Introduction: There is increased evidence that cancers of the upper GI tract are comprised of distinct epidemiological and molecular entities that may respond differently to anti-cancer therapy in Asian patients compared to North American patients. Everolimus, an oral inhibitor of the mammalian target of rapamycin (mTOR) showed interesting results in a randomized phase III trial of pre-treated metastatic upper GI cancers with a statistical improvement in PFS and RR but not OS. This study was designed to evaluate the efficacy and safety of everolimus in patients with pre-treated metastatic esophagus, gastro-esophageal junction and gastric adenocarcinomas in a US patient population with a focus on biomarker correlation that could inform the Phase III trial.

Methods: Patients with advanced upper GI adenocarcinomas who experienced disease progression despite 1-2 prior regimens were treated with everolimus 10 mg PO daily. The primary endpoint was disease control rate (DCR; CR + PR + SD). Secondary end points included progression free survival (PFS), toxicity, overall survival (OS) and translational correlates of the mTOR pathway. Target accrual was 50 patients based on a type I error of 10% and a power of 90%. Immunohistochemical staining was performed on formalin-fixed, paraffin-embedded tissues for correlates of the mTOR pathway. IHC results were scored based on the percentage of positive cells and the proportion of positive tumor cells were scored as 0 (0%), 1 (<25%), 2 (25-50%), 3 (50-75%) and 4 (>75%). Expression of pmTOR, pS6K1, pS6 and p4EBP1 were assessed and scored.

Results: 45 patients were evaluable with adequate correlative biomarkers. Of these, 21 gastric, 11 esophagus and 13 from the GEJ. The median age was 64 (range 38-73), all patients had an ECOG of 0 or 1; 18 (40%) had received 1 prior regimen and 27 (60%) received 2 prior regimens. We observed 1 PR with 39% of evaluable patients having stable disease. Median overall survival was 4.4 months (95% CI: 3.2-7.6) and PFS was 1.8 months, 95% CI (1.6, 2.2). 89% of all adverse events were grade 1-2, and 11% were grade 3-4. Grade 3-4 related adverse events include: fatigue (24%), thrombocytopenia (22%), anemia (9%). There was a strong correlation between those patients with ≥2 IHC staining for pS6 with both PFS (p < 0.0001) and DCR (p = 0.0001). There was no statistically significant correlation with the other IHC proteins and any clinical outcomes.

Conclusion: In this single arm phase II study, we did not achieve the same degree of overall survival as was seen in the Asian studies with everolimus which may reflect differences in the locations of the primary tumor or underlying geographic variation in this disease. However, there was a strong correlation of benefit in the patients with high pS6 for all clinical endpoints. Testing this biomarker in the randomized patient samples from the GRANITE trial may lead to a positive predictive marker for everolimus in upper GI cancers.