



Division head John Haanen

John Haanen MD PhD Head

Joke Baars MD PhD Academic staff

Paul Baas MD PhD Academic staff

André Bergman MD PhD Academic staff

Jos Beijnen PhD Academic staff

Christian Blank MD PhD Academic staff

Willem Boogerd MD PhD Academic staff

Henk Boot MD PhD Academic staff

Wieneke Buikhuisen MD PhD Academic staff

Sjaak Burgers MD PhD Academic staff

Annemieke Cats MD PhD Academic staff

Jan Paul De Boer MD PhD Academic staff

Dieta Brandsma MD PhD Academic staff

Elke Brouwers PhD Academic staff

Alwin Huitema PhD Academic staff

Martijn Kerst MD PhD Academic staff

Marjolein Klous PhD Academic staff

Sabine Linn MD PhD Academic staff

Anne Lukas MD PhD Academic staff

Serena Marchetti MD Academic staff

Bastiaan Nuijen PhD Academic staff

Sjoerd Rodenhuis MD PhD Head

Hilde Rosing PhD Academic staff

Jan Schellens MD PhD Academic staff

Gabe Sonke MD Academic staff

Neeltje Steeghs MD PhD Academic staff

Babs Taal MD PhD Academic staff

Margot Tesselaar MD Academic staff

Michel Van Den Heuvel MD PhD Academic staff

Marchien Van Der Weide MD PhD Academic staff

Roel Van Gijn PhD Academic staff

Marije Appels Temporary staff

Sandra Bakker Temporary staff

Marja Bonarius Temporary staff

Melanie Bos Temporary staff

Ilja Bot Temporary staff

Rogier Boshuizen Temporary staff

Annebeth Haringhuizen Temporary staff

Emile Kerver MD Temporary staff

Peter Kunst MD PhD Temporary staff

Alet Mager Temporary staff

Boelo Poppema Temporary staff

Josine Quispel Temporary staff

Quirine van Rossum-Schornagel Temporary staff

Dirkje Sommeijer Temporary staff

Teun van Strien Temporary staff

Suzan Vrijaldenhoven Temporary staff

Ralph de Backer PhD student

Karin Beelen PhD student

David Boss PhD student

DIVISION OF MEDICAL ONCOLOGY

CLINICAL PHARMACOLOGY OF ANTICANCER DRUGS

Jan Schellens, Henk Boot, Annemieke Cats, Bastiaan Nuijen, Hilde Rosing, Serena Marchetti, Neeltje Steeghs, Alwin Huitema, Jos Beijnen

BACKGROUND AND OBJECTIVES

The division of pharmacology is involved in research in different phases of anticancer drug development. This concerns: I) Pharmaceutical formulation, II) Bioanalytical method development and implementation in clinical pharmacological studies, III) Early clinical phase I/II studies and IV) supportive care studies in patients with breast cancer.

Research activities of the division of Clinical Pharmacology of the department of Medical Oncology, the department of Pharmacy & Pharmacology and the department of Experimental Therapy (group Schellens) are closely integrated. In 2010 we continued clinical research fully compliant with ICH-GCP guidelines, previously certified by the Dutch Ministry of Health. The department of Pharmacy & Pharmacology successfully continued its official governmental GLP (in the field of analytical chemistry), GMP (formulation and manufacturing of investigational cytotoxic drugs) and GDP (ISO9002 for worldwide distribution of clinical supplies) licenses.

I PHARMACEUTICAL FORMULATION

Clinical manufacturing (Thalidomide tablets) of oral formulations of anticancer agents was continued. A pharmaceutical development program of oral taxanes resulted in a first formulation composed of a solid dispersion of docetaxel that entered the clinic (ModraDoco01). A similar formulation of paclitaxel (ModraPaco01) was developed and is clinically tested.

A first formulation project aimed at the GMP-manufacture of ready-to-label molecular imaging agents is started with bevacizumab, which is now available as an off-the-shelf product for imaging studies. A second project with DOTATATE was initiated.

The Amsterdam BioTherapeutics Unit (AmBTU) is fully operational for the manufacture of GMP-grade DNA-plasmid. A phase I clinical study with the in-house manufactured DNA-plasmid pDERMATT (plasmid DNA Encoding Recombinant Mart-1 and Tetanus Toxin fragment-c) is ongoing in our institute. Currently, pharmaceutical products of HPV E6 and E7 pDNA vaccines are developed and manufactured. It is expected that these pDNA products will enter the clinic first half of 2011. Clean room facilities are in place to enable GMP-preparation of T-lymphocytes for TIL and T-cell receptor gene therapy. Clinical trials are expected to start beginning of 2011. The research program in collaboration with Utrecht University aiming at the pharmaceutical development of non-viral vectors (e.g. lipoplexes and polyplexes) for improvement of DNA-plasmid transfection is ongoing. An ex vivo human skin screening model is in place and has helped to identify important aspects of intradermal pDNA administration and non-viral vector composition. Ultimate aim of this program is translation of promising vectors to the clinic.

II BIOANALYTICAL METHOD DEVELOPMENT + IMPLEMENTATION IN PK STUDIES

The bioanalytical support of three mass balance studies (E7389, E7080 and bendamustine) has been completed this year. E7389 is a synthetic analog of Halichondrin B (HalB), acting by interfering with normal mitotic spindle formation, resulting in blockage of cells in mitosis, leading to cell death via apoptosis. Results showed that E7389 was slowly metabolised and only minor monooxygenated metabolites were detected using our LTQ XL MS instrument. Radioactive E7080, an orally active multi-tyrosine kinase inhibitor, was orally administered to 6 patients, followed by collection of blood and plasma samples and collection of all excreta for a period of at least 8 days. E7080 was quantified in plasma, urine and

faeces using LC-MS/MS. Furthermore, the collected samples were used for total radioactivity determination and metabolic profiling. The average total recovery of the radioactive dose in excreta was ~89%, of which ~25% was excreted in urine and ~64% in faeces. Comparison of total radioactivity results with LC-MS/MS results indicated large amounts of metabolites in urine and faeces. The metabolite profiling revealed products of E7080 oxidation and demethylation in both urine and faeces and products of demethylation and glucuronidation in urine and, in small amounts, in plasma. Bendamustine is an alkylating agent for the treatment of chronic lymphocytic leukemia (CLL), Hodgkin's lymphoma, non-Hodgkin's lymphoma (NHL) and with activity in small-cell lung cancers. We investigated bendamustine's disposition in a mass balance study. Mean total recovery of the radioactivity in excreta was ~76% of the radiochemical dose, with approximately half of the radiochemical dose recovered in the urine. Results of urinary metabolite profiling using LC-LTQ ion trap MS revealed that bendamustine is extensively metabolized via oxidative (*N*-dealkylation and hydroxylation), hydrolytic (chloride displacement and possibly hydrolysis of alkylated products), and conjugative (possibly glutathione conjugation) pathways.

A method for the quantification of tamoxifen and its phase I metabolites in plasma has been developed and validated to support a study in premenopausal women treated with adjuvant tamoxifen versus continued treatment.

New validated methods for the determination of capecitabine and its metabolite were developed and validated.

