A phase 2 study of EZN-2208 (PEG-SN38) administered with or without cetuximab in patients with metastatic colorectal carcinoma (mCRC)

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Primary Objective• For Arms A, B, and C: Determine the overall response rate (RR) of EZN-2208 for two distinct cohorts of patients with mCRC- Patients with mutated K-RAS tumors (Arm A)- Patients with wild-type K-RAS tumors (Arms B and C)• For Arms B...

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

Summary

ID

NL-OMON34687

Source
ToetsingOnline

Brief title
EZN-2208-004

Condition

- Malignant and unspecified neoplasms gastrointestinal NEC

Synonym
colorectal carcinoma; colorectal cancer

Research involving
Human

Sponsors and support

Primary sponsor: Enzon Pharmaceuticals, Inc.

Source(s) of monetary or material Support: Enzon

Intervention

Keyword: colon carcinoma, K-RAS, metastatic, PEG-SN38

Outcome measures

Primary outcome

For Arms A, B, and C: Determine the overall response rate (RR) of EZN-2208 for

two distinct cohorts of patients with mCRC

- Patients with mutated K-RAS tumors (Arm A)

- Patients with wild-type K-RAS tumors (Arms B and C)

For Arms B and C (wild-type K-RAS tumors): Determine the progression-free

survival (PFS)

Secondary outcome

• Evaluate the duration of response for each treatment arm

• Evaluate the PFS for Arm A

• Evaluate overall survival (OS) for each treatment arm

• Evaluate safety and toxicity for each treatment arm

• For patients with wild-type K-RAS tumors, benchmark the primary and secondary

endpoints observed in Arm B (EZN-2208 + cetuximab) with those observed in Arm C

(irinotecan + cetuximab)

• If possible, to evaluate the peripheral blood mononuclear cell (PBMC)

genotype (e.g., uridine diphosphate-glucuronosyl-transferase isoform 1A1

[UGT1A1]) to detect changes in genes that may affect how the anticancer drugs

work or are degraded, and to see if these changes affect the study treatment or

side effects. Patients may participate in this study even if they do not agree

to the molecular profile testing.

• If possible, to evaluate biomarkers in a sample of the original tumor biopsy.

Patients may participate in this study even if they do not agree to allow the

tumor biopsy testing.

Study description

Background summary

The treatment of patients with colorectal cancer that has spread or metastasized depends upon the extent and location of the tumor. Cure is not possible for most patients with metastatic colorectal cancer, although some patients who have limited involvement (particularly restricted to the liver or lung) can be cured with surgery. For others, chemotherapy is the most appropriate option. Chemotherapy does not cure metastatic colorectal cancer, but it can improve symptoms and prolong life.
The combination of cetuximab + irinotecan in the treatment of mCRC with wild-type K-RAS tumours has demonstrated a RR ranging from 21% to 65%. However, recent data demonstrate that cetuximab lacks efficacy in patients with mutated K-RAS tumors. Numerous studies have demonstrated that the combination of cetuximab + irinotecan has 0% response in patients with mutated K-RAS colorectal cancer (CRC) progressing after irinotecan therapy.
Of note, the lack of activity of cetuximab in this setting implies that no currently approved therapy is active for patients with metastatic CRC and K-RAS mutation who progress after therapy with irinotecan, oxaliplatin, and fluoropyrimidine.
Preclinical data suggest that EZN-2208 may be a promising anticancer agent in a wide variety of clinical settings, including tumors that are refractory to CPT-11 treatment.
In particular, in the HT-29 colorectal cancer model, EZN-2208 showed marked antitumor activity in mice that failed CTP-11 treatment.

