First-in-Human Phase 1 Study of PLN-101095, a First-in-Class Dual $\alpha_V\beta_8/\alpha_V\beta_1$ Integrin Inhibitor, as Monotherapy and in Combination With Pembrolizumab in Patients With Advanced Solid Tumors Refractory to Immune Checkpoint Inhibitors

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Timothy A. Yap Disclosure Information

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I have the following relevant financial relationships to disclose:

Employee of: University of Texas MD Anderson Cancer Center

Consultant for: AbbVie, Acrivon, Adagene, Almac, Aduro, Amphista, Artios, Astex, AstraZeneca, Athena, Atrin, Avenzo, Avoro, Axiom, Baptist Health Systems, Bayer, BeiGene, BioCity Pharma, Blueprint, Boxer, Bristol Myers Squibb, C4 Therapeutics, Calithera, Cancer Research UK, Carrick Therapeutics, Circle Pharma, Clovis, Cybrexa, Daiichi Sankyo, Dark Blue Therapeutics, Diffusion, Duke Street Bio, 858 Therapeutics, EcoR1 Capital, Ellipses Pharma, EMD Serono, Entos, F-Star, Genesis Therapeutics, Genmab, Glenmark, GLG, Globe Life Sciences, GSK, Guidepoint, Ideaya Biosciences, Idience, Ignyta, I-Mab, ImmuneSensor, Impact Therapeutics, Institut Gustave Roussy, Intellisphere, Jansen, Kyn, MEI pharma, Mereo, Merck, Merit, Monte Rosa Therapeutics, Natera, Nested Therapeutics, Nexys, Nimbus, Novocure, Odyssey, OHSU, OncoSec, Ono Pharma, Onxeo, PanAngium Therapeutics, Pegascy, PER, Pfizer, Piper-Sandler, Pliant Therapeutics Inc., Prolynx, Radiopharma Theranostics, Repare, resTORbio, Roche, Ryvu Therapeutics, SAKK, Sanofi, Schrodinger, Servier, Synnovation, Synthis Therapeutics, Tango, TCG Crossover, TD2, Terremoto Biosciences, Tessellate Bio, Theragnostics, Terns Pharmaceuticals, Tolremo, Tome, Thryv Therapeutics, Trevarx Biomedical, Varian, Veeva, Versant, Vibliome, Voronoi Inc, Xinthera, Zai Labs and ZielBio

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PLN-101095 Is a Novel, Orally Bioavailable Integrin αVβ8 and αVβ1 Inhibitor

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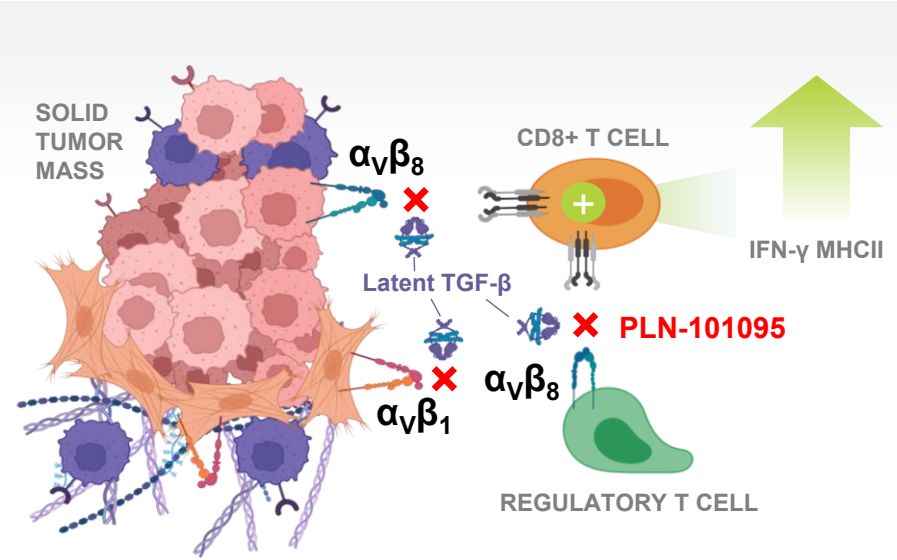
In response to sustained immune activity, solid tumors utilize integrin $\alpha_V\beta_8$ and $\alpha_V\beta_1$ activation of TGF-β to suppress and escape immune control[1,2]

PLN-101095 is designed to:

- Potently block integrin $\alpha_V\beta_8$- and $\alpha_V\beta_1$-driven activation of TGF-β locally in the TME
  - This differs from past strategies of systemically targeting the active TGF-β cytokine, TGF-β receptor kinase or specific isoforms of TGF-β
- Selectively enhance T cell IFN-γ effector function
- Reduce fibroblast activation and fibrotic tumor stroma
- Combine with orthogonal IO approaches like anti-PD-(L)1



Inhibition of integrin $\alpha_V\beta_8$ and $\alpha_V\beta_1$ blocks activation of TGF-β to reduce immunosuppression, leading to a new or reinvigorated cancer immune response[2,3]

1. Lainé A, et al. *Nat Comm.* 2021;12:6228; 2. Kothari V, et al. *J Immunother Cancer*. 2022;10(Suppl 2):Abstract 1352; 3. Kothari V, et al. *J Immunother Cancer*. 2023;11(Suppl 1):Abstract 464.
CD, cluster of differentiation; IFN, interferon; IO, immuno-oncology; MHC, major histocompatibility complex; PD-(L)1, programmed death (ligand) protein-1; TGF, transforming growth factor; TME, tumor microenvironment.

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

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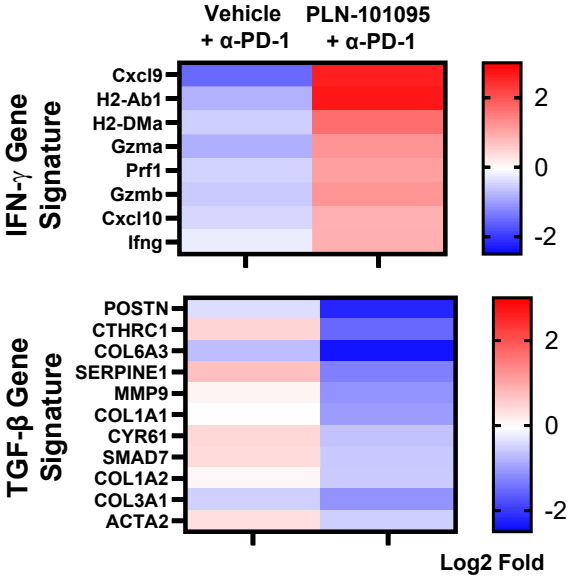
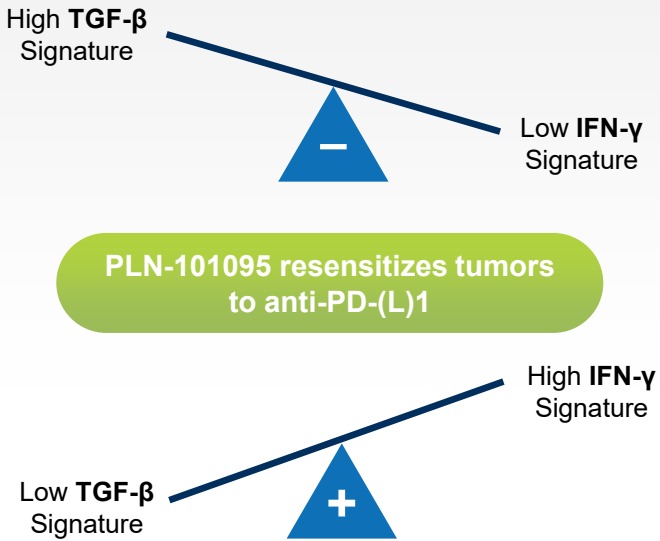
Tumor Gene Expression Change After Treatment

EMT6 tumor model, PLN-101095 dosed by minipump (144 mg/kg/day)



Anti-PD-(L)1 Nonresponsive Baseline Gene Signature



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

Daud A, et al. *J Immunother Cancer*. 2023;11(Suppl 1):Abstract 714.
ICI, immune checkpoint inhibitor.