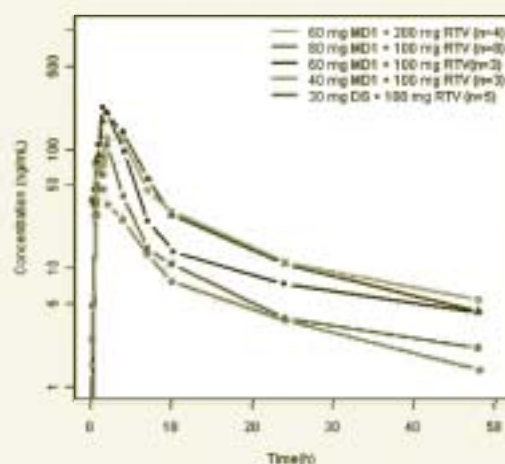
The following sample analysis were performed for clinical trials within and outside the Institute concerning paclitaxel, docetaxel, topotecan, irinotecan and its active metabolite SN-38, trabectedin, AS703026 (an inhibitor of MEK 1 and MEK2), lonafarnib, gemcitabine and dFdU, gemcitabine triphosphate, 5-hydroxy methyl uracil, cyclophosphamide (in combination with fludarabine) and its metabolite 4-hydroxy cyclophosphamide, and platinum (originating from cisplatin, carboplatin and oxaliplatin).

III EARLY CLINICAL PHASE I/II STUDIES

III-1 Novel approaches to improve oral bioavailability

The 'boosting' concept of oral docetaxel plus ritonavir, an efficacious inhibitor of gut wall and hepatic CYP3A4, has been further developed this year. The major step forward is that the oral capsule formulation of docetaxel, denoted ModraDoco01, turns out to have beneficial pharmaceutical properties in patients. The ongoing phase I study is approaching maximum tolerated dose (MTD) and now recruits patients at the level of 80 mg ModraDoco01 plus 200 mg ritonavir. Main toxicities are diarrhea and general malaise. The concentration-time profiles of docetaxel, administered as ModraDoco01, at the tested dose-levels administered together with ritonavir are shown in figure 1. The novel oral paclitaxel capsule formulation (ModraPaco01) showed excellent systemic exposure to paclitaxel and has therefore been taken further into the clinic. The phase I study with daily low-dose or metronomic ModraPaco01 plus booster drug ritonavir is being executed.

Figure 1: Plasma concentration-time profiles of patients who were treated with oral docetaxel formulated as capsules ModraDoco01 on all occasions taken together with one single dose of 100 mg or 200 mg of the boosting agent ritonavir.



Maarten Deenen PhD student
 Lot Devriese PhD student
 Thomas Dorlo PhD student
 Anne Charlotte Dubbelman PhD student
 Corinne Ekhart PhD student
 Geert Frederikx PhD student
 Andrew Goey PhD student
 Claudia Heijens PhD student
 Helgi Helgason PhD student
 Tine Janssens PhD student
 Eefje Jong PhD student
 Ron Keizer PhD student
 Heinz Josef Klumpen PhD student
 Stijn Koolen PhD student
 Nienke Lankheet PhD student
 Suzanne Leijen PhD student
 Jelte Meulenaar PhD student
 Johannes Moes PhD student
 Ruud van de Noll PhD student
 Philip Schouten PhD student
 Rik Stuurman PhD student
 Maurits Swellengrebel PhD student
 Bas Teunissen PhD student
 Linda Tulner PhD student
 Joost Van Den Berg PhD student
 Jolanda Van Den Hoven PhD student
 Coen Van Hasselt PhD student
 Evita Van Der Steeg PhD student
 Mariska Van Vliet PhD student
 Annemieke Van Winden PhD student
 Carolien Alderden Technical staff
 Abadi Gebretensae Technical staff
 Michel Hillebrand Technical staff
 Ciska Koopman-Kroon Technical staff
 Luc Lucas Technical staff
 Lianda Nan-Offeringa Technical staff
 Joke Schol Technical staff
 Bas Thijssen Technical staff
 Matthijs Tibben Technical staff
 Marja Merqui-Roelvink Clinical trial manager
 Sandra Adriaansz Nurse practitioner
 Roel Blanken Nurse practitioner
 Annelies Boekhout Nurse practitioner
 Karina Bucholtz Nurse practitioner
 Ria Dubbelman Nurse practitioner
 Joke Foekema Nurse practitioner
 Emmy Harms Nurse practitioner
 Marjo Holtkamp Nurse practitioner
 Marianne Keessen Nurse practitioner
 Annemieke Koenen Nurse practitioner
 Maria Kuiper Nurse practitioner
 Lisette Saveur Nurse practitioner
 Henk Mallo Nurse practitioner
 Annemarie Nol Nurse practitioner
 Suzanne Onderwater Nurse practitioner
 Margaret Schot Nurse practitioner
 Wilma Uyterlinde Nurse practitioner
 Jana Van der Sar Nurse practitioner
 Dick Visser Nurse practitioner
 Marion Zimmerman Nurse practitioner

Publications

Aleman BM, de Bruin ML, Dorresteyn LD, Krol AD, van 't Veer, Boogerd W, van Leeuwen FE. *Late effects of radiation therapy: the hits just keep on coming. J Natl Cancer Inst* 2010;102:576-577

Annema JT, Bohoslavsky R, Burgers S, Smits M, Taal B, Venmans B, Nabers H, van de Borne B, van Balkom R, Haitjema T, Welling A, Staaks G, Dekkers OM, van Tinteren H, Rabe KF. *Implementation of endoscopic ultrasound for lung cancer staging. Gastrointest Endosc.* 2010;71:64-70.70.e1

Baas P, Burgers JA. *Longkanker. In: van der Hoeven JJM, Wagener DTT, Dalmeijer JP, editors. Het oncologie formularium, een praktische leidraad. Houten: Bohn Stafleu van Loghum, 2010:39-52*

Bendle GM, Linnemann C, Hooijkaas AI, Bies L, de Witte MA, Jorritsma A, Kaiser AD, Pouw N, Debets R, Kieback E, Uckert W, Song JY, Haanen JB, Schumacher TN. *Lethal graft-versus-host disease in mouse models of T cell receptor gene therapy. Nat Med.* 2010;16:565-70

Van den Berg JH, Nuijen B, Schumacher TN, Haanen JB, Storm G, Beijnen JH, Hennink WE. *Synthetic vehicles for DNA vaccination. J Drug Target.* 2010;18:1-14

Van den Berg JH, Oosterhuis K, Hennink WE, Storm G, van der Aa LJ, Engbersen JF, Haanen JB, Beijnen JH, Schumacher TN, Nuijen B. *Shielding the cationic charge of nanoparticle-formulated dermal DNA vaccines is essential for antigen expression and immunogenicity. J Control Release.* 2010;141:234-40

Van den Berg JH, Oosterhuis K, Beijnen JH, Nuijen B, Haanen JB. *DNA vaccination in oncology: current status, opportunities and perspectives. Curr Clin Pharmacol.* 2010;5:218-25

Bergman AM, Kerst JM. *Rol van, en ontwikkelingen in, chemotherapie bij prostaatcancer. Nederlands Tijdschrift voor Oncologie (submitted)*

Bergman AM, Adema AD, Balzarini J, Bruheim S, Fichtner I, Noordhuis P, Fodstad O, Myhren F, Sandvold ML, Hendriks HR, Peters GJ. *Antiproliferative activity, mechanism of action and oral antitumor activity of CP-4126, a fatty acid derivative of gemcitabine, in vitro and in vivo tumor models. Invest New Drugs.* 2010 (in press)

III-2 Pharmacology (PK/PD, ADME, mass balance) of novel anticancer drugs

Currently, we perform twenty-eight phase I/II, pharmacological and proof of concept studies, which number is stable compared with last year. We recruited more than 240 new patients in these studies this year. Sixteen of these studies are two- or multicenter studies. Representative examples are described.

a. *Studies with the poly-ADP-ribose polymerase (PARP1) inhibitor olaparib (AZD2281)*

The ongoing two-center phase I trial to test the safety, optimal dose and schedule of AZD2281 when given daily BID in combination with three-weekly carboplatin and paclitaxel, or in combination with weekly paclitaxel has entered its 22nd dose-level. We demonstrated promising anticancer activity in a range of tumor types, but especially patients with tumors harboring BRCA1/2 mutations benefitted most. Prolonged myelosuppression is the main toxicity of the combination.

