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A phase 1 dose-escalation study of protein arginine methyltransferase 5 (PRMT5) inhibitor PRT543 in patients with advanced solid tumors and lymphoma

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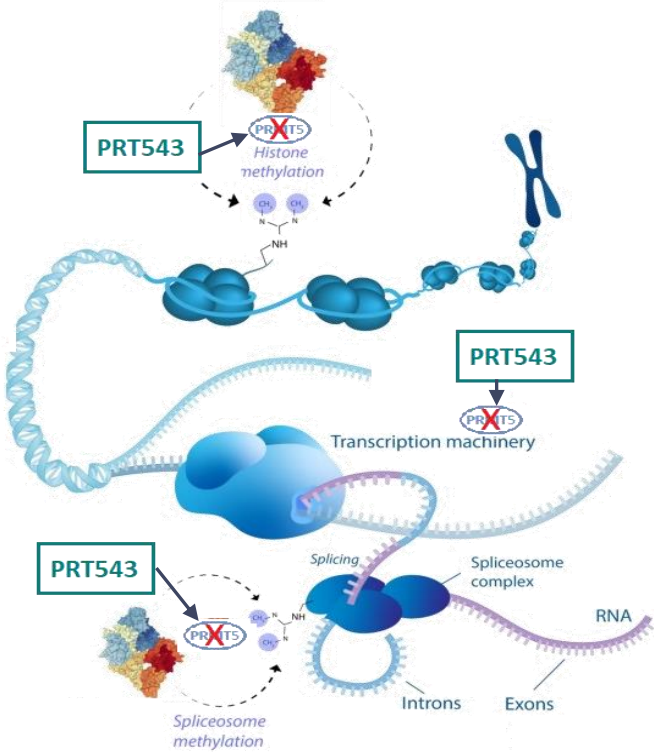
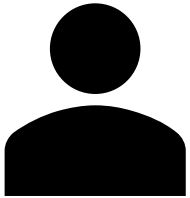
PRT543 is a Potent, Selective, Oral PRMT5 Inhibitor

- PRMT5 catalyzes symmetric arginine dimethylation of protein substrates with important roles in the cell cycle, including histone modification, transcription, and spliceosome assembly
- PRMT5 is overexpressed in a variety of cancers
- PRT543 inhibits PRMT5 enzymatic activity
  - Biochemical IC_{50}= 10.8 nM



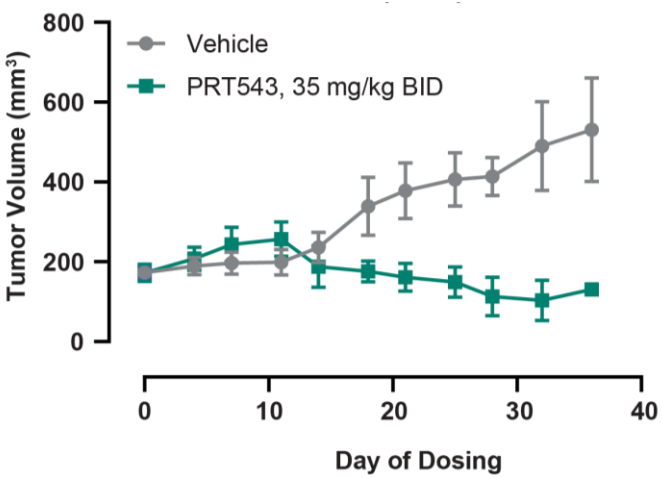


IC_{50}, half maximal inhibitory concentration; PRMT, protein arginine methyltransferase.
Adapted from Bhagwat N, et al. (2020, June 22-24). AACR Virtual Meeting. Poster 2915; Kim H. and Ronai ZA. *Cell Stress*. 4(8):199-215.

