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First-Line Treatment for Advanced SCLC: What Is Left Behind and Beyond Chemoimmunotherapy

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Small cell lung cancer (SCLC) is still a lethal disease. Three phase III randomized clinical trials (IMpower133, CASPIAN, and KEYNOTE-604) have highlighted the survival gain of adding immune checkpoint inhibitors to first-line standard chemotherapy in advanced SCLC patients. In this review, we discuss the data from the three trials above. Furtherly, we analyze issues that still need to be elucidated, like the role of biomarkers, poor performance status at baseline, the presence of brain metastases, and the platinum compound's choice. Moreover, we depict the future of SCLC first-line therapy management, focusing on new therapeutic strategies currently under investigation.

Keywords: small cell lung cancer (SCLC), immunotherapy, chemotherapy, biomarkers, first-line therapy

INTRODUCTION

Small cell lung cancer (SCLC), representing <20% of all cases of lung cancer worldwide, is still a lethal disease, with an estimated 5-year overall survival (OS) of 7% (1). The extensive stage (ES), which means the tumor is not amenable to radical radiotherapy due to its extent, is characterized by the poorest prognosis. Systemic treatments for ES disease have been implemented over the years, starting with single-agent chemotherapy (CT) in the 1970s (2). A platinum-based doublet with either etoposide or irinotecan became first-line standard CT, with a similar efficacy (i.e., median OS of ~10 months) but a different safety profile (3).

At the end of 2010s, results from three phase III randomized clinical trials, the IMpower133 (4), CASPIAN (5), and KEYNOTE-604 (6), were published. These studies have demonstrated a significant improvement in OS by adding immune checkpoint inhibitors (ICIs) to CT, thus, opening a new era in treating advanced SCLC patients.

This review will analyze some relevant aspects of the three trials above. Furtherly, we will focus on some related still open issues like potential biomarkers, poor performance status (PS), brain metastases, and the platinum compound's choice. We will then discuss the new lines of research about the first-line treatment of advanced SCLC, depicting the future in this therapeutic scenario.

EVIDENCE ON FIRST-LINE CHEMOIMMUNOTHERAPY

IMpower133 is a double-blind, placebo-controlled, phase 3 trial where treatment naïve patients with ES-SCLC were randomly assigned (1:1 ratio) to receive carboplatin and etoposide with or without atezolizumab, an anti-PD-L1 antibody (4). After an induction phase consisting of four 21-day cycles, a maintenance phase with atezolizumab or placebo was offered

until disease progression or unacceptable toxicity. Main patients' characteristics are resumed in **Table 1**. Co-primary endpoints were progression-free survival (PFS) and OS. Median PFS was 5.2 months [95% confidence interval (CI): 4.4–5.6] and 4.3 months (95% CI: 4.2–4.5) in the experimental and control arm, respectively ($p = 0.02$), while median OS was 12.3 months (95% CI: 10.8–15.9) and 10.3 months (95% CI: 9.3–11.3) in the experimental and control arm, respectively ($p = 0.007$). The objective response rate (ORR) among the two treatment groups was similar (60.2 vs. 64.4% in the experimental and control arm, respectively), as also the safety profile (4) (**Table 1**). The updated results with 22.9 months of median follow-up have confirmed a median OS of 12.3 and 10.3 months in the experimental and control arm, respectively (HR: 0.76, 95% CI: 0.60–0.95, $p = 0.0154$), with 34 and 21% of patients alive at 18 months in the two arms (7).

