A phase Ib/II multi-center, open-label, dose escalation study of LGX818 and cetuximab or LGX818, BYL719, and cetuximab in patients with BRAF mutant metastatic colorectal cancer.

Published: 15-10-2012
Last updated: 26-04-2024

Primary objectives Phase Ib: To estimate the MTD and/or RP2D of LGX818 in combination with cetuximab ± BYL719. Incidence of dose-limiting toxicities (DLTs). Phase II: To compare the efficacy of the dual (LGX818, cetuximab) and triple (LGX818, BYL719...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Gastrointestinal neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON47136

Source
ToetsingOnline

Brief title
LGX818 combination therapy in BRAF mutant colorectal cancer

Condition

- Gastrointestinal neoplasms malignant and unspecified

Synonym
metastatic colorectal cancer

Research involving
Human

Sponsors and support

Primary sponsor: Array Biopharma Inc.
Source(s) of monetary or material Support: Farmaceutische industrie

Intervention

Keyword: BRAF colorectal cancer, BYL719, cetuximab, LGX818

Outcome measures

Primary outcome

Incidence of DLTs, progression free survival

Secondary outcome

Incidence and severity of adverse events, pharmacokinetics, overall response

rate, duration of response, time to response, progression free survival and

overall survival.

Study description

Background summary

Colorectal cancer (CRC) is the fourth most frequently diagnosed cancer and second leading cause of cancer death in the EU and US. In 2009, an estimated 150,000 new cases and 50,000 deaths from CRC in the US have occurred. In the last decade, substantial advances in the treatment of metastatic CRC (mCRC) have resulted in an improvement in overall survival from 10-12 months to more than 20 months. This has occurred with the addition of irinotecan, oxaliplatin, bevacizumab, cetuximab, and panitumumab to the standard treatment with 5-FU/leucovorin. However, because many patients eventually develop resistance to these agents, new agents to treat resistant tumors are an important area of investigation.
The anti-EGFR monoclonal antibodies cetuximab and panitumumab were initially evaluated as monotherapy in patients with EGFR-expressing tumors after they became resistant to standard chemotherapy. Subsequent investigations discovered that oncogenic activation of signaling pathways downstream of the EGFR, such as mutations of KRAS and BRAF, play an important role in progression of CRC.
While the treatment of mCRC has improved significantly in patients whose tumors express wild-type KRAS, recent data indicate that patients with wild-type KRAS

that also carry the BRAFV600E mutation have worse outcome, highlighting the need for new therapies in this patient population. Evidence of clinical activity of the selective BRAF inhibitor vemurafenib in patients with BRAF mutant mCRC, supports that BRAF is a therapeutic target for this disease. However, the clinical activity has been more modest than that observed in patients with BRAF mutant melanoma, suggesting that additional factors may modulate the response to BRAF inhibitor in mCRC.
Preclinical work has shown that BRAF inhibition causes a rapid feedback activation of EGFR that supports continued proliferation of BRAF mutant CRC tumor cells, and can be effectively prevented by the combination of vemurafenib with anti-EGFR agents such as erlotinib or cetuximab. Activation of the PI3K/AKT signaling pathway was also shown to confer resistance to vemurafenib in BRAF mutant CRC cells. These reports suggest that both activation of EGFR and aberrant PI3K pathway signaling may explain the limited therapeutic effect of BRAF inhibitor monotherapy in patients with BRAF mutant mCRC.
The effect of combining the selective BRAF inhibitor LGX818 with the EGFR inhibitor cetuximab or erlotinib, or the PI3Kα-specific inhibitor BYL719 resulted in a strong synergistic anti-tumor activity consistent with the recent published reports. Furthermore, the results suggested that additional benefit may be gained through the simultaneous combination of all three inhibitors. The triple combination of LGX818, BYL719 and cetuximab effectively suppressed both RAF/MEK/ERK and PI3K/AKT pathways, and inhibited proliferation to a greater degree in vitro than did any of the dual combinations. These data provide a strong rationale to evaluate the combination of LGX818 and cetuximab ± BYL719 in patients with BRAF mutant mCRC that have a poor clinical outcome, and for whom no targeted therapeutic strategies are effective after failure of standard chemotherapeutic regimens.

