daNIS-3: An open-label, multi-center, phase II platform study evaluating the efficacy and safety of NIS793 and other new investigational drug combinations with standard of care (SOC) anti-cancer therapy for the second line treatment of metastatic colorectal cancer (mCRC)

Published: 10-05-2022
Last updated: 05-04-2024

Safety Run-in (SRI) part:To confirm the recommended phase 2 dose (RP2D) of NIS793 or any other investigational drug(s), in combination with SOC anti-cancer therapy. In protocol amendment 1, an arm with tislelizumab has been added. In this arm, the...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Malignant and unspecified neoplasms gastrointestinal NEC
Study type	Interventional

Summary

ID

NL-OMON52122

Source
ToetsingOnline

Brief title
CNIS793E12201 daNIS-3

Condition

- Malignant and unspecified neoplasms gastrointestinal NEC

Synonym
metastatic colorectal cancer

Research involving
Human

Sponsors and support

Primary sponsor: Novartis
Source(s) of monetary or material Support: Novartis Pharma B.V. (sponsor/verrichter van dit onderzoek)

Intervention

Keyword:), eta (TGF-&beta, metastatic colorectal cancer, NIS793, TGF-&beta, Tislelizumab

Outcome measures

Primary outcome

Primary estimand is defined only for the expansion part.

The primary scientific question of interest is:

• What is the relative effect of each investigational treatment arm relative to

the SOC anti-cancer therapy arm in prolonging PFS in the second line mCRC

setting, regardless of study treatment discontinuations or start of a new

subsequent antineoplastic therapy or prohibited medication which is not part of

assigned study treatment strategy?

Secondary outcome

none

Study description

Background summary

Colorectal cancer (CRC) is the 3rd most commonly diagnosed cancer in the world and the second highest cause of cancer death. Of newly diagnosed CRC patients, 75% have localized disease that is treated by surgical resection while 25% present with unresectable metastatic disease. Furthermore, approximately 30% of patients with localized CRC develop metastatic disease recurrence after the

surgical removal of the tumor. A worrying rise in patients presenting with colorectal cancer, younger than 50 years has been observed, especially rectal and left sided colon cancer. Patients with mCRC, after first line treatment, still have an important unmet medical need to improve current survival outcomes where median PFS is approximately 6 months and median overall survival (OS) is approximately 12 months with current available treatments.
The TME plays a critical role at the different stages of the disease. The TME confers to a CRC cell survival, immune evasion and a favorable environment to grow and metastasize . TGF-β pathway plays a critical role in immune regulations, stromal cell activation and fibrosis. It has been recognized that alteration and aberrant regulation of TGF-β pathway plays a crucial role in the initiation, proliferation, inflammation and invasiveness of CRC. Moreover, various studies have shown that TGF-β is responsible for reducing drug sensitivity and recurrence in patients with cancer supporting the therapeutic potency of TGF-β inhibitors in combination with other treatments in this setting.
Tislelizumab (also known as BGB-A317 and VDT482) is a humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) against human programmed cell death-1 (PD-1). Tislelizumab is being developed for treatment of human malignancies in multiple organs and tissues and is being investigated either as monotherapy or in combination with other therapies.

Study objective

Safety Run-in (SRI) part:
To confirm the recommended phase 2 dose (RP2D) of NIS793 or any other investigational drug(s), in combination with SOC anti-cancer therapy. In protocol amendment 1, an arm with tislelizumab has been added. In this arm, the patient can be treated with SoC, NIS793 and Tislelizumab. The RP2D of tislelizumab in combination with NIS793 is being investigated in the SRI.

Expansion part:
To evaluate preliminary efficacy of NIS793 or any other investigational drug(-s) (in arm 2 NIS793 + tislelizumab) in combination with SOC anti-cancer therapy versus SOC anti-cancer therapy in terms of progression-free survival (PFS)

