TPS2690

# Trial in Progress: Cohort Expansion of a Phase I Study of PLN-101095, a First-in-Class Dual $\alpha_v\beta_8$ /$\alpha_v\beta_1$ Integrin Inhibitor, in Combination with Pembrolizumab in Patients With Advanced Solid Tumors Refractory to Immune Checkpoint Inhibitors

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## BACKGROUND

- Although single-agent immune checkpoint inhibitors (ICIs) show antitumor activity across multiple tumor types, only a minority of patients respond and fewer achieve durable responses,[1,2] highlighting the need for additional immunomodulatory strategies to improve efficacy
- Transforming growth factor β (TGF-β) drives immunosuppression, T-cell exclusion and fibrogenesis in solid tumors, contributing to acquired ICI resistance[3,4]
  - The integrins $\alpha_v\beta_8$ (expressed by tumor and/or immune cells) and $\alpha_v\beta_1$ (expressed by cancer-associated fibroblasts) activate latent TGF-β in the tumor microenvironment (TME) to promote immune escape[3,4]
- PLN-101095 is a first-in-class, oral, dual $\alpha_v\beta_8$/$\alpha_v\beta_1$ inhibitor that is designed to block integrin $\alpha_v\beta_8$ and $\alpha_v\beta_1$–driven activation of TGF-β locally in the TME[3,5] (**Figure 1**)
- Inhibition of $\alpha_v\beta_8$ and $\alpha_v\beta_1$ integrins blocks the activation of TGF-β in solid tumors to reduce immunosuppression, leading to a new or reinvigorated cancer immune response (**Figure 1**)[3,5]
- PLN-101095 differs from past efforts to systemically target the active TGF-β cytokine or TGF-β receptor kinase, which have produced limited antitumor responses[6]
  - Latent TGF-β can signal through its receptors following integrin-induced localized conformational shifts, without the active cytokine being released from the latent complex[7]
  - PLN-101095 prevents integrin binding to the latent TGF-β complex, providing a novel point of intervention immediately upstream of the TGF-β signaling pathway in solid tumors blocking activation of multiple TGF-β isoforms **(Figure 2)**
- Preclinical studies showed that PLN-101095 resensitized tumors to programmed cell death protein 1 (PD-1) inhibitors by reversing an ICI-resistant gene signature (high TGF-β/low interferon gamma [IFN-γ]) to an ICI-responsive state. In combination with anti–PD-1, it dose dependently reduced tumor volume and increased $CD8^+$ T-cell infiltration in multiple murine models compared with anti–PD-1 alone[8]
- The Phase 1 trial of PLN-101095 (FORTIFY; NCT06270706) is an ongoing first-in-human, multicenter, open-label, dose-escalation/expansion study to evaluate the safety, tolerability, pharmacokinetics and preliminary evidence of antitumor activity of PLN-101095 as monotherapy (14 days) and in combination with pembrolizumab (anti–PD-1) in participants with advanced or metastatic solid tumors who have disease progression while on an ICI
  - The dose-escalation phase (Part 1) enrolled 16 participants across 10 solid tumor types at 5 dose levels (250 mg twice daily [BID] to 2000 mg BID) and has been completed, with all dose levels cleared[8]
  - PLN-101095 was generally well tolerated in Part 1, with no new safety concerns emerging when the integrin inhibitor was combined with pembrolizumab[9]
    - The most comment treatment-related adverse event (TRAE) was rash (38%). All occurrences of rash were Grade 1 or 2, and the majority of events occurred with the first dose of pembrolizumab
    - Two serious TRAEs occurred: keratoacanthoma (Grade 2) and an immune-mediated hepatitis event (Grade 3; the single dose-limiting toxicity that led to discontinuation)
    - One additional TRAE of bullous dermatitis (Grade 2) led to drug discontinuation
  - Early signals of antitumor activity of PLN-101095 plus pembrolizumab were observed in 4 participants in Part 1 with ICI secondary resistance at doses of 1000 mg BID or greater
    - In these participants with secondary resistance, the unconfirmed objective response rate (ORR) was 40% (confirmed ORR was 30%) and the disease control rate was 60% **(Figure 3)**[9]
    - Clinically significant and durable responses were observed in 3 of 4 responders (median duration of 19 months) (**Figure 4**)[9]
  - Elevated plasma IFN-γ and programmed death-ligand 1 (PD-L1) levels (known to be induced by IFN-γ) were observed only in responding participants during the monotherapy period[9]
  - The Part 2 expansion cohorts were determined based on Part 1 efficacy signals[9]

