A PHASE Ib/II, OPEN-LABEL, MULTICENTER, RANDOMIZED UMBRELLA STUDY EVALUATING THE EFFICACY AND SAFETY OF MULTIPLE TREATMENT COMBINATIONS IN PATIENTS WITH MELANOMA (MORPHEUS-MELANOMA)

Published: 07-10-2021
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• To evaluate the efficacy of treatment• To evaluate the safety of treatment

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

Summary

ID

NL-OMON55920

Source
ToetsingOnline

Brief title
Melanoma Treatment Combination

Condition

- Skin neoplasms malignant and unspecified

Synonym
Melanoma; Skin cancer

Research involving
Human

Sponsors and support

Primary sponsor: Hoffmann-La Roche
Source(s) of monetary or material Support: Industry

Intervention

Keyword: Cancer Immunotherapy (CIT), Melanoma, Oncology, Resectable Melanoma

Outcome measures

Primary outcome

• pRR (defined as the proportion of patients with pCR, pnCR, and pPR) at time

of surgery, as determined by independent pathologic review

Secondary outcome

• pRR (defined as the proportion of patients with pCR, pnCR, and pPR) at time

of surgery, as determined by local pathologic assessment

• EFS, defined as the time from randomization to any of the following events

(whichever occurs first): Disease progression that precludes surgery, as

assessed by the investigator according to RECIST v1.1; local, regional or

distant disease recurrence; or death from any cause

• RFS, defined as the time from surgery to the first documented recurrence of

disease or death from any cause

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

• ORR, defined as the proportion of patients with a CR or PR as determined by

the investigator according to RECIST v1.1, prior to surgery

Responses will be assessed and determined according to RECIST v1.1 but are not

required to be confirmed by later imaging studies.

• Incidence, nature, and severity of adverse events and laboratory

abnormalities, with severity determined according to NCI CTCAE v5.0

CRS severity will also be determined according to the ASTCT CRS Consensus

Grading Scale.

• Incidence and nature of immune-related adverse events Grade * 3 during the

first 12 weeks

• Rate and duration of delayed surgery due to treatment-related adverse events

• Surgical complication rates according to Clavien Dindo surgical

classification after CLND

Study description

Background summary

BACKGROUND ON MELANOMA
Melanoma is a malignant tumor of melanocytes. This potentially deadly form of skin cancer is one of the fastest growing malignancies (Algazi et al. 2010; Finn et al. 2012). More than 300,000 people worldwide are currently diagnosed with melanoma each year, and 57,000 people die of the disease (Ferlay et al. 2018). The clinical outcomes of patients with melanoma are highly dependent on the stage at presentation. When melanoma is diagnosed early (Stage I and II), it is generally curable with surgery as the treatment of choice, with a long term survival rate of around 90% for Stage I melanoma (Balch et al. 2009). However, most people with more advanced melanoma have a poor prognosis (Finn et al. 2012). Patients with lymph node involvement (Stage III) have a high risk of local and distant relapse after surgery, and the 5 year survival rate is 32%*93% in this patient group (Gershenwald et al. 2017). Few patients have metastatic disease (Stage IV) at presentation, but some develop metastases after their initial definitive treatment. Immunotherapy and targeted therapies have improved the outcomes of those patients, and the 5 year survival rate is around 50% (Larkin et al. 2015; Wolchok et al. 2017; Larkin et al. 2019; Robert et al. 2019; Long et al. 2020). Despite recent therapeutic advances, melanoma continues to be a serious health issue, with a high medical need and a steadily increasing incidence over the past 30 years (Bataille 2009).

IMMUNOTHERAPIES
A variety of immunotherapies have been approved for the treatment of melanoma, and immunotherapy has shown benefit regardless of PD L1 expression or BRAF

