A PHASE 3 TRIAL IN PROGRESS OF PLATINUM-CONTAINING COMBINATION CHEMOTHERAPY WITH OR WITHOUT TISLELIZUMAB AS FIRST-LINE THERAPY IN PATIENTS WITH UNTREATED EXTENSIVE-STAGE SMALL CELL LUNG CANCER

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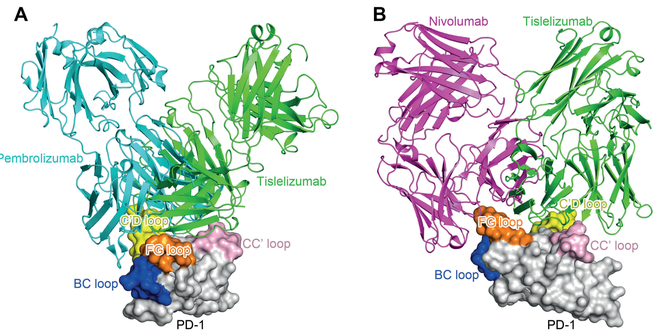
BACKGROUND

- In 2018, lung cancer was estimated to be the leading cause of cancer death in both men and women in China,[1] with small cell lung cancer (SCLC) accounting for approximately 15% of all lung cancers[2]
- Historically, the first-line standard of care for Chinese patients with untreated extensive-stage SCLC has been chemotherapy consisting of etopside plus cisplatin or carboplatin[3]
- Despite initial response rates of 60-70% in patients with extensive-stage SCLC treated with combination chemotherapy, the prognosis in these patients remains poor, with median overall survival (OS) of approximately 9-11 months and a 2-year survival rate of less than 5%, which calls to attention a significant unmet medical need[4]
- New therapeutic models have focused on targeting the immune system, including the programmed cell death-1/programmed cell death ligand-1 (PD-1/PD-L1) axis[5,6]
- The PD-1/PD-L1 axis plays a central role in suppressing antitumor immunity; dysregulation of the axis can be used by cancer cells to evade the immune system[7,8]
- Recent studies of immune checkpoint inhibitors targeting PD-1/PD-L1–both as monotherapy and/or in combination with chemotherapy–have shown antitumor activity in patients with SCLC[5,6,9,10]
- Tislelizumab is an investigational monoclonal antibody with high affinity and specificity for PD-1
  - Tislelizumab has shown higher affinity to PD-1 compared with pembrolizumab and nivolumab with an ~100- and 50-fold slower off-rate, respectively
- 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**)[11]

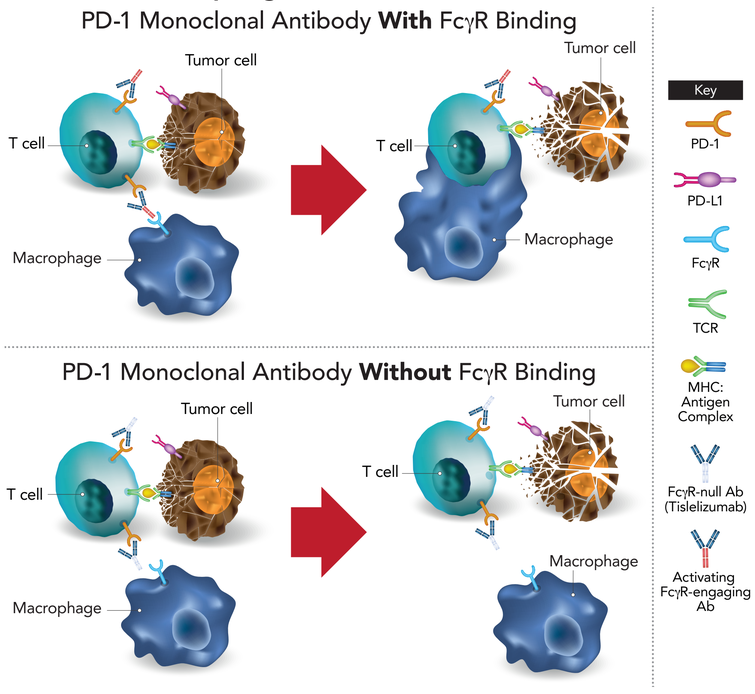
Figure 1: Tislelizumab Binds to PD-1 in an Orientation Different From Pembrolizumab (A) and Nivolumab (B)