Study objective

Primary objectives
Phase Ib: To estimate the MTD and/or RP2D of LGX818 in combination with cetuximab ± BYL719. Incidence of dose-limiting toxicities (DLTs).
Phase II: To compare the efficacy of the dual (LGX818, cetuximab) and triple (LGX818, BYL719, cetuximab) combinations.

Secondary objectives: safety and tolerability, PK, tumor activity, gene alterations/expression relevant to the RAF/MEK/ERK and EGFR/PI3K/AKT pathways in tumor tissue

Study design

Open-label phase Ib dose escalation and randomized phase II study.
Approximately 124 patients.
Screening for KRAS wild-type and BRAF V600 mutation.

The aim of phase Ib (n~24) is to determine the MTD and/or RP2D of LGX818 in combination with cetuximab (dual combination) and the MTD and/or RP2D of LGX818 in combination with BYL719 and cetuximab (triple combination). Cohorts of 3-6 patients. Cycle of 4 weeks.
Dose-escalation decision after 1 cycle.
After the MTD/RP2D of the dual combination has been determined, cohorts of patients will be enrolled to be treated with the triple combination.

Phase II (n~100) will be performed with the highest well-tolerated dose of the dual combination and the triple combination (randomized, 1:1).
Treatment until progression or unacceptable toxicity.
Follow-up for survival.

Intervention

Treatment with LGX818 in combination with cetuximab with or without BYL719.

Cetuximab will be administered intravenously. Startingdose: 400mg/m2 followed by 250 mg/m2 weekly
LGX818 will be supplied as capsules for oral use of 10, 25, 50, and 100 mg dosage strength and will be dosed on a flat scale of mg/day
BYL719 will be supplied as tablets for oral use of 10, 50, and 200 mg dosage strength and will be dosed on a flat scale of mg/day

Study burden and risks

Risks: Adverse events of study medication LGX818 in combination with cetuximab with or without BYL719. The combinations have not yet been tested in humans before.

Burden:
Treatment courses of 4 weeks with weekly cetuximab infusions.
5 visits during courses 1-2 and 4 visits in the subsequent courses. Visit duration 1-4 h. 3 visits of 8-10 h (PK sampling, for phase Ib only).
Weekly blood sampling during course 1 and bi-weekly thereafter. 3-40 ml of blood/occasion.
Additional PK for participants to phase Ib (7-8 samples of 2,5 ml each).
ECGs: 1 (course 2 and thereafter) and 2 during course 1.
Echocardiogram or MUGA-scan at screening and end of treatment.
Eye assessments at screening and every 4 cycles.
Tumor evaluations at screening and every 6 weeks thereafter until disease progression.
Tumor biopsy at screening (part II), during treatment and at disease progression.
Follow-up for survival (phone call every 8 weeks).

Contacts

Public
Array Biopharma Inc.

Cambridge Park Drive 100
Cambridge MA 02140
US
Scientific
Array Biopharma Inc.

Cambridge Park Drive 100
Cambridge MA 02140
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Histological or cytological proof of metastatic colorectal cancer (mCRC)
2. Progression after at least one prior standard of care regimen or be intolerant to irinotecan-based regimens
3. KRAS wild-type and BRAF V600E mutation, or any other BRAF V600 mutation
4. Phase II only: fresh tumor biopsy at baseline
5. Evidence of measurable disease, as determined by RECIST v1.1.
6. Life expectancy >= 3 months
7. ECOG performance status <= 2
Protocol amendment 4: Inclusion criteria 7: ECOG performance status <= 1

