Review

Check for updates

Advancements in Small-cell Lung Cancer: The Changing Landscape Following IMpower-133

Jose Pacheco, Paul A. Bunn

Abstract

The treatment landscape of small-cell lung cancer is rapidly evolving. Results of the first-line randomized trial comparing etoposide/carboplatin/placebo with etoposide/carboplatin/atezolizumab (IMpower-133) were recently published, showing a longer progression-free survival and overall survival for patients receiving atezolizumab. These results changed the standard first-line therapy for the first time in several decades. There are 4 additional ongoing randomized trials comparing chemotherapy alone with chemotherapy plus immune checkpoint inhibition as initial treatment. In addition to these major changes in first-line treatment, multiple second or later line options with new agents are likely to change therapeutic standards in these settings. In this article, we discuss the changing treatment landscape following IMpower-133, highlight new second/subsequent line approaches, and discuss the role of biomarkers in patient selection for these treatments.

Clinical Lung Cancer, Vol. 20, No. 3, 148-60 © 2018 Elsevier Inc. All rights reserved.
Keywords: Atezolizumab, Extensive stage, SCLC, Second line, Subsequent line

Introduction

For the past several decades, first-line therapy for extensive stage small-cell lung cancer (ES-SCLC) has been platinum-based chemotherapy (cisplatin or carboplatin) combined with etoposide.[1] Recent studies indicated that several immune checkpoint inhibitors (ICIs) were active in refractory SCLC. Subsequently, a phase III randomized trial (IMpower-133) demonstrated that adding the ICI atezolizumab to etoposide + carboplatin (EP) improved both progression-free survival (PFS) and overall survival (OS) (Figure 1).[2] These results have changed the standard of care for the first time in several decades. Ongoing randomized trials of other ICIs in the first line are likely to result in combinations of ICIs with EP being standard front-line therapy for the near future. Progress will still be made exploring new drugs and novel immune therapy combinations in second and subsequent line therapy.

Topotecan was approved in 1998 by the United States Food and Drug Administration (FDA) for second-line SCLC following progression on platinum-based chemotherapy, and both intravenous/oral topotecan remain the only FDA-approved therapy in this setting.[3] Based on studies described below, nivolumab became the only approved therapy for ≥ third-line SCLC.[3] However, many new options have emerged for post-platinum therapy (Figure 2). In this review, we discuss the changing treatment landscape following IMpower-133, highlight new second/subsequent line approaches, and discuss the role of biomarkers in patient selection for these treatments.

University of Colorado Cancer Center, Aurora, CO

Submitted: Oct 23, 2018; Revised: Dec 12, 2018; Accepted: Dec 25, 2018; Epub: Jan 2, 2019

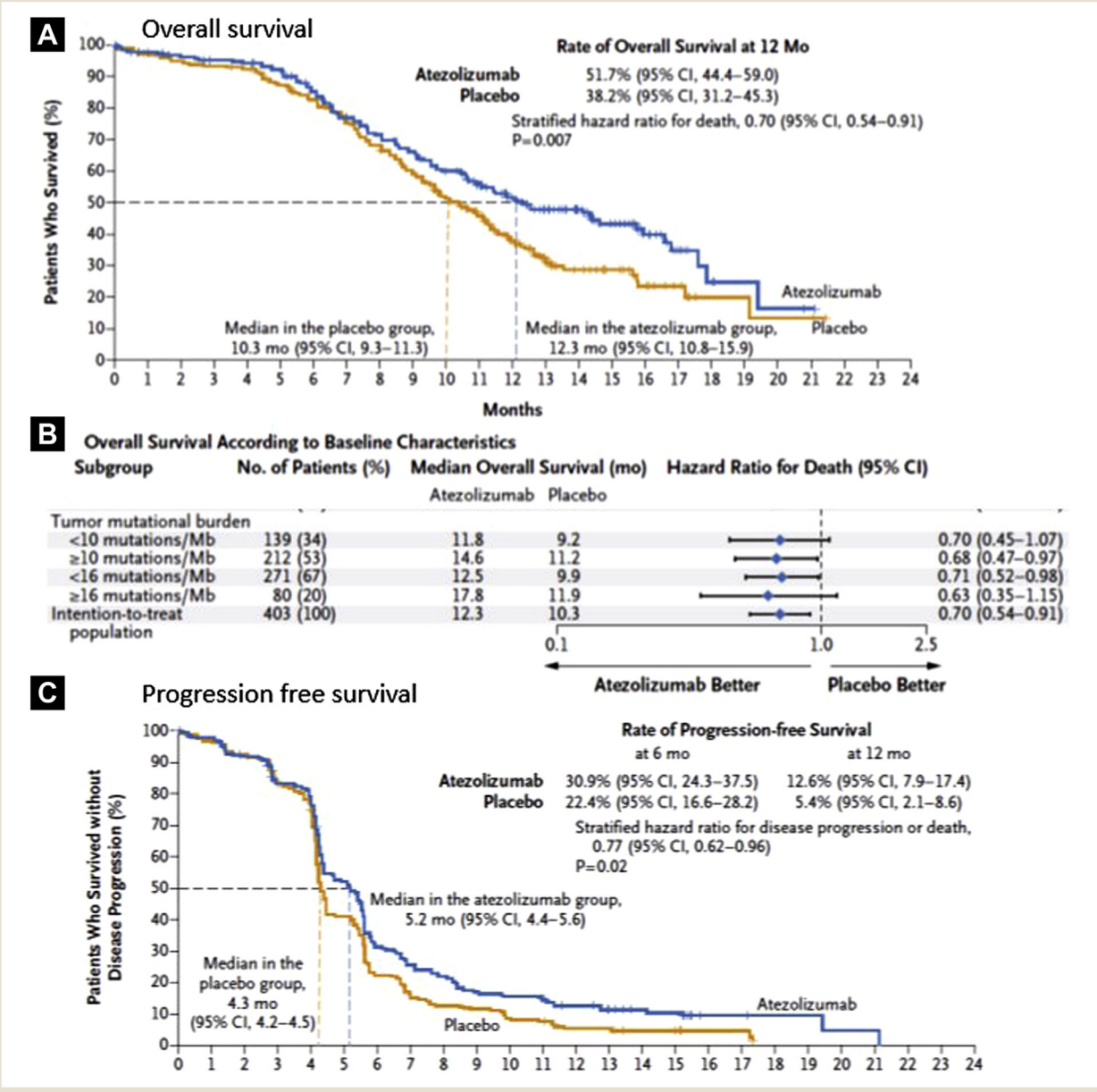
Address for correspondence: Jose Pacheco, MD, Department of Internal Medicine/Medical Oncology, University of Colorado Anschutz Cancer Center, 1665 Aurora Ct, Room 5309, Aurora, CO 80045
E-mail contact: jose.m.pacheco@ucdenver.edu

Methods

Trials were identified by searching PubMed without date limits, abstracts from major medical society meetings, and clinicaltrials.gov. Search terms included: AEB1102, Alisertib, Alisertib phase 2, Anlotinib, AZD2811, CASPIAN, CheckMate 032, CheckMate 451, durvalumab and SCLC, GSK2879552, IMpower133, INCB059872, ipilimumab and SCLC, lurbinectedin, KEYNOTE 158, KEYNOTE 604, Navitoclax and SCLC, nivolumab and platinum etoposide small cell, Pembrolizumab and maintenance SCLC, Pembrolizumab and paclitaxel SCLC, Rovalpituzumab tesirine, RRx-001, Sacituzumab Govitecan SCLC, Sunitinib maintenance SCLC, Talazoparib and SCLC, Temozolomide and Olaparib, temozolomide and small cell, Topotecan and CAV, and Topotecan and SCLC phase III. Additionally, the following sections of the 2018 International Association for Lung Cancer World Conference on Lung Cancer were reviewed: "Management of SCLC patients not represented in clinical trials," "Presidential Symposium," and "What is changing in the management of pulmonary neuroendocrine tumors?" Supplemental Table 1 (in the online version) provides information on the number of items identified by each search term and the reasons for exclusion of some studies.

1525-7304/$ - see frontmatter © 2018 Elsevier Inc. All rights reserved.
https://doi.org/10.1016/j.cllc.2018.12.019

Figure 1 Summary of IMpower-133 Results; Adapted From Horn et al.[2] A, Overall Survival Curves. B, Excerpt From a Forest Plot Showing that Different Cutoffs for Blood-Based Tumor Mutational Burden Testing Did Not Influence the Relative Overall Survival Benefit of Atezolizumab + Carboplatin + Etoposide When Compared With Carboplatin + Etoposide. C, Progression-free Survival Curves



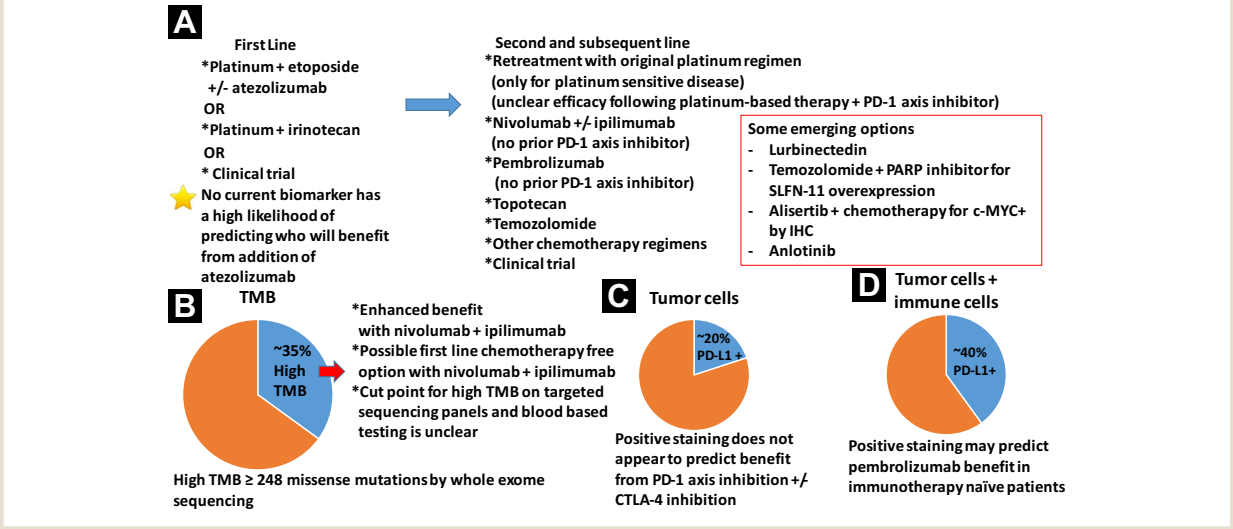
Abbreviations: CI = confidence interval; mo = months; no = number.

