Randomized Phase II Trial of Pazopanib versus Placebo in Patients (Pts) with Progressive Carcinoid Tumors (CARC) (Alliance A021202)

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BACKGROUND: Pts with progressive CARC have limited treatment options. Pazopanib (PZ) is an oral multi-kinase inhibitor (VEGFR-2,-3, PDGFR-a, and b, and c-KIT) with initial data suggesting efficacy in CARC.

METHODS: This was a multicenter, randomized, double-blind, phase II study of PZ (800 mg/day) versus placebo (PL) in progressive low-intermediate grade CARC with radiologic progressive disease (PD) <12 months (mo). Prior somatostatin analog (SSA) mandated for midgut tumors. Concurrent SSA allowed if previous PD on SSA documented. Primary endpoint-progression-free survival (PFS). Secondary endpoints—overall survival (OS), objective response rate (ORR) and safety. Trial had 85% power to detect a difference in median PFS 14 v 9 mo (hazard ratio [HR] 0.64) at 1-sided alpha=0.1. Stratified log-rank test based on intention-to-treat (ITT) principle used. Unblinding and crossover allowed if PD confirmed by central review.

RESULTS: 171 (97 PZ, 74 PL) pts randomized 6/2013-10/2015: median age 63; 56% female; 66% small bowel primary; 87% concurrent SSA. Median follow-up

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44 mo; 112 (56 PZ, 56 PL) PFS events observed. 6 pts (4 PZ, 2 PL) remain on initial treatment. Median PFS 11.6 in PZ and 8.5 mo in PL (HR=0.53, 1-sided 90% upper confidence limit [UCL] 0.69, p=0.0005), crossing pre-specified protocol efficacy boundary. 49 PL pts received PZ after PD. Median OS 41 and 42 mo in PZ and PL, respectively (HR=1.13, 1-sided 90% UCL 1.51, p=0.70). Notable treatment-related grade 3+ adverse events (PZ v. PL %): hypertension (27 v. 4), fatigue (8 v.3), ALT (9 v. 0), AST (9 v. 0), and diarrhea (5 v. 4).

**CONCLUSION:** PZ compared to PL associated with significant improvement in PFS in patients with progressive CARC. The results confirm VEGF signaling pathway is a valid target for therapy in CARC, but the potential benefit of PZ needs to be considered in the context of the risk of toxicity.

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