High levels of RSK2 in breast cancer patients is associated with longer PFS in patients treated with PMD-026, a first in class RSK inhibitor

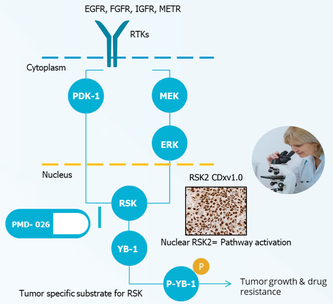
P4-01-16

JS Wang[1], M Beeram[2], P Chalasani[3], LA Mina[4] , RA Shatsky[5], SA Hurvitz[6], MS Trivedi[7], R Wesolowski[8], HS Han[9], A Patnaik[1], S Bahadur[4], A Jayanthan[10], G Los[11], SE Dunn[10,11], FA Dorr[11]

[1] Florida Cancer Specialists/Sarah Cannon Research Institute, Sarasota FL ; [2]START San Antonio, San Antonio, TX; [3]University of Arizona, Tucson, AZ; [4]Banner MD Anderson, Gilbert, AZ; [5]UCSD Medical Center, San Diego, CA; Columbia University Irving Medical Center, New York, NY; [6]David Geffen School of Medicine, University of California, Los Angeles/ Jonsson Comprehensive Cancer Center, Los Angeles, CA; [7]Columbia University Irving Medical Center, New York, NY; [8]The Ohio State University Comprehensive Cancer Center, Columbus, OH; [9]Moffitt Cancer Center, Tampa, FL; Phoenix Molecular Designs, [10]Vancouver, BC and [11]San Diego, CA

BACKGROUND

- RSK2 (p90 ribosomal S6 kinase 2) is an important driver for breast cancer (BC) and is associated with poorer prognoses
- RSK2 is highly activated in ~70% of cases, across all subtypes of BC[1]
- RSK2 was discovered as a novel drug target for triple negative breast cancer (TNBC)[2] and nuclear expression leads to the development of breast cancer in mice[3]
- PMD-026 is a first in class, oral RSK inhibitor being developed alongside a companion diagnostic measuring activated RSK2 in tumor tissue



STUDY OBJECTIVES

The objectives of this analysis of Phase 1/1b escalation/expansion cohorts from a first in human trial of PMD-026 were to:

- evaluate safety in metastatic BC patients
- identify subgroups, among 30 efficacy evaluable patients, who can benefit from PMD-026 treatment
- evaluate the pharmacokinetics of PMD-026 in breast cancer patients dosed at the RP2D of 200 mg Q12h
- evaluate the effect of food on the pharmacokinetics of PMD-026 following a single 200 mg dose

SAFETY AND TOLERABILITY

PMD-026 in heavily pre-treated mBC patients (n=41)

- Escalation 25 -200 mg QD; 200 – 300 mg Q12h
- Expansion RP2D 200 mg Q12h
- PMD-026 monotherapy was generally well-tolerated with mostly low grade TRAEs
- Fatigue and nausea were the most common TRAEs in the escalation and expansion patients
- G1/2 TRAEs were mostly GI related with no G4 events
- G3 TRAEs in the expansion patients dosed at the RP2D were AST & ALT increase and decreased lymphocytes

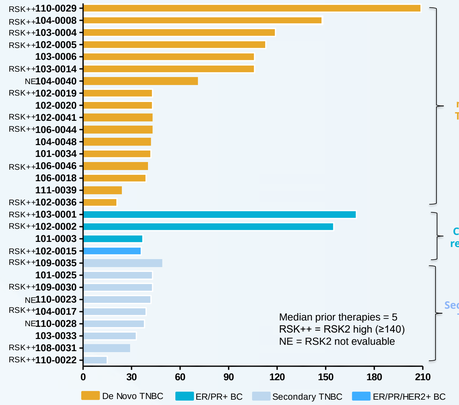
Table 1. Treatment related adverse events (TRAEs) in ≥10% of patients in the escalation and expansion cohorts

