Background: Both sorafenib and everolimus have activity in NETs. We performed a phase I study to evaluate the safety and feasibility of combining sorafenib and everolimus in pts with advanced NETs.

Methods: Patients were treated with everolimus 10 mg daily in combination with sorafenib (dose level 1: 200 mg BID; dose level 2: 200 mg in the morning, 400 mg in the evening) using a standard phase I dose escalation design. Treatment was continued until tumor progression, unacceptable toxicity, or withdrawal of consent.

Results: Enrolled pts had the following characteristics: M:F = 4:5; median age 56 (range 49-68); ECOG PS 0/1 = 5/4. All 9 pts had low-intermediate grade NETs (midgut, n=6; bronchial, n=2; gastric, n=1). Pts received a median of 2 cycles of treatment (range 1-6). One pt in Cohort 1 experienced DLT (grade 3 skin rash); the cohort was expanded to 6 pts with no further DLTs. Other ≥ grade 3 treatment-related adverse events at dose level 1 included grade 3 thrombocytopenia (n=2), grade 3 hypokalemia (n=2), grade 3 hypophosphatemia (n=1), grade 4 hypophosphatemia (n=1), grade 4 hypocalcemia (n=1). One pt treated at dose level 1 with gastric carcinoid tumor experienced fatal gastric perforation occurring after the DLT observation period. In the absence of additional DLT at dose level 1, enrollment to dose level 2 was initiated. All 3 pts in Cohort 2 experienced DLT (grade 3 thrombocytopenia requiring holding treatment for > 14 days, grade 3 hand-foot skin reaction, grade 3 skin rash/allergic reaction). Grade 3 hypophosphatemia (n=1) was also observed at dose level 2. Independently-reviewed best objective responses in 5 evaluable pts in Cohort 1 revealed stable disease in all 5 pts.

Conclusion: Sorafenib 200 mg BID in combination with everolimus 10 mg daily has been established as the MTD in pts with advanced NET. Further enrollment to confirm safety and assess antitumor activity at the MTD dose level is ongoing.