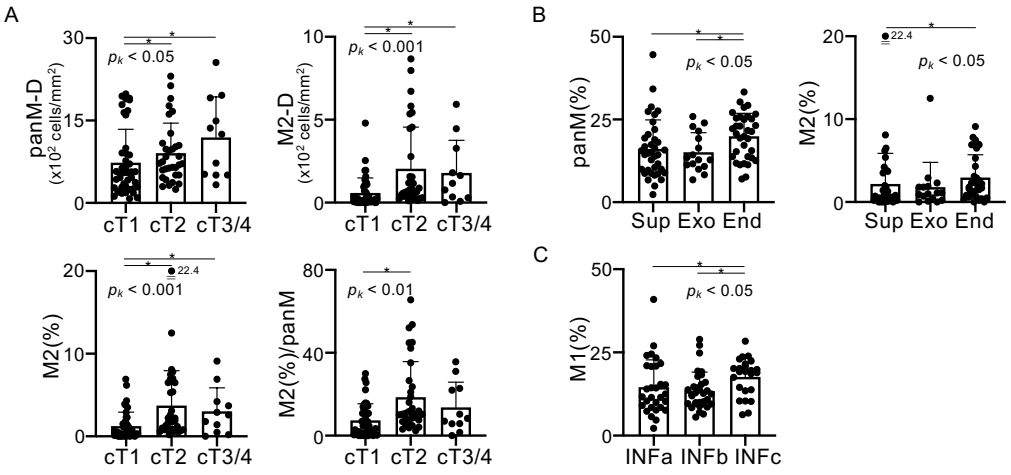
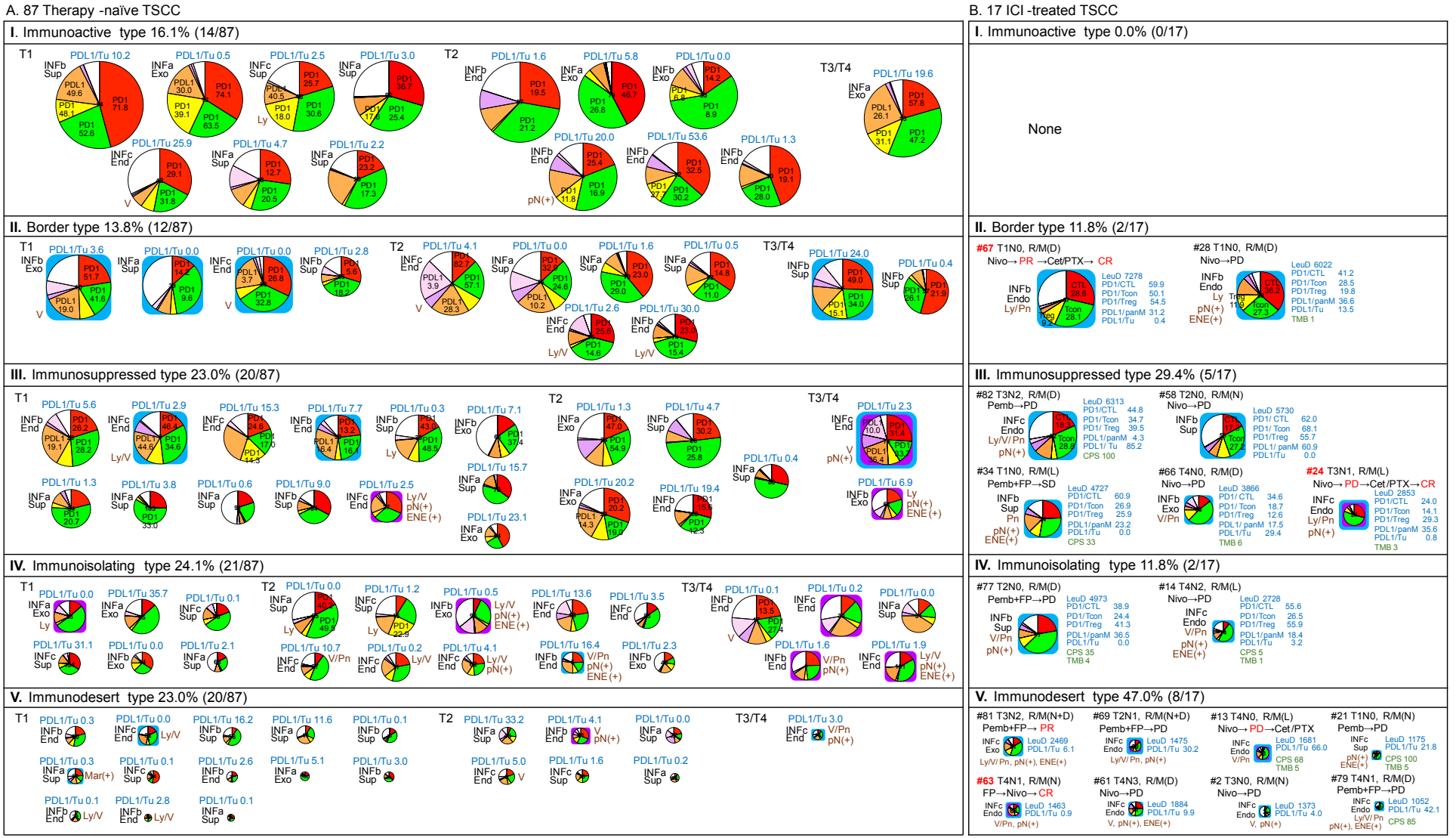
Supplementary Materials



