

P2.320: Phase Ib/II Study of Dual EZH2/EZH1 Inhibition With Pembrolizumab in Advanced NSCLC

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INTRODUCTION

Immune checkpoint inhibitors (ICIs) have transformed advanced NSCLC treatment, yet many patients exhibit primary ICI resistance or progression after initial response.

Epigenetic dysregulation, including aberrant EZH2-mediated trimethylation of histone H3 (H3K27me3), is implicated in tumor immune evasion and reduced ICI responsiveness.

Preclinical studies suggest EZH2 inhibition may enhance antitumor immunity and potentiate PD-1 blockade.

Tulimimetostat, a potent dual EZH2/EZH1 inhibitor, demonstrates favorable tolerability and antitumor activity across multiple solid tumors.

HYPOTHESIS: *Tulimimetostat + pembrolizumab may reverse pembrolizumab resistance in ICI-refractory NSCLC.*

METHODS

Design:

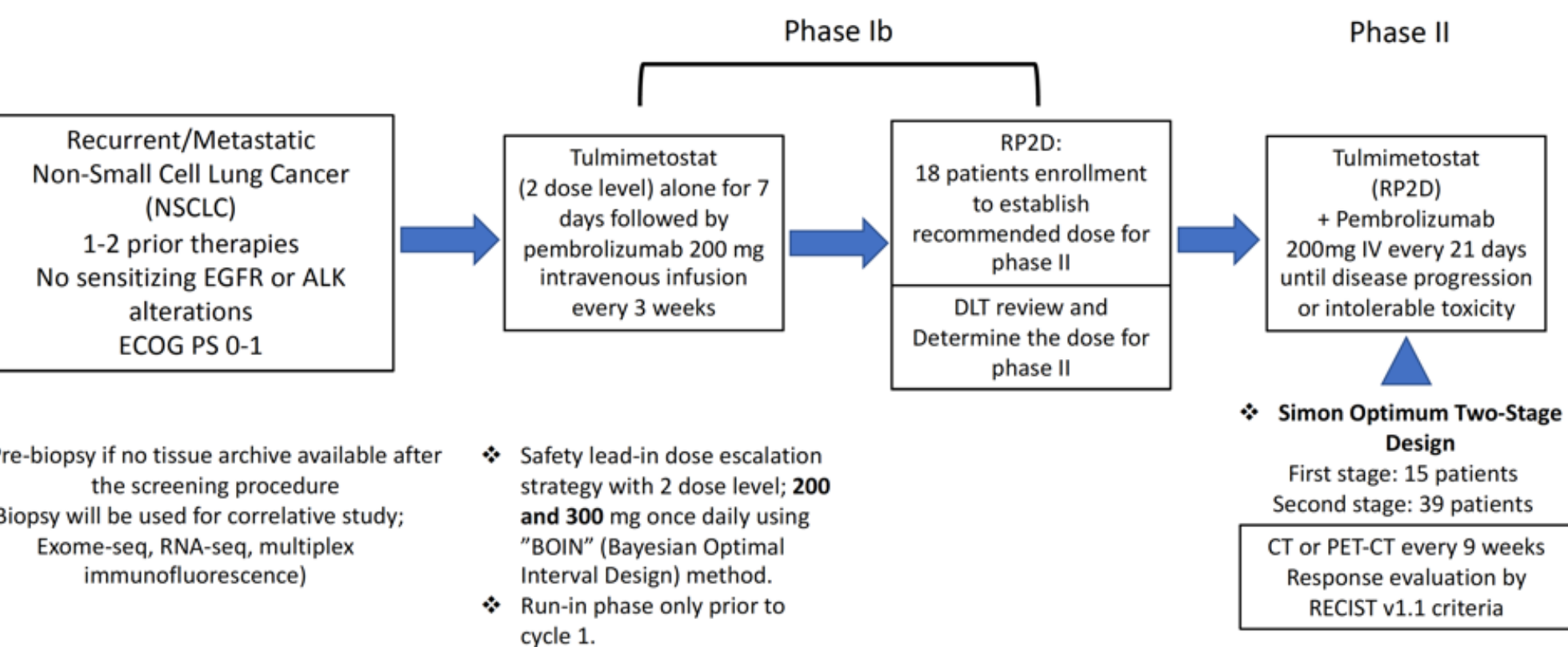
Phase Ib (BOIN dose-escalation): tulimimetostat 200 or 300 mg QD (7-day run-in) + pembrolizumab 200 mg IV Q3W; target DLT rate 20%; up to 18 patients to determine RP2D.

