A first-in-human, phase 1a, dose-escalation study of BGB-10188, a phosphatidylinositol 3-kinase delta (PI3Kδ) inhibitor, + tislelizumab (anti-PD-1) in patients with solid tumors

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Abstract

Background: PI3Kδ inhibition hampers regulatory T-cell proliferation and function, potentially optimizing $CD8^+$ T-cell activation for antitumor immunity in solid tumors. BGB-10188, a novel PI3Kδ inhibitor, showed high selectivity, potency, and an improved safety profile vs other PI3Kδ inhibitors in preclinical studies. Here, we present the results of BGB-10188 + tislelizumab in patients with solid tumors from the phase 1a dose-escalation part (Part D) of an open-label, multicenter, 5-part phase 1/2 study (NCT04282018).

Methods: Eligible patients were aged ≥18 years with ECOG PS of 0 or 1 and had previously treated unresectable locally advanced or metastatic solid tumors. BGB-10188 was given orally once daily (QD) at 6 dose levels (20, 40, 80, 160, 320, and 540 mg). Tislelizumab 200 mg IV was given on Day 8 of the 28-day Cycle 1 and Day 1 of all subsequent 21-day cycles. Primary objectives were to assess the safety and tolerability of BGB-10188 + tislelizumab. Select secondary/exploratory objectives were to evaluate preliminary antitumor activity, pharmacokinetics, and pharmacodynamics.

Results: As of August 30, 2023, 44 patients were treated with BGB-10188 + tislelizumab (median follow-up: 4.65 months; 3 patients remain on treatment). The median age was 61 years. Patients had a median of 2 prior lines of therapy (range, 1-11) and 97.7% of patients had metastatic disease at study entry. 84.1% (37 of 44) of patients had ≥1 adverse event (AE) related to either study drug. 81.8% (36) of patients had ≥1 BGB-10188-related AE, of which the most common (≥10%) were nausea (22.7%, n=10), decreased appetite (18.2%, n=8), fatigue (18.2%, n=8), alanine aminotransferase (ALT) increased (13.6%, n=6), aspartate aminotransferase (AST) increased (11.4%, n=5), and rash (11.4%, n=5). Two patients discontinued study drug treatment due to BGB-10188-related AEs. Three dose-limiting toxicities for BGB-10188 + tislelizumab were observed: grade (Gr) 5 pneumonia and Gr 5 intracranial hemorrhage at 160 mg, Gr 3 ALT/AST increase at 320 mg, and Gr 3 rash at 540 mg. Maximum tolerated dose was not reached. The confirmed objective response rate was 9.1% (4 of 44) and the disease control rate was 31.8% (14 of 44). The plasma exposure to BGB-10188 exhibited a dose-dependent increase across a range of 20 mg to 540 mg. The peak concentration of BGB-10188 typically occurred ~2 hours post dose. Additionally, the mean half-life was observed to be between 8 hours and 13 hours across dosages. Peripheral p-AKT inhibition increased with dose, suggesting valid target engagement of BGB-10188, and reached a plateau at ~84%.

Conclusions: BGB-10188 + tislelizumab showed preliminary antitumor activity and was generally safe and tolerable across doses in this heavily pretreated population of patients with solid tumors. BGB-10188 + tislelizumab will be further evaluated in dose expansion (Part E).