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REVIEW

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Current and future therapies for small cell lung carcinoma

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Abstract

Small cell lung cancer (SCLC) is an aggressive malignancy characterized by rapid proliferation and high metastatic potential. It is characterized by universal inactivation of and RB1, overexpression of the MYC family and dysregulation of multiple oncogenic signaling pathways. Among different patients, SCLCs are similar at the genetic level but exhibit significant heterogeneity at the molecular level. The classification of SCLC has evolved from a simple neuroendocrine (NE)/non-neuroendocrine (non-NE) classification system to a transcription factor-based molecular subtype system; lineage plasticity adds further complexity and poses challenges for therapeutic development. While SCLC is initially sensitive to platinum-based chemotherapy, resistance develops rapidly, leading to a dismal prognosis. Various antibodies, including PD-1/PD-L1 inhibitors and antibody–drug conjugates, have been introduced into clinical practice or are being evaluated in clinical trials. However, their therapeutic benefits for SCLC patients remain limited. This review summarizes SCLC carcinogenic mechanisms, tumor heterogeneity, and the immune microenvironment of SCLC, with a focus on recent advances in metastasis and resistance mechanisms. Additionally, the corresponding clinical progress in tackling these challenges is discussed.

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Introduction

Approximately 15% of lung cancer cases are small cell lung cancer (SCLC), which is typically characterized by rapid proliferation, early metastasis, and a poor prognosis [1]. Although low-dose computed tomography (CT) has been applied for early detection, 80–85% of patients present with extensive-stage SCLC (ES-SCLC) at first diagnosis, and less than 7% of them survive 5 years past diagnosis [2, 3]. SCLC is associated with heavy smoking or passive smoking, radon radiation, air pollutants, or older age (Fig. 1) [4, 5]. Thus, reducing the frequency of smoking is one of the main prevention methods for SCLC, and the ever-decreasing incidence confirms its effectiveness. However, SCLC is very difficult to treat SCLC patients rarely benefit from surgery. Etoposide-platinum (EP) is the current standard chemotherapeutic regimen. SCLC patients respond to chemotherapy initially, but most acquire resistance rapidly and relapse quickly [6]. Although there are additional therapies for relapsed patients, their response to further therapies is substantially reduced. As immunotherapy has been efficacious against in many other tumors, anti-PD-L1 or anti-PD-1 antibodies have also been used along with EP in the first-line treatment of SCLC and have improved overall survival, but the benefit is not significant [7]. SCLC patients have a median PFS of approximately 5 months and an average OS of 12 months, and there is an urgent need to find more effective therapies to prolong patient survival.

SCLC originates predominantly from pulmonary neuroendocrine cells (PNECs); major changes in the proliferative and metastatic potential of these cell lead to

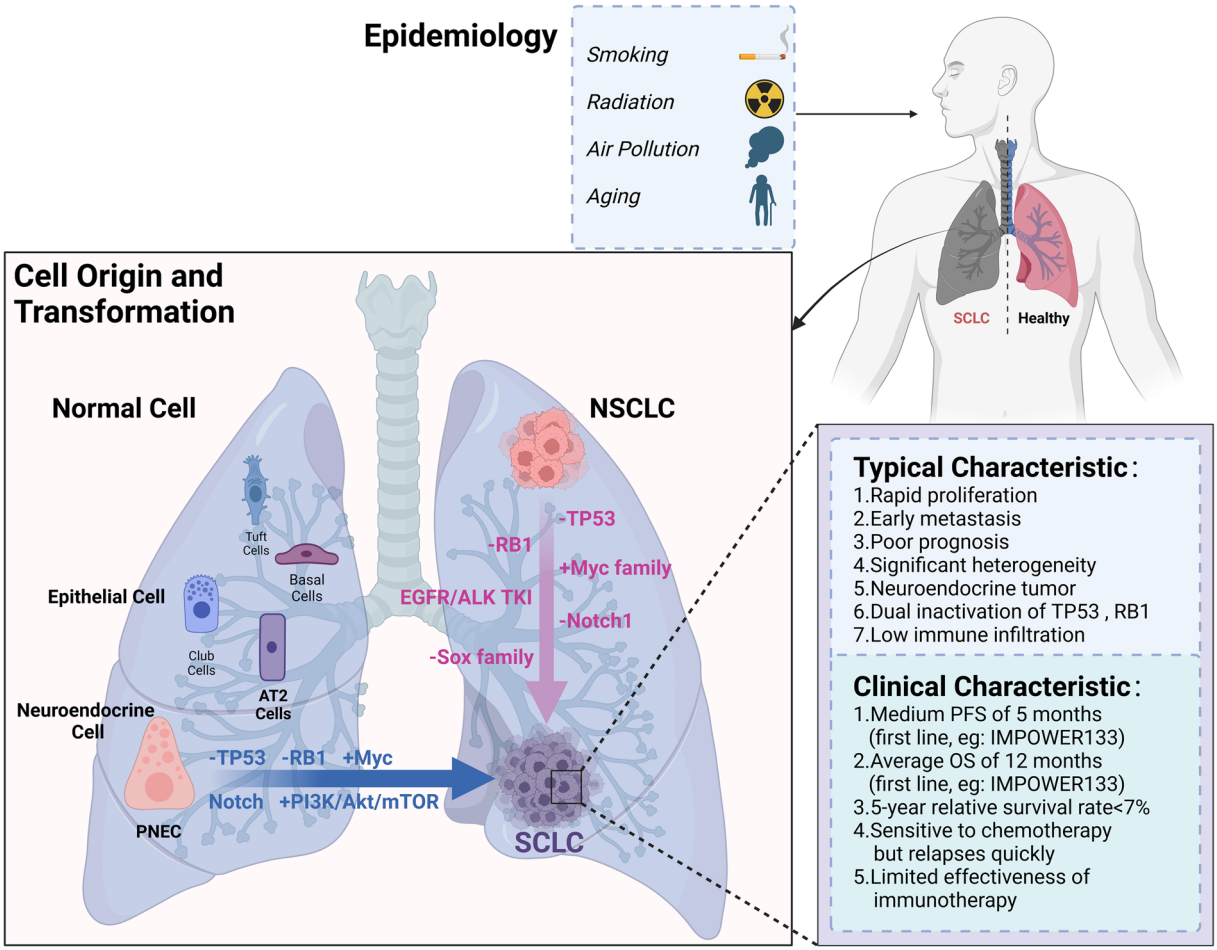


Fig. 1 The epidemiology, cell origin, and clinical characteristics of SCLC. The main epidemiological factors for SCLC include smoking, radiation, air pollution, and aging. On the one hand, the cellular origin of SCLC may be neuroendocrine cells within the lung. On the other hand, non-small cell lung cancer with tyrosine kinase inhibitor (TKI) resistance can transform into SCLC. SCLC has an oat cell shape and is sensitive to chemotherapy but is prone to recurrence. Abbreviations: ALK-TKIs, ALK tyrosine kinase inhibitors; AT2s, alveolar type II epithelial cells; EGFR-TKIs, EGFR tyrosine kinase inhibitors; PNECs, pulmonary neuroendocrine cells

paraneoplastic syndrome (PNS) [8, 9]. Barnard first mentioned SCLC in 1926 as "oat-cell sarcoma" on the basis of its morphological features; Azzopardi elaborated on the features of SCLC approximately 30 years later [10, 11]. The histopathological features of SCLC include small tumor cells with a round to fusiform shape loosely arranged or in a syncytial pattern, scant cytoplasm, rough chromatin, and obscure nucleoli [12, 13]. At the molecular level, unlike other solid tumors, SCLC is characterized by dual inactivation of the tumor suppressors P53 and RB1 rather than the activation of oncogenes, which leads to different changes in signaling pathways [14, 15]. Different SCLCs have different transcription factor expression profiles, so transcription factors can be assessed for molecular subtyping [16, 17]. SCLCs usually have a complicated tumor microenvironment, and the interaction of tumor cells with stromal cells in the microenvironment facilitates their strong immune evasion capacity [18].

Several new regimens have been developed on the basis of the biological characteristics of SCLC, as its cellular origins, metastatic properties, and genomic features have gradually been clairified. However, tumor heterogeneity and therapeutic resistance remain bottlenecks in clinical treatment [1, 7, 19–21].

This review summarizes new findings on SCLC clinical and biological features, including its pathogenesis, heterogeneity, drug resistance mechanism, and treatment options. We also discuss the possible resolution of drug resistance and screening efficiency.

Molecular characteristics of SCLC

Cell origins and transformation of SCLC

Transformation of normal cells

There are currently conflicting accounts of the origin of SCLC cells. Initially, SCLCs were thought to be derived from pulmonary neuroendocrine cells (PNECs) on the basis of the high expression of neuroendocrine markers, such as synaptophysin and chromogranin A, in SCLC tumors (Fig. 1) [22, 23]. In addition, PNECs differentiate early during lung development, suggesting that they may also possess the regenerative capacity of progenitor cells [24]. Many groups have investigated the mechanism by which PNECs affect tumor cell transformation. Using lineage tracing approaches in *Ascl1*$^{CreER/+}$, *Trp53*$^{f/f}$, and *Rb1*$^{f/f}$ mice, Ouadhah et al. found that SCLC is derived from a subset of PNECs with stem cell features. Specifically, Notch signaling pathway activation is necessary for reprogramming neuroendocrine cells in the lungs.

In contrast, deletion of Rb/p53 further promotes the dispersal and reprogramming of neuroendocrine cells in the lungs, ultimately giving SCLC cells early metastasis-promoting properties [25]. Furthermore, Chen et al. generated SCLC-like tumor cells by knocking down *TP53* and *RB1* and overexpressing *c-MYC* in human PNECs [26, 27]. However, PNECs are not the exclusive cell origin of SCLCs, and some studies have suggested that other epithelial cells, such as alveolar type II epithelial cells (AT2), club cells, and basal cells, may also differentiate into SCLC cells. Chen's group reported that SCLC tumors can be derived from multiple cell lineages, including PNECs, AT2 cells, and club cells, in the context of *Trp53*, *Rb1* loss, and *MYC* gain [28]. Ferone et al. reported that SCLC could be initiated from basal cells with inactivation of *Rb1* and *Trp53* and activation of *FGFR1* in the Ad5-K14-Cre mouse model [29]. However, the exact mechanism of tumorigenesis has not been explicitly investigated. Moreover, SCLCs derived from different cell lineages have distinct expression profiles and phenotypes that are correlated with SCLC molecular subtypes. For example, PNEC-initiated SCLC expresses SCLC-A subtype features such as highly upregulated ASCL1 [30]. Huang et al. suggested that the SCLC-P subtype may transform from tuft cells, a previously unrecognized cell lineage. Overall, there are still many unanswered questions about the origin of SCLC, but understanding the origin of SCLC will facilitate the identification of treatment targets and prevention strategies for SCLC.

NSCLC to SCLC histological transformation

The histological transformation of NSCLC to SCLC is thought to be another origin of SCLC. It has been observed after targeted therapeutic resistance in NSCLC (Fig. 1) [31]. Genealogical plasticity theory holds that NSCLC is transformed into SCLC through EGFR mutation or ALK rearrangement-mediated cell phenotypic transformation [32, 33]. Approximately 3%-14% of NSCLC patients undergo SCLC transformation during resistance to EGFR tyrosine kinase inhibitors (EGFR-TKIs). Genomic sequencing revealed that most post-transformed SCLC cells retained the original EGFR mutations in primary NSCLC, indicating the direct evolution of SCLC from original EGFR-mutated NSCLC tumor cells under the selective pressure of TKIs [34–36].

Furthermore, Offin et al. reported that *EGFR/TP53/RB1*-mutant lung cancers are at unique risk of histologic transformation, with 25% presenting with de novo SCLC or eventual small-cell transformation [37]. SCLC transformation is also commonly observed in patients with *ALK*-rearranged lung cancer after resistance to ALK inhibitors (ALKis). Levacq et al. reported a case in which *RB1*, *TP53*, *PTEN*, and *NOTCH1* inactivation in primary NSCLC induced SCLC transformation after ALKi therapies [38]. The transformation of NSCLC to SCLC with therapeutic resistance indicates that NSCLCs and SCLCs share the same cell origins. As mentioned above, some SCLCs can develop from AT2 cells, which are also

considered the origin cells of NSCLCs [39]. Another study revealed that cells with a transitional morphology expressed TTF-1 (a PNEC marker) on the border of SCLC and NSCLC, suggesting that they were possibly derived from the common PNEC ancestor [40]. As SCLC transformation commonly occurs during resistance to targeted therapies in NSCLC, novel treatments targeting the trunk mutation of the common ancestor are highly needed to overcome the current problem of therapeutic resistance.

Key pathways in SCLC tumorigenesis

In both normal cells and those transformed from other malignant tumors, many activations of oncogenic molecules or inactivation of oncogenic pathways occur during the process. For example, inactivation of the oncogenes *TP53* and *RB1* and activation of the *MYC* oncogene, as well as upregulation of the NOTCH pathway and activation of the PI3K/Akt/mTOR pathway and several other oncogenic pathways, contribute to the development of SCLC, ultimately leading to the distinctive characteristics of SCLC in terms of its rapid amplification and high metastasis efficiency (Fig. 2).

Dual inactivation of p53 and RB1

P53 is a major tumor suppressor transcription factor that responds to various cellular stresses, including DNA damage, hypoxia, and hyperproliferative stimuli, to maintain genome stability and inhibit cancer progression [41–43]. *RB1* is another important transcriptional regulator with tumor suppressor functions. It exerts its regulatory effects by forming protein complexes with the E2F family of transcription factors and binding to gene promoters that trigger cell cycle S-phase progression and cell proliferation [44]. Inactivation of *p53* and *RB1* occurs frequently in SCLC. Epidemiologically, a heavy smoking history and long-term tobacco-related carcinogen exposure are significantly associated with gene mutation accumulation in SCLC patients [14]. The two genes with the highest mutation rates in SCLC are *TP53* (75%-90%)

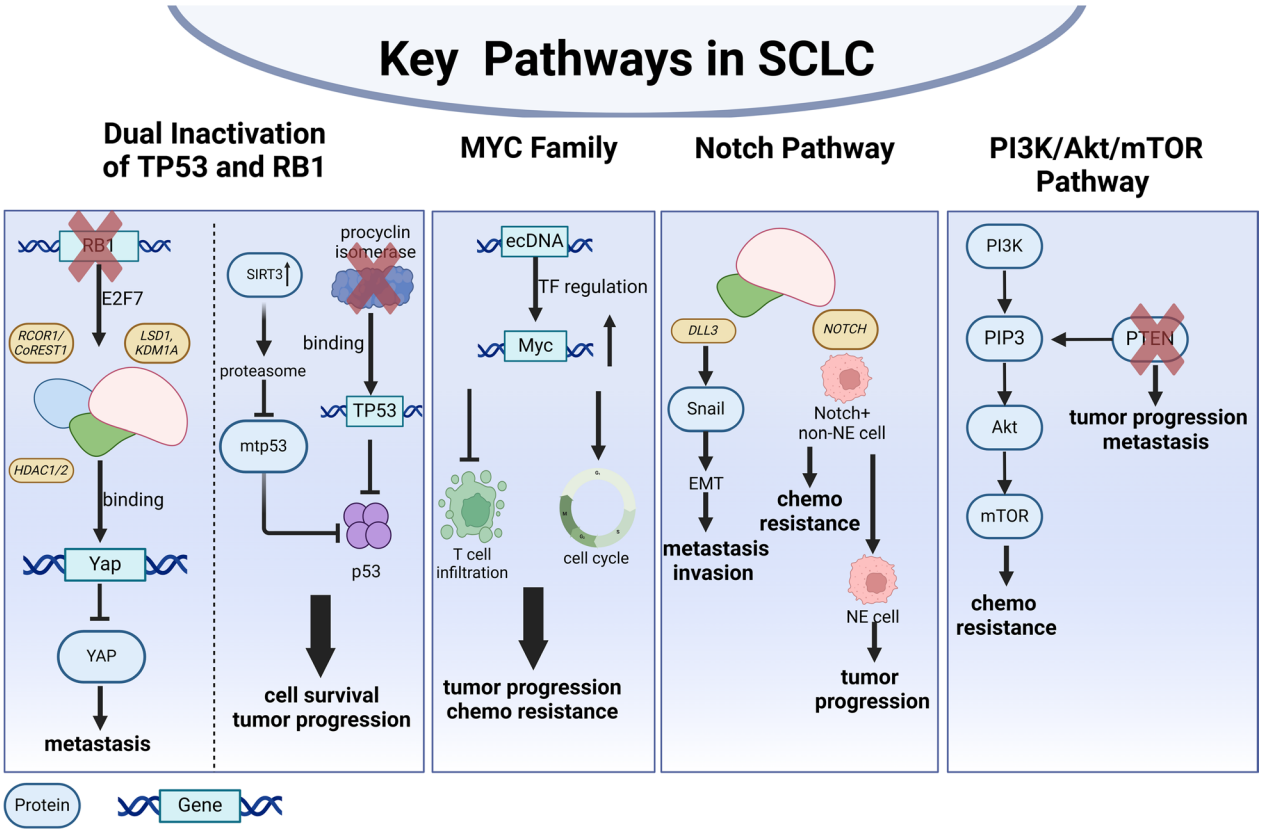


Fig. 2 Key pathways in SCLC. The dual inactivation of TP53 and RB1 can promote tumor progression and metastasis, whereas the overexpression of MYC facilitates the acquisition of drug resistance in tumors. Alterations in the Notch pathway promote metastasis and invasion, and the PI3K/Akt/mTOR pathway is associated with tumor formation and chemotherapy resistance. Abbreviations: DLL3, delta-like canonical notch ligand 3; HDAC1/2, histone deacetylases 1 and 2, LSD1/KDM1A, lysine-specific demethylase 1A; mTOR, mammalian target of rapamycin; PI3K, phosphatidylinositol-3-kinase; PIP3, phosphatidylinositol (3,4,5)-trisphosphate; RCOR1/CoREST1, corepressor protein 1; SIRT3, sirtuin 3; TSC, tuberous sclerosis complex; YAP, yes-associated protein

and *RB1* (93%) [14, 45]. For p53 inactivation, the inhibition of procyclin isomerase activity or genetic ablation of specific procyclin genes inhibits p53-mediated cell necrosis by restricting *p53* transcription without affecting *p53* chromatin binding, thereby ensuring SCLC survival [46]. Investigators have modulated the stability of mutant *p53* by controlling the ubiquitination-mediated proteasomal degradation of proteins after the deacetylase sirtuin 3 (SIRT3) is overexpressed in SCLC to promote necrosis and apoptosis in SCLC [47]. With respect to the regulatory effect of RB inactivation on SCLC, Wu et al. reported that the inactivation of *RB1* in SCLC allows the transcription factor E2F7 to recruit the repressive REST corepressor protein 1 (RCOR1/CoREST1)-lysine-specific demethylase 1A (LSD1, KDM1A)-histone deacetylases 1 and 2 (HDAC1/2) complexes to the gene promoter of *YAP* and to downregulate its expression, resulting in the repression of *YAP* transcription, which increases the metastatic potential of SCLC cells [48]. More importantly, many studies have shown that dual inactivation of *RB1* and Tp53 is required for SCLC development. Somatic inactivation of both *Trp53* and *Rb1* induces SCLC in mice [49], whereas depletion of Rb1 or p53 causes only lung adenocarcinoma [50]. Therefore, the *p53* and *RB1* double mutation, a unique feature of SCLC among solid tumors, has become a critical characteristic for SCLC diagnosis.

MYC family

MYC (c-Myc) is a major regulator of several biological programs; it exerts most of its functions as a transcription factor, regulating the expression of thousands of genes directly or indirectly, and is one of the most frequently activated products in human cancers [51]. In 20% of SCLCs, *MYC* family genes are amplified and overexpressed, and this phenotype is associated with aggressive tumor characteristics [14]. Pongor et al. reported that extrachromosomal DNA (cDNA) enables exceptionally high *Myc* gene levels by promoting its transcriptional amplification [52]. Recent studies have also shown that Myc amplification in SCLC tumors controls dysregulated lineage-specific gene expression programs and molecular features of tumor heterogeneity that drive subtype switching in SCLC. These molecular features may provide effective alternative therapeutic strategies for SCLC in addition to standard first-line treatments [53]. The *MYC* family includes two paralogs, *MYCL* and *MYCN*, and *c-Myc*. *L-MYC* expression was initially thought to be associated with SCLC risk; however, insights gained from genome sequencing studies suggest that *N-MYC* has a broader role in SCLC [54]. Grunblatt et al. constructed mouse models of SCLC with *MYCN* or *MYCL* overexpression and reported that *MYCN* overexpression inhibited the response to cisplatin-etoposide chemotherapy, with similar findings in the case of *MYCL* overexpression. Among them, in primed mice, *MYCN* overexpression promoted cell cycle progression, inhibited cytotoxic T-cell infiltration, and accelerated SCLC progression, whereas USP7 inhibition resensitized *MYCN*-overexpressing chemoresistant tumors to EP regimens (etoposide and cisplatin in combination), providing a genotype-specific strategy for targeting a subgroup of chemoresistant SCLCs [55]. These data suggest that Myc and Myc-dependent cellular mechanisms are strong candidates for therapeutic targets in SCLC.

Notch pathway

Notch signaling involves multiple aspects of postnatal animal life, including cell fate determination, embryonic and tissue development, tissue function and repair, and numerous cancerous diseases, including SCLC. Single-sample gene set enrichment analysis (ssGSEA) revealed that Notch signaling was the most significantly enriched gene set associated with clinical benefit in patients with recurrent SCLC [56]. Lim et al. reported that Notch signaling could be tumor-suppressive and protumorigenic in SCLCs [57]. These results showed that non-NE SCLC tumor cells with activated Notch are slow-growing, which is consistent with a tumor-suppressive role for Notch. However, these cells are chemoresistant and provide nutrient support for NE SCLC cells, indicating a protumorigenic role of Notch activation.

Notch signaling involves many typical ligands, and DLL3 is a unique ligand that is typically involved in only cis-inhibition [58]. Analysis of clinical trial populations confirmed that DLL3 is expressed in more than 80% of SCLCs. In preclinical models, DLL3 promoted SCLC cell migration and invasion by regulating expression of the epithelial–mesenchymal transition protein Snail [59]. DLL3 is the most promising target in the Notch pathway for developing drugs against SCLC because DLL3 is located mainly in the Golgi. However, some DLL3 escapes to the cell surface [60], and this surface DLL is the candidate target for treatment. Additionally, DLL3 expression is undetectable in normal tissues [60], which reduces the likelihood of adverse effects.

PI3K/Akt/mTOR pathway

The PI3K/Akt/mTOR pathway is involved in many cellular processes, including the cell cycle, cell growth, glucose metabolism, and protein synthesis. Genetic alterations in the PI3K/Akt/mTOR pathway, which are associated with tumor progression and chemoresistance, were observed in 36% of SCLCs. High mutation rates have been reported for many related genes, including *PIK3CA*, *PTEN*, *AKT2*, *AKT3*, *RICTOR*, and *MTOR*, in SCLC

patients [61]. The heterozygous loss of *PTEN* in Rb/P53-deleted mice led to accelerated SCLC with frequent metastasis to the liver. Activation of the PI3K/Akt/mTOR pathway promotes a phenotypic transition (from suspension to adherent growth patterns) and induces chemoresistance [62]. mTOR signaling is usually identified as an essential kinase in SCLC. Inhibition of mTOR signaling sensitized SCLC patient-derived xenografts (PDXs) to cisplatin and etoposide therapy, attenuating chemoresistance [63].

Furthermore, Horie et al. reported that SCLC cell lines with high expression of YAP and TAZ are more sensitive to mTOR inhibitors [64]. Subsequent studies have shown that PI3K/mTOR inhibitors in combination with chemotherapy synergistically inhibit the growth of SCLC cells [65], highlighting the effectiveness of this combination therapy. In conclusion, PI3K/mTOR inhibitors have shown limited efficacy in monotherapy, and more attention should be given to rational combination therapy strategies. Therefore, the PI3K/AKT/mTOR pathway will likely be the primary therapeutic focus for SCLC.

The SCLC tumor microenvironment (TME)

In addition to the activation and inactivation of key molecular pathways involved in the tumorigenesis of SCLC tumor cells, cell–cell interactions in the TME play important roles in tumorigenesis and progression (Fig. 3). SCLC has an angiogenic and hypoxic tumor microenvironment that supports an immunosuppressive phenotype; an immunosuppressive microenvironment is associated with SCLC development and a poor prognosis. A comprehensive understanding of the TME has the potential to reveal promising therapeutic opportunities for SCLC patients. Here, we dissected the TME into the stromal and immune microenvironments and explored the characteristics of the TME, conditions leading to a

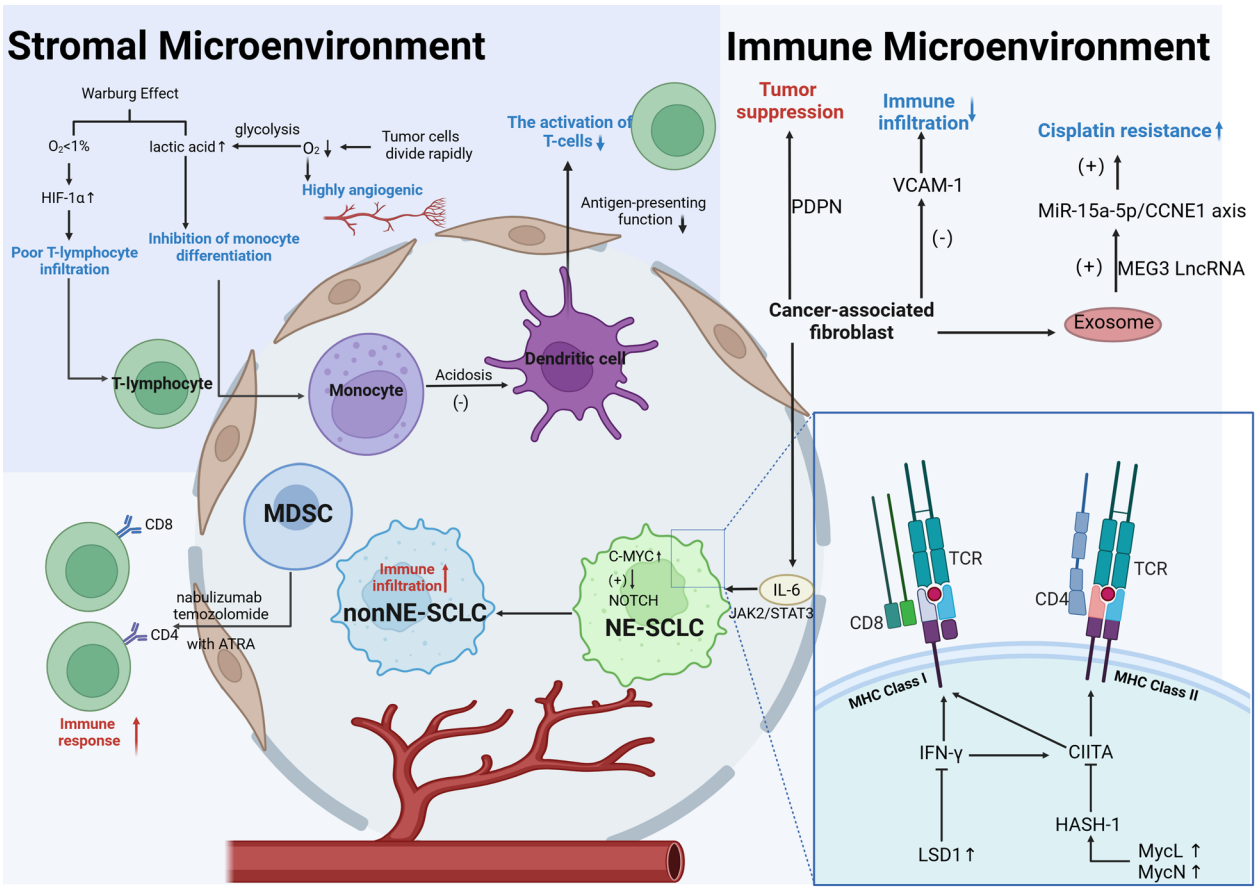


Fig. 3 The tumor microenvironment in SCLC. In the stromal microenvironment, factors such as oxygen levels and stromal cells contribute to tumor growth and metastasis. In the immune microenvironment, the inability of immune cells to infiltrate cancer nests leads to the formation of "cold tumors." Abbreviations: ATRA, all-trans retinoic acid; CCNE1, cyclin E1; CD4/8, cluster of differentiation 4/8; HIF-1α, hypoxia-inducible factor-1α; IL-6, interleukin-6; JAK2, Janus kinase 2; lncRNA, long noncoding RNA; MDSC, myeloid-derived suppressor cell; MEG3, maternally expressed gene 3; MHC, major histocompatibility complex; NE-SCLC, neuroendocrine small cell lung cancer; PDPN, podoplanin; STAT3, signal transducer and activator of transcription 3; TCR, T-cell receptor; VCAM-1, vascular cell adhesion molecule 1

suppressive immune microenvironment, and potential therapeutic targets of the TME.

