A Phase 1 Dose-Escalation Study of BGB-290 in Chinese Subjects with Advanced Ovarian, Fallopian, and Primary Peritoneal Cancer, or Advanced Triple-Negative Breast Cancer

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Background

BGB-290 is a selective inhibitor of poly (ADP-ribose) polymerases (PARP) 1 and 2 that crosses the blood-brain barrier, showed potent DNA-PARP trapping, and demonstrated robust antitumor activity in nonclinical models. In a first-in-human study (NCT02361723), BGB-290 was generally well tolerated and showed promising preliminary antitumor activity, notably in patients (pts) with high-grade non-mucinous ovarian cancer (HGOC). The recommended Phase 2 dose (RP2D) was established as 60 mg PO BID.

Methods

This ongoing dose-escalation (DE)/expansion study (NCT03333915) is enrolling Chinese pts with advanced HGOC, including fallopian and primary peritoneal cancer, or triple-negative breast cancer (TNBC). DE cohorts were designed to confirm the previously established RP2D. Patients with germline *BRCA1/2* mutation (BRCA+) were retrospectively identified by central testing. The primary endpoint was safety and tolerability of BGB-290 in Chinese patients as per CTCAE v4.03. Key secondary endpoints were pharmacokinetics (PK) and antitumor activity as per RECIST v1.1.

Results

As of 25 Sep 2017, 15 pts (HGOC: n=9; TNBC: n=6) were enrolled in DE. Median age was 49 years (range: 32–70), ECOG score was 0 (n=2) or 1 (n=13), and 7 of 15 pts were germline BRCA+ (HGOC: n=5; TNBC: n=2). BGB-290 BID dose levels of 20 mg (n=4), 40 mg (n=4), and 60 mg (n=7) were evaluated. Most common treatment-related adverse events (AEs) were asthenia (n=12), nausea (n=12), decreased appetite (n=9), decreased white blood cell (WBC) count (n=9), anemia (n= 8), and decreased neutrophil count (n=7). Grade 3 AEs occurring in ≥2 pts were anemia (n=5), decreased neutrophil count, and decreased WBC (n=2 each). No ≥ Grade 4 AEs were reported. Serious AEs (abdominal infection, ileus, and pleural effusion, n=1 each) were determined not related to BGB-290. No dose-limiting toxicities were reported, and the RP2D was confirmed as 60 mg PO BID. After a single dose, BGB-290 was rapidly absorbed (median T_{max}=1 hr) with a $t_{1/2}$ of ~12 hr and showed near dose-proportional increases for both C_{max} and $AUC_{0\text{-}inf}$. Preliminary activity showed 2 confirmed PRs (BRCA+=1) and 6 SD (BRCA+=4) in HGOC pts (all platinum-resistant/refractory); median duration of treatment is 133 days (range: 8–260) with 5 pts still on treatment. Best response in the 5 TNBC pts was PD (BRCA+ =1).

Conclusions

BGB-290 at 20, 40, and 60 mg PO BID was generally well tolerated in Chinese pts with advanced HGOC or TNBC. The previously established RP2D of 60 mg BID was confirmed. Preliminary antitumor activity in HGOC pts previously resistant or refractory to platinum is consistent with other reports. Enrollment in the expansion stage is ongoing.

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