Immunotherapy for Small Cell Lung Cancer: Established Applications and Novel Approaches

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Abstract: Small cell lung cancer (SCLC) is a devastating disease that has a case fatality rate of more than 90% despite best available treatments. As a result, patients with SCLC are in critical need of improved therapeutic approaches. Immunotherapies, in particular immune checkpoint inhibitors (ICIs), have transformed the treatment of many cancers and are of great interest in SCLC. In recent years, the addition of anti–programmed death ligand 1 (PD-L1) inhibitors to frontline platinum-based chemotherapy in extensive-stage SCLC has improved survival, and combination chemo-immunotherapy is now approved as the standard of care. ICIs are also under investigation in other settings, including as consolidation therapy in limited-stage SCLC following chemoradiation and in combination with chemoradiation. PD-L1 expression and tumor mutational burden are not reliably associated with ICI benefit in SCLC, and predictive biomarkers of ICI response in SCLC are actively sought. Novel immunotherapeutic approaches are under investigation in SCLC. Rational targets and combinations, which stem from investigations of SCLC biology and the immune tumor microenvironment, include combinations with inhibitors of TIGIT or LAG3; targeting alternative signaling pathways, such as DNA damage repair; and co-targeting SCLC-specific tumor antigens, such as fucosyl-GM1 and DLL3. This review summarizes approaches to immunotherapy in SCLC, including current evidence and approvals, as well as key questions and future directions.

Introduction

Lung cancer is the leading cause of cancer death worldwide,[1] and small cell lung cancer (SCLC) is the most aggressive and deadly form of this disease. SCLC affects more than 200,000 patients each year across the world, representing about 15% of lung cancer incidence.[1,2] It is a poorly differentiated neuroendocrine tumor that is characterized by rapid growth and early metastasis. Most patients present with incurable, extensive-stage disease. Despite high rates of response to initial platinum-based chemotherapy, most patients survive less than

1 year after a diagnosis, and fewer than 2% are alive at 5 years.[3,4] Even among the one-third of patients presenting with limited-stage disease, more than 75% will experience disease recurrence after curative-intent therapy, and the 5-year overall survival (OS) rate is 15% to 20%.[4]

Since the 1980s, platinum-based chemotherapy has served as the backbone of SCLC treatment. As first-line therapy for extensive-stage SCLC, etoposide plus platinum chemotherapy (EP) offers response rates of 60% to 70%. Prompt relapse is the rule, however, with median progression-free survival (PFS) of only 5 to 6 months.[5] Given the aggressive metastatic potential of SCLC, adjuvant systemic chemotherapy and prophylactic cranial irradiation (PCI) are recommended even in rare patients with completely resected stage I disease.[6] Definitive chemoradiotherapy with EP followed by PCI is the standard of care for patients with limited-stage IIB to IIIC disease, but it offers only 15-month median PFS.[6,7] For those with relapsed or refractory SCLC following platinum-based chemotherapy, available treatment options provide a short duration of response or stability with significant toxicity; standard agents include topotecan and the more recently approved lurbinectedin (Zepzelca, Jazz/PharmaMar). Both of these agents are associated with a median PFS of approximately 3 months and median OS of 6 to 9 months.[8,9]

The promising benefits of immunotherapy observed in non–small cell lung cancer (NSCLC) and many other tumors, coupled with the limited options for SCLC and the poor durability of SCLC therapies, have spurred considerable interest in immunotherapy approaches in SCLC. Immune checkpoint inhibitors (ICIs), in particular anti–programmed death 1 (PD-1) and anti–programmed death ligand 1 (PD-L1) antibodies, are under investigation in every stage of SCLC management, and they have been approved in combination with EP chemotherapy for the frontline treatment of extensive-stage SCLC and as single agents in relapsed disease. SCLC is strongly associated with tobacco smoking and frequently exhibits a high tumor mutational burden (TMB), which has been associated with response to ICI therapy.[10,11] However, compared with the ICI response rates and benefits in NSCLC, those in SCLC are less robust and less durable. Efforts to augment the immunotherapy response and identify biomarkers predictive of response are ongoing. Here, we review immunotherapy approaches in SCLC, including current evidence and approvals, as well as key questions and future directions.

