

REVIEW

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Advances in predictive biomarkers associated with immunotherapy in extensive-stage small cell lung cancer

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Abstract

Small cell lung cancer (SCLC) is a highly malignant and poor-prognosis cancer, with most cases diagnosed at the extensive stage (ES). Amidst a landscape marked by limited progress in treatment modalities for ES-SCLC over the past few decades, the integration of immune checkpoint inhibitors (ICIs) with platinum-based chemotherapy has provided a milestone approach for improving prognosis, emerging as the new standard for initial therapy in ES-SCLC. However, only a minority of SCLC patients can benefit from ICIs, which frequently come with varying degrees of immune-related adverse events (irAEs). Therefore, it is crucial to investigate predictive biomarkers to screen potential beneficiaries of ICIs, mitigate the risk of side effects, and improve treatment precision. This review summarized potential biomarkers for predicting ICI response in ES-SCLC, with a primary focus on markers sourced from tumor tissue or peripheral blood samples. The former mainly included PD-L1 expression, tumor mutational burden (TMB), along with cellular or molecular components related to the tumor microenvironment (TME) and antigen presentation machinery (APM), molecular subtypes of SCLC, and inflammatory gene expression profiles. Circulating biomarkers predominantly comprised circulating tumor DNA (ctDNA), circulating tumor cells (CTCs), cytokines, plasma autoantibodies, inflammation-related parameters, and blood TMB. We synthesized and analyzed the research progress of these potential markers. Notably, investigations into PD-L1 expression and TMB have been the most extensive, exhibiting preliminary predictive efficacy in salvage immunotherapy; however, consistent conclusions have yet to be reached across studies. Additionally, novel predictive markers developed based on TME composition, APM, transcriptomic and genomic features provide promising tools for precision immunotherapy. Circulating biomarkers offer the advantages of convenience, non-invasiveness, and a comprehensive reflection of tumor molecular characteristics. They may serve as alternative options for predicting immunotherapy efficacy in SCLC. However, there is a scarcity of studies, and the significant heterogeneity in research findings warrants attention.

Keywords Small cell lung cancer, Extensive stage, Immune checkpoint inhibitors, Immunotherapy, Efficacy, Predictive biomarkers

Background

Lung cancer is among the most prevalent malignant tumors globally and stands as the primary cause of cancer-related death. Lung cancer is histologically categorized into two major subtypes: non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) [1]. SCLC is identified as a poorly differentiated neuroendocrine tumor, accounting for approximately 13–15% of all

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lung cancers [2]. SCLC is closely associated with tobacco exposure and is characterized by high malignancy, rapid growth, early distant metastasis, elevated recurrence rate, and acquired drug resistance [3], with a 5-year survival rate of less than 7% [4]. The Veterans Administration Lung Cancer Study Group (VALCSG) proposed dividing SCLC into limited-stage (LS) and extensive-stage (ES) disease, based on whether the lesions are contained to one hemithorax and can be covered by a radiation field [5]. Approximately 70% of newly diagnosed SCLC patients have already progressed to ES-SCLC. The standard first-line treatment for ES-SCLC using a platinum-etoposide (EP) combination has remained mostly unchanged for decades. ES-SCLC initially shows high sensitivity to chemotherapy, with a response rate of up to 60–65%, but the response is of short duration [6]. The median progression-free survival (PFS) spans only about 5–6 months, with the median overall survival (OS) of approximately 9–10 months [7, 8].

The clinical development of immunotherapy, especially anti-programmed cell death protein 1/programmed cell death 1 ligand 1 (PD-1/PD-L1) therapy, has been a revolutionary milestone in the treatment landscape of ES-SCLC in recent years. Landmark research such as IMpower133 and CASPIAN has supported the approval of atezolizumab/durvalumab plus chemotherapy for initial therapy of ES-SCLC globally. The IMpower133 study demonstrated that at a median follow-up of 13.9 months, the median OS for the atezolizumab group and the placebo group were 12.3 months and 10.3 months, respectively, with a hazard ratio (HR) of 0.70 (95% confidence interval [CI] 0.54–0.91; $p = 0.007$). Atezolizumab group had a median PFS of 5.2 months compared to 4.3 months for the placebo group, with a HR of 0.77 (95% CI 0.62–0.96; $p = 0.02$) [6]. The results of the CASPIAN study indicated that adding durvalumab to chemotherapy conferred a significant OS benefit compared to EP regimen (median OS: 12.9 months vs. 10.5 months; HR, 0.71; 95% CI 0.60–0.86; $p = 0.0003$) [9, 10]. Despite these advancements, the improvement in PFS and OS with the addition of immune checkpoint inhibitors (ICIs) is modest, and the divergence of long-term survival curves after six months suggested that a limited subset of SCLC patients benefited from ICIs. Additionally, while immunotherapy offers benefits, it also comes with immune-related toxicities [11–13]. Therefore, it is urgent to find reliable biomarkers to effectively predict the efficacy of PD-1/PD-L1 inhibitors.

Novel immunomodulatory agents beyond PD-1/PD-L1 inhibitors have also been intensively evaluated preclinically and clinically in SCLC, among which delta-like ligand 3 (DLL3)-targeted bispecific T-cell engagers (BiTEs) have garnered the most extensive research and

demonstrated promising clinical efficacy [14–17]. Tarlatamab has received accelerated approval from the US Food and Drug Administration (FDA) for treating ES-SCLC following progression. Additionally, several other novel treatment strategies with promising preclinical results are undergoing corresponding clinical investigations, such as chimeric antigen receptor (CAR) based therapies [18–20], cancer vaccines [21, 22], and novel ICIs (anti-T cell immunoglobulin and mucin domain-containing protein 3 (TIM3), anti-T cell immunoreceptor with immunoglobulin and ITIM domain (TIGIT), anti-lymphocyte activation gene 3 (LAG3), anti-CTLA4-LAG-3 antibodies, etc.) [23–29]. However, the development of novel immunotherapies in SCLC largely remains in early-stage clinical trials, with limited exploration of biomarkers. The information of these trials was listed in Supplementary Table 1.

In this review, we aimed to summarize the latest advances in the predictive biomarkers for immunotherapy in ES-SCLC, with a primary focus on ICIs. Our primary emphasis, according to the types of markers that have been reported, lied on markers obtained from tumor tissue or peripheral blood (Fig. 1).

Tumor tissue-based biomarkers

PD-L1 expression

PD-L1 expression detected by immunohistochemistry (IHC) is considered a critical predictive factor for the immunotherapy response in NSCLC [30, 31]. Nonetheless, variations in PD-L1 expression levels in NSCLC arise from diverse clinical and genotypic characteristics among distinct study populations. Additionally, disparities in ICIs and corresponding detection platforms contribute to varying PD-L1 expression thresholds, resulting in inconsistent findings across studies [32]. In comparison to NSCLC patients, those with SCLC exhibit lower frequencies of PD-L1 expression, compounded by the scarcity of specimen cells which limits PD-L1 detection and research [33]. Reportedly, PD-L1 expression on tumor cells (TCs) in SCLC is quite low, with a range of 1.8% to 17%, whereas PD-L1 expression is more frequent on immune cells (ICs) compared to TCs, ranging from 25.8 to 40% [34–47]. Currently, the predictive role of PD-L1 expression in SCLC is still controversial (Table 1).

In the first-line treatment of ES-SCLC, the efficacy of ICIs combined with EP appears to be less dependent on PD-L1 expression. In the IMpower133 trial, OS benefits were observed with atezolizumab plus etoposide and carboplatin (EC) versus placebo plus EC in both the PD-L1 expression < 1% TC and IC subgroup (median OS: 10.2 months vs. 8.3 months; HR, 0.51; 95% CI 0.30–0.89) and the PD-L1 expression \geq 5% TC or IC subgroup (median OS: 21.6 months vs. 9.2 months; HR, 0.60; 95%

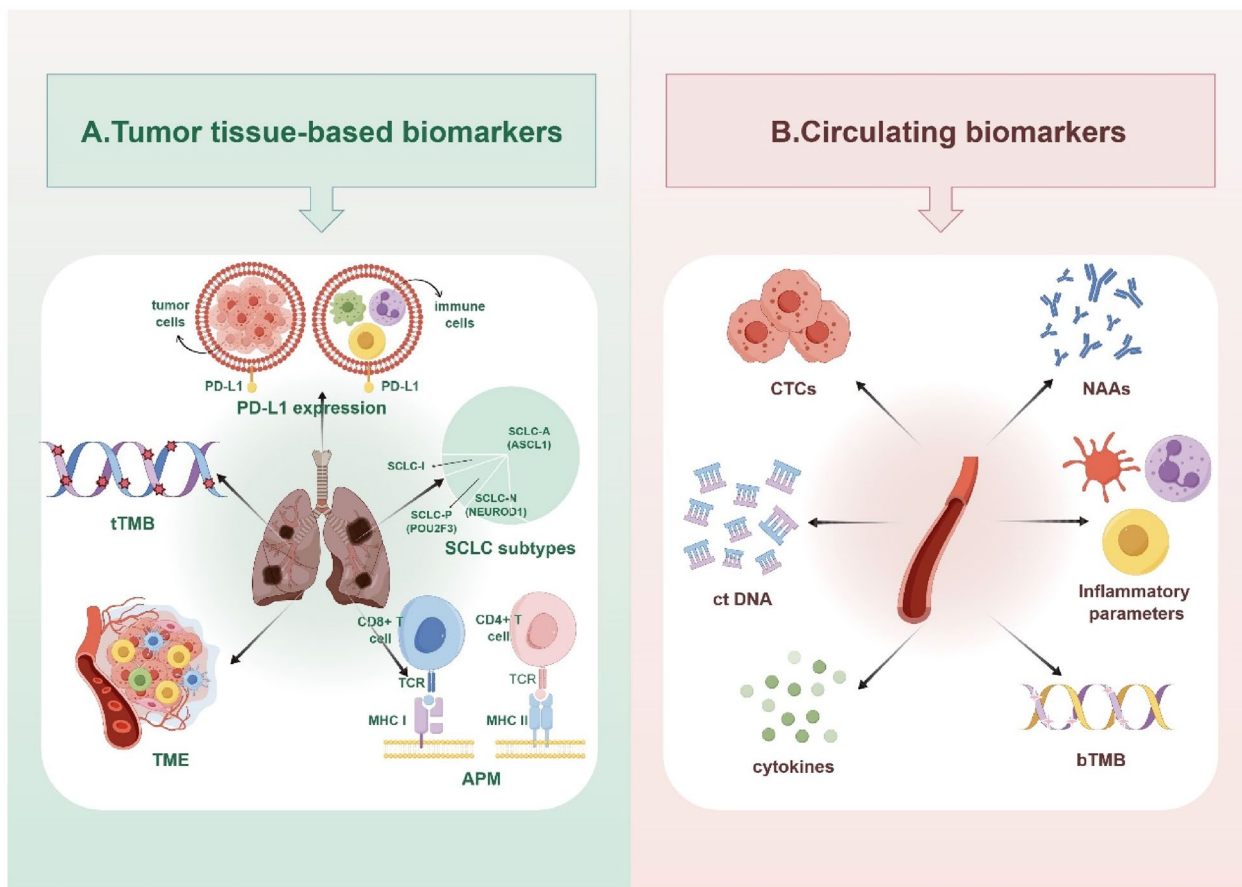


Fig. 1 Predictive biomarkers of ICI response in ES-SCLC. SCLC: small cell lung cancer; ES: extensive stage; PD-L1: programmed cell death 1 ligand 1; ICI: immune checkpoint inhibitor; TMB: tumor mutational burden; tTMB: tissue tumor mutational burden; bTMB: blood tumor mutational burden; TME: tumor microenvironment; APM: antigen presentation machinery; TCR: T cell receptor; MHC: major histocompatibility complex; ASCL1: achaete-scute homologue 1; NEUROD1: neurogenic differentiation factor 1; POU2F3: POU class 2 homeobox 3; ctDNA: circulating tumor DNA; CTCs: circulating tumor cells; NAAs: neuronal autoantibodies

CI 0.25–1.46). Patients with PD-L1 expression levels $\geq 1\%$ TC or IC, however, did not show a comparable outcome (median OS: 9.7 months vs. 10.6 months; HR, 0.87; 95% CI 0.51–1.49) [34, 35]. The KEYNOTE-604 study evaluated the efficacy of pembrolizumab plus EP in previously untreated ES-SCLC, revealing comparable HRs for PFS and OS between the PD-L1 combined positive score (CPS) ≥ 1 and PD-L1 negative subgroups [36]. The treatment regimens in the ASTRUM-005 trial [37] and CAPSTONE-1 trial [38] were respectively Serplulimab plus EC and Adebrelimab plus EC, and exploration of the predictive potential of PD-L1 expression yielded negative results consistent with previous studies. Interestingly, in exploratory analyses of the CASPIAN trial, OS benefit of durvalumab in combination with EP compared to EP alone appeared independent of PD-L1 expression, with HRs of 0.64 (95% CI 0.47–0.85) in the IC $< 1\%$ subgroup and 0.59 (95% CI 0.34–1.02) in the IC $\geq 1\%$ subgroup. However, in the PD-L1 $\geq 1\%$ subgroups, the OS benefit

seemed greater with durvalumab plus tremelimumab plus EP versus EP alone, with HRs of 0.88 (95% CI 0.66–1.19) in the IC $< 1\%$ subgroup and 0.53 (95% CI 0.31–0.90) in the IC $\geq 1\%$ subgroup, indicating that PD-L1 expression could potentially function as a promising biomarker for assessing the effectiveness of combination therapy involving PD-1/PD-L1 and cytotoxic T lymphocyte antigen 4 (CTLA-4) inhibition [39]. Whereas, further data from additional studies are required to bolster this proposition.

The available evidence on the predictive value of PD-L1 expression in first-line maintenance therapy for ES-SCLC remains insufficient. Exploratory analyses of the CheckMate451 study in the CPS-evaluable population demonstrated that PD-L1 expression levels (CPS ≥ 1 or < 1) were not associated with the benefits of nivolumab with or without ipilimumab compared to placebo as first-line maintenance therapy for ES-SCLC. However, across all treatment arms, including

Table 1 PD-L1 expression as predictive biomarker for ICI therapies in clinical trials involving ES-SCLC

Trial	Phase	Year ^a	Population	Treatment	N (BEP)	Antibody
First-line setting						
CASPIAN [39]	III	2017	Untreated ES-SCLC	Durvalumab plus etoposide and platinum (EP) (D+EP), Durvalumab plus Tremelimumab plus EP (D+T+EP), EP alone	D+EP: 152 D+T+EP: 157 EP: 129	SP263
IMpower133 [34]	I/III	2016	Untreated ES-SCLC	Atezolizumab plus etoposide and carboplatin (EC), Placebo plus EC	Atezolizumab arm: 64, Placebo arm: 73	SP263
KEYNOTE-604 [36]	III	2017	Untreated ES-SCLC	Pembrolizumab plus EP, Placebo plus EP	Pembrolizumab arm: 185, Placebo arm: 175	22C3
ASTRUM-005 [37]	III	2019	Untreated ES-SCLC	Serplulimab plus EC, Placebo plus EC	Serplulimab arm: 379, Placebo arm: 186	22C3
CAPSTONE-1 [38]	III	2018	Untreated ES-SCLC	Adebrelimab plus EC, Placebo plus EC	Adebrelimab arm: 220, Placebo arm: 220	E1L3N
SKYSCRAPER-02 [25]	III	2020	Untreated ES-SCLC	Tiragolumab plus Atezolizumab and CE, Placebo plus Atezolizumab and CE	Tiragolumab arm: 216 Placebo arm: 225	SP263
First-line maintenance						
CheckMate 451 [40]	III	2015	ES-SCLC first line maintenance	Nivolumab plus ipilimumab, Nivolumab monotherapy, Placebo	Combination arm: 116 Nivolumab arm: 124 Placebo arm: 114	28-8
NCT 02359019 [41]	II	2015	ES-SCLC first line maintenance	Pembrolizumab	TC assessed: 30, stroma interface assessed: 20	22C3
Second- and later-line settings						
CheckMate 331 [44]	III	2015	Relapsed ES-SCLC	Nivolumab, Chemotherapy (topotecan or amrubicin)	Nivolumab arm: 171 Chemotherapy arm: 150	28-8
KEYNOTE-158 [42]	II	2015	Relapsed ES-SCLC	Pembrolizumab	92	22C3
IFCT-1603 Trial [45]	II	2017	Relapsed SCLC	Atezolizumab, Chemotherapy (topotecan or re-induction of initial chemotherapy)	54	SP142
PASSION [46]	II	2018	Relapsed ES-SCLC	Camrelizumab plus apatinib	44	NR
CheckMate 032 [47]	I/II	2013	Relapsed SCLC	Nivolumab, Nivolumab plus ipilimumab	Nivolumab monotherapy: 78	28-8
KEYNOTE-028 [43]	Ib	2014	Relapsed ES-SCLC	Pembrolizumab	24	22C3

Table 1 (continued)

Trial	PD-L1 pattern	Cutoff	PD-L1 positivity	ORR%	mPFS (months)	mOS (months)
First-line setting CASPIAN [39]	ICs, TCs	1%	TC ≥ 1%: 5.7%, IC ≥ 1%: 25.8%, TC or IC ≥ 1%: 28.3%	D + EP vs. EP: ORs (95% CI) of 0.67 (0.06–5.87), 1.87 (0.64–5.88) and 1.68 (0.62–4.61), respectively, for the PD-L1 ≥ 1% subgroups based on TC, IC, and TC or IC expression; ORs of 2.26 (1.36–3.77), 2.21 (1.28–3.85), and 2.30 (1.32–4.07), respectively, for the PD-L1 < 1% subgroups; D + T + EP vs. EP: ORs of 3.89 (0.58–32.28), 0.82 (0.32–2.10) and 1.00 (0.40–2.42), respectively, for the PD-L1 ≥ 1% subgroups; ORs of 1.09 (0.67–1.77), 1.30 (0.75–2.25), and 1.22 (0.70–2.12), respectively, for the PD-L1 < 1% subgroups	D + EP vs. EP: HRs (95% CI) of 0.74 (0.22–2.24), 0.55 (0.32–0.96) and 0.55 (0.33–0.93), respectively, for the PD-L1 ≥ 1% subgroups based on TC, IC, and TC or IC expression; HRs of 0.69 (0.53–0.90), 0.74 (0.56–0.99), and 0.75 (0.56–1.00), respectively, for the PD-L1 < 1% subgroups; D + T + EP vs. EP: HRs of 0.13 (0.03–0.46), 0.66 (0.40–1.12) and 0.62 (0.38–1.01), respectively, for the PD-L1 ≥ 1% subgroups; HRs of 0.78 (0.60–1.01), 0.81 (0.60–1.08), and 0.83 (0.61–1.11), respectively, for the PD-L1 < 1% subgroups	D + EP vs. EP: HRs (95% CI) of 0.75 (0.24–2.27), 0.59 (0.34–1.02) and 0.61 (0.37–1.02), respectively, for the PD-L1 ≥ 1% subgroups based on TC, IC, and TC or IC expression; HRs of 0.62 (0.47–0.81), 0.64 (0.47–0.85), and 0.63 (0.47–0.85), respectively, for the PD-L1 < 1% subgroups; D + T + EP vs. EP: HRs of 0.42 (0.13–1.29), 0.53 (0.31–0.90) and 0.50 (0.31–0.83), respectively, for the PD-L1 ≥ 1% subgroups; HRs of 0.76 (0.58–0.99), 0.88 (0.66–1.19), and 0.91 (0.68–1.23), respectively, for the PD-L1 < 1% subgroups D + T + EP arm: TC or IC ≥ 1% subgroup vs. TC and IC < 1% subgroup: 15.5 vs. 8.9 (HR, 0.50; 95% CI 0.33–0.75)
IMpower133 [34]	TC or IC	1%, 5%	TC or IC ≥ 1%: 52.6%, TC or IC ≥ 5%: 21.2%	Atezolizumab arm vs. placebo arm: 75.0% vs. 62.2% in PD-L1 expression < 1% TC and IC (PD-L1 negative); 52.8% vs. 69.4% in PD-L1 expression ≥ 1% TC or IC	Atezolizumab arm vs. placebo arm: 5.4 vs. 4.2 (HR, 0.52; 95% CI 0.31–0.88) in PD-L1 negative; 5.1 vs. 5.5 (HR, 0.86; 95% CI 0.51–1.46) in PD-L1 expression ≥ 1% TC or IC	Atezolizumab arm vs. placebo arm: 10.2 vs. 8.3 (HR, 0.51; 95% CI 0.30–0.89) in PD-L1 negative; 9.7 vs. 10.6 (HR, 0.87; 95% CI 0.51–1.49) in PD-L1 expression ≥ 1% TC or IC; 21.6 vs. 9.2 (HR, 0.60; 95% CI 0.25–1.46) in PD-L1 expression ≥ 5% TC or IC;
KEYNOTE-604 [36]	CPS	1	40.8%	NR	Pembrolizumab arm vs. placebo arm: (HR, 0.73; 95% CI 0.54–1.01) in PD-L1 negative; (HR, 0.68; 95% CI 0.49–0.94) in PD-L1 CPS ≥ 1	Pembrolizumab arm vs. placebo arm: (HR, 0.80; 95% CI 0.58–1.11) in PD-L1 negative; (HR, 0.84; 95% CI 0.60–1.18) in PD-L1 CPS ≥ 1

