TRIAL IN PROGRESS: Part 2 Cohort Expansion of a Phase I Study of PLN-101095, a Dual αvβ8/αvβ1 Integrin Inhibitor, in Combination With Pembrolizumab in Immune Checkpoint Inhibitor–Refractory Advanced Solid Tumours

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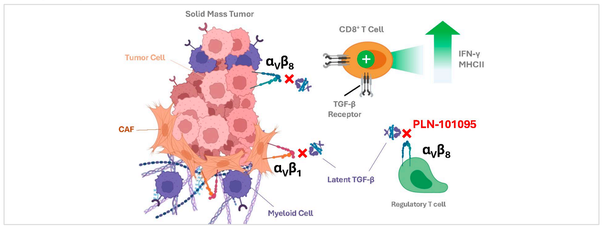
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BACKGROUND

- Although single-agent immune checkpoint inhibitors (ICIs) have demonstrated antitumour activity across multiple tumour types, only a minority of patients respond, fewer achieve durable responses, and some initial responders ultimately develop resistance,[1,2] highlighting the need for additional immunomodulatory strategies to improve efficacy and extend clinical benefit
- Transforming growth factor β (TGF-β) drives immunosuppression, T-cell exclusion and fibrogenesis in solid tumours, contributing to acquired ICI resistance[3,4]
  - The integrins $\alpha_v\beta_8$ (expressed by tumour and/or immune cells) and $\alpha_v\beta_1$ (expressed by cancer-associated fibroblasts) activate latent TGF-β in the tumour microenvironment (TME) thereby promoting immune escape[3,4]
- PLN-101095 is a potential 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 tumours to reduce immunosuppression, leading to a new or reinvigorated cancer immune response[3,5]

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.

- PLN-101095 differs from past efforts to systemically target free TGF-β cytokine, which have produced limited antitumour responses[6]
  - Latent TGF-β can signal through its receptors following integrin-induced active-domain exposure, without release of the cytokine from the latent complex[7]
  - PLN-101095 prevents integrin binding to the latent complex and active domain exposure—a novel point of intervention immediately upstream of TGF-β signalling that blocks activation of multiple isoforms in solid tumours
- Preclinical studies showed that PLN-101095 resensitised tumours 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 (high IFN-γ/low TGF-β). In combination with anti–PD-1, PLN-101095 dose dependently reduced tumour 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, multicentre, open-label, dose-escalation/expansion study to evaluate the safety, tolerability, pharmacokinetics and preliminary evidence of antitumour activity of PLN-101095 as monotherapy (14 days) and in combination with pembrolizumab (anti–PD-1) in participants with advanced or metastatic solid tumours who have disease progression while on an ICI
  - The dose-escalation phase (Part 1; Phase 1a) enrolled 16 participants across 10 solid tumour types at 5 dose levels (250 mg twice daily [BID] to 2000 mg BID) and has been completed, with all dose levels cleared[9]
  - 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 common treatment-related adverse event (TRAE) was rash (50.0%). All occurrences of rash were Grade 1 or 2, and most events occurred with the first dose of pembrolizumab (**Figure 2**)
    - 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

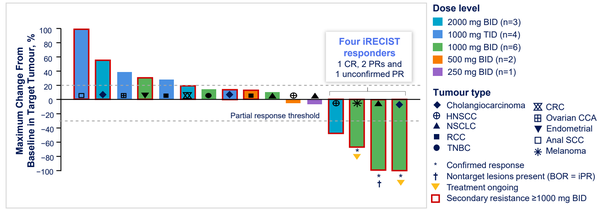
Figure 2. Adverse Events in Part 1

AST, aspartate aminotransferase.

- Early signals of antitumour 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 monotherapy treatment with PLN-101095 prior to combination with pembrolizumab[9]
- The Part 2 expansion cohorts were determined based on Part 1 efficacy signals[9]

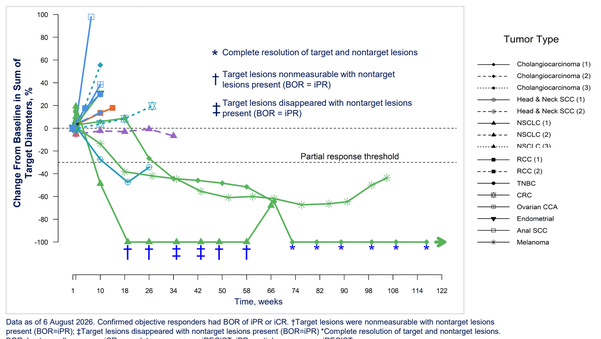
FORTIFY

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



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 Tumours (Including Those With Secondary Resistance to ICIs)in Part 1 of the Phase 1a Trial[9]

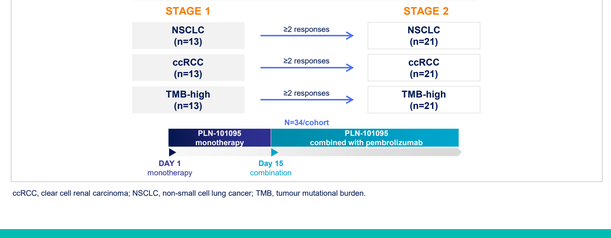


Data as of 6 August 2026. Confirmed objective responders had BOR of iPR or iCR. †Target lesions were nonmeasurable with nontarget lesions present (BOR=iPR); ‡Target lesions disappeared with nontarget lesions present (BOR=iPR) *Complete resolution of target and nontarget lesions. BOR, best overall response; iCR, complete response per iRECIST; iPR, partial response per iRECIST.

