PHOENIX MOLECULAR DESIGNS
DESIGNING PRECISE CANCER THERAPEUTICS

PMD-026, a first-in-class oral p90 ribosomal S6 kinase (RSK) inhibitor for triple-negative breast cancer (TNBC)

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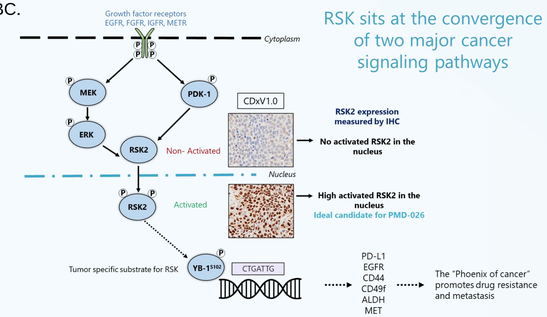
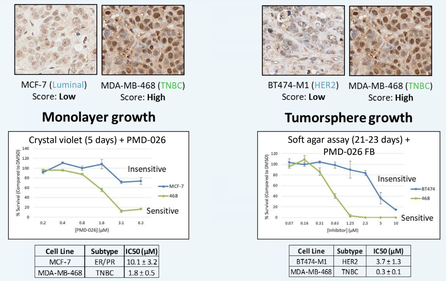
Background

Functional dependency of TNBC on RSK2 was discovered through unbiased kinome-wide screens across a heterogeneous panel of breast cancer cell lines [1]. Silencing RSK2 by siRNA in TNBC inhibited growth *in vitro* with induction of apoptosis and suppression of tumor growth in mice [2]. Pharmacological inhibition of RSK2 with RSK inhibitors further validated RSK2 as a TNBC target in xenografts in mice [2,3]. The challenge until now has been in developing an inhibitor that has favorable pharmacological and pharmacokinetic properties required for oral delivery. PMD-026, an oral first-in-class small molecule kinase inhibitor, is the first RSK inhibitor to be tested in a clinical trial for patients with breast cancer. We present non-clinical data on the specificity, potency and safety of PMD-026 and a clinical trial plan to support the first-in-human testing of this novel targeted therapy for TNBC.

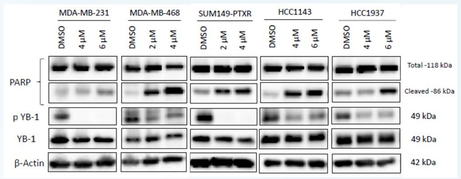


RSK sits at the convergence of two major cancer signaling pathways

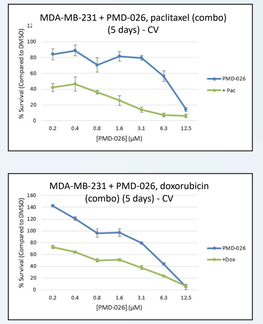
High RSK2 is associated with increased response to PMD-026



PMD-026 decreases pYB-1 and promotes apoptosis



PMD-026 synergizes with SOC chemotherapies



[PMD-026] (μM)	0.3 nM Paclitaxel
0.2	1.05
0.4	1.10
0.8	1.07
1.6	0.66
3.1	0.36
6.3	0.26
12.5	0.89

CDI	Interaction
>1.1	Antagonism
1.10 - 0.95	Additive
0.94 - 0.80	Weak Synergy
<0.80	Synergy

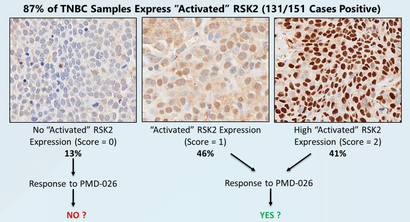
[PMD-026] (μM)	7 nM Doxorubicin
0.2	0.75
0.4	0.77
0.8	0.76
1.6	0.77
3.1	0.69
6.3	0.78
12.5	1.75

A. MCF-7 (ER/PR) and BT474-M1 (HER2) (low RSK) are less sensitive to treatment with PMD-026 compared to MDA-MB-468 (TNBC), as shown by cellular growth inhibition assays in monolayer (crystal violet staining) and under anchorage independent conditions (soft agar assay).
B. PMD-026 causes a decrease in pYB-1 expression associated with PARP cleavage (induction of apoptosis).
C. Treatment of MDA-MB-231 cells with PMD-026 alone or in combination with IC_{25} concentrations of paclitaxel or doxorubicin demonstrate synergy
- between 1.6 – 12.5 μM of PMD-026 with paclitaxel.
- between 0.2 – 6.3 μM of PMD-026 with doxorubicin.

RSK is activated in most TNBC

151 cases of TNBC were screened for RSK2 activation
- 131 cases were positive for RSK2
- 41% of those cases had high activation of RSK2

A CAP/CLIA certified IHC method will be used retrospectively to stain patient samples in our Phase 1/1b
- Does tumor response correlate with RSK2 activation?

