NEOADJUVANT TISLELIZUMAB OR PLACEBO + PLATINUM-BASED CHEMOTHERAPY FOLLOWED BY ADJUVANT TISLELIZUMAB OR PLACEBO IN PATIENTS WITH RESECTABLE NON-SMALL CELL LUNG CANCER: A PHASE 3 TRIAL IN PROGRESS

Changli Wang[1], Ruihua Wang[2], Yan Ma[2], Xiaofang Liang[2]

[1]*Tianjin Medical University Cancer Institute & Hospital, Tianjin, China;* [2]*BeiGene (Shanghai) Co., Ltd., Shanghai, China*

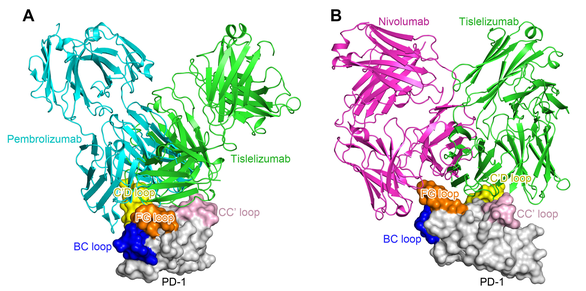
Abstract: 438

European Lung Cancer Congress
25-27 March 2021, Virtual Congress

BACKGROUND

- Globally, lung cancer is the leading cause of cancer death, with approximately 2.2 million new lung cancer cases and 1.8 million deaths in 2020[1]
- Current standard of care is adjuvant platinum-based doublet chemotherapy for fully resected (stage II or IIIA) non-small cell lung cancer (NSCLC)[2]
- Adjuvant and neoadjuvant chemotherapies have been proposed to improve the prognosis of patients with stage II/IIIA lung cancer, and have provided modest survival benefits[2,3]
  - Preoperative platinum-based doublet chemotherapy provides minimal (5%) improvement in 5-year overall survival (OS) rate[3]
- When added to chemotherapy, anti-PD-(L)1 antibodies have resulted in enhanced antitumor activity versus chemotherapy alone in locally advanced or metastatic NSCLC[4-6]
  - The ability of anti-PD-(L)1 antibodies to limit relapse in patients who have undergone surgical resection has not been fully elucidated
- Tislelizumab is a monoclonal antibody with high affinity and specificity for PD-1
  - Tislelizumab has shown higher affinity to PD-1 than pembrolizumab and nivolumab with an ~100- and 50-fold slower dissociation rate, respectively[7]
- Tislelizumab has a different binding orientation to PD-1 compared with pembrolizumab and nivolumab; the binding surface on PD-1 for tislelizumab partially overlaps with that for pembrolizumab, but differs significantly from that for nivolumab (**Figure 1**)[7]

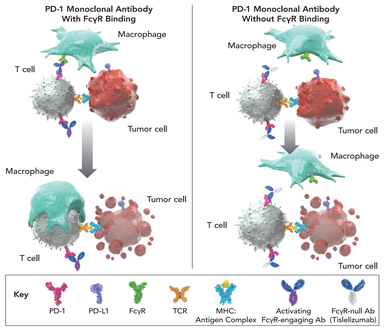
Figure 1: Tislelizumab Binds to PD-1 in an Orientation Different From Pembrolizumab (A) and Nivolumab (B)



Abbreviation: PD-1, programmed cell death protein 1.

- Tislelizumab was specifically engineered to minimize binding to FcγR on macrophages to abrogate antibody-dependent phagocytosis, a mechanism of T-cell clearance and potential resistance to anti PD-1 therapy (**Figure 2**)[8,9]
- In previous studies (NCT02407990; NCT04068519; NCT03432598; NCT03594747; NCT03663205), tislelizumab, as a single agent and in combination with chemotherapy, was generally well tolerated and had encouraging antitumor activity in patients with advanced NSCLC[5,6,10-12]
  - In RATIONALE 304 (NCT03663205; BGB-A317-304), addition of tislelizumab to chemotherapy resulted in significantly longer progression-free survival (PFS) compared to chemotherapy alone (median PFS: 9.7 versus 7.6 months; HR=0.645 [95% CI: 0.462, 0.902]; *P*=0.0044) in patients with stage IIIB/IV nonsquamous NSCLC[5]
  - Addition of tislelizumab to either chemotherapy backbone of paclitaxel and carboplatin (*Arm A*) or nab-paclitaxel and carboplatin (*Arm B*) for patients with advanced stage squamous NSCLC also resulted in significantly longer PFS compared to paclitaxel and carboplatin alone (*Arm C*) (7.6, 7.6, and 5.5 months, respectively; A vs C: HR=0.524 [95% CI: 0.370, 0.742] *P*=0.0001; B vs C: HR=0.478 [95% CI: 0.336, 0.679] *P*=0.0001) in RATIONALE 307 (NCT03594747; BGB-A317-307)[6]

