A prospective, international, multi-centre, open-label,single-arm phase II study investigating the predictive value of [68Ga]Ga-PentixaFor PET imaging in primary and isolated secondary CNS lymphoma patients

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Primary objective:1. To evaluate the negative predictive value (NPV) of [68Ga]Ga-PentixaFor (PTF) PET at interim examination (after 6 ± 2 weeks of induction chemotherapy) for progression-free survival (PFS). Secondary objectives:2. To evaluate the...

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

Summary

ID

NL-OMON51764

Source
ToetsingOnline

Brief title
Diagnostic imaging in CNS lymphoma patients.

Condition

- Other condition
- Lymphomas non-Hodgkin's unspecified histology

Synonym
Brain lymphoma, Brain tumor

Health condition

Central Nervous system lymphoma

Research involving
Human

Sponsors and support

Primary sponsor: PentixaPharm GmbH
Source(s) of monetary or material Support: Sponsor is PentixaPharm GmbH

Intervention

Keyword: CSN lymphoma, PentixaFor, radiopharmaceutical

Outcome measures

Primary outcome

The primary efficacy endpoint will be the NPV of [68Ga]Ga-PentixaFor (PTF) PET at interim examination (after 6 ± 2 weeks of induction chemotherapy, PTF-PET2) for the prediction of 16 (±1) month PFS.

Secondary outcome

Major secondary efficacy endpoints will be the PPV of PTF PET at interim examination (PTF-PET2) for prediction of 16 (±1) month PFS; NPV and PPV of PTF-PET at end-of-chemotherapy (PTF PET3) for prediction of 16 (±1) month PFS; NPV and PPV of PTF-PET2 and PTF-PET3 for the prediction of complete response. Exploratory analyses of the association between PTF PET variables (standardised uptake value, tumour-to-background ratio, metabolic tumour volume) and PFS and CR will be performed. Sensitivity of PTF-PET to detect CXCR4 overexpression will be assessed. Agreement between PTF-PET and MRI concerning CNSL-suspicion will be determined, and inter- and intra-reader agreement will be checked.

Study description

Background summary

The role of CXCR4/CXCL12 in CNS lymphoma is substantial: the tumour cells of both primary and secondary CNS lymphoma are characterised by their strong and consistent expression of this chemokine receptor and/or its ligand; moreover, CXCR4/CXCL12 play a key role as neurotrophic factors.
Different therapeutic agents targeting CXCR4/CXCL12 are currently in clinical development. Subsequently, various CXCR4-directed imaging tracers were developed. PTF is being developed for CXCR4-directed imaging. The tracer shows high affinity and selectivity for human CXCR4, rapid renal excretion, and very low non-specific background accumulation, allowing sensitive and high-contrast PET imaging of CXCR4-expressing tissues in vivo. Recent imaging studies have confirmed that a CXCR4-based PET tracer accumulated in the brain of patients with primary as well as of those with secondary CNS lymphoma.
In addition to the proposed indication, diagnosis of primary and secondary CNS lymphoma, PentixaFor application in the future might include staging (evaluating the extent of disease) and activities directed towards patient selection for personalised therapeutic concepts such as CXCR4-directed radio-ligand therapy and/or response assessment to anti-cancer therapy.
For CNS lymphoma, a major problem in therapy decisions is that it is not known which patients need an additional consolidation therapy (high-dose chemotherapy and/or radiation) if a (partial) remission is achieved. Both high-dose chemotherapy and whole-brain irradiation are very toxic.
A staging method with a high negative predictive value (NPV) might be very helpful for guiding the omission of consolidation therapies.
Moreover, a more precise staging method as compared with MRI might identify relapses earlier and therefore improve therapy by prompting earlier interventions.
Finally, a method with a high positive predictive value (PPV) might guide escalation of therapy at an early stage of treatment.

