A Phase II study of the efficacy and safety of tislelizumab plus lenvatinib in patients with advanced or metastatic hepatocellular carcinoma: results of safety run-in period

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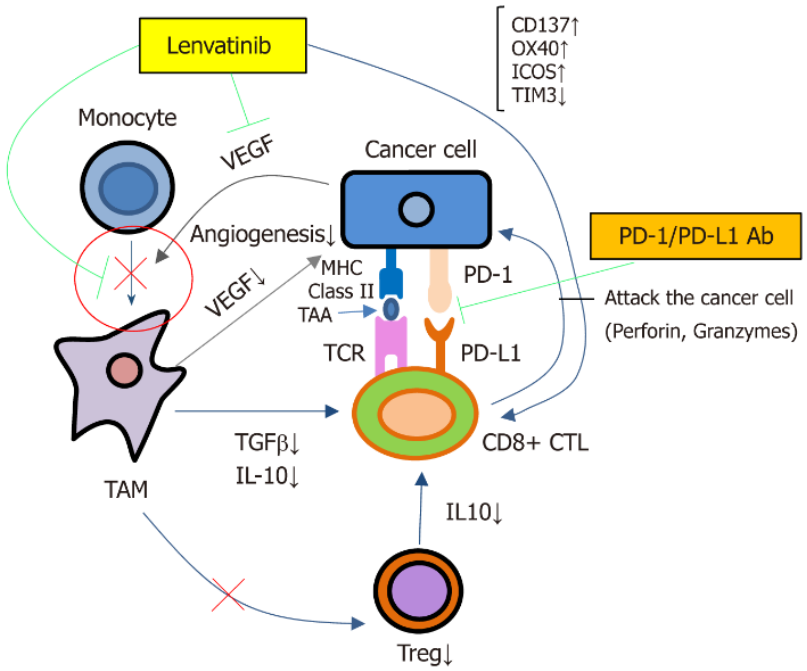
Introduction

- The effectiveness of monotherapy for advanced HCC is relatively limited, combination therapy is the development direction
- Lenvatinib, an oral small-molecule multikinase inhibitor, was approved as a first-line therapy for unresectable HCC
- Tislelizumab, an anti-PD-1 mAb, has preliminarily shown promising efficacy in HCC as monotherapy with acceptable safety profile[1,2]
- Lenvatinib has potential synergistical effects with immunotherapy, and the combined therapy with tyrosine kinase inhibitors (TKIs) and anti-PD-1 antibodies may improve the prognosis of patients with advanced HCC[3]

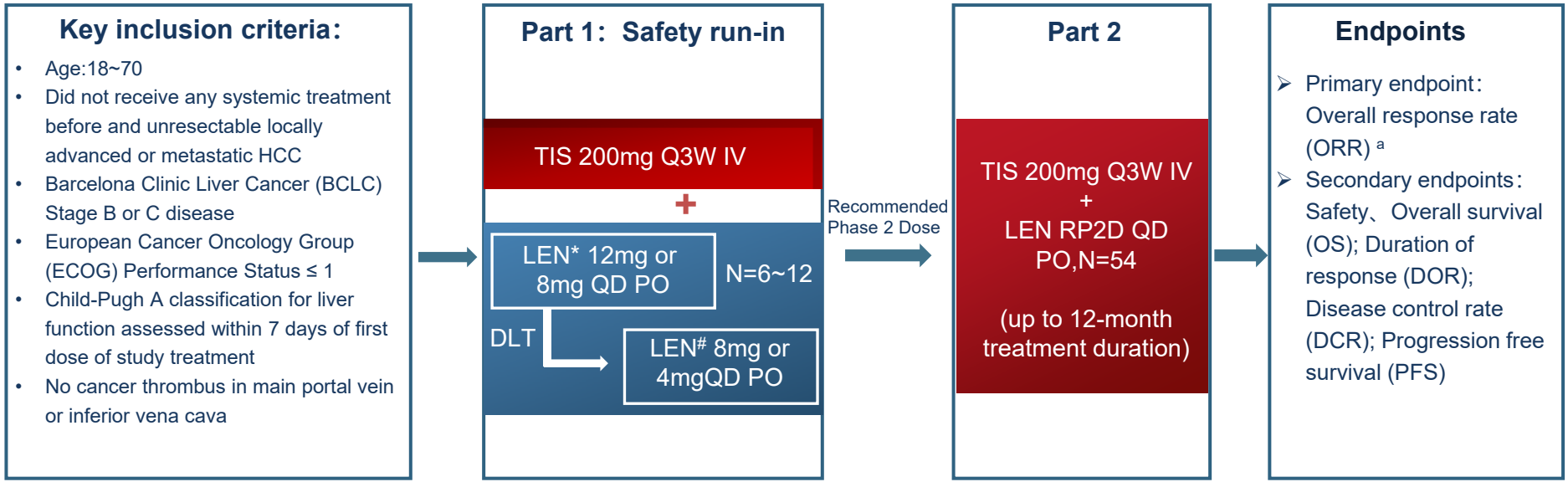


Lenvatinib + PD-1/PD-L1 antibody act synergistically to blocks PD-1/PD-L1 and inhibits formation of an immunosuppressive microenvironment [3]

