Received: 30 January 2023 | Revised: 30 March 2023 | Accepted: 4 April 2023

DOI: 10.3322/caac.21785

REVIEW ARTICLE

Clinical insights into small cell lung cancer: Tumor heterogeneity, diagnosis, therapy, and future directions

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Funding information

Hungarian National Research, Development, and Innovation Office, Grant/Award Numbers: 2020-1.1.6-JÖVŐ, FK-143751, KH130356, TKP2021-EGA-33, UNKP-20-3, UNKP-21-3;

Abstract

Small cell lung cancer (SCLC) is characterized by rapid growth and high metastatic capacity. It has strong epidemiologic and biologic links to tobacco carcinogens. Although the majority of SCLCs exhibit neuroendocrine features, an important subset of tumors lacks these properties. Genomic profiling of SCLC reveals genetic instability, almost universal inactivation of the tumor suppressor genes *TP53* and *RB1*, and a high mutation burden. Because of early metastasis, only a small fraction of patients are amenable to curative-intent lung resection, and these individuals require adjuvant platinum-etoposide chemotherapy. Therefore, the vast majority of patients are currently being treated with chemoradiation with or without immunotherapy. In patients with disease confined to the chest, standard therapy includes

The last two authors contributed equally to this work as senior authors.

American Society of Clinical Oncology : Young Investigator Award; International Association for the Study of Lung Cancer/International Lung Cancer Foundation : IASLC Early Career Education Award 2021; International Association for the Study of Lung Cancer/International Lung Cancer Foundation : Young Investigator Grant 2022; Cancer Research Prevention Institute of Texas : Early Clinical Investigator Award; Hungarian Respiratory Society, Grant/Award Number: MPA #2020; City of Vienna Fund for Innovative Interdisciplinary Cancer Research; Austrian Science Fund, Grant/Award Numbers: FWF I4677, FWF I3522, FWF I3977, FWF T 1062-B33; LUNGevity Foundation : Career Development Award

thoracic radiotherapy and concurrent platinum-etoposide chemotherapy. Patients with metastatic (extensive-stage) disease are treated with a combination of platinum-etoposide chemotherapy plus immunotherapy with an anti-programmed death-ligand 1 monoclonal antibody. Although SCLC is initially very responsive to platinum-based chemotherapy, these responses are transient because of the development of drug resistance. In recent years, the authors have witnessed an accelerating pace of biologic insights into the disease, leading to the redefinition of the SCLC classification scheme. This emerging knowledge of SCLC molecular subtypes has the potential to define unique therapeutic vulnerabilities. Synthesizing these new discoveries with the current knowledge of SCLC biology and clinical management may lead to unprecedented advances in SCLC patient care. Here, the authors present an overview of multimodal clinical approaches in SCLC, with a special focus on illuminating how recent advancements in SCLC research could accelerate clinical development.

KEYWORDS
chemotherapy, diagnosis, immunotherapy, molecular subtypes, small cell lung cancer

INTRODUCTION

Small cell lung cancer (SCLC) represents approximately 13%–15% of all lung cancer cases and remains one of the most lethal malignancies, with a 5-year survival rate <7%.[1,2] In addition to rapid proliferation, high vascularity, and apoptotic imbalance, SCLC is also characterized by early metastatic spread.[2,3] Mirroring this high metastatic capacity, two thirds of patients already present with tumor cell dissemination outside the chest at initial diagnosis. Thus only a small fraction of patients are amenable to potentially curative-intent multimodality therapy.[4] In the past decade, genotype-directed targeted therapies based on mutually exclusive subtypes defined by aberrant oncogenic drivers have dramatically improved treatment outcomes in patients with non-small cell lung cancer (NSCLC).[5] Nevertheless, because SCLC is biologically and clinically different from other types of lung cancer, the progress in its therapeutic armamentarium stands in sharp contrast to that seen in NSCLC.[6] However, after a nihilistic period lasting for decades, substantial progress in our understanding of SCLC biology and tumor heterogeneity has been made.[6,7] These advancements on several fronts might define new avenues in management protocols and provide renewed hope for patients with this hard-to-treat disease.

