BGB-LC-202 (NCT05577702): Phase 2 Umbrella Study of Tislelizumab (TIS) Monotherapy and TIS-Based Immunotherapy Combinations +/- Chemotherapy (CT) as Neoadjuvant Treatment in Chinese Patients (pts) with Resectable Stage II to IIIA Non-Small Cell Lung Cancer (NSCLC)

Jianxing He MD,[1] Peng Zhang MD,[2] Hongxu Liu MD,[3] Wenhua Liang MD,[1] Wentao Yu MD,[4] Jingwen Shi PhD,[5] Bo Wei PhD,[6] Wenjuan Zheng MD,[4] Zhirong Shen PhD,[5] Nan Wu MD[7]

[1]Department of Thoracic Surgery, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China; [2]Department of Thoracic Surgery, Shanghai Pulmonary Hospital, Shanghai, China; [3]Department of Thoracic Surgery, Cancer Hospital of China Medical University, Liaoning Cancer Hospital & Institute, Shenyang, China; [4]Department of Clinical Development, BeiGene (Beijing) Co., Ltd., Beijing, China; [5]Department of Clinical Biomarker Science and CDx Development, BeiGene (Beijing) Co., Ltd., Beijing, China; [6]Department of Global Statistics and Data Science, BeiGene USA. Inc., Cambridge, MA, USA; [7]Department of Thoracic Surgery, Beijing Cancer Hospital, Beijing, China

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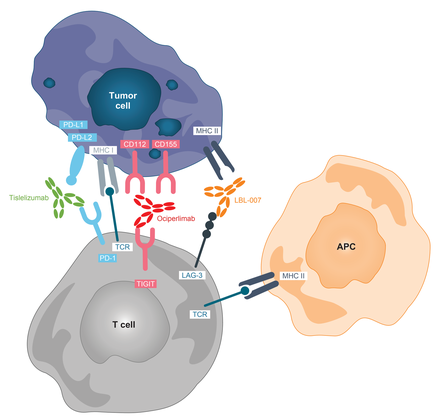
Background

- Lung cancer is the second most common cancer worldwide, with an estimated 2.2 million new cases and 1.8 million deaths in 2020[1]
  - Approximately 80–85% of lung cancers are non-small cell lung cancer (NSCLC)[2]
- At diagnosis, approximately 30% of patients have resectable stage II to IIIA NSCLC[3]
  - The most common cause of treatment failure for resectable NSCLC is tumor recurrence[4]
- Neoadjuvant immune checkpoint inhibitors + chemotherapy have shown promising efficacy versus chemotherapy alone; the combination is the current standard of care in patients with resectable NSCLC, followed by adjuvant platinum-based chemotherapy and subsequent therapy with immune checkpoint inhibitors[5,6,7]
- Despite improved efficacy with the addition of neoadjuvant immunotherapy to chemotherapy, the toxicity of such regimens should not be overlooked. Exploring neoadjuvant treatment containing novel agents that retain or improve efficacy and minimize safety risks may provide more clinical options for patients with resectable NSCLC

Investigational Agents

- Tislelizumab is a humanized immunoglobulin G4 (IgG4) anti-programmed cell death protein-1 (PD-1) monoclonal antibody (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[8]
  - Tislelizumab has been approved in China in combination with chemotherapy for the treatment of first-line NSCLC and as monotherapy for the treatment of second- or third-line NSCLC[9,10]
- Ociperlimab is a humanized anti-T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domains (TIGIT) mAb (**Figure 1**)
  - TIGIT is an immune checkpoint receptor upregulated on T cells and natural killer cells in multiple solid tumors, which can inhibit anticancer immune responses[11]
  - Ociperlimab blocks the interaction of TIGIT with ligands on tumor cells, resulting in activation of T-cell mediated antitumor immune responses
  - Ociperlimab also induces antibody-dependent cellular toxicity against regulatory T cells, and activates natural killer cells and monocytes[12]
- LBL-007 is an anti-lymphocyte activation gene-3 (LAG-3) mAb (**Figure 1**)
  - LAG-3 is an immune checkpoint receptor expressed on activated T cells that negatively regulates T-cell activity[13]
  - LBL-007 blocks the interaction of LAG-3 with ligands on tumor cells and antigen-presenting cells, resulting in T-cell activation

Figure 1. Targeting Tumor Cells with Anti-PD-1, Anti-TIGIT, and Anti-LAG-3 Antibodies



APC, antigen-presenting cell; CD112, poliovirus receptor-related 2; CD155, poliovirus receptor; 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; TIGIT, immunoreceptor tyrosine-based inhibitory motif domains.

