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\[^{177}\text{Lu}\]Lu-DOTA-TATE as First-line Therapy for Patients with Grade 2 and 3 Advanced Gastroenteropancreatic Neuroendocrine Tumors (GEP-NETs): the NETTER-2 Study

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BACKGROUND: The NETTER-1 study demonstrated that \[^{177}\text{Lu}\]Lu-DOTA-TATE, a radioligand therapy selectively targeting somatostatin receptors (SSTRs), plus 30 mg octreotide long-acting release (LAR), provided significantly increased progression-free survival (PFS) compared with 60 mg octreotide LAR in patients with GEP-NET who previously progressed on octreotide (HR, 0.21 [95% CI, 0.13-0.33]). However, the NETTER-1 population predominantly consisted of patients with grade 1 (G1) NET, and G3 patients were excluded. Five-year survival declines by ~44% for patients with G3 NET versus G1, with limited data and few therapy options available. The ongoing NETTER-2 study is evaluating \[^{177}\text{Lu}\]Lu-DOTA-TATE plus 30 mg octreotide LAR as a potential first-line radioligand therapy option in patients with advanced GEP-NET (G2 and G3) who have a high-risk profile and significant unmet medical need.

METHODS: This multicenter, randomized, open-label, phase III study (NCT03972488) is enrolling adult and adolescent patients (aged ≥15 years and body weight >40 kg) with SSTR-positive, high proliferative rate (G2 with Ki67 index ≥10% or G3 with Ki67 ≤55%), advanced GEP-NET diagnosed within 6 months
before screening. Patients are randomized 2:1 to receive $^{[177\text{Lu}]}$Lu-DOTA-TATE (7.4 GBq/200 mCi every 8 weeks [Q8W] x 4 cycles; cumulative dose: 29.6 GBq/800 mCi) plus octreotide LAR (30 mg Q8W with $^{[177\text{Lu}]}$Lu-DOTA-TATE then Q4W after last $^{[177\text{Lu}]}$Lu-DOTA-TATE treatment) or 60 mg octreotide LAR (Q4W). Both somatostatin analogue (SSA)-naïve and patients previously treated with SSAs without progression are eligible. Patients are excluded if other first-line therapies are considered more appropriate per investigator. Stratification factors are tumor grade and origin (pancreatic versus other NET). The primary endpoint is PFS (centrally assessed according to RECIST v1.1). Secondary endpoints include objective response rate, quality of life, overall survival, disease control rate, and safety. Cross-over is allowed for patients in the control arm who have centrally confirmed progression.

**RESULTS:** Study is in progress.

**CONCLUSION:** Study is in progress.

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