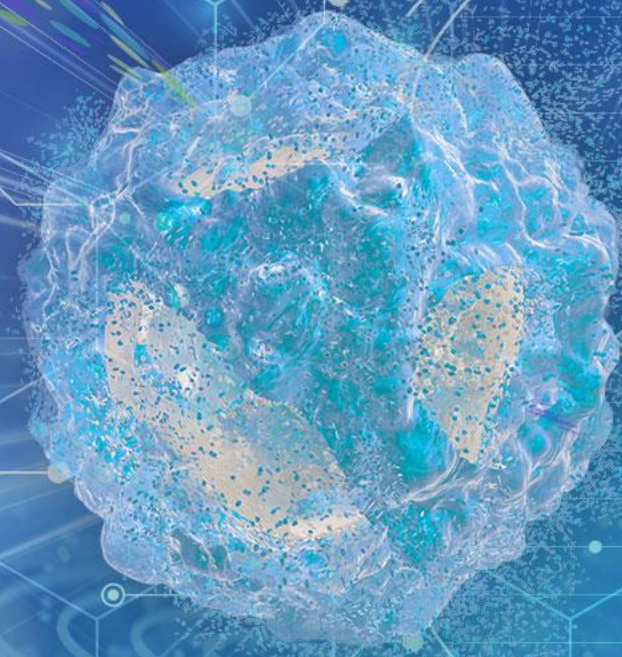
Prelude THERAPEUTICS

# PRT3789 Phase 1 Interim Clinical Data Update from 2024 ESMO Congress

**13 September 2024**

**Investor Presentation**



# Forward Looking Statements

This presentation contains “forward-looking” statements within the meaning of the “safe harbor” provisions of the Private Securities Litigation Reform Act of 1995, including, but not limited to, anticipated discovery, preclinical and clinical development activities for Prelude’s product candidates, including product candidates that are the subjects of the Company’s collaborations and partnerships, the potential safety, efficacy, benefits and addressable market for Prelude’s product candidates, the expected timeline for clinical trial results for Prelude’s product candidates including its SMARCA2 degrader molecules.

Any statements contained herein or provided orally that are not statements of historical fact may be deemed to be forward-looking statements. In some cases, you can identify forward-looking statements by such terminology as ‘‘believe,’’ ‘‘may,’’ ‘‘will,’’ ‘‘potentially,’’ ‘‘estimate,’’ ‘‘continue,’’ ‘‘anticipate,’’ ‘‘intend,’’ ‘‘could,’’ ‘‘would,’’ ‘‘project,’’ ‘‘plan,’’ ‘‘expect’’ and similar expressions that convey uncertainty of future events or outcomes, although not all forward-looking statements contain these words. Statements, including forward-looking statements, speak only to the date they are provided (unless an earlier date is indicated).

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Prelude THERAPEUTICS

# Opening Remarks

**Kris Vaddi, Ph.D., CEO**
**Prelude Therapeutics Incorporated**

Prelude THERAPEUTICS

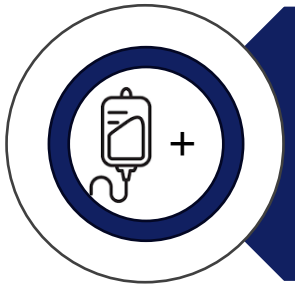
# *We are on a mission to extend the promise of precision medicine to every cancer patient in need*

***Strive for first- or best-in-class and anchor to patient unmet need***

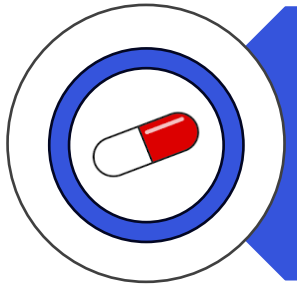
***Select the best modality to precisely target oncogenic mechanisms***

***Draw on decades of experience and proven leadership to drive innovation***

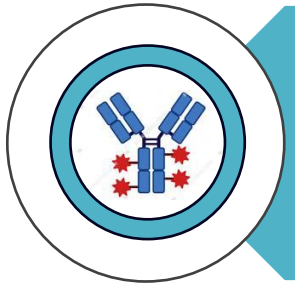
# Developing an Industry Leading Portfolio of SMARCA-Targeted Precision Medicines



**Lead SMARCA2 Degrader (PRT3789)**



**Oral SMARCA2 Degrader (PRT7732)**



**Precision ADCs with SMARCA2/4 Degrader Payload**

# PRT3789 Overview and Phase 1 Interim Data

**Dr. Jane Huang, President & Chief Medical Officer**
**Prelude Therapeutics Incorporated**

***A Phase 1 Trial of PRT3789, a First-in-Class SMARCA2 Degrader in Patients with Advanced Solid Tumors With a SMARCA4 Mutation***

*Guo, R. et. al., ESMO Congress, 13 Sept 2024*

# Expert Perspective on SMARCA4-*mutated* Cancer

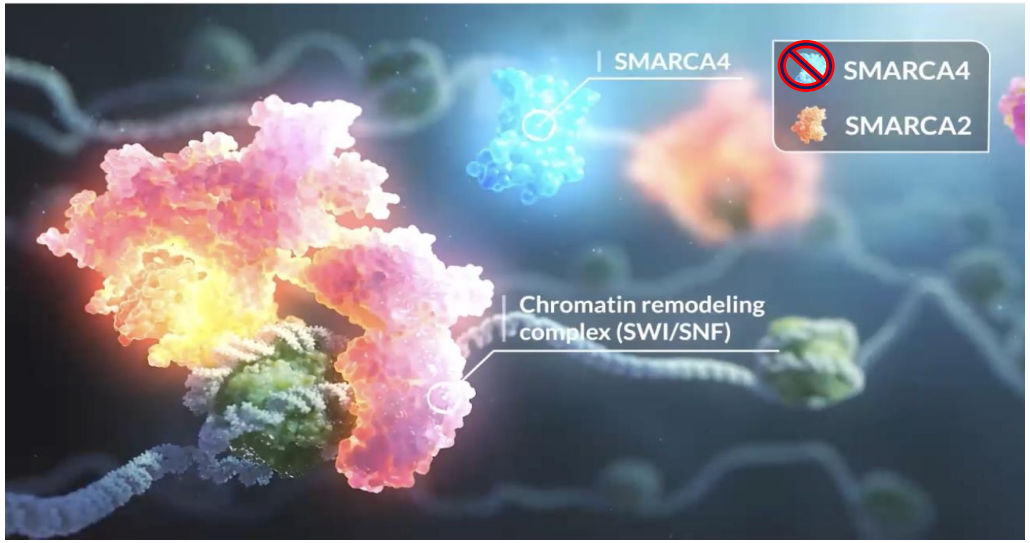
**Dr. Timothy Yap, University of Texas MD Anderson Cancer Center**

**Investigator on PRT3789-01:**

***A Phase 1 Trial of PRT3789, a First-in-Class SMARCA2 Degrader in Patients with Advanced Solid Tumors With a SMARCA4 Mutation***

