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REVIEW ARTICLE

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Application and mechanistic research of novel therapeutic strategies in cisplatin-resistant small cell lung cancer

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ABSTRACT

Introduction: Small cell lung cancer (SCLC) initially responds well to cisplatin-based chemotherapy, but rapid development of drug resistance limits long-term efficacy and subsequent treatment options. Understanding the multifactorial mechanisms of cisplatin resistance is essential for improving patient outcomes. This review synthesizes recent preclinical and clinical advances, focusing on seven key resistance mechanisms and emerging therapeutic strategies, including immunotherapy, targeted therapy, and novel chemotherapeutic agents.

Discussion: Cisplatin resistance in SCLC arises through multiple mechanisms. First, reduction of drug deposition due to altered uptake or enhanced efflux decreases intracellular cisplatin levels. Second, dysregulation of apoptotic pathways, including overexpression of anti-apoptotic proteins such as Bcl-2, allows tumor cells to evade chemotherapy-induced cell death. Third, enhanced DNA damage repair restores cisplatin-induced lesions, limiting cytotoxicity. Fourth, the tumor microenvironment can induce resistance through stromal and immune interactions. Fifth, metabolic adaptations enable tumor cells to survive under chemotherapeutic stress. Sixth, SCLC subtype transitions alter cellular phenotype and chemosensitivity. Seventh, epigenetic changes drive transcriptional programs that confer resistance.

Targeted therapies, such as multidrug resistance (MDR) inhibitors and Bcl-2 family inhibitors, can restore tumor sensitivity but are limited by toxicity and tumor-specific efficacy. Immunotherapy, including PD-1/PD-L1 and CTLA-4 inhibitors, shows potential, although effectiveness is constrained by the immunosuppressive tumor microenvironment and rapid progression. Targeted therapies, such as PARP inhibitors, demonstrate variable efficacy influenced by genetic heterogeneity, biomarker expression, and microenvironmental factors. Novel chemotherapeutic agents offer alternative options for cisplatin-resistant patients. Preclinical and early clinical studies suggest that combining these approaches may further enhance antitumor activity, potentially improving progression-free survival and quality of life. Biomarker-guided strategies may optimize personalized therapy and patient selection.

Conclusion: Cisplatin resistance in SCLC is a complex, multifactorial process involving cellular, molecular, and microenvironmental mechanisms. Integrating mechanistic insights with emerging therapies, including immunotherapy, targeted therapy, and novel chemotherapeutics, offers a promising path to overcome resistance, guiding future research and the development of more effective, personalized treatment strategies for patients with cisplatin-resistant SCLC.

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1. Introduction

SCLC is an aggressive form of lung cancer, accounting for 10–15% of cases and characterized by rapid growth and early metastasis, often diagnosed at an advanced stage [1–3]. Since its first evidence in 1985, cisplatin-etoposide combination chemotherapy has been established as the primary therapeutic regimen for extensive-stage small cell lung cancer (ES-SCLC) [4,5]. However, most patients experience relapse and

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resistance to further treatment [6,7]. While radiotherapy can control local tumours, it fails to prevent distant metastasis [8,9]. As a result, outcomes remain poor, with a median survival of 7–11 months and a 2-year survival rate below 5% [10–12].

Cisplatin is the cornerstone of SCLC treatment, forming DNA adducts that interfere with DNA replication and transcription, ultimately inducing apoptosis [13]. Cisplatin induces the formation of cross-links between DNA strands, which obstructs the activity of DNA helicase and DNA polymerase. This interference results in cell cycle arrest and ultimately leads to cellular apoptosis [14]. The combined use of cisplatin-based regimens has been proven to significantly enhance the initial treatment response rate in SCLC patients [15,16].

Despite the significant efficacy of cisplatin in initial SCLC treatment, resistance emergence is a common and serious problem. The mechanisms are complex and multifactorial, including increased drug efflux, altered apoptosis, enhanced DNA repair, changes in the tumour microenvironment, as well as tumour metabolism, epigenetic regulation and subtype transition. Resistance development significantly reduces treatment efficacy, making it difficult for relapsed patients to achieve effective subsequent treatment options [17]. Resistance not only limits the long-term efficacy of cisplatin but also significantly impacts patient survival and quality of life [10].

This review will delve into the following aspects: (1) the molecular mechanisms of cisplatin resistance, as illustrated in Figure 1; (2) current applications of immunotherapy in SCLC and its potential mechanisms for overcoming resistance, summarized in Figure 2; (3) applications and recent advances of targeted therapy in overcoming cisplatin resistance; (4) research progress on novel chemotherapeutic agents and their roles in mitigating resistance; (5) preclinical advances in overcoming cisplatin resistance, focusing on newly identified molecular targets and epigenetic regulators.

2. Mechanisms of cisplatin resistance

2.1. Mechanisms of drug deposition reduction leading to resistance

Studies have suggested that the drug efflux pumps of SCLC cells are greatly associated with their resistance feature to cisplatin-based therapies. The drug efflux pumps, including members of the ATP-binding

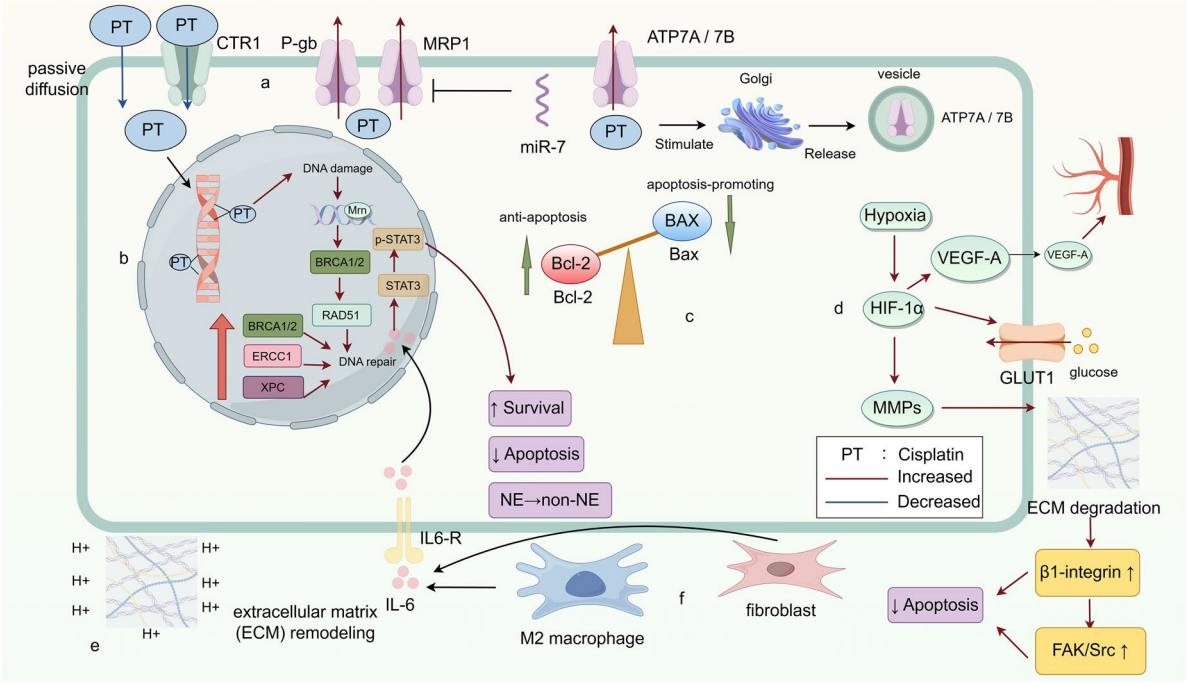

Figure 1. Mechanism of cisplatin resistance in small cell lung cancer.
(a) Decrease in DNA adduct levels. Inward transport: copper transporter 1 (CTR1) and passive diffusion. Outward transport: P-gp, MRP1 and ATP7A/7B.
(b) The DNA damage repair mechanism increases the resistance to cisplatin.
(c) The increase in anti-apoptotic signals and the decrease in pro-apoptotic signals enhance cisplatin resistance.
(d) Hypoxic conditions enhance resistance to cisplatin.
(e) Acidic microenvironment contributes to cisplatin resistance.
(f) Inflammation, tumour stroma and extracellular matrix contribute to cisplatin resistance. (Thanks for Figdraw).

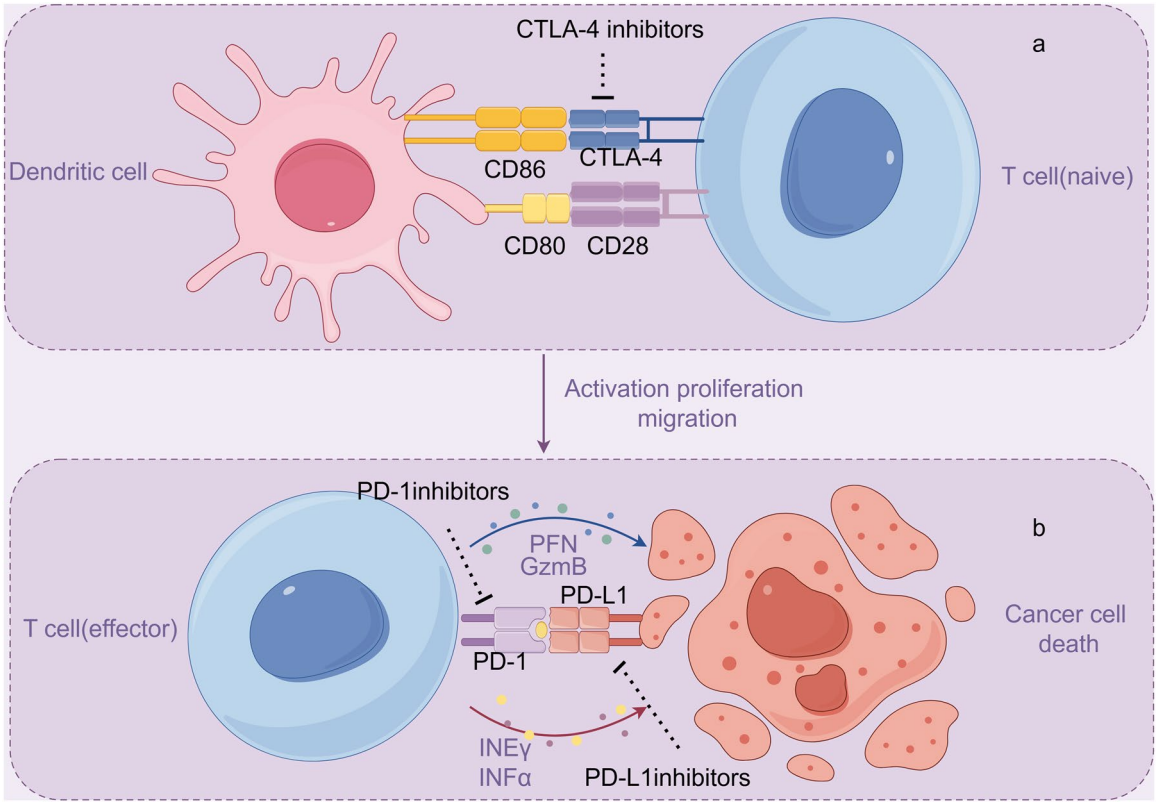

Figure 2. Molecular mechanism of immunotherapy.
(a) CTLA-4 inhibitors impede the binding of CTLA-4 to B7 (encompassing CD80 and CD86), thereby diminishing the transmission of inhibitory signals to T cells, which in turn enhances the activation and proliferation of T cell.
(b) PD-1/PD-L1 inhibitors disrupt the engagement of PD-1 with PD-L1, alleviating the suppression of T cells, and restoring their functionality, enabling them to secrete cytotoxic granules and cytokines to eliminate tumour cells. PFN, perforin; GzmB, GranzymeB; INEγ, Interferon γ; INEα, Interferon α

cassette (ABC) transporter family such as P-glycoprotein (P-gp) and multidrug resistance protein 1 (MRP1), along with copper-transporting ATPases (ATP7A/7B), function to actively pump cisplatin drugs out of the cells, reducing drug accumulation within the cells and consequently diminishing the cytotoxic effects of the drugs [18,19]. Compared to the original cisplatin-sensitive SCLC cells, resistant cells exhibit stronger drug efflux capabilities.

