



P2.239: Pretreatment IL-33 is Associated with Pathologic Response to Neoadjuvant Tislelizumab-Chemotherapy in Stage III Lung Squamous Cell Carcinoma



IASLC 2026 World
Conference on Lung Cancer
SEPTEMBER 12 - 15, 2026
SEOUL, REPUBLIC OF KOREA

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INTRODUCTION

Perioperative chemoimmunotherapy has improved outcomes in patients with resectable stage II-III NSCLC, yet pathological response remains highly heterogeneous. **PD-L1 alone is insufficient for pretreatment stratification**, particularly in lung squamous cell carcinoma (SCC), where robust predictive biomarkers remain lacking. Identifying biologically relevant markers that can distinguish patients likely to achieve deep pathological response may help refine perioperative treatment selection and guide future escalation or de-escalation strategies.

We therefore sought biomarkers beyond PD-L1 that were associated with pathological response and could be supported by both mechanistic evidence and independent external data.

METHODS

We analyzed the prospective phase II TACT trial (NCT05024266) of neoadjuvant tislelizumab plus chemotherapy in potential resectable stage III SCC. Among 35 treated patients, 29 underwent multi-omics profiling and 27 patients were evaluable for pathological response. Pretreatment multi-omics profiling and longitudinal ctDNA analyses were performed to identify response-associated biomarkers. The **IL-33/ST2 axis** was functionally evaluated using murine lung cancer models and single-cell RNA sequencing, and externally assessed in the Liu et al. (*Cell*, 2025) cohort of 234 Chinese patients with NSCLC.

DISCUSSION AND CONCLUSION

Integrated analyses identified a pretreatment **IL-33/ST2-associated immune state** enriched in patients achieving pCR despite limited discrimination by PD-L1. IL-33 enhanced PD-1 blockade by remodeling the tumor immune microenvironment, increasing **Xcl1⁺ effector CD8⁺ T cells** and reducing **ST2⁺ regulatory T cells**. Concordant enrichment in an independent Chinese NSCLC cohort supported cross-cohort reproducibility. The **IL-33/ST2 axis** may serve as a biomarker for response stratification beyond PD-L1 and warrants prospective evaluation in perioperative therapy. Larger multicenter SCC cohorts with predefined cutoffs are needed for validation

RESULTS

Of 56 patients screened, 35 were enrolled and received neoadjuvant treatment. Twenty-nine patients were included in the multi-omics biomarker cohort. Twenty-seven completed surgery and were evaluable for pathological response, of whom 12 achieved pCR, yielding a pCR rate of 44.4% (12/27). Two patients did not undergo surgery and were excluded from the pCR denominator. Median EFS was not reached, and the 36-month EFS rate was 65.5%. PD-L1 expression was not associated with pathological response or survival. Transcriptomic profiling identified an IL33-centered immune transcriptional program associated with pCR. A 42-gene signature discriminated pCR from non-pCR patients with high accuracy (AUC=0.956), while IL33 alone achieved an AUC of 0.825. ctDNA mutation frequency declined after treatment, with lower residual ctDNA levels observed in pCR patients. These findings were further supported in an independent neoadjuvant anti-PD-1-treated NSCLC cohort, where IL-33-positive and IL1RL1-positive cells were enriched in patients achieving pCR. In murine lung cancer models, exogenous IL-33 synergized with PD-1 blockade to suppress tumor growth. Single-cell RNA sequencing demonstrated enrichment of Xcl1-positive effector CD8-positive T cells and depletion of regulatory T cells following IL-33 treatment, supporting a role for IL-33/ST2 signaling in enhancing antitumor immunity.

