2. SYNOPSIS

Name of Sponsor/Company: BeiGene, Ltd.	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Active Ingredient: - Tislelizumab (BGB-A317) - Sitravatinib (BGB-9468)		
Title of Study: A Randomized Phase 3 Study of Tislelizumab in Combination With Sitravatinib in Patients With Locally Advanced or Metastatic Non-Small Cell Lung Cancer That Progressed on or After Platinum-Based Chemotherapy and Anti-PD-(L)1 Antibody		
Principal Investigator: [redacted]		
Study center(s): This study was conducted at 53 study centers in China, 12 study centers in Australia.		
Publications (reference): NA		
Studied period (years): Date first patient dosed: 27 July 2021 Date last patient completed: 20 December 2023 Data cutoff date: 20 December 2023	**Phase of development:** 3	

Objectives:

Primary:

- To compare the overall survival (OS) of tislelizumab and sitravatinib combination therapy with that of docetaxel monotherapy.
- To compare the progression-free survival (PFS) of tislelizumab and sitravatinib combination therapy with that of docetaxel monotherapy, as assessed by the Independent Review Committee (IRC).

Secondary:

- To compare the PFS of tislelizumab and sitravatinib combination therapy with that of docetaxel monotherapy, as assessed by the investigator.
- To compare the confirmed overall response rate (ORR) of tislelizumab and sitravatinib combination therapy with that of docetaxel monotherapy as assessed by the IRC.
- To evaluate the safety and tolerability of tislelizumab and sitravatinib combination therapy with that of docetaxel monotherapy.

Methodology:

This was an open-label, randomized, multicenter, Phase 3 clinical study evaluating the efficacy and safety of tislelizumab in combination with sitravatinib compared with docetaxel in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) whose disease progressed following platinum-based chemotherapy and anti-programmed cell death protein-1/programmed cell death protein ligand-1 (PD-[L]1) antibody, with the anti-PD-(L)1 antibody administered in combination with, or sequentially before or after the platinum-based chemotherapy.

Patients were randomized in a 1:1 ratio to receive the study treatment(s) in the following 2 arms:

- Arm A: tislelizumab 200 mg intravenously once every 3 weeks in combination with sitravatinib 100 mg orally once a day
- Arm B: docetaxel 75 mg/m^2 intravenously once every 3 weeks

Randomization was stratified according to histological subtype (nonsquamous versus squamous), PD-L1 expression (< 1% tumor cells [TC] versus ≥ 1% TC; patients whose tissues were unevaluable for PD-L1 expression were included in the < 1% TC group), and race (Asian versus non-Asian).

The study procedures occurred over the following periods and visits:

- A screening period (up to 28 days)
- A treatment period (until disease progression, intolerable toxicity, death, or withdrawal of consent, whichever occurred earlier)
- An End-of-Treatment (EOT) Visit (30 days [± 7 days] after the last dose of study drug[s], or before the initiation of a new anticancer treatment, whichever occurred first) and Safety Follow-up Visit
  - Patients returned to the clinic for the EOT Visit. In addition, telephone contacts (safety follow-up phone call) with patients were conducted to assess imAEs and concomitant medications (if appropriate, ie, associated with an imAE or is a new anticancer therapy) at 60 days (± 14 days) and 90 days (± 14 days) after the last dose of tislelizumab, regardless of whether or not the patient started a new anticancer therapy. If patients reported a suspected imAE at a telephone follow-up contact, the investigator would arrange an unscheduled visit if further assessment was indicated.
- A survival follow-up period (every 3 months [± 14 days] after the EOT Visit or as directed by the sponsor until death, withdrawal of consent, lost to follow-up, or end of study)

Number of patients (planned and analyzed):

Planned: approximately 420 patients

Enrolled: 377 patients

ITT Analysis Set: 377 patients

Safety Analysis Set: 363 patients

Diagnosis and Main Criteria for Inclusion:

The study enrolled adult patients aged ≥ 18 years on the day of signing the informed consent form or the legal age of consent if > 18 in the jurisdiction in which the study is taking place with metastatic or unresectable locally advanced histologically or cytologically confirmed NSCLC and having been previously treated with no more than 2 lines of prior systemic chemotherapy and anti-PD-(L)1 antibody therapy. Patients with known *EGFR* or *BRAF* sensitizing mutation, or *ALK* or *ROS1* rearrangement were ineligible for the study. All patients were required to have an ECOG Performance Status score of ≤ 1 and adequate organ function.

Criteria for Evaluation:

Study-specific assessments and procedures were performed as outlined in the Schedule of Assessments in the protocol.

Primary Endpoint:

- OS, defined as the time from randomization to death from any cause.
- PFS, defined as the time from randomization to the first occurrence of disease progression as determined by the IRC based on Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1), or death from any cause, whichever occurs first.

Secondary Endpoints:

- PFS, defined as the time from randomization to the first occurrence of disease progression as determined by the investigator based on RECIST v1.1, or death from any cause, whichever occurs first.
- ORR, defined as the proportion of patients with partial response or complete response as determined by the IRC based on RECIST v1.1.
- Incidence and severity of treatment-emergent adverse events (TEAEs) graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 (NCI-CTCAE v5.0).