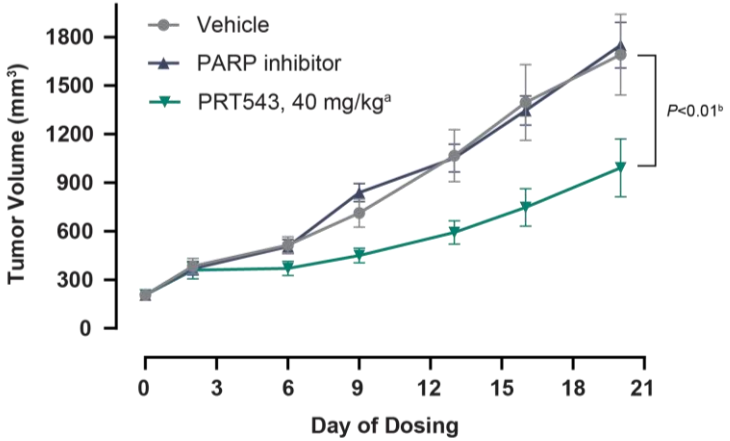
PRT543 Demonstrates Robust Preclinical Antitumor Activity

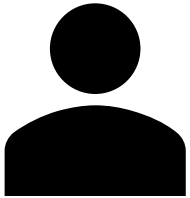
PRT543 Demonstrates Anti-tumor Activity
in Solid Tumor PDX Models of ACC and HRD+ Breast Cancer

ACC (PDX)[1]



HRD+ Breast Cancer (PDX)[2]





ACC, adenoid cystic carcinoma; BID, twice a day; HRD+, homologous recombination deficiency-positive; PARP, poly (ADP-ribose) polymerase; PDX, patient-derived xenograft.
1. Adapted from Bhagwat N, et al. (2020, June 22-24). AACR Virtual Meeting. Poster 2915. 2. Adapted from Ito K, et al. (2021, June 10-15; May 17-21). AACR Virtual Meeting. Poster 1185.
[a]Administered in mouse diet. [b]*P*-value for PRT543 versus vehicle.

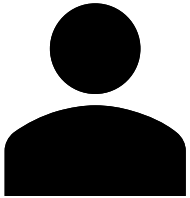
Study Design

Key Eligibility Criteria

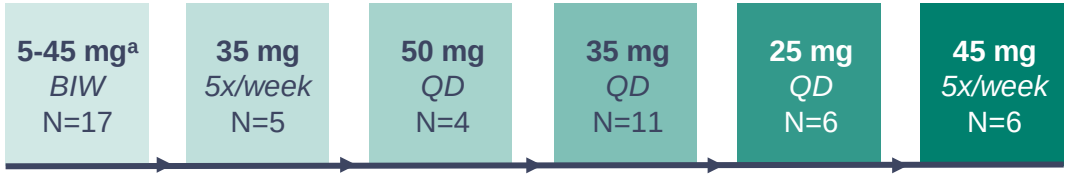
- Adults with advanced or metastatic solid tumors, including lymphoma
- Relapsed refractory disease
- ECOG PS 0 or 1

Key Objectives

- Safety/tolerability and RP2D
- Pharmacokinetic/pharmacodynamic profile
- Preliminary signals of efficacy (RECIST v1.1)



Part 1 Dose Escalation
Accelerated 3+3 Design (N=49)



Part 2 Dose Expansion
45 mg/5x Week Expansion Dose

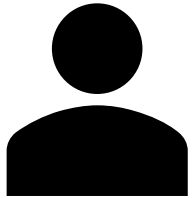
- Adenoid Cystic Carcinoma (N≈35)
- HRD+ Ovarian Carcinoma (N≈20)
- HRD+ Solid Tumors (N≈20)
- DLBCL, MCL, RT (N≈20)
- Solid Tumors with *MYC* or *MYB* alteration (N≈20)
- Solid Tumors with Spliceosome Mutation (N≈20)

[a]Dosing at 5, 10, 15, 22.5, or 45 mg BIW.
Data cutoff for these analyses was August 6, 2021. Part 2 Dose Expansion is ongoing.
BIW, biweekly; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; HRD+, homologous recombination deficiency-positive; MCL, mantle cell lymphoma; PRMT, protein arginine methyltransferase; QD, once daily; RP2D, Recommended Phase 2 Dose; RECIST, Response Evaluation Criteria In Solid Tumors; RT, rhabdoid tumor.
ClinicalTrials.gov. NCT03886831. Accessed August 18, 2021. https://www.clinicaltrials.gov/ct2/show/NCT03886831.

