PRT3789, a First-in-Class Intravenous SMARCA2 Degrader, in Advanced Solid Tumors With a *SMARCA4* Mutation: Phase 1 Trial

Timothy A. Yap,[1] Afshin Dowlati,[2] Ibiayi Dagogo-Jack,[3] Julien Vibert,[4] Alexander I. Spira,[5] Victor Moreno,[6] Salman R. Punekar,[7] Emiliano Calvo,[8] Guru P. Sonpavde,[9] Mark Awad,[10] Jonathan W. Riess,[11] Tatiana Hernández-Guerrero,[12] Benjamin Herzberg,[13] Antoine Italiano,[14] Aurelie Swalduz,[15] Ticiana A Leal,[16] Patricia LoRusso,[17] Egbert F. Smit,[18] Edward B. Garon,[19] William Novotny,[20] Robin Guo[21]

[1]Department of Investigational Cancer Therapeutics, The University of Texas, MD Anderson Cancer Center, Houston, TX, USA; [2]Department of Medicine, University Hospitals Seidman Cancer Center and Case Western Reserve University, Cleveland, OH, USA; [3] Department of Medicine, Massachusetts General Hospital, Boston, MA, USA; [4]Department of Oncology Medicine, Gustave Roussy, Villejuif, France; [5]Department of Clinical Research, Virginia Cancer Research (VCS) Research Institute, NEXT Oncology-Virginia, Fairfax, VA, USA; [6]Early Phase Clinical Trial Unit, START Madrid-FJD, Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain; [7]Division of Hematology and Oncology, NYU Langone Health, New York, NY, USA; [8]Early Phase Clinical Drug Development in Oncology, START Madrid-CIOCC, Centro Integral Oncológico Clara Campal, Madrid, Spain; [9]Department of Genitourinary Oncology, AdventHealth Cancer Institute, Orlando, FL, USA; [10]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA; [11]Department of Thoracic Oncology, UC Davis Comprehensive Cancer Center, Sacramento, CA, USA; [12]Department of Medical Oncology, START Barcelona - HM Nou Delfos, Barcelona, Spain; [13]Department of Medicine, Columbia University Herbert Irving Comprehensive Cancer Center, New York, NY, USA; [14]Early Phase Trials and Sarcoma Units, Institut Bergonié, Bordeaux, France; [15]Department of Medical Oncology, Léon Bérard Centre, Lyon, France; [16]Department of Hematology and Medical Oncology Winship Cancer Institute of Emory University, Atlanta, GA, USA; [17]Department of Developmental Therapeutics, Yale Cancer Center, New Haven, CT, USA; [18]Department of Pulmonology, Universiteit Leiden, Leiden, Netherlands; [19]Department of Medicine, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; [20]Clinical Development, Prelude Therapeutics Incorporated, Wilmington, DE, USA; [21]Department of Gynecologic Medical Oncology, Memorial Sloan Kettering Cancer Center, Commack, NY, USA

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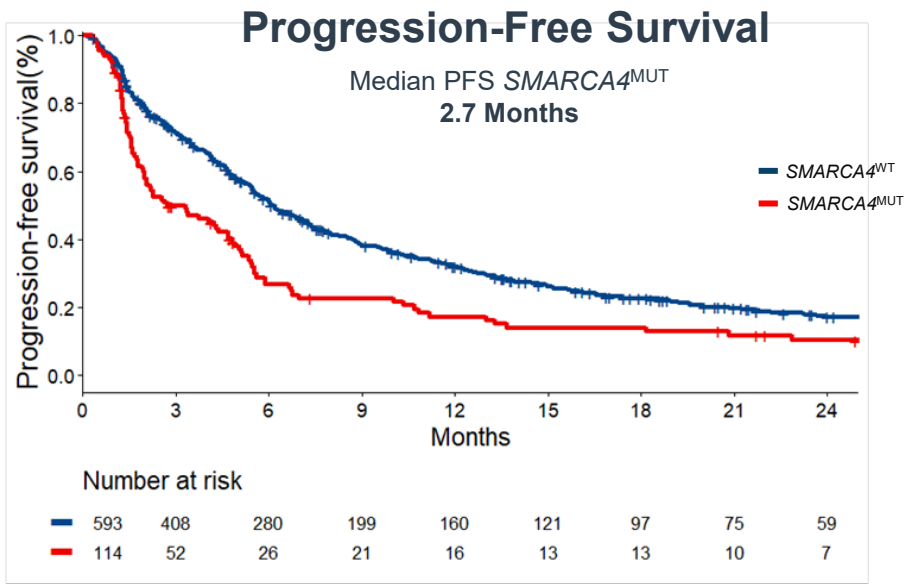
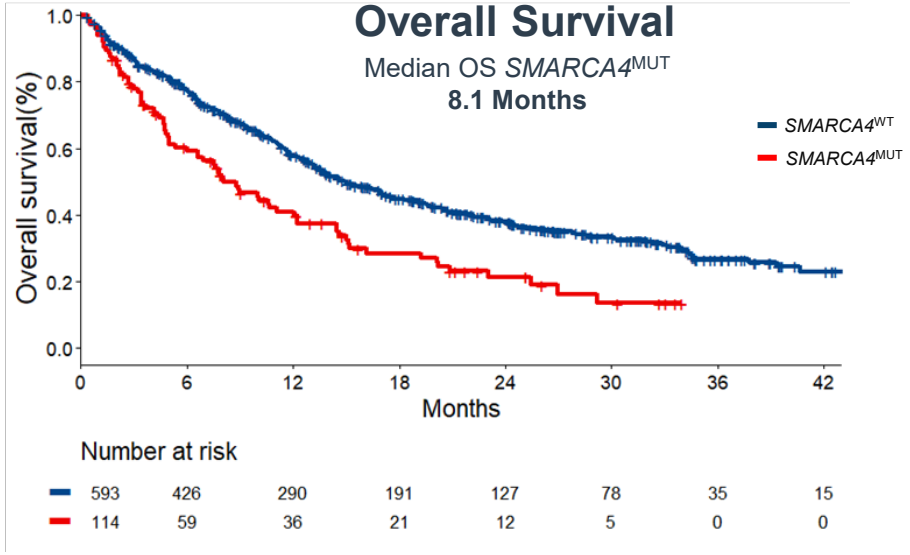
SMARCA4 Mutations in NSCLC and Other Solid Tumors





