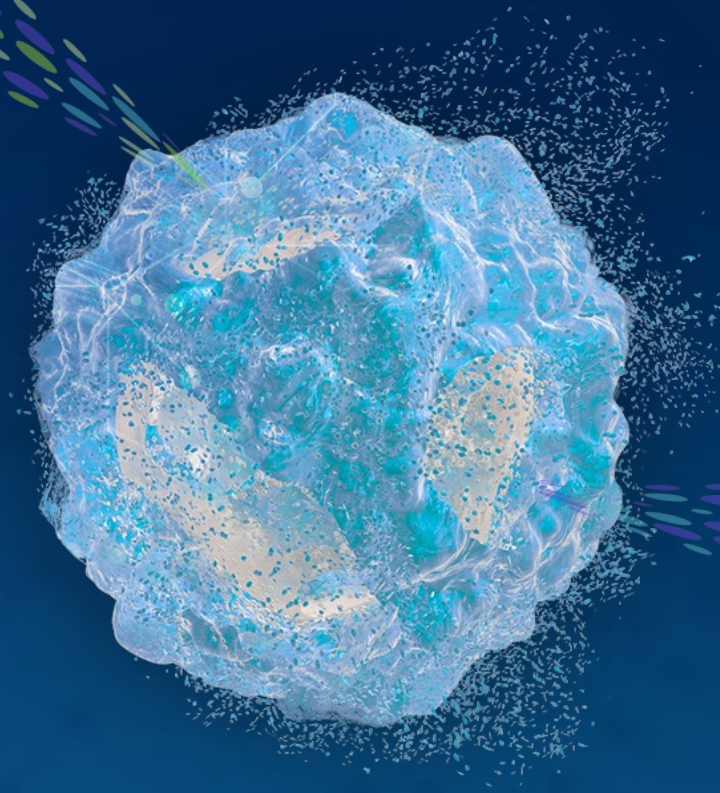
Highly Selective SMARCA2 Degraders



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, the potential safety, efficacy, benefits and addressable market for Prelude’s product candidates, the expected timeline for proof-of-concept data and 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).

Certain data in this presentation are based on cross-study comparisons and are not based on any head-to-head clinical trials. Cross-study comparisons are inherently limited and may suggest misleading similarities or differences. This presentation shall not constitute an offer to sell or the solicitation of an offer to buy, nor shall there be any sale of these securities in any state or other jurisdiction in which such offer, solicitation or sale would be unlawful prior to registration or qualification under the securities laws of any such state or other jurisdiction.

These forward-looking statements are based on the beliefs of our management as well as assumptions made by and information currently available to us. Although we believe the expectations reflected in such forward-looking statements are reasonable, we can give no assurance that such expectations will prove to be correct. If such assumptions do not fully materialize or prove incorrect, the events or circumstances referred to in the forward-looking statements may not occur. We undertake no obligation to update publicly any forward-looking statements for any reason after the date of this presentation to conform these statements to actual results or to changes in our expectations, except as required by law. Accordingly, readers are cautioned not to place undue reliance on these forward-looking statements. Additional risks and uncertainties that could affect our business are included under the caption “Risk Factors” in our filings with the Securities and Exchange Commission, including our Annual Report on Form 10-K for the year ended December 31, 2023.

- There is high unmet need in SMARCA4-*mutated* NSCLC (up to 10% of patients)
- These mutations are prevalent across a range of other cancers as well
- SMARCA2 is a promising new “synthetic lethal” target for these patients
- Targeting SMARCA2 is very challenging; selectivity over SMARCA4 is critical
- With PRT3789, our lead SMARCA2 degrader, Prelude scientists solved the selectivity challenge >1000-fold
- Industry-first clinical data validating this approach is coming soon
- Prelude’s first-in-class oral SMARCA2 degrader (PRT7732) and Precision ADCs further expand potential impact for patients

Learning Objectives

Learning Modules

Topic	Presenter
Advancing Our Understanding of SMARCA Science	Dr. Timothy Yap, MDACC
Discovery Deep Dive: Targeting SMARCA2	Andrew Combs & Peggy Scherle
Clinical Experience with SMARCA4-*mutated* NSCLC	Dr. Adam Schoenfeld, MSKCC
Clinical Development Plan and Future Directions	Dr. Jane Huang
Prelude Portfolio Strategy & Closing Remarks	Kris Vaddi

Prelude THERAPEUTICS

We are on a mission to extend the promise of precision medicine to every cancer patient

- *Follow the science and select the best modality to solve the problem*
- *Strive for first- or best-in-class and anchor to patient unmet need*
- *Draw on decades of experience and collaboration to drive innovation*

Our scientific leadership has deep experience in precision oncology

Kris Vaddi, PhD
Founder & Chief Executive Officer

Jane Huang M.D.
President & Chief Medical Officer

Peggy Scherle, PhD
Chief Scientific Officer

Andrew Combs, PhD
Chief Chemistry Officer

Jakafi® ruxolitinib (tablets) · olumiant® (baricitinib) tablets 2 mg · TABRECTA® (capmatinib) tablets 150 mg · 200 mg · VELCADE® (bortezomib)

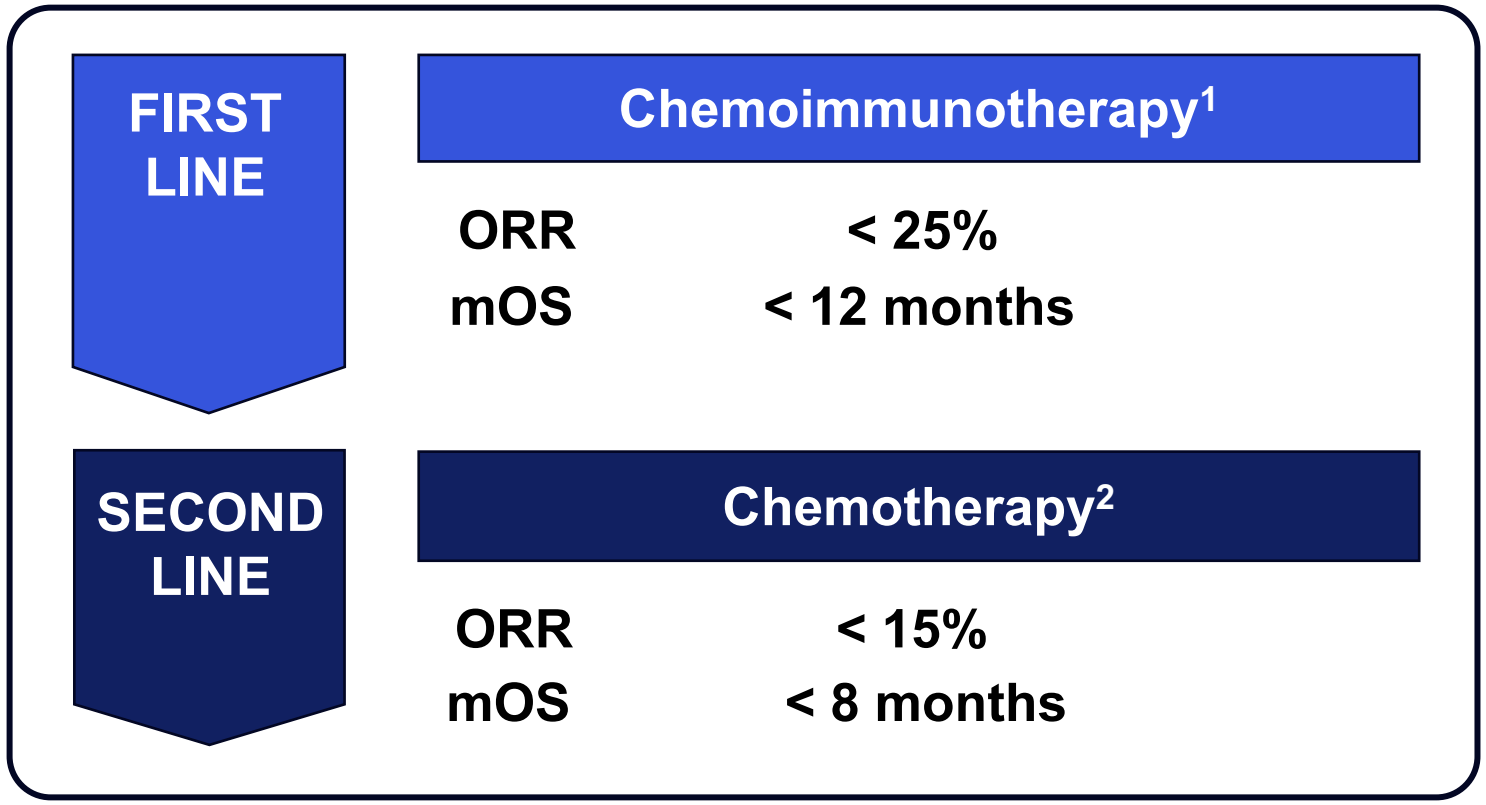
Brukinsa® zanubrutinib 80 mg capsules · CALQUENCE® (acalabrutinib) 100 mg capsules · VENCLEXTA® venetoclax tablets 10mg, 50mg, 100mg · GAZYVA® obinutuzumab injection | 1,000mg/40mL · Kadcyla® ado-trastuzumab emtansine · AVASTIN® bevacizumab 100 MG/4 ML INJECTION FOR IV USE

Jakafi® ruxolitinib (tablets) · olumiant® (baricitinib) tablets 2 mg · Pemazyre® pemigatinib (tablets) · TABRECTA® (capmatinib) tablets 150 mg · 200 mg

Jakafi® ruxolitinib (tablets) · olumiant® (baricitinib) tablets 2 mg

Prelude THERAPEUTICS

High unmet need in SMARCA4-*mutated* NSCLC



The prognosis for SMARCA4-*mutated* NSCLC patients is poor

A selective SMARCA2 degrader has the potential to transform outcomes for these patients

[1] Response Rate and Survival Data: Schoenfeld et al. *Clin Cancer Res.* (2020); 26(21):5701-5708
[2] Second line estimates based on docetaxel label and clinical experience

We are developing the industry's leading SMARCA-targeted pipeline

PROGRAM	POTENTIAL INDICATIONS	DISCOVERY	PHASE 1	PHASE 2/3	UPCOMING MILESTONES
Lead SMARCA2 Degrader *PRT3789*	Patients with SMARCA4-deficient advanced NSCLC and other cancers				**First Interim Phase I Data in 2H 2024**
Oral SMARCA2 Degrader *PRT7732*	Patients with SMARCA4-deficient NSCLC and other cancers				**File IND in 1H 2024; Phase I Start in 2024**
SMARCA "Precision ADCs" *(aka "DACs")*	Solid tumors & heme malignancies not addressed by selective SMARCA2 degraders				**Expand portfolio to target >90% of cancers without SMARCA4 mutations**

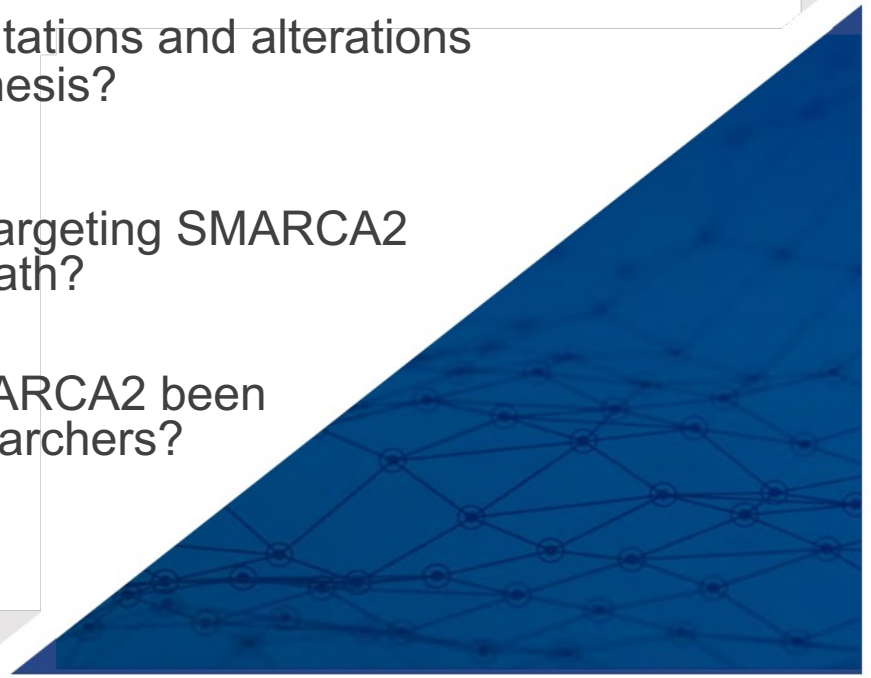
+ Full pipeline includes programs against other cancer targets in active clinical or preclinical development

Advancing our Understanding of SMARCA Science

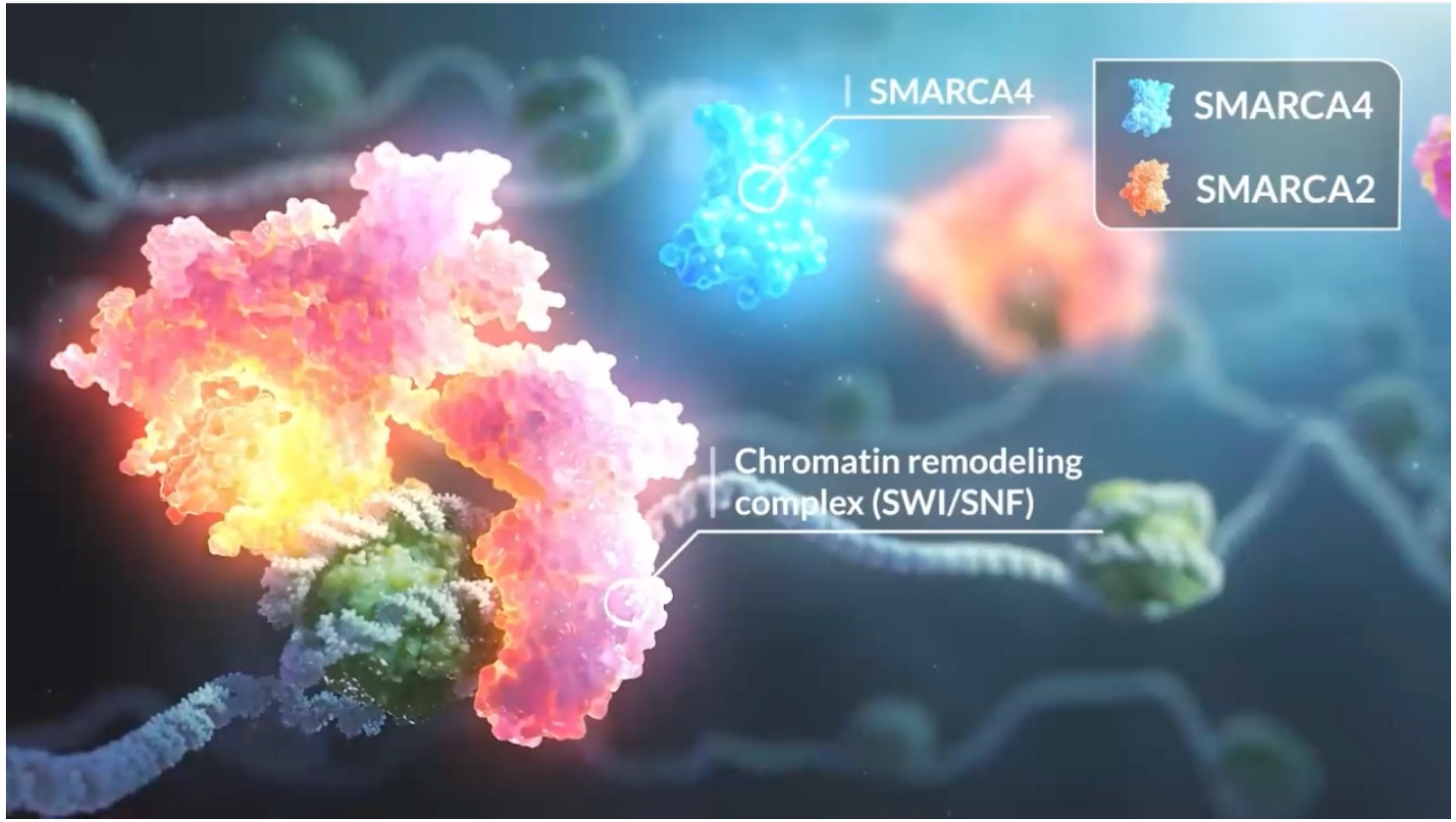
Dr. Timothy Yap, University of Texas
MD Anderson Cancer Center

Learning Objectives

- Why has SMARCA garnered such interest as a target for cancer research?
- What is the function of SMARCA2 and SMARCA4 in healthy cells?
- How do SMARCA4 mutations and alterations contribute to tumorigenesis?
- How does selectively targeting SMARCA2 result in cancer cell death?
- Why has targeting SMARCA2 been so challenging for researchers?



Chromatin Remodeling (CR) is an essential step in DNA replication, repair and gene expression



SMARCA: SWI/SNF-related, Matrix-associated, Actin-dependent Regulator of Chromatin, subfamily A.

