Tumor and immune cell dynamics at single-cell resolution on combined PARP inhibition and anti-PD-L1 therapy

Julien Vibert[1], Clémence Hénon[2], Patricia Martin-Romano[1], Lambros Tselikas[3], Léo Colmet-Daage[2], Roman Chabanon[2], Nicolas Dorvault[2], Anas Gazzah[1], Fanny Bouquet[4], Nathalie Droin[5], Karim Fizazi[6], Damien Vasseur[7], Etienne Rouleau[8], Sophie Postel-Vinay[1]

[1]Drug Development Department, Gustave Roussy, Villejuif, France, [2]U981 INSERM, Gustave Roussy, Villejuif, France, [3]Interventional Radiology Department, Gustave Roussy, Villejuif, France, [4]ImCORE, Roche S.A.S – France, Basel, Switzerland, [5]INSERM Research Unit, Gustave Roussy, Villejuif, France, [6]Cancer Medicine Department, Gustave Roussy, Villejuif, France, [7]Molecular Biology, Gustave Roussy, Villejuif, France, [8]Tumor Genetics, Gustave Roussy, Villejuif, France

BACKGROUND

Poly (ADP-ribose) polymerase inhibitors (PARPi) have immunomodulatory properties, which may enhance anti-PD-(L)1 therapy efficacy. However, the exact immunomodulatory mechanism is still debated.

OBJECTIVE

To explore this, we performed single-cell RNA and T cell receptor sequencing (scRNA + scTCR-seq) on sequential tumor biopsies collected at three timepoints in the ARIANES academic phase 2 basket trial, associating the PARPi rucaparib (R) to the anti-PD-L1 atezolizumab (A), in patients (pts) with DNA repair-deficient tumors.

PATIENTS AND METHODS

scRNA + scTCR-seq (10x) was performed on fresh biopsies collected at baseline, on R monotherapy, and on R + A. Using Cellranger, Seurat and Harmony, we identified and quantified the evolution over time of tumor and microenvironment (TME) cells, calculated differentially expressed genes and signatures within each cell population, and explored the clonal dynamics of tumor and T cells.

Two patients - BRCA2-mutant prostate (CRPC) and ATM-mutant lung (NSCLC) cancer – were successfully profiled on three sequential biopsies with 11,845 and 5,484 single cells analyzed, respectively.

Clinical trial identification: NCT04276376

RESULTS

scRNA-seq identifies tumor cells and microenvironment

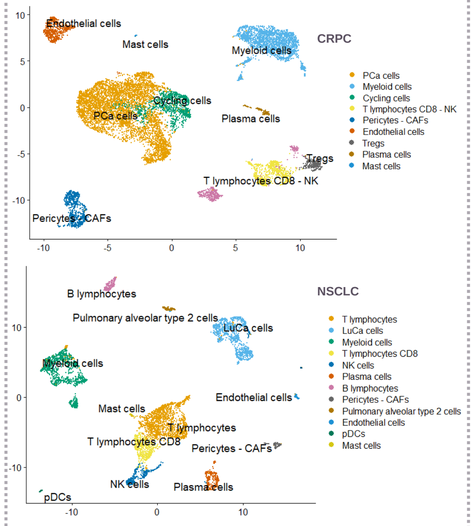

Fig. 1: UMAP plots of BRCA2-mutant prostate (CRPC) and ATM-mutant lung (NSCLC) cancer patients (Pca=prostate cancer LuCa= lung cancer) after integration of three timepoints

Cell composition varies upon therapy with R and R + A: e.g., increased myeloid cells (CRPC) and T cells (NSCLC)