CASPIAN is an open-label phase 3 trial in which untreated patients with ES-SCLC were randomly assigned (1:1:1 ratio) to receive durvalumab (anti-PD-L1 drug) plus platinum-etoposide or tremelimumab (anti-CTLA-4 antibody) and platinum-etoposide, or platinum-etoposide alone (5). Patients in the CT control arm received up to six cycles of platinum-etoposide. The immunotherapy was administered as maintenance in the experimental arms after four cycles of concomitant chemoimmunotherapy until disease progression or unacceptable toxicity. In **Table 1**, the main patients' characteristics are reported for the control arm and durvalumab plus platinum-etoposide arm. Median OS, the primary study endpoint, was 13.0 months (95% CI: 11.5–14.8) with durvalumab plus platinum-etoposide vs. 10.3 months (9.3–11.2) with platinum-etoposide ($p = 0.0047$). Median PFS was similar between the same two arms (5.1 vs. 5.4 months, respectively), whilst investigator-assessed ORR was higher in durvalumab than control arm (79 vs. 70%, respectively). No relevant difference in adverse events was highlighted between the two arms except for a slightly higher incidence of neutropenia and anemia in the control arm (5) (**Table 1**). The updated results published in 2021 substantially confirmed the OS improvement after a median follow-up time of 25.1 months, being 12.9 and 10.5 months in the experimental and control arm, respectively (HR: 0.75, 95% CI 0.62–0.91, $p = 0.0032$) (8). Notably, the addition of tremelimumab to durvalumab and platinum-based chemotherapy did not show a significant improvement in OS vs. platinum–etoposide, with a median OS of 10.4 months (95% CI: 9.6–12.0) vs. 10.5 months (9.3–11.2), respectively, but increased serious adverse events and treatment-related deaths (PMID: 33285097).

KEYNOTE-604 is a double-blind, placebo-controlled, phase 3 trial where untreated patients with ES-SCLC were randomly assigned (1:1 ratio) to receive platinum-etoposide with or without pembrolizumab, an anti-PD-1 antibody (6). The main patients' characteristics are resumed in **Table 1**. PFS and OS were the two primary endpoints of this study. The median PFS was 4.5 months (95% CI: 4.3–5.4) and 4.3 months (95% CI: 4.2-−4.4) in the experimental and control arm, respectively ($p = 0.0023$), while the median OS was 10.8 months (CI 95%: 9.2–12.9) and 9.7 months (95% CI: 8.6–10.7), in the experimental and control arm, respectively ($p = 0.0164$). A higher ORR was recorded

in the experimental arm (70.6%) compared to the control arm (61.8%). The safety profile was similar between the two arms (**Table 1**).

POTENTIAL BIOMARKERS

Among those biomarkers that have been explored to predict the efficacy of anti-PD-(L)1 antibodies as cancer therapy, PD-L1 is undoubtedly the most studied (9). Patients with PD-L1 positive SCLC, defined by immunohistochemical staining in over 5% of tumor cells, showed better survival in a retrospective series (10). However, another work pointed out that tumoral cells from SCLC specimens were negative for PD-L1 expression, whilst it was expressed in macrophages and correlated with tumor-infiltrating lymphocytes (TILs) (11). The different assays used to detect PD-L1 expression have made the scenario more complex (12). In the IMpower133 trial, PD-L1 testing was not performed during screening for two main reasons: an expected high rate of inadequate samples and the previous results from the phase I trial that had not shown an association between SCLC response and PD-L1 expression (4, 13). Likewise, in the CASPIAN trial, PD-L1 testing was not required for enrollment (8); it was optionally tested in archival tissue as a part of an ancillary analysis (14), confirming the low rate of PD-L1 positive tumoral cells and the lack of prognostic value when investigated as a continuous variable. In the KEYNOTE-604 trial, PD-L1 was retrospectively assessed using the combined positive score (CPS), defined as the number of PD-L1-staining cells divided by the total number of viable tumor cells times 100 (6). This estimate was based on the previous phase II KEYNOTE-158 trial (15). Patients with CPS ≥ 1%, CPS < 1% and unknown were about 40, 40, and 20%, respectively. The subgroup analyses did not observe differences between CPS ≥ 1% and CPS < 1% groups in PFS and OS. An exploratory analysis from the IMpower133 trial has not shown a predicted OS and PFS difference by each PD-L1 IHC subgroup (7).

