Liberty-201: Maintenance Fluoropyrimidine 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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Summary

Liberty-201 is an ongoing phase 1b/2 trial investigating the efficacy and safety of LBL-007 (anti-lymphocyte activation gene-3 [anti–LAG-3]) + tislelizumab (anti-programmed cell death protein-1 [anti–PD-1]) in combination with bevacizumab + fluoropyrimidine versus bevacizumab + fluoropyrimidine as maintenance therapy in patients with metastatic or unresectable MSS/pMMR colorectal cancer.

The trial will be conducted at approximately 46 sites in the US, Australia, China, and Puerto Rico.

Enrollment is ongoing.

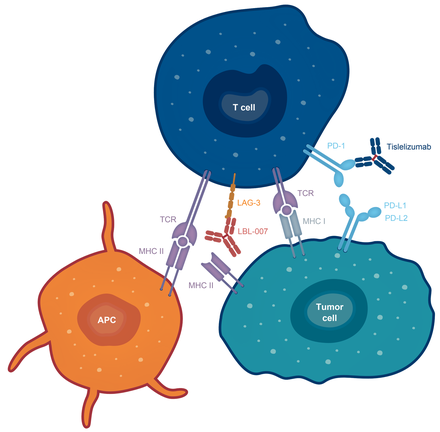
Background

- Colorectal cancer is the third most common cancer and the second highest cancer-related cause of death worldwide[1]
- Approximately 20% of patients with colorectal cancer have metastases at diagnosis and more than 50% of patients will develop metastatic disease[2]
- Patients diagnosed with metastatic colorectal cancer have a 5-year survival rate of approximately 14% in the US[3]
- Immunotherapy has only shown clinical benefit in patients with microsatellite instability-high (MSI H)/ mismatch repair (MMR)-deficient colorectal cancer, which accounts for 5% of patients with metastatic colorectal cancer[4]
- The current first-line standard of care for most patients with MSS/pMMR status is chemotherapy in combination with anti-VEGF or anti-EGFR antibodies
- There is a strong unmet need for improved therapy options for patients with MSS/pMMR colorectal cancer, which represents 95% of the patient population in the metastatic setting

Investigational Agents

- **LBL-007** is a fully humanized anti–LAG-3 IgG4 monoclonal antibody (mAb) that blocks the interaction of LAG-3 with ligands on tumor cells and antigen-presenting cells, resulting in T-cell activation (**Figure 1**)
  - LAG-3 is an immune checkpoint receptor predominantly expressed on activated T cells and natural killer (NK) cells in humans that negatively regulates T-cell activity, allowing tumor cells to escape immunosurveillance[5]
  - LAG-3 is frequently co-expressed with PD-1 on tumor-infiltrating T cells.[6] Co-blockade of PD-1 and LAG-3 restores the function of exhausted T cells and inhibits tumor growth by enhancing antitumor immunity[7]
- Emerging safety data of LBL-007 in combination with an anti–PD-1 antibody demonstrated a well-tolerated profile with no new safety signals identified[8]
- **Tislelizumab** is a humanized IgG4 anti–PD-1 mAb that blocks the PD-1/programmed death-ligand 1 (PD-L1) immune checkpoint, resulting in T-cell activation (**Figure 1**)
  - Tislelizumab was designed to minimize binding to FcγR on macrophages, reducing antibody-dependent macrophage-mediated killing of T cells[9]
  - Tislelizumab is approved for several indications in China, including for patients with advanced colorectal cancer with MSI-H or deficient MMR status who have been treated with fluoropyrimidine, oxaliplatin, and irinotecan
  - The safety profile of tislelizumab is similar to that of other anti–PD-1 antibodies in this class

Figure 1. LBL-007 + Tislelizumab Proposed Mechanism of Action



APC, antigen-presenting cell; LAG-3, lymphocyte activation gene-3; MHC, major histocompatibility complex; PD-1, programmed cell death protein-1; PD-L1, programmed death-ligand 1; PD-L2, programmed death-ligand 2; TCR, T-cell receptor.

