Background Across several cancer types, activated transforming growth factor-β (TGFβ) helps support an immuno-suppressive microenvironment that contributes to immune checkpoint blockade (ICB) resistance and treatment failure. Alpha-V integrins, specifically αVβ8, αVβ6, and αVβ1, are the primary activators of TGFβ from the latent complex. These integrins have a limited cell-expression profile that make them potential targets to safely and potently inhibit the activation of TGFβ in cancer. Targeting αVβ8 has recently emerged as a promising approach to realizing the potential of anti-TGFβ therapies to address ICB resistance. In the stroma, integrin αVβ1 is the major source of activated TGFβ. Here, we describe the development of PLN-1095, a dual small molecule inhibitor of αVβ8 and αVβ1 and characterize this approach in ICB-resistant mouse tumor models.

Methods In vivo efficacy and activities of a dual αVβ8 and αVβ1 integrin inhibitor, PLN-1095, in combination with anti-programmed death receptor-1 antibody (anti mPD-1) was evaluated in EMT6, Pan02, and CT26 cancer syngeneic mouse models by monitoring animal survival, tumor growth, gene expression, and infiltrating CD8+ lymphocytes. In addition, PLN-1095 single agent proinflammatory and antifibrotic activities was assessed using mouse EMT6 tumors in vivo and human breast tumor tissues ex vivo.

Results PLN-1095 showed selective inhibition of integrins αVβ8 and αVβ1 at nanomolar concentrations. Treatment of mice bearing EMT6 tumors with PLN-1095 alone and in combination with anti-mPD-1 significantly reduced tumor growth. Anti-mPD-1 treatment showed a peripherally restricted CD8+ and CD4+ pattern, whereas PLN-1095 treatment significantly increased intra-tumoral CD8+ T cell infiltration. PLN-1095 treatment, both alone and in combination with anti-mPD-1 was associated with elevated gene expression of CXCL9 and other pro-inflammatory cytokines, enhanced expression of genes involved in antigen presentation, reduced TGFβ signaling, diminished expression of pro-fibrogenic and angiogenic transcripts across the models tested. A significant increase in granzyme B positive T cells was observed in human breast cancer tissues treated with PLN-1095 ex vivo.

Conclusions PLN-1095 sensitized immunologically cold murine tumors to anti mPD-1 ICB. PLN-1095-mediated inhibition of integrins αVβ8 and αVβ1 effectively reduced the immunosuppressive effects of TGFβ by activating the immune system thereby promoting CD8+ cytotoxic T cell infiltration in the tumors. Based on these results, a first-in-human clinical trial investigating the effects of PLN-1095 is being planned.

Ethics Approval All the animal Studies were approved by Pliant IACUC protocol # PLI-010-2019. Fresh breast tumor samples were collected from the Biological Resource Center of the Centre Léon Bérard by Marie’s laboratory, according to the institutional review board and ethics committee and with fully informed patient consent (French Ministry of Research agreement number: AC-2013-1871 and AC-2019-3426).