SCLC and its bronchial origin were first described by Barnard in 1926 by referring to it as an unusual mediastinal *oat cell sarcoma* (Figure 1).[8] Some 30 years later, Azzopardi provided its light-microscopic description and distinguished SCLC from other types of lung cancer.[9,10] The finding in 1973 that SCLC cells spread through lymphatic and blood vessels earlier than malignant cells of other lung cancer histotypes receded surgical resection into the background.[11] Consequently, the therapeutic focus was shifted toward radiation and chemotherapy. Indeed, SCLC tumors are tantalizingly chemosensitive in the beginning.[12,13] Yet recurrence occurs rapidly, resulting in SCLC as an extremely challenging tumor type for oncologists to treat.[14] The concept of the currently used platinum-based combination chemotherapy was defined in the 1980s, when multiple studies demonstrated that the addition of combination platinum-based chemotherapy given concurrently with chest radiotherapy improved survival in patients with limited stage SCLC, and platinum-based combinations that included etoposide provided superior survival in those with extensive-stage disease (Figure 1).[15–17] Thus, the etoposide/platinum (EP) combination was standard until 2019, when it was demonstrated that the incorporation of antiprogrammed death-ligand 1 (anti–PD-L1) immunotherapy into EP chemotherapy improved survival, with a small percentage of patients remaining alive at 3 years.[18–20] Importantly, in addition to the lack of potentially targetable oncogenic drivers, therapeutic advancements were also hindered by the scarcity of surgically resected tissue specimens ideal for profiling studies.[2] This shortage of adequate patient materials ultimately increased the importance of preclinical models and patient-derived xenografts for understanding the biology of SCLC and supporting translational research.[2]

The emergence of multimodal approaches, the increased research funding, as well as the recent resurgence of profiling studies because of the development of representative disease models have enhanced SCLC research. In the context of these impressive advances, the objective of this in-depth review of the primary literature was to offer clinicians a comprehensive outlook on the most important challenges in tackling this highly recalcitrant disease. Specifically, here, we provide a synthesis of our understanding of SCLC, highlight the most recent translational discoveries, and summarize the current trends in epidemiology, diagnosis, screening, and treatment.

