Advances in novel molecular typing and precise treatment strategies for small cell lung cancer

Rilan Bai, Lingyu Li, Xiao Chen, Yuguang Zhao, Wei Song, Huimin Tian, Jiuwei Cui

Cancer Center, the First Hospital of Jilin University, Changchun 130021, China
Correspondence to: Jiuwei Cui. Cancer Center, the First Hospital of Jilin University, Changchun 130021, China. Email: cuijw@jlu.edu.cn.

Abstract
Small cell lung cancer (SCLC) is a high-grade neuroendocrine (NE) cancer characterized by high circulating tumor-cell burden and early extensive metastasis. Considering the complexity of SCLC genes and the immune microenvironment, their unique molecular heterogeneity profiles have been continuously explored. The understanding of SCLC subtypes has recently changed from traditional “classical” and “variant” types to “NE” and “non-NE” phenotypes and to the subtypes defined by major transcriptional regulators, which indicates the gradual revelation of high intratumoral heterogeneity and plasticity characteristics of SCLCs. Advances in genomics as well as the development of single-cell sequencing analysis and new preclinical models have helped investigators gain many new insights into SCLCs and the development of targeted therapy and immunotherapy strategies. This article provides an overview of changes in molecular typing, tumor heterogeneity, and plasticity and that of advances in the precise treatment of different subtypes of SCLC.

Keywords: Small cell lung cancer; transcription factors; tumor heterogeneity; plasticity; immune

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Introduction
Small cell lung cancer (SCLC) is a high-grade neuroendocrine (NE) lung cancer, accounting for approximately 15% of all lung cancers, and is strongly associated with severe tobacco exposure (1). SCLCs are characterized by a high proliferation rate, high circulating tumor-cell (CTC) burden, early and extensive metastasis, high mortality, and poor prognosis (2-4), with a survival time of approximately 10 months and a 5-year overall survival (OS) rate of 6% (5). Although cytotoxic chemotherapy has been the standard treatment for decades, it is only temporarily effective in a vast majority of patients; no substantial progress has been made in systemic therapy. SCLC has been considered a homogeneous disease owing to the almost universal loss of tumor protein p53 (TP53), retinoblastoma 1 (RB1), and NE or epithelial differentiation features (6-8). Increasing evidence has shown that SCLC is a genetically complex disease with significant genomic instability, which manifests as aneuploidy, multiple intra- and inter-chromosomal rearrangements, and various genetic changes affecting cell fate, including tumor suppressor gene mutations, copy number variations, and somatic mutations in transcription factors (9), such as v-MYC avian myelocytoma viral oncogene homolog (MYC) family gene mutations, inactivating mutations in NOTCH family members, and phosphatase tension protein homolog (PTEN) deletion. However, most targeted therapies for these genetic changes have failed. The tumor immune microenvironment of SCLC is complex, and most reports reveal that it is of “immune desert” type, which resulted in mostly discouraging responses of SCLCs to immunotherapy. Considering the complexity of genes and the immune microenvironment of SCLCs, their unique molecular heterogeneity profiles have been continuously explored. The understanding of SCLC subtypes has recently changed from the traditional “classical/variant” type to the “NE/non-NE” phenotype and to the subtypes defined by
dominant transcriptional regulators (6,10), which led to the gradual revelation of its different gene expression profiles. Moreover, studies have shown that different subtypes are dynamically changing, emphasizing the intratumoral heterogeneity (ITH) and strong plasticity of SCLCs, which are associated with tumor evolution, metastasis, and acquired drug resistance. Recent advances in genomics and the development of new preclinical models have helped researchers gain new insights into ITH, specific genetic alterations, and molecular methods for the classification of this disease, and a better understanding of these biological features has facilitated the identification of new targets and the development of potentially suitable targeted therapies.

**Transformation in molecular typing of SCLCs**

**Traditional classification of SCLCs**

Thirty years ago, SCLC cell lines were implanted as xenografts, and their subtypes were first distinguished based on morphological differences: “classical” phenotype, high expression of NE markers and anchorage-independent growth patterns; “variant” phenotype, low expression of NE features and adherent or loosely adherent growth patterns (3). However, the 2015 World Health Organization classification of lung tumors considers SCLCs to be histologically homogenous, with generalized loss of TP53, RB1, and NE/epithelial differentiation features (6-8). They are characterized by small cells with scanty cytoplasm and a nucleus showing fine granular chromatin and a lack of prominent nucleoli, which are similar to the features of “classical” SCLC subtype. They initially described that the “variant” subtype may represent a mixed type of SCLC with large cell NE carcinoma (LCNEC) in the current classification (11). At present, SCLCs are primarily classified into “NE” subtype and “non-NE” subtype based on different NE markers (3,12). Zhang et al. (12) developed a large scoring system for lung cancer based on 50 genes [25 genes positively correlated with NE differentiation, such as achaete-scute homolog 1 (ASCL1), neurogenic differentiation factor 1 (NEUROD1), insulinoma-associated protein 1 (INSM1), syntaxin protein (SYP), brain expressed X-linked 1 (BEX1), and Nkx homeobox-1 gene (NKX2-1); 25 genes negatively correlated with NE differentiation, such as RE1 silencing transcription (REST), ASCL2, and B-cell lymphoma/leukemia-2 (BCL2)], confirming that the NE scores can be used to separate NE-high and NE-low subtypes of human SCLC and SCLC cell lines, with more than 90% concordance with related genes and pathways (12). Different subtypes exhibit significant heterogeneity in morphology, growth characteristics, genetic alterations, and immune infiltration (12) and exhibit different sensitivities to platinum-based chemotherapy, targeted therapy, and immunotherapy. The subtypes with high NE scores were associated with classical morphology, high expression levels of NE markers, epithelial cell phenotype, and expression of NKX2-1, delta-like protein 3 (DLL3), and delta-like 1 homolog (DLK1), whereas phenotypes with low NE scores were associated with variant morphology, low or no expression of NE markers, the activation of MYC, REST, NOTCH, HIPPO and transforming growth factor-β (TGF-β) pathway, and epithelial-mesenchymal transition (EMT). In terms of chemosensitivity, NE-high SCLCs were reported to be more sensitive to cisplatin, whereas “non-NE” SCLCs were mostly resistant to cisplatin. With regard to immune infiltration, NE-high SCLCs have an “immune desert” phenotype, whereas NE-low SCLCs exhibit an “immune oasis” phenotype (13,14). Nevertheless, the classification of SCLCs remains insufficient to guide precise treatment.

