Plasma Biomarkers of Immune Activation Predict Sensitization to Immune Checkpoint Inhibition in Patients With Advanced Solid Tumors Receiving Dual $\alpha_v\beta_8/\alpha_v\beta_1$ Integrin Inhibitor PLN-101095

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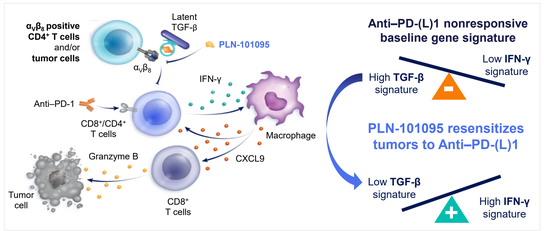
546

BACKGROUND

- Although single-agent immune checkpoint inhibitors (ICIs) show tumor 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 secondary ICI resistance[3,4]
- PLN-101095 is a potential first-in-class, oral, dual $\alpha_v\beta_8/\alpha_v\beta_1$ inhibitor designed to block integrin $\alpha_v\beta_8$ and $\alpha_v\beta_1$–driven activation of TGF-β locally in the tumor microenvironment[3,5]
- PLN-101095 prevents integrin binding to the latent TGF-β complex and the resulting active-domain exposure—a novel point of intervention upstream of integrin-based TGF-β signaling that blocks activation of multiple isoforms in solid tumors
  - Preclinical studies have shown that PLN-101095 can shift solid tumors from a TGF-β–high to an interferon γ (IFN-γ)–high gene signature, resulting in increased circulating C-X-C motif chemokine ligand 9 (CXCL9) levels and cytotoxic T-cell infiltration (**Figure 1**)[6]
- PLN-101095 FORTIFY (NCT06270706) is an ongoing first-in-human, multicenter, open-label, Phase 1 dose-escalation (Part 1)/expansion (Part 2) study evaluating the safety, tolerability, pharmacokinetics and preliminary evidence of tumor activity of a 14-day PLN-101095 monotherapy run-in followed by PLN-101095 plus pembrolizumab (anti–PD-1) in participants with advanced or metastatic solid tumors who have secondary ICI resistance
- **Objective:** characterize FORTIFY Part 1 baseline and on-treatment biomarkers

Figure 1. Mechanism of Action of PLN-101095 on $\alpha_v\beta_8$-Expressing Immune and/or Tumor Cells



CD, cluster of differentiation; CXCL, C-X-C motif chemokine ligand; IFN-γ, interferon γ; TGF-β, transforming growth factor β.

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METHODS

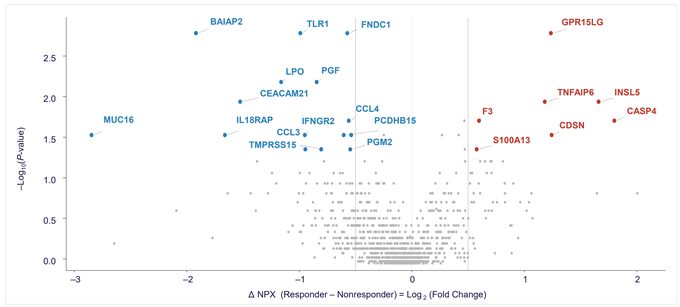
- FORTIFY included a 14-day PLN-101095 monotherapy run-in, followed by PLN-101095 in combination with pembrolizumab (200 mg every 3 weeks)
- Plasma samples from 15 participants were analyzed using the Olink Reveal proteomics platform
- Plasma protein expression was assessed at baseline, Day 14 (monotherapy) and Days 28 and 70 (combination therapy) to identify baseline and on-treatment pharmacodynamic biomarkers associated with subsequent clinical response to combination therapy
- Analytes were grouped a priori into 3 families with Benjamini-Hochberg FDR (q<0.05) applied within each: baseline exploratory (m=1034), mechanism-based postbaseline (m=5: IFN-γ, CXCL9, CXCL10, CXCL11, and granzyme B [GZMB]) and postbaseline exploratory (m=1029)
- Benjamini-Hochberg false discovery rate (FDR) correction was applied in each family independently at q<0.05
- Unsupervised clustering and random forests were conducted to identify differences at baseline and separately, post baseline

RESULTS

Baseline Differences in Plasma Proteins Between Responders and Nonresponders

- Four participants, all with secondary ICI resistance, achieved an objective clinical response following treatment with PLN-101095 plus pembrolizumab
- Of 1034 plasma proteins measured, 22 showed nominal differences at baseline between responders and nonresponders (*P*<0.05; |change in normalized protein expression [NPX]| ≥0.5; **Figure 2**)
  - Analytes with the largest baseline differences and higher levels in responders included CASP4, INSL5, GPR15LG, CDSN, and TNFAIP6
  - Analytes with the largest baseline differences and lower levels in responders included MUC16, CEACAM21, BAIAP2, IL18RAP, LPO, and TLR1