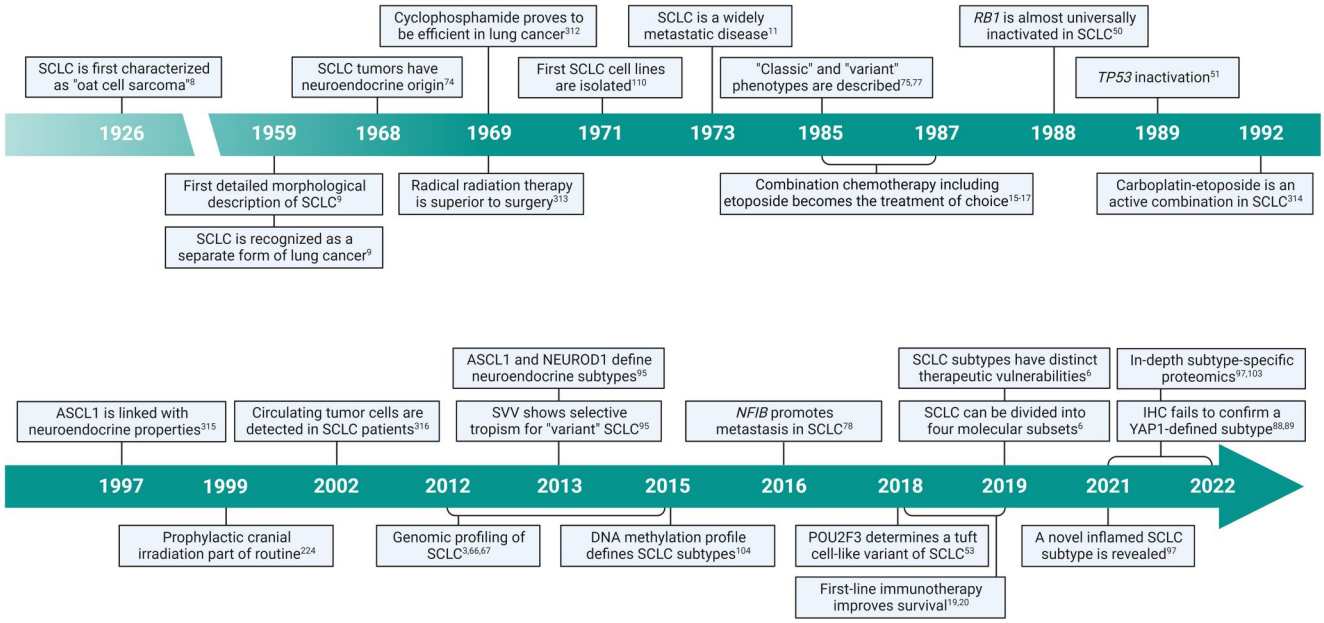

FIGURE 1 Major discoveries and therapeutic advancements in SCLC. ASCL1 indicates achaete-scute homolog 1; IHC, immunohistochemistry; NEUROD1, neurogenic differentiation factor 1; NFIB, nuclear factor IB; POU2F3, POU class 2 homeobox 3; RB1, retinoblastoma 1; SCLC, small cell lung cancer; SVV, Seneca Valley virus; YAP1, yes-associated protein 1.[3,6,8,9,11,15–17,19,20,50,51,53,66,67,74,75,77,78,88,89,95,97,103,104,110,224,312–316] Created with BioRender.com.

EPIDEMIOLOGY

Incidence and mortality

SCLC comprises an estimated 250,000 new cases globally each year and contributes to at least 200,000 deaths.[2,21] In the United States, approximately 30,000–35,000 new SCLC cases are diagnosed annually.[7,22] Because there is a strong epidemiologic link with heavy smoking, the worldwide incidence of SCLC tends to mirror smoking habits of certain time periods, with a lag time of approximately 30 years.[4,23] Accordingly, because of the adoption of clinical and public health interventions to discourage smoking initiation and encourage cessation programs as well as changes in cigarette composition and reduction of occupational hazards, the incidence rate of SCLC has declined steadily since the late 1980s.[4,24] SCLC incidence is slightly higher in males than in females; however, the incidence gap between sexes has narrowed down over the past 3 decades, again reflecting the changes in smoking habits.[4,24,25] The incidence of SCLC also varies according to geographic and racial/ethnic differences.[2] Reflecting trends in smoking prevalence, the incidence of SCLC is decreasing in high-income countries, but it is increasing in low-income and middle-income regions.[26] SCLC incidence is lower and the survival rates are higher in African American individuals compared with White individuals despite the lower smoking prevalence in the latter racial group.[24,27–29] Importantly, although the relative incidence of SCLC has indeed decreased over the past decades, patients' overall survival (OS) has remained notoriously poor.[30,31]

Risk factors

SCLC tumorigenesis is commonly linked to excessive tobacco exposure, and 94% and 93.9% of men and women with SCLC, respectively, are ever-smokers.[32] Smoking is associated with intrinsic aggressive disease, which is reflected by odds ratios (ORs) of 12.9 (95% confidence interval [CI], 9.79–17.1) and 42.0 (CI 21.7–81.2) in ever-smokers or current-smokers diagnosed with SCLC, respectively.[33] Compared with other types of lung cancer, patients who have SCLC display the highest smoking intensity (>30 cigarettes a day: OR, 18.3; 95% CI, 9.26–36.4) and the longest duration of smoking (≥40 years: OR, 38.6; 95% CI, 11.9–125).[33] Notably, secondhand smoking also contributes to SCLC carcinogenesis because the association between secondary smoke exposure and the development of SCLC is two to three times greater than that in other histologic types.[34] Interestingly, the fraction of never-smokers with SCLC appears to be somewhat higher in Asians, among whom >10% of patients are never-smokers.[35,36] Nevertheless, the risk of SCLC steadily decreases over the years after smoking cessation, underscoring the importance of quitting smoking as early as possible.[23] Regarding pathogenic mechanisms, the assault on lung cells of genotoxic carcinogens in cigarette smoke (e.g., polycyclic aromatic hydrocarbons, N-nitrosamines, aromatic amines) has disastrous effects on DNA, leading to miscoding and mutations in critical growth-control genes.[37,38] In addition, co-carcinogens and tumor promoters, such as undecane, pyrene, and fluoranthene, enhance the carcinogenicity of cigarette smoke carcinogens through mechanisms that usually lead to the stimulation of cell proliferation.[39] Finally, proinflammatory

