Overview of trials running in the Benelux

(Belg J Med Oncol 2010;4:23-8)

Multinational phase III, randomized, double-blind, placebo-controlled efficacy and safety study of oral MDV3100 in patients with progressive castration-resistant prostate cancer previously treated with docetaxel-based chemotherapy

after docetaxel - castration - phase III - resistant prostate cancer - small molecule androgen receptor antagonist

In clinical practice, treatment of advanced prostate cancer is limited by the development of resistance to anti-androgen therapies. Most patients receive 2 or more hormonal manipulations before offered docetaxel. Once patients progress on docetaxel, no approved second-line therapy is available. Because many of these resistant tumours continue to over-express androgen receptors, second generation anti-androgens that are more potent and pure antagonists, like MDV3100, may be effective in these patients. The primary objective of this study is to determine the benefit of MDV3100 (160 g/d orally) compared to placebo as assessed by overall survival.

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Phase I study of the combination of lapatinib and temozolomide for the treatment of progressive brain disease in HER2-positive breast cancer

brain metastasis - breast cancer - HER2-positive - lapatinib - phase I - temozolomide

This is a **phase I trial** that is being conducted at the Jules Bordet Institute to determine the maximum tolerated dose (MTD) for lapatinib combined with temozolomide and to evaluate the dose limiting toxicities (DLT) for this combination in HER2-positive breast cancer progressing after standard local therapy.

Lapatinib is an orally active, reversible dual inhibitor of HER1 and HER2 that has shown activity in HER2-positive breast cancer. Due to its small molecular structure, lapatinib has the potential advantage to better penetrate the blood brain barrier and may therefore offer a significant benefit in patients with CNS involvement. Temozolomide is an oral alkylating agent that has shown preliminary activity in brain metastases from breast cancer. Both oral agents offer ease of administration and possess an acceptable safety profile.

Eligibility criteria include women with proven HER2-positive metastatic breast cancer with recurrent/progressive measurable brain lesions, after standard local therapy. Previous treatment with trastuzumab and/or lapatinib is allowed. Patients must have normal cardiac and hepatic functions, ECOG status 0-2 and a life expectancy of more than 3 months.

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PathIES: Intergroup Exemestane Study – pathology sub-study

aromatase inhibitor - breast cancer - retrospective FFPE block collection - tamoxifen

The Intergroup Exemestane Study (IES) has shown improved disease-free survival in postmenopausal women with early breast cancer who switched to the aromatase inhibitor (AI) exemestane, after 2-3 years of tamoxifen therapy compared to those who

received tamoxifen alone for a total of 5 years of adjuvant therapy. Despite the overall benefit demonstrated, it is not yet possible to identify upfront which women would benefit from switching to exemestane.
PathIES is an academically led translational study that aims to address this question. It involves the retrospective collection of archived formalin-fixed, paraffin-embedded (FFPE) blocks containing tissue from the primary tumour, recurrent tumour and contralateral breast carcinomas from women participating in the IES. Tumour tissue will be analysed for a set of biomarkers that have been shown to impact on sensitivity to AIs and/or tamoxifen. By correlating the results of this analysis with patient outcome, we hope to identify those biomarkers that may be response determinants to these treatments, thereby taking a step towards individualising treatment selection in this patient group.
PathIES has been successfully set up in a number of European countries including Belgium. We would like to thank IES investigators for their continuous support in this important research and invite them to participate in PathIES by contributing archived, diagnostic tumour blocks from patients recruited in the IES. Participating pathologists will be compensated for their time and effort.