Immune Checkpoint Inhibitors in Relapsed SCLC

Early data for the efficacy of ICIs in relapsed SCLC came from the multicohort and basket trials KEYNOTE-028, KEYNOTE-158, and CheckMate 032, which studied inhibitors of PD-1 and cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) in the relapsed setting.[12-14] In KEYNOTE-028, a phase 1b multicohort study, 24 patients who had SCLC with PD-L1 expression of 1% or greater (by tumor proportion score, or TPS) and who were naive to immunotherapy were treated with single-agent pembrolizumab (Keytruda, Merck); the objective response rate (ORR) was 33%, with a median duration of response (DOR) of 19.4 months.[12] In the phase 2 basket trial KEYNOTE-158, 107 patients with relapsed SCLC, without PD-L1 selection, were treated with pembrolizumab and had an ORR of 18.7%.[14] The CheckMate 032 trial of nivolumab (Opdivo, Bristol Myers Squibb) with or without ipilimumab (Yervoy, Bristol Myers Squibb) also was not PD-L1–restricted, and pooled analysis of the initial nonrandomized cohort (n=216) and randomized expansion cohort (n=242) of patients with relapsed SCLC found an ORR of 11% (95% CI, 8%-16%) with nivolumab and 22% (95% CI, 16%-29%) with nivolumab/ipilimumab.[13,15] Importantly, grade 3 and 4 treatment-related adverse events (AEs) were observed in 12% of patients treated with nivolumab and 27% of patients treated with nivolumab/ipilimumab. The encouraging results of these early-phase trials in relapsed disease led to the investigation of ICIs in all stages of SCLC.

Despite these promising results in the third-line setting, ICI therapy has not been shown to offer benefit compared with chemotherapy in the second-line setting. In IFCT-1603, 73 ICI-naive patients were randomly assigned in a 2:1 ratio to atezolizumab (Tecentriq, Genentech) or up to 6 cycles of topotecan or re-induction with platinum-based chemotherapy.[16] The disease control rate (DCR) was 21% with atezolizumab vs 65% with chemotherapy, and these rates translated to a median PFS of 1.4 months with atezolizumab and 4.3 months with chemotherapy. Overall survival (OS) did not differ. In the larger CheckMate 331 trial, 569 ICI-naive patients with relapsed SCLC were randomly assigned to nivolumab or chemotherapy with topotecan or amrubicin. No significant improvement in the primary endpoint of OS was observed with nivolumab; median OS with nivolumab was 7.5 months vs 8.4 months with chemotherapy, and the ORRs did not differ (14% vs 17%).[17] The median DOR was 8.3 months with nivolumab vs 4.5 months with chemotherapy. As expected from the low response rates but longer DOR with nivolumab, there appeared to be an initial OS advantage with chemotherapy but a later advantage with nivolumab. For example, in an exploratory analysis, the hazard ratio (HR) for death at 6 months and beyond favored nivolumab.

Table 1. Randomized Controlled Trials of First-Line Combination Anti–PD-1/PD-L1 and Chemotherapy in ES-SCLC

Clinical Trial	Experimental Arm	Control Arm	Phase	N	Median Follow-up, mo	ORR, %	HR, PFS (95% CI)	Median PFS, mo	HR, OS (95% CI)	Median OS, mo	12-mo OS, %
IMpower133	Atezolizumab + carboplatin/ etoposide with atezolizumab maintenance	Carbo-platin/ etoposide	3	403	22.9	60 vs 64	0.77 (0.63-0.95)	5.2 vs 4.3	0.76 (0.60-0.95)	12.3 vs 10.3	52 vs 39
CASPIAN[a]	Durvalumab + platinum/ etoposide with durvalumab maintenance	Platinum/ etoposide	3	537	25.1	68 vs 58	0.78 (0.65-0.94)	5.1 vs 5.4	0.75 (0.62-0.91)	12.9 vs 10.5	54 vs 40
EA5161	Nivolumab + platinum/ etoposide with nivolumab maintenance	Platinum/ etoposide	2	160	NR	52 vs 48	0.65 (0.46-0.91)	5.5 vs 4.6	0.67 (0.46-0.98)	11.3 vs 8.5	
KEYNOTE-604	Pembrolizumab + platinum/ etoposide with pembrolizumab maintenance	Platinum/ etoposide	3	453	26.1	71 vs 62	0.75 (0.61-0.91)	4.5 vs 4.3	0.80 (0.64-0.98)	10.8 vs 9.7	45 vs 40

[a]Excluding the patients enrolled in durvalumab plus tremelimumab plus platinum/etoposide arm.

CI, confidence interval; ES-SCLC, extensive-stage small cell lung cancer; HR, hazard ratio; mo, months; N, number of patients; NR, not reached; ORR, objective response rate; OS, overall survival; PD-1, programmed death 1; PD-L1, programmed death ligand 1; PFS, progression-free survival.