Methods

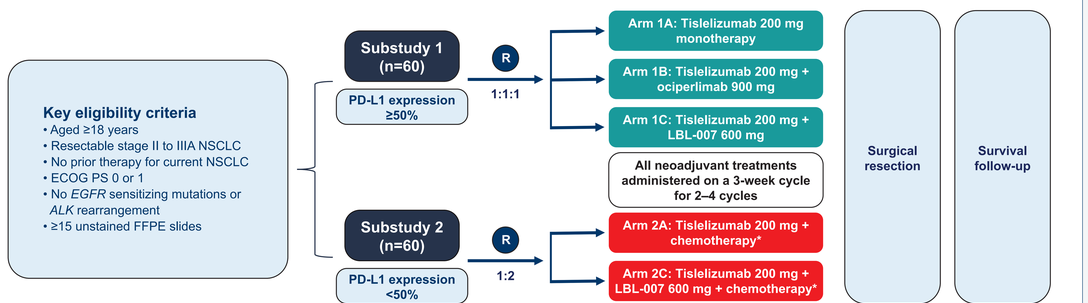
Study Design and Treatments

- This phase 2, randomized, open label, multicenter study aims to evaluate tislelizumab as monotherapy and in multiple immunotherapy combinations +/- chemotherapy as neoadjuvant treatment in Chinese patients with resectable NSCLC (**Figure 2**)
  - The umbrella trial design allows for multiple investigational drugs, administered alone or in combination in a single disease population
  - Treatment arms can be opened or closed during the study based on internal available data or external emerging data
- Substudy 1 will include 60 patients (PD-L1 ≥50%) randomized 1:1:1
  - Arm 1A: Tislelizumab monotherapy
  - Arm 1B: Tislelizumab + ociperlimab
  - Arm 1C: Tislelizumab + LBL-007
- Substudy 2 will include 60 patients (PD-L1 <50%) randomized 1:2
  - Arm 2A: Tislelizumab + histology-specific chemotherapy
  - Arm 2C: Tislelizumab + LBL-007 + histology-specific chemotherapy
- All treatments will be administered on a 3-week cycle for 2–4 cycles followed by surgical resection and survival follow-up

Study Population

- **Key inclusion criteria:**
  - Aged ≥18 years
  - Eastern Cooperative Oncology Group performance status of 0 or 1
  - Histologically confirmed stage II–IIIA NSCLC
  - Confirmed eligibility for a resection with curative intent
  - Patients must provide at least 15 freshly cut unstained formalin-fixed paraffin-embedded (FFPE) slides of the primary tumor, or an FFPE block containing equivalent tumor tissues

Figure 2. Study Design



The umbrella trial design allows for treatment arms to be opened or closed during the study based on internal available data or external emerging data.
*Chemotherapy consisted of cisplatin (75 mg/m²) or carboplatin (AUC=5 mg/mL/min) + pemetrexed (nonsquamous, 500 mg/m²)/paclitaxel (squamous, 175 mg/m²).
ALK, anaplastic lymphoma kinase; AUC, area under the curve; ECOG PS, Eastern Cooperative Oncology Group performance score; EGFR, epidermal growth factor receptor; FFPE, formalin-fixed paraffin-embedded; NSCLC, non-small cell lung cancer; PD-L1, programmed death-ligand 1; R, randomization.

- **Key exclusion criteria:**
  - Any prior antineoplastic therapy for current NSCLC
  - Prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-cytotoxic lymphocyte associated protein-4 (CTLA-4), anti-TIGIT, or anti-LAG-3 antibody
  - Mixed small cell lung cancer
  - Large cell neuroendocrine carcinoma
  - Epidermal growth factor receptor sensitizing mutations or *ALK*-rearrangement

Assessments and Endpoints

- Tumor assessment (by investigator per RECIST v1.1) will be performed during screening, after the neoadjuvant treatment phase, and after surgery (3 months post-surgery, then every 6 months for the first 2 years, then annually thereafter)
- Assessments will continue until disease recurrence or progression that precludes definitive surgery, withdrawal of consent, initiation of new anticancer therapy except the prespecified adjuvant treatment, death, loss to follow-up, or study termination, whichever comes first
  - The primary endpoint is major pathological response per blinded independent pathology review (BIPR) (**Table 1**)
  - Secondary and exploratory endpoints are listed in **Table 1**
  - The trial will be conducted at approximately 14 sites in China
- Enrollment is ongoing

Table 1. Study Endpoints

Primary endpoint	MPR per BIPR
Secondary endpoints	pCR per BIPR
	OS
	Investigator assessed EFS and DFS per RECIST v1.1
	Adverse events per CTCAE v5.0
	Proportion of patients who undergo resection
Exploratory endpoints	Pharmacodynamics and pharmacokinetics of the investigational agents
	Predictive, prognosis, and resistance-associated biomarkers
	Immunogenicity to the investigational agents

BIPR, blinded independent pathology review; CTCAE, Common Terminology Criteria for Adverse Events; DFS; disease-free survival; EFS, event-free survival; MPR, major pathological response; OS, overall survival; pCR, pathological complete response; RECIST, Response Evaluation Criteria in Solid Tumors.

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WY: Employee of BeiGene and may own company stock/stock options

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