A Randomized, Open-Label, Phase 2 Study of Nivolumab in Combination with Ipilimumab or Nivolumab Monotherapy in Participants with Advanced or Metastatic Solid Tumors of High Tumor Mutational Burden (TMB-H)

Published: 22-10-2018
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Primary Objectives:• To compare Blinded Independent Committee for Radiology (BICR)-assessed objective response rate (ORR) in participants of tissue Tumor Mutational Burden-High (tTMB-H) treated with nivolumab combined with ipilimumab • To compare...

Ethical review	Approved WMO
Status	Completed
Health condition type	Metastases
Study type	Interventional

Summary

ID

NL-OMON52919

Source
ToetsingOnline

Brief title
CA209-848

Condition

- Metastases

Synonym
Solid Tumors; Metastatic

Research involving

Human

Sponsors and support

Primary sponsor: Bristol-Myers Squibb
Source(s) of monetary or material Support: Pharmaceutical industry

Intervention

Keyword: High Tumor Mutational Burden, Ipilimumab, Nivolumab, Solid Tumor

Outcome measures

Primary outcome

BICR-assessed ORR using RECIST 1.1, and Response Assessment for Neuro-Oncology

(RANO) criteria in primary CNS tumors

Secondary outcome

Further efficacy endpoints will be assessed by BICR and the investigator and in

correlation with biomarker analysis.

Safety and tolerability will be assessed by review of Incidence of adverse

events, serious adverse events, and select adverse events

Study description

Background summary

Tumors with a high mutational burden may have a higher number of neo-antigens which, in principle, would be expected to be more immunogenic than tumors with comparatively low mutational burden. Therefore, high TMB has been hypothesized to correlate with improved efficacy in patients treated with immune-oncology (IO) therapies. This hypothesis has been supported by multiple publications across IO therapies, tumor types, and lines of treatment. The first published study of TMB as a biomarker of clinical outcomes was reported by Snyder et al, where high TMB (TMB-H) was found to be associated with efficacy in metastatic melanoma patients treated with anti-CTLA-4 therapy. Further studies by Rizvi et al reported TMB as a biomarker of pembrolizumab efficacy in second-line NSCLC patients. Additional studies of pembrolizumab and atezolizumab in NSCLC have

been generally consistent with these results.
This trial with nivolumab in combination with ipilimumab and nivolumab monotherapy will include participants with refractory, metastatic or unresectable TMB-H malignancy who have been treated with prior non-IO therapies. In general, malignancies included in this trial are the ones that have no standard of care after first line therapy showing an improved benefit over best supportive care. The low prevalence of TMB-H in these tumor types limits the feasibility of traditional large-scale randomized trials. As a result, a high unmet medical need exists for these patients, with no less expectation for immunotherapy activity.
The primary goal of this study is to demonstrate the clinical activity of nivolumab in combination with ipilimumab in multiple tumor types based on the status of TMB.

Study objective

Primary Objectives:
• To compare Blinded Independent Committee for Radiology (BICR)-assessed objective response rate (ORR) in participants of tissue Tumor Mutational Burden-High (tTMB-H) treated with nivolumab combined with ipilimumab
• To compare BICR-assessed ORR in participants of blood TMB-H treated with nivolumab combined with ipilimumab

Secondary Objectives:
- To estimate the duration of response (DOR), progression free survival (PFS), overall survival (OS) and time to response (TTR) in participants of tTMB-H treated with nivolumab combined with ipilimumab or nivolumab monotherapy assessed by BICR or investigator
- To estimate the duration of response (DOR), progression free survival (PFS), overall survival (OS) and time to response (TTR) in participants of bTMB-H treated with nivolumab combined with ipilimumab or nivolumab monotherapy assessed by BICR or investigator
- To assess the clinical benefit rate (CBR) in participants of tTMB-H treated with nivolumab combined with ipilimumab or nivolumab monotherapy
- To assess the clinical benefit rate (CBR) in participants of tTMB-H treated with nivolumab combined with ipilimumab or nivolumab monotherapy
- To evaluate the safety and tolerability of NKTR 214 combined with nivolumab and that of nivolumab monotherapy

Exploratory Objectives:
- To characterise the pharmacokinetics of ipilimumab combined with nivolumab and that of nivolumab monotherapy
- To characterise the immunogenicity of ipilimumab combined with nivolumab
- To assess the effect of ipilimumab combined with nivolumab and that of nivolumab monotherapy on quality of life

