Scientific Annual Report 2019

NETHERLANDS
CANCER
INSTITUTE
ANTONI VAN LEEUWENHOEK

Contents

Scientific Annual Report 2019

**Director of Research
René Medema**

Introduction

It is my pleasure to present the 2019 Scientific Annual Report of the Netherlands Cancer Institute. In it, we hope to convey how we have contributed to improving the prospects of cancer patients by integrating state-of-the-art fundamental research, translational research, and clinical research.

When I sat down to write these introductory words, I found it as difficult as each year to select just a few research highlights out of the many, with the aim of giving an idea of what we have learned and accomplished in 2019. We have all worked so hard, published beautiful papers or started or finished innovative clinical trials. But then I pictured the last or penultimate slide of all our PowerPoint presentations: the one in which we acknowledge all the people who have contributed to our project. And once again I realized the importance of collaboration in cancer research. Here are some examples of our collaborative efforts in 2019.

Collaboration between the lab and the clinic is part and parcel of daily life in our Comprehensive Cancer Centre, in which some 45 nationalities are represented. In 2019, this collaboration between individual researchers and oncologists has again resulted in new insights into the mechanisms of cancer and into new patient impact.

Since the summer of 2019, all oncologists within our hospital have been participating in a new clinical study in which we investigate, as the first hospital in the world and in collaboration with the Hartwig Medical Foundation, whether whole genome sequencing of tumour DNA can be implemented in standard cancer diagnostics.

Our lab and clinic also closely collaborate with our pharmacy. In 2019, we have been building a brand new pharmaceutical centre equipped with innovative facilities that include clean rooms for developing advanced cellular therapies. When this becomes operative, it will lead to an even more fruitful integration of our research labs, our clinical research and our pharmacy.

In 2019, the NKI and the Dutch Cancer Society designed a new cooperation agreement, covering the next five years. It devotes an annual €16.8 million for research at the Netherlands Cancer Institute. The link between the Dutch Cancer Society and the Netherlands Cancer Institute is a strong one and goes back to 1951. The fact that the Dutch Cancer Society is supporting us for another five years with this level of funding attests to their strong confidence in our work. In the years to come we will be working towards three common goals: making the results of scientific research accessible to patients more quickly, making both new and existing drugs more readily available, and improving the quality of life of everyone facing cancer or dealing with its aftermath.

We also highly cherish our collaboration with all Dutch universities, including their medical centres, where the vast majority of our group leaders have a chair. In 2019, in their inaugurals, our recently appointed professors presented exciting plans for multidisciplinary collaboration with their university colleagues, aimed at generating new knowledge not only about cancer but also about other diseases, new methodologies and technologies, or about the human immune system.

Many of our group leaders are also affiliated with the Oncode Institute, which unites top cancer research groups within the Netherlands and enables new collaboration in various domains. In November 2019, for instance, our institute hosted the launch of the Patient Perspective Program, which connects patients and cancer survivors to Oncode labs or individual Oncode researchers. This should decrease the distance between Oncode

researchers and patients so they can explore, investigate and understand each other's worlds.

Clinical research has always been impossible without collaboration with many professional partners, including pharmaceutical companies, health insurance companies, health care authorities, policy makers and thousands of patients. Collaboration has always been key in large randomized studies, but it is also becoming increasingly important in generating critical mass in innovative studies aimed at personalized medicine. These are studies with small cohorts of patients who often have rare molecular tumour profiles. At the European level, Cancer Core Europe, in which seven leading cancer centers, including the NKI, have joined forces, is a case in point.

Within the EU, preparations for Horizon Europe, the next Research and Innovation Framework Programme, are in full swing. We are proud and happy that Regina Beets-Tan, head of our Radiology department, has been selected by the European Commission to be a member of Horizon Europe's Mission Board for Cancer. Also, by working together in EU-LIFE with 13 other leading life science institutes, we can raise a powerful voice to convince the European Commission of the importance of fundamental research for the future health and well-being of Europe and its citizens.

Close collaboration is also required at a global level and our research groups collaborate with other groups all over the world. In 2019, the NKI signed a declaration of intent for collaboration in clinical research with the Sun Yat-sen University Cancer Centre, which is one of best comprehensive cancer centres in China. The year before, the Netherlands Cancer Institute already signed a collaboration agreement with the Renji Hospital in Shanghai for the training of postdocs.

In the Netherlands, average five-year survival rates for cancer have been rising by 1% over the past years, and the percentage of patients alive five years after diagnosis is now 65%, according to the Netherlands Cancer Registry. This is good news.

Journalists often ask us whether, at a certain point in time, we will have 'conquered' cancer or have made it into a chronic disease. Our oncologists, who know from day-to-day experience that there are still many patients they cannot help, tend to be very modest. We also know that cancer will always be part of life, in an ageing society.

FIGURE 1
CORE RESEARCH FUNDING THE NETHERLANDS CANCER INSTITUTE - ANTONI VAN LEEUWENHOEK HOSPITAL BY THE DUTCH CANCER SOCIETY AND THE MINISTRY OF HEALTH, WELFARE AND SPORT IN THE PERIOD 2007-2018 IN MILLION EUROS.

- DUTCH CANCER SOCIETY
- MINISTRY OF HEALTH, WELFARE & SPORT*
- TOTAL

* EXCLUDED ARE THE REIMBURSEMENTS FOR INTEREST
  AND DEPRECIATION OF BUILDINGS

And unfortunately, survival rates for certain cancers, such as ovarian and pancreas cancer are still depressingly low.

And yet, in the Netherlands Cancer Institute, we believe that cancer need not be a terminal disease. We believe that within decades, cancer will have become a chronic disease that can be controlled, with good quality of life for the patients. We dare express this vision because we, as a global research community, are making steady progress in understanding the biology of cancer and in exploiting its Achilles heels. I am convinced that there are many more fundamental and practice-changing breakthroughs to come that will sooner or later benefit individual patients all over the world.

However, whether we will be able to realize our vision partly depends on public investment in basic, curiosity-driven research. As I already mentioned, in 2019, the European Commission established the Mission Board for Cancer, as one of five mission boards established to help us solve our generation's biggest challenges.

This was a wise decision, in our opinion. But real health impact is not sustainable without strong and continued support for research aimed at understanding the fundamental mechanisms behind health and disease. Together with our partner institutes in EU-LIFE, we work hard to get this message along in Brussels.

I end by thanking all our employees and everyone who supported us and collaborated with us in 2019. Since the foundation of the Netherlands Cancer Institute in 1913, we have received enormous support and commitment from our employees, volunteers and sponsors. I thank Tom de Swaan, who retired as chair of our supervisory board in 2019 and I welcome his successor Lodewijk Hijmans van den Bergh. I also want to thank the Dutch Cancer Society for their renewed institutional support and the Ministry of Health, Welfare and Sport for their substantial core funding. And above all, I would like to extend my sincere gratitude to all our patients willing to take part in our clinical studies. Your confidence in our capacity to make progress has again been invaluable.

René Medema
Director of Research

RESEARCH HIGHLIGHTS

In all five of our research themes, much progress has been made in understanding cancer and bringing our knowledge to the clinic, to the patient, and to society. Often, these were small but crucial steps, but we also discovered important new mechanisms, new methodologies or new ways of diagnosing or treating patients. Here, I present just some of our highlights from the year 2019.

MOLECULAR ONCOLOGY

Which DNA variants really make a difference?

No two humans have the same DNA. But which of those millions of variants really affect the functioning of our cells? To find those needles in a haystack, the Bas van Steensel group developed a new powerful technique (named SuRE) that reveals which changes in the genetic code affect the activity of genes. They labelled billions of small pieces of DNA with a unique barcode, put them into another cell and then measured how active the built-in pieces of DNA were. This allowed them to identify more than 30,000 of these SNPs that alter the activity of enhancers or promotors. Since these are often mutated in cancer cells, this is valuable new knowledge for cancer researchers. (Joris van Arensbergen et al. *Nature Genetics,* June 2019*)*.

Compacting DNA from spaghetti to macaroni

Chromosome condensation is essential for accurate cell division. In 2019, the chromosome biology group of Benjamin Rowland, in a collaboration with nanobiologists at TU Delft, set some important steps in unraveling the mystery of how the condensin protein complex turns chromosomes from 'spaghetti' into 'macaroni'. They showed that condensin's ATPase has a dual, balancing, role that allows condensin to correctly structure chromosomes in chromosome condensation. Mutation of one ATPase site impairs condensation, while mutating the second site makes condensing hyperactive. This likely reflects a universal mechanism in all domains of life. (Ahmed Elbatsh et al., *Molecular Cell*, October 2019).

Solving a 3D molecular scissors structure

Microtubules are continuously modified to serve different purposes within the cell. For this, their tyrosine tails are cut and put back by different enzymes. After researchers from the Netherlands Cancer Institute and Oncode Institute, in 2017, found the identity of the scissors, a team, led by Thijn Brummelkamp and Tassos Perrakis now determined the 3D solved crystal structure and mechanism of these peculiar molecular end-tail scissors. Detyrosynation of tubulin has been implicated in correct segregation of chromosomes during mitosis. The cancer drug paclitaxel affects detyrosynation of microtubules. (Athanasios Adamopoulos et al., *Nature Structural & Molecular Biology*, July 2019).

Which genes drive BRCA1-mutated breast cancer?

BRCA1-mutated breast cancer is primarily driven by DNA copy-number alterations (CNAs) containing large numbers of candidate driver genes. But which genes are true drivers? To study this, novel approaches are needed for high-throughput in vivo manipulation of gene function. The Jos Jonkers group developed genetically engineered mouse models of BRCA1-deficient breast cancer that permit rapid introduction of putative drivers. Using this technique, they found two collaborating drivers (MYC and MCL1). Moreover, inhibition of the latter potentiates the efficacy of PARP inhibition in mice, underscoring the therapeutic potential of this combination. (Stefano Annunziato et. al, *Nature Communications*, January 2019).

New national infrastructure for genomic screening

The use of large-scale screening methods and implementation of new genome editing technologies requires extensive expertise, a lot of collaboration, and a dedicated infrastructure. Roderick Beijersbergen, together with researchers from Leiden University and the UMCG, received 2 million euros from the Dutch Cancer Society to build such an infrastructure. This will lead to the discovery of new therapeutic strategies for cancer.

European consortium for structural biology

The EU, through its Horizon 2020 program, has invested €10 million in the iNEXT-Discovery consortium, led by Anastassis Perrakis, for enabling European scientists to perform high-end structural biology research with state-of-the-art equipment that is often unavailable in their home countries.

PRECISION MEDICINE

A 'one-two-punch' strategy for precision medicine

Powerful drug combinations are becoming increasingly important for treating cancer and tackling drug resistance. However, many promising combinations will be too toxic for patients. In 2019, the Rene Bernards group with other NKI researchers showed that first inducing senescence in tumor cells and subsequently killing off the vulnerable senescent cells may be a promising way out of this problem. In mice, this so-called 'one-two-punch' strategy proved to be effective in treating liver cancer. Bernards is now looking for common vulnerabilities induced by senescence in other cancer types. (Cun Wang et al., *Nature*, September 2019).

World's largest data base of metastasized tumours

Dutch researchers, including Emile Voest, Neeltje Steeghs and Egbert Smit, have been the first to map the landscape of DNA errors in thousands of metastasized tumours. In 62% of the patients, actionable events were found that may lead to new treatment options targeting specific characteristics of individual tumors. The study was conducted by the Centre for Personal Cancer Treatment (CPCT), co-founded by the NKI, to which 46 Dutch hospitals are currently affiliated, in collaboration with Hartwig Medical Foundation. The publication highlights a decade-long Dutch effort in building the world's largest data base of metastasized tumours, aimed at putting an end to the 'one size fits all' approach in systemic treatment, based on tumour type. (Peter Priestly et al., *Nature*, October 2019).

The DRUP: from clinical to societal impact

The Drug Rediscovery Protocol (DRUP study) was launched in 2016 as part of the above-described Dutch pioneering effort. In this innovative pan-cancer clinical basket trial, patients with metastatic cancer without any further treatment options, are given an off-label medicine targeted at their molecular tumour profile. In 2019, the research team, co-led by Emile Voest, published the first results. From the first 215 patients, 34% benefited from the treatment. One specific cohort (nivolumab for MSI-tumours) even showed a response rate of 67%. To grant new patients access to this promising treatment, oncologists, the National Health Care Institute, health insurers and the drug producer together devised a new personalized reimbursement model, that already received a lot of interest from politicians and policy makers and the international research community. (Diana van der Velden et al., *Nature*, September 2019).

New research into sarcomas

Sarcomas are rare and under-researched tumours that come in many subtypes. Unfortunately, sarcomas are usually insensitive to existing therapies. Daniel Peeper and PhD student Julia Boshuizen received a grant from the Dutch Cancer Society to find out why this is the case and to hopefully lay the foundation for more effective treatments. A commonality of all sarcomas is that they produce a lot of the AXL protein, more than any other type of cancer. The researchers will investigate which role AXL plays in the growth and therapy resistance of sarcomas, and whether patients may benefit from AXL inhibitors that are already being developed.

IMMUNOTHERAPY

How one infamous oncogene hijacks the immune system

In 2015, Karin de Visser demonstrated that some breast tumours mobilise neutrophils in the patient's body via a chain reaction of signal molecules. These neutrophils promote metastasis, by counteracting T cells. But where does this chain reaction start? And why do some breast tumours abuse neutrophils for their own ends, while others do not? In 2019, her group with the Jos Jonkers group showed that the genetic make-up of a primary tumour itself determines if it can hijack the entire immune system. They saw that P53-defective tumour cells, via Wnt-signaling, trigger an inflammatory response in the blood, which in turn leads to metastasis. In p53-deficient mice, inhibiting these signals prevents the hijacking of neutrophils and also inhibits the metastasis process. (Max Wellenstein et. al. *Nature*, July 2019).

Neoadjuvant immonutherapy is conquering the clinic

Immunotherapy prior to surgery is thought to have several advantages. It will hopefully prevent metastasis, surgery will be easier, response to immunotherapy can be studied at molecular level in the resected material, and last but not least: the immune response induced by the immunotherapy is expected to be broader and better when the tumour is still present in the body. In the OpACIN-neo study, the Christian Blank group showed that neoadjuvant immunotherapy was effective in 77% of 89 patients, with acceptable side effects. Moreover, after 8 months, none of the responders had relapsed. The study earned researcher Lisette Rozeman the Antoni van Leeuwenhoek Award, and ASCO ranked it one of the highlights of the year (for surgery!). The NKI is also investigating this treatment strategy in a whole range of other cancer types. (Lisette Rozeman et. al, *Lancet Oncology*, May 2019).

Grant for personalized cellular therapy

Medical oncologist John Haanen, researcher Wouter Scheper and pharmacist Joost van den Berg received a €1,5 million ZonMW grant to set up a new T cell therapy in which genetically engineered T cells are multiplied and given back to the patient. In this exploratory clinical study, 5 patients with metastatic melanoma each receive a customized set of T cells each engineered to express a T cell receptor that specifically recognize their tumour. The researchers will each research in the Schumacher group, who set up a method to identify neo-antigens and find the associated T-cell receptors.

TABLE 1

SHORT TERM CITATIONS AND IMPACT OF SCIENTIFIC ARTICLES PUBLISHED BY
THE NETHERLANDS CANCER INSTITUTE RESEARCH STAFF 2005-2019

PUBLICATION YEAR	PUBLICATIONS*	CITATIONS	CITATIONS/ PUBLICATIONS	IMPACT
2005	405	6350	15,7	2461
2006	435	6336	14,6	2608
2007	430	5605	13,0	2969
2008	442	5657	12,8	2590
2009	511	7904	15,5	3074
2010	481	8788	18,3	2841
2011	459	8651	18,8	3110
2012	573	9268	16,2	3333
2013	512	8989	17,6	3228
2014	596	9599	16,1	3935
2015	659	19618	29,8	5234
2016	793	15087	19,0	5344
2017	727	18371	25,3	5891
2018	771			6024
2019	**896			**7129

*   SINCE 2014 A NEW STANDARD WAS USED TO PERFORM THE CITATION AND IMPACT FACTOR ANALYSES.
    CONSEQUENTLY THE NUMBERS CAN DIFFER FROM THE PREVIOUS YEARS.

** ANALYSIS WAS PERFORMED IN MARCH 2020. DATA CAN BE SUBJECT TO CHANGE.

Chemotherapy may help immunotherapy succeed

Preclinical research within and outside the NKI has shown that a low dose of chemotherapy or radiotherapy can stimulate the immune system and help immunotherapy succeed. In the phase 2 TONIC study, led by medical oncologist Marleen Kok, this has now been investigated in patients with metastases from triple-negative breast cancer. The results of part 1 of the study show that in particular, pretreatment with cisplatin and doxorubicin appears to increase the effect of immunotherapy. In the lab, researchers did indeed see T cells entering the tumour after pre-treatment with chemotherapy. (Leonie Voorwerk et al., *Nature Medicine*, May 2019)

IMAGE-GUIDED INTERVENTIONS

4D image helps radiotherapists target moving tumours

In a clinical trial, the NKI has become the first hospital in Europe to administer radiation therapy to a cancer patient using a 4D image generated by the MRI Linac. This allows radiotherapists to take into account the movements of a tumour during delivery of the radiation, due to the patient's breathing for example. The 4D technology was developed by PhD student Tessa van de Lindt, who, in 2019, defended her thesis, supervised by Jan Jakob Sonke and Uulke van der Heiden. A clinical trial led by Marlies Nowee will show whether it is technically feasible to treat all patients with limited liver metastases using this new method.

Cerenkov light reveals remaining cancer cells

Cerenkov radiation is a by-product of PET-scans. In 2016, nuclear medicine expert Marcel Stokkel came up with the idea of putting Cerenkov light imaging to use in the operating theatre. In May 2019, after some years of research, a clinical study was started with support of the Dutch Cancer Society, in which [68]Gallium-PSMA Cerenkov Imaging is used to better visualize cancer cells in the resection margins of an excised prostate. The surgeon can then continue surgery and remove any residual tumour tissue, thus sparing many patients another operation or additional radiotherapy. The technical study underlying this trial was published in 2019 by Judith olde Heuvel et al. (*EJNMMI Phys.*)

Augmented reality enters the operating theatre

In order to improve precision when excising malignancies, oncological surgeon Theo Ruers received a grant of €500.000 from the Dutch Cancer Society for developing an augmented reality system that adds previously recorded images of the tumour to live images on the operation monitor. If the development stage runs smoothly, he will use augmented reality in the final year of his research on colon cancer patients with liver metastases.

Image-guided immunotherapy

Only a subset of patients responds to immunotherapy, urging the quest for predictive biomarkers. Researchers led by Hugo Aerts and Regina Beets analyzed 1055 primary and metastatic lesions from 203 patients with advanced melanoma and non-small-cell lung cancer undergoing anti-PD1 therapy. Their results indicate that radiographic characteristics of lesions on standard-of-care imaging may function as noninvasive biomarkers for response, and be used for improved patient stratification. (Stefano Trebeschi et al. *Annals of Oncology*, March 2019).

New collaboration for advancing nuclear medicine

In 2019, internationally-operating nuclear service provider NRG-Petten, four university medical centres, the NKI and other partners, including the German Cancer Research Centre, initiated the so-called 'FIELD-LAB' for nuclear medicine. The 'Advancing Nuclear Medicine Consortium' was launched to speed up development and translation of new generation radiotracers.

SURVIVORSHIP AND EPIDEMIOLOGY

Does breast cancer treatment increase heart failure risk?

Now that a substantial group of cancer patients survive cancer, it is important to evaluate how late complications of treatment affect their long-term survival. In 2019, the Floor van Leeuwen epidemiology group published the first study to assess relationships between radiation dose to the heart, anthracycline dose and the risk of subsequent heart failure in women treated for early breast cancer. Breast cancer radiotherapy in itself was not associated with increased HF risk, but strongly elevated heart failure risks were observed after treatment with anthracyclines and also after treatment with trastuzumab. This emphasizes the need for ongoing efforts to evaluate preventative strategies. (Naomi Boekel et al., *Eur. Journal of Heart Failure*, 2019).

Young adults with cancer deserve more research

Every year, 3800 18-to-39-year-olds living in the Netherlands are diagnosed with cancer. For young adult cancer patients, referred to as AYAs, more research is sorely needed. In 2019, researcher Olga Husson received an NWO Vidi grant to examine which young adult cancer patients are at risk for poor health outcomes and why. This came on top of the Dutch Cancer Society Grant of €2,8 million that Husson and group leader Winette van der Graaff had already been awarded in December 2018 to set up a unique national research platform for collecting data from 4000 young adults.

Comparing cognitive function

Research suggests that non-central nervous system tumours may negatively impact the brain, apart from effects of cancer treatment. To study this, the Sanne Schagen group compared the course of cognitive functioning of participants who were diagnosed with cancer with the cognitive functioning of participants without cancer. However, unlike previous studies, they investigated cognitive functioning just *prior* to diagnosis, in order to minimise the effects of psychological factors surrounding a cancer diagnosis. These data were available through the Rotterdam Study, a prospective, population-based cohort study. Unlike studies that examined patients shortly *after* their diagnosis, they found no difference in cognitive functioning between participants with and without cancer. (Kimberley van der Willik et al., *Journal of the National Cancer Institute,* September 2019).

Keep moving!

In October 2019, an international team of exercise oncology experts issued new research-based standards for health care workers and fitness professionals, to help them design and deliver exercise programs that aim to lower the risk of developing certain cancers and best meet the needs, preferences and abilities of people with cancer. Martijn Stuiver, physical therapist and clinical epidemiologist in the NKI, was one of two experts from the Netherlands who participated in developing the new guidelines. (Kathryn Schmitz et al., *CA: A Cancer Journal for Clinician, 16 October 2019).*

HONOURS AND APPOINTMENTS

– Biologist Jacco van Rheenen was awarded the bi-annual Ammodo Science Award, a prize for fundamental science.
– Epidemiologist Floor van Leeuwen received the 17th Rosalind E. Franklin Award for Women in Science.
– Senior postdoc Daniela Thommen has been awarded the Pfizer Forschungspreis.
– Professor emeritus Piet Borst was awarded an honorary doctorate from the University of Bern.
– Radiologist Regina Beets-Tan has been selected by the European Commission to be a member of Horizon Europe's Mission Board for Cancer.
– Director of Research René Medema has been appointed chair of EU-LIFE, an alliance of thirteen leading life science institutes in Europe.
– Cancer researcher Rene Bernards has been elected to the American Academy of Arts and Science.

- Group leaders Emile Voest, Jannie Borst and Tassos Perrakis were selected to join Oncode Institute
- Immunologist and tumour biologist Karin de Visser has been awarded a VICI grant from the Netherlands Organisation for Scientific Research (NWO)
- The European Research Council (ERC) has assigned an advanced grant to Reuven Agami for gene regulation research.
- Researcher Elzo de Wit has been awarded a €2 million Consolidator Grant by the European Research Council for research on DNA folding.
- Researchers Olga Husson, Leila Akkari and Martin Fast each received an €800.000 Vidi grant from NWO to develop their own innovative line of research.
- Karin de Visser, Marjanka Schmidt, and Paul Baas were appointed professor at Leiden University. Fred van Leeuwen was appointed professor at the University of Amsterdam.

CLINICAL TRIALS:
CROSS-FERTILIZATION BETWEEN LAB AND CLINIC

Within the Netherlands Cancer Institute, almost 25% of our patients are involved in a clinical trial. Moreover, a substantial number of our clinical trials are either based on our own fundamental or translational research, or run in close collaboration with our basic or translational groups (see table 2). This cross-fertilization has frequently led to new diagnostic tools or therapies.

An example: from bench to BEACON

To give just one example: In September 2019, the New England Journal of Medicine published the results of the BEACON study. This was a large international study for patients with metastatic BRAF-mutated colorectal cancer who did not respond well to standard systemic treatment. The BEACON study, in which the NKI participated, compared standard treatment of chemotherapy plus an EGFR inhibitor with an experimental combination of BRAF and EGFR inhibitors, without chemotherapy. Part of the patients also received a MEK inhibitor. We are proud that this new rational combination treatment, which gives these patients some extra months of life, not only originated in the laboratory of Rene Bernards in the Netherlands Cancer Institute (results published in Nature in 2012) but was also tested in several clinical trials in our own hospital. In April 2020, the FDA has approved this treatment for patients with advanced BRAF-mutated colorectal cancer.

TABLE 2

TABLE 2 PRESENTS A SELECTION OF OUR CLINICAL TRIALS THAT ARE BASED ON THERAPEUTIC CONCEPTS DEVELOPED OR CO-DEVELOPED FROM OUR OWN FUNDAMENTAL AND TRANSLATIONAL RESEARCH. (THE COMPLETE LIST OF OUR CLINICAL TRIALS IS PRESENTED ELSEWHERE IN THIS SCIENTIFIC ANNUAL REPORT).

AVL CODE	REFERENCE	NOVEL TREATMENT	TUMOR TYPE
M06CRI	1,2,3	Chemoradiotherapy + surgery	Resectable Gastric Cancer
N10DMY	8	Dose reduction of preoperative RT	Liposarcoma
M11ART	9	Cisplatin + Adaptive High Dose Radiotherapy	Head & Neck Cancer
M13TNB	5-7; 12-16	Paclitaxel +/- VEGFi	BRCA21-like Breast Cancer
N13NAV	18, 36	Image-guided surgical navigation	Colorectal Cancer
M14HUM	25	Organoid biobank for drug discovery	Solid tumours
M14POS	20,21, 43	Tamoxifen + P13Ki	Breast Cancer
M14PRE	68.69,70	Predicting Response to Enzalutamide as 2nd line Treatment	Metastatic Castr. Resistant Prostate Cancer
M14TIL	19	TIL vs. Ipilimumab	Metastatic Melanoma
M14TUM	38	Tumor organoids: predict sensitivity to treatment	Colorectal Cancer
N14DAR	68, 69, 70	neoadjuvant enzalutamide	Prostate Cancer
N14ITO	34	Immunogenecity of tumor organoids	Colorectal cancer, Lung cancer
N14RCS		Smart tools during surgery	Colorectal cancer

Code	Refs	Title	Indication
M15CRI	1-3, 33	Preop. chemoradiotherapy vs chemo+radiotherapy	Resectable gastric cancer
M16BCR	10, 37	Binimetinib + Encorafenib + Cetuximab (BEACON)	BRAF-mutant metastatic Colorectal Cancer
M16OPN	32	Neoadjuvant Ipilimumab and Nivolumab (optimal combination)	Melanoma
M16OST	68,69,70	Finding biomarkers for optimal 2nd-line treatment secquence	
N16PRB		Pre-operative breast irradiation	Breast Cancer
N16IMC	44	Neoadjuvant ipilimumab & nivolumab	Advanced or recurrent head & neck cancer
N16NCI	47	Neoadjuvant nivo, ipi&COX2i	early-stage Colorectal Cancer
N16NEON		Personalized T-cell therapy	Various solid tumours
N16STS		Biobank of patient-derived xenografts of soft tissue sarcomas	Soft tissue Sarcomas
N16UMB		UMBRELLA-I MR guided Adaptive Radiation Therapy	all sites
N16VOM	45	HDACi vorinostat in resistant BRAF-mutated Melanoma	Advanced melanoma
M17GEL	71	Carboplatin + Atezolizumab (GELATO)	locally advanced or metastatic Lobular breast cancer
N17MRB		Monitoring MRI changes before and during Radiotherapy	Glioblastoma
M17SDM		Decision aid for breast cancer and DCIS patients	Breast Cancer
N17PSI	46, 50, 51	Increasing pazopanib exposure by splitting intake moments	Osteosarcoma
M17TDM	39	Therapeutic drug monitoring for oral anti-cancer drugs	All sites
M18CYP		Effect of erythromycin on pharmacokinetics of palbociclib	Breast Cancer
N18BREL	65, 66, 67	MR-guided adaptable radiation	all sites
M18IWO	58, 59	Internet-based cognitive rehabilitation for cancer survivors	
N18CLI	52	Cerenkov Luminescence Imaging during surgery	Prostate Cancer
M18LORD	61, 62, 63	Management of low-grade DCIS	DCIS/Breast Cancer
M18QUE	53, 54	Impact of the diagnostic trajectory on stage at diagnosis, primary treatment, clinical outcome and quality of life	Sarcoma
N18TRZ	55	Neoadjuvant radiotherapy + atezolizumab&bevacizumab	Rectal Cancer
N18ULN	18, 36, 60	Ultrasound-based navigation during liver surgery	Liver Tumours
N18WGS	48	WGS implimention in standard care diagnostics (WIDE)	All sites
M19CON	61, 62, 63	Control DCIS: ipsilateral invasive breast-cancer free rate after 10 years	Breast Cancer
M19DON	31, 32	Neoadjuvant Domatinostat + Nivolumab +Ipilimumab (DONIMI)	Melanoma stage III
M19STR		CYP3A4*22 genotype-guided dosing of TKIs	All sites
M19SUS	56, 57	Mapping of Sentinel lymph node Using SPECT/CT	Head & Neck Cancer

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Board members

**Chairman of
Board of Governors
LJ Hijmans van den Bergh**
as from May 2019

**Chairman of
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T de Swaan**
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**Board
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EE Voest
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M van der Meer
Director of Organisation,
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Vera Atema MSc PhD student
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Evalien Veldhuijzen MSc PhD student
Barbara Wollersheim MSc PhD student

Selected
publications

Koole S, Kieffer JM, Sikorska K,
Schagen van Leeuwen JH, Schreuder
HWR, Hermans RH, de Hingh IH,
van der Velden J, Arts HJ, van Ham
MAPC, Aalbers AG, Verwaal VJ, van
de Vijver KK, Sonke GS, van Driel WJ,
Aaronson NK. Health-related quality
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surgery with or without hyperthermic
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Behavioral interventions in clinical oncology and health-related quality of life assessment

This research line has two primary foci: (1) development and testing of behavioral and psychosocial interventions to reduce symptom burden and improve the HRQL of patients with cancer; and (2) development and use of health-related quality of life (HRQOL) assessments in clinical research and clinical practice.

Efficacy of internet-based cognitive behavioral therapy (iCBT) on treatment-Induced menopausal symptoms in breast cancer survivors

In this randomized, controlled trial, we randomly assigned 254 BC survivors to a therapist guided or a self-managed iCBT group or a waiting-list control group. Compared with the control group, both iCBT groups reported a significant decrease in the perceived impact of HF/NS (p<.001, ES=.63 and.56) and improvement in sleep quality (p<.001, ES=.57 and .41). The guided group also reported significant improvement in overall levels of menopausal symptoms (p=.003, ES=.33), and night sweats frequency (p<.0012, ES=.64). At longer-term (6-month) follow-up, the effects remained significant with smaller ES, and also included significantly reduced frequency of hot flushes. iCBT, with or without therapist support, has salutary effects on the perceived impact and frequency of HF/NS, overall levels of menopausal symptoms and sleep quality.

Sustained effects of Internet-based cognitive behavioral therapy (iCBT) on sexual functioning of breast cancer survivors

We evaluated the long-term efficacy of iCBT) for sexual dysfunctions in 84 breast cancer survivors (BCS). The positive immediate post-intervention effects of the intervention observed in our randomised controlled trial on overall sexual functioning, sexual desire, sexual arousal, vaginal lubrication, discomfort during sex, sexual distress and body image at immediate post-treatment were maintained at 3- and 9-month follow-up. Although sexual pleasure decreased during follow-up, it did not return to baseline levels. Our findings provide evidence that iCBT has a sustained, positive effect on sexual functioning and body image of BCS with a sexual dysfunction.

Patient-reported outcomes following treatment of localized prostate cancer and their association with regret about treatment choices

In this prospective, observational study we documented: (1) differences in physical and psychosocial patient-reported outcomes (PROs) following radical prostatectomy, external beam radiotherapy, brachytherapy, and active surveillance; and (2) how these PROs and other factors are associated with treatment decision regret. The sample included 434 men who completed validated PRO measures at baseline (pre-treatment) and 3, 6 and 12 months post-treatment. At one year follow-up, those men who had received: (1) radical prostatectomy reported significantly (*p*<0.01) more urinary incontinence, worse sexual function, more hormonal/masculinity-related symptoms, and less emotional distress; (2) external beam radiotherapy reported significantly worse sexual function, more hormonal/masculinity-related symptoms, and more physical distress; and (3) brachytherapy reported significantly more urinary obstruction and irritation symptoms, compared to patients under active surveillance. Decision regret was not significantly different across treatment groups. At one year follow-up 23% of the patients reported clinically relevant decision regret, which was associated with hormonal-related symptoms, educational level, and positive surgical margins.

Uncovering novel vulnerabilities of cancer

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Pierre-René Körner PhD student
Itamar Kozlovski PhD student
Jane Sun PhD student
Naomi Blommaert Technical staff
Remco Nagel PhD Technical staff

Selected publications

Milne K, Sun J, Zaal, EA, Mowat J, Celie PHN, Fish A, Berkers CR, Forlani G, Loayza-Puch F, Jamieson C, et al. A fragment-like approach to PYCR1 inhibition. Bioorg Med Chem Lett 2019;29:2626-2631

Sun J, Nagel R, Zaal EA, Ugalde AP, Han R, Proost N, Song JY, Pataskar A, Burylo A, Fu H, et al. SLC1A3 contributes to L-asparaginase resistance in solid tumors. EMBO J 2019;38:e102147

Korkmaz G, Manber Z, Lopes R, Prekovic S, Schuurman K, Kim Y, Teunissen H, Flach K, Wit E, Galli GG, et al. A CRISPR-Cas9 screen identifies essential CTCF anchor sites for estrogen receptor-driven breast cancer cell proliferation. Nucleic Acids Res 2019;47:9557-9572

Our main research objective is to identify novel cellular vulnerabilities that can be exploited for cancer therapies. For this purpose, we developed, and are still developing, innovative genomic and genetic tools. Key targets are regulatory DNA elements such as enhancers and chromatin domains, mRNA translation, and non-coding RNAs. In particular, we employ novel and unbiased functional genetic screening approaches, perform mechanistic studies to understand their connection with the cancerous phenotype, and use this information for the development of innovative cancer therapeutic approaches.

SLC1A3 contributes to L-asparaginase resistance in solid tumors

Treating cancer with amino acid deprivation schemes showed limited success so far. Only in the case of acute lymphoblastic leukemia a combined treatment of L-Asparaginase with chemotherapy increased patient cure to ~95%. Attempts to broaden this treatment to solid cancer have failed so far. In 2016, we have developed differential ribosome profiling technology (Diricore) to uncover treatment-induced cellular amino acid shortages. Now, we used this technology, in combination with a genome-wide CRISPR-Cas9 functional genetic screen and identified SLC1A3, an aspartate and glutamate transporter, as a novel contributor to L-Asparaginase resistance in cancer cells. Our findings identify a novel role for SLC1A3 in ASNase resistance and suggest that restrictive aspartate and glutamate uptake might improve ASNase efficacy with solid tumors. (see figure).

Targeting the proline production pathway in cancer

PYCR1 is the final enzyme involved in the biosynthesis of proline and has been found to be upregulated in various forms of cancer. Due to the role of proline in maintaining the redox balance of cells and preventing apoptosis, PYCR1 is emerging as an attractive oncology target. Previous PYCR1 knockout studies led to a reduction in tumor growth. We reported this year the design and synthesis of the first tool compounds as PYCR1 inhibitors, derived from pargyline. Structural activity studies have revealed the key determinants of activity, with the most potent compound showing improved activity in vitro in enzyme and pathway relevant effects in cell-based assays.

Functional genetic screens of regulatory DNA elements

Functional characterization of non-coding regulatory DNA elements in the human genome is a major genomic challenge and the maturation of genome-editing technologies is revolutionizing our ability to achieve this task. In 2016 we initiated a CRISPR-Cas9-based genetic approach to functionally annotate tumor suppressor and oncogenic regulatory DNA elements. In 2019 we continue to use this technology to identify key players in tumor progression.

A major determinant of chromatin structure is the CCCTC-binding factor (CTCF), that dimerizes and together with cohesin stabilizes chromatin loops and forms the boundaries of topologically associated domains. However, whether CTCF-binding elements (CBEs) are essential for ERα-driven cell proliferation is unknown. To address this question in a global manner, we implemented this year a CRISPR-based functional genetic screen targeting CBEs located in the vicinity of ERα-bound enhancers. Our data showed that distinct CTCF-mediated chromatin structures are required for ERα-driven breast cancer cell proliferation.
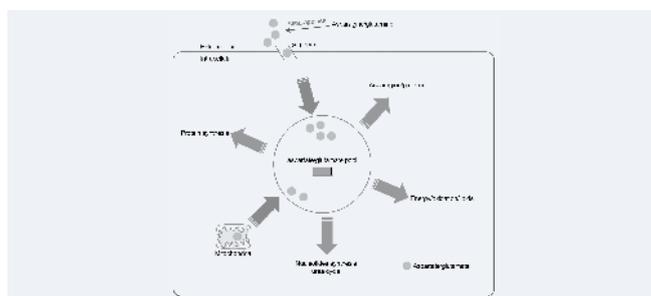
A novel role for the aspartate/glutamate transporter SLC1A3 in ASNase resistance. SLC1A3-mediated aspartate/glutamate fuels protein synthesis, energy and nucleotide synthesis to allow proliferation in the absence of Asparagine.

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Jeremy Tessier MSc PhD student
Marnix de Groot MSc Technical staff
Shanna Handgraaf MSc Technical staff

Publications

Kielbassa K#, Vegna S#, Ramirez C, Akkari L*. Understanding the Origin and Diversity of Macrophages to Tailor Their Targeting in Solid Cancers. Front Immunol, 2019;10:2215

Sanghvi VR, Leibold J, Mina M, Mohan P, Berishaj M, Li Z, Miele MM, Lailler N, Zhao C, de Stanchina E, Viale A, Akkari L, Lowe SW, Ciriello G, Hendrickson RC, Wendel HG. The Oncogenic Action of NRF2 Depends on De-glycation by Fructosamine-3-Kinase. Cell 2019;178(4):807-819.e21

Wang C#, Vegna S#, Jin H#, Benedict B#, Lieftink C, Ramirez C, de Oliveira RL, Morris B, Gadiot J, Wang W, du Chatinier A, Wang L, Gao D, Evers B, Jin G, Xue Z, Schepers A, Jochems F, Sanchez AM, Mainardi S, Te Riele H, Beijersbergen RL, Qin W*, Akkari L*, Bernards R*. Inducing and exploiting vulnerabilities for the treatment of liver cancer. Nature 2019;574 (7777)268-272

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Macrophage dynamics in cancer progression and response to treatment

Our laboratory is interested in the microenvironment-mediated mechanisms of tumor maintenance, progression and resistance to therapeutic intervention. We aim to uncover the vulnerabilities in the heterotypic communication between cancer cells and immune cells that can be targeted, in order to develop novel therapeutic alternatives for therapeutically challenging cancers, as brain and liver tumors.

Heterogeneity underlies glioma-associated macrophage functions during therapeutic response to standard of care radiotherapy

The role of tumor infiltrating bone marrow-derived macrophages (BMDM) and tissue-resident microglia (MG) in glioblastoma (GBM) has been studied mainly in primary gliomas, and remains poorly defined. We employed multiple genetically modified murine models combined with lineage tracing of macrophages to identify the transcriptional changes in BMDM/MG subpopulations during the course of radiotherapy treatment, a standard of care for glioma patients. We performed single-cell RNA sequencing combined with proteomics analyses to identify *de novo* education programs acquired by both macrophage subsets in recurrent GBM post radiotherapy. Interestingly, these transcriptional programs are reminiscent of neurodegenerative phenotypes. Moreover, our preliminary data suggest that this recurrence-specific rewiring of brain macrophages supports glioma relapse post treatment. Our current work now focuses on identifying which signaling pathways activation underlie these changes in order to target them pharmacologically and genetically and enhance the effect of radio/chemotherapy in aggressive gliomas.

Optimizing the combination between radio- and immunotherapy in glioblastoma

Incorporating anti-PD1 T-cell immunotherapy (IT) to the current standard of care treatment in glioblastoma has failed to provide therapeutic promises in recent clinical trials. In collaboration with Dr Gerben Borst, we are investigating the efficacy of concurrent as opposed to an adjuvant IT to radiotherapy. Importantly, we collaborate with Dr Dieta Brandsma and neurosurgeons at VUMC and Erasmus to obtain primary and recurrent human GBM, to identify additional alterations in the immune contexture of recurrent disease, including macrophage and T cell phenotype.

Analyses of the tumor microenvironment dynamics in hepatocellular carcinoma (HCC) initiation and progression

We have developed multiple HCC murine models using the relevant oncogenic drivers of this disease, by taking advantage of hydrodynamic gene delivery and the Sleeping Beauty-mediated somatic integration in mouse hepatocytes *in vivo*. By recapitulating the genetic diversity of this disease, we found that different oncogenic drivers distinctively shape the HCC tumor microenvironment, as seen in the human pathology. In this project, we generated aggressive or slow-growing HCC, thus providing a platform for immune-based therapies. We are currently examining the mechanisms responsible for genetic-dependent immune landscape shaping, and intervening on the dominant immune cell subset present at different stages of these genetically distinct HCCs.

Analyses of the tumor microenvironment dynamics in hepatocellular carcinoma (HCC) initiation and progression

In collaboration with Rene Bernards' lab, we have used a subset of our HCC models to successfully test novel pro-senescence/senolytic therapies. Our analyses of the tumor microenvironment response to induction of senescence *in vivo* revealed that both adaptive and innate immune cells are mobilized by senescent cancer cells. These findings are encouraging us to therapeutically target immune cells in the context of pro-senescence agents, to harness the potential of immune cells in this novel setting of treatment for HCC.

Oncologic Imaging Research

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**Group leader
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Paula Bos MSc PhD student
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Joost van Griethuysen MD PhD student
Kay van der Hoogt MD PhD student
Ieva Kurilova MD PhD student
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Niels Schurink MSc PhD student
Femke Staal MD PhD student
Marjanneh Taghavirazavizadeh MSc
PhD student
Teresa Tareco Bucho MD PhD student
Stefano Trebeschi MSc PhD student
Sophie Vollenbrock MD PhD student
Melda Yeghaian MD PhD student

Selected publications

Lambregts DMJ, […], Beets-Tan RGH.
Long-term imaging characteristics of
clinical complete responders during
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radiotherapy in oesophageal cancer.
British J Surg 2019;106(5):596-605

MR imaging for Personalised Treatment
Functional MRI for Organ preservation

Previous work in organ preservation of rectal cancer has shown that MRI can improve the selection of patients with clinical complete response after chemoradiotherapy. A multicenter rectal cancer Watch & Wait implementation trial, financed by the Dutch Cancer Society, aims to transfer the team's expertise to centers throughout The Netherlands and implement this treatment nationwide. Our organ preservation research was expanded to oesophageal cancer with clinical complete response after chemoradiotherapy. A study with 3 readers showed that diffusion weighted MRI reached AUCs of 0.70 for the detection of residual disease. A trial is currently running in collaboration with Erasmus MC, investigating the value of a multimodality approach towards selecting patients with clinical complete response.

Multiparametric MR imaging

Research projects in multiparametric MRI run in several cancer types.
In rectal cancer a multicenter study, funded by the Dutch Cancer society, aims to build models linking multiple MR parameters to clinical data to predict response and long-term outcome after treatment. In prostate cancer multiparametric imaging research investigates tumor phenotypes for advanced risk stratification and decision support systems for treatment management. In breast cancer deep learning modeling for lesion classification is executed using multiparametric breast MRI.

MRI of peritoneal carcinomatosis

Patients with limited peritoneal metastases from colorectal cancer may be candidates for cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS-HIPEC). Selection is based on surgical inspection during laparoscopy or laparotomy. The aim of our MR project, funded by the Netherlands Organisation of Scientific Research (NWO), is to investigate whether diffusion weighted MRI can be used to select these patients. The first studies showed that all patients with resectable disease were identified by MRI and none were overstaged. A second multicenter trial was recently funded by the NWO, addressing the role of diffusion weighted MRI in patients with peritoneal metastases from ovarian cancer.

Interventional Oncology

In a collaborative project with the interventional oncology team of MSKCC we identified factors that could improve patient selection and modify ablative treatment approach resulting in an increased local tumor control and reduction of complications following lung and liver thermal ablation. Image fusion guided FNA cytology - fusing real time US with pre-procedural CT, MR or PET-CT - showed improved detection of metastatic cervical nodes in head and neck cancer. Image fusion guidance of biliary drainage and of local liver lesion treatment have shown to improve treatment efficiency because of better visualization of the target.

Artificial Intelligence in Immunotherapy and Radiogenomics

Artificial Intelligence research is translational and leverages AI methodologies to develop non-invasive AI-biomarkers and bring clinically-usable algorithms into the clinic. The AI research focused on exploring predictive radiomics signatures of response to immunotherapy in several cancer types. Our study in 213 patients with melanoma and NSCLC treated with anti PD-1 showed that a radiomics signature derived from 1055 lesions at baseline CTs could predict response at 12 weeks with AUC up to 0.78.
A radio-genomics study - aiming to link radiomics signatures with clinically relevant genetic mutations - found in 400 colon cancer lesions certain radiomics signatures that were significantly correlated with four relevant genetic mutations in colon cancer.

Roderick Beijersbergen

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Roderick Beijersbergen PhD Group leader
Lorenzo Bombardelli PhD Post-doc
Cor Lieftink MSc Bioinformatician
Ben Morris Technical staff
Wouter Nijkamp Technical staff

Selected publications

Combès E, Andrade AF, Tosi D, Michaud HA, Coquel F, Garambois V, Desigaud D, Jarlier M, Coquelle A, Pasero P, Bonnefoy N, Moreaux J, Martineau P, Del Rio M, Beijersbergen RL, Vezzio-Vie N, Gongora C. Inhibition of Ataxia Telangiectasia Mutated and RAD3-Related (ATR) Overcomes Oxaliplatin Resistance and Promotes Antitumor Immunity in Colorectal Cancer. Cancer Res. 2019;79(11):2933-2946

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Wang C, Wang H, Lieftink C, du Chatinier A, Gao D, Jin G, Jin H, Beijersbergen RL, Qin W, Bernards R. CDK12 inhibition mediates DNA damage and is synergistic with sorafenib treatment in hepatocellular carcinoma. Gut. 2019

Cancer specific dependencies

Our research continues to evolve around the discovery of regulators of crucial pathways deregulated in cancer, genotype specific dependencies and synthetic lethal interactions that can be explored as drug targets in precision therapy. To achieve these goals, we develop and apply functional genomic technologies including large scale RNAi and CRISPR/CAS9 screening. Besides CRISPR-based gene-editing, we apply CRISPR-based transcriptional activation, -repression and -base-editing screening technologies. With the ability to efficiently manipulate genomes in mammalian cells, we have developed screening models based on sensors that report gene-transcription, protein activation or pathway regulation. Although many of our screening technologies are based on pooled screening, we have also established a platform for single well CRISPR screens using synthetic guide RNAs. With this platform we are able to screen for complex phenotypes but also for genes that upon inactivation affect specific DNA modifications or affect the levels of (allele) specific gene transcription. These advanced tools will allow for the discovery of novel components and pathways involved in cancer relevant phenotypes.
These approaches allow for the identification of specific dependencies in the context of tumor- and patient-specific alterations that can be explored for pathway-targeted therapeutics in cancer.

MAPK pathway hyper-activation as strategy to treat resistant cancers

Drug resistance is the largest factor limiting the success of targeted treatment. $BRAF^{V600E}$-mutant melanomas are strongly dependent on elevated MAPK signaling illustrated by the effectiveness of MAPK pathway inhibition using either single (BRAF) inhibitors or combinations of BRAF and MEK inhibitors. However, treatment with MAPK pathway inhibitors almost invariably leads to outgrowth of resistant disease in which both genomic and non-genomic mechanisms cooperate to restore MAPK pathway output to sufficient levels to compensate for the effect of the BRAF and MEK inhibitors. However, MAPK pathway output levels need to be tightly controlled as too much leads to anti-proliferative signals. We have previously shown that hyperactivation of the MAPK pathway using Prostratin, a PKC and MAPK pathway activator, results in enhanced cell death after BRAF/MEK inhibitor withdrawal in resistant BRAF-mutant melanoma cells. Although prostratin can be explored for clinical application, we have set out to identify negative regulators such as dual specificity phosphatases (DUSPs), which upon inhibition, result in deregulation and hyperactivation of the MAPK pathway. To study the relevance of DUSP4 and DUSP6 in MAPK hyperactivation in BRAF/MEK inhibitor resistant BRAF mutant melanoma cells, we have knocked-in an invertible intronic cassette (FLIP) in the first exon of both genes. After validation of the hyperactivation of MAPK pathway activation, we will study the consequence of inactivation of DUSP4 or DUSP6 expression after BRAF/MEK inhibitor withdrawal on proliferation and survival of BRAF/MEK inhibitor resistant BRAF mutant melanoma cells. This insight could to point to DUSPs as potential targets that can be explored to kill resistant melanoma cells upon drug withdrawal with potentially a more preferable therapeutic window than MAPK pathway activators such as Prostratin.

Pharmaceutical research: drug manufacturing – bioanalysis – pharmacokinetics and pharmacodynamics

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Our research programs focus on drug manufacturing including cellular immunotherapies, bioanalysis and pharmacokinetics-pharmacodynamics modelling and simulation of (anticancer) drugs for both preclinical and clinical projects. In 2020 we will move to a brand-new, 3,000 m^2 pharmacy building housing state-of-the-art drug storage, dispensing, manufacturing, laboratory and supportive facilities.

Drug manufacturing

In 2019 we supported more than 20 mono- and (international) multi-center clinical trials (*e.g.* DRUP, POSEIDON, SUBITO, SENSOR) with drug manufacturing, packaging and distribution. In-house manufacturing of vorinostat capsules and oral solid dispersion tablet formulations of docetaxel (ModraDoc006) continued for ongoing clinical studies. New formulation technologies are currently explored. In 2019, we continued the production of Tumour Infiltrating Lymphocytes (TIL) infusions for metastatic melanoma patients treated in the first multi-center phase III trial with TIL therapy in the world. This unique and fully academic trial now includes 96 enrolled patients (30 patients were included in 2019, a two-fold increase compared to 2017 and 2018). Previously produced DNA vaccines for HPV induced malignancies are currently tested by the Gynaecology department with promising results. Total enrolment is now almost finalized (13/14) for this phase I/II clinical trial. In-house manufacturing of radiopharmaceuticals for imaging of prostate cancer is currently explored in collaboration with the department of Nuclear Medicine.

Bioanalysis

We continued drug analysis for pre-clinical pharmaceutical research with carboplatin, cisplatin, endoxifen and olaparib. Samples from pharmacokinetic interaction studies with multidrug efflux transporters and multidrug metabolizing enzymes in *in vitro* transport systems and from knockout and transgenic mice were analysed (abemaciclib, ribociclib, milciclib, tivozanib, capecitabine, irinotecan, vinorelbine, morphine and ibogaine). Routine analysis to support clinical trials within and outside the Institute concerned docetaxel, capecitabine, vorinostat, doxorubicin, daunorubicin, etoposide, gemcitabine, vincristine and platinum (originating from cisplatin, carboplatin and oxaliplatin). Dihydropyrimidine dehydrogenase substrate uracil was quantified in serum of patients for a multicentre study to prevent the increased risk of developing severe fluoropyrimidine-related toxicity. This year we have received more than 6,000 (plasma) samples from treated patients in the context of Therapeutic Drug Monitoring (TDM). New LC-MS/MS equipment including a hyphenated LC-MS Q-TOF platform has been installed in the past year.

Pharmacokinetics and Pharmacodynamics (PK/PD)

We develop modelling methodologies to relate drug exposure to diverse measures of treatment outcome for both toxicity and efficacy. Research focusses mainly on PK and PD in special patient populations typically underrepresented in clinical trials *e.g.* in children. Further PK and PD studies with docetaxel were performed in castration resistant prostate cancer patients. Since 2010 a large scale TDM program is operational for precision dosing of oral anticancer agents increasing annually. Our program on treatment optimization of the repurposed anticancer PI3K/Akt inhibitor miltefosine for the neglected tropical parasitic disease leishmaniasis has been extended to other antibiotics. Besides we have expanded our modelling expertise and activities towards physiologically-based pharmacokinetic modelling (PBPK) to enable the prediction of target site/target tissue exposure, based on physicochemical properties of compounds, as well as translation of animal to human PK. In 2019 we started a project to introduce PK/PD modelling in nuclear medicine.

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Selected publications

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Interactions between prostate cancer and its microenvironment

The prostate cancer microenvironment consists of stromal and immune cells recruited to the microenvironment. Our lab has an interest in the interaction between normal prostate cells and prostate cancer. There is abundant evidence that these cells play a crucial role in the initiation and progression of prostate caner. In contrast to the tumor cells, the stroma and infiltratred immunecells in the tumor microenvironment consist of normally regulated cells and might hold promise for clinical valuable biomarkers and drug targets.

Androgen receptor signaling in prostate cancer associated fibroblasts and macrophages

Androgen Receptor (AR) signaling is essential for the development of the prostate and for prostate cancer development. Not only normal and malignant epithelial prostate cells express the AR, but also cells in the prostate cancer microenvironment, including Cancer Associated Fibroblasts (CAFs) and macrophages. CAFs were isolated from biopsies of cancer-affected areas in prostatectomies and cultured in vitro. The isolated cells express various CAF markers and the AR. The AR bound to the chromatin upon testosterone, which suggests transcriptional activity. Exposure of prostate cancer cells to medium of testosterone stimulated fibroblasts, resulted in decreased migration mediated by CCL2 and CXCL8.

Multiple macrophage differentiations have been described, including inflammation associated M1 and cancer promoting M2 macrophages. The amount and differentiation of infiltrating macrophages proved to be prognostic factors for prostate cancer development. Immunohistochemical studies showed co localization of AR and the pan-macrophage marker CD68 in human prostate cancer samples suggesting that macrophages express AR. Moreover, single cell mRNA sequencing of myeloid (CD14+) cells isolated from human prostate cancer biopsies showed AR expression. Further studies showed that AR in macrophages regulates the expression of multiple cytokines that stimulate prostate cancer cell migration and invasion. AR in macrophages also stimulated differentiation into M2. These results suggest that inhibition of AR in macrophages is a novel mechanism of action of androgen receptor inhibitors.

Interaction between prostate cancer cells and cells in the microenvironment

As we have shown in previous work, fibroblasts and macrophages affect prostate cancer cell growth. We're currently conducting a CRISPR knock out screen in prostate cancer cells cocultured with fibroblasts or macrophages or both. With this, we aim to identify genes in prostate cancer cells, essential for cellular killing.

Myeloid cell populations in human prostate cancer

Macrophages are among the most abundant non-cancerous cells in the tumor microenvironment and relatively recent studies introduced the concept of different subtypes of macrophages that are able to influence tumor progression. The overall aim of this project is to assess the phenotype of the myeloid cells compartment and their secreted factors in the tumor microenvironment of human prostate cancer. Myeloid cell populations are quantified in human prostate cancer specimen. Moreover, macrophages are isolated from biopsies from the cancer affected peripheral zone of human prostates and phenotypically characterized by single cell sequencing.

Functional genomics

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Selected
publications

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CDK12 inhibition mediates DNA damage
and is synergistic with sorafenib
treatment in hepatocellular carcinoma.
Gut. 2019

My group uses genome-wide functional genetic approaches to identify powerful drug combinations, new drug targets and mechanisms of resistance to cancer drugs. We aim to bring our discoveries to the clinic in close collaboration with the clinicians of our affiliated hospital.

### Pro-senescence therapies for the treatment of cancer
Induction of senescence represents a promising strategy for the treatment of cancer, especially when such pro-senescence therapy is followed by a second drug that selectively kills senescent cancer cells (senolytic agent). We published this year that such a "one-two punch" therapy is effective for the treatment of liver cancer. To make this approach more generally applicable, we have characterized a large panel of senescent cancer cells with the aim to find common vulnerabilities. We have performed CRISPR screens in senescent cancer cells to uncover such vulnerabilities. This resulted in the identification of several new candidate senolytic agents.

Multi Low Dose therapy
Targeted cancer drugs often elicit powerful initial responses, but generally fail to deliver long-term benefit due to the emergence of resistance. We hypothesized that partial inhibition of multiple components in the same oncogenic signaling pathway might add up to complete pathway inhibition, while at the same time decreasing the selective pressure on each individual component to acquire a resistance mutation (see figure). We tested this Multi Low Dose (MLD) model of drug administration in Epidermal Growth Factor Receptor (EGFR) mutant non-small cell lung cancer (NSCLC). We found that as little as 20% of the individual drug doses required for full inhibition of cell viability is sufficient to completely block MAPK signaling and proliferation when used in 3D (RAF+MEK+ERK inhibitors) or 4D (EGFR+RAF+MEK+ERK inhibitors) combinations. Importantly, EGFR mutant NSCLC cells treated with EGFR inhibitors at a high dose rapidly developed resistance in vitro, but the cells treated with 3D or 4D MLD therapy did not. Moreover, NSCLC cells that had gained resistance to high dose anti-EGFR therapies were still sensitive to MLD therapy. Using several animal models, including patient derived xenografts of NSCLC tumors that are resistant to EGFR inhibitors erlotinib and osimertinib, we found durable responses to MLD therapy without associated toxicity. These data support the notion that partial inhibition of multiple components of cancer-activated signaling pathways is difficult to circumvent and suggest that MLD therapy could deliver clinical benefit. We propose that MLD strategy could be an effective treatment option for EGFR mutant NSCLC patients, especially those having acquired resistance to even third generation EGFR inhibitor therapy.

PTPN11 as a drug target in RAS mutant cancers
In 2018, we published that combined inhibition of PTPN11 and MEK leads to dramatic therapeutic effects in *KRAS* mutant lung cancer. We have spent the past year to validate this concept in *KRAS* mutant pancreatic cancer with drugs that inhibit PTPN11 and the ERK kinases, in anticipation of the start of a clinical study with these drugs in pancreatic cancer in the course of 2020.
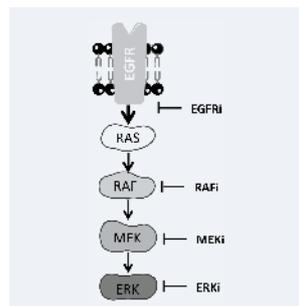
Multi low dose therapy of EGFR mutant lung cancer
While high dose single agent therapy often results in secondary mutations which ultimately lead to resistance, MLD therapy consisting of low dose EGFR, RAF, MEK and ERK inhibitors is able to minimize therapeutic resistance without apparent toxicity.

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Publications

Amaria RN, Menzies AM, [...], Blank CU, Tawbi HA, Long GV. Neoadjuvant systemic therapy in melanoma: recommendations of the International Neoadjuvant Melanoma Consortium. Lancet Oncol. 2019;20(7):e378-e389

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Understanding resistance upon immunotherapy

We aim to identify mechanisms of tumor immune escape and to develop therapeutic protocols to combine cancer immunotherapy with targeted and other therapies. Tumor immune escape mechanisms are often multifactor modulations of the tumor cells interacting with the immune cell network. In addition, systemic immune suppression seems to be an undervalued factor. The functional characterization of inhibitory networks, exploration of their inhibition and the examination of possible synergy with small molecule-based targeted and other immunotherapies may help in designing novel approaches to improve cancer immunotherapy.

Alteration of immune infiltrates to improve the outcome upon checkpoint inhibition
Targeted therapy does not only alter tumor signaling pathways, but also the tumor environment. Thus, it is crucial to simulate targeted therapies in immune-competent mouse models for cancer. Previously, we have tested combined targeting of the MAPK and the PI3K pathways (selective BRAF, MEK, PI3K and mTOR inhibitors) in murine melanoma. We found that short-term intermittent combination of BRAF and MEK inhibition was superior to all other targeted combinations when combined with PD-1 blockade. This has led to a phase 1b trial testing intermittent BRAF+MEK inhibition plus pembrolizumab in melanoma patients (IMPemBra, NCT02625337). It was presented as late braking abstract at this year's Melanoma Bridge meeting, showing excellent tolerability and for the first time a PFS benefit of intermittent short-term BRAF+MEK inhibition plus PD-1 blockade in comparison to anti-PD-1 monotherapy.
Currently, we are testing new approaches to alter the skewing towards low regulatory T cell content in tumors, more resistant T cells in the hostile tumor environment and improving the function of antigen presenting cells.

Biomarker identification for personalized immunotherapy
Immunotherapies like CTLA-4 or PD-1/PD-L1 blockade have revolutionized the treatment of late stage melanoma. We have postulated that immunotherapy works best when the tumor is still present, allowing the induction of a broader T cell immune response. Meanwhile, we have confirmed a nearly 80% pathologic response rate upon neoadjuvant CTLA-4 plus PD-1. Baseline biomarker analyses identified a neoadjuvant IFN-signature and tumor mutation burden as being associated with better outcome (100% response rate in double favorable patients). Pathologic response is also an excellent surrogate marker for long-term outcome, as only 1/71 (1.4%) responders has relapsed, while nearly 65% of non-responders have relapsed, so far. Extensive preclinical work trying to find the anti-tumor immune defects in these patients and a first trial testing alternative therapy approaches for these unfavorable patients have been set-up by our group.

Psychosocial oncology in clinical genetics and survivorship care

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**Selected
publications**

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EMA. The impact of an online patient
decision aid for women with breast
cancer considering immediate breast
reconstruction: study protocol of a
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trial. BMC Medical Inform Decis Mak,
2019;19(1):165

This psychosocial oncology group is concentrating on survivorship and quality of life in individuals with cancer, and those at high risk because of an inherited gene mutation. The overall aim of the research is to improve the quality of life and quality of care. The study designs vary from observational (uptake and impact studies) and prospective (long-term surveillance studies) to randomized controlled trials (psychosocial intervention studies to support decision making and improve quality of life and quality of care). Examples of ongoing studies on the two main themes of this group (clinical genetics and survivorship) are described.

Clinical genetics
Uptake of genetic testing after being informed by a clinical geneticist
A study about family communication, funded by the KWF, was initiated in 2016. This study aims to develop, test, and implement a new way to facilitate family communication of genetic test results to relatives of counselled individuals. First, a systematic review of the literature was done in which we critically evaluated studies on the uptake of pre-symptomatic genetic testing in hereditary breast-ovarian cancer (HBOC) or in Lynch syndrome (LS). We found that, based on information provided by the proband (15 studies), the uptake of pre-symptomatic genetic testing ranged from 15 to 57% in HBOC, while one study in LS kindreds reported an uptake of 70%. Based on information provided by genetics centers (15 studies) the uptake ranged from 21 to 44% in HBOC and from 41 to 94% in LS. However, when genetics centers contacted relatives directly a substantial number of additional family members could be tested. We are currently pilot-testing an additional strategy including the geneticist directly contacting relatives.

Survivorship and supportive care
Supporting women in making a well-informed decision about breast reconstruction: the development and evaluation of an online decision aid (TANGO-project)
In 2015, funding was received from Alpe d'HuZes/KWF for a five-year study which aims to develop and implement an interactive, online, patient decision aid (pDA) for the Dutch population of women who have to decide on breast surgery and reconstruction. Decisions about breast reconstruction are complex and largely depend on patients' personal preferences. We developed the online pDA in partnership with ZorgKeuzeLab and together with a national multidisciplinary working group, based on the literature and a needs assessment among patients (n=17) and professionals (n=33). The resulting pDA consists of six modules with information about the reconstructive options, pros and cons of the options and the most frequent complications. The pDA also includes experiences of other patients and value clarification exercises that stimulate women to weigh the options. The study runs in eight hospitals. In 2019 we enrolled the aimed 250 women who are treated for breast cancer or ductal carcinoma in situ, undergoing ablative surgery and eligible for an immediate breast reconstruction. In 2020, we will analyze the data and report on the effectiveness of the decision aid.

Improving sleep quality, psychosocial functioning, and cancer related fatigue with light therapy (SPARKLE-study)
Cancer related fatigue is a frequently reported symptom in survivors of (non-) Hodgkin lymphoma (40-60%). This fatigue impacts on the quality of life, even years after diagnosis. A novel and promising intervention to treat this symptom is *light therapy*. During a 4-week light therapy intervention, patients are exposed to bright white light every morning for 30 minutes. The SPARKLE-study (financially supported by the KWF) is a multi-center RCT to investigate the efficacy of this intervention in (non-)Hodgkin survivors. We also explore possible working mechanisms, including changes in sleep quality, psychological variables, biological circadian rhythms, circadian activity rhythms, and/or inflammation markers that have been identified as correlates and potential causes of fatigue. The study is coordinated by the Netherlands Cancer Institute and performed in close collaboration with the BETER-consortium, a nationwide survivorship care program for lymphoma survivors. In 2019 we enrolled the aimed 164 patients in our study, stemming from 10 hospitals. In 2020 we will report the first results.

B

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Publications

Hessen E, Nijkamp J, Damen P, Hauptmann M, Jasperse B, Dewit L, Lutkenhaus L, Lamers E, van der Heide U, Damen E, Hanssens P, Borst G. Predicting and implications of target volume changes of brain metastases during fractionated stereotactic radiosurgery. Radiother Oncol. 2019

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Optimizing treatment strategies for brain tumors, and uncovering irradiation escapes mechanisms

Glioblastoma (GBM) is the most common and aggressive brain cancer with a devastating prognosis due to the inevitable local tumor progression. Unfortunately, for many years the current standard treatment is still surgery followed by postoperative (chemo)radiation. Novel strategies of targeted agents enhancing the local (radiation) response are therefore needed, with an important role of advanced imaging techniques to optimize temporal-spatial modulating strategies.

Timing of immunotherapy
Following other disease sites that do benefit from immunotherapy (IT) this treatment modality is also tested for GBM patients. The first results of IT trials in GBM are however disappointing, both in the recurrent setting IT (CheckMate-143) as in the primary setting when combined with RT (CheckMate 498 and 548). This may be somewhat counterintuitive, because RT causes significant alterations in the tumor microenvironment that are thought to boost immunity. However, the working mechanism, optimal timing and sequence of IT in relation to RT are still unknown. In collaboration with the Akkari group we are investigating different timings of RT and IT in a pro-neural glioblastoma mouse model to further exploit the potential of IT in combination with RT in GBM patients.

Timing of cell cycle interfering agents during radiotherapy.
Mitotic enrichment has previously been clinically tested as radiosensitizing strategy with cytotoxic agents. However, both the compound(s) as the timing of the strategy were inappropriate and we want to revive mitotic enrichment as radiosensitizing strategy for GBM patients with better agents and scheduling. In collaboration with the Van Tellingen group we are currently evaluating the feasibility to introduce one of the candidate drugs in a clinical trial after promising in vivo data with repetitive dosing of mitotic inhibitors during fractionated radiotherapy.

Uncovering and exploiting new interphase effects of Tumor Treating Fields (TTF)
TTF is a new treatment modality for GBM patients improving the survival significantly by 5 months (to a median survival of 20,6 months). TTF is a local treatment using alternating electric fields that are delivered via insulated transducers. These electric fields are thought to specifically target dividing cells but research elucidating the exact working mechanism is still in progress. Our preliminary data uncovered additional effects of TTF in the interphase with an accumulation of cells in the G2 cell cycle phase. This effect is targetable with Wee1/Chk inhibitors showing a strong synergistic effect. We are currently optimizing a live cell imaging setup and preparing in vivo systems to move this promising combination strategy forward.

Anatomical and functional changes before and during radiotherapy
Surprisingly, limited data is available about anatomical and functional changes of the GBM tumors during fractionated RT. Both these aspects are of paramount importance to understand when and how to apply dose modifications and/or targeted agents to increase the treatment outcome. We study anatomical and functional changes of GBM patients throughout their treatment course for a better understanding of local response and how to improve this. Repeated MRI scans (with anatomical and functional MRI sequences) are made before, during and after the RT treatment in a prospective clinical trial. This study aims to identify markers that can be used for guidance of RT dose and timing of systemic treatment in combination with RT.

Experimental Biomedical Genetics

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Selected publications

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Glutaminyl cyclase is an enzymatic
modifier of the CD47-SIRPα axis and a
target for cancer immunotherapy. Nat
Med. 2019;25(4):612-619

Using a classical genetic approach we mutate the DNA of an organism and study the consequences. We use two improvements to apply this approach to human biology with high precision and throughput: the use of haploid human cells and the application of deep sequencing to measure the effects of millions of mutations in parallel. We apply this approach to study how genes collaborate to affect phenotypes and to link new genes to human disease.

Regulators of Molecular Phenotypes

As key executers of biological processes, the activity and abundance of proteins is subjected to extensive regulation. Using mutagenesis in haploid human cells we have developed an approach to couple genomic mutations to protein measurements within individual cells. Using this approach, which is both sensitive and scalable, genes can be identified that regulate any quantifiable protein phenotype in haploid human cells. Besides known regulators this also points out new genetic connections: the E3 ligase subunit KCTD5 was identified as new regulator of the AKT signaling pathway, CMTM6 as a new component of the PD1-PDL1 axis and Vasohibins were recognized as the long-sought tubulin detyrosinating enzymes.

In the future the ability to link genes to protein phenotypes using deep sequencing will enable us to build a genetic wiring map for haploid human cells. To better understand how genes collaborate we also study two types of genetic interactions that: synthetic lethality and genetic suppression.

Pathogen Portals

Our group studies viral families that cause the most-deadly human infections (Filovirus [eg. Ebola virus], Arenavirus [eg. Lujo virus], Bunyavirus [eg Hanta virus] as well as the most frequent human infections (Picornavirus [eg rhinovirus]). We use haploid genetics to gain insight into the entry tactics of these pathogens into human cells.

Genetic screens revealed that our mechanistic understanding of virus entry was incomplete, notably at the step that involves escape from the endo-lysosomal compartment. For Ebola and Lassa virus we revealed a 'receptor switch' to an intracellular transmembrane protein, recognized deep in the endo-lysosomal compartment. For Picornaviruses we identified PLA2G16 and demonstrated recruitment of this host factor to the perforated endosomal membrane. Loss of PLA2G16 led to a virus-resistance phenotype that could be reverted by ablation of a pathway previously linked to the clearance of intracellular bacteria. Thus, infection by picornaviruses involves two competing processes triggered by viral membrane perturbation: activation of a pore-activated clearance pathway and recruitment of a phospholipase to enable genome escape.

Studies on Coxsackie A and New World Hanta viruses identified new virus entry receptors at the cell surface. Haploid genetic screens identified the WNT-pathway component Kremen-1 as a critical host factor for infection, a finding that could be validated in mouse models deficient for KREMEN. Remarkably, Kremen-1 functions as entry receptor for a large subgroup of Coxsackie A viruses for which entry receptors remained unknown. In collaboration with other research groups PCDH1 was identified as entry receptor for New World Hantaviruses, a finding for which the relevance could be shown using blocking antibodies and PCDH1-deficient hamsters generated using CRISPR-CAS9.

D

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**Selected
publications**

Salvagno C, Ciampricotti M, Tuit S, Hau C-S, van Weverwijk A, Coffelt SB, Kersten K, Vrijland K, Kos K, Ulas T, Song J-Y, Ooi C-H, Rüttinger D, Cassier PA, Jonkers J, Schultze JL, Ries CH and de Visser KE. Therapeutic targeting of macrophages enhances chemotherapy efficacy by unleashing type I interferon response. Nature Cell Biology 2019;21(4):511-521

Wellenstein MD*, Coffelt SB*, Duits DEM, van Miltenburg MH, Slagter M, de Rink I, Henneman L, Kas SM, Prekovic S, Hau CS, Vrijland K, Drenth AP, de Korte-Grimmerink R, Schut E, van der Heijden I, Zwart W, Wessels LFA, Schumacher TN, Jonkers J, de Visser KE. Loss of p53 triggers WNT-dependent systemic inflammation to drive breast cancer metastasis. Nature 2019;572(7770):538-542

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Impact of the immune system on metastatic breast cancer and therapy response

Metastasis formation and unresponsiveness to conventional therapies are the challenges in cancer therapy that urgently need solutions. We study how the immune system influences breast cancer metastasis and therapy responsiveness. Through mechanistic understanding of the crosstalk between the immune system and cancer cells, we aim to contribute to the design of novel immunomodulatory strategies to fight metastatic breast cancer.

Impact of the genetic makeup of breast cancer on pro-metastatic inflammation

Cancer-associated systemic inflammation is strongly linked with poor disease outcome in cancer patients. For example, high neutrophil-to-lymphocyte ratios in blood of cancer patients are associated with increased metastasis, and we (Coffelt et al. Nature 2015) and others have previously demonstrated that neutrophils promote metastasis formation in mouse tumor models. Given the emerging interest in immunomodulatory therapies for cancer, it is crucial to understand the mechanisms by which tumors shape the systemic immune landscape. In collaboration with Prof. Jos Jonkers (NKI), we uncovered the impact of the genetic makeup of breast cancer on pro-metastatic inflammation. We have revealed a novel role for p53 as a key regulator of systemic inflammation in breast cancer. Mechanistically, p53 loss in cancer cells induces paracrine stimulation of tumor-associated macrophages in a Wnt dependent manner, which elicits an inflammatory cascade leading to the systemic accumulation of neutrophils, which facilitates metastasis formation (Wellenstein et al. Nature 2019). These insights illustrate the importance of the genetic makeup of cancer cells in dictating pro-metastatic systemic inflammation, and set the stage for personalized immune intervention strategies for cancer patients.

