A narrative review of current and potential prognostic biomarkers for immunotherapy in small-cell lung cancer

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Abstract: Small-cell lung cancer (SCLC) is a highly invasive and rapidly proliferating pathologic subtype that accounts for 13–15% of all lung cancer cases. Recently in extensive-stage SCLC, treatments that combine immunotherapy and chemotherapy showed increased efficacy compared to chemotherapy alone in several trials. However, the combination of immunotherapy and conventional chemotherapy regimens was introduced only recently for extensive-stage SCLC, with relatively little real-world data. The demand for reliable biomarkers that can predict the efficacy of immunotherapy in SCLC is high. Several studies evaluated various parameters including programmed cell death ligand-1 (PD-L1) expression, tumor mutation burden (TMB), gene expression profiling, autoantibody, and blood cytokines for predictive value for response to immunotherapy in SCLC. Despite some observed correlations, there is a lack of concrete support for the use of PD-L1 expression levels for readily available biomarker. High TMB in combination with smoking history is predictive of a better response to immunotherapy, but validation of cutoffs and testing methods is necessary before it can be widely applied in clinical settings. Other candidate biomarkers such as immune cell distribution among tumor microenvironment, and systemic inflammatory markers can also be evaluated, after an accumulation of real-life data from SCLC patients under immunotherapy.

Keywords: Small-cell lung cancer (SCLC); immunotherapy; biomarker; tumor

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Background

Small-cell lung cancer (SCLC) is a highly invasive and rapidly proliferating pathologic subtype that accounts for 13–15% of all lung cancer cases (1,2). SCLC is much more likely to develop in smokers than in non-smokers (3). About two-thirds of patients who are initially diagnosed with SCLC develop extensive-stage SCLC (ES-SCLC) (4). The prognosis for ES-SCLC is poor, with a median overall survival of 8–13 months (5). For the past two decades, etoposide in combination with either carboplatin or cisplatin has been the standard first-line regimen for ES-SCLC (6,7). Although response rates to this regimen have reached 60–65%, the median overall survival (OS) is only 10 months (8,9).

Immune cells, including cytotoxic T-cells, contain programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte associated protein 4 (CTLA-4). When programmed death-ligand 1 (PD-L1) on the surface of cancer cells binds to receptors on cytotoxic T-cells, immune
responses against tumor cells are inhibited. Studies of immune evasion by cancer cells have led to significant advances in the development of immunotherapies that block PD-1 and CTLA-4 on T cells from binding to PD-L1 on cancer cells (10,11).

Treatments that combine immunotherapy and chemotherapy can increase immune responses to tumor cells, resulting in increased efficacy compared to chemotherapy alone (11). Several recent trials have combined immunotherapy targeting the programmed cell death-1 (PD-1)/programmed cell death ligand-1 (PD-L1) pathway to a platinum-based regimen, resulting in improved overall survival (OS) in patients with ES-SCLC (12,13). The IMpower 133 and CASPIAN studies showed similar results, collectively suggesting a breakthrough in the treatment of SCLC. The addition of atezolizumab to the traditional etoposide–carboplatin regimen, followed by atezolizumab maintenance until progression, has shown a superior median OS of 12.3 months compared to 10.3 months in the placebo group, and a median progression free-survival (PFS) of 5.2 months compared to 4.3 months in the placebo group (12). In patients with advanced SCLC who were treated in CheckMate 032, the 2-year overall survival rate was 26% among those treated with nivolumab plus ipilimumab, compared to 14% in the nivolumab monotherapy group (14). This treatment was particularly enhanced in patients with high tumor mutation burden (TMB) (15). The combination of durvalumab and platinum-based regimens also showed promising results (13,16). However, the combination of immunotherapy and platinum-based chemotherapy regimens was introduced only recently, with relatively little real-world data. It is likely that not all patients with ES-SCLC would benefit from this combination treatment. Even though the impact of adding immunotherapy is modest in improving OS, it is beneficial to search for biomarker to predict clinical outcomes and personalize cancer treatment. Therefore, the demand for reliable biomarkers that can predict the efficacy of immunotherapy in SCLC is high, and efforts to identify predictive markers are ongoing.