Figure 2: Lack of FcγR Binding May Help Prevent Macrophage-Mediated T-Cell Clearance



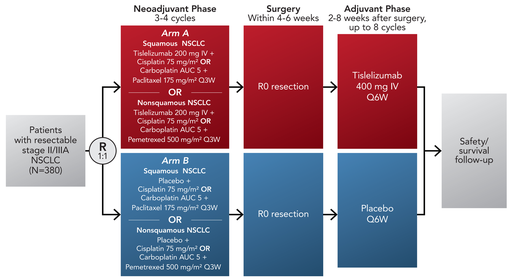
Abbreviations: Ab, antibody; FcγR, Fc-gamma receptor; MHC, major histocompatibility complex; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; TCR, T-cell receptor.

METHODS

Overall Design and Study Objectives

- This multicenter, double-blind, placebo-controlled, randomized, phase 3 study (NCT04379635; BGB-A317-315) is being conducted in about 30 sites with approximately 380 patients and is designed to compare the efficacy of neoadjuvant tislelizumab or placebo plus platinum-containing chemotherapy followed by surgery and adjuvant tislelizumab or placebo for patients with resectable, stage II or IIIA NSCLC (**Figure 3**)

Figure 3: Study Design



Abbreviations: AUC, area under the curve; IV, intravenous; NSCLC, non-small cell lung cancer; PD-L1, programmed death-ligand 1; Q3W, once every 3 weeks; Q6W, once every 6 weeks; R0, pathological complete resection of primary tumor.

- The dual primary endpoints are major pathological response rate as assessed by blinded independent pathology review (MPR_{BIPR}) and event-free survival as assessed by blinded independent central review (EFS_{BICR})
- Secondary endpoints will include OS, objective response rate (complete or partial response), pathological complete response rate by blinded independent pathology review, disease-free survival by blinded independent central review, investigator-assessed EFS, safety/tolerability profile, as well as health-related quality-of-life measures

Study Population

- Key inclusion/exclusion criteria are outlined in **Table 1**

Table 1: Patient Eligibility

Inclusion Criteria	Exclusion Criteria
• Adults (aged ≥18 years) • Histologically confirmed stage II/IIIA squamous or nonsquamous NSCLC • Eligible for a R0 resection with curative intent • ≥1 measurable/evaluable lesion per RECIST v1.1 • ECOG performance status score ≤1 • Must provide fresh or archival tumor tissue for assessment of various biomarkers (eg, PD-L1)	• Known *EGFR* mutation or *ALK* gene translocations • Prior treatments with: – Chemo- or radiotherapy for stage II or IIIA NSCLC – An antibody toward an immune checkpoint pathway inhibitor – Prior systemic treatment with either corticosteroids or other immunosuppressive medication ≤14 days before randomization • History of interstitial lung disease, noninfectious pneumonitis, or uncontrolled lung disease • Any active malignancy ≤2 years before randomization except for NSCLC or any locally recurring cancer that has been treated curatively

Abbreviations: ALK, anaplastic lymphoma kinase; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; PD-L1, programmed death-ligand 1; R0, pathological complete resection of primary tumor; RECIST, response evaluation criteria in solid tumors.

Treatment

- Patients will be randomized 1:1 to receive either tislelizumab plus histology-specific chemotherapy (*Arm A*) or placebo plus histology-specific chemotherapy (*Arm B*) followed by surgery and adjuvant treatment of tislelizumab (*Arm A*) or placebo (*Arm B*), respectively
- Neoadjuvant therapy will be administered for 3-4 cycles and consist of either:
  - Tislelizumab 200 mg plus either cisplatin 75 mg/m² or carboplatin AUC 5 plus paclitaxel 175 mg/m² IV once every 3 weeks (Q3W; Day 1 of each 21-day cycle) for squamous NSCLC; **or**
  - Tislelizumab 200 mg plus either cisplatin 75 mg/m² or carboplatin AUC 5 plus pemetrexed 500 mg/m² IV Q3W (Day 1 of each 21-day cycle) for nonsquamous NSCLC
- Surgery will be performed within 4-6 weeks after the last dose of neoadjuvant study treatment
- Adjuvant treatment will be initiated within 2-8 weeks after surgery and consist of tislelizumab (400 mg) or placebo once every 6 weeks (Day 1 of each 42-day cycle) for up to eight cycles

