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Pliant Therapeutics
PLN-101095 Overview

AACR Drug Discovery and Development

July 24, 2026

Problem Statement

- **Checkpoint inhibitor responders eventually relapse**
- These patients have limited next line options
- Integrin activity has been found to mediate checkpoint inhibitor relapse
- Pliant is developing PLN-101095 as a potential solid tumor treatment option to resensitize checkpoint inhibitor refractory subjects

High Burden of ICI Relapse

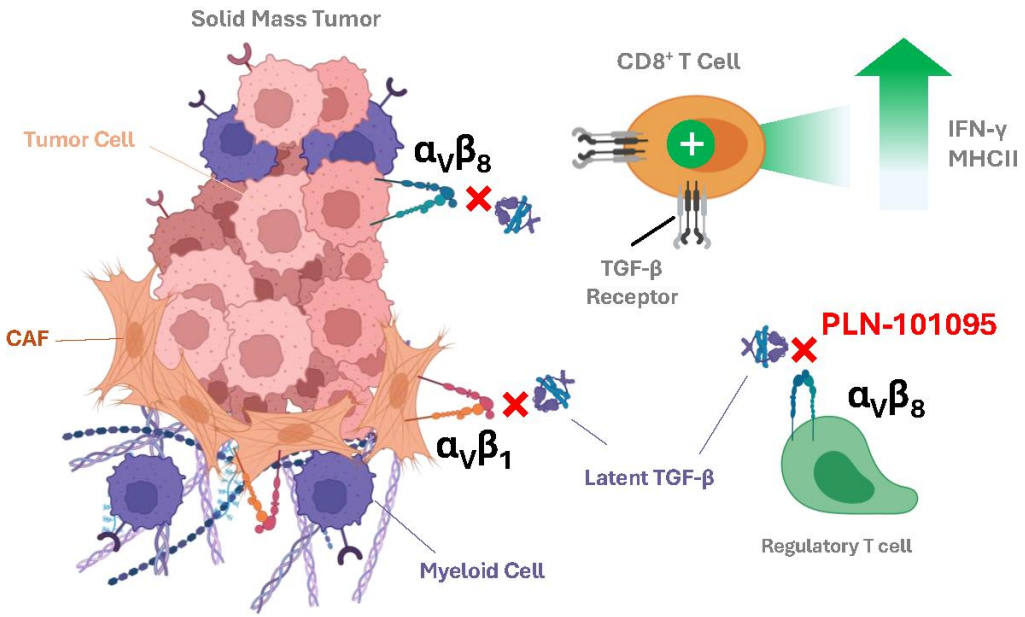
Tumor Type	Initial ICI Response	Secondary-resistance burden
Melanoma[1,2]	42%	30% of durable responders relapse by 5 years
NSCLC[3]	45%	Majority of responders progress
ccRCC[4]	≤42%	Most progress within a few years
Biliary Tract Carcinoma[5,6]	~27%	~75% progress in a year
Endometrial[7,8]	dMMR≤57% pMMR ~13%	pMMR (majority) low & non-durable; rapid relapse
Urothelial[9]	~21%	5-year OS ~15%; majority progress

1 KEYNOTE-006 (Lancet Oncol 2019)
2 KEYNOTE-006 (JCO 2022)
3 *KEYNOTE-024 (JCO 2021)*
4 *CHECKMATE 214 (NEJM 2018)*
5 TOPAZ-1 (NEJM Evid 2022)
6 KEYNOTE-966 (Lancet 2023)
7 *KEYNOTE-158 (J Clin Oncol 2022)*
8 GARNET (Clin Cancer Res 2023)
9 *KEYNOTE-045 (Ann Oncol 2023)*

Pliant's Solution

PLN-101095, A First-in-Class, Oral, Dual $\alpha_V\beta_8$ / $\alpha_V\beta_1$ Integrin Inhibitor

In response to sustained immune activity, solid tumors utilize integrin $\alpha_V\beta_8$ and $\alpha_V\beta_1$ activation of TGF-β to suppress and escape immune control[1,2]