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A phase I trial of sutent, a tyrosine kinase inhibitor combined with ionizing irradiation in rectal cancer: protocol KIRC 08-01

phase I - radiotherapy - rectal cancer - sunitinib - tyrosine kinase inhibitor

The standard treatment for locally advanced rectal cancer combines radiotherapy with surgery and chemotherapy. It has been demonstrated that neoadjuvant radiotherapy provides superior results compared to the postoperative setting. Sunitinib is a tyrosine kinase inhibitor (TKI) with anti-angiogenic properties. In murine models, the combination of sunitinib and fractionated radiotherapy inhibits tumour regrowth. This **phase I trial** is therefore designed to combine conventional radiotherapy with concomitant sunitinib in a preoperative approach for locally advanced rectal cancer.
Eligibility criteria include a cT3 or N+ (confined to mesorectum) rectal adenocarcinoma considered amenable to a R0 low anterior resection.
Three different doses of sunitinib (25, 37.5, and 50 mg) will be tested. The primary objective is to establish a recommended dose of sunitinib in these conditions. Secondary endpoints include overall survival, progression-free survival, downstaging and R0 resection rate, gene expression and proteomics. These results will pave the way for the design of a phase II trial that can potentially combine radiotherapy, chemotherapy, and sunitinib in the neoadjuvant setting.

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A dosimetric study comparing breast radiotherapy planned in prone versus supine position and via conformal 3D versus IMRT techniques: protocol B-POS

breast - dosimetry - gating - IMRT - prone - radiotherapy - supine

Breast cancer is the most frequently diagnosed cancer in women. Radiotherapy is an essential component of the curative treatment algorithm. The current standard of care is radiotherapy, in the supine position, to the whole breast by 3D conformal planning. However, several questions remain regarding dose delivery and technique optimization. Can patient positioning improve dose homogeneity? Can the prone position reduce error associated with patient breathing or decrease the dose to healthy organs and tissues? This study is designed to compare prone versus (conventional) supine treatment and the impact of respiratory motion in each position. The benefits of IMRT versus conventional 3D conformal planning (in each position) will be compared with regard to dose delivery to the breast, dose to healthy

organs and tissues and cost-efficiency regarding departmental resources. The results of this study will serve for the standardization of breast radiotherapy techniques within the Liège University Hospital.

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SORCE trial: a phase III randomized double-blind study comparing sorafenib with placebo in patients with resected primary renal cell carcinoma at high or intermediate risk of relapse

accrual ongoing - phase III - renal cell carcinoma - sorafenib

This **multicentre phase III trial** aims to assess the efficacy and tolerability of sorafenib in patients with resected renal cell carcinoma (RCC). Patients will be randomized to 3 treatment arms: 3 years placebo, 1 year sorafenib + 2 years placebo, or 3 years sorafenib. The main endpoints of the study are disease-free survival, RCC-specific survival, overall survival, and toxicity.

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EORTC 22043-30041 trial: postoperative external radiotherapy combined with concomitant and adjuvant hormonal treatment versus postoperative external radiotherapy alone in pathological stage pT3a-b R0-1 N0M0, Gleason score 5-10 prostate carcinoma

accrual start: May-June 2009 - hormonotherapy - phase III - prostate cancer - radiotherapy

This **multicentre phase III trial** aims to investigate the potential benefit of a combined adjuvant treatment (short-term androgen suppression and postoperative radiotherapy) for improving the biochemical progression-free survival of patients who have undergone radical prostatectomy for cT1-2-3a N0M0 prostate cancer with baseline prostate-specific antigen (PSA) level ≤5x upper limit of normal range, and who present postoperatively with pathologic stage pT2 R1 / pT3-b R0-1 N0M0, Gleason score 5-10, and an undetectable postoperative PSA level.
Patients will be randomized between postoperative irradiation alone or postoperative irradiation and short-term adjuvant androgen deprivation.
The main endpoints of the study are biochemical and clinical progression-free survival, distant metastasis-free survival, overall survival, and toxicity.

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Two trials with intra-arterial chemotherapy for unresectable isolated liver metastases from colorectal cancer

cetuximab - colorectal cancer - liver metastases - oxaliplatin - phase II

CHOICE study

The CHOICE study is a multicentre phase II study (promoter: Institute Gustave-Roussy (IGR), Villejuif, France) including 45 colorectal cancer patients with isolated liver metastases in whom the primary tumour has been removed (first-line treatment). Patients with K-RAS mutant tumours are excluded from this study. Patients will be treated as follows:

- intravenous chemotherapy: leukovorin (LV) + 5-fluorouracil (FU)2 + weekly cetuximab (provided by Merck);
- Intra-arterial chemotherapy: oxaliplatin (q 2 weeks).