In this mini-review, we assess and discuss biomarkers evaluated in previous studies of immunotherapy in SCLC, as well as other candidate markers that may predict clinical outcomes.

We present the following article in accordance with the Narrative Review reporting checklist (available at http://dx.doi.org/10.21037/atm-21-68).

Method

Search strategy

Using the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (17), an online search of literature on biomarkers for efficacy of immunotherapy in ES-SCLC was conducted. The National Center for Biotechnology Information (NCBI) PubMed, Cochrane Library, EMBASE and Google Scholar were searched. All literature published in English between January 2014 and November 2020 were included. Various combinations of search texts were used. Search word ‘SCLC’ or ‘small cell lung’ was combined with each of the following terms; ‘immunotherapy’, ‘immune checkpoint’, ‘nivolumab’, ‘atezolizumab’, ‘pembrolizumab’, ‘durvalumab’, ‘ipilimumab’, ‘biomarker’, ‘marker’, ‘prognosis’, ‘programmed cell death ligand-1’, ‘PD-L1’, and ‘tumor mutation burden’.

Current immunotherapy regimens in ES-SCLC

First line therapy

After decades without major breakthrough, immune checkpoint inhibitors (ICIs) are the notable agents to show an improvement in outcomes of patients with ES-SCLC. Clinical trials of single and combination regimens show some significant results.

The phase III study IMpower133 showed that a combination regimen including immunotherapy as first-line treatment improved both OS and PFS. A total of 403 treatment-naïve patients with ES-SCLC were assigned to carboplatin plus etoposide with either atezolizumab or placebo, followed by atezolizumab or placebo maintenance. The median OS was significantly longer in the atezolizumab group than the placebo group (12.3 vs. 10.3 months; HR 0.70, 95% CI: 0.54–0.91; P=0.007). The median PFS was 5.2 and 4.3 months, respectively (HR 0.77, 95% CI: 0.62–0.96, P=0.02) (12). The efficacy of ipilimumab in combination with carboplatin and etoposide as first-line therapy for ES-SCLC was also tested in both phase II and phase III studies (CA184-041, NCT01331525, and CA184-156), and the results suggested the possibility of a significant breakthrough. Even though median OS was not different between chemotherapy plus ipilimumab group and chemotherapy plus placebo group, median PFS was longer in the chemotherapy plus ipilimumab group (4.6 vs. 4.4 months, HR 0.85; 95% CI: 0.75–0.97, P=0.0161).
(18–20). The phase III CASPIAN study showed that the addition of durvalumab to a combination regimen of etoposide with either cisplatin or carboplatin (EP) significantly improved OS compared with EP alone in patients with treatment-naïve ES-SCLC (13.0 months vs. 10.3 months, HR 0.73; 95% CI: 0.59–0.91, P=0.0047) (13).

Second or higher line therapy

Several studies which evaluated the efficacy of immunotherapy for recurrent SCLC have been performed. In the Checkmate 032 study in which patients were eligible regardless of tumor PD-L1 expression, double checkpoint inhibitor combination of nivolumab and ipilimumab, and nivolumab monotherapy demonstrated anti-tumor activity with durable responses in previously treated patients with SCLC. Objective response rate (ORR) was 10% (95% CI: 5–18%) in the nivolumab monotherapy group and 23% (95% CI: 13–36%) in the combination group (21). However, median OS was similar between the groups (4.7, 95% CI: 3.1–8.3 vs. 5.7, 95% CI: 3.8–7.6) (14). Based on these data, FDA granted an accelerated approval to nivolumab for the treatment of metastatic refractory SCLC in August 2018. Furthermore, a randomized phase III trial (CheckMate 331) was conducted to evaluate the efficacy of nivolumab compared to a standard second-line treatment with either topotecan or amrubicin upon investigator’s decision in patients with relapsed SCLC following platinum-based chemotherapy, however, nivolumab did not show survival benefit when compared to the conventional chemotherapy regimens (median OS, 7.5 vs. 8.4 months; HR, 0.86; 95% CI: 0.72–1.04; P=0.11) (22).

