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

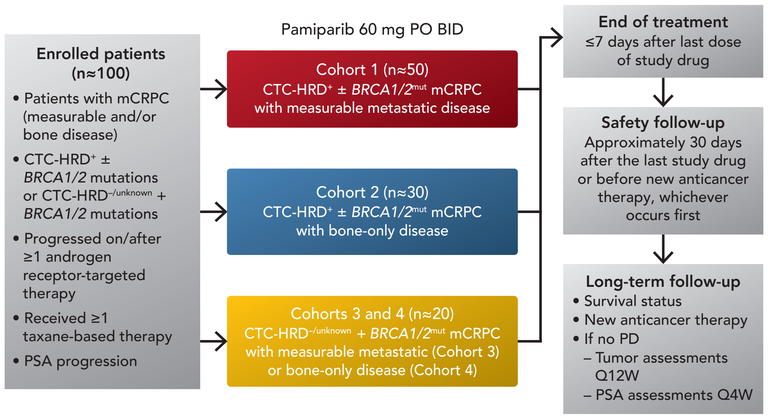
Overall Design and Study Objectives

- 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]

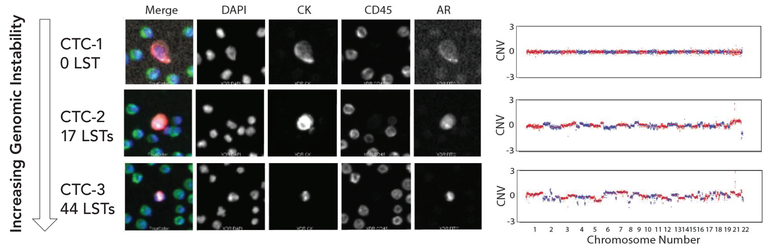
Figure 1: Study Design



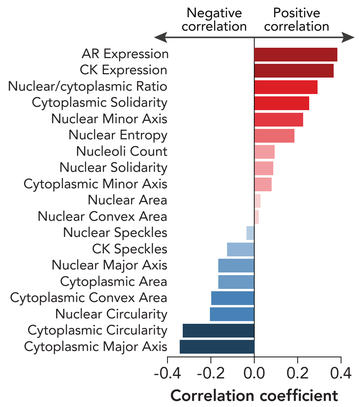
Abbreviations: BID, twice daily; *BRCA1/2*^{mut}, breast cancer 1/2 mutation; CTC-HRD$^+$, positive for circulating tumor cells with homologous recombination deficiency; mCRPC, metastatic castration-resistant prostate cancer; PD, progressive disease; PO, oral; PSA, prostate-specific antigen; Q4W, once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

Figure 2: Epic Sciences Liquid Biopsy CTC-HRD Assay

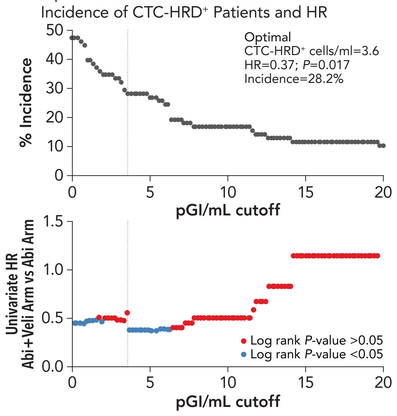
A. Example CTC images and corresponding single cell sequencing from the training set[7]



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

REFERENCES

1. Fitzmaurice C, Akinyemiju TF, Al Lami FH, et al. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 29 cancer groups, 1990 to 2016: A systematic analysis for the global burden of disease study. *JAMA Oncol*. 2018;4(11):1553-1568.
2. Chowdhury S, McDermott R, Piulats JM, et al. Genomic profiling of circulating tumour DNA (ctDNA) and tumour tissue for the evaluation of rucaparib in metastatic castration-resistant prostate cancer (mCRPC). *Ann Oncol*. 2018;29(suppl 8):Abstract 795PD.
3. Lupo B, Trusolino L. Inhibition of poly(ADP-ribosyl)ation in cancer: old and new paradigms revisited. *Biochim Biophys Acta*. 2014;1846(1):201-215.
4. Ledermann JA, Drew Y, Kristeleit RS. Homologous recombination deficiency and ovarian cancer. *Eur J Cancer*. 2016;60:49-58.
5. Tang Z, Jiang B, Shi Z, et al. BGB-290, a novel PARP inhibitor with unique brain penetration ability, demonstrated strong synergism with temozolomide in subcutaneous and intracranial xenograft models. *Cancer Res*. 2015;75(suppl 15):Abstract 1651.
6. Alix-Panabieres C, Pantel K. Circulating tumor cells: liquid biopsy of cancer. *Clin Chem*. 2013;59(1):110-118.
7. Dittamore R, Wang Y, Daignault-Newton S, et al. Phenotypic and genomic characterization of CTCs as a biomarker for prediction of veliparib therapy benefit in mCRPC. *J Clin Oncol*. 2018;36(suppl 15):Abstract 5012.
8. 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.
9. 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 13):Abstract CT050.
10. Scher HI, Graf RP, Schreiber NA, et al. Phenotypic heterogeneity of circulating tumor cells informs clinical decisions between AR signaling inhibitors and taxanes in metastatic prostate cancer. *Cancer Res*. 2017;77(20):5687-5698.
11. Sher HI, Schonhoft J, Hullings M, et al. Morphology-predicted, large-scale transition (LST) number in circulating tumor cells (CTC) as a biomarker of chromosomal instability (CIN) to assess early resistance to standard of care (SOC) drugs in mCRPC. *J Clin Oncol*. 2019;37(suppl 7):Abstract 225.

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