PLN-101095 blocks integrin binding to latent TGF-β in the TME to prevent pathway activation that results in loss of responsiveness to ICIs

1. **First-in-class oral dual integrin inhibitor**
   Potently block $\alpha_V\beta_8$- and $\alpha_V\beta_1$-driven activation of TGF-βin the TME while limiting systemic TGF-β inhibition

2. **Re-arms the anti-tumor immune response**
   Potential to reverse TGF-β–driven immunosuppression and T-cell exclusion by raising IFN-γ and $CD8^+$ T-cell infiltration, turning "cold" tumors hot

3. **Reduce fibroblast activation and fibrotic tumor stroma**
   Decrease physical and immunologic barriers in the TME

4. **Re-sensitizes tumors to anti–PD-(L)1**
   Designed to restore checkpoint responsiveness

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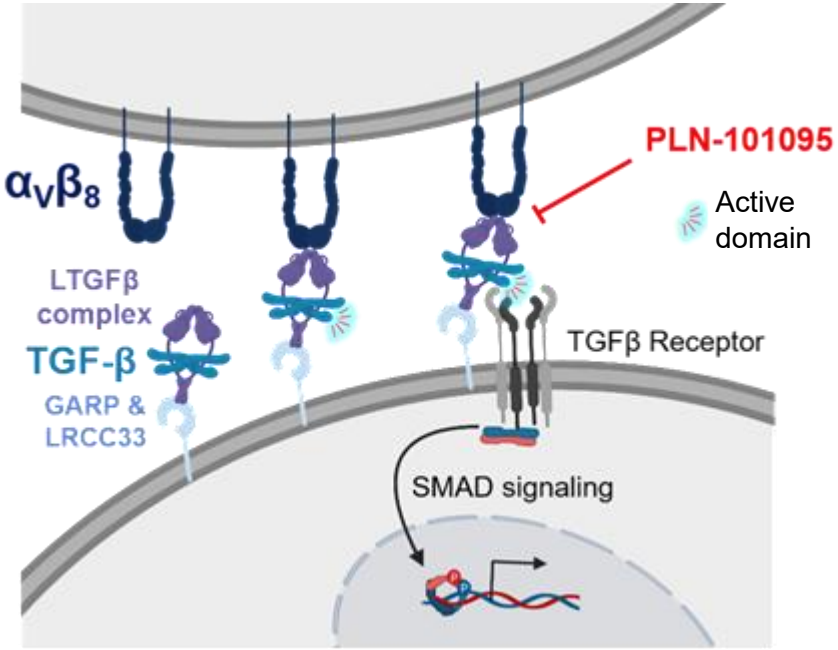
1 Lainé A, et al. Nat Comm. 2021; 2. Kothari V, et al. J Immunother Cancer. 2022

Differentiated Mechanism From Other TGF-β Inhibition Strategies

Emerging Consensus view on TGF-β

TGF-β can attenuate anti-tumor immunity via integrin binding, ***without*** being released from the latent TGF-β complex[1,2]



PLN-101095 prevents $\alpha_V\beta_8$ from binding to the latent TGF-β complex, preventing the active domain exposure that drives downstream signaling