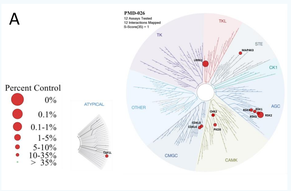


Pre-clinical summary: PMD-026 target profile

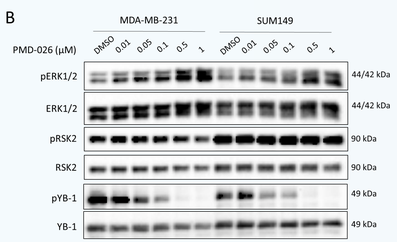
In vitro and in vivo preclinical summary		PMD-026
ADME	Metabolically stable in human microsomes and hepatocytes *in vitro*	✓
	Not a substrate of efflux transporters BCRP or MDR1 *in vitro*	✓
	Highly bound to human plasma proteins at >90 % *in vitro*	✓
DMPK	Moderate to high bioavailability (%F : ~99 % in mice, ~55% in dogs)	✓
	High volume of distribution, low clearance, half life ~ 2-6 hrs in animals	✓
	Low potential of drug to drug interactions due to CYPs	✓
Safety	Safety screen 44: no off target non-kinase activity	✓
	Does not inhibit cardiac channels hERG, CaV1.2 and NaV 1.5 channels *in vitro*	✓
	No apparent cardiotoxicity, ocular toxicity or neutropenia in mouse and dog GLP Tox studies	✓
Chemistry	CMC: Synthesis = medium difficulty, crystalline salt form	✓
	DS stability under ambient and stress conditions	✓

IND cleared by the FDA in Sept 2019, PMD-026 deemed safe to proceed to clinical trials

PMD-026 specifically targets RSK and does not affect kinases upstream in the MAPK pathway



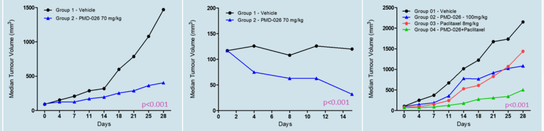
A. In a competition binding assay (KINOMEscan®) against 389 human kinases, PMD-026 has high specificity for the four RSK isoforms at IC_{50} values of 2 (RSK1), 0.7 (RSK2), 0.9 (RSK3) and 2 (RSK4) nM.



B. Following treatment with PMD-026 in TNBC cells,
- pYB-1 expression decreased in a dose-dependent manner
- pERK1/2 and pRSK2 expression did not change, therefore PMD-026 does not target MEK or ERK.

PMD-026 cuts across resistance and heterogeneous TNBC tumor models in mice

TNBC model	MDA-MB-231	MDA-MB-468	BR5015 PDx
Resistance	EGFR and mTOR inhibitors paclitaxel, sacituzumab govitecan	Gefitinib	AC-T: doxorubicin & cyclophosphamide-taxol
Mutations	KRAS, p53, EGFR, MSH3/4	p53, amplified EGFR, PTEN, RB1, SMAD4	BRCA-1, BRCA-2, EGFR, p53
Efficacy	TGI 72%	Regression 73%	Combo TGI 80%
RSK2 Score (20X magnification)	RSK2 ++	RSK2 ++	RSK2 ++

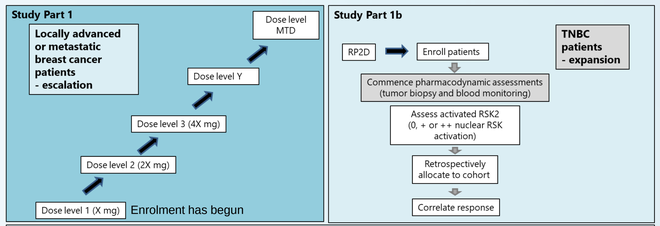


In vivo efficacy across genetically diverse models of TNBC. Models resistant to experimental and clinically approved therapies which harbor oncogenic mutations, all have high RSK2 expression. PMD-026 was well tolerated with no significant changes in body weight.
A. Female NCr nu/nu mice bearing established orthotopic MDA-MB-231 xenografts,
- Group 1 (vehicle), Group 2 (70 mg/kg PMD-026 po TID); 28 days.
- Tumor growth inhibition (TGI) 72% of control.

B. Female SCID Beige mice bearing established subcutaneous MDA-MB-468 xenografts,
- Group 1 (vehicle), Group 2 (70 mg/kg PMD-026 po TID; 14 days.
- PMD-026 treated tumors regressed 73%.

C. Female NOD-SCID mice bearing patient derived PDx BR5015 tumors,
- Group 1 (vehicle), Group 2 (100 mg/kg PMD-026 po BID), Group 3 (8 mg/kg paclitaxel iv QW), Group 4 (PMD-026 + paclitaxel comb); 28 days.
- Synergy observed in Group 4 with TGI of 80 %.

Phase 1/1b clinical trial study design



Primary objectives: safety, MTD and R2PD, efficacy
Secondary objectives: PK, time to and duration of response
Other outcomes: RSK2 expression, PMD-026 activity in tissue, correlate RSK2 expression and response

References

1. Brough R, Frankum JR, Sims D, et al. Functional viability profiles of breast cancer. Cancer Discov. 2011;1(3):260-73
2. Stratford AL, Reipas K, Hu K, et al. Targeting p90 ribosomal S6 kinase eliminates tumor-initiating cells by inactivating Y-box binding protein-1 in triple-negative breast cancers. Stem Cells. 2012;30(7):1338-48
3. Ludwik KA, Campbell JP, Li M, et al. Development of a RSK Inhibitor as a Novel Therapy for Triple-Negative Breast Cancer. Mol Cancer Ther. 2016;15(11):2598-608.

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