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

Objectives

Molecular targeted therapy has been reported to be able to act synergistically combined with immunotherapy in hepatocellular carcinoma (HCC). This single-arm, multi-center, phase II clinical study (NCT04401800) aims to evaluate the efficacy and safety of tislelizumab plus lenvatinib combination therapy in patients with advanced or metastatic HCC.

Methods

In this open-label, multicenter study, patients with locally advanced or metastatic HCC without any previous systemic treatment, BCLC stage B or C, Child-Pugh class A, and ECOG PS ≤1 received lenvatinib (bodyweight ≥60 kg: 12 mg/day; <60 kg: 8 mg/day) daily and 200 mg intravenous tislelizumb once every 3 weeks. Tolerability was evaluated by assessing dose-limiting toxicities (DLT) during the first cycle in patients (Part 1, 6~12 patients). Recommended phase II dose of lenvatinib (R2PD) was determined if ≤1/6 patient experienced dose limiting toxicity (DLT) within 21 days. Once tolerability of the combination was confirmed, additional eligible patients will be enrolled to receive lenvatinib (R2PD) plus tislelizumab until disease progression, unacceptable toxicities, or completion of a 12-month treatment duration (part 2).

The primary endpoint was objective response rate (ORR) assessed by the Independent Imaging Review Committee per RECIST v1.1; Secondary and exploratory endpoints included safety, disease control rate (DCR), progression-free survival (PFS), and duration of response (DOR), overall survival (OS), and serum concentration of tislelizumab during the safety run-in period. DLT was defined as the haematological toxicity associated with lenvatinib and/or tislelizumab (grade 4 neutropenia lasting more than 7 days, ≥ Grade 3 febrile neutropenia, ≥ Grade 3 thrombocytopenia with clinically significant bleeding, Grade 4 thrombocytopenia lasting more than 3 days and requiring blood transfusion, or any decreased platelet count <15,000/mm^3 or <15.0x10^9/ L, or ≥ grade 4 anaemia) or non-haematological toxicity (≥ grade 4 or clinically significant grade 3 toxicity that did not relieve to baseline or ≤ grade 1 within 7 days of optimal supportive treatment).

Results

A total of 6 patients were enrolled during the run-in period, with a median age of 48.5 (32-65) years old, and 4 patients with an ECOG score of 0. As of December 24, 2020, the median treatment duration was 43 (21~87) days. No DLT event was observed during the 21-day observation period after the first administration. Therefore, the R2PD of lenvatinib was determined as 12 mg

(body weight ≥60 kg) or 8 mg (bodyweight <60 kg). 6 patients had reported at least one treatment-emergent adverse event (TEAE); while no ≥grade 3 TEAE and no immune-mediated TEAE were observed. 5 of the 6 patients had at least one grade 1 or 2 treatment-related adverse event (TRAE). The TRAEs mainly included abnormal laboratory tests (n=3), hypertension (n=2), and renal and urinary disorders (n=2). Two patients decided to withdraw from the study, one after disease progression and the other after grade 1 sensorineural hearing loss and vaginal bleeding. The average C_{trough} (pre-dose) of tislelizumab in cycle 2 and 5 were 20.9 ± 3.02 μg/mL (n=5) and 37.2 ± 8.24 μg/mL (n=4), respectively.

Conclusion

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.