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Review

Chemo-immunotherapy as first-line treatment for small-cell lung cancer

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Saira Farid and Stephen V. Liu

***Abstract*:** Small-cell lung cancer (SCLC) is a highly lethal subtype of lung cancer. Despite concerted efforts over the past several decades, there have been limited therapeutic advances. Traditional chemotherapy offers a high response rate and rapid symptomatic improvement, but its benefit is fleeting, and relapse is quick and unforgiving. Immunotherapy has delivered improved outcomes for patients with many cancers and there was compelling rationale for development in SCLC. While initial efforts with cytotoxic T-lymphocyte protein-4 inhibitors failed to improve upon chemotherapy alone, the addition of programmed death ligand-1 (PD-L1) inhibitors to first-line chemotherapy finally provided long-awaited gains in survival. Atezolizumab, when added to carboplatin and etoposide, improved both progression-free survival and overall survival. Durvalumab, when added to platinum plus etoposide, similarly improved OS. Biomarker development has stalled as PD-L1 expression and tumor mutational burden have not been useful predictive biomarkers. However, based on the significant survival improvements, both atezolizumab and durvalumab were approved by the US Food and Drug Administration to be given with first-line chemotherapy, and these regimens represent the new standards of care for SCLC.

Keywords: atezolizumab, chemo-immunotherapy, durvalumab, immunotherapy, small-cell lung cancer

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Introduction

Small-cell lung cancer (SCLC) is a particularly lethal subtype of lung cancer, accounting for about 15% of all new lung cancer diagnoses but a disproportionate number of lung cancer deaths.[1] It is characterized by rapid growth and early spread; the vast majority (>70%) of patients present with stage IV or extensive-stage (ES) SCLC at diagnosis. The historic standard of care for ES-SCLC was platinum-doublet chemotherapy.[2] At first glance, platinum plus etoposide is a seemingly acceptable initial therapy. It is consistently well tolerated, easy to administer, and effective, in the sense that the response rate (RR) is high (>60%), responses occur quickly, and complete responses can be seen in about 10% of patients.[3] These initial responses, however, are frustratingly transient and chemotherapy alone is not associated with long-term survival. Progression-free survival (PFS) is well under 6 months and overall survival (OS) has been limited to 8–10 months.[3,4] Irinotecan was explored as a potentially more active platinum partner, but phase III trials showed no improvement in survival over platinum plus etoposide.[5] Despite the limited survival seen with standard chemotherapy however, the standard treatment remained unchanged for decades, as dozens of trials failed to offer any improvement in survival for patients with SCLC.

Change came with the development of immunotherapy, specifically, use of immune checkpoint inhibitors. Monoclonal antibodies targeting cytotoxic T-lymphocyte protein-4 (CTLA-4), programmed cell death protein-1 (PD-1), and programmed death ligand-1 (PD-L1) triggered a paradigm shift throughout oncology, introducing the potential for durable, meaningful responses with very favorable toxicity profiles.[6] The PD-1 inhibitors nivolumab and pembrolizumab and the

Correspondence to:
Stephen V. Liu
Lombardi Comprehensive Cancer Center, Georgetown University Hospital, 3800 Reservoir Road NW, Washington, DC 20007, USA
stephen.v.liu@gunet.georgetown.edu

Saira Farid
Department of Internal Medicine, MedStar Washington Hospital Center, Washington, DC, USA

PD-L1 inhibitor atezolizumab all showed efficacy in patients with previously treated SCLC.[7–9] In the third-line setting for SCLC, where there had been no approved options, anti-PD-1 antibodies emerged as appealing therapeutic options. Nivolumab monotherapy was associated with a modest RR of 11.9% but responses were durable, with a median duration of response (DOR) of 17.9 months.[7] While median OS was only 5.6 months, landmark survival rates were higher than would be expected with other agents, with an 18-month survival rate of 20%. Pembrolizumab offered similar outcomes. In patients with SCLC who had received at least two prior lines of therapy, pembrolizumab had an RR of 19.3% with 61% of responses ongoing at 18 months.[10] The 24-month survival rate was an impressive 20.7%. These single-arm studies led to approval by the US Food and Drug Administration (FDA) of nivolumab and pembrolizumab as third-line monotherapy for SCLC.

