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Unravelling the biology of SCLC: implications for therapy

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Abstract

Small-cell lung cancer (SCLC) is an aggressive malignancy associated with a poor prognosis. First-line treatment has remained unchanged for decades, and a paucity of effective treatment options exists for recurrent disease. Nonetheless, advances in our understanding of SCLC biology have led to the development of novel experimental therapies. Poly [ADP-ribose] polymerase (PARP) inhibitors have shown promise in preclinical models, and are being clinically tested in combination with cytotoxic therapies and inhibitors of cell-cycle checkpoints. Preclinical data indicate that targeting of histone-lysine *N*-methyltransferase EZH2, a regulator of chromatin remodelling implicated in acquired therapeutic resistance, might augment and prolong chemotherapy responses. High expression of the inhibitory Notch ligand Delta-like protein 3

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Author contributions

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Competing interests statement

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(DLL3) in most SCLCs has been linked to expression of Achaetescute homologue 1 (ASCL1; also known as ASH-1), a key transcription factor driving SCLC oncogenesis; encouraging preclinical and clinical activity has been demonstrated for an anti-DLL3-antibody–drug conjugate. The immune microenvironment of SCLC seems to be distinct from that of other solid tumours, with few tumour-infiltrating lymphocytes and low levels of the immune-checkpoint protein programmed cell death 1 ligand 1 (PD-L1). Nonetheless, immunotherapy with immune-checkpoint inhibitors holds promise for patients with this disease, independent of PD-L1 status. Herein, we review the progress made in uncovering aspects of the biology of SCLC and its microenvironment that are defining new therapeutic strategies and offering renewed hope for patients.

Graphical Abstract

For three decades, the treatment of small-cell lung cancer (SCLC) has remained essentially unchanged, and patient outcomes remain dismal. In the past 5 years, however, advances in our understanding of the disease, at the molecular level, have resulted in the development of new therapeutic strategies, encompassing immunotherapies and novel molecularly targeted agents. Herein, authors review the breakthroughs that hold the promise to improve SCLC outcomes.

Lung cancer is the most common cancer worldwide, with an estimated 1.8 million cases diagnosed each year and an estimated 1.6 million lung-cancer-related deaths annually[1,2]. Globally, small-cell lung cancer (SCLC) accounts for 13–15% of all lung cancers, with approximately 250,000 cases diagnosed annually, and is the sixth most common cause of cancer-related mortality[3–7]. SCLC is an aggressive high-grade neuroendocrine tumour associated with a short doubling time, a high growth fraction, and early development of widespread metastases, which contribute to the extremely poor prognosis of patients with the disease. The typical life expectancy for a patient diagnosed with SCLC, and the standard options for therapy, have not changed over the past three decades (FIG. 1); the median overall survival duration of patients with extensive-stage (ES)-SCLC is stalled, frustratingly, at <10 months, with a discouraging 5-year overall survival of 1–5%[4]. The incidence of SCLC in the developed world has decreased in parallel with the declining rates of smoking, although SCLC remains a substantial cause of cancer-related mortality worldwide[2,8]. Among the major lung-cancer subtypes, SCLC has the strongest association with smoking, with only 2% of cases occurring in never-smokers[9,10]. Consequently, SCLCs have a high load of somatic mutations induced by tobacco carcinogens[11–13]. The most common genetic alterations in SCLC include inactivation of the tumour-suppressor genes *TP53* and *RB1,* as well as copy-number gains of genes encoding MYC family members, enzymes involved in chromatin remodelling, receptor tyrosine kinases and their downstream effectors, and Notch family proteins[12,13]. Importantly, the high mutational burden of SCLC might provide opportunities for therapeutic intervention. In this Review, we explore the progress made in defining the molecular aetiology of SCLC and discuss the development of rational therapeutic strategies based on the disease biology.

Clinical overview

Pathology

SCLC is one constituent of a group of neuroendocrine lung tumours that also includes large-cell neuroendocrine carcinoma, and typical and atypical carcinoid tumours. The diagnosis of SCLC is based primarily on histological appearance by light microscopy, demonstrating dense sheets of small cells with neuroendocrine differentiation (characterized by scant cytoplasm; poorly defined cell borders; dispersed, finely granular nuclear chromatin; absent or inconspicuous nucleoli; and prominent nuclear moulding). Necrosis is typically extensive and the mitotic count is exceptionally high (>10 mitoses per 10 high-power fields), with a high Ki67 labelling index (using the MIB-1 antibody) of around 90–100% also indicating rapid cell proliferation[14]. Current classifications of SCLC subtypes include ‘small-cell carcinoma’ and ‘combined small-cell carcinoma’, with the latter comprising small-cell carcinomas harbouring an additional component of non-small-cell carcinoma (NSCLC), such as adenocarcinoma, squamous-cell carcinoma, or large-cell carcinoma[14]. Combined small-cell carcinoma accounts for approximately 10–25% of SCLC cases. Most SCLCs express the neuroendocrine markers CD45, CD56, chromogranin, and synaptophysin; fewer than 10% of SCLCs are negative for all neuroendocrine markers[14].

SCLC can be staged according to the conventional ‘TNM’ criteria, as defined by the Union for International Cancer Control and the American Joint Committee on Cancer[4]. Surgery can have a role in the treatment of patients with early, TNM stage I disease (tumours <5 cm in diameter with no lymph-node involvement or metastasis); however, disease presentation at such early stage is the exception to the norm. More commonly, SCLC is staged as limited-stage or extensive-stage disease; these distinctions are both prognostic and guide the use of the available treatment options.

Limited-stage disease

Limited-stage (LS)-SCLC is defined as disease confined to a single radiation port (that is, to a tolerable treatment field), with or without mediastinal lymph-node involvement. Only around one-third of patients diagnosed with SCLC present with LS-SCLC. In contrast to NSCLC, low-dose CT screening has not been shown to improve the survival of patients with SCLC, or to increase the number of patients diagnosed with early stage disease[15]. Treatment advances involving thoracic and cranial irradiation have led to improved outcomes for patients with LS-SCLC[6] (FIG. 1). The rapid proliferation rate of this malignancy confers an exquisite sensitivity to DNA-damaging therapies; thus, the standard of care for LS-SCLC is concurrent chemoradiotherapy with cisplatin and etoposide, which results in an objective response rate (ORR) of 70–90%[16], and has been associated with 44% survival at 2 years and 23% survival at 5 years[17,18]. The radiotherapy regimen best supported by randomized clinical trial data is 45 Gy delivered in 30 twice-daily (b.i.d.) 1.5-Gy fractions (over 3 weeks)[17]. In this practice-defining study[17], however, the b.i.d. fractionation schema was compared with a regimen comprising the same nominal dose of 45 Gy delivered in 25 once-daily 1.8-Gy fractions (over 5 weeks), which is not a biologically equivalent dose. Accordingly, in the ongoing EORTC 08072 CONVERT trial (NCT00433563) and the CALGB 30610/RTOG 0538 trial (NCT00632853), the standard b.i.d. regimen is being

compared to biologically equivalent doses: once-daily 2-Gy fractions to a total dose of 66 Gy and 70 Gy, respectively (over 6.5–7 weeks). Early results of the CONVERT trial, presented in abstract form at the ASCO 2016 meeting[19], indicate equivalent overall survival and toxicity between the two arms, providing some evidence to support the use of either regimen.