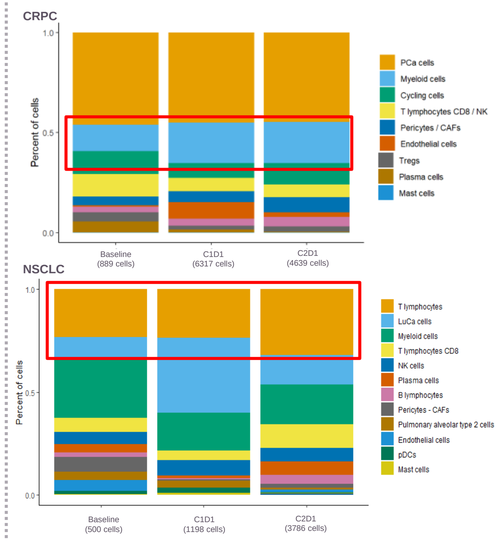

Fig. 2: Cell composition across timepoints of the two patients (as Fig.1) at baseline, C1D1 (on R) and C2D1 (on R + A)

R treatment upregulates *PARP1* in tumor cells and cytosolic DNA sensing in myeloid cells

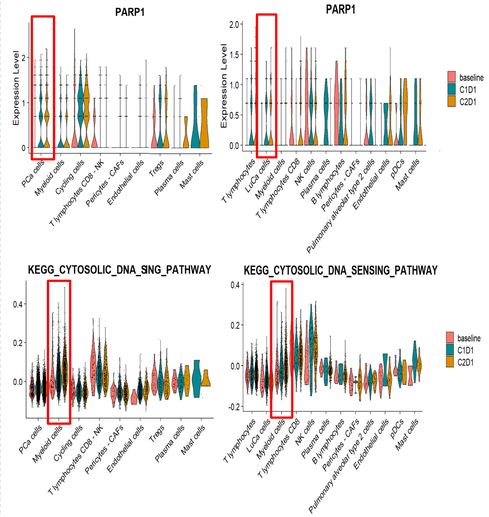

Fig. 3: Expression level of PARP1 and a cytosolic DNA sensing signature across timepoints in the two patients (left: CRPC, right: NSCLC)

R + A activates T cells and induces clonotype hyperexpansion

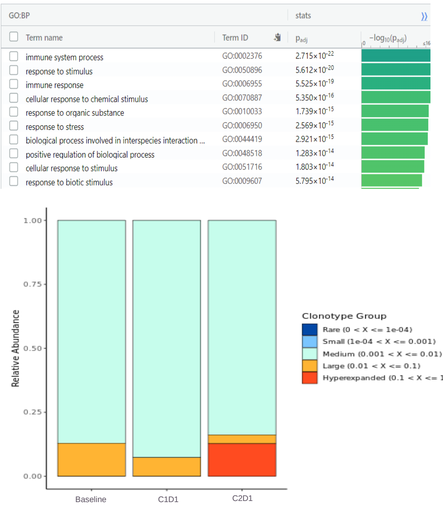

Fig 4: Gene Ontology (GO) analysis of upregulated genes upon R + A treatment in T lymphocytes (top); scTCR-seq quantification of clonotypes across timepoints (bottom)

CONCLUSION

- ScRNA + scTCR-seq allows the dynamic, quantitative and qualitative assessment of tumor cells and the microenvironment.
- These preliminary studies in two patients confirm the potential of R + A to induce T cell activation and clonal expansion.
- This is to our knowledge the first study depicting at a single-cell resolution the evolution of tumor and immune cells from patients on PARPi + anti-PD-L1 therapy.
- This study is ongoing with the profiling of further patients from the same clinical trial.

ACKNOWLEDGMENT

We wish to thank all the patients and staff from all the units that participated in this study. Translational work for this project is supported by the imCORE network on behalf of F. Hoffmann-La Roche.

CONTACTS

Julien VIBERT, PhD, MD student: julien.vibert@gustaveroussy.fr
Sophie POSTEL-VINAY, MD, PhD: sophie.postel-vinay@gustaveroussy.fr

PARIS 2022 ESMO congress
PARIS FRANCE
9-13 SEPTEMBER 2022