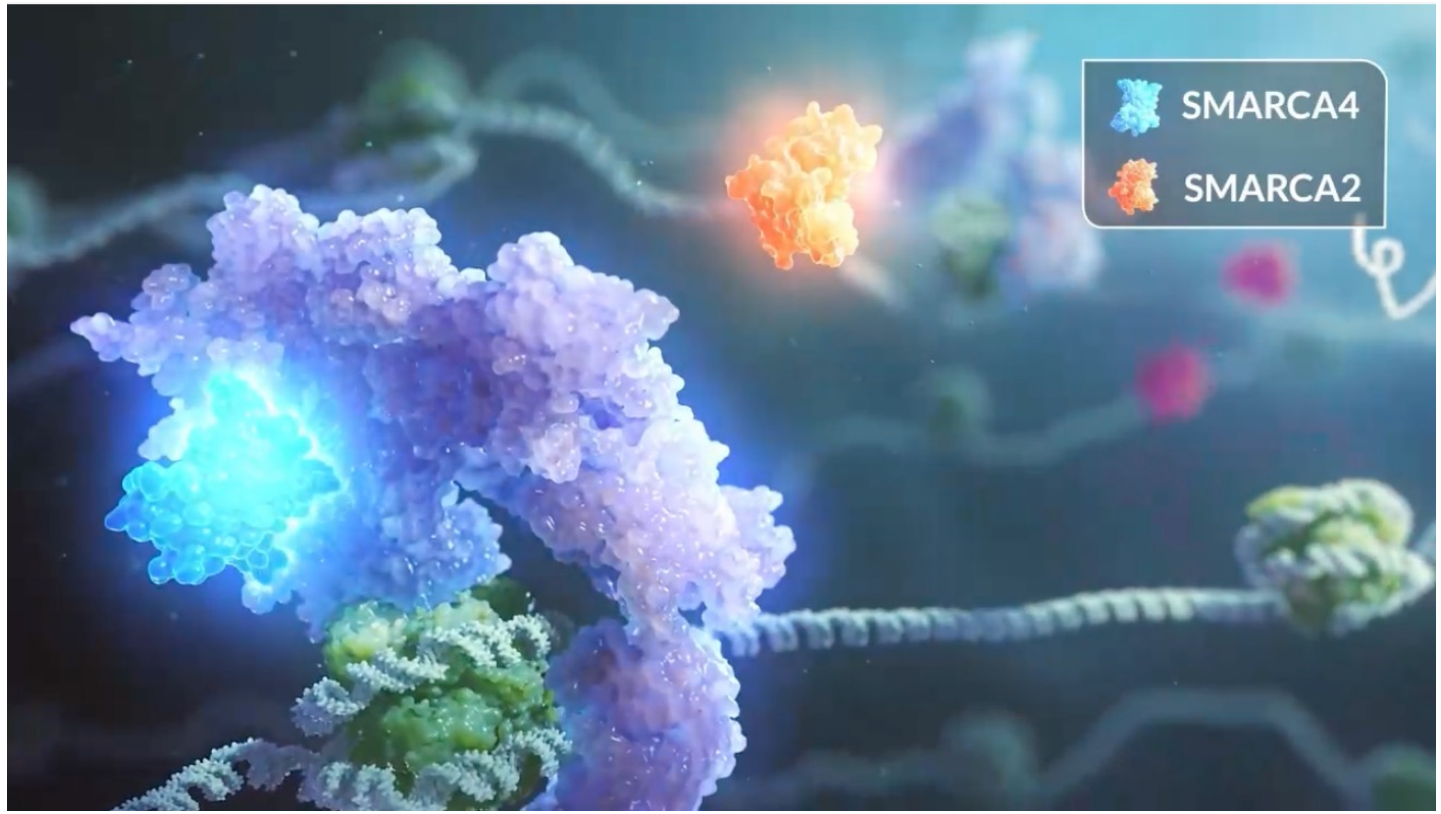
Chromatin Remodeling (CR) Complex (aka SWI/SNF)

Unwinds Chromatin

ATP-Dependent

> 20 Subunits

SMARCA2 and SMARCA4 are highly related, interchangeable ATPase subunits



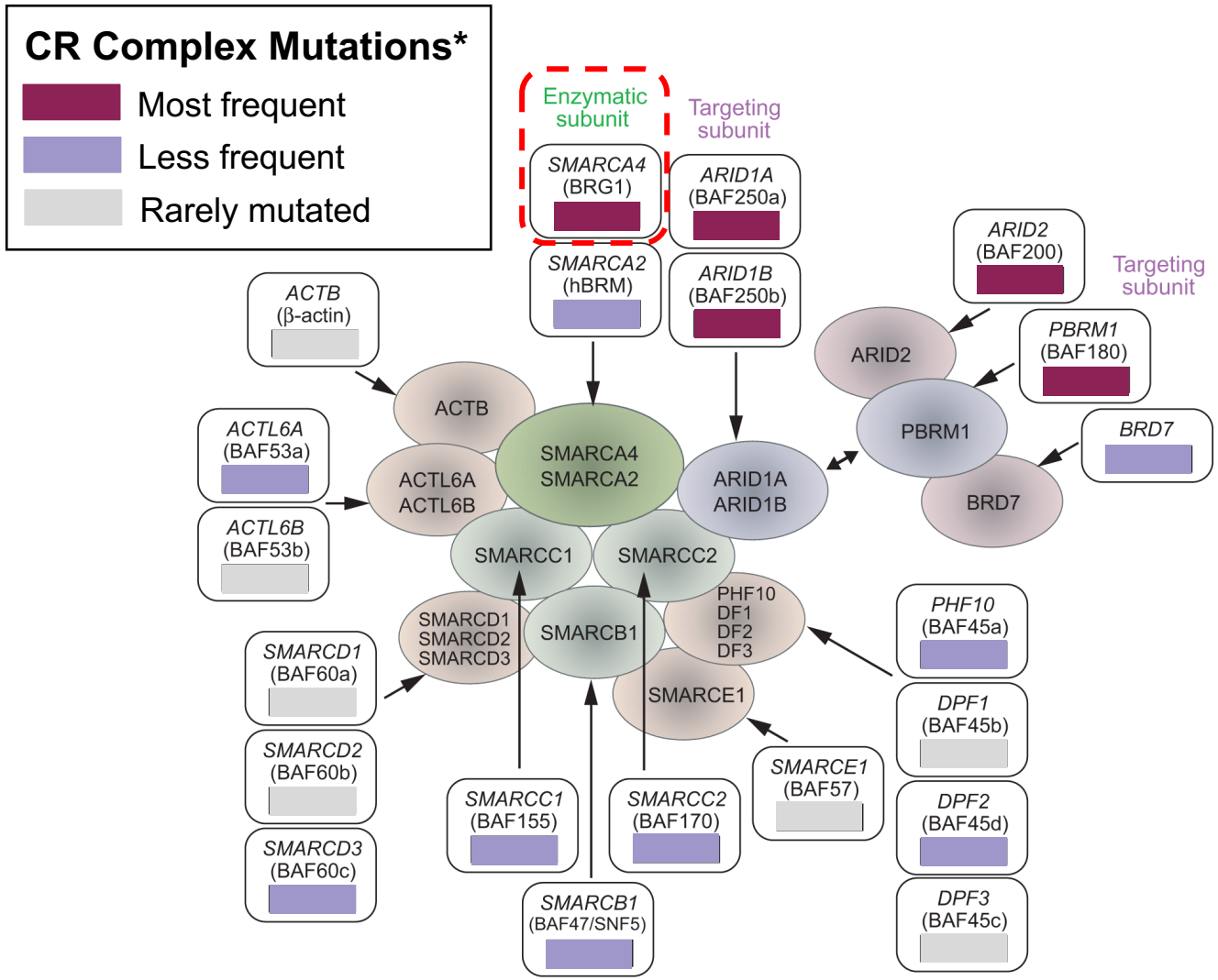
SMARCA2 is also known as “BRM”
SMARCA4 is also known as “BRG1”

SMARCA2 and SMARCA4 work in a complementary manner

Regulate gene expression and cell proliferation

Only one or the other is engaged at any given time

More than 20% of all human cancers harbor mutation(s) in at least one of the CR subunits



* Average frequency of subunit mutation across 18 distinct neoplasms tested

Shain AH, Pollack JR (2013) The Spectrum of SWI/SNF Mutations, Ubiquitous in Human Cancers. PLoS ONE 8(1): e55119

Mutations in the CR complex lead to cancer growth, resistance and poor prognosis

Implicated across a wide range of cancers

Challenging proteins to target for drug discovery

SMARCA4 mutations occur in ~10% of all NSCLC and to varying degrees across other cancers

NSCLC: 10%

Squamous cell lung: 8%

Esophageal: 8%

Colorectal: 6%

Gastric: 8%

Pancreatic: 3%

Endometrial: 13%

Urinary: 9%

Mostly non-overlapping with other "druggable" mutations

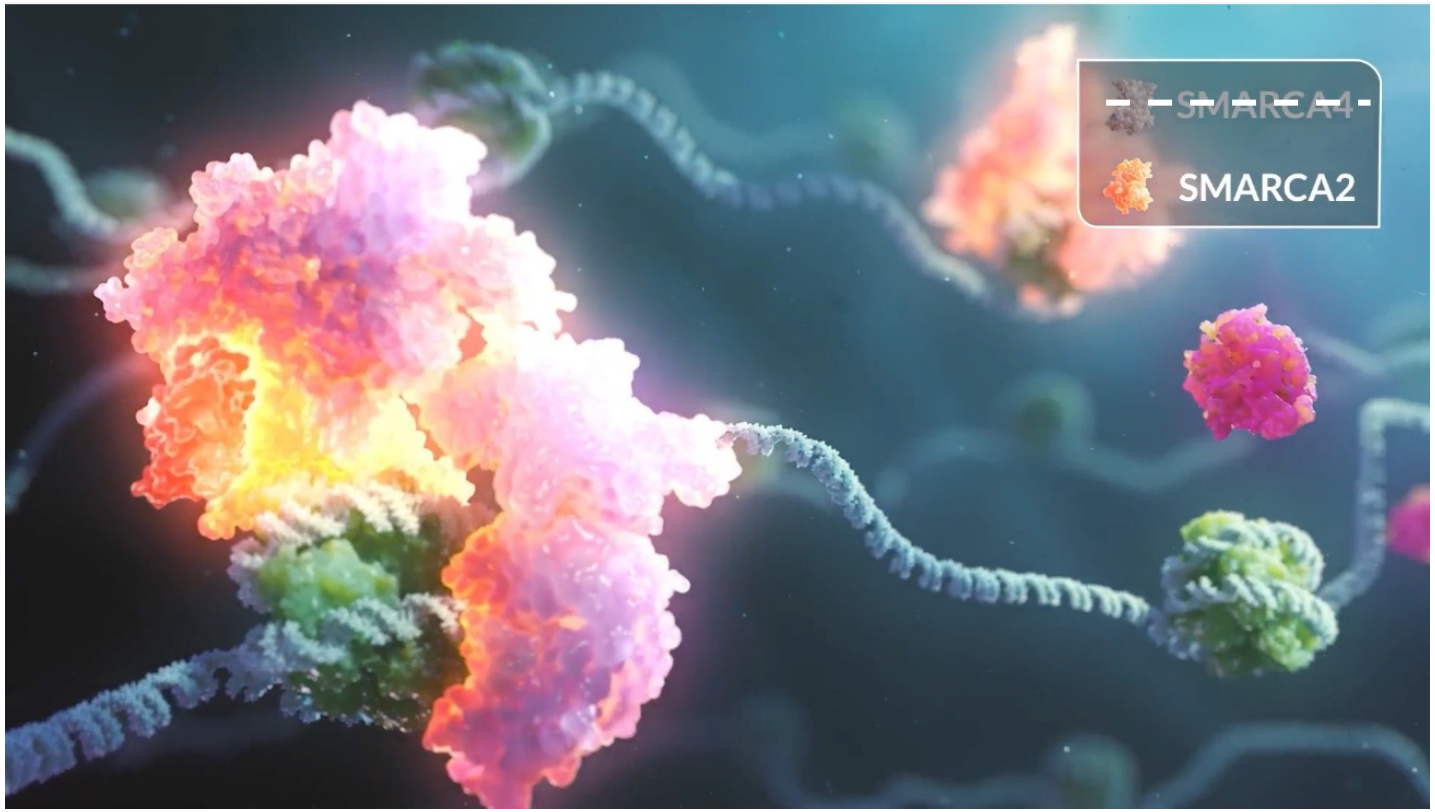
Types of mutations:

Class I (Loss-of-function)

Class II (Missense, other)

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

When SMARCA4 is mutated, tumors become reliant on SMARCA2 for growth and survival



SMARCA4-*mutated* cancers become reliant on SMARCA2

In these cancers, when SMARCA2 is depleted, the CR complex no longer functions

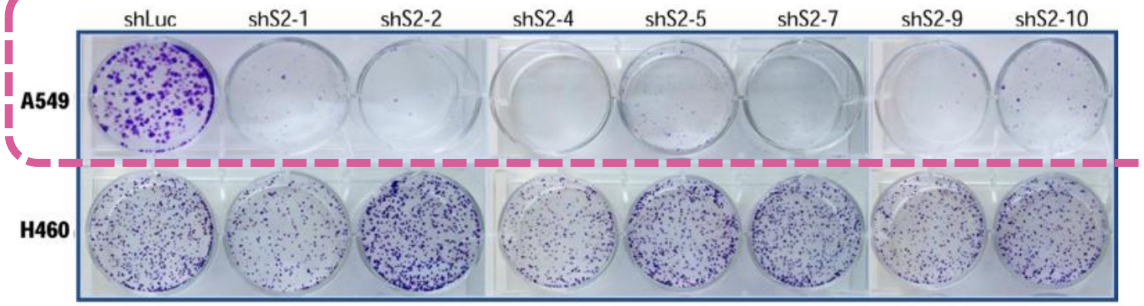
Cells can no longer survive and tumors regress

“Synthetic Lethality”

Selectively knocking out SMARCA2 induces synthetic lethality in SMARCA4-*mutated* cancers

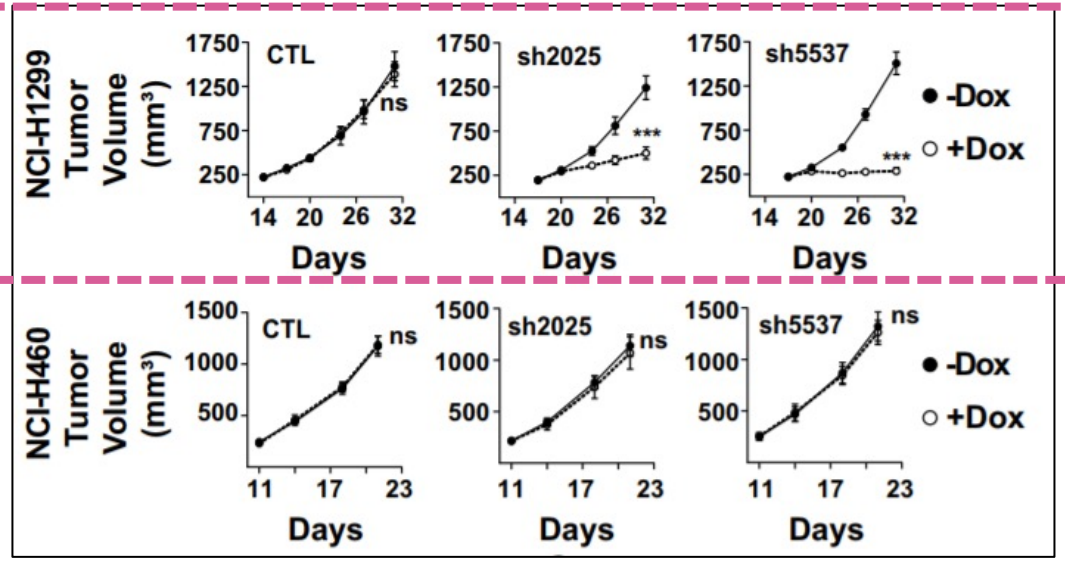
SMARCA4-*mut* cancer cells

SMARCA4 WT cancer cells



SMARCA4-*mut* cancer model

SMARCA4 WT cancer model

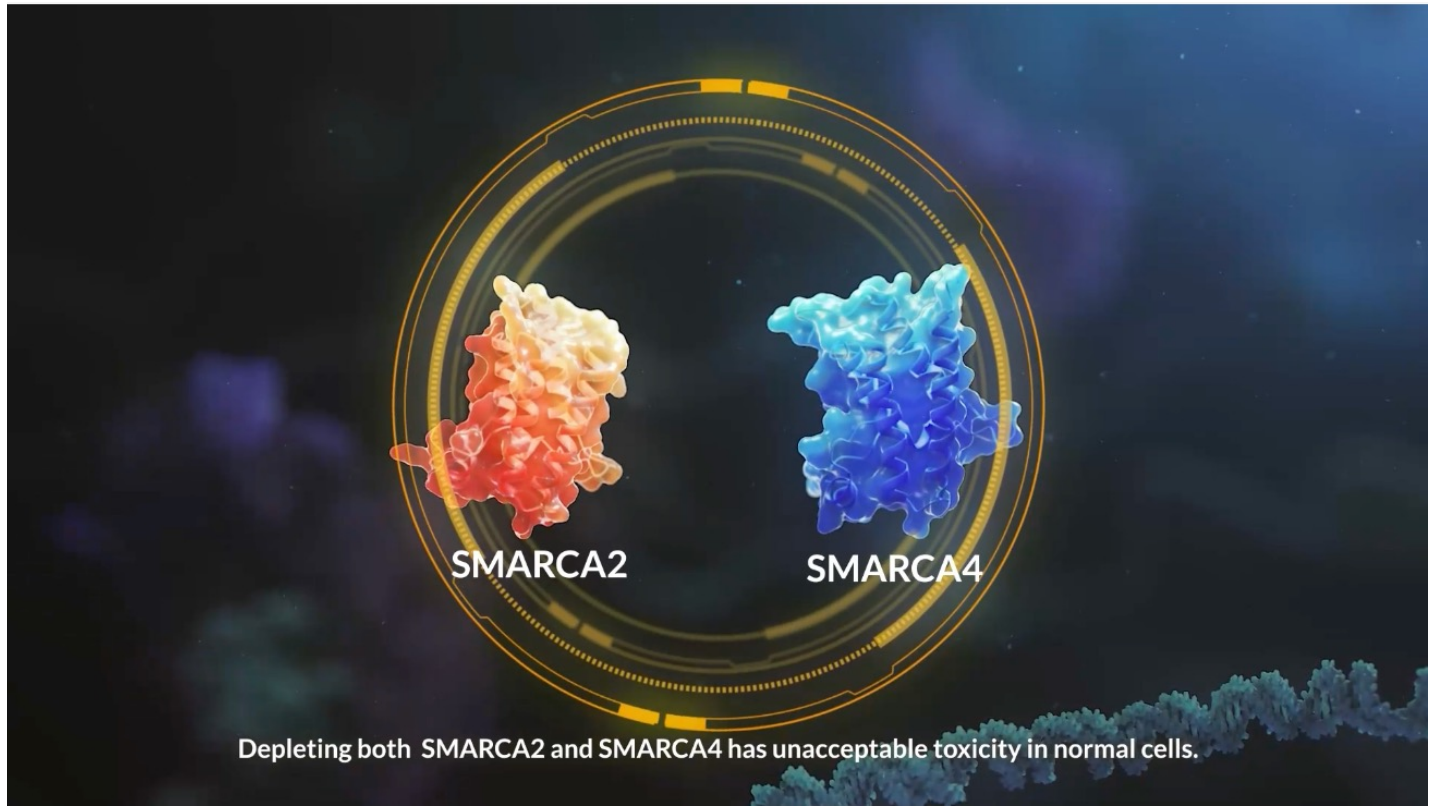


Hoffman GR et al. PNAS (2014); 111 (8): 3128-3133
Vangamudi et al. Cancer Res (2015); 75 (18): 3865-3878.

