A first-in-human, phase 1a/1b, open-label, dose-escalation and expansion study to investigate the safety, pharmacokinetics, and antitumor activity of the RAF dimer inhibitor BGB-3245 in patients with advanced or refractory tumors

Authors

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Background

BGB-3245 is a RAF dimer inhibitor with preclinical activity in MAPK-altered tumor models harboring BRAF V600 mutations, atypical BRAF mutations/fusions, and RAS mutations. This study is investigating the safety, pharmacokinetics, and preliminary antitumor activity of BGB-3245 in patients (pts) with advanced or refractory MAPK-altered solid tumors.

Methods

Eligible pts were ≥18 yrs old with ECOG 0-1 and had solid tumors harboring MAPK pathway alterations. Dose-escalation and cohort-size decisions were made using the Modified Toxicity Probability Interval Design. The starting dose was 5 mg QD.

Treatment emergent adverse events (TEAEs) were graded per NCI CTCAE v5.0. Tumor responses were assessed by investigators using RECIST v1.1.

Results

As of 1 Sep 2022, 42 pts were treated across 6 cohorts (5-60 mg QD). The median age was 60 yrs; pts had received a median of 3 prior lines of treatment.

All pts had TEAEs; 79% had treatment-related (TR) AEs. The most common TRAEs (≥ 10%) were rash acneiform (33%), rash maculopapular (24%), fever (17%), ALT elevations and nausea (both 12%). Gr ≥3 TRAEs were reported in 29% of pts, events in ≥ 2 pts included decreased platelet count and rash maculopapular (3 each), ALT and AST elevations, and fever (2 each). Dose reductions occurred in 5 pts: rhabdomyolysis (1), LVEF decreased (1), hand-foot syndrome (1), rash maculopapular (1), and liver function abnormalities (1). Dose interruptions due to AEs occurred in 60% of pts. Dose discontinuations occurred in 79% of pts, 57% due to disease progression or death, 21% due to AE. Dose limiting toxicities were observed at 10 mg, 40 mg, and 60 mg. 40 mg QD was determined as the MTD.

PK results showed generally dose-proportional increases in exposure. Tmax was at ~2 h; BGB-3245 had a long terminal half-life and 7.4-fold average accumulation in exposure at steady-state.

79% of pts were efficacy evaluable. The disease control rate was 48% with 1 CR, 5 cPR, 2 uPR and 8 SD≥24 wks. Objective responders included BRAF V600E melanoma pts post-BRAF/MEK and checkpoint inhibitors (2; 1 CR, 1 cPR), 1 NRAS G12S melanoma and 1 NRAS Q61K melanoma (post checkpoint inhibitors), 1 BRAF V600E LGSOC (progressed on BRAF

inhibitor), 1 BRAF V600E cholangiocarcinoma (progressed on BRAF/MEK inhibitors), 1 BRAF K601E/PIK3CA endometrial cancer, and 1 KRAS G12D appendiceal cancer.

Preliminary analysis of circulating tumor DNA showed correspondence to clinical response.

Conclusions

BGB-3245 has a manageable safety profile and a generally dose-proportional PK. Antitumor activity was observed in pts with no approved targeted therapy options. The safety and early efficacy profile of BGB-3245 supports further investigation in selected MAPK-altered tumors.