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

Fortunato Ciardiello[1], Yung-Jue Bang[2], Johanna C. Bendell[3], Andres Cervantes[4], Kathy Zhang[5], Mitch Raponi[5], Heinrich Farin[5], Lin Shen[6]

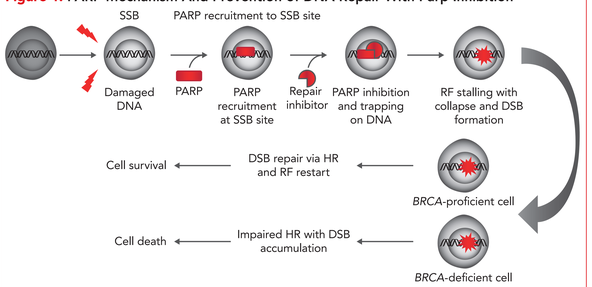
[1]*University of Campania "Luigi Vanvitelli", Naples, Italy;* [2]*Seoul National University Hospital, Seoul, Korea, Republic of (South);* [3]*Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN;* [4]*Instituto de Investigación Sanitaria INCLIVA, Valencia, Spain;* [5]*BeiGene USA, Inc., San Mateo, CA;* [6]*Beijing Cancer Hospital, Beijing, China*

BOARD N5: Abstract TPS173
Gastrointestinal Cancers Symposium of the American Society of Clinical Oncology
January 17–19, 2019, San Francisco, CA

BACKGROUND

- Gastric cancer (GC) is the fifth most common cancer, and is the third leading cause of cancer deaths worldwide[1]
  - A subset of GC exhibits platinum sensitivity and genomic instability,[2] characteristic of homologous recombination deficiency (HRD)[3]
- In patients with locally advanced or metastatic GC, fluoropyrimidine- and platinum-based combination chemotherapy is the first-line standard of care[4]
- Despite refinement in chemotherapy regimens, prognosis is poor with low response rates and short survival duration[5,6]
- Disease progression or toxicity can limit the duration of first-line therapy to less than 6 months[7]; however, there are no approved treatments for maintenance treatment after first-line therapy
- Poly(ADP-ribose) polymerase proteins 1 and 2 (PARP1/2) are critical to repairing collapsed replication forks resulting from HRD-associated single-strand breaks[8]
- PARP1/2 is involved in DNA damage repair, and their inhibition is cytotoxic for cells with HRD (Figure 1)[9]

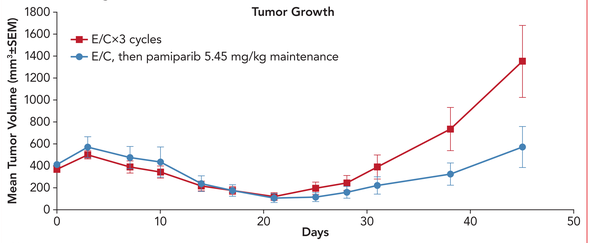
Figure 1: PARP Mechanism And Prevention of DNA Repair With Parp Inhibition



Adapted from Dziadkowiec KN, et al. *Prz Menopauzalny*. 2016;15:215–219.
Abbreviations: BRCA, breast cancer; DSB, double-strand break; DVL, disheveled; HR, homologous recombination; PARP, poly (ADP-ribose) polymerase; RF, replication fork; SSB, single-strand break.

