Background

RBN-2397 is a mono-AKT that is upregulated in response to cellular stress (e.g., viral infection, cigarette smoke), and suppresses the Type I interferon (IFN) response following cytotoxic nucleic acid sensing. RBN-2397 is a first-in-class PARP inhibitor,12 inducing cancer cell autonomous and immune stimulatory effects in preclinical models through enhanced type I IFN signaling in cancer cells. Moreover, RBN-2397 induces DDR T cell-dependent tumor-specific immune memory in an immunocompetent mouse cancer model.12 RBN-2397 is currently being tested in an ongoing Phase I clinical study (NCT04536737)13 and in combination with pembrolizumab (NCT02725900), and nivolumab (NCT03121037). Treatment of tumors with DNA damaging agents like chemotherapy can result in the accumulation of double-stranded (ds) DNA in the cytoplasm. Abrupt levels of cytotoxic dsDNA can activate innate immune signaling through the cGAS-STING pathway, leading to increased expression of type I interferons. Since PARP inhibitors, like RBN-2397, have a negative impact on nucleic acid sensing, the chemotherapy-induced activation of the Type I interferon response would be minimized. Combining RBN-2397 with chemotherapy agents in PARP-active tumors would lead to a synergistic type I IFN signaling in tumor and tumor-macrophage cells. We found that combining RBN-2397 with cisplatin led to increased cGAMP and pSTAT1 protein expression in CT26 tumors. In vivo, cisplatin alone modestly increased cytotoxic DNA and IFNα expression in CT26 tumors. Finally, the combination led to increased efficacy and survival of mice harboring CT26 tumors. Increased survival correlated with enhanced IFNα expression in the combination groups.

Methodology – In vitro assays

Cisplatin Increased CytosDNA and IFN Induced Genes

Conclusions

- Single agent cisplatin generates cytotoxic DNA that produces cGAMP by engaging the nucleic acid sensing pathway and leads to activation of the IFN response in CT26 tumor cells in vitro and in vivo.
- Combination of RBN-2397 with cisplatin or carboplatin robustly enhanced type I IFN signaling.
- Decreased tumor burden and extended survival observed with cisplatin plus RBN-2397 combination in CT26 tumor bearing mice.
- Enhanced expression of CXCL10 and CCL5 in combination (CPT 5) group correlated to highest efficacy.