A randomized, double-blind, phase III study comparing NIS793 in combination with gemcitabine and nab-paclitaxel versus placebo combined with gemcitabine and nab-paclitaxel for first line treatment of metastatic pancreatic ductal adenocarcinoma (mPDAC)

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The purpose of this study is to evaluate the efficacy and safety of NIS793 in combination with gemcitabine/nab-paclitaxel versus gemcitabine/nab-paclitaxel and placebo in first-line mPDAC.This study aims to explore whether blockade of Transforming...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON51502

Source
ToetsingOnline

Brief title
NIS793B12301

Condition

- Other condition

Synonym
metastatic pancreatic cancer

Health condition

alvleesklier kanker

Research involving
Human

Sponsors and support

Primary sponsor: Novartis
Source(s) of monetary or material Support: Novartis Pharma BV (sponsor van dit onderzoek)

Intervention

Keyword: First line treatment, Metastatic pancreatic cancer, Monoclonal antibody, Phase III

Outcome measures

Primary outcome

Safety run-in part:

The primary objective of the safety run-in part is to confirm the recommended

phase 3 dose (RP3D) of NIS793 in combination with gemcitabine and

nab-paclitaxel (SOC).

Randomized part:

The primary objective of the randomized part is to compare OS in participants

with mPDAC treated as the first line treatment with the combination of NIS793,

gemcitabine and nab-paclitaxel to the combination of placebo with gemcitabine

and nab-paclitaxel.

The primary clinical question of interest of the randomized part is to estimate

the treatment effect on the primary endpoint of OS of NIS793 in combination

with gemcitabine and nab-paclitaxel (arm A) compared to placebo in combination

with gemcitabine and nab-paclitaxel (arm B) for the target population,

regardless of discontinuation from study treatment, or start of a new subsequent antineoplastic therapy.

Secondary outcome

Safety run-in part:

To evaluate:

• Safety and tolerability of NIS793 in combination with gemcitabine and nab-paclitaxel

• Preliminary anti-tumor activity of NIS793 in combination with gemcitabine and nab-paclitaxel

• Pharmacokinetics (PK) of NIS793 in combination with gemcitabine and nab-paclitaxel

Randomized part:

• To evaluate the efficacy (progression-free survival (PFS), overall response rate (ORR), disease control rate (DCR), duration of response (DOR), time to response (TTR)) in participants treated as the first line treatment of NIS793 in combination with gemcitabine and nab-paclitaxel versus placebo plus gemcitabine and nab-paclitaxel

• To evaluate safety and tolerability in each treatment arm

• To explore PK of NIS793 in combination with gemcitabine and nab-paclitaxel

• To characterize the incidence of immunogenicity of NIS793 in combination with gemcitabine/nab-paclitaxel

• To evaluate health-related quality of life and other patient reported outcomes in each treatment arm

Study description

Background summary

Pancreatic ductal adenocarcinoma (PDAC) represents a significant public health burden, with a 5-year survival rate of approximately 2.9%. In the absence of improvements in early diagnosis and treatment, PDAC will likely become the second leading cause of death worldwide by 2030. There are two recommended first-line chemotherapy treatments for metastatic PDAC, FOLFIRINOX (a combination of 5-fluorouracil, folinic acid, irinotecan plus oxaliplatin) or gemcitabine plus nab-paclitaxel and the reported median overall survival (mOS) for both regimens is less than 12 months.

FOLFIRINOX is usually reserved for patients with good performance status (e.g., ECOG performance status 0-1) due to the toxicity associated with this combination regimen. Unlike other common cancers, survival gains have only improved slightly for advanced pancreatic cancer patients over the past decades and additional treatments are urgently needed.

One of the reasons for the poor response to therapeutic treatments in PDAC has been attributed to the extensive stromal response in this indication. PDAC displays in fact the most prominent desmoplastic reaction of all epithelial tumors, characterized by an abundance of activated stroma and progressive accumulation of extracellular matrix (ECM) proteins such as hyaluronic acid, which altogether contribute to tissue structural rigidity and poor perfusion. These structural aberrations significantly reduce penetration of macromolecules, hindering the tumor intake of therapeutics. Intra-tumoral fibrosis in PDAC is known to correlate with poor survival even after resection.

New agents targeting the desmoplastic tumor microenvironment may therefore represent an opportunity to establish novel therapeutic paradigms in the treatment of PDAC.
In this context, TGFβ-blockade offers the potential to address some of the aberrations of the PDAC microenvironment, due to its pleiotropic effects on stroma. In particular, TGFβ plays a pivotal role in the activation of pancreatic stellate cells (PSC), the most abundant type of fibroblasts in the pancreas and the chief organizers of the desmoplastic reaction. As the expression of TGFβ increases throughout disease progression, so does the conversion of stellate cells into myofibroblasts, as well as the fibrotic response.

Notably, studies have shown that TGFβ signaling components are often genetically silenced in the pancreatic cancer cells, disabling the tumor intrinsic suppressive activity of TGFβ and cooperating instead with other genetic alterations to promote tumor initiation and malignant progression.

