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

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Introduction

Sutent, (Sunitinib) is a multiple receptor tyrosine kinases (RTKs) inhibitor that may affect tumor growth, pathologic angiogenesis, and metastatic progression of cancer. In 2011, based on clinical trial NCT00428597, the FDA approved Sutent for the treatment of neuroendocrine tumors (NET). NCT00428597 reported 1) 11.4month median progression-free survival in sunitinib group vs 5.5months in controls 2) 9.3% objective response rate in sunitinib group versus 0% in controls, and 3) 9 deaths in sunitinib group (10%) versus 21 deaths in controls (25%).[1] The purpose of the proposed study is threefold. 1) Correlate ex-vivo surrogate of NET angiogenesis with overall survival (OS) in order to stratify risk and improve patient selection for anti-angiogenesis intervention. 2) Quantify NET SUTENT sensitivity in order to increase objective response by focusing on predicted responders. 3) Identify NETs that are "exceptional responders" (as defined NCI Division of Cancer Treatment and Diagnosis) to SUTENT that can be studied using OMIC analysis to advance new/novel therapies.

NET tumor samples, collected at during surgery in 2014, were tested using a previously published ex-vivo angiogenesis assays developed in our laboratory. Tumors were dissected into 1mm samples and cultured in thrombin-coated wells for 14days. Endothelial cell outgrowths, which are indicative of angiogenesis, were quantitated as 1) percentage initiation and 2) 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 sample 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.

Figure 1.

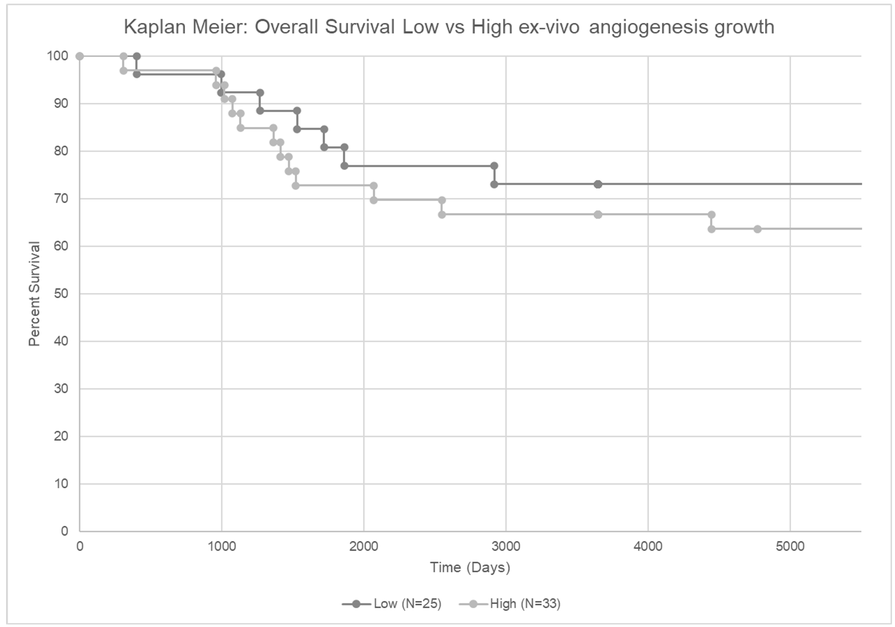

Figure 1. Kaplan Meier Curve Comparing Percent Survival in Low vs. High ex-vivo angiogenesis growth over 10 years. Percent Survival in the Low ex-vivo angiogenesis group was 63% at 10 years and 72% at 10 years for the High ex-vivo angiogenesis

Figure 2.

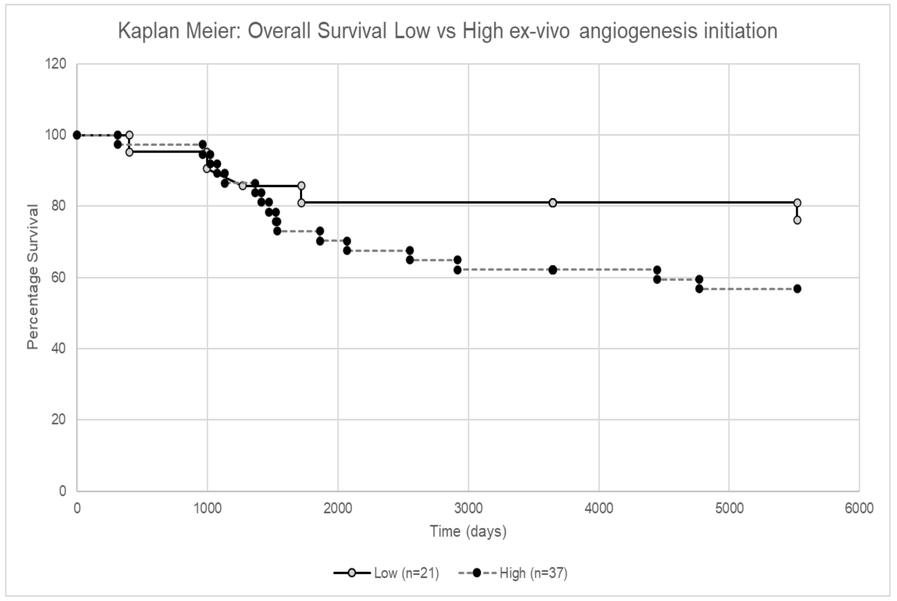

Figure 2. Kaplan Meier Curve Comparing Percent Survival in in Low vs. High ex-vivo angiogenesis initiation over 10 years. Percent Survival in the Low ex-vivo angiogenesis group was 79% at 10 years and 59% at 10 years for the High ex-vivo angiogenesis

Figure 3.

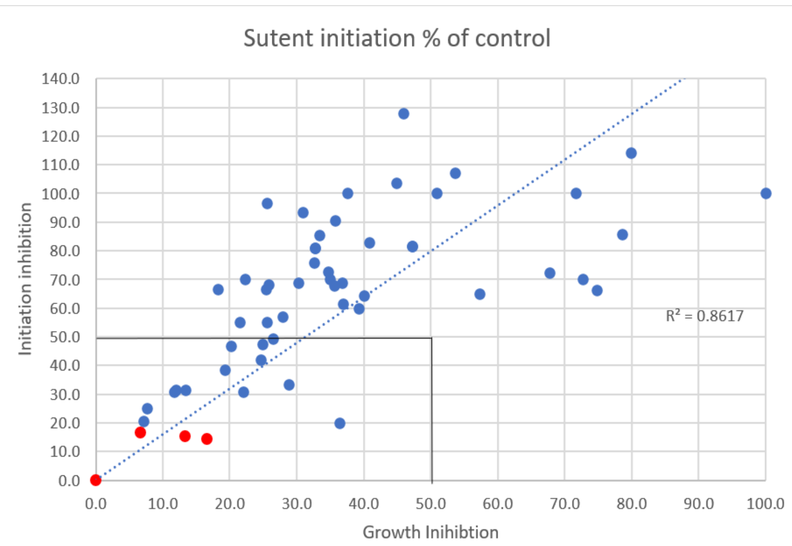

Figure 3. Relationship of tumor samples (n=58) Initiation Inhibition vs. Growth Inhibition. R=0.8617 Red dots denote exceptional responders.

Results

Ex-vivo angiogenesis and OS: The 10yr 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 were 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 currently pending.

Conclusion

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. Further study is required. In this initial study, correlation of SUTENT ex-vivo sensitivity with SUTENT oral use in patients was not performed. Future studies will cross reference patients records for SUTENT, especially for patients with exceptional responding NET tumors.