The tumor mutational burden (TMB), an indirect measure of the tumor's neoantigen load, has been deeply investigated as a potential biomarker for immunotherapy in human cancer (16). Concerning the SCLC, data from the Checkmate 032 trial, with nivolumab vs. nivolumab plus ipilimumab in pretreated patients, suggested a role for the TMB as a potential predictive biomarker, given the high tumor responses achieved by the combination therapy in patients with high TMB compared to nivolumab (17). Similarly, the TMB did not predict either OS or PFS by an exploratory analysis of the IMpower133 trial (7). The recent FDA's approval of pembrolizumab for patients with any cancer type characterized by ≥10 mutations/megabase (mut/Mb) who had progressed to one previous treatment line without a valid alternative option has raised several criticisms. Particularly for the SCLC, it seems unlikely that clinicians will offer pembrolizumab to their patients exclusively based on a high TMB (18–20).
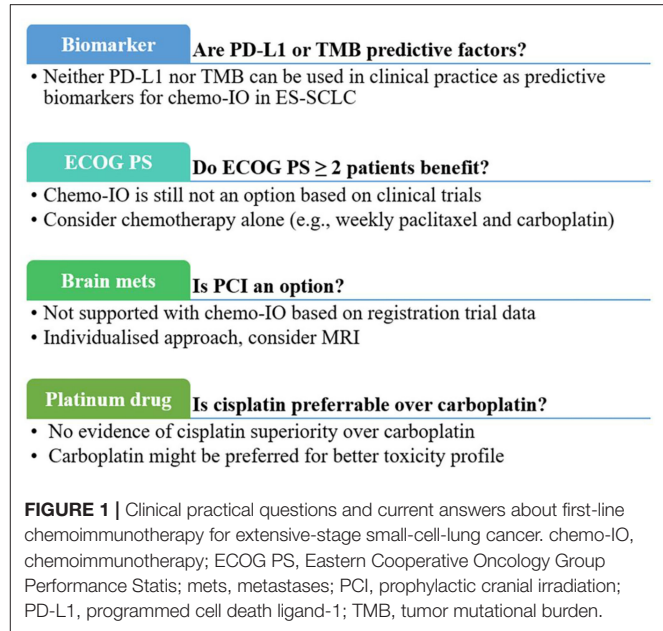
In conclusion, to date, neither PD-L1 nor TMB can be used in clinical practice as predictive biomarkers for ES-SCLC (**Figure 1**).

TABLE 1 | Main characteristics of enrolled patients in the phase III clinical trials Impower133, CASPIAN, and KEYNOTE-604.

Trial	IMpower133 (4)		CASPIAN (5)			KEYNOTE-604 (6)	
	Experimental arm	Control arm	Experimental arm1*	Experimental arm2*	Control arm	Experimental arm	Control arm
Therapy	CbE + atezolizumab	CbE + placebo	PE + durvalumab	PE + Durvalumab + Tremelimumab	PE	PE + pembrolizumab	PE + placebo
No of patients	201	202	268	268	269	228	225
PS				NR			
- 0	36.3%	33.2%	37%		33%	26.3%	24.9%
- 1	63.7%	66.8%	63%		67%	73.7%	75.1%
Brain metastases at baseline	8.5%	8.9%	10%	NR	10%	14.5%	9.8%
Platinum compound				NR			
- Cisplatin	0%	0%	78%		78%	27.9% (both arms)	
- Carboplatin	100%	100%	25%		25%	68.5% (both arms)	
PFS, median (range), mo.	5.2 (4.4–5.6)	4.3 (4.2–4.5)	5.1 (4.7–6.2)	NR	5.4 (4.8–6.2)	4.5 (4.3–5.4)	4.3 (4.2–4.4)
OS, median (range), mo.	12.3 (10.8–15.9)	10.3 (9.3–11.3)	13 (11.5–14.8)	NR	10.3 (9.3–11.2)	10.8 (9.2–12.9)	9.7 (8.6–10.7)
Grade ≥ 3 AEs	58.1%	57.6%	62%	NR	62%	76.7%	74.9%

AEs, adverse events; CbE, carboplatin + etoposide; mo, months; PE, cisplatin + etoposide; PFS, progression-free survival; NR, not reported; OS, overall survival; PS, performance status.
*Patients were allowed to switch between carboplatin and cisplatin at the investigator's discretion.

FIGURE 1 | Clinical practical questions and current answers about first-line chemoimmunotherapy for extensive-stage small-cell-lung cancer. chemo-IO, chemoimmunotherapy; ECOG PS, Eastern Cooperative Oncology Group Performance Statis; mets, metastases; PCI, prophylactic cranial irradiation; PD-L1, programmed cell death ligand-1; TMB, tumor mutational burden.