mutations.
Three CPIs, namely ipilimumab, pembrolizumab, and nivolumab, are now approved by the FDA for the treatment of unresectable or advanced disease. Each has shown improved OS against different comparators. Treatments shown to be effective in the unresectable or metastatic disease setting have also proven to be effective adjuvant therapies for patients with resectable Stage III melanomas. The current standard of care is surgery followed by adjuvant anti-PD 1 or targeted therapy.
Ipilimumab, a monoclonal antibody targeting CTLA 4, demonstrated significant improvement in OS in two randomized trials (Hodi et al. 2010; Robert et al. 2011), and was the first CPI approved for use in unresectable or metastatic melanoma. It was also the first CPI to be approved by the FDA as adjuvant therapy, and it has demonstrated improved OS at a dose of 10 mg/kg when compared with placebo in the European Organisation for Research and Treatment of Cancer 18071 study (Eggermont et al. 2016). The subsequent Intergroup E1609 trial demonstrated better outcomes with low dose (3 mg/kg) ipilimumab; this dose has been approved for metastatic disease (Tarhini et al. 2020). Anti-PD 1 monotherapy (pembrolizumab or nivolumab) shows improved efficacy outcomes with better safety profiles compared with treatment using single agent anti-CTLA 4 (ipilimumab) or the investigator*s choice of chemotherapy.
Pembrolizumab was initially approved for the treatment of patients with advanced or unresectable melanoma who progressed after ipilimumab and/or BRAF therapy (Ribas et al. 2015a; Robert et al. 2015b). It is now approved for the treatment of patients with unresectable or metastatic melanoma, as well as for the adjuvant treatment of patients with melanoma with lymph node involvement following complete resection.
Nivolumab was originally approved in advanced melanoma patients without BRAF mutation (Robert et al. 2015a). It is now approved for patients with unresectable or metastatic melanoma, and for patients with melanoma with lymph node involvement or metastatic disease who have undergone complete resection in the adjuvant setting.
The combination of anti-PD 1 and anti-CTLA 4 immunotherapies (nivolumab plus ipilimumab) further prolonged PFS and OS compared with ipilimumab or nivolumab alone, and this combination has been approved for previously untreated patients with unresectable or metastatic melanoma (Larkin et al. 2015). The CheckMate 238 study compared nivolumab with ipilimumab. At a median follow up of 51 months, nivolumab improved RFS and distant metastasis free survival while reducing toxicity. The OS was similar in the two groups (Ascierto et al. 2020).

NEOADJUVANT IMMUNOTHERAPY
Nonclinical studies demonstrated improved survival and increased anti tumor immunity when immune CPI therapy was given before surgery as compared with adjuvant application (Liu et al. 2016; Brockwell et al. 2017; Bourgeois-Daigneault et al. 2018; Brooks et al. 2018; O*Donnell et al. 2019).
Patients with clinically detectable Stage III melanoma are ideal candidates for neoadjuvant therapy because they represent a high risk patient population with poor outcomes when treated with upfront surgery alone. Neoadjuvant therapy

also has the advantage of providing information on pathologic response, which is valuable to estimate prognosis and to guide the choice of adjuvant therapy and follow up (Tetzlaff et al. 2018). Moreover, the availability of tumor tissue before and following therapy enables efficient exploration of possible mechanisms of resistance and response as well as identification of baseline biomarkers. Neoadjuvant therapy for melanoma is now an active area of research, with numerous completed and ongoing trials that have disparate designs, endpoints, and analyses (Menzies et al. 2021). The International Neoadjuvant Melanoma Consortium (INMC) was created by experts in medical oncology, surgical oncology, pathology, radiation oncology, radiology, and translational research who developed recommendations for investigating neoadjuvant therapy in melanoma to align future trial designs and correlative analyses (Amaria et al. 2019).
Six melanoma neoadjuvant trials were conducted recently with BRAF/MEK-targeted therapy or PD-1-based immunotherapy (reviewed by Amaria et al. 2019). These trials demonstrated that neoadjuvant therapies can achieve high pathologic complete response (pCR) rates and impressive RFS in Stage III melanoma (Menzies et al. 2021; Rozeman et al. 2021). The initial data are particularly promising for the neoadjuvant combination of nivolumab plus ipilimumab. Treatment with nivolumab plus ipilimumab results in pathologic response rates (pRRs) between 70%*80%, is well tolerated, and may reduce surgical morbidity (Rozeman et al. 2019; Blank et al. 2020).
This study protocol was developed in accordance with INMC guidelines to create the needed consistency amongst neoadjuvant trials in order to facilitate optimal data organization for future regulatory review. Its exploratory analysis plan will strengthen translational research across the melanoma disease continuum.

