A phase Ib/II, open-label, multi-center, dose escalation study of MEK162 in combination with panitumumab in adult patients with mutant RAS or wild-type RAS metastatic colorectal cancer

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

Summary

ID

NL-OMON41524

Source
ToetsingOnline

Brief title
MEK162+panitumumab in colorectal cancer (RAS mutant or WT)

Condition

- Gastrointestinal neoplasms malignant and unspecified

Synonym
metastatic colorectal cancer

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Colorectal cancer, MEK162 and panitumumab, RAS mutant, wild-tupe RAS

Outcome measures

Primary outcome

Phase Ib: Incidence of Dose Limiting Toxicities in Cycle 1

Phase II: Outcome: Overall response rate (ORR) as per RECIST v1.1

Secondary outcome

Phase Ib and Phase II: Frequency and severity of AEs, SAEs, changes in

laboratory values, vital signs, and electrocardiograms

Phase Ib only: Objective Response Rate (ORR), Progression-free survival, (PFS),

duration of response

(DOR), disease control rate (DCR) as per RECIST v1.1

Phase II only: Progression-free survival, (PFS), duration of response (DOR),

disease control rate (DCR) as per RECIST v1.1

Study description

Background summary

Colorectal cancer (CRC) is the fourth most frequently diagnosed cancer and second leading cause of cancer death in the United States (US) and in the European Union. In the last decade, substantial advances in the treatment of metastatic colorectal cancer (mCRC) have resulted in an improvement in overall survival (OS) This improvement has occurred with the addition of irinotecan,

oxaliplatin, bevacizumab, cetuximab, and panitumumab to the standard treatment with 5-fluorouracil (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, panitumumab and cetuximab, 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, in particular mutations of KRAS, play an important role in the progression of colorectal cancer. KRAS mutations, which may be present in up to 40% of patients with CRC, have emerged as important predictive markers of primary resistance to anti-EGFR monoclonal antibodies resulting in limited treatment options for metastatic CRC patients displaying KRAS mutations.
In patients with wild-type KRAS CRC, anti-EGFR monoclonal antibodies are an important treatment option. However, resistance to anti-EGFR monoclonal antibodies typically emerge after several months of treatment. The underlying mechanism is not known, but recent data identified KRAS mutations as potential and frequent drivers of acquired resistance to both anti-EGFR monoclonal antibodies, panitumumab and cetuximab. The addition of MEK inhibitors to anti-EGFR monoclonal antibodies may represent a rational strategy to overcome resistance to anti-EGFR monoclonal antibodies. Preliminary activity for this combination has been observed in a clinical trial (Deming 2012). These findings show that co-targeting the EGFR and the downstream molecule MEK might emerge as a potential therapeutic option for patients with mCRC who have progressed on existing standard therapies.

Study objective

The aim of the phase Ib part is to estimate the MTD and/or identify the RP2D for the combination MEK162 and panitumumab, followed by a phase II part to assess the clinical efficacy and to further assess the safety of the combination in selected patient populations.

Study design

This is a multi-center phase Ib/II study. The study has a dose escalation part and a phase II part. Patients will be treated until progression of disease, unacceptable toxicity develops, or withdrawal of informed consent, whichever occurs first.
Cohorts of patients will be treated in the doseescaltion part with the combination until the MTD/RP2D of the combination is identified.
Following MTD/RP2D declaration, additional patients will be enrolled in 4 phase II arms.
Arm 1: mutant RAS mCRC patients who have not been pretreated with an EGFR inhibitor (EGFRi), including EGFR tyrosine kinase inhibitor therapy and/or anti-EGFR monoclonal antibody therapy.

Arm 2: mutant RAS mCRC patients who have been pretreated with anti-EGFR monoclonal antibody therapy, but have not been pre-treated with EGFR tyrosine kinase inhibitor therapy.
Arm 3 patients with WT RAS mCRC who have been pretreated with anti-EGFR monoclonal antibody therapy, but have not been pretreated with EGFR tyrosine kinase inhibitor therapy.
Arm 4: patients with WT RAS mCRC who have not been pretreated with an EGFRi, including EGFR tyrosine kinase inhibitor therapy and/or anti-EGFR monoclonal antibody
therapy.