Phase 1, Open-Label, Dose-Escalation Study in Patients With Solid Tumors With Prior ICI Resistance

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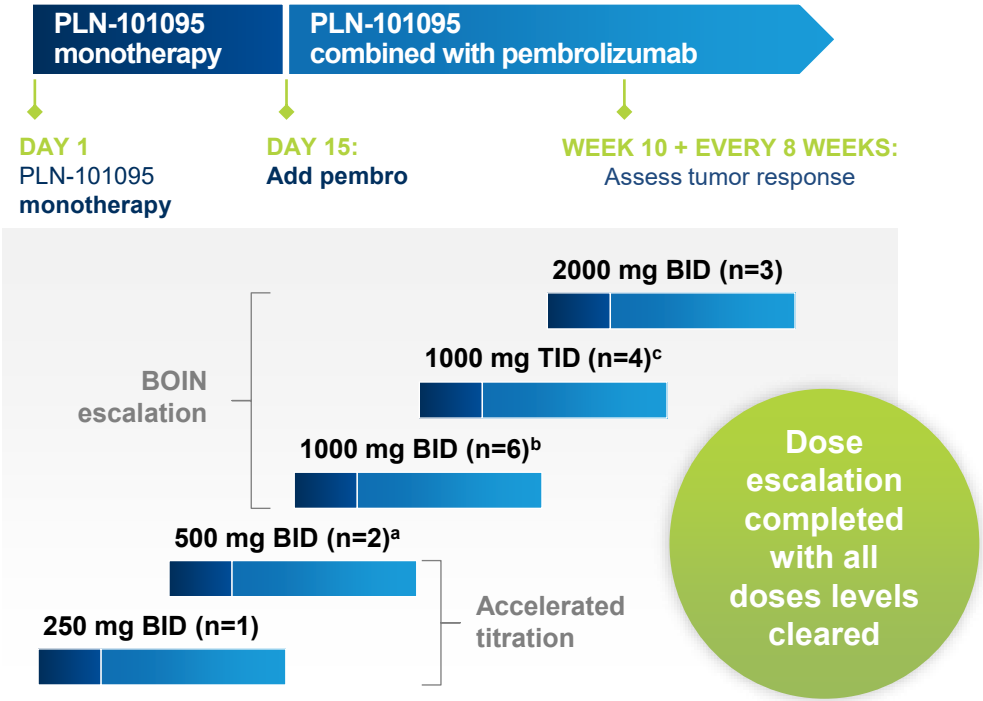

STUDY POPULATION

- Prior exposure to PD-1 therapy with documented PD
- Primary or secondary resistance by SITC definition[1,d]

PRIMARY AND SECONDARY ENDPOINTS

- TEAEs, serious TEAEs and DLTs
- Pharmacokinetics

EXPLORATORY ENDPOINTS

- Antitumor activity: ORR, DCR per iRECIST
- Changes in blood-based biomarkers

NCT06270706. 1. Kluger H, et al. *J Immunother Cancer*. 2023;11:e005921.
[a] One participant discontinued at Day 14 due to PD. [b] Cohort expanded due to single DLT. [c] One patient added as part of backfill. [d] SITC primary resistance: BOR of PD or SD <6 months despite adequate treatment exposure; secondary resistance: prior CR, PR or SD ≥6 months followed by progression during or after treatment.
BID, twice daily; BOIN, Bayesian optimal interval; BOR, best overall response; CR, complete response; DCR, disease control rate; DLT, dose-limiting toxicity; iRECIST, Immunological Response Evaluation Criteria in Solid Tumors; ORR, objective response rate; PD, disease progression; pembro, pembrolizumab; PR, partial response; SD, stable disease; SITC, Society for Immunotherapy of Cancer; TEAE, treatment-emergent adverse event; TID, three times daily.

Patient Baseline Characteristics

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	Cohort 1 250 mg BID (n=1)	Cohort 2 500 mg BID (n=2)	Cohort 3 1000 mg BID (n=6)	Cohort 4 1000 mg TID (n=4)	Cohort 5 2000 mg BID (n=3)	Total (n=16)
Age, year[a]	70 (70-70)	58 (53-63)	56 (53-63)	48 (41-60)	67 (66-72)	60 (52-68)
Male, n (%)	1 (100)	2 (100)	2 (33.3)	1 (25.0)	2 (66.7)	8 (50.0)
Tumor type, n (%)						
NSCLC	1 (100.0)	0	2 (33.3)	0	0	3 (18.8)
Cholangiocarcinoma	0	0	1 (16.7)	1 (25.0)	1 (33.3)	3 (18.8)
HNSCC	0	1 (50.0)	0	0	1 (33.3)	2 (12.5)
RCC	0	1 (50.0)	0	1 (25.0)	0	2 (12.5)
Melanoma	0	0	1 (16.7)	0	0	1 (6.3)
CRC	0	0	0	0	1 (33.3)	1 (6.3)
Endometrial	0	0	1 (16.7)	0	0	1 (6.3)
TNBC	0	0	1 (16.7)	0	0	1 (6.3)
Ovarian CCA	0	0	0	1 (25.0)	0	1 (6.3)
Anal SCC	0	0	0	1 (25.0)	0	1 (6.3)
Prior therapy lines[a]	2 (2-2)	3.5 (3-4)	3.5 (1-4)	3 (1.5-4)	3 (2-4)	3 (2-4)
ICI secondary resistance, n (%)[b]	0	2 (100)	4 (66.7)	3 (75.0)	3 (100)	12 (75.0)