Table 1 (continued)

Trial	PD-L1 pattern	Cutoff	PD-L1 positivity	ORR%	mPFS (months)	mOS (months)
ASTRUM-005 [37]	TPS	1%	17%	NR	NR	Serplulimab arm vs. placebo arm: 15.0 vs. 10.5 (HR, 0.58; 95% CI 0.44–0.76) in PD-L1 negative; not reached vs. 12.9 (HR, 0.92; 95% CI 0.44–1.89) in PD-L1 TPS ≥ 1%
CAPSTONE-1 [38]	TPS	1%	14%	NR	Adebrelimab arm vs. placebo arm: (HR, 0.68; 95% CI 0.54–0.85) in PD-L1 negative; (HR, 0.70; 95% CI 0.34–1.45) in PD-L1 positive	Adebrelimab arm vs. placebo arm: (HR, 0.66; 95% CI 0.52–0.83) in PD-L1 negative; (HR, 0.72; 95% CI 0.33–1.59) in PD-L1 positive
SKYSCRAPER-02 [25]	TC or IC	1%, 5%	TC or IC ≥ 1%: 58.0%, TC or IC ≥ 5%: 23.8%	NR	No significant difference reported (data not shown)	Tiragolumab arm vs. placebo arm: 10.8 vs. 12.0 (HR, 1.33; 95% CI 0.96–1.84) in PD-L1 < 1% TC and IC; 14.5 vs. 13.1 (HR, 1.01; 95% CI 0.75–1.37) in PD-L1 ≥ 1% TC or IC; 14.4 vs. 16.5 (HR, 1.56; 95% CI 0.97–2.51) in PD-L1 ≥ 5% TC or IC
First-line maintenance CheckMate 451 [40]	CPS	1%	46.0%	CPS ≥ 1% vs. CPS < 1%: 8.0% vs. 11.5% in combination arm, 9.8% vs. 13.2% in Nivolumab arm, 5.6% vs. 0% in placebo arm	CPS ≥ 1% vs. CPS < 1%: 2.8 (1.5–3.7) vs. 1.5 (1.4–2.5) in combination arm, 1.9 (1.4–4.1) vs. 1.6 (1.4–2.6) in Nivolumab arm, 1.4 (1.4–1.5) vs. 1.4 (1.4–1.5) in placebo arm	CPS ≥ 1% vs. CPS < 1%: 11.9 (6.9–15.2) vs. 8.6 (7.1–12.4) in combination arm, 14.1 (9.9–21.6) vs. 9.4 (5.8–11.3) in Nivolumab arm, 13.9 (8.9–16.5) vs. 6.1 (4.8–8.1) in placebo arm
NCT 02359019 [41]	TCs and stroma	1%	TCs: 10%, stroma interface: 40%	8.3% (95% CI 1.5–35.4) in stromal PD-L1 negative; 37.5% (95% CI 13.7–69.4) in stromal PD-L1 positive	1.3 (95% CI 0.6–2.5) in stromal PD-L1 negative; 6.5 (95% CI 1.1–12.8) in stromal PD-L1 positive	7.6 (95% CI 2.0–12.7) in stromal PD-L1 negative; 12.8 (95% CI 1.1–17.6) in stromal PD-L1 positive

Table 1 (continued)

Trial	PD-L1 pattern	Cutoff	PD-L1 positivity	ORR%	mPFS (months)	mOS (months)
Second- and later-line settings						
CheckMate 331 [44]	CPS	1	45.5%	NR	Nivolumab arm vs. chemotherapy arm: 1.4 vs. 4.1 (HR, 1.68; 95% CI 1.23–2.31) in PD-L1 negative; 1.5 vs. 4.3 (HR, 1.52; 95% CI 1.06–2.19) in PD-L1 CPS ≥ 1	Nivolumab arm vs. chemotherapy arm: 7.3 vs. 8.1 (HR, 0.91; 95% CI 0.66–1.25) in PD-L1 negative; 7.0 vs. 8.6 (HR, 0.96; 95% CI 0.67–1.38) in PD-L1 CPS ≥ 1
KEYNOTE-158 [42]	CPS	1	45.7%	6.0% in PD-L1 negative; 35.7% in PD-L1 positive	1.9 (95% CI 1.6–2.0) in PD-L1 negative; 2.1 (95% CI 2.0–9.9) in PD-L1 positive	7.7 (95% CI 3.9–10.4) in PD-L1 negative; 14.6 (95% CI 5.6–not estimable) in PD-L1 positive
IFCT-1603 Trial [45]	TCs, ICs, composite score	1% in ICs, 1% in TCs	TCs: 1.8%, ICs: 29.6%	6-week DCR in Atezolizumab arm: 0% in PD-L1 ≥ 1% IC; 25% in PD-L1 negative	PD-L1 negative vs. PD-L1 ≥ 1% IC: 1.4 (95% CI 1.2–1.5) vs. 1.6 (95% CI 1.4–4.1) (p=0.15) in the whole BEP	PD-L1 negative vs. PD-L1 ≥ 1% IC: 5.6 (95% CI 2.4–9.5) vs. 12.0 (95% CI 4.1–13.3) (p=0.39) in the whole BEP
PASSION [46]	NR	1%	23.4%	33.3% (95% CI 18.0–51.8) in PD-L1 negative; 45.5% (95% CI 16.7–76.6) in PD-L1 positive	3.7 (95% CI 1.2–4.6) in PD-L1 negative; 3.6 (95% CI 1.0–6.6) in PD-L1 positive	9.3 (95% CI 4.5–not reached) in PD-L1 negative; 6.6 (95% CI 1.9–12.3) in PD-L1 positive
CheckMate 032 [47]	TCs	1%	17%	Nivolumab monotherapy: 15.4% (95% CI 7.6–26.5%) in PD-L1 negative; 15.4% (95% CI 1.9–45.4%) in PD-L1 positive	NR	NR
KEYNOTE-028 [43]	TCs, ICs, stroma	1% of TCs and ICs or positive staining in stroma	only patients with PD-L1 positive tumors were enrolled	33.3% (95% CI 15.6%–55.3%)	1.9 (95% CI 1.7–5.9)	9.7 (95% CI 4.1–not reached)

PD-L1: programmed cell death 1 ligand 1; IC: immune checkpoint inhibitor; SCLC: small cell lung cancer; ES: extensive stage; EC: etoposide and carboplatin; EP: etoposide and platinum; TCs: tumor cells; ICs: immune cells; CPS: combined positive score; TPS: tumor proportion score; ORR: objective response rate; DCR: disease control rate; mPFS: median progression-free survival; mOS: median overall survival; N: number; biomarker-evaluable population; HR: hazard ratio; CI: confidence interval; OR: odds ratio; NR: not reported
^a“Year” refers to the first posted date in clinical trials

the placebo arm, patients with $\text{CPS} \geq 1$ showed longer OS compared to patients with $\text{CPS} < 1$, indicating that PD-L1 expression might serve as a prognostic biomarker for ES-SCLC [40]. A phase II clinical trial assessed the effectiveness of maintenance pembrolizumab in ES-SCLC patients following chemotherapy. The findings indicated that the 8 patients with tumors positive for stromal PD-L1 expression achieved a higher median PFS (6.5 months vs. 1.3 months) and a higher median OS (12.8 months vs. 7.6 months) than the 12 patients with PD-L1-negative tumors, suggesting a potential benefit trend for pembrolizumab maintenance therapy in PD-L1 positive patients. However, the sample size of this study was limited ($N = 20$), and the results did not reach statistical significance [41].

In second- or later-line treatment for SCLC, the relationship between PD-L1 expression and the efficacy of ICIs has not reached a consensus. The KEYNOTE-158 trial, a phase II basket study of 11 cancer types, observed that pembrolizumab exhibited superior antitumor effects and sustained responses in ES-SCLC patients with PD-L1 $\text{CPS} \geq 1$ compared to those who were PD-L1 negative, indicating that PD-L1 CPS could predict outcomes in ES-SCLC patients [42]. In the phase I, multicohort KEYNOTE-028 study, patients with PD-L1-positive recurrent or metastatic SCLC who received pembrolizumab monotherapy achieved an objective response rate (ORR) of up to 33.3%, with a median OS of 9.7 months (95% CI 4.1-not reached), indicating promising antitumor activity of pembrolizumab in PD-L1 positive SCLC patients [43]. Nonetheless, the pooled analysis of KEYNOTE-158 and KEYNOTE-028 explored the efficacy of pembrolizumab in recurrent SCLC patients who had undergone two or more lines of treatment. The results showed that pembrolizumab exhibited antitumor activity regardless of PD-L1 expression [48]. Likewise, in the CheckMate 331 study, the PD-L1 CPS status with a threshold of 1 did not impact the OS or PFS outcomes of nivolumab compared to chemotherapy [44]. Comparable findings were reported in the IFCT-1603 trial, which assessed the efficacy of atezolizumab as a second-line therapy for SCLC [45]. The PASSION study is a phase II trial of camrelizumab and apatinib in refractory ES-SCLC after platinum-based chemotherapy. The ORR (45.5% vs. 33.3%) was higher in the PD-L1-positive subgroup compared to the PD-L1-negative subgroup, but the median OS (6.6 months vs. 9.3 months) was shorter in patients with positive PD-L1, suggesting that the prognostic value of PD-L1 remained unvalidated [46]. The Phase I/II clinical trial CheckMate 032 evaluated the effectiveness of later-line nivolumab monotherapy or nivolumab plus ipilimumab, indicating that PD-L1 expression might not be a reliable indicator for the response to nivolumab [47].

In summary, the reliability of PD-L1 expression as a marker for immunotherapy response in ES-SCLC has not yet been supported by large-scale, high-quality randomized controlled trials (RCTs). The temporal and spatial heterogeneity of PD-L1 expression, variations in sensitivity among PD-L1 IHC detection antibodies, and the absence of standardized cutoff value for PD-L1 expression assessment may all impact its predictive value.

Tissue tumor mutational burden (tTMB)

Tumor mutational burden (TMB) typically refers to the total count of somatic mutations per coding region of a tumor genome, as detected by whole exome sequencing (WES) or next generation sequencing (NGS) [49]. Based on the source of samples, it can be categorized into tissue TMB (tTMB) and blood TMB (bTMB). TMB serves as an indirect indicator of a tumor's capacity to produce neoantigens and has been shown to predict immunotherapy response across various cancer types, such as NSCLC, melanoma, and urothelial carcinoma, etc. [50–55] SCLC is marked by high TMB, possibly due to its strong association with smoking [56]. Nevertheless, the application of TMB in predicting ICIs response in SCLC remains contentious, given the heterogeneous outcomes observed across different studies (Table 2). Herein, our primary focus was on the findings related to tTMB, while analyses of bTMB were deliberated separately in the "Circulating biomarkers" section.

The prospective biomarker analysis of the phase II KEYNOTE-158 study revealed that high tTMB was correlated with clinical benefit (ORR and OS) with pembrolizumab as later-line treatment in various tumor types, including SCLC [57]. The CheckMate 032 study [51] and CheckMate 451 study [40] evaluated the impact of TMB on the effectiveness of nivolumab alone or in combination with ipilimumab in the later-line treatment and maintenance therapy following first-line platinum-based chemotherapy for SCLC, respectively. The results of both studies suggested that TMB status could predict the response to these two treatment modalities. In the CheckMate 032 study, patients were stratified into low, medium, and high TMB tertiles on the basis of thresholds of 143 mutations and 247 mutations. It was reported that in both the monotherapy and combination therapy arms, patients with high TMB exhibited superior ORR, PFS, and OS than those with medium and low TMB [51]. In the CheckMate 451 study, OS was enhanced with both combination therapy (HR, 0.61; 95% CI 0.39–0.94) and monotherapy (HR, 0.67; 95% CI 0.45–1.01) compared to placebo in patients with $\text{TMB} \geq 13$ mutations per megabase (mut/Mb) but not in the other patients [40]. However, the CheckMate 331 study assessed the correlation between high/low TMB and the effectiveness of

Table 2 Evidence of TMB as an immunotherapy-related biomarker in clinical trials involving ES-SCLC

TMB type	Trial	Phase	Year ^a	Population	Treatment	TMB assay
tTMB	First-line setting CASPIAN [39]	III	2017	Untreated ES-SCLC	Durvalumab plus etoposide and platinum (EP) (D + EP), Durvalumab plus Tremelimumab plus EP (D + T + EP), EP alone	FoundationOne CDx
	KEYNOTE-604 [60]	III	2017	Untreated ES-SCLC	Pembrolizumab plus EP, Placebo plus EP	WES
	First-line maintenance CheckMate 451 [40]	III	2015	ES-SCLC first line maintenance	Nivolumab plus ipilimumab, Nivolumab monotherapy, Placebo	FoundationOne CDx
	Second- and later-line settings CheckMate 331 [44]	III	2015	Relapsed ES-SCLC	Nivolumab, Chemotherapy (topotecan or arubicin)	FoundationOne CDx
bTMB	KEYNOTE-158 [57]	II	2015	Relapsed ES-SCLC	Pembrolizumab	FoundationOne CDx
	CheckMate 032 [47, 51]	I/II	2013	Relapsed SCLC	Nivolumab, Nivolumab plus ipilimumab	WES
	IMpower133 [34]	I/III	2016	Untreated ES-SCLC	Atezolizumab plus carboplatin and etoposide (EC), Placebo plus EC	NR

Table 2 (continued)

TMB type	Trial	Cutoff	N (BEP)	ORR%	mPFS (months)	mOS (months)
tTMB	First-line setting					
	CASPIAN [39]	6–14 mut/Mb	D + EP arm: 107, D + T + EP arm: 105, EP arm: 71	D + EP vs. EP: ORs (95% CI) of 1.98 (0.99–4.01), 1.85 (0.87–3.92), 1.99 (0.88–4.54), 1.59 (0.67–3.73), 1.23 (0.46–3.22), 0.97 (0.34–2.69), 1.14 (0.38–3.29), 0.75 (0.22–2.39) and 0.46 (0.10–1.78), respectively, for the tTMB-high subgroups at cutoffs ranging from 6 to 14 mut/Mb; ORs of 1.39 (0.32–6.36), 1.96 (0.60–6.71), 1.76 (0.66–4.79), 2.42 (0.95–6.36), 2.73 (1.17–6.59), 2.90 (1.29–6.72), 2.53 (1.16–5.67), 2.90 (1.36–6.31) and 2.86 (1.40–5.95) for the tTMB-low subgroups; D + T + EP vs. EP: ORs of 0.87 (0.43–1.75), 0.78 (0.36–1.64), 0.71 (0.31–1.61), 0.64 (0.27–1.49), 0.46 (0.17–1.22), 0.32 (0.11–0.90), 0.30 (0.09–0.91), 0.33 (0.09–1.07) and 0.30 (0.07–1.11) for the tTMB-high subgroups; ORs of 0.81 (0.24–2.76), 1.04 (0.37–2.94), 1.09 (0.44–2.70), 1.19 (0.50–2.85), 1.32 (0.60–2.90), 1.50 (0.70–3.26), 1.41 (0.67–2.96), 1.25 (0.61–2.57) and 1.18 (0.59–2.36) for the tTMB-low subgroups;	D + EP vs. EP: HRs (95% CI) of 0.75 (0.53–1.09), 0.83 (0.56–1.23), 0.76 (0.50–1.17), 0.76 (0.49–1.20), 0.79 (0.48–1.32), 0.82 (0.49–1.40), 0.79 (0.46–1.38), 0.79 (0.43–1.45) and 0.79 (0.39–1.62), respectively, for the tTMB-high subgroups at cutoffs ranging from 6 to 14 mut/Mb; HRs of 0.67 (0.30–1.43), 0.45 (0.23–0.85), 0.70 (0.42–1.15), 0.70 (0.44–1.12), 0.68 (0.44–1.05), 0.68 (0.45–1.02), 0.69 (0.46–1.04), 0.71 (0.48–1.04) and 0.70 (0.49–1.01) for the tTMB-low subgroups; D + T + EP vs. EP: HRs of 0.90 (0.62–1.32), 0.93 (0.62–1.40), 0.94 (0.61–1.47), 0.91 (0.57–1.45), 1.04 (0.63–1.75), 1.22 (0.73–2.11), 1.25 (0.72–2.21), 1.14 (0.63–2.12) and 1.24 (0.65–2.46) for the tTMB-high subgroups; HRs of 0.62 (0.33–1.20), 0.66 (0.38–1.16), 0.73 (0.45–1.18), 0.78 (0.49–1.23), 0.73 (0.48–1.11), 0.67 (0.44–1.02), 0.69 (0.47–1.04), 0.74 (0.51–1.10) and 0.74 (0.51–1.08) for the tTMB-low subgroups;	D + EP vs. EP: HRs (95% CI) of 0.72 (0.50–1.03), 0.80 (0.54–1.18), 0.71 (0.47–1.09), 0.72 (0.46–1.13), 0.68 (0.42–1.14), 0.69 (0.41–1.19), 0.65 (0.37–1.15), 0.66 (0.36–1.24) and 0.62 (0.30–1.32), respectively, for the tTMB-high subgroups at cutoffs ranging from 6 to 14 mut/Mb; HRs of 0.76 (0.34–1.66), 0.58 (0.31–1.09), 0.75 (0.45–1.26), 0.72 (0.45–1.18), 0.77 (0.50–1.20), 0.77 (0.50–1.17), 0.80 (0.53–1.20), 0.77 (0.52–1.13) and 0.76 (0.53–1.10), respectively, for the tTMB-low subgroups; D + T + EP vs. EP: HRs (95% CI) of 0.80 (0.55–1.17), 0.85 (0.56–1.28), 0.80 (0.52–1.25), 0.79 (0.50–1.26), 0.77 (0.46–1.30), 0.86 (0.51–1.49), 0.86 (0.49–1.54), 0.80 (0.43–1.52) and 0.86 (0.44–1.75), respectively, for the tTMB-high subgroups at cutoffs ranging from 6 to 14 mut/Mb; HRs of 0.84 (0.43–1.68), 0.76 (0.43–1.35), 0.81 (0.50–1.35), 0.82 (0.51–1.33), 0.83 (0.54–1.29), 0.78 (0.51–1.19), 0.79 (0.53–1.18), 0.82 (0.56–1.22) and 0.82 (0.56–1.20), respectively, for the tTMB-low subgroups;
	KEYNOTE-604 [60]	175 mut/exome	Pembrolizum arm: 167, Placebo arm: 151	NR	NR	Pembrolizum arm vs. placebo arm: 12.3 (8.3–15.5) vs. 12.0 (9.8–13.9) in TMB ≥ 175 mut/exome (HR, 1.02; 95% CI 0.72–1.45); 10.2 (8.5–14.4) vs. 7.7 (6.6–9.3) in TMB < 175 mut/exome (HR, 0.60; 95% CI 0.43–0.85)