**Novel SCLC subtypes defined by transcriptional regulators**

Recently, based on the findings of large-scale gene expression profiling conducted using samples collected from patients with SCLC (15), patient-derived xenografts (PDXs) (16), cell lines (17,18), and genetically engineered mouse models (GEMMs) (19,20), researchers have proposed that different SCLCs can be defined based on unique transcription-factor expression profiles overlapping with RNA sequencing (RNA-seq) profiles. Moreover, they have identified several target genes that are differentially regulated by these transcription factors and are related to SCLC biology (6). SCLC-A is defined based on the expression of transcription factor ASCL1. High ASCL1 expression is considered to be associated with high NE marker expression and to have the potential to regulate stemness, cell-cycle progression, and mitosis (19,21). The target genes of ASCL1 include MYCL of the MYC family, BCL2, SOX2, rearranged during transfection (RET), oncogene nuclear factor IB (NFIB), and NOTCH ligands/inhibitors DLL3 and DLK1. The expression of the NKX2-1 gene (encoding TTF-1) is also positively regulated by ASCL1 (19). Subsequent analysis revealed that SCLC-A is divided into two clusters (SCLC-A and SCLC-A2), which differ in the expression of hairy and enhancer of split 1 (HES1) (17). SCLC-N is defined based on the expression
of NEUROD1, with an overall low expression level of NE markers (19,20). NEUROD1 promotes neurogenic differentiation of cells during their development and malignant behavior of SCLC cell lines, and its target genes MYC (19) and oncogenic MycT58A can promote tumor development (20). The common target genes of ASCL1 and NEUROD1 are INSM1, a zinc finger transcription factor that acts as a driver of NE differentiation by inhibiting the NOTCH signaling pathway (22) and HES6, an inhibitor of the HES1 transcription factor. SCLC-P is dependent on POU class 2 homeobox 3 (POU2F3), a transcription factor required for the generation, chemosensation, and immune function of specialized clusters of cells in the skin, oropharynx, gastrointestinal, and respiratory tracts (15). SCLC-P is ASCL1/NEUROD1 double-negative “non-NE” SCLC, which involves the receptor tyrosine kinase insulin growth factor receptor 1 (IFGRI) pathway and is associated with the expression of TF SOX9, ASCL2, and MYC. Finally, the key transcriptional regulator yes-associated protein 1 (YAP1) in the HIPP0 growth signaling pathway was found to drive the fourth subtype, SCLC-Y (6). YAP1 nuclear activity is associated with cancer stem cell renewal, metastasis, and chemo-resistance (18,23,24) and is considered one of the subtype-defining markers of “non-NE” SCLCs. SCLC-Y is associated with reduced expression of INSM1, enrichment of intact RB1, and possible overexpression of MYC (18); however, the expression of replication and proliferation genes is lower than that of other subtypes. Thus, some studies classify SCLC into the four subtypes “A, N, P, and Y” that is, SCLC-A (ASCL1), SCLC-N (NEUROD1), SCLC-P (POU2F3), and SCLC-Y (YAP1) (6). Studies have confirmed that there are significant differences in NE differentiation programs among these subtypes of transcriptional programs, with both ASCL1+ and NEUROD1+ subtypes being associated with a high NE program (NE marker^high/TF-1^high/DLL3^high) and POU2F3 and other ASCL1/NEUROD1 double-negative subtypes being associated with a low NE program (NE marker^low/TF-1^low/DLL3^low) (25).

Notably, it has been reported that YAP1 expression is completely absent or only present at low levels in patients with SCLC (26), and recent studies on SCLC CTC-derived xenografts (CDXs) have not found significant YAP1 subtypes (27). Subsequent immunohistochemical analysis results have also failed to confirm the unique YAP1 subtypes (25). In addition, although YAP1 is primarily expressed in “non-NE” cells, it can also be present at a low level in NE-low cells. Therefore, YAP1 may not define a unique SCLC subtype, and its role as a marker for typing transcription factors needs to be further clarified in future studies. Some investigators have further explored the association between YAP1 and immunity. Owonikoko et al. (28) found that SCLCs with YAP1 positive was enriched in long-term survivors, and associated with high expression levels of interferon-γ (INF-γ) gene, human leukocyte antigen (HLA) gene, and T-cell receptor gene, and high scores of T-cell inflammatory gene expression profile (GEP). They subsequently replicated this inflammatory phenotype using SCLC cell lines and tumor samples in two independent validation datasets (28). Similarly, another study revealed that although SCLC is a cancer with the lowest expression of immune-related genes, SCLC-Y cell lines evidently show a tendency for better antigenic presentation and innate immune response. The expression of innate immune effector genes cGAS, stimulator of interferon genes STING, HLA-E, and INF-induced genes is positively correlated with YAP1 expression, whereas NE subtypes represented by SCLC-N and SCLC-A are negatively correlated with those genes (29). Therefore, although YAP1 may not be a key transcription factor that can facilitate the precise definition of SCLC subtypes, these key findings suggest that, in patients with triple-negative SCLC, there may be a population of immunomarker-rich phenotype cells that are characterized by the loss of ASCL1/NEUROD1/POU2F3 and may be responsive to immunotherapy.

Recently, Gay et al. (30) identified four transcriptionally distinct SCLC subtypes by using non-negative matrix factorization (NMF) analysis of RNAseq from 81 resected SCLC samples and 62 SCLC cell lines, three of which were confirmed to present the characteristics defined by Rudin et al. (6) (including SCLC-A/ASCL1, SCLC-N/NEUROD1 and SCLC-P/POU2F3). The fourth is a previously undescribed subtype with NE marker negativity, generally low or no transcription factor levels, and moderately elevated RB1 protein expression. Interestingly, the expression of immune checkpoints [including programmed death-ligand 1 (PD-L1), cytotoxic T lymphocyte-associated antigen-4 (CTLA-4), cluster of differentiation (CD) 38, indoleamine 2,3-dioxygenase 1 (IDO1), T-cell immunoreceptor with Ig and ITIM domain protein (TIGIT), VISTA, inducible T-cell co-stimulator (ICOS), and lymphocyte activation gene 3 (LAG3)], HLA genes, STING, INF-γ signaling pathway, T-cell inflammatory GEPs, and a variety of other inflammatory...
markers on this novel subtype are up-regulated (30); therefore, it was named SCLC-inflamed or SCLC-I subtype. This is consistent with the findings of George et al. (21), who showed significantly high expression levels of genes encoding HLAs and other antigen presentation mechanisms in SCLC-I tumors. Another study, using CIBERSORTx deconvolution (31), quantified various immune populations according to gene expression and found that SCLC-I tumors had the highest total immune cell infiltration, including cytotoxic T cells, NK cells, and macrophages, as well as cytolytic activity scores. In addition, Gay et al. (30) showed that SCLC-I cell lines comprised “mesenchymal” tumors that lost cytokeratin and expressed vimentin (VIM), with the highest mean score of EMT, while SCLC-A was the most epithelial subtype, with the lowest score of EMT. The results of reverse-phase protein array (RPPA) of 62 SCLC cell lines support the conclusion that SCLC-I tumors express very low levels of the epithelial marker, E-cadherin (CDH1), and high levels of the mesenchymal markers, VIM and AXL (a member of the TAM family of receptor tyrosine kinases), which suggests the possibility of using EMT markers for discriminating SCLC subtypes (30). Notably, Gay et al. (30) observed higher expression of YAP1 and its transcriptional targets in both SCLC-P and SCLC-I subtypes than in the other two subtypes; therefore, SCLC-I was not specifically defined by YAP1 expression, which is consistent with recent analyses of two clinical samples (25) and CDXs (27). The proposal of novel SCLC-I may become the key to a more precise definition of SCLC subtypes, which may facilitate the effective prediction of the benefit of immunotherapy in specific patients with SCLC; however, this hypothesis needs further validation. This evidence reveals advances in novel SCLC molecular subtyping and heterogeneous biology, driving the design of biomarker-driven clinical trials. In the future, development of new models must be continued to provide strong evidence for further identification of SCLC subtypes and to dispense precise and effective subtype-based treatment for patients with SCLC.

