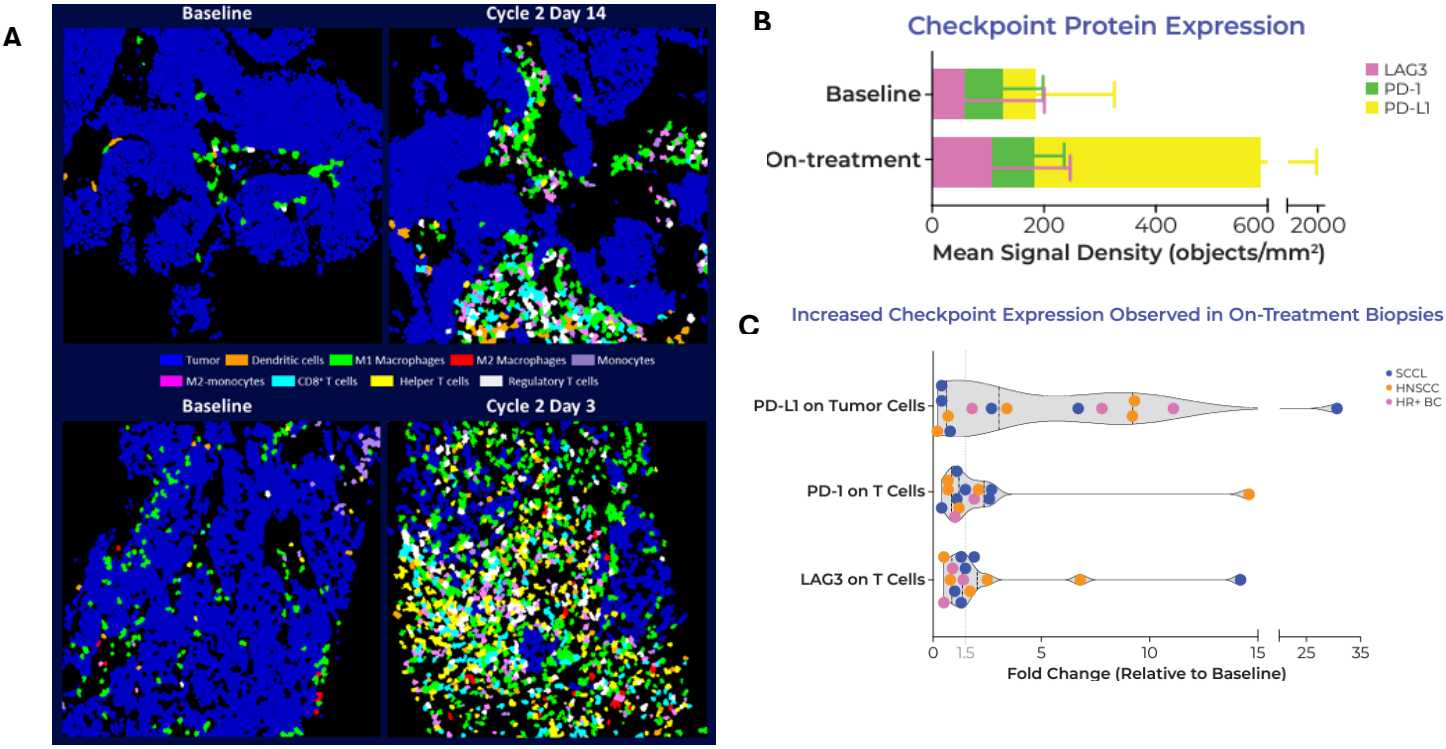
Unveiling the Immunological Impact of RBN-2397: A First-in-Class PARP7 Inhibitor in Cancer Therapy

The research team at Ribon set out to investigate the immunological effects of RBN-2397, a PARP7 inhibitor, in patients with advanced solid tumors. As part of a Phase 1 clinical trial, they aimed to understand how RBN-2397 reactivates Type I interferon signaling, enhances immune cell infiltration and increases checkpoint protein expression. The study focused on its impact across various cancers, including head and neck squamous cell carcinoma and hormone receptor-positive breast cancer.

The study's **key findings** revealed key immunological shifts post-treatment with RBN-2397:

- **Increased immune infiltration:** Significant increases in CD8+ T cells, M1 macrophages, and monocytes in the tumor microenvironment suggest an enhanced ability of the immune system to recognize and attack tumor cells, supporting sustained antitumor activity.
- **Spatial proximity improvement:** A marked reduction in the distance between immune and tumor cells allows for more effective immune engagement and destruction of cancer cells, promoting a stronger response.
- **Checkpoint protein expression boost:** Elevated levels of PD-1, LAG3, and PD-L1 indicate RBN-2397 primes tumors for greater responsiveness to immune checkpoint inhibitors, enhancing the potential for combination therapies.



