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REVIEW

Extensive-Stage Small-Cell Lung Cancer: Current Landscape and Future Prospects

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Abstract: Small-cell lung cancer (SCLC) is characterized by aggressive disease progression and tendency to metastasize. Although chemotherapy for extensive-stage SCLC (ES-SCLC) has remained unchanged for decades, immune checkpoint inhibitors have become the primary therapy for ES-SCLC. However, the number of patients benefiting from immunotherapy is limited, and the treatment outcomes remain unsatisfactory. In addition, predictive biomarkers for immunotherapy have not yet been identified. Recent reports have shed light on the genomics of SCLC and defined four distinct molecular subtypes based on transcription factor expression. This may increase our understanding of the biology of SCLC and identify novel therapeutic targets and drugs. In this article, we review the current standard management of ES-SCLC and present the most recent reports to further our understanding of molecular classification, predictive biomarkers, and prospective therapies, including immunotherapy, chemotherapy, and targeted therapy.

Keywords: small-cell lung cancer, extensive-stage, immunotherapy, targeted therapy

Introduction

Small-cell lung cancer (SCLC) accounts for 10–15% of all lung cancers.[1,2] SCLC is characterized by aggressive disease progression and a tendency to metastasize to multiple organs and lymph nodes. Approximately 70–80% of patients with SCLC have ES-SCLC at the initial diagnosis.[3] Although most cases of ES-SCLC are initially sensitive to chemotherapy, local or distant recurrence frequently occurs, resulting in a poor prognosis. However, the addition of immune checkpoint inhibitors to platinum-based chemotherapy has prolonged the survival of SCLC patients in recent years. Genomic and transcriptomic analyses have recently revealed different SCLC molecular subtypes, suggesting their potential for personalized treatment. This article reviews the current strategies and future landscapes based on a new understanding of SCLC biology.

Molecular Classification of SCLC

Despite its histological heterogeneity, SCLC has been clinically treated as a single pathological disease. In the 1980s, morphological analysis suggested that SCLC cell lines could be classified into classical and variant subtypes.[4,5] Interestingly, the variant subtype grew faster than the classical subtype, and lacked expression of several neuroendocrine (NE) markers. Achaete-scute homolog 1 (ASCL1), an NE transcription factor, plays an important role in tumor development in SCLC.[6] A study that used cell lines reported that the classical subtype highly expressed ASCL1; conversely, the variant subtype highly expressed neurogenic differentiation 1 (NEUROD1), another NE transcription factor.[7] Subsequently, transcriptomic and epigenomic analyses of SCLC cell lines suggested that ASCL1 and NEUROD1 regulate distinct transcriptional programs and can be used to define SCLC subtypes.[8]

In addition, an SCLC population with low expression of both ASCL1 and NEUROD1 is recognized as a non-NE subtype. Clustered regularly interspaced short palindromic repeat (CRISPER) screening identified a third transcription factor, POU class 2 homeobox 3 (POU2F3), as a non-NE tuft cell-like variant of SCLC.[9] The fourth transcription factor, yes-associated protein 1 (YAP1), a regulator of the HIPPO growth signaling pathway, was preferentially expressed in

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a subset of patients with non-NE SCLC.[10] According to a study of these transcription factors using immunohistochemistry, however, YAP1 did not exclusively define the putative forth subtype "SCLC-Y" because of the low expression of each subtype.[11] In 2021, Gay et al defined a new subtype, SCLC-I, in addition to the known subtypes, SCLC-A, SCLC-N, and SCLC-P, based on ASCL1, NEUROD1, and POU2F3 expressions, respectively.[12] SCLC-I is characterized by epithelial–mesenchymal transition (EMT) and an inflammatory phenotype, with high expression of genes related to human leukocyte antigens, interferon-γ activation, and immune checkpoints, consistent with the association between EMT and immune-related gene expression.

SCLC-A and SCLC-N, both NE phenotypes, highly express two common NE markers, chromogranin A and synaptophysin, whereas SCLC-P and SCLC-I, which are non-NE phenotypes, highly express RE1 silencing transcription factor, an NE gene repressor.[13] SCLC can be comprehensively classified into four subtypes: SCLC-A, SCLC-N, SCLC-P, and SCLC-I.

Genomics of SCLC

Genomic profiling of various cancers using next-generation sequencing technology became widely used in the 2010s, and large-scale whole-exon and whole-genome sequencing analyses of human SCLC have been reported.

Inactivation of tumor protein 53 (TP53) and retinoblastoma 1 (Rb1) is almost universally detected in SCLC.[14–16] Both are known tumor suppressor genes which encode proteins that regulate cell cycle and survival. TP53 and Rb1 inactivation is also observed in the transformation to SCLC from lung adenocarcinomas with epidermal growth factor receptor mutations and from castration-resistant prostate cancer;[17,18] therefore, this phenomenon is considered a key event in the pathogenesis of small-cell carcinoma.

Amplification of SRY-box transcription factor 2 (SOX2), which encodes a transcriptional regulator of stem cells, has been observed in approximately 27% of patients with SCLC, especially in the SCLC-A subtype.[14] However, currently no therapies targeting SOX2 amplification exist.

Alterations in MYC family members, most commonly gene amplification and mutually exclusive, were observed in 20% of the SCLC cases (9% MYCL1, 4% MYCN, and 6% MYC).[16] The MYC gene is characterized by abnormalities in many cancers, whereas the MYCN gene is frequently altered in nervous system and NE tumors, and the MYCL gene is altered exclusively in some tumors, including SCLC. The SCLC-A subtype is highly associated with MYCL expression, whereas the upregulation of MYC is related to the SCLC-N subtype; replacing MYCL with MYC in the SCLC cell line induces a differentiation shift from the ASCL1 subtype to the NEUROD1 subtype.[10,19] In addition, it reportedly activates NOTCH to promote the temporal transition of SCLC subtypes from ASCL1 through NEUROD1 to the YAP1 state,[20] suggesting that the SCLC phenotype is dynamic during survival, proliferation, or treatment. Molecular subtypes of SCLC are summarized in Figure 1.

First-Line Treatments

Immune Checkpoint Inhibitors

Platinum plus etoposide (ETP) or cisplatin (CDDP) plus irinotecan[22–25] is the standard first-line treatment for ES-SCLC. Several clinical trials of immune checkpoint inhibitors, in addition to platinum plus ETP, have been reported over the past 5 years. The trial results for first-line chemoimmunotherapy in ES-SCLC are summarized in Table 1.

