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. TGF-β promotes stromal cell reprogramming, imunosuppression, and fibrinogenesis in cancers, including PDA. Integrins αVβ8 and αVβ1 are important activators of TGF-β signaling. Selective integrin blockade has recently emerged as a promising therapeutic approach to address TGF-β-mediated immunotherapy resistance, and improve anti-tumor response across cancer models. Here, we assessed the in vivo efficacy of PLN-101095, a dual selective small molecule inhibitor of αVβ8 and αVβ1, in well-annotated models of advanced PDA.

Methods} We determined the pre-clinical efficacy of PLN-101095 in genetically-defined (LSL-KrasG12D/+, LSL-Trp53R172H/++; 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 αβ8 (ITGB8) within the T-reg and NK cell subsets, while components of TGF-β signaling were more widely represented across cancer and stromal cell subsets. Dual targeting of αVβ8 and αVβ1 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-β 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/Abbraxane, 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.