A PHASE 3, OPEN-LABEL, MULTICENTER, RANDOMIZED STUDY TO INVESTIGATE THE EFFICACY AND SAFETY OF TISLELIZUMAB, AN ANTI-PD-1 ANTIBODY, VERSUS DOCETAXEL IN PATIENTS WITH NON-SMALL CELL LUNG CANCER WHO HAVE PROGRESSED ON A PRIOR PLATINUM-CONTAINING REGIMEN

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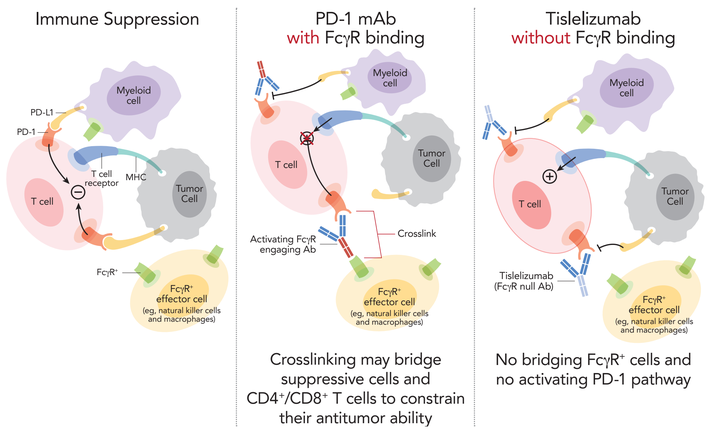
BACKGROUND

- Lung cancer is the most common cancer worldwide, with non-small cell lung cancer (NSCLC) accounting for 80–85% of all lung cancers[1]
- The prognosis for patients with NSCLC is relatively poor, particularly when it is diagnosed in later stages where 5-year survival rates are approximately 36% for Stage IIIA, 26% for Stage IIIB, and 1% for Stage IV[2]
- Recent studies of immune checkpoint inhibitors have shown efficacy in patients with advanced NSCLC[3–5]
- Tislelizumab (also known as BGB-A317) is a humanized, IgG4 monoclonal antibody with high affinity and binding specificity for programmed cell death receptor-1 (PD-1). It was specifically engineered to minimize FcγR binding on macrophages, thereby abrogating antibody-dependent phagocytosis, a potential mechanism of T-cell clearance (**Figure 1**)

Figure 1: Lack of FcγR Binding Prevents Macrophage-Mediated T-Cell Clearance



Abbreviations: Ab, antibody; CD, cluster of differentiation; FcγR, Fc-gamma receptor; mAb, monoclonal antibody; MHC, major histocompatibility complex; PD-1, programmed cell death-1; PD-L1, programmed death-ligand 1.

- In a first-in-human, phase 1A/1B study (NCT02407990), single-agent tislelizumab was generally well tolerated and demonstrated evidence of antitumor activity in patients with solid tumors, including NSCLC.[6] Phase 2 and 3 studies in patients with solid tumors are currently recruiting[7–9]
- A recommended dose of 200 mg administered intravenously (IV) every 3 weeks (Q3W) has been identified for tislelizumab

METHODS

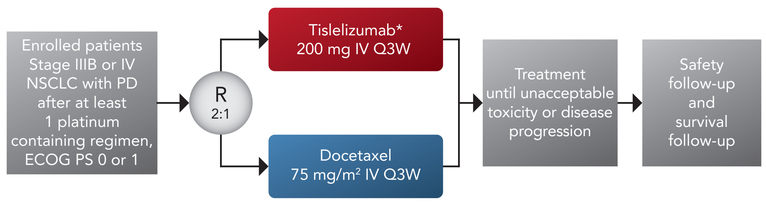
Overall Design and Study Objectives

- This phase 3, randomized, multicenter study (NCT03358875) was designed to evaluate the efficacy, safety, and tolerability of tislelizumab compared with docetaxel in the second- or third-line treatment of NSCLC (**Figure 2**)
- The primary objective will be to compare overall survival (OS) for tislelizumab versus docetaxel in the intent-to-treat (ITT) population and in those who tested positive for programmed cell death ligand-1 (PD-L1)
- Secondary objectives will include a comparison of tislelizumab and docetaxel for objective response rate (ORR), duration of response (DoR), and progression-free survival (PFS) in both the ITT and PD-L1-positive populations; health-related quality of life, and safety and tolerability will also be assessed
- Approximately 800 patients will be enrolled from Asian Pacific countries

Study Population

- Adult patients, aged ≥18 years, with locally advanced or metastatic NSCLC (Stage IIIB or IV, squamous or nonsquamous), who have progressed on at least one prior platinum-containing regimen will be eligible to enroll if:
  - Nonsquamous NSCLC with documentation of wild type epidermal growth factor receptor (EGFR) by tissue-based test; for those without such documentation, fresh or archival tumor tissues will be required for central EGFR mutation assessment. In addition, all patients are required to have fresh or archival tumor tissues with an associated pathological report (squamous or nonsquamous) for biomarker analysis, including PD-L1 testing
  - Adequate hematologic and end-organ function, and an Eastern Cooperative Oncology Group performance status score of 0 or 1

Figure 2: Study Design



Randomization stratified by histology (squamous versus nonsquamous), lines of therapy (second versus third), and PD-L1 expression (≥25% TC versus <25% TC)

*The initial infusion (Cycle 1, Day 1) will be administered over 60 minutes; if well tolerated, subsequent infusions may be administered over 30 minutes. After tislelizumab infusion, patients will be monitored for 2 hours during Cycles 1 and 2, and for at least 30 minutes from Cycle 3 onward.