# Targeting SMARCA4-*mutated* Cancer By Selectively Degrading SMARCA2

**Mutations in the chromatin remodeling complex drive cancer growth and resistance**




**SMARCA4 (BRG1) mutations occur in approximately 5% of all cancers**

**NSCLC: 10%**

SCLC: 8%

Esophageal: 8%

Colorectal: 6%

Gastric: 8%

Pancreatic: 3%

Endometrial: 13%

Urinary: 9%

**Cancer cells with deleterious SMARCA4 mutations become highly dependent on SMARCA2 for survival**

**Selectively degrading SMARCA2 induces "synthetic lethality" in SMARCA4-*deficient* cancers**

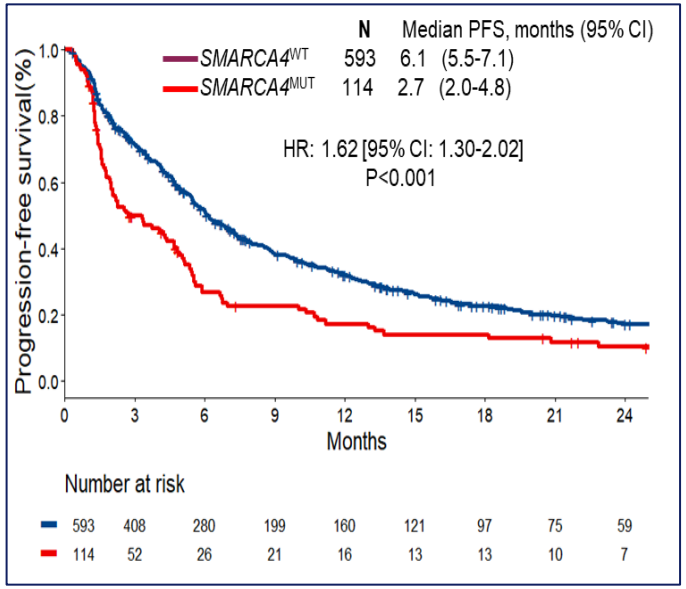
**Patients with SMARCA4 mutations are not typically eligible for other targeted therapies**

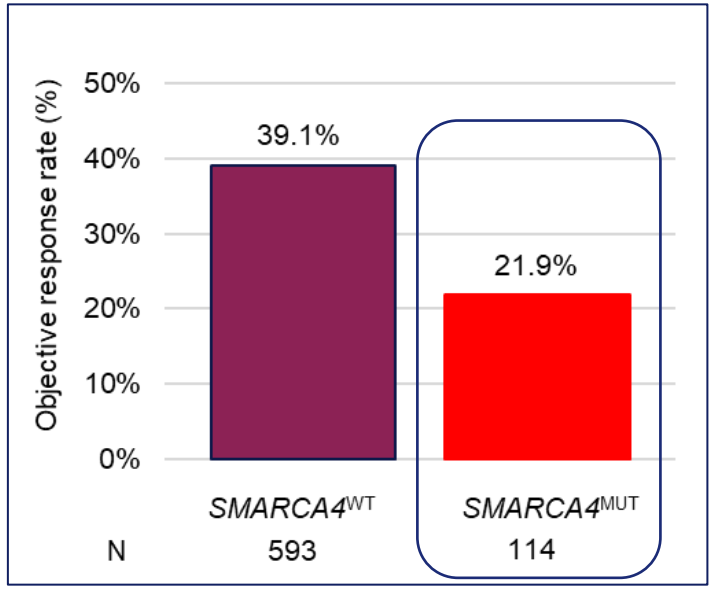
**Currently treated with standard of care chemotherapy or chemo-immunotherapy**

Dagogo-Jack et al. Journal of Thoracic Oncology. 2020 Foundation Medicine dataset

# Outcomes for Patients with SMARCA4-*mutated* NSCLC are Poor with Current Standard of Care

## *Patients treated with first-line chemoimmunotherapy*



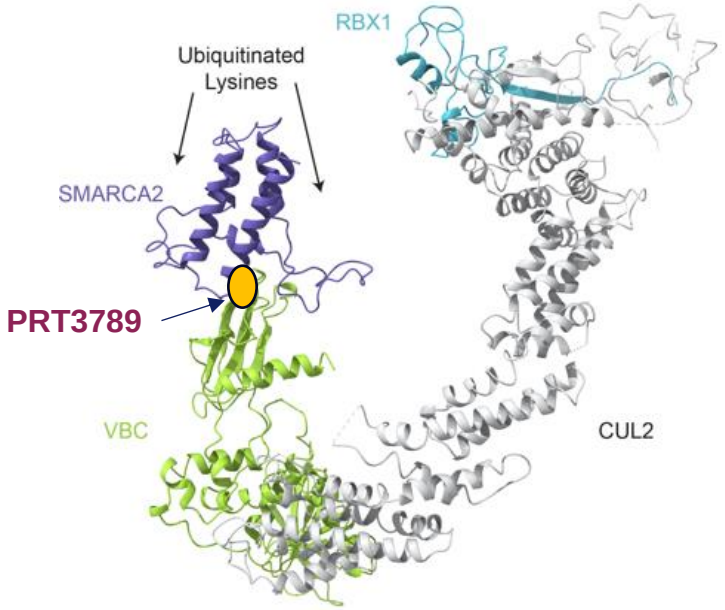

**Median progression free survival for first-line SMARCA4-mutated NSCLC treated with chemoimmunotherapy is 2.7 months and response rates approximately 22%**

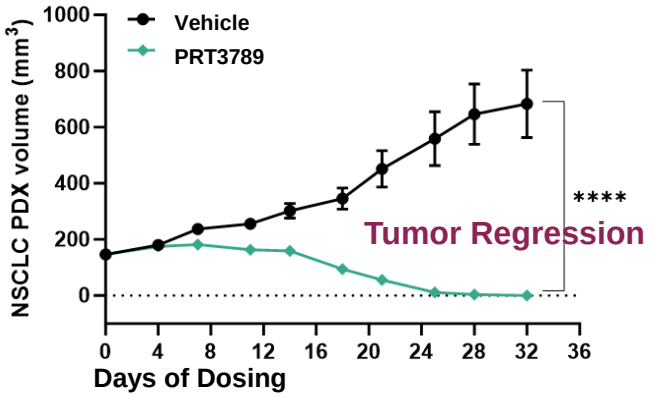
**There is even greater unmet need in second-line and beyond**

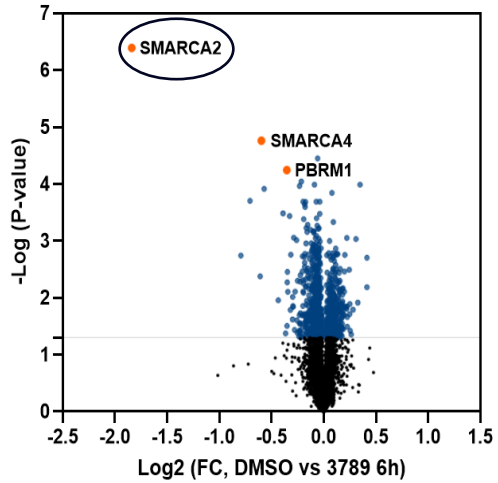
Alessi JV, et al. Clinicopathologic and genomic factors impacting efficacy of first-line chemoimmunotherapy in advanced non-small cell lung cancer (NSCLC). J Thorac Oncol. 2023 Feb 10:S1556-0864(23)00121-1. doi: 10.1016/j.jtho.2023.01.091. PMID: 36775193.

