A Phase 3, Randomized, Open-label Study to Compare Adjuvant Immunotherapy of Bempegaldesleukin Combined with Nivolumab Versus Nivolumab After Complete Resection of Melanoma in Patients at High Risk for Recurrence (PIVOT-12)

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

Summary

ID

NL-OMON55317

Source
ToetsingOnline

Brief title
PIVOT-12

Condition

- Skin neoplasms malignant and unspecified
- Pigmentation disorders

Synonym

Melanoma, Skin cancer

Research involving
Human

Sponsors and support

Primary sponsor: Nektar Therapeutics
Source(s) of monetary or material Support: Nektar Therapeutics en Bristol-Myers Squibb.

Intervention

Keyword: Adjuvant immunotherapy, Bempegaldesleukin, High risk for Recurrence, Resected Melanoma

Outcome measures

Primary outcome

The primary objective is:

To compare the efficacy, as measured by recurrence-free survival (RFS) by

blinded independent central review (BICR), of bempegaldesleukin plus nivolumab

versus nivolumab in patients with completely resected Stage IIIA (lymph node

[LN] metastasis > 1 mm), Stage IIIB/C/D, or Stage IV (American Joint Committee

on Cancer [AJCC] 8th edition) cutaneous melanoma with no evidence of disease

(NED) who are at high risk for recurrence.

Secondary outcome

The secondary objectives are:

• To compare the overall survival (OS) of bempegaldesleukin plus nivolumab

versus nivolumab in patients with completely resected Stage IIIA (LN metastasis

> 1 mm), Stage IIIB/C/D, or Stage IV NED melanoma

• To evaluate distant metastasis-free survival (DMFS) by Investigator in

patients who have Stage IIIA (LN metastasis > 1 mm) or IIIB/C/D melanoma at

study entry

• To assess the overall safety and tolerability of bempegaldesleukin plus nivolumab versus nivolumab in study patients

• To describe changes in patient-reported outcomes (PROs) as assessed by the global health/quality of life (GH/QoL) and physical functioning subscales of the 30-item European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30)

• To evaluate the association between programmed cell death ligand 1 (PD-L1) expression status and RFS by BICR

• To assess the efficacy, as measured by RFS by Investigator, of bempegaldesleukin plus nivolumab versus nivolumab in patients with completely resected Stage IIIA (LN metastasis > 1 mm), Stage IIIB/C/D, or Stage IV NED melanoma

Study description

Background summary

Bempegaldesleukin (NKTR-214) is a prodrug of a conjugated cancer immunotherapy cytokine that exerts its biological activity by binding to the IL-2 receptor and subsequent activation of effector T cells. As a PEGylated human recombinant IL-2 molecule of aldesleukin with approximately six releasable polyethylene glycol (PEG) chains, bempegaldesleukin can be administered conveniently in the outpatient setting using an antibody-like dosing regimen. It is pharmacologically classified as an immunostimulatory interleukin cytokine.

The immunogenic properties of bempegaldesleukin with the induction of tumor-infiltrating

lymphocytes and upregulation of the PD-1/PD-L1 axis makes bempegaldesleukin a potentially
promising combination therapy for use with checkpoint inhibitors that target and inhibit the
PD-1/PD-L1 pathway. Moreover, the side effect profile of bempegaldesleukin generally does
not overlap with that of checkpoint inhibitors, further supporting the use of bempegaldesleukin
as a potentially complimentary combination partner with checkpoint inhibitors.

See protocol for more details regarding previous trials

Study objective

The primary objective is to compare the efficacy, as measured by recurrence-free survival (RFS) by blinded independent central review (BICR), of bempegaldesleukin plus nivolumab versus nivolumab in patients with completely resected Stage IIIA (lymph node [LN] metastasis > 1 mm), Stage IIIB/C/D, or Stage IV (American Joint Committee on Cancer [AJCC] 8th edition) cutaneous melanoma with no evidence of disease (NED) who are at high risk for recurrence.

