MLN0264, AN INVESTIGATIONAL, FIRST-IN-CLASS ANTIBODY-DRUG CONJUGATE TARGETING GUANYLYL CYCLASE C (GCC): FIRST-IN-HUMAN STUDY IN PATIENTS WITH ADVANCED GASTROINTESTINAL MALIGNANCIES

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Background: GCC is a transmembrane cell surface receptor expressed on the apical side of epithelial cell tight junctions in normal intestinal tissue. It is also expressed on approximately 95% of metastatic colorectal cancer (mCRC) tumors, and subsets of gastric and pancreatic cancer. In tumor tissue, epithelial tight junctions are altered, and therefore it is expected that systemically delivered GCC-targeting agents would not affect GCC receptors in normal intestinal tissue but would have access to those in tumor tissue. The investigational antibody–drug conjugate MLN0264 consists of a fully human monoclonal antibody targeting GCC linked to monomethyl auristatin E (MMAE) via a protease-cleavable linker. MMAE and the linker technology are licensed from Seattle Genetics. MLN0264 has shown antitumor activity in xenograft models of GCC-expressing tumors.

Methods: The aim of this first-in-human study (NCT01577758) is to evaluate the safety, tolerability, maximum tolerated dose (MTD), and clinical pharmacokinetics (PK) of MLN0264 administered via IV infusion on Day 1 of a 21-day cycle in patients aged ≥18 years with gastrointestinal malignancies expressing GCC who have measurable disease by RECIST and ECOG performance status of 0–1. Dose escalation from 0.3 mg/kg is proceeding via an adaptive Bayesian continual reassessment method in 2-patient cohorts based on dose-limiting toxicities (DLTs) in cycle 1. Approximately 6–10 ascending dose cohorts are anticipated to reach the MTD. Following determination of the MTD, additional mCRC patients will be enrolled for further characterization of MLN0264. Toxicities were graded by NCI-CTCAE v4.03. Blood samples for PK analysis were taken pre-dose and at various time points post dose.

Results: As of 18 Jan 2013, 10 patients (male, n = 7; median age 60 [range 30–69 years]) were enrolled and received MLN0264 at 0.3, 0.6, 1.2, 1.5, and 1.8 mg/kg (n = 2 per cohort). Diagnoses include 8 mCRC, 1 pancreatic and 1 esophageal cancer. No DLTs have been observed to date; dose escalation is ongoing. 9 patients reported grade 1 and 2 adverse events (AEs); including diarrhea (50%), fatigue (40%), nausea (20%), pyrexia (20%), anemia (20%), constipation (10%), pain (10%), and dyspepsia (10%). No infusion reaction AEs were reported. 3 patients reported grade 3 AEs; including abdominal abscess (10%), anemia (10%), hyponatremia (10%), increased gamma-glutamyltransferase (10%), increased white blood cell count (10%), and intestinal obstruction (10%). No grade 4 AEs have been reported; 3 patients reported unrelated SAEs consisting of intestinal obstruction (n = 1), convulsion (n = 1), and pyrexia (n = 1, occurred twice). Preliminary PK data show that MLN0264 exposure appears greater at increased dose levels.

Conclusion: These preliminary data indicate that MLN0264 appears to be generally well tolerated and not associated with infusion reactions within the five dose-escalation