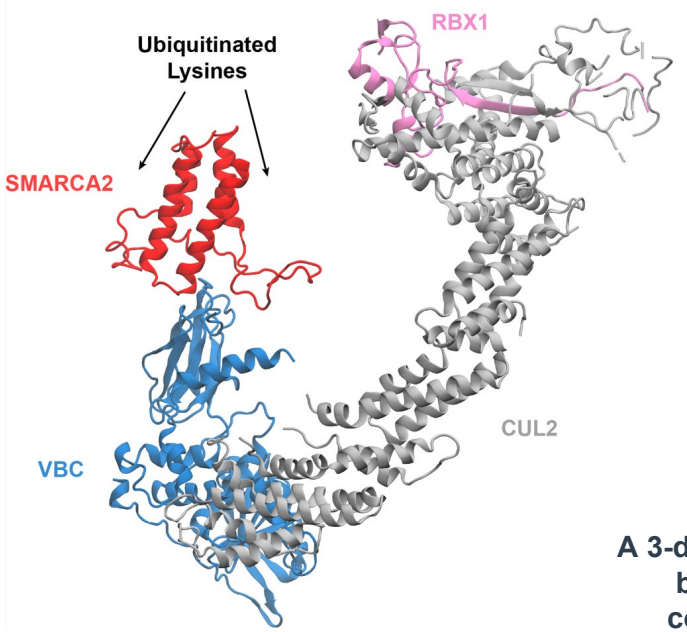
- SMARCA4 is inactivated in a variety of cancers and considered a tumor suppressor[1]
- In NSCLC, *SMARCA4* mutations are observed in ~10% of cases, and are associated with more aggressive and invasive disease and poor clinical outcomes[2,3]
- *SMARCA4* mutations are classified as class 1 mutations (truncating mutations, fusions, and homozygous deletion) and class 2 mutations (missense mutations)[2]
- Therapies that target *SMARCA4*-deficient cancers are not available. However, *SMARCA4*-mutated cancers become reliant on *SMARCA2* and selectively degrading *SMARCA2* offers an attractive approach to induce synthetic lethality in *SMARCA4*-mutant tumors

MUT, mutated; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; WT, wildtype.

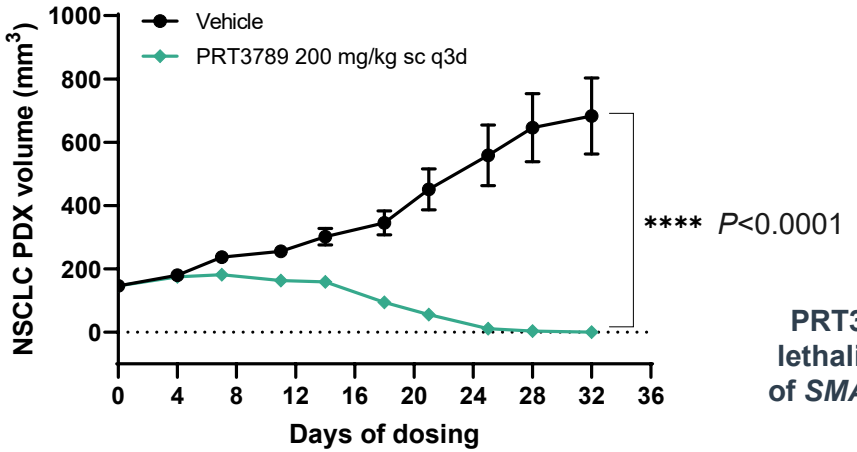
1. Wang X, et al. *Clin Cancer Res*. 2013;20(1):21-27. 2. Schoenfeld AJ, et al. *Clin Cancer Res*. 2020;26(21):5701-5708. 3. Alessi JV, et al. *J Thorac Oncol*. 2023;18(6):731-743.

PRT3789: An Intravenous SMARCA2 Degrader

- Highly potent (plasma DC_{50} = 21 nM)
- Selective for SMARCA2 over SMARCA4
- Induces synthetic lethality in various CDX and PDX mouse models of *SMARCA4*-deficient cancer at well-tolerated doses
- Unlike an inhibitor, a SMARCA2 degrader achieves prolonged chromatin regulation through disrupting the SWI/SNF complex in SMARCA4-deficient cancer cells
- In our experience, we are able to achieve greater selectivity with a degrader as compared with an inhibitor



A 3-dimensional model of SMARCA2 bromodomain and E3 ligase complex formed by PRT3789.



PRT3780-induced synthetic lethality in PDX mouse model of *SMARCA4*-deficient NSCLC.

CDX, cell line-derived xenograft; DC_{50}, half-maximal degradation concentration; NSCLC, non-small cell lung cancer; PDX, patient-derived xenografts; q3d, every 3 days; sc, subcutaneously; VBC, von Hippel-Lindau, elongin B, and elongin C complex.
Ito K, et al. 6th Annual TPD Summit 2023.

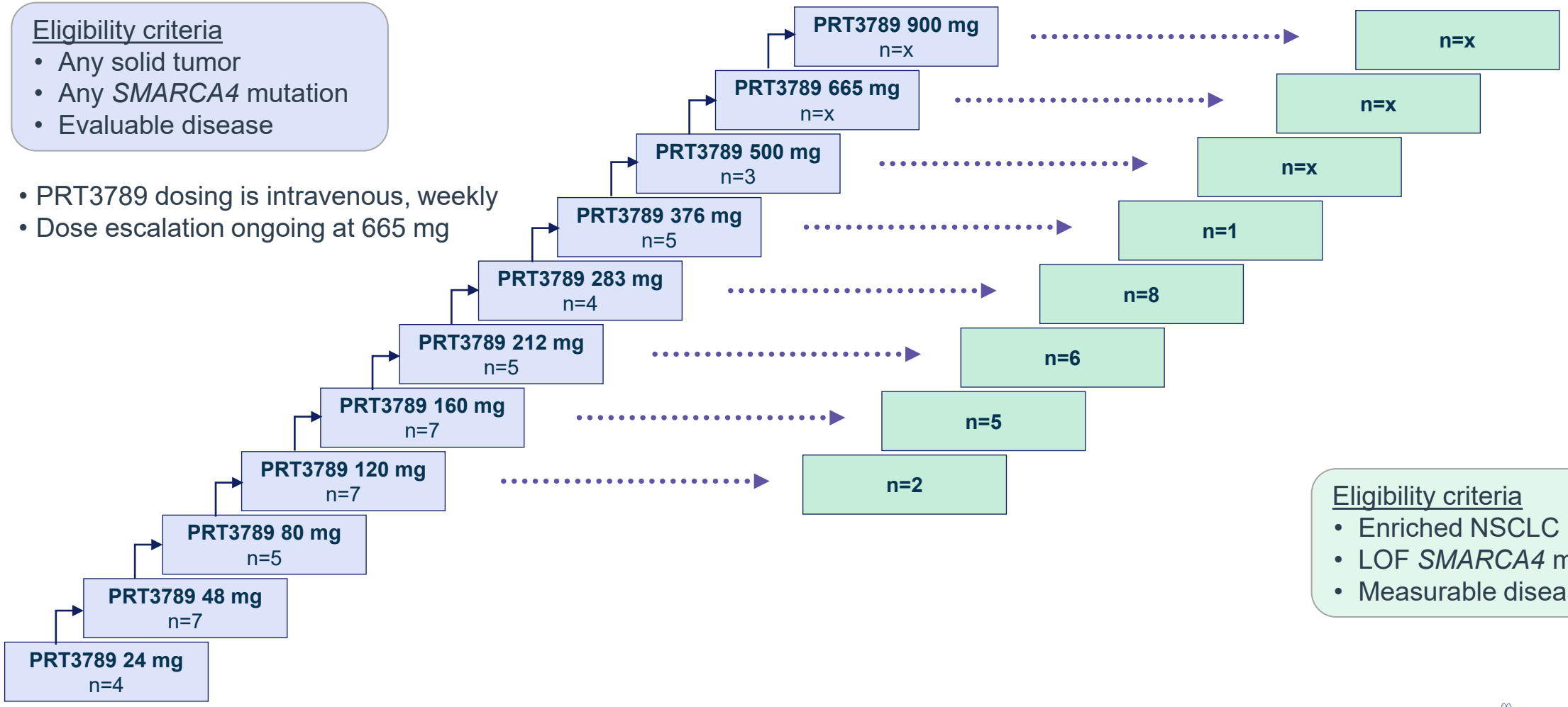
Study Schema and Enrollment
PRT3789 Monotherapy

Dose-Escalation Cohorts

Eligibility criteria
- Any solid tumor
- Any *SMARCA4* mutation
- Evaluable disease

- PRT3789 dosing is intravenous, weekly
- Dose escalation ongoing at 665 mg

Backfill Cohorts



Eligibility criteria
- Enriched NSCLC
- LOF *SMARCA4* mutation
- Measurable disease

Data cutoff: 30 November 2024 and patients enrolled by 31 August 2024.
LOF, loss of function; NSCLC, non-small cell lung cancer.

