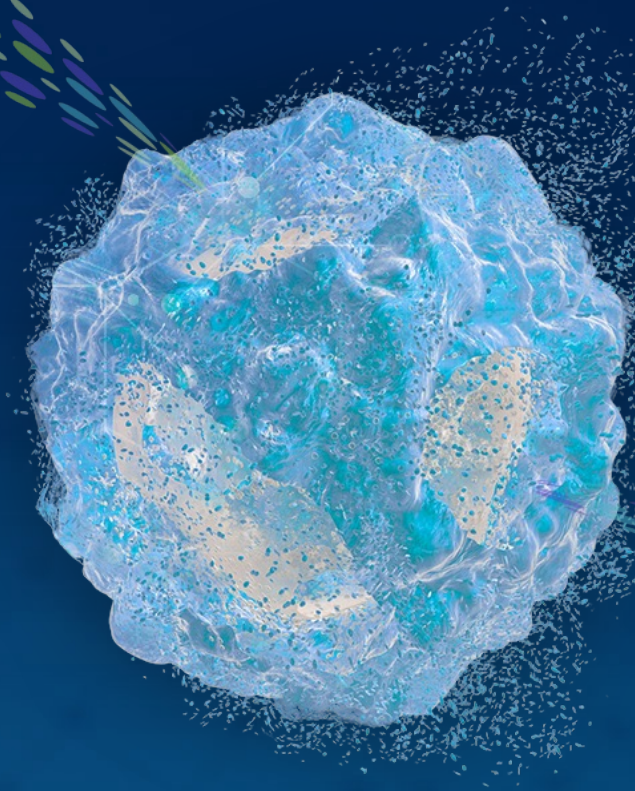
Highly Selective SMARCA2 Degraders



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).

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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)

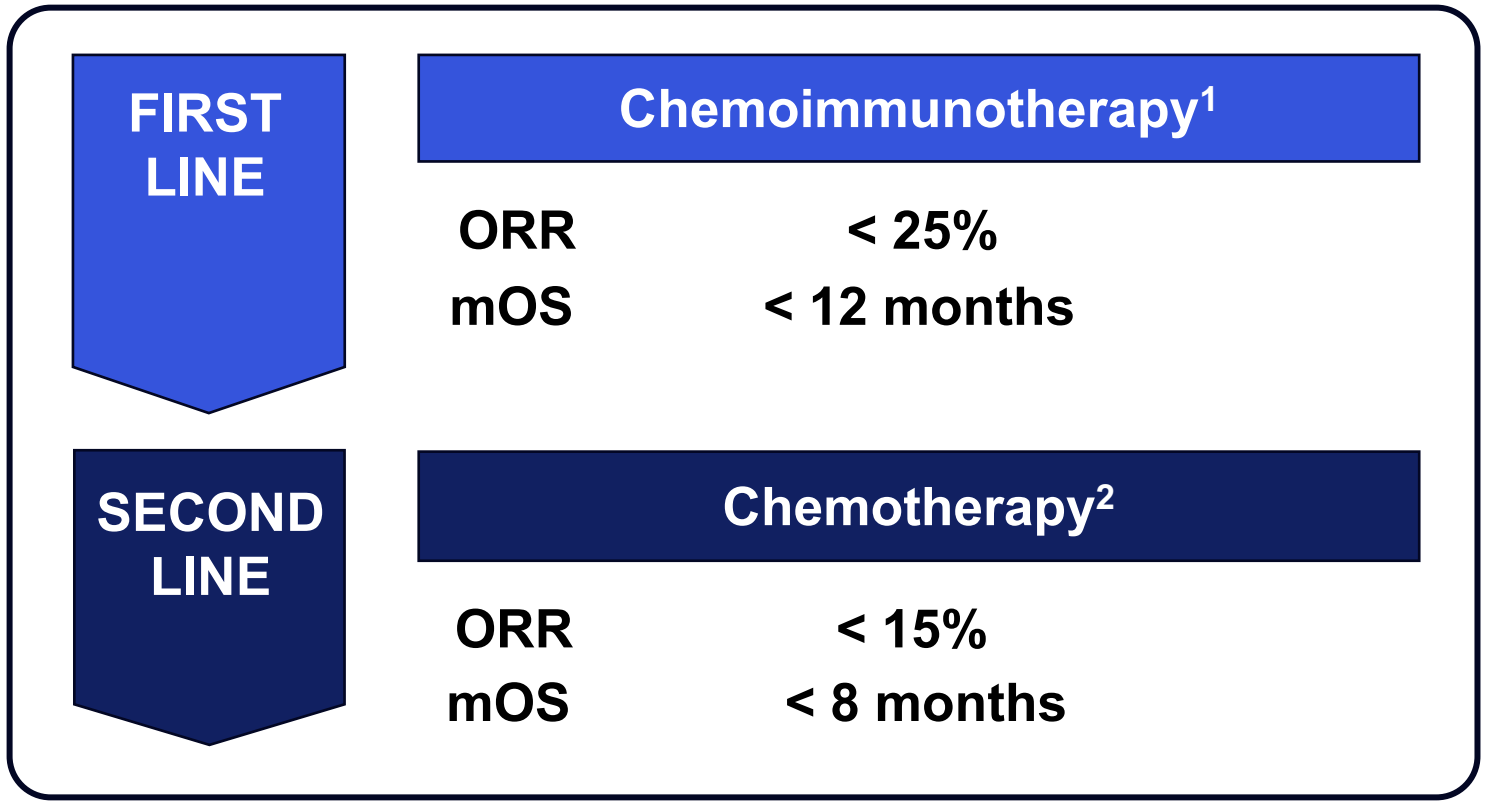
Brukinsa® zanubrutinib 80 mg capsules · CALQUENCE® (acalabrutinib) 100 mg capsules · VENCLEXTA® venetoclax tablets 10mg, 50mg, 100mg · GAZYVA® obinutuzumab injection | 1,000mg/40mL · Kadcyla® ado-trastuzumab emtansine · AVASTIN® bevacizumab 100 MG/4 ML INJECTION FOR IV USE

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