Figure 1. Study design and patient cohort

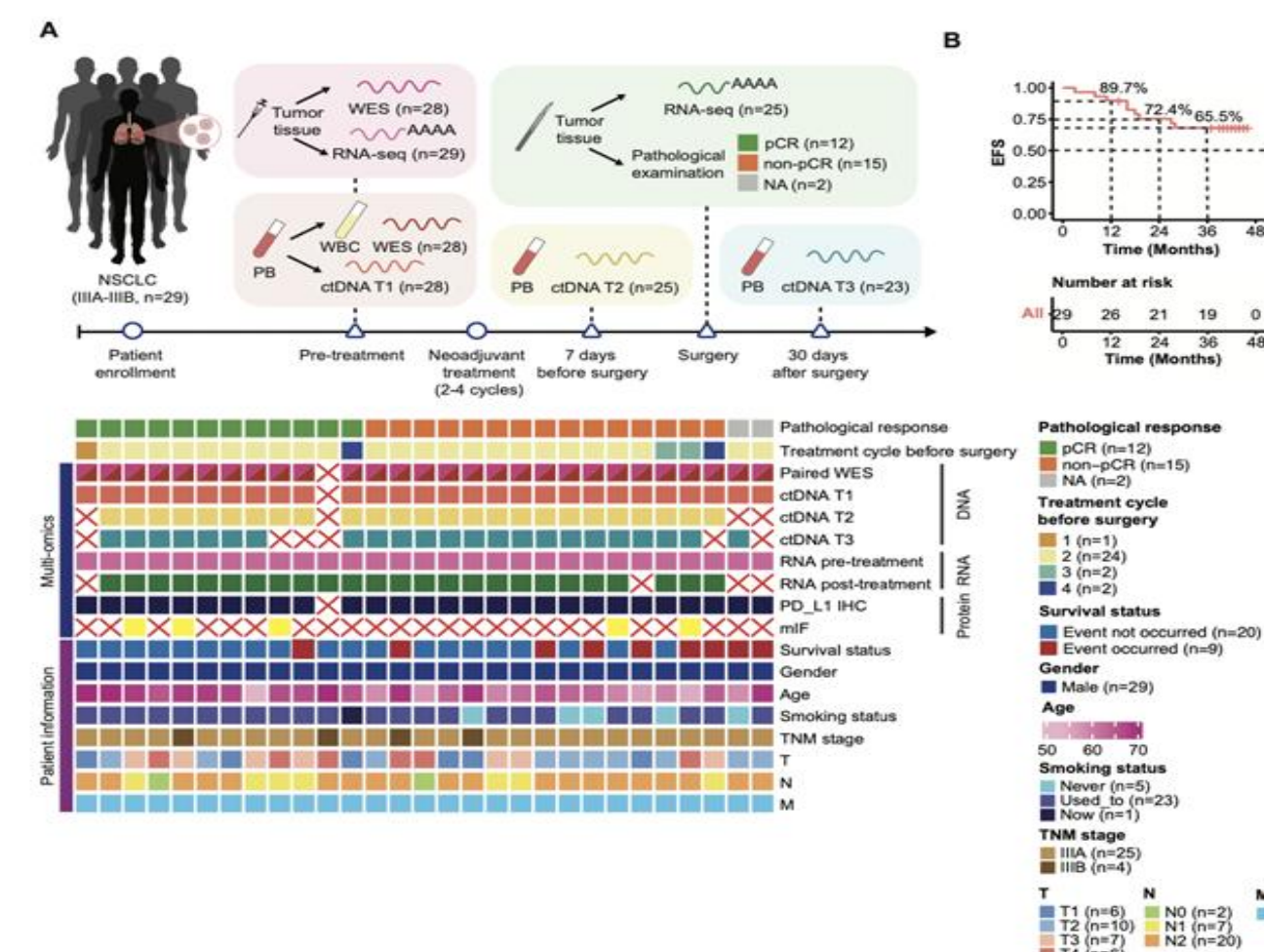


Figure 1. Study design, patient disposition, longitudinal sampling and multi-omics profiling. Of 56 screened patients, 35 were enrolled and treated; 29 entered the multi-omics biomarker cohort. Twenty-seven completed surgery and were evaluable for pathological response, including 12 patients who achieved pCR (44.4%). Two patients who did not undergo surgery were excluded from pCR assessment. Red crosses indicate missing data; ctDNA T1/T2/T3 denote pretreatment, presurgical and postsurgical timepoints.