Stromal microenvironment

The stromal microenvironment comprises the vascular system, tumor stroma cells, and biochemical components [66]. The rapid division of tumor cells leads to an increase in oxygen consumption. Moreover, tumor angiogenesis is insufficient to provide enough oxygen to tumor cells; in turn, this incomplete vascularization ultimately leads to an oxygen concentration of less than 1%, creating a hypoxic environment [67]. Histological analysis of biopsy samples revealed areas of hypoxia in more than 50% of patients with newly diagnosed SCLC, a higher percentage than in most other tumor types and a value that may be even greater given the small size of the samples analyzed and the failure to reveal complete intratumor heterogeneity [68]. Lin et al. showed, by immunohistochemistry, that the presence of hypoxic areas in SCLC is strongly associated with tumor progression and poor survival [69]. Upon hypoxia, hypoxia-inducible factor HIF-1α is upregulated in SCLC, which further upregulates the expression of immune checkpoint ligands in SCLC tumors and stromal cells, leading to low infiltration of CD8+ and CD4+ T cells within the tumor [70]. These findings indicate that the hypoxia-inducible factor HIF-1α is a favorable target for improving the immune microenvironment of SCLC and increasing the efficacy of immunotherapy. Researchers have successfully inhibited the progression and spread of in situ human small-cell lung cancer in mice via the use of HIF-1α antagonists [71]. In addition, SCLC tends to have an acidic chemical environment, which is caused by the "Warburg effect" [72], and acidification of the chemical environment of SCLC is closely related to tumor immune escape. For example, acidosis affects the differentiation of monocytes into dendritic cells, inhibits the antigen-presenting function of dendritic cells, and thus inhibits the activation of T cells [73]. SCLC cells tend to utilize glucose through the glycolytic process due to the hypoxic environment, which leads to the accumulation of lactic acid and a decrease in the microenvironmental pH [74], promoting angiogenic invasion and tumor metastasis, which is associated with resistance to chemotherapy and radiotherapy [75]. In summary, targeting tumor hypoxia and lactate accumulation could be a potential therapeutic strategy.

Other components of the stromal microenvironment of SCLC, such as tumor-associated fibroblasts (CAFs) and myeloid-derived suppressor cells (MDSCs), also play essential roles in shaping the SCLC microenvironment. CAFs, as critical cellular components of the tumor stromal microenvironment, play multiple roles in tumor progression, drug resistance, and immune regulation. For example, CAFs mainly inhibit vascular cell adhesion molecule 1 (VCAM-1) expression to prevent immune cell infiltration [76]. MEG3 lncRNA in exosomes released from CAFs enhances cisplatin resistance in SCLC via the miR-15a-5p/CCNE1 axis [77]. However, in SCLC, CAFs have also been found to play a role in promoting antitumor immunity. For example, Lu et al. reported that CAF-rich SCLCs can undergo phenotypic reprogramming from NE tumors to non-NE tumors. In this process, fibroblast-derived IL-6 activates JAK2/STAT3 signaling, upregulates c-MYC expression, and subsequently activates the NOTCH pathway, driving non-NE phenotypic reprogramming [78]; these changes are accompanied by an increased inflammatory gene signature and immune cell infiltration in SCLC, which contributes to a better response to immune checkpoint inhibitors [79]. In addition, Takahashi et al. cocultured CAFs overexpressing PDPN with SCLC cells and reported that the number of SCLC cells was reduced in the coculture group vs. the control group. Moreover, inhibition of PDPN expression in CAFs with shRNA led to an increase in the number of SCLC cells, suggesting that PDPN-expressing CAFs are tumor-suppressive stromal cells in SCLC [80]. The controversial role of CAFs in SCLC complicates the concept of treatments targeting CAFs, and more studies are needed to further elucidate the function of CAFs in SCLC.

Immune microenvironment

Most primary SCLCs are considered to have an immunosuppressive microenvironment, with many T cells surrounding the tumor margins rather than infiltrating the tumor nests [81–83], which explains the poor prognosis of SCLC treated with immunotherapy. In addition to the physical barrier driving the "cold" tumor phenotype of SCLC, defective antigen presentation (MHC-l and MHC-ll), which impedes the immune-killing process, is another reason for the extremely low immunogenicity of SCLC [84]. Burr et al. reported that transcriptional silencing of the MHC-I antigen processing pathway (MHC-I APP) in SCLC promoted evasion of T-cell-mediated antitumor immunity [85]. Moreover, targeted inhibition of LSD1 (a lysine-specific demethylase) in SCLC restored cell surface MHC-I expression, further induced interferon signaling, induced intrinsic immunogenicity and enhanced the antitumor immune response against immune checkpoint blockade in SCLC [86]. Notably, MHC class II molecules are not expressed in SCLC cells because of the lack of IFN-γ-induced expression of class II transcription factor (cIITA), which hinders the antitumor immune effects of CD4 T cells and contributes to tumor immunosuppression [87, 88].

To combat the immunosuppressive microenvironment, researchers have focused on two aspects: increasing immune cell infiltration and promoting immune cell antitumor immunity. To promote T-cell infiltration, Hiatt et al. reported inhibited EZH2 or LSD1 expression, which significantly upregulated MHC-I expression in SCLC, resulting in increased CD8+ T-cell infiltration and an enhanced therapeutic response to PD-1 inhibitor treatment [89]. Another group reported that 6TdG, a nucleoside analog with a high affinity for telomerase, can promote antitumor immunity by activating STING and type-I interferon signaling, leading to tumor recognition by the immune system [90]. Furthermore, recent studies have shown that the degree of immune cell infiltration in SCLC is also associated with the neuroendocrine (NE) phenotype. Cai et al. reported that SCLCs with high NE signatures have repressed expression of interferon-stimulated genes (ISGs). In contrast, SCLCs with low NE scores presented increased CD4+ or CD8+ T-cell infiltration and immune interactions [91], indicating the importance of SCLC subtyping when immunotherapy is considered.

In addition, some immunosuppressive cells in the immune microenvironment, such as myeloid-derived suppressor cells (MDSCs), have immunosuppressive functions in the antitumor process and may decrease the sensitivity to immunotherapy [92]. In one clinical trial of SCLC, compared with 37 healthy subjects, 42 SCLC patients exhibited a significant increase in the number and frequency of circulating CD14+ HLA-DR-/low MDSCs, which suggests that an increase in CD14(+) HLA-DR-/low myeloid-derived suppressor cells is associated with a poor prognosis [93]. In a clinical trial (ClinicalTrials.gov Identifier: NCT03728361), a patient with refractory SCLC treated with the combination of natalizumab and temozolomide had reduced early MDSCs, thus enhancing the high proliferative capacity of CD8+ and CD4+ T cells [94]. Another clinical trial in patients with extensive-stage SCLC revealed a significant increase in the immune response after MDSC depletion was induced by vaccination combined with all-trans retinoic acid (ATRA) [95]. In conclusion, immunosuppressive cells are also topics of interest in developing research on SCLC.

Metastasis of SCLC

Metastasis occurs when genetically unstable malignant cells acquire the adaptive capacity to thrive within distant tissue microenvironments. The most common modes of invasion and metastasis of lung cancer are shedding of tumor cells in the extracellular matrix (ECM), invasion of adjacent tissues and basement membranes, infiltration of blood vessels or lymphatic vessels, transport by blood and lymphatic means, extravasation from distant sites, and the formation of metastatic lesions. This complex pathophysiology involves tumor stem cells, the proliferation of tumor cells, apoptosis, immune escape, angiogenesis, extravasation, and the proliferation of distant metastatic cells (Fig. 4) [96].

SCLC is highly metastatic, and more than 60% of patients have metastases to the liver, brain, bone, or elsewhere in the lungs [97, 98]. Determining the specific mechanism of metastasis is important for developing new therapies to prolong the survival of SCLC patients.

Type of SCLC metastasis

SCLC has the most substantial metastatic potential of any cancer, with metastasis occurring in more than 60% of patients [97]. As Paget's "seed and soil" theory explains, some sites are preferred for SCLC metastasis [99]. The main sites of SCLC metastasis include the bone (20–25%), liver (20–30%), and brain (15–20%) [100]. Notably, a clinical study on the site of bone metastasis of SCLC revealed that spinal metastasis accounted for 64.7% of all bone metastases, whereas metastasis to the tibia or hand bone did not occur in any patients [101]. The selectivity of metastatic SCLC cells for the bone deserves some degree of investigation.

Furthermore, the median survival time (MST) of SCLC patients with bone metastases has significantly decreased; for example, the MST of SCLC patients with bone metastasis (MST = 6 months, 95% CI = 5.441–6.559 months) was shorter than that of SCLC patients without bone metastasis (MST = 10 months, 95% CI = 9.507–10.493 months) [102]. Patients with concurrent liver metastases are less likely to benefit from first-line immunotherapy in combination with chemotherapy, resulting in greater resistance [103]. SCLC with metastases is relatively more drug resistant and more malignant. Finally, the development of different markers may facilitate the clinical diagnosis of these metastases. Currently, different clinical markers have been developed for these metastases to facilitate diagnosis, such as annexin A1 (bone metastasis) [104], APOH (liver metastasis) [105], and MBP (brain metastasis) [106, 107]. However, these markers are still in the exploratory stage and are far from clinical application, and more research is still needed for the early detection and diagnosis of SCLC metastasis.

SCLC metastasis model

To better study SCLC metastasis, scientists have established various in vivo mouse models of spontaneous SCLC metastasis. The most common ones are the SCLC mouse model constructed with complete deletion of *Trp53* and *Rb1* with high expression of ASCL1 and the mouse model with additional MYC overexpression and

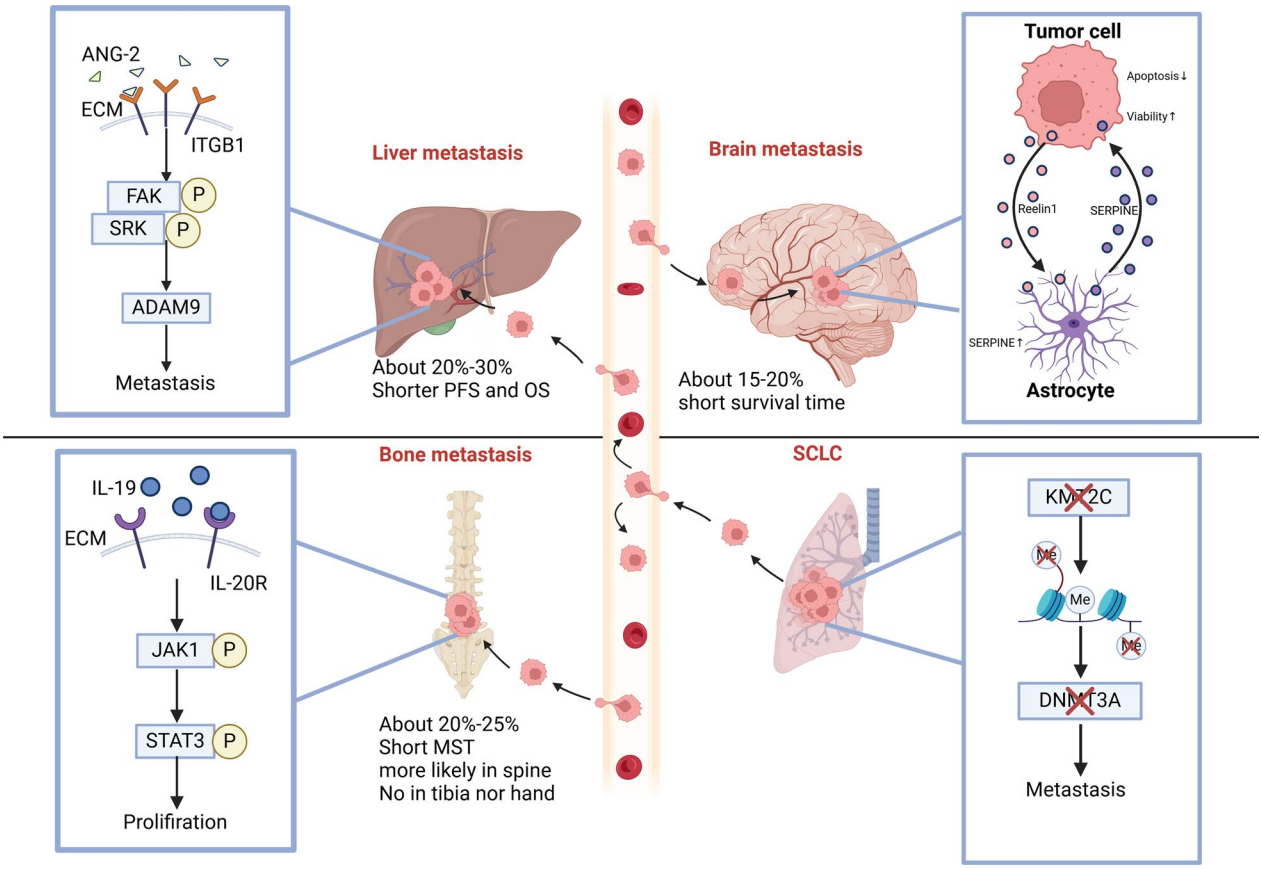


Fig. 4 Mechanisms of SCLC metastasis. Different mechanisms mediate metastasis to different sites. For example, KMY2C mediates multiple-organ metastases in the lungs, the ANG-2/ITGB1 pathway mediates liver metastasis, Reelin1 mediates brain metastasis, and IL-19 mediates bone metastasis. Abbreviations: ADAM9, A distegrinin and metalloprotease 9; ANG-2, angiopoietin 2; DNMT3A, DNA methyltransferase 3 alpha; ECM, extracellular matrix; FAK, focal adhesion kinase; IL-19, interleukin-19; IL-20R, interleukin-20 receptor; ITGB1, integrin β-1; JAK1, Janus kinase 2; KMT2C, lysine methyltransferase 2C; MST, median survival time; OS, overall survival; PFS, progression-free survival; SERPINE, serpin family E member; STAT3, signal transducer and activator of transcription 3

high expression of NeuroD1 [17, 49, 108]. Rapid metastasis can occur in all of these models, but the organ specificity of metastasis is low. However, mouse models for SCLC-Y and SCLC-P have not been constructed successfully [17]. Therefore, better metastasis models are urgently needed.

In recent years, on the basis of the standard deletion of *Trp53* and *Rb1*, researchers have further knocked out *Pten*, *Crebbp*, or *Rbl2*, also known as *p130,* and constructed triple-knockout genetically engineered mice, which exhibit rapid tumor growth and have a 50%-60% probability of liver metastasis [50, 109, 110]. In addition to multiple-gene knockout, 3D printing technology is also an idea for improving models. One group utilized a combination of 3D printing technology and bone-on-a-chip technology to centralize the ecological niche prior to bone metastasis on a single chip, simulating bone metastasis with high fidelity and proof of concept while being portable [111]. This approach is less likely to be widely used because of the high degree of technical requirements. Because brain metastasis is rare in mouse models of SCLC, SCLC brain metastasis experiments in mice are usually performed by injecting SCLC cells directly into the striatum or left ventricle [49, 112, 113]. Since zebrafish can be conveniently injected at the embryo stage, tumor cells can be injected when the blood–brain barrier is not fully developed, thus realizing the construction of tumor brain metastasis models; therefore, a recent study in which zebrafish were used as an animal model revealed that cordycepin can efficiently inhibit the brain metastasis of SCLC [114, 115]. Zebrafish have been proven to be a rapid and accurate model for displaying a wide range of biological tumor characteristics and assessing tumor response to therapy [116]. The model can be used for basic research and clinical precision medicine, with many future applications.

Mechanisms of SCLC metastasis

Cells in SCLC metastases exhibit significant changes at the cellular level compared to premetastatic SCLC cells. SCLC can show varying degrees of up- or downregulation of different genes, which affects SCLC metastasis. Ma et al. reported that the upregulation of *COTE1*, a gene encoding a membrane protein, can mediate the AMPK/mTOR pathway to promote cellular autophagy and thus promote SCLC cell invasion by promoting invasion of the basement membrane [117]. Moreover, *RB1* loss promotes SCLC metastasis by silencing YAP transcription via increased E2F7, which recruits RCOR repressors [48]. SCLC also increases the likelihood of colonization to specific organs by altering gene expression levels, e.g., tumor cell invasion and liver metastasis in SCLC are triggered by the angiopoietin 2 (ANG-2)/integrin β-1-dependent pathway in tumor cells, while blockade of integrin β-1 signaling by anti-ANG-2 treatment blocks the formation of liver metastases in vivo [118]. In addition, many genes, such as PLCG2 and ANXA, are associated with metastasis from the perspective of tumor samples and may be targets for metastatic SCLC treatment in the future [104, 119].

In addition to alterations at the genetic level, epigenetic modifications may also regulate SCLC metastasis. H3 lysine 4 methyltransferase (KMT2C) converts unmethylated H3K4 to methylated H3K4 via monomethylation of lysine 4 on the subunit of the histone H3 protein. It is considered a core protein in the COMPASS complex. Defects in this gene affect the epigenomic landscape, thereby affecting the growth or metastasis of, for example, breast cancer, colorectal cancer, and other cancers [120, 121]. In SCLC, Na et al. reported that deletion of *KMT2C* could cause SCLC to exhibit histone and DNA hypomethylation, inhibiting the expression of DNMT3A and promoting SCLC metastasis [122]. Furthermore, NFIB is a component of the NFI protein, which interacts with DNA in a dimerized manner to regulate gene transcription. In human SCLC cell lines, NFIB is highly expressed in approximately 50% of primary human SCLC metastases, and its high expression is associated with worse patient survival cycles [123–125]. NFIB can promote the metastasis of SCLC by increasing chromatin plasticity, thereby promoting the expression of neural-related genes [124]. The genealogical plasticity of SCLC also affects metastasis. For example, vasculogenic mimicry (VM), a process by which cancer cells acquire endothelial cell characteristics and can form a tumor-derived vascular network from scratch, has been demonstrated to be associated with tumor progression and metastasis in other cancers [126]. Some circulating tumor cells in SCLC can express the VM marker VE-cadherin and cytokeratins [127]. Once non-VM SCLC cells leave the primary tumor and circulate in the bloodstream, VM-expressing and non-VM-expressing SCLC cells continue interacting, potentially promoting their survival and metastasis [100]. Different subtypes of SCLC can also undergo a certain degree of transformation. SCLC-A can transform into SCLC-N, which exhibits fewer epithelial features and lower expression of EPCAM, and SCLC-N shows stronger metastatic potential as a whole [128]. Finally, in SCLC patients, higher levels of neuronal markers such as neuron-specific enolase (NSE) are associated with shorter survival and a greater metastatic disease burden [129, 130]. Yang et al. also reported that axon-like protrusions in SCLC cells can increase the metastatic and invasive ability of SCLC cells [9]. These studies suggest that a high neuroendocrine state can instead promote SCLC metastasis.

Metastasis is a very complex process; in addition to changes in SCLC itself, its interaction with the surrounding environment affects the occurrence and progression of metastasis. Several studies have demonstrated the importance of cytoplasmic matrix alterations in SCLC metastasis. For example, SCLC cells can overexpress CEMIP, a novel hyaluronidase that promotes the breakdown of hyaluronic acid (HA) and the accumulation of low-molecular-weight (LMW)-HA, which activates its receptor, TLR2, and subsequently recruits c-Src to activate ERK1/2 signaling, which promotes the rearrangement of F-actin and ultimately leads to the migration and invasion of SCLC cells [131]. Moreover, Kim et al. revealed that the overexpression of syntenin, a PDZ domain-containing junction protein, can lead to the overexpression of membrane type 1-matrix metalloproteinase (MT1-MMP) and matrix metalloproteinase 2 (MMP2), which are capable of degrading the ECM and thus lead to transduction through p38 MAPK and PI3K/AKT, activating SP1 and promoting SCLC metastasis [132]. Alterations in the ECM can also promote SCLC metastasis. Burnier et al. reported that type IV collagen promotes liver-specific metastasis in an α2 integrin/FAK-dependent manner [133]. Increased deposition of collagen IVα1 and α2 in the liver is also characteristic of the pathological condition of the liver and is indicative of the tissue repair response of this organ [134, 135]. However, it has been hypothesized that tumor cell entry into the liver may trigger this repair process through local tissue injury; in turn, these changes in the TME may provide additional scaffolds for tumor cell adhesion and migration [136].

In addition to changes in the cytoplasmic matrix, tumor cells can interact with other cells, thus promoting metastasis. In bone metastasis, osteoclasts can secrete IL-19, which binds to IL20RB in tumor cells and activates the intracellular JAK/STAT signaling pathway, thus

promoting the proliferation of tumor cells [137]. During brain metastasis, SCLC cells can secrete the brain development factor Reelin, which masquerades other neuronal cells in the developing brain to recruit reactive astrocytes. The recruited astrocytes can secrete neuronal prosurvival factors such as SERPINE1, which, in turn, promote SCLC growth and metastasis. The SERPINE1 inhibitor tiplaxtinin attenuates the pro-growth, anti-apoptosis, pro-metastasis effects of SERPINE1 in SCLC [113]. Disruption of the blood–brain barrier by tumor cells is a critical step in the formation of brain metastases. In this step, the interaction between human brain microvascular endothelial cells (HBMECs) and SCLC cells in the BBB can increase endostatin serum levels. Lactone rapidly upregulates CCL2 expression in SCLC cells in an autocrine manner. This factor destroys the BBB and promotes the passage of tumor cells mediated by HBMECs [138].

In addition, in experiments on mice with NFIB-driven metastasis, tumors formed from lung epithelial cells transduced with adenovirus-CMV-cre, whereas when the same tumors formed by adenovirus-CGRP-cre in lung neuronal cells expressing the neuroendocrine marker CGRP, the metastatic tumors that arose did not upregulate NFIB [124, 139]. These observations suggest that the cell type of origin may also influence the mechanism of SCLC metastasis. With respect to the four types of SCLC and extensive tumor heterogeneity, the exploration of the mechanism of metastasis still requires further research [140].

SCLC subtypes and evolution

Recent advances in SCLC studies highlight the importance of tumor heterogeneity and cancer subtyping in the design of personalized therapeutic regimens. In 1985, SCLCs were classified into classic and mutant phenotypes [141]. Subsequently, tumor cells were further classified into neuroendocrine and non-neuroendocrine types on the basis of their neuroendocrine signatures [83]. Recently, four SCLC subtypes were identified on the basis of tumor expression data via non-negative matrix factorization (NMF). These subtypes include SCLC-A (high expression of ASCL1), SCLC-N (high expression of NEUROD1), SCLC-P (high expression of POU2F3) and SCLC-I (low expression of the three transcription factors) (Fig. 5) [16]. These subtypes can also be distinguished according to DNA methylation profiles using machine learning approaches [142]. In addition, the latest research suggests that SCLC can also be classified on the basis of treatment outcomes and therapeutic targets into the NSCLC group (featuring genetic alterations associated

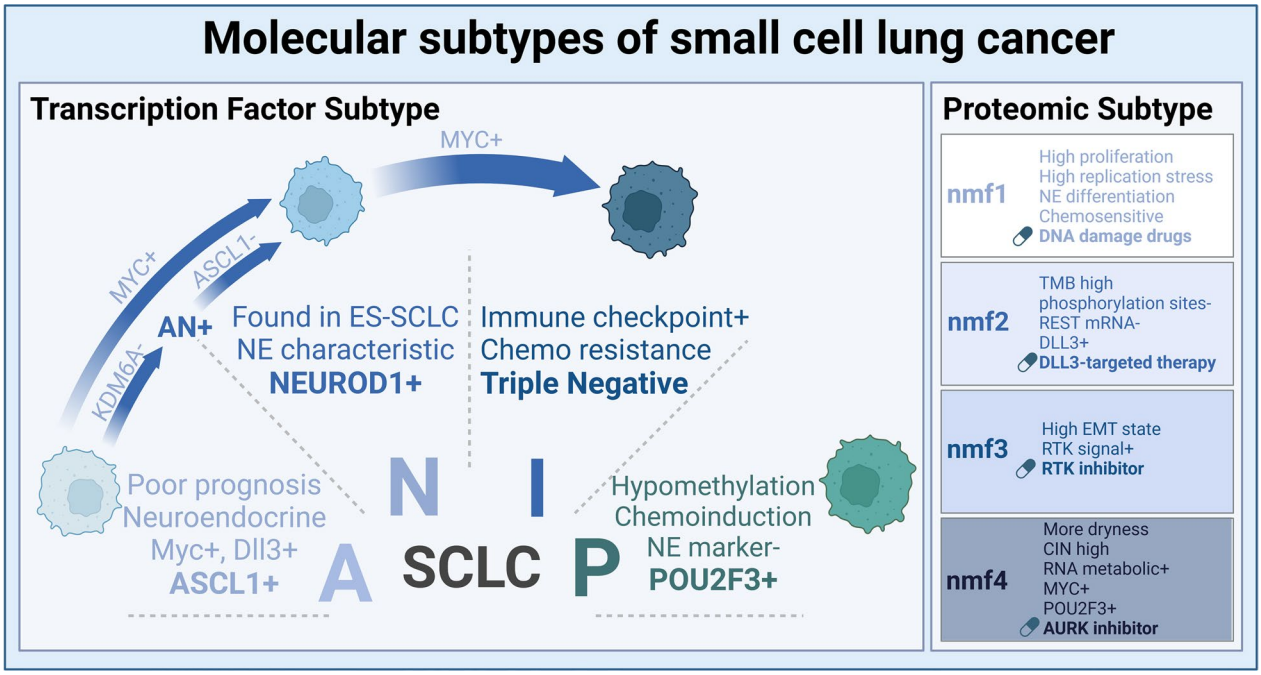


Fig. 5 Transformation between molecular subtypes of SCLC. SCLC can be classified into four subtypes according to the expression of different transcription factors: A, N, I, and P. SCLC can be divided into four subtypes on the basis of varying protein expression levels: nmf1, nmf2, nmf3, and nmf4. Abbreviations: ASCL1, achaete-scute family BHLH transcription factor 1; AURK, aurora kinase A; CIN, chromosome instability; DLL3, delta-like canonical notch ligand 3; ES-SCLC, extensive stage small cell lung cancer; KDM6A, lysine demethylase 6A; NE, neuroendocrine; NEUROD1, neuronal differentiation 1; POU2F3, POU class 2 homeobox 3; REST, repressor element 1-silencing transcription factor; RTK, receptor tyrosine kinase; TMB, tumor mutation burden

with NSCLC), the hotspot mutation group (harboring common hotspot targetable mutations in tumors), the MYC group (with MYC amplification), the PI3K group (with alterations in the PI3K/AKT/mTOR pathway), and the HME subgroup (with mutations in histone-modifying enzymes) [143]. More importantly, SCLC can exhibit genealogical plasticity, represented by switching between subtypes at the single-cell level, which ultimately leads to the temporal evolution of SCLC, suggesting that combinatorial or plasticity-targeting therapeutic approaches are needed to counteract these features of SCLC tumors.