b. *Phase I studies with oral fibroblast growth factor receptor (FGFR) inhibitors*

Two trials are being executed, with BGJ398 and AZD4547 respectively. The study with AZD4547 has reached its MTD, which is hyperphosphatemia, skin and nail toxicity and general malaise. The hyperphosphatemia seems to indicate that the FGFR mediates phosphate excretion in the kidneys.

c. *Studies with angiogenesis inhibitor pazopanib*

We continued the trial with the angiogenesis agent pazopanib given in combination with topotecan. Of interest, significant antitumor activity is observed in this study in a range of heavily pretreated patients.

d. *Other phase I studies*

This year we started a number of first-in-man phase I studies, including the novel androgen receptor down regulating molecule AZD3514, indicated for hormone refractory prostate cancer. This is an orally available drug given on a daily continuous schedule. The first-in-man study with the combination of erlotinib and the PI3K inhibitor GDC0941 progressed. Intermittent dosing of GDC0941, together with continuous daily dosing of erlotinib, was implemented as continuous dosing of both compounds was found unsafe. Main toxicity is skin toxicity. This study is especially of interest for patients progressing but previously responding to erlotinib. The first in man study with the MEK inhibitor BO21189 was put on hold as the DLT had been reached. Main toxicity is EGFR-inhibitor-like skin toxicity. This is also a daily continuous schedule. We continued the phase I study with the Wee1 inhibitor in combination with or gemcitabine, cisplatin or carboplatin. Main toxicities are general malaise, nausea and vomiting, which can be controlled well with intensive antiemetic medication. This concept is currently been tested in tumors with p53 pathway mutation, especially refractory ovarian cancer and advanced melanoma.

III-3 Pharmacokinetic and pharmacodynamic (PK/PD) modelling and simulation
PK/PD modelling and simulation was used to investigate whether a relevant therapeutic dose was reached in a first-in-human phase I study of a novel integrin inhibitor (E7820). For this purpose, preclinical data on PK, tumor growth inhibition in xenografts and biomarker data were combined with clinical biomarker and PK data. The required level of biomarker inhibition for tumor stasis in the preclinical experiments was used as target for the phase I study. At the recommended dose level from the phase I study indeed this level of biomarker inhibition was reached. A semi-mechanistic PK model for the complex interaction between orally administered docetaxel and ritonavir has been developed both on human as on preclinical data. Excellent extrapolation from preclinical experiments to humans was found using allometric scaling.

In clinical research, often datasets are obtained which contain some degree of missing data. We investigated several methods to deal with two commonly encountered types of missing data (data below the limit of quantitation and missing categorical data) on the outcome of PK/PD analyses and applied these methods to some real datasets. Appropriate handling of missing data may heavily reduce bias in PK/PD analyses.

Publications (continued)

Bex A, van der Veldt AA, Boven E, Haanen JB. *Re: Surgical resection of renal cell carcinoma after targeted therapy.* Thomas AA, Rini BI, Stephenson AJ, Garcia JA, Fergany A, Krishnamurthi V, Novick AC, Gill IS, Klein EA, Zhou M and Campbell SC. *J Urol* 2009;182:881-886. *J Urol* 2010;183:1646-7;author reply 1647

Bex A, Sonke GS, Pos FJ, Brandsma D, Kerst JM, Horenblas S. *Symptomatic brain metastases from small-cell carcinoma of the urinary bladder: The Netherlands Cancer Institute experience and literature review.* *Ann Oncol*. 2010

Bex A, Van der Veldt AA, Blank C, Meijerink MR, Boven E, Haanen JB. *Progression of a caval vein thrombus in two patients with primary renal cell carcinoma on pretreatment with sunitinib.* *Acta Oncol*. 2010;49:520-3

Borkner L, Kaiser A, van de Kastelee W, Andreesen R, Mackensen A, Haanen JB, Schumacher TN, Blank C. *RNA interference targeting programmed death receptor-1 improves immune functions of tumor-specific T cells.* *Cancer Immunol Immunother*. 2010;59:1173-83

Brandsma D, Dorlo TP, Haanen JH, Beijnen JH, Boogerd W. *Severe encephalopathy and polyneuropathy induced by dichloroacetate J Neurol*. 2010

Buikhuisen WA, Burgers JA, Vincent AD, Schellens JHM, Beijnen JH, Smit EF, Joerger M. *Pemetrexed Pathway-Associated Germline Polymorphisms: A Useful Tool for Treatment Individualization?* *JCO* 2010

Cats A, Verheij M, van Grieken NCT, van de Velde CJH. *Maagcarcinoom. In: Oncologie. van de Velde, van der Graaf, van Krieken, Marijnen, Vermorken, eds. Bohn Stafleu, 2010:353-359 (in press)*

Courrech Staal EF, Aleman BM, van Velthuysen ML, Cats A, Boot H, Jansen EP, van Coevorden F, van Sandick JW. *Chemoradiation for Esophageal Cancer: Institutional Experience With Three Different Regimens.* *Am J Clin Oncol*. 2010

Courrech Staal EF, van Sandick JW, van Tinteren H, Cats A, Aaronson NK. *Health-related quality of life in long-term esophageal cancer survivors after potentially curative treatment.* *J Thorac Cardiovasc Surg*. 2010;140:777-83

III-4 Pharmacogenomics to identify patients at risk for toxicity or undertreatment

Pharmacogenetic screening of patients treated with 5-FU/Capecitabine.

DYPD*2 genotyping in routine clinical practice was continued. To date a population of more than 1600 patients has been genotyped prior to start of capecitabine therapy, amongst which seventeen heterozygotes have been identified. Dose-adaptation could be performed in twelve of these patients. Safety was excellent. No major toxicities were reported and no toxic deaths occurred. The cost analysis of the genotyping approach testing demonstrated that the adaptive dosing in DPYD*2A patients is cost-effective.

IV SUPPORTIVE CARE STUDIES IN PATIENTS WITH BREAST CANCER

The intervention study in female patients with menopausal complaints induced by treatment for breast cancer with placebo, venlafaxine (Efexor®) and clonidine hydrochloride demonstrated that both venlafaxine and clonidine significantly reduced hot flash scores. Side-effects were manageable in most patients. We continued the multicenter cardiac protection trial with the angiotensin II (ATI) receptor antagonist candesartan in patients with Her 2 positive breast cancer who received adjuvant treatment with trastuzumab. This is a double blind randomized trial versus placebo. There are 19 centers actively recruiting and in total 198 of the planned 200 patients have been registered. The recruitment rate has significantly increased over the past year.

We started a retrospective analysis to assess the severity of cardiac toxicity induced by trastuzumab in patients who received trastuzumab in the adjuvant or metastatic disease setting. Data of more than 130 patients are available for this analysis. Left ventricular ejection fraction data illustrate that about 20% of the patients who started with normal LVEF (>50%) drop to values < 50% and 15 % reduction in LVEF. This confirms that trastuzumab induces significant cardiac toxicity.

V COLLABORATION WITH THE DUTCH MEDICINES EVALUATION BOARD

We performed the following dossiers for the CBG/EMA this year: Co-rapporteur report about erlotinib (Tarceva) for first line treatment of patients with NSCLC with EGFR activating mutations (type II variation), Rapporteur report about mifamurtide (Mepact) for osteosarcoma (type II variation) and Co-rapporteur report about vandetanib (Zactima) for metastasized or locally advanced medullary thyroid cancer. In addition Scientific advices were given about PF00299804 (HER1,2,4 TKI) in NSCLC, about MGN901 (maytansinoid immunoconjugate) in Merkel cell carcinoma, about AMG479 (anti IGF-1R antibody) in pancreas cancer, about pazopanib (Votrient) in NSCLC and ovarian cancer, about RO5185426 (Braf inhibitor) for metastasized or locally advanced melanoma and about tivantinib (ARQ197; C-Met inhibitor) for NSCLC

We continued the scientific advices to the minister of Health and the Dutch Health Insurance Authority (NZA) as chairperson of the "Committee for Pharmaceutical Aid".

