PAMIPARIB, AN INVESTIGATIONAL PARP 1/2 INHIBITOR MONOTHERAPY FOR PATIENTS WITH RECURRENT OVARIAN, FALLOPIAN, AND PRIMARY PERITONEAL CANCER WITH GERMLINE *BRCA* MUTATIONS: AN OPEN-LABEL, MULTICENTER, PHASE 2 TRIAL IN CHINA

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BACKGROUND

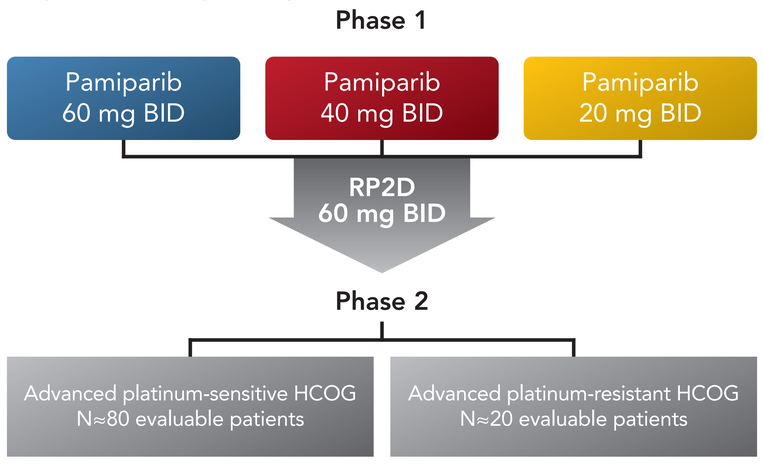
- Poly (ADP-ribose) polymerase (PARP) proteins are involved in DNA repair, genome stability, and programmed cell death[1]
- Inhibition of PARP proteins allows for accumulation of unrepaired single-strand breaks, which are converted to double-strand breaks during cell division and can lead to apoptosis/cell death[1]
  - Double-strand break repair can be compromised by the absence of homologous recombination components (eg, *BRCA1*, *BRCA2*)[1]
- PARP inhibitors (PARPi) bind directly to, and inhibit activity of, PARP enzymes, preventing DNA damage repair and trapping PARP–DNA complexes at DNA damage site[1]
  - The lack of homologous recombination makes *BRCA*-deficient cells acutely sensitive to PARPi[2]
- Ovarian cancer is the tenth most common cancer among Chinese women[3] with 28.5% of these patients reporting germline *BRCA* mutation (*BRCA*^{mut})[4]
  - For carriers of *BRCA1* and *BRCA2* mutations, the lifetime risk of ovarian cancer is between 40% and 11%, respectively[5]
- PARPi have shown anticancer activity in patients with ovarian cancer with a germline or somatic *BRCA*^{mut} [6–8]
- Several studies have also revealed that patients with ovarian cancer who are sensitive to platinum therapy demonstrate susceptibility to PARPi[9–12]
- Pamiparib (also known as BGB-290) is a selective PARP1/2 inhibitor that penetrates the blood–brain barrier, has shown PARP trapping, and has demonstrated antitumor activity in both in vitro and in vivo nonclinical tumor models harboring *BRCA* gene mutations and other homologous recombination deficiencies
- In early phase clinical studies (NCT02361723; NCT03333915), pamiparib was generally well tolerated and showed preliminary antitumor activity in both Caucasian and Chinese patients; these studies also established 60 mg orally twice daily (PO BID) as the recommended pivotal dose
- Presented here is the study design from the dose-expansion phase of an ongoing phase 1/2 trial in Chinese patients with advanced ovarian, fallopian, and primary peritoneal cancer (NCT03333915)

METHODS

Overall Design and Study Objectives

- This ongoing study consists of two phases (**Figure 1**):
- Phase 1 was a dose-escalation phase that followed a 3+3 design to confirm the recommended phase 2 dose (RP2D) of pamiparib in Chinese patients (aged ≥18 years) with locally advanced or metastatic high-grade ovarian cancer (HGOC), including fallopian and primary peritoneal cancer, who had disease progression following at least one line of chemotherapy; this phase of the study is now closed to enrollment
  - Patients with germline *BRCA*^{mut} will be retrospectively identified by central testing
- Phase 2 is an ongoing RP2D-expansion phase investigating the safety and tolerability, as well as antitumor activity, of oral pamiparib in adult patients (aged ≥18 years) with platinum-sensitive/platinum-resistant HGOC with known or suspected deleterious germline *BRCA*^{mut} as identified by central testing
  - Antitumor activity of pamiparib is being assessed in patients with advanced platinum-sensitive (n=80) or platinum-resistant (n=20) high-grade, non-mucinous, epithelial ovarian cancer (including fallopian or primary peritoneal cancer) harboring *BRCA1/2* mutations according to separate evaluations based on the Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST v1.1) by independent radiology review (IRR) and investigators

Figure 1: Study Design



Abbreviations: BID, twice daily; HGOC, high-grade ovarian cancer; RP2D, recommended phase 2 dose.