Study design

This is an open-label, multi-center, phase II platform study.
The platform design of this study is adaptive to allow flexibility in the introduction of additional treatment arms with new investigational drugs in combination with SOC anticancer therapy for the second line treatment of mCRC. The study will include control arm that will enroll participants treated with SOC anticancer therapy (bevacizumab with mFOLFOX6 or FOLFIRI) for the second

line treatment of mCRC. Each investigational arm will include a combination of an investigational drug and the SOC anti-cancer therapy.
Investigational arm #1 will include combination of NIS793 with SOC anti-cancer therapy.
Investigational arm #2 will include combination of NIS793 + NIS793 with SOC anti-cancer therapyn (protocol amendment 1)
Combinations of other investigational drug(-s) with SOC anti-cancer therapy may be added later by protocol amendment as new investigational arms (i.e, investigational arm #2, investigational arm #3 etc).
Each investigational arm will start with a Safety run-in (SRI) followed by an Expansion part. The purpose of SRI is to confirm the dose of investigational drug with SOC anticancer therapy.
* Each SRI will enroll up to approximately 20 participants to have at least 12 evaluable participants (6 treated by NIS793 [or any other new investigational drug] + mFOLFOX6 + bevacizumab and 6 by NIS793 [or any other new investigational drug] + FOLFIRI +bevacizumab)
* Each expansion will enroll approximately 75 participants in each treatment arm
The decision to open the expansion part of the study will be based on dose confirmation of investigational drug(-s) with available safety, relevant PK and other relevant clinical and laboratory data from the safety run-in part.

Intervention

Safety run-in:
combination of NIS793 and SOC (FOLFIRI or mFOLFOX) + bevacizumab
combination of NIS793, and tislelizumab, SOC (FOLFIRI or mFOLFOX) + bevacizumab
Expansion part:
Investigational arm 1: NIS793 and SOC (FOLFIRI or mFOLFOX) + bevacizumab
investigational arm 2: NIS793,and tislelizumab, SOC (FOLFIRI or mFOLFOX) + bevacizumab
control arm: alone SOC FOLFIRI or mFOLFOX) + bevacizumab
Treatment cycle is defined as 28 days. Treatment will be given at day 1 and day 15.

Study burden and risks

The extra burden for the patient is mainly the duration of the visits, the extra blood samples (especially PK and biomarker test, if applicable pregnancy tests, eye examinations and the completion of the questionnaires. The visits take longer because of extra blood draws, observation period after NIS793 and tislelizumab administration.
There are a number of additional visits such as screening, end trial and if applicable the follow-up and PK sampling visits (day 2 of the first cycles).
The frequency of visits follows the dosing schedule of the standard of care bevacizumab + FOLFIRI/mFOLFOX.

As with any administration of drugs, side effects may occur. However, the patient is observed before being allowed to go home and vital signs are checked regularly.

If patient gives consent, additional biopsies are taken

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. Signed informed consent must be obtained prior to participation in the study.
2. Age 18 years or older at the time of informed consent.
3. Histologically or cytologically confirmed (by local laboratory and local clinical guidelines) metastatic colorectal adenocarcinoma that is not amenable to potentially curative surgery in the opinion of the investigator and

progressed on or within 6 months after the last dose of one prior line of systemic anti-cancer therapy administered for metastatic disease.
4. Presence of at least one measurable lesion assessed by CT and/or MRI according to RECIST 1.1.
5. Eastern Cooperative Oncology Group (ECOG) Performance Status 0 or 1.
6. Adequate organ function as defined by the following laboratory values (assessed by central laboratory for eligibility except where indicated):
• Absolute neutrophil count >= 1.5 × 109/L
• Platelets count >= 100 × 109/L
• Hemoglobin >= 9 g/dL
• Calculated creatinine clearance >= 60 mL/min (e.g. by using Cockcroft-Gault equation)
• Albumin >= 3 g/dL
• PT/INR and PTT <= 1.5 x ULN. Participants requiring therapeutic anticoagulants are eligible if coagulation parameters are within therapeutic range.
• Total bilirubin <= 1.5 X ULN
• Aspartate aminotransferase/serum glutamic oxaloacetic transaminase (AST/SGOT) and alanine aminotransferase /serum glutamic pyruvic transaminase (ALT/SGPT) <= 3.0 x ULN (<=5 x ULN in presence of liver metastasis). In participants with elevated ALT or AST, the values must be stable for at least 2 weeks and with no evidence of biliary obstruction by imaging.
7. Women of child-bearing potential must have negative pregnancy tests during the screening period and before starting study treatment.
8. Able to adhere to study visit schedule and other protocol requirements.
9. Participant must have recovered from treatment related toxicities of prior anticancer therapies to grade <=1 (CTCAE v5.0) at the time of screening, except alopecia.

