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

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Background:
PD-(L)1 inhibitors have improved outcomes for melanoma, but many patients do not respond or develop resistance. Sitravatinib, a spectrum-selective tyrosine kinase inhibitor targeting TAM receptors (Tyro3/Axl/MerTK) and VEGFR2, decreases 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 response. Tislelizumab is an anti-PD-1 antibody engineered to minimize binding to FcγR on macrophages to abrogate antibody-dependent phagocytosis. Tislelizumab showed clinical activity as monotherapy and combined with chemotherapy for 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. 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, -OX40, or -CD137) or anti-BRAF/MEK therapy. Patients received oral sitravatinib 120 mg once daily and intravenous tislelizumab 200 mg Q3W until discontinuation. 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 October 13, 2020, 25 patients were enrolled; 16 patients (64%) remained on treatment. All patients received one 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 study follow-up was 5.5 months (range: 1.5-13.3). Adverse events (AEs) were reported in 25 patients (100%); the most common grade ≥3 AE was hypertension (n=3; 12%). One patient (4%) reported serious AEs. Dose reductions of sitravatinib due to AEs occurred in 13 patients. No AEs led to death. Confirmed ORR was 24.0% (95% CI: 9.36-45.13; all partial responses, n=6); 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 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.