changes have been observed in smokers that are closely associated with tumor promotion and NF-κB signaling, a pathway that regulates multiple aspects of innate and adaptive immune functions.[40–43] Although never-smokers lack mutational signatures related to tobacco exposure and their tumors have a lower tumor mutational burden (TMB), there are no differences in the survival of patients who have SCLC between never-smokers and smokers.[44] Indoor radon exposure and air pollution are most likely the second most important risk factors for SCLC worldwide and the main risk factor for never-smokers.[45,46] Indeed, radon disintegration emits alpha radiation, which damages cells in the lung lining and produces mutations.[46] Meanwhile, air pollutants, such as particulate matter with an aerodynamic diameter <10 μm and nitrogen dioxide, have direct carcinogenic effects, especially in the case of SCLC and squamous cell lung cancer.[47,48] This is mainly because the wretched effects of these air pollutants are more evident in the central sites of the bronchial tree (the place of origin of most SCLCs and squamous cell carcinomas) than in the peripheral bronchi.[34] Among respiratory comorbidities, chronic obstructive pulmonary disease is an independent risk factor for SCLC development.[23] Studies of familial aggregation suggest a higher risk of SCLC among first-degree relatives.[38] Yet, this is mostly because of shared smoking patterns rather than the consequence of hereditary germinal mutations.[49]

PATHOLOGY AND GENOMICS

Cell of origin and pathogenesis of SCLC

In contrast to NSCLC, in which precancerous conditions offer valuable insights into the cellular origin of both lung adenocarcinoma and squamous cell carcinoma, the explosive tumor growth in SCLC precludes the detection of these lesions; therefore, oncogenesis remains poorly understood.[7] However, it is thought that concomitant inactivation of the tumor suppressors p53 and RB (encoded by *TP53* and *RB1*, respectively) is necessary for tumorigenesis in the vast majority of patients (Figure 2A).[3,50,51] These dual inactivation events usually target achaete-scute homolog 1 (ASCL1)-expressing pulmonary neuroendocrine (NE) cells located predominantly in larger airways and initiate molecular events necessary for tumor development. Actually, a comprehensive preclinical study suggests that loss of *Trp53* and *RB1* transforms both NE cells and type 2 alveolar cells to SCLC, albeit the latter are transformed with much lower efficiency.[52] Accordingly, SCLC arises with greatest efficiency from pulmonary NE cells but could also arise seldom from epithelial cells, such as type 2 alveolar cells, basal cells, or club cells (Figure 2A).[7,52] Recent studies suggest that certain SCLC tumors harbor tuft cell-like gene expression signatures.[53] These tumors most likely originate from the chemosensory epithelial cells of the respiratory tract and have widely different morphologic features compared with the classical NE form of this disease (Figure 2A).[53] Undifferentiated stem cells also have the potential to form SCLC-like tumors through *NOTCH*, *TP53*, and *RB1* inactivation.[54] Finally, although uncommon, epidermal growth factor receptor (EGFR)-driven, ALK-driven, or RET-driven lung adenocarcinomas can also transdifferentiate to an SCLC phenotype through lineage plasticity upon treatment with targeted therapies, as discussed below.[55–57]