STUDY RATIONALE
This randomized Phase Ib/II umbrella study is designed to accelerate the development of treatments or treatment combinations by identifying early signals and establishing proof of concept clinical data in patients with resectable melanoma. Single agent immune CPIs or targeted therapies, dual CPI combinations, and CPIs in combination with targeted therapies have shown promising objective response rates (ORRs) and OS and are approved for use in patients with melanoma.

Study objective

• To evaluate the efficacy of treatment
• To evaluate the safety of treatment

Study design

Description of the Study
This is a Phase Ib/II, open label, multicenter, randomized, umbrella study in

patients with resectable Stage III (Cohort 1) or Stage IV (Cohort 2) melanoma. The study is designed with the flexibility to open new treatment arms as new treatments become available, close existing treatment arms that demonstrate minimal clinical activity or unacceptable toxicity, modify the patient population (e.g., with regard to prior anti cancer treatment or biomarker status), or introduce additional cohorts of patients with other types of melanoma.
When additional treatment options become available, patients may be eligible to receive treatment with a different treatment combination in an additional study stage (Stage 2). When a Stage 2 treatment is available, this will be introduced by amending the protocol.
Two cohorts will be enrolled in parallel in this study. Cohort 1 will enroll patients with resectable Stage III melanoma with measurable lymph node metastases according to Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) that can be biopsied, who have no history of intransit-metastases within the last 6 months, and who have not received systemic CIT for their disease, e.g., PD 1/PD-L1 and/or CTLA-4 blocking agents or other agents. Cohort 2 will enroll patients with Stage IV melanoma who experienced disease progression during or after at least one but not more than two lines of treatment for metastatic disease. Up to two lines of checkpoint inhibition therapy (monotherapy or combination therapy) are allowed. Patients with BRAF-mutant disease may have received an additional line of targeted therapy (either before, intermittent with, or after the checkpoint inhibition therapy) or may have received targeted therapy and checkpoint inhibition therapy concurrently as one combination treatment. Patients with BRAF-mutant melanoma with rapidly progressive disease who have not been previously treated with approved targeted therapies are not eligible.

Treatment Assignment
In Cohort 1, patients will be randomly assigned to a control arm (nivolumab plus ipilimumab [Nivo * Ipi]) or an experimental arm consisting of RO7247669, atezolizumab in combination with tiragolumab (Atezo * Tira), or RO7247669 in combination with tiragolumab (RO7247669 * Tira). Patients will be stratified by geographic region (Australia vs. Rest of the World) and baseline LDH (* the upper limit of normal [ULN] vs. * ULN).
In Cohort 2, patients will be enrolled into an experimental arm consisting of RO7247669 in combination with tiragolumab (RO7247669 * Tira). Enrollment will begin with a 6 patient safety run-in phase. Patients from French investigational sites are excluded from the safety run-in phase and may only be enrolled into the preliminary phase, which succeeds the safety-run-in.
Approximately 61*191 patients will be enrolled during the study, including approximately 6 patients who will be enrolled in the safety run-in phase of Cohort 2. Enrollment within the experimental arms will take place in two phases: a preliminary phase, followed by an expansion phase. Approximately 15*20 patients will be enrolled in each treatment arm during the preliminary phase. If clinical activity (pathologic response in Cohort 1) is observed in an experimental arm during the preliminary phase, approximately 20 additional

patients may be enrolled in that arm during the expansion phase.
The Sponsor may decide to delay or suspend enrollment within a given treatment arm. Experimental arms with insufficient clinical activity or unacceptable toxicity will not be expanded. Additional patients may be enrolled to ensure balance among treatment arms with respect to demographic and baseline characteristics, including potential predictive biomarkers, in order to enable further subgroup analyses. New experimental arms may be added during the study by amending the protocol.
The randomization ratio will depend on the number of experimental arms that are available (e.g., if an arm is added or enrollment in an arm is suspended, pending analysis of results from the preliminary phase), with the stipulation that the likelihood of being allocated to the control arm is no more than 35%.
Randomization will take into account arm-specific exclusion criteria. Patients will be ineligible for a specific arm if they meet any of the exclusion criteria outlined for that arm.
Details on the treatment regimens are provided in Table 3.

