Improving peptide receptor radionuclide therapy with poly ADP ribose polymerase inhibitor.

Published: 18-11-2021
Last updated: 14-09-2024

This study has been transitioned to CTIS with ID 2024-513007-14-00 check the CTIS register for the current data. The current trial aims to asses the safety of this combination in a phase I trial with olaparib dose escalation during two cycles of...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Neoplastic and ectopic endocrinopathies
Study type	Interventional

Summary

ID

NL-OMON54089

Source
ToetsingOnline

Brief title
The PRRT-PARPi study

Condition

- Neoplastic and ectopic endocrinopathies
- Endocrine neoplasms malignant and unspecified

Synonym
neuroendocrine tumors

Research involving
Human

Sponsors and support

Primary sponsor: Moleculaire geneeskunde
Source(s) of monetary or material Support: Oncode Instituut

Intervention

Keyword: dose-escalation, Neuroendocrine tumor, PARPi, PRRT

Outcome measures

Primary outcome

To determine the maximum tolerated dose (MTD) of olaparib in combination with PRRT in patients with a well-differentiated advanced NET, progressive after treatment with PRRT.

Secondary outcome

To evaluate the efficacy, pharmacokinetics (PK) and biomarker response of olaparib in combination with PRRT in patients with a well-differentiated advanced NET, progressive after treatment with PRRT.

Study description

Background summary

Neuroendocrine tumors (NETs) are well-differentiated cancers that originate from the sensory and secretory neuroendocrine cells, predominantly located in the bronchopulmonary and gastrointestinal tracts. The rarity and heterogeneity of NET disease has hampered drug development and clinical trials in this field. Consequently, patients presenting with advanced stages of NET have a limited prognosis as systemic treatment options are limited.
Peptide receptor radionuclide therapy (PRRT) with 177Lutetium-DOTA-Tyr3,octreotate (177Lu-DOTATATE) is an effective treatment for patients with locally advanced or metastatic NETs.
A large multicenter phase III trial (NETTER-1)using the Rotterdam protocol was successfully completed. Patients randomized to PRRT with 4 cycles of 177Lu-DOTATATE displayed a significantly improved progression-free survival of 28 months compared to 8 months in the control arm. The risk of progression or death was 79% lower in patients treated with PRRT and quality of life was improved. However, partial and complete response rates after PRRT are limited at 17% and 1% of patients, respectively, and disease progression occurs after

approximately 2.5 years. Therefore, adaptations of the therapeutic regimen of PRRT are urgently needed. As administering a higher PRRT dose will lead to radiation-induced side effects in healthy tissues, especially the bone marrow and kidneys, many groups have focused on other targeted therapeutic strategies capable to stimulating tumor cell death.
Following our preclinical work on molecular mechanisms of the DNA damage response to radiation, we aim to overcome the current limitations of PRRT by enlarging the therapeutic window. During PRRT of NETs, therapeutic radionuclides are coupled to peptides (177Lu-DOTATATE) that can specifically bind to the somatostatin receptors (SSTs) overexpressed on the tumor surface. The β-particle radiation emitted by 177Lu-DOTATATE induces both single-strand breaks (SSBs) and double-strand breaks (DSBs) in the tumor cell*s DNA. While a certain amount of DNA damage can be repaired, a higher level will induce cell death. In order to force more cancer cells to reach the lethal threshold, we will prevent repair of PRRT-induced DNA damage using the PARP-1 inhibitor (PARPi) olaparib. PARP-1 is essential for SSB repair and when SSBs are not repaired, they will be converted into DSBs during cell division. The combination of PRRT with olaparib can potentially increase the rate at which the tumor cells accumulate PRRT-induced DSBs and thereby increase the tumor cell death rate.
Furthermore, ongoing studies in xenografted mice show a significant decrease in tumor size in mice treated with PRRT and olaparib compared to PRRT alone as well as a delay in tumor regrowth (Figure 2). Excitingly, we have reached 13% completed response in the PRRT and olaparib combination group while none of the mice treated with PRRT alone were cured. Olaparib alone did not influence tumor growth and no acute toxicity was observed in the mice.
Together, these clinical data provide sufficient justification to pursue clinical development of a combination of a PARP inhibitor with PRRT.

Study objective

This study has been transitioned to CTIS with ID 2024-513007-14-00 check the CTIS register for the current data.

The current trial aims to asses the safety of this combination in a phase I trial with olaparib dose escalation during two cycles of 177Lu-DOTATATE in salvage setting in patients with advanced GEP NET, progressive after initial PRRT.

Study design

This is a phase I dose-escalation, single arm, prospective study among patients with advanced NETs that have progressive disease according to RECIST v1.1 following initial or salvage PRRT. The study will be initiated at Erasmus MC, but based upon recruitment and interest additional centers may be added after approval of a submitted amendment.

