A phase III, open-label, multicenter, two-arm, randomized study to investigate the efficacy and safety of cobimetinib plus atezolizumab versus pembrolizumab in patients with previously untreated advanced BRAFv600 wild-type melanoma

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To evaluate the efficacy of cobimetinib plus atezolizumab compared with pembrolizumab, as measured by the primary endpoint of progression-free survival (PFS) by independent review

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

Summary

ID

NL-OMON46404

Source
ToetsingOnline

Brief title
CO39722

Condition

- Skin neoplasms malignant and unspecified

Synonym
melanoma, skin cancer

Research involving
Human

Sponsors and support

Primary sponsor: Roche Nederland B.V.
Source(s) of monetary or material Support: Farmaceutische industrie

Intervention

Keyword: atezolizumab, cobimetinib, melanoma, pembrolizumab

Outcome measures

Primary outcome

Progression-free survival, as measured by independent review

Secondary outcome

1. Overall survival

2. Two-year landmark survival

3. Objective response rate

4. PFS, as determined by the investigator

5. Disease control rate

6. Duration of objective response as determined by indenpendent review

7. Duration of objective response as determined by the investigator

8. Change from baseline in HRQoL scores

9. Occurrence and severity of adverse events

10. Change from baseline in selected vital signs

11. Change from baseline in selected clinical laboratory test results

12. Plasma concentration of cobimetinib at specified timepoints

13. Serum concentration of atezolizumab at specified timepoints

14. Incidence of anti-drug antibodies (ADAs) during the study relative to the

prevalence of ADAs at baseline

Study description

Background summary

Although the outcome for promptly diagnosed superficial tumors is good, in the metastatic setting, melanoma is associated with high rates of mortality and disease-related morbidity. The clinical outcome of patients with melanoma is highly dependent on the stage at presentation. Despite recent therapeutic advances, metastatic melanoma continues to be one of the most deadly cancers, with a relative 5-year survival rate of 15%*17%. In 2012, there were around 232,000 new cases and 55,000 deaths from melanoma worldwide, with more than 100,000 new cases and 22,000 deaths in Europe. Moreover, the number of melanoma cases worldwide is increasing faster than any other cancer, especially in fair-skinned, Caucasian populations; estimates suggest a doubling of melanoma incidence every 10*20 years. Immunotherapeutic agents currently approved for advanced BRAF wild-type melanoma, ipilimumab, nivolumab and pembrolizumab, have led to a better progression-free survival. However combining immunotherapeutic agents leads to challenging toxicity. Thus, despite recent advances in treatments for patients with advanced melanoma, a significant unmet medical for more efficacious treatment options with less toxicity remains.

Study objective

To evaluate the efficacy of cobimetinib plus atezolizumab compared with pembrolizumab, as measured by the primary endpoint of progression-free survival (PFS) by independent review

Study design

Study CO39722 is a Phase III, multicenter, open-label, randomized study. BRAFV600 wild-type status will be determined using local testing, and enrollment based on local testing will be subsequently confirmed with central testing after enrollment. This study will be conducted globally and approximately 450 patients will be randomized
in a 1:1 ratio to one of two treatment arms:
* Arm A: Patients will receive 60 mg of cobimetinib by mouth (PO) on a 21 days on, 7 days off (21/7) schedule (dosing on Days 1*21, followed by no dosing on Days 22*28) plus 840 mg of atezolizumab by intravenous (IV) infusion on Days 1 and 15 of each 28-day cycle (n = 225).
* Arm B: Patients will receive 200 mg of pembrolizumab administered by IV infusion every 3 weeks (Q3W) (n = 225).
Stratification factors are PD-L1 status (IC0 vs. IC1, 2, 3), baseline plasma LDH level (less than or equal to the upper limit of normal [ULN] vs. greater than the ULN), and geographic region (North America vs. Europe vs. Australia,

New Zealand, and others).

Intervention

The investigational medicinal products (IMPs) for this study are cobimetinib, atezolizumab, and pembrolizumab.

Patients randomized to Arm A will receive cobimetinib 60 mg (three tablets of 20 mg each) by mouth QD on Days 1*21 of each 28-day cycle. This 4-week period is considered a treatment cycle. Cobimetinib should be taken at the same time every day. It can be taken with or without food. If a daily dose of cobimetinib is missed or if vomiting occurs when the dose is taken, resume dosing with the next scheduled dose. Patients randomized to Arm A will also receive atezolizumab 840 mg by IV infusion on Day 1 and Day 15 of each 28-day cycle. This 4-week period is considered a treatment cycle.

Patients randomized to Arm B will receive 200 mg fixed-dose of pembrolizumab by IV infusion Q3W as monotherapy. A 3-week period is considered a treatment cycle.

Study burden and risks

The safety plan for patients in this study is based on clinical experience with cobimetinib and atezolizumab in completed and ongoing studies, and published data from similar molecules. The risks associated with cobimetinib, atezolizumab, and pembrolizumab are detailed in Sections 5.1.1, 5.1.2, and 5.1.3, respectively. Adverse events will be reported as described in Sections 5.2*5.6. In addition to the oversight provided by the Medical Monitor and drug safety personnel for this trial, an iDMC will monitor and evaluate patient safety throughout the study.