Molecular subtypes

SCLC-A is the most common SCLC subtype and is characterized by the expression of the transcription factor ASCL1. ASCL1 is a major regulator of NE fate, regulating oncogenes such as MYCL1, RET, SOX2, and NFIB128. Therefore, SCLC-A is highly neuroendocrine. In addition, ASCL1 is highly expressed in PNECs, the main cell of origin of SCLCs, suggesting that the majority of SCLCs may be derived from PNECs. Increased ASCL1 expression is associated with a poor prognosis and poor survival [144].

SCLC-N accounts for approximately 12% of all tumors. The characteristic transcription factor NEUROD1 of this subtype is involved in neuronal, neuroendocrine, and pancreatic beta cell differentiation [145]. NEUROD1 overexpression in nonendocrine lung cancer cell lines can induce an NE-associated phenotype and increase cell proliferation [146]. Thus, despite having low NE markers, SCLC-N still shows NE characteristics. NEUROD1 is upregulated in extensive-stage SCLCs, and overexpression of NEUROD1 is associated with cell migration, suggesting that NEUROD1 may promote SCLC metastasis [147]. Osborne et al. demonstrated that nicotine-induced upregulation of NEUROD1 in immortalized normal bronchial epithelial cells and that increased expression of NEUROD1 subsequently led to the modulation of the expression and function of the nicotinic acetylcholine receptor subunit clusters α3, α5, and β4, which ultimately increased migration and invasion capacity [148], which is consistent with epidemiological studies and suggests that SCLC-N may originate from lung epithelial cells.

SCLC-P is associated with low levels of classical neuroendocrine markers (synaptophysin, chromogranin A, CD56, and INSM1), accounting for 12% of SCLCs [149]. The SCLC-P-specific transcription factor POU2F3 is usually selectively expressed in tufted cells, a rare chemosensory cell type in the lung epithelium [150]. POU2F3 expression is correlated with chemosensitivity and favorable prognosis [144]. SCLC-P cells have similar expression profiles to tufted cells [151].

SCLC-I is a subtype with no expression of three transcription factors in the other three subtypes (ASCL1, NEUROD1, POU2F3). Instead, it specifically expresses many immune checkpoints and human leukocyte antigens (HLAs). The expression of immune cell markers such as CD8A and CD8B is significantly greater in SCLC-I, suggesting greater cytotoxic T-cell infiltration. The upregulated expression of immune checkpoint molecules, such as CD274 and PDCD1, suggests that SCLC-I tumors may benefit from immune checkpoint blockade (ICB) [16].

In addition to the four subtypes mentioned above, another study defined an SCLC subtype characterized by the transcription factor YAP1 (SCLC-Y), although this finding was not confirmed by IHC [152]. However, YAP1-defined SCLC is still valuable for basic experimental and clinical trial studies. For example, Chen et al. reported that, compared with other subtypes, SCLC-Y has higher PD-L1 expression and suppressed T-cell activation, leading to immune escape. SCLC-Y patients usually have the worst clinical outcomes [153].

Currently, transcription factor-based molecular typing of SCLC, although widely recognized, has a limited direct impact on subtype-based therapy selection. Thus, proteomics-based SCLC typing may be more relevant for treatment. Liu et al. used unsupervised clustering to classify SCLC tumors into four subtypes, with respective biological differences and therapeutic vulnerabilities among the subtypes [154]. The nmf1 subtype is associated with high proliferation rates, replication stress, and NE differentiation, suggesting that this subtype is potentially responsive to agents that exacerbate DNA damage. This hypothesis was validated by E/P-based chemotherapy treatments [154]. The nmf2 subtype shows high expression of DLL3, suggesting a potential response to anti-DLL3 therapies, such as the T-cell splicer (TCE) molecule tarlatamab [155]. High DLL3 expression was also detected in SCLC-A and SCLC-N subtypes, but an increase was not detected in other subtypes [152]. The nmf3 subtype is characterized by a high EMT state and elevated RTK signaling and may therefore benefit from treatment with RTK inhibitors such as amilorotinib, which has been validated in the cell-derived xenograft (CDX)/PDX model [154]. Among non-NE tumors, nmf4 tumors highly express MYC and POU2F3 and may be sensitive to AURK inhibitors [108], as also demonstrated in in vitro cell cultures and in vivo PDX/CDX models [154]. In addition, they assessed the expression patterns of the transcription factor ANPY (ASCL1, NEUROD1, POU2F3, and YAP1) in the four subtypes of nmf1-4 on the basis of mRNA expression and reported that the nmf1–4 subtypes did not show a complete one-to-one correspondence with ANPY. These findings suggest that

proteomics-based subtyping of SCLC is uniquely valuable in guiding therapeutic decision making for SCLC.

Temporal evolution between subtypes

Initially, SCLC subtypes were thought to be mutually exclusive. However, recent evidence suggests that intratumoral heterogeneity means that multiple SCLC phenotypes can exist within the same tumor and can evolve during disease progression [142]. Using single-cell RNA sequencing (scRNA-seq), Gay et al. that numerous cells coexpressed ASCL1 and NEUROD1, indicating a transition state from SCLC-A to SCLC-N [16]. Subsequent studies revealed that KDM6A normally maintains an active chromatin state in favor of ASCL1 isoforms, but KDM6A/UTX inactivation in mice induced a decrease in H3K4me1 on neuroendocrine gene enhancers and an increase in the expression of the neuroendocrine gene enhancer H3K27me3, resulting in a decrease in SCLC tumors expressing both ASCL1 and NEUROD1. NEUROD1 in SCLC tumors suggests a transition of subtypes from SCLC-A to SCLC-N [156]. In another study, Ireland et al. performed time series single-cell transcriptome analysis using mouse and human models and found that MYC dedifferentiated tumor cells by activating the Notch pathway; in neuroendocrine cells, this led to temporal subtyping of SCLC from the ASCL1 to NEUROD1 to the YAP1 state. Temporal subtype transition from ASCL1 to YAP1 status was also observed [157].

In addition, cisplatin treatment of SCLC-A PDXs induced tumor transition to the SCLC-I subtype, suggesting that subtype switching is a mechanism related to acquired platinum resistance in SCLC. For example, with the transition of SCLC subtypes, there are significant differences in the promoter methylation of immune-related genes, such as CXCL12 (T-cell recruitment), CIITA (antigen-presentation mechanism transcription), STAT1 (inflammatory gene transcription), and interferon α and γ receptors (IFNRA1, IFNRA2, and IFNGR1). These results highlight profound changes in the tumor immunophenotype [142].

SCLC resistance

Platinum-based chemotherapy is the mainstay treatment for SCLC. While the objective response rate (ORR) is high, patients develop recurrence and progression within 6 months [158, 159]. Although the combination of chemoimmunotherapy is being approved as a new first-line treatment for SCLC, there are only modest improvements in overall survival compared with chemotherapy alone [160]. The main factors of SCLC therapeutic resistance are a lack of targetable genomic alterations, inter- and intratumor heterogeneity, and a cold tumor microenvironment (TME) (Fig. 6). To resolve rapid resistance and identify therapeutic vulnerabilities, an increasing number of researchers have focused on epigenetic regulation, metabolic changes, lineage plasticity, and TME remodeling.

Genomic alterations

Investigating tumor evolution through longitudinal genomic profiling of treatment-naïve and recurrent samples is one of the main strategies for studying the mechanisms of drug resistance. An increasing number of studies have shown that primary SCLC exhibits clonal homogeneity at different tumor sites, whereas first-line platinum-based chemotherapy leads to a burst of genomic intratumor heterogeneity and spatial clonal diversity [161]. For example, Wagner et al. used whole-exome sequencing data from 12 paired SCLC samples at diagnosis and recurrence to identify significant similarities and differences before and after chemotherapy. Mutations such as those in *TP53* and *RB1* were found in treatment-naïve and recurrent samples, suggesting that these mutations occur early in SCLC tumorigenesis [162]. However, *ABCC1* gains and *MYCL*, *MSH2*, and *MSH6* deletions were observed only in relapse samples [162]. George et al. reported *TP53*-damaging alterations and features such as coalterations of *CREBBP/EP300*, *TP73* or *FMN2* in SCLC cells after the course of treatment [161]. These studies further suggest that drug resistance in SCLC may be a process of ongoing evolutionary adaptation. Under treatment-induced stress, some inherently drug-resistant cells survive and develop into subclones that lead to clinical relapse and drug resistance.

Molecular heterogeneity and lineage plasticity

The four molecular subtypes of SCLC have been gradually recognized since 2019 [17]. Unique molecular signatures in SCLC subtypes indicate distinct therapeutic vulnerabilities. For example, SCLC-A cells exhibit increased sensitivity to a BCL-2 inhibitor (a transcriptional target of ASCL1) [16]. In SCLC-N, c-MYC protein expression is a predictive biomarker for the response to AURK inhibitors [16, 163]. SCLC-P has an increased dependence on IGF-1R and PARP [164, 165]. In SCLC-Y, the high expression of PD-L1 and CD38 suggests sensitivity to PD-1/PD-L1 inhibitors and immune checkpoint inhibitors [165, 166]. However, SCLC subtype transformation, which is one of the key drivers of cancer progression and therapeutic resistance, is frequently observed in both longitudinal human samples and mouse models [167]. Acquired resistance was observed in the cisplatin treatment of SCLC-A PDXs, where the tumor subtype shifted toward SCLC-I, a highly platinum-resistant subtype [16]. After chemotherapy in patients with predominantly SCLC-N tumors, the tumors transform to

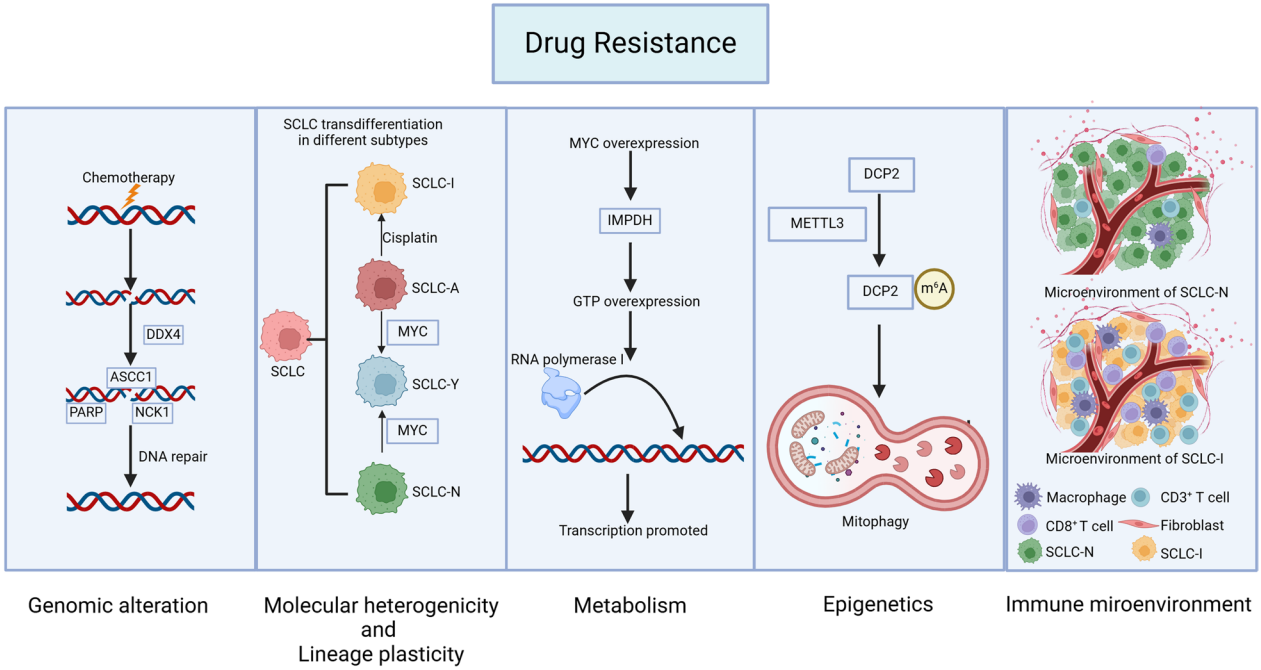


Fig. 6 Mechanisms of therapeutic resistance in SCLC. SCLC cells acquire drug resistance through genomic alterations; molecular heterogenicity; lineage plasticity; and changes in metabolism, epigenetics and the unique immune microenvironment. Abbreviations: ASCC1, activating signal cointegrator 1 complex subunit 1; CD3/8, cluster of differentiation 3/8; GTP, guanosine triphosphate; IMPDH, inosine 5′-monophosphate dehydrogenase; METTL3, methyltransferase-like 3; NCK1, NCK adaptor protein 1; PARP, poly ADP—ribose polymerase

predominantly SCLC-A tumors, so the transformation from SCLC-N to SCLC-A at the tumor level may also lead to chemoresistance [168]. In addition, MYC can drive the conversion of SCLC-A and SCLC-N to SCLC-Y, which exhibits a higher degree of chemoresistance and a worse prognosis [157, 169]. Mechanically, key regulatory factors driving the transformation of SCLC subtypes have been gradually identified. For example, studies have revealed that SMARCA4 can increase the expression of neuroendocrine genes by interacting with ASCL1 and NEUROD1, whereas the inhibition of SMARCA4 leads to a reduction in neuroendocrine gene expression and the activation of non-neuroendocrine factors [170]. In addition to transformation among SCLC subtypes, SCLC cells can acquire resistance to therapy through dedifferentiation. Studies have shown that WNT activation is associated with SCLC chemoresistance, where the number of $CD133^+$ (upstream genes of WNT) cancer stem-like cells (CSCs) is increased in mouse and human SCLC after chemotherapy [5, 171]. Moreover, WNT-induced transcription factors include TWIST1, one of the most upregulated genes related to chemotherapy resistance [162, 172]. Additionally, signaling pathways induced downstream of WNT include the PI3K/AKT and mTOR pathways, which have previously been found to alter chemoresistance in SCLC, and inhibition of the mTOR pathway in combination with etoposide reversed chemoresistance in myc-driven SCLC cells [173, 174]. Interestingly, SCLC is involved in NSCLC therapeutic resistance through lung adenocarcinoma neuroendocrine transdifferentiation, especially after targeted treatments, including anti-EGFR therapy and ALK inhibition [37, 167, 175].

DNA damage repair

Since the main drugs used for chemotherapy (e.g., platinum and DNA topoisomerase inhibitors such as etoposide or irinotecan) and high doses of radiation mainly kill tumor cells through DNA damage, SCLC cells can acquire greater DNA damage repair capacity by altering the expression of genes and proteins related to DNA repair, thus leading to resistance to chemotherapy and radiotherapy [176, 177]. Noyes et al. reported that DEAD-box helicase 4 (DDX4), a conserved regulator of mRNA translation, upregulated the expression of proteins related to DNA repair and immune/inflammatory responses, such as PARP2, ASCC2, and NCK1, which increased the survival of SCLC cells and promoted resistance to cisplatin. Moreover, high expression of DDX4 was associated with decreased survival time, and low expression of DDX4 was associated with longer survival [178–180]. Additionally, the upregulation of Rad51 is a potential strategy for SCLC patients to cope with

etoposide. Rad51 is an ATPase that forms nucleoprotein filaments on single-stranded DNA, enabling accurate and timely double-stranded DNA repair by searching for and invading homologous DNA, which is a key regulator of DNA fidelity [181]. Dysregulation of Rad51 has been shown to be correlated with cancer development [182]. Although the specific mechanism by which the Rad51 protein resists etoposide in SCLC still needs to be investigated, Hansen et al. reported that aberrant expression of Rad51 alters the efficacy of etoposide by reversing etoposide-induced DNA breaks [183]. In addition, nonhomologous end joining (NHEJ) in tumor cells also plays a role in chemoresistance. Hansen et al. reported that the efficacy of etoposide varies with the expression level of DNA-dependent protein kinase (DNA-PK), an important enzyme in the NHEJ process [183]. Therefore, synergistically targeting DNA repair pathways with chemotherapy might be a way to increase SCLC chemosensitivity in the future.

Metabolism

SCLC can also resist therapies by undergoing metabolic reprogramming, including dysregulation of amino acid metabolism, energy programs, and GTP, purine, and pyrimidine biosynthesis. Tumors with these metabolic alterations become resistant through DNA repair and autophagy dysfunction. Notably, MYC-overexpressing SCLCs are associated with multiple metabolic vulnerabilities. Studies have shown that MYC-amplified SCLC is often chemoresistant to increased Aurora kinase, arginine, and leucine levels [173]. The use of arginine inhibitors and Aurora inhibitors has also been shown to significantly inhibit the growth of MYC-amplified SCLC [108, 173]. SCLC can also develop therapeutic resistance through alteration of energy metabolic programs. Chen et al. reported that the activation of PIK3/AKT is associated with radioresistance through the inhibition of G6PD, which promotes the pentose phosphate pathway (PPP) and further induces the increase in NADPH levels and resistance to oxidative effects mediated by ROS. Inhibition of PIK3/AKT also increases oxidative damage stress in cells, thereby resensitizing SCLC cells to radiotherapy [184–187]. In addition, MYC-overexpressing SCLC exhibited increased glycolysis. Inhibition of glycolysis with PFK158 preferentially attenuated glucose uptake, ATP production, and lactate production in SCLC cells, delaying xenograft tumor growth [188]. Furthermore, MYC-hi SCLC cells with acquired chemoresistance presented increased levels of GTP synthesis, and these cells were sensitive to an inhibitor of the GTP synthesis enzyme IMPDH. IMPDH inhibition suppressed tumor growth by preventing Pol I from binding to rDNA and thus prevented pre-RNA synthesis [189]. These findings indicate that MYC plays a crucial role in SCLC metabolism and that inhibiting these metabolic pathways can significantly suppress tumor growth, suggesting the potential value of metabolic therapies in the development of resistance in MYC-hi SCLC.

In SCLC, there is also widespread abnormal overexpression of purine and pyrimidine metabolic pathway components. The mRNA levels encoding hypoxanthine phosphoribosyl transferase 1 (HPRT1), a key component of the purine salvage pathway, are lower in gedatolisib (a dual mTOR/PI3K inhibitor)-sensitive SCLC cells than in gedatolisib-resistant SCLC cells, which suggests that the activation of the purine salvage pathway may contribute to SCLC resistance to PI3K inhibitors [190]. Recent studies have revealed that the loss of the HPRT1 gene, which encodes the rate-limiting enzyme of the purine salvage pathway, significantly suppresses tumor growth in SCLC. This loss is accompanied by a compensatory increase in metabolic flux through the PPP and de novo purine synthesis. Additionally, high expression of HPRT1 is linked to resistance to lemetrexol (LMX), an inhibitor of de novo purine synthesis [191]. Numerous studies have indicated that pyrimidine synthesis has a particular impact on SCLC drug resistance. Leanne et al. reported that SCLC has a relatively greater sensitivity to pyrimidine biosynthesis pathway inhibitors than other cancers do. Dihydroorotate dehydrogenase (DHODH) inhibition effectively suppressed the growth of SCLC tumors in PDX models [192]. Similarly, William et al. discovered through patient-derived organoid (PDO) models that dysregulation of pyrimidine synthesis in SCLC can lead to resistance to thymidylate synthase (TS) inhibitors [193]. Purine synthesis supports the high proliferative capacity of tumors, and targeting de novo nucleotide biosynthesis, including both purine and pyrimidine synthesis, is a highly effective strategy for treating a variety of malignant tumors. Therefore, genes regulating the purine and pyrimidine synthesis pathways may serve as potential therapeutic targets for SCLC in the future [193, 194].

SCLC can develop therapeutic resistance through the upregulation of autophagy-related pathways. Shen et al. reported that nuclear receptor binding factor 2 (NRBF2) can positively regulate autophagy by increasing the formation of autophagosome P62, thus leading to the development of chemoresistance in SCLC. Knocking down NRBF2 can restore the sensitivity of SCLC cells to chemotherapy, indicating that NRBF2 can be used as a combination therapy to attenuate chemotherapy resistance [195]. Furthermore, another study revealed that SR9009, a drug that targets the core autophagy gene *Atg5*, strongly inhibits the proliferation of chemosensitive and chemoresistant cells [196]. Guo et al. reported that statins can overcome chemotherapy resistance in SCLC by reducing

geranylgeranyl diphosphate (GGPP), thereby inhibiting the function of RAB7A and suppressing the formation and maturation of autophagosomes [197]. Although cellular autophagy can suppress the cellular stress response to drugs and thus lead to drug resistance; the overexpression of autophagy-related genes can also lead to the conversion of cell fate from survival to accelerated cell death [198–200]. How tumors control the expression of autophagy-related genes to promote acquisition of drug-resistant phenotype is still unclear and needs to be studied.

Epigenetics

Drug resistance in SCLC cannot solely be explained in terms of genetic factors because "the fate of each cell is not always written in the genes" [201]. Epigenetic variability, including histone modifications and DNA methylation, can contribute directly to the development or progression of cancer and therapeutic resistance [202, 203].

Altered gene methylation status was found to be associated with SCLC therapeutic resistance. N6-methyladenosine (m6A), a form of methylation that occurs at the N6 position of adenosine, is involved in SCLC resistance to multiple treatments [204]. A low m6A score is associated with a longer overall survival time [205]. Several studies have indicated that METTL3, an m6A methyltransferase, is highly expressed in chemotherapy-resistant SCLC cells [206–208]. For example, Sun et al. reported that METTL3 induced m6A methylation of DCP2, leading to DCP2 degradation, which promoted mitochondrial autophagy via the Pink1-Parkin pathway, resulting in chemoresistance [209]. *SLFN11* is a gene involved in replication fork blockade during DNA damage [210]. *SLFN11* inactivation was found to be associated with SCLC resistance through hypermethylation of the *SLFN11* promoter [211, 212]. Furthermore, Zhai et al. reported that aberrant methylation of the hTERT promoter induced radioresistance in SCLC through the upregulation of EZH2 [213], a gene associated with nucleotide excision repair and SCLC cisplatin resistance [214]. In summary, SCLC cells can regulate the DNA methylation of genes associated with DNA repair and, therefore, achieve therapeutic resistance.

Alterations in histone modifications may also contribute to treatment resistance in SCLC. KAT6B encodes an acetyltransferase that acetylates lysine 23 of histone H3. KAT6B was found to be associated with irinotecan resistance in SCLC. Deletion of KAT6B led to an enhanced ATM-mediated DNA damage response and, therefore, sensitized tumor cells to irinotecan treatment [215, 216]. In addition, radioresistant SCLC cells presented lower levels of histone H3K9 acetylation and higher levels of MRE11-RAD50-NBS1 (MRN) complex expression and exhibited more potent DNA damage repair ability [66]. In addition to acetylation, the histone methylation status can also be changed, leading to altered gene expression levels. In SCLC with low MHC-I expression, the MHC-I antigen processing and presentation (APP) gene promoter contains bivalent activating H3K4me3 and H3K27me3 histone modifications; silencing of basal MHC-I expression and suppression of cytokine-induced upregulation leads to immunotherapy resistance in SCLC [85, 217–219]. The use of lysine-specific demethylase 1 (LSD1) to remove the methyl group on monomethylated and dimethylated lysines 4 and 9 of histone H3 also activates interferon signaling and sensitizes SCLC cells to immunotherapy [86].

The immune microenvironment

The main challenge of applying immunotherapy to SCLC is the cold immune microenvironment, where very few immune cells infiltrate SCLC tumors. Compared with NSCLC cells, SCLC cells have lower ratios of B cells and CD3+ and CD8+ cells [220–222]. Compared with SCLC patients with short survival times, long-term SCLC survivors have relatively lower ratios of suppressor immune cells (e.g., monocytes, regulatory T cells (T-regs), and macrophages) to CD3+ lymphocytes in their tumors. Unlike most SCLC tumors, the SCLC-I subtype is characterized by increased infiltration of NK cells, T cells, and macrophages; increased expression of checkpoint molecules (e.g., PD-L1 and CTLA4); relatively increased expression of antigen-presenting genes; and increased tumor mutational burden (TMB), which are markers of increased sensitivity to immunotherapy [16, 17]. Studies have also revealed that SCLC patients with high neuroendocrine expression, such as SCLC-N patients (approximately 31%), exhibit increased tolerance to immunotherapy, as demonstrated by a decrease in CD8+ T cells and a decrease in the infiltration of NK cells compared with SCLC-I patients [16, 17, 119, 223, 224].

Moreover, most studies have shown that SCLC has relatively low expression of PD-L1 [222, 225, 226]. PD-L1 expression on tumor-infiltrating immune cells is greater than that on tumor cells [158]. These findings suggest that SCLC may not rely on PD-L1 for immune escape and that PD-L1-targeted immunotherapy does not apply to SCLC. Therefore, the identification of other key factors that suppress the antitumor immune response is urgently needed. For example, CD47, a protein that can inhibit macrophage and monocyte expansion, is highly expressed on the membrane of SCLC cells. Blockade of CD47 promotes the phagocytosis of SCLC cells by macrophages and effectively kills SCLC tumor cells [227, 228].

