



P3.153: TREM2⁺ Macrophages Mediate Anticancer Therapy-Induced Immune Evasion in Non-small Cell Lung Cancer via the CCL5/CCL22-Treg Axis

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

INTRODUCTION

Tumor-associated macrophages (TAMs) contribute to immune suppression and therapeutic resistance in non-small cell lung cancer (NSCLC). TREM2⁺ TAMs represent an immunosuppressive macrophage population, but how anticancer therapies reshape TREM2-mediated myeloid–T-cell interactions remains unclear.

Objective: To determine whether TREM2⁺ macrophages promote treatment-induced immune evasion through recruitment of regulatory T cells (Tregs) and to identify the underlying molecular mediators.

METHODS

Integrated multi-platform analysis

- **Human scRNA-seq:** TREM2⁺ myeloid and T/NK-cell populations were characterized in paired NSCLC and adjacent normal lung tissues; cell–cell interactions were analyzed using CellChat.

- **Human tissue validation:** TREM2⁺ and FOXP3⁺ cells were quantified by immunohistochemistry in a tissue microarray of 116 treatment-naïve lung adenocarcinomas.

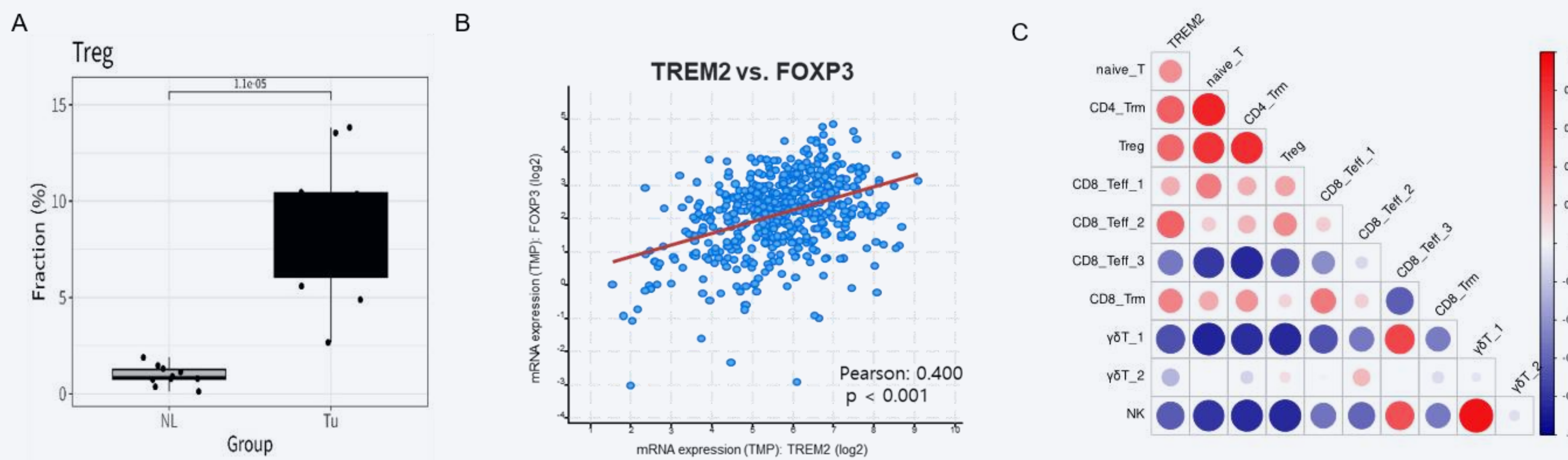
- **Mechanistic studies:** THP-1-derived macrophages and murine bone marrow–derived macrophages were exposed to cisplatin or osimertinib. CCL5/CCL22 regulation was evaluated using TREM2 knockdown, TREM2 overexpression, the TREM2-inhibitory peptide IA9, and pathway inhibitors.

- **In vivo validation:** The effects of TREM2 inhibition on chemotherapy-associated Treg enrichment were assessed in orthotopic immunocompetent lung cancer models.