PD-1, tislelizumab, pembrolizumab, and nivolumab are colored in gray, green, cyan, and magenta, respectively. The BC, CC′, C′D, and FG loops of PD-1 are colored in blue, pink, yellow, and orange, respectively.
Abbreviation: PD-1, programmed death-1 receptor.

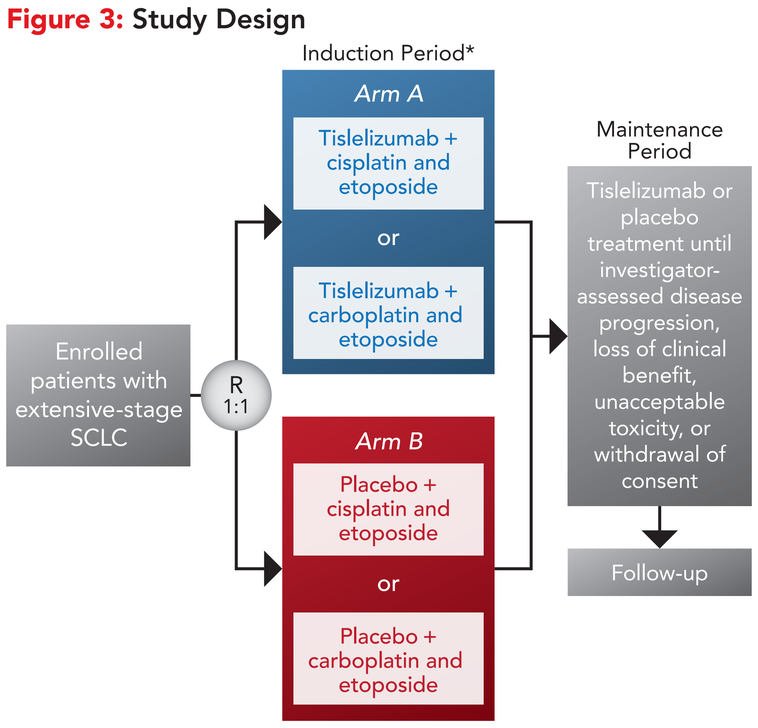
- Tislelizumab was specifically engineered to minimize binding to FcγR on macrophages to abrogate antibody-dependent phagocytosis, a mechanism of T-cell clearance and potential resistance to anti-PD-1 therapy (**Figure 2**)[7,12]
- Early phase studies (NCT02407990; NCT03432598) have reported that tislelizumab, as a single agent and in combination with platinum-containing chemotherapy, was generally well tolerated and demonstrated preliminary antitumor activity in patients with advanced lung cancer, including SCLC[13,14]

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



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

Figure 3: Study Design



Randomization was stratified by Eastern Cooperative Oncology Group performance status score, investigator-chosen chemotherapy (carboplatin versus cisplatin), and brain metastasis.
*Chemotherapy regimen will be administered up to 4 cycles.
Abbreviations: R, randomization; SCLC, small cell lung cancer.

