#1047 MORPHEUS-Lung: Biomarkers and Clinical Response to Atezolizumab + Bevacizumab + Stereotactic Body Radiotherapy in Patients With Metastatic Non-Small Cell Lung Cancer.

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 # Principal investigators

HIGHLIGHTS

- Atezolizumab+bevacizumab+SBRT showed improved efficacy outcomes vs docetaxel in the MORPHEUS-Lung study.
- Activation of T cells and macrophages was associated with benefit to Atezolizumab+bevacizumab+SBRT.
- CD8 T_{RM}, CD8 T_{EX}, and CXCL10^{+} were also identified as potential biomarkers.

BACKGROUND

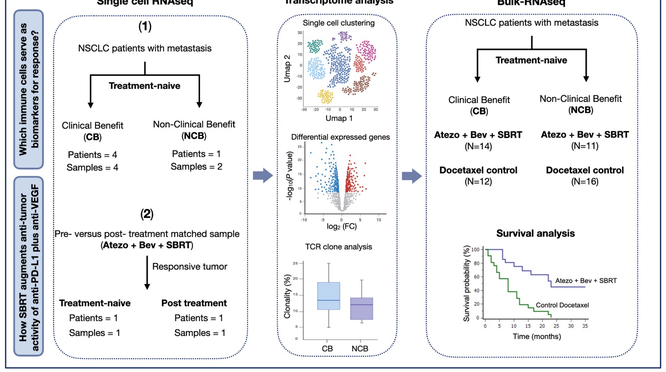
Within the tumor microenvironment (TME) of metastatic NSCLC, response to immune checkpoint inhibitors (CPIs) remains variable, particularly in CPIs-exposed patients with limited therapeutic options. Combination strategies integrating anti–PD-L1 therapy, anti-angiogenic agents, and radiotherapy have shown potential to enhance antitumor immunity through vascular normalization and immune activation. However, predictive biomarkers for response to such triplet therapies remain poorly defined. Here, we aimed to characterize the immune landscape associated with clinical benefit to atezolizumab + bevacizumab + SBRT and identify potential biomarkers to guide patient selection.

METHODS & MATERIALS

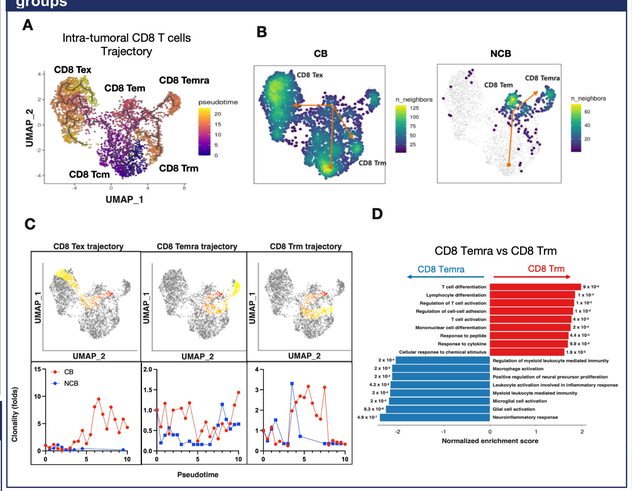
We performed integrated single-cell RNA sequencing (scRNA-seq) and bulk RNA sequencing analyses on tumor samples from patients with metastatic NSCLC enrolled in the MORPHEUS-Lung study. scRNA-seq was conducted as a discovery analysis to characterize immune cell subsets and transcriptional programs associated with clinical benefit (CB) versus non-benefit (NCB). Bulk RNA-seq from a larger cohort was used for validation of T cell– and macrophage-associated gene signatures. Patients were stratified based on treatment response, and survival outcomes were analyzed in relation to biomarker-defined subgroups.

RESULTS

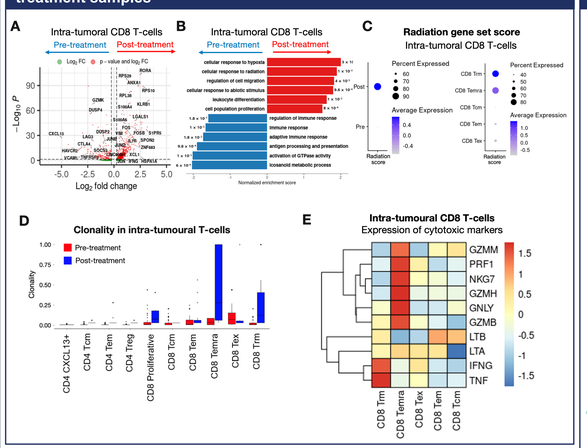
Research Overview



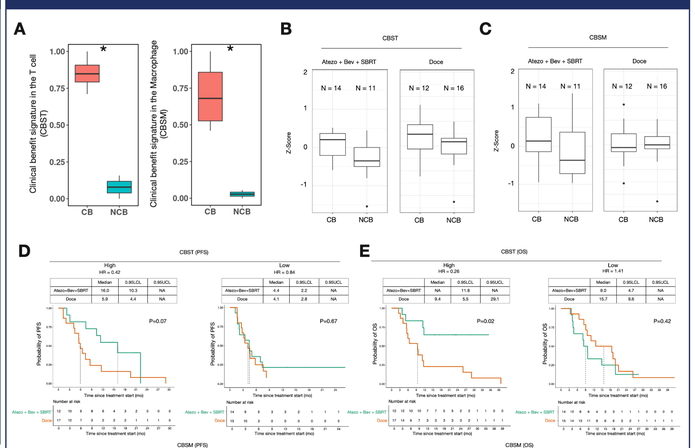
Intratumoral differentiation trajectory analysis of CD8 T cells in the CB and NCB groups



