

**Phase 1 Expansion Study of an Oral TORC1/TORC2 Inhibitor (CC-223)
in Non-Pancreatic Neuroendocrine Tumors (NET)**

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Background: Clinical efficacy of everolimus, an allosteric TORC1-selective inhibitor, has been established in pancreatic NET. CC-223, an ATP-competitive inhibitor of the mTOR kinase, inhibits both TORC1 and TORC2 complexes.

Methods: Subsequent to MTD determination, non-pancreatic NET subjects enrolled in two expansion cohorts using CC-223 starting doses of 45 or 30 mg QD, administered in 28-day cycles until disease progression.

Results: Preliminary results on June 16, 2014 are reported for both dosing cohorts combined. Forty-seven subjects with progression within the prior 12 months while receiving somatostatin analogs (SSA) were treated. The majority of tumors (58%) were midgut with liver metastases; 30/43 (64%) subjects had refractory carcinoid syndrome despite SSA use. The most common (> 20%) related adverse events were diarrhea, stomatitis and fatigue (70% each), rash (65%), nausea (43%), pruritus (39%), hyperglycemia (30%), anorexia (26%), thrombocytopenia and xerostomia (22% each). Dose reduction (30, 20 or 15 mg QD) was required for 74% subjects, usually during cycle 1 or 2; thereafter treatment was well tolerated. Inhibition of TORC1 and TORC2 biomarkers was confirmed in blood cells. Although not prospectively collected, 12/15 (80%) subjects with carcinoid reported marked reduction of flushing and 11/20 (49%) had reduced bowel movements. Symptomatic improvement generally occurred early and persisted despite dose reduction. 9/23 (39%) subjects showed $\geq 50\%$ reduction in NET-related hormone levels elevated at baseline. Reduction in FDG-PET glucose uptake ($\geq 25\%$ SUV) at day 15 was observed in 18/34 (53%) paired scans. Best tumor response (RECIST1.1) in 39 subjects with restaging CTs included stable disease in 35, partial response in 3 and progressive disease in 1. Median treatment duration was 8 cycles (range 1-25 cycles) with a 6-month PFS rate of 85% (68%, 94%).

Conclusions: Encouraging signals of biomarker and clinical activity were observed in NET, including prolonged stable disease in the majority of subjects and symptomatic improvement in those with refractory carcinoid syndrome.