A Phase 2, Open Label, Multicenter, Randomized Trial Comparing Tivozanib in Combination with mFOLFOX6 with Bevacizumab in Combination with mFOLFOX6 in Stage IV Metastatic Corectal Cancer (mCRC) Subjects

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PrimaryTo compare progression-free survival (PFS) between tivozanib in combination with mFOLFOX6 and bevacizumab in combination withmFOLFOX6 based on investigator radiological tumor assessmentSecondary• Progression Free Survival (PFS) based on...

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

Summary

ID

NL-OMON39372

Source
ToetsingOnline

Brief title
4130-CL-0201

Condition

- Gastrointestinal neoplasms malignant and unspecified

Synonym
Bowel cancer, Metastatic colorectal cancer (CRC)

Research involving

Human

Sponsors and support

Primary sponsor: Astellas Pharma
Source(s) of monetary or material Support: Farmaceutische industrie

Intervention

Keyword: Bevacizumab, Metastatic Colorectal Cancer, Stage IV, Tivozanib

Outcome measures

Primary outcome

Primary efficacy analysis: median Progression Free Survival (PFS). PFS is

defined as the time from randomization until radiological

progression assessed by the investigator or death due to any cause. PFS will be

compared between two treatment arms.

Secondary outcome

Secondary efficacy analyses: objective response rate (ORR), progression free

survival (PFS) based on independent radiological review (IRR), overall survival

(OS), time to treatment failure (TTF), and the duration of the response (DoR)

will be compared between two treatment arms.

Study description

Background summary

Metastatic coloncancer (mCRC) is the third most diagnosed cancer in men, the second in women and the second most commonly leading cause of cancer death in Europe. This number is only rising.

The Vascular Endothelial Growth Factor (VEGF) pathway is a well-defined signaling pathway known to be required for normal development of the vasculature as well as for the pathologic angiogenesis that accompanies cancer

and other diseases.

Tivozanib has demonstrated activity against all 3 VEGF receptors. Tivozanib inhibits the development of new blood vessels. The use of Tivozanib with mFOLFOX6 might be responsible for the cancer cells to stop growing.

Study objective

Primary
To compare progression-free survival (PFS) between tivozanib in combination with mFOLFOX6 and bevacizumab in combination with mFOLFOX6 based on investigator radiological tumor assessment

Secondary
• Progression Free Survival (PFS) based on Independent Radiological Review (IRR)
• Overall survival (OS)
• Objective Response Rate (ORR)
• Duration of Response (DoR)
• Time to Treatment Failure (TTF)
• Health-Related Quality of Life (HRQoL)
• Safety and tolerability
• Assess relationships that may be predictive of the level of response to tivozanib/mFOLFOX6 vs. bevacizumab/mFOLFOX6
• Lactate Dehydrogenase (LDH)
• Vascular Endothelial Growth Factor (VEGF) A, C, D
• CD68 and myeloid-derived gene signature (MGS)
• Serum soluble cytokines

Exploratory
• Tivozanib exposure and relation to clinical outcome
• Pharmacogenomic evaluation of the association of genetic variations in the host DNA and response (safety, tolerability, pharmacokinetics and efficacy) following treatment with each regimen
• Pharmacogenomic exploratory relationship of dihydropyrimidine dehydrogenase (DPD) and thymidylate synthase (TS) to toxicity and efficacy
• Evaluation of the association of the hypoxia multigene signature and clinical response
• The association between change in tumor size and PFS/OS outcome

Study design

This is a Phase 2, open label, multicenter, randomized trial comparing tivozanib in combination with mFOLFOX6 to bevacizumab in combination with mFOLFOX6 as first line therapy in Stage IV metastatic colorectal cancer (mCRC). There are two treatment arms: Arm A (tivozanib/mFOLFOX6) and Arm B

(bevacizumab/mFOLFOX6).

Intervention

Tivozanib will be administered orally at a dose of 1.5 mg daily beginning on Day 1 of each Cycle for 21 days followed by 7 days off treatment. One Cycle will be defined as 28 days.

Bevacizumab will be administered as an intravenous infusion at a dose of 5 mg/kg every 2 weeks beginning on Day 1 of Cycle 1. Subjects will receive 2 treatments of bevacizumab in each treatment Cycle, Day 1 and Day 15.