Exclusion criteria

1. Phase II only: previous treatment with cetuximab, panitumumab, other EGFR inhibitors, RAF-inhibitors, PI3K-inhibitors, and/or MEK-inhibitors
2. Symptomatic or untreated leptomeningeal disease
3. Symptomatic brain metastasis.
4. Patients with diabetes mellitus requiring insulin treatment and/or with clinical signs or with fasting glucose >=7.8 mmol/L, history of clinically significant gestational diabetes mellitus or documented steroid-induced diabetes mellitus
5. Known acute or chronic pancreatitis
6. Clinically significant cardiac disease including any of the following:
Congestive heart failure requiring treatment (NYHA grade >= 2), LVEF < 45%), history or presence of clinically significant ventricular arrhythmias or atrial fibrillation, clinically significant resting bradycardia, unstable angina pectoris <= 3 months prior to starting study drug, Aacute Myocardial Infarction (AMI) <= 3 months prior to starting study drug, QTcF > 480 msec
7. Any of the following laboratory values at Screening/baseline:
•Absolute neutrophil count (ANC) <1.5 x 109/L
•Platelets < 100 x 109/L
•Hemoglobin < 5,58 mmol/L
•Serum creatinine >1.5 x ULN or Creatinin Clearance < 50% LLN (lower limit of normal)
•Serum total bilirubin >1.5 x ULN, except for patients with Gilbert*s syndrome, who may be included if total bilirubin is <= 3.0 x ULN and direct bilirubin is <= 1.5 x ULN
•AST/SGOT and/or ALT/SGPT > 2.5 x ULN, or > 5 x ULN if liver metastases are present
8. Impairment of gastrointestinal (GI) function or GI disease which may alter the absorption of LGX818
9. Previous or concurrent malignancy. Exceptions: adequately treated basal cell or squamous cell skin cancer; in situ carcinoma of the cervix without evidence of recurrence for at least 3 years prior to study entry; or other solid tumor treated curatively, and without evidence of recurrence for at least 3 years prior to study entry.
10. Pregnant or nursing (lactating) women
11. History of thromboembolic or cerebrovascular events within the last 6 months, including transient ischemic attack, deep vein thrombosis, or pulmonary embolism.
12. Radiation therapy (> 30% of the bone marrow reserve), chemotherapy, biological therapy (e.g., antibodies) within <= 4 weeks
13. Any major surgery within the last 2 weeks prior to starting study drug or who would not have fully recovered from previous surgery
14. Known human immunodeficiency virus (HIV) infection
15. Other severe, acute, or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or study drug administration or that may interfere with the interpretation of study results

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	19-11-2012
Enrollment:	25
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Erbitux
Generic name:	cetuximab
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	niet van toepassing
Generic name:	encorafenib
Product type:	Medicine
Brand name:	niet van toepassing
Generic name:	niet van toepassing

Ethics review

Approved WMO

Date:	15-10-2012
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO Date:	02-11-2012
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	19-12-2012
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	21-12-2012
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	16-01-2013
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	29-01-2013
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	08-02-2013
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	02-08-2013
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	19-08-2013
Application type:	Amendment

Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	18-12-2013
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	09-01-2014
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	10-01-2014
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	14-03-2014
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	25-03-2014
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	23-04-2014
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	24-04-2014
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO	

Date:	30-04-2014
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	22-05-2014
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	30-05-2014
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	05-06-2014
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	12-06-2014
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	19-09-2014
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	17-11-2014
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	09-01-2015
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van

	Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	22-01-2015
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	30-01-2015
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	04-02-2015
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	24-03-2015
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	22-06-2015
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	25-06-2015
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	19-08-2015
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	12-11-2015

Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	02-02-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	12-05-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	25-08-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	31-08-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	11-11-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	01-02-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	09-02-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO Date:	11-04-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	13-04-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	08-11-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	31-01-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	19-04-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Not approved Date:	26-04-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	24-05-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	20-09-2018
Application type:	Amendment

Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	27-09-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	21-03-2019
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	12-04-2019
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

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	EUCTR2012-002138-35-NL
ClinicalTrials.gov	NCT01719380
CCMO	NL41787.031.12

Study results

Results posted: 28-01-2020

First publication
17-12-2019