Efficacy, Safety, and Pharmacokinetics of the Anti-Programmed Cell Death Receptor-1 Monoclonal Antibody, Tislelizumab (BGB-A317), in a Phase 2, Open-label, Multicenter Study in Patients with Unresectable Hepatocellular Carcinoma: A Trial-in-Progress

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INTRODUCTION

- Hepatocellular carcinoma (HCC) is a leading cause of cancer-related death worldwide,[1] with more than two-thirds of patients presenting with advanced disease at diagnosis[2]
- Immune checkpoints have gained attention as potential targets in HCC with several immune checkpoint inhibitors including programmed cell death protein 1 (PD-1), PD ligand 1 (PD-L1), and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) currently targeted for HCC treatment[3]
- Expression of PD-L1 is also significantly increased in HCC tumor cells and tumor-associated immune cells in the presence of stimulating cytokines[3], and monoclonal antibodies against PD-1 have demonstrated antitumor activity in HCC[4]

TISLELIZUMAB: AN ANTI-PD-1 ANTIBODY

- Tislelizumab (also known as BGB-A317) is a humanized, IgG4 monoclonal antibody with high affinity and binding specificity for PD-1
- Tislelizumab was specifically engineered to minimize binding to FcγR on macrophages, thereby abrogating antibody-dependent phagocytosis, a potential mechanism of T-cell clearance and resistance to anti-PD-1 therapy (**Figure 1**)

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

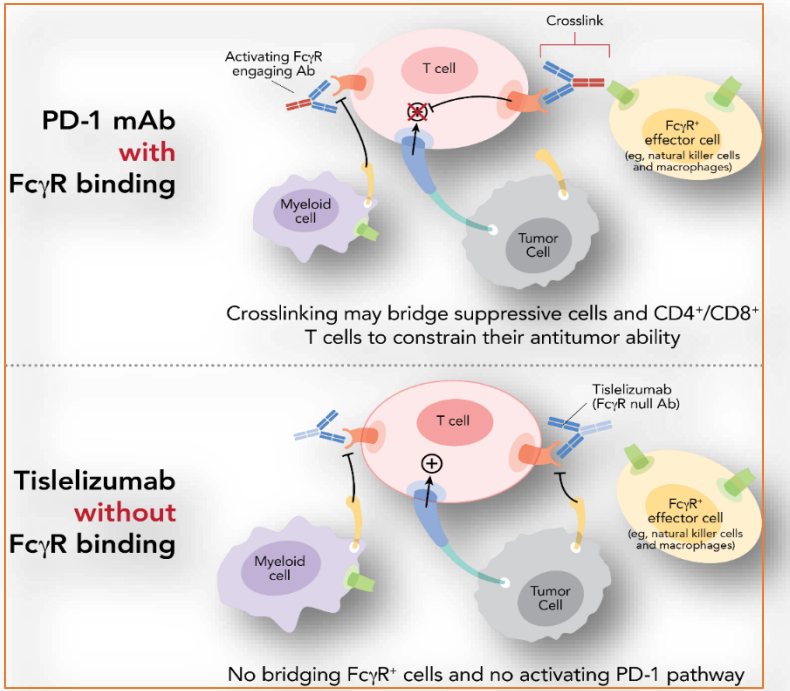
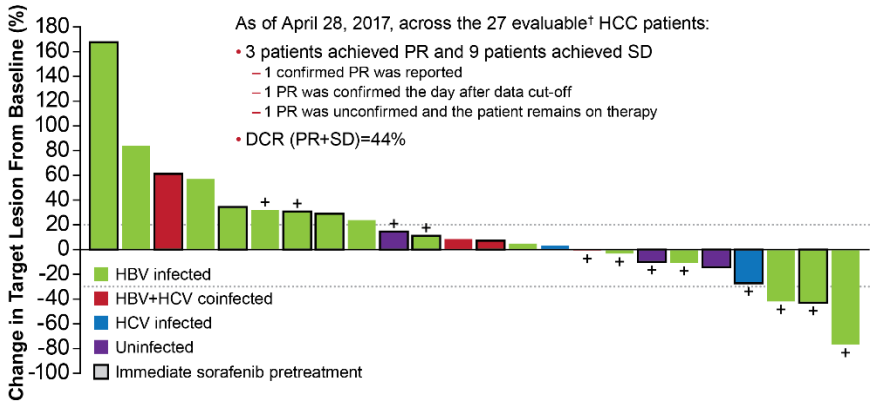


Figure modified from Dahan R, et al. *Cancer Cell*. 2015;28:285–295.

ANTITUMOR ACTIVITY OF TISLELIZUMAB AS SINGLE-AGENT TREATMENT FOR HCC

- In a first-in-human, phase 1A/1B study (NCT02407990), single-agent tislelizumab was generally well tolerated and demonstrated evidence of antitumor activity in patients with solid tumors, including HCC (**Figure 2**)[5]
  - Recommended dose for registration of 200 mg administered intravenously (IV) every 3 weeks (Q3W) has been established for tislelizumab
- Clinical trials evaluating tislelizumab in patients with HCC are ongoing, including a global phase 3 study (see ILCA 2018 P-207)[6]

Figure 2: Maximum Tumor Reduction by Hepatitis Infection Status*



+ Indicates patient still on treatment; *Includes 24 of 25 evaluable patients; 1 patient, who progressed due to a new lesion, had no post-baseline target lesion measurement; †Evaluable is defined as a patient who had at least 1 tumor assessment after enrolment on study or had progressed or died prior to the initial tumor assessment after enrollment on study or had progressed or died prior to the initial tumor assessment.