# PRT3789: A Highly Potent SMARCA2 Degrader with >1000-fold Selectivity Over SMARCA4

| Preclinical Assay | PRT3789 |
|---|---|
| SMARCA2 Degradation (nM) | 0.73 |
| Selectivity: Cell Proliferation (SMARCA4 / SMARCA2) | >1000 fold |



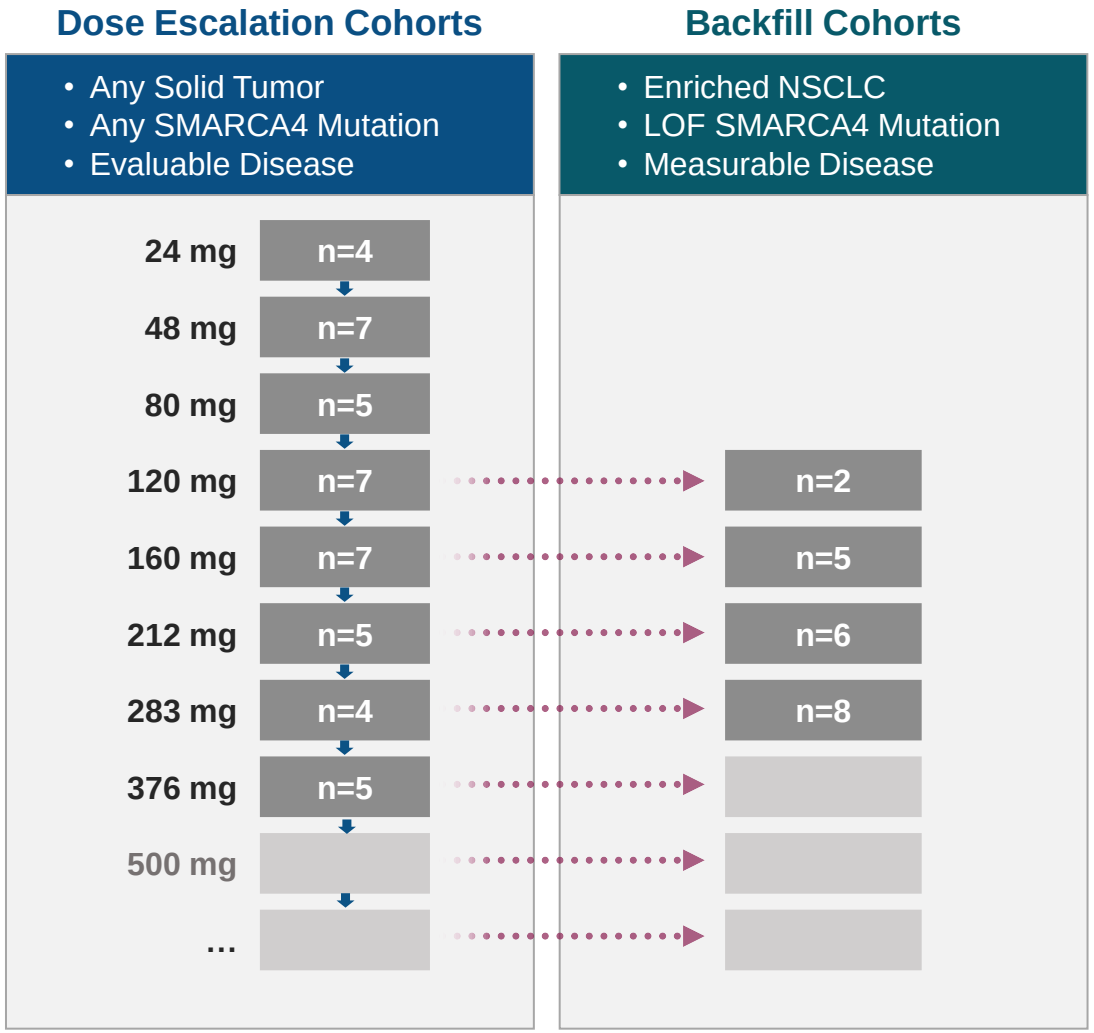

**Sub-nanomolar SMARCA2 degradation potency in cell lines**

**Anti-tumor activity, including regressions, in SMARCA4 mutant models *in vivo***

**Highly selective for SMARCA2 vs SMARCA4 (>1000 fold) and selective across the proteome**

Hulse et al. *Cancer Res*. (2022); 82 (12_Suppl) :3263.
AACR 2022: https://preludetx.com/wp-content/uploads/2022/05/Prelude_AACR_Hulse-SMARCA2-FINAL-21Mar2022.pdf

# PRT3789-01: Study Schema and Enrollment




**Phase 1 dose escalation study enrolled patients who had evaluable disease, any solid tumors, and any type of SMARCA4 mutation**

**All patients received PRT3789 intravenously once weekly**

**Patients treated in escalating doses from 24 to 376 mg and backfill cohort patients who had SMARCA4 (Class 1) loss of function mutations**

LOF, loss of function; NSCLC, non-small cell lung cancer

Guo, R. *et al.*, ESMO Congress, 13 Sept 2024

Data cutoff: 05 August 2024

# PRT3789-01: Demographics and Disease Characteristics

| Characteristics | Patients (N=65) |
|---|---|
| **Age (years)** | |
| Median | 62.0 |
| **Sex, n (%)** | |
| Male | 36 (55.4) |
| Female | 29 (44.6) |
| **Prior lines of systemic anti-cancer therapy, n** | |
| Median (min, max) | 3 (1, 10) |
| **Tumor type, n (%)** | |
| Non-small cell lung cancer | 34 (52.3) |
| Pancreatic cancer | 6 (9.2) |
| Breast cancer | 4 (6.2) |
| Cholangiocarcinoma | 2 (3.1) |
| Colorectal cancer | 2 (3.1) |
| Esophageal cancer | 2 (3.1) |
| Ovarian cancer | 2 (3.1) |
| Other | 13 (20.0) |
| **Type of SMARCA4 mutation, n (%)** | |
| Class 1 (loss of function) | 34 (52.3) |
| Class 2 (missense, VUS) | 24 (36.9) |
| Loss of SMARCA4 protein (BRG1) by IHC | 7 (10.8) |

**65 patients were safety evaluable**

**Primary tumor type was NSCLC (n = 34) patients along with a range of other solid tumors**

**34 patients had Class 1 loss of function mutations and additional 7 patients had loss of SMARCA4 protein by IHC**

IHC, immunohistochemistry; VUS, variant of uncertain significance.

Guo, R. *et al.*, ESMO Congress, 13 Sept 2024

Data cutoff: 05 August 2024

# PRT3789-01: Patient Disposition

| | 24 mg (n=4) | 48 mg (n=7) | 80 mg (n=5) | 120 mg (n=9) | 160 mg (n=12) | 212 mg (n=11) | 283 mg (n=12) | 376 mg (n=5) | Total (N=65) |
|---|---|---|---|---|---|---|---|---|---|
| **Treated, n (%)** | 4 (100) | 7 (100) | 5 (100) | 9 (100) | 12 (100) | 11 (100) | 12 (100) | 5 (100) | 65 (100) |
| On treatment | 0 | 1 (14.3) | 0 | 0 | 0 | 2 (18.2) | 7 (58.3) | 4 (80.0) | 14 (21.5) |
| Off treatment | 4 (100) | 6 (85.7) | 5 (100) | 9 (100) | 12 (100) | 9 (81.8) | 5 (41.7) | 1 (20.0) | 51 (78.5) |
| **Reason for treatment discontinuation, n (%)** | | | | | | | | | |
| Adverse event | 0 | 0 | 0 | 0 | 1 (8.3) | 0 | 0 | 0 | 1 (1.5) |
| Physician decision | 0 | 0 | 0 | 1 (11.1) | 0 | 0 | 0 | 0 | 1 (1.5) |
| Disease progression | 4 (100) | 6 (85.7) | 5 (100) | 8 (88.9) | 11 (91.7) | 8 (72.7) | 5 (41.7) | 1 (20.0) | 48 (73.8) |
| Withdrawal of consent | 0 | 0 | 0 | 0 | 0 | 1 (9.1) | 0 | 0 | 1 (1.5) |
| **Duration of treatment (weeks)** | | | | | | | | | |
| Median | 7.5 | 5.9 | 3.1 | 6.0 | 3.9 | 6.0 | 2.4 | 4.1 | 5.0 |
| Min, Max | 6.0, 9.7 | 1.0, 54.6 | 1.0, 16.0 | 2.0, 30.0 | 1.0, 18.0 | 0.1, 23.1 | 0.1, 16.0 | 1.0, 6.0 | 0.1, 54.6 |

