PHOENIX MOLECULAR DESIGNS
DESIGNING PRECISE CANCER THERAPEUTICS

A first-in-human Phase 1/1b multicenter, open-label dose escalation study to assess safety and tolerability of PMD-026, a first-in-class oral RSK inhibitor, in metastatic breast cancer patients

PS11-33

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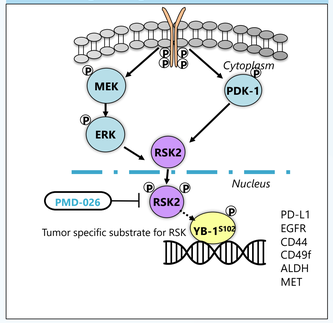
BACKGROUND

- PMD-026 is a First-in-Class RSK2 inhibitor
  - Small molecule, **orally** available, highly selective
  - Lead indication: triple-negative breast cancer (TNBC)
  - Preclinical efficacy in TNBC models[1]
  - p90 ribosomal S6 kinase (RSK) is a highly sought-after target for cancer
- RSK2 is expressed in 87% of triple negative breast cancers (TNBC) and nuclear location of RSK2 indicates activation of the MEK/ERK/RSK pathway (Fig 1).
- Here we describe PMD-026, a first-in-human oral RSK inhibitor for TNBC

Figure 1. PMD-026 interference in the cancer signaling.



STUDY DESIGN

- **Primary objectives:** determine safety and tolerability of PMD-026, maximum tolerated dose (MTD), recommended phase 2 dose (RP2D)
- **Secondary objectives:** evaluate pharmacokinetics (PK), time to and duration of response
- **Exploratory objectives:** evaluate RSK2 expression in tumor tissues retrospectively and determine relationship with response

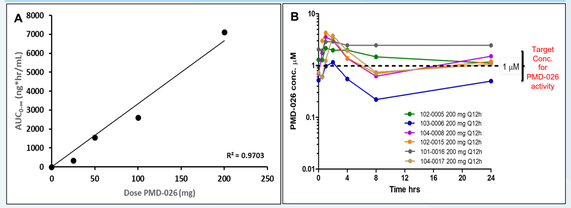
DEMOGRAPHICS OF DOSE ESCALATION PATIIENTS

- 7 TNBC patients and 8 hormone positive patients (total n=15) were treated on study from November 14, 2019 to September 15, 2020
- Patients were enrolled in a total of 6 PMD-026 dose levels: 25 mg QD, 50 mg QD, 100 mg QD, 200 mg QD, 200 mg Q12h (400 mg/day) and 300mg Q12h (600 mg/day)[2]
- Median ECOG performance status (range): 0 (0-1)
- Median number of prior regimens was 5 (range 1-11)

PHARMACOKINETICS

- Good plasma exposure to PMD-026 following oral dosing
- Dose linearity between 25-200 mg QD (Fig. 2A)
- Q12h dosing is favored to sustain desired preclinical efficacious concentrations (Fig. 2B)
- $T_{1/2}$ ~6 h (range 4-8 h)
- High V_d (volume of distribution)
- T_{max} is ~2 h (range 1-4 h)
- C_{max} median is 1242 ng/mL (range 477-1799 ng/mL)

Figure 2. PMD-026 pharmacokinetics on Cycle 1 Day 15.



SAFETY

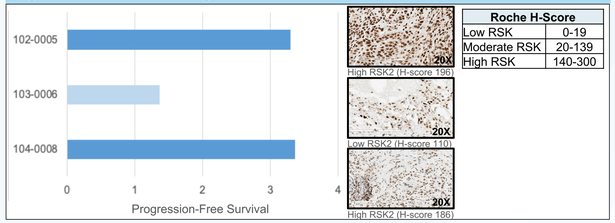
- PMD-026 was generally well-tolerated; adverse events were largely low grade and reversible
- The most common AEs were fatigue and GI (nausea, vomiting, constipation, GERD, stomatitis) side effects as the most common symptoms
- The Recommended Phase 2 Dose (RP2D) is 200 mg Q12h
- Dose Limiting Toxicities (DLTs): G3 dehydration 2º to N/V at the MTD/RP2D. Above the RP2D one G3 acute kidney injury (AKI) associated with N/V and one G3 syncope of uncertain etiology
- Most common G3 treatment-related AEs (TRAEs) were neutropenia (13.3%) and fatigue (13.3%)
- Dose reductions occurred in n=2 (G1 elevated AST and G1 pyrexia) and treatment discontinuations occurred in n=2 (unrelated G3 dyspnea and G3 AKI)
- No alopecia nor peripheral neuropathy was observed

Table 2. Adverse events at all doses ≥ 10% (N=15).

