A phase III, double-blinded, randomized, placebo-controlled study of atezolizumab plus cobimetinib and vemurafenib versus placebo plus cobimetinib and vemurafenib in previously untreated BRAF V600 mutation-positive patients with unresectable locally advanced or metastatic melanoma

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This study will evaluate the efficacy, safety, and pharmacokinetics of atezo + cobi + vem compared with placebo plus cobimetinib plus vemurafenib (placebo+ cobi + vem) in patients with previously untreated, BRAFV600 mutation*positive, metastatic or…

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

Summary

ID

NL-OMON47276

Source
ToetsingOnline

Brief title
CO39262 TRILOGY

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, Vemurafenib

Outcome measures

Primary outcome

PFS, defined as the time from randomization to the first occurrence of disease progression, as determined by the investigator according to RECIST v1.1, or death from any cause, whichever occurs first.

Secondary outcome

• PFS, defined as the time from randomization to the first occurrence of disease progression, as determined by an IRC according to RECIST v1.1, or death from any cause, whichever occurs first

• Objective response, defined as a CR or PR on two consecutive occasions >= 4 weeks apart, as determined by the investigator according to RECIST v1.1.

• DOR, defined as the time from the first occurrence of a documented objective response to disease progression, as determined by the investigator according to RECIST v1.1, or death from any cause, whichever occurs first.

• OS, defined as the time from randomization to death from any cause.

• 2-year landmark survival, defined as survival at 2 years.

More secondary study parameters and corresponding endpoints are described in

protocol paragraph 2 on page 35-37.

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. Approximately 50% of all cutaneous melanomas harbor an activating mutation in BRAF, a major driver of signaling in the RAS/RAF/MEK/ERK MAP kinase (MAPK) pathway. In the past several years, new agents, including targeted therapies and immunotherapies, have been approved in the European Union and the United States for the treatment of BRAFV600 mutation*positive advanced melanoma. Melanoma cells are also highly immunogenic and thus an appropriate target for immunotherapy. Despite recent advances in treatments for patients with advanced melanoma, a significant unmet medical for more efficacious treatment options remains.

Study objective

This study will evaluate the efficacy, safety, and pharmacokinetics of atezo + cobi + vem compared with placebo plus cobimetinib plus vemurafenib (placebo+ cobi + vem) in patients with previously untreated, BRAFV600 mutation*positive, metastatic or unresectable locally advanced melanoma.

Study design

Approximately 500 patients will be randomized in the study. Patients will be randomized in a 1:1 ratio to Arm A (placebo + cobi + vem) or Arm B (atezo + cobi + vem). Patients in both arms will be treated with cobimetinib and vemurafenib during a run-in period of 28 days. Patients in Arm A (control arm) will receive atezolizumab placebo, cobimetinib, and vemurafenib (960 mg twice daily [BID]). Patients in Arm B (experimental arm) will receive active

atezolizumab, cobimetinib, and vemurafenib (720 mg BID). As the vemurafenib doses are different between in the two treatments arms, vemurafenib will be blinded in both study arms. To ensure adequate blinding, patients in both arms will receive the same number of vemurafenib tablets, with patients in Arm A receiving all active vemurafenib tablets and patients in Arm B receiving a combination of active vemurafenib tablets and vemurafenib placebo tablets. Following randomization, patients will enter a 28-day run-in period to receive treatment with cobi + vem, followed by treatment with either atezo placebo + cobi + vem (Arm A) or atezo + cobi +vem+ vem placebo (Arm B) in the triple combination period.

Intervention

Atezolizumab 840 mg or placebo will be administered by IV infusion on Days 1 and 15 of Cycle 1 and Days 1 and 15 (every 2 weeks) of subsequent cycles.
All patients will receive cobimetinib at a dose of 60 mg (three 20-mg tablets) orally (PO) once daily on Days 1*21 of each 28-day cycle during the run-in and triple combination periods. Cobimetinib should be taken approximately the same time each day, with the morning vemurafenib dose, and no later than 4 hours after the scheduled time. Cobimetinib may be taken with or without a meal. Cobimetinib should be swallowed whole with a glass of water and should not be chewed, cut, or crushed. If a dose of cobimetinib is missed (i.e., not taken within 12 hours after the scheduled dosing time), the patient should resume dosing with the next scheduled dose. Missed or vomited doses will not be made up.
Each dose of vemurafenib will consist of four tablets, with patients in Arm A (atezo placebo + cobi + vem) receiving four active tablets and patients in Arm B (atezo + cobi + vem+ vem placebo) receiving three active tablets plus one placebo tablet. All patients will receive vemurafenib at a dose of 960 mg (four 240-mg tablets) PO BID on Days 1*21 of the run-in period. Patients in Arm A will continue to receive vemurafenib at a dose of 960 mg PO BID on Days 22*28 of the run-in period and Days 1*28 of each 28-day cycle during the triple combination period. Patients in Arm B will receive vemurafenib at a dose of 720 mg (three 240-mg tablets) plus vemurafenib placebo (one tablet) PO BID on Days 22*28 of the run-in period and Days 1*28 each 28-day cycle during the triple combination period.

Study burden and risks

The safety plan for patients in this study is based on clinical experience with atezolizumab, cobimetinib, and vemurafenib in completed and ongoing studies. The anticipated important safety risks are outlined in Sections 5.1.1 [atezolizumab], 5.1.2 [cobimetinib], 5.1.3 [vemurafenib], and 5.1.4 [combination use] of the protocol. Guidelines for dose modifications and treatment interruption, as well as management of patients who experience specific adverse events, are provided in Section 5.1.5.