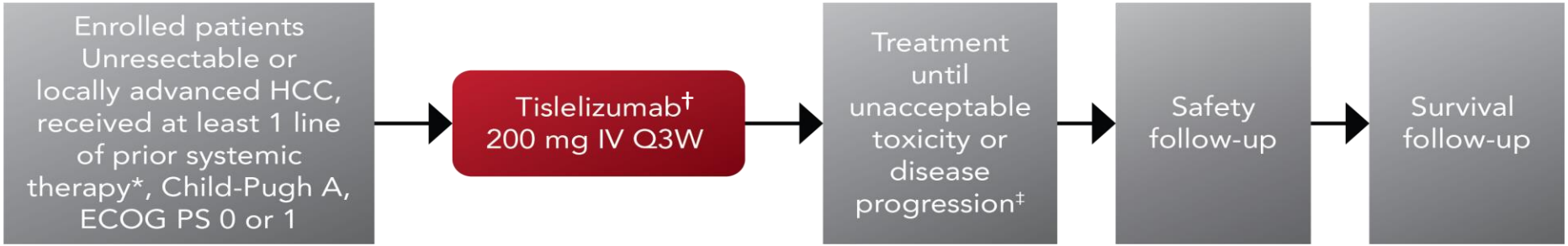
Abbreviations: DCR, disease control rate; PR, partial response; SD, stable disease.

Figure from Yen et al. 2017. *Ann Oncol.* 28 (suppl_3).

OVERALL STUDY DESIGN

- 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 (**Figure 3**)
  - A total of 228 patients will be enrolled globally

Figure 3: 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 ad ministered 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.

STUDY ENDPOINTS

- The primary endpoint will be objective response rate (ORR), as assessed by Independent Review Committee (IRC) per RECIST v1.1
- Duration of response (DOR), as assessed by IRC per RECIST v1.1, is a key secondary endpoint
- Other secondary endpoints will include:
  - Efficacy assessments (eg, progression-free survival [PFS], disease control rate [DCR], and clinical benefit rate [CBR] by IRC and by the investigators; ORR and DoR by the investigators and overall survival [OS])
  - Measures of health-related quality of life
  - Safety and tolerability profile
- Pharmacokinetic profile will also be evaluated as an exploratory endpoint

STUDY POPULATION

Key Inclusion Criteria

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

Key Exclusion Criteria

- 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 any prior therapies targeting PD-1 or PD-L1, locoregional therapy to the liver (within 4 weeks of enrollment), sorafenib, regorafenib, or any Chinese herbal or patent medicines to control cancer within 14 days of enrollment, chemotherapy, investigational therapies or immunotherapy within 28 days prior to enrollment
- Grade ≥2 hepatic encephalopathy (at screening or prior history), or known brain or leptomeningeal metastasis
- Active or history of autoimmune diseases that may relapse, history of HIV infection, clinically significant ascites at screening or 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

STUDY TREATMENT

- After screening, eligible patients will receive tislelizumab 200 mg IV Q3W
- Treatment will be administered until disease progression, intolerable toxicity, or treatment discontinuation for other reasons
- There will be no dose reduction of tislelizumab allowed in this study; dose delays or interruptions of less than 12 weeks will be permitted

STUDY ASSESSMENTS AND STATISTICAL ANALYSIS

- Tumor response will be evaluated every 6 weeks in the first 18 weeks and every 9 weeks thereafter, with tumor response assessed by an IRC and by investigators
- The primary efficacy endpoint (ORR) is defined as complete response (CR) plus partial response (PR) based on RECIST v1.1 as evaluated by an IRC
  - Significance will be determined if the one-sided P-value is ≤0.025
- Secondary endpoints (eg, PFS, DoR, DCR, and CBR) will be evaluated by the IRC and investigators; OS and ORR will be assessed by the investigators; time-to-event variables will be analyzed using the Kaplan–Meier method
- Safety and tolerability will be assessed by monitoring adverse events (AEs), serious adverse events (SAEs), physical examination, vital signs, ECG, and laboratory assessments
- The European Organisation for Research and Treatment of Cancer Quality of Life Cancer Questionnaire (EORTC QLQ) Hepatocellular Carcinoma 18 Questions (EORTC QLQ-HCC18), EORTC QLQ Core 30 (EORTC QLQ-C30), and 5-level version of the European Quality of Life 5-Dimensional Questionnaire (EQ-5D-5L) will be used to assess health-related quality-of-life
- Tislelizumab plasma concentrations from patients at sites able to adequately perform PK sampling, handling, and processing procedures will be included in pharmacokinetic analyses

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