A Phase III study (IMpower133 study) conducted in patients with ES-SCLC with PS 0–1 compared carboplatin (CBDCA) + ETP + atezolizumab (a PD-L1 inhibitor) followed by maintenance therapy with atezolizumab with CBDCA + ETP + placebo.[26] The atezolizumab group showed significantly prolonged overall survival (OS), the primary endpoint, compared with the placebo group (median, 12.3 vs 10.3 months; HR 0.70, 95% CI: 0.54–0.91, $P = 0.007$). Progression-free survival (PFS), the secondary endpoint, was also significantly prolonged in the atezolizumab arm (median, 5.2 vs 4.3 months; HR 0.77, 95% CI: 0.62–0.96, $P = 0.02$). Although CBDCA was used as a platinum-based regimen in this study, the median OS in the placebo group was comparable to the previously reported median OS of 9.1–10.3 months in patients who received the CDDP + ETP regimen.[27–29] The updated 18-month OS was 34.0% in the atezolizumab arm and 21.0% in the placebo arm (HR 0.76 [95% CI: 0.60–0.95]).[30]

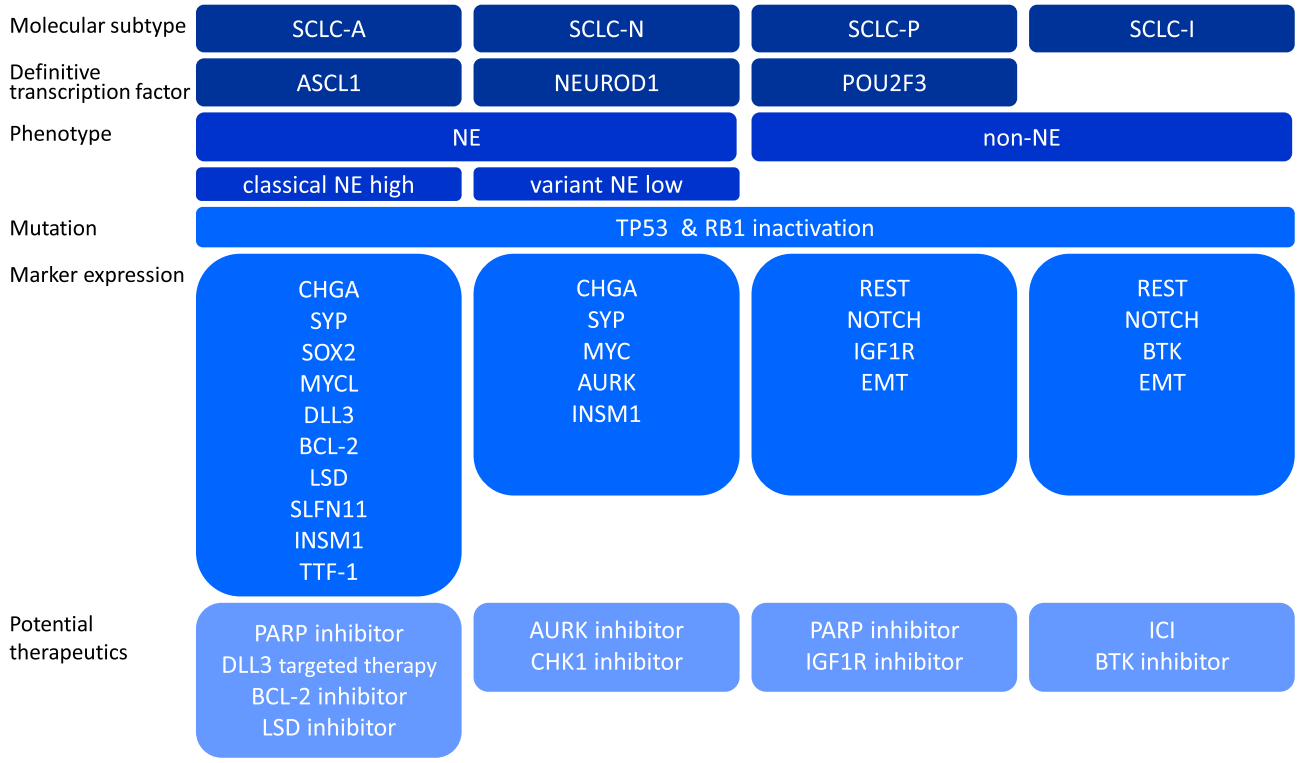

Figure 1 Molecular subtypes of small cell lung cancer with key transcription factors and potential therapeutics.
Note: Data from Lantuejoul S, Fernandez-Cuesta L, Damiola F, et al. New molecular classification of large cell neuroendocrine carcinoma and small cell lung carcinoma with potential therapeutic impacts. Transl Lung Cancer Res 2020;9(5):2233-2244, doi:10.21037/tlcr-20-269.[21]
Abbreviations: ASCL1, achaete-scute homolog 1; NEUROD1, neurogenic differentiation 1; POU2F3, POU class 2 homeobox 3; NE, neuroendocrine; TP53, tumor protein 53; RB1, retinoblastoma 1; CHGA, chromogranin A; SYP, synaptophysin; SOX2, SRY-box transcription factor 2; DLL3, delta-like protein 3; BCL-2, B-cell lymphoma 2; LSD, lysine-specific histone demethylase; SLFN11, Schlafen family member 11; INSM1, insulinoma-associated protein 1; TTF-1, thyroid transcription factor-1; AURK, Aurora kinase; REST, RE1 silencing transcription factor; IGF1R, insulin-like growth factor 1 receptor; EMT, epithelial–mesenchymal transition; BTK, Bruton tyrosine kinase.

