AACR-NCI-EORTC Virtual International Conference on
MOLECULAR TARGETS AND CANCER THERAPEUTICS
October 7-10, 2021

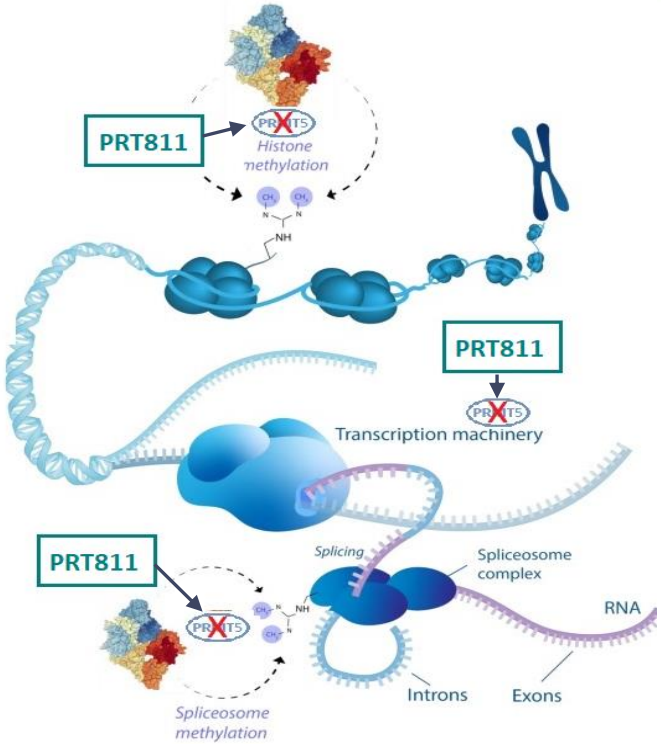
A phase 1 dose-escalation study of protein arginine methyltransferase 5 (PRMT5) brain-penetrant inhibitor PRT811 in patients with advanced solid tumors, including recurrent high-grade gliomas

Gerald S. Falchook, MD[1]; Jon Glass, MD[2]; Varun Monga, MD[3]; Pierre Giglio, MD[4]; David Mauro, MD[5]; John Viscusi[5]; Peggy Scherle, PhD[5]; Neha Bhagwat, PhD[5]; William Sun, PhD,[5] Rachel Chiaverelli, PhD,[5] Eric Mintah, PhD,[5] Lydia Clements, MD[6]; Tanner M. Johanns, MD, PhD[7]; Meredith McKean, MD, MPH[8]

[1]Sarah Cannon Research Institute at HealthONE, Denver, CO; [2]Sidney Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, Pennsylvania; [3]University of Iowa Hospitals and Clinics, Iowa City, IA; [4]Ohio State University Wexner Medical Center, Columbus, OH; [5]Prelude Therapeutics, Research & Development, Wilmington, DE; [6]Christiana Care Health Services, Christiana, DE; [7]Washington University School of Medicine, St Louis, MO; [8]Sarah Cannon Research Institute, Tennessee Oncology, Nashville, TN

PRT811 is a Brain-penetrant, 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
- PRT811 inhibits PRMT5 enzymatic activity
  - In preclinical studies, the biochemical and cellular sDMA IC_{50} were 3.9 nM and 17 nM, respectively
  - Importantly, PRT811 is brain-penetrant



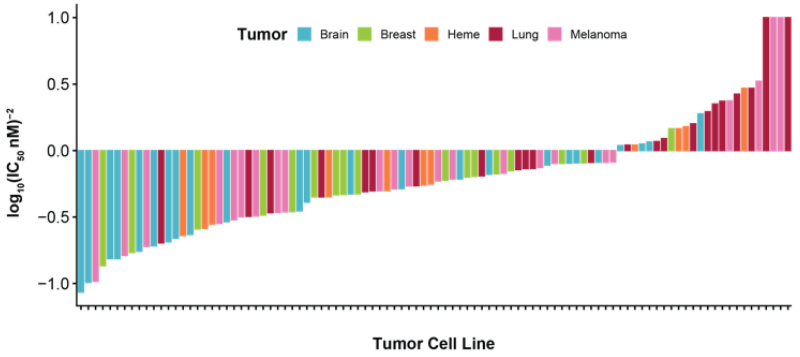
>2-fold Higher Brain Exposure Compared to Plasma in Rodents