Baseline Characteristics

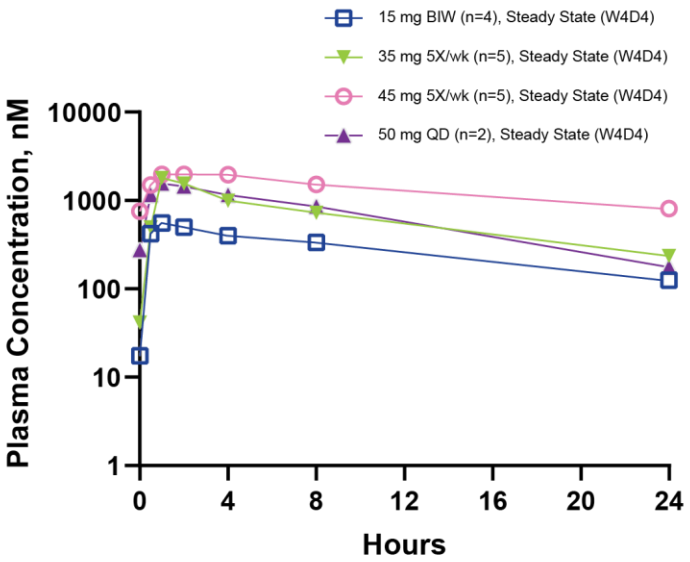
Demographics	Total Patients (N=49)
Age, years, median (range)	63.0 (31-82)
Female, n (%)	31 (63)
ECOG PS, n (%)	
0	24 (49)
1	25 (51)
Race, n (%)	
White or Caucasian	42 (86)
Black or African American	5 (10)
Asian	1 (2)
Other	1 (2)
Prior lines of systemic therapy, median (range)	3 (0-6)

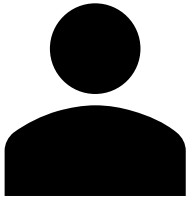
Primary Cancer Diagnosis, n (%)	Total Patients (N=49)
Colon cancer	9 (18)
ACC	7 (14)
Uveal melanoma	6 (12)
Ovarian cancer	5 (10)
Pancreatic cancer	4 (8)
Prostate cancer	4 (8)
DLBCL	2 (4)
SCLC	2 (4)
Anal cancer	1 (2)
Appendiceal cancer	1 (2)
Breast cancer	1 (2)
Cholangiocarcinoma	1 (2)
Esophageal cancer	1 (2)
Gallbladder cancer	1 (2)
Melanoma	1 (2)
NSCLC	1 (2)
Renal cell carcinoma	1 (2)
Sarcoma	1 (2)



ACC, adenoid cystic carcinoma; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; NSCLC, non-small cell lung cancer; PRMT, protein arginine methyltransferase; SCLC, small cell lung cancer.

Pharmacokinetics





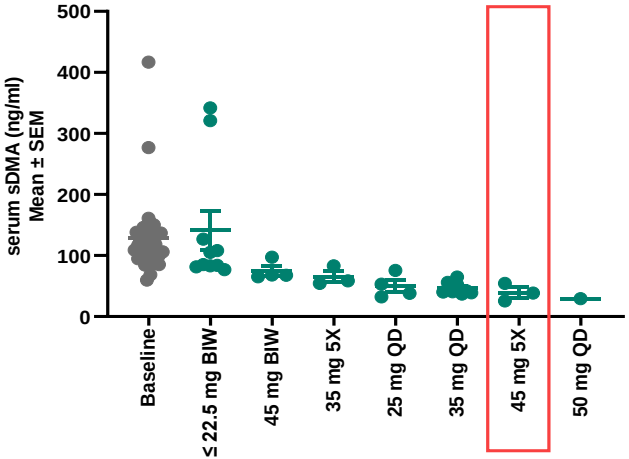
Expansion Dose (45 mg 5x/week)	Parameter Values (CV%)
C_{max}, nM	2,142 (32)
$AUC_{0\text{-}t}$, hr.nM	26,293 (33)
$T_{1/2}$, hrs	15 (7)

- PRT543 demonstrated dose-dependent increases in C_{max} and AUC
- Drug accumulation was seen at the highest dose (50 mg QD)