RESULTS

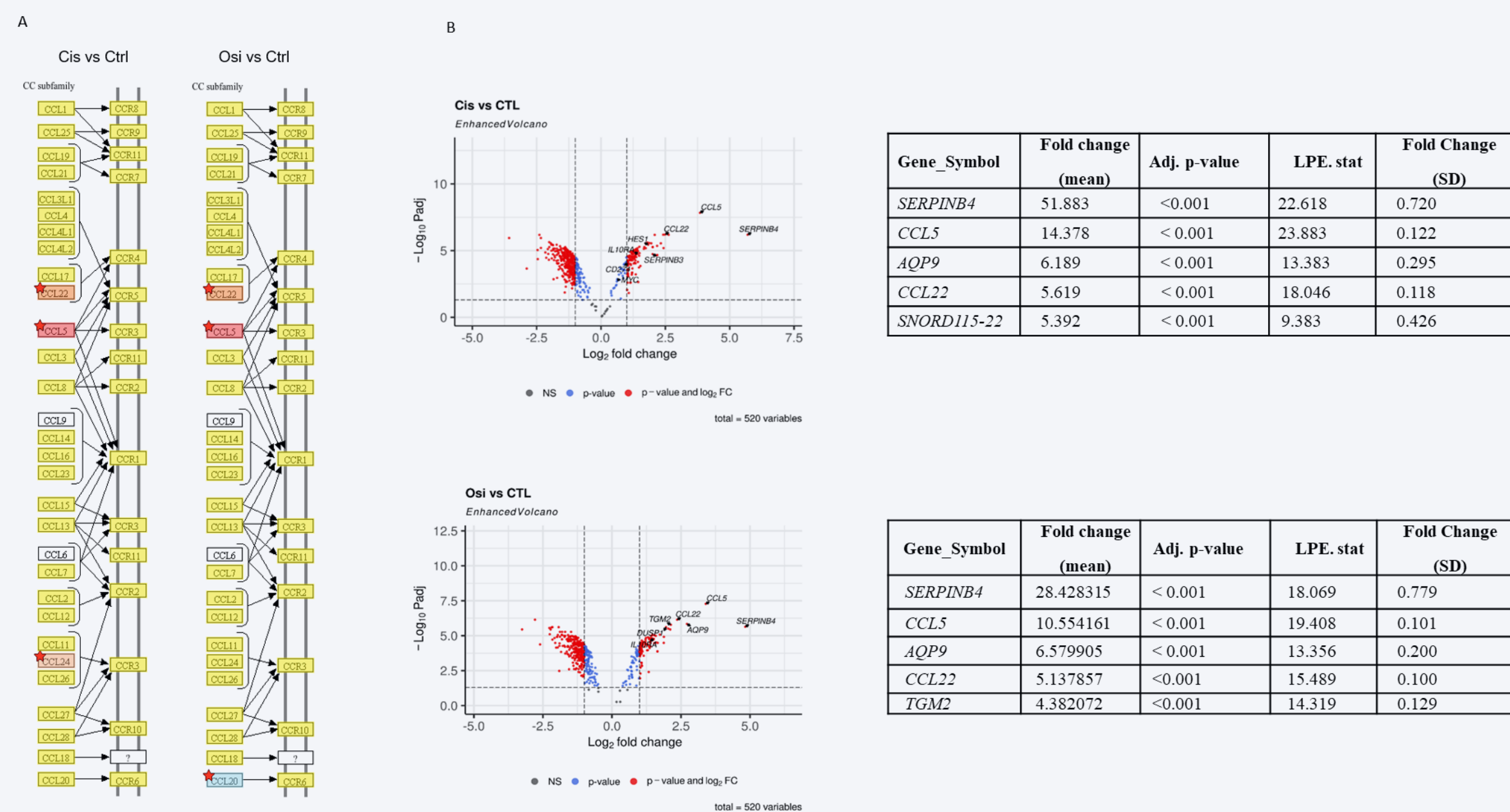
① TREM2⁺ macrophages are associated with Treg enrichment in NSCLC

- Tregs were significantly enriched in NSCLC tumors compared with adjacent normal lung.
- TREM2⁺ myeloid-cell abundance strongly correlated with Treg abundance (Spearman $\rho = 0.7323$, $P < 0.001$).
- TREM2 and FOXP3 expression were also positively correlated in the TCGA-LUAD cohort.
- Human lung adenocarcinoma tissue microarrays independently demonstrated a positive association between TREM2⁺ and FOXP3⁺ cell densities.