Unfortunately, there is significant attrition after each line of therapy for SCLC. In a series of 432 patients with SCLC who received initial systemic therapy, only 50% received second-line therapy and only 22% received third-line therapy.[11] To maximize the impact of this potentially transformative class of agents, earlier use was eagerly explored. In the second-line setting, however, nivolumab monotherapy failed to improve survival when compared with standard chemotherapy.[12] Median OS with standard chemotherapy was 8.4 months compared with 7.5 months with nivolumab. While the 12-month OS rate numerically favored nivolumab (37% *versus* 34%), the 6-month OS rate numerically favored chemotherapy (60% *versus* 54%), with no statistically significant difference in survival between the two arms. Second-line atezolizumab monotherapy was similarly disappointing, offering an RR of only 2.3% in an unselected population.[13] Maintenance immunotherapy also failed to impact outcomes. In patients who completed platinum-doublet chemotherapy and had not yet progressed, nivolumab given with the CTLA-4 antibody ipilimumab did not improve OS compared with placebo.[14] It was only with integration of PD-L1 inhibitors concurrently with platinum-doublet chemotherapy followed by maintenance therapy that the elusive improvement in OS was achieved, creating a new standard of care for patients with SCLC.[15,16]

Rationale for chemo-immunotherapy in SCLC

Even before early clinical studies of immunotherapy showed activity in SCLC, there was a compelling rationale to integrate immunotherapy in treatment algorithms, despite the lack of strong preclinical evidence for the approach in SCLC. Early studies of pembrolizumab in patients with non-small-cell lung cancer (NSCLC) noted improved outcomes in patients whose tumors harbored a high number of non-synonymous somatic mutations, referred to as a high tumor mutational burden (TMB).[17] Patients whose tumors had a high TMB had a higher RR and significantly longer PFS. Carcinogen-related cancers, in particular smoking-related cancers, also seemed to derive greater benefit from use of immune checkpoint inhibitors based on reported tobacco use[18] or a molecular signature associated with smoking.[19] SCLC is strongly associated with a history of smoking and is characterized by a relatively high TMB, providing an early impetus to develop checkpoint inhibitors in SCLC.[20–22]

Immune-mediated clinical events associated with SCLC also generated interest in checkpoint inhibitors. There is a strong association with SCLC and the development of immune-mediated paraneoplastic syndromes.[23,24] The development of onconeural antibodies (anti-Hu, anti-Yo, anti-amphiphysin, anti-Ri, and others) is associated with various neurologic paraneoplastic syndromes, including encephalitis, cerebellar degeneration, opsoclonus-myoclonus, optic neuropathy, and many more.[23] For example, Lambert–Eaton myasthenic syndrome (LEMS) is a neurologic paraneoplastic syndrome mediated by antibodies targeting voltage-gated calcium channels.[24,25] One series compared patients with SCLC and LEMS with matched controls who had SCLC alone and found that the presence of LEMS was associated with greater survival (17.3 months *versus* 10 months, $p = 0.048$).[26] In another retrospective analysis, the presence of anti-Hu antibodies in patients with SCLC was strongly predictive of complete response to therapy.[27] Several other studies support a better prognosis for patients with SCLC and a coexisting, immune-mediated paraneoplastic syndrome.[28,29] Exploring the pathologic basis for this relationship, biopsies were analyzed from patients with concurrent SCLC and paraneoplastic syndromes. These tumors were found to have a higher ratio of antitumor

effector T cells to regulatory T cells, promoting antitumor immunity, and delaying tumor growth.[30] In a more recent analysis of 145 patients with SCLC, the presence of a neurologic paraneoplastic syndrome was associated with greater tumoral T-cell infiltration and higher degrees of PD-1/PD-L1 interaction.[24] This supported the pursuit of enhancing immune-mediated antitumor responses for patients with SCLC.