Study objective

Primary objective:
1. To evaluate the negative predictive value (NPV) of [68Ga]Ga-PentixaFor (PTF) PET at interim examination (after 6 ± 2 weeks of induction chemotherapy) for progression-free survival (PFS).
Secondary objectives:
2. To evaluate the positive predictive value (PPV) of PTF PET at interim examination (after 6 ± 2 weeks of induction chemotherapy) for PFS.
3. To evaluate the safety and tolerability of PTF PET imaging.
4. To evaluate the predictive values of PTF PET at the end of induction chemotherapy for PFS.

5. To evaluate the predictive values of PTF PET at interim examination (after 6 ± 2 weeks of induction chemotherapy) and end-of-chemotherapy-treatment for complete response (CR).
6. To evaluate the predictive values of pre-treatment PTF PET imaging parameters for PFS and CR.
7. To evaluate the predictive values of interim (after 6 ± 2 weeks of induction chemotherapy) PTF PET imaging parameters for PFS and CR.
8. To evaluate the predictive values of changes between pre-treatment and interim (after 6 ± 2 weeks of induction chemotherapy) PTF PET imaging parameters for PFS.
9. To determine the sensitivity of pre-treatment PTF PET for CXCR4-positivity in the fraction of patients from whom biopsy tissue is available, by using histopathology (CXCR4 overexpression by immunohistochemistry, IHC) as the reference standard on a patient basis.
10. To evaluate the diagnostic agreement between PTF PET and MRI at baseline imaging on a patient level.
11. To evaluate the observer agreement of PTF PET (inter- and intra-reader agreement).

Study design

This will be an open, single-arm, international, multicentre, phase II imaging study to assess the predictive value of [68Ga]Ga PentixaFor PET imaging in primary and isolated secondary central nervous system lymphoma (CNSL) patients scheduled to undergo induction chemotherapy.
At each of three time points, each patient will receive two scans, a CXCR4-directed PTF PET scan and an MRI scan. The time points are baseline (before the initiation of induction chemotherapy), an interim scan (Week 6 ± 2 after the inception of induction chemotherapy) and a final scan in Week 12-18 (after the completion of induction chemotherapy).
After the three pairs of scans (PTF PET and MRI) have been performed the patients will enter the follow-up phase of the study. This will comprise four further MRI imaging procedures at 3 month intervals.
This is an imaging-only study, and the study procedures do not include any therapeutic measures or decisions. Patients will be treated according to *standard of care*.

Intervention

The study product is [68Ga]Ga-PentixaFor, otherwise referred to as PTF. It is a positron emitter and is used in this study as a PET tracer. It will be administered to each patient by bolus injection shortly before PET scanning. In all, three PTF PET scans will be performed. The short decay half-life of 68Ga will ensure an appropriately short exposure of the patients to radiation.

Imaging with [68Ga]Ga-PentixaFor PET/CT and MRI is planned for the following

time points:
1) Before the start of standard therapy (induction chemotherapy),
2) Halfway through standard therapy (induction chemotherapy) and
3) After the end of standard therapy (induction chemotherapy).

Study burden and risks

For the nature and extent of the burden and risks associated with participation, please refer to section E.9.
Probably no short-term personal benefit for participating patients will be gained in the study, but it may be that more accurate information about the disease and treatment response can be obtained. In any case participation in the study will deliver valuable information about whether imaging with 68Ga-PentixaFor PET/CT can provide additional information for CNS lymphoma follow-up.

