A Phase 3, Randomized, Open-label Study of NKTR-214 Combined with Nivolumab Versus Nivolumab in Participants with Previously Untreated Unresectable or Metastatic Melanoma

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Primary Objectives:- To compare ORR (objective response rate) using RECIST 1.1 for NKTR-214 combined with nivolumab and that of nivolumab monotherapy in participants with previously untreated unresectable or metastatic melanoma- To compare PFS (...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Skin neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON52577

Source
ToetsingOnline

Brief title
CA045-001

Condition

- Skin neoplasms malignant and unspecified

Synonym
Melanoma

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Melanoma, Metastatic, Nivolumab, NKTR-214

Outcome measures

Primary outcome

The efficacy endpoints of ORR, PFS and OS were assessed by a BICR.

The addition of bempegaldesleukin to nivolumab did not result in a statistically significant improvement in PFS (HR 1.09, 97% CI, 0.88-1.35) or ORR compared to nivolumab monotherapy as assessed by Blinded Independent Central Review (BICR), and the significance threshold for OS was also not crossed at the combined first and second OS analyses.

Furthermore, there was added toxicity with bempegaldesleukin plus nivolumab compared to nivolumab monotherapy including NK a higher incidence of drug-related adverse events (AEs), drug-related serious adverse events (SAEs) and drug-related AEs leading to study treatment discontinuation.

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.

Per Protocol Amendment 03, the secondary and exploratory objectives except

biomarker parameters are no longer applicable. Biomarker sample collection will not be applicable per Protocol Amendment 03. However, exploratory analysis of biomarkers on previously collected specimens may be conducted.

Study description

Background summary

PD-1 blockade is the recommended first-line therapy for treatment of BRAF WT and BRAF Mutant unresectable or metastatic melanoma in the National Comprehensive Cancer Network (NCCN) Guidelines.
Although first-line treatment with checkpoint inhibitors significantly improved clinical outcome for melanoma patients, a significant portion of patients progress or discontinue treatment due to treatment-related toxicities. These data support the need for combinations such as NKTR-214 and nivolumab that may yield greater clinical efficacy without adding significant treatment related toxicities.
The PIVOT-02 study of nivolumab and NKTR-214 included an expansion cohort in patients with treatment-naive melanoma. Previous analysis of the dose escalation part showed the response rate in this cohort was 69% (11 out of 16 participants) with 1 complete response and 10 partial responses with all responders maintaining their response. With 3 years of follow-up, nivolumab monotherapy in the Checkmate 067 study demonstrated an ORR of 44%, a 3-year PFS of 32% and a 3-year OS of 52%.13 The 3-year analysis of Checkmate 067 reaffirmed that responses to checkpoint inhibitors continue to evolve with longer follow-up as the number of participants achieving a complete response to nivolumab increased from 28 to 52 patients out of 316 total (9% to 16%) with a median duration of response that has still not been reached. It was anticipated that a similar evolution of responses would be seen in the combination of NKTR-214 and nivolumab as evolution of responses over time has been reported in the setting of high dose IL-2.
CA045001 was a Phase 3 randomized study of NKTR-214 combined with nivolumab vs Nivolumab monotherapy in participants with unresectable or metastatic melanoma that is previously untreated.
Study data were recently analyzed as planned and showed that the combination of bempegaldesleukin with nivolumab did not add benefit but could add side effects. Because of this, participant on Arm A and receiving bempegaldesleukin and nivolumab, will stop bempegaldesleukin and continue nivolumab alone. Participants on arm B can continue receiving nivolumab alone.
The study remains open so that participants can recieve nivolumab alone. Blood and urine samples will be taken before each treatment to assess how

participants are responding to the treatment.

Study objective

Primary Objectives:
- To compare ORR (objective response rate) using RECIST 1.1 for NKTR-214 combined with nivolumab and that of nivolumab monotherapy in participants with previously untreated unresectable or metastatic melanoma
- To compare PFS (progression free survival) using RECIST 1.1 of NKTR-214 combined with nivolumab and that of nivolumab monotherapy in participants with previously untreated unresectable or metastatic melanoma

Secondary Objectives:
- To evaluate efficacy of NKTR-214 combined with nivolumab and that of nivolumab monotherapy
- To evaluate the association between PD-L1 tumor expression on tumor cells (>= 1% or < 1%/indeterminate) and efficacy measures including PFS and ORR by blinded independent committee for radiology (BICR) and OS.
- To evaluate the safety and tolerability of NKTR 214 combined with nivolumab and that of nivolumab monotherapy

Exploratory Objectives:
- To characterise the pharmacokinetics of NKTR-214 combined with nivolumab and that of nivolumab monotherapy
- To characterise the immunogenicity of NKTR-214 combined with nivolumab and that of nivolumab monotherapy
- To assess the effect of NKTR-214 combined with nivolumab and that of nivolumab monotherapy on quality of life
- To assess the effect of NKTR-214 combined with nivolumab and that of nivolumab monotherapy on tumor and blood based biomarkers

Per Protocol Amendment 03, the secondary and exploratory objectives except biomarker parameters are no longer applicable. Biomarker sample collection will not be applicable per Protocol Amendment 03. However, exploratory analysis of biomarkers on previously collected specimens may be conducted.

