COMPOSE: Pivotal phase III trial of ^{177}Lu-edotreotide versus best standard of care in well-differentiated aggressive grade 2 and grade 3 gastroenteropancreatic neuroendocrine tumors

Halfdanarson TR,[1] Reidy D,[2] Vijayvergia N,[3] Halperin D,[4] Goldstein G,[5] Kong G,[6] Michael M,[6] Leyden S,[7] Grozinsky-Glasberg S,[8] Sorbye H,[9] Öberg K,[10] Thevenet T, [11] Herrmann M[11]

1. Presenter: Mayo Clinic, Rochester, MN, USA; 2. Memorial Sloan Kettering Cancer Center, New York, NY, USA; 3. Fox Chase Cancer Center, Philadelphia, PA, USA; 4. MD Anderson Cancer Center, Houston, TX, USA; 5. Carcinoid Cancer Foundation, Mt Kisco, NY, USA; 6. Peter MacCallum Cancer Centre, Melbourne, VIC, Australia; 7. NeuroEndocrine Cancer, Australia; 8. Hadassah Medical Center, Jerusalem, Israel; 9. Haukeland University Hospital, Bergen, Norway; 10. Akademiska Sjukhuset, Uppsala, Sweden; 11. ITM Oncologics GmbH, Garching/Munich, Germany.

Background

Gastroenteropancreatic neuroendocrine tumors (GEP-NETs), which represent approximately 70% of NETs, frequently develop metastatic disease with limited treatment options.[1]

Current standard therapies for the subset of well-differentiated high grade 2 and grade 3 GEP-NETs include cytoreductive procedures, somatostatin analogues, molecular targeted therapies (everolimus or sunitinib), chemotherapy and peptide receptor radionuclide therapy (PRRT), with no specified sequence of use.[2–4]

PRRT may stabilize disease and induce objective tumor responses. This treatment uses radiolabeled somatostatin analogues to selectively target tumor cells expressing somatostatin receptor 2.[5]

As demonstrated in the Bad Berka study, PRRT in the form of non-carrier added (n.c.a.) ^{177}Lu-edotreotide is an innovative radiolabeled somatostatin analogue with a favorable safety profile and promising efficacy in treating patients with NETs (Figure 1 and Figure 2).[6]

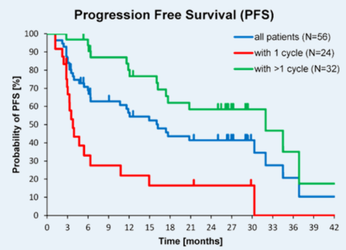


Figure 1. Kaplan-Meier estimates of PFS in the study population depending on number of n.c.a. ^{177}Lu-edotreotide PRRT cycles.[6]

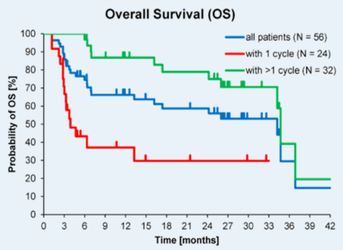


Figure 2. Kaplan-Meier estimates of OS in the study population depending on number of n.c.a. ^{177}Lu-edotreotide PRRT cycles.[6]

Mode of Action

Lock and Key Principle

PRRT contains a targeting molecule, which binds to the tumor specific receptor according to the lock and key principle (Figure 3), and a radioisotope. The targeting molecule can be used for both therapeutics and diagnostics, only the radioisotope has to be changed. This opens up the way for theranostics in precision oncology.