[a] Median (IQR). [b] SITC secondary resistance: prior CR, PR or SD ≥6 months followed by progression during or after treatment.
CCA, clear cell adenocarcinoma; CRC, colorectal cancer; HNSCC, head and neck squamous cell carcinoma; IQR, interquartile range; NSCLC, non-small cell lung cancer; RCC, renal cell carcinoma; SCC, squamous cell carcinoma; TNBC, triple-negative breast cancer.

PLN-101095 Was Generally Well Tolerated

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n (%)	Cohort 1 250 mg BID (n=1)	Cohort 2 500 mg BID (n=2)	Cohort 3 1000 mg BID (n=6)	Cohort 4 1000 mg TID (n=4)	Cohort 5 2000 mg BID (n=3)	Total (n=16)
Any TRAE	**1 (100)**	**1 (50)**	**4 (67)**	**4 (100)**	**2 (67)**	**12 (75)**
Grade 3/4[a]	0	0	1 (17)[c]	0	0	1 (6)
Serious	1 (100)[b]	0	1 (17)[c]	0	0	2 (13)
Led to discontinuation	0	0	1 (17)[c]	1 (25)[d]	0	2 (13)
Most common TRAEs (in >1 participant)						
Rash[e]	0	1 (50)	2 (33)	2 (50)	1 (33)	6 (38)
Fatigue	0	0	2 (33)	0	0	2 (13)
Hypomagnesemia	0	0	0	1 (25)	1 (33)	2 (13)
Pruritus	0	0	0	1 (25)	1 (33)	2 (13)

The most common TRAE was rash[e]

- All rashes were grade 1 or 2
- One treatment-related rash was reported during the monotherapy period, but otherwise these were primarily observed within 2 days of starting combination treatment

[a] No Grade 5 TRAEs occurred. [b] Keratoacanthoma (Grade 2). [c] Immune-mediated hepatitis (Grade 3), considered a DLT. [d] Dermatitis bullous (Grade 2). [e] Includes rash, rash erythematous, rash maculo-papular, dermatitis acneiform and dermatitis bullous.
TRAE, treatment-related adverse event.

PLN-101095 Monotherapy Demonstrated Dose-Ordered Exposure at Day 14

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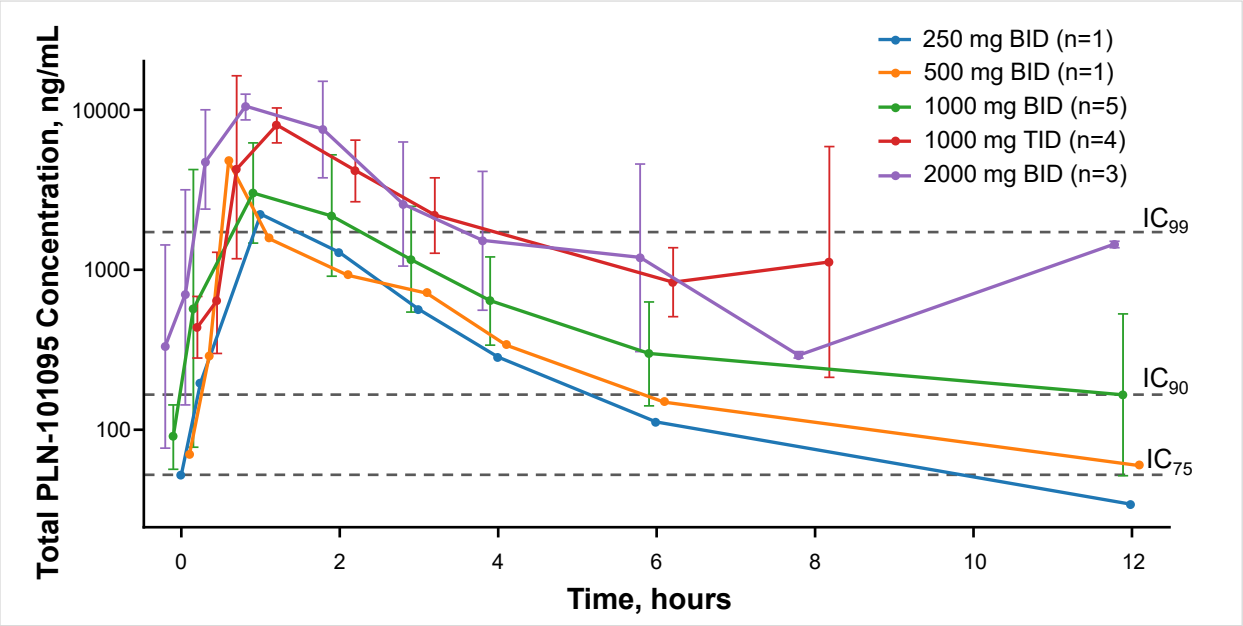