CLINICAL IMMUNOTHERAPY AND TARGETED THERAPY

John Haanen, Christian Blank, Sandra Adriaansz, Henk Mallo, Loes Pronk

BACKGROUND AND OBJECTIVES

The clinical immuno- and targeted therapy group is responsible for the treatment of melanoma and renal cell carcinoma patients. Translational immunotherapy research focuses on adoptive cellular therapies, such as T-cell receptor gene therapy and treatment with tumor-infiltrating lymphocytes (TIL) for melanoma and DNA and peptide vaccination studies for HPV-related squamous cell cancers. For renal cell cancer our group is leading in the development of investigator-initiated phase II/III trials to improve the treatment with small molecule receptor tyrosine kinase inhibitors (RTKI), mTOR kinase inhibitors and combinations of cytokines and anti-angiogenesis drugs.

Publications (continued)

Deenen MJ, Terpstra WE, Cats A, Boot H, Schellens JHM. *Standard dose UFT is not a safe treatment alternative after severe toxicity to capecitabine or 5-FU in DPD-deficient patients. Ann Int Med.* 2010 (in press)

Dikken JL, Jansen EP, Cats A, Bakker B, Hartgrink HH, Kranenbarg EM, Boot H, Putter H, Peeters KC, van de Velde CJ, Verheij M. *Impact of the extent of surgery and postoperative chemoradiotherapy on recurrence patterns in gastric cancer. J Clin Oncol.* 2010;28:2430-6

Douma KFL, Aaronson NK, Vasen HFA, Gerritsma MA, Gundy CM, Janssen E, Vriends AHJT, Cats A, Verhoef S, Bleiker EMA. *Psychological distress and use of professional psychosocial support in families at high risk for familial adenomatous polyposis Psycho-Oncology* 2010;19:289-298

Douma KF, Bleiker EM, Aaronson NK, Cats A, Gerritsma MA, Gundy CM, Vasen HF. *Long-term compliance with endoscopic surveillance advice for familial adenomatous polyposis (FAP). Colorectal Dis* 2010;12(12):1198-207.

Van Erp NP, Mathijssen RH, van der Veldt AA, Haanen JB, Reyners AK, Eechoute K, Boven E, Wessels JA, Guchelaar HJ, Gelderblom H. *Myelosuppression by sunitinib is flt-3 genotype dependent. Br J Cancer.* 2010;103:757-8

Gadiot J, Hooijkaas AI, Kaiser ADM, Tinteren H, van Boven H, Blank C. *Overall survival and PD-L1 expression in metastasized malignant melanoma. Cancer (in press)*

Geurts TW, Klomp HM, Burgers JA, van Tinteren H, Roukema BY, Balm AJ. *Resection of secondary pulmonary malignancies in head and neck cancer patients. J Laryngol Otol.* 2010:1-6

Giovannetti E, Zucali PA, Peters GJ, Cortesi F, D'Incecco A, Smit EF, Falcone A, Burgers JA, Santoro A, Danesi R, Giaccone G, Tibaldi C. *Association of polymorphisms in AKT1 and EGFR with clinical outcome and toxicity in non-small cell lung cancer patients treated with gefitinib. Mol Cancer Ther.* 2010;9:581-93

MELANOMA

Translational research with DNA vaccination in melanoma patients

In January 2009 we started a first in man study with DNA tattoo vaccination. In this dose-escalating phase I clinical study advanced-stage HLA-A*0201-positive melanoma patients are treated with an in-house manufactured DNA vaccine, pDERMATT, encoding Tetanus Toxin Fragment C (TTFC) fused to an immunodominant epitope of the melanocyte differentiation antigen MART-1. The DNA vaccine (5 mg/ml) is being tattooed into the epidermis of patients on days 0, 3 and 6 and a booster vaccination is administered at days 28, 31 and 34. The starting dose is 1 mg of DNA applied to a total skin surface of 2 x 2 cm. Dose escalation is performed by increasing the skin area that is being tattooed (8 cm², 16 cm² and 32 cm²). In 2010 the 2nd dose cohort (8 cm²) with three patients was finished. The study is now also open for enrolment at the Leiden University Medical Center. So far, only local vaccination site toxicity (grade 1 and 2) was observed. In biopsies taken one week after the last tattoo (both priming and booster) from the vaccination site showed the presence of CD8+ MART-1-specific T cells, indicating that a cellular immune response had been induced. We are awaiting the final results from peripheral blood samples (both MART-specific and TTFC-specific responses).

Translational research with tumor-infiltrating lymphocytes in melanoma patients

We are preparing for a clinical phase II study using tumor-infiltrating lymphocytes for patients with metastatic melanoma. This is based on results from a single arm, single institution trial performed at the Surgery Branch of the NIH, Bethesda, USA, which showed a 50% objective response rate in heavily pre-treated stage IV melanoma patients. Recently, these impressive response rates were confirmed in a trial performed in Israel, using the exact same protocol as was used at the NIH. Again a 50% objective response rate was found in heavily pre-treated stage IV melanoma patients. Ours will be the first trial in Europe with TIL and the first trial comparing TIL treatment to standard dacarbazine chemotherapy. As of September 2008 the Division of Immunology, Medical Oncology and Pharmacy is working closely together to prepare for this high impact trial. A new clean room for the culturing of TIL according GMP guidelines has been added to the AM-BTU and all steps in the production of the TIL product are being validated (figure 2). The full protocol including IMPD is under review of the Central Committee on Research involving Human Subjects (CCMO). We expect to enrol patients in this study in early 2011.



Anti-CTLA4 treatment

In 2006 we participated (European top includer) in the randomized double-blind placebo-controlled phase III trial comparing the combination of Ipilimumab, a fully human anti-CTLA4 monoclonal antibody, and gp100 peptide vaccine, to Ipilimumab or gp100 vaccine alone. In June 2010, the results were presented at ASCO, showing a statistical significant and meaningful overall survival improvement of both Ipilimumab arms compared to gp100 vaccine arm. As of June 2010, Ipilimumab is available at our institute in a Named Patient Program for treatment of patients with metastatic melanoma, who have failed 1st line treatment. In 2010 over 50 patients have been enrolled in this program and a novel research project (see section IV) is being developed to analyze the immune response changes upon Ipilimumab treatment.

BRAF V600E mutated melanoma

In 2010 we participated in the multicenter randomized controlled phase III trial, BRIM3, comparing standard dacarbazine with an oral BRAF V600E inhibitor in metastatic melanoma patients with tumors harbouring this BRAF mutation. Close to 80 patients were screened and in about 40% this mutation was present. 23 patients were randomized. Impressive objective responses were seen, some of which were unfortunately short-lived. Enrolment was closed in November 2010.

RENAL CELL CARCINOMA

In the renal cell carcinoma program we closely collaborate with Dr Axel Bex from the urology-oncology group.

In 2005 we started participation in a treatment-use program of the small molecule sunitinib, a multiple receptor tyrosine kinase inhibitor with high affinity for VEGF-R, PDGF-R, c-KIT and FLT3. Since VEGF and PDGF play prominent roles in the pathogenesis of sporadic clear cell renal cell cancer, inhibition of kinase activity of their receptors appeared to be a rational therapy in this patient population. In 2010, still 2 out of 53 patients that were treated in this study were on study medication, indicating that in a minority of patients sunitinib can induce long-term disease stabilization. Serum samples from amongst others these 53 patients were used in a collaborative study to perform a genome wide association study, analyzing single nucleotide polymorphisms that are correlated with toxicity of sunitinib treatment.

