A first-in-human phase 1a dose-escalation study of BGB-15025 (HPK1 inhibitor) as monotherapy and in combination with tislelizumab (TIS; anti-PD-1 antibody) in patients (pts) with advanced solid tumors

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Background: Hematopoietic progenitor kinase 1 (HPK1), a critical negative feedback regulator of T-lymphocyte and dendritic cell activation, is a potential target for IO treatment (tx). BGB-15025, a potent, selective, small-molecule HPK1 inhibitor, showed preliminary antitumor effects in preclinical studies as monotherapy (mono tx) and enhanced antitumor effects in combination with TIS. We present dose-escalation results from an open-label, multicenter, phase 1 study (NCT04649385) of BGB-15025 mono tx and in combination with TIS in pts with advanced solid tumors.

Methods: Eligible pts (≥18 yrs) with previously treated (pts with prior exposure to CPIs were eligible) locally advanced/metastatic solid tumors and ECOG PS ≤1 were enrolled. Oral BGB-15025 mono tx was escalated through 7 doses (20 mg QD–240 mg BID); 5 doses (60 mg QD–240 mg QD) were given in combination with TIS 200 mg IV Q3W (combo tx). Primary objectives were assessment of safety and tolerability, determination of the maximum tolerated/administered dose (MTD/MAD) and recommended dose(s) for expansion (RDFE) for mono tx or combo tx. Select secondary and exploratory objectives included preliminary antitumor activity, PK, and PD.

Results: As of Nov 21, 2023, 60 and 49 pts received mono tx and combo tx, respectively (median age: 59.0 yrs and 62.0 yrs; median follow-up: 2.3 months and 2.8 months). Most pts were male (56.7% [mono tx]; 67.3% [combo tx]) and received a median of 2 lines of systemic therapy in the metastatic setting (range: 0–7 [mono tx]; 0–5 [combo tx]). The most common tumors were RCC, NSCLC, cervical cancer, CRC, GC/GEJC, and HNSCC.

The most common TRAEs (**Table**) for mono tx were diarrhea (18.3%), vomiting (15.0%), and blood creatinine increased (15.0%); and for combo tx were nausea (30.6%), diarrhea (28.6%), and fatigue (20.4%). No DLTs were observed with mono tx. 5 DLTs were observed with combo tx (2 ALT/AST increased, 1 colitis, 1 immune-related hepatitis, 1 GGT increased). The MAD was 200 mg BID for mono tx and MTD was 150 mg QD for combo tx. For mono tx, there were no responders and disease control rate (DCR) was 35.0%; 3 pts remained on tx for >6 months (2 pts are still on tx for >60 and 84 weeks). For combo tx, the unconfirmed ORR was 18.4% for all doses combined and 31.3% for RDFE, DCR was 57.1% for all doses combined and 56.3% for RDFE.

Conclusions: These preliminary results show BGB-15025 mono tx or combo tx with TIS was generally tolerable. The antitumor activity of BGB-15025 was improved when given in combination with TIS. Further investigation of BGB-15025 + TIS +/- chemotherapy is ongoing in the expansion phase.

Table

Pts, n (%)	**BGB-15025 (N=60)**	**BGB-15025 + TIS (N=49)**
TRAEs		
Any	42 (70.0)	35 (71.4)
Grade ≥3	7 (11.7)	10 (20.4)
Serious	4 (6.7)	10 (20.4)
Leading to death	0 (0)	0 (0)
Leading to tx discontinuation	0 (0)	6 (12.2)
Immune-related AEs	7 (11.7)	13 (26.5)