PS11-33

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First-in-Human Expansion Study of Oral PMD-026 in Metastatic Triple Negative Breast Cancer Patients

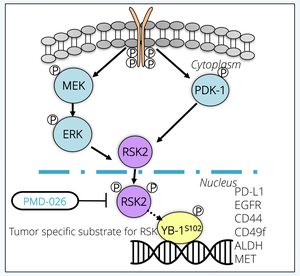
M Beeram[1], JS Wang[2], LA Mina[3], P Chalasani[4], RA Shatsky[5], R Wesolowski[6], SA Hurvitz[7], MS Trevedi[8], HS Han[9], A Patnaik[1], M Huynh[10], A Jayanthan[10], MR Pambid[10], L Yue[10], G Los[11], SE Dunn[10,11], FA Dorr[11]

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

BACKGROUND

- RSK (p90 ribosomal S6 kinase 2) is a novel target kinase for TNBC
- PMD-026 is a first in class, oral inhibitor of RSK
- PMD-026 showed a favorable safety profile in metastatic breast cancer patients in the escalation phase of our FIH trial
- Here we describe interim safety and efficacy of PMD-026 monotherapy in metastatic TNBC patients whose disease had progressed on standard therapy

Figure 1. PMD-026 inhibits critical tumor signaling pathways in TNBC



STUDY OBJECTIVES

In this expansion phase of the FIH study of the oral RSK inhibitor, PMD-026, the objectives were to further evaluate the anti-tumor activity of PMD-026 in patients with TNBC dosed at the recommended phase 2 dose (RP2D) of 200 mg Q12h.

Other objectives were to evaluate the relationship between activated RSK2 expression (companion diagnostic, CDx) and patient response to PMD-026 across heterogeneous TNBC histologies and to further assess safety of PMD-026.

DEMOGRAPHICS

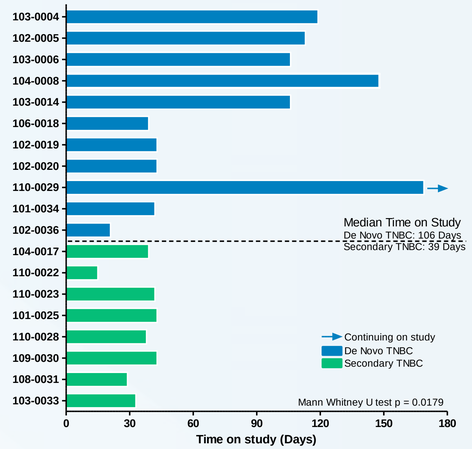
- Patients (n=19) were treated on study between Nov 2 2020 to Sep 14 2021 (data cut)
- Patients represented women from diverse ethnic/racial backgrounds
- **"*De novo*" TNBC**: patients with <10% ER, PR and HER2 at initial diagnosis; **"Secondary" TNBC**: patients who were initially diagnosed with ER+, PR+ or HER2+ BC but lost ER/PR/HER2 expression
- Patients had been heavily pre-treated with up to 13 prior lines of therapy including ADC/IO targeted agents

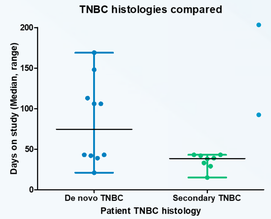
Table 1: Patient demographics from the Dose Expansion

Characteristic	Patients (n=19)
Median age, year (range)	63 (32 - 77)
Female Sex - n (%)	19 (100)
Race or ethnic group	
Non-Hispanic white	10 (53)
Hispanic/ Latino	3 (16)
Non-Hispanic black	2 (11)
Non-Hispanic mixed race	1 (5)
Asian/ Pacific Islander	1 (5)
American Indian/ Alaska Native	1 (5)
Middle Eastern/Indian	1 (5)
mTNBC status	
De novo	9 (47)
Secondary	10 (53)
Median prior lines of therapy - n (range)	7 (2 - 13)
De novo	6 (2 - 7)
Secondary	7 (3 - 13)
Prior targeted therapies - n (%)	
sacituzumab (ADC)	10 (53)
pembrolizumab (IO)	8 (42)
atezolizumab (IO)	6 (32)

PRECISION MEDICINE: CLINICAL ACTIVITY (Phase 1/1b)

Figure 2. De *novo* TNBC patients stay on PMD-026 treatment longer than Secondary TNBC patients





- *De novo* TNBC patients stay on PMD-026 treatment **3x** longer than patients with Secondary TNBC
- *De novo* TNBC patients were on study for a median of **3.5 months** vs 1.3 months for Secondary TNBC (phase 1/1b patients)