The secondary objectives are:
• To compare the overall survival (OS) of bempegaldesleukin plus nivolumab versus nivolumab in patients with completely resected Stage IIIA (LN metastasis > 1 mm), Stage IIIB/C/D, or Stage IV NED melanoma
• To evaluate distant metastasis-free survival (DMFS) by Investigator in patients who have Stage IIIA (LN metastasis > 1 mm) or IIIB/C/D melanoma at study entry
• To assess the overall safety and tolerability of bempegaldesleukin plus nivolumab versus nivolumab in study patients
• To describe changes in patient-reported outcomes (PROs) as assessed by the global health/quality of life (GH/QoL) and physical functioning subscales of the 30-item European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30)
• To evaluate the association between programmed cell death ligand 1 (PD-L1) expression status and RFS by BICR
• To assess the efficacy, as measured by RFS by Investigator, of bempegaldesleukin plus nivolumab versus nivolumab in patients with completely resected Stage IIIA (LN metastasis > 1 mm), Stage IIIB/C/D, or Stage IV NED.

Study design

This is a multicenter, randomized, open-label, Phase 3 study that will evaluate the efficacy and safety of bempegaldesleukin plus nivolumab compared with nivolumab after complete resection of melanoma in patients at high risk for recurrence. Patients will be randomized in a 1:1 ratio to one of two treatment

arms:
• Arm A: bempegaldesleukin plus nivolumab every 3 weeks (q3w)
• Arm B: nivolumab monotherapy every 4 weeks (q4w)

Randomization will be stratified by:
• PD-L1 status by Dako PD-L1 PharmDx 28-8 assay: PD-L1 >= 1% vs PD-L1 < 1% vs indeterminate/not evaluable
Note: PD-L1 indeterminate/not evaluable will be capped at a maximum of 25% of the total patient population
• Stage: IIIA(LN metastases > 1 mm)/IIIB vs IIIC vs IIID/IV

Patients will be treated for approximately 1 year (maximum of 17 cycles for Arm A and 13 cycles for Arm B) or until disease recurrence, death, unacceptable toxicity, decision by Investigator to discontinue treatment, decision by patient to discontinue treatment or withdraw consent from the study, patient is lost to follow-up, or decision by Sponsor to terminate the trial, whichever is earlier. Efficacy, safety, pharmacokinetic (PK), immunogenicity, and biomarker assessments will be performed during treatment as presented in the On-Treatment Schedules of Events (Table 2 for Arm A; Table 3 for Arm B).
Patients will undergo Safety Follow-up Visits for 100 (± 7) days after the last dose of study treatment and imaging assessments for up to 5 years from randomization (Table 4). Patients will be followed for survival until death, the patient withdraws consent from all further study assessments including survival follow-up, the patient is lost to follow-up, or the study is terminated by the Sponsor.
The end of study will be no more than 5 years from randomization of the last patient or Sponsor decision to terminate the study, whichever comes first.

Intervention

The study includes a screening period, treatment period and follow-up period.
Patient will recieve once of the following treatments:
• Arm A: NKTR-214 0,006 mg/kg IV and nivolumab 360 mg IV q3w (on Day 1 of each 3-week cycle) or 4.5 mg/kg IV q3w for patients < 40 kg.
• Arm B: Nivolumab 480 mg IV q4w (on Day 1 of each 4-week cycle) or 6.0 mg/kg IV q4w for patients < 40 kg.

Screening:
Patients will provide written informed consent to participate in the study before completing any protocol-specified procedures or evaluations not considered to be part of the patient*s standard care. For adolescent patients unable to give their written consent, in accordance with local regulations, one or both parents, a guardian, or a legally acceptable representative must be informed of the study procedures and must document permission by signing the ICF approved for the study prior to clinical study participation.

