

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 is an ATP-competitive inhibitor of the mTOR kinase, inhibiting both TORC1 and TORC2 complexes.

Methods: Following earlier establishment of the MTD, subjects with non-pancreatic NET enrolled in an expansion cohort. CC-223 dose started with 45 or 30 mg QD, administered in 28-day cycles until disease progression.

Results: Preliminary results to June 1, 2013 are reported. Twenty-six subjects with progression within prior 12 months and receiving somatostatin analogs (SSA) were treated. The majority of tumors (58%) were midgut with liver metastases; 15/21 (71%) subjects had refractory carcinoid syndrome despite SSA use. The most common (> 20%) related adverse events (all grades) were diarrhea (73%), stomatitis (42%), fatigue (42%), rash (35%), nausea (35%), hyperglycemia (27%), anorexia (23%) and pruritus (23%). One related serious adverse event (diarrhea) was reported. CC-223 dose reduction (30 or 15 mg QD) was required for 77% 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 symptoms reported marked reduction of flushing and 4/7 (57%) also had reduced bowel movements. Symptomatic improvement generally occurred early and persisted despite dose reduction in 92% subjects. 4/15 (27%) subjects showed $\geq 50\%$ reduction in NET-related hormone levels that were elevated at baseline. Reduction in FDG-PET glucose uptake ($\geq 25\%$ SUV) at day 15 was observed in 8/14 (57%) paired scans. All 20 subjects with restaging evaluations showed stable disease with median treatment of 9 cycles (range 2-14 cycles).

Conclusions: Encouraging signals of biomarker and clinical activity were observed in NET, including prolonged SD and symptomatic improvement in subjects with refractory carcinoid syndrome. Further exploration using the starting dose of 30 mg QD is ongoing.