



REVIEW

Immune Checkpoint Inhibitors in Small Cell Lung Cancer: A Partially Realized Potential

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Received: April 23, 2019 / Published online: June 17, 2019
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ABSTRACT

Small cell lung cancer (SCLC) is a highly lethal subtype of lung cancer that has seen few therapeutic advances, despite ongoing concerted efforts. Immunotherapy has been an effective option in other carcinogen-related cancers and has shown modest activity in SCLC. Monotherapy with the anti-PD-1 antibody nivolumab in patients with at least two prior lines of therapy was associated with a response rate of 11.9% and a median duration of response of 17.9 months, leading to accelerated approval by the Food and Drug Administration (FDA) as third-line therapy for SCLC. Second-line checkpoint inhibitors have not performed well enough to change the standard of care, and maintenance immunotherapy has not shown significant benefit. However, the incorporation of concurrent immunotherapy in the first-line treatment of SCLC has improved outcomes. The addition of the anti-PD-L1 antibody atezolizumab to standard carboplatin plus etoposide led to an improvement in progression free survival (PFS) and overall survival, the first such improvement in over 30 years leading to the

approval of atezolizumab as part of first-line therapy for advanced SCLC. While these landmark approvals offer promising novel treatment options for this recalcitrant disease, more work is needed to optimize their delivery and to build upon these important advances.

Keywords: Atezolizumab; Checkpoint inhibitors; Immunotherapy; Nivolumab; SCLC

INTRODUCTION

Small cell lung cancer (SCLC) is a highly lethal subtype of lung cancer. It is characterized by a rapid onset, an aggressive course, and a uniquely predictable response pattern. Initially, SCLC is highly responsive to chemotherapy; even monotherapy with numerous agents can induce a response [1]. Unfortunately, relapse is just as predictable as response, and in contrast to treatment-naïve SCLC, relapsed SCLC is highly refractory to most agents.

Standard initial therapy for advanced, extensive-stage (ES) SCLC is platinum-based chemotherapy, typically cisplatin or carboplatin combined with etoposide or irinotecan [2]. The response rate is high (51–67%) but responses are transient, with progression free survival (PFS) typically limited to 4–5.5 months [3]. Survival remains about 10 months or shorter in most series. Despite these poor

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outcomes, treatment has been relatively static for decades, with dozens of phase III trials failing to improve survival. Progress has been elusive as SCLC is a challenging disease to properly study. Fortunately, advances in immunotherapy, specifically implementation of checkpoint inhibitors, have finally changed the treatment landscape for SCLC.

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

IMMUNOTHERAPY RATIONALE

As checkpoint inhibitors began to show promising activity in melanoma and non-small cell lung cancer (NSCLC), their application to SCLC was highly anticipated. SCLC seemed poised to be a highly immune-responsive tumor. A consistent predictor of immune-mediated antitumor response has been a high number of somatic tumor mutations. Among patients with NSCLC treated with pembrolizumab, those with a higher tumor mutational burden (TMB) were more likely to respond to therapy [4]. Tumors with the highest rates of mutations per megabase include melanoma, NSCLC, and bladder cancer—all tumors with responses to immunotherapy [5]. SCLC is a carcinogen-associated tumor and has among the highest rates of mutations per megabase [5, 6], which generated enthusiasm for an immunotherapy approach in SCLC.

Furthermore, there is already a strong relationship between SCLC and the immune system. SCLC, perhaps more than nearly any other cancer, is associated with neurologic paraneoplastic syndromes. Host antibodies recognizing a mal-expressed neuronal antigen on the tumor interact with normal host cells causing a litany of potentially disabling symptoms [7]. Many series have reported that the presence of these syndromes is associated with a better cancer prognosis. Lambert–Eaton syndrome, which occurs in 2–3% of SCLC patients, is associated with improved prognosis, with a median survival of 17.3 months compared to 10 months in patients without Lambert–Eaton [8]. Longer

survival has also been associated with SCLC patients affected by anti-Yo cerebellar syndrome [9]. Furthermore, some patients with idiopathic anti-Hu encephalomyelitis or sensory neuropathy were found to have small SCLC lesions only noted at autopsy [10]. These observations suggest that immune-mediated neurologic syndromes may be associated with immune-mediated anti-tumor responses, responses that could perhaps be induced with checkpoint inhibitors.