POOR PERFORMANCE STATUS AT BASELINE

One of the challenging issues in treating advanced SCLC patients is their deterioration of PS before starting first-line therapy. The NCCN guidelines suggest the exclusive use of supportive care when poor PS (≥2) is not due to SCLC. In contrast, the use of systemic therapy is not discouraged when poor PS is a consequence of SCLC (21); given the high chemosensitivity of SCLC, rapid response and symptomatic improvement with CT is expected, even if at the cost of higher toxicity than patients with good PS (22, 23). However, some specific situations may require a delay in systemic treatment start, like the presence of symptomatic brain metastases or epidural/cord compression. In these cases, a priority to radiotherapy (RT) is given (21).

Chemoimmunotherapy should not be offered to ES-SCLC patients with PS ≥2 as they were not enrolled in the three mentioned phase 3 trials (4–6). A single-arm phase 2 trial is currently recruiting PS 2 patients with ES-SCLC to investigate the impact on OS of adding atezolizumab to carboplatin-etoposide, adopting the schedule of the IMpower133 trial (NCT04221529). On the other hand, there are several reports about CT alone in patients with poor PS. A single-arm phase 2 clinical trial enrolled advanced SCLC patients with PS 2 or age ≥ 70 years, showing that the combination of weekly paclitaxel (80 mg/m^2) and carboplatin [area under the curve (AUC) 2], given on days 1, 8, 15 every 4-week cycle for up to six cycles, was feasible with few toxicities and led to a median OS of 7.2 months (24). A Japanese phase 3 randomized trial compared carboplatin plus etoposide with split doses of cisplatin plus etoposide in elderly or poor-risk SCLC patients (25). Eighteen and eight percent of enrolled patients were PS 2 and 3, respectively. Notably, PS 2-3 patients had a median OS of 8 months and PS 3

patients aged <70 years of 7 months, regardless of treatment allocation (25).

Similarly, in PS ≥ 2 non-small cell lung cancer (NSCLC) patients, the benefit of ICIs is still controversial. However, adopting frailty-assessing scales (26) or prognostic models, including the inflammatory indexes (27, 28), could assist clinical decisions. Likewise, those could be explored as helpful tools for PS2 SCLC patients (**Figure 1**).

BRAIN METASTASES IN THE CHEMOIMMUNOTHERAPY ERA

Another critical aspect in the clinical management of SCLC patients is relative to their high risk of developing synchronous or metachronous brain metastases (29). Brain metastases could be symptomatic or incidental lesions at the imaging, particularly at the contrast-enhanced magnetic resonance imaging (MRI), which is more sensitive than the computed tomography scan (CT scan) (30).

Prophylactic cranial irradiation (PCI) has been offered since the 1970s to reduce the intracranial failure rate following CT in SCLC patients (31). Two randomized clinical trials demonstrated that PCI minimizes the risk of developing symptomatic brain metastases after CT, although this did not translate into a statistically significant OS benefit (32, 33). The percentage of enrolled patients who received PCI in the IMpower133 and KEYNOTE-604 was 11 and 13%, respectively, whilst in the CASPIAN trial, PCI was allowed only in the control arm after completion of CT, and 8% of patients in this arm received it (4–6). Noteworthy, in the IMpower133 trial, time to intracranial progression was longer in patients receiving CT + atezolizumab vs. CT only (20.2 vs. 10.5 months, respectively), even though they did not receive PCI (16.7 vs. 9.8 months, respectively) (34). This evidence further questioned the role of PCI in the era of chemoimmunotherapy. Furthermore, the optimal timing of PCI (before or after the CT induction phase) and the subsequent follow-up schedule remain controversial.

Therefore, in the absence of robust data supporting PCI use in patients eligible for chemoimmunotherapy, an individualized approach should be pursued considering brain magnetic resonance imaging (MRI) follow-up as a valid alternative option (35).

Moreover, brain metastases at baseline were not an exclusion criterion for the three randomized trials (4–6), provided they were asymptomatic or treated and stable off steroids and anticonvulsants. It means we do not currently have data about chemoimmunotherapy in SCLC patients with active symptomatic brain metastases, which represents a considerable proportion of diagnosed patients and remains an unmet clinical need (**Figure 1**).