While there was early activity with checkpoint inhibitors in SCLC, there was additional rationale to combine these agents with platinum-based chemotherapy in the first-line setting. Cancer cell death induced by cytotoxic chemotherapy can lead to the release of neoantigens and facilitate antigen presentation and tumor recognition.[31] Cytotoxic chemotherapy can deplete the tumor microenvironment of myeloid-derived cells such as T-regulatory cells, which would otherwise suppress immune effector cell function.[32] Chemotherapy can also promote intratumoral T-cell infiltration and activation.[33,34] These combinatorial strategies had been very effective and well tolerated in NSCLC.[35] Practically, combinations of immunotherapy and chemotherapy in the first-line setting for SCLC would help circumvent the high rates of attrition and leverage the initial response seen with chemotherapy. It was this strategy that would ultimately provide the greatest impact in SCLC (Table 1).

Chemotherapy and CTLA-4 inhibitors in SCLC

CTLA-4 is a transmembrane protein receptor expressed on the surface of T cells which regulates responses in the early stages of T-cell activation.[40] Combinations of ipilimumab with chemotherapy were explored in SCLC with initial enthusiasm. A randomized phase II study investigated carboplatin and paclitaxel alone or in combination with ipilimumab in patients with treatment-naïve SCLC ($n = 130$).[36] The study explored two different strategies of ipilimumab delivery: a concurrent approach and a phased approach. Patients were randomized 1:1:1 to receive chemotherapy with placebo, with concurrent ipilimumab, or with phased ipilimumab. All patients received carboplatin area under the curve (AUC) 6 and paclitaxel 175 mg/m^2 intravenously (IV) every 3 weeks for six cycles. Patients in the concurrent arm ($n = 43$) received ipilimumab 10 mg/kg IV with cycles 1–4 and placebo with cycles 5–6. Patients in the phased arm ($n = 42$) received placebo with cycles 1–2 and ipilimumab 10 mg/kg IV with cycles 2–6. Patients in the control arm ($n = 45$) received placebo with cycles 1–6. Patients without progression could then continue ipilimumab or placebo every 12 weeks as maintenance therapy until progression, death, or intolerance. Using standard assessment criteria, RR was 57% with phased ipilimumab, 33% with concurrent ipilimumab, and 49% with placebo. The median PFS was similar across the three arms: phased 5.2 months, concurrent 3.9 months, and placebo 5.2 months. Using a modified assessment plan, the immune-related response criteria, outcomes favored the phased approach. The immune-related RR was 71% with phased ipilimumab, 49% with concurrent ipilimumab, and 53% with placebo. The median PFS using immune-related criteria was also higher with the phased ipilimumab regimen (6.4 months) compared with concurrent groups (5.7 months) and control groups (5.3 months; HR 0.64; 95% CI 0.40–1.02; $p = 0.03$).

The OS was 12.5 months with phased ipilimumab, 9.1 months with concurrent ipilimumab, and 10.5 months in the control group. The incidence of grade 3–4 treatment-related adverse events (TRAEs) was higher in the ipilimumab-containing arms [phased ipilimumab (50%), concurrent ipilimumab (43%)] compared with the control (30%). The most common grade 3–4 TRAEs in the phased cohort were fatigue (12%), diarrhea (10%), neutropenia (10%), anemia (10%), and transaminitis [AST (7%), ALT (4%)]. Grade 3–4 TRAEs in the concurrent ipilimumab group were fatigue (7%), rash (5%), thrombocytopenia (8%), anemia (5%), neutropenia (3%), and transaminitis [AST (13%), ALT (18%)]. The common grade 3–4 TRAEs in the control group were fatigue (5%), diarrhea (5%), nausea (2%), anemia (7%), neutropenia (2%), and thrombocytopenia (2%).

Ipilimumab was then studied in combination with first-line platinum plus etoposide in a randomized phase III trial. This study included 954 patients with treatment-naïve ES-SCLC but unfortunately observed no survival benefit with the addition of ipilimumab to chemotherapy.[37] All patients received standard chemotherapy with etoposide 100 mg/m^2 IV on days 1–3 and either cisplatin 75 mg/m^2 IV or carboplatin AUC 5 IV on day 1. Patients were randomized 1:1 to receive concurrent ipilimumab (10 mg/kg IV) or placebo. This induction regimen was given every 3 weeks for

Table 1. Summary of randomized first-line chemo-immunotherapy trials in extensive-stage small-cell lung cancer.