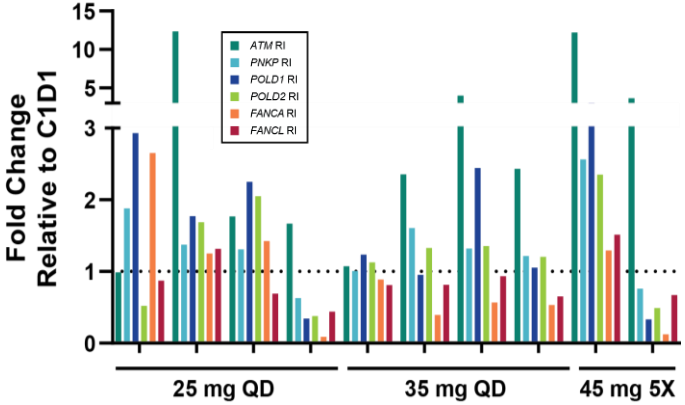
AUC, area under the curve; BIW, biweekly; C_{max}, highest concentration in blood; CV, coefficient of variation; D, day; PRMT, protein arginine methyltransferase; QD, once daily; $T_{1/2}$, half-life; W, week.

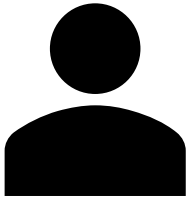
Pharmacodynamics

PRT543 Exhibited Dose-Dependent Inhibition of Serum sDMA: 69% Decrease Observed at the Expansion Dose (45 mg/5x Week)[a]



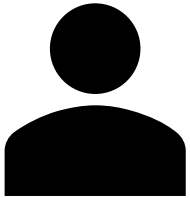
Intron Retention, a Marker of PRMT5-Mediated mRNA Splicing Fidelity, was Observed with PRT543 Treatment at Higher Dose Levels[b,c]





Most Common Treatment-Related Adverse Events (TRAEs) of Any Grade Occurring in ≥5% of Patients

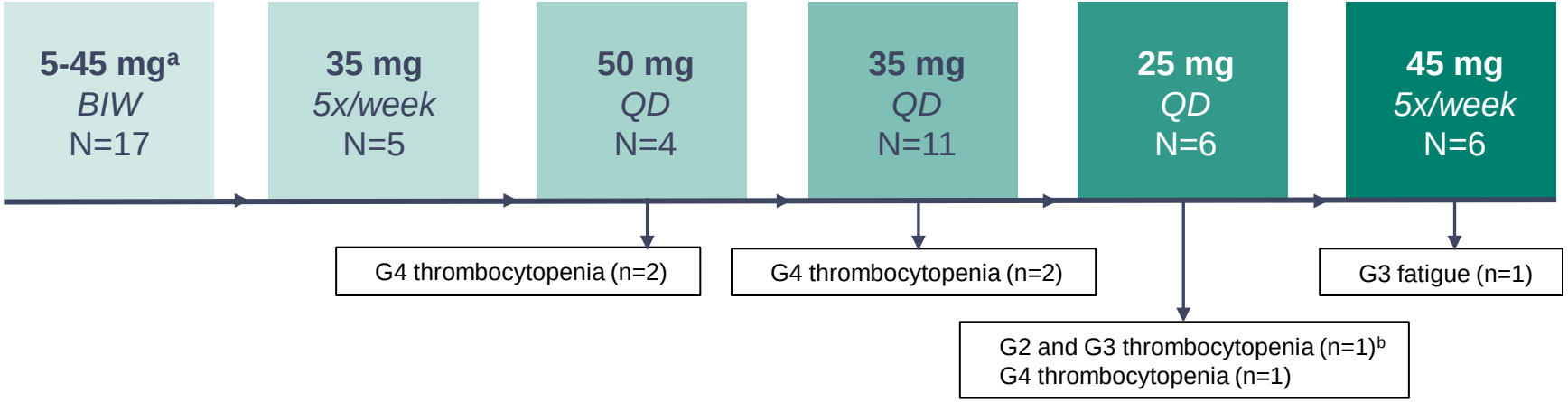
	All Patients (N=49)[a]		Expansion Dose 45 mg 5x/week (N=6)	
AE, n (%)	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Patients with events	36 (73)	20 (41)	4 (67)	3 (50)
Fatigue	20 (41)	2 (4)	1 (17)	1 (17)
Thrombocytopenia[b]	19 (39)	13 (27)	2 (33)	1 (17)
Anemia	14 (29)	6 (12)	2 (33)	2 (33)
Nausea	14 (29)	0	2 (33)	0
Diarrhea	6 (12)	1 (2)	0	0
Alopecia	4 (8)	0	0	0
Anorexia	4 (8)	0	2 (33)	0
Back pain	4 (8)	0	0	0
Oral mucositis	4 (8)	0	0	0
Vomiting	4 (8)	0	1 (17)	0
Headache	3 (6)	0	0	0
Leukopenia	3 (6)	2 (4)	1 (17)	1 (17)
Macropapular rash	3 (6)	0	0	0