Immune Checkpoint Inhibition

First-line Therapy

Atezolizumab + EP. IMpower-133 compared EP with EP + atezolizumab. Four cycles of platinum-based doublet chemotherapy ± atezolizumab were administered as induction, each cycle being given every 21 days. Carboplatin was administered at area under the curve 5 on day 1 and etoposide at 100 mg/m^2 on days 1 to 3. Atezolizumab was administered at 1200 mg every 3 weeks on day 1. After the 4 cycles of induction therapy, patients without progressive disease continued every 3-week atezolizumab or placebo as maintenance until disease progression or unacceptable toxicity. The median number of cycles of atezolizumab in the experimental group (induction + maintenance) was 7, and 11.6% of patients received atezolizumab for > 12 months (ie, > 17 cycles). Prophylactic cranial radiation was permitted on this trial, but not mandated. Consolidative thoracic radiotherapy was not allowed. Twenty-two patients on each study arm (about 11%) received prophylactic cranial radiation.[2]

Figure 2 Treatment Options for Small-Cell Lung Cancer and Potential Utility of TMB/PD-L1 as Biomarkers.[1,4-11] A. Schema of Treatment Options. B, TMB as a Potential Biomarker. C, PD-L1 on Tumor Cells as a Potential Biomarker. D, PD-L1 on Tumor Cells and Immune Cells as a Potential Biomarker. Platinum-Sensitive Disease is Defined as Progression/Relapse ≥ 90 Days Following Last Dose of Platinum-Based Chemotherapy. Some Other Chemotherapy Regimens Include: Amrubicin, Cyclophosphomide + Doxorubicin + Vincristine, Gemcitabine, Irinotecan, Paclitaxel, and Vinorelbine



Abbreviations: CTLA-4 = Cytotoxic T lymphocyte-associated protein 4; IHC = immunohistochemistry; PARP = poly ADP ribose polymerase; PD-1 = programmed cell death protein 1; PD-L1 = programmed death ligand 1; SLFN-11 = Schlafen family member 11; TMB = tumor mutational burden.

Figure 1 summarizes the results from IMpower-133. The objective response rate (ORR) was similar in the 2 arms, as was median duration of response. However, ongoing responses at the time of data reporting were greater in the EP + atezolizumab arm at 14.9% versus 5.4%. Additionally, the OS curves were nearly identical until about 7 to 8 months, after which they began to separate in favor of EP + atezolizumab; this separation was still increasing at the median follow-up of 13.9 months.[2] The increased duration of response and prolonged survival outcomes seen with other chemotherapy + ICI combinations in first-line treatment of non–small-cell lung cancer (NSCLC) suggests the OS curves in IMPOWER-133 may separate further with longer follow-up and that the hazard ratio (HR) is likely to improve more in favor of EP + atezolizumab.[12-15]

With respect to PFS, the fact that the results were almost identical through the median indicates that nearly 50% of the patients had no benefit from the addition of atezolizumab and emphasizes the need to identify a biomarker distinguishing patients likely or unlikely to benefit. Unfortunately, blood-based tumor mutational burden (TMB) did not associate with benefit in this trial (Figure 1).[2] The superiority of EP + atezolizumab is likely to result in this regimen remaining a standard, at least until the results of other ICI randomized trials are known. Table 1 summarizes the other ongoing first-line randomized trials with ICIs in ES-SCLC.[16] Trials summarized in Table 1 are based on data from earlier phase studies in second or later line therapy described below. A press release recently indicated that the phase III randomized maintenance trial comparing nivolumab and nivolumab + ipilimumab versus placebo failed to meet its primary endpoint.[17] Although details of the study are not currently available, this maintenance approach will likely not be utilized unless other agents show a positive result.

Second and Later Line Therapy

Nivolumab ± Ipilimumab. Ipilimumab was the first ICI tested in SCLC. Unfortunately, a phase III randomized trial of platinum-based chemotherapy ± ipilimumab showed no benefit from adding ipilimumab.[18] Trials showing benefit of combining ipilimumab with nivolumab in melanoma and NSCLC lead to trials of nivolumab alone and with ipilimumab in ES-SCLC. The CheckMate-032 trial evaluated nivolumab ± ipilimumab in previously treated SCLC. Nivolumab was administered at 3 mg/kg every 2 weeks. Nivolumab + ipilimumab was administered every 3 weeks for 4 cycles followed by nivolumab maintenance at 3 mg/kg every 2 weeks, with nivolumab and ipilimumab being dosed at either 1 mg/kg and 3 mg/kg, or 3 mg/kg and 1 mg/kg, respectively.[4-7] The trial originally used any of these 3 regimens and subsequently randomized patients between nivolumab alone or nivolumab 1 mg/kg + ipilimumab 3 mg/kg.

The ORR with single agent nivolumab was 11% (n = 245) in the combined cohorts (randomized and non-randomized).[7] In the non-randomized cohort, the ORR was 19% with nivolumab 3 mg/kg + ipilimumab 1 mg/kg (n = 54), whereas it was 23% for nivolumab 1 mg/kg + ipilimumab 3 mg/kg (n = 61) (Table 2).[5] The ORR was 22% in the combined cohorts with nivolumab 1 mg/kg + ipilimumab 3 mg/kg (n = 156) (Table 2).[7] Although the ORR was numerically higher for nivolumab + ipilimumab when compared with nivolumab, no statistical comparisons were made

Table 1 Ongoing Randomized Trials of Immune Checkpoint Inhibitors in First-line Small-cell Lung Cancer

Trial Phase	Patient Population	Treatments	Primary Outcome	Estimated Completion Date
Phase III (IMpower-133)[2,16]	First-line therapy with platinum-based doublets ± ICI	a) Atezolizumab + carboplatin + etoposide, OR b) Carboplatin + etoposide	PFS and OS	Aug 1, 2019
Phase II[16]	First-line therapy with platinum-based doublets ± ICI	a) Nivolumab + platinum + etoposide, OR b) Platinum + etoposide	PFS	Jun 2, 2020
Phase III (CheckMate-451)[16]	Maintenance therapy after platinum-based doublets	a) Nivolumab, OR b) Nivolumab + ipilimumab, OR c) Placebo	OS	Nov 20, 2019
Phase III (CASPIAN)[16]	First-line therapy with platinum based-doublets ± ICIs	a) Durvalumab + tremelimumab + platinum + etoposide, OR b) Durvalumab + platinum + etoposide, OR c) Platinum + etoposide	PFS and OS	Feb 28, 2020
Phase III (KEYNOTE-604)[16]	First-line therapy with platinum-based doublets ± ICI	a) Pembrolizumab + platinum + etoposide, OR b) Platinum + etoposide	PFS and OS	Oct 5, 2021

Abbreviations: ICI = immune checkpoint inhibitor; OS = overall survival; PFS = progression-free survival.

between the 3 dosing regimens and the confidence intervals (CIs) for ORR overlapped for each of the different arms.[4-7] Nine patients crossed over at time of progression on nivolumab to nivolumab + ipilimumab, none of whom had subsequent confirmed responses.[5]

The PFS and OS in the non-randomized cohort were numerically higher for nivolumab 1 mg/kg + ipilimumab 3 mg/kg when compared with nivolumab or nivolumab 3 mg/kg + ipilimumab 1 mg/kg (Table 2). However, there were no statistical comparisons between groups; additionally, the CIs for PFS and OS overlapped for each of the regimens.[4-7] The most striking feature of this trial was not the median survival but the high survival rates at 1 and 2 years, indicating that, although a minority of patients benefited, those that benefited had long-term benefit.

Although CheckMate-032 treated patients with ES-SCLC in second or later lines, the results in third or later lines were similar, and the long-term survival with nivolumab alone was superior to that observed with historical controls treated in the third-line setting. As a result, the FDA approved nivolumab monotherapy for third-line SCLC.[3,22] However, there was a recent press release that the phase III randomized trial (CheckMate-331) comparing nivolumab with standard of care (topotecan or amrubicin) in second-line therapy of ES-SCLC did not meet the primary endpoint of OS.[23] When the data is presented, it will be important to see if there were any differences between the treatment arms with regard to key subgroups (eg, patients with high TMB or platinum-resistant disease).

TMB seemed to predict benefit from nivolumab + ipilimumab in NSCLC.[24] As a result, patients in CheckMate-032 were divided into TMB tertiles, with the upper tertile being designated as high TMB. For those with high TMB, the ORR to nivolumab (n = 47) was 21.3% and for nivolumab 1 mg/kg + ipilimumab 3 mg/kg (n = 26), it was 46.2%. For low and intermediate TMB, the ORR to nivolumab was only 4.8% and 6.8%, respectively, whereas for nivolumab 1 mg/kg + ipilimumab 3 mg/kg, the ORR in low and intermediate TMB were 22.2% and 16%, respectively (Table 3).

Table 2 Efficacy of Second and Subsequent Line Immune Checkpoint Inhibitors

Regimen	ORR, % (95% CI)	Median PFS, mos (95% CI)	1-year PFS, % (95% CI)	Median OS, mos (95% CI)	1-year OS, % (95% CI)	Adverse Events
Nivolumab[4-7]	11[a] (8.0-16) (n = 245)	1.4[b] (1.4-1.9) (n = 98)	11	4.1[b] (3.0-6.8) (n = 98)	27	Grade 3-4 TRAEs, 13%: diarrhea, 0%; pneumonitis, 1%; ↑ lipase, 0%
Nivolumab 1 mg/kg + ipilimumab 3 mg/kg every 3 weeks × 4 cycles, then nivolumab maintenance[4-7]	22[a] (16-29) (n = 156)	2.6[b] (1.4-4.1) (n = 61)	19	7.8[b] (3.6-14.2) (n = 61)	40	Grade 3-4 TRAEs, 30%: diarrhea, 5%; pneumonitis, 2%; ↑ lipase, 9%
Nivolumab 3 mg/kg + ipilimumab 1 mg/kg every 3 weeks × 4 cycles, then nivolumab maintenance[5-7]	19[b] (9.0-31) (n = 54)	1.4[b] (1.3-2.2)	N/A	6.0[b] (3.6-11)	35	Grade 3-4 TRAEs, 19%: diarrhea, 2%; pneumonitis, 2%; ↑ lipase, 0%
Pembrolizumab[8]	18.7 (11.8-27.4) (n = 107)	2.0 (1.9-2.1)	17	8.7 (5.6-12)	40	Grade 3-4 TRAEs, 12%: pancreatitis, 2%; colitis, 1%; pneumonitis, 1%
Durvalumab[19]	9.5 (1.2-30.4) (n = 21)	1.5 (0.9-1.8)	14	4.8 (1.3-10.4)	28	Grade 3-4 TRAEs, 0%
Durvalumab + tremelimumab[20]	13.3 (3.8-30.7) (n = 30)	1.8 (1.0-1.9)	16.3 (5.4-32.6)	7.9 (3.2-15.8)	41.7 (23.3-59.2)	Grade 3-4 TRAEs, 23.3%: ↑ lipase, 6.7%; pituitary dysfunction, 6.7%; adrenal insufficiency, 3.3%; diarrhea, 0%
Atezolizumab[21]	6 (n = 17)	N/A	N/A	N/A	N/A	N/A

Nivolumab maintenance was 3 mg/kg every 2 weeks.
Abbreviations: CI = confidence interval; N/A = not available; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; TRAEs = treatment-related adverse events.
[a]Randomized and non-randomized cohorts.
[b]Non-randomized cohort.