Treatment period:

Following Screening and confirmation of a patient*s eligibility, patients will be randomized 1:1 to Arm A (bempegaldesleukin in combination with nivolumab) or Arm B (nivolumab alone) using the IRT system. Within 5 calendar days following randomization, the patient should receive the first dose of study treatment. Patients will be treated up to approximately 1 year (maximum of 17 cycles for Arm A and 13 cycles for Arm B) or until disease recurrence, death, unacceptable toxicity, decision by Investigator to discontinue treatment, decision by patient to discontinue treatment or withdraw consent from the study, patient is lost to follow-up, or decision by Sponsor to terminate the trial.
Study treatment is administered q3w (Arm A) or q4w (Arm B), and patients will have clinic visits for dose administration and/or study assessments approximately 3 times a month (see Table 2 for Arm A and Table 3 for Arm B details).

Follow-up period:
Long-term follow-up comprises 2 Safety Follow-up Visits and Survival Follow-up visits. Long-term follow-up will continue until the patient withdraws consent, dies or is lost to follow-up, or the study is terminated by the Sponsor. Additional subsequent cancer therapy details such as regimen, setting of the regimen, line of therapy, start date and end date of each regimen, best response to the regimen, and date of progression after next line of therapy will be collected.

Study burden and risks

Benefit/Risk Aspects
Bempegaldesleukin has been generally well-tolerated in the clinical studies to date, both as monotherapy as well as in combination with nivolumab, with promising evidence of clinical efficacy and a potentially favorable benefit-risk profile. Bempegaldesleukin has been safely administered in an outpatient setting supported by appropriate clinical monitoring.

Hypotension has been characterized as an identified risk of bempegaldesleukin and can be effectively mitigated by prophylaxis and hydration guidelines. Other risks associated with bempegaldesleukin include cytokine-related toxicities (e.g., flu-like symptoms, rash, pruritus, fatigue, hepatic transaminase elevations, and creatinine elevation), infusion-related reactions, thyroid dysfunction, eosinophilic disorder, and arthralgia; these AEs are generally mild or moderate in severity and can be monitored and managed in clinical setting. Cases of thyroid dysfunction (hypothyroidism, hyperthyroidism, thyroiditis), dermatitis, pneumonitis, hepatitis, myocarditis, myositis/myasthenia gravis and vitiligo/hypopigmentation consistent with immune-mediated mechanism have been observed in patients receiving bempegaldesleukin in combination with nivolumab; however, there is no evidence that bempegaldesleukin increases the frequency or severity of immune-mediated AEs associated with nivolumab with the limitation of small sample size and relatively shorter treatment duration for bempegaldesleukin-treated patients.

The continued development of bempegaldesleukin in combination with nivolumab for the treatment of various cancers is warranted based on a positive benefit-risk profile. The encouraging manageable and generally non-overlapping toxicity profile of the combination of bempegaldesleukin and nivolumab, together with the clinical evidence of activity of this combination in melanoma and the demonstrated importance of adjuvant treatment options for patients with resected melanoma at high risk for recurrence, suggest a positive benefit-risk for this study in the adjuvant setting.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Provide written, informed consent to participate in the study and follow the study procedures. The Investigator takes responsibility for ensuring that all vulnerable patients are protected and participate voluntarily in an environment free from coercion or undue influence. (See Section 5.2 for details about obtaining informed consent for adolescent patients.)

2. Male or female patients age 18 years or older at the time of signing the informed consent form (ICF) (age 18 years or older where local regulations or institutional policies do not allow for patients < 18 years of age to participate).

3. Patients must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (>= 17 years of age)/Lansky Performance Score >= 80% (12 to 16 years of age, inclusive) (for details, see Appendix 3).

4. Histologically confirmed Stage IIIA (LN metastasis > 1 mm [i.e., at least one LN metastasis measuring > 1 mm at greatest diameter]), IIIB/C/D, or IV (M1a/b/c/d) cutaneous melanoma by AJCC (8th edition) at study entry that has been completely surgically resected within 12 weeks prior to randomization. Patients with presence of in transit or microsatellite disease will be allowed if disease has been completely surgically resected. Patients must have been surgically rendered free of disease with negative surgical margins documented, as applicable. (Please refer to Section 5.2 for details of minimum documentation requirements and Appendix 2 for AJCC 8th edition definitions of TNM and staging.)