Improving response to platinum-based chemotherapy by targeting macrophages

Poor chemotherapy response is a major obstacle to successful cancer treatment. There is a growing realization that the immune system influences the success of chemotherapy, however, the exact underlying mechanisms are largely unknown. Utilizing mouse tumor models that faithfully recapitulate human breast tumorigenesis, we discovered that targeting macrophages by CSF-1 receptor (CSF-1R) blockade enhances the anti-cancer efficacy of platinum-based chemotherapeutics. We mechanistically uncovered that CSF-1R inhibition stimulates intratumoral type I interferon signaling which is essential for the therapeutic synergy between cisplatin and CSF-1R blockade. Further elimination of immunosuppressive neutrophils was required to engage an efficacious anti-tumor immune response that further improved therapeutic benefit of cisplatin (Salvagno et al. Nature Cell Biology 2019). These findings illustrate the importance of breaching multiple layers of immunosuppression during cytotoxic therapy to engage anti-tumor immunity in breast cancer.

Translating our findings to breast cancer patients

In collaboration with medical oncologist and researcher Marleen Kok (NKI-AVL) we have established an extensive immunomonitoring program to perform in-depth profiling of the immune landscape in fresh blood samples of patients with different subtypes of breast cancer. Through these analyses, we validate the findings from our pre-clinical studies in patients, and we hope to gain a deeper understanding of the complex cancer-immune crosstalk in breast cancer patients.

Genome dynamics and function

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Selected publications

Braccioli, L, and de Wit, E.
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organization and transcription
regulation. Essays Biochem.
2019;63:157-165

Kaaij, LJT, Mohn, F, van der Weide, RH,
de Wit, E, and Bühler, M.
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chromatin looping at CTCF sites that
emerged from SINE expansions in
mouse. Cell 2019;178:1437-1451.e14

Van der Weide, RH, and de Wit, E.
Developing landscapes: genome
architecture during early
embryogenesis. Curr. Opin. Genet.
Dev. 2019;55:39-45

Our research centers around the question: how are genes regulated within the context of the three-dimensional (3D) genome? We use a combination of genetic and acute perturbation experiments in combination with genomics tools to understand how distal regulatory elements (e.g. enhancers) contribute to the regulation of genes. In addition to implementing and developing genomics methods we also develop software for the analysis of chromosome conformation capture data.

Acute protein depletion

It is becoming increasingly appreciated that chromatin inside the nucleus is highly dynamic. Both the proteins binding to DNA and the DNA itself are in a constant flux. These dynamic processes contribute to the regulation of genes. However, because of the highly dynamic nature of nuclear organization it is difficult to determine cause and effect. The reason for this is that whereas the folding of chromosomes influences expression, expression in turn also influences the folding of chromosomes. In order to study the consequences of changes in genome folding we now make use of methods that can acutely (<1hr) and uniformly deplete a protein from cells. This is achieved by fusing a degron tag to a protein of interest which is sensitive to a small molecule. Following the addition of a small molecule the protein is then rapidly degraded.

We have performed acute depletion in mouse embryonic stem cells of a number of proteins that are important for nuclear organization. Our experiments show a rapid change in nuclear organization, reshaping the nucleus within a few hours. Changes in the 3D genome are followed by changes in gene expression. Our experiments are consistent with a model in which the 3D genome, driven by cohesin, is crucial for maintaining proper gene expression and the maintenance of the cellular state (see figure).

In vitro early differentiation models

A key event in the differentiation of multi-cellular organisms is gastrulation. During gastrulation the blastula which is single-layered and symmetrical reorganizes itself into a multilayered and asymmetric gastrula. The process of symmetry breaking leads to the establishment of different cell types in the early embryo. The gene regulatory factors that control this process in mammalian cell systems are still not fully delineated. This is in part due to the difficulty to obtain sufficient material from *in utero* or *in vitro* developing embryos. However, this can be overcome by using an *in vitro* culture system that uses embryonic stem cells that aggregate into so-called gastruloids. These undergo the process of symmetry breaking *in vitro*.

Gastruloids will allow us to study the role of the 3D genome during the process of gastrulation. By making gastruloids of our acute depletion mouse embryonic stem cell lines, we can influence key regulators of expression during early development and delineate the key transcriptional response. We have set up single cell ATACseq that allows us to measure the open chromatin landscape of single cells, enabling us to deconvolve the different cell types and their regulators in gastruloids.
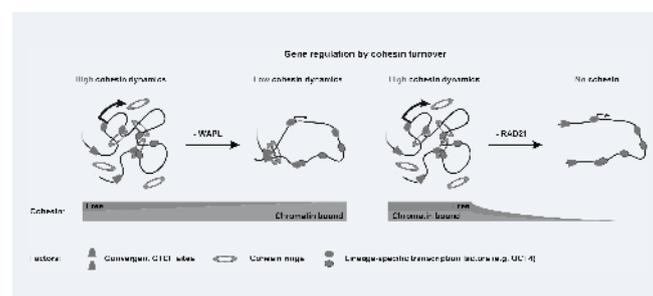
Cohesin mediated loops drive cell type specific expression.

F

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**Selected
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Rohwer N, Jumpertz S, Erdem M,
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Kühl AA, Kramann R, Neuss S, Rudolph
I, Endermann T, Zasada C, Apostolova
I, Gerling M, Kempa S, Hughes R,
Lewis CE, Brenner W, Malinowski MB,
Stockmann M, Schomburg L, Faller W,
Sansom OJ, Tacke F, Morkel M,
Cramer T. Non-canonical HIF-
1 stabilization contributes to
intestinal tumorigenesis. Oncogene
2019;38(28):5670-5685

Regulation of translation in the intestinal epithelium

The main interest of our lab is in the role that RNA translation plays in normal and cancer cells. Understanding this mechanism of gene regulation, and how it is hijacked in cancer, will allow us to uncover proteins and pathways involved in cancer phenotypes.

RNA translation in intestinal stem cells

In particular we are focused on the stem cell populations in the intestine, and cancers of the same organ. We study this using genetically modified mouse models (GEMMS), and 3d organoid culture, which allow us to maintain the complexity of the organ, while still providing tractable systems to study. In particular, we use a tagged ribosome approach which allows us to isolate the ribosomes, and associated mRNA, in our cell type of choice. This gives us the ability to study RNA translation (via ribosome profiling) in specific cellular populations in a complex tissue like the intestine.
Stem cells are the drivers of CRC development and resistance to therapy. Previous studies have suggested that there are global changes in protein synthesis in stem cells compared to differentiated cells. Using the above mentioned *in vivo* and *in vitro* tools, we have shown that multiple pathways are translationally regulated in intestinal stem cells. In particular, RNA translation controls metabolic pathways, resulting in increased mitochondrial metabolism and oxygen consumption in these cells.

Inhibiting translation reverses this metabolic switch, and causes the stem cells to change identity, driving the appearance of a normally rare population of fetal stem cells with distinct characteristics. We are now studying this stem cell population to understand their function in the normal intestine and cancer. These fetal stem cells also bear a similarity to Kras-driven colon cancer cells, so we have also translationally profiled these and are working to understand the similarities, including the role that they play in the resistance to therapy.
Additionally, we are working to understand how translation is regulated in these cells, and whether this process can be targeted by therapy.

Ribosomal heterogeneity in normal and cancer tissue

We have developed a bioinformatics method for increasing the efficiency of ribosome profiling experiments, called Ribo-ODDR. This has allowed is to carry out these experiments in difficult to work with tissue (such as the intestine). Interestingly, we have found that the same pipeline can also be used as a novel method to analyze ribosome populations in the cell.

Ribosomes have always been thought of as homogenous protein production factories. Recent work suggests that this is not the case however, and shows that differences in ribosomal populations can cause major changes in phenotypes. Using ribosome profiling data and Ribo-ODDR, we are beginning to understand what populations are present in different cell types, and how oncogenic mutations can change them. As this work progresses we can also begin to dissect how these different populations affect what is being translate in the cell.

Immunotherapy, immunomonitoring and production facility

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Publication

Bex A, Mulders P, Jewett M, Wagstaff J, van Thienen JV, Blank CU, van Velthoven R, Del Pilar Laguna M, Wood L, van Melick HHE, Aarts MJ, Lattouf JB, Powles T, de Jong IJ, Rottey S, Tombal B, Marreaud S, Collette S, Collette L, Haanen J. Comparison of Immediate vs Deferred Cytoreductive Nephrectomy in Patients With Synchronous Metastatic Renal Cell Carcinoma Receiving Sunitinib: The SURTIME Randomized Clinical Trial. JAMA Oncol. 2019;5(2):164-170

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Scheper W, Kelderman S, Fanchi LF, Linnemann C, Bendle G, de Rooij MAJ, Hirt C, Mezzadra R, Slagter M, Dijkstra K, Kluin RJC, Snaebjornsson P, Milne K, Nelson BH, Zijlmans H, Kenter G, Voest EE, Haanen JBAG, Schumacher TN. Low and variable tumor reactivity of the intratumoral TCR repertoire in human cancers. Nat Med. 2019;25(1):89-94

This research line is aimed at developing novel T cell-based immunotherapies that can be applied in cancer patients. The focus is on patients with solid tumors, especially melanoma, renal cell carcinoma, and HPV-associated cancers. These immunotherapies comprise DNA-based vaccines and T cell products, including Tumor Infiltrating Lymphocytes (TILs) and genetically modified peripheral blood T cells. GMP production of these therapeutic agents takes place in the Biotherapeutics Unit (BTU), situated in the hospital pharmacy. A second objective concerns immunomonitoring, primarily to evaluate the effects of novel immunotherapies. These studies are conducted together with the Schumacher, Kvistborg and Blank labs at the NKI-AVL and with national and international collaborators.

HIGHLIGHTS 2019

In collaboration with Sanquin and one European cancer center in Copenhagen, Denmark, we are continuing our international, randomized controlled phase III trial in stage IV melanoma patients, comparing Tumor Infiltrating Lymphocytes (TIL) with standard of care for second line treatment. Enrollment of patients started in October 2014. Up to date 97 patients have been randomized. Materials (liquid and tumor biopsies) are being collected for translational research. We have established additional funding from KWF to open additional clinical centers to speed up recruitment.

In pre-clinical studies, we have developed highly immunogenic and safe HPV 16 E6- and E7-containing DNA vaccines for which we have produced GMP grade vaccines. These vaccines are currently been tested in a phase I clinical trial (Prof. G. Kenter, gynaecologic oncologist and co-workers). Patients with HPV 16-positive Vulvar Intraepithelial Neoplasia Grade III (VIN III) are vaccinated using a novel and potent intradermal DNA vaccination strategy. Immunomonitoring is being performed by us, and vaccine induced E6 and E7 directed T cell responses have been detected directly *ex vivo* in blood to monitor the immunogenicity of these therapeutic vaccines.

Together with a third party and the Voest lab, we are working on strategies to extract tumor reactive cells from the blood as novel treatment option.
In addition, we have an exciting collaboration with NEON therapeutics (Cambridge, MA), in which we develop new T cell therapies directed against patient specific neo-antigens. For this collaboration, large scale enginering runs have been successfully executed.

In 2019, we obtained a large translational ZonMW grant to develop a fully personalized TCR gene therapy. In a Proof-of-Concept study in melanoma patients, neoantigen-specific TCRs will be identified using technology developed by Ton Schumacher and Wouter Scheper, and transferred to patient T cells using CRISPR/Cas9 technology.

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**Selected
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Nederlof I, De Bortoli D, Bareche Y, Nguyen B, de Maaker M, Hooijer GKJ, Buisseret L, Kok M, Smid M, Van den Eynden GGGM, Brinkman AB, Hudecek J, Koster J, Sotiriou C, Larsimont D, Martens JWM, van de Vijver MJ, Horlings HM, Salgado R, Biganzoli E, Desmedt C. Comprehensive evaluation of methods to assess overall and cell-specific immune infiltrates in breast cancer. Breast Cancer Res. 2019;21(1):151

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Voorwerk L, Slagter M, Horlings HM, Sikorska K, van de Vijver KK, de Maaker M, Nederlof I, Kluin RJC, Warren S, Ong S, Wiersma TG, Russell NS, Lalezari F, Schouten PC, Bakker NAM, Ketelaars SLC, Peters D, Lange CAH, van Werkhoven E, van Tinteren H, Mandjes IAM, Kemper I, Onderwater S, Chalabi M, Wilgenhof S, Haanen JBAG, Salgado R, de Visser KE, Sonke GS, Wessels LFA, Linn SC, Schumacher TN, Blank CU, Kok M. Immune induction strategies in metastatic triple-negative breast cancer to enhance the sensitivity to PD-1 blockade: the TONIC trial. Nat Med. 2019;25(6):920-928

Computational Pathology

Our team focuses on the development of Computational Pathology approaches that combine clinical, pathology and genomics data with image analysis of solid tumors to identify biomarkers for prediction of treatment response. We train powerful computers to recognize tumor and their microenvironment by annotating pathology samples from the clinic. Combining these image-based quantitative results with genetic analysis of the cancer-immune interactions can be complementary or offer completely new observations to empower precision oncology.

Predicting response to immunotherapy by deep learning of quantitative tissue analysis

Currently, immunotherapy treatment decision making is based on quantification of Program Death Ligand 1 (PD-L1) or in clinical trials based on the percentage of tumor-infiltrating lymphocytes in pathology samples. Pathologists apply thresholds to assessments visually, which are image-dependent and operator-dependent. As a result, the critical decision of administering immunotherapy is made by applying very sensitive thresholds to a possibly inaccurate and subjective quantification of a largely variable stain. Therefore, there is an urgent need for reliable and more accurate biomarkers that can aid in the selection of cancer patients eligible for immunotherapy.

Last year, we developed a deep learning algorithm to quantify tumor infiltrating lymphocytes, PD-L1 and CD8 positive cells in digitized histopathology images of cancer patients treated with immunotherapy. The tool is based on deep learning algorithms, trained using multiple stainings of retrospective cancer cohorts. The resulting tool will allow accurate, objective and reproducible quantification of imaging biomarkers for the prediction of treatment response both in a metastatic and in an early-stage scenario. The system is currently being validated and applied to ongoing prospective clinical trials of cancer patients treated with immunotherapy.

Histogenomics: An Integrative deep learning approach of histopathology and genomics to personalize cancer treatment

The last decade, genomic and molecular sub-classification of solid tumors potentially have important clinical implications, including identification of new therapeutic targets. However, these subclassifications are based on labor-intensive assays with fresh frozen samples and long turnaround times, limiting their routine use as treatment must start soon after diagnosis. The semi-quantitative morphological interpretation of histological sections of solid tumors by a pathologist is still the cornerstone of diagnosis and assessing cancer prognosis and response to treatment for more than 100 years. This phenotypic information reflects the aggregate effect of molecular / genomic alterations on cells and provides an inexpensive as well as convenient visual read-out of disease biology.

To combine genetic and histology markers, we have built a web-based platform (Slide Score) for characterizing solid tumors, based on artificial intelligence (AI) techniques, by combining genetic and histology markers. In more detail, in the coming years we will build automated AI-tools to investigate the relationship between genetic markers, histology and clinical outcome and treatment response, and combine these data for a comprehensive profile of each tumor. This approach has the potential to provide immuno- and targeted therapy to a much broader subset of patients with cancer. We will train and validate this on samples with Whole genome sequencing results (N-CIA, CPCT) and we will be validated and applied to ongoing daily clinical genomic testing of cancer patients (WIDE).

Programming mutagenesis and epigenetics in lymphocyte biology

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Selected publications

Pilzecker B, Buoninfante OA, Jacobs H. DNA damage tolerance in stem cells, ageing, mutagenesis, disease and cancer therapy. Nucleic Acids Res. 2019;47:7163-7181

Pilzecker B, Jacobs H. Mutating for Good: DNA Damage Responses During Somatic Hypermutation. Front Immunol. 2019;10:438

Vlaming H, McLean CM, Korthout T, Alemdehy MF, Hendriks S, Lancini C, Palit S, Klarenbeek S, Kwesi-Maliepaard EM, Molenaar TM, Hoekman L, Schmidlin TT, Altelaar AM, van Welsem T, Dannenberg JH, Jacobs H, van Leeuwen F. Conserved crosstalk between histone deacetylation and H3K79 methylation generates DOT1L-dose dependency in HDAC1-deficient thymic lymphoma. EMBO J. 2019;38:e101564

Lymphocytes and their precursors are licensed to transiently activate specific mutation pathways that enable efficient remodeling of antigen-receptor genes. To generate the enormous diversity of clonotypic antigen receptors, specific DNA lesions are generated and resolved in an error-prone fashion at defined stages of lymphocyte development. These characteristics provide ideal model systems to study not only the role of DNA damage response (DDR) and DNA damage tolerance (DDT) pathways in resolving specific DNA lesions and shaping the immunoglobulin (Ig) repertoire but also in maintaining genome stability and tissue homeostasis.
Our research activities are focused on two subjects:
(i) DDT in physiology and precision cancer medicine
(ii) Genetic and epigenetic regulation of lymphocyte development

DNA damage tolerance is essential for hematopoietic stem cell maintenance and mammalian life

Stem cells are key players in central biological processes, such as tissue homeostasis, ageing, and cancer formation. Stem cells depend on genome maintenance to prevent disease formation. DDT pathways enable DNA replication in the presence of replication impediments and are regulated by $PCNA^{K164}$ ubiquitination and REV1. The failure to generate $Pcna^{K164R/K164R};Rev1^{-/-}$ deficient mice revealed DDT as essential for mammalian life. The compound mutation rendered hematopoietic stem cells (HSCs) and the hematopoietic precursors genetically unstable, instigating a pathological process where the associated HSC depletion culminated in a severe, embryonic-lethal anemia. Single cell RNA-sequencing of the remaining HSCs and progenitors identified $CD24A^{high}$ and $CD93^{low}$ erythroid-biased progenitors (EBP) within the Lineage$^-$, Sca1$^+$, cKit$^-$ (LSK) population. In line, this subset was found to depend on the erythroid transcription factor Klf1. In conclusion, DDT is an essential activity within the DDR network and in maintaining HSC fitness. By studying this system, we identified a novel erythroid-biased progenitor subset within the LSK compartment.

Histone methyltransferase DOT1L controls state-specific identity during B cell differentiation

Differentiation of naïve peripheral B cells into terminally differentiated plasma cells is characterized by epigenetic alterations, yet the epigenetic mechanisms that control B cell fate remain unclear. We identified a central role for the histone H3K79 methyltransferase DOT1L in controlling B cell differentiation. Naïve and activated murine B cells lacking Dot1L prematurely acquired plasma cell features and failed to establish germinal centers (GC) and normal humoral immune responses *in vivo*. Mechanistically, combined epigenomics and transcriptomics analysis revealed that DOT1L promotes expression of a pro-proliferative (Myc) and pro-GC program (Bach2) and supports the expression of the H3K27 methyltransferase Ezh2, the catalytic component of Polycomb Repressor Complex 2 (PRC2). Thereby, DOT1L ensures PRC2-mediated repression of anti-proliferative and plasma cell differentiation program. Our findings show that DOT1L is a critical regulator of the core transcriptional and epigenetic landscape in B cells and establishes an epigenetic barrier warranting B cell naivety (details, see bioRxiv: doi.org/10.1101/826370). Similar observations were made in the CD8$^+$ T cell lineage. (details, see bioRxiv: doi.org/10.1101/826255).
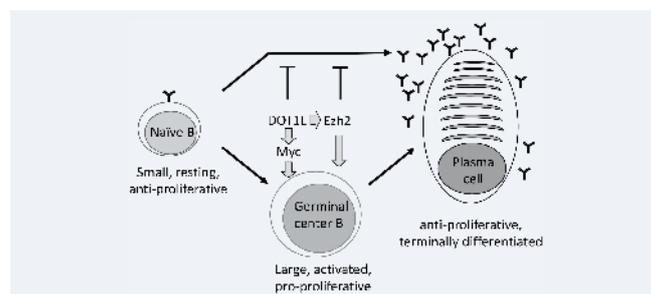
DOT1L has a key function in the generation and maintenance of pro-proliferative germinal center B cells and preventing premature differentiation towards terminally differentiated plasma cells.

J

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Telomere and genome integrity

Tight control of DNA repair is critical in maintaining genome integrity and preventing or treating pathology, but the underlying processes are not well understood. Therefore we lack important knowledge about the causes underlying cancer development and the consequences of DNA-damaging anti-cancer therapies. Our work focuses on (erroneous) DNA damage response and repair activities at telomeres and DNA double-strand breaks (DSBs) and how they contribute to cancer and aging by causing cell death, cell senescence, loss of genome integrity or genomic instability.

DNA repair pathway choice at telomeres and DNA DSBs

The main mechanisms by which cells repair DSBs are non-homologous end-joining (NHEJ) and homology-directed repair (HDR). These operate mutually exclusive and are activated by 53BP1 and BRCA1, respectively. The appropriate choice for engaging these two pathways is critical for genome stability and regulated at the level of DNA end-resection. End-resection inhibits NHEJ while committing to HDR. A few years ago we identified MAD2L2, a.k.a. REV7, as an unexpected protein that promotes NHEJ and inhibits HDR at telomeres and DSBs by counteracting 5' DNA end-resection downstream of 53BP1. Thereby MAD2L2 contributes to repair pathway choice between NHEJ and HDR and to the synthetic lethality of BRCA1-deficient cancer cells treated with PARP-inhibitors. In subsequent efforts to further understand MAD2L2 function we identified two previously uncharacterized factors, SHLD1 and SHLD2, that act with MAD2L2 and a third factor SHLD3, identified in parallel work by others. Together MAD2L2, SHLD1, -2 and -3 form a complex called shieldin that protects DNA ends against excessive resection, thereby promoting NHEJ and counteracting HDR (see figure). Loss of SHLD1 or SHLD2 renders BRCA1-deficient cells resistant to PARP-inhibitors, but increases their sensitivity to cisplatin, suggesting how defining the SHLD1/2 status of BRCA1-deficient tumors might aid patient stratification and expose new treatment opportunities.

Our most recent work addresses potential regulation of shieldin. For this we examined specific amino acid residues of MAD2L2 possibly critical for its role in DNA repair and searched for additional factors that might promote or counteract shieldin. Through a functional genetic screen for NHEJ regulators and mass-spectrometry for MAD2L2 interacting proteins we identified a potential regulator of MAD2L2 complex assembly with other factors. In this ongoing work we are assessing the role of this potential regulator on the different activities associated with MAD2L2 and on shieldin assembly and function.

Ubiquitin-mediated control of NHEJ at telomeres

Over the last year we also made significant progress on understanding how an E2 ubiquitin-conjugating enzyme, that we identified in a functional genetic screen, promotes NHEJ at telomeres. We discovered that this E2 contributes to DNA damage-dependent chromatin ubiquitylation and recruitment of DNA damage response proteins critical for NHEJ. Moreover, we found that it prevents excessive accumulation of the RNF168 ubiquitin-ligase and inactivation of a protein essential for heterochromatic DNA repair.
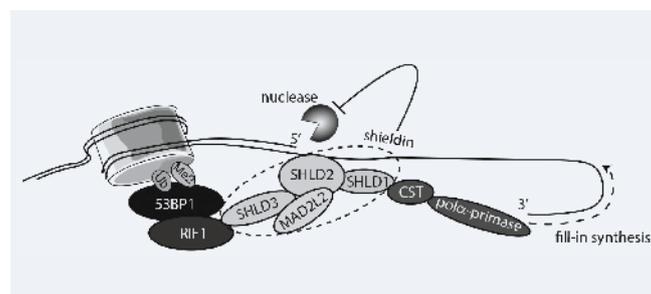
Model of how shieldin promotes NHEJ and inhibits HDR at DSBs by suppressing nuclease activity and/or promoting fill-in synthesis to counteract formation of 3' single-stranded DNA.

Biophysics of Cell signaling

Kees Jalink

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Selected publications

Broertjes J, Klarenbeek J, Habani Y, Langeslag M, Jalink K. TRPM7 residue S1269 mediates cAMP dependence of Ca2+ influx. PLoS One. 2019;14(1):e0209563

Kamermans A, Planting KE, Jalink K, van Horssen J, de Vries HE. Reactive astrocytes in multiple sclerosis impair neuronal outgrowth through TRPM7-mediated chondroitin sulfate proteoglycan production. Glia. 2019;67(1):68-77

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We use advanced microscopy and spectroscopy techniques to study cell signaling events and cytoskeletal dynamics with high spatial and temporal resolution. Our expertise is predominantly in advanced functional imaging and Super Resolution microscopy. Functional imaging techniques like FRET, FLIM and FCCS aim to provide information about the function of molecules, rather than just static images of their position within the cell. We also develop methods, hard- and software for various advanced microscopy applications. These techniques are used in research projects in our group as well as in collaborations within and outside our institute.

FLIM imaging on wide-field and confocal microscopes

Having completed construction and testing of instruments for ultrafast Fluorescence Lifetime Imaging (FLIM) in our lab on both confocal and widefield microscopes, we have now moved forward to apply these developments in automated FLIM screens. FLIM records the fluorescence lifetime of a fluorophore, i.e. the average time that a fluorophore remains in the excited state following excitation and is an intrinsically quantitative method to detect molecular interactions in living cells. We use FLIM, in conjunction with a variety of Fluorescence Resonance Energy Transfer (FRET) sensors to dynamically read out various signal transduction pathways in individual single cells. In single cells we have characterized the sensitivity, response kinetics and cell-to-cell variability in well-known signaling pathways, including the cAMP-PKA axis, ERK signaling, PLC/Ca^{2+} signals, receptor tyrosine kinase activity and caspase signaling. Of particular interest is that with the current palette of FRET sensors, we can now follow activity of different nodes within the same signaling cascade, for example following GPCR activation, activation of the G-protein Gq, PIP2 hydrolysis, IP3 formation and Ca^{2+} release with individual FRET sensors. Being able to study these with sub-second temporal and micro-meter spatial resolutions will allow us to uncover cross-talk between signaling cascades, as well as feedback- and feed-forward mechanism that affect intensity and longevity of these signals. We also study the distribution of signaling activity in multi-cell preparations such as spheroids and organoids.

How does hypoxia affect activity of signal transduction cascades?

Until now, microscopy studies on living cells have been conducted exclusively at athmospheric oxygen levels (i.e., 20% of oxygen). This is remarkable, because the cells in our body are never exposed to 20% O2; rather, they experience between 2% and 7 % of O2 (normoxia). Solid tumours in our bodies almost invariably lack well-developed blood vessels, and large parts of the tumor are therefore devoid of O2 (<1 % of O2; hypoxia). Importantly, a large body of literature shows that hypoxic tumors are much less sensitive to clinical therapies, particularly to irradiation and to systemic cytostatic agents. We therefore adapted our screening microscopes to allow imaging at arbitrarily set O2 and CO2 levels, thus mimicking the natural conditions of cells in our body much better. With these adaptations, we are studying cell growth and differentiation, signal transduction and migration in several model systems, partly with collaborators at the NKI-AVL.
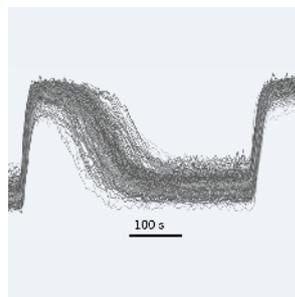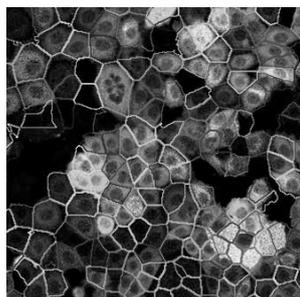
High content characterization of cAMP signaling at the single-cell level. Cells are stimulated with isoproterenol.

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**Selected
publications**

Annunziato S, et al. Comparative
oncogenomics identifies combinations
of driver genes and drug targets
in BRCA1-mutated breast cancer.
Nat Commun. 2019;10(1):397

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actomyosin contractility enables
mammary tumor formation upon
loss of E-cadherin. Nat Commun.
2019;10(1):3800

Mouse models of breast cancer

My group studies human breast cancer development and progression, as well as therapy response and resistance, in genetically engineered mouse models (GEMMs) and patient-derived tumor xenograft models (PDX). We have developed mouse models for BRCA1/2-associated breast cancer and invasive lobular carcinoma (ILC), which are used to (1) study tumor cell-intrinsic and -extrinsic mechanisms of breast cancer development and progression; (2) develop novel therapeutic strategies for prevention and treatment of breast tumors; (3) study mechanisms of acquired resistance to targeted therapeutics.

Driver genes in BRCA1-associated breast cancer
We have developed several GEMMs for somatic modeling of BRCA1-associated breast cancer using intraductal injection of lentiviral vectors for stable overexpression of exogenous genes and CAS9-mediated disruption or APOBEC-CAS9n-UGI (BE3)-mediated base editing of endogenous genes. We have used these GEMMs to validate RB, PTEN, PIK3CA, MYC and MCL1 as bona fide driver genes in BRCA1-associated breast cancer. Moreover, MCL1 inhibition potentiated the *in vivo* efficacy of the PARP inhibitor (PARPi) olaparib, underscoring the therapeutic potential of this combination for treatment of BRCA1-associated cancer patients with poor response to PARPi monotherapy.

Therapy resistance in BRCA1-deficient breast cancer
BRCA1-deficient cancers are defective in homologous recombination repair and therefore hypersensitive to DNA-damaging agents, including platinum drugs and PARP inhibitors (PARPi). However, these treatments do not result in tumor eradication and eventually resistance develops. To study mechanisms of PARPi resistance, we combined functional genetic screens in BRCA1-deficient cells with multi-omics analysis of PARPi-resistant tumors from our GEMMs of BRCA1-deficient breast cancer. These studies have shown that PARPi resistance can be induced by loss of components of the 53BP1-RIF1-SHLD or CST complexes that govern protection of DNA double-strand breaks.

Driver genes in ILC
Using *in vivo* transposon-based insertional mutagenesis, we have found that overexpression of hyperactive truncated forms of MYPT1/2 and ASPP2 reduces actomyosin contractility and thereby promotes malignant transformation of E-cadherin deficient mammary epithelial cells, resulting in ILC formation in mice. This work highlights actomyosin hypercontractility induced by E-cadherin loss as a critical barrier to ILC development.

In vivo models of DCIS
Since the advent of breast screening, Ductal Carcinoma In Situ (DCIS) accounts for 25% of all breast neoplasms detected. This increased detection rate has resulted in overtreatment since most DCIS lesions will not progress into invasive breast cancer. Better insight into the biology of DCIS is required to distinguish indolent lesions from potentially hazardous ones. To this end, we are using intraductal injections of lentiviruses encoding (combinations of) DCIS driver genes to generate genetically engineered rat models of DCIS. We are also using intraductal injections of patient-derived DCIS cells to generate mouse PDX models of DCIS. These approaches will enable the identification of DCIS driver genes and yield models to study disease progression and response to targeted therapeutics.

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Selected publications

Nederlof I, De Bortoli D, Bareche Y,
Nguyen B, de Maaker M, Hooijer GKJ,
Buisseret L, Kok M, et al.
Comprehensive evaluation of methods
to assess overall and cell-specific
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Breast Cancer Res. 2019;21(1):151

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Kruger DT, Beelen KJ, van der Noort V,
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Kok M. Immune induction strategies
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cancer to enhance the sensitivity to
PD-1 blockade: the TONIC-trial. Nature
Medicine 2019;25(6):920-928

Improving breast cancer immunotherapy

Cancer immunotherapy, especially PD1-blockade, has resulted in durable anti-tumor responses in a subgroup of breast cancer patients. However, the overall response rates are still modest. Using innovative clinical trial approaches as well as applying state-of-the-art knowledge from fundamental cancer immunology, we work on i) the identification of those breast cancer patients that will benefit from immunotherapy, and ii) a better understanding of the interactions between breast cancer and tumor-associated as well as circulating immune cells in order to develop novel immunomodulatory strategies.

Modulation of the tumor microenvironment to improve response to PD-1 blockade
The response rate of triple negative breast cancer (TNBC) patients to PD-1 blockade is low, highlighting an urgent clinical need for strategies that render the TNBC tumor microenvironment (TME) more sensitive to PD-1 blockade. Immunomodulatory mechanisms have been proposed for both chemotherapy and irradiation, but it has not been established whether these therapies can favorably changing the TME. Patients with metastatic TNBC were randomized to anti-PD1 without induction or to one of four induction treatments, consisting of irradiation or a two- week low-dose regimen of cyclophosphamide, cisplatin or doxorubicin, all followed by anti-PD-1. The majority of clinical responses were observed on anti-PD1 in the cisplatin and doxorubicin induction cohorts. After doxorubicin and cisplatin induction, we detected an upregulation of immune-related genes, involved in PD-1/PD-L1, and T-cell cytotoxicity pathways. This was supported by enrichment among upregulated genes related to inflammation, JAK-STAT and TNFα-signaling after doxorubicin. In addition, we observed a trend towards increased T-cell infiltration, measured using T-cell receptor (TCR) sequencing, after doxorubicin. Together, this suggests that short-term doxorubicin and cisplatin may induce a more favorable TME and increase the likelihood of response to PD-1 blockade in TNBC (Voorwerk et al. Nature Medicine 2019).

PI3K-pathway and tumor-infiltrating lymphocytes (TILs)
TILs are correlated with good outcome in TNBC and HER2-positive BC. However, the role of TILs in luminal breast cancer is less clear. Emerging evidence has now demonstrated that genetic aberrations influence the immune landscape of tumors. Phosphatidylinositol 3-kinase (PI3K) is the most common altered pathway in ER-positive BC. It is unknown whether changes in the PI3K pathway result in a different composition of the breast TME. In a randomized trial in 563 ER-positive BC we found that CD8-positive TILs were significantly more abundant in PIK3CA-mutated tumors. While CD4 and FOXP3 were not significantly associated with prognosis, patients with tumors classified as CD8-high had increased risk of recurrence (Sobral-Leite et al. Breast Cancer Res 2019)

Systemic immune characteristics in breast cancer patients
There is substantial evidence that suppressive immune cells and soluble immune mediators can blunt the anti-cancer T cells response. Right now the question is whether this immunosuppressive phenomenon is present in BC patients. In collaboration with the group of prof Karin de Visser we have set-up a pipeline for analyses of these systemic immunosuppressive components using flow cytometry combined with functional assays on fresh material from BC patients who receive various combinations of chemo-immunotherapy in our clinical trials.

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Hogan SA, Courtier A, Cheng PF, Jaberg-Bentele NF, Goldinger SM, Manuel M, Perez S, Plantier N, Mouret JF, Nguyen-Kim TDL, Raaijmakers MIG, Kvistborg P, Pasqual N, Haanen J, Dummer R, Levesque MP. Peripheral Blood TCR Repertoire Profiling May Facilitate Patient Stratification for Immunotherapy against Melanoma. Cancer Immunol Res 2019;7(1):77-85

Lugli E, Kvistborg P, Galletti G. Cancer neoantigens targeted by adoptive T cell transfer: private no more. J Clin Invest 2019;129(3):949-951

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How checkpoint targeting therapy alters the tumor-reactive T cells

The immune checkpoint blockade ICB therapies are undoubtfully a massive success in treatment of many solid malignancies and have changed standard of care treatment for a large proportion of patients over the last years. Approximately 60% of stage IV melanoma patients respond to anti-CTLA-4/anti-PD-1 treatment. In spite of this success, 40% are not responding, and at 4 year follow up 58% of initial responders have relapsed. Even though a part of the heterogeneity in response to therapy may be explained by tumour cell intrinsic properties, it is known that T cell intrinsic properties contribute to lack of responses. To expand the success of these therapies it is of key importance to understand how the the tumour-specific T cell compartment is composed in different malignancies, and the therapy induced alterations. Our team is focused on understanding how the tumour-reactive T cell response rendered dysfunctional in cancer can be improved with adequate support in terms of e.g. immunotherapies.

We have a strong interest in how the state of the tumour specific T cell response differ between patients and malignancies, and how therapies change the state of these cells. We are in particular interested in the effect of ICB alone or in combination with conventional therapies such as chemotherapy, and the ultimate aim is to identify novel targets and provide rationale for new combination therapies to broaden the success of immunotherapy. We are addressing these questions in two different manners: 1. Dissecting mechanism of action of checkpoint targeting therapies by analysing larger patient cohorts with high throughput strategies focusing on T cell responses restricted towards shared self-tumor antigens, and 2. In depth characterization of T cell responses specific for patient private neoantigens, and how therapy can alter these or not.

Immunocompetence in cancer

An important limitation of ICB is the occurrence of serious adverse events (SAEs) in a large proportion of treated patients. Data obtained from clinical trials show that approximately 60% of stage IV and 90% of stage III melanoma patients treated with dual CTLA-4/PD-1 blockade experiences grade 3/4 SAEs. A large proportion of these immune related toxicities are mediated by T cells not specific for the disease (bystander T cells). There is consensus among clinical oncologists that many patients are currently overtreated with ICB, which is likely to in part explain the high level of toxicity that is observed, however, tools are lacking to drive patient specific dosing of these drugs. The observation that SAEs occur more frequently in patients with a lower disease stage strongly suggests that the occurrence of events is related to general immune function, i.e. immunocompetence, of patients. In support of this model, prior work has provided evidence for immunosuppression in cancer patients, as based on analyses of dendritic cells from peripheral blood. Furthermore, this immunosuppression was shown to increase with disease progression, indicating that immune reactivity not related to the tumor-specific T cell response, is dependent on disease stage, and is a systemic phenomenon. On the basis of these observations it is of interest to examine the relationship between the activity/ transcriptome of bystander T cells (allowing high throughput analysis across patients) and disease stage as well as the SAEs to ICB. Such knowledge could be highly useful to predict potential SAEs for each individual and adjust the dosing schedule per patient to ensure treatment can be given in a safer manner. The main questions we are working on addressing are: 1) Do systemic bystander T cells change during disease progression? and 2. Does the immunocompetence correlate with toxicity to ICB?

Transcription dynamics
in single cells

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Publications

Brouwer I, Lenstra TL. Visualizing transcription: key to understanding gene expression dynamics. Curr Opin Chem Biol. 2019;51:122-129

Donovan BT, Huynh A, Ball DA, Patel HP, Poirier MG, Larson DR, Ferguson ML, Lenstra TL. Live-cell imaging reveals the interplay between transcription factors, nucleosomes, and bursting. EMBO J. 2019;38(12)

Gene expression is tightly regulated to ensure that genes are transcribed in the right cell at the right time. Single-cell studies have shown that cells in a population can show considerable heterogeneity in gene expression, and that even at steady state concentrations of individual RNAs and proteins randomly fluctuate from one moment to the next. This stochastic heterogeneity can influence essential cell-fate decisions, and can also contribute to heterogeneity in tumors. We use cutting-edge single-molecule imaging approaches to visualize transcription fluctuations in living cells, in order to understand the mechanisms and regulation of transcription dynamics in single cells.

Understanding the mechanisms of transcriptional bursting

Previous studies on transcription dynamics have shown that genes are often not transcribed in a continuous fashion, but show transcriptional bursting, with periods of gene activity followed by periods of inactivity. Transcriptional bursting is a conserved property that occurs from bacteria to yeast to human cells. However, the origin and regulators of bursting remain largely unknown. Our lab uses a single-molecule RNA labeling technique to directly visualize and measure transcriptional bursts in both yeast and mammalian cells to understand how different levels of regulation control bursting.

Interplay between transcription factors, nucleosomes, and bursting

A combination of *in vitro* and *in vivo* single-molecule imaging was used to study the interplay between transcription factor dwell time, nucleosome binding and transcriptional bursting at the galactose responsive genes in budding yeast. We directly correlated the binding of the transcription factor Gal4 with the transcriptional bursting kinetics of its target genes in living yeast cells, which showed that Gal4 dwell time sets the transcriptional burst size. The dwell time of Gal4 is determined by the affinity of the binding site. Moreover, Gal4 dwell time *in vivo* is reduced by several orders of magnitude by promoter nucleosomes. Using a novel imaging platform called orbital tracking, we simultaneously tracked Gal4 binding and transcription at one locus, revealing the timing and correlation between Gal4 binding and transcription. Our data support a model where multiple polymerases initiate during a burst as long as the transcription factor is bound to DNA, and a burst terminates upon transcription factor dissociation.

Bursting of neighboring genes

Closely positioned genes may affect each other's transcription, for example by shared binding sites or propagation of supercoils generated by transcription. We have set up a dual-color imaging assay technique to simultaneously monitor bursting of divergent and tandem gene pairs in the same cell. Transcriptional bursts of divergent genes show correlated transcription initiation. Rapid conditional degradation of enzymes that relieve supercoiling, called topoisomerases, decreases this correlation. Interestingly, the transcription of tandem gene pairs becomes mutually exclusive upon topoisomerase degradation, indicating that the inability to release supercoiling inhibits simultaneous expression of neighboring genes. We are currently using different perturbation approaches to determine the mechanism of this regulation.

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**Selected
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Baird RD, van Rossum AGJ, Oliveira M,
Beelen K, Gao M, Schrier M, Mandjes
IAM, Garcia-Corbacho J, Vallier AL,
Dougall G, van Werkhoven E, Linossi
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J, Eichler C, Thangarajah F, Malter W,
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Lohuizen M, Hauptmann M, Rhiem K,
Hahnen E, Reinhardt HC, Buttner R,
Mallmann P, Schomig-Markiefka B,
Schmutzler R, Linn S, Jonkers J.
EZH2 Is Overexpressed in BRCA1-like
Breast Tumors and Predictive for
Sensitivity to High-Dose Platinum-
Based Chemotherapy. Clin Cancer
Res 2019; 25: 4351-4362

Molecular dissection of cancer by differential drug sensitivity

In the clinic, we mainly use anticancer drugs based on outcomes of clinical trials that have identified the best treatment for the average breast cancer patient, not considering differential patient and tumor characteristics that define the case mixes studied. Hence, this approach serves only those patients whose outcome improves substantially with 'the best treatment' identified, while harming patients that do not derive benefit, or even develop metastasis or progress due to the same treatment.

The focus of our research line is to unravel underlying tumor and host mechanisms that ultimately define treatment efficacy and develop tests that will guide individualized treatment decisions in the clinic and eventually improve survival. For this purpose, we use several genome-wide approaches and molecular techniques, in order to dissect the mechanisms that divide clinically well-defined cohorts of breast cancer patients into resistant and sensitive to a particular treatment. We have a close collaboration with the groups of Jos Jonkers and Jacco van Rheenen, who use genetically engineered mouse models for breast cancer, to study differential drug sensitivity in a controlled fashion. In addition, we collaborate with the group of Wilbert Zwart, focusing on molecular mechanisms underlying endocrine therapy resistance.

A second research line focuses on prognostic molecular classifiers for adjuvant systemic treatment advice in breast cancer in collaboration with the groups of Lodewyk Wessels and Rene Bernards.

Molecular mechanisms underlying sensitivity to alkylating agents

Our institute previously described characteristic DNA copy number aberrations of *BRCA1*- and *BRCA2*-mutated breast cancers. We called these profiles BRCA-like profiles. In posthoc analyses of several randomized controlled trials we have demonstrated that BRCA1-like breast cancer patients derive significant benefit from alkylating agents and PARP inhibition in the (neo)adjuvant setting. These findings are now investigated in a prospective, randomized trial (NCT02810743). Recently, we demonstrated that EZH2 is overexpressed in human BRCA1-deficient breast cancers and might predict sensitivity to high-dose, alkylating chemotherapy in HER2-negative, non-BRCA1-like, EZH2 overexpressing stage III breast cancers. Furthermore, EZH2 inhibition potentiated cisplatin efficacy in Brca1-deficient murine mammary tumors.

Endocrine therapy resistance in the adjuvant and metastatic setting

We showed that IGF-1R pathway activation contributes to adjuvant tamoxifen resistance in early breast cancer patients. Next, we showed that treating breast cancer cells with linsitinib can thwart IGF-1R signaling and restore tamoxifen's efficacy. Patients with activated IGF-1R pathways may therefore do better with tamoxifen combined with linsitinib than tamoxifen alone.
Combining endocrine therapy with PI3K/mTOR inhibition has shown promise in metastatic, estrogen receptor (ER)–positive breast cancer. In a phase 1b trial we investigated the combination of tamoxifen with taselisib, a potent, selective, PI3kinase inhibitor. Twelve of 30 patients (40%) had disease control for 6 months or more. Circulating tumor DNA studies using next-generation tagged amplicon sequencing identified early indications of treatment response and mechanistically relevant correlates of clinical drug resistance (e.g., mutations in KRAS, ERBB2) in some patients.

Cell cycle checkpoints and chromosome segregation

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Jeroen van den Berg MSc PhD student
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Chantal Vaarting Technical staff

Selected publications

Krenning L, van den Berg J,
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Mol. Cell 2019;76:346-358

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Wiegant WW, van den Broek B, Rother
MB, Wolthuis RM, Freire R, van Attikum
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and G2 checkpoint recovery. EMBO
Rep. 2019

The research in the Medema group aims to gain a better understanding of the cellular response to classic anti-cancer drugs that damage the DNA or interfere with chromosome segregation. The ultimate aim is to identify vulnerabilities of cancer cells that could be exploited to selectively target the fitness of cancer cells. Our group uses the knowledge that is generated to define and experimentally test new anti-cancer strategies.

The cellular response to DNA damage
Our work on the DNA damage response aims to identify and characterize determinants of DNA damage sensitivity. We strive to answer questions such as: are there differences in cellular sensitivity to a single double strand break, and if so, what causes such differential DNA damage sensitivity? What factors contribute to the differences in DNA damage sensitivity in normoxic and hypoxic conditions? Can we identify novel factors that contribute to limiting the toxicity of DNA damage? Answering these important questions may help to better understand the response of a tumor to DNA damaging agents that are commonly used to treat cancer.

In an effort to identify novel chromatin-associated players that are involved in limiting the toxicity of DSBs we have identified PHF6 (Warmerdam *et al.*, EMBO J, 2019). We showed that PHF6 is required for the efficient repair of DSBs by regulating the recruitment of 53BP1 and classical Non-Homologous End-Joining DNA repair. As such, PHF6 allows for efficient DNA repair and timely recovery of a damage-induced cell cycle arrest.

Using CRISPR/Cas9-technology to introduce DSBs at a defined set of locations, we investigated whether there are location-dependent differences in the response to a single DSB (van den Berg, bioRxiv, 2019). We showed that DSBs that occur in regions of accessible chromatin are much more likely to undergo excessive DNA end-resection. Such DSBs have a more detrimental effect on cellular outgrowth compared to breaks in less accessible regions, and we could show that his is due to the excessive resection of such breaks. These data imply that the cellular toxicity of a single DSB is in part determined by its nuclear location. Current efforts aim to identify additional determinants of DSB toxicity.

Chromosome segregation errors
The other aim of the lab is to unravel the causes and consequences of chromosome segregation errors, a trait that is very common to cancer cells. To reveal the liabilities of genomically unstable cells, we have performed multiple haploid genetic screens in collaboration with the Brummelkamp lab. In one of these screens we previously identified BUB1 as a synthetic lethal interactor with mitotic checkpoint deficiency. This was received as a surprising finding as BUB1 was suggested to be an essential player of the mitotic checkpoint itself. To exclude an essential role for BUB1 in the mitotic checkpoint, we now deleted the entire BUB1 gene in HAP1 cells and we verified that these full BUB1 KO cells are still able to elicit a functional mitotic checkpoint response (Raaijmakers and Medema, EMBO J, 2019). We are further exploiting the haploid genetics approach to study synthetic lethal interactions with genomic instability as a consequence of replication stress.

We also have a strong interest in understanding the consequences of segregation errors and the resulting abnormal karyotypes on cell fate. We reviewed the latest advances in this field (Soto et al. Trends Genet. 2019 and Lens and Medema, Nat. Rev. Cancer, 2019), and are currently addressing a major open question in the field: how are cancer cells able to tolerate abnormal karyotypes while this is such a detrimental condition in normal cells. As such, we are now studying the short-term consequences of segregation errors in single cells to understand how abnormal karyotypes are eliminated under normal conditions. Besides, we aim to get insight into how cells can adapt to the negative consequences associated to abnormal karyotypes on the long term.

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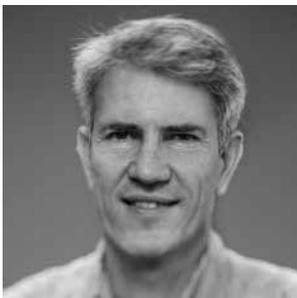
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Translational gastrointestinal oncology

Translating disease biology into new diagnostic applications holds great promise for improving outcome for patients. We characterize gastrointestinal pre-malignant and malignant lesions at DNA, RNA, and protein level by tumor profiling using multiple -omics techniques for biomarker development, to improve colorectal cancer screening as well as to stratify patient groups and arrive at individually tailored therapies. Disease biology is studied using pre-clinical model systems such as organoid cultures. Clinical validation is performed by making use of large series of patient sample collections derived from screening programs and multi-center clinical trials. To facilitate the logistics that are needed for these validation studies, we are involved in several (inter)national research infrastructure programs.

Early detection of colorectal cancer
Colorectal cancer screening programs using the fecal immunochemical test have a high sensitivity for cancer (80%) but <30% for advanced adenomas (i.e. precursors). We aim to improve on this by unravelling the biology of adenoma to carcinoma progression, and identifying and clinically validating novel biomarkers. This includes improved stratification of patients in groups at low- or high-risk of developing CRC.

Candidate protein biomarkers for *colorectal cancer screening* were identified using shotgun mass spectrometry on stool samples of individuals with or without cancer or adenomas, detected by colonoscopy. For these candidate biomarkers antibody-based assays were developed, and clinical utility was validated in a large series of 1298 FIT samples. Currently, we are preparing a prospective trial among 10,000 participants of the Dutch national bowel screening program. This study is planned to start by the end of 2020.

Inclusion of the MOCCAS (MOlecular stool testing for Colorectal CAncer Surveillance) study, where the performance of molecular markers in *surveillance after polypectomy or cancer* resection is evaluated, almost is complete (3736 out of 4000). An interim analysis has shown promising results to support the potential use of molecular markers in surveillance. A full Health Technology Assessment will be conducted after completion of the inclusion.

Our understanding of the natural history of colorectal adenoma to cancer progression still is incomplete. Previously, we observed specific DNA copy number alterations to be associated with adenoma to cancer progression risk. In the IntEnd study we aim to further substantiate this, by evaluating these same features in a large retrospective series of adenoma patients with detailed follow-up, and model alternative surveillance strategies. Within the same study we will also validate POFUT1, which we identified as a biomarker for risk of progression.

To conduct functional studies to address the same research questions, we have established a library of ~50 human adenoma organoids, representing both high-risk and low-risk adenomas, as defined by specific DNA copy number alterations. An extensive phophoproteomics analysis of adenomas and cancers pinpointed several molecular pathways specifically active in adenoma to carcinoma progression. These pathways are being functionally tested in a series of adenoma organoids.

Patient stratification
With DNA-, RNA-, and protein-profiling we aim to stratify patients to optimize treatment outcomes. Whole Genome Sequencing (WGS) captures an accurate, unbiased and complete view of genomic characteristics of a tumor in one single test on a relatively low amount of tumor material. WGS can identify 'clinically actionable' targets in more patients than regular diagnostics, allowing a match with a registered and approved therapy. Yet, so far, WGS has been mainly evaluated in clinical trials, i.e. outside the routine clinical setting. In the WIDE (WGS Implementation in standard cancer Diagnostics for Every cancer patient) project we will together with Hartwig Medical Foundation

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and UMCU investigate the (i) feasibility and (ii) impact of WGS-based diagnostics in routine clinical practice. Nine months underway, accrual for the WIDE study is fully on schedule with >450 of the planned 1200 patients enrolled.

Liquid biopsies (i.e. blood samples) contain minute amounts of tumor material, can be obtained longitudinally and are less burdensome than tissue biopsies. We investigate whether analysis of liquid biopsy circulating tumor DNA (ctDNA) can be applied as biomarkers to better determine who to treat, how to treat, and when to treat patients. After surgery most stage II CRC patients do not receive systemic adjuvant chemotherapy (ACT), while still ~15% develop a recurrence and might have benefitted from ACT (undertreatment). Most stage III CRC patients do receive ACT, while ~50% of stage III CRC patients are cured by surgery alone (overtreatment). Detection of ctDNA after surgery is highly prognostic for disease recurrence, and may therefore guide decisions who (not) to treat with ACT. To validate these observations, we collect and analyze blood samples longitudinally from stage II (MEDOCC study) and stage III (PROVENC3 study) CRC patients making use of the infrastructure of the Prospective Dutch CRC cohort (PLCRC). An interventional trial (CrEATE study) will start early 2020.

Detection of ctDNA in CRC patients with metastatic disease allows to monitor treatment response and to detect therapy resistance. We are collecting and analyzing blood samples longitudinally from patients with CRC metastases in the liver or in the peritoneum.

Highly sensitive technologies for detecting ctDNA are being developed by our collaborator prof. Velculescu (Johns Hopkins University, Baltimore), such as TEC-seq and DELFI.

The COIN (ctDNA on the way to Implementation in the Netherlands) project establishes a clinical validation framework for effciently investigating clinical utility of ctDNA towards clinical implementation.

Translational research infrastructure
Succesfully developing biomarkers to clinical implementation is critically dependent on dedicated infrastructure for facilitating study logistics and FAIR data stewardship. Rather than just using, we are heavily involved in co-developing this infrastructure, both locally as well as nationally (Health-RI, https://trait.health-ri.nl/trait-tools). This is of critical importance as user input is crucial to make sure that the needs of end users are met by the solutions built. These solutions comprise a series of applications to accommodate the different types of research data generated. For view and query of 'final' data cBioPortal now is used as the main data integration platform. Internationally, we align our activities with initiatives such as Cancer Core Europe and AACR GENIE.

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Selected
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**Vredevoogd DW, Kuilman T, Ligtenberg
MA, Boshuizen J, Stecker KE, de Bruijn
B, Krijgsman O, Huang X, Kenski JCN,
Lacroix R, Mezzadra R, Gomez-Eerland
R, Yildiz M, Dagidir I, Apriamashvili G,
Zandhuis N, van der Noort V, Visser
NL, Blank CU, Altelaar M, Schumacher
TN, Peeper DS.** Augmenting
Immunotherapy Impact by Lowering
Tumor TNF Cytotoxicity Threshold.
Cell. 2019;178(3):585-599.e15

Functional genomics for cancer
and immune cell therapy

We use function-based, genome-wide experimental strategies to develop rational combinatorial cancer treatment, targeting both cancer and immune cells. By screening for novel therapeutic targets and predictive biomarkers, we aim to achieve more durable clinical responses for patients. On the one hand, we are increasing our understanding of how cancer cells rewire their signaling networks, to expose and exploit new pharmacologically tractable tumor susceptibilities, also in the context of immunotherapy. On the other hand, we are manipulating various cell types from the patient's own immune system to boost their specific cytotoxicity towards tumor cells. With these function-based approaches, we develop new rational combinatorial therapies, which simultaneously eliminate the patients' tumors and harness their immune systems.

CRISPR screening to break tumor resistance to immunotherapy

Notwithstanding clinical advances, it is clear that large groups of patients will not durably benefit from immunotherapy, mostly because of resistance. Therefore, in collaboration with the group of Ton Schumacher, we have built *in vitro* and *in vivo* systems to study interactions between tumor cells and T cells. We have used these systems to perform function-based screens to develop combinatorial targeted and immunotherapy regimens to achieve more durable clinical responses. For example, we have used this approach to break intrinsic resistance of melanoma to T cell killing. Whereas the interferon (IFN)g pathway harbors both ICB resistance factors and therapeutic opportunities, this has not been systematically investigated for IFNg-independent signaling routes. A genome-wide CRISPR/Cas9 screen to sensitize IFNg receptor-deficient tumor cells to CD8 T cell elimination uncovered several hits mapping to the tumor necrosis factor (TNF) pathway. Clinically, we have shown that TNF antitumor activity is only limited in tumors at baseline and in ICB non-responders, correlating with its low abundance. Taking advantage of the genetic screen, we have also demonstrated that ablation of the top hit, TRAF2, lowers the TNF cytotoxicity threshold in tumors by redirecting TNF signaling to favor RIPK1-dependent apoptosis. TRAF2 loss greatly enhanced the therapeutic potential of pharmacologic inhibition of its interaction partner cIAP, another screen hit, thereby cooperating with ICB. Our results suggest that selective reduction of the TNF cytotoxicity threshold increases the susceptibility of tumors to immunotherapy.

Reversal of pre-existing NGFR-driven tumor and immunotherapy resistance

Continuing on this theme, we considered that little is known about mechanisms of intrinsic immune resistance. To mimic recurrent T cell attack, we chronically exposed a panel of (patient-derived) melanoma cell lines to cytotoxic T cells. This led to strong enrichment of a pre-existing cell population that exhibited immune resistance in vitro and in mice. These fractions showed high expression of NGFR, were maintained stably, and were found to be present in patients' melanomas prior to treatment. Remarkably, these cells exhibited multidrug-resistance to other therapies including BRAF + MEK inhibition, suggesting that they exist in a stable and distinct cellular state. We are currently clinically corroborating these findings, and exploring how to translate this findings therapeutically.
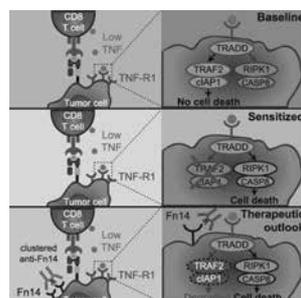
New opportunities are needed to increase immune checkpoint blockade (ICB) impact for cancer patients. A genome-wide CRISPR/Cas9 screen uncovered several hits in the TNF pathway sensitizing tumor cells to T cell elimination. TNF antitumor activity was generally limited in tumors at baseline and in ICB non-responders, correlating with its low abundance. Selective inactivation of TNF signaling lowered melanoma and lung cancer thresholds to low TNF levels, thereby increasing tumor susceptibility to T cell attack and augmenting benefit from anti-PD-1 treatment.

Structural biology

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Selected publications

Adamopoulos A, Landskron L, Heidebrecht T, Tsakou F, Bleijerveld OB, Altelaar M, Nieuwenhuis J, Celie PHN, Brummelkamp TR, Perrakis A. Crystal Structure of the Tubulin Tyrosine Carboxypeptidase Complex VASH1-SVBP. Nat Struct Mol Biol. 2019;26(7):567-570

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Salgado-Polo F, Perrakis A. The Structural Binding Mode of the Four Autotaxin Inhibitor Types That Differentially Affect Catalytic and Non-Catalytic Functions. Cancers (Basel) 2019;11(10)

We aim to provide molecular insight to macromolecular interactions and structures, understanding how these regulate specific biological activities in space and in time. In parallel we develop concepts, algorithms, and software for strive for improving the methods for this work. Our work enables the development of new specific drugs and biologics.

Structural studies of Autotaxin
ATX produces the signalling phospholipid LPA; LPA and ATX are involved in cancer metastasis and other pathogenic situations. Our detailed evaluation of the kinetics of the enzymatic activity of ATX, taking into account allosteric activation, allowed us to understand better how new types of inhibitors affect ATX action. Our focus remains in understanding how different inhibitors, targeting catalytic and non-catalytic activities of ATX, can have different clinical results in specific pathologies.

Structural studies of microtubule interacting proteins
Our major interest revolves around our collaboration with the group of Geert Kops, studying the spindle assembly checkpoint (SAC) and how the Mps1 kinase competes with microtubules for binding to the NDC80 complex in the outer kinetochores, regulating SAC activity. We also study the dynein adaptor Spindly that drives kinetochore expansion in a dynein-independent manner, promoting initial microtubule capture and subsequent correct maturation of attachments.
The discovery of the long-sought tubulin detyrosination enzyme by the group of Thijn Brummelkamp, the complex between VASH1/2 and SVBP, has prompted us to extend our research to this tubulin-modifying enzyme complex. We determined the crystal structure of VASH1:SVBP, explaining how SVBP acts as a unique structural chaperone of the VASH1 catalytic subunit, stabilising the N- and C-terminal VASH1 domains by inserting between them a long helix. Together with mutagenesis experiments and cell-based assays, we deciphered the specificity determinants for the C-terminal tyrosine of the α-tubulin tail.

Structural studies of J-base binding proteins
The JBP1 protein binds to DNA that contains base J (β-D-glucosyl-hydroxymethyluracil) and is also a thymidine hydroxylase. Well into the second decade since its discovery by Piet Borst and colleagues, we now understand the function of JBP1 and have published the characterisation of the low-resolution shape of the J-DNA complex with JBP1. In 2019, we have established a low-resolution model of JBP1 by electron microscopy and are working on a medium-resolution model and X-ray structures of JBP3, a new protein in J-base biosynthesis that likely assists glucosylation of the JBP1 hydroxylation product to create base J.

Methods for X-ray crystallography
PDB-REDO is a project we lead together with Robbie Joosten in my group. We strive to make better crystallographic structure models by improving published structures and making them available through the PDB_REDO data bank and providing a web-server that allows practicing crystallographers to take full advantage of the PDB_REDO procedure.

This year we took our work on using structural homology one step further, towards building a new web service (https://lahma.pdb-redo.eu) allowing researchers to look interactively for unusual – and thus potentially functionally interesting – features between structural homologues.

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Selected
publications

Elbatsh AMO, Kim E, Eeftens JM,
Raaijmakers JA, van der Weide RH,
García-Nieto A, Bravo S, Ganji M,
uit de Bos J, Teunissen H, Medema RH,
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turning heads, bending elbows, and
fixed anchors. Curr Opin Genet Dev.
2019;55:11-18

Chromosome biology

Human chromosomes are centimetres in length, but are organized such that they fit into a cell of micrometre-scale dimensions. Within this confined setting, chromosomes allow for tightly controlled cellular processes such as mitosis and transcription. These processes are made possible by two conserved protein complexes known as cohesin and condensin. Both cohesin and condensin are so-called SMC complexes that by building DNA loops, and by holding together DNA elements, can provide structure to chromosomes.

Research in our lab centres on the mode of action of cohesin and condensin. How do these complexes form DNA loops and shape the genome in 3D? How do these complexes entrap and release DNA? How does cohesin stably lock together the sister chromatids? How does condensin drive mitotic chromosome condensation? And how does loop formation by these complexes affect nuclear organization and gene expression? We are addressing these questions using a multi-disciplinary approach that covers genetics, genomics, biochemistry and imaging.

Chromosome organization by cohesin and CTCF

The cohesin complex is essential for the formation of chromatin loops across the genome. We recently discovered that the interphase genome is structured through a highly dynamic process that involves a continuous cycle of formation, loss and re-formation of loops by cohesin. We also found that the cohesin release factor WAPL limits the degree by which loops can be enlarged. Together, our findings support the model that cohesin structures chromosomes through the processive enlargement of DNA loops (Haarhuis et al., Cell 2017).

Cohesin is required for the formation of loops between CTCF sites along chromosomes. How cohesin and CTCF together enable the formation of such loops has remained unknown. This year we had a fruitful collaboration with the laboratory of Daniel Panne (University of Leicester), and found that a segment of the CTCF N-terminus interacts with the SA2-SCC1 subunits of cohesin. CTCF turns out to bind to a conserved surface on cohesin and hereby stabilizes cohesin on chromatin. This key interaction is essential for CTCF-anchored loops, and contributes to the positioning of cohesin at CTCF binding sites. We suggest that CTCF enables chromatin loop formation by protecting cohesin against loop release. Our results provide fundamental insights into the molecular mechanism that enables chromatin folding by cohesin and CTCF.

Chromosome condensation by condensin

As cells enter mitosis, condensin complexes convert the genome into compact and rigid chromosomes. Condensin drives chromosome condensation through the formation of loops along the DNA. This vital process ensures that chromosomes are shortened enough to allow the splitting in half of the cell during cytokinesis without DNA getting caught in the middle. Cohesin and condensin are enzymes with highly conserved ABC-like ATPases at their basis. In a productive collaboration with colleagues from Delft and Heidelberg, we discovered this year that one of condensin's ATPase sites promotes the initiation of loops, while the other site determines the type of loops that condensin forms. Mutation of this latter site yields hyper-active condensin that compacts DNA faster than wild type, both in vivo and in vitro. Asymmetric ATPases with distinct roles for each ATPase site are likely to reflect a universal principle for SMC complexes that enables these ancient molecular machines to intricately control chromosome architecture.

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**Selected
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Klaver KM, Duijts SFA, Engelhardt
EG, Geusgens CAV, Aarts MJB, Ponds
RWHM, van der Beek AJ, Schagen SB.
Cancer-related cognitive problems at
work: experiences of survivors and
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Van der Willik KD, Hauptmann M,
Jóźwiak K, Vinke EJ, Ruiter R, Stricker
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to cancer diagnosis: a population-based
study. J Natl Cancer Inst. 2019

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J, Hogewoning SJ, Timmermans
KCAA, Visser O, Schagen SB, Ikram
MA, Stricker BHC. Ascertainment of
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concordance between the Rotterdam
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Registry. Int J Cancer. 2019

Cognitive function
in cancer patients

The projects constituting our lines of research center around the characterization of the incidence, pattern and course of cognitive problems associated with cancer and cancer therapies, the risk factors for cognitive problems and the mechanisms that underlie cognitive problems in patients with tumours either inside or outside the CNS. Our research is also directed to develop, evaluate and implement interventions to minimize and manage cognitive problems.

Internet based Work-related cognitive Rehabilitation for Cancer survivors
Cognitive problems are common in non-CNS cancer survivors. These problems are perceived as an important contributor to affect job performance and work ability. Various interventions for cancer-related cognitive impairment have been proposed, but effectiveness for work-related outcomes is not yet established. We therefore developed and internet-based cognitive intervention programme for occupationally active cancer survivors.

A three-armed randomized controlled trial including two intervention groups and a waitlist control group is currently in progress. 300 cancer survivors who have returned to work and who experience cognitive problems are recruited. Patients with and without cognitive dysfunction are eligible. The high-intensity arm will contain a comprehensive training programme (including psycho-education, fatigue management and cognitive strategy training) with individual guidance. The low-intensity arm will contain a brief cognitive training programme (including psycho-education and fatigue management) without individual guidance. The primary outcome will be accomplishment of an individually defined work-related treatment goal.

Accelerated brain aging after chemotherapy for breast cancer?
Chemotherapy for non-CNS cancer is associated with brain abnormalities that are compatible with a premature brain aging framework. Using machine learning we evaluated whether chemotherapy for breast cancer is associated with accelerated brain aging in a datapooling project initiated by the ICCTF Neuroimaging Working Group.

T1-weighted MRI scans from 6 sites (USA and Europe) acquired at 3 Tesla were included for brain age estimations in BC patients exposed to chemotherapy (CT+, n=182), BC patients who did not receive chemotherapy (CT-, n=154) and no-cancer controls (NC, n=145). Brain age was estimated with the brainageR toolbox. Subtracting brain age at baseline (preCT) from brain age at follow-up (postCT) provided a longitudinal estimate of brain aging. By dividing this with the interscan interval, we obtained a brain aging coefficient with percentages > 100% indicating accelerated brain aging. The mean brain aging coefficient was 144% for CT+ patients, 103% for CT- patients and 76% for NC (p=ns). Next, analyses were restricted to participants who showed longitudinal brain aging (i.e., positive numbers) between the time points (61% of participants). The brain aging coefficient for these subgroups was 498% for CT+ patients, 325% for CT- patients and 300% for NC (p<0.001), indicating that among participants who showed brain aging, BC patients exposed to chemotherapy showed more accelerated brain aging than patients not exposed to chemotherapy and no-cancer controls. Brain age estimations, particularly in longitudinal settings, are a new field of research with many unexplored avenues. They are a promising tool to study chemotherapy-associated neurotoxicity.

Genes and proteins involved in anticancer drug resistance and pharmacokinetics

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Selected publications

Durmus S, van der Valk M, Teunissen SF, Song JY, Wagenaar E, Beijnen JH, Schinkel AH. ABC transporters Mdr1a/1b, Bcrp1, Mrp2 and Mrp3 determine the sensitivity to PhIP/DSS-induced colon carcinogenesis and inflammation. Arch Toxicol. 2019;93:775-90

Li W, Tibben M, Wang Y, Lebre MC, Rosing H, Beijnen JH, Schinkel AH. P-glycoprotein (MDR1/ABCB1) controls brain accumulation and intestinal disposition of the novel TGF-β signaling pathway inhibitor galunisertib. Int J Cancer. 2019 (in press)

Martínez-Chávez A, van Hoppe S, Rosing H, Lebre MC, Tibben M, Beijnen JH, Schinkel AH. P-glycoprotein Limits Ribociclib Brain Exposure and CYP3A4 Restricts Its Oral Bioavailability. Mol Pharm. 2019;16:3842-52

We study genes and proteins that affect drug resistance in tumors, or influence the pharmacological and toxicological behavior of (anticancer) drugs and toxins, including carcinogens. Of special interest are multispecific drug efflux and uptake transporters, as well as drug-metabolizing enzymes. Insight into these systems may: i) improve pharmacotherapy approaches for cancer and other diseases; ii) increase insights into factors determining susceptibility to toxins and carcinogens, and; iii) allow elucidation of physiological functions. To understand the roles of these proteins we generate and analyze knockout or transgenic mice lacking or overexpressing the relevant genes. Below we describe a few recent studies illustrating our approach.

ABC transporters Mdr1a/1b, Bcrp1, Mrp2 and Mrp3 determine the sensitivity to PhIP-induced colon carcinogenesis

2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP) is an abundant dietary carcinogen. We investigated whether clinically relevant ATP binding cassette (ABC) efflux transporters can modulate PhIP-induced colorectal carcinogenesis using wild-type (WT), $Bcrp1^{-/-};Mrp2^{-/-};Mrp3^{-/-}$ and $Bcrp1^{-/-};Mdr1a/b^{-/-};Mrp2^{-/-}$ mice. Both knockout strains were more sensitive to DSS-induced colitis than WT mice. Lack of these transporters also led to altered disposition of activated PhIP metabolites. The results suggest that Mdr1a/1b, Bcrp1 and Mrp2 contributed to biliary excretion and Mrp3 to sinusoidal secretion of the pre-carcinogenic metabolite N2-OH-PhIP. A genotoxicity marker, PhIP-5-sulphate, was at least 4- and 17-fold reduced in the intestinal tissue and intestinal content of both knockout strains. The level of colon carcinogenesis was reduced by 2- to 4-fold in both knockout strains compared to WT mice. Thus, reduced activity of these ABC transporters may in part protect from PhIP-induced colon carcinogenesis. It thus appears that ABC transporters are important in protecting the body from inflammatory agents such as DSS, in the disposition of carcinogenic metabolites, and in determining the sensitivity to dietary PhIP-induced carcinogenesis.

P-glycoprotein (MDR1/ABCB1) controls brain accumulation and intestinal disposition of the novel TGF-β signaling pathway inhibitor galunisertib

Galunisertib is currently in trials for various cancers. Using genetically modified mouse models, we investigated the roles of the multidrug efflux transporters ABCB1 and ABCG2, the OATP1A/1B uptake transporters, and the drug-metabolizing CYP3A complex in galunisertib pharmacokinetics. Orally administered galunisertib was very rapidly absorbed in mice. Galunisertib brain-to-plasma ratios were increased by 24-fold in $Abcb1a/1b^{-/-}$ and $Abcb1a/1b;Abcg2^{-/-}$ mice compared to wild-type mice. Galunisertib oral availability was not affected, but recovery of galunisertib in the small intestinal lumen was strongly reduced in $Abcb1a/1b^{-/-}$ and $Abcb1a/1b;Abcg2^{-/-}$ mice. Oral coadministration of the ABCB1/ABCG2 inhibitor elacridar boosted galunisertib brain accumulation in wild-type mice. Oatp1a/1b deficiency did not alter oral galunisertib pharmacokinetics or liver distribution. $Cyp3a^{-/-}$ mice showed a 1.9-fold higher plasma AUC_{0-1h} than wild-type mice, but this difference disappeared over 8 h. Also transgenic human CYP3A4 overexpression did not significantly alter oral galunisertib pharmacokinetics. Abcb1 thus dramatically restricts galunisertib brain penetration and affects its intestinal disposition, possibly through biliary excretion.

