

## RBN-2397, A NOVEL, POTENT, AND SELECTIVE PARP7 INHIBITOR, INDUCES TUMOR-INTRINSIC TYPE I INTERFERON RESPONSES AND ADAPTIVE IMMUNITY IN PRECLINICAL MODELS AND PATIENT TUMORS

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**Background** PARP7 is a mono-ART that is upregulated in response to cellular stress (e.g., viral infection, cigarette smoke), and suppresses the Type I interferon (IFN) response following cytosolic nucleic acid sensing. RBN-2397 is a first-in-class PARP7 inhibitor, inducing cancer cell autonomous and immune stimulatory effects in preclinical models through enhanced Type I IFN signaling in cancer cells. Moreover, RBN-2397 induces CD8 T cell-dependent tumor-specific immune memory in an immunocompetent mouse cancer model.<sup>1</sup> RBN-2397 is currently being tested in an ongoing Phase I clinical study (NCT04053673).<sup>2</sup> Here we aimed to compare biomarker results from preclinical models and patient samples.

**Methods** In preclinical models, interferon-stimulated gene (ISG) expression was assessed by qPCR, NanoString, or ELISA. Plasma CXCL10 from patients was measured by MSD while ISG expression in PBMCs was measured by NanoString. Baseline and on-treatment patient tumor biopsies were analyzed by NanoString, CD8/GZMB IHC, and MIBI-TOF to characterize immune changes in the tumor microenvironment.

**Results** RBN-2397 potently restored tumoral Type I IFN signaling in preclinical models as demonstrated by increases in ISGs, namely CXCL10, which were not observed in non-tumor tissue (e.g. spleen, PBMCs). In peripheral blood from patients treated with RBN-2397, neither plasma nor PBMC CXCL10 increased more than 2-fold over baseline. Expression of 42 ISGs was not consistently induced in a dose-dependent manner in PBMCs. However, in tumor types of interest (e.g. cancers of the upper aerodigestive tract), CXCL10 expression increased 1.5 to 8-fold, with similar effects observed for a subset of ISGs in 5 evaluable paired biopsy samples. Confirming preclinical studies [1], up to 8-fold increases in CD8 T cell infiltration along with induction of granzyme B expression were observed in 4 of 5 paired patient tumor biopsies by immunohistochemistry. Using the MIBI-TOF technology, we observed up to 50-fold increases in intratumoral activated T cells as well as monocytes and M1 macrophages, most strikingly in two NSCLC patients.

**Conclusions** Inhibition of PARP7 with RBN-2397 restores tumor-intrinsic Type I IFN signaling in preclinical models leading to enhanced adaptive immunity, resulting in CD8 T cell-dependent durable tumor regressions. These observations are mirrored in samples from patients treated with RBN-2397 in that pharmacodynamic effects of RBN-2397 were preferentially observed in tumor tissue relative to the periphery, including an increase in immune infiltration into the tumor microenvironment. These data provide evidence for induction of an adaptive immune response and confirm the tumor-intrinsic, immunomodulatory mechanism of action of RBN-2397 in patients.

## REFERENCES

1. Gozgit, *et al.* PARP7 negatively regulates the type I interferon response in cancer cells and its inhibition triggers antitumor immunity. *Cancer Cell* 2021; In press.
2. Falchook, *et al.* A first-in-human phase 1 study of a novel PARP7 inhibitor RBN-2397 in patients with advanced solid tumors. *ASCO* 2021; oral presentation.

<http://dx.doi.org/10.1136/jitc-2021-SITC2021.866>