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# Neuroendocrine tumor ex-vivo angiogenesis; correlation with overall survival and SUTENT sensitivity

**Introduction:** Sutent, (Sunitinib) is a multiple receptor tyrosine kinases inhibitor that may affect tumor growth, angiogenesis, and metastatic progression of cancer. In the clinical NCT00428597 Sunitinib was associated with increased median progression-free survival, greater objective response rate, and fewer deaths. The purpose of the proposed study is threefold. 1) Correlate ex-vivo surrogate of NET angiogenesis with overall survival (OS) to stratify risk and improve patient selection for anti-angiogenesis intervention. 2) Quantify NET SUTENT sensitivity in to increase objective response by focusing on predicted responders. 3) Identify exceptional responders for analysis to advance new/novel therapies.

**METHODS:** NET tumor samples, were tested using a previously published ex-vivo angiogenesis assay. Tumors were dissected into 1mm samples and cultured in thrombin-coated wells for 14 days. Endothelial cell outgrowths were quantitated as an assay for angiogenesis, percentage initiation, and growth intensity. *Ex-vivo angiogenesis and OS:* OS was calculated based on dates of diagnosis and dates of death extracted from medical and public records. Patients were stratified into two groups for Kaplan Meier curves. *Group 1. Low angiogenesis*. Angiogenesis initiation and/or growth (< average-2SEM). *Group 2. High angiogenesis*. Angiogenesis initiation and/or growth (> average-2SEM). NET *SUTENT Sensitivity:* Matched NET tumor samples were treated with 188nM SUTENT. Initiation and growth were compared to untreated tumors to calculate percentage inhibition. *SUTENT exceptional responders:* Were identified by three criteria. 1) Ex-vivo angiogenesis growth and initiation greater than mean-2SEM, 2) SUTENT-induced inhibition of initiation and growth >80%, and 3) SUTENT ex-vivo angiogenesis initiation and growth < mean-2SEM.

**RESULTS:** *Ex-vivo angiogenesis and OS*: The 10-year survival for NET patients was 62% (N=58). In non-survivors the ex-vivo NET angiogenesis initiation and growth were greater (58.3±1.4 and 3.4±0.1 $p<0.05$) when compared to surviving patients (50.9±4.9, 2.6±0.36). NET tumors with low ex-vivo angiogenesis was linked to an increased OS when compared to high ex-vivo angiogenesis. *SUTENT Sensitivity*: Ex-vivo response to SUTENT was inconsistent. In some samples, SUTENT had no effect. In contrast, some tumors, that grew in control conditions, had 100% inhibition of sprouting. SUTENT reduced ex-vivo angiogenesis initiation and growth > 50% in 29% of tumors *3) SUTENT exceptional responders:* Four tumors were identified for genomic & proteomic analysis; results are currently pending.

**CONCLUSIONS:** Quantification of NET tumor ex-vivo angiogenesis activity has the potential to inform and improve clinical prognosis and direct personalized medicine treatment plans. In particular, the appropriateness of anti-angiogenesis treatment.