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Selected publications

Escala-Garcia M et al. A network
analysis to identify mediators of
germline-driven differences in breast
cancer prognosis. Nat Commun.
2020;16;11(1):312

Giardiello D et al. Prediction and
clinical utility of a contralateral breast
cancer risk model. Breast Cancer Res
2019;21:144 (online)

Sobral-Leite M et al. Cancer-immune
interactions in ER-positive breast
cancers: PI3K pathway alterations and
tumor-infiltrating lymphocytes. Breast
Cancer Res. 2019;21(1):90

Molecular breast cancer epidemiology

Our work spans the themes of precision medicine (and precision prevention) and survivorship. We investigate germline genetic variants for their role in breast cancer subtype development and prognosis. We strive to translate and implement our findings in models and tools to facilitate shared decision-making by patients and physicians with overarching goals to prevent breast cancer and recurrence of cancer, to reduce overtreatment, and to improve outcome. We also investigate and try to implement the best Ethical, Legal, and Societal (ESLI) practices related to the (secondary) use of human data and materials.

Identification of hereditary variants relevant for breast cancer prognostication

We are using genome wide genetic data of the Breast Cancer Association Consortium for over 95,000 women with breast cancer to study the impact of germline variants on breast cancer outcome. We adapted a network-based approach to handle this underpowered complex dataset to provide new insights into the potential function of germline variants in breast cancer prognosis[1]. We used this adapted network-based analysis to study ~7.3 million variants in 84,457 breast cancer patients in relation to breast cancer survival and confirmed the results on 12,381 independent patients. Aggregating the prognostic effects of genetic variants across multiple genes, we identified four gene modules associated with survival in estrogen receptor (ER)-negative and one in ER-positive disease. The modules showed biological enrichment for cancer-related processes such as G-alpha signaling, circadian clock, angiogenesis, and Rho-GTPases in apoptosis.

Understanding and predicting risk of contralateral breast cancer

Contralateral breast cancer (CBC), a new primary tumor in the opposite breast, is a rare event (10-year cumulative incidence 4%) with potential for poor outcome. We need improved risk prediction and understanding of the disease etiology to identify high and low risk to develop CBC and to optimize the decision making around contralateral preventive mastectomy or tailored follow up. Therefore, we developed and validated a CBC risk prediction model, PredictCBC, using multiple studies including patient, oncogenetics and tumor and treatment information[2]. Although in breast cancer patients with *BRCA1/2* germline mutations, PredictCBC is potentially useful for clinical decision making, CBC risk prediction in the general breast cancer population remains challenging.

To address this remaining challenge, we are expanding the model with additional informative factors, such as a polygenic risk score (PRS). We investigated the impact of a PRS of 313 common genetic variants on CBC risk. Based on of 56,068 breast cancer patients, we showed that the PRS is an independent factor associated with CBC risk; hazard ratio per standard deviation = 1.25 (95%CI = 1.18-1.33). Patients in the lowest and highest decile of the PRS distribution had 0.59 fold (95%CI=0.45-0.78) and 1.38 fold (95%CI=1.13-1.69) risk of CBC, respectively, compared with patients in the 40-60% group.

More transparency and facilitating research by improving consent procedures

We made a significant contribution towards improving consent procedures for the (secondary) use of residual tissue, images, and data for scientific research. Although most patients agree with the use of their materials and data for research, previous research of our group showed that patients felt that transparency around this topic should be improved. Moreover, changing societal norms increased the number of research studies for which the opt-out procedure does not suffice anymore. Since mid-2018, the Antoni van Leeuwenhoek hospital therefore informs all patients about this use, and asks their consent (www.avl.nl/toestemming). We conducted patient and employee interviews, and evaluated the decisions patients took, which led to changes in patient information brochures (www.avl.nl/media/3645/gebruik-van-uw-gegevens-en-materiaal-voor-wetenschappelijk-onderzo.pdf), employee information, and technical systems.

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Maarten Slagter MSc PhD student
Paula Voabil MSc PhD student
Marjolein de Bruijn Technical staff
Mireille Toebes Technical staff
Jos Urbanus Technical staff

Selected publications

Dijkgraaf FE et al. Tissue patrol by
resident memory CD8(+) T cells in
human skin. Nat Immunol 2019;20:756-
764

Li H et al. Dysfunctional CD8 T Cells
Form a Proliferative, Dynamically
Regulated Compartment within Human
Melanoma. Cell 2019;176:775-789 e718

Schumacher TN, Scheper W &
Kvistborg P. Cancer Neoantigens. Annu
Rev Immunol 2019;37:173-200

Dissecting and manipulating tumor-specific immunity

The aim of our research is simple 1). To design novel technologies to examine and modify immune responses 2). To subsequently use these technologies to unravel and manipulate immune recognition of human cancer. Some of the highlights of the past year have been the following:

Dissecting and enhancing T cell recognition in human cancer

There is now widespread evidence for the clinical value of T cell-based immunotherapies in a number of human cancers. However, our ability to carry out mechanistic studies on the immune infiltrates in human tumors has historically been limited. To overcome this limitation, we have over the past years invested heavily in technologies to dissect and perturb aspects of human intratumoral immune function, with the expectation that this will yield novel biomarkers of response and an improved understanding of the functional capacity of the intratumoral immune pool, both in steady state and upon therapy. The two main platforms that have been spawned by this effort have been a technology to recover and functionally test intratumoral TCR repertoires, and a technology to measure immunotherapy response of human tumor fragments upon ex vivo perturbation. The former platform has over the past years proven useful to demonstrate that human tumors can contain very large fractions of 'bystander T cells' that appear irrelevant to tumor control. With the goal to, for instance, understand whether tumor reactivity can be accurately predicted by T cell phenotype, this technology has subsequently been adapted to allow high-throughput screening of very large collections of TCRs, an effort now led by Wouter Scheper in the Haanen lab. With the aim to, for instance, understand whether clinical response of tumors to immune checkpoint blockade is predicted by immunological response, and whether distinct subtypes of immunological non-responding tumors can be distinguished, we have profiled the ex vivo tumor fragment response of a large set of human cancers to PD-1 blockade. Key findings of this work led by Daniela Thommen have been the establishment of a relationship between clinical and immunological response of cancers, and the definition of a set of baseline parameters that predict the capacity of PD-1 blockade to rekindle intratumoral immune function.

An aspect of intratumoral T cell function that has received little attention is the putative effect of T cell-secreted cytokines as modifiers of the tumor micro-environment (TME) beyond the target cells that are directly contacted. In collaboration with the van Rheenen group, we have documented that T cell-secreted IFNg can modify bystander tumor cell behavior over very large distances, and in future work it will be of interest to expand this concept of 'cytokine sensing' to other cytokines and chemokines within the TME.

Development of T cell memory

In addition to our work in which we aim to dissect immune function in cancer tissue, we remain interested in the dissection of fundamental aspects of the formation of antigen-specific T cell memory. One highlight in the past year has been the development and use of technology to measure the replicative age of memory T cells in vivo. Data obtained demonstrate that, contrary to some of the prevailing models, memory T cells are derived from a cell pool that has undergone extensive proliferation, but that the capacity to induce recall responses is biased towards a more nascent subset of memory T cells.

Structural biology

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Selected publications

Bhairosing-Kok D, Groothuizen FS, Fish A, Dharadhar S, Winterwerp HHK, Sixma TK. Sharp kinking of a coiled-coil in MutS allows DNA binding and release. Nucleic Acids Res. 2019;47(16):8888-8898

Horn V, Uckelmann M, Zhang H, Eerland J, Aarsman I, le Paige UB, Davidovich C, Sixma TK, van Ingen H. Structural basis of specific H2A K13/K15 ubiquitination by RNF168. Nat Commun. 2019;10(1):1751

Kim RQ, Geurink PP, Mulder MPC, Fish A, Ekkebus R, El Oualid F, van Dijk WJ, van Dalen D, Ovaa H, van Ingen H, Sixma TK. Kinetic analysis of multistep USP7 mechanism shows critical role for target protein in activity. Nat Commun. 2019;10(1):231

Development of cancer is generally due to errors that occur in cellular pathways. Understanding the mechanisms of underlying processes will help to determine where the errors occur and how they can be treated. We combine biochemical and biophysical methods, including X-ray crystallography and cryo-EM (electron microscopy) to study protein function. This leads to insights in molecular mechanisms that we validate in cells. In addition, our structures provide targets for drug design studies. In this work we focus primarily on proteins involved in mismatch repair and ubiquitin conjugation, particularly in stress response and DNA repair pathways.

DNA mismatch repair

DNA mismatch repair (MMR) plays a crucial role in maintaining genome stability. Defects in the mismatch repair proteins in humans predispose to Lynch syndrome (or hereditary non-polyposis colorectal cancer) and are associated with a variety of sporadic cancers.

DNA mismatch repair is initiated by recognition of a mismatch or an unpaired base by MutS (in Escherichia coli) or its MSH homologs (in humans). Initial recognition of the mismatch is followed by an ATP-dependent conformational change of MutS into a sliding clamp state that is recognized specifically by the next protein in the mismatch repair cascade, MutL. We studied how full length MutS is organized in the absence of DNA, and found that its coiled coil region can kink. Further analysis showed that this ability to kink is necessary for DNA binding, but does not affect MutL interaction (Bhairosing-Kok et al, 2019).

In collaboration with Meindert Lamers and Rafael Fernandez-Leiro we study different MMR states by cryo-EM. This generated unexpected insight into the conformational changes. Apparently, DNA positioning and the asymmetry of the MutS dimer are critical steps in the licensing of the mismatch repair.

Ubiquitin conjugation

Ubiquitin conjugation is an important signal in cellular pathways, changing the fate of a target protein, by degradation, relocalisation or complex formation. Deregulation of ubiquitin-dependent processes often leads to cancer. Ubiquitin signals are balanced by deubiquitinating enzymes (DUBs), which antagonize ubiquitination of specific protein substrates. Because ubiquitination pathways are critically important, we focus on mechanisms of ubiquitin conjugation to aid the process of drug design.

We are interested in the selectivity of the ubiquitination process, studying how three E3 ligases each modify a different set of lysines on H2A. In collaboration with Hugo van Ingen we used NMR to explain the selectivity of RNF168 for the N-terminal lysines K13 and K15 (Horn et al, 2019). We present a model for interaction that was validated with cross-link mass spectrometry and mutagenesis. We mutated a site on H2B that interfered with RNF168 and not with PRC1 modification. Intriguingly, this site is relatively frequently mutated in cancer.

DUB activity is often carefully controlled. We focus on the role of the target in this regulation. We found that intrinsic activation mechanisms and target interaction collaborate for full activity of the pleiotropic DUB USP7. Based on biophysical analysis on a series of different enzyme constructs we defined a model for USP7 activation on a peptide target-Ub conjugate. We validated our kinetic model by stopped-flow kinetic analysis and simultaneous fitting of all data, which elucidated kinetic constants for the different steps (Kim et al, 2019).

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**Selected
publications**

Heukelom J, Kantor ME, Mohamed ASR,
Elhalawani H, Kocak-Uzel E, Lin T,
Yang J, Aristophanous M, Rasch CR,
Fuller CD, Sonke JJ. Differences
between planned and delivered dose
for head and neck cancer, and their
consequences for normal tissue
complication probability and treatment
adaptation, Radiother Oncol. 2019

Lønning K, Putzky P, Sonke JJ,
Reneman L, Caan MWA, Welling M.
Recurrent inference machines for
reconstructing heterogeneous MRI
data, Med Image Anal. 2019;53:64-78

Van Diessen JNA, Kwint M, Sonke JJ,
Walraven I, Stam B, de Langen AJ,
Knegjens J, Belderbos JSA. Safety and
efficacy of reduced dose and margins
to involved lymph node metastases
in locally advanced NSCLC patients,
Radiother Oncol. 2019

Adaptive radiation therapy

Geometrical uncertainties such as setup error, posture change, organ motion, deformations and treatment response limit the precision and accuracy of radiation therapy (RT). Consequently, the actually delivered dose typically deviates from the planned dose. To minimize the deleterious effects of geometrical uncertainties, adaptive radiation therapy (ART) aims to characterize the patient's specific variation through an image feedback loop and adapt the patients' treatment plan accordingly. Adaptive radiation therapy research therefore includes 1) improving in room imaging, 2) patient variability characterization, 3) treatment plan modification and 4) outcome modeling.

AI based MRI reconstruction
Accelerating MRI acquisition and reconstruction time is important for efficient MR-guided radiotherapy systems. While sparse sampling accelerates the acquisition process, state of the art reconstruction using compressed sensing (CS) from sparsely sampled data is typically slow. We developed and characterized deep learning based reconstruction using recurrent Inference Machines (RIM) as a framework. We demonstrate the ability of RIM to generalize well by reconstructing different anatomies, different contrast and resolution, at different field strength, subjected to varying acceleration levels. We showed that RIMs outperform CS not only with respect to quality metrics, but also according to a rating given by an expert in a double blinded experiment.

Differences between planned and delivered dose for head and neck cancer
Anatomical changes induce differences between planned and delivered dose. Adaptive radiotherapy (ART) may reduce these differences but the optimal implementation is insufficiently clear. In this study the difference between planned and delivered dose in head-and-neck cancer (HNC) patients were quantified and the value of differences in normal tissue complication probabilities (ΔNTCP) as an objective selection strategy for ART was evaluated. To that end, daily doses were accumulated to estimate the delivered dose for 52 HNC patients. ΔNTCP was calculated for xerostomia, dysphagia, parotid gland dysfunction and tube feeding dependency at 6 months. ART was deemed necessary if ΔNTCP was >5%. The positive predictive value was 0.86 and 0.38 for ΔNTCP at fraction 10 and clinical judgement respectively. The negative predictive value was 0.93 and 0.9 respectively. To identify patients accurately for ART, ΔNTCP based on the differences between planned and delivered dose at fraction 10 were superior to clinical judgement.

Dose and margin reduction
Considerable safety margins and high doses to central structures in radiation treatment of locally advanced lung cancer patients is associated with substantial toxicity. In an observational cohort study we evaluated the combined impact of margin and dose reduction. 308 locally advanced lung cancer patients were included in an observational study. A reduction in safety-margins and dose from 70 Gy to 60 Gy to the involved lymph nodes in LA-NSCLC patients receiving (chemo) radiotherapy did not result in an increase in regional failures. Moreover, significantly lower acute toxicities and an improved OS were observed in the reduction-cohort.

Receptors for matrix adhesion
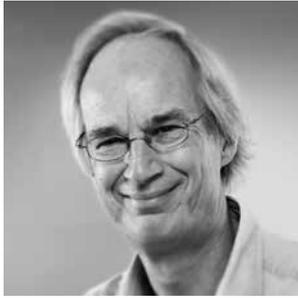
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Selected publications

Manso JA, Gómez-Hernández M, Carabias A, Alonso-García N, García-Rubio I, Kreft M, Sonnenberg A, and De Pereda JM. Integrin α6β4 recognition of a linear motif of Bullous Pemphigoid Antigen BP230 controls its recruitment to hemidesmosomes. Structure 2019;27(6):952-964.e6

Ramovs V, Secades P, Song J-Y, Thijssen B, Kreft M, and Sonnenberg A. Absence of integrin α3β1 promotes HER2-driven breast cancer *in vivo*. Breast Cancer Res. 2019;21(1):63

Te Molder L, Juksar J, Harkes R, Wang W, Kreft M, and Sonnenberg A. Tetraspanin CD151 and integrin α3β1 contribute to the stabilization of integrin α6β4 containing cell-matrix adhesions. J Cell Sci. 2019;132(19)

Our main aim is to understand the molecular mechanisms that regulate the interaction of cells with components of the extracellular matrix and to establish the role of cell adhesion receptors in health and disease. A major class of cell adhesion receptors are formed by members of the integrin family. We would like to understand how integrins interact with their ligands and assemble multiprotein complexes at the cell-substratum site in normal and pathological conditions, define the interplay among different integrins and understand the underlying molecular mechanisms.

Assembly of different integrin-based adhesion structures

Integrins are obligate heterodimers composed of α and β subunits. In mammals 18 α and 8 β subunits have been characterized. We are investigating three integrins that are clustered in different adhesion structures and associate with distinct cytoskeletal elements. These are laminin-binding α3β1 and α6β4, and αVβ5, a receptor for vitronectin. While the integrins α3β1 and αVβ5 are connected to the actin cytoskeleton in focal adhesions, α6β4 associates with the intermediate filament system in hemidesmosomes. Additionally, integrins α3β1 and αVβ5 can localize to adhesion structures that are seemingly not connected with the actin cytoskeleton; αVβ5 can be found in flat clathrin lattices and α3β1, when in complex with CD151, resides in tetraspanin webs. We study the dynamic regulation of these adhesion structures, how they mediate cellular mechanotransduction and define the molecular mechanisms underlying mechanosensing. We found a novel role of α6β4-containing hemidesmosomes in resisting actomyosin-generated cellular tension, which is dependent on mechanical coupling of focal adhesions to hemidesmosomes and inhibition of mechanosensitive signalling. Furthermore, through their ability to influence cellular tension, α6β4 also controls the localization of integrin αVβ5 in flat clathrin lattices.

Role of integrins in health and disease

Integrin α3β1, which mediates the adhesion of epithelial cells to laminin-332 and -511 in the basement membrane and plays a role in the maintenance of cell-cell contacts, has been implicated both as a promoter and suppressor of tumorigenesis and metastasis in different types of tumors. Among others, we observed such dual role in cancer in a model of chemically induced skin tumorigenesis (DMBA/TPA treatment) in mice, where α3β1 is required for the initiation and development of the disease. However, during the later stages of skin carcinogenesis, the loss of integrin α3β1 resulted in increased invasiveness and metastases formation. The correlation between α3β1 and breast cancer development is even less clear, as independent studies of human samples have reported all possible outcomes – positive, negative and lack of correlation between α3β1 and tumor formation and progression. This reflects the complex role of this integrin during the lifespan of cancer. Our current work focuses on understanding the often opposing function of α3β1 in cancer by studying its role in specific stages and types of tumors. Our primary focus is to determine the mechanisms behind α3β1-dependent onset of skin tumors induced by DMBA/TPA treatment. To this end we are investigating the role of α3β1 in the proliferation, differentiation and dynamics of different skin cell populations during homeostatic conditions and during skin tumorigenesis and are studying the related α3β1 dependent signalling pathways and interactors. We are also interested in the role of α3β1 in breast cancer, which we investigated using a mouse model overexpressing the HER2 oncogene. We showed that the downregulation of α3β1 in a HER2-driven mouse model and in HER2-overexpressing human mammary carcinoma cells promotes progression and invasiveness of tumors. This invasion suppressive role of α3β1 was not observed in triple-negative mammary carcinoma cells, once again illustrating the tumor type specific function of α3β1 in cancer.

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**Selected
publications**

Houlleberghs H, Dekker M, Lusseveld J,
Pieters W, van Ravesteyn T, Verhoef S,
Hofstra RMW, Te Riele H. Three-step
site-directed mutagenesis screen
identifies pathogenic MLH1 variants
associated with Lynch syndrome.
J Med Genet. 2019

Van de Vrugt HJ, Harmsen T,
Riepsaame J, Alexantya G, van Mil SE,
de Vries Y, Bin Ali R, Huijbers IJ,
Dorsman JC, Wolthuis RMF, Te Riele H.
Effective CRISPR/Cas9-mediated
correction of a Fanconi anemia defect
by error-prone end joining or templated
repair. Sci Rep. 2019;9:768

Van Ravesteyn TW. Replication-coupled
gene editing in mammalian cells.
Thesis VU University Amsterdam 2019

Genomic instability and carcinogenesis

How does genomic instability develop and impact the initiation and progression of cancer? We study two causes of genomic instability: *(1)* loss of DNA mismatch repair (MMR) and *(2)* defective G_1/S control causing unscheduled S-phase entry and replication stress. We develop novel gene modification tools to study genomic instability in cell culture and mouse models.

Unclassified variants of MMR genes

Carriers of a deleterious MMR gene variant (deletion, stop codon) are cancer prone (Lynch syndrome, LS) and need surveillance to reduce cancer risk. However, single codon variants are difficult to interpret complicating the counseling of carriers. We developed a functional test to study such 'Variants of uncertain significance' (VUS): "oligonucleotide-directed mutation screening" (ODMS) (Houlleberghs et al., PNAS 2016; PLoS Genet 2017; J Med Genet 2019). We first introduce the VUS into ±0.01% of mouse embryonic stem cells (ESCs), hemizygous for an MMR gene, by a replication-coupled process only using short (21-25 nt) single-stranded DNA oligonucleotides (ssODN) (Van Ravesteyn et al., PNAS 2016). When the VUS is deleterious, modified cells form colonies in 6-thioguanine (6TG)-containing medium. This protocol identified 64 deleterious VUS among 149 MMR gene variants.
Further optimization of 'oligo targeting' and application in human cells allows us to also address extra-exonic variants (promoter and intron sequences) and to implement ODMS in clinical practice in the context of a nationwide KWF-sponsored consortium, termed INVUSE (investigating variants of uncertain significance for use in clinical practice).

CRISPR/Cas9-assisted gene modification

ssODN-directed gene modification is stimulated by a CRISPR/Cas9-induced DNA break. Strikingly, DNA MMR impacts ssODN-directed gene modification *without* and *with* nuclease activity differently: while suppressing oligo targeting without nuclease, in the presence of a break MMR activity promoted break-distal nucleotide substitution instructed by the 3'-half of the ssODN. This finding implies templated break repair rather than oligonucleotide integration to underlie CRISPR/Cas9-mediated nucleotide substitution (Harmsen et al., NAR 2018). Additional strategies, including a 'co-CRISPR' protocol, improved recovery of single-nucleotide substitutions.

We corrected a disruptive mutation in the Fanconi anemia (FA) gene *Fancf* using CRISPR/Cas9 and a 120-nt ssODN template in mouse ESCs and fibroblasts. Although the frequency was low (3-6%) FA corrected ESCs rapidly overgrew non-corrected cells, which even allowed recovery of very rare templated gene editing events obtained by using Cas9D10A nickase. Notably, unlike wild-type Cas9, nickase activity resulted in mono-allelic gene editing without undesired mutagenesis (Van de Vrugt et al., Sci Rep 2019).

Replication stress

Unscheduled S-phase entry of G_1/S checkpoint defective, mitogen-starved cells causes replication stress, revealed by slow fork progression, low origin firing, DNA breakage and proliferative arrest (Van Harn et al., Genes Dev 2010). Strikingly, mitogen-independent proliferation was promoted by disruption of the Tp53/p21^{CIP1} axis, not only by attenuated DNA damage response, but rather by restored origin firing and reduced DNA breakage (Benedict et al., Elife 2018). However, replication speed remained low, and genetic screens divulged pathways that were critical for proliferation in the absence but not the presence of mitogens. An example is the requirement for WAPL-dependent removal of cohesion rings to allow rapid RAD51-dependent repair of broken replication forks (Benedict et al., Developmental Cell, 2020, in press). Furthermore, we found cohesion loss in many cancer cell lines, suggesting that active cohesion removal from newly synthesized sister chromatids is necessary for cancer cells to handle oncogene-induced DNA replication stress.

Cancer survivorship

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Selected
publications

**Van Eenbergen M, Vromans RD, Boll D,
Kil PJM, Vos CM, Krahmer EJ, Mols F,
van de Poll-Franse LV.** Changes in
internet use and wishes of cancer
survivors: A comparison between 2005
and 2017. Cancer. 2019

**Van Kleef JJ, Ter Veer E, van den
Boorn HG, Schokker S, Ngai LL, Prins
MJ, Mohammad NH, van de Poll-Franse
LV, Zwinderman AH, van Oijen MGH,
Sprangers MAG, van Laarhoven HWM.**
Quality of life during palliative systemic
therapy for oesophagogastric cancer:
systematic review and meta-analysis.
J Natl Cancer Inst. 2019

**Van der Hout A, Van Uden-Kraan CF,
Holtmaat K, Jansen F, Lissenberg-
Witte B, Nieuwenhuijzen G, Hardillo J,
Baatenburg de Jong R, Tiren-Verbeet N,
Sommeijer D, de Heer K, Schaar C,
Sedee RJ, Bosscha K, van den Brekel M,
Petersen J, Westerman M, Honings J,
Takes R, Houtenbos I, van den Broek W,
de Bree R, Jansen P, Eerenstein S,
Leemans R, Zijlstra R, Cuijpers P,
van de Poll-Franse LV, Verdonck-
de Leeuw I.** Efficacy of an eHealth
application 'Oncokompas' that supports
cancer survivors to self-manage their
symptoms and health-related quality of
life: results of a randomized controlled
trial. Lancet Oncology. 2019

Our research objective is to understand the impact of cancer, treatment and supportive care
strategies on physical and psychosocial functioning of cancer survivors.

Patient Reported Outcomes Following Initial treatment and
Long-term Evaluation of Survivorship (PROFILES)

In 2009 we initiated the PROFILES registry for the study of the physical and psychosocial impact
of cancer and its treatment. Today we have evaluated patient reported outcomes (PRO's) of
more than 25.000 cancer survivors in 80 hospitals in the Netherlands, resulting in 148 scientific
publications. In 2016 we obtained a large investment grant from NWO to upgrade the PROFILES
registry to facilitate studies of the *mechanisms* of declining health after cancer. We are currently
collecting novel data that includes biological markers, biosensor data, online food diaries and body
composition.

International development of quality of life questionnaires

We have developed disease-specific EORTC QoL questionnaires for patients with (non) Hodgkin
lymphoma (N-HL) or chronic lymphocytic leukaemia (CLL). Furthermore, in the past years we have
been developing an EORTC cancer survivorship questionnaire that includes physical, emotional and
socio-economic functioning. We are currently conducting international validation studies for both
(sets of) questionnaires.

Effectiveness of patient-reported outcome feedback and a web-based
intervention on lymphoma patients' self-management skills

The objective of the multicentre Lymphoma InterVEntion (LIVE) RCT is to examine whether feedback
to patients on their PROs and access to the web-based self-management intervention *Living with
lymphoma* will increase self-management skills and satisfaction with information and reduce
psychological distress.
Patients with (non) Hodgkin lymphoma are invited via their haemato-oncologist 6 to 15 months after
diagnosis. The intervention is based on cognitive-behavioural therapy components and includes
information, assignments, assessments, and videos. Patient recruitment has been completed,
analyses are currently ongoing.

Efficacy of the eHealth application 'Oncokompas' to support cancer survivors
to self-manage their symptoms and health-related quality of life

Oncokompas is a web-based eHealth application that supports survivors in self-management by
1) monitoring health-related quality of life (HRQOL) and (cancer-generic and tumour-specific)
symptoms; and 2) obtaining tailored feedback with a personalized overview of supportive care
options. In this RCT, survivors diagnosed with head and neck, colorectal, and breast cancer, and
(non-)Hodgkin lymphoma were randomised to the intervention group (access to Oncokompas:
N=320) or wait-list control group (N=305). After a median follow-up of 6 months, Oncokompas did
not significantly improve knowledge, skills and confidence for self-management (possibly because
the study population was already performing relatively well), but seems effective to reduce
symptom burden and improve HRQOL.

GERSOC and PROSPEC trials

In 2019 we furthermore continued data collection for the pragmatic cluster randomized GERSOC
(GERiatric Screening in the treatment of elderly patients with Ovarian Carcinoma) trial and the
individually randomized PROSPEC (PROstate cancer follow-up care in Secondary and Primary hEalth
Care) trial.

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Personalized Oncology in sarcoma and adolescent and young adult (AYA) cancer patients

The personalized oncology group is currently concentrating on two principal research lines: (1) the short-, long-term and late consequences of cancer at adolescent and young adult age; (2) diagnosis, treatment, outcome and health-related quality of life issues of people with sarcoma.

Adolescents and Young Adults

Adolescent and Young Adult (AYA) cancer patients, diagnosed with cancer between the age of 18-39 years old, suffer from delay in diagnosis, lack of centralization of care, age-adjusted expertise and follow-up care. This group presents with a unique spectrum of cancers, distinctive tumor biology, cancer risk factors, developmental challenges and treatment regimens that are different compared to children. There will be a burden of medical and psychosocial problems, that could result in compromised health-related quality of life and reduced life expectancy. Findings derived from childhood cancer survivors cannot be extrapolated to AYA. It is imperative for advances in the field of AYA oncology to pool data sources (patient-reported outcomes, clinical, genetic and biological data) across institutions and create large cohorts that include the full range of AYA ages and diagnoses to be able to address the many pressing questions that remain unanswered in this vulnerable population. We are currently running the SURVAYA study to examine the long-term consequences of cancer at AYA age among people who were diagnosed 5-20 years ago. Additionally, we are working on a unique nationwide infrastructure (COMPRAYA) for research into the prevalence, predictive and prognostic markers (risk factors) and underlying mechanisms of (age-specific) medical and psychosocial outcomes, and to facilitate the development and testing of (early) intervention strategies to improve these outcomes for patients (at risk). We will establish a prospective observational cohort of 1-year AYA cancer survivors followed prospectively for 20+ years or until death. Within COMPRAYA we will pay special attention to AYA cancer patients living with life-limiting cancer: how does this diagnosis impacts normal (daily) life and what are the challenges they face within the health care system?

Sarcoma
Health-related quality Of Life In patients with advanced Soft TIssue sarcomas treated with Chemotherapy: the HOLISTIC study

Chemotherapy is the mainstay of treatment for patients with metastatic soft tissue sarcomas (STS). Treatment intent is usually palliative, aiming to improve symptoms, stabilize or reduce tumour-burden and extend life. Clinical trials for advanced STS have traditionally used radiological response, time to progression and survival as measures of treatment efficacy. Treatment decisions are often challenging due to modest response rates and potential adverse side-effects. Health-related quality of life (HRQoL) is at least equally- or more important than survival for many patients with advanced cancer. Systematically collecting HRQoL data during chemotherapy can provide greater insight into treatment efficacy from the patient perspective. The primary aims of this study are to evaluate HRQoL in patients with advanced STS treated with chemotherapy over time, explore the decision-making process and patient reflections post-treatment.

Quality of life and Experiences of Sarcoma Trajectories: the QUEST study

The prognosis of patients with rare cancers in general and sarcomas in particular suffers from delay in diagnosis. Routes to diagnosis have neither been studied in detail in larger numbers before, nor in a direct comparison between two countries with different health systems. Comprehensive assessment of diagnostic delays and its determinants, including demographic, clinical, psychosocial and health care system factors, is necessary to improve referral pathways and come to best practice and patient reported outcomes for sarcoma patients. This study aims to quantify diagnostic delay (including patient, general practitioner and system delay) and evaluates routes to diagnosis and referral to sarcoma expert centers in the Netherlands and England; to comprehensively evaluate risk factors of diagnostic delay; determine the association between diagnostic delay and outcomes (HRQoL, quality adjusted life years, patient satisfaction, TNM classification, time to local/distant relapse and overall survival); and to assess differences between both countries.

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Incorporating the patient voice in sarcoma research: how can we assess health-related quality of life in this heterogeneous group of patients

There is limited high-quality HRQoL data in sarcoma. Previous studies have predominantly used generic HRQoL instruments, which cover some relevant issues but do not capture all the unique experiences of patients with sarcoma, and thus lack content validity. A sarcoma-specific questionnaire or validated items should be able to detect, with more sensitivity, side-effects, symptoms and problems with function that are particularly relevant to patients with different presentations and subtypes of sarcomas. Given the heterogeneity of the disease in terms of subtype, location, age and treatment, the development of a single sarcoma questionnaire is impossible. Therefore, we have started a study to develop standards of HRQoL measurements in the broad spectrum of patients with sarcoma. This is a collaborative project between the EORTC Quality of Life Group (QLG) and the EORTC Soft Tissue and Bone Sarcoma Group (STBSG).

Sarcoma Priority Setting Partnership Study

Research in sarcoma has historically been the domain of scientists and clinicians attempting to understand the disease in an effort to develop effective treatments. There is growing recognition of the importance of integrating patient perspectives (e.g., preferences, expectations, and expanded definitions of what constitutes "successful" outcomes) into clinical research. This evolution is reflected in the growth of patient-centered organizations and patient advocacy groups that seek to meaningfully integrate patients into the process of prioritizing research needs and creating alliances wherein patients and researchers can partner together to accomplish research goals. The group leaders are leading a project together with the patient advocacy group SPAEN aiming to identify the unanswered questions about sarcoma from patient, carer and clinical perspectives and then prioritise those that patients, carers and clinicians agree are the most important for research to address.

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publications

Dinis Fernandes C, Simões R, Ghobadi
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Imaging technology in radiation oncology

Dose painting for prostate cancer

The FLAME trial, a multi-center phase III randomized trial of dose escalation in prostate cancer using external-beam radiotherapy, will reach its primary endpoint of 5y biochemical failure free survival in 2020. In this study, a focal boost to the visible tumor inside the prostate to a dose of 95 Gy was given and compared to the standard treatment of 77 Gy to the gland. In total 571 patients have been randomized. To allow a pattern-of-failure analysis, we image patients with recurrent prostate cancer (PCa) with PET and/or multi-parametric (mp-)MRI to delineate local recurrences.
We trained a tumor probability model for recurrent cancer based on mp-MRI on a cohort of patients with recurrent PCa. The model was tested on another cohort of patients who received salvage prostatectomy, allowing for whole-mount section histological validation of the model predictions. We found an area under the curve of 0.77, and an accuracy of automatically derived tumor delineations that was comparable to delinations by trained radiologists.

Quantitative MRI for radiotherapy

While many imaging biomarker studies have been conducted to establish their prognostic value after radiotherapy, the vast majority of studies is small and the methodology between studies varies widely. On the Unity MR-linac system patients receive an MRI as part of each treatment fraction. Acquisition of quantitative MRI sequences is feasible without prolonging the treatment time. This makes the Unity system uniquely suitable for MRI biomarker studies for response assessment. Within the MR-linac consortium, we established the feasibility of multi-parametric MRI on the Unity system, applying relaxometry, diffusion-weighted MRI and dynamic contrast-enhanced MRI during a radiation treatment session. The repeatability of these quantitative techniques was measured in a study with 4 centers and showed results consistent with diagnostic MRI scanners.
Within the MR-linac consortium we recently formed a collaborative working group with the aim of initiating MRI biomarker studies using consistent methods for quantitative MRI.

MRI-guided radiotherapy

The department of Radiation Oncology has now treated about 100 patients on the MR-linac. Studies to improve image quality are ongoing. The Umbrella-II trial has started, allowing us to investigate the feasibility of multiple techniques and software for MR-guided adaptive radiation therapy on the Elekta Unity MR-linac. We validated that the system for electronic portal imaging dosimetry is reliable for dose verification in patients.
The introduction of systems for MRI-guided radiotherapy has resulted in an increased interest in the use of MRI within all phases of radiotherapy. With a team of authors form various institutes, we published a book on MRI in radiotherapy, describing its use for planning, delivery and response assessment.

Image-guided radiotherapy of rectal cancer

To improve the results of radiotherapy for rectal cancer, we investigated various image-guidance strategies using brachytherapy and external-beam radiotherapy. We demonstrated that fiducial markers, implanted around the tumor, can serve as a surrogate for the tumor position despite small displacements of the markers relative to the tumor volume. In particular in patients with tumors located in the mid and upper rectum, this may result in a reduction of PTV margins when boosting the tumor.

Personalized treatment of urological cancers

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Selected publications

Gomez de Liano Lista A, van Dijk N, de Velasco Oria de Rueda G, Necchi A, Lavaud P, Morales-Barrera R, Alonso Gordoa T, Maroto P, Ravaud A, Duran I, Szabados B, Castellano D, Giannatempo P, Loriot Y, Carles J, Anguera Palacios G, Lefort F, Raggi D, Gross Goupil M, Powles T, Van der Heijden MS. Clinical outcome after progressing to frontline and second-line Anti-PD-1/PD-L1 in advanced urothelial cancer. Eur Urol. 2019

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Individualized therapy in bladder cancer: molecular targets and biomarkers

Bladder cancer is a common cancer, with a worldwide prevalence of 2.7 million patients. Although bladder cancer is often superficial at diagnosis, 30-40% of patients present with more advanced disease or progress to more aggressive disease. For patients with locally advanced or metastatic bladder cancer, platinum-based chemotherapy is the mainstay of treatment. Most patients will eventually die of their disease. In recent years, immunotherapy has shown to be active in bladder cancer. Impressive responses are seen, however only a minority of patients benefits from these treatments and it is unclear which patients respond. We aim to advance the development of a personalized approach to bladder cancer by exploring novel molecular targets, mechanisms of resistance and biomarkers that can guide systemic therapy. Our key focus is on the neoadjuvant setting, as we believe the highest gains in cure rates can be achieved here. Through the large number of bladder cancer patients, excellent multidisciplinary collaboration and broad availability of clinical trials with novel therapeutics at the NKI-AVL, discoveries can rapidly be translated into clinical trials.

Neoadjuvant treatment with combination Immunotherapy

In 2019, we completed the first cohort of the NABUCCO study. In this study, we investigate the feasibility of pre-operative ipilimumab/nivolumab in locoregionally advanced bladder cancer. 24 patients (14 cT3-4N0; 10 cN+) were enrolled, of whom 23 (96%) had resection <12 weeks from 1st cycle, meeting the primary endpoint. One patient, responding radiologically, had a delay in surgery because of immunotherapy-related (irAE) hemolysis. Grade 3/4 irAEs occurred in 54% of pts; 42% when excluding clinically insignificant lab deviations. 11/24 patients (46%) achieved a pCR. 3 additional pts (12%) had a small focus of noninvasive cancer at resection (2 CIS, 1 pTa), resulting in an overall rate of 58% (13/22) without invasive cancer cells at resection. In a subset of the remaining patients, clear signs of response were noted. Response was associated with PD-L1 positivity and massive infiltration of CD8+ T-cells in the tumor bed. Translational analysis of this unique set of 24 paired pre/post tumor samples is ongoing and a follow-up cohort of 30 patients, testing adjusted dosing schedules, has been initiated.

Genetic mechanisms of resistance to androgen receptor inhibitors

Novel androgen receptor (AR) inhibitors have clinical benefit in castration-resistant prostate cancer patients. Still, cancer cells eventually develop resistance to these therapies. We are investigating genetic resistance to these drugs through several means.

In a genome-wide CRISPR-Cas9 screen using LNCaP prostate cancer cells, loss of the co-repressor *TLE3* conferred resistance to AR antagonists apalutamide and enzalutamide. Genes differentially expressed upon *TLE3* loss shared AR as the top transcriptional regulator, and *TLE3* loss rescued the expression of a subset of androgen-responsive genes upon enzalutamide treatment. Of this subset, GR expression was strongly upregulated upon AR inhibition in a *TLE3*-negative background. In another component of this project, clinical samples are being collected through the CPCT network and sequenced using WGS. In addition, plasma is collected to analyze development of genetic resistance throughout treatment.

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Selected publications

Franzen N, van Harten WH, Retèl VP, Loskill P, van den Eijnden-van Raaij J, IJzerman M. Impact of organ-on-a-chip technology on pharmaceutical R&D costs. Drug Discov Today. 2019;24(9):1720-1724

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Early stage technology assessment, operations research and cancer rehabilitation

Early Stage Technology Assessment

As healthcare costs are continuously increasing sustainability of future oncology services will inevitably become an issue. Gradually we can expect Health Technology Assessment (HTA) not only to be involved in policy and coverage decisions, but also in earlier stages in the translational research process.

From 2003 through 2010, an HTA study was conducted on the introduction of the 70-gene micro array test as a prognostic tool in the treatment of node negative breast cancer (the RASTER-study) and as a side study of the European randomized controlled trial (the MINDACT-study). We continued the series of Cost Effectiveness Analyses of this test with the results of the MINDACT trial. In 2015 an early stage technology assessment of TIL-adoptive cell technology in advanced melanoma started in a Coverage with Evidence Development project, as well as in 2017 for gastric HIPEC and on high-dose chemotherapy for triple negative breast cancer, and recently HIPEC for Ovarian cancer was accepted as well. The CED programs are coordinated by Valesca Retèl, and Joost Verbeek started a PhD project on the HTA in the ongoing CED programs. Valesca Retèl works as Senior Scientist 50% employed by NKI and 50% for the Health Technology and Services Research group at the University of Twente. She is primary investigator of the TANGO project in the Personalized Medicine program of ZonMw (HTA coordinator: Wim van Harten) on a specific HTA model regarding implementation of Whole Genome Sequencing. As part of Tango the work package on ethics and legal aspects, produced a comment in Nature Reviews Genetics.

Ann-Jean Beck works on HTA of various interventions in Head & Neck survivorship care. Melanie Lindenberg is evaluating early stage translational technologies in oncology including image guided interventions and the TIL study (ATMP). In the CERA-Pro study we compare historic cohorts of laparoscopic versus Robot Assisted Prostatectomies on cost-effectiveness in 2020. Danalyn Bing is active in the field of HTA in de-escalating treatment for early stage breast cancer and DCIS in the PRECISION consortium. Nora Franzen is working on research and modelling of alternatives for the present system of patents and pricing in expensive cancer drugs. In 2019 it was decided to host the European Fair Pricing Network in our group at the NKI.

Improving Oncology Services

Benchmarking is a possibly powerful tool to inform management on improvement options and patients on the quality of services. In 2013 the EU-subsidized project BENCH-CAN started to develop and pilot a European benchmarking system on Comprehensive Cancer Care. Anke Wind started a follow-up project on pathway benchmarking, including value-based health care principles. Bruno Vieira is conducting a PhD project on improving radiotherapy logistics by use of Operations Research methods. After developing a number of algorithms to improve various aspects of RT logistics, an implementation project was started which is innovative as most OR projects have shown mainly theoretical improvements so far.

Rehabilitation, Physical Activity and Cancer

As follow-up to the major ACARE2, Alpe d'Huzes funded KWF project Laura Kooij performs research into e-health interventions and survivorship care, such as IT-supported stepped care and video consultation.

A PhD student works at IQ-Healthcare in Nijmegen on the structured implementation of physical activity interventions for cancer survivors in ten Dutch hospitals and is expected to finalize her PhD in 2020.

The PABLO trial involves a web-based and blended intervention on physical activity in breast and prostate cancer survivors. Wim Groen is PI and PhD student Hester van de Wiel focuses on aspects that influence effectiveness from both physical as psychological perspective. Willeke Naaktgeboren performs a PhD project (KWF-funded) on cardiovascular status and late effects after physical activity interventions during chemotherapy in the PACT-PACES-HEART study.

Cancer epidemiology

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The cancer epidemiology group is currently concentrating on two principal research lines: (1) the long-term health consequences of cancer treatment, particularly in terms of the risk of developing second malignancies or cardiovascular disease; and (2) the etiology of hormone related cancers, with a focus on breast and ovarian cancer. Special interest is in cancer etiology in BRCA1/2 families and late effects of ovarian stimulation for in vitro fertilization.

Late effects of cancer treatment

Now that curative treatment is available for a substantial group of cancer patients, it is increasingly important to evaluate how the occurrence of late complications of treatment affects their long-term survival. We aim to evaluate the risk of second malignant neoplasms (SMNs) and cardiovascular disease (CVD) after radiotherapy (RT), chemotherapy (CT) and immunotherapy for Hodgkin lymphoma (HL, n=8,500), non-Hodgkin lymphoma (n=3,200), testicular cancer (n=7,100) and breast cancer (n~23,000) over a period of up to 40 years after primary treatment.

In 2019 we reported on two studies assessing the risk of CVD after treatment for breast cancer and one study assessing subclinical cardiac dysfunction after anthracycline-chemotherapy for breast cancer.

In the first study we assessed the relationship between radiation dose to the heart and risk of myocardial infarction (MI). We included 183 patients diagnosed with MI after breast cancer and 183 matched controls with breast cancer, but no CVD. For all patients our Oxford colleagues (Prof. Darby's group) retrospectively estimated mean heart dose (MHD). We found that the MI rate increased linearly with increasing MHD, with an excess rate ratio (ERR) per Gray of 6.4%. Patients who received >20 Gy MHD had a 3.4-times higher MI rate than non-irradiated patients. The ERRs were higher for younger women. As radiation oncologists nowadays strive for a much lower MHD, we expect lower MI risk among current survivors. The second study assessed the dose-response relationships between anthracyclines, trastuzumab, radiation dose and risk of heart failure (HF). HF was defined as either dilated cardiomyopathy or HF with reduced ejection fraction (LVEF<50%). 102 HF cases and 306 controls were included. HF risk was most strongly increased among patients treated with anthracyclines and trastuzumab compared to no chemotherapy (Relative risk=35). HF risk increased linearly with increasing anthracycline dose (ERR=1.5% per mg/m^2). MHD was only associated with HF risk among anthracycline-treated women. Compared to women with MHD <10 Gy and no anthracyclines, women with a MHD <10 Gy and anthracyclines had a RR of 6.3, while women with MHD >10 Gy and anthracyclines had 12.4-fold increased risk.

These results emphasize the need to evaluate preventative strategies. The prevalence of subclinical cardiotoxicity in young breast cancer survivors treated with anthracyclines is currently unknown. Subclinical measures of left ventricular dysfunction are needed to early identify patients at increased risk of symptomatic cardiac disease. Echocardiography-based cardiac deformation imaging may be a promising technique to identify survivors at high risk of cardiac disease.

In the HARBOR study, we therefore assessed subclinical cardiotoxicity among breast cancer patients diagnosed at ages 40-50 years, who were 5-12 years after initial treatment. At clinic visit, transthoracic tissue Doppler echocardiography was performed and global longitudinal strain (GLS) was measured.

In total, 569 women were included, of whom 313 received anthracycline-chemotherapy and 256 were not treated with anthracyclines. Median ages at breast cancer diagnosis and at cardiac assessment were 46.7 and 55.5 years, respectively. Anthracycline-treated patients more often had low LVEF (10% versus 4%), impaired GLS (34% versus 27%) and elevated NT-proBNP (23% versus 8%) compared to patients not treated with anthracyclines. 54% of anthracycline-treated women had at least one indicator of subclinical cardiotoxicity. Both GLS and LVEF worsened in a linear fashion with increasing cumulative anthracycline dose; GLS was worse for patients who had received left breast irradiation. Patients who received 241-300mg/m^2 anthracycline had the highest probability to have a NT-proBNP>125ng/L compared to patients without anthracyclines (RR 3.3). The study shows that a substantial proportion of young survivors treated with anthracyclines has signs of subclinical cardiotoxicity. GLS may be a promising measurement to identify survivors at high risk of

V

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Selected publications

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cardiac disease but we plan to perform longitudinal assessment to determine its precise prognostic value.

Etiology of hormone-related cancers

In our nationwide cohort study among families tested for a BRCA1/2 mutation (HEBON study; 48,757 relatives, including 41,707 women (6,293 BRCA1/2 mutation carriers) and 6,508 men (including 1,821 BRCA1/2 mutation carriers), we are studying whether 1) hormonal/life-style factors modify cancer risk in BRCA1/2 families, and 2) common genetic alterations are associated with the risk of breast cancer among BRCA1/2 carriers.

To improve breast cancer risk prediction for BRCA1 and BRCA2 mutation carriers, we investigated hormonal/lifestyle risk factors of breast cancer as established in the general population. We coordinated an international cohort consortium, including HEBON (5,983 BRCA1/2 mutation carriers), to examine reproductive risk factors, alcohol and smoking using data of 5,707 BRCA1 mutation carriers and 3,525 BRCA2 mutation carriers in Cox proportional hazards models. For BRCA1 mutation carriers, there was no overall association with parity when compared with nulliparity. However, relative to being nulliparous, uniparous BRCA1 mutation carriers were at a 69% increased BC risk in the prospective cohort. Relative to being uniparous, an increasing number of full-term pregnancies was associated with a decreasing breast cancer risk. An increasing duration of breastfeeding was associated with decreasing risk of breast cancer as well. For BRCA2 mutation carriers, being parous was associated with a 33% increase in BC risk and there was no apparent decrease in risk associated with multiparity except for the 28% decreased risk of women with 4 or more full term pregnancies. These findings suggest differential associations with parity between BRCA1 and BRCA2 mutation carriers, with higher risk for uniparous BRCA1 carriers and parous BRCA2 carriers.

When compared to parous women who never smoked, smoking for more than five years before a first full-term pregnancy (FFTP) was associated with a 19%-36% increased risk for BRCA1 mutation carriers and a 25%-30% increased risk for BRCA2 mutation carriers. Similar associations between early smoking and breast cancer have been found in the general population. For both carrier groups, alcohol consumption was not associated with BC risk, although the weakly increased risk as known for the general population could not be excluded.

In HEBON we investigated the breast cancer-specific mortality reduction for BRCA1/2 mutation carriers undergoing a bilateral risk-reducing mastectomy (BRRM) or breast surveillance. During a mean follow-up of 10 years, 722 out of 1712 BRCA1 (42%) and 406 out of 1145 BRCA2 (35%) mutation carriers underwent BRRM. For BRCA1 mutation carriers, we observed 20 breast cancer deaths in the surveillance group, and 1 breast cancer death after BRRM (HR 0.06). Breast cancer-specific survival at age 65 was 93% for surveillance and 99.7% for BRRM. For BRCA2 mutation carriers more follow-up is needed.

The aim of the Nightingale Study, a cohort of 59,947 nurses, is to assess the association between shift work and risk of breast cancer. The first prospective analyses are ongoing using 626 incident cases of breast cancer identified through a recent linkage with the Netherlands Cancer Registry.

The aim of the nationwide OMEGA study is to assess risk of hormone-related cancers after fertility treatment in a nationwide cohort of 30,800 women treated with in-vitro fertilization (IVF) 1983-2001 and 10,000 women treated with subfertility treatments other than IVF. Analyses on the effect of IVF treatment on risk of ovarian cancer are ongoing, as are analyses on childhood cancer in an expanded cohort of 30,000 children conceived by intracytoplasmic sperm injection or IVF compared with 13,761 children that were naturally conceived.
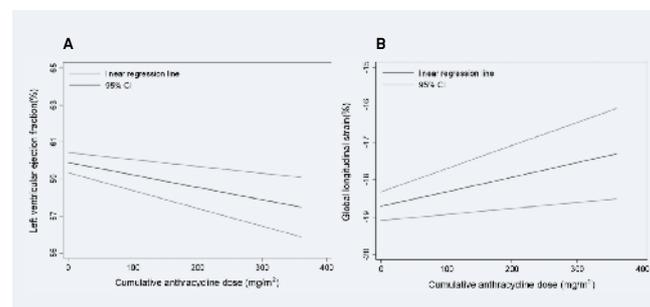
Associations between cumulative anthracycline dose and left ventricular ejection fraction (LVEF) (A) and global longitudinal strain (GLS) (B). Bold lines depict linear associations and regular lines depict 95% confidence intervals (CI). Associations can be described by LVEF = 59.9–0.40 per cycle of 60 mg/m2 anthracycline dose; GLS = -18.7 + 0.23 per cycle of 60 mg/m2 anthracycline dose; NT-proBNP = 72 + 7.2 per cycle of 60 mg/m2 anthracycline dose.

Chromatin Dynamics

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**Selected
publications**

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TM, Babala N, de Vries E, Bovens A,
Wessels L, van Leeuwen F, Borst J.
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Palit S, Klarenbeek S, Kwesi-Malie-
paard EM, Molenaar TM, Hoekman L,
Schmidlin TT, Altelaar M, van Welsem
T, Dannenberg J-H, Jacobs H, van
Leeuwen F. Conserved crosstalk
between histone deacetylation
and H3K79 methylation generates
DOT1L-dose dependency in HDAC1-
deficient thymic lymphoma. EMBO J.
2019;38(14):e101564

Switching genes on or off and keeping them in that state involves packaging of the genome by wrapping it around histone proteins. Histones carry different chemical modifications that affect the packaging of DNA by epigenetic mechanisms. The Van Leeuwen lab studies mechanisms and principles of epigenetic regulation using innovative proteomic, genetic, and (epi)genomics approaches. Our general strategy is to develop new tools and technologies, most recently two DNA-barcoding approaches to discover epigenetic regulators and to decode proteomes of specific genomic loci (figure 1). These innovations enable us to explore new areas of chromatin biology and to dissect specific chromatin processes in high molecular detail. We take advantage of yeast as a powerful model system. In parallel we are developing tools in mice and cultured human cells using CRISPR-Cas9 to translate our findings to mammals.

Function and regulation of histone methylation

Errors in chemical modifications of histones can lead to changes in gene expression and cancer. We previously discovered the histone methyltransferase Dot1, which methylates lysine 79 of histone H3 (H3K79). This modification influences gene regulation and oncogenic transformation in mammals. A major goal of our research is to understand the regulation of H3K79 methylation and its function in gene control. We recently discovered a conserved regulatory mechanism of Dot1 in yeast and DOT1L in mouse T cells with relevance for lymphomagenesis (figure 2). We are currently studying DOT1L in lymphoma and in epigenetic control of normal T- and B-lymphocyte fate and differentiation.

Decoding chromatin proteomes by DNA sequencing

Gene regulation involves interactions of specific genomic loci with many different proteins. How these interactions are orchestrated at any given location over time is largely unknown because systematically measuring protein-DNA interactions at a specific locus in the genome is challenging. To address this problem, we developed DNA barcode-based Epigenetics technologies in yeast. Epi-Decoder, a method orthogonal to proteomics, enables decoding of local chromatin proteomes and has identified hundreds of chromatin-interacting proteins at actively transcribed barcoded loci (figure 1). Epi-ID, which is aimed at identifying regulators of known chromatin marks or chromatin-binding proteins, recently led to the discovery that H3K79 methylation is regulated by a histone deacetylase in yeast and mice (figure 2).

Together, the aim of our studies is to provide a deep molecular understanding of the dynamics and inheritance of protein-based epigenetic information in dividing cells and the impact of chromatin-based information on gene regulation in normal development and disease.
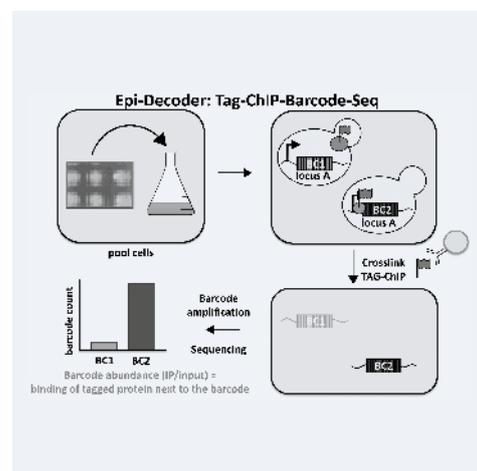
Figure 1
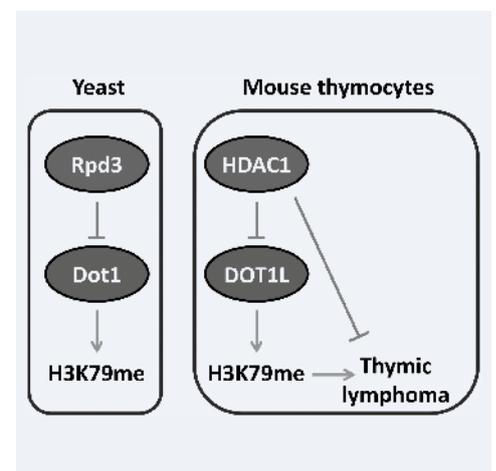
Figure 2

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Publications

**Gisler S, Gonçalves JP, Akhtar W, de
Jong J, Pindyurin AV, Wessels LFA, van
Lohuizen M.** Multiplexed Cas9 targeting
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Józ′wiak K, Lips E, Severson T, van de
Ven M, Brambillasca C, Bouwman P,
van Tellingen O, Bernards R, Wesseling
J, Eichler C, Thangarajah F, Malter W,
Pandey GK, Ozretić L, Caldas C, van
Lohuizen M, Hauptmann M, Rhiem K,
Hahnen E, Reinhardt HC, Büttner R,
Mallmann P, Schömig-Markiefka B,
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2019;4351-4362

Role of polycomb-group genes in transcriptional repression, stem cell fate and tumorigenesis

We study transcriptional repression by Polycomb-group (PcG) protein complexes, and the effects of deregulation of PcG genes on development, cell cycle control, cancer and stem cell maintenance. For this a range of conditional polycomb transgenic and knockout mouse models are used in combination with specific cancer-predisposing mutations mimicking closely cognate human cancers. Recent focus is on using CISPR screens in selected polycomb-dependent tumor models to uncover new synthetic lethal interactions and vulnerabilities.

Context-dependent roles of PRC2 in tumorigenesis

We recently demonstrated an oncogenic role for *Ezh2* (histone methyltransferase and catalytic subunit of Polycomb repressive complex 2 (PRC2) in *Kras* driven non-small cell lung cancer. However, prolonged inactivation of PRC2 in aggressive *Kras;P53* mutant NSCLC uncovered a profound tumor suppressive function for PRC2 loss resulting in tumor cell identity change, driven by inflammatory responses and EMT. This resulted in new vulnerabilities that can be exploited using combined inhibition of PRC2 and inflammatory responses. Ezh2 is overexpressed in glioblastoma multiforme (GBM) suggesting a possible oncogenic role. In a mouse model for GBM we demonstrated using inducible Ezh2 shRNAs and specific Ezh2 inhibitors that short-term intermitted inhibition indeed slowed tumor growth and prolonged survival. However, prolonged Ezh2 inhibition caused a robust switch in cell fate, resulting in enhanced proliferation and invasion, enhanced DNA repair and activation of a stem cell pluripotency network, resulting in therapy-resistant aggressive GBM. This illustrates that dosing of Ezh2 inhibition is critical, and Ezh2 inhibitors need to be used with caution. We are using these GBM models with CRISPR screens to find more effective combination therapies.

Modeling and investigating BAP1-deficient malignant mesothelioma

Besides PRC2, also a variety of PRC1 complexes contribute to dynamic polycomb repression. These PRC1 complexes differ in subunit constitution but all harbor a critical E3 ubiquitin ligase monoubiquitylates H2A at K119. This mark can be removed by the de-ubiquitylase BAP1. Interestingly, BAP1 is a prominent tumor suppressor that is frequently mutated in malignant mesothelioma (MM), uveal melanoma and clear cell renal cancers. Together with the Berns lab we have generated a conditional mouse model that closely mimics BAP1-deficient human MM. Interestingly, BAP1 deficient MM shows increased polycomb repression and recruitment and dependency on PRC2 and Ezh2. We are using this model and tumor cell lines to screen for the underlying cancer relevant polycomb targets and pathways. This model is also used to screen for new vulnerabilities and targeted combination therapies.

Genome wide Chromatin profiling using a transposon-reporter system

In collaboration with the Wessels and van Steensel labs we have developed high-throughput chromatin profiling by using Thousands of PiggyBac transposon-based Reporters In Parallel (TRIP). The power of TRIP lies in combining different (inducible) transcriptional reporters in transposons with random barcoding and high throughput sequencing to study position effects and influences of local chromatin and epigenetic states on reporter expression. As an example, we recently used TRIP to test the genome-wide influence of epigenomic context on CRISPR-Cas9 activity.

Intravital Microscopy of cancer plasticity

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Selected publications

Alieva M, Leidgens V, Riemenschneider MJ, Klein CA, Hau P, van Rheenen J. Intravital imaging of glioma border morphology reveals distinctive cellular dynamics and contribution to tumor cell invasion. Sci Rep. 2019;9(1):2054

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Our laboratory studies the identity, behavior, and fate of cells that drive tumor initiation, progression, metastasis and the development of therapy resistance. These population of cells are difficult to study since they are rare, and their behavior (e.g. migration) and traits (e.g. stemness) change over time. To be able to study these dangerous cells, we have developed intravital microscopy techniques to visualize individual cells in real-time in living animals, often referred to as intravital microscopy. In order to trace specific cell types (e.g. stem cells, EMT cells, proliferative cells) within the primary tumor and at distant organs for several weeks, we combine genetic mouse models for breast and colorectal cancer with fluorescent mouse models in which identity, behavior or lineage is labeled by fluorescent colors.

Tumor initiation and progression revealed at the single cell level
Adult stem cells (SCs) are long-lived, able to self-renew and differentiate into specialized cells to drive tissue homeostasis and tissue repair, and in addition are considered to be crucial for the initiation of tumors. Using intravital microscopy, we have identified the behavior of the adult stem cells that drive the development and homeostasis of intestinal and breast tissues. By developing new fluorescent mouse models, intravital microscopy, mathematical modelling, and single cell sequencing we are currently investigating how the dynamic behavior and fate of these SCs can be manipulated to reduce the initiation and progression of colon and breast tumors. For example, we have shown that the competition between mutant and wild-type stem cells can be enhanced by diet (e.g. calorie restriction). Moreover, we investigate if and how benign breast lesions (DCIS) can progress to malignant lesions (IDC).

Metastasis and minimal residual disease revealed at the single cell level
Only a minority of cells within a tumor acquire traits and are surrounded by microenvironments that enable them to resist therapy, gain long-term clonogenic capacity, and/or to disseminate and form distant metastases. We have established genetic colorectal and breast cancer mouse models in which cells that possess or acquire these states, such as stemness and epithelial-to-mesenchymal-transition (EMT), are fluorescently marked. We are currently filming these cells during the metastatic cascade and during and after therapy. Moreover, we try to identify the tumor microenvironment that induces the deleterious cellular states that cancer cells can acquire, and how these states and microenvironment be manipulated to inhibit metastases and the recurrence of therapy resistant tumors.

Cellular mechanisms that drive therapy resistance
The cellular composition of tumors is highly heterogeneous, and can have a large influence on how tumors respond to therapy. We have related the cellular composition of tumors in breast cancer patients to their response to different therapies and showed that the cellular composition can be used to select the most optimal treatment. In mouse models, we are currently dissection the cellular and molecular explanation for these observations. Combined with this work we hope to identify new biomarkers for personalized medicine.

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Selected publications

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Chromatin genomics

Gene expression is controlled by promoters, enhancers and other regulatory elements, and by packaging of DNA into chromatin. In addition, the spatial organization of interphase chromosomes is thought to be of key importance for genome expression and maintenance. In order to gain insight into these fundamental processes, we develop and apply new genomics techniques to reveal the interplay of chromatin and regulatory elements, and to study the architecture of chromosomes inside the nucleus.

Nuclear lamina interactions and gene regulation

We previously found that the genome of mammalian cells is associated with the nuclear lamina through ~1,300 large Lamina-Associated Domains (LADs). By gene expression analysis and systematic promoter transplantation approaches we identified hundreds of genes that are repressed inside LADs. Another set of genes is much less sensitive to the LAD context. We found that these differences are in part encoded in the promoters, and in part due to local variation in the repressive potential of LADs. Conversely, we found that forced activation of genes inside LADs can lead to local detachment of these genes from the lamina. This detachment is restricted to the activated gene plus several tens of kilobases of flanking DNA.

Furthermore, we have improved the temporal resolution of the DamID mapping method. Using this approach, we have studied the dynamics of LAD - lamina interactions during the cell cycle. This revealed that these interactions are mostly established in the first hour after mitosis with a preference for distal chromosome regions, and show a transient increase during DNA replication. Finally, we have begun to map association of the genome with other nuclear compartments, such as nucleoli and pericentric heterochromatin domains. This extends our understanding of the dynamic spatial architecture of chromosomes in relation to gene regulation.

Genomics tools to study regulatory elements

We previously developed SuRE, a genome-wide method to study how regulatory elements are functioning. We recently applied SuRE to study the impact of human genetic variation on gene regulation. Among ~6 million single-nucleotide variants we identified ~30,000 that alter the activity of enhancers and promoters. These data can help to overcome the limited mapping resolution of large genome-wide association studies, to pinpoint genetic variants responsible for various human traits and predisposition to disorders such as cancer. Furthermore, we are developing new approaches to study the communication between enhancers and promoters.

How enhancers 'choose' their target promoter(s) is still poorly understood. We have begun to dissect this logic by testing thousands of enhancer-promoter pairs in a multiplexed reporter assay. This will provide insight into the rules that determine compatibility of enhancers and promoters. In addition, we are developing a method to disrupt the physical interaction (looping) of selected enhancer-promoter pairs. This method is based on the parMRC segrosome, which can push apart two DNA molecules in prokaryotes. We are introducing this system in mammalian cells and test its ability to physically disrupt enhancer-promoter pairing and other genomic loops. Together, these approaches provide insights into fundamental principles of gene regulation, which are needed to better understand defects in gene expression in cancer.
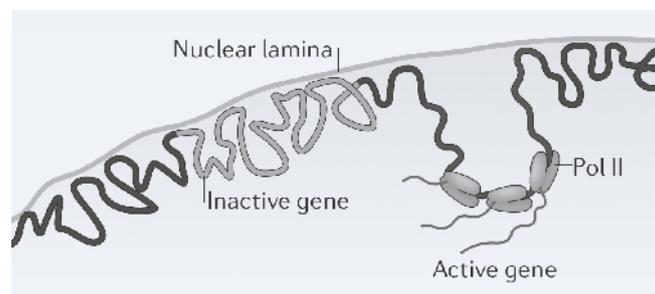
Activated genes detach from the nuclear lamina.

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Publication

Meel MH, Guillen Navarro M, de Gooijer
MC, Metselaar DS, Waranecki P, Breur
M, Lagerweij T, Wedekind LE, Koster J,
van de Wetering MD, Schouten-van
Meeteren N, Aronica E, van Tellingen O,
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Neuro Oncol. 2019

Glioblastomas and the quest for better therapies

Glioblastoma (GBM) is a uniformly fatal brain tumor. The location and invasive nature of GBM renders complete surgical resection impossible, side effects prohibit the delivery of curative doses of radiotherapy (RT) and the blood-brain barrier (BBB) hinders the adequate delivery of drugs. Our mission is to develop more effective pharmacotherapies for this disease.

We have made further progress with our research concerning so called multi-targeted combination therapy. GBM is characterized by over-activation of the PI3K, MAPK and CDK4/6-Rb pathways, being a major reason why single-targeted therapies are not very efficacious. We have observed meaningful responses in GBM models with a combination of three drugs targeting these pathways: buparlisib, PD0325901 and palbociclib. The drugs were given at dose levels that resulted in clinically relevant plasma levels and were well-tolerated. Importantly, sustained exposure to this combination of inhibitors not just inhibits proliferation, but also triggered cells to undergo senescence, which was observed both *in vitro* and *in vivo*.

The transport proteins ABCB1 and ABCG2 are important components of the BBB and restrict the brain penetration of many drugs. Our aim is to repurpose elacridar, a dual ABCB1/ABCG2 inhibitor, as a platform to improve the drug delivery to the brain. To inhibit ABCB1/ABCG2 at the BBB, the plasma levels should be sufficient. Unfortunately, the bioavailability of elacridar is restricted by poor solubility and first-pass metabolism. We have now increased the metabolic stability of elacridar by replacing hydrogens for deuterium at selected sites in the molecule. In rat, which is a more predictive species than mice, this resulted in a 30-40% increased systemic exposure.

The groups of van Tellingen and Borst have intensified their collaborations on the treatment of GBM, following the relocation of the Gerben Borst group to H3. We are conducting studies with tumor Treating Fields (TTFields); a novel treatment modality for GBM. TTFields is perceived as a black box therapy, especially since the mechanism of action is largely unknown. Interestingly, we observed an accumulation of cells in G2 when synchronized cells were exposed to TTFields, which did not occur when combined with a Wee1 or Chk1 inhibitor. When combining TTFields with a G2 checkpoint inhibitor we observed a striking synergy in proliferation and colony forming assays. We are now using live cell imaging to achieve a more in-depth insight into the kinetics of cell cycling and cell fate and will further investigate if this boosting of TTFields can be confirmed in *in vivo* models.

These last years, we have been working on the concept of "mitotic enrichment" to enhance the efficacy of radiotherapy (RT) in GBM. Dividing tumor cells are most vulnerable to RT when in mitosis and much less in other phases of the cell cycle. However, only a minor fraction of cells will be in mitosis when irradiating an asynchronous population of tumor cells. Combination of RT with mitotic inhibitors such as vincristine have been tried in the past, but were unsuccessful due to unacceptable side effects and poor blood-brain barrier (BBB) penetrance. We have identified better candidate drugs for this mitotic enrichment strategy. These have already been clinically tested, but abandoned due to insufficient single-agent antitumor efficacy. One of these compounds is an oral drug, has sufficient BBB penetrance and can safely be given daily at a dose level providing mitotic enrichment of tumor cells in the brain. This PK-PD profile matches perfectly with the standard daily RT of GBM with dosing of our drug 8 h prior to RT. We have demonstrated efficacy in experimental GBM models and are currently confirming these finding in other clinically relevant models. Based on these results we are planning to initiate a clinical trial.

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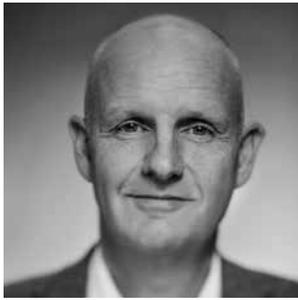
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**Selected
publications**

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2019;574(7776):127-131

Personalized medicine by employing tumor organoids and genomics

Emile Voest's laboratory group is devoted to bringing personalized medicine to patients and is focused on mechanistic studies and identification of biomarkers that predict treatment efficacy. The results from these studies are subsequently translated in clinical studies. These translational approaches are performed across tumor types with emphasis on epithelial tumors.

Genomics, immunotherapy and (tumor)organoids
Genomic guided personalized medicine
In 2019 we published several papers in high ranking journals that were the fruits of a long-standing vision on creating a data base of clinical and genomic data of patients with metastatic cancer. By employing whole genome sequencing we have not only generated significantly more insight in the genomic landscape of several cancer types but also created treatment opportunities for patients with cancer. The Drug Rediscovery Protocol, in short the DRUP study, is now a brand name for defined off lable use of approved drugs. In this multi-pharma (12 companies to date), multi-drug (27 drugs to date), multi-center (37 centers to date) study we now have created a platform through which patients can get access to approved medication based on a genomic profile coupled to a tumor type. These drugs are provided for free by pharma and the number of drugs and hospitals are expanding. At the closure of 2019, we have received and reviewed >1150 patient submissions of which 520 patients are actively treated with targeted agents. We have encountered a stable clinical benefit ratio (defined as complete or partial remission or stable disease >16 weeks) of ~30%. This is surprisingly high and reflects that patient selection is key in such a personalized medicine approach.

A true highlight of the DRUP approach is the agreement with the Dutch Healthcare Institute and national health care insurers to reimburse on a pay for performance basis successful cohorts of DRUP, starting with MSI tumors treated with nivolumab. This model is now mentioned as an example of more sustainable drug development (by parliament, regulatory bodies and pharma).

Taken together, WGS is here to stay and I am very excited that, in collaboration with Hartwig Medical Foundation, in 2019 all patients of the NKI had access to WGS, an unprecedented step in the implementation of precision medicine.

Immunotherapy
Several trials and translational studies have continued to accrue patients in 2019. The NICHE trial is a unique study that investigates the use of neoadjuvant immunotherapy in colorectal cancer. First results are now coming in which allows the assessment of safety and initial outcome. We also invested a great deal of time and energy in obtaining paired biopsies from tumors such as melanoma or lung patients treated with e.g. immunotherapy. This is extremely challenging but we feel that (with the help of the Nefkens Foundation) this will be very rewarding in better understanding resistance pathways.

Organoids as a tool to personalize medicine
In 2019 we have published our autologous T cell-organoid protocol. This will facilitate researchers to use this innovative platform. Next, we have completed several clinical trials to investigate the value of these organoids as predictive tools. These trials included validation studies in patients with chemotherapy and targeted therapy in lung and colorectal cancer (TUMOROID), organoid-guided experimental treatment studies (SENSOR) and more. We have now shown that tumor organoids can predict non-responsiveness to irinotecan-based chemotherapy but not to oxaliplatin-based treatment. Unfortunately, studies with breast cancer organoids have been terminated due to very slow growth rate and success rate to create organoids of biopsies (44%). We also stopped using lung cancer organoids because of the potential overgrowth of normal epithelial organoids.

In summary, my group is strongly committed to develop a better understanding of individual tumors and their responsiveness to immunotherapy and targeted therapy.

Molecular pathology
of breast cancer

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Selected
publications

**Van Seijen M, Lips EH, Thompson AM,
Nik-Zainal S, Futreal A, Hwang ES,
Verschuur E, Lane J, Jonkers J, Rea
DW, Wesseling J; PRECISION team.**
Ductal carcinoma in situ: to treat or
not to treat, that is the question. Br J
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**Visser LL, Elshof LE, Van de Vijver K,
Groen EJ, Almekinders MM, Sanders
J, Bierman C, Peters D, Hofland I,
Broeks A, van Leeuwen FE, Rutgers
EJT, Schmidt MK, Schaapveld M,
Lips EH, Wesseling J.** Discordant
Marker Expression between Invasive
Breast Carcinoma and Corresponding
Synchronous and Preceding DCIS. Am J
Surg Pathol. 2019;43:1574-82

**Visser LL, Groen EJ, Van Leeuwen FE,
Lips EH, Schmidt MK, Wesseling J.**
Predictors of an invasive breast
cancer recurrence after DCIS: A
Systematic Review and Meta-analyses.
Cancer Epidemiol Biomarkers Prev.
2019;28:835-45

Breast cancer is a heterogeneous disease. Accurate pathological and molecular analyses are key to make accurate predictions regarding prognosis and response to treatment. We aim to find, validate, and implement biomarkers to optimize precise and personalized predictions regarding prognosis and treatment response.