Species	Time (hr)	Plasma (μM)	Brain (μM)	Brain/ plasma
Mouse	2	0.196	0.408	2.08
	4	0.105	0.261	2.49
	8	0.018	0.082	4.56
Rat	4	2.02	4.11	2.26

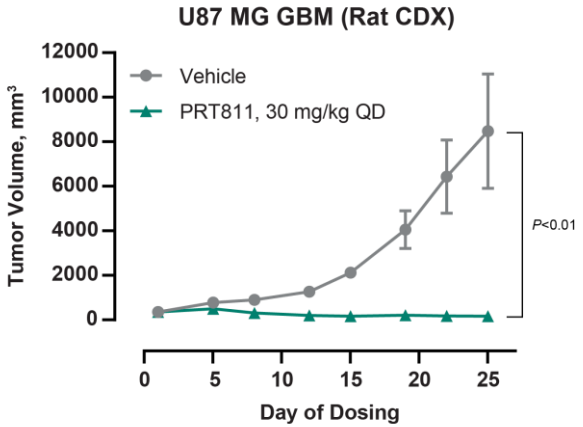
IC_{50}, half maximal inhibitory concentration; PRMT, protein arginine methyltransferase; sDMA, symmetric dimethylarginine.
Adapted from Zhang Y, et al. (2020, June 22-24). AACR Virtual Meeting. Poster 2919; Kim H. and Ronai ZA. *Cell Stress*. 4(8):199-215.

PRT811 Induces Significant Antitumor Activity in Advanced Solid Tumor and GBM Models

Broad Antiproliferative Activity in a Panel of 87 Cancer Cell Lines



Significant Antitumor Activity in a GBM Model



CDX, cell line-derived xenograft; IC_{50}, half maximal inhibitory concentration; GBM, glioblastoma multiforme; QD, once daily.
Adapted from Zhang Y, et al. (2020, June 22-24). AACR Virtual Meeting. Poster 2919.

