Phase I/II study with galunisertib (LY2157299) combined with capecitabine in patients with advanced chemotherapy resistant colorectal cancer and an activated TGF-* signature

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Part I of this study is designed to identify the recommended phase 2 dose of the combination regimen of galunisertib/capecitabine as second line treatment in patients with 5-FU or capecitabine resistant colorectal carcinoma. Part II is designed to...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Gastrointestinal neoplasms malignant and unspecified
Study type	Observational invasive

Summary

ID

NL-OMON46888

Source
ToetsingOnline

Brief title
M16TGA: Galunisertib and capecitabine in resistent colorectal cancer

Condition

- Gastrointestinal neoplasms malignant and unspecified

Synonym
bowel cancer, colorectal carcinoma

Research involving
Human

Sponsors and support

Primary sponsor: Antoni van Leeuwenhoek Ziekenhuis
Source(s) of monetary or material Support: europese unie

Intervention

Keyword: activated TGF-beta signature, capecitabine, colorectal carcinoma, galunisertib

Outcome measures

Primary outcome

Phase I: To determine the recommended phase 2 dose (RP2D) of galunisertib plus capecitabine in patients with chemotherapy resistant activated TGF-* signature-like CRC.

Phase II: To determine the anti-tumor activity, as measured by response rate (RR) of galunisertib in combination with capecitabine in patients with chemotherapy resistant activated TGF-* signature-like CRC.

Secondary outcome

- To characterize the safety and tolerability of galunisertib in combination with chemotherapy regimens, as assessed by the incidence and severity of adverse events
- To assess anti-tumor activity of galunisertib in combination with chemotherapy, as measured by duration of response, time to response and, progression free survival (phase II only) and overall survival (phase II only)
- To determine the pharmacokinetic profile of galunisertib in combination with chemotherapy, as measured by plasma concentrations
- To explore genetic determinants of response to galunisertib in combination

with chemotherapy, as measured by baseline molecular status of potential

predictive markers of tumor response

- To explore the potential mechanism of resistance to galunisertib in

combination with chemotherapy, as measured by gene alterations/expression

profiles (e.g. baseline, relapse) in tumor tissue upon progression

Study description

Background summary

A pre-clinical study, using a large-scale RNAi screen, identified MED12, a component of the transcriptional MEDIATOR complex that is mutated in cancers, as a determinant of response to chemotherapy drugs such as 5-Fluorouracil (5-FU). Loss of MED12 induces an epithelial-mesenchymal transition (EMT) like phenotype and leads to activation of the tumor growth factor * receptor (TGF-*R), which is sufficient to cause drug resistance against multiple anti-cancer drugs.(1) Chemotherapy with 5-FU did not lead to noticeable change in disease specific survival (DSS) of patients with MED12 knockdown (MED12KD) -like colorectal tumors, whereas it did cause a significant increase in DSS of patients with MED12 wild-type (MED12WT) -like tumors. This indicates that the MED12KD signature predicts response to 5-FU-based chemotherapy in patients with colorectal cancer (CRC), consistent with the finding that MED12KD confers resistance to 5-FU. Inhibition of TGF-* signalling in MED12KD cells with small-molecule drugs can reverse this resistance to anti-cancer drugs.(2)

Hence, there is a strong rationale for combining chemotherapeutic agents with TGF-* inhibitor galunisertib in patients with chemotherapy resistant TGF-* signature tumors.

Study objective

Part I of this study is designed to identify the recommended phase 2 dose of the combination regimen of galunisertib/capecitabine as second line treatment in patients with 5-FU or capecitabine resistant colorectal carcinoma. Part II is designed to obtain proof of principle of the galunisertib plus capecitabine combination in patients with chemo-resistant colorectal carcinoma.

Study design

This is a multi-center pharmacological open-label non randomized proof of

principle study consisting of two parts: a phase I dose-finding study evaluating the recommended phase II dose of galunisertib in combination with capecitabine; and a phase II study with Simon two-stage design investigating the anti-tumor activity and safety of galunisertib (LY2157299) in combination with capecitabine.

Phase I:
Dose-finding of the galunisertib/capecitabine combination
This study will first explore the optimal dose and safety of the combination of galunisertib and capecitabine when given together. After inclusion and treatment of 6 patients we will evaluate toxicity and decide whether or not to start with phase II of this study.

DOSE-LEVEL 1
The galunisertib dose will be 150 mg twice daily (BID) for the first 14 days of every 4-week cycle, which is the maximum tolerated dose when given as single agent. Capecitabine will also be dosed during the first 14-days on time of galunisertib at 1000 mg/m2 twice daily (BID) and will in case of toxicities be reduced according to standard care.

MAXIMUM DOSES
Dose levels beyond the single agent MTD will not be investigated. If necessary the dose of galunisertib can be decreased according to protocol guidelines.