**As of the data cutoff, 21.5% patients remained on treatment**

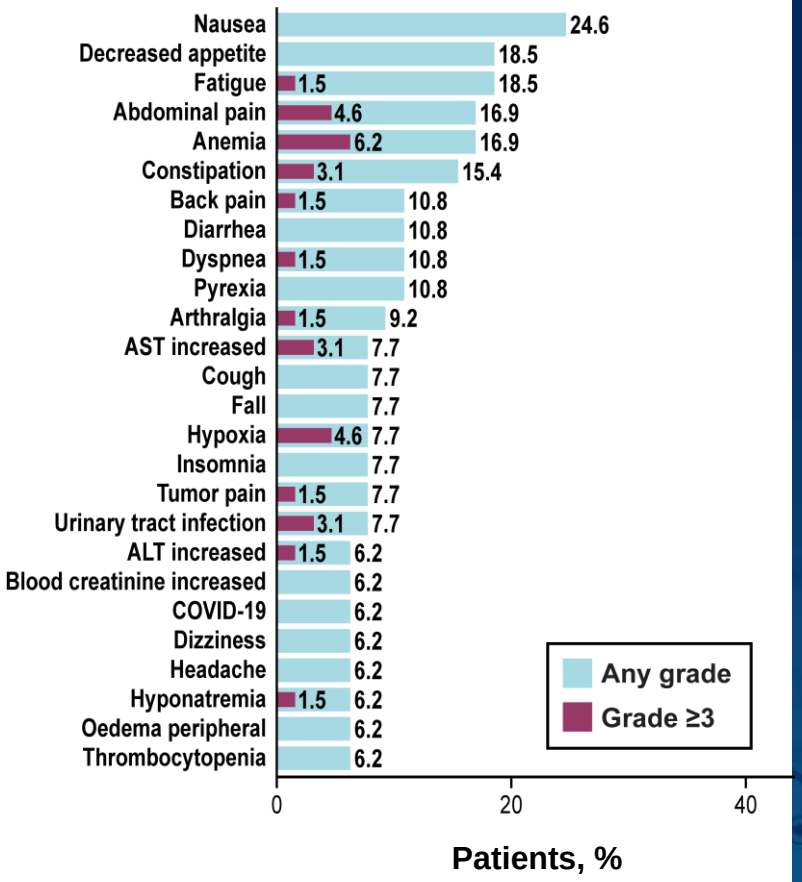
**Only one patient discontinued treatment due to an adverse event, considered unrelated to study drug**

Guo, R. *et al.*, ESMO Congress, 13 Sept 2024

Data cutoff: 05 August 2024

# PRT3789-01: Summary of Adverse Events

| Adverse events, n (%) | Patients (N=65) |
|---|---|
| **Any adverse event** | 58 (89.2) |
| Treatment related | 37 (56.9) |
| **Grade ≥3 adverse event** | 33 (50.8) |
| Treatment related | 3 (4.6) |
| **Serious adverse event** | 19 (29.2) |
| Treatment related | 0 |
| **Adverse event leading to** | |
| Dose hold | 18 (27.7) |
| Dose reduction | 0 |
| Treatment discontinuation | 2 (3.1) |
| Death | 0 |
| **Any dose-limiting toxicity** | 0 |




**65 patients were safety evaluable**

**PRT3789 was generally well tolerated; no drug related SAEs or dose limiting toxicities to date**

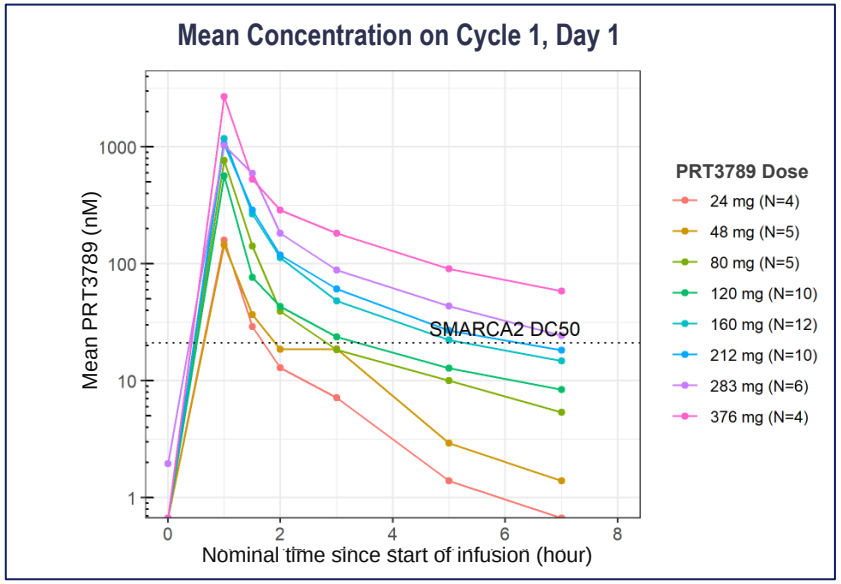
**Of all adverse events, nausea, decreased appetite and fatigue had the highest incidence**

Patients receiving at least one dose of PRT3789
ALT, alanine aminotransferase; AST, aspartate aminotransferase.

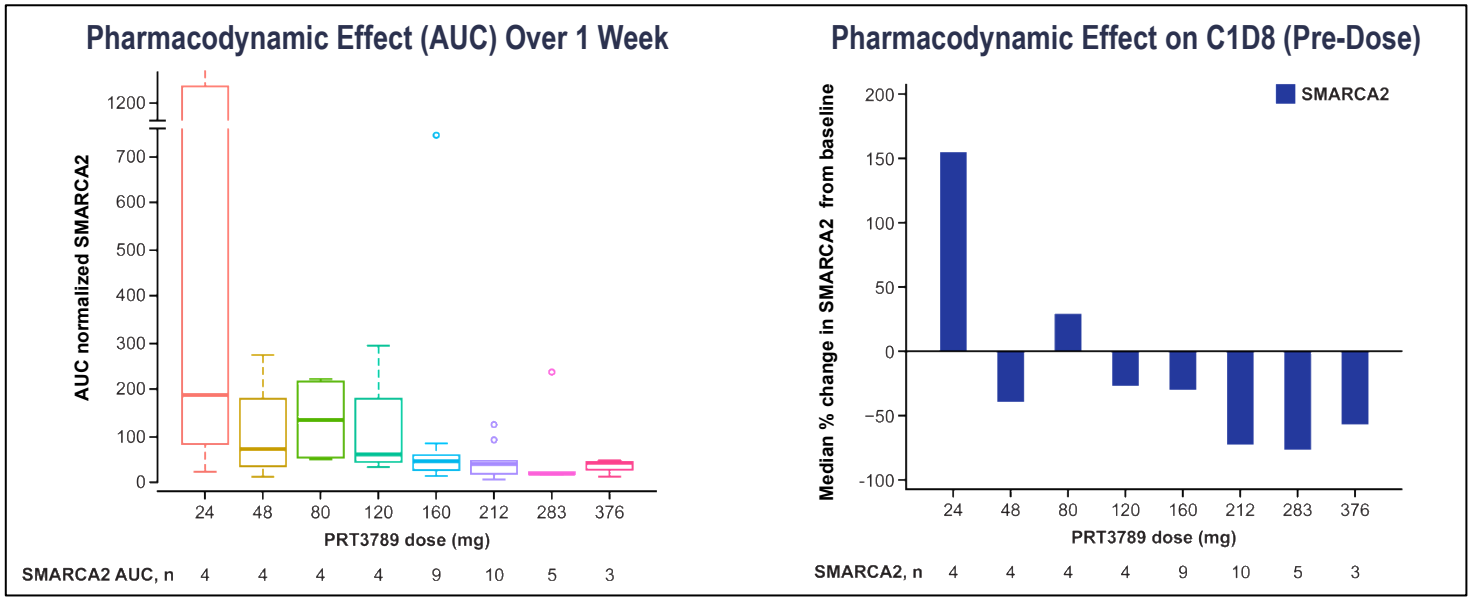
Guo, R. *et al.*, ESMO Congress, 13 Sept 2024