Different clinical trials evaluated the efficacy of immunotherapy for refractory SCLC, but they did not show encouraging results. Atezolizumab was evaluated in the IFCT-1,603 non-comparative phase II study and resulted in ORR of 2.3% and median PFS of 1.4 months (23). In KEYNOTE-028 study, pembrolizumab treatment for PD-L1 expressing (≥1%) recurrent SCLC showed ORR of 33% (95% CI: 16% to 55%), but limited PFS of 1.9 months (95% CI: 1.7 to 5.9 months) (24). Also, durvalumab failed to show satisfactory results, ORR of 10% and PFS of 1.5 months (25).

PD-L1 and PD-1 expression

One of the immune escape mechanisms of tumor cells is the interaction of PD-L1 with PD-1 on T cells, which inhibits T cell activation and cytotoxicity (26). The understanding of ICIs is based on the PD-1/PD-L1 axis, and PD-L1 expression has been evaluated as a potential predictive biomarker for ICI efficacy in several studies (27,28). However, despite some observed correlations, there is a lack of concrete support for the use of PD-L1 expression levels in SCLC as a predictive biomarker for immunotherapy response (29). First, the pooled prevalence of PD-L1 expression is lower compared to those reported in non-small cell lung cancer (NSCLC), which are influenced by IHC evaluation cut-off values, PD-L1 staining pattern, the quality of the study’s methodological characteristics, specimen acquisition, and other technical problems such as antibody staining and tissue fixation (14,30,31). Second, PD-L1 expression heterogeneity is not fully captured by small piece of tissue. Circulating tumor cells (CTCs) can represent tumor PD-L1 expression on the whole, but technical problem such as CTCs isolation and validation with matched biopsy and resected tumor are remained (32). Although positive PD-L1 expression appears to show better OS in SCLC patients, using it as a reliable predictive marker requires further large scaled studies. In a meta-analysis, the pooled HR of all studies was 0.86 (95% CI: 0.49–1.50, P=0.588) indicating that positive PD-L1 expression demonstrated a trend towards longer OS in SCLC patients (14). However, in the Checkmate 032 study, only 17% of patients had ≥1% PD-L1 expression and 5% had ≥5% PD-L1 expression, and the response to nivolumab monotherapy or a combination with ipilimumab occurred irrespective of the PD-L1 expression levels (21).

Tumor mutation burden

Like NSCLC, SCLC is characterized by high TMB, which has been shown to predict the efficacy of nivolumab in NSCLC treatment (33), suggesting a potential significant benefit for TMB as a biomarker for immunotherapy in SCLC. In SCLC cohort of CheckMate 032, nivolumab ± ipilimumab showed an improved efficacy in patients with high TMB. In this study, TMB was defined as the total number of somatic missense mutations, and patients were divided into tertiles. Tertile boundaries were defined as: low, 0 to <143 mutations; medium, 143 to 247 mutations, and high, ≥248 mutations (15). Previous studies on immunotherapy in SCLC have shown that high TMB in combination with smoking history is predictive of a better response to immunotherapy (31,34). However, exploratory subgroup analyses performed in the IMpower 133 study showed that blood-based TMB levels at a cutoff
of 10 or 16 mutations per megabase had no clear predictive power for atezolizumab response. The authors explained that the highly active and myelosuppressive nature of the combination of platinum and etoposide affected the predictability of blood-based TMB (12). TMB is not readily available as a biomarker for clinical practice yet, because a larger population study is necessary to validate reliable cutoffs and testing methods before it can be widely applied in clinical settings. In addition, tissue acquisition is an important issue in TMB assessment, because many patients with SCLC are likely to receive only small cytology sample biopsies. Therefore, core biopsies are necessary for patients with SCLC in order to perform routine TMB testing (35). Also, clinical use of circulating free DNA (cfDNA) for TMB evaluation instead of tissue sample is needed. Many problems such as low cfDNA concentration in patients with low tumor burden and low variant allelic frequency affecting the test results remain (36).