Figure 3. IL-33 enhanced anti-PD-1 efficacy through immune remodeling

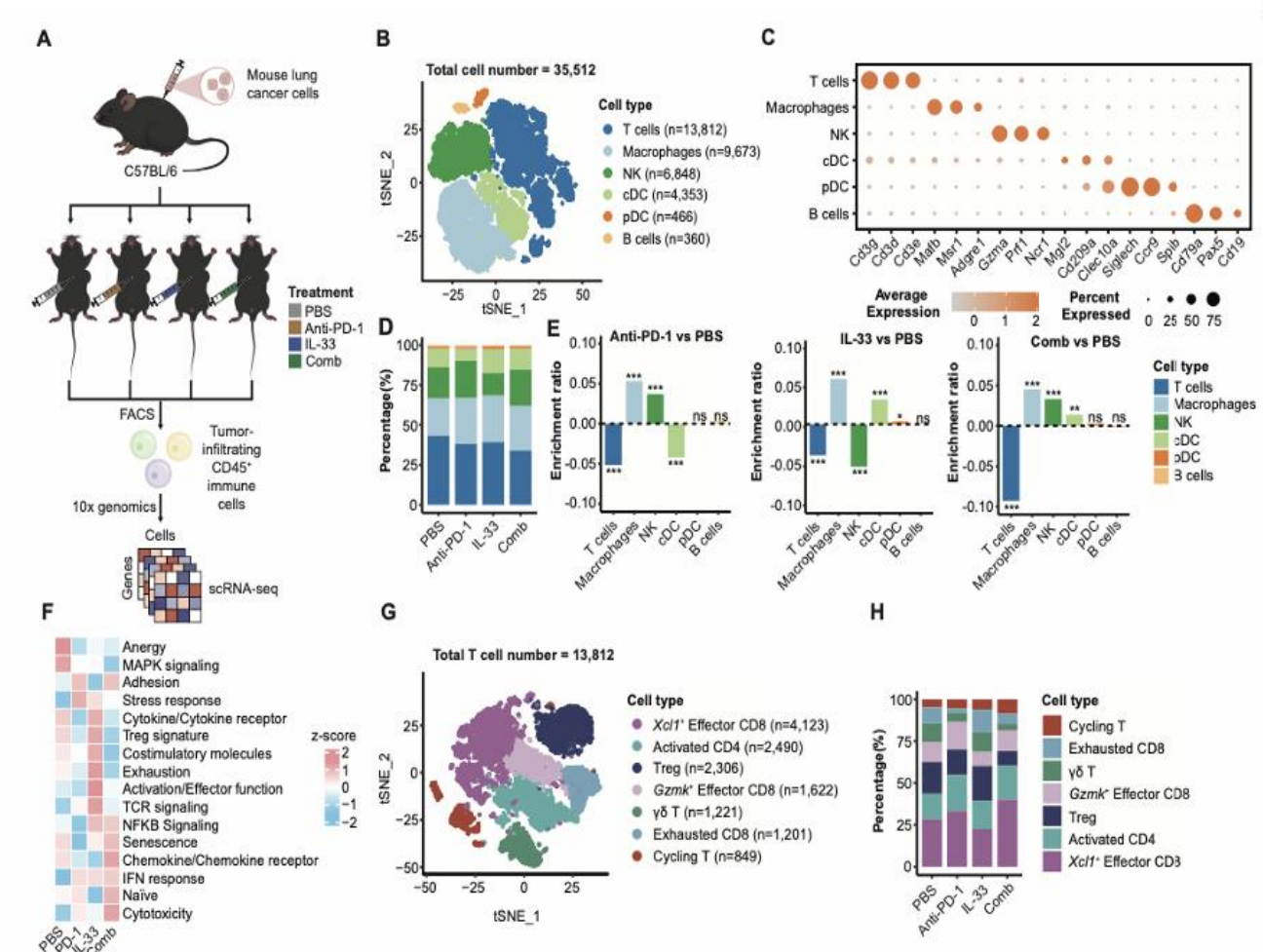


Figure 3. IL-33 enhanced anti-PD-1 efficacy through immune remodeling in murine lung cancer models. Combination treatment suppressed tumor growth and reshaped the tumor immune microenvironment, characterized by enrichment of Xcl1⁺ effector CD8⁺ T cells and reduction of regulatory T-cell populations. These findings provide functional support for IL-33-mediated potentiation of PD-1 blockade.

