

Overview of trials running in the Benelux

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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) $\geq 1500/\text{mm}^3$
- Platelets $\geq 100,000/\text{mm}^3$
- Hemoglobin $\geq 9 \text{ g/dL}$
- Bilirubin ≤ 1.5 times ULN (excluding pts with

Gilbert's syndrome)

- Serum creatinine $\leq 1.5 \text{ mg/dL}$
- ALT & AST ≤ 2.5 times ULN
- Sexually active (male & female) must agree to use medically accepted contraception during and 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 $\geq 25\%$ 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 $>2.5 \text{ mL}$ 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 tumour 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. Continuous follow-up information of these patients will be provided.

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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 tu-

mor 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 tumour. Patients will be treated as follows:

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

OPTILIV study

The OPTILIV study is multicentric 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 tumour was removed (Xth treatment line)

No amendments regarding the K-ras status of the tumour. 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 – deacetylase 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 deacetylase 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 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 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 tumours 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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FIELD study: First line Inhibitor of EGFR in Lung cancer Treatment

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

The FIELD 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 maxi-

mally 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 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:** 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 cisplatin based chemotherapy

The study comprises a translational component including

- Baseline plasma levels of VEGF-A, sVEGFR-2, sVEGFR-3 and PlGF (placenta growth factor)
- 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

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 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 endpoints 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

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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The SUCON trialphase II – multicentre – metastatic breast cancer – SU11248 – accrual ongoing

The SUCON trial is a Belgian multicentre, phase II randomised trial in HER2 negative metastatic breast cancer with SU11248 (sunitinib malate), evaluating consolidation antiangiogenic therapy after response to taxane chemotherapy induction. This phase II trial has been open since February 2006 and

41 patients have been included in 20 participating centres by March 2008. The accrual target is 60 patients.

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GORTEC 2006-01: A phase II study of SU11248 in patients with recurrent and/or metastatic squamous head and neck carcinomaphase 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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An open-label, multicentre phase I trial in order to determine the safety and pharmacokinetics of Bay43-9006 (sorafenib) in combination with docetaxel as first-line treatment in metastatic hormone refractory prostate cancer patientsphase I – open label – multicentre – prostate cancer – recurrent or metastatic – sorafenib

Sorafenib is the new first-line treatment for metastatic hormone refractory prostate cancer patients. Anti-VEGF strategies are studied in different cancer types. Combining these new treatments with standard chemotherapy is appealing. **This phase I mul-**

ticentre study will examine toxicity.

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