Finding the balance between over and undertreatment
of breast Ductal Carcinoma In Situ (DCIS)

Ductal carcinoma in situ (DCIS) now represents 20-25% of all breast neoplasia due to large-scale detection by population-based breast cancer screening programs. Uncertainty as to which DCIS lesions will progress to invasive drives massive overtreatment of this often harmless disease. Distinguishing DCIS that may progress to lethal disease from the majority of harmless DCIS is therefore an urgent need to save thousands of women with low risk DCIS the burden of radical treatment without any survival benefit. Therefore, we started the PRECISION (PREvent ductal Carcinoma In Situ Overtreatment Now) initiative in 2015, to distinguish harmless DCIS from hazardous DCIS. In 2017 the PRECISION team received the Cancer Research UK Grand Challenge Award, co-funded by the Dutch Cancer Society.

We aim to reduce the burden of overtreatment of DCIS (surgery, radiation therapy, hormonal therapies) through the development of novel tests that promote informed and shared decision-making between patients and clinicians, without compromising the excellent outcomes for DCIS management presently achieved. We collected a nation-wide, population-based cohort of about 20,000 women treated for primary DCIS between 1989 and 2015 in the Netherlands with long-term follow-up. Within this cohort we assess which factors of the patients, the DCIS lesion and its treatment relate to the risk of developing recurrences in the same breast. We showed that women with HER-positive and overexpressed COX-2 had a fourfold increased risk of developing a subsequent invasive breast cancer. In a comprehensive multiplex immunohistochemistry study, no differences were found in the density, number and type of periductal lymphocytes between DCIS in patients developing subsequent invasive breast cancer compared to those that did not. Yet, we did find a higher number of these cells for ER-positive, HER2-negative, and/or higher grade DCIS. We are now continuing our efforts to unravel DCIS progression. In addition, the prospective active surveillance LORD-trial to test safety of active surveillance for low risk DCIS is ongoing.

Development of clinically useful molecular tests to predict
chemotherapy response of primary breast cancers

We continued our work to identify predictive biomarkers for neoadjuvant chemotherapy treatment in breast cancer (collaboration with Lodewyk Wessels and Gabe Sonke). An extensive molecular characterization of matched pre- and post-treatment samples of 22 luminal and triple negative patients showed a multitude of differences between pre- and post-chemotherapy samples, revealing a wide range of potential, distinct mechanisms of resistance. Among these, proliferation- and stroma-related genes play a prominent role. The large degree of heterogeneity in possible resistance mechanisms makes effectively targeting chemotherapy resistant cells challenging. New projects are ongoing to unravel treatment resistance mechanisms in HER2 positive breast cancer. In addition, we are focusing on liquid biopsies to diagnose breast cancer and predict treatment benefit.

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Selected
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**Gisler S, Gonçalves JP, Akhtar W, de
Jong J, Pindyurin AV, Wessels LFA, van
Lohuizen M.** Multiplexed Cas9 targeting
reveals genomic location effects
and gRNA-based staggered breaks
influencing mutation efficiency. Nat
Commun. 2019;10(1):1598

**Mourragui S, Loog M, van de Wiel MA,
Reinders MJT and Wessels LFA.**
PRECISE: a domain adaptation
approach to transfer predictors
of drug response from pre-clinical
models to tumors. Bioinformatics.
2019;35(14):i510-i519

**Van de Haar J, Canisius S, Yu MK,
Voest EE, Wessels LFA, Ideker T.**
Identifying Epistasis in Cancer
Genomes: A Delicate Affair. Cell.
2019;177(6):1375-1383

Computational cancer biology

We aim to quantify and understand treatment response in model systems and human patients. To this end we focus on three themes. In Theme 1, Cell decisions, we employ single cell profiling and (combinatorial) perturbation techniques to infer the regulatory machinery employed by (cancer) cells to regulate the transitions between different cellular states such as proliferation, senescence and apoptosis. Theme 2, Cell maps, aims to map the regulatory circuitry in (cancer) cells by performing network inference on large scale screens combined with experimental validation. Finally, in Theme 3, Treatment response, we aim to understand treatment response by performing analyses on pre-treatment and on-treatment measurements and employing these insights to build better predictors of treatment response. Below we present some exemplary projects from these themes.

Modeling mTOR inhibitor response by multi-omics integration

Invasive lobular carcinoma (ILC) is the second most common type of breast cancer. Recent studies revealed that PI3K/AKT/mTOR signaling is frequently activated in ILC. Therefore, inhibition of this pathway is the promising therapeutic strategy. However, prolonged inhibition of this pathway results in resistance. We are investigating such resistance mechanisms using an in-vivo mouse model of human ILC: K14Cre; CDH1F/F;P53F/F. With this mouse model, we are tracking transcriptional and proteomic dynamics upon the treatment of dual mTORC1/2 inhibitor, AZD8055, from pre- and post-treatment tumors that are sensitive and resistant to AZD8055. We found that the immune response was initially induced by treatment, while the tumors lost this response when they acquired resistance. Interestingly, we also found that a subset (43%) of resistant tumors showed high expression of Myc, mainly driven by genomic amplification of Myc. These tumors had distinct molecular profiles, showing stronger downregulation of immune response and stronger upregulation of proliferation. Additionally, a recurrent focal amplification of Chromosome 2 appears in 24% of the resistant tumors, and is mutually exclusive with Myc activation, indicating an independent mechanism. We expect that these leads will provide avenues to overcome intrinsic and acquired resistance to mTOR inhibitors in ILC tumors.

PRECISE: Transfer of response prediction from cell lines to tumors

Cell lines have been used extensively to understand the molecular underpinnings of cancer. However, important differences with human tumors hamper the translation of findings from cell lines to the human setting. In particular, transfer of cell line derived drug response predictors to the clinical setting remains a challenging task. As very large drug response datasets have been collected for cell lines, and patient drug response is sparse, there is an urgent need for methods that can achieve this transfer efficiently. We developed PRECISE, a novel methodology based on domain adaptation, that captures the common information shared amongst cell lines and human tumors in a consensus representation. Employing this representation, we train predictors of drug response on pre-clinical data and apply these predictors to stratify human tumors. We show that the resulting domain-invariant predictors show a small reduction in predictive performance on cell lines, but, importantly, reliably recover known associations between independent biomarkers and their companion drugs on human tumors.

Improving treatment responses
in head and neck cancer

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Selected publications

**Duinkerken C, Rohaan MW, De Weger VA,
Lohuis PJFM, Latenstein MN,
Theunissen EAR, Balm AJM,
Dreschler WA, Haanen, JBAG,
Zuur C.** Sensorineural hearing loss
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2019;40:e674-e678

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Immuno-radiotherapy with cetuximab
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results from a phase-IB trial
(NCT02938273). Radiother Oncol. 2019

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Vogel W, Smit L, Willems S,
Al-Mamgani A, Nijkamp J, Schumacher T,
Blank C, de Boer JP, Haanen J.**
Immuno-modulation by the combination
of ipilimumab and nivolumab
neoadjuvant to (salvage) surgery in
advanced or recurrent head and neck
carcinoma, IMCISION, an investigator-
initiated phase-Ib/II trial (N16IMC,
NCT03003637). J Clin Oncol, 2019

Novel treatments to improve clinical outcome in head and neck cancer

Head and neck cancer can be categorized by two distinct aetiologies: tobacco and/or alcohol use in combination with genetic predisposition, or infection and activity of viral oncogenes. Head and neck cancers are characterized by a microenvironment invaded by various immune cells (see figure) that each may play a role in treatment response and resistance. Despite intensive treatment regimens of surgery w/wo (chemo-)radiotherapy (RT), prognosis in our patients remains relatively poor.

To improve clinical outcome in our patients, my group designed the phase Ib/II *IM*CISION trial (EudraCT 2016_002366_31) concerning toxicity and feasibility of T-cell checkpoint inhibitors nivolumab w/wo ipilimumab immunotherapy neoadjuvant to standard of care (extensive surgery) in patients with advanced disease. This trial has been completed end of 2019, and we are currently analysing the data.

Also, we identified a promising novel lead compound that showed tumor selective radiosensitizing activity in vitro, while having no effect on cell viability in the absence of irradiation. The target was found to be ATM, part of the DNA repair pathway. We are currently chemically optimizing the lead compound in collaboration with the Division of Chemical Immunology of Prof Neefjes and Prof Ovaa in het LUMC in Leiden, the Netherlands, and should define better options for radiotherapy in our patients.

In 2018 we have also completed a phase 1 trial providing trans-tympanic administration of an oto-protective drug to rescue patients from irreversible hearing loss due to high-dose cisplatin anti-cancer treatment. The idea is that the rescue drug will diffuse from the middle ear to the inner ear via the round window. In this phase 1 trial we could safely administer the drug in all patients. Moreover, to our great enthusiasm, our protocol and mode of administration of the drug indeed resulted in successful oto-protection in single patients.
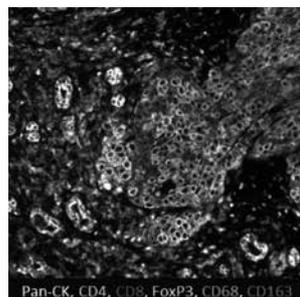
Tumor microenvironment of oropharyngeal cancer. Various coloured cells represent the various immune cells that surround and invade the squamous cell carcinoma (courtesy Bianca Cioni, Jan Paul de Boer, André Bergman, Erik Hooijberg).

Z

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**Selected
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**Kim Y, Bismeijer T, Zwart W, Wessels
LFA, Vis DJ.** WON-PARAFAC: a genomic
data integration method to identify
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T, Ahmed M, Zhou S, Severson TM,
Guilhamon G, Huang V, Yamaguchi
TN, Fraser M, Bergman AM, van der
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RG, Zwart W, Lupien M.** Cistrome
Partitioning Reveals Convergence of
Somatic Mutations and Risk Variants
on Master Transcription Regulators in
Primary Prostate Tumors. Cancer Cell.
2019;36(6):674-689.e6

**Stelloo S, Linder S, Nevedomskaya E,
Valle-Encinas E, de Rink I, Wessels L,
van der Poel H, Bergman AM, Zwart W.**
Androgen modulation of XBP1 is
functionally driving part of the AR
transcriptional program. Endocr Relat
Cancer. 2019

Hormones in cancer

Hormonal therapies represent the first and most-successful targeted therapeutics in cancer.
In most breast and prostate cancers, hormonal therapy forms the very backbone of systemic
treatment, both in adjuvant and metastatic treatment. However, resistance to hormonal intervention
is common, and many patients relapse despite treatment.
We study hormonal action in multiple tumor types; breast cancer, prostate cancer, endometrial
cancer and lung cancer. Our ultimate goal is to better understand hormonal signaling and elucidate
therapy resistance in cancer, contributing to personalized clinical decision-making, optimized
treatment selection, identification of novel therapeutic options and minimized over-treatment.
By enhancing our knowledge on steroid hormone receptor function in cancer and elucidating
mechanisms of treatment resistance, our research will be instrumental to fully tailor endocrine
treatment selection in the future, selecting the most-suitable therapy for the individual patient.

Glucocorticoid Receptor signaling axis in lung cancer

As hormone receptors are expressed in a wide spectrum of tumor types, we explored wider
applicability of hormonal therapies beyond their regular use. We found expression of the
glucocorticoid receptor (GR) is associated with favorable outcome in lung cancer patients, with
activation of this receptor inducing cellular quiescence in a subset of lung cancer cell lines (Prekovic
et al., submitted). By integrating functional genomic studies on GR activity, transcriptomics and
CRISPR knockout methods, we identified GR-controlled CDKN1C expression as the key-driver to
dictate drug response. A small compound screen revealed a novel drug-drug synergy between GR
activation and IGF1R inhibition to eradicate lung cancer cells. In vivo studies are ongoing to explore
the therapeutic potential of this novel drug-drug combination in lung cancer treatment.

Genome-wide Androgen Receptor profiling in prostate cancer

Prostate cancer is the second-most prevalent malignancy in men, in which the Androgen
Receptor (AR) is considered the sole-driving factor in cancer development and progression. In
collaboration with the lab of Mathieu Lupien (Princess Margaret Cancer Centre, Toronto), we
integrated AR chromatin interactome analyses in healthy prostate tissue and primary tumors with
somatic mutation data and prostate cancer risk SNPs. Both somatic and germline variants were
enriched in the tumor-specific AR DNA interactome, shared with other prostate cancer driving
transcription factors, including FOXA1 and HOXB13. While most variants did not functionally alter
AR activity, convergence of somatically acquired and germline risk factors was observed at specific
enhancer elements that driver tumor progression (Mazrooei et al., 2019). We are currently
performing analogous studies in two Phase II clinical trials, in which patients receive AR-targeting
Enzalutamide treatment in the neo-adjuvant (DARANA; Dynamics of Androgen Receptor Genomics
and Transcriptomics After Neoadjuvant Androgen Ablation. NCT03297385. PI: Henk van der Poel)
and metastatic (PRESTO; Predicting Response to Enzalutamide as a Second Line Treatment for
Metastasized Castration Resistant Prostate Cancer Patients: a biomarker design study. PI: Andre
Bergman) setting, aimed elucidate the cellular plasticity of AR function in prostate cancer and
treatment resistance, and to better understand the impact of DNA mutations on transcriptional
regulation in cancer.
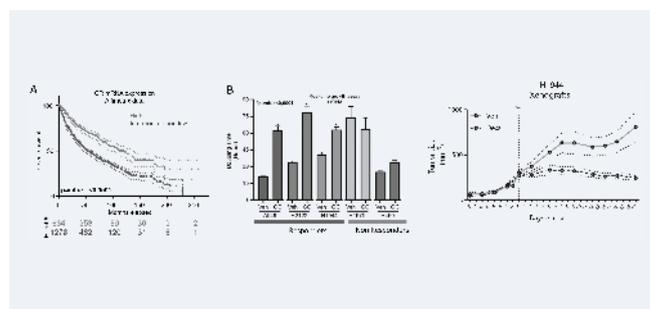
**Glucocorticoid Receptor signaling axis
as therapeutic inroad for lung cancer
treatment.**
A. GR expression is correlated with
lung cancer patient outcome.
B. GR activation induces cellular
quiescence in vitro (left) and in vivo
(right).

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Division of Diagnostic Oncology

DEPARTMENT OF CLINICAL CHEMISTRY AND LABORATORY MEDICINE

The department of clinical chemistry and laboratory medicine is responsible for the routine analysis of laboratory diagnostics for patient care. The department has the objective to bridge basal biomarker research and routine clinical application of meaningful biomarkers. Furthermore, the institutional biobank for blood and urinary based samples is hosted and run from this department.

Liquid Biopsies

An important focus of the department is translational research and implementation of innovative diagnostics into clinical practise. Such an innovative approach to cancer diagnostics are liquid biopsies. Liquid biopsies are increasingly used in clinical care, with our department involving in biobank initiatives and numerous studies exploring this biomarker. In 2019 the COIN (ctDNA on the road to implementation in the Netherlands) was granted by ZonMW. We initiated a multidisciplinary consortium in the Netherlands to come to evidence-based implementation of ctDNA. In addition, two studies focusing on the added value of ctDNA were finished focussing at pre-treatment evaluation and in patients with progressive disease under TKI treatment.

Clinical and diagnostic validation of biomarkers

For monitoring of cancer, tumor biomarkers are often used. Unfortunately for many of these markers used in daily practice objective insights in what consecutive obtained results clinically mean, is lacking. A platform called Re-marker was developed to support clinical studies validating the diagnostic performance of longitudinal tumour biomarkers. Investigations focus amongst others on early detection of immunotherapy non-responsiveness in melanoma and non-small cell lung cancer.

State-of-the-art steroid analysis for breast and prostate cancer

In (advanced) breast and prostate cancer steroid hormones are important drivers of tumour growth. Most systematic treatments are therefore aimed at interfering with these signalling pathways. At the department of clinical chemistry and laboratory medicine new state-of-the-art, LC-MS/MS based assays for amongst others testosterone and estrogens have been developed for routine clinical diagnostics. These offer superior analytical performance and enable studying the relevance of these steroid concentrations as prognostic and predictive markers.

DEPARTMENT OF MEDICAL PHYSICS AND TECHNOLOGY

Our department actively participates in several hospital-wide research lines. We introduce new techniques, facilitate their implementation, and advise on regulatory issues. A mechanical workshop is part of our department, where we build, adapt, and design devices used in several clinical and pre-clinical research projects.

Our expertise and skills:
- MR physics: develop, implement, and evaluate new MRI sequences for biomarkers and image-guided therapy applications.
- Medical imaging: develop segmentation, registration, and visualization algorithms for image-guided therapy applications. PACS interface to facilitate large-scale imaging studies (in collaboration with the Radiomics group).
- Pharmacokinetic modeling and radiation dose calculations.
- Optical and physiological measurement techniques: development, implementation, and evaluation.
- We are member of the medical ethics committee to guard the patient safety studies involving patients.

THE NETHERLANDS CANCER INSTITUTE FAMILY CANCER

For many of the 1450 patients (families) visiting the Family Cancer Clinic the indication for referral is a possible genetic predisposition for breast and/or ovarian cancer. Other indications include suspected Lynch syndrome, colorectal polyposis syndromes, Li-Fraumeni syndrome and a possible genetic predisposition for stomach cancer, renal cancer, melanoma and pancreatic cancer.

Increasingly, results of DNA-analysis have implications for the treatment of cancer. This development results in more referrals and, sometimes, a different way of genetic counselling.

The DNA-diagnostic laboratory of the Family Cancer Clinic

The implementation of Next Generation Sequencing (NGS) for the BRCA1/2 genes in 2016 made it possible to offer BRCA testing for germline and somatic DNA, isolated from blood cells and more importantly FFPE fixed tumor or normal cells. Several clinical trials require rapid testing of tumor DNA for a BRCA1 specific or a BRCAness profile. In this respect, we are able to offer a complete test panel for BRCAness: germline and somatic BRCA1/2 testing, BRCA1 promotor methylation and CNV seq to assess the genomic tumor profile for BRCAness features (in collaboration with P. Nederlof, head Molecular Diagnostics). In the last quarter of 2019 we started to implement an NGS test containing 17 genes which is suitable for FFPE isolated DNA and can be used for breast and ovarian cancer. In 2019 the following genes were added to our NGS tests: CHEK2, ATM and PALB2 for breast cancer. Using Sanger Sequencing CDK4 and MITF for melanoma were added. January 1st 2020 we will start with an NGS panel specific for ovarian cancer and this panel contains BRCA1, BRCA2, BRIP1, RAD51 C and RAD51D.

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Meta van Lanschot MD PhD student
Iris van 't Erve PhD student
Carmen Rubio PhD student

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Charlotte van Rooijen Technical staff
Marianne Tijssen Technical staff
Menno de Vries MSc Technical staff
Rianne van der Wiel Technical staff

Selected publications

DEPARTMENT OF CLINICAL CHEMISTRY AND LABORATORY MEDICINE

Colak S, Tasdemir O, van der Schaar M, Opdam F, van den Noort V, van den Broek D, van Rossum HH. Design, validation and performance of aspartate aminotransferase- and lactate dehydrogenase-reporting algorithms for haemolysed specimens including correction within quality specifications. Ann Clin Biochem 2019

Hummelink K, Muller M, Linders TC, van der Noort V, Nederlof PM, Baas P, Burgers S, Smit EF, Meijer GA, van den Heuvel MM, van den Broek D, Monkhorst K. Cell-free DNA in the supernatant of pleural effusion can be used to detect driver and resistance mutations, and can guide tyrosine kinase inhibitor treatment decisions. ERJ Open Res 2019;5(1):00016-2019

Van Rossum HH, Spruit J, Korse CM, de Vries F, Tesselaar M. Antidepressant use limit serotonin as marker for neuroendocrine tumor disease activity by lowering of circulating serotonin concentrations. Clin Chem Lab Med 2019 (accepted)

DEPARTMENT OF MEDICAL PHYSICS AND TECHNOLOGY

De Boer L, Kho E, Nijkamp J, Van de Vijver K, Sterenborg HJC, Ter Beek L, Ruers TJ. Method for coregistration of optical measurements of breast tissue with histopathology: the importance of accounting for tissue deformations. J Biomed Opt. 2019;24(7):1-12

Kooreman ES, van Houdt PJ, Nowee ME, van Pelt VWJ, Tijssen RHN, Paulson ES, Gurney-Champion OJ, Wang J, Koetsveld F, van Buuren LD, Ter Beek LC, van der Heide UA. Feasibility and accuracy of quantitative imaging on a 1.5 T MR-linear accelerator. Radiother Oncol. 2019;133:156-162

Vollenbrock SE, Voncken FEM, van Dieren JM, Lambregts DMJ, Maas M, Meijer GJ, Goense L, Mook S, Hartemink KJ, Snaebjornsson P, Ter Beek LC, Verheij M, Aleman BMP, Beets-Tan RGH, Bartels-Rutten A. Diagnostic performance of MRI for assessment of response to neoadjuvant chemoradiotherapy in oesophageal cancer. Br J Surg. 2019 Apr;106(5):596-605

THE NETHERLANDS CANCER INSTITUTE FAMILY CANCER

Aalbersberg EA, Rossi MM, de Wit-van der Veen LJ, Walraven I, van den Heuvel MM, Sonke JJ, Belderbos JS, Vogel WV. Pre-hydration in cisplatin-based CCRT: effects on tumour concentrations and treatment outcome. Radiother Oncol. 2019;134:30-36

Olde Heuvel J, de Wit-van der Veen BJ, Vyas KN, Tuch DS, Grootendorst MR, Stokkel MPM, Slump CH. Performance evaluation of Cerenkov luminescence imaging: a comparison of 68Ga with 18F. EJNMMI Phys. 2019;6(1):17

Saadani H, van der Hiel B, Aalbersberg EA, Zavrakidis I, Haanen JBAG, Hoekstra OS, Boellaard R, Stokkel MPM. Metabolic Biomarker-Based BRAFV600 Mutation Association and Prediction in Melanoma. J Nucl Med. 2019;60(11):1545-1552

DEPARTMENT OF PATHOLOGY

Bosch LJW, Melotte V, Mongera S, Daenen KLJ, Coupe VMH, van Turenhout ST, Stoop EM, de Wijkerslooth TR, Mulder CJJ, Rausch C, Kuipers EJ, Dekker E, Domanico MJ, Lidgard GP, Berger BM, van Engeland M, Carvalho B, & Meijer GA. Multitarget Stool DNA Test Performance in an Average-Risk Colorectal Cancer Screening Population. Am J Gastroenterol. 2019;114:1909-18

Research projects

We contribute to national (HEBON) and international (BCAC, CIMBA) efforts to understand the etiology, risk and outcome of breast cancer. We are involved in international efforts to establish polygenic risk scores for breast cancer and we are looking for opportunities for implementation studies in the clinic, in collaboration with group Schmidt. In 2017 a unique prospective breast cancer study was granted by Pink Ribbon/KWF (in close cooperation with M.J. Hooning and A. Hollestelle, ErasmusMC, M.K. Schmidt, and M.A. Adank, NKI-AVL) to assess all aspects of breast cancer in women from families with a CHEK2 c.1100delC mutation. For this study, women are currently invited to participate.

TP53-mutation carriers from Li-Fraumeni syndrome families nation-wide are screened by total body MRI in the NKI. Data on the MRI-results and on the psychosocial impact of this screening tool (M. Ruijs, E. Bleiker, G. Sonke (Division of Medical Oncology) and Loo Division of Radiology)) are continuously collected. In close cooperation between the PSOE (E. Bleiker) and the Family Cancer Clinic (F. Menko, L. vd Kolk) new methods for informing family members are developed and evaluated aimed at improving the communication of cancer risk and better use of preventive measures.

Furthermore, we participate in ongoing collaborations (inter) nationally to elucidate the clinical role of DNA variants found by the DNA diagnostic laboratory (INVUSE, BRCA1/2 VUS, ENIGMA). Our department is also interested in the ethical, legal and social aspects of unsolicited genomic findings, particularly in the context of tumor testing (WIDE study) and clinical genetic testing and counseling; Lizet van der Kolk is a member of the core team of the ELSI Servicedesk and of the WIDE study team.

DEPARTMENT OF NUCLEAR MEDICINE

In the past year, the department of nuclear medicine has further elaborated on some important topics as advanced image analysis and quantification. The aim of such studies is to enable better characterization of primary tumors and metastases as well as to predict response to therapy. A study on this by Saadani et al. (J Nucl Med. 2019;60(11):1545-1552) for the first time showed that BRAFV600 mutation status of melanoma is not associated with, nor can it be predicted with, conventional PET features, as radiomic features were of low predictive value (AUC = 0.62). Recently, comparable results were also found in breast cancer and lung cancer, again indicating that radiomics in nuclear medicine might differ from radiology. These studies were performed in close collaboration with AUMC-VUMC. One of the prerequisites for advanced image analysis is an optimal standardization. In this respect, close collaboration has been established with multiple academic partners resulting in a recent publication by Huizing et al., which revealed a leading role of our department in the field of ^{68}Ga-labeled PET/CT (EJNMMI Phys. 2019;6(1):19).

Several studies have been performed last year in which the value of FDG PET/CT was evaluated in patients scheduled for radiotherapy. In one of these studies by Gouw et al. (Clin Nucl

Med. 2019;44(5):e323-e328), increased baseline TLG was associated with worse DFS in HPV-negative Oropharyngeal cancer and it might be used as biomarker for risk stratification in these patients. Interestingly, it was not possible to confirm this association in HPV-positive patients. Furthermore, FDG-PET/CT has excellent performance for the detection of recurrent disease in oropharyngeal cancer, with a sensitivity and negative predictive value approaching 100%. Due to these excellent results is examination under anesthesia today in the vast majority of the PET-negative cases not necessary anymore. Some new tracers and isotopes have been studied in the past years, leading up to the first thesis covering translational studies on [195m]Pt-Cisplatin. This successful work formed the basis of an ongoing collaboration with among others NRG-Petten, four UMC's and the NKI-AVL, the so-called 'FIELD-LAB'. This consortium was launched in 2019 to speed up development and translation of the new generation radiotracers. Consequently, our department gained access to several upcoming diagnostic and therapeutic tracers that will be evaluated for clinical practice within this institute. One example of an on-going project is ^{177}Lu-PSMA, a small molecule directed towards the prostate specific membrane antigen, that was tested at our department as part of an international multicenter study. The outcomes will be published next year.

Finally, several methodological and clinical studies (funded by NWO-KWF) related to Cerenkov Light Imaging (CLI) were initiated, of which the technical part was already published this year by Olde Heuvel et al. (EJNMMI Phys. 2019;6(1):17). In the upcoming months the first clinical results will become available, and a close collaboration with colleagues from the University Hospital in Essen is being set up.

DEPARTMENT OF PATHOLOGY

Pathology is all about diagnosing the nature of disease processes, to guide clinical decision-making and optimize personalized and precision treatment of cancer patients. Our challenge is to generate as much relevant information from tissue, cell and DNA samples aimed at the best personalized treatment for patients today and in the future. Important questions to be answered relate to finding, validating, and implementing prognostic and predictive biomarkers, combined with tumor classification issues. The progress of the research by the Translational Gastrointestinal Oncology group (PI's, Beatriz Carvalho, Remond Fijneman and Gerrit Meijer), and the lung group (PI Kim Monkhorst), as carried out in the Division of Diagnostic Oncology and the translational mamma research (PI Jelle Wesseling) and the computational pathology research (PI Hugo Horlings), as carried out in the Division of Molecular Pathology, can be found in the first part of this report. The progress of the Laboratory of Familiar Tumors (head Frans Hogervorst) is summarized in the chapter of the Department of Clinical Genetics. In addition to the major lines of research the department is further developing its role as a key player in translational research through the Pathology Translational Research Core (PTRC). The PTRC provides research services for both basic, translational and clinical researchers to accelerate laboratory discoveries into patient care. The PTRC

Rozeman EA, Menzies AM, van Akkooi ACJ, Adhikari C, Bierman C, van de Wiel BA, Scolyer RA, Krijgsman O, Sikorska K, Eriksson H, Broeks A, van Thienen JV, Guminski AD, Acosta AT, Ter Meulen S, Koenen AM, Bosch LJW, Shannon K, Pronk LM, Gonzalez M, Ch'ng S, Grijpink-Ongering LG, Stretch J, Heijmink S, van Tinteren H, Haanen J, Nieweg OE, Klop WMC, Zuur CL, Saw RPM, van Houdt WJ, Peeper DS, Spillane AJ, Hansson J, Schumacher TN, Long GV, & Blank CU. Identification of the optimal combination dosing schedule of neoadjuvant ipilimumab plus nivolumab in macroscopic stage III melanoma (OpACIN-neo): a multicentre, phase 2, randomised, controlled trial. Lancet Oncol. 2019;20:948-60

Theelen W, Peulen HMU, Lalezari F, van der Noort V, de Vries JF, Aerts J, Dumoulin DW, Bahce I, Niemeijer AN, de Langen AJ, Monkhorst K, & Baas P. Effect of Pembrolizumab After Stereotactic Body Radiotherapy vs Pembrolizumab Alone on Tumor Response in Patients With Advanced Non-Small Cell Lung Cancer: Results of the PEMBRO-RT Phase 2 Randomized Clinical Trial. JAMA Oncol. 2019

DEPARTMENT OF RADIOLOGY

Detering R, Borstlap WAA, Broeders L, Hermus L, Marijnen CAM, Beets-Tan RGH, Bemelman WA, van Westreenen HL, Tanis PJ; Dutch Snapshot Research Group. Cross-Sectional Study on MRI Restaging After Chemoradiotherapy and Interval to Surgery in Rectal Cancer: Influence on Short- and Long-Term Outcomes. Ann Surg Oncol. 2019;26(2):437-448

Mann RM, Pinker K. Is Background Parenchymal Enhancement an Important Risk Factor for Breast Cancer Development in Women with Increased Risk? Radiology. 2019;292(3):562-563

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Trebeschi S, Drago S, Birkbak N, Kurilova I, Călin A, Pizzi A, Lalezari F, Lambregts D, Rohaan M, Parmar C, K Hartemink, C Swanton, J Haanen, C Blank, E Smit, R Beets-Tan, H Aerts. Predicting Response to Cancer Immunotherapy using Non-invasive Radiomic Biomarkers. Annals of Oncology 2019;30(6):998–1004

offers state of the art expertise from pathologists, molecular biologists, biomedical scientists and bioinformaticians. The PTRC also offers data services related to pathology. An important asset to this is the Core Facility Molecular Pathology (CFMPB, head Annegien Broeks) which is key to tissue biobanking as well as laboratory support for translational studies. CFMPB has developed automated staining protocols for multiplex fluorescent marker panels. More details about the CFMPB are reported in the first part of this report. The clinical studies unit of the PTRC supports the logistics of the pathology part of clinical studies, sample handling and shipping of tissues. In the context of the PTRC and in close collaboration with CFMPB, multi spectral imaging, employing Vectra-3 hardware (Akoya and HALO image analysis software (Indica Labs), is further developed (coordinated by Erik Hooijberg). In order to meet the increasing demand for image analysis the number of modulesand the number of license seats is increased. Data analysis is supported as well. Moreover, NanoString technology has been introduced, coordinated by Linda Bosch. Researchers from in- and outside NKI have successfully analyzed their samples using this robust technology and the first results have been published in Lancet Oncology (see below) for publication. In close collaboration with Daan van den Broek of the department of Clinical Chemistry, Remond Fijneman and Kim Monkhorst make use of clinical trials to perform translational research studies of cell-free circulating tumor DNA as prognostic and predictive biomarkers for colorectal cancer and lung cancer, respectively. Most staff members are actively involved in multidisciplinary research activities in the field of thoracic oncology, urology, gastrointestinal oncology, melanoma, ovarian cancer, head and neck cancer and immunotherapy. In 2019, the department was involved in 181 clinical trials and 419 translational studies. The scientific output includes 108 publications. Three projects were granted by ZONMW and KWF, with a total budget of €3.3 M.

DEPARTMENT OF RADIOLOGY

Imaging Research at the department of Radiology is multidisciplinary clinical and translational. It focuses on functional MRI for Organ preservation, Image guided intervention, Artificial intelligence, Imaging for Immunotherapy and Radiogenomics. The research team consists of 18 PhD students, 3 postdoc scientists and 19 postdoc radiologists. Rectal Cancer Imaging research focuses on modern imaging technology and Artificial Intelligence models for noninvasive assessment and prediction of response to improve the selection and monitoring of patients for organ-preserving treatments such as Watch-and-Wait and Papillon contact radiotherapy. An implementation study in NL of the Watch and Wait is funded by the Dutch Cancer Society, resulting in two dissertations. Organ preservation is also the focus of research in oesophageal cancer. It validates MRI as part of a multimodality approach to identify patients with complete response after neoadjuvant treatment, aiming towards better selection of patients for non-operative treatment. The project resulted in several publications and will be completed with a dissertation. Research in breast imaging revolved around several major themes. The collaborative research in MRI screenings has resulted in publications of outcomes in respectively the New England Journal of Medicine

(DENSE) and Lancet Oncology (FamRisc). Research explored the potential of breast MR biomarkers for prognosis, risk prediction and stratification of screening populations. Another study shows that AI for mammography can improve radiologist's performance in correct interpretation of these images. AI modeling projects for breast MRI are ongoing including deep learning for multiparametric breast MR for lesion classification. Other projects aim at de-escalating treatment burden, image guided excision of small breast cancers and MRI for treatment evaluation after neoadjuvant therapy. Further studies are in the validation of dedicated breast CT for the evaluation of micro-calcifications, primary breast cancer and systemic therapy monitoring.

MRI of peritoneal carcinomatosis research determines the impact of DW-MRI for the detection of peritoneal carcinomatosis in CRC and ovarian cancer. The Dutch Organisation of Science funded a randomized multicentre trial to evaluate whether DW-MRI can replace diagnostic laparoscopies in colorectal cancer CRS/HIPEC candidates. A second multicenter trial funded by the Dutch Organisation of Science is running, evaluating its role in patients with peritoneal mets from ovarian cancer. Multiparametric imaging research aims to build models linking MRI to clinical, CT and PET data to predict response and long-term outcome in various cancers and treatments, including a large multicenter trial in rectal cancer with additional Radiomics analysis (funded by two research grants from the Dutch Cancer Society). In Prostate cancer multiparametric imaging research focuses on identifying tumor characteristics and phenotypes for advanced risk stratification and decision support systems in biopsy and treatment management. Ultrasound image fusion projects fusing real time US with CT, MR or PET-CT aim to improve the characterization of cervical nodes in Head and Neck ca and imaging guidance in treatment of vanishing liver metastases. Interventional radiology research group reported the results of intra-hepatic Mitomycine-C in breast cancer liver metastases also in combination with Y90 radioembolization. Kidney ablation projects reported on the safety and efficacy of MWA. The combination of local therapies plus immunotherapy is one of the main focus of the interventional research. A prospective registration of the combined use of cryo-ablation and embolization for kidney T1b tumors is running. Prospective registry studies for image fusion (Percunav) during biliary drainage and for LUMI (radio-opaque) beads for transarterial embolization in NET tumours are running. Studies including new treatment approaches for the patients with colorectal liver metastases will start including neoadjuvant ablative dose in Y-90 radioembolization and combined treatment of MWA plus transarterial chemoembolization. A multidisciplinary project has started for interventional treatment of complex painful bone metastases non responsive to conventional treatments. This year a collaborative project with MSKCC analyzing biomarkers associated with local control and survival following treatment of CRC limited metastatic disease has been completed and results in a dissertation.

Radioimmunotherapy study for prostate cancer is in collaboration with the nuclear medicine and urology department to investigate the feasibility of direct intraarterial embolization of prostate cancer. AI Immunotherapy research focuses on therapeutic response assessment and predictionas well as

biological profiling of immune-relevant tumours. The research showed predictive radiomics signatures for response to immunotherapy in melanoma and NSCLC, and to clinically relevant genetic mutations in colorectal carcinoma. We have expanded our research to include further cancer types, and external validation cohorts in collaboration with international cancer centers. AI-powered analysis was executed to assess brain metastasis response to immunotherapy in melanoma. Studies on deep learning-derived of brain metastases have shown both prognostic and predictive values in immunotherapy. Furthermore, AI model is being built to improve imaging diagnostic of immune-related adverse effects. As of this year technically oriented questions addressing clinically relevant questions have started being investigated, most prominently integrative approaches for the development of novel AI-biomarkers for evaluation of treatment response in liver, head and neck, colon, breast and lung cancer.

Gabe Sonke

Head Research Division of Medical Oncology

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Ruby van Stein MD PhD student
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Marit Vermunt MD PhD student
Judith Versluis PhD student

Division of Medical Oncology

The Division of Medical Oncology includes the Departments of Gastroenterology, Internal Medicine, Neurology, Pharmacology, Psychiatry, and Pulmonology. The Division has a capacity of 60 in-patient beds, a day clinic hosting 54 beds for chemotherapy, a large outpatient clinic, and a GCP certified Clinical Research Unit (CRU) for the conduct of phase I-IV clinical trials with 16 beds. The Division treats about 13,000 patients per year, accommodates a staff of 57 medical specialists, and offers a training program for residents in gastroenterology, medical oncology, neurology, and pulmonology.

Research at the Division of Medical Oncology

The Division aims to combine high quality care with cutting edge research. These ambitions are matched by a strong focus on clinical and translational research and close collaborations between clinical and research staff within the institute. A selection of clinicians serves as group leaders of laboratory-based research and spend 25-50% of their time on laboratory research. The NKI funds part of their salary and research staff. In addition, the Division actively stimulates other clinicians to initiate clinical research.

Translational research in Medical Oncology requires laboratory space and expertise, which is provided by the research sections (NKI), such as Divisions of Experimental Therapy, Immunology, Molecular Biology, Molecular Carcinogenesis, and Molecular Genetics. There is also strong interaction with the Departments of Pathology and Molecular Pathology.

There are 69 PhD students currently employed, while 64 PhDs successfully defended their theses over the last five years. All our PhD students participate in the oncology graduate school of Amsterdam (OOA) accredited by the Royal Netherlands Academy of Sciences (KNAW). At the moment, 91 research grants are active with a total budget of 62.4 million euro. Approximately 125 clinical trials are actively recruiting patients. All new clinical trials are reviewed by an internal committee on clinical and translational research (CKTO). This committee is composed of a number of research oriented medical specialists from the Division and selects potential studies based on alignment with the Institute's research themes, study methodology, translational research opportunities, competing studies, and financial and logistical arrangements.

BREAST AND OVARIAN CANCER

Vincent Dezentjé, Marloes van Dongen, Marleen Kok, Sabine Linn, Lemonitsa Mammatas, Carolien Smorenburg, Marcel Soesan, Gabe Sonke, Jacqueline Stouthard, Leonora de Boo, Marieke Bruggeman, Marjolein Delfos, Maxime Duijst, Marjo Holtkamp, Chaja Jacobs, Lisette Janssen, Vincent de Jong, Inge Kemper, Chris Klaver, Simone Koole, Marte Liefaard, Ingrid Mandjes, Lennart Mulder, Annemiek van Ommen, Iris Nederlof, Margaret Schot, Mariette Schrier, Tessa Steenbruggen, Ruby van Stein, Sonja Vliek, Anna van der Voort, Leonie Voorwerk

Background and objectives

The objective of this research program is to develop and improve systemic therapy for patients with early breast cancer and to improve treatment options in (oligo-) metastatic breast cancer. Our studies are in close collaboration with the Dutch Breast Cancer Research Group, the EORTC Breast Cancer Group, the Breast International Group, and Cancer Core Europe. In 2019, we included 196 patients in 15 clinical studies. The team is also involved in optimizing the treatment of ovarian cancer.

(Neo)adjuvant systemic treatment

The neoadjuvant chemotherapy program is the core of a multidisciplinary research effort to optimize systemic treatment and response prediction. It currently comprises studies for ER+/HER2- tumors (AFTER, NEOLBC, BELLINI), triple negative tumors (SUBITO, BELLINI) and HER2+ tumors (TRAIN-3). The 20-year follow-up data of the N4+ study will be published in JAMA Oncology early 2020, showing that overall survival benefit of high dose chemotherapy is maintained at 20 years in patients with >10 involved axillary lymph nodes, most notably in triple negative breast cancer (TNBC). Building on the N4+ results, the SUBITO study currently evaluates high-dose chemotherapy with stem cell transplant in women with high-risk triple negative breast cancer harboring homologous recombination deficiency. The BELLINI study has started in 2019 and evaluates the value of PD1-blockade in HER2-negaive breast tumors with high levels of tumor-infiltrating lymphocytes. The TRAIN-3 study investigates if the number of pre-operative chemotherapy cycles can safely be reduced in case of an early radiologic complete pathologic remission. In addition, 3-year follow-up data of the earlier TRAIN-2 study is collected and will be presented in 2020.

Metastatic breast cancer

The OLIGO study, Triple B-study, and ABC study investigate the treatment of patients whose tumors harbor DNA repair defects as interrogated with the BRCA-like test. The triple B-study evaluates the addition of anti-PDL1 (atezolizumab) to a backbone of paclitaxel or platinum-based chemotherapy as first line treatment for metastatic TNBC. The NKI led international phase Ib/II POSEIDON and nationwide SONIA studies investigate the optimal use of an isoform selective PI3K inhibition and CDK4/6 inhibition, respectively, added to endocrine therapy in advanced ER+/HER2- breast cancer. In 2019, we published the final clinical data and the first translational data of the TONIC trial in Nature Medicine. The data showed that induction with doxorubicin or cisplatin can result in a more favorable tumor microenvironment and more responses on nivolumab. The GELATO study is a

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Berbel Ykema MD PhD student
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Yvonne Schuller Research physician
Matthijs Tibben Technical staff
Sandra Adriaansz Nurse practitioner
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Simone Dokter Nurse practitioner
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Marjo Holtkamp Nurse practitioner
Lisette Jansen Nurse practitioner
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Anoesjka Lechner Nurse practitioner
Judith Lijnsvelt Nurse practitioner
Henk Mallo Nurse practitioner
Suzanne Onderwater Nurse practitioner
Saskia Pulleman Nurse practitioner
Lisette Saveur Nurse practitioner
Bodien Schilder Nurse practitioner
Margaret Schot Nurse practitioner
Wilma Uyterlinde PhD Nurse practitioner
Jana van der Sar Nurse practitioner
Marion Zimmerman Nurse practitioner

Selected publications

SELECTED PUBLICATIONS DEPARTMENT BREAST AND OVARIAN CANCER

Koole SN, van Lieshout C, van Driel WJ, van Schagen E, Sikorska K, Kieffer JM, Schagen van Leeuwen JH, Schreuder HW, Hermans RH, de Hingh IH, van der Velden J, Arts HJ, Massuger LF, Aalbers AG, Verwaal VJ, van de Vijver KK, Aaronson NK, van Tinteren H, Sonke GS, van Harten WH, Retèl VP. Cost effectiveness of interval cytoreductive surgery with hyperthermic intraperitoneal chemotherapy in stage III ovarian cancer on the basis of a randomized phase III trial. J Clin Oncol 2019;37:2041-50

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Voorwerk L, Slagter M, Horlings HM, Sikorska K, van de Vijver KK, de Maaker M, Nederlof I, Kluin RJC, Warren S, Ong S, Wiersma TG, Russell NS, Lalezari F, Schouten PC, Bakker NA, Ketelaars SL, Peters D, Lange CA, van Werkhoven E, van Tinteren H, Mandjes IA, Kemper I, Onderwater S, Chalabi M, Wilgenhof S, Haanen JB, Salgado R, de Visser KE, Sonke GS, Wessels LF, Linn SC, Schumacher TN, Blank CU, Kok M. Immune induction strategies in metastatic triple-negative breast cancer to enhance the sensitivity to PD-1 blockade: the TONIC trial. Nat Med 2019;25:920-8

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multicenter phase 2 trial initiated for invasive lobular breast cancer (ILC) patients with metastatic disease. Based on preclinical data we hypothesize synergy between platinum and immune checkpoint blockade in a subgroup of immune-related ILC.

Ovarian cancer

In 2019, we ensured reimbursement for all patients receiving hyperthermic intraperitoneal chemotherapy (HIPEC) added to interval debulking surgery, based on our previous work that was published in the New England Journal of Medicine. This treatment option is now also included in the NCCN and other international guidelines. Furthermore, we published in the Journal of Clinical Oncology that the addition of HIPEC to interval debulking is cost-effective. We currently perform translational studies looking at homologous recombination deficiency and immune signatures as predictors for HIPEC efficacy and started the OVHIPEC-2 study that evaluates HIPEC added to primary surgery. We also continue our investigator-initiated study on neo-adjuvant chemo-immunotherapy in stage IV ovarian cancer.

GASTROENTEROLOGY

Tineke Buffart, Annemieke Cats, Myriam Chalabi, Jolanda van Dieren, Cecile Grootscholten, Monique van Leerdam, Margot Tesselaar, Wieke Verbeek, Marieke Vollebergh, Thomas de Wijkerslooth, Sonja van Veenendaal, Elvira Nuijten, Lisette Al, Berbel Ykema, Esther Toes, Arthur Kooyker

Background and objectives

The Department of Gastroenterology is involved in early detection and prevention of and innovative multimodality treatments for gastrointestinal cancers including neuro-endocrine tumors (NET) and hereditary GI-cancer syndromes.

Upper GI cancer

For esophageal cancer several imaging studies are being performed including the evaluation of fiducials, MRI and 4D-PET. We started a neo-adjuvant pilot study with immunotherapy for GI-junction and gastric cancer. Furthermore, we are evaluating a watch-and-wait policy for esophageal cancer. The first studies have been published. In 2015, 788 patients with primary resectable gastric cancer were enrolled in the international, randomized, phase III CRITICS study. The results were published in Lancet Oncology and subgroup analyses are being done.

Lower GI cancer

We are responsible for evaluation of the Dutch population-based CRC screening program (www.rivm.nl) in collaboration with the Erasmus MC in Rotterdam. We published data on quality and yield of the screening program and influence on stage distribution. Furthermore, we are expert center for hereditary GI cancer syndromes and run several research projects in patients with hereditary CRC syndromes, serrated polyposis syndrome, and second primary CRCs (MLDS grants). Other studies focus on DPD activity. Genotype-guided dosing resulted in adequate systemic drug exposure and improved safety and was cost-effective. A meta-analysis of 7365 patients treated

with fluoropyrimidines estimated the prevalence of various DPYD genotypes. Prospective studies are ongoing. We are involved in translational and multicenter clinical studies with targeted and immunotherapy for CRC in all stages. The first data about neo-adjuvant Immunotherapy for CRC has been presented, showing (near) complete responses in all MMR deficient CRCs.

Neuro-endocrine tumors (NET)
In close collaboration with the UMCU Utrecht, we are an ENETs center of excellence and a Dutch NFU GEP-NET expertise center. Since the start of PRRT in March 2016 we have all techniques to diagnose and treat GEP-NET patients. Several research projects are going such as exploring new blood biomarkers in patients with metastatic NET as well as GEP-NEC.

THORACIC ONCOLOGY

Paul Baas, Sjaak Burgers, Wieneke Buikhuisen,
Maria Disselhorst, Wanda de Kanter,
Joop de Langen, Egbert Smit, Willemijn Theelen

Background and objectives
The Department of Thoracic Oncology stands for optimizing patient care, performing translation research and introducing new systemic therapies.

Immune checkpoint inhibition
Following implementation of immunotherapy in 1st line setting in lung cancer, we now focus on treatment of recurrent disease. We published in JAMA Oncology that stereotactic body radiotherapy prior to pembrolizumab was well tolerated and lead to a doubling of response rate. New studies investigate the combination of IO agents before start of surgery or chemo-radiation in patients with locally advanced stages. Using compounds targeting different pathways we hope to improve outcome and better understand the involved pathways. In collaboration with the AUMC biomarker studies investigate the usefulness of immuno- and small molecule PD-(L)1 PET/CT for response prediction and pharmacodynamic changes during IO (combination) treatment. Outcome of the pilot study of PD-1 and PD-L1 PET/CT have been published in Nature Communications. A perspective on pembrolizumab for the treatment of advanced NSCLC has been published in the Lancet.

Malignant pleural mesothelioma
The DENIM phase III vaccination study after chemotherapy in first line is currently running, in collaboration with Erasmus MC in Rotterdam. Our INITIATE study (anti-PDL1 + anti-CTL4) in patients with recurrent mesothelioma has been published in Lancet Respiratory Medicine. The Mesoscape Database (ETOP) has recruited almost 500 patients and data on epidemiology and treatment outcomes have been presented.

Neuro endocrine tumors (ENETS center of excellence)
We continue to focus on the diagnosis and treatment of patients with neuro endocrine tumors. Recently, a phase 2 study with a PD1 inhibitor in patient with low grade metastatic neuro endocrine tumors has been finalized. Other studies like the phase 3 with lanreotide versus placebo have been completed.

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Targeted agents

We optimized the molecular work-up for NSCLC, which now includes all known molecular drivers and genetic alterations of resistance to targeted treatment. Six investigator-initiated and ten externally sponsored mutation defined studies are open.

The NKI is one of the referral centers in the Netherlands for patients with rare (incidence less than 5%) genetic alterations. The European Thoracic Oncology Platform (ETOP) initiated dedicated studies, such as alectinib in RET rearranged tumors. We actively participate in the CPCT-02 and DRUP studies and co-authored two seminal papers that were published in Nature this year. Over 200 patients were included in the national LEMA study (Early Molecular Assessment) analyzing the mutational status in all patients with primary adenocarcinoma of the lung.

Small cell lung cancer

A randomized study with lurbenectedin (a tubulin inhibiting agent) with chemotherapy versus chemotherapy alone in second line has finished accrual.

Smoking cessation

The current focus is the prevention of smoking in adolescents. A manipulation of filter cigarettes leading to higher toxic products during inhalation was discovered. Although a criminal lawsuit to file charges against the tobacco companies was rejected, recommendations to politicians to defer from tobacco lobbyists continues.

CLINICAL PHARMACOLOGY

Neeltje Steeghs, Frans Opdam, Serena Marchetti, Marloes van Dongen, Roos Achterbergh, Bastiaan Nuijen, Hilde Rosing, Alwin Huitema, Jos Beijnen

Background and objectives

Research activities of the Departments of Clinical Pharmacology, the Department of Pharmacy & Pharmacology and the Division of Pharmacology are closely integrated. Currently, we perform 48 phase I/II, pharmacological and proof of concept studies. We are referral center for phase I studies in the Netherlands. We annually screen over 350 and recruit over 200 new patients in early phase industry sponsored and investigator initiated clinical trials. In 2019, the main themes of our investigator-initiated research were the personalized dosing of oral anti-cancer drugs, drug-drug interaction, and genomic profile selected phase I/II studies.

Personalized dosing of oral anti-cancer drugs

Oral targeted anti-cancer agents have a complex pharmacological profile, narrow therapeutic index, and a marked pharmacokinetic interpatient variability. Individual patients have a high probability to be either underdosed (>30%) or overdosed (>15%). Therapeutic drug monitoring (TDM) refers to personalized dosing based on measured drug levels. We have started a nationwide project to study and implement TDM in the Netherlands. Over 450 patients have been included so far and first results were presented at several international meetings, i.e. ESMO conference in Madrid.

Genomic profile selected phase I/II studies

Based on preclinical work done in the lab of Rene Bernards, three clinical trials study the combination of pan-HER and MEK inhibitors in KRAS mutant and PIK3CA wildtype lung cancer, pancreatic cancer, and colorectal cancer. We initiated a phase II study with the WEE-1 inhibitor AZD1775 plus carboplatin for TP53 mutated platinum refractory ovarian cancer. We also initiated an international study (MoTriColor consortium) to treat colorectal cancer patients according to molecular defined subtypes. Finally, we initiated the Basket of Basket trial within the Cancer Core Europe Consortium that treats a pancancer population according to molecular targets.

Improving doctor-patient dialogue in early phase clinical trial participation

With a consortium grant from the Dutch Cancer Society we started the OnVaCT study. This study aims to qualitatively evaluate life values of patients with advanced cancer facing the choice to participate in early phase clinical trials. We aim to develop a value clarification tool that helps the decision-making processes of patients and working routines of oncologists.

UROLOGIC ONCOLOGY

André Bergman, Martijn Kerst, Michiel van der Heijden, Vincent Dezentje, Jeantine de Feijter, Elsbeth van der Laan, Anoesjka Lechner, Suzanne van der Kolk, Helga Schrijver, Helga Hoogenhout, Rebecca Louhanepessy, Sushil Badrising, Marit Vermunt, Nick van Dijk, Jeroen van Dorp, Hielke-Martijn de Vries

Background and objectives

Our group focusses on the treatment of prostate, bladder, testicular, penile, and rare urological cancer. We aim to contribute to international trials and to play a leading role in initiation of national trials and translational research.

Prostate cancer

in 2019, multiple investigator initiated- and industry sponsored trials in metastatic castration resistant prostate cancer (mCRPC) patients were open for recruitment. Investigator initiated trials included the national OSTRICh study, randomizing patients between cabazitaxel and abiraterone or enzalutamide as a second line treatment. Biomarker studies include serum levels of cytokines involved in neutrophil homeostasis and analysis of cfDNA. In the PRESTO study, biopsies of metastatic sites are taken prior to enzalutamide treatment. In the biopsies, chromatin accessibility and binding profiles of transcription factors to the chromatin are assessed, which may hold biomarker properties as a predictor of response to enzalutamide. The ROTOR registry aimed to assess activity of radium-223 in contemporary patients and the course of pain in a non-study population treated with radium-223. Multiple biomarker studies are connected to this study.

Bladder cancer

In 2019, we completed the first cohort of the NABUCCO study. In this study, we investigate the feasibility of pre-operative ipilimumab/nivolumab in locoregionally advanced bladder cancer.

24 patients were enrolled, of whom 23 (96%) had resection <12 weeks from 1st cycle, meeting the primary endpoint. Eleven patients (46%) achieved a pCR. Three additional patients only had a small focus of non-invasive cancer at resection, resulting in an overall rate of 58% without invasive cancer cells at resection. Translational analysis of this unique set of 24 paired pre/post tumor samples is ongoing and a follow-up cohort of 30 patients, testing adjusted dosing schedules, has been initiated. ICRA is another investigator-initiated trial, which investigates paclitaxel in combination with anti-CTLA4 (tremelimumab) for urothelial cancer progressing to chemotherapy and checkpoint blockade.

Testicular cancer

The NKI multidisciplinary testicular cancer group (*Expert Centre for rare urological diseases*) has an ongoing focus on patient treatment, including salvage chemotherapy and robotic laparoscopic surgery and on studies on long-term effects of platinum-containing therapy (cardio-vascular risks and second tumors). In addition, the group works on Introducing the sentinel-node procedure in clinical stage I testicular cancer.

Penile cancer

We initiated the PERICLES study. In this study, advanced penile cancer patients are treated with atezolizumab (anti-PDL1). A subset of patients with locoregional lymph node metastases receive additional radiotherapy.

CLINICAL IMMUNOTHERAPY

John Haanen, Christian Blank, Hans van Thienen, Sofie Wilgenhof, Aafke Meerveld, Sandra Adriaansz, Henk Mallo, Wilma Uyterlinde, Judith Lijnsvelt, Marieke Groot-Obbink, Lisette Rozeman, Irene Reijers, Judith Versluis, Maartje Rohaan

Background and objectives

Our group is primarily involved in the treatment of melanoma and renal cell carcinoma patients. Research focuses on neo-adjuvant targeted and immunotherapies, dissection of immunological changes upon immune checkpoint inhibition plus targeted agents, combination with local therapy (RFA, oncolytic viruses), and on adoptive cellular therapies.

Clinical adoptive T cell transfer program

There is an unmet medical need for patients with stage IV melanoma who have failed anti-PD-1 treatment. Based on promising data from our and other institutes, we initiated the first phase 3 TIL trial worldwide, which compares efficacy of TIL therapy versus ipilimumab as 1st or 2nd line treatment in stage IV melanoma. Collaborating with Herlev Hospital in Denmark and Sanquin, 97 patients have been randomized so far. We received financial support from the Dutch Cancer Society to increase accrual by opening the study in CHUV in Lausanne and DKFZ in Heidelberg. Together with Neon Therapeutics we are developing a strategy to induce and augment neoantigen-specific T cell populations from metastatic melanoma patients for adoptive transfer. The idea is that using adoptive T cell therapy with products enriched for neoantigen-specific T cells can overcome resistance to immune checkpoint blockade. A proof-of-concept phase Ib trial is being planned for 2020.

Neoadjuvant immune checkpoint inhibition in melanoma

Anti-PD-1 (nivolumab, pembrolizumab) with or without anti-CTLA4 (ipilimumab) has become standard therapy for metastatic melanoma. Nivolumab and pembrolizumab are also used as adjuvant therapy in stage III melanoma, improving recurrence-free survival of many patients. We have pioneered in developing neoadjuvant checkpoint inhibition studies, with the idea of inducing broader immune responses with checkpoint when the primary tumor is in situ. The three-year update of the initial OpACIN trial was presented at ESMO 2019 and confirmed long-term relapse free survival in patients achieving a pathologic response. The OpACIN-neo trial established high efficacy with a combination regimen that has reduced toxicity and therefore allows broad application. The subsequent PRADO extension cohort closed inclusion in 2019 and aims to confirm the observed responses and toxicities and addresses whether a complete lymph node dissection can be omitted in patients achieving a major pathologic response. Based on these data, a phase 3 registration trial, comparing neoadjuvant versus standard adjuvant checkpoint inhibition, is currently developed. Novel combinations, like HDACi + PD-1-blockade +/- CTLA-4 blockade or oncolytic virus therapy (T-VEC) + PD-1 blockade, are currently set-up as investigator-initiated trials with the aim to develop alternatives for patients not responding to neoadjuvant ipilimumab + nivolumab. This will lead eventually to personalized neoadjuvant immunotherapy. Together with MD Anderson Houston and Melanoma Institute Australia, the NKI has set-up the International Neoadjuvant Melanoma Consortium. Together, we recently published our framework on neo-adjuvant on study design and translational research. In addition, we presented full PFS results from the ImPemBra trial at the Melanoma Bridge Congress 2019. This feasibility trial combines pembrolizumab with short-term dabrafenib/trametinib in BRAF V600 mutated metastatic melanoma patients. The short course targeted therapy added to PD-1 blockade was better tolerated than continuous combinations, and a promising PFS benefit was observed. This novel approach will also be tested in a neoadjuvant study for patients with an unfavorable baseline biomarker profile who are unlikely to respond to ipilimumab + nivolumab.

Renal cell cancer

Our group is involved in implementing or participating in trials to improve the treatment with small molecule receptor tyrosine kinase inhibitors (RTKI) in combination with checkpoint inhibitors in the metastatic disease setting, and in the neoadjuvant setting with high-risk clear cell RCC. We participate in adjuvant immunotherapy trials and in a trial for patients with non-clear cell metastatic RCC patients.

Theo Ruers

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Division of Surgical Oncology

IMAGE GUIDED SURGERY

This research line aims to optimize surgical procedures by better surgical guidance during operative procedures. To this end new imaging technologies are developed and tested to improve tumor mapping and staging pre and intra-operative. These imaging and surgical guidance procedures should lead to more radical resections while sparing normal tissue and organ function. The research line is a strong collaboration between the NKI-AVL, Technical University Twente and industrial partners. For the moment 3 project lines are running. In the first project we are developing tools for optical guidance during surgery by means of spectroscopy. We published for the first time that both techniques can be used seamlessly in the current workflow for the detection of breast cancer, colon cancer, lung cancer and head and neck tumors. Accuracy to detect malignancies varied from 90-95%. We will further concentrate to incorporate the developed technology into surgical tools and we started a STW project to further develop this technology in combination with ultrasound as well as with laparoscopy. In a second project we aim to improve the balance between radical surgery and preventing morbidity in extensive surgery, by bringing innovative navigation technology to the OR. We introduced this first in world electromagnetic navigation system for abdominal and pelvic surgery into clinical practice. Over 150 patients have been operated this way with great success and enthusiasm amongst the surgeons working with the system. The project team was able to obtain funding from the KWF/Alp d'HuZes and the Vriendenloterij. We published the first in man navigation study for abdominal tumor tracking.
A third project line concentrates on the introduction of hyperspectral imaging for cancer surgery. This project is funded by the European project Astonish and received a grant from the Dutch Cancer Society (KWF), TKI and recently also from STW/KWF. We aim that in the near future all tumor resection samples can be analyzed almost real time within the OR enabling additional resection when necessary.

SURGICAL ONCOLOGY

Patient care and clinical research is largely organized in subunits who work in multidisciplinary teams: breast, melanoma, sarcoma, thoracic tumors, upper gastro-intestinal, and a combined unit of lower gastro-intestinal, liver, and colorectal peritoneal metastases. The goal of our research is twofold: to improve the survival for patients with more advanced disease, and to improve the quality of life of all patients by minimizing the side-effects and trauma of oncological treatment. A first common theme is to explore better combinations of systemic therapy, radiotherapy and surgery, and to incorporate the recent advances in immunotherapy. These therapies are

increasingly applied in a neo-adjuvant setting, and with a focus on a better assessment of the response it becomes possible to individually tailor the extent of the surgery to the type of response. Some well-responding tumors can be removed with less extensive surgery, and in some patients, surgery can be omitted altogether. Some very advanced unresectable tumors may become resectable after neoadjuvant therapy.

A second common theme is the technical development and clinical use of intra-operative imaging and tissue differentiation techniques that allow more precise identification of tumor tissue, allowing both a better complete removal of the tumor and sparing of non-involved tissues. The department of surgery has initiated many phase I and II trials, and is participating in multicenter phase III trials, some of which have been initiated by NKI-AVL. In addition to the surgical staff, over 40 researchers were associated with the department. In 2019 this resulted in 172 publications in peer reviewed journals, PhD theses, and regular media coverage.

Upper GI cancer

Translational research focuses on the identification of genetic patterns based on copy number variation in relation to treatment response of the tumor, immune activity, and patients' survival. The results of the multicenter clinical NKI-AVL study on (neo)-adjuvant multimodality treatment in gastric cancer was internationally well recognized with a major Lancet Oncology publication. Ongoing studies in this field are further investigating the role of multimodality neo-adjuvant treatment, e.g. neoadjuvant chemoradiotherapy and immunotherapy for gastric cancer and a surgery-as-needed protocol for oesophageal cancer. An ongoing clinical and research focus is on the role of hyperthermic intraperitoneal chemotherapy (HIPEC) in gastric cancer patients with peritoneal metastases.

Thoracic surgery

Clinical innovations in surgical treatment for NSCLC include minimally invasive surgical techniques such as 3D-video assisted thoracoscopic surgery (VATS), robotic surgery and segmental resections. Scientific research focuses on multimodality treatment, including the role of chemoradiation followed by surgery and the role of neoadjuvant and adjuvant immunotherapy and targeted therapies in combination with surgery. There are ongoing studies on response evaluation after chemoradiotherapy and immunotherapy. Another research focus is on the role of Tumor Infiltrating lymphocytes (TIL) therapy and organoids.

Colorectal – Liver – Peritoneal metastases

In both rectal cancer and liver tumors there are many ongoing intraoperative imaging studies. In rectal cancer NKI-AVL is recognized as a world leader in organ preservation. The program is continuously expanded with ongoing multicenter trials, and with a fully operational contact radiotherapy device. The concept of neoadjuvant immunotherapy is tested in an exploratory study in colonic cancer, and combined with radiotherapy in a new trial for organ preservation in rectal cancer. For liver metastases the concept of adjuvant intra-arterial chemotherapy was first tested in a phase II trial, and now in a phase III trial. Advanced MR imaging studies are continued in the field of rectal cancer and peritoneal metastases. New studies on the use of liquid biopsies in primary and metastatic colorectal cancer have been explored and will be initiated.

Anne Heirman MD PhD student
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Kilian Kappert MSc PhD student
Rebecca Karsten MD PhD student
Liset Lansaat MsC PhD student
Maartje Leemans MSc PhD student
Inge Oskam MD PhD student
Ellen Passchier MsC PhD student
Marije Petersen MD PhD student
Neslisah Seyrek MD PhD student
Matthijs Valstar MD PhD student
Martijn van der Heijden MD PhD student
Manon van der Laaken MSc PhD student
Tessa van Doeveren PhD student
Michel van Harten MD PhD student
Klaske van Sluis PhD student/SLP
Joris Vos MD PhD student
Luuk Voskuilen MSc PhD student
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Kees Hendricksen MD PhD Academic staff
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Maaike van de Kamp MD Academic staff
Ton Roeleveld MD Academic staff
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Selected publications

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Breast

The breast cancer group focuses their main research activities on three programs. The first is personalized breast cancer treatment with the goal to de-escalate breast cancer treatment. In close collaboration with the Radiology and Pathology departments, we work on trials investigating which patients are eligible for active surveillance instead of local treatment both in the primary surgery setting and in the neo-adjuvant systemic treatment setting. Together with the Division of Medical Oncology we work on multicenter trials to personalize (neoadjuvant) systemic treatment based on response prediction and monitoring. The second research focus is on the development of 'shared decision making' programs for breast cancer patients. Our third research focus is on outcome of breast cancer care; we actively participate in the NBCA and in close collaboration with the Department of Quality of Care we invest in research focused on both the long term psychological and physical outcome of breast cancer care.

Melanoma and skin tumors

Together with the Division of Medical Oncology the melanoma unit has invested in the development of new neo-adjuvant therapies in stage III disease, allowing a reduction of the extent of surgery. Other areas of interest have been the treatment and outcome of Merkel Cell Carcinoma (MCC), and loco-regional therapies such as oncolytic viruses. In all these areas our unit has established itself as leaders in the field with high-ranking publications in NEJM, Lancet and Nat Med.

Soft tissue tumors

The sarcoma unit focuses its research activities on three programs. The first is the development of (international) neo-adjuvant trials for angiosarcoma and retroperitoneal sarcoma. The second is the development of a multi-disciplinary translational research collaboration on the prediction of response to neo-adjuvant systemic therapy, radiotherapy and isolated limb perfusion, and on exploring new therapeutic options. The third is outcome research on different surgical strategies in DFSP, angiosarcoma and retroperitoneal sarcoma.

HEAD AND NECK SURGERY AND ONCOLOGY

The department has research lines in image guided treatment. Projects on radiomics, image guided research in SN detection, tumor margin optimization and mandibular reconstruction are carried out. We have a 3D lab and in collaboration with the University Twente, many students do their master thesis at our department. In this lab, new techniques in mandibular and maxillary reconstruction are being developed. In the field of personalized medicine, several PhD's work on tumor profiling using many histopathological and genetic techniques. We mainly study the relationship between (chemo)radiosensitivity and tumor characteristics, with an emphasis on DNA repair deficits. In a project of the Dutch Head and Neck Society (DESIGN project) we are combining many prognosticators from genetics, radiomics and the clinic to build a prediction model.

The department has a long-standing tradition in survivorship research. Most research focuses on rehabilitation and counseling and several PhD students are working in this field. Laryngectomy is a major topic, but also swallowing after chemoradiation and other modalities are being studied. Different aspects of rehabilitation are studied, such as cost-effectiveness, new devices, improving fitness, organization of care. Voice, swallowing, general fitness, pulmonary rehabilitation, body image and lymphedema are major topics of interest. In the field of patient counseling, we are developing decision aid tools and personalized prediction of outcome, both in terms of survival as well as functioning. In several projects, functional outcome models are being developed using computer animations of the actual patient with input from imaging, EMG and speech.

In 2019 there were several highlights:
– Michiel van den Brekel was visiting professor at the University of Toronto and program chairman of the IAOO World Conference in Rome.
– In the biomarker studies, we have recently identified several important pathways playing a role in both response as well as survival. DNA repair deficits predict a poor survival, but only when suboptimal cisplatin doses are administered. Hypoxia and EMT were also identified as possible targets for future personalized treatment. These profiles not only help in predicting outcome, but might also direct targeted therapies.
– In patient counseling we are the first to develop decision aid tools, both for advanced laryngeal and hypopharyngeal cancer as well as early oropharyngeal cancer. Involving the patients' association is a crucial factor. These tools will become more precise when more accurate prediction models are added. We also will try to make them more personal by adding prediction of speech and swallowing.
– In the field of rehabilitation, we have shown that preventive rehabilitation as well as a structured multidisciplinary program for rehabilitation, addressing function as well as social and coping aspects is optimal for the patient. Many aspects of speech and swallowing have been clarified and long-term functional results after chemoradiation are also dependent on optimal rehabilitation.
– The phase II study on induction immunotherapy before surgery (IMCISION), led by C.L. Zuur was completed. The results are very promising with several major clinical responses and will be published shortly.
– The 3D lab was able to get funding for developing new mandibular reconstruction plates together with Mobius Industries: a 214K grant: TKI-LSH PPP allowance Health Holland: 2019

UROLOGY

In 2019 urology welcomed 3 new urologists of which 2 MD PhD and one preparing her thesis. The number of clinical and preclinical studies increased to over 15. Further subspecialisation lead to core research groups for renal, bladder and prostate cancer research, whereas joint efforts drove penile and testicular cancer research. The main focus research lines in at the department in 2019 were:

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Bladder preserving strategies in patients with muscle invasive bladder cancer

Brachytherapy for bladder cancer was shown to be associated with good survival in patients with <5 cm cT1G3-T2N0M0 bladder tumor and was associated with a reduced complication rate compared to radical cystectomy in a retrospective series. (Radiother Oncol. 2019 Dec;141:130-136). Neoadjuvant immunotherapy with ipilimumab and nivolumab showed an impressive complete response rate of 46% in patients with muscle invasive bladder cancer, opening the discussion on the need of cystectomy for selected patients (ESMO 2019).

Cytoreductive nephrectomy may improve survival in metastasized renal cancer after response sunitinib

The SURTIME trial with a primary endpoint of progression-free survival found an overall survival benefit, a secondary endpoint of deferred cytoreductive nephrectomy after sunitinib (JAMA Oncol 5 (2), 164-170).

In prostate cancer staging the PSMA-PET

scan improved metastases detection and when combined with a sentinel node procedure has the highest predictive value for nodal metastases (J Nucl Med. 2019 Sep 27. BJU Int. 2019 Jul;124(1):62-68). PSMA tracers can be used for image guided surgery in prostate cancer (Eur Urol. 2019;76(4):517-523).

GYNAECOLOGY

Center for Gynecologic Oncology Amsterdam (CGOA)

The integration of the clinical groups at the NKI-AVL and Amsterdam UMC into *Center for Gynecologic Oncology Amsterdam* was further structured. Interdisciplinary teams with members from both locations are now established per organ. The teams aim to facilitate guideline writing, conduct clinical and translational research, contribute to teaching and collaborate on (inter)national level. In 2020 we will further focus on overarching projects we considered as pivotal in an academic clinical setting. The ultimate goal remains to install CGOA on one location in Amsterdam.

Ovarian carcinoma

Ovarian carcinoma is a disease with a high mortality due to the fact that symptoms are often only present when the disease has spread in the abdomen. In 2019, steps were made to implement HIPEC into daily clinical practice to improve overall survival for women with advanced ovarian cancer. More knowledge about the peritoneum and the mechanism of development of metastases is indispensable. Another method to improve patient outcome, is early detection of ovarian cancer. Research in molecular biomarkers can contribute to this. Ovarian carcinoma is a heterogenous disease with different histological subtypes. Research to clinical characteristics and molecular background of ovarian cancer and the subtypes is another focus of research.

Endometrial cancer

Endometrial cancer is the most common gynecological malignancy in high-income countries. Although the overall prognosis is relatively good, high-grade endometrial cancers tend to recur. Our focus is to develop a risk stratification based on molecular and other tumor characteristics and imaging that helps us to identify patients with extra-uterine disease. Minimal invasive surgery including the studies with sentinel node biopsy are ongoing. We contribute in the development of European (ESMO) and national guidelines (oncoline)

Cervical Cancer

Cervical cancer yearly affects 700 women in the Netherlands. One third of these women are younger than 40 years and a significant amount of these women still wish to have children. Current treatment modalities to preserve fertility in early stage cervical cancer consist of an operation with poor pregnancy outcomes. In 2018, we started an observational trial for treatment with chemotherapy to reduce the size of the tumor enabling less radical surgery. We expect the number of women who will be able to carry a child after this treatment to increase 5-fold. Besides, we aim to improve the current procedure to screen for cervical cancer by introduction of molecular markers as a triage test in hrHPV positive women in urine and cervical scrapes because many women do not attend the screening program, possibly because of fear for a gynecological examination.

Vulva

Vulvar cancer is a relatively uncommon disease. Surgery is treatment of choice, causing frequently postoperative morbidity in patients with high stage disease. An alternative treatment, starting with neo-adjuvant chemotherapy, could reduce tumor size, thereby diminishing the chance for morbidity. In case of lymph node metastases, prognosis is worse. Tumor-derived factors are an important factor in these metastases and we investigate how this mechanism works and determine if immunotherapeutic strategies could be useful. Also, pre-malignant vulvar disease is investigated to determine optimal treatment.