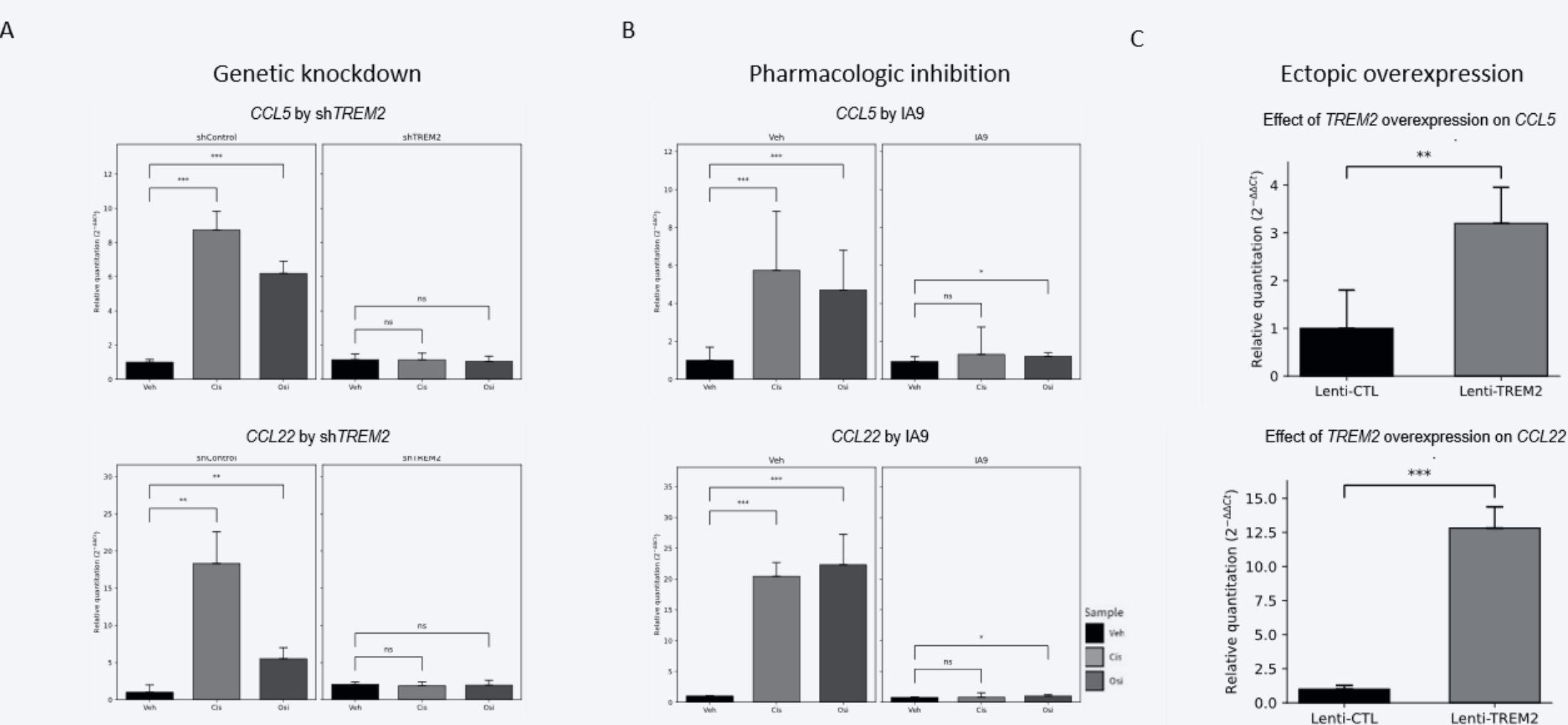
② CCL5 and CCL22 emerge as key treatment-induced mediators

- CellChat analysis identified signaling interactions between TREM2⁺ macrophages and Treg/NK-cell subsets.
- Transcriptomic profiling of macrophages exposed to anticancer therapy revealed enrichment of leukocyte chemotaxis and CCR-related pathways.
- **CCL5 and CCL22 emerged as prominent treatment-induced chemokines linking TREM2⁺ macrophages to Treg recruitment.**