The blood–brain barrier can restrict access of systemically delivered therapies into the brain and, therefore, most patients with LC-SCLC experience recurrent disease in the central nervous system (CNS). Thus, prophylactic cranial irradiation (PCI) is recommended for patients with LS-SCLC who respond to upfront concurrent chemoradiotherapy and have no evidence of brain metastasis on MRI, in order to eliminate undetectable micrometastatic disease that might be present[20]. Results of a large meta-analysis have confirmed the survival benefit of this approach[21]. In summary, the preferred therapeutic strategy for patients with LS-SCLC is concurrent chemoradiotherapy (with cisplatin and etoposide)[16], followed by PCI in those who achieve complete remission[21]; the associated 5-year survival ranges from 20–40% depending on disease stage and degree of nodal involvement[22].

Extensive-stage disease

ES-SCLC, defined as disease that has spread beyond a single radiation port — generally synonymous with distant metastasis — accounts for two-thirds of all SCLC diagnoses[6,23]. As described previously, the outcomes of patients with ES-SCLC are dismal, with median overall survival durations of <10 months and 5-year survival <5%[4]. First-line treatment for such patients, which has remained unchanged for more than three decades (FIG. 1), generally consists of 4–6 cycles of chemotherapy with a platinum-based agent (either cisplatin or carboplatin) and etoposide. ORRs associated with this regimen approach 70%; however, most patients suffer rapid disease relapse within 6 months[24–30]. The use of a platinum-based drug in combination with irinotecan is also an acceptable first-line treatment, and this regimen is commonly used in Japan[28,29]. Results of the largest North American study reported to date[31], however, did not confirm the clinical benefit of cisplatin and irinotecan versus cisplatin and etoposide previously reported in Japanese cohorts[28,29].

Despite the inevitable and rapid disease relapse after first-line treatment, topotecan is the only systemic therapy approved by the FDA for the treatment of recurrent ES-SCLC. Furthermore, the activity of this agent is, in general, limited to patients with chemosensitive relapse, defined as those with an objective response to first-line chemotherapy that persisted for at least 3 months after completion of therapy[32]. Unfortunately, the mechanisms of acquired chemoresistance in SCLC are poorly understood.

The roles of thoracic radiation therapy and PCI in the treatment of ES-SCLC remain controversial. A randomized phase III trial of post-chemotherapy consolidative chest radiation was negative for its primary end point of an improvement in overall survival at 1 year compared with that observed without thoracic radiotherapy (33% versus 28%; $P = 0.066$), but results of a post-hoc analysis indicated an overall survival benefit at 2 years (13% versus 3%; $P = 0.004$)[33]. A survival benefit from consolidative thoracic radiotherapy was also later reported for the subgroup of patients with residual intrathoracic disease (HR 0.81,95% CI 0.66–1.00; $P = 0.044$)[34]. The low-dose radiation regimen used (30 Gy in 10

fractions) was well tolerated, with no marked differences in toxicities between the control and experimental groups[33]. Further work is necessary to confirm these results, and to identify additional subsets of patients with ES-SCLC who are most likely to benefit from consolidative thoracic radiotherapy. In this study[33], all patients received PCI, which has been reported to improve overall survival in patients with ES-SCLC (27.1% at 1 year versus 13.3% without PCI)[35]; however, radiological assessment before PCI was not mandated in this study[35], and thus the inclusion of patients with overt brain metastases might have contributed to the apparent clinical benefit. In a more recent Japanese phase III trial[36], in which pretreatment brain imaging was mandated, PCI did not improve the overall survival of patients with ES-SCLC. Of note, both patients and physicians have concerns regarding the potential for delayed PCI-related neurotoxicity, which must be balanced with the need to achieve disease control[37,38].

Essentially, the management of ES-SCLC has remained unchanged for the past 20 years — since the approval of topotecan for recurrent and/or refractory disease in 1996 (FIG. 1) — and effectiveness of the few available treatment options is limited; therefore, novel, targeted, and biomarker-guided therapies an important unmet need. Advances in genomic, epigenetic, and proteomic profiling, tumour immunology, and tumour biology have led to exciting new experimental therapies, some of which have been shown to provide a meaningful clinical benefit in early phase clinical trials. In the following sections, we discuss the breakthroughs in our understanding of the molecular and cellular biology of SCLC, and highlight the emerging targets for novel treatments.

SCLC developmental regulatory pathways

SCLCs display poorly differentiated neuroendocrine features[14]; three distinct molecular subtypes have been defined by gene-expression profiles determined by differential expression of the neuronal basic helix–loop–helix transcription factors achaetescute homologue 1 (ASCL1, also known as ASH-1) and neurogenic differentiation factor 1 (NEUROD1)[39–41]. A subgroup defined by expression of ASCL1 has been described as the ‘classic’ subtype, while a subgroup defined by high expression levels of NEUROD1 has been described as the ‘variant’ subtype[41–43]. The third, minor subgroup lacks expression of either of these neuroendocrine markers. These subgroups are clearly distinct disease entities based on gene-expression profiling, although the clinical implications of this molecular classification have not been defined — for example, whether these subtypes have differential capacities for invasion or metastasis, or differential responses to standard therapies is unknown.

In a genetically engineered mouse model, conditional Cre-mediated excision of the *Tp53* and *Rb1* gene in lung epithelial cells gives rise to lung tumours resembling the classic subtype of SCLC[44]. Interestingly, tumours resembling variant subtype SCLC are not observed in this model[45]. The results of subsequent experiments have revealed that ASCL1 activates pulmonary neuroendocrine differentiation[46]; regulates the expression of multiple Notch-pathway genes, including that encoding the inhibitory Notch ligand Delta-like protein 3 (DLL3)[39]; and is required for tumour initiation in this model, whereas NeuroD1 is dispensable[47,48]. In 2017, however, Mollaoglu *et al.*[49] demonstrated that overexpression of

an oncogenic *Myc*^{T58A} allele in this context promotes the development of 'neuroendocrine-low' tumours resembling variant subtype SCLC, characterized by a high level of NeuroD1 expression and low ASCL1 expression. Importantly, a targeted drug screen in this model revealed the therapeutic potential of aurora kinase inhibitors, in combination with cisplatin and etoposide chemotherapy, in MYC-driven variant subtype SCLC[49]. ASCL1 drives the expression of many proto-oncogenes implicated in SCLC progression and cell survival, including *MYCL1*, *RET*, *SOX2*, *NF-IB*, and *BCL2* (REFS 39,50). Although NEUROD1 does not seem to be required for the tumorigenesis of classic subtype SCLC, this transcription factor has been shown to induce migratory signalling pathways in human SCLC cells[51], and can activate a neuroendocrine differentiation programme in a mouse lung epithelial (non-neuroendocrine) cell line[52].

