**Liberty-201: maintenance capecitabine and bevacizumab with or without anti-lymphocyte activation gene 3 (LAG-3) antibody LBL-007 plus anti-programmed cell death protein 1 (PD-1) antibody tislelizumab (TIS) for patients (pts) with metastatic or unresectable microsatellite stable (MSS)/mismatch repair proficient (pMMR) colorectal cancer (CRC)**

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**Background:**

LBL-007 is a fully human IgG4 monoclonal antibody targeting LAG-3. LAG-3 is a receptor expressed on immune cells, and negatively regulates T-cell proliferation and effector T-cell function. LAG-3 is frequently co-expressed with PD-1 on tumor infiltrating T cells and dual inhibition of these two molecules synergistically prevents tumor growth in mouse models. CRC is the second-highest cancer-related cause of death worldwide; pts diagnosed with metastatic CRC have a 5-year survival rate of 14%. Immunotherapy has only demonstrated clinical benefit in pts with microsatellite instability high (MSI-H)/MMR deficient CRC, which accounts for 5% of CRC pts; however, improved therapy options for patients with MSS CRC remain limited. In a phase 1b study (NCT02720068), anti-LAG-3 therapy combined with anti-PD-1 therapy demonstrated promising antitumor activity and a manageable safety profile in pts with MSS CRC.

**Methods:**

This is a phase 1b/2 randomized, open-label study (NCT05609370). Adults with histologically confirmed metastatic or unresectable CRC, measurable per RECIST v1.1, are eligible. Pts with pMMR or MSS tumors, who had no disease progression after induction treatment in first-line therapy are also eligible. Using a modified 3+3 scheme, ~6-12 pts will be enrolled in phase 1b (safety run-in) to receive LBL-007 300 mg (Cohort 1) or 600 mg (Cohort 2) intravenously (IV) and TIS 200 mg IV, combined with the maintenance backbone of BEV 7.5 mg/kg IV once every 3 weeks and CAP 1000 mg/m$^2$ twice daily orally [days 1-14]. In phase 2, ~130 pts will be enrolled in the programmed death-ligand 1 (PD-L1) positive group and 60 patients in the PD-L1 negative group. Pts with a PD-L1 positive status will be randomized 2:1:2 to receive: LBL-007 recommended phase 2 dose (RP2D) IV, plus TIS 200 mg IV and maintenance

backbone (Arm A); LBL-007 RP2D IV, plus maintenance backbone (Arm B), or maintenance backbone (Arm C). Pts with a PD-L1 negative status will be randomized 1:1 to receive: LBL-007 RP2D IV, plus TIS 200 mg IV and maintenance backbone (Arm D), or maintenance backbone (Arm E). Treatment will continue until disease progression or unacceptable toxicity. The primary endpoint is safety in phase 1b and investigator-assessed progression-free survival (PFS) per RECIST v1.1 in phase 2. Secondary endpoints include overall survival, PFS2, overall response rate, duration of response, safety and pharmacokinetics. Exploratory endpoints include potential biomarkers (including but not limited to PD-L1 and LAG-3) and immunogenicity.