- To assess the effect on tumor and blood based biomarkers

Study design

The study will enroll participants diagnosed with select advanced or metastatic solid tumors of TMB-H with either tissue (tTMB) or blood TMB (bTMB) >= 10 mut/Mb. Both tissue and blood TMB will be assessed prior to randomization. Participants without a prior known tTMB-H status available via F1CDx assay, or a prior known bTMB result available from Foundation Medicine, will provide consent for pre-screening and TMB status determination, but consent for further screening procedures and study treatment should be deferred until TMB-H status is established. Screening process can continue when the participant is TMB-H. Participants with a prior known result of tTMB-H via F1CDx assay or bTMB-H from Foundation Medicine may proceed immediately with full screening procedures. Both tissue and blood TMB will be assessed prior to randomization. Prior results of tTMB or bTMB obtained from any other assays except the ones described above are not acceptable, including prior result of tTMB obtained via Foundation One assay.
Once the TMB-H status is determined, this study will consist of three phases: screening, treatment, and follow-up.
Approximately 210 patients will be treated globally.
Participants will receive either nivolumab (240 mg) every 2 weeks combined with ipilimumab (1 mg/kg) every 6 weeks or Nivolumab alone (480mg) every 4 weeks until disease progression, unacceptable toxicity, withdrawal of consent, the study ends or a maximum treatment duration of 2 years, whichever occurs first.
After treatment, all subjects will enter the follow-up phase of the study.
Subjects will have 2 visits within the first 100days after stopping treatment.
The remaining follow-up visits can be conducted over the phone and will occur every 3 months.
Participants will be permitted to continue on nivolumab +/- ipilimumab beyond initial defined progression, as long as they meet the protocol criteria.

Intervention

Participants will receive either nivolumab (240 mg) every 2 weeks combined with ipilimumab (1 mg/kg) every 6 weeks or Nivolumab alone (480mg) every 4 weeks. Both nivolumab and ipilimumab are provided by the sponsor.

Study burden and risks

As part of the trial, patients will be expected to attend multiple clinic visits, where they will undergo physical examinations, vital sign measurements, blood tests for safety assessment, pregnancy testing (for females of child bearing potential), and monitoring for adverse events. If there is no archive tumour tissue available or the sample was taken too long ago (more than 3 months), patients will be required to have a biopsy in order to participate. In

addition, every 12 weeks, patients will undergo radiographic assessment of their tumors (by CT or MRI) until disease progression or treatment discontinuation whichever occurs later. Blood will also be collected at certain visits for research purposes (PK, immunogenicity and biomarker studies). The frequency of visits and number of procedures carried out during this trial would typically be considered over and above standard of care. These procedures are conducted by medically trained professionals and every effort will be made to minimise any risks or discomfort to the patient.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

a) Participants with a refractory, metastatic, or unresectable
histologically or cytologically
confirmed solid malignant tumor with TMB-H who are refractory to standard local

therapies, or for which no standard treatment is available., b)Either a formalin-fixed, paraffin-embedded (FFPE) tissue block or unstained tumor tissue sections, obtained within 9 months and no additional intervening therapy (excluding
palliative therapy) prior to enrollment, with an associated pathology report, must be
submitted to the core laboratory for inclusion. Biopsy should be excisional, incisional or
core needle. Fine needle aspiration is unacceptable for submission., c) The IRT must be provided with the results of both tissue and blood TMB-H testing for eligible participants prior to randomization. Both results are utilized for stratification purposes.
d) Prior TMB-H results obtained with F1CDx assay (tissue) or assay from Foundation Medicine (blood) are acceptable for eligibility purposes. When these prior results are not available, tissue and / or blood samples must be provided for central TMB-H testing, and results must be available prior to randomization.
i) Participants must have either tTMB or bTMB >= 10 mut/Mb (tTMB >= 10 mut/Mb or the
new cutoff value of bTMB determined by the 1st interim analysis). Should one of the
two populations (tTMB-H or bTMB-H) reach the targeted sample size before the other,
then enrollment will continue only with participants for the other TMB-H population.
ii) TMB results obtained from any other methodologies are not acceptable for eligibility.
d) Participants must have measurable disease for response assessment as per RECIST 1.1 for solid tumors other than CNS, and RANO criteria for primary CNS malignancies.

Exclusion criteria

a) Active brain metastases or leptomeningeal metastases. Participants with brain metastases are eligible if these have been treated and there is no MRI evidence of progression for at least 8 weeks after treatment is complete and within 28 days prior to first dose of study treatment administration.
b) There must also be no requirement for immunosuppressive doses of systemic corticosteroids (> 10 mg/day prednisone equivalents) for at least 2 weeks prior to study treatment administration. Stable dose of anticonvulsants is allowed.
c) Patient who received whole brain radiation therapy are not eligible.
d) Participants who received prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti CD137, or anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	30-01-2019
Enrollment:	13
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Opdivo
Generic name:	Nivolumab
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Yervoy
Generic name:	Ipilimumab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	22-10-2018
Application type:	First submission
Review commission:	METC NedMec

Approved WMO

Date:	07-01-2019
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	01-03-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	04-03-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	19-06-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	11-07-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	13-01-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	30-04-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	14-05-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	11-06-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO	

Date:	15-01-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	04-02-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	24-06-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	16-07-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	23-11-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	09-12-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	08-04-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	10-06-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	28-06-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO	

Date:	16-09-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	11-10-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	04-01-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	11-01-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	26-05-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	06-06-2023
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	EUCTR2016-002898-35-NL
CCMO	NL67171.031.18
Other	U1111-1185-1326

Study results

Date completed: 10-07-2023

Results posted: 01-08-2024

First publication
01-01-1900