- All participants receiving ≥1000 mg BID maintained IC_{75} coverage over 24 hours, supporting consistent target engagement
- PK profile supports continuous pharmacologic inhibition with BID dosing at steady state

All participants treated with ≥1000 mg BID maintained IC_{75} coverage over 24 hours, supporting consistent target engagement

IC75, 75% maximal inhibitory concentration; IC90, 90% maximal inhibitory concentration; IC99, 99% maximal inhibitory concentration; PK, pharmacokinetics.

Responses Were Observed in Patients With Secondary ICI Resistance

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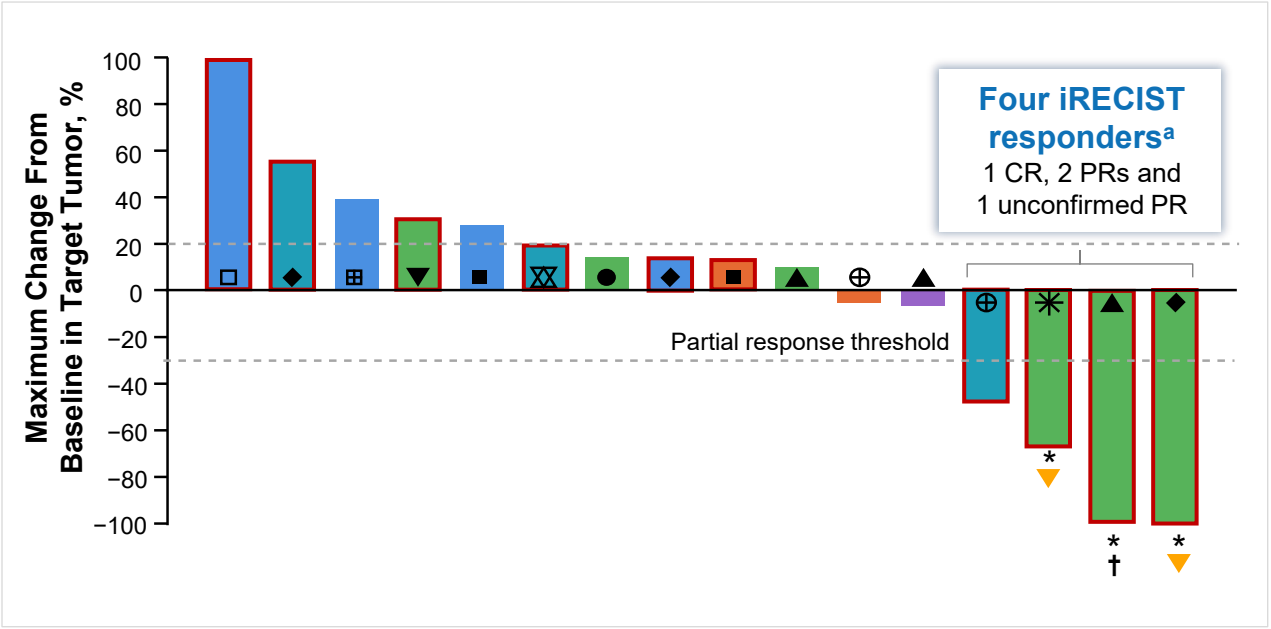

Dose level
- 2000 mg BID
- 1000 mg TID
- 1000 mg BID
- 500 mg BID
- 250 mg BID

Tumor type
- Cholangiocarcinoma
- HNSCC
- NSCLC
- RCC
- TNBC
- CRC
- Ovarian CCA
- Endometrial
- Anal SCC
- Melanoma

† Nontarget lesions present (BOR=iPR)
* Confirmed response
▼ Treatment ongoing
Secondary Resistance ≥ 1000 mg BID

Overall study population: 19% ORR | 56% DCR
ICI secondary resistance: 30% ORR | 60% DCR

[a] As of Feb 27, 2026.