The SCLC genome, epigenome, and proteome

Genetic landscape

SCLC cells are typically aneuploid, with a high incidence of chromosomal deletions of 3p, 4q, 5q, 10q, 13q, and 17p, and copy-number gains of 3q, 5p, 6p, 8q, 17q, 19, and 20q (REFS 53–55). The genetic mutational landscape of SCLC is complex and varied, but functional inactivation of both *TP53* and *RB1* is essentially universal[12,13]. Other molecular abnormalities detected in SCLCs include amplification and overexpression of *MYC* family oncogenes[56], overexpression of *BCL2* (REF. 57) and *KIT*[58], as well as activation of autocrine loops through bombesin-like peptides[59]. Gene-expression profiling data suggest that several neuroendocrine genes are expressed in SCLCs, including those encoding chromogranins A, B and C (*CHGA*, *CHGB*, and *CHGC* (*SCG2*))[60], insulinoma-associated gene 1 (*INSM1*)[61], as well as *ASCL1* (REF. 62); however, the relevance of many of these markers, with respect to improving the diagnosis or directing therapy for the disease, remains unclear.

In the past 5 years, comprehensive genomic studies, including exome, whole-genome, transcriptome, and copy-number alteration analyses of primary human SCLC samples, have provided the first overview of genomic landscape of this disease[12,13,63,64]. SCLCs have a mean mutation rate of 7.4 nonsynonymous mutations per million base pairs — similar to that of other tobacco-associated lung cancers[12,65]. As noted, biallelic inactivation of *TP53* and *RB1* is near-ubiquitous in SCLC[12,13,63,64]. Recurrent mutations in *CREBBP*, *EP300*, *MLL* (also known as *KMT2A*), *PTEN*, *SLIT2*, *EPHA7*, and *Notch* genes, and amplification of *FGFR1* and *SOX2,* have also been reported[12,13,63]. In particular, mutations affecting Notch receptors have been detected in 25% of SCLCs, and these receptors have been validated as tumour suppressors in mouse models of SCLC[12]. Indeed, alterations in tumour-suppressor genes were the most-frequent finding in SCLC samples. Lastly, RNA-sequencing data have identified multiple fusion transcripts in primary SCLC specimens, including a recurrent *RLF–MYCL1* fusion[13]. Further work is needed to better understand how individual genomic alterations associated with SCLC relate to patient response to therapy and outcome.

Epigenetic landscape

Epigenetic processes have a central role in carcinogenesis, and tumour maintenance, progression, and responses to treatment[66]. Most early cancer epigenetics studies focused on DNA methylation at CpG-dinucleotide islands[67,68]. DNA-methylation patterns are associated with gene expression, and promoter hyper-methylation has been shown to lead to a heterochromatin state and repressed gene expression[69]. Repression of tumour-suppressor genes and genes required for programmed cell death in this manner, as well as de-repression of oncogenes, can provide a fitness advantage for cancer cells[67,68]. Evidence for this paradigm in SCLC was provided by the finding that several SCLC cell lines were insensitive to TNF-related apoptosis-inducing ligand (TRAIL)-mediated apoptosis owing to epigenetic silencing of genes encoding caspase-8, FAS, and TRAIL-R1 via promoter CpG-island methylation[70]. Interestingly, treatment with the DNA methyltransferase (DNMT) inhibitor decitabine, in combination with IFNγ (which has been shown to upregulate expression of caspase-8), partially restored caspase-8 expression and increased the sensitivity of the SCLC cell lines to TRAIL-induced apoptosis[70]. Subsequently, the combination of DNMT inhibition using decitabine and histone deacetylase (HDAC) inhibition using either valproic acid or CI-994 could restore expression of caspase-8, sensitizing the cell lines to TRAIL-mediated cell death[71]. These findings provide insight into the mechanisms by which DNA-methylation events can impair the extrinsic apoptosis pathway and provided early evidence of the potential for pharmacological reversibility of such events in SCLC cells.

In the first genome-scale analysis of methylation changes in SCLC[72], 73 genes that were methylated in >77% of SCLC tumours were identified. Methylated gene promoters were enriched in binding sites for the neurogenic transcription factors NEUROD1, heart and neural crest derivatives-expressed protein 1 (HAND1), zinc finger protein 423 (ZNF423), and RE1-silencing transcription factor (REST), which the authors interpreted as being indicative of a defect in neuroendocrine differentiation[72]. Results of a subsequent genome-wide study, performed at single-nucleotide resolution, demonstrated overall DNA hypomethylation in primary SCLC samples compared with non-neoplastic lung specimens; however, CpG-island-containing promoters were found to be hypermethylated in SCLC to a greater degree than most tumour types included in The Cancer Genome Atlas[40]. Hypermethylated sites were concentrated focally at transcription start sites, whereas hypomethylated sites were distributed diffusely throughout promoter regions, suggesting a functional role for hypermethylation in cancer-specific gene silencing[40]. The authors further demonstrated that a major subgroup of SCLC has increased promoter methylation in a manner similar to what has been described in other tumour types as the ‘CpG-island methylator phenotype’ (CIMP)[40]. Of note, the CIMP has been associated with an unfavourable prognosis across multiple tumour types[73,74]. Neither initial genome-scale study in SCLC reported relationships of methylation profiles with patient outcome data[40,72]. In an ensuing study, however, SCLC samples could be similarly stratified according to CIMP status, and patients with CIMP-positive tumours had a poorer prognosis than those with CIMP-negative disease[75]. These data suggest that clinically relevant subtypes of SCLC are defined by DNA-methylation patterns, consistent with observations among other lung carcinoma epitypes[74].

Proteomic landscape

Proteomic and transcriptomic analyses of 34 SCLC and 74 NSCLC cell lines revealed a number of proteins of potential therapeutic interest that are differently expressed between these tumour types[76]. In comparison to NSCLCs, SCLCs had substantially increased levels of the growth-factor receptor KIT; the antiapoptotic protein Bcl-2 and the pro-apoptotic Bcl-2 family members BIM (Bcl-2-like protein 11) and BAX (Bcl-2-like protein 4); Upregulated histone-lysine *N*-methyltransferase EZH2 (also known as enhancer of zeste homologue 2), a chromatin-remodelling factor; thymidylate synthase; and DNA-repair proteins, including poly [ADP-ribose] polymerase (PARP) enzymes[76].

Potential therapeutic targets in SCLC

Many of the new insights into the biology of SCLC are now being actively translated into clinical trials of novel treatments for patients with this disease. In the following sections of this Review, we highlight some of the particularly attractive targets for clinical investigation.

PARP inhibitors

PARP enzymes were first identified in 1963 (REF. 77). To date, 17 structural PARP enzymes have been described[78]. PARP1 — the most abundantly expressed isoform in humans — and PARP2 function to detect and mark DNA single-strand breaks (SSB) by binding to the site of DNA damage and synthesizing poly [ADP-ribose] chains, which recruit a host of scaffold proteins and DNA-repair enzymes to mend the break[79]. As alluded to, PARP protein levels are upregulated in SCLC relative to other lung cancers[76]. In particular, PARP1 has been found to be highly expressed at both the mRNA and protein levels in SCLC samples[76]. In addition to DNA repair, this protein is a co-activator of the transcription factor E2F1 (FIG. 2), and has been implicated in various cellular processes involved in tumorigenesis — including cell differentiation, proliferation, and transformation[80]. The results of initial *in vitro* studies indicated that SCLC cell lines are sensitive to PARP inhibitors, and provided preclinical validation that PARP inhibition enhances the anticancer activity of chemotherapy (and perhaps other DNA-damaging therapies) by downregulating key DNA-repair mechanisms[76]. These preclinical data supported the inclusion of a cohort of patients with SCLC in a phase I study of monotherapy with the PARP inhibitor talazoparib; the reported ORR was 9% and the clinical benefit rate at ≥16 weeks was 26%[81]. Indeed, clinical trials of a number of PARP inhibitors, in a range of treatment settings, are ongoing in patients with SCLC (TABLE 1).

