SAFFRON-301: A Phase 3 Study of Tislelizumab With Sitravatinib Versus Chemotherapy in Patients With Locally Advanced or Metastatic Non-Small Cell Lung Cancer Previously Treated With Platinum-Based Chemotherapy and an Anti-PD-1/PD-L1 Antibody

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Qing Zhou*,[1] Jun Zhao,[2] Bo Gao,[3] Mengzhao Wang,[4] Jianhua Chang,[5] Jie Hu,[6] Jian Li,[7] Juan Zhang,[7] Qiuyang Zhang,[7] Yanyan Peng,[8] Yi-Long Wu[†1]

[1]Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou, China; [2]Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education, Beijing), Department of Thoracic Medical Oncology, Peking University Cancer Hospital & Institute, Beijing, China; [3]Blacktown Cancer and Hematology Centre, Blacktown, NSW, Australia; [4]Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing, China; [5]Cancer Hospital Chinese Academy of Medical Sciences, Shenzhen Center, Shenzhen, China; [6]Department of Pulmonary Medicine, Shanghai Respiratory Research Institute Zhongshan Hospital, Fudan University, Fudan, China; [7]BeiGene (Beijing) Co., Ltd., Beijing, China; [8]BeiGene (Shanghai) Co., Ltd., Shanghai, China.

*Presenting author; †Corresponding author

Conclusions

This is 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 who have disease progression following treatment with platinum-based chemotherapy and an anti-PD-1/PD-L1 antibody.

Background

Lung cancer carries a poor prognosis and is the leading cause of cancer death worldwide.[1] Despite the advent of immuno-oncology, there is an unmet need for new therapies.[2]

Most patients with advanced non-small cell lung cancer (NSCLC) do not respond to programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) inhibitor monotherapy.[3] Of the patients who do respond, most develop resistance over time with disease progression usually occurring within 2-17 months of treatment initiation.[3]

More effective treatment options capable of combating resistance and increasing the duration of response are needed.

Introduction to Tislelizumab and Sitravatinib

Tislelizumab

Tislelizumab is a monoclonal antibody with high binding affinity to the PD-1 receptor, which was engineered to minimize binding to Fcγ receptors on macrophages.[4,5]

In two phase 3 trials, the addition of tislelizumab to chemotherapy led to increased progression-free survival (PFS) and longer duration of response (DoR) compared with chemotherapy alone in patients with advanced NSCLC.[2,6]

Sitravatinib

Sitravatinib is an oral spectrum-selective tyrosine kinase inhibitor targeting TAM family receptors (TYRO3, AXL, MER) and split tyrosine-kinase domain containing receptors (VEGFR2/KIT), which may help to reduce the number of myeloid-derived suppressor cells and regulatory T cells and increase the ratio of M1/M2 polarized macrophages, promoting an antitumor immune microenvironment.[7-9]

Rationale for Combination of Tislelizumab and Sitravatinib

- Combining an immunotherapeutic PD-1 checkpoint inhibitor with a receptor tyrosine kinase inhibitor that has both immunomodulatory and antitumor properties could potentially produce a synergistic effect and enhance the antitumor activity observed with either agent alone[10,11]

Methods

Figure 1. Study Design (NCT04921358)

Inclusion criteria:
- Age ≥18 years
- Unresectable locally advanced or metastatic histologically confirmed NSCLC
- No known *EGFR* or *BRAF* sensitizing mutation, or *ALK* or *ROS1* rearrangement
- Prior treatment must include platinum-based chemotherapy and an anti-PD-1/PD-L1 antibody
- ≤2 lines of prior systemic therapy for advanced/metastatic disease
- ≥1 measurable lesion (RECIST v1.1)
- ECOG PS ≤1

N~420

R 1:1

Tislelizumab 200 mg IV Q3W + Sitravatinib 100 mg PO QD

Docetaxel 75 mg/m² IV Q3W

Continue until:
- Withdrawal
- Disease progression
- Intolerable toxicity
- Death

Stratification factors

- Histological subtype (squamous vs nonsquamous)
- PD-L1 expression (<1% TC[a] vs ≥1% TC)
- Race (Asian vs non-Asian)

Assessments

- Tumor imaging (CT or MRI) will be performed within 28 days before randomization and while on study, ~every 6 weeks (± 7 days) from Day 1 of Cycle 1 in the first 12 months and ~every 9 weeks (± 7 days) thereafter. Tumor assessment will be based on RECIST v1.1
- Patients will be evaluated for AEs, serious AEs, and immune-mediated AEs
  - Safety follow-up will occur until 30 days after the last dose of the study drug (90 days after the last dose of tislelizumab for immune-mediated AEs)
- Patients are enrolling in Australia and China with plans to enroll in the US and Europe

[a]Patients with unevaluable PD-L1 expression in tissues will be included in the <1% TC group. Abbreviations: AE, adverse event; ALK, anaplastic lymphoma kinase; BRAF, B-Raf proto-oncogene serine/threonine kinase; CT, computed tomography; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR; epidermal growth factor receptor; IV, intravenous; MRI, magnetic resonance imaging; NSCLC, non-small cell lung cancer; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PO, orally; Q3W, every 3 weeks; QD, every day; R, randomized; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; ROS1, ROS proto-oncogene 1, receptor tyrosine kinase; TC, tumor cell.

Study Endpoints

- **Primary endpoints**
  - OS
  - PFS, IRC-assessed, based on RECIST v1.1
- **Secondary endpoints**
  - PFS, INV-assessed, based on RECIST v1.1
  - ORR, DoR, and DCR, IRC-assessed, based on RECIST v1.1
  - HRQoL, defined as changes in PROs
  - Incidence and severity of TEAEs
  - PK parameters for sitravatinib[a]
- **Exploratory endpoints**
  - ORR, DoR and DCR, INV-assessed, based on RECIST v1.1
  - The predictive and prognostic effect of PD-L1 expression level
  - Plasma concentrations and the derived PK parameters of the active sitravatinib metabolite M10[a]
  - Serum concentrations of tislelizumab and incidence of anti-drug antibodies
  - Potential biomarkers and their association with disease status, and response/resistance to combination treatment

[a]If data permit. Abbreviations: DCR, disease control rate; DoR, duration of response; HRQoL, health-related quality of life; INV, investigator; IRC, independent review committee; ORR, objective response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PK, pharmacokinetic; PRO, patient-reported outcome; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; TEAE, treatment-emergent adverse event.

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***Author contact details: gzzhouqing@126.com (Qing Zhou)**