SMARCA2 gene knockdown shows tumor growth inhibition in SMARCA4-mutated cancers

… but NOT in SMARCA4 wild-type cancers

Selective SMARCA2 targeted treatments could have utility treating SMARCA4-mutated cancers



Selectively targeting SMARCA2 should induce tumor regression in SMARCA4-mutated cancers

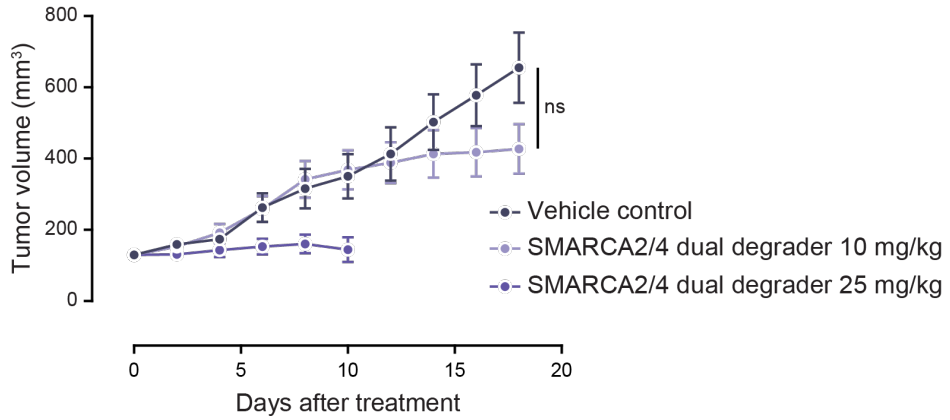
In healthy tissue, SMARCA4 should compensate for selectively depleted SMARCA2

If both are depleted, there would likely be adverse effects

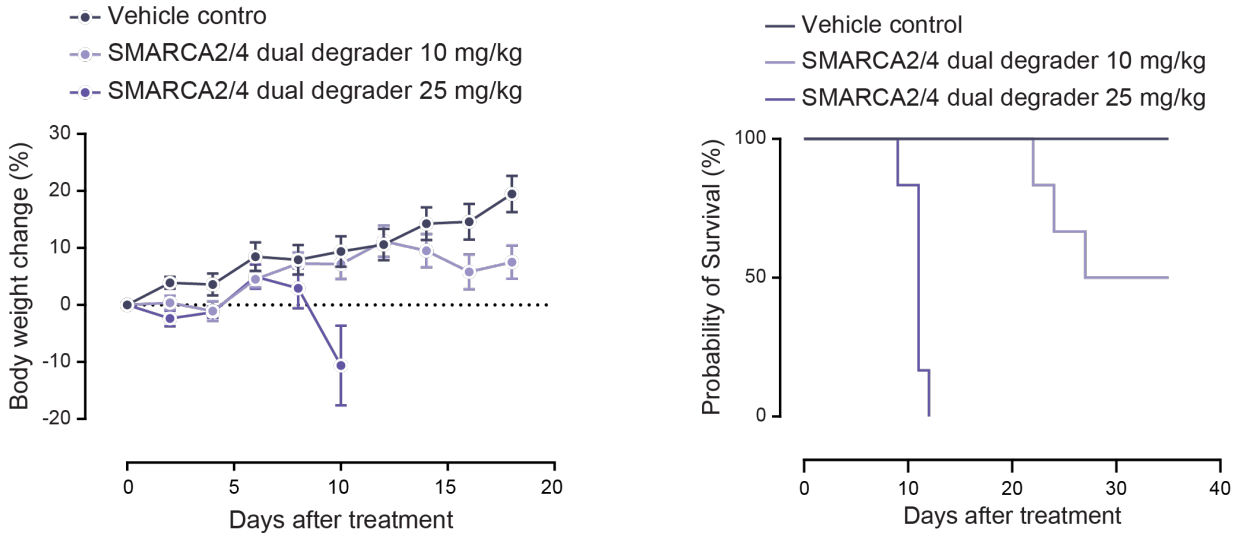
Selectivity is critical

SMARCA2/4 dual degraders show rapid tumor regressions, but may cause unacceptable toxicity

Rapid cell death and tumor regression



… but with unacceptable toxicity in animal models



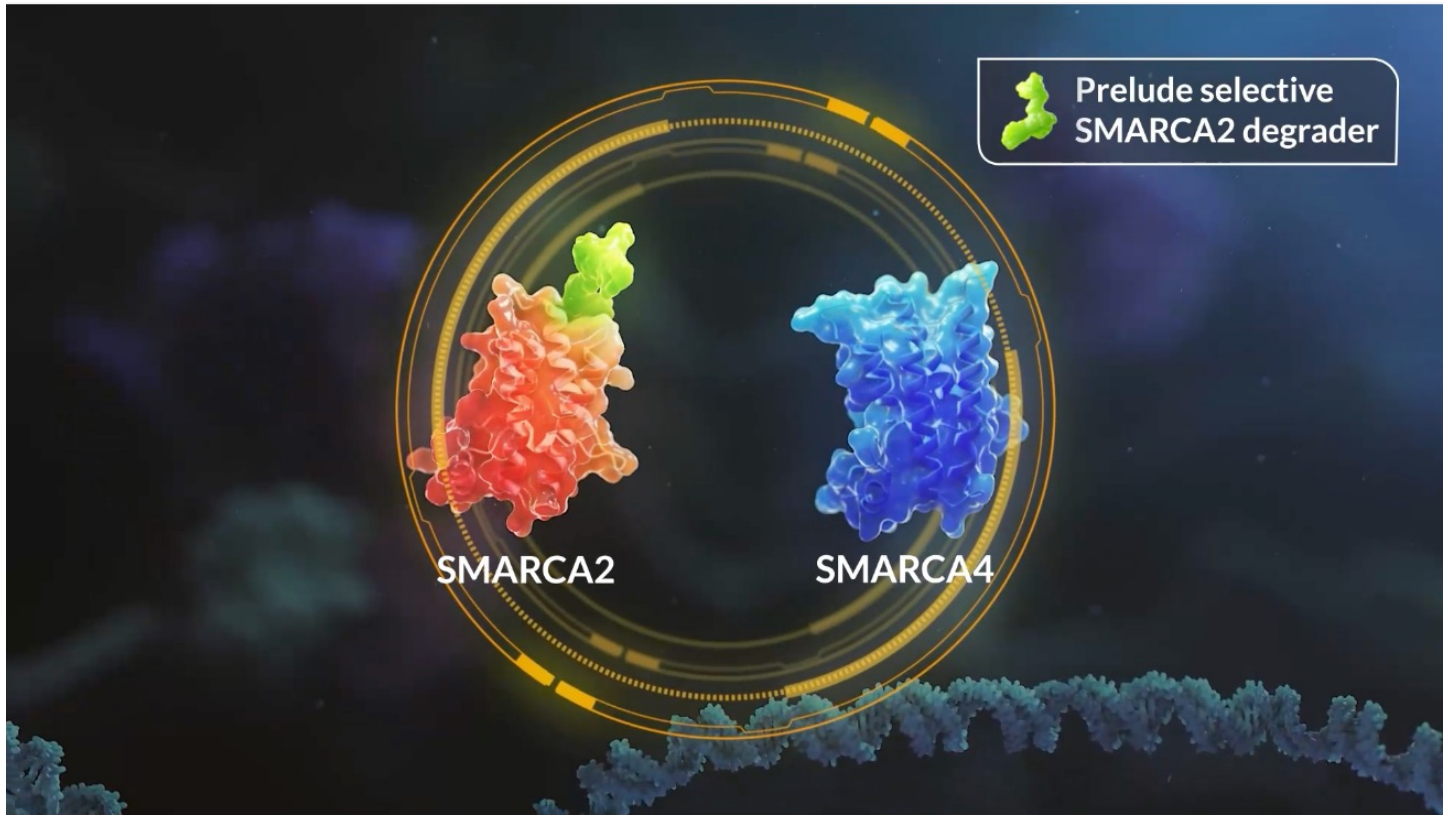
Prelude Data on File. Presented at 6th TPD Summit, 2023

SMARCA2/4 dual degraders showed rapid cell death and tumor regression

However, dual degraders also showed toxicity, body weight changes and shorter survival

Selectivity is key for a better therapeutic window

Achieving SMARCA2 selectivity has been a challenge for industry, until recently



Hard to achieve selectivity with inhibitors to the ATPase active site

Recent advances in targeted protein degrader technology allows for both potency and selectivity

Once "undruggable" target → now in human clinical trials

Targeting SMARCA2 represents an important new field of cancer research

- Mutations in the Chromatin Remodeling (CR) complex drive cancer growth and resistance
- SMARCA4 mutations are present in up to 10% of all NSCLC and across other cancers
- Cancer cells with loss of SMARCA4 expression through mutations or alteration are highly dependent on SMARCA2 for survival
- Selective SMARCA2 degraders have the potential to induce "synthetic lethality" in SMARCA4-*mutated* cancers
- Discovering new agents with high selectivity for SMARCA2 is critical

Key Takeaways

Discovery Deep Dive: Prelude's Lead SMARCA2 Degrader (PRT3789)

Andrew Combs, Ph.D.
Chief Chemistry Officer
Prelude Therapeutics

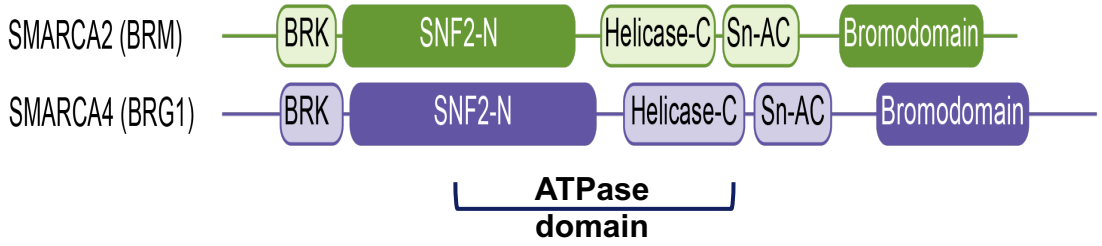
Peggy Scherle, Ph.D.
Chief Scientific Officer
Prelude Therapeutics

Learning Objectives

- Why has SMARCA2 selectivity been so hard to achieve? How did Prelude succeed?
- Why are we so excited about the profile and potency of our lead program, PRT3789?

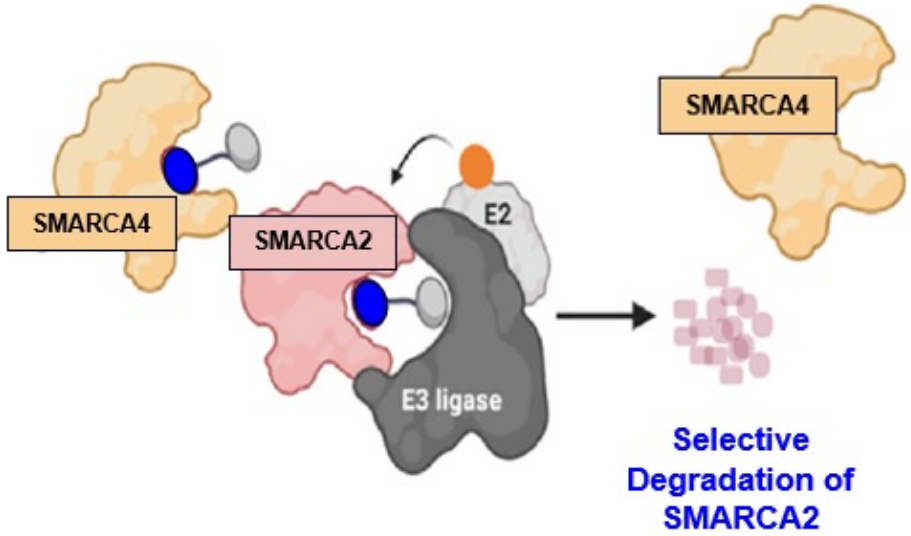
Selectively targeting SMARCA2 has been a significant challenge for industry

Selective SMARCA2 Inhibition is an Unmet Medicinal Chemistry Challenge



- **Bromodomain Binders**
  - Non-selective and inactive in SMARCA4 mutated cancer cells[1]
- **ATPase Inhibitors**
  - Inhibitors show low selectivity for SMARCA2 in cell proliferation assays (<10 fold[2] and ~33 fold[3])

Prelude's Targeted Protein Degradation (TPD) Approach



- **SMARCA2 Selective Degradation** is possible through differences in ternary complexes and subsequent ubiquitination of unique lysine residues

[1] Vangamudi et al, Cancer Res. **2015** (Pfizer); Taylor et al J. Med. Chem **2022** (Genentech)
[2] Papillon et al, J. Med. Chem **2018** (Novartis) [3] AACR **2024** (Foghorn/Lilly)

When it comes to targeting SMARCA2, degraders offer distinct advantages

	Inhibitors	Degraders
Potency	☑	☑
High Selectivity	X	☑
Extended PD	X	☑
Oral Bioavailability	☑	☑

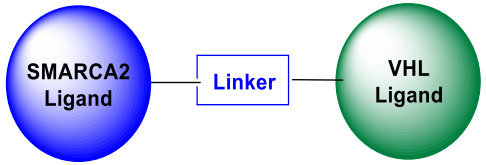
Early attempts at achieving both potency and selectivity with inhibitor approaches had challenges

Inhibitors do not degrade the target and need to be dosed at levels that retain IC_{90} coverage continuously

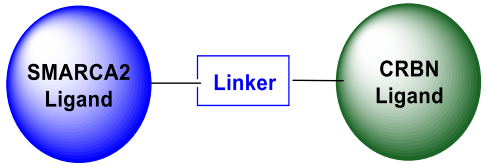
Degraders demonstrate sustained PD effect as it takes ~72h for SMARCA2 to resynthesize

Prelude scientists solved the SMARCA2 selectivity enigma

Parallel VHL- and CRBN-based SMARCA2 Degrader Programs



PRT3789
(IV or SC formulation)



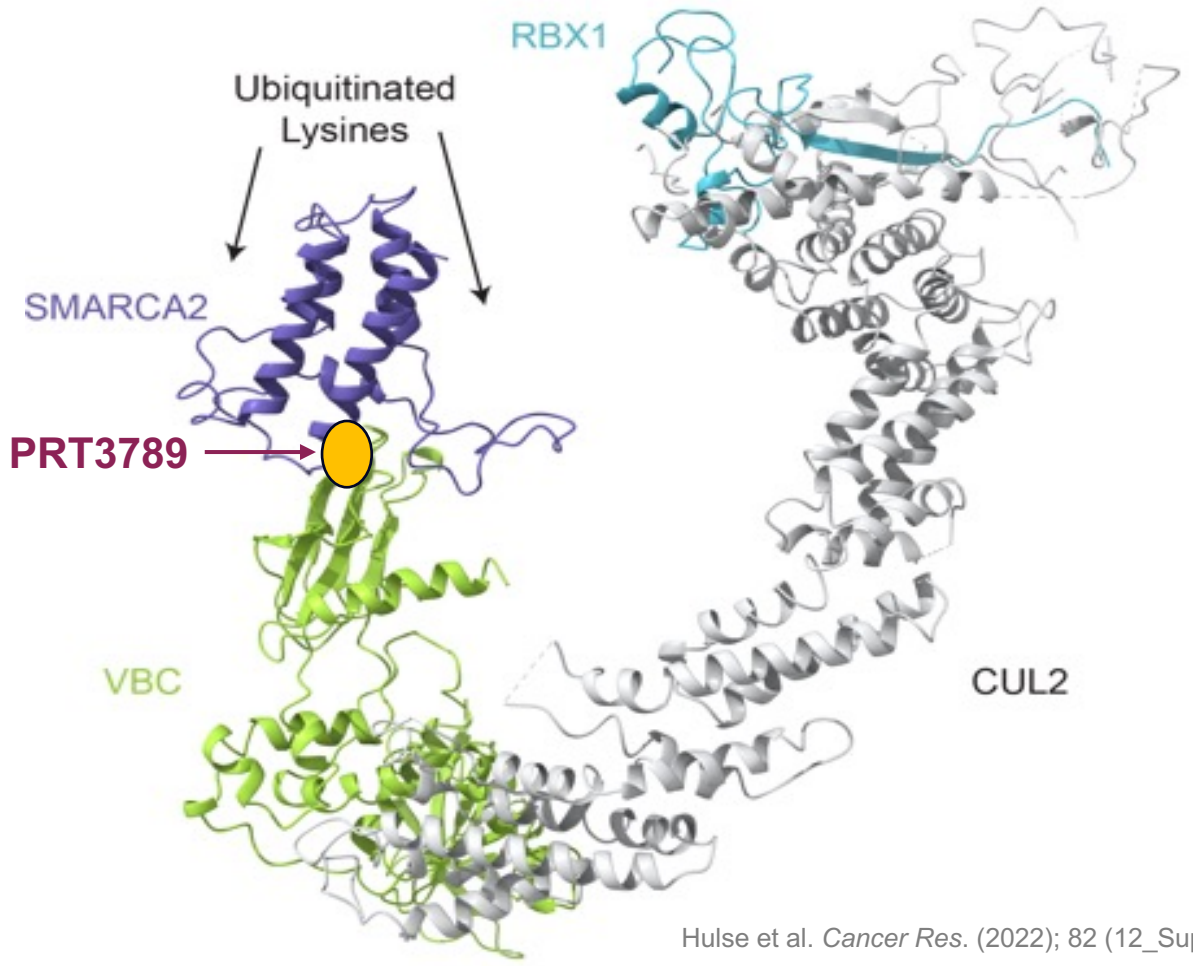
PRT7732
(Oral Candidate)

- **IV or SC Candidate** - **VHL-TPD**s provided an expedited path to potential clinical development with QW dosing
- **Oral Candidate** - **CRBN-TPD**s provided oral candidates, but required extensive lead optimization with balancing of potency, selectivity and oral PK properties

Our lead IV and oral clinical candidates both have sub-nanomolar degradation potencies and very high selectivity (>1000 fold) for SMARCA2 over SMARCA4

PRT3789: Our Lead SMARCA2 Degrader

Tertiary Complex of SMARCA2/ PRT3789/VHL E3 Ligase



Hulse et al. *Cancer Res*. (2022); 82 (12_Suppl) :3263.

