2023 ASCO ANNUAL MEETING

A Phase 1 Study of the Protein Arginine Methyltransferase 5 (PRMT5) Brain-Penetrant Inhibitor PRT811 in Patients with Recurrent High-Grade Glioma or Uveal Melanoma

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Abstract # 3008

Background

- PRMT5 catalyzes symmetric arginine dimethylation of protein substrates and controls key cellular processes[1-4]
- Overexpression of PRMT5 has been correlated with tumor cell growth and is associated with poor clinical outcomes[3,4]
- PRT811 is brain penetrant and has demonstrated potent and selective inhibition of PRMT5 in *IDH1*-mutant GBM cells[2]
- In the previously reported dose escalation phase of the current study, patients treated with PRT811 at 600 mg QD had a mean sDMA inhibition of 83%, and 1 patient with Grade IV *IDH*+ glioma had a complete response[5]
- Herein, we report the safety and efficacy of PRT811 monotherapy in all patients with recurrent high-grade glioma or uveal melanoma with limited treatment options

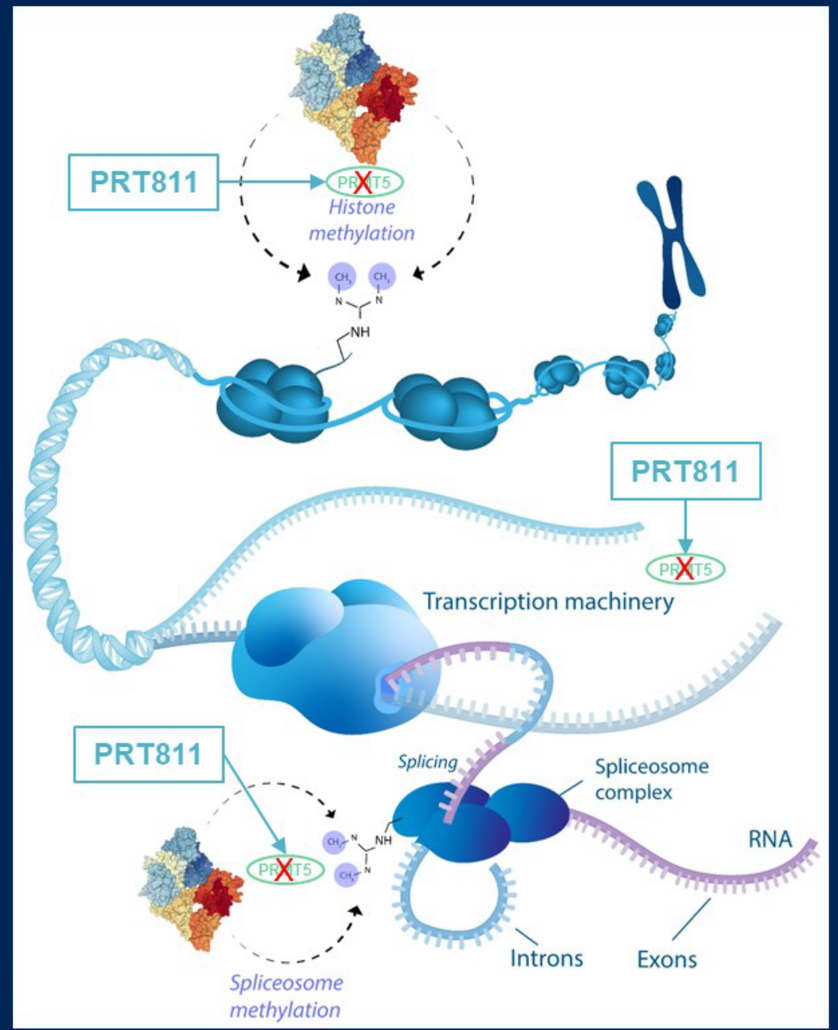


Figure adapted with permission from Zhang Y, et al.[1]

QD, once daily; sDMA symmetrical dimethylated arginine; GBM, glioblastoma; *IDH*, isocitrate dehydrogenase.