A phase III study (CASPIAN) compared platinum combination therapy (CDDP + ETP or CBDCA + ETP) + durvalumab (PD-L1 inhibitor) followed by maintenance therapy with durvalumab (durvalumab arm) or platinum combination therapy + durvalumab + tremelimumab (CTLA-4 inhibitor) followed by maintenance therapy with durvalumab (durvalumab + tremelimumab arm) with platinum combination therapy in patients with ES-SCLC with PS 0–1. In the interim analysis of OS, the durvalumab arm showed significantly prolonged OS compared with the chemotherapy arm (median, 13.0 vs 10.3 months; HR 0.73, 95% CI: 0.59–0.91, $P = 0.0047$).[31] PFS showed an HR of 0.73 (median, 5.1 vs 5.4 months; 95% CI: 0.65–0.94). The updated 18-month OS rate was 32.0% in the durvalumab arm and 24.8% in the chemotherapy arm (HR 0.75 [95% CI: 0.62–0.91]).[32]

Furthermore, the CAPSTONE-1 phase III trial recently compared CBDCA + ETP + adebrelimab, a novel PD-L1 antibody, with CBDCA + ETP + placebo.[33] The median OS was significantly improved in the adebrelimab arm compared with the placebo arm (median, 15.3 vs 12.8 months; HR 0.72, 95% CI: 0.58–0.90, $P = 0.0017$). Thus, the current recommendations for patients with ES-SCLC with PS 0–1 are treatment with platinum + ETP + PD-L1 inhibitor.

In contrast to PD-L1 inhibitors, the indications of which have been steadily expanded, researchers studying PD-1 inhibitors have struggled to demonstrate efficacy in patients with ES-SCLC. The KEYNOTE-604 study was a randomized, double-blind, placebo-controlled Phase 3 trial that compared the efficacy and safety of platinum + ETP + pembrolizumab with chemotherapy alone.[34] The results of the final analysis showed a significant improvement in PFS (median, 4.5 vs 4.3 months; HR 0.75, 95% CI: 0.65–0.91, $P = 0.0023$). The OS was prolonged in the pembrolizumab arm although did not meet the pre-specified significance level of superiority (median, 10.8 vs 9.7 months; HR 0.8, 95% CI: 0.64–0.98, $P = 0.0164$). The ECOG-ACRIN EA5161 Phase II study of 160 patients with ES-SCLC used 1:1 randomization to evaluate platinum + ETP + nivolumab followed by nivolumab maintenance therapy or platinum + ETP alone and showed that the addition of nivolumab improved the primary PFS endpoint (median, 5.5 vs 4.6 months; HR 0.65, 95%

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Table 1 Clinical Trials for First-Line Chemoimmunotherapy in ES-SCLC

Trial	Phase	N	Treatment	Endpoint	ORR (%)	mPFS (Months)	mOS (Months)	Result of Trial
Impower133	III	403	CE + Atezolizumab CE + Placebo	PFS, OS	60.2 64.4	5.2 (HR 0.77, *P* = 0.02) 4.3	12.3 (HR 0.70, *P* = 0.007) 10.3	Positive
CASPIAN	III	805	CE/PE + Durvalumab CE/PE + Durvalumab + Tremelimumab vs CE/PE + Placebo	OS	68 58 58	5.1 (HR 0.80, 95% CI: 0.66–0.96) 4.9 (HR 0.84, 95% CI: 0.70–1.01) 5.4	12.9 (HR 0.75, *P* = 0.003) 10.4 (HR 0.82, *P* = 0.045) 10.5	Positive
CAPSTONE-1	III	462	CE + Adebrelimab CE + placebo	OS	70.4 65.9	5.8 (HR 0.67, *P* < 0.0001) 5.6	15.3 (HR 0.72, *P* = 0.0017) 12.8	Positive
KEYNOTE-604	III	453	CE/PE + Pembrolizumab CE/PE + Placebo	PFS, PS	70.6 61.8	4.5 (HR 0.75, *P* = 0.002) 4.3	10.8 (HR 0.80, *P* = 0.016) 9.7	Positive
ECOG-ACRIN EA5161	II	160	CE/PE + Nivolumab CE/PE + Placebo	PFS	52.3 47.7	5.5 (HR 0.65, *P* = 0.047) 4.6	11.3 (HR 0.67, *P* = 0.14) 8.5	Positive
ASTRUM-005	III	585	CE + Serplulimab CE + Placebo	OS	80.2 70.4	5.7 (HR 0.47, *P* < 0.001) 4.3	15.4 (HR 0.63, *P* < 0.001) 10.9	Positive
NCT00527735	II	130	CBDCA + PTX + phased Ipilimumab CBDCA + PTX + concurrent Ipilimumab vs CBDCA + PTX	irPFS	71 49 53	6.4[a] (HR 0.64, *P* = 0.03) / 5.22[b] (HR 0.93, *P* = 0.37) 5.7 (HR 0.75, *P* = 0.11) / 3.89 5.3 / 5.19	12.9 (HR 0.75, *P* = 0.13) 9.1 (HR 0.95, *P* = 0.41) 9.9	Positive (phased Ipilimumab vs control)
CA184-156	III	1132	CE/PE + Ipilimumab CE/PE + Placebo	OS	62 62	4.6 (HR 0.85, *P* = 0.016) 4.4	11.0 (HR 0.94, *P* = 0.37) 10.9	Negative
CheckMate 451 (Maintenance)	III	834	Ipilimumab + Nivolumab Nivolumab vs Placebo as maintenance	OS	9.1 11.5 4.2	1.7 (HR 0.72, 95% CI: 0.60–0.87) 1.9 (HR 0.67, 95% CI: 0.56–0.81) 1.4	9.2 (HR 0.92, 95% CI: 0.75–1.12) 10.4 (HR 0.84, 95% CI: 0.69–1.02) 9.6	Negative

Notes: [a]irPFS, [b]Modified World Health Organization PFS.

Abbreviations: ORR, objective response rate; PFS, progression free survival; OS, overall survival; irPFS, immune-related progression free survival; HR, hazard ratio; CI, confidence interval; CE, carboplatin + etoposide; PE, cisplatin + etoposide; CBDCA, carboplatin; PTX, paclitaxel.

CI: 0.46–0.91, $P = 0.047$) although failed to significantly improve OS (median, 11.3 vs 8.5 months; HR 0.67, 95% CI: 0.46–0.98, $P = 0.14$).

However, the recent ASTRUM-005 phase III trial evaluated CBDCA + ETP + serplulimab, another PD-1 antibody, and reported significantly improved PFS (median, 5.7 vs 4.3 months; HR 0.47, 95% CI: 0.38–0.59, $P < 0.001$) and OS (median, 15.4 vs 10.9 months; HR 0.63, 95% CI: 0.49–0.82, $P < 0.001$) relative to the placebo arm, with tolerable toxicity.[35] Based on these results, the FDA granted serplulimab, an orphan drug designation for the treatment of patients with SCLC.

