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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PHOENIX MOLECULAR DESIGNS
DESIGNING PRECISE CANCER THERAPEUTICS

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1. Background

Ribosomal S6 kinase (RSK) is situated at the convergence of the PI3K and ERK-MAPK pathways and plays a crucial role in cell growth and survival[1]. It has been reported that up to 70% of breast tumors have a high expression of RSK2[2,3], which is an indicator of poor prognosis in patients with breast cancer[4]. RSK2 binds directly to estrogen receptor alpha (ERα) to promote tumor growth and the development of breast cancer in mice[5] (**Figure 1A**). RSK1-4 have been linked to endocrine therapy (ET) and CDK4/6 inhibitor (CDK4/6i) resistance, which are common in patients with HR+/HER2- advanced or metastatic breast cancer (mBC)[6]. RSK drives resistance by promoting the G2/M phase of the cell cycle and bypassing G1/S control. PMD-026 is a first-in-class oral small molecule RSK inhibitor that halts G2/M progression and blocks growth in pre-clinical models of CDK4/6i resistance (**Figure 1B**). In addition, PMD-026 inhibits the nuclear translocation of RSK2 (with no change to levels of nuclear ERα) (**Figure 2A**). Combining PMD-026 and fulvestrant reduced ERα transcription by 84% as demonstrated by ELISA (**Figure 2B**). Taken together, the working model for overcoming CDK4/6i resistant in mBC patients is to combine PMD-026 and fulvestrant (**Figure 3**). In MCF-7 IBR (a CDK4/6i resistant ESR1 WT breast cancer model), PMD-026 synergizes with fulvestrant to yield a 7000-fold improvement in the inhibition of tumor growth in soft agar (**Figure 4A**). Likewise, PMD-026 was synergistic with all oral selective estrogen receptor degraders (SERDs) or vepdegestrant (ARV-471) in this model (**Figure 4B**).

Figure 1: PMD-026 is a highly differentiated approach to breaking through CDK4/6i resistance

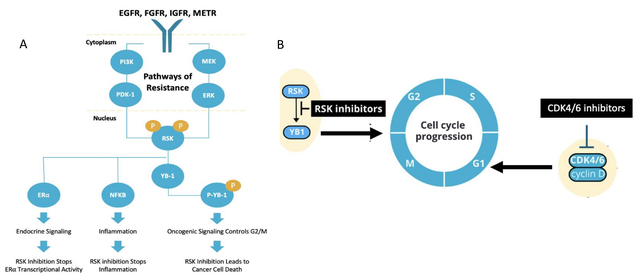


Figure 2: PMD-026 inhibits RSK and ERα transcriptional activity in the ESR1 WT HR+ MCF-7 cell line

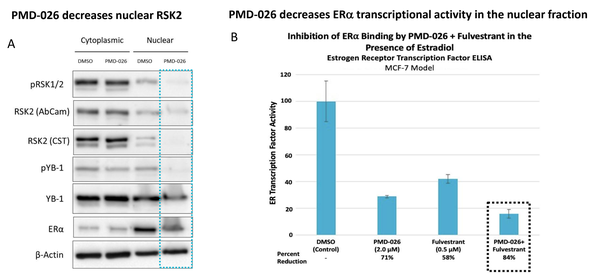


Figure 3: Working model for the combination of PMD-026 and Fulvestrant

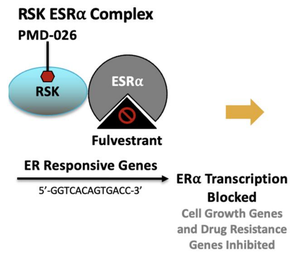
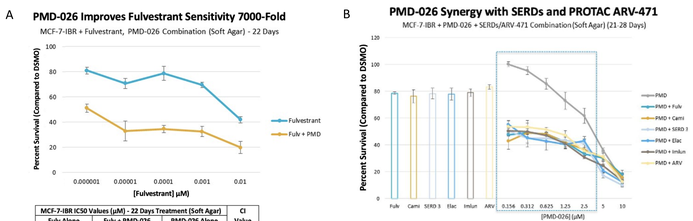


Figure 4: PMD-026 combined with endocrine therapies are highly synergistic in CDK4/6 inhibitor resistant models demonstrating a class effect



MCF-7-IBR IC50 Values (μM) - 22 Days Treatment (Soft Agar)			CI
Fulv Alone	Fulv + PMD-026	PMD-026 Alone	Value
7.0×10^{-3}	1.0×10^{-4}	3 μM - 80% Survival	0.65