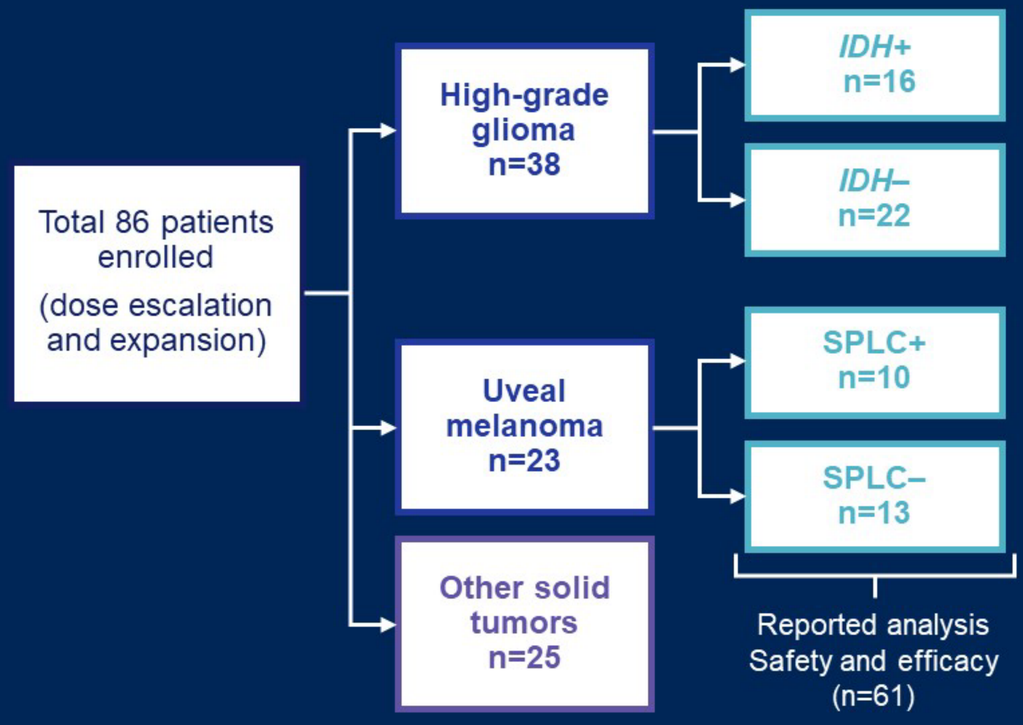
1. Chen Y, et al. *Biomed Pharmacother.* 2021;144:112252. 2. Zhang Y, et al. *Cancer Res.* 2020;80(16_Supplement):2919. 3. Hwang JW, et.al. *Exp Mol Med.* 2021;53:788-808. 4. Kim H, Ronai ZA. *Cell Stress.* 2020;4:199-215.
5. Falchook GS, et al. *Mol Cancer Ther.* 2021;20(12_Supplement):P044.

Study Design
NCT04089449

- Phase 1, first-in-human, open-label, multi-center study
- Dose escalation (3+3 design) followed by expansion
- Patients received 15-800 mg of PRT811 orally
- The RP2D was determined to be 600 mg orally once daily
- The majority of patients reported in this analysis (n=42) received 600 mg PRT811 orally once daily

Key Eligibility Criteria

- Age ≥18 years
- Biopsy-confirmed high-grade glioma with recurrence/progression or advanced/metastatic uveal melanoma
- Resistant, refractory, or ineligible to receive standard treatment
- **Dose escalation:**
  - WHO grade III-IV glioma irrespective of *IDH* mutation status
  - Uveal melanoma
  - Other solid tumors
- **Expansion:**
  - WHO grade III-IV *IDH+* glioma
  - SPLC+ uveal melanoma (e.g., *SF3B1*, *U2AF1*, *SRSF2*, *ZRSR2*, *EIF1AX*)
  - SPLC– uveal melanoma
- Patients with uveal melanoma were required to have measurable disease per RECIST v1.1



Study Objectives

Primary Objectives:
- DLTs of PRT811
- Determine the MTD and RP2D of PRT811

Secondary Objectives:
- Safety and tolerability of PRT811
- PK of PRT811
- Anti-tumor activity of PRT811 (investigator assessed)

DLT, dose-limiting toxicity; *IDH+/–*, isocitrate dehydrogenase 1/2 mutant-positive/negative; MTD, maximum tolerated dose; ORR, objective response rate; PFS, progression-free survival; PK, pharmacokinetics; RECIST, Response Evaluation Criteria in Solid Tumours; RP2D, recommended phase 2 dose; QD, once daily; SPLC+, splicing mutation positive (per protocol tumors must display at least one splicing mutation (e.g., *SF3B1*, *U2AF1*, *SRSF2*, *ZRSR2*, *EIF1AX*); SPLC–, splicing mutation negative; WHO, World Health Organization.