Demographics and Disease Characteristics
PRT3789 Monotherapy

Demographics and Disease Characteristics

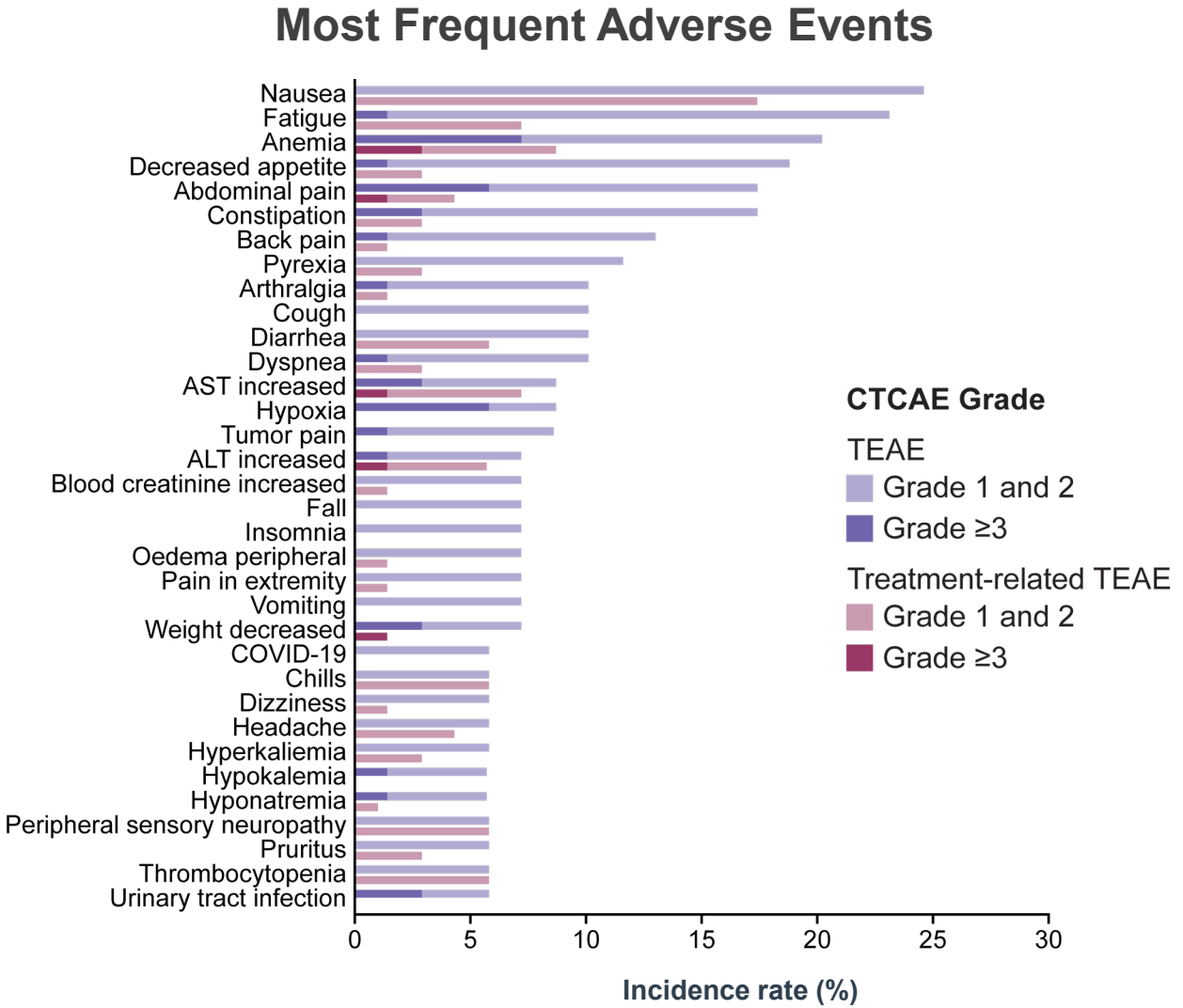
Characteristics	Patients (N=69)
Age, years	
Median	62
Sex, n (%)	
Male	37 (53.6)
Female	32 (46.4)
Prior lines of systemic anticancer therapy, n	
Median (min, max)	3 (1, 10)
Tumor type, n (%)	
Non-small cell lung cancer	32 (46.4)
Pancreatic cancer	6 (8.7)
Breast cancer	4 (5.8)
Thoracic undifferentiated	3 (4.3)
Cholangiocarcinoma	2 (2.9)
Colorectal cancer	2 (2.9)
Esophageal cancer	2 (2.9)
Gastric cancer	2 (2.9)
Small intestine cancer	2 (2.9)
Other	14 (20.3)
Type of *SMARCA4* mutation, n (%)	
Class 1 (loss of function)	39 (56.5)
Class 2 (missense, VUS)	22 (31.9)
Loss of SMARCA4 protein (BRG1) by IHC	8 (11.6)

Data cutoff: 30 November 2024 and patients enrolled by 31 August 2024.
IHC, immunohistochemistry; VUS, variant of uncertain significance.

