INCREASED SERUM LEVELS OF EBI3 ARE ASSOCIATED WITH POOR OUTCOME IN HEPATOCELLULAR CARCINOMA PATIENTS AND SRF388, A FIRST-IN-CLASS IL-27 BLOCKING ANTIBODY, INHIBITS THE GROWTH OF MURINE LIVER TUMORS

Background IL-27 is a heterodimeric cytokine consisting of IL-27p28 and Epstein-Barr virus-induced gene 3 (EBI3) that binds the IL-27 receptor subunit alpha and glycoprotein 130. IL-27 is produced by activated macrophages and dendritic cells and limits the intensity and duration of immune responses in the tumor microenvironment by inducing the expression of immunoregulatory receptors (PD-L1, TIM3, LAG-3, TIGIT) and inhibiting production of proinflammatory cytokines (IFNγ, IL-17, TNFα). The IL-27 subunit EBI3 is elevated in plasma from patients with certain cancers including renal cell carcinoma, where it correlates with poor outcome. Based on high expression of IL-27 transcript in tumors from patients with hepatocellular carcinoma (HCC), the role of IL-27 was further explored in patient samples and a mouse model of HCC.

Methods Gene expression profiles from the Cancer Genome Atlas (TCGA) were analyzed to identify tumors with elevated IL-27 transcripts. Serum from patients with HCC was analyzed for levels of the IL-27 subunit EBI3. The ability of SRF388, a first-in-class IL-27-blocking antibody that binds to IL-27p28, to reverse IL-27-induced inhibition of cytokine production in human immune cell cultures from patients with HCC was assessed in vitro. Finally, the anti-tumor activity of SRF388 was assessed in an orthotopic murine model of HCC.

Results TCGA expression data revealed that IL-27p28 transcripts were elevated in tumors from patients with HCC relative to other indications. Serum levels of EBI3 were: 1) elevated in a subset of HCC patients; 2) inversely correlated with survival; 3) independent of serum alpha-fetoprotein levels; and 4) elevated in both hepatitis B/C virus positive and negative patients. Treatment with SRF388 stimulated increased cytokine production in activated peripheral blood mononuclear cells from patients with HCC that was further enhanced when combined with PD-1 blockade. Furthermore, SRF388 inhibited the growth of orthotopic Hepa1-6 liver tumors. mRNA transcriptional profiling of treated tumors revealed that SRF388 profoundly altered the transcriptional landscape in this model. In particular, treatment with SRF388 inhibited expression of immunoregulatory receptors PD-L1 and TIGIT, repressed transcripts associated with TGF-β signaling, and altered myeloid and natural killer cell transcripts.

Conclusions These data indicate that elevated IL-27 subunit EBI3 is a hallmark of HCC and is associated with poor outcomes in these patients. Blockade of IL-27 with SRF388, currently being evaluated in a Phase I clinical trial in patients with advanced solid tumors (NCT04374877), may represent a promising therapy for patients with HCC where it can potentiate anti-tumor immune responses.

INCREASED ANTIMICROBIAL RESISTANCE IS ASSOCIATED WITH POOR OUTCOME IN ADVANCED NSCLC PATIENTS AND SRF388, A FIRST-IN-CLASS IL-27 BLOCKING ANTIBODY, INHIBITS THE GROWTH OF MURINE LIVER TUMORS

Background Immune checkpoint inhibitors (ICI) have altered the therapeutic paradigm of advanced non-small cell lung cancer (NSCLC) and have become an attractive treatment strategy in several malignancies. The identification of reliable predictors associated with resistance is essential to dictate new approaches to broaden responder groups. Growing evidence has shown that the gut microbiome is an important regulator of the systemic immune system and is involved in the response to ICI. The aim of the study was to evaluate the association between antibiotics use & ICI efficacy in advanced NSCLC.

Methods A retrospective, single-centre study of unselected patients with advanced NSCLC treated with ICI between June 2016 to May 2019. We included consecutive patients who received at least one dose of PD-1 inhibitors (Nivolumab or pembrolizumab) and with at least 6 months of follow-up. The primary endpoint was progression-free survival (PFS). Secondary endpoints included overall survival (OS) and objective response rate (ORR). Antibiotics use was defined as antibiotic treatment at any time during and 4 weeks post the start of ICI. Antibiotics use was compared to ICI treatment with SRF388 (a first-in-class IL-27-blocking antibody).

Results After a median follow-up of 8.5 months [0.3–56.4], a significant improvement in PFS was observed in treated group compared to Antibiotics treated group. 12.4 months (95%CI, 9.1–15.7) vs 4.1 months (95%CI, 2.6–5.6) (p < 0.001; figure 1). Similarly, OS among patients with no Antibiotic usage was significantly higher: 28.2 months (95%CI, not calculated) vs 12.5 months (95%CI, 10.8–14.2) (p < 0.001; figure 2).

Antibiotics use was associated with poor outcome in advanced NSCLC.