Cancer and pregnancy

On behalf of the International Network on Cancer Infertility and Pregnancy, we reported that women with Hodgkin lymphoma did not have worse outcome. This information is important regarding maternal safety and cancer treatment during pregnancy. At the same time, we continue to follow up children who were antenatally exposed to chemotherapy. This allows us to both look into maternal and fetal safety. We further elaborate on the survey estimating maternal mental health and emotional needs when cancer is treated during pregnancy.

Gestational Trophoblastic Disease

Gestational trophoblastic disease (GTD) is a heterogeneous group of disorders characterized by abnormal proliferation of trophoblastic tissue. Since GTD is a rare disease, little evidence is available from randomized controlled trials on optimal treatment and follow up. In Amsterdam, the Amsterdam Trophoblastic Team was founded in 2018 to advice on treatment and follow-up of GTD. We cooperate with the European Organisation for Treatment of Trophoblastic diseases and International Society for the Studies on Trophoblastic Disease. In 2019, we finalized an RCT on providing digital information for these patients. We are also finetuning therapy for very rare subtypes of GTD.

PLASTIC AND RECONSTRUCTIVE SURGERY

Our research is focused on innovative reconstructive techniques after ablative surgery by other specialists. Additionally, multi-disciplinary research is being executed in collaboration with the Division of Psychosocial Research and Epidemiology, as well as with the oncologic breast task force of the Erasmus University - Daniel den Hoed Clinic in Rotterdam, the Netherlands. We participated actively in the development of the Dutch Breast Implant Registry (DBIR).

A nation-wide DBIR was established in 2015 as one of the first up-and-running breast implant registries worldwide to evaluate breast implant surgery and increase our knowledge of implant performance. Initial DBIR outcomes and experiences over the first years were evaluated. DBIR show high national participation rates (95% and 78% for hospitals respectively private clinics in 2016). Between 2015 and 2017, a total of 15,049 patients and 30,541 breast implants were included. A minimum breast implant incidence rate of 1 per 1,691 women could be determined for 2017. Devices were inserted for a cosmetic (85.2%) or reconstructive (14.8%) indications. Patient, device, and surgery characteristics differed per indication group. Substantial variation was seen in the use of infection control measures (range 0-100%). These preliminary observations support further developments toward the improvement of breast implant surgery and patient safety.

The general advice against immediate implant-based breast reconstruction in women who need to undergo post-mastectomy radiotherapy (PMRT) has never been justified to date by any evidence that PMRT causes short-term complications in these women. Therefore, we compared the type and prevalence of all complications, any unscheduled surgical intervention, and implant loss occurring during the first 16 post-operative weeks after 235 combined skin-sparing mastectomy and such reconstruction in 232 women receiving PMRT, to those occurring after 656 similar combined surgical interventions in 630 women who did not undergo PMRT (control group). We found the prevalence of minor complications (p= 0.00), major complications (p= 0.04) and the fraction of total number of interventions (p= 0.02) were significantly lower after PMRT than in the control group. The fraction of breasts needing unscheduled surgery (p= 0.16) and the prevalence of implants loss (p = 0.69) was lower in the interventional group, but not significantly so. We concluded that that women who might need to undergo PMRT after combined skin-sparing mastectomy and immediate implant-based breast reconstruction ought to be treated as those who need not.

DERMATOLOGY

Reflectance confocal microscopy
The diagnosis and management of skin cancer has become a burden on both patients and health care systems due to the increasing incidence worldwide. Through the routine use of dermatoscopy we have seen a significant increase in diagnostic accuracy of skin malignancies compared to naked-eye examination alone. With the arrival of *in vivo* diagnostic devices such as reflectance confocal microscopy (RCM) and optical coherence tomography (OCT) there is now the potential for an additional non-invasive diagnostic step prior to histological examination. Reflectance confocal microscopy is a noninvasive imaging technique that allows the in vivo visualization of cutaneous structures at a cellular-level up to the level of the superficial reticular dermis. In (retrospective) studies we aim to determine the diagnostic accuracy and added value of RCM in the management of skin cancer in a clinical setting.

Skin problems in patients started with targeted and immune checkpoint inhibitors
Oncodermatology is the dermatologic field aimed at the dermatologic health in cancer patients. Due to rapid developments in cancer treatment there are now over 50 described dermatologic side effects. Traditional cytostatic treatment is aimed at inhibiting cell division (mitosis) and can result in cytotoxic side effect like toxic erythema of chemotherapy, mucositis, extravasation injuries, nail disorders, and alopecia. Following the arrival of targeted therapies, and to a lesser extend immune checkpoint inhibitors, a significant amount of new mucocutaneous side-effects have been described. These new agents block the growth of cancer cells by inhibiting specific molecules involved in tumor pathogenesis pathways. The side effects of targeted therapy are the direct result of the pharmacological drug effects, as the molecular targets are also present in the mucosal and cutaneous tissues. In the case of immune checkpoint inhibitors, most are immunological side effects secondary to immune system modulation. In both types of cancer treatments, true immunological allergic reactions are rare. A multidisciplinary approach to these dermatological side effects is important as they could potentially influence the continuation of the cancer treatment, in addition to having a significant effect on the patient's quality of life. Due to the large number of these side effects a lot of more time is spend in treating these skin problems in the (outpatient) clinic. In 2019 we have started with retrospective studies in the group of metastatic melanoma patients who are treated with targeted and immunotherapy in our hospital.

ANESTHESIOLOGY, INTENSIVE CARE MEDICINE AND PAIN MEDICINE

The principal aim of our department is to deliver the highest standard of anesthesiological care, intensive care and pain therapy and to continually work on the development of best practices in everyday patient care.

In 2019 there has been ongoing work on a comprehensive review on the effects of anesthetics on cancer recurrence and patient outcome.
A prospective study investigating an intervention to decrease hospital admissions at the end of life is currently running. Furthermore, clinical studies in the surgical field involve optimal treatment after prostatectomy and breast cancer surgery.

Corrie Marijnen

Head Division of Radiation Oncology

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Marnix Witte PhD Post-doc
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Saskia Cooke PhD student
Catarina Dinis Fernandes PhD student
Theo Driever PhD student
Roelant Eijgelaar PhD student
Elselien Frijlink PhD student
Beatrix Gomez Solsona PhD student
Celia Juan de la Cruz PhD student
Edzo Klawer PhD student
Chavelli Kensen PhD student
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Tessa van de Lindt PhD student
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Vineet Mohan PhD student
Daniel Muñoz PhD student
Marcel van Schie PhD student
Lukas Schröder PhD student
Astrid Slagter PhD student
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Uros Stankovic PhD student
Iban Torres Xirau PhD student
Evalien Veldhuijzen PhD student
Anke Wiersma PhD student

Selected publications

Al-Mamgani A, Navran A, Walraven I, Schreuder WH, Tesselaar MET, Klop WMC. Organ-preservation (chemo) radiotherapy for T4 laryngeal and hypopharyngeal cancer: is the effort worth? Eur Arch Otorhinolaryngol. 2019;276(2):575-583

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Division of Radiation Oncology

INTRODUCTION

Following the change of leadership, the division of Radiation Oncology has redefined his research ambitions for the coming 10 years. In 2030, we will be a leading example for large international centers because we are pushing the boundaries in our search for the best possible options for our patients. In addition to that, we are frontrunner in the area of personalized medicine, through continuous adaptation of the treatment according to the characteristics of the tumor and the patients' preferences. These ambitions can be summarized in the following:

Mission 2030
Through the **comprehensive approach** of clinical care and research the department offers the most progressive treatment worldwide

Vision 2030
We will **continuously** take **all relevant factors** into account to ensure a **personal and tailored** treatment for **every patient**.

To achieve this vision, we aim to individualize treatment through genetic profiling and biology-driven imaging for patient selection and the use of chemotherapy, targeted agents or immunotherapy during radiotherapy. Besides, patients' preferences will be taken into account. To ensure optimal shared decision making, data on both tumor control and toxicity profiles will be made available.

Based on this 2030 vision, the ongoing and future research addresses 1) optimization of the therapeutic window by increasing efficacy and decreasing toxicity, 2) better patient selection for better individualized treatment management, and 3) acquisition of information for shared decision making. The research activities within the division of radiation oncology are mostly clustered within four of the five institution wide

HIGHLIGHTS

- In October 2019, we treated the first patient with liver metastases with motion compensation on our Elekta Unity MR-Linac system.
- Prof. dr. C.A.M. Marijnen has been appointed as chair of the cluster of Radiation Oncology
- The 2030 research vision has been defined

themes: personalized treatment, immunotherapy, image guided treatment and survivorship. Most research projects have a multi-disciplinary character, combining clinical, physics, biological and/or epidemiology efforts, with a strong focus on translational research and innovation.

PERSONALIZED RADIOTHERAPY

Personalized radiotherapy aims to individualize treatment through the use of genetic profiling and biology driven imaging for patient selection and the use of targeted agents during radiotherapy. The ongoing and future research addresses 1) novel insights in the irradiation response of tumors, 2) better patient selection for better individualized treatment management, and 3) optimization of combined-modality-targeted therapeutics to increase the therapeutic window. Our research follows the bench to bedside approach with the focus on the clinical needs and opportunities in our daily clinical practice. Importantly, we initiated new and promising collaborations with other research groups to use state-of-the-art pre-clinical tools and to enable innovative translational studies contributing to the personalized radiotherapy treatment approach.

Translational research
Modulation of targeted agents to optimize the radiotherapy outcome

To further improve the success of radiotherapy treatments we develop novel strategies that enhance the local (radiation) response using targeted agents. Besides the underlying mechanism of radiosensitization, the timing of administration of targeted agents during radiotherapy is also crucial. Therefore we study also the potential of advanced MRI imaging techniques to develop MRI guided radiosensitization strategies.

For different radiosensitization strategies we have observed that the timing of administration relative to the RT is critical; 1) In collaboration with the Akkari group we observed different outcomes of the combination of RT and immunotherapy dependent on the timing of the two modalities. We are currently exploiting why this is, and the optimal sequence of this combination treatment. 2) Also, for the radiosensitization strategy of increasing the number of mitotic cells during RT ("mitotic enrichment strategy") we observed both *in vitro* and *in vivo* very promising outcome in which the timing of the agents relative to the RT was critical (and explains the failures of previous historical attempts). This work is done in collaboration with the Van Tellingen group and we are working to move this strategy into clinical trials.

Insight in the different parameters (e.g. oxygenation, cell density) that are important for the radiotherapy outcome before and during the radiotherapy treatment will support guidance of the selection and timing of agents in combination with the radiotherapy dose. In our prospective clinical trial of glioblastoma patients, we collect all these parameters to evaluate how these parameters change during treatment and what critical parameters are in correlation with tumor recurrence. This will be an important first step towards MRI guided radiosensitization strategies.

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Identification and exploitation of DNA repair defects

DNA damage response and repair processes play a role in tumorigenesis and cellular resistance to cancer treatments. We previously identified DNA crosslink repair defects in HNSCC that can be exploited by PARP and other DNA repair inhibitors. This prompted the development of predictive models to identify such defects in tumor specimen of advanced HPV-negative HNSCC patients prior to chemoradiotherapy. We find that such repair defects are associated with poor prognosis and an increased risk for metastasis. These patients however benefit most from high cumulative cisplatin doses, revealing relevance in treatment outcome. Enabled by a multicentric study with 197 HNSCC samples, we further evaluated individual biological determinants of patient outcomes in a multifactorial context and demonstrate a differential role in distant metastasis risk or locoregional control.

Clinical research
Interaction study

High dose radiotherapy is often indicated for patients on systemic targeted agents (including immunotherapy). However, the combination of radiotherapy with a potential radiosensitizer could easily lead to normal tissue damage, while discontinuation of the drug during radiotherapy could lead to rapid disease progression. We currently face a lack of consensus about the optimal strategy in this situation. Although case reports and several phase I/II studies exist, mostly evidence-based data are missing to easily write the urgently needed guideline. Therefore, we developed a draft guideline based on an extensive literature search, combined with all available clinical, pharmacological and radiobiological knowledge. By disseminating this as a dynamic, easily accessible online guideline a standardized approach will be established, including the option to add new drugs. This guideline will be implemented in a national study using a registry of treatment-related toxicity, facilitating an iterative process of toxicity registration and protocol adaptation.

Reducing side effects in breast cancer: PAPBI study

Partial breast irradiation (PBI) instead of whole breast irradiation is a safe alternative for women with low risk breast cancer and has been shown to give less toxicity and better cosmesis. However, with standard postoperative PBI still large volumes are irradiated. When radiotherapy is given preoperatively, more accurate tumor delineation can be performed, resulting in smaller radiotherapy volumes. The results of our phase II PAPBI trial, in which all patients received preoperative PBI are very promising; low complication rates, limited fibrosis/induration in a small volume and good-excellent cosmetic results. The aim of PAPBI-2, a randomized phase III trial, is to confirm the hypothesis that preoperative PBI leads to significantly and clinically relevant less toxicity and better cosmesis compared to postoperative PBI.

Individualizing preoperative radiation for sarcoma patients

After preoperative radiotherapy, with the exception of myxoid liposarcomas, in other sarcoma subtypes the rate of treatment response (defined as less than 5% remaining viable tumor cells) is as low as 8%. Increasing the radiation dose in patients that still have to undergo definitive surgery is probably not clinically feasible. Obviously, investigations into radiation sensitizers maintaining radiation dose are warranted. For this purpose angiogenesis inhibitors seemed logic candidates. After observing the feasibility of the combination of 25 x 2 Gy preoperative radiotherapy with pazopanib, (NCT01985295), a subsequent phase II study confirmed our prior observations of a high pathological complete remission rate (NCT02575066). However, this efficacy was no longer observed after a radiation dose reduction to 18 x 2 Gy, while maintaining pazopanib dose. Further investigations, combining novel targeted drugs (e.g. interfering with the DNA Damage Response pathways) with preoperative radiotherapy are currently being designed and will start to accrue patients in 2020. Obviously, careful monitoring of the treatment response is obligatory is such new combined modality clinical trials. Especially correlating observations by bio-imaging (e.g. perfusion and diffusion weighted MRI imaging) with pathology are imperative.

SURVIVORSHIP

In the last decades, cancer treatments have improved significantly, leading to improved cure rates. Consequently, increasing numbers of cancer survivors are at risk of developing (late) adverse effects, which in turn may affect quality of life (QOL) and long-term survival. Therefore, treatment individualization and optimization to decrease adverse event risk, as well as early detection and monitoring strategies of adverse events are warranted.

Identification of risk groups at increased risk of treatment related adverse events

In 2019 we published two studies assessing the risk of cardiovascular disease after treatment for breast cancer. We showed that myocardial infarction rate after radiation for breast cancer increased linearly with mean whole heart dose (MWHD), with an excess rate ratio (ERR) per Gray of 6.4%. In addition, we showed that heart failure risk increased linearly with increasing anthracycline dose (ERR=1.5% per mg/m^2). MWHD was only associated with heart failure risk among anthracycline-treated women. The results of these studies are currently implemented in risk prediction models. In addition, we published a study assessing subclinical cardiac dysfunction after anthracycline-chemotherapy for breast cancer. We showed that a substantial proportion of young survivors treated with anthracyclines has signs of subclinical cardiotoxicity. For detailed information, please see epidemiology section. Furthermore, performed a prospective study aimed at evaluating the prevalence of colorectal neoplasia in Hodgkin lymphoma survivors at increased risk of colorectal neoplasia. We showed that Hodgkin lymphoma survivors treated with abdominal radiotherapy and/or procarbazine have a high prevalence of advanced colorectal neoplasia.

The results of these studies show that development of preventive strategies should be considered for patients at increased risk of late treatment-related effects.

Treatment optimization to reduce side effects

The results of the multicenter randomized phase III trial (NCT01780675) to investigate neuro-cognitive functioning and safety of prophylactic cranial irradiation (PCI) with or without

hippocampus avoidance in Small Cell Lung Cancer (SCLC) were analyzed in collaboration with the PSOE department. In between April 2013 and March 2018, 168 patients were recruited in 10 centers in the Netherlands and Belgium. 84 patients were randomly assigned to receive conventional PCI and 84 to receive HA-PCI. The stage distribution was 70% limited- and 30% extensive stage. In this randomized phase III trial of SCLC patients HA-PCI compared to conventional PCI did not affect neuro-cognitive decline. No increase in brain metastases was observed. Conventional PCI remains the standard of care.

Accurate monitoring and modeling of adverse event development

Recent trials showed that the use of patient reported outcomes (PROs) to monitor symptoms during and after cancer treatment does not only improve adverse event management but also significantly improves QOL and overall survival. These promising results emphasize the increasingly important role of the PRO symptom monitoring tools and the need to implement these tools within clinical practice. To implement patient-reported symptom monitoring, we work on implementation of PROs for all relevant tumor types in the department.

Gaining more knowledge on who develops which toxicity and when, will facilitate dynamic modeling to update toxicity risks. By both incorporating time-varying covariates and allowing for time-varying effects, more accurate and real-time toxicity risks can be generated for each patient during treatment and follow-up.

These models will enable physicians to more precisely assess a patients' real time toxicity risk at each follow-up moment during and after treatment, allowing for direct treatment adaptation. Tailoring treatment to the individual risk of developing a specific toxicity from a specific point in time will lead to real-time personalized decision making. Therefore, we are working on developing such models by incorporating longitudinal and dynamic information of, for example, MRI scans derived from the MR-linac during treatment.

IMAGE GUIDED RADIOTHERAPY

Spatiotemporal inter- and intra-tumor variability challenge optimal treatment selection and delivery. Imaging allows to quantify such variability non-invasively. Image guided radiotherapy is the process of image acquisition, image processing and treatment modification for optimal treatment selection and delivery. Our image guided research activities span a broad range of disease sites and all major imaging modalities.

Adaptive Radiotherapy

Day-to-day shape variation in the rectum CTV results in considerable geometric uncertainties during rectal cancer radiotherapy. The purpose of this study was to increase the accuracy of treatment delivery by building a population-based library of planning CTVs for rectal cancer patients and to evaluate its potential for rectum PTV margin and PTV volume reduction. We created signed distance maps from the planning rectum CTV to each of the repeat CTVs to create the library of nine planning CTVs. For each of the repeat CTVs the best

fitting CTV structure in the library was automatically selected and residual distance maps were calculated from which a new PTV margin was constructed. Residual errors were found to decrease with the number of plans in the library, but adding more than five plans yields negligible further error reduction. Margin reduction of up to 50% was achieved at the upper-anterior site of the mesorectum. In conclusion, a library of plans strategy for rectal cancer based on population statistics is feasible and results in a considerably reduced average rectum PTV volume compared to conventional radiotherapy.

MRI-guided radiotherapy

To improve the precision of dose delivery in the clinic, the department of Radiation Oncology has started MRI-guided radiotherapy with the Elekta Unity system. The department participates in the MR-linac consortium to further develop the methodology and conduct joint clinical trials. The NKI leads the consortium tumor site groups on rectal cancer and oligo-metastases.

The first year of clinical use has focused on the development of treatment techniques and establishing strategies for daily on-line adaptation of varying complexity. As the continuous presence of a radiation oncologist and a medical physicist during adaptive radiotherapy is not sustainable, we spend considerable effort to develop more efficient workflows that can safely be executed by radiotherapy technologists. Adapt-to-rotation was introduced for prostate cancer, resulting in an accurate treatment without the need for daily contouring. Decision tools were developed to assess the quality and physical reliability of adapted treatment plans.

Clinically, these methods are now applied for prostate cancer, rectal cancer and oligometastases. For treatment of rectal cancer, we have started with daily plan adaptation based on the anatomy of a given day. For treatment of cancers in the abdomen, a 4D-MRI technique was developed from which the mid position of the tumor during breathing motion can be derived, as well as the amplitude of the motion. In 2019, we were the first to treat patients with liver cancer with this technique worldwide. While the regulatory environment has become challenging, we aim to continue to bring these novel technologies to routine clinical care.

Quantitative MRI for radiotherapy

To realize our vision of daily adaptive treatments, the development of imaging biomarkers is necessary to track changes in relevant characteristics of the cancer and healthy tissue. The work on quantitative MRI techniques has been expanded to the MR-linac, demonstrating that daily acquisition of quantitative MRI sequences is feasible without prolonging the treatment time. This makes the Unity system uniquely suitable for MRI biomarker studies for response assessment.

EPID Dosimetry

In vivo EPID dosimetry is meant to trigger relevant differences between delivered and planned dose distributions. As part of the project to develop *in vivo* portal dosimetry for the Unity MR-linac, we performed a study characterizing the device for EPID dosimetry in 2018. We have now demonstrated the feasibility of two-dimensional (2D) EPID dosimetric verification for the Unity

MR-linac by comparing back-projected EPID doses to ionization chamber (IC) array dose distributions.

Despite the availability and simplicity of use of EPIDs, detector arrays are regarded as gold standard for patient specific QA. The purpose of this study was to perform a direct comparison of (transit and non-transit) EPID dosimetry against absolute dose measurements in 3D, made with the Octavius 4D system (PTW Freiburg, Germany). Two detector arrays were used: the Octavius 1500 and Octavius 1000SRS. 3D dose distributions for 68 VMAT arcs, and 10 IMRT plans were reconstructed within the same phantom geometry using both methods, and compared by means of γ evaluation. The γ-pass rate values were higher than 95% in 150 of 156 cases, demonstrating that both transit and non-transit EPID dosimetry are equivalent in dosimetric terms to conventional detector arrays for patient specific QA.

Individualizing irradiation treatment for Head and Neck patients

The SPECT-guided elective unilateral nodal irradiation was completed in January 2018. In this proof-of-concept study, 50 patients with T1-3N02b head and neck squamous cell carcinoma limited to the midline were treated electively to one side of the neck instead of the current standard of care where patients with these tumors are electively treated to both sides of the neck in order to reduce the risk of contralateral recurrence. The preliminary results are very promising. After a median follow-up of 33 months, only one patient (2%) developed contralateral regional failure after unilateral elective irradiation. Furthermore, the severity, frequency and duration of different troublesome acute and late radiation-related toxicities such as the need for tube feeding and xerostomia were significantly reduced, compared to the historical cohort treated to both sides of the neck at our institute. The follow up study (SUSPECT II) has started and will investigate in 90 patients whether the contralateral draining lymph node harbor malignancy by performing sentinel node procedure in patients with contralateral hot spot on the SPECT/CT.

Dose painting for prostate cancer

The FLAME trial, a multi-center phase III randomized trial of dose escalation in prostate cancer using external-beam radiotherapy, will reach its primary endpoint of 5y biochemical failure free survival in 2020. In this study, a focal boost to the visible tumor inside the prostate to a dose of 95 Gy was given and compared to the standard treatment of 77 Gy to the gland. In total 571 patients have been randomized.
Preparing for the analysis of the primary endpoint, we have validated the contouring of the tumors inside the gland, investigated the boost dose that actually was delivered to the tumors and developed methods for localization and contouring of recurrent prostate cancers. Moreover, in collaboration with Dr. Ivo Schoots, we used a cohort of patients who received multi-parametric MRI prior to prostatectomy, to investigate the histological characteristics of the cancers that were partially missed during contouring.

Artificial intelligence

Artificial intelligence in general and deep learning specifically is a rapidly developing field that is likely to impact many aspects of the radiotherapy chain. Therefore, we are expanding our AI related research where currently 9 PhD students and postdocs are focusing on AI related projects. Similarly, our high-performance computing capacity is rapidly expanding. AI related projects range from image reconstruction and image analysis to outcome prediction. More specifically, deep learning based reconstruction of under-sampled MRI acquisition using recurrent inference machines improves image quality compared to state of the art reconstruction approaches and is robust against changes in contrast and field strength. Similar approaches are evaluated for 4D MRI methods as well as in-room cone beam CT reconstruction. U-net based net-work designs are being optimized for auto-segmentation of both organs at risk and target volumes as well as for deformable image registration. Convolutional neural nets also were shown to improve portal dosimetry reconstruction accuracy in the Elekta Unity MR-linac. Finally, deep learning is being explored to predict treatment outcome based on multi-modality imaging.

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Division of
Pharmacology & Biometrics

The division of Pharmacology & Biometrics was founded in 2016. Every year, we organize a symposium to exchange information and tighten cohesion between the Pharmacology and Biometrics departments. Drug research is one of the major themes that connects us. In 2019, Immunotherapy was the theme of our annual symposium. Research programs in the *Pharmacology* team focus on drug manufacturing, including cellular immunotherapies, bioanalysis and pharmacokinetics - pharmacodynamics of (anticancer) drugs for both preclinical and clinical projects. In the *Biometrics* team, we focus on collection and analyzing of clinical data and interpretation.
A major event in 2020 will be the move of the Pharmacy department, after more than 40 years, from the old Slotervaart hospital building next door to a brand-new building (Building I) on the NKI premises. The new pharmacy building houses modern, state-of-the-art facilities for drug storage, dispensing, manufacturing, laboratory and support services. This enables us to continue our work and to provide daily pharmaceutical patient care and research in accordance with the highest international standards.

PHARMACOLOGY

Drug manufacturing

In 2019 we continued to support >20 mono- and (international) multi-center clinical trials (*e.g.* DRUP, POSEIDON, SUBITO, SENSOR) with drug manufacturing, packaging and distribution. In-house manufacturing of vorinostat capsules and oral solid dispersion tablet formulations of docetaxel (ModraDoc006) proceeded for ongoing clinical studies. The BioTherapeutics Unit (BTU, headed by pharmacist Joost van den Berg) is the biotech facility from the Antoni van Leeuwenhoek Pharmacy where biotechnological products are developed and manufactured for clinical trials. In the past year, we continued the production of Tumor Infiltrating Lymphocytes (TIL) infusions for metastatic melanoma patients treated in the first multi-center phase III trial with TIL therapy in the world. This unique and fully academic trial now includes 96 enrolled patients (30 patients were included in 2019, a two-fold increase compared to 2017 and 2018). In 2019, BTU produced 7 TIL products in-house and guided the production of another 6 productions by neighbouring blood bank Sanquin. BTU has previously produced DNA vaccines for HPV induced malignancies. The second generation of vaccines are currently tested by the Gynaecology department (prof. G. Kenter). In 2019, 4 patients have been treated in this trial. Total enrolment is now almost finalized (13/14) for this phase I/II clinical trial. No substantial toxicity has been observed and vaccine-induced T cell responses have been observed.

In parallel to current clinical production activities, BTU is preparing itself for future clinical trials. We are aiming to apply TIL therapy in other malignancies. In our collaboration with NEON therapeutics (Cambridge, MA), we develop new T cell therapies directed against patient specific neo-antigens. In this product, patient-unique, neo-antigen directed T cells are cultured from autologous peripheral blood by several rounds of peptide stimulation. For this collaboration, large scale engineering runs have been successfully executed. Submission of the Investigational Medicinal Product Dossier (IMPD) and clinical study is scheduled for end 2019. The pharmacy holds a governmental GMP (Good Manufacturing Practice) license for these manufacturing activities of pharmaceutical products.

Bioanalytical method development + implementation in pharmacokinetic studies

Therapeutic Drug Monitoring (TDM) is a useful tool to optimize the dose of orally-administered anticancer drugs if a clear relationship between the dose and exposure, exposure-response and/or exposure-toxicity has been established. According to several clinical studies, such relationships might exist for poly (ADP-ribose) polymerase (PARP) inhibitors. To support the TDM of this relatively new class of compounds, a liquid chromatography-mass spectrometry (LC-MS/MS) assay was developed and validated for the combined analysis of the five PARP inhibitors niraparib, olaparib, rucaparib, talazoparib and veliparib. A simple and fast sample pre-treatment method was applied by protein precipitating of plasma samples with acetonitrile and dilution of the supernatant with formic acid (0.1% v/v in water). This was followed by chromatographic separation on a reversed-phase UPLC BEH C18 column and detection with a triple quadrupole mass spectrometer operating in the positive mode. Beside PARP inhibitors, we supported the TDM programme of another 39 orally-administered anticancer drugs and in 2019 more than 6,000 plasma samples were analysed for this purpose.

For a proof-of-concept study to determine the absolute bioavailability of oral imatinib (Glivec®) during steady state plasma pharmacokinetics in cancer patients, we developed an LC-MS/MS method to quantify orally-administered imatinib (400 mg once daily) and deuterium-labelled imatinib (imatinib-D_8), administered intravenously as a single 100 μg microdose. For both analytes, imatinib-$^{13}C,D_3$ was used as an internal standard. After concomitant administration of an intravenous microdose and an oral therapeutic dose, large differences in systemic plasma concentrations of these analytes emerge. This requires adequate drug labelling of the microdose, as the unlabelled drug might interfere in higher mass transition channels because of the presence of naturally abundant isotopes. Furthermore, the labelling locations should be selected outside the metabolic hot spots to prevent a kinetic isotope effect. The results of the study demonstrate the potential to use a stable isotopically-labelled microdose in combination with LC-MS/MS for the assessment of absolute bioavailability. By using the stable isotope labelled microdose trial design, the number of dose events and collected plasma samples can be reduced when compared to a conventional crossover design. Furthermore, it is no longer required to use ^{14}C-radiolabeled drug as the microdose.

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Selected publications

DIVISION PHARMACOLOGY

Arnamo AH, Huitema ADR, Beijnen JH, Nuijen B. Use of leftovers of monoclonal antibody products after partial extraction – A microbiological safety study. J Oncol Pharm Pract 2019

Crombag MRBS, Dorlo TPC, van der Pan E, van Straten A, Bergman AM, van Erp NP, Beijnen JH, Huitema ADR. Exposure to Docetaxel in the Elderly Patient. Pharm Res 2019;36:181(1-9)

Martínez-Chávez A, Rosing H, Hillebrand MJX, Tibben MM, Schinkel AH, Beijnen JH. Development and validation of a bioanalytical method for the quantification of the CDK4/6 inhibitors abemaciclib, palbociclib, and ribociclib in human and mouse matrices using liquid chromatography-tandem mass spectrometry. Anal Bioanal Chem 2019;411:5331-5345

Roosendaal J, Rosing H, Lucas L, Gebretensae A, Huitema ADR, van Dongen MG, Beijnen JH, Oganesian A. Mass balance and metabolite profiling of (14)C guadecitabine in patients with advanced cancer. Invest New Drugs. 2019

BIOMETRICS DEPARTMENT

Van der Velden DL, Hoes LR, van der Wijngaart H, et al. The Drug Rediscovery protocol facilitates the expanded use of existing anticancer drugs. Nature 2019;574(7776):127-31

Hol JA, Lopez-Yurda MI, Van Tinteren H, et al. Prognostic significance of age in 5631 patients with Wilms tumour prospectively registered in International Society of Paediatric Oncology (SIOP) 93-01 and 2001. PLoS One 2019;14(8):e0221373

Irtan S, Van Tinteren H, Graf N, et al. Evaluation of needle biopsy as a potential risk factor for local recurrence of Wilms tumour in the SIOP WT 2001 trial. Eur J Cancer 2019;116:13-20

Rozeman EA, Menzies AM, van Akkooi ACJ, et al. Identification of the optimal combination dosing schedule of neoadjuvant ipilimumab plus nivolumab in macroscopic stage III melanoma (OpACIN-neo): a multicentre, phase 2, randomised, controlled trial. Lancet Oncol 2019;20(7):948-60

Voorwerk L, Slagter M, Horlings HM, et al. Immune induction strategies in metastatic triple-negative breast cancer to enhance the sensitivity to PD-1 blockade: the TONIC trial. Nat Med 2019;25(6):920-8

To date more than 30 anti-cancer monoclonal antibodies (mAbs) have been approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA). The increasing popularity of these therapeutic proteins has led to a growing demand for accurate and reliable bioanalytical methods of these macromolecules to support clinical studies. The data generated by these methods could help in better understanding of the drug pharmacokinetics including concentration of the drug over time and distribution of the drug in different bio fluids. These data might aid in optimizing treatment and assessing appropriate dosing schedules. Quantitative LC-MS analysis of mAbs faces great analytical challenges. Plasma and serum contain an abundance of endogenous proteins and their concentrations may vary more than 10 orders of magnitude. These compounds could potentially interfere with the MS signal and complicate the analysis of relatively low levels of therapeutic mAbs. Besides, high molecular weight proteins such as mAbs are likely to distribute over many charge states in the MS, dropping the signal intensity per charge state significantly. In order to reduce interferences and improve sensitivity, sample clean-up and enzymatic digestion yielding peptide markers was selected for the quantification of nivolumab and pembrolizumab in human serum. Our newly obtained quadrupole time-of-flight accurate mass spectrometer is now used to setup a method for the quantification of these MAbs in human serum.

We continued to support pre-clinical pharmaceutical research with carboplatin, cisplatin, endoxifen and olaparib. Samples from pharmacokinetic interaction studies with multidrug efflux transporters and multidrug metabolizing enzymes in vitro transport systems and from knockout and transgenic mice were analysed (abemaciclib, ribociclib, milciclib, tivozanib, capecitabine, irinotecan, vinorelbine, morphine and ibogaine). Routine analysis to support clinical trials within and outside the Institute concerned docetaxel, capecitabine, vorinostat, doxorubicin, daunorubicin, etoposide, gemcitabine, vincristine and platinum (originating from cisplatin, carboplatin and oxaliplatin). Dihydropyrimidine dehydrogenase substrate uracil was quantified in serum of patients for a multicentre study to prevent the increased risk of developing severe fluoropyrimidine-related toxicity.

In recent years, we have been involved in designing the new pharmacy facility and we are looking forward to move into the new building in 2020.

Pharmacokinetic and Pharmacodynamics (PK/PD) modelling and simulation

The modelling and simulation group of the department of Pharmacy & Pharmacology maintains a high-performance computational server, part of the NKI Research HPC facility, dedicated to PK/PD modelling and simulation purposes. The group develops modelling methodologies to relate drug exposure to diverse measures of treatment outcome for both toxicity and efficacy. PK/PD modelling and simulation has been applied to optimize therapy of approved anticancer and novel agents used in clinical trials. This research focussed mainly on PK and PD in special patient populations typically underrepresented in clinical trials. We have developed a PK/PD model for bortezomib in children. In this model the relationship between body size and PK was studied and the relationship between PK and proteasome inhibition in PBMCs was quantified. For docetaxel further PK

and PD studies were performed: (i) showing that castration-resistant prostate cancer patients have a lower exposure to docetaxel and consequently less neutropenia and (ii) the complex pharmacokinetics of oral docetaxel in combination with ritonavir has been described in a population PK model.

Since 2010, a large-scale Therapeutic Drug Monitoring program is operational for precision dosing of oral anticancer agents. Most kinase inhibitors have a narrow therapeutic index. However, the currently approved dosing paradigm is a "one-size-fits-all" approach. We implemented TDM for these drugs in clinical practice, where plasma concentrations are routinely measured and reported to the treating physician together with a clinical pharmacological review and dosing advice. In 2019 this program has been expanded with newly introduced compounds. We have shown that exposure to abiraterone and pazopanib in patients with low exposure can be increased in a cost-neutral way by concomitant intake with food (abiraterone) or by splitting the dose (pazopanib).

In collaboration with the Department of Nuclear Medicine, a program was started to use PK/PD modelling and simulation for optimization of the use of radio-pharmaceuticals for diagnostic and therapeutic purpose. Within this program we aim to optimize 1) the selection of peptide, 2) peptide content and 3) administered radioactivity for radionuclide labelled peptides used in clinical practice.

Our program on treatment optimization of the repurposed anticancer PI3K/Akt inhibitor miltefosine for the neglected tropical parasitic disease leishmaniasis has been extended to other antibiotics, with various clinical PK/PD studies initiated and ongoing in 2019 in India, Bangladesh, Sudan and Kenya, funded partially through H2020. We showed that children with leishmaniasis require a higher mg/kg miltefosine dose to effectively treat the disease. To support the translation of preclinical drug candidates to the clinic, we have expanded our modelling expertise and activities towards physiologically-based pharmacokinetic modelling (PBPK) to enable the prediction of target site/target tissue exposure, based on physicochemical properties of compounds, as well as translation of animal to human PK.

BIOMETRICS

The Biometrics Department serves as the medical data center of the institute and provides the infrastructure for clinical research through biostatistical support, centralized patient data collection and documentation, data processing and coordinated administration and monitoring of clinical trials. The statisticians and projects managers collaborate in clinical research projects both within the institute and in national and international multicenter studies. Working procedures follow Good Clinical Practice and reporting and data sharing follow National and International laws and guidelines.

Tumor Registries

Three important types of registries are maintained by the tumor registry group. Traditionally, and since 1977 electronically, the group collects data from dossiers of patients visiting the hospital with benign tumors, pre-malignant, and malignant tumors. Depending on the clinical involvement at the hospital with respect to the diagnosis and therapy of the tumor, the number of items collected ranges from minimal to very extensive. The registry allows querying medical information for indicators, research projects and policy matters. From July 2018 until July 2019, 10.505 tumors were added to the register. A selection of cases of about 3500 tumors, who have been diagnosed and/or treated primarily in the Netherlands Cancer Institute, is sent to the National Cancer Registry at regular intervals.

A second series of registries belongs to the category of quality registers. Most of these registries are developed by the Dutch Institute for Clinical Auditing (DICA). DICA aims at creating valid monitoring systems for quality in healthcare by collecting a fixed set of items of interest per area over time. The system is set up to continuously audit quality of care through online benchmarking, taking patient- and disease characteristics into account. Between July 2018 and July 2019, 2498 patients were registered in 12 different specialized cancer registries, i.e. breast (NBCA), colorectal (DCRA), upper gastro-intestinal (DUCA), lung surgery (DLCA-S) and lung radiotherapy (DLCA-R), melanoma (DMTR), gynecologic (DGOA) and gynecologic radiotherapy, liver (DHBA) and head and neck cancer (DHNA). An implant registry (DBIR) is generated directly from the electronic sources and last year a bladder cancer registry (BlaZib) was started, organized by the IKNL. A substantial amount of data in the registries is recorded in an unstructured way. In collaboration with information specialists from the department I&A, efforts are made to complete the registries more efficiently by connecting various electronic sources and writing sophisticated queries.

A third registry, starting from July 2015 is the Landelijke Basisregistratie Ziekenhuiszorg (LBZ). This is a registry of medical, administrative and financial data of patients at the outpatient clinic, the daycare department or who have been hospitalized. Key aspects are the use of ICD-10, an international coding system for diagnosis, and a standardized list of medical activities.

In 2018 the DataDesk was introduced in the institute. The DataDesk is a virtual desk for data- and information requests from anywhere in the institute: e.g. scientific research, business and management questions and clinical questions in general (quality-, diagnostics-, treatment related). The idea is to facilitate researchers, clinicians and staff by providing one single point of access for all questions. Questions can be asked by completing in a web-form. Questions and answers are recorded, stored and are thus retrievable. A team is available to answer questions either directly, by using the tumor registry or other sources from the data warehouse (DWH) or to relay the questions to the relevant subdesks, i.e. experts in particular areas with access to specific sources of data. Before answering, a request is checked for the necessary approval, which is, in case of individual personal data permission of the Institutional Review Board (IRB) or the Medical Research Ethics Committee (MREC). The department plays a central role in this process and is training new desk employees. In 2018, 500 questions were centrally recorded and in 2019 more than 600.
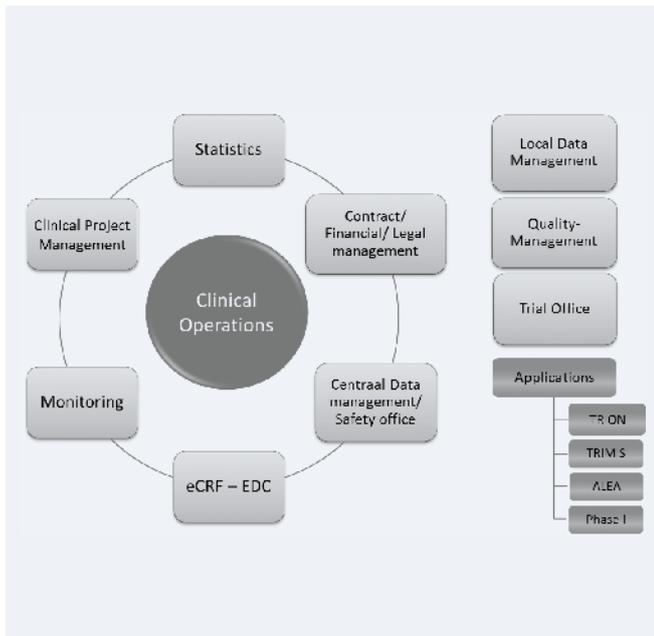
Figure 1. Clinical Trial Service Unit
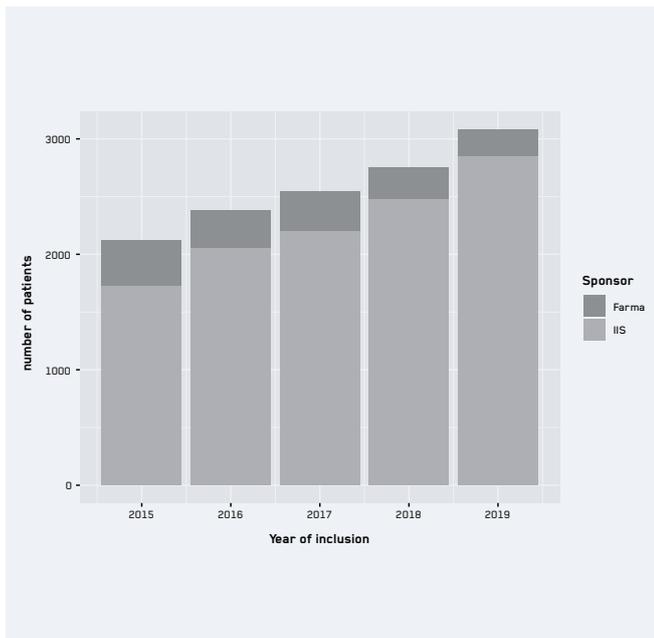
Figure 2. Number of patients enrolled in
WMO-studies in the past 5 years

Clinical Trial Service Unit

The Biometrics Department provides logistic support for clinical trials performed in and by the institute. For a full investigator-initiated trial there is a line-up of people involved: Clinical Project Managers facilitate the development of protocols and submission to Medical Research-Ethics Committee (MREC) and coordinate the projects; local data managers facilitate the initiation of studies and perform the registration of pre-screening, screening and entry of patients into clinical trials. They perform drug resupplies and are the source of information with regard to clinical trials in general. Central data management designs the Case Record Forms and takes care of the quality of the central data bases of investigator-initiated studies and monitors these to ensure that the clinical trials are conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP) and the applicable regulatory requirement(s). All processes follow a Quality Management System which was formally introduced in 2018 and is based on ICH-GCP(R2) and published on the internal document management system (figure 1).

The number of studies – approved according to the Medical Research Involving Human Subjects Act (WMO) – open for patient inclusion over the past 5 years is ranging between 230 and 250, while the number of patients registered still increases. In 2019 well over 3,000 patients were registered centrally in one of the WMO-approved studies (figure 2).

Methodological support to clinical trials

In October, the first results of the Drug Rediscovery Protocol Study (DRUP) were published in Nature. The study is an adaptive, precision-oncology trial that aims to identify signals of activity in cohorts of patients, with defined tumor types and molecular variants, who are being treated with anticancer drugs outside of their approved label. Currently more than 140 cohorts are opened and over 500 patients have been included. The study makes use of a novel design called a master protocol, e.g. multiple hypotheses are investigated through concurrent and adaptive sub-studies. The DRUP study is actually a combination of basket trials (targeted therapy is evaluated on multiple diseases) and umbrella trials (multiple targeted therapies for a single disease that is stratified into subgroups on the basis of specific molecular alterations). Each single cohort has a Simon-like, two-stage design in which for the first stage 8 patients need to be enrolled and at least 1 response needs to be observed to continue to the next stage, where up to 24 need to be enrolled and 5 or more patients have to experience clinical benefit to call it a successful cohort. Similar master protocols are running in North America and Canada. Together with statisticians from the other groups, we are working on solutions for the fact that due to low prevalence of many genomic variants there is a finite number of patients that can be enrolled in a specific cohort. Our aim is to provide practical guidance on how best to share or combine efficacy data across the three trials (TAPUR, DRUP and CAPTUR) and which will enable each group to achieve their objectives. A PhD student is studying unbiased estimators of (incomplete) cohorts, multiplicity of inference and methods for combining and sharing in the context of master protocols.

Within the international pediatric renal tumour study group (SIOP-RTSG), data of both the 9301 and the 2001 study are an important source for unique analyzes. For example, the prognostic significance of age was studied in a cohort of 5631 patients with Wilms tumour (WT)[2] and needle biopsy was studied as a potential risk factor for local recurrence in 969 biopsies out of 2971 patients. The UMBRELLA protocol was approved in the summer of 2019. This is a registration study and trial providing a detailed treatment plan for primary and recurrent WT and a randomized trial for metastatic patients. Biobanking of material is part of the standard procedure for participating. The department has created the ALEA database that makes it possible to collect detailed clinical data, but also allows uploading DICOM images. A 'trusted-third-party'-solution guarantees the privacy and security of the data. Currently, data on the first 100 patients from 8 different countries have been entered, including for example Brazil and China. A large number of countries around the world is lined-up to be initiated.

The number of immunotherapy studies and the number of patients included in those studies is ever-increasing. In 2019, the OpACIN-neo trial was published and identified - echoing the earlier OPACIN trial - a feasible combination dosing schedule for broader clinical use in melanoma patients. Also, the results of the randomized multi-cohort TONIC trial were published. The TONIC trial aimed at identifying a treatment strategy that may be utilized as priming strategies to improve the efficacy of PD-1/PD-L1 blockade in Triple Negative Breast Cancer. The study applied a 'pick-the-winner' strategy, considering clinical responses and translational findings, with a Simon's two-stage design to decide which cohorts would be expanded. Mostly based on the translational results of the TONIC study, the TONIC-2 study will be opened in 2020.

Koen Verhoef

Head Technology Transfer Office

Koen Verhoef Manager
Marije Marsman Senior business developer
Tim Moser Senior business developer
Anje Raven Business developer
Hylke Galama Senior legal counsel
Marin Hubertus Legal counsel
Tim de Jong Legal counsel
Stephanie de Meza Legal counsel

INTRODUCTION

The Technology Transfer Office (TTO) helps NKI-AVL researchers and clinicians in concluding contractual agreements around research collaborations and -materials, both with other academic research institutions as well as with industry.
TTO is charged with advancing the application of NKI research results in healthcare. One of the major aims of the NKI is to see its scientific breakthroughs being turned into novel products and services that benefit cancer patients and their families. On occasion, NKI applies for patent protection for promising new technology developed within the institution as a means to attract investment from companies for new product development. TTO manages the patent portfolio and other intellectual property assets of the institute and actively engages with life science and healthcare companies and investors who have the commitment and resources to bring our innovations to the market. TTO also handles all consultancy agreements for the institute and has a sizeable portfolio of research materials which it licenses to industry.

COLLABORATIONS ON KNOWLEDGE TRANSFER

Since 2014, NKI-AVL has supported **Maastro Clinic** – a radiotherapy clinic and research centre – in Maastricht with both legal and business development support for Maastro's clinical and pre-clinical research programmes. While the support provided by the NKI-AVL TTO was initially underpinned by temporary contracts, Maastro and NKI-AVL signed a long-term support agreement in 2019.
Also in 2019, NKI-AVL and the Prinses Máxima Centrum (PMC; the dedicated pediatric cancer hospital in the Netherlands) signed a multi-year collaboration on tech transfer, under which PMC and NKI-AVL jointly selected and appointed three legal FTE to work at PMC, supported by further legal and business development expertise from the TTO of NKI-AVL. And NKI-AVL formalized a support agreement with Oncode Institute, under which a number of staff members of NKI-AVL are seconded part-time to Oncode and legal support for the Valorization Team at Oncode is provided by the NKI-AVL TTO.

SELECTED ACHIEVEMENTS
Pyrophosphate drug development for calcification disorders and Pseudoxanthoma elasticum (PXE)
Pyrophosphate (PPi) treatment has potential to treat calcification disorders including the rare genetic disorder PXE, and the research group of Piet Borst played a role in discovering that PPi drugs could be given orally for reduced patient burden and improved treatment. This discovery nonetheless requires further elaboration to be turned into a drug. In late 2019, NKI-AVL entered into an option agreement with **Panorama Research Inc.** to evaluate PPi drug development. In lieu of a full license, we agreed that a lower-risk option evaluation period would allow Panorama to pursue development of improved formulation and dosing of new PPi treatments, as well as to determine the requirements for clinical trials to measure safety and efficacy of these treatments. This option ensured that they would provide best efforts and also established eventual licensing terms. If further development is deemed feasible, Panorama will convert the option agreement to a license, establish a new company, and obtain adequate funding to cover development through clinical proof-of-concept (Phase 2a/b). The eventual license will include socially responsible licensing milestone payments as further development stages are achieved, as well as eventual royalties if the drug reaches the market.

Magnetic localization for improved navigation to biopsied tumors

The research group of Theo Ruers had developed tiny, implantable localization magnets which allow surgeons to return to previously biopsied breast cancer tissue in the event that the biopsy identified malignancy. This technology was the subject of a shared NKI-AVL & University of Twente patent application and was subsequently the basis for a spinoff company – **Sirius Medical** – to be founded. In 2019, NKI-AVL TTO, in conjunction with University of Twente, negotiated a license agreement with Sirius to enable them to use this IP, and if Sirius acquires sufficient funding capital for further investment, the company takes legal ownership of the IP. NKI-AVL is a minority shareholder in Sirius, which expects to achieve CE-marking of its combination beacon-sensor system by mid-2020, and for commercialization immediately thereafter.

HEALTHY IDEAS, HEALTHY RETURNS VENTURE PLATFORM

In 2016, the TTO of NKI-AVL initiated and organized the first joint meeting of venture teams from all Dutch academic hospitals, the Hubrecht Institute and NKI-AVL where these teams pitched their investment proposals to specialized, early-stage life science venture capital investors. Since then, the platform has grown very rapidly and in 2019 crossed international borders when first the Flemish academic research organizations and subsequently the Walloon and Luxemburg life science research centres joined the platform as well. 'Healthy Ideas, Healthy Returns', as the platform is called, is now supported by 28 public research organizations in the Benelux and 38 investment funds and is expanding its activities to become a network organization for early-stage health ventures (www.hihr.eu). The platform receives further support from J&J Innovation through sponsoring and training of venture teams.

TTO 2019 IN NUMBERS*
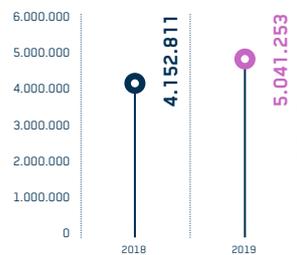
License income: € 5.041.253
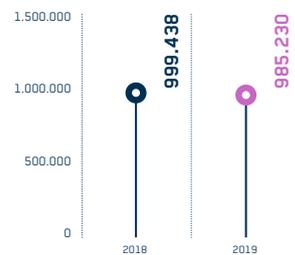
Freely disposable income from commercial research and consulting: € 985.230

In total, 1327 contracts were negotiated and executed in 2019, of which 22 were license agreements.

TTO received 25 invention disclosures and filed 10 priority patent applications in 2019.

Number of research & KT contracts concluded

* some numbers are still provisional at this stage as financial records for 2019 are still to be finalized.

Research facilities

Modern day biomedical research depends on expensive equipment and extensive experience with very specialized techniques. Individual researchers need to use a wide range of techniques for their work. It is impossible for anyone to master them all or to be given the budget to buy all the equipment they are likely to need. The NKI has resolved this problem, and used its funding in the most efficient way, by creating dedicated, centralized technology (core) facilities that serve the whole institute. These research facilities play an essential role in almost all research performed at the NKI. All NKI scientists have direct access to these facilities. Involvement of user committees and periodic review of the facilities ensure that the facilities maintain a high standard and cater to the needs of the researchers.

The facilities of the NKI are offered free of charge to NKI-researchers. In some cases, the costs of consumables are charged to the budget of the research group. There is in principle no restriction on the amount of time one can utilize a certain facility. When extensive support from a facility is required, this is discussed beforehand and in some cases group leaders transfer some of their budget to the facility in order to finance extra support (e.g. for recruitment of extra staff).

Most facilities of the NKI are supervised by a user committee. The Research Council installs these user committees. The user committees consist of faculty members and postdocs, PhD students and/or technicians. They meet at least once a year and they see to the quality of the service provided by the facility and make sure that the facility caters to the need of the researchers. They also review requests for new equipment for the facility and discuss implementing new technologies. The head of the facility and the director of operations are invited to the user committee meetings.

The research facilities of the NKI are presented on the next pages. In addition, the institute has a biometrics facility and a clinical trial unit that both support clinical research (see description under Division of Pharmacology & Biometrics and under Division of Medical Oncology) and a pharmacy which is licensed to manufacture drugs and cell therapies for use in humans (see description under the Division of Pharmacology & Biometrics). In addition to these facilities we also provide the researchers with the following facilities:
– the Biostatistics Center provides statistical expertise to researchers and doctors on diverse topics from all areas of observational and experimental biomedical cancer research. This involves developing and implementing statistical approaches to cover a wide range of subjects including the design and analysis of epidemiologic studies and clinical trials, the identification of prognostic and predictive biomarkers, sample size calculations, risk prediction, as well as animal and in vitro experiments. Members of the Biostatistics Center routinely employ the following statistical methods: parametric and non-parametric hypothesis testing, linear and non-linear regression models for binary responses, continuous and time-to-event outcomes, mixed models for longitudinal data, propensity scores, missing data imputation techniques, competing risk modelling, weighting, exact methods for small sample sizes, simulation studies, cross-validation, and receiver operating characteristic methodology;
– the Data Desk provides access to the fast amount of data collected at our institute over the years: data about diagnosis, treatment, treatment outcome, patient characteristics, et cetera. All these data are collected via different systems, such as the electronic patient records (HiX), pathology databases, clinical laboratory systems. These systems are mined via a data warehouse that brings together the data from a patient or tumor for the different applications. Researchers can ask for a dataset to be retrieved via the data warehouse through the data desk. First, they fill out a brief request form and then a data steward will discuss what they precisely need. This leads to retrieval of the actual information needed to answer their research question and also supports data-minimalization (a requirement of the General Data Protection Regulation). The dataset is handed out after being registered and after a check

has been performed on consent of the patients for use of their data (General Data Protection Regulation requirements). Afterwards, enriched data can be fed into the data warehouse for later use;

– the Sequencing Facility performs DNA sequence and fragment analysis for users in the research divisions and the DNA-diagnostics laboratory of the Department of Human Pathology. The Sequencing Facility has an important role in the diagnostic analysis of patient samples. Its procedures and protocols are therefore accredited by the Accreditation Council (RvA). Researchers from all divisions make use of the service provided by the facility. The facility is equipped with a 3730 DNA analyzer capillary sequence machine, which can handle up to 96 samples simultaneously, and a 3500xL Genetic Analyzer capillary sequence machine. The sequence facility handled approximately 35,000 samples. This type of sequencing can now be done as good, as efficient and for a lower price outside the institute and therefore we will close this facility early 2020;

– in 2019 the NKI got its own Electron Microscope (EM) again. From June until August this system was assembled in the basement. When the built-up was finished people were trained. We now have a 200 kV JEOL F200 EM mounted with a refurbished K2 high resolution camera and software for doing cryoEM on protein complexes. We also have access to EM's at the Amsterdam University Medical Center for morphology in plastic embedded material and quality checking of cryoEM grids that needed to be imaged at NECEN (Leiden) on the 300 kV Titans;

– IT support for the development of software and databases and access to high performance computing facilities. This support is provided through the general IT department of the institute but also through a dedicated group of IT specialists;

– library with dedicated support for data management and literature searches and providing access to a large collection of electronic journals and books;

– cryogenic storage of cells and tissues in a centralized liquid nitrogen storage facility;

– culture labs at different containment levels;

– dedicated labs for working with radionuclides or carcinogens;

– technical workshop that can make modifications to existing equipment or develop new tools;

– glassware cleaning.

Furthermore, researchers are supported by the finance, HR, training, IT, communication and general services departments.

Proteomics Facility
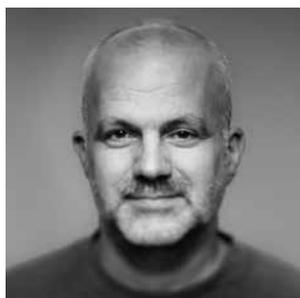
Maarten Altelaar

Head Proteomics Facility

Maarten Altelaar PhD Head
Onno Bleijerveld PhD Senior post-doc
Liesbeth Hoekman BSc Technical staff

Selected publications

Adamopoulos A, Landskron L, Heidebrecht T, Tsakou F, Bleijerveld OB, Altelaar M, Nieuwenhuis J, Celie PHN, Brummelkamp TR, Perrakis A. Crystal structure of the tubulin tyrosine carboxypeptidase complex VASH1-SVBP. Nat Struct Mol Biol. 2019;26(7):567-570

Vlaming H, McLean CM, Korthout T, Alemdehy MF, Hendriks S, Lancini C, Palit S, Klarenbeek S, Kwesi-Maliepaard EM, Molenaar TM, Hoekman L, Schmidlin TT, Altelaar AM, van Welsem T, Dannenberg JH, Jacobs H, van Leeuwen F. Conserved crosstalk between histone deacetylation and H3K79 methylation generates DOT1L-dose dependency in HDAC1-deficient thymic lymphoma. EMBO J 2019;38(14):e101564

The NKI Proteomics Facility supports users from all over the institute to address proteomics questions within their research projects. The facility provides advice, performs proteomics sample preparation, runs the LC-MS/MS systems and performs data analysis. The facility is involved in many research projects and reports on these subjects in scientific publications with NKI investigators.

Equipment and Workflow

Our Facility operates a Thermo Orbitrap Fusion hybrid mass spectrometer equipped with a Proxeon nLC1000 nano-LC system for LC-MS/MS-based peptide/protein identification and quantification. Aided by funding from the NWO X-Omics Initiative, a second, state-of-the-art Thermo Q Exactive HF-X hybrid Quadrupole-Orbitrap mass spectrometer with a Proxeon nLC1200 nano-LC system was installed early 2019.

Researchers contact our facility with their proteomics question(s) and we discuss the optimal experimental design with them. Samples are then typically delivered as either gel (bands), immunoprecipitation beads, cell pellets or lysates. In all cases, the facility then performs sample preparation which involves enzymatic digestion of proteins to peptides for bottom-up proteomics. Depending on sample complexity or the specific research question, samples are pre-fractionated at the protein level by SDS-PAGE, or at the peptide level using a dedicated offline High-pH HPLC fractionation system (Agilent 1200) in order to increase depth of proteome coverage. Peptide samples are run on one of the LC-MS/MS systems, after which data analysis is performed using dedicated software. Finally, data sheets containing identified and/or quantified proteins, protein modification sites, identified protein interactors, regulated proteins/modification sites or pathways are communicated with the researcher.

Over 50 experiments

Projects to which the facility has provided their services include mostly immunoprecipitation experiments aimed at unraveling protein-protein interactions, global proteome profiling of cell lines and post-translational modification-focused profiling such as protein phosphorylation and ubiquitination. In 2019 we have performed over 50 experiments for researchers from 20 research groups within the institute. We saw a clear increase in the number of larger-scale discovery projects employing both whole proteome and phosphoproteome profiling and we expect this trend to continue.

The NKI Robotics and Screening Center

Roderick Beijersbergen

Head Robotics and Screening Center

Roderick Beijersbergen PhD Head
Cor Lieftink MSc Bioinformatician
Ben Morris Technical staff

Selected publications

Tuijnenburg P, Aan de Kerk DJ, Jansen MH, Morris B, Lieftink C, Beijersbergen RL, van Leeuwen EMM, Kuijpers TW. High-throughput compound screen reveals mTOR inhibitors as potential therapeutics to reduce (auto)antibody production by human plasma cells. Eur J Immunol. 2020;50(1):73-85

Wang C, Vegna S, Jin H, Benedict B, Lieftink C, Ramirez C, de Oliveira RL, Morris B, Gadiot J, Wang W, du Chatinier A, Wang L, Gao D, Evers B, Jin G, Xue Z, Schepers A, Jochems F, Sanchez AM, Mainardi S, Te Riele H, Beijersbergen RL, Qin W, Akkari L, Bernards R. Inducing and exploiting vulnerabilities for the treatment of liver cancer. Nature. 2019;574(7777):268-272

Wang C, Wang H, Lieftink C, du Chatinier A, Gao D, Jin G, Jin H, Beijersbergen RL, Qin W, Bernards R. CDK12 inhibition mediates DNA damage and is synergistic with sorafenib treatment in hepatocellular carcinoma. Gut. 2019

The NKI Robotics and Screening Center (NRSC) accelerates research by providing integrated services ranging from functional genomic screening, small molecule screening, high-throughput liquid handling and robotics to data analysis and integration. A major focus of the NRSC is to develop technology platforms for the discovery of gene function, the unraveling of molecular pathways, the identification of novel drug targets and to support small molecule screening. In addition, the NRSC is a resource center that provides automated technologies for medium to high throughput applications, provides support and expertise for automated cell and biochemical assays and is used for the development, production and maintenance of large functional genomic screening reagent collections.

Since the generation of the first NKI human shRNA library in 2002, we have extended our RNAi platform with several large (genome-wide) collections for human and mouse. These collections are available as individual reagents and can be used to generate smaller sub-collections for specific screening projects. We have generated several sub-collections representing gene-sets of interest. In addition to our RNAi platforms we also provide access to CRISPR/CAS9 technologies. We have a pipeline for the production of custom libraries for subsets of genes for specific applications using custom vector designs. We have also acquired different genome-wide sgRNA libraries for human and mouse. In addition, we have incorporated technologies that allow for the (inducible) inhibition (CRISPRi) or activation (CRISPRa) of gene expression in mammalian cells.

In 2019, we have assisted more than 30 researchers with their screening projects. The majority of these projects involved our pooled CRISPR screening platforms and support was given in the design of the screens, providing screening reagents and protocols, the generation of custom sgRNA libraries and data-analysis and interpretation of the screening results. We have also provided individual reagents for validation and follow-up.

We have supported seven small molecule screening projects in 2019. The majority of compound screening projects made use of our compound screening library of ~2500 compounds including those present in the LOPAC collection (1,250 pharmacological active compounds), the NCI diversity and oncology sets, the John Hopkins FDA and foreign approved drugs and bioactive compounds (1,450 compounds) and several enzyme specific collections including kinase, apoptosis, epigenetic modifiers and a collection of protease inhibitors. Recently, we have extended our platform with a drug repurposing collection of more than 5500 compounds that are either approved or in clinical testing. The small molecule collections have been used for cell-based screening for the discovery of synergistic combinations, synthetic lethal interactions, drug-sensitizers, senescence inducers, stress-inducers and drugs affecting cross-presentation.

During 2019, we continued to improve and extend our technology platforms. We have improved our data analysis pipeline for screening results. Originally, pooled screens were largely based on cell proliferation and survival but recently we have extended our pooled screening platforms using other types of read-outs based on single cell markers, protein expression or make use of cellular reporters that reflect cellular processes such as DNA damage and repair. The NRSC is further extending its genome editing capabilities with improved generation of (conditional) knock-out cell lines, single well screens with sequencing-based read-outs using multiplexing and barcoding and single cell technologies.

Jos Jonkers

**Head (ad int.)
Laboratory
Animal Center**

Jos Jonkers PhD Head (ad int.)
Leo Ennen BSc Team leader T2
Marianne Lubbers MSc Team leader T3
Jan Kleinsma Team leader Logistics &
Training
Sin-ming Sit BSc Information manager
Roel Sneepers DVM Veterinarian
Anne Marie Rhebergen DVM
Veterinarian
Mijke de Vreij-Kruidenier DVM
Veterinarian

25 animal caretakers
4 logistics employees

Laboratory Animal Center

The NKI aims to make a significant contribution to solving the cancer problem by conducting excellent research. An essential part of this research involves preclinical experiments with the help of laboratory animals. Thanks to the unique knowledge and expertise, the state-of-the-art facilities, the development and implementation of innovations, and the support of excellent research, the NKI Laboratory Animal Center (LAC) plays an (inter)national leading role in preclinical cancer research with laboratory animals; all this with specific attention to hygiene and safety and respect for our employees and the animals.

Activities
The LAC is a state-of-the-art animal facility housed in a new 8,000 m^2 building that was established in 2013 and became fully operational in 2016. The LAC has a maximum capacity of 21,000 individually ventilated cages (IVCs) for holding wild-type and genetically engineered mice and rats. All animals are housed in disposable IVC systems, which minimizes the risk of cross-infection and obviates the need for a robotics infrastructure for cage-washing.

The LAC provides services to approximately 200 NKI researchers working with mouse and rat models of human cancer. The LAC also provides cancer research services to a growing number of external academic customers and several small pharmaceutical companies in the Netherlands.

The LAC consists of five independent microbiological units:
– The T3 breeding unit is dedicated to nucleus- and production breeding of mice under specific and opportunistic pathogen free (SOPF) conditions. This unit is only accessible for authorized staff of the animal facility. All mouse lines that are rederived via caesarian section or embryo transfer, or recovered from frozen sperm or embryos, are imported into this unit.
– The T3 BSL2 unit is a negative barrier area for BSL2 experiments and infection studies. Depending on the infectious agent, mice are housed in IVCs or isolators.
– The T2 unit is a combined experimental and breeding unit where mice are kept under specific pathogen free (SPF) conditions. T2 supports the Animal Model facility that creates custom-made genetically engineered mouse strains for researchers and performs cryopreservation of mouse strains by freezing sperm or embryos.
– The T1 unit is a negative barrier area that houses the Mouse Cancer Clinic for preclinical imaging and intervention studies with mice and rats. This unit is equipped with small-animal systems for image-guided radiation therapy (IGRT), bioluminescence and fluorescence imaging, MRI, PET-CT, SPECT-CT, and intravital imaging.
– The T0 quarantine and sanitation unit is dedicated to importing mice from non-approved vendors or other research facilities. All mice are sanitized either via embryo transfer or caesarian section.

A team of 25 animal care takers and 2 team leaders are responsible for the day-to-day care of the animals and biotechnical support on T0, T2 and T3. General support is provided by a dedicated logistics team and two office managers. An information manager is responsible for various laboratory animal related IT systems and its output towards end users. Three veterinarians supervise the health and welfare of the laboratory animals. They also support the researchers by contributing to the responsible design and implementation of animal experiments and by proposing possible alternatives.

Lenny Brocks

Facility manager

Marjolijn Mertz

Facility manager

Lenny Brocks PhD Facility manager
Marjolijn Mertz MSc Facility manager
Bram van den Broek PhD Post-doc
Amalie Dick PhD Microscopy manager

Publications

Alvarez L, et al. APPLICATION NOTE: SP8 FALCON: a novel concept in fluorescence lifetime imaging enabling video-rate confocal FLIM. Nature Methods. 2019;16(10)

Dijkgraaf FE, et al. Tissue patrol by resident memory CD8⁺ T cells in human skin. Nat Immunol 2019;20:756-764

Gogola E, et al. Selective Loss of PARG Restores PARylation and Counteracts PARP Inhibitor-Mediated Synthetic Lethality. Cancer Cell. 2019;35(6):950-952

BioImaging Facility

The BioImaging Facility provides scientific and technical support in basic and advanced light microscopy and image processing and analysis. We manage a diverse collection of light microscopes systems for brightfield and fluorescence applications, including widefield, confocal, and superresolution systems. We provide dedicated application trainings to microscope users of the institute and offer courses in light microscopy and image analysis. The BioImaging Facility is part of LCAM (van Leeuwenhoek Centre for Advanced Microscopy, Amsterdam), a formal collaboration between three innovative microscopy centres, located at the University of Amsterdam (UvA), the Academic Medical Centre (AMC) and the Netherlands Cancer Institute (NKI). The BioImaging Facility, together with the Jalink lab and Van Rheenen lab constitute the NKI part of LCAM.

The BioImaging staff provide the following services:
– Setup daily maintenance and regular quality checks of the microscopes
– Expert advice on experimental design and sample preparation
– Microscopy and image analysis training (introductions, workshops, courses)
– Custom solutions for image processing and quantification
– Data storage and backup on a central server
– Small maintenance of microscopes in other departments
– Technical advice for grant applications and microscopy purchases
– Access to and assistance with functional and/or advanced imaging techniques (FRET, FLIM, FCS, SuperResolution, Multiphoton, Intravital Imaging)

Training and courses
– Introduction to microscopy (1,5-day course; eight to ten times a year)
– In the footsteps of Antoni van Leeuwenhoek (5-day graduate school basic microscopy course; twice a year)
– ImageJ/Fiji (Image processing & Analyses course; two to three times a year)
– We regularly (~annually) participate in FEBS- and EMBO-sponsored advanced imaging courses (organized via LCAM)

Equipment list
– A Spinning Disk Confocal (Andor Dragonfly)
– Four Confocal Microscopes: Leica SP5 (2x), Leica SP8, Zeiss Airyscan LSM 980
– A TIRF microscope (Leica)
– Three (live imaging) widefield microscopes (Zeiss Axio Observer Z1)
– A color widefield microscope (Zeiss AxioVert 200M)
– AxioScan slide scanner (Brightfield and Fluorescence) (Zeiss)
– A Macroscope (Zeiss AxioZoom V16 Stereo microscope)
– Three high-end workstations with image processing & analysis software (Huygens, Imaris, Matlab, Leica en Zeiss Zen)
– HIVE: High Speed Centralized Data Repository

Annegien Broeks

Head Core Facility Molecular Pathology & Biobanking

Annegien Broeks PhD Head
Maartje Alkemade Technical staff
Laurie Borghuis Technical staff
Linde Braaf Technical staff
Sten Cornelissen Technical staff
Willem Hoefakker Technical staff
Ingrid Hofland Technical staff
Donne Majoor Technical staff
Dennis Peters Technical staff
Shiva Vonk Technical staff
Lars Leezenberg Datamanager
Wouter Kievit IT staff
Yush Lam IT staff
Sharon Hinrich Logistics staff
Esther Holman Logistics staff
Jose Overwater Logistics staff

Selected publications

Cioni B, Jordanova ES, Hooijberg E, van der Linden R, de Menezes RX, Tan K, Willems S, Elbers JBW, Broeks A, Bergman AM, Zuur CL, de Boer JP. HLA class II expression on tumor cells and low numbers of tumor-associated macrophages predict clinical outcome in oropharyngeal cancer. Head Neck. 2019;41(2):463-478

Rozeman EA, Menzies AM, van Akkooi ACJ, Hansson J, Schumacher TN, Long GV, Blank CU. Identification of the optimal combination dosing schedule of neoadjuvant ipilimumab plus nivolumab in macroscopic stage III melanoma (OpACIN-neo): a multicentre, phase 2, randomised, controlled trial. Lancet Oncol. 2019;20(7):948-960

Visser LL, Elshof LE, Van de Vijver K, Groen EJ, Almekinders MM, Sanders J, Bierman C, Peters D, Hofland I, Broeks A, van Leeuwen FE, Rutgers EJT, Schmidt MK, Schaapveld M, Lips EH, Wesseling J. Discordant Marker Expression Between Invasive Breast Carcinoma and Corresponding Synchronous and Preceding DCIS. Am J Surg Pathol. 2019;43(11):1574-1582

BioImaging Core Facility
Molecular Pathology
& Biobanking Facility

Activities

The Core Facility Molecular Pathology & Biobanking (CFMPB) registers, coordinates, supports and facilitates (translational) research involving human biospecimens (serum, blood, circulating DNA, FFPE and fresh frozen biopsies, DNA, RNA etc.) in the context of optimally controlled medical-ethical issues using the Application & Request tool (ART-IRB for registration and review of studies with human biospecimens & data and new Biobanks).

The CFMPB has fully equipped and dedicated Molecular and a Histology/Immunohistochemistry (IHC) labs. All routine IHC and newly developed IHC protocols (single & multiplex, brightfield and fluorescent), RNA scope and FISH are performed using the BenchMark & Discovery (Ventana) automated stainers (320 protocols; 227 in research setting), all in close collaboration with the Pathology department and the pathologists. The new 3D Histech P1000 & Vectra-3 scanners in combination with slidescore and HALO software tools enable digital pathology and multi-spectral image analysis. In 2020 we will explore new potential high throuput biomarker discovery immune profiling techniques (e.g. MACsima and TissueCytoff). All DNA and RNA isolations from human biospecimens are performed by the CFMPB technicians and in collaboration with clinical chemistry, using the Qiacube or Qiasymphony, according to standard protocols and QC. Molecular analysis techniques like e.g. (RT)-PCR, MLPA, HPV, Sequenom, nCounter Nanostring FLEX are offered. In 2019 we have registered 87 new studies (421 studies up and running) and handled 917 lab requests (including e.g. 30.767 FFPE & 1736 FF numbers, 7831 DNA/RNA isolations and 10.695 IHC & 8570 HE stains).