Various PARP inhibitors have received FDA approval or a ‘breakthrough therapy’ designation for the treatment of patients with ovarian cancer harbouring deleterious *BRCA1* or *BRCA2* mutations[82,83]. *BRCA1/2* are critical mediators of the DNA double-strand break repair pathway involving homologous recombination (HR). HR-deficient (HRD) tumour cells depend on PARP-mediated SSB-repair pathway[84,85], as well as other back-up pathways involving RAD52 (REFS 86,87) and DNA polymerase θ, for survival[88,89]. This synthetic lethal dependency can be exploited therapeutically; thus, PARP inhibition leads to selective lethality of *BRCA1/2*-mutated tumour cells. However, *BRCA1/2* mutations are notably rare in primary human SCLCs, occurring in <2% of cases[12,13]. Beyond *BRCA1/2* mutations,

HRD can be assessed using allele specific copy-number analysis of data generated from single-nucleotide polymorphism (SNP) microarrays and now next-generation sequencing (NGS) approaches that quantify the resulting characteristic large-scale chromosomal aberrations[90], and which have been shown to predict PARP inhibitor sensitivity in patients with *BRCA1/2*-wild-type ovarian cancer[91]. Surprisingly, however, HRD-assay scores do not seem to correlate with sensitivity to PARP inhibitors in SCLC cell lines[92].

A distinct mechanism, high expression levels of schlafen family member 11 (SLFN11), has been identified as a critical determinant of PARP-inhibitor sensitivity in SCLC cell lines and patient-derived xenografts[92,93]. SLFN11 is actively recruited to sites of DNA damage, inhibits HR[94], and activates a cellular replication-stress response[93]. Notably, SLFN11 expression correlates with sensitivity to DNA-damaging agents (such as irinotecan, etoposide, and cisplatin) in other malignancies[95–98]. In line with the preclinical evidence[92], high levels of SLFN11 expression (H-score ≥1) was associated with favourable tumour responses, progression-free survival (PFS), and overall survival in patients with SCLC who were treated with temozolomide and the PARP inhibitor veliparib, but not temozolomide plus placebo, in a randomized phase II clinical trial[99]. Of note, SLFN11 expression levels were defined using tumour samples obtained at initial diagnosis, and all patients enrolled had received at least one prior treatment[99], which could have led to downregulation of SLFN11 at the time of study treatment; thus, this population might not have had ideal responses to PARP inhibition. Indeed, mechanisms to upregulate SLFN11 in chemoresistant patients are currently being considered. The utility of SLFN11 expression as a predictive biomarker for PARP-inhibitor therapy in SCLC will require validation in prospective biomarker-stratified trials.

EZH2 inhibition

The polycomb repressor complex 2 (PRC2) is a multiprotein chromatin-modifying complex that inhibits gene expression by promoting local histone methylation. EZH2 is the enzymatic histone-lysine *N*-methyltransferase subunit of PRC2, and mediates histone H3 lysine 27 dimethylation and trimethylation (H3K27me2 and H3K27me3)[100] (FIG. 2). EZH2 is mutated in some human cancers at gain of function hotspots that increase its enzymatic activity and thereby promote H3K27me3 (REF. 101). EZH2 is not commonly mutated in SCLC but the level of EZH2 expression is higher in SCLCs than in any tumour type included in The Cancer Genome Atlas[40,76]. Expression of the *EZH2* gene is under the direct control of E2F family of transcription factors, including E2F1 (REF. 102) (for which PARP1, itself overexpressed in SCLC cells[76], acts a co-activator). E2F transcriptional activity is negatively regulated by product of the *RB1* tumour-suppressor gene (Rb); the nearly universal loss of *RB1* — and thus functional Rb — in SCLC cells results in a high level of E2F transcriptional activity, and consequent high EZH2 expression levels[103]. These observations define a model in which EZH2 expression is primarily promoted by one of the pathognomonic genetic alterations of SCLC (FIG. 2).

In 2017, findings from multiple patient-derived xenografts linked the upregulation of EZH2 with H3K27me3-associated *SLFN11* gene silencing as a frequent mechanism of acquired chemoresistance in SCLC[104]. EZH2-mediated suppression of *SLFN11* was observed in 40%

of SCLC models selected *in vivo* for acquired chemotherapeutic resistance[104]. Mechanistically, loss of SLFN11 expression increases HR efficiency and, therefore, augments repair of DNA damage induced by cytotoxic chemotherapy. Importantly, EZH2 inhibition was found to prevent *SLFN11* silencing and maintain the sensitivity of SCLC xenografts to chemotherapy[104], suggesting a potential combinatorial strategy to enhance the effectiveness of current standard therapies for this recalcitrant disease. Various EZH2 inhibitors are undergoing clinical testing in the treatment of a range of malignancies; although clinical trials enrolling patients with SCLC are a research priority, at present, no such studies are underway.

WEE1-targeted cell-cycle vulnerabilities

The protein product of *TP53*, p53, has a critical role in the DNA-damage-response network, inducing cell-cycle arrest and initiation of apoptosis in cells exposed to genotoxic stress. Accordingly, *TP53* deficiency leads to defective cell-cycle arrest at the G1/S checkpoint (FIG. 2), blunts the DNA-damage response, and contributes to replication stress[105–107]. In SCLC cells, combined loss of *RB1* and *TP53* result in markedly defective G1/S cell-cycle checkpoint capacity and, consequently, increased dependency on the G2/M checkpoint for adequate DNA repair and ultimately cell survival; rational targeting of the G2/M checkpoint might exploit this tumour-specific vulnerability[107].

The tyrosine kinase WEE1 is an important gatekeeper of G2/M checkpoint (FIG. 2), and induces G2 arrest via inhibitory phosphorylation of cyclin-dependent kinases 1 and 2 (REF. 108). The combination of a WEE1 inhibitor with any of several classes of DNA-damaging agents, including antimetabolites (gemcitabine or 5-fluorouracil), topoisomerase inhibitors (camptothecin or doxorubicin), DNA-crosslinking agents (cisplatin or carboplatin), and PARP inhibitors, results in synergistic efficacy in *TP53*-deficient cervical, colon, pancreatic, and NSCLC cell lines[109–111]. As such, WEE1 is a promising target for SCLC therapy. Single-agent and combination studies of WEE1 inhibitors are now active in the clinic[112,113], and include studies in patients with relapsed and/or refractory SCLC (TABLE 1). The role of *TP53/RB1* status (that is, context dependency) and WEE1 expression as predictive biomarkers of response to WEE1-inhibitor therapy are of great interest, and remain an area of substantial controversy in preclinical studies[109,111,114,115].

