PAMIPARIB, A NOVEL PARP 1/2 INHIBITOR, MONOTHERAPY FOR g*BRCA*^{mut} PATIENTS WITH RECURRENT OVARIAN, FALLOPIAN, AND PRIMARY PERITONEAL CANCER: AN OPEN-LABEL, MULTICENTER, PHASE 2 TRIAL IN CHINA

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BACKGROUND

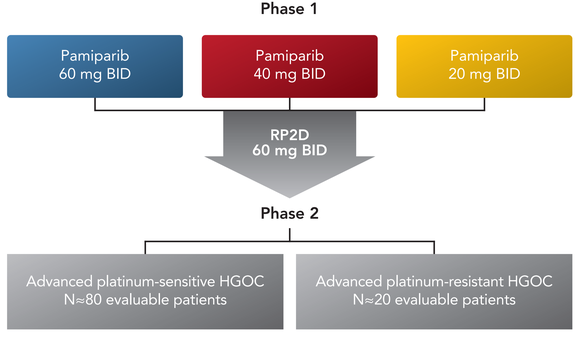
- Poly (ADP-ribose) polymerase (PARP) proteins are involved in DNA repair, genome stability, and programmed cell death[1]
- Inhibition of PARP proteins allows for accumulation of unrepaired single-strand breaks, which are converted to double-strand breaks during cell division and can lead to apoptosis/cell 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 the 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 histologically or cytologically confirmed, locally advanced or metastatic triple negative breast cancer, or high-grade epithelial ovarian cancer (HGOC) including fallopian or primary peritoneal cancer for which no effective standard therapy is available; 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
  - The 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 received at least 2 lines of standard chemotherapy, currently with relapsed/progressive disease or have withdrawn due to unacceptable toxicity from 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 21 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

REFERENCES

1. Lupo B, Trusolino L. Inhibition of poly(ADP-ribosyl)ation in cancer: old and new paradigms revisited. *Biochim Biophys Acta*. 2014;1846(1):201–215.
2. Dziadkowiec KN, et al. PARP inhibitors: review of mechanisms of action and BRCA1/2 mutation targeting. *Prz Menopauzalny*. 2016;15(4):215–219.
3. Reid BM, et al. Epidemiology of ovarian cancer: a review. *Cancer Biol Med*. 2017;14(1):9–32.
4. Wu X, et al. The first nationwide multicenter prevalence study of germline *BRCA1* and *BRCA2* mutations in chinese ovarian cancer patients. *Int J Gynecol Cancer*. 2017;27(8):1650–1657.
5. Antoniou A, et al. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case series unselected for family history: a combined analysis of 22 studies. *Am J Hum Genet*. 2003;72(5):1117–1130.
6. Lynparza (olaparib) [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2018.
7. Zejula (niraparib) [package insert]. Waltham, MA: Tesaro, Inc.; 2017.
8. Rubraca (rucaparib) [package insert]. Boulder, CO: Clovis Oncology, Inc.; 2018.
9. Kristeleit R, et al. Clinical activity of the poly(ADP-ribose) polymerase (PARP) inhibitor rucaparib in patients (pts) with high-grade ovarian carcinoma (HGOC) and a BRCA mutation (BRCAmut): analysis of pooled data from study 10 (parts 1, 2a, and 3) and ARIEL2 (parts 1 and 2). *Ann Oncol*. 2016;27(suppl 6):8560.
10. Kristeleit R, et al. A phase III study of the oral PARP inhibitor rucaparib in patients with germline BRCA1/2-mutated ovarian carcinoma or other solid tumors. *Clin Cancer Res*. 2017;23(15):4095–4106.
11. Steffensen KD, et al. Veliparib monotherapy to patients with BRCA germ line mutation and platinum-resistant or partially platinum-sensitive relapse of epithelial ovarian cancer: a phase I/II study. *Int J Gynecol Cancer*. 2017;27(9):1842–1849.
12. Gelmon KA, et al. Olaparib in patients with recurrent high-grade serous or poorly differentiated ovarian carcinoma or triple-negative breast cancer: a phase 2, multicentre, open-label, non-randomised study. *Lancet Oncol*. 2011;12(9):852–861.

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