Randomized Phase II Study of Everolimus (E) versus Everolimus plus Bevacizumab (E+B) in Patients (Pts) with Locally Advanced or Metastatic Pancreatic Neuroendocrine Tumors (pNET), CALGB 80701 (Alliance)

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Support: U10CA180821, U10CA180882, CA31946, CA025224

Background: It is not known if the addition of a VEGF pathway inhibitor to an mTOR inhibitor enhances antitumor activity in pNET. This randomized phase II study evaluated E or E+B in pts with advanced pNET.

Methods: Pts were randomized 1:1 to E (10 mg po qd) or E (10 mg po qd) with B (10 mg/kg IV q 2 wks). All pts received octreotide. The primary endpoint was PFS. Potential superiority of E+B vs. E was assessed using a stratified log-rank test with 90% power (1-sided α=0.15) to detect a HR of 0.64. Secondary endpoints included overall survival (OS), response rate (RR), and safety.
**Results:** 150 pts were randomized: median age was 59 years (21-86), 56% male, ECOG PS 0 (57%)/1 (43%), prior chemotherapy 24%. Median number of 28-day treatment cycles were 13 (E+B) and 12 (E); range 1-44. Median follow up was 25.9 months. Pts on E+B experienced more grade 3 AEs, including diarrhea (14% vs. 3%; \( p = 0.01 \)), hyponatremia (12% vs. 3%; \( p = 0.02 \)), hypophosphatemia (11% vs. 3%; \( p = 0.04 \)), proteinuria (16% vs. 1%; \( p = 0.001 \)), and hypertension (41% vs. 12%; \( p < 0.0001 \)). The frequency of grade 4 AEs was 11% in both arms. Median PFS was 16.7 mos (E+B) vs. 14 mos (E); HR=0.80 (95% CI: 0.55, 1.17; 116 PFS events), 1-sided \( p = 0.12 \). Median OS was 36.7 mos (E+B) vs. 35.0 mos (E), HR =0.75 (95% CI: 0.42-1.33; 49 OS events), 1-sided \( p=0.16 \). E+B was associated with a significantly higher RR (31%) compared to E alone (12%), \( p=0.005 \).

**Conclusions:** Treatment with E+B led to superior PFS compared to E but with more adverse events in this randomized phase II study. The RR was significantly higher in pts treated with E+B. The combination of E+B warrants further investigation in pts with advanced pNET.