On the basis of the early-phase trials KEYNOTE-028, KEYNOTE-158, and CheckMate 032, described above, nivolumab in August 2018 and pembrolizumab in June 2019 were granted accelerated approval as monotherapy in relapsed SCLC after 2 prior lines of therapy. These indications, however, were later withdrawn (nivolumab in December 2020 and pembrolizumab in March 2021) owing to lack of benefit observed in subsequent randomized studies of nivolumab and pembrolizumab.[17-20] Furthermore, with the widespread adoption of anti–PD-L1 therapy in the first-line setting, described below, the role of subsequent ICI monotherapy in patients previously exposed to ICIs has not been established.

Checkpoint Inhibitors in First-Line Therapy for Extensive-Stage SCLC

The first ICI studied in the frontline setting for SCLC was ipilimumab. In two phase 2 studies, ipilimumab was administered with either carboplatin plus paclitaxel or carboplatin plus etoposide, with promising results.[21,22] A subsequent randomized phase 3 study of ipilimumab or placebo in combination with EP in the first-line setting,

however, failed to demonstrate an improvement in OS, the primary endpoint of the study, compared with EP plus placebo (median OS, 11.0 vs 10.9 months, respectively; HR, 0.94; 95% CI, 0.81-1.09).[23]

After 3 decades without improvement in first-line SCLC treatment, several recent phase 3 trials have established the role of chemoimmunotherapy with PD-L1 inhibition in the frontline treatment of extensive-stage SCLC (Table 1). The IMpower133 trial randomly assigned 403 patients with extensive-stage SCLC and no prior systemic therapy to the anti–PD-L1 monoclonal antibody atezolizumab or placebo concurrently with carboplatin and etoposide chemotherapy for 4 cycles.[24] Atezolizumab or placebo was continued as maintenance until disease progression or untoward toxicity. The primary endpoint of median OS was 12.3 months (95% CI, 10.8-15.8) in the atezolizumab arm vs 10.3 months (95% CI, 9.3-11.3) in the placebo arm, and the HR for death was reduced by 24% (HR, 0.76; 95% CI, 0.60-0.95).[25]

The OS rate at 12 months was higher in the chemo-immunotherapy arm (52% vs 39%). This difference was maintained at 18 months (34% vs 21%), suggesting that a proportion of patients experienced a durable

response. The difference in median PFS benefit was statistically significant, at 5.2 months in the atezolizumab arm vs 4.3 months in the placebo arm (HR, 0.77; 95% CI, 0.63-0.95). Furthermore, there was a separation of the PFS curves after the median, and the 1-year PFS was 12.6% for the atezolizumab arm vs 5.4% for the placebo arm. ORR and median DOR were similar in the 2 groups, likely owing to the high rates of response to platinum chemotherapy. In an exploratory analysis of 35 patients with treated brain metastases at diagnosis, no clear benefit of added atezolizumab was found, with an HR of 0.96 (95% CI, 0.46-2.01). Further studies are needed to determine the role of chemo-immunotherapy in this setting. Grade 3 or 4 immune-related AEs occurred in 8.1% of those in the atezolizumab arm and 2.6% of those in the placebo arm.[25]

The randomized open-label phase 3 CASPIAN trial compared the addition of the anti–PD-L1 antibody durvalumab (Imfinzi, AstraZeneca) or both durvalumab and the anti–CTLA-4 antibody tremelimumab to an EP backbone as first-line treatment in extensive-stage SCLC.[26] In contrast to IMpower133, the CASPIAN trial design allowed up to 6 cycles of EP chemotherapy (either carboplatin or cisplatin) and PCI in the control arm, whereas the combination immunotherapy arms received a maximum of 4 cycles of chemo-immunotherapy followed by durvalumab maintenance without PCI. Still, the durvalumab/chemotherapy arm demonstrated a significantly improved OS, with an HR 0.75 (95% CI, 0.62-0.91) and median OS of 12.9 months vs 10.5 months for chemotherapy alone.[27] The study was not powered for PFS, but a higher PFS rate at 12 months (18% vs 5%) suggested sustained clinical benefit with the addition of durvalumab. Again, subgroup analysis did not show a clear benefit in 10% of patients with asymptomatic brain metastases at diagnosis (HR, 0.79; 95% CI, 0.44-1.41). Grade 3 or 4 immune-mediated AEs were reported in 5% of patients who received durvalumab. More recently, post hoc analysis demonstrated consistent OS and PFS benefit from the addition of durvalumab in patients with both thoracic-only and extrathoracic disease at baseline, reiterating the potential of this systemic approach in distantly metastatic disease.[28] The third preplanned arm, which included durvalumab and tremelimumab with chemotherapy, did not demonstrate significantly improved OS vs chemotherapy alone (HR, 0.82; 95% CI, 0.68-1.00; median OS, 10.4 vs 10.5 months, respectively).[27] These 2 landmark trials led to US Food and Drug Administration (FDA) approval for atezolizumab and durvalumab in combination with platinum-based chemotherapy in the first-line treatment of extensive-stage SCLC.