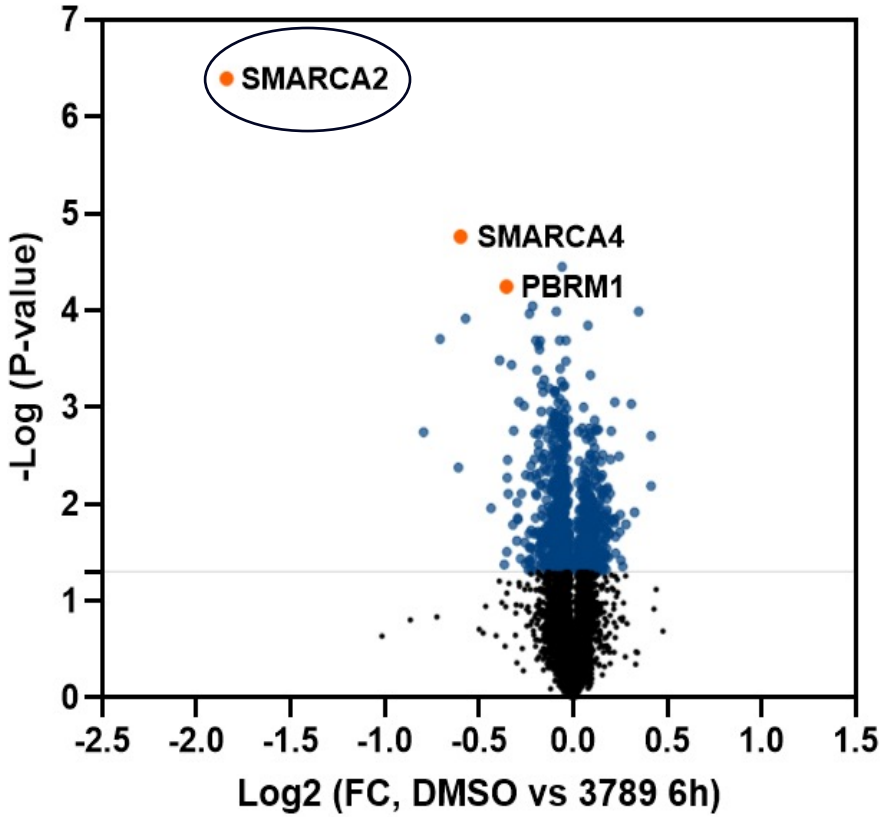
PRT3789 has been shown to catalyze the polyubiquitination of unique lysine residues expressed only in SMARCA2 and not SMARCA4

Unique conformational bias promotes selective ubiquitination and degradation of only SMARCA2

Presented at AACR 2023; https://preludetx.com/wp-content/uploads/2023/05/Ito_SMARCA2_AACR-2023_Poster_6277_01MAY23_CORRECTION.pdf

PRT3789 is highly potent and highly selective

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



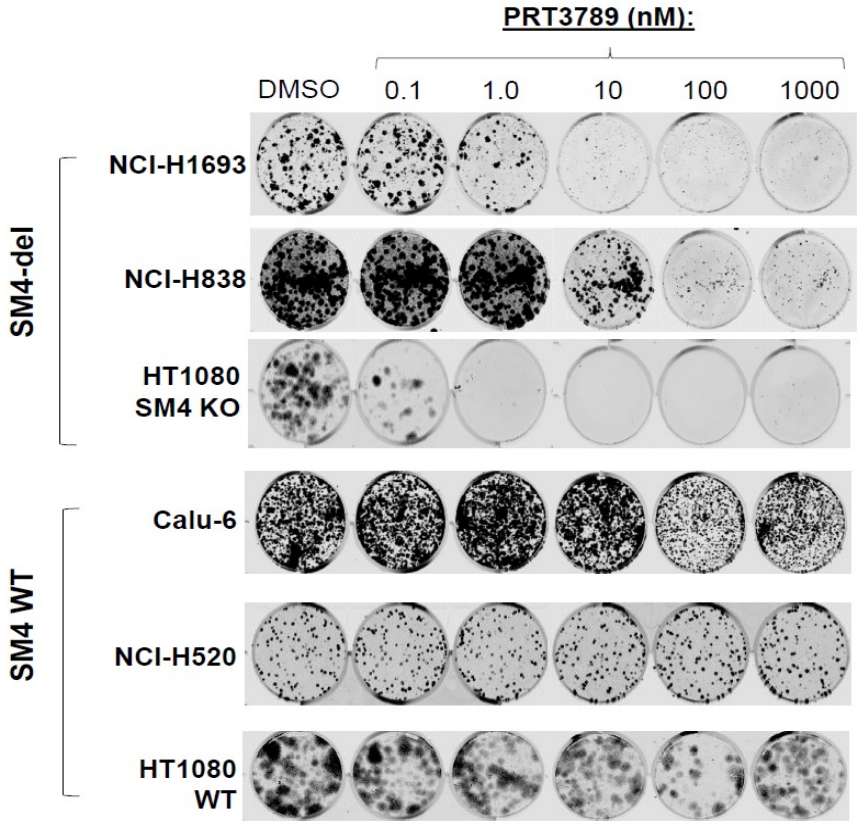
Sub-nanomolar SMARCA2 degradation potency

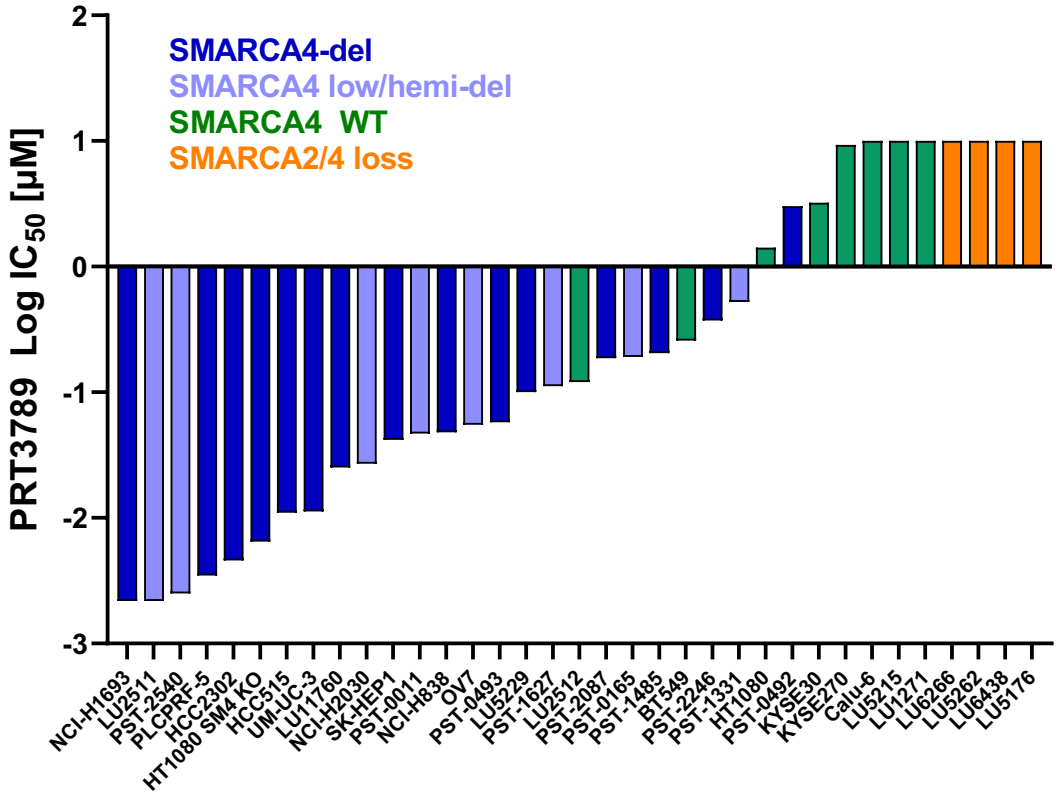
Highly selective for SMARCA2 vs SMARCA4 (>1000 fold)

High selectivity across the proteome

Presented at AACR 2022; https://preludetx.com/wp-content/uploads/2022/05/Prelude_AACR_Hulse-SMARCA2-FINAL-21Mar2022.pdf

PRT3789 induces synthetic lethality in SMARCA4-deficient cancer cells *in vitro*



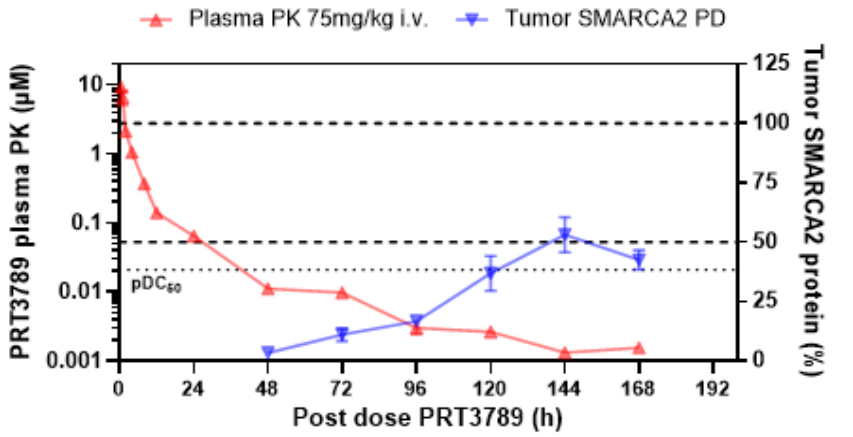


- PRT3789 selectively inhibits SMARCA4 deficient cancer cell proliferation *in vitro*
- None or limited response in SMARCA4 WT and SMARCA2/4 dual loss cancer cells
- >1000x selectivity in cell proliferation assays

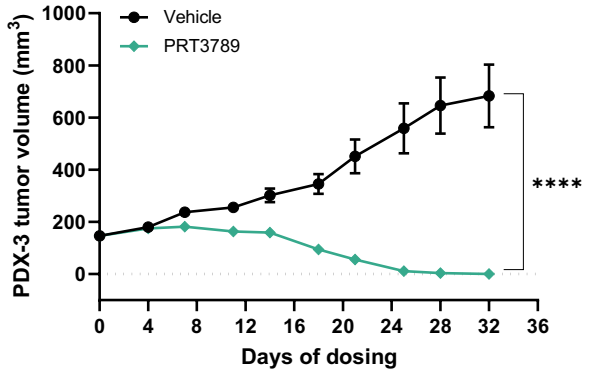
1. Data on file. 2. Hulse et al. *Cancer Res.* (2022); 82 (12_Suppl) :3263.

PRT3789 demonstrates selective tumor regression *in vivo*

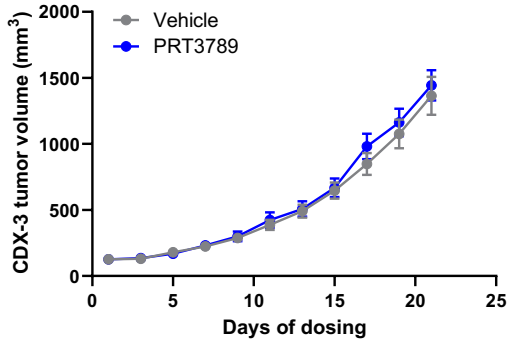
PK/PD - Highly Selective for SMARCA2 Degradation



Robust Tumor Growth Inhibition of SMARCA4 mutated but not WT Xenograft



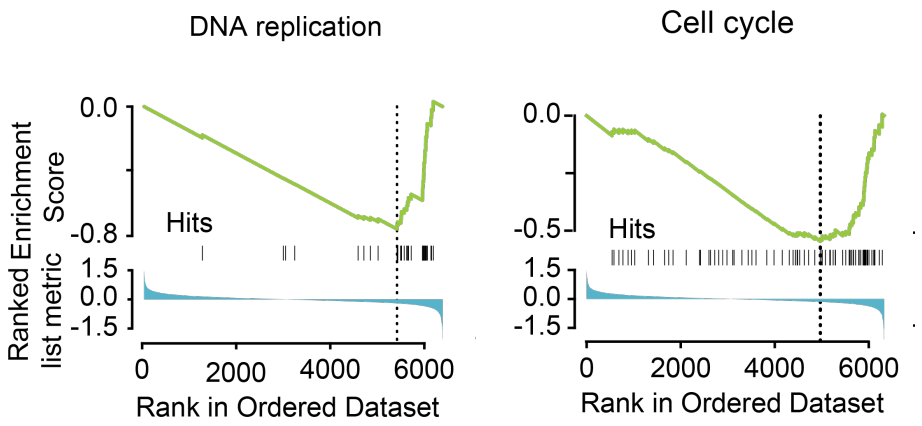
SMARCA4 mutant



SMARCA4 WT

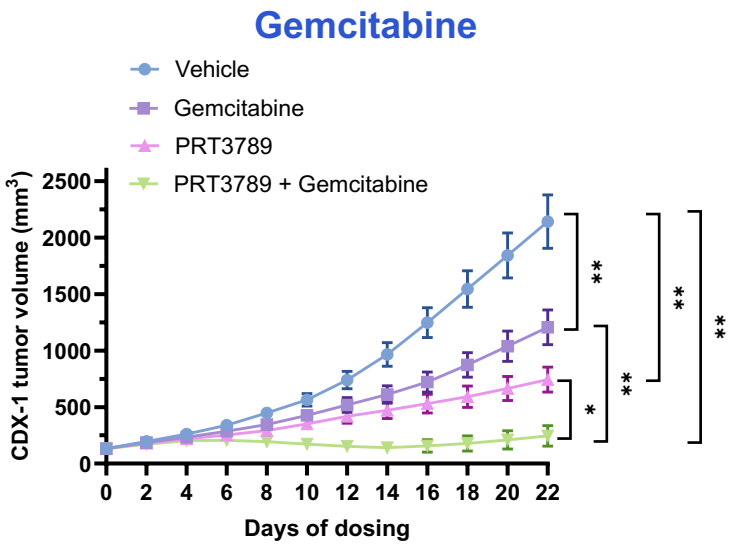
Presented at AACR 2023; https://preludetx.com/wp-content/uploads/2023/04/Hulse_SMARCA2_AACR-2023_Poster-6270_04APR23.pdf
Presented at AACR 2022; https://preludetx.com/wp-content/uploads/2022/05/Prelude_AACR_Hulse-SMARCA2-FINAL-21Mar2022.pdf

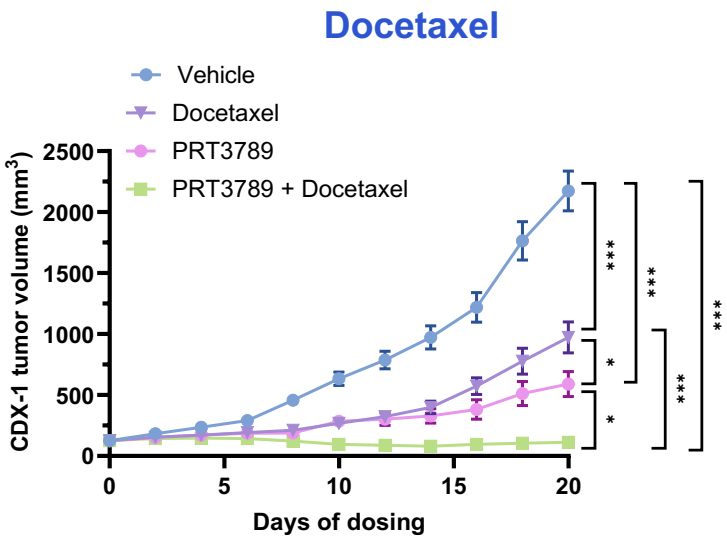
PRT3789 demonstrates potential for synergy with chemotherapy and apoptosis-inducing agents



FEN1, LIG1, MCM, PCNA, POLA1/2, POLD1/2/3, POLE/2/3

BUB1B, CCNA2/B2, CDC25C, CDK1/2, CHEK1/2





AACR 2022, 2023

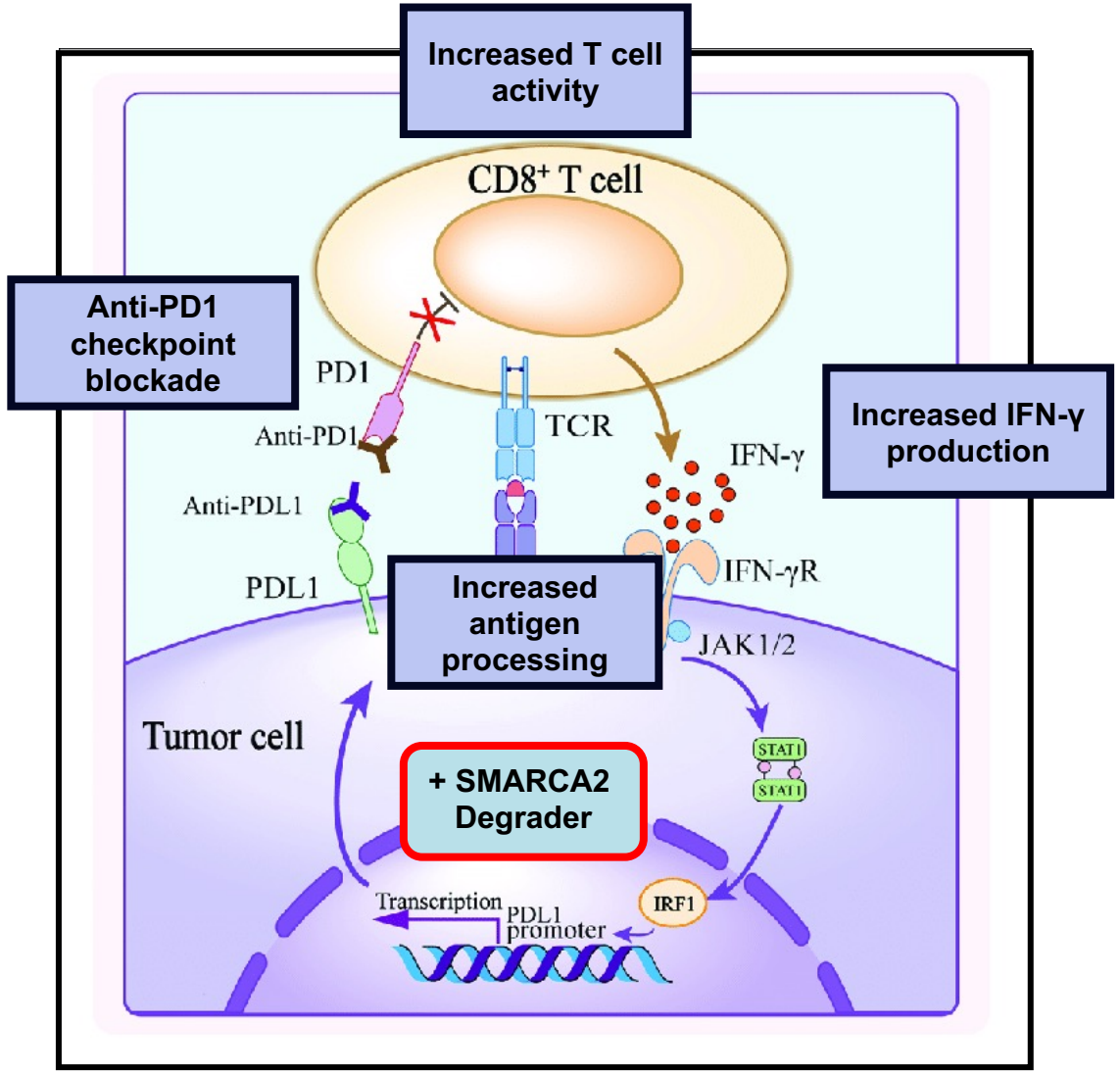
Several oncogenic gene sets regulated by PRT3789

