Small cell lung cancer (SCLC) is an extremely aggressive subtype of lung cancer, which accounts for approximately 15% of all lung cancer cases. The disease is characterized by rapid growth and early metastasis to distant organs; thus, most patients with SCLC are diagnosed in advanced stages. Despite frequently observed good initial responses to systemic chemotherapy, almost all advanced SCLC cases eventually relapse, becoming nonresponsive to chemotherapy within months, and the prognosis is dismal. Compared with non-small-cell lung cancer (NSCLC), there have been fewer advances in the treatment of SCLC in the past few decades.

Immunotherapy with checkpoint inhibitors targeting the programmed death 1 (PD-1) and PD-1 ligand 1 (PD-L1), which provide specific co-inhibitory signaling to effector T cells to suppress immune surveillance, has shown unprecedented treatment benefits to systemic chemotherapy, almost all advanced SCLC cases eventually relapse, becoming nonresponsive to chemotherapy within months, and the prognosis is dismal. Compared with non-small-cell lung cancer (NSCLC), there have been fewer advances in the treatment of SCLC in the past few decades.

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71.6% of SCLCs and 58.8% of pulmonary neuroendocrine tumors. According to recent information from Abcam (Cambridge, UK), the clone EPR1161 seems to be inappropriate for the detection of PD-L1 expression and is no longer available. In clear contrast to these studies describing relatively high PD-L1 positive rates in SCLC, another study using the antibody clones 5H1 and E1L3N showed that SCLC tumor cells did not express PD-L1 (13). In the CheckMate 032 trial using 28-8, ≥1% tumor PD-L1 expression was detected in 17% of SCLC specimens and ≥5% tumor PD-L1 expression was detected in only 5% of specimens (7 of 148 patient samples) (8). In the KEYNOTE-028 trial that evaluated the efficacy of pembrolizumab for multicohort PD-L1-positive solid tumors, PD-L1 positivity was assessed using the 22C3 antibody and was defined as staining in ≥1% of the tumor and associated inflammatory cells or positive staining in the stroma. These criteria were fulfilled in 28.6% (42 of 147) of the extensive-disease SCLC cohort (14). Collectively, new biomarkers for SCLC are needed that are more reliable and less arbitrary than immunohistochemistry (IHC) analysis for PD-L1.

In a recent study by George et al. (15), genomic amplification of the CD274 (PD-L1) was rigorously explored in SCLC using a Taqman copy number assay and an SNP array from two independent cohorts with 210 patients in total. Focal CD274 amplification was observed in four (1.9%) tumors, which is a slightly lower frequency than determined in NSCLC using fluorescence in situ hybridization assay in a previous study (10). PD-L1 expression in SCLC was evaluated in a subset of the cohort with IHC using the well-validated E1L3N clone. Surprisingly, PD-L1 was positive in only the four CD274-amplified tumor specimens. Interestingly, CD274-polysomic cases showed no tumor PD-L1 expression in contrast to our previous study, which demonstrated that CD274 polysomy as well as CD274 amplification was significantly associated with PD-L1 expression in NSCLC (10). In addition, George et al. (15) found that amplification of the 9p24 locus, where CD274 and PDCD1LG2 (PD-L2) reside, led to increased expression of CD274 but not of PDCD1LG2, indicating that CD274 was the target of the 9p24 amplification. Similarly, the PD-L2 copy number gains were not linked to increased PD-L2 expression in our previous study on NSCLC (10) and in another study on diffuse large B-cell lymphoma (16). The different regulation mechanisms between CD274 and PDCD1LG2 need to be further investigated.

George et al. (15) found multiple intra- and inter-chromosomal rearrangements affecting the 9p24.1 segment in two CD274-amplified SCLC cases. In one case, a genomic rearrangement was observed in the upstream promoter and 5’-UTR region of CD274, resulting in a tandem duplication of the upstream region of CD274. In another case, intra- and inter-chromosomal rearrangements were detected, but the copy number of the CD274 open reading frame was not affected. Therefore, the authors speculated that genomic rearrangements in the 9p24 locus upstream of CD274 might cause the deregulation of CD274 expression. Translocations and chimeric fusions of CD274 augment the expression of transcripts in several types of lymphomas (16-19), among which the chromosome 9p24.1 cytoband was rearranged to several fusion partners, such as the immunoglobulin heavy-chain (IGH) gene locus and the major histocompatibility complex class II transactivator CIITA. It is of interest to explore the relevance of CD274-rearranged tumors in other cancers and to clarify whether there are any biological or clinical differences between CD274-rearranged tumors and nonrearranged but amplified tumors.

George et al. (15) also showed that CD274 amplification was correlated with immune cell infiltration using transcriptome sequencing data and IHC. The relationships of CD274 copy number changes with tumor mutation load and specific tumor microenvironment were previously discussed in other cancers (20). In our study, CD274 copy number gains were significantly associated with increased infiltration of CD8- or PD-1-positive lymphocytes in NSCLC (unpublished data). However, it remains unclear whether CD274 amplification is correlated with further tumor mutation load in SCLC, which usually harbors high mutation burden. It is also unknown whether the complicated chromosomal changes influence other biomarkers and clinical outcomes.

SCLC treatment, which has experienced relatively few advances in the past decade, has entered a new era of immunotherapy. In view of the PD-L1 positive rates for SCLC in the CheckMate 032 and KEYNOTE-028 trials, there should be other mechanisms that induce PD-L1 expression in SCLC besides CD274 amplification. However, CD274 amplification is a recurrent genomic change observed in a variety of malignancies in addition to SCLC, implying its important role in the biology of cancer cells. Although the frequency in SCLC is quite low, the significance of CD274 amplification and rearrangement should be further evaluated, especially in the context of the
anti-PD-1/PD-L1 therapy. CD274 genomic changes might interact with the distinct tumor microenvironment and predict sensitivity to the therapy, possibly in combination with other indices. Ultimately, it would be another challenge for oncologists to translate these rare but important genetic findings into feasible and practical clinical tests.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References