Lineage plasticity and transdifferentiation

Histologic transformation to SCLC may occur in up to 15% of EGFR-mutant lung adenocarcinomas and is mostly triggered by acquired resistance to tyrosine kinase inhibitors.[58–60] The median elapsed time from the initiation of anti-EGFR therapy to the transformation to SCLC is approximately 16–19 months, and it mostly affects a subset of tumors characterized by concomitant biallelic loss of *TP53* and *RB1*.[55,58,61,62] Genomic sequencing of tumor samples from repeated biopsies suggests that transformed SCLCs harbor the original activating EGFR mutation present in the adenocarcinoma counterpart, but EGFR protein expression is downregulated after transdifferentiation.[56] The clinical behavior of transdifferentiated tumors mimics the characteristics of primary SCLCs, exhibiting rapid tumor growth and early metastatic spread.[55] Likewise, survival outcomes concerning both progression-free survival (PFS) and OS are also comparable to those seen in classical extensive-stage SCLC.[61] Importantly, SCLC transdifferentiation can also occur in patients who have ALK-translocated NSCLC treated with ALK inhibitors and even in those who have wild-type EGFR or ALK tumors treated with immunotherapy.[63,64] The potential mechanisms underlying this SCLC phenotype conversion are poorly understood, yet a possible explanation might lie in the shared ancestry of some SCLC and NSCLC tumors.[59] Accordingly, as elaborated previously, type 2 alveolar cells (the cellular origin of some adenocarcinomas) also have the capacity to become SCLC (Figure 2A).[59] Of note, a similar transdifferentiation can also occur in prostate cancer when prostate adenocarcinoma acquires the histologic features of small cell NE cancer after developing resistance to traditional systemic therapies. These castration-resistant NE cancers are clonally derived from prostate adenocarcinomas but possess a unique NE-differentiated phenotype and have recurrent *TP53* and *RB1* alterations.[65]

Genomic landscape, key genetic alterations, and pathways

In addition to the loss of *TP53* and *RB1*, genome sequencing has revealed several other recurrent genetic alterations in SCLC particularly linked with NE differentiation and either therapeutic resistance or therapeutic sensitivity.[3] A small but significant fraction of SCLC is characterized by recurrent amplification of *BCL2* and the MYC family of proto-oncogenes as well as by the loss of the tumor suppressor *PTEN*.[3,66,67] The amplification of *MYC*, *MYCL*, and *MYCN* and the inactivating mutations in MYC-regulatory factors *MAX*,

