LUTETIUM (^{177}LU) OXODOTREOTIDE (LUTATHERA®) FOR THE TREATMENT OF UNRESECTABLE OR METASTATIC, PROGRESSIVE, WELL-DIFFERENTIATED GRADE 1 OR GRADE 2, SOMATOSTATIN RECEPTOR-POSITIVE GASTROENTEROPANCREATIC NEUROENDOCRINE TUMOURS IN ADULTS

Results from the phase III NETTER-1 study of lutetium (^{177}Lu) oxodotreotide

Introduction

Neuroendocrine tumours (NETs) are heterogeneous malignancies arising from the diffuse neuroendocrine system.[1,2] Approximately two-thirds of NETs derive from the gastrointestinal system and represent the group of gastroenteropancreatic neuroendocrine tumours (GEP-NETs).[3] In the USA, it is estimated that GEP-NETs have an annual incidence of 3.56/100,000.[4] Quality of life (QoL) in these patients may be considerably affected by symptoms related to tumour growth and hormone production.[5] Most patients with GEP-NETs are diagnosed when the disease is metastatic, and as such are not amenable to curative surgery; therefore, systemic therapies may be used as treatments to suppress tumour growth and relieve symptoms.[6]

Radioligand therapy (RLT) for the treatment of GEP-NETs

Lutetium (^{177}Lu) oxodotreotide (LUTATHERA®) is the first RLT approved for use by the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) for the treatment of unresectable or metastatic, progressive, well-differentiated (grade 1 and grade 2), somatostatin receptor (SSTR)-positive GEP-NETs in adults.[3,7] RLT (also known as Peptide Radioreceptor Therapy – PRRT) is one of the systemic therapies that can be used to treat GEP-NETs.[8] lutetium (^{177}Lu) oxodotreotide comprises the radioisotope lutetium-^{177} chelated to the somatostatin analogue octreotide.[3,7] Octreotide binds with high affinity to SSTR2, the most frequently expressed SSTR subtype in GEP-NETs.[7,9] Octreotide is internalised into the cell by endocytosis, where it emits beta radiation from lutetium-^{177}.[3,7] This induces single- and double-stranded DNA breaks leading to cell death.[3,7] Lutetium-^{177} has a maximum penetration range in tissue of 2.2 mm (mean penetration range of 0.67 mm), which is sufficient to kill targeted tumour cells with a limited effect on neighbouring healthy cells.[7]

The European Society for Medical Oncology and the European Neuroendocrine Tumor Society Clinical Practice Guidelines recommend RLT as a therapeutic option in progressive SSTR-positive GEP-NETs with homogeneous SSTR expression.[4,10,11] RLT is recommended as a second-line treatment in midgut NETs after progression on somatostatin analogues; it can also be considered for later-line therapy.[4,10,11] In pancreatic NETs, RLT can be given to patients after the failure of other approved therapies.[4,10] RLT may also be considered to improve symptoms in patients with carcinoid syndrome and progressive disease.[4,10,11]

Progression-free survival (PFS) in NETTER-1

NETTER-1 (NCT01578239) was a phase III, open-label, randomised controlled trial involving 231 adult patients with locally advanced or metastatic, well-differentiated, SSTR-positive midgut NETs with disease progression on fixed-dose long-acting octreotide.[2,12] The study originally enrolled 229 patients to receive either ^{177}Lu-Dotatate (116 patients) or long-acting octreotide (113 patients), and these were included in the primary analysis with the cut-off date of July 24, 2015.[13] Two additional patients were randomised after the prespecified primary PFS analysis data cut-off date, meaning that the final analysis included 231 patients.[2] Patients were randomised to receive four cycles of lutetium (^{177}Lu) oxodotreotide plus long-acting octreotide 30 mg every eight weeks (every four weeks after completion of lutetium (^{177}Lu) oxodotreotide) or high-dose long-acting octreotide 60 mg alone every four weeks (control arm).[2] High-dose long-acting octreotide 60 mg is an unlicensed dose.

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Figure 1: Progression-free survival of patients receiving lutetium (^{177}Lu) oxodotreotide + long-acting octreotide 30 mg versus high-dose long-acting octreotide 60 mg in NETTER-1.