IMMUNOTHERAPY FOR RELAPSED SCLC

Despite the high anticipation of success with immunotherapy, outcomes have been modest. Pembrolizumab, an anti-PD-1 antibody, has been explored in SCLC in two notable studies. KEYNOTE-028 was a phase Ib basket study that included 24 patients with relapsed ES-SCLC whose tumor expressed PD-L1 in at least 1% of cells by immunohistochemistry [11]. In this cohort, the response rate was a promising 33% with a duration of response of 19.4 months. Overall median PFS, though, was only 1.9 months. A larger phase II study included 107 patients with previously treated SCLC, unselected for PD-L1 expression [12]. The response rate was 18.7% in this larger study; median PFS was still only 2.0 months and median survival was 8.7 months. A pooled analysis of these two studies reported a response rate of 19.3%, a median PFS of 2.0 months [13], and a median survival of 7.7 months. While pembrolizumab clearly had activity in relapsed SCLC, benefit was limited to a minority of patients.

Perhaps the most experience in this setting has been with the anti-PD-1 antibody nivolumab, alone or with the anti-CTLA-4 antibody ipilimumab. Checkmate-032 was a phase I/II study that initially included a non-randomized cohort of patients with relapsed SCLC. Patients were treated with nivolumab alone or in combination with ipilimumab, employing various dosing schedules [14]. Nivolumab alone had a response rate of 10% with a median PFS of 1.4 months. The addition of ipilimumab

increased the response rate to 19–23% but also increased the rate of grade 3 or higher adverse events. PFS was still limited to only 1.4–2.3 months with the combination. Survival was 4.4–7.7 months across these cohorts. A randomized cohort was then added, with 242 patients randomized 3:2 to nivolumab monotherapy or in combination with ipilimumab. Response patterns were similar: 12% with monotherapy and 21% with the combination [15]. Outcomes were also reported for the 109 patients treated with nivolumab monotherapy in the third-line setting [16]. With a median follow-up of 28.3 months, the response rate was 11.9% with a median duration of response of 17.9 months. On the basis of these data, nivolumab was granted accelerated approval by the Food and Drug Administration (FDA) on August 16, 2018 for the third-line treatment of advanced SCLC.

Unfortunately, most patients are not eligible for third-line therapy. In an analysis of 432 patients with ES-SCLC treated in Germany, only 22% of patients received a third line of treatment [17]. Earlier efforts are certainly appealing. Attempts to introduce immunotherapy in the second-line setting, however, have been disappointing. Checkmate 331 was a randomized phase III trial in patients with SCLC that progressed on or relapsed after platinum-based therapy [18]. In this study, 568 patients were randomized 1:1 to receive nivolumab monotherapy or investigator's choice between topotecan and amrubicin. Nivolumab did not improve survival, with a median OS of 7.5 months compared to 8.4 months with chemotherapy. Both response rate (13.7% vs. 16.5%) and PFS (1.4 months vs. 3.8 months) numerically favored chemotherapy. A non-comparative, randomized phase II study of atezolizumab monotherapy was also disappointing [19]. Among the 43 eligible patients treated with atezolizumab, there was only one response (2.3%) with a median PFS of 1.4 months and median survival of 9.5 months.

MAINTENANCE IMMUNOTHERAPY

Immunotherapy has clear activity in SCLC but failed to improve outcomes compared to

standard second line therapy, despite a seemingly low bar. As SCLC becomes significantly more refractory to therapy at relapse, earlier introduction was explored with maintenance strategies. These have been similarly disappointing. A single-arm phase II trial exploring maintenance pembrolizumab included 45 patients with ES-SCLC who had a response or stable disease after first line platinum-etoposide chemotherapy [20]. The target PFS was 3.0 months, based on historical standards. The observed PFS was only 1.4 months.