## PART 2 STUDY DESIGN AND OBJECTIVES

- Part 2 **(Figure 5)** is being conducted in indication-expansion cohorts of participants who meet the Society for Immunotherapy of Cancer (SITC) criteria for secondary resistance to prior ICI therapy[10] using a Simon's 2-stage design
  - Three cohorts at a single dose level (1000 mg BID) are initially planned: non-small cell lung cancer, clear cell renal carcinoma and a tumor mutational burden (TMB)–high mixed-tumor cohort
  - Initially, 13 participants will be enrolled in each cohort
  - If ≤1 participant demonstrates a partial response per iRECIST (iPR) or a complete response per iRECIST (iCR) in Stage 1, the cohort will be stopped early for futility
  - If ≥2 participants demonstrate an iPR or iCR, 21 additional participants will be enrolled in that cohort in Stage 2
- The target ORR is 25% in each of the part 2 cohorts
- Part 2 objectives and endpoints are summarized in **Table 1**

## PATIENT ELIGIBILITY AND TREATMENT IN PART 2

- Based on Part 1 safety data and efficacy signals,[9] the PLN-101095 dose of 1000 mg BID is being evaluated in Part 2 in three patient cohorts **(Table 2)**
- Part 2 will be conducted in adults with histologically or cytologically confirmed advanced or metastatic solid tumors and evidence of secondary resistance to an anti–PD-(L)1 treatment **(Table 3)**

## ENROLLMENT

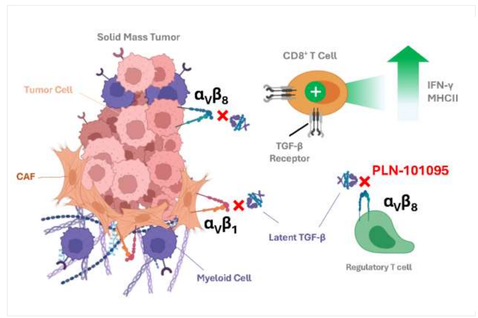
- FORTIFY is currently enrolling participants in the US **(Figure 6)**, with additional sites opening globally this year

## FURTHER INFORMATION

- Further information on FORTIFY (PLN-101095-ONC-101) can be found at: https://clinicaltrials.gov/study/NCT06270706
- **Contact email:** clintrials@pliantrx.com

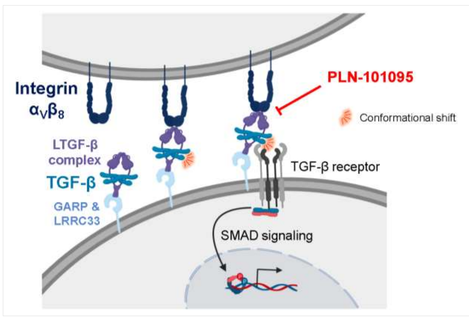
**References:** 1. Mariniello A, et al. *BioDrugs*. 2025;39:215-235. 2. Marei HE, et al. *Cancer Cell Int.* 2023;23:64. 3. Kothari V, et al. *J Immunother Cancer.* 2022;10(suppl 2). Abstract 1352. 4. Lainé A, et al. *Nat Comm.* 2021;12:6228. 5. Kothari V, et al. *J Immunother Cancer.* 2023;11(suppl 1). Abstract 464. 6. Jing H, et al. *Front Oncol.* 2025;15:1489701. 7. Campbell MG, et al. *Cell.* 2020;180:490-501.e16. 8. Daud A, et al. *J Immunother Cancer.* 2023;11(suppl 1). Abstract 714. 9. Yap TA, et al. AACR 2026. 10. Kluger H, et al. *J Immunother Cancer*. 2023;11(3):e005921.