Intervention

Study Treatments for Cohort 1
1. Nivolumab + ipilimumab (control, CIT combination treatment)
2. RO7247669 (CIT single agent treatment)
3. Atezolizumab + tiragolumab (CIT combination treatment)
4. RO7247669 + tiragolumab (CIT combination treatment)

Study Treatments for Cohort 2
1. RO7247669 + tiragolumab (CIT combination treatment)

Additional CIT treatments or treatment combinations may be added in the future, and enrollment may be delayed or suspended for some CIT treatments or treatment combinations. Thus, the number of available CIT treatments or treatment combinations may increase or decrease over the course of the study. The control group CIT treatments or treatment combination will be available for enrollment throughout the study.

Study burden and risks

Screening: Taking part in the screening and treatment assignment procedures for this study will not cause the patient's health to improve, but the screening procedures may show that he/she is eligible for the study.

Treatment: The study treatment may improve the patient's condition or bring him/her to remission, but that is not certain. The skin cancer may come back or get worse at any time during this study.

In Cohort 1, there is a risk of delaying a potentially curative surgery

(removal of lymph nodes) due to side effects from the study drugs.
In Cohort 2, the patient may be foregoing an approved, standard therapy with proven survival benefit.

In addition:
- The patient may experience the side effects or adverse effects of the study treatment, as described in Section 6 of the ICF.
- There may be some discomfort from the measurements during the study, as described in Section 7 of the ICF.
- Taking part in the study will cost extra time.
- The patients have to comply with the study agreements.

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

Shared Inclusion Criteria for Cohort 1 and Cohort 2 Patients must meet all of the following criteria to qualify for Cohort 1 and Cohort 2: • Signed Informed Consent Form • Age >= 18 years at the time of signing Informed Consent Form • ECOG performance status (PS) of 0 or 1 • Ability to comply with the protocol, in the investigator*s judgment • Availability of a representative tumor specimen that is suitable for biomarker testing via central laboratory Baseline tumor tissue samples will be collected from all patients (except patients in the Cohort 2 safety run-in phase) by biopsy of a metastatic lymph node (Cohort 1) or other metastatic lesion (Cohort 2) at screening. In addition, archival primary tumor tissue will be submitted from all patients if available. In case no archival primary tissue is available (e.g., for patients with unknown primary tumor), enrollment is permitted. For archival tissue, a formalin-fixed, paraffin-embedded (FFPE) tumor specimen in a paraffin block (preferred) with sufficient size and tumor content representation, preferably including the invasive margin, or if available at least 16 slides containing unstained, freshly cut, serial sections must be submitted along with an associated pathology report. • Adequate hematologic and end-organ function, defined by the following laboratory test results, obtained within 14 days prior to initiation of study treatment: - ANC >= 1.5 x 109/L (1500/uL) - Lymphocyte count >= 0.5 x 109 cells/L (500/uL) Borderline machine lymphocyte counts may be confirmed by a manual count. - Platelet count >= 100 x 109/L (100,000/uL) - Hemoglobin >= 90 g/L (9 g/dL) - AST, ALT, and ALP <= 2.5 x ULN with the following exceptions: For Cohort 2, patients with documented liver metastases: AST and ALT <= 5 x ULN. For Cohort 2, patients with documented liver or bone metastasis: ALP <= 5 x ULN. - Total bilirubin <= 1.5 x ULN, with the following exception: Patients with known Gilbert disease: bilirubin level <= 3 x ULN - Creatinine <=1.5 x ULN or creatinine clearance >= 30 mL/min (calculated using the Cockcroft-Gault formula) - Serum albumin >= 25 g/L (2.5 g/dL) - For patients not receiving therapeutic anticoagulation: INR and aPTT <= 1.5 x ULN • For patients receiving therapeutic anticoagulation: stable anticoagulant regimen (i.e., no new thrombosis, thromboembolic event, or bleeding episode within 3 months prior to study treatment start) • Negative HIV test at screening with the following exception: Patients with a positive HIV test at screening are eligible provided they are stable on anti-retroviral therapy, have a CD4 count >= 200/uL, and have an undetectable viral load. Patients without a prior positive HIV test result will undergo an HIV test at screening, unless not permitted per local regulations. • Negative hepatitis B surface antibody (HBsAb) and negative total hepatitis B core antibody (HBcAb) test at screening. If a patient has a negative hepatitis B surface antigen (HBsAg) test and a positive total HBcAb test at screening, a hepatitis B virus (HBV) DNA test must also be performed to rule out active HBV. • Negative hepatitis C virus (HCV) antibody test at screening, or positive HCV antibody test followed by a negative HCV RNA test at screening The HCV RNA test will be performed only for patients who have a positive HCV antibody test. • For women