Table 2 (continued)

TMB type	Trial	Cutoff	N (BEP)	ORR%	mPFS (months)	mOS (months)
First-line maintenance						
	CheckMate 451 [40]	10, 13 mut/Mb	Nivolumab plus Ipilimumab: 192 Nivolumab: 196 Placebo: 192	Nivolumab plus Ipilimumab vs. Nivolumab vs. placebo: 14.0% vs. 14.3% vs. 5.3% in TMB ≥ 13mut/Mb; 6.5% vs. 9.5% vs. 4.0% in TMB < 13mut/Mb	Nivolumab plus Ipilimumab vs. Nivolumab vs. placebo: 2.7 (1.5–3.6) vs. 2.8 (1.6–4.1) vs. 1.6 (1.4–2.6) in TMB ≥ 13mut/Mb; 1.5 (1.4–2.0) vs. 1.6 (1.4–2.6) vs. 1.4 (1.4–1.4) in TMB < 13mut/Mb	Nivolumab plus Ipilimumab vs. placebo: 13.5 (9.3–21.8) vs. 9.5 (6.2–13.5) in TMB ≥ 13mut/Mb (HR, 0.61; 95% CI 0.39–0.94), 7.8 (6.7–9.7) vs. 10.0 (7.7–11.5) in TMB < 13mut/Mb (HR, 1.04; 95% CI 0.79–1.37); Nivolumab vs. placebo: 13.2 (10.0–17.9) vs. 9.5 (6.2–13.5) in TMB ≥ 13mut/Mb (HR, 0.67; 95% CI 0.45–1.01), 10.1 (8.7–11.3) vs. 10.0 (7.7–11.5) in TMB < 13mut/Mb (HR, 0.92; 95% CI 0.70–1.22)
Second- and later-line settings						
	CheckMate 331 [44]	10, 11, 13, 14, 15 mut/Mb	Nivolumab arm: 155, Chemotherapy arm: 157	No significant difference reported (data not shown)	No significant difference reported (data not shown)	No significant difference reported (data not shown)
	KEYNOTE-158 [57]	10mut/Mb	SCLC cohort: 76	High TMB vs. non-high-TMB: 29.4% vs. 9.5%	No specific data of SCLC cohort; No significant difference reported in ten tumor-type-specific cohorts	High TMB vs. non-high-TMB: 9.4(5.6–19.1) vs. 6.3(3.9–7.7)
	CheckMate 032 [47, 51]	143, 247 mutations	Nivolumab arm:133, Nivolumab plus Ipilimumab arm: 78	Nivolumab arm vs. Nivolumab plus Ipilimumab arm: 21.3% vs. 46.2% in high TMB, 6.8% vs. 16.0% in medium TMB, 4.8% vs. 22.2% in low TMB	low TMB vs. medium TMB vs. high TMB: 1.3 (95% CI 1.2–1.4) vs. 1.3 (95% CI 1.2–1.4) vs. 1.4 (95% CI 1.3–2.7) in Nivolumab arm; 1.5 (95% CI 1.3–2.7) vs. 1.3 (95% CI 1.2–2.1) vs. 7.8 (95% CI 1.8–10.7) in Nivolumab plus Ipilimumab arm	low TMB vs. medium TMB vs. high TMB: 3.1 (95% CI 2.4–6.8) vs. 3.9 (95% CI 2.4–9.9) vs. 5.4 (95% CI 2.8–8.0) in Nivolumab arm; 3.4 (95% CI 2.8–7.3) vs. 3.6 (95% CI 1.8–7.7) vs. 22.0 (95% CI 8.2-not reached) in Nivolumab plus Ipilimumab arm
bTMB	IMpower133 [34]	10, 16 mut/Mb	346	NR	NR	Atezolizumab arm vs. placebo arm: 11.8 vs. 9.4 in bTMB < 10mut/Mb (HR, 0.73; 95% CI 0.49–1.08), 14.9 vs. 11.2 in bTMB ≥ 10mut/Mb (HR, 0.73; 95% CI 0.53–1.00); 12.5 vs. 10.0 in bTMB < 16mut/Mb (HR, 0.79; 95% CI 0.60–1.04), 17.1 vs. 11.9 in bTMB ≥ 16mut/Mb (HR, 0.58; 95% CI 0.34–0.99)

TMB: tumor mutational burden; tTMB: tissue TMB; bTMB: blood TMB; SCLC: small cell lung cancer; ES: extensive stage; N: number; BEP: biomarker-evaluable population; ORR: objective response rate; mPFS: median progression-free survival; mOS: median overall survival; EC: etoposide and carboplatin; EP: etoposide and platinum; mut/Mb: mutations per megabase; WES: whole exome sequencing; HR: hazard ratio; CI: confidence interval; NR: not reported; OR: odds ratio

^a“Year” refers to the first posted date in clinical trials

Table 3 Other biomarkers for response or resistance to immunotherapy in ES-SCLC

Biomarker	Study	Author, year ^a	Population	Treatment	Assay
Tumor infiltrating lymphocytes, TILs	NCT02484404 (phase II trial) [70]	Thomas et al. 2015	Relapsed SCLC	Durvalumab and Olaparib	IHC
	CheckMate 032 (phase I/II trial) [68]	Rudin et al. 2013	Relapsed SCLC	Nivolumab, Nivolumab plus Ipilimumab	IHC
	A cohort study [69]	Shirasawa et al. 2023	Untreated SCLC	Atezolizumab plus carboplatin and etoposide (EC)	IHC
	A cohort study [71]	Pasello et al. 2023	Untreated ES-SCLC	Atezolizumab plus EC	9-color multiplex immunofluorescence
	A cohort study [72]	Kanemura et al. 2022	ES-SCLC	Chemotherapy plus an ICI (ICI combo-cohort); chemotherapy alone (chemo-cohort)	IHC
Molecular subtypes	CheckMate 032 (phase I/II trial) [68]	Rudin et al. 2013	Relapsed SCLC	Nivolumab alone, Nivolumab plus Ipilimumab	RNA sequencing
	KEYNOTE-604 (phase III trial) [60]	Rudin et al. 2017	Untreated ES-SCLC	Pembrolizumab plus EP, Placebo plus EP	RNA sequencing
	A cohort study [110]	Gay et al. 2021	Untreated ES-SCLC	Atezolizumab plus EC, Placebo plus EC	RNA sequencing
	IMpower133 (phase I/III trial) [111]	Liu et al. 2016	Untreated ES-SCLC	Atezolizumab plus EC, Placebo plus EC	RNA sequencing
Antigen presentation machinery (APM)	A cohort study [69]	Shirasawa et al. 2023	Untreated ES-SCLC	Atezolizumab plus EC	IHC
	CheckMate 032 (phase I/II trial) [68]	Rudin et al. 2013	Relapsed SCLC	Nivolumab alone, Nivolumab plus Ipilimumab	RNA sequencing
	CASPAN (phase III trial) [105]	Garassino et al. 2017	Untreated ES-SCLC	Durvalumab plus Tremelimumab plus EP (D+T+EP), Durvalumab+EP (D+EP), EP	NGS
T cell-inflamed gene expression profile (TcellinfGEP)	KEYNOTE-604 (phase III trial) [60]	Rudin et al. 2017	Untreated ES-SCLC	Pembrolizumab plus EP, Placebo plus EP	RNA sequencing
	KEYNOTE-028 (phase Ib trial) [113]	Ott et al. 2014	Relapsed ES-SCLC	Pembrolizumab	RNA sequencing
RB1	A cohort study [117]	Dowlati et al. 2022	SCLC	Data set A: single-agent ICI combination; Data set B (CheckMate 032) as validation: nivolumab, nivolumab plus ipilimumab	DNA and RNA sequencing

Table 3 (continued)

Biomarker	Study	Author, year ^a	Population	Treatment	Assay	
Circulating biomarkers	ctDNA	IFCT-1603 (phase II trial) [132]	Herbreteau et al. 2017	Relapsed SCLC	Atezolizumab, Chemotherapy (topotecan or re-induction of carboplatin-etoposide doublet)	NGS
		A cohort study [133]	Sivapalan et al. 2023	ES-SCLC	Immunotherapy-containing regimens, Chemotherapy	NGS
	Cytokines	NCT02484404 (phase II trial) [70]	Thomas et al. 2015	Relapsed SCLC	Durvalumab plus Olaparib	MSD U-PLEX
		A cohort study [166]	Hardy-Werbin et al. 2019	SCLC	EP (cohort 1), Ipilimumab plus EP (cohort 2)	Luminex assay
	neuronal auto-antibodies (NAAs)	NCT01331525 (phase II trial) [181]	Arriola et al. 2011	Untreated ES-SCLC	Ipilimumab plus EP	radioimmunoprecipitation assays; indirect IHC; immunoblotting, and a semiautomated enzyme-linked immunosorbent assay
Biomarker		A cohort study [182]	Hardy-Werbin et al., 2018	Untreated SCLC	Cohort 1: EP; cohort 2: ipilimumab plus EC	Commercial immunoblotting assay
	NLR	A cohort study [192]	Xiong et al. 2021	Relapsed SCLC	ICIs	blood test
		A cohort study [193]	Riemann et al. 2023	Advanced SCLC	Atezolizumab plus EC	multi-color flow cytometry
		A cohort study [194]	Stratmann et al. 2022	Relapsed SCLC	Single-agent ICI ICI combination	blood test
	LPI	A cohort study [195]	Li et al. 2021	Untreated advanced SCLC	ICIs plus chemotherapy	blood test
Tumor infiltrating lymphocytes, TILs		N (BEP)	ORR%	mPFS (months)	mOS (months)	
		14	Inflamed phenotype: tumor responses in all instances, immune-desert or immune-excluded phenotype: no tumor responses observed	NR	NR	
	Nivolumab arm: 46, Nivolumab plus ipilimumab arm: 32	NR	NR	NR	CD8 positivity ($\geq 1\%$ infiltrating CD8+ T cells) vs. CD8 negative: (HR, 0.51; 95%CI 0.27–0.95) in Nivolumab arm; (HR, 0.70; 95%CI 0.32–1.49) in Nivolumab plus ipilimumab arm	
	37	NR	TIL-high (above median TIL density $\geq 69/\text{mm}^2$) vs. TIL-low: 7.3 (95% CI 4.2–10.4) vs. 4.0 (95% CI 2.7–5.3), $p < 0.001$		NR	

Table 3 (continued)

Biomarker	N (BEP)	ORR%	mPFS (months)	mOS (months)
	39	Correlated with better RR: lower CD163 + M2-polarized macrophages density and ratio on CD8+ cells in the total and tumoral areas ($p < 0.05$)	Correlated with longer PFS: lower CD163 + M2-polarized macrophages density and ratio on CD8+ cells ($p < 0.05$); high intra-tumoral CD4 + FOXP3 + density ($p = 0.004$); CD20 + interaction with CD8+ ($p = 0.038$); high percentage (%) of stromal CD163+ close to CD8+ cells ($p = 0.045$)	Correlated with longer OS: lower CD163 + M2-polarized macrophages density and ratio on CD8+ cells in the total and tumoral areas ($p < 0.05$); high intra-tumoral CD4 + FOXP3 + density ($p = 0.026$); CD20 + interaction with CD8+ ($p = 0.032$); high % of CD4 + closed to CD8+ cells in the total area ($p = 0.025$) and in the stroma ($p = 0.002$); intra and peri-tumoral interaction between CD163+ ($p = 0.020$) and CD8+ cells ($p = 0.008$); CD8+ and tumor cells interaction ($p = 0.012$)
	ICI combo-cohort: 63, chemo-cohort: 70	NR	Inflamed tumors (PD-L1-positive [CPS $\geq 1\%$] and CD8+TIL-high [$> 85/\text{mm}^2$] vs. noninflamed tumors: 10.8 (95% CI 3.5–not reached) vs. 5.1 (4.3–5.6) ($p = 0.002$, HR, 0.26; 95% CI 0.09–0.74) in the ICI combo-cohort; 3.6 (95% CI 3.1–5.5) vs. 4.8 (4.4–5.7) ($p = 0.11$, HR, 1.70; 95% CI 0.92–3.14) in chemo-cohort	NR
Molecular subtypes	Nivolumab arm: 156, Nivolumab plus Ipilimumab arm: 130	NR	No significant difference reported (data not shown) based on subtype assignment (SCLC-A, -N, -P, and -Y)	No significant difference reported (data not shown)
	Pembrolizumab arm: 159, Placebo arm: 157	NR	NR	No significant difference reported (pembrolizumab arm, $p = 0.960$; placebo arm, $p = 0.999$) based on subtype assignment (SCLC-A, -N, -P, and -Y)

Table 3 (continued)

Biomarker	N (BEP)	ORR%	mPFS (months)	mOS (months)
	Atezolizumab arm: 132 Placebo arm: 139	NR	NR	Atezolizumab arm vs. placebo arm: (HR, 0.572; 95%CI 0.284–1.15) in SCLC-I, (HR, 0.807; 95%CI 0.547–1.189) in SCLC-A, (HR, 0.631; 95%CI 0.353–1.129) in SCLC-N, (HR, 0.595; 95%CI 0.223–1.589) in SCLC-P; SCLC-I vs. all other tumors: (HR, 0.566; 95%CI 0.321–0.998) in atezolizumab arm, (HR, 0.75; 95%CI 0.46–1.221) in placebo arm
	Atezolizumab arm: 122 Placebo arm: 131	Proportion of SCLC-I in long-term survivors (LTS) vs. non-LTS: Atezolizumab arm: 28% vs. 11% Placebo arm: 32% vs. 18%		
	34	NR	Pathological SCLC-A (pSCLC-A) vs. pSCLC-N vs. pSCLC-P: 4.8 (95% CI 3.9–5.7) vs. 4.0 (0.8–7.2) vs. 4.2 (2.9–5.5) (p value NR)	NR
Antigen presentation machinery (APM)	Nivolumab arm: 170 Nivolumab plus ipilimumab arm: 151	NR	NR	APM-high vs. APM-med vs. APM low: p = 3.2×10^{-4} (Cox proportional hazards model) in nivolumab arm; p = 0.19 in nivolumab plus ipilimumab arm LSD1-low vs. LSD1-med vs. LSD1-high: p = 0.035 in nivolumab arm; p = 0.02 in nivolumab plus ipilimumab arm EZH2-low vs. EZH2-med vs. EZH2-high: p = 0.076 in nivolumab arm; p = 0.27 in nivolumab plus ipilimumab arm
	D+T+EP arm: 142, D+EP arm: 143, EP arm: 129	NR	NR	HLA-DQB1*03:01-positive vs. HLA-DQB1*03:01-negative: 14.9 (95% CI 10.4–21.2) vs. 10.5 (7.6–12.9) (HR, 0.59; 95% CI 0.39–0.88) in D+T+EP arm; 14.7 (11.5–16.3) vs. 14.3 (9.4–17.2) (HR, 0.93; 95% CI 0.63–1.37) in D+EP arm; 9.7 (7.7–11.7) vs. 10.5 (8.9–11.3) (HR, 0.94; 95% CI 0.61–1.40) in EP arm;

Table 3 (continued)

Biomarker	N (BEP)	ORR%	mPFS (months)	mOS (months)
T cell-inflamed gene expression profile (TcellinfGEP)	Pembrolizumab arm: 159, Placebo plus EP: 157	NR	NR	Pembrolizumab arm vs. placebo arm: 8.5 (95% CI 8.1–12.5) vs. 7.9 (95% CI 6.5–9.8) (HR, 0.74; 95% CI 0.49–1.11) in Tcell _{inf} GEP < 1st tertile; 13.1 (95% CI 9.7–17.5) vs. 10.6 (95% CI 8.2–12.9) (HR, 0.77; 95% CI 0.56–1.06) in Tcell _{inf} GEP > 1st tertile; Tcell _{inf} GEP < 1st tertile vs. Tcell _{inf} GEP > 1st tertile: p = 0.003 in pembrolizumab arm; p < 0.005 in placebo arm
RB1	All tumors: 313, SCLC: 8 Data set A: 42; Data set B: 155 in nivolumab mon- otherapy arm, 124 in nivolumab plus ipilimumab arm	Higher Tcell _{inf} GEP score was asso- ciated with ORR across all tumors evaluated (p value NR) NR	Higher Tcell _{inf} GEP score was asso- ciated with longer PFS across all tumors evaluated (p value NR) Data set A: RB1 wild-type (WT) vs. RB1 mutant: 18 (95% CI 7-not reached) vs. 3 (1.5–24.1) (p = 0.05) in the entire cohort; Data set B: RB1 mutant vs. RB1 WT: (HR, 1.20; 95% CI 0.85–1.69; p = 0.294) in nivolumab monotherapy arm	NR Data set A: RB1 WT vs. RB1 mutant: 23.1 (95% CI 9–37.5) vs. 5 (2.5–26) (p = 0.04) in the entire cohort; Data set B: RB1 mutant vs. RB1 WT: (HR, 1.46; 95% CI 1.02–2.01; p = 0.041) in nivolumab monotherapy arm; (HR, 1.03; 95% CI 0.68–1.69; p = 0.9) in nivolumab plus ipilimumab arm
Circulating biomarkers	Atezolizumab arm: 46, Chemo- therapy arm: 22	6-week DCr: detectable circulat- ing mutation vs. no detectable mutation: 29.5% vs. 58.8% (p = 0.030) in all patients; 64.3% vs. 71.4% (p = 0.672) in chemotherapy arm; 13.3% vs. 50% (p = 0.0145) in atezolizumab arm	Low ctDNA abundance vs. high ctDNA abundance: 1.6 (95% CI 1.3–3.1) vs. 1.3 (1.1– 1.5) (HR _{VAF≥median} = 2.57; 95% CI 1.31–5.07; p = 0.0063) in patients with a detectable circulating mutation	Low ctDNA abundance vs. high ctDNA abundance (median relative abundance = 44.5%): 12 (95% CI 6.6–15.3) vs. 2.5 (1.4–8.1) (HR _{VAF≥median} = 5.09; 95% CI 2.13–12.16; p = 0.0002) in patients with a detectable circulating muta- tion; 12.5 vs. 2.1 (HR _{VAF≥median} = 8.11; 95% CI 2.20–29.91; p = 0.0017) in atezolizumab arm; 9.4 vs. 7.7 (HR _{VAF≥median} = 0.91; 95% CI 0.21–3.98, p = 0.8996) in chemo- therapy arm