Study design

This study was an open-label, phase 3 trial that aimed to assess the impact on response rate and overall survival in patients treated with nivolumab in combination with NKTR-214 when compared to patients treated with monotherapy nivolumab in subjects, with no prior systemic anticancer therapy given as primary therapy for advanced or metastatic melanoma.
783 patients were treated globally.
Participants received either nivolumab (360 mg) combined with NKTR-214 (0.006 mg/kg) or Nivolumab alone as an iv infusion every 3 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 entered the follow-up phase of the study. Subjects had 2 visits within the first 100 days after stopping treatment. Remaining follow-up visits occured very 3 months and could be conducted over the phone.
Participants were permitted to continue on NKTR-214 +/- nivolumab beyond initial defined progression, as long as they met the protocol criteria.

Following analysis that showed the addition of bempegaldesleukin to nivolumab did not result in a statistically significant improvement in progression free survival or overall survival rate compared to nivolumab monotherapy and added toxicity, protocol amendment 3 will be implemented to allow participants who are currently receiving bempegaldesleukin plus nivolumab to discontinue bempegaldesleukin and continue nivolumab monotherapy. All participants will receive nivolumab monotherapy at 480 mg IV once every 4 weeks. Participants < 40 kg will be administered a body weight adjusted nivolumab dose of 6 mg/kg IV once every 4 weeks. Study treatment will be until disease progression, unacceptable toxicity, withdrawal of consent, the study ends or a maximum treatment duration of 2 years, whichever occurs first. After completing treatment patients will be followed for 100 days then study participation ends unless they have side effects that require further follow up.

Intervention

Subjects received open-label treatment with nivolumab (flat dose 360 mg every 3 weeks) in combination with NKTR-214 (0.006 mg/kg every 3 weeks) or Nivolumab monotherpy (flat dose 360 mg every 3 weeks). Both nivolumab and NKTR-214 are provided by the sponsor.

Following analysis that showed the addition of bempegaldesleukin to nivolumab did not result in a statistically significant improvement in progression free survival or overall survival rate compared to nivolumab monotherapy and added toxicity, protocol amendment 3 will be implemented to allow participants who are currently receiving bempegaldesleukin plus nivolumab to discontinue bempegaldesleukin and continue nivolumab monotherapy. All participants will receive nivolumab monotherapy at 480 mg IV once every 4 weeks. Participants < 40 kg will be administered a body weight adjusted nivolumab dose of 6 mg/kg IV once very 4 weeks.

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 9 weeks until week 52 and then 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) as well as optional stool samples for microbiome analysis. 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.

Upon implementation of protocol amendment 3: Nivolumab treatment will be every 4 weeks until unacceptable toxicity, withdrawal of consent, the study ends or a maximum treatment duration of 2 years, whichever occurs first. After completing treatment patients will be followed for 100 days then study participation ends unless they have side effects that require further follow up.
Patients will undergo physical examinations, weight and vital sign measurements, blood and urine tests for safety assessment and to asses response to treatment, pregnancy testing (for females of child bearing potential), review of medications and monitoring for adverse events. Scans will be performed per standard of care.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

a) Participants must have an Eastern Cooperative Oncology Group (ECOG) performance status of <= 1 (adults 18 years or older) or/Lansky Performance Score >= 80% (for minors (ages 12-17 only)
b) Histologically confirmed stage III (unresectable) or stage IV melanoma, as per American Joint Committee on Cancer (AJCC) staging system, 8th edition
c) Treatment-naïve participants (ie, no prior systemic anticancer therapy for unresectable or metastatic melanoma) with the exception of prior adjuvant treatment for melanoma with approved agents (eg, BRAF/MEK inhibitors, ipilimumab, nivolumab, pembrolizumab or interferon). Participants who have had a recurrence within the 6 months of completing adjuvant treatment are not eligible.
d) Measurable disease by computed tomography (CT) or magnetic resonance imaging (MRI) per Response Evaluation Criteria in Solid Tumors (RECIST 1.1) criteria
e) Either a formalin-fixed, paraffin-embedded (FFPE) tissue block or unstained tumor tissue sections, obtained within 3 months prior to enrollment, with an associated pathology report, must be submitted to the core laboratory for inclusion. FFPE tissue block and unstained slides submitted should be from biopsy obtained within 6 months prior to enrollment. Unstained slides should be sectioned within 3 months prior to submission.
i) To be randomized, a participant must be classified as PD-L1 positive (>= % tumor cell membrane staining) vs PD-L1 negative (< 1% tumor cell membrane staining)/PD-L1 indeterminate (tumor cell membrane scoring hampered by high cytoplasmic staining or melanin content). Not evaluable participants are not eligible for randomization.
f) Participants must have known BRAF V600 mutation status or consent to BRAF V600 mutation testing per local institutional standards by approved methodology during the Screening period.

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) Uveal melanoma is excluded.

Study design

Design

Study phase:	3
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	10-12-2020
Enrollment:	35
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO

Date:	16-10-2018
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Approved WMO

Date:	07-01-2019
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	20-06-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	26-06-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	23-07-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	13-08-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	08-10-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	23-10-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	10-08-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	22-09-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO	

Date:	04-05-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	24-06-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	29-07-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	08-09-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	13-09-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	18-03-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	19-05-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	20-09-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	17-10-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	EUCTR2018-001423-40-NL
ClinicalTrials.gov	NCT03635983
CCMO	NL67164.091.18