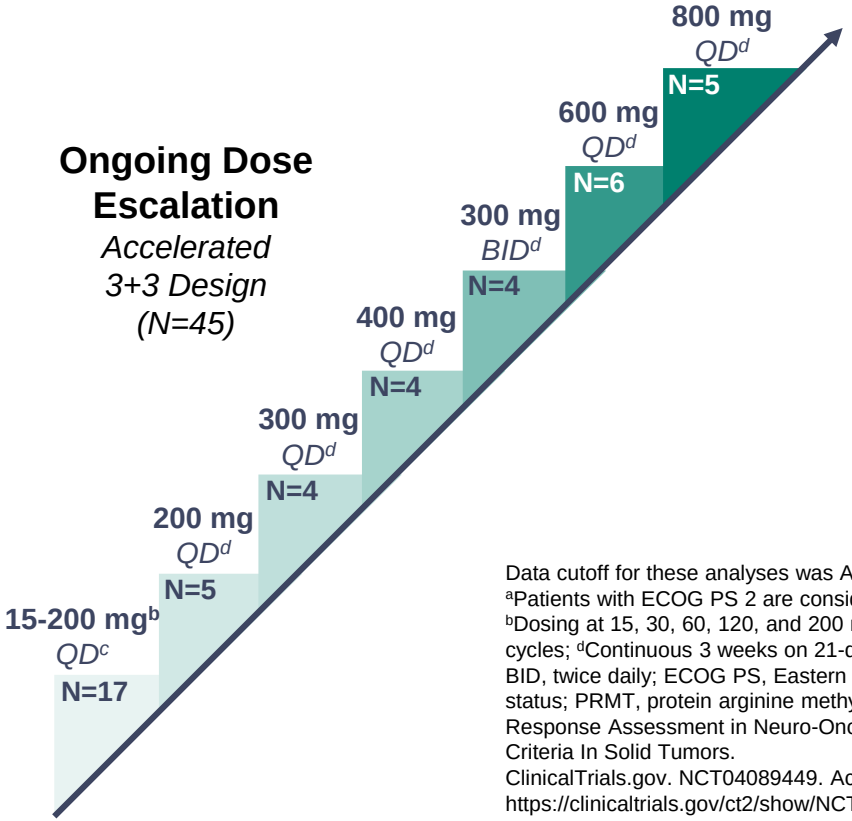
Study Design

Key Eligibility Criteria

- Adults with advanced solid tumors and recurrent high-grade glioma
- Refractory disease
- ECOG PS 0 or 1[a]

Key Objectives

- Safety/tolerability and recommended phase 2 dose
- Pharmacokinetic/pharmacodynamic profile
- Preliminary signals of efficacy (RECIST v1.1 & RANO)



Data cutoff for these analyses was August 13, 2021. Dose escalation is ongoing.
[a]Patients with ECOG PS 2 are considered eligible at physician's discretion; [b]Dosing at 15, 30, 60, 120, and 200 mg QD; [c]2 weeks on/1 week off 21-day cycles; [d]Continuous 3 weeks on 21-day cycles.
BID, twice daily; ECOG PS, Eastern Cooperative Oncology Group performance status; PRMT, protein arginine methyltransferase; QD, once daily; RANO, Response Assessment in Neuro-Oncology; RECIST, Response Evaluation Criteria In Solid Tumors.
ClinicalTrials.gov. NCT04089449. Accessed August 18, 2021. https://clinicaltrials.gov/ct2/show/NCT04089449.

Baseline Characteristics

Primary cancer diagnosis, n (%)	Total N=45
Advanced solid tumors	27 (60)
ACC	4 (9)
Uveal melanoma	4 (9)
Breast cancer	2 (4)
CRC	2 (4)
Gallbladder cancer	2 (4)
Melanoma	2 (4)
NSCLC	2 (4)
Acinar cell pancreatic cancer	1 (2)
Appendiceal cancer	1 (2)
Bladder	1 (2)
Cholangiocarcinoma	1 (2)
Chondrosarcoma	1 (2)
Esophageal adenocarcinoma	1 (2)
Large cell neuroendocrine lung cancer	1 (2)
Penile cancer	1 (2)
Prostate cancer	1 (2)
High-grade gliomas	18 (40)
GBM	17 (38)
Anaplastic astrocytoma	1 (2)

ACC, adenoid cystic carcinoma; CRC, colorectal cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; GBM, glioblastoma multiforme; NSCLC, non-small cell lung cancer.

Demographics	Total N=45
Age, years, median (range)	60 (28-82)
Female, n (%)	22 (49)
ECOG PS, n (%)	
0	12 (27)
1	32 (71)
2	1 (2)
Race, n (%)	
White or Caucasian	40 (89)
American Indian or Alaska Native	1 (2)
Asian	1 (2)
Black or African American	1 (2)
Other	2 (4)
Prior lines of systemic therapy, median (range)	2 (0-9)
Advanced solid tumors	2 (0-9)
High-grade gliomas	1 (0-5)