Research has demonstrated that activation of multiple signalling pathways has been implicated in the upregulation of efflux transporters that mediate cisplatin resistance. Specifically, activation of the MCAM–PI3K/Akt–SOX2 signalling axis promotes transcriptional upregulation of MRP1 (ABCC1), enhancing cisplatin efflux and reducing intracellular drug accumulation [20]. In addition, the Nrf2–ARE pathway has been identified as another critical regulatory mechanism of MRP1 expression in multidrug-resistant SCLC cells. Compared with the parental H69 cell line, H69AR cells exhibit significantly higher Nrf2 activity and MRP1 expression, and Nrf2 knockdown markedly decreases MRP1 levels while restoring chemosensitivity. Promoter analysis further identified two antioxidant response elements (ARE1 and ARE2) in the MRP1 gene that directly bind Nrf2, confirming its transcriptional regulation of MRP1 [21]. Cisplatin-resistant SCLC cells can also redistribute ATP7A/B, originally residing in the trans-Golgi network, to more peripheral vesicles in the cytosol, insulating cisplatin away from the nuclei of resistant cells [22,23], thus enhancing cellular drug tolerance. Research has shown that miR-495 can directly attach to the 3′ untranslated region (3′UTR) of ATP7A/B mRNA, leading to a reduction in ATP7A/B expression. This interaction was found to inhance the response of non-small cell lung cancer (NSCLC) cells to cisplatin, highlighting the involvement of ATP7A/B in the process of cisplatin efflux [24]. Similarly, in SCLC, miR-7 has been identified as a critical post-transcriptional regulator of MRP1/ABCC1. Reduced expression of miR-7 in chemoresistant SCLC tissues and H69AR cells is inversely correlated with MRP1 levels, while transfection with miR-7 mimics suppresses MRP1 expression and restores cisplatin sensitivity. Dual-luciferase reporter assays further confirmed that miR-7 directly targets the 3′UTR of MRP1/ABCC1 mRNA, thereby repressing its translation and mitigating drug resistance [25]. Simultaneously,

some scholars propose that the lower accumulation of cisplatin is a result of diminished drug uptake instead of heightened drug efflux [26]. It is widely recognized that passive diffusion and the copper transport protein Ctr1 play key roles in the influx of cisplatin. In mouse fibroblasts, it was further confirmed that cisplatin triggers the rapid degradation of copper membrane transporter CTR1, reducing cisplatin influx and leading to drug resistance [27]. The knockout of the CTR1 gene resulted in *in vivo* resistance to cisplatin, whereas cells with higher levels of CTR1 expression exhibited greater accumulation of cisplatin and, in most instances, heightened sensitivity to the drug [28].

2.2. Mechanisms of resistance through apoptotic pathways

In lung cancer cells that exhibit resistance to cisplatin-based therapies, modifications in apoptotic pathways play an essential part in the formation of this resistance. Cisplatin-based chemotherapeutic agents generally induce cytotoxicity in cancer cells by triggering apoptotic signalling cascades, which encompass both the extrinsic death receptor pathway and the intrinsic mitochondrial pathway [29,30].

Tumour necrosis factor-α (TNFα) ligands attach to their receptor families to create the death-inducing signalling complex (DISC), which in turn activates the extrinsic apoptosis pathway by recruiting and aggregating adaptor proteins and procaspase-8. The intrinsic apoptosis pathway is activated by cellular stress factors such as DNA damage, leading to the release of cytochrome c from mitochondria, which interacts with apoptotic protease activating factor-1 (APAF-1) to trigger and activate precursor caspase-9, forming an active apoptotic complex. The Bcl-2 protein family further regulates the release of cytochrome c from mitochondria, thereby controlling apoptosis that is triggered by DNA damage [31,32].

In SCLC, however, multiple molecular alterations disrupt these apoptotic pathways, leading to pronounced cisplatin resistance. Nearly all SCLCs harbour biallelic inactivation of TP53 and RB1, impairing DNA damage sensing and downstream activation of apoptosis after platinum treatment [33]. Dysregulation of BCL-2 family proteins further attenuates the intrinsic pathway: overexpression of BCL-2 and MCL-1 prevents mitochondrial outer membrane permeabilization, whereas MCL-1 inhibition restores BAK-mediated apoptosis and re-sensitizes resistant SCLC cells to chemotherapy [34]. Reduced expression of pro-apoptotic BAX has similarly been detected in cisplatin-resistant SCLC cells, resulting in suppressed caspase activation and mitochondrial cytochrome c release [35]. In parallel, overexpression of inhibitors of apoptosis proteins (IAPs), particularly survivin (BIRC5), correlates with poor prognosis and decreased sensitivity to chemotherapeutic agents [36]. Additionally, activation of prosurvival signalling cascades such as the PI3K/Akt and TRIB2 pathways further suppresses apoptosis and promotes chemoresistance [37]. At the post-transcriptional level, dysregulation of apoptosis-related microRNAs has also been implicated. For instance, miR-7 downregulation in resistant SCLC cells leads to upregulation of MRP1 (ABCC1), which not only enhances drug efflux but also suppresses cisplatin-induced apoptosis by reducing intracellular drug accumulation and subsequent DNA damage. Conversely, miR-7 restoration restores chemosensitivity by promoting apoptosis [25]. Together, these findings indicate that SCLC cells develop a multifaceted anti-apoptotic phenotype through genetic inactivation, signalling reprogramming and microRNA-mediated regulation, collectively driving cisplatin resistance.

2.3. Mechanisms of resistance through DNA damage repair

Enhanced DNA damage repair mechanisms are central to the acquisition of cisplatin resistance SCLC. Cisplatin induces apoptosis primarily by forming DNA adducts that disrupt replication and transcription [38]. However, resistant SCLC cells adapt by upregulating multiple DNA repair pathways, thereby mitigating drug-induced genotoxicity. Among these, homologous recombination repair (HR) and nucleotide excision repair (NER) play key roles.

For example, HR is a precise mechanism for repairing DNA double-strand breaks, maintaining genetic information integrity by using homologous sequences as templates. When this pathway is enhanced, it can effectively repair DNA damage induced by cisplatin, reducing the drug's lethal effect [39]. BRCA1 and BRCA2, core components of HR, are frequently dysregulated in SCLC. While low BRCA1 expression correlates with initial chemosensitivity, reactivation during relapse enhances HR efficiency and promotes platinum

resistance [40]. Moreover, loss of SLFN11 – an essential determinant of replication stress response – confers tolerance to DNA-damaging agents by allowing continued replication despite unrepaired lesions [41].

The nucleotide excision repair (NER) pathway plays a crucial role in the repair of substantial DNA damage induced by chemical agents. In SCLC, the efficient operation of the NER pathway can remove cisplatin-DNA adducts, reducing their cytotoxicity [42]. At the molecular level, the upregulation of key NER pathway proteins such as ERCC1 and XPC is an important factor in enhancing resistance. These proteins augment the cellular capacity to repair DNA damage induced by cisplatin-based chemotherapeutic agents and their interactions with signalling pathways, such as the PI3K/Akt pathway, further contribute to enhanced cell survival and resistance [43]. Empirical studies have demonstrated that the enhancement of the NER pathway, particularly the activation of ERCC1 and XPC, is crucial for maintaining SCLC cell resistance to cisplatin. Specifically, ERCC1 and XPC facilitate the ability of SCLC cells to evade the cytotoxic effects of cisplatin-based chemotherapeutics by participating in the repair of DNA cross-link damage induced by these drugs [44]. The upregulation of ERCC1 expression in SCLC treatment is positively correlated with weakened chemotherapy effects, highlighting its core role in the chemotherapy resistance mechanism [45].

Targeting the key molecules in these DNA repair mechanisms, such as using BRCA or ERCC1 inhibitors, can potentially reduce SCLC cell resistance to cisplatin and enhance the efficacy of chemotherapy [45,46]. This approach has demonstrated promise in clinical trials for enhancing sensitivity to cisplatin-based chemotherapeutics, thereby offering novel avenues for the management of cisplatin-resistant SCLC.

2.4. Mechanisms of tumour microenvironment-induced resistance

Various elements present in the tumour microenvironment, including hypoxia, acidity, inflammation and alterations in the tumour stroma and extracellular matrix, significantly influence the effectiveness of cisplatin.

2.4.1. Hypoxia

Hypoxia, is a common feature in SCLC, as highlighted by multiple studies. Immunohistochemical investigations have shown that SCLC tumours frequently contain regions of low oxygenation [47]. This hypoxic microenvironment stabilizes hypoxia-inducible factors, enabling cells to adapt and survive under low oxygen.

Analyses of hypoxia-inducible factors in SCLC reveal distinct patterns: HIF-2α is generally absent, whereas HIF-1α is strongly expressed, especially near necrotic tumour areas. Consistently, SCLC cell lines under hypoxic conditions display accumulation of HIF-1α but minimal or no HIF-2α, enabling cell survival even under moderate or severe oxygen deprivation [48]. Clinically, HIF-1α and HIF-2α were detected in 48.9% and 24.4% of patients, respectively. HIF-2α tends to localize around necrotic regions and is associated with tumour progression and distant metastasis, while HIF-1α is more diffusely distributed within tumour nests. Overexpression of either factor has been linked to poorer overall survival [49]. Functional studies demonstrate that HIF-1α upregulation enhances the expression of VEGF-A, MMPs and GLUT1, thereby promoting angiogenesis and metabolic adaptation in SCLC [50]. Targeting HIF-1α with the inhibitor PX-478 significantly suppresses tumour growth and prolongs survival in multiple SCLC xenograft models, confirming HIF-1α as a viable therapeutic target [51]. Clinically, high HIF-1α expression correlates with poor prognosis in SCLC patients, reinforcing its functional relevance [52].

