# TLR ligand matured dendritic cell vaccination in melanoma patients: the key towards a more potent immune induction?

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

## Summary

### ID

NL-OMON37090

**Source**
ToetsingOnline

**Brief title**
TLR-ligand matured DC vaccinations in melanoma patients

### Condition

- Skin neoplasms malignant and unspecified

**Synonym**
malignant melanoma

**Research involving**
Human

### Sponsors and support

**Primary sponsor:** Universitair Medisch Centrum Sint Radboud

**Source(s) of monetary or material Support:** KWF en Stichting Nijmeegs Offensief Tegen Kanker

## Intervention

**Keyword:** DC vaccination, immune therapy, melanoma, Toll like receptors

## Outcome measures

### Primary outcome

The primary objective of the study is to investigate the toxicity of TLR-DC by

dose escalation of the number of cells.

### Secondary outcome

The secondary objectives of the study are:

(a) The migratory capacity of the TLR-ligand matured DC.

(b) Activation of immune cells in vivo.

(c) The immunological response induced in melanoma patients vaccinated with

TLR-ligand matured DC loaded with mRNA encoding melanoma-associated tumor

antigens (gp100 and tyrosinase).

(d) The clinical efficacy of vaccination with TLR-ligand matured DC.

# Study description

### Background summary

Immunotherapy applying ex vivo generated and tumor-antigen-loaded dendritic cells (DC) has now successfully been introduced in the clinic. A limited, but consistent, number of objective immunological and clinical responses have been observed. Thusfar it remains unclear why some patients respond and others not, but there is a general consensus that the current protocols applied to generate DC may not result in the induction of optimal Th1 responses. We and others have demonstrated that DC maturation is one of the crucial factors, not only for effective DC migration but also to induce effective anti-tumor immune responses in cancer patients. Currently, the *golden standard* used to mature DC consists

of a cocktail of pro-inflammatory cytokines (IL-1β, IL-6, TNFα) and prostaglandin E2 (PGE2). Recent mouse data demonstrated, however, that maturation of DC by solely pro-inflammatory cytokines yielded DC that supported T cell clonal expansion, but failed to efficiently direct effector T cell differentiation. Interestingly, DC matured in the presence of Toll like receptor (TLR) ligands were able to induce full T cell effector function and unleashed more potent immune responses. We recently identified vaccines against infectious diseases that contain TLR ligands and are capable of inducing DC maturation. This knowledge provides a new application for these clinical applicable agents: clinical grade DC stimulators. A clinical grade DC maturation protocol is developed in which TLR ligands (preventive vaccines) and PGE2 are combined which resulted in the generation of mature DC that secrete high levels of the key cytokine IL-12. Moreover, these TLR-ligand matured DC induced T cells secreting at least 20-fold higher levels of the effector cytokines IFNγ and TNFα as compared to DC matured in the absence of TLR ligands. In conclusion, these in vitro data demonstrate that TLR-ligand matured DC are promising candidates to improve immunological and clinical responses in cancer immunotherapy.

**Study objective**

This is an exploratory study, consisting of two parts. In part I a dose escalation is performed and the primary objective is the safety of different doses of TLR-DC. In part II TLR-DC vaccination will be compared with cytokine-matured DC vaccination and the primary objective of this part is the immunological response to TLR-DC vaccination, with toxicity and clinical efficacy being secondary objectives. These studies will provide important data on the safety and immuniological effects of TLR-matured DC.

**Study design**

This study is an open label prospective exploratory intervention study.

**Intervention**

HLA-A2.1+ stage III and IV melanoma patients will be vaccinated with mature DC loaded with mRNA encoding tumor-associated antigens gp100 and tyrosinase and pulsed with KLH as an immune control. First, we will perform a dose-finding study in 5 stage IV patients with DC matured in the presence of the vaccines BCG, Typhim and Act-HIB (TLR-matured DC) (see Outline of study). If no toxicity is observed, we will continue with the study and aim to randomly include 20 evaluable patients in arm A (TLR-matured DC) and 12 patients in arm B (cytokine-matured DC). Furthermore, 5 stage III melanoma patients scheduled for lymph node dissection will be vaccinated once before surgery and three times thereafter. In these patients the immune activating potential in vivo of TLR-matured DC will be studied. In all patients biopsies from DTH sites will be

investigated for the presence of specific anti-tumor immunity.

**Study burden and risks**

Based on the experience with our cytokine-matured DC and the studies performed by Dr. Pawel Kalinski (PhD, MD) exploiting TLR-ligand matured DC, we expect that the TLR-matured DC will be well tolerated. Common and expected side effects of DC vaccination are usually mild and include flu-like symptoms and local reaction at injection site, both CTC grade 1. Furthermore a few patients showed allergic reactions (4 patients) and/or depigmentation of the skin (3 patients).
Aferesis is a safe procedure. Patients will have to visit our outpatient clinic (aferese, vaccination 1-3, skin test), extra blood will be drawn (vaccination 2 and 3 and skin test) and 6 mm biopsies will be taken from skin tests.

# 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

For both stage III and IV melanoma;- histologically documented evidence of melanoma;- stage III or IV melanoma according to the 2001 AJCC criteria;- HLA-A2.1 phenotype is required;- melanoma expressing gp100 (compulsory) and tyrosinase (non-compulsory);- WHO performance status 0-1 (Karnofsky 100-70%);- life expectancy >3 months;- age 18-70 years;- no clinical signs or symptoms of CNS metastases;- WBC >3.0×109/l, lymphocytes >0.8×109/l, platelets >100×109/l, ;serum crea-tinine <150 µmol/l, serum bilirubin <25 µmol/l;- normal serum LDH (<=450 U/l);- expected adequacy of follow-up;- no pregnant or lactating women;- written informed consent;For stage III melanoma;- interval since regional lymph node dissection is <2 months, or radical lymph node ;dissection is planned;For stage IV melanoma;- at least one unidimensional measurable target lesions according to RECIST, not previously irradiated, and limited tumor burden, according to the responsible physician

### Exclusion criteria

- prior chemotherapy, immunotherapy or radiotherapy <4 weeks prior to planned ;vaccination or presence of treatment-related toxicity;- history of any second malignancy in the previous 5 years, with the exception of adequately treated basal cell carcinoma or carcinoma in situ of the cervix ;serious active infections, HbsAg or HIV positive or autoimmune diseases or organ allografts ;- concomitant use of immunosuppressive drugs;- known allergy to shell fish (since it contains KLH);- rapidly progressive disease;- any serious clinical condition that may interfere with the safe administration of DC

## Study design

### Design

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| Study type: | Interventional |
| Intervention model: | Parallel |
| Allocation: | Randomized controlled trial |
| Masking: | Open (masking not used) |
| Control: | Active |
| Primary purpose: | Treatment |

### Recruitment

NL

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|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 12-08-2009 |
| Enrollment: | 34 |
| Type: | Actual |

### Medical products/devices used

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|---|---|
| Product type: | Medicine |
| Generic name: | Somatic cells autologous |

## Ethics review

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| Approved WMO Date: | 14-04-2009 |
| Application type: | First submission |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 27-04-2009 |
| Application type: | First submission |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 11-05-2010 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 06-12-2011 |
| 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 | EUCTR2008-001973-14-NL |
| CCMO | NL22750.000.08 |

# Study results

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| Date completed: | 01-08-2012 |
| Actual enrolment: | 20 |