Prelude THERAPEUTICS

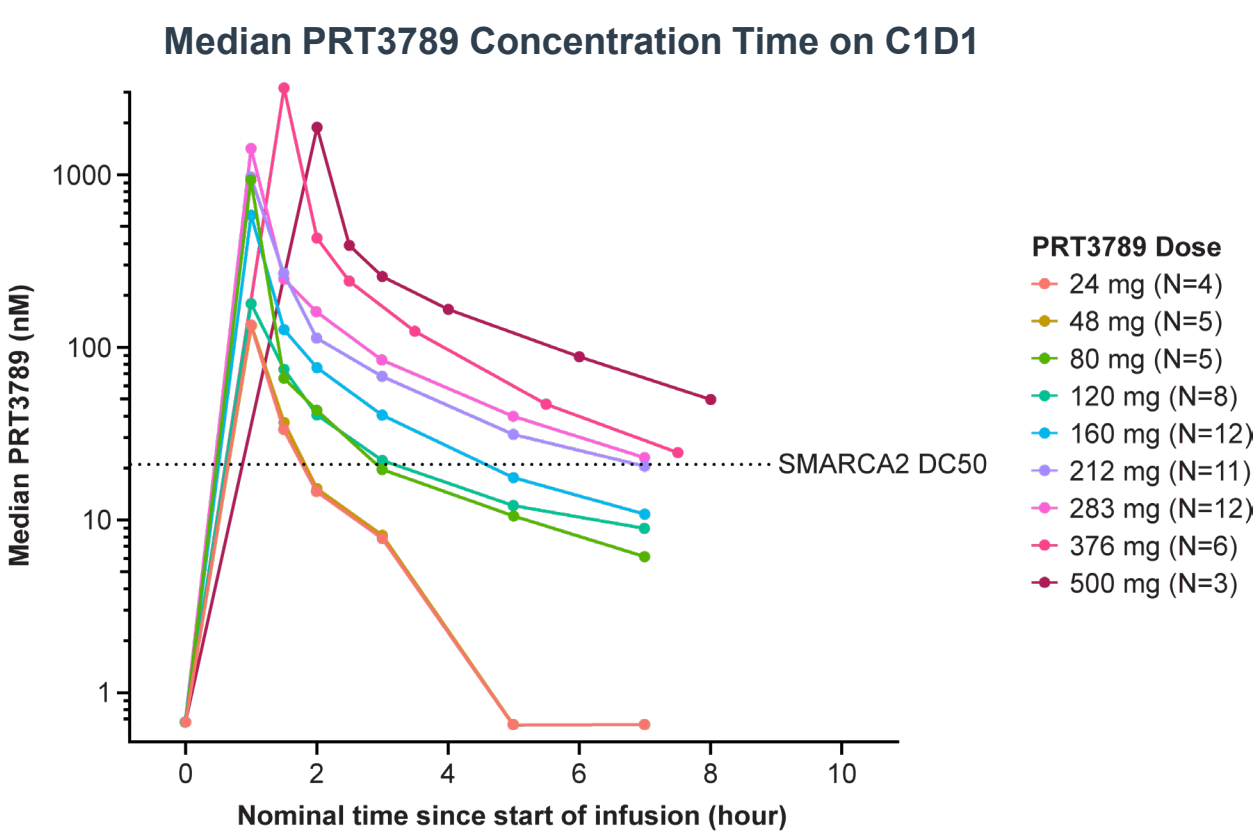
Summary of Adverse Events
PRT3789 Monotherapy

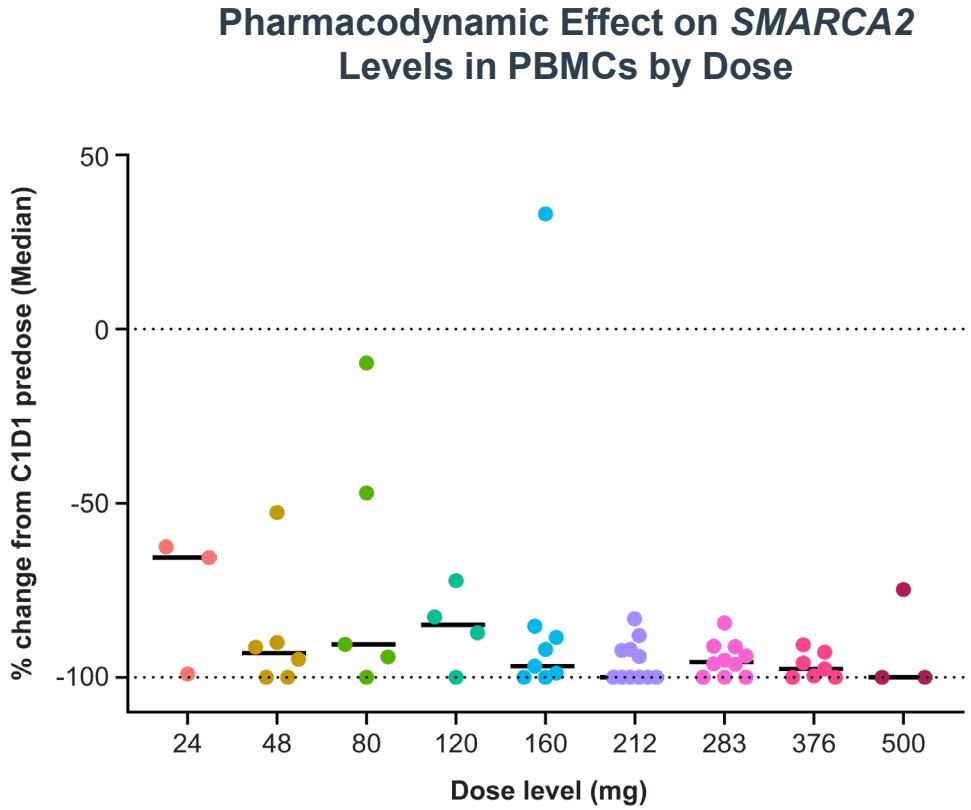
Adverse Events, n (%)	PRT3789 Monotherapy (N=69)
Any adverse event	67 (97.1)
Treatment related	43 (62.3)
Grade ≥3 adverse event	35 (50.7)
Treatment related	4 (5.8)
Serious adverse event	20 (29.0)
Treatment related	0
Adverse event leading to	
Dose hold	23 (33.3)
Treatment related	6 (8.7)
Dose reduction	4 (5.8)
Treatment discontinuation	5 (7.2)
Death	0
Any dose-limiting toxicity	0



Data cutoff: 30 November 2024 and patients enrolled by 31 August 2024.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTCAE, common terminology criteria for adverse events; TEAE, treatment emergent adverse events.

Pharmacokinetics and Pharmacodynamics Target Engagement Confirmed by SMARCA2 Reduction





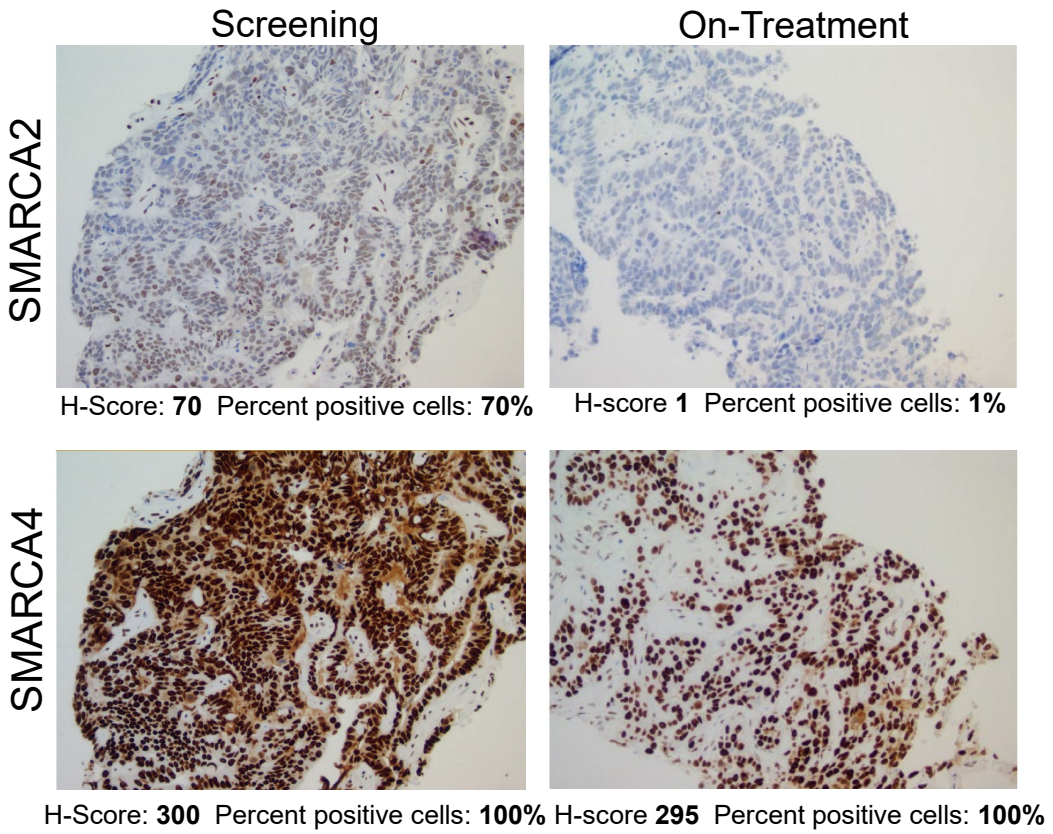
Pharmacodynamic effect is more prolonged than pharmacokinetics
Increasing doses show deeper and more prolonged pharmacodynamic effects