Table 3 Biomarkers and Efficacy of Immune Checkpoint Inhibitors in Small-cell Lung Cancer

Regimen	Biomarker	Patients, n	ORR, % (95% CI)	Median PFS, mos (95% CI)	1-year PFS. %	Median OS, mos (95% CI)	1-year OS, %
Nivolumab[4,6]	High TMB	47	21.3	1.4 (1.3-2.7)	21	5.4 (2.8-8.0)	35
	Intermediate TMB	44	6.8	1.3 (1.2-1.4)	3	3.9 (2.4-9.9)	26
	Low TMB	42	4.8	1.3 (1.2-1.4)	0	3.1 (2.4-6.8)	22
Nivolumab 1 mg/kg + ipilimumab 3 mg/kg every 3 weeks × 4 cycles, then nivolumab maintenance[4,6]	High TMB	26	46.2	7.8 (1.8-10.7)	30	22 (8.2-NR)	62
	Intermediate TMB	25	16	1.3 (1.2-2.1)	8	3.6 (1.8-7.7)	20
	Low TMB	27	22.2	1.5 (1.3-2.7)	6	3.4 (2.8-7.3)	23
Nivolumab[4-7]	PD-L1 positive	11	9	N/A	N/A	N/A	N/A
	PD-L1 negative	64	14	N/A	N/A	N/A	N/A
Nivolumab 1 mg/kg + ipilimumab 3 mg/kg every 3 weeks × 4 cycles, then nivolumab maintenance[4-7]	PD-L1 positive	10	10	N/A	N/A	N/A	N/A
	PD-L1 negative	31	32	N/A	N/A	N/A	N/A
Nivolumab 3 mg/kg + ipilimumab 1 mg/kg every 3 weeks × 4 cycles, then nivolumab maintenance[4-7]	PD-L1 positive	5	40	N/A	N/A	N/A	N/A
	PD-L1 negative	29	21	N/A	N/A	N/A	N/A
Pembrolizumab[8]	PD-L1 positive	42	35.7 (21.6-52.0)	2.1 (2.0-8.1)	29	14.9 (5.6-NR)	53
	PD-L1 negative	50	6 (1.3-16.5)	1.9 (1.6-2.0)	8	5.9 (3.3-10.1)	31

High TMB was defined as ≥ 248 missense mutations by whole exome sequencing.
Nivolumab maintenance is 3 mg/kg every 2 weeks.
PD-L1-positive was defined as ≥ 1% staining by the respective assay.
The PD-L1 test and cell types stained differed for nivolumab ± ipilimumab AND pembrolizumab.
Abbreviations: CI = confidence interval; N/A = not available; NR = not reached; ORR = objective response rate; OS = overall survival; PD-L1 = programmed death ligand 1; PFS = progression-free survival; TMB = tumor mutational burden.

The ORR appeared to be greater for nivolumab 1 mg/kg + ipilimumab 3 mg/kg compared with nivolumab across the different TMB tertiles; however, there was no statistical comparison made between the dosing regimens.[4,6]

High TMB may also help predict for better PFS and OS with nivolumab 1 mg/kg + ipilimumab 3 mg/kg (Table 3) (Figure 2). However, there did not appear to be any substantial differences in PFS or OS for patients with low/intermediate TMB given either nivolumab or nivolumab 1 mg/kg + ipilimumab 3 mg/kg (Table 3). Although survival did appear to be better for those with high TMB treated with nivolumab 1 mg/kg + ipilimumab 3 mg/kg when compared with nivolumab, no statistical comparison was made between the regimens.[4,6]

Adverse events were higher with nivolumab + ipilimumab when compared with nivolumab (Table 2). Immune-related neurologic toxicities and deaths were uncommon: 1% grade 4 limbic encephalitis with nivolumab, 2% grade 3 myasthenia gravis and 2% grade 1 to 2 limbic encephalitis with nivolumab 1 mg/kg + ipilimumab 3 mg/kg.[5,25] There was concern for increased risk of autoimmune adverse events with ICIs in SCLC when compared with other tumor types because of the paraneoplastic syndromes seen in SCLC; however, higher rates of autoimmune adverse events were not seen with nivolumab ± ipilimumab or with the other ICIs discussed below (Table 2).[4-7]

Based on these results, a first-line maintenance trial was initiated comparing nivolumab alone with nivolumab + ipilimumab with placebo shown in Table 1.[16] Unfortunately, as discussed above, a recent press release indicated that the trial failed to meet the primary endpoint.[17]

Pembrolizumab. KEYNOTE-158 examined pembrolizumab 200 mg every 3 weeks. Ninety-four patients were evaluable for response; 42 were programmed death ligand-1 (PD-L1)-positive (combined positive score ≥ 1% by the 22C3 assay), and 50 were PD-L1-negative. Independent review committee-assessed ORR was 18.7% (Table 2). The response differed by PD-L1 positivity; ORR was 35.7% in positive patients and 6% in negative patients (Table 3).[8]

The median PFS was 2 months and the 1-year PFS was 17%, whereas the median OS was 8.7 months and the 1-year OS was 40% (Table 2). The median PFS did not differ when comparing PD-L1-positive patients with PD-L1-negative patients; however, the 1-year PFS was better in PD-L1-positive patients. The OS was improved in PD-L1-positive patients when compared with PD-L1-negative patients (Table 3) (Figure 2). As with the nivolumab studies, the long-term survival in a subset of patients was the most remarkable finding. Pembrolizumab was relatively well-tolerated; any grade treatment-related adverse events (TRAEs) were 60%, and grade 3 to 4 TRAEs were 12% (Table 2). Immune-mediated neurologic toxicities were uncommon: 1% grade 5 encephalitis.[8] There is an ongoing phase II study comparing pembrolizumab with topotecan as second-line therapy.[16] In the ongoing

KEYNOTE-604 trial, pembrolizumab is being evaluated in combination with platinum-based doublets as first-line therapy (Table 1).[16]

PD-L1 Inhibitors. Atezolizumab and durvalumab were studied as monotherapies in previously treated ES-SCLC having progressed on prior platinum-based doublets (Table 2).[19,21] Additionally, durvalumab has been evaluated in combination with tremelimumab (Table 2).[20] The first-line IMpower-133 study with atezolizumab and the first-line Caspian study with durvalumab are highlighted in Table 1.[16]

ICIs With Chemotherapy Post-platinum Doublets. A trial combining pembrolizumab + paclitaxel (n = 26) has presented results. The ORR was 23%, the median PFS was 5.0 months, and the median OS was 9.2 months. The median PFS did not differ by PD-L1 positivity (5.0 months in PD-L1-positive [n = 4] and 3.9 months in PD-L1-negative [n = 22]; $P = .897$); however, the relative numbers in each group were small. The OS for PD-L1-positive versus PD-L1-negative patients was not provided. This trial suggested patients with MET amplification (n = 3) may have improved median PFS at 10.5 months versus patients without MET amplification (n = 9) with a median PFS of 3.4 months ($P = .019$). However, the numbers were small for comparison by MET amplification status. This treatment combination was relatively well-tolerated, most adverse events were grade 1 to 2, and no grade 3 to 4 adverse event occurred with an incidence > 8%.[26] There are ongoing trials of combinations of ICIs with other chemotherapies, but no results are available at the time of this review.

Standard Second-line Therapy

Retreatment With Platinum-based Doublets. For patients with platinum-sensitive disease (most commonly defined as progression/relapse ≥ 90 days following last dose of platinum-based therapy), retreatment with the original platinum-based regimen may be efficacious (Figure 2). Response rates of 34% to 65% have been reported in this setting. The median PFS was 5.5 months in 1 study, and the median OS ranged from 6.3 to 14.4 months across studies. The majority of the literature suggesting a benefit to this approach is based on retrospective analysis.[27-29] How such an approach would compare to other available therapies in similar patient populations undergoing randomization is unclear.

Topotecan. Topotecan is the only FDA-approved second-line therapy for SCLC after progression on platinum-based chemotherapy (Figure 2).[3] This agent is most effective in platinum-sensitive disease, defined as progression/relapse ≥ 90 days following platinum-based chemotherapy. The ORR was 10% to 24% in unselected patients; platinum-sensitive patients had an ORR of 17% to 27%, and platinum-resistant patients had an ORR of 5% to 13%. Without regards to platinum sensitivity, the median PFS ranged from 2.8 to 3.5 months and the median OS from 5.8 to 8.2 months (Table 4). Across studies, the OS appeared to be higher in platinum-sensitive patients versus platinum-resistant patients.[30-32] The most common grade ≥ 3 treatment-emergent adverse events were hematologic: neutropenia, 54% to 88%; thrombocytopenia, 41% to 58%; and anemia, 24% to 42% (Table 4).[30-32]

Amrubicin, CAV (Cyclophosphamide, Doxorubicin, Vincristine), Gemcitabine, Irinotecan, Paclitaxel, Vinorelbine. Topotecan was originally compared with CAV. Topotecan had similar antitumor efficacy but greater symptom improvement.[32] Amrubicin was compared with topotecan in a randomized phase III trial of second-line therapy for patients previously receiving platinum-based chemotherapy. Although the ORR was numerically higher with amrubicin (31.1% vs. 16.9% with topotecan), the median PFS and OS were similar. Amrubicin had more febrile neutropenia and grade ≥ 3 infections.[31] Amrubicin is not FDA-approved for SCLC, but it is utilized in some parts of the world as a second-line treatment option. There are reports of activity of a variety of chemotherapies in patients with SCLC who progressed after first-line platinum-based chemotherapy, including gemcitabine, irinotecan, paclitaxel, vinorelbine, and others. For the most part, these agents produced a median PFS of 2 to 4 months and a median OS of 4 to 7 months; however, they were never included in randomized trials.[27] Although not FDA-approved, these agents are sometimes used (Figure 2).

