A PHASE 3, RANDOMIZED, OPEN-LABEL, MULTICENTER STUDY TO COMPARE THE EFFICACY AND SAFETY OF TISLELIZUMAB, AN ANTI-PD-1 ANTIBODY, VERSUS SORAFENIB AS FIRST-LINE TREATMENT IN PATIENTS WITH ADVANCED HEPATOCELLULAR CARCINOMA

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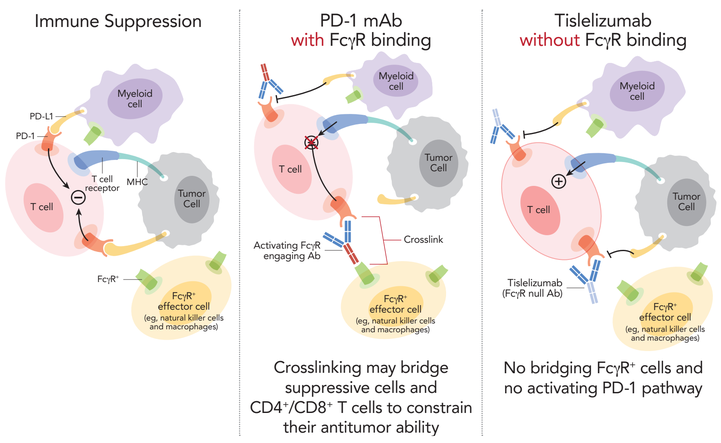
BACKGROUND

- Hepatocellular carcinoma (HCC) is a leading cause of cancer-related death,[1] with more than two-thirds of patients presenting with advanced disease at diagnosis[2]
- The multitargeted tyrosine kinase inhibitor sorafenib is currently the only globally approved first-line treatment for advanced HCC[3]; however, it has shown only modest efficacy in HCC and is difficult for patients to tolerate[4]
- Monoclonal antibodies against the immune checkpoint inhibitory receptor programmed cell death-1 (PD-1) have demonstrated antitumor activity across multiple malignancies,[5] including HCC[6,7]
- Tislelizumab (also known as BGB-A317) is a humanized, IgG4 monoclonal antibody with high affinity and binding specificity for PD-1
- Tislelizumab is specifically engineered to minimize FcγR binding on macrophages that, based on preclinical evidence, is believed to minimize potentially negative interactions with other immune cells (**Figure 1**)
- In a first-in-human, phase 1A/1B study (NCT02407990), single-agent tislelizumab was generally well tolerated and showed evidence of antitumor activity in patients with advanced solid tumors, including HCC.[8–12] Phase 2 and 3 studies in patients with solid tumors are ongoing
- A recommended phase 3 dose of 200 mg administered intravenously (IV) every 3 weeks (Q3W) has been established for tislelizumab

Figure 1: Lack of FcγR Binding Prevents Macrophage-Mediated T-Cell Clearance



Adapted from Dahan, et al. *Cancer Cell*. 2015;28:285–295.

Abbreviations: Ab, antibody; CD, cluster of differentiation; FcγR, Fc-gamma receptor; mAb, monoclonal antibody; MHC, major histocompatibility complex; PD-1, programmed cell death-1; PD-L1, programmed death-ligand 1.

