Phase I/II study with galunisertib combined with capecitabine in patients with advanced chemotherapy resistant colorectal cancer with peritoneal metastases

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This study has been transitioned to CTIS with ID 2024-518980-37-00 check the CTIS register for the current data. With this clinical study, we aim to gain more information about the pharmacological characteristics, safety profile, tolerability and...

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

Summary

ID

NL-OMON53340

Source
ToetsingOnline

Brief title
Galunisertib combined with capecitabine in advanced CRC with PM

Condition

- Malignant and unspecified neoplasms gastrointestinal NEC

Synonym
colorectal cancer with peritoneal metastases

Research involving
Human

Sponsors and support

Primary sponsor: Antoni van Leeuwenhoek Ziekenhuis
Source(s) of monetary or material Support: Fase 1 gelden Antoni van Leeuwenhoek

Intervention

Keyword: capecitabine, colorectal cancer, galunisertib, peritoneal metastases

Outcome measures

Primary outcome

The main endpoints of part 1 of this study (phase I) is the safety profile of galunisertib and capecitabine when given together and finding the optimal doses for continuation in part 2 (RP2D). The main endpoint of phase II is to evaluate the anti-tumor activity of the combination as measured by ORR according to RECIST 1.1 criteria. With 6 or more responses out of 25, the treatment will be declared to be effective in the selected patient population

Phase I: To determine the RP2D of galunisertib plus capecitabine in patients with advanced chemotherapy resistant CRC with PM.

Phase II: To determine the anti-tumor activity as measured by ORR of galunisertib in combination with capecitabine in patients with advanced chemotherapy resistant CRC with PM

Secondary outcome

Phase II:

- To characterize the safety and tolerability of galunisertib in combination with capecitabine as assessed by the incidence and severity of adverse

events.

- To assess anti-tumor activity of galunisertib in combination with

capecitabine, as measured by DOR, TTR, PFS and OS (phase II only).

- To determine pharmacokinetics of galunisertib in combination with

capecitabine as measured by plasma concentrations.

Study description

Background summary

Colorectal cancer (CRC) is globally a commonly diagnosed type of cancer. Treatment options are heterogeneous. Survival rates depend among other on the extent of the disease at time of diagnosis, molecular characteristics and the presence of specific genetic alterations. According to IKNL (Integraal Kankercentrum Nederland) the 5-years survival rates of patients with stage IV colorectal carcinoma decreases by 80% compared with patients diagnosed in stage I (96% vs. 12%). Patients with mesenchymal subtype CRC (CMS4) have the worst outcome, since these patients experience a limited benefit from chemotherapy because of resistance to most cytotoxic agents. The majority of these patients have peritoneal metastases (PM). Previous preclinical research showed that the CMS4 subtype has elevated TGF-β signaling causing drug resistance against multiple anticancer drugs. Inhibition of TGF-β signaling in CMS4 CRCs could be a beneficial approach to revert the unresponsiveness of the tumor cells to 5-fluorouracil(5-FU)-based chemotherapy.

Study objective

This study has been transitioned to CTIS with ID 2024-518980-37-00 check the CTIS register for the current data.

With this clinical study, we aim to gain more information about the pharmacological characteristics, safety profile, tolerability and efficacy of galunisertib in combination with capecitabine in patients with PM from CRC.

The ultimate goal is to utilize the findings of this trial to improve the survival rates of a subgroup of patients with metastatic CRC (mCRC) who otherwise have no treatment options left.

Phase I: To determine the safety and recommended phase 2 dose (RP2D) of galunisertib plus capecitabine in patients with advanced chemotherapy resistant

CRC with PM, who progressed after standard chemotherapy.

Phase II: To determine the anti-tumor activity, as measured by objective response rate (ORR) of galunisertib in combination with capecitabine in patients with advanced chemotherapy resistant CRC with PM. Secondary objectives include the safety and tolerability of the combination therapy, duration of response (DOR), time to response (TTR), progression free survival (PFS), overall survival (OS), the pharmacokinetic profile of galunisertib in combination with capecitabine and exploratory genetic determinants of response and resistance.

Study design

This is a two-center open-label non-randomized proof of principle study consisting of a dose-finding part (phase I) and phase II study with Simon two-stage design investigating the anti-tumor activity of the combination of capecitabine and galunisertib.

Intervention

Galunisertib will be dosed 150 mg twice daily (BID) for the first 14 days of every 4-week cycle. If necessary, the dose of galunisertib and the dose of capecitabine can be decreased. Capecitabine will be dosed during the first 14 days of every cycle at 1000 mg/m2 BID.

Study burden and risks

Patients are at risk for capecitabine and galunisertib related side effects and side effects of other interventions such as blood draw and/or tissue biopsies. As both drugs can be safely given in monotherapy and have little overlapping toxicities, we expect we will be able to use full monotherapy RP2D*s also in the combination. A structured risk analysis including all study details is given in chapter 13 of the protocol.

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

1. Histological or cytological proof of CRC with at least confirmed peritoneal metastases (presence of additional extraperitoneal metastases is allowed);
2. Disease progression or relapse upon treatment for advanced CRC with fluoropyrimidine containing chemotherapy as single agent or in combination with other anti-cancer drugs, with no treatment options at time of inclusion (combinations with oxaliplatin, irinotecan, bevacizumab and cetuximab/panitumumab are allowed);
3. Age >= 18 years;
4. Able and willing to give written informed consent and informed consent form must have been signed before start of the trial;
5. WHO performance status of <=1;
6. Able and willing to undergo blood sampling for PK analysis;
7. Able and willing to undergo tumor biopsy before start, during treatment and at the end of treatment;
8. Life expectancy > 3 months allowing adequate follow up of toxicity and anti-tumor activity;
9. Evaluable disease according to RECIST 1.1 criteria (measurable disease for the phase II part; evaluable disease is sufficient for the phase I part);
10. Minimal acceptable safety laboratory values
a. ANC of >=1.5 x 109 /L
b. Platelet count of >=100 x 109 /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);
11. Negative pregnancy test (urine or serum) for female patients with childbearing poten-tial.
12. Able and willing to swallow tablets.

Exclusion criteria

1. Any treatment with investigational drugs within 30 days prior to receiving the first dose of investigational treatment and/or radio- or chemotherapy within the last 2 weeks prior to receiving the first dose of investigational treatment. Palliative radia-tion (1x 8Gy) is allowed; except radiotherapy focused on the liver;
2. Known or suspected complete or partial dihydropyrimidine dehydrogenase deficien-cy (Mutant for DPD*2A genotype, 1236G>A genotype, 1679T>G 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 al-lowed to enrol. Brain metastasis must be stable with verification by imaging (e.g. brain MRI or CT completed at screening demonstrating no current evidence of pro-gressive 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 first dose of study medication, unstable angina pectoris, New York Heart Associa-tion 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. Treatment with CYP3A4 inducers or inhibitors and/or concomitant treatment with CYP2C9 substrates with narrow therapeutic window, including but not limited to vit-amin K antagonizing anticoagulants (e.g. acenocoumarol, phenprocoumon and war-farin) and phenytoin is not allowed;
7. 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, major small bowel surgery);
8. Woman who are pregnant or breast feeding;
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 abnor-mality 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.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	28-07-2023
Enrollment:	31
Type:	Actual

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:	06-03-2023
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	04-05-2023
Application type:	First submission
Review commission:	METC NedMec

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
EU-CTR	CTIS2024-518980-37-00
EudraCT	EUCTR2022-004167-25-NL
CCMO	NL83627.041.23