BGB-LC-201 (NCT05635708): A Phase 2, Open-Label, Multi-Arm Study of Tislelizumab (TIS; Anti-PD-1) in Combination With Investigational Agents +/- Chemotherapy as First-Line Treatment for Patients With Locally Advanced, Unresectable, or Metastatic Non-Small Cell Lung Cancer (NSCLC)

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Summary

BGB-LC-201 (NCT05635708) is a phase 2 umbrella study investigating the efficacy and safety of tislelizumab in combination with BGB-A445, BGB-15025, or LBL-007 with or without histology-appropriate chemotherapy as first-line treatment of patients with NSCLC without actionable driver mutations.

The study is currently enrolling patients at 61 sites across the Asia-Pacific (Australia, China, Malaysia, Singapore, South Korea, Thailand), Brazil, Canada, the European Union (France, Georgia, Italy, Moldova, Romania, Spain), and the United States.

Background

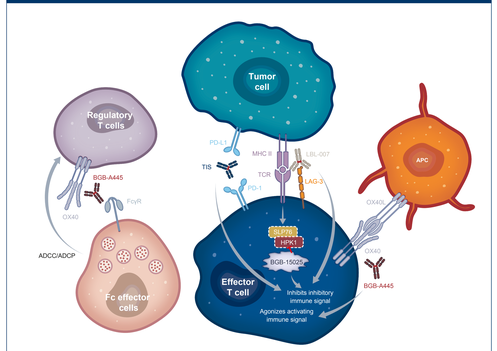
Unmet Need in NSCLC

- 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]
  - Non-small cell lung cancer (NSCLC) accounts for 80%–85% of all lung cancer cases, with approximately 55% of patients diagnosed with metastatic disease[2]
- Immune checkpoint inhibitor-based therapeutic strategies have significantly improved clinical outcomes for patients with advanced or metastatic NSCLC; however, prognosis remains poor, partly due to innate or adaptive resistance to immune checkpoint inhibitors[3]
  - Single-agent anti-programmed cell death protein-1 (PD-1)/programmed death-ligand 1 (PD-L1) inhibitors are the preferred first-line therapy for patients with advanced or metastatic NSCLC with PD-L1 expression of ≥50% (PD-L1–high) without targetable genetic aberrations, irrespective of histology[4]
  - Anti-PD-1/PD-L1 inhibitors in combination with histology-specific platinum-doublet chemotherapy is currently the preferred first-line therapy in patients with advanced or metastatic NSCLC without targetable genetic aberrations, regardless of PD-L1 expression[4]
- However, only a small proportion of patients develop long-term responses[5]
- Combination therapies targeting distinct biological pathways aim to overcome resistance to PD-1/PD-L1 therapy and thus improve anticancer activity[3]

Introduction to Tislelizumab (TIS) and Investigational Agents (Figure 1)

- TIS is a humanized IgG4 anti-PD-1 monoclonal antibody (mAb) engineered to minimize FCγ receptor (FCγR) binding on macrophages to abrogate antibody-dependent phagocytosis, a mechanism of T-cell clearance and potential resistance to anti-PD-1 therapy[6]
  - TIS, as monotherapy or in combination with chemotherapy, is approved for the treatment of NSCLC and esophageal squamous cell carcinoma (ESCC) in China, and as monotherapy for the treatment of ESCC in China, the European Union, and the United States
- BGB-A445 is a potent humanized IgG1 mAb directed against OX40, and is differentiated from most clinical stage OX40 agonists by not competing with the binding of endogenous OX40[7]
  - Preclinical studies have shown that OX40 is expressed on tumor-infiltrating effector T cells and regulatory T cells (T_{reg}), with particularly high expression on T_{reg}. OX40 agonists have the potential to mediate antitumor effects by promoting the effector function of T cells and diminish suppressive effects of T_{reg} through antibody-dependent cellular cytotoxicity/antibody-dependent cellular phagocytosis[8]
- LBL-007 is a fully humanized IgG4 mAb directed against lymphocyte activation gene-3 (LAG-3),[9] which is upregulated inpatient-derived xenografts with NSCLC resistant or non-responsive to anti-PD-1 therapy, suggesting that co-inhibition of these immune checkpoints may improve antitumor activity[10]
- BGB-15025, a first-in-class, potent, selective, small-molecule inhibitor of hematopoietic progenitor kinase 1 (HPK1), showed preliminary antitumor effects in preclinical studies as monotherapy and enhanced antitumor effects in combination with anti-PD-1[11]
  - HPK1, a hematopoietic cell-restricted serine/threonine protein kinase prominently expressed on T and NK cells, is a negative regulator of T-cell receptor-induced T-cell activation, making it a potential target for immuno-oncology therapy[12]