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

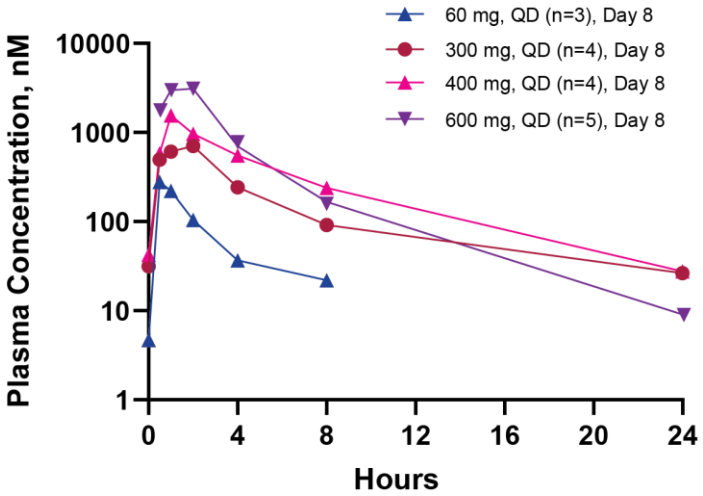
	All Patients (N=45)		Advanced Solid Tumors (n=27)		High-grade Gliomas (n=18)	
AE, n (%)	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Patients with events	31 (69)	5 (11)	22 (81)	3 (11)	9 (50)	2 (11)
Nausea	17 (38)	0	11 (41)	0	6 (33)	0
Vomiting	12 (27)	1 (2)	7 (26)	1 (4)	5 (28)	0
Fatigue	9 (20)	1 (2)	6 (22)	1 (4)	3 (17)	0
Thrombocytopenia[a]	8 (18)	3 (7)	6 (22)	2 (7)	2 (11)	1 (6)
Anemia	7 (16)	1 (2)	6 (22)	1 (4)	1 (6)	0
Anorexia	6 (13)	1 (2)	5 (19)	1 (4)	1 (6)	0
Diarrhea	5 (11)	0	4 (15)	0	1 (6)	0
Hypophosphatemia	4 (9)	0	4 (15)	0	0	0
Pruritus	3 (7)	0	2 (7)	0	1 (6)	0
Weight loss	3 (7)	0	3 (11)	0	0	0

- No grade 5 TRAEs (death)

- 6 (13%) and 2 (4%) patients had dose interruptions and reductions, respectively, due to AEs
- 34 (76%) patients discontinued treatment[b]
  - 28 (82%) due to PD
  - 1 (3%) each due to AE, withdrawal by subject, and other

[a]Term thrombocytopenia defined as thrombocytopenia plus platelet count decreased; [b]Missing reason for 3 (9%) patients.
AE, adverse event; PD, progressive disease; PRMT, protein arginine methyltransferase; QD, once daily.

Pharmacokinetics



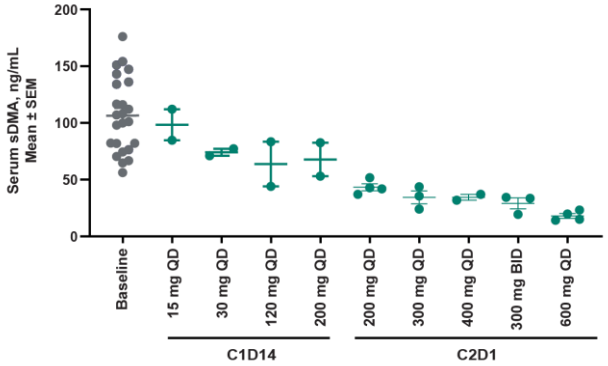
Dose (600mg, QD)	Parameter Values (CV%)
C_{max}, nM	3,777 (63)
AUC_{0-t}, hr.nM	12,487 (71)
$T_{1/2}$, hrs	5.8 (59)

- PRT811 demonstrated dose-dependent increases in C_{max} and AUC
- PRT811 did not accumulate in systemic circulation