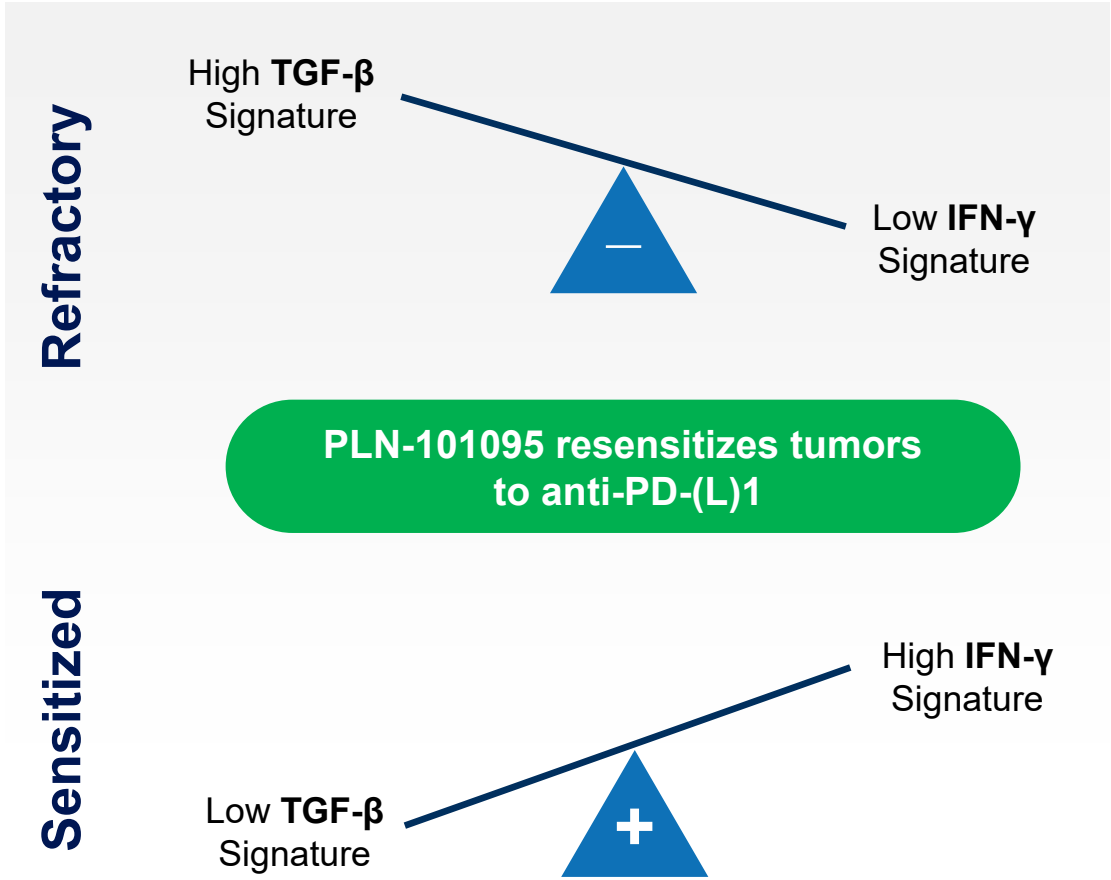
PLN-101095 presents a differentiated mechanism to potently address activation of TGF-β in the TME

Approach	Blocks $\alpha_V\beta_8$-driven TGF-β Signaling	Blocks $\alpha_V\beta_1$-driven TGF-β Signaling (Fibroblasts)	Spares global TGF-beta inhibition	Modality
PLN-101095	✓	✓	✓	Small molecule
ALK5 / TGF-β receptor inhibitor[3,4]	↓	↓	✗	Small molecule
TGF-β ligand traps / antibodies[2,5,6]	◑	?	✗	Antibody / complex protein
Anti-Latent TGF-β1 antibody[7]	◑	◑	◑	Antibody / complex protein
Anti-GARP antibody[8]	◑	✗	✓	Antibody / complex protein
Anti-$\alpha_V\beta_8$ antibody[2,9]	✓	✗	✓	Antibody / complex protein