An investigator-initiated study to define the optimal time point for tumor nephrectomy in primary metastatic renal cell carcinoma patients is ongoing. A total of 20 patients have been treated in this small proof of principle trial. The idea of defining the optimal timing for nephrectomy in primary metastatic RCC was adopted by the EORTC GU group and has been approved as a randomized controlled multicenter phase III trial (NCT01099423) that has started enrolment in 2010. Patients will be randomized to receive either 3 cycles of sunitinib treatment prior to tumor nephrectomy or immediate nephrectomy. Post surgery both groups will (re) start sunitinib treatment until disease progression. Study endpoint: Progression-free and overall survival.

In addition, we participated in a phase I study: sorafenib + IL-2 as second line treatment for metastatic clear cell renal cell cancer and in a randomized controlled multicenter phase III trial in metastatic clear cell renal cell cancer comparing two receptor tyrosine kinase inhibitors, pazopanib and sunitinib, the latter being the standard of care at the moment.

BREAST CANCER THERAPY AND RESPONSE PREDICTION

Sabine Linn, Sjoerd Rodenhuis, Gabe Sonke, Karin Beelen, Jos Beijnen, Jorma De Ronde, Marjo Holtkamp, Alwin Huitema, Rutger Koornstra, Esther Lips, Ingrid Mandjes, Lennart Mulder, Paula Nederlof, Margaret Schot, Philip Schouten, Marieke Vollebergh, Jelle Wesseling, Lodewyk Wessels

BACKGROUND AND OBJECTIVES

The objective of this program is to develop and improve potentially curative therapy for patients with locoregional or oligometastatic breast cancer. For all studies, close collaborations are maintained with many other clinical departments and research divisions. In 2010, about 140 patients were entered in sixteen medical studies in breast cancer, either focusing on the treatment of early breast cancer or on advanced disease.

PREOPERATIVE CHEMOTHERAPY

The preoperative chemotherapy program continues to accrue over nearly 100 patients per year and now includes data and tissues of some 500 patients. The program is the core of a multidisciplinary research effort to optimize response prediction and to improve response monitoring. A pCR (pathologic complete remission) is rare in luminal tumors (usually characterized by a positive estrogen receptor and the absence of a HER2 amplification). The expression of the Progesterone Receptor and the molecular subtype were shown to be weakly predictive of response but cannot be used to withhold chemotherapy. In addition to the Dutch multicenter phase II study of Trastuzumab, Carboplatin and Paclitaxel in HER2+ disease, a second multicenter study was launched for triple-negative breast cancers (NCT01057069). In October, it had recruited the first 16 patients while additional centers were still being added to the list of investigators. It studies the efficacy of intensive alkylating agents in tumors that have a defect in the DNA repair mechanism called 'Homologous Recombination' in a phase III setting. Attempts to develop a chemotherapy sensitivity gene expression signature using mRNA expression arrays have not yet been successful and the same is true for the

Graafland NM, Valdés Olmos RA, Teertstra HJ, Kerst JM, Bergman AM, Horenblas S. *18F-FDG PET/CT for monitoring induction chemotherapy in patients with primary inoperable penile carcinoma: first clinical results.* *Eur. J. Nucl. Med Mol Imaging.* 2010;37:1474-80

Hamberg P, Steeghs N, Loos WJ, van de Biessen D, den Hollander M, Tascilar M, Verweij J, Gelderblom H, Sleijfer S. *Decreased exposure to Sunitinib due to concomitant administration of ifosfamide: results of a phase I and pharmacokinetic study on the combination of Sunitinib and Ifosfamide in patients with advanced solid malignancies.* *Br J Cancer.* 2010;102:1699-706

Heemskerk B, Jorritsma A, Gomez-Eerland R, Toebe M, Haanen JB, Schumacher TN. *Microbead-assisted retroviral transduction for clinical application.* *Hum Gene Ther.* 2010;21:1335-42

Helgason HH, Engwegen JYMN, Zapatka M, Vincent A, Cats A, Boot H, Beijnen JH, Schellens JHM. *Identification of serum proteins as prognostic and predictive markers of colorectal cancer using surface-enhanced laser desorption ionization – time of flight mass spectrometry (SELDI-TOF MS).* *Oncology Reports* 2010;24:57-64

Helgason HH, Engwegen JYMN, Zapatka M, Cats A, Boot H, Beijnen JH, Schellens JHM. *Serum proteomics and disease-specific biomarkers of patients with advanced gastric cancer.* *Oncol Letters* 2010;1:327-333

Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, Gonzalez R, Robert C, Schadendorf D, Hassel JC, Akerley W, van den Eertwegh AJ, Lutzky J, Lorigan P, Vaubel JM, Linette GP, Hogg D, Ottensmeier CH, Lebbé C, Peschel C, Quirt I, Clark JI, Wolchok JD, Weber JS, Tian J, Yellin MJ, Nichol GM, Hoos A, Urba WJ. *Improved survival with ipilimumab in patients with metastatic melanoma.* *N Engl J Med.* 2010;363:711-23. *Erratum in: N Engl J Med.* 2010;363:1290

Jansen EPM, Boot H, Dubbelman R, Verheij M, Cats A. *Postoperative chemoradiotherapy in gastric cancer. A phase I-II study of radiotherapy with dose-escalation of weekly cisplatin and daily capecitabine chemotherapy.* *Ann Oncol.* 2010;21:530-534

Publications (continued)

Kappers I, van Sandick JW, Burgers JA, Belderbos JS, van Zandwijk N, Klomp HM. *Surgery after induction chemotherapy in stage IIIA-N2 non-small cell lung cancer: why pneumonectomy should be avoided. Lung Cancer.* 2010;68:222-7

Kerst JM, Moonen L, Graafland NM, Bergman AM, Pos FJ, Horenblas S. *The role of chemotherapy and radiotherapy in the treatment of penile cancer. Springer Verlag (in press)*

Kluijt I, Sijmons RH, Hoogerbrugge N, Vasen HFA, Cats A. *Familiaire maagkanker: diagnostiek en periodieke controles Namens de Nederlandse werkgroep erfelijke maagkanker. Ned Tijdschr Geneesk.* 2010 (in press)

Knauer M, Mook S, Rutgers EJ, Bender RA, Hauptmann M, van de Vijver MJ, Koornstra RH, Bueno-de-Mesquita JM, Linn SC, van 't Veer LJ. *The predictive value of the 70-gene signature for adjuvant chemotherapy in early breast cancer. Breast Cancer Res Treat.* 2010;120:655-61

Kok M, Zwart W, Holm C, Fles R, Hauptmann M, Van 't Veer LJ, Wessels LF, Neefjes J, Stål O, Linn SC, Landberg G, Michalides R. *PKA-induced phosphorylation of ERalpha at serine 305 and high PAK1 levels is associated with sensitivity to tamoxifen in ER-positive breast cancer. Breast Cancer Res Treat* 2010

Kroep JR, Linn SC, Boven E, Bloemendal HJ, Baas J, Mandjes IAM, van den Bosch J, Smit WM, de Graaf H, Schröder CP, Vermeulen GJ, Hop WCJ, Nortier JWR. *Lapatinib: clinical benefit in patients with HER2-positive advanced breast cancer. Neth J Med.* 2010;68:371-6

Lammens CR, Bleiker EM, Aaronson NK, Wagner A, Sijmons RH, Ausems MG, Vriends AH, Ruijs MW, van Os TA, Spruijt L, Gómez García EB, Cats A, Nagtegaal T, Verhoef S. *Regular surveillance for Li-Fraumeni syndrome: advice, adherence and perceived benefits. Fam Cancer.* 2010;9:647-54

Lee SM, Baas P, Wakelee H. *Anti-angiogenesis drugs in lung cancer. Respirology.* 2010;15:387-92

validation of signatures published by other groups. A chemotherapy resistance test based on gene expression may be a more realistic goal, as resistance may be caused by abnormal activity of a single gene. First hypothetical results that should be testable in future patients have been generated.

