Background Pancreatic ductal adenocarcinoma (PDA) has a 5-year survival of less than 10% and remains the 3rd leading cause of cancer-related death in Western societies. New treatment options are urgently needed. We previously characterized molecular subsets of PDA, including fibrotic elements of the disease, associated with pre-clinical and clinical response to selected tailored treatment strategies.\(^1\)\(^-\)\(^4\) TGF-\(\beta\) promotes stromal cell reprogramming, immunosuppression, and fibrinogenesis in cancers, including PDA.\(^5\)\(^-\)\(^6\) Integrins \(\alpha\)\(\beta\)\(3\) and \(\alpha\)\(\beta\)\(1\) are important activators of TGF-\(\beta\) signaling. Selective integrin blockade has recently emerged as a promising therapeutic approach to address TGF-\(\beta\)-mediated immunotherapy resistance, and improve anti-tumor response across cancer models.\(^7\)\(^-\)\(^9\) Here, we assessed the in vivo efficacy of PLN-101095, a dual selective small molecule inhibitor of \(\alpha\)\(\beta\)\(8\) and \(\alpha\)\(\beta\)\(1\), in well-annotated models of advanced PDA.

Methods We determined the pre-clinical efficacy of PLN-101095 in genetically-defined (LSL-Kras\(\text{G12D}^+\); LSL-Trp53\(\text{R172H}^+\); Pdx1-Cre (KPC), and Pan02) and genomically diverse patient-derived PDA xenograft models, testing clinically-relevant combinations with standard of care (SoC) chemotherapy and anti-programmed death receptor-1 antibody (anti mPD-1), by monitoring tumor growth, metastasis, and animal survival. Mechanistic assessment of alterations in the tumor microenvironment (TME) was performed using comprehensive transcriptomic, immunohistochemical, and immunofluorescence approaches.

Results Single cell analysis of KPC pancreatic tumors revealed restricted expression of integrin \(\alpha\)\(\beta\)\(8\) (ITGB8) within the T-reg and NK cell subsets, while components of TGF-\(\beta\) signaling were more widely represented across cancer and stromal cell subsets. Dual targeting of \(\alpha\)\(\beta\)\(8\) and \(\alpha\)\(\beta\)\(1\) with PLN-101095 in this setting effectively reduced tumor growth (45% reduction in tumor weight compared with Vehicle; \(P=0.003\)) and significantly delayed disease progression in vivo (median OS Vehicle 29.5 days vs PLN-101095 45 days, \(P<0.0001\)). Of note, combining PLN-101095 with anti mPD-1 antibody further improved survival in this aggressive model of metastatic PDA (median OS anti mPD-1 33 days vs PLN-101095 + anti mPD-1 51 days, 22% CR; \(P<0.0001\)). In a second syngeneic model of PDA (Pan02), PLN-101095 in combination with immune checkpoint blockade (ICB) significantly reduced tumor growth, TGF-\(\beta\) signaling, and fibrosis, while increasing CD8+ lymphocyte infiltration. Finally, utilizing patient-derived models of metastatic PDA revealed that PLN-101095 significantly blocked tumor growth, improved the response to SoC chemotherapy Gemcitabine/Abraxane, and reduced the number and size of lung metastases.

Conclusions These data demonstrate that PLN-101095 significantly enhances ICB or SoC chemotherapy response in advanced PDA models and provide scientific rationale for future combination studies testing PLN-101095 in pancreatic cancer.

REFERENCES
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