Randomized phase III study comparing a non-myeloablative lymphocyte depleting regimen of chemotherapy followed by infusion of tumor infiltrating lymphocytes and interleukin-2 to standard ipilimumab treatment in metastatic melanoma

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

Summary

ID

NL-OMON53098

Source
ToetsingOnline

Brief title
TIL treatment is compared to ipilimumab in melanoma patients

Condition

- Skin neoplasms malignant and unspecified

Synonym
malignant melanoma, skin cancer

Research involving
Human

Sponsors and support

Primary sponsor: Nederlands Kanker Instituut
Source(s) of monetary or material Support: Ministerie van OC&W,De studie wordt voor het Nederlandse aandeel gefinancierd uit 3e geldstroom (KWF Kankerbestrijding subsidie) en 1e geldstroom (Academische Budget component). We zijn nog in afwachting van beoordeling van een CVZ aanvraag voor voorlopige toelating tot het basispakket. Besluit valt in juni 2014 en indien positief zal dat per 1 jan 2015 ingaan voor een periode van 4 jaar.

Intervention

Keyword: interleukin 2, ipilimumab, melanoma, TIL treatment

Outcome measures

Primary outcome

Progression free survival (according to RECIST 1.1).

Secondary outcome

PFS at 6 months (according to RECIST 1.1) and PFS according to irRC. Overall

response rate (RECIST 1.1 and immune related response criteria (irRC)),

complete response rate, overall survival and safety.

Study description

Background summary

Prior preclinical and clinical studies have shown that tumors from patients with advanced melanoma contain tumor-infiltrating lymphocytes (TIL) with anti-tumor reactivity targeting a variety of melanoma-associated antigens. Prior clinical trials have shown that these TIL can be expanded in vitro using interleukin-2 with anti-CD3 antibody stimulation and can cause regression of melanoma when adoptively transferred back to the patient.
Preclinical mouse models and clinical studies have shown that host immunosuppression prior to the adoptive transfer of tumor-reactive lymphocytes greatly enhances their anti-tumor effect.
Using a preparative non-myeloablative regimen of cyclophosphamide and

fludarabine, a single institution phase II study in 43 patients showed a 51% objective response rate to TIL and interleukin-2, with complete and durable partial responses in a patient population that was heavily pretreated.
Thus, in this trial we will investigate whether TIL treatment improves progression free survival (PFS) in a randomized phase III study compared to the current standard of care (ipilimumab). If PFS is indeed significantly improved, application of this approach for patients with advanced melanoma should be pursued.

Study objective

In this randomized controlled phase III study we will evaluate whether TIL infusion preceded by non-myeloablative chemotherapy and followed by high dose bolus interleukin-2 can result in an improved progression free survival when randomly compared to ipilimumab in stage IIIc and IV melanoma patients. A health technology assessment (HTA) will be performed to evaluate the impact of the TIL treatment on patients and organizational processes and cost-effectivity.

Study design

Patients with irresectable or metastatic (stage IIIc or IV) melanoma and a resectable metastasis will be randomized between arm A, standard treatment (ipilimumab) and arm B, TIL treatment.

• Arm A: standard ipilimumab (3 mg/kg x 1 day i.v., q 3 weeks, maximal 4 times).

• Arm B: non-myeloablative chemotherapy (cyclophosphamide 60 mg/kg/day x 2 days i.v., fludarabine 25 mg/m2/day x 5 days i.v.) followed by intravenous adoptive transfer of at least 5 x 109 TIL followed by high dose interleukin-2 (Proleukin) (600.000 IU/kg/dose every 8 hours for up to 15 doses).

Intervention

Eligible patients (n=168) will be randomized between arm A and B. Patients that are randomized in arm A will receive standard therapy with ipilimumab , 3 mg/kg, q 3 weeks, maximal 4 times. Patients that are randomized for arm B will receive TIL treatment as described above. The patients for whom no TIL can be generated, will be taken off-study. They will be treated with ipilimumab according to the standard treatment arm but will be included in the intension to treat analysis.