All subjects will receive mFOLFOX6 chemotherapy every two weeks starting on Day 1 of Cycle 1. Subjects will receive 2 treatments of mFOLFOX6 in each treatment Cycle, Day 1 and Day 15. The mFOLFOX6 regimen is described below:
Oxaliplatin: Days 1 and 15
• 85 mg/m2 IV bolus in 500 mL of D5W over 2 hours
Leucovorin Calcium: Days 1 and 15
• 400 mg/m2 IV bolus in 500 mL of D5W over 2 hours (may be given concurrently with oxaliplatin through a separate IV line)
Fluorouracil Bolus: Days 1 and 15
• 400 mg/m2 IV bolus over 5-15 minutes
Fluorouracil Infusion: Days 1-3 and 15-17
• 2400 mg/m2continuous IV infusion via infusion pump over 46-48 hours or infusion duration per institutional guidelines

Study burden and risks

Tivozanib has been tested already in several human studies.The most frequent side effects experienced by patients receiving tivozanib was high blood pressure.
The study drug Tivozanib can have the following side effects:
*occurred at > 5% of subjects: • High blood pressure • Hoarseness (rough sounding voice) • Feeling tired or weak • Diarrhea • Shortness of breath • Feeling sick to the stomach • Changes in urine tests (protein in the urine) that may indicate kidney problems • Sores in the mouth or other mucous membranes • Headache • Not feeling hungry • Redness, pain/swelling or blisters on the hands and feet • Vomiting • Weight loss • Joint aches and pain • Rash • Changes in thyroid tests that may be associated with symptoms like feeling tired, weight gain and feeling cold • Bleeding (nose bleeds, coughing up blood, blood in the urine and other types of bleeding)

*occurred at 2%-5% of subjects: • Heart attack and stroke • Blood clots in your arteries

*occurred at <2% subjects: • Blood clots in your veins Chest pain related to

decrease of blood flow to the heart • Dehydration (due to vomiting and/or diarrhea)

Other Side Effects seen in less than 2% of subjects and are not considered expected with tivozanib monotherapy, but are also seen with other similar drugs: • The heart is not able to pump blood properly (called *Congestive Heart Failure* or *CHF*), which can cause weakness and tiredness, fluid retention, and fluid build-up in the lungs, which can cause shortness of breath. This may be serious or life-threatening • Perforation of the intestine (gut) • Changes in liver tests that may indicate liver problems

Combining tivozanib and mFOLFOX6 chemotherapy was done in a small population of patients. The most common side effects experienced were feeling sick to one*s stomach, tiredness, vomiting, and numbness and tingling and cramping of the hands or feet often triggered by cold.

Procedures during the study (the amount of procedures depends on the study duration of the patient):
* 6 times (ECG (screening cycle 1 D1 + D15 and cycle 2 D15 (2 times), end of treatment)
* 1 time (stored) tumorbiopsy
* physical examination and vital signs (screening, day 1 and 15 of every cycle, end of treatment)
* urinalyses (screening, day 1 and 15 of every cycle (except for cycle 1; only day 15), end of treatment)
* CT/MRI scan (screening, day 15 of every cycle (except for cycle 1), end of treatment, follow-up visits)
*FACT-C-, the FCSI- and the EQ-5D-questionnaire (screening, day 1 of every cycle (except for cycle 1), end of treatment)

Contacts

Public
Astellas Pharma

Sylviusweg 62
Leiden 2333 BE
NL
Scientific
Astellas Pharma

Sylviusweg 62
Leiden 2333 BE
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. The subject is male or female, aged 18 years or older.
2. The subject has histologically or cytologically confirmed mCRC for which bevacizumab/ mFOLFOX6 chemotherapy regimen would be the appropriate treatment per the investigator.
3. The subject has at least one measurable lesion by RECIST Version 1.1. A lesion that has received prior radiotherapy may only be counted as
a target lesion if it has progressed since radiotherapy as determined by
PI or radiologist assessment.
4. The subject has had no prior systemic chemotherapy for advanced colorectal cancer; no fluorouracil containing adjuvant therapy in previous 6 months.
5. The subject has an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
6. Female subject must be either:
-post-menopausal (defined as at least 1 year without any mensus) prior to Screening, or
- premenarchal prior to Screening, or
- documented surgically sterile or status post hysterectomy (at least 1 month prior to Screening), or
- if of childbearing potential, must have a negative serum or urine pregnancy test at Screening and must be using highly effective contraception
7. Male subject and their female spouses/partners who are of childbearing potential must be using highly effective contraception consisting of two forms of birth control (one of which must be a barrier method) starting Screening and continue throughout the study period and for 90 days after final study drug administration.
8) Female subject must not be breastfeeding at Screening or during the study period and for 90 days after final study drug administration.
9) Female subject must not donate ova starting at Screening and throughout the study period and for 90 days after final study drug administration.
10) Male subject must not donate sperm starting at Screening and throughout the study period and for 90 days after final study drug administration.

