LBA588 Oral Abstract Session

[^{177}Lu]Lu-DOTA-TATE in newly diagnosed patients with advanced grade 2 and grade 3, well-differentiated gastroenteropancreatic neuroendocrine tumors: Primary analysis of the phase 3 randomized NETTER-2 study.

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Background: Currently, there is no universally accepted first line (1L) therapy for higher grade, well-differentiated gastroenteropancreatic neuroendocrine tumors (GEP-NETs) and an unmet medical need remains in these patients (pts). Radioligand therapy (RLT) is an innovative cancer treatment that crosses the traditional domains of systemic, radiation or surgical therapies. The Phase 3 NETTER-2 study (NCT03972488) evaluated [^{177}Lu]Lu-DOTA-TATE (hereafter ^{177}Lu-DOTATATE) as 1L treatment in pts with Grade (G) 2 and G3 advanced GEP-NETs. This is the first trial to assess 1L RLT in any solid tumor. **Methods:** Eligible pts were newly diagnosed with somatostatin receptor-positive high G2 or G3 (Ki-67 $\geq$10% and $\leq$55%) advanced GEP-NETs within the last 6 months prior to enrollment. Pts were randomized (2:1) to receive 4 cycles of ^{177}Lu-DOTATATE (4 $\times$ 7.4 GBq) plus 30 mg octreotide long-acting release (LAR) at 8-weekly intervals during ^{177}Lu-DOTATATE treatment then every 4 weeks (^{177}Lu-DOTATATE arm), or 60 mg octreotide LAR every 4 weeks (control arm), stratified by grade (G2 vs G3) and tumor origin (pancreas vs other). The primary endpoint was progression-free survival (PFS), centrally assessed using RECIST 1.1. Objective response rate (ORR), a key secondary endpoint, was tested hierarchically after PFS. **Results:** Overall, 226 pts were randomized to the ^{177}Lu-DOTATATE (n = 151) or control (n = 75) arms. Most tumors originated in the pancreas (54.4%) or small intestine (29.2%); G3 tumors were reported in 35.0% of pts. Median cumulative dose of ^{177}Lu-DOTATATE was 29.2 GBq, with 87.8% of pts receiving all 4 doses. Median PFS (95% confidence interval [CI]) was significantly prolonged by ~14.3 months from 8.5 months (7.7, 13.8) in the control arm to 22.8 months (19.4, not estimable) in the ^{177}Lu-DOTATATE arm; stratified hazard ratio 0.276 (95% CI: 0.182, 0.418; $p < 0.0001$). The ORR was significantly higher in the ^{177}Lu-DOTATATE arm (43.0%) vs the control arm (9.3%); stratified odds ratio 7.81 (95% CI: 3.32, 18.4; $p < 0.0001$). PFS and ORR results were consistent across all pre-specified demographic and prognostic subgroups. Among adverse events of special interest to RLT, G3/4 leukopenia, anemia and thrombocytopenia occurred in $\leq$3 pts each in the ^{177}Lu-DOTATATE arm. One case of myelodysplastic syndrome was reported (^{177}Lu-DOTATATE arm). **Conclusion:** ^{177}Lu-DOTATATE significantly prolonged PFS and demonstrated a clinically meaningful ORR, compared with high-dose octreotide LAR, in pts with newly diagnosed advanced G2 and G3 GEP-NETs. Safety was in line with the established profile of ^{177}Lu-DOTATATE. This is the first randomized study to demonstrate efficacy of RLT as 1L treatment in any malignancy and will change clinical practice. Further investigations of RLT as a therapeutic option in other settings is warranted. Clinical trial information: NCT03972488. Research Sponsor: Advanced Accelerator Applications, a Novartis company.