Immunity against neoantigens in CMMRD

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In this explorative study, we aim to:Analyze neoantigens expressed on different tumors of CMMRD patients, to identify more possible target antigens for DC vaccination studies and to select the antigens that are most frequent. Investigate...

Ethical review	Approved WMO
Status	Pending
Health condition type	Chromosomal abnormalities, gene alterations and gene variants
Study type	Observational invasive

Summary

ID

NL-OMON57508

Source
Onderzoeksportaal

Brief title
Immunity against neoantigens in CMMRD

Condition

- Chromosomal abnormalities, gene alterations and gene variants

Synonym
bi-allelic Lynch Syndrome, bi-allelic mismatch repair deficiency (BMMRD)

Research involving
Human

Sponsors and support

Primary sponsor: Radboud Universitair Medisch Centrum
Source(s) of monetary or material Support: Derde geldstroom (anders, zoals collectebussenfondsen, Europese Unie, vakministeries of bedrijven)

Intervention

- No intervention

Explanation

N.a.

Outcome measures

Primary outcome

The primary endpoints of the study are identification of neoantigens on different tumors of CMMRD patients and the detection of pre-existing immune responses against neoantigens in these patients.

Secondary outcome

Not applicable

Study description

Background summary

CMMRD

In 1999, a recessive paediatric tumor predisposition syndrome called Constitutional Mismatch Repair Deficiency (CMMRD) syndrome was recognized. CMMRD is caused by homozygous or compound heterozygous germline mutations in one of the DNA mismatch (MMR) genes. Mainly three types of malignancy characterize this syndrome: gastrointestinal tract cancer, haematological malignancies and brain tumors, which occur in childhood or adolescence. If patients survive the first malignancy, they have a high chance of developing a second or even a third malignancy. To date, patients with CMMRD are intensively screened but this does not guarantee the detection of precancerous lesions or cancer at a curable stage. A preventive treatment modality would therefore be a major step forward .

Due to germline mutations in MMR genes coding for proteins involved in repair of nucleotide mismatches, truncated proteins with impaired function are formed. These aberrant proteins can be recognized by the immune system and they might be excellent targets for immunotherapy since only tumor cells express them.

DC vaccination

Dendritic cells (DCs) play a central role in the induction of immune responses. During an infection, DCs become activated and migrate to the lymph nodes where they stimulate specific killer T cells. Their decisive role in inducing immunity formed the rationale for DC immunotherapy: DCs loaded with tumor antigens are injected into cancer patients to

stimulate T cells to eradicate tumors . In experimental clinical studies, DC vaccination has led to effective anti-tumor immune responses and increased survival in patients with melanoma . In healthy Lynch syndrome carriers, who have only a mono-allelic mutation in their DNA mismatch repair system, DC vaccination has led to induction of neoantigen-specific T cells, without inducing serious side effects.

DC vaccination of CMMRD

In this study we want to develop a preventive treatment for children with CMMRD. We aim to induce immune responses against neoantigens with DC vaccines, to prevent the formation of new lesions. For this, we need more knowledge of the presence of neoantigens and immune responses in tumors of CMMRD patients. In a pilot study (METC Oost-Nederland dossier no. 2020-6330) we made an inventory of neoantigens expressed by 42 tumors of 17 patients with CMMRD syndrome, to select/identify possible target antigens for DC vaccination studies. In addition, in pilot study NL73648.091.20 (dossier no. 2020-6355), we collected blood and serum samples of 10 CMMRD patients to investigate the presence and specificity of pre-existing immune responses against neoantigens CMMRD. In the present follow-up study, we aim to expand the cohort of patients, by including newly diagnosed CMMRD patients in the Netherlands and in Europe via the European Consortium Care for CMMRD (C4CMMRD). The results of this study will be translated into the development of a preventive DC vaccine for children with CMMRD in a follow-up study.

Study objective

In this explorative study, we aim to:

- Analyze neoantigens expressed on different tumors of CMMRD patients, to identify more possible target antigens for DC vaccination studies and to select the antigens that are most frequent.
- Investigate the presence of pre-existing immune responses against neoantigens in CMMRD carriers.

Study design

This is a single-arm, exploratory, multicentre study.

Intervention

Not applicable

Study burden and risks

There are no additional risks to participation in this study other than that of regular blood collection. The burden for the participants is minimal, as blood collection for the study will take place during regular blood collection. The results of this study will provide insight in the potential to induce immunological responses in CMMRD. Knowledge obtained will be directly translated in a clinical study with DC loaded with the identified target antigens.

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Trial sites

Trial sites in the Netherlands

Prinses Maxima Centrum voor Kinderoncologie
Target size: 25

Radboud Universitair Medisch Centrum
Target size: 5

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (16-17 years)
Babies and toddlers (28 days-23 months)
Children (2-11 years)
Adolescents (12-15 years)
Adults (18-64 years)

Inclusion criteria

- Patients with genetically proven Constitutional Mismatch Repair Deficiency (CMMRD)
- Signed informed consent

Exclusion criteria

- Any form of comorbidity interfering with safe collection of blood
- Having objectives against coded storage of tissue

Study design

Design

Study phase:	N/A
Study type:	Observational invasive
Intervention model:	Single
Allocation:	Non controlled trial
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-04-2025
Enrollment:	30
Type:	Anticipated

Medical products/devices used

Product type:	N.a.

IPD sharing statement

Plan to share IPD: Undecided

Plan description

N.a.

Ethics review

Approved WMO Date:	14-04-2025
Application type:	First submission
Review commission:	METC Oost-Nederland

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
Research portal	NL-009203