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

Disease-Specific Inclusion Criteria
- Histologically confirmed locally advanced and unresectable or metastatic melanoma
- Naive to prior systemic anti-cancer therapy for melanoma with the following exeptions:
* adjuvant treatment with IFN-alpha, IL-2 or vaccine therapies, if discontinued at least 28 days prior to initiation of study treatment
* adjuvant treatment with ipilimumab, if discontinued at least 90 days prior to initiation of study treatment
- Documentation of BRAFV600 wild-type status in melanoma tumor tissue through use of a clinical mutation test approved by the local health authority
- A representative, formalin-fixed, paraffin-embedded (FFPE) tumor specimen in a paraffin block (preferred) or 20 slides containing unstained, freshly cut, serial sections must be submitted along with an associated pathology report prior to study entry. If 20 slides are not available or the tissue block is not of sufficient size, the patient may still be eligible for the study, after discussion with and approval by the Medical Monitor. If archival tissue is unavailable or is determined to be inadequate , tumor tissue must be obtained from a biopsy performed at screening.
- Measureable disease according to RECIST v1.1;General Inclusion Criteria
- Age ><=18 years at time of signing Informed Consent Form
- Ability to comply with the study protocol, in the investigator's judgment
- Histologically or cytologically confirmed BRAFV600 wild-type melanoma
- ECOG Performance Status of 0 or 1
- Life expectancy ><=3 months
- Adequate hematologic and end-organ function
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use at least two forms of effective contraceptive with a failure rate of < 1% per year during the treatment period and for at least 3 months after the last

dose of cobimetinib and at least 5 months for after the last dose of atezolizumab and pembrolizumab.
- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures (e.g. condom), and agreement to refrain from donating sperm, for at least 3 months after the last dose of cobimetinib
- Willingness and ability of patients to report selected study outcomes using an electronic device or paper backup questionnaires

Exclusion criteria

General Exclusion Criteria
- Inability to swallow medications
- Malabsorption condition that would alter the absorption of orally administered medications
- Pregnancy, breastfeeding, or intention of becoming pregnant during the study
- History of severe hypersensitivity reactions to components of the cobimetinib, atezolizumab or pembrolizumab formulations
- Administration of a live, attenuated vaccine within 4 weeks before randomization or anticipation of need for such a vaccine during the study
- Any anti-cancer therapy, including chemotherapy or hormonal therapy, within 2 weeks prior to initiation of study treatment
- Treatment with systemic immunostimulatory agents within 28 days or 5 half-lives of the drug, whichever is shorter, prior to Day 1 of Cycle 1
- Treatment with systemic immunosuppressive medications within 2 weeks prior to Day 1 of Cycle 1
- Any serious medical condition or abnormality in clinical laboratory tests that, in the investigator's judgment, precludes the patient's safe participation in and completion of the study;Cancer-Related Exclusion Criteria
- Ocular melanoma
- Major surgery or radiotherapy within 21 days prior to Day 1 of Cycle 1 or anticipation of needing such procedure while receiving study treatment
- Uncontrolled tumor-related pain
- Uncontrolled pleural effusion, pericardial effusion, or ascites requiring repeated drainage more than once every 28 days
- Active or untreated CNS metastases;Exclusions Related to Cardiovascular Disease
- Unstable angina, new-onset angina within the last 3 months, myocardial infarction within the last 6 months prior to Day 1 of Cycle 1, or current congestive heart failure classified as New York Heart Association Class II or higher
- LVEF below institutional lower limit of normal or <50%, whichever is lower
- Poorly controlled hypertension, defined as sustained, uncontrolled, non-episodic baseline hypertension consistently above 159/99 mmHg despite optimal medical management
- History or presence of an abnormal ECG that is clinically significant in the investigator's opinion, including complete left bundle branch block, second- or third degree heart block, or evidence of prior myocardial infarction;Exclusions Related to Infections
- HIV infection
- Active tuberculosis infection

- Severe infections within 4 weeks prior to Day 1 of Cycle 1, including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia
- Signs or symptoms of clinically relevant infection within 2 weeks prior to Day 1 of Cycle 1
- Treatment with oral or IV antibiotics within 2 weeks prior to Day 1 of Cycle 1
- Active or chronic viral hepatitis B or C infection ;Exclusions Related to Ocular Disease
- Known risk factors for ocular toxicity ;Exclusions Related to Autoimmune Conditions and Immunomodulatory Drugs
- Active or history of autoimmune disease or immune deficiency
- Prior allogeneic stem cell or solid organ transplantation
- History of idiopathic pulmonary fibrosis, organizing pneumonia, druginduced or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan
- Treatment with systemic immunosuppressive medications within 2 weeks prior to Day 1, Cycle 1 ;Exclusions Related to Other Medical Conditions or Medications
- Active malignancy (other than melanoma) or a prior malignancy within the past 3 years
- No previous cancer immunotherapy including anti-PD-1 or anti-PD-L1
- Any Grade >=3 hemorrhage or bleeding event within 28 days of Day 1 of Cycle 1
- History of stroke, reversible ischemic neurological defect, or transient ischemic attack within 6 months prior to Day 1
- Proteinuria >3.5 g/24 hr
- Consumption of foods, supplements, or drugs that are strong or moderate CYP3A4 enzyme inducers or inhibitors at least 7 days prior to Day 1 of Cycle 1 and during study treatment

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:	Recruitment stopped
Start date (anticipated):	07-05-2018
Enrollment:	18

Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Cotellic
Generic name:	Cobimetinib
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Keytruda
Generic name:	Pembrolizumab
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Tecentriq
Generic name:	Atezolizumab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	05-09-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	28-11-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-12-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	02-02-2018

Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-02-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	11-04-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	17-04-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	09-01-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	16-05-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	11-10-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-03-2020
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	EUCTR2016-004387-18-NL
CCMO	NL62569.056.17