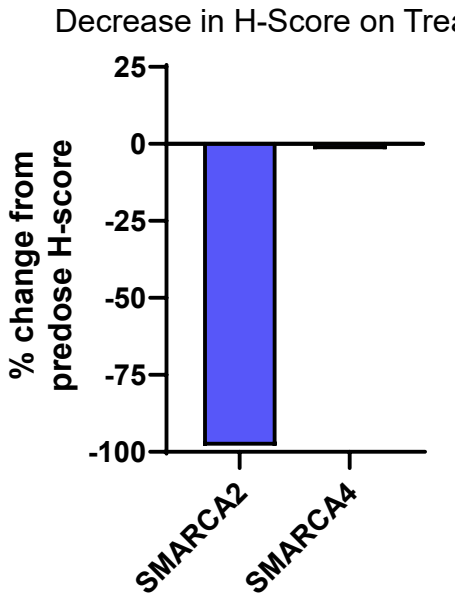
Data cutoff: 30 November 2024 and patients enrolled by 31 August 2024.
AUC, area under the curve over 1 week; C, cycle; D, day; DC50, half-maximal degradation concentration; PBMC, peripheral blood mononuclear cells.

Prelude THERAPEUTICS

Tumor SMARCA2 Degradation Confirms Target Engagement and Selectivity

41-year-old female with ovarian cancer with missense *SMARCA4* class 2 mutation receiving **500 mg PRT3789 monotherapy.**
Fresh baseline and on-treatment lung biopsies taken 23 days apart.
On-treatment biopsy taken on C2D2, **1-day postdose.**

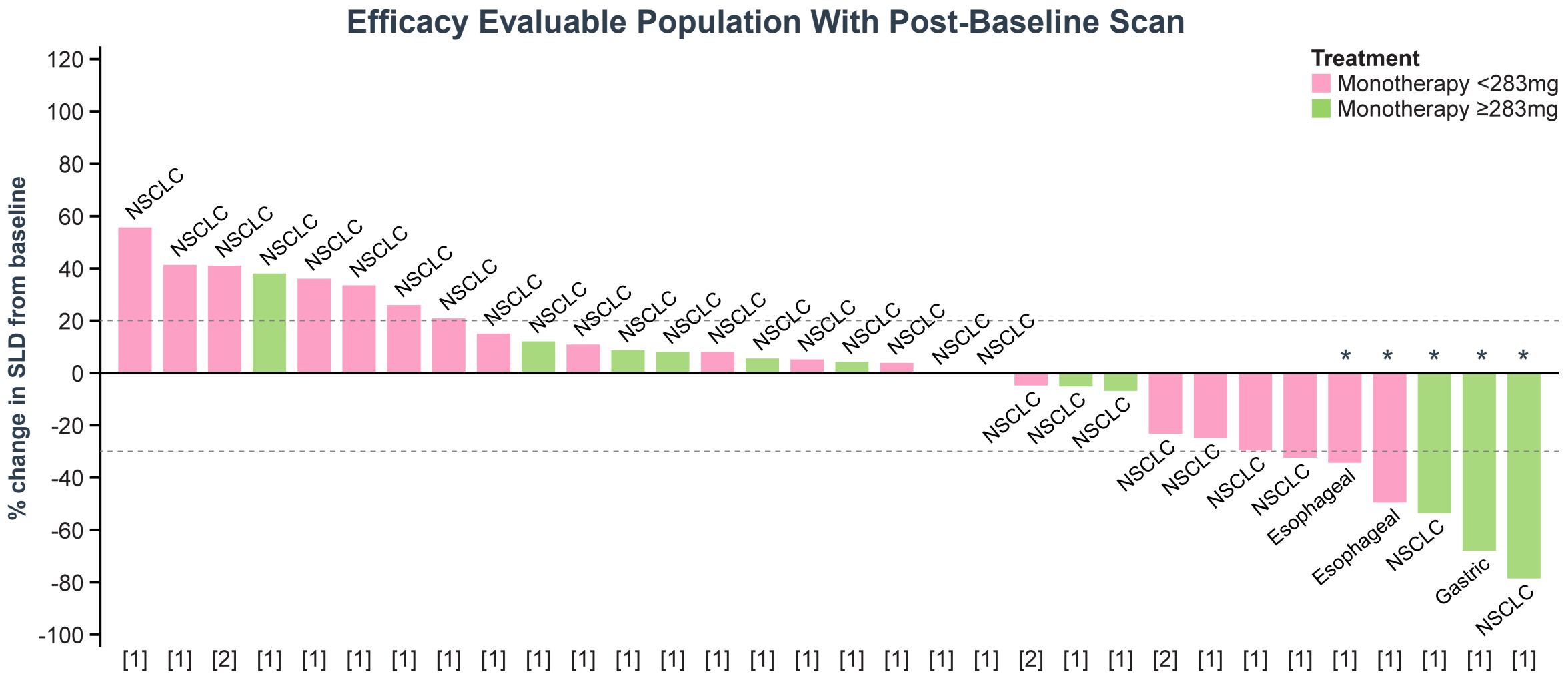




- ✓ **Selective degradation of SMARCA2 in tumor tissue**
- ✓ **99% decrease in SMARCA2 expression (H-score) with treatment**

C, cycle; D, day.