Study objective

Primary Objective
• For Arms A, B, and C: Determine the overall response rate (RR) of EZN-2208 for two distinct cohorts of patients with mCRC
- Patients with mutated K-RAS tumors (Arm A)
- Patients with wild-type K-RAS tumors (Arms B and C)

• For Arms B and C (wild-type K-RAS tumors): Determine the progression-free survival (PFS)

Secondary Objectives
• Evaluate the duration of response for each treatment arm
• Evaluate the PFS for Arm A
• Evaluate overall survival (OS) for each treatment arm
• Evaluate safety and toxicity for each treatment arm
• For patients with wild-type K-RAS tumors, benchmark the primary and secondary endpoints observed in Arm B (EZN-2208 + cetuximab) with those observed in Arm C (irinotecan + cetuximab)
• If possible, to evaluate the peripheral blood mononuclear cell (PBMC) genotype (e.g., uridine diphosphate-glucuronosyl-transferase isoform 1A1 [UGT1A1]) to detect changes in genes that may affect how the anticancer drugs work or are degraded, and to see if these changes affect the study treatment or side effects. Patients may participate in this study even if they do not agree to the molecular profile testing.
• If possible, to evaluate biomarkers in a sample of the original tumor biopsy. Patients may participate in this study even if they do not agree to allow the tumor biopsy testing.

Study design

A Phase 2, multicenter, multiple-arm, open-label study to evaluate the efficacy, safety, and tolerability of EZN-2208 (polyethylene glycol [PEG]-SN38).
EZN-2208 will be administered weekly for 3 weeks in 4-week cycles with or without cetuximab to patients who have failed regimens containing irinotecan (Camptosar®, CPT-11), oxaliplatin (Eloxatin®), and fluoropyrimidine.

Approximately 220 patients with mCRC will be enrolled to obtain 192 assessable patients.
All patients will have their tumor tissue tested for K-RAS status (mutated versus wild type) during the prestudy period. Patients will be stratified on the basis of the tumor K-RAS status.
• Patients with mutated K-RAS tumors will be treated with single-agent EZN-2208 in Arm A.
• Patients with wild-type K-RAS tumors will be randomly assigned in a 2:1 ratio to Arm B or Arm C. Patients with indeterminate K-RAS genotype will be randomized as are patients with wild-type K-RAS tumors.
- Patients in Arm B will receive EZN-2208 + cetuximab (Erbitux®).
- Patients in Arm C (benchmark) will receive irinotecan + cetuximab.

If patients provide separate consent, a sample from the tumor biopsy used to make the original diagnosis may be collected and tested for biomarkers. Patients may participate in this study even if they do not agree to allow the tumor biopsy testing.

Patients will continue to be followed for disease progression, subsequent anticancer therapy, and survival for at least 6 months after enrollment of the last patient in the study.

The study treatments are summarized below:
* Arm A (single-agent Ezn 2208)
Premedication with anti-emetics such as 5-HT3 blockers (eg odansetron or granisetron) are to be given 30 minutes before administration of Ezn-2208.
9 mg/m2 Ezn-2208 will be administered as a 60 minutes iv infusion on days 1, 8 and 15 and repeated every 28 days.

* Arm B (EZN-2208 cetuximab)
Premedication with an H1 antagonist (eg 50 mg diphenhydramine) should be given iv 30 to 60 minutes before the first cetuximab dose. Premedication should be administered before the next dose cetuximab based on clinical findings and presence / severity of infusion reactions occurred previously.
The use of preventive skin protection such as moisturizing skin cream, sunscreen, topical steroids (1% hydrocortisone cream) and doxycycline 100 mg twice daily administered from 1 to 6 weeks, starting on day -1 and with the option to continue, is recommended. [41]
Cetuximab 400 mg/m2 will be administered as a 2-hour iv infusion on days 1, then weekly cetuximab 250 mg/m2 will be administered as 1-hour infusion.
Premedication with anti-emetics such as 5-HT3 blockers (eg odansetron or granisetron) are to be given 30 minutes before administration of Ezn-2208.
9 mg/m2 Ezn-2208 will be administered as a 60 minutes iv infusion on days 1, 8 and 15 and repeated every 28 days.

