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Progression-Free Survival in Patients with Bronchopulmonary Neuroendocrine Tumors Treated with Lanreotide or Placebo: Adjustment for Crossover Effects in Placebo Arm

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BACKGROUND

SPINET was a phase 3 trial (NCT02683941) in patients with well-differentiated, advanced bronchopulmonary neuroendocrine tumors (NETs; typical and atypical carcinoids [TCs and ACs]). During the double-blind (DB) period, patients were randomized (2:1) to receive lanreotide autogel/depot (LAN; 120 mg) or placebo (PBO) every 28 days; in the optional open-label (OL) phase, all patients received LAN. Recruitment was stopped early due to slow accrual; all eligible patients transitioned to OL-LAN. The adapted primary endpoint was centrally confirmed progression-free survival (PFS) during the DB or OL phases in patients randomized to LAN. The aim of this *post hoc* analysis was to compare PFS data during the DB and OL phases between PBO and LAN, adjusting for the crossover using the rank-preserving structural failure time (RPSFT) model.

METHODS

RPSFT is one of the most common statistical methods used to adjust overall survival (OS) data for crossover in oncology trials (Jack Ishak K et al. *Pharmacoeconomics* 2014;32:533; Bennett I *et al. Value Health* 2018;21:105) and has been used previously in a *post hoc* analysis of a phase 3 study in pancreatic NETs (Faivre S *et al. Ann Oncol* 2017;28:339). RPSFT is a non-parametric model that provides a treatment-effect estimate that is corrected for the confounding effect of crossover. Kaplan-Meier estimates were generated and the hazard ratio (HR) estimated using the multivariate Cox proportional-hazards model, stratified for tumor subtype.

RESULTS

Overall, 77 patients were randomized; this analysis accounted for the 19/26 patients in the PBO arm (73%) who transitioned to OL-LAN. Over the DB+OL-LAN phase, median (95% CI) centrally assessed PFS based on RPSFT was 13.5 (11.0; not calculable [NC]) months for PBO and 16.6 (11.3; 21.9) months for LAN (HR [95% CI]: 0.78 [0.48; 1.52]; p=0.601). Data by NET subtype are shown in the table.

Median (95% CI) PFS (months)

	LAN (observed; DB+OL)	**PBO (with RPSFT)**	**HR (95% CI)**
All patients	16.6 (11.3; 21.9) [n=50]	13.5 (11.0; NC) [n=26]	0.78 (0.48; 1.52) p=0.601
TCs	21.9 (12.8; NC) [n=28]	13.9 (13.4; NC) [n=16]	–
ACs	13.8 (5.4; 16.6) [n=22]	11.0 (2.8; 16.9) [n=10]	–

CONCLUSIONS

The risk of disease progression or death was lower with LAN versus PBO in patients with advanced, well-differentiated bronchopulmonary NETs (HR=0.78). However, despite adjusting for PBO crossover, the HR 95% CI included 1.00, reflecting the lack of statistical significance in this small sample. LAN may provide some clinical activity for TCs.

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