A) MIBI-TOF cell classification images illustrate infiltration of multiple T cell populations, M1 macrophages, and monocytes into the tumor regions of on-treatment biopsies from the baseline and on-treatment biopsies of two lung cancer patients, Patient 2 (top) and Patient 5 (bottom). Quantification of the density of each cell type for three regions of interest per samples is shown on the right. **B)** Quantification of total signal density for the proteins of interest for the patient shown in panel A. **C)** Checkpoint expression increases observed in the three cohorts for PD-1 and LAG3 on T cells and PD-L1 on tumor cells across all biopsies via MIBI-TOF analysis (n = 14).

MIBI's Role in the Study: provided a critical detailed visualization and quantification of immune responses within the tumor microenvironment:

- **Multiplexed immune profiling:** Enabled simultaneous detection of multiple immune cell types, offering an in-depth understanding of the immune landscape and how various immune cells respond to RBN-2397.
- **Spatial context:** Revealed how immune cells, such as CD8+ T cells and macrophages, interact closely with tumor cells, which is imperative to understanding immune activation.
- **Quantitative analysis:** Provided reproducible, quantitative data showing significant immune cell infiltration and checkpoint protein expression changes after treatment.

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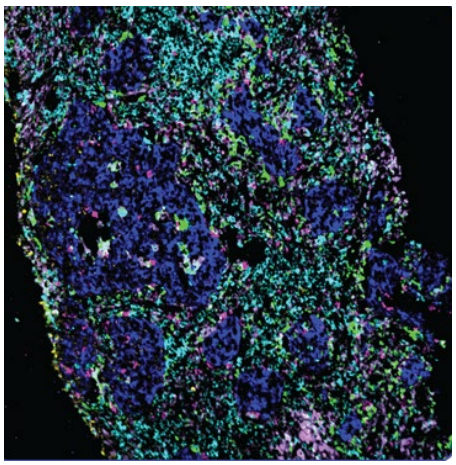

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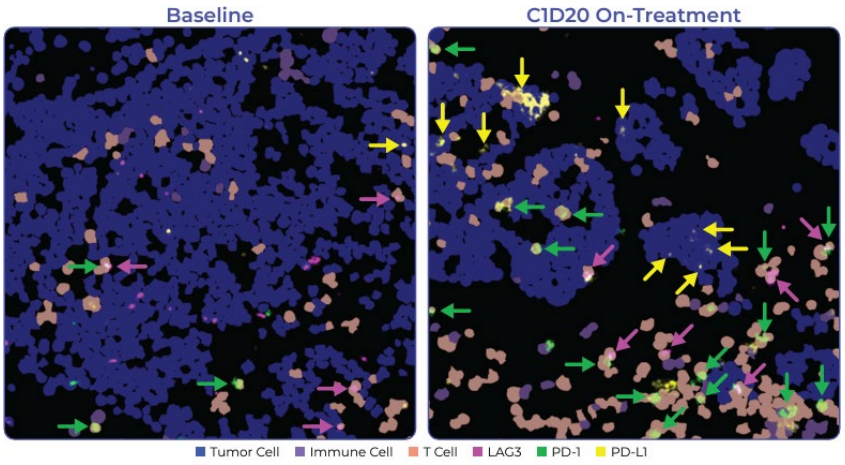

D) Documented disease progression on immediate prior line of therapy (pembrolizumab and investigational STING agonist) • Baseline biopsy showed: • High CD8 and Granzyme B density (744 and 167 objects/mm2, respectively) • TMB = 2.5 muts/Mb; SMARCB1 deletion; MSS **E)** MIBI-TOF cell classification images illustrate increased expression of multiple checkpoint proteins in the on-treatment lung biopsy of an HNSCC patient. Images are representative of 12 (baseline) and 7 (on-treatment) regions of interest.

Impact on Cancer Therapy Development:

The study highlights RBN-2397's potential as a leading candidate for immunotherapy by enhancing immune cell infiltration, activating adaptive immune responses, and increasing checkpoint protein expression. These findings support its use in combination with immune checkpoint inhibitors, offering a promising path for more targeted and durable cancer treatments.

References

1. First-in-Class Human Phase 1 Trial and Translational Study of the Mono (ADP-Ribose) Polymerase-7 (PARP7) Inhibitor RBN-2397 in patients With Selected Advanced Solid Tumors, Yap, T., AACR poster CT109, 2023
2. RBN-2397, a novel, potent, and selective PARP inhibitor, induces tumor-intrinsic Type I interferon responses and adaptive immunity in preclinical models and patient tumors, Kuplast-Barr, K., Abstract 866, SITC 2021
3. PARP7 negatively regulates the type I interferon response in cancer cells and its inhibition triggers antitumor immunity, Gozgit, Joseph M. et al., Cancer Cell, Volume 39, Issue 9, 1214 - 1226.e10