A larger, phase III maintenance study reported similar results. Checkmate-451 included 834 patients with ES-SCLC who had an ongoing response or stable disease after four cycles of platinum-based chemotherapy [21]. Patients were randomized 1:1:1 to receive nivolumab 1 mg/kg plus ipilimumab 3 mg/kg every 3 weeks (with maintenance nivolumab 240 mg every 2 weeks after four cycles of induction therapy), nivolumab 240 mg every 2 weeks as monotherapy or placebo. The primary endpoint was an improvement in survival with nivolumab plus ipilimumab as compared to placebo. This endpoint was not met. The OS HR was 0.92 (95% CI 0.8–1.1) with a median OS of 9.2 months with nivolumab plus ipilimumab and 9.6 months with placebo. PFS was marginally improved at 1.7 months vs. 1.4 months (HR 0.72, 95% CI 0.60–0.87) but toxicity was significantly worse, with treatment-related adverse events leading to discontinuation in 29% of patients, compared to < 1% with placebo. Comparisons of nivolumab monotherapy to chemotherapy were exploratory, given the hierarchical analysis, but provided similar results. Nivolumab had a median OS of 10.4 months compared to 9.6 months with placebo (HR 0.84, 95% CI 0.7–1.0) with a PFS of 1.9 months vs. 1.4 months (HR 0.67, 95% CI 0.56–0.81).

FIRST-LINE IMMUNOTHERAPY STRATEGIES

While second-line and maintenance efforts have been disappointing, the greatest potential for impact has always been as first-line therapy. SCLC has a very high rate of attrition with fewer

patients eligible for therapy in later lines. Treatment-naïve patients also lack the cumulative toxicity of prior therapy, and the impact of this prior therapy on the likelihood of generating an immune response is not clear. Given the aggressive natural history of SCLC, however, and the relatively low response rates previously noted, immunotherapy alone carried too great a risk in an unselected population. If response was not seen, patients would likely forfeit the reliable, though admittedly transient, benefit of chemotherapy. This was one reason why combinations of chemotherapy and immunotherapy were explored as first-line therapy (Table 1). Chemotherapy can provide a reliable initial benefit and the immediate addition of immunotherapy could potentially improve long-term outcomes. There is also a potential synergy with chemotherapy–immunotherapy combinations. Chemotherapy can impact myeloid-derived suppressor cells and facilitate tumor antigen release; chemotherapy is a known immune modulator and its effects may promote an immune response [22].

FIRST-LINE ANTI-CTLA-4

The first combination efforts were with chemotherapy and anti-CTLA-4 therapy and were decidedly negative. The addition of ipilimumab to carboplatin plus paclitaxel, as a first-line therapy for ES SCLC, showed no improvement in PFS (3.9 months with ipilimumab vs. 5.2 months with placebo) or overall survival

(9.1 months vs. 9.9 months) [23]. A phase III trial of platinum plus etoposide with ipilimumab or placebo was also negative [24]. This study included 954 patients and ipilimumab compared to placebo did not improve survival (11.0 months vs. 10.9 months), PFS (4.6 months vs 4.4 months), or response rate (62% in both arms). It did increase toxicity, with treatment-related discontinuation noted in 18% of patients compared to 2% with placebo.

FIRST-LINE ANTI-PD-L1

Fortunately, survival was improved with the addition of the anti-PD-L1 antibody atezolizumab to chemotherapy. IMpower 133 was a global, randomized, placebo-controlled, double blind phase I/III trial that included 403 patients with treatment-naïve ES-SCLC [25]. All patients received four cycles of carboplatin AUC 5 on day 1 with etoposide 100 mg/m² on days 1–3 and were randomized to receive concurrent atezolizumab 1200 mg on day 1 or placebo, followed by maintenance atezolizumab or placebo. The co-primary endpoints were overall survival and investigator-assessed PFS; IMpower 133 met both of its primary endpoints.

The addition of atezolizumab improved overall survival, with an improvement in median OS from 10.3 months to 12.3 months and an HR for death of 0.70 (95% CI 0.54–0.91). Atezolizumab improved the 1-year survival rate from 38.2% to 51.7%. PFS was also superior with atezolizumab, with an HR of 0.77 (95% CI

Table 1 Select randomized trials featuring concurrent chemotherapy and immunotherapy