* Arm C (irinotecan + cetuximab)
Premedication with an H1 antagonist (eg 50 mg diphenhydramine) should be given iv 30 to 60 minutes before the first cetuximab dose. Premedication should be administered before the next dose cetuximab based on clinical findings and presence / severity of infusion reactions occurred earlier.
The use of preventive skin protection such as moisturizing skin cream, sunscreen, topical steroids (1% hydrocortisone cream) and doxycycline 100 mg twice daily administered from 1 to 6 weeks, starting on day -1 and with the option to continue, is recommended.
Cetuximab 400 mg/m2 will be administered as a 2-hour iv infusion on days 1, then weekly cetuximab 250 mg/m2 will be administered as 1-hour infusion.
Irinotecan 125 mg/m2 will be administered by an iv infusion lasting 90 minutes on days 1 and 8.

General:
Ezn-2208 will be administered as a 60-minute iv infusion weekly for 3 weeks in 4-week cycles. Cycles may be repeated on every 4 weeks (28 days).
The cetuximab infusion will be administered before the Ezn-2208 (Arm A) or irinotecan (Arm C) infusion.
Study treatment will continue untill disease progression reveals, unacceptable

toxicity, or withdrawal of consent for participation in the study of the patient.
After cycle 1, the "safety analysis" for the first 6 patients treated in Arm B will be performed to ensure the safety of the combination of cetuximab + Ezn-2208.

Intervention

- Arm A (single-agent EZN-2208)
9 mg/m2 EZN-2208 will be administered as a 60-minute i.v. infusion on Days 1, 8, and 15 repeated every 28 days.

- Arm B (EZN-2208 + cetuximab)
400 mg/m2 cetuximab will be administered as a 2-hour i.v. infusion on Day 1; subsequently, 250 mg/m2 cetuximab will be administered weekly as a 1-hour i.v. infusion.
9 mg/m2 EZN-2208 will be administered as a 60-minute i.v. infusion on Days 1, 8, and 15 repeated every 28 days.

- Arm C (irinotecan + cetuximab)
400 mg/m2 cetuximab will be administered as a 2-hour i.v. infusion on Day 1; subsequently, 250 mg/m2 cetuximab will be administered weekly as a 1-hour i.v. infusion.
125 mg/m2 irinotecan will be administered i.v. over 90 minutes on Days 1 and 8.

Study burden and risks

During screening a standar physical exaination will be done. Furthermore extensive blood analysis will be done. The physical examination will be repeated during the study at every first day of the next cycle. Bloodanalysis will be repeated at days 1, 8, 15 and 22 of every cycle in patients in arm A en arm B. Patients in arm C will have blood analysis on repeated on days 1,8 and15 of every cycle.
At least every two months a scan will be made for tumor evaluation.
Patients treated in arm A and C will get intravenous administration of study treatment on days 1, 8 and 15 of every cycle. Patients treated in arm B will get intravenous administration of study treatment on days 1, 8 15 and 22 of every cycle.
Depending on the arm in which the patient is being treated the total duration of the infusion is ranging from minimaal 1,5 hours to a maximum of 4 hours, including administration of pre-medication.
Survival status will be collected every 3 months and until the end of study.
See protocol pages 49-52.

Contacts

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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

Patients must meet all of the following criteria to be eligble for enrollment in the study.
1. capable of understanding the protocol requirements and risks and providing written informed consent.
2. histologically confirmed CRC adenocarcinoma that is metastatic or locally recurrent CRC that is nonresectable.
3. patients must agree to genetic testing of the original or metastatic CRC tumor biopsy tissue for K-RAS mutational status. Participation in study requires the availability of the tumor biopsy and written patient consent for K-RAS genotyping of the tumor tissue. Lack of tumor tissue or patient refusal to allow genotyping makes the patient ineligible for the study.
4. disease progression.
5. previous therapy with irinotecan, oxaplatin and fluoropyrimidine either alone or in any combination(s). Patients must have radiographically documented progressive disease while