Figure 2. Multi-omics analyses identified IL33 as a key predictor of pCR

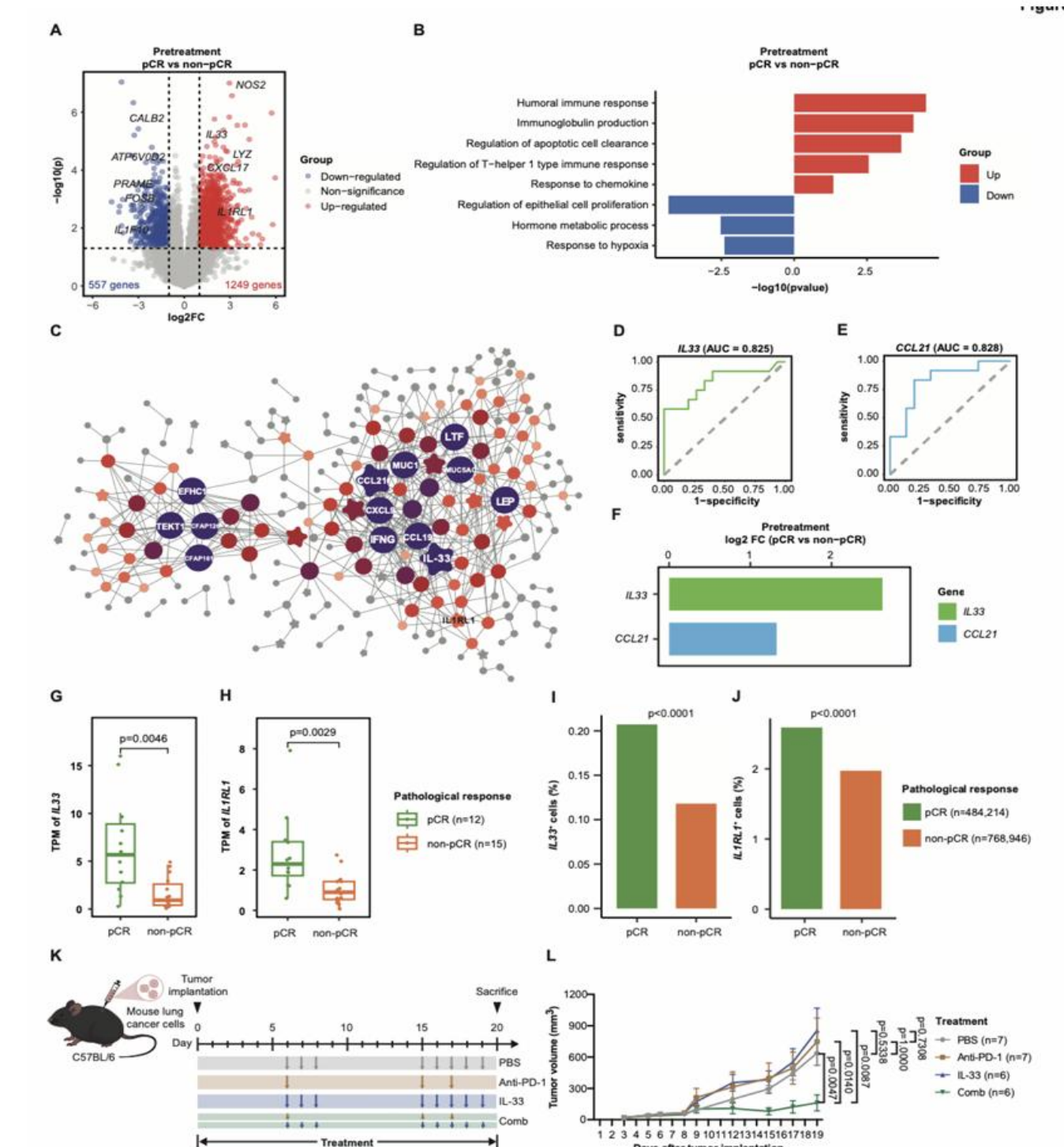
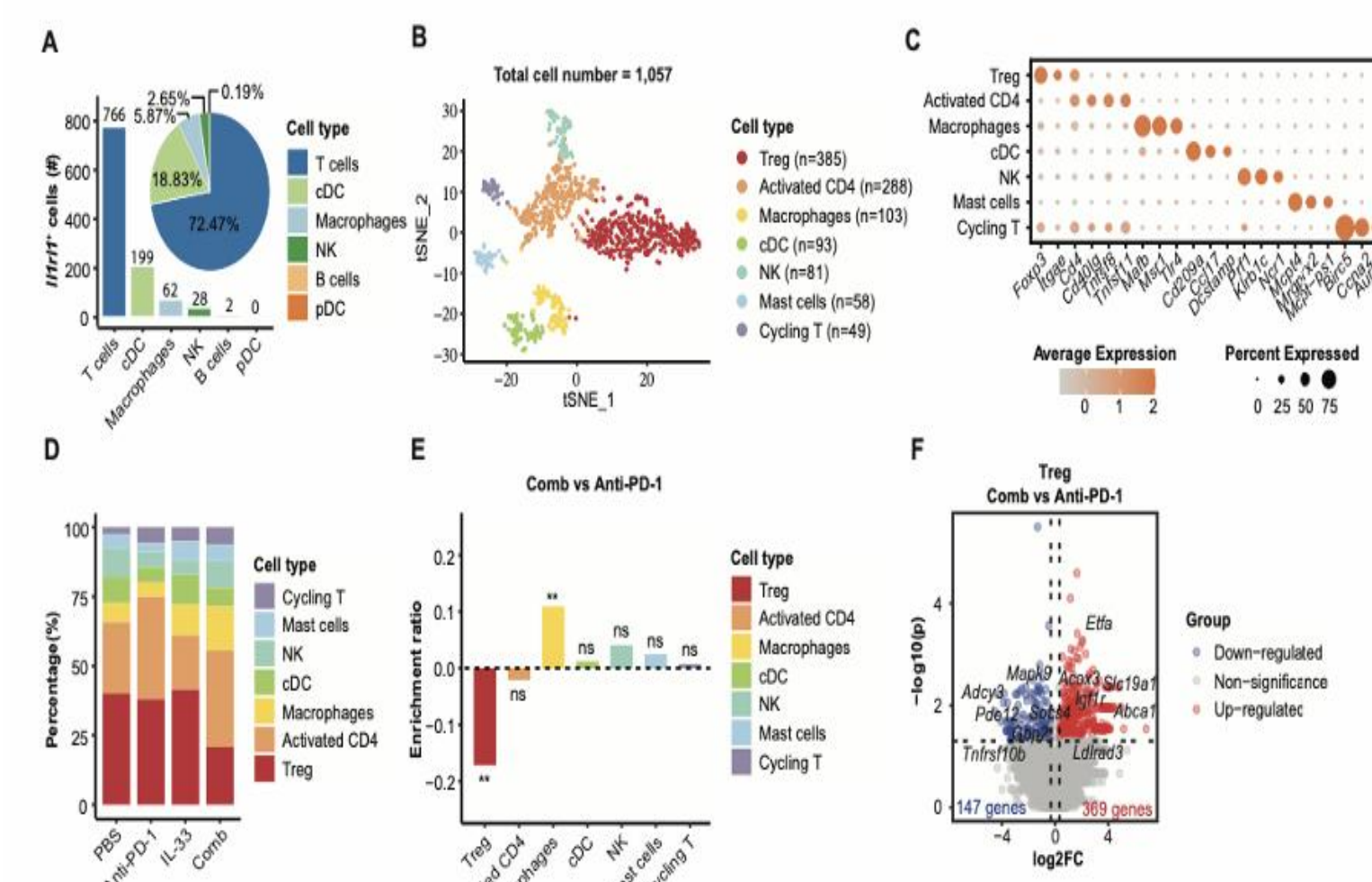