ADJUVANT SYSTEMIC THERAPY, PROGNOSIS AND PREDICTION

The primary objective of the Matador study is to identify predictive gene expression profiles for a disease-free survival benefit of either a docetaxel-containing regimen (docetaxel-doxorubicin-cyclophosphamide (TAC)) or an accelerated doxorubicin-cyclophosphamide (ACdd) regimen (ISRCTN61893718). As such, frozen tissue of the primary tumor is mandatory to be eligible. The study, open since 2004, is running in over 30 centers in the Netherlands and ~460 patients of the planned 600 patients have been included.

The preoperative window trial to study responsiveness of hormone-receptor positive breast cancers to tamoxifen, anastrozole or anastrozole in combination with fulvestrant in postmenopausal patients has been extended to other centers (NCT00738777). Blood and tumor tissue is collected pre and post treatment for translational research, including gene expression profiling. Changes in Ki67 expression, in combination with changes in TUNEL labeling as a marker for apoptosis are used as a read-out for hormonal therapy responsiveness. Chromosome immune precipitation (ChIP-seq) studies on the first paired samples of patients exposed to the combination of fulvestrant and anastrozole revealed changes in estrogen receptor binding to the DNA in over 3000 sites.

In collaboration with Leiden University Medical Center and the TEAM study group, the TEAM II study has been initiated to investigate the optimal duration of neoadjuvant exemestane therapy (currently ~40 patients included) and to study the benefit of three years adjuvant oral ibandronate in addition to standard adjuvant systemic therapy in postmenopausal patients with hormone-receptor positive early breast cancer (currently ~500 patients included) (ISRCTN17633610).

THORACIC ONCOLOGY

Paul Baas, Sjaak Burgers, Michel van den Heuvel, Wieneke Buikhuisen, Josine Quispel-Janssen, Houke Klomp, Michel Wouters, Jose Belderbos, Petra Nederlof, Jacques Neefjes

The department's clinical research focuses on immunological studies, combined modality approaches and mesothelioma treatment.

NON SMALL CELL LUNG CANCER (NSCLC)

Patients with resectable early stage NSCLC are included in a neo-adjuvant study with erlotinib given for 3 weeks. This study is led by Dr Klomp and shows that this short course of targeted agent treatment already induces significant apoptosis. The study is now under evaluation with 55 patients entered.

Several I and II clinical trials in locally advanced disease focus on concurrent chemoradiotherapy and explore the usage of both innovating new radiation strategies and the implementation of agents such as Cetuximab and Olaparib. A clinical care pathway has been established and several studies aim to improve supportive care in this group of patients.

In 3 different vaccination trials are ongoing: a maintenance study with Selectikine after a short course of RT has just ended; two phase 3 randomized trials, one testing the peptide vaccine Stimuvax after chemoradiotherapy, the other testing a tumor-cell vaccin Lucanix in an adjuvant setting.

In second line in advanced NSCLC a national randomized study of erlotinib vs. erlotinib + chemotherapy is ongoing (PI: S Burgers) with pharmaco-kinetic and genomic studies.

For 2011 we are planning to construct a SOP in order to profile tumors with regard to relevant signalling pathways and chemosensitivity. Finally, tumor tissue from patients is cultured in mice and as cell lines in order to test multiple compound libraries and. We hope to elucidate molecular pathways involved in thoracic malignancies and to develop an *ex vivo* drug sensitivity screening method.

SMALL CELL LUNG CANCER (SCLC)

In patients with Limited Stage disease we join the European phase 3 CONVERT study which investigates the effects of concurrent twice daily RT with chemotherapy vs. sequential chemotherapy and RT. For patients with Extensive Stage a window of opportunity EORTC phase 2 study with Sunitinib induction therapy has just been finished. The results of this study are being analyzed.

PLEURAL DISEASES

In 2007 the pleura bank study was initiated to allow the development of innovative diagnostic and treatment algorithms. All patients presenting with a pleural effusion are asked to participate and to allow research in the near future with frozen serum and pleural fluid samples. Currently we have patient data and matched samples in over 600 patients. A national pleurodesis study has been initiated to compare the primary pleurodesis with the use of indwelling catheters. A total of 120 patients is planned for this study.

MALIGNANT PLEURAL MESOTHELIOMA (MPM)

The national randomized phase 3 maintenance study of thalidomide after standard chemotherapy in MPM is now prepared for publication. A subgroup of patients in both arms will be analyzed for predictive and prognostic factors of serial serum samples including VEGF, bFGF, IL-6 and Cytokeratin markers. Independent radiology monitoring is ongoing.

For second and third line therapy we offer patients a international randomized phase 3 study of Vorinostat vs. placebo. Of the 660 planned patients we are the top recruiting centre with over 40 patients included.

We have started a randomized phase-2 study examining the effect of Axitinib (a potent oral anti vascular drug) to standard chemotherapy in patients with MPM. Biopsies are taken before and after 3 courses of chemotherapy and will be used to evaluate the effect of the addition of Axitinib. The randomized phase II part is currently ongoing. The translational research in this study will focus on vascular staining, apoptosis and circulating endothelial/tumor cells.

Fresh tumor samples are currently used to prepare cell lines in the lab of A Berns. In special immuno-compromised mice human tissue samples are implanted in order to test specific promising compounds.

GASTROENEROLOGY

Henk Boot, Annemieke Cats, Babs Taal, Margot Tesselaar, Hans Bonfrer, Maarten Deenen, Luc Dewit, Tiny Korse, Jan Schellens, Maurits Swellengrebel, Marcel Verheij

GASTRIC CANCER

New treatment regimens are indicated for the treatment of gastro-esophageal cancer. In a phase I/II dose-finding study we explored the safety and preliminary activity of the combination of docetaxel, oxaliplatin and capecitabine. In 22 patients treated at the maximal tolerated dose level, toxicity mostly remained grade ≤ 2 , with grade 3 toxicity consisting of fatigue, diarrhea and infection (1 patient each). Overall response rate was 46% (95% CI: 27-66%). Median progression-free and overall survival were 6.9 months (95% CI: 5.6 – 8.2) and 11.6 months (95% CI: 8.7 – 14.5), respectively. The polymorphisms GSTP1 313A>G and CDA 79C>A were individually predictive for hematological toxicity, and three patients homozygous polymorphic for GSTP1 313A>G experienced a prolonged progression-free survival.

In another study, we evaluated the effect of gastric surgery and radiotherapy on the systemic exposure to oral capecitabine and its primary metabolites. Patients with a total or partial resection absorbed capecitabine significantly more rapidly, and showed significantly higher peak plasma concentrations of capecitabine, 5'-dFCR and 5'-dFUR compared with non-gastrectomized patients. Esophagocardiac resection had no significant effect on capecitabine pharmacokinetics.

