

SMALL CELL LUNG CANCER MOLECULAR SUBTYPES AND VULNERABILITY TO IMMUNE CHECKPOINT BLOCKADE

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Background Extensive-stage (ES) small cell lung cancer (SCLC) disproportionately contributes to annual lung cancer-related deaths.^{1,2,3} Following the pivotal Phase III IMpower133 study, the PD-L1 inhibitor atezolizumab, combined with carboplatin and etoposide (CE), was the first immune checkpoint inhibitor approved for first-line treatment of ES-SCLC and is now a standard-of-care.⁴ In general, SCLC tumors are immunological deserts with limited tumor cell PD-L1 expression.^{5,6} Previous subtyping define SCLC tumors as neuroendocrine (NE) (ASCL1 or NEUROD1-driven) and non-neuroendocrine (nonNE) (POU2F3 or an Inflamed subtype).^{5,7,8,9} Subtyping approaches have been limited to small cohorts and cell lines, with associated clinical outcomes suggesting improved benefit of the inflamed subtype with immunotherapy.⁵

Methods We analyzed pre-treatment RNA-sequencing (RNA-seq) from 271 patient tumors from IMpower133. We applied nonnegative matrix factorization (NMF) to define SCLC classes within this dataset and correlated these new subtypes with clinical outcomes to atezolizumab+CE versus placebo+CE. We defined cell-intrinsic and -extrinsic hallmarks of each subtype with differential gene expression analyses.

Results We identify four subtypes that can be characterized by both cell-intrinsic and tumor microenvironmental features. The subtypes include NEUROD1-driven (NE-N, 31%), ASCL1-driven (NE-A, 33%), NE inflamed (NE-I, 14%), and nonNE inflamed (nonNE-I, 22%). Prior classification schema had one inflamed subgroup, whereas we identify two clusters with inflamed hallmarks. We observe both a NE-I and nonNE-I group with enrichment for T cells, B/plasma cells, antigen presentation machinery, and immune cell PD-L1 expression.

We find that while the NE-A and NE-N subtypes show similar atezolizumab+CE benefit compared to placebo, the inflamed subtypes have markedly distinct outcomes. The NE-I subtype shows a near doubling of median overall survival (OS) with atezolizumab+CE compared to placebo+CE (OS HR, 0.45 [0.22-0.89]), while the nonNE-I subtype shows no benefit despite hallmarks of lymphocyte inflammation and PD-L1 expression (OS HR, 1.02 [0.55-1.91]). The balance of T-effector to tumor-associated macrophage (TAM) signals distinguish these two inflamed subtypes (NE-I and nonNE-I). Tumors with high T-effector and high TAM signals have similar OS with atezolizumab+CE and placebo+CE (OS HR, 0.85 [0.53-1.37]), while tumors with high T-effector, but low TAM signals demonstrate markedly longer OS with atezolizumab+CE compared to placebo+CE (OS HR, 0.26 [0.12-0.57]).

Conclusions We further refine SCLC subtypes and describe a spectrum of heterogeneity. We identify two inflamed subtypes with distinct clinical outcomes to atezolizumab+CE therapy dependent on the balance of T-effector to TAM infiltration. These results demonstrate the potential for personalization of therapy for SCLC patients based on molecular subtypes.

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Ethics Approval The study protocol for IMpower133 was approved by the institutional review board or independent ethics committee for each study site and was performed in full accordance with the Guideline for Good Clinical Practice and the Declaration of Helsinki. All human tumor specimens in this study, and subsequent evaluations, were used in accordance with the informed consent agreements obtained from all subjects.

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