PHASE 1A TRIAL OF PLN-101095, AN INTEGRIN $\alpha_v\beta_8$ AND $\alpha_v\beta_1$ INHIBITOR, AS MONOTHERAPY AND IN COMBINATION WITH PEMBROLIZUMAB, IN TREATMENT-RESISTANT PATIENTS WITH ADVANCED OR METASTATIC SOLID TUMORS

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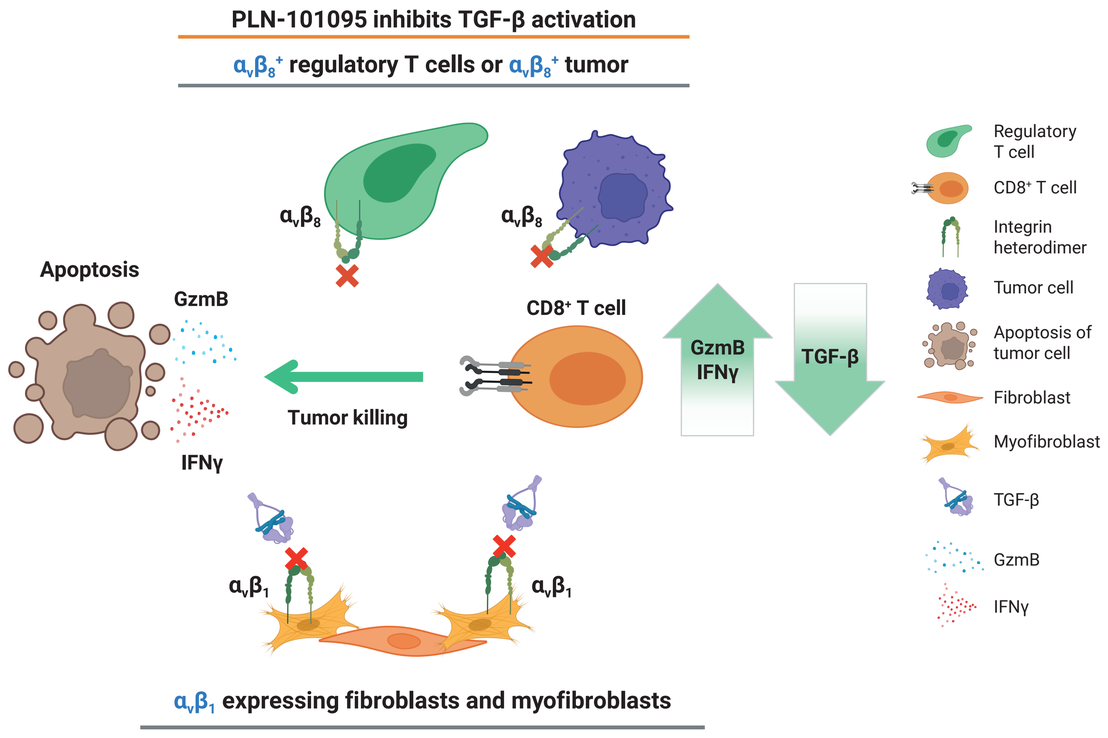
BACKGROUND

- PLN-101095 is a novel, orally bioavailable small molecule that effectively inhibits integrins alpha-V-beta 8 ($\alpha_v\beta_8$) and alpha-V-beta 1 ($\alpha_v\beta_1$) by preventing binding to the latency-associated peptide of transforming growth factor-beta (TGF-β)
- Blocking $\alpha_v\beta_8$ and $\alpha_v\beta_1$ prevents the activation of TGF-β and may impede immunosuppression by increasing immune cell infiltration into the tumor microenvironment
- PLN-101095 blocks inhibitory pathways on T cells and the tumor stroma, resulting in antitumor activity and tumors becoming more susceptible to immune checkpoint inhibitor (ICI) therapies (**Figure 1**)
- As such, PLN-101095 has the potential for use in combination with ICI therapies, such as anti-programmed cell death protein 1 (PD-1) monoclonal antibodies (mAbs), to target ICI-resistant tumors