Exclusion criteria

1. Previously administered of anti-cancer immunotherapy or TGF-β targeted therapies.
2. Microsatellite instability-high (MSI-H)/mismatch repair-deficient (dMMR) and/or BRAFV600 mutation positive colorectal cancer.
3. Known complete or partial dipyrimidine dehydrogenase (DPD) enzyme deficiency
4. For participants treated with irinotecan: Known history or clinical evidence of reduced UGT1A1 activity.
5. Presence of symptomatic CNS metastases, or CNS metastases that requires directed therapy (such as focal radiotherapy or surgery), or increasing doses of corticosteroids 2 weeks prior to study entry. Participants with treated symptomatic brain metastases should be neurologically stable for 4 weeks post-treatment and prior to study entry, and at a dose of <= 10 mg per day prednisone or equivalent for at least 2 weeks before administration of any study treatment.
6. Known history of severe allergy or hypersensitivity to any of the study

drugs or its excipients or to drugs of similar chemical classes (e.g. monoclonal antibodies), or contraindication to any of the study drugs as outlined in the *Contraindications* or *Warnings and Precautions* sections of the SOC local prescribing information
7. Participant is currently receiving other anti-cancer therapy (medication or radiotherapy), or received other investigational product within 30 days or 5 half-lives prior to initiation of study treatment, whichever is longer.
8. Participant is currently receiving any of the prohibited medications as outlined in the protocol or in the SOC anti-cancer therapy local prescribing information, and these cannot be discontinued >= 7 days or 5 half-lives, whichever is longer, before the first dose of that drug.
9. Participant has not recovered from a major surgery performed prior to start of study treatment or has had a major surgery within 4 weeks days prior to start of study treatment.
10. Radiation therapy <= 4 weeks or brain-radiotherapy <= 4 weeks prior to start of study treatment
11. Impaired cardiac function or clinically significant cardio-vascular disease, such as:
• Congestive heart failure requiring treatment (NYHA grade >=2), or clinically significant arrhythmia (including uncontrolled atrial flutter/fibrillation)
• Acute myocardial infarction, unstable angina pectoris, coronary stenting, or bypass surgery 6 months prior to study entry
• LVEF < 50%
• Elevated cardiac enzymes troponin I > 2 x ULN
• Cardiac valvulopathy>= grade 2
• Uncontrolled hypertension defined by a systolic blood pressure >=160 mg and/or diastolic blood pressure >=100 mg Hg
• Medical history or current diagnosis of myocarditis
12. History of positive test for human immunodeficiency virus (HIV) infection
13. Active or chronic hepatitis B virus (HBV) or hepatitis C virus infections.
14. Active untreated or uncontrolled systemic fungal, bacterial or viral infection (including COVID-19), which in the opinion of the investigator places the study participant at an unacceptable risk.
15. Use of hematopoietic growth factors or transfusion support <= 2 weeks prior to start of study treatment.
16. Participant has conditions that are considered to have a high risk of clinically significant gastrointestinal tract bleeding or any other condition associated with or history of significant bleeding.
17. Serious non-healing wounds.
18. Stroke or transient ischemic attack, or other ischemic event, or thromboembolic event (e.g., deep venous thrombosis, pulmonary embolism) within 3 months before start of study treatment.
19. Concurrent malignancy other than the disease under investigation with exception of malignancy that was treated curatively and has not recurred within 2 years prior to the date of screening. Fully resected basal or squamous cell skin cancers and any carcinoma in situ are eligible.
20. Any significant medical condition, laboratory abnormality or psychiatric or

social condition that would constitute unacceptable safety risks to the participants, contraindicate participant participation in the clinical study, limit the participant*s ability to comply with study requirements, or compromise participant*s compliance with the protocol and all requirements of the study as stated in the Informed Consent Form.
21. Women of child-bearing potential, unless they are willing to use highly effective methods of contraception during treatment with study drugs and for at least 120 days after stopping treatment with tislelizumab.
22. Pregnant or breast-feeding women.
23. Use of live/attenuated vaccines within 4 weeks of initiation of study treatment
24. Active, known or suspected autoimmune disease or history thereof
25. Systemic chronic steroid therapy (>10 mg/day prednisone or equivalent) or any immunosuppressive therapy
26. History of allogeneic bone marrow or solid organ transplant

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:	Will not start
Enrollment:	3
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	NIS793

Generic name:	NIS793
Product type:	Medicine
Brand name:	tislelizumab
Generic name:	tislelizumab

Ethics review

Approved WMO Date:	10-05-2022
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	11-02-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	09-03-2023
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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	EUCTR2021-000553-40-NL
ClinicalTrials.gov	NCT04952753
CCMO	NL79023.056.22