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

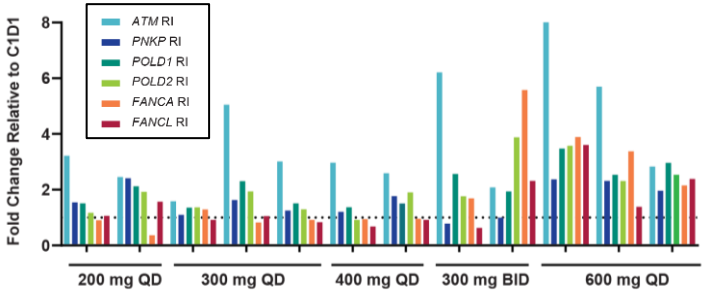
Pharmacodynamics

Dose-dependent Inhibition of Serum sDMA



- 83% decrease observed at 600 mg QD by C2D1

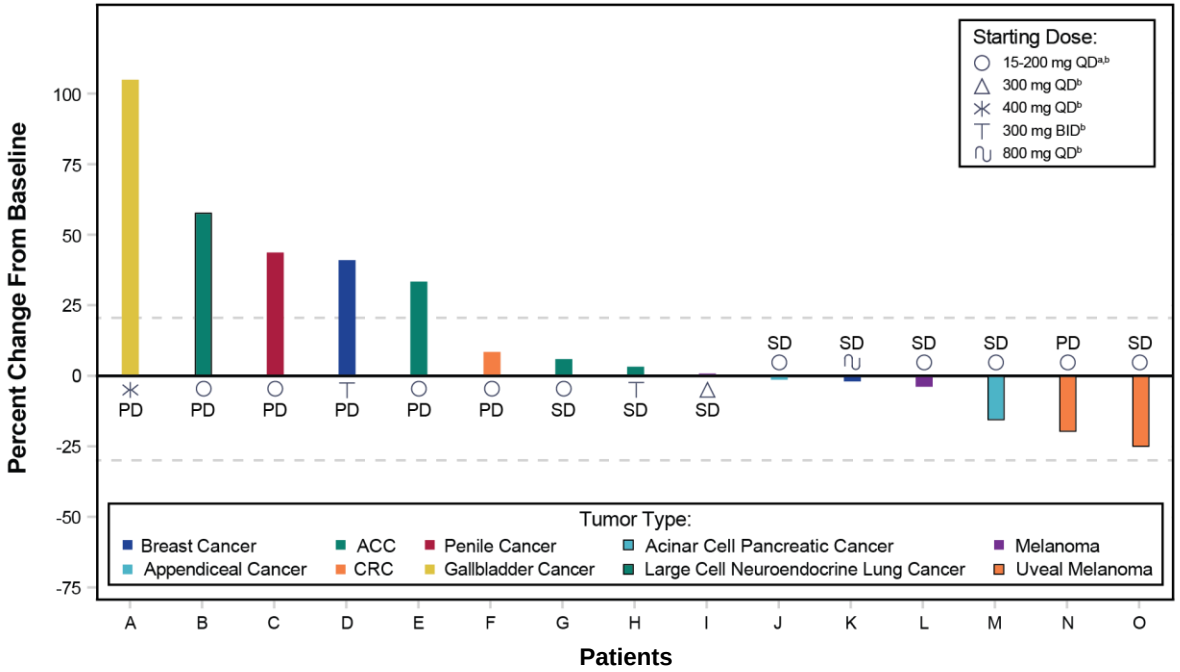
Intron Retention in PBMCs[a]



- PRMT5 plays a crucial role in mRNA splicing fidelity
- At higher dose levels, PRT811 treatment induced retention of introns in transcripts regulated by PRMT5

[a]Expression of retained introns was evaluated on Cycle 2 Day 1.
BID, twice daily; C, cycle; D, day; PBMC, peripheral blood mononuclear cells; PRMT, protein arginine methyltransferase; QD, once daily; RI, retained intron; sDMA, symmetric dimethylarginine; SEM, standard error of the mean.