Study	Chemotherapy	Intervention	PFS (months)	PFS HR	OS (months)	OS HR
Reck et al. [23]	Carboplatin plus paclitaxel	Ipilimumab	3.9	0.93 (0.59–1.48)	9.1	0.89 (0.57–1.39)
		Placebo	5.2		10.5	
Reck et al. [24]	Platinum plus etoposide	Ipilimumab	4.6	0.85 (0.75–0.97)	11.0	0.94 (0.81–1.09)
		Placebo	4.4		10.9	
Horn et al. [25]	Carboplatin plus etoposide	Atezolizumab	5.2	0.77 (0.62–0.96)	12.3	0.70 (0.54–0.91)
		Placebo	4.3		10.3	

0.63–0.96). There was no difference in response rate and no new safety signals were identified. Patients in both arms received a median of four doses of carboplatin and 12 doses of etoposide, suggesting that the addition of atezolizumab did not compromise the ability to deliver four full cycles of chemotherapy. These landmark results represent the first improvement in survival in several decades, establishing atezolizumab plus carboplatin plus etoposide as the new standard of care in ES-SCLC. The IMpower 133 regimen was approved by the FDA as first-line therapy for ES-SCLC on March 18, 2019. Two other large phase III SCLC trials have completed accrual with results pending. KEYNOTE 604 randomized patients to chemotherapy alone or with pembrolizumab (NCT03066778) and CASPIAN features three arms: chemotherapy alone, chemotherapy with the anti-PD-L1 antibody durvalumab, or chemotherapy with durvalumab and the CTLA-4 inhibitor tremelimumab (NCT03043872).

BIOMARKERS

In previously treated patients, there is an impressive duration of response to checkpoint inhibitors that is balanced by a very short median PFS. This suggests that most of the benefit is carried by a small subset of patients. Identification of that subset is critical to optimize therapy—not only to ensure patients receive the proper therapy but also to understand why most patients do not respond. The search for a predictive biomarker has been challenging. PD-L1 expression has been explored. In KEYNOTE-158, expression of PD-L1 on either tumor or stromal cells was explored and tumors with expression had superior outcomes [12]. Response in PD-L1-positive tumors (using this combined proportion score, CPS) was 35.7% vs. 6% in the PD-L1-negative tumors. This also translated to a superior survival of 14.9 months vs. 5.9 months and a 1-year survival rate of 53.1% vs. 30.7%. This pattern was not seen in the Checkmate-032 study, where patients with PD-L1 expression had an inferior response rate with nivolumab monotherapy (9% vs. 14%) or in combination with

ipilimumab 3 mg/kg (10% vs. 32%) [15]. In Checkmate-032, however, TMB was associated with a higher response rate. With nivolumab alone, the response rate in patients with high TMB was 21.3% compared to 4.8% in patients with low TMB [26]. With nivolumab and ipilimumab, responses were noted in 46.2% of patients with high TMB and 22.2% with low TMB. However, blood-based TMB, explored in IMpower 133, was not associated with a difference in outcome, with patients above and below pre-specified thresholds all favoring the addition of atezolizumab [24].

CONCLUSION

Small cell lung cancer is a recalcitrant, unforgiving disease whose course can only be minimally altered by our current interventions. Chemotherapy has provided reliable initial responses for decades, but its transient nature underscores the need for newer treatment strategies. Immunotherapy has finally improved outcomes. While nivolumab is an approved option in the third-line space, the failures of immunotherapy in the second-line and maintenance settings have been disappointing. Fortunately, outlook is now buoyed by the success of IMpower 133. The addition of concurrent atezolizumab to carboplatin and etoposide has finally delivered on improving survival, offering patients a long-awaited novel approach. We now look to the field to build upon this success, confident that the next advance will not take decades to materialize.

ACKNOWLEDGEMENTS

Funding. No funding or sponsorship was received for publication of this article.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Disclosures. SAA reports no relevant conflicts. SVL reports serving as a paid consultant and/or advisory board member for Apollomics, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, G1 Therapeutics, Genentech/Roche, Heron, Ignyta, Inivata, Janssen, Lilly, Merck, Pfizer, Regeneron, Taiho (DSMB), Takeda/Ariad, and Tempus. SVL has received research funding from AstraZeneca, Bayer, Blueprint, Bristol-Myers Squibb, Clovis, Corvus, Esanex, Genentech/Roche, Ignyta, Lilly, Lycera, Merck, Molecular Partners, OncoMed, Pfizer, Rain Therapeutics, and Threshold.

Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

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