Extensive-Stage Small-Cell Lung Cancer

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Contributor: Ivy Riano

Small-cell lung cancer (SCLC) is an aggressive subtype of lung cancer characterized by a rapid initial response and early development of resistance to systemic therapy and radiation. The management of SCLC significantly changed for the first time in decades with the introduction of immune checkpoint inhibitors.

Keywords: small-cell lung cancer ; pembrolizumab ; immunotherapy ; PD-1 ; checkpoint inhibitor

1. Introduction

Small-cell lung cancer (SCLC) is a neuroendocrine tumor that represents about 13% of all lung cancers and occurs predominantly in smokers [1]. In general, SCLC grows rapidly and has high metastatic potential. These two properties contribute to a particularly high mortality rate. Most patients have advanced disease and present with distant metastases, malignant effusions, and/or contralateral supraclavicular or hilar lymph node involvement. In these patients, systemic chemotherapy is typically the primary therapeutic modality, with some patients also drawing benefit from radiation therapy [2]. Although the tumor–node–metastasis (TNM) classification is preferred to the staging system of the Veterans Administration Lung Study Group (VALSG), which separates limited-stage (LS) disease (tumor confined to one hemithorax and one radiation port; no malignant pleural or pericardial effusion) from extensive-stage (ES) disease (not meeting criteria for LS), the latest staging system is still widely used in both designing clinical trials and presenting data from them, as it effectively distinguishes patients treated primarily with chemotherapy (LS disease) from those treated with systemic chemotherapy or chemoimmunotherapy (ES disease) [3][4][5].

The initial approach to SCLC treatment varies substantially by stage. In non-metastatic SCLC, the therapeutic goals are to achieve durable control of thoracic disease and reduce the risk of metastatic dissemination. Local treatment options include surgery and radiotherapy. Chemotherapy can both augment the local efficacy of radiation and potentially treat micrometastatic disease. The standard chemotherapy regimen in this setting is cisplatin–etoposide. In patients who respond to initial treatment, prophylactic cranial irradiation (PCI) is also part of the standard management with non-metastatic disease [3][6]. For ES disease, the first-line chemotherapy for newly diagnosed metastatic SCLC consisted of a platinum agent (cisplatin or carboplatin) with etoposide. Radiotherapy is traditionally reserved for the palliation of symptoms in patients with ES disease, and PCI remains controversial [3][7]. Despite a typically dramatic initial response to therapy, most patients with SCLC experience relapse within 6 months despite chemotherapy and radiation and the 5-year survival rates for patients with ES disease remain low (5%) [2]. As outcomes are poor, therapeutic options after relapse are limited.

Several groups have pursued comprehensive genomic profiling of SCLC with hopes of identifying actionable genomic targets. Studies have shown high somatic mutation rates and copy number alterations in the tumor tissues with a near-universal bi-allelic inactivation of TP53 and RB1 [8][9]. Unfortunately, there has been a notable lack of activating mutations in driver oncogenes in SCLC, and molecularly targeted agents have yet to find a place in the treatment of SCLC. This is not to say alterations are uncommon; a comprehensive analysis of 236 cancer genes in 98 patients using next-generation sequencing demonstrated that all patients had at least one genomic alteration, and an average of 3.9 alterations was seen per tumor [10]. These high mutation rates suggest that these tumors may respond to immune checkpoint inhibition, as previous work has correlated the rate of somatic mutations to the efficacy with programmed cell death protein 1 (PD-1) inhibitors [11].

The advent of immune checkpoint inhibitors has changed the landscape of oncology care over the past decade. The mainstay of treatment for ES-SCLC has been platinum-based chemotherapy with etoposide [12]. Nivolumab monotherapy was the first immune checkpoint inhibitor to show durable responses, leading to its accelerated approval in the United States (U.S.) as third-line monotherapy in patients with ES-SCLC [13]. Pembrolizumab showed similar results, leading to its accelerated approval as third-line monotherapy [14].

The interest in immunotherapy for SCLC, however, is undeniable. This is largely based on the durability of response and the potential for long-term survival. These features coupled with the high attrition rate seen in SCLC [15] prompted the earlier introduction of immunotherapy in subsequent prospective trials. Two randomized phase 3 clinical trials demonstrated an improvement in survival with the addition of an anti-programmed death-ligand 1 (PD-L1) antibody, either atezolizumab or durvalumab, to standard first-line platinum-based chemotherapy [16][17]. These outcomes led to the U.S. Food and Drug Administration (FDA) full approval of atezolizumab and durvalumab in the first-line setting. Pembrolizumab given with platinum-doublet chemotherapy was also studied in the first-line setting but did not demonstrate a survival benefit [18].