Table 3 (continued)

Biomarker	N (BEP)	ORR%	mPFS (months)	mOS (months)
	ICI's arm: 17, Chemotherapy arm: 16	NR	Patients with sustained early ctDNA elimination followed by recurrence vs. ctDNA burden persisted: not reached vs. 6.18 vs. 1.74 (p < 0.0001)	Patients with sustained early ctDNA elimination (ctDNA molecular responses) vs. ctDNA elimination followed by recurrence vs. ctDNA burden persisted: not reached vs. 12.35 vs. 6.48 (p = 0.0006); ctDNA molecular responses vs. radiographic assessments: predictive performance for OS at 12 months (AUC 78.1% vs. 73.3%), 36 months (AUC 80.8% vs. 71.8%), and 64 months (AUC 87.3% vs. 67.6%)
Cytokines	18	No significant difference reported (data not shown)	NR	NR
	Cohort 1: 47, cohort 2: 37	NR		Baseline high IL-8 level vs. low IL-8 level: 9.2 vs. 16.8 (p = 0.028) in cohort 1; 5.3 vs. 17 (p = 0.031) in cohort 2; baseline high IL-2 level vs. low IL-2 level: 12.2 vs. 12.6 (p = 0.273) in cohort 1; 30.5 vs. 8 (p = 0.015) in cohort 2; baseline high IL-6 level vs. low IL-6 level: 15 vs. 12.6 (p = 0.073) in cohort 1; 9.5 vs. 18.5 (p = 0.026) in cohort 2; baseline high TNFα level vs. low TNFα level: 14.1 vs. 12.6 (p = 0.222) in cohort 1; 7.8 vs. 18.5 (p = 0.004) in cohort 2; IL-4 increased ≥ 23% from baseline to response vs. IL-4 increased < 23%: 9.5 vs. 16.3 (p = 0.002) in cohort 1; IL-4 increased ≥ 32% vs. IL-4 increased < 32%: 18.5 vs. 8.8 (p = 0.042) in cohort 2

Table 3 (continued)

Biomarker	N (BEP)	ORR%	mPFS (months)	mOS (months)
neuronal auto-antibodies (NAAs)	38	ORR based on immune-related response criteria (irRC): Any positive autoantibody at baseline vs. negative autoantibody: 100% (14/14) vs. 73.7% (14/19) (p=0.049)	PFS by irRC (irPFS): Any positive autoantibody at baseline vs. negative autoantibody: 8.8 (95%CI 5.1–10.7) vs. 7.3 (2.9–7.9, p=0.036); positive antinuclear antibody vs. negative antinuclear antibody: 10.2 vs. 6.9 (p=0.032)	Any positive autoantibody vs. negative autoantibody: 18.5 vs. 17 (p=0.144)
	Cohort 1: 47, cohort 2: 38	NAAs+ (patients with at least 1 baseline positive NAA) vs. NAAs-: 96% vs. 91% (p=0.451) in cohort 1; 90% vs. 93% (p=0.635) in cohort 2	NAAs+ vs. NAAs-: 7.4 (95% CI 6.2–8.6) vs. 6.2 (5.5–7) (p=0.279) in cohort 1; 6.9 (6.6–7.2) vs. 6.9 (2.7–11.1) (p=0.762) in cohort 2; The presence of only 1 NAA vs. > 1 NAA: 7.3 (5.9–8.6) vs. 5.5 (2.8–8.2) (p=0.005) in cohort 2; Positive anti-Yo vs. negative anti-Yo: 4.3 (2.5–6.0) vs. 6.9 (6.4–7.5) in cohort 2	NAAs+ vs. NAAs-: 15.1 (95%CI 10.2–20) vs. 11.7 (7.5–15.9) (p=0.032) in cohort 1; 12.3 (5.3–19.3) vs. 17.0 (0–36.1) (p=0.796) in cohort 2; The presence of only 1 NAA vs. > 1 NAA: 12.3 (4.7–19.9) vs. 7.9 (4.9–11) (p=0.180) in cohort 2; Positive anti-Yo vs. negative anti-Yo: 7.8 (2.2–13.4) vs. 17.0 (8.7–25.4) in cohort 2; patients with decreased or remained stable NAA during treatment vs. patients with increased NAA: 18.5 (15.8–21.2) vs. 12.3 (8.1–16.5) (p=0.049) in both cohorts; 17.2 (12.4–22.1) vs. 12.6 (8.3–17) (p=0.090) in cohort 1; 18.5 (9.1–27.8) vs. 9.5 (7.0–12.0) (p=0.143) in cohort 2
NLR	41	NLR < 5 vs. NLR ≥ 5 at 6 weeks post treatment: 67.9% vs. 46.2%	NLR < 5 vs. NLR ≥ 5 at 6 weeks post treatment: not reached vs. 3.2 (HR, 0.29; 95%CI 0.09–0.96; p=0.04); NLR < 5 vs. NLR ≥ 5 at baseline: not reached vs. 4.8 (HR, 0.75; 95% CI 0.24–2.26; p=0.58); PLR < 169 vs. PLR ≥ 169 at baseline: not reached vs. 5.1 (HR, 0.67; 95% CI 0.25–1.80; p=0.43); PLR < 169 vs. PLR ≥ 169 at 6 weeks post treatment: not reached vs. 5.1 (HR, 0.69; 95% CI 0.25–1.86; p=0.46)	NR
	40	NR	NLR ≥ 6.1 vs. NLR < 6.1: 5.1 ± 0.77 vs. 12.3 ± 1.8 (p=0.001) (HR, 3.04; 95%CI 1.46–6.54; p=0.003)	NLR ≥ 6.1 vs. NLR < 6.1: 7.1 ± 1.0 vs. 14.0 ± 1.7 (p=0.001) (HR, 3.18; 95%CI 1.45–6.99; p=0.004)

Table 3 (continued)

Biomarker	N (BEP)	ORR%	mPFS (months)	mOS (months)
	Single ICI arm: 64 ICI combination arm: 47	No significant difference reported (data not shown)	NR	NLR ≥ median vs. NLR < median: 3.5 (95% CI 2.6–4.4) vs. 12.4 (3.6–21.3) (HR, 1.9; 95% CI 1.2–3.2; p = 0.008) in the whole cohort
LIP1	100	NR	Pretreatment LIP1 intermediate/ poor vs. LIP1 good (dNLR < 4.0 and LDH < 283U/L): 4.7 vs. 8.4 (p = 0.02) (multi- variate analysis; HR, 1.42; 95% CI 0.84–2.39; p = 0.19)	Pretreatment LIP1 intermediate/ poor vs. LIP1 good: 1.33 vs. 23.8 (p = 0.0006) (multi- variate analysis; HR, 2.34; 95% CI 1.13–4.86; p = 0.02)

SCLC: small cell lung cancer; ES: extensive stage; N: number; BEP: biomarker-evaluable population; ORR: objective response rate; DCR: disease control rate; RR: response rate; mPFS: median progression-free survival; mOS: median overall survival; ICI: immune checkpoint inhibitor; PD-L1: programmed cell death 1 ligand 1; TILs: tumor infiltrating lymphocytes; FOXP3: forkhead box P3; APM: antigen presentation machinery; TcellinfGEP: T cell-inflamed gene expression profile; RB: retinoblastoma; WT: wild type; ctDNA: circulating tumor DNA; VAF: variant allele fraction; NAAs: neuronal autoantibodies; NLR: neutrophil-to-lymphocyte ratio; LIP1: lung immune prognostic index; LDH: lactate dehydrogenase; dNLR: derived neutrophils/ (leukocytes minus neutrophils) ratio; irRC: immune-related response criteria; EC: etoposide and carboplatin; EP: etoposide and platinum; CPS: combined positive score; IHC: immunohistochemistry; NGS: next generation sequencing; MSD: meso-scale discovery; LTS: long-term survivor; HR: hazard ratio; CI: confidence interval; NR: not reported

^a“Year” refers to the first posted date in clinical trials, and to the date of publication in non-clinical-trial studies

later-line nivolumab using multiple cutoff values (10, 11, 13, 14, 15 mut/Mb), with results showing that TMB did not emerge as a predictor of clinical outcomes (p-value for interaction of TMB by treatment > 0.20 for all cutoffs) [44]. In conclusion, TMB holds promise as a predictive marker in ICI monotherapy or dual immunotherapy for previously treated advanced SCLC, and further validation is needed.

In other clinical settings, results may differ. Chemotherapy has the potential to elevate TMB, thereby complicating the assessment of the relationship between TMB and immunotherapy efficacy when combined with chemotherapy [58, 59]. Current clinical studies have yet to affirm the predictive capacity of TMB in first-line chemotherapy plus immunotherapy. The tTMB subgroups in the CASPIAN study were defined according to various tTMB thresholds ranging from 6 to 14 mut/Mb. Durvalumab in combination with EP or durvalumab plus tremelimumab plus EP showed consistent advantages over EP across these subgroups [39]. The phase III KEYNOTE-604 study in untreated ES-SCLC unveiled a positive correlation between high TMB and favorable OS in the placebo group ($p=0.005$) but not in the pembrolizumab plus EP group ($p=0.450$). Additionally, pembrolizumab plus EP demonstrated clinical benefit compared to placebo plus EP for $TMB < 175$ mut/exome, but not for $TMB \geq 175$ mut/exome [60]. Both studies have indicated that tTMB was not an ideal predictive biomarker.

According to current research, tTMB holds potential as a predictive marker for the efficacy of ICI monotherapy in later-line setting, but its role in first-line immunotherapy plus chemotherapy lacks supportive evidence. Furthermore, research on tTMB as a predictive biomarker is constrained by some limitations. The majority of existing studies are retrospective exploratory analyses with restricted sample sizes, along with a lack of standardized detection methods, platforms, and cutoff values. Therefore, further prospective studies with expanded sample sizes are warranted to clarify the prognostic role of tTMB in immunotherapies.

Tumor microenvironment (TME)

The tumor microenvironment (TME) is a complex and dynamic network primarily comprised of tumor cells, immune cells (such as T lymphocytes, B lymphocytes, dendritic cells, and macrophages), stromal cells (including fibroblasts, endothelial cells, and pericytes), as well as various metabolites and cytokines [61]. The immune landscape within the TME exerts a pivotal influence on tumor initiation, progression, invasion, and resistance, thereby impacting patient prognosis [62, 63]. It has been reported that the TME of SCLC exhibited features of immune suppression, largely attributed to limited

immune cell infiltration, low PD-L1 expression levels, and deficient antigen presentation [64–66]. Recent studies have explored TME-related predictive biomarkers to identify patients who may benefit from immunotherapy (Table 3). However, owing to the scarcity of both resected tumor samples and biopsy samples, such studies remain limited in number and are mostly retrospective in design.

It is widely believed that tumor infiltrating lymphocytes (TILs) within the TME serve multiple functions. TILs produce soluble cytokines that regulate tumor cell proliferation and metastasis, and directly participate in the immune-mediated anti-tumor mechanisms. Research has confirmed the correlations between TILs with superior prognosis in a variety of tumors, such as melanoma, colorectal cancer, and breast cancer [67]. Some studies have demonstrated that the degree of lymphocytes infiltration could predict ICIs response in ES-SCLC. For instance, the post hoc analysis of the CheckMate 032 study indicated that $CD8^+T$ cell infiltration $\geq 1\%$ was correlated with better survival in relapsed SCLC patients receiving nivolumab monotherapy (HR, 0.51; 95% CI 0.27–0.95), with a similar trend seen in patients receiving nivolumab plus ipilimumab (HR, 0.7; 95% CI 0.32–1.49) [68]. A retrospective study conducted by Shirasawa et al. validated the predictive value of TILs density in patients with treatment-naive ES-SCLC receiving atezolizumab plus EC [69]. Classification of immune phenotypes based on the presence and infiltration patterns of $CD3^+$ and $CD8^+$ lymphocytes has also been shown to predict their response to ICIs. An exploratory analysis of a single-arm phase II study revealed that tumors exhibiting an inflamed phenotype all experienced tumor remission following treatment with durvalumab combined with olaparib, while non-responding tumors displayed either an immune-desert or immune-excluded pattern [70]. Interestingly, Pasello et al. proposed a connection of immune cell distribution and their spatial indicators with the efficacy of first-line immunochemotherapy. Lower density of $CD163^+M2$ polarized macrophages and its ratio on $CD8^+$ cells in both the overall and tumor regions were found to be favorably linked to PFS and OS ($p < 0.05$). Moreover, a high ratio of $CD4^+$ to $CD8^+$ cells adjacent in the entire region ($p=0.025$) and stroma ($p=0.002$), along with interaction between $CD8^+$ cells and tumor cells ($p=0.012$), were associated with longer OS. These findings highlighted the importance of the TME and cellular interactions in tumor response and survival prognosis [71]. Additionally, Kanemura et al. conducted a preliminary investigation into the potential of combining PD-L1 expression and TILs density as a prognostic indicator for ES-SCLC patients. They defined tumors with PD-L1 positivity ($CPS \geq 1\%$) and high $CD8^+$ TILs ($> 85/mm^2$) as “inflamed tumors,” while others were categorized as

“non-inflamed tumors.” In the ICI plus chemotherapy cohort, median PFS for patients with inflamed tumors and non-inflamed tumors were 10.8 months (95% CI 3.5–not reached) and 5.1 months (95% CI 4.3–5.6), respectively ($p=0.002$, HR, 0.26; 95% CI 0.09–0.74), indicating the predictive value of this combined biomarker [72].

Regulatory T cells (Tregs) expressing transcription factor forkhead box P3 (FOXP3) are crucial for maintaining dominant self-tolerance and immune homeostasis, typically inhibiting anti-tumor immune reactions and supporting tumor progression. However, FOXP3-TILs represent a heterogeneous population, comprising not only suppressive subsets but also non-suppressive subsets with anti-tumor activity [73, 74]. Two retrospective studies, involving 102 cases and 66 cases, respectively, have reported that FOXP3+ cells infiltration had an independently positive prognostic impact on patients with stages I to III SCLC [75, 76]. Unfortunately, immunotherapy was not included in the treatment modalities for these patients. Further research is needed to investigate the predictive value of FOXP3+ cells for immunotherapy response.

Tumor-associated macrophages (TAMs), a crucial component of the TME, can be generally categorized into anti-tumor M1 phenotype and pro-tumor M2 phenotype. The activity and phenotypes of TAMs can be dynamically regulated by integrating signals within the TME [77, 78]. Most clinical studies have observed that TAM infiltration was associated with the M2-phenotype-related gene expressions in solid tumors, where M2-like TAMs promoted angiogenesis and induced immune suppression [79–81]. However, there were also studies suggesting that macrophage infiltration might confer benefits to patients with solid tumors like NSCLC [82], colorectal cancer [83], and prostate cancer [84]. Eerola et al. evaluated samples from surgically treated SCLC patients, reporting that a higher concentration of macrophages was linked to better survival ($p=0.05$) [85]. Another case-control study compared surgically resected tumor specimens from long-term SCLC survivors (survival >4 years) and SCLC patients with expected survival time (survival <2 years), revealing higher numbers of CD14+ monocytes, FOXP3+ lymphocytes, and CD68+ macrophages in long-term survivors (LTS). However, the relative counts of these cells in relation to CD3+ T lymphocytes were typically lower [86]. Both studies utilized surgical specimens and did not explore the correlation between macrophage infiltration and immunotherapy effect.

Chemokines exert a vital role in the migration of immune cells towards tumors, thereby modulating the immune landscape of the TME, usually favoring a pro-tumorigenic state [87]. Additionally, chemokines are involved in various cancer progression processes

including cancer cell proliferation, tumor metastasis, angiogenesis, among others, thereby emerging as pivotal mediators of disease advancement with substantial implications for patient prognosis and treatment response [88, 89]. Chemokine (C–C motif) ligand 5 (CCL5), a member of the CC motif chemokine family, has been the subject of conflicting conclusions regarding its role in tumors. Some studies suggested that CCL5 served as an adverse prognostic indicator in cancer [90], while others proposed its protective role [91]. Tang et al. conducted a study using two published cohorts comprising 159 SCLC patients. Through the analysis of differentially expressed genes (DEGs) between high and low immune score, they observed a positive association between CCL5 expression with both survival and immunotherapy response in SCLC patients [92].

The exploration of TME-related biomarkers continues to encounter several challenges. Currently, most of the research remains exploratory and relies on retrospective data, lacking validation from RCTs. There is an urgent need to investigate standardized detection platforms. Furthermore, the constraints of single biomarkers underscore the necessity for developing composite predictive models that comprehensively reflect the immune status. Such an approach may act as an effective strategy for enhancing biomarker development.

Antigen presentation machinery (APM)

The antigen presentation machinery (APM) is a crucial process for the correct identification, processing, and presentation of tumor antigens to CD8+ T cells, thereby triggering T cell immune-mediated cytotoxic killing [93]. Various factors that modify antigen display on tumor cells, such as genetic variations in genes encoding major histocompatibility complex (MHC) or other APM components, transcriptional and translational modulation, as well as epigenetic regulation, can impact the effectiveness of immune responses [94]. Thus, identifying the regulatory mechanisms of APM in tumors holds significant potential for the precise administration of immunotherapy.

MHC, also known as human leukocyte antigen (HLA), is a critical component of the APM, can be primarily divided into MHC class I and MHC class II molecules. The presentation of antigens by MHC class I molecules to CD8+ T cells is a key mechanism of immune surveillance [93]. Downregulation of MHC class I expression and subsequent decrease in antigen presentation contribute to immune escape by intracellular pathogens and malignant cells. SCLC exhibits poor immunogenicity, with most cases showing low expression or loss of MHC class I [95, 96]. A study has identified a specific subset of SCLC that exhibited high MHC I expression and

displayed non-neuroendocrine features. Utilizing multiplexed immunofluorescence (mIF), spatial characterization in this subset revealed increased immune infiltration by CD3+/CD8+T cells and CD45+/PD-L1+ immune cells, suggesting that the TME of such tumors might be poised for an anti-tumor response. Mahadevan et al. further corroborated a significant correlation between high MHC I expression and sustained clinical benefits from ICIs, indicating that MHC I could function as a marker for ICI response in SCLC [97]. Conversely, epigenetic silencing of MHC-I in SCLC leads to poor response to ICIs. A preclinical study conducted by Nguyen et al. illustrated that inhibition of lysine-specific demethylase 1 (LSD1) could restore cell surface expression of MHC-I, activate antigen presentation pathways, and enhance anti-tumor response to ICIs in SCLC [98].