New Agents Being Studied in Second-line or Greater SCLC

Temozolomide ± Poly ADP Ribose Polymerase (PARP) Inhibition. Veliparib + temozolomide produced an ORR of 39% versus 14% with temozolomide monotherapy. However, the combination did not significantly increase PFS (median, 3.8 months vs. 2.0 months; $P = .39$) or OS (median, 8.2 months vs. 7.0 months; $P = .50$). The 1-year OS was similar with veliparib + temozolomide at 35% versus temozolomide alone at 30% (Table 4).[9]

Schlafen family member 11 (SLFN-11) recognizes DNA damage and may limit DNA replication through binding to DNA. SLFN-11 may be found in any type of cell; however, it is inactivated in some cancers through hypermethylation. Higher levels of SLFN-11 are believed to be associated with enhanced sensitivity to DNA damaging agents.[39] SLFN-11 expression was evaluated in 48 patients treated with temozolomide ± veliparib; 23 patients (48%) had overexpression and 25 patients (52%) lacked overexpression. SLFN-11 overexpression was not associated with survival on the temozolomide monotherapy arm. However, for those receiving temozolomide + veliparib, the median PFS ($P = .009$) and the median OS ($P = .014$) were improved in patients with SLFN-11 overexpression (n = 12) (Table 5) (Figure 2).[9]

Across different dose levels, the confirmed ORR was 35% with olaparib + temozolomide, which was numerically greater in platinum-sensitive patients (progression/relapse ≥ 90 days following platinum-based therapy) versus platinum-resistant patients. The median PFS was 2.8 months, and the median OS was 7.3 months (Table 4).[33] The addition of temozolomide to a PARP inhibitor in both of these trials resulted in more grade ≥ 3 cytopenias than temozolomide monotherapy: neutropenia, 37% to 51%; thrombocytopenia, 29% to 50%; and anemia, 11% to 29% (Table 4).[9,33]

Table 4 Efficacy of Second and Subsequent Line Chemotherapies

Regimen	Patients, N	ORR, % (95% CI)	Median PFS, mos (95% CI)	1-year PFS, %	Median OS, mos (95% CI)	1-year OS, %	Adverse Events
Topotecan[30-32]	624	10-24[a]	2.8-3.5[a,b]	0-15[c]	5.8-8.2[a]	14.2-32.6[c]	Grade ≥ 3 AEs,[d] 89%
Temozolomide + veliparib[9]	49	39 (25-54)	3.8 (3.0-4.1)	N/A	8.2 (6.4-12.2)	35[c]	Grade 3-4 TEAEs: mainly cytopenias
Temozolomide + olaparib[33]	20	35[e]	2.8 (1.7-5.2)	5-10[c]	7.3 (4.6-11.3)	30-35[c]	Grade 3-4 TRAEs: mainly cytopenias
Lurbinectedin[10]	61	39.3 (27-53)	4.1 (2.6-5.7)	10-15[c]	11.8 (9.6-15.9)	43	Grade 3-4 AEs:[f] mainly cytopenias
Lurbinectedin + doxorubicin[34]	27	37[e]	3.4 (2.0-6.0)	N/A	7.9 (5.0-12.0)	22.4	Grade 3-4 AEs[f]: mainly cytopenias
Rovalpituzumab tesirine[35]	339	12.4 (9.1-16.4)	N/A	N/A	5.6 (4.9-6.1)	N/A	Grade 3-4 TRAEs, 40%; thrombocytopenia, 11%; photosensitivity, 7%; pleural effusion, 4%
Anlotinib[36]	81	4.9 (0.2-9.7)	4.1 (2.8-4.8)	N/A	7.3 (6.5-10.5)	N/A	Grade ≥ 3 TRAEs, 35.8%
Alisertib[37]	48	21 (10-35)	2.1 (1.4-3.4)	5[c]	N/A	N/A	Grade 3-4 TRAEs, 53%
Alisertib + paclitaxel[11]	89	22[e]	3.3[e]	N/A	6.9[e]	10-15[c]	Grade ≥ 3 TEAEs, 76%
Sacituzumab govitecan[38]	50	14[e]	3.7 (2.1-4.3)	5-10[c]	7.5 (6.2-8.8)	25[c]	Grade 3-4 TEAEs, mainly neutropenia and diarrhea

Abbreviations: CI = confidence interval; N/A = not available; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; TEAE = treatment-emergent adverse event; TRAE = treatment-related adverse event.
[a]Confidence intervals were not provided as results were determined from multiple separate trials and/or different patient populations.
[b]This included time to progression and progression-free survival as the 3 trials included had different endpoint measures.
[c]Estimated from survival curves as not reported in reference.
[d]Multiple trials, some reporting TEAEs and others reporting TRAEs.
[e]Confidence intervals were not available.
[f]Not reported if TEAEs or TRAEs.

This later trial with olaparib and temozolomide is ongoing. Another PARP inhibitor, talazoparib, is similarly being investigated in combination with temozolomide in relapsed/refractory ES-SCLC. Temozolomide is also being studied in SCLC in combination with novel immunotherapies (eg, M7824, which is a fusion protein with antibodies against both PD-L1 and transforming growth factor-β). Additionally, temozolomide monotherapy is being investigated for prevention of brain metastasis in patients with SCLC, as maintenance after platinum-based chemotherapy and in relapsed/refractory disease for patients with O-6-methylguanine-DNA-methyltransferase (MGMT) methylation.[16]

Lurbinectedin. Lurbinectedin may promote apoptosis through inhibiting transcription of protein-encoding genes and inducing double-stranded DNA breaks. Lurbinectedin produced an ORR of 39.3% in a phase II trial of 61 previously treated patients without baseline brain metastasis. For platinum-sensitive patients (progression/relapse ≥ 90 days following platinum-based therapy), the ORR was 44%, and for platinum-resistant patients, the ORR was 33%. The median PFS was 4.1 months; 4.2 months in platinum-sensitive patients and 3.4 months in platinum-resistant patients. The median OS was 11.8 months; 15.8 months in platinum-sensitive patients and 8.1 months in platinum-resistant patients. The 1-year OS was 43%; 59% for platinum-sensitive patients and 23% for platinum-resistant patients (Table 4).[10]

Lurbinectedin may be better tolerated than a similar drug, trabectedin, that is approved in sarcoma.[10,40] Grade 3 to 4 adverse events with lurbinectedin included neutropenia, 39%; febrile

Table 5 Association Between Biomarkers and Efficacy of New Chemotherapies in Small-cell Lung Cancer

Biomarker	Patients, N	Regimen	ORR, %	Median PFS, mos (95% CI)	Median OS, mos (95% CI)
SLFN-11 overexpression by IHC[9]	12	Temozolomide + veliparib	58[a,b]	5.7[b] (3.7-N/A)	12.2[b] (9.7-N/A)
No SLFN-11 overexpression by IHC[9]	13	Temozolomide + veliparib	38[a,b]	3.6[b] (2.0-6.0)	7.5[b] (5.6-N/A)
c-MYC positive by IHC[11]	17	Alisertib + paclitaxel	N/A	4.6 HR 0.29 (0.12-0.72)	N/A
	16	Paclitaxel	N/A	2.3	N/A
c-MYC negative by IHC[11]	6	Alisertib + paclitaxel	N/A	3.3 HR 11.8 (1.52-91.2)	N/A
	7	Paclitaxel	N/A	5.2	N/A

Abbreviations: CI = confidence interval; HR = hazard ratio; IHC = immunohistochemistry; N/A = not available; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; SLFN-11 = Schlafen family member 11.
[a]Confidence intervals not provided.
[b]Hazard ratios not provided.

neutropenia, 9%; thrombocytopenia, 7.5%; alanine aminotransferase increase, 4.6%; and aspartate aminotransferase increase, 4.5% (Table 4).[10]

A phase Ib expansion cohort evaluated lurbinectedin + doxorubicin as second-line therapy. One of the 28 enrolled patients had baseline brain metastasis. The ORR was 37%, being higher in platinum-sensitive patients at 50% versus 11% in platinum-resistant patients. The median PFS was 3.4 months; 5.7 months in platinum-sensitive patients and 1.5 months in platinum-resistant patients. The median OS was 7.9 months; 11.5 months in platinum-sensitive patients and 4.9 months in platinum-resistant patients. The main grade $\geq$ 3 adverse events were hematologic: neutropenia, 93%; anemia, 21%; thrombocytopenia, 18%; and febrile neutropenia, 14%.[34] The reasons for the differences in survival outcomes between this trial and the phase II mentioned above are unclear. However, there were fewer patients on this expansion cohort, and the dose of lurbinectedin utilized in combination with doxorubicin was less than in the phase II monotherapy study.[10,34] It is possible these differences could explain part of the variability in results. A randomized phase III trial (ATLANTIS) is evaluating lurbinectedin + doxorubicin compared with investigator's choice (topotecan or CAV) as second-line therapy in ES-SCLC.[16] Randomized trials evaluating the monotherapy dose of lurbinectedin in a similar setting are likely to be initiated as well.

Rovalpituzumab Tesirine (Rova-T). Rova-T is an antibody drug conjugate (ADC) with an antibody against delta-like ligand 3 (DLL3), a cleavable linker and a pyrrolobenzodiazepine dimer toxin. Approximately 85% of SCLC expresses DLL3. DLL3 may be expressed in normal tissues; however, its level of expression in normal tissues is much lower than in SCLC. DLL3 inhibits NOTCH activation, resulting in increased tumor growth in SCLC.[41]

The phase II TRINITY trial examining Rova-T as third- or later-line therapy in DLL-positive patients with ES-SCLC did not meet the primary endpoint, and as a result, accelerated FDA approval was not pursued.[42] DLL3-positive was defined as $\geq$ 25% of tumor cells staining any intensity, and DLL3 high was defined as $\geq$ 75% of tumor cells staining any intensity. Three hundred thirty-nine patients were DLL3-positive, 238 of which were DLL3-high.[35]

Rova-T was administered at 0.3 mg/kg every 6 weeks for 2 doses. The ORR was 12.4% in all subjects and 14.3% in DLL3-high patients. The median OS was 5.6 months in all participants. DLL3-high patients had a median PFS of 3.8 months and a median OS of 5.7 months. Grade $\geq$ 3 TRAEs were experienced by 40%. Common TRAEs of any grade included photosensitivity, 35%; pleural effusion, 28%; peripheral edema, 26%; thrombocytopenia, 22%; and pericardial effusion, 12%. Grade 3 to 4 TRAEs included thrombocytopenia, 11%; photosensitivity, 7%; and pleural effusion, 4% (Table 4).[35] Problems with fluid balance (capillary leak syndrome, serosal effusions, and peripheral edema) have prevented safe administration of more than 2 cycles of Rova-T.[43]

There are several ongoing trials of Rova-T. It is being evaluated in first-line treatment as either monotherapy, in combination with platinum-based chemotherapy, or as sequential administration before or after platinum-based chemotherapy. The randomized phase III MERU trial is comparing Rova-T with placebo as a maintenance strategy following platinum-based chemotherapy.[16] A second-line trial evaluating Rova-T compared with topotecan (TAHOE) was recently stopped early after interim analysis showed inferior OS with Rova-T.[44] Rova-T is also being evaluated as part of novel combinations with nivolumab $\pm$ ipilimumab.[16]