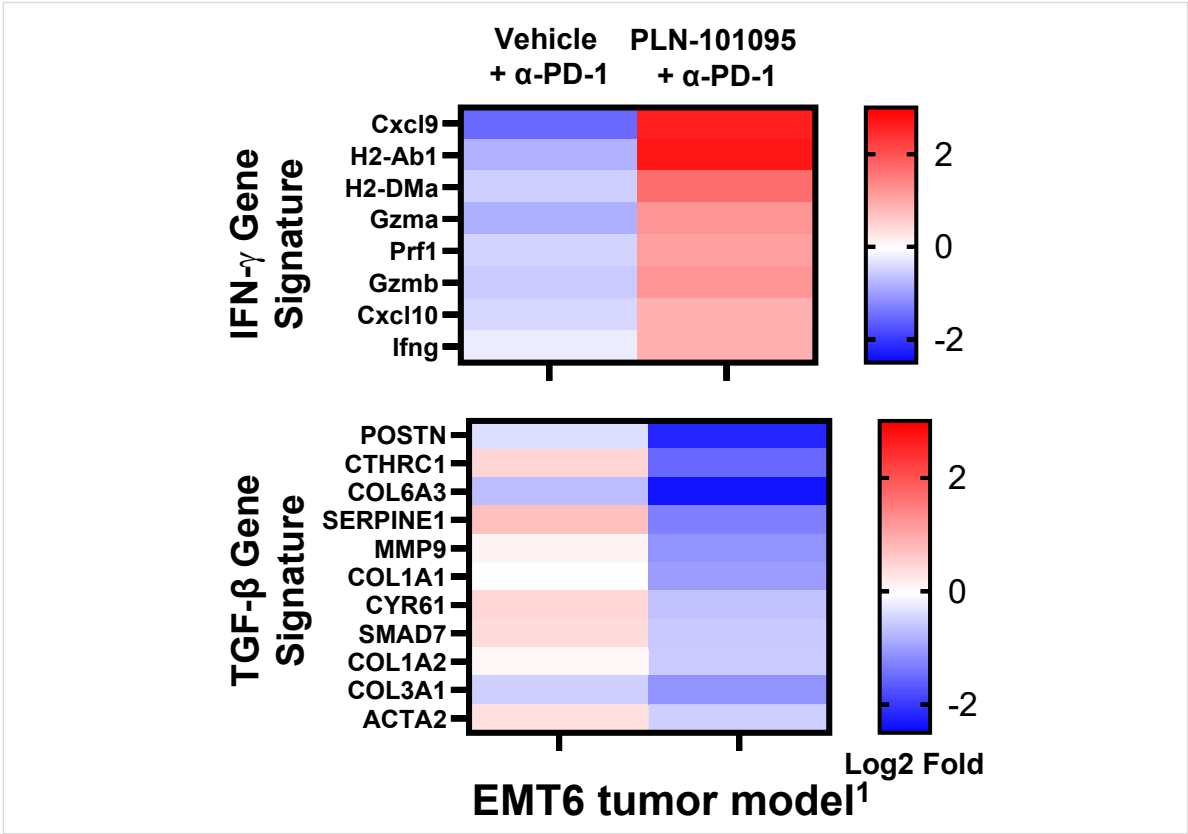
↓ Downstream/receptor level blockade ◑ Partially Small molecule Antibody / complex protein

1 Campbell MG, et al. Cell. 2020
2 Williams K, et al. Preprint, bioRxiv. 2026
3 Herbertz S, et al., Drug Des Devel Ther. 2015
4 Anderton MJ, et al., Toxicol Pathol. 2011
5 Lan Y, et al. Sci Transl Med. 2018
6 Martin CJ, et al. Sci Transl Med. 2020
7 Liénart S, et al. Science. 2018
8 Takasaka N, et al. JCI Insight. 2018
9 Larrick JW, et al. Preprint, Research Square. 2022

PLN-101095 Promotes ICI Responsiveness by Inhibiting TGF-β and Increasing IFN-γ Expression in Mouse Models



Tumor Gene Expression Change After Treatment



By inhibiting TGF-β, PLN-101095 shifts solid tumors to a high–IFN-γ signature, ICI-responsive state

