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A Randomized Phase II Trial of Irinotecan With Hyaluronan (HYCAMP) versus Irinotecan Alone as Treatment for Patients With Metastatic Colorectal Cancer Who Have Failed 5-Fluorouracil-Based Chemotherapy

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Background: Single-agent irinotecan is a standard therapy for patients with metastatic colorectal cancer (CRC) who have failed 5-fluorouracil (5-FU)–based therapy. In an attempt to reduce the dose-limiting toxicities of diarrhea and neutropenia often associated with irinotecan (CPT-11) therapy, the naturally ubiquitous polysaccharide, hyaluronan (HA), has been formulated with this cytotoxic inhibitor of topoisomerase-1, resulting in a proprietary product [HyCAMP]. This product utilizes the unique physiochemical and biologic properties of HA, where HA targets and transports the entrained anticancer agent(s) to the CD44 receptor, which is overexpressed on CRC. The HA derivitized drug forms a vascular microembolism within tumors, increasing drug retention, with preclinical studies demonstrating both an increase in treatment efficacy and reduced toxicity across a range of cytotoxic agents. Following promising phase I data, we have

completed a randomized phase II study comparing irinotecan and hyaluronan [HyCAMP] vs. irinotecan alone.

Method: Eligibility criteria included metastatic CRC, previous treatment with 5-FU, adequate major organ function, and Eastern Cooperative Oncology Group performance status (ECOG PS) of 0-1. Patients were randomized to receive irinotecan 350 mg/m^2 formulated with hyaluronan 1,000 mg/m^2 [HyCAMP] every 3 weeks, or to receive irinotecan alone 350 mg/m^2 every 3 weeks.

Results: A total of 80 patients (48 male/32 female) were enrolled in the study and 76 were randomized; 41 patients received HyCAMP (24 male/17 female, median age of 63 years, ECOG 0/1 = 19/22, 34 had previously received oxaliplatin) and 35 received irinotecan alone (21 male/14 female, median age of 64 years, ECOG 0/1 = 16/19, 30 had previously received oxaliplatin). Confirmed responses were seen in 3 of 41 (7.3%) HyCAMP patients compared with 1 of 35 (2.9%) irinotecan-alone patients (P=NS). Fourteen of 41 (34%) HyCAMP patients compared with 5 of 35 (14%) irinotecan patients completed 8 cycles (P=.064). Median number of cycles completed was 6 for HYCAMP patients and 2 for irinotecan-alone patients (P=.005). Median progression-free survival (PFS) was 5.2 months for HyCAMP patients compared with 2.4 months for those receiving irinotecan alone, a statistically significant difference (P=.014). Median overall survival (OS) was 10.1 months vs. 8.0 months for HyCAMP and irinotecan-alone patients, respectively (P=.196). There were no significant differences in any grade 3 or 4 toxicities. Three patients in the irinotecan-alone group died on study, one due to febrile neutropenia, compared with none in the investigational arm. The incidence of grade 3 diarrhea in HyCAMP-treated patients was 19.5% (8 patients) vs. 5.7% (2 patients) in the irinotecan-alone arm. Consistent with this, four patients (9.7%) in the HYCAMP arm vs. one patient (2.9%) in the control arm had the UGT1A1*28 polymorphism.

Conclusion: Patients treated with HyCAMP had a significantly increased PFS duration compared with those treated with irinotecan alone. No difference in OS was seen, possibly due to the effect of further lines of therapy. The two treatment arms appear to be

well balanced for known prognostic factors. Analysis continues, and further studies of HyCAMP are warranted.