# feasibility of immunotherapy in children with high-risk neuroblastoma

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Primary objectives: we aim to investigate the feasibility of NK cell immunotherapy by evaluating the expression of activating and inhibitory NK cell receptor ligands on primary tumor cells. secondary objectives: we aim to evaluate the cytotoxic...

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| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Miscellaneous and site unspecified neoplasms malignant and unspecified |
| **Study type** | Observational invasive |

## Summary

### ID

NL-OMON42169

**Source**
ToetsingOnline

**Brief title**
Immunotherapy in children with HR NBL

### Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

**Synonym**
immunotherapy

**Research involving**
Human

### Sponsors and support

**Primary sponsor:** Academisch Medisch Centrum
**Source(s) of monetary or material Support:** KIKA

## Intervention

**Keyword:** BM, Immunotherapy, neuroblastoma, NK cells

## Outcome measures

### Primary outcome

if the BM sample is infiltrated by NBL cells, the expression of activating NK cell receptor ligands on the tumor itself; such as MIC (MICA/B) and ULBP (ULBP1-4) proteins and CD112-/ CD155 as well as the expression of HLA class I (inhibitory liogand), CD54-/CD58 (adhesion) will be evaluated bij FACS analysis using multiple markers.

NK cell sensitivity will be determined by labelling primary NBL cells with 51-Chromium or by chemo luminescent methods and adding resting and cytokine actyivated NK cells. Furthermore, if NK cell cytotoxicity occurs, activating NK cell receptors will be blocked by monocklonal antibodies (NKG2D, DNAM-1), thereby allowing amnalysis of the activating signals involved. peripheral blood samples of newly diagnosed, treated and during FU of HR NBL patients will allow analysis of NK cell phenotype and function in these patients.

Phenotyping

The presence of a variety of lymphocyte subsets (e.g. standard T-cell subset, dendritic cells, lineages of suppressor cells) has been described to be associated with either response or failure of therapy in cancer patients, including those treated with IL-2 or GM-CSF. For the present proposal we will study the number and differentiation of each subset present in the HR NBL patients in different stages of the disease/treatment regimen.

Immunophenotyping will be performed on biobanked peripheral blood and available

bone marrow aspirates using flow cytometry to visualize subsets of:

1. T cells (naïve, central/effector memory, resting or activated CD4, CD8 and gamma/delta TCR)
2. Regulatory T cells (CD3/CD4/CD127/CD25/FoxP3)
3. T helper subsets (Th1, Th2, Th17, Th22)
4. B cells (naïve, memory, transitional, plasmablasts)
5. NK/NKT cells (CD16/CD56, CD3, Va24/Vb11)
6. DC/mono ((non-)classismal monocytesm, cDC and pDC)
7. Myeloid-derived (suppressor) cells and Tr1 cells

Secretome

Analyzing the profile of secreted cytokines, chemokines and growth factors represents an integral part of immunomonitoring during immunotherapeutic treatments. These biomarkers can distinguish diverse disease/response patterns and identify surrogate markers of efficacy. Our home-made designed panel of 100+ markers include biomarkers for general inflammatory activation (e.g. IL-1, IL-6, IL-18, TNF-a, sIL-2R etc.), Th cell skewing (e.g. IFN-g, IL-5, IL-13, IL-17, IL-10), chemo attraction (full panel of CCL and CXCL), granulocyte activation (e.g. elastase), etc. We will assess the dynamics of these markers in time in each individual patient to study a profile of biomarkers that may be diagnostic/prognostic for efficacy versus toxicity and that will be included in immunomonitoring programs of future clinical trials.

**Secondary outcome**

N/A

# Study description

### Background summary

The defining characteristics of high risk (HR) NBL include an age of more than one year, with regional or metastatic disease, unfavourable Shimada histology or Myc-N amplification (NMA). Patients with HR NBL have a 5-year survival rate of only 30-40%, even if there is a favourable response to initial therapy. For the majority of patients with relapsed refractory solid tumors, there are currently no further treatment options other than phase I/ II studies or palliation. Therefore, we aim to explore the feasibility of adoptive immunotherapy (AIT) as an additional treatment modality for this tumor, with a focus on natural killer (NK) cells.

### Study objective

Primary objectives: we aim to investigate the feasibility of NK cell immunotherapy by evaluating the expression of activating and inhibitory NK cell receptor ligands on primary tumor cells.
secondary objectives: we aim to evaluate the cytotoxic potential of unstimulated and cytokine stimulated NK cells towards primary NBL tumor cells. Cytotoxic activity of NK cells towards NBL cells in vitro and additional stimulation methods (cytokines, irradiation, tumor manipulation). This will encourage the development of novel AIT strategies as an additional treatment for high risk or relapsed NBL next to conventional or other novel therapies

### Study design

Prospective analysis, in newly diagnosed HR NBL patients, as well during therapy and FU of bone marrow (BM) samples that are infiltrated with NBL cells and immune cells (i.e. NK cells) obtained from blood, in order to perform immunological analysis.

### Study burden and risks

No additional burden, risks, the patients will undergo a bone amrrow aspirate and bloods will be taken as a routine procedure in a newly diagnosed patient (at diagnosis, during treatment and FU, max. 8 times). In this study additional material will be taken during the same procedure: bone marrow 3-5 ml and blood 5-10 ml.

# Contacts

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# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

**Age**
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

## Inclusion criteria

High risk neuroblastoma, between 1 and 18 years at diagnosis
Neuroblastoma histological proven diagnosis
Informed consent
Initial staging of the tumor
No pregnancy

## Exclusion criteria

Any prior anticancer treatment

# Study design

## Design

**Study type:** Observational invasive

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

## Recruitment

NL

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|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 13-11-2014 |
| Enrollment: | 20 |
| Type: | Actual |

# Ethics review

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| Approved WMO Date: | 29-10-2014 |
| Application type: | First submission |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 08-01-2016 |
| 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 |
|---|---|
| CCMO | NL50762.018.14 |