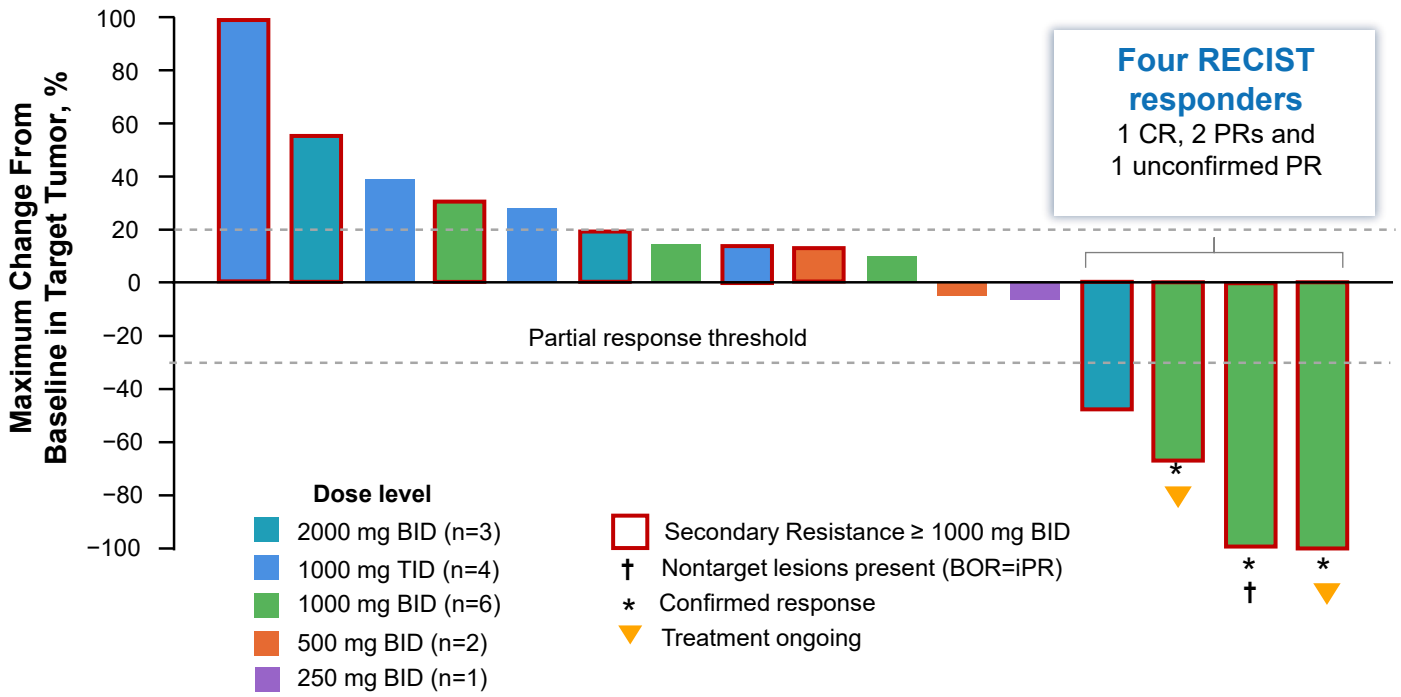
1 Daud A, et al. *J Immunother Cancer*. 2023

PLN-101095 with Pembrolizumab Demonstrated Responses in Secondary ICI Resistance

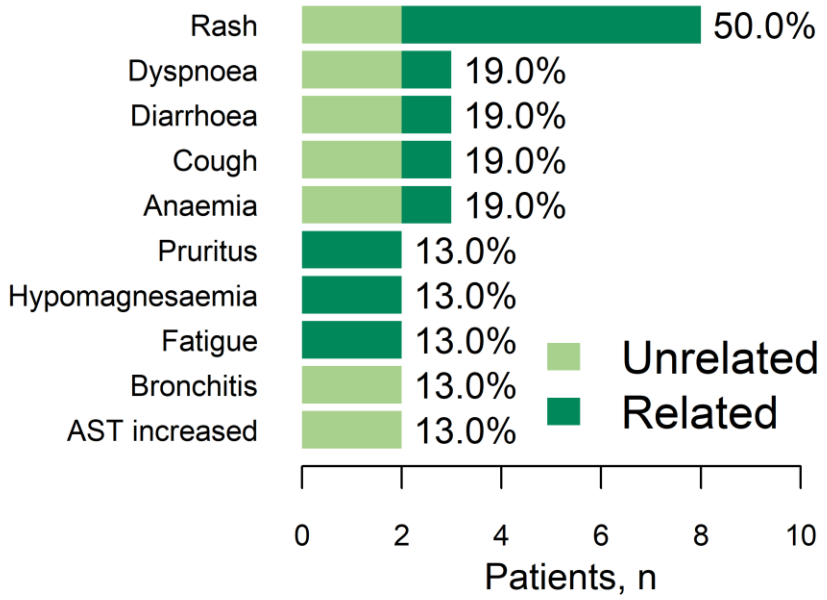
FORTIFY

Clinical Response[1]

cORR	DCR	Avg Reduction	mTOT
30%	60%	89%	19 mo



Safety and Tolerability



Any TRAE	75%
Grade ≥3 TRAE	6% (1)
Serious TRAE	13% (2)
TRAE → discontinuation	13% (2)