Anlotinib. Anlotinib is a multi-kinase inhibitor that most strongly inhibits vascular endothelial growth factor receptor, c-KIT, platelet-derived growth factor receptor, and fibroblast growth factor receptor. It was examined as $\geq$ third-line therapy for patients with ES-SCLC. Eighty-one patients received anlotinib, and 38 patients received placebo. The ORR was low with anlotinib at 4.9%. However, the median PFS was significantly improved when compared with placebo at 4.1 months versus 0.9 months (HR, 0.19; 95% CI, 0.12-0.32; $P < .0001$). Twenty-six percent of patients receiving anlotinib had brain metastasis. The relative PFS benefit of anlotinib versus placebo did not differ by presence or absence of brain metastasis. The HR was 0.15 ($P = .003$) for patients with brain metastasis, and the HR was 0.20 ($P < .001$) in patients without brain metastasis. The OS analysis was immature but suggested a possible OS benefit at a median OS of 7.3 months with anlotinib versus 4.9 months with placebo (HR, 0.53; 95% CI, 0.30-0.92; $P = .0210$). Grade 3 to 5 adverse events occurred in 35.8% of patients: 13.6% hypertension and 4.9% hand-foot syndrome (Table 4).[36]

Aurora Kinase Inhibition. Alisertib is an inhibitor of Aurora A Kinase. As a single agent in relapsed SCLC, the ORR was 21% (10 of 48), which did not differ by platinum sensitivity. The main grade $\geq$ 3 adverse events were neutropenia, 37%; anemia, 12%; and thrombocytopenia, 8% (Table 4).[37]

Alisertib with paclitaxel was compared with paclitaxel alone in a randomized phase II trial. The ORR was 22% with alisertib + paclitaxel (20 of 89) and 18% with paclitaxel alone (16 of 89). The PFS was greater with alisertib + paclitaxel (median, 3.3 months) versus with paclitaxel (median, 2.2 months; HR, 0.71; $P = .038$). This PFS difference seemed to be driven by those with platinum resistant disease, who had median PFS 2.9 months with alisertib + paclitaxel (n = 60) versus 1.6 months with paclitaxel (n = 49) (HR, 0.66; $P = .04$). The OS was not significantly different between the 2 treatments; median of 6.9 months with alisertib + paclitaxel versus 5.6 months with paclitaxel (HR, 0.73; $P = .06$). Grade $\geq$ 3 treatment-emergent adverse events were greater with the addition of alisertib to paclitaxel at 76% versus 51% (Table 4).[11]

Preclinical studies indicate alisertib and other aurora kinase inhibitors are more effective in cells with amplification or high expression of myc.[45,46] Myc functions in cancer to increase metabolism and cellular proliferation.[47] In normal tissues, myc has low-level expression and minimal activation; however, in SCLC and some other tumors, there is sustained activation/increased expression of myc.[46] Patients who were c-myc positive ($\geq$ 1+) by immunohistochemistry (IHC) had significantly improved PFS with alisertib + paclitaxel (median, 4.6 months; n = 17) versus with paclitaxel (median 2.3 months; n = 16) (HR, 0.29; 95% CI, 0.12-

0.72) (Figure 2).[11] In contrast, those who were c-myc negative had a significantly worse PFS with alisertib + paclitaxel (median, 3.3 months; n = 6) versus with paclitaxel (median, 5.2 months; n = 7) (HR, 11.8; 95% CI, 1.5-91) (Table 5).[11] Other aurora kinase inhibitors, such as the nanoparticle aurora kinase B inhibitor AZD2811, are being investigated in early trials and may have efficacy in patients with myc amplification or overexpression.[16]

RRx-001. RRx-001 targets tumor associated macrophages and cancer stem cells. It may re-sensitize patients to platinum-based chemotherapy. Twenty-six patients were treated with RRx-001 on a phase II study, all having prior exposure to platinum-based chemotherapy and all of whom received ≥ 2 previous systemic treatments.[48]

RRx-001 was administered until development of progressive disease, after which patients were to be started on platinum-based chemotherapy. Twelve (46%) of the 26 enrolled patients subsequently received platinum-based chemotherapy and were evaluable for response. It is unclear why the other 14 patients were not evaluable. It was not reported whether any of these 14 non-evaluable patients received subsequent platinum-based therapy, whether any of them never progressed on RRx-001, or whether some became too sick owing to their disease and/or drug toxicities to be candidates for platinum-based chemotherapy. Four of the 12 evaluable patients who were subsequently treated with platinum-based chemotherapy obtained an objective response; all of these 4 were platinum-resistant at enrollment. The median OS of 7.5 months and the 1-year OS of 46% for the 12 evaluable patients treated with RRx-001 followed by platinum-based chemotherapy was encouraging. However, information was not provided as to what the survival outcomes were for the whole enrolled population of 26 patients.[48] Although RRx-001 may benefit a subset of patients with ES-SCLC, its actual benefit is unclear owing to small patient numbers and a lack of information on the 14 enrolled patients who were not evaluable for response. However, based on the encouraging results in the 12 evaluable patients on this study, a phase III trial has been initiated evaluating RRx-001 followed by platinum-based chemotherapy versus platinum-based chemotherapy alone in third or later lines of therapy.[16]

Sacituzumab Govitecan. Sacituzumab govitecan is an ADC with an antibody against tumor-associated calcium signal tranducer 2, a cleavable linker and the cytotoxic SN-38 (which is the active metabolite of irinotecan). This ADC delivers 136-fold greater SN-38 to tumor cells than irinotecan, based on preclinical studies.[49] In a phase Ib trial, 53 patients with SCLC were treated, and the ORR was 14%, the median PFS was 3.7 months, and the median OS was 7.5 months. The main grade ≥ 3 adverse events were neutropenia, 34%; diarrhea, 9%; and febrile neutropenia, 2% (Table 4).[38]

Nanoliposomal Irinotecan-based Therapy. There are 2 nanoliposomal drugs, nanoliposomal irinotecan and nanoliposomal SN-38, that are being evaluated in previously treated ES-SCLC.[16] Similar to sacituzumab govitecan, these drugs are attempting to achieve antitumor efficacy by delivering higher doses of SN-38 to tumors than traditional irinotecan.

Pegzilarginase (AEB1102). Argininosuccinate synthase (ASS) is responsible for cellular synthesis of arginine. Preclinical studies suggest that SCLC with low ASS expression is sensitive to extracellular arginine depletion. Limited data from 16 human SCLC specimens suggested low to no ASS expression by IHC may be found in around 45% of cases. Polymerase chain reaction analysis suggested a similar incidence of low to no ASS RNA expression in 50% of 10 evaluated SCLC cell lines.[50]

AEB1102 depletes extracellular arginine. There is currently an ongoing expansion cohort examining AEB1102 monotherapy in previously treated patients with ES-SCLC.[16] A separate study is evaluating AEB1102 + pembrolizumab in immunotherapy-naive patients with ES-SCLC based on preclinical studies showing enhanced efficacy of this combination when compared with either monotherapy.[16]

Lysine-specific Demethylase 1 (LSD1) Inhibitors. LSD1 is responsible for demethylating histone H3 lysine 4. LSD1 helps in maintaining a stem cell-like phenotype. LSD1 was overexpressed by IHC in 98 of 100 formaldehyde-fixed paraffin-embedded SCLC specimens. Thirty-two percent of 28 SCLC cell lines had their growth inhibited by an experimental LSD1 inhibitor known as GSK2879552. Multiple SCLC xenograft models also demonstrated growth inhibition with GSK2879552.[51] Twenty-nine patients were enrolled on a phase I study examining this agent in SCLC; this study was stopped early owing to toxicity and lack of benefit.[16]

Preclinical data suggest LSD1 inhibition with PD-1 axis inhibition may be more effective than either monotherapy.[52] There is another LSD1 inhibitor, INCB059872, in clinical development. This agent is being evaluated as monotherapy in a dose-escalation study and in combination with nivolumab for patients with SCLC progressing on/after platinum-based therapy.[16]

Bromodomain and Extra-terminal (BET) Inhibitors. Preclinical studies have suggested SCLC may be sensitive to inhibition of BET proteins. BET proteins may bind to the enhancer region of achaete-scute homolog 1 (ASCL1), leading to increased ASCL1 expression. ASCL1 is a transcription factor that promotes formation of neuroendocrine tumors. ASCL1 was very highly overexpressed in > 50% of 15 SCLC cases, and increased ASCL1 is hypothesized to be associated with enhanced sensitivity to BET inhibitors. An experimental BET inhibitor demonstrated significant growth inhibition in 15 of 18 SCLC cell lines examined.[53] BET inhibitors are currently in clinical trials, and SCLC is a tumor type of interest in these trials.[16]

Other Epigenetic Modifiers. Certain segments of the genome in SCLC are heavily methylated, which may result in inactivation of several genes that function in cell cycle arrest and repair of DNA damage. Such hypermethylation has been correlated with high expression of E2F and EZH2.[54] Because of this, EZH2 inhibitors are being evaluated in early phase trials as potential antitumor therapies in ES-SCLC.[16] DNA methyltransferase inhibitors and alkylating deacetylase inhibitors are also being evaluated owing to their potential to cause epigenetic modifications that may have antitumor efficacy.[16,55,56]

DNA Damage Response Inhibitors. SCLC has a high proliferation rate, and large numbers of genomic alterations tend to accumulate with time. SCLC is also relatively resistant to DNA-damaging agents. Continued cellular proliferation may be dependent on pathways that recognize and repair certain types of DNA damage. PARP is one of many proteins involved in repairing DNA damage, and it functions primarily through base excision repair. Higher PARP expression has been demonstrated in SCLC when compared with either normal lung or other types of lung cancer. In this context, DNA damage response inhibitors (eg, PARP inhibitors and Wee1 inhibitors) may have efficacy and are currently being evaluated in SCLC as monotherapy and in combination.[16,55,56]

A randomized phase II trial evaluated 4 cycles of cisplatin + etoposide with or without veliparib as first-line treatment. Although there was a difference in PFS with the addition of veliparib (median, 6.1 months vs. 5.5 months; HR, 0.63; $P = .01$), there was no significant difference in ORR ($P = .57$) or OS ($P = .17$). Efficacy outcomes and their relationship to specific biomarkers (eg, SLFN-11) were not reported. Additionally, maintenance PARP inhibition after the 4 cycles of induction therapy was not administered, and whether this would have led to a greater difference in OS is unclear.[57,58]

Bcl-2 and Bcl-xl Inhibitors. Bcl-2 and Bcl-xl are proteins limiting apoptosis. Inhibitors of these proteins have demonstrated efficacy in SCLC cell lines and mouse models. Navitoclax was evaluated in 39 patients with SCLC having received ≥ 1 prior systemic therapy and demonstrated little efficacy: ORR, 2.9%; median PFS, 1.5 months; and median OS, 3.2 months. Thrombocytopenia was a significant toxicity with navitoclax; grade 3 to 4 in 41% of patients.[59] Other bcl-2 inhibitors that are thought to cause less thrombocytopenia than navitoclax are being studied, and potentially these agents could be escalated to a higher effective dose than navitoclax, which could lead to better responses. Additionally, ADCs with bcl-2 inhibitor payloads are also being evaluated.[16]