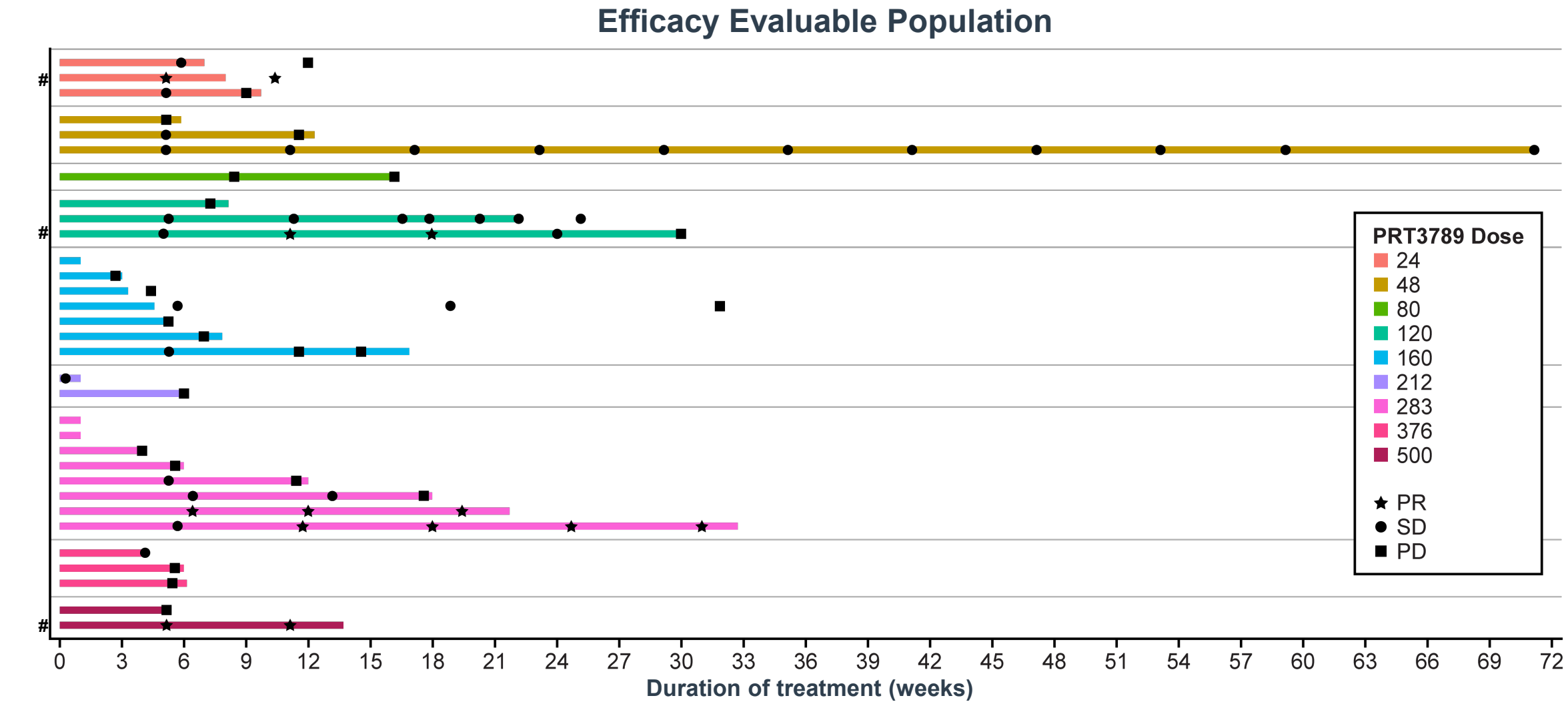
Change in Tumor Burden in Patients With NSCLC or Upper GI Cancer



Data cutoff: 30 November 2024 and patients enrolled by 31 August 2024.
GI, gastrointestinal; NSCLC, non-small cell lung cancer; SLD, sum of longest diameter.
* Confirmed partial response; [1], class 1 mutation; [2], class 2 mutation.

Prelude THERAPEUTICS

Duration of Treatment in Patients With NSCLC or Upper GI Cancer With a Class 1 Mutation



Data cutoff: 30 November 2024 and patients enrolled by 31 August 2024.
GI, gastrointestinal; NSCLC, non-small cell lung cancer; PD, progressive disease; PR, partial response; SD, stable disease.
Patients with esophageal or gastric cancer.

Prelude THERAPEUTICS

Response Rate in NSCLC or Upper GI Cancer
Efficacy Evaluable, With Class 1 Mutations

Patients With Class 1 *SMARCA4* Mutations

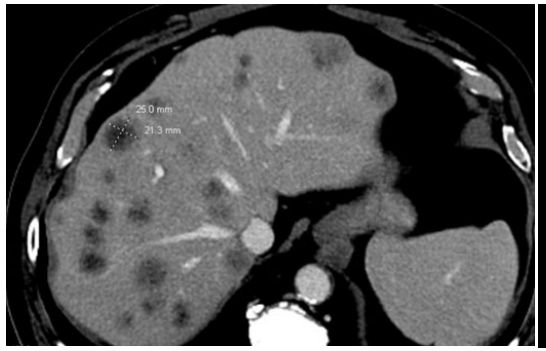
Response Rate	PRT3789 Doses <283 mg (n=19)	PRT3789 Doses ≥283 mg (n=13)	All Doses (n=32)
Objective response rate, n (%)	2 (10.5)	3 (23.1)	5 (15.6)
95% CI	1.3, 33.1	5.0, 53.8	5.3, 32.8
Best overall response, n (%)			
PR	2 (10.5)	3 (23.1)	5 (15.6)
SD	7 (36.8)	3 (23.1)	10 (31.3)
PD	8 (42.1)	5 (38.5)	13 (40.6)
Symptomatic deterioration	2 (10.5)	2 (15.4)	4 (12.5)
Duration of follow-up,[a] weeks			
Median	50.9	18.9	36.8
Min, max	31.7, 82.7	13.7, 32.7	13.7, 82.7

Data cutoff: 30 November 2024 and patients enrolled by 31 August 2024.
CI, confidence interval; CR, complete response; GI, gastrointestinal; NSCLC, non-small cell lung cancer; PD, progressive disease; PR, partial response; SD, stable disease.
[a] Duration of follow-up defined as time from date of first dose to date of data cutoff.

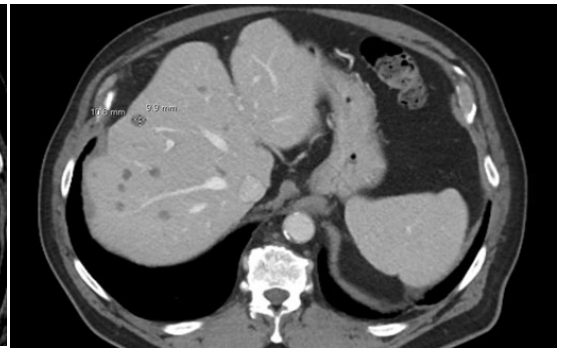
Examples of Responses in NSCLC

Patient 1

Baseline



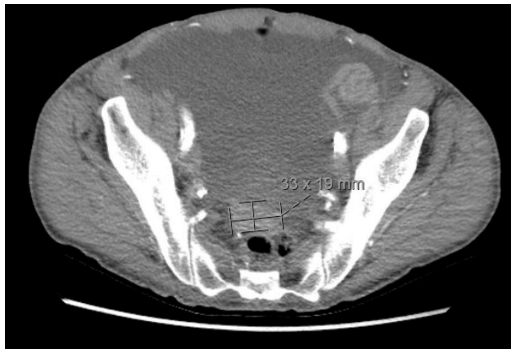
Week 12



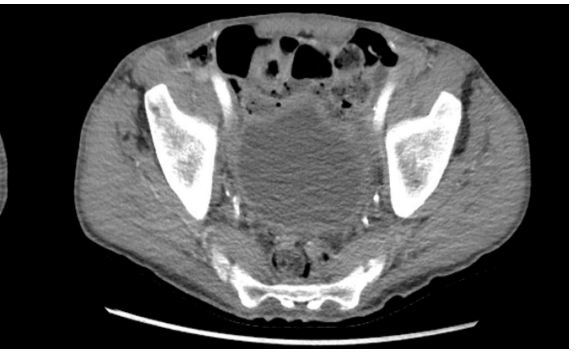
- 72-year-old man with metastatic, poorly differentiated carcinoma of the lung with squamous differentiation
- Class 1 *SMARCA4* splice-site alteration (c1246-2A>G)
- Prior therapy included carboplatin/paclitaxel and carboplatin/pemetrexed/pembrolizumab, followed by progression
- Started on PRT3789 283 mg
- RECISTv1.1 PR on second follow-up scan, with reduction in liver, adrenal, and lymph nodes