Table 1 Pivotal clinical trials evaluating the efficacy of FDA/NMPA-approved agents for SCLC

Drug Name	Trial number	Phase	Patients	Strategy	Drugs	N	Median OS	Median PFS	Status	Indication
Atezolizumab	NCT02763579	3	ES-SCLC	PD-L1 inhibitor + Chemo	Atezolizumab + Chemo vs. Chemo	201 vs. 202	12.3 vs. 10.3 months	5.2 vs. 4.3 months	FDA approved	First line
Tislelizumab	NCT04005716	3	ES-SCLC	PD-L1 inhibitor + Chemo	Tislelizumab + Chemo vs. Chemo	457	15.5 months vs. 13.5 months	4.8 months vs. 4.3 months	NMPA approved	First line
Pembrolizumab	NCT03066778	3	ES-SCLC	Chemo + PD-1 inhibitor	Pembrolizumab + Chemo vs. Chemo	228 vs. 225	10.8 vs. 9.7 months	4.5 vs. 4.3 months	FDA approved	Second line
Adebrelimab	NCT03711305	3	ES-SCLC	Chemo + PD-L1 inhibitor	Chemo + Adebrelimab vs. Chemo	230 vs. 232	15.3 vs. 12.8 months	5.8 vs. 5.6 months	NMPA approved	First line
Serplulimab	NCT04063163	3	ES-SCLC	Chemo + PD-1 inhibitor	Chemo + Serplulimab vs. Chemo	389 vs. 196	15.4 vs. 10.9 months	5.7 vs. 4.3 months	NMPA approved	First line
Anlotinib + Benmelstobart	NCT04234607	3	ES-SCLC	Chemo + anti-Angiogenesis + PD-L1 inhibitor	Chemo + Anlotinib + Benmelstobart vs. Chemo	246 vs. 247	19.3 vs. 11.9 months	6.9 vs. 4.2 months	NMPA approved	First line
Toripalimab	NCT04012606	3	ES-SCLC	Chemo + PD-1 inhibitor	Chemo + Toripalimab vs. Chemo	213 vs. 219	14.6 vs. 13.3 months	5.8 vs. 5.6 months	NMPA approved	First line

Abbreviations: Chemo, chemotherapy; NCT, ClinicalTrials.gov identifier; FDA, U.S. Food and Drug Administration; NMPA, National Medical Products Administration; ORR, objective response rate; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PFS, progression-free survival

New treatment options for SCLC

Clinical management

The clinical management of SCLC depends substantially on the stage of the disease. According to the Veterans Administration Lung Cancer Study Group (VALCSG) staging system, patients are grouped into limited stage (LS-SCLC) and extensive stage (ES-SCLC) [229]. The VALCSG-limited stage refers to a disease affecting only one hemithorax, and extensive stage refers to disease that affects both the lungs or has extrathoracic metastases. The VALCSG staging system is an important tool in routine clinical practice. The tumor, node, metastasis (TNM) staging system, initially applied for classifying NSCLC samples, provides a precise definition of tumor spread by describing the size of the primary tumor, the degree of evasion of lymph nodes and distant metastasis [230]. The TNM staging system can also be applied in SCLC; stage I-III SCLC according to the TNM staging system corresponds to LS-SCLC in the VALCSG system, whereas ES-SCLC is considered TNM stage IV [231].

Patients with T1-2N0 LS-SCLC are recommended to undergo surgery followed by adjuvant chemoradiation therapy [232]. The 5-year survival rate of patients with early-stage SCLC who received surgery and adjuvant therapy was 47.4% [233]. However, the main treatment approach for non-T1-2N0 LS-SCLC is etoposide with platinum (cisplatin or carboplatin, EP) chemotherapy concurrent with thoracic radiotherapy (TRT) followed by prophylactic cranial irradiation (PCI) for responsive disease. For those patients, the median OS has improved to 25–30 months [234]. For ES-SCLC, EP chemotherapy combined with PD-1/PD-L1 inhibitors, including atezolizumab, durvalumab, adebelimab, and serplulimab, has been the standard first-line treatment (Table 1) [159, 235]. The median OS and PFS were 14.0 months and 5.6 months, respectively, when ES-SCLC patients received EP chemotherapy and anti-PD-L1 therapy [236]. Owing to the high likelihood of relapse in SCLC patients, patients who experience relapse more than 6 months after first-line treatment are considered sensitive and can be retreated with the first-line regimen [237]. Patients who experience relapse within 6 months after first-line treatment are considered resistant or refractory to treatment and are generally given later-line regimens such as paclitaxel, docetaxel, irinotecan, temozolomide, CAV, oral etoposide, vinorelbine, gemcitabine, nivolumab, and pembrolizumab.

Chemotherapy combined with immunotherapy

EP chemotherapy has been the cornerstone therapy for SCLC for the past 30 years. Recently, immune checkpoint inhibitors combined with EP chemotherapy became a breakthrough for SCLC, improving the OS of ES-SCLC patients [7]. Humanized anti-PD-L1/PD-L1 antibodies inhibit PD-L1-PD-1 and PD-L1-B7-1 signaling and promote the restoration of tumor-adapted immunity. Clinical studies have demonstrated that combination therapy confers a more favorable prognosis than does chemotherapy alone, but the mechanism by which chemotherapy increases immune efficacy remains unclear (Tables 2, 3) [238, 239]. The combination of atezolizumab and EP chemotherapy improved OS from 10.3 to 12.3 months, which may not be considered a prominent improvement. Nevertheless, the 18-month survival rate was 34.0% in the combination group compared with 21.0% in the chemo-only group, which implies that only a subset of SCLC patients benefit from the addition of atezolizumab in the long term, whereas the majority do not [240].

Atezolizumab

Atezolizumab is a monoclonal antibody that targets PD-L1 and was developed by Roche [241]. Atezolizumab was the first PD-L1 inhibitor approved by the US Food and Drug Administration (FDA). It is considered the first-line treatment in combination with EP chemotherapy for patients with ES-SCLC on the basis of the results of the IMpower 133 trial [7]. In this trial, the median OS was 12.3 months, and the median PFS was 5.2 months in the atezolizumab combined with chemotherapy group, which was 2 months and 0.9 months longer than that in the placebo group. The addition of atezolizumab to first-line therapy revolutionized the history of SCLC treatment and marked the beginning of immunotherapy for SCLC. Recently, outcomes of the phase III extension study IMbrella A were reported for patients with ES-SCLC who received atezolizumab every three weeks following the closure of the IMpower133 trial. The 3-, 4- and 5-year estimated OS rates of 18 patients who received atezolizumab plus EP treatment were 16%, 13%, and 12%, respectively [242]. The MAURIS phase IIIb trial is ongoing to evaluate the efficacy of adding atezolizumab to the EP strategy in a patient population more similar to that in the real-world and to further discuss the efficacy and safety of cycles of induction therapy. The data presented thus far corroborate the conclusion of the IMpower133 trial.

Durvalumab

Durvalumab is a fully human monoclonal antibody against PD-L1. It is now approved as the first-line treatment for patients with ES-SCLC in combination with etoposide on the basis of data from the planned interim analysis of the multicenter phase III CASPIAN trial [243]. The median OS and PFS were 13.0 months and 5.1 months, respectively, for durvalumab plus

Table 2 Completed clinical trials evaluating the safety and efficacy of immune checkpoint inhibitors in patients with SCLC

Study name	Trial number	Phase	Patients	Strategy	Drugs	N	ORR	Median OS	Median PFS	Safety (grade 3–4)
IMPOWER133	NCT02763579	3	ES-SCLC	PD-L1 inhibitor + Chemo	Atezolizumab + Chemo vs. Chemo	201 vs. 202	–	12.3 vs. 10.3 months	5.2 vs. 4.3 months	63% vs. 58%
RATIONALE 206	NCT03432598	2	ES-SCLC	PD-L1 inhibitor + Chemo	Tislelizumab + Chemo	17	77%	15.6 months	6.9 months	76.5%
RATIONALE 312	NCT04005716	3	ES-SCLC	PD-L1 inhibitor + Chemo	Tislelizumab + Chemo vs. Chemo	457	68.3% vs. 61.7%	15.5 months vs. 13.5 months	4.8 months vs. 4.3 months	85.5% vs. 86%
CheckMate 032	NCT01928394	1/2	LS/ES-SCLC	PD-1 inhibitor + CTLA-4 inhibitor	Nivolumab + Ipilimumab vs. Ipilimumab	147 vs. 96	11.6% vs. 21.9%	5.7 vs. 4.7 months	–	12.9% vs. 37.5%
CheckMate 451	NCT02538666	3	ES-SCLC	PD-1 inhibitor + CTLA-4 inhibitor	Nivolumab + Ipilimumab vs. Nivolumab vs. Placebo	279 vs. 280 vs. 275	9.1% vs. 11.5% vs. 4.2%	9.2 vs. 10.4 vs. 9.6 months	1.7 vs. 1.9 vs. 1.4 months	(85.6%/52.2%) vs. (60.9%/11.5%) vs. (50.2%/8.4%)
CheckMate 331	NCT02481830	3	Relapsed SCLC	PD-1 inhibitor vs. chemo	Nivolumab vs. Chemo	284 vs. 285	13.7% vs. 16.5%	7.5 vs. 8.4 months	1.4 vs. 3.8 months	13.8% vs. 73.2%
ETOP/IFCT 4–12 STIMULI	NCT02046733	2	LS-SCLC	PD-1 + CTLA-4 inhibitor vs. obsrvation after CRT plus PCI	Nivolumab + Ipilimumab vs. obsrvaton after CRT plus PCI	78 vs. 75	–	not reached	10.7 vs. 14,5 months	62% vs. 25%
-	NCT03026166	1/2	ES-SCLC	Rova-T + PD-1 inhibitor or CTLA-4 inhibitor	Rova-T + Nivolumab + Ipilimumab vs. Rova-T + Nivolumab	42	–	–	–	Not tolerated
-	NCT03325816	1	Relapsed ES-SCLC	Chemo + PD-1 inhibitor	Lutathera + Nivolumab	9	–	–	–	55.6%
KEYNOTE-604	NCT03066778	3	ES-SCLC	Chemo + PD-1 inhibitor	Pembrolizumab + Chemo vs. Chemo	228 vs. 225	70.6% vs. 61.8%	10.8 vs. 9.7 months	4.5 vs. 4.3 months	76.7% vs. 74.9%
CAPSTONE-1	NCT03711305	3	ES-SCLC	Chemo + PD-L1 inhibitor	Chemo + adebrelimab vs. Chemo	230 vs. 232	–	15.3 vs. 12.8 months	5.8 vs. 5.6 months	85% vs. 84%
ASTRUM-005	NCT04063163	3	ES-SCLC	Chemo + PD-1 inhibitor	Chemo + Serplulimab vs. Chemo	389 vs. 196	–	15.4 vs. 10.9 months	5.7 vs. 4.3 months	33.2% vs. 27.6%
CTR20192538/ ETER701	NCT04234607	3	ES-SCLC	Chemo + anti-Angiogenesis + PD-L1 inhibitor	Chemo + anlotinib + benmelstobart vs. Chemo	246 vs. 247	81.3% vs. 66.8%	19.3 vs. 11.9 months	6.9 vs. 4.2 months	94.3% vs. 89%
EXTENTORCH	NCT04012606	3	ES-SCLC	Chemo + PD-1 inhibitor	Chemo + Toripalimab vs. Chemo	213 vs. 219	78% vs. 73.1%	14.6 vs. 13.3 months	5.8 vs. 5.6 months	89.6% vs. 89.4%

Abbreviations: Chemo, chemotherapy; CRT, chemoradiation treatment; CTLA-4, cytotoxic T-lymphocyte–associated protein 4; NCT, ClinicalTrials.gov identifier; ORR, objective response rate; OS, overall survival; PCI, postoperative prophylactic cranial irradiation; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PFS, progression-free survival; Rova-T, rovalpituzumab tesirine

Table 3 Ongoing clinical trials evaluating the safety and efficacy of immune checkpoint inhibitors in patients with SCLC

Trial number	Phase	Patients	Strategy	Drugs	N	ORR	Median OS	Median PFS	Safety (grade 3–4)
NCT03043872	3	ES-SCLC	PD-L1 inhibitor + Chemo	Durvalumab + Chemo vs. Chemo	268 vs. 269	–	13.0 vs. 10.3 months	5.1 vs. 5.4 months	62% vs. 62%
NCT03728361	2	Metastatic NEN	PD-1 inhibitor + chemo	Nivolumab + temozolomide	11(Lung) vs. 17(Others)	64% vs. 18%	NR vs. 32.3 months	11.1 vs. 7.2 months	43% (of all)
NCT02402920	1	ES-SCLC	Chemo + TRT + PD-1 inhibitor	Chemo + TRT + Pembrolizumab	38	–	8.4 months	6.1 months	0%
NCT04624204	1/2	LS-SCLC	CRT + PD-1 inhibitor	CRT + Pembrolizumab	40	–	39.5 months	19.7 months	45/40

Abbreviations: Chemo, chemotherapy; CRT, chemoradiation treatment; NCT, ClinicalTrials.gov identifier; NEN, neuroendocrine neoplasms; ORR, objective response rate; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PFS, progression-free survival; TRT, thoracic radiotherapy

standard chemotherapy, which were better than those of patients who received platinum–etoposide alone (OS 10.3 months, PFS 5.4 months) [238]. Thus, durvalumab plus chemotherapy is recommended for ES-SCLC patients according to the NCCN [244]. A retrospective comparative cohort study estimated the efficacy of durvalumab plus chemotherapy and atezolizumab plus chemotherapy. The median OS of patients who received durvalumab plus chemotherapy (22.0 months) was significantly longer than that of patients who received atezolizumab plus chemotherapy (10.0 months), whereas the median PFS was not significantly different [245]. Another retrospective study was performed to analyze the outcomes of patients who received durvalumab/atezolizumab plus standard chemotherapy combined with radiotherapy. Although the 1-year OS (33% vs. 28%, $p=0.066$) was not significantly different from that of the group without radiotherapy, the 2-year OS results were significantly promising (13% vs. 3%, $p=0.004$), indicating that durvalumab plus chemotherapy combined with radiotherapy might be a better choice than durvalumab plus chemotherapy [246].

Adebrelimab

Adebrelimab is a human anti-PD-L1 monoclonal antibody independently developed by Hengrui Pharmaceutical, which is based on CAPSTONE-1 research and was approved for marketing in China in 2023. The CAPSTONE-1 study evaluated the efficacy and safety of adebrelimab versus standard chemotherapy as the first-line treatment for ES-SCLC. The median OS was significantly longer in the adebrelimab group (median 15.3 months) than in the placebo group (12.8 months) [247]. An analysis comparing the survival data from the CASPIAN, Impower133, and CAPSTONE-1 trials and reconstructing patient-level data revealed that adebrelimab significantly prolonged survival outcomes compared with atezolizumab and durvalumab. The median OS was 15.3 months in the adebrelimab group and 12.9 months and 12.3 months in the durvalumab and atezolizumab groups, respectively [236]. Adebrelimab is expected to be the best agent for combination with chemotherapy for ES-SCLC patients, although further study is needed.

Serplulimab

Serplulimab, a novel PD-1 inhibitor developed by Shanghai Henlius Biotech, Inc., was evaluated in combination with EP chemotherapy as a first-line treatment in ES-SCLC patients in the ASTRUM-005 randomized clinical trial (ClinicalTrials.gov identifier: NCT04063163).

To date, the median OS and PFS times are significantly longer in the serplulimab group than in the placebo group, with 15.4 vs. 10.9 months and 5.7 vs. 4.3 months, respectively [248]. A meta-analysis of data from seven articles on the CA184-156, ECOG-ACRIN EA5161, KEYNOTE-604, IMpower133, CASPIAN, CAPSTONE-1, and ASTRUM-00520 trials was performed. Serplulimab plus chemotherapy was compared with several approved ICIs, including atezolizumab, durvalumab, adebrelimab, nivolumab, pembrolizumab, and ipilimumab, in terms of OS, PFS, ORR, and safety. Serplulimab plus chemotherapy resulted in substantially better outcomes, especially in terms of PFS [249].

Serplulimahas has shown promising results in ES-SCLC treatment and is likely to be the best first-line treatment option for ES-SCLC patients in the future [249]. However, some analyses have shown that serplulimab plus chemotherapy is not cost effective [250, 251]. The high price might be an obstacle to its wide-range promotion.

Tislelizumab

Tislelizumab (BGB-A317) is a humanized IgG4 anti-PD-1 monoclonal antibody made by Beigene. The greatest difference between the anti-PD-1 antibody tislelizumab and other antibodies is that tislelizumab was engineered with a constant region that cannot bind to the FcγR receptor. As a result, it can no longer bind to type II macrophages with the Fcγ receptor, preventing the macrophages from attacking T cells. This eliminates or at least reduces the adverse effects of immunotherapy [252]. In a phase II clinical study of tislelizumab in combination with chemotherapy in Chinese patients with advanced lung cancer (RATIONALE 206), the ORR was 77%, the median PFS was 6.9 months, and the median OS was 15.6 months (ClinicalTrials.gov identifier: NCT03432598) [253]. The most impressive recent trial is RATIONALE 312 (ClinicalTrials.gov identifier: NCT04005716). Compared with placebo plus chemotherapy, tislelizumab plus chemotherapy significantly improved OS. The median OS was 15.5 vs. 13.5 months in the tislelizumab and placebo arms, respectively, and the OS rates at 1, 2, and 3 years were 62.7%, 33.2%, and 25.0%, respectively, in the tislelizumab arm and 58.4%, 22.4%, and 9.3%, respectively, in the placebo arm [239]; however, the incidence of treatment-related adverse events (TRAEs) was greater in the tislelizumab group. Tislelizumab plus chemotherapy is expected to become a first-line treatment for ES-SCLC, providing patients with long-term survival benefits with a good safety profile.

Tislelizumab is not only expected to be a first-line treatment for ES-SCLC but also has the potential to be used in LS-SCLC patients. A group from Shanghai Pulmonary Hospital applied tislelizumab plus EP in LS-SCLC, followed by surgical treatment. The seven patients who completed four cycles of therapy had an ORR of 85.7%, with five patients undergoing surgery. At a median follow-up of 18 months, all patients were alive [242] (ClinicalTrials.gov identifier: NCT04542369). Therefore, tislelizumab is not only expected to be a first-line treatment for ES-SCLC but also has the potential to be used in LS-SCLC.

Toripalimab

Toripalimab, a selective recombinant humanized PD-1 monoclonal antibody, binds to the heavy chain of the former and the FG loop of the latter [254]. It was developed by Shanghai Junshi Bioscience Co., Ltd., in China and was recently approved for SCLC on 4th June 2024 by the China National Medical Products Administration (NMPA). Approval was based on the EXTENTORCH study (ClinicalTrials.gov identifier: NCT04012606), a randomized, double-blind, phase III clinical trial designed to evaluate the efficacy and safety of toripalimab in combination with chemotherapy versus placebo in combination with chemotherapy for the first-line treatment of ES-SCLC. Data published in October 2023 revealed that patients in the toripalimab-chemotherapy arm exhibited a survival benefit, with PFS times of 5.8 vs. 5.6 months. OS was prolonged by 1.3 months in patients in the toripalimab arm (14.6 vs. 13.3 months) [255]. In addition, toripalimab was the first PD-1 inhibitor to induce PFS and OS benefit in a phase III trial for first-line ES-SCLC treatment, but whether it is suitable for other combinations, such as TRT or targeted drugs, needs further investigation.

Nivolumab

Nivolumab combined with ipilimumab was the first approved dual immunotherapy with a potentially synergistic mechanism targeting PD-1 and CTLA-4. This technique successfully prolonged survival for over 5 years for patients with many solid tumors [256]. Therefore, this combination has been studied extensively in SCLC. For ES-SCLC first-line treatment, CheckMate 451, a double-blind phase III trial testing nivolumab plus ipilimumab as maintenance therapy after chemotherapy, showed that the median OS was 9.2 months in the nivolumab plus ipilimumab arm compared with 9.6 months in the placebo arm [257]. In summary, the combination of nivolumab and ipilimumab failed to prolong survival in SCLC patients.

However, for recurrent LS/ES SCLC patients, CheckMate 032, a phase 1/2 trial, was performed to assess the effects of treatment with nivolumab with or without ipilimumab. The ORR was 11.6% with nivolumab vs. 21.9% with nivolumab plus ipilimumab, and the median OS times were 5.7 vs. 4.7 months [258]. The combination of PD-1 and CTLA-4 inhibitors significantly increased the response rate, although the incidence of TRAEs increased to 17.9% (nivolumab) vs. 37.5% (nivolumab plus ipilimumab). On the basis of these data, the FDA approved the third-line indication of nivolumab for ES-SCLC in 2018. However, in CheckMate 331, no significant improvement in OS was observed with nivolumab versus chemotherapy, with median OS times of 7.5 vs. 8.4 months [259]. In 2020, the FDA withdrew the approval of nivolumab for ES-SCLC patients on the basis of those trials.

In addition, other novel therapeutic combinations have been explored. The randomized phase II ETOP/IFCT 4-12 STIMULI trial aimed to evaluate the superiority of nivolumab plus ipilimumab combination immunotherapy after chemoradiotherapy plus PCI as the first-line treatment for LS-SCLC patients. The median PFS was 10.7 months in the experimental arm and 14.5 months in the observation arm. The median OS was not reached in

the experimental arm by 03 June 2021. Sixty-two percent of patients in the experimental arm experienced Grade ≥3 TRAEs, and 25% in the observation arm experienced Grade ≥3 TRAEs [260]. In a phase I study, lutathera [175], a lutetium-labeled somatostatin analog, combined with nivolumab was used to treat relapsed ES-SCLC patients; this combination showed signs of antitumor activity, so further exploration is needed (ClinicalTrials.gov identifier: NCT03325816) [261]. Nivolumab not only has demonstrated promising efficacy in the treatment of SCLC but also has been studied in many clinical trial results as a part of various combination regimens, laying an important foundation for the development of new anti-PD-1 drugs.

Pembrolizumab

Pembrolizumab is a highly selective humanized anti-PD-1 monoclonal IgG4-κ isotype antibody. Preclinical models have revealed that its pharmacokinetics are very similar to those of nivolumab. In June 2019, the FDA approved pembrolizumab for SCLC patients who progressed after prior platinum-based chemotherapy and at least one other treatment, on the basis of the results of a phase 1b study (KEYNOTE-028) and a phase 2 study (KEYNOTE-158).

In a combined analysis of the KEYNOTE-028 and KEYNOTE-158 studies involving recurrent SCLC patients who received pembrolizumab after two or more lines of treatment, the ORR was 19.3%, whereas 61% of responders had a durational response of more than 18 months [262]. However, in the phase III KEYNOTE-604 study comparing pembrolizumab plus EP with placebo plus EP for ES-SCLC, the median OS was 10.8 vs. 9.7 months in the pembrolizumab arm and EP arm, respectively. The median PFS was 4.5 vs. 4.3 months, which did not reach prespecified efficacy boundaries [263]. On the basis of these results, the FDA withdrew the third-line treatment indication of pembrolizumab for ES-SCLC in 2021. Like nivolumab, pembrolizumab has been employed in a range of clinical trials investigating combination therapies. A phase I study assessing the safety of combining pembrolizumab with TRT after induction chemotherapy for ES-SCLC patients revealed that the median PFS and OS were 6.1 months and 8.4 months, respectively [264]. The combination of concurrent chemoradiotherapy and pembrolizumab for the treatment of LS-SCLC was evaluated in a phase I/II trial, in which the median PFS was 19.7 months and the median OS was 39.5 months [265]. Recent studies have shown that the combination of TRT and immunotherapy exerts synergistic effects by upregulating major histocompatibility complex class I expression and promoting CD8-positive T-cell infiltration, which may indicate a new research hotspot and a highly promising therapeutic approach in the future [266].

Taken together, although the FDA has withdrawn the indications for nivolumab and pembrolizumab treatment, the NCCN panel recommends them as a subsequent therapy option for patients who have relapsed 6 months or less after primary therapy [244].

Ongoing clinical trials

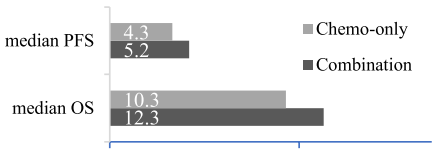
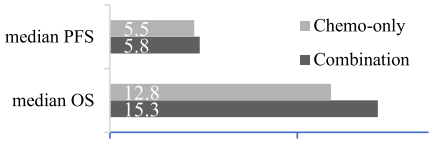
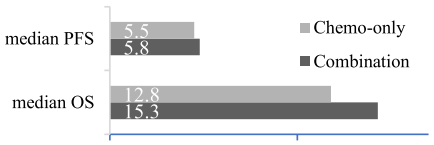
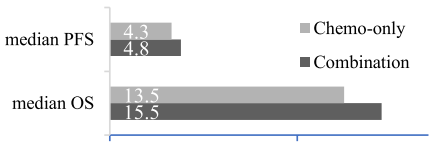
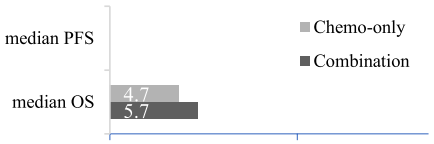
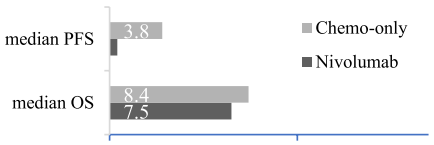
More ongoing clinical trials are being performed to evaluate the efficacy of the combination of PD-1 monoclonal antibodies with EP chemotherapy, such as avelumab (ClinicalTrials.gov identifier: NCT03568097) and toripalimab (ClinicalTrials.gov identifier: NCT04012606), as first-line treatments for patients with ES-SCLC. The quadruple-drug combination regimen has drawn increasing attention. A randomized, double-blind, phase III trial (ClinicalTrials.gov identifier: NCT04234607) combined Benmelstobart, a novel PD-L1 inhibitor, with anlotinib, an antivascular agent, plus standard chemotherapy in ES-SCLC as the first-line treatment was performed. According to the current data, benmelstobart + anlotinib + EC significantly improved the median PFS (6.9 months vs. 4.2 months, $p < 0.0001$), median OS (19.3 months vs. 11.9 months, $p = 0.0002$), objective response (81.3% vs. 66.8%), and duration of response (5.8 months vs. 3.1 months) compared with that in the placebo group. Benmelstobart plus anlotinib and chemotherapy significantly improved OS and PFS at approximately 7.4 months and 6 months, respectively [239]. Currently, patients are being recruited for a trial evaluating the efficacy of the combination in LS-SCLC as a first-line treatment (ClinicalTrials.gov Identifier: NCT04539977).

