

NETTER-1 Phase III in Patients with Midgut Neuroendocrine Tumors Treated with 177Lu-Dotatate: Efficacy, Safety, QoL Results and Subgroup Analysis

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Background: Therapeutic options for patients are currently limited with advanced midgut neuroendocrine tumors progressing on first-line somatostatin analog therapy.

Methods: NETTER-1 is the first phase III, randomized trial evaluating 177Lu-DOTA0-Tyr3-Octreotate (Lutathera®) in patients with progressive, somatostatin receptor positive midgut NETs. 230 patients were randomized to receive Lutathera 7.4 GBq every 8 weeks (x4 administrations) versus Octreotide LAR 60 mg every 4 weeks. The primary endpoint was PFS (RECIST 1.1). Secondary objectives included ORR, OS, toxicity, and quality of life (QoL) based upon EORTC QLQ-C30 and QLQ-G.I.NET21 questionnaires. Subgroup analysis of PFS was performed to assess impact of potential prognostic factors.

Results: Centrally confirmed disease progressions or deaths were 23 in the Lutathera arm and 68 in the Octreotide LAR 60 mg arm. The median PFS was not reached for Lutathera and was 8.4 months with control, $p < 0.0001$, HR 0.21. At the time of the NDA/MAA submission, interim OS analysis (14 deaths in Lutathera group and 26 in control group; $p = 0.0043$) suggested an improvement in OS. Subgroup analyses for PFS confirmed consistent benefits of Lutathera irrespective of stratification and prognostic factors including tumor grade, age, gender, tumor marker levels, and levels of radiotracer uptake. Grade 3 or 4 neutropenia, thrombocytopenia and lymphopenia occurred in 1%, 2% and 9% of patients in Lutathera arm vs. none in controls. Health related QoL surveys indicated a moderate improvement in the global health status in the Lutathera treatment arm, demonstrating that the treatment benefit of Lutathera is not offset by a negative impact on patient quality of life.

Conclusion: The phase III NETTER-1 trial provides evidence for a clinically meaningful and statistically significant increase in PFS, and suggests an OS benefit in patients with advanced midgut NETs treated with Lutathera. Subgroup analysis demonstrates consistent benefit across prognostic factors. The Lutathera safety and QoL profile was found to be favorable.