Author	Therapy	Patients (*n*)	RR (%)	PFS (months)	OS (months)	12-month OS rate (%)
Reck *et al.*[36]	Carboplatin and paclitaxel with phased ipilimumab	42	57	5.2	12.5	NR
	Carboplatin and paclitaxel with concurrent ipilimumab	43	33	3.9	9.1	NR
	Carboplatin and paclitaxel with placebo	45	49	5.2	10.5	NR
Reck *et al.*[37]	Platinum-etoposide plus ipilimumab	478	62	4.6	11	40
	Platinum-etoposide plus placebo	476	62	4.4	10.9	40
Horn *et al.*[15]	Platinum-etoposide plus atezolizumab	201	60	5.2	12.3	51.7
	Platinum-etoposide plus placebo	202	64	4.3	10.3	38.2
Paz-Ares *et al.*[16,38]	Platinum-etoposide plus durvalumab	268	68	5.1	12.9	52.8
	Platinum-etoposide plus durvalumab and tremelimumab	268	58	4.9	10.4	43.8
	Platinum-etoposide	269	58	5.4	10.5	39.3
Rudin *et al.*[39]	Platinum-etoposide plus pembrolizumab	228	71	4.5	10.8	45.1
	Platinum-etoposide plus placebo	225	62	4.3	9.7	39.6

NR, not reported; OS, overall survival; PFS, progression-free survival; RR, response rate.

four cycles, followed by maintenance with either ipilimumab or placebo every 12 weeks until progression, unacceptable toxicity, or death, for a maximum of 3 years. The RR was 62% in both arms; PFS was 4.6 months with chemotherapy and ipilimumab ($n = 478$) and 4.4 months with chemotherapy and placebo ($n = 476$; HR 0.85; 95% CI 0.75–0.97; $p = 0.0161$). Median DOR was 4.01 months with chemotherapy plus ipilimumab, and 3.45 months with chemotherapy plus placebo. The modest improvement in PFS, however, did not translate into any improvement in survival. Median OS was 11.0 months with chemotherapy plus ipilimumab and 10.9 months with chemotherapy plus placebo (HR 0.94; 95% CI 0.81–1.09; $p = 0.3775$). Grade 3–4 TRAEs were similar in the two arms: 48% with chemotherapy and ipilimumab and 44% with chemotherapy and placebo; however, the addition of ipilimumab led to higher rates of treatment-related discontinuation (18% *versus* 2%). Ipilimumab did not impact survival with first-line chemotherapy: fortunately, targeting the PD-1/PD-L1 axis in this fashion did meet with success.

Chemotherapy and PD-1/PD-L1 inhibitors in SCLC

Whether synergistic or additive, combinations of platinum-based chemotherapy and PD-(L)1 inhibitors have emerged as a standard option for patients with advanced NSCLC. This strategy also changed the standard of care for SCLC. It was the addition of the PD-L1 inhibitor atezolizumab to standard carboplatin and etoposide in the IMpower 133 trial that led to the first improvement in OS for SCLC in decades.[15] IMpower 133 was a global phase I/III, randomized, double-blind, placebo-controlled trial for patients with treatment-naïve ES-SCLC. Patients with treated, asymptomatic brain metastases were included, and PD-L1 expression was not mandated for study entry. All patients ($n = 403$) received standard carboplatin AUC 5 IV on day 1 and etoposide 100 mg/m^2 IV on days 1–3 and were randomized 1:1 to receive either concurrent atezolizumab 1200 mg IV ($n = 201$) or placebo ($n = 202$) on day 1 for four cycles, followed by maintenance atezolizumab or placebo. Prophylactic cranial irradiation (PCI) was permitted during the maintenance phase, but consolidative thoracic

radiation was not allowed. The co-primary endpoints were PFS and OS and this study met both endpoints.

