Overview of trials running in the Benelux

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CYPTAM-BRUT 2 and 3 trials: prospective, multicentric studies to evaluate the relation between CYP450 mutations, metabolisation and response to tamoxifen in breast cancer patients.

Breast cancer – tamoxifen – CYP450 – response – biomarkers

A lot of variation regarding clinical response and side effects is seen among women receiving tamoxifen for an estrogen-receptor positive breast cancer. A possible explanation for this is the presence of mutations in enzymes important for converting tamoxifen to its active metabolites. The aim of these studies is to assess the predictive value of CYP450 mutations in patients planned to receive tamoxifen as endocrine therapy in early and advanced breast cancer. Both studies were approved by the central UZ Leuven Commission for Medical Ethics and patient inclusion is started.

CYPTAM-BRUT 2 (NCT00965939) is a prospective, multicentric study including postmenopausal women receiving tamoxifen for metastatic, locally advanced (stage IIIB/C) or in the neoadjuvant setting for measurable estrogen-receptor positive breast cancers. The primary endpoint is the difference in efficacy of tamoxifen, defined as the objective response rate using RECIST criteria, between women with a normal versus low Tamoxifen Activity Score (TAS) after 3-6 months of tamoxifen use. The TAS score is based on the presence of genetic variations and drug interactions. Secondary endpoints are time to progression, clinical benefit, serum metabolite concentrations, endometrial changes and menopausal symptoms. Patients using tamoxifen in the neoadjuvant setting need to be operated between 4-6 months following the start of tamoxifen.

CYPTAM-BRUT 3 (NCT00966043) is a prospective, multicentric study in Belgium within the CYPTAM study of the Leiden University Medical Center (NTR1509) including postmenopausal women receiving tamoxifen for estrogen-receptor positive breast cancer in the adjuvant setting. The primary endpoint is the difference in uterine changes between women with a normal versus low TAS after 3 months of tamoxifen use. Secondary endpoints are serum metabolite concentrations, serum follicle-stimulating hormone level, serum sex hormone-binding globulin level and menopausal symptoms. These patients are registered in the Leiden protocol with time to breast cancer event as primary endpoint.

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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

Lapatinib – temozolomide - phase I - HER-2 positive - brain metastasis - breast cancer

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 evaluate the dose limiting toxicities (DLT) for this combination in HER-2 positive breast cancer progressing after standard local therapy.

Lapatinib is an orally active, reversible dual inhibitor of HER-1 and HER-2 that has shown activity in HER-2 positive breast cancer. Its small molecular structure has the potential advantage in better penetrating the blood brain barrier and may 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 agents are oral and offer ease of administration and possess an acceptable safety profile.

Eligibility criteria include women with proven HER-2 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 of 0-2 and a life-expectancy of more than 3 months.

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PathIES: Intergroup Exemestane Study – Pathology Sub-study

Retrospective FFPE block collection – breast cancer – aromatase inhibitor – 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 2-3years of tamoxifen therapy compared to those who received tamoxifen alone for a total of five 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 tumor, recurrent tumor and contralateral breast carcinomas from women participating in the IES. Tumor 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 identity those biomarkers that may be determinants of response 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 the IES investigators for their continuous support in this important research and invite them to participate in PathIES by contributing archived, diagnostic tumor 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 (TKI) combined with ionizing irradiation in rectal cancer ; protocol KIRC 08-01

Rectal cancer – radiotherapy – phase I – 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 post-operative setting. Sunitinib is a tyrosine kinase inhibitor with anti-angiogenic properties. In murine models, the combination of sunitnib and fractionated radiotherapy inhibits tumor 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 50mg) 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 the prone versus supine positions and via conformal 3D versus IMRT techniques; protocol B-POS

Dosimetry – breast - radiotherapy – prone – supine – IMRT – gating

Breast cancer is the most frequently diagnosed cancer in women. Radiotherapy is an essential component in 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 regards 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 CHU-Liege.

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

Phase III – sorafenib – renal cell carcinoma – accrual ongoing

This **multi-center phase III tria**l aims to assess the efficacy and tolerability of sorafenib in patients with resected renal cell carcinoma. 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: Post-operative external radiotherapy combined with concomitant and adjuvant hormonal treatment versus post-operative external radiotherapy alone in pathological stage pT3a-b R0-1 N0M0, Gleason score 5-10 prostatic carcinoma

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

This **multi-center phase III trial** aims to investigate the potential benefit of a combined adjuvant treatment (short term androgen suppression and post-operative radiotherapy) for improving the biochemical progression free survival of patients who have undergone radical prostatectomy for cT1-2-3a N0M0 prostate cancer with baseline PSA ≤ 5 x upper limit of normal range and who present post-operatively with pathologic stage pT2 R1 / pT3-b R0-1 N0M0, Gleason score 5-10 and an undetectable post-operative PSA.

Patients will be randomized between post-operative irriadiation alone or post-operative irradiation and short term adjuvant androgen deprivation.
The main endpoints of the study are biochemical and clinical progression-free survival, distant-metastases-free survival, overall survival and toxicity.