Patient 2

Baseline



Week 6



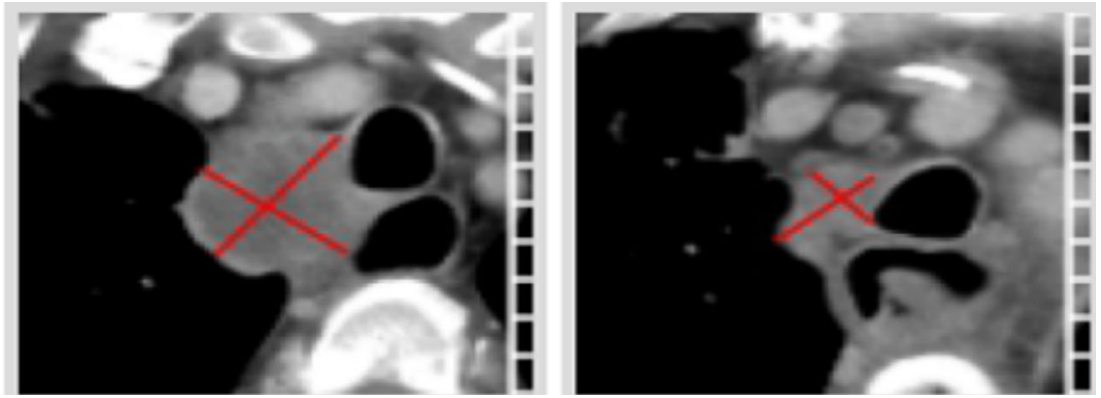
- 72-year-old man with moderately well-differentiated lung adenocarcinoma. Metastases to brain and malignant pleural effusion and ascites
- Class 1 *SMARCA4* splice variant (c3874-1G>T)
- Prior therapy included carboplatin, pemetrexed, pembrolizumab, followed by progression
- Started on PRT3789 283 mg
- RECISTv1.1 PR on first follow-up scan, with reduction in lung, lymph node, pelvic lesions, and resolution of ascites

C, cycle; ctDNA, circulating tumor DNA; D, day; NSCLC, non-small cell lung cancer; PR, partial response.

Example of Responses in Esophageal and Gastric Cancer

Patient 3

Baseline | **Week 6**



- 53-year-old man with metastatic, poorly differentiated esophageal carcinoma with squamous differentiation
- *SMARCA4* deletion-frameshift (c2732delG, pG911fs)
- Prior therapy included cisplatin, 5-FU, pembrolizumab, followed by progression
- Started on PRT3789, 24 mg
- Partial response on first follow-up scan, with reduction in liver, adrenal, and lymph node lesions

Patient 4

- 78-year-old woman with metastatic, poorly differentiated adenocarcinoma of the stomach
- *SMARCA4* missense mutation in ATPase domain
- Prior therapy included FLOT, gastrectomy, FOLFOX + nivo, FOLFOX + ramucirumab, followed by progression
- Started on PRT3789, 500 mg
- Partial response on first follow-up scan

Nivo, nivolumab; NSCLC, non-small cell lung cancer; PR, partial response.

Study Schema and Enrollment
Docetaxel + PRT3789

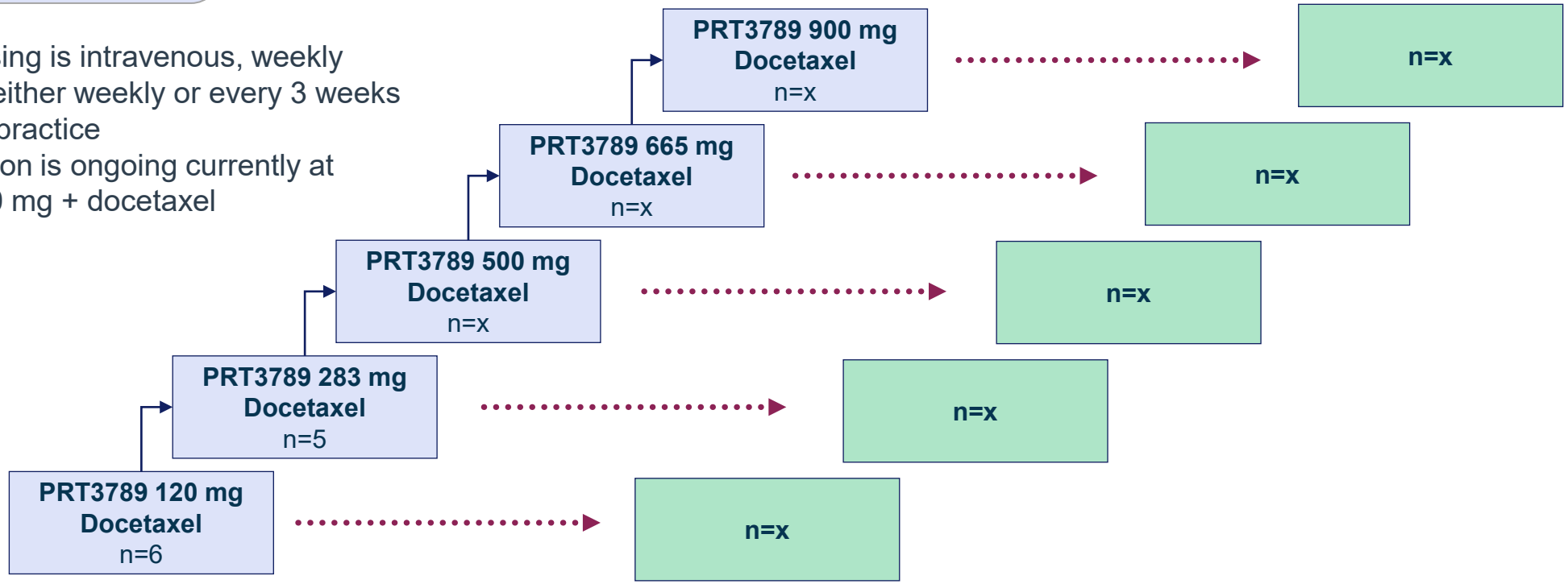
Dose-Escalation Cohorts

Eligibility criteria
- Any solid tumor
- Any *SMARCA4* mutation
- Evaluable disease

- PRT3789 dosing is intravenous, weekly
- Docetaxel is either weekly or every 3 weeks per standard practice
- Dose escalation is ongoing currently at PRT3789 500 mg + docetaxel

Backfill Cohorts

Eligibility criteria
- Enriched NSCLC
- LOF *SMARCA4* mutation
- Measurable disease



Data cutoff: 30 November 2024 and patients enrolled by 24 September 2024.
LOF, loss of function; NSCLC, non-small cell lung cancer.

