Patient selection for high RSK2 expression is key for achieving improved PFS in metastatic breast cancer in the PMD-026 Phase I/Ib study

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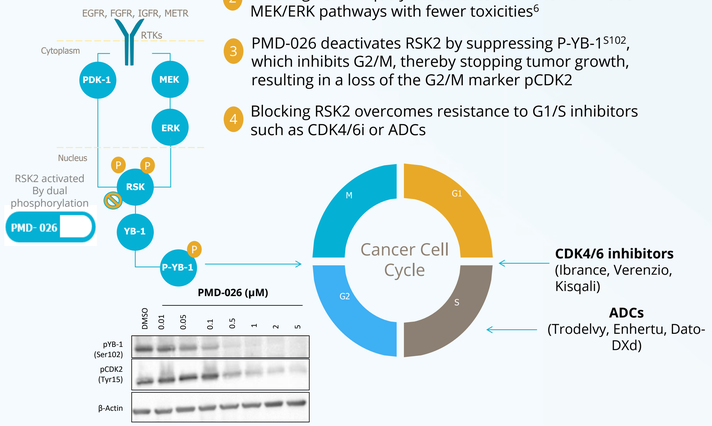
Judy S. Wang[1], Hyo S. Han[2], Robert Wesolowski[3], Murali Beeram[4], Amita Patnaik[4], Shakeela Bahadur[5], Nicolaos J. Palaskas[6], Aarthi Jayanthan[7], Gerrit Los[7], Sandra E. Dunn[7], and Andrew Dorr[7]

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

BACKGROUND

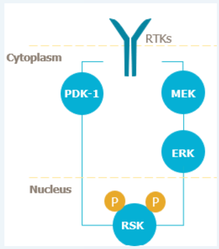
1. RSK2 was originally identified as a novel drug target for TNBC.[1-4] It is also a driver in the genesis of HR+ breast cancer[5]
2. Blocking RSK uniquely deactivates both the PDK-1 and MEK/ERK pathways with fewer toxicities[6]
3. PMD-026 deactivates RSK2 by suppressing P-YB-1^{S102}, which inhibits G2/M, thereby stopping tumor growth, resulting in a loss of the G2/M marker pCDK2
4. Blocking RSK2 overcomes resistance to G1/S inhibitors such as CDK4/6i or ADCs



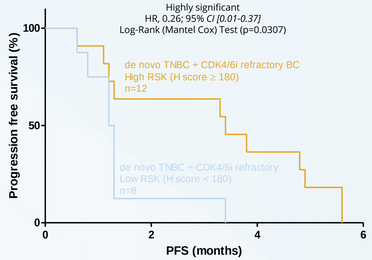
PRECISION MEDICINE WITH RSK2 COMPANION DIAGNOSTIC (CDx)

Companion Diagnostic (CDx)

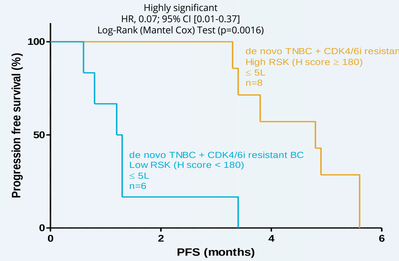
- Activated RSK2 translocates from the cytoplasm into the nucleus and nuclear RSK2 is measured by immunohistochemistry (IHC)
- A total of 37 tumor samples were evaluated
- Tumors were considered RSK2 high if they had an H- Score of ≥180 and a RSK2 staining intensity of 2+ or 3+ in ≥75% of the tumor nuclei.