Methods

- Liberty-201 (NCT05609370) is a phase 1b/2, randomized, open-label study evaluating LBL-007 + tislelizumab in combination with bevacizumab + fluoropyrimidine versus bevacizumab + fluoropyrimidine as maintenance backbone in patients with unresectable or metastatic MSS/pMMR colorectal cancer
- The dosing of LBL-007 + tislelizumab will match the dose frequency of the 5-fluorouracil/leucovorin or levoleucovorin (a 2-week regimen) + capecitabine (a 3-week regimen)–based maintenance backbones

Design and Treatments

Phase 1b

- Phase 1b aims to assess the safety and tolerability of LBL-007 + tislelizumab in combination with bevacizumab + fluoropyrimidine, and to confirm the recommended phase 2 dose for LBL-007 in combination with tislelizumab and maintenance backbone (**Figure 2A**)

Phase 2

- Phase 2 aims to evaluate the efficacy of LBL-007 + tislelizumab in combination with bevacizumab + fluoropyrimidine versus bevacizumab + fluoropyrimidine in PD-L1–positive and –negative populations (**Figure 2B**)
- PD-L1–positive population (tumor area positivity [TAP] ≥1%)
  - Approximately 130 patients will be randomized in a 2:1:2 ratio to 1 of 3 treatment arms:
    - Arm A: LBL-007 + tislelizumab + maintenance backbone
    - Arm B: LBL-007 + maintenance backbone
    - Arm C: Maintenance backbone
- PD-L1–negative population (TAP <1%)
  - Approximately 60 patients will be randomized in a 1:1 ratio to 1 of 2 treatment arms:
    - Arm D: LBL-007 + tislelizumab + maintenance backbone
    - Arm E: Maintenance backbone
- Treatment for phases 1b and 2 will continue until disease progression, unacceptable toxicity, or withdrawal of consent, followed by safety and survival follow-up

Trial Population

Eligibility criteria include the following:

- Age ≥18 years
- Eastern Cooperative Oncology Group performance status ≤1
- Histologically confirmed colorectal adenocarcinoma with metastatic or unresectable disease
- MSS or pMMR status (local laboratory assessment is acceptable for enrollment)
- No prior systemic therapy for colorectal cancer in the metastatic setting, except for the induction treatment of first-line therapy
- No disease progression after induction treatment in first-line therapy
- No *BRAF* V600E mutation
- No prior treatment with an anti-EGFR antibody
- No prior therapy targeting T-cell stimulation or checkpoint pathways

Endpoints

Phase 1b

- The primary endpoint for phase 1b is the incidence and severity of adverse events and serious adverse events per National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, and adverse events meeting dose-limiting toxicity (DLT) criteria
- The secondary endpoint for phase 1b is pharmacokinetic parameters of LBL-007

Phase 2

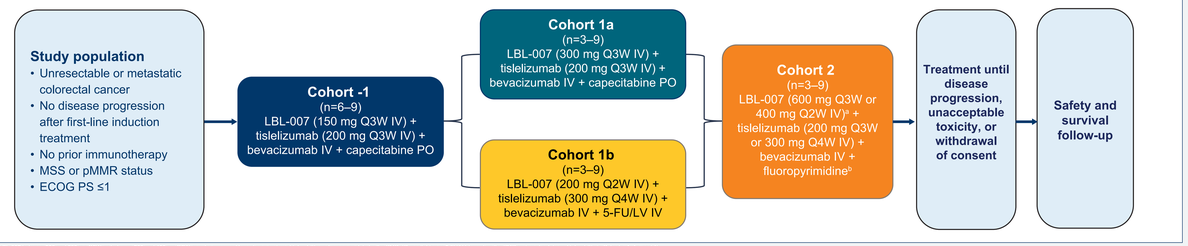
- The primary and selected secondary endpoints for phase 2 are listed in **Table 1**

Table 1. Phase 2 Endpoints

Primary endpoint	Selected secondary endpoints	
Investigator-assessed progression-free survival per RECIST v1.1	Overall survival	Pharmacokinetics
	Investigator-assessed objective response rate and duration of response	Immunogenicity
	Incidence and severity of adverse events per CTCAE v5.0	

