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Multivariate Analysis of Progression-Free Survival in the CLARINET Study of Lanreotide Autogel/Depot vs Placebo Identifies Prognostic Factors in Neuroendocrine Tumors

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Background: Progression-free survival (PFS) in metastatic pancreatic and intestinal neuroendocrine tumors (NETs) was significantly increased with lanreotide Autogel (Depot in USA) 120 mg vs placebo (hazard ratio [HR] for progressive disease [PD]/death 0.47 [95% CI: 0.30, 0.73]) in the CLARINET study. This was a preplanned exploratory covariate analysis to identify prognostic factors for PFS.

Methods: Patients with metastatic grade 1/2 (Ki-67<10%) nonfunctioning pancreatic/intestinal NETs received lanreotide Autogel 120 mg (n=101) or placebo (n=103) for 96 weeks or until PD/death (NCT00353496), with data analyses stratified according to PD (yes/no) and prior therapy for NET (yes/no) at baseline. These factors, alongside treatment, were tested here in separate Cox proportional hazards (PH) models for several baseline covariates (as listed in the table). Factors potentially significant in univariate analysis ($p \leq 0.1$, Wald chi-square test) were included in stepwise multivariate analysis to obtain a final model. Treatment interaction was investigated.

Results: With adjustment for covariates, treatment with lanreotide vs placebo reduced the risk of PD/death by 60% in the final model (Table). The adjusted effect of prior therapy was not significant, whereas PD at baseline was associated with higher risk of PD/death. Other baseline factors associated with an increased risk of PD/death were: hepatic tumor load (HTL) >25%; primary tumor type of pancreas (risk increased by 20–60% vs midgut, hindgut and other types); and below-median BMI (Table). No covariate-by-treatment interaction was significant.

Conclusions: Lanreotide extends PFS across patient subgroups; patients without PD at baseline have the lowest risk of PD. Among other potential prognostic factors in this exploratory analysis, several covariates (including tumor grade, prior therapy and time since diagnosis) had no effect. Conversely, HTL and primary tumor type were identified as the most important prognostic factors for PFS.

Table		
Term (reference)	**HR [95% CI)***	***p* value***

Lanreotide (placebo)	0.40 [0.25, 0.63]	< 0.0001
PD (no PD)	4.57 [1.67, 12.54]	0.0032
Prior therapy (no prior	1.29 [0.72, 2.31]	0.3914
HTL, % (0):		0.0005
>0, ≤10	0.81 [0.42, 1.59]	
>10, ≤25	1.22 [0.59, 2.52]	
>25, ≤50	2.82 [1.41, 5.63]	
>50	2.47 [1.21, 5.03]	
Primary tumor type		0.0289
Midgut	0.80 [0.33, 1.94]	
Hindgut	0.53 [0.32, 0.88]	
Other / unknown	0.39 [0.17, 0.86]	
BMI >median[#] (≤median)	0.64 [0.41, 1.00]	0.0483

*From final multivariate Cox PH model; [#]26.2 kg/m^2; intent-to-treat population.

Other baseline terms (sex, age, race, US/ex-US, region, time since diagnosis, Ki67, tumor grade, CgA, prior chemotherapy, prior surgery) had no prognostic value (p>0.1) either in individual models or in presence of other terms in final model.