Open-label single arm phase II study on pembrolizumab for recurrent primary central nervous sytem lymphoma

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Primary objective To evaluate the Overall Response Rate (CR/PRrate) in patients treated with pembrolizumab for recurrent or progressive PCNSL after MTX-based first-line therapy To evaluate the safety of pembrolizumab in subjects diagnosed with...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Nervous system neoplasms malignant and unspecified NEC
Study type	Interventional

Summary

ID

NL-OMON47301

Source
ToetsingOnline

Brief title
PCNSL

Condition

- Nervous system neoplasms malignant and unspecified NEC

Synonym
Primary central nervous system lymphoma

Research involving
Human

Sponsors and support

Primary sponsor: University Vienna, Department of Internal Medicine I, Division of Oncology
Source(s) of monetary or material Support: Ministerie van OC&W,industry,Merck Sharp & Dohme (MSD)

Intervention

Keyword: Pembrolizumab, Primary central nervous system lymphoma, recurrent, treatment

Outcome measures

Primary outcome

The primary study outcome is to evaluate the Overall Response Rate (CR/PR) and

safety in patients treated with pembrolizumab for recurrent or progressive

PCNSL after MTX-based first-line therapy.

Secondary outcome

- To describe Best Overall Response categories (CR, PR, SD, PD) in patients

treated with pembrolizumab for relapsed PCNSL after MTX-based

first-line therapy.

- To describe individual duration of response over time.

- To assess progression-free survival in this patient population.

- To assess overall survival in this patient population.

Study description

Background summary

Primary central nervous system lymphoma (PCNSL) is a malignant lymphoma, most commonly of the diffuse large B-cell lymphoma (DLBCL) type, that is confined to the central nervous system (CNS) at time of diagnosis.

The median progression-free survival time is around 12 months from the initial diagnosis and the median overall survival is approximately 3 years in most series. The standard therapy at diagnosis is based on high-dose methotrexate (MTX) chemotherapy, which may be combined with other chemotherapeutics (e.g. cytarabine) and followed by consolidation therapies such as whole-brain radiotherapy (WBRT), intensified chemotherapy or autologous stem cell transplantation (ASCT). Therapeutic options for recurrent/progressive PCNSL after MTX-based first-line therapy are poorly defined and novel treatment

concepts based on biological insights are urgently needed to improve patient outcomes.

Activating the immune system against PCNSL might be a promising therapeutic strategy. In this regard, the development and clinical availability of immune checkpoint blockers that interfere with immune-inhibiting signals represents a novel and promising therapeutic option. Among the most promising compounds are drugs that inhibit the interaction between the receptor, PD-1, and its ligands. The administration of antibodies which block PD-1 such as pembrolizumab has provided very promising results in patients with metastatic melanoma and other advanced cancers including lymphomas and was overall well tolerated .Pembrolizumab was approved by the US health authority FDA for therapy of metastatic melanoma. Several clinical trials are evaluating pembrolizumab in lymphomas, however, CNS involvement is an exclusion criterion in these studies.

In summary, there is a high medical need for patients suffering from recurrent/progressive PCNSL. Targeting the PD-1 pathway may represent a very promising novel approach for the treatment of these patients.

Study objective

Primary objective
To evaluate the Overall Response Rate (CR/PRrate) in patients treated with pembrolizumab for recurrent or progressive PCNSL after MTX-based first-line therapy
To evaluate the safety of pembrolizumab in subjects diagnosed with recurrent PCNSL

Secondary objectives
To describe Best Overall Response categories (CR, PR, SD, PD) in patients treated with pembrolizumab for relapsed PCNSL after MTX-based first-line therapy
To describe individual duration of response over time
To assess median progression-free survival in this patient population
To assess median overall survival in this patient population

Exploratory objectives
To assess PD-L1 as a predictive marker for response to pembrolizumab
Examination of PD-L1 expression in tumor tissue, including infiltrating immune cells, obtained during biopsy of primary tumor (and recurrent tumor if available)
To investigate neuro-radiological response patterns

Study design

Prospective, single-arm, phase II

Intervention

Pembrolizumab 200 mg every 3 weeks until disease progression, unacceptable toxicity or withdrawal of consent.

Study burden and risks

Before inclusion into the study standard blood tests need to be performed including tests for liver infections (hepatitis B and C) and HIV. Additionally, an ECG, tumor evaluation by MRI scan of the brain and, in women of reproductive potential, a pregnancy test will be performed. Patients will also need to be examined by a neurologist and an ophthalmologist. This does not entail a significant risk. Pembrolizumab is administered as an 30-minute infusion in out-patient setting. Generally, pembrolizumab is usually well-tolerated with mostly treatable and reversible side-effects such as diarroea, nausea, itching, skin rash, painful joints and fatigue. Occasionally auto-immune disease occur such as inflammation of kidneys, lung, thyroid or pituitary gland. These are a result of the mechanism of action of pembrolizumab (enhancement of immunity) and are rare (less than 2/100) but may be severe. Pembrolizumab is administered once every 3 weeks as long as it is tolerated and no tumor progression occurs. Prior to each cycle standard blood tests and a physical examination are performed. Every 8 weeks an MRI scan will be made to evaluate the effect of treatment and every 3 weeks a pregnancy test will be done in women of reproductive potential.

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

- Histologically confirmed diagnosis of PCNSL (DLBCL) at initial diagnosis.
- Documented progression of recurrence in cranial MRI after prior MTX-based first line therapy (with or without prior radiotherapy).
- The patient demonstrates adequate organ function.

Exclusion criteria

- Concurrent administration of any other antitumor therapy except steroids.
- Known additional malignancythat is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer.
- Active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency etc.) is not considered a form of systemic treatment.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	7
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Keytruda
Generic name:	Pembrolizumab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	17-01-2019
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-02-2019
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	EUCTR2015-005103-89-NL
ClinicalTrials.gov	NCT02779101
CCMO	NL60211.078.18