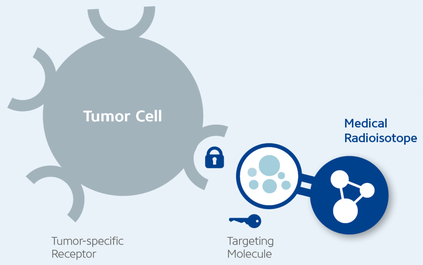


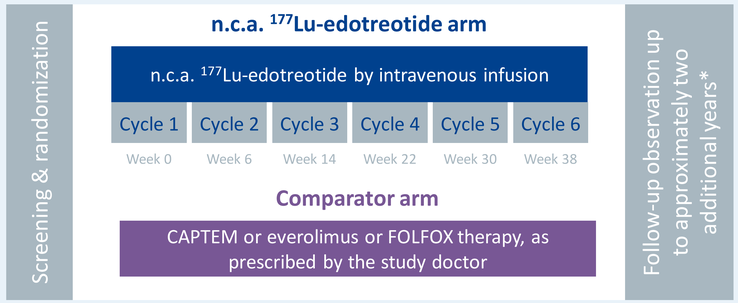
Figure 3. Lock and key mode of action

Method

Trial Design

COMPOSE is a prospective, randomized, controlled, open-label, multi-center, Phase III study to evaluate the efficacy, safety and patient-reported outcomes of first-or later-line treatment with n.c.a. ^{177}Lu-edotreotide PRRT compared to best standard of care in patients with well-differentiated, high grade 2 and grade 3 (Ki-67 index 15–55), somatostatin receptor-positive (SSTR+) GEP-NETs.

The study was recently opened and is planned to recruit patients in 10 countries. It aims to randomize 202 patients 1:1 to receive one of two treatment options (Figure 4).



*Treatment response, tumor progression, survival data, information on further antineoplastic treatments and secondary malignancies

Figure 4: Summary schedule of treatments and follow-up consultation

As shown above, patients will receive either:

- PRRT with n.c.a. ^{177}Lu-edotreotide consisting of six cycles (7.5 GBq n.c.a. ^{177}Lu-edotreotide per cycle), administered as i.v. infusion (101 patients) or
- Either CAPTEM, everolimus, or FOLFOX, administered according to local prescribing information, until diagnosis of progression or end of study (101 patients). The appropriate standard therapy will be determined by the study doctor.

Main Inclusion/Exclusion criteria

Inclusion Criteria include:

- Patients aged ≥18 years
- Histologically confirmed diagnosis of unresectable, well-differentiated (high grade 2 and grade 3) GEP-NETs
- SSTR+ disease

Exclusion Criteria include:

- Prior PRRT
- Any major surgery within 4 weeks prior to randomization in the trial
- Therapy with an investigational compound and/or medical device
- Other known malignancies
- Serious non-malignant disease
- Renal, hepatic, cardiovascular, or hematological organ dysfunction, potentially interfering with the safety of the trial treatments

Study Outcomes

Primary

- Progression-free survival assessed every 12 weeks until disease progression (RECIST v1.1) or death, whichever occurs earlier.

Secondary

- Overall survival assessed up to 2 years after disease progression

Conclusion

Study recruitment for COMPOSE commenced in September 2021. It is expected that COMPOSE will increase treatment options for patients with well-differentiated high grade 2 and grade 3 GEP-NETs, including first-line therapy.

References

1. Severi S, et al. Onco Targets Ther 2017;10:551–557; 2. Uri I & Grozinsky-Glasberg S. Clin Diabetes Endocrinol 2018;4:16; 3. Pavel M, et al. Ann Oncol 2020;31:844 – 860; 4. Sonbol MB & Halfdanarson TR. Curr Treat Options Oncol 2019;20:74; 5. Strosberg J, et al. N Engl J Med 2017;376:125–135; 6. Baum RP, et al. Theranostics 2016;6:501-510.

Clinical Phase III Trial COMPOSE: Find more trial information on www.itm-gep-net-trials.com; *ClinicalTrials.gov* NCT04919226

CAPTEM: capecitabine-temozolomide; DOTA: dodecane tetraacetic acid; FOLFOX: folinic acid, fluorouracil and oxaliplatin; GEP-NETs: gastroenteropancreatic neuroendocrine tumors; i.v.: intravenous; n.c.a: non-carrier added; PRRT: Peptide Receptor Radionuclide Therapy; RECIST: response evaluation criteria in solid tumors; SSTR+: somatostatin receptor-positive