The anti–PD-1 antibodies pembrolizumab and nivolumab have also been evaluated in the first-line setting with chemotherapy. In the randomized phase 3 KEYNOTE-604 trial, the addition of pembrolizumab to EP resulted in a PFS benefit (HR, 0.75; 95% CI, 0.61-0.91).[29] The trial did not meet the prespecified endpoint for OS, although the HR for OS favored the addition of pembrolizumab (HR, 0.80; 95% CI, 0.64-0.98; median OS, 10.8 vs 9.7 months), and compelling improvement in OS was noted at 24 months (22.5% vs 11.2% with chemotherapy alone). The addition of nivolumab to chemotherapy was investigated in the randomized phase 2 ECOG-ACRIN trial EA5161, which met its primary endpoint of PFS (HR, 0.65; 95% CI, 0.46-0.91).[30] Results from this smaller phase 2 trial align with those of the previously mentioned phase 3 trials, with median PFS of 5.5 vs 4.6 months and median OS of 11.3 vs 8.5 months (HR for OS 0.67; 95% CI, 0.46-0.98), suggesting a class effect for PD-1 and PD-L1 inhibition in combination with chemotherapy.

In contrast to the benefit of combining an ICI with first-line chemotherapy, 2 studies have failed to show a benefit of initiating an ICI as maintenance after the completion of frontline EP. A phase 2 trial of pembrolizumab in 45 patients with stable disease after induction EP chemotherapy demonstrated a median PFS of only 1.4 months, although 4 patients continued ICI therapy beyond 18 cycles.[31] Similarly, CheckMate 451 randomly assigned 834 patients with stable disease or response after 4 cycles of EP chemotherapy to nivolumab, nivolumab plus ipilimumab, or placebo. No improvement in OS occurred in either immunotherapy arm in comparison with the placebo arm.[19] Asking a slightly different question, the phase 2 REACTION trial investigated whether benefit was derived from the addition of pembrolizumab in patients with an objective response to 2 cycles of EP chemotherapy. In this trial, responding patients received pembrolizumab concurrently with chemotherapy for an additional 4 cycles and as maintenance for up to 35 cycles. PFS did not differ in the patients who responded to chemotherapy; however, early OS analysis suggested a possible durable benefit from pembrolizumab in a small subset of patients.[32]

Immune Checkpoint Inhibitors in Limited-Stage SCLC

The potential of systemic therapy to reduce recurrence after the definitive treatment of locally advanced tumors, combined with the durability of the immune-mediated antitumor response to ICI therapy, is of great interest in the treatment of solid tumors. Among the 30% of patients with SCLC who present with limited-stage disease, the median PFS after definitive EP chemotherapy and concurrent radiotherapy followed by PCI remains

approximately 15 months.[7] In NSCLC, the PACIFIC trial demonstrated a significant benefit of 12 months of durvalumab following definitive chemoradiation in patients with unresectable stage III disease. The improvement in median PFS from 5.6 to 17.2 months (HR, 0.51; 95% CI, 0.41-0.63) translated to a 4-year OS rate of 49.6% with durvalumab vs 36.3% with placebo.[33,34] These promising results in stage III NSCLC, coupled with ICI responses in extensive-stage SCLC, have led to studies of ICI therapy in patients with limited-stage SCLC.