of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures • For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating sperm Inclusion Criteria for Cohort 1 Patients must meet all of the following criteria to qualify for Cohort 1: • Histologically confirmed resectable Stage III melanoma (T: T0, Tx, or T-14; N: cN1-3, pN1b/2b/3b; M: M0 according to AJCC-8) and no history of in-transit metastases within the last 6 months Patients may present with primary melanoma with concurrent regional nodal metastasis, or a history of primary melanoma or unknown primary melanoma with clinically detected regional nodal recurrence, and may belong to any of the following groups: - Primary cutaneous melanoma with concurrent clinically/radiologically apparent regional lymph node metastases - Clinically/radiologically detected recurrent melanoma at the proximal regional lymph node(s) basin - Clinically/radiologically detected nodal melanoma (if single site) arising from an unknown primary • Fit and planned for CLND (as assessed by surgeon prior to randomization according to local guidelines) • Measurable disease (at least one target lesion) according to RECIST v1.1 At least one macroscopic lymph node metastasis (measurable according to RECIST v1.1) to be biopsied. Inclusion Criteria for Cohort 2 Patients must meet all of the following criteria to qualify for Cohort 2: • Life expectancy >= 3 months, as determined by the investigator • Histologically confirmed Stage IV (metastatic) cutaneous melanoma according to AJCC-8 • Disease progression during or following at least one but no more than two lines of treatment for metastatic disease Up to two lines of checkpoint inhibition therapy (monotherapy or combination therapy) are allowed. Patients with BRAF-mutant disease may have received an additional line of targeted therapy (either before, intermittent with, or after the checkpoint inhibition therapy), or may have received targeted therapy and checkpoint inhibition therapy concurrently as one combination treatment. Patients with BRAF-mutant melanoma with rapidly progressive disease who have not been previously treated with approved targeted therapies are not eligible. Patients who received adjuvant treatment with checkpoint inhibition therapy for localized melanoma require an additional line of checkpoint inhibition therapy in the metastatic setting. Patients who relapse or systemically progress during or within 6 months of completion of adjuvant therapy are eligible and do not require an additional line of checkpoint inhibition therapy. • Measurable disease (at least one target lesion) according to RECIST v1.1 At least one metastasis (measurable according to RECIST v1.1).

Exclusion criteria

Exclusion Criteria for Cohort 1 and Cohort 2 Patients who meet any of the following criteria will be excluded from study entry: • Mucosal and uveal melanoma Acral lentiginous melanoma is excluded for Cohort 1. For Cohort 2, acral lentiginous melanoma is permitted; however, the proportion of patients

should not exceed 20% of response-evaluable patients. • Treatment with investigational therapy within 28 days prior to initiation of study treatment • Treatment with systemic immunostimulatory agents (including, but not limited to, interferon [IFN] and interleukin [IL]-2) within 4 weeks or 5 drug-elimination half-lives (whichever is longer) prior to initiation of study treatment • Prior allogeneic stem cell or solid organ transplantation • Known immunodeficiency or conditions requiring treatment with systemic immunosuppressive medication (including, but not limited to, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor** agents), or anticipation of need for systemic immunosuppressant medication during study treatment, with the following exceptions: Patients on replacement doses of corticosteroids to manage hypopituitary or adrenal insufficiency are eligible for the study. Patients who received acute, low-dose, systemic immunosuppressant medications, or a one-time pulse dose of systemic immunosuppressant medication (e.g., 48 hours of corticosteroids for a contrast allergy) are eligible for the study. Patients requiring chronic low-dose systemic corticosteroid treatment (i.e., a maximal dose of corticosteroids <= 10mg/day equivalent prednisone) are eligible. Patients who received mineralocorticoids (e.g., fludrocortisone), corticosteroids for chronic obstructive pulmonary disease or asthma, or low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for the study. • Treatment with a live, attenuated vaccine within 4 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during study treatment or within 5 months after the final dose of study treatment • Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener granulomatosis, Sjo*gren syndrome, Guillain-Barre* syndrome, or multiple sclerosis, with the following exceptions: Patients with a history of autoimmune-related hypothyroidism who are on thyroid-replacement hormone are eligible for the study. Patients with controlled Type 1 diabetes mellitus who are on a stable insulin regimen are eligible for the study. Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis are excluded) are eligible for the study provided all of following conditions are met: - Rash must cover < 10% of body surface area. - Disease is well controlled at baseline and requires only low-potency topical corticosteroids. - There is no occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high-potency or oral corticosteroids within the previous 12 months. • 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 computed tomography (CT) scan. Patients with a history of CIT-related pneumonitis Grade < 2 are eligible. • History of malignancy other than malignant melanoma within 2 years prior to screening, with the exception of malignancies with a negligible risk of

