A PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER TRIAL OF MAINTENANCE TREATMENT WITH PAMIPARIB VERSUS PLACEBO IN CHINESE PATIENTS WITH PLATINUM-SENSITIVE RECURRENT OVARIAN CANCER

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BACKGROUND

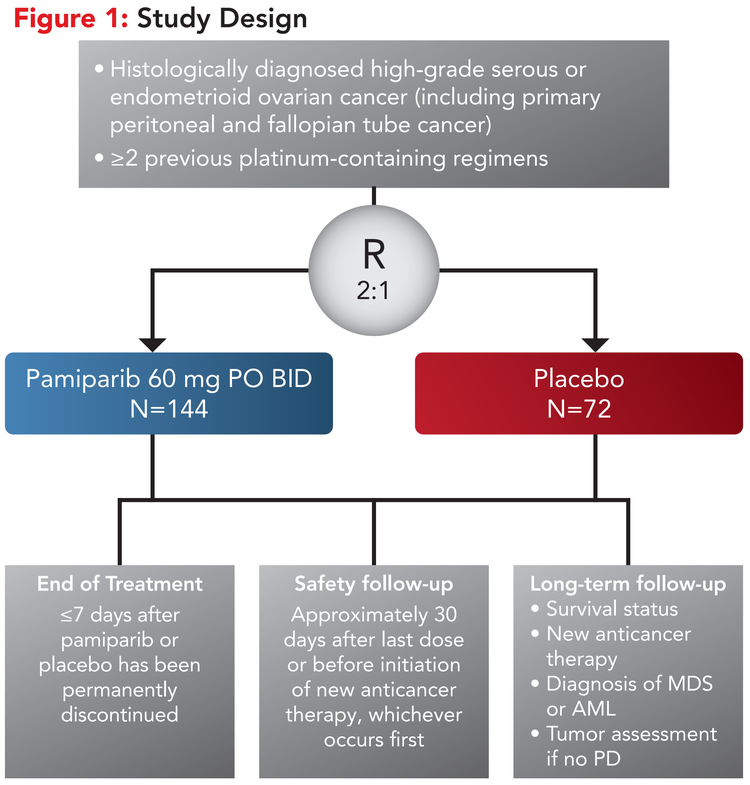
- Poly (ADP-ribose) polymerase (PARP) proteins are involved in DNA repair, genome stability, and programmed cell death[1]
- Inhibition of PARP proteins allows for accumulation of unrepaired single-strand breaks (SSBs), which are converted to double-strand breaks (DSBs) during cell division and can lead 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 PARP inhibitors[2]
- Ovarian cancer is the tenth most common cancer among Chinese women[3] with 28.5% of these patients reporting germline *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* mutation (*BRCA*^{mut})[6–8]
- Several studies have 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 double-blind, placebo-controlled, phase 3 study (NCT03519230) of pamiparib versus placebo as maintenance therapy in Chinese patients with recurrent high-grade, serous, or endometrioid ovarian cancer (HGOC)

METHODS

Overall Design and Study Objectives

- This randomized, double-blind, placebo-controlled, multicenter, phase 3 study (NCT03519230) is designed to evaluate the efficacy and safety of maintenance therapy with pamiparib versus placebo in patients with recurrent ovarian cancer who achieved a complete response (CR) or partial response (PR) after platinum-based chemotherapy (**Figure 1**)
- The primary endpoint is progression-free survival (PFS) by blinded independent review committee (BIRC) assessment
- Secondary endpoints will include comparisons of pamiparib versus placebo for other efficacy endpoints as assessed by the investigator (including PFS, overall survival [OS], objective response rate [ORR] , duration of response [DoR], and time to response), as well as safety and tolerability

Figure 1: Study Design



Key assessments during treatment phase:
- Pamiparib and placebo are to be administered continuously
- Tumor assessments every 8 weeks in the first year and then once every 12 weeks until PD
- Tumor marker, CA-125, will be assessed locally from blood samples taken every 8 weeks in the first year and then every 12 weeks until objective PD
- Adverse events recorded at each visit

Abbreviations: AML, acute myeloid leukemia; BID, twice daily; MDS, myelodysplastic syndrome; PD, progressive disease; PO, oral; R, randomized.

Study Population

- To be eligible for participation in the study, patients aged ≥18 years must have
  - Histologically diagnosed high-grade serous or endometrioid ovarian cancer (including primary peritoneal and fallopian tube cancer)
  - Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
  - Completed ≥2 prior lines of platinum-containing regimens (eg, carboplatin or cisplatin) and achieved a CR or PR with their last platinum-based chemotherapy regimen as determined by investigator according to RECIST v1.1
    - For the penultimate platinum-based regimen before enrollment on the study: patients must have platinum-sensitive disease, defined as disease progression >6 months after the last dose of platinum
    - For the last platinum-based regimen before enrollment on the study: patients must have received a platinum-containing regimen for ≥4 cycles and bevacizumab could not have been part of the last regimen
- Patients will be excluded if they have:
  - Progressive disease (PD) as per the definition given in the CA-125 criteria
  - Diagnosis of myelodysplastic syndrome
  - Active infection requiring systemic treatment, active viral hepatitis, or active tuberculosis

TREATMENT

- Patients will be randomized 2:1 to receive pamiparib 60 mg PO BID or placebo given as 28-day treatment cycles; randomization will be stratified by time to progression after penultimate platinum chemotherapy (6–12 months vs >12 months), best overall response (CR vs PR) to last platinum therapy, and germline *BRCA* mutation status (*BRCA*^{mut} vs wild type)
- Patients will receive treatment until occurrence of progressive disease, unacceptable toxicity, death, or treatment discontinuation for other reasons
- Up to two dose reductions of the study drug will be permitted during the study and treatment can be withheld for up to 28 consecutive days
- Patients are not allowed to receive other anticancer therapies, including surgery, radiation therapy, immunotherapy, investigational agents, cytotoxic, biologic or hormone therapy, anticancer Chinese medicine, or anticancer herbal remedies

STUDY ASSESSMENTS AND STATISTICAL ANALYSIS

- Radiologic assessments will be centrally evaluated per RECIST v1.1 at screening, every 8 weeks after first dose during the first year, and then every 12 weeks to evaluate disease progression
- The primary endpoint will be PFS by BIRC assessment
  - A two-sided, stratified log-rank test using a significance level of 0.05 will be used to analyze the distribution of PFS in the two arms
  - An interim analysis will be performed when 93 PFS events have occurred (estimated to be at approximately 16.1 months after first patient's randomization); final analysis will be performed when 139 PFS events have occurred (estimated to be at about 22 months post first patient's randomization)
- For time-to-event endpoints, a stratified Cox regression analysis will be used to estimate the hazard ratio; KM curves will be plotted to display the treatment arm comparison over time
- The ORR and its exact two-sided 95% confidence interval (CI) will be reported for each treatment arm; a Cochran-Mantel-Haenszel score test will be used to compare treatment arms
- Median DoR and its two-sided 95% CI for each treatment arm will be provided
- 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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