PMD-026 plasma levels in mBC patients cover the synergy range

2. PMD-026 Phase 2a Clinical Trial Dauntless-1 Study Design

Dauntless-1 is a Phase 2a study of PMD-026 plus fulvestrant in locally advanced or metastatic HR+/HER2- breast cancer patients with high RSK expression (≥50%) previously treated with a CDK4/6i + ET combination (NCT04115306). PMD-026 was evaluated at two dose levels of 200 mg Q12h or 100 mg Q12h combined with fulvestrant. The recommended Phase 3 dose for a registrational trial will be established. Outcomes will be compared to a historic control. Historic control studies indicate that fulvestrant as a single agent post CDK4/6i delivers median progression-free survival (mPFS) of 2.35 months (Range: 1.8 – 5.3 months) and an overall response rate of 5.4% (Range 2.9% - 11%) in patients (**Table 1**)

Figure 5: PMD-026 Phase 2a clinical trial Dauntless-1 study schema

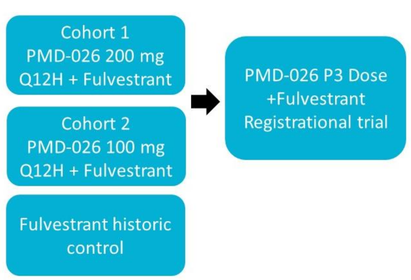


Table 1: Fulvestrant historic control from 1436 patients across 12 clinical trials[7]

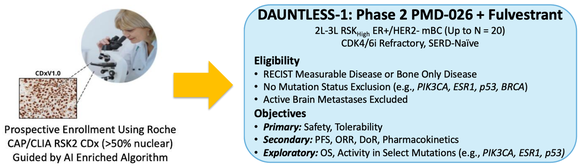
Trial	Phase	n = 1436	ESR1m %	Median Prior Tx	Prior %CDK4/6i	Prior % Fulv	mPFS post-CDK4/6i	ORR%
ELAINE-1	II	20	100	1	100	0	3.7	2.9
CAPItello-291	III	248	NA	1	70	0	2.6	NA
VERONICA	II	52	30	1	100	0	1.94	5.9
EMERALD	III	165	47.8	1	100	3.6 #	1.9	4.4 †
SERENA-2	II	73	48	1	51	0	2.1	NA
MAINTAIN	II	50	41.6 *	1	100	0	2.76	11 **
SOLAR +	III	20 +	NA	1	100 ^	0	1.8	NA
PACE	II	55	54	1	100	0	4.8	7.3
postMONARCH	III	186	42.3	1	100	0	5.3	5.4 [b]
VERITAC-2	III	311	43	1	100	0	3.6	3.6
FINER	III	125 ‡	NA	1	100	0	1.9	NA
VIKTORIA-1	III	131	NA	1	100	0	2.0	NA
						Median	**2.35**	**5.4**

* 15/36 (41.6%) from Fig. 4
+ *PIK3CA*m
^ From [8] re: SOLAR (p.495)
† For SOC, which was 69% Fulv., 31% AI
** 85% received Fulv., 15% an AI
[b] From the ITT

2. Design (Continued)

Figure 6. Dauntless-1 is a single arm phase 2a trial of PMD-026 plus fulvestrant in 2L-3L ER+/HER2- mBC patients with RSK2 high expression (>50%) previously treated with CDK4/6i + ET and with no prior exposure to a SERD. A CAP/CLIA RSK CDx is used to screen patients for RSK expression. ESR1 mutations are quantified via ctDNA testing.

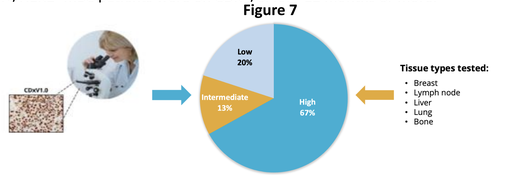
Figure 6



3. Results

Figure 7. The distribution of RSK expression levels in 30 ER+/HER2- 2L mBC patients screened for DAUNTLESS-1 was universally expressed at different levels in the primary breast tumor as well as in distant metastases, with the frequency of high expression (67%) comparable to those reported historical in the literature (70%). The majority of RSK2+/HR+/HER2- mBC patients were on CDK4/6i for ~12 months or more.

Figure 7



3. Results (Continued)

Table 2. Treatment-Related Adverse Events (TRAEs). Two doses of PMD-026: 200 mg po BID and 100 mg po BID. Grade 3 rash and elevated transaminases led to a reduction in the starting dose of PMD-026 from 200 mg BID to 100 mg BID.