Figure 2. Baseline Protein Expression Differences

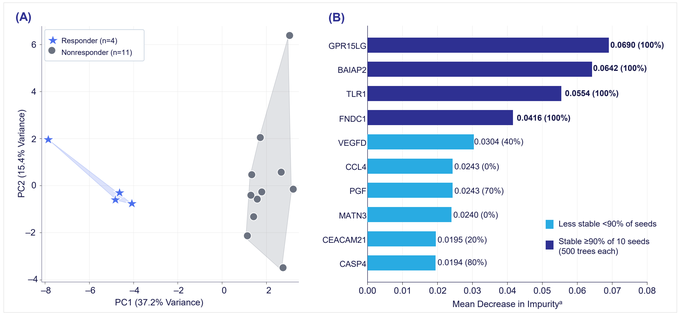


BAIAP2, brain-specific angiogenesis inhibitor 1-associated protein 2; CASP4, caspase 4; CCL3, C-C motif chemokine 3; CCL4, C-C motif chemokine 4; CEACAM21, carcinoembryonic gen-related cell adhesion molecule 21; CDSN, corneodesmosin; F3, tissue factor (ie, coagulation factor III); FNDC1, fibronectin type III domain-containing protein 1; GPR15LG, G protein-coupled receptor 15 ligand; IFNGR2, interferon-γ receptor 2; IL18RAP, interleukin-18 receptor accessory protein; INSL5, insulin-like peptide 5; LPO, lactoperoxidase; MUC16, mucin-16; NPX, normalized protein expression; PCDHB15, protocadherin beta-15; PGF, placenta growth factor; PGM2, phosphoglucomutase-2; S100A13, S100 calcium-binding protein A13; TLR1, toll-like receptor 1; TMPRSS15, transmembrane serine protease 15; TNFAIP6, tumor necrosis factor-inducible gene 6 protein.

Potential Discrimination of Part 1 Responders and Nonresponders at Baseline

- Of the 22 proteins that showed nominal differences at baseline (no *P* values were significant post FDR correction) between responders and nonresponders (**Figure 3**):
  - Unsupervised clustering identified a set of analytes that separated responders from nonresponders
  - Random forest analysis identified GPR15LG, BAIAP2, TLR1, and FNDC1 as the 4 most important proteins for distinguishing responders from nonresponders
  - These findings are hypothesis generating and require validation in a larger cohort

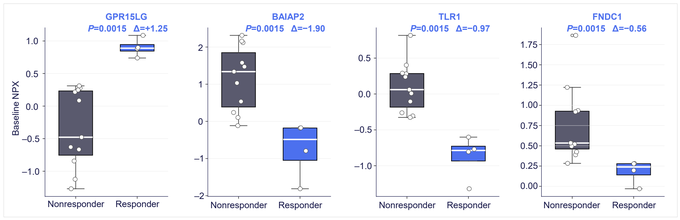
Figure 3. Principal Component Analysis of Baseline Plasma Protein Expression in Responders and Nonresponders: (A) Unsupervised Clustering and (B) Random Forest



BAIAP2, brain-specific angiogenesis inhibitor 1-associated protein 2; CASP4, caspase 4; CCL4, C-C motif chemokine ligand 4; CEACAM21, carcinoembryonic gen-related cell adhesion molecule 21; FNDC1, fibronectin type III domain-containing protein 1; GPR15LG, G protein-coupled receptor 15 ligand; MATN3, matrilin 3; PC, principal component; PGF, placental growth factor; TLR1, toll-like receptor 1; VEGFD, vascular endothelial growth factor D.
[a]Percentage is the seed stability across 10 seeds × 500 trees.

- Baseline NPX values for the 4 key proteins are shown in **Figure 4**

Figure 4. Baseline NPX of Key Proteins

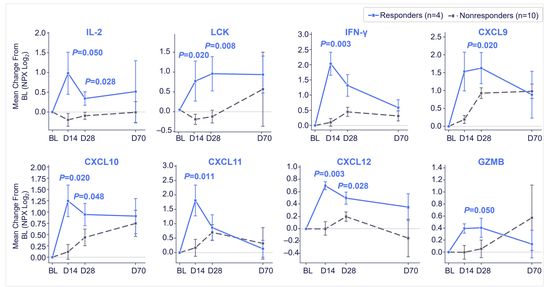


BAIAP2, brain-specific angiogenesis inhibitor 1-associated protein 2; FNDC1, fibronectin type III domain-containing protein 1; GPR15LG, G protein-coupled receptor 15 ligand; NPX, normalized protein expression; TLR1, toll-like receptor 1.
P values: exact Wilcoxon rank sum test. Error bars represent standard deviation.