Data cutoff: 05 August 2024

# PRT3789-01: Phase 1 Interim PK/PD Findings




- Preliminary PK data are available from 24mg to 376mg
- General trend of increases in exposure ($C_{max}$, AUC) with dose were seen
- Mean concentrations were above SMARCA2 plasma $DC_{50}$ (21 nM) for approximately 8 hours at 376 mg
- Mean half-life was 4.7 hours at the 376 mg dose level
- No accumulation seen with repeat dose administration; consistent with the half-life and once-weekly administration




**As expected with a potent degrader, the observed pharmacodynamic effect was more prolonged than pharmacokinetic half-life**

**Increasing doses showed deeper and more prolonged SMARCA2 degradation in the peripheral blood monocytes (PBMCs) of patients**

**PRT3789 showed selective SMARCA2 degradation with minimal observed effect on SMARCA4 levels**

AUC, area under the curve; $C_{max}$, maximum concentration; $DC_{50}$, half-maximal degradation concentration; PK, pharmacokinetics. C1D8, cycle1 day 8.

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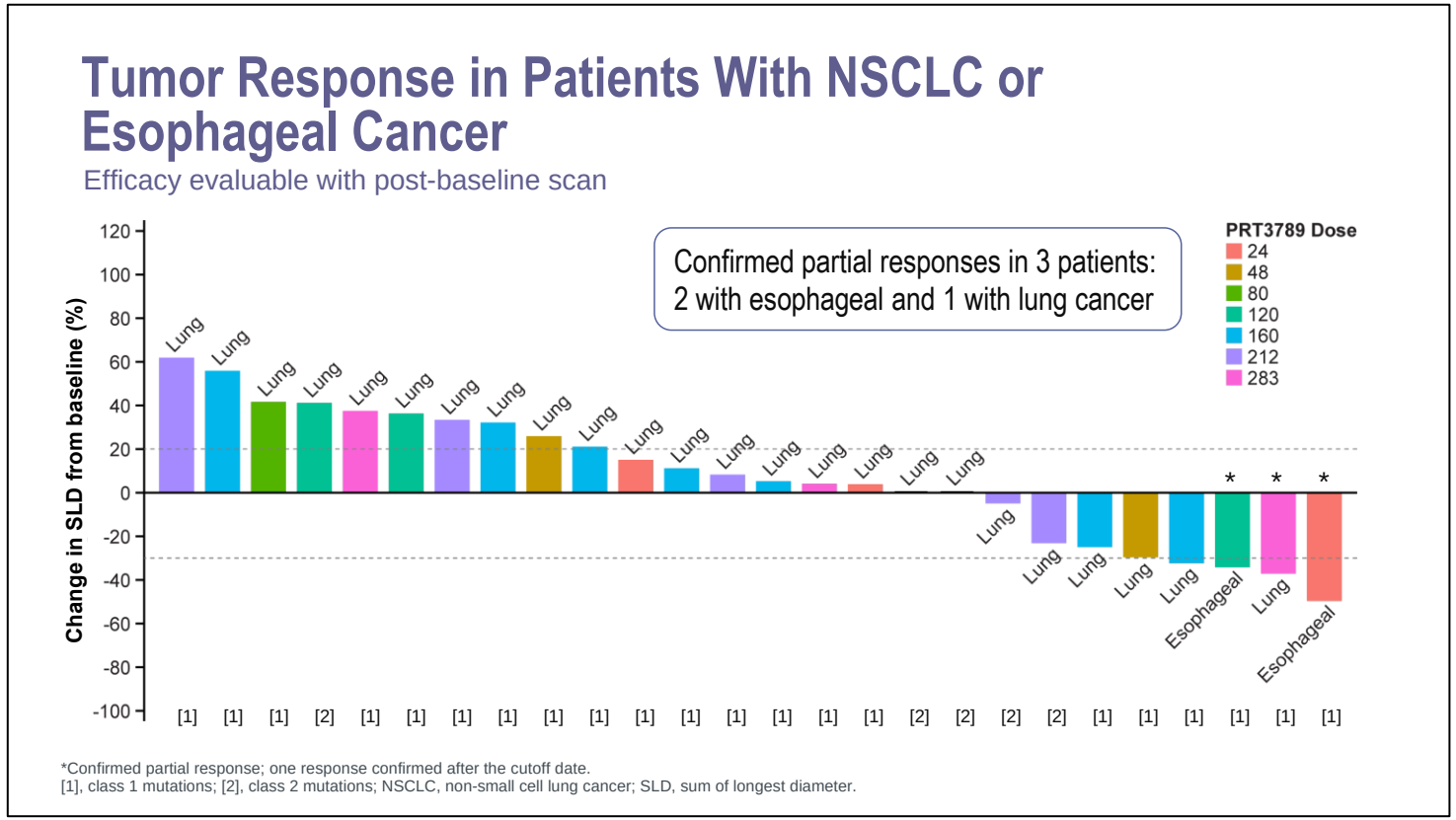
# PRT3789-01: Phase 1 Interim Clinical Activity




- Positive correlation observed between tumor shrinkage and a higher level of sustained SMARCA2 degradation
- Enrollment is now into dose cohort 9 (500 mg QW)

**Of the 26 NSCLC or esophageal patients with at least one post baseline scan who were evaluable for efficacy, 7 had tumor shrinkage**

**RECIST confirmed partial responses (PRs) were observed in 3 patients (2 esophageal, 1 NSCLC)**

**Tumor shrinkage was observed in patients with both Class 1 and Class 2 SMARCA4 mutations**

Tumor shrinkage defined as 5% or greater decrease in sum of longest diameters of target lesions.