**Tumor heterogeneity and plasticity of SCLCs**

**Tumor heterogeneity of SCLCs**

SCLCs that look similar at the histopathological level may represent different tumor subtypes. SCLC tumors and cell lines exhibit significant differences in tumor morphology, growth characteristics, and molecular properties owing to the expression or absence of NE, presenting significant intertumoral heterogeneity. The NE-high subtype lineage is primarily driven by the transcription factors ASCL1 and NEUROD1, which express NKX2-1 but lack the expression of REST (12). The NE-low subtype lacks most NE markers but can express REST; it shows activation of the NOTCH, HIPPO, TGF-β pathways and MYC oncogenes (12). Recently, emerging evidence supports a model in which biologically relevant ITH can occur within SCLC tumors and during SCLC progression, including distinct subpopulations of interacting cells. Several findings suggest that multiple transcriptional subtypes may exist in a single tumor (32-34). A study with comprehensive immunohistochemical and histopathological characterization of SCLC subtypes showed that 69% and 17% of tumors were ASCL1-dominant and NEUROD1-dominant, respectively, and 22% expressed both the factors at high levels (IHC H-score >50 for both markers) (25), which is in good agreement with the findings of Zhang et al. (12), who showed a 19.8% double high expression of ASCL1 and NEUROD1. In a study by Gay et al. (30), while <1% of cells expressed POU2F3 in any model, these rare POU2F3+ cells all showed co-expression of ASCL1; in addition, in MDA-SC39, approximately 10% of cells expressed both ASCL1 and NEUROD1, although this proportion was lower than that in other tumors. The expression profiles of these markers showed more heterogeneity in native samples than in experimental models, particularly in terms of the high incidence of ASCL1/NEUROD1 co-expression. Together, these data suggest that while most tumors or cells express only one of these transcription factors, their expression is not mutually exclusive, and this co-expression can occur on the same tumor or on the same cell.

**Plasticity transformation and associated mechanisms of SCLCs**

Single-cell and bioinformatic analyses revealed that SCLC subtype-specific ITH may be a dynamic transition process. Single-cell RNA sequencing (scRNA-seq) analysis of SCLC GEMM revealed that single tumor cells can gradually undergo evolution from one transcription factor-defined subtype/phenotype to another (32,35). For example, mesenchymal, inflamed descendants can appear spontaneously in cultures of SCLC-A cell lines (36,37). Data from SCLC cell lines of mice suggest that there may be a developmental hierarchy among subtypes that evolve
from SCLC-A to SCLC-N and subsequently to SCLC-Y (32). This indicates the possibility that these subtypes may represent the development of lineages or the existence of a continuum. ITH subtypes may underlie the natural history of SCLC. Notably, this subtype plasticity shift in SCLC is accompanied by the emergence of resistance to treatment. ScRNA-seq analysis of SCLC CTC-derived CDX models exhibited higher transcriptional ITH after platinum resistance (38). The emergence of SCLC-Y may be associated with chemo-resistance (18,23), and it has been shown that YAP1-positive “non-NE” cells cultured with CDX30P and CDX31P exhibit 5- to 7.5-fold higher resistance to cisplatin than YAP1-negative NE cells (27). A study by Song et al. (23) found that patients exhibiting high YAP1 expression had shorter survival and more advanced disease stages than those exhibiting low YAP1 expression. YAP1 may induce multidrug resistance by inhibiting apoptosis of SCLCs, and this process may be involved in the expression of CD74. Gay et al. (30) performed scRNA-seq on two SCLC-A CDX models before and after platinum treatment and observed a decrease in the proportion of ASCL1+ cells and the appearance of triple-negative (ASCL1-/NEUROD1-/POU2F3-) SCLC-I cells with EMT scores in the post-treatment relapse model; although HLA expression was almost universally absent in naïve model cells, the expression of HLA class II genes, including HLA-DRB1 and HLA-DQA1, was observed in the relapse model, and this was accompanied by platinum resistance, suggesting that the continuous evolution of decreased ASCL1 expression and increased SCLC-I characteristics (e.g., EMT) of tumors may underlie platinum resistance. Researchers have found that the expression of MYC genes increased and that of MYCL and ASCL1 decreased in chemo-resistant mice and humans with SCLC (38,39). A higher expression of MYC is associated with a shorter patient survival and a more aggressive resistance phenotype (10,40), suggesting that this phenotypic transformation and the development of resistance may be driven by the genes of the MYC family.