OPTILIV study

The OPTILIV study is a muliticentre phase II study (promoter: 'Association pour la Recherche sur le

temps Biologique et la Chronotherapie (ARTBC) internationale-Hopital P. Brousse', Villejuif, France) in which 60 colorectal cancer patients with isolated liver metastases are recruited in whom the primary tumour was removed (x^{th} treatment line).
Patients with K-RAS mutant tumours are excluded from this study. Patients will be treated as follows:

- IV: bi-weekly cetuximab (provided by Merck)
- IA: 5FU + irinotecan + oxaliplatin (q 2 weeks); chronomodulated schedule optional.

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A phase I trial on LBH589 (panobinostat), a histone deacetylase inhibitor in combination with external radiotherapy for the treatment of prostate cancer, oesophageal cancer and head and neck cancer: protocol CLBH589CBE01

deacytase inhibitor - histones - phase I trial - radiotherapy

Radiotherapy is a keystone in the treatment of prostate cancer (PC), oesophageal cancer (EC) and head and neck cancer (HNC). In PC, LBH589 degrades androgen receptors, a key regulator for cancer cell survival and proliferation. In squamous cell cancer, LBH589 is synergistic with radiation in preclinical models. Generally, there is a strong rationale to use pan-histone deacytelase inhibitor (HDACi) in HNC and gastrointestinal cancer. A **phase I trial** designed to assess the feasibility of combined administration of different oral LBH589 dosages in combination with ionizing irradiation in a selection of patients with PC, HNC and EC is currently starting at CHU-Liège. This will allow the optimal dose-establishment for further studies.

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Assessing the efficacy of the combination of gemcitabine and cetuximab (ECHO) in advanced cholangiocarcinoma

BGDO - cetuximab - cholangiocarcinoma - gemcitabine - phase II

The Belgian Group of Digestive Oncology (BGDO) is launching a **phase II trial** assessing the efficacy of the combination of gemcitabine and cetuximab in advanced cholangiocarcinoma: the **ECHO trial**. These rare tumours represent an orphan disease, with no standard treatment and only phase II trials in the literature. If efficacy is shown after the first 13 patients, this study will hopefully include 45 patients. The aim of the study is to assess progression-free survival at 6 months, hoping to improve it from 20% (as estimated from the trials using gemcitabine) to 40% with the combined regimen. As biliary tract tumours express K-RAS in 50% of the cases, translational research will also be performed to see if mutated K-RAS can be predictive of response.

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FIELT study: first-line inhibitor of EGFR in lung cancer treatment

EGFR mutation - EGFR-1 tyrosine kinase inhibition - NSCLC - phase II

The FIELT study is a multicentre prospective phase II study evaluating small molecule EGFR-1 tyrosine kinase inhibition as first-line treatment in patients with advanced non-small cell lung cancer (NSCLC) harbouring a mutant EGFR gene. Patients with adenocarcinoma of the lung with a little (<15 pack years) or non-smoking history are genotyped for mutations in the EGFR gene in the central laboratory of the Free University of Brussels. This is performed on the normal formalin-fixed lung cancer biopsies used for diagnosis. The results are returned within maximally 2 weeks. The patients with an EGFR gene mutation are then eligible for first-line

treatment with erlotinib. The primary endpoint of this trial is progression-free survival. FISH analysis and additional genotyping is also performed to identify potential eligibility for other targeted therapies in patients that do not have an EGFR gene mutation in their tumour. This study continues to recruit patients.

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Single-arm trial of BIBW2992 in demographically and genotypically selected non-small cell lung cancer patients

BIBW2992 - EGFR inhibitor - HER2-neu inhibitor - NSCLC - phase II

The primary objective of this **phase II trial** is to explore the efficacy of **BIBW2992**, a dual inhibitor of EGFR and HER2-neu, in patients with advanced non-small cell lung cancer (NSCLC) stage IIIB or IV whose tumours:

1. harbour activating **mutations** within exon 18 to exon 21 of the **EGFR receptor** and who have become **resistant to treatment with gefitinib or erlotinib**;
2. are **EGFR FISH-positive** and who have become resistant to treatment with **gefitinib or erlotinib**;
3. harbour **activating mutations in the HER2-neu receptor.**

The HER2 mutation screens are routinely performed in patients who were screened in the Laboratory of Molecular Oncology, Oncology Centre, University Hospital Brussels, and who were EGFR mutation negative.
The laboratory can also perform **HER2 mutation screens in phenotypically selected lung adenocarcinomas in never or past smokers** who have failed prior chemotherapy and were not previously considered for the FIELT study.
These mutation screens are performed on paraffin-embedded, formalin-fixed tissues.