Genetically Modified T-cells and Bispecific T-cell Engagers. Genetically modified chimeric antigen receptor (CAR) T-cells have revolutionized the care of patients with B-cell acute lymphoblastic leukemia (ALL) and certain types of lymphoma.[60,61] CAR T-cells have recently gained FDA approvals for these diseases.[3] However, initial trials in solid tumors targeting proteins such as Her2 have faced toxicity challenges.[62] Because DLL-3 is highly expressed on SCLC and lacking significant expression on normal tissues, there are trials evaluating DLL-3 targeting CAR T-cells in SCLC.[41,63] Similarly, a bispecific T-cell engager has demonstrated efficacy in ALL and gained FDA approval in this disease.[3,64] Bispecific T-cell engager antibodies have also been developed against DLL-3 and are being explored in SCLC.[63]

Discussion

SCLC was once a disease with few treatments. Fortunately, there are new options for first-line management, with the addition of an ICI to standard chemotherapy, as well as several emerging treatments for patients after progression on first-line systemic therapies (Figure 2). Many of these options are in the National Comprehensive Cancer Network guidelines, and new FDA approvals are likely in the near future.[1]

Advanced SCLC is a disease where maintenance therapy after completion of first-line chemotherapy has generally not been practiced. Maintenance with pembrolizumab or sunitinib after platinum-based doublets did not appear to improve survival.[65,66] Additionally, a recent press release suggested no OS benefit with maintenance nivolumab + ipilimumab following platinum-based chemotherapy.[17] However, with the recent release of the IMpower-133 data, continuation atezolizumab is likely to be increasingly implemented as maintenance after completion of atezolizumab + platinum-based doublets.[2] Whether consolidation radiation to the thorax ± oligometastatic sites would be of benefit for patents with no or limited sites of extrathoracic disease upon starting atezolizumab maintenance has not been determined.

Similar to NSCLC, in SCLC, the question about whether it is best to give atezolizumab + platinum-based chemotherapy to patients upfront versus sequencing platinum-based chemotherapy followed by an ICI at progression will become increasingly common. Although we do not have a randomized trial showing which of these is the best option, it may be better to give platinum-based doublets + atezolizumab with atezolizumab maintenance for a few reasons. One, in randomized trials, there are an estimated 35% of patients who do not get second-line therapy.[67] Additionally, we can get some insight into this question from patients with NSCLC on KEYNOTE-021. This was a phase II randomized trial comparing carboplatin + pemetrexed + pembrolizumab versus carboplatin + pemetrexed. At a median follow-up of 24 months, there was a significant difference in 2-year OS for chemotherapy + pembrolizumab at 67% versus 48% for chemotherapy alone (HR, 0.56; $P = .0151$), and this was despite a 73% cross-over rate at time of progression on the chemotherapy-alone arm to subsequently receive an ICI.[12,14] However, looking at the IMpower-133 data, it is hard to make any conclusions in this regard, as only 7.4% of the patients progressing on chemotherapy alone subsequently received an ICI.[2] Also, neoadjuvant studies in small patient populations with NSCLC have suggested much higher major pathologic response with PD-1 axis inhibitors plus platinum-based doublets versus platinum-based doublets alone; 50% to 80% versus 20% to 45%.[68-71] Because of the possible benefit of vascular endothelial growth factor inhibition with ICIs that has been suggested in other tumor types, would there be a role of adding bevacizumab to atezolizumab as a maintenance strategy after completion of platinum-based doublets + atezolizumab?[72-74] Similarly, giving bevacizumab with atezolizumab + EP as induction in the front-line setting followed by atezolizumab + bevacizumab maintenance could potentially improve even further on the IMpower-133 results.

EP + ICIs will likely be utilized increasing in the near future for first-line therapy given the positive survival results from IMpower-133 and the ongoing phase III first-line trials. There is no evidence that changing to a different PD-1 axis inhibitor after

progression on PD-1 inhibitor-based therapy will be efficacious. Additionally, data is lacking in both NSCLC and SCLC to suggest cytotoxic T-lymphocyte-associated protein 4 inhibitors have meaningful efficacy following progression on a PD-1 axis inhibitor. Thus, use of PD-1 axis inhibitors ± cytotoxic T-lymphocyte-associated protein 4 inhibitors in second or later lines of therapy are not likely to be a recommended strategy in the coming years. Rather, other immunotherapies and novel combinations will be evaluated in clinical trials.

Many of the trials discussed in this review excluded patients with central nervous system (CNS) disease. For trials that allowed enrollment of patients with CNS disease, the vast majority of patients had to have brain metastasis that were stable and previously treated. This is unfortunate as CNS involvement occurs in up to 80% of patients during the first 2 years following a diagnosis of ES-SCLC.[75] Thus, for a significant proportion of patients with SCLC, the ORR and median survival reported in many of the trials discussed above may not be applicable. For the agents/regimens discussed in this review, temozolomide has the most CNS efficacy data; however, based on literature in melanoma, there is reason to think nivolumab + ipilimumab may also have efficacy in CNS disease for patients who have not been exposed to ICIs previously.[9,76,77]

Although there is yet to be a great biomarker that helps select treatment for patients with SCLC, there are many candidates. High TMB has been suggested to predict benefit from nivolumab + ipilimumab; however, its application is challenging and not ready for routine clinical implementation (Figure 2).[4,6] CheckMate-032 utilized whole exome sequencing to define high TMB.[4,6] Unfortunately, whole exome sequencing is only available at select research institutions, is costly, and is time consuming. Foundation Medicine has a targeted sequencing panel that estimates TMB based on evaluation of a much smaller panel of genes than whole exome sequencing (324 vs. 21,522). Foundation Medicine testing also identifies some types of mutations that may not necessarily code for different amino acids (eg, synonymous mutations) as opposed to whole exome sequencing, which only identifies mutations that code for different amino acids. Whether Foundation Medicine testing can be used to identify patients with SCLC with high TMB that would have greater benefit from nivolumab + ipilimumab remains to be determined (Figure 2).[78] The role of blood-based TMB testing to predict benefit of this combination is also unclear. Whether high TMB could predict a population of patients with SCLC that may forgo frontline chemotherapy and who would benefit most from initial treatment with nivolumab + ipilimumab as in CheckMate-227 remains to be seen (Figure 2).[24]

Although c-myc is not thought of as an emerging biomarker in SCLC, there is a strong signal that positive c-myc IHC staining may predict benefit from aurora kinase A inhibition + chemotherapy (Figure 2).[11] A biomarker based trial to select patients with c-myc positive IHC staining for treatment with such a combination would be of interest. Although there is a signal that SLNF-11 overexpression may predict for those more likely to benefit from combinations involving PARP inhibitors, the data is limited and more clinical information is needed in this regard (Figure 2).[9]

A PD-L1 combined positive score ≥ 1% by the Dako 22C3 assay did appear to predict increased response and improved survival with pembrolizumab when compared with PD-L1-negative patients, the same was not true of the Dako 28-8 assay where PD-L1 positivity was not associated with improved outcomes with nivolumab ± ipilimumab (Figure 2). However, these 2 assays are not testing the same thing. With the 22C3 assay, a combined positive score is calculated from staining on tumor cells, lymphocytes, and macrophages, whereas with the Dako 28-8 assay, only staining on tumor cells is used to determine positivity.[4-8] The different cell types that are used to determine the PD-L1 score for each of these assays could affect the predicative value of the respective test. Further study is thus needed to determine the true utility of the various PD-L1 assays, and a standardized testing method would be useful.

DLL-3 staining may be necessary for effectiveness of Rova-T; however, the degree of positivity may not matter, as ORR and OS were not significantly different in the TRINITY trial when comparing high DLL3 (≥ 75% of tumor cells staining positive) with 25% to 74% of tumor cells staining positive.[35] It is unclear whether certain degrees of positivity for a cell surface marker will be better for predicting benefit of other ADCs in SCLC or whether positive staining of any magnitude will suffice. Data about utility of MGMT methylation status to predict response and survival with temozolomide in SCLC is conflicting, and thus this test is not ready for clinical use.[9,76,79]

Novel combinations of ICIs with agents (eg, with LSD1 inhibitors, with lurbinectedin, or with drugs that deplete extracellular arginine, or with other experimental therapies) will be important to evaluate in patients who have progressed on ICIs ± chemotherapy. Many of these trials are already ongoing.[16] As we have illustrated in this review, SCLC is a disease where outcomes may improve over historical numbers owing to new developments in first-line management and increasing therapeutic options in later lines of therapy. Additionally, as we have suggested biomarker testing may make its way into care of patients with SCLC in the not so distant future. It is an exciting time for SCLC treatment, with a lot of new developments that may translate into improved patient outcomes.

Acknowledgments

Dr Bunn was partially supported by the University of Colorado Lung Cancer SPORE (P50CA058187; PI: R.C. Doebele)

Disclosures

Dr Pacheco reports consulting fees from AstraZeneca and Novartis; honorarium from Takeda; and research funding from Pfizer. Dr Bunn reports consulting fees from AstraZeneca, Guardant, Lilly, Merck, Pfizer, and Takeda; and prior limited research funding from AstraZeneca.

Supplemental Data

Supplemental table accompanying this article can be found in the online version at https://doi.org/10.1016/j.cllc.2018.12.019.

References

1. National Comprehensive Cancer Network. Small Cell Lung Cancer. Version 2. 2018, Available at: https://www.nccn.org/professionals/physician_gls/pdf/sclc.pdf. Accessed on December 4, 2018.
2. Horn L, Mansfield AS, Szczesna A, et al, IMpower133 Study Group. First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. *N Engl J Med* 2018; 379:2220-9.

