Phase III Double-blinded, Placebo Controlled Study of Xilonix* for Improving Survival in Metastatic Colorectal Cancer

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Malignant and unspecified neoplasms gastrointestinal NEC
Study type	Interventional

Summary

ID

NL-OMON45233

Source
ToetsingOnline

Brief title
2012-PT023

Condition

- Malignant and unspecified neoplasms gastrointestinal NEC

Synonym
Metastatic Colorectal Cancer - Cancer of the colon or the rectum that has spread

Research involving
Human

Sponsors and support

Primary sponsor: XBiotech Germany GmbH

Source(s) of monetary or material Support: De opdrachtgever van dit onderzoek XBiotech Germany GmbH

Intervention

Keyword: Colorectal Cancer, Oncology, XBiotech, Xilonix

Outcome measures

Primary outcome

Primary Efficacy Endpoint

* Overall survival (OS) will be the primary endpoint of this study, which will

be measured from the date of randomization until death or last follow-up.

Secondary outcome

Secondary Efficacy Endpoints

* Secondary efficacy variables will include change in lean body mass (LBM)

measured by dual-energy X-ray absorptiometry (DEXA) scans, change in Quality of

Life assessed through the cancer-specific EORTC QLQ-C30 questionnaire,

stabilization of platelet counts, progression free survival (PFS), objective

response rate (ORR) and disease control rate (DCR).

Study description

Background summary

In the setting of refractory, metastatic disease a complete resolution of tumor burden is not a reasonable expectation. Instead, the primary goal of anti-tumor therapy at this stage is to eliminate or reduce the symptomatic effects of the tumor, while trying to prolong survival for as long as possible. Due to treatment related morbidity however, few treatment modalities are ideal for

this objective. Even with the most recent targeted agents (such as multi-kinase inhibitors), drug related toxicities frequently lead to relatively short treatment durations. With discontinuation of therapy, disease progression is uncontrolled and prognosis is poor.

New agents that control disease progression*while improving tumor-related symptoms, rather than causing significant therapy related morbidity*are vitally needed to treat patients with advanced cancer, including those with colorectal cancer. An approach has been taken to develop such an agent using a monoclonal antibody to block the chronic inflammation involved in both malignant disease progression and constitutional symptoms.

Xilonix* is expected to inhibit tumor growth and metastasis by interrupting crucial signals that drive angiogenesis and invasiveness. The antibody therapy may also block tumor microenvironment infiltration by leukocytes (such as myeloid suppressor cells) that suppress antitumor immunity, enabling better host immune control of the disease. In addition to local effects on the tumor, Xilonix* is expected to work systemically to correct the metabolic dysregulation, fatigue and anxiety mediated by chronic inflammatory signaling to the central nervous system.

We have reported the first observation that increases in lean body mass (LBM) in patients with advanced metastatic disease are associated with a very substantial survival benefit. In the recent clinical study where these observations were made, patients were treated with an anti-IL-1* therapeutic antibody (Xilonix*) to block tumor-related inflammation. Dual energy X-ray absorptiometry was used to accurately and objectively measure changes in body mass, and discriminate between changes in lean mass (i.e. muscle) and fat. LBM increased an average of 1.9±2kg within 8 weeks in 70% of the per-protocol population ($p<0.001$). In the colorectal carcinoma cohort, patients that gained lean body mass had dramatic improvement in survival (19.3 months vs 6.6 $p=0.098$) compared to those that lost lean mass .

Dramatic improvement in survival in patients with increasing LBM after treatment with an anti-IL-1* therapeutic antibody suggests new hope for treating patents that are currently considered refractory. The use of this antibody monotherapy to target chronic inflammation is proposed as a safe, effective treatment for patients with metastatic colorectal cancer.

Study objective

The study will compare the overall survival (OS) between the MABp1 treated and placebo arms. Secondary endpoints will include change in lean body mass from screening to the cycle 5 assessment and change in quality of life.

Study design

This is a phase III, multicenter, double blind, randomized, placebo controlled pivotal trial of the True Human monoclonal antibody MABp1 (Xilonix*) in subjects with metastatic colorectal cancer who are refractory to standard therapy.