- Pamiparib (BGB-290) is a selective PARP1/2 inhibitor that crosses the blood–brain barrier, has shown potent DNA–PARP trapping, and has demonstrated robust antitumor activity in preclinical models[10,11]
- To investigate the antitumor activities of BGB-290, small cell lung cancer xenograft models were established in BALB/c Nude mice using patient biopsy samples[12]
  - Pamiparib maintenance delayed relapses in mice treated with etopiside/carboplatin and demonstrated sustained tumor growth inhibition versus mice receiving no further treatment (Figure 2)
- In clinical studies (NCT02361723; NCT03333915), pamiparib was generally well tolerated and showed preliminary antitumor activity as a single agent and established 60 mg orally twice daily as the recommended dose[10,13]
- Here we describe a trial-in-progress of pamiparib as maintenance therapy in patients with locally advanced or metastatic GC that responded to platinum-based first-line chemotherapy

Figure 2: Pamiparib as Maintenance Therapy in the BCLU-080 Small Cell Lung Cancer Xenograft Model



Abbreviations: ESCC, esophageal squamous cell carcinoma; 5-FU, 5-fluorouracil; G/GEJ, gastric/gastroesophageal junction.

METHODS

Overall Design and Study Objectives

- This ongoing, global, double-blind, placebo-controlled, randomized, multicenter phase 3 study (NCT03427814) is designed to compare the efficacy, safety, and tolerability of pamiparib with placebo as maintenance therapy in patients with advanced GC who have responded to first-line platinum-based chemotherapy (Figure 3)
- The primary objective will be to evaluate the efficacy of maintenance with pamiparib versus placebo in terms of progression-free survival (PFS) assessed by a Blinded Independent Review Committee (BIRC)
- Key secondary objectives include comparisons of pamiparib versus placebo for other efficacy assessments (overall survival [OS]; PFS by investigator assessment; time from randomization to second disease progression or death from any cause, whichever is first [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

Patient Population

- Approximately 540 patients will be enrolled at 110 study centers in Asia, Australia, Europe, and North America
- Key inclusion/exclusion criteria are provided in Table 1

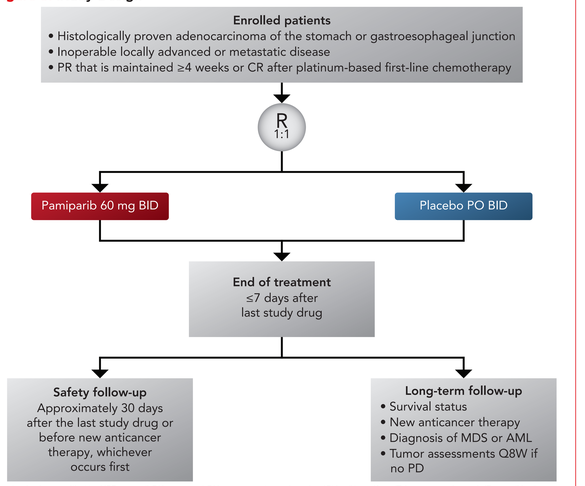
Treatment

- Patients will be randomized 1:1 to receive either pamiparib 60 mg twice daily or placebo, given as 28-day cycles
- Patients will receive treatment until the occurrence of progressive disease, unacceptable toxicity, 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

- Primary and key secondary endpoints are presented in Table 2
- Radiologic assessments will be centrally evaluated per RECIST v1.1 at screening and then every 8 weeks after first dose to evaluate disease progression
- Long-term follow-up assessments will include survival status, new anticancer therapy, diagnosis of myelodysplastic syndrome or acute myeloid leukemia, and tumor assessments every 8 weeks for patients without progressive disease

Figure 3: 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.

Table 1: Key Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
• Aged ≥18 years	• GC overexpressing HER2
• Histologically confirmed adenocarcinoma of the stomach/gastroesophageal junction	• Prior treatments ≤14 days before randomization – Chemotherapy, biologic therapy, immunotherapy, investigational agent, anticancer Chinese medicine, or herbal remedies – Major surgical procedure, open biopsy, gastric resection, or significant traumatic injury
• Received platinum-based first-line chemotherapy – Achieved CR or PR maintained for ≥4 weeks	• Comorbidities – Leptomeningeal disease, brain metastasis, or MDS – Clinically significant cardiovascular disease – Chronic diarrhea, active inflammatory GI disease, or any disease resulting in malabsorption syndrome
• Archival tumor tissue for central laboratory determination of HRD status	• Concomitant medications – Strong/moderate CYP3A inhibitors or strong CYP3A inducers within 10 days before randomization
• ECOG performance status ≤1	

Abbreviations: CR, complete response; CYP3A, cytochrome P450 3A; ECOG, Eastern Cooperative Oncology Group; GC, gastric cancer; GI, gastrointestinal; HER2, human epidermal growth factor receptor 2; HRD, homologous recombination deficiency; MDS, myelodysplastic syndrome; PR, partial response.

