COMPETE Phase III Trial – Peptide Receptor Radionuclide Therapy (PRRT) with Lutetium (^{177}Lu) Edotreotide vs. Everolimus in Patients with Progressive GEP-NETs

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Background

Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are relatively rare and complex neoplasms. Their incidence and prevalence are continuously rising[1]. Current standard treatment options for metastasized GEP-NETs include somatostatin (SST) analogs (due to NETs strongly expressing SST receptors) and targeted drugs such as the mTOR inhibitor everolimus and the tyrosine kinase inhibitor sunitinib. While these treatments rarely induce objective tumor remission, disease stabilization may be achieved for a limited time, for instance, median progression free survival (mPFS) with everolimus in prospective phase III trials is 11 months[2]. Some patients may also benefit from systemic chemotherapy.

Peptide Receptor Radionuclide Therapy (PRRT) uses IV-infused radiolabeled ligands to deliver cytotoxic dose of radiation to tumor cells while sparing the surrounding tissue. This therapy is emerging as a promising option, providing more durable response and potentially higher objective response rates than currently approved therapies. PRRT with ^{177}Lu-DOTATATE has increased PFS and achieved higher response rates than high dose octreotide in patients with advanced SSTR$^+$ midgut NETs[3]. These results call for additional prospective, randomized and controlled study of other PRRTs in SSTR$^+$ NETs of the midgut and other locations.

Lutetium (^{177}Lu) edotreotide (^{177}Lu-DOTATOC), tested in the COMPETE trial, is an innovative octreotide-derived somatostatin analog containing the chelator DOTA radiolabeled with the medical radioisotope lutetium (^{177}Lu). Its favorable safety profile and promising efficacy have been demonstrated in a phase II study in 56 patients[4]. Lutetium (^{177}Lu) edotreotide PRRT in metastasized GEP-NETs achieved a median PFS of 34.5 months in patients who received ≥2 treatment cycles (Figures 1 and 2). The COMPETE trial is the first to undertake a direct comparison of PRRT vs. an approved therapeutic.

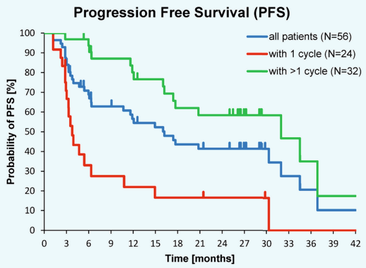


Figure 1: Kaplan-Meier estimates of PFS in the study population depending on number of lutetium (^{177}Lu) edotreotide PRRT cycles (Baum et al, 2016)

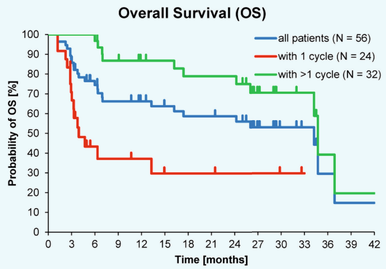


Figure 2: Kaplan-Meier estimates of OS in the study population depending on number of lutetium (^{177}Lu) edotreotide PRRT cycles (Baum et al, 2016)

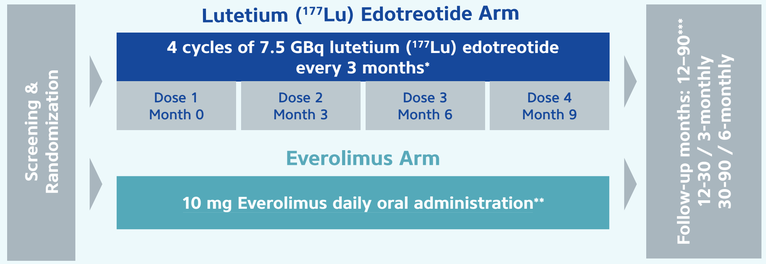
Method

Trial design

COMPETE is a prospective, randomized, controlled, open-label, multi-center, phase III clinical trial to evaluate the efficacy and safety of lutetium (^{177}Lu) edotreotide PRRT compared to targeted molecular therapy with everolimus in patients with inoperable, progressive, somatostatin receptor-positive (SSTR$^+$) GEP-NETs. The study is ongoing and currently recruiting patients in at least 14 countries[5].

