A PHASE 2, OPEN-LABEL, MULTICENTER STUDY TO INVESTIGATE THE EFFICACY, SAFETY, AND PHARMACOKINETICS OF THE ANTI-PROGRAMMED CELL DEATH RECEPTOR-1 (PD-1) MONOCLONAL ANTIBODY TISLELIZUMAB (BGB-A317) IN PATIENTS WITH UNRESECTABLE HEPATOCELLULAR CARCINOMA

Ann-Lii Cheng[1], Ghassan K. Abou-Alfa[2], Zhenggang Ren[3], Eric Assenat[4], Antonio Cubillo[5], Stefan Pluntke[6], Lorenza Rimassa[7], Paul J. Ross[8], Lucjan Wyrwicz[9], Jeannie Hou[10], Cindy Li[11], John Wu[12], Michel Ducreux[13]

[1]National Taiwan University Hospital, Taipei, Taiwan; [2]Memorial Sloan Kettering Cancer Center, New York, NY; [3]Zhongshan Hospital, Fudan University, Shanghai, China; [4]CHRU Saint Eloi, Montpellier, France; [5]HM Universitario Sanchinarro, Centro Integral Oncológico Clara Campal (CIOCC), Madrid, Spain; [6]Kliniken Essen-Mitte, Essen, Germany; [7]Humanitas Clinical and Research Center, Rozzano, Italy; [8]Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom; [9]Centrum Onkologii-Instytut im. M. Sklodowskiej Curie, Warszawa, Poland; [10]BeiGene USA, Inc., Emeryville, CA; [11]BeiGene (Beijing) Co., Ltd., Chaoyang District, Beijing, China; [12]BeiGene, Ltd., Fort Lee, NJ; [13]Gustave Roussy, Villejuif, France

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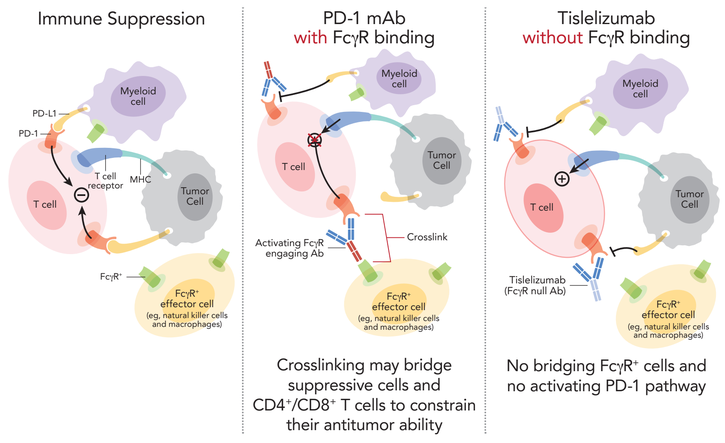
BACKGROUND

- Hepatocellular carcinoma (HCC) is a leading cause of cancer-related mortality.[1] Most patients present with unresectable disease at diagnosis,[2] leaving few treatment options
- Immune checkpoints have gained attention as potential targets in HCC with several immune checkpoint inhibitors including PD-1, programmed cell death protein ligand-1 (PD-L1), and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) currently targeted for HCC treatment[3]
- The expression of PD-L1 is also significantly increased in tumor cells and tumor-associated immune cells in the presence of stimulating cytokines[3]
- Monoclonal antibodies against PD-1 have demonstrated antitumor activity in HCC[4]
- Tislelizumab (also known as BGB-A317) is a humanized IgG4 monoclonal antibody with high affinity and specificity for PD-1 that was specifically engineered to minimize FcγR binding on macrophages, thereby abrogating antibody-dependent phagocytosis, a potential mechanism of T-cell clearance (**Figure 1**)
- A first-in-human, phase 1A/1B study (NCT02407990) demonstrated that single-agent tislelizumab was generally well tolerated and had preliminary antitumor effects in patients with solid tumors, including HCC.[5–7] Other trials in patients with HCC are ongoing[8]
- A recommended phase 2 dose of 200 mg tislelizumab administered intravenously (IV) every 3 weeks (Q3W) has been established

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

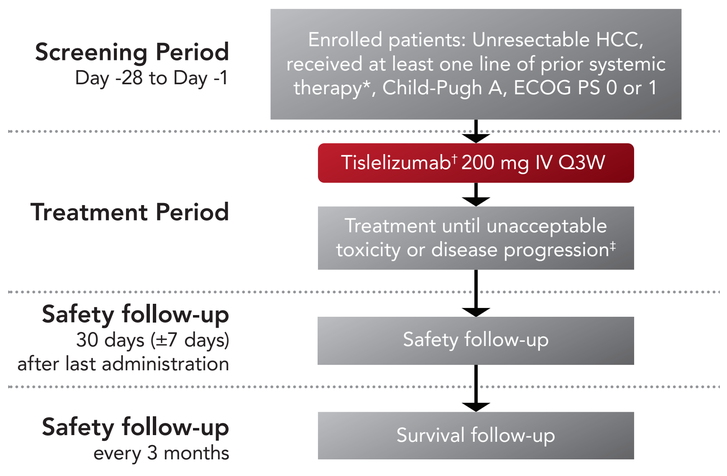
Overall Design and Study Objectives

- This phase 2, open-label, multicenter study (NCT03419897) was designed to evaluate the efficacy, safety, tolerability, and pharmacokinetics of tislelizumab in patients with previously treated unresectable HCC
- The primary endpoint will be endpoint response rate (ORR), as assessed by an Independent Review Committee (IRC)
- Secondary endpoints will include efficacy assessments (such as duration of response [DoR], progression-free survival [PFS], disease control rate [DCR], clinical benefit rate [CBR], and overall survival [OS]), along with safety and tolerability, and health-related quality of life
- The pharmacokinetics of tislelizumab will also be evaluated
- Two hundred twenty-eight patients will be enrolled globally