Patients eligible for salvage PRRT will receive 18 days of olaparib starting 3 days before PRRT until 14 days after. Patients will receive a fixed standard dose of salvage PRRT, consisting of 2 cycles of 7.4 GBq 177Lu-DOTATATE. Four dose tiers of olaparib will be evaluated in a dose escalation sequence next to the two cycles of PRRT according to the following regime:
- 100 mg q.d.
- 100 mg b.i.d.
- 200 mg b.i.d.
- 300 mg b.i.d.
Patients discussed at the multidisciplinary team and accepted for salvage PRRT will be approached for participation if they fulfil the inclusion and exclusion criteria.

Study design is a classic 3+3 dose escalation with 3 patients per dose tier. The 3+3 design with fixed doses per patient and opening of a higher dose tier after complete evaluation of all safety data until day 57 was chosen because of the sub-acute toxicity observed after PRRT. A dose tier will open for 3 patients. In case no dose-limiting toxicity (DLT) is observed in the first cycle of PRRT, successive participants will escalate the olaparib dose to the next tier.
In case of the occurrence of 1 DLT, inclusion of up to 3 additional patients at the same dose is pursued, after which dose escalation can follow if no additional DLT is observed. In case of >=2/3 or >=2/6 DLTs at a given dose level, further dose escalation will be stopped and an additional 3 patients will be treated at the previous dose level. In case of unexpected toxicity (>=2/3 or >=2/6 DLTs) at the starting dose of 100mg q.d., a single de-escalation step to 50 mg q.d. is allowed.
The maximum tolerated dose of olaparib is the highest dose level at which 0 or 1 DLTs are encountered in 6 patients.

Intervention

2x18 days taking tablets of olaparib, 2 biopsies of the tumor, 29 additional venipunctures, 7 ECG*s, 4 additional SPECT/CT scans.

Study burden and risks

PRRT with 177Lu-DOTATATE and olaparib are treatments which are already used in therapy for cancer and of which the side-effects are known. However, the effects and side-effects of this combination are still unknown, therefore this phase 1 dose-escalation study is necessary. The patients receive de PRRT as known and have to take tablets of olaparib for 18 days in addition. They will be checked frequently for effects and side-effects of this combination therapy to reduce the risk as much as possible.
It is necessary to draw blood to determine the toxicity and take biopsies to evaluate the effect on the tumor cells.

There will be drawn approximately 350 ml of blood in total.

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 proven locally advanced or metastatic, well-differentiated (grade 1, 2 or 3) NET
- Disease progression based on RECIST v1.1 following initial or salvage treatment with PRRT with 177Lu-DOTATATE with a progression free interval of at least 12 months since first cycle of previous administration of PRRT or with no suitable systemic alternative treatment options
- The patient is eligible for two cycles of salvage PRRT
- Measurable disease according to RECIST v1.1 on CT/MRI
- Confirmed presence of somatostatin receptors on all target lesions on CT/MRI,

based on positive uptake on a 68Ga-DOTATATE/-TOC/-NOC PET-CT/MRI scan
- Age >= 18 years
- Karnofsky Performance Score (KPS) > 60

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:
- Hb concentration <6.2 mmol/L; white blood cell count <3x109/L; platelets <100x109/L; neutrophil count <1.5x109/L
- Renal insufficiency defined as a creatinine clearance <50 mL/min, measured in 24-hour urine collection
- Liver function or enzyme abnormalities defined as a total bilirubin >3 x ULN, Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2.5 x ULN or serum albumin <3.0 g/dL unless prothrombin time is within the normal range.
- Pregnancy, lactation and inability to comply with effective means of contraception in females of child-bearing age.
- Neuroendocrine carcinoma of any origin.
- Any surgery, radioembolization, chemoembolization, chemotherapy and radiofrequency ablation within 12 weeks prior to inclusion in the study. Interferons, everolimus, sunitinib or other systemic therapies within 4 weeks prior to inclusion in the study.
- Uncontrolled congestive heart failure (NYHA II, III, IV).
- Patients with any other significant medical, psychiatric, or surgical condition, currently uncontrolled by treatment, which may interfere with the completion of the study.
- Prior external beam radiation therapy to more than 25% of the bone marrow.
- Other known co-existing malignancies except non-melanoma skin cancer and carcinoma in situ of the uterine cervix, unless definitively treated and proven no evidence of recurrence for 5 years.
- Patients who use a strong CYP3A4 inhibitor within 1 week before start of the treatment or a CYP3A4 inducer within 4 weeks before start of the treatment.
- History or evidence of any other clinically significant disorder, condition or disease (with the exception of those outlined above) that, in the opinion of the investigator would pose a risk to subject safety or interfere with the study evaluation, procedures or completion.
- Known allergy or intolerance for the (non-)investigational drugs
- Inability to provide informed consent
- End of life care

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	24-03-2022
Enrollment:	24
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Lutathera
Generic name:	177Lu-DOTATATE
Product type:	Medicine
Brand name:	Lynparza
Generic name:	Olaparib
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	18-11-2021
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO

Date:	20-01-2022
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO

Date:	17-05-2023
Application type:	Amendment
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
EU-CTR	CTIS2024-513007-14-00
EudraCT	EUCTR2021-001064-15-NL
CCMO	NL79259.078.21
Other	NL9857