Measures will be taken to ensure the safety of patients participating in this study, including the use of stringent inclusion and exclusion criteria and close monitoring of patients during the study. Administration of atezolizumab will be performed in a monitored setting in which there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. 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

Public
Roche Nederland B.V.

Beneluxlaan 2a
Woerden 3446 GR
NL
Scientific
Roche Nederland B.V.

Beneluxlaan 2a
Woerden 3446 GR
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- Age >= 18 years

- Histologically confirmed Stage IV (metastatic) or unresectable Stage IIIc (locally advanced) melanoma, as defined by the American Joint Committee on Cancer, 7th revised edition
- Naïve to prior systemic anti-cancer therapy for melanoma (e.g., chemotherapy, hormonal therapy, targeted therapy, immunotherapy, or other biologic therapies), with the following exeptions: neoadjuvant and or adjuvant treatment with chemotherapy, if discontinued at least 28 days prior to initiation of study treatment
- Documentation of BRAFV600 mutation*positive status in melanoma tumor tissue (archival or newly obtained) through use of a clinical mutation test approved by the local health authority
- Eastern Cooperative Oncology Group Performance Status of 0 or 1 (see Appendix 3)
- Measurable disease according to RECIST v1.1
- Willingness to undergo tumor biopsies of accessible lesions during treatment and at progression for exploratory biomarker analyses
- Life expectancy >= 18 weeks
- Adequate hematologic and end-organ function, defined by standard laboratory test results, obtained within 14 days prior to initiation of study treatment, with the exception of amylase, lipase, and LDH where up to 28 days is acceptable (using central laboratory result).
- For patients not receiving therapeutic anticoagulation: INR or aPTT <= 1.5×ULN within 28 days prior to initiation of study treatment
- For patients receiving therapeutic anticoagulation: stable anticoagulant regimen and stable INR during the 28 days immediately preceding initiation of study treatment
- For women of childbearing potential: agreement to remain abstinent or use a contraceptive method with a failure rate of <1% per year during the treatment period and for 6 months after the last dose of study treatment
- For men: agreement to remain abstinent or use contraceptive measures, and agreement to refrain from donating sperm

Exclusion criteria

Cancer-Related Exclusion Criteria
- Major surgical procedure other than for diagnosis within 4 weeks prior to initiation of study treatment, or anticipation of need for a major surgical procedure during the course of the study
- Traumatic injury within 2 weeks prior to initiation of study treatment
- Palliative radiotherapy within 14 days prior to initiation of study treatment
- Active malignancy (other than BRAFV600 mutation*positive melanoma) or malignancy within 3 years prior to screening are excluded, with the exception of resected melanoma, resected basal cell carcinoma (BCC), resected cutaneous squamous cell carcinoma (SCC), resected carcinoma in situ of the cervix, resected carcinoma in situ of the breast, in situ prostate cancer, limited-stage bladder cancer, or any other curatively treated malignancies from which the patient has been disease-free for at least 3 years;Ocular Exclusion Criteria
- History of or evidence of retinal pathology on ophthalmologic examination that is considered a risk factor for neurosensory retinal detachment, central serous chorioretinopathy, retinal vein occlusion (RVO), or neovascular macular degeneration;Cardiac Exclusion Criteria

- History of clinically significant cardiac dysfunction including the following: poorly controlled hypertension, defined as sustained, uncontrolled, nonepisodic baseline hypertension consistently above 159/99 mmHg despite optimal medical management.;Central Nervous System Exclusion Criteria
- Untreated or actively progressing CNS lesions (carcinomatous meningitis)
- History of metastases to brain stem, midbrain, pons, or medulla, or within 10 mm of the optic apparatus (optic nerves and chiasm)
- History of leptomeningeal metastatic disease
- History of intracranial hemorrhage;Additional Exclusion Criteria
- Current severe, uncontrolled systemic disease (including, but not limited to, clinically significant cardiovascular, pulmonary, or renal disease) other than cancer
- Anticipated use of any concomitant medication during or within 7 days prior to initiation of study treatment that is known to cause QT prolongation (which may lead to torsades de pointes)
- Any psychological, familial, sociological, or geographical condition that may hamper compliance with the protocol and follow-up after treatment discontinuation
- History of malabsorption or other clinically significant metabolic dysfunction that may interfere with absorption of oral study treatment
- Pregnant or breastfeeding, or intending to become pregnant during the study
- Prior allogeneic stem cell or solid organ transplantation
- History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan
- History of autoimmune disease;For all exclusion criteria, see section 4.1.2 on pages 50-54 of the protocol

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:	Recruiting
Start date (anticipated):	14-04-2017
Enrollment:	14
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Cotellic
Generic name:	Cobimetinib
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Tecentriq
Generic name:	Atezolizumab
Product type:	Medicine
Brand name:	Zelboraf
Generic name:	Vemurafenib
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	25-10-2016
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	27-12-2016
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	07-02-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date:	07-09-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	11-09-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	19-10-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-11-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-01-2018
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:	15-02-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-04-2018
Application type:	Amendment

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	24-05-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-01-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	24-06-2019
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:	30-03-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-07-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-12-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO	

Date:	18-04-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-07-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	25-10-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	27-11-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-03-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	24-06-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	30-08-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	29-10-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek

	(Assen)
Approved WMO Date:	10-11-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	02-12-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	06-04-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-08-2023
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	EUCTR2016-002482-54-NL

Register	ID
ClinicalTrials.gov	NCT02908672
CCMO	NL59004.056.16