Enhancement of immune response by combining immune checkpoint blockade and radiation in patients with recurrent / refractory malignant lymphoma (re-directing the immune system).

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This translational study focusses on the altered / improved immune response triggered by the addition of radiation to immune checkpoint blockade therapy. The study is investigative in nature.Main study parameters/endpoints:a) Alteration / increase...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Lymphomas NEC
Study type	Interventional

Summary

ID

NL-OMON50953

Source
ToetsingOnline

Brief title
RIMAL1

Condition

- Lymphomas NEC
- Lymphomas NEC

Synonym
malignant lymphoma; lymph node cancer

Research involving
Human

Sponsors and support

Primary sponsor: Radboud Universitair Medisch Centrum
Source(s) of monetary or material Support: financiering wordt gezocht

Intervention

Keyword: immune checkpoint blockade, irradiation, malignant lymphoma

Outcome measures

Primary outcome

Enhancement of the immune response by radiation, and thereby treatment efficacy, in patients with recurrent / refractory malignant lymphomas treated with immune checkpoint blockade (ICB). As a measure for immune activation, interferon I and II signature alterations will be correlated with clinical response measured by [18F]FDG PET-CT scans and the amount of circulating tumour DNA (ctDNA).

Secondary outcome

- To correlate amplification of 9p24.1 in malignant lymphoma with response to (radio-) immune checkpoint inhibition therapy. The 9p24.1 amplification contains several genes; we focus mainly on the genes PDCD1LG1 (encoding programmed cell death 1 ligand 1) and PDCD1LG2 (encoding programmed cell death 1 ligand 2) responsible for IC resistance.

- To correlate tumour mutational burden with response to treatment.

- To investigate additional factors either influencing or revealing the immune response: changes in blood leukocyte subsets, T-cell receptor repertoire, functional T- and NK-cell assays, gut microbiome.

- To correlate *myeloid regulatory cell number and function* with immune

response as measured by [18F]FDG PET-CT scans and the amount of ctDNA.

- To compare, using [18F]FDG PET-CT scans, irradiated and non-irradiated

lesions in the same patient (abscopal effect).

- To investigate whether re-treatment with radio-immune checkpoint blockade

will undo CI resistance in patients who show progression in the study protocol.

- Optional: in selected cases, patients will be asked to undergo an extra

biopsy during treatment. Immune response in the tumour tissue will be

correlated with the immune response measured in blood.

Study description

Background summary

After 2 - 3 lines of standard therapy, patients with recurrent / refractory malignant lymphoma have a dismal prognosis. Immune checkponit blockade is one of the remaining options and has shown encouraging results. Best results are seen in malignant lymphomas with 9p24.1 amplification. This 9p24.1 amplification contains several genes of which PDCD1LG1 (encoding programmed cell death 1 ligand 1) and PDCD1LG2 (encoding programmed cell death 1 ligand 2) are responsible for immune checkponit resistance.
Although malignant lymphomas with 9p24.1 amplification and also malignant lymphomas without this amplification (albeit at a lesser extent) are sensitive for immune checkpoint blockade, in the end they become resistant. Mainly case reports have shown that this resistance can be overcome by irradiating (part of) the tumour bulk.
Tumour cell disruption by radiation generates a surplus of neo-antigens that enhances the effect of immunotherapy in solid malignancies as well as malignant lymphomas. The hypothesis is that the combination of immune checkpoint inhibitors and radiation will lead to better responses and longer survival in patients with recurrent / refractory malignant lymphoma, compared with either modality given alone.

Study objective

This translational study focusses on the altered / improved immune response triggered by the addition of radiation to immune checkpoint blockade therapy.
The study is investigative in nature.

Main study parameters/endpoints:
a) Alteration / increase in interferon I and II (INF I and II) signatures in blood, measured 3 weeks after radiotherapy and after every 3 consecutive courses of immune checkpoint blockade (ICB). It is anticipated that the addition of radiotherapy will lead to an extra / more pronounced response.
b) [18F]FDG PET-CT response 3 weeks after radiotherapy and after every 3 consecutive courses of ICB, related to the presence of 9p24.1 amplification. It is expected that lymphomas that harbour a 9p24.1 amplification and therefore an overexpression of PD-L1 will be more sensitive to (radio-) ICB therapy resulting in a more pronounced response.
c) Changes in ctDNA, based on the presence of tumour-specific somatic genomic characterizations of the lymphoma; reflecting lymphoma activity or tumour cell death, measured 3 weeks after radiotherapy and after every 3 consecutive courses of ICB. After an initial increase, a larger decrease in ctDNA is expected in the irradiated group.

