Overview of trials running in the Benelux

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A phase I trial of sunitinib, 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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Exelixis trial 184-301: a promising experimental treatment option for patients with medullary thyroid carcinoma (MTC)

XL-184 – medullary thyroid carcinoma – tyrosine kinase inhibitor

XL-184 is a multi-targeted oral tyrosine kinase inhibitor against RET, MET, VEGFR2/KDR and KIT. The drug is available since 29-01-2009 (trial initiation date) in the framework of a double-blind, randomized, placebo-controlled phase III study for a global total of 315 patients. This is a registration trial. In a previous landmark phase I study performed by Exelixis, a biotech company from the United States, the vast majority of patients showed significant shrinkage of their MTC metastasis including objective RECIST responses, achieved excellent symptom control and impressive biochemical responses. This work has been featured at various prestigious meetings, including ASCO 2008 in Chicago and the EORTC NCI AACR Symposium in Geneva last year.
The drug "competes" with similar agents from other companies, which have recently been explored in Phase II/III trials, which do not recruit further patients anymore. Patients who failed treatment with other agents (or screening for similar trials), including various tyrosine kinase inhibitors or monoclonal antibodies, are not automatically excluded from participation in this trial.
The exelixis trial 184-301 recruits patients with MTC who fulfill the following major inclusion criteria:

- Histologically confirmed MTC that is unresectable, locally advanced or metastatic & measurable or non-measurable by modified RECIST
- 18 years old or older
- ECOG 0, 1 or 2
- Progressive disease on CT, MRI, bone scan or X-ray per mRECIST at screening compared to an image done within previous 14 months
- Clinically significant adverse events due to anti-neoplastic agents, investigational drugs or other medications have recovered to CTCAE v3.0 Grade ≤ 1
- ANC (Absolute Neutrophil Count) ≥ 1500/mm^3

- Platelets ≥ 100,000/mm^3
- Hemoglobin ≥ 9 g/dL
- Bilirubin ≤ 1.5 times ULN (excluding pts with Gilbert's syndrome)
- Serum creatinine ≤ 1.5 mg/dL
- ALT & AST ≤ 2.5 times ULN
- Sexually active (male & female) must agree to use medically accepted contraception during & for 3 months after treatment (excludes women not of childbearing potential and men who have been sterilized)
- No other malignancy & currently no evidence of malignancy (except non-melanoma skin cancer or carcinoma in situ of the cervix).
- Female subjects of childbearing potential must have a negative pregnancy test at screening. Females of childbearing potential are defined as sexually mature women without prior hysterectomy or who have had any evidence of menses in the past 12 months. Women who have been amenorrheic for 12 or more months are still considered to be of childbearing potential if the amenorrhea is possibly due to prior chemotherapy, anti-estrogens or ovarian suppression

Patients are excluded from trial participation in case of:

- Systemic anti-tumor therapy (chemotherapy, biologic modifiers or anti-angiogenic therapy) within 4 weeks of randomization (6 weeks - Nitrosoureas or mitomycin C)
- Radiation to ≥ 25% of bone marrow
- Treatment with other investigational agents within 4 weeks of randomization
- Previous treatment with XL184
- Brain metastases or spinal cord compression, unless radiation completed ≥ 4 weeks before randomization & stable without steroid or anti-convulsant for ≥ 10 days
- Clinically significant hematemesis or recent history of hemoptysis of >2.5 mL of red blood or other signs of pulmonary hemorrhage or endobronchial lesion(s)
- Urine protein/creatinine ratio of ≥ 1
- Serious intercurrent illness such as: Hypertension (> 2 readings at screening of > 140 mmHg systolic or > 90 mmHg diastolic) despite optimal treatment; unhealed wounds from recent surgery; cardiac arrhythmias
- Recent history of serious disease such as: symptomatic congestive heart failure or unstable angina pectoris within the past 3 months or; MI, stroke or TIA within the past 6 months
- Pregnant or breastfeeding
- Active infection requiring systemic treatment
- Known allergy or hypersensitivity to any of the components of the XL184 or placebo formulations
- Incapable of understanding and complying with the protocol or unable to provide informed consent

The experimental compound is given daily at a dose of 175 mg p.o. (4 capsules). Due to the good safety profile of this drug treatment does not require any co-medication.

The trial has a few methodological pitfalls:

- Deviations from the patient selection criteria described above will not be allowed (no waivers).
- FDA requested not to cross-over patients from the placebo arm to the experimental treatment arm (1:2 randomization) in case of disease progression, which means that 1/3 of patients will receive no active treatment.
- The complex screening procedures must be completed within 28 days, including shipment of biological samples, central review of digital images etc.
- At least 10 unstained slides of archival tumor tissue are required within a very tight deadline .
- All study-specific procedures will have to be performed on site in Leuven.
- The selection of sites participating in this global registration study has been completed.

Patients with MTC, who basically comply with the patient selection criteria mentioned above, can be send to the consultation of prof Schöffski, accompanied by 10 unstained, archived tumor slides (or a paraffin block) and previous spiral CT scans on CD-ROM demonstrating disease progression. They will received detailed information about all aspects of the complex trial and – if interested in participation – will undergo the informed consent and screening procedures. You will receive continuous follow-up information of these patients.

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

Phase II – sunitinib - esophageal cancer – melanoma - sarcoma

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 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 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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The VLK trial

Prospective trial - dose de-escalation – HNC – phase III – IG-IMRT – swallowing dysfunction

The VLK trial is an academic, multicentre, randomized, prospective phase III trial using image-guided, intensity-modulated radiotherapy (IG-IMRT) with dose de-escalation to the elective nodal sites, the swallowing apparatus and neck soft tissues for head and neck cancer. The hypothesis is that dose de-escalation on the elective nodal sites will decrease the rate and severity of swallowing disturbances while loco-regional control will remain equal.

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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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The department of general medical oncology of the University Hospitals Leuven has generated a list of recently closed, currently ongoing and prospective clinical trials of our department. This overview can be consulted through the following link: **http://www.uzleuven.be/nl/ig-algemeen-medische-oncologie/klinische-studies**

The list provides an overview of the clinical trials in non-disease specific, disease-specific and compassionate use programs.

It is a useful tool for general practitioners as well as patients themselves looking for more information on the internet.