Statistical Analysis Method

Efficacy and safety analyses were performed on Intent-to-Treat (ITT) Analysis Set and Safety Analysis Set, respectively, whose definitions were provided in the statistical analysis plan (SAP). No inferential hypothesis testing was performed in the efficacy analysis because the study was terminated before the planned efficacy interim analysis. Further details can be found

in the report body and SAP.

SUMMARY – CONCLUSIONS

For patients with NSCLC who have received prior checkpoint inhibitors and platinum-based chemotherapy, treatment options are limited and mainly involve docetaxel, which is associated with poor survival outcomes (about 10 to 12 months' median OS and severe toxicities, including neutropenia, febrile neutropenia, anemia, and neuropathy).

BGB-A317-Sitravatinib-301 was an open-label, randomized, multicenter, Phase 3 clinical study evaluating the efficacy and safety of tislelizumab in combination with sitravatinib compared with docetaxel in patients with locally advanced or metastatic NSCLC whose disease progressed following platinum-based chemotherapy and anti-PD-(L)1 antibody, with the anti-PD-(L)1 antibody administered in combination with, or sequentially before or after the platinum-based chemotherapy.

A total of 377 patients were randomized in a 1:1 ratio to receive the study treatment(s) in either arm. The demographics and baseline disease characteristics of the 2 arms were generally well balanced, representing the target patient population.

EFFICACY RESULTS:

Although a numerically favorable PFS assessed by IRC was observed in Arm A (median: 4.4 months, 95% CI: 4.0 to 5.7 months) over Arm B (2.9 months, 95% CI: 2.6 to 4.2 months), the OS was generally similar. The median OS was 11.5 months (95% CI: 9.4 to 14.6 months) in Arm A and 11.4 months (95% CI: 9.9 to 15.0 months) in Arm B. No clear OS improvement favoring Arm A over Arm B was observed in any prespecified subgroups. To be noted, in this trial, the OS data should be interpreted with caution due to the early termination of this study and the survival data are not yet mature.

Several studies are evaluating docetaxel compared with combinations of checkpoint inhibitor (CPI) and agents targeting tumor-associated macrophages (TAM) receptors and/or VEGFR2 with the aim of modulating the immunosuppressive tumor microenvironment (TME) and overcoming CPI resistance. But all of them, including SAPPHIRE, CONTACT-01, and LEAP-008, failed to show significant improvement when compared with docetaxel.

The only positive readout in this setting comes from Dato-DXd, which is a TROP2-directed antibody-drug conjugate (ADC) that selectively delivers topoisomerase I inhibitor payload into tumor cells. In TROPION-Lung01 study, Dato-DXd showed a statistically significant longer PFS results compared to docetaxel, but the benefit was only limited to non-squamous populations (5.6 months versus 3.7 months; HR = 0.63). A numerically favorable OS trend was also observed in this subpopulation (HR = 0.77; 74% maturity). However, the success was not repeated in EVOKE-01, in which trial Sacituzumab govitecan (SG), another TROP2-directed ADC, was investigated and compared with docetaxel in the same setting. Although a numerical improvement in OS favoring SG in both squamous and non-squamous histologies was observed, the difference failed to achieve any statistical significance.

Resistance to CPI therapy is a complex process associated with various mechanisms, not only related to an immunosuppressive TME and TAM receptor activation, but also with co-inhibitory checkpoints, defects in antigen processing or neoantigen loss, and tumor-mediated

immune suppression. Emerging therapies with novel and diverse mechanisms of action are poised to enter this setting for patients with NSCLC who have been previously treated with CPI and platinum-based chemotherapy.

SAFETY RESULTS:

As of the data cutoff date, the median duration of exposure to tislelizumab was 4.140 months (range: 0.46 to 24.80 months), and that to sitravatinib was 4.123 months (range: 0.03 to 24.28 months). The median duration of exposure to docetaxel was 2.103 months (range: 0.10 to 25.79 months), which was relatively shorter than Arm A.

Treatment-emergent adverse events incidences were similar in patients in the 2 arms (98.4% in Arm A and 91.5% in Arm B), while higher incidences were noted in Arm A than Arm B for treatment emergent adverse events of ≥ Grade 3 (65.1% versus 56.5%), serious adverse events (44.6% versus 37.3%), treatment emergent adverse events leading to treatment discontinuation of any component (24.2% versus 8.5%), and treatment emergent adverse events leading to death (8.1% versus 2.8%).

There was a numerical imbalance of both serious and fatal haemoptysis related to study treatment reported between Arm A and Arm B (serious: 2.2% versus 0%, fatal: 1.6% versus 0%, respectively) in this study. Therefore, pulmonary hemorrhage was considered an important identified risk of sitravatinib when used in combination with tislelizumab, especially in this study population with locally advanced or metastatic NSCLC. However, the same risk was not identified in other studies of the combination of sitravatinib and tislelizumab.

CONCLUSION:

In conclusion, this study showed a numerically favorable PFS assessed either by IRC or the investigator in the tislelizumab plus sitravatinib combination therapy compared with docetaxel in patients with locally advanced or metastatic NSCLC who had been treated with anti-PD-(L)1 antibody and platinum-based chemotherapy while no such trend of OS and ORR was observed.

Considering the safety risk of pulmonary haemorrhage in the investigational arm in this study, it was assessed that the overall risk-benefit assessment was unfavorable to the study population, and the study was terminated early.

Date of the report:

08 May 2024