PAMIPARIB, AN INVESTIGATIONAL PARP1/2 INHIBITOR, FOR THE TREATMENT OF PATIENTS WITH HER2-NEGATIVE METASTATIC BREAST CANCER HARBORING GERMLINE *BRCA1/2* MUTATIONS: AN OPEN-LABEL, MULTICENTER, PHASE 2 TRIAL IN CHINA

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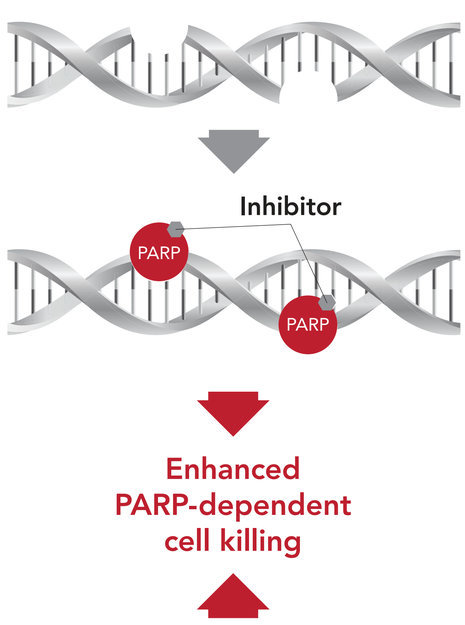
Chinese Society of Clinical Oncology
18-22 September 2019 | Xiamen, Fujian, China

BACKGROUND

- Breast cancer is the most prevalent malignancy among women in China and one of the main causes of tumor-related death[1]
- Poly(ADP-ribose) polymerase (PARP) proteins are involved in DNA repair, and their inhibition can lead to an accumulation of double-strand DNA breaks and cell toxicity[2-4]
  - DNA repair can be compromised by the absence of homologous recombination components, such as BRCA1 or BRCA2[4]
- PARP inhibitors (PARPi) represent a new class of therapeutic agents for the treatment of malignancies associated with *BRCA1/2* mutations (*BRCA*^{mut})
  - PARPi bind directly to, and inhibit activity of, PARP enzymes by preventing DNA repair and by trapping PARP-DNA complexes[4] (**Figure 1**)
- Breast cancers with germline *BRCA*^{mut}, including triple-negative breast cancer (TNBC) and hormone receptor–positive (HR$^+$)/human epidermal growth receptor 2–negative (HER2$^-$) cancers, have been shown to respond to PARP inhibitors[5,6]
- Pamiparib is an investigational selective PARP1/2 inhibitor that has been shown to cross the blood-brain barrier, have potent DNA-PARP trapping, and have robust antitumor activity in nonclinical models[7,8]
- 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 phase 2 dose[7,9]

Figure 1: Mechanism of Action of PARP Inhibitors



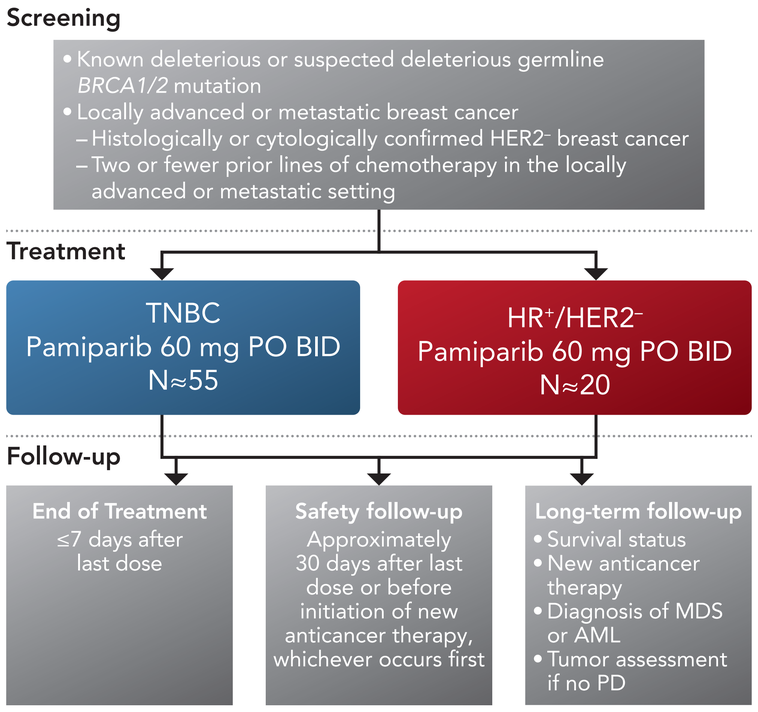
Abbreviations: *BRCA*, breast cancer susceptibility gene; HRD, homologous recombination deficiency; PARP, poly (ADP-ribose) polymerase.