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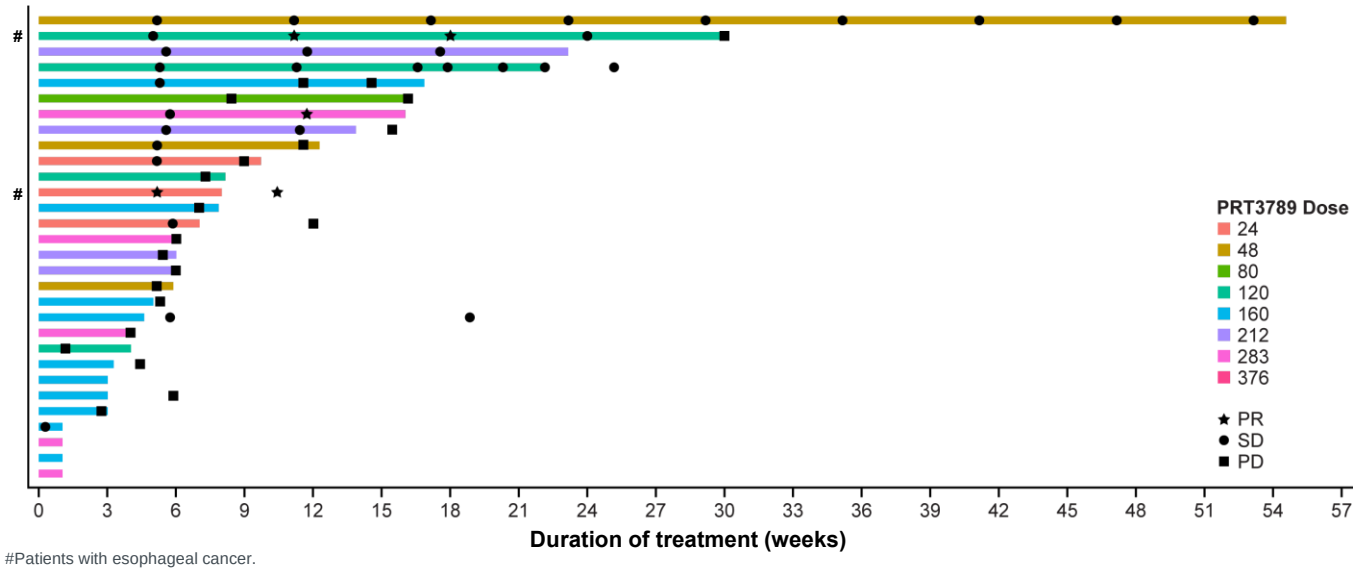
# PRT3789-01: Phase 1 Interim Clinical Activity

## Duration of Treatment for Patients With NSCLC and Esophageal Cancer

Efficacy evaluable




#Patients with esophageal cancer.
NSCLC, non-small cell lung cancer; PD, progressive disease; PR, partial response; SD, stable disease.

**The median progression free survival for first-line SMARCA4-*mutated* NSCLC treated with chemo-immunotherapy is 2.7 months[1]**

**In this heavily pretreated patient population of SMARCA4-*mutated* patients, some have demonstrated clinical benefit as measured by prolonged stable disease (SD) and confirmed responses**

**One patient remains on study having been on treatment for more than 1 year**

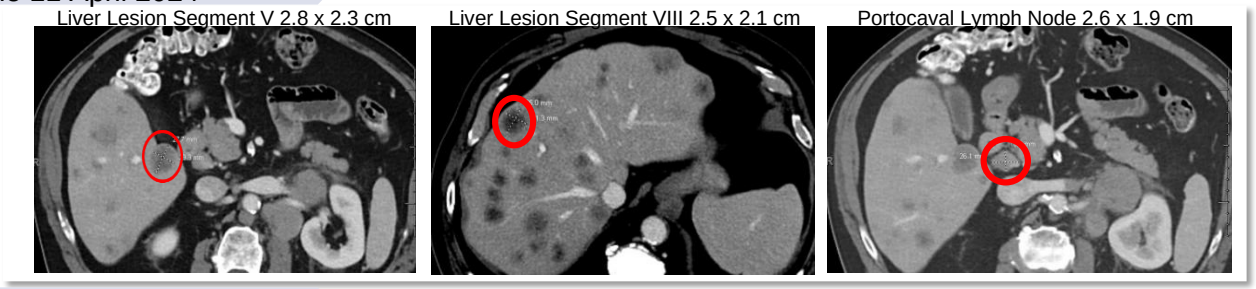
1 Alessi JV, et al. Clinicopathologic and genomic factors impacting efficacy of first-line chemoimmunotherapy in advanced non-small cell lung cancer (NSCLC). J Thorac Oncol. 2023 Feb 10:S1556-0864(23)00121-1. doi: 10.1016/j.jtho.2023.01.091. PMID: 36775193.

Guo, R. *et al.*, ESMO Congress, 13 Sept 2024

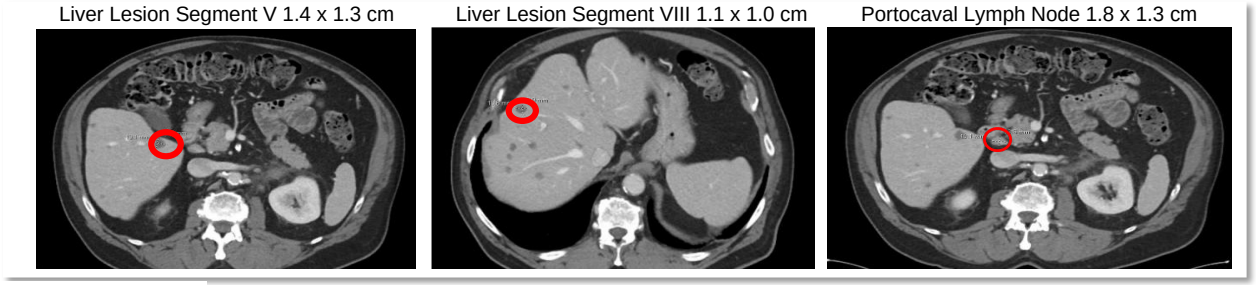
# PRT3789-01: Patient Case Study

## 72-Year-Old Man With Metastatic, Poorly Differentiated Carcinoma of the Lung With Squamous Differentiation; Prior Therapy Included Carbo/Paclitaxel and Carbo/Docetaxel/Pembrolizumab

Baseline 11 April 2024




Second restaging 6 July 2024




**The patient images depicted here are representative of a "classical" patient with SMARCA4 mutations: poorly differentiated, aggressive disease**

**This patient experienced a confirmed PR, with tumor shrinkage in liver lesions and lymph nodes**

**This patient was treated at 283 mg and is ongoing on the trial**

Guo, R. *et al.*, ESMO Congress, 13 Sept 2024

# PRT3789-01: Key Takeaways

## Summary and Conclusions

- PRT3789, a first-in-class, selective SMARCA2 degrader is being developed to treat SMARCA4-deficient cancer
- At doses studied, PRT3789 is generally well tolerated, with no dose-limiting toxicities or study drug-related serious adverse events reported to date
- Pharmacokinetic analysis shows increases in exposure ($C_{max}$, AUC) with dose
- Pharmacodynamic effect is more prolonged than pharmacokinetic half-life; increasing doses show deeper and more prolonged pharmacodynamic effect
- Encouraging signs of anti-tumor activity are seen in patients with NSCLC or esophageal cancer
- RP2D not reached, dose escalation and backfill enrollment ongoing
- Combinations of PRT3789 + docetaxel and PRT3789 + pembrolizumab will also be tested

AUC, area under the curve; $C_{max}$, maximum concentration; NSCLC, non-small cell lung cancer.

**These data represent initial proof of concept that selective SMARCA2 degradation can yield anti-tumor activity in certain SMARCA4-*mutated* cancers**

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# What's Next for PRT3789?