Supports combination strategies with both cytotoxic and apoptosis-inducing agents (*e.g.*, RAS)

***In vivo* CDX models show strong tumor regression in combination with gemcitabine or docetaxel**

SMARCA degraders may also have synergy with and help to potentiate PD1/PDL1 immunotherapy

"Turning Cold Tumors Hot"



In SMARCA4-deficient cancer cell lines, SMARCA2 degradation…

Induces presentation of unique MHC-I peptide

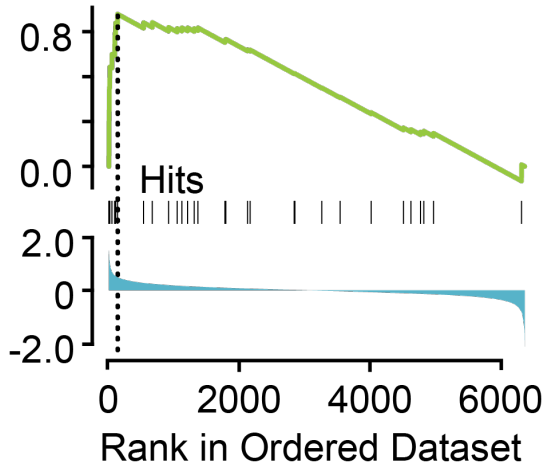
Upregulates antigen processing and presentation machinery

Increases cytokine production

Promotes T-cell activity and accelerates tumor cell killing

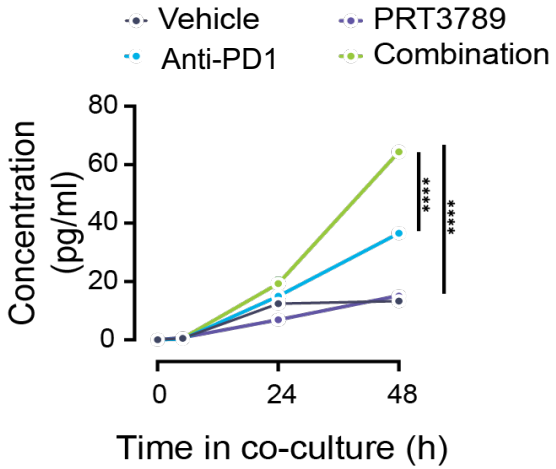
Preclinical data for PRT3789 support rationale for anti-PD1 combination

PRT3789 Upregulates Genes for Antigen Processing and Presentation

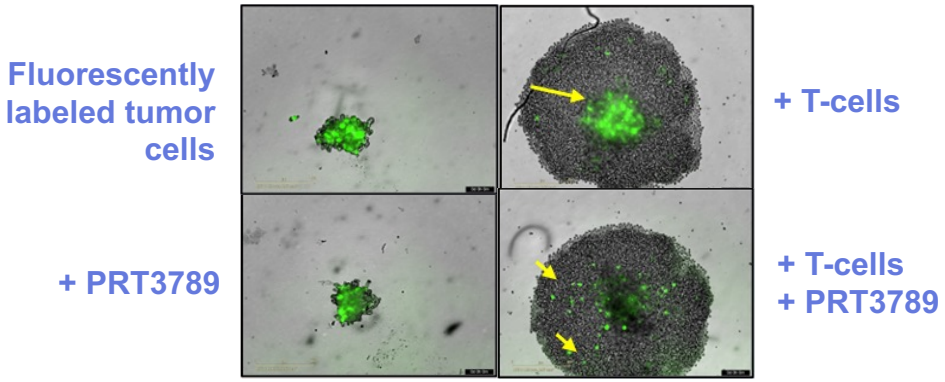


TAP1/2, HLA-A/C/G/F, B2M

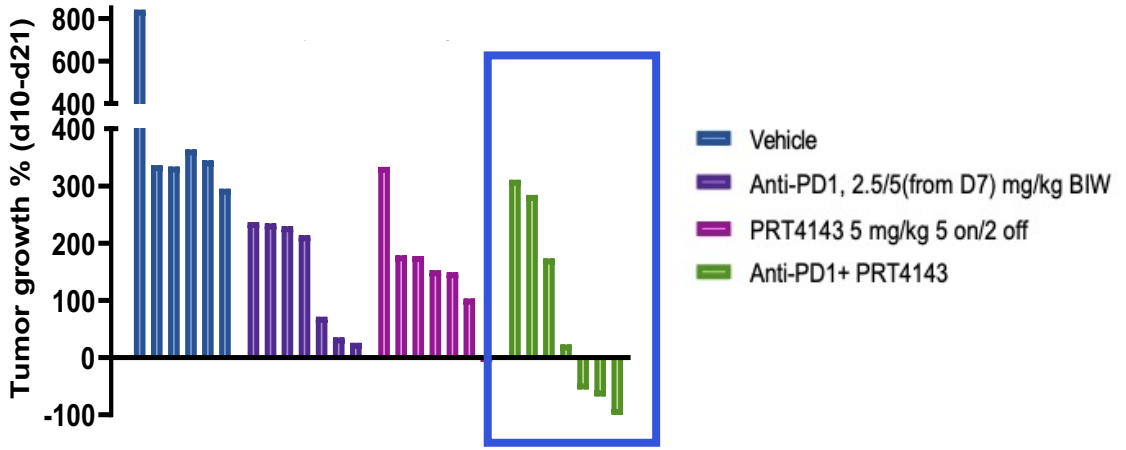
PRT3789 Increases IFN-g Levels in Combination with anti-PD1 *In Vitro*



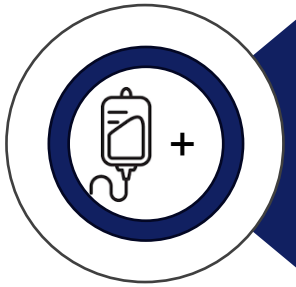
PRT3789 Promotes T-cell mediated Tumor Cell Killing *In Vitro*



SMARCA2 Degrader + Anti-PD1 Demonstrates Tumor Regression *In Vivo*

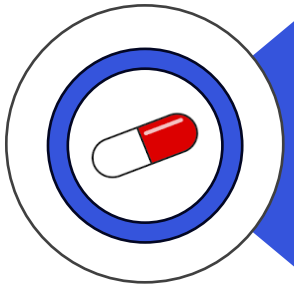


PRT3789 was the industry's first selective SMARCA2 degrader to enter the clinic



Lead SMARCA2 Degrader (PRT3789)

- ✓ Highly potent, selective degrader with once-weekly IV dosing
- ✓ Phase 1 trial underway, advancing well in clinic
- ✓ Generally well tolerated with no dose limiting toxicities observed to date
- ✓ Synergy with chemotherapy and immunotherapy



Oral SMARCA2 Degrader (PRT7732)

We solved SMARCA2 selectivity challenge >1000 fold

- Targeting SMARCA2 has been challenging due to the high homology between SMARCA2 and SMARCA4
- We have identified both IV and oral candidates with sub-nanomolar degradation potencies and high selectivity for SMARCA2 over SMARCA4
- Our lead program, PRT3789, is the first selective SMARCA2 degrader to enter clinical development
- Preclinical data for ‘3789 shows significant tumor regression in animal models, favorable safety, and high potential for chemoimmunotherapy synergy

Key Takeaways

Discovery Deep Dive: Prelude's Oral SMARCA2 Degrader (PRT7732)

Andrew Combs, Ph.D.
Chief Chemistry Officer
Prelude Therapeutics

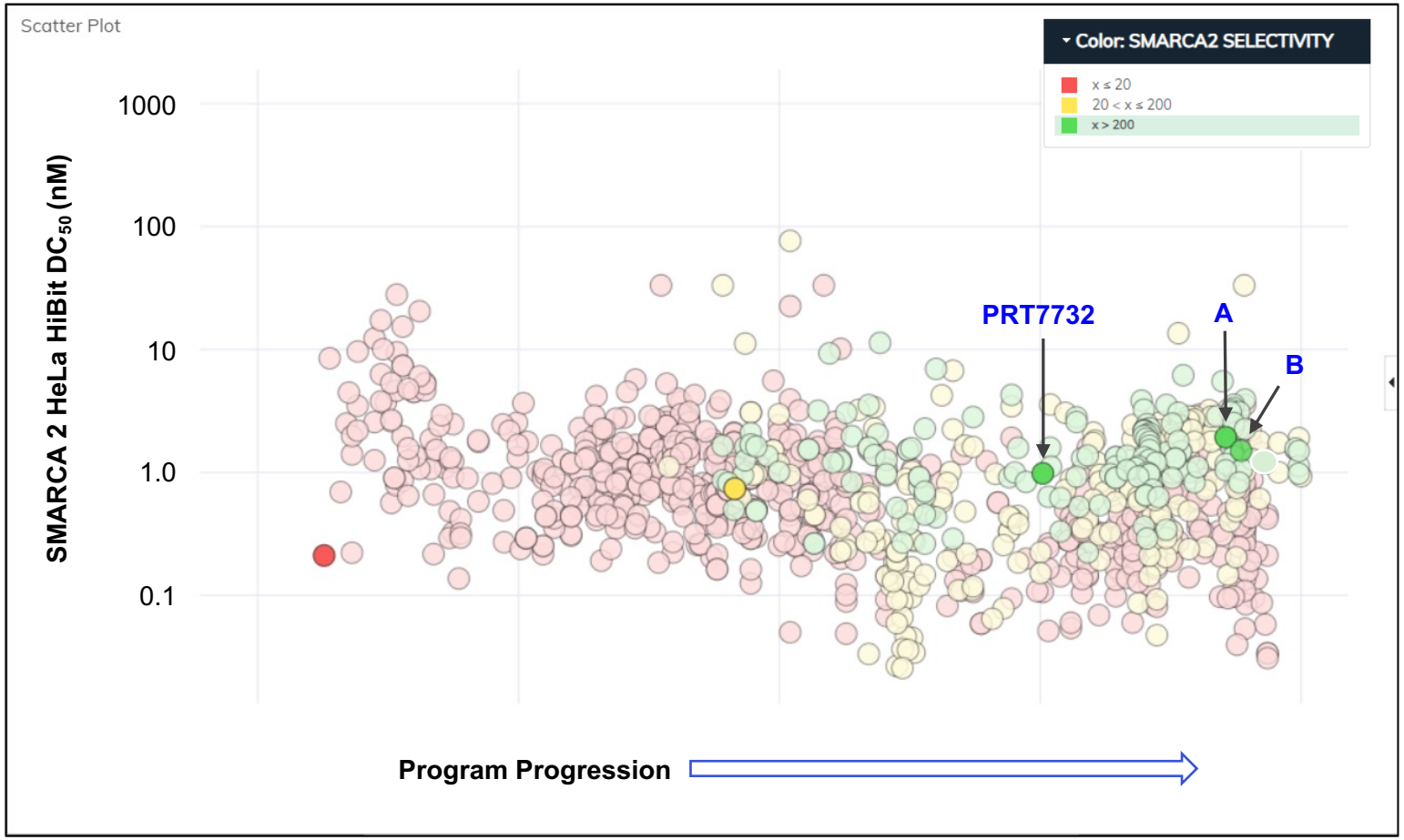
Peggy Scherle, Ph.D.
Chief Scientific Officer
Prelude Therapeutics

Learning Objectives

- What is the status of our oral SMARCA2 degrader program, and lead oral candidate PRT7732?
- Where is the science leading us next to further expand the reach of our SMARCA portfolio for patients?

Our SMARCA2 oral degrader program has progressed rapidly and systematically

SMARCA2 HiBit DC_{50} & SMARCA4 Selectivity



*Inactive & weakly potent compounds removed for clarity

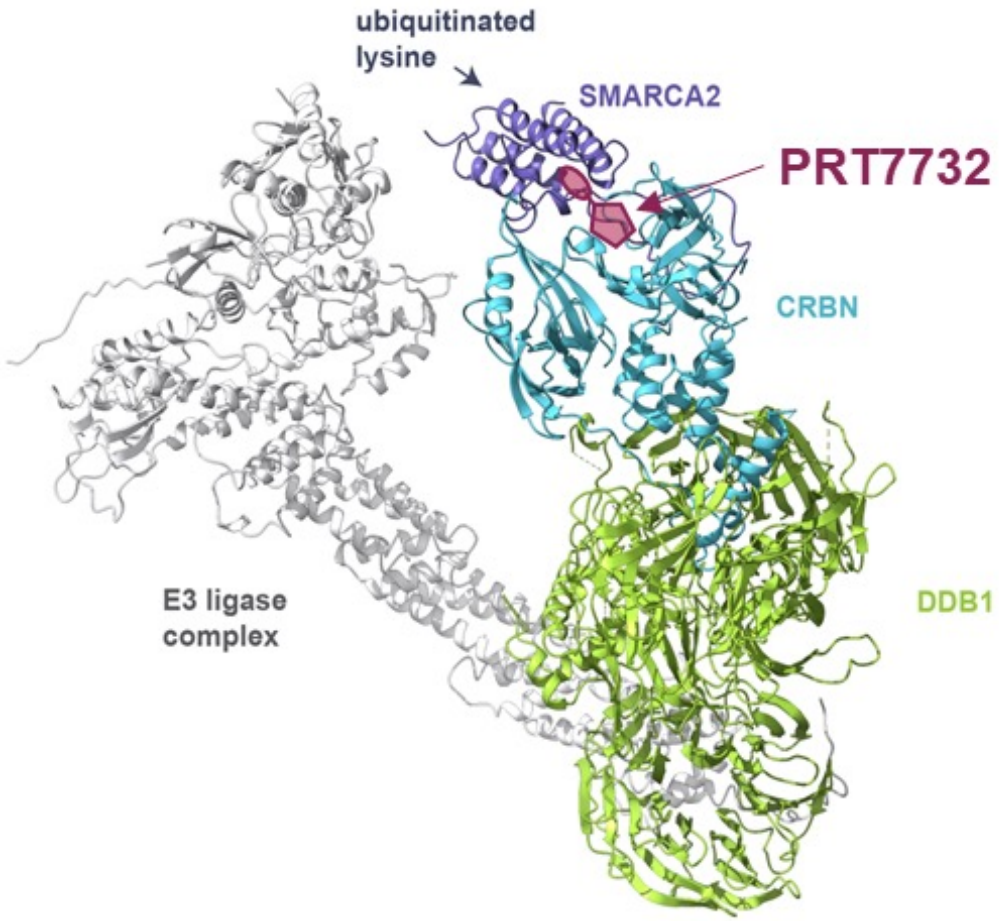
Solving for potency, selectivity and oral bioavailability was a challenge

PRT7732: Lead Oral Candidate with >3000-fold Selectivity

A and B: Two additional structurally distinct oral back-up candidates

PRT7732: Our Lead Oral SMARCA2 Degrader

Tertiary Complex of SMARCA2/ PRT7732/CRBN-DDB1 E3 Ligase



Source: Shvartsbart, K. Ito et al., AACR Poster, April 2024. Available here: Preclinical Characterization Of PRT7732: A Highly Potent, Selective, And Orally Bioavailable Targeted Protein Degrader Of SMARCA2

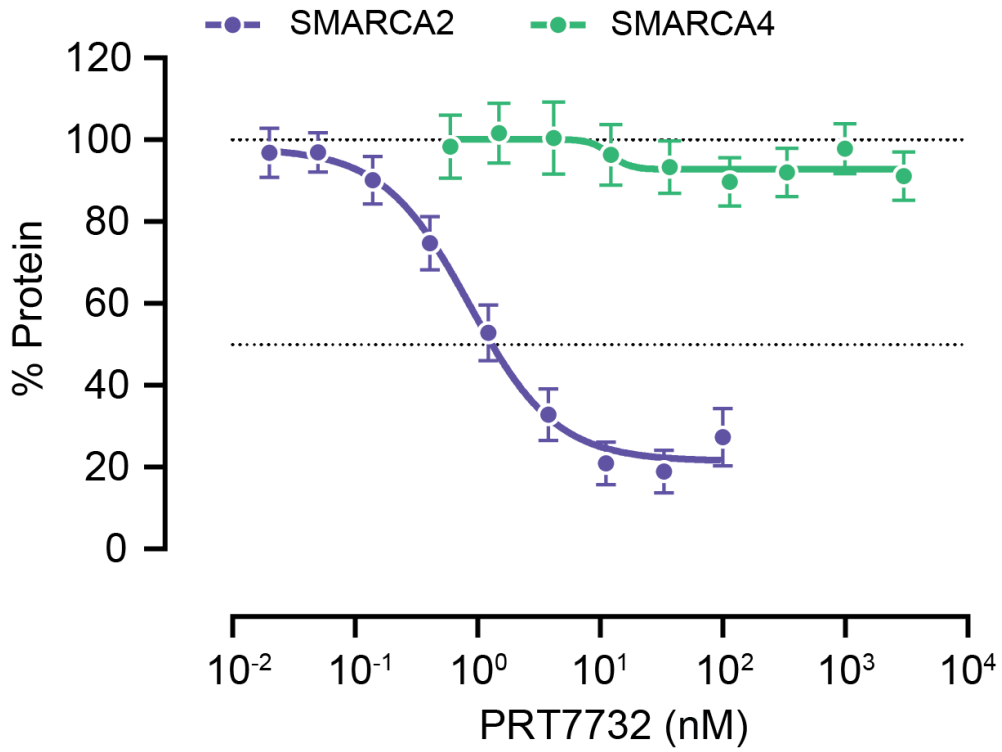
PRT7732 binds to the SMARCA2 bromodomain and CRBN-DDB1 E3 ligase complex

PRT7732 has been shown to catalyze the polyubiquitination of unique lysine residues expressed only in SMARCA2 and not SMARCA4