In summary, combining immunotherapy and chemotherapy has led to a significant change in the treatment strategy for SCLC, but many limitations remain (Table 4). For example, in immune-cold tumors, the infiltration of immune cells into the SCLC tumor mass is limited. Thus, given the low number of immune cells in tumors, how anti-PD-1/PD-L1 antibodies improve the survival of SCLC patients is currently unclear. Several clinical trials are currently underway to evaluate the efficacy of combining radiotherapy with immunotherapy, with a goal of exploring more effective and safer clinical treatment options in the future. Increasing attention has been given to the selection of patients who are more likely to benefit from immunotherapy on the basis of their molecular subtype or biomarker expression profile.

Radiotherapy

In addition to chemotherapy and immunotherapy, radiotherapy plays a vital role in the therapeutic management of patients with SCLC, as does palliative therapy.

Table 4 Comparison of the efficacy of immune checkpoint inhibitors in SCLC

Drug	Company	Target	Status	Approval Year	Trial	Strategy	Efficacy
Atezolizumab	Roche	IgG1 targeting PD-L1	FDA approved	2019/3/1	IMpower133	Combined with chemotherapy for first-line	
Durvalumab	AstraZeneca UK Ltd	IgG1 targeting PD-L1	FDA approved	2020/3/1	CASPIAN	Combined with chemotherapy for first-line	
Adebelimab	Hengrui Pharmaceutical	IgG1 targeting PD-L1	NMPA approved	2023/3/1	CAPSTONE-1	Combined with chemotherapy for first-line	
Serplulimab	Shanghai Henlius Biotech, Inc	IgG4 targeting PD-1	NMPA approved	2022/1/1	ASTRUM-005	Combined with chemotherapy for first-line	
Tislelizumab	Beigene	IgG4 targeting PD-1	NMPA approved	–	RATIONALE 312	Combined with chemotherapy for first-line	
Nivolumab	Bristol-Myers Squibb Company	IgG4 targeting PD-1	FDA approved	2018/8/1	CheckMate032	Combined with ipilimumab for second/multi lines	
			Withdrawn	2020/12/1	CheckMate 451	Combined with ipilimumab for first-line	
					CheckMate 331	Monotherapy for second/multi-lines	
Pembrolizumab	MSD	IgG4 targeting PD-1	FDA approved	2019/6/1	KEYNOTE-028 and KEYNOTE-158	Monotherapy for second/multi-lines	
			Withdrawn	2020/1/1	KEYNOTE-604	Combined with chemotherapy for first-line	

Abbreviations: FDA, U.S. Food and Drug Administration; IgG1/4, immunoglobulin G 1/4; NMPA, National Medical Products Administration; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PFS, progression-free survival

As we mentioned previously, for patients with postoperative pathology suggestive of N1 and N2 disease, adjuvant chemotherapy combined with chest radiotherapy is recommended. In contrast, radiotherapy in those with ES-SCLC consists of consolidative TRT or PCI after first-line treatment according to their physical condition. It has been shown that radiochemotherapy is important for maintaining long-term efficacy after surgery [1]. In patients with localized and extensive SCLC, in addition to the combination of etoposide and cisplatin, daily chest radiotherapy with radiation doses between 50 and 60 Gy has a higher survival rate than conventional chemotherapy regimens do [267]. Notably, for early-stage (node-negative) disease, the debate regarding optimal local management has increased in recent years with increased utilization of stereotactic body radiotherapy (SBRT) and advances in thoracic surgical techniques. However, both therapeutic approaches lack supporting prospective data. In the context of immunotherapy, the effects of radiotherapy and chemotherapy combination regimens are expected to be elucidated. The question remains whether the immunogenic cell death caused by radiotherapy is sufficient to convert the immunosuppressive microenvironment into a pro-immunogenic state. Related clinical trials, such as the RAPTOR trial (ClinicalTrials.gov identifier: NCT04402788) for assessing the addition of therapy to the usual immune therapy (atezolizumab) for ES-SCLC, are ongoing.

Novel therapeutic approaches

Angiogenesis

Angiogenesis is initiated at the early stage of tumorigenesis and remains activated throughout the progression of the disease. The inhibition of angiogenesis has been demonstrated to be an effective antitumor strategy [268]. Vascular endothelial growth factor (VEGF), the most crucial protein with proangiogenic functions, is overexpressed in SCLC [269–271].

Bevacizumab, a humanized monoclonal antibody that inhibits angiogenesis, has been approved for treating several malignant tumors, including SCLC. It was investigated as a first-line treatment in combination with EP chemotherapy for ES-SCLC. A phase II trial revealed prolonged PFS with bevacizumab, although the difference was not statistically significant, and there was no improvement in OS [272] (Table 5). Similarly, a recent phase III trial assessing the efficacy of adding bevacizumab to EP chemotherapy as the first-line therapy reported that the median OS was 9.8 vs. 8.9 months, and the median PFS was 6.7 vs. 5.7 months in the bevacizumab arm and placebo arm, respectively [273]. The BEAT-SC study, a phase III study evaluating the efficacy of bevacizumab combined with atezolizumab plus platinum-based chemotherapy in patients with ES-SCLC, recently met its endpoint. The median PFS was 5.7 months (bevcizumab + atezolizumab + EP) vs. 4.4 months (placebo + atezolizumab + EP), while no improvement in OS was observed [274]. Overall, bevacizumab combined with EP chemotherapy may not be warranted as a first-line treatment for ES-SCLC patients. A meta-analysis revealed that bevacizumab, in combination with standard chemotherapy, improved PFS compared with chemotherapy alone. Moreover, there was no superiority in terms of OS or response rate in ES-SCLC patients.

Anlotinib is a small-molecule TKI that targets VEGFR, FGFR, PDGFR, and C-KIT, inhibiting angiogenesis [275]. A phase II study (ALTER1202) investigated the efficacy of anlotinib as a third- or fourth-line therapy in patients with short-term relapsed SCLC. Compared with placebo, anlotinib significantly improved the median PFS and OS (4.0 vs. 0.7 months, $p < 0.0001$ and 7.3 vs. 4.4 months, $p = 0.006$, respectively) [276]. When combined with the PD-L1 inhibitor Benmelstobart as a first-line therapy for ES-SCLC, anlotinib has shown promising results, with a median PFS of 6.9 months in the combined group and 4.2 months in the EP alone group [239]. Owing to these encouraging results, additional clinical trials are ongoing to evaluate the efficacy of anlotinib in combination with anti-PD-1 inhibitors. A phase II study is assessing the efficacy of tislelizumab combined with anlotinib as maintenance therapy following tislelizumab and chemotherapy for first-line treatment of ES-SCLC (ClinicalTrials.gov Identifier: NCT05896059). The use of anlotinib combined with other regimens is also under investigation. Compared with other single-agent regimens, the irinotecan single-agent regimen appears to have acceptable toxicity and significant palliative effects for second-line treatment. A single-arm trial evaluating the combination of irinotecan liposomes and anlotinib (ClinicalTrials.gov Identifier: NCT06258642) is active. After many rounds of failed clinical trials, anlotinib finally showed superiority in combination with an anti-PD-L1 antibody in SCLC in 2023, indicating a potential breakthrough in the treatment of SCLC.

Cell cycle checkpoints

Both P53 and RB play key roles in cell cycle regulation. However, deletion of the *TP53* and *RB1* genes occurs frequently in SCLC tumor cells, and dual inactivation events lead to elimination of G1/S checkpoint activity, resulting in SCLC proliferation. DNA repair at the G2/M checkpoint appears to be particularly important. Therefore, cell cycle regulators, such as Aurora kinase A/B and WEE1, are interesting targets.

Table 5 Completed and ongoing clinical trials evaluating the safety and efficacy of targeted drugs in patients with SCLC

Study name	Trial number	Phase	Patients	Strategy	Drugs	N	ORR	Median OS	Median PFS	Safety (grade 3–4)
SALUTE	NCT00403403	2	ES-SCLC	chemo + anti-Angiogenesis	Chemo + bevacizumab vs. Chemo	52 vs. 50	58% vs. 48%	9.4 vs. 10.9 months	5.5 vs. 4.4 months	75% vs. 60%
GOIRC-AIFA FARM-6PMFJM	EudraCT number 2007-007949-13	3	ES-SCLC	chemo + anti-Angiogenesis	Chemo + bevacizumab vs. Chemo	101 vs. 103	–	9.8 vs. 8.9 months	6.7 vs. 5.7 months	6.3% vs. 1.0%
ALTER1202	NCT0305979	2	Relapsed SCLC	Angiogenesis only	Anlotinib vs. Placebo	67 vs. 34	4.5% vs. 3.9%	7.3 vs. 4.4 months	4.0 vs. 0.7 months	51.9% vs. 34.6%
–	NCT02038647	2	Relapsed SCLC	Aurora Kinase A inhibitor + chemo	Paclitaxel + Alisertib vs. Paclitaxel	89 vs. 89	22% vs. 18%	6.11 vs. 5.42 months	3.32 vs. 2.17 months	67% vs. 22%
–	NCT02499770	1b/2	ES-SCLC	CDK4/6 inhibitor + chemo	Chemo + Trilaciclib vs. Chemo	39 vs. 39	66.7% vs. 56.8%	10.9 vs. 10.6 months	6.2 vs.5.0 months	50% vs. 83.8%
–	NCT02289690	2	ES-SCLC	PARP inhibitor + chemo	Chemo + Veliparib vs. Chemo	61 vs. 61	77% vs. 64%	10.1 bs 12.4 months	5.8 vs. 5.6 months	83% vs. 68%
ECOG-ACRIN 2511 Study	NCT01642251	2	ES-SCLC	PARP inhibitor + chemo	Chemo + Veliparib vs. Chemo	64 vs. 64	71.9% vs. 65.6%	10.3 vs. 8.9 months	6.1 vs. 5.5 months	49% vs. 32%
–	NCT01901653	1	Relapsed SCLC	ADC(DLL3)	Rova-T	74	18%	4.6 months	3.1 months	–
TAHOE	NCT03061812	3	Second-Line	ADC(DLL3)	Rova-T vs. Topotecan	296 vs. 148	15% vs. 21%	6.3 vs. 8.6 months	3.0 vs. 4.3 months	64% vs. 88%
MERU	NCT03033511	3	ES-SCLC	ADC(DLL3)	Rova-T vs. Placebo	372 vs. 376	9% vs. 4%	8.8 vs. 9.9 months	3.7 vs. 1.4 months	59% vs. 30%
–	NCT03319940	1	Relapsed SCLC	TCE(DLL3)	Tarlatamab	107	23.40%	13.2 months	3.7 months	–
DeLLphi-301	NCT05060016	2	Relapsed SCLC	TCE(DLL3)	10-mg Tarlatamab vs. 100-mg Tarlatamab	88 vs. 88	40% vs. 32%	14.3 vs. NE months	4.9 vs. 3.9 months	59% vs. 64%

Abbreviations: ADC, antibody–drug conjugates; Chemo, chemotherapy; CDK4/6, cyclin-dependent kinases 4/6; DLL3, delta-like ligand 3; NCT, ClinicalTrials.gov identifier; NE, not evaluable; ORR, objective response rate; OS, overall survival; P, placebo; PARP, Poly ADP-ribose polymerase; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PFS, progression-free survival; Rova-T, rovalpituzumab tesirine; TCE, T cell engager

Alisertinib, an Aurora kinase A inhibitor, is used in the subsequent treatment of SCLC. Aurora kinase A/B is highly expressed in *RB1*-inactivated SCLC cells in a mouse model, maintaining cell survival. Aurora kinase interferes with the cell cycle check function, enabling DNA-damaged cells to progress into the G2/M phase normally and inhibiting the p53 pathway, thereby preventing apoptosis from proceeding [277, 278]. Alisertinib combined with paclitaxel was evaluated in a phase II study in the second-line setting for SCLC. Compared with the placebo plus paclitaxel, the combination arm with alisertinib improved the median PFS (3.32 vs. 2.17 months) without significantly affecting the ORR (22% vs. 18%) or median OS (6.17 vs. 5.42 months) [279]. Another phase II study focusing on the efficacy of alisertib in patients with ES-SCLC following progression on or after chemoimmunotherapy is underway (ClinicalTrials.gov Identifier: NCT06095505). Other aurora kinase inhibitors, such as LSN3321213 combined with a PD-L1 inhibitor, have shown enhanced effects in immunocompetent SCLC GEMMs [280]. Chiauranib, a novel orally active multitarget inhibitor that targets VEGFR/Aurora B/CSF-1R, is undergoing a phase III clinical trial for patients with refractory SCLC (ClinicalTrials.gov Identifier: NCT04830813).

The Wee1 kinase is a critical member of the serine/threonine protein kinase family and plays a vital role in cell cycle regulation and DNA damage repair. Owing to the high frequency of p53 inactivating mutations in SCLC cells, these cells predominantly rely on the G2/M checkpoint [53]. Inhibiting WEE1 forces tumor cells to undergo continuous division without DNA repair, ultimately leading to cell death. In in vitro experiments, the inhibition of WEE1 has been shown to activate the STING-TBK1-IRF3 or STAT1 pathway, facilitating $CD8^+$ cytotoxic T-cell infiltration and PD-1 expression [281]. Combining the WEE1 inhibitor AZD1775 with other DNA-damaging agents or immune checkpoint inhibitors induced a synergistic effect [282, 283]. Although this combination is theoretically feasible and promising in vitro, clinical trial data supporting its efficacy are lacking. A phase II study evaluating the efficacy of AZD1775 in combination with EP chemotherapy or PARP inhibitors has been completed, with outcomes pending publication (ClinicalTrials.gov Identifier: NCT02937818).

Trilaciclib, an inhibitor of CDK4/6 that is primarily used for cell cycle inhibition, is currently used for bone marrow preservation in patients with ES-SCLC undergoing standard chemoimmunotherapy. Preclinically, trilaciclib transiently arrested HSPCs in the G1 phase and protects them from chemotherapy-induced damage, leading to faster hematopoietic recovery and enhanced antitumor immunity [284]. A phase II trial (ClinicalTrials.gov identifier: NCT02499770) revealed that patients who received trilaciclib before EP chemotherapy each cycle had a lower likelihood of having ≥ G3 TRAEs than did those who received placebo (50% vs. 83.8%) [285]. Another phase II trial revealed that patients who received trilaciclib before chemotherapy and atezolizumab had a significantly lower incidence and duration of grade 4 neutropenia (1.9% vs. 49.1%) than did those who received placebo [286].

DNA repair proteins

PARP is currently an active drug target that acts as a DNA damage response (DDR) protein. PARP inhibitors can cause DNA double-strand breaks via two mechanisms: by inhibiting the formation of poly-ADP ribose at the single-strand break and by preventing the release of PARP complexes at the single-strand break. As a result, when DNA repair is impaired, cells often resort to alternative repair mechanisms that can lead to extensive genome recombination, leading to cell death [287]. The ECOG-ACRIN 2511 study evaluated the combination of veliparib with cisplatin and etoposide in untreated ES-SCLC patients. The results revealed a median PFS of 6.1 months for the veliparib arm compared with 5.5 months for the placebo arm, and the median OS was 10.3 months vs. 8.9 months, respectively, suggesting a benefit of veliparib combined with chemotherapy as the first-line treatment [288]. Another phase II study demonstrated that significantly prolonged PFS (5.7 vs. 3.6 months; $p = 0.009$) and OS (12.2 vs. 7.5 months; $p = 0.014$) were observed in patients with SLFN11-positive SCLC treated with temozolomide (TMZ) and veliparib, indicating that PARP inhibitors improved therapeutic efficacy in SCLC patients with high SLNF11 expression [289]. Notably, different PARP inhibitors vary in their ability to trap PARP and thus cause various degrees of cytotoxicity [290]. Compared to TMZ, veliparib has a weaker cytotoxic effect and a reduced likelihood of TRAEs in clinical trials because of its lower affinity for PARP [275, 291]. Combining PARP inhibitors with immunotherapy is considered to overcome drug resistance because tumors with homologous recombination repair (HRR) defects mostly harbor more mutations and are likely to generate more neoantigens, potentially enhancing the anticancer immune response. Several ongoing clinical trials are being performed to evaluate the efficacy of PD-1/PD-L1 inhibitors combined with PARP inhibitors, such as camrelizumab (ClinicalTrials.gov Identifier: NCT04701307), durvalumab (ClinicalTrials.gov Identifier: NCT04728230) and dostarlimab (ClinicalTrials.gov Identifier: NCT04701307). And the outcome of the combination therapy is promising, with extending OS by 4.7 months in patients with high

SLFN11 expression, indicating promising results. Additional clinical trials for more combination therapies are currently underway.

CHK1, a serine–threonine kinase, is pivotal in DNA damage-dependent cell cycle arrest [292]. It has been reported that overexpression of the CHK1 protein has been observed in a portion of SCLC cases, indicating that CHK1 inhibition is a target of interest. Notably, CHK1 inhibition shows promise in overcoming chemoresistance. Early preclinical data indicated that the CHK1 inhibitor prexasertib (LY260638) had significant single-agent activity in chemoresistant preclinical models and augmented the effects of cisplatin or the PARP inhibitor olaparib, particularly in the MYC-overexpressing subset [293]. Similar results from other preclinical studies further underscore the potential clinical relevance of CHK1 inhibition [294, 295].

Targeting of DLL3

DLL3 is an atypical Notch ligand whose overexpression supports the growth of SCLC cells, promoting their migratory and invasive capacity [59]. Notably, up to 85% of human SCLC tumors express the DLL3 protein on their cell surface [60], positioning DLL3 as a potential therapeutic target for SCLC. This is particularly evident in nmf2-type SCLC, in which DLL3 is highly expressed, suggesting that therapeutics targeting DLL3 may be especially beneficial for patients with this subtype [154]. From Rova-T to tarlatamab, much progress has been made in the field of DLL3-targeting therapies.

The rovalpituzumab tesirine (Rova-T), a pioneer ADC for SCLC treatment, is composed of a humanized DLL3-specific IgG1 monoclonal antibody, the DNA cross-linking agent pyrrolobenzodiazepine (PDB), and a protease-cleavable linker [21]. Rova-T binds to DLL3 on the tumor surface, causing internalization of the ADC-target complex via endocytosis. Lysosome-associated cathepsin B cleaves the linker, releasing PBD into the cytoplasm, where it subsequently enters the nucleus and induces tumor cell apoptosis [296]. Rova-T has been administered to more than 1000 patients as monotherapy and in combination with other chemotherapies and immunotherapies in at least 10 clinical trials, including two phase III clinical trials. The first-in-human study of Rova-T yielded an ORR of 18%, which increased to 38% in DLL3-high SCLC patients [297], which was promising. However, phase III trials comparing Rova-T as a second-line treatment against topotecan or as maintenance therapy after first-line treatment have failed to meet primary activity endpoints due to high toxicity [298, 299]. In addition to these setbacks, Rova-T has paved the way for new therapeutic strategies in SCLC.

Tarlatamab is a bimolecular T-cell phagocytosis agent that targets both DLL3 on tumor cells and CD3 on T cells. It induces apoptosis in tumor cells by simultaneously binding to tumor cells and T cells to form a cytolytic synapse, activating T cells to release pore-forming enzymes, such as perforin and granzyme B [300, 301]. In a phase II study involving patients with refractory SCLC, a 10 mg dose of tarlatamab administered biweekly resulted in a durable ORR of 40% and improved survival outcomes, with a median PFS of 4.9 months [302]. The drug has now entered a phase three clinical trial (ClinicalTrials.gov Identifier: NCT05740566). Tarlatamab therapy is associated with a significantly increased risk of cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS), which are adverse events commonly observed in T-cell redirecting immunotherapies. Clinical trial data revealed that CRS occurred in 61% of patients receiving the 100 mg dose, although predominantly low-grade (Grades 1–2) manifestations were effectively mitigated through optimized management protocols, including stepwise dosing regimens and prophylactic glucocorticoid administration [302]. While the mechanisms remain incomplete, emerging evidence suggests that CRS pathogenesis may involve IFNγ-mediated hyperinflammatory responses. Conversely, ICANS development appears to be associated with IL18-driven neuroinflammatory pathways. These mechanistic insights position IL18 blockade as a rational therapeutic strategy warranting clinical investigation for ICANS management [303].

Cellular therapy

Cell therapy for lung cancer has become a research hotspot in recent years. Researchers have developed a variety of cell therapies for SCLC that target DLL3. AMG 119, an anti-DLL3 CAR-T-cell therapy with a CD28 and 4-1BB costimulatory structural domain and a CD3 intracellular structural domain, demonstrated no dose-limiting toxicity or ≥ grade 4 TRAEs in a phase I clinical trial with five SCLC patients. One patient in the group achieved a PR and a 43% decrease in tumor diameter from baseline, laying a solid foundation for future development (Table 6) [304]. HPN328, a trispecific T-cell-activating construct (TriTAC), targets CD3, DLL3, and human serum albumin. Data presented at the 2022 ASCO annual meeting from a phase I/II study (ClinicalTrials.gov Identifier: NCT04471727) revealed that among the 9 SCLC patients treated with all doses of HPN328, 3 (33%) had a greater than 30% reduction in summed target lesion diameter, including one confirmed PR. In patients receiving doses greater than 1.215 mg, the cumulative reduction in target lesion diameter exceeded 30%, which was observed

Table 6 Promising basic research, case reports and important clinical trials of cellular treatment in SCLC

Publication	Trial number	Phase	Patients	Strategy	Drugs	N	Response	Median OS	Median PFS
Byers et al. [304]	NCT03392064	1	Relapsed SCLC	DLL3 CAR-T	AMG 119	41	–	7.4 months	3.7 months
Wermke et al. [305]	NCT04471727	1	SCLC	TriTAC	HPN328	24	OR:50%	–	–
Wang et al. [306]	Case report	–	ES-SCLC	NK cell therapy + anti PD-L1 + antiangiogenic	NK cell + Atezolizumab + Anlotinib	1	PR	–	–
Liu et al. [307]	Case report	–	ES-SCLC	CIK therapy + Chemo	CIK cell + Chemo	1	PR	–	–
Liu et al. [308]	Pre-clinic	–	–	DLL3 CAR-NK	–	–	–	–	–
Tian et al. [309]	Pre-clinic	–	–	CDH17 CAR-T	–	–	–	–	–

Abbreviations: TriTAC, tri-specific T-cell activating construct; CIK, Cytokine-Induced Killer Cell Therapy; Chemo, chemotherapy; NK cell, natural killer cell; DLL3, delta-like ligand 3; OS, overall survival

in 2 out of 4 SCLC patients (50%), and a 20% reduction was observed in another patient. Other drugs, such as BI 764532, provide valuable insights into DLL3-targeted therapies [305].

In addition to clinical trials, case reports have shown that patients have tried a wider variety of cell therapies with remarkable results. Wang et al. reported a patient with ES-SCLC in 2023 who achieved satisfactory short-term results after PD-L1-enhanced adoptive transfer of NK cells combined with antiangiogenic targeted therapy, with most of the metastases disappearing and the remaining metastases significantly shrinking [306]. Cytokine-induced killer (CIK) cell therapy is an immunotherapy method that mainly involves activating and expanding patients' immune cells, especially natural killer cells and cytotoxic T lymphocytes (CTLs), to increase their ability to kill tumor cells. Liu et al. reported in 2024 a patient with ES-SCLC who significantly controlled tumor progression and prolonged survival by combining chemotherapy, radiotherapy, and cytokine-induced killing (CIK) immune cell therapy [307]. The above cases illustrate the importance of cell therapy in treating SCLC.

In addition, researchers are working hard to target different proteins and target different kinds of cells. Liu et al. developed DLL3-specific NK-92 cells and explored their potential in treating SCLC. Coculture of the DLL3 SCLC cell line with DLL3-CAR NK-92 cells resulted in significant in vitro cytotoxicity and cytokine production. DLL3-CAR-NK-92 cells induce tumor regression in an H446-derived lung metastasis model with a reasonable safety threshold. The potent antitumor activity of DLL3-CAR-NK-92 cells was observed in SCLC subcutaneous tumor models. In addition, significant numbers of DLL3-CAR NK-92 cells infiltrating tumors were detected in DLL3 SCLC xenografts. These findings suggest that DLL3-CAR NK-92 cells may be a potential strategy for treating SCLC [308]. Tian et al. established CDH17 CAR-T cells and cocultured them with SCLC cells, and the results showed that CDH17 CAR-T cells exhibited potent cytotoxic activity against CDH17-expressing SCLC cells in vitro. In addition, CDH17 CAR-T-cell treatment significantly slowed the growth rate of SCLC-derived xenograft tumors in vivo. Notably, there was no significant difference in body weight between the control group and the CDH17 CAR-T-cell-treated group. The above phenomena indicate the efficacy and safety of CDH17 CAR-T-cell therapy in preclinical models [309].

Conclusion and outlook

In this review, we comprehensively explored recent advancements in SCLC research, focusing on pathogenesis, subtype, clinical management and therapeutic resistance. Significant progress has been made in the understanding of SCLC biology with the development of engineered models and extensive genomic data analysis, bringing new hope for improving the overall survival of SCLC patients. However, substantial knowledge gaps and challenges remain, so further investigation is needed to address these issues fully.

SCLC is aggressive and rapidly develops resistance to standard therapy. While immunotherapies and targeted therapies have recently been included in clinical trials and clinical regimens, the OS remains limited, with an average of 12 months. Surgery is currently considered a potential addition to advanced treatment for limited-stage SCLC. The efficacy of neoadjuvant chemoimmunotherapy combined with surgery or radiotherapy is under investigation in multiple clinical trials. A phase II trial is being performed to evaluate the benefits of neoadjuvant therapy with toripalimab and JS004 combined with EP chemotherapy for LS-SCLC (ClinicalTrials.gov Identifier: NCT06256237). Another phase III trial is being performed to compare the efficacy of surgery and radiotherapy following adebrelimab and platinum-containing doublet induction therapy for LS-SCLC (ClinicalTrials.gov Identifier: NCT05496166). This approach capitalizes

on the rapid tumor remission induced by chemoimmunotherapy, followed by surgical removal of the primary site and immune-mediated clearance of potential distal metastatic cells, representing a very promising advancement in SCLC treatment. ES-SCLC patients face persistent challenges of therapeutic resistance and relapse driven by tumor heterogeneity. Although EP chemotherapy has been the cornerstone for 30 years, its limited efficacy necessitates novel strategies. Emerging evidence highlights the survival benefits and multitarget synergy of immunotherapy. A quadruple regimen (benmelstobart + anlotinib + EP) achieved a landmark, with a median OS of 19.3 months [239]. Concurrently, the use of chemoradiotherapy and pembrolizumab in SCLC patients has led to unprecedented outcomes (median PFS: 19.7 months; OS: 39.5 months) [265]. These findings highlight combination therapies including drugs targeting multiple molecular mechanisms as the most promising approach.