The addition of atezolizumab to chemotherapy improved PFS from a median of 4.3 months to 5.3 months (HR 0.77; 95% CI 0.62–0.96; $p = 0.02$). Importantly, atezolizumab also improved survival; median OS with atezolizumab plus chemotherapy was 12.3 months compared with 10.3 months with placebo plus chemotherapy (HR 0.70; 95% CI 0.54–0.91; $p = 0.007$). There was a notable improvement in landmark survival rates: the 12-month OS rate was 51.7% with atezolizumab and 38.2% with placebo. RR was comparable in the two arms (60% with atezolizumab, 64% with placebo). The addition of atezolizumab to chemotherapy for SCLC improved PFS and OS but did not significantly increase toxicity; grade 3–4 TRAEs were reported in 56.6% of patients with chemotherapy plus atezolizumab, and 56.1% of patients with chemotherapy plus atezolizumab.

In IMpower 133, patient-reported outcomes (PROs) were assessed every 3 weeks during treatment using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) and the Lung Cancer 13 (QLQ-LC13) questionnaires.[41] Results were compiled from 394 patients in the induction phase and 318 patients in the maintenance phase. The incidence of TRAEs affecting the patients' quality of life (such as nausea, vomiting, diarrhea, loss of appetite, or dyspnea) was similar in both arms. The incidence of these TRAEs was lower in the maintenance phase with both atezolizumab and placebo. Patient function and quality of life improved in both arms with treatment but quality-of-life improvements were more pronounced and persistent in the atezolizumab arm. Patients receiving atezolizumab achieved meaningful improvements in quality of life that persisted through week 54, while those receiving placebo had their improvements taper off after week 21. In March 2019, atezolizumab was approved by the US FDA in combination with carboplatin and etoposide as first-line treatment for ES-SCLC.

The CASPIAN trial, which reported 1 year after IMpower 133, showed strikingly similar results with the addition of the anti-PD-L1 antibody durvalumab to chemotherapy in ES-SCLC. CASPIAN was an open-label trial where patients with ES-SCLC were randomized to one of three arms: chemotherapy alone, chemotherapy with durvalumab, or chemotherapy with durvalumab and the anti-CTLA-4 antibody tremelimumab.[16] Patients in the chemotherapy arm received either cisplatin (75–80 mg/m^2) or carboplatin (AUC 5–6) IV on day 1 and etoposide 80–100 mg/m^2 on days 1–3 every 3 weeks for at least four and up to six cycles, followed by the option of PCI. Patients in the durvalumab arm received chemotherapy as above given with durvalumab 1500 mg IV for four cycles followed by maintenance durvalumab 1500 mg IV every 4 weeks. Patients in the durvalumab plus tremelimumab arm also received tremelimumab 75 mg every 3 weeks with chemotherapy for four cycles; tremelimumab was not given with maintenance therapy. PCI was not delivered in the experimental arms and crossover was not allowed. Consolidative thoracic radiation was not permitted in any arm. Patients with untreated, asymptomatic brain metastases were eligible. The primary endpoint was OS and CASPIAN was a positive trial. The addition of durvalumab to chemotherapy improved OS; full results from the durvalumab plus tremelimumab arm have not yet been presented.

Durvalumab, when added to platinum plus etoposide, improved survival; median OS with chemotherapy alone was 10.5 months and median OS with chemotherapy plus durvalumab was 12.9 months (HR 0.75; 95% CI 0.62–0.91; *p*-0.0032).[38] PFS with durvalumab was 5.1 months and PFS with chemotherapy alone was 5.4 months, though due to the multiple-testing procedure at the interim analysis, this could not yet be tested for significance. Responses were more frequent in the durvalumab arm (RR 67.9% *versus* 58%). As seen with atezolizumab, the improvement in outcomes did not worsen the incidence of grade 3–4 TRAEs, which were seen in about 62% of patients in both groups. PROs, health-related quality of life, and functioning were assessed *via* EORTC QLQ-C30/LC13 questionnaires.[16] Baseline PRO scores (symptoms and functionality) were comparable between both the study arms. Global health status was superior with the addition of durvalumab over chemotherapy alone (HR 0.81; 95% CI 0.626–1.054), cognitive functioning (HR 0.61; 95% CI 0.472–0.776), emotional functioning (HR 0.61; 95% CI 0.464–0.800), and social functioning (HR 0.70; 95% CI 0.549–0.897) favored combination treatment, though the open-label nature of the study could influence results. The OS benefit

achieved was comparable to that seen with atezolizumab and led to the approval by the US FDA of durvalumab with platinum plus etoposide as first-line treatment for ES-SCLC in March 2020.