Protein Facility

Patrick Celie

Head Protein Facility

Patrick Celie PhD Head
Alexander Fish PhD Research associate
Justina Kazokaitè PhD Technical staff
John de Widt Technical staff

Publications

Adamopoulos A, Landskron L, Heidebrecht T, Tsakou F, Bleijerveld OB, Altelaar M, Nieuwenhuis J, Celie PHN, Brummelkamp TR, Perrakis A. Crystal structure of the tubulin tyrosine carboxypeptidase complex VASH1-SVBP. Nat Struct Mol Biol. 2019;26:567-70

Kim RQ, Geurink PP, Mulder MPC, Fish A, Ekkebus R, El Oualid F, van Dijk WJ, van Dalen D, Ovaa H, van Ingen H, Sixma TK. Kinetic analysis of multistep USP7 mechanism shows critical role for target protein in activity. Nat Commun. 2019;10:231

Milne K, Sun J, Zaal EA, Mowat J, Celie PHN, Fish A, Berkers CR, Forlani G, Loayza-Puch F, Jamieson C, Agami R. A fragment-like approach to PYCR1 inhibition. Bioorg Med Chem Lett. 2019;29:2626-31

The genes within the DNA encode all the proteins that a cell requires to stay vital and function properly within a living organism. Proteins are essential molecules involved in almost all biological processes. DNA damage – as occurs in cancer – may cause mutations within genes and hence can lead to generation of dysfunctional proteins. These mutated proteins could become inactive or even hyper-active and cause deregulation of cellular function and -growth. To understand the (dys) function of proteins, recombinant proteins can be designed, produced, purified and subsequently be characterized by a variety of functional and structural methods *in vitro*. The Protein Facility provides dedicated equipment, knowledge and experienced personnel to support all these experiments. Access is offered to both internal and external academic researchers.

Equipment

The facility houses multiple shakers and incubators for protein expression in E. coli, Sf9 insect cells and mammalian cells. Automated chromatography systems are available for purification of proteins at analytical- or preparative scale. Access to a selection of biophysical instruments is offered for protein characterization, including: A Prometheus thermal analysis system (Nanotemper); Biacore T200 SPR (GE Healthcare), VP-ITC (Microcal) and MST (Nanotemper) for protein interaction studies; PHERAstar and CLARIOstar (BMG Labtech) plate readers for fluorescent experiments; SEC-MALLS (GE Healthcare and Wyatt) for determination of molecular weight and composition of protein complexes. The facility also supports high throughput protein crystallization screening and optimization using a CyBi-SELMA (CyBio) liquid dispenser, a Mosquito (TTP Labtech) nanoliter drop setter, a Formulator (Formulatrix) for liquid preparation and two RockImager systems (Formulatrix) for storage and automated imaging of crystallization trials at 4 ˚C and 20 ˚C.

Projects

Within the past year, the facility has provided support to multiple projects filed by more than 10 research groups within the NKI-AVL. Together these projects covered all facets of the facility, from protein- and antibody production to biophysical characterization and crystallization. The facility also maintains a repository of reagents that are of common use to many researchers. These include generally used proteins (enzymes, proteases, antibodies), cloning utilities (expression vectors, cloning reagents) and stock cell cultures.
About 20% of annual facility time has been spent on external projects. These were either initiated through direct collaboration or via access through Instruct-ERIC (https://instruct-eric.eu/), a European infrastructure in structural biology which provides access to high-end technology, and through iNEXT (Infrastructure for NMR, EM and X-rays for Translational Research; www.inext-eu.org/), funded by the Horizon2020 program.

EU Networks

Implementation of new methods and technologies is essential to keep up-to-date with the latest developments in protein research. A useful source has been provided by two EU networks in which the facility participates as an active member: P4EU, a consortium of protein expression facilities in Europe and the biophysical network ARBRE MOBIEU. Both networks organize courses, meetings, benchmarking experiments, sharing of reagents/protocols and discussion of new methods. This year, the facility hosted the first P4EU workshop together with the 15th (bi)annual P4EU meeting here at NKI.

Animal Model Facility
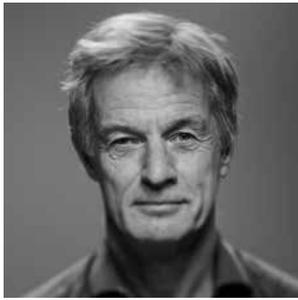
Paul Krimpenfort

Head Animal Model Facility (ad int.)

Ivo Huijbers PhD Head of facility
Paul Krimpenfort PhD Head of facility
(ad int.)
Fina van de Ahé Technical staff
Rahmen Bin Ali BSc Technical staff
Linda Henneman PhD Technical staff
Lona Kroese MSc Technical staff
Jan Paul Lambooij BSc Technical staff
Colin Pritchard MSc Technical staff
Tanya Vermeeren-Braumuller BSc
Technical staff

Selected publications

Annunziato S, de Ruiter JR, Henneman L, Brambillasca CS, Lutz C, Vaillant F, Ferrante F, Drenth AP, van der Burg E, Siteur B, van Gerwen B, de Bruijn R, van Miltenburg MH, Huijbers IJ, van de Ven M, Visvader JE, Lindeman GJ, Wessels LFA, Jonkers J. Comparative oncogenomics identifies combinations of driver genes and drug targets in BRCA1-mutated breast cancer. Nat Commun. 2019;10(1):397

Mørkholt AS, Trabjerg MS, Oklinski MKE, Bolther L, Kroese LJ, Pritchard CEJ, Huijbers IJ, Nieland JDV. CPT1A plays a key role in the development and treatment of multiple sclerosis and experimental autoimmune encephalomyelitis. Sci Rep. 2019;9(1):13299

Van de Vrugt HJ, Harmsen T, Riepsaame J, Alexantya G, van Mil SE, de Vries Y, Bin Ali R, Huijbers IJ, Dorsman JC, Wolthuis RMF, Te Riele H. Effective CRISPR/Cas9-mediated correction of a Fanconi anemia defect by error-prone end joining or templated repair. Sci Rep. 2019;9(1):768

Activities

During 2019, the organizational structure of the NKI Animal Facility has been modified, leading to a change in position of the Transgenic Facility within the organization. This has been a challenging operation asking flexibility and full commitment from all the people involved. While the Transgenic Facility remains a key user at the T2 unit for animal-related procedures, it is no longer an integral part of the Laboratory Animal Center. The decision for this change was based on the fact that a large part of the activities of the Transgenic Facility are executed in the NKI research laboratories. Animal-related procedures are still carried out in close collaboration with the team of animal care takers on T2. In addition, the Transgenic Facility has been renamed Animal Model Facility because its activities also include cryopreservation and revitalization of genetically engineered mouse (GEM) strains, congenic gene mapping and somatic cancer modelling.

In 2019, the activities of Animal Model Facility continue to show an increase of the application of CRISPR/Cas technology in the generation of GEM strains together with a decline of ES cell-based strategies. CRISPR/Cas9-based procedures have now become a routine to generate genetic modifications initially only possible by ES cell manipulation, such as introduction of loxP sites to produce conditional knockout alleles and targeted knock-in of reporter alleles. Consequently, creating mouse strains carrying a wide range of different types of genetic alterations has become much more efficient in terms of generation time and number of mice involved. Nearly all GEM strains are made under full-service conditions covering all steps from vector design to screening of the founder mice and their respective offspring.

During 2019, the Animal Model Facility finalized 22 projects by delivering the modified mouse strains to the client, while it is involved in 35 ongoing projects.
The total number of projects run by the Facility did not change significantly when compared to the previous year. However, there is a shift in customer origin: the number of projects for NKI researchers has declined, whereas the number of projects for researchers from outside the NKI, both from national and international academia, is steadily increasing.

Robbie Joosten

Manager Research High-Performance Computing facility

Robbie Joosten PhD Facility manager
Ismail Koraichi BSc Technical staff
Torben Wriedt MSc Technical staff

Selected publications

Janssen JM, Dorlo TPC, Niewerth D, Wilhelm AJ, Zwaan CM, Beijnen JH2, Attarbaschi A, Baruchel A, Fagioli F, Klingebiel T, De Moerloose B, Palumbo G, von Stackelberg A, Kaspers GJL, Huitema ADR. A semi-mechanistic population pharmacokinetic/pharmacodynamic model of Bortezomib in pediatric patients with relapsed/refractory acute lymphoblastic leukemia. Clin. Pharmacokinet. 2019

Logtenberg MEW, Jansen JHM, Raaben M, Toebes M, Franke K, Brandsma AM, Matlung HL, Fauster A, Gomez-Eerland R, Bakker NAM, van der Schot S, Marijt KA, Verdoes M, Haanen JBAG, van den Berg JH, Neefjes J, van den Berg TK, Brummelkamp TR, Leusen JHW, Scheeren FA, Schumacher TN. Glutaminyl cyclase is an enzymatic modifier of the CD47-SIRPα axis and a target for cancer immunotherapy Nat Med. 2019;25(4):612-619

Van Beusekom B, Wezel N, Hekkelman ML, Perrakis A, Emsley B, Joosten RP. Building and rebuilding N-glycans in protein structure models. Acta Cryst. D 2019;75(4):416-425

Research High-Performance Computing facility

Our facility deploys, maintains, and secures High-Performance Computing solutions for eighteen research groups in the NKI and two research facilities. The facility takes care of the backbone infrastructure and the group-owned computing platforms, so the research groups have the freedom to focus on the science of their computational work.

2019 was a year of consolidation and growth for the facility. The addition of the new electron microscopy facility as a stakeholder required the opening of a second server room in the basement with hardware to process the large amount of microscope data. A fast direct network connection between the server rooms ensures rapid data exchange. This also allowed moving all GPU-computing machines to the downstairs server room. A new 8-way GPU server was deployed for the radiology department, tripling radiology's GPU capacity. This server is the first of its kind at the NKI and can be used as a reference model for further expansion of GPU-computing within the institute. Another new server was added for the pharmacy which, in terms of CPU power, is the largest system in RHPC thus far. More efficient use of existing (and new) hardware was achieved by the setup of queueing systems for GPU and CPU computing.

The facility now has 220 users of 19 machines with in total 1250 CPUs, 3 TB of RAM, and 990 TB of storage. Next to the compute nodes, the facility features 5 high-end GPU-computing workstations, two code repositories, and a lab equipment booking system.

The growth in scale of the facility is more than matched by the growth in scientific output by the facility's users, with a selection of papers highlighted here. In addition to the output in scientific papers, there are several scientific web servers and services plus a large scientific databank hosted by RHPC, see for instance https://phenosaurus.nki.nl and https://pdb-redo.eu. The increasing importance of computing in the NKI's research is apparent in the broadening of our user base and its requirements. To continue to meet the needs and demands of our stakeholders, the RHPC facility will be reorganised over the course of 2020.

Ron Kerkhoven

**Head Genomics
Core Facility**

Ron Kerkhoven PhD Head
Marja Nieuwland MSc Wet-lab team
leader
Arno Velds MSc Bioinformatic team
leader
Roel Kluin MSc Bioinformatician
Iris de Rink MSc Bioinformatician
Shan Baban MSc Technical staff
Wim Brugman MSc Technical staff
Gijs van Riel MSc Technical staff
Charlaine van Steenis MSc Technical
staff
Dilani Sellathurai MSc Technical staff
Jessica Sieljes MSc Technical staff

Selected publications

Scheper W, [...], Schumacher TN.
Low variable tumor reactivity of the
intratumoral TCR repertoire in human
cancers. Nat Med. 2019;25(1):89-94

Voorwerk L, [...], Kok M. Immune
induction strategies in metastatic
triple-negative breast cancer to
enhance the sensitivity to PD-1
blockade: the TONIC trial. Nat Med.
2019;25(6):920-928

Xue Y, [...], Huang S. CDK4/6 inhibitors
target SMARCA4-determined cyclin D1
deficiency in hypercalcemic small cell
carcinoma of the ovary. Nat Commun.
2019;10(1):558

Genomics Core Facility

The Genomics Core Facility (GCF) supports users in all aspects of Next Generation Sequencing experiments in their research projects. The facility is equipped with two Illumina HiSeq2500, a NextSeq550Dx and a MiSeq machine. Support comes from the NKI, the AVL foundation and from the Oncode Institute. We aim to maintain high data quality at lower sequencing costs per base. The facility provides advice, performs library preparation at consumable cost prize, runs the sequencing machines, manages the data storage and performs data analysis. The facility is involved in research projects and reports on these subjects in lectures, scientific publications and conference presentations. The facility makes new technologies and innovative sequencing applications available. Education of students and post-docs is supported by the core. This year we performed the 1000th Hiseq run.

Experiment types
The facility aims to be flexible regarding the types of samples that can be delivered as well as the workflows that are available. A user can hand in tissue, cells, extracted nucleic acids or libraries ready for sequencing. The facility has acquired a lot of expertise in library preparation both from fresh samples as well as from formalin fixed (FFPE) samples. Users receive gene expression profiles, functional synthetic lethal screens, chromatin binding profiles, full genome copy number plots, tumor mutational load (TMB) scores and detected mutation events in tumor-normal whole exome data sets. Common experiment types are RNAseq, miRNAseq, ChIPseq, CNVseq, PCRseq, Methyl-seq and Target Enrichment strategies (exomes, kinomes). We have seen an increase in the TruSeq RNA Exome prep (human FFPE-RNAseq). Besides preparing sequence libraries in house, the facility also performs sequencing on custom prepared libraries (TRC short hairpin screens, functional screens, CRISPR/Cas9 screens and screens for nuclear organization and epigenetics). The knowledge to fine-tune sequencing strategies like sequencing with "dark cycles", multiple primers, barcodes, indices with minimal use of chemistry is much appreciated by users. The facility now also works with smaller inputs (1-10 ng RNA in Smart-seq2) and separate cells are studied in the 10X Single Cell Sequencing.

Workflows, sample database, primary analysis
Standard routine is that users register new samples from their own PC in the sample tracking database GCFdb using a web-based portal. Sample tracking, sequencing monitoring, billing administration, reporting and data maintenance are the main features of this in-house designed software package.

During the actual sample delivery to the core, sequencing setup, settings and expected results are discussed with the user. Projects are assigned to lab technicians keeping users informed of subsequent steps like sample preparation, pooling, sequencing and analysis. We rely on the 8 tube Covaris machine for fragmentation of nucleic acids and are looking into enzymatic fragmentation. User prepared libraries are quantification by qPCR. Data generated by the sequencing machines is stored centrally and secured at the NKI-IT department. Users receive links to primary data files (FASTQ) and have the choice to perform data analysis on their own or to collaborate with the facility for more in-depth analysis. In the last year, new features for data sharing and for easy data transport to in-house network systems were added. Upon finalization of the work, the system calculates the costs for the work done, and a money transfer order is sent out.

Sjoerd Klarenbeek

**Head Experimental
Animal Pathology**

Sjoerd Klarenbeek Pathologist
Ji-Ying Song Pathologist
Lex de Vrije Technical staff
Britt Janssen Technical staff
Ellen Riem Technical staff
Jelrik van der Meer Technical staff
Joost van Ooij Technical staff

Selected
publications

Krimpenfort P, Snoek M, Lambooij JP, Song JY, van der Weide R, Bhaskaran R, Teunissen H, Adams DJ, de Wit E, Berns A. A natural WNT signaling variant potently synergizes with Cdkn2ab loss in skin carcinogenesis. Nat Commun. 2019;10(1):1425

Böttger F, Semenova EA, Song JY, Ferone G, van der Vliet J, Cozijnsen M, Bhaskaran R, Bombardelli L, Piersma SR, Pham TV, Jimenez CR, Berns A. Tumor Heterogeneity Underlies Differential Cisplatin Sensitivity in Mouse Models of Small-Cell Lung Cancer. Cell Rep. 2019;27(11):3345-3358.e4

Klarenbeek S, Doornebal CW, Kas SM, Bonzanni N, Bhin J, Braumuller TM, van der Heijden I, Opdam M, Schouten PC, Kersten K, de Bruijn R, Zingg D, Yemelyanenko J, Wessels LFA, de Visser KE, Jonkers J. Response of metastatic mouse invasive lobular carcinoma to mTOR inhibition is partly mediated by the adaptive immune system. Oncoimmunology (in press)

Experimental
Animal Pathology

Activities

The Experimental Animal Pathology facility provides broad pathology support for research projects involving the use of animals. Our activities include consultancy and collaboration with scientists in all phases of a project, from study design to publication. We help with the dissection of animals and tissue sampling, our technicians process and embed tissues, cut slides and perform a wide range of histochemistry and immunohistochemistry stains. We develop and optimize methods such as immunohistochemistry protocols. We can also process organoids or cells, and provide support for other institutes as well.

Our pathologists partner with researchers in their projects, train and educate personnel, help to perform dissections, and provide detailed microscopic analysis of pathologic changes. Through these activities, we provide content for scientific presentations and publications. In addition, the pathologists perform diagnostic pathology analysis of sick animals, for the benefit of the health and welfare of animals in the institute.

Our pathologic findings play a pivotal role in several projects, revealing temporal and spatial events in the process of tumorigenesis, which leads to a better understanding of tumor heterogeneity and its relationship with therapeutic outcome. For example, it has been shown that different subpopulations of tumor cells in a mouse model of small cell lung cancer (SCLC) responded differently to cytostatic treatment. The re-populating/re-seeding tumor cells in the lung and its surroundings, which were identified by their distribution patterns as well as by immunohistochemistry (negative for E-cadherin, left photograph), were sensitive to the initial chemotherapy by cisplatin. In contrast, the primary lesions of SCLC (positive for E-cadherin) were not sensitive to cisplatin treatment (right photograph). This study was published in Cell Reports in 2019.
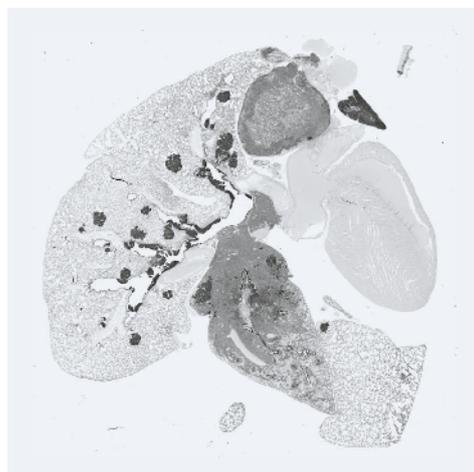
Vehicle treatment of SCLC
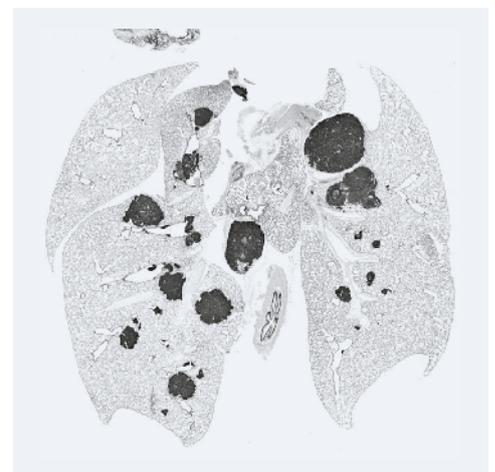
After cisplatin treatment of SCLC

Flow Cytometry Facility

Martijn van Baalen

**Head Flow
Cytometry Facility**

Martijn van Baalen Head
Debajit Bhowmick Operator
Frank van Diepen Operator
Anita Pfauth Operator

Selected
publications

Li H, van der Leun AM, Yofe I, Lubling Y, Gelbard-Solodkin D, van Akkooi ACJ, van den Braber M, Rozeman EA, Haanen JBAG, Blank CU, Horlings HM, David E, Baran Y, Bercovich A, Lifshitz A, Schumacher TN, Tanay A, Amit I. Dysfunctional CD8 T Cells Form a Proliferative, Dynamically Regulated Compartment within Human Melanoma. Cell 2019;176(4):775-789

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The Flow Cytometry Facility provides access to high-end flow cytometers and state-of-the-art cell sorting equipment. We actively support investigators of the NKI with tailored advice and practical assistance in all phases of their experiments with regard to analytical flow cytometry and cell sorting.

The Flow Cytometry Facility maintains six analytical flow cytometers for basic and high-parameter interrogation of biological samples on a single cell level, and five high-end cell sorters for isolation of the cells of interest with high purity. All instruments are housed in BSL 2 lab environment. We are responsible for interactions with instrument manufacturers to schedule routine maintenance and unexpected repairs. Furthermore, routine Quality Assurance and Quality Control is performed to ensure consistent and robust performance. The available equipment provides flexibility and allows for tailored approaches to address a wide range of scientific problems and biological questions.

Our full cell sorting service by expert sort operators allows for bulk isolation and (indexed) single cell sorting of specific cell subsets from heterogeneous samples, based on scatter parameters up to complex immunological panels with 18 fluorescent labels, for a wide range of post-isolation applications. Some examples of post bulk sorting applications are: *in vitro* expansion and functional assays; *in vivo* transplantation; protein, DNA and RNA extraction for applications such as mass spectrometry, sequencing for genetic screens and mRNA expression respectively. Common post-sort single cell applications include: cloning; DamID assays; qPCR; and sequencing.

We strive to meet the investigators' specific needs by providing tailored assistance with experimental design, sample preparation, data acquisition and analysis, enabling the highest possible resolution, data quality and reproducibility. We provide introductory courses to allow independent use of the available analytical instruments and to ensure a high level of theoretical knowledge, optimal instrument use, and data quality. Additionally, we provide introductory and advanced training sessions on theoretical and technical topics related to flow cytometry, and independent operation of cell sorting instruments. We also organize specialized workshops and seminars on topics such as tumor dissociation and other sample preparation methods, optimizing protocols for staining of intracellular targets, and data analysis methods.

Finally, we are actively involved in (inter)national and virtual cytometry networks and instrument user groups to exchange knowledge with colleagues from the wider community, allow investigators of the NKI to benefit from the latest developments and insights in the field of cytometry.

Marieke van de Ven

Head Mouse Cancer Clinic - Animal Facility (T1)

Marieke van de Ven PhD Head Mouse Cancer Clinic
Ben van de Graaff Team leader Mouse Cancer Clinic
Niels de Wit BSc Head of imaging facility
Olaf van Tellingen Head of Pharmacology facility
Manon Boeije BSc Technical staff
Artur Burylo Technical staff
Myrthe Hoogeland BSc Technical staff
Coen Joling BSc Technical staff
Jason Keet BSc Technical staff
Renske de Korte-Grimmerink BSc Technical staff
Ashley Pascual BSc Technical staff
Natalie Proost BSc Technical staff
Bjørn Siteur Technical staff
Justin Sprengers BSc Technical staff
Seven animal caretakers

Selected publications

Annunziato S, de Ruiter J, et al. Comparative oncogenomics identifies combinations of driver genes and drug targets in *BRCA1*-mutated breast cancer. Nat Commun. 2019;10 (1):397

Kopper O, De Witte CJ, et al. An organoid platform for ovarian cancer captures intra- and interpatient heterogeneity. Nat Med. 2019;25(5):838-849

Sun J, Nagel R, et al. SLC1A3 contributes to L-asparaginase resistance in solid tumors. EMBO J. 2019;38(21)

Mouse Cancer Clinic - Animal Facility (T1)

Activities

The Mouse Cancer Clinic / T1 is a facility where advanced mouse models are used as surrogate for cancer patients to identify and validate targets that can be exploited by anti-cancer therapy. The Mouse Cancer Clinic is composed of an intervention unit, a preclinical imaging facility and a Bio-Pharmacy Unit working together in close collaboration with research groups at the NKI, other academic partners and pharmaceutical companies. The main objective is to find and test novel anti-cancer treatments, using the advanced cancer models, such as transgenic (spontaneous) mouse models, orthotopic transplantation models, human xenograft models that have been developed/ established at the NKI.

The knowledge of the molecular pathology of cancer cells is rapidly expanding and this now helps to design interventions that specifically interfere in the critical steps that drive cancer cells. This holds the promise of generating more efficacious therapies with fewer side effects. In order to more accurately translate preclinical studies to clinical outcome, it is essential to use cancer models that faithfully recapitulate the human disease. Moreover, when the treatment involves testing of new agents, it is necessary to consider the pharmacokinetic behavior of the experimental drugs in relation to their pharmacodynamics effects (target inhibition), especially since species-differences in pharmacokinetics of drugs is a potentially confounding factor. Obviously, it is not very useful when a drug demonstrates pre-clinical efficacy only at a dose level that results in plasma concentrations that cannot be achieved in patients. Therefore, we include the collection of data on plasma exposure (C_{max} and AUC, half-life) of test compounds in these intervention studies.

With the knowledge on pharmacokinetic behavior being established, an intervention study using one of our advanced mouse models can be designed guided by novel insights from basic research and clinical demands. Various approaches to treat cancer with classical chemotherapy, molecularly targeted agents, immuno-modulators, radiotherapy or combinations thereof are currently ongoing. In addition to systemically administered agents, we are also investigating loco-regional applications of drugs, surgery and radiation. The pre-clinical Intervention Unit can take care of the whole trajectory of preclinical trial design and execution, including support in the design/setup of the study, design suitable drug formulations, planning and execution of treatments, follow-up of tumor growth and/or metastasis formation, assessment of therapy response, collection of tissues and reporting of data. The longitudinal follow-up of tumors is greatly facilitated by dedicated state-of-the-art small animal imaging systems, including SPECT/CT, PET/CT and 7T MRI. Local and precise radiation beams can be delivered using the image-guided radiation therapy system for small animals. The lab of the bio-pharmacy unit is equipped with analytical instruments (LC-MS/MS, LC-UV/PDA, LC-FD and GFAAS) to execute bioanalytical assays.

This year the Mouse Cancer Clinic carried out more than 120 projects for more than 20 groups inside the NKI. 22 of the projects were for external academic customers and 15 for small pharmaceutical companies.

Next to that the Imaging Facility made 3944 scans in 2019. (Counting one time point per mouse as one scan, not counting the different sequences.) Approximately 70% of these scans were made by the personnel of the Imaging Unit, the remaining 30% was made by technicians or researchers themselves.

Education in oncology

The Netherlands Cancer Institute offers a variety of opportunities for practical and theoretical training to (trainee) technicians, University Master students, PhD students and post-doctoral fellows. Research and clinical staff and their group members are involved in theoretical and practical training. Many staff members have joint appointments as professors at Dutch universities and even more contribute to the regular curriculum at various universities. The research divisions attract students from universities throughout the The Netherlands. The NKI has a formal affiliation with the Science faculty of the University of Amsterdam (UvA) and is committed to make a contribution to Master student teaching. The institute participates in the Oncology Graduate School Amsterdam, together with the medical faculties of the UvA and the VU University (VU), referred to as Academic Medical Center (AMC) and VU medical center (VUmc), respectively. All educational activities are supervised by the Teaching Committee, which consists of Roderick Beijersbergen (chair and dean Master students), Hein te Riele (general affairs and dean PhD students), Fred van Leeuwen (dean post-docs), Wilbert Zwart (HLO students and publicity), and Fons Balm (clinical teaching).

MASTER STUDENTS

The program in Experimental Oncology attracts Master students of all national universities (see www.nki.nl/topmenu/master-students/). Students generally have a background in (Medical) Biology, Health Sciences, Chemistry, Pharmacology, Medicine, or Psychology. The program offers combined practical and theoretical training in various aspects of experimental oncology. Practical training includes participation in ongoing research projects for a minimum of 4 months.

In 2019, 73 Dutch university Master students completed a placement of 6-10 months at the biomedical research divisions. The students came primarily from the University of Amsterdam (UvA) (16) and the VU University Amsterdam (VU) (25), but also from the universities of Utrecht (6), Leiden (17), Amsterdam University College (1), Wageningen (1), TU Delft (1), Groningen (1) and Universities outside The Netherlands (5). The institute also provides practical training opportunities for Bachelor students of the HLO (Universities of Applied Science), who stay for similar periods of time as the university students and like these, often make significant contributions to research progress of the PhD students and post-docs who supervise them.

The core element of theoretical training is the course in Experimental Oncology (Table 1). This master course is a compulsory course for UvA Master students in Biomedicine, track Oncology. It is also offered as an elective to master students who do an internship at the NKI or follow a masterprogram in a biomedical area at a Dutch university. Other interested parties such as PhD students are welcome to attend the lectures as listener upon enrollment as attendee. The master course has a interactive program consisting of tutorials, student presentations and discussion and assignments. In addition, the students have to pass four exams in order to get study points. The course evolved around four main themes for which assignments and exams were organized, in addition to lectures covering the latest developments in the respective fields.

TABLE 1

COURSE IN EXPERIMENTAL ONCOLOGY

LECTURES

Epidemiology	Fl van Leeuwen
Radiotherapy	Monique de Jong
Next generation sequencing	R Kerkhoven
Conventional chemotherapy	F Opdam
Radiotherapy	R Haas
Early diagnostics	B Carvallo, R Fijneman
Telomerase and cancer	J Jacobs
Chromosome morphogenesis	B Rowland
Epigenetics in cancer	B van Steensel, Fr van Leeuwen
Cancer genomics	L Wessels
Non-coding landscape and cancer	R Agami
RNA translation and the ribosome	W Faller
Protein structure and design	T Sixma
Functional genomics	T Brummelkamp
Targeted therapy in melanoma	D Peeper
Mouse models of cancer	J Jonkers, I Huijbers
Tumor microenvironment	K de Visser
Radioimmunotherapy	I Verbrugge
Macrophages in the microenvironment	L Akkari

THEMATIC BLOCKS

Introductory lecture, state-of-the art lectures, student presentations and questions, research proposals and exams

Hormone regulated cancers	W Zwart, A Bergman
DNA damage and genomic instability	H te Riele, H. Jacobs
Targeted therapy and resistance	R Beijersbergen, R Bernards
Immunology and immunotherapy	L Akkari, J Haanen, J den Haan (guest)

PHD STUDENTS

PhD students at the NKI-AVL participate in the Oncology Graduate School Amsterdam (OOA), an alliance of the oncology research divisions of the NKI-AVL and the Amsterdam University Medical Centers. The number of PhD students has been rising rapidly in the past years. In 2019, the institute had 329 PhD students registered at the OOA. 40 students defended a PhD thesis at a Dutch university.

Besides joining interdepartmental work discussions, the students follow the OOA training program that offers courses, meet-the-expert sessions and an annual retreat (Table 2). The OOA course program includes in-depth courses on different topics in cancer research, but also technical courses in English writing, biostatistics and -informatics, microscopy and animal handling. Students with an insufficient background in cancer research can attend the Experimental Oncology course for Master students. PhD students also have the opportunity to meet with experts in the field of oncology: the Friday morning seminar speakers are invited to a lunch meeting with a delegation of PhD students. Each PhD student can participate several times a year.

The annual PhD student retreat is entirely focused on the research of the PhD students themselves. First year students present their work in the form of a poster, advanced students give oral presentations. Importantly, students are in charge of chairing sessions, monitoring discussions and selecting prizewinners for the best posters and presentations. In this way, the retreat not only provides an overview of the research in the OOA at an early stage of the student's career, but also training in presentation and interaction skills. We hope to stimulate translational interactions and bottom-up research, in which PhD students actively establish collaborations with other research groups, strengthening scientific exchange between the Amsterdam oncology centers.

TABLE 2.

OOA PHD STUDENT COURSES AND EVENTS 2019

DATE	COURSE	ECTS	ORGANIZERS	# STUDENTS	RATING
Feb 17	Indesign Thesis printing	0.1	N Nijhuis (Gildeprint)	21	4.1
March 25-29	Radiation Oncology	1.5	P Sminia, L Stalpers, (Amsterdam UMC) JJ Sonke (NKI-AVL)	29	4.2
April 8-12	Mouse morphology, genetics and function	1.5	J Seppen, V Christoffels (Amsterdam UMC)	-	-
May 6-10	In the footsteps of Antoni van Leeuwenhoek – Basic microscopy	1.5	E Reits, N van der Wel, (Amsterdam UMC), M Mertz, H Janssen, L Brocks (NKI-AVL)	16	4.3
May 13-17	O2Flow Cytometry	1.5	J Garcia Vallejo (Amsterdam UMC)	14	4.6
May 20-24	Epigenetics and epitranscriptomics	1.5	Fred van Leeuwen, R Agami (NKI-AVL)	35	4.5
June 17-21	Genetic engineering in model organisms	1.5	E Robanus Maandag, P Hohenstein, L Clemens-Daxinger (LUMC), H te Riele (NKI-AVL)	9	4.1
Sept 12-13	Histopathology of human tumors	0.6	N Donner (Amsterdam UMC)	29	4.0
Sept & Oct	Ethics and Integrity in Science	0.15	P Borst, M Schmidt, B van Steensel (NKI-AVL)	30	4.3
October 10-12	Annual Graduate Student Retreat	2.0	P Lagerweij, K van der Heijden, H te Riele (NKI-AVL)	145	4.2
Oct 28-Nov 8	BioBusiness	3.0	A Griffioen, E Huijber, J van Beijnum (Amsterdam UMC), Zuhir Elkarghali (NKI-AVL)	10	4.0
Nov 7-May 20 (2020)	Intervision group	0.4	E. Ruhé (Amsterdam UMC), H te Riele (NKI-AVL)	6	
Nov 11-15	O2Flow Cytometry	1.5	J Garcia Vallejo (Amsterdam UMC)	14	4.2
Nov 25-29	In the footsteps of Antoni van Leeuwenhoek – Basic microscopy	1.5	E Reits, N van der Wel, (Amsterdam UMC), M Mertz, H Janssen, L Brocks (NKI-AVL)	14	4.8
Nov 25-29	How to write research papers and grant proposals – a guide to successful scientific writing	1.5	E. Ruhé, A Griffioen (Amsterdam UMC), H te Riele (NKI-AVL)	20	4.4
Dec 2-6	Basic Medical Statistics / SPSS	1.5	M Hauptmann, K Jozwiak, S Roberti, A Morra, D Giardiello (NKI-AVL)	95	4.1
Throughout the year	Lunch meetings with NKI-AVL seminar speakers	-	NKI seminar committee	150	ND

PhD student retreat 2019

Senior graduate students can participate in a joint retreat with other cancer institutes in Europe. In 2019, this event was held in Amsterdam, organized by the students from the Netherlands Cancer Institute, with participants from:
– The CRUK Institutes (Cambridge, Glasgow, London, Manchester and Oxford)
– The Institute of Cancer Research (ICR)
– German Cancer Research Center (DKFZ)
– The Max Delbruck Center for Molecular Medicine (MDC)
– The Netherlands Cancer Institute (NKI, 7 participants)
– The European School of Molecular Medicine (SEMM: IFOM-IEO)
who attended and contributed to a program of scientific lectures and posters as well as an enthusiastic social session. This retreat gives students the opportunity to become acquainted with oncology centers of excellence throughout Europe.

Once a year, the PhD student meets with a supervisory committee to evaluate the progress of research. Each committee has independent members from within and outside the division. The committee discusses progress with the supervisor and the student jointly and separately. Two years after the appointment of the PhD student, a midterm review takes place. At this more elaborate meeting the likelihood of achieving a PhD within a reasonable time frame is discussed. This meeting can be used to redefine goals if necessary.

Each research division of the NKI-AVL has a delegate in the PhD student council that meets with the Dean of graduate students on a regular basis, as well as upon request. They also mediate communication between the graduate students and the board of directors. In addition, an OOA PhD council has been installed consisting of representatives of the Amsterdam oncology centers, which organizes events specifically focused on career development of graduate students.

POSTDOCS

In 2019 the NKI-AVL hosted approximately 150 postdoctoral fellows, almost half of which are from abroad and with equal gender representation. The postdocs at the NKI are represented by a very active postdoc committee (postdocs@nki). They organize workshops and special events such as (alumni) career development seminars and workshops about intellectual property and entrepreneurship. In addition, they regularly bring issues that matter to postdocs and others to the attention of NKI management.

The postdoc committee is also actively involved in the NKI Postdoc Career Development Program that is offered by the NKI to all its postdocs. This program has been developed together with AVL Academy and the postdoc dean. During their first year at the NKI, postdocs participate in a basic program, which consists of three one-day workshops. The basic program is mandatory for new NKI postdocs. In 2019, 41 postdocs started in the basic program.

Basic Postdoc Career Development Program 2019
Day 1.   Personal effectiveness: time and project management
Day 2.   Communication & cooperation
Day 3.   Creating your future, take ownership

All postdocs that have completed the basic program are invited in subsequent years to follow one of the one-day workshops as part of the Advanced Postdoc Career Development Program. In 2019, 67postdocs registered for a workshop of the advanced program.
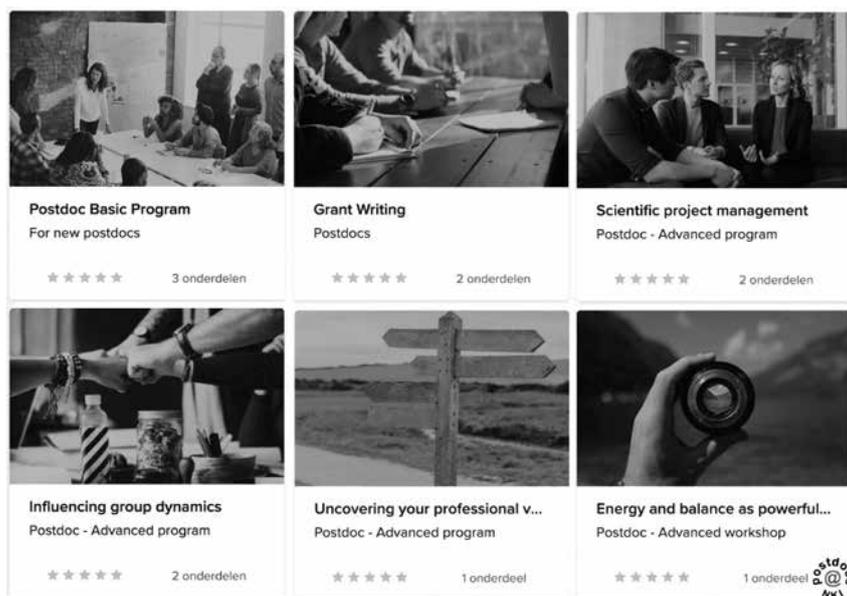
Advanced Postdoc Career Development Program 2019
1. Shaping your career
2. Influence & impact
3. Uncovering your professional value
4. Scientific project management
5. Energy and balance as powerful tools to increase your impact at work
6. Scientific Grant Writing

The goals of the program are to provide postdocs with the tools to take charge of their professional and personal development at the NKI, to promote maximum achievement of postdocs at the NKI, and to prepare postdocs for the next steps in their careers. The program, which is tailored to NKI postdocs, consists of special workshops of about 12 participants given by professional trainers but with input and active participation of NKI group leaders. The trainers all have a background in science and are fluent in English. The program is flexible and adjusted every year based on the evaluations of the workshops and suggestions from the postdocs.

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Clinical trials

Type of cancer study (nick name)	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
ALL SITES				
M09NIB	The NIB-Cohort study, therapeutic drug monitoring of tyrosine kinase inhibitors	Neeltje Steeghs	other	09/06/2009
M11PCT (CPCT-02)	Development of a platform for next-generation DNA sequencing based personalized treatment for cancer patients: protocol to obtain biopsies from patients with metastatic cancer (CPCT-02 biopsy protocol)	Neeltje Steeghs	other	24/01/2012
M12SEN (senior)	Observational study to evaluate pharmacokinetics and pharmacodynamics of docetaxel,paclitaxel, doxorubicine, gemcitabine, vinorelbine and capecitabine in elderly patients	Neeltje Steeghs	other	13/09/2012
M14CDP (BP29392)	An open-label, multicenter, dose-escalation phase Ib study to investigate the safety, pharmacokinetics, pharmacodynamics, and therapeutic activity of RO7009789 (CD40 agonist) in combination with MPDL3280a (anti-PD-L1) in patients with locally advanced and/or metastatic solid tumors	Neeltje Steeghs	I	23/1/2015 (7/12/2018)
M14CIP (CIP-study)	Cancer in Pregnancy (CIP-study)	Christianne Lok	other	17/02/2015
M14HUM	Hubrecht Organoid Technology-Metastasis, a resource for functional studies on drug development for cancer treatment	Emile Voest	other	11/8/2014 (13/11/2019)
M14HUP	Biobank Hubrecht Institute, a resource for functional studies on drug development for cancer treatment	Emile Voest	other	11/8/2014 (31/10/2019)
M14MCL	A Phase I Study of MCLA-128, a Human IgG1 Bispecific Antibody Targeting HER2 and HER3, in Patients with Solid Tumours	Frans Opdam	I/II	11/03/2015
M15CEG	A phase I/II, multicenter, open-label study of EGFRmut–TKI EGF816, administered orally in adult patients with EGFRmut solid malignancies	Egbert Smit	I/II	28/6/2016 (30/10/2019)
M15DRU (DRUP)	A National Study to Facilitate Patient Access to Commercially Available, Targeted Anti-cancer Drugs to determine the Potential Efficacy in Treatment of Advanced Cancers with a Known Molecular Profile; The Drug Rediscovery Protocol	Emile Voest	I	25/07/2016
M15FAP (BP29842)	An open-label, multicenter, dose-escalation, Phase I study to evaluate safety, pharmacokinetics, and therapeutic activity of RO6874281, an immunocytokine consisting of interleukin 2 variant (IL-2v) targeting fibroblast activation protein- (FAP), in patients with advanced and/or metastatic solid tumors	Neeltje Steeghs	I	18/12/2015
M15KEY (KEYNOTE 158)	A clinical trial of Pembrolizumab (MK-3475) evaluating predictive biomarkers in subjects with advanced solid tumors	Marloes van Dongen	II	29/02/2016
M15MBG	A phase I-Ib/II, open-label, multi-center study of the safety and efficacy of MBG453 as single agent and in combination with PDR001 in adult patients with advanced malignancies	Sofie Wilgenhof	I/II	28/07/2017
M15MSR	An Open Label, Phase Trial of the DNA-PK Inhibitor MSC2490484A in Combination with Radiotherapy in Patients with Advanced Solid Tumors	Baukelien van Triest	I	17/07/2015
M15PEM (ENGAGE-1)	A Phase I, open-label study of GSK3174998 administered alone and in combination with anticancer agents including Pembrolizumab in subjects with selected advanced solid tumors	Frans Opdam	I	4/5/2016 (18/4/2019)
M15PRM (PRMT5i)	A phase I, open-label, dose escalation study to investigate the safety, pharmacokinetics, pharmacodynamics and clinical activity of GSK3326595 in subjects with solid tumors and non-Hodgkin's lymphoma	Frans Opdam	I	27/10/2016

Type of cancer study (nick name)	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
M15RVA (BP29889)	An open-label, multicenter, dose escalation phase 1b study with expansion cohorts to evaluate the safety, pharmacokinetics, pharmacodynamics and therapeutic activity of RO7009789 (CD40 agonistic monoclonal antibody) in combination with Vanucizumab (anti-ANG2 and anti-VEGF bi-specific monoclonal antibody) in patients with metastatic solid tumors	Neeltje Steeghs	I	26/02/2016
M16BAN	A Phase 1/2a Study of BMS-986179 Administered in Combination with Nivolumab (BMS-936558, anti-PD-1 Monoclonal Antibody) in Advanced Solid Tumors	Neeltje Steeghs	I/II	02/09/2016
M16GAC	A Phase I Open Label study of GSK3359609 administered alone and in combination with anticancer agents in subjects with selected advanced solid tumors	Frans Opdam	I	30/05/2017
M16LAG	A phase 1/2a dose escalation and cohort expansion study of the safety, tolerability, and efficacy of anti-LAG-3 monoclonal antibody (BMS-986016) administered alone and in combination with anti-PD-1 monoclonal antibody (Nivolumab, BMS-936558) in advanced solid tumors	Sofie Wilgenhof	I/II	06/12/2016
M16NFC	Multicenter study evaluating the hybrid approach using a novel fluorescence camera – Identifying the value of intraoperative fluorescence imaging during sentinel node biopsy procedures	Simon Horenblas	other	09/11/2017
M16STT (STARTRK-2)	An open-label, multicenter, global phase 2 basket study of Entrectinib for the treatment of patients with locally advanced or metastatic solid tumors that harbour NTRK1/2/3, ROSI or ALK gene rearrangements	Egbert Smit	II	24/08/2016
M16TEM (Kameleon)	Phase II, exploratory, multicenter, non randomized, single agent study to determine best tumor response with Trastuzumab Emtansine in HER2 overexpressing solid tumors	Michiel van der Heijden	II	26/1/2017 (12/12/2019)
M17AFE	A randomised, open-label, phase I study to determine the effect of food on the pharmacokinetics of AZD1775 after oral dosing of a capsule formulation in patients with advanced solid tumours	Frans Opdam	I	27/9/2017 (30/10/2019)
M17AVM	A phase Ib open-Label, dose-finding trial to evaluate the safety, tolerability, and pharmacokinetics of Avelumab in combination with M9241 (NHS-IL12) in subjects with locally advanced, unresectable, or metastatic solid tumors	Frans Opdam	I	25/07/2019
M17AZD	An open-label, non-randomised, multicentre study to allow continued access to and assess the safety and tolerability of AZD1775 for patients enrolled in AZD1775 clinical pharmacology studies	Frans Opdam	other	02/10/2017 (30/10/2019)
M17CAN (CANFOUR)	An open label, dose escalation followed by dose expansion, safety and toler-ability trial of CAN04, a fully humanized monoclonal antibody against IL1RAP, in subjects with solid malignant tumors	Neeltje Steeghs	I/II	14/11/2017
M17CIP	INCIP fertility substudy	Christianne Lok	other	25/04/2019
M17ITR	An open-label, Phase I study to asses the effect of itraconazole (CYP3A4 and P-gp inhibitor) on the pharmacokinetics of anetumab ravtansine and to asses the ECG effects, safety and immunogenicity of anetumab ravtansine given as a single agent and together with itraconazole in subjects with mesothelin-expressing advanced solid cancers	Neeltje Steeghs	I	6/10/2017 (30/10/2019)
M17LET	An open-label, multi-center, roll-over study to assess long term safety of lenvatinib monotherapy or lenvatinib combination regimen or comparator treatment arm to cancer patients in Eisai sponsored lenvatinib trials	Marloes van Dongen	II	15/08/2018
M17MIW	A Phase Ib, open label, multicenter study of the safety and efficacy of MIW815 (ADU-S100) administered by intratumoral injection with PDR001 to patients with advanced/metastatic solid tumors or lymphomas (CheckMate 592)	Neeltje Steeghs	I	2/2/2018 (11/12/2019)

Type of cancer study (nick name)	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
M17MPE	A Phase 1 Study of MK-5890 as Monotherapy and in Combination with Pembrolizumab in Participants with Advanced Solid Tumors	Marloes van Dongen	I	15/05/2018
M17PCV	A phase Ia/Ib open-label, dose-escalation study of the safety and pharmacokinetics of RO7198457 as a single agent and in Ccombination with Atezolizumab in patients with locally advanced or metastatic tumors	Neeltje Steeghs	I	04/10/2018
M17QLQ	Validation of the EORTC computerized adaptive testing (CAT) instrument – Feasibilty and field study	Neil Aaronson	other	28/11/2017
M17QOL	Phase III development of an EORTC QoL cancer survivorship questionnaire	Lonneke van de Poll - Franse	III	12/06/2018
M17RIT	A phase I/II study of safety and efficacy of ribociclib (LEE011) in combination with trametinib (TMT212) in patients with metastatic or advanced solid tumors	Neeltje Steeghs	I/II	23/5/2017 (8/5/2019)
M17TDM	Therapeutic drug monitoring for oral anti-cancer drugs	Neeltje Steeghs	other	09/08/2017
M18AXL	First-in-human, open-label, dose-escalation trial with expansion cohorts to evaluate safety of Axl-specific antibody-drug conjugate (HuMax®-AXL-ADC) in patients with solid tumors	Christian Blank	I	21/01/2019
M18BOB	Basket of Baskets: A modular, open-label, phase II, multicentre study to evaluate targeted agents in molecularly selected populations with advanced solid tumours	Frans Opdam	II	08/02/2019
M18BRM	A phase I drug-drug interactions study between Brigatinib and the CYP3A substrate Midazolam in patients with ALK-postive or ROSI-postive solid tumors	Egbert Smit	I	13/06/2019
M18COM (SO-CDM)	Communication in Second Opinions	Gemma de Kenter	other	29/3/2018 (3/12/2019)
M18COP (COP)	Prospective, multi-centre trial to evaluate effectiveness of 45-min and 20-min postinfusion cooling time for patients treated with scalp cooling to prevent Paclitaxel-induced alopecia	Carolien Smorenburg	other	19/06/2018
M18FLH (FLUYT-Prevent)	Fluid Hydration to prevent: Post-ERCP Pancreatitis. A randomized, superiority multicenter trial	Thomas de Wijkerslooth	III	04/02/2019
M18GSK	A Phase I First Time in Human Open Label Study of GSK3745417 administered with and without Anticancer Agents in Participants with Selected Advanced Solid Tumors	Neeltje Steeghs	I	31/10/2019
M18INB	Safety, Pharmacokinetics, and Pharmacodynamics of Escalating Oral Doses of the Arginase Inhibitor INCB001158 (formerly known as CB001158) as a Single Agent and in Combination with Immune Checkpoint Therapy in Patients with Advanced/Metastatic Solid Tumors	Christian Blank	I	07/03/2019
M18IWO (i-WORC studie)	Internet-based Work-related cognitive Rehabilitation for Cancer survivors: a randomised controlled trial	Sanne Schagen	III	08/03/2019
M18SPX (SPHINX)	Endoscopic sphincterotomy before fully covered self-expandable metal stent placement for malignant extrahepatic biliary obstruction to prevent pancreatitis: a randomised controlled trial	Thomas de Wijkerslooth	nvt	28/02/2019
M18TAK	A Phase 1, Open-Label Study to Assess the Relative Bioavailability, Effect of Food, and Gastric pH Modification on the Pharmacokinetics of TAK-931 in Patients With Advanced Solid Tumors	Neeltje Steeghs	I	9/5/2019 (28/8/2019)
M18TLO	A Phase I, Open-Label Study of GSK1795091 Administered in Combination with Immunotherapies in Participants with Advanced Solid Tumors	Neeltje Steeghs	I	25/09/2018
M18TMB (CheckMate 848)	A Randomized, Open-Label, Phase 2 Study of Nivolumab in Combination with Ipilimumab or Nivolumab Monotherapy in Participants with Advanced or Metastatic Solid Tumors of High Tumor Mutational Burden	Neeltje Steeghs	II	14/01/2019

Type of cancer study (nick name)	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
M18TNO	An open-label, multi-center, phase I, dose finding study of oral TNO155 in adult patients with advanced solid tumors	Neeltje Steeghs	I	13/02/2019
M19ALP (Alphe2U)	Improving the safety of fluoropyrimidine-based chemotherapy by combined DPYD genotype-guided and DPD phenotype-guided dose-individualization	Annemieke Cats	other	14/08/2019
M19EQP (eQuiPe)	Experienced Quality of Care and Life in advanced oncological patients and their relatives, a prospective observational cohort study	Lonneke van de Poll - Franse	other	07/11/2019
M19MOM (MOMENTUM)	The Multiple Outcome Evaluation of Radiation Therapy using the MR-Linac	Marlies Nowee	other	27/03/2019
M19OVC (OnVaCT)	Realizing better doctor-patient dialogue about choices in palliative care and early phase clinical trial participation	Neeltje Steeghs	other	10/07/2019
M19PCC (PROSPECT)	Hope for the best, prepare for the worst: Towards a better understanding of unawareness of prognosis in advanced cancer patients	Sjaak Burgers	other	23/07/2019
M19SFV	Phase I/II pharmacokinetic multi-tumor study of subcutaneous formulation of nivolumab monotherapy	Marloes van Dongen	I/II	01/05/2019
M19STR (STAR22)	CYP3A4*22 genotype-guided dosing of TKI's in cancer patients: a new way of personalized therapy	Neeltje Steeghs	IV	07/06/2019
N12MTG	Middle ear thiosulfate-gel protection against cisplatin-induced hearing loss in patients carrying a single nucleotide polymorphism in the TPMT, COMT or LRP2 gene	Serena Marchetti	other	11/4/2013 (12/3/2019)
N14CCT	Phase I pharmacological study of continuous and intermittent chronomodulated capecitabine therapy	Serena Marchetti	I	18/06/2014
N15LDC	The effect of prehydration on the pharmacokinetics of low-dose Cisplatin	Wouter Vogel	other	06/11/2015
N16CLT (COLIT-1)	The use of fecal calprotectin in detecting immunotherapy induced colitis and feasibility for the use of immunohistochemical markers in patients receiving checkpoint inhibitors'	Jolanda van Dieren	other	23/5/2016 (2/5/2019)
N16CRY	The effect of Cryotherapy in preventing oral mucositis associated with doxorubicin treatment	Carolien Smorenburg	other	09/05/2016
N16GEM	Phase 0 proof of concept study: a clinical pharmacokinetic microdosing trial with gemcitabine	Serena Marchetti	other	19/4/2017 (18/2/2019)
N16LND (TALENT)	Targeted Abdominal Lymph nodE dissections randomized for surgical NavigaTion	Theo Ruers	other	25/01/2017
N16PDA	Validation of Pharmacokinetic Assays for determination of Nivolumab and Pembrolizumab concentrations in serum	Serena Marchetti	other	16/01/2017
N16UMB (UMBRELLA-I)	MR-sequence optimization and Workflow development for treatment guidance, using the integrated MR scanner of the MR Linac system. Towards MR guided Adaptive Radiation Therapy	Marlies Nowee	other	26/04/2017
N17MRB	Monitoring MRI changes before and during Radiotherapy Treatment of Brain Tumors	Gerben Borst	other	31/08/2017
N17ROW	Reiniging van gecontamineerde postoperatieve oncologische wonden met kraanwater of antiseptische spoelvloeistof - een gerandomiseerde klinische studie	Rob Kuin	other	5/2/2018 (6/11/2019)
N17SAN	Studie naar immunotherapie voor de behandeling van kankerpatient	Koen Hartemink	other	16/01/2019
N18BREL (UMBRELLA-2)	The MR-Linac Technical Feasibility Protocol For Development of MR-guided Adaptive Radiation Therapy	Marlies Nowee	other	26/09/2018

Type of cancer study (nick name)	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
N18MRC	Development of MRCAT: electron density maps for radiotherapy dose calculations from MR images as alternative for planning CT scans	Abrahim Al-Mamgani	other	21/03/2018
N18POR	Comparison of preoperative and intraoperative image registration using an ultrasound-based navigation system during liver surgery	Theo Ruers	other	28/06/2019
N18TIME	Idle time scanning on the MR-linac	Marlies Nowee	other	7/3/2019 (8/10/2019)
N18ULN	Ultrasound-based navigation during liver surgery	Theo Ruers	other	10/08/2018
N18WGS (WIDE)	WGS implementation in standard care Diagnostics for Each cancer patient	Geerard Beets	other	10/04/2019

BIOBANK

Type of cancer study (nick name)	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
B09BIO (Biobank)	NKI-AVL biobank - patienten	Daan van den Broek	biobank	22/01/2020
B15CTD	Circulating tumor DNA in cancer patients: development of a clinical diagnostic tests and establishment of a biobank	Michiel van der Heijden	biobank	07/10/2015
B15HHC	Analyse van weefsel van patienten met een tumor in het hoofd-halsgebied	Lotje Zuur	biobank	03/09/2015
B15IMM	Longitudinal tumor and blood sampling in patients with advanced stage urothelial cancer of the bladder for the analysis of mechanisms of response to immunotherapy	Michiel van der Heijden	biobank	07/10/2015
B15OES (Together)	Tissue sampling of oesophagogastric cancer to enable tailored therapies	Johanna van Sandick	biobank	17/06/2015
B16BBC	Melanoma transcriptome protocol; Blood collection NETest	Margot Tesselaar	biobank	14/04/2016
B16BHW	Blood sampling of healthy women and early stage breast cancer patients	Jelle Wesseling	biobank	11/07/2016
B16CIT	Antigenic specificity and functional properties of colorectal cancer infiltrating human T cells, biobank protocol	Ton Schumacher	biobank	23/1/2017 (6/11/2019)
B16CLM	Determining the sensitivity and specificity of circulating tumor cells and cytology in cerebrospinal fluid of patients with suspicion of leptomenigual matastases	Dieta Brandsma	biobank	19/09/2017
B16IMM	Biobank Immunotherapy baseline samples	Huub van Rossum	biobank	03/10/2016
B16MEL	Understanding tumor immune escape in patients with stage III melanoma	Alexander van Akkooi	biobank	28/08/2017
B16NBC	Tissue and blood sampling to find predictive markers for neoadjuvant chemotherapy benefit in breast cancer – Neoadjuvant Therapy Breast Cancer Biobank	Gabe Sonke	biobank	27/06/2016
B16PON	Paired healthy & tumor organoid Biobank (adenomas)	Emile Voest	biobank	14/7/2016 (13/11/2019)
B16TGT	Translational Gastrointestinal Oncology – tissue	Gerrit Meijer	biobank	14/07/2016
B17CON	CONventional TReatment Or Leave DCIS	Jelle Wesseling	biobank	27/12/2017 (12/11/2019)

Type of cancer study (nick name)	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
B17GEN	Biomarker analyse van weefsel/bloed van patiënten met een HPV-negatieve tumor in het hoofdhalsgebied	Michiel van den Brekel	biobank	27/9/2017 (6/12/2019)
B17PRE (PRECISION)	Prevent Ductal Carcinoma In Situ Invasive Overtreatment Now	Jelle Wesseling	biobank	28/11/2017
B18HIR	Blood sampling of healthy volunteers for immunological research	Marleen Kok	biobank	08/02/2019
B18NCI (N-CIA)	The Netherlands facility for Cancer-Immune Analysis: studying the immune landscape of tumors	John Haanen	biobank	22/05/2019
B18UBC	Longitudinal tumor, urine and blood sampling in patients with urinary tract cancer treated with chemotherapy	Michiel van der Heijden	biobank	15/10/2018
B19BIO	Blood Biobank healthy volunteers	Daan van den Broek	biobank	19/08/2019

BRAIN / CNS

Type of cancer study (nick name)	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
E1709	A phase III trial of Marizomib in combination with standard Temozolomide-based radiochemotherapy versus standard Temozolomide-based radiochemotherapy alone in patients with newly daignosed glioblastoma	Dieta Brandsma	III	30/10/2018
M15NTG (CheckMate 498)	A Randomized Phase 3 Open Label Study of Nivolumab vs Temozolomide Each in Combination with Radiation Therapy in Newly Diagnosed Adult Subjects with Unmethylated MGMT (tumor O-6-methylguanine DNA methyltransferase) Glioblastoma	Dieta Brandsma	III	06/06/2016
M16NMG	A Randomized Phase 2 Single Blind Study of Temozolomide plus Radiation Therapy combined with Nivolumab or Placebo in Newly Diagnosed Adult Subjects with MGMT-Methylated (tumor O6-methylguanine DNA methyltransferase) Glioblastoma	Dieta Brandsma	II	17/06/2016
M19IPA (IPAX-1)	A multi-centre, open label, single arm, dose-finding phase I/II study to evaluate safety, tolerability, dosing schedule, and preliminary efficacy of carrier-added 4-L-[131I]iodo-phenylalanine (^{131}I-IPA), administered as a single or repetitive injections in patients with recurrent glioblastoma multiforme (GBM), concomitantly to 2nd line external radiation therapy (XRT)	Wouter Vogel	I/II	15/07/2019
M19VAX (VAXIMM)	An open-label, phase I/II multicenter clinical trial of VXM01 in combination with Avelumab in patients with progressive glioblastoma following standard treatment, with or without second surgery	Dieta Brandsma	I/II	28/08/2019
N17ICO	Position stability during radiosurgery of brain tumours	Gerben Borst	other	18/1/2018 (24/1/2019)
N17MRB	Monitoring MRI changes before and during Radiotherapy Treatment of Brain Tumors	Gerben Borst	other	31/08/2017
N18POB (POBIG)	Dose and Volume Escalation of Preoperative Brain Irradiation in GBM Patients	Gerben Borst	I/II	19/06/2018

BREAST

Type of cancer study (nick name)	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
M05BRI (BRIGHT)	Long term risk of breast cancer following treatment of Hodgkin's disease	Nicola Russell	other	05/01/2006
M12DEN (DENSE)	Early detection of breast cancer in women with dense breasts	Claudette Loo	other	19/09/2012

Type of cancer study (nick name)	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
M12SSU	Detectie van onstekingsgeassocieerde eiwitprofielen in het serum, speeksel en urine van patienten met mammatumoren	Emiel Rutgers	other	17/04/2012
M13TNB (TRIPLE-B)	Biomarker discovery randomized phase IIb trial with Carboplatin-Cyclophosphamide versus Paclitaxel with or without Bevacizumab as first-line treatment in advanced triple negative breast cancer	Sabine Linn	II	09/07/2013
M14ABC (ABC)	A feasibility study of niraparib for advanced, BRCA1-like, HER2-negative breast cancer patients	Sabine Linn	II	15/01/2018
M14CNB (BOOG 2013-08)	Clinically node negative breast cancer patients undergoing breast conserving therapy: Sentinel lymph node procedure versus follow-up. A Dutch randomized controlled multicentre trial	Frederieke van Duijnhoven	III	14/09/2016
M14HAR (HARBOR)	Identifying subgroups with high cardiovascular risk in breast cancer survivors	Floor van Leeuwen	other	13/04/2015
M14POS (POSEIDON)	Phase I/prospective randomized phase II trial Of the Safety and Efficacy of tamoxifen in combination with the Isoform selective Pi3K inhibitor GDC-0032 compared with tamoxifen alONe in hormone receptor positive, HER2 negative, metastatic breast cancer patients with prior exposure to endocrine treatment	Sabine Linn	I/II	31/10/2014
M15INF (INFLAME)	Inflame; Towards optimal treatment of inflammatory breast cancer patients	Gabe Sonke	other	10/5/2016 (31/12/2018)
M15OLY (olympia)	A randomised double-blind parallel group placebo controlled multicenter phase III study to assess the efficacy and safety of olaparib versus placebo as adjuvant treatment in patients with germline BRCA1/2 mutations and high risk HER2 negative primary breast cancer who have completed definitive local treatment and neoadjuvant or adjuvant chemotherapy	Gabe Sonke	III	3/6/2015 (29/4/2019)
M15PAP (PAPBI-2)	Pre- versus Postoperative Accelerated Partial Breast Irradiation in early stage breast cancer patients; A randomized phase III trial	Astrid Scholten	III	17/08/2016
M16BRC (SUBITO)	Substantially improving the cure rate of high-risk BRCA1-like breast cancer patients with personalized therapy, an international randomized phase III trial	Sabine Linn	III	13/10/2016
M16PLE	Phase Ib, open-label, multi-center study to characterize the safety, tolerability and pharmacodynamics (PD) of PDR001 in combination with LCL161, Everolimus (RAD001) or Panobinostat (LBH589)	Neeltje Steeghs	I	01/11/2016
M17GEL (GELATO)	AssessinG Efficacy of carboplatin and ATezOlizumab in metastatic Lobular breast cancer	Marleen Kok	I/II	06/10/2017
M17PAB (PABLO)	Effect of a physical activity promotion program offered online or via blended care on physical activity level in breast and prostate cancer survivors	Wim Groen	other	19/10/2017
M17PRP (PRECiSE Project)	Discovery of prognostic molecular markers within an early stage breast cancer patient population A study of the Dutch Breast Cancer Research Group	Gabe Sonke	other	22/08/2017
M17SDM	Implementing a decision aid for breast cancer and DCIS patients deciding on their radiation treatment: A pre- and post-intervention study	Nicola Russell	other	26/10/2017
M17SJA (SONIA)	Endocrine therapy plus CDK 4/6 inhibition in first or second line for hormone receptor positive advanced breast cancer	Gabe Sonke	other	09/11/2017
M17TAN (Tango)	Impact of a web-based decision aid for women considering breast reconstruction:a randomized controlled trial	Eveline Bleiker	other	02/08/2017
M17TOP (TOP-1)	Tailored treatment in Older Patients (TOP-1): Omission of radiotherapy in elderly patients with low risk breast cancer	Marie Jeanne Vrancken Peeters	other	28/02/2018

Type of cancer study (nick name)	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
M18BEL (BELLINI)	Pre-operative phase II trial for breast cancer with nivolumab in combination with novel IO	Marleen Kok	II	22/07/2019
M18CYP	Effect of the moderate CYP3A4 inhibitor erythromycin on the pharmacokinetics of palbociclib	Neeltje Steeghs	IV	13/02/2019
M18HAR (HARMony)	Favorable and unfavorable effects of risk-reducing salpingo-oophorectomy (RRSO) in women with a high genetic risk of ovarian cancer	Floor van Leeuwen	other	12/09/2018
M18LBC (NEOLBC)	Tailoring Neoadjuvant therapy in hormone receptor positive, HER2 negative, luminal breast cancer	Sabine Linn	II	15/11/2018
M18LORD (E1401)	Management of low grade ductal carcinoma in situ (low-grade DCIS): a randomized, multicenter, non-inferiority trial, standard therapy versus active surveillance	Jelle Wesseling	III	02/02/2017
M18MTE	Phase 2 study of MCLA-128-based combinations in metastatic breast cancer (MBC): MCLA-128/trastuzumab/chemotherapy in HER2-positive MBC and MCLA-128/endocrine therapy in estrogen receptor positive and low HER2 expression MBC	Vincent Dezentjé	II	03/07/2019
M18TRD (TRAIN-3)	Image-guided de-escalation of systemic neoadjuvant treatment in HER2-positive breast cancer	Gabe Sonke	II	15/02/2019
M19CAD	Phase Ib, multicenter, open-label dose escalation and expansion platform study of select immunotherapy combinations in adult patients with triple negative breast cancer	Neeltje Steeghs	I	23/05/2019
M19CON (CONTROL DCIS)	Ipsilateral invasive breast cancer-free rate at 10 years; A prospective non-randomized comparison observational study of screen-detected low-risk DCIS between active surveillance and conventional treatment	Jelle Wesseling	other	31/10/2019
N08AFT (AFTER)	A randomized prospective trial of 2-6 weeks pre-operative hormonal treatment for hormone receptor positive breast cancer: Anastrozole +/- fulvestrant or tamoxifen exposure - response in molecular profile	Sabine Linn	II	04/08/2008
N12OLG (OLIGO)	High-dose alkylating chemotherapy in oligo-metastatic breast cancer harboring homologous recombination deficiency	Gabe Sonke	III	03/07/2012
N13ORB	Olaparib dose escalation combined with radiotherapy in patients with inoperable breast cancer	Gabe Sonke	I	23/8/2013 (12/2/2019)
N15PPP	Prediction of persisting postmastectomy pain by psycho-somato-sensory profiling	Anne Lukas	other	25/01/2016
N15TON (TONIC)	Adaptive phase II randomized non-comparative trial of nivolumab after induction treatment in triple-negative breast cancer (TNBC) patients	Marleen Kok	II	10/09/2015
N16MIC (MICRA)	Minimally Invasive Complete Response Assessment of the breast after neoadjuvant chemotherapy	Marie Jeanne Vrancken Peeters	other	06/04/2016
N16PRB (PROBI)	Pre-operative Breast Irradiation	Astrid Scholten	I/II	18/4/2017 (26/9/2019)
N16SEN (SENTIMAP)	Simplifying the sentinel node procedure in breast cancer using a portable gamma camera in order to replace conventional preoperative lymphatic mapping	Marcel Stokkel	other	6/7/2017 (8/1/2019)
N18CPB	Ervaren beperkingen ten gevolge chronische pijn na borstkanker: een kwalitatieve studie naar het perspectief van de patiënt	Kisten Nienhuys	other	25/04/2018
N19IPT	Contributing to research in a time of privacy: information provision and transparency	Marjanka Schmidt	other	07/11/2019

Type of cancer study (nick name)	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
GASTRO INTESTINAL				
E1560	Phase II of immunotherapy plus local tumor ablation (RFA or stereotactic radiotherapy) in patients with colorectal cancer liver metastases	Theo Ruers	II	18/01/2019
M09OCB	A pilot evaluating response to induction chemotherapy with oxaliplatin, capecitabine and bevacizumab in patients with extensive peritoneal carcinomatosis of colorectar origin	Arend Aalbers	pilot	25/03/2010
M12DEC (ART DECO)	A randomized trial of dose escalation in definitive chemoradiotherapy for patients with oesophageal cancer	Berthe Aleman	III	12/2/2013 (26/3/2019)
M13ORC (ORCHESTRA)	A randomized multicenter clinical trial for patients with multi-organ, colorectal cancer metastases comparing the combination of chemotherapy and maximal tumor debulking versus chemotherapy alone	Cecile Grootscholten	III	09/06/2015
M14CR5 (CAIRO-5)	Treatment strategies in colorectal cancer patients with initially unresectable liver-only metastases - a randomised phase 3 study of the Dutch Colorectal Cancer Group	Cecile Grootscholten	III	09/06/2015
M14NEC (NEC)	Phase II Study of cisplatin and everolimus in patients with metastatic or unresectable neuroendocrine carcinomas of extrapulmonary origin	Margot Tesselaar	II	10/02/2016
M14TUM (TUMOROID)	Tumor organoids: feasibility to predict sensitivity to treatment in cancer patients	Emile Voest	pilot	22/07/2014
M15CRI (CRITICS-II)	A multicentre randomised phase II trial of neo-adjuvant chemotherapy followed by surgery vs. neo-adjuvant chemotherapy and chemoradiotherapy followed by surgery vs. neo-adjuvant chemoradiotherapy followed by surgery in resectable gastric cancer	Marcel Verheij	II	23/06/2017
M15HPV (BMS-936558)	Non-Comparative, Two-Cohort, Single-Arm, Open-Label, Phase 1/2 Study of Nivolumab in Subjects with Virus-Positive and Virus-Negative Solid Tumors	Jan Paul de Boer	I/II	27/10/2015
M15INN (INNOVATION)	INtegratioN of trastuzumab, with or without pertuzumab, into periOperatiVe chemotherApy of HER-2 posiTIve stOmach caNcer	Annemieke Cats	II	09/05/2019
M15MOC (MOCCAS)	Molecular stool test for colorectal cancer surveillance	Monique van Leerdam	other	20/01/2016
M15MOD (MODUL)	A multi-centre randomised clinical trial of biomarker-driven maintenance treatment for first-line metastatic colorectal cancer	Cecile Grootscholten	II	14/1/2016 (5/9/2019)
M15PEC (PERISCOPE II)	Treatment of peritoneal dissemination in stomach cancer patients with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. A multicentre randomised phase III trial	Johanna van Sandick	III	23/08/2017
M15SCA (SCAPURA)	The sensitivity of scar-biopsies for residual colorectal adenocarcinoma after endoscopic resection with uncertain radicality	Monique van Leerdam	other	27/8/2015 (19/8/2019)
M16BAC (E1604)	A phase II open-label study with the anti-PDL1 Atezolizumab monoclonal antibody in combination with Bevacizumab in patients with advanced chemotherapy resistant colorectal cancer and MSIlike molecular signature	Neeltje Steeghs	II	19/12/2017
M16BCR (BEACON CRC)	A multicenter, randomized, open-label, 3-arm phase 3 study of Encorafenib +Cetuximab plus or minus Binimetinib vs. Irinotecan/Cetuximab or Infusional 5-Fluorouracil (5-FU)/Folinic Acid (FA) /Irinotecan (FOLFIRI)/Cetuximab with a safety lead-in of Encorafenib + Binimetinib + Cetuximab in patients with BRAF V600E-mutant metastatic colorectal cancer: Binimetinib, Encorafenib, And Cetuximab COmbined to Treat BRAF-mutant ColoRectal Cancer	Neeltje Steeghs	III	23/9/2016 (13/12/2018)
M16EEW	Expectations and experiences of clinical complete responders after chemoradiation for rectal cancer, regarding the Wait-and-See policy: a qualitative multicenter study	Geerard Beets	other	3/5/2016 (4/12/2019)