1. Jayesh Desai, et al. J Immunother Cancer. 2020 Jun;8(1):e000453; 2. Lin Shen, et al. J Immunother Cancer. 2020 Jun;8(1):e000437; 3. Masatoshi Kudo, World J Gastroenterol 2019 February 21; 25(7): 789-807.

Study Design (BGB-A317-211)

A Phase 2 Study to Investigate the Preliminary Antitumor Activity, Safety and Tolerability of Tislelizumab in Combination with Lenvatinib in Patients with Unresectable Locally Advanced or Metastatic Hepatocellular Carcinoma

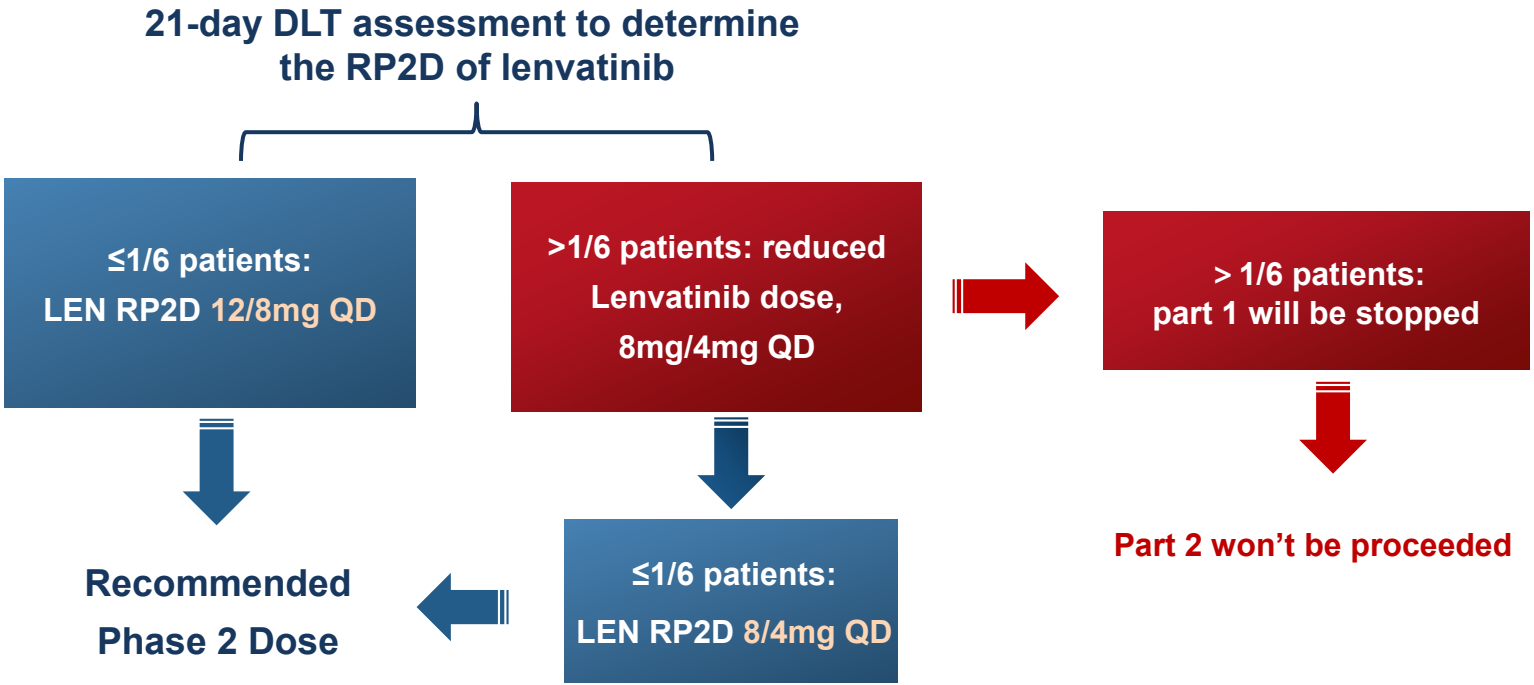


All patients will receive study treatments until confirmed progressive disease (iCPD) assessed by investigator based on iRECIST, unacceptable toxicity, 12-month treatment duration completion, death, withdrawal of consent, study termination by sponsor or patients meet any discontinuation criterion described in protocol.