PRESENTED BY: Varun Monga, MD

Patient Disposition

Disposition	Patients with glioma (n=38)	Patients with uveal melanoma (n=23)	Total (N=61)
Study phase enrolled, n (%)			
Escalation	18 (47.4)	4 (17.4)	22 (36.1)
Confirmation/expansion	20 (52.6)	19 (82.6)	39 (63.9)
Duration of treatment, median (range), months	1.38 (0.03-32.23)	1.41 (0.16-26.68)	1.38 (0.03-32.23)
Patients continuing treatment, n (%)[a]	1 (2.6)	2 (8.7)	3 (4.9)
Reason for treatment discontinuation, n (%)			
AE	3 (7.9)	2 (8.7)	5 (8.2)
Physician's decision	1 (2.6)	1 (8.7)	2 (3.3)
PD	31 (81.6)	15 (65.2)	46 (75.4)
Withdrawal by patient	2 (5.3)	1 (4.4)	3 (4.9)
Study terminated by Sponsor	0	2 (8.7)[b]	2 (3.3)

[a]Patients continuing treatment under an investigator-led single-patient study. [b]Patients who discontinued treatment due to termination of the study by the Sponsor transitioned to an investigator-led single-patient study.
Data cut-off date: March 31, 2023.
AE, adverse event; PD, progressive disease.

Patient Baseline Characteristics

Characteristic	Patients with glioma		Patients with uveal melanoma		
	IDH+ (n=16)	*IDH*– (n=22)	SPLC+ (n=10)	SPLC– (n=13)	Total (N=61)
Age					
Median (range), years	43.0 (25.0-73.0)	60.5 (28.0-79.0)	56.0 (24.0-76.0)	61.0 (42.0-83.0)	56.0 (24.0-83.0)
≥65, n (%)	1 (6.3)	5 (22.7)	3 (30.0)	6 (46.2)	15 (24.6)
<65, n (%)	15 (93.8)	17 (77.3)	7 (70.0)	7 (53.8)	46 (75.4)
Gender, n (%)					
Female	9 (56.3)	12 (54.5)	7 (70.0)	7 (53.8)	35 (57.4)
Male	7 (43.8)	10 (45.5)	3 (30.0)	6 (46.2)	26 (42.6)
Race, n (%)					
White or Caucasian	14 (87.5)	21 (95.5)	9 (90.0)	13 (100.0)	57 (93.4)
ECOG performance status, n (%)					
0-1	11 (68.8)	19 (86.4)	10 (100.0)	13 (100.0)	53 (86.9)

Patient Disease Characteristics

	Patients with glioma	
	IDH+ (n=16)	*IDH*– (n=22)
WHO Grade at study entry, n (%)		
Grade III	9 (56.3)	2 (9.1)
Grade IV	7 (43.8)	20 (90.9)
Lines of prior systemic therapy, median (range)	2.0 (1.0-6.0)	2.0 (1.0-5.0)
0, n (%)	0	0
1, n (%)	6 (37.5)	10 (45.5)
2, n (%)	3 (18.8)	5 (22.7)
≥3, n (%)	7 (43.8)	7 (31.8)
Prior therapy, n (%)		
Temozolomide	15 (93.8)	22 (100.0)
Radiation	16 (100.0)	22 (100.0)

	Patients with uveal melanoma	
	SPLC+ (n=10)	SPLC– (n=13)
Stage at study entry, n (%)		
Stage IA	1 (10.0)[a]	0
Stage IV	9 (90.0)	13 (100.0)
Hepatic metastases, n (%)	8 (80.0)	12 (92.3)
Lines of prior systemic therapy, median (range)	2.0 (1.0-5.0)	2.0 (0-5.0)
0, n (%)	0	2 (15.4)
1, n (%)	5 (50.0)	4 (30.8)
2, n (%)	1 (10.0)	2 (15.4)
≥3, n (%)	4 (40.0)	5 (38.5)

[a]Stage reported in the database for time of initial diagnosis but patient was Stage IV at the time of study entry with metastases to muscle.