Overall, the copy number amplification of MYC family genes accounts for approximately 20% of SCLCs [MYCL (MYCL1 or L-MYC), 9%; MYCN, 4%; and MYC (c-MYC), 6%] (41,42), suggesting that this gene family is involved in tumor carcinogenesis (21). Among them, MYCL overexpression is associated with the classical NE status of SCLC (primarily ASCL1 subtype) (19), while the amplification or overexpression of c-MYC is required to maintain the NEUROD1 subtype lineage status and can also appear in SCLC-P and SCLC-Y subtypes (6,21). In this study, replacement of c-MYC with MYCL gene in c-MYC SCLC cells induced cell transition to NE lineage state, which is highly similar to ASCL1-SCLC but could not lead to a complete transition to ASCL1-SCLC, suggesting that it could not completely control the trans-differentiation from NE-low or variant state to NE-high or classical state (43). However, in human SCLC cell lines and PDX models, c-MYC induced the trans-differentiation from ASCL1-SCLC to variant morphology with NEUROD1 expression (33,40), accompanied by LCNEC-like/variant SCLC histological transition. Furthermore, findings of scRNA-seq analysis indicate that the MYC gene in GEMM could drive ASCL1+ NE cells to YAP1+ “non-NE” phenotype through NEUROD1+ intermediates (32), while ASCL1/NEUROD1 double-positive cells identified by Gay et al. (30) may support the hypothesis of this transition state and reveal the dynamic, potential transcriptional pattern transition of SCLC subtypes defined by different transcription-factor expressions. Drivers that regulate this unique transcriptional program and achieve lineage plasticity of molecular and histological subtypes may be the oncogenes c-MYC and MYCL, in which MYCL regulates the NE developmental pathway and c-MYC regulates EMT and NOTCH signaling.

NOTCH is considered to be a tumor suppressor associated with SCLCs, and approximately 25% of SCLCs (primarily NE-high type) have functionally inactivating mutations in the NOTCH pathway (21). In the absence of R81 and TP53, the loss of NOTCH function is postulated to lock cells in a self-renewing NE stem-like state (44), which leads to the development of SCLC. Activation of NOTCH can induce the transition from MYCL-associated NE SCLC model to “non-NE” SCLC fate in mouse and human SCLC cells by inhibiting the expression of ASCL1 (35), which can slow down tumor-cell growth but typically leads to chemo-resistance (21,35); in mouse and human models, studies using time-series single-cell RNA-seq analysis showed that the activation of NOTCH signaling by MYC dedifferentiated NE tumor cells and promoted a continuous transition of SCLC from ASCL1+ to NEUROD1+ and to YAP1+ state (32), revealing the dynamic evolutionary mechanism of SCLC subtypes. Regulation of SCLC by the NOTCH signaling pathway may be achieved by the transcriptional repression of the differentiation effector gene hASH1 by the downstream target molecule of NOTCH signaling, HESI (45), which has also been shown to be particularly enriched in MYC-driven tumor-cell
transition to a “non-NE” fate (32). Another study found that the loss of NE differentiation and concomitant activation of NOTCH signaling is promoted by the activation of the REST factor, a transcriptional repressor of NE and neuronal differentiation (46), which could further lead to the specific expression of HES1 in “non-NE” phenotype cells. Consistently, REST is absent in most NE SCLCs, which also leads to the inhibition of NOTCH signaling (3,12,35,47). The above studies propose a transcriptional network linking SCLC subtypes to MYC and its paralogs as well as the NOTCH and HIPPO pathways. Thus, it has been proposed that one of the mechanisms by which the NE differentiation program is absent in SCLC, may be mediated by e-MYC in a NOTCH signaling pathway-dependent manner, and the activation of NOTCH signaling is promoted by the activation of its target gene REST, which further promotes HES1 transcription, ultimately leading to “non-NE” phenotype SCLC. However, it has also been proposed that this transdifferentiation can be mediated independent of NOTCH signaling or can be directly activated by REST (43).

In addition, researchers have proposed that epigenetic regulation might control a continuum of expression ranging from ASCL1-only to NEUROD1-only, with co-expression representing a transition state and driving NE differentiation. Gay et al. (30) revealed that different subtypes can be distinguished by methylation β values in the region upstream of the NEUROD1 transcription start site (TSS). Specifically, the ASCL1-only cell line exhibited a relatively high methylation of sites both proximal and distal to the NEUROD1 TSS, and the NEUROD1-only cell line exhibited almost no methylation of proximal sites and little methylation of highly distal sites; furthermore, the double-positive cell line exhibited low methylation of proximal sites and high methylation of highly distal sites. As predicted, the manipulation of epigenetic mechanisms modulates NEUROD1 expression, and, to some extent, ASCL1 expression. Treatment with lysine-specific histone demethylase 1 (LSD1) inhibitors revealed little change in NEUROD1 expression, whereas treatment with decitabine, an inhibitor targeting DNA methyltransferase 1 (DNMT1), resulted in a significant and consistent upregulation of NEUROD1, including cell lines with no detectable NEUROD1 expression at baseline (30); furthermore, both LSD1 inhibitors and decitabine can lead to a modest downregulation of ASCL1 (30), indicating that epigenetic mechanisms may regulate transformation between SCLC-A and SCLC-N models.

A comprehensive analysis of the identification of molecular subtypes of SCLCs in a previous study revealed the association between different molecular subtypes and cellular programs (e.g., “stemness,” “interstitial,” or “NE” programs), and their evolution over time and treatment may explain the prominent plasticity and strong metastatic potential of SCLCs (48,49). These studies provide evidence of SCLC tumor heterogeneity and transcriptional plasticity as well as clues to investigate tumor evolution, responsiveness to specific therapeutic agents, and the development of acquired resistance; additionally, they help investigators focus on the development of therapies for patients who may benefit from a particular therapeutic approach.

**Precision treatment strategies for different SCLC subtypes**

Currently, no significant benefits of targeted therapy and immunotherapy for patients with SCLC have been observed. The association of SCLCs with the selective activation of major transcriptional regulators has recently attracted interest in transcriptional regulatory strategies. Identifying subtype-specific molecular signatures and clinically meaningful biomarkers and improving the understanding of the key signaling pathways that play a role in specific SCLC subtypes may help explore new targets and corresponding targeted therapeutic strategies for SCLCs.

**Treatments for SCLC-A**

Inactivating mutations in NOTCH family members and abnormally high expression of DLL3, a key negative regulator of NOTCH signaling, are commonly observed in SCLC-A subtype (50). DLL3 is a direct transcriptional target of ASCL1. DLL3 inhibitors selectively target SCLC-A tumors (50,51). The antibody-drug conjugate, rovalpituzumab teserine (Rova-T), was the first targeted therapy that used DLL3 as a novel biomarker for the treatment of SCLC (52,53). First-in-human clinical trials of Rova-T on patients with recurrent SCLC have shown encouraging activities despite causing serious adverse events. Subsequent studies including the phase II TRINITY study and the phase III TAHOE trial of second-line therapy revealed discouraging efficacy data, leading to the discontinuation of the development of Rova-T (53,54). Nevertheless, DLL3 remains an important target for the
development of SCLC drugs, and other active strategies include bispecific antibody T-cell technology (BiTE), AMG 757 (NCT03139940), chimeric antigen receptor (CAR)-T, and AMG119 (NCT03392064). BCL-2 is another direct transcriptional target of ASCL1. BCL2 inhibitors (venetoclax) have been the focus of research and development of multiple targeted inhibitors in SCLC clinical trials; however, these may exhibit high activity only against SCLC-A (16,51). In addition, recent data suggest that the inhibition of another epigenetic modifier, LSD1, drives NOTCH1 activation and leads to ASCL1 inhibition in patients with SCLC (55), indicating the selective activity of LSD1 inhibitors in patients with SCLC-A, which is being explored in patients with SCLC (NCT02034123).