Event	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Fatigue	16(39)	3(7)	
Nausea	14(34)		
AST increased	10(24)	5(12)	
ALT increased	8(20)	3(7)	
Vomiting	7(17)		
Rash maculo-papular	6(15)		
Diarrhea	6(15)		
Lymphocytes decreased	5(12)	2(5)	
Constipation	5(12)		
Dehydration	4(10)	1(2)	
Decreased appetite	4(10)		
Stomatitis	4(10)		

Possibly/Definitely related events

TUMOR RESPONSE AND TREATMENT RESULTS

Figure 1. Time on treatment (all evaluable patients n=30)

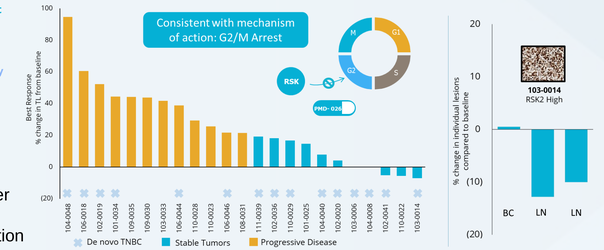


- *De novo* TNBC and CDK4/6i refractory HR+ patients had longer time on PMD-026 treatment (Fig. 1)
- The disease control rate (DCR) was 40% and there was reduction in measurable tumor in 20% of patients (n=30) (Table 2)
- Subgroup analysis revealed specific subsets of patients that responded to PMD-026 treatment (Table 2)
- Best response was observed in *de novo* TNBC with high RSK2* (n=10) with DCR of 70% and tumors decreasing in size in 40% of that subgroup (Table 2) based on H:Score 140.

Table 2. Subgroup analysis of evaluable patients to identify best disease and tumor responses to PMD-026 treatment

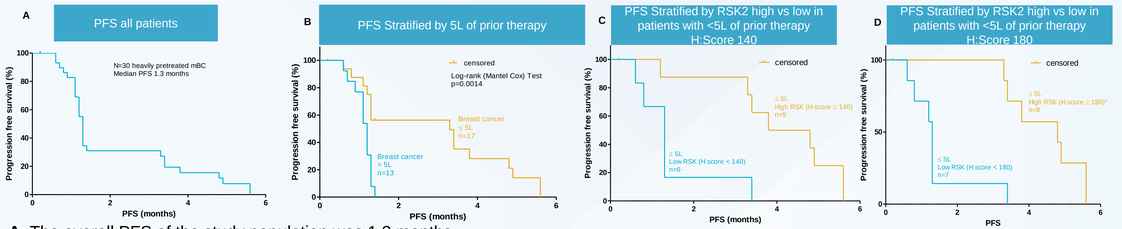
Patient subgroup analysis (evaluable)	n	PMD-026 dose	DCR (%)	Tumor shrinkage <30%
Safety (mBC)	41	All doses	NA	NA
Efficacy evaluable (mBC)	30	All doses	12/30 (40%)	6/30 (20%)
TNBC (secondary and *de novo*)	26	200 mg QD/Q12h (RP2D)	10/26 (38%)	6/26 (23%)
De novo TNBC	17	200 mg QD/RP2D	9/17 (53%)	4/17 (24%)
TNBC with high RSK2	15	200 mg QD/RP2D	8/15 (53%)	6/15 (40%)
De novo TNBC with high RSK2	10	200 mg QD/RP2D	7/10 (70%)	4/10 (40%)

Figure 2. Stable tumors and tumor shrinkage in heavily pretreated TNBC (patients with measurable disease n=23)



- Stabilized tumor growth in 48% (11/23) of heavily pre-treated TNBC patients with measurable disease, is consistent with the mechanism of action (MoA) of PMD-026 (Fig. 2)
- Best patient response was in *de novo* TNBC with high RSK2*; stable breast /lymph node lesion size decrease were observed following PMD-026 treatment (Fig. 2)

