

# Efficacy and Safety of Tislelizumab, an Anti-PD-1 Antibody, Versus Sorafenib as a Potential First-Line Treatment in Patients With Advanced Hepatocellular Carcinoma in a Phase 3, Randomized, Multicenter Study: A Trial-in-Progress

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# INTRODUCTION

- Hepatocellular carcinoma (HCC) is a leading cause of cancer-related death worldwide,<sup>1</sup> with more than two-thirds of patients presenting with advanced disease at diagnosis<sup>2</sup>
- The multitargeted tyrosine kinase inhibitor, sorafenib, is currently the only globally approved first-line treatment for advanced HCC<sup>3</sup>; however, it has shown only modest efficacy in HCC and is difficult for patients to tolerate<sup>4</sup>
- Monoclonal antibodies against the immune checkpoint inhibitory receptor programmed cell death-1 (PD-1) have demonstrated antitumor activity across multiple malignancies,<sup>5</sup> including HCC<sup>6,7</sup>

# 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

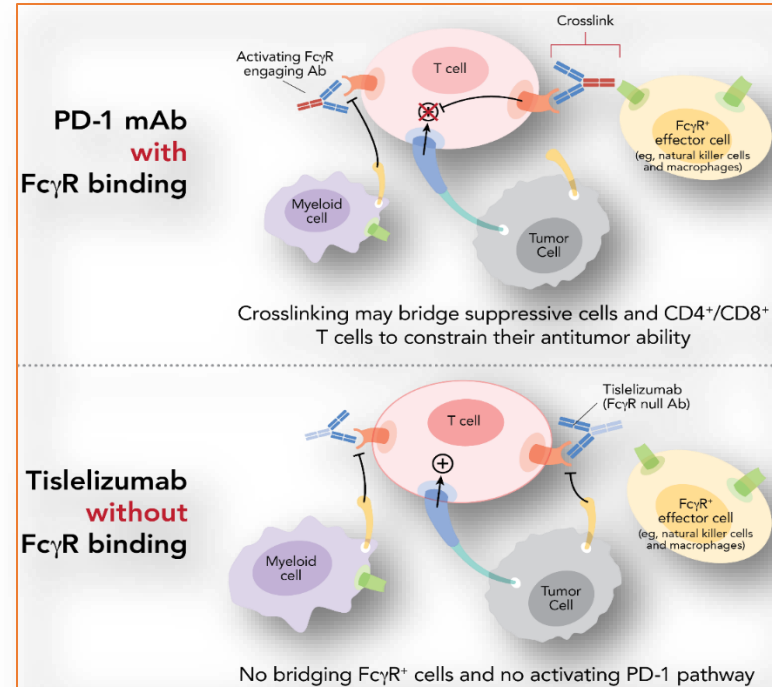


Figure modified from Dahan R, et al. *Cancer Cell*. 2015;28:285–295.

# 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**)<sup>8</sup>
  - Recommended phase 3 dose 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 2 study (see ILCA 2018 P-204)<sup>9</sup>