**Treatments for SCLC-N**

SCLC-N is typically associated with c-MYC amplification, which can serve as a potential target for therapeutic agents. Tumors characterized by high c-MYC expression are preferentially sensitive to aurora kinase (AURK) A/B, checkpoint kinase (CHK) 1, and IMPDH (inosine-5’-monophosphate dehydrogenase) 1/2 inhibition (39,51, 56,57). MYC-driven SCLC cells are highly dependent on arginine-regulated pathways, including polyamine biosynthesis and mammalian target of rapamycin (mTOR) pathway activation. Selective arginine depletion appears to be significantly effective in MYC-driven preclinical models of SCLC-N (39). Oncolytic Seneca Valley virus (SVV), which selectively targets SCLC-N tumor cells, could have selective efficacy either as a single agent or as a strategy to enhance immunotherapy by selectively introducing viral antigens in tumor cells (58). Alternatively, the SCLC-N model is highly sensitive to multiple AURK inhibitors (AURKi), and c-MYC protein expression is a predictive biomarker of AURKi sensitivity (34,59). The phase II clinical trial (NCT01045421) tested the activity and safety of AURKi and alisertib in patients with relapsed or refractory SCLCs or other cancers (60,61). Aurora amplification is associated with taxane resistance. A recent clinical trial showed that, compared with paclitaxel alone, alisertib combined with paclitaxel was associated with a significantly higher progression-free survival (PFS) in patients with c-MYC-positive SCLCs (59), while patients with low c-MYC expression showed a better response to paclitaxel alone. Phase II clinical trials of alisertib, alone or in combination with other drugs, for the treatment of multiple tumor types, have shown its antitumor activity and provided therapeutic strategies for recurrent SCLCs (61). Other strategies for SCLC-N may involve inhibition of the phosphatidylinositol 3-kinase (PI3K)/mTOR pathway and heat shock protein 90 (HSP90) (51).

**Treatments for SCLC-P**

SCLC-P may be the most sensitive subtype to antimetabolites and poly ADP-ribose polymerase (PARP) inhibitors that target DNA damage repair pathways. A phase II trial of veliparib in combination with temozolomide in patients with previously treated SCLC did not meet its primary endpoint of PFS improvement but showed an improvement in objective response rate of 39% (NCT01638549). Previous studies have demonstrated that the expression of Schlafen11 (SLFN11) is the most sensitive predictive biomarker of efficacy in studies on DNA-damaging chemotherapy and PARP inhibitors (62-64). Approximately 40% of 116 SCLC cell lines from a global drug and genomic database (SCLC-Global) do not express SLFN11, which predicts resistance to DNA-damaging agents (29). Notably, it was also found that most of the models showing the highest expression of SLFN11 were SCLC-A and showed a bimodal expression pattern (29), and when the expression level of SLFN11 distinguished SCLC-A groups, there was a significant difference in sensitivity to cisplatin and olaparib. Therefore, additional biomarker analysis may be required to further identify sensitive drug-target candidates after the identification of SCLC subtypes using transcription-factor markers. In addition, on the basis of results of clustered regularly interspaced short palindromic repeats (CRISPR) screening, SCLC-P cells may be sensitive to insulin-like growth factor 1 receptor (IGF1R) inhibitors (15); however, no such inhibitors are currently used in clinical practice.

**Treatment for SCLC-Y**

The SCLC-Y cell line shows the highest resistance to standard chemotherapy, and an obvious resistance phenotype between YAP1 expression and the response of etoposide and camptothecin can be observed throughout the database of the Cancer Cell Line Encyclopedia (CCLE)/Cancer Therapeutics Response Portal (CTRP) (29). SCLC-Y cells express the “non-NE” markers CD151 and ephrin type-A receptor (EPHA2) and may respond to inhibitors targeting YAP1 and NOTCH in clinical development (65,66). In addition, considering the
association of SCLC-Y with immunity, the likelihood of its response to immune checkpoint inhibitors (ICIs) is high (67). On the basis of the results of gene expression and recent in silico studies, SCLC-Y shows the highest sensitivity to mTOR, polo-like kinase 1 (PLK1), and potentially to cyclin-dependent kinase (CDK) 4/6 inhibitors (18,68).

Treatment for SCLC-I

Although the current scenario of immunotherapy for SCLC is not optimistic as a whole, with a response rate of only approximately 15% (69-71), evidence suggests that SCLCs have immunogenic potential, and an in-depth exploration of SCLC immunophenotypes and molecular subtypes may improve the understanding of the potential immunological characteristics of patients with SCLC to facilitate effective immunotherapy. Recently, the newly identified SCLC-I subtype was found to potentially have a high response to immunotherapy, and this finding will revolutionize SCLC immunotherapy. Gay et al. (30) divided patients in the IMpower133 study (72) into four groups and reanalyzed patient survival to explore whether patients with SCLC-I tumors may preferentially benefit from ICIs. Patients with SCLC-I were found to have a significantly higher OS benefit than those with other subtypes in the chemotherapy combined with atezolizumab group (hazard ratio (HR): 0.566; 95% confidence interval (95% CI): 0.321–0.998), but not in the control group (placebo combined with chemotherapy), indicating that SCLC-I could predict the benefit of ICIs (30). Although this trial was not designed for this analysis, a trend toward a preferential response to immune combination chemotherapy was observed in patients with SCLC-I, and these data deserve further validation in future SCLC-based umbrella trials. Interestingly, Bruton’s tyrosine kinase (BTK), another target commonly associated with immune cells, is highly expressed in SCLC-I tumors (30). Therefore, this subtype may be sensitive to the BTK inhibitor, imbruvica. Furthermore, EMT is another potentially targetable feature of SCLC-I tumors. It was found that mocetinostat, a histone deacetylase inhibitor, reduced VIM expression and increased E-cadherin expression in the SCLC-I (H841) cell line, which is consistent with EMT reversal (30) and might be a future direction for therapeutic development. Table 1 summarizes the different subtypes of SCLC, genes/pathways related to each subtype, and the corresponding treatment strategies.