Figure 1. Targeting Tumor Cells With BGB-15025, BGB-A445, LBL-007, and TIS



ADCC, antibody-dependent cellular cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; APC, antigen-presenting cell; BGB-A445, OX40 agonistic monoclonal antibody; BGB-15025, HPK1 inhibitor; LAG-3, lymphocyte activation gene-3; HPK1, hematopoietic progenitor kinase 1; LBL-007, anti-lymphocyte activation gene-3 monoclonal antibody; MHC, major histocompatibility complex; OX40L, OX40 ligand; PD-1, programmed cell death protein-1; PD-L1, programmed cell death-ligand 1; SLP76, lymphocyte cytosolic protein 2; TCR, T-cell receptor; TIS, tislelizumab.

Methods

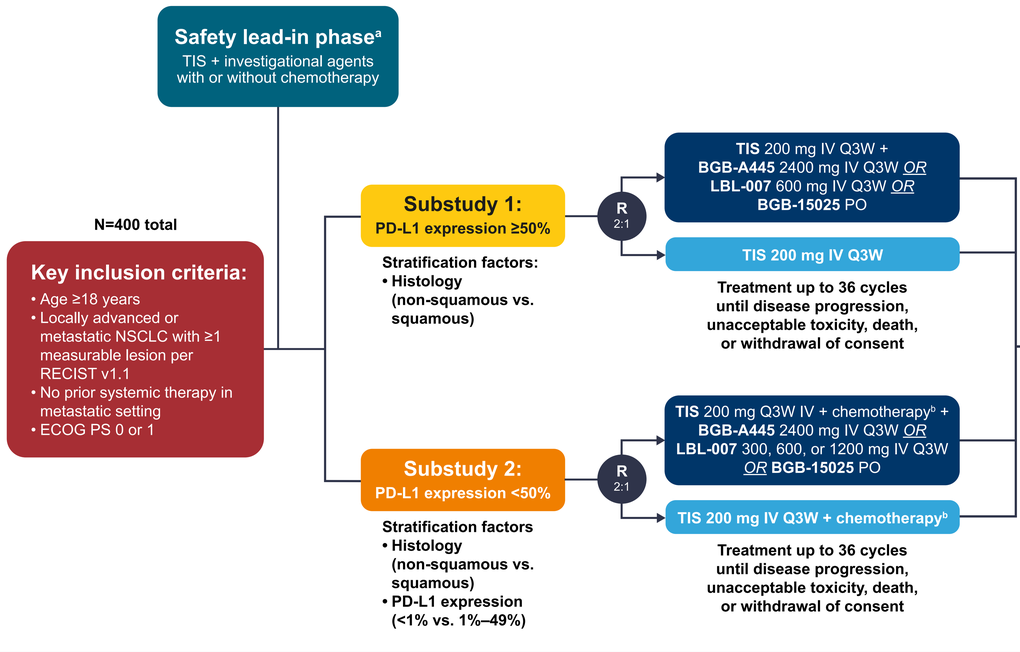
Study Design and Treatment

- BGB-LC-201 (NCT05635708) is a phase 2, open-label, multi-arm, multicenter umbrella study investigating the efficacy and safety of TIS in combination with BGB-A445, LBL-007, or BGB-15025 with or without histology-appropriate chemotherapy as first-line treatment of patients with NSCLC without actionable driver mutations
- Approximately 400 patients with previously untreated, locally advanced, unresectable, or metastatic NSCLC will be enrolled (**Figure 2**). The randomization ratio is 2:1 between each of the experimental arms and the reference arm within each substudy
- Additional study arms, with other investigational drugs, may be added in the future