Type of cancer study (nick name)	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
M16EGJ (CheckMate 577)	A Randomized, Multicenter, Double Blind, Phase III Study of Nivolumab or Placebo in Subjects with Resected Lower Esophageal, or Gastroesophageal Junction Cancer: CHECKpoint pathway and nivoluMab clinical Trial Evaluation	Cecile Grootscholten	III	27/10/2016 (12/8/2019)
M16EPS (EPoS I/II/III)	The European Polyp Surveillance study (EPoS). Two randomized controlled trials and an observational cohort study	Monique van Leerdam	other	29/03/2017
M16INC (INCA)	Intensive therapy for esophageal anastomotic strictures (INCA)	Jolanda van Dieren	II	12/4/2017 (31/10/2019)
M16PLE	Phase Ib, open-label, multi-center study to characterize the safety, tolerability and pharmacodynamics (PD) of PDR001 in combination with LCL161, Everolimus (RAD001) or Panobinostat (LBH589)	Neeltje Steeghs	I	01/11/2016
M16PTO (PEPTONE)	Preferences, barriers and facilitators for pre-operative exercise participation for elderly treated for colorectal cancer and their social network	Carla Agasi-Idenburg	other	20/4/2017 (4/12/2018)
M16SCR (Motricolor)	Screening protocol to molecularly identify MSI-like, BRAF-like and TGFβ-like classifiers in patients with metastatic colorectal cancer (mCRC), to potentially participate in any of the H2020 MoTriColor Clinical Trials	Neeltje Steeghs	other	25/01/2017
M16STA (STAR-TREC)	Can we Save the rectum by watchful waiting or TransAnal microsurgery following (chemo)Radiotherapy versus Total mesorectal excision for early REctal Cancer?	Geerard Beets	II	26/07/2017
M16TGA (MoTriColor1)	Phase I/II study with galunisertib combined with chemotherapy regimens in patients with advanced chemotherapy resistant colorectal cancer and a TGFbeta signature	Neeltje Steeghs	I/II	16/5/2018 (2/9/2019)
M16TSR (TESAR)	Rectal preserving treatment for early rectal cancer. A multi-centred randomised trial of radical surgery versus adjuvant chemoradiotherapy after local excision for early rectal cancer	Monique van Leerdam	III	17/08/2016
M16VIB (MoTriColor2)	A phase II study of vinorelbine in advanced BRAF-like colon cancer	Neeltje Steeghs	II	02/02/2018
M16WAS	Multicentre evaluation of the "wait-and-see" policy for complete responders after chemoradiotherapy for rectal cancer	Geerard Beets	other	24/02/2017
M17CR6 (CAIRO6)	Investigating the benefit of perioperative systemic therapy in patients undergoing cytoreductive surgery with HIPEC for peritoneal metastases of colorectal cancer: the multicentre, phase II-III, prospective, randomised study	Arend Aalbers	other	07/09/2017
M17CRC (PLCRC)	Prospective data collection initiative on colorectal cancer - a prospective obeservational cohort study	Geerard Beets	IV	22/08/2017
M17HCR (pump)	Adjuvant hepatic arterial infusion pump chemotherapy after resection of colorectal liver metastases - a feasibility study	Koert Kuhlmann	pilot	13/2/2018 (31/10/2019)
M17PLA (PLASTIC)	Evaluation of PET and Laparoscopy in STagIng advanced gastric Cancer: a multicenter prospective study	Johanna van Sandick	other	16/10/2017
M18LUT (LUTIA)	Intra-arterial lutetium-177-dotatate for treatment of patients with neuro-endocrine tumor liver metastases	Marcel Stokkel	II	29/01/2019
M18PIE (PRIDE)	Preoperative Image-guided Identification of Response to neoadjuvant chemoradiotherapy in Esophageal cancer	Marcel Verheij	nvt	31/05/2018
M18PUMP	Adjuvant hepatic arterial infusion pump chemotherapy after resection of colorectal liver metastases in patients with a low clinical risk score – a randomized controlled trial	Kurt Kuhlmann	III	19/02/2019
M18SAN (SANO)	Neoadjuvant chemoradiotherapy plus surgery versus active surveillance for oesophageal cancer	Johanna van Sandick	III	25/06/2018

Type of cancer study (nick name)	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
M18SPO	The (ir)relevance of WHO criterion 2 for the diagnosis of Serrated Polyposis Syndrome	Monique van Leerdam	other	29/11/2018
M18STAR (*STAR-LNPCP)	Standardizing TrAining for endoscopic Resection of Large Non-Pedunculated Colorectal Polyps: it is prime-time to change practice	Monique van Leerdam	other	03/04/2019
M19AHW (CheckMate 8HW)	Phase 3b Randomized Clinical Trial of Nivolumab Alone, or in Combination with Ipilimumab in Participants with Microsatellite Instability High (MSIH) or Mismatch Repair Deficient Metastatic Colorectal Cancer (dMMR): CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 8HW)	Cecile Grootscholten	III	24/09/2019
M19CLP (COLOPEC II)	Second and third look laparoscopy in pT4 colon cancer patients for early detection of peritoneal metastases; the COLOPEC II randomized multicentre trial	Arend Aalbers	III	24/05/2019
M19DSC (DISCO)	Dedicated MR imaging vs surgical staging of peritoneal carcinomatosis in colorectal cancer patients: a randomized multicenter trial	Max Lahaye	other	31/10/2019
M19FTR	Prospective Registration of endoscopic Full Thickness Resection in the Netherlands	Thomas de Wijkerslooth	other	22/11/2019
M19FTRO	Long-term oncological outcomes of endoscopic fullthickness resection after previous (potential) incomplete resection of T1 CRC. A national prospective cohort study	Thomas de Wijkerslooth	other	22/11/2019
M19IMP (IMPACT - CRC)	Image guided treatment optimalization with cetuximab for patients with metastatic colorectal cancer. As part of the imaging program: Towards patient tailored cancer treatment supported by molecular imaging IMPACT: Imaging Patients for Cancer drug selecTion	Tineke Buffart	II	19/07/2019
M19TGR (TIGER)	Distribution of lymph node metastases in esophageal carcinoma	Johanna van Sandick	other	10/07/2019
N12INT	Pilot study to evaluate the tumor-reactiviity of infiltrating T cells in human malignancies	Wouter Scheper	pilot	05/09/2012
N13NAV (NAVIGATION 1)	IImage-guided navigation during abdominal surgery	Theo Ruers	pilot	17/10/2013
N14ITO	Immunogenicity of Tumor Organoids, a feasibility study	Emile Voest	other	22/07/2014
N14RCS (ColoSpect)	In vivo identification of rectum and coloncarcinoma during surgery using optical spectroscopy techniques	Theo Ruers	other	31/07/2014
N14SNS (SENSOR)	Selecting cancer patients for treatment using Tumor Organoids	Emile Voest	other	16/8/2016 (31/10/2019)
N16BTC	Blood Transcript Analysis in colorectal cancer patients	Margot Tesselaar	other	23/08/2016
N16DWI (DISPERSE)	DWI MR imaging for dedicated staging of patients with peritoneal seeding	Max Lahaye	other	26/05/2016
N16GMR	A Feasibility Study of MR-based target delineation for Radiotherapy Treatment Planning For Gastric Cancer	Marcel Verheij	pilot	02/09/2016
N16NCI (NICHE)	Nivolumab, Ipilimumab and COX2-inhibition in early stage colon cancer: an unbiased approach for signals of sensitivity	Myriam Chalabi	other	20/01/2017
N16OCR	A prospective observational cohort for the clinical evaluation of innovative image guided surgical interventions in rectal cancer	Theo Ruers	other	13/10/2016

Type of cancer study (nick name)	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
N16TRS	Real-time in vivo sensor tracking of rectal tumours during colorectal cancer surgery	Theo Ruers	other	16/9/2016 (25/9/2019)
N17PND (PANDA)	Neoadjuvant capecitabine, oxaliplatin, docetaxel and atezolizumab in non-metastatic, resectable gastric and GE-junction cancer	Myriam Chalabi	II	27/02/2018
N18TRZ (TARZAN)	Neoadjuvant treatment in rectal cancer with radiotherapy followed by atezolizumab and bevacizumab	Myriam Chalabi	I/II	26/09/2019
N18UIF	Ultrasound image fusion during percutaneous biliary drainage in patients with malignant obstruction of the biliary tree	Brigit Aarts	other	13/02/2019
N18ULN	Ultrasound-based navigation during liver surgery	Theo Ruers	other	10/08/2018
N19IPT	Contributing to research in a time of privacy: information provision and transparency	Marjanka Schmidt	other	07/11/2019
N19RNA	The identification and characterization of predictive markers of chemotherapy resistance in metastatic colorectal cancer using single-cell RNA sequencing	Emile Voest	other	30/09/2019

GYNAECOLOGICAL

Type of cancer study (nick name)	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
E55102 (ENGOT-EN2-DGCG)	A phase III Trial of postoperative chemotherapy or no further treatment for patients with node-negative stage I-II intermediate or high risk endometrial cancer	Hans Trum	III	24/8/2016 (8/4/2019)
M10MKO	Phase II and pharmacological study with WEE-1 inhibitor MK-1775 combined with carboplatin in patients with p53 mutated epithelial ovarian cancer	Frans Opdam	II	08/07/2010
M14BBB (tripleB)	The Blood-Belly Barrier	Christianne Lok	nvt	03/05/2016
M15HPV (BMS-936558)	Non-Comparative, Two-Cohort, Single-Arm, Open-Label, Phase 1/2 Study of Nivolumab in Subjects with Virus-Positive and Virus-Negative Solid Tumors	Jan Paul de Boer	I/II	27/10/2015
M15RHY (SHAPE)	A randomized phase III trial comparing radical hysterectomy and pelvic node dissection vs simple hysterectomy and pelvic node dissection in patients with low-risk early-stage cervical cancer	Willemien van Driel	III	29/12/2015
M16HE4 (HE4 prediction)	Prospective evaluation of Human Epididymal protein 4 (HE4) as predictor of malignancy in patients with a ovarian mass	Christianne Lok	other	(02/12/2019)
M16RTE (PORTEC 4a)	Randomised Phase III Trial of molecular profile-based versus standard recommendations for adjuvant radiotherapy for women with early stage endometrial cancer	Monique Bloemers	III	08/02/2017
M16SOL (SOLUTION)	Biomarker detection in cytology samples of women with gynaecologic cancer: a multicentric study	Gemma Kenter	other	30/1/2017 (3/12/2019)
M16SON (SONAR-2)	Sentinel node in ovarian cancer	Willemien van Driel	I	15/09/2016
M16TUB (TUBA)	Early salpingectomy (Tubectomy) with delayed oophorectomy to improve quality of life as alternative for risk-reducing salpingo-oophorectomy in BRCA1/2 mutation carriers	Marc van Beurden	other	01/06/2016
M17CPF (NEOCON-F)	Neo-Adjuvant Chemotherapy and Conservative Surgery in Cervical Cancer to Preserve Fertility	Nienke van Trommel	II	04/12/2018
M17EBR (EMBRACE-II)	Image guided intensity modulated External beam radiochemotherapy and MRI based adaptive Brachytherapy in locally advanced Cervical cancer	Monique Bloemers	other	04/06/2018

Type of cancer study (nick name)	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
M17GINC (GINA-Cervix)	The state of the (sentinel) lymph node microenvironment in patients with cancer of the cervix	Henry Zijlmans	other	28/02/2018
M17GINV (GINA-Vulva)	The state of the (sentinel) lymph node microenvironment in patients with HPV-positive and HPV-negative cancer of the vulva	Henry Zijlmans	other	28/02/2018
M17GSC (GERSOC)	GERiatric Screening in the treatment of elderly patients with Ovarian Carcinoma	Hans Trum	other	07/06/2018
M17MRO	Clinical impact of dedicated MR staging of ovarian cancer	Max Lahaye	other	17/04/2018
M17OVH (OVHIPEC-2)	Randomized clinical trial for stage III epithelial ovarian cancer randomizing between primary cytoreductive surgery with or without hyperthermic intraperitoneal chemotherapy	Willemien van Driel	III	21/06/2019
M17PDV (PADOVA)	Physical Activity and Dietary intervention in OVArian cancer: a RCT evaluating effects on body composition, physical function, and fatigue	Willemien van Driel	other	01/05/2018
M17SNX (Sentix)	A prospective observational trial on sentinel lymph node biopsy in patients with early stage cervical cancer	Hans Trum	other	22/10/2018 (10/7/2019)
M18BAM	An open-label, first-in-human, multi-center study to evaluate the safety, tolerability, pharmacokinetics and anti-tumor activity of a thorium-227 labeled antibody-chelator conjugate, BAY 2287411 injection, in patients with solid tumors known to express mesothelin	Egbert Smit	I	13/02/2019
M18CRA	Cancer risk assessment in women with vulvar intraepithelial neoplasia. Historic cohort study + Prospective study	Marc van Beurden	other	06/11/2018
M18FUG (FUCHSia)	An open-label, single arm, prospective, multi-center, tandem two stage designed, phase II study to evaluate the efficacy of Fulvestrant in women with recurrent/metastatic estrogen receptor positive gynecological malignancies	Frederic Amant	II	13/06/2019
M18IQM (IQ-EMBRACE)	Quantitative MR Imaging in Locally Advanced Cervical Cancer -Sub-study under the EMBRACE II protocol	Monique Bloemers	other	26/09/2019
M18KZH	Ontwikkeling option grid/keuzehulp t.b.v. behandeling gevorderd ovariumcarcinoom	Willemien van Driel	other	31/7/2018 (13/11/2019)
M19GRA (GRANULOSA)	Granulosa cell tumors: a step towards targeted therapy	Christianne Lok	other	23/04/2019
N12INT	Pilot study to evaluate the tumor-reactiviity of infiltrating T cells in human malignancies	Wouter Scheper	pilot	05/09/2012
N15TCH	Isolation of T cell receptors from human papilloma virus (HPV)-reactive or other tumor-reactive T cells from patients with oropharyngeal, cervical or vulvar cancer	Lotje Zuur	other	13/07/2016
N16DWI (DISPERSE)	DWI MR imaging for dedicated staging of patients with peritoneal seeding	Max Lahaye	other	26/05/2016
N16NEON	Personalized adoptive T-cell therapy protocol	John Haanen	other	09/11/2016
N16OPE	Feasibility study of neo-adjuvant treatment with carboplatin, paclitaxel and pembrolizumab in primary stage IV serous ovarian cancer	Gabe Sonke	I	19/07/2017
N16SIG	Safety, immunogenicity and clinical response of sig-HELP-E6SH/E7SH-kdel, injected in the epidermis by DNA tattoo vaccination, in HPV16-positive vulvar intraepithelial neoplasia: a phase I/II study	Gemma Kenter	I/II	09/11/2016

Type of cancer study (nick name)	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
HEAD AND NECK				
M11ART (ARTFORCE)	Adaptive and innovative radiation treatment for improving cancer treatment outcome	Olga Hamming-Vrieze	II	20/12/2011 (4/12/2019)
M14PAR	TachoSil patch application as replacement of closed suction wound drainage by parotid gland surgery: a prospective study	Fons Balm	other	22/01/2015
M15HPV (BMS-936558)	Non-Comparative, Two-Cohort, Single-Arm, Open-Label, Phase 1/2 Study of Nivolumab in Subjects with Virus-Positive and Virus-Negative Solid Tumors	Jan Paul de Boer	I/II	27/10/2015
M16OPS	Optical properties of the sinonasal cavity after surgical tumor resection	Baris Karakullukcu	other	01/03/2017
M16SPS	Combination of salvage surgery and adjuvant photodynamic therapy in management of recurrent or residual sinonasal tumors	Baris Karakullukcu	other	26/01/2017
M17CPI	Validation and psychometric properties of the Dutch version of the Communicative Participation Item Bank (CPIB) short form	Michiel van den Brekel	other	16/10/2017
M17MOV (Move-FIT)	Optimising physical fitness in patients receiving chemo radiotherapy for head and neck cancer: a feasibility study	Martijn Stuiver	other	01/03/2018
M17OSA	Prevalence of Obstructive Sleep Apnea Syndrome (OSAS) after treatment for advanced stage head and neck cancer	Ludi Smeele	other	28/02/2019
M18EAC	External Auditory Canal Carcinoma, a retrospective study on treatment outcome	Michiel van den Brekel	other	16/1/2019 (16/1/2019)
M18ISA	A randomized, double-blind, placebo-controlled, phase 2 study of Cemiplimab versus the combination of Cemiplimab with ISA101b in the treatment of subjects with HPV16-positive Platin-resistant oropharyngeal cancer (OPC)	Jan Paul de Boer	other	01/05/2019
M18KOC	Ontwikkeling van een keuzehulp voor patiënten met een orofarynxtumor waarbij curatieve chirurgie een behandeloptie is	Ludi Smeele	other	22/02/2019
M18TUN (TUNE)	Validation of TUNE criteria in patients treated with chemoradiotherapy using cisplatin for head and neck squamous cell carcinoma	Lotje Zuur	other	15/05/2018
M19SUS (SUSPECT-2)	Mapping of sentinel lymph node drainage Using Spect/CT to tailor highly selective elective nodal irradiation in node-negative neck of patientens with head and neck cancer	Abrahim Al-Mamgani	II	25/06/2019
N12MAC (M&M)	Exploring the contribution of Macrophages in the microenvironment of HPV-induced squamous cell carcinoma of the head and neck	Jan Paul de Boer	other	31/08/2012
N13ORH	Olaparib dose escalation trial in patients treated with radiotherapy for stage II-III laryngeal and stage II-III HPV-negative oropharyngeal squamous cell carcinoma	Marcel Verheij	I	20/02/2014
N14IMR (IMRAD)	The immunological aspects of conventional therapies for the treatment of head and neck squamous cell carcinoma (HNSCC). An exploratory study to study the mmunological effects of (chemo)radiotherapy in HNSCC patients	Lotje Zuur	other	23/03/2015
N14LMN	Lymphatic mapping of the neck in patients with oral cavity malignancies using ICG-nanocolloid	Martin Klop	other	10/06/2015
N15HTC	Longitudinal analysis of head and neck cancer-specific immunity in patients treated with (salvage) surgery	Lotje Zuur	other	16/12/2015
N15PAH	Feasibility of position averaged planning-CT for head-neck tumours	Wouter Vogel	other	16/12/2015 (15/1/2019)

Type of cancer study (nick name)	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
N15SHA (SHAFE)	Effect of a silicone foam dressing (XtraSorb Foam) and hydrocolloid dressing (XtraSorb HCS) compared to silicone foam dressing (Mepilex) or an alginate (Kaltostat) combined with a semipermeable film (Tegaderm) on the donor site after split-thickness skin graft: a randomized controlled trial	Peter Lohuis	other	31/05/2016
N15TCH	Isolation of T cell receptors from human papilloma virus (HPV)-reactive or other tumor-reactive T cells from patients with oropharyngeal, cervical or vulvar cancer	Lotje Zuur	other	13/07/2016
N16IGM	Intraoperative verification of maxillary malignancy resection with cone-beam computed tomography	Baris Karakullukcu	pilot	21/2/2017 (31/10/2019)
N16IMC (IMCISION)	ImmunoModulation by the Combination of Ipilimumab and nivolumab neoadjuvant to Surgery In advanced Or recurrent head and Neck carcinoma	Lotje Zuur	I	08/12/2016
N16NEON	Personalized adoptive T-cell therapy protocol	John Haanen	other	09/11/2016
N17ADM (ADMIRE)	Adaptive Dose-Escalated Multi-modality Image-guided RadiothErapy for head and neck cancer by twice reimaging, re-delineation and re-planning during the course of radiotherapy	Abrahim Al-Mamgani	other	31/8/2017 (24/4/2019)
N17BTM	Personalization of a biomechanical tongue model for the prediction of treatment outcome: a feasibility study	Ludi Smeele	other	22/06/2017
N17DSI	Determining the dose-effect relation of salivary gland irradiation and cell loss with PSMA PET	Wouter Vogel	other	23/05/2017
N17LFO	Effectiveness of lipofilling in patients with oropharyngeal dysfunction (speech and/or swallowing) after treatment for head and neck cancer	Ludi Smeele	other	19/12/2017
N17SPE (SPEAT)	The timed Swallowing Performance EATing and drinking test to objectify dysphagia in head and neck cancer patients	Ludi Smeele	other	24/04/2018
N17SSF	Prospective assessment of swallowing and speech function 10 years after preventive swallowing rehabilitation and chemoradiotherapy for head and neck cancer	Ludi Smeele	other	9/3/2018 (30/10/2019)
N17SWU	Shear wave ultrasound elastography of the tongue – a feasibility study	Ludi Smeele	other	14/6/2017 (8/5/2019)
N17TOT	Tracking of oral cavity carcinomas in head and neck surgery	Baris Karakullukcu	other	18/04/2017
N18EMT	Active and passive elasticity measurements of the tongue using in vivo measurement techniques	Ludi Smeele	other	10/08/2018
N18HME	HME attachment Study	Michiel van den Brekel	other	10/1/2019 (19/2/2019)
N18HSP	Are circulating hematopoietic stem and progenitor cells a potential biomarker for therapy response and disease progression in patients with squamous cell carcinoma of the head and neck?	Lotje Zuur	other	06/07/2018
N18PCN (PECAN)	Prospective study Evaluating CtDNA as a biomarker for treatment failure in head and Neck squamous cell carcinoma	Abrahim Al-Mamgani	other	15/05/2018
N18VOQ	Voice quality and voice related quality of life in patients treated with totallaryngectomy; A prospective data collection	Klaske van Sluis	other	20/02/2018
N19IFC (INFLUENCE)	INtra-operative evaluation of a novel FLUorescENt CmEt tracer in penile and tongue cancer	Baris Karakullukcu	other	13/11/2019

Type of cancer study (nick name)	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
LUNG				
E1205	EORTC randomized phase II study of pleurectomy/decortication (P/D) preceded or followed by chemotherapy in patients with early stage malignant pleural mesothelioma	Paul Baas	II	15/03/2018
M13N19 (NVALT19)	Switch maintenance treatment with gemcitabine for patients with malignant mesothelioma who do not progress after 1st line therapy with a pemetrexed-platinum combination. A randomised open label phase II	Sjaak Burgers	II	4/3/2014 (19/2/2019)
M14AFS	Phase I/II study with the combination of afatinib and selumetinib in advanced KRAS mutant positive and PIK3CA wildtype colorectal, non-small cell lung and pancreatic cancer	Frans Opdam	I/II	19/05/2015
M14ENI	A phase II, multicenter, open-label study of EGF816 in combination with Nivolumab in adult patients with EGFR mutated non-small cell lung cancer and of INC280 in combination with Nivolumab in adult patients with cMet positive non-small cell lung cancer	Willemijn Theelen	II	9/6/2015 (20/03/2019)
M14LTK	Phase I/II study with lapatinib plus trametinib in patients with metastatic KRAS mutant colorectal, non-small cell lung and pancreatic cancer	Frans Opdam	I/II	4/8/2014 (29/5/2019)
M14TUM (TUMOROID)	Tumor organoids: feasibility to predict sensitivity to treatment in cancer patients	Emile Voest	pilot	22/07/2014
M15CIN (CINC280A2201)	A phase II, multicenter, three-cohort study of oral cMET inhibitor INC280 in adult patients with EGFR wild-type (wt), advanced non-small cell lung cancer (NSCLC) who have received one or two prior lines of systemic therapy for advanced/matastatic disease	Egbert Smit	II	15/09/2015
M15LEM (LEMA)	Lung cancer Early Molecular Assessment trial	Sjaak Burgers	other	29/06/2016
M15N22 (NVALT 22)	First line chemotherapy in KRAS mutated non-small cell lung cancer patients: a phase III comparing cisplatin-pemetrexed with carboplatin-paclitaxelbevacizumab	Egbert Smit	III	05/07/2016
M16N24 (NVALT 24)	A phase III prospective double blind placebo controlled randomized study of adjuvant MEDI4736 in completely resected non-small cell lung cancer	Sjaak Burgers	III	28/3/2017 (18/10/2019)
M16PLE	Phase Ib, open-label, multi-center study to characterize the safety, tolerability and pharmacodynamics (PD) of PDR001 in combination with LCL161, Everolimus (RAD001) or Panobinostat (LBH589)	Neeltje Steeghs	I	01/11/2016
M16STT (STARTRK-2)	An open-label, multicenter, global phase 2 basket study of Entrectinib for the treatment of patients with locally advanced or metastatic solid tumors that harbour NTRK1/2/3, ROSI or ALK gene rearrangements	Egbert Smit	II	24/08/2016
M17ARC (ARCS-Multi)	Phase Ib multi-indication study of Anetumabrav tensine (BAY 94-9343) in patients with mesothelin expressing advanced or recurrent malignancies	Egbert Smit	I	07/09/2017
M17DNM (DENIM)	A randomized, open-label phase II/III study with dendritic cells loaded with allogenic tumor cell lysate (PheraLys) in subjects with mesothelioma as maintenance treatment (MesoPher) after chemotherapy	Paul Baas	II	15/11/2018
M17FNN	^{18}F-PD-L1 PET/CT to predict response to Nivolumab in patients with NSCLC	Joop de Langen	other	26/10/2018
M17IMG	[89]Zr-pembrolizumab-PET imaging in patients with locally advanced or metastatic melanoma or nonsmall cell lung cancer	John Haanen	pilot	23/07/2018
M17IPL	Repeatability of 18F FDG/CT and immunological profiling of lymph nodes in NSCLC	Joop de Langen	pilot	23/01/2018
M17PPD	PDR001 in combination with platinum-doublet chemotherapy in PD-L1 unselected metastatic NSCLC patients	Sjaak Burgers	I	2/11/2017 (11/2/2019)

Type of cancer study (nick name)	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
M17RLC	Reirradiation for recurrent lung cancer in the thorax: overall survival, local control, and toxicity: a phase 2 trial	Joost Knegjens	II	07/11/2018
M17SAT (SATIN)	Safety of TKI concurrent with cranial radiotherapy in NSCLC patients	Egbert Smit	IV	27/05/2019
M17ZML	Companion biomarker development for MEDI4736 treated non-small-cell lung cancer patients using [89]Zirconium-labeled MEDI4736 - a feasibility study	Joop de Langen	pilot	13/06/2018
M18ACX	Phase II study of afatinib in combination with cetuximab in EGFR exon 20 insertion positive non-small-cell lung cancer	Joop de Langen	II	11/12/2018
M18ALE (ALERT-lung)	A single arm phase II trial evaluating the activity of alectinib for the treatment of pretreated RETrearranged advanced NSCLC	Egbert Smit	II	17/05/2019
M18AMG (AMG 757)	A Phase I study evaluating the safety, tolerability and pharmacokinetics of AMG 757 in subject with small cell lung cance	Neeltje Steeghs	I	27/02/2019
M18BAM	An open-label, first-in-human, multi-center study to evaluate the safety, tolerability, pharmacokinetics and anti-tumor activity of a thorium-227 labeled antibody-chelator conjugate, BAY 2287411 injection, in patients with solid tumors known to express mesothelin	Egbert Smit	I	13/02/2019
M18BNI (CheckMate 592)	An Exploratory Study of the Biologic Effects and biomarkers of Nivolumab Combined With Ipilimumab in Subjects With Treatment-Naive Stage IV or Recurrent Non-Small Cell Lung Cancer (NSCLC)	Joop de Langen	II	23/10/2018
M18BRM	A phase I drug-drug interactions study between Brigatinib and the CYP3A substrate Midazolam in patients with ALK-postive or ROSI-postive solid tumors	Egbert Smit	I	13/06/2019
M18COS	11C-osimertinib-PET/CT to identify T790M positive tumors in patients that are T790M negative in a single tumor biopsy and a circulating tumor DNA sample	Joop de Langen	I/II	10/04/2019
M18DSN	A phase 2, multicenter, open-label, 2-cohort study of trastuzumab deruxtecan (DS-8201a), an anti-HER2 antibody drug conjugate (ADC), for HER2-overexpressing or-mutated, unresectable and/or metastatic non-small cell lung cancer	Egbert Smit	II	14/11/2018
M18IOP	An open-label, randomized, phase I/II trial investigating the safety and efficacy of IO102 in combination with pembrolizumab, with or without chemotherapy, as first-line treatment for patients with metastatic non-small cell lung cancer	Paul Baas	I/II	02/09/2019
M18IRL (ImmunoSABR)	Phase II study examining the activity of L19-IL2 immunotherapy and stereotactic ablative radiotherapy in metastatic non-small cell lung cancer	Monique de Jong	II	26/09/2019
M18MPR (IMPROVE)	Individualized pemetrexed dosing in patients with non-small cell lung cancer or mesothelioma based on renal function to improve treatment response	Sjaak Burgers	II	23/01/2019
M18OSI (OSIRIS)	OSIRIS: Osimertinib resistance analysis in patients with EGFR mutation positive non-small-cell lung carcinoma that have progressed on osimertinib treatment	Joop de Langen	other	23/07/2019
M18PDL	A phase II, mullticenter, randomized, open-label controlled study of M7824 versus Pembrolizumab as a first treatment in patients with PD-L1 expressing advanced non-small cell lung cancer	Egbert Smit	II	15/03/2019
M18PST (Position-20)	Patients on osimertinib with EGFR mutation exon 20, non-T790M. The position-20 trial	Joop de Langen	II	21/01/2019
M18SPR (SPUTUM)	Sputum analysis for diagnosis of malignancy in the differential of radiotherapy induced changes on CT	Egbert Smit	other	05/04/2019
M18SRP	Combining SBRT and immunotherapy in early stage NSCLC patients planned for surgery: exploring safety and immunological proof of principle	Joop de Langen	other	25/05/2018

Type of cancer study (nick name)	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
M18TAT (TATIN)	Track and treat in NSCLC – ctDNA guided treatment of early resistance to targeted treatment in patients with EGFR positive NSCLC	Joop de Langen	II	17/07/2019
M18TEO	Trastuzumab-emtansine and osimertinib combination treatment to target HER2 bypass track resistance in EGFR mutation poitive NSC	Joop de Langen	II	19/12/2018
M18TEP (VISION)	A phase II single-arm trial to investigate tepotinib in advanced (Stage IIIB/IV) non-small cell lung cancer with MET exon 14 (METex14) skipping alterations or MET amplifications	Egbert Smit	II	03/04/2019
M19EBL	A phase 2, open-label study with Encorafenib + Binimetinib in patients with BRAF V600F-mutant nonsmall cell lung cancer	Egbert Smit	II	27/11/2019
M19SYM (SYMPRO-Lung)	Symptom monitoring with patient-reported outcomes using a web application among lung cancer patients in the Netherlands	José Belderbos	other	24/09/2019
M19TPO	A phase II single-arm study to investigate tepotinib combined with osimertinib in MET amplified, advanced or metastatic non-small cell lung cancer (NSCLC) harboring activating EGFR mutations and having acquired resistance to prior 1st to 3rd generation EGFR-tyrosine kinase inhibitor therapy	Egbert Smit	II	03/12/2019
N13FPB	Fluid phase biopsy (circulating tumour DNA and serum tumour markers) in patients with non-small cell lung cancer	Sjaak Burgers	other	17/12/2013
N14ITO	Immunogenicity of Tumor Organoids, a feasibility study	Emile Voest	other	22/07/2014
N14PLU (PROOF)	Personalized treatment with combination therapy for patients with pleural effusion due to malignant pleural mesothelioma or lung cancer in second or third line. An open label phase II study	Paul Baas	II	03/10/2014
N16NEON	Personalized adoptive T-cell therapy protocol	John Haanen	other	09/11/2016
N17DTL (Induction-1)	A Phase Ib, Open-label, Single-center study to assess the safety of cancer-immunotherapy induction with Tremelimumab and Durvalumab prior to Chemoradiotherapy and/or Resection in the treatment of locally advanced NSCLC	Willemijn Theelen	I	05/10/2018
N18NUA (NUANCE)	NUtritional Assessment in Non-small Cell lung cancer patients	Martijn Stuiver	other	29/06/2018
N18PET	Novel Ga68-PSMA PET tracer to differentiate between radiation necrosis and tumor progression in stereotactic irradiated brain metastases	Dieta Brandsma	other	14/08/2019
N19RER	A Open-label Single-arm pharmacokinetic Trial, Investigating the Effect of CYP3A4 inhibitor Ritonavir on the Pharmacokinetics of Erlotinib	Neeltje Steeghs	other	25/04/2019

LYMPHOMA - HODGKIN'S DISEASE

Type of cancer study (nick name)	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
M13SOP (SOPHIA)	Study of Menopause in ex-patients with Hodgkin Lymphoma: influence on long-term adverse events	Floor van Leeuwen	other	17/01/2014
M17MIW	A Phase Ib, open label, multicenter study of the safety and efficacy of MIW815 (ADU-S100) administered by intratumoral injection with PDR001 to patients with advanced/metastatic solid tumors or lymphomas	Neeltje Steeghs	I	2/2/2018 (11/12/2019)
M17SPA (SPARKLE)	The effect of light therapy on fatigue and psychosocial functioning in long-term survivors of (non-)Hodgkin lymphoma: a randomized controlled trial	Eveline Bleiker	other	13/07/2017

Type of cancer study (nick name)	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
LYMPHOMA - NON-HODGKIN'S				
M15PRM (PRMT5i)	A phase I, open-label, dose escalation study to investigate the safety, pharmacokinetics, pharmacodynamics and clinical activity of GSK3326595 in subjects with solid tumors and non-Hodgkin's lymphoma	Frans Opdam	I	27/10/2016
M17MIW	A Phase Ib, open label, multicenter study of the safety and efficacy of MIW815 (ADU-S100) administered by intratumoral injection with PDR001 to patients with advanced/metastatic solid tumors or lymphomas	Neeltje Steeghs	I	2/2/2018 (11/12/2019)
M17SPA (SPARKLE)	The effect of light therapy on fatigue and psychosocial functioning in long-term survivors of (non-)Hodgkin lymphoma: a randomized controlled trial	Eveline Bleiker	other	13/07/2017
M18CNH (CLARITY)	Cardiotoxicity and other Late effects After Radiotherapy and Immuno-chemoTherapy for nonHodgkin lYmphoma	Floor van Leeuwen	other	07/10/2019
MELANOMA / SKIN				
E1208MG (Minitub)	Minitub: Prospective registry of Sentinel Node (SN) positive melanoma patients with minimal SN tumor burden who undergo Completion Lymph Node Dissection (CLND) or Nodal Observation	Alexander van Akkooi	other	23/04/2015
E1612 (EBIN)	Combination of targeted therapy (encorafenib and binimetinib) followed by combination of immunotherapy (ipilimumab and nivolumab) vs immediate combination of immunotherapy in patients with unresectable or metastatic melanoma with BRAF V600 mutation: an EORTC randomized phase II study	Alexander van Akkooi	II	27/05/2019
M14REP (REPOSIT)	A Phase II, Open-Label, Multicenter Study of Vemurafenib plus Cobimetinib (GDC-0973) in Unresectable Stage IIIc or Metastatic Melanoma - Response Monitoring and Resistance Prediction with Positron Emission Tomography and Tumor Characteristics	Bernies van der Hiel	II	24/11/2014 (15/3/2019)
M14TIL	Randomized phase III study comparing a non-myeloablative lymphocyte depleting regimen of chemotherapy followed by infusion of tumor infiltrating lymphocytes and interleukin-2 to standard ipilimumab treatment in metastatic melanoma	John Haanen	III	06/08/2014
M15HPV (BMS-936558)	Non-Comparative, Two-Cohort, Single-Arm, Open-Label, Phase 1/2 Study of Nivolumab in Subjects with Virus-Positive and Virus-Negative Solid Tumors	Jan Paul de Boer	I/II	27/10/2015
M16COW (COWBOY)	Phase 2 Study testing the COmbination of Vemurafenib With Cobimetinib in BRAF V600 mutated Melanoma Patients to Normalize LDH and Optimize immunotherapY with Nivolumab and Ipilimumab	Christian Blank	II	06/07/2017
M16OPN (OpACIN-neo)	Multicenter Phase 2 Study to Identify of the Optimal neo-Adjuvant Combination Scheme of Ipilimumab and Nivolumab	Christian Blank	II	01/11/2016
M17IMG	[89]Zr-pembrolizumab-PET imaging in patients with locally advanced or metastatic melanoma or nonsmall cell lung cancer	John Haanen	pilot	23/07/2018
M17IVR	In vivo reflectance confocal microscopy, a novel non-invasive tool for diagnosing skin cancer - a randomized controlled trial	Marianne Crijns	other	12/6/2017 (5/3/2019)
M17PTS (POINTING)	Towards patient-tailored cancer immunotherapy supported by a multifaceted predictive signature composed of integrative omics and molecular imaging	John Haanen	other	12/11/2018
M18NKN	A Phase 3, Randomized, Open-label Study of NKTR214 Combined with Nivolumab Versus Nivolumab in Participants with Previously Untreated Unresectable or Metastatic Melanoma	Christian Blank	III	27/05/2019

Type of cancer study (nick name)	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
M18PDR	A randomized, open-label, phase II open platform study evaluating the efficacy and safety of novel spartalizumab (PDR001) combinations in previously treated unresectable or metastatic melanom	John Haanen	II	01/03/2019
M19PCX (PROCLAIM)	A Phase 2, Open-Label, Multi-cohort Study of PD-L1 Probody™ Therapeutic CX-072 in Combination With Other Anticancer Therapy in Adults With Solid Tumors	Christian Blank	II	04/11/2019
M19SST (Safe Stop Trial)	Observational study of the STOP & GO strategy of PD-1 blockade in advanced melanoma patients upon achieving a complete or partial response	John Haanen	II	10/05/2019
N03LAM	Longitudinal analysis of melanoma-specific immunity in stage III and IV melanoma patients	John Haanen	other	22/08/2003
N13GEN	Regulation of skin tumorgenesis by integrin alpha3beta1	Arnoud Sonnenberg	other	27/11/2013
N13NDT (REDuCTOR)	Cytoreductive treatment of dabrafenib combined with trametinib to allow complete surgical resection in patients with BRAF mutated, prior unresectable stage III or IV melanoma	John Haanen	II	6/12/2013 (3/7/2019)
N16IGM	Intraoperative verification of maxillary malignancy resection with cone-beam computed tomography	Baris Karakullukcu	pilot	21/2/2017 (31/10/2019)
N16MME	Magnetic Marker Localization for Melanoma Surgery. A feasibility study	Theo Ruers	other	25/1/2017 (31/10/2019)
N16VOM	HDAC inhibitor vorinostat in resistant BRAF V600 mutated advanced melanoma	Sofie Wilgenhof	other	24/06/2016
N17BCC (BCC-COMI)	Noninvasive diagnostics and subtyping of basal cell carcinoma in the head and neck by dermoscopy and handheld reflectance confocal microscopy	Fons Balm	other	19/04/2017
N17LMC (LM-COMI)	Lentigo maligna: Diagnostic accuracy of in vivo handheld reflectance confocal microscopy for pigmented macules in the head and neck	Marianne Crijns	other	19/04/2017
N18PET	Novel Ga68-PSMA PET tracer to differentiate between radiation necrosis and tumor progression in stereotactic irradiated brain metastases	Dieta Brandsma	other	14/08/2019

MISCELLANEOUS

Type of cancer study (nick name)	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
E1525 (nivothym)	Single-arm, multicenter, phase II study of nivolumab in patients with type B3 thymoma and thymic carcinoma previously treated with chemotherapy	Sjaak Burgers	II	20/02/2019
M15GRA (GRAFITI)	Prospective registration study on growth behavior of aggressive fibromatosis without therapeutic intervention	Frits van Coevorden	other	15/9/2015 (12/12/2018)
M16STT (STARTRK-2)	An open-label, multicenter, global phase 2 basket study of Entrectinib for the treatment of patients with locally advanced or metastatic solid tumors that harbour NTRK1/2/3, ROSI or ALK gene rearrangements	Egbert Smit	II	24/08/2016
M17ARC (ARCS-Multi)	Phase Ib multi-indication study of Anetumab ravtensine (BAY 94-9343) in patients with mesothelin expressing advanced or recurrent malignancies	Egbert Smit	I	07/09/2017
M17CLE	CLE in diagnosing Pleural Malignancies, a comparison with pathology	Paul Baas	other	16/8/2017 (31/10/2019)
M17CMT (EXAMINER)	A Randomized, Double-blind Study to Evaluate the Efficacy and Safety of Cabozantinib (XL184) at 60 mg/Day Compared to 140 mg/Day in Progressive, Metastatic Medullary Thyroid Cancer Patients	Jan Paul de Boer	IV	15/05/2018

Type of cancer study (nick name)	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
M17LAN	A phase 3, prospective, randomized, double-blind, multi-center study of the efficacy of lanreotide Autogel/Depot 120 mg plus BSC vs placebo plus BSC for tumour control in subjects with the well differentiated, metastatic and/or unresectable, typical or atypical, lung neuroendocrine tumors	Wieneke Buikhuisen	III	05/07/2017
N18DAF (DeFi)	A randomized, double-blind, placebo-controlled, phase 3 trial of Nirogacestat versus placebo in adult patients with progressing Desmoid Tumors/Aggressive Fibromatosis	Winette van der Graaf	III	25/09/2019
N15HNT (HEP-NET)	Hepatic NET metastasis embolization biomarker evaluation	Margot Tesselaar	other	13/1/2016 (13/11/2019)
N17ICO	Position stability during radiosurgery of brain tumours	Gerben Borst	other	18/1/2018 (24/1/2019)
N17MRD	Healthy volunteer imaging techniques development for motion management in MR-guided adaptive radiotherapy	Gabe Sonke	other	09/11/2017
N18ISI	Inhibition of salivary glands to reduce uptake of radioactive Iodine	Wouter Vogel	pilot	29/01/2019
N18SEA	Muscle activation during strengthening exercises with the Swallow Exercise Aid: visualization using Magnetic Resonance Imaging	Ludi Smeele	other	15/02/2019
M18ORG	Modeling neuroendocrine tumors using adult stem cellderived organoids (NET organoids)	Margot Tesselaar	other	23/11/2018

SOFT TISSUE / OSTEOSARCOMA

Type of cancer study (nick name)	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
E1202	Phase II trial of cabazitaxel in metastatic or inoperable locally advanced dedifferentiated liposarcoma	Neeltje Steeghs	II	7/11/2018 (22/3/2019)
E1402 (Euro Ewing 2012)	International randomised controlled trial for the treatment of newly diagnosed Ewing's sarcoma family of tumours	Martijn Kerst	other	18/1/2018 (18/1/2019)
E1506 (ANITA)	A Phase II multicenter study comparing the efficacy of the oral angionenesis inhibitor Nintedanib with the intravenous cytotoxic compound Ifosfamide for treatment of patients with advanced metastatic soft tissue sarcoma after failure of systemic nonoxazaphosporine- based first line chemotherapy for inoperable disease	Neeltje Steeghs	II	03/11/2017
M15GCD (GALLOP)	Gastrointestinal stromal tumors (GIST): assessment of mutation in tumors and in circulating tumor DNA and measurement of TKI plasma exposure to optimize treatment	Neeltje Steeghs	other	12/03/2015
M15PAS (PASART-2)	Phase II clinical study of concurrent PAzopanib for non-metastatic SArcoma patients to be treated with RadioTherapy, localized in the extremities, trunk and chest wall or the head and neck region	Rick Haas	II	30/12/2015 (31/10/2019)
M16GTDM (GIST-TDM)	Persoonlijk aangepast doseren van anti-tumormedicatie in GIST patiënten op basis van geneesmiddel-spiegels	Neeltje Steeghs	other	08/08/2016
M16ITF (SSG XXII)	Three versus five years of adjuvant imatinib as treatment of patients with operable GIST with a high risk for recurrence: A randomised phase III study	Neeltje Steeghs	III	04/07/2017
M17BLU (VOYAGER)	An International, Multicenter, Open-label, Randomized, Phase 3 Study of BLU-285 vs Regorafenib in Patients with Locally Advanced Unresectable or Metastatic Gastrointestinal Stromal Tumor (GIST)	Neeltje Steeghs	III	27/5/2019 (4/11/2019)
M18HOL (HOLISTIC)	Health-related quality Of Life In patients with advanced Soft Tissue sarcomas treated with Chemotherapy	Neeltje Steeghs	other	22/01/2019

Type of cancer study (nick name)	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
M18QUE (Quest)	The impact of the diagnostic trajectory in sarcoma patients on stage at diagnosis, primary treatment, clinical outcome and quality of life	Rick Haas	other	05/06/2018
N10DMY (DOREMY)	Dose reduction of preoperative radiotherapy in Myxoid liposarcomas	Rick Haas	II	15/12/2010
N16STS	Development of a platform of Patient Derived Xenografts (PDX) of Soft Tissue Sarcomas (STS): Protocol to obtain biopsies from patients with nonmetastatic STS	Rick Haas	other	30/01/2017
N17PSI	Increasing pazopanib exposure by splitting intake moments	Neeltje Steeghs	IV	22/5/2017 (30/10/2019)
N18IBA	Absolute bioavailability trial of oral imatinib (Glivec®) using a stable isotope labeled intravenous imatinib microdose	Neeltje Steeghs	I	4/2/2019 (2/9/2019)
N19PCA	Neoadjuvant trial on the efficacy of propranolol monotherapy in cutaneous angiosarcoma	Neeltje Steeghs	other	03/12/2019

URO-GENITAL

Type of cancer study (nick name)	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
E1407 (TIGER)	A randomised phase III trial comparing conventional-Dose chemotherapy using paclitaxel, ifosfamide, and cisplatin (TIP) with high dose chemotherapy using mobilizing paclitaxel followed by High-dose carboplatin and etoposide (TI-CE) as first salvage treatment in relapsed or refractory germ cell tumours	Martijn Kerst	III	20/10/2016
M10PCM (PCMM)	Prostate cancer molecular medicine	Henk van der Poel	other	17/02/2011
M13PSN	Prospective randomized multicenter comparison of indocyanine green (ICG)-99mTc-nanocolloid vs. 99mTcnanocolloid plus an intraoperative injection of ICG for the detection and surgical resection of the sentinel nodes in patients with prostate cancer	Henk van der Poel	II	17/04/2014
M14HSN	Sentinel node biopsy for bladder cancer using the hybrid tracer	Bas van Rhijn	other	26/02/2015
M15MPO	A phase III, open-label, multicenter, randomized study of MPDL3280A (anti-PDL-1 antibody) versus observation as adjuvant therapy in patients with PD-L1-selected, high-risk muscle-invasive bladder cancer after cystectomy	Michiel van der Heijden	III	16/11/2015
M15RTO (ROTOR)	Registry of Treatment Outcomes in a non-study population of Symptomatic Metastasized Castration Resistant Prostate Cancer (mCRPC) Patients Treated with Radium-223. WMO-protocol	André Bergman	other	30/10/2015
M15VPM	A phase I/II open label clinical trial assessing safety and efficacy of intravesical instillation of VPM1002BC in patients with recurrent non-muscle inasive bladder cancer after standard BCG therapy	Kees Hendricksen	II	18/1/2018 (31/10/2019)
M16ARA (ARASENS)	A randomized, double-blind, placebo-controlled Phase III study of ODM-201 versus placebo in addition to standard androgen deprivation therapy and docetaxel in patients with metastatic hormonesensitive prostate cancer	André Bergman	III	10/05/2017
M16FPV (Fingerprint)	Vascular fingerprint to identify patients at risk for arterial cardiovascular events within the first year after start of cisplatin-based chemotherapy for testicular cancer: a validation study	Martijn Kerst	other	07/10/2016
M16OST (OSTRICh)	A randomized, open label, Phase IIB trial of Optimal Sequencing of Treatment Options for Poor Risk Metastasized Castration Resistant Prostate Cancer Previously Treated with Docetaxel	André Bergman	II	01/06/2017

Type of cancer study (nick name)	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
M16PMP (KEYNOTE-199)	Phase II Trial of Pembrolizumab (MK-3475) in Subjects with Metastatic Castration-Resistant Prostate Cancer (mCRPC) Previously Treated with Chemotherapy	André Bergman	II	13/10/2016 (8/2/2019)
M17AAT	A phase III, multicenter, randomized, placebo-controlled double-blind study of Atezolizuamb (anti-PD-L1 antibody) as adjuvant therapy in patients with renal cell carcinoma at high risk of developing metastasis following nephrectomy	Axel Bex	III	9/6/2017 (29/4/2019)
M17AIR	A Phase 3 Randomized Study Comparing Nivolumab and Ipilimumab Combination vs Placebo in Participants with Localized Renal Cell Carcinoma Who Underwent Radical or Partial Nephrectomy and Who Are at High Risk of Relapse	Hans van Thienen	III	21/08/2017
M17CAP (CABAZIPET)	Towards early identification of response to CABAZItaxel in patients with metastatic castrationresistant prostate cancer: potential of 18F-Choline PET-CT	Marcel Stokkel	II	30/8/2017 (31/10/2019)
M17DOC	Multicenter safety, feasibility and pharmacokinetic phase I-II trial of ModraDoc006/r in patients with metastatic castration-resistant prostate cancer	André Bergman	I	26/4/2017 (13/3/2019)
M17EPC (ECHO-303)	A Phase 3 Randomized, Double-Blind Clinical Study of Pembrolizumab + Epacadostat vs Pembrolizumab + Placebo as a Treatment for Recurrent or Progressive Metastatic Urothelial Carcinoma in Patients who have Failed a First-Line Platinumcontaining Chemotherapy Regimen for Advanced/Metastatic Disease	Michiel van der Heijden	III	12/04/2018
M17EPP (ECHO-307)	A Phase 3 Randomized, Double-Blind Trial of Pembrolizumab (MK-3475) in Combination with Epacadostat (INCB024360) or Placebo in Participants with Cisplatin-ineligible Urothelial Carcinoma	Michiel van der Heijden	III	02/02/2018
M17LUC (DaBlaCa)	Lymphadenectomy in urothelial carcinoma in the renal pelvis and ureter - A randomized international clinical trial on lymphadenectomy in urothelial carcinoma in the renal pelvis and ureter	Kees Hendricksen	other	15/1/2018 (17/10/2019)
M17MDN	A Phase 1/2, Open-label Study to Evaluate the Safety and Antitumor Activity of MEDI0680 (AMP-514) in Combination with Durvalumab versus Nivolumab Monotherapy in Subjects with Select Advanced Malignancies	Hans van Thienen	I/II	13/2/2018 (6/3/2019)
M17MRP (MR PROPER)	Risk assessment and MR imaging in prostate cancer diagnosis: an impact analysis	Henk van der Poel	other	23/01/2018
M17NIU (CheckMate 90)	A Phase 3, Open-label, Randomized Study of Nivolumab Combined with Ipilimumab versus Standard of Care Chemotherapy in Participants with Previously Untreated Unresectable or Metastatic Urothelial Cancer	Michiel van der Heijden	III	29/05/2017
M17PAB (PABLO)	Effect of a physical activity promotion program offered online of via blended care on physical activity level in breast and prostate cancer survivors	Wim Groen	other	19/10/2017
M17PRO (PROSPEC)	Prostate cancer follow-up care in secondary and primary health care	Lonneke van de Poll - Franse	other	12/04/2018
M17RCU (FORT-1)	A randomized, open label, multicenter Phase 3 study to evaluate the efficacy and safety of Rogaratinib (BAY 1163877) compared to chemotherapy in patients with FGFR-positive locally advanced or metastatic urothelial carcinoma who have received prior platinum-containing chemotherapy	Michiel van der Heijden	III	25/4/2018 (10/9/2019)
M17REB (REBACARE)	REduce BlAdder CAncer REcurrence in patients treated for upper urinary tract urothelial carcinoma	Kees Hendricksen	other	24/11/2017
M17SFC (Sunniforecast)	A Phase 2, Randomized, Open-Label Study of Nivolumab Combined with Ipilimumab Versus Sunitinib Monotherapy in Subjects with Previously Untreated and Advanced (unresectable or metastatic) non-clear Cell Renal Cell Carcinoma	John Haanen	II	27/03/2019
M18ASG	A single-arm, open-label, multicenter study of enfortumab vedotin (ASG-22CE) for treatment of patients with locally advanced or metastatic urothelial cancer who previously received immune checkpoint inhibitor therapy	Michiel van der Heijden	II	13/12/2018

Type of cancer study (nick name)	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
M18CLR (CLEAR)	A Multicenter, Open-label, Randomized, Phase 3 Trial to Compare the Efficacy and Safety of Lenvatinib in Combination with Everolimus or Pembrolizumab Versus Sunitinib Alone in First-Line Treatment of Subjects with Advanced Renal Cell Carcinoma	Hans van Thienen	III	23/10/2018
M18ERC (EASE RCC)	European Active Surveillance of Renal Cell Carcinoma study	Axel Bex	other	07/08/2018
M18EVU	An Open-Label, Randomized Phase 3 Study to Evaluate Enfortumab Vedotin vs. Chemotherapy in Subjects with Previously Treated Locally Advanced or Metastatic Urothelial Cancer	Michiel van der Heijden	III	24/01/2019
M18ICR (ICRA)	Improve Checkpoint-blockade Response in Advanced urothelial cancer: an adaptive clinical study to determine efficacy of combining weekly paclitaxel with tremelimumab +/- durvalumab (MEDI4736)	Michiel van der Heijden	I/II	25/04/2019
M18IMB (IMBrella)	An open label, multicenter extension study in patients previously enrolled in a Genentech- and/or F. Hoffmann-La Roche LTD-sponsored Atezolizumab study	Michiel van der Heijden	other	03/10/2018
M18JNJ	An Open-label, Multicenter, Phase 1b Study of JNJ-63723283, a PD-1 inhibitor, administered in combination with apalutamide in subjects with metastatic castration-resistant prostate cancer	André Bergman	I/II	29/11/2018
M18JNJ (KRONOS)	An Open-label, Multicenter, Phase 1b Study of JNJ63723283, a PD-1 inhibitor, administered in combination with apalutamide in subjects with metastatic castration-resistant prostate cancer	André Bergman	I/II	14/03/2019
M18NBB	A Phase 2, Randomized, Open-label Study of Nivolumab or Nivolumab/BMS-986205 Alone or Combined with Intravesical BCG in Participants with BCG-Unresponsive, High-Risk, Non-Muscle Invasive Bladder Cancer	Michiel van der Heijden	II	16/11/2018
M18NIA (NIAGARA)	A phase III, randomized, open-label, multi-center, global study to determine the efficacy and safety of Durvalumab in combination with Gemcitabine+Cisplatin for neoadjuvant treatment followed by Durvalumab alone for adjuvant treatment in patients with muscleinvasive bladder cancer	Michiel van der Heijden	III	25/04/2019
M18RAP (CERA-PRO)	Cost-Effectiveness of Robot-Assisted Prostatectomy versus laparoscopic prostatectomy a 5 year multi-institutional study of PROMs from a Dutch perspective	Henk van der Poel	other	12/04/2018
M18RES (RESPONDER)	Biomarker discovery study to identify patients with advanced urothelial cancer benefitting from pembrolizumab treatment	Michiel van der Heijden	II	21/08/2019
M18TGC (SENATOR)	Sentinel Lymph Node Procedure in Testicular Germ Cell Tumour	Simon Horenblas	other	31/08/2018
M18ZIR (ZIRCON)	A confirmatory, prospective, open-label, multi-centre phase 3 study to evaluate diagnostic performance of 89Zirconium-labelled girentuximab(89Zr-TLX250) to non-invasively detect clear cell renal cell carcinoma (ccRCC) by positron emission tomography/CT (PET/CT) imaging in patients with indeterminate renal masses	Marcel Stokkel	III	12/07/2019
M19CTR (CATCHER)	Diagnostic yield of colonoscopy surveillance in testicular cancer survivors treated with platinumbased chemotherapy	Monique van Leerdam	other	27/11/2019
M19KLK (KEYLYNK-010)	A Phase 3, Randomized Open-label study of Pembrolizumab (MK-3475) Plus Olaparib Versus Abiraterone Acetate or Enzalutamide in Participants with Metastatic Castration-resistant Prostate Cancer (mCRPC) Who are Unselected for Homologous Recombination Repair Defects and Have Failed Prior Treatment with One Next-generation Hormonal Agent (NHA) and Chemotherapy	André Bergman	III	09/05/2019
M19KNT (KEYNOTE-921)	A Phase 3, Randomized, Double-blind Study of Pembrolizumab (MK-3475) Plus Docetaxel Plus Prednisone versus Placebo Plus Docetaxel Plus Prednisone in Participants with Chemotherapy-naïve Metastatic Castration-Resistant Prostate Cancer (mCRPC) who have Progressed on a Next Generation Hormonal Agent (NHA)	André Bergman	III	27/06/2019

Type of cancer study (nick name)	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
M19MAG (MAGNITUDE)	A phase 3 randomized, placebo-controlled, doubleblind study of Niraparib in combination with Abiraterone acetate and Prednisone versus Abiraterone acetate and Prednisone for treatment of subjects with metastatic prostate cancer	André Bergman	III	03/07/2019
M19NEK (NEKTAR)	A Phase 2, randomized, non-comparative, openlabel study of NKTR-214 in combination with nivolumab and of chemotherapy in cisplatin ineligible, locally advanced or metastatic urothelial cancer patients with low PD-L1 expression	Michiel van der Heijden	II	12/08/2019
M19OTE (PROTEUS)	Randomized, double-blind, placebo-controlled, phase 3 study of Apalutamide in subjects with highrisk, localized or locally advanced prostate cancer who are candidates for radical prostatectomy	Henk van der Poel	III	28/10/2019
M19PCX (PROCLAIM)	A Phase 2, Open-Label, Multi-cohort Study of PD-L1 Probody™ Therapeutic CX-072 in Combination With Other Anticancer Therapy in Adults With Solid Tumors	Christian Blank	II	04/11/2019
M19VIS (VISION)	An international, prospective, open label, multicenter, randomized phase 3 study of 177LuPSMA-617 in the treatment of patients with progressive PSMA-positive metastatic castrationresistant prostate cancer (mCRPC).	Wouter Vogel	III	28/06/2019
N12LAR	Longitudinal analysis of RCC-specific immunity in renal cell carcinoma patients	Christian Blank	other	14/12/2012 (13/11/2019)
N13KCM	Longitudinal kinetics of cancer mutations in the plasma, urine and tumor of patients with urothelial cancer treated with chemotherapy	Michiel van der Heijden	other	24/01/2014
N14DAR (DARANA)	Dynamics of Androgen Receptor genomics and transcriptomics after neoadjuvant androgen ablation	Henk van der Poel	other	27/08/2014
N14ITO	Immunogenicity of Tumor Organoids, a feasibility study	Emile Voest	other	22/07/2014
N15DOP	Weekly ModraDoc/r in combination with hormonal treatment and high-dose intensity-modulated radiation therapy in patients with high-risk early stage prostate cancer	Baukelien van Triest	I	12/05/2016
N15PEN	Chemoradiation in the treatment of loco-regionally advanced Penile Cancer	Floris Pos	other	31/8/2015 (9/7/2019)
N16DIP	Clinical evaluation of a prototype drop-in gamma probe for (robot-assisted) laparoscopic sentinel node biopsy	Henk van der Poel	other	18/12/2017 (24/1/2019)
N16NEON	Personalized adoptive T-cell therapy protocol	John Haanen	other	09/11/2016
N17DIP	Clinical pharmacokinetics of intravenous docetaxel in patients with castration-resistant prostate cancer and non-castration-resistant prostate cancer	André Bergman	other	27/12/2017
N17JAV (NEOJAVALIN)	Neoadjuvant AXITINIB plus AVELUMAB for patients with localized RCC and a moderate to high risk of recurrence. A phase II study	Axel Bex	II	16/05/2018
N17NAB (NABUCCO)	Phase 1B Study to assess safety and efficacy of Neo-Adjuvant Bladder Urothelial Carcinoma COmbination-immunotherapy	Michiel van der Heijden	I	04/12/2017
N17PSA	Finger prick PSA	Huub van Rossum	other	13/09/2019
N17PSI	Increasing pazopanib exposure by splitting intake moments	Neeltje Steeghs	IV	22/5/2017 (30/10/2019)
N18CLI (CLIPPS)	A feasibility study on Cerenkov Luminescence Imaging during prostate cancer surgery using Gallium-68 PSMA	Marcel Stokkel	other	12/02/2019
N18ISG	Inhibition of salivary gland function to reduce uptake and toxicity of PSMA-ligands	Wouter Vogel	pilot	28/05/2018

Type of cancer study (nick name)	Title	Study coordinator in NKI-AVL	Phase	Activated (closed)
N18PER (PERICLES)	PEnile cancer Radio- and Immunotherapy Clinical Exploration Study – a Phase 1B study of atezolizumab with or without radiotherapy in penile cancer	Michiel van der Heijden	I	21/09/2018
N18PSM	Variatie in PSMA receptor expressie over de tijd in prostaatkanker	Marcel Stokkel	other	19/12/2018
N18TAE	Trans arterial embolization for the optimization of percutaneous thermal ablation of primary renal cell carcinoma	Brigit Aarts	other	17/01/2019
N19IFC (INFLUENCE)	INtra-operative evaluation of a novel FLUorescENt CmEt tracer in penile and tongue cancer	Baris Karakullukcu	other	13/11/2019
N19IPT	Contributing to research in a time of privacy: information provision and transparency	Marjanka Schmidt	other	07/11/2019
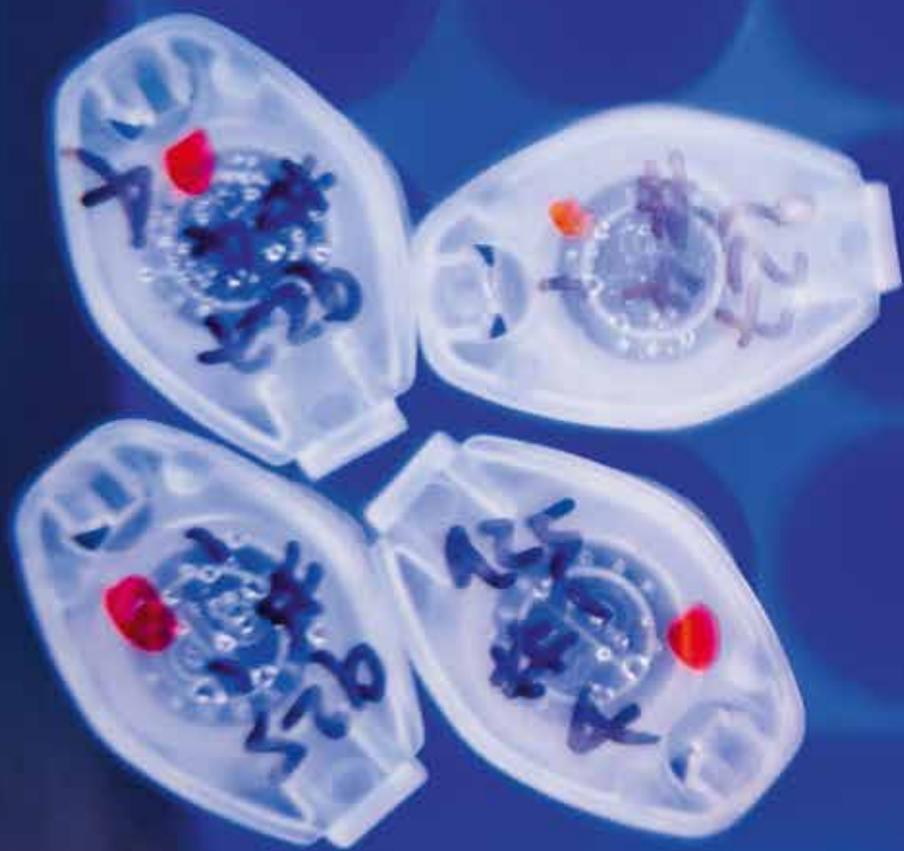
Invited speakers

Andrea Alimonti
Institute of Oncology Research, Bellinzona, Switzerland
Aberrant activation of the tumour immune response drives
resistance to prostate cancer therapy

Ido Amit
Weizmann Institute of Science, Rehovot, Israel
Single-cell genomics: a stepping stone for future immunology
discoveries

Michal Besser
Ella Institute, Ramat Gan, Israel
Adoptive cell therapy with on-site produced TIL or
CD19 CAR T cells - Updated results of 300 enrolled patients

Christoph Bock
CeMM, Vienna, Austria
High-throughput dissection of epigenome regulation in cancer
and immune cells

Carlos Caldas
Cancer Research UK, Cambridge Institute,
Cambridge, United Kingdom
Breast cancer: from tumour tissue to single cells and back

Keith Caldecott
University of Sussex, Brighton, United Kingdom
DNA strand break-induced ADP-ribosylation and
human genetic disease

Gerard Evan
University of Cambridge, Cambridge, United Kingdom
Where cancer phenotypes come from and how to make
them go away

Silvia Formenti
Weill Cornell, New York, NY, USA
DNA damage response and immune rejection of cancer

Susan Gasser
Friedrich Miescher Institute for Biomedical Research,
Basel, Switzerland
The crucial importance of silencing repeats for genome
stability: Synergy between BRCA1/BARD1 and H3K9
methylation

Thomas Gregor
Princeton University, Princeton, NJ, USA
Visualizing chromatin dynamics and its effect on transcription

James Haber
Brandeis University, Waltham, MA, USA
Genome stability and instability during repair of
a broken chromosome

Hiroshi Kimura
Tokyo Institute of Technology, Kanagawa, Japan
Chromatin modification dynamics during gene activation
and inactivation in living cells

Puck Knipscheer
Hubrecht Institute, Utrecht, The Netherlands
Alcohol-derived DNA interstrand crosslinks are repaired
by two distinct mechanisms

Philip Kranzusch
Dana-Farber Cancer Institute, Boston, MA, USA
cGAS-like enzymes in human immunity and
host-microbe signaling

Jason Locasale
Duke University School of Medicine, Durham, NC, USA
How metabolism shapes epigenetics

Madelon Maurice
UMC Utrecht, Utrecht, The Netherlands
Mutation-guided insights in Wnt signalling alterations in cancer

Nick Navin
MD Anderson Cancer Center, Houston, TX, USA
Insights into Premalignant Breast Cancer Progression
with Single Cell Genomics

Emmanuelle Passegué
Columbia University, New York, NY, USA
Hematopoietic stem cells in stress, disease and aging

Ze'ev Ronai
**Sanford Burnham Prebys Medical Discovery Institute,
La Jolla, CA, USA**
Epigenetic regulators of anti-tumor immunity, from ubiquitin
ligases to methyl-transferases

Matti Rookus
Netherlands Cancer Institute, Amsterdam, The Netherlands
Which factors push the risk of breast cancer to be this high? –
the population and individual perspective

Davide Ruggero
University of California San Francisco, San Francisco, CA, USA
Translating the cancer genome one codon at a time and its
therapeutic implications

Agnel Sfeir
Skirball Institute, NYU School of Medicine, New York, NY, USA
Maintaining genome stability: nuclear and mitochondrial

Peter Sicinski
Dana-Farber Cancer Institute, Boston, MA, USA
Cell cycle machinery in development and in cancer

Arnoud Sonnenberg
Netherlands Cancer Institute, Amsterdam, The Netherlands
What have we learned from over 30 years of integrin research?