* Enrolled subjects will be randomized (2:1) to receive either MABp1 plus best supportive care (BSC) versus placebo plus BSC.
* BSC is defined as those measures intended to provide palliation of symptoms and improve quality of life. This includes, but is not limited to, antibiotics, anti-emetics, narcotics, and parenteral nutrition.
* Subjects randomized to MABp1 or placebo will receive 7.5 mg/kg of study drug via intravenous infusion once every 2 weeks (one cycle).
* Study drug will be administered under close observation in a facility equipped to handle medical emergencies. Subjects must be observed for at least 1 hour with stable vital signs following the end of the infusion.
* Efficacy will be assessed by comparing overall survival (OS) between the MABp1 and placebo groups.
* Secondary endpoints will include change in lean body mass and quality of life from screening to the cycle 5 assessment. Other secondary endpoints will be progression-free survival, objective response rate (ORR), disease control rate (DCR), and stabilization of platelet counts. Lean body mass measurements will be obtained through the use of dual-energy X-ray absorptiometry (DEXA) scans. Quality of life will be assessed with the EORTC QLQ-C30 (v. 3). Response and progression will be evaluated using the Immune Related Response Criteria (irRC).
* Safety assessments will include physical examinations, vital signs, standard clinical laboratory evaluations (blood chemistry, urinalysis, and hematology), allergic reaction monitoring and adverse event monitoring.
* Pharmacokinetic samples will be taken in all patients. The pharmacokinetics of MABp1 in plasma will be randomly analyzed. Plasma samples will also be randomly monitored for the development of anti-MABp1 antibodies.

Intervention

Consented eligible subjects will be enrolled and randomly assigned to treatment arm or placebo arm with 2:1 ratio respectively.
Subjects randomized to treatment arm will receive Xilonix* and those in control arm will receive placebo 7,5mg/kg via intravenous infusion every 2 weeks (one cycle) plus BSC.
BSC is defined as those measures intended to provide palliation of symptoms and improve quality of life. This includes, but is not limited to, antibiotics, anti-emetics, narcotics, and parenteral nutrition.

Study burden and risks

To date, over 140 patients have been treated with Xilonix* and over 700 doses

have been administered. The safety profile observed so far has been excellent. There have been no infusion reactions reported with the i.v. administration of the antibody (subjects are not pre-medicated with antihistamines or steroids) and there have been few injection site reactions reported with the subcutaneous formulation. These observations are highly consistent with the fact that there have been no human anti-human antibodies against Xilonix* detected.

The adverse events reported vary by disease indication, but most of the events appear related to the underlying disease and there are no severe or serious toxicities that are obviously related to therapy with Xilonix*.

IL-1* is a key mediator of sterile inflammatory responses, however immunosuppression had been considered as a theoretical risk of the antibody. To date there is no evidence of immunosuppression or increased susceptibility to infection of any kind in patients treated with Xilonix*.

Platelets and other peripheral blood cells, including neutrophils and macrophages, may express IL-1* and thus may be targeted by Xilonix*. While there is no evidence that Xilonix* induces antibody-directed cellular cytotoxicity, there may be the potential for Xilonix* to cause thrombocytopenia, monocytopenia or neutropenia in some patients, however, this has not been observed to date.

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Dramatic improvement in survival in patients with increasing LBM after treatment with an anti-IL-1* therapeutic antibody suggests new hope for treating patents that are currently considered refractory. The use of this antibody monotherapy to target chronic inflammation is proposed as a safe, effective treatment for patients with metastatic colorectal cancer.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Subjects are included in the study if they meet all of the following criteria:;1. Subjects with pathologically confirmed colorectal carcinoma that is metastatic or unresectable and which is refractory to standard therapy. To be considered refractory, a subject must have experienced progression (or intolerance) after treatment with at least all of the following agents: oxaliplatin, irinotecan, flouropyrimidine, and cetuximab or panitumumab if KRAS wildtype.
2. Subjects will not be treated with any radiation, chemotherapy, or investigational agents while enrolled in this protocol.
3. Eastern Cooperative Oncology Group (ECOG) performance status 0, 1, or 2.
4. At least 2 weeks since the last previous cancer treatment including: chemotherapy, radiation therapy, immunotherapy, surgery, hormonal therapy, or targeted biologics and 4 weeks for patients who received treatment immediately prior to the study with anti-IL-1 or anti-TNF agents.
5. Age * 18 years, male or female subjects.
6. Serum potassium and magnesium levels within Central Lab normal limits. Total serum calcium or ionized calcium level must be greater than or equal to the lower limit of normal. Subjects with low potassium, calcium and magnesium levels may be replenished to allow for protocol entry.
7. Adequate renal function, defined by serum creatinine * 1.5 x Central Lab ULN.
8. Adequate hepatic function defined as:

* total bilirubin * 1.5 times the Central Lab ULN
* alanine aminotransferase (ALT) * 2.0 times the Central Lab ULN
Exception: subjects with known liver metastases: * 3.0 times the Central Lab ULN for ALT.
9. Adequate bone marrow function as defined as:
* absolute neutrophil count (neutrophil and bands) of * 1,500/mm3 (* 1.5 x 109/L)
* platelet count of * 100,000/mm3 (* 100 x109/L)
* hemoglobin of * 9 g/dL
10. For women of childbearing potential (WOCBP), a negative serum pregnancy test result at Screening and monthly thereafter.;For women who are not postmenopausal (24 months of amenorrhea) or surgically sterile (absence of ovaries and/or uterus): agreement to use adequate methods of contraception, during the treatment period and for at least 1 month after the last dose of study drug.
Acceptable contraceptive measures include:
- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation: Oral, Intravaginal or transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation; Oral, injectable or implantable
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Barrier or sterilization methods such as condoms, bilateral tubal occlusion, vasectomized partner or sexual abstinence ;For men: agreement to use a barrier method of contraception during the treatment period and for at least 1 month after the last dose of study drug
11. Signed and dated institutional review board (IRB)-approved informed consent before any protocol-specific screening procedures are performed.
12. Patients enrolled must, in the Investigator*s judgment, be healthy enough to stay on the clinical trial for three months.

Exclusion criteria

Subjects with ANY of the following will be excluded from the study:;1. Mechanical obstruction that would prevent adequate oral nutritional intake.
2. Serious uncontrolled medical disorder, or active infection, that would impair the ability of the patient to receive protocol therapy.
3. Uncontrolled or significant cardiovascular disease, including:
* A myocardial infarction within the past 6 months.
* Uncontrolled angina within the past 3 months.
* Congestive heart failure within the past 3 months, defined as New York Heart Association (NYHA) Classes II or higher.
* Diagnosed or suspected congenital long QT syndrome.
* Any history of clinically significant ventricular arrhythmias (such as ventricular tachycardia, ventricular fibrillation, Wolff-Parkinson-White (WPW) syndrome, or torsade de pointes).
* Any history of second or third degree heart block (may be eligible if currently have a pacemaker).
* Uncontrolled hypertension (blood pressure >140 mm Hg systolic and >90 mm Hg diastolic).
4. Dementia or altered mental status that would prohibit the understanding or rendering of

informed consent.
5. Subjects who have not recovered from the adverse effects of prior therapy at the time of enrollment to * grade 1; excluding alopecia and grade 2 neuropathy.
6. Immunocompromised subjects, including subjects known to be infected with human immunodeficiency virus (HIV).
7. Known hepatitis B surface antigen and/or positive hepatitis C antibody and presence of hepatitis C RNA.
8. History of tuberculosis (latent or active) or known positive Interferon-gamma release assay (IGRA).
9. Receipt of a live (attenuated) vaccine within 1 month prior to Screening.
10. Subjects with history of hypersensitivity to compounds of similar chemical or biologic composition of Xilonix*.
11. Women who are pregnant or breastfeeding.
12. WOCBP or men whose sexual partners are WOCBP who are unwilling or unable to use an acceptable method of contraception for at least 1 month prior to study entry, for the duration of the study, and for at least 1 month after the last dose of study medication.
13. Weight loss >20% in the previous 6 months.
14. History of progressive multifocal leukoencephalopathy or other demyelinating disease
15. Subjects on immunosuppressive therapy, including transplant patients

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	21-06-2016
Enrollment:	12
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Xilonix
Generic name:	MABp1

Ethics review

Approved WMO Date:	25-11-2015
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-02-2016
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-07-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-07-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-09-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-10-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-01-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Approved WMO Date:	01-02-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-07-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	31-07-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2012-005287-10-NL
ClinicalTrials.gov	NCT01767857
CCMO	NL54551.018.15

Study results

Date completed:	01-01-1900
Results posted:	10-11-2017
Actual enrolment:	12

First publication
10-11-2017