Safety/tolerability and preliminary antitumor activity of sitravatinib plus tislelizumab in patients with PD-(L)1 refractory/resistant unresectable or metastatic melanoma from a phase 1b study

[1]Chuanliang Cui, [2]Hongming Pan, [3]Matteo Carlino, [4]Jiuwei Cui, [1]Xuan Wang, [5]Cheng Chen, [5]Xiao Xiang, [5]Liu Yang, [1]Jun Guo

[1]Beijing Cancer Hospital, Beijing, China; [2]Sir Run Run Shaw Hospital, Zhejiang University, Hangzhou, China; [3]Blacktown Hospital, Blacktown NSW, Australia; [4]The First Hospital of Jilin University, Changchun, China; [5]BeiGene (Beijing) Co., Ltd., Beijing, China

Background: While PD-(L)1 inhibitors have improved outcomes for melanoma, a substantial proportion of patients do not respond or develop resistance. Sitravatinib, a spectrum-selective TKI targeting TAM receptors (Tyro3/Axl/MerTK) and VEGFR2, reduces the number of myeloid-derived suppressor cells and regulatory T cells while increasing the ratio of M1/M2-polarized macrophages, which may overcome an immunosuppressive tumor microenvironment and augment antitumor immune responses. Tislelizumab, an anti-PD-1 antibody engineered to minimize binding to FcγR on macrophages to abrogate antibody-dependent phagocytosis, has shown clinical activity as a single agent and in combination with chemotherapy in patients with advanced solid tumors, including melanoma.

Methods: We report results from the melanoma cohort of an ongoing multicohort phase 1b study (BGB-900-103; NCT03666143) assessing safety/tolerability and preliminary antitumor activity of sitravatinib + tislelizumab in advanced solid tumors. Eligible patients had unresectable or metastatic melanoma refractory/resistant to PD-(L)1 inhibitors and had not received other prior immunotherapy (eg, anti-CTLA-4, -OXO40, or -CD137) or anti-BRAF/MEK therapy. Patients received oral sitravatinib 120 mg once daily and tislelizumab 200 mg IV Q3W until a discontinuation criterion was met. The primary endpoint was safety/tolerability; key secondary endpoints included investigator-assessed objective response rate (ORR), disease control rate (DCR), and progression-free survival (PFS).

Results: As of Oct 13, 2020, 25 patients were enrolled; 16 patients (64%) remained on treatment. All patients received 1 prior line of PD-(L)1 therapy, median age was 51 years (range: 23-79), and baseline histology included cutaneous (n=12; 48%), acral (n=7; 28%), and mucosal (n=4; 16%) subtypes. Median duration of study follow-up was 5.5 months (range: 1.5-13.3). Adverse events (AEs) were reported in 25 patients (100%); the most

commonly reported grade ≥3 AE was hypertension (n=3; 12%). Serious AEs were reported in 4% (n=1/25) of patients. Dose reductions of sitravatinib due to AEs occurred in 13 patients. No AEs led to death. Six patients achieved a confirmed partial response. Confirmed ORR was 24.0% (95% CI: 9.36-45.13); DCR was 88.0% (95% CI: 68.78-97.45). Median PFS was 6.7 months (95% CI: 4.07, not evaluable).

Conclusions: Sitravatinib + tislelizumab was generally well tolerated, had a manageable safety/tolerability profile, and demonstrated preliminary antitumor activity in patients with refractory/resistant unresectable or metastatic melanoma. Further investigation of sitravatinib + tislelizumab in these patients is warranted.