5. Prior treated central nervous system (CNS) metastases must have magnetic resonance imaging (MRI) evidence of no recurrence for at least 4 weeks after treatment, subjects must be off immunosuppressive doses of systemic steroids (> 10 mg/day or equivalent) for at least 14 days prior to study drug administration and must have returned to neurologic baseline post-operatively. (The 4-week period of stability is measured after the completion of the neurologic interventions [i.e., surgery and/or radiation]). (Note: Leptomeningeal disease is excluded.)

6. In addition to neurosurgery to treat CNS metastases, adjuvant radiation after the resection of CNS metastasis is allowed. Immunosuppressive doses of systemic steroids (doses >= 10 mg/day prednisone or equivalent) must be discontinued at least 14 days before study drug administration.

7. Tumor tissue from biopsy or resected disease must be provided to central laboratory for PD-L1 status analysis. Must have PD-L1 expression classification (>= 1%, < 1%, indeterminate, or not evaluable) prior to randomization.

8. Disease-free status documented by a complete physical examination and imaging studies within 28 days prior to randomization (see Table 1 for details of required assessments).

9. Demonstrated adequate organ function, as defined below:
a. White blood cells >= 2000/µL
b. Absolute neutrophil count >= 1500/µL (1.5 × 109/L)
c. Hemoglobin >= 9.0 g/dL (90 g/L)
d. Platelet count >= 100 × 109/L
e. Total bilirubin <= 1.5 × upper limit of normal (ULN) (except patients with Gilbert Syndrome, who must have total bilirubin < 3.0 mg/dL)
f. Alanine aminotransferase (ALT) <= 3 × ULN
g. Aspartate aminotransferase (AST) <= 3 × ULN
h. Serum creatinine <= 1.5 × ULN (133 µmol/L) OR calculated creatinine clearance >= 50 mL/min (using Cockcroft-Gault formula and actual body weight)

10. A documented left ventricular ejection fraction (LVEF) > 45% using standard echocardiogram or multigated acquisition (MUGA) scan test.

11. Reproductive Status
a. Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin [HCG]) within 14 days prior to the start of study treatment.
b. Women must not be breastfeeding
c. WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study treatment and for 5 months after bempegaldesleukin and/or nivolumab treatment completion. Women should use an adequate method(s) of contraception as indicated in Appendix 4. WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements, and still must undergo pregnancy testing as described in this section.
d. Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study treatment(s) and 7 months after bempegaldesleukin and/or nivolumab treatment completion. In addition, male patients must be willing to refrain from sperm donation during this time (Appendix 4).

12. Patients must be able and willing to comply with the study visit schedule and study procedures.

Exclusion criteria

1. Use of an investigational agent or an investigational device within 28 days before randomization.

2. Female patients who are pregnant or lactating, who plan to get pregnant, or who have a positive serum or urine pregnancy test.

3. History of ocular/uveal melanoma or mucosal melanoma.

4. Active, known or suspected autoimmune disease. Patients with Type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.

5. Conditions requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of randomization. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.

6. Prior therapy for melanoma. Exceptions include surgery for the melanoma lesion(s) and/or adjuvant radiation therapy for CNS lesions at least 28 days prior to randomization. Patients must have recovered from all Grade >= 2 radiation-related toxicities.

7. Prior therapy with interferon, talimogene laherparepvec (Imylgic®), IL-2 directed therapy, anti-PD-1, anti PD L1, anti PD L2, anti-CD137, or anti-CTLA-4 antibody (including ipilimumab or any other antibody or drug specifically targeting T cell co stimulation or checkpoint pathways).

8. History of leptomeningeal disease.

9. History of hypersensitivity or allergy to study drug components (for nivolumab, bempegaldesleukin, or any of their excipients).

10. History of severe hypersensitivity reaction to any monoclonal antibody.

11. Prior malignancy active within the previous 3 years except for locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer or prior melanoma, superficial bladder cancer, or carcinoma in situ of the prostate, cervix, or breast. Consult with the Medical Monitor about other potential exceptions.