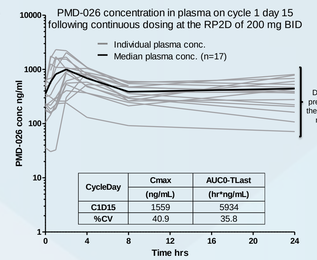
Figure 3. Kaplan-Meier progression free survival (PFS) analysis in subsets of patients dosed with PMD-026



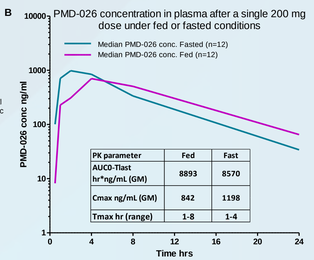
A. The overall PFS of the study population was 1.3 months.
B. Median PFS is significantly longer in BC patients that had ≤5 compared with >5 lines of prior therapies (HR, 0.19; 95% CI [0.06–0.52], p=0.0014).
C. Median PFS with ≤5 prior therapies and high RSK2 H-score was longer than with a low RSK2 H-score, 4.3 vs 1.3 months, respectively (HR, 0.12; 95% CI [0.02-0.06], p=0.0075).
D. Median PFS with ≤5 prior therapies and high RSK2 H-score was longer than with a low RSK2 H-score, 4.8 vs 1.3 months, respectively (HR, 0.07;95% CI [0.02-0.36], p=0.0012).

PHARMACOKINETICS

Figure 4. PK at the RP2D and food effect on PK of PMD-026



CycleDay	Cmax (ng/mL)	AUC0-TLast (hr*ng/mL)
C1D15	1559	5934
%CV	40.9	35.8



PK parameter	Fed	Fast
AUC0-Tlast hr*ng/mL (GM)	8893	8570
Cmax ng/mL (GM)	842	1198
Tmax hr (range)	1-8	1-4

A. Exposure was achieved in the desired preclinical range is seen following oral dosing of PMD-026 at the RP2D of 200 mg Q12h on cycle 1 day 15 (continuous dosing)
B. A food effect (FE) sub-study of 12 patients showed:
   - there was no significant change in exposure AUC in fed vs fasted
   - there was greater variability in Tmax and a decrease in Cmax in fed vs fasted

Based on the FE data PMD-026 will continue to be administered without food.

CONCLUSIONS

Safety – TRAEs were generally mild (G1/2) with some G3, but no G4 events

Clinical activity - subgroup analysis of patients treated with PMD-026 demonstrates:

- **Longer time on treatment** in BC patients with high RSK2 in both *de novo* TNBC and refractory CDK4/6i HR+ patients
- **Longer PFS** in BC patients who had very high RSK2 (H:Score 180) and ≤5 prior therapies.
- **Disease stabilization** in 48% of heavily pre-treated TNBC patients
- **PK:** the first orally available RSK inhibitor, PMD-026 exposure was achieved in the desired range in patients and was better administered without food

In Summary:
PMD-026 has promising activity in RSK2+ breast cancer patients with fewer lines of prior therapies.

ACKNOWLEDGMENTS

- We thank the patients and their families who took part in this study, as well as the staff, research coordinators, and investigators at each participating institution.
- SciQuus Oncology, Inc. and Cardiff Clinical, Inc. provided support in the development of this poster.

REFERENCES

1 Phase 1/1b clinical trial results of 37 patients retrospectively assessed for RSK2 activation by CAP/CLIA assay (Roche Diagnostics).
2 Brough R, Frankum JR, Sims D, et al. Functional viability profiles of breast cancer. Cancer Discov. 2011;1(3):260-73
3 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

*Definitions: "*De novo*" TNBC (patients with <10% ER, PR and HER2 at initial diagnosis) and "Secondary" TNBC (patients who were initially diagnosed with ER+, PR+ or HER2+ BC but lost ER/PR/HER2 expression). RSK2 IHC H scores are high (≥140) and low (<140) based on a bridging study conducted with Roche (post submission of SABCS 2022 abstract). 103-0001 was considered borderline high with HScore:140 and 10% 3+ nuclear staining. Unaudited data cut Sep 2022

CONTACT

ClinicalTrials.gov ID: NCT04115306
clinical@sciquus.com