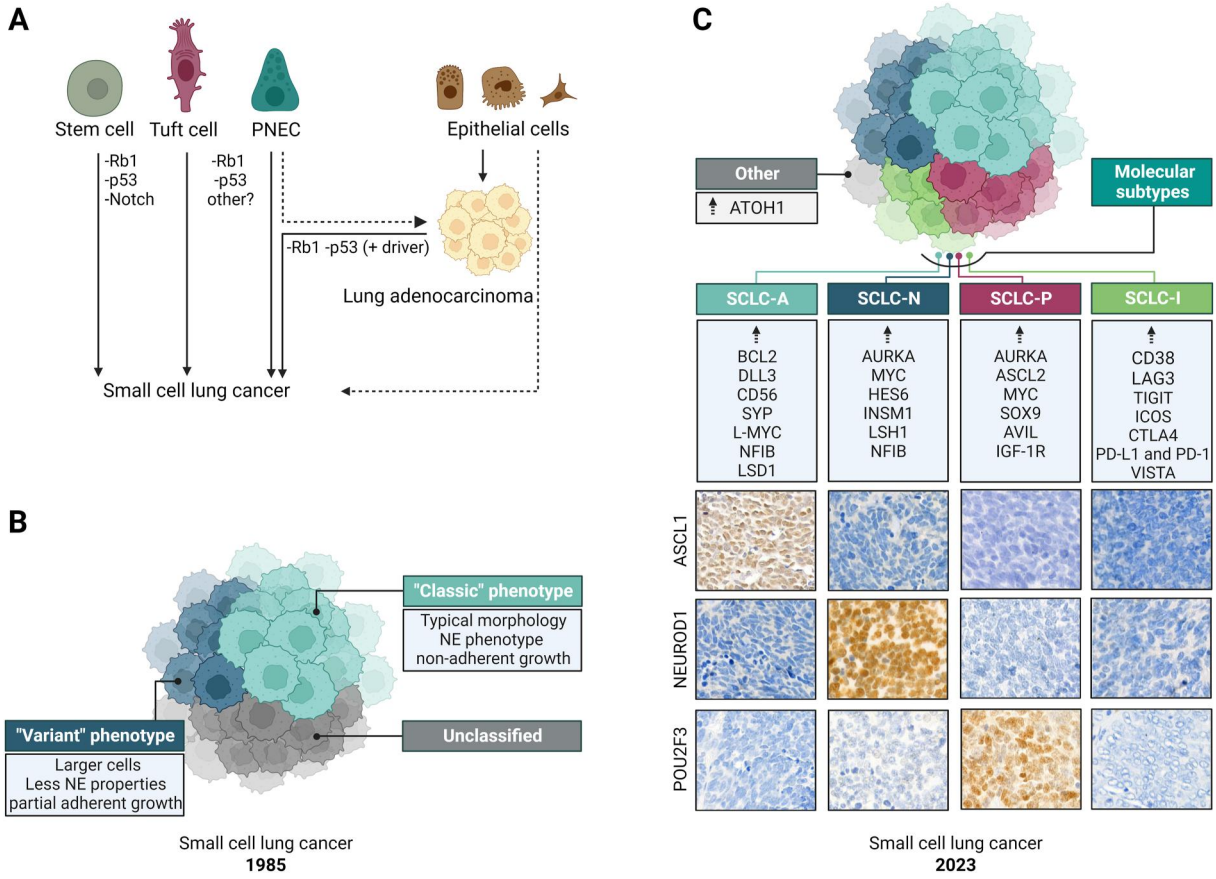

FIGURE 2 (A) Cellular origin and concepts on tumoral heterogeneity in SCLC concerning morphology, key characteristics, and genomic alterations (B) in 1985 and (C) today. ASCL1 indicates achaete-scute homolog 1; ATOH1, atonal bHLH transcription factor 1; NE, neuroendocrine; NEUROD1, neurogenic differentiation factor 1; PNEC, pulmonary neuroendocrine cells; POU2F3, POU class 2 homeobox 3; Rb1, retinoblastoma 1; SCLC, small cell lung cancer. Created with BioRender.com.

MGA, and *BRG1* result in tumors with distinct morphologies, expression profiles, and gene dependencies.[7,68] Specifically, amplification of *MYC* (i.e., c-Myc) promotes an NE-low phenotype associated with high expression of neurogenic differentiation factor 1 (NEUROD1) and thus with variant morphology (as discussed below).[69] In line with this, c-Myc induces transition from ASCL1-defined to NEUROD1-defined SCLC.[70] Meanwhile, increased *MYCL* expression is associated with high NE marker expression and elevated levels of the transcription factor ASCL1.[4] Accordingly, by activating Notch signaling, *MYC* plays a prominent role in mediating NE plasticity.[52] Suppression of apoptosis is a hallmark of SCLC. This is mainly achieved by elevated expression of the antiapoptotic gene *BCL2*, which acts as a promoter of carcinogenesis and cancer progression through cell death resistance.[71] Importantly, *BCL2* is a conserved transcriptional target of ASCL1.[71] In addition to influencing NE fate, Notch signaling also acts as a tumor suppressor in SCLC.[72] In the vast majority of tumors, Notch appears to be inactivated, especially in those expressing the full set of NE markers.[3] Nevertheless, Notch-active SCLCs also exist. Consistent with the tumor suppressive role of Notch, these tumors grow slowly and are characterized by loss of NE differentiation.[73] Other recurrent genetic alterations in SCLC include the activating mutation of *PIK3A* and the deletion of *KMT2D*, *PTEN*, and *CREBBP*.

Neuroendocrine features of SCLC

Because of the presence of sparse, fairly small, dense-core granules in the majority of SCLC cells, which are all part of the ultrastructural hallmark of NE cells, SCLC was historically regarded as an NE malignancy.[74] Indeed, this *classic* form of SCLC is associated with typical morphology, high expression of NE markers, and nonadherent growth patterns in cell cultures (Figure 2B).[75] These SCLCs share histologic features with extrapulmonary small cell carcinomas arising from the gastrointestinal and genitourinary systems.[76] Although they are relatively rare, extrapulmonary small cell carcinomas have an aggressive natural history and a dismal prognosis, similar to SCLCs. Importantly, in 1985 (Figure 1), Gazdar et al. also provided evidence for a distinct SCLC phenotype with *variant* morphology (Figure 2B). This subset of SCLC tumors is characterized by larger cells with prominent nucleoli, partial or complete loss of NE cell properties, and epithelial-mesenchymal transition (EMT).[77]