**Figure 1.** PLN-101095 Mechanism of Action: Inhibition of Integrin $\alpha_V\beta_8$ and $\alpha_V\beta_1$ Blocks Activation of TGF-β, Reinvigorating the Immune Response



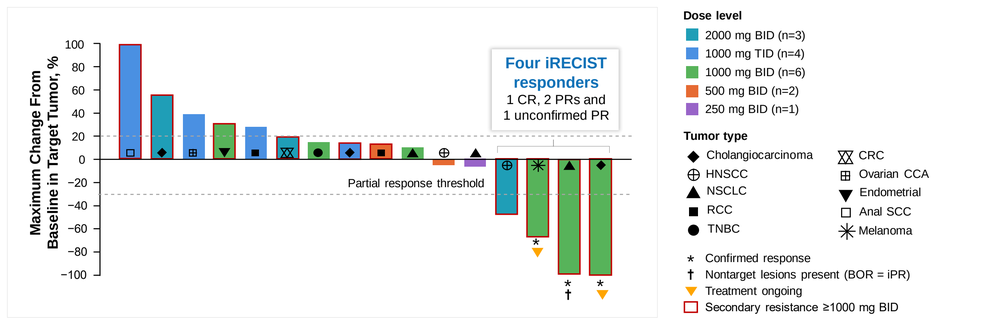

CAF, cancer-associated fibroblast; IFN-γ, interferon gamma; MHC, major histocompatibility complex; TGF-β, transforming growth factor beta.

**Figure 2.** Integrin Inhibition Represents a Novel Point of Intervention in the TGF-β Signaling Pathway in Solid Tumors



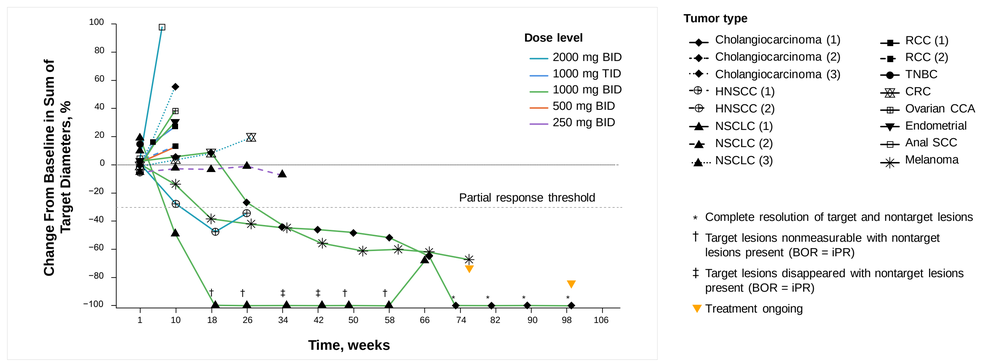

GARP, glycoprotein A repetitions predominant; LRRC33, leucine-rich repeat-containing protein 33; LTGF-β, latent transforming growth factor beta; TGF-β, transforming growth factor beta.

**Figure 3.** Clinical Activity of PLN-101095 in Combination With Pembrolizumab as Treatment for Solid Tumors (Including Those With Secondary Resistance to ICIs) in Part 1 of the Phase 1a/1b Trial[9]



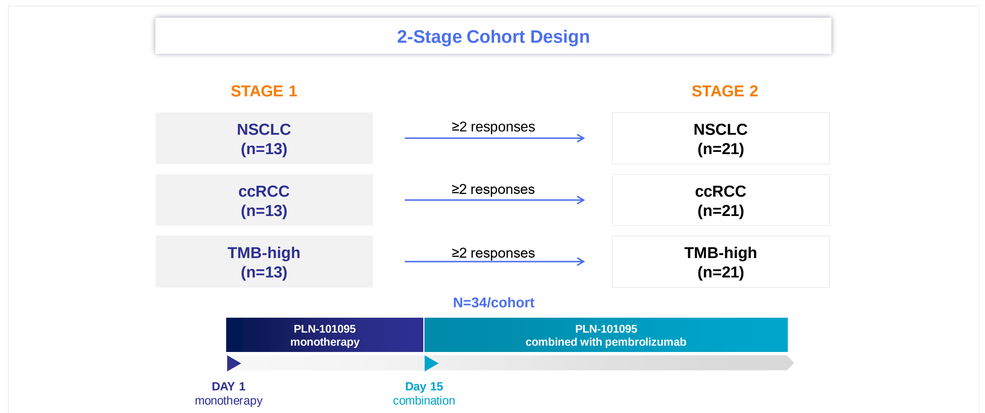

Data as of Feb 27, 2026.
BID, twice daily; BOR, best overall response; CCA, clear cell adenocarcinoma; CR, complete response; CRC, colorectal cancer; HNSCC, head and neck squamous cell carcinoma; ICI, immune checkpoint inhibitor; iPR, partial response per iRECIST; iRECIST, Immune Response Evaluation Criteria in Solid Tumors; NSCLC, non-small cell lung cancer; PR, partial response; RCC, renal cell carcinoma; SCC, squamous cell carcinoma; TID, 3 times daily; TNBC, triple-negative breast cancer.