## '3789 Monotherapy Dose Confirmation

- Currently enrolling patients in dose escalation cohort 9 (500 mg QW)
- Backfill cohorts continue to enroll
  - Enriching for NSCLC and esophageal cancer w/ Class I LOF mutations
- Expecting dose confirmation by YE24
- Additional information to be presented at plenary session of Triple Meeting, October 24th, 2024

## '3789 + Docetaxel

- Docetaxel combination cohorts continue to enroll
- Goal is to assess safety and clinical activity in combination
- Docetaxel is the chemotherapy most often used in 2L+ NSCLC
- Seeking to improve upon poor outcomes observed with current standard of care

## '3789 + KEYTRUDA®

- Phase 2 pembrolizumab combination trial on track to initiate in 2H 2024
- Subject of recent clinical collaboration agreement with Merck
- Goal is to assess safety and clinical activity in combination

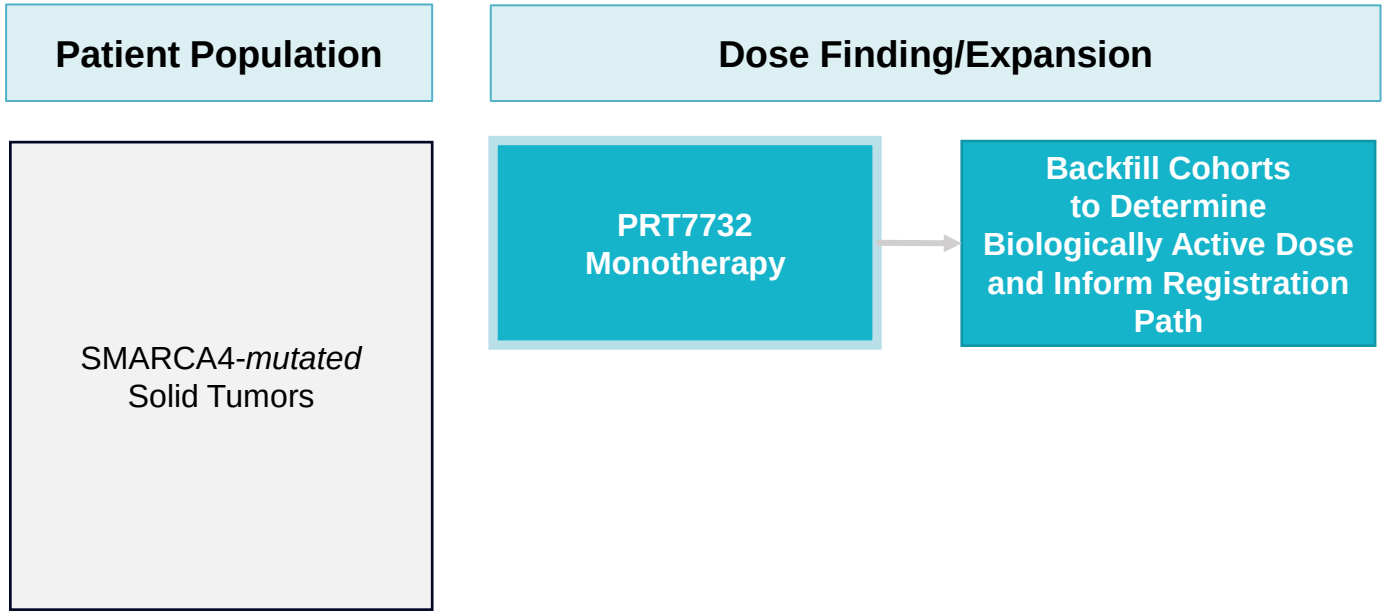
**'3789 Program Priorities:**

- Confirm biologically active dose as monotherapy
- Further characterize activity in Class 1 (LOF) vs. Class 2 patients at biologically active doses
- Share initial data on combination with docetaxel

*KEYTRUDA® is a registered trademark of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.*
LOF = "Loss-of-function"; QW = once weekly; DLT = dose limiting toxicity; NSCLC – non-small cell lung cancer; 2L = second-line

# PRT7732: First-in-Class, Highly Selective Oral SMARCA2 Degrader – *Phase I Trial Initiated*

| Preclinical Assay | PRT7732 |
|---|---|
| SMARCA2 Degradation (nM) | 0.98 |
| Selectivity: Degradation (SMARCA4 / SMARCA2) | >3000 fold |
| Selectivity: Cell Proliferation (SMARCA4 / SMARCA2) | >1000 fold |




**Goal: Establish Initial Proof-of-Concept and Identify Biologically Active Dose as Monotherapy**

**Sub-nanomolar SMARCA2 degradation potency in cell lines**

**Very high selectivity for SMARCA2 over SMARCA4**

**Good oral bioavailability observed across species supporting once-daily projected human dose**

ClinicalTrials.gov Identifier: NCT06560645

# Closing Remarks

**Kris Vaddi, Ph.D., CEO**
**Prelude Therapeutics Incorporated**

# Open for Questions

**Kris Vaddi, PhD**
*Chief Executive Officer*

**Jane Huang M.D.**
*President and Chief Medical Officer*

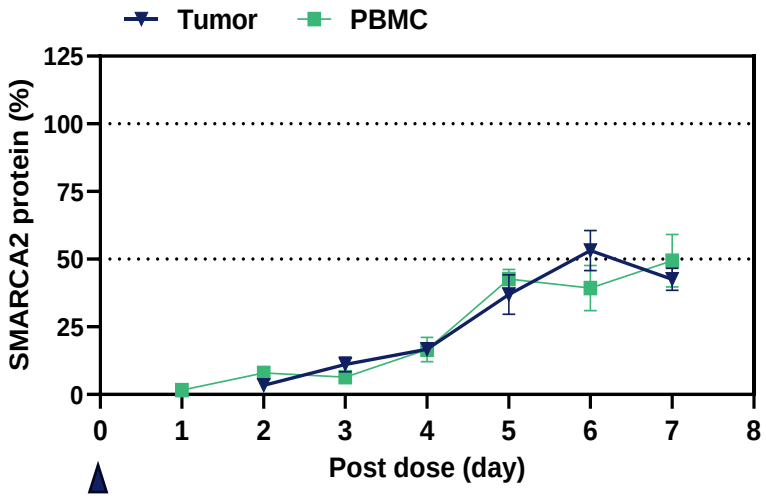
**Peggy Scherle, PhD**
*Chief Scientific Officer*

**Sean Brusky, MBA**
*Chief Business Officer*

**Bryant Lim, J.D.**
*Chief Legal Officer, Corporate Secretary and Interim CFO*

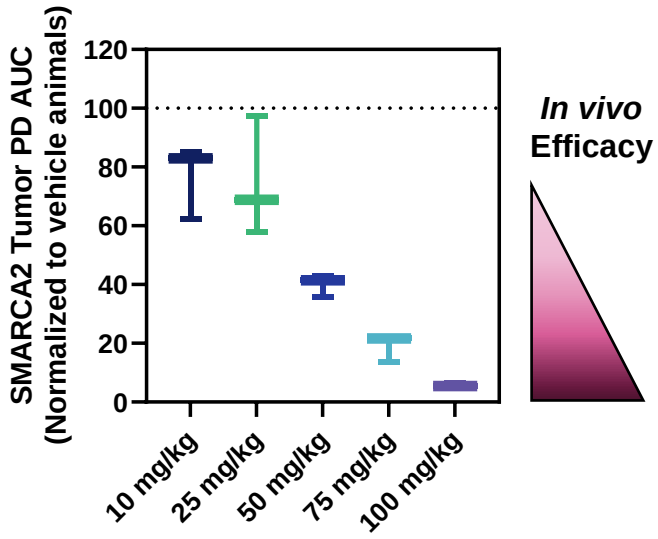
# PD Correlates with Efficacy in Preclinical Models