The four-drug regimen of platinum, etoposide, durvalumab, and tremelimumab did not improve OS compared with chemotherapy alone.[38] Median OS with durvalumab and tremelimumab was 10.4 months compared with 10.5 months with chemotherapy alone (HR 0.82; 95% CI 0.68–1.00). There was also no difference in PFS between the experimental and control arms (median 4.9 months *versus* 5.4 months, respectively; HR 0.84; 95% CI 0.70–1.01). There were more grade 3/4 TRAEs with the addition of durvalumab and tremelimumab (70.3%) compared with chemotherapy alone (62.8%), and 21.4% of patients receiving the four-drug regimen discontinued treatment due to a TRAE.

In contrast to IMpower 133 and CASPIAN, the phase III KEYNOTE-604 study did not meet its primary endpoint.[39] This study randomized 453 patients with ES-SCLC to first-line platinum (either cisplatin 75 mg/m^2 or carboplatin AUC 5 given on day 1) plus etoposide 100 mg/m^2 on days 1–3 with either pembrolizumab 200 mg or placebo for four cycles followed by pembrolizumab or placebo maintenance. Patients with brain metastases were included if they had been treated with radiation at least 14 days before study entry. The dual primary endpoints were PFS and OS. The addition of pembrolizumab did improve PFS from a median of 4.3 months to 4.5 months with a PFS HR of 0.73 (95% CI 0.60—0.88). The study did not, however, meet its survival endpoint. Median OS was 9.7 months with placebo and 10.8 months with pembrolizumab with an OS HR of 0.80 (95% CI 0.64–0.98), not crossing the predetermined threshold for a survival benefit. Landmark survival rates did favor pembrolizumab, with 1-year and 2-year survival rates of 45.1% and 22.5% compared with 39.6% and 11.2% with placebo. While these results were disappointing, the trends were consistent with other chemo-immunotherapy efforts and they do not detract from the positive survival results seen with atezolizumab and durvalumab. The addition of these PD-L1 inhibitors to platinum-doublet chemotherapy has set a new survival benchmark and established new standards of care upon which to build. While it is not appropriate to directly compare results across the IMpower 133 and CASPIAN trials, both provide validity to the strategy: the addition of a PD-L1 inhibitor to platinum plus etoposide chemotherapy improves survival.

There are many limitations to the available data for chemo-immunotherapy in ES-SCLC. Longer follow up is needed to appreciate long-term survival differences as well as patterns of progression and the impact of subsequent therapy. The patient population included in these phase III trials may not represent the full spectrum of patients with SCLC encountered in clinical practice. Studies exploring the benefit in patients with poor performance status, organ dysfunction, or with underlying paraneoplastic disorders are needed. Consolidative radiation therapy was associated with an improvement in 2-year landmark survival but was not permitted in these phase III trials and warrants further exploration.[42] Despite these welcome advances, there remains much room for improvement and a need to deliver more effectively long-term benefit to more patients with advanced SCLC.

Biomarkers for chemo-immunotherapy in SCLC

Concurrent chemo-immunotherapy with a PD-L1 inhibitor is the new standard of care for ES-SCLC and while this approach does offer a survival advantage over chemotherapy alone, the true benefit of immunotherapy is likely carried by a subset of patients. Identification of that subset of patients is paramount to drug development. A reliable biomarker to guide chemo-immunotherapy in SCLC, however, has been elusive.

