Novel next generation PARP1 selective and CNS penetrant inhibitor DSB2455: A Phase Ia/Ib Open Label, Multi-Centre Dose Escalation Study with Expansion Cohorts to Assess the Safety, Tolerability, and Activity as Monotherapy in Participants with Advanced Malignancies

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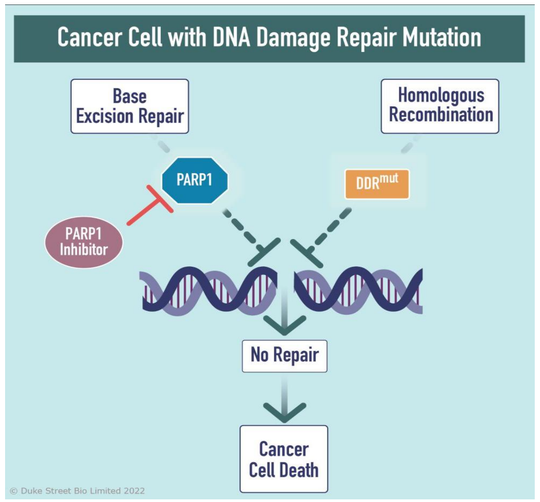
Background

PARP1 is primarily involved in the detection and repair of DNA damage, as well as in the regulation of gene expression. It is found in the nucleus and is activated by single-strand DNA breaks. Closely related PARP2 is also involved in this pathway; however, its inhibition is associated with haematotoxicity.

DSB2455 is a next-generation PARP1 inhibitor with high selectivity over PARP2, expected to reduce haematological toxicity, while providing a therapeutic benefit in participants with tumours with BRCA1/2 mutations or Homologous Recombination Deficiency (HRD). Preclinically, DSB2455 monotherapy has demonstrated strong anti-tumour activity[1], high rat CNS penetrance[2] , and a safe haematotoxicity profile. These data provide the rationale to explore DSB2455 as monotherapy in participants with these molecular alterations. Study objectives are to assess safety and tolerability, establish a recommended dose range (RDR) and evaluate early clinical efficacy. DSB2455 is administered orally.

1. **Safety advantage – selectivity for PARP1 vs PARP2 anticipated to reduce risk of haematotoxicity**
2. **Tumour penetrance – excellent preclinical PK residency time**
3. **CNS penetrance**



Objectives

Dose Escalation Phase

Primary Objectives

- Evaluate the safety, tolerability, and dose-limiting toxicities (DLTs) of DSB2455 as monotherapy
- Determine the RDR for DSB2455 in participants with selected solid tumours*

Secondary Objectives

- Describe the pharmacokinetics (PK) of **DSB2455** in participants with selected solid tumours
- Evaluate the efficacy of DSB2455 in participants with selected solid tumours*

*Metastatic castrate-resistant prostate cancer (mCRPC), advanced ovarian cancer, metastatic breast cancer, and secondary brain metastases (Expansion Phase only)

Dose Expansion Phase

Primary Objectives

- Assess the objective response rate (ORR) per Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 associated with DSB2455 treatment

Secondary Objectives

- Evaluate the safety and tolerability of DSB2455 treatment
- Evaluate the efficacy of DSB2455 in participants with selected solid tumours*
- Describe the PK of DSB2455 in participants with selected solid tumours*
- Assess the prostate specific antigen decline of >50% (PSA50) response rate (Cohort A)
- Assess changes in CA125 levels (Cohort B)
- Evaluate the efficacy of DSB2455 treatment using the response assessment in neuro-oncology brain metastases (RANO BM) criteria (Cohort D)

Dose Escalation and Dose Expansion Phases (All Cohorts)

Exploratory Objectives

- To evaluate potential predictive biomarkers of activity of DSB2455
- To explore the PK-pharmacodynamic relationship between PK and efficacy, safety, blood-borne and tissue biomarkers
- Exploratory research into genes and genetic variations that may influence response to DSB2455 (i.e., distribution, safety, tolerability, and efficacy).
- Explore the relationship between DSB2455 PK and safety, anti-tumour activity, and biological activity and the impact of participant characteristics on PK