Intervention

MEK162 tablet for oral use 15mg. Starting dose 45mg BID
Panitumumab intravenous infusion starting dose 6mg/kg Q2W

Study burden and risks

Side effects of the combination of MEK162 and panitumumab.
This combination has not been tested in humans before.
The main side effects of MEK162 (single agent) sofar are: rash or skin irritation, diarrhea, fluid retention, increased creatine phosphokinase (that may indicate muscle inflammation or damage), fatigue, nausea with or without vomiting, changes in vision (such as blurred vision, seeing *floaters* or swelling in or around the eye, constipation, dry mouth, dry skin, stomatitis/mucositis, loss or reduction of appetite, hair loss, taste alteration, high blood pressure, indigestion, muscle weakness, fever, anemia, increase in the value of liver enzymes.
The main side effects of panitumumab are: infusion reactions , allergic reactions , rash, dry skin, itchy skin,
anemia, hypokalemia, hypomagnesaemia, conjunctivitis, alopecia, stomatitis, diarrhea, nausea, vomiting, abdominal pain, constipation, anorexia, decreased weight, fatigue. Pyrexia, asthenia, peripheral edema, back pain, insomnia, cough, dyspnea
The risks related to some study assessments as taking blood and imaging as MUGA-scans and CT-scans.

Burden:
4 visits during Cycle 1 and 2, and 2 visits during the subsequent Cycles. Visit duration 1-4 h.
Blooddraws at each visit (5 to 15 mL blood/each visit, depending on the analysis that will be done).
ECG monitoring: weekly during Cycle 1, bi-weekly during Cycle 2 and once every Cycle thereafter. Echocardiogram or MUGA-scan at screening and cycle 2 and every 3rd cycle thereafter.

Contacts

Public
Array Biopharma

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Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Histological or cytological confirmation of mCRC
2. Progression on or following standard therapy or for whom no standard therapy exists.
3. Written documentation of WT RAS or somatic mutation in exon 2 (codons 12/13), 3 (codons 59/61) or 4 (codons 117/146) in either KRAS or NRAS in medical history.
4. Phase Ib only: Availability of a representative tumor sample at Screening/baseline (newly obtained or if not feasible, archival with a corresponding pathology report)
5. Phase II only: A newly obtained tumor sample must be collected to document the WT RAS or somatic mutation status (as described above) during the molecular pre-screening period at a local or a Novartis designated central laboratory. The tumor sample must be collected after the last anti-neoplastic treatment, and within 3 months prior to start of treatment on this study.
6. Evidence of measurable disease, as determined by RECIST v1.1.

7. ECOG performance status <= 2.

Exclusion criteria

1. Phase II arms 1 and 4 only: previous treatment with cetuximab, panitumumab, and/or other EGFR inhibitors
2. Previous treatment with MEK-inhibitors
3. History of severe infusion reactions to monoclonal antibodies.
4. Known hypersensitivity and/or contraindication to any of the study medications or their excipients
5. Symptomatic or untreated leptomeningeal disease.
6. Symptomatic brain metastasis.
7. History or current evidence of retinal disease or ophthalmopathy as assessed by ophthalmologic examination at baseline that would be considered a risk factor for CSR/RVO
8. History of keratitis or ulcerative keratitis.
9. Known acute or chronic pancreatitis.
10. Clinically significant cardiac disease including any of the following:
• Congestive heart failure (NYHA grade >= 2),
• Left ventricular ejection fraction (LVEF) < 45%
• Uncontrolled arterial hypertension (as defined > 140 (systolic) /100 (diastolic) mmHg
• 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
• Acute Myocardial Infarction (AMI) <= 3 months prior to starting study drug
• QTcF > 480 msec
11. Patients with any of the following laboratory values at Screening/baseline:
• Absolute neutrophil count (ANC) <1,500/mm3 [1.5 x 109/L]
• Platelets < 100,000/mm3 [100 x 109/L]
• Hemoglobin < 9.0 g/dL
• Serum creatinine >1.5 x ULN (upper limit of normal) or calculated or directly measured CrCl < 50% LLN (lower limit of normal)
• Serum total bilirubin >1.5 x ULN
• AST/SGOT or ALT/SGPT > 2.5 x ULN, or > 5 x ULN if liver metastases are present
• Magnesium < the lower limit of normal
12. Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of oral MEK162.
13. Previous or concurrent malignancy. Exceptions: adequately treated basal cell or squamous cell skin cancer; in situ carcinoma of the cervix, treated curatively and 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.
14. History of thromboembolic or cerebrovascular events within the last 6 months.
15. Patients who have received 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 (or <= 4

weeks when half-life is unknown) prior to starting study drug or who have not recovered to grade <= 1 from the side effects of such therapy (except alopecia).
16. Any major surgery within the last 2 weeks prior to starting study drug or who would not have fully recovered from previous surgery.
17. Known human immunodeficiency virus (HIV) infection.
18. Other severe, acute, or chronic medical or psychiatric condition or laboratory abnormality

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	26-02-2014
Enrollment:	7
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Vectibix
Generic name:	panitumumab
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	18-10-2013
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO Date:	29-01-2014
Application type:	First submission
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:	14-05-2014
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	15-10-2014
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	17-10-2014
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	14-11-2014
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	20-11-2014
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:	26-06-2015
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:	12-11-2015
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	EUCTR2013□001986□18-NL
ClinicalTrials.gov	NCT01927341
CCMO	NL46448.031.13