Clinically Significant, Durable Responses Observed in 3 of 4 iRECIST Responders at Doses ≥1000 mg BID

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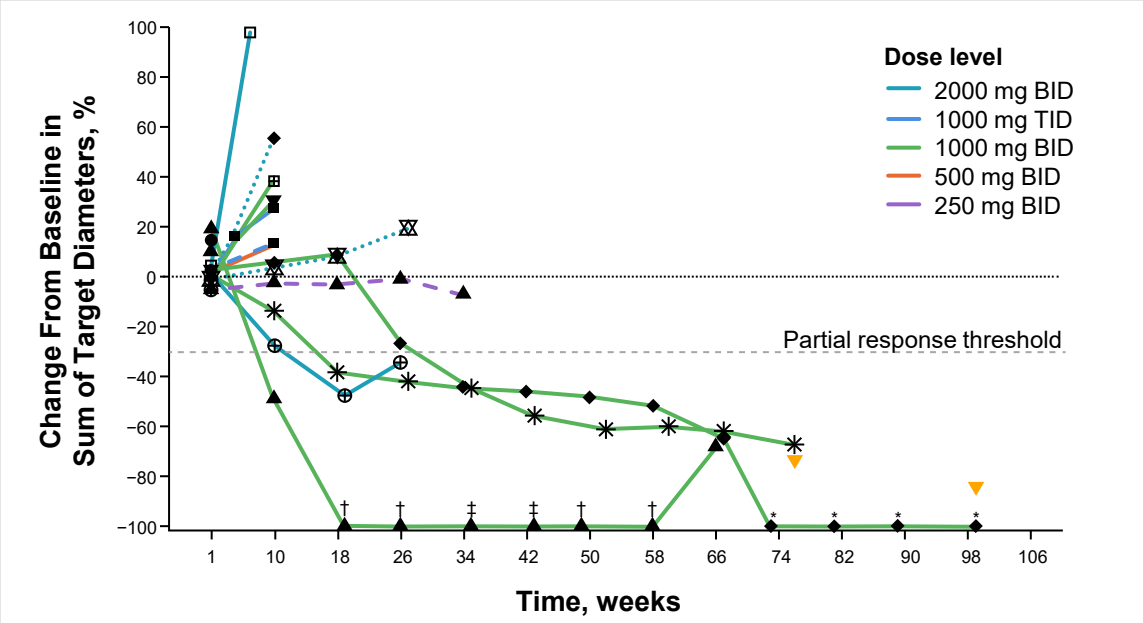

Tumor type

- Cholangiocarcinoma (1)
- Cholangiocarcinoma (2)
- Cholangiocarcinoma (3)
- HNSCC (1)
- HNSCC (2)
- NSCLC (1)
- NSCLC (2)
- NSCLC (3)
- RCC (1)
- RCC (2)
- TNBC
- CRC
- Ovarian CCA
- Endometrial
- Anal SCC
- Melanoma

† Target lesions nonmeasurable with nontarget lesions present (BOR=iPR)

‡ Target lesions disappeared with nontarget lesions present (BOR=iPR)

* Complete resolution of target and nontarget lesions

▼ Treatment ongoing

Median time on treatment is 19 months for the 3 confirmed objective responders, who had an average maximum tumor reduction of -89%

Data as of Feb 27, 2026. Confirmed objective responders had BOR of iPR or iCR.
iCR, complete response per iRECIST; iPR, partial response per iRECIST.

Tumor Shrinkage Over Time – Case #1 (CR)
iRECIST CR (106+ weeks on trial)

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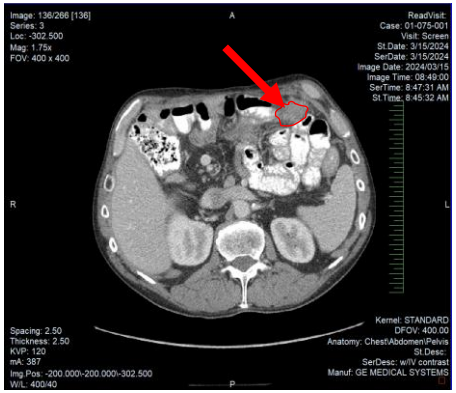
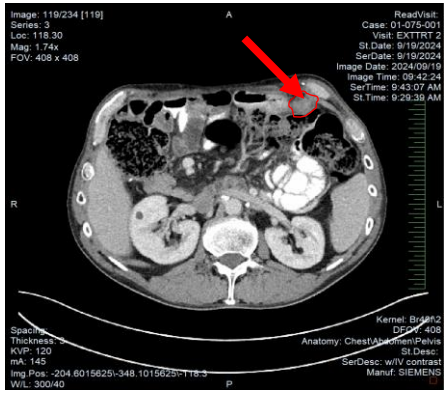
- 63-year-old male
- Cholangiocarcinoma, 2019
- Lynch Syndrome
  - Prior Hx of CRC, basal and SCC of skin
- TL: Left peritoneal implant