Several studies are evaluating the role of ICIs as consolidation after definitive chemotherapy and radiation. The European Thoracic Oncology Platform (ETOP)/ Intergroupe Francophone de Cancerologie Thoracique (IFCT) 4-12 STIMULI trial randomly assigned patients after chemoradiation to nivolumab plus ipilimumab for 4 cycles followed by nivolumab for up to 12 months or to observation.[35] In the 153 of the 222 enrolled patients who were randomly assigned to consolidation, the study found no improvement in median PFS, which was 10.7 months with dual ICI consolidation vs 14.5 months with observation (HR, 1.02; 95% CI, 0.66-1.58). Of note, 49% of the patients in the ICI consolidation arm discontinued treatment owing to treatment-related AEs, with a median time to discontinuation of only 1.7 months. The overall rate of grade 3 or higher adverse events was 62% in the ICI arm compared with 25% in the observation arm. Longer-term outcomes, including OS, are awaited and might reveal a small subset of durable responses. In unselected patients, however, the toxicity of combination ICI treatment after chemoradiation outweighs the potential benefit. ADRIATIC (NCT03703297) is an ongoing phase 3 study that will randomly assign approximately 600 patients with inoperable limited-stage SCLC that is stable after 4 cycles of concurrent chemoradiation to durvalumab for up to 2 years, durvalumab plus tremelimumab for 4 cycles followed by durvalumab for up to 2 years, or placebo.[36] PCI will be offered at the investigators' discretion and is a prespecified stratification, along with stage. The primary endpoints are PFS in the durvalumab and the durvalumab/tremelimumab arms vs the placebo arm and OS in the durvalumab/tremelimumab arm vs the placebo arm. The contemporaneous randomized phase 2 ACHILES trial (NCT03540420) has a planned enrollment of 212 patients, who will be randomly assigned to atezolizumab for up to 12 months or observation after the completion of chemoradiation. The primary endpoint for this study is 2-year OS.

The concurrent use of ICIs with chemoradiation is also an area of active investigation, with an added focus on safety and tolerability, given the potential for radiation-induced lung injury coupled with the risk for immune-related pneumonitis due to ICI therapy. A recent single-center phase 1/2 trial investigated the safety and efficacy of EP chemotherapy plus pembrolizumab with concurrent radiation followed by up to 12 months of pembrolizumab and optional PCI in 36 patients with limited-stage SCLC and 4 others with neuroendocrine tumors of the lung.[37] The primary safety outcome was favorable, with fewer toxicities than in the concurrent chemoradiation-only CONVERT trial. For example, pneumonitis was observed in 15% of patients in the phase 1/2 trial, vs 21% in the CONVERT trial.[7] PFS and OS were secondary endpoints. The study had a relatively short follow-up of 23 months at publication but an encouraging signal, with a median PFS of 20 months and a median OS of 40 months.[37] Among the 68% of patients who received PCI, median OS was not reached. NRG LU005 (NCT03811002), an ongoing phase 2/3 trial with a planned enrollment of 506 patients who have SCLC, is comparing concurrent atezolizumab and chemoradiation plus up to 1 year of maintenance atezolizumab with chemoradiation followed by observation. The primary endpoint of the phase 2 portion of this study is PFS, and the primary endpoint of the phase 3 portion is OS.

Biomarkers for Immune Checkpoint Inhibitor Benefit in SCLC

In current practice, no biomarker-based trials or predictive tools for patient selection in SCLC therapies are available. Across immunotherapy studies in SCLC, the modest efficacy of treatment and the small subset of patients with favorable responses highlight the need to identify biomarkers indicating the patients most likely to benefit from ICI therapy, and to characterize better the mechanisms of ICI response in SCLC, so that novel combinations that will expand the use of ICIs in this setting can be explored.

PD-L1 expression is a predictive biomarker in NSCLC,[38,39] but it has not consistently been correlated with ICI response or survival in patients with SCLC. More than 60% of NSCLC cases are PD-L1 tumor proportion score (TPS)–positive (TPS ≥1% by the SP142 or 28-8 assays). A significantly lower percentage of SCLC cases are TPS-positive, but reports are quite variable, ranging from 7% to 32% in various studies.[39] In KEYNOTE-028, in which patients with extensive-stage SCLC were treated with single-agent pembrolizumab, 32% of the tumors with evaluable tissue were PD-L1 TPS-positive. The ORR among these patients was impressive, at 33%, and the median DOR exceeded 19 months in a population pretreated with platinum-based chemotherapy.[12] In KEYNOTE-158, which used a combined proportion score (CPS) for PD-L1, patients whose tumors had a PD-L1