Phase II (Simon two-stage): single-arm, up to 66 patients across multiple VA sites; primary endpoint ORR (RECIST v1.1); allows early stopping for futility. Phase Ib patients treated at RP2D are included in the efficacy analysis.

Eligibility Criteria

INCLUSION	EXCLUSION
✓ Biopsy-proven advanced NSCLC	✗ ICI-naïve patients
✓ Progressed after 1st/2nd-line Rx (incl. ICI)	✗ EGFR/ALK-mutated NSCLC
✓ Measurable disease (RECIST v1.1)	✗ Low/intermediate-grade neuroendocrine tumor
✓ ECOG PS 0–1	✗ Active brain metastases
✓ Adequate organ function	✗ Active autoimmune disease (>10 mg prednisone/day)
✓ Tumor biopsy ≤1 yr or willing to biopsy	

Trial Schema



Treatment continues until progression, unacceptable toxicity, or withdrawal. Optional on-treatment biopsies; safety per CTCAE v5.0.

DISCUSSION AND CONCLUSION

Key Conclusions

- First VA-based multicenter trial combining dual EZH2/EZH1 inhibition with anti-PD-1 therapy in ICI-refractory NSCLC.
- Addresses a critical unmet need: no standard of care exists for ICI-refractory NSCLC.
- Mechanistically rational: EZH2 inhibition may reverse epigenetic immunosuppression to restore ICI sensitivity.

Future Directions

A comprehensive biomarker strategy (H3K27me3, PD-L1, ctDNA, MIF, CyTOF, TCR clonality) aims to identify predictive markers of response.

Positive findings may support a novel therapeutic paradigm for NSCLC progressing after immunotherapy or chemo-immunotherapy and inform the design of a future randomized trial.

REFERENCES & ACKNOWLEDGEMENTS

ClinicalTrials.gov: NCT05467748

Reference: Zhou L, et al. Combined inhibition of EZH2 and PD-1 enhances antitumor immunity. Clin Cancer Res. 2020.

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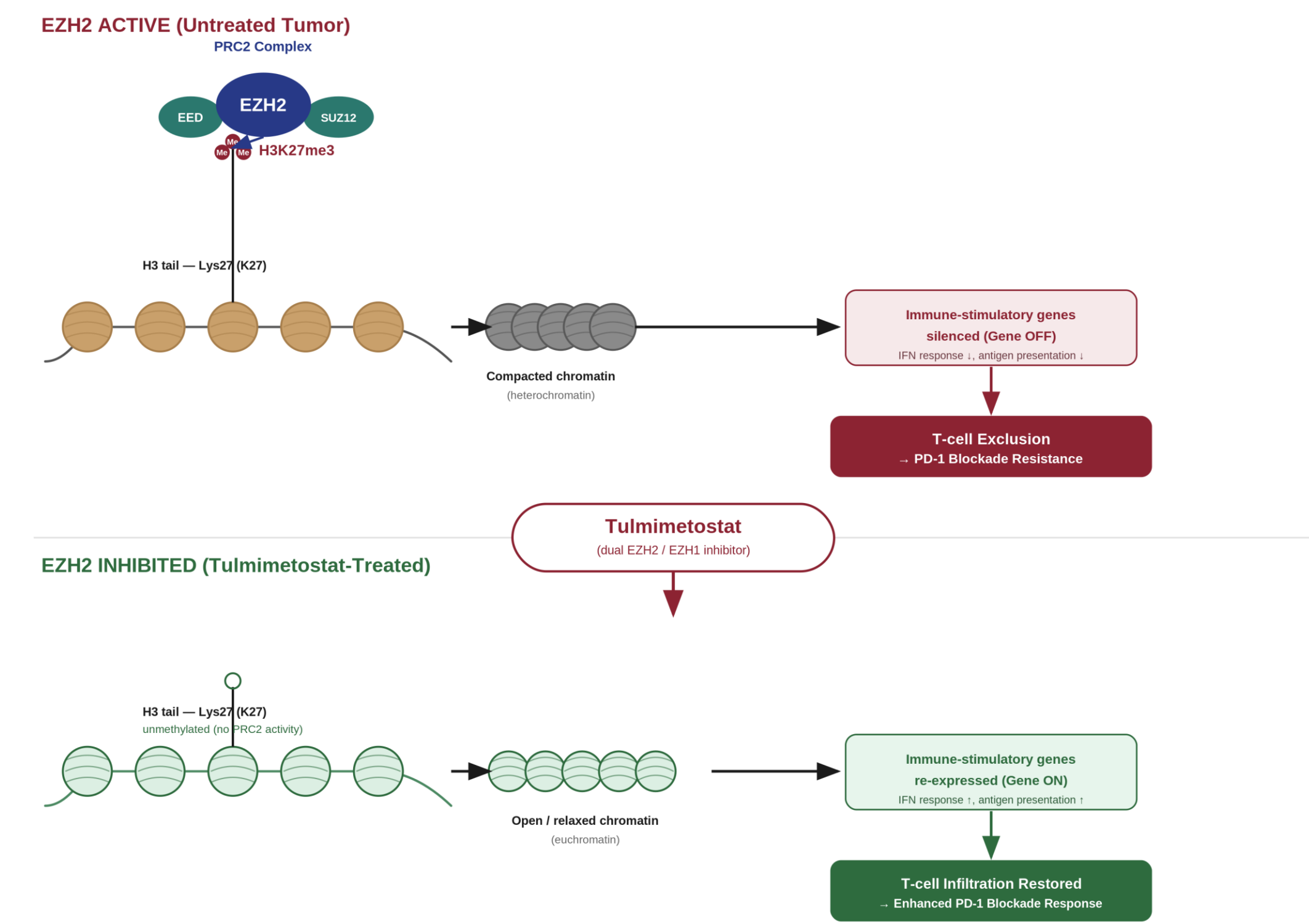
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STUDY RATIONALE, DESIGN & TRIAL STATUS