Demographics and Disease Characteristics
Docetaxel + PRT3789

Demographics and Disease Characteristics

Characteristics	Patients (N=11)
Age, years	
Median	65
Sex, n (%)	
Male	8 (72.7)
Female	3 (27.3)
Prior lines of systemic anticancer therapy, n	
Median (min, max)	1 (1, 6)
Tumor type, n (%)	
Non-small cell lung cancer	5 (45.5)
Pancreatic cancer	2 (18.2)
Esophageal cancer	1 (9.1)
Large cell neuroendocrine cancer	1 (9.1)
Stomach	1 (9.1)
Thoracic SMARCA4 deficient undifferentiated	1 (9.1)
Type of *SMARCA4* mutation, n (%)	
Class 1 (loss of function)	8 (72.7)
Class 2 (missense, VUS)	3 (27.3)

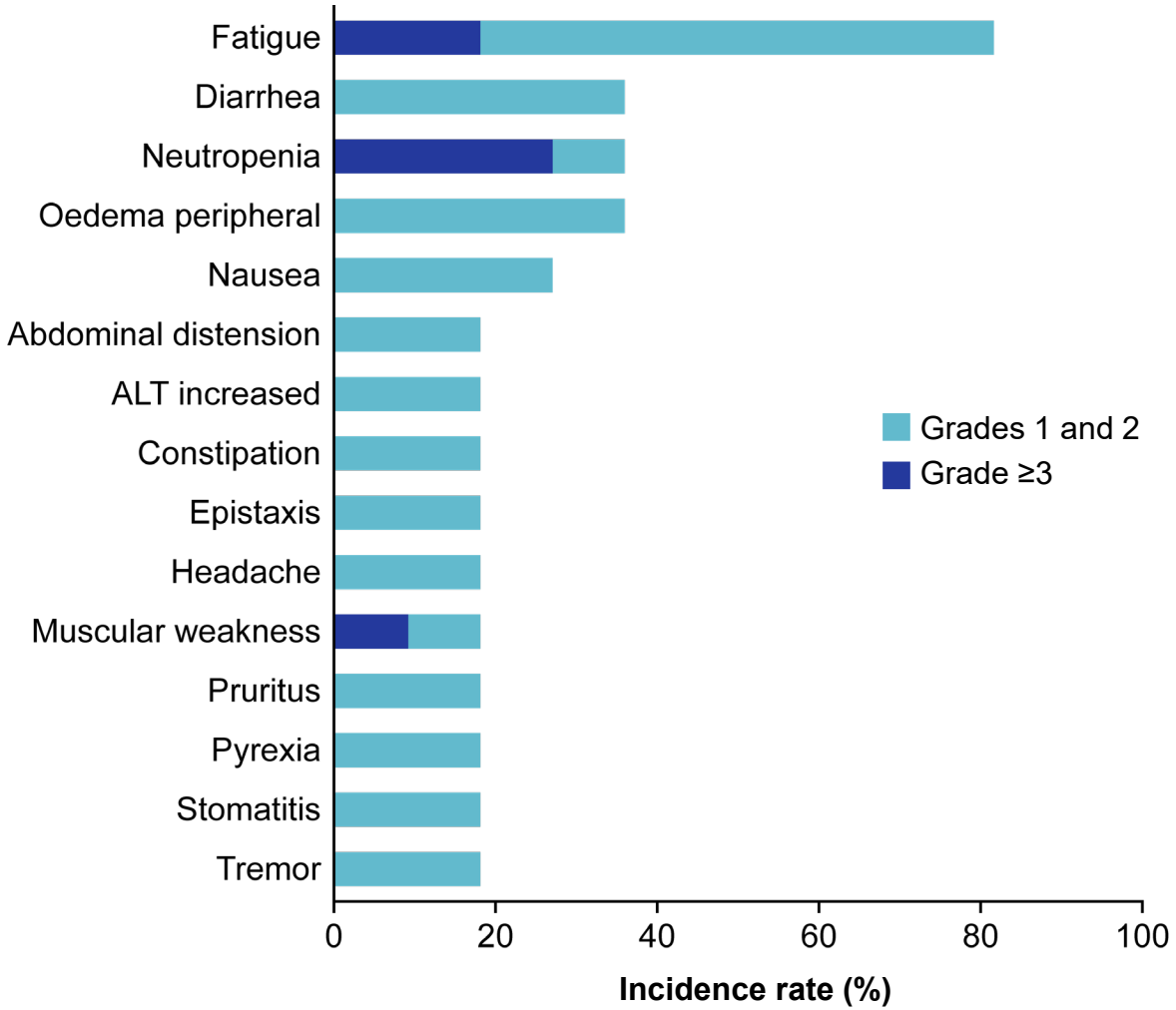
Data cutoff: 30 November 2024 and patients enrolled by 24 September 2024.
VUS, variant of uncertain significance.

Adverse Events
Docetaxel + PRT3789

Summary of Adverse Events

Adverse Events, n (%)	PRT3789 + Docetaxel (N=11)
Any adverse event	11 (100.0)
PRT3789 treatment related	7 (63.6)
Docetaxel treatment related	11 (100.0)
Grade ≥3 adverse event	8 (72.7)
Serious adverse event	4 (36.4)
PRT3789 treatment related	0
Docetaxel treatment related	1 (9.1)
Adverse event leading to	
PRT3789 dose hold	8 (72.7)
PRT3789 treatment related	2 (18.2)
Docetaxel dose hold	8 (72.7)
Dose reduction[a]	1 (9.1)
Treatment discontinuation	0
Death	0
Any dose-limiting toxicity	2 (18.2)

Most Frequent Adverse Events



Data cutoff: 30 November 2024 and patients enrolled by 24 September 2024.
ALT, alanine aminotransferase.
[a] Patient had both docetaxel dose hold and dose reduction.

Summary and Conclusions

- PRT3789 represents a first-in-class, novel, targeted therapeutic designed to induce synthetic lethality in *SMARCA4*-deficient cancer, while sparing normal tissue
- PRT3789 monotherapy demonstrates an acceptable safety profile, with no dose limiting toxicities or study drug-related SAEs to date. The safety profile of PRT3789 in combination with docetaxel consistent with the safety profile of docetaxel alone
- Degradation of SMARCA2 was observed in PBMCs and tumor tissue confirming target modulation
- First early clinical proof of concept in effectively drugging SMARCA2 was demonstrated by tumor responses and prolonged stable disease in patients with NSCLC, esophageal, and gastric cancer

- Dose escalation is ongoing in monotherapy and combination with docetaxel, with the optimal RP2Ds still to be identified
- A clinical trial testing the combination of PRT3789 and pembrolizumab has initiated (NCT06682806)
- Prelude Therapeutics Incorporated is also developing an oral, selective SMARCA2 degrader to treat *SMARCA4*-deficient cancer (PRT7732). A phase 1 study of PRT7732 in patients with *SMARCA4*-deficient solid tumors is underway (NCT06560645)

NSCLC, non-small cell lung cancer; PBMC, peripheral blood mononuclear cell; RP2D, recommended phase 2 dose; SAE, serious adverse event.

Acknowledgments

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