Phase Ib study of PDR001 in combination with regorafenib in adult patients with previously treated metastatic microsatellite stable (MSS) colorectal cancer

Published: 07-06-2017
Last updated: 12-04-2024

Primary: Dose escalation part: To determine the MTD and/or RP2D of PDR001 in combination with regorafenib in patients with metastatic MSS CRC. Expansion part: To evaluate the efficacy based on overall response rate (ORR) of PDR001 in combination...

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

Summary

ID

NL-OMON45600

Source
ToetsingOnline

Brief title
PDR001 and regorafenib in MSS colorectal cancer

Condition

- Gastrointestinal neoplasms malignant and unspecified

Synonym
Colorectal carcinoma

Research involving
Human

Sponsors and support

Primary sponsor: Novartis
Source(s) of monetary or material Support: Farmaceutisch bedrijf Novartis

Intervention

Keyword: Colorectal carcinoma, PDR001, Phase Ib, regorafenib

Outcome measures

Primary outcome

Escalation phase: Incidence of DLT during the first 8 weeks of treatment

Expansion phase: ORR as per RECIST 1.1

Secondary outcome

ORR, adverse events, PK parameters, Antidrug antibodies, OS.

Study description

Background summary

Regorafenib is an oral multi-kinase inhibitor that blocks the activity of several protein kinases, including kinases involved in the regulation of tumor angiogenesis, oncogenesis, and the tumor micro-environment (PDGFR and FGFR). Regorafenib has been demonstrated to improve overall survival by decreasing the risk of death by 33% compared to placebo in patients with pretreated metastatic colorectal cancer (CRC).
In spite of the treatment improvements and clinical outcome observed with the approved agents; there is still a need to investigate treatments that could further improve the benefit risk profile providing longer disease stabilization, and tumor response together with a tolerable safety profile.
In addition, the subset of patients presenting with CMS4 like subtype are not likely to respond to available treatments as they typically have a poor clinical outcome.
For this reason, new treatment combination strategies that modify the immune contexture with antiangiogenic agents may facilitate the activity of checkpoint blockade restoring immunogenicity.
This is a Phase Ib study to evaluate the safety and efficacy of the combination PDR001/regorafenib in previously treated patients with metastatic Microsatellite Stable (MSS) CRC. The study will have a dose escalation (up to 2

dose levels of regorafenib in combination with PDR001 at a fixed dose) and an expansion part.

Study objective

Primary:
Dose escalation part: To determine the MTD and/or RP2D of PDR001 in combination with regorafenib in patients with metastatic MSS CRC.
Expansion part: To evaluate the efficacy based on overall response rate (ORR) of PDR001 in combination with regorafenib.

Secondary:
Efficacy. Safety and tolerability. Pharmacokinetic (PK) profile, immunogenicity. Overall survival (OS).

Study design

Multicenter, open label, phase Ib study with a dose escalation part and a dose expansion part. Treatment with up to 2 dose levels of regorafenib in combination with PDR001 at a fixed dose until disease progression or unacceptable toxicity.
Follow-up for safety (5 months) and survival.
Approx. 72 subjects (12 dose escalation part, 60 expansion part).

Intervention

Treatment with PDR001 in combination with regorafenib.
PDR001 (intraveneus) - 400mg per 4 weken
Regorafenib (oraal): startdosering 120mg/ dag. Volgende dosisnieveau: 160mg/dag.

Study burden and risks

Risk: Adverse effects of PDR001 in combination with regorafenib.
Burden: Cycles of 4 weeks. Cycle 1: 3 visits, cycle 2: 2 visits, thereafter 1 visit per cycle.
PDR001: 1 infusion (250 mL) per cycle.
Physical examination: once per cycle (cycle 1: 3 times, cycle 2: 2 times).
Blood tests (5-15 mL/occasion): every visit up to follow-up (cycle 1: 4 times).
Extra blood draws for PK and antidrug antibodies (in total 76 mL) and biomarkers (in total 225 mL).
Urine testing every visit up to follow-up.
Pregnancy test: every cycle and every visit during safety follow-up.
ECG: 5 times and every 2nd cycle.
CT-/MRI scan: baseline, every 8 weeks thereafter.
Echocardiography: Twice.

Optional examinations: Pharmacogenetic substudy (6 ml blood). Cytokine substudy in case of adverse events (20 mL blood). Tumor biopsy during study treatment.

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. Metastatic microsatellite stable colorectal adenocarcinoma.
2. Subjects must provide a newly obtained or an archival tumor sample corresponding to CRC diagnosis (primary tumor) with sufficient tissue quality for analysis.
3. Subjects must provide a newly obtained tumor tissue sample from a metastatic site.
4. At least one measurable lesion.
5. Previously treated with two prior regimen as per standard of care and have experienced disease progression.
6. ECOG performance status 0-1

Exclusion criteria

1. High level Microsatellite Instable (MSI-H) colorectal adenocarcinoma as defined per local standard of care testing.
2. Metastatic disease amenable to be resected with potentially curative surgery.
3. Chemotherapy, radiation, or biological cancer therapy within 14 days prior to the first dose of study treatment.
4. Prior treatment with anti-PD-1, anti-PD-L1, anti-PDL2, anti-CTLA-4 antibodies, other checkpoint inhibitors.
5. Any untreated CNS lesion. Exceptions: see protocol page 39.
6. Use of any live vaccines against infectious diseases within 4 weeks of initiation of study treatment.
7. Use of G-CSF and comparable, see protocol page 39 for details.
8. Systemic chronic steroid therapy (* 10mg/day prednisone or equivalent) or any immunosuppressive therapy 7 days prior to start of study treatment.
9. History of severe hypersensitivity reactions to other monoclonal antibodies, see protocol page 39 for details.
10. HIV positive, HBsAg positive, hepatitis positive.
11. Active, known or suspected autoimmune disease or a documented history of autoimmune disease, see protocol page 40 for details.

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	6
Type:	Anticipated

Medical products/devices used

Product type:	Medicine

Brand name:	Stivarga
Generic name:	rigorafenib
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	07-06-2017
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	22-06-2017
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	12-07-2017
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	14-08-2017
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	28-08-2017
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	21-11-2017
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	21-06-2018
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

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	EUCTR2017-000466-30-NL
ClinicalTrials.gov	NCT03081494
CCMO	NL61135.058.17