Releasing the brakes on CD8+ T cells in the melanoma sentinel lymph node by pre-operative local administration of low-dose anti-CTLA-4 (tremelimumab)

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1) To determine clinical safety and tolerability of local i.d. administration of a single dose of tremelimumab in clinical stage II melanoma patients scheduled to undergo a SLN procedure. 2) To ascertain the immunological effects of local i.d.…

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

Summary

ID

NL-OMON39041

Source
ToetsingOnline

Brief title
Anti-CTLA-4 in the melanoma sentinel node

Condition

- Skin neoplasms malignant and unspecified

Synonym
melanoma

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum

Source(s) of monetary or material Support: Een grant van Harry J. Loyd

Intervention

Keyword: anti-CTLA-4, immunity, melanoma, sentinel node

Outcome measures

Primary outcome

1) To determine clinical safety and tolerability of local i.d. administration

of a single dose of tremelimumab in Stage II melanoma patients scheduled to

undergo a SLN procedure.

2) To ascertain the immunological effects of local i.d. injection of

tremelimumab on the frequency and functionality of tumor-specific T cells and

Tregs -in the SLN and in blood- and on the number and activation state of DC

subsets in the SLN.

Secondary outcome

not applicable

Study description

Background summary

Cutaneous melanoma is the most aggressive type of skin cancer, the incidence of which has increased rapidly over the past decades. Adjuvant therapy options for melanoma are still limited and complete surgical excision at an early stage remains the only curative treatment option. Although of limited therapeutic value, the sentinel lymph node (SLN) procedure has proven a useful prognostic tool for the assessment of melanoma relapse and mortality risk. However, the SLN is of at least equal or perhaps even greater value for the assessment of immunological interventions for melanoma. The routine SLN procedure as carried out in the VUmc in early stage melanoma patients provides us with an ideal platform to test options for pre-operative modulation of SLN immune effector functions to maximize protection against possible micrometastases. In two previous Phase II trials carried out at the VUmc, we observed immune-activating

effects in the SLN, following the local intradermal (i.d.) administration of GM-CSF or the CpG type-B oligodeoxynucleotide around the excision site of the primary melanoma. Isolation and T cell expansion techniques were developed to obtain sufficient numbers of immune effector cells from the SLN for functional monitoring without interfering with standard diagnostic procedures. These studies provided insight into the different DC subsets present in melanoma SLN and how these could be targeted through the means of cytokines and/or Toll-like receptor ligands (TLR-L) in order to (re)activate melanoma-specific CD8+ T cells. Such local immune modulation strategies may afford local as well as systemic control of metastatic.The CTL Antigen-4 (CTLA-4) receptor represents a crucial checkpoint. It is expressed on activated T cells and binds to CD80 and CD86 on DC with higher avidity than its competitor ligand CD28. In contrast to CD28, CTLA-4 relays inhibitory signals to the T cell and blocks activating signals originating from CD28-CD86/CD80 interactions. Numerous pre-clinical and clinical studies have clearly indicated enhanced anti-tumor efficacy upon blocking of CTLA-4 and strongly support further implementation of anti-CTLA-4 in immunotherapeutic approaches to the treatment of melanoma. We now propose to conduct a phase I dose escalation trial of local administration of a single low dose of anti-CTLA4 (tremelimumab) and to monitor the immunological effects on the SLN in a correlative study. If this strategy is able to induce a strong anti-tumor immunity, it would be applicable in the neo-adjuvant treatment melanoma without the risk of serious toxicity. Hopefully this new approach could improves the prognosis of high risk melanoma patients.

Study objective

1) To determine clinical safety and tolerability of local i.d. administration of a single dose of tremelimumab in clinical stage II melanoma patients scheduled to undergo a SLN procedure.
2) To ascertain the immunological effects of local i.d. injection of tremelimumab on the frequency and functionality of tumor-specific T cells and Tregs -in the SLN and in blood- and on the number and activation state of DC subsets in the SLN

Study design

After resection of primary melanoma and seven days before surgery, clinical stage II melanoma patients undergoing a triple-technique SLN procedure will be treated by local i.d. injections, around the excision site of the primary tumor, of escalating doses of 2, 5, 10 or 20 mg tremelimumab (3 patients per dose level with an expansion at the optimal dose level with an additional 5 patients). Immunomonitoring of T cells and dendritic cells will be performed on blood before and 7 days after administration of tremelimumab and on cells derived from the SLN 7 days after administration of tremelimumab. These results will also be compared with control patients from previous studies.

Intervention

After resection of primary melanoma and seven days before surgery, clinical stage II melanoma patients undergoing a triple-technique SLN procedure will be treated by local i.d. injections, around the excision site of the primary tumor, of escalating doses of 2, 5, 10 or 20 mg tremelimumab (3 patients per dose level with an expansion at the optimal dose level with an additional 5 patients).

Study burden and risks

As can be seen in the investigator brochure no toxicity was observed in the 1 mg/kg i.v. cohort. Therefore, the low dosage (highest fixed dose of ipilimumab is 20 mg) used in this trial makes the emergence of toxicity very unlikely.

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

Stage II melanoma
WHO 0-1 performance

Exclusion criteria

no auto-immune disease
no immune deficiency

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	13-03-2012
Enrollment:	17
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	NA
Generic name:	tremelimumab

Ethics review

Approved WMO Date:	12-05-2011
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-07-2011
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-09-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-09-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-05-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2011-000139-10-NL

Register	ID
CCMO	NL35200.029.11