Figure 5. PMD-026 provides stable disease (SD) in 67% (6/9) of *de novo* TNBC patients vs all patients which was 50% (8/16)

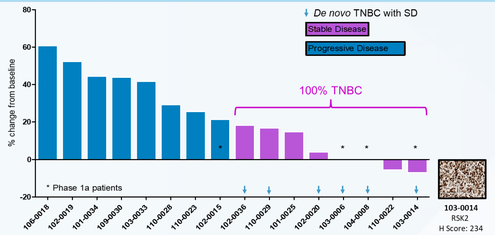
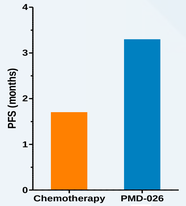


Figure 3. PMD-026 doubles PFS relative to chemotherapy in evaluable patients with high RSK2 activation (CDx)



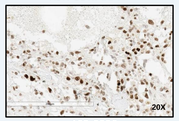
(Bardia et al 2021)[1] 3L therapy

PMD-026 De novo, high RSK2 ≤5L therapy

- *De novo* TNBC patients with high RSK2 (CDx), with ≤5L of prior therapies (n=4) were on PMD-026 for a median PFS of **3.3 months**, compared to 1.7 months in a similar patient cohort on chemotherapy[1]

Roche H score	
Low RSK	180 <
High RSK	180 ≥

RSK CDx: **LOW**



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RSK CDx: **HIGH**

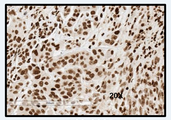

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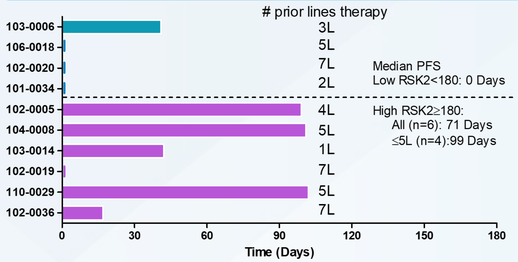
Figure 4. Median PFS of *de novo* TNBC patients with low versus high activated RSK2 (CDx)

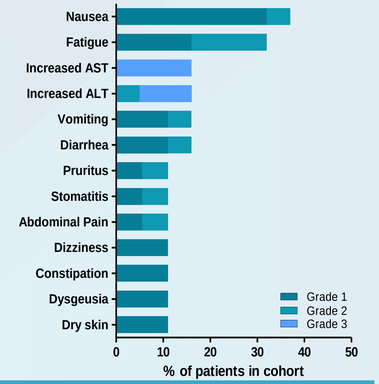


- Median progression free survival (PFS) is longer in *de novo* TNBC patients with high RSK2 in tumor tissues compared with low RSK2
- *De novo* TNBC patients (6/9) have more SD on PMD-026 (67%) compared to our general breast cancer population with measurable tumors, where PMD-026 provides SD in 50% (8/16) of patients dosed at RP2D
- Best tumor response in RSK2 high/*de novo* TNBC patients

SAFETY

- PMD-026 was generally well-tolerated with Grade 1/2 nausea and fatigue as the most common symptoms
- No alopecia was observed
- Low incidence of symptoms often observed in MAPK pathway inhibitors, such as rash (5%) and ocular disorders (5%).
- Low incidence of GI related symptoms
- G3 treatment-related AEs (TRAEs) ≥10% were elevated AST (16%) and ALT (16%)
- One related SAE (G3 colitis) was reported for the expansion cohort
- Comparable safety profile to our escalation cohort[2]

Figure 6. Treatment related adverse events ≥10% patients



CONCLUSIONS

Clinical activity - We identified TNBC patients in this interim analysis, that may be most likely to benefit the most from PMD-026 in this diverse patient cohort:

- *De novo* TNBC with high RSK2 with ≤5 prior lines of therapy had the longest PFS when treated with PMD-026.
- Time on study was longer for *de novo* compared with secondary TNBC patients
- *De novo* TNBC patients with high RSK2 had longer PFS than those with low RSK2 expression (by CDx: tumor IHC staining)
- Stable disease is higher in *de novo* TNBC patients compared to all patients with breast cancer

Safety - We established the safety of PMD-026

- PMD-026 dosed at the RP2D of 200 mg Q12h has a relatively benign safety profile: mostly low grade (G1/2) with the most common being nausea and fatigue

ACKNOWLEDGMENTS

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REFERENCES

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2 Beeram et al. PS11-33: 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. SABCS (2020).

CONTACT

ClinicalTrials.gov ID: NCT04115306

clinical@sciquus.com

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