Metabolically, hypoxic SCLC cells primarily depend on glycolysis [53]. This reliance makes lactate transporters, such as monocarboxylate transporter 1 (MCT1), attractive therapeutic targets. In approximately 21% of SCLC tumours, MCT1 and the hypoxia-associated marker carbonic anhydrase IX are expressed without detectable MCT4. Inhibition of MCT1 using AZD3965 significantly suppresses tumour growth and elevates intratumoural lactate levels in hypoxic SCLC cells lacking MCT4, highlighting a potential vulnerability in lactate-dependent metabolic adaptation [54].

2.4.2. Acidity

Although acidic tumour microenvironments have been implicated in chemotherapy resistance in several tumour types, direct evidence in SCLC of extracellular acidity contributing to cisplatin resistance remains

limited. For example, a retrospective cohort of SCLC patients found that alkalization therapy (an alkaline diet and bicarbonate therapy) combined with intravenous vitamin C treatment was associated with longer survival but did not explore the underlying pH-modulated cellular mechanisms [55]. In lung carcinoma models, long modelling of acidosis showed enhanced extracellular matrix remodelling and side-population cell survival under low pH conditions [56]. These findings suggest that acidification may support survival and therapeutic tolerance, but further SCLC-specific mechanistic work – such as pH perturbation in SCLC cell lines or xenografts – is needed.

2.4.3. Inflammation

In the context of SCLC, emerging evidence indicates that the inflammatory tumour microenvironment contributes not only to tumour progression but also to the acquisition of platinum-based chemoresistance by altering specific signalling axes in tumour cells and immune stromal elements. For example, tumour-associated macrophages (TAMs), especially M2-polarized macrophages, accumulate in SCLC and secrete interleukin-6 (IL-6), which in turn activates STAT3 signalling in adjacent SCLC cells, promoting survival, reduced apoptosis and enhanced resistance to chemotherapy [57]. Indeed, TAM-derived IL-6 was shown to drive STAT3 phosphorylation in SCLC cell lines (SBC-3, SBC-5) and a small-molecule inhibitor of STAT3 (the natural compound onionin A) reduced macrophage-induced SCLC proliferation [58].

Furthermore, in SCLC the enrichment of M2-type macrophages ($CD206^+$) correlates with poorer prognosis and is associated with activation of the NF-κB pathway *via* the NLRP6 inflammasome in macrophages, triggered by tumour-derived exosomes [59]. This provides a link between tumour inflammation and metastatic spread, and by extension may contribute to therapy resistance.

While there is still limited direct data on inflammation-driven cisplatin resistance specifically in SCLC, analogous mechanisms from other lung-cancer subtypes point to key candidate pathways. For instance, in NSCLC, up-regulation of NF-κB in cisplatin-resistant lines was documented and pharmacologic NF-κB inhibition restored cisplatin sensitivity [60].

2.4.4. Tumour stroma and extracellular matrix

The tumour stroma and extracellular matrix (ECM) play a pivotal role in shaping the chemoresistant phenotype of SCLC. Fibroblast-rich stroma promotes a transition of tumour cells from the classical neuroendocrine to a non-neuroendocrine phenotype through cytokine-driven activation of JAK2/STAT3 and NOTCH signalling pathways. This phenotypic shift enhances cellular plasticity, suppresses apoptosis and contributes to reduced responsiveness to cytotoxic therapy [61]. In parallel, ECM remodelling alters integrin-mediated adhesion dynamics. Increased expression of β1-integrin and activation of focal adhesion kinase (FAK) and Src signalling sustain tumour cell survival, invasion and metastasis, while attenuating chemotherapy-induced cell death [62]. Impaired ubiquitin-mediated degradation of β1-integrin further amplifies these effects, maintaining persistent FAK/Src signalling and promoting resistance. Moreover, cancer-associated fibroblasts (CAFs) communicate with SCLC cells *via* exosomal transfer of long noncoding RNAs that regulate the miR-15a-5p/CCNE1 axis, thereby facilitating cell-cycle progression and cisplatin tolerance [63]. Together, stromal fibroblasts and ECM remodelling cooperate to establish a protective microenvironment that promotes tumour adaptability, survival and therapeutic resistance. Targeting the ECM–integrin axis and CAF-derived signalling pathways offers a promising strategy to overcome chemoresistance in SCLC.

2.5. Tumour metabolism

Metabolic reprogramming is a recurring and functionally important feature of cisplatin-resistant lung cancer and contributes to therapeutic failure in SCLC. Cisplatin-resistant cells frequently display elevated reactive oxygen species (ROS) together with a metabolic switch away from strict glycolytic dependence toward increased mitochondrial oxidative phosphorylation (OXPHOS) and alternative substrate utilization. They often exhibit enhanced glutamine uptake and oxidation, which supports ATP production for energy-intensive resistance mechanisms such as drug efflux and DNA repair while maintaining redox

homeostasis [64]. In several tumour models, acquired cisplatin resistance is also associated with decreased de novo lipogenesis accompanied by increased uptake and β-oxidation of exogenous fatty acids. Blocking fatty acid oxidation (FAO) resensitizes resistant cells to platinum both *in vitro* and *in vivo*, indicating FAO as a targetable metabolic vulnerability [65]. In SCLC, mitochondrial quality control mechanisms (such as mitophagy) are up-regulated in chemoresistant cells, implicating altered mitochondrial metabolism in resistance phenotypes [66]. Finally, metabolic reprogramming generates therapeutic liabilities because pharmacologic or genetic inhibition of glutamine metabolism, FAO, or components of OXPHOS selectively impairs cisplatin-resistant cells in preclinical studies [67]. These findings provide a rationale to combine metabolic inhibitors with platinum-based chemotherapy to overcome or prevent resistance in SCLC.

2.6. SCLC subtype transition

SCLC exhibits pronounced lineage plasticity, in which tumours transition between neuroendocrine (NE) and non-neuroendocrine (non-NE) states. This plasticity contributes directly to therapeutic failure by generating cell populations with distinct survival programs and drug sensitivities. Experimental models demonstrate that activation of Notch signalling and cooperating oncogenic drivers can induce a shift from the NE to the non-NE phenotype, producing distinct cells that display reduced chemosensitivity and an increased propensity for vasculogenic mimicry and dissemination [68]. Transcriptional control underlies these shifts. Suppression of NE lineage factors leads to the emergence of a SOX9-positive neural-crest-like program, while disruption of lineage-defining transcriptional networks remodels cell identity toward states with enhanced stress tolerance and altered cell-cycle control [69]. Longitudinal profiling of preclinical and clinical samples reveals that subtype composition can evolve during disease progression or after therapy, with MYC activation and downstream pathway changes driving sequential transitions among subtype programs [70]. Functionally, non-NE states exhibit distinct interactions with the tumour microenvironment and immune milieu, and the coexistence or cooperation between NE and non-NE compartments promotes metastatic outgrowth [71]. Collectively, these primary-research findings support a model in which dynamic subtype transition is a mechanistic contributor to SCLC relapse and indicate that therapeutic strategies should account for lineage plasticity to prevent or overcome resistance.

2.7. Epigenetic changes

Epigenetic alterations are fundamental to the development and progression of SCLC, influencing lineage identity, tumour heterogeneity and therapeutic resistance. Recent genome-wide methylation analyses have demonstrated that tumour and circulating cell-free DNA methylation profiles accurately classify molecular SCLC subtypes and reflect treatment-induced evolution, highlighting DNA methylation as both a mechanistic driver and a potential biomarker [72]. Aberrant activation of the polycomb repressive complex 2, particularly through overexpression of EZH2, promotes H3K27me3-mediated repression of differentiation and DNA-repair genes; inhibition of EZH2 restores gene expression and enhances chemosensitivity in SCLC models [72]. Moreover, loss or functional inactivation of SWI/SNF chromatin-remodelling components, especially SMARCA4, disrupts enhancer accessibility and facilitates transitions between neuroendocrine and non-neuroendocrine phenotypes, contributing to intratumoural plasticity and drug tolerance [73]. Dysregulated expression of microRNAs, including miR-1 (which attenuates the growth and metastasis of SCLC through the CXCR4/FOXM1/RRM2 axis) and miR-375, has been shown to regulate key oncogenic pathways associated with proliferation, metastasis and chemoresistance in experimental models of SCLC [74]. Together, these findings underscore that DNA methylation dynamics, histone modifications and non-coding RNA perturbations cooperate to shape the SCLC epigenome, offering potential targets for epigenetic-based therapeutic interventions.

3. The novel therapeutic approaches

3.1. Immunotherapy

Immunotherapy utilizes the patient's immune system to recognize and target cancer cells by stimulating or augmenting the immune response. Prominent forms of immunotherapy encompass immune

Table 1. Clinical trials of immunotherapy for cisplatin-resistant small cell lung cancer.

Phase	Study	Treatment arms	Patients (n)	ORR (%)	PFS (months)	OS (months)
First line						
II	NCT01331525	Ipilimumab + carboplatin + cisplatin; maintained with ipilimumab	42	72.4	6.9 (95% CI: 5.5–7.9)	17 (95% CI: 7.9–24.3)
III	NCT01450761	Ipilimumab + etoposide + platinum vs. placebo + etoposide + platinum	954	62 vs. 62	4.6 vs. 4.4 (HR: 0.85; 95% CI: 0.75–0.97; $p = 0.016$)	11.0 vs. 10.9 (HR: 0.94; 95% CI: 0.81–1.09; $p = 0.38$)
III	Impower133	Atezolizumab + carboplatin + etoposide vs. placebo + etoposide + platinum; maintained with atezolizumab vs. placebo	403	60.2 vs. 64.4	5.2 vs. 4.3 (HR: 0.77; 95% CI: 0.62–0.96; $p = 0.02$)	12.3 vs. 10.3 (HR: 0.70; 95% CI: 0.54–0.91; $p = 0.007$)
III	NCT04256421	Tiragolumab + atezolizumab + CE vs. placebo + atezolizumab + CE; maintenance: tiragolumab + atezolizumab vs. placebo + atezolizumab.	490	73.5 vs. 66.7	5.4 vs. 5.6 (HR = 1.11; $p = 0.3504$)	13.1 vs. 13.1 (HR = 1.14; $p = 0.2859$)
III	KEYNOTE-604	Pembrolizumab + etoposide + platinum vs. placebo + etoposide + platinum	453	70.6 vs. 61.8	13.6 vs. 3.1 (HR: 0.75; 95% CI: 0.61–0.91; $p = 0.0023$) 12-month PFS	22.5 vs. 11.2 (HR: 0.80; 95% CI: 0.64–0.98; $p = 0.0164$) 24-month OS
III	NCT03043872	Durvalumab + platinum-etoposide vs. platinum-etoposide alone	537	68 vs. 58	5.1 vs. 5.4 (HR: 0.78; 95% CI: 0.65–0.94)	13 vs. 10.3 (HR: 0.73; 95% CI: 0.59–0.91; $p = 0.0047$)
III	NCT03703297	Durvalumab vs. placebo	530	30.3 vs. 32	55.9 vs. 33.4 (HR 0.73)	16.6 vs. 9.2 (HR 0.76)
Maintenance						
II	NCT02359019	Pembrolizumab	45	11.1	1.4	9.6
III	CheckMate 451	Nivolumab + ipilimumab vs. nivolumab vs. placebo	789	0.09 vs. 0.11 vs. 0.04	1.7 vs. 1.9 vs. 1.4 (HR: 0.72; 95% CI: 0.60–0.87) (HR: 0.67; 95% CI: 0.56–0.81)	9.2 vs. 10.4 vs. 9.6 (HR: 0.92; 95% CI: 0.75–1.12; $p = 0.37$) (HR: 0.84; 95% CI: 0.69–1.02)
Relapsed						
I/II	CheckMate 032	Nivolumab 3 mg/kg vs. nivolumab 1 mg/kg + ipilimumab 3 mg/kg vs. nivolumab 3 mg/kg + ipilimumab 1 mg/kg	213	10 vs. 23 vs. 19	1.4 vs. 2.6 vs. 1.4	4.4 vs. 7.7 vs. 6.0
IB	KEYNOTE-028	Pembrolizumab	24	33.3	1.9	9.7