11) Subject agrees not to participate in another investigational study while on study treatment.

Exclusion criteria

The subject has;
1.- had any prior VEGF-directed therapy including VEGF antibody or any other agent or investigational agent targeting the VEGF pathway.
2.- has primary CNS malignancies or CNS metastases; subjects with previously treated brain metastases will be allowed if the brain metastasis have been stable without steroid treatment for at least 3 months following prior treatment (radiotherapy or surgery).
3.- has any of the following hematologic abnormalities: • Hemoglobin >= 9.0 g/dL (90 g/L, 5.5854 mmol/L) • ANC <2000 per mm3 • Platelet count <100,000 per mm3 • PT or PTT > 1.5 X ULN
4.-has any of the following serum chemistry abnormalities: • Total bilirubin > 1.5 X ULN (or > 2.5 X ULN for subjects with Gilbert*s syndrome) • AST or ALT > 2.5 X ULN (or > 5 X ULN for subjects with liver metastasis) • Alkaline phosphatase > 2.5 X ULN (or > 5 X ULN for subjects with liver or bone metastasis) • Serum albumin < 2.0 g/dL • Creatinine > 1.5 X ULN (or calculated creatinine clearance < 60mL/min/1.73m2) • Proteinuria > 2+ by urine dipstick; protein greater than 2+ must have 24-hour urine collection that is less than 2 gm/24hr
5. The subject has significant cardiovascular disease
6. The subject has significant thromboembolic or vascular disorders within 6 months prior to administration of first dose of study drug.
7. The subject has a non-healing wound, bone fracture, or skin ulcer.
8. The subject has inadequate recovery from any prior surgical procedure or major surgical procedure within 4 weeks prior to administration of first dose of study drug, or anticipation of major surgical procedure during the course of the study.
9. The subject has history of significant gastrointestinal (GI) toxicity, diarrhea, or stomatitis within the last 6 weeks.
10. The subject has an active peptic ulcer disease, inflammatory bowel disease, ulcerative colitis, or other gastrointestinal condition with increased risk of perforation.
11. The subject has history of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 4 weeks prior to administration of first dose of study drug.
12. The subject has a serious/active infection or infection requiring antibiotics.
13. The subject has significant bleeding disorders within 6 months prior to administration of first dose of study drug.
14. The subject has currently active second primary malignancy, including hematologic malignancies, other than non-melanoma skin cancers, non-metastatic prostate cancer and in situ cervical cancer and ductal or lobular carcinoma in situ of the breast. Subject is not considered to have currently active malignancy if they have completed anti-cancer therapy and have been disease free for > 5 years.
15. The subject has history of allergic reactions, or intolerance, attributed to compounds of similar chemical or biologic composition to 5-fluorouracil, history of Grade 3 hypersensitivity to oxaliplatin, history of allergic reaction to folic acid.
The subject has a;

17.- known history of genetic or acquired immune suppression disease including HIV; subjects on immune suppressive therapy for organ transplant.
18. - an inability to swallow pills, malabsorption syndrome or gastrointestinal disease that would severely affect the absorption of tivozanib, major resection of the stomach or small bowel, or gastric bypass.
19.- uncontrolled neuro-psychiatric disorder or altered mental status precluding informed consent or necessary testing.
20.- peripheral neuropathy >= Grade 2.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	06-02-2013
Enrollment:	17
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Tivozanib hydrochloride monohydrate
Generic name:	-

Ethics review

Approved WMO Date:	21-02-2012
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	10-07-2012
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	19-12-2012
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	31-01-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	28-02-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	16-05-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	05-06-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	11-07-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	01-08-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO	

Date:	22-10-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	03-03-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	10-04-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	03-06-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	19-06-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	15-07-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	EUCTR2011-003502-24-NL
ClinicalTrials.gov	NCT01478594
CCMO	NL38959.042.12