Summary and prospects

Over the past three decades, no significant progress has been made in the systemic treatment of SCLCs, primarily because of tumor heterogeneity and high plasticity. Recently, substantial progress has been made in understanding the biology of SCLC, defining different SCLC subtypes using major transcriptional regulators, clarifying their different gene expression profiles, and indicating that different subtypes are dynamically changing, emphasizing the strong plasticity and ITH of SCLC. Recently, advances in genomics, the development of single-cell sequencing analysis, and the development of new preclinical models have helped researchers gain new insights into the disease-specific genetic alteration, molecular typing, and tumor heterogeneity of SCLCs and better explain the similarity, diversity, and biological behavior of different subtypes. These biologically distinct subtypes may define unique therapeutic vulnerabilities and resistance, facilitating the development of molecular targeted therapies and immunological strategies.

Future research should focus on the following: First, further insight into SCLC genetic characteristics, tumor heterogeneity, and molecular subtypes should be sought to analyze different SCLC subtype-specific treatment vulnerabilities and the correlation of each subtype classification with specific treatment outcomes and corresponding predictive biomarkers; new targets and innovative biomarkers should be used to guide the stratification of patients with SCLC to develop and integrate corresponding targeted or immuno-personalized treatment strategies, to provide clinical insights into the prognostic significance of subtype classification and the predictive significance of standard and investigational therapies, and ultimately to expand the therapeutic benefit to a larger proportion of patients. Second, the development of new drugs, such as blocking the transition of different SCLC-phenotypes by targeting epigenetic regulators and the combination of different subtype-specific therapies, may have a substantial effect on this fatal disease. Furthermore, considering the emerging preclinical data on functional plasticity and phenotypic diversity, it is recommended that in future studies, liquid biopsy techniques should be fully combined (e.g., CTCs, peripheral immune cell profiling, and circulating tumor DNA) to dynamically and continuously monitor the spatiotemporal heterogeneity of tumors before and during treatment, which may be suggestive of treatment benefits.
Table 1 Different subtypes of SCLC, related genes/pathways, and corresponding treatment strategies

| Traditional classification of SCLCs | Characteristics | Novel SCLC subtypes defined by transcriptional regulators | Major transcriptional factor | Related genes/pathways | Treatments |
|-----------------------------------|-----------------|----------------------------------------------------------|----------------------------|------------------------|------------|
| NE-high subtype                   | Classic SCLC morphology; Epithelial phenotype | ASCL1, INSM1, SYP, BEX1, CHGA, NXX2-1, DLL3, DLK1, HES6, TTF-1 | SCLC-A | ASCL1 | MYCL, BCL2, SOX2, RET, NF1B, DLL3, DLK1, NXX2-1, INSM1, HES6, TTF-1 | DLL3 inhibitors: Antibody-drug conjugate, rovalpituzumab teserine (Rova-T); Bispecific antibody T-cell technology (BiTE), AMG 757 (NCT03319940); Chimeric antigen receptor (CAR)-T, AMG119 (NCT03392064); BCL2 inhibitors: venetoclax; LSD1 inhibitors: (NCT02034123) |
| NE-low subtype/non-NE SCLC        | Variant form of SCLC; Mesenchymal phenotype | NOTCH, HES1, MYC, REST, ASCL2, HIPPO/YAP1, TGF-β, EMT (vimentin, SMA2, CD44), MYB, BCL2 | SCLC-P | POU2F3 | IFGR1 pathway, SOX9, ASCL2, MYC | Antimetabolites: anti-folates and nucleoside analogues; PARP inhibitors (veliparib, olaparib) |
|                                   |                 | SCLC-Y | YAP1 | HIPPO signaling, intact RB1, overexpress MYC | mTOR inhibitors, PLX inhibitors*; CDK4/6 inhibitors*; YAP1 and NOTCH inhibitors*; ICIs* |
|                                   |                 | SCLC-I/infamed | ASCL1*/NEUR OD1*/POU2F3 | Inflamed: immune checkpoints, HLA genes, STING, INFγ pathway, T-cell inflammatory GEPs, immune cell infiltration | ICIs (atezolizumab); BTK inhibitor (imbruvica)* |

*, Therapeutic agents have only preliminary exploration results in SCLC subtypes or may become one of the treatments in the future; SCLC, small cell lung cancer; NE, neuroendocrine.
Finally, the development of new experimental models combining various genetic alterations and different putative cell-of-origin types will be the key to modeling all subtypes. In the future, SCLC patient-relevant preclinical models spanning different subtypes should be developed and characterized, with an emphasis on expanding the number of models to evaluate the molecular characteristics and treatment sensitivity of different SCLC subtypes. The availability of large biobanks of relevant models for patients with SCLC, including longitudinal models, could allow the fields to explore inter- and intratumoral heterogeneity in further detail to find optimized and personalized therapies for this aggressive cancer.