Table 2. Ongoing or New Immunotherapy Trials in SCLC

Regimen	Phase	Identifier	Primary Endpoint(s)
First-line with chemo-immunotherapy			
Atezolizumab + EP +/- tiragolumab (anti-TIGIT)	3	NCT04256421	PFS and OS
Nivolumab + EP +/- BMS-986012 (anti–fucosyl-GM1)	RPh2	NCT04702880	PFS, AEs, SAEs
Olaparib + durvalumab + EP +/- radiation therapy	1/2	NCT04728230	DLT
Maintenance after induction chemo-immunotherapy			
Vorolanib + atezolizumab	2	NCT04373369	PFS
Atezolizumab +/- talazoparib in SFLN11-positive SCLC	2	NCT04334941	PFS
Niraparib + temozolomide + atezolizumab	1b/2	NCT03830918	RP2D (Ph1), PFS (Ph2)
Relapsed disease			
Nivolumab + ipilimumab	2	NCT03670056	Change in Teff:Treg ratio
AZD2811 (WEE1 inhibitor) + durvalumab (SUKSES-N5)	2	NCT04525391	DCR
Durvalumab + topotecan	2	NCT04607954	6-month OS
Nivolumab + temozolomide	2	NCT03728361	ORR
Lurbinectedin + pembrolizumab	1/2	NCT04358237	RP2D (Ph1), ORR (Ph2)
Lurbinectedin + nivolumab + ipilimumab	1/2	NCT04610658	RP2D (Ph1), DCR (Ph2)
Nivolumab + ipilimumab + plinabulin	1/2	NCT03575793	Safety

AEs, adverse events; DCR, disease control rate; DLT, dose-limiting toxicity; EP, etoposide/platinum chemotherapy; ORR; objective response rate; OS, overall survival; PFS, progression-free survival; Ph1, phase 1; Ph2, phase 2; RP2D, recommended phase 2 dose; RPh2, randomized phase 2; SAEs, serious adverse events; SCLC, small cell lung cancer; Teff, effector T cell; Treg, regulatory T cell.

CPS of 1% or greater (42/107; 39%) had an ORR of 35.7%, whereas those who had a CPS of less than 1% (50/107; 47%) had an ORR of 6%.[40] Conversely, in CheckMate 032, a PD-L1 TPS of 1% or greater was seen in 18% of tumors tested and did not correlate with response to ICI therapy.[13] In contrast to the expected increased benefit in PD-L1–expressing tumors, in a subgroup analysis of 137 patients with PD-L1 biomarker–evaluable tumors in IMpower133 (34% of patients in the study), the addition of atezolizumab was associated with an OS benefit in the PD-L1–negative (<1%) group (HR, 0.51; 95% CI, 0.30-0.89) but not in the PD-L1–positive (≥1%) group (HR, 0.87; 95% CI, 0.51-1.49).[25] A significant OS benefit was not seen in either the PD-L1–high or the PD-L1–low group when a PD-L1 expression cutoff of less than 5% was used. In summary, PD-L1 is not recommended as a predictive biomarker for response to ICI therapy in SCLC.

Similarly, in multiple tumor types—including NSCLC—a higher TMB in the tumor or blood has been associated with an increased response to ICI therapy independently of PD-L1 expression.[41,42] The increase in somatic mutations is postulated to increase the presentation of tumor-associated antigens, thus promoting a more robust antitumor adaptive immune response. SCLC tumors typically have high TMBs, are associated with tobacco exposure, and are driven by canonical *TP53* and *RB1* mutations.[43] In a comprehensive genomic profiling assessment of 913 SCLC tumors, the median TMB was 9.9 mutations per megabase, with TMBs exceeding 20 mutations per megabase observed in 9% of cases (95% CI, 7.3-11).[11] In the CheckMate 032 study of nivolumab and nivolumab/ipilimumab in relapsed SCLC, a high tissue TMB (the top tertile) was associated with greater clinical benefit with both regimens, including a higher ORR and 1-year OS rate.[44] However, more recently, in an exploratory analysis of the IMpower133 trial of first-line EP chemotherapy combined with atezolizumab, blood TMB cutoff levels of 10 and 15 mutations per megabase were not predictive of response to combination therapy.[24] Several ongoing and upcoming studies will continue to explore TMB as a predictive biomarker for ICI response in SCLC, including NRG LU005, which is investigating ICI therapy with concurrent chemoradiotherapy in limited-stage SCLC.[45]

Insights From Studies of the SCLC Immune Tumor Microenvironment and SCLC Biology

There is a significant focus on augmenting the therapeutic activity of ICIs in SCLC in the first-line and relapsed settings. Current strategies center predominantly on

combination immunotherapy approaches, co-targeting molecules highly expressed in SCLC to enhance ICI responses or to redirect T cells. Several of these novel strategies have emerged from studies of the SCLC immune tumor microenvironment and have provided new insights into SCLC biology, including a proposed classification of SCLC in subsets based on molecular profiles and expression of immune inhibitory proteins. In one analysis of 90 tumor samples, PD-L1 protein expression was detected in only 7%, and the expression of tumor-infiltrating lymphocytes (CD3+, CD8+, and CD20+) was significantly lower in SCLC than in NSCLC.[46] B7-H3, or CD276, a member of the B7 superfamily that inhibits T cell–mediated responses, is expressed in 65% of SCLCs and is another potential immunotherapeutic target of interest.[46] Expression of the inhibitory T-cell immunoreceptor TIGIT was found in 75% of samples of limited-stage SCLC. In a study of 32 primary early-stage SCLC tumors designated as either neuroendocrine (NE)–high or NE-low, higher numbers of CD8+ T effector cells and greater expression of immunosuppressive molecules, including TIM3, PVR, and IDO, were found in NE-low tumors than in NE-high tumors.[47] Several current clinical trials are designed to overcome ICI resistance by addressing these co-expressed inhibitory molecules.

