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[3]
  - DNA repair can be compromised by the absence of homologous recombination (HR) components, such as *BRCA1* or *BRCA2*[4]
- Pamiparib (BGB-290) is a selective PARP1/2 inhibitor that demonstrated brain penetration, PARP-DNA complex trapping, and antitumor activity in preclinical models[5]
- In patients with metastatic castration-resistant prostate cancer (mCRPC), determination of HRD mutational status is highly challenging using standard approaches
  - DNA sequencing using tumor tissue is hampered by insufficient tissue availability and high DNA-sequencing failure rates[2]
  - 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[2]
- Circulating tumor cells (CTCs) are shed from primary tumors during cancer progression and can be collected via liquid biopsy for further analysis[6]
- The novel EPIC liquid biopsy assay uses phenotypic characterization to identify CTCs with HRD (CTC-HRD$^+$)[7]
- In early phase clinical studies (NCT02361723; NCT03333915), pamiparib was generally well tolerated and showed preliminary antitumor activity as a single agent[8,9]
  - These studies also established 60 mg orally twice daily as the recommended investigational dose

METHODS

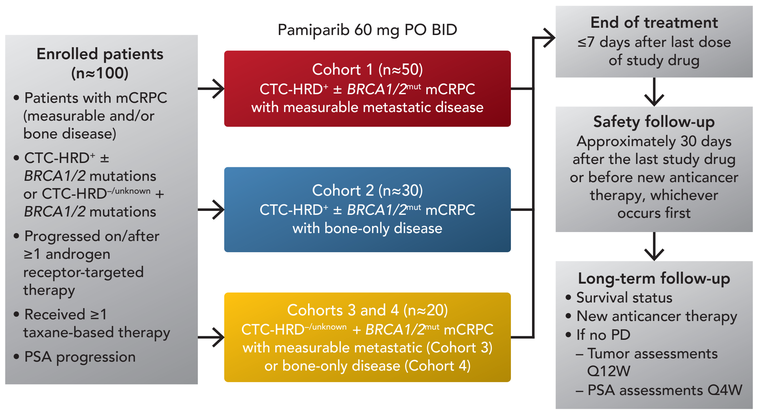
Overall Design and Study Objectives

- 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 1)
- 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
- 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
- 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 identify genomic alterations associated with HRD, such as large scale transitions (LSTs; Figure 2A)
- Phenotypic features of CTCs harboring LSTs are correlated to the sequencing data to build a microscopy-based classification model (Figure 2B)
- The final assay utilizes analytically validated microscopy-based CTC detection technology and automated digital pathology methods to identify CTCs with an HRD phenotype
- 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)
  - The threshold used represents an optimized threshold of CTC-HRD$^+$ cells vs univariate hazard ratios for clinical responses to PARPi (using data from the NCI-9012 trial that compared abiraterone to abiraterone + veliparib in men with mCRPC; NCT01576172)
- A similar assay platform was used to identify AR-V7 splice variants and inform clinical decisions in men with mCRPC[10]
- This assay was also used to investigate LST as a biomarker of chromosomal instability and resistance to standard-of-care drugs in mCRPC[11]

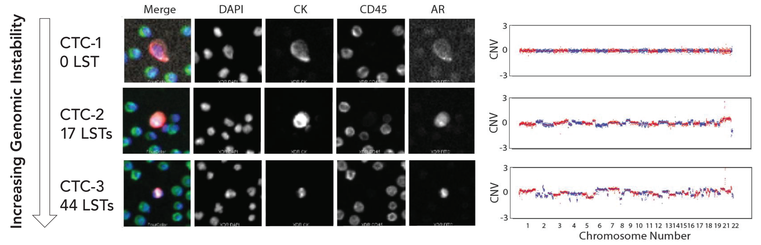
Figure 1: Study Design



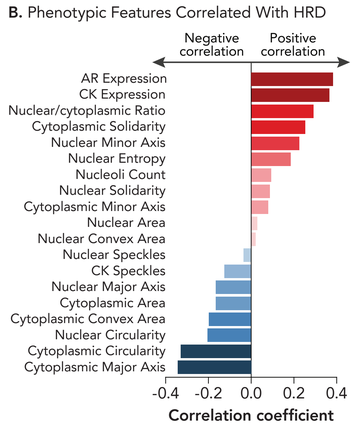
Abbreviations: BID, twice daily; *BRCA1/2*^{mut}, breast cancer 1/2 mutation; CTC-HRD$^+$, positive for circulating tumor cells with homologous recombination deficiency; mCRPC, metastatic castration-resistant prostate cancer; PD, progressive disease; PO, oral; PSA, prostate-specific antigen; Q4W, once every 4 weeks; Q12W, once every 12 weeks.