Unique conformational bias promotes selective ubiquitination and degradation of SMARCA2

PRT7732 is highly potent and orally bioavailable with near-absolute selectivity for SMARCA2

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



* Based on highest concentration tested

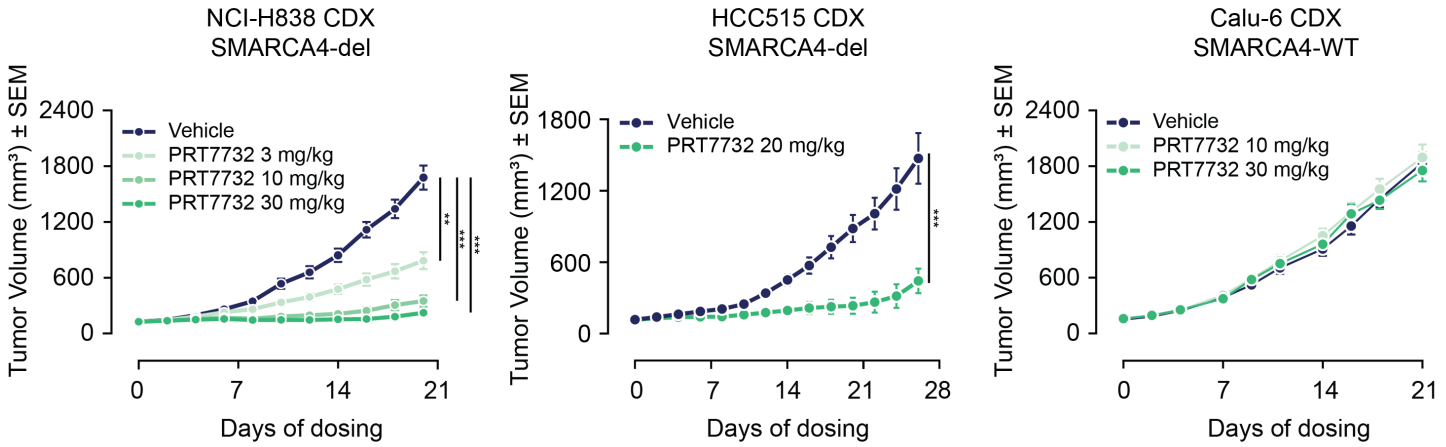
Source: Shvartsbart, K. Ito et al., AACR Poster, April 2024. Available here: Preclinical Characterization Of PRT7732: A Highly Potent, Selective, And Orally Bioavailable Targeted Protein Degrader Of SMARCA2

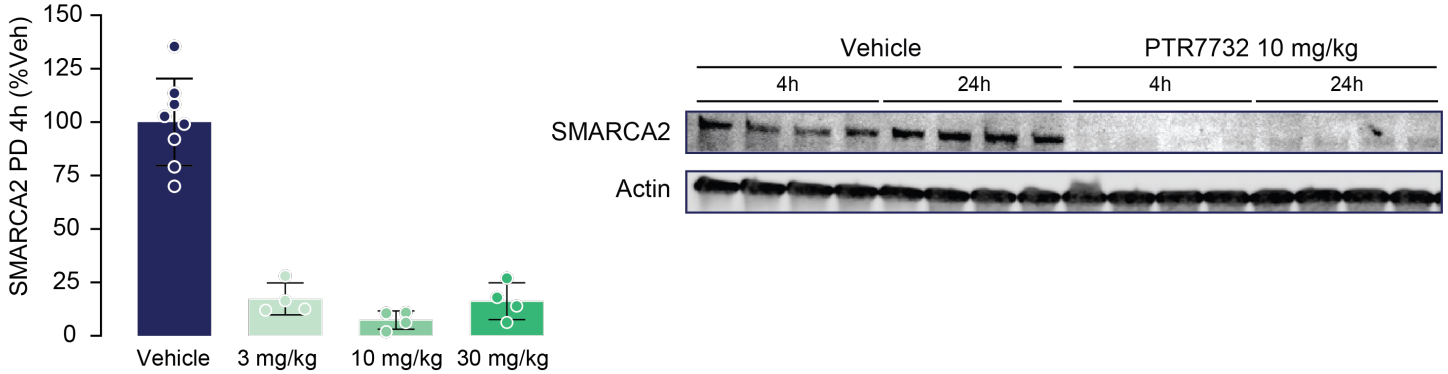
Sub-nanomolar SMARCA2 degradation potency

Near-absolute cellular selectivity for SMARCA2 vs SMARCA4 (>3000 fold) in HiBit cell lines and >1000-fold in cell proliferation assays

Good oral bioavailability across species

PRT7732 has significant anti-tumor activity in SMARCA4-deficient cancer xenograft models



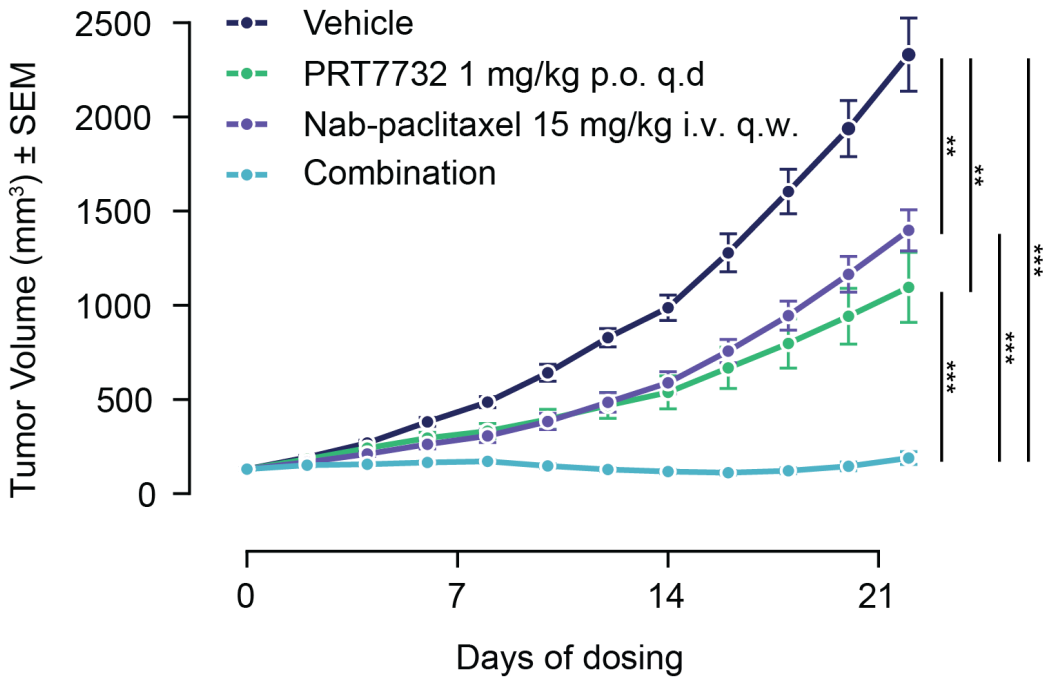


Daily oral administration of PRT7732 inhibits growth of SMARCA4-deficient tumors but not SMARCA4 WT tumors

PRT7732 decreases SMARCA2 protein levels in NCI-H838 tumor tissues

Source: Shvartsbart, K. Ito et al., AACR Poster, April 2024. Available here: Preclinical Characterization Of PRT7732: A Highly Potent, Selective, And Orally Bioavailable Targeted Protein Degrader Of SMARCA2

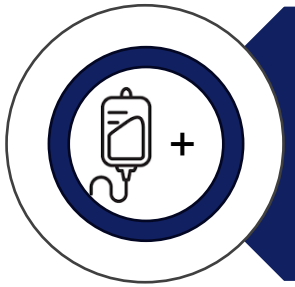
PRT7732 also shows high potential for synergy with other common anti-cancer agents



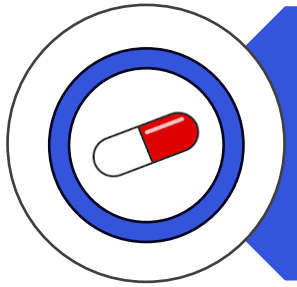
Oral daily administration of PRT7732 1 mg/kg in combination with nab-paclitaxel (Abraxane®) induces tumor regression in the NCI-H838 tumor model in mice

Source: Shvartsbart, K. Ito et al., AACR Poster, April 2024. Available here: Preclinical Characterization Of PRT7732: A Highly Potent, Selective, And Orally Bioavailable Targeted Protein Degrader Of SMARCA2

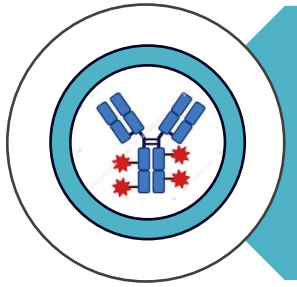
Expanding our portfolio of SMARCA-targeted therapeutics



Lead SMARCA2 Degrader (PRT3789)



Oral SMARCA2 Degraders (PRT7732)



SMARCA Degrader-Antibody Conjugates (“DACs”)

Prelude is continuing to lead the field

- Our lead oral SMARCA2 degrader PRT7732 shows >3000-fold selectivity and a PK/PD profile supporting a low-mg once daily projected human dose
- PRT7732 is advancing to Phase I in 2H 2024
- SMARCA Degrader-Antibody-Conjugates (“DACs”) have potential to dramatically expand the reach of this platform, including patients without SMARCA4 mutations

Key Takeaways

Clinical Experience with SMARCA4-*mutated* NSCLC

Dr. Adam Schoenfeld
Memorial Sloan Kettering Cancer Center

Learning Objectives

- How is SMARCA4-*mutated* advanced NSCLC treated today?
- What has been our clinical experience in treating these patients?
- Where would a SMARCA2 degrader fit in clinical practice? How could it change SoC?
- Where is the unmet need greatest in the treatment of advanced NSCLC?

SMARCA4 mutations occur in ~10% of all NSCLC and to varying degrees across other cancers

NSCLC: 10%

Squamous cell lung: 8%

Esophageal: 8%

Colorectal: 6%

Gastric: 8%

Pancreatic: 3%

Endometrial: 13%

Urinary: 9%

Types of mutations:

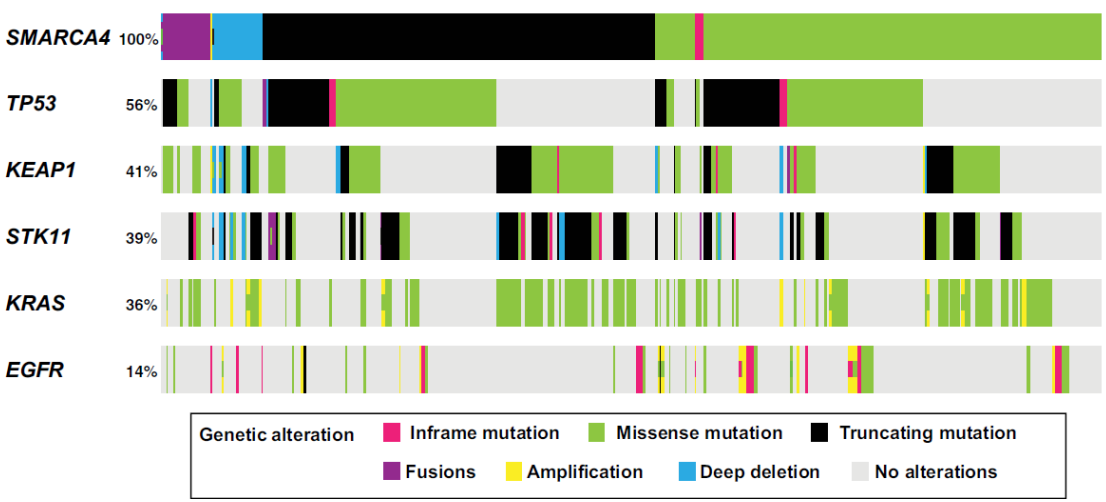
Class I (Loss-of-function)

Class II (Missense, other)

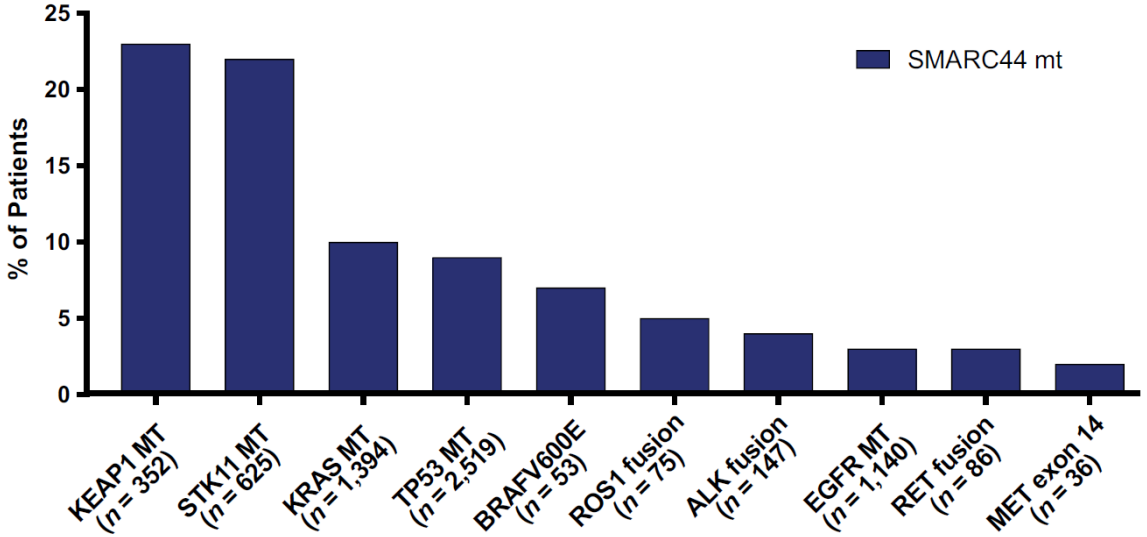
[1]Dagogo-Jack et al. Journal of Thoracic Oncology. 2020 Foundation Medicine dataset

SMARCA4 mutations are sometimes concurrent with other driver oncogenes

Most Frequent Co-Occurring Mutations



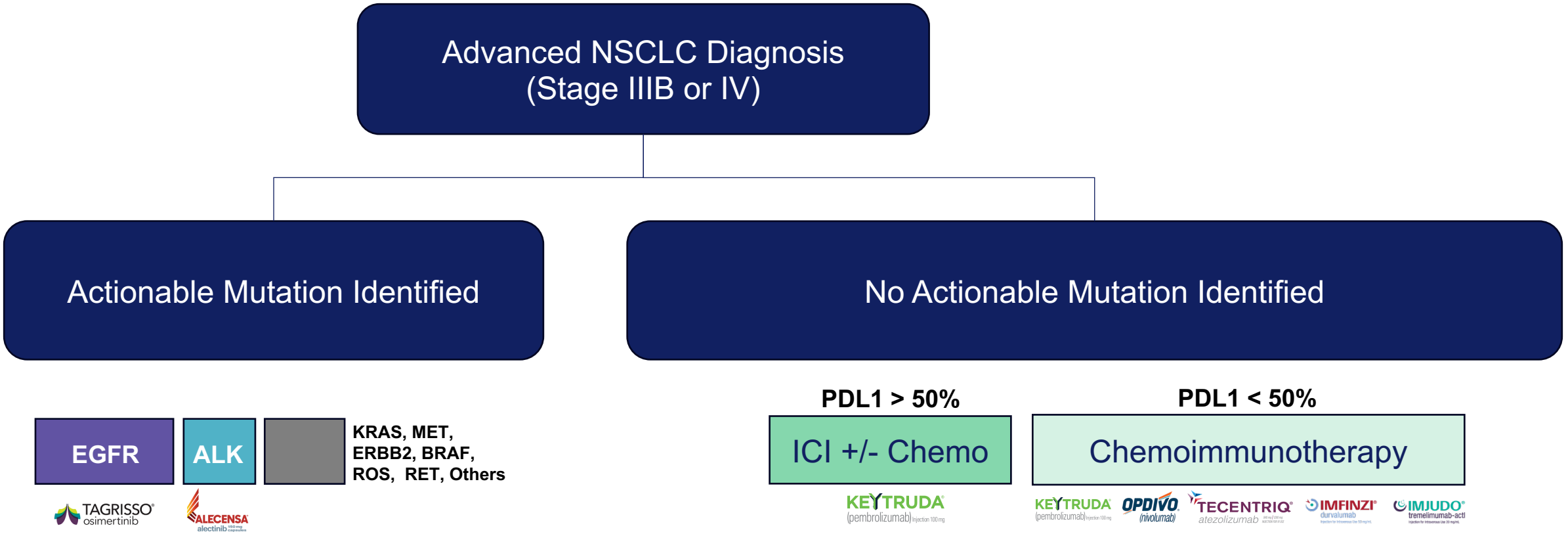
Distribution of *SMARCA4* Mutation by Commonly Altered Gene Subgroup



Schoenfeld et al. *Clin Cancer Res.* (2020); 26(21):5701-5708.

