798 TGFβ BLOCKADE IN PANCREATIC CANCER ENHANCES SENSITIVITY TO COMBINATION CHEMOTHERAPY

[1]Li Qiang*, [2]Megan Hoffman, [2]Lestat Ali, [2]Jaime Ivan Castillo Silva, [4]Ayantu Temesgen, [2]Patrick Lenehan, [3]Lauren Kageler, [2]Jennifer Wang, [2]Elisa Bello, [2]Victoire Cardot-Ruffino, [2]Giselle Uribe, [2]Annan Yang, [4]Michael Dougan, [2]Andrew J Aguirre, [2]Srivatsan Raghavan, [5]Marc Pelletier, [6]Viviana Cremasco, [2]Stephanie Dougan. *[1]Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA; [2]Dana-Farber Cancer Institute, Boston, MA, USA; [3]Harvard Medical School, Boston, MA, USA; [4]Massachusetts General Hospital, Boston, MA, USA; [5]Novartis Institute for Biomedical Research, Cambridge, MA, USA; [6]Novartis Institutes of BioMedical Resear, Cambridge, MA, USA*

Background TGFβ plays pleiotropic roles in pancreatic cancer including promoting metastasis, attenuating CD8 T cell activation, and enhancing myofibroblast differentiation and deposition of extracellular matrix. However, single-agent TGFβ inhibition has shown limited efficacy against pancreatic cancer in mice or humans.

Methods We evaluated the TGFβ blocking antibody NIS793 in combination with either gemcitabine/n(ab)-paclitaxel or FOLFIRINOX chemotherapy in orthotopic pancreatic cancer models.[1] Single-cell RNA-seq and immunofluorescence were used to evaluate changes in tumor cell state and the tumor microenvironment.

Results Blockade of TGFβ with chemotherapy reduced tumor burden in poorly immunogenic pancreatic cancer, without affecting the metastatic rate of cancer cells. Surprisingly, efficacy of combination therapy was not dependent on CD8 T cells, as response to TGFβ blockade was preserved in CD8-depleted or RAG2-/- mice. TGFβ blockade decreased total αSMA+ fibroblasts but had minimal effect on fibroblast heterogeneity. Bulk RNA-seq on tumor cells sorted ex vivo revealed that tumor cells treated with TGFβ blockade adopted a classical lineage consistent with enhanced chemosensitivity, and immunofluorescence for cleaved caspase 3 confirmed that TGFβ blockade increased chemotherapy-induced cell death in vivo.

Conclusions TGFβ regulates pancreatic cancer cell plasticity along the classical to basal lineage. TGFβ blockade in orthotopic mouse models of pancreatic cancer synergizes with chemotherapy by maintaining a classical-like chemotherapy-sensitive state. This study provides scientific rationale for evaluation of NIS793 with either FOLFIRINOX or gemcitabine/n(ab)paclitaxel chemotherapy backbone in the clinical setting (NCT04390763, NCT04935359, NCT05546411, NCT05417386). We also support the concept of manipulating cancer cell plasticity to increase efficacy of combination therapy regimens.

REFERENCE

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