Recent analysis of SCLC gene expression profiles has elucidated 4 molecular SCLC subtypes driven by global transcription regulators (ASCL1, NEUROD1, POU2F3, and YAP1), which may serve as the basis for identifying predictive biomarkers in SCLC.[48] Each of the transcriptional programs has predicted targetable vulnerabilities, such as BCL-2 and DLL3 in ASCL1-dominant tumors and Aurora kinase in NEUROD1-dominant tumors. Additional studies using circulating tumor cell xenografts and single-cell RNA sequencing analyses have reported both intertumoral and intratumoral heterogeneity of gene expression within SCLC, and importantly, changes in gene expression profile may track with the development of therapeutic resistance.[49,50] Using a combination of RNA sequencing and immunohistochemistry in a discovery set of neuroendocrine tumors, the YAP1 SCLC subtype (SCLC-Y) was found to be associated with a T cell–inflamed gene expression score.[51] Further, an inflamed subtype (SCLC-I) characterized by a low expression of signatures for ASCL1, NEUROD1, and POU2F3 has been described and is predicted to be more sensitive to ICI therapy.[52] This study included a retrospective analysis of patients enrolled to IMpower133, of whom 18% were classified as having the SCLC-I subtype. In this analysis, the SCLC-I subtype was associated with a more significant magnitude of benefit from the addition of atezolizumab than were the other SCLC subtypes.[52] Correlation of outcomes with SCLC molecular subtypes of patients receiving immunotherapy in ongoing studies may enable a better understanding of the predictive or prognostic value of this subtype classification and ultimately lead to the development of prospective biomarker-based studies.

Ongoing Studies of Immunotherapy Combinations in SCLC

Further investigation into immunogenomic features and the tumor microenvironment of SCLC has provided more insight into potentially targetable vulnerabilities of this cancer and combinatorial strategies to augment ICI responses. ICIs are also under evaluation in combination with a recently approved agent in SCLC, lurbinectedin. Selected ICI-based studies are highlighted in Table 2.

Tiragolumab, a monoclonal antibody targeting TIGIT, is combined with chemo-immunotherapy as part of frontline therapy in the phase 3 randomized SKYSCRAPER-02 study (NCT04256421). In this study, 470 patients with therapy-naive extensive-stage SCLC are randomly assigned to receive EP/atezolizumab plus either tiragolumab or placebo for 4 cycles, followed by tiragolumab plus atezolizumab or placebo. The primary endpoints of this study are PFS and OS. This study has completed enrollment; results are pending. In a phase 2 study of LAG525 (anti-LAG3) in combination with the anti–PD-1 agent spartalizumab, the SCLC cohort met the criteria for expansion on the basis of the clinical benefit rate.[53]

Other novel approaches combine ICIs or chemotherapy/ICIs with inhibitors of proteins that are highly (or selectively) expressed in SCLC, including fucosyl-GM1 and poly(ADP-ribose) polymerase (PARP). For several of these combinations with ICIs, additive or better effects have been demonstrated preclinically or in earlier-phase studies. Fucosyl-GM1 is an SCLC-selective tumor antigen that is expressed in approximately 65% to 90% of SCLC tumors.[54] In an ongoing phase 1/2 clinical trial, the combination of the anti–fucosyl-GM1 monoclonal antibody BMS-986012 and nivolumab yielded an ORR in 11 of 29 patients (38%) with relapsed SCLC and no prior ICI therapy, a result that was favorable in comparison with a historical control of nivolumab monotherapy (12% ORR in CheckMate-032).[15,55] The median OS in this pretreated SCLC population was an encouraging 18.7 months. BMS-986012 is also under investigation in combination with chemotherapy and nivolumab in the frontline treatment of advanced SCLC (NCT04702880). PARP is a DNA damage response gene that is overexpressed in most SCLC cases. Preclinical studies have demonstrated that PARP inhibition can sensitize tumors to immunotherapy.[56] Although a small phase 2 study of durvalumab plus olaparib (Lynparza, AstraZeneca) did