2. Pembrolizumab for Previously-Treated ES-SCLC

Pembrolizumab is a selective, humanized, monoclonal anti-PD-1 antibody that disrupts the interaction between the PD-1 and its ligand, PD-L1, allowing activation and expansion of cytotoxic T-cells to facilitate an immune-mediated, anti-tumor response [17]. Pembrolizumab has demonstrated relevant clinical activity in patients with previously treated ES-SCLC. Most of the evidence regarding the use of pembrolizumab in previously treated SCLC comes from two single-arm trials—KEYNOTE-028 cohort C1 (NCT02054806) [19] and KEYNOTE-158 cohort G1 (NCT02628067) [20]. A comparison between the designs of pembrolizumab clinical trials in ES-SCLC is included in **Table 1**.

Table 1. Comparison between designs of published pembrolizumab clinical trials in extensive-stage small-cell lung cancer.

Trial	Design	End Points	PD-L1 Expression	Key Eligibility Criteria	Pembrolizumab Dose	Response Assessment
KEYNOTE-028 [19]	Multicohort Phase 1b open-label for previously treated SCLC	Primary: ORR; secondary: PFS, OS, DOR, safety, and tolerability	PD-L1 expression was required	SCLC or pulmonary neuroendocrine tumor that had failed standard therapy	Pembrolizumab 10 mg/kg every 2 weeks	Every 8 weeks for 6 months; every 12 weeks thereafter
KEYNOTE-158 [20]	Multicohort Phase 2 open-label for previously treated SCLC	Primary: ORR; secondary: PFS, OS, DOR, and safety	No PD-L1 expression required	Evaluable tumor sample for biomarker assessments	Pembrolizumab 200 mg IV every 3 weeks	Every 9 weeks for 12 months; every 12 weeks thereafter
Gadgeel et al. [21]	Phase 2 open-label, single-arm maintenance pembrolizumab after 1st line chemotherapy	Primary: PFS; secondary: OS and safety	No PD-L1 expression required	Response or stable disease after chemotherapy and enrollment within 8 weeks of last chemotherapy dose	Pembrolizumab 200 mg IV every 3 weeks	Every 6 weeks (two cycles) for the first six cycles and then at the discretion of the treating physician
KEYNOTE-604 [18]	Phase 3 randomized, double-blind, placebo-controlled for the 1st-line treatment of ES-SCLC	Primary: PFS, OS; secondary: ORR, DOR, and safety	PD-L1 expression was assessed retrospectively	SCLC not previously treated with systemic therapy	Pembrolizumab 200 mg IV every 3 weeks + platinum/etoposide	At baseline, every 6 weeks for the first 48 weeks, and every 9 weeks thereafter
Kim et al. [22]	Phase 2, multi-center, open label, single-arm for ES-SCLC that had not responded to 1st line	Primary: ORR; secondary: OS, PFS, safety and analysis of biomarkers	PD-L1 expression was required	ED SCLC that progressed after 1st line standard treatment regardless of their initial best response	Pembrolizumab 200 mg IV every 3 weeks + paclitaxel	At baseline, every two cycles until six cycles. Thereafter, every three cycles

ORR, objective response rate; PFS, progression-free survival; OS, overall survival; DOR, duration of response; PD-L1, programmed death-ligand 1; SCLC, small-cell lung cancer; mg, milligrams; kg, kilograms; IV, intravenous.

The phase 1b open-label KEYNOTE-028 was a multicohort trial that explored the safety and efficacy of pembrolizumab in patients with various PD-L1-positive tumors [19]. In this study, patients received pembrolizumab 10 mg/kg every two weeks for 24 months or until documented disease progression or intolerable toxicity. Cohort C1 included patients with ES-SCLC or primary pulmonary neuroendocrine tumors that had failed standard therapy. Tumor PD-L1 expression assayed by immunohistochemistry (IHC) using the Dako 22C3 PD-L1 clone was required for entry. PD-L1 positivity was defined by membranous PD-L1 expression in ≥1% of tumor cells and associated inflammatory cells or positive staining in stroma [19].

A total of 163 patients were screened for enrollment, 31.7% tested positive for PD-L1 expression, and 24 patients were treated. At the time the data was presented, the study median follow-up was 9.8 months (range, 0.5–24.4 months). Patients were heavily pretreated; 87.5% of patients had received two or more lines of therapy. The confirmed overall response rate (ORR) was 33.3% (95% confidence interval (CI), 15.6–55.3), and the median duration of response (DOR) was 19.4 months (range, ≥3.6–≥20.0 months) with three patients remaining in treatment at the time of data cutoff. The median progression-free survival (PFS) was limited to 1.9 months (95% CI, 1.7–5.9), but the median OS was 9.7 months (95% CI, 4.1—not reached). Treatment-related adverse events (AEs) were seen in 16 (66.7%) of 24 patients. Eight patients (33.3%) had grade 3 to 5 AEs, two of whom had AEs related to treatment. One patient experienced grade 3 bilirubin elevation, and another patient experienced grade 3 asthenia and grade 5 colitis/intestinal ischemia [19].