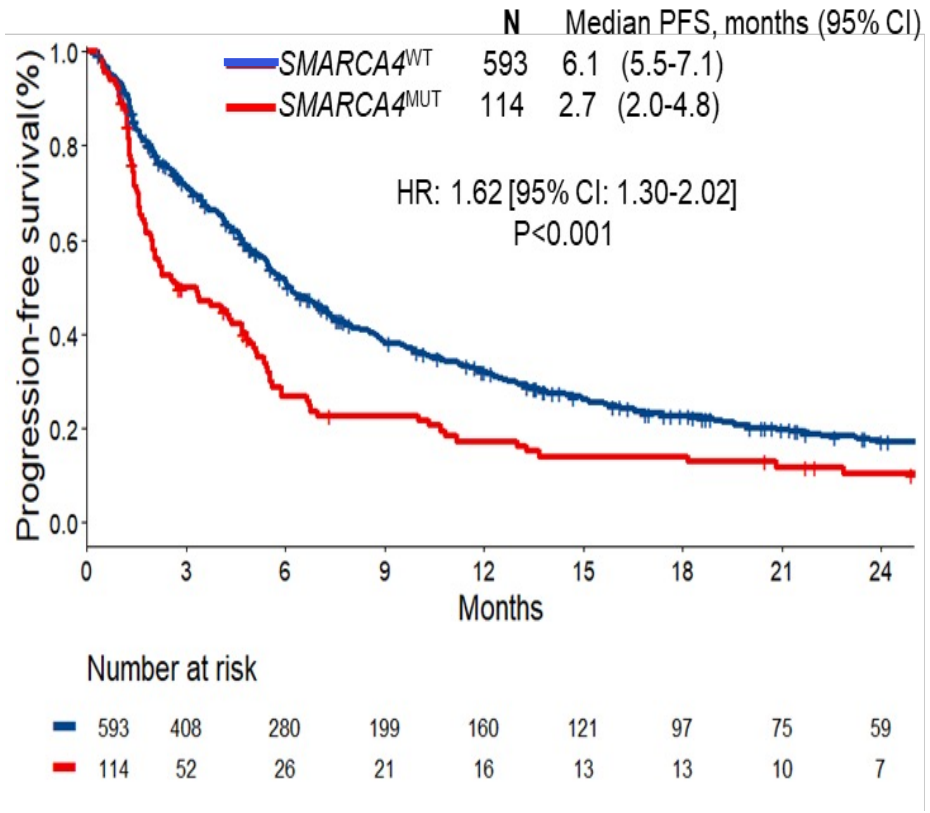
Prelude THERAPEUTICS

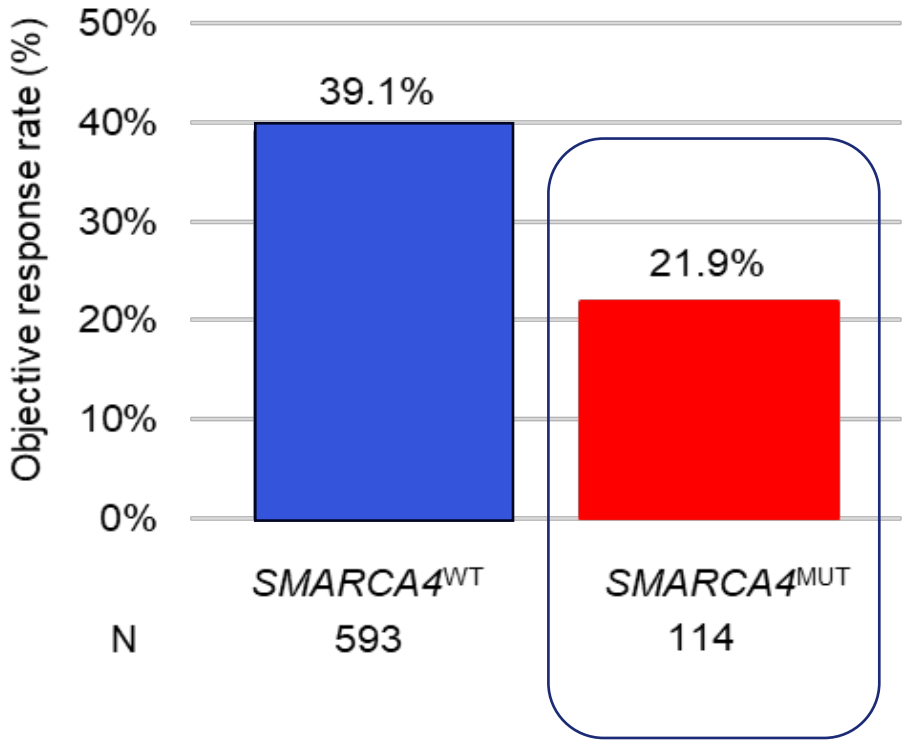
Majority of advanced NSCLC patients are currently treated with chemoimmunotherapy



Note: Simplified schematic based on current ESMO and NCCN Clinical Practice Guidelines and current clinical experience at MSKCC

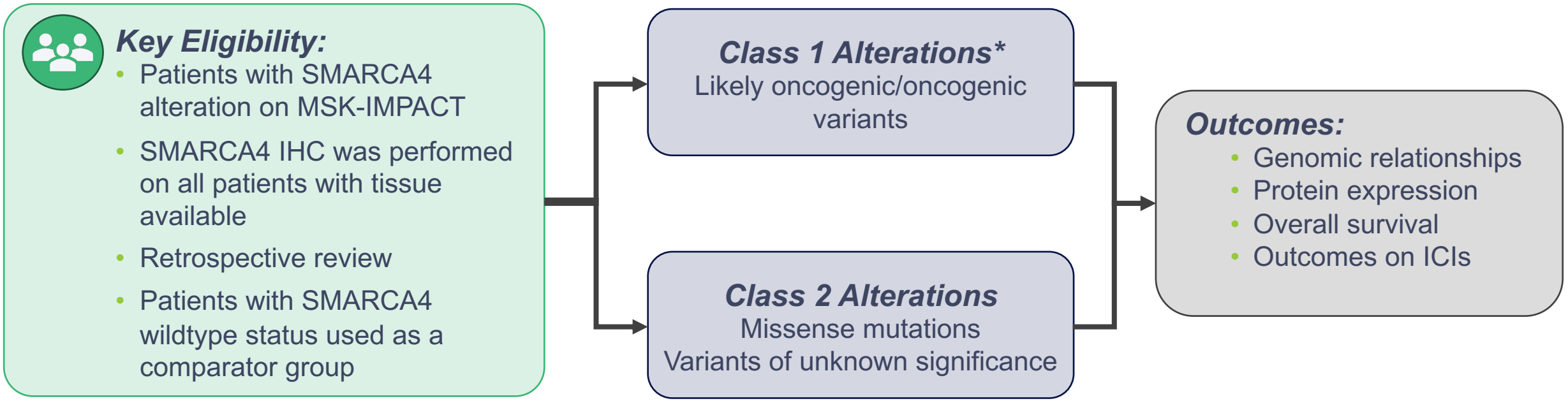
SMARCA4-*mutated* NSCLC patients have significantly worse prognosis





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 (attached).

Impact of SMARCA4 mutations on clinical outcomes for NSCLC patients

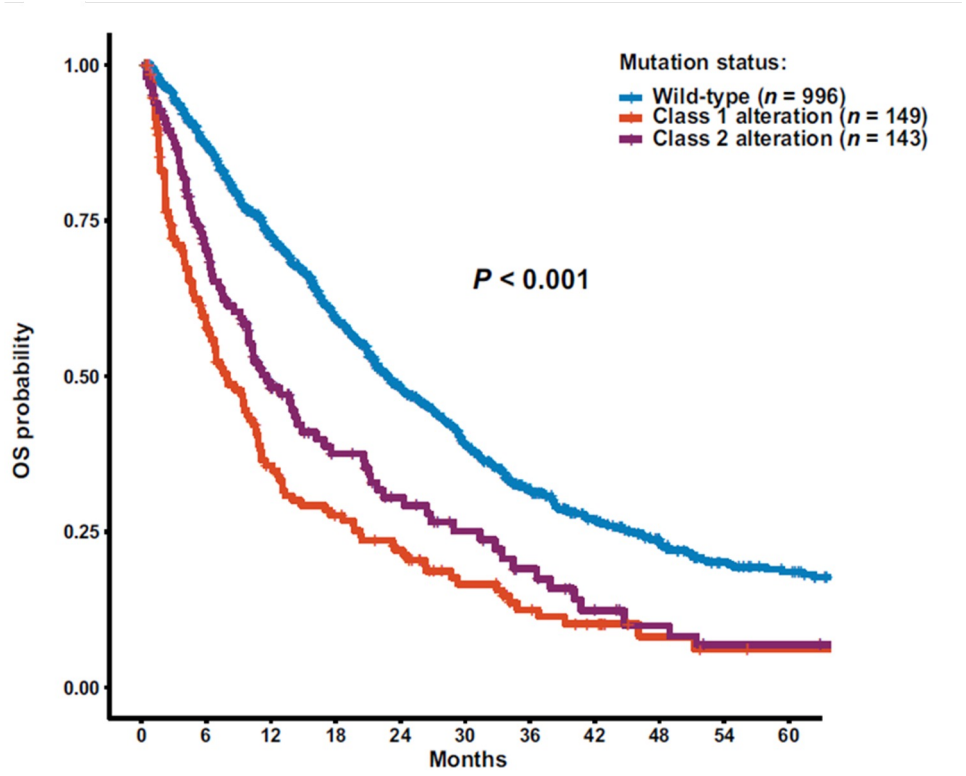


* Class 1 includes chromosomal rearrangements, truncating mutations, and likely oncogenic variants as determined by Oncokb

Schoenfeld et al. *Clin Cancer Res.* (2020); 26(21):5701-5708.

SMARCA4-*mutated* NSCLC patients (Class I & II) associated with worse prognosis

OS Among All Patients

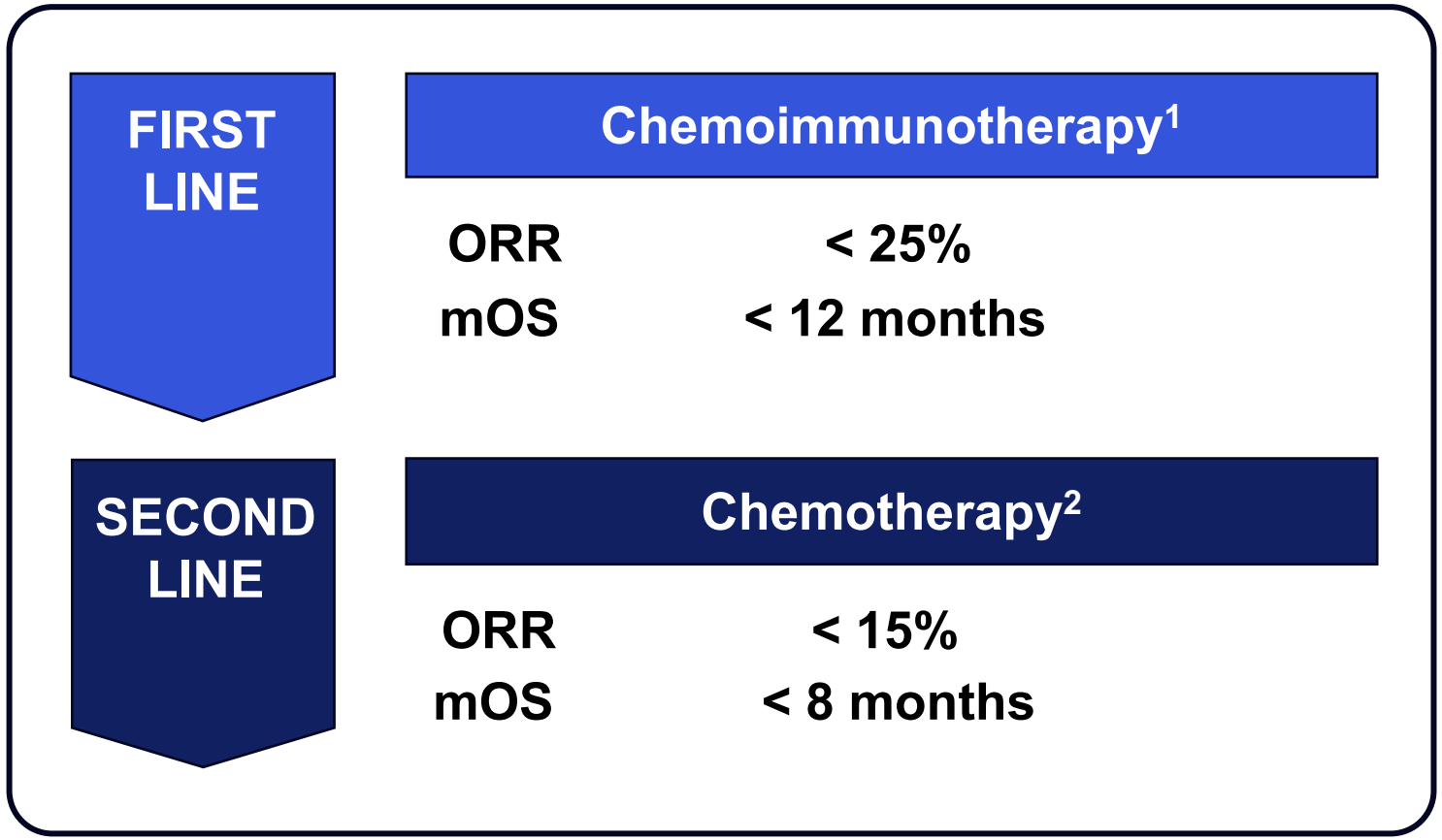


N = 1288	Hazard Ratio	95% CI	p value
SMARCA4 mutation type			<0.001
Wild type	--	--	
Class 2	2.01	1.58, 2.55	
Class 1	1.59	1.25, 2.04	
Sex			0.2
Female	--	--	
Male	1.12	0.95, 1.31	
Age (10 years)	1.22	1.13, 1.32	<0.001
Smoking status			0.005
Never smoker	--	--	
Former light (<15 pack-year)	1.58	1.23, 2.03	
Former heavy (>15 pack year)	1.21	0.96, 1.51	
Current smoker	1.27	0.96, 1.69	
Histology			<0.001
Adenocarcinoma	--	--	
Non-adenocarcinoma	1.79	1.38, 2.33	
Tumor mutation burden (TMB)	0.98	0.97, 0.99	<0.001
STK11			<0.001
Negative	--	--	
Positive	1.52	1.23, 1.88	
KEAP1			0.036
Negative	--	--	
Positive	1.26	1.02, 1.55	

Schoenfeld et al. *Clin Cancer Res.* (2020); 26(21):5701-5708.

Prelude THERAPEUTICS

Substantial unmet need in the treatment of patients with SMARCA4-*mutated* NSCLC



Response rates are less than 25% and expected median OS is less than a year

Even greater unmet need in 2nd line where fewer effective treatment options are available

[1] Response Rate and Survival Data: Schoenfeld et al. *Clin Cancer Res.* (2020); 26(21):5701-5708
[2] Second line estimates based on docetaxel label and clinical experience

There is high unmet need in NSCLC for patients with SMARCA4 mutations

- In NSCLC, SMARCA4 mutations are observed in ~10% of cases and are associated with more aggressive and invasive disease and shorter survival
- The majority of these patients are not eligible for other targeted therapies, and therefore are typically treated with chemoimmunotherapy combinations
- In patients with metastatic NSCLC, SMARCA4 mutations (both Class I & II) have been associated with poor prognosis when given first-line chemo-immunotherapy
- The unmet need is even greater in 2L NSCLC where few treatment options are approved

Key Takeaways

Prelude THERAPEUTICS

Clinical Development Plan & Future Directions

Jane Huang, M.D., President & Chief Medical Officer

Learning Objectives

- What is the current clinical development status of our SMARCA portfolio?
- What is the design of the PRT3789 Phase I trial and what have we learned to date?
- How are we thinking about the potential for monotherapy and combination approaches?
- What should we expect to see when interim Phase I data is released later this year?
- What could the future hold for the development of SMARCA2 degrader therapies over time?

Our first-in-class IV and oral SMARCA2 degrader programs are advancing

PROGRAM	POTENTIAL INDICATIONS	DISCOVERY	PHASE 1	PHASE 2/3	UPCOMING MILESTONES
Lead SMARCA2 Degrader *PRT3789*	Patients with SMARCA4-*mutated* advanced NSCLC and other cancers				**First Interim Phase I Data in 2H 2024**
Oral SMARCA2 Degrader *PRT7732*	Patients with SMARCA4-*mutated* NSCLC and other cancers				**File IND in 1H 2024; Phase I Start in 2H 2024**

+ Full pipeline includes programs against other cancer targets in active clinical or preclinical development

What is the design of the PRT3789 Phase 1 trial?

Study Population

Advanced, recurrent, or metastatic disease in solid tumors with *any* SMARCA4 mutation*

Dosing

PRT3789 IV once weekly for 3 weeks (1 cycle)

DLTs assessed during first 21 days of dosing during cycle 1

Dose Escalation + Backfill Cohorts + Expansion Cohorts

Monotherapy PRT3789 Dose Escalation^

- Dose level 1
- Dose level 2
- Dose level 3
- Dose level 4
- Dose level 5
- Dose level 6
- Dose level 7
- Dose level 8

Backfill Cohorts

Up to 10 participants in each cohort (minimum of 6 with NSCLC) with a SMARCA4 *loss-of-function* mutation

Criteria to Enroll Backfill Cohorts

1. All participants have cleared the DLT observation period; **AND**
2. An objective response per RECIST v1.1 has been observed; **OR**
3. The dose level is safe and biologically effective taking into account safety, PK, and pharmacodynamic data

Backfill cohorts allow for deeper assessment of clinical activity in the 6-8% of advanced NSCLC patients with SMARCA4 loss-of-function mutations

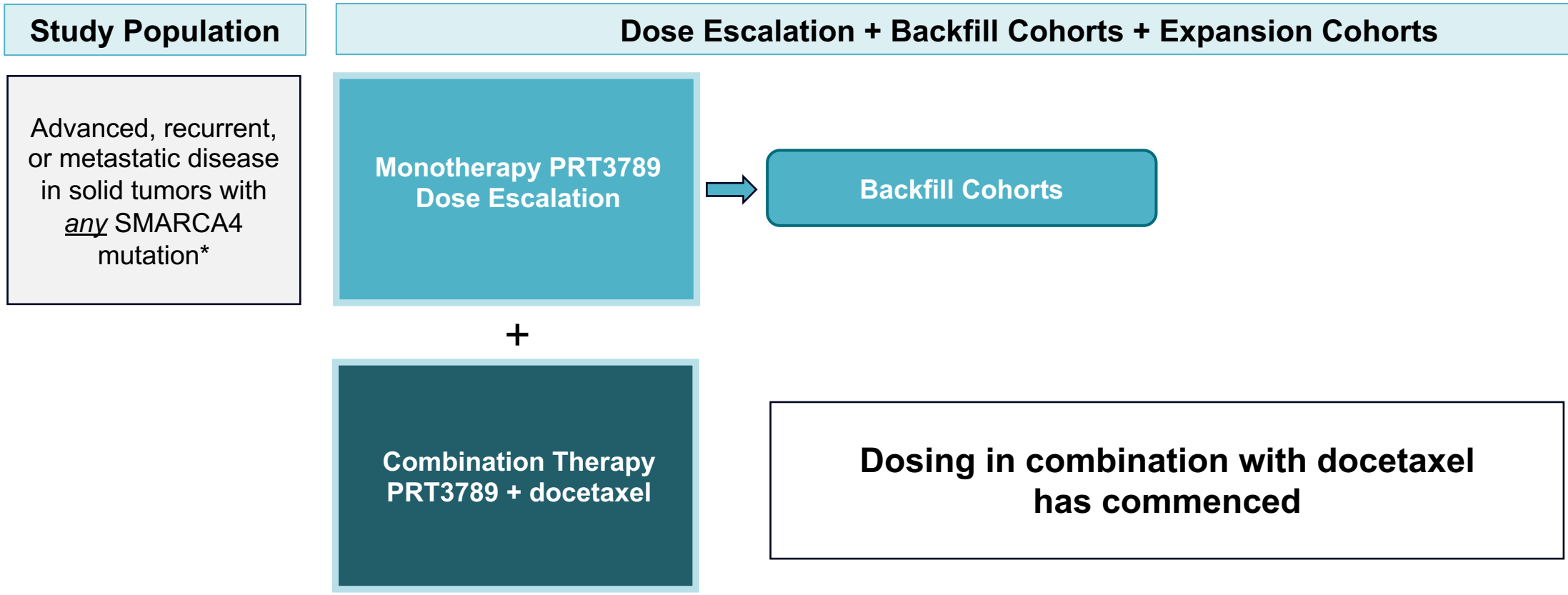
^ Dose Finding: Bayesian Optimal Interval (BOIN) Design Method

* *any* mutation (Class I or Class II), including participants with SMARCA4 *loss-of-function* mutation due to truncating mutation and/or deletion

ClinicalTrials.gov Identifier: NCT05639751; ESMO 2023 Poster: https://preludetx.com/wp-content/uploads/2023/10/Dagogo-Jack_ESMO-2023_PRT3789-01-TiP-Poster_Final_9Oct2023.pdf

Prelude THERAPEUTICS

Study expanded to evaluate potential for PRT3789 + docetaxel in combination



**any* mutation (Class I or Class II), including participants with SMARCA4 *loss-of-function mutation* due to truncating mutation and/or deletion.
ClinicalTrials.gov Identifier: NCT05639751; ESMO 2023 Poster: https://preludetx.com/wp-content/uploads/2023/10/Dagogo-Jack_ESMO-2023_PRT3789-01-TiP-Poster_Final_9Oct2023.pdf

Prelude THERAPEUTICS

What do we hope to learn from the Phase I study?