MHC class II molecules are primarily expressed on professional antigen-presenting cells (APCs) and participate in the presentation of exogenous antigens to CD4+T cells [99, 100]. Evidence suggested that HLA class II molecules on tumor cells influence tumor immunogenicity, tumor invasion, and immune responses [101, 102], while those on TILs are associated with antigen presentation, interactions with immune cells, and cancer prognosis [103]. In LS-SCLC patients, a retrospective study observed low expression of HLA class II on tumor cells while relatively high expression on TILs (positivity rates of 8.8% and 44.1% respectively). HLA class II on TILs was negatively correlated with lymph node metastasis and associated with longer recurrence-free survival (RFS), underscoring the prognostic and clinical significance of HLA class II in SCLC patients [104]. A post-hoc analysis of the phase III open-label CASPIAN study reported an association between the MHC class II allele DQB1*03:01 and longer OS in the durvalumab plus tremelimumab plus EP arm (HR, 0.59; 95%CI 0.39–0.88), but not in the durvalumab plus EP (HR, 0.93; 95%CI 0.63–1.37) or EP (HR, 0.94; 95%CI 0.61–1.40) arms [105].

The post-hoc analysis of the CheckMate 032 study preset a gene expression signature consisting of genes encoding the APM, such as HLA-A, HLA-B, HLA-C, B2M, TAP1, and TAP2. Rudin et al. assessed patient clinical outcomes by classifying cohorts of SCLC patients receiving nivolumab alone or with ipilimumab into tertiles based on APM gene signature. The results revealed a significant positive correlation ($p=3.2\times 10^{-4}$) between APM-related genes expression and OS for patients who received nivolumab. Furthermore, APM in SCLC is often subjected to epigenetic repression, with EZH2 and LSD1 identified as two critical negative epigenetic regulators. The study showed that elevated LSD1 expression was strongly linked to poorer OS in both the nivolumab and nivolumab plus ipilimumab arms ($p=0.035$ and $p=0.02$

respectively), with similar trends observed for EZH2 ($p=0.076$ and $p=0.27$ respectively) [68].

Research on the correlation of APM with benefit from ICIs in SCLC is still in its early stages (Table 3), necessitating further investigation and exploration.

Molecular subtypes and gene expression profiling

As high-throughput sequencing technologies advance, whole-genome analysis of SCLC has revealed the complexity of its genomic landscape [106]. Research on the epigenetic and gene expression of preclinical models and human SCLC samples has identified distinct SCLC subtypes, uncovering significant heterogeneity within tumors, which correlated with tumor evolution, metastasis, and treatment resistance [107]. In 2019, Rudin et al. introduced a novel model of SCLC subtypes—A, N, P, and Y—defined by differential expression of four key transcription regulators: achaete-scute homologue 1 (ASCL1), neurogenic differentiation factor 1 (NEUROD1), POU class 2 homeobox 3 (POU2F3), and yes associated protein 1 (YAP1) [107, 108]. The first two are neuroendocrine subtypes, while the latter two are non-neuroendocrine subtypes. Diverse immune profiles exist among different SCLC subtypes, thus leading to varied benefits from immunotherapy. The exploratory analysis in the CheckMate 032 study investigated the relationship between these four subtypes and the survival benefits of ICIs. Unfortunately, statistical significance was not observed across all subtypes, but the APM gene signature was enriched in SCLC-Y ($p<10^{-5}$) [68]. Interestingly, Shirasawa proposed a pathological classification of SCLC on the basis of IHC evaluation of ASCL1, NEUROD1, POU2F3, and YAP1 expression: pathological SCLC-A (pSCLC-A), pSCLC-N, pSCLC-P, and pSCLC-Y. However, this retrospective study did not discover a connection between pathological subtypes and immunotherapy [69].

Nevertheless, subsequent IHC analyses failed to confirm a distinct TAP1-driven subtype [109]. Consequently, Gay et al. proposed a unique SCLC-I subtype, characterized by low expression of ASCL1, NEUROD1, and POU2F3, but with features of inflammatory genes and mesenchymal traits [110]. The research indicated that, compared to other subtypes, the SCLC-I subtype exhibited higher levels of CD8+T cells, natural killer (NK) cells, macrophages, and B lymphocytes, along with increased expression of immune checkpoints and HLAs, illustrating superior responses to ICIs. The SCLC-I subtype was validated in tumor samples from IMpower-133 study. Although improvement trends were observed in the atezolizumab plus EC arm compared to the placebo plus EC arm across all four subtypes, the median OS and the magnitude of benefit with the addition

of atezolizumab was numerically greater in SCLC-I (18.2 months vs. 10.4 months, HR, 0.57; 95% CI 0.28–1.15) compared to the other three subtypes. Additionally, the study noted a remarkable survival advantage of SCLC-I in OS over all other tumors in the atezolizumab plus EC arm (HR, 0.566; 95% CI 0.321–0.998) but not the placebo arm (HR, 0.75; 95% CI 0.46–1.221), suggesting that the SCLC-I subtype might be predictive of ICI benefits [110]. Subsequently, exploratory analysis in IMpower-133 classified patients who survived for at least 18 months after randomization as LTS, evaluating the distribution of SCLC transcriptional subtypes in LTS and non-LTS groups. The results unveiled a greater percentage of LTS, especially in the atezolizumab group, with the SCLC-I subtype [111].

The 18-gene T cell–inflamed gene expression profile (TcellinfGEP) contains interferon (IFN)- γ -responsive genes linked to antigen presentation, chemokine expression, cytotoxic activity, and adaptive immune resistance, all crucial for clinical benefit [112]. TcellinfGEP has been developed into a clinical-grade assay and has been validated in some studies. For instance, the KEYNOTE-028 study, which encompassed patients with 20 distinct solid tumors including SCLC receiving pembrolizumab, revealed that patients achieving higher ORR and longer PFS had elevated TcellinfGEP scores. This underscored the predictive capability of TcellinfGEP for clinical benefits in PD-1 inhibitors [113]. However, this trial exclusively enrolled patients with PD-L1-positive solid tumors, thereby introducing bias in the distribution of biomarkers evaluated in the dataset, which posed limitations to its generalizability. Subsequent exploratory biomarker analyses in the KEYNOTE-604 study assessed the correlation of TcellinfGEP and SCLC transcriptional subtypes with survival outcomes. The findings indicated that SCLC subtypes were not linked to OS in either treatment group (pembrolizumab plus EP, $p=0.960$; placebo plus EP, $p=0.999$). However, a positive correlation between TcellinfGEP and OS was observed in both the pembrolizumab arm ($p=0.003$) and the placebo arm ($p<0.005$). Notably, there was no additional OS benefit with pembrolizumab plus EP [60].

The molecular hallmarks of SCLC encompass the inactivation of retinoblastoma gene (RB1), resulting in the absence of Rb protein expression, along with concomitant TP53 alterations [114]. SCLC exhibits near-universal biallelic functional inactivation of both RB1 and TP53 genes. RB1 is primarily involved in cell cycle regulation and cellular differentiation. Additionally, studies have highlighted the immunological significance of RB1, as evidenced by the downregulation of immune-related gene expression observed in preclinical models with RB1 inactivation [115, 116]. To assess the association between

RB1 mutation or inactivation and the benefit of ICIs in SCLC, Dowlati et al. retrospectively collected data from 42 SCLC patients receiving either single-agent ICI or ICI combination therapy. They found that the median OS for patients with RB1 wild-type (WT) receiving ICI was 23.1 months (95% CI 9–37.5), compared to 5 months (95% CI 2.5–26; $p=0.04$) for patients with RB1 mutation [117]. These results were further confirmed in CheckMate 032, where patients with RB1 mutant receiving nivolumab showed significantly inferior outcome compared to RB1 WT patients (HR, 1.41; 95% CI 1.02–2.01; $p=0.041$). Moreover, a significant correlation was noted between a high RB1 loss-of-function signature score and the neuroendocrine subtype (ASCL1 and NEUROD1) [117].

In general, the development of predictive biomarkers for immunotherapy based on SCLC transcriptomic and genomic features is a promising field (Table 3). Such biomarkers hold the potential to guide the selection of more effective treatment strategies for SCLC patients. However, the role of molecular subtypes or inflammatory gene expression requires more RCTs to be substantiated.

Circulating biomarkers

The conventional approach for clinical biomarker detection is tissue biopsy. However, this method presents certain limitations: (1) it is an invasive procedure; (2) tumors exhibit complex spatial and temporal heterogeneity, and a single biopsy may not encompass the full molecular characteristics of the tumor; (3) acquiring a sufficient quantity and quality of tumor specimens poses challenges [118]. In response to these constraints, liquid biopsy has gained growing prominence in recent years. Liquid biopsy primarily involves blood sampling but can also analyze cerebrospinal fluid, urine, pleural effusions, etc. It mainly detects circulating tumor DNA (ctDNA) and circulating tumor cells (CTCs) shed from primary or metastatic tumors into body fluids [119]. Liquid biopsy offers advantages such as low invasiveness, cost-effectiveness, and short detection time. It allows for repeated sampling to reflect tumor heterogeneity, as well as dynamic monitoring of treatment efficacy [120]. Liquid biopsy is often considered a rapid, minimally invasive alternative to tissue biopsy. In this chapter, we focused on the latest advancements in circulating biomarkers related to immunotherapy for SCLC (Table 3).

Circulating tumor DNA (ctDNA)

ctDNA refers to specific DNA fragments released into the circulation either through active secretion of tumor cells or during tumor cell apoptosis or necrosis. ctDNA harbors genetic features derived from the tumor, such as gene mutations, methylation, copy number alterations

(CNAs), etc. [121], serving as an important indicator for tumor screening [122], companion diagnostics [123], assessment of treatment efficacy and monitoring of recurrence [124–126]. Typically constituting a minor portion of cell-free DNA (cfDNA) in plasma, ctDNA can be identified using polymerase chain reaction (PCR) or NGS assays [127, 128].

Some studies have documented statistically significant correlations of quantified ctDNA variant allele fraction (VAF) and CNAs with OS, suggesting ctDNA as a prognostic biomarker for SCLC [129–131]. However, these studies did not include populations undergoing ICI therapy. Data on the predictive value of ctDNA in ES-SCLC patients receiving immunotherapy are limited.

According to an ancillary analysis of the phase II IFCT-1603 trial, high ctDNA abundance was significantly associated with poor OS outcomes ($HR_{VAF \geq median} 8.11$; 95% CI 2.20–29.91; $p=0.0017$) in SCLC patients with atezolizumab as second-line treatment. Researchers observed that patients with high baseline ctDNA levels appeared to derive less benefit from atezolizumab than chemotherapy, while the reverse trend was observed in patients with low baseline ctDNA levels. This trial underscored the predictive role of ctDNA in second-line immunotherapy for SCLC [132].

Sivapalan et al. conducted a comprehensive longitudinal analysis of somatic sequence and plasma aneuploidy in ctDNA, identifying three distinct molecular response patterns reflecting different clinical outcomes in metastatic SCLC patients treated with either chemotherapy or immunotherapy-based regimens. Patients with sustained ctDNA elimination attained significantly longer OS (median OS: not reached) and PFS (median PFS: not reached) compared to those with ctDNA elimination followed by recrudescence (median OS: 12.35 months, median PFS: 6.18 months) or persistent ctDNA burden (median OS: 6.48 months, median PFS: 1.74 months) ($p=0.0006$ and $p<0.0001$, respectively). These findings suggested that longitudinal ctDNA dynamics assessment could provide a basis for early identification of persistent molecular response or resistance, guiding decisions to either continue or switch to alternative therapies for maximal clinical benefit [133, 134]. Similarly, in a phase II clinical trial evaluating the efficacy of durvalumab plus olaparib for relapsed SCLC, a case with a deleterious BRCA1 mutation was described, where the patient achieved a complete response (CR) accompanied by a sharp decline in cfDNA levels [70].

These studies supported the predictive significance of baseline and dynamic monitoring of ctDNA in SCLC patients undergoing immunotherapy, albeit with small cohorts. Prospective research is warranted to fully assess the reliability of ctDNA for clinical decision-making.

Circulating tumor cells (CTCs)

CTCs are tumor cells that are shed from primary or metastatic sites into the peripheral blood. These cells carry vital information concerning the genetic and molecular characteristics of the tumor, facilitating real-time, dynamic, and non-invasive monitoring of the patient's condition [135]. They have shown prognostic significance across various cancer types, including breast cancer [136–138], NSCLC [139, 140], prostate cancer [141, 142], colorectal cancer [143, 144], and others.

Research confirmed that due to the short cell cycle and rapid proliferation of SCLC cells, which easily enter circulation leading to distant metastasis, the detection rate of CTCs in SCLC populations is approximately 60–94% [129, 145–150], significantly higher than in other tumors. Similar to ctDNA, studies on CTCs in SCLC primarily focused on their prognostic value, predominantly including SCLC cohorts treated with chemotherapy in the pre-immunotherapy era. Although specific thresholds have not been definitively established, these studies have documented a correlation between elevated levels of CTCs and unfavorable prognosis [146–153], with higher levels observed in ES-SCLC compared to LS-SCLC [146, 148, 150]. Furthermore, changes in CTC levels during treatment seem to predict clinical outcomes [149, 153, 154]. Additionally, the role of CTC detection in clinical disease differentiation [155], chemotherapy sensitivity evaluation [156, 157], and analysis of resistance molecular mechanisms [158] is supported by some research. The predictive potential of CTCs in immunotherapy remains to be further explored.

Cytokines

Cytokines represent a class of soluble immune signaling proteins, including interleukins (IL), IFN, tumor necrosis factor (TNF), chemokines, and growth factors, which play pivotal roles in either promoting or inhibiting inflammation through various biochemical pathways and interactions [159, 160]. Preliminary data suggested that soluble factors such as IL-6 [161], IL-8 [162, 163], IL-10 [164, 165], etc., may serve as predictive or prognostic factors for ICI response in solid tumors such as NSCLC. However, there is limited research on the biological impact of cytokine levels in SCLC.

Hardy-Werbin and the team analyzed Th1, Th2, and proinflammatory cytokines in two independent cohorts of SCLC patients before and during treatment with chemotherapy with or without ipilimumab and correlated them with survival. The study noted an overall increase in all cytokines following treatment initiation in patients receiving ipilimumab. Irrespective of the treatment regimen, a high baseline IL-8 level was linked to poorer prognosis. Elevated baseline levels of IL-2 were indicative of

sensitivity to ICIs, while high IL-6 and TNF- α predicted resistance. Additionally, an increase in IL-4 concentration during treatment in the immune-chemotherapy cohort correlated with improved OS [166]. However, a phase II clinical trial assessing the combination of durvalumab and olaparib for recurrent SCLC did not yield similar correlations [70]. Consequently, there remains no consensus regarding the role of cytokines in predicting ICI efficacy for SCLC, underscoring the need for further investigation.

Serum neuronal autoantibodies (NAAs)

Paraneoplastic neurological syndromes (PNSs) are recognized as immune-mediated disorders, characterized by antibodies induced by tumor antigens that exhibit cross-reactivity with neural antigens [167]. Among patients with PNSs caused by SCLC, the most frequently detected onconeural autoantibodies are anti-Hu antibodies, also referred to as type 1 antineuronal nuclear antibodies (ANNA1) [168]. Additional onconeural autoantibodies implicated in PNSs include those targeting collapsin response mediator protein 5 (CRMP5), SOX1, microtubule-associated protein 1B (MAP1B), and amphiphysin [169]. PNSs manifest in 5–10% of SCLC patients, often accompanied by the detection of multiple autoantibodies. However, about half of patients without PNSs also carry at least one autoantibody [170–172].

In cases of PNSs related to SCLC, distinctive neurological dysfunction typically precedes respiratory symptoms, facilitating early cancer screening. Evidence suggested that SCLC patients with PNSs had a better prognosis than those without PNSs [173, 174]. Furthermore, several studies indicated potential prognostic value of certain neuronal autoantibodies (NAAs) such as ANNAs in SCLC [175, 176]. However, two other studies failed to observe prognostic differences between serum autoantibody-positive and -negative SCLC patients [170, 177].

Reportedly, SCLC patients with PNSs exhibit a "hot" TME marked by increased TILs, elevated PD-L1 expression, and increased PD-1/PD-L1 interactions, suggesting that such patients may represent an ideal population for receiving ICIs [178]. Additionally, immunotherapy can induce irAEs, and identifying serum characteristics before treatment commencement may help predict the risk of immune-mediated complications [179, 180].

In a biomarker analysis from a phase II clinical trial assessing ipilimumab plus EC as first-line treatment for ES-SCLC, autoimmune profile positivity at baseline was observed to be associated with improved outcomes and severe neurotoxicity [181]. Based on this study, Hardy-Werbin et al. expanded the research to include a control cohort receiving standard chemotherapy in order to evaluate the predictive and prognostic roles of NAAs.

In both cohorts, the most prevalent autoantibody was anti-SOX1, succeeded by anti-HuD and anti-Yo. In the chemotherapy-alone cohort, positive NAAs at baseline correlated with better OS (15.1 months vs. 11.7 months, $p=0.032$), whereas no such difference was observed in chemotherapy plus ipilimumab cohort (12.3 months vs. 17 months, $p=0.796$). Furthermore, patients with a decrease in NAAs titer post-treatment experienced longer OS (18.5 months; 95%CI 15.8–21.2) compared to those with elevated NAAs (12.3 months; 95%CI 8.1–16.5; $p=0.049$), indicating a correlation between antibody levels and tumor burden [182]. The findings demonstrated the function of NAAs as prognostic markers for SCLC and reflections of tumor burden, yet there was no conclusive evidence supporting their predictive role in ICI response. Further research is warranted to determine whether neuronal antibodies can serve as reliable predictors of immunotherapy efficacy and toxicity.

Inflammatory hematologic parameters

Hematologic parameters, such as the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), are described as general prognostic indicators for immunotherapy in several cancer types, reflecting the balance between pro-tumor inflammation and anti-tumor immune response [183–185]. Additionally, the lung immune prognostic index (LIPI), an index calculated from the lactate dehydrogenase (LDH) level and derived neutrophils/ (leukocytes minus neutrophils) ratio (dNLR), is believed to be linked with ICI outcomes in patients with melanoma and NSCLC [186–188].

The correlation of inflammation-related biomarkers with clinical outcomes in SCLC has been documented. NLR has been proposed as a significant prognostic marker for ES-SCLC patients across various treatments, excluding immunotherapy [189]. Sonehara et al. demonstrated LIPI as a prognostic factor for SCLC patients [190], a conclusion echoed by Qi et al. [191], although both studies involved patients who did not receive ICIs.

A retrospective study including 41 patients with SCLC who received anti-PD-1/PD-L1 antibodies as second- or later-line treatment evaluated NLR and PLR at baseline and 6 weeks post-treatment. Patients with $NLR < 5$ had significantly prolonged median PFS compared to those with $NLR \geq 5$ at 6 weeks post treatment (HR, 0.29; 95%CI 0.09–0.96; $p=0.04$), while a similar trend was not observed at baseline (HR, 0.75; 95% CI 0.24–2.26; $p=0.58$), suggesting that the NLR at 6 weeks after start of treatment may predict early response in SCLC patients receiving ICIs [192]. Riemann et al. conducted an exploratory prospective study, identifying a high baseline NLR ($NLR \geq 6.1$) as a risk factor for advanced SCLC patients' response to chemotherapy combined with

immunotherapy (median OS: HR, 3.18; 95%CI 1.45–6.99; $p=0.004$) [193]. Similarly, Stratmann et al. proposed that NLR above the median was strongly correlated with inferior OS (3.5 months vs. 12.4 months; HR, 1.9; 95% CI 1.2–3.2; $p=0.008$) in relapsed/refractory SCLC patients treated with ICIs [194]. A retrospective study explored the prognostic effect of LIPI on advanced SCLC patients undergoing first-line ICIs plus chemotherapy. The researchers found that the pretreatment LIPI good ($dNLR < 4.0$ and $LDH < 283U/L$) group had superior PFS (median: 8.4 months vs. 4.7 months, $p=0.02$) and OS (median: 23.8 months vs. 13.3 months, $p=0.0006$) than the LIPI intermediate/poor group, suggesting LIPI as a potential predictive biomarker [195]. Additional prospective research is required to evaluate the predictive capacity of these inflammatory markers for ICIs.

