



P2.015: PFKFB3⁺ Invasive-Margin CAFs Drive Resistance to Neoadjuvant PD-1 Blockade in lung cancer

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INTRODUCTION

Neoadjuvant PD-1-based therapy has become an important treatment strategy for resectable NSCLC, yet 60% patients fail to achieve major pathologic response. Although cancer-associated fibroblasts are key regulators of the tumor microenvironment, the spatially restricted metabolic programs by which CAFs impair anti-tumor immunity at the invasive margin remain defined.

METHODS

We assembled a cohort comprising 30 paired clinical samples and integrated single-cell transcriptomic data from 105 NSCLC patients. We integrated RNA sequencing, spatial transcriptomics, and metabolomics to define features of the tumor microenvironment. The primary clinical endpoint was MPR. Therapeutic relevance was further evaluated in a humanized patient-derived xenograft (PDX) model.

REFERENCES

Reference

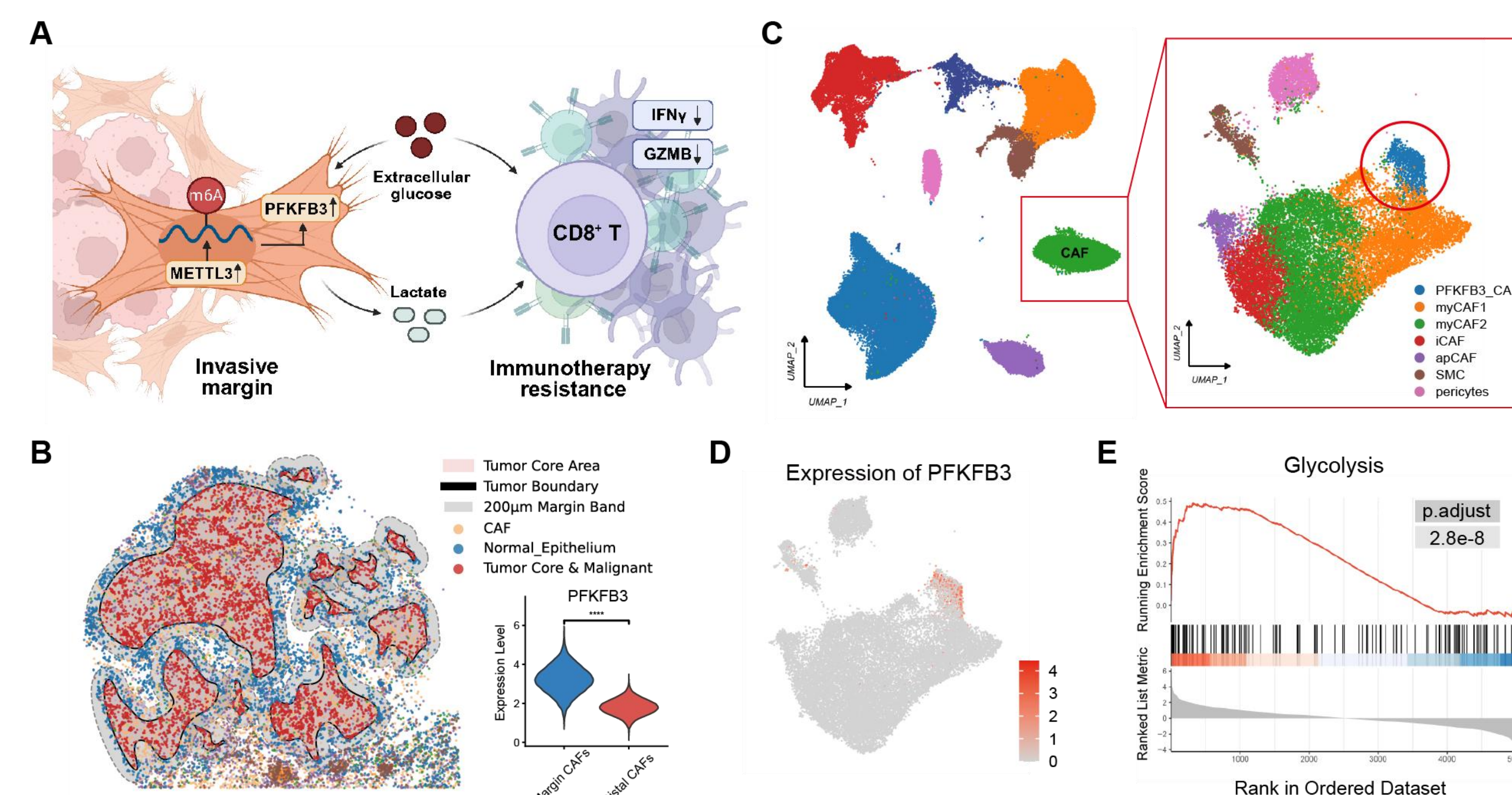
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Artificial Intelligence (AI) Use Disclaimer