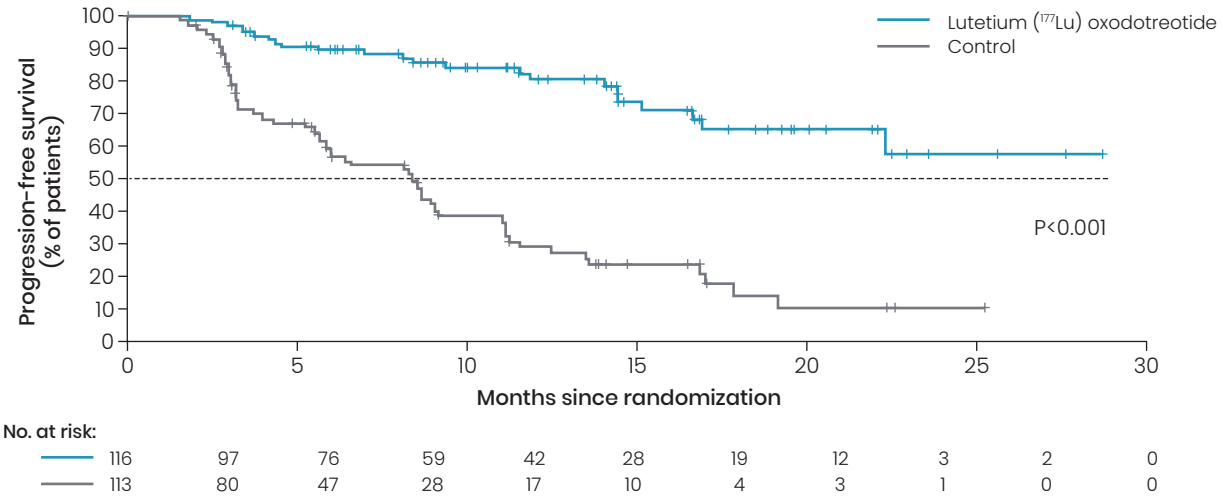


Figure sourced from: Strosberg, et al. 2017[13]

The primary endpoint of NETTER-1 was PFS, which differed significantly between treatment arms (p<0.001) (**Figure 1**).[13] The median PFS was not reached at the cut-off date in the lutetium (^{177}Lu) oxodotreotide arm compared with 8.5 months in the control arm.[7] The hazard ratio was 0.18 (95% confidence interval [CI]: 0.11–0.29), indicating an 82% reduction in the risk of progression or death for the lutetium (^{177}Lu) oxodotreotide arm compared with the control arm (p<0.0001).[7]

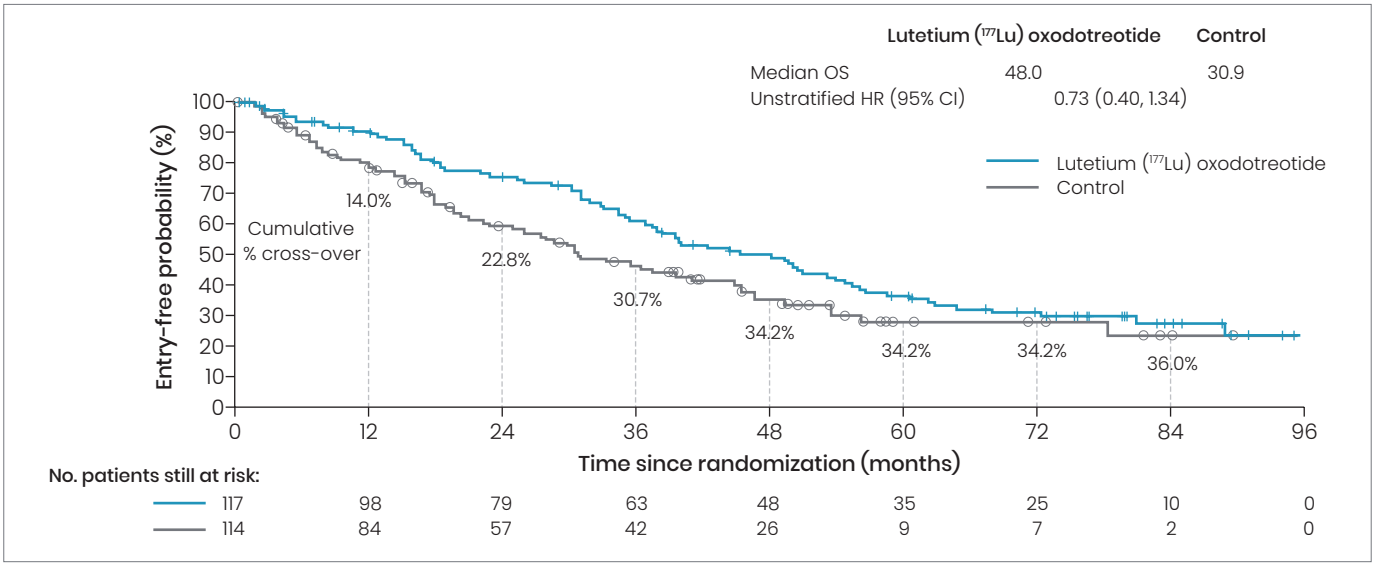
In a NETTER-1 post hoc subgroup analysis, lutetium (^{177}Lu) oxodotreotide demonstrated significant prolongation in PFS compared with high-dose long-acting octreotide in patients with advanced, progressive midgut NET, regardless of baseline liver tumour burden, elevated alkaline phosphatase, or the presence of a large target lesion.[14]