Drivers of metastatic spread

The transcription factor NFIB is frequently overexpressed and amplified in SCLC and has been shown to function as a major determinant driving tumor progression, invasion, and metastasis (Figure 1).[78,79] In addition to being associated with several gene expression programs related to metastasis, such as cell migration, cell adhesion, and neuronal differentiation, *NFIB* also promotes multiple steps of the metastatic cascade through a widespread increase in chromatin accessibility.[78,80] Accordingly, high *NFIB* expression is generally associated with late-stage disease and, consequently, worse patient survival.[79] Recently, EMT has also been associated with metastasis. Because yes-associated protein 1 (YAP1) is frequently linked with EMT, its elevated expression might endow SCLC cells with the ability to metastasize.[81] Other mechanisms underlying the ability of malignant cells to metastasize remain relatively poorly understood, but factors associated with migration and neuronal differentiation might as well be implicated in the metastatic spread of SCLC.[4,82]

AN EMERGING MOLECULAR CLASSIFICATION AND ITS CLINICAL IMPACT

Neuroendocrine and molecular subtypes of SCLC

Except for minor attempts in classifying the disease by its dominant phenotype (*classic* vs. *variant*),[75,77] SCLC was considered a single, monolithic entity in both clinics and laboratories for decades. Consequently, clinical study protocols are still generally based on disease stage, with no consideration of predefining distinct molecular marker expressions that have predictive or prognostic significance.[6,30] However, the recent worldwide resurgence of profiling studies and the development of the preclinical models highlighted below led to the refinement of the SCLC classification scheme.[7] Accordingly, based on the expression pattern of certain well established NE cell markers, SCLC tumors can be classified either as *NE-high* or *NE-low* subtypes.[2,6,83,84] In addition, a further subset of SCLC lacks any sign of NE differentiation; therefore, these termed *non-NE tumors*.[6] These subtypes can also be characterized by NE-related scoring systems and EMT.[83] Importantly, NE subtypes have major differences concerning their immunologic landscape because NE-high SCLCs are considered *immune desert* tumors characterized by low numbers of infiltrating immune cells, whereas NE-low tumors have an *immune oasis* phenotype with increased immunogenicity.[85]