- 45 (92%) patients discontinued treatment[c]
  - 29 (64%) progressive disease
  - 3 (7%) physician decision
  - 2 (4%) adverse event
  - 1 (2%) death[d]
  - 1 (2%) withdrawal by subject
- 13 (27%) patients drug interrupted
- 11 (22%) patients dose reduced

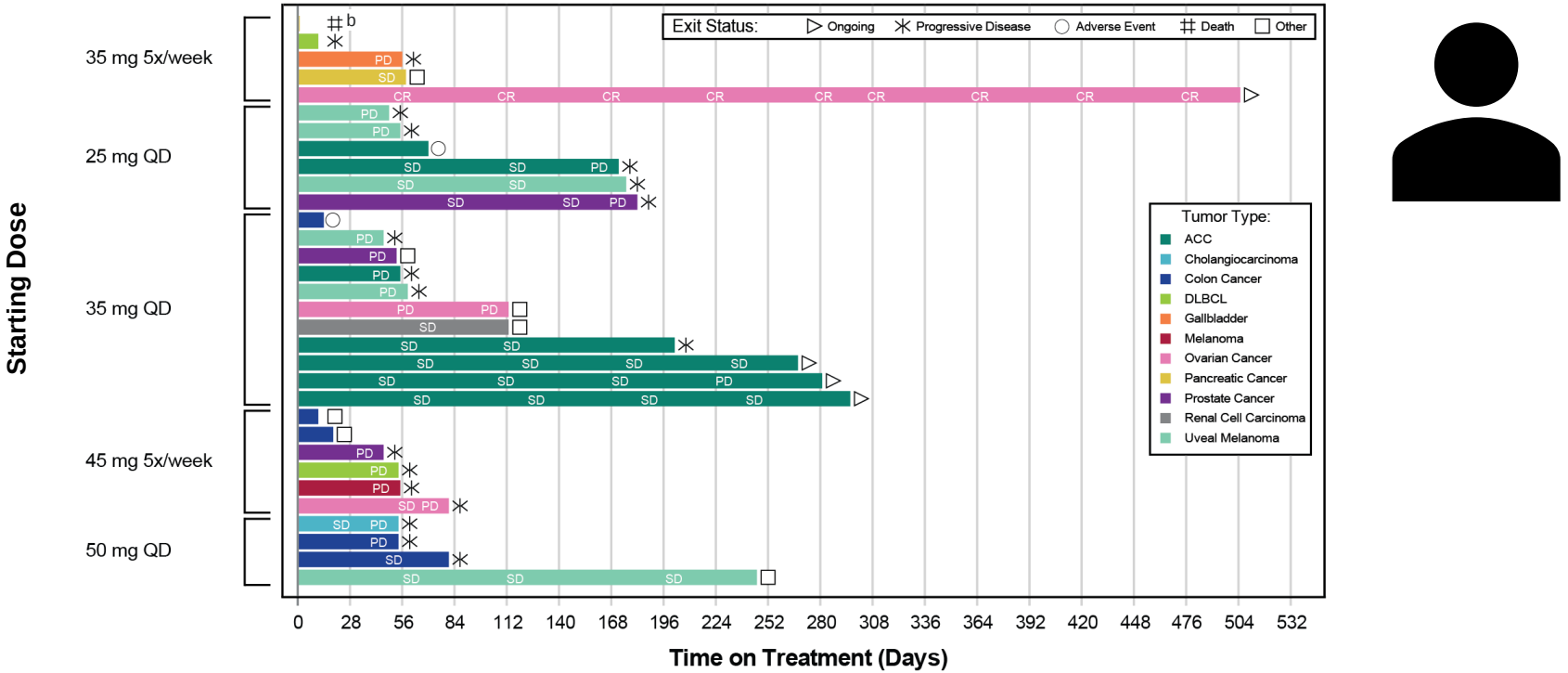
[a]No grade 5 TRAEs (death); [b]The term thrombocytopenia is defined as thrombocytopenia plus platelet count decreased; [c]9 (18%) missing reason or other; [d]Patient enrolled but did not take study drug. AE, adverse event; PRMT, protein arginine methyltransferase.