Contrary to our expectations, CTLA-4 inhibitors failed to show clear efficacy in patients with ES-SCLC. Ipilimumab was first investigated in 2013 in a phase II study that randomized 130 patients 1:1:1 (CBDCA + paclitaxel + phased ipilimumab, CBDCA + paclitaxel + concurrent ipilimumab, or CBDCA + paclitaxel only).[36] Primary endpoint of this study was immune-related PFS (time from randomization to immune-related progressive disease or death according to immune-related response criteria). Median immune-related PFS was 6.4, 5.7, and 5.3 months, and the median OS was 12.9, 9.1, and 9.9 months in patients receiving phased ipilimumab or concurrent ipilimumab and controls, respectively. Phased ipilimumab improved immune-related PFS compared with controls (HR 0.64, $P = 0.03$) although not according to modified World Health Organization criteria (5.22 vs 5.19 months) (HR 0.93, 95% CI: 0.59–1.45, $P = 0.37$). No improvement in PFS (HR 0.93, $P = 0.37$) or OS (HR 0.75, $P = 0.13$) was observed. Furthermore, the CA184-156 trial, a phase III study that randomized 1132 patients to receive four cycles of platinum + ETP + ipilimumab or placebo followed by maintenance therapy of ipilimumab or placebo showed no differences in OS (median, 11.0 vs 10.9 months; HR 0.94, 95% CI: 0.81–1.09, $P = 0.3775$), with a higher frequency of adverse events (AEs) and treatment-related deaths (TRDs).[37]

The Checkmate 451 study evaluated ipilimumab and nivolumab or nivolumab monotherapy as maintenance therapy following first-line treatment for ES-SCLC. A total of 834 patients were randomly assigned 1:1:1 to the ipilimumab + nivolumab, nivolumab, or placebo group. OS was not significantly prolonged with ipilimumab + nivolumab vs placebo (median, 9.2 vs 9.6 months; HR 0.92, 95% CI: 0.75–1.12, $P = 0.37$).[38] Notably, serious treatment-related AEs of any grade were more common with combination therapy compared with monotherapy or placebo (37.4% vs 6.1% and 2.9%, respectively), as were AEs of any grade that led to discontinuation (28.8% vs 7.9% and 0.4%, respectively). Moreover, TRDs were more frequent in the combination therapy group (7 [2.5%], 1 [0.4%], and 1 [0.4%], respectively).

The CASPIAN trial evaluated platinum +ETP + durvalumab + tremelimumab (a CTLA-4 inhibitor) followed by maintenance therapy with durvalumab (durvalumab + tremelimumab arm). Unfortunately, the durvalumab + tremelimumab arm did not show a superior PFS (median, 4.9 vs 5.4 months; HR 0.84, 95% CI: 0.70–1.01) or OS (median, 10.4 vs 10.5 months; HR 0.82, 95% CI: 0.68–1.00, $P = 0.045$) compared with the chemotherapy arm and was even correlated with immune-related AEs, treatment-related terminations, and deaths.[31]

Poor PS

Currently, no evidence exists for the use of immune checkpoint inhibitors in ES-SCLC patients with poor PS, since the population with PS 2–4 was excluded in both the IMpower133 and CASPIAN trials. In general, when PS is impaired because of cancer progression and is expected to improve with treatment, chemotherapy is considered, even in ES-SCLC patients with PS 2–3. Hence, the addition of ICI to chemotherapy for patients with poor PS should be considered in daily practice. A Phase II, non-randomized, open-label, single-arm trial is ongoing to investigate the efficacy and safety of CBDCA + ETP + durvalumab in ES-SCLC patients with PS 2 and 3 (NEJ045A study).[39]

Biomarkers

Kaplan–Meier curves in both the IMpower 133 and CASPIAN trials reported a difference between the ICI and control arms after approximately 6 months.[26,31] The additional benefit in 1-year OS from ICI is only 14%. These results imply that the clinical benefit is not only attributed to the maintenance of ICI but also indicates that there might be a mixture of ES-SCLC subsets that benefit from ICI and those that do not. However, predictive biomarkers for ICI have not yet been established.

In both the IMpower 133 and CASPIAN trials, patients derived clinical benefits from the addition of ICI regardless of PD-L1 expression. With regard to tumor mutation burden (TMB), a retrospective analysis of the CheckMate 032 trial suggested improved objective response rate (ORR), PFS, and OS with nivolumab or nivolumab + ipilimumab therapy in patients with high compared with low/medium TMB.[40] Blood-based and tissue-based TMB were also explored as predictive biomarkers in the IMpower 133 and CASPIAN trials, respectively; however, both analyses showed no correlation between TMB and OS.[30] Tumor infiltrating lymphocytes (TILs) are one of the plausible predictive biomarkers of non-SCLC.[41] A retrospective study evaluating tumor PD-L1 expression in patients with SCLC with paraneoplastic syndrome (PNS) showed that patients with neurological PNS had increased TILs and PD-1/PD-L1 interactions and a better prognosis compared with patients with or without endocrinological PNS, suggesting a prognostic biomarker.[42]

Gay et al assigned 276 samples from the IMpower133 trial to the aforementioned four molecular subtypes and investigated the benefits of ICI by subtype.[12] A significant OS benefit was observed for SCLC-I relative to all other tumors (HR 0.566, 95% CI: 0.321–0.998) in the atezolizumab arm, although not in the placebo arm, suggesting that SCLC-I subtype assignment may be predictive of ICB benefit.

Second-Line or Later Treatment

Two clinical patterns of ED-SCLC relapse are considered for second-line treatment: sensitive and refractory. Patients with a longer time between initial drug therapy and relapse reportedly have a higher response to second-line therapy; patients who respond to initial therapy and have a longer time until relapse (usually defined as later than 60–90 days) are defined as sensitive relapse and others as refractory relapse. The recent clinical trials for second-line or later treatment in ES-SCLC are summarized in Table 2.

