1319P Post-hoc analysis of CLARINET phase III study to investigate the influence of diabetic status on progression-free survival (PFS) of patients with neuroendocrine tumours (NETs) treated with lanreotide (LAN) or placebo (PBO)

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Background: Diabetes mellitus (DM) is a risk factor for pancreatic NETs, but its prognostic role in stage IV NETs is less defined. We evaluated the impact of diabetes on PFS in patients with advanced, non-functioning GEP-NETs.

Methods: Post hoc analysis of data from the phase III double-blind, placebo-controlled CLARINET study (NCT00353496) to investigate association between DM (any of: medical history of type 1 or 2; use of antihyperglycemic medication; HbA1c $\geq$6.5%, fasting plasma glucose $\geq$7mmol/L; non-fasting plasma glucose $\geq$11.11mmol/L [at baseline or during study]) and PFS (Kaplan-Meier). Multivariate Cox analysis including treatment (LAN vs PBO), DM at baseline, previous therapy and progression at baseline was used to test interaction between DM and LAN efficacy.

Results: The overall population (total, n = 204; LAN, n = 101; PBO, n = 103) had well-differentiated (Ki-67 <10%) foregut (45%), midgut (36%), or hindgut (7%) and unknown (13%) NET. 79 patients had DM, 125 did not (N-DM); 24 received metformin in combination with LAN (n = 14) or PBO (n = 10). Median PFS (mPFS) was 96.0 months (mo) [95% CI: 70.4; not reached (NR)] for DM vs 98.0 mo [72.1;NR] for N-DM (HR 1.20 [0.79;1.82], p = 0.38). For DM, mPFS with LAN (n = 42) was NR [95.9;NR] vs 60.0 mo [48.0;74.4] with PBO (n = 37) (HR 0.27, [0.13-0.57], p = 0.0002). For N-DM, mPFS with LAN (n = 59) was NR [96.0;NR] vs 72.1 mo [52.0;NA] with PBO (n = 66) (HR 0.64 [0.35-1.15], p = 0.04). In multivariate analysis, DM at baseline was not significantly associated with PFS (HR 1.64 [0.95;2.84], p = 0.08). Significant impact of LAN on PFS was confirmed (HR 0.53 [0.31;0.89], p = 0.02), without significant interaction between LAN efficacy and DM (p = 0.62).

Conclusions: DM did not emerge as a negative prognostic factor in advanced stage IV NETs. Efficacy of LAN in DM and N-DM was confirmed. Although LAN–DM interaction was not significant, LAN efficacy seemed particularly favorable in DM compared to N-DM patients, in terms of HR. These findings, along with a potential favorable association with hypoglycemic drugs such as metformin, should be evaluated and validated in prospective biomarker studies.

Clinical trial identification: Post hoc analisys of phase III double-blind, placebo-controlled CLARINET study (NCT00353496).

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