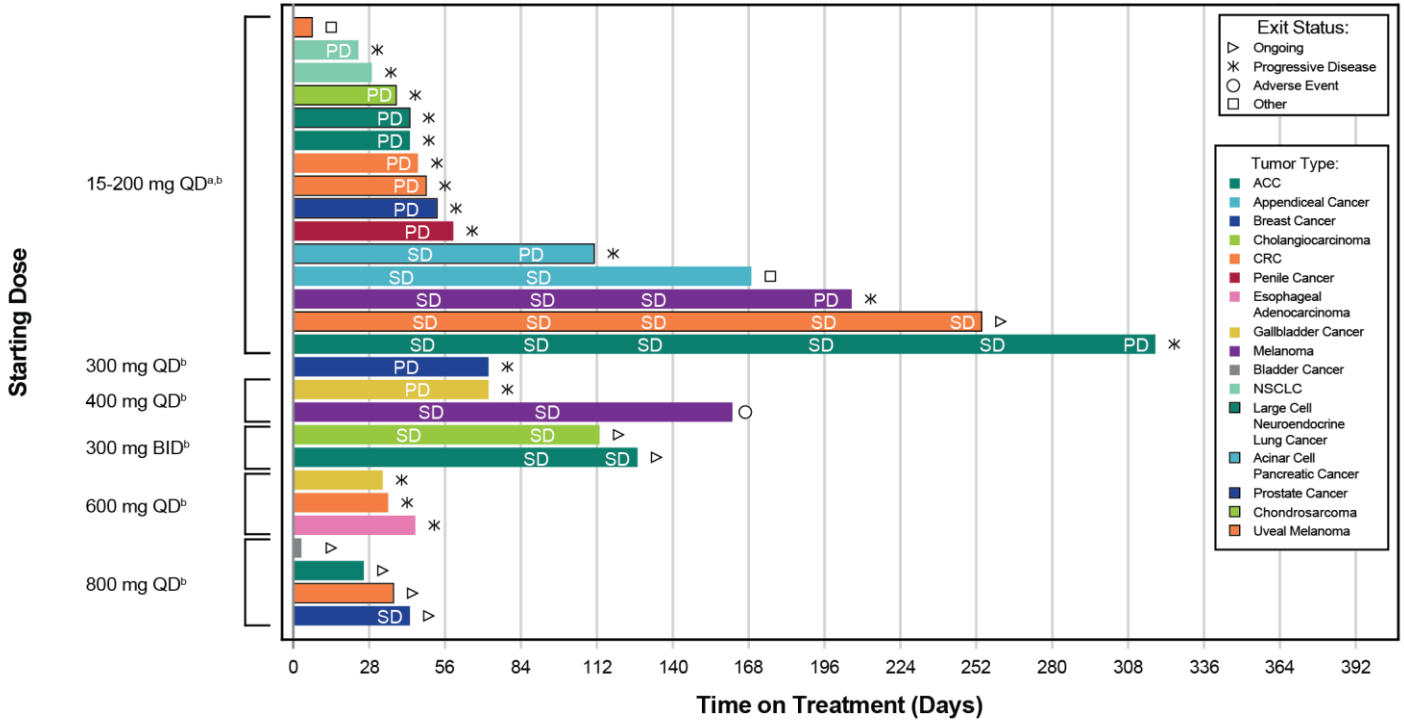
Best Target Lesion Response (RECIST v1.1) in Patients with Advanced Solid Tumors



- At a *post-data-cutoff exploration* on September 20, 2021
  - One additional patient (800 mg QD) with splicing-mutant (SF3B1) uveal melanoma had an unconfirmed PR with a 47% decrease in the target lesion
  - A patient with triple negative breast cancer (800 mg QD) had a 27% decrease in target lesions
  - Both patients continue on treatment