Sensitive Relapse

Topotecan, a topoisomerase I inhibitor, has been the only FDA-approved drug for the second-line treatment of ES-SCLC for decades. A phase III trial comparing oral topotecan monotherapy with best supportive care in relapsed SCLC including sensitive relapse showed superior OS in the oral topotecan arm (median, 13.9 vs 25.9 weeks; HR 0.64, 95% CI: 0.45–0.90, $P = 0.01$).[43] A phase III trial comparing topotecan monotherapy with cyclophosphamide+ doxorubicin + vincristine (CAV) in patients with sensitive relapse showed that the OS with topotecan monotherapy and that of CAV were comparable, with superior symptom improvement in the topotecan monotherapy arm.[44]

Amrubicin (AMR) is a topoisomerase I inhibitor. Three clinical trials comparing AMR with topotecan have been conducted.[45–47] A randomized controlled phase II trial for sensitive relapse only showed a comparable median OS (9.2 vs 7.6 months).[46] Moreover, a subgroup analysis of patients with sensitive relapse in a phase III trial showed that AMR was not superior to topotecan, with a median OS of 9.2 vs 9.9 months (HR 0.936, 95% CI: 0.724–1.211).[47] Based on these findings, AMR is not considered a standard therapy for patients with sensitive relapsed ES-SCLC.

A phase III trial (JCOG0605) comparing CDDP + ETP + irinotecan (PEI) with topotecan monotherapy for patients with sensitive relapsed ES-SCLC was conducted in Japan and demonstrated superior OS with PEI (median, 18.2 vs 12.5 months; HR 0.67, 95% CI: 0.51–0.88, $P = 0.0079$).[48] However, grade 3 or higher febrile neutropenia occurred in 31% of patients in the PEI arm (7% of patients in the topotecan arm) despite prophylactic administration of Granulocyte Colony Stimulating Factor. PEI therapy is considered a second-line therapy option for patients with sensitive relapsed ES-SCLC if the patient's condition permits.

A phase III study (GFPC01-13) comparing CBDCA + ETP rechallenge with oral topotecan was conducted in patients with sensitive relapse after platinum + ETP therapy.[49] The primary endpoint, PFS, was significantly prolonged in the CBDCA + ETP arm (median, 4.7 vs 2.7 months; HR 0.57, 90% CI: 0.41–0.73, $P = 0.0041$), whereas OS was similar with a median OS of 7.5 vs 7.4 months (HR 1.03, 95% CI: 0.87–1. 19). The main grade 3 or higher adverse events in both groups were hematological toxicity and febrile neutropenia, with similar frequencies. The rechallenge of platinum-based doublet is another valid option for patients with sensitive relapsed ES-SCLC.

Table 2 Clinical Trials for Second-Line or Later Treatment in ES-SCLC

Trial	Phase	N	Treatment	Endpoint	ORR (%)	mPFS (Months)	mOS (Months)	Result of Trial
Topotecan vs CAV	III	107	Topotecan CAV	ORR, Response duration	24.3 18.3	3.1 (P = 0.552) 2.8	5.8 (P = 0.795) 5.7	Better symptom control
NCT00547651	III	637	Amrubicin Topotecan	OS	31.1 16.9	4.1 (HR 0.802, P = 0.018) 3.5	7.5[a] (HR 0.88, P = 0.17) / 6.2[b] (HR 0.77, P = 0.047) 7.8 / 5.7	Negative
JCOG0605	III	180	CDDP + ETP + Irinotecan Topotecan	OS	84 27	5.7 (HR 0.50, P < 0.0001) 3.6	18.2 (HR 0.67, P = 0.0079) 12.5	Positive
GFPC01-13	III	164	CBDCA + ETP rechallenge Oral Topotecan	PFS	39 19	4.7 (HR 0.57, P = 0.0041) 2.7	7.5 (HR 1.03, 95% CI: 0.87–1.19) 7.4	Positive
NCT02454972	II	105	Lurbinectedin	ORR	35.2	3.5 (95% CI: 2.6–4.3)	9.3 (95% CI: 6.3–11.8)	Positive
ATLANTIS	III	613	Lurbinectedin + Doxorubicin Topotecan or CAV	OS	31.6 29.7	4.0 (HR 0.831, P = 0.043) 4.0	8.6 (HR 0.967, P = 0.70) 7.6	Negative
CheckMate 032 Randomized cohort	I/II	243	Nivolumab Nivolumab + Ipilimumab	ORR	11.6 21.9	1.4 (95% CI: 1.3–1.4) 1.5 (95% CI: 1.4–2.2)	5.7 (95% CI: 3.8–7.6) 4.7 (95% CI: 3.1–8.3)	–
KEYNOTE-028 and 158	Ib/II	83	Pembrolizumab	ORR	19.3	2.0 (95% CI: 1.9–3.4)	7.7 (95% CI: 5.2–10.1)	–
CheckMate 331	III	569	Nivolumab Topotecan or Amrubicin	OS	13.7 16.5	1.4 (95% CI: 1.4–1.5, HR 1.41) 3.8 (95% CI: 3.0–4.2)	7.5 (HR 0.86, P = 0.11) 8.4	Negative

Notes: [a]ITT patients, [b]Refractory patients.

Abbreviations: ORR, objective response rate; PFS, progression free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; CAV, cyclophosphamide + doxorubicin + vincristine; CDDP, cisplatin; ETP, etoposide; CBDCA, carboplatin.

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Refractory Relapse

A subgroup analysis of phase III trials of topotecan versus AMR in patients with recurrent SCLC showed prolonged OS with AMR monotherapy in patients with refractory relapse, with a median OS of 5.7 vs 6.2 months (HR 0.776, 95% CI: 0.589–0.997).[47] Based on these findings, AMR monotherapy is recommended for patients with refractory-relapsed ES-SCLC.

Several retrospective studies have assessed the efficacy and safety of AMR for relapsed SCLC after a first-line regimen, including ICI.[50–52] An ORR of 47%, median PFS of 3.8 months, and median OS of 10 months was reported. Toxicity was manageable; 73% of patients had grade 3 or 4 neutropenia and only one case (3%) of interstitial lung disease resulting in discontinuation of AMR.[52]

Because the combination of chemotherapy with ICI is now mainly used as the first-line treatment for ES-SCLC, evidence of the efficacy and safety of other subsequent therapies for relapse after the ICI regimen is needed. In addition, the definition of sensitive and refractory relapse may be reconsidered now that the clinical outcome of first-line therapy for ES-SCLC has been improved by chemotherapy with ICI.

