A Phase Ib, multicenter, open-label dose escalation and expansion platform study of select druk combinations in adult patients with advanced or metastatic BRAF V600 colorectal cancer.

Published: 02-04-2020
Last updated: 08-04-2024

Primary objective:To characterize safety and tolerability of each treatment arm tested and identify recommended doses (RD) and regimens for future studies, by assessing the incidence and severity of AEs and SAEs; including changes in laboratory...

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

Summary

ID

NL-OMON52799

Source
ToetsingOnline

Brief title
CADPT01C12101 (CRC)

Condition

- Gastrointestinal neoplasms malignant and unspecified

Synonym
advanced or metastatic BRAF V600

Research involving
Human

Sponsors and support

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

Intervention

Keyword: BRAF, Colorectal, metastatic, Phase Ib

Outcome measures

Primary outcome

Incidence and severity of AEs and SAEs, including changes in laboratory values,

vital signs, and ECGs

Incidence and nature of DLTs in the first cycle (dose escalation only)

Dose interruptions, reductions, and dose intensity

Secondary outcome

Tumor MAPK pathway suppression (change from baseline) within combination

treatment arms

Tumor mutational changes throughout treatment course

Tumor immune phenotyping within combination treatment arms (e.g. CD8, PD-L1)

BOR per RECIST v1.1

For individual investigational drug, compare the PK in combination regimen vs.

as a single agent

Study description

Background summary

The purpose of this study is to inhibit the MAPK pathway in BRAF V600 colorectal cancer by leveraging the potential for approved and novel agents to uniquely target mechanisms of intrinsic and acquired resistance in BRAF

V600-driven cancer cells. Furthermore, targeted MAPK inhibition in tumor immune cells may complement the mechanism of action of anti-PD-1 antibodies in mismatch-repair deficient CRC, thereby potentially increasing anti-cancer immunomodulation. Therefore, RAF and ERK inhibition will be combined with the anti-PD-1 antibody spartalizumab in CRC harboring concurrent activated BRAF and microsatellite instability, with the future potential to explore targeted immune approaches in the mismatch repair proficient setting as well.Given the number of potentially active agents and the inability to predict which combination may be most beneficial for patients, this trial will investigate the safety, tolerability, and preliminary anti-tumor effect using an adaptive platform design to improve efficiency

Study objective

Primary objective:
To characterize safety and tolerability of each treatment arm tested and identify recommended doses (RD) and regimens for future studies, by assessing the incidence and severity of AEs and SAEs; including changes in laboratory values, vital signs, and ECGs; the incidence and nature of DLTs in the first cycle (dose escalation only); and by assessing dose interruptions, dose reductions, and dose intensity

Secondary objective:
To characterize the PK of each investigational drug within each treatment arm by assessing serum/plasma concentrations and PK parameters of individual investigational drugs within combination treatments.
To evaluate preliminary anti-tumor activity of each treatment arm by assessing best overall response (BOR), progression free survival (PFS), overall response rate (ORR), and disease control rate (DCR) per RECIST v1.1.
To evaluate PD effect in their respective combinations in tumor by assessing the change from baseline of the PD marker DUSP6 in tumor tissue (dose escalation only)

Study design

This is a phase Ib, multi-center, open-label study with multiple treatment arms. The open platform design of this study is adaptive to allow removal of combination treatment arm(s) based on emerging data and facilitate introduction of new candidate combinations. The study is comprised of a dose escalation part and may be followed by a dose expansion part for any combination treatment arm.

The study will initially enroll subjects into the dabrafenib + LTT462 treatment arm.

The dose escalation of the triplet combination treatment arms will start after

the first dose level of the dabrafenib + LTT462 treatment arm has been determined to be safe and tolerable. This will be when at least two cycles of therapy have been received by patient at the first dose level, and writen confirmation has been received by the investigators that the second dose level has been evaluated. Dabrafenib + LTT462 will be used as the initial backbone doublet to which partner investigational drugs will be added to comprise triplet combination treatment arms. It is possible that planned combination treatment arm(s) may not be initiated based on emerging clinical data.