③ TREM2 drives anticancer therapy-induced CCL5/CCL22 expression

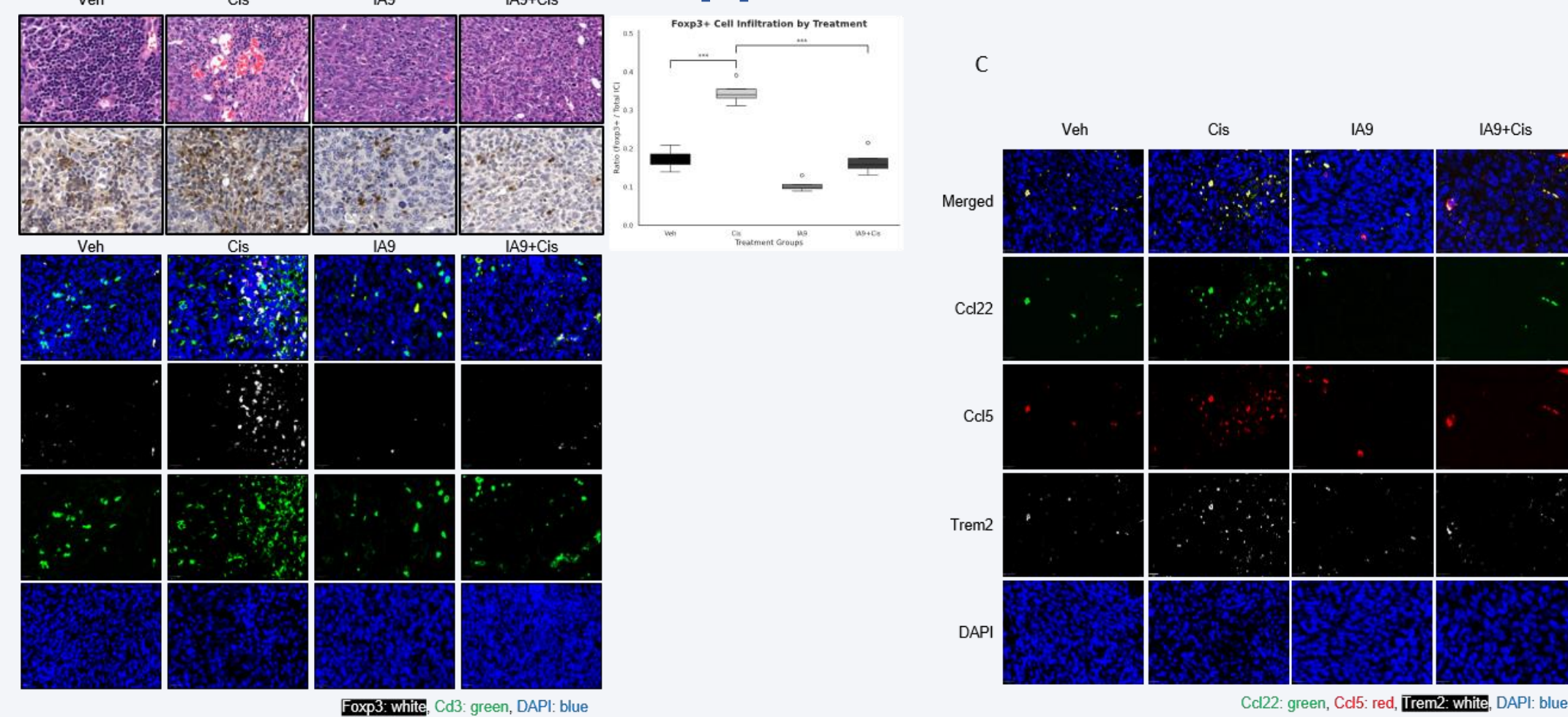
- Cisplatin and osimertinib markedly induced CCL5 and CCL22 in macrophages.
- **TREM2 knockdown abolished treatment-induced CCL5/CCL22 upregulation.**
- Pharmacologic disruption of TREM2–DAP12 signaling with IA9 similarly suppressed chemokine induction.
- Conversely, **TREM2 overexpression alone was sufficient to induce CCL5 and CCL22**, supporting a causal role for TREM2 signaling.



RESULTS

④ TREM2 inhibition attenuates chemotherapy-associated Treg enrichment in vivo

- Cisplatin increased Foxp3⁺ T-cell infiltration within orthotopic lung tumors.
- Increased Trem2⁺ cells and Ccl22/Ccl5 signals were observed around chemotherapy-induced tumor cell death.
- **IA9-mediated TREM2 inhibition reduced Foxp3⁺ T-cell enrichment and attenuated the chemotherapy-associated immunosuppressive niche.**



DISCUSSION AND CONCLUSIONS

Anticancer therapy promotes a TREM2-dependent macrophage program that induces CCL5 and CCL22 and facilitates FOXP3⁺ Treg recruitment in NSCLC.

Our findings establish a mechanistic link between anticancer treatment and secondary immune suppression:

Anticancer therapy → TREM2⁺ macrophages → CCL5/CCL22 → CCR5/CCR4 → FOXP3⁺ Treg recruitment → immune evasion

Genetic and pharmacologic inhibition of TREM2 suppressed this chemokine program, while TREM2 overexpression was sufficient to activate it. Importantly, TREM2 inhibition also reduced chemotherapy-associated Treg enrichment in vivo.

These findings identify the TREM2–CCL5/CCL22–Treg axis as a potential therapeutic target for preventing treatment-induced immune evasion in NSCLC.