METHODS

Overall Design and Study Objectives

- This open-label, multicenter, phase 2 study (CTR20171623; NCT03575065) is designed to evaluate the safety, tolerability, and antitumor activity of pamiparib administered 60 mg PO BID in patients with locally advanced or metastatic TNBC or HR$^+$/HER2$^-$ breast cancer with germline *BRCA*^{mut} (**Figure 2**)
- The primary endpoint will be the efficacy of pamiparib as measured by objective response rate (ORR) by independent radiology review (IRR)

Figure 2: Study Design



Key assessments during treatment phase:

- Tumor assessments every 8 weeks in the first year and once every 12 weeks in the second year and beyond
- Weekly hematology tests for the first 3 cycles during the study; for all grade ≥2 anemia, hematology tests weekly thereafter until adequate recovery
- Adverse events recorded at each visit

Pamiparib is to be administered continuously.

Abbreviations: AML, acute myeloid leukemia; BID, twice daily; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; MDS, myelodysplastic syndrome; PD, progressive disease; PO, oral; TNBC, triple-negative breast cancer.

- Secondary endpoints will include:
  - ORR by investigator assessment
  - Progression-free survival and duration of response by IRR and investigator assessment
  - Disease control rate, best overall response, and clinical benefit rate assessment by IRR and investigator assessment
  - Overall survival
  - Incidence, timing, and severity of treatment-emergent adverse events
- Exploratory objectives will assess potential predictive biomarkers of efficacy and resistance, examine changes in tumor microenvironment (such as PD-L1 and CD8) and other markers (such as PARP inhibition) in response to pamiparib in breast cancer patients, and further characterize the pharmacokinetic (PK) profile of pamiparib

Patient Population

- Approximately 75 patients from ~25 centers will be enrolled
- Key inclusion/exclusion criteria are provided in **Table 1**
- This study is currently enrolling

Table 1: Key Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
• Adult patients ≥18 years • Histologically or cytologically confirmed, locally advanced or metastatic HER2$^-$ breast cancer (TNBC or HR$^+$/HER2$^-$) harboring germline *BRCA*^{mut} • Received ≤2 prior lines of chemotherapy in the locally advanced or metastatic setting • For HR$^+$/HER2$^-$ breast cancer, patients must have received and progressed on ≥1 endocrine therapy either in an adjuvant or metastatic setting, or have disease that the treating physician believes to be inappropriate for endocrine therapy • ECOG performance status ≤1	• Prior treatments – Other PARP inhibitors – Prior platinum therapy allowed if there was no disease progression while on treatment, or, if given in the neoadjuvant/adjuvant setting, ≥6 months had passed between the last platinum therapy and relapse – Major surgical procedure, open biopsy, previous gastric resection or significant traumatic injury ≤14 days before first dose • Comorbidities – Diagnosis of MDS – Untreated and/or active brain metastases – Active infection requiring systemic treatment, active viral hepatitis, or active tuberculosis – Clinically significant cardiovascular disease – Active bleeding disorder

Abbreviations: *BRCA*^{mut}, breast cancer susceptibility gene 1/2 mutation; ECOG, Eastern Cooperative Oncology Group; HER2$^-$, human epidermal growth factor receptor 2-negative; HR$^+$, hormone receptor-positive; MDS, myelodysplastic syndrome; PARP, poly(ADP-ribose) polymerase; TNBC, triple-negative breast cancer.