checkpoint inhibitors (ICIs), cancer vaccines and adoptive cell therapies [75]. SCLC has historically been recognized as an immunogenic neoplasm. Immune-mediated paraneoplastic syndromes, including Lambert-Eaton myasthenic syndrome and encephalomyelitis, manifest in approximately 15–20% of patients with SCLC. These syndromes are linked to autoimmune responses targeting antigens that are expressed by both SCLC cells and normal neuronal tissues, such as HuD, HuC and Hel-N1 [76,77]. SCLC is distinguished by a high tumour mutation burden (TMB), closely linked to the carcinogenic effects of extensive tobacco exposure [78,79], which results in the exposure of numerous potentially immunogenic neoantigens. Therefore, immunotherapy for SCLC could theoretically target these characteristics.

The introduction of immune checkpoint inhibitors has significantly transformed the conventional treatment protocols for various solid tumours, including SCLC. The predominant immune checkpoint inhibitors utilized in clinical practice are those targeting PD-1, PD-L1 and CTLA-4, which have proved promising efficacy in clinical studies, as summarized in Table 1.

3.1.1. Ipilimumab

Due to the role of CTLA-4 in regulating T cell activation at lymphoid sites [80], CTLA-4 became one of the earliest studied immune co-inhibitory targets [81]. Ipilimumab is a human monoclonal antibody targeting CTLA-4, blocking its interaction with the ligands CD80 and CD86. This mechanism facilitates the activation and growth of T cells [82]. Early clinical trials showed durable inhibitory effects of Ipilimumab in various tumour types [83–85].

The CheckMate 032 trial investigated the efficacy of combining ipilimumab and nivolumab in patients with relapsed SCLC. Among the 61 patients who were treated with nivolumab at a dosage of 1 mg/kg

in conjunction with ipilimumab at 3 mg/kg, 23% achieved an objective response rate (ORR), significantly higher than the 10% in the nivolumab 3 mg/kg monotherapy group (98 patients). Nevertheless, the occurrence of grade 3 or higher adverse events was elevated in the group receiving combination therapy, with a rate of 30% reported [86]. The findings indicate that although combination therapy demonstrates a degree of efficacy, it is imperative to thoroughly evaluate safety considerations.

An open-label clinical trial examined the efficacy of ipilimumab in conjunction with carboplatin and etoposide as a first-line therapeutic approach aimed at enhancing progression-free survival (PFS) and overall survival (OS) in patients diagnosed with ES-SCLC. A total of 42 patients were enrolled in this phase II clinical trial. Among these participants, 72.4% demonstrated an objective response, while 84.8% exhibited an immune-related objective response. The median PFS was recorded at 6.9 months (95% CI: 5.5–7.9), and the median immune-related PFS was noted to be 7.3 months (95% CI: 5.5–8.8). Furthermore, the median OS was determined to be 17.0 months (95% CI: 7.9–24.3) [87]. These data preliminarily demonstrate the potential efficacy of ipilimumab combined with chemotherapy.

A comprehensive phase III clinical trial, encompassing 1,132 participants, examined the effectiveness of ipilimumab in conjunction with etoposide and cisplatin chemotherapeutic agents in patients with cisplatin-resistant SCLC. Results showed that both groups had the same ORR of 62%. The median OS in the ipilimumab cohort was recorded at 11.0 months, in contrast to 10.9 months in the control group (HR 0.94, 95% CI: 0.81–1.09; $p = 0.3775$), indicating that the inclusion of ipilimumab did not result in a statistically meaningful improvement in OS. However, the median PFS exhibited a modest improvement, with values of 4.6 months for the ipilimumab group compared to 4.4 months for the control group (HR 0.85, 95% CI: 0.75–0.97) [88]. These results suggest that while ipilimumab offers some improvement, overall efficacy requires further validation.

In the STIMULI trial, the administration of ipilimumab and nivolumab as maintenance treatment after initial chemotherapy did not demonstrate a statistically significant enhancement in PFS or OS among patients diagnosed with limited-stage SCLC. The trial results indicated that the median PFS was 14.5 months for the observation group, while it was 10.7 months for the control group. Additionally, the median OS for the observation group was reported as 32.1 months, whereas the experimental group had not yet reached a median OS value [89]. These results indicate that combined maintenance therapy has limited effectiveness in improving patient outcomes. The CheckMate 451 study conducted a further assessment of the effectiveness of the combination of nivolumab and ipilimumab as maintenance therapy following initial chemotherapy in patients with ES-SCLC. A total of 789 patients participated in this study and were randomly assigned in a 1:1:1 ratio to receive either the combination of nivolumab and ipilimumab, nivolumab monotherapy, or a placebo. Results showed ORRs of 0.09, 0.11 and 0.04; PFS of 1.7, 1.9 and 1.4 months (HR:0.72; 95% CI: 0.60–0.87) (HR:0.67; 95% CI: 0.56–0.81); and median OS of 9.2, 10.4 and 9.6 months (HR:0.92; 95% CI: 0.75–1.12; $p = 0.37$) (HR:0.84; 95% CI: 0.69 to 1.02), respectively. Results did not demonstrate a statistically significant enhancement in OS and PFS with combined therapy [90]. This study further underscores the challenges and limitations of combination therapy in clinical application.

3.1.2. Atezolizumab

Atezolizumab is a humanized monoclonal antibody that specifically binds to programmed death ligand 1 (PD-L1), which inhibits T cell activation and growth by interacting with the PD-1 receptor [91]. The phase III IMpower133 trial was the first to demonstrate a significant survival advantage with immune checkpoint inhibition in ES-SCLC. In this study, 403 previously untreated patients were randomized to receive atezolizumab or placebo in combination with carboplatin and etoposide (CP/ET), followed by maintenance therapy. The initial analysis reported an ORR of 60.2% in the atezolizumab group and 64.4% in the control group, with a median OS of 12.3 months versus 10.3 months, respectively (HR = 0.70; 95% CI: 0.54–0.91; $p = 0.007$). Median PFS was 5.2 months versus 4.3 months (HR = 0.77; 95% CI: 0.62–0.96; $p = 0.02$) [12]. Updated data confirmed consistent benefit, with an 18-month OS rate of 34.0% in the atezolizumab arm compared to 21.0% in the placebo arm, irrespective of PD-L1 expression or blood tumour mutational burden (bTMB) [92]. A comprehensive safety analysis revealed comparable incidences of grade 3–4 and serious adverse events between both groups [93].

Long-term outcomes were subsequently assessed in the IMbrella A extension study, which included 18 rollover patients from IMpower133 who continued atezolizumab therapy. With a median follow-up of

59.4 months, the 3-, 4- and 5-year OS rates were 16% (95% CI: 11–21%), 13% (8–18%) and 12% (7–17%), respectively. Only three patients (16.7%) experienced serious adverse events, and a single grade 2 hypothyroidism event was reported [94]. Despite the limited sample size, these data provide the first evidence of 5-year survival durability in ES-SCLC treated with first-line chemoimmunotherapy.

Given the established benefit of PD-L1 inhibition, attention has turned to dual immune checkpoint blockade. Tiragolumab, a fully human anti-TIGIT antibody [95], was evaluated in combination with atezolizumab and chemotherapy in the phase III SKYSCRAPER-02 trial. In this study, 490 untreated ES-SCLC patients were randomized to receive tiragolumab or placebo plus atezolizumab and CP/ET, followed by maintenance therapy. However, the trial did not demonstrate additional efficacy with the addition of tiragolumab. Median PFS was 5.4 months versus 5.6 months (HR = 1.11; $p = 0.3504$), and median OS was 13.1 months in both groups (HR = 1.14; $p = 0.2859$). The safety profile remained acceptable, with immune-related adverse events observed in 54.4% of tiragolumab-treated and 49.2% of control patients, and grade 3–4 events in 7.9% and 7.7%, respectively [96].

In summary, atezolizumab combined with carboplatin and etoposide remains the standard first-line therapy for ES-SCLC, providing durable survival benefits with manageable toxicity. Although tiragolumab failed to improve outcomes beyond PD-L1 inhibition, its good tolerability warrants further study of TIGIT blockade in selected populations or in combination strategies to overcome immune resistance.

3.1.3. Pembrolizumab

Pembrolizumab is a humanized monoclonal antibody designed to targets the PD-1 receptor, thereby obstructing the negative signalling that happens when PD-1 interacts with its ligands [97]. The KEYNOTE-028 trial, a Phase Ib study, assessed the effectiveness and safety of pembrolizumab in a cohort of 24 patients diagnosed with PD-L1-positive recurrent SCLC. The findings revealed that treatment with pembrolizumab yielded an ORR of 33%. Additionally, the median PFS was recorded at 1.9 months (95% CI: 1.7–5.9 months), while the median OS was observed to be 9.7 months (95% CI: 4.1 months to not reached). The adverse events that were reported most often included fatigue, weakness and coughing. All participants experienced treatment-related adverse events, with two individuals encountering grade 3–5 adverse events: one patient exhibited grade 3 elevated bilirubin levels, while another presented with grade 3 fatigue and grade 5 colitis. Notably, fewer than 10% of participants reported grade 3–5 treatment-related adverse events [98]. This trial indicates that pembrolizumab has a safety profile consistent with other tumour types and demonstrates encouraging anti-tumour efficacy in patients with pre-treated SCLC.