Safety Summary

n, (%)	Patients with glioma (n=38) Any Grade	Patients with glioma (n=38) Grade ≥3	Patients with uveal melanoma (n=23) Any Grade	Patients with uveal melanoma (n=23) Grade ≥3	Total (N=61) Any Grade	Total (N=61) Grade ≥3
TEAEs	38 (100.0)	22 (57.9)	22 (95.7)	10 (43.5)	60 (98.4)	32 (52.5)
Related TEAEs	28 (73.7)	7 (18.4)	20 (87.0)	5 (21.7)	48 (78.7)	12 (19.7)
TEAEs leading to dose reduction/interruption	12 (31.6)	8 (21.1)	9 (39.1)	6 (26.1)	21 (34.4)	14 (23.0)
Related TEAEs leading to dose reduction/interruption	7 (18.4)	4 (10.5)	6 (26.1)	4 (17.4)	13 (21.3)	8 (13.1)
Serious TEAEs	10 (26.3)	8 (21.1)	3 (13.0)	2 (8.7)	13 (21.3)	10 (16.4)
Related SAEs	1 (2.6)	1 (2.6)	1 (4.4)	1 (4.4)	2 (3.3)	2 (3.3)
Grade 5 TEAEs	2 (5.3)[a]	2 (5.3)[a]	0 (0)	0 (0)	2 (3.3)[a]	2 (3.3)[a]
Related Grade 5 TEAEs	0	0	0	0	0	0

TEAE, treatment-emergent AE; SAE, serious adverse event
[a]1 patient died from cardiac arrest (unrelated); 1 patient died from acute hypoxic respiratory failure (unrelated).

Treatment-Emergent AEs ≥15%

Events by preferred term, n (%)	Patients with glioma (n=38)		Patients with uveal melanoma (n=23)		Total (N=61)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Nausea	23 (60.5)	0	15 (65.2)	0	38 (62.3)	0
Vomiting	17 (44.7)	0	12 (52.2)	0	29 (47.5)	0
Fatigue	12 (31.6)	2 (5.3)	11 (47.8)	1 (4.4)	23 (37.7)	3 (4.9)
Constipation	9 (23.7)	0	10 (43.5)	1 (4.4)	19 (31.1)	1 (1.6)
Fall	13 (34.2)	0	2 (8.7)	0	15 (24.6)	0
Thrombocytopenia	9 (23.7)	4 (10.5)	5 (21.7)	2 (8.7)	14 (23.0)	6 (9.8)
Headache	11 (28.9)	1 (2.6)	1 (4.4)	0	12 (19.7)	1 (1.6)
Anemia	4 (10.5)	0	6 (26.1)	5 (21.7)	10 (16.4)	5 (8.2)
Muscular weakness	9 (23.7)	3 (7.8)	1 (4.4)	0	10 (16.4)	3 (4.9)

Best Overall Response

Response, n (%)	Patients with glioma *IDH*+ (n=16)	Patients with glioma *IDH*– (n=22)	Patients with glioma Total (N=38)	Patients with uveal melanoma SPLC+ (n=10)	Patients with uveal melanoma SPLC– (n=13)	Patients with uveal melanoma Total (N=23)
ORR	2 (12.5)	0	2 (5.3)	1 (10.0)	0	1 (4.4)
CR	2 (12.5)	0	2 (5.3)	0	0	0
PR	0	0	0	1 (10.0)	0	1 (4.4)
PRu	1 (6.3)	0	1 (2.6)	1 (10.0)	0	1 (4.4)
SD	8 (50.0)	3 (13.6)	11 (28.9)	4 (40.0)	4 (30.8)	8 (34.8)
PD	4 (25.0)	16 (72.7)	20 (52.6)	2 (20.0)	8 (61.5)	10 (43.5)
NE[a]	1 (6.3)	3 (13.6)	4 (10.5)	2 (20.0)	1 (7.7)	3 (13.0)

Durable objective responses observed

Patients with glioma:

- 1 CR with a DOR of 31.0 months (ongoing)
- 1 CR with a DOR of 7.5 months (PD)