3. United States Food and Drug Administration, Available at: www.fda.gov. Accessed: October 16, 2018.
4. Antonia SJ, Callahan MK, Awad MM, et al. *Impact of tumor mutation burden on the efficacy of nivolumab or nivolumab + ipilimumab in small cell lung cancer: an exploratory analysis of CheckMate 032*, Presented at: IASLC 18th World Conference on Lung Cancer; October 15-18 2017, Yokohama, Japan; abstract 11063.
5. Antonia SJ, López-Martin JA, Bendell J, et al. Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): a multicentre, open-label, phase 1/2 trial. *Lancet Oncol* 2016; 17:883-95.
6. Hellmann MD, Callahan MK, Awad MM, et al. Tumor mutational burden and efficacy of nivolumab monotherapy and in combination with ipilimumab in small-cell lung cancer. *Cancer Cell* 2018; 33:853-61.
7. Hellman MD, Ott PA, Zugazagoitia J, et al. Nivolumab (nivo) +/- ipilimumab (ipi) in advanced small-cell lung cancer (SCLC): first report of a randomized expansion cohort from CheckMate 032. *J Clin Oncol* 2017; 35(Suppl), abstract 8503.
8. Chung HC, Lopez-Martin JA, Kao SCH, et al. Phase 2 study of pembrolizumab in advanced small-cell lung cancer (SCLC): KEYNOTE-158. *J Clin Oncol* 2018; 36(Suppl), abstract 8506.
9. Pietanza MC, Waqar SN, Krug LM, et al. Randomized, double-blind, phase II study of temozolomide in combination with either veliparib or placebo in patients with relapsed-sensitive or refractory small-cell lung cancer. *J Clin Oncol* 2018; 36: 2386-94.
10. Trigo Perez JM, Leary A, Besse B, et al. Efficacy and safety of lurbinectedin (PM1183) in small cell lung cancer (SCLC): results from a phase 2 study. *J Clin Oncol* 2018; 36(Suppl), abstract 8570.
11. Owonikoko TF, Nackaerts K, Csoszi T, et al. *Randomized phase 2 study of the investigational aurora a kinase (AAK) inhibitor alisertib (MLN8237) + paclitaxel vs placebo + paclitaxel as second-line therapy for small cell lung cancer*, IASLC 17th World Conference on Lung Cancer; Vienna, Austria; December 4-7 2016, abstract 4855.
12. Borghaei H, Langer CJ, Gadgeel S, et al. 24-Month overall survival from KEYNOTE-021 cohort g: pemetrexed and carboplatin with or without pembrolizumab as first-line therapy for advanced nonsquamous non-small-cell lung cancer. *J Thorac Oncol* 2019; 14:124-9.
13. Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al, KEYNOTE-189 Investigators. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. *N Engl J Med* 2018; 378:2078-92.
14. Gentzler RD, Langer CJ, Borghaei H, et al. 24-month overall survival from KEYNOTE-021 cohort G: Pemetrexed-carboplatin plus pembrolizumab as first-line therapy for advanced nonsquamous NSCLC. *J Clin Oncol* 2018; 36(Suppl), abstract 9206.
15. Socinski MA, Jotte RM, Cappuzzo F, et al, IMpower150 Study Group. Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. *N Engl J Med* 2018; 378:2288-301.
16. National Institutes of Health; United States National Library of Medicine. Available at: Clinicaltrials.gov. Accessed on October 16, 2018.
17. Available at: https://news.bms.com/press-release/corporatefinancial-news/bristol-myers-squibb-announces-checkmate-451-study-did-not-mee. Accessed: December 10, 2018.
18. Reck M, Luft A, Szczesna A, et al. Phase III randomized trial of ipilimumab plus etoposide and platinum versus placebo plus etoposide and platinum in extensive-stage small-cell lung cancer. *J Clin Oncol* 2016; 34:3740-8.
19. Goldman JW, Dowlati A, Antonia SJ, et al. Safety and antitumor activity of durvalumab monotherapy in patients with pretreated extensive disease small-cell lung cancer (ED SCLC). *J Clin Oncol* 2018; 36(Suppl), abstract 8518.
20. Cho DC, Mahipal A, Dowlati A, et al. Safety and clinical activity of durvalumab in combination with tremelimumab in extensive disease small-cell lung cancer (ED-SCLC). *J Clin Oncol* 2018; 36(Suppl), abstract 85170.
21. Leighl N. *SCLC: progress at last?*, Presented at the IASLC 19th Annual World Conference on Lung Cancer; Toronto, Ontario, Canada; September 23-26 2018.
22. Ready N, Farago AF, de Braud F, et al. Third line nivolumab monotherapy in recurrent SCLC: CheckMate 032. *J Thorac Oncol* 2018. https://doi.org/10.1016/j.jtho.2018.10.003 [Epub ahead of print].
23. Bristol-Myers Squibb Press Release. Bristol-Myers Squibb announces phase 3 CheckMate-331 study does not meet primary endpoint of overall survival with opdivo versus chemotherapy in patients with previously treated relapsed small cell lung cancer, Available at: https://news.bms.com/press-release/corporatefinancial-news/bristol-myers-squibb-announces-phase-3-checkmate-331-study-doe. Accessed: October 16, 2018.
24. Hellmann MD, Ciuleanu TE, Pluzanski A, et al. Nivolumab plus ipilimumab in lung cancer with a high tumor mutational burden. *N Engl J Med* 2018; 378:2093-104.
25. Owonikoko TK. *Role of immunotherapy in small cell lung cancer*, Presented at the American Society of Clinical Oncology Annual Meeting; Chicago, IL; June 1-5 2018.
26. Kim Y, Keam B, Ock CY, et al. A phase II study of pembrolizumab and paclitaxel in refractory extensive disease small cell lung cancer. *J Clin Oncol* 2018; 36(Suppl), abstract 8575.
27. Butts CA. *Retreatment with platinum-etoposide and treatment beyond second-line*, Presented at the IASLC 19th Annual World Conference on Lung Cancer; Toronto, Ontario, Canada; September 23-26 2018.
28. Garassino MC, Torri V, Michetti G, et al. Outcomes of small-cell lung cancer patients treated with second-line chemotherapy: a multi-institutional retrospective analysis. *Lung Cancer* 2011; 72:378-83.
29. Genestreti G, Tiseo M, Kenmotsu H, et al. Outcomes of platinum-sensitive small-cell lung cancer patients treated with platinum/etoposide rechallenge: a multi-institutional retrospective analysis. *Clin Lung Cancer* 2015; 16:e223-8.
30. Eckardt JR, von Pawel J, Pujol JL, et al. Phase III study of oral compared with intravenous topotecan as second-line therapy in small-cell lung cancer. *J Clin Oncol* 2007; 25:2086-92.
31. von Pawel J, Jotte R, Spigel DR, et al. Randomized phase III trial of amrubicin versus topotecan as second-line treatment for patients with small-cell lung cancer. *J Clin Oncol* 2014; 32:4012-9.
32. von Pawel J, Schiller JH, Shepherd FA, et al. Topotecan versus cyclophosphamide, doxorubicin, vincristine for the treatment of recurrent small-cell lung cancer. *J Clin Oncol* 1999; 17:658-67.
33. Farago AF, Drapkin BJ, Charles A, et al. Safety and efficacy of olaparib (O) and temozolomide (T) in small cell lung cancer (SCLC). *J Clin Oncol* 2018; 36(Suppl), abstract 8571.
34. Moreno V, Calvo E, Olmedo ME, et al. *Overall survival with lurbinectedin plus doxorubicin in relapsed SCLC. Results from an expansion cohort of a phase Ib trial*, Presented at the IASLC 19th Annual World Conference on Lung Cancer; Toronto, Ontario, Canada; September 23-26 2018, abstract P1.12-20.
35. Carbone DP, Morgensztern D, Moulec SL, et al. Efficacy and safety of rovalpituzumab tesirine in patients with DLL3-expressing, ≥ 3rd line small cell lung cancer: results from the phase 2 TRINITY study. *J Clin Oncol* 2018; 36(Suppl), abstract 8507.
36. Cheng Y, Wang Q, Li K, et al. *Anlotinib as third-line or further-line treatment in relapsed SCLC: a multicentre, randomized, double-blind phase 2 trial*, Presented at the IASLC 19th Annual World Conference on Lung Cancer; Toronto, Ontario, Canada; September 23-26 2018.
37. Melichar B, Adenis A, Lockhart AC, et al. Safety and activity of alisertib, an investigational aurora kinase A inhibitor, in patients with breast cancer, small-cell lung cancer, non-small-cell lung cancer, head and neck squamous-cell carcinoma, and gastro-oesophageal adenocarcinoma: a five-arm phase 2 study. *Lancet Oncol* 2015; 16:395-405.
38. Gray JE, Heist RS, Starodub AN, et al. Therapy of small cell lung cancer (SCLC) with a topoisomerase-I-inhibiting antibody-drug conjugate (ADC) targeting trop-2, sacituzumab govitecan. *Clin Cancer Res* 2017; 23:5711-9.
39. Murai J, Tang SW, Leo E, et al. SLFN11 blocks stressed replication forks independently of ATR. *Mol Cell* 2018; 69:371-84.
40. Demetri GD, von Mehren M, Jones RL, et al. Efficacy and safety of trabectedin or dacarbazine for metastatic liposarcoma or leiomyosarcoma after failure of conventional chemotherapy: results of a phase III randomized multicenter clinical trial. *J Clin Oncol* 2016; 34:786-93.
41. Saunders LR, Bankovich AJ, Anderson WC, et al. A DLL3-targeted antibody-drug conjugate eradicates high grade pulmonary neuroendocrine tumor-initiating cells in vivo. *Sci Transl Med* 2015; 7:302ra136.
42. AbbVie News Center. AbbVie announces results from phase 2 study evaluating rovalpituzumab tesirine (Rova-T) for third-line treatment of patients with DLL3-expressing relapsed/refractory small cell lung cancer, Available at: https://news.abbvie.com/news/abbvie-announces-results-from-phase-2-study-evaluating-rovalpituzumab-tesirine-rova-t-for-third-line-treatment-patients-with-dll3-expressing-relapsedrefractory-small-cell-lung-cancer.htm. Accessed: October 16, 2018.
43. Rudin CM, Pietanza MC, Bauer TM, et al. Rovalpituzumab tesirine, a DLL3-targetted antibody-drug conjugate, in recurrent small-cell lung cancer: a first-in-human, first-in-class, open-label, phase 1 study. *Lancet Oncol* 2017; 18:42-51.
44. AbbVie News Center. Phase 3 trial of Rova-T as second-line therapy for advanced small-cell lung cancer (TAHOE Study) halted, Available at: https://news.abbvie.com/news/press-releases/phase-3-trial-rova-t-as-second-line-therapy-for-advanced-small-cell-lung-cancer-tahoe-study-halted.htm. Accessed: December 7, 2018.
45. Sos ML, Dietlein F, Peifer M, et al. A framework for identification of actionable cancer genome dependencies in small cell lung cancer. *Proc Natl Acad Sci U S A* 2012; 109:17034-9.
46. Hook KE, Pavlicek A, Garza SJ, et al. *Amplification and/or high expression of Myc family genes sensitizes tumor cells to aurora kinase inhibitors*, Presented at the AACR Annual Meeting; Washington DC; April 17-21 2010, abstract 2615.
47. Miller DM, Thomas SD, Islam A, Muench D, Sedoris K. c-Myc and cancer metabolism. *Clin Cancer Res* 2012; 18:5546-53.
48. Padda SK, Brzezniak CE, Waqar SN, et al. QUADRUPLE THREAT: A phase II trial of RRx-001 followed by etoposide-platinum re-challenge in previously treated small cell lung cancer. *J Clin Oncol* 2018; 36(Suppl), abstract e20575.
49. Pacheco JM, Camidge DR. Antibody drug conjugates in thoracic malignancies. *Lung Cancer* 2018; 124:260-9.
50. Kelly MP, Jungbluth AA, Wu B-W, Bomalaski J, Old LJ, Ritter G. Arginine deiminase PEG20 inhibits growth of small cell lung cancers lacking arginino-succinate synthetase. *Br J Cancer* 2012; 106:324-32.
51. Mohammad HP, Smitheman KN, Kamat CD, et al. A DNA hypomethylation signature predicts antitumor activity of LSD1 inhibitors in SCLC. *Cancer Cell* 2015; 28:57-69.
52. Sheng W, LaFleur MW, Nguyen TH, et al. LSD1 ablation stimulates anti-tumor immunity and enables checkpoint blockade. *Cell* 2018; 174:549-63.
53. Lenhart R, Kirov S, Desilva H, et al. Sensitivity of small cell lung cancer to BET inhibition is mediated by regulation of ASCL1 gene expression. *Mol Cancer Ther* 2015; 14:2167-74.
54. Gazdar AF, Bunn PA, Minna JD. Small-cell lung cancer: what we know, what we need to know and the path forward. *Nat Reviews Cancer* 2017; 17:725-37.