metastasis or death (e.g., 5-year overall survival [OS] rate > 90%), such as adequately treated carcinoma in situ of the cervix, non melanoma skin carcinoma, localized prostate cancer, ductal carcinoma in situ, or Stage I uterine cancer • Active tuberculosis (TB) • Severe infection within 4 weeks prior to initiation of study treatment, including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia, or any active infection that, in the opinion of the investigator, could impact patient safety • Treatment with therapeutic or prophylactic oral or IV antibiotics within 2 weeks prior to initiation of study treatment • Significant cardiovascular disease such as New York Heart Association cardiac disease (Class II or greater), myocardial infarction or cerebrovascular accident within 3 months prior to initiation of study treatment, unstable arrhythmia, or unstable angina • Uncontrolled hypertension (defined as resting systolic blood pressure * 150 mmHg and/or diastolic blood pressure > 100 mmHg in two or more serial measurements) • 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 other than CLND, during the study Placement of central venous access catheter (e.g., port or similar) is not considered a major surgical procedure and is therefore permitted. • Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of an investigational drug, may affect the interpretation of the results, impair the ability of the patient to participate in the study, or may render the patient at high risk from treatment complications • History of severe allergic reactions to chimeric or humanized antibodies or fusion proteins • Known hypersensitivity to Chinese hamster ovary cell products or recombinant human antibodies • Known allergy or hypersensitivity to any of the study drugs or their excipients • Known intolerance to any of the drugs required for premedication (acetaminophen, ranitidine, diphenhydramine, and methylprednisolone) • Pregnancy or breastfeeding, or intention of becoming pregnant during the study Women of childbearing potential must have a negative serum pregnancy test result within 14 days prior to initiation of study treatment. • Eligible only for the control arm Exclusion Criteria for Cohort 1 Patients who meet any of the following criteria will be excluded from Cohort 1: • Distantly metastasized melanoma • History of in-transit metastases within the last 6 months • Prior radiotherapy • Prior immunotherapy, including anti-CTLA-4, anti-PD-1, and anti-PD-L1 therapeutic antibodies, and other systemic therapy for melanoma Exclusion Criteria for Cohort 2 Patients who meet any of the following criteria will be excluded from Cohort 2: • Symptomatic, untreated, or progressing CNS metastases Asymptomatic patients with treated CNS lesions are eligible, provided that all of the following criteria are met: - Measurable disease, per RECIST v1.1, must be present outside the CNS. - The patient has no history of intracranial hemorrhage or spinal cord hemorrhage. - CNS metastases are stable for >= 4 weeks prior to initiation of study, or neurosurgical resection occurred >= 28 days prior to initiation of study treatment. - The patient has no requirement for corticosteroids as therapy for CNS disease for at least 14 days prior to initiation of study treatment. - Anti-convulsant therapy at a stable

dose is permitted. • Active or history of carcinomatous meningitis/leptomeningeal disease • Uncontrolled tumor-related pain Patients requiring pain medication must be on a stable regimen at screening. Symptomatic lesions (e.g., bone metastases or metastases causing nerve impingement) amenable t

Study design

Design

Study phase:	2
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):	25-03-2022
Enrollment:	30
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:	PD1-LAG3
Generic name:	RO7247669
Product type:	Medicine
Brand name:	Tecentriq

Generic name:	Atezolizumab
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	tiragolumab
Generic name:	Tiragolumab (RO7092284)
Product type:	Medicine
Brand name:	Yervoy
Generic name:	Ipilimumab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	07-10-2021
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	25-03-2022
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	14-05-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	17-05-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	25-02-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek

	(Assen)
Approved WMO Date:	06-03-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-06-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-06-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-11-2023
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	EUCTR2021-002147-29-NL

Register	ID
CCMO	NL78989.056.21