* lenvatinib dose: body weight ≥ 60 kg (3 subjects enrolled), 12mg; < 60 kg (3 subjects enrolled), 8mg; # reduced lenvatinib dose : body weight ≥ 60 kg, 8mg; < 60 kg, 4mg;

[a] objective response rate (ORR) assessed by the Independent Imaging Review Committee per RECIST v1.1; TIS, Tislelizumab; LEN, Lenvatinib; DLT, dose limiting toxicity; QD, once a day; Q3W, every 3 weeks; PO, orally; IV, intravenous injection; SMC, Safety Monitoring Committee

Recommended Phase 2 Dose (RP2D)



LEN: Lenvatinib;

Dose Limiting Toxicity (DLT) Definition

Any of the following toxicities occurring during the DLT assessment window and considered by the investigator to be related to lenvatinib and/or tislelizumab

Hematologic	Non-Hematologic
➢ **Grade 4 neutropenia lasting > 7 days** ➢ **≥ Grade 3 febrile neutropenia** ➢ **Grade 3 thrombocytopenia with clinically significant bleeding** ➢ **Grade 4 thrombocytopenia lasting > 3 days and requiring transfusion, or any decreased platelet count < 15,000/mm^3 or < 15.0 x 10^9/L** ➢ **≥ Grade 4 anemia**	➢ **≥ Grade 4 toxicity** ➢ **Grade 3 toxicity that is clinically significant and does not resolve to baseline or ≤ Grade 1 within 7 days of initiating optimal supportive care** **Note: The following AEs will not be considered DLTs:** ✓ Grade 3 endocrinopathy that is adequately controlled by hormonal replacement ✓ Grade 3 of tumor flare (defined as local pain, irritation, or rash localized at sites of known or suspected tumors) ✓ Grade 3 rash ✓ Grade 3 infusion-related AE that is transient (resolving within 6 hours of onset) ✓ Grade 3 hypertension that is resolving within 7 days of optimal supportive care ✓ Clinically insignificant or transient abnormal laboratory findings, including but not limited to following : • Grade 3-4 alanine aminotransferase elevation, aspartate aminotransferase elevation or hyperbilirubinemia without significant related clinical symptoms and judged by investigators and medical monitors as non-fatal risk • Grade 3-4 hyperamylasemia or hyperlipasemia that is not associated with symptoms or clinical manifestations of pancreatitis and judged by investigators and medical monitors as non-fatal risk • Grade 3 proteinuria that is resolving within 7 days of optimal supportive care

DLT, dose limiting toxicity; Adverse events graded per CTCAE v5.0

Demographics and Baseline Disease Characteristics

	Total (N = 6)
Sex, n (%)	
Male	5 (83.3)
Female	1 (16.7)
Age (years)	
Median (range)	48.5 (32- 65)
Age Group, n (%)	
< 65 years	5 (83.3)
≥65 years	1 (16.7)
Weight (kg)	
Median (range)	59.75 (39.0- 73.5)

	Total (N = 6)
ECOG PS, n (%)	
0	4 (66.7)
1	2 (33.3)
BCLC，n (%)	
C	6 (100.0)
Hepatitis B, n (%)	
Yes	6 (100.0)
No	0 (0.0)
Hepatitis C, n (%)	
Yes	0 (0.0)
No	6 (100.0)

ECOG PS : Eastern Cooperative Oncology Group Performance Status; BCLC : Barcelona Clinic Liver Cancer
Body weight < 60kg: 3 patients (39.0, 56.5 and 59.0kg), received 8 mg lenvatinib; Body weight ≥60kg: 3 patients (60.5, 63.0 and 73.5kg), received 12 mg lenvatinib.

Data cutoff: 24DEC2020

Study Treatment Exposure

	Tislelizumab(N=6)	Lenvatinib(N=6)
Duration of Exposure (days)		
Median	43.5	43.0
Min, Max	21,87	21,87
Actual Cumulative Dose Administered (mg)		
Median	500.0	420.0
Min, Max	200, 1000	168, 1020
Patients with Dose Modification*, n (%)		
Yes	0 (0.0)	0 (0.0)
No	6 (100.0)	6 (100.0)

* Dose modification: dose interruption or delay for tislelizumab, dose interruption or reduction for lenvatinib

Data cutoff: 24DEC2020

Two patients decided to withdraw from the study:

- One after immune unconfirmed progressive disease (iUPD)
- the other when adverse events (**deafness neurosensory and vaginal bleeding, grade 1**) occurred

Summary of Treatment-Emergent Adverse Events (TEAEs)

	Total (N=6) n (%)
Patients With at Least One TEAE	6 (100.0)
Grade 3 or Higher	0 (0.0)
Serious Adverse Events (SAE)	0 (0.0)
Potential Immune-Mediated TEAE (imTEAE)	0 (0.0)
Treatment Related	5 (83.3)
Treatment Related Grade 3 or Higher	0 (0.0)
Treatment Related Leading to Tislelizumab Discontinuation	0 (0.0)
Treatment Related Leading to Lenvatinib Discontinuation	0 (0.0)