PD-L1 expression is an effective, though imperfect, predictive biomarker for use of first-line checkpoint inhibitors in NSCLC.[43] It does not play the same role in SCLC. In IMpower 133, a *post hoc* exploratory analysis was conducted to correlate OS with PD-L1 expression by immunohistochemistry using the VENTANA SP-263 PD-L1 assay (Ventana Medical Systems, Oro Valley, AZ, USA).[44] Only 34% of patient samples were evaluable for PD-L1 expression. There was limited expression of PD-L1 on tumor cells: 94.2% were PD-L1 negative, 5.8% were PD-L1 positive, and only 1.5% had expression on at least 5% of tumor cells. Expression of PD-L1 on immune cells was much more common: 49.6% were PD-L1 negative, 50.4% were PD-L1 positive, and 20.4% had expression on at least 5% of immune cells. PD-L1 expression, however, did

not predict survival as all subgroups (whether a 1% or 5% cutoff was used) had a survival advantage with atezolizumab. Similar results were seen with PD-L1 expression analyses in CASPIAN.[45] In that study, 52% of samples were evaluable: 96% were PD-L1 negative based on tumor-cell expression and 78% were PD-L1 negative based on immune-cell expression. Again, whether PD-L1 expression on tumor cells or immune cells was analyzed, outcomes favored the addition of durvalumab for both PD-L1 positive and negative tumors. In addition, more recently, in KEYNOTE-604, PD-L1 expression using the combined proportion score and the Dako 22C3 PD-L1 clone similarly did not predict OS benefit with the addition of pembrolizumab.[39]

TMB also carries predictive value for immunotherapy in NSCLC[43] but its role in selecting optimal first-line therapy for SCLC is unclear. Early studies showed greater efficacy of nivolumab alone or with ipilimumab in previously treated patients whose tumors had high TMB.[46] These results have not been confirmed in the first-line setting. Biopsy specimens in patients with SCLC are often scant and unlikely to yield TMB results. To maximize testing feasibility, blood-based TMB (bTMB) was used in the IMpower 133 study.[15] Cutoffs for bTMB were extrapolated from studies in NSCLC, where high bTMB predicted superior PFS with atezolizumab in the OAK and POPLAR randomized trials.[47] Blood was collected at entry for patients on IMpower 133 and analyzed using cutoffs of 10 mutations/Mb and 16 mutations/Mb. Unfortunately, bTMB did not have predictive utility at either cutoff, with all subgroups achieving superior survival with atezolizumab. The need for a predictive biomarker for chemo-immunotherapy in SCLC is clear but it has not yet been identified. PD-L1 expression and bTMB do not have value in this setting and more prospective work is needed. The current approach remains delivery of first-line chemo-immunotherapy to an all-comer population with ES-SCLC.

Conclusion

The management of ES-SCLC has undergone remarkably little change in the past 40 years. Doublet chemotherapy is initially effective, but the benefit is transient; response is routinely expected but so is relapse. Upon relapse, SCLC is highly recalcitrant to therapy and almost uniformly lethal. Efforts to evolve first-line therapy in SCLC have consistently failed. It was only with the addition of PD-L1 inhibitors to first-line chemotherapy that the OS benchmark was cleared. Atezolizumab, when added to carboplatin and etoposide, significantly improved PFS and OS without greatly increasing toxicity.[15] Durvalumab, when added to platinum and etoposide, also improved OS without introducing significant toxicity.[16] These regimens represent new standards of care, though long-term outcomes still lag behind those achieved in NSCLC. Biomarker identification and rational drug development will hopefully build upon these advances. Chemo-immunotherapy may not provide the lofty outcomes we had hoped for, but the strategy is clearly better than that for which we had previously been settling. This hopefully represents the first of many improvements in the management of SCLC, and one of many gains made for patients facing this highly lethal disease.

Conflict of interest statement

SVL reports serving as an advisory board member and/or consultant for AstraZeneca, Blueprint, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, G1 Therapeutics, Genentech, Guardant Health, Inivata, Janssen, Jazz, Eli Lilly, LOXO, Merck/MSD, PharmaMar, Pfizer, Regeneron, and Takeda and receiving research grant funding (to institution) from Alkermes, AstraZeneca, Bayer, Blueprint, Bristol Myers Squibb, Corvus, Debiopharm, Genentech, Eli Lilly, Lycera, Merck, Molecular Partners, Pfizer, Rain Therapeutics, RAPT Therapeutics, Spectrum, and Turning Point Therapeutics.

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ORCID iD

Stephen V. Liu https://orcid.org/0000-0002-4852-3914

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