A phase Ib/II multi-center, open label, dose escalation study of WNT974, LGX818 and cetuximab in patients with BRAFV600-mutant KRAS wild-type metastatic colorectal cancer harboring Wnt pathway mutations

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Primary: Phase Ib: To estimate the MTD(s) and/or RP2D(s) of the triple combination of WNT974, LGX818 andcetuximab in patients with BRAFV600-mutant CRC harboring Wnt pathway mutations.Phase II: To estimate the preliminary anti-tumor activity of the...

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

Summary

ID

NL-OMON45070

Source
ToetsingOnline

Brief title
CWNT974X2102C

Condition

- Gastrointestinal neoplasms malignant and unspecified

Synonym
colorectal cancer; cancer of the intestine

Research involving

Human

Sponsors and support

Primary sponsor: Array Biopharma
Source(s) of monetary or material Support: Array BioPharma Inc

Intervention

Keyword: cetuximab, colorectal cancer, LGX181, WNT974

Outcome measures

Primary outcome

Phase 1b: DLTs.

Phase II: overall response rate (ORR).

Secondary outcome

Phase 1b: ORR.

Both phases: overall survival, time to and duration of response, progression

free survival, disease control rate, adverse effects, frequency of dose

modifications,

Study description

Background summary

Patients with metastatic BRAF-mutant colorectal cancer (CRC) have a very poor prognosis, with a median survival of only 10 months. Initial studies of BRAF inhibitors in this disease have been disappointing, with few objective responses. Based on pre-clinical data demonstrating the importance of an EGFR feedback loop for BRAF inhibitor resistance as well as synergistic activity with the combination of BRAF and EGFR inhibitors in BRAF-mutant CRC models, clinical trials of BRAF inhibitors and EGFR antibodies were initiated. Preliminary clinical efficacy data of LGX818 and cetuximab suggest promising activity with 4 confirmed and 3 unconfirmed PRs of 27 evaluated patients (26%). In addition to BRAFV600 mutations and EGFR activation, Wnt pathway alterations (inactivating mutations in RNF43 and RSPO fusions) are likely to be important

oncogenic drivers in BRAF-mutant CRC. These alterations activate Wnt signals and importantly, are markers for WNT974 sensitivity in preclinical models.
Preclinical studies of the triple combination of WNT974+LGX818+cetuximab in BRAF-mutant, RNF43-mutant or RSPO-fusion positives, using CRC xenograft models demonstrate increased anti-tumor activity as compared to double combinations of LGX818 with cetuximab or LGX818 with WNT974.
These data suggest that the inhibition of the Wnt pathway in addition to inhibition of BRAF and EGFR signals may offer additional clinical benefit to patients with BRAF-mutant CRC.
Based on this rationale, the specific purpose of this Phase Ib/II study is to 1) identify safe and tolerable doses of WNT974+LGX818+cetuximab; and 2) explore the anti-tumor activity of the triple combination.

Study objective

Primary:
Phase Ib: To estimate the MTD(s) and/or RP2D(s) of the triple combination of WNT974, LGX818 and
cetuximab in patients with BRAFV600-mutant CRC harboring Wnt pathway mutations.
Phase II: To estimate the preliminary anti-tumor activity of the RP2D(s) of WNT974 in combination with LGX818 and cetuximab in patients with BRAFV600-mutant CRC harboring Wnt pathway mutations.
Secondary: To assess additional parameters of clinical activity of WNT974 in combination with LGX818 and cetuximab and to characterize the safety and tolerability. To characterize pharmacokinetics of WNT974, its pharmacologically active metabolite LHA333, and LGX818 when used in combination therapy with cetuximab.

Study design

Multicenter phase 1b dose escalation study, for the triple combination of WNT974, LGX818 and cetuximab, followed by a single arm phase II part.
The study treatment will be administered during 28-days cycles. WNT974 and LGX818 will be administered daily orally. Cetuximab will be administered weekly i.v., as recommended by the label.
Treatment period until disease progression or unacceptable side effects.
Patients who discontinue study treatment for any reason other than disease progression will be followed up for progression of disease and all patients will be followed for survival.
Approx. 60 patients.

Intervention

Treatment with WNT974, LGX818 and cetuximab.

Study burden and risks

Risk: Adverse effects of the combination of combination of WNT974-LGX818 and cetuximab. The adverse effects of this combination is not known.
The patient may receive no direct benefit from being in this study. Other disadvantages are the inconveniences of the several tests such as extra blood sampling, intravenous administration of cetuximab, eye exams and skin- and tumorbiopsy.

Burden: The patient needs to go to the hospital more often and will undergo more tests such as ECG, echocardiogram or MUGA, eye exams, more (frequent) blood sampling and imaging scans. The visits may take more time (1-8 hours).Cycles of 4 weeks. Cycle 1: 6 visits, from cycle 2 onwards: 4 visits. Duration mostly 1-4 hours. Some visits 8-9 hours.

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

• Histological or cytological confirmed metastatic colorectal cancer.
• Written documentation of KRAS-wild-type status and BRAFV600 mutation with RNF43 mutations and/or RSPO fusions. See protocol page 37 for details.
• Progression of disease after at least one prior standard of care regimen or intolerance to irinotecan based regimens. See protocol page 37 for details.
• Measurable disease.
• ECOG performance status 0, 1, 2.

Exclusion criteria

• Phase II only: Prior treatment with RAF inhibitors, Wnt pathway inhibitors, cetuximab, panitumumab, and/or other EGFR inhibitors.
• Symptomatic brain metastasis. See protocol page 38 for details.
• Use of strong inhibitors or inducers of CYP3A4/5 or herbal medications. See protocol page 38 for details.
• Acute and chronic pancreatitis, clinically significant cardiac disease. See protocol page 38 for details.
•History of thromboembolic or cerebrovascular events within the last 6 months.
• Radiation therapy that includes >30% of the bone marrow reserve, chemotherapy, biological therapy (e.g., antibodies) within <= 4 weeks (6 weeks for nitrosourea, mitomycin-C), or who have been treated with continuous or intermittent small molecule therapeutics or investigational agents within 5 half-lives of the agent.
• Pregnancy, lactation, inadequate contraception (males and females). See protocol page 39 for details.

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruiting

Start date (anticipated):	18-12-2014
Enrollment:	4
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:	Nog niet van toepassing
Generic name:	encorafenib
Product type:	Medicine
Brand name:	Nog niet van toepassing
Generic name:	Nog niet van toepassing

Ethics review

Approved WMO Date:	08-12-2014
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	10-02-2015
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	13-02-2015
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	26-02-2015

Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	29-07-2015
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	13-08-2015
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:	26-10-2015
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	29-10-2015
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:	13-06-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO Date:	01-07-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	06-09-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	15-09-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	10-11-2016
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:	09-05-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	11-05-2017
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	EUCTR2014-002826-11-NL
CCMO	NL51259.031.14