Table 2

DAUNTLESS-1 TRAEs

Dermatologic and Hepatic

PMD-026 200 mg BID (N = 2)	All Grades	Grade 3
AST Increase	2 (100%)	2 (100%)
ALT Increase	2 (100%)	2 (100%)
Rash (Maculopapular)	2 (100%)	2 (100%)
PMD-026 100 mg BID (N = 6)		
AST Increase	0 (0%)	0 (0%)
ALT Increase	0 (0%)	0 (0%)
Rash (Maculopapular)	1 (17%)	1 (17%)

Figure 8. Pharmacokinetics Synergy Range: In two patients, one at PMD-026 200 mg po BID and the other at PMD-026 100 mg po BID, plasma levels of PMD-026 fall within the synergy range when combined with fulvestrant. The median plasma concentration of PMD-026 200 mg po BID as a monotherapy was 1 μM. **Figure 9.** Synergy range with fulvestrant is predicted by PK modelling to be fully covered by PMD-026 100 mg BID, supporting a reduction in the starting dose of PMD-026 from 200 mg po BID to 100 mg po BID.

Figure 8

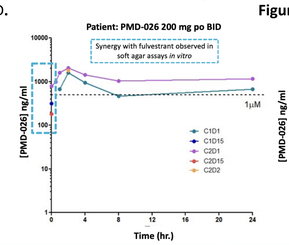
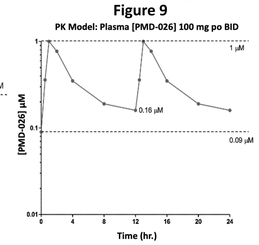


Figure 9



3. Results (Continued)

Figure 10. Preliminary efficacy results: Early and durable anti-tumor activity in *ESR1$_{wt}$* patients. **Figure 11.** Duration of treatment in those patients that exceeds the historical mPFS for fulvestrant monotherapy (2.35 months).

Figure 10

Tumor Response

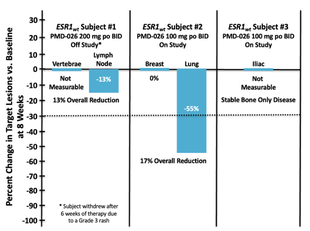
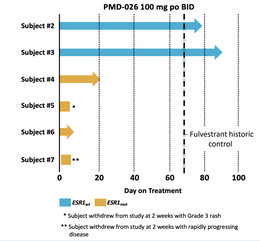


Figure 11

Duration of Treatment
PMD-026 100 mg po BID



4. Discussion

Key Points:

- RSK cooperates with ERα to drive malignant transformation, is highly expressed in ~70% of patients with ER+/HER2- mBC, and high expression (RSK$_{High}$) is associated with poor prognosis.
- PMD-026 monotherapy in heavily pre-treated RSK$_{High}$ mBC patients demonstrated mPFS of 4.3 months and an 88% reduction in the risk of disease progression and death compared with low RSK expressing patients (mPFS = 1.3 months)[3].
- In a CDK4/6i resistant, *ESR1$_{wt}$* breast cancer model, PMD-026 synergizes with fulvestrant to yield a 7000-fold improvement in the inhibition of tumor growth.
- The pharmacokinetics of 2 patients receiving PMD-026 at the initial starting dose of 200 mg BID with fulvestrant and compared to Phase 1 monotherapy showed a median of 2.5 μM across 24 hours for PMD-026 compared to 1 μM for PMD-026 as a monotherapy, resulting in a higher than expected exposure for the combination relative to PMD-026 monotherapy, which was associated with G3 rash and elevated transaminases that resolved when PMD-026 was held.
- PMD-026 100 mg po BID plus fulvestrant is currently being studied in RSK$_{High}$ 2L-3L ER+/HER2- mBC patients previously treated with CDK4/6i + ET.
- Preliminary results indicate the combination is tolerable with promising early signs of durable anti-tumor activity in CDK4/6i refractory RSK$_{High}$ *ESR1$_{wt}$* mBC patients.
- oSERDs alone or in combination with other drugs are becoming the standard of care in 2L *ESR1$_{mut}$* ER+/HER2- mBC.
- Trials evaluating an oSERD plus CDK4/6i retreatment are underway or completed in the 2L *ESR1$_{wt}$* ER+/HER2- mBC setting, but to date the results have not yet led to regulatory approvals in this setting.

4. Discussion (Continued)

- A potential alternative approach for the 2L *ESR1$_{wt}$* ER+/HER2- mBC is to use a novel but related cell cycle arrest mechanism (G2/M) with PMD-026 versus a redundant G1 cell cycle arrest mechanism that utilizes CDK4/6i retreatment, which could be explored in future studies of PMD-026 combinations.

5. References

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7. References available upon request

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