**Figure 4.** Duration of Response of PLN-101095 in Combination With Pembrolizumab as Treatment for Solid Tumors (Including Those With Secondary Resistance to ICIs) in Part 1 of the Phase 1a/1b Trial[9]




Data as of Feb 27, 2026.
Confirmed objective responders had BOR of iPR or iCR. BID, twice daily; BOR, best overall response; CCA, clear cell adenocarcinoma; CRC, colorectal cancer; HNSCC, head and neck squamous cell carcinoma; ICI, immune checkpoint inhibitor; iCR, complete response per iRECIST; iPR, partial response per iRECIST; iRECIST, Immune Response Evaluation Criteria in Solid Tumors; NSCLC, non-small cell lung cancer; RCC, renal cell carcinoma; SCC, squamous cell carcinoma; TID, 3 times daily; TNBC, triple-negative breast cancer.

**Figure 5.** Study Design of Part 2 in Participants With Select Advanced Solid Tumors




ccRCC, clear cell renal carcinoma; NSCLC, non-small cell lung cancer; TMB, tumor mutational burden.

**Figure 6.** Enrolling FORTIFY Study Sites

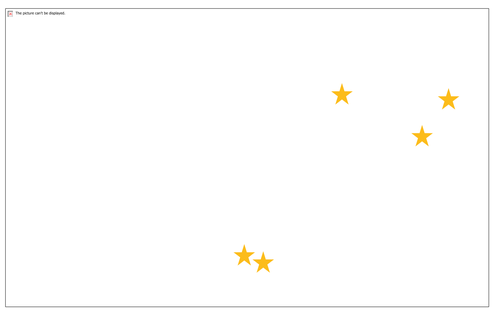



**Table 1.** Study Objectives and Endpoints for Part 2

| OBJECTIVES | ENDPOINTS |
|---|---|
| **PRIMARY** | |
| To evaluate the preliminary antitumor activity of PLN-101095 in combination with pembrolizumab in adults with advanced solid tumors who had PD while on previous anti–PD-(L)1 treatment | • ORR per iRECIST<br>• DCR per iRECIST<br>• Proportion of participants with SD per iRECIST |
| To further assess the safety and tolerability of PLN-101095 | • Incidence and severity of TEAEs and SAEs<br>• Cumulative toxicity leading to discontinuation<br>• Incidence of DLTs through Day 35 (DLT evaluation period) |
| **SECONDARY** | |
| To further characterize the pharmacokinetics of PLN-101095 | • PLN-101095 pharmacokinetic parameters |
| To further evaluate the durability of antitumor responses | • Duration of response in objective responders<br>• Time to response in objective responders<br>• Duration of stable disease in participants with best overall response of SD<br>• Time on treatment |
| **EXPLORATORY** | |
| To characterize potential pharmacodynamic and prognostic biomarkers of response to PLN-101095 | • Change from baseline in plasma IFN-γ and PD-L1 levels at Days 14 and 28<br>• Proportion of objective responders with increased plasma IFN-γ or PD-L1 levels at Days 14 and 28 |
| To further characterize the preliminary pharmacodynamic activity in blood-based and tumor-based biomarkers associated with PLN-101095 | • Change from baseline in circulating blood-based biomarkers, including immune cytokines, ctDNA and peripheral blood immune cell subsets<br>• Baseline and/or change from baseline in tumor tissue–based biomarkers, including integrin expression, markers of TGF-β pathway activity, TME composition and immune response |
| To assess the pharmacokinetic/pharmacodynamic relationships of PLN-101095 | • Relationship between pharmacokinetic parameters, biomarkers and clinical and safety outcomes |

ctDNA, circulating tumor DNA; DCR, disease control rate; DLT, dose-limiting toxicity; IFN-γ, interferon gamma; iRECIST, immune Response Evaluation Criteria in Solid Tumors; ORR, objective response rate; PD, progressive disease; PD-(L)1, programmed cell death 1 (ligand 1); SAE, serious adverse event; SD, stable disease; TEAE, treatment-emergent adverse event; TGF-β, transforming growth factor beta; TME, tumor microenvironment.