Blood TMB (bTMB)

tTMB has been discussed in Section “Tumor tissue-based biomarkers” before. In contrast to tTMB, assessing bTMB may offer a more precise depiction of the overall disease characteristics, covering both primary and metastatic sites. Additionally, obtaining bTMB is more convenient and less invasive [196]. Retrospective analyses of the OAK and POPLAR studies have showcased consistency between bTMB and tTMB [197]. The correlation between bTMB and clinical outcomes of immunotherapy has been established in NSCLC [197–200]. Nevertheless, the predictive potential of bTMB in SCLC appears less promising. In the exploratory analysis of the IMpower133 trial, using 10 and 16 mut/Mb as bTMB thresholds, it was observed that atezolizumab plus EC exhibited enhanced efficacy over placebo plus EC, independent of bTMB levels [34]. Currently, there is a paucity of research exploring the predictive value of bTMB in SCLC patients with ICI monotherapy. Therefore, further investigation is warranted to elucidate the predictive role of bTMB on the efficacy of SCLC immunotherapy and its relationship with tTMB.

Conclusions

The advent of immunotherapy has shown promise in improving outcomes for SCLC patients, although conferring benefits primarily to a small subset. Moreover, immunotherapy is accompanied by nearly unavoidable immune-related toxicities. Hence, there is a pressing clinical imperative to pinpoint suitable biomarkers to predict immunotherapy response so as to facilitate individualized treatment in SCLC. Conventional markers such as PD-L1 expression and TMB did not show consistent and robust predictive power for immunotherapy response in SCLC, though they played significant indicative roles

in various cancer types. Notably, biomarkers based on TME, transcriptional and genetic characteristics may offer valuable guidance for immunotherapy. Specifically, TILs and RB1 mutation appear to hold promising predictive value. Moreover, given the advantages in convenience and reproducibility, circulating biomarkers, such as ctDNA, hold potential as alternative predictors of therapeutic efficacy. However, corresponding research data remains limited. Ultimately, owing to the pronounced heterogeneity of SCLC, the predictive utility of individual biomarker is constrained. The exploration of composite predictive models, integrating multi-omics information encompassing genomics, transcriptomics, proteomics, and epigenomics, may indeed represent a future trend.

Abbreviations

SCLC	Small cell lung cancer
NSCLC	Non-small cell lung cancer
VALCSG	Veterans Administration Lung Cancer Study Group
ES	Extensive stage
LS	Limited stage
EP	Platinum and etoposide
PFS	Progression-free survival
OS	Overall survival
RFS	Recurrence-free survival
ICIs	Immune checkpoint inhibitors
HR	Hazard ratio
CI	Confidence interval
irAEs	Immune-related adverse events
PD-L1	Programmed cell death 1 ligand 1
PD-1	Programmed cell death protein 1
CAR	Chimeric antigen receptor
DLL3	Delta-like ligand 3
BiTEs	Bispecific T-cell engagers
FDA	The US Food and Drug Administration
TIM3	T cell immunoglobulin and mucin domain-containing protein 3
TIGIT	T cell immunoreceptor with immunoglobulin and ITIM domain
LAG3	Lymphocyte activation gene 3
IHC	Immunohistochemistry
TCs	Tumor cells
ICs	Immune cells
EC	Etoposide and carboplatin
CPS	Combined positive score
CTLA-4	Cytotoxic T lymphocyte antigen 4
CR	Complete response
ORR	Objective response rate
RCTs	Randomized controlled trials
TMB	Tumor mutational burden
tTMB	Tissue tumor mutational burden
bTMB	Blood tumor mutational burden
WES	Whole exome sequencing
NGS	Next generation sequencing
mut/Mb	Mutations per megabase
TME	Tumor microenvironment
TILs	Tumor infiltrating lymphocytes
Tregs	Regulatory T cells
FOXP3	Forkhead box P3
TAMs	Tumor-associated macrophages
LTS	Long-term survivor
CCL5	Chemokine (C–C motif) ligand 5
DEGs	Differentially expressed genes
APM	Antigen presentation machinery
MHC	Major histocompatibility complex
HLA	Human leukocyte antigen
mIF	Multiplexed immunofluorescence

LSD1	Lysine-specific demethylase 1
APCs	Antigen-presenting cells
ASCL1	Achaete-scute homologue 1
NEUROD1	Neurogenic differentiation factor 1
POU2F3	POU class 2 homeobox 3
YAP1	Yes associated protein 1
NK cells	Natural killer cells
TcellinfGEP	T cell-inflamed gene expression profile
RB1	Retinoblastoma
WT	Wild-type
ctDNA	Circulating tumor DNA
CNAs	Copy number alterations
VAF	Variant allele fraction
cfDNA	Cell-free DNA
CTCs	Circulating tumor cells
PCR	Polymerase chain reaction
IL	Interleukin
IFN	Interferon
TNF	Tumor necrosis factor
NAAs	Neuronal autoantibodies
PNSs	Paraneoplastic neurological syndromes
ANNA1	Type 1 antineuronal nuclear antibody
CRMP5	Collapsin response mediator protein 5
MAP1B	Microtubule-associated protein 1B
NLR	Neutrophil-to-lymphocyte ratio
PLR	Platelet-to-lymphocyte ratio
LPI	Lung immune prognostic index
LDH	Lactate dehydrogenase
dNLR	Derived neutrophils/(leukocytes minus neutrophils) ratio

Supplementary Information

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Supplementary Material 1.

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Author contributions

TC and YL conceived the review. TC provided data curation and wrote the manuscript. TC and MW provided review and editing. TC, YC and YC designed the figures and tables. YL supervised the manuscript. YL solicited for funding. All authors read and approved the final manuscript.

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References

1. Thai AA, Solomon BJ, Sequist LV, Gainor JF, Heist RS. Lung cancer. *Lancet*. 2021;398(10299):535–54.
2. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. *CA Cancer J Clin*. 2022;72(1):7–33.
3. Alexandrov LB, Ju YS, Haase K, Van Loo P, Martincorena I, Nik-Zainal S, et al. Mutational signatures associated with tobacco smoking in human cancer. *Science*. 2016;354(6312):618–22.
4. Gazdar AF, Bunn PA, Minna JD. Small-cell lung cancer: what we know, what we need to know and the path forward. *Nat Rev Cancer*. 2017;17(12):765.
5. Micke P, Faldum A, Metz T, Beeh KM, Bittinger F, Hengstler JG, et al. Staging small cell lung cancer: Veterans Administration Lung Study Group versus International Association for the Study of Lung Cancer—what limits limited disease? *Lung Cancer*. 2002;37(3):271–6.
6. Horn L, Mansfield AS, Szczesna A, Havel L, Krzakowski M, Hochmair MJ, et al. First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. *N Engl J Med*. 2018;379(23):2220–9.
7. Lally BE, Urbanic JJ, Blackstock AW, Miller AA, Perry MC. Small cell lung cancer: have we made any progress over the last 25 years? *Oncologist*. 2007;12(9):1096–104.
8. Pietanza MC, Byers LA, Minna JD, Rudin CM. Small cell lung cancer: will recent progress lead to improved outcomes? *Clin Cancer Res*. 2015;21(10):2444–55.
9. Paz-Ares L, Dvorkin M, Chen Y, Reinmuth N, Hotta K, Trukhin D, et al. Durvalumab plus platinum-etoposide versus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial. *Lancet*. 2019;394(10212):1929–39.
10. Paz-Ares L, Chen Y, Reinmuth N, Hotta K, Trukhin D, Statsenko G, et al. Durvalumab, with or without tremelimumab, plus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer: 3-year overall survival update from CASPIAN. *ESMO Open*. 2022;7(2):100408.
11. Kumar V, Chaudhary N, Garg M, Floudas CS, Soni P, Chandra AB. Current diagnosis and management of immune related adverse events (irAEs) induced by immune checkpoint inhibitor therapy. *Front Pharmacol*. 2017;8:49.
12. Naidoo J, Wang X, Woo KM, Iyriboz T, Halpenny D, Cunningham J, et al. Pneumonitis in patients treated with anti-programmed death-1/programmed death ligand 1 therapy. *J Clin Oncol*. 2017;35(7):709–17.
13. Puzanov I, Diab A, Abdallah K, Bingham CO 3rd, Brogdon C, Dadu R, et al. Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. *J Immunother Cancer*. 2017;5(1):95.
14. Su PL, Chakravarthy K, Furuya N, Brownstein J, Yu J, Long M, et al. DLL3-guided therapies in small-cell lung cancer: from antibody-drug conjugate to precision immunotherapy and radioimmunotherapy. *Mol Cancer*. 2024;23(1):97.
15. Wermke M, Kuboki Y, Felip E, Alese OB, Morgensztern D, Sayehli C, et al. OA01.05 phase I dose escalation trial of the DLL3/CD3 IgG-like T cell engager BI 764532 in patients with DLL3+ tumors: focus on SCLC. *J Thorac Oncol*. 2023;18(11):545–6.
16. Rudin CM, Reck M, Johnson ML, Blackhall F, Hann CL, Yang JC, et al. Emerging therapies targeting the delta-like ligand 3 (DLL3) in small cell lung cancer. *J Hematol Oncol*. 2023;16(1):66.
17. Paz-Ares L, Champiat S, Lai WW, Izumi H, Govindan R, Boyer M, et al. Tarlatamab, a first-in-class DLL3-targeted bispecific T-cell engager, in recurrent small-cell lung cancer: an open-label, Phase I Study *J Clin Oncol*. 2023;41(16):2893–903.
18. Byers LA, Heymach JV, Gibbons DL, Zhang J, Chiappori AA, Rasmussen ER, et al. 697 A phase 1 study of AMG 119, a DLL3-targeting, chimeric antigen receptor (CAR) T cell therapy, in relapsed/refractory small cell lung cancer (SCLC). *Regul Young Investig Award Abstr*. 2022. <https://doi.org/10.1136/jitc-2022-SITC2022.0697>.
19. Giffin M, Cooke K, Lobenhofer E, Friedrich M, Raum T, Coxon A. P3.12–03 targeting DLL3 with AMG 757, a BiTE® antibody construct, and AMG 119, a CAR-T, for the treatment of SCLC. *J Thorac Oncol*. 2018;13:S971.

20. Liu M, Huang W, Guo Y, Zhou Y, Zhi C, Chen J, et al. CAR NK-92 cells targeting DLL3 kill effectively small cell lung cancer cells in vitro and in vivo. *J Leukoc Biol*. 2022;112(4):901–11.
21. Giaccone G, Debruyne C, Filip E, Chapman PB, Grant SC, Millward M, et al. Phase III study of adjuvant vaccination with Bec2/bacille Calmette-Guerin in responding patients with limited-disease small-cell lung cancer (European Organisation for Research and Treatment of Cancer 08971–08971B; Silva Study). *J Clin Oncol*. 2005;23(28):6854–64.
22. Neningen E, Díaz RM, de la Torre A, Rives R, Díaz A, Saurez G, et al. Active immunotherapy with 1E10 anti-idiotype vaccine in patients with small cell lung cancer: report of a phase I trial. *Cancer Biol Ther*. 2007;6(2):145–50.
23. Zhang Q, Bi J, Zheng X, Chen Y, Wang H, Wu W, et al. Blockade of the checkpoint receptor TIGIT prevents NK cell exhaustion and elicits potent anti-tumor immunity. *Nat Immunol*. 2018;19(7):723–32.
24. Dixon KO, Schorer M, Nevin J, Ertman Y, Amoozgar Z, Kondo T, et al. Functional anti-TIGIT antibodies regulate development of autoimmunity and antitumor immunity. *J Immunol*. 2018;200(8):3000–7.
25. Rudin CM, Liu SV, Soo RA, Lu S, Hong MH, Lee JS, et al. SKYSCRAPER-02: tiragolimumab in combination with atezolizumab plus chemotherapy in untreated extensive-stage small-cell lung cancer. *J Clin Oncol*. 2024;42(3):324–35.
26. Deng WW, Mao L, Yu GT, Bu LL, Ma SR, Liu B, et al. LAG-3 confers poor prognosis and its blockade reshapes antitumor response in head and neck squamous cell carcinoma. *Oncoimmunology*. 2016;5(11):e1239005.
27. Lichtenegger FS, Rothe M, Schnorfeil FM, Deiser K, Krupka C, Augstberger C, et al. Targeting LAG-3 and PD-1 to enhance T cell activation by antigen-presenting cells. *Front Immunol*. 2018;9:385.
28. Uboha NV, Milhem MM, Kovacs C, Amin A, Magley A, Purkayastha DD, et al. Phase II study of spartalizumab (PDR001) and LAG525 in advanced solid tumors and hematologic malignancies. *J Clin Oncol*. 2019;37(15_suppl):2553.
29. Powderly JD, Hamid O, Gutierrez ME, Balmanoukian AS, Janik J, Hoyle P, et al. 742P First-in-human phase I study of INCAGN02385, a LAG-3 monoclonal antibody antagonist in patients with advanced malignancies. *Ann Oncol*. 2022;33:883.
30. Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csósz T, Fülöp A, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. *N Engl J Med*. 2016;375(19):1823–33.
31. Keppens C, Dequeker EM, Pauwels P, Ryska A, t'Hart N, von der Thüsen JH. PD-L1 immunohistochemistry in non-small-cell lung cancer: unraveling differences in staining concordance and interpretation. *Virchows Arch*. 2021;478(5):827–39.
32. Hirsch FR, McElhinny A, Stanforth D, Ranger-Moore J, Jansson M, Kulangara K, et al. PD-L1 immunohistochemistry assays for lung cancer: results from phase 1 of the blueprint PD-L1 IHC assay comparison project. *J Thorac Oncol*. 2017;12(2):208–22.
33. Schultheis AM, Scheel AH, Ozretić L, George J, Thomas RK, Hagemann T, et al. PD-L1 expression in small cell neuroendocrine carcinomas. *Eur J Cancer*. 2015;51(3):421–6.
34. Liu SV, Reck M, Mansfield AS, Mok T, Scherpereel A, Reinmuth N, et al. Updated overall survival and PD-L1 subgroup analysis of patients with extensive-stage small-cell lung cancer treated with atezolizumab, carboplatin, and etoposide (IMpower133). *J Clin Oncol*. 2021;39(6):619–30.
35. Mansfield AS, Kaźarnowicz A, Karaseva N, Sánchez A, De Boer R, Andric Z, et al. Safety and patient-reported outcomes of atezolizumab, carboplatin, and etoposide in extensive-stage small-cell lung cancer (IMpower133): a randomized phase I/III trial. *Ann Oncol*. 2020;31(2):310–7.
36. Rudin CM, Awad MM, Navarro A, Gottfried M, Peters S, Csósz T, et al. Pembrolizumab or placebo plus etoposide and platinum as first-line therapy for extensive-stage small-cell lung cancer: randomized, double-blind, phase III KEYNOTE-604 study. *J Clin Oncol*. 2020;38(21):2369–79.
37. Cheng Y, Han L, Wu L, Chen J, Sun H, Wen G, et al. Effect of first-line serplulimab vs placebo added to chemotherapy on survival in patients with extensive-stage small cell lung cancer: the ASTRUM-005 randomized clinical trial. *JAMA*. 2022;328(12):1223–32.
38. Wang J, Zhou C, Yao W, Wang Q, Min X, Chen G, et al. Adebrelimab or placebo plus carboplatin and etoposide as first-line treatment for extensive-stage small-cell lung cancer (CAPSTONE-1): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2022;23(6):739–47.
39. Paz-Ares L, Garassino MC, Chen Y, Reinmuth N, Hotta K, Poltoratskiy A, et al. Durvalumab ± tremelimumab + platinum-etoposide in extensive-stage small cell lung cancer (CASPIAN): outcomes by PD-L1 expression and tissue tumor mutational burden. *Clin Cancer Res*. 2024;30(4):824–35.
40. Owonikoko TK, Park K, Govindan R, Ready N, Reck M, Peters S, et al. Nivolumab and ipilimumab as maintenance therapy in extensive-disease small-cell lung cancer: CheckMate 451. *J Clin Oncol*. 2021;39(12):1349–59.
41. Gadgeel SM, Pennell NA, Fidler MJ, Halmos B, Bonomi P, Stevenson J, et al. Phase II study of maintenance pembrolizumab in patients with extensive-stage small cell lung cancer (SCLC). *J Thorac Oncol*. 2018;13(9):1393–9.
42. Chung HC, Lopez-Martin JA, Kao SC-H, Miller WH, Ros W, Gao B, et al. Phase 2 study of pembrolizumab in advanced small-cell lung cancer (SCLC): KEYNOTE-158. *J Clin Oncol*. 2018;36(15_suppl):8506.
43. Ott PA, Elez E, Hirt S, Kim DW, Morosky A, Saraf S, et al. Pembrolizumab in patients with extensive-stage small-cell lung cancer: results from the phase Ib KEYNOTE-028 study. *J Clin Oncol*. 2017;35(34):3823–9.
44. Spigel DR, Vicente D, Ciuleanu TE, Gettinger S, Peters S, Horn L, et al. Second-line nivolumab in relapsed small-cell lung cancer: CheckMate 331(★). *Ann Oncol*. 2021;32(5):631–41.
45. Pujol JL, Greillier L, Audigier-Valette C, Moro-Sibilot D, Uwer L, Hureauux J, et al. A randomized non-comparative phase II study of anti-programmed cell death-ligand 1 atezolizumab or chemotherapy as second-line therapy in patients with small cell lung cancer: results from the IFCT-1603 trial. *J Thorac Oncol*. 2019;14(5):903–13.
46. Fan Y, Zhao J, Wang Q, Huang D, Li X, Chen J, et al. Camrelizumab plus apatinib in extensive-stage SCLC (PASSION): a multicenter, two-stage, phase 2 trial. *J Thorac Oncol*. 2021;16(2):299–309.
47. Ready N, Farago AF, de Braud F, Atmaca A, Hellmann MD, Schneider JG, et al. Third-line nivolumab monotherapy in recurrent SCLC: CheckMate 032. *J Thorac Oncol*. 2019;14(2):237–44.
48. Chung HC, Piha-Paul SA, Lopez-Martin J, Schellens JHM, Kao S, Miller WH Jr, et al. Pembrolizumab after two or more lines of previous therapy in patients with recurrent or metastatic SCLC: results from the KEYNOTE-028 and KEYNOTE-158 studies. *J Thorac Oncol*. 2020;15(4):618–27.
49. Steuer CE, Ramalingam SS. Tumor mutation burden: leading immunotherapy to the era of precision medicine? *J Clin Oncol*. 2018;36(7):631–2.
50. Carbone DP, Reck M, Paz-Ares L, Creelan B, Horn L, Steins M, et al. First-line nivolumab in stage iv or recurrent non-small-cell lung cancer. *N Engl J Med*. 2017;376(25):2415–26.
51. Hellmann MD, Callahan MK, Awad MM, Calvo E, Ascierto PA, Atmaca A, et al. Tumor mutational burden and efficacy of nivolumab monotherapy and in combination with ipilimumab in small-cell lung cancer. *Cancer Cell*. 2018;33(5):853–61.e4.
52. Rizvi H, Sanchez-Vega F, La K, Chatila W, Jonsson P, Halpenny D, et al. Molecular determinants of response to anti-programmed cell death (PD)-1 and anti-programmed death-ligand 1 (PD-L1) blockade in patients with non-small-cell lung cancer profiled with targeted next-generation sequencing. *J Clin Oncol*. 2018;36(7):633–41.
53. Hellmann MD, Ciuleanu TE, Pluzanski A, Lee JS, Otterson GA, Audigier-Valette C, et al. Nivolumab plus ipilimumab in lung cancer with a high tumor mutational burden. *N Engl J Med*. 2018;378(22):2093–104.
54. Van Allen EM, Miao D, Schilling B, Shukla SA, Blank C, Zimmer L, et al. Genomic correlates of response to CTLA-4 blockade in metastatic melanoma. *Science*. 2015;350(6257):207–11.
55. Rosenberg JE, Hoffman-Censits J, Powles T, van der Heijden MS, Balar AV, Necchi A, et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. *Lancet*. 2016;387(10031):1909–20.
56. George J, Lim JS, Jang SJ, Cun Y, Ozretić L, Kong G, et al. Comprehensive genomic profiles of small cell lung cancer. *Nature*. 2015;524(7563):47–53.
57. Marabelle A, Fakih M, Lopez J, Shah M, Shapira-Frommer R, Nakagawa K, et al. Association of tumour mutational burden with outcomes in patients with advanced solid tumours treated with pembrolizumab:

- prospective biomarker analysis of the multicohort, open-label, phase 2 KEYNOTE-158 study. *Lancet Oncol.* 2020;21(10):1353–65.
58. Crisafulli G, Sartore-Bianchi A, Lazzari L, Pietrantonio F, Amatu A, Macagno M, et al. Temozolomide treatment alters mismatch repair and boosts mutational burden in tumor and blood of colorectal cancer patients. *Cancer Discov.* 2022;12(7):1656–75.
 59. Cao Y, Ma Y, Yu J, Sun Y, Sun T, Shao Y, et al. Favorable response to immunotherapy in a pancreatic neuroendocrine tumor with temozolomide-induced high tumor mutational burden. *Cancer Commun.* 2020;40(12):746–51.
 60. Rudin CM, Kim HR, Navarro A, Gottfried M, Peters S, Csozsi T, et al. Exploratory biomarker analysis of the phase 3 KEYNOTE-604 study of pembrolizumab plus etoposide for extensive-stage SCLC. *J Clin Oncol.* 2023;41(16_suppl):8503.
 61. Giraldo NA, Sanchez-Salas R, Peske JD, Vano Y, Becht E, Petitprez F, et al. The clinical role of the TME in solid cancer. *Br J Cancer.* 2019;120(1):45–53.
 62. Galon J, Bruni D. Tumor immunology and tumor evolution: intertwined histories. *Immunity.* 2020;52(1):55–81.
 63. Liu H, Zhao H, Sun Y. Tumor microenvironment and cellular senescence: understanding therapeutic resistance and harnessing strategies. *Semin Cancer Biol.* 2022;86(Pt 3):769–81.
 64. Remon J, Aldea M, Besse B, Planchard D, Reck M, Giaccone G, et al. Small cell lung cancer: a slightly less orphan disease after immunotherapy. *Ann Oncol.* 2021;32(6):698–709.
 65. Spigel DR, Socinski MA. Rationale for chemotherapy, immunotherapy, and checkpoint blockade in SCLC: beyond traditional treatment approaches. *J Thorac Oncol.* 2013;8(5):587–98.
 66. Tian Y, Zhai X, Han A, Zhu H, Yu J. Potential immune escape mechanisms underlying the distinct clinical outcome of immune checkpoint blockades in small cell lung cancer. *J Hematol Oncol.* 2019;12(1):67.
 67. Fridman WH, Pagès F, Sautès-Fridman C, Galon J. The immune contexture in human tumours: impact on clinical outcome. *Nat Rev Cancer.* 2012;12(4):298–306.
 68. Rudin CM, Balli D, Lai WV, Richards AL, Nguyen E, Egger JV, et al. Clinical benefit from immunotherapy in patients with SCLC is associated with tumor capacity for antigen presentation. *J Thorac Oncol.* 2023;18(9):1222–32.
 69. Shirasawa M, Yoshida T, Shiraishi K, Takigami A, Takayanagi D, Imabayashi T, et al. Identification of inflamed-phenotype of small cell lung cancer leading to the efficacy of anti-PD-L1 antibody and chemotherapy. *Lung Cancer.* 2023;179:107183.
 70. Thomas A, Vilimas R, Trindade C, Erwin-Cohen R, Roper N, Xi L, et al. Durvalumab in combination with olaparib in patients with relapsed SCLC: results from a phase II study. *J Thorac Oncol.* 2019;14(8):1447–57.
 71. Pasetto G, Lorenzi M, Tosi A, Roma A, Pavan A, Scapinello A, et al. 164P Immune cells distribution and spatial relationship within microenvironment as predictive biomarkers of benefit in extended stage small cell lung cancer patients receiving atezolizumab plus carboplatin and etoposide as first-line treatment. *J Thorac Oncol.* 2023;18(4):S130–1.
 72. Kanemura H, Hayashi H, Tomida S, Tanizaki J, Suzuki S, Kawanaka Y, et al. The tumor immune microenvironment and frameshift neoantigen load determine response to PD-L1 blockade in extensive-stage SCLC. *JTO Clin Res Rep.* 2022;3(8):100373.
 73. Sakaguchi S, Miyara M, Costantino CM, Hafler DA. FOXP3+ regulatory T cells in the human immune system. *Nat Rev Immunol.* 2010;10(7):490–500.
 74. Miyara M, Yoshioka Y, Kitoh A, Shima T, Wing K, Niwa A, et al. Functional delineation and differentiation dynamics of human CD4+ T cells expressing the FoxP3 transcription factor. *Immunity.* 2009;30(6):899–911.
 75. Jiang M, Wu C, Zhang L, Sun C, Wang H, Xu Y, et al. FOXP3-based immune risk model for recurrence prediction in small-cell lung cancer at stages I–III. *J Immunother Cancer.* 2021;9(5):e002339.
 76. Bonanno L, Pavan A, Dieci MV, Di Liso E, Schiavon M, Comacchio G, et al. The role of immune microenvironment in small-cell lung cancer: distribution of PD-L1 expression and prognostic role of FOXP3-positive tumour infiltrating lymphocytes. *Eur J Cancer.* 2018;101:191–200.
 77. Garrido-Martin EM, Mellows TWP, Clarke J, Ganesan AP, Wood O, Cazaly A, et al. M1(hot) tumor-associated macrophages boost tissue-resident memory T cells infiltration and survival in human lung cancer. *J Immunother Cancer.* 2020;8(2):e000778.
 78. Loyher PL, Hamon P, Laviron M, Meghraoui-Kheddar A, Goncalves E, Deng Z, et al. Macrophages of distinct origins contribute to tumor development in the lung. *J Exp Med.* 2018;215(10):2536–53.
 79. Wanderley CW, Colón DF, Luiz JPM, Oliveira FF, Viacava PR, Leite CA, et al. Paclitaxel reduces tumor growth by reprogramming tumor-associated macrophages to an M1 profile in a TLR4-dependent manner. *Cancer Res.* 2018;78(20):5891–900.
 80. Cassetta L, Fragkogianni S, Sims AH, Swierczak A, Forrester LM, Zhang H, et al. Human tumor-associated macrophage and monocyte transcriptional landscapes reveal cancer-specific reprogramming, biomarkers, and therapeutic targets. *Cancer Cell.* 2019;35(4):588–602.e10.
 81. Ginhoux F, Guilliams M. Tissue-resident macrophage ontogeny and homeostasis. *Immunity.* 2016;44(3):439–49.
 82. Welsh TJ, Green RH, Richardson D, Waller DA, O'Byrne KJ, Bradding P. Macrophage and mast-cell invasion of tumor cell islets confers a marked survival advantage in non-small-cell lung cancer. *J Clin Oncol.* 2005;23(35):8959–67.
 83. Forssell J, Oberg A, Henriksson ML, Stenling R, Jung A, Palmqvist R. High macrophage infiltration along the tumor front correlates with improved survival in colon cancer. *Clin Cancer Res.* 2007;13(5):1472–9.
 84. Shimura S, Yang G, Ebara S, Wheeler TM, Frolov A, Thompson TC. Reduced infiltration of tumor-associated macrophages in human prostate cancer: association with cancer progression. *Cancer Res.* 2000;60(20):5857–61.
 85. Eerola AK, Soini Y, Pääkkö P. A high number of tumor-infiltrating lymphocytes are associated with a small tumor size, low tumor stage, and a favorable prognosis in operated small cell lung carcinoma. *Clin Cancer Res.* 2000;6(5):1875–81.
 86. Muppa P, Parrilha Terra SBS, Sharma A, Mansfield AS, Aubry MC, Bhinge K, et al. Immune cell infiltration may be a key determinant of long-term survival in small cell lung cancer. *J Thorac Oncol.* 2019;14(7):1286–95.
 87. Ozga AJ, Chow MT, Luster AD. Chemokines and the immune response to cancer. *Immunity.* 2021;54(5):859–74.
 88. Crespo J, Sun H, Welling TH, Tian Z, Zou W. T cell anergy, exhaustion, senescence, and stemness in the tumor microenvironment. *Curr Opin Immunol.* 2013;25(2):214–21.
 89. Zou W, Wolchok JD, Chen L. PD-L1 (B7–H1) and PD-1 pathway blockade for cancer therapy: mechanisms, response biomarkers, and combinations. *Sci Transl Med.* 2016;8(328):328rv4.
 90. Yamaguchi M, Takagi K, Narita K, Miki Y, Onodera Y, Miyashita M, et al. Stromal CCL5 promotes breast cancer progression by interacting with CCR3 in tumor cells. *Int J Mol Sci.* 2021;22(4):1918.
 91. Chen D, Bao X, Zhang R, Ding Y, Zhang M, Li B, et al. Depiction of the genomic and genetic landscape identifies CCL5 as a protective factor in colorectal neuroendocrine carcinoma. *Br J Cancer.* 2021;125(7):994–1002.
 92. Tang Y, Hu Y, Niu Y, Sun L, Guo L. CCL5 as a prognostic marker for survival and an indicator for immune checkpoint therapies in small cell lung cancer. *Front Med.* 2022;9:834725.
 93. Oliveira CC, van Hall T. Alternative antigen processing for MHC class I: multiple roads lead to rome. *Front Immunol.* 2015;6:298.
 94. Yang K, Halima A, Chan TA. Antigen presentation in cancer—mechanisms and clinical implications for immunotherapy. *Nat Rev Clin Oncol.* 2023;20(9):604–23.
 95. Burr ML, Sparbier CE, Chan KL, Chan YC, Kersbergen A, Lam EYN, et al. An evolutionarily conserved function of polycomb silences the MHC class I antigen presentation pathway and enables immune evasion in cancer. *Cancer Cell.* 2019;36(4):385–401.e8.
 96. Restifo NP, Esquivel F, Kawakami Y, Yewdell JW, Mulé JJ, Rosenberg SA, et al. Identification of human cancers deficient in antigen processing. *J Exp Med.* 1993;177(2):265–72.
 97. Mahadevan NR, Knelson EH, Wolff JO, Vajdi A, Saigi M, Campisi M, et al. Intrinsic immunogenicity of small cell lung carcinoma revealed by its cellular plasticity. *Cancer Discov.* 2021;11(8):1952–69.
 98. Nguyen EM, Taniguchi H, Chan JM, Zhan YA, Chen X, Qiu J, et al. Targeting lysine-specific demethylase 1 rescues major histocompatibility complex class I antigen presentation and overcomes programmed

- death-ligand 1 blockade resistance in SCLC. *J Thorac Oncol.* 2022;17(8):1014–31.
99. Marty Pyke R, Thompson WK, Salem RM, Font-Burgada J, Zanetti M, Carter H. Evolutionary pressure against MHC class II binding cancer mutations. *Cell.* 2018;175(7):1991.
 100. Reith W, LeibundGut-Landmann S, Waldburger JM. Regulation of MHC class II gene expression by the class II transactivator. *Nat Rev Immunol.* 2005;5(10):793–806.
 101. van den Hoorn T, Paul P, Jongsma ML, Neeffjes J. Routes to manipulate MHC class II antigen presentation. *Curr Opin Immunol.* 2011;23(1):88–95.
 102. Zagzag D, Salnikow K, Chiriboga L, Yee H, Lan L, Ali MA, et al. Down-regulation of major histocompatibility complex antigens in invading glioma cells: stealth invasion of the brain. *Lab Invest.* 2005;85(3):328–41.
 103. He Y, Rozeboom L, Rivard CJ, Ellison K, Dziadziszko R, Yu H, et al. MHC class II expression in lung cancer. *Lung Cancer.* 2017;112:75–80.
 104. Chen P, Zhao L, Wang H, Zhang L, Zhang W, Zhu J, et al. Human leukocyte antigen class II-based immune risk model for recurrence evaluation in stage I-III small cell lung cancer. *J Immunother Cancer.* 2021;9(8):e002554.
 105. Garassino MC, Shrestha Y, Xie M, Lai Z, Spencer S, Dalvi T, et al. MA16.06 durvalumab ± tremelimumab + platinum-etoposide in 1L ES-SCLC: exploratory analysis of HLA genotype and survival in CASPIAN. *J Thorac Oncol.* 2021;16(10):939.
 106. Rudin CM, Brambilla E, Faivre-Finn C, Sage J. Small-cell lung cancer. *Nat Rev Dis Primers.* 2021;7(1):3.
 107. Rudin CM, Poirier JT, Byers LA, Dive C, Dowlati A, George J, et al. Molecular subtypes of small cell lung cancer: a synthesis of human and mouse model data. *Nat Rev Cancer.* 2019;19(5):289–97.
 108. Rudin CM, Poirier JT, Byers LA, Dive C, Dowlati A, George J, et al. Author Correction: molecular subtypes of small cell lung cancer: a synthesis of human and mouse model data. *Nat Rev Cancer.* 2019;19(7):415.
 109. Baine MK, Hsieh MS, Lai WV, Egger JV, Jungbluth AA, Daneshbod Y, et al. SCLC subtypes defined by ASCL1, NEUROD1, POU2F3, and YAP1: a comprehensive immunohistochemical and histopathologic characterization. *J Thorac Oncol.* 2020;15(12):1823–35.
 110. Gay CM, Stewart CA, Park EM, Diao L, Groves SM, Heeke S, et al. Patterns of transcription factor programs and immune pathway activation define four major subtypes of SCLC with distinct therapeutic vulnerabilities. *Cancer Cell.* 2021;39(3):346–60.e7.
 111. Liu SV, Mok TSK, Nabat BY, Mansfield AS, De Boer R, Losonczy G, et al. Clinical and molecular characterization of long-term survivors with extensive-stage small cell lung cancer treated with first-line atezolizumab plus carboplatin and etoposide. *Lung Cancer.* 2023;186:107418.
 112. Ayers M, Lunceford J, Nebozhyn M, Murphy E, Loboda A, Kaufman DR, et al. IFN- γ -related mRNA profile predicts clinical response to PD-1 blockade. *J Clin Invest.* 2017;127(8):2930–40.
 113. Ott PA, Bang YJ, Piha-Paul SA, Razak ARA, Bennouna J, Soria JC, et al. T-cell-inflamed gene-expression profile, programmed death ligand 1 expression, and tumor mutational burden predict efficacy in patients treated with pembrolizumab across 20 cancers: KEYNOTE-028. *J Clin Oncol.* 2019;37(4):318–27.
 114. Febres-Aldana CA, Chang JC, Ptashkin R, Wang Y, Gedvilaite E, Baine MK, et al. Rb tumor suppressor in small cell lung cancer: combined genomic and IHC analysis with a description of a distinct Rb-proficient subset. *Clin Cancer Res.* 2022;28(21):4702–13.
 115. Markey MP, Bergseid J, Bosco EE, Stengel K, Xu H, Mayhew CN, et al. Loss of the retinoblastoma tumor suppressor: differential action on transcriptional programs related to cell cycle control and immune function. *Oncogene.* 2007;26(43):6307–18.
 116. Rivadeneira DB, Mayhew CN, Thangavel C, Sotillo E, Reed CA, Graña X, et al. Proliferative suppression by CDK4/6 inhibition: complex function of the retinoblastoma pathway in liver tissue and hepatoma cells. *Gastroenterology.* 2010;138(5):1920–30.
 117. Dowlati A, Abbas A, Chan T, Henick B, Wang X, Doshi P, et al. Immune checkpoint blockade outcome in small-cell lung cancer and its relationship with retinoblastoma mutation status and function. *JCO Precis Oncol.* 2022;6:e2200257.
 118. Russano M, Napolitano A, Ribelli G, Iuliani M, Simonetti S, Citarella F, et al. Liquid biopsy and tumor heterogeneity in metastatic solid tumors: the potentiality of blood samples. *J Exp Clin Cancer Res.* 2020;39(1):95.
 119. Pantel K, Alix-Panabières C. Real-time liquid biopsy in cancer patients: fact or fiction? *Cancer Res.* 2013;73(21):6384–8.
 120. Lone SN, Nisar S, Masoodi T, Singh M, Rizwan A, Hashem S, et al. Liquid biopsy: a step closer to transform diagnosis, prognosis and future of cancer treatments. *Mol Cancer.* 2022;21(1):79.
 121. Bettegowda C, Sausen M, Leary RJ, Kinde I, Wang Y, Agrawal N, et al. Detection of circulating tumor DNA in early- and late-stage human malignancies. *Sci Transl Med.* 2014;6(224):224ra24.
 122. Campos-Carrillo A, Weitzel JN, Sahoo P, Rockne R, Mokhnatkun JV, Murtaza M, et al. Circulating tumor DNA as an early cancer detection tool. *Pharmacol Ther.* 2020;207:107458.
 123. Luo H, Zhao Q, Wei W, Zheng L, Yi S, Li G, et al. Circulating tumor DNA methylation profiles enable early diagnosis, prognosis prediction, and screening for colorectal cancer. *Sci Transl Med.* 2020;12(524):eaax7533.
 124. Parkinson CA, Gale D, Piskorz AM, Biggs H, Hodgkin C, Addley H, et al. Exploratory analysis of TP53 mutations in circulating tumour DNA as biomarkers of treatment response for patients with relapsed high-grade serous ovarian carcinoma: a retrospective study. *PLoS Med.* 2016;13(12):e1002198.
 125. Tie J, Kinde I, Wang Y, Wong HL, Roebert J, Christie M, et al. Circulating tumor DNA as an early marker of therapeutic response in patients with metastatic colorectal cancer. *Ann Oncol.* 2015;26(8):1715–22.
 126. Chaudhuri AA, Chabon JJ, Lovejoy AF, Newsum AM, Stehr H, Azad TD, et al. Early detection of molecular residual disease in localized lung cancer by circulating tumor DNA profiling. *Cancer Discov.* 2017;7(12):1394–403.
 127. Alix-Panabières C, Pantel K. Clinical applications of circulating tumor cells and circulating tumor DNA as liquid biopsy. *Cancer Discov.* 2016;6(5):479–91.
 128. Abbosh C, Birkbak NJ, Swanton C. Early stage NSCLC—challenges to implementing ctDNA-based screening and MRD detection. *Nat Rev Clin Oncol.* 2018;15(9):577–86.
 129. Mohan S, Foy V, Ayub M, Leong HS, Schofield P, Sahoo S, et al. Profiling of circulating free DNA using targeted and genome-wide sequencing in patients with SCLC. *J Thorac Oncol.* 2020;15(2):216–30.
 130. Almodovar K, Iams WT, Meador CB, Zhao Z, York S, Horn L, et al. Longitudinal cell-free DNA analysis in patients with small cell lung cancer reveals dynamic insights into treatment efficacy and disease relapse. *J Thorac Oncol.* 2018;13(11):112–23.
 131. Gonzalez R, Silva JM, Sanchez A, Dominguez G, Garcia JM, Chen XQ, et al. Microsatellite alterations and TP53 mutations in plasma DNA of small-cell lung cancer patients: follow-up study and prognostic significance. *Ann Oncol.* 2000;11(9):1097–104.
 132. Herbreteau G, Langlais A, Greillier L, Audigier-Valette C, Uwer L, Hureau J, et al. Circulating tumor DNA as a prognostic determinant in small cell lung cancer patients receiving atezolizumab. *J Clin Med.* 2020;9(12):3861.
 133. Sivapalan L, Iams WT, Belcaid Z, Scott SC, Niknafs N, Balan A, et al. Dynamics of sequence and structural cell-free DNA landscapes in small-cell lung cancer. *Clin Cancer Res.* 2023;29(12):2310–23.
 134. Pellini B, Chaudhuri AA. ctDNA monitoring for small cell lung cancer: ready for prime time? *Clin Cancer Res.* 2023;29(12):2176–8.
 135. Crowley E, Di Nicolantonio F, Loupakis F, Bardelli A. Liquid biopsy: monitoring cancer-genetics in the blood. *Nat Rev Clin Oncol.* 2013;10(8):472–84.
 136. Cristofanilli M, Budd GT, Ellis MJ, Stopeck A, Matera J, Miller MC, et al. Circulating tumor cells, disease progression, and survival in metastatic breast cancer. *N Engl J Med.* 2004;351(8):781–91.
 137. Cristofanilli M, Hayes DF, Budd GT, Ellis MJ, Stopeck A, Reuben JM, et al. Circulating tumor cells: a novel prognostic factor for newly diagnosed metastatic breast cancer. *J Clin Oncol.* 2005;23(7):1420–30.
 138. Bidard FC, Peeters DJ, Fehm T, Nolé F, Gisbert-Criado R, Mavroudis D, et al. Clinical validity of circulating tumour cells in patients with metastatic breast cancer: a pooled analysis of individual patient data. *Lancet Oncol.* 2014;15(4):406–14.
 139. Krebs MG, Sloane R, Priest L, Lancashire L, Hou JM, Greystoke A, et al. Evaluation and prognostic significance of circulating tumor cells in patients with non-small-cell lung cancer. *J Clin Oncol.* 2011;29(12):1556–63.

