Improving Peptide Receptor Radionuclide Therapy with PARP inhibitors.

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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.

Ethische beoordeling	Positief advies
Status	Werving gestart
Type aandoening	-
Onderzoekstype	Interventie onderzoek

Samenvatting

ID

NL-OMON21221

Bron
NTR

Verkorte titel
PRRT-PARPi study

Aandoening

well-differentiated advanced gastroenteropancreatic neuro-endocrine tumors.

Ondersteuning

Primaire sponsor: Erasmus MC, Rotterdam, the Netherland
Overige ondersteuning: Erasmus MC

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

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.

Toelichting onderzoek

Achtergrond van het onderzoek

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.

Doel van het onderzoek

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.

Onderzoeksopzet

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

Onderzoeksproduct en/of interventie

Olaparib (18 days) during 2 PRRT cycles.

Contactpersonen

Publiek

Erasmus MC
Nina Becx

-

Wetenschappelijk

Erasmus MC
Nina Becx

-

Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

- 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

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

- 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

Onderzoeksopzet

Opzet

Type:	Interventie onderzoek
Onderzoeksmodel:	Anders
Toewijzing:	N.v.t. / één studie arm
Blindering:	Open / niet geblindeerd
Controle:	N.v.t. / onbekend

Deelname

Nederland

Status:	Werving gestart
(Verwachte) startdatum:	01-01-2022
Aantal proefpersonen:	24
Type:	Verwachte startdatum

Voornemen beschikbaar stellen Individuele Patiënten Data (IPD)

Wordt de data na het onderzoek gedeeld: Nog niet bepaald

Ethische beoordeling

Positief advies

Datum:	04-11-2021
Soort:	Eerste indiening

Registraties

Opgevolgd door onderstaande (mogelijk meer actuele) registratie

Geen registraties gevonden.

Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

In overige registers

Register	ID
NTR-new	NL9857
Ander register	METC EMC : 79259

Resultaten