Study Assessments, Populations, and Statistical Analysis

- Tumor assessments will occur at baseline, before Cycle 3 of neoadjuvant treatment and surgery, and then every 3 months after surgery for the first 2 years; assessments will occur every 6 months from Years 3-5 and annually thereafter
- The dual primary endpoints of MPR_{BIPR} and EFS_{BICR} will be assessed using the Cochran-Mantel-Haenszel chi-square test methodology and the stratified log-rank test methodology, respectively
  - All efficacy analyses will be assessed in the intent-to-treat analysis set, defined as all patients who have been randomized to treatment
- Safety/tolerability will be assessed by evaluating the incidence and severity of adverse events (AEs), physical examinations, vital signs, electrocardiograms, and laboratory test results
  - Adverse events are defined as those reported ≤30 days after the last dose of study drug or until initiation of new systemic anticancer treatment, whichever occurs first
  - In the tislelizumab containing arm, AE classification also applies to immune-mediated AEs that are reported ≤90 days after the last dose of study treatment, regardless of whether the patient starts a new anticancer therapy
  - Safety and tolerability will be assessed in the safety analysis set, consisting of all subjects who receive ≥1 dose of any component of study treatment
- Quality of life will be analyzed based on change from baseline

REFERENCES

1. Lung Cancer Fact Sheet, 2020. Global Cancer Observatory. https://gco.iarc.fr/today/data/factsheets/cancers/15-Lung-fact-sheet.pdf. Published December 2020. Accessed February 5, 2021.
2. Liang Y, Wakelee HA. Adjuvant chemotherapy of completely resected early stage non-small cell lung cancer (NSCLC). *Transl Lung Cancer Res.* 2013;2(5):403-410.
3. NSCLC Meta-analysis Collaborative Group. Preoperative chemotherapy for non-small-cell lung cancer: a systematic review and meta-analysis of individual participant data. *Lancet.* 2014;383(9928):1561-1571.
4. Carlisle JW, Ramalingam SS. A banner year for immunotherapy and targeted therapy. *Nat Rev Clin Oncol.* 2019;16(2):79-80.
5. Lu S, Yu Y, Xinmin Y, et al. Tislelizumab plus chemotherapy versus chemotherapy alone as first-line treatment for locally advanced/metastatic nonsquamous non-small cell lung cancer. *Ann Oncol.* 2020;31(suppl 4):S816-S817.
6. Wang J, Lu S, Yu X, et al. Tislelizumab plus chemotherapy versus chemotherapy alone as first-line treatment for advanced squamous non-small cell lung cancer (RATIONALE 307): randomized phase 3 trial. *JAMA Oncol.* 2021:In Press.
7. Feng Y, Hong Y, Sun H, et al. Abstract 2383: The molecular binding mechanism of tislelizumab, an investigational anti-PD-1 antibody, is differentiated from pembrolizumab and nivolumab; Presented at: American Association of Cancer Research; March 29-April 3, 2019; Atlanta, Georgia. Abstract 2383.
8. Zhang T, Song X, Xu L, et al. The binding of an anti-PD-1 antibody to FcγRI has a profound impact on its biological functions. *Cancer Immunol Immunother.* 2018;67(7):1079-1090.
9. Dahan R, Sega E, Engelhardt J, et al. FcγRs modulate the anti-tumor activity of antibodies targeting the PD-1/PD-L1 axis. *Cancer Cell.* 2015;28(4):543.
10. Desai J, Deva S, Lee JS, et al. Phase IA/IB study of single-agent tislelizumab, an investigational anti-PD-1 antibody, in solid tumors. *J Immunother Cancer.* 2020;8(1):e000453.
11. Shen L, Guo J, Zhang Q, et al. Tislelizumab in Chinese patients with advanced solid tumors: an open-label, non-comparative, phase 1/2 study. *J Immunother Cancer.* 2020;8(1):e000437.
12. Wang Z, Zhao J, Ma Z, et al. A phase 2 study of tislelizumab in combination with platinum-based chemotherapy as first-line treatment for advanced lung cancer in Chinese patients. *Lung Cancer.* 2020;147:259-268.

CONFLICT OF INTEREST

CW has nothing to disclose.

ACKNOWLEDGMENTS

The authors wish to acknowledge the investigative center study staff and to recognize those from BeiGene, Ltd. who have substantially contributed to the development of this presentation. BeiGene, Ltd. provided financial support for this presentation, including writing and editorial assistance by Agnieszka Laskowski, PhD, and Elizabeth Hermans, PhD, from Peloton Advantage, LLC, an OPEN Health company (Parsippany, NJ).

Please address any questions or comments regarding this poster to Clinicaltrials@beigene.com