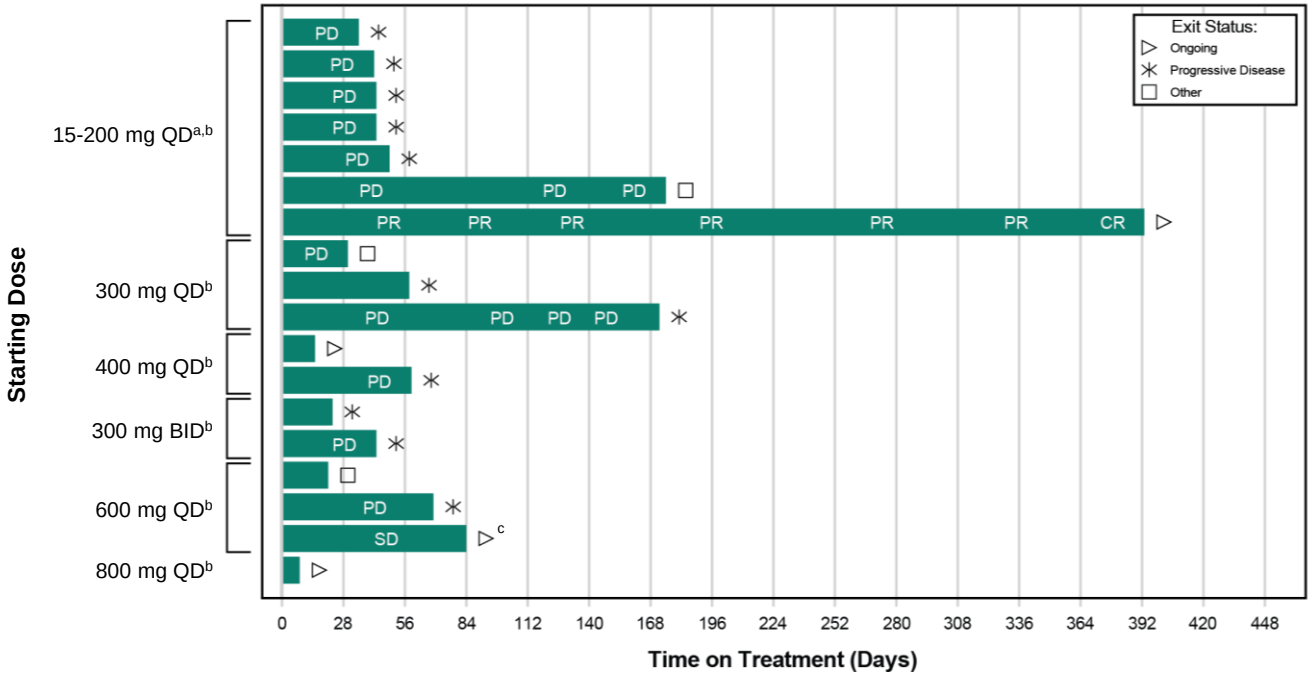
[a]2 weeks on/1 week off 21-day cycles for ≤200 mg; [b]Continuous 3 weeks on 21-day cycles for ≥200 mg.
This analysis includes patients with target lesions at baseline and at least 1 post-baseline percentage change (from baseline to PD). RECIST v1.1 assessment by investigator. 4 patients had insufficient lesion measurements to allow calculation of percentage change from baseline, thus data not shown.
ACC, adenoid cystic carcinoma; BID, twice weekly; CRC, colorectal cancer; PD, progressive disease; PRMT, protein arginine methyltransferase; QD, once daily; RECIST, Response Evaluation Criteria In Solid Tumors; SD, stable disease.

Overall Response and Response Duration by Dose/Schedule and Diagnosis in Patients with Advanced Solid Tumors



[a]2 weeks on/1 week off 21-day cycles for ≤200 mg; [b]Continuous 3 weeks on 21-day cycles for ≥200 mg.
ACC, adenoid cystic carcinoma; BID, twice daily; CRC, colorectal cancer; NSCLC, non-small cell lung cancer; PD, progressive disease; PRMT, protein arginine methyltransferase; QD, once daily; SD, stable disease.