Sohail Tavazoie
Rockefeller University, New York, NY, USA
Cancer metastasis and gene regulation

Nicolas Thomä
**Friedrich Miescher Institute for Biomedical Research,
Basel, Switzerland**
CUL4 ubiquitin ligases: from DNA damage detection in
chromatin to new modality in drug discovery

Andrew Wood
University of Edinburgh, Edinburgh, UK
Condensin (dys)function during development and disease

Research projects
supported by the
Dutch Cancer Society

Principal investigator	Number of projects	Title	Started	Ended / Ends
Aaronson, N.K.	NKI 2014-6788	A randomized controlled trial of internet-based cognitive behavioral therapy for breast cancer patients with climacteric symptoms	01/02/15	31/07/19
Agami, R.	11574	Exploring the role of serine metabolism adaptations in platinum resistant high grade serous ovarian cancer	01/09/18	31/08/22
Agami, R.	10315	Diricore, a platform for the discovery of novel amino acid vulnerabilities in aggressive cancer	01/01/17	31/12/20
Agami, R.	11037	Exploiting proline vulnerability for cancer therapy	01/11/17	31/10/21
Akkari, L.	12049	Investigating the Cancer Cell-Mediated Shaping of the Liver Immune Environment	01/01/19	31/12/22
Akkari, L.	10658	Improving the effects of standard of care therapy in glioma by modulating tumor-associated macrophages and microglia functions	01/06/17	31/05/22
Al-Mamgani, A.	NKI 2015-8054	Dutch randomized multicenter trial COmparing twO PalliativE RAdiaTION schemes for incurable head and neck cancer (COOPERATION)	18/12/15	18/12/19
Amant, F.C.H.	10094	CRADLE: Cancer tReAtment During pregnancy: from fetaL safety to maternal Efficacy	01/05/17	30/04/21
Amant, F.C.H.	11132	Postpartum breast cancer diagnosed during involution: a distinct entity with unique clinicopathological, molecular and immunological features?	01/01/18	31/12/21
Baas, P.	NKI 2015-7823	Defining new and personalized treatment options for patients with malignant mesothelioma	01/01/16	31/12/19
Beets-Tan, R.G.H.	10138	Development and validation of a multiparametric imaging model for pre-treatment response prediction in rectal cancer: the road towards organ-preservation.	01/10/17	30/09/21
Beets-Tan, R.G.H.	10611	Radiomics for the prediction of response to neoadjuvant treatment in rectal carcinoma	01/10/17	30/09/19
Beets, G.L.	UM 2015-7738	Multicentre evaluation of the 'wait-and-see' policy for complete responders after chemoradiotherapy for rectal cancer	01/10/15	30/09/21
Beets, G.L.	10513	Multicenter evaluation of the 'wait-and-see' policy for complete responders after chemoradiotherapy for rectal cancer	01/09/17	31/08/21
Beijersbergen, R.L.	12539	ScreeninC: a national infrastructure for functional genome editing and large scale functional genomic screening	01/06/20	31/05/24
Bernards, R.	NKI 2015-7803	Evolution of resistant clones to novel target-directed drugs in colorectal tumors. - A genetic and epigenetic study of intratumoral heterogeneity dynamics	01/11/16	31/10/19
Bernards, R.	NKI 2013-5859	Engineering a liver cancer model on a chip	01/09/17	31/08/19
Bleiker, E.M.A.	NKI 2014-7031	Choices in breast surgery and reconstruction: implementation and testing of a web-based psycho-educational intervention to facilitate decision making. TANGO.	01/11/15	31/10/20
Bleiker, E.M.A.	NKI 2015-7909	The effect of light-therapy on fatigue and psychosocial functioning in long-term survivors of (non-) Hodgkin lymphoma: a randomized controlled trial. M17SPA	01/08/16	31/07/20
Borst, G.R.	10902	New era of radiosensitization by modulating radio sensitizing agents during RT	01/02/18	31/01/23

Principal investigator	Number of projects	Title	Started	Ended / Ends
Borst, J.G.	NKI 2013-5951	Enhancing the anti-tumor efficacy of immunotherapy by localized radiotherapy.	01/05/14	30/04/20
Borst, J.G.	11079	Cytotoxic T-cell programming at the dendritic cell interface	01/09/17	31/08/21
Borst, J.G.	10894	Achieving synergy between radiotherapy and immunotherapy to increase control of metastatic cancer.	01/02/18	31/01/23
Borst, J.G.	10764	Inducing and sustaining anti-tumor immunity by chemo-radiotherapy.	01/01/18	31/12/19
Brummelkamp, T.R.	11352	identification and validation of genetic factors that determine sensitivity to Weel inhibition in high-grade ovarian cancer and related cancers	01/10/18	30/09/23
Brummelkamp, T.R.	NKI 2015-7609	A mutation-based approach to examine the principles of synthetic lethality in human cells.	01/04/16	31/03/20
Cats, A.	NKI 2013-6249	Safety, feasibility and cost-effectiveness of genotype- and phenotype-directed individualized dosing of fluoropyrimidines	01/09/14	31/08/20
de Visser, K.E.	VU 2015-7864	Targeting the right dendritic cell for the job: leveraging antitumor immunity to enhance the efficacy of chemotherapy.	01/07/19	01/12/19
de Visser, K.E.	10083	Enhancing the success of immunotherapy for metastatic breast cancer by overcoming tumor associated immunosuppressive mechanisms	01/05/17	30/04/21
de Visser, K.E.	10623	Dissecting how tumor-associated myeloid cells counteract chemotherapy response of breast cancer.	01/04/18	31/03/22
Faller, W.J.	10535	The role of translation elongation in models of intestinal cancer	01/07/17	30/06/22
Haanen, J.B.A.G.	11877	Overcoming anti-PD1 failure with adoptive cell therapy using tumor-infiltrating lymphocytes in metastatic melanoma: requirements for a randomized controlled trial.	01/01/19	31/12/21
Haanen, J.B.A.G.	NKI 2013-5924	Feasibility study using T-cell receptor gene therapy in metastatic melanoma	05/02/13	05/02/19
Haanen, J.B.A.G.	10034	POINTING: Towards patient-tailored cancer immunotherapy supported by a multifaceted predictive signature composed of integrative omics and molecular imaging	01/09/17	31/08/22
Haanen, J.B.A.G.	NKI 2017-8244	Netherlands Facility for Cancer Immune Analysis (N-CIA)	01/05/18	30/04/23
Haas, R.L.M.	NKI 2015-8069	Dose Reduction of preoperative radiotherapy in Myxoid liposarcomas.	01/01/16	31/12/19
Hauptmann, M.	10004	Statistical assessment of cancer risks from therapeutic radiation exposure incorporating the spatial distribution of radiation dose in the target organ	01/12/17	30/11/21
Hauptmann, M.	10603	Novel statistical methods for efficient identification of biomarkers for personalized cancer treatment	01/09/17	31/08/21
Horlings, H.M.	10510	Genetic properties of breast carcinomas associated with cancer-immune interactions.	01/11/17	31/10/21
Huijbers, I.J.G.	NKI 2017-8231	CustoMICE: a facility for production and distribution of engineered mouse models for cancer research	01/01/18	31/12/20
Husson, O.	NKI 2015-7527	Psychosocial and physical problems and needs of adolescents and young adults (AYAs) with cancer: Towards comprehensive patient-centered care.	01/10/18	01/08/20
Jacobs, H.B.	12825	Targeting epigenetic crosstalk in Diffuse Large B Cell Lymphoma	01/06/20	31/05/24
Jacobs, H.B.	NKI 2012-5713	Exploring DNA-Damage Tolerance as a Drug-Target for Chemosensitization and a Mechanism of Chemoresistance.	01/06/13	31/05/19

Principal investigator	Number of projects	Title	Started	Ended / Ends
Jacobs, H.B.	10032	Precision Cancer Therapy: Profiting from Tumor Specific Defects and Synthetic Lethality in the DNA Damage Tolerance System	01/03/17	28/02/21
Jacobs, H.B.	10796	Role of DNA Damage Tolerance Pathways in Genome Maintenance, Tissue Homeostasis, and Cancer Suppression	01/10/17	30/09/21
Jacobs, J.J.L.	11905	Mechanisms to overcome replication challenges at telomeres	01/08/19	31/07/23
Jacobs, J.J.L.	12826	Revealing novel modes of DNA repair control by ubiquitin(-like) reversal	01/06/20	31/05/24
Jacobs, J.J.L.	10999	Mechanisms of DNA repair pathway control at DNA double-strand breaks and telomeres	01/10/17	30/09/21
Jonkers, J.M.M.	NKI 2014-7048	Ex vivo assays for selection of breast and ovarian cancer patients for PARP inhibitor treatment	01/09/15	31/08/20
Jonkers, J.M.M.	NKI 2015-7589	Cancer-associated fibroblasts as therapeutic targets in invasive lobular breast carcinoma.	01/01/16	30/06/20
Jonkers, J.M.M.	NKI 2015-7877	Functional analysis of BRCA1 variants and domains to improve genetic counselling and treatment strategies.	01/01/16	31/12/19
Jonkers, J.M.M.	NKI 2015-7835	Combatting therapy resistance by integrating genomic, transcriptomic and proteomic data from mouse models of invasive lobular breast carcinoma	01/01/17	31/12/20
Kok, M.	NKI 2015-7542	KWF fellowship	01/06/15	31/05/19
Kok, M.	10653	Mapping immunosuppressive cascades in breast cancer patients treated with immunotherapy	01/09/17	31/01/20
Kvistborg, P.	NKI 2015-7978	How checkpoint blockade alters the quality of tumor specific T cells	01/09/16	31/08/21
Linn, S.C.	NKI 2014-7052	The substantially improving the cure rate of high-risk BRCAi-like breast cancer patients with personalized therapy (SUBITO) trial; an international randomized phase III trial. SUBITO studie.	01/02/16	31/01/21
Linn, S.C.	NKI 2015-7808	Clinical Impact of Intratumor heterogeneity in metastatic breast cancer. Transcan	01/04/16	31/03/19
Lok, C.A.R.	12694	OVI-DETECT; Liquid biopsies for improving the pre-operative diagnosis of ovarian cancer.	01/06/20	31/05/24
Marijnen, C.A.M.	12612	Pre-versus postoperative accelerated partial breast irradiation in early stage breast cancer patients (PAPBI-2). A randomized phase III trial.	01/06/20	31/05/24
Marijnen, C.A.M.	12702	INTERACTION of hypofractionated radiotherapy with targeted agents, antibodies and immunotherapy	01/06/20	31/05/24
Medema, R.H.	12233	Unbalanced genomes: why do cancer cells not care?	01/11/19	31/10/23
Medema, R.H.	NKI 2014-6787	Determinants of cell fate after DNA damage.	01/04/15	31/03/19
Medema, R.H.	NKI 2015-7742	Enhancing chromosome segregation errors in cancer therapy.	01/07/15	30/06/19
Medema, R.H.	NKI 2015-7832	Exploring the vulnerabilities of chromosome unstable tumor cells	01/05/16	30/04/20
Meijer, G.A.	11809	Towards implementation of liquid biopsy cell-free circulating tumor DNA as prognostic biomarker for stage I II colon cancer patients	01/01/19	31/12/22
Meijer, G.A.	NKI 2013-6338	MOCCAS; Molecular Stool test for postpolypectomie surveillance	01/07/15	30/06/20
Meijer, G.A.	NKI 2014-6813	Identifying signaling pathways	01/09/15	31/08/19

Principal investigator	Number of projects	Title	Started	Ended / Ends
Meijer, G.A.	2013-5885	Fellowship Linda Bosch;DCR1 and its role in response of colorectal cancer patients to irinotecan treatment	01/04/15	31/05/20
Meijer, G.A.	NKI 2014-6635	Deciphering diagnostic and companion therapies for mesenchymal colorectal cancer.	01/04/15	31/03/19
Meijer, G.A.	8166	Translational research IT (TraIT) in transition Health RI - Sustaining FAIR data stewardship support for translational cancer research	01/02/17	31/01/20
Meijer, G.A.	10438	Liquid biopsy analyses of cell-free circulating tumor DNA as predictive and prognostic biomarker for colorectal cancer patients with metastatic disease	01/10/17	30/09/21
Opdam, F.L.	11352	Identification and validation of genetic factors that determine sensitivity to Weel inhibition in high-grade ovarian cancer and related cancers	01/10/18	30/09/23
Peeper, D.S.	12188	AXL as an anchor to combat therapy-refractory Soft Tissue Sarcoma	01/09/19	31/08/23
Peeper, D.S.	NKI 2014-7241	In vivo cancer drug target discovery screens exploiting T cell immunity.	01/09/15	31/08/19
Peeper, D.S.	NKI 2015-7595	Function-based unbiased discovery of clinically exploitable metabolic vulnerabilities of cancer cells.	01/10/16	30/09/20
Peeper, D.S.	10425	Targeting phenotype switching as a therapy for melanoma	01/09/17	31/08/21
Peeper, D.S.	10304	Increasing drug holiday impact on therapy-refractory cancers for more durable responses	01/01/17	31/12/20
Perrakis, A.	10215	Membrane glycerophosphodiesterases: novel players in cell differentiation and cancer biology	01/01/17	31/12/20
Rookus, M.A.	12535	Nationwide infrastructure integrating research and health care to improve management for Dutch women with familiar breast cancer risk	01/06/20	31/05/25
Rookus, M.A.	12560	The potential association between circadian disruption and hormone-related cancer risk; prospective cohort study among 59,947 female nurses	01/06/20	31/05/24
Rookus, M.A.	NKI 2014-6987	A nationwide prospective cohort study among 59,947 female nurses to elucidate the potential association between shift work and risk of breast cancer.	01/02/16	31/01/20
Rowland, B.D.	11665	SWI/SNF-mediated cohesin loading: A dual role in tumorigenesis?	01/07/19	30/06/23
Rowland, B.D.	12687	A universal binding hub on cohesin to control the genome?	01/06/20	31/05/24
Rowland, B.D.	NKI 2015-7657	Locking Together the Sister Chromatids.	01/11/15	31/10/19
Ruers, T.J.M.	12815	Augmented reality for precision surgery in cancer	01/06/20	31/05/24
Ruers, T.J.M.	NKI 2014-6596	Clinical implementation of image-guided surgery in rectal cancer. Tevens studie N14RCS.	01/05/15	30/04/19
Ruers, T.J.M.	NKI 2016-8162	TomTom voor de OK (via Vriendenloterij)	01/01/17	31/05/21
Ruers, T.J.M.	10747	Improving the outcome of breast cancer surgery by real time assessment of resection margins using Hyperspectral Imaging (10396).	01/01/18	31/12/21
Schagen, S.B.	NKI 2015-7737	Trajectories of cognitive decline in survivors of non-CNS cancers: from precancer diagnosis to late life after cancer.	01/09/16	31/08/20
Schagen, S.B.	NKI 2015-7937	Monitoring, understanding and managing cognitive problems in cancer patients without central nervous system disease: putting knowledge into practice	01/01/17	31/12/22

Principal investigator	Number of projects	Title	Started	Ended / Ends
Schagen, S.B.	UU 2015-7954	Effect of physical exercise on cognitive function after chemotherapy in patients with breast cancer	01/09/16	31/08/20
Schmidt, M.K.	10758	Risk prediction, screening and Therapy of breast cancer in women from CHEK2 c.1100delC families in the Netherlands (in ART).	01/11/17	31/10/21
Schmidt, M.K.	11655	Balancing risks of under- and overtreatment in young breast cancer patients: a focus on the triple negative subtype	01/02/19	31/01/23
Schmidt, M.K.	NKI 2013-6253	Risk management of contralateral breast cancer: development and validation of an online decision aid for physicians and patients.	01/10/14	30/09/19
Schmidt, M.K.	NKI 2015-7632	Breast cancer prognosis: identification of hereditary genetic variants.	01/03/16	29/02/20
Schumacher, A.N.M.	NKI 2013-6122	Linking cancer exomes to cancer immunotherapy	01/08/14	31/07/20
Sixma, T.K.	NKI 2015-8082	Elucidating regulation of tumor suppressor BAP1 in genome stability maintenance	01/12/16	30/11/20
Sonke, G.S.	NKI 2012-5685	High-dose alkylating chemotherapy in oligo-metastatic breast cancer harboring homologous recombination deficiency	01/07/12	01/04/21
Sonke, G.S.	NKI 2014-6838	Improving the outcome of ovarian cancer patients: when and why to use neoadjuvant chemotherapy or primary surgery in advanced ovarian cancer.	01/10/15	30/09/19
Sonke, J.J.	RUG 2017-8254	Proton Therapy Research Infrastructure - ProTRAIT	01/09/19	31/08/22
Sonke, J.J.	11964 ALPE	Cardiac changes after radiotherapy with high fraction doses for early stage lung cancer. M19CCR.	01/09/19	28/02/22
Sonke, J.J.	RUG 2017-8254	Proton Therapy Research Infrastructure - ProTRAIT	01/02/18	31/01/21
Sonnenberg, A.	12143	Analysis of the role of PEAK1, an integrin-associated pseudokinase, in the initiation and progression of colorectal carcinomas	01/10/19	30/09/23
te Riele, H.P.J.	NKI 2014-6702	Replication stress in cancer: mechanisms and consequences for therapy.	01/10/14	30/09/19
te Riele, H.P.J.	NKI 2014-7176	Development of prevention strategies for intestinal cancer in lynch syndrome using novel mouse models.	01/08/15	31/07/19
te Riele, H.P.J.	10645	INVUSE: Investigation of variants of uncertain clinical significance for use in clinical practice	01/02/18	31/01/22
te Riele, H.P.J.	11074	Targeting replication rescue pathways	01/03/18	28/02/23
Thommen, D.S.	12046	Dysfunctional T cells in predicting and modulating the response to PD-1 blockade in human cancer	01/06/19	31/05/23
van de Poll, L.V.	NKI 2015-7932	A randomized study, PROstate cancer follow-up care in secondary and Primary health care (PROSPEC)	01/09/17	31/08/22
van der Graaf, W.T.A.	11788	COMPRAYA: Dutch nationwide infrastructure for COMPRehensive health outcome and intervention research among Adolescent and Young Adult cancer survivors.	01/01/20	31/12/24
van der Heide, U.A.	NKI 2013-6311	Brachytherapy for rectal cancer: a better balance between tumor control and side effects.	01/11/14	31/10/20
van der Heide, U.A.	10088	Focal escalation of the radiation dose to the tumor in prostate cancer	01/04/17	31/03/21
van der Heijden, M.S.	NKI 2014-7080	Genetic causes of resistance to new androgen receptor signaling inhibitors in circulating tumor DNA of metastasized castration resistant prostate cancer patients.	01/06/15	31/05/20

Principal investigator	Number of projects	Title	Started	Ended / Ends
van Driel, W.J.	11540	Primary cytoreductive surgery with or without hyperthermic intraperitoneal chemotherapy for stage III ovarian cancer: a randomized phase III trial (OVHIPEC-2). M17OVH	01/12/19	30/11/26
van Driel, W.J.	11910	Implementation of HIPEC for patients with stage III ovarian carcinoma treated with neoadjuvant chemotherapy and interval debulking in the Netherlands	01/01/19	31/12/22
van Harten, W.H.	NKI 2014-6078	Advanced Logistics Optimization of the Radiotherapy Treatment (ALORT)	01/02/15	31/01/20
van Harten, W.H.	NKI 2015-7904	A randomized controlled trial of an internet-based tailored physical activity support program in breast and prostate cancer survivors. PABLO.M17PAB	01/09/16	31/08/20
van Harten, W.H.	10325	Does physical exercise during adjuvant cardiotoxic chemotherapy protect against cardiac injury among women with breast cancer? HEART	01/09/17	31/08/20
van Houdt, W.J.	12686	Development of a translational ex-vivo model of zD cells and organoids as a predictive tool for soft tissue sarcoma	01/06/20	31/05/24
van Leerdam, M.E.	10274	Evaluation of optimal intervals for colonoscopy surveillance: a randomized trial. M16EPS	01/02/17	31/01/29
van Leeuwen, F.	11490	DOT1L as a druggable epigenetic writer in T cell programming and immunotherapy	01/12/18	31/05/20
van Leeuwen, F.	NKI 2014-7232	Epigenetic Pathways in Cancer Development and Treatment: Crosstalk between Conserved Histone Modifiers in T-cell Lymphoma.	01/11/15	31/10/19
van Leeuwen, F.E.	12710	Prediction tools for Hodgkin lymphoma patients to weigh benefits and harms of different treatment and survivorship care strategies	01/06/20	31/05/24
van Leeuwen, F.E.	10164	Favorable and unfavorable effects of risk-reducing salpingo-oophorectomy(RRSO) in women at high genetic risk of ovarian cancer	01/07/17	30/06/21
van Leeuwen, F.E.	10424	Cardiotoxicity and second cancer risk after treatment of aggressive B-cell Non-Hodgkin lymphoma (M18CNH)	01/01/18	31/12/21
van Leeuwen, F.E.	NKI 2017-8237	The BETER-REFLECT biobank: A REsource For studies on Late Effects of CancerTreatment	01/02/18	31/01/22
van Leeuwen, F.E.	10933	A risk prediction tool for cardiovascular disease in breast cancer patients. PREDICT	01/12/17	31/08/21
van Leeuwen, F.E.	VU 2017-8288	Psychosocial factors and cancer incidence: a pre-planned meta-analysis of the psychosocial	01/12/17	30/11/21
van Lohuizen, M.M.S.	11700	Identifying and testing new intervention therapies for mesotheliomas.	01/09/18	31/08/22
van Lohuizen, M.M.S.	NKI 2014-7208	Testing therapeutic responses to Polycomb inhibition in preclinical mouse models of Kras mutant lung cancer.	01/07/15	30/06/19
van Rheenen, J.E	11491	Mechanistic insight in the role of cell competition in growth of colorectal cancer liver metastases	01/01/19	31/12/22
van Rheenen, J.E	UU 2015-7838	Understanding the role of SOX4 in educating the mammary tumor niche: the potential for personalized therapeutic targeting.	01/10/17	31/12/19
van Rheenen, J.E	10123	The intermediate filament network in glioma invasion	01/05/17	30/04/21
van Tellingen, O.	11165	Radiosensitization of glioma through induction of mitotic enrichment	01/01/18	30/06/20
van Trommel, N.E.	12674	Neo-Adjuvant Chemotherapy and Less Extensive Surgery in Cervical Cancer to Preserve Fertility (CONTESSA/NEOCON-F)	01/06/20	01/05/24

Principal investigator	Number of projects	Title	Started	Ended / Ends
Vens, C.	VU 2014-7072	A multiparameter radiogenomics-based decision support system for personalized treatment of advanced stage head and neck cancer patients (DESIGN)	01/11/15	31/10/20
Verheij, M.	NKI 2017-8287	Multicentre randomized phase II trial of neo-adjuvant chemotherapy vs. chemotherapy/chemoradiotherapy vs. chemoradiotherapy followed by surgery in resectable gastric cancer (CRITICS-II)	01/12/17	30/11/21
Voest, E.E.	NKI 2015-7732	Tumor organoids : feasibility to predict sensitivity to treatment in cancer patients (TUMOROID trial M14TUM)	01/07/15	31/12/21
Voest, E.E.	HUBR 2014-7006	Exploring The Use Of Lung Cancer Organoids In Personalized Medicine	01/02/16	31/01/20
Voest, E.E.	10014	The Drug Rediscovery Protocol (DRUP trial)	01/06/17	31/05/20
Vogel, W.V.	10606	Comprehensive functional salivary gland management to avoid an iatrogenic dry mouth	01/11/17	31/10/21
Wesseling, J.	NKI 2014-6250	Management of low risk ductal carcinoma in situ: watchful waiting or not? A randomized, non-inferiority trial. (LORD Trial)	01/02/15	31/01/21
Wesseling, J.	NKI 2014-7167	Secondary prevention of breast cancer: risk stratification for personalized management of screen-detected ductal carcinoma in situ(DCIS).	01/10/15	30/09/19
Wesseling, J.	NKI 2015-7711	Management of low grade ductal carcinoma in situ: active surveillance or not? A randomized, non-inferiority phase III trial (LORD studie) (BOOG). Datamanagement	01/07/15	30/06/19
Wesseling, J.	11105	Improving breast cancer screening among young high risk women by blood-based methods.	01/02/18	31/01/22
Wessels, L.F.A.	11741 ALPE	From fixed to functional pathology: defining intermediate phenotypes that determine prognosis and therapy response	01/12/18	30/11/20
Wessels, L.F.A.	12516	Phosphoproteomics and integrative analysis to enable precision medicine for anti-EGFR therapy in colorectal cancer	01/01/20	31/12/23
Wessels, L.F.A.	NKI 2015-7835	Combatting therapy resistance by integrating genomic, transcriptomic and proteomic data from mouse models of invasive lobular breast carcinoma	01/01/17	31/12/20
Wessels, L.F.A.	NKI 2014-7080 A	Genetic causes of resistance to new androgen receptor signaling inhibitors in circulating tumor DNA of metastasized castration resistant prostate cancer patients.	01/06/15	31/05/20
Zwart, W.T.	12018	Unraveling DNA repair / Estrogen Receptor interplay in breast cancer	01/06/19	31/05/23
Zwart, W.T.	12128	Exploiting the Glucocorticoid Receptor signaling axis to induce growth arrest in lung cancer.	01/11/19	31/10/23
Zwart, W.T.	NKI 2015-7733	Companion diagnostics for endocrine treatment selection in breast cancer	01/07/15	30/06/19
Zwart, W.T.	10084	Biomarker discovery for prognostication and treatment selection in prostate cancer through Androgen Receptor profiling	01/06/17	31/05/21

Research projects supported by other organisations

Principal investigator	Granting agency	Title	Started	Ended / Ends
Aaronson, N.K.	Pink Ribbon	Zorg op maat om fysieke fitheid en welzijn van vrouwen met gemetastaseerde borstkanker te bevorderen	01/09/15	01/02/19
Agami, R.	EEG-CEC / EU	Breaking borders, Functional genetic screens of structural regulatory DNA elements	01/09/19	31/08/24
Agami, R.	EMBO	Two-year EMBO Long-Term Fellowship of Dr. A. Pataskar	01/01/19	30/04/19
Agami, R.	Stichting Oncode Institute	Oncode Agami	01/09/17	31/08/22
Agami, R.	ZonMw	Uncovering cancerous enhancers of prostate and breast cancers	01/03/17	28/02/21
Akkari, L.	AVL Foundation	Immunologie & Kanker Akkari	01/01/18	31/12/19
Akkari, L.	NWO	Zwaartekracht programma 2012 Akkari	01/01/17	31/12/21
Akkari, L.	Stichting Oncode Institute	Oncode Akkari	01/01/19	31/08/22
Akkari, L.	The Royal Institution for the Advancement of Learning/McGill University	Harnessing the brain tumor immune-microenvironment to enhance therapeutic efficacy	01/01/19	31/12/21
Akkari, L.	ZonMw	Investigating the Consequences of Macrophage Evolution in Brain Tumor Recurrence Post-Radiotherapy	01/11/19	31/10/23
Altelaar, M.	NWO	X-omics	01/09/18	31/08/23
Altelaar, M.	NWO	Proteins@Work; A large-scale proteomics research facility for the life sciences	01/05/13	30/06/19
Amant, F.C.H.	EEG-CEC / EU	CRADLE: Cancer tReAtment During pregnancy: from fetaL safety to maternal Efficacy	01/10/15	30/09/20
Baas-Vrancken Peeters, M.J.T.F.D.	Innovatiefonds	Towards omitting breast surgery in patients with pathologic complete response after neoadjuvant systemic therapy.	01/03/18	31/12/20
Baas-Vrancken Peeters, M.J.T.F.D.	Pink Ribbon	Towards patient tailored locoregional treatment of breast cancer in patients treated with neoadjuvant systemic therapy. N16MIC	01/09/16	31/08/19
Baas, P.	AVL Foundation	E-Nose	01/11/19	31/10/20
Baas, P.	AVL Foundation	Uitbreiding Longgroep	01/03/18	28/02/20
Baas, P.	EEG-CEC / EU	DC-based immunotherapy to treat Malignant Mesothelioma	01/01/16	31/12/21
Beets-Tan, R.G.H.	EEG-CEC / EU	Active Monitoring of Cancer As An Alternative To Surgery	01/11/19	31/10/23
Beets-Tan, R.G.H.	Nederlandse Vereniging voor Radiologie (NVvR)	Optimalisatie van MRI diagnostiek bij behandeling van rectumcarcinoom	01/07/18	31/12/19
Beets-Tan, R.G.H.	ZonMw	MR imaging vs surgical staging of peritoneal carcimatosis in colorectal cancer patients; a randomized multicenter trial	01/09/19	31/08/23
Beets-Tan, R.G.H.	ZonMw	Clinical impact of dedicated MR staging of ovarian cancer patients	28/12/17	28/12/21
Beijersbergen, R.L.	Merck Sharp & Dohme Corp.	Identification of chromatin modifiers genes that upon inactivation show a synthetic lethal phenotype with Switch/Sucrose NonFermentable (SWI/SNF) chromatin-remodeling complex mutations in tumor cell lines.	08/09/15	08/09/19

Principal investigator	Granting agency	Title	Started	Ended / Ends
Beijnen, J.H.	EEG-CEC / EU	Efficacy and Safety of a newly registered Artemisinin-Based Combination for the treatment of uncomplicated malaria in African pregnant women	01/03/19	29/02/24
Beijnen, J.H.	EEG-CEC / EU	Afri-KA-DIA: Towards an adapted, safe, effective combination treatment for African visceral leishmaniasis (Kala Azar) and improved diagnostic tools	18/12/17	18/12/21
Beijnen, J.H.	ZonMw	Optimizing drug development for the neglected tropical disease visceral leishmaniasis through a systems pharmacology model	01/12/16	30/11/20
Belderbos-Candiff, J.S.A.	IKNL (Utrecht)	Implementatie van patient-gerapporteerde (PRO) monitoring van bijwerkingen en therapietrouw van systemische behandeling.	01/08/18	31/07/21
Belderbos-Candiff, J.S.A.	Ned Ver v Radioth en Ocologie NVRO	Ontwikkeling en implementatie van PRO-CTCAE-subsets voor longkankerpatienten	01/09/19	31/08/20
Bergman, A.M.	AVL Foundation	CRISPR screen to identify genes critical for prostate cancer cells faith in a context with macrophages and cancer associated fibroblasts	01/01/19	31/12/24
Bergman, A.M.	Stichting DUOS	Zijn er in prostaatkankermetastasen van eerder op de prostaat bestraalde patientenmutaties te vinden passend bij ioniserende bestraling?	01/06/19	31/05/21
Bernards, R.	Astex UK	ERN1 inhibition in KRAS mutant solid tumors and in BRAF mutant melanoma	01/09/14	30/06/19
Bernards, R.	Astex UK	SHP2 inhibition in KRAS mutant solid tumors	01/03/16	22/12/19
Bernards, R.	CGC	POC clinical trial voor melanoma patienten	01/12/15	31/12/21
Bernards, R.	EEG-CEC / EU	Senescence therapy for cancer	01/10/18	30/09/23
Bernards, R.	EEG-CEC / EU	Molecularly guided trials with specific treatment strategies in patients with advanced newly molecular defined subtypes of colorectal cancer (MoTriColor)	01/10/15	30/09/19
Bernards, R.	Eli Lilly Cork Limited	CDK4/6 mesylate salt synthetic lethal interactions in KRAS mutant colorectal cancer.	12/01/16	31/03/20
Bernards, R.	NWO	Zwaartekracht programma 2012	01/01/13	31/12/21
Bernards, R.	NWO	NWO Diamond Graduate Program J. Kahn	01/09/15	31/08/19
Bernards, R.	Stand up to cancer (SU2C)	SU2C - Targeting SHP2 in pancreatic cancer	01/11/18	31/12/19
Bernards, R.	Stichting Oncode Institute	Oncode Bernards	01/09/17	31/08/22
Bernards, R.	University of California (UCLA)	Interrogation of Resistance Mechanisms to Checkpoint Inhibitors Using Functional Genomics	01/11/17	31/10/19
Berns, A.J.M.	EEG-CEC / EU	Combination therapies for personalized cancer medicine	01/05/13	30/04/19
Berns, A.J.M.	Stichting Oncode Institute	Oncode Berns	01/09/17	31/05/19
Blank-de Hoop, C.U.	AVL Foundation	Impulsplan Immuuntherapie	01/04/18	31/03/22
Blank-de Hoop, C.U.	Bristol Myers Squibb Company	3D analyses of melanoma treated with Ipilimumab + Nivolumab neoadjuvant	01/01/19	30/06/20
Blank-de Hoop, C.U.	Bristol Myers Squibb Company	Improve the understanding of systemic melanoma-mediated immune suppression by deep serum profiling	01/06/17	31/05/19
Blank-de Hoop, C.U.	Bristol Myers Squibb France	A prospective multicenter cohort study of late physical, psychological and social effects in patients treated with IO for advance melanoma.	01/07/16	31/12/19

Principal investigator	Granting agency	Title	Started	Ended / Ends
Blank-de Hoop, C.U.	Bristol Myers Squibb USA	Systematic analysis of Cutaneous and Uveal Melanoma.	01/06/17	31/12/19
Blank-de Hoop, C.U.	Bristol Myers Squibb USA	Impact of NSAIDs on the response to checkpoint therapy.	02/08/17	02/08/19
Bleiker, E.M.A.	EORTC	EORTC kwaliteit van leven data.	01/12/15	31/12/20
Bleiker, E.M.A.	Stichting Roparun	Het optimaliseren en implementeren van de online borstreconstructie keuzehulp voor vrouwen met borstkanker.	01/07/19	30/06/20
Bleiker, E.M.A.	Zorginstituut Nederland	Mannen met Borstkanker	15/02/18	30/11/19
Borst, G.R.	AACR	Uncovering and exploiting interphase effects of tumor treating fields	01/07/19	30/06/20
Borst, J.G.	Aduro Biotech, Europe B.V.	Identification and validation of novel T-cell modulators in Immune Oncology	01/07/17	30/06/19
Borst, J.G.	AVL Foundation	Dendritic Cell project	01/01/18	31/12/22
Borst, J.G.	Elekta Ltd	Radio-immunotherapy in cancer treatment	01/06/16	24/01/19
Borst, J.G.	Fonds Wetenschappelijk Onderzoek	Refining cancer cell death and danger signals for the improvement of immunotherapy	01/01/18	31/12/21
Borst, J.G.	LUMC	Mutation-bearing (G)MOPD Cells: Drivers of LCH Pathology?	01/03/18	28/02/19
Borst, J.G.	NWO	Mechanisms of action of the Ubiquitin-like modifier ISG15 in immune regulation	01/01/15	31/08/19
Borst, J.G.	ZonMw	Discriminating signaling nodes in conventional and regulatory T cells to guide clinical targeting of costimulatory receptors in cancer, autoimmunity and transplant rejection.	01/04/14	31/07/19
Brummelkamp, T.R.	CIHR-IRSC / Canadian Institutes of Health Research	Exploiting proline vulnerability for cancer therapy	01/05/19	30/04/21
Brummelkamp, T.R.	EEG-CEC / EU	A global alliance for Zika virus control and prevention	01/10/16	30/09/20
Brummelkamp, T.R.	EMBO	Two-year EMBO Long-Term Fellowship Dr. Abdelghani Mazouzi	01/07/18	30/06/20
Brummelkamp, T.R.	Health-Holland	Exploiting proline vulnerability for cancer therapy	01/09/19	31/08/23
Brummelkamp, T.R.	NWO	Zwaartekracht programma 2012	01/01/13	31/12/21
Brummelkamp, T.R.	NWO	Human Genes and Intracellular Phenotypes.	01/03/17	28/02/22
Brummelkamp, T.R.	Stichting Ammodo	Ammodo Award 2015 voor Biomedical Sciences	04/03/16	04/03/19
Brummelkamp, T.R.	Stichting Oncode Institute	Oncode Brummelkamp	01/09/17	31/08/22
Brummelkamp, T.R.	University of Copenhagen	Benchfee Peter Haahr	01/07/19	30/06/22

Principal investigator	Granting agency	Title	Started	Ended / Ends
Chalabi, M.	Bristol-Myers Squibb International Belgie	Towards deciphering immune escape mechanisms of early colon cancers and developing rationales for future treatment strategies.	01/10/17	30/09/20
de Langen, A.J.	Merus N.V.	Collaboration for identification of NRG1-fusion cases in Lung Cancer.	01/03/19	31/12/20
de Visser, K.E.	EEG-CEC / EU	Mechanistic insights into the impact of tumor-associated neutrophils on metastatic breast cancer	01/03/14	28/02/20
de Visser, K.E.	F. Hoffmann-LaRoche Ltd	Rational identification and in vivo validation of effective immunotherapy opportunities for metastatic breast cancer	12/04/19	12/10/22
de Visser, K.E.	Fonds National Suisse De La Recherche Scientfique	Fellowship Spagnuolo	01/02/19	31/07/20
de Visser, K.E.	NWO	OOA NWO Diamond K.Kos	01/10/16	30/09/20
de Visser, K.E.	Roche Diagnostics GMBH	To study the anti-cancer efficacy of a triple combination treatment consisting of the Roche murinized antibody against CSF-1 receptor, cisplatin, and another modulator in a spontaneous mammary tumor mouse model.	01/05/13	31/08/19
de Visser, K.E.	Stichting Oncode Institute	Oncode - Deciphering the Cancer-Immune Landscape; towards personalized immune intervention strategies	01/08/18	31/07/21
de Visser, K.E.	Stichting Oncode Institute	Oncode de Visser	01/09/17	31/08/22
de Visser, K.E.	ZonMw	Dissecting cancer cell-intrinsic mechanisms dictating the immune landscape of breast cancer; towards personalized immune intervention strategies	01/09/19	31/08/24
de Wit, E.	EEG-CEC / EU	From haplotype to phenotype: a systems integration of allelic variation, chromatin state and 3D genome data	01/09/15	31/08/20
de Wit, E.	NWO	The role of transcription factors in 3D genome organization.	01/10/16	30/09/21
de Wit, E.	NWO	Impact of sequential driver mutations on epigenetic regulation during intestinal carcinogenesis.	01/09/17	31/08/20
de Wit, E.	Stichting Oncode Institute	Oncode de Wit	01/09/17	31/08/22
Faller, W.J.	EMBO	Two-year EMBO Long-Term Fellowship Dr. Joana Da Silva	01/07/18	30/06/20
Faller, W.J.	NWO	Zwaartekracht programma 2012	01/01/17	31/12/21
Fast, M.F.	NWO Applied and Engineering Sciences	Breathe easy: adapting lung radiotherapy in a heartbeat	01/09/19	31/08/24
Haanen, J.B.A.G.	AVL Foundation	ACT with TCR gene modified T-cells	01/01/19	31/12/21
Haanen, J.B.A.G.	Bristol Myers Squibb Company	Analysis of PD-1T TILs as biomarker for response to anti-PD-1 therapy in non-small cell lung cancer	01/09/18	01/09/19
Haanen, J.B.A.G.	Bristol Myers Squibb Company	REsPonses to noveL Immunotherapies in ex vivo Cultured tumor frAgments (REPLICA)	14/02/18	14/02/20
Haanen, J.B.A.G.	Merck (MSD)	Dissection of the role of pembrolizumab (MK-3475) on the circulating tumor-specific T cell pool specific for shared tumor-associated antigens	01/11/14	31/08/19

Principal investigator	Granting agency	Title	Started	Ended / Ends
Haanen, J.B.A.G.	Neon Therapeutics	T Cell Program, Stimulation of neo-antigen specific T cell responses from patient PBMC. N16NEON	01/02/16	31/12/19
Haanen, J.B.A.G.	ZonMw	Individualized T cell receptor (TCR) gene therapy, from bench to men	01/09/19	31/08/25
Haanen, J.B.A.G.	ZonMw	Randomized controlled trial comparing TIL treatment to ipilimumab for the treatment of advanced stage melanoma. M14TIL.	01/07/15	30/06/22
Haanen, J.B.A.G.		Precision Cell Therapy: the next wave in personalized cancer treatment	01/12/19	30/11/20
Hauptmann, M.	AVL Foundation	Startgeld Hauptmann	17/07/17	01/08/20
Hauptmann, M.	EEG-CEC / EU	Implications of Medical Low Dose Radiation Exposure	01/06/17	28/02/22
Hofland, L.	AVL Foundation	AVL Foundation hoofdhuidkoeling	01/11/18	30/06/20
Horenblas, S.	AVL Foundation	Testis onderzoek	01/01/19	31/12/20
Horenblas, S.	AVL Foundation	Immunological aspects of the microenvironment of primary tumours, tumour-positive and tumour-negative lymph nodes in HPV+ and HPV- penile cancer patients (CFMPB-522)	01/01/17	31/12/20
Horlings, H.M.	AVL Foundation	Start-up package Horlings	01/09/19	31/08/24
Huijbers, I.J.G.	EEG-CEC / EU	Towards enduring mouse resources and services advancing research into human health and disease	01/01/17	31/12/20
Huitema, A.D.R.	Merus B.V.	Support of (pre)-clinical development program of the Merus HER2/HER3 bispecific monoclonal antibody (MCLA-128)with PK/PD modeling and simulation.	18/04/14	31/08/19
Huitema, A.D.R.	Merus B.V.	Support of clinical development program of the Merus bispecific monoclonal antibody MCLA-117 with PK/PD modeling and simulation	01/09/16	01/01/19
Huitema, A.D.R.	Radboudumc	Individualized PeMetRexed dOsing in lung cancER and mesothelioma patients to improVE treatment response and allow treatment of patients with impaired renal function.	01/12/17	30/11/21
Husson, O.	EORTC	Incorporating the patient voice in sarcoma research: How can we assess health-related quality of life in this heterogeneous group of patients?	01/01/19	31/12/20
Husson, O.	NWO	Facing the unthinkable in the prime of life: Prevalence, risk factors and mechanisms of impaired medical and psychological health outcomes among adolescents and young adults with cancer	01/12/19	30/11/24
Husson, O.	Sarcoma Patients EuroNet e.V./ Assoc.	SPAEN sarcoomonderzoek	01/05/19	30/04/21
Husson, O.	Stichting Vrienden Integrale Oncologische Zorg	Onderzoek naar het effect van de Match app, een online interventie om het menselijk contact en begrip tussen jongvolwassenen met kanker en hun omgeving te verbeteren	01/10/18	30/09/20
Jacobs, H.B.	ZonMw	The role of stable immunoglobulin transcripts in establishing allelic exclusion.	01/04/14	31/03/19
Jacobs, J.J.L.	EEG-CEC / EU	Joint Training and Research Program on Chromatin Dynamics and the DNA Damage Response - aDDRess	01/03/19	28/02/23
Jacobs, J.J.L.	EMBO	EMBO Small Grant for funding of research materials.	01/01/17	31/12/20
Jacobs, J.J.L.	NWO-ALW	EMBO Young Investigators	01/01/13	31/12/20

Principal investigator	Granting agency	Title	Started	Ended / Ends
Jalink, C.	EEG-CEC / EU	Microscopy of living cancer cells at physiological oxygen levels: the MICROX platform	15/09/19	14/09/22
Jalink, C.	STW	New Film Camera for molecular microscopy	01/09/16	15/06/20
Jonkers, J.M.M.	EEG-CEC / EU	Combination Therapies for personalized medicine	01/05/13	30/04/19
Jonkers, J.M.M.	EEG-CEC / EU	Generation of the CanPath prototype - a platform for predictive cancer pathway modeling	01/03/16	28/02/21
Jonkers, J.M.M.	EEG-CEC / EU	Targeting SYNthetic lethal interactions for new cancer treatments	01/09/16	31/08/20
Jonkers, J.M.M.	NWO	Zwaartekracht programma 2012	01/01/13	31/12/21
Jonkers, J.M.M.	NWO	Finding novel Achilles 'heels to prevent and target BRCA1-associated breast cancer.	01/02/14	31/01/20
Jonkers, J.M.M.	Stand up to cancer (SU2C)	2018 Stand up to cancer Laura Ziskin Price Award, A high -risk, high-rewarded breast cancer research project.	01/02/18	31/01/19
Jonkers, J.M.M.	Stichting Oncode Institute	Oncode Jonkers	01/09/17	31/08/22
Jonkers, J.M.M.	University of Copenhagen	Unraveling the genetic background of familial breast cancer	01/01/18	31/12/22
Jonkers, J.M.M.	ZonMw	Deciphering the contribution of cancer-associated fibroblasts to invasive lobular carcinoma development, progression and tumor microenvironment	01/01/19	31/12/21
Karakullukcu, M.B.	AVL Foundation	3D Lab	01/04/17	31/12/21
Karakullukcu, M.B.	Health-Holland	PPS-toeslag	11/03/19	31/03/21
Kok, M.	AVL Foundation	Materiaal budget TONIC-Trial	01/09/15	31/03/20
Kok, M.	AVL Foundation	How breast cancer cells escape from the immune system	01/04/19	30/06/20
Kok, M.	AVL Foundation	Hoe omzeilt borstkanker het immuunsysteem?	01/01/19	31/12/20
Kok, M.	AVL Foundation	Start-up package Marleen Kok	01/12/18	30/11/28
Kok, M.	Breast Cancer Research Foundation	Exploiting the Foreign Antigenic Space in Breast Cancer	01/10/17	31/10/19
Kok, M.	Pink Ribbon	Discovery of biomarkers to select metastatic breast cancer patients for immunotherapy using anti-PD1	01/09/16	30/06/20
Kok, N.F.M.	AVL Foundation	PUMP-IT Trial (M19PIT)	01/11/19	31/12/24
Kvistborg, P.	Bristol Myers Squibb Company	Quantitative and qualitative changes in tumor-specific T cells upon anti-PD-1 therapy	01/02/16	18/08/19
Kvistborg, P.	Merck Sharp & Dohme Corp.	To compare the tumor reactivity and antigenic determinants of CD8+ TCR clones in tumor tissue from KN161 participants who respond to pembrolizumab compared to KN161 participants who do not respond to pembrolizumab	02/11/18	01/11/23
Kvistborg, P.	Merck Sharp & Dohme Corp.	Feasibility study of neo-adjuvant treatment with carboplatin, paclitaxel and pembrolizumab in stage IV epithelial ovarian cancer	01/10/16	30/09/20

Principal investigator	Granting agency	Title	Started	Ended / Ends
Lenstra, T.L.	EEG-CEC / EU	Single-molecule visualization of transcription dynamics to understand regulatory mechanisms of transcriptional bursting and its effects on cellular fitness.	01/01/18	31/12/22
Lenstra, T.L.	NWO	Zwaartekracht programma 2012	01/01/17	31/12/21
Lenstra, T.L.	NWO Exacte en Natuurweten-schappen	Unravelling how DNA organization is linked to transcriptional dynamics	01/09/18	31/12/21
Lenstra, T.L.	Stichting Oncode Institute	Oncode Lenstra	01/01/19	31/12/23
Lenstra, T.L.	Stichting Oncode Institute	3D orbital tracking microscope	01/08/19	31/07/20
Linn, S.C.	A Sister's Hope	Toward personalized medicine by using the nationwide population-based breast cancer registry (1989-2009) couple with biobanking: NBCP	01/06/12	31/08/19
Linn, S.C.	A Sister's Hope	PI3K pathway activation in primary and metastatic estrogen receptor alpha (ERa) positive breast cancer and the association with drug response	01/12/12	31/08/21
Linn, S.C.	A Sister's Hope	Mutational analysis and BRCA1-like classification in WSG-ADAPT TN-Trial	01/01/17	31/12/20
Linn, S.C.	Agendia N.V.	Validation of Ultralow threshold MammaPrint in the IKA trial	01/03/19	29/02/20
Linn, S.C.	AVL Foundation	Breast cancer research aimed at saving lives	01/11/17	01/11/21
Linn, S.C.	AVL Foundation	ADAPT BRCA-like project Zaan aan de Wandel	01/01/17	31/12/20
Linn, S.C.	AVL Foundation	STARZ Foundation	01/01/14	31/12/20
Linn, S.C.	AVL Foundation	Zaan Peeper-Linn 'Learning from unexpected cures'	01/04/14	31/08/21
Linn, S.C.	AVL Foundation	Materiaal budget TONIC-Trial	01/09/15	31/12/20
Linn, S.C.	Daiichi Sankyo Oncology Europe GmbH	ENDEAVOUR-Breast	01/06/18	31/05/21
Linn, S.C.	ZonMw	Substantiele verbetering van de overleving van stadium III, BRCA1-like borstkanker patienten met doelgerichte behandeling. SUBITO	01/01/17	31/12/22
Marijnen, C.A.M.	AVL Foundation	Prospective study evaluating ctDNA as a biomarker for treatment response in head and neck squamous cell carcinoma	01/05/19	30/04/22
Marijnen, C.A.M.	AVL Foundation	Image Guided Therapy onderzoek met de Gamma Knife	01/01/17	31/12/20
Marijnen, C.A.M.	Ned Ver v Radioth en Ocologie NVRO	De ontwikkeling van een PRO-bijwerkingensubset voor prostaatkankerpatienten	01/09/19	31/08/20
Medema, R.H.	NWO	Zwaartekracht programma	01/01/13	31/12/21
Medema, R.H.	Stichting Oncode Institute	Oncode Medema	01/09/17	31/08/22
Medema, R.H.	ZonMw	Impact of chromatin context on DNA double-strand break repair kinetics, fidelity and signaling.	01/07/16	30/06/20
Meijer, G.A.	AACR	AACR GENIE Project	01/07/16	31/12/23
Meijer, G.A.	AVL Foundation	Darmkanker en biomarkers (research / translationeel deel van CAIRO 6 studie, M17CR6)	01/03/17	28/02/20

Principal investigator	Granting agency	Title	Started	Ended / Ends
Meijer, G.A.	BBMRI-NL	X-omics BBMRI	01/09/18	31/08/23
Meijer, G.A.	EEG-CEC / EU	Coordinated Research Infrastructures Building Enduring Life-science services	01/11/16	31/05/20
Meijer, G.A.	EIT Health e.V.	Convention for distributing funds Subvention by Philantropia	01/03/19	31/03/20
Meijer, G.A.	Health-Holland	CRCBioscreen3.0	10/07/19	09/07/20
Meijer, G.A.	Health-Holland	Liquid biopsy-based molecular diagnostics to monitor therapy response in metastatic colorectal cancer: PLCRC-ORCA EXTended beyond RAS	01/01/17	31/12/20
Meijer, G.A.	Stichting Sacha Swarttouw-Hijmans	Vrij circulerend tumor DNA (ctDNA) als biomarker voor monitoring van patienten met rectumkanker	01/05/18	30/04/20
Meijer, G.A.	Stichting Sacha Swarttouw-Hijmans	Securing Blood from Colon Adenoma Patients in the CLIPPER Trial to Enable Development of Biomarkers for Early Detection of High-Risk Colon Adenomas and CRC. The SAMPLE Study.	01/05/18	30/04/20
Meijer, G.A.	ZonMw	Molecular adenoma features to predict colorectal cancer risk	10/06/19	10/12/21
Meijer, G.A.	ZonMw	WGS implementation in standard cancer Diagnostics for Each cancer patient (WIDE) N18WGS	15/07/19	14/01/22
Meijer, G.A.	ZonMw	Voorlichtingsvideo kiembaanbevindingen	04/11/19	04/03/20
Monkhorst, K.	AstraZeneca BV (NL)	Primary Molecular Profiling in NSCLC using Plasma cfDNA from the LEMA cohort	07/05/19	01/07/20
Nederlof, P.M.	Roche Nederland BV	Roche CGH Array	01/10/12	30/11/19
Neefjes, J.J.C.	NWO	Visualizing macromolecular complexes in MHC antigen presentation	01/10/14	31/12/19
Neefjes, J.J.C.	NWO	Discovery of novel cancer therapies(oncodrugs)	01/01/16	31/12/19
Nuijen, B.	Modra Pharmaceuticals B.V.	For Chemistry, Manufacturing and Control of ModraDoc006 tablets	28/05/18	31/05/19
Nuijen, B.	Modra Pharmaceuticals B.V.	To provide clinical services for Study: Multicenter safety, feasibility and pharmacokinetic phase I-II trial of ModraDoc006/r in patients with metastatic castration-resistant prostate cancer (M17DOC)	25/05/17	30/06/19
Nuijen, B.	Modra Pharmaceuticals B.V.	A multicentre phase IIa study to evaluate the efficacy and tolerability of ModraDoc006/r in patients with recurrent or metastatic HER-2 negative breast cancer, suitable for treatment with a taxane (M18DMB)	01/01/19	31/12/19
Ovaa, H.	NWO	Covalent Enzyme Capture	01/06/14	31/05/19
Ovaa, H.	NWO	Discovery of novel cancer therapies(oncodrugs)	01/01/16	31/12/19
Ovaa, H.	NWO Chemische Wetenschappen	Exploring and exploiting activity-based protein profiling in chemical biology and medicinal chemistry	01/03/15	28/02/21
Peeper, D.S.	AVL Foundation	Screening novel therapeutic targets for immuno oncology	01/12/17	30/11/19
Peeper, D.S.	Bristol Myers Squibb USA	Defining and tackling immunotherapy resistance in melanoma and lung cancer	01/08/17	31/07/21
Peeper, D.S.	EEG-CEC / EU	Combination Therapies for personalized medicine	01/05/13	30/04/19
Peeper, D.S.	Genmab	Research into cell signal pathways and oncogenic divers.	01/05/15	30/09/20

Principal investigator	Granting agency	Title	Started	Ended / Ends
Peeper, D.S.	Josephine Nefkens Stichting	Identificatie van nieuwe immuuntherapie met Itellicyt Screener PLUS	01/03/18	28/02/22
Peeper, D.S.	Merck Sharp & Dohme Corp.	Identify tumor-intrinsic factors that induce resistance to anti PD-1 antibody treatment in vivo (Keytruda resistome) in the D10 system.	13/11/18	13/11/19
Peeper, D.S.	Merck Sharp & Dohme Corp.	Identification of chromatin modifiers genes that upon inactivation show a synthetic lethal phenotype with Switch/Sucrose NonFermentable (SWI/SNF) chromatin-remodeling complex mutations in tumor cell lines.	08/09/15	08/09/19
Peeper, D.S.	Stichting Oncode Institute	Oncode Peeper	01/09/17	31/08/22
Perrakis, A.	EEG-CEC / EU	INEXT JRA	01/09/15	31/08/19
Perrakis, A.	Janssen Research & Development	Enhancement of PDB_REDO algorithms and software	01/01/16	30/04/19
Perrakis, A.	NWO Chemische Wetenschappen	Structural and chemical basis for the biosynthesis and propagation of base J.	01/09/14	31/08/19
Perrakis, A.	NWO Chemische Wetenschappen	Optimized protein knowledge through transfer of evolutionary conserved features and chemical knowledge.	15/11/14	14/11/19
Perrakis, A.	STFC Science & Technology Facilities Council C/O UK SBS Ltd	CCP4 Software Derivative Work	01/06/19	31/05/20
Perrakis, A.	Stichting Oncode Institute	Oncode Perrakis	01/01/19	31/08/22
Perrakis, A.	Universiteit Utrecht	Releasing the full potential of Instruct to expand and consolidate infrastructure services for integrated structural life science research	01/01/17	31/12/20
Rosing, H.	Neon Therapeutics	Qualification of an UPLC-MS method for the identity analysis of neo-antigen peptides drug products and the quality control of these products	01/03/18	31/12/19
Rowland, B.D.	EEG-CEC / EU	Cohesin-mediated chromosomal looping: from linear paths to 3D effects	01/04/18	31/03/23
Ruers, T.J.M.	AVL Foundation	Fluorescence Life Time Imaging	01/09/19	31/08/21
Ruers, T.J.M.	AVL Foundation	Optical guided surgery	01/11/14	31/05/20
Ruers, T.J.M.	AVL Foundation	Pixelanalyse voor (vroeg)detectie van dikkedarmkanker	01/01/17	31/12/20
Ruers, T.J.M.	EEG-CEC / EU	Photonics Manufacturing Pilot Lines for Photonic Components and Devices	01/01/20	31/12/23
Ruers, T.J.M.	EEG-CEC / EU	Advancing Smart Optical Imaging and Sensing for Health.	01/06/16	31/05/19
Ruers, T.J.M.	Health-Holland	TomTom project van Venture Challenge Fall 2016	01/12/16	30/11/20
Ruers, T.J.M.	Holland High Tech	ECSEL project ASTONISH.	01/06/16	31/05/19
Ruers, T.J.M.	Innovation Exchange Amsterdam	Magnetische Marker voor Chirurgische Lokalisatie. Amsterdam Science & Innovation Award.	01/06/16	31/05/20
Ruers, T.J.M.	Intuitive Surgical Operations Inc.	Improving robotic surgery of prostate cancer by real time tissue characterrization using Diffuse Reflection Spectroscopy. Development of clinical implementation of existing technology.	01/01/20	31/12/20

Principal investigator	Granting agency	Title	Started	Ended / Ends
Ruers, T.J.M.	Nijbakker-Morra Stichting	Fiber probe; steriliseerbare instrument voor in vivo spectroscopisch onderzoek van resectiemarges.	01/02/18	31/03/19
Ruers, T.J.M.	Philips	Research collaboration Philips	01/04/10	30/06/20
Ruers, T.J.M.	Stichting Life Science Health Tki	Hyperspectral Imaging for Improving Cancer Surgery	01/04/19	31/03/22
Ruers, T.J.M.	STW	Combining Optics and Acoustics For Real-time Guidance during Cancer Surgery	01/04/18	31/03/22
Schellens, J.H.M.	aCBG	Convenant CBG	01/05/17	30/04/22
Schellens, J.H.M.	NWO	Zwaartekracht programma 2012	01/01/13	31/12/21
Schmidt, M.K.	BBMRI-NL	Personalized medicine: servicedesk ethiek en recht	01/09/18	31/12/19
Schmidt, M.K.	BBMRI-NL	X-omics	01/09/18	31/08/23
Schmidt, M.K.	EEG-CEC / EU	Breast CAncer STratification: understanding the determinants of risk and prognosis of molecular subtypes.	01/09/15	31/08/20
Schmidt, M.K.	Ministerie van VWS	Verkenning niet-WMO-onderzoek	06/05/19	30/11/19
Schmidt, M.K.	ZonMw	Practical help towards responsible use of residual bio specimens and data in medical research in the Netherlands	01/10/19	30/09/20
Schmidt, M.K.	ZonMw	Fostering the responsible use of residual bio specimens and data in medical	01/05/17	30/04/19
Schmidt, M.K.	ZonMw	Personalized medicine: servicedesk ethiek en recht	01/09/17	31/08/21
Schmidt, M.K.		Servicedesk 2	01/09/19	31/08/21
Schumacher, A.N.M.	Cancer Research Institute	Unraveling the biology of CMTM6: A novel regulator of PD-Li identified through genome-wide genetic screening	01/01/17	31/12/19
Schumacher, A.N.M.	EEG-CEC / EU	Sensitivity of human tumors to T cell attack	01/12/17	30/11/22
Schumacher, A.N.M.	Kristian Gerhard Jebsen foundation	Jebsen grant	01/06/13	31/12/19
Schumacher, A.N.M.	Merck KGaA	Single cell analysis of the tumor-immune ecosystem in human cancer: Dissecting the dynamics of immune-tumor cross talk following checkpoint blockade.	01/06/17	31/05/20
Schumacher, A.N.M.	NWO	Zwaartekracht programma 2012	01/10/14	30/09/19
Schumacher, A.N.M.	Roche Nederland BV	T cell responses and mapping of neo-antigen-specific T cell repertoires in follicular lymphoma patients after local anti-CD20 therapy	01/04/14	30/06/19
Schumacher, A.N.M.	Stichting Oncode Institute	Oncode Schumacher	01/09/17	31/08/22
Sixma, T.K.	EEG-CEC / EU	Regulated Assembly of Molecular Machines for DNA REPAIR: a Molecular Analysis training Network	01/01/17	31/12/20
Sixma, T.K.	NWO	Structure-function analysis of transcription-associated DNA repair	01/06/18	31/05/24
Sixma, T.K.	NWO	Zwaartekracht programma 2012	01/01/13	31/12/21

Principal investigator	Granting agency	Title	Started	Ended / Ends
Sixma, T.K.	NWO	Thermophoresis HPLC imager	01/04/13	31/12/21
Sixma, T.K.	NWO	The molecular mechanism of USP48, a BRCA1 antagonist during DNA damage response	01/09/18	31/08/23
Sixma, T.K.	NWO	A program to enable discovery of catalytic and/or inhibitors of the USP4/11/15 family of deubiquitinating enzymes	01/10/18	30/09/23
Sixma, T.K.	NWO Chemische Wetenschappen	A movie of DNA mismatch repair: how information is transmitted by conformational change	01/01/17	31/12/22
Sixma, T.K.	NWO Exacte en Natuurweten-schappen	The mechanism of USP1 activation	01/06/20	31/05/24
Sixma, T.K.	NWO-ALW	Cellular activation of the allosterically inhibited UCHL5/INO80G complex	01/12/16	30/11/19
Sixma, T.K.	Stichting Life Science Health Tki	Development of activity-based probes for metalloDUBs	01/09/19	31/08/21
Sixma, T.K.	Stichting Oncode Institute	Oncode Sixma	01/09/17	31/08/22
Sonke, G.S.	AVL Foundation	Long-term survival in HER2+ Breast Cancer project Zaan de Wandel	01/01/18	30/06/20
Sonke, G.S.	Pink Ribbon	Learning from long-term survivors in metastatic breast cancer	01/11/16	31/10/20
Sonke, J.J.	Elekta Ltd	Framework Research Agreement between Elekta and NKI/AvL	10/08/10	10/08/20
Sonnenberg, A.	DEBRA AUSTRIA	High-content screening for new therapies for Epidermolysis Bullosa Simplex associated with Muscular Dystrophy (EBS-MD)	01/04/17	31/03/19
Steeghs, N.	EEG-CEC / EU	Molecularly guided trials with specific treatment strategies in patients with advanced newly molecular defined subtypes of colorectal cancer (MoTriColor).	01/10/15	31/05/20
Steeghs, N.	Glaxo Smith Kline Durham	Oncology Clinical and Translational consortium (OCTC)	22/10/13	22/10/20
Stokkel, M.P.M.	AVL Foundation	Tumour specific imaging of prostate cancer using PSMA-PET	01/07/16	30/06/19
Stokkel, M.P.M.	STW	A feasibility study on Cerenkov Luminescence Imaging during prostate cancer surgery using Gallium-68 PSMA	01/08/17	31/10/19
Stuiver, M.M.	EEG-CEC / EU	Project on Exercise for Fatigue Eradication in Advanced Breast cancer to improve quality of life - PREFERABLE	01/01/19	31/12/23
Stuiver, M.M.	Nutricia Nederland B.V.	Voedingsstatus en het beloop van de behandeling van stadium III longkanker.	01/11/17	31/12/20
te Riele, H.P.J.	STW	Phenotypic assessment of intra- and extra-exonic variants of disease-related genes present in the human population.	01/01/17	31/12/20
Tesselaar, M.E.T.	Ipsen Farmaceutica BV	NEN database	15/12/19	14/12/20
Tesselaar, M.E.T.	Merck BV	Database of retrospectively and subsequent prospectively gathered data of all MCC patients treated in the Netherlands as platform for a national MCC database.	01/09/18	31/12/22
Thommen, D.S.	AVL Foundation	DNA gala	01/09/19	31/08/24

Principal investigator	Granting agency	Title	Started	Ended / Ends
Thommen, D.S.	Bristol Myers Squibb Company	Simultaneous versus sequential combination of nivolumab and ipilimumab in human tumor explants	01/10/19	31/03/20
Trum, J.W.	ZonMw	GERiatric Screening in the treatment of elderly patients with Ovarian Carcinoma (GERSOC)	15/08/17	15/08/21
van Akkooi, A.C.J.	Amgen B.V.	the infra structure registry: prospective melanoma stadium III registry	01/07/17	30/06/20
van Akkooi, A.C.J.	EORTC	Transitional study moving towards logical and personal combination therapies in the treatment of melanoma in-transit metastases and improving understanding of underlying biology.	01/05/18	31/12/20
van Beurden, M.	AVL Foundation	Onderzoek naar vrouwen met LS die kanker ontwikkelen	01/05/18	30/04/20
van de Poll, L.V.	EEG-CEC / EU	Cancer Patients Better Life Experience (CAPABLE)	01/01/20	31/12/23
van de Poll, L.V.	EORTC	Phase II and III development of an EORTC QOL cancer survivorship questionnaire	01/02/17	31/07/19
van de Poll, L.V.	Stichting Roparun	Project CALM Roparun	01/10/18	30/09/20
van de Ven, H.W.M.	EEG-CEC / EU	EurOPDX Distributed Infrastructure for Research on patient-derived cancer Xenografts	01/02/18	31/01/22
van den Berg, J.H.	Bristol Myers Squibb Company	Urelumab to improve tumor reactivity of Tumor Infiltrating Lymphocytes (TIL) derived from ovarian cancer and NSCLC using urelumab	31/07/17	31/01/19
van den Berg, J.H.	MedImmune	Immunomagnetic selection of PD1 + Peripheral Blood Mononuclear Cells.	10/07/17	10/07/20
van den Berg, J.H.	Neon Therapeutics	NEON manufacturing agreement	28/08/19	27/08/22
van den Brekel, M.W.M.	ATOS	ATOS research and new product development NKI-AVL	01/01/14	30/06/20
van den Brekel, M.W.M.	AVL Foundation	Hoofd-Hals Targeted therapy	01/01/15	31/12/20
van den Brekel, M.W.M.	EEG-CEC / EU	Training Network on Automatic Processing of PAthological Speech	01/11/17	31/10/21
van den Brekel, M.W.M.	Patienten-vereniging Hoofd-Hals	De ontwikkeling van een keuzehulp voor patienten met een orofarynxcarcinoom waarvoor een chirurgisch curatieve behandeling mogelijk is.	01/07/18	31/01/20
van den Broek, D.	Roche Nederland BV	Roche AVENIO first evaluation and validation NKI-AVL	01/09/18	01/09/19
van den Broek, D.	ZonMw	ctDNA on the way to implementation in the Netherlands(COIN)	27/03/19	26/03/23
van den Heuvel, M.M.	Bristol Myers Squibb USA	Introducing an easily accessible biomarker based on an active immune expression array can optimize personalized immunotherapy.	01/11/16	31/12/20
van der Heide, U.A.	Health-Holland	Magnetic en Momentum	01/06/18	28/02/23
van der Heide, U.A.	Philips Finland	Feasibility of MR-only in Radiation Oncology.	13/12/17	30/04/22
van der Heide, U.A.	Rijksdienst voor Ondernemend Nederland	ARTWORK	01/11/19	30/11/21
van der Heide, U.A.	ZonMw	Quantivision project - perfect cut	15/05/15	15/05/19
van der Heijden, M.S.	Stichting DUOS	Translationeel onderzoek immunotherapie bij peniskanker	01/06/19	31/05/21

Principal investigator	Granting agency	Title	Started	Ended / Ends
van der Poel, H.G.	Intuitive Surgical Operations Inc.	Robot-assisted radioguided surgery using a drop-in gamma probe	01/03/18	29/02/20
van Driel, W.J.	AVL Foundation	Onderzoek voor ovarium carcinoom	01/10/17	30/09/20
van Driel, W.J.	ZonMw	Implementation of diagnostic laparoscopy in advanced stage ovarian cancer to guide initial treatment; either primary debulking surgery or neo-adjuvant chemotherapy.	01/01/20	31/12/20
van Harten, W.H.	AVL Foundation	Monopolie met maatschappelijk rendement - Verantwoord omgaan met patenten in de oncologie	01/01/17	28/02/21
van Harten, W.H.	Intuitive Surgical Operations Inc.	CERA-PRO: cost-effectiveness of robot-assisted prostatectomy compared to laparoscopic prostatectomy: 6-8 year multi institutional PROM's follow-up study out of a Dutch perspective.	01/09/19	31/08/27
van Harten, W.H.	ZonMw	Technology Assessment of Next Generation Sequencing in Personalized Oncology (TANGO)	31/12/16	13/02/21
van Leerdam, M.E.	MAAG LEVER DARM Stichting	Diagnostic yield of colonoscopy surveillance in testicular cancer survivors treated with platinum-based chemotherapy	01/01/20	31/12/21
van Leerdam, M.E.	MAAG LEVER DARM Stichting	DICHOS project: Diagnostic yield of screening colonoscopy in Hodgkin lymphoma survivors at increased risk of treatment-induced colorectal cancer.	01/05/15	30/04/19
van Leeuwen, F.	NWO	Principles of epigenetic inheritance.	23/07/13	23/07/19
van Leeuwen, F.	NWO Chemische Wetenschappen	Development of antibodies targeted at site-specific protein ubiquitylation Phase 1 & Phase 2	01/09/16	31/08/19
van Leeuwen, F.	ZonMw	Epigenetic control of cytotoxic T cells to modulate immune responses	01/06/19	31/05/24
van Leeuwen, F.E.	AVL Foundation	Beter Project	01/06/18	31/05/20
van Leeuwen, F.E.	DES	Onderzoek CCAC van DES-dochters ouder dan 50 jaar	01/10/17	31/03/19
van Leeuwen, F.E.	EEG-CEC / EU	Implications of Medical Low Dose Radiation Exposure	01/06/17	28/02/22
van Leeuwen, F.E.	Pink Ribbon	Assessment of myocardial strain: a novel method for early detection of subclinical cardiotoxicity after anthracycline-based chemotherapy in young breast cancer patients.	01/12/16	30/11/19
van Leeuwen, F.E.	Social & Scientific Systems inc.	Preparing and providing tissue samples and clinical data from histologically confirmed second gastric tumor cases among survivors of Hodgkin lymphoma and testicular cancer for a study characterizing the molecular characteristics of second primary gastric cancers.	02/09/16	31/05/20
van Leeuwen, F.E.	The General Hospital Corporation D b/a Massachussetts General Hospital	LIFT-OMEGA	01/09/17	30/11/19
van Leeuwen, F.E.	Vlissingen Lymfoomfonds	Evaluatie BETER poliklinieken	01/03/18	31/12/19
van Lohuizen, M.M.S.	NWO	Zwaartekracht programma 2012	01/01/13	31/12/21
van Lohuizen, M.M.S.	Stichting Oncode Institute	Oncode van Lohuizen	01/09/17	31/08/22
van Lohuizen, M.M.S.		EZH2 + FGFR inhibitor Combination Therapy to Treat BAPI. Deficient Tumors	01/07/19	30/06/20

Principal investigator	Granting agency	Title	Started	Ended / Ends
van Luenen, H.G.A.M.	AVL Foundation	Junior groepsleider 2019	01/10/19	30/09/24
van Luenen, H.G.A.M.	EEG-CEC / EU	Libra	01/10/15	31/03/19
van Luenen, H.G.A.M.	NWO	Stimulering Europees Onderzoek	01/12/15	30/11/20
van Rheenen, J.E	CGC	CGC	01/10/17	31/12/21
van Rheenen, J.E	Dr. Josef Steiner Krebsstiftung	Research Award 2017	01/10/17	30/09/21
van Rheenen, J.E	EEG-CEC / EU	Tumor cell death supports recurrence of cancer (Cancer-Recurrence)	01/10/17	31/08/20
van Rheenen, J.E	EMBO	Two-year EMBO Long-Term Fellowship Dr. Miguel Vizoso Patino	01/09/18	31/12/19
van Rheenen, J.E	EMBO	EMBO Long-Term Fellowship H. Messal	01/08/19	31/07/21
van Rheenen, J.E	H.F.S.P.O.	HFSPO Fellowship Claire Vennin	01/06/18	31/05/21
van Rheenen, J.E	Stichting Oncode Institute	Oncode van Rheenen	01/09/17	31/08/22
van Sandick, J.W.	Vrolijk	Slokdarmkankeronderzoek Stichting Vrolijk	01/01/08	30/06/20
van Sandick, J.W.	Vrolijk	Lab slokdarmkankeronderzoek Stichting Vrolijk	01/09/09	30/06/20
van Sandick, J.W.	ZonMw	Combinatie behandeling van cytoreductieve chirurgie en hypertherme intraperitoneale chemotherapie (HIPEC) bij patienten met een maagcarcinoom en synchrone buikvliesmetastasen en/of tumorpositief buikvocht.	01/10/17	30/09/22
van Steensel, B.	AIRC	Twisting the boundaries: Role of Topoisomerase1 at the nuclear lamina iCARE-2 fellowship	01/01/19	31/12/21
van Steensel, B.	AVL Foundation	Ontwikkeling Chromatin Genomics	01/11/14	31/10/24
van Steensel, B.	EEG-CEC / EU	Genomics of Chromosome Architecture and Dynamics in Single Cells	01/03/17	28/02/22
van Steensel, B.	Stichting Oncode Institute	Oncode van Steensel	01/09/17	31/08/22
van Steensel, B.	University of Illinois	NIH 4DNucleome deel 1 Mapping and Technology Development	28/09/15	31/07/20
van Steensel, B.	University of Illinois	NIH 4DNucleome deel 2 Additional Tool Development or Data Generation module	01/09/17	31/08/20
van Steensel, B.	ZonMw	Impact of chromatin context on DNA double-strand break repair kinetics, fidelity and signaling.	28/07/16	28/07/20
van Tellingen, O.	AVL Foundation	Improving chemoradiation therapy of GBM by inhibition of glioma invasion: A Proof-of-Concept study	01/12/17	30/11/20
van Tellingen, O.	AVL Foundation	Multi-Targeted Combination Therapy for treatment of glioblastoma: in vivo proof-of-concept study	01/06/18	31/05/20
van Tellingen, O.	Debiopharm International SA	Efficacy study of Wee1 inhibitor Debio 0123 and radiotherapy against orthotopic intracranial tumor models.	01/10/18	30/09/20
van Tellingen, O.	Izumi Biosciences INC	Modulation of the metabolism of elacridar by deuteration	01/10/18	30/09/20
van Tellingen, O.	Numeric Biotech Holding BV	Collaboration to test the validity of using senolytic peptides in combination with radiotherapy for the treatment of cancer	01/10/18	30/09/20

Principal investigator	Granting agency	Title	Started	Ended / Ends
van Tellingen, O.	Reneuron Limited	Efficacy study of exosomes against orthotopic intracranial tumor models	01/06/16	31/05/19
van Tinteren, H.	IKNL	Overeenkomst zelfregisterend melanoomcentrum DMTR	01/05/16	31/12/20
van Tinteren, H.	IKNL (Utrecht)	Dutch Oncology Research Platform (DORP)	01/06/19	31/05/23
van Tinteren, H.	Modra Pharmaceuticals B.V.	Work order 1 Multicenter safety, feasibility and pharmacokinetic phase II trial of ModraDoc006/r in patients with metastatic castration-resistant prostate	01/06/17	31/03/20
van Tinteren, H.	Modra Pharmaceuticals B.V.	Food effect of weekly administration of (bi) daily Oral Docetaxel(ModraDoc006) in combination with ritonavir	01/07/17	31/03/20
van Tinteren, H.	Modra Pharmaceuticals B.V.	Safety of extended use of the weekly oral docetaxel formulation ModraDoc006/r in patients with advanced solid tumors (N17DEX)	01/07/17	30/09/20
van Tinteren, H.	NVALT	A phase III prospective double blind placebo controlled randomized study of adjuvant MEDI4736 in completely resected non-small cell lung cancer.	08/02/18	08/08/22
van Trommel, N.E.	AVL Foundation	Onderzoek ADP Cervixcarcinoom, tevens M17CPF	01/09/17	31/08/21
van Trommel, N.E.	AVL Foundation	Onderzoek ADP Ovariumcarcinoom	01/09/17	31/08/21
Vens, C.	AstraZeneca BV (NL)	Olaparib- Radiation combination studies: evaluating the potential of Olaparib to mitigate RT-induced lung toxicity and comparing this combination to conventional chemo-radiation	01/01/14	01/07/19
Verheij, M.	EEG-CEC / EU	Clinical proof of concept through a randomized phase II study: a combination of immunotherapy and stereotactic ablative radiotherapy as a curative treatment for limited metastatic lung cancer.	01/01/17	31/12/22
Voest, E.E.	NWO	Zwaartekracht programma 2012	01/03/14	31/12/21
Voest, E.E.	Stichting Oncode Institute	Oncode Voest	01/01/19	31/08/22
Voest, E.E.	ZonMw	COLOSYS: A systems approach to preventing drug resistance in colon cancer	01/05/16	30/11/19
Wesseling, J.	Cancer Research UK	Prevent Ductal Carcinoma in Situ Invasive Overtreatment Now - PRECISION	01/06/18	31/12/19
Wesseling, J.	HeritX, Inc	Immunoprevention of BRCA1-associated mammary cancer	01/03/18	28/02/21
Wesseling, J.	Pink Ribbon	Preventing overtreatment of microcalcification-associated in situ breast lesions by implementing more accurate prognostic biomarkers.	01/04/14	31/03/19
Wesseling, J.	Pink Ribbon	Low Risk Ductal carcinoma In Situ - a Randomized, Non-inferiority trial. (LORD Trial)	01/04/14	31/03/19
Wessels, L.F.A.	CGC	Bioinformatica CGC	01/11/13	31/12/21
Wessels, L.F.A.	EEG-CEC / EU	Combination Therapies for personalized medicine	01/05/13	30/04/19
Wessels, L.F.A.	Genmab	Identification of Biomarkers for HexaBodyR-DR5/DR5 therapy.	01/09/17	31/12/20
Wessels, L.F.A.	GlaxoSmith Kline	Computational analyses to unravel the mechanism of action of BET and EZH2 inhibitors and define biomarkers	01/02/16	31/01/19
Wessels, L.F.A.	Health-Holland	A genomics compendium to identify therapeutic targets	01/09/19	31/08/23
Wessels, L.F.A.	NWO	Zwaartekracht programma 2012	01/01/13	31/12/21

Principal investigator	Granting agency	Title	Started	Ended / Ends
Wessels, L.F.A.	Stichting CPCT	Tumor Organoids: A new preclinical model for drug sensitivity analysis	01/05/14	30/04/19
Wessels, L.F.A.	Stichting Oncode Institute	Oncode Wessels	01/09/17	31/08/22
Wessels, L.F.A.	Vall D'Hebron Institute of Oncology	Basket of Baskets: A modular, open-label, phase II, multicentre study to evaluate targeted agents in molecularly selected populations with advanced solid tumors	01/11/18	31/10/22
Wessels, L.F.A.	ZonMw	COLOSYS: A systems approach to preventing drug resistance in colon cancer	01/02/17	31/01/20
Wessels, L.F.A.	ZonMw	Targeting theHER2 receptor: finding biomarkers for optimal anti-HER2 treatment.	01/02/18	31/01/19
Zuur, C.L.	W.M. de Hoopstichting	Aanschaf en opzetten laboratoriummaterialen voor het onderzoeken van bloedaanmaak bij hoofd-hals kankerpatienten voor en na behandeling.	01/04/18	30/09/21
Zwart, W.T.	A Sister's Hope	Ex-vivo intervention of metastatic breast cancers for novel drug testing and development in endocrine therapy-resistance.	01/12/17	31/05/20
Zwart, W.T.	AVL Foundation	Integrative Androgen Receptor genomics as a readout for recurrence risk and treatment resistance of prostate cancer	01/09/17	31/01/19
Zwart, W.T.	EEG-CEC / EU	Training network in drug discovery targeting TRIM Ubiquitin ligases in disease.	01/01/19	31/12/22
Zwart, W.T.	Stichting Oncode Institute	Oncode - Validation of a novel 9-gene-classifier to guide adjuvant treatment for prostate cancer	01/01/19	31/12/20
Zwart, W.T.	Stichting Oncode Institute	Oncode Zwart	01/09/17	31/08/22
Zwart, W.T.	The Mark Foundation for Cancer Research	Short-term 3D-printing-based cultures of metastatic breast cancer for tailored therapy selection.	01/12/18	30/04/20
Zwart, W.T.	ZonMw	Proteomic and genomic evaluation of metastatic breast cancer to facilitate personalized treatment selection	01/12/16	30/11/21

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