One of the challenges in overcoming SCLC aggressiveness and rapid drug resistance is tumor heterogeneity, both intratumoral and intertumoral. The identification of four SCLC subtypes on the basis of transcription factors has laid a foundation for addressing the heterogeneity of SCLC, enabling the alignment of therapies with specific tumor subtypes. Additionally, subtype switching is also a main factor in therapeutic resistance. As reported by Gay et al. SCLC-A tumors can evolve into the SCLC-I subtype after chemotherapy, indicating the importance of longitudinal monitoring of SCLC subtypes during treatment [16]. In addition to molecular subtypes, genomic diversity also contributes to SCLC heterogeneity and therapeutic resistance. Spatial- and temporal-tumor evolution genomic studies on SCLC identified the common ancestral and main driver of resistance [161]. Although temporal heterogeneity remains less understood than spatial heterogeneity, newly developed time-logging tools based on scRNA-seq might facilitate a breakthrough regarding this bottleneck [310]. In the future, molecular biomarker and mutation assessment at baseline in SCLC patients and personalized approaches guided by the SCLC subtype framework are highly expected in clinical practice.

Early screening for SCLC is particularly important, given that most patients present with advanced disease at diagnosis. However, low-dose CT (LDCT), the current recommended screening method, is insufficient to address this issue [311]. A more effective approach involves the combination of radiography techniques with other highly specific biomarkers [312]. Numerous molecular biomarkers from liquid biopsies are used for early detection in SCLC, including circulating tumor cells (CTCs), circulating tumor DNA (ctDNA) (including DNA methylation), miRNAs, and proteins [313]. Approximately 70–95% of SCLC patients have detectable CTCs [314]. In addition, whole-genome sequencing of ctDNA can reveal the cellular origins of SCLC and establish a diagnostic model [315, 316]. Furthermore, methylome analysis of ctDNA fosters early detection, subtyping and longitudinal tumor monitoring during treatment [142, 317–319]. However, background noise from noncancerous signals limits the clinical application of the above early detection approaches [320]. miRNA-based assays tend to have increased specificity. Both a miRNA signature classifier (MSC) based on individual miRNA and miRNA panels with multiple miRNAs can effectively distinguish lung cancer samples from controls and differentiate SCLC from NSCLC [321, 322]. Nevertheless, these findings are based on a small proportion of SCLC patients, which requires further validation in larger-scale studies [323]. In summary, the relatively low sensitivity and specificity of these markers have limited their clinical application in screening or diagnosing SCLC. The recent application of multiomics and machine learning strategies in early detection studies is anticipated to improve the predictive value of biomarkers and bolster their future clinical applications.

To conclude, although the biological features of SCLC are gradually being elucidated, their translation into clinical practice is lacking. The stagnation in SCLC treatment optimization is largely related to the heterogeneous nature of SCLC and subtype evolution during therapeutic resistance. Continued exploration of SCLC subtyping and pathogenesis is fundamental for guiding clinical therapeutic decision making. Furthermore, the development of subtype-specific targeted drugs and the integration of subtype-specific regimens with standard therapies are crucial for improving patient outcomes. Future efforts are expected to reveal novel and precise biomarkers for early SCLC detection, enabling timely and effective interventions before the disease progresses to a lethal stage.

Author contributions

XZ initiated the idea and revised the manuscript. ZZ,YC,YW and CZ retrieved the data and drafted the manuscript. YL(Lin),YL (Liu)and CC revised the manuscript.

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No datasets were generated or analysed during the current study.

Declarations

Competing interests
The authors declare no competing interests.

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References

1. Megyesfalvi Z, et al. Clinical insights into small cell lung cancer: tumor heterogeneity, diagnosis, therapy, and future directions. CA A Cancer J Clin. 2023;73:620–52. https://doi.org/10.3322/caac.21785.
2. Oronsky B, et al. A 2022 update on extensive stage small-cell lung cancer (SCLC). J Cancer. 2022;13:2945–53. https://doi.org/10.7150/jca.75622.
3. Gazdar AF, Bunn PA, Minna JD. Small-cell lung cancer: what we know, what we need to know and the path forward. Nat Rev Cancer. 2017;17:725–37. https://doi.org/10.1038/nrc.2017.87.
4. Wang S, et al. Survival changes in patients with small cell lung cancer and disparities between different sexes, socioeconomic statuses and ages. Sci Rep. 2017;7:1339. https://doi.org/10.1038/s41598-017-01571-0.
5. Torres-Durán M, et al. Small-cell lung cancer in never-smokers. ESMO Open. 2021;6: 100059. https://doi.org/10.1016/j.esmoop.2021.100059.
6. Reguart N, Marin E, Remon J, Reyes R, Teixido C. In search of the long-desired "copernican therapeutic revolution" in small-cell lung cancer. Drugs. 2020;80:241–62. https://doi.org/10.1007/s40265-019-01240-8.
7. Horn L, et al. First-line Atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. N Engl J Med. 2018;379:2220–9. https://doi.org/10.1056/NEJMoa1809064.
8. Gandhi L, Johnson BE. Paraneoplastic syndromes associated with small cell lung cancer. J Natl Compr Canc Netw. 2006;4:631–8. https://doi.org/10.6004/jnccn.2006.0052.
9. Yang D, et al. Axon-like protrusions promote small cell lung cancer migration and metastasis. Elife. 2019. https://doi.org/10.7554/eLife.50616.
10. Barnard WG. The nature of the "oat-celled sarcoma" of the mediastinum. J Pathol Bacteriol. 1926;29:241–4. https://doi.org/10.1002/path.1700290304.
11. Azzopardi JG. Oat-cell carcinoma of the bronchus. J Pathol Bacteriol. 1959;78:513–9. https://doi.org/10.1002/path.1700780218.
12. Rudin CM, Brambilla E, Faivre-Finn C, Sage J. Small-cell lung cancer. Nat Rev Dis Primers. 2021;7:3. https://doi.org/10.1038/s41572-020-00235-0.
13. Raso MG, Bota-Rabassedas N, Wistuba II. Pathology and classification of SCLC. Cancers. 2021;13:820. https://doi.org/10.3390/cancers13040820.
14. George J, et al. Comprehensive genomic profiles of small cell lung cancer. Nature. 2015;524:47–53. https://doi.org/10.1038/nature14664.
15. Yuan M, et al. Signal pathways and precision therapy of small-cell lung cancer. Signal Transduct Target Ther. 2022;7:187. https://doi.org/10.1038/s41392-022-01013-y.
16. Gay CM, et al. Patterns of transcription factor programs and immune pathway activation define four major subtypes of SCLC with distinct therapeutic vulnerabilities. Cancer Cell. 2021;39:346-360.e347. https://doi.org/10.1016/j.ccell.2020.12.014.
17. Rudin CM, et al. Molecular subtypes of small cell lung cancer: a synthesis of human and mouse model data. Nat Rev Cancer. 2019;19:289–97. https://doi.org/10.1038/s41568-019-0133-9.
18. Li T, Qiao T. Unraveling tumor microenvironment of small-cell lung cancer: implications for immunotherapy. Semin Cancer Biol. 2022;86:117–25. https://doi.org/10.1016/j.semcancer.2022.09.005.
19. Haddadin S, Perry MC. History of small-cell lung cancer. Clin Lung Cancer. 2011;12:87–93. https://doi.org/10.1016/j.cllc.2011.03.002.
20. Megyesfalvi Z, et al. Unfolding the secrets of small cell lung cancer progression: novel approaches and insights through rapid autopsies. Cancer Cell. 2023;41:1535–40. https://doi.org/10.1016/j.ccell.2023.08.007.
21. Owen DH, et al. DLL3: an emerging target in small cell lung cancer. J Hematol Oncol. 2019;12:61. https://doi.org/10.1186/s13045-019-0745-2.
22. Drivsholm L, Paloheimo LI, Osterlind K. Chromogranin A, a significant prognostic factor in small cell lung cancer. Br J Cancer. 1999;81:667–71. https://doi.org/10.1038/sj.bjc.6690745.
23. Jensen SM, Gazdar AF, Cuttitta F, Russell EK, Linnoila RI. A comparison of synaptophysin, chromogranin, and L-dopa decarboxylase as markers for neuroendocrine differentiation in lung cancer cell lines. Can Res. 1990;50:6068–74.
24. Semenova EA, Nagel R, Berns A. Origins, genetic landscape, and emerging therapies of small cell lung cancer. Genes Dev. 2015;29:1447–62. https://doi.org/10.1101/gad.263145.115.
25. Ouadah Y, et al. Rare pulmonary neuroendocrine cells are stem cells regulated by Rb, p53, and Notch. Cell. 2019;179:403-416.e423. https://doi.org/10.1016/j.cell.2019.09.010.
26. Chen HJ, et al. Generation of pulmonary neuroendocrine cells and SCLC-like tumors from human embryonic stem cells. J Exp Med. 2019;216:674–87. https://doi.org/10.1084/jem.20181155.
27. Chen HJ, Gardner EE, Shah Y, Zhang K, Thakur A, Zhang C, Elemento O, Varmus H. Formation of malignant, metastatic small cell lung cancers through overproduction of cMYC protein in TP53 and RB1 depleted pulmonary neuroendocrine cells derived from human embryonic stem cells. bioRxiv. 2024:2023-10. https://doi.org/10.1101/2023.10.06.561244.
28. Chen J, et al. Lineage-restricted neoplasia driven by Myc defaults to small cell lung cancer when combined with loss of p53 and Rb in the airway epithelium. Oncogene. 2022;41:138–45. https://doi.org/10.1038/s41388-021-02070-3.
29. Ferone G, et al. FGFR1 oncogenic activation reveals an alternative cell of origin of SCLC in Rb1/p53 mice. Cell Rep. 2020;30:3837-3850.e3833. https://doi.org/10.1016/j.celrep.2020.02.052.
30. Sutherland KD, et al. Cell of origin of small cell lung cancer: inactivation of Trp53 and Rb1 in distinct cell types of adult mouse lung. Cancer Cell. 2011;19:754–64. https://doi.org/10.1016/j.ccr.2011.04.019.
31. Gardner EE, et al. Lineage-specific intolerance to oncogenic drivers restricts histological transformation. Science. 2024;383:eadj1415. https://doi.org/10.1126/science.adj1415.
32. Yin X, et al. Small cell lung cancer transformation: from pathogenesis to treatment. Semin Cancer Biol. 2022;86:595–606. https://doi.org/10.1016/j.semcancer.2022.03.006.
33. Clamon G, Zeitler W, An J, Hejleh TA. Transformational changes between non-small cell and small cell lung cancer-biological and clinical relevance—a review. Am J Clin Oncol. 2020;43:670–5. https://doi.org/10.1097/coc.0000000000000720.
34. Marcoux N, et al. EGFR-mutant adenocarcinomas that transform to small-cell lung cancer and other neuroendocrine carcinomas: clinical outcomes. J Clin Oncol. 2019;37:278–85. https://doi.org/10.1200/jco.18.01585.
35. Sequist LV, et al. Genotypic and histological evolution of lung cancers acquiring resistance to EGFR inhibitors. Sci Transl Med. 2011;3:75ra26. https://doi.org/10.1126/scitranslmed.3002003.
36. Lee JK, et al. Clonal history and genetic predictors of transformation into small-cell carcinomas from lung adenocarcinomas. J Clin Oncol. 2017;35:3065–74. https://doi.org/10.1200/jco.2016.71.9096.
37. Offin M, et al. Concurrent RB1 and TP53 alterations define a subset of EGFR-mutant lung cancers at risk for histologic transformation and inferior clinical outcomes. J Thorac Oncol. 2019;14:1784–93. https://doi.org/10.1016/j.jtho.2019.06.002.
38. Levacq D, D'Haene N, de Wind R, Remmelink M, Berghmans T. Histological transformation of ALK rearranged adenocarcinoma into small cell lung cancer: a new mechanism of resistance to ALK inhibitors. Lung Cancer. 2016;102:38–41. https://doi.org/10.1016/j.lungcan.2016.10.012.
39. Sainz de Aja J, Dost AFM, Kim CF. Alveolar progenitor cells and the origin of lung cancer. J Intern Med. 2021;289:629–35. https://doi.org/10.1111/joim.13201.
40. Fukui T, et al. Epidermal growth factor receptor mutation status and clinicopathological features of combined small cell carcinoma with adenocarcinoma of the lung. Cancer Sci. 2007;98:1714–9. https://doi.org/10.1111/j.1349-7006.2007.00600.x.

41. Kapoor M, Lozano G. Functional activation of p53 via phosphorylation following DNA damage by UV but not gamma radiation. Proc Natl Acad Sci U S A. 1998;95:2834–7. https://doi.org/10.1073/pnas.95.6.2834.
42. Su D, et al. Interactions of chromatin context, binding site sequence content, and sequence evolution in stress-induced p53 occupancy and transactivation. PLoS Genet. 2015;11: e1004885. https://doi.org/10.1371/journal.pgen.1004885.
43. Verfaillie A, et al. Multiplex enhancer-reporter assays uncover unsophisticated TP53 enhancer logic. Genome Res. 2016;26:882–95. https://doi.org/10.1101/gr.204149.116.
44. Burke JR, Deshong AJ, Pelton JG, Rubin SM. Phosphorylation-induced conformational changes in the retinoblastoma protein inhibit E2F transactivation domain binding. J Biol Chem. 2010;285:16286–93. https://doi.org/10.1074/jbc.M110.108167.
45. Miller CW, et al. p53 mutations in human lung tumors. Can Res. 1992;52:1695–8.
46. Acosta J, et al. p53 restoration in small cell lung cancer identifies a latent cyclophilin-dependent necrosis mechanism. Nat Commun. 2023;14:4403. https://doi.org/10.1038/s41467-023-40161-9.
47. Tang X, et al. Sirtuin 3 induces apoptosis and necroptosis by regulating mutant p53 expression in small-cell lung cancer. Oncol Rep. 2020;43:591–600. https://doi.org/10.3892/or.2019.7439.
48. Wu Z, et al. YAP silencing by RB1 mutation is essential for small-cell lung cancer metastasis. Nat Commun. 2023;14:5916. https://doi.org/10.1038/s41467-023-41585-z.
49. Meuwissen R, et al. Induction of small cell lung cancer by somatic inactivation of both Trp53 and Rb1 in a conditional mouse model. Cancer Cell. 2003;4:181–9. https://doi.org/10.1016/s1535-6108(03)00220-4.
50. Schaffer BE, et al. Loss of p130 accelerates tumor development in a mouse model for human small-cell lung carcinoma. Can Res. 2010;70:3877–83. https://doi.org/10.1158/0008-5472.can-09-4228.
51. Schaub FX, et al. Pan-cancer alterations of the MYC oncogene and its proximal network across the cancer genome atlas. Cell Syst. 2018;6:282-300.e282. https://doi.org/10.1016/j.cels.2018.03.003.
52. Pongor LS, et al. Extrachromosomal DNA amplification contributes to small cell lung cancer heterogeneity and is associated with worse outcomes. Cancer Discov. 2023;13:928–49. https://doi.org/10.1158/2159-8290.Cd-22-0796.
53. Patel AS, et al. Prototypical oncogene family Myc defines unappreciated distinct lineage states of small cell lung cancer. Sci Adv. 2021. https://doi.org/10.1126/sciadv.abc2578.
54. Williamson D, et al. Relationship between MYCN copy number and expression in rhabdomyosarcomas and correlation with adverse prognosis in the alveolar subtype. J Clin Oncol. 2005;23:880–8. https://doi.org/10.1200/jco.2005.11.078.
55. Grunblatt E, et al. MYCN drives chemoresistance in small cell lung cancer while USP7 inhibition can restore chemosensitivity. Genes Dev. 2020;34:1210–26. https://doi.org/10.1101/gad.340133.120.
56. Roper N, et al. Notch signaling and efficacy of PD-1/PD-L1 blockade in relapsed small cell lung cancer. Nat Commun. 2021;12:3880. https://doi.org/10.1038/s41467-021-24164-y.
57. Lim JS, et al. Intratumoural heterogeneity generated by Notch signalling promotes small-cell lung cancer. Nature. 2017;545:360–4. https://doi.org/10.1038/nature22323.
58. Ladi E, et al. The divergent DSL ligand Dll3 does not activate Notch signaling but cell autonomously attenuates signaling induced by other DSL ligands. J Cell Biol. 2005;170:983–92. https://doi.org/10.1083/jcb.200503113.
59. Furuta M, et al. DLL3 regulates the migration and invasion of small cell lung cancer by modulating Snail. Cancer Sci. 2019;110:1599–608. https://doi.org/10.1111/cas.13997.
60. Saunders LR, et al. A DLL3-targeted antibody-drug conjugate eradicates high-grade pulmonary neuroendocrine tumor-initiating cells in vivo. Sci Transl Med. 2015;7:302ra136. https://doi.org/10.1126/scitranslmed.aac9459.
61. Umemura S, et al. Therapeutic priority of the PI3K/AKT/mTOR pathway in small cell lung cancers as revealed by a comprehensive genomic analysis. J Thorac Oncol. 2014;9:1324–31. https://doi.org/10.1097/jto.0000000000000250.
62. Li X, et al. PI3K/Akt/mTOR signaling orchestrates the phenotypic transition and chemo-resistance of small cell lung cancer. J Genet Genomics. 2021;48:640–51. https://doi.org/10.1016/j.jgg.2021.04.001.
63. Kern JA, et al. Role of mTOR As an essential kinase in SCLC. J Thorac Oncol. 2020;15:1522–34. https://doi.org/10.1016/j.jtho.2020.05.026.
64. Horie M, Saito A, Ohshima M, Suzuki HI, Nagase T. YAP and TAZ modulate cell phenotype in a subset of small cell lung cancer. Cancer Sci. 2016;107:1755–66. https://doi.org/10.1111/cas.13078.
65. Mao G, et al. DRBin: metagenomic binning based on deep representation learning. J Genet Genomics. 2022;49:681–4. https://doi.org/10.1016/j.jgg.2021.12.005.
66. Liu YT, Sun ZJ. Turning cold tumors into hot tumors by improving T-cell infiltration. Theranostics. 2021;11:5365–86. https://doi.org/10.7150/thno.58390.
67. Patel SA, Simon MC. Biology of hypoxia-inducible factor-2alpha in development and disease. Cell Death Differ. 2008;15:628–34. https://doi.org/10.1038/cdd.2008.17.
68. Lee GW, et al. Hypoxia-inducible factor-1α and excision repair cross-complementing 1 in patients with small cell lung cancer who received front-line platinum-based chemotherapy: a retrospective study. J Thorac Oncol. 2012;7:528–34. https://doi.org/10.1097/JTO.0b013e3182417830.
69. Lin CS, Liu TC, Lee MT, Yang SF, Tsao TC. Independent prognostic value of hypoxia-inducible factor 1-alpha expression in small cell lung cancer. Int J Med Sci. 2017;14:785–90. https://doi.org/10.7150/ijms.19512.
70. Kasahara N, et al. Fluorodeoxyglucose uptake is associated with low tumor-infiltrating lymphocyte levels in patients with small cell lung cancer. Lung Cancer. 2019;134:180–6. https://doi.org/10.1016/j.lungcan.2019.06.009.
71. Jacoby JJ, et al. Treatment with HIF-1alpha antagonist PX-478 inhibits progression and spread of orthotopic human small cell lung cancer and lung adenocarcinoma in mice. J Thorac Oncol. 2010;5:940–9. https://doi.org/10.1097/JTO.0b013e3181dc211f.
72. Bononi G, et al. Historical perspective of tumor glycolysis: a century with Otto Warburg. Semin Cancer Biol. 2022;86:325–33. https://doi.org/10.1016/j.semcancer.2022.07.003.
73. Gottfried E, et al. Tumor-derived lactic acid modulates dendritic cell activation and antigen expression. Blood. 2006;107:2013–21. https://doi.org/10.1182/blood-2005-05-1795.
74. Siska PJ, Singer K, Evert K, Renner K, Kreutz M. The immunological Warburg effect: Can a metabolic-tumor-stroma score (MeTS) guide cancer immunotherapy? Immunol Rev. 2020;295:187–202. https://doi.org/10.1111/imr.12846.
75. Liu A, Curran MA. Tumor hypermetabolism confers resistance to immunotherapy. Semin Cancer Biol. 2020;65:155–63. https://doi.org/10.1016/j.semcancer.2020.01.009.
76. Bouzin C, Brouet A, De Vriese J, Dewever J, Feron O. Effects of vascular endothelial growth factor on the lymphocyte-endothelium interactions: identification of caveolin-1 and nitric oxide as control points of endothelial cell anergy. J Immunol. 2007;178:1505–11. https://doi.org/10.4049/jimmunol.178.3.1505.
77. Sun Y, et al. MEG3 LncRNA from exosomes released from cancer-associated fibroblasts enhances cisplatin chemoresistance in SCLC via a MiR-15a-5p/CCNE1 Axis. Yonsei Med J. 2022;63:229–40. https://doi.org/10.3349/ymj.2022.63.3.229.
78. Lu Y, et al. Dynamic phenotypic reprogramming and chemoresistance induced by lung fibroblasts in small cell lung cancer. Sci Rep. 2024;14:2884. https://doi.org/10.1038/s41598-024-52687-z.
79. Tian Y, et al. Single-cell transcriptomic profiling reveals the tumor heterogeneity of small-cell lung cancer. Signal Transduct Target Ther. 2022;7:346. https://doi.org/10.1038/s41392-022-01150-4.
80. Takahashi A, et al. Podoplanin-expressing cancer-associated fibroblasts inhibit small cell lung cancer growth. Oncotarget. 2015;6:9531–41. https://doi.org/10.18632/oncotarget.3371.
81. Dora D, et al. Neuroendocrine subtypes of small cell lung cancer differ in terms of immune microenvironment and checkpoint molecule distribution. Mol Oncol. 2020;14:1947–65. https://doi.org/10.1002/1878-0261.12741.
82. Sun Y, et al. Characterization of PD-L1 protein expression and CD8(+) tumor-infiltrating lymphocyte density, and their associations with