	All AEs (related and unrelated), n (%)	AEs (Treatment-Related), n (%)
Fatigue	10 (66.7)	9 (60.0)
Nausea	7 (46.7)	6 (40.0)
Aspartate aminotransferase increased	5 (33.3)	4 (26.7)
Rash maculo-papular	5 (33.3)	3 (20.0)
Neutrophil count decreased	4 (26.7)	3 (20.0)
Muscular weakness	4 (26.7)	3 (20.0)
Constipation	4 (26.7)	2 (13.3)
Alanine aminotransferase increased	3 (20.0)	3 (20.0)
Gastroesophageal reflux disease	3 (20.0)	2 (13.3)
Diarrhea	3 (20.0)	2 (13.3)
Stomatitis	2 (13.3)	2 (13.3)
Dyspepsia	2 (13.3)	2 (13.3)
Vomiting	2 (13.3)	2 (13.3)
Platelet count decreased	2 (13.3)	2 (13.3)
Anemia	2 (13.3)	2 (13.3)
Decreased appetite	2 (13.3)	2 (13.3)
Dehydration	2 (13.3)	2 (13.3)
Alopecia	0 (0)	0 (0)
Peripheral neuropathy	0 (0)	0 (0)

RSK2 EXPRESSION

Figure 3. RSK2 IHC images in TNBC samples at RP2D.



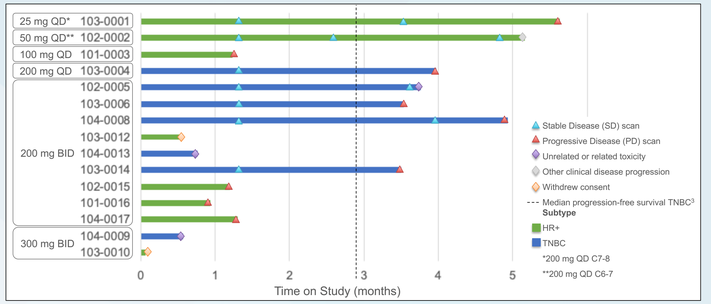
Roche H-Score	
Low RSK	0-19
Moderate RSK	20-139
High RSK	140-300

- Nuclear RSK2 was detectable by immunohistochemistry (IHC) in all evaluable patients (n=14); one sample was not evaluable
- Of evaluable tissue, RSK2 was found to be expressed at moderate levels in n=3 (20%) and high levels n=11 (73.3%)
- In the Phase 1b Expansion, retrospective analysis will be performed between the expression of nuclear RSK2 and response to treatment

CLINICAL ACTIVITY

- Initial signs of efficacy:
  - n=1 decrease in non-target lesion (102-0005)
  - n=2 decrease in tumor biomarker (103-0004, 103-0014)
  - n=2 decrease in target lesions (104-0008, 103-0014)

Figure 4. Time on study for completed escalation portion.



CONCLUSIONS

- PK: analysis showed a linear PK profile and supported Q12h dosing
- Safety: The RP2D of PMD-026 is 200 mg Q12h
  -The safety profile consists of low-grade reversible AEs with fatigue and nausea being the most common
  -DLT at the RP2D was G3 dehydration secondary to GI toxicity
  RSK2 expression: detectable in 100% of evaluable samples
- Clinical activity: continue to assess as the trial progresses
- Dose Expansion in metastatic TNBC patients with measurable disease is open to enrolment (9 clinical sites as of Q4 2020)

ACKNOWLEDGMENTS

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