A larger Phase II clinical trial involving 45 participants assessed the effectiveness of pembrolizumab as a maintenance therapy subsequent to treatment with cisplatin and etoposide in individuals diagnosed with ES-SCLC. The findings indicated that, irrespective of PD-L1 expression status, the median PFS for the overall cohort was 1.4 months (95% CI: 1.3–2.8), with a 1-year PFS rate of 13%. The median overall OS was recorded at 9.6 months (95% CI: 7.0–12), accompanied by a 1-year OS rate of 37%. The ORR was determined to be 11.1%. Among the eight patients exhibiting PD-L1 expression at the stromal interface, the median PFS and OS were 6.5 months (95% CI: 1.1–12.8) and 12.8 months (95% CI: 1.1–17.6). Conversely, among the 12 patients with PD-L1-negative tumour stroma, the median PFS and OS were significantly lower, at 1.3 months (95% CI: 0.6–2.5) and 7.6 months (95% CI: 2.0–12.7) [99].

Pembrolizumab has been evaluated in conjunction with etoposide and cisplatin as a first-line therapeutic option for ES-SCLC. The randomized, double-blind, phase III KEYNOTE-604 trial investigated the effectiveness of pembrolizumab combined with etoposide and cisplatin (EP) versus a placebo combined with EP in previously untreated patients with ES-SCLC. A total of 453 participants were enrolled, with 228 allocated to the pembrolizumab plus EP cohort and 225 to the placebo plus EP cohort. The findings revealed an ORR of 70.6% in the pembrolizumab plus EP group, compared to 61.8% in the placebo plus EP group. The 12-month PFS estimates were 13.6% for the pembrolizumab plus EP group and 3.1% for the placebo plus EP group, indicating a statistically significant enhancement in PFS with pembrolizumab plus EP (HR 0.75; 95% CI: 0.61–0.91; $p = .0023$). The 24-month OS estimates were 22.5% for the pembrolizumab plus EP group and 11.2% for the placebo plus EP group. Although the combination of pembrolizumab and EP extended OS, it did not achieve statistical significance (HR, 0.80; 95% CI: 0.64–0.98; $p = .0164$). The most frequently reported adverse events included neutropenia, anaemia, nausea and

alopecia, with no unexpected toxicities noted [100]. These results underscore the potential of pembrolizumab in conjunction with EP to enhance the prognosis for patients with ES-SCLC.

3.1.4. Durvalumab

Durvalumab is a human monoclonal antibody that selectively binds to PD-L1, with the objective of inhibiting the interaction between PD-L1 and its receptors, PD-1 and CD80 [101]. A phase III clinical trial published in The Lancet in 2019 evaluated the effectiveness of durvalumab in conjunction with cisplatin-etoposide as a first-line treatment for ES-SCLC. In this trial, 268 participants were allocated to receive a treatment regimen consisting of durvalumab and cisplatin-etoposide, while 269 participants were assigned to the cisplatin-etoposide monotherapy group. The findings indicated an ORR of 68% in the durvalumab plus cisplatin-etoposide cohort, compared to 58% in the cisplatin-etoposide group. Furthermore, the median OS was reported as 13.0 months (95% CI: 11.5–14.8) for the durvalumab plus cisplatin-etoposide group, in contrast to 10.3 months (95% CI: 9.3–11.2) for the cisplatin-etoposide group. Grade 3 or 4 adverse events were reported in 163 (62%) of the 268 patients treated with durvalumab in combination with cisplatin-etoposide, as well as in 166 (62%) of the 269 patients receiving cisplatin-etoposide alone [102]. These results indicate that the incorporation of durvalumab into first-line cisplatin-etoposide chemotherapy significantly enhances OS outcomes for patients with ES-SCLC, while the safety profile aligns with previously established data.

A midterm analysis of patient-reported outcomes (PROs) from the CASPIAN trial evaluated the addition of durvalumab to etoposide-platinum (EP) as first-line therapy for ES-SCLC. Among 261 patients receiving durvalumab plus EP and 260 on EP alone, durvalumab delayed deterioration of key symptoms (cough HR 0.78; dyspnoea 0.79; chest pain 0.76; fatigue 0.82; appetite loss 0.70), improved functional abilities and maintained better overall health-related quality of life, suggesting enhanced survival without compromising QoL [103].

An exploratory CASPIAN analysis assessed PD-L1 expression and tissue tumour mutational burden (tTMB) as potential predictors of response. The OS benefit of durvalumab plus EP was comparable across PD-L1 expression levels (HRs 0.47–0.79), and no interaction was observed between tTMB and treatment effect (durvalumab plus EP vs. EP, $p = 0.916$) [104], indicating that first-line durvalumab efficacy is independent of PD-L1 or tTMB status.

Beyond ES-SCLC, the phase III ADRIATIC trial evaluated durvalumab as adjuvant therapy after concurrent platinum-based chemoradiotherapy in limited-stage SCLC. Durvalumab significantly prolonged OS (median 55.9 vs. 33.4 months; HR 0.73) and PFS (16.6 vs. 9.2 months; HR 0.76) compared with placebo, with a manageable safety profile, supporting its use in the adjuvant setting [105].

3.2. Targeted therapy

Targeted therapy represents a therapeutic approach that aims to impede the proliferation and dissemination of cancer cells by specifically targeting molecules and signalling pathways that are unique to tumour cells. Compared to conventional chemotherapy, targeted therapy inflicts less damage on normal cells and is associated with fewer side effects. Common targeted therapeutic agents include PARP inhibitors, angiogenesis inhibitors and DLL3 inhibitors [106]. These therapeutic strategies have demonstrated varying degrees of efficacy in clinical trials, offering new hope and treatment options for patients with cisplatin-resistant SCLC. A summary of the current targeted therapeutic agents and their clinical outcomes is presented in Table 2.

3.2.1. DLL3 inhibitor

In SCLC, inactivating mutations are commonly observed in the key components of the Notch signalling pathway. Furthermore, the overexpression of delta-like protein 3 (DLL3), a significant negative regulator of Notch signalling, is prevalent in the majority of SCLC tumours, while its expression is minimal in healthy adult tissues [107]. The dysregulation of the Notch pathway plays a critical role in the tumourigenesis, progression and chemoresistance of SCLC, with studies indicating that its inhibition is effective in *in vivo* animal models [108]. Therefore, DLL3 emerges as a potential therapeutic target for SCLC that is resistant to cisplatin-based treatments.

Table 2. Clinical trials of targeted therapy for cisplatin-resistant small cell lung cancer.

Phase	Study	Treatment arms	Patients (n)	ORR (%)	PFS (months)	OS (months)
First line						
II	ECOG-ACRIN 2511	Veliparib + etoposide + cisplatin vs. placebo + etoposide + cisplatin	128	71.9 vs. 65.6 ($p = 0.57$)	6.1 vs. 5.5 (HR: 0.75; $p = 0.06$)	10.3 vs. 8.9 (HR: 0.83; $p = 0.17$)
II	GOIRC-01-2019 CeLEBrATE	Carboplatin + etoposide + bevacizumab + atezolizumab	53	83.3	6.2(95% CI: 5.4-6.6)	12.9 (95% CI: 11.6–17.5)
II	NCT05001412	Camrelizumab + apatinib + EC	40	88.9 (95% CI: 73.9%-96.9%)	7.3 (95% CI: 6.6–9.2)	17.3 (95% CI: 11.8-not reached)
II/III	NCT00930891	Bevacizumab + induction chemotherapy vs. induction chemotherapy	74	91.9 vs. 89.2	5.3 vs. 5.5 (HR: 1.1; 95% CI: 0.7–1.7; $p = 0.82$)	11.1 vs. 13.3 (HR: 0.8; 95% CI: 0.5–1.3; $p = 0.35$)
III	NCT04234607	Benmelstobart + anlotinib + etoposide/carboplatin(EC) vs. anlotinib + EC vs. EC	738	81.3 vs. 81.2 vs. 66.8	6.9 vs. 5.6 vs. 4.2	19.3 vs. 13.3 vs. 11.9
Maintenance						
IB	NCT06211036	Tarlatamab with atezolizumab or durvalumab	88	24	5.6(3.5–9.0)	25.3(20.3-NE)
Relapsed						
I	NCT01901653	Rovalpituzumab tesirine	74	18 (60 assessable patients)	3.1 (95% CI: 2.5–8.3)	4.6 (95% CI: 3.9–7.1)
I	NCT03319940	Tarlatamab	107	23.4	3.7 (95% CI: 41.5–61.2)	13.2 (95% CI: 10.5-not reached)
I/II	NCT 02446704	Olaparib + temozolomide	50	41.7 (48 assessable patients)	4.2 (95% CI: 2.8–5.7)	8.5 (95% CI: 5.1–11.3)
II	NCT02674568	Rovalpituzumab tesirine 0.3 mg/kg	339	12.1	3.5 (95% CI: 3.0–3.9)	5.6 (95% CI: 4.9–6.1)
II	ALTER1202	Anlotinib vs. placebo	120	71.6 vs. 13.2	4.1 vs. 0.7 (HR: 0.19; 95% CI: 0.12–0.32; $p < 0.0001$)	7.3 vs. 4.9 (HR: 0.53; 95% CI: 0.34–0.81; $p = 0.0029$)
II	ChiCTR2100049390	Sintilimab + anlotinib + nab-paclitaxel	25	60	6.0 (95% CI: 5.4–9.7)	13.4 (95% CI: 11.8-NR)
II	NCT03732846	Anlotinib	45	11	4.1 (95% CI: 2.4–5.8)	6.1 (95% CI: 2.2–10.0)
II	NCT02945852	Apatinib 500 mg per day	40	17.5	3.0 (95% CI: 2.2–3.7)	5.8 (95% CI: 3.7–7.9)
II	NCT03547804	Apatinib	29	27.6	7.4 (95% CI: 5.39–9.33)	14.2 (95% CI: 9.52–18.80)
II	NCT03009682 + NCT0328607	Olaparib vs. olaparib and ceralasertib	41	6.7 vs. 3.8	1.4 vs. 2.8	8.6 vs. 7.2
II	NCT01638546	Veliparib + temozolomide vs. placebo + temozolomide	104	39 vs. 14 ($p = 0.016$)	3.8 vs. 2.0 ($p = 0.39$)	8.2 vs. 7.0 ($p = 0.50$)
III	NCT05740566	Tarlatamab vs. chemotherapy (topotecan, lurbinectedin, or amrubicin)	509	35 vs. 20	5.3 vs. 4.3 (HR: 0.71; 95% CI: 0.59–0.86; $p = 0.002$)	13.6 vs. 11.1 (HR: 0.6; 95% CI: 0.47–0.77; $p < 0.001$)

Rovalpituzumab tesirine (Rova-T, SC16LD6.5) is an antibody-drug conjugate specifically engineered to target the DLL3 protein. *In vivo* studies demonstrate that Rova-T interacts with DLL3 receptors located on the surface of tumour cells. Following this binding, ROVA-T undergoes endocytosis, allowing it to enter the cell and subsequently induce the release of its cytotoxic payload in the form of pyrrolobenzodiazepine (PBD) dimers. The PBD dimers migrate to the cell nucleus, where they cause DNA damage, subsequently facilitating the process of apoptosis [109]. A phase I trial in 2017 involving 74 patients with relapsed SCLC showed that Rova-T achieved objective responses in 18% of evaluable patients, with median PFS and OS of 3.1 and 4.6 months, respectively [110]. However, the phase II TRINITY study demonstrated limited efficacy, with ORRs of 12.4–14.3% in DLL3-positive patients, and significant toxicities including fatigue, photosensitivity, pleural effusion and peripheral oedema; grade 3–4 adverse events occurred in 54%, and 10% experienced grade 5 events [111,112]. A maintenance trial was terminated early due to no survival benefit and higher toxicity [113]. Although Rova-T failed due to its specific and substantial toxicities, DLL3 remains a critical target in SCLC.