140. Lindsay CR, Blackhall FH, Carmel A, Fernandez-Gutierrez F, Gazzaniga P, Groen HJM, et al. EPAC-lung: pooled analysis of circulating tumour cells in advanced non-small cell lung cancer. *Eur J Cancer*. 2019;117:60–8.
141. Miyamoto DT, Lee RJ, Kalinich M, LiCausi JA, Zheng Y, Chen T, et al. An RNA-based digital circulating tumor cell signature is predictive of drug response and early dissemination in prostate cancer. *Cancer Discov*. 2018;8(3):288–303.
142. Scher HI, Lu D, Schreiber NA, Louw J, Graf RP, Vargas HA, et al. Association of AR-V7 on circulating tumor cells as a treatment-specific biomarker with outcomes and survival in castration-resistant prostate cancer. *JAMA Oncol*. 2016;2(11):1441–9.
143. Huang X, Gao P, Song Y, Sun J, Chen X, Zhao J, et al. Meta-analysis of the prognostic value of circulating tumor cells detected with the cell search system in colorectal cancer. *BMC Cancer*. 2015;15:202.
144. Veyrone L, Naumann DN, Christou N. Circulating tumour cells as prognostic biomarkers in colorectal cancer: a systematic review. *Int J Mol Sci*. 2021;22(8):3437.
145. Hou JM, Greystoke A, Lancashire L, Cummings J, Ward T, Board R, et al. Evaluation of circulating tumor cells and serological cell death biomarkers in small cell lung cancer patients undergoing chemotherapy. *Am J Pathol*. 2009;175(2):808–16.
146. Hiltermann TJN, Pore MM, van den Berg A, Timens W, Boezen HM, Liesker JJW, et al. Circulating tumor cells in small-cell lung cancer: a predictive and prognostic factor. *Ann Oncol*. 2012;23(11):2937–42.
147. Hou JM, Krebs MG, Lancashire L, Sloane R, Backen A, Swain RK, et al. Clinical significance and molecular characteristics of circulating tumor cells and circulating tumor microemboli in patients with small-cell lung cancer. *J Clin Oncol*. 2012;30(5):525–32.
148. Naito T, Tanaka F, Ono A, Yoneda K, Takahashi T, Murakami H, et al. Prognostic impact of circulating tumor cells in patients with small cell lung cancer. *J Thorac Oncol*. 2012;7(3):512–9.
149. Messaritakis I, Nikolaou M, Politaki E, Koinis F, Lagoudaki E, Koutsopoulos A, et al. Bcl-2 expression in circulating tumor cells (CTCs) of patients with small cell lung cancer (SCLC) receiving front-line treatment. *Lung Cancer*. 2018;124:270–8.
150. Aggarwal C, Wang X, Ranganathan A, Torigian D, Troxel A, Evans T, et al. Circulating tumor cells as a predictive biomarker in patients with small cell lung cancer undergoing chemotherapy. *Lung Cancer*. 2017;112:118–25.
151. Wang PP, Liu SH, Chen CT, Lv L, Li D, Liu QY, et al. Circulating tumor cells as a new predictive and prognostic factor in patients with small cell lung cancer. *J Cancer*. 2020;11(8):2113–22.
152. Hodgkinson CL, Morrow CJ, Li Y, Metcalf RL, Rothwell DG, Trapani F, et al. Tumorigenicity and genetic profiling of circulating tumor cells in small-cell lung cancer. *Nat Med*. 2014;20(8):897–903.
153. Messaritakis I, Politaki E, Kotsakis A, Dermitzaki EK, Koinis F, Lagoudaki E, et al. Phenotypic characterization of circulating tumor cells in the peripheral blood of patients with small cell lung cancer. *PLoS ONE*. 2017;12(7):e0181211.
154. Normanno N, Rossi A, Morabito A, Signoriello S, Bevilacqua S, Di Maio M, et al. Prognostic value of circulating tumor cells' reduction in patients with extensive small-cell lung cancer. *Lung Cancer*. 2014;85(2):314–9.
155. Ni X, Zhuo M, Su Z, Duan J, Gao Y, Wang Z, et al. Reproducible copy number variation patterns among single circulating tumor cells of lung cancer patients. *Proc Natl Acad Sci USA*. 2013;110(52):21083–8.
156. Carter L, Rothwell DG, Mesquita B, Smowton C, Leong HS, Fernandez-Gutierrez F, et al. Molecular analysis of circulating tumor cells identifies distinct copy-number profiles in patients with chemosensitive and chemorefractory small-cell lung cancer. *Nat Med*. 2017;23(1):114–9.
157. Su Z, Wang Z, Ni X, Duan J, Gao Y, Zhuo M, et al. Inferring the evolution and progression of small-cell lung cancer by single-cell sequencing of circulating tumor cells. *Clin Cancer Res*. 2019;25(16):5049–60.
158. Lallo A, Gulati S, Schenk MW, Khandelwal G, Berglund UW, Pateras IS, et al. Ex vivo culture of cells derived from circulating tumour cell xenograft to support small cell lung cancer research and experimental therapeutics. *Br J Pharmacol*. 2019;176(3):436–50.
159. Berraondo P, Sanmamed MF, Ochoa MC, Etxeberria I, Aznar MA, Pérez-Gracia JL, et al. Cytokines in clinical cancer immunotherapy. *Br J Cancer*. 2019;120(1):6–15.
160. Propper DJ, Balkwill FR. Harnessing cytokines and chemokines for cancer therapy. *Nat Rev Clin Oncol*. 2022;19(4):237–53.
161. Keegan A, Ricciuti B, Garden P, Cohen L, Nishihara R, Adeni A, et al. Plasma IL-6 changes correlate to PD-1 inhibitor responses in NSCLC. *J Immunother Cancer*. 2020;8(2):e000678.
162. Sanmamed MF, Perez-Gracia JL, Schalper KA, Fusco JP, Gonzalez A, Rodriguez-Ruiz ME, et al. Changes in serum interleukin-8 (IL-8) levels reflect and predict response to anti-PD-1 treatment in melanoma and non-small-cell lung cancer patients. *Ann Oncol*. 2017;28(8):1988–95.
163. Yuen KC, Liu LF, Gupta V, Madireddi S, Keerthivasan S, Li C, et al. High systemic and tumor-associated IL-8 correlates with reduced clinical benefit of PD-L1 blockade. *Nat Med*. 2020;26(5):693–8.
164. Tarhini AA, Zahoor H, Lin Y, Malhotra U, Sander C, Butterfield LH, et al. Baseline circulating IL-17 predicts toxicity while TGF- β 1 and IL-10 are prognostic of relapse in ipilimumab neoadjuvant therapy of melanoma. *J Immunother Cancer*. 2015;3:39.
165. Giunta EF, Barra G, De Falco V, Argenziano G, Napolitano S, Vitale P, et al. Baseline IFN- γ and IL-10 expression in PBMCs could predict response to PD-1 checkpoint inhibitors in advanced melanoma patients. *Sci Rep*. 2020;10(1):17626.
166. Hardy-Werbin M, Rocha P, Arpi O, Taus Á, Nonell L, Durán X, et al. Serum cytokine levels as predictive biomarkers of benefit from ipilimumab in small cell lung cancer. *Oncoimmunology*. 2019;8(6):e1593810.
167. Darnell RB, Posner JB. Paraneoplastic syndromes involving the nervous system. *N Engl J Med*. 2003;349(16):1543–54.
168. Graus F, Keime-Guibert F, Reñe R, Benyahia B, Ribalta T, Ascaso C, et al. Anti-Hu-associated paraneoplastic encephalomyelitis: analysis of 200 patients. *Brain*. 2001;124(Pt 6):1138–48.
169. Graus F, Delattre JY, Antoine JC, Dalmau J, Giometto B, Grisold W, et al. Recommended diagnostic criteria for paraneoplastic neurological syndromes. *J Neurol Neurosurg Psychiatry*. 2004;75(8):1135–40.
170. Titulaer MJ, Klooster R, Potman M, Sabater L, Graus F, Hegeman IM, et al. SOX antibodies in small-cell lung cancer and Lambert-Eaton myasthenic syndrome: frequency and relation with survival. *J Clin Oncol*. 2009;27(26):4260–7.
171. Gozzard P, Woodhall M, Chapman C, Nibber A, Waters P, Vincent A, et al. Paraneoplastic neurologic disorders in small cell lung carcinoma: a prospective study. *Neurology*. 2015;85(3):235–9.
172. Sodeyama N, Ishida K, Jaeckle KA, Zhang L, Azuma A, Yamada M, et al. Pattern of epitopic reactivity of the anti-Hu antibody on HuD with and without paraneoplastic syndrome. *J Neurol Neurosurg Psychiatry*. 1999;66(1):97–9.
173. Maddison P, Newsom-Davis J, Mills KR, Souhami RL. Favourable prognosis in Lambert-Eaton myasthenic syndrome and small-cell lung carcinoma. *Lancet*. 1999;353(9147):117–8.
174. Maddison P, Gozzard P, Grainge MJ, Lang B. Long-term survival in paraneoplastic Lambert-Eaton myasthenic syndrome. *Neurology*. 2017;88(14):1334–9.
175. Gozzard P, Chapman C, Vincent A, Lang B, Maddison P. Novel humoral prognostic markers in small-cell lung carcinoma: a prospective study. *PLoS ONE*. 2015;10(11):e0143558.
176. Graus F, Dalmau J, Reñe R, Tora M, Malats N, Verschuuren JJ, et al. Anti-Hu antibodies in patients with small-cell lung cancer: association with complete response to therapy and improved survival. *J Clin Oncol*. 1997;15(8):2866–72.
177. Monstad SE, Drivsholm L, Storstein A, Aarseth JH, Haugen M, Lang B, et al. Hu and voltage-gated calcium channel (VGCC) antibodies related to the prognosis of small-cell lung cancer. *J Clin Oncol*. 2004;22(5):795–800.
178. Iams WT, Shiuan E, Meador CB, Roth M, Bordeaux J, Vaupel C, et al. Improved prognosis and increased tumor-infiltrating lymphocytes in patients who have SCLC with neurologic paraneoplastic syndromes. *J Thorac Oncol*. 2019;14(11):1970–81.
179. Chen DS, Mellman I. Oncology meets immunology: the cancer-immunity cycle. *Immunity*. 2013;39(1):1–10.
180. Mammen AL, Rajan A, Pak K, Lehky T, Casciola-Rosen L, Donahue RN, et al. Pre-existing antiacetylcholine receptor autoantibodies and B cell lymphopenia are associated with the development of myositis in patients with thymoma treated with avelumab, an immune checkpoint inhibitor targeting programmed death-ligand 1. *Ann Rheum Dis*. 2019;78(1):150–2.
181. Arriola E, Wheeler M, Galea I, Cross N, Maishman T, Hamid D, et al. Outcome and biomarker analysis from a multicenter phase 2 study of

- ipilimumab in combination with carboplatin and etoposide as first-line therapy for extensive-stage SCLC. *J Thorac Oncol.* 2016;11(9):1511–21.
182. Hardy-Werbin M, Arpi O, Taus A, Rocha P, Joseph-Pietras D, Nolan L, et al. Assessment of neuronal autoantibodies in patients with small cell lung cancer treated with chemotherapy with or without ipilimumab. *Oncoimmunology.* 2018;7(2): e1395125.
 183. Saccalan DB, Lucero JA, Saccalan DL. Prognostic utility of baseline neutrophil-to-lymphocyte ratio in patients receiving immune checkpoint inhibitors: a review and meta-analysis. *Onco Targets Ther.* 2018;11:955–65.
 184. Ameratunga M, Chénard-Poirier M, Moreno Candilejo I, Pedregal M, Lui A, Dolling D, et al. Neutrophil-lymphocyte ratio kinetics in patients with advanced solid tumours on phase I trials of PD-1/PD-L1 inhibitors. *Eur J Cancer.* 2018;89:56–63.
 185. Qi Y, Liao D, Fu X, Gao Q, Zhang Y. Elevated platelet-to-lymphocyte corresponds with poor outcome in patients with advanced cancer receiving anti-PD-1 therapy. *Int Immunopharmacol.* 2019;74:105707.
 186. Mezquita L, Auclin E, Ferrara R, Charrier M, Remon J, Planchard D, et al. Association of the lung immune prognostic index with immune checkpoint inhibitor outcomes in patients with advanced non-small cell lung cancer. *JAMA Oncol.* 2018;4(3):351–7.
 187. Ferrucci PF, Ascierto PA, Pigozzo J, Del Vecchio M, Maio M, Antonini CapPELLINI GC, et al. Baseline neutrophils and derived neutrophil-to-lymphocyte ratio: prognostic relevance in metastatic melanoma patients receiving ipilimumab. *Ann Oncol.* 2018;29(2):524.
 188. Diem S, Kasenda B, Spain L, Martin-Liberal J, Marconcini R, Gore M, et al. Serum lactate dehydrogenase as an early marker for outcome in patients treated with anti-PD-1 therapy in metastatic melanoma. *Br J Cancer.* 2016;114(3):256–61.
 189. Xie D, Marks R, Zhang M, Jiang G, Jatoi A, Garces YI, et al. Nomograms predict overall survival for patients with small-cell lung cancer incorporating pretreatment peripheral blood markers. *J Thorac Oncol.* 2015;10(8):1213–20.
 190. Sonehara K, Tateishi K, Komatsu M, Yamamoto H, Hanaoka M. Lung immune prognostic index as a prognostic factor in patients with small cell lung cancer. *Thorac Cancer.* 2020;11(6):1578–86.
 191. Qi W, Zhao S, Chen J. Prognostic role of pretreatment lung immune prognostic index in extensive-stage small-cell lung cancer treated with platinum plus etoposide chemotherapy. *Cancer Biomark.* 2021;31(2):177–85.
 192. Xiong Q, Huang Z, Xin L, Qin B, Zhao X, Zhang J, et al. Post-treatment neutrophil-to-lymphocyte ratio (NLR) predicts response to anti-PD-1/PD-L1 antibody in SCLC patients at early phase. *Cancer Immunol Immunother.* 2021;70(3):713–20.
 193. Riemann D, Turzer S, Ganchev G, Schütte W, Seliger B, Möller M. Monitoring blood immune cells in patients with advanced small cell lung cancer undergoing a combined immune checkpoint inhibitor/chemotherapy. *Biomolecules.* 2023;13(2):190.
 194. Stratmann JA, Timalisina R, Atmaca A, Rosery V, Frost N, Alt J, et al. Clinical predictors of survival in patients with relapsed/refractory small-cell lung cancer treated with checkpoint inhibitors: a German multicentric real-world analysis. *Ther Adv Med Oncol.* 2022;14:17588359221097192.
 195. Li L, Pi C, Yan X, Lu J, Yang X, Wang C, et al. Prognostic value of the pretreatment lung immune prognostic index in advanced small cell lung cancer patients treated with first-line PD-1/PD-L1 inhibitors plus chemotherapy. *Front Oncol.* 2021;11:697865.
 196. Chae YK, Davis AA, Agte S, Pan A, Simon NI, Iams WT, et al. Clinical implications of circulating tumor dna tumor mutational burden (ctDNA TMB) in non-small cell lung cancer. *Oncologist.* 2019;24(6):820–8.
 197. Gandara DR, Paul SM, Kowanetz M, Schleifman E, Zou W, Li Y, et al. Blood-based tumor mutational burden as a predictor of clinical benefit in non-small-cell lung cancer patients treated with atezolizumab. *Nat Med.* 2018;24(9):1441–8.
 198. Wang Z, Duan J, Cai S, Han M, Dong H, Zhao J, et al. Assessment of blood tumor mutational burden as a potential biomarker for immunotherapy in patients with non-small cell lung cancer with use of a next-generation sequencing cancer gene panel. *JAMA Oncol.* 2019;5(5):696–702.
 199. Nie W, Wang ZJ, Zhang K, Li B, Cai YR, Wen FC, et al. ctDNA-adjusted bTMB as a predictive biomarker for patients with NSCLC treated with PD-(L)1 inhibitors. *BMC Med.* 2022;20(1):170.
 200. Kim ES, Velcheti V, Mekhail T, Yun C, Shagan SM, Hu S, et al. Blood-based tumor mutational burden as a biomarker for atezolizumab in non-small cell lung cancer: the phase 2 B-F1RST trial. *Nat Med.* 2022;28(5):939–45.

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