Overall Response and Response Duration by Dose/Schedule and Diagnosis in Patients with High-grade Gliomas



MGMT status, n (%)	Total (n=18)
Methylated	4 (22)
Unmethylated	7 (39)
Indeterminate	1 (6)
Unknown	6 (33)
***IDH* status, n (%)**	
*IDH1*m	1 (6)
IDH1/2 WT	17 (94)

[a]2 weeks on/1 week off 21-day cycles for ≤200 mg; [b]Continuous 3 weeks on 21-day cycles for ≥200 mg; [c]Patient has H3 K27M mutation.
BID, twice weekly; CR, complete response; IDH, isocitrate dehydrogenase; m, mutant; PD, progressive disease; PR, partial response; PRMT, protein arginine methyltransferase; QD, once daily; SD, stable disease; MGMT, O^6-methylguanine-DNA methyltransferase; WT, wild type.

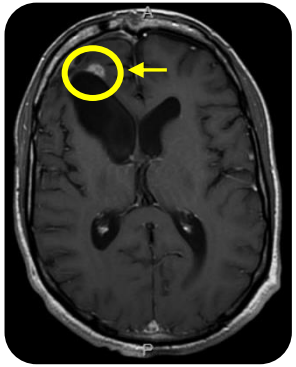
Confirmed CR in GBM

Patient History

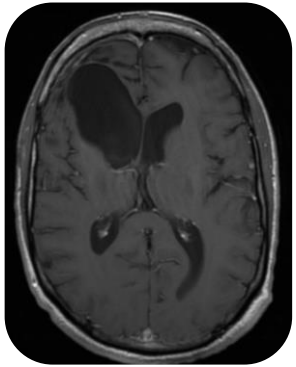
- 2019 recurrent GBM diagnosis
  - *IDH1*m
  - *MGMT* unmethylated
- Baseline: one target lesion per RANO
- Prior treatment: surgery and chemoradiation + temozolomide
- PRT811:
  - July 2020: Enrolled at 200 mg QD (2 weeks on/1 week off)
  - April 2021: Escalated to 300 mg QD (continuously)

Patient Response (per RANO)

- September 2020: 66% reduction in target lesion
- November 2020: 77% reduction of target lesion, confirmed PR
- August 2021: confirmed CR
  - T2/FLAIR sequence remains stable
  - Clinical status remains stable



Baseline



Aug 2021

CR, complete response; FLAIR, fluid-attenuated inversion recovery; GBM; glioblastoma multiforme; IDH, isocitrate dehydrogenase; m, mutant, MGMT, O^6-methylguanine–DNA methyltransferase; PR, partial response; PRMT, protein arginine methyltransferase; QD, once daily; RANO, Response Assessment in Neuro-Oncology; T2, transverse relaxation time.

Conclusions

PRT811 was well tolerated
- Most common TRAEs were fatigue, vomiting, and nausea
- No grade 5 TRAEs occurred

PRT811 demonstrated dose-dependent target engagement and inhibition of PRMT5 functional activity

PRT811 demonstrated preliminary clinical activity
- At the data cutoff of August 13, 2021
  - One patient with uveal melanoma with splicing-mutant (SF3B1) had SD for >6 months and a 25% decrease in tumor burden
  - Two other patients with advanced solid tumors also had SD >6 months
  - One patient with GBM experienced a durable PR that evolved into a CR
- At a *post-data-cutoff exploration* on September 20, 2021
  - One additional patient (800 mg QD) with splicing-mutant (SF3B1) uveal melanoma had an unconfirmed PR with a 47% decrease in the target lesion
  - A patient with triple negative breast cancer (800 mg QD) had a 27% decrease in target lesions
  - Both patients continue on treatment

The expansion phase of the study will be initiated in select tumor types upon establishing the recommended expansion dose

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

AE, adverse event; CR, complete response; DLT, dose-limiting toxicity; GBM, glioblastoma multiforme; PR, partial response; PRMT, protein arginine methyltransferase; QD, once daily; SD, stable disease; TRAE, treatment-related adverse event.