Recent advances have shifted focus to DLL3-targeted T-cell engaging strategies. Tarlatamab (AMG 757) is a first-in-class bispecific T-cell engager (BiTE) that binds both DLL3 and CD3, directing T-cell mediated cytotoxicity toward DLL3-expressing tumour cells [108]. In a 2023 phase I study of 107 heavily pretreated relapsed/refractory SCLC patients, tarlatamab monotherapy achieved an ORR of 23.4%, a disease control rate of 51.4% and a median duration of response of 12.3 months. Median PFS and OS were 3.7 and 13.2 months, respectively [114]. Building on these results, a recent multinational, open-label phase III trial (DeLLphi-304) evaluated tarlatamab versus standard chemotherapy (topotecan, lurbinectedin, or amrubicin) in 509 patients with SCLC whose disease progressed during or after platinum-based chemotherapy. Tarlatamab significantly improved OS compared with chemotherapy (median OS 13.6 vs. 8.3 months; HR 0.60; $p < 0.001$), and also demonstrated superior PFS and patient-reported outcomes. Notably, grade ≥3 adverse events and treatment discontinuations due to toxicity were less frequent with tarlatamab than chemotherapy (54% vs. 80% and 5% vs. 12%, respectively)[115].

In 2025, the DeLLphi-303 study evaluated tarlatamab in combination with a PD-L1 inhibitor (atezolizumab or durvalumab) as first-line maintenance therapy in ES-SCLC patients who had not progressed after standard platinum-etoposide plus PD-L1 inhibitor chemotherapy. Among 88 patients, the grade 3–4 adverse events included hyponatremia (10%), anaemia (8%) and neutropenia (7%). Serious adverse events occurred in 57% of patients, most commonly cytokine release syndrome (24%), fever (7%), immune effector cell-associated neurotoxicity syndrome (5%) and pneumonia (5%). Importantly, no treatment-related deaths were reported. Median OS was 25.3 months (95% CI: 20.3–not estimable), highlighting both manageable safety and promising anticancer activity [116]. Overall, although early studies of Rova-T were unsuccessful, novel DLL3-targeted strategies – particularly tarlatamab and its combination with PD-L1 inhibitors – have demonstrated greater potential in both efficacy and tolerability, offering a new therapeutic avenue for cisplatin-resistant SCLC.

3.2.2. Anti-angiogenic drugs

Anti-angiogenic agents predominantly function by inhibiting vascular endothelial growth factor (VEGF) and its associated receptors VEGFR. VEGF is a key signalling protein that facilitates angiogenesis, and by binding to VEGF receptor tyrosine kinases (VEGFR1–3), VEGF activates VEGF signalling in endothelial cells, thereby enhancing tumour vascularization [117]. By inhibiting this process, anti-angiogenic drugs can deprive the tumour of its nutrient supply, thus inhibiting its growth. In SCLC, common anti-angiogenic drugs include bevacizumab, anlotinib and apatinib. These drugs can be used alone or in combination with chemotherapy to enhance therapeutic efficacy.

3.2.2.1. Bevacizumab. Bevacizumab, a monoclonal antibody that targets angiogenesis, impedes tumour growth and metastasis in small cell lung cancer by obstructing the VEGF signalling pathway, which in turn inhibits the formation of new blood vessels [118,119]. A number of investigations have shown that the administration of bevacizumab in conjunction with carboplatin can enhance both median survival and overall survival rates in patients with NSCLC. However, subsequent efforts to implement this combination therapy in SCLC, especially among patients with ES-SCLC, have not yielded any notable enhancements in median PFS or median OS [120]. Furthermore, bevacizumab use is associated with severe adverse events; for example, an increased risk of tracheoesophage [121]. In a study of recurrent

SCLC, 34 patients received paclitaxel plus bevacizumab followed by bevacizumab maintenance after 4–6 cycles, yielding an ORR of 18.1%, median PFS of 14.7 weeks (95% CI: 7–15.7) and median OS of 30 weeks (95% CI: 18–48), indicating no substantial improvement over paclitaxel alone [122]. A systematic review and meta-analysis of seven phase II/III trials involving 1,322 patients found that bevacizumab modestly improved PFS (HR = 0.73, 95% CI: 0.42–0.97, $p = 0.04$) but did not significantly enhance OS (HR = 0.99, 95% CI: 0.88–1.12, $p = 0.91$) or ORR (OR = 1.12, 95% CI: 0.85–1.47, $p = 0.41$), and 1- and 2-year survival rates showed no clear benefit [123]. Subgroup analyses suggested a potential PFS benefit (HR = 0.74, 95% CI: 0.59–0.92, $p = 0.007$) and a trend toward improved OS (HR = 0.84, 95% CI: 0.67–1.06, $p = 0.14$) [124]. Overall, bevacizumab may provide limited benefit in select SCLC patients, but its broad incorporation into standard chemotherapy regimens has not demonstrated consistent long-term survival improvements, and risks such as constipation and thrombosis warrant careful consideration [123].

Notably, the 2025 CeLEBrATE study evaluated the combination of carboplatin, etoposide, bevacizumab and the PD-L1 inhibitor atezolizumab as first-line treatment in patients with ES-SCLC. This Italian multicentric single-arm phase II trial enrolled 53 patients (median age 65 years), who received four to six cycles of induction therapy consisting of carboplatin (AUC 5 ml/min), etoposide (100 mg/m^2), bevacizumab (7.5 mg/kg) and atezolizumab (1,200 mg) every 3 weeks, followed by maintenance with bevacizumab and atezolizumab. At a median follow-up of 23.4 months (95% CI: 21.1–26.0), the 1-year OS rate was 61.8% (90% CI 50.7–72.8%), median OS was 12.9 months (95% CI: 11.6–17.5), median PFS was 6.2 months (95% CI: 5.4–6.6) and the ORR was 83.3% (95% CI: 69.8–92.5%). Grade 3–4 adverse events occurred in 64.2% of patients, with dose reductions and delays observed during both induction and maintenance phases, and 35.8% of patients experienced treatment-related serious adverse events [125].

Overall, these findings suggest that while bevacizumab alone has shown limited and inconsistent benefits in SCLC, its combination with carboplatin, etoposide and the PD-L1 inhibitor atezolizumab in the CeLEBrATE study demonstrates promising antitumour activity and a manageable safety profile, indicating that VEGF inhibition may enhance the efficacy of standard first-line chemo-immunotherapy in patients with ES-SCLC.

3.2.2.2. Anlotinib. Anlotinib is a recently developed oral small-molecule multi-target tyrosine kinase inhibitor. Its antitumour efficacy is mediated through the inhibition of several receptors that are essential for tumour angiogenesis and cellular proliferation, including the vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), fibroblast growth factor receptor (FGFR), among other associated targets [126].

Anlotinib has been authorized for the treatment of several malignancies, including NSCLC, soft tissue sarcoma and metastatic renal cell carcinoma [127–129]. Recent findings from the phase II ALTER 1202 trial evaluated anlotinib as a third-line or later treatment for recurrent SCLC. This randomized, double-blind, placebo-controlled, multicentre study enrolled 120 patients, who were assigned in a 2:1 ratio to receive either anlotinib ($n = 82$) or placebo ($n = 38$). The median PFS was 4.1 months (95% CI: 2.8–4.2) in the anlotinib group versus 0.7 months (95% CI: 0.7–0.8) in the placebo group (HR = 0.19; $p < 0.0001$), with a significantly higher disease control rate (71.6% vs. 13.2%; $p < 0.0001$). Updated OS data indicated a survival advantage for anlotinib (7.3 vs. 4.9 months) [130,131]. In another prospective phase II trial including 45 patients with recurrent SCLC, anlotinib achieved an ORR of 11%, a median PFS of 4.1 months and a median OS of 6.1 months. The most common treatment-related adverse events were hypertension (13%), decreased appetite (9%) and fatigue (9%), reflecting a manageable safety profile [132].

Building upon these monotherapy results, the phase III ETER701 trial further evaluated anlotinib in combination therapy for first-line treatment of ES-SCLC. In this multicentre, double-blind, randomized, placebo-controlled study, treatment-naïve patients received either benmelstobart (a novel PD-L1 inhibitor) plus anlotinib and standard etoposide/carboplatin (EC) chemotherapy, anlotinib plus EC, or EC alone, followed by corresponding maintenance therapy. The addition of benmelstobart and anlotinib to EC significantly prolonged OS compared with EC alone (19.3 vs. 11.9 months; HR = 0.61; $p = 0.0002$), representing the longest OS reported in randomized ES-SCLC trials. In contrast, the anlotinib + EC arm showed a median OS of 13.3 months versus 11.9 months for EC alone, but this improvement did not reach statistical significance (HR = 0.86; $p = 0.1723$). Grade ≥3 treatment-related adverse events occurred in 93.1%, 94.3% and 87.0% of patients in the benmelstobart + anlotinib + EC, anlotinib + EC and EC-alone groups, respectively [133]. These results highlight that the triple combination achieved the longest OS reported to date in randomized ES-SCLC trials, with a tolerable and manageable safety profile.

Meanwhile, a 2024 phase II study evaluated sintilimab (a PD-1 inhibitor) combined with anlotinib and nab-paclitaxel as a second-line or later therapy for relapsed ES-SCLC. Among 25 enrolled patients, the confirmed ORR was 60%, with a median PFS of 6.0 months and a median OS of 13.4 months. Grade ≥3 adverse events occurred in only 12% of patients, indicating good tolerability [134]. These findings support the growing potential of anlotinib-based strategies across multiple treatment lines in SCLC.