References
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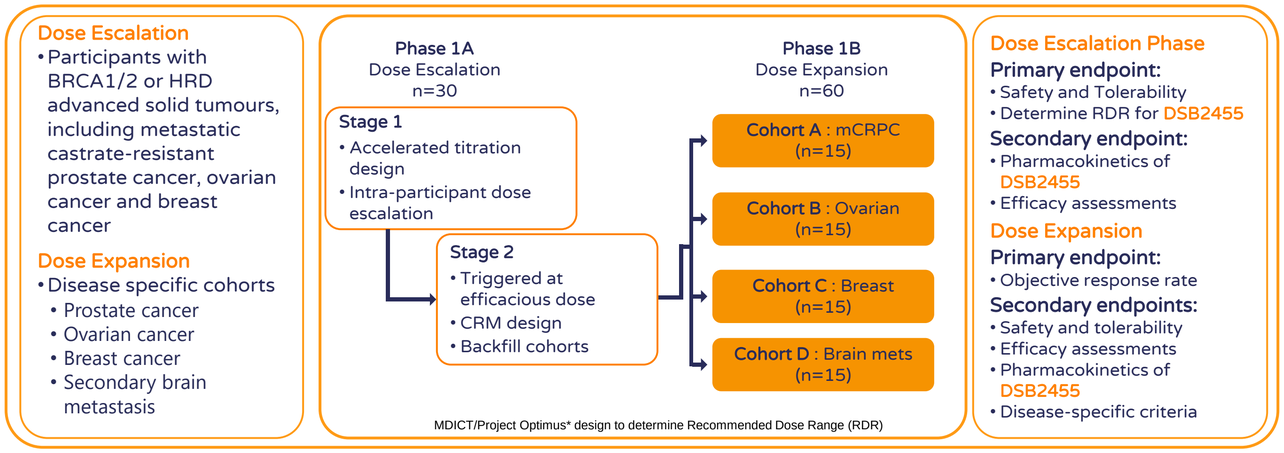
2. Cowley PM, McGuinness BE, Campbell GM, Wise A. "Abstract B055: Characterization of highly selective and CNS-penetrant PARP1 inhibitors." Molecular Cancer Therapeutics 22.12_Supplement (2023): B055-B055, https://doi.org/10.1158/1535-7163.TARG-23-B055
3. U.S. Department of Health and Human Services, Food and Drug Administration. *Optimizing the Dosage of Human Prescription Drugs and Biological Products for the Treatment of Oncologic Diseases: Guidance for Industry.* Washington, DC: FDA; August 2024. Docket No. FDA-2022-D-2827. Available from: FDA website (FDA Media 164555)

Methods

This is a Phase Ia/Ib study design, in line with Project Optimus[3] and will enrol up to 90 participants. It consists of two parts. **Part A Dose Escalation** with two stages, **Stage 1: Accelerated Titration Design** and **Stage 2: Continuous Reassessment Model (CRM) Design**. Intraparticipant dose escalation and backfill cohorts are permitted. **Part B Dose Expansion** will consist of 4 cohorts: **mCRPC, advanced ovarian cancer, advanced breast cancer** and **secondary brain metastasis with BRCA1/2 mutations or HRD**. The study incorporates a Bayesian CRM to identify a recommended dose and RDR. It will also investigate pharmacodynamic (PD) and exploratory biomarker profiles and study their relationship to PK and efficacy. Eligible patients are aged ≥18 years with prostate, ovarian or breast cancer who have failed prior PARP inhibitor and/or standard therapies. The starting dose is DSB2455 5 mg OD.

Figure 1: DSB2455 Study Design



* https://doi.org/10.1016/j.annonc.2022.09.158

Key Inclusion Criteria

1. Aged ≥18 years of age on the day of signing the informed consent
2. Provision of formalin-fixed and paraffin embedded (FFPE) sample is mandatory. If an FFPE sample is not available, then a baseline fresh biopsy is required
3. Histologically confirmed diagnosis of locally advanced and/or metastatic breast cancer, prostate cancer or ovarian cancer.
4. Deleterious frameshift or truncating or if results in loss of function alterations in BRCA1, BRCA2, or HRD
5. Measurable disease per RECIST v1.1
6. ECOG performance status of 0 to 1 and life expectancy >12 weeks.
7. Participants may have received up to one prior line of therapy with a PARP inhibitor-based regimen
8. Must have known asymptomatic or symptomatic brain metastasis, as confirmed by an MRI brain scan, from a primary tumour (Cohort D)

Key Exclusion Criteria

1. Myelodysplastic syndrome (MDS), acute myeloid leukaemia (AML) or features suggestive of MDS/AML
2. Has received a prior PARP1-selective inhibitor
3. Has received prior systemic anti-cancer therapy including investigational agents within 4 weeks prior to study intervention
4. Received prior radiotherapy within 2 weeks of the start of study intervention or has a history of radiation pneumonitis

Current Status

- Phase 1a Dose Escalation part of the study was initiated on 26th November 2024 and Stage 2 has commenced
- Participants enrolled in dose level cohorts 1 – 4 (5mg – 40mg)
- 7 sites are currently active across EU & US
- Approximately 20 sites will be active during the remainder of Phase 1a and Phase 1b.

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Presenting author disclosure statement
No conflicts of interest.

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