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Footnote

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References

1. Pesch B, Kendzia B, Gustavsson P, et al. Cigarette smoking and lung cancer -- relative risk estimates for the major histological types from a pooled analysis of case-control studies. Int J Cancer 2012;131:1210-9.
2. Rudin CM, Poirier JT. Small-cell lung cancer in 2016: Shining light on novel targets and therapies. Nat Rev Clin Oncol 2017;14:75-6.
3. Gazdar AF, Bunn PA, Minna JD. Small-cell lung cancer: what we know, what we need to know and the path forward. Nat Rev Cancer 2017;17:725-37.
4. Sen T, Gay CM, Byers LA. Targeting DNA damage repair in small cell lung cancer and the biomarker landscape. Transl Lung Cancer Res 2018;7:50-68.
5. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin 2019;69:7-34.
6. Rudin CM, Poirier JT, Byers LA. Molecular subtypes of small cell lung cancer: a synthesis of human and mouse model data. Nat Rev Cancer 2019;19:289-97.
7. D’amico D, Carbone D, Mitsudomi T, et al. High frequency of somatically acquired p53 mutations in small-cell lung cancer cell lines and tumors. Oncogene 1992;7:339-46.
8. Meder L, König K, Ozretić L, et al. NOTCH1, ASCL1, p53 and RB alterations define an alternative pathway driving neuroendocrine and small cell lung carcinomas. Int J Cancer 2016;138:927-38.
9. Arcaro A. Targeted therapies for small cell lung cancer: Where do we stand? Crit Rev Oncol Hematol 2015;95:154-64.
10. Carney DN, Gazdar AF, Bepler G, et al. Establishment and identification of small cell lung cancer cell lines having classic and variant features. Cancer Res 1985;45:2913-23.
11. Travis WD, Brambilla E, Nicholson AG, et al. The 2015 World Health Organization Classification of Lung Tumors: Impact of Genetic, Clinical and Radiologic Advances Since the 2004 Classification. J Thorac Oncol 2015;10:1243-60.
12. Zhang W, Girard L, Zhang YA, et al. Small cell lung cancer tumors and preclinical models display heterogeneity of neuroendocrine phenotypes. Transl Lung Cancer Res 2018;7:32-49.
13. Gazdar A. Molecular phenotypes of SCLC. J Thorac Oncol 2018;13(suppl 10):S309.
14. Dora D, Rivard C, Yu H, et al. Neuroendocrine subtypes of small cell lung cancer differ in terms of immune microenvironment and checkpoint molecule distribution. Mol Oncol 2020;14:1947-65.
15. Huang YH, Klingbeil O, He XY, et al. POU2F3 is a master regulator of a tuft cell-like variant of small cell lung cancer. Genes Dev 2018;32:915-28.
16. Poirier JT, Gardner EE, Connis N, et al. DNA methylation in small cell lung cancer defines distinct disease subtypes and correlates with high expression of EZH2. Oncogene 2015;34:5869-78.
17. Wooten DJ, Groves SM, Tyson DR. Systems-level network modeling of small cell lung cancer subtypes identifies master regulators and destabilizers. PLoS Comput Biol 2019;15:e1007343.
18. McColl K, Wildey G, Sakre N, et al. Reciprocal expression of INSM1 and YAP1 defines distinct disease subtypes in small cell lung cancer. Oncotarget 2017;8:73745-56.
19. Borromeo MD, Savage TK, Kollipara RK, et al. ASCL1 and NEUROD1 reveal heterogeneity in pulmonary neuroendocrine tumors and regulate...
distinct genetic programs. Cell Rep 2016;16:1259-72.
20. Mollaoglu G, Guthrie MR, Böhm S, et al. MYC drives progression of small cell lung cancer to a variant neuroendocrine subtype with vulnerability to aurora kinase inhibition. Cancer Cell 2017;31:270-85.
21. George J, Lim JS, Jang SJ, et al. Comprehensive genomic profiles of small cell lung cancer. Nature 2015;524:47-53.
22. Fujino K, Motooka Y, Hassan WA, et al. Insulinoma-associated protein 1 is a crucial regulator of neuroendocrine differentiation in lung cancer. Am J Pathol 2015;185:3164-77.
23. Song Y, Sun Y. YAP1 promotes multidrug resistance of small cell lung cancer by CD74-related signaling pathways. Cancer Med 2020;9:258-69.
24. Lee HJ, Diaz MF, Price KM, et al. Fluid shear stress activates YAP1 to promote cancer cell motility. Nat Commun 2017;8:14122.
25. Baine MK, Hsieh MS, Lai WV, et al. SCLC subtypes defined by ASCL1, NEUROD1, POU2F3, and YAP1: A comprehensive immunohistochemical and histopathologic characterization. J Thorac Oncol 2020;15:1823-35.
26. Ito T, Matsubara D, Tanaka I, et al. Loss of YAP1 defines neuroendocrine differentiation of lung tumors. Cancer Sci 2016;107:1527-38.
27. Pearssal SM, Humphrey S, Revill M, et al. The rare YAP1 subtype of SCLC revisited in a biobank of 39 circulating tumor cell patient derived explant models: A brief report. J Thorac Oncol 2020;15:1836-43.
28. Owonikoko TK, Dwivedi B, Chen Z, et al. YAP1 expression in SCLC defines a distinct subtype with T-cell-inflamed phenotype. J Thorac Oncol 2021;16:464-76.
29. Tiemsani C, Pongor L, Elloumi F, et al. SCLC-CellMiner: A resource for small cell lung cancer cell line genomics and pharmacology based on genomic signatures. Cell Rep 2020;33:108296.
30. Gay CM, Stewart CA, Park EM, et al. Patterns of transcription factor programs and immune pathway activation define four major subtypes of SCLC with distinct therapeutic vulnerabilities. Cancer Cell 2021;39:346-60.e7.
31. Newman AM, Steen CB, Liu CL, et al. Determining cell type abundance and expression from bulk tissues with digital cytometry. Nat Biotechnol 2019;37:773-82.
32. Ireland AS, Micinski AM, Kastner DW, et al. MYC drives temporal evolution of small cell lung cancer subtypes by reprogramming neuroendocrine fate. Cancer Cell 2020;38:60-78.e12.
33. Simpson KL, Stoney R, Frese KK, et al. A biobank of small cell lung cancer CDX models elucidates inter- and intratumoral phenotypic heterogeneity. Nat Cancer 2020;1:437-51.
34. Gay CM, Tong P, Cardnell RJ, et al. Differential sensitivity analysis for resistant malignancies (DISARM) identifies common candidate therapies across platinum-resistant cancers. Clin Cancer Res 2019;25:346-57.
35. Lim JS, Ibaseta A, Fischer MM, et al. Intratumoural heterogeneity generated by Notch signalling promotes small-cell lung cancer. Nature 2017;545:360-4.
36. Cañadas I, Thummalapalli R, Kim JW, et al. Tumor innate immunity primed by specific interferon-stimulated endogenous retroviruses. Nat Med 2018;24:1143-50.
37. Krohn A, Ahrens T, Yalcin A, et al. Tumor cell heterogeneity in small cell lung cancer (SCLC): phenotypical and functional differences associated with Epithelial-Mesenchymal Transition (EMT) and DNA methylation changes. PLoS One 2014;9:e100249.
38. Stewart CA, Gay CM, Xi Y, et al. Single-cell analyses reveal increased intratumoral heterogeneity after the onset of therapy resistance in small-cell lung cancer. Nat Cancer 2020;1:423-36.
39. Chalishazar MD, Wait SJ, Huang F, et al. MYC-driven small-cell lung cancer is metabolically distinct and vulnerable to arginine depletion. Clin Cancer Res 2019;25:5107-21.
40. Johnson BE, Battey J, Linnoila I, et al. Changes in the phenotype of human small cell lung cancer cell lines after transfection and expression of the c-myc proto-oncogene. J Clin Invest 1986;78:525-32.
41. Nau MM, Carney DN, Battey J, et al. Amplification, expression and rearrangement of c-myc and N-myc oncogenes in human lung cancer. Curr Top Microbiol Immunol 1984;113:172-7.
42. Saksela K, Bergh J, Lehto VP, et al. Amplification of
the c-myc oncogene in a subpopulation of human small cell lung cancer. Cancer Res 1985;45:1823-7.