receiving, or within 3 months of receiving these agents alone or in combination.
6. No more than 2 prior cytotoxic chemotherapy regimes. Biologic agents and target non-cytotoxic therapies do not count with respect to the number of prior regimes.
7. age 18 years and older
8. measurable disease by RECIST version 1.1 is required.: >= 1 tumor with >= 10 mm (assuming computed tomography [CT] slice thickness of 5 mm minimum) If the CT slice thickness is >5 mm, the measurable lesion minimum is 2x slice thickness. Measurable disease is defined as at least one lesion for which the longest diameter can be accurately measured. The only evidence of metastasis must not be nonmeasurable disease such as leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, or abdominal masses/abdominal organomegaly identified by physical examination that is not measureable by reproducible imaging techniques.
9. ECOG performance status of 0 or 1.
10. Adequate bone marrow, renal and hepatic function. : - Hemoglobin>= 9.0 g/dl (no history of blood transfusion in prior 2 weeks)
- absolute neutrophil count (ANC)>= 1,000/microL
- Platelet count >= 75,000/ microL
- Serum creatinine <= 1.5 times the upper limit of normal (ULN)
- Total bilirubine within normal limits.
- Transaminases (aspartate aminotransferase [AST] and alanine aminotransferase [ALT})<= 2.5 times the ULN (may be <= 5 times the ULN if the increase is due to metastatic disease to the liver)

Exclusion criteria

Patients meeting any of the following exclusion criteria will not be eligible for enrollment.
1. concurrent serious medical illness that could potentially interfere with protocol compliance.
2. previous cancer treatment with cetuximab(Erbitux®) , panitumumab (Vectibix®) or any other anti-EGFR therapies. Patients previously treated with such therapy who are found to have mutated K-RAS tumors and who meet all other eligibility criteria are eligible for participation in Arm A of the study.
3. positive screening pregnancy test or is breast-feeding.
4. female or male patient of reproductive capacity unwilling to use methods appropriate to prevent pregnancy during this study.
5. Known chronic infectious disease, such as acquired immunodeficiency syndrome (AIDS).
6. Major surgery within 3 weeks before study start.
7. known or suspected brain metastases requiring intervention with steroids and/or radiotherapy. Patients with previously treated brain metastases who are currently asymptomatic and not requiring steroids are eligble.
8. prior chemotherapy, immunotherapy, non-investigational agent, or other therapy used to treat the cancer within 3 weeks (6 weeks for prior treatment with mitomycin C) before the scheduled administration of EZN-2208.
9. History of other primary cancer within 5 years of enrollment, unless
a. curatively resected non-melanomatous skin cancer,or

b. curatively resected cervical cancer.
10. lack of recovery to Grade 1 from any reversible side effects (except alopecia or grade 2 senory neuropathy) related to administration of an investigational agent, chemotherapy, immunotherapy, surgery, radiotherapy, or other treatments for the cancer.
11. any condition, such as uncontrolled diabetes, uncontrollable hypertension, or active infection that, in the opinion of the principal investigator (PI) or Enzon, makes the patient unsuitable for the study. The PI must consider the potential side effects of SN38 therapy when evaluating a prospective study patient previously treated with irinotecan.
12. current participation in another clinical study with investigational agent and/ or use of an investigational drug (not including investigational use of an approved drug) in the 30 days before the first administration of EZN-2208.
13. Inability to comply with the study protocol.

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):	18-02-2010
Enrollment:	20
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:	geen
Generic name:	irinotecan
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	geen
Generic name:	polyethylene glycol- SN38

Ethics review

Approved WMO Date:	04-01-2010
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-05-2010
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-07-2010
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-09-2010
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-05-2011
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	

Date:	24-06-2011
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	EUCTR2009-014876-23-NL
ClinicalTrials.gov	NCT00931840
CCMO	NL30464.078.09