The inhibitory Notch ligand DLL3

DLL3 is normally expressed in the developing CNS and has a key role in somitogenesis, the process by which somites (bilaterally paired blocks of mesoderm tissue) form along the anterior–posterior axis of the developing embryo[116,117]. The Notch pathway has been implicated in regulating neuroendocrine versus epithelial-cell differentiation in embryonic lung development[118] and, more recently, in SCLC oncogenesis[12]. Notch activation is oncogenic in some tumour types; however, in neuroendocrine tumours, Notch signalling suppresses oncogenesis and tumour growth[12,119]. Unlike other mammalian Notch family members, DLL3 is predominantly located in the Golgi apparatus and inhibits Notch 1 signalling in cis[120]. In high-grade neuroendocrine tumours, including SCLC, DLL3 is highly upregulated and aberrantly expressed on the cell surface, making it a potential therapeutic target[121].

Rovalpituzumab tesirine (Rova-T) is a novel, first-in-class, antibody–drug conjugate with high specificity for DLL3. Rova-T binds to DLL3 expressed on the cell surface, is internalized, and subsequent cleavage of a linker moiety releases the pyrrolobenzodiazepine (PBD) dimer cytotoxic payload from the anti-DLL3 antibody, resulting in tumour-specific DNA damage and cell death. PBDs, originally discovered in *Streptomyces* species of bacteria, are a class of sequence-selective, DNA-minor-groove-binding agents that form covalent crosslinks between the N2 of guanine and the C11 position of the PBD[122,123]. The resulting PBD–DNA adduct leads to replication-fork stalling, preventing DNA replication and causing cell-cycle arrest. PBDs are not inherently tumour specific; thus, conjugation of PBDs to an anti-DLL3 antibody enables a potential targeted therapeutic approach in SCLC. Preclinical findings demonstrated *in vivo* efficacy of Rova-T in patient-derived xenograft models of SCLC, with a strong correlation between the level of DLL3 expression and therapeutic activity[121].

Results of the first-in-human phase I clinical trial of Rova-T in patients with recurrent metastatic SCLC and large-cell neuroendocrine lung cancers were published in 2017 (REF. 124). The study investigators defined a recommended phase II dose and schedule (0.3 mg/kg every 6 weeks), and identified dose-limiting toxicities, including thrombocytopenia, liver-test abnormalities, and serosal effusions. Among the evaluable patients, 17% (11 of 65) had a confirmed objective response and 54% (35 of 65) had stable disease. The median duration of response was 5.6 months (95% CI 2.5–8.3 months), median PFS was 3.1 months (95% CI 2.7–4.1 months), and the median overall survival was 4.6 months (95% CI 3.9–7.1 months). In patients with a high level of DLL3 expression (defined immunohistochemically as detectable protein expression in at least 50% of tumour cells), the ORR was 39% (10 of 26) and the disease-control rate (stable disease or objective response) was 89% (22 of 26). Most notably, among those patients with tissue available for protein analysis, responses were observed exclusively in those with a high DLL3 expression level, further supporting the preclinical observation that the efficacy of Rova-T correlates with the level of DLL3 expression. In an exploratory analysis, median PFS was 4.5 months (95% CI 3.0–5.4 months) in the DLL3-high patient subgroup compared with 2.3 months (95% CI 1.3–3.3 months) in the DLL3-low subgroup; overall survival differences between the DLL3-high and DLL3-low subgroups were not reported[124]. These data support DLL3 as a candidate predictive bio-marker for this therapy — potentially the first such bio-marker in SCLC. These results, in a heavily pretreated patient population, seem promising; however, additional studies are needed to determine the clinical benefits of Rova-T treatment and multiple trials of this agent are ongoing (TABLE 1), including an open-label, multicentre, phase II study of the efficacy of Rova-T in the third-line and later-line treatment of patients with DLL3-positive ES-SCLC (NCT02674568). Further proposed studies of Rova-T in patients with ES-SCLC encompass frontline treatment of DLL3-high disease (NCT02819999), maintenance therapy following first-line platinum-based chemotherapy (NCT03033511), and combination treatment with nivolumab — with or without ipilimumab — in the second-line setting (NCT03026166).

Aurora kinase

The aurora kinase family proteins have key roles in mitosis. Aurora kinase A is essential for centrosome function, spindle assembly, chromosome alignment, and mitotic entry[125]. Knockdown of Aurora A expression induces G2/M-phase arrest and thereby inhibits the proliferation of human SCLC cells[126]. Moreover, targeted drug screens have indicated that the neuroendocrine-low, variant subtype of SCLC with high MYC and NEUROD1 expression is vulnerable to aurora kinase inhibition, which strongly suppressed tumour progression when combined with chemotherapy in the aforementioned mouse model of this disease subtype[49]. Alisertib, an investigational, orally administered, selective inhibitor of aurora kinase A, has preclinical therapeutic activity across multiple tumour types[127]. In a multicentre phase I/II study of this agent in patients with various solid tumours[128], a recommended phase II dose and schedule was defined, and dose-limiting toxicities, including neutropenia, leukopenia, and anaemia, were noted. In a phase II study expansion cohort comprising patients with relapsed and/or refractory SCLC, single-agent alisertib therapy resulted in an ORR of 21% (10 of 48 patients; 95% CI 10–35)[128]. Furthermore, in a randomized phase II study of paclitaxel plus either alisertib or placebo in the second-line treatment of patients with SCLC, the ORR was 22% in the experimental arm (20 of 89) and 18% in the control arm (16 of 89); the median PFS was 101 days versus 66 days (HR 0.71,95% CI 0.51–0.99; P= 0.04)[129]. Further clinical investigations are needed to better study and optimize the therapeutic utility of this compound in SCLC.

Immunotherapy for SCLC

Escape from immune surveillance is a well-recognized feature of cancer[130]. The development of therapies to enhance antitumour immune responses — particularly antagonistic antibodies targeting the inhibitory immune-checkpoint proteins cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), programmed cell death protein 1 (PD-1), or its ligand PD-L1 (FIG. 2) — has led to exciting new treatment options for patients, across multiple tumour types[131,132]. The high mutational burden of SCLCs, resulting in a large number of potential tumour-specific antigens, has raised hope that immunotherapy might be effective in this disease. At present, only limited data have been reported on immune-checkpoint blockade in patients with SCLC, although a number of clinical trials of this promising therapeutic approach are underway (TABLE 2).

CTLA-4

Ipilimumab, a fully human monoclonal IgG1, binds to CTLA-4 expressed by T cells and blocks the interaction of this receptor with its ligands CD80 and CD86 on antigen-presenting cells (FIG. 2). Upon ligand binding, CTLA-4 transmits signals that suppress T-cell priming, and thus blockade of this interaction using ipilimumab can promote T-cell activation and an anticancer immune response[133]. In a randomized phase II study, investigators evaluated the activity of ipilimumab in combination with paclitaxel and carboplatin versus paclitaxel and carboplatin alone in patients with ES-SCLC[134]; 133 patients with previously untreated ES-SCLC were randomly assigned (1:1:1) to receive either concurrent ipilimumab and chemotherapy, phased-ipilimumab and chemotherapy, or the control regimen of chemotherapy alone. This study was not stratified by PD-L1 expression status, and the

immune-related response criteria (irRC) were used to assess response to therapy. The irRC are modified RECIST criteria that capture the unique tumour response patterns observed with immunotherapy, including regression of index lesions coincident with the appearance of new lesions, and initial progression followed by tumour stabilization or a decrease in tumour burden[135]. The phased administration of ipilimumab in combination with paclitaxel and carboplatin, after induction with the same chemotherapy regimen plus placebo, resulted in an improvement in immune-related PFS (as per the iRC) compared with that observed with induction and maintenance chemotherapy plus placebo (HR 0.64; P= 0.03); however, no significant improvement in PFS (HR 0.93; P= 0.37) or overall survival (HR 0.75; P= 0.13) was demonstrated[134]. Moreover, induction therapy with concurrent ipilimumab plus chemotherapy with maintenance chemotherapy plus placebo did not improve patient outcomes. In the same setting, a follow-up phase III trial of phased ipilimumab in combination with more-conventional first-line chemotherapy (comprising etoposide and a platinum-based agent) versus the same chemotherapy regimen plus placebo was negative for its primary end point of overall survival: median 11.0 months versus 10.9 months (HR 0.94, 95% CI 0.81–1.09; P= 0.38)[136]. Furthermore, ipilimumab was associated with a high frequency of some toxicities, including diarrhoea, rash, and colitis[136].