3.2.2.3. Apatinib. Apatinib is a tyrosine kinase inhibitor (TKI) that is administered orally and specifically targets and inhibits the vascular endothelial growth factor receptor-2 (VEGFR-2). Previous studies have indicated that apatinib displays promising antitumour activity and a tolerable safety profile across a range of solid tumours, including SCLC [135]. A retrospective study conducted at a single centre in China found that apatinib (250 mg daily) as maintenance therapy for ES-SCLC showed promising effectiveness (PFS of 4.1 months and OS of 12.5 months) and an acceptable safety profile. The most frequently observed adverse events associated with treatment were hand-foot syndrome (43.5%, 10/23) and secondary hypertension (30.4%, 7/23), followed by fatigue, proteinuria, nausea and oral mucositis (17.4%, 13.0%, 13.0% and 8.7%, respectively), with no new toxicity observed [136]. A phase II prospective study carried out in 2019 assessed the efficacy and safety of apatinib in patients diagnosed with ES-SCLC who had undergone two to three previous treatment regimens. In this study, 40 patients were recruited and administered 500 mg apatinib once daily. As of the data cutoff date of November 15, 2018, the study results showed that 7 out of 40 intention-to-treat patients (17.5%) achieved an objective response, while 7 out of 38 patients in the per-protocol group (18.4%) achieved an objective response. The median PFS was recorded at 3.0 months (95% CI: 2.2–3.7), while the median OS was noted to be 5.8 months (95% CI: 3.7–7.9). The most frequently reported grade 3 or higher treatment-related adverse events included hypertension, hand-foot syndrome and elevated levels of gamma-glutamyl transferase [137]. A phase II prospective study evaluated the effectiveness of apatinib in conjunction with chemotherapy as a second-line treatment for advanced small cell lung cancer. The findings indicated that following treatment with apatinib and chemotherapy, along with maintenance therapy, the ORR and DCR were 27.59% (8 out of 29 patients) and 96.55% (28 out of 29 patients), respectively. Furthermore, the median PFS and OS were reported as 7.36 and 14.16 months, respectively, suggesting an improved efficacy relative to standard second-line chemotherapy. The most frequently occurring adverse events (AEs) were neutropenia (41.94%, 13/31), followed by leukopoenia (35.48%, 11/31) and thrombocytopenia (25.81%, 8/31). Nearly all patients experienced various AEs, but most AEs were mild and tolerable [138]. Recently, a 2025 multicentre, single-arm trial investigated induction chemotherapy followed by camrelizumab plus apatinib and chemotherapy as first-line treatment for untreated ES-SCLC. Among 36 evaluable patients, the confirmed ORR reached 88.9%, with a median PFS of 7.3 months and median OS of 17.3 months. Grade ≥3 adverse events occurred in 75% of patients, mainly neutropenia, anaemia and elevated alanine aminotransferase, with no treatment-related deaths. RB1 mutations, high tumour mutation burden, increased levels of natural killer cells and interferons, and low levels of cancer-associated fibroblasts were associated with prolonged PFS [139]. These studies indicate that apatinib has potential in treating cisplatin-resistant SCLC patients, particularly in prolonging PFS and OS. Nonetheless, additional phase III clinical trials are required to thoroughly assess its efficacy and safety.

3.2.3. PARP inhibitors

The majority of SCLC cells harbour genetic alterations, particularly in TP53 and RB1, leading to impaired DNA repair capacity [33]. This defect partly explains the initial chemosensitivity of SCLC to DNA-damaging agents, including alkylators (cisplatin, temozolomide) and topoisomerase inhibitors (etoposide, topotecan, irinotecan). Consequently, targeting DNA repair pathways has emerged as a promising therapeutic strategy.

Poly (ADP-ribose) polymerase (PARP) is a key enzyme in the base excision repair (BER) pathway, essential for repairing single-strand DNA breaks and maintaining genomic stability [140,141]. PARP inhibitors (PARPi) block DNA repair, sensitizing tumour cells to cytotoxic agents. In preclinical SCLC models, the potent PARPi talazoparib (BMN673) demonstrated significant single-agent antitumour activity across multiple SCLC cell lines [142]. However, the clinical efficacy of PARPi monotherapy remains limited. In a phase II trial evaluating olaparib alone or in combination with the ATR inhibitor ceralasertib (AZD6738), only modest activity was observed: ORRs were 6.7% and 3.8%, DCR were 33.3% and 42.3%, and median PFS was 1.4 and 2.8 months, respectively [143]. These findings suggest that PARPi-based combination strategies may provide greater clinical benefit.

PARP inhibitors have undergone extensive investigation in combination with various therapeutic regimens for SCLC [144]. A randomized, double-blind phase II trial further evaluated temozolomide (TMZ) plus veliparib versus TMZ plus placebo in patients with recurrent SCLC ($n = 104$). Although PFS and OS were not significantly different, the ORR was higher in the veliparib arm (39% vs. 14%, $p = 0.016$). In SLFN11-positive tumours, PFS (5.7 vs. 3.6 months, $p = 0.009$) and OS (12.2 vs. 7.5 months, $p = 0.014$) were significantly prolonged, highlighting SLFN11 as a predictive biomarker for PARPi response. Increased grade 3–4 haematologic toxicities (thrombocytopenia 50%, neutropenia 31%) were observed [145].

Building upon this biomarker-driven strategy, a phase II randomized trial (S1929) investigated whether adding the PARP inhibitor talazoparib to maintenance atezolizumab could improve outcomes in SLFN11-positive ES-SCLC following initial chemoimmunotherapy. A total of 106 eligible patients were enrolled and randomized to receive atezolizumab alone or atezolizumab plus talazoparib. The combination regimen resulted in a significant improvement in PFS (HR = 0.66, 80% CI: 0.50–0.86, one-sided $p = 0.019$), with median PFS of 2.9 vs. 2.4 months, while OS was not significantly different (HR = 0.98, 80% CI: 0.71–1.36, one-sided $p = 0.47$). Grade ≥3 haematologic adverse events occurred more frequently with the combination (50% vs. 4%, $p < 0.001$), mainly due to anaemia, whereas non-haematologic toxicities were comparable (17% vs. 14%)[146]. These results further validate the concept of PARP inhibition in biomarker-selected SLFN11-positive SCLC, highlighting that precision-based therapeutic selection may yield tangible clinical benefit despite increased haematologic toxicity.

Additionally, a phase I/II study of olaparib plus TMZ in recurrent SCLC ($n = 50$) reported an ORR of 41.7%, median PFS of 4.2 months, and median OS of 8.5 months [147],further supporting the potential synergy of PARPi with alkylating agents.

In the frontline setting, a phase II trial enrolling 128 patients with ES-SCLC compared cisplatin and etoposide plus veliparib versus cisplatin and etoposide plus placebo. Patients receiving the combination of cisplatin and etoposide plus veliparib achieved a slightly higher ORR compared with the placebo arm (71.9% vs. 65.6%, $p = 0.57$), although the difference was not statistically significant. Median PFS was modestly prolonged in the veliparib arm (6.1 vs. 5.5 months; HR = 0.63, $p = 0.01$), and median OS was also increased but did not reach statistical significance (10.3 vs. 8.9 months; stratified HR = 0.83; 80% CI, 0.64–1.07; one-sided $p = 0.17$). Notably, male patients with elevated lactate dehydrogenase (LDH) levels derived substantial benefit in PFS from the combination therapy (HR = 0.34; 80% CI, 0.22–0.51), whereas no significant advantage was observed in other patient subgroups (HR = 0.81; 80% CI, 0.60–1.09). Haematologic toxicities were increased in the combination arm, particularly neutropenia and CD4 lymphopenia. Collectively, these findings indicate that PARPi monotherapy provides limited benefit but holds greater potential when combined with chemotherapy or immunotherapy, particularly in SLFN11-positive subgroups. Ongoing biomarker-driven trials may further optimize patient selection and combination treatment strategies in SCLC. A comprehensive summary of clinical trials evaluating PARP inhibitor–based combination therapies in SCLC is presented in Table 3.

Table 3. Clinical trial of PARR inhibitor combination therapy for cisplatin-resistant small cell lung cancer.

Phase	Study	Treatment arms	Patients (n)	ORR (%)	PFS (months)	OS (months)
First line						
I	NCT02289690	Veliparib + chemotherapy vs. placebo + chemotherapy; maintained with veliparib vs. placebo	181	77 vs. 59 vs. 64	5.8 vs. 5.7 vs. 5.6	10.1 vs. 10.0 vs. 11.4
II	ECOG-ACRIN 2511	Veliparib + etoposide + cisplatin vs. placebo + etoposide + cisplatin	128	71.9 vs. 65.6 ($p = 0.57$)	6.1 vs. 5.5 (HR: 0.75; $p = 0.06$)	10.3 vs. 8.9 (HR: 0.83; $p = 0.17$)
II	S1929	Atezolizumab vs. atezolizumab + talazoparib	106	19 vs. 11	2.9 vs. 2.4 (HR = 0.66,80% CI: 0.50-0.86, $p = 0.019$)	9.5 vs. 9.7 (HR = 0.98,80% CI: 0.71–1.36; $p = 0.47$)
Relapsed						
I/II	NCT02446704	Olaparib + temozolomide	50	41.7 (48 assessable patients)	4.2 (95% CI: 2.8–5.7)	8.5 (95% CI: 5.1–11.3)
I/II	NCT02734004	Olaparib + durvalumab	40	10.5 (95% CI: 2.9–24.8)	2.4 (95% CI: 0.9–3.0)	7.6 (95% CI: 5.6–8.8)
II	NCT03009682 + NCT0328607	Olaparib vs. olaparib and ceralasertib	41	6.7 vs. 3.8	1.4 vs. 2.8	8.6 vs. 7.2
II	NCT01638546	Veliparib + temozolomide vs. placebo + temozolomide	104	39 vs. 14 ($p = 0.016$)	3.8 vs. 2.0 ($p = 0.39$)	8.2 vs. 7.0 ($p = 0.50$)

3.3. The novel chemotherapy

3.3.1. Lurbinectedin

Lurbinectedin is an innovative anticancer agent belonging to the ecteinascidin class of compounds. It binds to DNA, obstructing access to transcription factors and essential transcription machinery such as RNA polymerase II, thereby disrupting the transcription process, causing the buildup of DNA double-strand breaks, which ultimately leads to cell death [148,149]. Furthermore, lurbinectedin may influence the tumour microenvironment by diminishing both the quantity and transcriptional activity of tumour-associated macrophages, which could result in a reduction in tumour cell survival, angiogenesis and an enhancement of antitumour immunity. A single-arm, open-label, phase II basket trial assessed the efficacy and safety of lurbinectedin in a cohort of 105 patients diagnosed with SCLC who had previously failed cisplatin-based chemotherapy. Among these participants, 37 individuals (35.2%, 95% CI: 26.2–45.2) exhibited an overall response to the treatment. The ORR was recorded at 35.2%, with a median PFS of 3.5 months and a median OS of 9.3 months. The most frequently observed grade 3–4 adverse events were haematologic disorders, which included anaemia (9%), leukopoenia (29%), neutropenia (46%), thrombocytopenia (7%) and febrile neutropenia (5%) [150]. In light of these favourable clinical outcomes, lurbinectedin received accelerated approval from the U.S. Food and Drug Administration (FDA) in 2020 for the management of relapsed small cell lung cancer.