Dose-limiting Toxicities (DLTs)



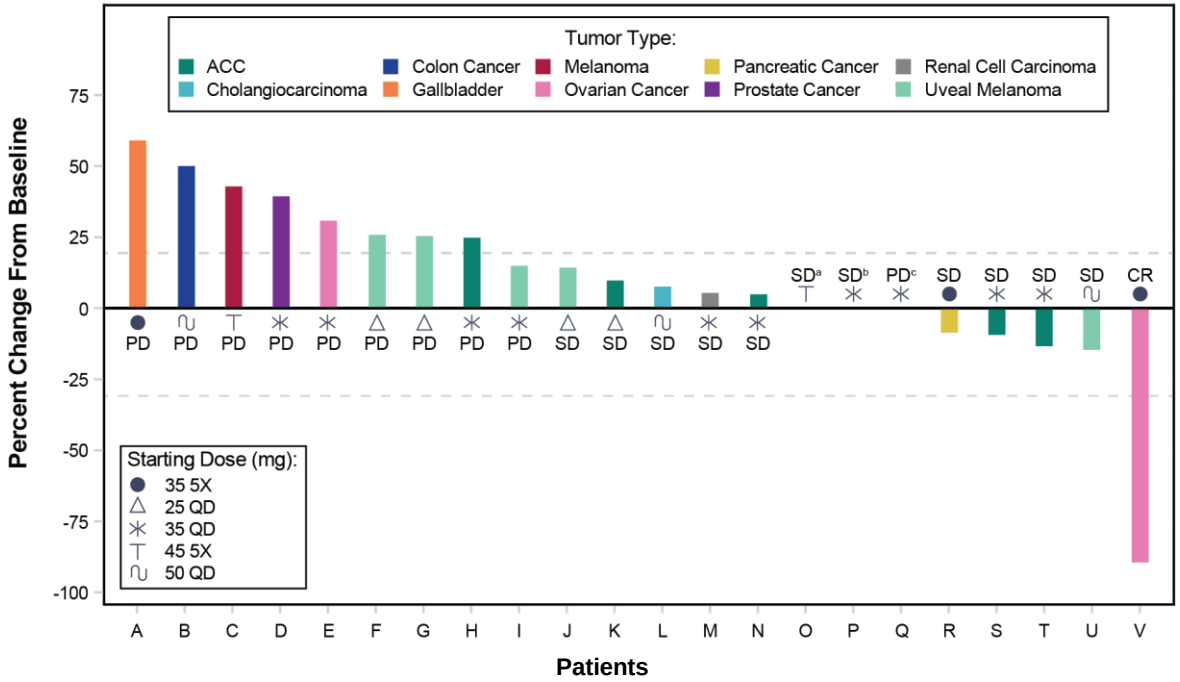
[a]Dosing at 5, 10, 15, 22.5, or 45 mg BIW.
[b]The same patient (dosed 25 mg QD) reported DLT thrombocytopenia Grade 3, and then 3 days later, DLT thrombocytopenia Grade 2.
BIW, biweekly; DLT, dose-limiting toxicity; G2, Grade 2; G3, Grade 3; G4, Grade 4; PRMT, protein arginine methyltransferase; QD, once daily.

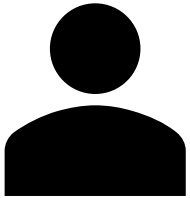
Overall Response and Response Duration by Dose/Schedule and Diagnosis[a]



[a]Analysis for patients treated with weekly dose higher than 175 mg. [b]Patient with pancreatic cancer enrolled but did not take study drug.
ACC, adenoid cystic carcinoma; CR, complete response; DLBCL, diffuse large B-cell lymphoma; PD, progressive disease; PRMT, protein arginine methyltransferase; QD, once daily; SD, stable disease.