PD-1 and PD-L1 blockade

PD-L1 is expressed on a range of cell types, including some neoplastic and non-neoplastic cells within tumours, and interaction of this protein with PD-1 on T cells results in local suppression of T-cell activation and cytotoxicity, and promotes T-cell exhaustion (FIG. 2). Nivolumab, a fully human IgG4, binds to PD-1 and blocks its interaction with PD-L1, which can reinvigorate T-cell activity and potentially unleash suppressed antitumour immunity. Although ipilimumab alone did not improve chemotherapy responsiveness of patients with SCLC[136], preclinical data from the melanoma literature suggests that combined PD-1 and CTLA-4 blockade can synergistically enhance activation of tumour-specific T cells and antitumour activity through complementary mechanisms[137]. Outcome data from CheckMate 032, a multicentre, open-label, phase I/II trial of nivolumab with or without ipilimumab in patients with recurrent ES-SCLC[138], was reported in 2016. The study investigators enrolled 216 patients, including 98 patients treated with nivolumab alone and the remainder with alternative schedules incorporating both nivolumab and ipilimumab. The toxicity profiles were similar to those observed in prior studies of these agents, including grade 3–4 events in 13% of patients receiving nivolumab alone, and between 19% and 30% of patients receiving nivolumab and ipilimumab. The ORRs were 10% in the nivolumab arm and 19–23% in the combination arms, translating into an encouraging 1-year survival of 33% and 35–43%, respectively[138]. These results have led to the incorporation of the nivolumab and ipilimumab combination as a National Comprehensive Cancer Network (NCCN) guideline recommendation for the second-line treatment of ES-SCLC[20]. However, the efficacy of checkpoint inhibitors in patients with SCLC needs to be confirmed in randomized trials, and these treatments have not been formally approved for the treatment of SCLC in the USA or elsewhere and, therefore, remain experimental. Potential toxicity remains an ongoing concern with combination immunotherapy, and physicians should have a substantive discussion with their patients regarding potential risks and benefits of treatment. Close monitoring of the endocrine axis and early detection of immune-related adverse events, such

as colitis and pneumonitis, are critical because patients can benefit from early intervention with high-dose steroids and/or drug discontinuation.

A high mutational burden has been identified as a potential predictor of effective immunotherapy[139]; however, despite the fact that SCLCs have among the highest mutational burdens of all tumour types[11], the clinical efficacy of checkpoint inhibitors in this disease seems to be far less pronounced than would be expected based on the experiences in other highly mutated cancers, such as melanoma and NSCLC. In stark contrast to other tumour types, SCLCs rarely express PD-L1, which might at least partially explain this disparity. In an immunohistochemical analysis of archival formalin-fixed paraffin-embedded SCLC specimens using two different assays (VENTANA PD-L1 (SP142) and 28–8 pharmDx)[140], the overall prevalence of PD-L1 expression in tumour cells was found to be low (16.5%) and was not markedly different between LS-SCLC and ES-SCLC samples. Importantly, PD-L1 positivity does not seem to be predictive of immunotherapy response in this setting[138]. Work to define predictive biomarkers of immunotherapy response and the characteristics of the SCLC immune microenvironment is ongoing. In addition, multiple clinical trials of combination strategies to bolster the efficacy of immune-checkpoint inhibition are underway in patients with SCLC (TABLE 2).

CD47

CD47 is a cell-surface molecule that inhibits activation and phagocytic activity of macrophages by engaging signal-regulatory protein α[141] (SIRPα; FIG. 2). In fact, CD47 is involved in regulating a wide variety of physiological processes, including platelet and neutrophil activation, T-cell function, vascular signalling by nitric oxide, suppression of dendritic cell activity, and inhibition of monocyte activation[142]. This protein is expressed on many normal cells, but is highly upregulated on the surface of human SCLC cells and has been implicated in immune escape by tumours[143]. In particular, disruption of the interaction of CD47 and SIRPα using anti-CD47 antibodies induced macrophage-mediated phagocytosis of human SCLC cell lines *in vitro* and in mouse xenograft models[143]. Moreover, CD47 blockade has been shown to trigger T-cell-mediated destruction of immunogenic tumours[144], and thus combination strategies with immune-checkpoint blockade might enhance the antitumour effects of anti-CD47 antibodies. Clinical exploration of CD47/SIRPα inhibition as a therapeutic strategy for SCLC is expected to begin in 2017.

Conclusions

Large-scale genomic, proteomic, and transcriptomic analyses have led to the identification of new druggable targets in SCLC (FIG. 2). PARP1, EZH2, WEE1, and DLL3 are all examples of novel targets implicated as vulnerabilities, and tractable therapeutic opportunities, in SCLC; drugs for each of these targets are under active clinical investigation. Rapid progress in the field of immuno-oncology has similarly opened a door to new treatment options. Treatment with the combination of ipilimumab and nivolumab is now NCCN-recommended for patients with recurrent SCLC after platinum-based therapy. Nevertheless, the immune microenvironment of SCLC seems to be distinct from that of other solid tumours, with alternative targets, such as CD47, coming to the fore. Defining

predictive biomarkers for targeted therapies and optimizing activation of antitumour immune response in SCLC are areas of intensive ongoing investigation. The progress made in defining novel therapeutic targets in SCLC has renewed hope for advances in combatting this recalcitrant disease. Several ongoing and upcoming clinical trials will test whether these new insights into tumour biology can be successfully translated into major therapeutic breakthroughs in what has been a singularly challenging and deadly disease.