Figure 4. IL-33/ST2 signaling depleted Treg cells and promoted antitumor immunity



PD-L1 versus IL-33/ST2

- Pretreatment PD-L1 was not associated with pCR (P=0.643)
- IL-33 and IL1RL1 (ST2) were significantly elevated in pCR patients
- IL-33 achieved an AUC of 0.825.
- A 42-gene immune-response signature achieved an AUC of 0.956.

Independent Validation Cohort (GSE243013)

- 243 neoadjuvant anti-PD-1-treated NSCLC patients (85 pCR, 157 non-pCR).
- IL-33+ cells were enriched in pCR patients
- IL1RL1+ cells were enriched in pCR patients.
- Supports reproducibility of the IL-33/ST2 response-associated axis.
- Provides external biological validation but not prospective biomarker validation.

Figure 4. IL1RL1/ST2 was predominantly expressed in T-cell populations. IL-33 plus anti-PD-1 reduced ST2⁺ Treg cells and suppressed tolerance-associated programs, supporting activation of the IL-33/ST2 axis.

Mechanistic Summary:
IL-33/ST2 signaling enhanced PD-1 blockade through dual immune remodeling: enrichment of Xcl1⁺ effector CD8⁺ T cells and depletion of ST2⁺ Treg cells, collectively shifting the tumor microenvironment toward antitumor immunity.