Recently, another study in ES-SCLC without central nervous system (CNS) metastases found that lurbinectedin had a statistically significant higher ORR compared to the topotecan control group (41.0% vs. 25.5%; $p = 0.0382$). The lurbinectedin group also had a higher ORR (33.7% vs. 25.5%), longer median duration of response (5.3 months vs. 3.9 months) and longer median OS (10.2 months vs. 7.6 months). Additionally, the lurbinectedin group had significantly lower grade 3 haematologic abnormalities compared to the control group: anaemia (12.0% vs. 54.1%), leukopoenia (30.1% vs. 68.4%), neutropenia (47.0% vs. 75.5%) and thrombocytopenia (6.0% vs. 52.0%) [151]. These results indicate that lurbinectedin used alone is safe and shows considerable effectiveness as a second-line therapy for SCLC.

Following confirmation of lurbinectedin's efficacy as monotherapy, combination strategies have been explored. A phase III trial assessed lurbinectedin plus doxorubicin in 613 patients with relapsed SCLC, compared with topotecan or CAV (cyclophosphamide, doxorubicin, vincristine) control. Median OS was 8.6 months versus 7.6 months (HR 0.97, $p = 0.70$), without statistical significance, but haematologic toxicities – including anaemia, neutropenia and thrombocytopenia – were lower in the combination arm, suggesting a potential safety advantage [152]. Building on this, the phase 3 IMforte trial evaluated first-line maintenance therapy with lurbinectedin plus atezolizumab versus atezolizumab alone in 483 ES-SCLC patients who had not progressed after induction with atezolizumab, carboplatin and etoposide. Lurbinectedin plus atezolizumab significantly prolonged PFS (HR 0.54; 95% CI: 0.43–0.67; $p < 0.0001$) and OS (HR 0.73; 95% CI: 0.57–0.95; $p = 0.017$) compared with atezolizumab alone. Grade 3–4 adverse events were more frequent with the combination (38% vs. 22%), mainly anaemia, neutropenia and thrombocytopenia, while grade 5 events occurred in 5% versus 3% [153]. These findings indicate that lurbinectedin, particularly in combination with doxorubicin or atezolizumab, represents a promising therapeutic option for relapsed and first-line maintenance treatment of ES-SCLC.

3.3.2. Alisertib

Aurora kinase A (AURKA) serves as a critical regulator of mitotic processes and is frequently found to be amplified or overexpressed in various solid tumours, including SCLC, suggesting its potential involvement in tumourigenesis [154,155]. The AURKA inhibitor alisertib has demonstrated effectiveness as a standalone treatment in a phase II clinical trial, where 10 out of 48 patients (21%; 95% CI: 10–35) attained an objective response, with a median PFS of 2.1 months (95% CI: 1.4–3.4) [156]. Furthermore, the combination of alisertib and paclitaxel has been evaluated as a second-line therapeutic option for SCLC. The findings indicated an ORR of 22% in the alisertib/paclitaxel cohort, in contrast to 18% in the placebo/paclitaxel cohort. The median OS was recorded at 6.86 months for the combination therapy group, compared to 5.58 months for the placebo group (HR = 0.93, 95% CI: 0.652–1.341, $p = 0.714$), revealing no statistically significant difference in OS between the two groups. Additionally, the median PFS was 3.32 months for the combination therapy group, as opposed to 2.17 months for the placebo group (HR:

0.77; 95% CI: 0.557–1.067, $p = 0.113$). Notably, a subset of patients expressing c-Myc showed a marked enhancement in PFS when treated with alisertib/paclitaxel [157]. These results align with the proposed mechanism of action of alisertib as a mitotic inhibitor, which has the capacity to disrupt the cell cycle. Consequently, c-Myc expression may function as a biomarker for predicting the therapeutic efficacy of alisertib in the treatment of SCLC. Despite the promising outcomes observed in clinical trials, the combination therapy approach involving alisertib has yet to be comprehensively validated through large-scale clinical studies, necessitating further exploration of its efficacy and safety profile. A summary of recent clinical and experimental studies investigating lurbinectedin and alisertib in SCLC is presented in Table 4.

4. Preclinical advances in overcoming cisplatin resistance

Recent preclinical investigations have converged on a multifactorial model of platinum resistance in SCLC in which oncogenic drivers, epigenetic reprogramming, altered mitophagy and checkpoint dependence create distinct but potentially targetable vulnerabilities. Functionally, both acquired and enforced MYC overexpression drive platinum resistance in cell lines and autochthonous models, and high-throughput screening identified the dual PI3K–HDAC inhibitor fimepinostat as an agent that downregulates MYC and produces potent single-agent efficacy in xenograft and patient-derived models while significantly prolonging survival when combined with platinum–etoposide [158]. Targeting cell-cycle checkpoints offers a complementary approach. CHK1 inhibition (prexasertib, AZD7762) synergizes with cisplatin to induce mitotic catastrophe in p53-deficient SCLC and restores sensitivity in resistant models [159]. Integrative methylome–transcriptome analyses further nominate epigenetic biomarkers and druggable interactions: hypomethylation and upregulation of PCDHB4 associate with stemness/EMT phenotypes, reduced immune infiltration and poorer outcomes after platinum therapy [160], while an epigenome-wide study across 66 SCLC cell lines revealed methylation–expression correlations (e.g. TREX1, SLFN11, CEP350, EPAS1, KDM1A, EZH2, YAP1) that predict sensitivity or resistance to specific classes of agents (Aurora kinase inhibitors, PLK1 inhibitors, PARP/ATR pathway agents and microtubule poisons) [161].

5. Perspective

While therapies targeting the four mechanisms of resistance to cisplatin-based drugs, such as multidrug resistance (MDR) inhibitors and Bcl-2 family inhibitors, have been developed to address specific resistance pathways, their substantial side effects and efficacy limited to specific tumour types have restricted

Table 4. Clinical trials of novel chemotherapy drugs for cisplatin-resistant small cell lung cancer.

Phase	Study	Treatment arms	Patients (n)	ORR (%)	PFS (months)	OS (months)
First line						
III	NCT05091567	Lurbinectedin + atezolizumab vs. atezolizumab	483	59.1 vs. 74.0	5.4 vs. 2.1 (HR: 0.54; 95% CI: 0.43–0.67; $p < 0{\cdot}0001$)	13.2 vs. 10.6 (HR: 0.73; 95% CI: 0.57–0.95; $p = 0.017$)
Relapsed						
II	NCT02454972	Lurbinectedin	105	35.2	3.5 (95% CI: 2.6–4.3)	9.3 (95% CI: 6.3–11.8)
II	NCT01045421	Alisertib	48	10	2.1 (95% CI: 1.4–3.4)	/
II	NCT02038647	Alisertib + paclitaxel vs. placebo + paclitaxel	178	22 vs. 18	3.32 vs. 2.17 (HR: 0.77; 95% CI: 0.557–1.067; $p = 0.113$)	6.86 vs. 5.58 (HR: 0.93; 95% CI: 0.652–1.341; $p = 0.714$)
II/III	NCT02454972 + NCT02566993	Lurbinectedin vs. topotecan	181	IA: 41 vs. 25.5 IRC: 33.7 vs. 25.5	IA: 5.3 vs. 3.9 ($p = 0.7323$) IRC: 5.1 vs. 4.3 ($p = 0.6102$)	10.2 vs. 7.6 ($p = 0.3037$)
III	NCT02566993	Lurbinectedin + doxorubicin vs. topotecan or CAV	613	32 vs. 30	4.0 vs. 4.0 (HR: 0.83; 95% CI: 0.69–1.00)	8.6 vs. 7.6 (HR: 0.97; 95CI%: 0.82–1.15; $p = 0.70$)

their widespread use in the treatment of cisplatin-resistant SCLC. Currently, immunotherapy and targeted therapy remain the mainstream treatments for this type of lung cancer.

Studies have shown that the MDR inhibitor Cyclosporine A can reduce the activity of P-gp, enhancing the sensitivity of lung cancer cells to cisplatin-based drugs, but its immunosuppressive effects and renal toxicity limit its clinical application [162]. Similarly, the Bcl-2 family inhibitor Venetoclax has shown significant therapeutic effects in clinical trials on various haematological malignancies, such as chronic lymphocytic leukaemia and multiple myeloma, particularly displaying an overall response rate of up to 70% when used in combination with other drugs [163,164]. However, its effects in solid tumours are relatively weak, possibly due to the more complex anti-apoptotic mechanisms in these tumours [165].

In this context, immunotherapy and targeted therapy have emerged as significant areas of research, each with unique mechanisms and potential advantages. Immunotherapy, particularly inhibitors targeting the PD-1/PD-L1 pathway (such as nivolumab and pembrolizumab), although effective in some patients, still shows limited overall response rates and improvements in survival. This variability in effectiveness may be related to the significant immunosuppressive environment in SCLC, characterized by restricted T-cell infiltration and impaired antigen presentation [166]. Although SCLC generally exhibits a high tumour mutation burden (TMB), the immune suppressive factors limit the response to immunotherapy, which may explain why PD-1/PD-L1 blockade is not as effective in SCLC as expected [167]. Similarly, CTLA-4 inhibitors such as Ipilimumab have not significantly improved ORR, PFS, or OS in SCLC. This may be due to CTLA-4 inhibitors primarily modulating T cell activation within lymph nodes, and the insufficient immune activation signals in the SCLC tumour microenvironment, combined with the rapid progression nature of the tumour, limits the effectiveness of such immunotherapy [168].

On the other hand, targeted therapy, such as PARP inhibitors (PARPi), although theoretically potent against SCLC, has not yet become a recommended standard treatment. This is partly because the response of SCLC patients to PARPi varies, and even in clinical trials involving combination therapies, some patients show significantly better responses than others. The variability in response can be attributed to several factors, including genetic heterogeneity, expression levels of relevant biomarkers like BRCA mutations and RAD51, differences in the tumour microenvironment that affect drug metabolism and efficacy, and the complexities of drug interactions in combination therapies. Therefore, future research should focus on identifying specific patient groups through biomarkers to optimize the application of PARPi in SCLC treatment, enhancing personalized therapy approaches to improve clinical outcomes.

Combining immunotherapy with targeted treatments such as PARP inhibitors provides a promising therapeutic strategy for platinum-resistant SCLC by targeting multiple pathways simultaneously. PARP inhibitors disrupt the DNA repair mechanisms of tumour cells, thereby enhancing the immune system's attack on these cells, which in turn strengthens the effect of immunotherapy. This combined strategy not only overcomes the immunosuppressive microenvironment of the tumour but also leverages the genetic predisposition of patients to enhance the overall effectiveness of the treatment. Future clinical trials should focus on utilizing biomarkers such as TP53 and RB1 genes to identify patients most likely to benefit from these combined therapies, aiming for more precise treatment. This approach seeks to advance treatment toward greater personalization and efficacy by improving response rates and extending survival times.

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Data availability statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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