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Key points

- Small-cell lung cancer (SCLC) is a high-grade neuroendocrine tumour associated with a poor overall survival, and limited progress has been made in the treatment of this disease over the past three decades
- Over the past 5 years, advances in our understanding of multiple aspects of the biology of SCLC have led to the development of new therapies that are currently under clinical investigation
- Poly [ADP-ribose] polymerase (PARP) is abundantly expressed in SCLC and is involved in DNA-damage repair; clinical trials of the PARP inhibitors veliparib, olaparib, and talazoparib are ongoing in patients with SCLC
- Enhancer of zeste homologue 2 (EZH2) is a regulator of chromatin remodelling that can drive acquired chemoresistance; therapeutic targeting of EZH2 might augment and extend the durability of chemotherapy responses
- Delta-like protein 3 (DLL3) is an inhibitory Notch ligand that is overexpressed in many SCLCs; rovalpituzumab tesirine (Rova-T), an anti-DLL3-antibody drug conjugate, has shown promising activity in preclinical and early phase clinical studies
- SCLC has a high mutational burden, raising hopes regarding immunotherapy, and immune-checkpoint blockade has shown encouraging clinical activity in patients with this disease, despite typically low tumoural expression of immune-checkpoint proteins

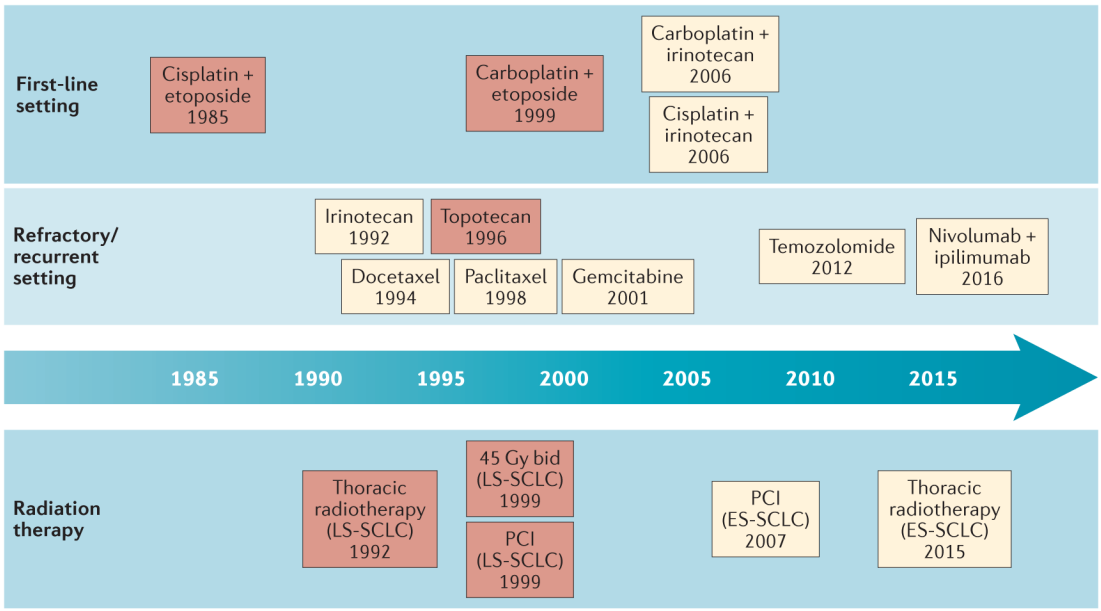

Figure 1. Timeline of therapeutic advances for small-cell lung cancer (SCLC)

This timeline illustrates the paucity of new treatment options for patients with SCLC over the past three decades. The red-shaded boxes represent standard-of-care therapies that have been approved by the FDA; the yellow-shaded boxes represent therapies that have been recommended by the National Comprehensive Cancer Network (NCCN)[20], but are not currently approved by the FDA. Since 1985, the cisplatin and etoposide chemotherapy regimen has remained the standard-of-care first-line systemic treatment for patients with extensive-stage (ES)-SCLC. Subsequent regimens, in which carboplatin or irinotecan substitute for cisplatin or etoposide, respectively, have comparable effectiveness, but differing toxicity profiles. Second-line therapies that are recommended in the NCCN guidelines include topoisomerase inhibitors, taxols, alkylating agents, and, since 2016, immunotherapy, although only topotecan is approved by the FDA for use in this setting. For limited-stage (LS)-SCLC, radiation treatment early in the course of chemotherapy is recommended, classically at a total dose of 45 Gy delivered in 30 twice-daily (b.i.d.) fractions of 1.5 Gy (over the course of 3 weeks), with additional prophylactic cranial irradiation (PCI). More recently, thoracic irradiation has been shown to be of benefit for some patients with ES-SCLC; however, the role of thoracic radiation and PCI in the treatment of ES-SCLC remains controversial.

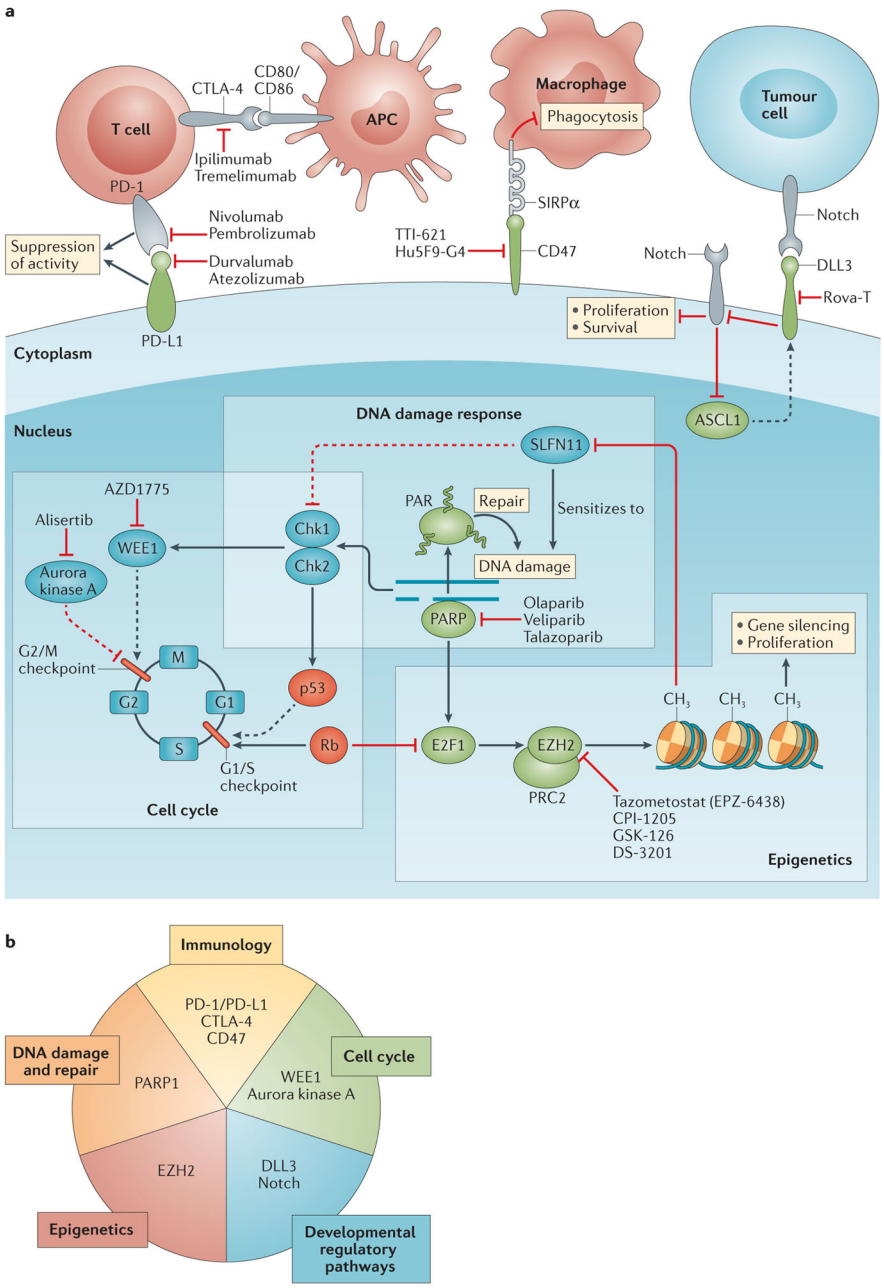

Figure 2. Signalling pathways and physiological domains that are the focus of experimental targeted therapies for small-cell lung cancer (SCLC)