Study Population

- Patients who are ≥18 years of age with histologically confirmed, unresectable HCC will be enrolled if they meet the following criteria:
  - Have Barcelona Clinic Liver Cancer (BCLC) Stage C disease or BCLC Stage B disease that is not amenable to or has relapsed after locoregional therapy, and is not amenable to a curative treatment approach
  - Have a Child-Pugh classification A
  - Have an Eastern Cooperative Oncology Group performance status (ECOG PS) ≤1
  - Have received at least one line of prior systemic therapy containing either sorafenib, an experimental therapy that has demonstrated efficacy in a phase 3 study, or chemotherapy (oxaliplatin-based regimen)

Figure 2: Study Design



*At least 100 patients will be enrolled who have had no more than one line of prior systemic therapy and at least 100 patients will be enrolled who have had at least two lines of prior systemic therapy.

†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 at least 1 hour after infusion during Cycles 1 and 2, and for at least 30 minutes from Cycle 3 onward.

‡Treatment beyond the initial investigator-assessed disease progression will be permitted if pseudo progression is suspected or if patients have evidence of clinical benefit.

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; HCC, hepatocellular carcinoma; IV, intravenously; Q3W, once every 3 weeks.

- Patients will be excluded if they have the following:
  - Participated in a prior clinical trial by the sponsor for the treatment of HCC
  - Known fibrolamellar HCC, sarcomatoid HCC, or mixed cholangiocarcinoma and HCC
  - Prior therapies targeting PD-1 or PD-L1
  - Known brain or leptomeningeal metastasis
  - Locoregional therapy to the liver (within 4 weeks of enrollment)
  - Sorafenib, regorafenib, Chinese herbal medicine, or Chinese patent medicines to control cancer within 14 days of study drug administration, and any chemotherapy or immunotherapy within 28 days or 5 half-lives of study drug administration
  - Tumor thrombus involving the main trunk of the portal vein
  - Grade 2 or higher hepatic encephalopathy (prior history or at screening)
  - Clinically significant ascites
  - Active autoimmune diseases or history of autoimmune diseases that may relapse
  - Any condition requiring systemic treatment with corticosteroids (>10 mg daily of prednisone or equivalent) or other immunosuppressive medication within 14 days of study drug administration
  - A history of interstitial lung disease, non-infectious pneumonitis, or uncontrolled systemic diseases
  - A known history of HIV infection
  - Prior allogeneic stem cell transplantation or organ transplantation
  - Cardiovascular risk factors, such as cardiac chest pain or symptomatic pulmonary embolism, within 28 days prior to study drug administration, or a history of acute myocardial infarction, history of heart failure meeting New York Heart Association (NYHA) Classification III or IV, any event of ventricular arrhythmia grade ≥2, or a history of cerebrovascular accident, all within 6 months before study drug administration

TREATMENT

- After screening, eligible patients will receive tislelizumab 200 mg IV Q3W until intolerable toxicity, withdrawal of informed consent, or until they are no longer benefiting from therapy as assessed by the investigator (**Figure 2**)
- There will be no dose reduction of tislelizumab in this study; dose delays or interruptions of less than 12 weeks will be permitted

STUDY ASSESSMENTS AND STATISTICAL ANALYSIS

- Radiological assessments of tumor response status will be performed every 9 weeks in the first year and then every 12 weeks thereafter, with tumor response assessed by an IRC and by investigators
- ORR, defined as complete response (CR) plus partial response (PR) based on RECIST v1.1 as evaluated by an IRC, will be assessed as the primary efficacy endpoint; significance will be determined if the one-sided *P*-value is ≤0.025
- Secondary efficacy endpoints will include DoR, PFS, DCR, and CBR evaluated by the IRC or investigators; OS and ORR will be assessed by the investigators; time event variables will be analyzed using the Kaplan–Meier method
- Safety and tolerability assessments, also a secondary endpoint, will include monitoring of adverse events (AEs) occurring up to 30 days after the last dose of the study drug or until initiation of a new anticancer treatment, and immune-related AEs occurring up to 90 days after the last dose of the study drug. Physical examinations, vital signs, laboratory measurements, and electrocardiograms will also be assessed
- Health-related quality of life will be assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Hepatocellular Carcinoma 18 Questions index score, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 index-score, and the 5-level version of the European Quality of Life 5-Dimensional Questionnaire
- Tislelizumab plasma concentrations will be used in pharmacokinetic analyses for all patients

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