A PHASE 3, DOUBLE-BLIND, RANDOMIZED STUDY OF PAMIPARIB VERSUS PLACEBO AS MAINTENANCE THERAPY IN PATIENTS WITH INOPERABLE, LOCALLY ADVANCED, OR METASTATIC GASTRIC CANCER THAT RESPONDED TO PLATINUM-BASED FIRST-LINE CHEMOTHERAPY

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BACKGROUND

- Gastric cancer is one of the most commonly diagnosed cancers, and is among the leading causes of cancer deaths worldwide[1]
- Chemotherapy regimens containing a platinum and fluoropyrimidine are typically given to patients with newly diagnosed, inoperable, locally advanced, or metastatic disease[2,3]
- However, even in those responding to treatment, chemotherapy usually does not exceed 6 months because of cumulative toxicities[4]
- A subset of gastric cancers exhibit platinum sensitivity and genomic instability that is characteristic of homologous recombination deficiency (HRD)
- Poly(ADP-ribose) polymerase proteins 1 and 2 (PARP1/2) are involved in DNA damage repair, and their inhibition is cytotoxic for cells with HRD,[5] suggesting that PARP inhibitors may be effective in cancers with platinum sensitivity and higher levels of HRD[6]
- Pamiparib (previously known as BGB-290) is a selective PARP1/2 inhibitor that crosses the blood-brain barrier; it has shown potent DNA–PARP trapping, and has demonstrated antitumor activity in preclinical models
- In early phase clinical studies (NCT02361723; NCT03333915; NCT02660034), pamiparib was generally well tolerated and showed antitumor activity as a single agent or in combination regimens[7–9]
- These studies also established 60 mg orally twice daily as the recommended pivotal dose

METHODS

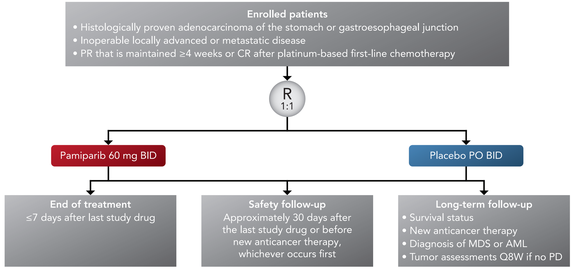
Overall Design and Study Objectives

- This phase 3, double-blind, placebo-controlled, randomized, multicenter study was designed to compare the efficacy, safety, and tolerability of pamiparib with placebo as maintenance therapy in patients with advanced gastric cancer who have responded to first-line platinum-based chemotherapy (Figure 1)
- The primary objective will be to evaluate the efficacy of maintenance therapy with pamiparib versus placebo in terms of progression-free survival (PFS) assessed by a Blinded Independent Review Committee (BIRC)
- Secondary objectives will include comparisons of pamiparib versus placebo for other efficacy assessments (overall survival [OS]; time from randomization to second disease progression, or death [PFS2]; time to second subsequent treatment [TSST]; and objective response rate [ORR], duration of response [DoR], and time to response, all by investigator assessment), along with safety and tolerability
- Approximately 540 patients will be enrolled globally

Study Population

- To be eligible for participation in the study, patients aged ≥18 years must have the following:
  - Histologically confirmed adenocarcinoma of the stomach or gastroesophageal junction with inoperable locally advanced or metastatic disease (patients with gastric cancer overexpressing HER2 or who received irradiation as part of prior first-line treatment will not be eligible)
  - Received platinum-based first-line chemotherapy with a total of ≥8 platinum-containing 14-day cycles, ≥5 platinum-containing 21-day cycles, or ≥4 platinum-containing 28-day cycles for ≤28 weeks
  - Achieved a partial response (PR) that is maintained for ≥4 weeks or a complete response (CR) as determined by the investigator according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 with platinum-based first-line chemotherapy
  - Archival tumor tissue for central laboratory determination of HRD status
  - Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1
- Patients will be excluded if they have the following:
  - Chemotherapy, biologic therapy, immunotherapy, investigational agent, anticancer Chinese medicine, or herbal remedies ≤14 days (or ≤5 half-lives, whichever is shorter) before randomization
  - Major surgical procedure, open biopsy, or significant traumatic injury ≤14 days before randomization, or are likely to need a major surgical procedure during the course of the study
  - Diagnosis of myelodysplastic syndrome (MDS)
  - Other diagnosis of malignancy
  - Leptomeningeal disease or brain metastasis
  - Cardiac chest pain or symptomatic pulmonary embolism within 28 days of randomization; or history of acute myocardial infarction, history of heart failure meeting New York Heart Association Classification III or IV, grade ≥2 ventricular arrhythmia event, or history of cerebral vascular accident, all within 6 months of randomization
  - 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 of randomization
  - Use within 10 days (or ≤5 half-lives, whichever is shorter) of randomization, or anticipated need for food or drugs known to be strong or moderate cytochrome P450 (CYP) 3A inhibitors or strong CYP3A inducers

Figure 1: Study Design



Randomization stratified by HRD status (LOH_{high} versus LOH_{low} versus unknown), region (China/Hong Kong/Taiwan versus Australia/Europe/North America versus Japan/South Korea versus ROW), and ECOG PS (0 versus 1).

