C-17

A Randomized Study of Temozolomide or Temozolomide and Capecitabine in Patients with Advanced Pancreatic Neuroendocrine Tumors: A Trial of the ECOG-ACRIN Cancer Research Group (E2211)

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BACKGROUND: Retrospective and small, prospective studies suggest that temozolomide-based therapies for pancreatic neuroendocrine tumors (pNETs) may have activity and the combination of temozolomide and capecitabine (TC) is associated with high RRs and long PFS. However, there are no randomized, prospective studies of these agents and this trial was initiated to establish a role for the combination of TC.

METHODS: E2211 was a randomized, phase II trial comparing T (200 mg/m2 PO QD days 1-5) vs. TC (T 200 mg/m2 PO QD days 10-14; C 750 mg/m2 PO BID days

1-14) in patients with advanced pNETs. Eligibility criteria included: metastatic or unresectable, low or intermediate grade pNETs, progression within preceding 12 months, and no prior T, C, DTIC, or 5-FU. The primary endpoint was PFS; secondary endpoints were Overall Survival (OS), RR, safety, and predictive value of MGMT by IHC and promoter methylation. This trial had at least 81% power to detect a difference in median PFS of 9 vs. 14 months (hazard ratio of 0.64) using a two-sided log-rank test at the 0.20 significance level.

RESULTS: 144 patients were enrolled between 8/2013 to 3/2016 to T (n = 72) or TC (n= 72) (intention to treat population). Median age, 62 years; women, 44%. Median PFS was 22.7 months for TC vs. 14.4 months for T (HR=0.58, p=0.023). Median OS was 38.0 months for T and has not been reached for TC (HR=0.41, p=0.012). RR was 33% for TC and 28% for T (p=0.47). Adverse events were as expected, though double in the combination arm.

CONCLUSION: In E2211, TC is associated with improved PFS and OS compared to T alone in advanced low or intermediate grade pNETs. There is no significant difference in RR between arms. This is the first prospective randomized trial of these agents and shows the longest PFS reported for pNET-directed therapy. NCT01824875.