Study design

The study population consists out of 2 groups, 10 patients each:
A. 10 patients with recurrent / refractory 9p24.1 amplified malignant lymphomas eligible for immune checkpoint inhibition; alternate assignment to either:
a1 radiation followed by immune checkpoint inhibition or
a2 start with immune checkpoint inhibition alone
resulting in 2 groups of 5 patients each.

B. 10 patients with recurrent / refractory malignant lymphoma without 9p24.1 amplification who do not qualify for standard treatment; alternate assignment to either:
b1 radiation followed by immune checkpoint inhibition or
b2 start with immune checkpoint inhibition alone
resulting in 2 groups of 5 patients each

For patients treated with combined radio-immunotherapy (groups a1 and b1), radiation will be given prior to immune checkpoint inhibition.
Radiation (5 daily fractions of 4 Gy = 20 Gy; in 1 week) will not be given to achieve local control, necessarily. Radiation will be given to induce fragmentation of tumour cell components to generate neo-tumour antigens allowing the adaptive immune system to generate a more profound and more specific anti-tumour response.

At progression or insufficient response (in both study groups A and B), patients will be examined whether they are eligible for (re-)introduction of radiation followed by ICB. For patients that were assigned to the initial *no radiotherapy arm* (groups a2 and b2) this means that radiation will be introduced in the treatment for the first time (= delayed radio-immunotherapy).

Intervention

The intervention is up-front or delayed radiation, in patients with recurrent / refractory malignant lymphoma treated with immune checkpoint blockade.

Study burden and risks

Burden: Extra blood samples. Extra [18F]FDG PET-CT scans. Stool collection. Optional: extra lymph node biopsy.

Risk: Checkpoint inhibitors and radiation have their own, well-known, toxicity profiles. Combination of both therapies does not seem to lead to an excess of toxicity. Side effects will be monitored.

Benefit: radiation may improve the effectiveness of immunotherapy in patients with recurrent / refractory lymphoma treated with immune checkpoint blockade.

Group relatedness: Checkpoint inhibition (immune checkpoint blockade = ICB) is standard therapy for patients with recurrent / refractory classical Hodgkin lymphoma (cHL). Almost all these patients have amplification of 9p24.1 in their tumour cells, harbouring amongst others the genes encoding the inhibitory PD-L1 and PD-L2 checkpoint proteins. It is very likely that all patients with 9p24.1 amplificated lymphomas (not only patients with cHL but also patients with non Hodgkin lymphomas) will benefit from ICB therapy. Patients with recurrent / refractory lymphoma without amplification of 9p24.1, are expected to have a lower response rate to ICB. Radiation prior to ICB will be tested to increase the immune response and overcome resistance.

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

- patients with refractory / recurrent malignant lymphoma eligible for ICB therapy
- aged 18 - 75 year
- WHO score >=2
- adequate organ function
neutrophil count
serum creatinine
ASAT, ALAT
albumin
- no prior treatment with checkpoint inhibitors
- no non-infectious pneumonitis requiring steroids
- not pregnant
- patients of childbearing/reproductive potential should use 2 birth control methods
- written informed consent

Exclusion criteria

- Not fit (mentally or physically) to undergo the proposed treatment.
- Patients with connective tissue diseases (inflammatory myopathy (polymyositis and ermatomyositis), systemic lupus erythematosus, Sjögren syndrome, systemic sclerosis, antisynthetase syndrome, rheumatoid arthritis, severe psoriasis and mixed CTDs), vasculitis (granulomatosis with polyangiitis (Wegener*s granulomatosis), microscopic polyangiitis, eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome), severe Behçet disease, Takayasu arteritis, giant cell arteritis, Buerger disease, Kawasaki disease, polyarteritis nodosa, severe immunoglobulin A (IgA) vasculitis (Henoch-

Schönlein purpura), severe cutaneous vasculitis, polymyalgia rheumatica, severe cryoglobulinaemia and undifferentiated systemic vasculitis) and other autoimmune diseases (primary biliary cirrhosis, severe autoimmune hepatitis, multiple sclerosis, severe antiphospholipid syndrome, myasthenia gravis, Guillain-Barré syndrome, inflammatory bowel disease, Miller-Fisher syndrome, Vogt-Koyanagi-Harada syndrome, eosinophilic fasciitis (Shulman syndrome), relapsing polychondritis and severe autoinflammatory diseases) (Martins et al. 2019).
- Sensory or motor peripheral neuropathy > grade 2.

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	20
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	KEYTRUDA 50 mg powder for concentrate for solution for infusion
Generic name:	pembrolizumab
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	OPDIVO 10 mg/mL concentrate for solution for infusion.
Generic name:	nivolumab
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	08-04-2021
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
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Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

ID: 22178
Source: NTR
Title:

In other registers

Register	ID
EudraCT	EUCTR2021-001270-34-NL
CCMO	NL75774.091.21
OMON	NL-OMON22178