Other Options

Irinotecan, a topoisomerase I inhibitor, is frequently used to treat relapsed SCLC in clinical practice. We previously reported the results of a phase II study of irinotecan for relapsed SCLC, showing a high response rate, PFS, and OS (41.3%; median, 4.1 and 10.4 months, respectively), with tolerable adverse events.[53]

Only two FDA-approved drugs are available as standard therapies for relapsed SCLC: topotecan and lurbinectedin. Lurbinectedin is a novel RNA polymerase II inhibitor that binds to CG-rich DNA sequences and inhibits oncogenic transcription, leading to tumor cell apoptosis. A phase II basket trial assessing lurbinectedin as a second-line therapy in 105 patients with relapsed SCLC after first-line platinum + ETP reported an ORR of 35% (95% CI: 26.2–45.2), a median PFS of 3.5 months, and a median OS of 9.3 months, with manageable adverse events.[54] Lurbinectedin was administered at a dose of 3.2 mg/m^2 every 3 weeks. Therefore, the FDA granted approval for lurbinectedin at a dose of 3.2 mg/m^2 every 3 weeks based on these clinical data in June 2020. The phase III randomized ATLANTIS trial assessed lurbinectedin plus doxorubicin versus control therapy with either CAV (cyclophosphamide, doxorubicin, and vincristine) or topotecan in 613 patients with relapsed SCLC.[55] Unfortunately, lurbinectedin + doxorubicin failed to improve outcomes compared with CAV or topotecan, with a median OS 8.6 months (95% CI: 7.1–9.4) for lurbinectedin + doxorubicin and 7.6 months (95% CI: 6.6–8.2) for CAV or topotecan (HR 0.97, 95% CI: 0.82–1.15). Notably, the dose of lurbinectedin was 2 mg/m^2 in the ATLANTIS trial, which was less than that used in the phase II trial. Hence, the NCCN Panel continued to recommend lurbinectedin at the higher dose in the 2023 update (Version 1), and the panel revised the preference stratification for lurbinectedin to "other recommended" from preferred status.

ICIs have not shown clear efficacy in second-line or later treatments. The CheckMate 032 Phase 1/2 trial compared nivolumab alone (n = 147) and nivolumab plus ipilimumab (n = 96) in patients with relapsed SCLC.[56,57] A combined analysis of phase Ib (KEYNOTE-028) and Phase 2 (KEYNOTE-158) trials evaluated the activity of pembrolizumab in 83 patients with relapsed SCLC.[58] Based on data from these reports, both nivolumab and pembrolizumab monotherapies were initially approved by the FDA as third-line treatments for SCLC. However, the CheckMate 331 randomized phase III trial comparing nivolumab monotherapy with topotecan or AMR in 569 patients with relapsed SCLC failed to show superiority in both PFS (median, 1.4 vs 3.8 months; HR 1.41, 95% CI: 1.18–1.69) and OS (median, 7.5 vs 8.4 months; HR, 0.86, 95% CI: 0.72–1.04, P = 0.11).[59] The OS was similar regardless of PD-L1 levels. The response rates were 13.7% and 16.5% for nivolumab and chemotherapy, respectively. Based on these results, the FDA withdrew subsequent therapeutic indications for nivolumab or pembrolizumab for patients with relapsed SCLC.

Emerging Strategies

Immunotherapy

Many studies have explored methods to augment ICI-based immunotherapy. The phase III SKYSCRAPER-02 study comparing CBDCA + ETP + atezolizumab + tiragolumab, an anti- T cell immunoreceptor with Ig and ITIM domains

(TIGIT) antibody, with CBDCA + ETP + atezolizumab + placebo is ongoing. A recent interim analysis revealed no improvement in the primary endpoint of PFS. The median PFS was 5.4 months with tiragolumab vs 5.6 months with placebo (HR 1.11, 95% CI: 0.89–1.38 $P = 0.3504$). The other co-primary endpoint, OS, was unlikely to reach statistical significance in the planned final analysis.[60] The median OS was 13.6 months for both cohorts (HR 1.04, 95% CI: 0.79–1.36, $P = 0.7963$).

In addition to anti-TIGIT antibody, LAG525, an anti-LAG3 antibody (NCT03365791); utomilumab, an anti-4-1BB antibody (NCT02554812); and other agents are currently under investigation in clinical trials for ES-SCLC. The clinical trials for emerging strategies in ES-SCLC are summarized in Table 3.

PARP Inhibitor

Previous data suggest that the loss of G1/S cell cycle checkpoint control due to the inactivation of RB1 and TP53 increases the susceptibility of SCLC to DNA damage.[16] Poly-ADP-ribose polymerase (PARP) is a protein involved in several cellular processes, such as DNA repair, genomic stability, and programmed cell death, and is highly expressed in patients with SCLC.[61] PARP inhibitors induce DNA damage and apoptosis in tumor cells by inhibiting the repair process. Currently, several PARP inhibitors are under investigation for SCLC such as olaparib, veliparib, and niraparib. Although PARP inhibitors seem to be promising targeted therapies, PARP inhibitor monotherapy has shown only modest efficacy.[62,63] Combination therapy with other chemotherapies was also evaluated. A phase II trial of temozolomide (TMZ) + veliparib or placebo in previously treated SCLC patients was conducted (N = 104) although failed to meet its primary endpoint of 4-month PFS (36% vs 27%, $P = 0.19$) or OS (8.2 months, 95% CI: 6.4–12.2, vs 7.0 months, 95% CI: 5.3–9.5, $P = 0.50$), while the ORR was significantly higher with TMZ + veliparib (39% vs 14%, $P = 0.016$).[64] However, the exploratory analysis of the veliparib arm showed significantly prolonged PFS (median, 5.7 vs 3.6 months; $P = 0.009$) and OS (median, 12.2 vs 7.5 months, $P = 0.014$) were observed in patients with Schlafen family member 11 (SLFN11)-positive tumors, suggesting that SLFN11 is a potential predictive biomarker for PARP inhibitors in patients with SCLC. SLFN11 is a member of the Schlafen family involved in the control of cell proliferation and induction of the immune response. A randomized phase II study of maintenance atezolizumab versus atezolizumab + talazoparib in patients with SLFN11 positive ES-SCLC (SWOG S1929) met its primary endpoint, demonstrating that maintenance atezolizumab + talazoparib improved PFS (median, 4.2 vs 2.8 months; HR 0.70, $P = 0.056$).[65]