Table 2: Primary and Secondary Endpoints

Primary Endpoints	Key Secondary Endpoints
• PFS by BIRC assessment • Treatment groups in the 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 HR and its 2-sided 95% CI will be estimated using the stratified Cox proportional hazards model • An interim analysis will be performed when 242 PFS events have occurred, with a final analysis performed when 363 PFS events have occurred	• Investigator-assessed PFS in the per-protocol analysis population • Overall survival (OS) – Treatment groups in the ITT population will be compared using a stratified log-rank test; incorporating the randomized stratification factors; the HR will be estimated using the stratified Cox proportional hazards model – Median OS will be estimated using the Kaplan–Meier method • Objective response rate – Treatment groups in the ITT population will be compared using a Cochran-Mantel-Haenszel score test • Progression-free survival at 2 y • Time to second subsequent treatment • Duration of response • Safety/tolerability

Abbreviations: AE, Adverse events; HR, hazard ratio; ITT, intent-to-treat; PFS, progression-free survival.

REFERENCES

1. Ansari S, Gantuya B, Tuan VP, Yamaoka Y. Diffuse gastric cancer: A summary of analogous contributing factors for its molecular pathogenicity. *Int J Mol Sci*. 2018;19(8).
2. Fang DC, Jass JR, Wang DX, Zhou XD, Luo YH, Young J. Infrequent loss of heterozygosity of APC/MCC and DCC genes in gastric cancer showing DNA microsatellite instability. *J Clin Pathol*. 1999;52(7):504–508.
3. Deans B, Griffin CS, O'Regan P, Jasin M, Thacker J. Homologous recombination deficiency leads to profound genetic instability in cells derived from Xrcc2-knockout mice. *Cancer Res*. 2003;63(23):8181–8187.
4. 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):v38–v49.
5. Hess LM, Michael D, Mytelka DS, Beyrer J, Liepa AM, Nicol S. 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.
6. Catalano V, Graziano F, Santini D, et al. Second-line chemotherapy for patients with advanced gastric cancer: who may benefit? *Br J Cancer*. 2008;99(9):1402–1407.
7. Van Cutsem E, Moiseyenko VM, Tjulandin S, et al. Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group. *J Clin Oncol*. 2006;24(31):4991–4997.
8. Ledermann JA, Drew Y, Kristeleit RS. Homologous recombination deficiency and ovarian cancer. Eur J Cancer. 2016;60:49–58.
9. Rouleau M, Patel A, Hendzel MJ, Kaufmann SH, Poirier GG. PARP inhibition: PARP1 and beyond. *Nat Rev Cancer*. 2010;10(4):293–301.
10. 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*. 2015;78(suppl):Abstract CT050.
11. 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.
12. Tang Z, Liu Y, Zhen Q, et al. BGB-290: A highly potent and specific PARP1/2 inhibitor potentiates anti-tumor activity of chemotherapeutics in patient biopsy derived SCLC models. *Cancer Res*. 2015;78(suppl):Abstract 1653.
13. 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 investigative center study staff and study patients, as well as recognize those from BeiGene who have substantially contributed to the development of this presentation. BeiGene, Ltd. provided financial support for this presentation, including writing and editorial assistance by Stephan Lindsey, PhD, at SuccinctChoice Medical Communications (Chicago, IL).

Please address any questions or comments regarding this poster to Clinicaltrials@beigene.com