METHODS

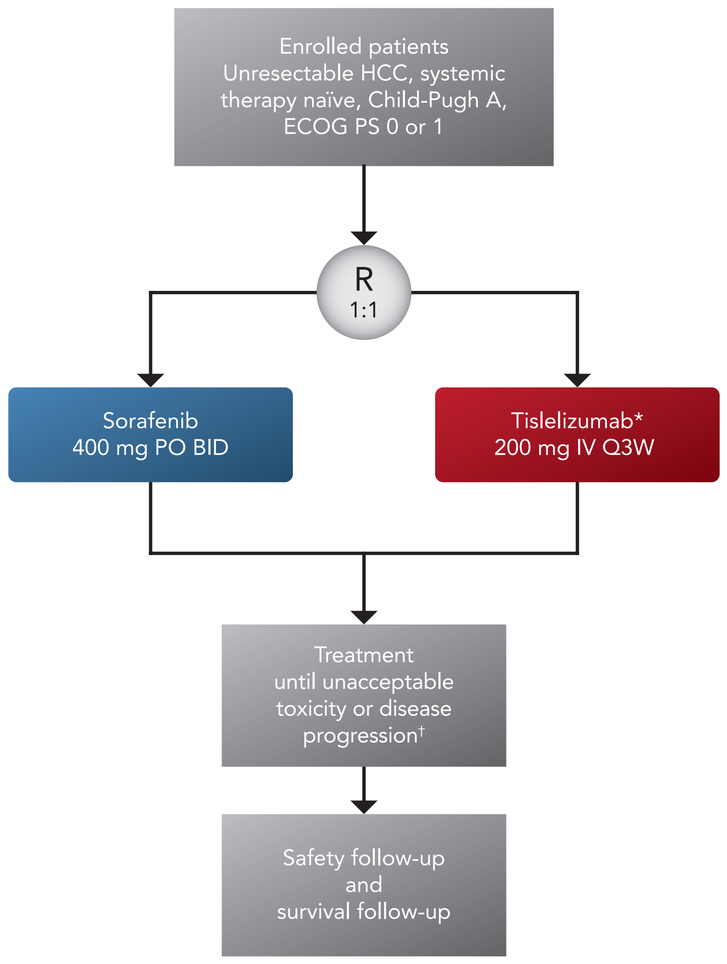
Overall Design and Study Endpoints

- This global, phase 3, randomized, multicenter study (NCT03412773) was designed to evaluate the efficacy and safety of tislelizumab compared with sorafenib as a first-line treatment of advanced HCC (**Figure 2**)
- The primary endpoint will be to compare overall survival (OS) between the two treatment groups
- ORR, as assessed by blinded independent review committee per RECIST v1.1, is a key secondary endpoint
- Other secondary endpoints will include a comparison of tislelizumab and sorafenib in terms of various efficacy assessments (progression-free survival [PFS], duration of response [DoR], time to progression [TTP], disease control rate [DCR], and clinical benefit rate [CBR]), measures of health-related quality of life, and safety and tolerability
- Approximately 640 patients will be enrolled globally

Study Population

- Adult patients, aged ≥18 years, will be enrolled if:
  - Unresectable, histologically confirmed HCC
  - An Eastern Cooperative Oncology Group (ECOG) score ≤1 and Child-Pugh A classification
  - Barcelona Clinic Liver Cancer (BCLC) Stage C disease or BCLC Stage B disease that is not amenable to, or has progressed after, loco-regional therapy, and is not amenable to a curative treatment approach
  - Not received prior systemic therapy

Figure 2: Study Design



Randomization stratified by: macrovascular invasion (present vs absent); extrahepatic spread (present vs absent); ECOG PS (0 vs 1); etiology (HCV vs other [includes HBV]); geography (Asia vs Japan vs Rest of World).

*The initial infusion (Cycle 1, Day 1) will be administered over 60 minutes; if well tolerated, subsequent infusions may be administered over 30 minutes. After tislelizumab infusion, patients will be monitored for 2 hours during Cycles 1 and 2, and for ≥30 minutes from Cycle 3 onward.

†Treatment beyond the initial investigator-assessed disease progression will be permitted in both treatment arms if pseudo progression is suspected or there is reasonable belief that the patient could derive benefit from the treatment.

Abbreviations: BID, twice daily; ECOG PS, Eastern Cooperative Oncology Group performance status; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IV, intravenously; PO, orally; 3W, once every 3 weeks; R, randomization.

- Patients will be excluded if:
  - Known fibrolamellar HCC, sarcomatoid HCC, or mixed cholangiocarcinoma and HCC histology
  - Tumor thrombus involving the main trunk of the portal vein or inferior vena cava
  - Received loco-regional therapy to the liver or any prior immunotherapy within 28 days prior to randomization, or any Chinese herbal medicine or patent medicine used to control cancer within 14 days of randomization
  - Grade 2 or higher hepatic encephalopathy (at screening or prior history)
  - Pericardial effusion, uncontrollable pleural effusion, or clinically significant ascites at screening

TREATMENT

- Patients will be randomized 1:1 to receive tislelizumab 200 mg IV Q3W or sorafenib 400 mg orally twice daily, with randomization stratified by the presence of macrovascular invasion, the presence of extrahepatic spread, ECOG performance status, etiology, and geography
- Treatment will be administered until disease progression, intolerable toxicity, or treatment discontinuation for other reasons

STUDY ASSESSMENTS AND STATISTICAL ANALYSIS

- Tumor response will be evaluated every 9 weeks during Year 1 and every 12 weeks from Year 2 onwards, in accordance with RECIST v1.1
- The primary efficacy endpoint of OS for tislelizumab versus sorafenib will be assessed for non-inferiority
- Secondary endpoints (such as ORR, PFS, DoR, and TTP assessed by a blinded independent review committee) will be evaluated for treatment comparisons
- All tests will be performed at one-sided α=0.025 (or 2-sided α=0.05)
- Safety and tolerability (a secondary endpoint) will be assessed by monitoring adverse events (AEs), including immune-related AEs, and through physical examinations, vital signs, and electrocardiograms
- The European Organisation for Research and Treatment of Cancer Quality of Life Cancer Questionnaire-Hepatocellular Carcinoma 18 Questions (EORTC QLQ-HCC18) and European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 will be used to assess health-related quality of life between the two treatment arms using a mixed model. The European Quality of Life 5-Dimensions will also be summarized

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