METHODS

Overall Design and Study Objectives

- This randomized, double-blind, placebo-controlled, phase 3 study (NCT04005716) is being conducted in 50 centers across China and is designed to compare tislelizumab plus etoposide and platinum with placebo plus etoposide and platinum as first-line treatment for patients (N≈364) with untreated extensive-stage SCLC (**Figure 3**)
- Primary objectives are to compare investigator-assessed survival (progression-free survival [PFS] and OS) in patients treated with tislelizumab plus chemotherapy versus those treated with placebo plus chemotherapy
- Secondary objectives are to evaluate investigator-assessed overall response rate (ORR), disease control rate (DCR), and duration of response (DoR), per RECIST v1.1 criteria, quality-of-life outcome measures (eg, European Organization for Research and Treatment of Cancer [EORTC] Quality of Life Questionnaire-Score 30 Score [QLQ-C30] and EORTC Supplemental Lung Cancer Module Questionnaire-Score), as well as the safety/tolerability profile of combination therapy

Study Population

- The study population included adult patients (≥18 years) with histologically or cytologically confirmed extensive-stage SCLC, an Eastern Cooperative Oncology Group performance status (ECOG PS) score of ≤1, and adequate hematologic, renal, and hepatic function
  - Patients may not have received prior treatment for extensive-stage SCLC
    - Patients treated with curative intent for limited-stage SCLC must have experienced a treatment-free interval of ≥6 months between the completion of chemotherapy, radiotherapy, or chemoradiotherapy and diagnosis of extensive-stage SCLC
- Patients will also be excluded if they have active leptomeningeal disease or uncontrolled, untreated brain metastasis, or have a history of interstitial lung disease, non-infectious pneumonitis, or uncontrolled systemic disease, have any other active malignancy ≤2 years before randomization, or have received prior therapy with drug specifically targeting T-cell co-stimulation or checkpoint pathways

Treatment

- Patients will be randomized 1:1 to receive either tislelizumab 200 mg IV every 3 weeks (Q3W; Day 1 of each 21-day cycle) plus investigator-chosen chemotherapy (*Arm A*) or placebo IV Q3W plus investigator-chosen chemotherapy (*Arm B*)
  - Investigators can choose from two chemotherapy options:
    - Cisplatin 75 mg/m^2 IV Q3W (Day 1 of each 21-day cycle) plus etoposide 100 mg/m^2 IV Q3W (Days 1-3 of every 21-day cycle); **or**
    - Carboplatin AUC 5 IV Q3W (Day 1 of each 21-day cycle) plus etoposide 100 mg/m^2 IV Q3W (Days 1-3 of every 21-day cycle)
- Randomization will be stratified by ECOG PS score, investigator-chosen chemotherapy, and brain metastasis
- The chemotherapy regimen will be administered for up to four cycles
- Patient crossover will not be allowed between *Arm A* and *Arm B*
- Maintenance therapy of tislelizumab or placebo will be administered until investigator-assessed disease progression, loss of clinical benefit, unacceptable toxicity, withdrawal of informed consent, or other discontinuation criterion is met

Study Assessments and Statistical Analysis

- Tumor assessments will occur at baseline, every 6 weeks (±7 days) for 48 weeks, and every 9 weeks (±7 days) thereafter until radiographic disease progression
- The primary endpoints—PFS and OS—will be assessed using the intention-to-treat (ITT) analysis set, which includes all randomized patients; treatment effect will be estimated by log rank test, Kaplan-Meier method, and Cox regression model
  - Progression-free survival is defined as the time from date of randomization to date of first investigator-documented disease progression or death from any cause
  - Overall survival is defined as the time from date of randomization until date of death from any cause
  - An interim analysis of OS will be performed when at least 189 OS events are observed in the ITT analysis set
- Safety/tolerability of tislelizumab or placebo with chemotherapy will be assessed by the incidence and severity of adverse events according to National Cancer Institute Common Terminology Criteria for adverse events v5.0 criteria, physical examinations, vital signs, electrocardiogram, ECOG PS scores, and laboratory test results up to 30 days (±7 days) after the last dose of study drugs including chemotherapy
  - Immune-related adverse events will be reported up to 90 days after the last dose of tislelizumab or placebo
  - Safety and tolerability assessments will be performed in the safety analysis set, which will consist of all subjects who receive ≥1 dose of any of the assigned treatments
- Quality-of-life assessments will be performed in the ITT analysis set and reported using summary statistics

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