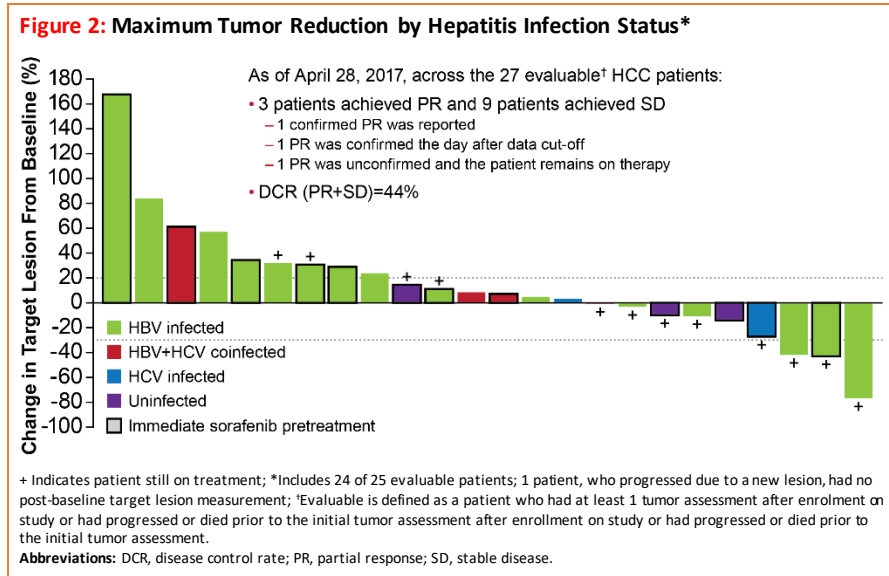
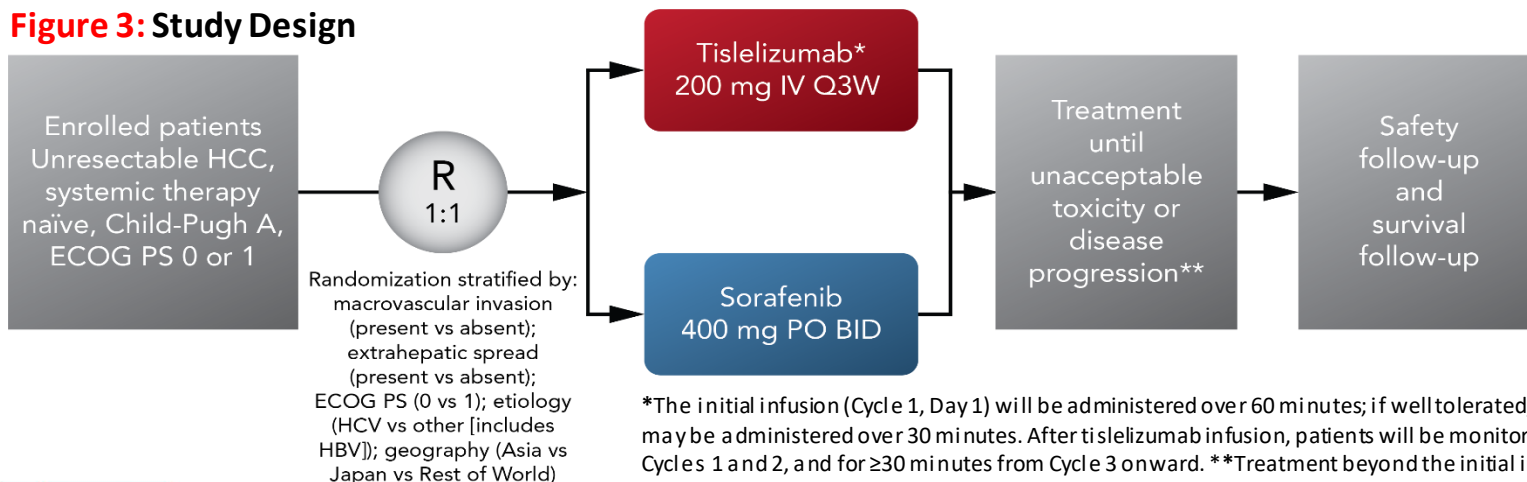


Figure from Yen et al. 2017. *Ann Oncol.* 28 (suppl\_3):iii13-iii136.

# OVERALL STUDY DESIGN

- 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 3**)
  - Approximately 640 patients will be enrolled globally

**Figure 3: Study Design**



\*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  $\geq 30$  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.

# STUDY ENDPOINTS

- The primary endpoint will be to compare overall survival (OS) between the two treatment groups
- Objective response rate (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 including:
  - Efficacy (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
  - Safety and tolerability profile

# STUDY POPULATION

## Key Inclusion Criteria

- Adult patients, aged  $\geq 18$  years, will be enrolled if they have:
  - Unresectable, histologically confirmed HCC
  - An ECOG score  $\leq 1$  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

## 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 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

# TREATMENTS

- Patients will be randomized 1:1 to receive tislelizumab 200 mg IV Q3W or sorafenib 400 mg orally twice daily
  - Randomization will be stratified by the presence of macrovascular invasion, presence of extrahepatic spread, ECOG performance status, etiology, and geography
- Treatment will be administered until intolerable toxicity, withdrawal of informed consent, or the time point at which, in the opinion of the Investigator, the patient is no longer benefiting from study therapy



# 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 (OS) for tislelizumab versus sorafenib will be assessed at the interim and final analyses
- Secondary endpoints (eg, ORR, PFS, DoR, and TTP) will be evaluated for treatment comparisons
  - All tests will be performed at one-sided  $\alpha=0.025$  or 2-sided  $\alpha=0.05$
- Safety and tolerability 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 (EORTC QLQ) Hepatocellular Carcinoma 18 Questions and EORTC QLQ 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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