Data cut as of Feb 27, 2026
1 BOR metrics based on secondary resistance participants dosed at 1000 mg or above
cORR: confirmed objective response rate; DCR, disease control rate; mTOT, median time on treatment

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PLN-101095 Monotherapy Produces a Coordinated T-cell Reactivation Cascade

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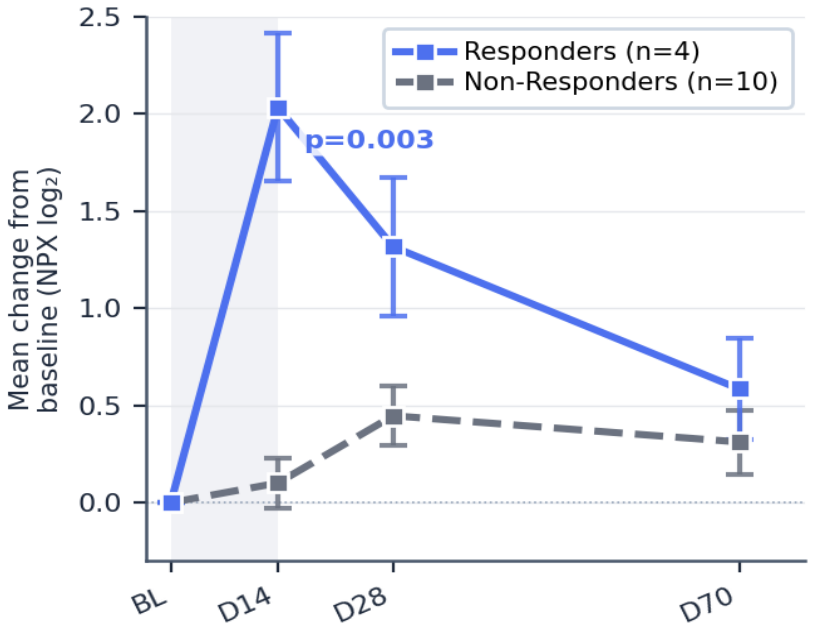
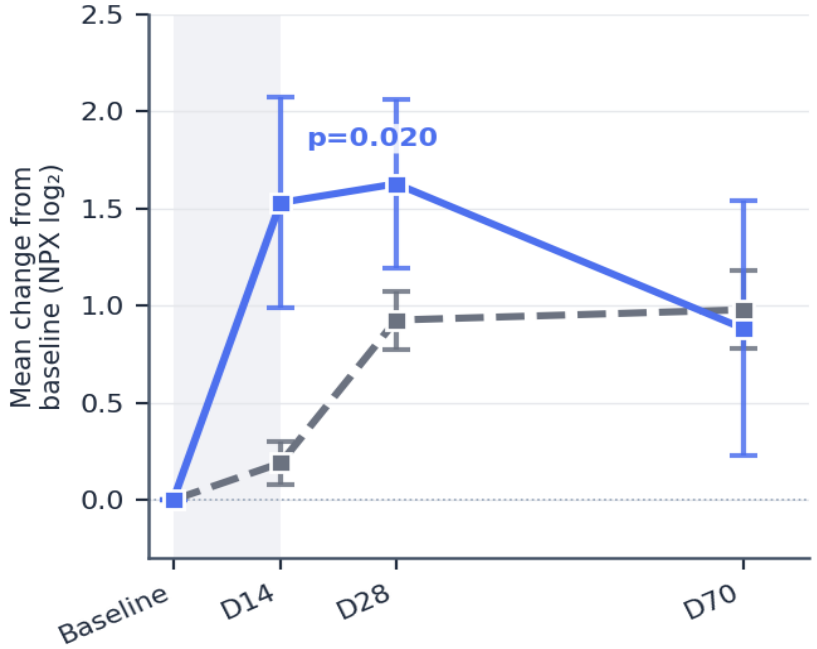
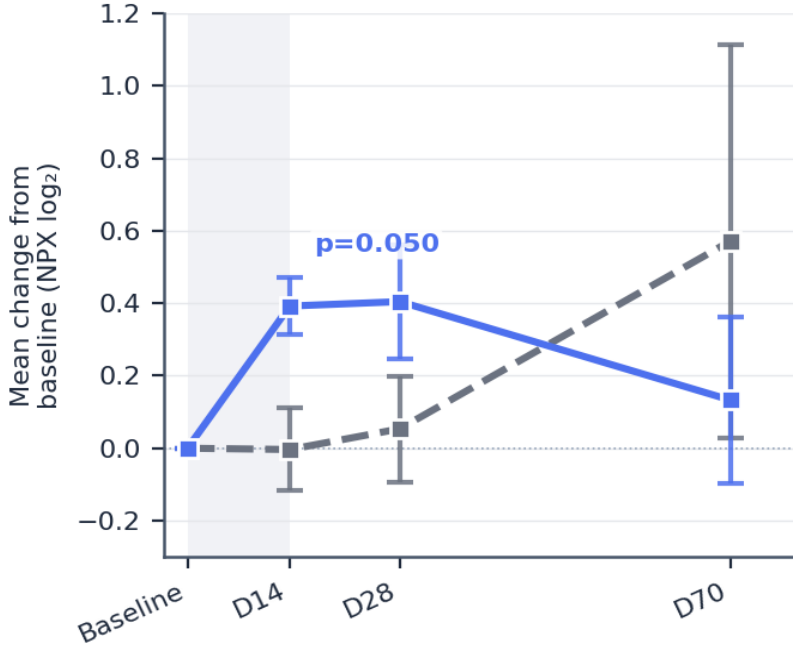
IFN-γ



