**A PHASE 2 TRIAL IN PROGRESS: PAMIPARIB, AN INVESTIGATIONAL PARP INHIBITOR IN PATIENTS WITH METASTATIC CASTRATION-RESISTANT PROSTATE CANCER AND A CIRCULATING TUMOR CELL HOMOLOGOUS RECOMBINATION DEFICIENCY PHENOTYPE OR BRCA DEFECTS**

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**BACKGROUND**

- Prostate cancer is one of the leading causes of cancer deaths in men.1
- Mutations in genes associated with homologous recombination deficiency (HRD), including BRCA1/2, are strongly associated with an aggressive phenotype and poor clinical outcomes.2
- Poly (ADP-ribose) polymerase (PARP) proteins are a family of proteins involved in DNA repair, genome stability, and programmed cell death.3
- 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.4
- DNA repair can be compromised by the absence of homologous recombination (HR) components, such as BRCA1 or BRCA2.5
- Pamiparib (BGB-290) is a selective PARP1/2 inhibitor that demonstrated brain penetration, PARP-DNA complex trapping, and antitumor activity in preclinical models.6
- In patients with metastatic castration-resistant prostate cancer (mCRPC), determination of HRD mutational status is highly challenging using standard approaches.7
- DNA sequencing using tumor tissue is hampered by insufficient tissue availability and high DNA-sequencing failure rates.8
- Detection of homozygous BRCA1/2 deletions from circulating tumor DNA is challenging, and could result in missing a group of patients who could benefit from PARP inhibitor therapy.9
- Circulating tumor cells (CTCs) are shed from primary tumors during cancer progression and can be collected via liquid biopsy for further analysis.10
- The novel EPIC liquid biopsy assay uses phenotypic characterization to identify CTCs with HRD (CTC-HRD).11
- In early phase clinical studies (NCT02361723; NCT03333315), pamiparib was generally well tolerated and showed preliminary antitumor activity as a single agent.12
- These studies also established 60 mg orally daily as the recommended investigational dose.

**METHODS**

**Overall Design and Study Objectives**

- This ongoing, open-label, single-arm, global multicenter phase 2 study (NCT03712930) was designed to evaluate the efficacy and safety of pamiparib monotherapy in patients with mCRPC who are either 1) CTC-HRD+ (≥3 CTC-HRD/ml) regardless of germline or somatic BRCA1/2 mutations or 2) who have BRCA1/2 mutations regardless of CTC-HRD status (Figure 1A).13
- The primary objectives are to evaluate the efficacy of pamiparib, using Prostate Cancer Clinical Trials Working Group 3 (PCWG3) criteria, in terms of objective response rate (ORR), assessed by an Independent Review Committee (IRC), and prostate-specific antigen (PSA) response rate.14
- Key secondary objectives include duration of response by IRC, investigator-assessed ORR, time to objective response, time to PSA response/progression, duration of PSA response, time to symptomatic skeletal event, radiographic progression-free survival, overall survival, and safety/tolerability of pamiparib.15
- An exploratory objective of this study is to determine the clinical utility of the CTC-HRD assay to identify patients with mCRPC, who will derive clinical benefit from pamiparib.

**CTC-HRD Test Development (Figure 2)**

- Initial development of this assay used DNA sequencing of individual CTCs to build a microscopy-based classification model (Figure 2B).16
- Phenotypic features of CTCs harboring LSTs are correlated to the sequencing data to build a microscopy-based classification model (Figure 2B).17
- The final assay utilizes validated microscopy-based CTC detection technology and automated digital pathology methods to identify CTCs with an HRD phenotype.18
- Preliminary data indicates that when a threshold of ≥3 CTC-HRD+ cells/mL blood is used, ~30% of mCRPC patients are CTC-HRD+ with a hazard ratio of 0.37 (P<0.017; Figure 2C).
- This threshold was optimized in three patients with HRD+ cells vs non-HRD cells to derive a scoring system for clinical responses to PARP inhibitors (data from the NCI-9012 trial that compared abiraterone to abiraterone + veliparib in men with mCRPC; NCT01576172).19
- A similar assay platform was used to identify AR-V7 splice variants and inform clinical decisions in men with mCRPC.20
- This assay was also used to investigate LST as a biomarker of chromosomal instability and resistance to standard-of-care drugs in mCRPC.21

**Patient Population**

- Approximately 100 patients will be enrolled at 45 study centers in Asia, Australia, Europe, and North America.22
- Key inclusion/exclusion criteria are provided in Table 123

**Treatment**

- Patients will receive pamiparib 60 mg twice daily as 28-day cycles until disease progression; PO, oral; PSA, prostate-specific antigen.24

**Abbreviations:** BID, twice daily; BRCA1/2, breast cancer 1/2; CTC-HRD+, positive for circulating tumor cells with homologous recombination deficiency; DAPI, 4,6-diamidino-2-phenylindole; LST, large scale transitions; pGI, phenotypic genomic instability; veliparib, poly(ADP-ribose)polymerase; PSA, prostate-specific antigen; RECIST, Response Evaluation Criteria in Solid Tumors.

**REFERENCES**


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