Figure 1. PLN-101095 blocks multiple resistance mechanisms, leading to tumor killing

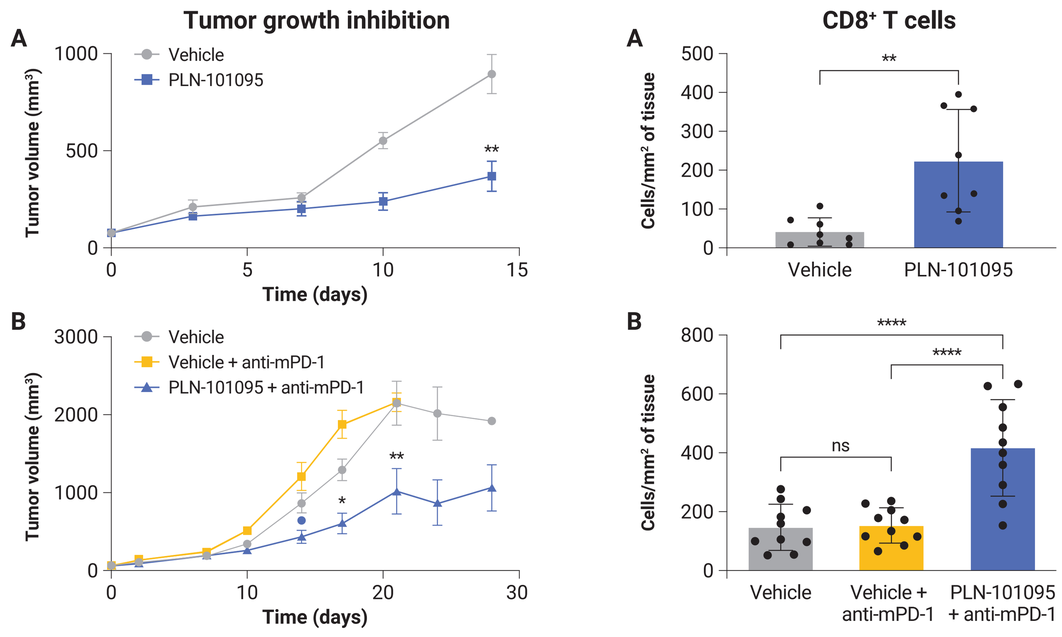


$\alpha_v\beta_1$, alpha-V-beta 1; $\alpha_v\beta_8$, alpha-V-beta 8; CD, cluster of differentiation; GzmB, granzyme B; IFNγ, interferon gamma; TGF-β, transforming growth factor-beta
Figure developed by Pliant Therapeutics, Inc. and created with BioRender.com

PRECLINICAL ANTITUMOR ACTIVITY

- The *in vivo* antitumor activity of PLN-101095 in combination with ICI therapy (anti-murine [m]PD-1 mAb) was assessed in the anti-PD-1 therapy-resistant orthotopic EMT6 breast cancer mouse model (**Figure 2**)
  - PLN-101095 demonstrated monotherapy activity in reduction of tumor volume and increased cluster of differentiation (CD)8+ T cell infiltration
  - PLN-101095 in combination with an anti-mPD-1 mAb elicited a dose-dependent reduction in tumor volume and increased CD8+ T cell tumor infiltration in the tumor microenvironment compared with anti-mPD-1 mAb therapy alone