Best Target Lesion Response (RECIST v1.1)





This analysis includes patients with target lesions at baseline and at least 1 post-baseline percentage change (from baseline to PD). RECIST v1.1 assessment by investigator. 4 patients had insufficient lesion measurements to allow calculation of percentage change from baseline, thus data not shown.

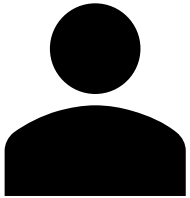
[a]Ovarian cancer; [b]ACC; [c]Uveal Melanoma.

ACC, adenoid cystic carcinoma; CR, complete response; DLBCL, diffuse large B-cell lymphoma; PD, progressive disease; PRMT, protein arginine methyltransferase; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

Response in Patient With HRD+ High-grade Serous Ovarian Cancer

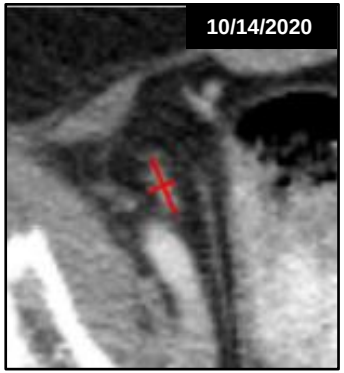
Patient History

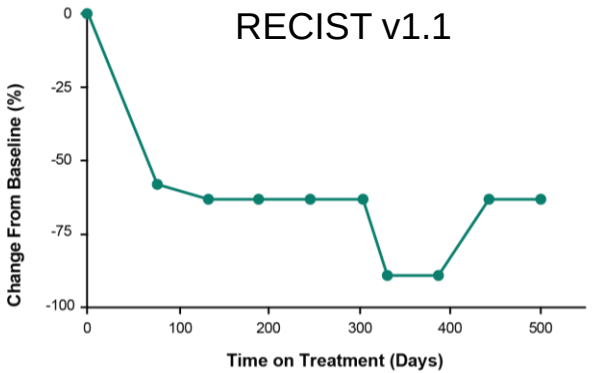
- 2014 diagnosis (tumor origin in fallopian tube)
- Multiple lines of prior therapy, including PARPi
- HRD+
  - DNA damage response (DDR) mutations: *ATR*, *RAD51D*, *BRCA1*
  - Plans to confirm HRD in validated clinical assay
- Baseline: One target lesion per RECIST v1.1; CA125 level 37.8 U/mL
- Enrolled at, and continues on, 35 mg 5x/week



Patient Response

- RECIST v1.1 CR at first follow-up tumor assessment (7 weeks), maintained throughout the study
- CA125 was reduced and remained below 5 U/mL at the last assessment
- The patient remains on study following 18 months of treatment

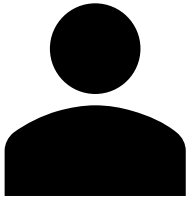




CR, complete response; HRD+, homologous recombination deficiency-positive; PARPi, poly (ADP-ribose) polymerase inhibitor; PRMT, protein arginine methyltransferase; RECIST, Response Evaluation Criteria In Solid Tumors.

Conclusions

- PRT543 exhibited target engagement and inhibited PRMT5 activity
- PRT543 was well tolerated
  - Most common treatment-related adverse events (TRAEs) of any grade in at least 10% of patients were fatigue, thrombocytopenia, anemia, nausea, and diarrhea
  - The most common dose-limiting toxicity was thrombocytopenia
- Preliminary clinical activity was suggested
  - Durable complete response (CR) in a patient with HRD+ ovarian cancer
  - Stable disease for at least 6 months in 5 other patients
- 45 mg/5x week was selected as the recommended phase 2 dose (RP2D)
  - The expansion phase in biomarker-selected solid tumor cohorts is ongoing



We would like to thank the patients who participated in this study and their families, as well as the study teams at each participating institution

HRD+, homologous recombination deficiency positive; PRMT, protein arginine methyltransferase.