12. History of allogeneic stem cell transplant; history of solid organ or tissue transplant that requires systemic use of immune suppressive agents.

13. Prior surgery that required general anesthesia within 28 days before the first dose of study treatment; surgery requiring local/epidural anesthesia within 72 hours before first dose.

14. Active infection requiring systemic therapy within 14 days prior to randomization.

15. History of idiopathic pulmonary fibrosis (including pneumonitis), drug-induced pneumonitis, organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia), or evidence of active pneumonitis on Screening chest CT scan.

16. Any positive test result for hepatitis B virus or hepatitis C virus indicating presence of virus (e.g., hepatitis B surface antigen [HBsAg, Australia antigen] positive, or hepatitis C antibody [anti-HCV] positive [except if HCV-RNA negative]).

17. Any positive test result for immunodeficiency or active human immunodeficiency virus (HIV 1/2 antibodies).

18. Prolonged Fridericia*s corrected QT interval (QTcF) > 450 ms for men and > 470 ms for women at Screening.

19. Known cardiovascular history including unstable or deteriorating cardiac disease within the previous 12 months prior to Screening including, but not limited to, the following:
a. Unstable angina or myocardial infarction
b. Transient ischemic attack (TIA)/CVA
c. Congestive heart failure (New York Heart Association Class III or IV)
d. Uncontrolled clinically significant arrhythmias

20. Need for > 2 antihypertensive medications for management of hypertension (including diuretics). Patients with hypertension must be on a stable antihypertensive regimen for the 14 days prior to randomization.
Note: An antihypertensive medication that contains 2 drugs under one formulation is counted as 2 antihypertensive medications (e.g., angiotensin-converting-enzyme [ACE] inhibitor and diuretic, calcium channel blocker and ACE inhibitor).

21. History of pulmonary embolism, deep vein thrombosis, or prior clinically significant venous or non-CVA/TIA arterial thromboembolic event (e.g., internal jugular vein thrombosis) within 3 months prior to randomization.
Note: Patients with a history of a venous or arterial thromboembolic event must be asymptomatic for at least 2 weeks prior to randomization and must be receiving a stable regimen of therapeutic anticoagulation (preferably low molecular weight heparin [LMWH] or direct oral anticoagulation [DOAC]; see Section 5.14.3.3 for further guidance). Note: Unless there is a new medical contraindication observed after Cycle 1 Day 1, a patient with a history of venous or arterial thromboembolic event must be willing to maintain therapeutic anticoagulation throughout participation on the treatment phase of the study.

22. Patients with inadequately controlled adrenal insufficiency.

23. Patients who have received a live / attenuated vaccine within 30 days of randomization.

24. Known current drug or alcohol abuse.

25. Receiving any medication prohibited in combination with study treatments as described in the respective product labels, unless medication was stopped within 7 days prior to randomization.

26. Any condition including medical, emotional, psychiatric, or logistical that, in the opinion of the Investigator, would preclude the patient from adhering to the protocol or would increase the risk associated with study participation or study drug administration or interfere with the interpretation of safety results (e.g., a condition associated with diarrhea or acute diverticulitis).

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	05-02-2021
Enrollment:	70
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	bempegaldesleukin (NKTR-214)
Generic name:	bempegaldesleukin (NKTR-214)
Product type:	Medicine
Brand name:	Opdivo
Generic name:	Nivolumab
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	13-08-2020
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	17-11-2020
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	14-12-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	15-12-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	10-02-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	22-02-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)

Approved WMO Date:	02-04-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	03-06-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	08-08-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	18-10-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	28-12-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	10-01-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	01-04-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	30-05-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)

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	EUCTR2020-000917-34-NL
CCMO	NL74477.028.20
Other	US IND nro 125471

Study results

Date completed:	19-04-2022
Results posted:	02-03-2023
Actual enrolment:	12

Summary results
Trial ended prematurely

First publication
24-02-2023