PFS for *de novo* TNBC and ER+ CDK4/6i Refractory Patients, Stratified by High vs. Low RSK



PFS for *de novo* TNBC and ER+ CDK4/6i Refractory Patients with ≤5 Prior Therapies, Stratified by High vs. Low RSK



PFS: 1.3 months
RSK2 low

PFS:4.8 months
RSK2 high

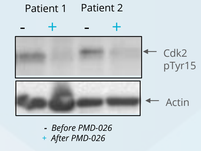
Best response in patients with a) high nuclear RSK2:, b) de novo TNBC & CDK4/6i refractory, c) 5L or less of therapy

Patient population to be enrolled in Phase 2/3 trials

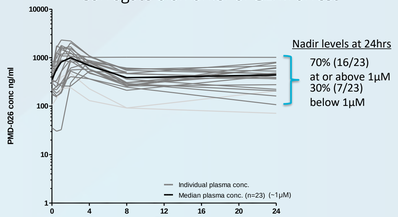
PMD-026 INHIBITS P-CDK2 IN PBMCs CONSISTENT WITH THE MECHANISM OF ACTION

PMD-026 inhibits p-CDK2, a surrogate marker of G2/M arrest, at concentrations achieved in plasma

PBMCs from TNBC Patients before and after PMD-026



PMD-026 plasma concentrations sufficient to inhibit p-CDK2, linking PK with a surrogate biomarker of G2/M arrest



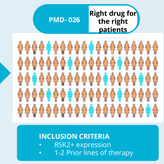
PMD-026 Plasma Concentrations:
Patient 1 D15 = 1.3 μM
Patient 2 D15 = 0.6 μM

Individual and median PMD-026 plasma concentrations in patients dosed 200mg Q12h on C1D15

NEXT STEPS

- Model of how the RSK2 CDx will be used to prospectively enroll patients
  - FFPE tissue stained for RSK2 at centralized lab (Roche-Ventana)
  - Pathology training
  - LIMS system reporting
  - Prospective enrollment

FFPE mBC sample



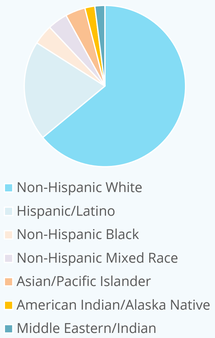
Companion Diagnostic Co-developed with Roche

5 day turn around Integrated digital pathology communications system

Precision medicine Phase 2 enrollment

PATIENT DIVERSITY

Diversity and Inclusion

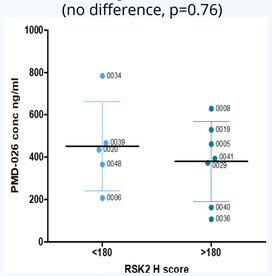


Race or Ethnic groups	Escalation	Expansion	All
Non-Hispanic White	13 (87%)	13 (50%)	26 (63%)
Hispanic/Latino	2 (13%)	6 (23%)	8 (20%)
Non-Hispanic Black	0	2 (8%)	2 (5%)
Asian/Pacific Islander	0	2 (8%)	2 (5%)
Non-Hispanic Mixed Race	0	1 (4%)	1 (2%)
American Indian/Alaska Native	0	1 (4%)	1 (2%)
Middle Eastern/Indian	0	1 (4%)	1 (2%)
Total patients	*15*	*26*	*41*

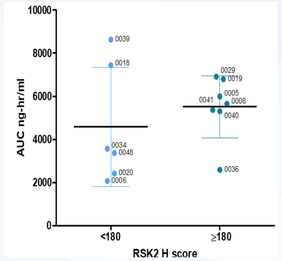
Breast cancer subtypes	Evaluable
TNBC; de novo	18 (60%)
TNBC; secondary	8 (27%)
HR+; CDK4/6i resistant	3 (10%)
HER-2+	1 (3%)
Total patients	*30*

PHARMACOKINETICS

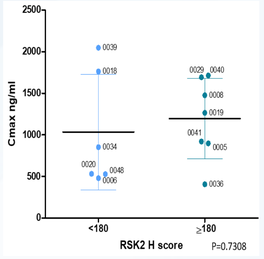
Plasma concentrations: RSK high vs RSK low (no difference, p=0.76)



AUC: RSK high vs RSK low (no difference, p=0.53)



Cmax: RSK high vs RSK low (no difference, p=0.73)



Patient benefit was unrelated to differences in PK

ACKNOWLEDGMENTS

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CONTACT

ClinicalTrials.gov ID: NCT04115306
clinical@sciquus.com

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