445PD | CLINICAL ACTIVITY AND PHARMACOKINETICS (PK) OF CABOZANTINIB (XL184) IN PATIENTS WITH PROGRESSIVE MEDULLARY THYROID CARCINOMA (MTC)

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Background

Cabozantinib (cabo) is a potent oral therapy that inhibits MET, VEGFR2, and RET. In a phase 1 study, cabo demonstrated anti-tumor activity in patients with MTC, and a long terminal half-life of 120 hours. We report clinical activity and PK analyses from a Phase 3 study of cabo versus placebo (P) in patients with progressive, unresectable, locally advanced or metastatic MTC.

Methods

Patients with MTC and documented RECIST progression within 14 months (mo) of screening were randomized 2:1 to receive cabo (140 mg freebase qd, n = 219) or placebo (n = 111). Blood samples for PK were collected on days 1 and 29. Baseline tumor and blood samples were evaluated for RET mutation status. Tumor assessments occurred every 12 weeks, and the primary efficacy measure was progression-free survival (PFS), assessed by an independent radiology committee using RECIST.

Results

Statistically significant PFS prolongation was observed, with median PFS for cabo of 11.2 mo versus 4.0 mo for P (HR 0.28, 95% CI 0.19-0.40, $p < 0.0001$). PFS results favored the cabo group across all RET mutation subgroups with hazard ratios 0.24, 0.47, and 0.30 for RET mutation positive, negative, and unknown subgroups. The 12-mo progression-free landmark estimate is 47.3% for cabo and 7.2% for P; objective response rate was 28% for cabo vs 0% for P. Cabo demonstrated moderate accumulation, with plasma Cmax ~3.6-fold increased at steady-state (Day 29) relative to Day 1. Plasma concentrations did not fluctuate markedly over the 24 hr dosing interval on Day 29. In a population-PK analysis, moderate inter-subject variability in clearance (CL/F) was observed (CV of ~35%). No clinically significant covariates on PK were identified which would require dose adjustment, and PFS for cabo-treated subjects did not correlate with individual subject steady-state AUC predicted for uninterrupted 140 mg qd dosing.

Conclusions

Cabo significantly prolonged PFS compared to placebo in a patient population with progressive MTC. PK analysis supports administration of cabo as a fixed dose without adjustment for patient covariates.

Disclosure

M.J. Schlumberger: MJ Schlumberger has been a compensated consultant for Exelixis.

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L.T. Nguyen: Linh Nguyen is an employee and stockholder in Exelixis.

S. Sherman: Dr. Sherman is a compensated consultant to Exelixis.

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