This encouraging activity prompted development of the larger KEYNOTE-158 study—a phase 2 open-label multi-cohort study of eleven cancer types, including a cohort for patients with ES-SCLC who had progressed after or were ineligible for standard therapy [20]. Having an evaluable tumor sample for biomarker assessment was an eligibility criterion, but tumor PD-L1 expression was not required. The pembrolizumab dose in this trial was a fixed dose of 200 mg every three weeks. A total of 107 patients with ES-SCLC were included in the study; 36 patients (34%) were continuing on-study at the data cutoff date. Again, patients were heavily pretreated; 79% had one or two prior therapies. Median follow-up was 10.1 months (range, 0.5–17.5). Tumors were PD-L1–positive in 42 patients (39%); this was determined using the combined positive score (CPS), defined as the ratio of PD-L1–positive cells (including tumor cells, lymphocytes, and macrophages) to the total number of tumor cells × 100. PD-L1 positivity was defined as a CPS ≥ 1. Of the total study population, 14% were unevaluable for CPS evaluation. The ORR with pembrolizumab in this trial was modest at 18.7% (95% CI, 11.8–27.4). Differences in response were observed in patients with PD-L1–positive tumors (using CPS) with an ORR of 35.7% (95% CI, 21.6–52.0) versus 6.0% (95% CI, 1.3–16.5) in patients with PD-L1-negative tumors. Median DOR had not been reached at the time of data cutoff (range, 2.1–18.7 months), but twelve patients had a DOR of over 9 months. Median OS was 8.7 months and median PFS was 2.0 months (95% CI, 1.9–2.1) in all patients, without significant difference in PFS between patients with PD-L1-positive and PD-L1-negative tumors (2.1 versus 1.9 months). Treatment-related AEs occurred in 63 patients (59%) and led to four treatment discontinuations and one death (pneumonia) [20].

Results from a pooled analysis of these two clinical trials, KEYNOTE-028 cohort C1 and KEYNOTE-158 cohort G1 are described in **Table 2** [14]. Of the 131 patients included from both cohorts, this pooled efficacy and safety analysis included 83 patients with ES-SCLC (19 from KEYNOTE-028 and 64 from KEYNOTE-158) who had previously received ≥2 lines of therapy for advanced disease. Including both trials, 47 patients (57%) had PD-L1-positive tumors, and 30 (36%) had received ≥3 lines of therapy. In the third-line-and-beyond setting, the ORR to pembrolizumab was 19.3% (95% CI, 11.4–29.4). Two patients (2.4%) had a complete response, and 14 had a partial response; 14 of 16 responders (88%) had PD-L1-sitive tumors. Median DOR was not reached (range, 4.1–35.8 months). Median time to response was 2.1 (range, 1.7–4.1) months; 54% of patients had disease progression at the time of data cutoff. Median PFS was 2 months (95% CI, 1.9–3.4). The median OS with pembrolizumab was 7.7 months (95% CI, 5.2–10.1), with impressive landmark survival rates at 12 months (34.3%) and 24 months (20.7%). In the sum of AEs, no significant differences were observed between patients with one or two lines of prior therapy. Treatment-related AEs occurred in 83 patients (61.4%). The most common adverse events included fatigue (12%), pruritus (12%), rash (12%), hypothyroidism (10.8%), and arthralgia (9.6%). Grade 3 immune-related AEs (7.2%) included colitis, severe skin reaction, adrenal insufficiency, pneumonitis, and pancreatitis [14].

Table 2. Summary KEYNOTE-028 and KEYNOTE-158 trial results.

Clinical Study	ORR	DOR	PFS	OS
KEYNOTE-028 [19]	**33.3% (95% CI, 15.6–55.3)**	**19.4 mo (range, 3.6–20.0)**	**1.9 mo (95% CI, 1.7–5.9)**	**9.7 mo (range, 4.1-NR)**
KEYNOTE-158 [20]	**18.7 % (95% CI, 11.8–27.4)**	**NR (range, 2.1–18.7)**	**2.0 mo (95% CI, 1.9–2.1)**	**8.7 mo**
Pooled analysis * [14]	**19.3% (95% CI, 11.4–29.4)**	**NR (range, 4.1–35.8)**	**2.0 mo (95% CI, 1.9–3.4)**	**7.7 mo (95% CI, 5.2–10.1)**

* Pooled analysis: KEYNOTE-028 and KEYNOTE-158. ORR, objective response rate; PFS, progression-free survival; OS, overall survival; DOR, duration of response; CI, confidence interval; mo, months; NR, not reached.

In summary, the pooled analysis suggested pembrolizumab had antitumor activity among patients with ES-SCLC who had received ≥2 previous lines of therapy, regardless of PD-L1 expression. Responses were durable for 12 months or longer in 67.7% of patients, and 18 months or longer in 60.9% of the responders [14]. Based on the durability of the response, the U.S. FDA granted accelerated approval to pembrolizumab as third-line treatment for patients with ES-SCLC and disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy.

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