Safety, Tolerability, and Preliminary Antitumor Activity of Sitravatinib Plus Tislelizumab in Patients With Unresectable Locally Advanced or Metastatic Hepatocellular Carcinoma

Authors: Feng Zhang,[1] Yuxian Bai,[2] Weijia Fang,[3] Zhiqiang Meng,[4] Jianping Xiong,[5] Yabin Guo,[6] Tao Zhang,[7] Jingdong Zhang,[8] Jieer Ying,[9] Zhendong Chen,[10] Zhenggang Ren,[11] Yajin Chen,[12] Chunyi Hao,[13] Liu Yang,[14] Jun Wang,[15] Juan Zhang,[15] Fan Yu,[14] Cong Fei,[14] Xikun Wu,[14] Shukui Qin[16†]

Affiliations: [1]Hubei Cancer Hospital, Wuhan, China; [2]Harbin Medical University Cancer Hospital, Harbin, China; [3]The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, China; [4]Fudan University Shanghai Cancer Center, Shanghai, China; [5]The First Affiliated Hospital of Nanchang University, Nanchang, China; [6]Nanfang Hospital, Southern Medical University, Guangzhou, China; [7]Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; [8]Liaoning Cancer Hospital & Institute, Cancer Hospital of China Medical University, Shenyang, China; [9]Zhejiang Cancer Hospital, Hangzhou, China; [10]The Second Hospital of Anhui Medical Hospital, Hefei, China; [11]Zhongshan Hospital, Fudan University, Shanghai, China; [12]Sun Yat-Sen Memorial Hospital, Sun Yat-Sen University, Guangzhou, China; [13]Beijing Cancer Hospital, Beijing, China; [14]BeiGene (Shanghai) Co., Ltd., Shanghai, China; [15]BeiGene (Beijing) Co., Ltd., Beijing, China; [16]The 81st Hospital of PLA, Nanjing, China

Objectives: Sitravatinib is a selective tyrosine kinase inhibitor that reduces the number of myeloid-derived suppressor and regulatory T cells and increases the ratio of M1/M2-polarized macrophages. This may help to overcome an immunosuppressive tumor microenvironment and augment antitumor responses. Tislelizumab, an anti-programmed cell death protein-1 (PD-1) antibody, has shown activity in multiple advanced solid tumors. This multicohort, phase 1/2 study assessed the safety/tolerability and efficacy of sitravatinib alone or with tislelizumab (BGB-900-104; NCT03941873). We report results from the phase 2 hepatocellular carcinoma (HCC) cohort receiving sitravatinib plus tislelizumab.

Methods: Eligible patients were aged ≥18 years, had unresectable locally advanced or metastatic HCC, had received 1 or 2 prior lines of systemic treatment, had an ECOG PS of 0-1, ≥1 measurable lesion (per RECIST v1.1), and had Barcelona Clinic Liver Cancer (BCLC) stage B or C disease. Patients with anti-PD-1/PD-L1 antibody-naïve HCC must have failed or been ineligible for current standard of care. Patients received sitravatinib 120 mg orally once daily and tislelizumab 200 mg intravenously every 3 weeks. The primary endpoint was objective response rate (ORR) (RECIST v1.1; by investigator). Secondary endpoints included duration of response (DoR), disease control rate (DCR), progression-free survival (PFS) (all per RECIST v1.1; by investigator), and safety and tolerability. Exploratory endpoints included overall survival (OS).

Results: As of July 12, 2021, 43 patients were treated (21 patients were anti-PD-1/PD-L1 antibody-naïve and 22 patients were refractory/resistant [R/R]) and 10 patients (23.3%) remained on treatment. The median age of patients was 55 years (range: 29-71), 88.4% were male, and 74.4% had BCLC stage C disease at study entry. With a median study follow-up of 8.6 months (range: 0.7-10.6), confirmed ORR was 10.0% (four patients) (95% CI: 2.8-23.7); all four patients achieved partial responses. Median DoR and PFS were 5.4 months (95% CI: 4.1-5.7) and 4.8 months (95% CI: 3.2-6.9), respectively. DCR was 85.0% (95% CI: 70.2-94.3). Median OS was not estimable (95% CI: 8.6

months-NE); the landmark OS rate at 9 months was 71.4% (95% CI: 47.2-86.0) and 52.7% (95% CI: 23.2-75.5) in patients with anti-PD-1/PD-L1 antibody-naïve HCC and R/R HCC, respectively. Treatment-emergent adverse events (TEAEs) of any grade/grade ≥3 were reported in 97.7%/48.8% of patients. Serious TEAEs were observed in 27.9% of patients (n=12). The most common grade ≥3 TEAE was palmar-plantar erythrodysesthesia (n=4; 9.3%). Patients experienced ≥1 TEAE that led to discontinuation of sitravatinib (n=4; 9.3%) and tislelizumab (n=4; 9.3%). Dose reductions of sitravatinib due to TEAEs occurred in 15 patients (34.9%).

Conclusions: Sitravatinib plus tislelizumab was tolerable and showed preliminary antitumor activity in pre-treated, advanced HCC. Further investigation in this patient population is warranted.