Abbreviations: AML, acute myeloid leukemia; BID, twice daily; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; HRD, homologous recombination deficiency; MDS, myelodysplastic syndrome; PD, progressive disease; PO, oral; PR, partial response; Q8W, once every 8 weeks; R, randomization; ROW, rest of world.

TREATMENT

- Patients will be randomized 1:1 (using central interactive response technology) to receive either pamiparib 60 mg twice daily or placebo, given as 28-day cycles; randomization will be stratified by genomic loss of heterozygosity status (ie, high versus low), region, and ECOG PS
- Patients will receive treatment until the 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 approximately 28 consecutive days
- Treatments and supportive care (such as antiemetic therapy, hematopoietic growth factors, and/or red blood cell/platelet transfusions) considered necessary for a patient's welfare will be permitted in keeping with the local standards of medical care

STUDY ASSESSMENTS AND STATISTICAL ANALYSIS

- Radiologic assessments will be centrally evaluated per RECIST v1.1 at screening and then every 8 weeks after first dose to evaluate disease progression, with tumor assessments continuing every 8 weeks in long-term follow-up
- The primary endpoint will be PFS by BIRC assessment
  - Treatment groups in the intent-to-treat (ITT) population will be compared using a stratified 1-sided log-rank test at a 0.025 significance level, incorporating the randomized stratification factors; the hazard ratio (HR) and its 2-sided 95% confidence interval (CI) will be estimated using the stratified Cox proportional hazards model
  - An interim analysis will be performed when 242 PFS events have occurred at approximately 23 months after start of randomization, with a final analysis performed when 363 PFS events have occurred (about 29 months post randomization)
- Key secondary endpoints include an additional efficacy endpoint (such as PFS assessed by the investigator, OS, ORR, PFS2, TSST, and DoR), along with safety/tolerability
  - Secondary analysis of PFS will be conducted in the per-protocol analysis population and also by investigator assessment
  - OS will be compared across treatment groups in the ITT population using a stratified log-rank test, incorporating the randomized stratification factors, with the HR estimated using the stratified Cox proportional hazards model; median OS will be estimated using the Kaplan–Meier method
  - Other secondary time-to-event endpoints, such as PFS2, TSST and DoR, will be analyzed in a similar manner to OS
  - ORR will be reported for the ITT population, with treatment groups compared using a Cochran-Mantel-Haenszel score test
- Safety will be monitored throughout the study (Day 1 of each cycle, on Day 15 of Cycles 1 and 2, and as needed), with safety assessments including adverse event monitoring, physical examinations, vital sign measurements, electrocardiograms, and clinical laboratory tests
- Adverse events will be documented during treatment for approximately 30 days after the last dose of study drug or until initiation of new anticancer therapy

REFERENCES

1. Global Burden of Disease Cancer Collaboration, Fitzmaurice C, Allen C, Barber RM, et al. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 32 cancer groups, 1990 to 2015: a systematic analysis for the global burden of disease study. *JAMA Oncol.* 2017;3(4)524–548.
2. Smyth EC, Verheij M, Allum W, et al. Gastric cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2016;27(suppl 5):38–49.
3. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Gastric Cancer (Version 1.2017). https://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf. Accessed April 12, 2018.
4. Hess LM, Michael D, Mytelka DS, et al. Chemotherapy treatment patterns, costs, and outcomes of patients with gastric cancer in the United States: a retrospective analysis of electronic medical record (EMR) and administrative claims data. *Gastric Cancer.* 2016;19(2):607–615.
5. Underhill C, Toulmonde M, Bonnefoi H. A review of PARP inhibitors: from bench to bedside. *Ann Oncol.* 2011;22(2):268–279.
6. Fong PC, Yap TA, Boss DS, et al. Poly(ADP)-ribose polymerase inhibition: frequent durable responses in BRCA carrier ovarian cancer correlating with platinum-free interval. *J Clin Oncol.* 2010;28(15):2512–2519.
7. Friedlander M, Meniawy T, Markman B, et al. A phase 1b study of the anti-PD-1 monoclonal antibody BGB-A317 in combination with the PARP inhibitor BGB-290 in advanced solid tumors. *J Clin Oncol.* 2018;36(suppl 5S): Abstract 48.
8. Friedlander M, Meniawy T, Markman B, et al. A phase 1b study of the anti-PD-1 monoclonal antibody BGB-A317 (A317) in combination with the PARP inhibitor BGB-290 (290) in advanced solid tumors. *J Clin Oncol.* 2017;35(suppl): Abstract 3013.
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.

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