not meet its primary endpoint of PFS in patients with relapsed SCLC in exploratory correlative studies, the tumors of responders at biopsy demonstrated a dense T-cell infiltrate and increased PD-L1 expression that was consistent with an inflamed phenotype.[57] Subsequent preclinical and exploratory correlative analyses from a phase 2 study of temozolomide plus the PARP inhibitor veliparib in relapsed SCLC report that the expression of SFLN11, a putative DNA/RNA helicase, is associated with responses to PARP inhibition.[58,59] Combining these concepts of selection for PARP inhibitor sensitivity and combinatorial activity of immune checkpoint inhibition plus inhibition of DNA damage repair, S1929 (NCT04334941) is a phase 2 randomized study of maintenance atezolizumab vs atezolizumab plus the PARP inhibitor talazoparib (Talzenna, Pfizer) in patients with SFLN11-positive extensive-stage SCLC. The primary endpoint is PFS. Preclinically, the combination of talazoparib and the alkylating agent temozolomide demonstrated synergy in vitro and combinatorial activity in vivo in SCLC animal models.[59] TRIO-US L-06 (NCT03830918) is a phase 1b/2 study of the PARP inhibitor niraparib (Zejula, Tesaro) plus temozolomide and atezolizumab vs atezolizumab as maintenance therapy in extensive-stage SCLC after induction chemoimmunotherapy. In early reports, dose-limiting toxicities occurred at the first dose level, and additional dose levels are currently being explored.[60]

Delta-like 3 (DLL3) is a Notch family member that is both highly and selectively expressed in SCLC.[61] It is therefore an attractive candidate for targeting therapies such as antibody-drug conjugates (ADCs) and T cell–redirecting therapy. Bispecific antibodies have been developed to engage DLL3 on tumor cells and CD3 on T cells simultaneously and induce T cell–mediated cell death. In preclinical studies, the DLL3 bispecific antibody AMG-757 demonstrated potent cytotoxic activity against SCLC cell lines and antitumor activity against SCLC xenograft models. Consistent with the proposed mechanism, this molecule was able to activate T cells, induce cytokine production, and induce T cell–mediated lysis.[62] AMG-757 is being evaluated in relapsed SCLC both alone and in combination with pembrolizumab (NCT03319940); a favorable safety profile and early evidence of antitumor activity of AMG-757 monotherapy have been reported recently.[63] HPN328, an anti-DLL3 T-cell engager, has demonstrated similar activity preclinically and is being studied more broadly in a phase 1 study of subjects with DLL3-expressing tumors (NCT04471727).[64]

Studies of combinations of ICIs with other established chemotherapy agents are also under way. Lurbinectedin is a transcriptional inhibitor that in 2020 received accelerated approval from the FDA for the treatment of relapsed SCLC on the basis of the ORR (35%) and DOR

in a phase 2 single-arm study.[9] Studies are currently investigating combinations of lurbinectedin plus pembrolizumab (NCT04358237) and nivolumab plus ipilimumab (NCT04610658) in patients with relapsed SCLC.

Conclusion

ICI therapy leads to a modest but statistically significant improvement in outcomes for some patients with SCLC and is now included in standard-of-care therapy for extensive-stage disease. The PD-L1 inhibitors atezolizumab and durvalumab are FDA-approved in combination with platinum-based chemotherapy for the first-line treatment of extensive-stage SCLC, with acceptable toxicity and similar OS benefit, as seen in the IMpower133 and CASPIAN trials. The PD-1 inhibitors nivolumab and pembrolizumab are not approved in this setting, but the available data suggest they are likely beneficial in a subset of patients and may be incorporated as ICI backbones in future studies. The benefit of adding ICIs in the treatment of patients with brain metastases at diagnosis remains unproven. Because of a lack of clear benefit when ICIs are added after 2 cycles of chemotherapy or as maintenance following 4 to 6 cycles of chemotherapy, the early inclusion of atezolizumab or durvalumab with the first or second cycle of EP chemotherapy is recommended for the first-line treatment of extensive-stage SCLC. In limited-stage disease, the addition of ICIs as consolidation following or concurrently with chemoradiation is under investigation in several studies. Finally, the modest improvements in survival with ICI therapy in SCLC are likely reflective of a small subset of patients with durable responses, highlighting the need for predictive biomarkers and rational combinations targeting mechanisms of immunotherapy resistance. Advances in our understanding of SCLC biology and the nuanced immune tumor microenvironment in SCLC should guide the pursuit of novel approaches.

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