AE: adverse event; TEAE: treatment-emergent adverse events

Data cutoff: 24DEC2020

A TEAE is defined as an AE that had an onset date or a worsening in severity from baseline (pretreatment) on or after the first dose of study drug(s) and up to 30 days following study drug(s) discontinuation or initiation of new anti-cancer therapy, whichever occurs first

Summary of Treatment-Emergent Adverse Events (TEAEs)

System Organ Class Preferred Term	Total (N=6) n (%)
Patients with at Least One TEAE	6 (100.0)
Investigations	5 (83.3)
Aspartate aminotransferase increased	3 (50.0)
Blood alkaline phosphatase increased	3 (50.0)
Blood bilirubin increased	2 (33.3)
Alanine aminotransferase increased	1 (16.7)
Bilirubin conjugated increased	1 (16.7)
Blood creatine phosphokinase MB increased	1 (16.7)
Blood creatine phosphokinase increased	1 (16.7)
Blood lactate dehydrogenase increased	1 (16.7)
C-reactive protein increased	1 (16.7)
Gamma-glutamyltransferase increased	1 (16.7)
Platelet count decreased	1 (16.7)
Gastrointestinal disorders	2 (33.3)
Diarrhoea	2 (33.3)

System Organ Class Preferred Term	Total(N=6)n (%)
Renal and urinary disorders	2 (33.3)
Haematuria	1 (16.7)
Proteinuria	1 (16.7)
Vascular disorders	2 (33.3)
Hypertension	2 (33.3)
Ear and labyrinth disorders	1 (16.7)
Deafness neurosensory	1 (16.7)
Metabolism and nutrition disorders	1 (16.7)
Hyperkalaemia	1 (16.7)
Psychiatric disorders	1 (16.7)
Insomnia	1 (16.7)
Reproductive system and breast disorders	1 (16.7)
Vaginal haemorrhage	1 (16.7)

Data cutoff: 24DEC2020

SOC, system organ class; TEAE, treatment-emergent adverse events

Summary of Treatment Related Adverse (TRAEs)

System Organ Class Preferred Term	Total (N=6) n (%)
Patients with at Least One Any Treatment Related TEAE	5 (83.3)
Investigations	3 (50.0)
Aspartate aminotransferase increased	1 (16.7)
Bilirubin conjugated increased	1 (16.7)
Blood alkaline phosphatase increased	1 (16.7)
Blood bilirubin increased	1 (16.7)
Blood creatine phosphokinase MB increased	1 (16.7)
Blood creatine phosphokinase increased	1 (16.7)
Blood lactate dehydrogenase increased	1 (16.7)
C-reactive protein increased	1 (16.7)
Platelet count decreased	1 (16.7)
Reproductive system and breast disorders	1 (16.7)
Vaginal haemorrhage	1 (16.7)

System Organ Class Preferred Term	Total (N=6) n (%)
Renal and urinary disorders	2 (33.3)
Haematuria	1 (16.7)
Proteinuria	1 (16.7)
Vascular disorders	2 (33.3)
Hypertension	2 (33.3)
Ear and labyrinth disorders	1 (16.7)
Deafness neurosensory	1 (16.7)
Gastrointestinal disorders	1 (16.7)
Diarrhoea	1 (16.7)
Metabolism and nutrition disorders	1 (16.7)
Hyperkalaemia	1 (16.7)

Data cutoff: 24DEC2020

SOC, system organ class; TRAE, treatment related adverse

No Dose Limiting Toxicity (DLT) Events Occurred

No DLT event reported by cutoff date; None of the 6 patients experienced DLT by cutoff date.

DLT	Outcome
Total number of DLT events	0
Number (%) of patients with DLT events	0/6 (0%)

DLT: dose limiting toxicity

Data cutoff: 24DEC2020

Summary

Tislelizumab plus lenvatinib shows no dose-limiting toxicity in the first-line treatment of patients with advanced or metastatic HCC, supporting for patients enrollment in the expansion part of this study to further explore the efficacy, safety and tolerability of the combination

- As of December 24, 2020, the median treatment duration of lenvatinib was 43.0 (21~87) .
- 6 patients had reported at least one TEAE, but none were ≥grade 3 or immune-mediated. No SAE were observed.

  5 patients had at least one grade 1 or 2 TRAE including abnormal laboratory tests (n=3), hypertension (n=2), and renal and urinary disorders (n=2).
- No dose limiting toxicities (DLTs) were observed.
- The RP2D of lenvatinib was determined as 12 mg (body weight ≥60 kg) or 8 mg (bodyweight <60 kg), PO, QD.