55. Goss G. *The management of small cell lung cancer following first line treatment failure*, Presented at the IASLC 19th Annual World Conference on Lung Cancer; Toronto, Ontario, Canada; September 23-26 2018.
56. Foy V, Schenk MW, Baker K, et al. Targeting DNA damage in SCLC. *Lung Cancer* 2017; 114:12-22.
57. Owonikoko TK, Dahlberg SE, Sica G, et al. Randomized phase II trial of cisplatin and etoposide in combination with veliparib or placebo for extensive-stage small-cell lung cancer: ECOG-ACRIN 2511 Study. *J Clin Oncol* 2019; 37:222-9.
58. Owonikoko TK, Dahlberg SE, Sica G, et al. Randomized trial of cisplatin and etoposide in combination with veliparib or placebo for extensive stage small cell lung cancer: ECOG-ACRIN 2511 study. *J Clin Oncol* 2017; 35(Suppl), abstract 8505.
59. Rudin CM, Hann CL, Garon EB, et al. Phase II study of single-agent navitoclax (ABT-263) and biomarker correlates in patients with relapsed small cell lung cancer. *Clin Cancer Res* 2012; 18:3163-9.
60. Park JH, Rivière I, Gonen M, et al. Long-term follow-up of CD19 CAR therapy in acute lymphoblastic leukemia. *N Engl J Med* 2018; 378:449-59.
61. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. *N Engl J Med* 2017; 377:2531-44.
62. Liu X, Zhang N, Shi H. Driving better and safer HER2-specific CARs for cancer therapy. *Oncotarget* 2017; 8:62730-41.
63. Giffin M. *Targetting DLL3 with BITE antibody constructs and cell-based therapies for the treatment of SCLC*, Presented at the American Association for Cancer Research Annual Meeting, 2018; Chicago, IL; April 14-18 2018.
64. Kantarjian H, Stein A, Gökbuget N, et al. Blinatumomab versus chemotherapy for advanced acute lymphoblastic leukemia. *N Engl J Med* 2017; 376:836-7.
65. Gadgeel SM, Pennell NA, Fidler MJ, et al. Phase II study of maintenance pembrolizumab in patients with extensive-stage small cell lung cancer (SCLC). *J Thorac Oncol* 2018; 13:1393-9.
66. Ready NE, Pang HH, Gu L, et al. Chemotherapy with or without maintenance sunitinib for untreated extensive-stage small-cell lung cancer: a randomized, double-blind, placebo-controlled phase II study-CALGB 30504 (Alliance). *J Clin Oncol* 2015; 33:1660-5.
67. Hanna N, Bunn PA Jr, Langer C, et al. Randomized phase III trial comparing irinotecan/cisplatin with etoposide/cisplatin in patients with previously untreated extensive-stage disease small-cell lung cancer. *J Clin Oncol* 2006; 24:2038-43.
68. Forde PM, Chaft JE, Smith KN, et al. Neoadjuvant PD-1 blockade in resectable lung cancer. *N Engl J Med* 2018; 378:1976-86.
69. Provencio M, Nadal E, Insa A, et al. *Neo-adjuvant chemo-immunotherapy for the treatment of stage IIIa resectable non-small-cell lung cancer (NSCLC): a phase II multicenter exploratory study*, Presented at the IASLC 19th Annual World Conference on Lung Cancer; Toronto, Ontario, Canada; September 23-26 2018.
70. Rusch VW, Chaft JE, Johnson BE, et al. *Neoadjuvant atezolizumab in resectable non-small cell lung cancer (NSCLC): updated results from a multicenter study (LCMC3)*, Presented at the IASLC 19th World Conference on Lung Cancer; Toronto, Ontario, Canada; September 23-26 2018, abstract MA04.09.
71. Shu CA, Grigg C, Chiuzan C, et al. Neoadjuvant atezolizumab + chemotherapy in resectable non-small cell lung cancer (NSCLC). *J Clin Oncol* 2018; 36(Suppl), abstract 8532.
72. Atkins MB, Plimack ER, Puzanov I, et al. Axitinib in combination with pembrolizumab in patients with advanced renal cell cancer: a non-randomised, open-label, dose-finding, and dose-expansion phase Ib trial. *Lancet Oncol* 2018; 19:405-15.
73. Motzer R, Powles T, Atkins MB, et al. IMmotion151: a randomized phase III study of atezolizumab plus avastin vs sunitinib in untreated metastatic renal cell carcinoma (mRCC). *J Clin Oncol* 2018; 36(Suppl):578.
74. Stein S, Pishvaian MJ, Lee MS, et al. Safety and clinical activity of 1L atezolizumab + bevacizumab in a phase Ib study in hepatocellular carcinoma (HCC). *J Clin Oncol* 2018; 36(suppl), abstract 4074.
75. Slotman B, Faivre-Finn C, Kramer G, et al. Prophylactic cranial irradiation in extensive small-cell lung cancer. *N Engl J Med* 2007; 357:664-72.
76. Pietanza MC, Kadota K, Huberman K, et al. Phase II trial of temozolomide in patients with relapsed sensitive or refractory small cell lung cancer, with assessment of methylguanine-DNA methyltransferase as a potential biomarker. *Clin Cancer Res* 2012; 18:1138-45.
77. Tawbi HA, Forsyth PA, Algazi A, et al. Combined nivolumab and ipilimumab in melanoma metastatic to the brain. *N Engl J Med* 2018; 379:722-30.
78. Rizvi N. *Discussant on nivolumab (nivo) + ipilimumab (ipi) vs platinum-doublet chemotherapy (PT-DC) as first-line (1L) treatment (tx) for advanced non-small cell lung cancer (NSCLC): initial results from CheckMate 227*, Presented at the American Association for Cancer Research Annual Meeting, 2018; Chicago, IL; April 14-18 2018.
79. Zauderer MG, Drilon A, Kadota K, et al. Trial of a 5-day dosing regimen of temozolomide in patients with relapsed small cell lung cancers with assessment of methylguanine-DNA methyltransferase. *Lung Cancer* 2014; 86:237-40.

Supplemental Data

Supplemental Table 1 Detailed Information on Methods of Identification of Studies

Search Term	Database	Number of Items Identified	Number of Items Included	Reasons for Exclusion
AEB1102	ClinicalTrials.gov	5	2	Trial in hematologic malignancies, no information about SCLC patient inclusion
Alisertib	2016 IASLC World Conference on Lung Cancer	2	1	Not SCLC patient population
Alisertib phase 2	PubMed	16	1	Not SCLC patient population, not clinical trial
Anlotinib	2018 IASLC World Conference on Lung Cancer	7	1	Not SCLC patient population, not clinical trial
AZD2811	ClinicalTrials.gov	3	1	Not SCLC patient population, study terminated and no results
CASPIAN	ClinicalTrials.gov	4	1	Not SCLC patient population
CheckMate 032	2017 ASCO Annual Meeting	2	1	Not SCLC patient population
CheckMate 032	PubMed	6	3	Not SCLC patient population
CheckMate 032	2017 IASLC World Conference on Lung Cancer	2	1	Did not evaluate TMB as a biomarker, only looked at health status via a patient questionnaire
CheckMate 451	ClinicalTrials.gov	1	1	N/A
Durvalumab and SCLC	2018 ASCO Annual Meeting	24	2	Not SCLC patient population, not clinical trial, not durvalumab
GSK2879552	ClinicalTrials.gov	3	1	Not SCLC patient population
IMpower133	PubMed	2	1	Trials in progress abstract
INCB059872	ClinicalTrials.gov	4	1	Not SCLC patient population
Ipilimumab and SCLC	PubMed	26	3	Not SCLC patient population, not clinical trial, no ipilimumab, trials in progress abstract, non-randomized phase II trial when there was a randomized phase III trial, phase II trial without platinum/etoposide backbone
Lurbinectedin	2018 ASCO Annual Meeting	7	1	Not SCLC patient population, used updated data from a later meeting
Lurbinectedin	2018 IASLC World Conference on Lung Cancer	1	1	N/A
KEYNOTE 158	2018 ASCO Annual Meeting	3	1	Not SCLC patient population
KEYNOTE 604	ClinicalTrials.gov	1	1	N/A
Navitoclax and SCLC	PubMed	12	1	Not clinical trial, phase I trial when there was a phase II trial
Nivolumab and platinum etoposide small cell	ClinicalTrials.gov	2	1	Not SCLC patient population
Pembrolizumab and maintenance SCLC	PubMed	1	1	N/A
Pembrolizumab and paclitaxel SCLC	2018 ASCO Annual Meeting	13	1	Not SCLC patient population, not clinical trial
Rovalpituzumab tesirine	2018 ASCO Annual Meeting	4	1	Not clinical trial
Rovalpituzumab tesirine	PubMed	19	1	Not clinical trial, included completed trial and not incomplete trial
RRx-001	2018 ASCO Annual Meeting	1	1	N/A
Sacituzumab govitecan SCLC	PubMed	2	1	Not clinical trial
Sunitinib maintenance SCLC	PubMed	6	1	Not clinical trial, induction regimen did not use platinum/etoposide
Talazoparib and SCLC	ClinicalTrials.gov	3	1	Not SCLC patient population
Temozolomide and olaparib	2018 ASCO Annual Meeting	5	1	Not SCLC patient population, not clinical trial
Temozolomide and small cell lung	PubMed	106	3	Not SCLC patient population, not clinical trial, only included patients with brain metastasis
Temozolomide and small cell lung	ClinicalTrials.gov	14	12	Not SCLC patient population

Supplemental Table 1 Continued

Search Term	Database	Number of Items Identified	Number of Items Included	Reasons for Exclusion
Topotecan and CAV	PubMed	22	1	Not clinical trial, did not compare with CAV, did not involve topotecan
Topotecan and SCLC phase III	PubMed	42	3	Not clinical trial, not phase III trial, not second or subsequent line therapy, only included brain metastasis, only included poor performance status patients

Abbreviations: ASCO = American Society of Clinical Oncology; CAV = cyclophosphamide + doxorubicin + vincristine; IASLC = International Association for the Study of Lung Cancer; N/A = not applicable; SCLC = small-cell lung cancer; TMB = tumor mutational burden.