Commentary

CD274 (PD-L1) genomic change: another marker for small cell lung cancer?

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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 and has been established as the standard of care for several malignancies, including NSCLC (1-4). The presence and amount of tumor-specific antigens generated via somatic mutations are considered candidate predictors of benefits from the PD-1/PD-L1 inhibitory agents (5). Among many carcinogens, SCLC is strongly correlated with smoking (6). SCLC possesses an extremely high mutation rate of 7.4 protein-changing mutations per million base pairs, and these mutations are likely associated with tobacco carcinogens (7). Autoimmune paraneoplastic syndromes that are sometimes observed in patients with SCLC also support the immunogenicity of this disease. Therefore, the PD-1/PD-L1 blockade strategy is expected to be effective for SCLC. A phase 1/2 multicenter, multi-arm prospective trial (CheckMate 032) in which nivolumab (an anti-PD-1 antibody) monotherapy and nivolumab and ipilimumab (an antibody against cytotoxic T-lymphocyte antigen-4) combination therapy were applied to previously treated SCLC patients, has recently demonstrated clinically meaningful antitumor activity, with durable responses and acceptable feasibility (8). Several studies are also currently evaluating immune checkpoint blockade therapies for SCLC (9). However, responses to immune checkpoint blockade are not universal for SCLC, similar to other cancers, signaling the urgency of identifying predictive biomarkers for sensitivity to the therapy.

PD-L1 expression in tumor cells and/or tumor-infiltrating immune cells is regarded as a potentially useful guide for selecting patients with NSCLC likely to respond to anti-PD-1/PD-L1 inhibitors (2-4). However, tumor responses were observed in SCLC patients irrespective of tumor PD-L1 expression in the CheckMate 032 trial (8). There are several issues in the evaluation of tumor PD-L1 expression using immunohistochemical staining as previously described (10). The reported prevalence of PD-L1 expression in SCLC tumor tissue varies widely. In studies using the anti-PD-L1 antibody clones EPR1161 (11) and 28-8 (12), tumor PD-L1 expression was detected in 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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