Study Population

- Key eligibility criteria are summarized in **Figure 2**. Other key criteria include:
  - Histologically confirmed locally advanced or metastatic NSCLC (non-squamous or squamous)
  - ≥1 measurable lesion, as per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1)[13]
  - No prior therapy with anti-TIGIT anti-LAG-3, or any other antibody or drug specifically targeting T-cell costimulation or immune checkpoint pathways
  - Patients must agree to provide archival tumor tissue from screening or be willing to undergo fresh tumor biopsy to evaluate tumor PD-L1 expression, either by a local laboratory (using 22C3, SP263, or 28-8; E1L3N [US patients only]), or by a central laboratory (using SP263 Ventana assay)
    - Patients with unknown PD-L1 expression will not be eligible for this study
  - No known actionable mutations (including, but not limited to, *EGFR*, *ALK*, *BRAF*, *RET*, and *ROS1* mutations)

Figure 2. Study Design of BGB-LC-201



[a]Safety lead-in phase will be included for any combinations not previously evaluated. [b]Histology-appropriate chemotherapy includes platinum (carboplatin or cisplatin) plus pemetrexed, or paclitaxel or nab-paclitaxel.
CBR, clinical benefit rate; DCR, disease control rate; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; IV, intravenous; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PK, pharmacokinetics; PO, oral; Q3W, once every 3 weeks; QD, once daily; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors; TIS, tislelizumab; TTR, time to response.

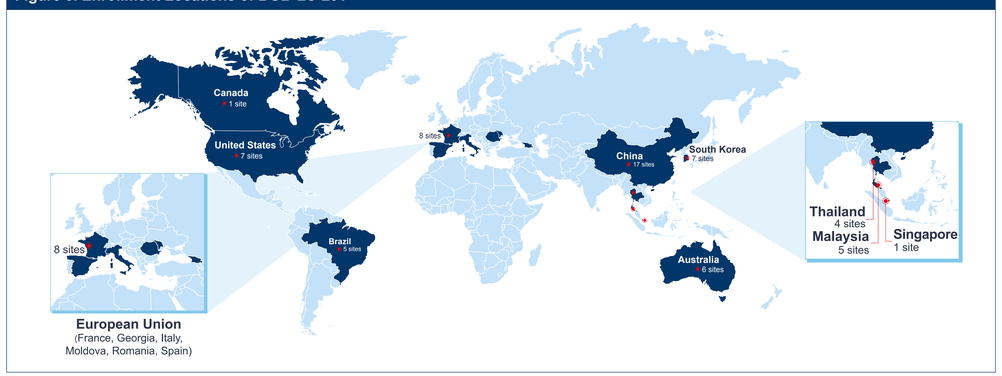
Endpoints and Assessments

- The primary endpoint is objective response rate, defined as the proportion of patients with a complete response or partial response, as assessed by the investigator using RECIST v1.1
- Select secondary endpoints include progression-free survival, disease-control rate safety, and pharmacokinetics (**Figure 2**)
- Tumor imaging will be performed within 28 days before randomization/enrollment. On-study tumor assessments will occur every 6 weeks for the first 52 weeks and every 12 weeks thereafter
- Safety will be assessed through monitoring of the incidence and severity of adverse events (graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0), laboratory results, and clinical symptoms and signs
  - The safety population will include all patients who receive ≥1 dose of study drug(s)
  - An independent Safety Oversight Committee will periodically assess safety throughout the study

Enrollment Status

- Enrollment is ongoing at 61 sites (**Figure 3**)

Figure 3. Enrollment Locations of BGB-LC-201



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Disclosures

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