**Targeted gene sequencing and gene expression profiling**

In a multicenter phase II study, 26 patients with ES-SCLC who showed progression after etoposide plus platinum chemotherapy received six cycles of paclitaxel every 3 weeks. Pembrolizumab was added after the first cycle of paclitaxel and maintained until progression. In this study, targeted gene sequencing (TGS) designed to detect 90 cancer-related genes was performed in 14 patients. Favorable survival outcomes were obtained in the group harboring MET copy number gain (PFS 10.5 vs. 3.4 months, P=0.019) (37).

A pan-cancer, T-cell-inflamed gene-expression profile (GEP) comprised of 18 genes indicative of a T-cell-activated tumor microenvironment (TME) was associated with pembrolizumab response in multiple cancers. T cell-inflamed TME characterized by active IFN-γ signaling, cytotoxic effector molecules, antigen presentation, and T-cell active cytokines, is a common feature of tumor biology that are responsive to PD-1 checkpoint blockade (38). In the phase Ib Keynote 028 trial, which enrolled 475 patients with PD-L1-positive advanced solid tumors, the patient group with SCLC showed an ORR of 33% following treatment with pembrolizumab. The study showed that tumor T cell-inflamed GEPs were a potential predictive biomarker of pembrolizumab response (39). T cell-inflamed GEP scores were higher in patients showing good responses and longer PFS. However, since Keynote 028 examined various solid tumors, a separate study enrolling a large number of SCLC patients should be conducted for validation.

**Autoantibodies and cytokines**

Other clinical parameters, such as autoantibody and inflammatory cytokine levels, have been evaluated for their potential values as biomarker. In a multicenter phase 2 study of ipilimumab in combination with carboplatin and etoposide as first-line therapy for ES-SCLC, a positive autoimmune profile at baseline was associated with better PFS according to immune response criteria. Patients with any positive autoantibody detected at baseline showed a significantly longer median PFS [8.8 months (95% CI: 5.1–10.7) versus 7.3 months (95% CI: 2.9–7.9), P=0.036]. Also, an association between anti-SOX2 and anti-Hu autoantibody levels, and severe neurological toxicities was observed (19).

Predictive values of inflammatory cytokines for the immunotherapy response have been studied in NSCLC (40), and one such study including two cohorts of SCLC patients evaluated the predictive value of cytokines in SCLC patients under immunotherapy. Changes in the levels of various cytokines, including IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, and IFN-γ, were compared between the patients treated with chemotherapy only and those treated with chemotherapy plus ipilimumab. Compared with the chemotherapy-only group, patients treated with ipilimumab showed a global increase of all cytokines after treatment initiation. Increased baseline IL-2 levels were predictive of the ipilimumab response. Patients with a high serum IL-2 concentration had a median OS of 30.5 months while those with lower concentration had a median OS of 8 months (P=0.015). A serial increase in the IL-4 levels was associated with improved OS in the combination treatment group. Patients whose IL-4 increased more than 32% had a significantly better OS (18.5 vs. 8.8 months; P=0.042) (41).

**Other candidate biomarkers**

A study of resected samples from long-term survivors (survival >4 years) and survivors with the expected survival time (survival ≤2 years) who were diagnosed with SCLC applied quantitative immunostaining to confirm differences in immune cell distribution among tumor microenvironments. The number of tumor-infiltrating and associated lymphocytes was higher
throughout tumors of long-term survivors than in those of expected survivors with an OS of <2 years, irrespective of clinical variables including TNM staging and curative-versus non-curative-intent surgery (42). Considering that immune response activation against tumor cells is the main mechanism of ICIs, the distribution of CD markers which reflect immune cell profiles in the tumor microenvironment may be a potential biomarker.

The lung immune prognostic index (LIPI), which is calculated from the serum lactate dehydrogenase levels and the ratio of derived neutrophils to lymphocytes (dNLR), is also a potential biomarker in SCLC patients under immunotherapy. A study of 171 patients with SCLC who underwent anticancer treatment modalities other than immunotherapy (concurrent chemoradiotherapy, conventional chemotherapy, radiotherapy) showed that LIPI had prognostic value in terms of OS and PFS (43). The authors hypothesized that systemic inflammation may have an adverse effect on the efficacy of chemotherapy, which may be reflected in the LIPI scores. Other systemic inflammatory biomarkers such as NLR and the platelet-to-lymphocyte ratio (PLR) may have prognostic value in SCLC patients under immunotherapy, since they are associated with OS or PFS in SCLC patients under conventional anticancer treatment including etoposide combination regimens (44,45). The publication of further studies of SCLC under immunotherapy using systemic inflammatory biomarkers is anticipated following an accumulation of survival data.