RECTAL CANCER

According to national guidelines, neoadjuvant (chemo)radiotherapy should be given to all rectal cancer patients >T1Mo. Between 2006-2008 we evaluated the additional

Lips EH, Mulder L, Hannemann J, Laddach N, Vrancken Peeters MT, van de Vijver MJ, Wesseling J, Nederlof PM, Rodenhuis S. *Indicators of homologous recombination deficiency in breast cancer and association with response to neoadjuvant chemotherapy.* *Ann Oncol.* 2010

Loo C, Straver ME, Rodenhuis S, Muller S, Wesseling J, Vrancken Peeters MJ, Gilhuijs K. *MRI response monitoring of breast cancer during neoadjuvant chemotherapy: Relevance of breast cancer subtype.* *J Clin Oncol.* 2010 (in press)

Mook S, Knauer M, Bueno-de-Mesquita JM, Retel VP, Wesseling J, Linn SC, Van't Veer LJ, Rutgers EJ. *Metastatic Potential of T1 Breast Cancer can be Predicted by the 70-gene MammaPrint Signature.* *Ann Surg Oncol* 2010

Van Meerbeeck JP, Scherpereel A, Surmont VF, Baas P. *Malignant pleural mesothelioma: The standard of care and challenges for future management.* *Crit Rev Oncol Hematol.* 2010

Oosterhuis K, van den Berg JH, Schumacher TN, Haanen JB. *DNA Vaccines and Intradermal Vaccination by DNA Tattooing.* *Curr Top Microbiol Immunol.* 2010

Van der Poel HG, Zevenhoven J, Bergman AM. *Pim1 regulates androgen-dependent survival signaling in prostate cancer cells.* *Urol Int.* 2010;84:212-20

Quaak SG, Haanen JB, Beijnen JH, Nuijen B. *Naked plasmid DNA formulation: effect of different disaccharides on stability after lyophilisation.* *AAPS PharmSciTech.* 2010;11:344-50

Rasch, CR, Hauptmann M, Schornagel J, Wijers O, Buter J., Gregor T, Wiggenraad R, De Boer JP, Ackerstaff AH, Kroger R, Hoebbers FJ, Balm AJ, Hilgers FJ. *Intra-arterial versus intravenous chemoradiation for advanced head and neck cancer: Results of a randomized phase 3 trial.* *Cancer* 2010;116:2159

Retel VP, Joore MA, Knauer M, Linn SC, Hauptmann M, Harten WH. *Cost-effectiveness of the 70-gene signature versus Sankt Gallen guidelines and Adjuvant Online for early breast cancer.* *Eur J Cancer* 2010

Publications (continued)

Rodenhuis S, Mandjes IA, Wesseling J, van de Vijver MJ, Peeters MJ, Sonke GS, Linn SC. *A simple system for grading the response of breast cancer to neoadjuvant chemotherapy.* *Ann Oncol.* 2010;21:481-7

De Ronde JJ, Hannemann J, Halfwerk H, Mulder L, Straver ME, Vrancken Peeters MJ, Wesseling J, van de Vijver M, Wessels LF, Rodenhuis S. *Concordance of clinical and molecular breast cancer subtyping in the context of preoperative chemotherapy response.* *Breast Cancer Res Treat.* 2010;119:119-26

De Ruyter MB, Reneman L, Boogerd W, Veltman DJ, van Dam FS, Nederveen AJ, Boven E, Schagen SB. *Cerebral hyporesponsiveness and cognitive impairment 10 years after chemotherapy for breast cancer.* *Hum Brain Mapp* 2010

Scherpereel A, Astoul P, Baas P, Berghmans T, Clayson H et al. *Guidelines of the European Respiratory Society and the European Society of Thoracic Surgeons for the management of malignant pleural mesothelioma.* *Eur Respir J* 2010;35:479-495

Van Schil PE, Baas P, Gaafar R, Maat AP, van de Pol M, Hasan B, Klomp HM, Abdelrahman AM, Welch J, Van Meerbeeck J; on behalf of the EORTC Lung Cancer Group. *Phase II trial of trimodality therapy for malignant pleural mesothelioma (EORTC 08031).* *Eur Respir J.* 2010

Schilder CM, Seynaeve C, Linn SC, Boogerd W, Beex LV, Gundy CM, Nortier JW, van de Velde CJ, van Dam FS, Schagen SB. *Cognitive functioning of postmenopausal breast cancer patients before adjuvant systemic therapy, and its association with medical and psychological factors.* *Crit Rev Oncol Hematol* 2010;76:133-141

Schilder CM, Seynaeve C, Beex LV, Boogerd W, Linn SC, Gundy CM, Huizenga HM, Nortier JW, van de Velde CJ, van Dam FS, Schagen SB. *Effects of tamoxifen and exemestane on cognitive functioning of postmenopausal patients with breast cancer: results from the neuropsychological side study of the tamoxifen and exemestane adjuvant multinational trial.* *J Clin Oncol* 2010;28:1294-1300

value of discussing rectal cancer patients in a multidisciplinary team (MDT) in the greater Amsterdam region. The primary endpoint was the number of positive circumferential resections margins (CRM \leq 1 mm). MDT discussion took place in 116 patients (55%). The proportion of patients with advanced disease was higher in the MDT+ group (88% \geq T3/N+ versus 68%, $p=0.001$). The overall CRM+ rate was 13% and did not differ between the MDT+ and the MDT- group.

In locally advanced rectal cancer, we test the feasibility of preoperative chemoradiotherapy with capecitabine and bevacizumab. Currently, 36 patients are included in the study and toxicity is evaluated by an independent data monitoring committee.

NEUROENDOCRINE TUMORS (NET)

In patients with hypervascular metastases of NET beyond surgical resection hepatic artery embolization induces tumor regression. However, embolization causes hypoxia, which may stimulate angiogenesis and therefore tumor growth. This hypothesis was studied in 12 patients. Multiple blood samples were drawn before and daily after embolization. The vascular endothelial growth factor (VEGF), endothelin-1 (ET-1) and C-terminal pro-Endothelin-1 (CTproET-1) showed indeed a clear increase at day 6.

GENOTYPING OF THE *DPYD* GENE IN PATIENTS TREATED WITH CAPECITABINE

DPYD coding region was sequenced in 45 metastasized colorectal cancer cases with grade \geq 3 capecitabine-related toxicity and in 100 randomly selected controls having been treated with capecitabine, oxaliplatin, bevacizumab \pm cetuximab. *DPYD* IVS14+1G>A and 2846A>T showed to be predictive markers for severe toxicity to capecitabine, for which patients require dose reductions of up to 50%.

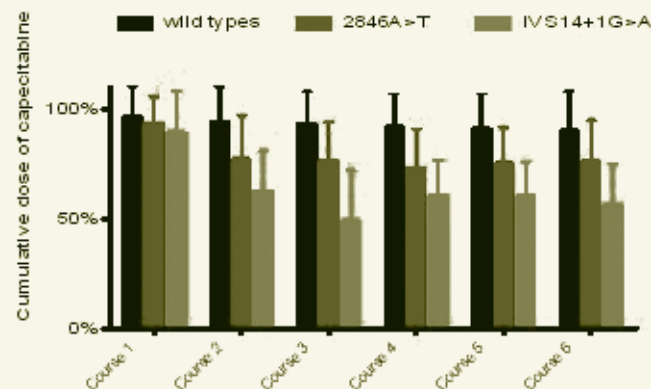


Figure 3: Dose modifications of capecitabine by genotype. Mean cumulative doses of capecitabine (plus standard deviations) expressed as a percentage of the planned dose according to the protocol for wild type and mutant patients for IVS14+1G>A and 2846A>T.