**Table 2.** Patient Cohorts and Treatment in Part 2 of the Phase 1a/1b Study

| | COHORT 1 | COHORT 2 | COHORT 3 |
|---|---|---|---|
| **TUMOR TYPE** | NSCLC<br>• Participants with both TMB-high and TMB-low tumors will be enrolled | ccRCC | TMB-high tumors[a]<br>• Limited to melanoma; CRC; BTC limited to cholangiocarcinoma and gallbladder cancers; endometrial; and urothelial cancers |
| **PLANNED COHORT SIZE** | 34 participants | 34 participants | 34 participants |
| **TREATMENT** | • PLN-101095 1000 mg orally BID from Day 1 (14-day monotherapy lead-in period)<br>• Concomitant pembrolizumab 200 mg IV Q3W from Day 15<br>• Duration is up to 9 weeks[b] initially, extended to duration of study in participants receiving clinical benefit[c] | | |
| **STRATIFICATION FACTOR** | • Prior duration on PD-(L)1 inhibitor therapy (<1 vs ≥1 year) | | |

BID, twice daily; BTC, biliary tract carcinoma; ccRCC, clear cell renal carcinoma; CRC, colorectal cancer; CT, computed tomography; iUPD, unconfirmed progressive disease per iRECIST; IV, intravenous; MRI, magnetic resonance imaging; NSCLC, non-small cell lung cancer; PD, progressive disease; PD-(L)1, programmed cell death 1 (ligand 1); Q3W, every 3 weeks; TMB, tumor mutational burden.
[a] Historical ≥10 mutations/megabase, as determined by local testing with a Clinical Laboratory Improvement Amendments–certified next-generation sequencing assay. [b] Participants who have iUPD at Week 9 may continue study treatment for an additional 4 weeks while awaiting results of a repeat CT/MRI scan to assess for PD by iRECIST. [c] Defined as iCR, iPR or iSD.

**Table 3.** Key Eligibility Criteria for Part 2 of the Phase 1a/1b study

| INCLUSION CRITERIA | EXCLUSION CRITERIA |
|---|---|
| • Age ≥18 years<br>• Confirmed advanced/metastatic NSCLC, ccRCC or TMB-high tumors as described in **Table 2**<br>• Previously received ≥12 weeks of continuous anti–PD-(L)1 treatment as monotherapy or in combination with other anticancer therapies[a]<br>• Documented prior clinical benefit with anti–PD-(L)1 treatment (defined as CR or PR at any time during treatment or SD lasting ≥6 months[b])<br>• Subsequently developed radiographic PD[b] during anti–PD-(L)1 treatment or within ≤12 weeks after the last dose<br>• Measurable disease at baseline<br>• Life expectancy ≥3 months<br>• ECOG performance status of 0 or 1<br>• Adequate bone marrow and organ function<br>• For women, not pregnant or breastfeeding | • History of life-threatening or permanently disabling immune-mediated adverse reaction(s) requiring permanent discontinuation of prior anti–PD-(L)1 treatment<br>• A known additional malignancy that is progressing or has required active treatment within the past 2 years<br>• Received prior radiotherapy within 2 weeks of study start for palliative bone-directed therapy and 4 weeks for all other radiotherapy<br>• Immunodeficiency or use of systemic steroids >10 mg/day (oral prednisone equivalent) within 2 weeks<br>• Active autoimmune disease that required systemic treatment in the past 2 years<br>• Known active brain and/or leptomeningeal CNS metastases<br>• Significant cardiac disease (i.e., MI within 6 months of study start, unstable angina pectoris, CCF, major abnormalities, LVEF <40%)<br>• Active infection requiring systemic therapy, including uncontrolled HIV, or hepatitis B or C<br>• Treatment with moderate or strong inducer or inhibitor of CYP3A4/5 and/or any strong inhibitor of BCRP, P-gp or OATP1A2 |

BCRP, breast cancer resistance protein; CCF, congestive cardiac failure; ccRCC, clear cell renal carcinoma; CNS, central nervous system; CR, complete response; CRC, colorectal cancer; CYP3A4/5, cytochrome P450 3A4/5; ECOG, Eastern Cooperative Oncology Group; HIV, human immunodeficiency virus; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSCLC, non-small cell lung cancer; OATP1A2, organic anion transporting polypeptide 1A2; PD, progressive disease; PD-(L)1, programmed cell death (ligand) 1; P-gp, P-glycoprotein; PR, partial response; SD, stable disease; TMB, tumor mutational burden.
[a] Need not be the most recent prior treatment. [b] As determined by the investigator.

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FORTIFY

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