Supplementary Fig. 1 Comparison of macrophage-related indices .

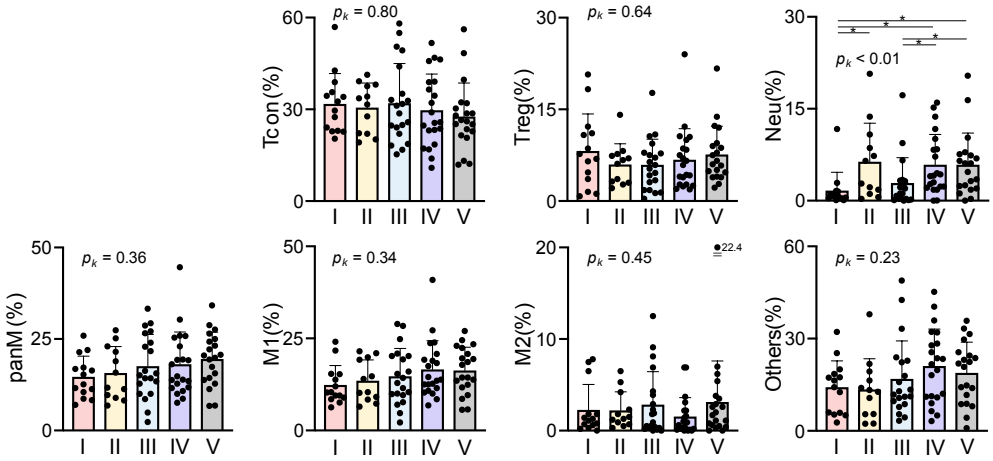
The indicated macrophage-related immune parameters were compared among groups according to clinical T stage (cT) (A), clinical growth pattern (B), and INF classification (C). The Kruskal–Wallis test was performed, followed by the uncorrected Dunn test (*p < 0.05). Clinical growth patterns: Sup (superficial), Exo (exophytic), and End (endophytic).