Publications (continued)

- Sigmond J, Bergman AM, Leon LG, Loves WJ, HOebe EK, Peters GJ. *Staurosporine increases toxicity of gemcitabine in non-small cell lung cancer cells: role of protein kinase C, deoxycytidine kinase and ribonucleotide reductase. Anticancer Drugs.* 2010;21:591-9
- Sleijfer S, Ouali M, van Glabbeke M, Krarup-Hansen A, Rodenhuis S, Le Cesne A, Hogendoorn PC, Verweij J, Blay JY. *Prognostic and predictive factors for outcome to first-line ifosfamide-containing chemotherapy for adult patients with advanced soft tissue sarcomas: an exploratory, retrospective analysis on large series from the European Organization for Research and Treatment of Cancer-Soft Tissue and Bone Sarcoma Group (EORTC-STBSG). Eur J Cancer.* 2010;46:72-83
- Snoeren N, Voest EE, Bergman AM, Dalesio O, Verheul HM, Tollenaar RA, van der Sijp JR, Schouten SB, Borel Rinkes IH, van Hilligersberg R. *A randomized two arm phase III study in patients post radical resection of liver metastases of colorectal cancer to investigate bevacizumab in combination with capecitabine plus oxaliplatin (CAPOX) vs CAPOX alone as adjuvant treatment. BMC Cancer.* 2010;10:545
- Sonke GS, Wesseling J. *Moeten we mammacarcinoom patiënten met (sub) micrometastasen in de schildwachtklier adjuvant systemisch behandelen? Ned Tijdschr Oncol* 2010;7:19-20
- Sonke GS, Rottenberg S, Linn SC, Jonkers J. *PARP remmers bij de behandeling van BRCA1/2 mutatie draagsters. Kanker Breed* 2010;2:3-8
- Stahel R, Baas P, Faivre-Finn C, Dooms C, Passlick B, Mazières J, Cappuzzo F, Früh M, Sorensen JB, Blackhall F, Taron M, Gridelli C, O'Byrne K, Rosell R. *Meeting report: 2nd meeting of the European Thoracic Oncology Platform (ETOP). Lung Cancer.* 2010;68:121-4
- Steeghs N, Mathijssen, RH, Wessels JA, de Graan AJ, van der Straaten T, Mariani M, Laffranchi B, Comis S, de Jonge MJ, Gelderblom H, Guchelaar HJ. *Influence of pharmacogenetic variability on the pharmacokinetics and toxicity of the aurora kinase inhibitor danusertib. Invest New Drugs.* 2010
- Steeghs N, Rabelink TJ, op 't Roodt J, Batman E, Cluitmans FH, Weijl NI, de Koning E, Gelderblom H. *Reversibility of capillary density after discontinuation of bevacizumab treatment. Ann Oncol.* 2010;21:1100-5
- Steeghs N, van Coevorden F, Luykx SA, Cats A. *Complicaties van bevacizumab behandeling. Nederl Tijdschr Oncol* 2010;7:27-36
- Straver ME, Glas AM, Hannemann J, Wesseling J, van de Vijver MJ, Rutgers EJ, Vrancken Peeters MJ, van Tinteren H, van 't Veer LJ, Rodenhuis S. *The 70-gene signature as a response predictor for neoadjuvant chemotherapy in breast cancer. Breast Cancer Res Treat.* 2010;119:551-8
- Straver ME, Rutgers EJ, Rodenhuis S, Linn SC, Loo CE, Wesseling J, Russell NS, Oldenburg HS, Antonini N, Vrancken Peeters MT. *The relevance of breast cancer subtypes in the outcome of neoadjuvant chemotherapy. Ann Surg Oncol.* 2010;17:2411-8
- Swellengrebe HAM, Marijnen CAM, Vincent A, Cats A. *Evaluating long-term attachment of two endoclips in the human gastrointestinal tract. World J Gastroenterol.* 2010 (in press)
- Swellengrebel HA, Marijnen CA, Verwaal VJ, Vincent A, Heuff G, Gerhards MF, van Geloven AA, van Tets WF, Verheij M, Cats A. *Toxicity and complications of preoperative chemoradiotherapy for locally advanced rectal cancer. Br J Surg.* 2010
- Tol J, Koopman M, Miller MC, Tibbe A, Cats A, Creemers GJM, Vos AH, Nagtegaal ID, Terstappen LWMM, Punt CJA. *Circulating tumour cells early predict progression-free and overall survival in advanced colorectal cancer patients treated with chemotherapy and targeted agents. Ann Oncol* 2010;21:1006-12
- Vasen HF, Abdirahman M, Brohet R, Langers AM, Kleibeuker JH, van Kouwen M, Koornstra JJ, Boot H, Cats A, Dekker E, Sanduleanu S, Poley JW, Hardwick JC, de Vos Tot Nederveen Cappel WH, van der Meulen-de Jong AE, Tan TG, Jacobs MA, Mohamed FL, de Boer SY, van de Meeberg PC, Verhulst ML, Salemans JM, van Bentem N, Westerveld BD, Vecht J, Nagengast FM. *One to 2-year surveillance intervals reduce risk of colorectal cancer in families with Lynch syndrome. Gastroenterology.* 2010;138:2300-6
- Van der Veldt AA, Meijerink MR, van den Eertwegh AJ, Haanen JB, Boven E. *Choi response criteria for early prediction of clinical outcome in patients with metastatic renal cell cancer treated with sunitinib. Br J Cancer.* 2010;102:803-9
- Van der Veldt AA, Eechoute K, Gelderblom H, Gietema JA, Guchelaar HJ, van Erp N, Van den Eertwegh AJ, Haanen JB, Mathijssen RH, Wessels JA. *Genetic Polymorphisms Associated With a Prolonged Progression-Free Survival in Patients With Metastatic Renal Cell Cancer Treated With Sunitinib. Clin Cancer Res.* 2010
- Vermaat JS, van der Tweel I, Mehra N, Sleijfer S, Haanen JB, Roodhart JM, Engwegen JY, Korse CM, Langenberg MH, Kruit W, Groenewegen G, Giles RH, Schellens JH, Beijnen JH, Voest EE. *Two-protein signature of novel serological markers apolipoprotein-A2 and serum amyloid alpha predicts prognosis in patients with metastatic renal cell cancer and improves the currently used prognostic survival models. Ann Oncol.* 2010;21:1472-81
- Vollebergh MA, Lips EH, Nederlof PM, Wessels LFA, Schmidt MK, van Beers EH, Cornelissen S, Holtkamp M, Froklage FE, de Vries EGE, Schrama JG, Wesseling J, van de Vijver MJ, van Tinteren H, de Bruin M, Hauptmann M, Rodenhuis S, Linn SC. *An aCGH classifier derived from BRCA1-mutated breast cancer and benefit of high-dose platinum-based chemotherapy in HER2-negative breast cancer patients. Ann of Oncol.* 2010 (in press)
- Vollebergh MA, Kappers I, Klomp HM, Buning-Kager JC, Korse CM, Hauptmann M, de Visser KE, van den Heuvel MM, and Linn SC. *Ligands of EGFR and the insulin-like growth factor family as serum biomarkers for response to EGFR-inhibitors in patients with advanced NSCLC. J Thorac Onc* 2010 (in press)
- Vyth-Dreese FA, Sein J, Van De Kastele W, Dellemijn TA, Van Den Bogaard C, Nooijen WJ, De Gast GC, Haanen JB, Bex A. *Lack of anti-tumour reactivity despite enhanced numbers of circulating natural killer T cells in two patients with metastatic renal cell carcinoma. Clin Exp Immunol.* 2010;162:447-59
- Van Winden A, van den Broek I, Gast M-C, Engwegen J, Sparidans R, van Dulken E, Depla, A, Cats A, Schellens J, Peeters PHM, Beijnen J, van Gils C. *Serum degradome markers for the detection of breast cancer. Journal of Proteome Research* 2010;9:3781-3788
- Yang TJ, Aukema TS, van Tinteren H, Burgers S, Valdés Olmos R, Verheij M. *Predicting early chemotherapy response with technetium-99m methoxyisobutylisonitrite SPECT/CT in advanced non-small cell lung cancer. Mol Imaging Biol.* 2010;12:174-80