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CUP trial: molecular profiling as a strategy for the identification of primary solid tumor in metastatic cancer patients

Carcinoma of unknown primary - phase II - molecular profiling - CupPrint®

Carcinoma of unknown primary (CUP) is defined by the presence of biopsy proven metastatic disease without an identifiable primary tumor site on its presentation. Molecular profiling of the tumor is a promising tool for helping clinicians to better decide the patients' diagnosis and treatment.
Gene expression analysis of the tumor is a promising new approach to identify the tumor origin. This technique (CupPrint®) can accurately predict the site of primary tumor in 78 to 90% of cases.
The CUP trial, is a prospective phase II clinical trial that will evaluate the accuracy and costs of molecular profiling as a diagnostic method, compared to the traditional standard investigations in patients with metastatic tumors for whom the primary tumor is identified by routine exams. The results of molecular profiling will not affect the treatment decision. Investigators will have access to CupPrint® results only after they have identified and reported the primary tumor. If no primary tumor is found by all means of clinical investigation, physicians will be allowed to access CupPrint® result to help defining treatment.

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2 trials with intra-arterial (IA) chemotherapy for unresectable isolated liver metastases from colorectal cancer.

Phase II – colorectal cancer – liver metastases – cetuximab - oxaliplatin

CHOICE study

The CHOICE study is a multicentric Phase II study (Promotor: IGR – Villejuif, France) including 45 colorectal cancer patients with liver isolated metastases in which the primary tumor was removed (first line of treatment). No amendments regarding the K-ras status of the tumor. Patients will be treated as follows:

IV: LV5FU2 + weekly cetuximab (provided by Merck)
IA: oxaliplatin (q 2 weeks)

OPTILIV study

The OPTILIV study is muliticentric phase II study (Promotor: ARTBC international- Hop. P.Brousse, Villejuif, France) in which 60 colorectal cancer patients with liver isolated metastases are recruited in which the primary tumor was removed (Xth treatment line)
No amendments regarding the K-ras status of the tumor. 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 LBH 589 (panobinostat), a histone deacetylase inhibitor (HDACi) in combination with external radiotherapy for the treatment of prostate cancer, esophageal cancer and head and neck cancer. Protocol CLBH589CBE01.

histones - deacytase inhibitor - radiotherapy - phase I trial

Radiotherapy is a keystone in the treatment of prostate cancer (PC), esophageal cancer (EC) and head and neck cancer (H&N). 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-HDACi (Histone deacytelase inhibitor) in H&N 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, H&N 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

Gemcitabine – cetuximab – cholangiocarcinoma – BGDO – 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 tumors 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 will be 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 tumors express Ki-Ras in 50% of the cases, translational research will also be performed to see if mutated Ki-Ras can be predictive of response.

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FIELT study: First line Inhibitor of EGFR in Lung cancer Treatment

NSCLC – EGFR mutation - EGFR-1 tyrosine kinase inhibition –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 little (< 15 packyears) or no smoking history are genotyped for mutations in EGFR in the central VUB lab. This is performed on the normal formalin fixed lung cancer biopsies used for diagnosis. The results are returned within maximally 2 weeks. FISH analysis will also be performed The patients with an EGFR mutation are then eligible for first-line treatment with erlotinib. The primary endpoint of this trial is progression free survival.

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Single-arm Trial of BIBW 2992 in Demographically and Genotypically Selected NSCLC Patients

Phase II – BIBW2992 – NSCLC – EGFR inhibitor – HER2-ney inhibitor

The primary objective of this **Phase II trial** is to explore the efficacy of **BIBW 2992**, a dual inhibitor of EGFR and HER2-neu, in patients with advanced 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 mutations are routinely performed in patients that were screened in the Laboratory of Molecular Oncology, Oncologisch Centrum UZ Brussel, and who were EGFR mutation negative.
The Laboratory can also perform **HER2 mutation screen in phenotypically selected patients lung adenocarcinoma in never or past smokers** that have failed prior chemotherapy and were not previously considered for the FIELT study.
These mutations are performed on paraffin embedded, formalin fixed tissues.

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

Phase II – sunitinib - esophageal cancer – melanoma - sarcoma

The melanoma and sarcoma cancer cohorts have been completed. Accrual continues in oesophageal cancer.
Therapeutic options in patients with advanced esophageal cancer, melanoma and sarcoma are limited after failure of standard first line chemotherapy. In the present, **multicentric two-stage phase II trial** the activity of single agent sunitinib malate (Sutent®) administered orally at 50mg/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 tumor marker
- Disease progression on prior treatment and anti-cancer therapy-free period of > 4 weeks before baseline examination for current study.
- Tumor- specific inclusion criteria:
  - **Sarcoma:** Second line, after one line of anthracycline based chemotherapy
  - **Melanoma:** Second line, after one line chemotherapy containing DTIC (combination or single agent). Prior vaccination and anti-CTLA4 immune therapy allowed (requires establishment of progressive disease under treatment).
  - **Esophageal 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 PlGF (placenta growth factor)
- Tumor gene copy number of VEGFR-2
- Evolution during treatment of circulating endothelial and tumor cells. Perfusion imaging with dynamic contrast enhanced MRI.

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The PATSGO trial

Temozolomide – Phase II – chemotherapy – glioblastoma – progression-free survival

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 tumors 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 tumor 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 tumor response in patients when they are rechallenged with temozolomide.

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The SOLE trial

Letrozole – phase III trial – endocrine therapy – early stage breast cancer – disease free survival

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

phase II – open label – multicentre – head and neck cancer – 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 website with information on recruiting trials

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