Figure 2: Epic Sciences Liquid Biopsy CTC-HRD Assay

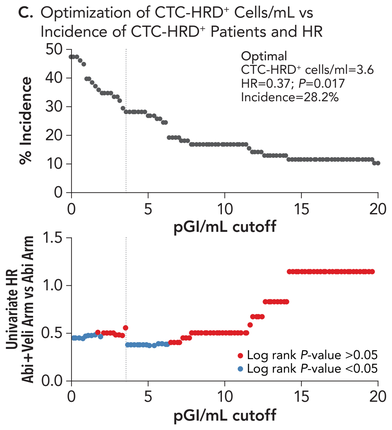
A. Example CTC images and corresponding single cell sequencing from the training set[7]



B. Phenotypic Features Correlated With HRD



C. Optimization of CTC-HRD$^+$ Cells/mL vs Incidence of CTC-HRD$^+$ Patients and HR



Abbreviations: Abi, abiraterone; AR, Androgen receptor; CK, cytokeratin; CNV, copy number variation; CTC-HRD+, positive for circulating tumor cells with homologous recombination deficiency; DAPI, 46-diamidino-2-phenylindole; HR, hazard ratio; HRD, homologous recombination deficiency; LST, large scale transitions; pGI, phenotypic genomic instability; veli, veliparib.

Patient Population

- Approximately 100 patients will be enrolled at 45 study centers in Asia, Australia, Europe, and North America
- Key inclusion/exclusion criteria are provided in Table 1
- This trial is currently enrolling; the first patient was recruited in December 2018

Treatment

- Patients will receive pamiparib 60 mg twice daily as 28-day cycles 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 (eg, 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

Table 1: Key Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
• Adult males ≥18 years • Histologically or cytologically confirmed adenocarcinoma or poorly differentiated adenocarcinoma of the prostate without neuroendocrine differentiation • mCRPC with at least one of the following: – Measurable disease per RECIST v1.1 involving viscera and/or extrapelvic nodes – Bone disease • Prostate cancer progression defined by PSA progression with ≥3 rising PSA levels (≥1 week between determinations) and a screening PSA level of ≥2 µg/L • CTC-HRD$^+$ (≥3 CTC-HRD/ml) ± *BRCA1/2* mutations **OR** CTC-HRD$^{-/unknown}$ + *BRCA1/2* mutations • ECOG performance status ≤1	• Prior treatments – Other PARP inhibitors, platinum-based therapies, cyclophosphamide, or mitoxantrone – Prior treatment with sipuleucel-T or a checkpoint inhibitor is allowed – Radiotherapy ≤21 days before first dose or ≤14 days if a single fraction was administered – Major surgical procedure, open biopsy, previous gastric resection, or significant traumatic injury ≤14 days before first dose • Comorbidities – Leptomeningeal disease, brain metastasis, or MDS – Clinically significant cardiovascular disease – Active bleeding disorder • Concomitant medications – Strong/moderate CYP3A inhibitors or strong CYP3A inducers ≤14 days before first dose

Abbreviations: *BRCA1/2*, breast cancer 1/2; CTC-HRD$^+$, positive for circulating tumor cells with homologous recombination deficiency; CYP3A, cytochrome P450 3A; ECOG, Eastern Cooperative Oncology Group; mCRPC, metastatic castration-resistant prostate cancer; MDS, myelodysplastic syndrome; PARP, poly(ADP-ribose) polymerase; PSA, prostate-specific antigen; RECIST, Response Evaluation Criteria in Solid Tumors.

Study Assessments and Statistical Analysis

- The co-primary endpoints across all cohorts are ORR by IRC assessment and PSA response rate
- Safety and tolerability will be assessed as secondary endpoints in all cohorts
- In Cohorts 1 and 2, additional secondary endpoints include time to and duration of PSA response, time to PSA progression or symptomatic skeletal event, radiographic progression-free survival, and overall survival
  - Cohort 1 will also examine duration of response by IRC and investigator-assessed ORR
- Tumor assessments will be evaluated at screening and every 8 weeks for the first 24 weeks, then every 12 weeks
- Levels of PSA will be evaluated at screening and every 4 weeks after the first dose of study drug
- Blood samples for CTC assessment will be collected at screening and every 8 weeks for the first 24 weeks, then every 12 weeks

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