CHEMOTHERAPY BACKBONE: CISPLATIN OR CARBOPLATIN

Platinum compounds are the mainstay of chemotherapeutic regimens in SCLC patients. The COCIS meta-analysis halted the long debate about the best platinum compound for ES-SCLC, showing substantial equivalence in efficacy between carboplatin and cisplatin, albeit with different safety profiles (3). Nevertheless, in the chemoimmunotherapy era, the question reappeared. In the Impower133 trial, only carboplatin was allowed (4). In the other two trials, about one-quarter of enrolled patients received cisplatin (5, 6), reflecting the clinical practice of broader adoption of carboplatin. Subgroups analyses from the two trials showed a substantial similarity between the two drugs (5, 6). Therefore, carboplatin might be favored in this setting, considering the heavier side effects of cisplatin and the need for corticosteroids as antiemetic prophylaxis (**Figure 1**).

THE FUTURE OF FIRST-LINE THERAPY IN SCLC

Several ongoing trials are evaluating the addition of an anti-PD(L)1 agent to CT in the first-line setting (**Table 2**). However, what is new in this setting is the investigation of other molecules in addition to chemoimmunotherapy.

The role of neoangiogenesis in SCLC is well-established, with the vascular endothelial growth factor (VEGF) and its receptor (VEGFR) as the central molecular axis involved (36–38); a higher serum concentration of VEGF correlates with poor survival (39). Bevacizumab, a humanized anti-VEGF monoclonal antibody, did not prolong the survival of advanced SCLC patients when added to CT compared to CT alone (40, 41). Antiangiogenic tyrosine kinase inhibitors (TKIs), like sorafenib and vandetanib, failed to improve the survival of chemorefractory patients (42), although they are currently under evaluation in association with CT in the first-line setting (**Table 2**). In the latest years, combining immunotherapy and antiangiogenic agents has been explored as a therapeutic strategy in several cancer types based on the potential synergy between these two drug classes (43); the antiangiogenic drugs could promote T-cell infiltration in tumors and reduce immunosuppression, thus enhancing the effect of immunotherapy. To date, several clinical trials have been investigating the association of chemoimmunotherapy with antiangiogenic drugs in the first-line setting and the association of ICIs and antiangiogenic agents as maintenance therapy (**Table 2**). Notably, the AK112, a bispecific antibody against PD-1 and VEGF, is currently being investigated with carboplatin and etoposide in a phase I trial (NCT05116007).

Other novel drugs are currently being tested with chemoimmunotherapy in the first-line setting (23). New immunomodulatory agents under investigation could potentiate the effect of anti-PD-(L)1 antibodies though their effect on specific immune targets like: the LAG3, expressed on activated T and NK cells (44); TIGIT, upregulated by activated T cells and regulatory cells (45); ILT4, expressed in myeloid cells (46); CD27, involved in T cell proliferation and differentiation to memory and effector cells (47) (**Table 2**). Poly ADP-ribose polymerase inhibitors (PARPi) have been approved in ovarian cancer, prostate cancer and breast cancer

TABLE 2 | Ongoing clinical trials evaluating new combination strategies as first-line or maintenance therapy.