PART 2: STUDY DESIGN AND OBJECTIVES

- Part 2 (Phase 1b; **Figure 5**), the indication-expansion portion of the study, 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 2-stage design
  - Part 2 objectives and endpoints are summarised in **Table 1**
  - Three cohorts at a single dose level (1000 mg BID) are initially planned: non-small cell lung cancer, clear cell renal carcinoma and a tumour mutational burden (TMB)–high mixed-tumour cohort (**Table 2**)
  - 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 treatment and eligibility criteria are summarised in **Tables 2 and 3**

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



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

Table 1. Part 2: Study Objectives and Endpoints of the FORTIFY Study

OBJECTIVES	ENDPOINTS
PRIMARY	
To evaluate the preliminary antitumour activity of PLN-101095 in combination with pembrolizumab in adults with advanced solid tumours who had PD while on previous anti–PD-(L)1 treatment	• ORR per iRECIST • DCR per iRECIST • Proportion of participants with SD per iRECIST
To further assess the safety and tolerability of PLN-101095	• Incidence and severity of TEAEs and SAEs • Cumulative toxicity leading to discontinuation • Incidence of DLTs through Day 35 (DLT evaluation period)
SECONDARY	
To further characterise the pharmacokinetics of PLN-101095	• PLN-101095 pharmacokinetic parameters
To further evaluate the durability of antitumour responses	• DOR in objective responders • TTR in objective responders • Duration of stable disease in participants with best overall response of SD • Time on treatment
EXPLORATORY	
To characterise 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 • Proportion of objective responders with increased plasma IFN-γ or PD-L1 levels at Days 14 and 28
To further characterise the preliminary pharmacodynamic activity in blood-based and tumour-based biomarkers associated with PLN-101095	• Change from baseline in circulating blood-based biomarkers, including immune cytokines, ctDNA and peripheral blood immune cell subsets • Baseline and/or change from baseline in tumour 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 tumour DNA; DCR, disease control rate; DLT, dose-limiting toxicity; DOR, duration of response; 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, tumour microenvironment; TTR, time to response.

PART 2: TREATMENT AND ELIGIBILITY CRITERIA

Table 2. Patient Cohorts and Treatment in Part 2 of the FORTIFY Study

	COHORT 1	COHORT 2	COHORT 3
TUMOUR TYPE	NSCLC • Participants with both TMB-high and TMB-low tumours will be enrolled	ccRCC	TMB-high tumours[a] • 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) • Concomitant pembrolizumab 200 mg IV Q3W from Day 15 • 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, tumour 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 FORTIFY Study

INCLUSION CRITERIA	EXCLUSION CRITERIA
• Age ≥18 years • Confirmed advanced/metastatic NSCLC, ccRCC or TMB-high tumours as described in **Table 2** • Previously received ≥12 weeks of continuous anti–PD-(L)1 treatment as monotherapy or in combination with other anticancer therapies[a] • 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]) • Subsequently developed radiographic PD[b] during anti–PD-(L)1 treatment or within ≤12 weeks after the last dose • Measurable disease at baseline • Life expectancy ≥3 months • ECOG performance status of 0 or 1 • Adequate bone marrow and organ function • 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 • A known additional malignancy that is progressing or has required active treatment within the past 2 years • Received prior radiotherapy within 2 weeks of study start for palliative bone-directed therapy and 4 weeks for all other radiotherapy • Immunodeficiency or use of systemic steroids >10 mg/day (oral prednisone equivalent) within 2 weeks • Active autoimmune disease that required systemic treatment in the past 2 years • Known active brain and/or leptomeningeal CNS metastases • Significant cardiac disease (i.e., MI within 6 months of study start, unstable angina pectoris, CCF, major abnormalities, LVEF <40%) • Active infection requiring systemic therapy, including uncontrolled HIV, or hepatitis B or C • 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 1 (ligand 1); P-gp, P-glycoprotein; PR, partial response; SD, stable disease; TMB, tumour mutational burden.
[a] Need not be the most recent prior treatment. [b] As determined by the investigator.

ENROLMENT

- FORTIFY is currently enrolling participants in the US and Spain (**Table 4**)

Table 4. Study Sites

Institution	Location
Spain Sites	
Centro Integral Oncologico Clara Campal (START Madrid)	Madrid
Hospital Universitario San Pedro (START La Rioja)	Logroño (Rioja Salud)
Hospital Universitario Quironsalud Madrid (NEXT Madrid)	Pozuelo de Alarcón
Hospital Universitario Fundacion Jimenez Diaz (START FJD)	Madrid
Hospital Quironsalud Barcelona (NEXT Barcelona)	Barcelona
HM Nou Delfos (START Barcelona)	Barcelona
US Sites	
Arizona Clinical Research Center - MAIN	Tucson, AZ
Avera Medical Group Gynecologic Oncology Sioux Falls	Sioux Falls, SD
Carolina Cancer Research Center	Wilson, NC
Emory University Hospital	Atlanta, GA
Inova Schar Cancer Institute	Fairfax, VA
NEXT Austin	Austin, TX
NEXT Houston	Houston, TX
NEXT Virginia	Fairfax, VA
Rutgers Cancer Institute of New Jersey	New Brunswick, NJ
South Texas Accelerated Research Therapeutics (START), LLC	Grand Rapids, MI
START Astera, LLC	East Brunswick, NJ
START Dallas Fort Worth	Irving, TX
START Mountain Region	West Valley City, UT
START New York Long Island LLC	Lake Success, NY
Tennessee Oncology, PLLC - Elliston Place Plaza	Nashville, TN
The University of Texas MD Anderson Cancer Center	Houston, TX
University of Iowa Health Care	Iowa, IA
Washington University School of Medine	St. Louis, MO

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

Presenting author email: TYap@mdanderson.org

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