Introduction In pancreatic ductal adenocarcinoma, the desmoplastic response is predominant. VEGF-A165b causes resistance to bevacizumab.

Methods We established a clinically relevant model of PDAC in animals by orthotopically inoculating human PDAC cells overexpressing VEGF-A165b and bcl-2. We treat the PDAC models with siRNA VEGF-A165b, termed as SEVINA-VI. We co-administer docetaxel. As control, we used only bevacizumab.

Results Post-treatment, the RNAi induced by long dsRNA processed into 23 bp dsRNA by DICER has incorporated siRNA into RISC blocking VEGF-A165b mRNA. The formulation SEVINA-VI (under patent) allowed bevacizumab to inhibit VEGF-A blocking VEGFR-1, VEGFR2, angiogenesis and lymphangiogenesis reducing LYVE-1, Prox-1, podoplanin, 5-nucleotidase and LVD. Calcineurin and NFATc1 were blocked, inhibiting Csp1Ex4 and COX-2 and IL-1b. Inhibition of TAMs blocked production of MCP-1, IL-6 and RANTES. DC maturation produced IFN- γ inducing Th1, IL-2, CTL, cellular immunity, phosphorylation of STAT3, p38 and JNK. Also, DCs reduced CD1a/CD208 and with IKDC expressed S-100, CD83, CD86, CD80, Cd40, CCR7, and MHC-II inducing Teff, and Trg. In blood, there was enhancement of IL-1b, IL-6, IP-10, TNF-a and IL-12p70. Bevacizumab induced ADCC and CDC. Docetaxel phosphorylated bcl-2 at ser70 and released beclin1 in cytoplasm interacting with Vps34/Vps15. Autophagy or type II PCD was induced, where LC3II and ATG8 relocated to autophagosomes inhibiting PKCe, PI3K/AKT/mTOR and MAPK. Docetaxel by inhibiting bcl-2 blocks BAG1, TIMP3, AKT1, FAIM, BIM, PUMA, MEK/ERK, Mcl-1, NF-kB, FOXM1, TF and FVIIa circumventing Trousseau's syndrome, and inhibition of type I PCD activating caspase 3, 8, 9 and PARP cleavage after inhibition of JAK/STAT5. Bevacizumab's action was antagonised by VEGF-A165b in controls.

Conclusion AICT formulation composed of antiVEGF-A165b siRNA (SEVINA-VI), anti-VEGF Mab (bevacizumab), and docetaxel would be a novel strategy against PDAC.

Competing interests None.

Keywords PDAC, antisense immunochemogene therapy, siRNA, VEGF-A165b, PCD, trousseau's syndrome.

PTU-108

ANTISENSE IMMUNOCHEMOGENE THERAPY COMPOSED OF SIRNA TARGETING VEGF-A165B MRNA, ANTIVEGF MAB AND TXT INHIBITED VEGF MEDIATED DESMOPLASTIC RESPONSE, ANGIOGENESIS AND LYMPHANGIOGENESIS INDUCING MATURATION OF DCS, ADCC, CMC, AUTOPHAGY AND PCD IN PDAC

doi:10.1136/gut.2011.239301.236

J Giannios* *Translational Cancer Medicine, Erasimio Oncology Hospital, Athens, Greece*