Study Population

- To be eligible for participation in the phase 2 portion of the study, patients aged ≥18 years with an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1 must have the following:
  - Histologically or cytologically confirmed high-grade (grade 2 or grade 3 endometrioid epithelial cancer is also acceptable), non-mucinous, epithelial ovarian cancer (including fallopian cancer or primary peritoneal cancer) harboring germline *BRCA1/2*^{mut}
    - Patients must have relapsed/progressive disease and must have received ≥2 lines of therapy in the advanced or metastatic setting or have withdrawn due to unacceptable toxicity from the most recent standard treatment
    - Patients must have platinum-sensitive (defined as disease progression by RECIST v1.1, having occurred >6 months after their last platinum treatment) or platinum-resistant (defined as disease progression occurring <6 months after the last platinum treatment) disease
    - If mixed histology is present, >50% of the primary tumor had to be confirmed to be high-grade (grade 2 or grade 3 endometrioid epithelial cancer), non-mucinous, epithelial ovarian cancer
  - Must undergo germline *BRCA1/2*^{mut} testing using blood samples prior to enrollment; archival tumor tissues will be collected from all patients if available
- Patients will be excluded if they have:
  - Diagnosis of myelodysplastic syndrome, untreated or active brain metastasis, or other diagnosis of malignancy, except for surgically excised non-melanoma skin cancer, adequately treated carcinoma in situ of the cervix, adequately treated low-stage bladder cancer, ductal carcinoma in situ treated surgically with curative intent, or a malignancy diagnosed ≥5 years ago with no current evidence of disease and no therapy ≥5 years prior to Day 1
  - Treatment with radiotherapy, chemotherapy, biologic therapy, immunotherapy, investigational agent, anticancer Chinese medicine, or anticancer herbal remedies ≤14 days (or ≤5 half-lives, whichever is shorter), or if they have not adequately recovered from the side effects of such therapy
  - Major surgical procedure for any cause ≤4 weeks prior to starting study drug
  - Previous complete gastric resection, chronic diarrhea, active inflammatory gastrointestinal disease, or any other disease causing malabsorption syndrome
  - Active bleeding disorder, including gastrointestinal bleeding, as evidenced by hematemesis, significant hemoptysis, or melena within 6 months before Day 1

TREATMENT

- The patients will receive pamiparib 60 mg BID daily until the occurrence of confirmed progressive disease, intolerable toxicity, or treatment discontinuation for other reasons
  - Up to two dose reductions of the study drug will be permitted during the study; reescalation may be possible with acceptable tolerability
  - Treatment can be withheld for up to 28 consecutive days

STUDY ASSESSMENTS AND STATISTICAL ANALYSIS

- Radiologic assessments of tumor response will be assessed separately by IRR and investigator's review based on RECIST v1.1 every 6 weeks for the first 18 weeks, thereafter once every 9 weeks for the remaining period in the first year, and then once every 12 weeks starting with the second year
  - For patients whose first response is a complete (CR) or partial response (PR), a response confirmation will need to be performed during the following 4–6 weeks
- The primary endpoint will be overall response rate (ORR) by IRR
  - A two-sided binomial exact 95% CI of ORR will be constructed to assess the precision of the rate estimate
- Overall response rate, progression-free survival (PFS), overall survival (OS), and duration of response (DoR) will be assessed by the investigator using RECIST v1.1 criteria
  - The Kaplan–Meier method will be used to estimate the key secondary endpoints, DoR, PFS, and OS, and corresponding quartiles (including the median) in the responders
    - For DoR, two-sided 95% CIs of the median will be constructed with a generalized Brookmeyer and Crowley method
    - Progression-free survival and OS will be estimated using the Kaplan–Meier method along with the corresponding 95% CI constructed using Greenwood's formula
- Tolerability will be assessed by monitoring and recording all adverse events; clinical laboratory values, vital signs, physical examinations, and ECG findings will also be used in determining the safety of the study drug

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