TPS1130 **Poster Session**

Dauntless-1, a phase 2 clinical trial to evaluate PMD-026, a first-in-class pan-RSK inhibitor, combined with fulvestrant to overcome resistance to CDK4/6 inhibitors in advanced or metastatic HR+/HER2- breast cancer.

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Background: Resistance to CDK4/6 inhibitors (CDK4/6i) is common for many patients with HR+/HER2- advanced or metastatic breast cancer, therefore new strategies are urgently needed to overcome this challenge. Ribosomal S6 kinases (RSK1-4) are implicated in breast cancer growth and resistance, and they are activated by the PI3K and MAPK pathways, which are linked to CDK4/6i resistance. As a convergence point of these pathways, RSK drives resistance by promoting the G2/M phase of the cell cycle and bypassing G1/S control. Inhibiting RSK with PMD-026, a first-in-class oral small molecule inhibitor, halts G2/M progression and blocks growth in CDK4/6i-resistant models, including those cross-resistant to abemaciclib and palbociclib. RSK also complexes with estrogen receptor alpha (ERα), enhancing transcription and tumor growth. PMD-026 disrupts this interaction, showing activity in both ESR1 wild-type and mutant HR+/HER2- models, making it a promising partner for endocrine therapies. It synergizes with fulvestrant and oral SERDs, achieving significant growth inhibition in pre-clinical models, including a 7000-fold improvement with fulvestrant in soft agar assays. Nuclear translocation of RSK is a key driver of breast cancer in mice and serves as a biomarker for RSK signalling activity. In the Phase 1/1b monotherapy study, PMD-026 was generally well-tolerated, and it reduced the risk of progression or death in patients by 93% in a subset of RSK2 high metastatic breast cancer patients. **Methods:** Dauntless-1 is a Phase 2a study for locally advanced or metastatic HR+/HER2- breast cancer patients previously treated with a CDK4/6i in combination with endocrine therapy (NCT04115306). It is designed to prospectively enroll RSK2+ (≥50% nuclear staining with ≥2+ staining intensity) patients to evaluate PMD-026 in combination fulvestrant. Fulvestrant will be dosed per the package insert (500 mg IM, Day 1 and 15 of the first 28-day cycle, then Day 1 of every cycle thereafter) in combination with PMD-026 at the RP2D (200 mg, PO, Q12h), determined in the dose-finding portion of the study. The combination regimen will have a safety lead-in cohort of 6 patients. The SRC will review the safety data after the sixth patient has been treated for at least 28 days. If determined to be safe, up to 14 additional patients will receive the combination for a total of 20 patients. A Bayesian safety monitoring rule will be used to evaluate the rate of DLTs during expansion. Primary objectives will be safety, pharmacokinetics, and progression free survival. Secondary objectives include duration of response, overall response and overall survival. Exploratory objectives will evaluate PMD-026 in the context of mutations (ESR1, PIK3CA, AKT1, p53, KRAS) at baseline using ctDNA. Clinical trial information: NCT04115306. Research Sponsor: None.