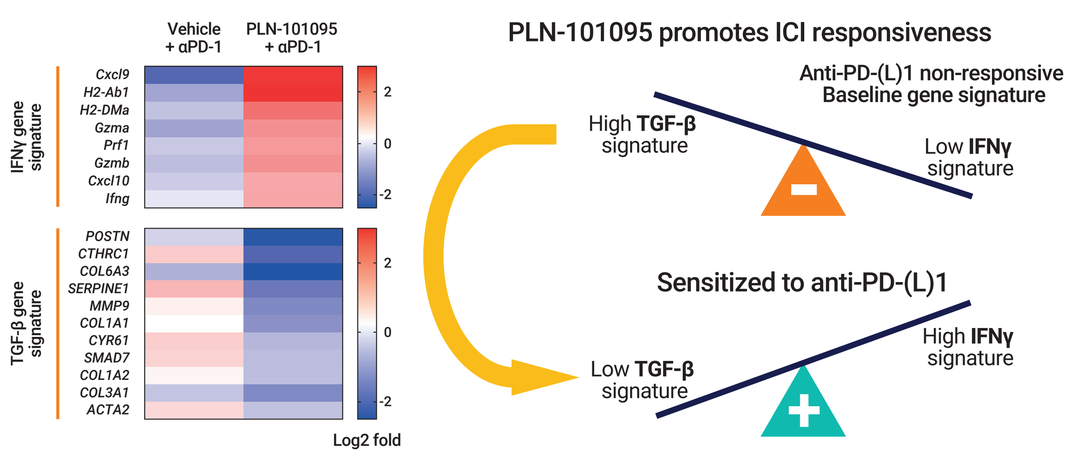
Figure 2. PLN-101095 (**A**) alone (N=8) and (**B**) in combination (N=10) with anti-mPD-1 mAb inhibited tumor growth and promoted CD8+ T cell infiltration in the anti-PD1 therapy-resistant EMT6 breast cancer mouse model



Error bars represent standard error (line graphs) or standard deviation (bar graphs); *p<0.05; **p<0.01; ****p<0.0001 vs. vehicle
CD, cluster of differentiation; mAb, monoclonal antibody; mPD-1, murine programmed cell death protein 1; ns, not significant

- Tumors resistant to ICIs tend to have gene signatures high in TGF-β response genes and low in interferon gamma (IFNγ) response genes[1–3]
- PLN-101095 in combination with anti-PD1 reverses this ICI-resistant tumor gene signature to be ICI responsive, namely a TGF-β-low and IFNγ-high gene signature (**Figure 3**)

Figure 3. PLN-101095 potently increases IFNγ and TGF-β gene signatures



ICI, immune checkpoint inhibitor; IFNγ, interferon gamma; L, ligand; PD, programmed cell death protein; TGF-β, transforming growth factor-beta