Supplementary Fig. 2

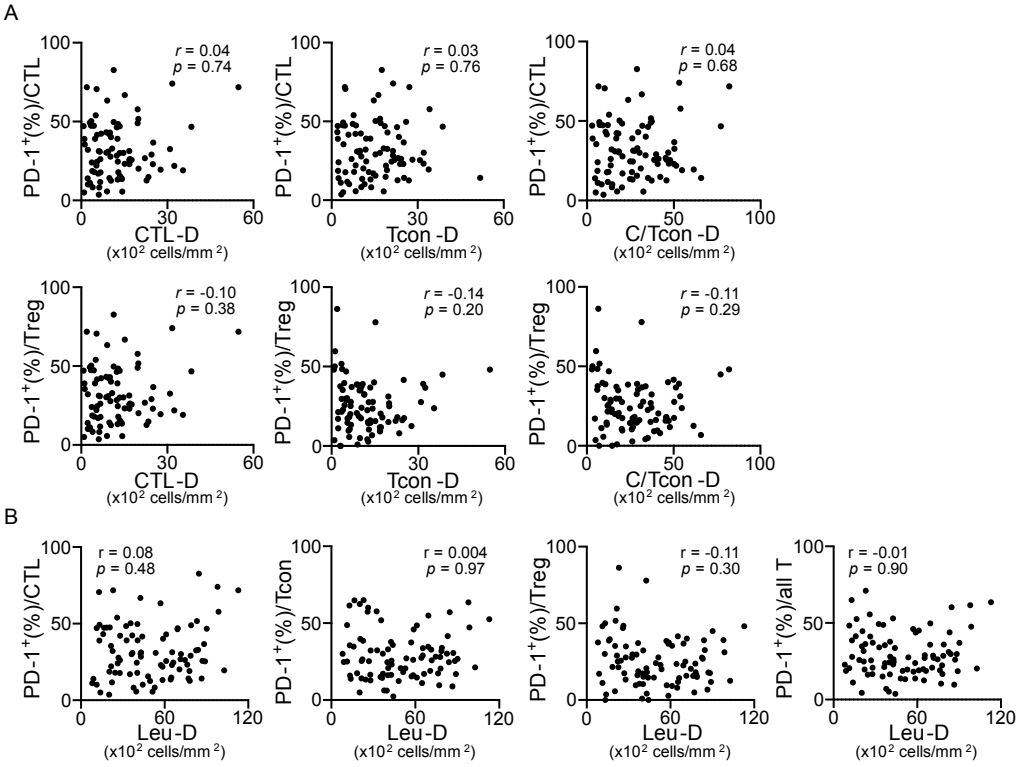


Supplementary Fig. 2 TSCC immune profiles by immunotype.

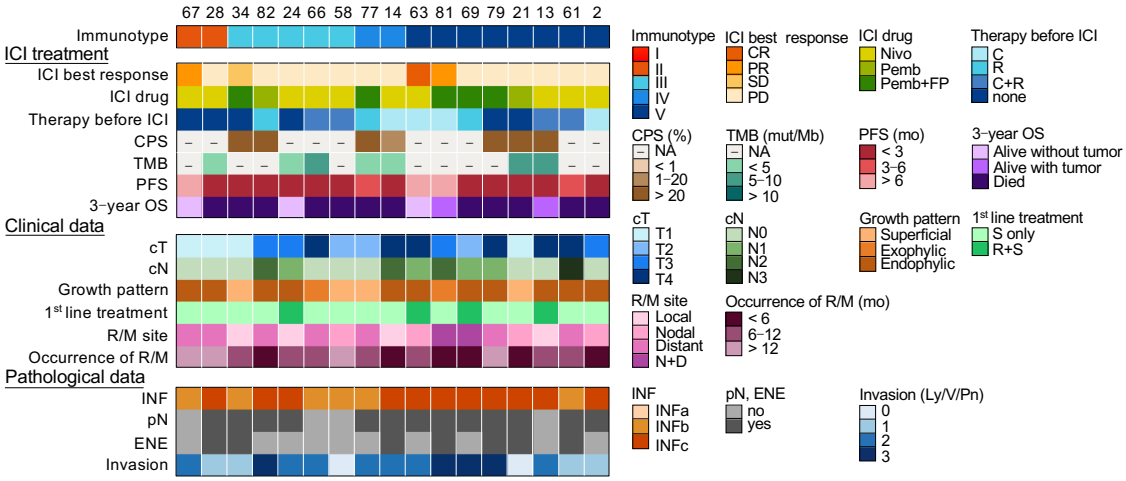
Immune profiles of 87 therapy-naïve (A) and 17 ICI-treated (B) TSCC patients. The placement of each pie chart is based on the immunotype classification. The "pie chart diameters" indicate $CD45^+$ Leu density values and relative proportions of CTL (red), Tcon (green), Treg (yellow), M1 (orange), M2 (purple), Neu (pink), and Others (white) are shown. Cases that developed R/M status and received adjuvant therapy are indicated by blue and purple squares, respectively. In (A), the values within the pie chart are the percentages of $PD\text{-}1^+$ or $PD\text{-}L1^+$ cells. The proportions (%) of $PD\text{-}L1^+$ cells within CK^+ tumor cells (PDL1/Tu) are shown in blue. Clinical growth patterns: Sup (superficial), Exo (exophytic), and End (endophytic); pathological invasion: Ly (lymphatic vessel), V (venous), Pn (perineural), ENE (extranodal extension), pN (pathological node metastasis). Mar (+): margin-positive. In (B), Leu-D, $PD\text{-}1^+$ cell (%) within the indicated T-cell subsets, $PD\text{-}L1^+$ (%) within panM (PDL1/panM) or Tu cells (PDL1/Tu), TMB (tumor mutation burden) and CPS (combined positive score) are shown on the right. R/M (L), local recurrence; R/M (N), lymph node metastasis; R/M (D), distant metastasis. The flow of clinical treatments and outcomes are shown in the upper regions of the pie charts. Nivo, Nivolumab; Pemb, Pembrolizumab; Cet, Cetuximab; PTX, Paclitaxel; FP, 5-Fluorouracil plus Cisplatin.