These molecular alterations likely represent a mechanism for pancreatic cancer cells to grow and spread in an overly high TGFβ microenvironment.

Study objective

The purpose of this study is to evaluate the efficacy and safety of NIS793 in combination with gemcitabine/nab-paclitaxel versus gemcitabine/nab-paclitaxel and placebo in first-line mPDAC.
This study aims to explore whether blockade of Transforming Growth Factor β (TGFβ) in combination with gemcitabine/nab-paclitaxel can reduce fibrosis in PDAC, restore chemo-sensitivity and ultimately lead to improvements in overall survival (OS) and other clinically relevant outcomes. A safety run-in part will be conducted before opening a randomized part to confirm the recommended phase 3 dose (RP3D) of NIS793 in combination with SOC anti-cancer therapy.

Study design

This is a multicenter, double-blind, two-arm, randomized phase III study that will have two parts: a safety run-in part and a 2-arm randomized part. The study will be conducted in multiple geographical regions.
Safety run-in part: Approximately 10 participants will be enrolled at the starting dose to achieve at least 6 evaluable patients; however, if the starting dose is not recommended and a lower dose level is tested, 10 additional participants will be enrolled
Randomized part: Approximatively 480 participants will be recruited and randomized
(1:1 ratio) to the two treatment arms (~240/per arm). Participants will be stratified at randomization by performance status (0 vs. 1), presence of liver metastasis (yes vs. no), and region (North America, Europe, and Australia vs. other countries).

Intervention

Safety run-in:
combination of NIS793, gemcitabine and nab-paclitaxel
Randomized part:
Participants will be randomized to one of two treatment arms:
• Investigational arm (Arm A): combination of NIS793, gemcitabine and nab-paclitaxel
• Control arm (Arm B): combination of placebo, gemcitabine and nab-paclitaxel
A cycle of treatment is defined as 28 days.

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 tests), if applicable

pregnancy tests, and the completion of the questionnaires. The visits take longer because of extra blood draws, observation period after NIS793 administration. There are a number of additional visits such as screening, end of trial and if applicable the folllow up visits. The frequency of visits follows the dosing schedule of standard of care gemcitabine and nab-paclitaxel, however visits take longer.

As with any administration of the drugs, side effects may occur. However, the patient is observed before being allowed to go home and blood values are checked regularly. If necessary, a dose reduction of chemo treatment may be given. Also, chemo and NIS793 gift can be skipped delayed if physician deems it medically necessary/or justified.

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

- Age >= 18 years
- Histologically or cytologically confirmed mPDAC eligible for treatment in first line setting and not amenable for potentially curative surgery
- Presence of at least one measurable lesion assessed by CT and/or MRI according to RECIST 1.1
- ECOG performance status 0-1
- Adequate organ function
- WCBP must have negative pregnancy test during screening and before starting study treatment
- Must have recovered from treatment-related toxicities of prior anticancer therapies to grade <= 1 (CTCAE v 5.0), except alopecia

Exclusion criteria

- previous systemic anti-cancer treatment for mPDAC
- pancreatic neuroendocrine, acinar or inslet tumors
- known status of MSI-H or MMR-deficient pancreatic cancer
- presence of symptomatic CNS metastases, or CNS metastases that requires direct therapy or increasing doses of corticosteroids 2 weeks prior to study entry
- known history of severe allergy or hypersensitivity to any of the study drug or their excipients
- currently receiving any of the prohibited medications which cannot be discontinued within >= 7 days or 5 half-lifes, whichever is longer
- not recovered from a major surgery or has a major surgery within 4 weeks prior to start of the study
- radiation therapy or brain radiotherapy <= 4 weeks prior to study start
- impaired cardiac function or clinically significant cardio-vascular disease
- history of positive test for HIV infection
- active or chronic HBV or HCV infections (patients with a history of HCV infection must have been treated with confirmation of cure to be eligible)
- active untreated or uncontrolled systemic fungal, bacterial or viral infections
- use of hematopoietic growth factors or transfusion support <= 2 weeks prior to start the study
- conditions that are considered to have a high risk of clinically significant gastrointestinal track bleeding or any other condition associated with or history of significant bleeding
- serious, non-healing wounds
- pre-existing peripheral neuropathy > grade 1
- concurrent malignancy other than disease under treatment

- pregnant or breast-feeding woman
- WCBP, unless using highly effective method of contraception during and up to 90 days after the study drug treatment NIS793
- currently receiving other anti-cancer therapy or received other investigational product within 30 days or 5 half-lives prior to study treatment, whichever is longer

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	10-01-2023
Enrollment:	12
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	gemcitabine
Generic name:	gemcitabine
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	nab-paclitaxel
Generic name:	nab-paclitaxel
Registration:	Yes - NL intended use

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

Ethics review

Approved WMO Date:	23-02-2022
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-04-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	16-06-2022
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	14-09-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-10-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	16-02-2023
Application type:	Amendment
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	EUCTR2021-000591-10-NL
ClinicalTrials.gov	NCT04935359
CCMO	NL80537.056.22