TREATMENT

- Patients will receive pamiparib 60 mg PO BID as 28-day treatment cycles until disease progression (as assessed by the investigator), unacceptable toxicities, death, withdrawal of consent, loss to follow-up, or study termination by sponsor
- Up to two dose reductions of pamiparib will be permitted during the study, and treatment can be withheld for up to 28 consecutive days for medical events (56 days for anemia)
- Patients are not allowed to receive other anticancer therapy, including surgery, radiation therapy (except palliative radiation therapy to a non-target lesion), immunotherapy, investigational agents, cytotoxic, biologic or hormone therapy, anticancer Chinese medicine, or anticancer herbal remedies

STUDY ASSESSMENTS AND STATISTICAL ANALYSIS

- The safety and tolerability of pamiparib will be evaluated in all patients who received ≥1 dose of pamiparib
  - Survival status will be assessed approximately every 12 weeks until study completion
- Radiologic assessments will be evaluated per RECIST v1.1 at screening, every 8 weeks in the first year, and every 12 weeks thereafter
  - A two-sided binomial exact 95% confidence interval of ORR will be constructed to assess the precision of the rate estimate for both cohorts
- The PK profile of pamiparib will be assessed in patients for whom valid pamiparib PK parameters can be estimated

REFERENCES

1. Chen W, Zheng R, Zhang S, et al. Cancer incidence and mortality in China, 2013. *Cancer Lett.* 2017;401:63-71.
2. Thomas C, Tulin AV. Poly-ADP-ribose polymerase: machinery for nuclear processes. *Mol Aspects Med.* 2013;34:1124-1137.
3. Dziadkowiec KN, Gasiorowska E, Nowak-Markwitz E, Jankowska A. PARP inhibitors: review of mechanisms of action and BRCA1/2 mutation targeting. *Prz Menopauzalny.* 2016;15:215-219.
4. Lupo B, Trusolino L. Inhibition of poly(ADP-ribosyl)ation in cancer: old and new paradigms revisited. *Biochim Biophys Acta.* 2014;1846:201-215.
5. Robson M, Im SA, Senkus E, et al. Olaparib for metastatic breast cancer in patients with a germline BRCA mutation. *N Engl J Med.* 2017;377:523-533.
6. Litton JK, Rugo HS, Ettl J, et al. Talazoparib in patients with advanced breast cancer and a germline BRCA mutation. *N Engl J Med.* 2018;379:753-763.
7. Xu B, Yin Y, Song Y, et al. A phase I dose escalation study of BGB-290 in Chinese subjects with advanced ovarian, fallopian, and primary peritoneal, or advanced triple-negative breast cancer. *Cancer Res.* 2018;78(suppl):Abstract CT050.
8. Gupta SK, Carlson BL, Schroeder MA, Bakken KK, C. TA, N. SJ. Inhibition of PARP activity by BGB-290 potentiates efficacy of temozolomide in patient derived xenografts of glioblastoma multiforme. *Cancer Res.* 2015;78(suppl):Abstract CT050.
9. Lickliter JD, Gan HK, Meniawy T, et al. A phase I dose-escalation study of BGB-290, a novel PARP1/2 selective inhibitor in patients with advanced solid tumors. *J Clin Oncol.* 2016;34(suppl):Abstract e17049.

ACKNOWLEDGMENTS

The authors wish to acknowledge the study patients and investigative center study staff, including the following site principle investigators: Xi Yan, Chuan Wang, Xiuli Wang, Shouman Wang, Gang Hu, Jifeng Feng, Ying Cheng, Min Yan, Dequan Liu, Shu Wang, Xiuping Du, and Yongsheng Wang. Acknowledgement is also provided to those from BeiGene, Ltd. who have substantially contributed to the development of this presentation. This study was sponsored by BeiGene, Ltd. Writing and editorial assistance was provided by Stephan Lindsey, PhD, and Elizabeth Hermans, PhD (OPEN Health Medical Communications, Chicago, IL), and funded by the study sponsor.

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