Abstract CT002: A Phase IB study of RAF dimer inhibitor BGB-283 in patients with B-RAF or K-RAS/N-RAS mutated solid tumors

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Abstract

Background: BGB-283 is a novel inhibitor of the RAF dimer with potent and reversible inhibitory activities against RAF family kinases including wild type A-RAF, B-RAF, C-RAF and B-RAF V600E, as well as EGFR. BGB-283 demonstrated acceptable safety and early clinical activity in its Phase 1A study. In this Phase IB dose expansion study, we further evaluated safety and tolerability of BGB-283 and investigated efficacy in pre-selected patients (pts) with B-RAF or K-RAS/N-RAS-mutated solid tumors.

Methods: This Phase 1B study was a multicenter, open-label, multiple-arm, dose expansion study. Pts were treated at the RP2D of BGB-283 at 30 mg/day. There were 10 different expansion arms for: B-RAF V600-mutated melanoma (not previously treated with a B-RAF or MEK inhibitor, and B-RAF and/or MEK inhibitor-resistant pts), colorectal cancer (CRC), non-small cell lung cancer (NSCLC), papillary thyroid cancer (PTC) and other solid tumors with B-RAF mutations; K-RAS/N-RAS-mutated endometrial cancer, NSCLC, CRC, and other solid tumors with K-RAS/N-RAS or NF-1 mutations. The primary end point was the response rate based on RECIST Version 1.1. Adverse events (AEs) are reported per CTCAE V4.03.

Results: As of 19th Sep 2016, 96 pts were enrolled: median age was 63 years (range: 20 to 82 years) with all pts having baseline ECOG PS of 0 or 1. Forty-seven (49.0%) subjects had received ≥3 prior lines of treatment, 22 (22.9%) had received 2 prior lines of treatment, and 18 (18.8%) had received 1 prior line of treatment. BGB-283 was generally well-tolerated. Drug-related AEs were mostly Grade 1/2 in severity; the most common were fatigue in 37 (38.5%) subjects, nausea in 16 (16.7%), decreased appetite in 21 (21.9%), and diarrhea in 17 (17.7%). A total of 34 (35.4%) subjects experienced study drug-related Grade 3/4 AEs, notably drug-related thrombocytopenia (6.3%), palmar- plantar erythrodysesthesia syndrome (1.0%) and hypertension (8.3%). In the cohorts with previously-untreated B- RAF V600-mutated melanoma (n=7), PTC with B-RAF mutation (n=3) and NSCLC with K-RAS mutation (n=6), the response rates were 42.9% (95% confidence interval [CI], 9.9, 81.6), 33.3% (95% CI, 0.8, 90.6) and 16.7% (95% [0.4, 64.1]), respectively. Confirmed PR was seen in the single case of ovarian cancer with B-RAF mutation enrolled and also in one of 4 melanoma subjects with a confirmed B-RAF V600 mutation, who had not responded to B-RAF and/or MEK inhibitor(s). One unconfirmed PR was found in two NSCLC subjects with a B-RAF mutation.

Conclusions: BGB-283 was generally well-tolerated during the Phase 1B stage of the study. Antitumor activity was not only observed in subjects with B-RAF V600-mutated solid tumors including melanoma, PTC, and ovarian cancer, but also in subjects with K-RAS-mutated NSCLC. When added to the efficacy data in the Phase IA portion of this study, with objective responses noted in these tumor subtypes as well as in K-RAS-mutated endometrial carcinoma, BGB-283 demonstrated a desirable risk-benefit profile for further efficacy and safety investigation.