Overall survival (OS) in NETTER-1

One of the secondary endpoints of the NETTER-1 trial was OS.[2,13] The prespecified final analysis of OS was done 5 years after the last patient was randomised because this occurred before the alternative cut-off of 158 deaths (data cut-off date, Jan 18, 2021).[2] lutetium (^{177}Lu) oxodotreotide demonstrated a positive trend in OS; however, the difference between treatment arms was not statistically significant.[2] Median OS was 48.0 months (95% CI: 37.4–55.2) in the lutetium (^{177}Lu) oxodotreotide arm compared with 36.3 months (95% CI: 25.9–51.7) in the control arm.[2] The hazard ratio was 0.84 (95% CI: 0.60–1.17) with a p-value of 0.30 (hazards non-proportional).[2] The five-year survival rate was 37.1% (95% CI: 27.8–46.4) in the lutetium (^{177}Lu) oxodotreotide arm compared with 35.4% (95% CI: 25.7–45.2) in the control arm.[15]

In the control arm, 41 of 114 patients (36%) crossed over to RLT.[2] This crossover may have influenced the OS data.[2] Thirty-six of 114 patients (32%) received lutetium (^{177}Lu) oxodotreotide; the remaining five patients received [^{177}Lu]Lu-DOTA-NOC, [90Y]Y-DOTA-NOC, [90Y]Y-DOTA-TOC or [90Y]Y-DOTA-TATE.[2] In a post-hoc sensitivity analysis using the rank-preserving structural failure time method, which adjusted survival of those patients in the control arm who crossed over to RLT, the adjusted hazard ratio for OS was 0.73 (95% CI: 0.40–1.34).[15] The adjusted median OS in the control arm was 30.9 months (**Figure 2**).[15]

Figure 2: Overall survival of patients receiving lutetium (^{177}Lu) oxodotreotide + long-acting octreotide 30 mg versus high-dose long-acting octreotide 60 mg in NETTER-1, accounting for the crossover to RLT (rank-preserving structural failure time method).



CI = confidence interval; HR = hazard ratio; OS = overall survival; RLT = radioligand therapy. Figure sourced from: Strosberg, et al. 2021[15]

Safety of lutetium (^{177}Lu) oxodotreotide in NETTER-1

No new safety signals were reported during the long-term follow-up of patients in the NETTER-1 trial (safety analysis cut-off date June 30, 2016).[2] During the trial, 95% of patients in the lutetium (^{177}Lu) oxodotreotide arm and 86% of patients in the control arm had at least one adverse event (AE).[13] The most common AEs among patients receiving lutetium (^{177}Lu) oxodotreotide were nausea (59%) and vomiting (47%).[13] As a result of the bone marrow toxicity of lutetium (^{177}Lu) oxodotreotide, the most expected adverse reactions were related to haematological toxicity: thrombocytopenia (25%), lymphopenia (22.3%), anaemia (13.4%), pancytopenia (10.2%).[7] Other very common adverse reactions reported include fatigue (27.7%) and decreased appetite (13.4%).[7] Grade 3 or 4 AEs occurred in 41% of patients receiving lutetium (^{177}Lu) oxodotreotide and 33% of patients in the control arm.[13] During the whole study, seven patients (6%) in the lutetium (^{177}Lu) oxodotreotide arm had a grade 3 or worse treatment-related serious AE.[2] At the time of the NETTER-1 final analysis, after a median follow-up duration of 76 months in each study arm, the safety profile remained consistent with that previously reported.[7] Two patients (2%) in the lutetium (^{177}Lu) oxodotreotide arm developed myelodysplastic syndrome, one of whom died (grade 5).[2]

