# PHASE 3 STUDY COMPARING TISLELIZUMAB IN COMBINATION WITH CISPLATIN/CARBOPLATIN + GEMCITABINE WITH PLACEBO IN COMBINATION WITH CISPLATIN/CARBOPLATIN + GEMCITABINE AS TREATMENT FOR CHINESE PATIENTS WITH ADVANCED UROTHELIAL CARCINOMA: A TRIAL IN PROGRESS

Feng Bi[1], Han-Zhong Li[2], Shaoxing Zhu[3], Qing Zou[4], Jia Tang[5], Wei Zhang[5], Ding-Wei Ye[6]

*[1]West China Hospital, Sichuan University, Sichuan, China; [2]Peking Union Medical College Hospital, Beijing, China; [3]Zhejiang Cancer Hospital, Hangzhou, China; [4]Jiangsu Cancer Hospital, Jiangsu, China; [5]BeiGene (Shanghai) Co., Ltd., Shanghai, China; [6]Fudan University Shanghai Cancer Center, Shanghai, China*

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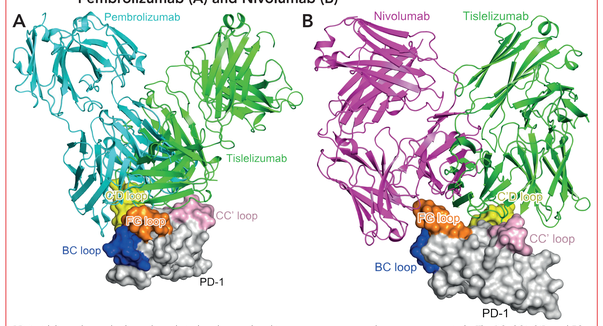
## BACKGROUND

- Urothelial carcinoma (UC) is the most common histologic type of bladder cancer, one of the most common urologic malignancies in China[1]
  - In China, bladder cancer accounted for approximately 80,500 new cancer cases and 32,900 deaths in 2015[2]
- Cisplatin-based chemotherapy (objective response rate [ORR]: 36%-71%)[3] is standard first-line treatment for patients with advanced UC; however, carboplatin-based regimens (ORR: 28%-56%)[3] are options for patients who are unable to receive cisplatin due to medical frailty or comorbidities[4,5]
- The programmed cell death-1/programmed cell death ligand-1 (PD-1/PD-L1) axis plays a central role in suppressing antitumor immunity; dysregulation of this axis may be exploited by cancer cells in order to help evade the immune system[6]
  - In bladder cancer, expression of PD-L1 has been associated with poor prognosis[7]
- Although there is evidence suggesting that anti-PD-1/PD-L1 antibodies are beneficial as first-line treatment in cisplatin-ineligible patients with UC (ORR: 23%-24%, complete response rate: 5%-9%, median overall survival [OS]: 16 months),[8,9] there is a lack of clinical evidence regarding the benefit of anti-PD-1/PD-L1 antibodies as first-line therapy for Chinese patients with UC who are platinum-eligible
  - In a different trial of 10 patients with UC, treatment with atezolizumab + gemcitabine + cisplatin resulted in grade 3-4 neutropenia in six patients, grade 3-4 anemia in seven patients, and febrile neutropenia in two patients[10]
    - One patient met initial criteria for partial response (PR), eight had confirmed PR, and one had progressive disease[10]
- Patients with UC receiving second-line tislelizumab had an ORR of 23% (95% CI: 15.4, 32.4)[11]
- Several studies examining anti-PD-1/PD-L1 antibodies as part of combination therapy in patients with UC are ongoing[12-15]
- Tislelizumab is an investigational monoclonal antibody with high affinity and specificity for PD-1
  - Tislelizumab shows higher affinity for PD-1 than pembrolizumab and nivolumab, with an approximate 100- and 50-fold slower off-rate, respectively (**Figure 1**)[16]

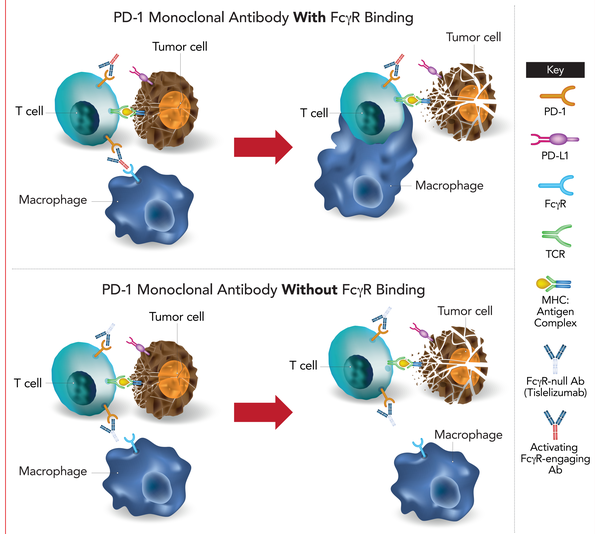
**Figure 1: Tislelizumab Binds to PD-1 in an Orientation Different From Pembrolizumab (A) and Nivolumab (B)**




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 engineered to minimize binding to FcγR on macrophages in order to abrogate antibody-dependent phagocytosis, a mechanism of T-cell clearance and potential resistance to anti-PD-1 therapy[17,18] (**Figure 2**)