To evaluate the safety, tolerability, and dose limiting toxicities of PRT3789 and to determine the biologically active dose

To evaluate the antitumor activity of PRT3789

To evaluate the pharmacokinetic profile of PRT3789

To evaluate the pharmacodynamic effect of PRT3789

What should we expect to see when data is released later this year?

Initial Data Readout: 2H 2024

1. Initial safety and tolerability data for monotherapy dose escalation cohorts
2. Initial assessment of clinical activity across different tumor types at the various dosing levels under evaluation
3. Early look at pharmacokinetic profile and pharmacodynamic effects

Full Trial Results and Next Steps: 2025+

1. Full safety and tolerability data for monotherapy dose escalation, backfill, and chemotherapy combination cohorts
2. Detailed assessment of clinical activity for all trial participants
3. Detailed PK profile and PD effects including recommended Phase 2 dose
4. Engagement with regulators on potential registrational trial pathways

Future Directions: Expanding the patient impact of selective SMARCA2 degraders

1

Assess Combinations with Chemo, I/O or Other Targeted Therapies

SMARCA2 Degrader +

Chemotherapy *Immunotherapy*

Chemoimmunotherapy

Establish safety and efficacy in combination

Improve outcomes, expand utility across multiple lines

2

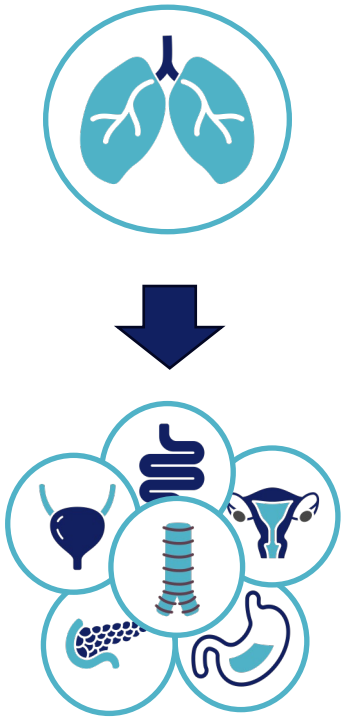
Generate Evidence in Earlier Stages of NSCLC (Adj. / Neo-Adj.)

Stage at Initial Diagnosis	Incidence (% of Pts)[1,2]	Treatment Modalities
Stage I / Stage IIA	~20-30%	Radiation and/or Resection → Adjuvant Tx
Stage IIB / Stage IIIA	~20-30%	Neo Adj. Tx → Resection → Adjuvant Tx
Stage IIIB/ Stage IV	~40-50%	Systemic Treatment

1. SEER 2022; 2. American Cancer Society – Cancer Facts & Figures

3

Generate Evidence Across Additional Tumor Types

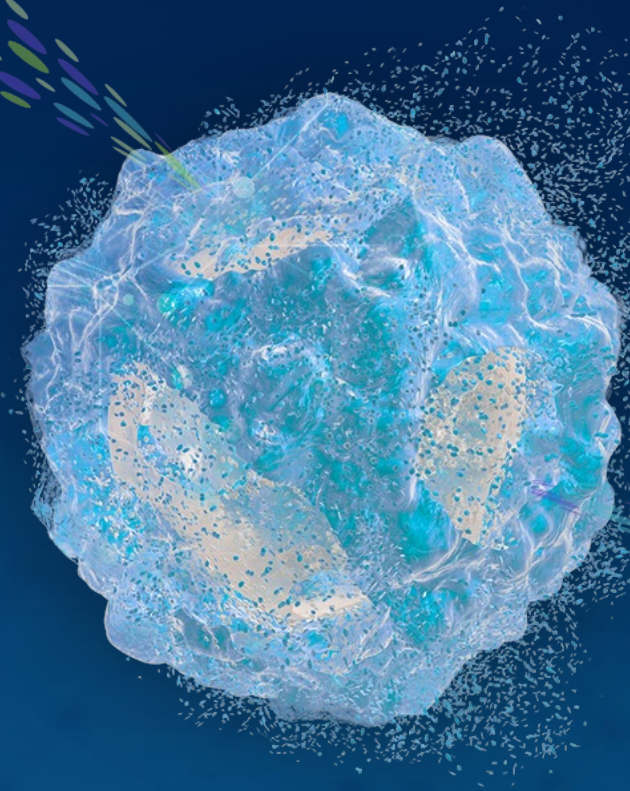


Prelude's first-in-class SMARCA2 degraders are advancing

- Prelude's lead SMARCA2 degrader PRT3789 is advancing well in the clinic with no dose limiting toxicities observed to date
- Initial Phase I data in 2H 2024 will be the industry's first look at safety and clinical activity for the SMARCA2 targeted approach
- PRT3789 represents our fastest path to address the high unmet need in advanced NSCLC
- PRT7732, our first-in-class oral degrader, will advance to Phase I start in 2H 2024 pending IND approval

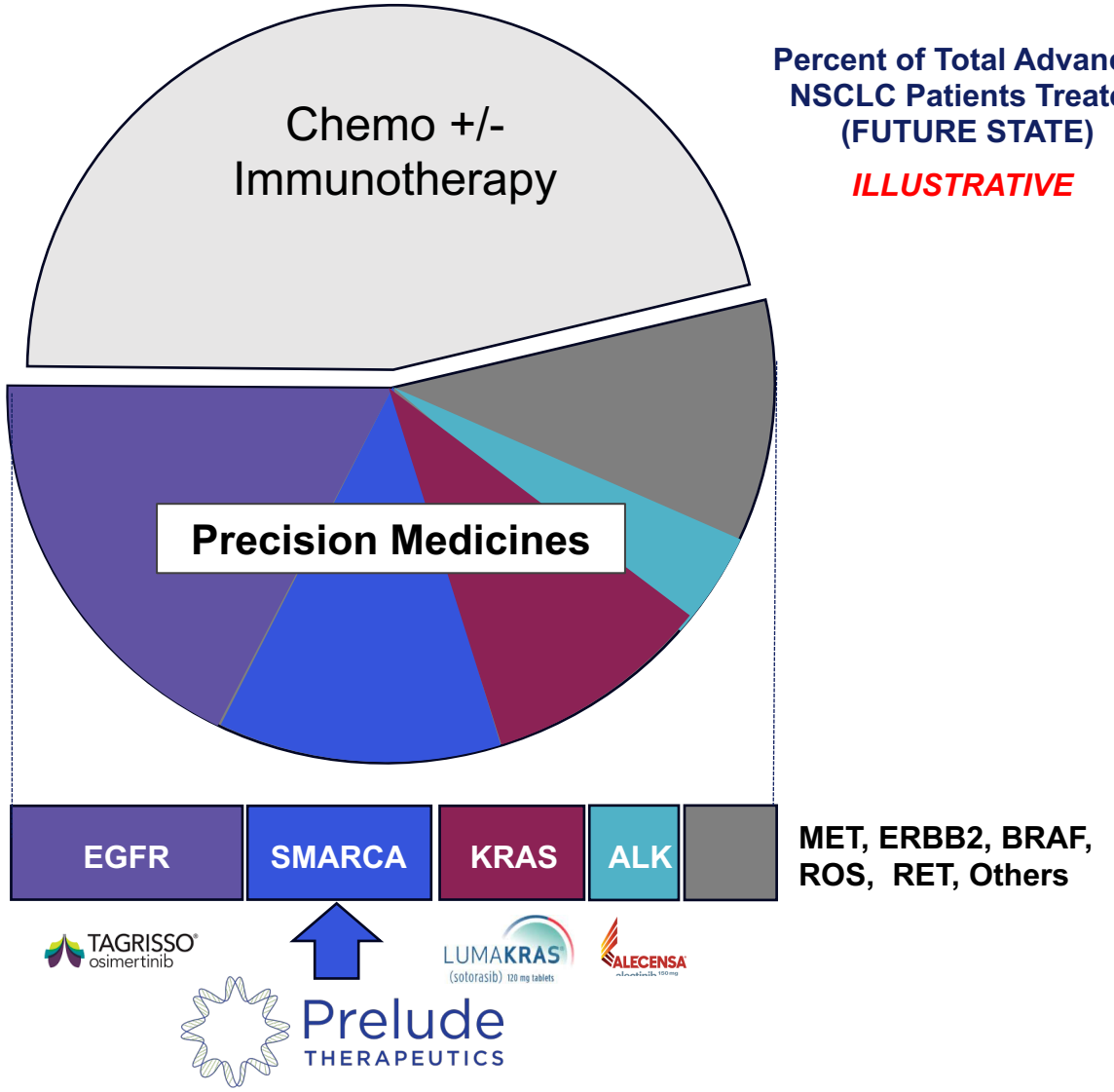
Key Takeaways

Highly Selective SMARCA2 Degraders:
Portfolio Strategy & Closing Remarks



- What could a highly selective SMARCA2 degrader mean for patients if we get this right?
- Why develop an IV version, oral versions, and Precision ADCs?
- What makes this is a strategic portfolio opportunity?

SMARCA has the potential to significantly expand precision medicine for even more NSCLC patients



Percent of Total Advanced NSCLC Patients Treated (FUTURE STATE)

ILLUSTRATIVE

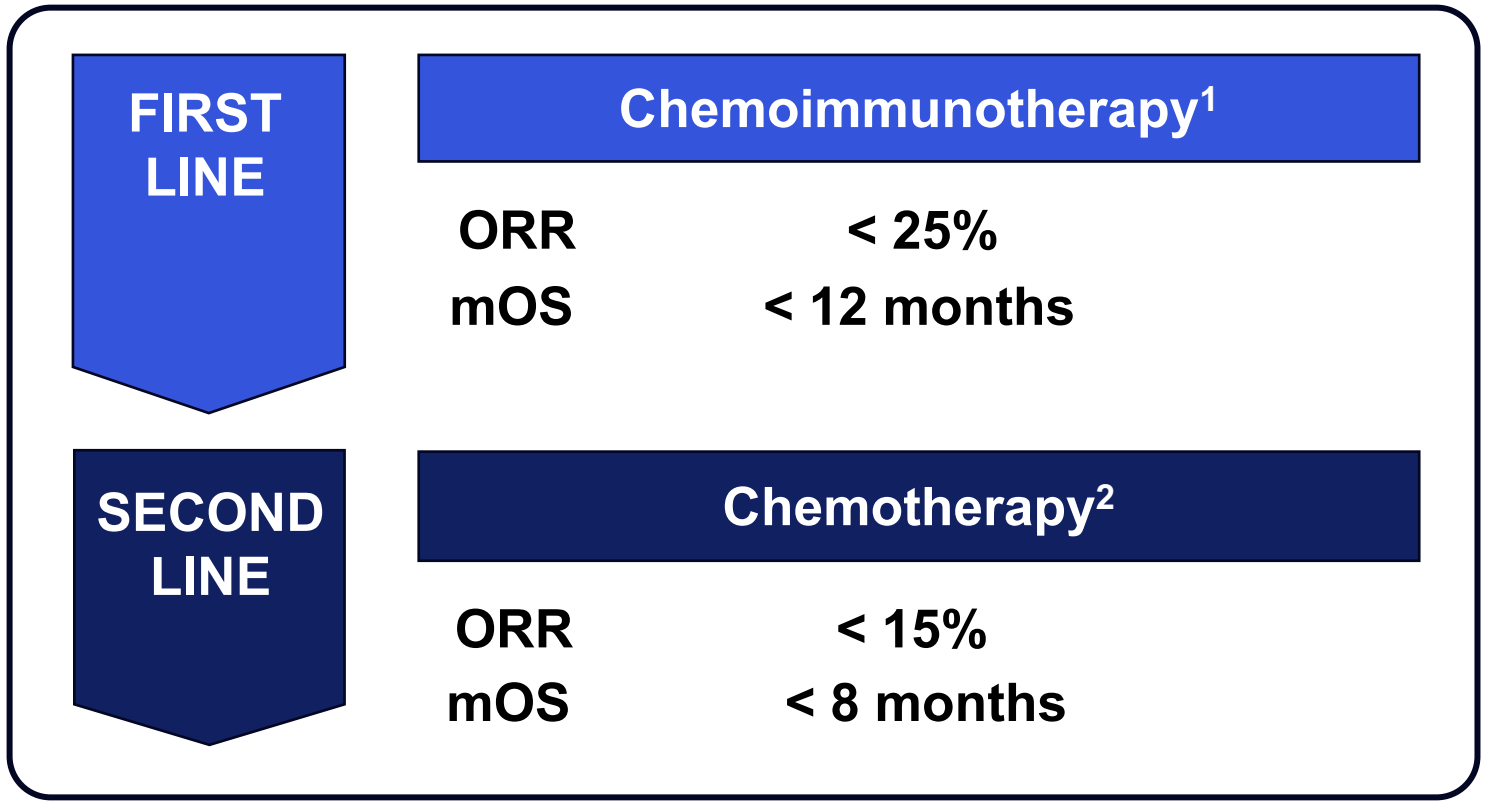
Potentially more patients than ALK, MET, BRAF, ROS and RET combined [1]

Reinforces need for comprehensive genomic profiling

More patients tested = More patients eligible

[1] Relative future utilization: Datamonitor 2023 Lung Cancer Report; Analysis on File

What could this mean for patients?

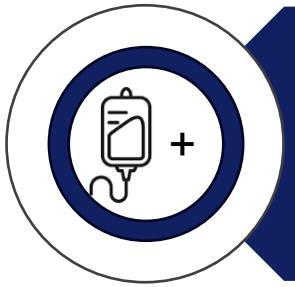


The prognosis for SMARCA4-*mutated* NSCLC patients is poor

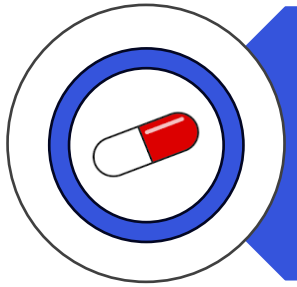
A selective SMARCA2 degrader has the potential to transform outcomes for these patients

[1] Response Rate and Survival Data: Schoenfeld et al. *Clin Cancer Res.* (2020); 26(21):5701-5708
[2] Second line estimates based on docetaxel label and clinical experience

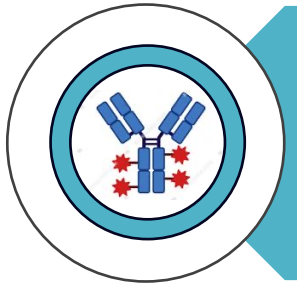
Why develop IV degraders, oral degraders, and “Precision ADCs”?



Lead SMARCA2 Degrader (PRT3789, IV)
- High unmet need supports seeking fastest possible path to approval
- Establishes proof-of-concept (mono or combo)
- Solidifies SMARCA as new standard of care



Oral SMARCA2 Degrader (PRT7732)
- Expands access for advanced NSCLC patients (first-line)
- Enables use in earlier stage disease (adjuvant / neo-adjuvant)
- Provides optionality across other SMARCA4-*mutated* cancers



SMARCA Degrader-Antibody Conjugates (“DACs”)
- All cancers depend on chromatin remodeling
- Independent of SMARCA4-mutation status
- Initial focus of AbCellera collaboration

What makes this such a strategic portfolio opportunity?

Addressable Patient Populations[1-4]

SECOND LINE	~150,000 pts/year	Up to 15,000 SMARCA4-*mutated*
FIRST LINE	~220,000 pts/year	Up to 22,000 SMARCA4-*mutated*
EARLIER STAGE (Adjuvant / Neo-Adj.)	~270,000 pts/year	Up to 27,000 SMARCA4-*mutated*

SMARCA4-*mutated*	TBD based on selected tumors[3,4]
Solid Tumors and/or Heme Malignancies	TBD based on antibody targets / tumor types

[1] US & EU5 only: Journal of Thoracic Oncology (US, 2021): https://doi.org/10.1016/j.jtho.2021.01.485; Globocan (EU5); [2] Datamonitor 2023 Lung Cancer Report; Analysis on File
[3] Schoenfeld et al. *Clin Cancer Res.* (2020); 26(21):5701-5708. [4] Dagogo-Jack et al. *J Thorac Oncol.* (2020); 15(5):766-776.

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- There is high unmet need in SMARCA4-*mutated* NSCLC (up to 10% of patients)
- These mutations are prevalent across a range of other cancers as well
- SMARCA2 is a promising new “synthetic lethal” target for these patients
- Targeting SMARCA2 is very challenging; selectivity over SMARCA4 is critical
- With PRT3789, our lead SMARCA2 degrader, Prelude scientists solved the selectivity challenge >1000-fold
- Industry-first clinical data validating this approach is coming soon
- Prelude’s first-in-class oral SMARCA2 degrader (PRT7732) and Precision ADCs further expand potential impact for patients

Key Takeaways

Prelude THERAPEUTICS

We are on a mission to extend the promise of precision medicine to every cancer patient

THANK YOU