Multiple triplet combination treatment arms may enroll in parallel during dose escalation. Those treatment arms that reach a maximum tolerated dose (MTD)/recommended dose (RD) may, but are not required to, proceed to dose expansion to further explore safety, tolerability, and preliminary anti-tumor activity. Another possibility is that a triplet combination treatment arm reaching an MTD/RD could be studied as a new backbone regimen to which other investigational drugs would be added by protocol amendment to generate quadruplet treatment arms. In the case that all dose levels of a given combination treatment arm are not considered tolerable, then no MTD/RD for that treatment arm will be defined, and enrollment in that treatment arm will be discontinued

Intervention

Dabrafenib (DRB436), LTT462, trametinib (TMT212), LXH254, TNO155, spartalizumab (PDR001), tislelizumab (VDT482) in various combinations.

Study burden and risks

Risks and side-effects associated with the treatment provided.

Risks associated with the study assessments such as blooddraws, imaging and tumor biopsy.

Burdens: 4 week cycles. Cycle 1: 5-6 visits depending on schedule. C2: 2-3 visits depending on schedule.
From Cycle 3 onward: 1 visit. Duration of visits: usually 1-2 hours unless blooddraws for farmacokinetic profiling is planned. Depending on the given combination therapy a visit may extend from minimally 2 to max 9 hours.

Assessments during visits, depending on combination therapy and type of visit: physical exam, blooddraws, ECG's / vital signs, imaging, pregnancy testing, tumor biopsy.

Contacts

Public
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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 be >= 18 years of age.
ECOG performance status <= 1.
Patients must have a site of disease amenable to biopsy, and be a candidate for tumor biopsy according to the treating institution*s guidelines.
All patients must have a BRAF V600 mutation confirmed by local assessment.
Patients with unresectable advanced/metastatic BRAF V600 cancer of the colon or rectum with measurable disease as determined by RECIST v1.1
See for more details protocol section 5.1

Exclusion criteria

Impairment of gastrointestinal function or gastrointestinal disease that may significantly alter the absorption of study drugs
Patients with CNS tumor involvement, unless > 2 weeks after completion of CNS-therapy, stable with respect to CNS-involvement, not receiving steroids or on stable dose of < 10 mg/day for two weeks.
Out of range laboratory values:
Hemoglobin (Hgb) < 9.0 g/dL
Platelets < 75 x 109/L
Serum total bilirubin > 1.5 x upper limit of normal (ULN),
Asparate aminotransferase (AST) > 3 x ULN
Alanine aminotransferase (ALT) > 3 x ULN
Serum creatinine > 1.5 x ULN OR Creatinine Clearance < 60 mL/min
Other exclusion criteria may apply, please see protocol section 5.2

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	28-07-2021
Enrollment:	21
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Mekinist
Generic name:	Trametinib
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	N/A

Generic name:	Spartalizumab
Product type:	Medicine
Brand name:	Tafinlar
Generic name:	Dabrafenib
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	02-04-2020
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	23-06-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	11-08-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	07-09-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	16-09-2020
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	27-10-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	19-11-2020
Application type:	Amendment

Review commission:	METC NedMec
Approved WMO Date:	30-12-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	29-01-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	01-02-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	22-03-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	26-03-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	09-04-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	16-04-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	30-04-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	01-05-2021
Application type:	Amendment

Review commission:	METC NedMec
Approved WMO Date:	10-06-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	11-06-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	21-06-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	25-06-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	07-09-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	23-09-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	24-09-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	23-02-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	17-03-2022
Application type:	Amendment

Review commission:	METC NedMec
Approved WMO Date:	23-03-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	30-03-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	28-04-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-06-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	22-06-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	14-09-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	04-10-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	09-11-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	10-11-2022
Application type:	Amendment

Review commission:	METC NedMec
Approved WMO Date:	28-12-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	03-01-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	05-01-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	10-01-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	10-02-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	22-02-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	04-03-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-03-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	03-05-2023
Application type:	Amendment

Review commission:	METC NedMec
Approved WMO Date:	19-05-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	16-08-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	12-10-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	17-10-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	15-11-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	29-11-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

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	EUCTR2019-004688-27-NL
CCMO	NL73014.031.20