**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.

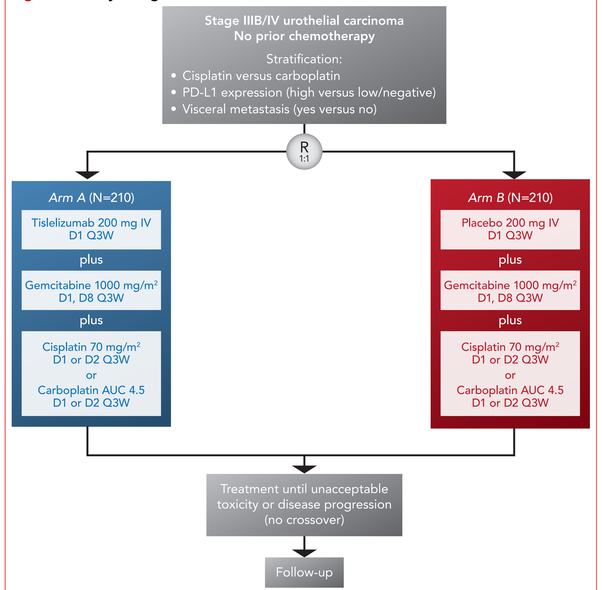
- Previous reports from a first-in-human phase 1A/1B study (NCT02407990) suggested that single-agent tislelizumab was generally well tolerated and had antitumor activity in patients with UC[19,20]

## METHODS

### Overall Design and Study Objectives

- This phase 3, randomized, double-blind, placebo-controlled study (NCT03967977), conducted in 25-36 centers in China, is designed to compare the efficacy and safety/tolerability of tislelizumab versus placebo in combination with cisplatin/carboplatin + gemcitabine as first-line treatment for locally advanced or metastatic UC (**Figure 3**)
- The primary objective is to compare the OS of tislelizumab versus placebo in combination with cisplatin/carboplatin + gemcitabine
- Secondary efficacy endpoints include investigator-assessed ORR (per Response Evaluation Criteria in Solid Tumors [RECIST] v1.1), duration of response, progression-free survival, and OS at 1 and 2 years
- Safety/tolerability profile of combination treatment as well health-related quality-of-life (HRQoL) questionnaire scores (eg, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Score 30 Score and EurQol 5-Dimension 5-Level) are also secondary endpoints

**Figure 3: Study Design**




*Or until investigator-assessed disease progression, unacceptable toxicity, or withdrawal for other reasons.
**Abbreviations:** cCRT, concurrent chemoradiotherapy; ESCC, esophageal squamous cell carcinoma; R, randomized.

### Study Population

- The study population will include UC patients who are eligible to receive cisplatin or carboplatin and have not received prior systemic therapy
  - Patients will be 18-75 years old
  - Patients must have histologically confirmed, inoperable, locally advanced, or metastatic UC
- Patients cannot have received prior therapies targeting PD-1, PD-L1, PD-L2, CTLA4, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways

### Treatment

- Patients will be randomized 1:1 to either chemotherapy plus tislelizumab (*Arm A*) or chemotherapy plus placebo (*Arm B*)
  - The study arm will receive tislelizumab 200 mg IV every 3 weeks (Q3W) with standard of care chemotherapy (gemcitabine 1000 mg/m$^2$ Day 1, Day 8, in combination with cisplatin 70 mg/m$^2$ Day 1 or carboplatin AUC 4.5 Day 1)
  - The placebo arm will receive placebo with standard of care chemotherapy
- The chemotherapy regimen will be administered for up to six cycles; tislelizumab (*Arm A*) or placebo (*Arm B*) will be administered until disease progression per RECIST v1.1, unacceptable toxicity, or death—whichever occurs first

### Study Assessments and Statistical Analysis

- During the study, tumor imaging will be performed per RECIST v1.1 approximately every 9 weeks for the first 54 weeks, then every 12 weeks thereafter
- Patients will be evaluated for adverse events (AEs) and infusion-related AEs (all grades according to NCI-CTCAE v5.0)
- Serious AEs or any AE that leads to treatment discontinuation will be followed and documented
  - An Independent Data Monitoring Committee (IDMC) will be established to assess the safety/tolerability of tislelizumab/placebo plus cisplatin/carboplatin + gemcitabine
- Patient-reported HRQoL questionnaires will be completed at baseline, at every other cycle through Cycle 12, then every four cycles thereafter, and at the end-of-treatment visit
- All efficacy analyses will be assessed in the intention-to-treat analysis set, which includes all randomized patients
- The primary efficacy analysis of OS will compare *Arm A* versus *Arm B* in a stratified log-rank test
- Kaplan-Meier survival probabilities for each arm will be plotted over time
- The hazard ratio between *Arm A* and *Arm B* and its 95% confidence interval will be estimated using a Cox proportional hazard model
- Safety will be assessed by monitoring and recording all AEs graded by NCI-CTCAE v5.0
  - Laboratory values, vital signs, electrocardiograms, and physical examinations will also be used in determining safety
  - Descriptive statistics will be used to analyze all safety data in the safety analysis set, which includes all patients who received at least one dose of study drug

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