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Randomized run-in study of Bevacizumab and Everolimus in low- to intermediate- grade neuroendocrine tumors (LGNETs) using perfusion CT (pCT) as functional biomarker

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Background: Studies have shown promising results for mTOR inhibitor, everolimus, and VEGF inhibitor, bevacizumab, in LGNETs. In our prior study, decrease in tumor blood flow (BF) following bevacizumab was proportional to baseline BF suggesting bevacizumab decreased BF by a fixed percentage.

Methods: LGNET patients with lesion(s)≥3 cm were randomized to bevacizumab or everolimus for one 21-day cycle. On Cycle 2 day 1, the alternate agent was added. pCTs assessing tumor BF, blood volume (BV), mean transit time (MTT), and permeability surface (PS) were mandatory. Primary objectives were to determine the effects of bevacizumab or everolimus as well as bevacizumab + everolimus on BF.

Results: 112 pCTs were performed among 39 patients. 65 lesions among 36 patients were evaluated at 3 time points. Bevacizumab led to 47% decrease in BF (P<.01). Everolimus was associated with 13% increase in MTT (P=.02) and 12% decrease in BF (P=.16). Addition of everolimus to bevacizumab led to a further decrease in BF (15%; P=.02). Addition of bevacizumab to everolimus resulted in 28% further decrease in BF (P<.01) and no significant change in MTT. By ITT analyses, there were 10 PR (26%), 27 SD (69%), 1 PD (3%), 1 unknown (3%). PFS rate at 6-month was 92%; median was 14.6 months. The 12- and 24-month overall survival rates were 92% and 80%. pCT parameters (all P<.05) associated with RECIST response included: high baseline permeability surface, higher post-treatment MTT, higher percentage decrease in BF, BV, and higher percentage increase in MTT. CTC G3/4 AE occurring in ≥10% patients included: neutropenia (15%), proteinuria (12%), hyperglycemia (10%).

Conclusions: Bevacizumab decreased tumor BF. Addition of everolimus was associated with further decrease in BF. Bevacizumab + everolimus demonstrated anti-tumor activity in LGNET. fCT is a promising for selection of patients likely to benefit from therapy.