Study burden and risks

The TIL treatment will involve surgery of a melanoma metastasis of 2-3 cm, in-hospital non-myeloablative chemotherapy, infusion of TIL and intravenous

high dose bolus IL-2 treatment. Although this treatment and toxicity has been demonstrated to be well manageable, common toxicities from non-myeloablative chemotherapy (transient bone marrow suppression requiring G-CSF for neutropenia, red cell and platelet support, increased chance of bacterial, viral and fungal infections, requiring antibiotics) and high dose IL-2 (high fever, rash, low blood pressure and decreased urinary output, edema requiring saline infusion support) may or will occur. Due to the infusion of TIL, patients may develop signs of melanoma associated autoimmune diseases such as vitiligo and uveitis. The latter, which is the more serious side effect, has been shown to respond promptly to topical corticosteroid treatment. One patient experienced prolonged toxicity after TIL treatment consisting of heart and kidney failure, anemia and thrombocytopenia, possibly due to cyclophosphamide and/or autoimmune effects of TIL. However, the fact that these patients may have a high chance of durable objective responses, which otherwise would not occur, justifies for the burden and possible toxicities.

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age

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

Inclusion criteria

• Histologically confirmed unresectable AJCC stage IIIc or stage IV melanoma
• Patients must have metastatic melanoma with a resectable metastatic lesion(s) of sufficient size (>= 2-3 cm in total) and must be willing to undergo such a resection for experimental purposes.
• Patients should have received no previous systemic therapy for unresectable or metastatic melanoma or one line of any kind of systemic treatment, except for ipilimumab.
• Patients must be >= 18 years and <= 75 years of age and must have measurable disease by CT or MRI per RECIST 1.1 criteria (in addition to the resected lesion).
• Patients must have a clinical performance status of ECOG 0 or 1.
• Patients of both genders must be willing to practice a highly effective method of birth control during treatment and for four months after receiving the preparative regimen.
• Patients must be able to understand and sign the Informed Consent document.

Exclusion criteria

• Life expectancy of less than three months.
• Patients with metastatic ocular/ mucosal or other non-cutaneous melanoma.
• Adjuvant treatment with ipilimumab within 6 months prior to randomization.
• Requirement for immunosuppressive doses of systemic corticosteroids (>10 mg/day prednisone or equivalent) or other immunosuppressive drugs within the last 3 weeks prior to randomization.
• Patients who have a more than two CNS metastases.
• Patients who have any CNS lesion that is symptomatic, greater than 1 cm in diameter or show significant surrounding edema on MRI scan will not be eligible until they have been treated and demonstrated no clinical or radiologic CNS progression for at least 2 months.
• All patients* toxicities due to prior non-systemic treatment must have recovered to a grade 1 or less. Patients may have undergone minor surgical procedures or focal palliative radiotherapy (to non-target lesions) within the past 4 weeks, as long as all toxicities have recovered to grade 1 or less.
• Women who are pregnant or breastfeeding, because of the potentially dangerous effects of the preparative chemotherapy on the fetus or infant.
• Any active systemic infections, coagulation disorders or other active major medical illnesses.
• Any autoimmune disease

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:	Health services research

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	23-09-2014
Enrollment:	110
Type:	Actual

Medical products/devices used

Product type:	Medicine
Generic name:	Somatic cells autologous
Product type:	Medicine
Brand name:	TIL treatment
Generic name:	tumor infiltrating lymphocytes
Product type:	Medicine
Brand name:	Yervoy
Generic name:	ipilimumab
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	03-04-2014

Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	10-06-2014
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	13-01-2015
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	28-01-2015
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	02-06-2015
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	04-06-2015
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	08-11-2016
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	27-01-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO Date:	20-02-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	30-04-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	01-08-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	03-08-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

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	EUCTR2013-005406-54-NL
ClinicalTrials.gov	NCT02278887

Register	ID
CCMO	NL47475.000.14