43. Patel AS, Yoo S, Kong R, et al. Prototypical oncogene family Myc defines unappreciated distinct lineage states of small cell lung cancer. Sci Adv 2021;7:eabc2578.

44. Ouadah Y, Rojas ER, Riordan DP, et al. Rare pulmonary neuroendocrine cells are stem cells regulated by Rb, p53, and Notch. Cell 2019;179:403-16.e23.

45. Zhang XM, Wang JX, Lei XG, et al. Regulation and mechanism of Notch signaling pathway in small cell lung cancer. Zhonghua Bing Li Xue Za Zhi (in Chinese) 2010;39:95-9.

46. Thiel G, EKici M, Rossler OG. RE-1 silencing transcription factor (REST): a regulator of neuronal development and neuronal/endocrine function. Cell Tissue Res 2015;359:99-109.

47. Hassan KA. Small cell lung cancer heterogeneity: elevated a Notch above the Rest! J Thorac Dis 2018;10:554-6.

48. Shue YT, Lim JS, Sage J. Tumor heterogeneity in small cell lung cancer defined and investigated in pre-clinical mouse models. Transl Lung Cancer Res 2018;7:21-31.

49. Yang D, Denny SK, Greenside PG, et al. Intertumoral heterogeneity in SCLC is influenced by the cell type of origin. Cancer Discov 2018;8:1316-31.

50. Saunders LR, Bankovich AJ, Anderson WC, et al. A DLL3-targeted antibody-drug conjugate eradicates high-grade pulmonary neuroendocrine tumor-initiating cells in vivo. Sci Transl Med 2015;7:302 ra136.

51. Cardnell RJ, Li L, Sen T, et al. Protein expression of TTF1 and cMYC define distinct molecular subgroups of small cell lung cancer with unique vulnerabilities to aurora kinase inhibition, DLL3 targeting, and other targeted therapies. Oncotarget 2017;8:73419-32.

52. Rudin CM, Pietanza MC, Bauer TM, et al. Rovaaltuzumab tesirine, a DLL3-targeted antibody-drug conjugate, in recurrent small-cell lung cancer: a first-in-human, first-in-class, open-label, phase 1 study. Lancet Oncol 2017;18:42-51.

53. Morgensztern D, Besse B, Grellier L. Efficacy and safety of rovaaltuzumab tesirine in third-line and beyond patients with DLL3-expressing, relapsed/refractory small-cell lung cancer: Results from the phase II TRINITY study. Clin Cancer Res 2019;25:6958-66.

54. Phase 3 trial of Rova-T as second-line therapy for advanced small-cell lung cancer (TAHOE study). Available online: https://news.abbvie.com/news/phase-3-trial-rova-t-as-second-line-therapy-for-advanced-small-cell-lung-cancer-tahoe-study-halted.htm

55. Augert A, Eastwood E, Ibrahim AH. Targeting NOTCH activation in small cell lung cancer through LSD1 inhibition. Sci Signal 2019;12:eaau2922.

56. Huang F, Ni M, Chalishazar MD, et al. Inosine monophosphate dehydrogenase dependence in a subset of small cell lung cancers. Cell Metab 2018;28:369-82.e5.

57. Dammert MA, Brägelmann J, Olsen RR, et al. MYC paralog-dependent apoptotic priming orchestrates a spectrum of vulnerabilities in small cell lung cancer. Nat Commun 2019;10:3485.

58. Poirier JT, Dobromilskaya I, Moriarty WF, et al. Selective tropism of Seneca Valley virus for variant subtype small cell lung cancer. J Natl Cancer Inst 2013;105:1059-65.

59. Owonikoko TK, Niu H, Nackaerts K, et al. Randomized phase II study of paclitaxel plus alisertib versus paclitaxel plus placebo as second-line therapy for SCLC: Primary and correlative biomarker analyses. J Thorac Oncol 2020;15:274-87.

60. Sabari JK, Lok BH, Laird JH, et al. Unravelling the biology of SCLC: implications for therapy. Nat Rev Clin Oncol 2017;14:549-61.

61. Melichar B, Adenis A, Lockhart AC, et al. Safety and activity of alisertib, an investigational aurora kinase A inhibitor, in patients with breast cancer, small-cell lung cancer, non-small-cell lung cancer, head and neck squamous-cell carcinoma, and gastroesophageal adenocarcinoma: a five-arm phase 2 study. Lancet Oncol 2015;16:395-405.

62. Byers LA, Krug L, Waqar S, et al. MA11.07 improved small cell lung cancer (SCLC) response rates with veliparib and temozolomide: Results from a phase II trial. J Thorac Oncol 2017;12:S406-S407.

63. Lok BH, Gardner EE, Schneeberger VE, et al. PARP inhibitor activity correlates with SLFN11 expression and demonstrates synergy with temozolomide in small
cell lung cancer. Clin Cancer Res 2017;23:523-35.
64. Gardner EE, Lok BH, Schneeberger VE, et al. Chemosensitive relapse in small cell lung cancer proceeds through an EZH2-SLFN11 axis. Cancer Cell 2017;31:286-99.
65. Crawford JJ, Bronner SM. Hippo pathway inhibition by blocking the YAP/TAZ-TEAD interface: a patent review. Expert Opin Ther Pat 2018;28:867-73.
66. Leonetti A, Facchinetti F, Minari R, et al. Notch pathway in small-cell lung cancer: from preclinical evidence to therapeutic challenges. Cell Oncol (Dordr) 2019;42:261-73.
67. Shibata M, Ham K, Hoque MO. A time for YAP1: Tumorigenesis, immunosuppression and targeted therapy. Expert Opin Ther Pat 2018;143:2133-44.
68. Horie M, Saito A, Ohshima M, et al. YAP and TAZ modulate cell phenotype in a subset of small cell lung cancer. Cancer Sci 2016;107:1755-66.
69. Ready NE, Ott PA, Hellmann MD, et al. Nivolumab monotherapy and nivolumab plus ipilimumab in recurrent small cell lung cancer: results from the CheckMate 032 randomized cohort. J Thorac Oncol 2020;15:426-35.
70. Chung HC, Piha-Paul SA, Lopez-Martin J, et al. Pembrolizumab after two or more lines of previous therapy in patients with recurrent or metastatic SCLC: Results from the KEYNOTE-028 and KEYNOTE-158 studies. J Thorac Oncol 2020;15:618-27.
71. Guo H, Li L, Cui J. Advances and challenges in immunotherapy of small cell lung cancer. Chin J Cancer Res 2020;32:115-28.
72. Horn L, Mansfield AS, Szczęsna A, et al. First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. N Engl J Med 2018;379:2220-9.

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