clinical outcome in small-cell lung cancer. Transl Lung Cancer Res. 2019;8:748–59. https://doi.org/10.21037/tlcr.2019.10.09.
83. Zhang W, et al. Small cell lung cancer tumors and preclinical models display heterogeneity of neuroendocrine phenotypes. Transl Lung Cancer Res. 2018;7:32–49. https://doi.org/10.21037/tlcr.2018.02.02.
84. Chen Y, Li H, Fan Y. Shaping the tumor immune microenvironment of SCLC: mechanisms, and opportunities for immunotherapy. Cancer Treat Rev. 2023;120: 102606. https://doi.org/10.1016/j.ctrv.2023.102606.
85. Burr ML, et al. An evolutionarily conserved function of polycomb silences the MHC class I antigen presentation pathway and enables immune evasion in cancer. Cancer Cell. 2019;36:385-401.e388. https://doi.org/10.1016/j.ccell.2019.08.008.
86. Nguyen EM, et al. Targeting lysine-specific demethylase 1 rescues major histocompatibility complex class I antigen presentation and overcomes programmed death-ligand 1 blockade resistance in SCLC. J Thorac Oncol. 2022;17:1014–31. https://doi.org/10.1016/j.jtho.2022.05.014.
87. Yazawa T, et al. Complicated mechanisms of class II transactivator transcription deficiency in small cell lung cancer and neuroblastoma. Am J Pathol. 2002;161:291–300. https://doi.org/10.1016/s0002-9440(10)64181-8.
88. He Y, et al. MHC class II expression in lung cancer. Lung Cancer. 2017;112:75–80. https://doi.org/10.1016/j.lungcan.2017.07.030.
89. Hiatt JB, et al. Inhibition of LSD1 with bomedemstat sensitizes small cell lung cancer to immune checkpoint blockade and T-cell killing. Clin Cancer Res Off J Am Assoc Cancer Res. 2022;28:4551–64. https://doi.org/10.1158/1078-0432.Ccr-22-1128.
90. Eglenen-Polat B, et al. A telomere-targeting drug depletes cancer initiating cells and promotes anti-tumor immunity in small cell lung cancer. Nat Commun. 2024;15:672. https://doi.org/10.1038/s41467-024-44861-8.
91. Cai L, et al. Cell-autonomous immune gene expression is repressed in pulmonary neuroendocrine cells and small cell lung cancer. Commun Biol. 2021;4:314. https://doi.org/10.1038/s42003-021-01842-7.
92. Yang Z, et al. Myeloid-derived suppressor cells-new and exciting players in lung cancer. J Hematol Oncol. 2020;13:10. https://doi.org/10.1186/s13045-020-0843-1.
93. Tian T, et al. Increased circulating CD14(+)HLA-DR-/low myeloid-derived suppressor cells are associated with poor prognosis in patients with small-cell lung cancer. Cancer Biomark. 2015;15:425–32. https://doi.org/10.3233/cbm-150473.
94. Owen DH, et al. Deep and durable response to nivolumab and temozolomide in small-cell lung cancer associated with an early decrease in myeloid-derived suppressor cells. Clin Lung Cancer. 2021;22:e487–97. https://doi.org/10.1016/j.cllc.2020.10.018.
95. Iclozan C, Antonia S, Chiappori A, Chen DT, Gabrilovich D. Therapeutic regulation of myeloid-derived suppressor cells and immune response to cancer vaccine in patients with extensive stage small cell lung cancer. Cancer Immunol Immunother. 2013;62:909–18. https://doi.org/10.1007/s00262-013-1396-8.
96. Ying X, et al. Research progress on the molecular mechanisms of hepatic metastasis in lung cancer: a narrative review. Ann Palliat Med. 2021;10:4806–22. https://doi.org/10.21037/apm-20-1675.
97. Nakazawa K, et al. Specific organ metastases and survival in small cell lung cancer. Oncol Lett. 2012;4:617–20. https://doi.org/10.3892/ol.2012.792.
98. Riihimäki M, et al. Metastatic sites and survival in lung cancer. Lung Cancer. 2014;86:78–84. https://doi.org/10.1016/j.lungcan.2014.07.020.
99. Akhtar M, Haider A, Rashid S, Al-Nabet A. Paget's, "seed and soil" theory of cancer metastasis: an idea whose time has come. Adv Anat Pathol. 2019;26:69–74. https://doi.org/10.1097/pap.0000000000000219.
100. Ko J, Winslow MM, Sage J. Mechanisms of small cell lung cancer metastasis. EMBO Mol Med. 2021;13: e13122. https://doi.org/10.15252/emmm.202013122.
101. Gong L, et al. Clinical outcome for small cell lung cancer patients with bone metastases at the time of diagnosis. J Bone Oncol. 2019;19:100265. https://doi.org/10.1016/j.jbo.2019.100265.
102. Chen Q, et al. Deep learning of bone metastasis in small cell lung cancer: a large sample-based study. Front Oncol. 2023;13:1097897. https://doi.org/10.3389/fonc.2023.1097897.
103. Lin Y, Jiang W, Su CY, Pan XB. Impact of liver metastases status on survival outcomes of first-line immunotherapy in extensive stage small cell lung cancer: a systematic review and meta-analysis. Aging. 2023;15:9561–71. https://doi.org/10.18632/aging.205035.
104. Chen P, et al. Annexin A1 is a potential biomarker of bone metastasis in small cell lung cancer. Oncol Lett. 2021;21:141. https://doi.org/10.3892/ol.2020.12402.
105. Li S, et al. Comparative proteomic profiling of plasma exosomes in lung cancer cases of liver and brain metastasis. Cell Biosci. 2023;13:180. https://doi.org/10.1186/s13578-023-01112-5.
106. Zhu Y, Cui Y, Zheng X, Zhao Y, Sun G. Small-cell lung cancer brain metastasis: From molecular mechanisms to diagnosis and treatment. Biochim Biophys acta Mol Basis Dis. 2022;1868:166557. https://doi.org/10.1016/j.bbadis.2022.166557.
107. Sarkis GA, et al. Generation and release of Neurogranin, Vimentin, and MBP proteolytic peptides, following traumatic brain injury. Mol Neurobiol. 2022;59:731–47. https://doi.org/10.1007/s12035-021-02600-w.
108. Mollaoglu G, et al. MYC drives progression of small cell lung cancer to a variant neuroendocrine subtype with vulnerability to aurora kinase inhibition. Cancer Cell. 2017;31:270–85. https://doi.org/10.1016/j.ccell.2016.12.005.
109. Cui M, et al. PTEN is a potent suppressor of small cell lung cancer. Mol Cancer Res MCR. 2014;12:654–9. https://doi.org/10.1158/1541-7786.mcr-13-0554.
110. Gazdar AF, et al. The comparative pathology of genetically engineered mouse models for neuroendocrine carcinomas of the lung. J Thorac Oncol Off Publ Int Assoc Study Lung Cancer. 2015;10:553–64. https://doi.org/10.1097/jto.0000000000000459.
111. Ji X, et al. Premetastatic niche mimicking bone-On-A-Chip: a microfluidic platform to study bone metastasis in cancer patients. Small. 2023;19:e2207606. https://doi.org/10.1002/smll.202207606.
112. Lukas RV, Gondi V, Kamson DO, Kumthekar P, Salgia R. State-of-the-art considerations in small cell lung cancer brain metastases. Oncotarget. 2017;8:71223–33. https://doi.org/10.18632/oncotarget.19333.
113. Qu F, et al. Crosstalk between small-cell lung cancer cells and astrocytes mimics brain development to promote brain metastasis. Nat Cell Biol. 2023;25:1506–19. https://doi.org/10.1038/s41556-023-01241-6.
114. Fan RY, et al. Zebrafish xenograft model for studying mechanism and treatment of non-small cell lung cancer brain metastasis. J Exp Clin Cancer Res CR. 2021;40:371. https://doi.org/10.1186/s13046-021-02173-5.
115. Zhang SR, et al. Efficacy and mechanism study of cordycepin against brain metastases of small cell lung cancer based on zebrafish. Phytomed Int J Phytother Phytopharmacol. 2023;109: 154613. https://doi.org/10.1016/j.phymed.2022.154613.
116. Fior R, et al. Single-cell functional and chemosensitive profiling of combinatorial colorectal therapy in zebrafish xenografts. Proc Natl Acad Sci USA. 2017;114:E8234-e8243. https://doi.org/10.1073/pnas.1618389114.
117. Ma Y, et al. COTE-1 promotes the proliferation and invasion of small cell lung cancer by regulating autophagy activity via the AMPK/mTOR signaling pathway. Mol Cell Probes. 2023;71: 101918. https://doi.org/10.1016/j.mcp.2023.101918.
118. Meder L, et al. Blocking the angiopoietin-2-dependent integrin β-1 signaling axis abrogates small cell lung cancer invasion and metastasis. JCI Insight. 2024. https://doi.org/10.1172/jci.insight.166402.
119. Chan JM, et al. Signatures of plasticity, metastasis, and immunosuppression in an atlas of human small cell lung cancer. Cancer Cell. 2021;39:1479-1496.e1418. https://doi.org/10.1016/j.ccell.2021.09.008.
120. Seehawer M, et al. Loss of Kmt2c or Kmt2d drives brain metastasis via KDM6A-dependent upregulation of MMP3. Nat Cell Biol. 2024;26:1165–75. https://doi.org/10.1038/s41556-024-01446-3.
121. Liu R, et al. Association of KMT2C/D loss-of-function variants with response to immune checkpoint blockades in colorectal cancer. Cancer Sci. 2023;114:1229–39. https://doi.org/10.1111/cas.15716.
122. Na F, et al. KMT2C deficiency promotes small cell lung cancer metastasis through DNMT3A-mediated epigenetic reprogramming. Nat Cancer. 2022;3:753–67. https://doi.org/10.1038/s43018-022-00361-6.
123. Dooley AL, et al. Nuclear factor I/B is an oncogene in small cell lung cancer. Genes Dev. 2011;25:1470–5. https://doi.org/10.1101/gad.2046711.
124. Denny SK, et al. Nfib promotes metastasis through a widespread increase in chromatin accessibility. Cell. 2016;166:328–42. https://doi.org/10.1016/j.cell.2016.05.052.

125. Böttger F, et al. Tumor heterogeneity underlies differential cisplatin sensitivity in mouse models of small-cell lung cancer. Cell Rep. 2019;27:3345-3358.e3344. https://doi.org/10.1016/j.celrep.2019.05.057.
126. Wagenblast E, et al. A model of breast cancer heterogeneity reveals vascular mimicry as a driver of metastasis. Nature. 2015;520:358–62. https://doi.org/10.1038/nature14403.
127. Williamson SC, et al. Vasculogenic mimicry in small cell lung cancer. Nat Commun. 2016;7:13322. https://doi.org/10.1038/ncomms13322.
128. Zhang X, et al. Molecular features and evolutionary trajectory of ASCL1(+) and NEUROD1(+) SCLC cells. Br J Cancer. 2023;128:748–59. https://doi.org/10.1038/s41416-022-02103-y.
129. Carney DN, et al. Serum neuron-specific enolase: a marker for disease extent and response to therapy of small-cell lung cancer. Lancet (London, England). 1982;1:583–5. https://doi.org/10.1016/s0140-6736(82)91748-2.
130. van Zandwijk N, Jassem E, Bonfrer JM, Mooi WJ, van Tinteren H. Serum neuron-specific enolase and lactate dehydrogenase as predictors of response to chemotherapy and survival in non-small cell lung cancer. Semin Oncol. 1992;19:37–43.
131. Li L, et al. CEMIP-mediated hyaluronan metabolism facilitates SCLC metastasis by activating TLR2/c-Src/ERK1/2 axis. Biochim Biophys Acta Mol Cell Res. 2023;1870:119451. https://doi.org/10.1016/j.bbamcr.2023.119451.
132. Kim WY, et al. Syntenin increases the invasiveness of small cell lung cancer cells by activating p38, AKT, focal adhesion kinase and SP1. Exp Mol Med. 2014;46: e90. https://doi.org/10.1038/emm.2014.1.
133. Burnier JV, et al. Type IV collagen-initiated signals provide survival and growth cues required for liver metastasis. Oncogene. 2011;30:3766–83. https://doi.org/10.1038/onc.2011.89.
134. Neubauer K, Saile B, Ramadori G. Liver fibrosis and altered matrix synthesis. Can J Gastroenterol. 2001;15:187–93. https://doi.org/10.1155/2001/870205.
135. Yang C, et al. Liver fibrosis: insights into migration of hepatic stellate cells in response to extracellular matrix and growth factors. Gastroenterology. 2003;124:147–59. https://doi.org/10.1053/gast.2003.50012.
136. Habeck M. Targeting the extracellular matrix to stop tumour progression. Drug Discov Today. 2001;6:1077–8. https://doi.org/10.1016/s1359-6446(01)02023-2.
137. He Y, et al. IL-20RB mediates tumoral response to osteoclastic niches and promotes bone metastasis of lung cancer. J Clin Investig. 2022. https://doi.org/10.1172/jci157917.
138. Umar MI, et al. The adipokine component in the molecular regulation of cancer cell survival, proliferation and metastasis. Pathol Oncol Res POR. 2021;27:1609828. https://doi.org/10.3389/pore.2021.1609828.
139. Yang D, et al. Intertumoral heterogeneity in SCLC is influenced by the cell type of origin. Cancer Discov. 2018;8:1316–31. https://doi.org/10.1158/2159-8290.cd-17-0987.
140. Rudin CM, et al. Comprehensive genomic analysis identifies SOX2 as a frequently amplified gene in small-cell lung cancer. Nat Genet. 2012;44:1111–6. https://doi.org/10.1038/ng.2405.
141. Carney DN, et al. Establishment and identification of small cell lung cancer cell lines having classic and variant features. Can Res. 1985;45:2913–23.
142. Heeke S, et al. Tumor- and circulating-free DNA methylation identifies clinically relevant small cell lung cancer subtypes. Cancer Cell. 2024;42:225-237.e225. https://doi.org/10.1016/j.ccell.2024.01.001.
143. Umemura S, et al. Clinical significance of a prospective large genomic screening for SCLC: the genetic classification and a biomarker-driven phase 2 trial of gedatolisib. J Thorac Oncol Off Publ Int Assoc Study Lung Cancer. 2025;20:177–93. https://doi.org/10.1016/j.jtho.2024.10.004.
144. Megyesfalvi Z, et al. Expression patterns and prognostic relevance of subtype-specific transcription factors in surgically resected small-cell lung cancer: an international multicenter study. J Pathol. 2022;257:674–86. https://doi.org/10.1002/path.5922.
145. Miyata T, Maeda T, Lee JE. NeuroD is required for differentiation of the granule cells in the cerebellum and hippocampus. Genes Dev. 1999;13:1647–52. https://doi.org/10.1101/gad.13.13.1647.
146. Neptune ER, et al. Targeted disruption of NeuroD, a proneural basic helix-loop-helix factor, impairs distal lung formation and neuroendocrine morphology in the neonatal lung. J Biol Chem. 2008;283:21160–9. https://doi.org/10.1074/jbc.M708692200.
147. Ikematsu Y, et al. NEUROD1 is highly expressed in extensive-disease small cell lung cancer and promotes tumor cell migration. Lung Cancer. 2020;146:97–104. https://doi.org/10.1016/j.lungcan.2020.05.012.
148. Osborne JK, et al. NeuroD1 mediates nicotine-induced migration and invasion via regulation of the nicotinic acetylcholine receptor subunits in a subset of neural and neuroendocrine carcinomas. Mol Biol Cell. 2014;25:1782–92. https://doi.org/10.1091/mbc.E13-06-0316.
149. Baine MK, et al. POU2F3 in SCLC: clinicopathologic and genomic analysis with a focus on its diagnostic utility in neuroendocrine-low SCLC. J Thorac Oncol. 2022;17:1109–21. https://doi.org/10.1016/j.jtho.2022.06.004.
150. Yamashita J, Ohmoto M, Yamaguchi T, Matsumoto I, Hirota J. Skn-1a/Pou2f3 functions as a master regulator to generate Trpm5-expressing chemosensory cells in mice. PLoS ONE. 2017;12: e0189340. https://doi.org/10.1371/journal.pone.0189340.
151. Huang YH, et al. POU2F3 is a master regulator of a tuft cell-like variant of small cell lung cancer. Genes Dev. 2018;32:915–28. https://doi.org/10.1101/gad.314815.118.
152. Baine MK, et al. SCLC subtypes defined by ASCL1, NEUROD1, POU2F3, and YAP1: a comprehensive immunohistochemical and histopathologic characterization. J Thorac Oncol Off Publ Int Assoc Study Lung Cancer. 2020;15:1823–35. https://doi.org/10.1016/j.jtho.2020.09.009.
153. Chen P, et al. YAP1 expression is associated with survival and immunosuppression in small cell lung cancer. Cell Death Dis. 2023;14:636. https://doi.org/10.1038/s41419-023-06053-y.
154. Liu Q, et al. Proteogenomic characterization of small cell lung cancer identifies biological insights and subtype-specific therapeutic strategies. Cell. 2024;187:184-203.e128. https://doi.org/10.1016/j.cell.2023.12.004.
155. Giffin MJ, et al. AMG 757, a half-life extended, DLL3-targeted bispecific T-cell engager, shows high potency and sensitivity in preclinical models of small-cell lung cancer. Clin Cancer Res Off J Am Assoc Cancer Res. 2021;27:1526–37. https://doi.org/10.1158/1078-0432.Ccr-20-2845.
156. Duplaquet L, et al. KDM6A epigenetically regulates subtype plasticity in small cell lung cancer. Nat Cell Biol. 2023;25:1346–58. https://doi.org/10.1038/s41556-023-01210-z.
157. Ireland AS, et al. MYC drives temporal evolution of small cell lung cancer subtypes by reprogramming neuroendocrine fate. Cancer Cell. 2020;38:60-78.e12. https://doi.org/10.1016/j.ccell.2020.05.001.
158. Berghoff AS, et al. Tumor infiltrating lymphocytes and PD-L1 expression in brain metastases of small cell lung cancer (SCLC). J Neurooncol. 2016;130:19–29. https://doi.org/10.1007/s11060-016-2216-8.
159. Sundstrøm S, et al. Cisplatin and etoposide regimen is superior to cyclophosphamide, epirubicin, and vincristine regimen in small-cell lung cancer: results from a randomized phase III trial with 5 years' follow-up. J Clin Oncol. 2002;20:4665–72. https://doi.org/10.1200/jco.2002.12.111.
160. Zhang S, Cheng Y. Immunotherapy for extensive-stage small-cell lung cancer: current landscape and future perspectives. Front Oncol. 2023;13:1142081. https://doi.org/10.3389/fonc.2023.1142081.
161. George J, et al. Evolutionary trajectories of small cell lung cancer under therapy. Nature. 2024;627:880–9. https://doi.org/10.1038/s41586-024-07177-7.
162. Wagner AH, et al. Recurrent WNT pathway alterations are frequent in relapsed small cell lung cancer. Nat Commun. 2018;9:3787. https://doi.org/10.1038/s41467-018-06162-9.
163. Owonikoko TK, et al. Randomized phase II study of paclitaxel plus alisertib versus paclitaxel plus placebo as second-line therapy for SCLC: primary and correlative biomarker analyses. J Thorac Oncol. 2020;15:274–87. https://doi.org/10.1016/j.jtho.2019.10.013.
164. Wang Z, et al. Increased insulin-like growth factor 1 receptor (IGF1R) expression in small cell lung cancer and the effect of inhibition of IGF1R expression by RNAi on growth of human small cell lung cancer NCI-H446 cell. Growth Factors (Chur, Switzerland). 2015;33:337–46. https://doi.org/10.3109/08977194.2015.1088533.
165. Caliman E, et al. Challenges in the treatment of small cell lung cancer in the era of immunotherapy and molecular classification. Lung Cancer. 2023;175:88–100. https://doi.org/10.1016/j.lungcan.2022.11.014.

166. Shibata M, Ham K, Hoque MO. A time for YAP1: tumorigenesis, immunosuppression and targeted therapy. Int J Cancer. 2018;143:2133–44. https://doi.org/10.1002/ijc.31561.
167. Davies A, Zoubeidi A, Beltran H, Selth LA. The Transcriptional and epigenetic landscape of cancer cell lineage plasticity. Cancer Discov. 2023;13:1771–88. https://doi.org/10.1158/2159-8290.cd-23-0225.
168. Lo YC, Rivera-Concepcion J, Vasmatzis G, Aubry MC, Leventakos K. Subtype of SCLC Is an intrinsic and persistent feature through systemic treatment. JTO Clin Res Rep. 2023;4: 100561. https://doi.org/10.1016/j.jtocrr.2023.100561.
169. McColl K, et al. Reciprocal expression of INSM1 and YAP1 defines subgroups in small cell lung cancer. Oncotarget. 2017;8:73745–56. https://doi.org/10.18632/oncotarget.20572.
170. Redin E, et al. SMARCA4 controls state plasticity in small cell lung cancer through regulation of neuroendocrine transcription factors and REST splicing. J Hematol Oncol. 2024;17:58. https://doi.org/10.1186/s13045-024-01572-3.
171. Sarvi S, et al. CD133+ cancer stem-like cells in small cell lung cancer are highly tumorigenic and chemoresistant but sensitive to a novel neuropeptide antagonist. Can Res. 2014;74:1554–65. https://doi.org/10.1158/0008-5472.can-13-1541.
172. Gardner EE, et al. Chemosensitive relapse in small cell lung cancer proceeds through an EZH2-SLFN11 axis. Cancer Cell. 2017;31:286–99. https://doi.org/10.1016/j.ccell.2017.01.006.
173. Chalishazar MD, et al. MYC-driven small-cell lung cancer is metabolically distinct and vulnerable to arginine depletion. Clin Cancer Res Off J Am Assoc Cancer Res. 2019;25:5107–21. https://doi.org/10.1158/1078-0432.Ccr-18-4140.
174. Tsurutani J, West KA, Sayyah J, Gills JJ, Dennis PA. Inhibition of the phosphatidylinositol 3-kinase/Akt/mammalian target of rapamycin pathway but not the MEK/ERK pathway attenuates laminin-mediated small cell lung cancer cellular survival and resistance to imatinib mesylate or chemotherapy. Can Res. 2005;65:8423–32. https://doi.org/10.1158/0008-5472.can-05-0058.
175. Rubin MA, Bristow RG, Thienger PD, Dive C, Imielinski M. Impact of lineage plasticity to and from a neuroendocrine phenotype on progression and response in prostate and lung cancers. Mol Cell. 2020;80:562–77. https://doi.org/10.1016/j.molcel.2020.10.033.
176. Pommier Y, Leo E, Zhang H, Marchand C. DNA topoisomerases and their poisoning by anticancer and antibacterial drugs. Chem Biol. 2010;17:421–33. https://doi.org/10.1016/j.chembiol.2010.04.012.
177. Zheng X, et al. Nanomedicine combats drug resistance in lung cancer. Adv Mater (Deerfield Beach Fla). 2024;36:e2308977. https://doi.org/10.1002/adma.202308977.
178. Linder P. Dead-box proteins: a family affair–active and passive players in RNP-remodeling. Nucleic Acids Res. 2006;34:4168–80. https://doi.org/10.1093/nar/gkl468.
179. Sengoku T, Nureki O, Nakamura A, Kobayashi S, Yokoyama S. Structural basis for RNA unwinding by the DEAD-box protein drosophila vasa. Cell. 2006;125:287–300. https://doi.org/10.1016/j.cell.2006.01.054.
180. Noyes C, et al. The germline factor DDX4 contributes to the chemoresistance of small cell lung cancer cells. Commun Biol. 2023;6:65. https://doi.org/10.1038/s42003-023-04444-7.
181. Bonilla B, Hengel SR, Grundy MK, Bernstein KA. RAD51 gene family structure and function. Annu Rev Genet. 2020;54:25–46. https://doi.org/10.1146/annurev-genet-021920-092410.
182. Meindl A, et al. Germline mutations in breast and ovarian cancer pedigrees establish RAD51C as a human cancer susceptibility gene. Nat Genet. 2010;42:410–4. https://doi.org/10.1038/ng.569.
183. Hansen LT, Lundin C, Spang-Thomsen M, Petersen LN, Helleday T. The role of RAD51 in etoposide (VP16) resistance in small cell lung cancer. Int J Cancer. 2003;105:472–9. https://doi.org/10.1002/ijc.11106.
184. Tripathi P, Soni R, Antra, Tandon V. Pixantrone confers radiosensitization in KRAS mutated cancer cells by suppression of radiation-induced prosurvival pathways. Free Radic Biol Med. 2022;190:351–62. https://doi.org/10.1016/j.freeradbiomed.2022.08.015.
185. Cheng J, et al. TRIM21 and PHLDA3 negatively regulate the crosstalk between the PI3K/AKT pathway and PPP metabolism. Nat Commun. 2020;11:1880. https://doi.org/10.1038/s41467-020-15819-3.
186. Meijer TW, Kaanders JH, Span PN, Bussink J. Targeting hypoxia, HIF-1, and tumor glucose metabolism to improve radiotherapy efficacy. Clin Cancer Res Off J Am Assoc Cancer Res. 2012;18:5585–94. https://doi.org/10.1158/1078-0432.ccr-12-0858.
187. Deng H, et al. PI3K/mTOR inhibitors promote G6PD autophagic degradation and exacerbate oxidative stress damage to radiosensitize small cell lung cancer. Cell Death Dis. 2023;14:652. https://doi.org/10.1038/s41419-023-06171-7.
188. Cargill KR, et al. Targeting MYC-enhanced glycolysis for the treatment of small cell lung cancer. Cancer Metab. 2021;9:33. https://doi.org/10.1186/s40170-021-00270-9.
189. Huang F, et al. Guanosine triphosphate links MYC-dependent metabolic and ribosome programs in small-cell lung cancer. J Clin Investig. 2021. https://doi.org/10.1172/jci139929.
190. Makinoshima H, et al. Metabolic determinants of sensitivity to phosphatidylinositol 3-kinase pathway inhibitor in small-cell lung carcinoma. Can Res. 2018;78:2179–90. https://doi.org/10.1158/0008-5472.can-17-2109.
191. Tabata S, et al. Metabolic hallmarks for purine nucleotide biosynthesis in small cell lung carcinoma. Mol Cancer Res MCR. 2024;22:82–93. https://doi.org/10.1158/1541-7786.mcr-23-0386.
192. Li L, et al. Identification of DHODH as a therapeutic target in small cell lung cancer. Sci Transl Med. 2019. https://doi.org/10.1126/scitranslmed.aaw7852.
193. Gmeiner WH, et al. Dysregulated pyrimidine biosynthesis contributes to 5-FU resistance in SCLC patient-derived organoids but response to a novel polymeric fluoropyrimidine, CF10. Cancers. 2020. https://doi.org/10.3390/cancers12040788.
194. Yang M, Vousden KH. Serine and one-carbon metabolism in cancer. Nat Rev Cancer. 2016;16:650–62. https://doi.org/10.1038/nrc.2016.81.
195. Shen W, et al. NRBF2 regulates the chemoresistance of small cell lung cancer by interacting with the P62 protein in the autophagy process. iScience. 2022;25:104471. https://doi.org/10.1016/j.isci.2022.104471.
196. Shen W, et al. SR9009 induces a REV-ERB dependent anti-small-cell lung cancer effect through inhibition of autophagy. Theranostics. 2020;10:4466–80. https://doi.org/10.7150/thno.42478.
197. Guo C, et al. Therapeutic targeting of the mevalonate-geranylgeranyl diphosphate pathway with statins overcomes chemotherapy resistance in small cell lung cancer. Nat Cancer. 2022;3:614–28. https://doi.org/10.1038/s43018-022-00358-1.
198. Leidal AM, Levine B, Debnath J. Autophagy and the cell biology of age-related disease. Nat Cell Biol. 2018;20:1338–48. https://doi.org/10.1038/s41556-018-0235-8.
199. White E. The role for autophagy in cancer. J Clin Investig. 2015;125:42–6.
200. Li X, et al. Autophagy: a novel mechanism of chemoresistance in cancers. Biomed Pharmacother. 2019;119:109415. https://doi.org/10.1016/j.biopha.2019.109415.
201. Langevin SM, Kelsey KT. The fate is not always written in the genes: epigenomics in epidemiologic studies. Environ Mol Mutagen. 2013;54:533–41. https://doi.org/10.1002/em.21762.
202. Duruisseaux M, Esteller M. Lung cancer epigenetics: from knowledge to applications. Semin Cancer Biol. 2018;51:116–28. https://doi.org/10.1016/j.semcancer.2017.09.005.
203. Shi YX, Sheng DQ, Cheng L, Song XY. Current landscape of epigenetics in lung cancer: focus on the mechanism and application. J Oncol. 2019;2019:8107318. https://doi.org/10.1155/2019/8107318.
204. Huang H, Weng H, Chen J. m(6)A modification in coding and non-coding RNAs: roles and therapeutic implications in cancer. Cancer Cell. 2020;37:270–88. https://doi.org/10.1016/j.ccell.2020.02.004.
205. Zhang Z, et al. m(6)A regulators as predictive biomarkers for chemotherapy benefit and potential therapeutic targets for overcoming chemotherapy resistance in small-cell lung cancer. J Hematol Oncol. 2021;14:190. https://doi.org/10.1186/s13045-021-01173-4.
206. Yang Y, Hsu PJ, Chen YS, Yang YG. Dynamic transcriptomic m(6)A decoration: writers, erasers, readers and functions in RNA metabolism. Cell Res. 2018;28:616–24. https://doi.org/10.1038/s41422-018-0040-8.
207. Kong H, Sun J, Zhang W, Zhang H, Li H. Long intergenic non-protein coding RNA 1273 confers sorafenib resistance in hepatocellular carcinoma via regulation of methyltransferase 3. Bioengineered. 2022;13:3108–21. https://doi.org/10.1080/21655979.2022.2025701.
208. Lin Z, et al. RNA m(6) A methylation regulates sorafenib resistance in liver cancer through FOXO3-mediated autophagy. EMBO J. 2020;39:e103181. https://doi.org/10.15252/embj.2019103181.