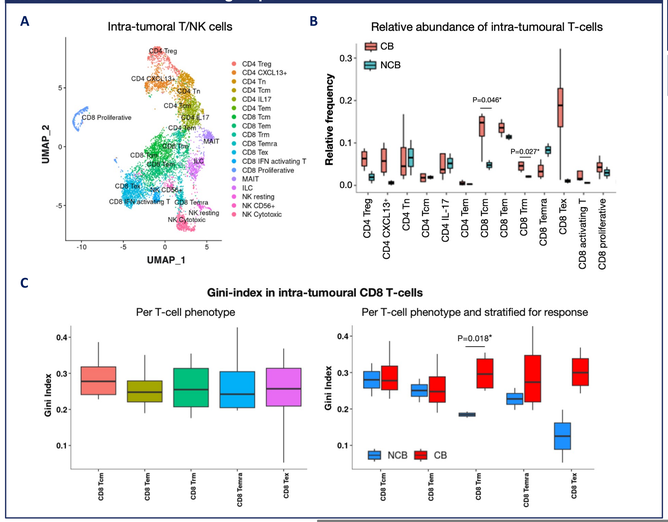
Phenotypic distribution of T/NK cells in the TME of the pre- and post-treatment samples



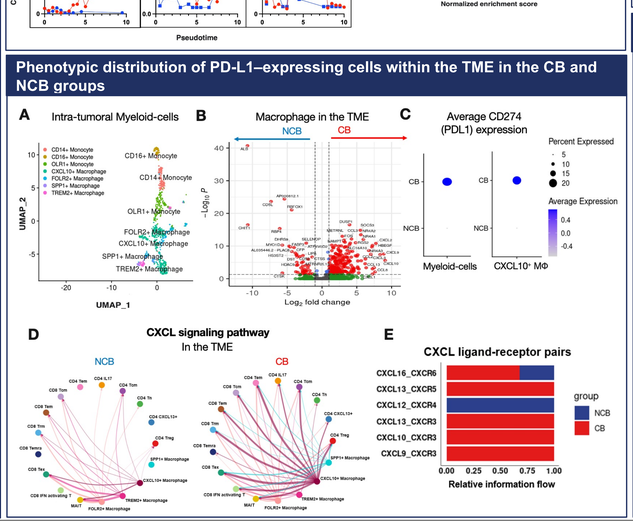
Survival outcomes in the CB and NCB groups and stratified by treatment arm



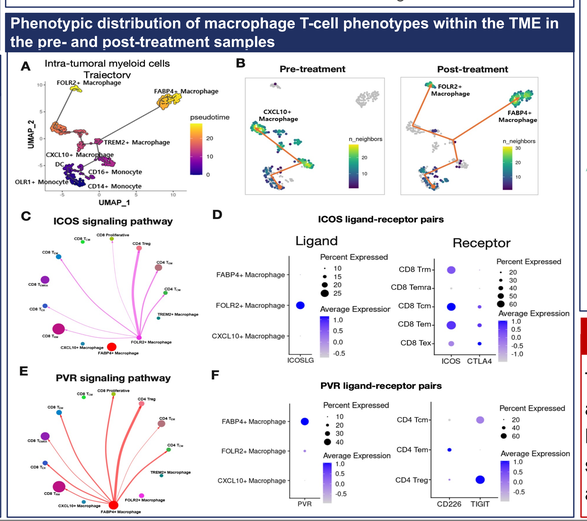
Phenotypic distribution of T/NK cells within the tumor microenvironment (TME) of mNSCLC in the CB and NCB groups



Phenotypic distribution of PD-L1–expressing cells within the TME in the CB and NCB groups



Phenotypic distribution of macrophage T-cell phenotypes within the TME in the pre- and post-treatment samples



Survival outcomes in the CB and NCB groups and stratified by treatment arm

Signature	Gene content
Clinical benefit signature in the T cell (CBST)	*DUSP4, CXCR4, NR4A3, METRNL, CXCL13, CSRNP1, PFKFB3, RGS1, DUSP8, TNFAIP3*
Clinical benefit signature in the Macrophage (CBSM)	*CXCL10, CXCL9, CXCL3, CXCL2, CCL8, CCL13, CXCL1, CCL4L2, HBEGF, NR4A3*

Conclusion

These results suggest that activation of T cells and macrophages are associated with a favorable clinical response to atezo+bev+SBRT. Moreover, CD8 T_{RM}, CD8 T_{EX} cells, and CXCL10^{+} macrophages may serve as potential biomarkers of response to atezo+bev+SBRT treatment and potentially aid in tailored, precision medicine for individual patients.

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