Improving Peptide Receptor Radionuclide Therapy with PARP inhibitors.

No registrations found.

Ethical review	Positive opinion
Status	Recruiting
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON21221

Source
NTR

Brief title
PRRT-PARPi study

Health condition

well-differentiated advanced gastroenteropancreatic neuro-endocrine tumors.

Sponsors and support

Primary sponsor: Erasmus MC, Rotterdam, the Netherland
Source(s) of monetary or material Support: Erasmus MC

Intervention

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

Peptide receptor radionuclide therapy (PRRT) with the beta-emitting radiopharmaceutical 177Lutetium-DOTA-Tyr3,octreotate (177Lu-DOTATATE) is an effective and safe treatment option for patients with metastatic neuroendocrine tumors (NETs). In advanced NET patients, 177Lu-DOTATATE has been proven to secure long-term survival in several large retrospective series and was superior to high-dose somatostatin analogs in a randomized phase 3 clinical trial, with a 79% decrease in the risk of progression or death. However, objective response rates are limited and fewer than 1% of the patients can achieve complete response following PRRT. Administering a higher cumulative dose than currently applied will induce more toxicity in healthy tissues, and therefore probably will be detrimental to patients. Therefore, adaptations to the currently applied PRRT regimen are needed. The repair of PRRT-induced DNA damage constitutes a viable target to enhance its antitumor effects. In a number of preclinical models, inhibitors of the enzyme poly ADP ribose polymerase (PARP), essential for repair of single-strand DNA breaks, have been shown to improve the cytotoxic effects of PRRT without signs of added toxicity. Various PARP inhibitors are registered for the treatment of human cancers, such as ovarian cancer, and BRCA- or HRD-dependent prostate and pancreatic cancer and are under investigation in several clinical trials as radiosensitizer. Based on preclinical in vitro and in vivo data, we hypothesize that PARP inhibitors can potentiate radiation-induced tumor cell death in patients treated with PRRT. To determine the maximin tolerated dose (MTD) of this combination, a phase 1 dose-escalation study is needed.

Study objective

We hypothesize that PARP inhibitors can potentiate radiation-induced tumor cell death in patients treated with PRRT. To determine the maximin tolerated dose (MTD) of this combination, a phase 1 dose-escalation study is needed.

Study design

Screening, 2 cycle of PRRT with olaparib, weekly blood draws, 4 appointments out patient clinic.

Intervention

Olaparib (18 days) during 2 PRRT cycles.

Contacts

Public
Erasmus MC
Nina Becx

-
Scientific
Erasmus MC
Nina Becx

-

Eligibility criteria

Inclusion criteria

- Histologically proven locally advanced or metastatic, well-differentiated 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
- Two cycles of PRRT are considered by the treating physician
- 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

- 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
Intervention model:	Other
Allocation:	Non controlled trial
Masking:	Open (masking not used)
Control:	N/A , unknown

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	01-01-2022
Enrollment:	24
Type:	Anticipated

IPD sharing statement

Plan to share IPD: Undecided

Ethics review

Positive opinion

Date:	04-11-2021
Application type:	First submission

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
NTR-new	NL9857
Other	METC EMC : 79259

Study results