An examination of the immune evasion mechanism of tumor cells can provide clues to predicting the immune response to SCLC at the cellular level. The interaction between SCLC tumor cells and T regulatory (Treg) cells, which modulate the activity of other T cells, may be involved in SCLC immunotherapy. Patients with SCLC showing higher ratios of FOXP3+ cells in tumor infiltrates have been reported to have a poorer prognosis. Some SCLC tumor cell lines induce de-novo differentiation of functional FOXP3+ Treg cells in healthy blood lymphocytes. SCLC tumor cells can induce CD4 T cell-mediated immunosuppression, suggesting a potential mechanism by which SCLC cells downregulate immune responses against tumor cells, in turn leading to poorer survival (46). Downregulation of the major histocompatibility complex (MHC) has also been suggested as a main mechanism of immunotherapy resistance (47). MHC class I expression has been reported to be lower in SCLC tumor samples than in NSCLC cell lines (48), and decreased interferon-γ secretion is thought to greatly contribute to the reduction of MHC in SCLC (49).

Finally, the associations between galectin-9 (Gal-9) and the tumor-immune microenvironment and immune infiltration in SCLC patients under concurrent chemoradiotherapy, conventional chemotherapy or radiotherapy, were studied. The Gal-9 expression levels on tumor-infiltrating lymphocytes (TILs) were found to be correlated with the PD-1, PD-L1, CD3, CD4, CD8, and FOXP3 levels, and high Gal-9 protein expression on TILs was correlated with superior recurrence-free survival, suggesting the potential of Gal-9 as a biomarker in SCLC patients under immunotherapy (50). In addition, other biomarkers which had shown potential predictive values in other cancers including NSCLC and skin cancer, and not yet tested in ES-SCLC can also be evaluated. T cell receptor clonality, TILs, blood soluble cytokine concentrations, and immune gene signature had shown association with ICI response in melanoma, breast, and lung cancer (51-53) (Table 1).

Conclusions
Besides TMB, no reliable biomarker has been discovered that can predict the immunotherapy response in SCLC patients. Future studies focused on understanding of basic biology of SCLC and the identification of novel predictive biomarkers of response to immunotherapy in SCLC are essential.
Table 1 Predictive biomarkers of anti-PD-1/PD-L1 therapy in SCLC in comparison to NSCLC

<table>
<thead>
<tr>
<th>Candidate biomarker</th>
<th>SCLC</th>
<th>NSCLC</th>
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<tr>
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<td>Nivolumab ± ipilimumab showed an improved efficacy in patients with high TMB</td>
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<td><strong>Mutation</strong></td>
<td>MET copy gain</td>
<td>Twenty-six patients who show progression after 1st line chemotherapy were treated with pembrolizumab and paclitaxel. Favorable survival outcomes obtained in the group of ES-SCLC harboring MET copy number gain</td>
</tr>
<tr>
<td><strong>Immune cell T cell-inflamed distribution</strong></td>
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IL, interleukin; IFN, interferon; PD, programmed death; ICI, immune checkpoint inhibitor; SCLC, small cell lung cancer; NSCLC, non-small cell lung cancer; ES, extensive-stage; PFS, progression-free survival; ORR, objective response rate; OS, overall survival; GEP, gene-expression profile; TMB, tumor mutation burden; CI, confidence interval; TIL, tumor-infiltrating lymphocytes; CTLA, cytotoxic T-lymphocyte-associated protein 4; MET, mesenchymal-to-epithelial transition.

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**Footnote**

**Reporting Checklist:** The authors have completed the Narrative Review reporting checklist. Available at [http://dx.doi.org/10.21037/atm-21-68](http://dx.doi.org/10.21037/atm-21-68)

**Ethical Statement:** The authors are accountable for all
aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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