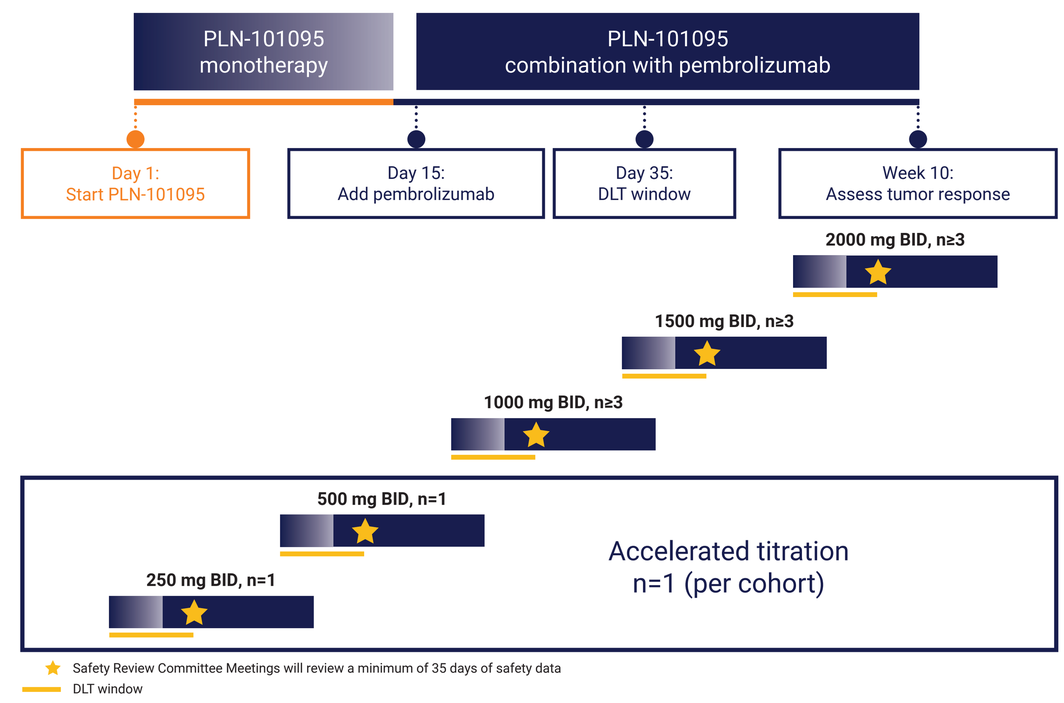
STUDY DESIGN

- This is a first-in-human, open-label, dose-escalation study designed to evaluate the safety, tolerability, and pharmacokinetics of PLN-101095 as monotherapy and in combination with pembrolizumab in adult patients with advanced or metastatic solid tumors and documented disease progression after at least 3 months from the start of treatment with pembrolizumab, and with no other available effective treatment options (**Figure 4**)
- PLN-101095 will be administered as monotherapy twice daily (BID) for 14 days, followed by PLN-101095 BID in combination with pembrolizumab every 3 weeks, starting on Day 15
- Up to 5 dose levels are planned as follows: level 1, 250 mg BID; level 2 500 mg BID; level 3 1000 mg BID; level 4, 1500 mg BID; and level 5, 2000 mg BID

DOSE ESCALATION

- Dose escalation will be conducted using a Bayesian optimal interval (BOIN) dose escalation design with accelerated titration (n=1) permitted for dose levels 1 and 2 (**Figure 4**)
- Dose limiting toxicities (DLTs) will be evaluated over the first 35 days of dosing for dose escalation/de-escalation decisions
- A minimum of 3 participants will be enrolled at dose levels 3 to 5
- Following the dose-escalation cohorts, dose-expansion cohorts using a Simon's Two-Stage design are planned

Figure 4. Study design



BID, twice daily; DLT, dose-limiting toxicity

INCLUSION CRITERIA

- ≥18 years of age
- Estimated survival of ≥3 months
- Advanced or metastatic solid tumor for which pembrolizumab is indicated
- Received ≥3 doses (200 mg once every 3 weeks) of pembrolizumab
- Evidence of disease progression (relapsed [secondary resistance] or refractory [primary resistance]) ≥3 months after initiation of pembrolizumab
- No other available effective treatment options
- Eastern Cooperative Oncology Group performance status of 0 or 1
- Adequate bone marrow and organ function

ENDPOINTS

PRIMARY ENDPOINTS

- Incidence and severity of treatment-emergent adverse events and serious adverse events
- Incidence of DLTs and cumulative toxicities leading to discontinuation

SECONDARY ENDPOINT

- Pharmacokinetics of PLN-101095 given as monotherapy and in combination with pembrolizumab

KEY EXPLORATORY ENDPOINTS

- Change from Baseline in blood-based biomarkers (cytokines, circulating tumor DNA, blood cell profile)
- Objective response rate per Immunological Response Evaluation Criteria in Solid Tumours (iRECIST)
- Disease control rate per iRECIST
- Proportion of participants with stable disease per iRECIST

CONCLUSIONS

- This first-in-human trial will evaluate the safety and tolerability of PLN-101095, administered first as monotherapy, and subsequently in combination with pembrolizumab in participants with advanced or metastatic solid tumors who have disease progression while on pembrolizumab
- Enrolled participants will have demonstrated primary or acquired resistance to pembrolizumab and, therefore, will serve as their own control for assessing antitumor activity and pharmacodynamic effects
- This BOIN dose escalation trial design with a monotherapy period followed by a combination therapy period in the same study participants enables the efficient conduct of dose escalation trials involving ICI-sensitizing drugs in participants with resistance to ICIs

Ethics approval: The protocol and all amendments are approved by the appropriate institutional review board or independent ethics committee at each participating study site. The study is being conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines

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