CXCL9



Granzyme-B



During monotherapy (Days 1- 14), PLN-101095 increased IFN-γ, CXCL9 (recruitment of T cells) and granzyme-B (cytotoxic arming) in responders relative to non-responders

Plasma biomarkers from OLINK REVEAL assay
One participant had no post baseline biomarker data and one participant excluded due to confounding AE (immune mediated hepatitis)
Mean non-responder Granzyme-B response at Day 70 driven by single outlier; without outlier, non-responder response is flat

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Next Steps For PLN-101095 Development

FORTIFY Phase 1b is enrolling

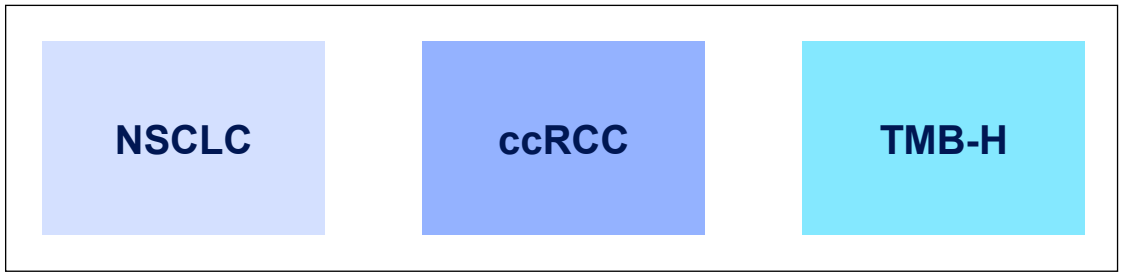
Evaluating a Single PLN-101095 Dose Level

1000 mg BID

DAY 1–14	DAY 15 ONWARDS
PLN-101095 Monotherapy	PLN-101095 + Pembrolizumab

Three Cohorts

(n = up to 34 per cohort)



Future Development Options

Biomarker-guided path

Use the IFN-γ signature to select patients and support expedited development in high-unmet tumors

Combine broadly

Evaluate combinations with other ICIs and IO-directed therapies

Explore monotherapy

Characterize single-agent activity

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