This abstract describes a **trial in progress**; efficacy results are not yet available. Below: scientific rationale, statistical design, biomarker strategy, and current trial status.

Scientific Rationale



Statistical Design

Phase Ib	Phase II
• BOIN dose-escalation	• Simon two-stage design
• 2 dose levels: 200 & 300 mg	• Early stopping for futility
• Target DLT rate: 20%	• Up to 66 pts, multi-VA site
• Up to 18 pts; determine RP2D	• Primary endpoint: ORR

Safety Profile (Preliminary, N = 10 Enrolled)

AE Term	Grade 1	Grade 2	Grade 3	Total
Anorexia	0	1	0	1
Fatigue	0	2	0	2
Generalized Pruritic Rash	0	1	0	1
Glucosuria	0	1	0	1
Hemoglobin (low)	0	0	1	1
Hyponatremia	1	1	0	2
Leukopenia	1	0	0	1
Proteinuria	0	1	0	1
Sepsis	0	0	1	1
Thrombocytopenia	2	0	0	2
Total	4 (30.8%)	7 (53.8%)	2 (15.4%)	13

Biomarker / Correlative Studies

Primary Biomarker: H3K27me3 (methyl mark) and PD-L1 expression in tumor biopsies — to explore epigenetic/immunologic correlates of response.

Correlative studies:

- Tumor mutational burden (tumor + ctDNA); ctDNA dynamics
- Multiplex immunofluorescence (MIF)
- Immune monitoring (peripheral blood): CD8+ T-cell clonality (TCR-β CDR3), CyTOF immunophenotyping, NanoString PanCancer Immune Profiling, ELISPOT for NSCLC antigens

Enrollment Status

As of August 2026		
11 Screened	10 Enrolled	6 Active on Treatment

Participating VA Sites

- Michael E. DeBakey VAMC (Lead) — Dr. D. Shin
- San Diego VAMC — Dr. P. Cheng
- Sacramento VAMC — Dr. T. Li
- Long Beach VAMC — Dr. P. Gupta
- Ann Arbor VAMC — Dr. G. Strohbehn

Serious Adverse Event (SAE)

1 event: Grade 3 worsening fatigue, possibly attributable to both study medications. No Grade 4/5 events.

Drug Attribution (all AEs)

- Tulimimetostat alone: 8/13 (61.5%)
- Both agents: 4/13 (30.8%)
- Pembrolizumab alone: 1/13 (7.7%)

Relatedness: 12/13 (92.3%) possibly attributable; 1/13 (7.7%) attributable.