**SMARCA2 Levels over Time After a Single IV Dose of PRT3789**




*Tumor levels from mouse xenograft model and PBMC levels from normal rat after single doses that provide equivalent exposure*

**PD AUC/Efficacy Correlation**



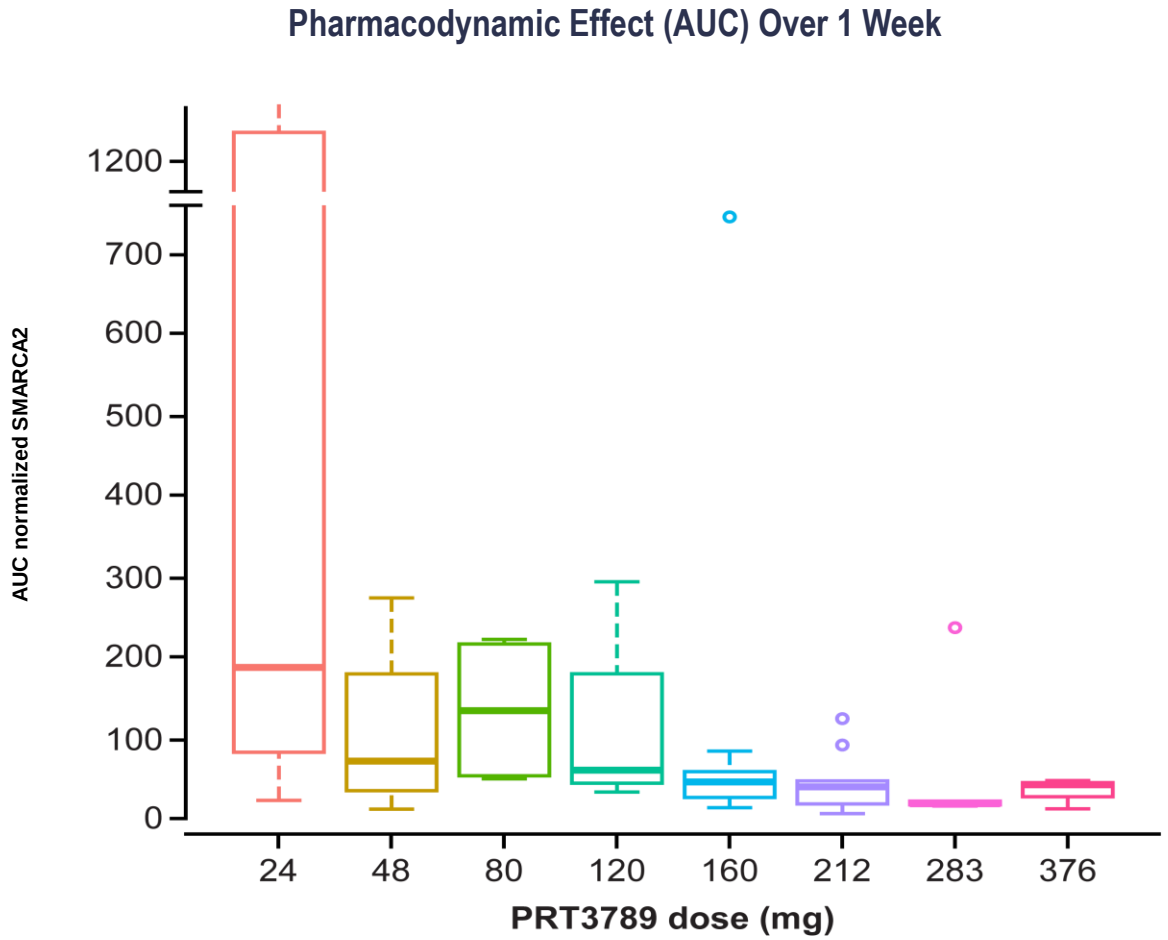

*50 mg/kg = 243 mg human dose equivalent*
*75 mg/kg = 365 mg human dose equivalent*
*100 mg/kg = 487 mg human dose equivalent*

**Correlation observed between peripheral blood monocyte (PBMC) and tumor SMARCA2 degradation levels at efficacious doses**

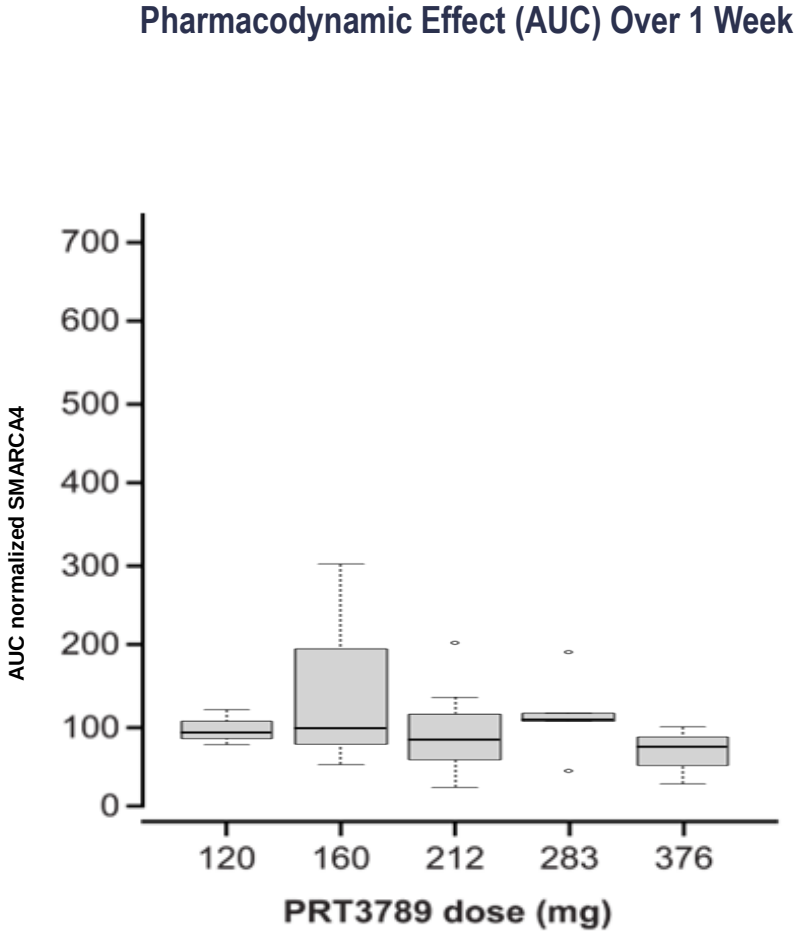
**Increasing doses result in increased reduction in SMARCA2 PD AUC in tumors and were associated with higher efficacy**

AUC, area under curve
Source: Wang et al. ENA 2023; Data on file

# Dose Dependent Degradation of SMARCA2, but not SMARCA4




| SMARCA2 AUC, n | 4 | 4 | 4 | 4 | 9 | 10 | 5 | 3 |
|---|---|---|---|---|---|---|---|---|




| SMARCA4 AUC, n | 3 | 8 | 10 | 5 | 3 |
|---|---|---|---|---|---|