Phase II:
The optimal dose-level as determined in Phase I will be taken to evaluate the anti-tumor activity and safety of galunisertib/capecitabine combination.
A total of 15 evaluable patients will be treated in the first stage of the phase II study with galunisertib plus capecitabine chemotherapy. This concerns 15 patients with CRC who will be treated with galunisertib + capecitabine. If at least 2 responses are obtained, an additional 10 patients with CRC will be treated in stage two of the study. However, if less than 2 responses are obtained the study will be terminated. The treatment will be declared effective if 6 or more responses are observed in total.

Study burden and risks

- Blood will be drawn for pharmacokinetic, pharmacodynamic and pharmacogenetic research
- Tumor biopsies will be taken pre-, upon and at end of treatment for histological analyses of biomarkers, genetics and immune infiltration
- Patients will be asked to keep a diary and note daily what they ate and when they took the medication.

Contacts

Public
Antoni van Leeuwenhoek Ziekenhuis

Plesmanlaan 121
Amsterdam 1066 CX
NL
Scientific
Antoni van Leeuwenhoek Ziekenhuis

Plesmanlaan 121
Amsterdam 1066 CX
NL

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 CRC;
2. Disease progression or relapse upon at least one line of treatment for advanced CRC with fluoropyrimidine containing chemotherapy as single agent or in combination (combinations with oxaliplatin, irinotecan, bevacizumab and cetuximab/panitumumab are allowed);
3. Written documentation of activated TGF-* signature-like gene signature, as determined by the validated assay of Agendia;
4. Age * 18 years;
5. Able and willing to give written informed consent;
6. WHO performance status of * 1;
7. LVEF * 55%;
8. Able and willing to undergo blood sampling for PK and PD analysis;
9. Able and willing to undergo tumor biopsies before start, during treatment and at the end of

treatment
10. Life expectancy * 3 months allowing adequate follow up of toxicity evaluation and anti-tumor activity;
11. Evaluable disease according to RECIST 1.1 criteria (measurable disease for the phase II part; evaluable disease is sufficient for the phase I part);
12. Minimal acceptable safety laboratory values
a. ANC of * 1.5 x 10^9 /L
b. Platelet count of * 100 x 10^9 /L
c. Hepatic function as defined by serum bilirubin * 1.5 x ULN, ALAT and ASAT * 3.0 x ULN, or ALAT and ASAT * 5 x ULN in patients with liver metastases
d. Renal function as defined by serum creatinine *1.5 x ULN
e. Creatinine clearance * 50 ml/min (by Cockcroft-Gault formula or MDRD);
13. Negative pregnancy test (urine or serum) for female patients with childbearing potential.

Exclusion criteria

1. Any treatment with investigational drugs within 30 days prior to receiving the first dose of investigational treatment;
2. Known or suspected dihydropirimidine dehydrogenase deficit (Mutant for DPD*2A genotype, 1236 GA genotype, 1679TG genotype and 2846A>T genotype);
3. Symptomatic or untreated leptomeningeal disease;
4. Symptomatic brain metastasis. Patients previously treated or untreated for these conditions that are asymptomatic in the absence of corticosteroid therapy are allowed to enrol. Brain metastasis must be stable with verification by imaging (e.g. brain MRI or CT (<21 days before start of treatment) completed at screening demonstrating no current evidence of progressive brain metastases). Patients are not permitted to receive enzyme inducing anti-epileptic drugs or corticosteroids;
5. History of cardiac disease, including myocardial infarction within 6 months before study entry, unstable angina pectoris, New York Heart Association Class III/IV congestive heart failure, or uncontrolled hypertension, major cardiac abnormalities, a predisposition for developing aneurysms including family history of aneurysms, Marfan syndrome, bicuspid aortic valve, or evidence of damage to the large vessels of the heart.
6. Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of oral galunisertib (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, small bowel resection);
7. Woman who are pregnant or breast feeding;
8. Radio- or chemotherapy within the last 2 weeks prior to receiving the first dose of investigational treatment. Palliative radiation (1x 8Gy) is allowed;
9. Patients who have undergone any major surgery within the last 2 weeks prior to starting study drug or who would not have fully recovered from previous surgery;
10. Active infection requiring systemic antibiotics or uncontrolled infectious disease;
11. Patients with a known history of hepatitis B or C or known Human Immunodeficiency Virus HIV-1 or HIV-2 type patients;
12. 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 and, in the judgment of the investigator, would make the patient inappropriate for the study;
13. Known hypersensitivity to one of the study drugs or excipients.
14. For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods with a failure rate of <1% per year (when used consistently and correctly) during the treatment period and for at least 90 days after the last dose of galunisertib and/or capecitabine.
15. For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating sperm, as defined in section 5.2.4.

Study design

Design

Study phase:	2
Study type:	Observational invasive
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	10
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	galunisertib
Generic name:	galunisertib
Product type:	Medicine
Brand name:	Xeloda
Generic name:	capecitabine
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	30-12-2016
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	29-09-2017
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	03-11-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	09-11-2017
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:	29-08-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	30-08-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO	

Date:	17-10-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	25-10-2018
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	EUCTR2016-002349-50-NL
CCMO	NL59103.031.16