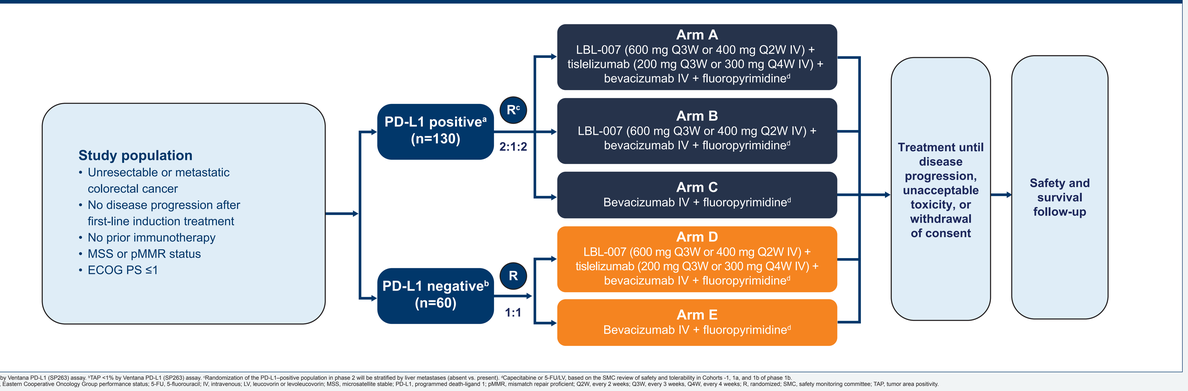
CTCAE, Common Terminology Criteria for Adverse Events; RECIST, Response Evaluation Criteria in Solid Tumors.

Figure 2A. Liberty-201: Phase 1b Design



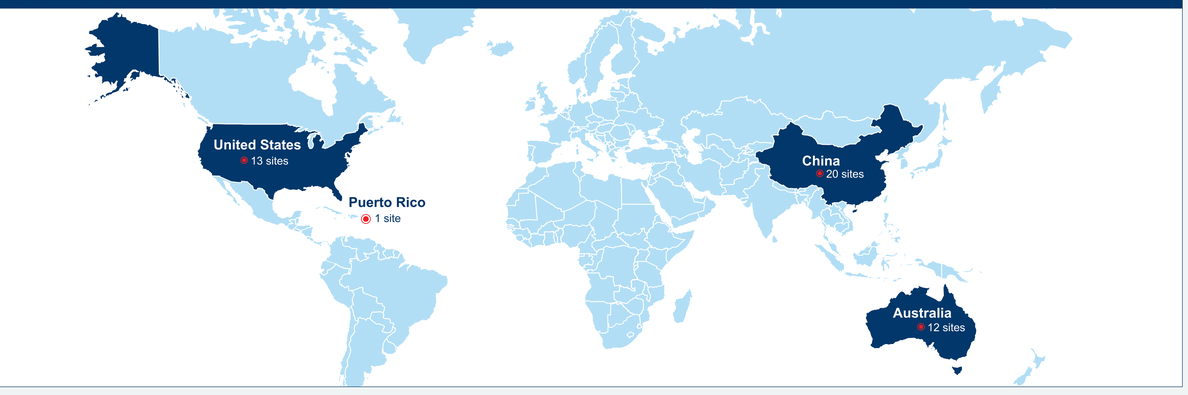
[a]Doses of LBL-007 between 300 and 600 mg Q3W, or between 200 and 400 mg Q2W, may be assessed based on a review of tolerability and exposure data by the SMC. [b]Capecitabine or 5-FU/LV, based on the SMC review of safety and tolerability in Cohorts -1, 1a, and 1b of phase 1b.
ECOG PS, Eastern Cooperative Oncology Group performance status; 5-FU, 5-fluorouracil; IV, intravenous; LV, leucovorin or levoleucovorin; MSS, microsatellite stable; pMMR, mismatch repair proficient; PO, orally; Q2W, every 2 weeks; Q3W, every 3 weeks, Q4W, every 4 weeks; SMC, safety monitoring committee.

Figure 2B. Liberty-201: Phase 2 Design



[a]TAP ≥1% by Ventana PD-L1 (SP263) assay. [b]TAP <1% by Ventana PD-L1 (SP263) assay. [c]Randomization of the PD-L1–positive population in phase 2 will be stratified by liver metastases (absent vs. present). [d]Capecitabine or 5-FU/LV, based on the SMC review of safety and tolerability in Cohorts -1, 1a, and 1b of phase 1b.
ECOG PS, Eastern Cooperative Oncology Group performance status; 5-FU, 5-fluorouracil; IV, intravenous; LV, leucovorin or levoleucovorin; MSS, microsatellite stable; PD-L1, programmed death-ligand 1; pMMR, mismatch repair proficient; Q2W, every 2 weeks; Q3W, every 3 weeks, Q4W, every 4 weeks; R, randomized; SMC, safety monitoring committee; TAP, tumor area positivity.

Figure 3. Trial Locations



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Acknowledgments

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Presenter disclosures

Lubna Jamal is an employee of BeiGene and may own company stock/stock options.

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