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A Phase Ib study of the nanoparticle-drug conjugate (NDC) CRLX101 in combination with weekly paclitaxel in patients with advanced neoplasms including platinum-resistant tumors

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Background: Cerulean Pharma, Inc. is developing CRLX101, an investigational NDC with a camptothecin payload. CRLX101 has been investigated in more than 350 patients to date. Regimens administered have included monotherapy and combination therapy with bevacizumab in patients with renal cell carcinoma (Keefe, ASCO 2015, abstract #4543) and platinum-refractory ovarian cancer (Krasner, ASCO 2014, abstract #5581). Based on preclinical and early clinical data suggesting synergy between taxanes and topoisomerase 1 inhibitors, we started a Phase 1b trial for this combination in patients with platinum-resistant ovarian cancer.

Methods: Cohorts of 3 patients were accrued in this trial. Two dose levels were planned as dose level 1: CRLX101 12 mg/m^2 (every other week) in combination with paclitaxel 80 mg/m^2 (weekly, 3 weeks on/1 week off); and dose level 2: CRLX101 15 mg/m^2 (every other week) in combination with the same regimen of paclitaxel 80 mg/m^2. The primary objective was to determine the maximum tolerated dose (MTD) administered in combination with weekly paclitaxel. Secondary objectives included pharmacokinetics, overall safety, tolerability, and initial signs of clinical activity of CRLX101 with weekly paclitaxel.

Results: As of March 11, 2016, a total of 9 patients have been enrolled and treated at dose levels one (n=3) and two (n=6) and all 9 patients are evaluable for safety and response. Median age is 61 years (range, 49–73); median number of previous regimens was 3 (range, 1–4); GOG score performance status was 0 (6 patients) or 1 (3 patients). No dose-limiting toxicities have been reported at either dose level, thus the RP2D for this schedule is CRLX101 15 mg/m^2 (every other week) and paclitaxel 80 mg/m^2 (3 weeks on/1 week off). Adverse events (AEs) suspected to be related to study treatment were fatigue (6 patients, 67%), neutrophil count decreased (4 patients, 44%), nausea (4 patients, 44%), vomiting, alopecia, headache, infusion-related reaction, and urinary tract infection (all seen in 2 patients, 22%), as well as dizziness, sinusitis, ALT increased, AST increased, constipation, cystitis noninfective, dyspnea, anemia, and peripheral sensory neuropathy (all seen in 1patient, 11%). The only grade ≥3 treatment-related AE was neutropenia, which occurred in 2 patients (one grade 3 and one grade 4). Partial response and stable disease rates were 56% (5/9), and 11% (1/9), respectively. Moreover, CA125 responses (≥50% decline from baseline) were demonstrated in 33% of patients (3/9). As of March 11, 2016, 2 patients (at 15 mg/m^2) are still receiving therapy.

Conclusions: CRLX101 given every other week in combination with weekly paclitaxel (3 weeks on/1 week off) has demonstrated early signs of antitumor activity and has been generally welltolerated to date in patients with platinum-resistant ovarian cancer.

Biography

Adrian has served as Senior Vice President and Chief Medical Officer since September 2015. Dr. Senderowicz was most recently Chief Medical Officer and Senior Vice President, Clinical Development and Regulatory Affairs at Ignyta, Inc. Previously, he was Vice President, Global Regulatory Oncology at Sanofi, Chief Medical Officer at Tokai Pharmaceuticals, and Senior Medical Director, Oncology Clinical Development at AstraZeneca. Before his tenure at AstraZeneca, Dr. Senderowicz held a variety of leadership positions at the U.S. Food and Drug Administration Division of Oncology Drug Products in the Center for Drug Evaluation and Research and a variety of clinical and research positions with the National Cancer Institute/National Institutes of Health (NCI), including Investigator and Chief, Molecular Therapeutics Unit. He currently serves as a director of Puma Biotechnology, Inc., a publicly traded biopharmaceutical company. He completed his Internal Medicine residency training at the Icahn School of Medicine at Mount Sinai, and a Clinical Oncology Fellowship at the NCI. Dr. Senderowicz holds an M.D. degree from the School of Medicine at the Universidad de Buenos Aires in Argentina.

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