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenous; NSCLC, non-small cell lung cancer; PD, progressive disease; PD-L1, programmed cell death ligand-1; Q3W, once every three weeks; R, randomized; TC, tumor cell.

- Patients will be excluded if:
  - Prior docetaxel treatment or therapies targeting PD-1, PD-L1 or cytotoxic T-lymphocyte-associated protein 4
  - A diagnosis of NSCLC that harbors EGFR sensitizing mutation or anaplastic lymphoma kinase (ALK) gene translocation
  - Unresolved toxicity of prior therapy of grade ≥2, except for adverse events (AEs) not constituting a likely safety risk
  - Prior chemotherapy, radiation, biologic therapy, immunotherapy or an investigational agent, or Chinese herbal medicines used to control cancer within 28 days (or ≤5 half-lives) of randomization
  - Uncontrolled or untreated brain metastases or active Leptomeningeal disease
  - History of interstitial lung disease or non-infectious pneumonitis (except for those induced by radiation therapies)
  - Clinically significant pericardial effusion
  - Clinically uncontrolled pleural effusion or ascites requiring pleurocentesis or abdominal tapping for drainage within 2 weeks before randomization

TREATMENT

- Patients will be randomized (2:1) to receive tislelizumab 200 mg IV Q3W or docetaxel 75 mg/m^2 IV Q3W, administered on Day 1 of each 21-day cycle, with randomization stratified by histology, lines of therapy, and PD-L1 expression
- Study treatment will be administered until disease progression, intolerable toxicity, or treatment discontinuation for other reasons. Patients on the tislelizumab arm will be permitted to continue tislelizumab treatment beyond radiographic progression till loss of clinical benefit
- There will be no dose reduction for tislelizumab in this study; dose delays or interruptions of less than 12 weeks will be permitted
- Dose reductions of docetaxel will be made for the management of general and hepatic toxicities

STUDY ASSESSMENTS AND STATISTICAL ANALYSIS

- Dual primary endpoints are OS in the ITT population (all randomized patients) and PD-L1-positive population (defined as those with ≥25% of tumor cells with PD-L1 membrane staining via the Ventana SP263 assay)
- Secondary efficacy endpoints include ORR, DoR, and PFS, in the ITT and PD-L1-positive populations as assessed by the investigator using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1
- Health-related quality of life (secondary endpoint) will be assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Lung Cancer (EORTC QLQ-LC13) and Core 30 (EORTC QLQ-C30), and will be compared between the two treatment groups
- Safety/tolerability will be assessed by monitoring AEs occurring up to 30 days after the last dose of the study drug, monitoring immune-related AEs occurring up to 120 days after the last dose of the study drug, and through physical examinations, vital signs, and electrocardiograms

REFERENCES

1. PDQ Adult Treatment Editorial Board. Small cell lung cancer treatment (PDQ®): Health professional version. 2017 Jan 20. In: PDQ cancer information summaries [Internet]. Bethesda (MD): National Cancer Institute (US); 2002 Available from: https://www.ncbi.nlm.nih.gov/books/NBK65909/. Accessed April 2018.
2. Non-small cell lung cancer survival rates, by stage. American cancer society. 2017. https://www.cancer.org/content/cancer/en/cancer/non-small-cell-lung-cancer/detection-diagnosis-staging/survival-rates.html. Accessed May 2018.
3. Gettinger SN, Horn L, Gandhi L, et al. Overall survival and long-term safety of nivolumab (anti-programmed death 1 antibody, BMS-936558, ONO-4538) in patients with previously treated advanced non-small-cell lung cancer. *J Clin Oncol.* 2015;33(18):2004–2012.
4. Rizvi NA, Mazières J, Planchard D, et al. Activity and safety of nivolumab, an anti-PD-1 immune checkpoint inhibitor, for patients with advanced, refractory squamous non-small-cell lung cancer (CheckMate 063): a phase 2, single-arm trial. *Lancet Oncol.* 2015;16(3):257-265.
5. Herbst RS, Bass P, Kim DW, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet.* 2016;387(10027):1540-1550.
6. Desai J, Markman B, Sandhu SK, et al. Updated safety, efficacy, and pharmacokinetics (PK) results from the phase I study of BGB-A317, an anti-programmed death-1 (PD-1) mAb in patients with advanced solid tumors. *J Immunother Cancer.* 2016;4(Suppl 1):P154.
7. US National Library of Medicine. Clinicaltrials.gov. https://clinicaltrials.gov/ct2/show/NCT03419897. Accessed April 13, 2018.
8. US National Library of Medicine. Clinicaltrials.gov. https://clinicaltrials.gov/ct2/show/NCT03412773. Accessed April 13, 2018.
9. US National Library of Medicine. Clinicaltrials.gov. https://clinicaltrials.gov/ct2/show/NCT03358875. Accessed April 13, 2018.

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