Supplementary Fig. 3 Immune parameters by immunotype. The Kruskal–Wallis test was performed. Bars: mean ± SD.



Supplementary Fig. 4 Correlations between the percentages of PD-1⁺ T cell subsets and the densities of T cell subsets. No correlations were observed among the percentages of PD-1⁺ T-cells and the CTL-, Tcon-, and C/Tcon-D values (A), or between the percentages of PD-1⁺ T-cells and the Leu-D values (B). Spearman's rank correlations were conducted. r, correlation coefficient.



Supplementary Fig. 5 Heatmap of data of the 17 ICI-treated TSCC patients.

All ICI treatment-related issues and clinicopathological characteristics are shown. S, surgery; C, chemotherapy; R, radiotherapy; CPS, combined positive score; TMB, tumor mutation burden; PFS, progression-free survival; OS, overall survival; pN, pathological node metastasis; ENE, extranodal extension; Ly, lymphatic vessel; V, venous; Pn, perineural. NA, not available.

Supplementary Table

Immunological characteristics, PD-1 ICI sensitivity, and possible combined treatments by immunotype

Immunotype	Immunological characteristics	PD-1 ICI sensitivity	Possible combined treatments
Type I	High CTL-D High PD-1/PD-L1	Sensitive	Not required
Type II	CTL-D (Type I > II) PD-1/PD-L1 (Type 1 > II)	Less sensitive	Targeting additional ICIs + anti-CTLA-4 + anti-TIM-3 or anti-LAG3
Type III	Moderate~low CTL CTL-D (Type III > IV) **Immunoregulatory cell-dominant status** (Treg, TAMs, Neu, Others)	Resistant	Targeting Treg recruitment + CCR4 antagonists (Mogamulizumab) Targeting TAMs generation and recruitment + CSF1R inhibitors (Emactuzumab, Pexidartinib) + multispecific CSF1R/CCR2/TGF-β Ab Targeting TAN/PMN-MDSC + Gemcitabine + IDO1 inhibitors
Type IV	Moderate~low CTL Long CTL–tumor distance **Alterations of stromal architecture**	Resistant	Targeting CAFs /Tumor cells /Endothelial cells + EGFR inhibitors (Cetuximab, Gefitinib) + VEGFR inhibitors (Bevacizumab) + TGF-βR inhibitors (Vactosertib) + dual TGF-βRII/PD-L1 inhibitor (Bintrafusp alfa) + STAT3 inhibitors
Type V	No antitumor response **Lack of tumor antigens (neoantigens)**	Resistant	Require tumor-Ag modification

TAMs: tumor-associated macrophages, TAN: tumor-associated neutrophils, MDSC: myeloid-derived suppressor cells, CSF1R: colony-stimulating factor 1 receptor, PMN: polymorphonuclear, IDO: indoleamine 2,3-dioxygenase, EGFR: epidermal growth factor receptor, VEGFR: vascular endothelial growth factor receptor, TGF-β: transforming growth factor beta, STAT3: signal transducer and activator of transcription 3.