Liberty-201: Maintenance fluoropyrimidine (FP) 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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Abstract

Background: LBL-007 is a monoclonal antibody targeting LAG-3, a receptor expressed on immune cells that 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 LAG-3/PD-1 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 (IO) has only demonstrated clinical benefit in pts with microsatellite instability-high/MMR-deficient CRC, which accounts for 5% of CRC pts; however, improved therapy options for patients with MSS CRC remain limited. The combination of anti-LAG-3 + anti-PD-1 IO is currently being tested in clinical trials in pts with MSS CRC.

Methods: This is a phase 1b/2, randomized, open-label study (NCT05609370). Pts with unresectable or metastatic CRC with locally or centrally confirmed pMMR or MSS status and no disease progression after induction treatment in first-line therapy are eligible. A maximum of 36 pts will be enrolled in phase 1b (safety run-in) to determine the recommended phase 2 dose. All pts will receive intravenous dual IO (LBL-007 + TIS) in combination with maintenance backbone (FP + bevacizumab). The dose of LBL-007 will be escalated from 150 mg every 3 weeks (Q3W) to 600 mg Q3W/400 mg Q2W using a Bayesian optimal interval design with informative prior. In phase 2, ~130 pts will be enrolled in the programmed death-ligand 1 (PD-L1)–positive group (tumor area positivity [TAP] ≥1%) and 60 patients in the PD-L1–negative group (TAP <1%). Pts with a PD-L1–positive status will be randomized 2:1:2 to receive dual IO + maintenance backbone (Arm A), LBL-007 + maintenance backbone (Arm B), or maintenance backbone only (Arm C). Pts with a PD-L1–negative status will be randomized 1:1 to receive dual IO + maintenance backbone (Arm D) or maintenance backbone only (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 Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 in phase 2. Secondary endpoints include overall survival, PFS2, overall response rate, duration of response, safety, pharmacokinetics, and immunogenicity. Exploratory endpoints include potential biomarkers (including but not limited to PD-L1 and LAG-3).