A PHASE 2 TRIAL IN PROGRESS TO EVALUATE THE EFFICACY AND SAFETY OF TISLELIZUMAB IN CHINESE PATIENTS WITH PREVIOUSLY TREATED LOCALLY ADVANCED UNRESECTABLE OR METASTATIC SOLID TUMORS WITH MICROSATELLITE INSTABILITY-HIGH OR MISMATCH REPAIR DEFICIENCY

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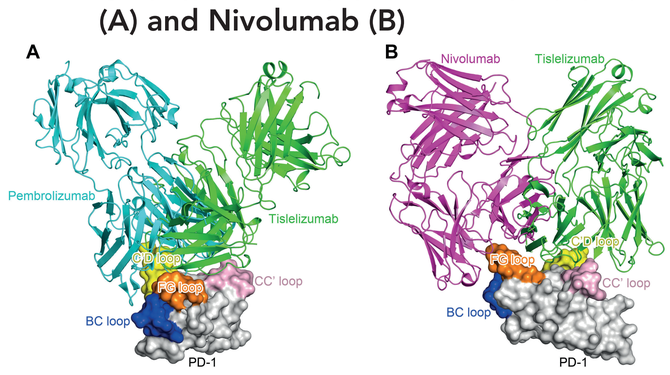
BACKGROUND

- Microsatellite instability (MSI) is a molecular tumor phenotype resulting from genomic hypermutability[1]
  - The gain or loss of nucleotides from microsatellite tracts—DNA elements composed of short repeating motifs—is the diagnostic hallmark of MSI[2]
- Mismatch repair deficiency (dMMR) refers to deficiency in proteins responsible for DNA mismatch repair (MMR), including MSH2, MSH6, MLH1, and PMS2[1]
  - dMMR leads to the MSI-high (MSI-H) phenotype
- The programmed cell death-1/programmed cell death-1 ligand (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[3]
- Tumors with dMMR/MSI-H are sensitive to PD-1 blockade as they have a significant upregulation of immune checkpoint proteins (including PD-1 and PD-L1) and increased mutation-associated neoantigen load[3,4]
- 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**)[5]

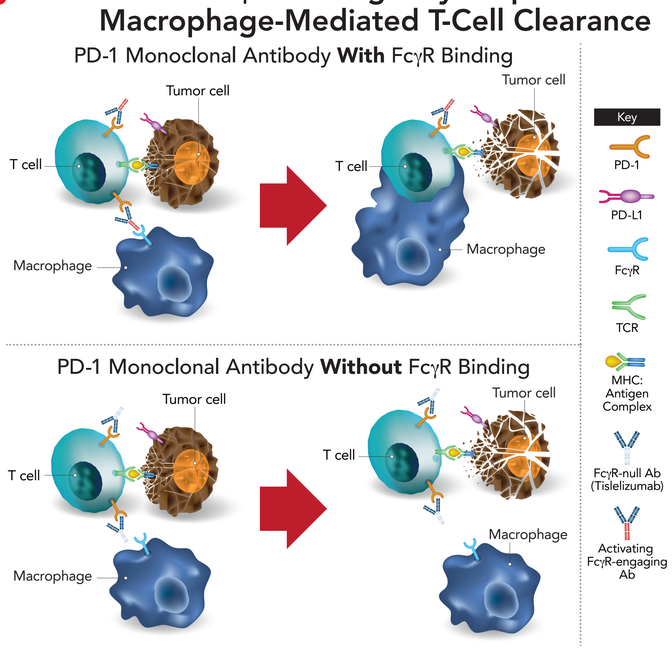
Figure 1: Tislelizumab Binds to PD-1 in an Orientation Different From Pembrolizumab (A) and Nivolumab (B)



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 (**Figure 2**)