Patient with uveal melanoma:

- 1 PR with a DOR of 10.0 months (PD)

[a]Patients who were not evaluable discontinued treatment prior to having a post-treatment scan
Glioma response was determined per RANO criteria. Uveal melanoma response was determined per RECIST v1.1.
CR, complete response; DOR, duration of response; NE, not evaluable; PR, partial response; PRu, partial response unconfirmed; RANO, Response Assessment in Neuro-Oncology; SD, stable disease; PD, progressive disease

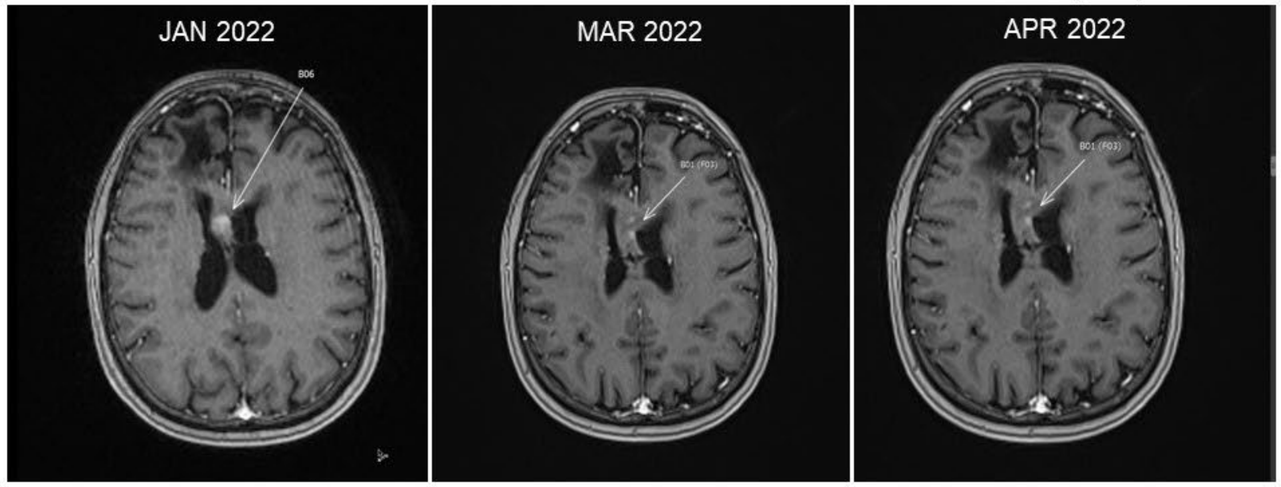
Confirmed CR in a Patient With Glioma

Patient history:

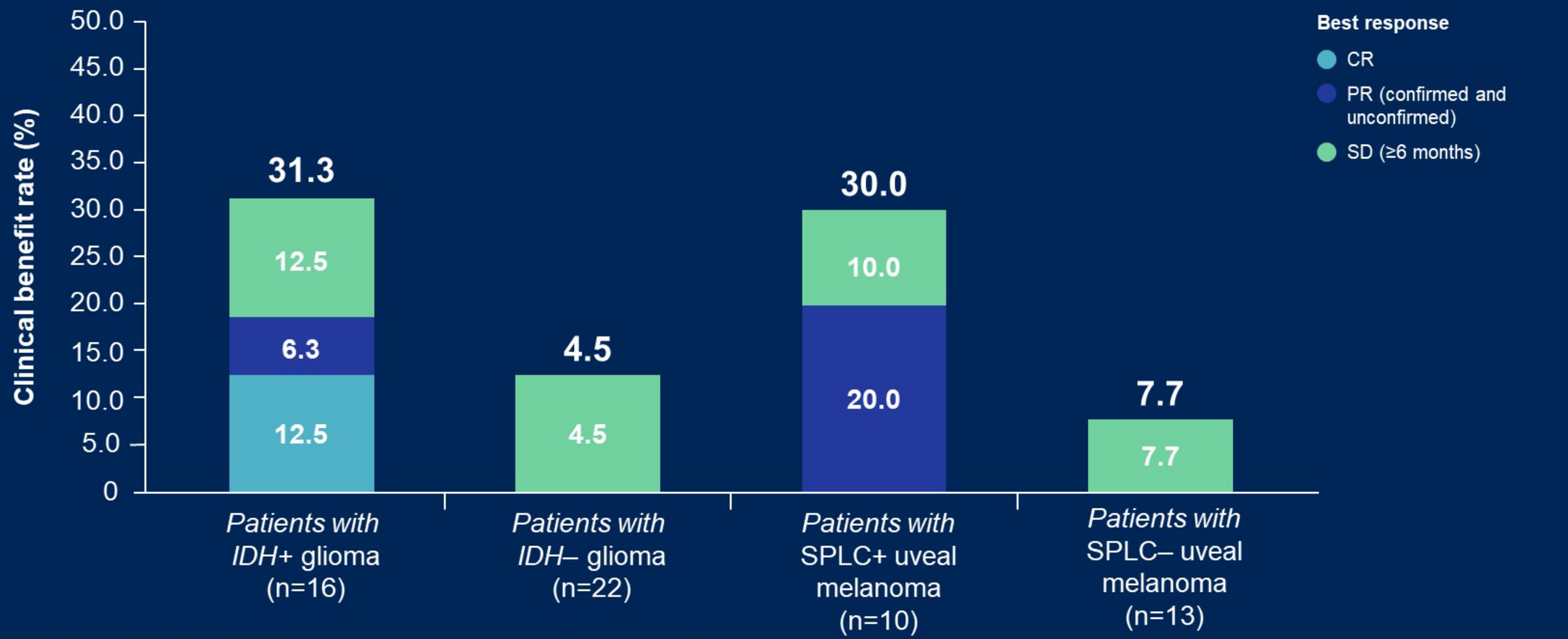
- 57-year-old Caucasian female
- Initial diagnosis: August 2004
  - Prior treatment: surgery, radiation, temozolomide, irinotecan + thalidomide
- Disease characteristics at study entry:
  - WHO Grade III oligodendroglioma (*IDH* mutant, 1p/19q co-deleted)
- Baseline: 1 target lesion and 2 NTLs per RANO criteria
- Received 600 mg QD PRT811
- Patient had disease progression with enhancing NTLs despite continued CR of target lesion

NTL, non-target lesion.