300 patients with progressive Grade 1 and Grade 2 GEP-NETs are being randomized: 200 patients receive up to 4 cycles of lutetium (^{177}Lu) edotreotide PRRT (7.5 GBq/cycle) every 3 months or until diagnosis of progression; 100 patients receive 10 mg everolimus until EOS or diagnosis of progression.
Study duration per patient is 30 months (Figure 3).

Treatment Schedule



* unless diagnosis of progression or EOS
** until diagnosis of progression or EOS
*** or until diagnosis of progression, whichever is earlier

Figure 3: Summary schedule of treatments and follow-up consultation

Study Objectives

Primary Objective

Progression-free survival (PFS). Diagnosis of progression will be established based on morphological imaging (MRI and/or CT) according to RECIST 1.1.

Key Secondary Objectives

Objective response rates (ORR) as best outcome; overall survival (OS); duration of disease control (DDC); safety and tolerability; health-related quality of life (HRQL); dosimetry; pharmacokinetics.

Main Inclusion Criteria

- Written informed consent
- Male or female ≥18 years of age
- Histologically and clinically confirmed diagnosis of well-differentiated NET of non-functional gastrointestinal origin (GI-NET) or both functional or non-functional pancreatic origin (P-NET), tumor grade G1 or G2 (Ki-67 ≤20%), unresectable or metastatic
- Measurable disease per RECIST 1.1, on CT/MRI scans, defined as at least 1 lesion with ≥1 cm in longest diameter and ≥2 radiological tumor lesions in total
- SSTR$^+$ disease, as evidenced by SSTR imaging within 4 months prior to randomization
- Radiological disease progression, defined as progressive disease per RECIST 1.1 criteria, evidenced by CT/MRI with ≥90 days interval during 12 months prior to randomization

Mode of Action

Lock and Key Principle

Targeted radiopharmaceuticals contain a targeting molecule and a medical radioisotope. The targeting molecule binds to the tumor specific receptor according to the lock and key principle (Figure 4). In most cases, the targeting molecule can be used for both diagnostics and therapy, only the radioisotope needs to be changed. This enables the application of theranostics in precision oncology.

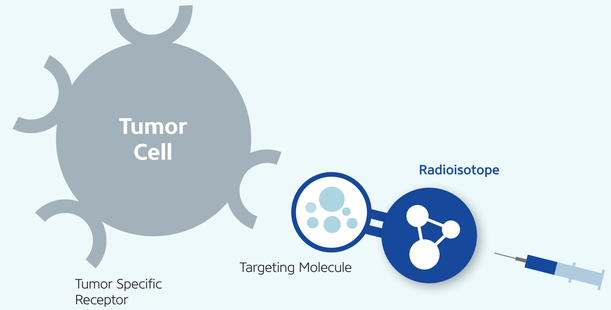


Figure 4: Lock and key principle of PRRT with targeting molecule and medical radioisotope

Conclusion

COMPETE is the first pivotal study to compare PRRT with an approved therapeutic in patients with Grade 1 and Grade 2 GEP-NETs. It is expected that COMPETE will increase treatment options, including first-line therapy. Further studies with lutetium (^{177}Lu) edotreotide in patients with NETs and high unmet medical needs are under review.

References

[1]Dasari A et al., JAMA 2017
[2]Yao JC et al., Lancet 2016
[3]Strosberg et al., NEJM 2017
[4]Baum et al., Theranostics 2016
[5]Phase III Trial COMPETE

Access via QR code or find more trial information on www.compete-clinical-trial.com

Access via QR code or find more trial information on ClinicalTrials.gov NCT03049189: https://bit.ly/3uccXds

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