Prior Treatment History	
Gemcitabine/Cisplatin	Feb 2019 - Jul 2019
FOLFIRI	Oct 2019 - Jan 2020
Capecitabine	Feb 2019 - Mar 2020
Pembrolizumab	Mar 2021 - Feb 2024 **(Confirmed PD)**

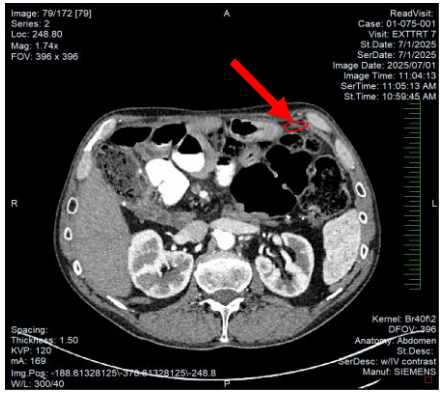
Screening
Mar 15, 2024
34 mm



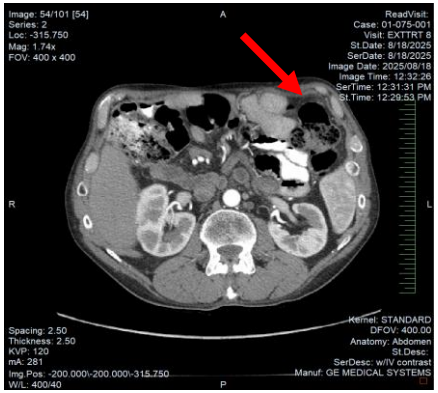
Week 26
Sep 19, 2024
25 mm



Week 66
Jul 1, 2025
12 mm



Week 74
Aug 18, 2025



Courtesy of Dr Manish Sharma. Patient had a confirmed response.
FOLFIRI, folinic acid, fluorouracil and irinotecan; Hx, history; TL, target lesion.

Tumor Shrinkage Over Time – Case #2
iRECIST PR (66 weeks on trial)

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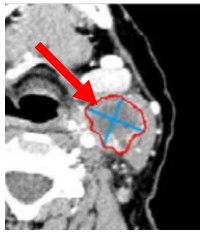
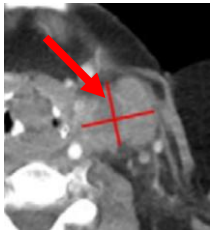
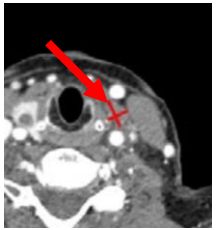
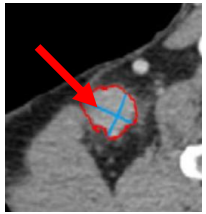
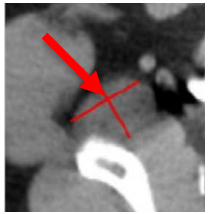
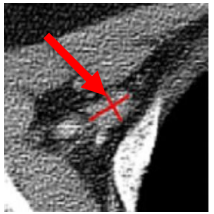
- 57-year-old female
- TMB-H NSCLC adenocarcinoma, 2020
- One prior line of treatment

Prior Treatment History
Pembrolizumab for 35 months (followed by confirmed PD)
RT for metastatic disease in brain and mediastinum

	Screening Oct 24, 2024 SA1: 23.1 mm SA2: 15.9 mm	Week 2 Nov 18, 2024 SA1: 27.9 mm SA2: 18.6 mm	Week 10 Jan 15, 2024 SA1: 8.9 mm SA2: 11.1 mm
T01 – Lymph node Cervical upper left (Level II)			
T02 – Lymph node Supraclavicular right (Level V)			

Courtesy of Dr Alexander Spira.
RT, radiotherapy.