A randomized phase II trial compared CDDP + ETP +veliparib with CDDP + ETP + placebo. In the first-line treatment of ES-SCLC, the veliparib arm showed significantly prolonged PFS (median, 6.1 vs 5.5 months; HR 0.63, $P = 0.01$) although did not result in a statistically significant difference in OS compared with the placebo arm (median 10.3 vs 8.9 months; HR 0.83, $P = 0.17$).[66] Stratified analysis showed significantly prolonged PFS (HR 0.34, 80% CI: 0.22–0.51) in the veliparib arm in male patients with high lactate dehydrogenase (LDH) although no significant differences between groups in the other patient populations (HR 0.81, 80% CI: 0.60–1.09). A single-arm phase II trial of olaparib plus durvalumab in patients with relapsed SCLC showed an ORR of 10.5%, a median PFS of 1.8 months, and a median OS of 4.1 months.[67] Tumor responses were observed in all cases in which pretreatment tumors showed an inflammatory immune phenotype. Clinical trials of PARP inhibitors in combination with ICIs are currently ongoing. In a previous report, SCLC cell line in vitro drug response data for over 500 drugs were utilized to investigate SCLC subtype-specific vulnerabilities.[12] SCLC-P models were significantly more sensitive to all five PARP inhibitors tested in these datasets.

Thus, PARP inhibitors are attracting attention as targeted therapies for ES-SCLC. However, their efficacy is unsatisfactory. The discovery of potential biomarkers, such as SLFN11 and LDH, or the phenotype of tumors may support the utility of PARP inhibitors in ES-SCLC.

DLL3 Targeted Agent

Delta-like protein 3 (DLL3), a key negative regulator of NOTCH signaling, is highly expressed on the cell surface of SCLC of NE origin.[68] DLL3 expression is regulated by ASCL1.[11] Correspondingly, DLL3 was the most highly expressed in the SCLC-A subtype and least expressed in SCLC-P and SCLC-I.[12] Hence, DLL3 targeted therapy is expected to be effective against the SCLC-A phenotype.

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Table 3 Emerging Strategies in ES-SCLC

Trial	Phase	N	Patients	Treatment	Endpoint	ORR (%)	mPFS (Months)	mOS (Months)	Result of Trial
Anti-TIGIT antibody									
SKYSCRAPER-02	III	490	First-line	CE + Atezolizumab + Tiragolumab CE + Atezolizumab + Placebo	PFS, OS	70.8 65.6	5.4 (HR 1.11; *P* = 0.35) 5.6	13.6 (HR 1.04, *P* = 0.79) 13.6	Negative
Anti-LAG3 antibody									
NCT03365791	II	76	Solid and hematologic malignancies, second- to sixth-line	PDR001 (anti-PD-1 antibody) + LAG525 (anti-LAG3 antibody)	CBR at 24 Weeks				Ongoing
Anti-4-1BB antibody									
NCT02554812	Ib/II	409	Solid tumor	Avelumab + Utomilumab	DLT, ORR				Ongoing
PARP inhibitor									
ECOG-ACRIN 2511	II	128	First-line	PE + Veliparib PE + Placebo	PFS	71.9 65.6	6.1 (HR = 0.63; *P* = 0.01) 5.5	10.3 (HR = 0.83; *P* = 0.17) 8.9	Positive
NCT02484404	II	20	Relapsed	Olaparib + Durvalumab	ORR	10.5	1.8 (95% CI, 0.9–2.4)	4.1 (95% CI, 2.4–9.2)	–
SWOG S1929 (NCT04334941)	II	106	SLFN11 positive, Maintenance following chemotherapy + Atezolizumab Atezolizumab	Atezolizumab + Talazoparib	PFS	12 16	4.2 (HR 0.70; *P* = 0.056) 2.8	9.4 (HR 1.17; *P* = 0.30) 8.5	Positive
DLL3 targeted agent									
TAHOE	III	444	Second-line	Rova-T (antibody drug conjugate) Topotecan	ORR	15 21	3.0 (95% CI: 2.9–3.6) 4.3 (95% CI: 3.8–5.4)	6.3 (95% CI, 5.6–7.3) 8.6 (95% CI: 7.7–10.1)	Negative
NCT03319940	I	107	Relapsed	Tarlatamab, AMG757 (BiTE)	Safety	23.4	3.7 (95% CI, 2.1–5.4)	13.2 (95% CI, 10.5-not reached)	–
DeLLphi-301	II	222	Third-line or later	Tarlatamab, AMG757 (BiTE)	ORR				Ongoing
NCT03392064	I	6	Relapsed	AMG119 (CAR-T)	Safety				Ongoing
Liposomal Irinotecan									
RESILIENT part 1	II	30	Second-line	Liposomal Irinotecan	Safety	44	3.98 (95% CI, 1.45–4.24)	8.08 (95% CI, 5.16–9.82)	–
RESILIENT part 2	III	450	Second-line	Liposomal Irinotecan Topotecan	OS				Ongoing
Angiogenesis inhibitor									
ALTER1202	II	120	Third-line or later	Anlotinib Placebo	PFS	4.9 2.6	4.1 (HR 0.19, *P*< 0.0001) 0.7	7.3 (HR 0.53, *P* =.0029) 4.9	Positive

Abbreviations: ORR, objective response rate; PFS, progression free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; CE, carboplatin + etoposide; PE, cisplatin + etoposide; Rova-T, Rovalpituzumab tesirine; BiTE, bispecific T-cell engager; CAR-T, chimeric antigen receptor-T cell; CBR, clinical benefit rate.