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

All study patients must meet all the following criteria:
1.Written informed consent obtained according to international guidelines and local laws by patient (or legally acceptable representative if the patient is temporarily legally not competent owing to his/her disease). [Note: No invasive study-specific procedures may be carried out until this consent has been given.]
2.Patient aged 18 years or above (either sex).
3.Histologically confirmed primary or secondary CNSL based on cytology/flow cytometry of cerebrospinal fluid (CSF) or brain biopsy.
4.Disease exclusively located in the CNS (primary CNSL or secondary CNSL with isolated CNS relapse). Subjects who had undergone allogeneic stem cell transplant > 12 months prior to first dose of study drug, have no evidence of active graft versus host disease, and are not on systemic immunosuppressive therapy are allowed to participate in the study.
5.At least one measurable parenchymal lesion. [Note: parenchymal CNSL is a *must*, and additional locations such as leptomeningeal disease are permitted.]
6.Previously untreated CNS disease.[Note: Previous or ongoing steroid treatment is permitted. Prophylaxis chemotherapy is not necessary, as induction chemotherapy will start within 72 hours after PTF-PET.]
7.At least one morphologically measurable lesion according to the IPCG criteria (Appendix 1).
8.Patients scheduled to undergo induction chemotherapy based on one of the following: High-dose methotrexate (HD-MTX)-based chemotherapy, ICE/DeVIC or High-dose cytarabine (HD-AraC)-based chemotherapy.
9.ECOG performance status <= 2 for patients aged >=65 years;ECOG performance status <= 3 for patients aged <65 years.
10.Life expectancy of at least 3 months, as estimated by the investigator.
11.For women of child-bearing potential: negative pregnancy test.
12.For sexually active female patients of child-bearing potential: The patient agrees to take adequate contraceptive measures during study participation and also agrees to continue use of this method for the duration of the study and for 6 months after the last dose of PTF.
13.For male patients whose partner is of child-bearing potential: The patient is willing to ensure that he and his partner use effective contraception during the study and for 6 months after the last dose of PTF.

Exclusion criteria

Any patient meeting one or more of the following criteria will not be included:
1.Known hypersensitivity to [68Ga]Ga-PentixaFor or its components.
2.Contraindication for contrast-enhanced MRI as set out in the relevant

institutional guidelines (e.g., pacemaker, defibrillator, aneurysm clip, metal in the body, renal insufficiency, severe claustrophobia etc.).
3.Contraindication for the use of gadolinium contrast for MRI.
4.Contraindication for PET according to institutional guidelines (weight-based, e.g. weight > 180 kg).
5.Inability to lie still for the entire imaging time.
6.Systemic lymphoma manifestation (outside the CNS).
7.Presence of active infection at screening or history of serious infection within the previous 6 weeks (except HIV infection: patients with HIV-associated primary CNSL are considered eligible).
8.Administration of another investigational medicinal product within the 30 days (or 5 excretion half-lives, whichever period is the longer) before first treatment with PTF.
[Note: Re screening may be performed to accept washout of prior agents.]
9.Current toxicity of Grade >2 from previous standard or investigational therapies (grade according to the NCI Common Terminology Criteria for Adverse Events, version 5.0 (CTCAE 5.0).
10.For female patients: Pregnancy (existing or intended) or breast-feeding.
11.Renal impairment: Both of the following: Estimated glomerular filtration rate (eGFR) < 30 ml/min/1.73 m2 Creatinine clearance < 60 ml/min
12.Hepatic impairment: Both of the following: Aspartate aminotransferase (AST) > 3 upper limit of normalAlanine aminotransferase (ALT) > 3 upper limit of normal
13.Presence of any unstable systemic disease (including, but not limited to, active infection, uncontrolled hypertension, unstable angina, congestive heart failure, serious cardiac arrhythmia requiring medication, hepatic, renal or metabolic disease.
14.Presence of psychiatric disease, alcohol abuse or any other medical condition(s) that, in the opinion of the investigator, makes the patient unable to comply with study procedures and visits.
15. Patient weight <= 48 kg

Study design

Design

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

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	6
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	[68Ga]Ga-PentixaFor
Generic name:	[68Ga]Ga-PentixaFor

Ethics review

Approved WMO Date:	29-03-2022
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	12-07-2022
Application type:	First submission
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	EUCTR2021-001711-85-NL
ClinicalTrials.gov	NCT05222269
CCMO	NL80452.000.22