Target Lesion Response

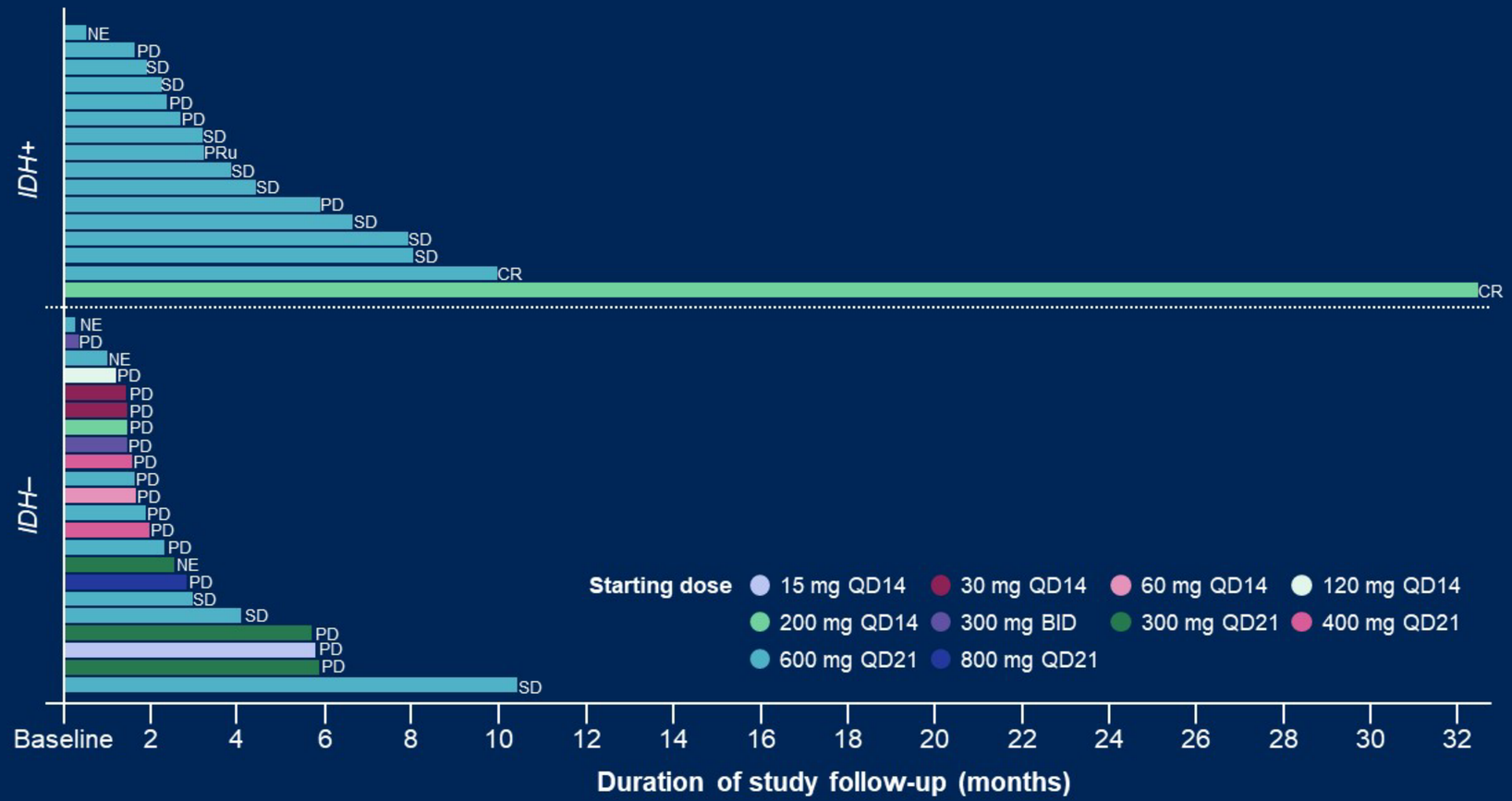


Clinical Benefit Rate



Clinical benefit rate is defined as any CR/PR or durable SD (≥6 months) prior to any PD, as assessed by Investigators per the criteria for corresponding disease.

Treatment Duration and PFS in Patients With Glioma (n=38)