209. Sun Y, et al. METTL3 promotes chemoresistance in small cell lung cancer by inducing mitophagy. J Exp Clin Cancer Res CR. 2023;42:65. https://doi.org/10.1186/s13046-023-02638-9.
210. Scattolin D, et al. The emerging role of Schlafen-11 (SLFN11) in predicting response to anticancer treatments: focus on small cell lung cancer. Cancer Treat Rev. 2024;128: 102768. https://doi.org/10.1016/j.ctrv.2024.102768.
211. Nogales V, et al. Epigenetic inactivation of the putative DNA/RNA helicase SLFN11 in human cancer confers resistance to platinum drugs. Oncotarget. 2016;7:3084–97. https://doi.org/10.18632/oncotarget.6413.
212. Krushkal J, et al. Epigenome-wide DNA methylation analysis of small cell lung cancer cell lines suggests potential chemotherapy targets. Clin Epigenetics. 2020;12:93. https://doi.org/10.1186/s13148-020-00876-8.
213. Zhai G, et al. hTERT promoter methylation promotes small cell lung cancer progression and radiotherapy resistance. J Radiat Res. 2020;61:674–83. https://doi.org/10.1093/jrr/rraa052.
214. Koyen AE, et al. EZH2 has a non-catalytic and PRC2-independent role in stabilizing DDB2 to promote nucleotide excision repair. Oncogene. 2020;39:4798–813. https://doi.org/10.1038/s41388-020-1332-2.
215. Simó-Riudalbas L, et al. KAT6B is a tumor suppressor histone H3 lysine 23 acetyltransferase undergoing genomic loss in small cell lung cancer. Can Res. 2015;75:3936–45. https://doi.org/10.1158/0008-5472.can-14-3702.
216. Vonlaufen N, Naguleswaran A, Coppens I, Sullivan WJ Jr. MYST family lysine acetyltransferase facilitates ataxia telangiectasia mutated (ATM) kinase-mediated DNA damage response in Toxoplasma gondii. J Biol Chem. 2010;285:11154–61. https://doi.org/10.1074/jbc.M109.066134.
217. Restifo NP, et al. Identification of human cancers deficient in antigen processing. J Exp Med. 1993;177:265–72. https://doi.org/10.1084/jem.177.2.265.
218. Doyle A, et al. Markedly decreased expression of class I histocompatibility antigens, protein, and mRNA in human small-cell lung cancer. J Exp Med. 1985;161:1135–51. https://doi.org/10.1084/jem.161.5.1135.
219. Schumacher TN, Schreiber RD. Neoantigens in cancer immunotherapy. Science. 2015;348:69–74. https://doi.org/10.1126/science.aaa4971.
220. Tian Y, Zhai X, Han A, Zhu H, Yu J. Potential immune escape mechanisms underlying the distinct clinical outcome of immune checkpoint blockades in small cell lung cancer. J Hematol Oncol. 2019;12:67. https://doi.org/10.1186/s13045-019-0753-2.
221. Muppa P, et al. Immune cell infiltration may be a key determinant of long-term survival in small cell lung cancer. J Thorac Oncol. 2019;14:1286–95. https://doi.org/10.1016/j.jtho.2019.03.028.
222. Carvajal-Hausdorf D, et al. Expression and clinical significance of PD-L1, B7–H3, B7–H4 and TILs in human small cell lung Cancer (SCLC). J Immunother Cancer. 2019;7:65. https://doi.org/10.1186/s40425-019-0540-1.
223. Liu SV, et al. Clinical and molecular characterization of long-term survivors with extensive-stage small cell lung cancer treated with first-line atezolizumab plus carboplatin and etoposide. Lung Cancer. 2023;186:107418. https://doi.org/10.1016/j.lungcan.2023.107418.
224. Best SA, et al. Harnessing Natural killer immunity in metastatic SCLC. J Thorac Oncol Off Publ Int Assoc Study Lung Cancer. 2020;15:1507–21. https://doi.org/10.1016/j.jtho.2020.05.008.
225. Yu H, et al. PD-L1 expression by two complementary diagnostic assays and mRNA in situ hybridization in small cell lung cancer. J Thorac Oncol. 2017;12:110–20. https://doi.org/10.1016/j.jtho.2016.09.002.
226. Kim HS, et al. Association of PD-L1 expression with tumor-infiltrating immune cells and mutation burden in high-grade neuroendocrine carcinoma of the lung. J Thorac Oncol. 2018;13:636–48. https://doi.org/10.1016/j.jtho.2018.01.008.
227. Zhang W, et al. Advances in anti-tumor treatments targeting the CD47/SIRPα Axis. Front Immunol. 2020;11:18. https://doi.org/10.3389/fimmu.2020.00018.
228. Weiskopf K, et al. CD47-blocking immunotherapies stimulate macrophage-mediated destruction of small-cell lung cancer. J Clin Investig. 2016;126:2610–20. https://doi.org/10.1172/jci81603.
229. Micke P, et al. Staging small cell lung cancer: veterans administration lung study group versus international association for the study of lung cancer–what limits limited disease? Lung Cancer. 2002;37:271–6. https://doi.org/10.1016/s0169-5002(02)00072-7.
230. Nicholson AG, et al. The international association for the study of lung cancer lung cancer staging project: proposals for the revision of the clinical and pathologic staging of small cell lung cancer in the forthcoming eighth edition of the TNM classification for lung cancer. J Thorac Oncol. 2016;11:300–311. https://doi.org/10.1016/j.jtho.2015.10.008.
231. Williams R, Eskandari N, Kendall A. Staging of small cell lung cancer (SCLC): comparison of two criteria by survival analysis. J Clin Oncol. 2006;24:17030–17030. https://doi.org/10.1200/jco.2006.24.18_suppl.17030.
232. Lee JH, Saxena A, Giaccone G. Advancements in small cell lung cancer. Semin Cancer Biol. 2023;93:123–8. https://doi.org/10.1016/j.semcancer.2023.05.008.
233. Yang CF, et al. Role of adjuvant therapy in a population-based cohort of patients with early-stage small-cell lung cancer. J Clin Oncol. 2016;34:1057–64. https://doi.org/10.1200/jco.2015.63.8171.
234. Faivre-Finn C, et al. Concurrent once-daily versus twice-daily chemoradiotherapy in patients with limited-stage small-cell lung cancer (CONVERT): an open-label, phase 3, randomised, superiority trial. Lancet Oncol. 2017;18:1116–25. https://doi.org/10.1016/s1470-2045(17)30318-2.
235. Evans WK, et al. VP-16 and cisplatin as first-line therapy for small-cell lung cancer. J Clin Oncol. 1985;3:1471–7. https://doi.org/10.1200/jco.1985.3.11.1471.
236. Wang BC, Fu C, Lin GH. The efficacy of adebrelimab compared with durvalumab and atezolizumab in untreated extensive-stage small-cell lung cancer: a survival analysis of reconstructed patient-level data. Front Immunol. 2023;14:1185577. https://doi.org/10.3389/fimmu.2023.1185577.
237. Owonikoko TK, et al. A systematic analysis of efficacy of second-line chemotherapy in sensitive and refractory small-cell lung cancer. J Thorac Oncol. 2012;7:866–72. https://doi.org/10.1097/JTO.0b013e31824c7f4b.
238. Paz-Ares L, et al. Durvalumab plus platinum-etoposide versus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial. Lancet (London, England). 2019;394:1929–39. https://doi.org/10.1016/s0140-6736(19)32222-6.
239. Cheng Y, et al. OA01.06 first-line chemotherapy with or without tislelizumab for extensive-stage small cell lung cancer: rationale-312 phase 3 study. J Thorac Oncol. 2023;18:S46. https://doi.org/10.1016/j.jtho.2023.09.027.
240. Liu SV, et al. Updated overall survival and PD-L1 subgroup analysis of patients with extensive-stage small-cell lung cancer treated with atezolizumab, carboplatin, and etoposide (IMpower133). J Clin Oncol. 2021;39:619–30. https://doi.org/10.1200/jco.20.01055.
241. Inman BA, Longo TA, Ramalingam S, Harrison MR. Atezolizumab: A PD-L1-blocking antibody for bladder cancer. Clin Cancer Res Off J Am Assoc Cancer Res. 2017;23:1886–90. https://doi.org/10.1158/1078-0432.Ccr-16-1417.
242. Reck M, et al. Five-year survival in patients with extensive-stage small cell lung cancer treated with atezolizumab in the Phase III IMpower133 study and the Phase III IMbrella A extension study. Lung Cancer. 2024;196: 107924. https://doi.org/10.1016/j.lungcan.2024.107924.
243. Al-Salama ZT. Durvalumab: a review in extensive-stage SCLC. Target Oncol. 2021;16:857–64. https://doi.org/10.1007/s11523-021-00843-0.
244. Ganti AKP, et al. Small cell lung cancer, version 2.2022, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw. 2021;19:1441–64. https://doi.org/10.6004/jnccn.2021.0058.
245. Zou Y, et al. Efficacy and safety of durvalumab + chemotherapy vs. atezolizumab + chemotherapy in the treatment of small-cell lung cancer: a retrospective comparative cohort study. J Thorac Dis. 2023;15:3339–49. https://doi.org/10.21037/jtd-23-588.
246. Li L, et al. First-line atezolizumab/durvalumab plus platinum-etoposide combined with radiotherapy in extensive-stage small-cell lung cancer. BMC Cancer. 2023;23:318. https://doi.org/10.1186/s12885-023-10784-8.
247. Wang J, et al. Adebrelimab or placebo plus carboplatin and etoposide as first-line treatment for extensive-stage small-cell lung cancer (CAPSTONE-1): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2022;23:739–47. https://doi.org/10.1016/s1470-2045(22)00224-8.
248. Cheng Y, et al. Effect of first-line serplulimab vs placebo added to chemotherapy on survival in patients with extensive-stage small

cell lung cancer: the ASTRUM-005 randomized clinical trial. JAMA. 2022;328:1223–32. https://doi.org/10.1001/jama.2022.16464.
249. Zhu Y, Liu K, Zhu H, Cao H, Zhou Y. Comparative efficacy and safety of novel immuno-chemotherapy for extensive-stage small-cell lung cancer: a network meta-analysis of randomized controlled trial. Ther Adv Med Oncol. 2023;15:17588359231206148. https://doi.org/10.1177/17588359231206147.
250. Liang X, Chen X, Li H, Li Y. Cost-effectiveness analysis of first-line serplulimab combined with chemotherapy for extensive-stage small cell lung cancer. Front Public Health. 2023;11:1156427. https://doi.org/10.3389/fpubh.2023.1156427.
251. Xiang G, et al. Cost-effectiveness of serplulimab as first-line therapy for extensive-stage small cell lung cancer in China. Front Immunol. 2023;14:1223020. https://doi.org/10.3389/fimmu.2023.1223020.
252. Zhang L, Geng Z, Hao B, Geng Q. Tislelizumab: a modified anti-tumor programmed death receptor 1 antibody. Cancer Control. 2022;29:10732748221111296. https://doi.org/10.1177/10732748221111296.
253. Wang Z, et al. A phase 2 study of tislelizumab in combination with platinum-based chemotherapy as first-line treatment for advanced lung cancer in Chinese patients. Lung Cancer. 2020;147:259–68. https://doi.org/10.1016/j.lungcan.2020.06.007.
254. Keam SJ. Toripalimab: first global approval. Drugs. 2019;79:573–8. https://doi.org/10.1007/s40265-019-01076-2.
255. Cheng Y, et al. Toripalimab plus chemotherapy as a first-line therapy for extensive-stage small cell lung cancer: the phase 3 EXTENTORCH randomized clinical trial. JAMA Oncol. 2025;11:16–25. https://doi.org/10.1001/jamaoncol.2024.5019.
256. Kooshkaki O, et al. Combination of ipilimumab and nivolumab in cancers: from clinical practice to ongoing clinical trials. Int J Mol Sci. 2020. https://doi.org/10.3390/ijms21124427.
257. Owonikoko TK, et al. Nivolumab and ipilimumab as maintenance therapy in extensive-disease small-cell lung cancer: CheckMate 451. J Clin Oncol. 2021;39:1349–59. https://doi.org/10.1200/jco.20.02212.
258. Ready N, et al. Third-line nivolumab monotherapy in recurrent SCLC: CheckMate 032. J Thorac Oncol. 2019;14:237–44. https://doi.org/10.1016/j.jtho.2018.10.003.
259. Spigel DR, et al. Second-line nivolumab in relapsed small-cell lung cancer: CheckMate 331(☆). Ann Oncol. 2021;32:631–41. https://doi.org/10.1016/j.annonc.2021.01.071.
260. Peters S, et al. Consolidation nivolumab and ipilimumab versus observation in limited-disease small-cell lung cancer after chemo-radiotherapy - results from the randomised phase II ETOP/IFCT 4–12 STIMULI trial. Ann Oncol. 2022;33:67–79. https://doi.org/10.1016/j.annonc.2021.09.011.
261. Kim C, et al. Phase I study of the (177)Lu-DOTA(0)-Tyr(3)-Octreotate (lutathera) in combination with nivolumab in patients with neuroendocrine tumors of the lung. J Immunother Cancer. 2020. https://doi.org/10.1136/jitc-2020-000980.
262. Chung HC, et al. Pembrolizumab after two or more lines of previous therapy in patients with recurrent or metastatic SCLC: results from the KEYNOTE-028 and KEYNOTE-158 studies. J Thorac Oncol. 2020;15:618–27. https://doi.org/10.1016/j.jtho.2019.12.109.
263. Rudin CM, et al. Pembrolizumab or placebo plus etoposide and platinum as first-line therapy for extensive-stage small-cell lung cancer: randomized, double-blind, phase III KEYNOTE-604 study. J Clin Oncol. 2020;38:2369–79. https://doi.org/10.1200/jco.20.00793.
264. Welsh JW, et al. Phase I trial of pembrolizumab and radiation therapy after induction chemotherapy for extensive-stage small cell lung cancer. J Thorac Oncol. 2020;15:266–73. https://doi.org/10.1016/j.jtho.2019.10.001.
265. Welsh JW, et al. Phase 1/2 trial of pembrolizumab and concurrent chemoradiation therapy for limited-stage SCLC. J Thorac Oncol. 2020;15:1919–27. https://doi.org/10.1016/j.jtho.2020.08.022.
266. Donlon NE, Power R, Hayes C, Reynolds JV, Lysaght J. Radiotherapy, immunotherapy, and the tumour microenvironment: Turning an immunosuppressive milieu into a therapeutic opportunity. Cancer Lett. 2021;502:84–96. https://doi.org/10.1016/j.canlet.2020.12.045.
267. Stupp R, Monnerat C, Turrisi AT 3rd, Perry MC, Leyvraz S. Small cell lung cancer: state of the art and future perspectives. Lung Cancer. 2004;45:105–17. https://doi.org/10.1016/j.lungcan.2003.12.006.
268. Cao Y, Langer R, Ferrara N. Targeting angiogenesis in oncology, ophthalmology and beyond. Nat Rev Drug Discov. 2023;22:476–95. https://doi.org/10.1038/s41573-023-00671-z.
269. Liu Y, et al. A prospective study of apatinib in patients with extensive-stage small cell lung cancer after failure of two or more lines of chemotherapy. Oncologist. 2020;25:e833–42. https://doi.org/10.1634/theoncologist.2019-0391.
270. Lucchi M, et al. Small cell lung carcinoma (SCLC): the angiogenic phenomenon. Eur J Cardiothorac Surg. 2002;21:1105–10. https://doi.org/10.1016/s1010-7940(02)00112-4.
271. Zhao J, Zhang X, Gong C, Zhang J. Targeted therapy with apatinib in a patient with relapsed small cell lung cancer: a case report and literature review. Medicine. 2017;96:e9259. https://doi.org/10.1097/md.0000000000009259.
272. Spigel DR, et al. Randomized phase II study of bevacizumab in combination with chemotherapy in previously untreated extensive-stage small-cell lung cancer: results from the SALUTE trial. J Clin Oncol. 2011;29:2215–22. https://doi.org/10.1200/jco.2010.29.3423.
273. Tiseo M, et al. Italian, multicenter, Phase III, randomized study of cisplatin plus etoposide with or without bevacizumab as first-line treatment in extensive-disease small-cell lung cancer: the GOIRC-AIFA FARM6PMFJM trial. J Clin Oncol. 2017;35:1281–7. https://doi.org/10.1200/jco.2016.69.4844.
274. Ohe Y, et al. BEAT-SC: a randomized phase III study of bevacizumab or placebo in combination with atezolizumab and platinum-based chemotherapy in patients with extensive-stage small cell lung cancer (ES-SCLC). J Clin Oncol. 2024;42:8001–8001. https://doi.org/10.1200/JCO.2024.42.16_suppl.8001.
275. Shen G, et al. Anlotinib: a novel multi-targeting tyrosine kinase inhibitor in clinical development. J Hematol Oncol. 2018;11:120. https://doi.org/10.1186/s13045-018-0664-7.
276. Shi J, et al. Anlotinib as third- or further-line therapy for short-term relapsed small-cell lung cancer: subgroup analysis of a randomized phase 2 study (ALTER1202). Front Med. 2022;16:766–72. https://doi.org/10.1007/s11684-021-0916-8.
277. Gong X, et al. Aurora A kinase inhibition is synthetic lethal with loss of the RB1 tumor suppressor gene. Cancer Discov. 2019;9:248–63. https://doi.org/10.1158/2159-8290.Cd-18-0469.
278. Oser MG, et al. Cells lacking the RB1 tumor suppressor gene are hyperdependent on aurora B kinase for survival. Cancer Discov. 2019;9:230–47. https://doi.org/10.1158/2159-8290.Cd-18-0389.
279. Owonikoko T, et al. OA05.05 randomized phase 2 study: alisertib (MLN8237) or Placebo + Pac litaxel as second-line therapy for small-cell lung cancer (SCLC). J Thorac Oncol. 2017;12:S261–2. https://doi.org/10.1016/j.jtho.2016.11.253.
280. Li Y, et al. Aurora A kinase inhibition induces accumulation of SCLC tumor cells in mitosis with restored interferon signaling to increase response to PD-L1. Cell Rep Med. 2023;4: 101282. https://doi.org/10.1016/j.xcrm.2023.101282.
281. Taniguchi H, et al. WEE1 inhibition enhances the antitumor immune response to PD-L1 blockade by the concomitant activation of STING and STAT1 pathways in SCLC. Cell Rep. 2022;39: 110814. https://doi.org/10.1016/j.celrep.2022.110814.
282. Lallo A, et al. The combination of the PARP inhibitor olaparib and the WEE1 inhibitor AZD1775 as a new therapeutic option for small cell lung cancer. Clin Cancer Res Off J Am Assoc Cancer Res. 2018;24:5153–64. https://doi.org/10.1158/1078-0432.Ccr-17-2805.
283. Zhao X, et al. Acquired small cell lung cancer resistance to Chk1 inhibitors involves Wee1 up-regulation. Mol Oncol. 2021;15:1130–45. https://doi.org/10.1002/1878-0261.12882.
284. Lai AY, et al. CDK4/6 inhibition enhances antitumor efficacy of chemotherapy and immune checkpoint inhibitor combinations in preclinical models and enhances T-cell activation in patients with SCLC receiving chemotherapy. J Immunother Cancer. 2020. https://doi.org/10.1136/jitc-2020-000847.
285. Weiss JM, et al. Myelopreservation with the CDK4/6 inhibitor trilaciclib in patients with small-cell lung cancer receiving first-line chemotherapy: a phase Ib/randomized phase II trial. Ann Oncol. 2019;30:1613–21. https://doi.org/10.1093/annonc/mdz278.
286. Weiss J, et al. Effects of trilaciclib on chemotherapy-induced myelosuppression and patient-reported outcomes in patients with

extensive-stage small cell lung cancer: pooled results from three phase II randomized, double-blind. Placebo-Controlled Stud Clin Lung Cancer. 2021;22:449–60. https://doi.org/10.1016/j.cllc.2021.03.010.
287. Slade D. PARP and PARG inhibitors in cancer treatment. Genes Dev. 2020;34:360–94. https://doi.org/10.1101/gad.334516.119.
288. Owonikoko TK, 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. https://doi.org/10.1200/jco.18.00264.
289. Lok BH, et al. PARP inhibitor activity correlates with SLFN11 expression and demonstrates synergy with temozolomide in small cell lung cancer. Clin Cancer Res Off J Am Assoc Cancer Res. 2017;23:523–35. https://doi.org/10.1158/1078-0432.Ccr-16-1040.
290. Murai J, et al. Trapping of PARP1 and PARP2 by clinical PARP inhibitors. Can Res. 2012;72:5588–99. https://doi.org/10.1158/0008-5472.Can-12-2753.
291. Penson RT, et al. Olaparib versus nonplatinum chemotherapy in patients with platinum-sensitive relapsed ovarian cancer and a germline BRCA1/2 mutation (SOLO3): a randomized phase III trial. J Clin Oncol. 2020;38:1164–74. https://doi.org/10.1200/jco.19.02745.
292. Zhang Y, Hunter T. Roles of Chk1 in cell biology and cancer therapy. Int J Cancer. 2014;134:1013–23. https://doi.org/10.1002/ijc.28226.
293. Sen T, et al. CHK1 inhibition in small-cell lung cancer produces single-agent activity in biomarker-defined disease subsets and combination activity with cisplatin or olaparib. Can Res. 2017;77:3870–84. https://doi.org/10.1158/0008-5472.Can-16-3409.
294. King C, et al. LY2606368 causes replication catastrophe and antitumor effects through CHK1-dependent mechanisms. Mol Cancer Ther. 2015;14:2004–13. https://doi.org/10.1158/1535-7163.Mct-14-1037.
295. Hong D, et al. Phase I study of LY2606368, a checkpoint kinase 1 inhibitor, in patients with advanced cancer. J Clin Oncol. 2016;34:1764–71. https://doi.org/10.1200/jco.2015.64.5788.
296. Hafeez U, Parakh S, Gan HK, Scott AM. Antibody-drug conjugates for cancer therapy. Molecules. 2020. https://doi.org/10.3390/molecules25204764.
297. Rudin CM, et al. Rovalpituzumab tesirine, a DLL3-targeted 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. https://doi.org/10.1016/s1470-2045(16)30565-4.
298. Johnson ML, et al. Rovalpituzumab tesirine as a maintenance therapy after first-line platinum-based chemotherapy in patients with extensive-stage-SCLC: results from the phase 3 MERU study. J Thorac Oncol. 2021;16:1570–81. https://doi.org/10.1016/j.jtho.2021.03.012.
299. Blackhall F, et al. Efficacy and safety of rovalpituzumab tesirine compared with topotecan as second-line therapy in DLL3-High SCLC: results from the phase 3 TAHOE study. J Thorac Oncol. 2021;16:1547–58. https://doi.org/10.1016/j.jtho.2021.02.009.
300. Offner S, Hofmeister R, Romaniuk A, Kufer P, Baeuerle PA. Induction of regular cytolytic T cell synapses by bispecific single-chain antibody constructs on MHC class I-negative tumor cells. Mol Immunol. 2006;43:763–71. https://doi.org/10.1016/j.molimm.2005.03.007.
301. Haas C, et al. Mode of cytotoxic action of T cell-engaging BiTE antibody MT110. Immunobiology. 2009;214:441–53. https://doi.org/10.1016/j.imbio.2008.11.014.
302. Ahn MJ, et al. Tarlatamab for patients with previously treated small-cell lung cancer. N Engl J Med. 2023;389:2063–75. https://doi.org/10.1056/NEJMoa2307980.
303. Diorio C, et al. comprehensive serum proteome profiling of cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome patients with B-Cell all receiving CAR T19. Clin Cancer Res Off J Am Assoc Cancer Res. 2022;28:3804–13. https://doi.org/10.1158/1078-0432.Ccr-22-0822.
304. Byers L, et al. 697 A phase 1 study of AMG 119, a DLL3-targeting, chimeric antigen receptor (CAR) T cell therapy, in relapsed/refractory small cell lung cancer (SCLC). J Immunother Cancer. 2022;10:A728–A728. https://doi.org/10.1136/jitc-2022-SITC2022.0697.
305. Wermke M, et al. Phase I trial of the DLL3/CD3 bispecific T-cell engager BI 764532 in DLL3-positive small-cell lung cancer and neuroendocrine carcinomas. Future Oncol. 2022;18:2639–49. https://doi.org/10.2217/fon-2022-0196.
306. Wang Z, et al. Investigation of the efficacy and feasibility of combined therapy of PD-L1-enhanced exogenous peripatetic adoptive natural killer (NK) cells in combination with antiangiogenic targeted therapy in the treatment of extensive-stage small cell lung cancer. Thoracic cancer. 2023;14:2877–85. https://doi.org/10.1111/1759-7714.15040.
307. Liu T, et al. Long-term, 13-year survival after immune cell therapy combined with chemotherapy for extensive-stage small-cell lung cancer: a case report. Front Oncol. 2024;14:1389725. https://doi.org/10.3389/fonc.2024.1389725.
308. Liu M, et al. CAR NK-92 cells targeting DLL3 kill effectively small cell lung cancer cells in vitro and in vivo. J Leukoc Biol. 2022;112:901–11. https://doi.org/10.1002/jlb.5ma0122-467r.
309. Tian W, Zhao J, Wang W. Targeting CDH17 with chimeric antigen receptor-redirected T cells in small cell lung cancer. Lung. 2023;201:489–97. https://doi.org/10.1007/s00408-023-00648-0.
310. Kirschenbaum D, et al. Time-resolved single-cell transcriptomics defines immune trajectories in glioblastoma. Cell. 2024;187:149-165.e123. https://doi.org/10.1016/j.cell.2023.11.032.
311. Thomas A, Pattanayak P, Szabo E, Pinsky P. Characteristics and outcomes of small cell lung cancer detected by CT screening. Chest. 2018;154:1284–90. https://doi.org/10.1016/j.chest.2018.07.029.
312. Kunihiro AG, et al. CD133 as a biomarker for an autoantibody-to-ImmunoPET paradigm for the early detection of small cell lung cancer. J Nucl Med. 2022;63:1701–7. https://doi.org/10.2967/jnumed.121.263511.
313. Wang Q, et al. SCLC: epidemiology, risk factors, genetic susceptibility, molecular pathology, screening, and early detection. J Thorac Oncol. 2023;18:31–46. https://doi.org/10.1016/j.jtho.2022.10.002.
314. Foy V, Fernandez-Gutierrez F, Faivre-Finn C, Dive C, Blackhall F. The clinical utility of circulating tumour cells in patients with small cell lung cancer. Transl Lung Cancer Res. 2017;6:409–17. https://doi.org/10.21037/tlcr.2017.07.05.
315. Shields MD, Chen K, Dutcher G, Patel I, Pellini B. Making the rounds: exploring the role of circulating tumor DNA (ctDNA) in non-small cell lung cancer. Int J Mol Sci. 2022;23:9006. https://doi.org/10.3390/ijms23169006.
316. Mohan S, et al. Profiling of circulating free DNA using targeted and genome-wide sequencing in patients with SCLC. J Thorac Oncol. 2020;15:216–30. https://doi.org/10.1016/j.jtho.2019.10.007.
317. Baca SC, et al. Liquid biopsy epigenomic profiling for cancer subtyping. Nat Med. 2023;29:2737–41. https://doi.org/10.1038/s41591-023-02605-z.
318. Chemi F, et al. cfDNA methylome profiling for detection and subtyping of small cell lung cancers. Nat Cancer. 2022;3:1260–70. https://doi.org/10.1038/s43018-022-00415-9.
319. Missiaglia E, et al. Distal and proximal colon cancers differ in terms of molecular, pathological, and clinical features. Ann Oncol Off J Eur Soc Med Oncol. 2014;25:1995–2001. https://doi.org/10.1093/annonc/mdu275.
320. Fernandez-Cuesta L, et al. Identification of circulating tumor DNA for the early detection of small-cell lung cancer. EBioMedicine. 2016;10:117–23. https://doi.org/10.1016/j.ebiom.2016.06.032.
321. Fehlmann T, et al. Evaluating the use of circulating MicroRNA profiles for lung cancer detection in symptomatic patients. JAMA Oncol. 2020;6:714–23. https://doi.org/10.1001/jamaoncol.2020.0001.
322. Yu Y, et al. Plasma miR-92a-2 as a biomarker for small cell lung cancer. Cancer Biomark. 2017;18:319–27. https://doi.org/10.3233/CBM-160254.
323. Pastorino U, et al. Baseline computed tomography screening and blood microRNA predict lung cancer risk and define adequate intervals in the BioMILD trial. Ann Oncol. 2022;33:395–405. https://doi.org/10.1016/j.annonc.2022.01.008.

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