Overall Design and Study Objectives

- **Primary objectives** are to evaluate the efficacy of pamiparib, using Prostate Cancer Clinical Circulating tumor cells (CTCs) are shed from primary tumors during carcinogenesis and are involved in DNA repair. Poly (ADP-ribose) polymerase (PARP) proteins are a family of proteins involved in DNA repair, genome stability, and programmed cell death. CTCs are shed from primary tumors in circulating tumor DNA (ctDNA) and can be collected via liquid biopsy for further analysis. DNA sequencing using tumor tissue is hampered by insufficient tissue availability and high DNA-sequencing failure rates.

- **Secondary objectives** include duration of response by IRC, investigator-assessed ORR, and safety/tolerability of pamiparib.

METHODS

**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.

**Study Design**

- 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.

**Tumor assessments** will be evaluated at screening and every 8 weeks for the first 24 weeks, then every 12 weeks thereafter.

**CTC-HRD Test Development**

- The initial validation of the approach involved the testing of individual CTCs to identify genomic alterations associated with HRD, such as large scale transitions (LOI).

- Phenotypical features of CTCs harboring LOIs are correlated to the sequencing data to support the development of a reliable bioinformatics classification model.

- The final assay utilizes analytically validated microfluidic-based CTC detection technology and Cytoplasmic Convex Area, Cytoplasmic Circularity, and Nuclear Major Axis. The thresholds used represent an optimized threshold of CTCs harboring an HRD phenotype.

- The assays were also used to investigate LSTR as a biomarker of chromosome instability and resistance to standard-of-care drugs in mCRPC and is presented at Board K4: Abstract 225.

**Study Assessments and Statistical Analysis**

- The co-primary endpoints across all cohorts are ORC by IRC assessment and PSA response.

- Safety and tolerability will be assessed as secondary endpoints in all cohorts.

- In cohorts 1 and 2, additional secondary endpoints include time to PSA progression, time to PSA progression or symptomatic skeletal events; radiographic progression-free survival, overall survival.

- Time to PSA progression or symptomatic skeletal events; radiographic progression-free survival, overall survival.

- The assay 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 thereafter.

- 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.

**Key Inclusion/Exclusion Criteria**

- **Outcome measures**:
  - Other PARP inhibitors, platinum-, taxane-based therapy, or taxane-based therapy, whichever comes first. Rucaparib therapy, for patients with germline or somatic *BRCA1* or *BRCA2* mutations.
  - Median duration of therapy is 5-10 months.

**References**


**Acknowledgments**

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**Table 1: Key Inclusion and Exclusion Criteria**

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
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<tbody>
<tr>
<td>• ECOG performance status ≤1</td>
<td>• History of significant neurologic disease that is untreated or uncontrolled</td>
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<tr>
<td>• Measurable disease per RECISTv1.1</td>
<td>• Previous treatment with PARP inhibitors, platinum-, taxane-based therapy, or taxane-based therapy, whichever comes first</td>
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<td>• Adult males ≥18 years</td>
<td>• Current or prior history of leptomeningeal disease</td>
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<tr>
<td>• Histologically or cytologically confirmed</td>
<td>• At least one of the following: multiple medical conditions that, in the investigator’s opinion, would prejudice the patient’s ability to participate in the study</td>
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