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Activity of sunitinib in oesophageal cancer, melanoma and sarcoma (SEMS)

melanoma - oesophageal cancer - phase II - sarcoma - sunitinib

The melanoma and sarcoma cancer cohorts have been completed. Accrual continues in oesophageal cancer.
Therapeutic options in patients with advanced oesophageal cancer, melanoma and sarcoma are limited after failure of standard first-line chemotherapy. In the present, **multicentre 2-stage phase II trial** the activity of the single agent sunitinib malate (Sutent®) administered orally at 50 mg/day, 4 weeks on followed by 2 weeks off, will be examined.
Inclusion criteria:

- advanced cancer, locally or metastatic;
- presence of plasma and tissue sample;
- life expectancy of >3 months;
- measurable disease or disease evaluable with non-measurable lesions or tumour marker;
- disease progression on prior treatment and anti-cancer therapy-free period of >4 weeks before baseline examination for current study;
- Tumour-specific inclusion criteria:
  - **sarcoma and melanoma cohorts are closed (recruitment completed)**;
  - **oesophageal cancer**: second line after cisplatinum based chemotherapy.

The study comprises a translational component including

- baseline plasma levels of VEGF-A, sVEGFR-2, sVEGFR-3 and placenta growth factor (PlGF);
- tumour gene copy number of VEGFR-2;
- evolution during treatment of circulating endothelial and tumour cells. Perfusion imaging with dynamic contrast enhanced MRI.

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The PATSGO trial

chemotherapy - glioblastoma - phase II - progression-free survival - temozolomide

The PATSGO trial is a randomized phase II trial evaluating the benefit of a prolonged adjuvant treatment in glioblastoma patients. Some patients present at the end of the 6 months adjuvant treatment with residual tumours that are still regressing. These patients could benefit from prolonged treatment. This study will also evaluate the efficacy of rechallenging patients with temozolomide when their tumour progresses. As temozolomide is thought to be inactive at relapse most relapsing patients do not receive it. However, some responses have been reported. The major enpoints of this trial are (1) progression-free and overall survival at 6 months; (2) safety and adverse event profile of prolonged adjuvant temozolomide; (3) comparison of the health-related quality of life of the patients randomized in the 2 arms; (4) overall tumour response in patients when they are rechallenged with temozolomide.

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The SOLE trial

disease free survival - early stage breast cancer - endocrine therapy - letrozole - phase III trial

The SOLE trial is a phase III trial evaluating the role of continuous letrozole versus intermittent letrozole following 4 to 6 years of prior adjuvant endocrine therapy in postmenopausal women with hormone receptor-positive, node-positive, early stage breast cancer (SOLE / IBCSG 35-07 / BIG 1-07).

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GORTEC 2006-01: a phase II study of SU11248 in patients with recurrent and/or metastatic squamous head and neck carcinoma

head and neck cancer - multicentre - open label - phase II - recurrent or metastatic disease - toxicity and efficacy of sunitinib

Recurrent or metastatic head and neck cancer patients will receive sunitinib, an anti-VEGFR after they fail platinum-salt chemotherapy. Patients should have measurable lesions accessible to biopsy. This is the first time that such treatment is given to these patients. Therefore, this **European multicentre phase II study** examines toxicity and efficacy.

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Institutional websites with information on recruiting trials

Medische Oncologie UZ Leuven
http://www.uzleuven.be/nl/ig-algemeen-medische-oncologie/klinische-studies

Medische Oncologie UZ Brussel
http://www.uzbrussel.be/u/view/nl/2555295-Medische+oncologie.html

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