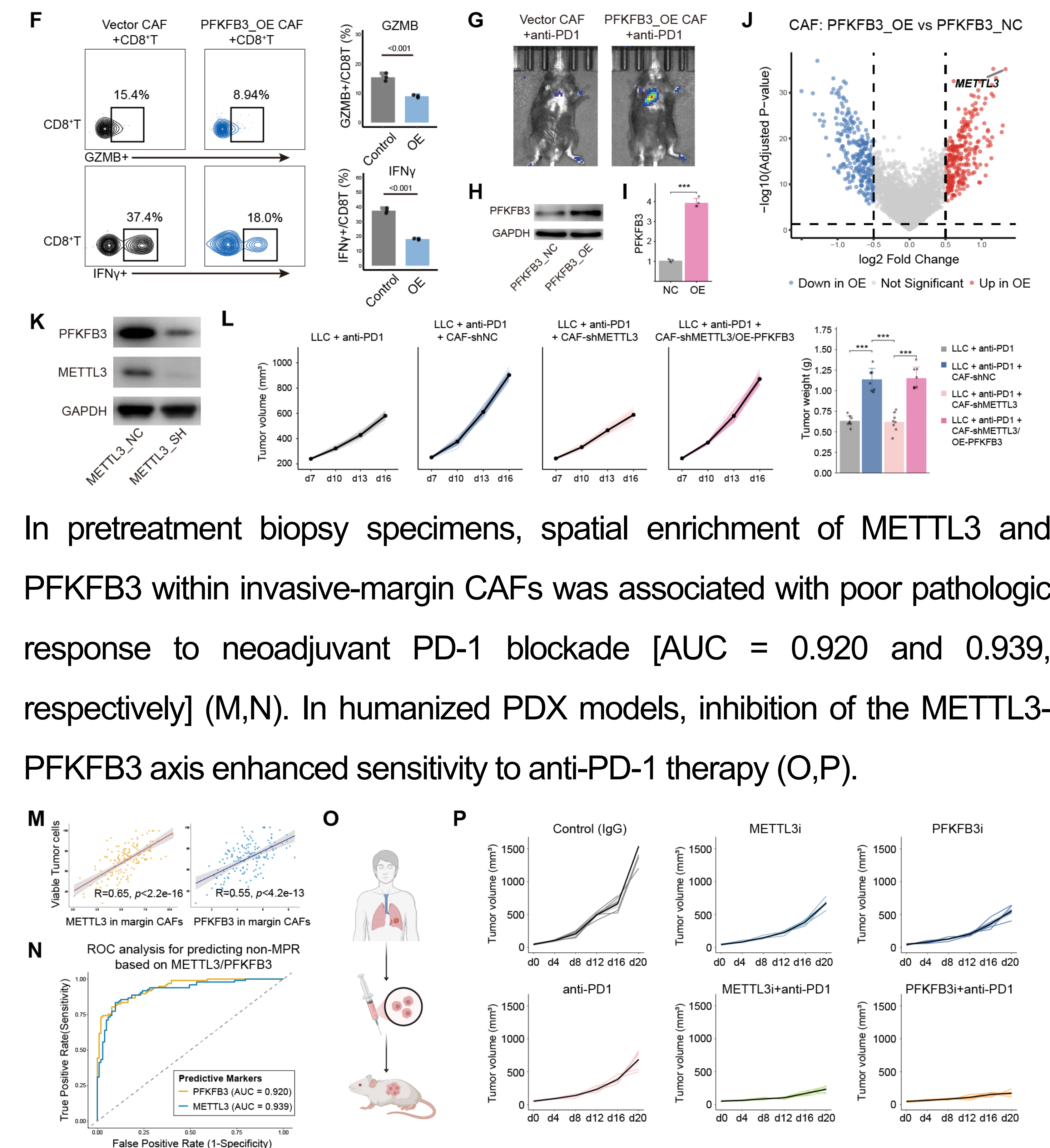
No artificial intelligence (AI) tools were used in the development of this presentation.

RESULTS

Multi-omics integration identified a glycolytic PFKFB3⁺ CAF subset enriched at the tumor-stroma invasive margin in non-MPR tumors (A). Spatially, these marginal CAFs localized adjacent to exhausted CD8⁺ T cells and defined a metabolically restrictive niche (B). Integrative pathway analysis suggested reduced extracellular glucose and increased lactate accumulation within this niche, correlating with impaired CD8⁺ T cell metabolic fitness and effector function (C,D,E).



Flow cytometric analysis confirmed that co-culturing with PFKFB3⁺ CAFs exacerbated terminal exhaustion in CD8⁺ T cells (F,G,H,I). Mechanistically, METTL3 was identified as an upstream regulator stabilizing PFKFB3 expression (J,K,L).



DISCUSSION AND CONCLUSION

A spatially restricted METTL3-driven PFKFB3⁺ CAF program at the invasive margin promotes resistance to neoadjuvant PD-1 blockade in NSCLC through local metabolic competition with CD8⁺ T cells. Quantification of this CAF-specific epigenetic-metabolic axis in pretreatment biopsy samples may help identify patients less likely to achieve MPR. These findings also support further evaluation of combined targeting of the METTL3-PFKFB3 axis and PD-1 blockade as a therapeutic strategy in resistant NSCLC.