Biomarkers Consistent With PLN-101095 Mechanism of Action

- Postbaseline analyses showed that LCK, IL-2, IFN-γ, CXCL9, CXCL10, CXCL11, GZMB, and CXCL12 distinguished responders from nonresponders (**Figure 5**)
  - **T-cell activation (upstream):** increased LCK and IL-2, consistent with proximal T-cell receptor signaling and IL-2–driven proliferation, both repressed by TGF-β[7-9]
  - **Effector cytokine:** increased IFN-γ
  - **T-cell recruitment:** increased IFN-γ–inducible C-X-C chemokine receptor 3 ligands CXCL9, CXCL10, and CXCL11[10]
  - **Cytolysis:** increased GZMB[11]
  - **Cancer-associated fibroblast (CAF) phenotype**: Increased CXCL12 at Day 14 may reflect a treatment-induced shift in CAF phenotype following TGF-β pathway inhibition; this hypothesis requires confirmation

Figure 5. Biomarker Changes Consistent With Immune Activation During PLN-101095 Treatment



IL-2, LCK and CXCL12 were not significant post FDR correction. IFN-γ, CXCL9, CXCL10, CXCL11 and GZMB were significant (q<0.05) post FDR correction. BL, baseline; CXCL, C-X-C motif chemokine ligand; D, day; GZMB, granzyme B; IFN-γ, interferon gamma; IL-2, interleukin-2; LCK, lymphocyte-specific protein tyrosine kinase. *P* values: exact Wilcoxon rank sum test. Error bars represent standard deviation.

CONCLUSIONS

- Early induction of immune activation biomarkers during PLN-101095 monotherapy was associated with subsequent clinical response following pembrolizumab initiation, supporting a potential mechanism of immune resensitization in patients with secondary ICI-resistant solid tumors
- Collectively, these findings support the hypothesis that TGF-β pathway inhibition promotes immune activation, T-cell recruitment into the tumor microenvironment, and enhanced cytotoxic effector function
- These hypothesis-generating findings support further evaluation of candidate baseline predictive and on-treatment pharmacodynamic biomarkers in tumor-specific expansion cohorts of patients with secondary ICI-resistant disease

Disclosures: M. Decaris, R. Sharma, J. Amaya-Amaya and **C. Barnes** are employees of Pliant Therapeutics. **M. Sharma** reports stock and other ownership interests with AADi, AbbVie, Abbott Laboratories, Amgen, Bristol Myers Squibb, Eli Lilly, Enlaza Therapeutics, Gilead Sciences, Johnson & Johnson, Merck, Pfizer, Pliant Therapeutics Inc., Regeneron, Vertex and Whitehawk Therapeutics. Research funding with AbbVie, Adcentrx Therapeutics, ALX Oncology, Alkermes, Arcus Biosciences, Artios, Arvinas, Astellas Pharma, AstraZeneca, BioNTech, Black Diamond Therapeutics, Boehringer Ingelheim, Bolt Biotherapeutics, Boundless Bio, Bristol Myers Squibb, Chugai Pharma, Circle Pharma, Context Therapeutics, Compugen, Cullinan Oncology, Daiichi Sankyo/UCB Japan, Day One Biopharmaceuticals, Debiopharm Group, Deciphera, Eli Lilly, Enlaza Therapeutics, EvolveImmune Therapeutics, Exelixis, Exscientia, FoRx Therapeutics, Genentech/Roche, Genmab, Gilead Sciences, GlaxoSmithKline/Tesaro, Halda Therapeutics, Helsinn Therapeutics, Iambic Therapeutics, IDEAYA Biosciences, Ikena Oncology, Incyte, InhibRx, Ipsen, Johnson & Johnson/Janssen, Kùs Pharma, Kumquat Biosciences, MacroGenics, MBrace Therapeutics, MedLink Therapeutics, Menarini Group, Merck, Mirati Therapeutics, Moderna Therapeutics, Monte Rosa Therapeutics, NGM Biopharmaceuticals, NiKang Therapeutics, Olema Pharmaceuticals, Opna Bio, Pfizer, Pliant Therapeutics Inc., Quanta Therapeutics, Regeneron, Repare Therapeutics, Seagen, Takeda, Third Arc Bio, Treeline Biosciences, VelaVigo Bio, Vividion Therapeutics and Zymeworks.

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