Clinical Response to PLN-101095 Is Associated With Elevated Plasma IFN-γ and PD-L1 Levels After 14 Days' Monotherapy

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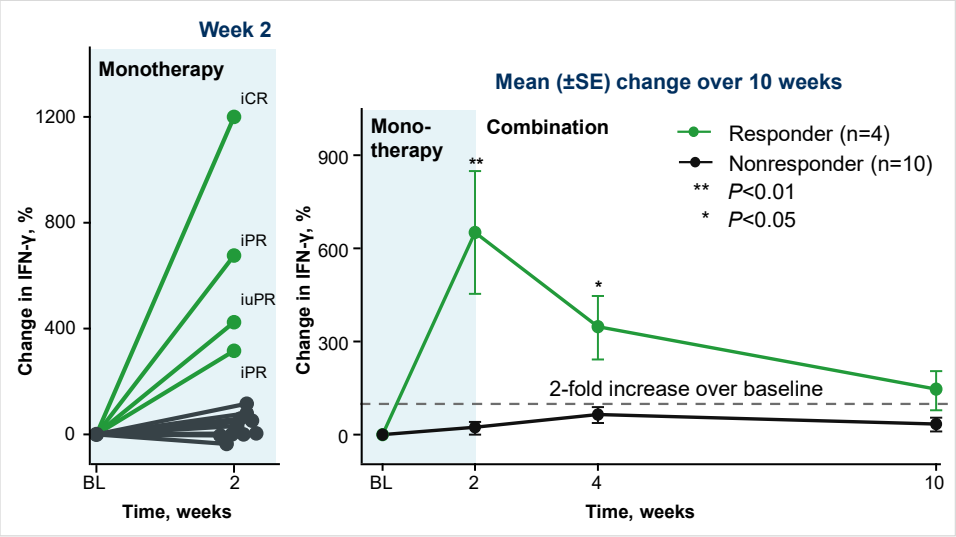
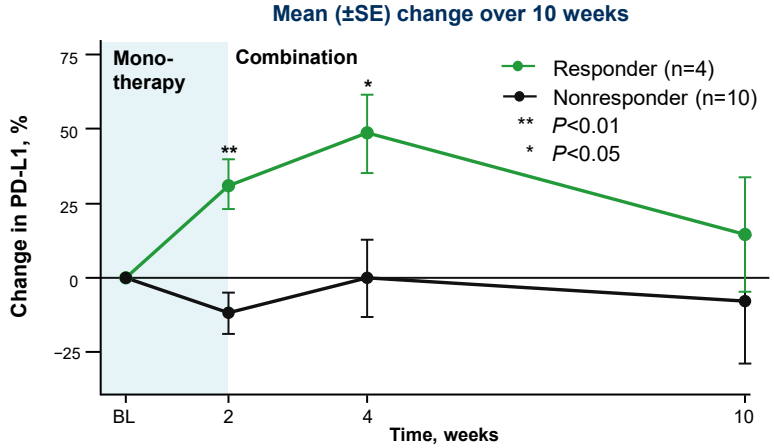
Change in Plasma IFN-γ



- Elevated plasma IFN-γ was observed in responders

Change in PD-L1



- Elevated plasma PD-L1 was observed in responders
  - Known to be induced by IFN-γ; higher tumor PD-L1 expression predicts improved response to ICIs[1]

Increase in IFN-γ during monotherapy may act as a potential biomarker of TGF-β inhibition; this will be studied further in dose-expansion cohorts

1. Incorvaia I, et al. *Adv Ther.* 2019;36:2600-2617.
Responders: PR and CR. Nonresponders: SD and PD. One patient with immune-mediated hepatitis and resultant increase in IFN-γ (nonresponder) was excluded from the mean change analyses.
iuPR, unconfirmed partial response per iRECIST.

Conclusions

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- PLN-101095 was generally well tolerated in the dose-escalation part of this Phase 1 study, with no new safety concerns emerging when the integrin inhibitor was combined with pembrolizumab
- Early signals of antitumor activity were observed in patients with ICI secondary resistance (ORR, 30%; DCR, 60%) treated with PLN-101095 in combination with pembrolizumab
- Circulating IFN-γ may be a potential biomarker for early prediction of treatment response
- Dose-expansion cohorts have been initiated in advanced NSCLC, ccRCC and TMB-H cancers

These data for PLN-101095 with pembrolizumab suggest the potential to meet a high unmet clinical need among patients with secondary ICI resistance, with no new safety concerns

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