Prelude THERAPEUTICS

Clinical Development Plan & Future Directions

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Forward Looking Statements

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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

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Study expanded to evaluate potential for PRT3789 + docetaxel in combination

Study Population

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

Dose Escalation + Backfill Cohorts + Expansion Cohorts

Monotherapy PRT3789 Dose Escalation → **Backfill Cohorts**

+

Combination Therapy PRT3789 + docetaxel

Dosing in combination with docetaxel has commenced

**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

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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

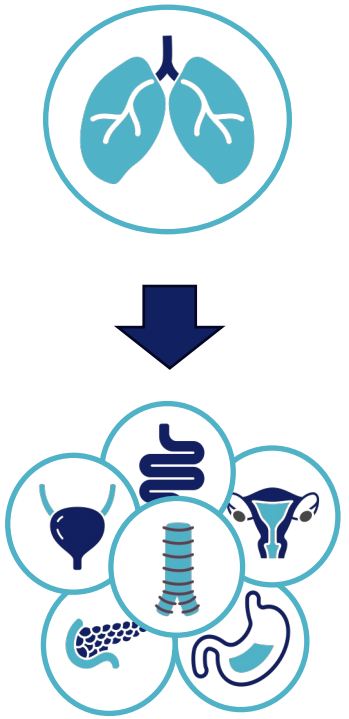
Improve outcomes, expand utility across multiple lines

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