Rovalpituzumab tesirine (Rova-T) is an antibody drug conjugate consisting of a monoclonal antibody targeting DLL3, a cathepsin cleavable linker, and a pyrrolobenzodiazepine warhead, and is the first therapeutic agent targeting DLL3. In the phase III TAHOE study comparing Rova-T with topotecan as second-line therapy for DLL3-high SCLC, Rova-T exhibited inferior OS and higher rates of serosal effusions, photosensitivity reactions, and peripheral edema.[69] Another DLL3 targeted agent, tarlatamab (AMG757), is a half-life-extended bispecific T-cell engager that binds to both DLL3 and CD3, leading to T-cell-mediated tumor lysis. A Phase I study of tarlatamab in 107 patients with relapsed SCLC (DeLLphi-300) was recently reported.[70] Grade 3 and higher AEs occurred in 30.8% of patients, including grade 5 pneumonitis in one patient (1%). Cytokine release syndrome was the most common AE, occurring in 51.4% of the patients, including grade 3 in one patient (1%). The maximum tolerated dose was not achieved. The ORR was 23.4% (95% CI: 15.7–32.5) including two complete responses. The median response was 12.3 months (95% CI: 6.6–14.9). The median PFS and OS were 3.7 (95% CI: 2.1–5.4) and 13.2 (95% CI: 10.5-not reached) months, respectively. Notably, the median number of prior lines of anticancer therapy was two (range, 1–6); 49.5% received PD-1/PD-L1 therapy. Based on these results, tarlatamab is anticipated to exhibit antitumor efficacy and durability in heavily treated SCLC patients. A Phase 2 study of tarlatamab, DeLLphi-301 (NCT05060016), is ongoing for the third-line treatment of SCLC and beyond. Novel chimeric antigen receptor-T cell therapies targeting DLL3 (AMG119) are also underway.

Other Targeted Therapies

Ataxia telangiectasia and RAD3-related protein (ATR), a central DNA damage repair mediator, is also a promising target, and ATR inhibitor is expected to act synergistically when combined with topotecan. In a proof-of-concept study, berzosertib, a first-in-class ATR inhibitor, showed a 36% ORR when combined with topotecan.[71] Durable tumor regression has been observed in patients with platinum-resistant SCLC. A randomized phase II study of berzosertib plus topotecan versus topotecan alone is underway for patients with relapsed small-cell NE cancers, including SCLC (NCT03896503).

Proteins from the B-cell lymphoma 2 (BCL-2) family inhibit cell death and regulate the critical step of apoptosis. BCL-2 proteins are overexpressed in patients with SCLC and are another direct transcriptional target of ASCL1, suggesting a potential therapeutic target, especially in the SCLC-A subtype.[12] BCL2 inhibitors such as navitoclax and venetoclax have also been investigated.[72,73]

Inhibition of lysine-specific histone demethylase results in the downregulation of ASCL1 via NOTCH1 activation.[12,74] The SCLC-N variant expresses high levels of MYC and NEUROD1 and is sensitive to Aurora kinase inhibition.[75] Higher expression or amplification of MYC also predicts sensitivity to inhibitor of checkpoint kinase 1.[76] The POU2F3 subtype is vulnerable to insulin-like growth factor 1 receptor inhibition based on the results of CRISPR screens.[9] SCLC-I cells highly express Bruton tyrosine kinase (BTK), suggesting a potential therapeutic target. BTK inhibitors such as ibrutinib, which is approved for hematologic malignancies, may be candidates for this subtype.

Liposomal Irinotecan

Irinotecan has been widely used to treat relapsed SCLC in clinical practice as mentioned above. Liposomal irinotecan (nal-IRI) is a long-circulating liposomal-encapsulated formulation of irinotecan that was developed to overcome the pharmacological and clinical limitations of conventional (non-liposomal) formulations of the drug, with the overall aim of maximizing antitumor efficacy while minimizing drug-related toxicities. Phase II of the RESILIENT trial reported encouraging data with an ORR of 44.0% (95% CI: 24.40–65.07), median PFS of 3.98 (95% CI: 1.45–4.24) months, and median OS of 8.08 (95% CI: 5.16–9.82) months.[77] A randomized phase III trial comparing nal-IRI with topotecan for patients with SCLC after platinum-based first-line therapy is ongoing (NCT03088813).

Angiogenesis Inhibitor

Two randomized studies confirmed that a monoclonal vascular endothelial growth factor antibody, bevacizumab, in combination with platinum-based chemotherapy failed to improve OS as a first-line treatment for patients with ES-SCLC.[78,79]

To date, only anlotinib improved the OS and PFS in Chinese patients with SCLC as third-line therapy, which was approved for this indication in China. Anlotinib is an oral multi-kinase inhibitor that targets vascular endothelial growth factor receptor, platelet-derived growth factor receptor, fibroblast growth factor receptor, and c-kit. The randomized phase II ALTER1202 study comparing anlotinib with placebo as a third-line or later treatment for ES-SCLC showed significantly longer PFS (median, 4.1 vs 0.7 months; HR 0.19, 95% CI: 0.12–0.32, $P < 0.0001$) and OS (median, 7.3 vs 4.9 months; HR 0.53, 95% CI: 0.34–0.81, $P = 0.0029$).[80] Large-scale randomized controlled phase III studies are currently ongoing.

Summary and Prospective

Genomic profiling using next-generation sequencing revealed distinct SCLC subtypes. Four molecular subtypes of SCLC are now known: SCLC-A, SCLC-N, SCLC-P, and SCLC-I. SCLC-A, SCLC-N, and SCLC-P are defined by the key transcription factors ASCL1, NEUROD1, and POU2F3, respectively. SCLC-I is characterized by EMT and a highly inflammatory signature. Interestingly, each subtype exhibited distinct vulnerabilities to inhibitors, mainly corresponding to each expression marker. This approach may lead to the discovery of novel therapeutic targets and drugs, based on subtype-specific therapies. Several targeted therapeutics are under investigation, such as PARP inhibitors, DLL3 targeted agents, and Aurora kinase inhibitors, and the clinical trial results are anticipated.

The addition of PD-L1 inhibitors to pre-existing cytotoxic regimens prolongs survival in ES-SCLC patients. However, the additional benefit of immunotherapy in patients with SCLC is unsatisfactory relative to that in patients with non-SCLC, which is understandable if immunotherapy-sensitive and -resistant subtypes exist. Hence, the elucidation of predictive biomarkers or methods to select sensitive populations is required. Moreover, research efforts should continue to augment immunotherapy. Currently, new immune checkpoint inhibitors (anti-TIGIT and anti-LAG3), small molecules, and their combinations have been investigated. Future clinical trials on ES-SCLC should be designed to gain insights into the biology of SCLC.

Disclosure

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