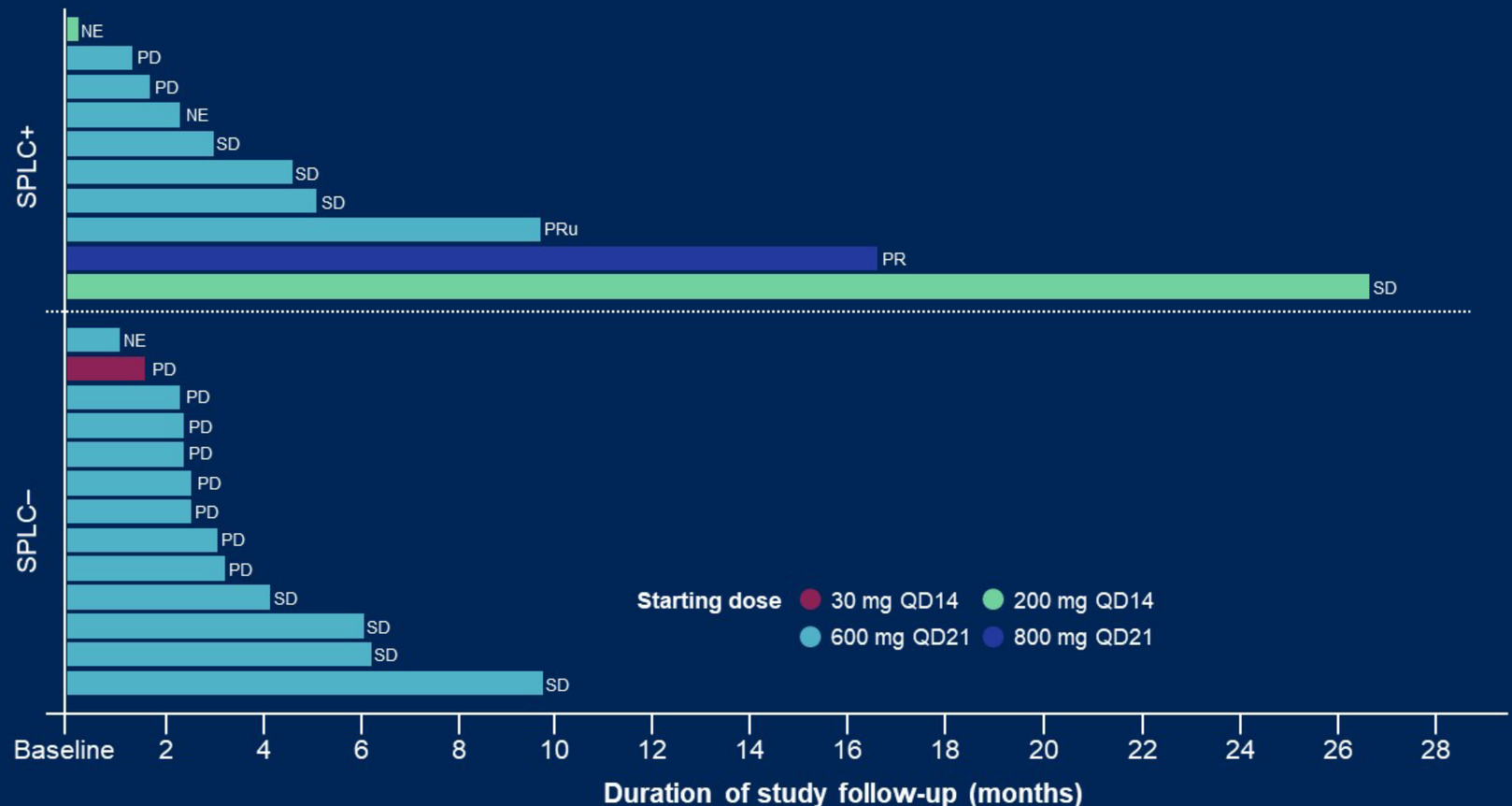


Median Duration on Treatment (months, range)	
IDH+	2.49 (0.33- 32.23)
IDH–	1.15 (0.03- 10.05)

PFS	*IDH+* glioma (n=16)	*IDH–* glioma (n=22)
Events, n (%)	13 (81.3)	20 (90.9)
Median (95% CI), months	2.46 (1.41-5.62)	1.38 (1.15-1.58)
6-month rate, % (95% CI)	22.0 (5.0-46.0)	5.0 (0-21.0)

BID, twice daily; CI, confidence interval; PRu, partial response unconfirmed; QD14, once daily for 14 days; QD21, once daily for 21 days

Treatment Duration and PFS in Patients With Uveal Melanoma (n=23)



Median Duration on Treatment (months, range)	
SPLC+	2.74 (0.16- 26.68)
SPLC–	1.41 (0.23-9.23)

PFS	SPLC+ uveal melanoma (n=10)	SPLC– uveal melanoma (n=13)
Events, n (%)	5 (50.0)	11 (84.6)
Median (95% CI), months	4.14 (1.31-NE)	1.4 (1.28-4.93)
6-month rate, % (95% CI)	45.0 (11.0-75.0)	13.0 (1.0-40.0)

PRu, partial response unconfirmed; QD14, once daily for 14 days; QD21, once daily for 21 days

Summary

- Consistent with findings from the dose-escalation component of the study,[1] PRT811 continues to be associated with an acceptable safety profile
  - The majority of treatment-emergent AEs were Grade 1 and 2; the most common were gastrointestinal (nausea, vomiting, constipation), fatigue, fall, and myelosuppression (anemia, thrombocytopenia)

- PRT811 monotherapy demonstrated clinical activity in patients with high-grade *IDH*+ glioma and SPLC+ metastatic uveal melanoma
  - ***IDH*+ glioma:** 12.5% ORR (2 durable CRs); 31.3% clinical benefit rate; median PFS of 2.46 months
  - **SPLC+ uveal melanoma:** 10.0% ORR (1 durable PR); 30.0% clinical benefit rate; median PFS of 4.14 months

- Minimal clinical activity was observed in patients with high-grade *IDH*– glioma or SPLC– metastatic uveal melanoma

1. Falchook GS, et al. *Mol Cancer Ther.* 2021;20(12_Supplement):P044.

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THANK YOU