a | Dashed and solid lines indicate indirect and direct interactions, respectively. Proteins in green are typically upregulated in SCLCs compared with nonmalignant lung tissue, while those in red are downregulated or absent. Examples of the investigational molecularly targeted agents or antibody-based treatments targeting each signalling node are provided. **b** | The novel, investigational, targeted therapeutics for SCLC are predicated on five aspects of cancer biology. Immune-checkpoint blockade with antibodies targeting programmed cell death protein 1 (PD-1), programmed cell death 1 ligand 1 (PD-L1), and/or cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) can prime the adaptive immune response to

SCLC cells, whereas antibody-mediated blockade of the ‘don’t eat me’ protein CD47 can enable phagocytosis of tumour cells by macrophages. The use of small-molecule inhibitors of key regulators of the cell cycle, such as the protein kinases WEE1 and aurora kinase A, exploits the inherent lack of the G1/S-checkpoint activity resulting from loss of the tumour suppressors p53 and retinoblastoma-associated protein (Rb) in most SCLC cells. WEE1 regulates the G2/M cell-cycle checkpoint that is essential for ensuring the integrity of the genome in such cancer cells and, thus, inhibition of this kinase can lead to mitotic catastrophe and apoptosis, particularly if combined with DNA-damaging therapies. By contrast, aurora kinase A has essential roles in mitosis, and inhibitors of this protein results in cell-cycle arrest, preventing cell proliferation. Inhibitors of Notch have demonstrated antitumour effects in preclinical studies. Moreover, Delta-like protein 3 (DLL3), an inhibitory Notch ligand, is specifically upregulated in SCLC and can, therefore, be leveraged for selective tumour targeting with the antibody–drug conjugate rovalpituzumab tesirine (Rova-T). Inhibitors of the histone-lysine *N*-methyltransferase EZH2 (also known as enhancer of zeste homologue 2), the enzymatic histone-lysine *N*-methyltransferase subunit of the polycomb repressive complex 2 (PRC2) chromatin-remodelling machinery, can prevent chemoresistance and cell proliferation by counteracting epigenetic gene silencing, in particular, of schlafen family member 11 (SLFN11) — a protein that negatively regulates homologous recombination DNA repair. Poly [ADP-ribose] polymerase (PARP) inhibitors prevent the activation of DNA-repair proteins by PARP1 and trap this enzyme on DNA, which causes further DNA damage that can eventually result in cell death. APC, antigen-presenting cell; ASCL1, achaetescute homologue 1 (also known as ASH-1); Chk1/2, checkpoint kinase 1/2; E2F1, transcription factor E2F1 (also known as retinoblastoma-associated protein 1); PAR, poly-ADP-ribosylation.

Table 1

Selected ongoing studies of targeted therapy for extensive stage small-cell lung cancer

Therapy	Molecular target	Study name	Study phase	ClinicalTrials.gov study identifier	Estimated primary completion date
First line					
Veliparib (plus carboplatin and etoposide)	PARP	M14-361/2014-001764-35	I/II	NCT02289690	August 2017
Rova-T (± cisplatin and etoposide)	DLL3	SCRX001-004	I	NCT02819999	October 2020
Maintenance					
Olaparib plus cediranib or no maintenance treatment (after cis/carboplatin and etoposide ± cediranib)	PARP; VEGF-RTKs	SUKSES-B	II	NCT02899728	December 2018
Rova-T plus dexamethasone versus placebo (after cis/carboplatin and etoposide)	DLL3	MERU	III	NCT03033511	August 2019
Second line and beyond					
Olaparib plus CRLX101 (nanoparticle camptothecin)	PARP	160107/16-C-0107	I/II	NCT02769962	June 2018
Olaparib plus cediranib	PARP; VEGF-RTKs	NCI-2015-01097/9881	II	NCT02498613	May 2018
Olaparib plus durvalumab	PARP; PD-L1	MEDIOLA	I/II	NCT02734004	October 2018
Olaparib plus AZD1775	PARP; WEE1	D6010C00005/REFMAL 384	I	NCT02511795	January 2018
AZD1775	WEE1	2015-10-178	II	NCT02593019	March 2017
AZD1775 plus carboplatin	WEE1	D419QC00002/2016-001202-42	II	NCT02937818	May 2020
Rova-T	DLL3	TRINITY	II	NCT02674568	March 2017
Rova-T	DLL3	SCRX001-007	I	NCT02874664	June 2017

Cis/carboplatin, cisplatin or carboplatin; DLL3, Delta-like protein 3; PARP, poly [ADP-ribose] polymerase; PD-L1, programmed cell death 1 ligand 1; Rova-T, rovalpituzumab tesirine; VEGF-RTKs, vascular endothelial growth factor receptor tyrosine kinases; WEE1, Wee1-like protein kinase.

Table 2

Ongoing studies of immune-checkpoint blockade in small-cell lung cancer

Immunotherapy	Study name	Study phase	ClinicalTrials.gov study identifier	Estimated primary completion date
LS-SCLC				
Nivolumab plus ipilimumab	STIMULI	II	NCT02046733	October 2019
Pembrolizumab and concurrent radiotherapy ± chemotherapy (cis/carboplatin and etoposide)	NA	I	NCT02402920	July 2023
ES-SCLC: first line				
Pembrolizumab with cis/carboplatin and etoposide	KEYNOTE-011	I	NCT01840579	June 2019
Cis/carboplatin and etoposide ± pembrolizumab	REACTION	II	NCT02580994	June 2020
ES-SCLC: maintenance				
Nivolumab ± ipilimumab versus placebo	CheckMate 451	III	NCT02538666	September 2018
ES-SCLC: second line and beyond				
Nivolumab versus topotecan or amrubicin	CheckMate 331	III	NCT02481830	March 2018
Carboplatin and etoposide plus atezolizumab or placebo	IMpower133	I/III	NCT02763579	June 2019
Tremelimumab and durvalumab ± radiation	NCI-2016-00026/Winship3112-15/ESR-14-10531	II	NCT02701400	April 2019
Pembrolizumab versus topotecan	AFT-17	II	NCT02963090	May 2019
BMS-986012 ± nivolumab	CA001-030	I/II	NCT02247349	October 2018
Pembrolizumab	KEYNOTE-158	II	NCT02628067	September 2017
Pembrolizumab plus irinotecan	PembroPlus	Ib/II	NCT02331251	December 2016
Durvalumab plus olaparib	MEDIOLA	I/II	NCT02734004	October 2018

Cis/carboplatin, cisplatin or carboplatin; ES-SCLC, extensive-stage SCLC; LS-SCLC, limited-stage SCLC; NA, not applicable.