Setting	Chemotherapy	Investigational drug(s)	National clinical trial number
CT + anti-PD-(L)1			
First-line therapy	CbE	HLX10 (anti-PD-1)	NCT04063163
First-line therapy	PE	Toripalimab (anti-PD-1)	NCT04012606
First-line therapy	Paclitaxel-albumin + Carboplatin	Shr-1210 (anti-PD-1)	NCT04790539
First-line therapy	CbE	ZKAB001 (anti-PD-L1)	NCT04878016
First-line therapy	CbE	SHR-1316 (anti-PD-L1)	NCT03711305
First-line therapy	CbE	LP002 (anti-PD-L1)	NCT04740021
CT + anti-VEGF			
First-line therapy	PE	Anlotinib	NCT04675697
First-line therapy	PE	AL3810	NCT04254471
CT + anti-PD-(L)1 + anti-VEGF			
First-line therapy	PE	AK112 (Anti-PD-1 and VEGF Bispecific Antibody)	NCT05116007
First-line therapy	PE	Durvalumab + Anlotinib	NCT04660097
First-line therapy	PE	Toripalimab + Anlotinib	NCT04731909
First-line therapy	PE	Camrelizumab + Apatinib	NCT05001412
Maintenance therapy	No	Vorolanib + Atezolizumab	NCT04373369
Maintenance therapy	No	Camrelizumab + Apatinib	NCT04901754
Maintenance therapy	No	Tislelizumab + Anlotinib	NCT04620837
CT + Anti-PD-1 + other drugs			
First-line therapy	PE	Pembrolizumab + MK-4830 (anti-ILT4)	NCT04924101 (KEYNOTE-B99)
First-line therapy	PE	Pembrolizumab + MK-5890 (anti-CD27)	NCT04924101 (KEYNOTE-B99)
First-line therapy	PE	Sintilimab + IBI110 (anti-LAG3)	NCT05026593
First-line therapy	PE	Atezolizumab + Tiragolumab (anti-TIGIT)	NCT04256421 (SKYSCRAPER-02)
First-line therapy	PE	Durvalumab + Olaparib (PARPi)	NCT04728230
First-line therapy	PE	Tislelizumab + 177Lu-DOTATATE	NCT05142696
First-line therapy	PE	Nivolumab + BMS-986012 (fucosyl-GM1)	NCT04702880
First-line therapy	PE	Atezolizumab + LB-100 (PP2Ai)	NCT04560972
Maintenance therapy	No	Durvalumab + Ceralasertib (ATRi)	NCT04699838
Maintenance therapy	No	Atezolizumab + Lurbinectedin	NCT05091567
Maintenance therapy	No	Atezolizumab + Niraparib + Temozolomide	NCT03830918
Maintenance therapy	No	Camrelizumab + Fluzoparib (PARPi)	NCT04782089
Maintenance therapy	No	Atezolizumab + Talazoparib (PARPi)	NCT04334941
Maintenance therapy	No	Durvalumab + AZD2811 (AurKBi)	NCT04745689

ATRi, ATR inhibitor; AurKBi, Aurora Kinase B inhibitor; CbE, carboplatin + etoposide; CT, chemotherapy; PARPi, PARP inhibitor; PE, cisplatin + etoposide; PP2Ai, Protein phosphatase 2 A inhibitor.

and are currently under investigation in SCLC, given their potential of enhancing cytotoxic response to chemotherapy, radiotherapy, and immunotherapy (48). A clinical trial with the PARPi olaparib added to chemoimmunotherapy as first-line therapy in ES-SCLC patients (NCT04728230) is ongoing. However, PARPi have currently shown limited activity in SCLC patients, suggesting that a better selection of patients is needed (49). Other drugs investigated in combination with chemoimmunotherapy are the 177Lu-DOTATATE, a somatostatin receptor-targeted radionuclide therapy; BMS-986012, an anti-fucosyl-GM1 monoclonal antibody; and LB-100, a protein phosphatase 2A (PP2A) inhibitor (**Table 2**).

In parallel, translational research focused on identifying specific subgroups of patients who do benefit—or do not—from immunotherapy. In the latest years, immune signatures have been developed and studied in several cancer types (50). Specifically for SCLC, two recently published works shed light on this topic. Xie et al. have built up a prognostic 10-gene immune-related signature (ARAF, HDGF, INHBE, LRSAM1, NR1D2, NR3C1, PLXNA1, PML, SP1, and TANK), able to predict SCLC patients' survival; however, this model needs validation as a predictive tool for immunotherapy (51). Gay et al. have identified four SCLC subtypes based on the expression of three transcription factors (i.e., ASCL1, NEUROD1, and POU2F3); if those are all not expressed, an inflamed gene signature showed a similar correlation between SCLC subtypes and their vulnerability to specific drugs (52). Also for this molecular classification, validation is needed mandatory.

CONCLUSIONS

The addition of ICIs to standard chemotherapy represents a milestone in the first-line therapeutic scenario of ES-SCLC. Results from the three phase III randomized clinical trials are consistent, with OS gain across all patients' subgroups. However, primary resistance to chemoimmunotherapy is still challenging for ES-SCLC patients. More research efforts are needed to answer specific questions, like identifying responding patient according to their clinical and molecular characteristics, adding novel anticancer drugs to chemoimmunotherapy, and optimizing the therapeutic strategy for patients with symptomatic brain metastases.

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