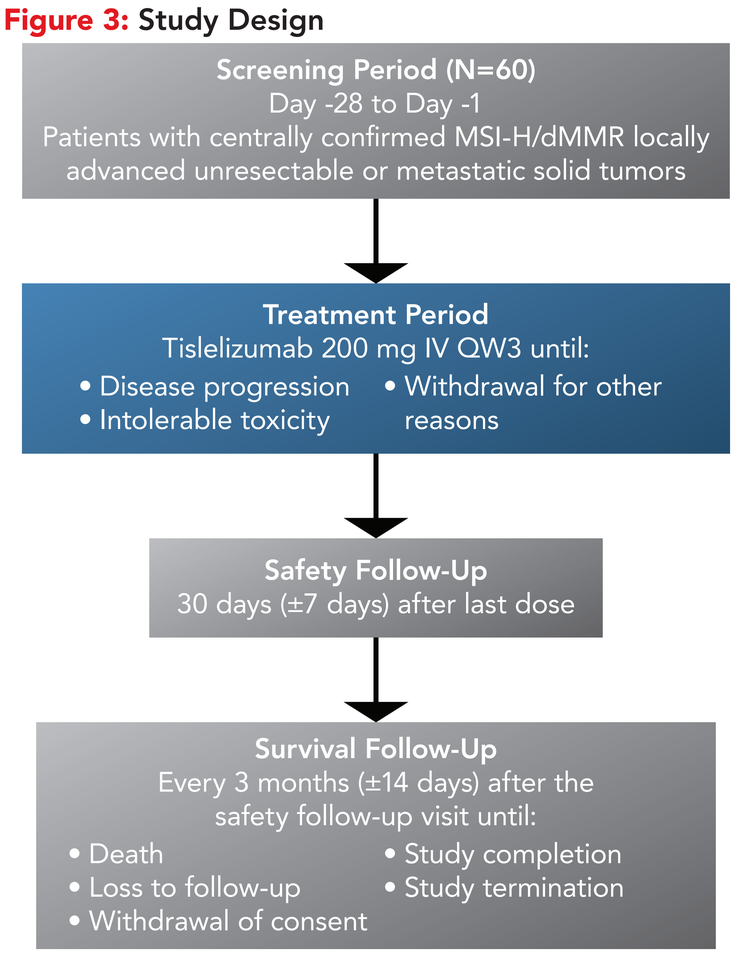
Figure 2: Lack of FcγR Binding May Help Prevent Macrophage-Mediated T-Cell Clearance



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 showed single-agent tislelizumab was generally well tolerated and had antitumor activity in patients with advanced solid tumors, including tumors with MSI-H/dMMR[6,7]

Figure 3: Study Design



Abbreviations: dMMR, mismatch repair deficient; IV, intravenous; MSI-H, microsatellite instability-high; Q3W, once every three weeks.

METHODS

Overall Design and Study Objectives

- This single-arm, open-label, phase 2 study (NCT03736889) is designed to evaluate the efficacy and safety of tislelizumab in patients with previously treated locally advanced unresectable or metastatic MSI-H or dMMR solid tumors from approximately 25 sites in China (**Figure 3**)
- The primary objective is to evaluate the efficacy of tislelizumab assessed by Independent Review Committee (IRC) as measured by objective response rate (ORR) per RECIST v1.1 in patients with previously treated locally advanced unresectable or metastatic solid tumors that are centrally confirmed as MSI-H or dMMR
- Secondary objectives include IRC-assessed time to response and duration of response, disease control rate, and progression-free survival per RECIST v1.1, as well as overall survival and safety and tolerability of tislelizumab

Study Population

- Adult patients (≥18 years) with locally advanced unresectable or metastatic MSI-H or dMMR solid tumors with measurable disease (per RECIST v1.1), who have progressed following prior treatment, have no satisfactory alternative treatment options, and have an Eastern Cooperative Oncology Group performance status ≤1 are eligible
  - Patients must be able to provide whole blood and archived tumor samples or fresh biopsies for determining MMR or MSI status using a validated polymerase chain reaction (PCR) assay by a central laboratory
- Patients will be excluded if they have had prior anti-PD-1, anti-PD-L1, anti-PD-L2, or any other antibody/drug specifically targeting T-cell co-stimulation or checkpoint pathways, or any condition that required systemic treatment with either corticosteroids (>10 mg daily of prednisone or equivalent) or other immunosuppressive medication ≤14 days before the first dose of study drug

Treatment

- Approximately 60 patients will receive tislelizumab 200 mg by IV infusion every 3 weeks (Q3W; Day 1 of each 21-day cycle)
  - Dose delays or interruptions of less than 12 weeks will be permitted; dose reductions are not permitted
- Treatment will be administered until disease progression, intolerable toxicity, or withdrawal for other reasons
  - Treatment beyond the initial investigator-assessed, RECIST v1.1-defined disease progression is permitted provided that the patient has investigator-assessed clinical benefit and is tolerating tislelizumab

Study Assessments and Statistical Analysis

- Tumor assessment will occur at baseline, after 9 weeks following initial assessment, every 6 weeks for the first year, and every 12 weeks thereafter
- Clinical response will be assessed by the IRC using RECIST v1.1 criteria
- Safety/tolerability profile of tislelizumab will be assessed by monitoring the incidence and severity of adverse events according to National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5, and by physical examinations, electrocardiograms, vital signs, and laboratory test results

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