In patients treated with lutetium (^{177}Lu) oxodotreotide, the rate of severe nephrotoxicity was low (5%); which was similar to that reported in the control group (4%).[2] Both the lutetium (^{177}Lu) oxodotreotide and control groups recorded similar changes in creatinine clearance over time, indicating no long-term adverse effects of lutetium (^{177}Lu) oxodotreotide on kidney function in the patients in this study.[2] This suggests that there was no apparent longterm nephrotoxicity with lutetium (^{177}Lu) oxodotreotide treatment.[2]

QoL results from NETTER-1

A post-hoc analysis also reported the longitudinal change in health-related quality of life (HRQoL) by comparing time to deterioration (TTD) in both arms of the study to determine the overall impact of treatment on HRQoL.[5] Patients completed two questionnaires every 12 ± 1 weeks: the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ C-30) and the neuroendocrine carcinoid module (G.I.NET-21).[5] Patients were required to complete the questionnaires until disease progression or until a maximum of 72 weeks from random assignment had elapsed.[5] The questionnaire results were converted to a 100-point scale per the EORTC manual.5 TTD was defined as the time from random assignment to the first deterioration of ≥10 points (on a 100-point scale) compared with the baseline score for the same domain.[5]

TTD was significantly longer in the lutetium (^{177}Lu) oxodotreotide arm for several domains including global health (p<0.001), physical functioning (p=0.0147) and role functioning (p=0.0298) compared with the control arm.[5] Median TTD in global health status was 28.8 months in the lutetium (^{177}Lu) oxodotreotide arm compared with 6.1 months in the control arm (demonstrating a 22.7-month prolongation).[5] Median TTD in physical functioning was 25.2 months compared with 11.5 months in the lutetium (^{177}Lu) oxodotreotide arm versus control arm, respectively.[5] A key limitation of this HRQoL analysis is that patients in the NETTER-1 study were not blinded to treatment.[5] This was due to significant differences in treatment modalities between the two trial arms. It is possible that knowledge of which treatment they were assigned to may have affected the patients' perceptions of HRQoL.[5]

Conclusion

Most patients with GEP-NETs are diagnosed when the disease is metastatic, and as such may not be candidates for curative surgery; therefore, systemic treatment such as RLT may be used as a treatment to suppress tumour growth and relieve symptoms.[6] lutetium (^{177}Lu) oxodotreotide is the first RLT agent approved for use by the EMA and FDA.3 The phase III NETTER-1 trial demonstrated that treatment with lutetium (^{177}Lu) oxodotreotide can improve PFS as well provide patients with significant QoL benefits compared with high-dose long-acting octreotide.[2,5,13] The study also found lutetium (^{177}Lu) oxodotreotide to have a favourable long-term safety profile in patients with unresectable or metastatic, progressive, well-differentiated (grade 1 and grade 2), somatostatin receptor-positive GEP-NETs.[2]

This report was developed as part of the touchFEATURE activity, **'Results from the LUTATHERA® NETTER-1 trial'**. To view the full touchFEATURE activity, which also includes engaging videos, please visit: http://www.touchoncologytmc.com/neuroendocrine-tumours/learning-zone/results-from-NETTER-1-trial/.

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Abbreviations: AE, adverse event; EMA, European Medicines Agency; EORTC QLQ C-30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; FDA, Food and Drug Administration; G.I.NET-21, neuroendocrine carcinoid module; GEP-NET, gastroenteropancreatic neuroendocrine tumour; NET, neuroendocrine tumour; OS, overall survival; PFS, progression free survival; PRRT, peptide receptor radionuclide therapy; QoL, quality of life; RLT, radioligand therapy; SSTR, somatostatin receptor.

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