Emerging knowledge suggests that SCLC subtypes are defined not necessarily by their mutational landscape but, instead, by the expression of certain transcription factors and features of inflammation that can provide a biologic framework for the distinct SCLC entities.[86] SCLC tumors originating both from limited stage and extensive-stage disease have recently been stratified into different subtypes based on the elevated expression of transcription factors ASCL1, NEUROD1, and POU class 2 homeobox 3 (POU2F3) and on inflammatory characteristics (Figures 1 and 2C).[6,87–89] Of note, it has been demonstrated that ASCL1, NEUROD1, and POU2F3 expression levels define distinct SCLC subtypes in metastatic lymph nodes as well.[90] These novel subtypes are of clinical importance because they correlate with therapeutic responsiveness and have major differences in morphology, growth properties, genetic alterations, and prognosis.[87,89] The most common is the ASCL1-defined SCLC-A subtype, comprising approximately 40%–50% of all SCLCs.[6,88,89] Pathologically, these tumors are associated with elevated expression of NE markers and classic morphology.[30] Importantly, recent studies on patients with surgically treated SCLC suggest that high ASLC1 expression is associated with impaired survival outcomes in surgically treated individuals.[89,91,92] Indeed, high-grade NE features and elevated ASCL1 levels have been described as a potential sign of poor prognosis in other histologic subtypes of lung cancer, including lung adenocarcinoma.[93] Further subdivision of ASCL1-driven tumors into two subclusters (namely, SCLC-A and SCLC-A2) is suggested based on expression differences concerning other factors, such as HES1.[94] SCLC-N was originally described as a distinct, NEUROD1-defined subtype susceptible to the Seneca Valley virus.[95] These tumors are associated with lower overall NE marker expression and thus with variant phenotype.[6,30] Importantly, combined SCLC-AN tumors also exist.[88,89] POU2F3 is a master transcriptional regulator of tuft cells, a rare cell type thought to have chemosensory and immunomodulatory functions.[53] These cells can be found in a wide variety of epithelia and are alternatively referred to as brush cells in the lung airways.[96] Accordingly, POU2F3-driven SCLCs (SCLC-P subtype) might represent a specific tuft-cell variant of SCLC and thus might have a distinct cellular origin compared with SCLC-A and SCLC-N.[53] These tumors do not express classical NE markers. Therefore, from a clinical point of view, these tumors may represent diagnostic challenges and often require an extensive immunohistochemical (IHC) work-up to exclude other entities.[96] Interestingly, in-depth analyses of basaloid squamous cell carcinomas revealed strong and diffuse POU2F3 immunoreactivity, suggesting a possibly closer biologic relationship between SCLC-P and this primitive phenotype of lung squamous cell carcinoma than expected.[96] High POU2F3 expression was recently associated with improved survival outcomes in patients with surgically treated SCLC.[89,91] However, survival analyses in patients with extensive-stage disease yielded conflicting results.[96,97] Accordingly, our current understanding concerning its clinical relevance is still limited. Initially, a putative fourth molecular subtype driven by the transcription factor YAP1 was also proposed,[6] yet multiple independent studies (including those from the investigators originally proposing YAP1 as a candidate subtype) failed to confirm the existence of a major, distinct SCLC-Y subtype.[88,89,98] Instead, a recent study based on RNA sequencing data and subsequent IHC validation provided evidence for an SCLC-inflamed subtype (SCLC-I). In addition to the lack of prominent ASCL1, NEUROD1 and POU2F3 expression, SCLC-I is accompanied by an inflamed gene signature and mesenchymal characteristics (Figure 2C).[97] Concerning the nomenclature, an alternative for SCLC-I might be the newly proposed quadruple-negative subtype (SCLC-QN) characterized by

low expression of all four (ASCL1, NEUROD1, POU2F3, and YAP1) transcription regulators.[89] Although neither of these is defined by YAP1 expression, currently it is still debatable whether SCLC-I and SCLC-QN are identical subtypes or they form two distinct subsets within the scale of non-NE SCLCs. Finally, it is worth mentioning that a rare subtype demonstrating elevated expression of the transcription factor ATOH1 might also exist; yet, to date, little is known about its specific genomic features.[99]

Phenotype switching and tumoral heterogeneity

Although a dominant molecular subtype can be distinguished in the majority of cases, recent studies described substantial heterogeneity.[88,89,97] Pathologically, two manifestation forms of intratumoral heterogeneity were detected. In some cases, tumors have both subtype-specific marker-expressing and nonexpressing cells within the same areas, whereas, in other cases, clusters of these cells can be found in spatially distinct regions.[89,97] In addition to raising diagnostic issues, this also indicates a potential temporal evolution between subtypes. Indeed, several studies suggest a potential sequential hierarchy between subtypes, with SCLC-A being a necessary precursor for SCLC-N.[69,100] The dominant phenotype might as well be influenced by systemic therapy. High YAP1-expressing tumor cells are thought to be resistant to the majority of standard-of-care chemotherapeutics.[89,97] Accordingly, after chemotherapy, YAP1-high cells have the potential to replenish the tumor.[97,101] Subtype switching was also described during metastatic spread in mediastinal lymph nodes.[84] In this form of intertumoral heterogeneity, some NE-low primary tumors gave rise to NE-high metastases, suggesting that tumor cells with NE differentiation tend to be more aggressive and thus more metastatic than NE-low cells.[84]

It is also important to mention that, apart from subtypes, dynamic heterogeneity can be observed in the expression of several SCLC candidate targets, such as DLL3, aurora kinase (AURK) A and B (AURKA)/(AURKB), and poly(ADP-ribose) 1 (PARP1).[102] This may contribute to therapeutic resistance and the lower-than-expected response rates, despite biomarker-guided patient selection.

Subtype-specific therapeutic targets

The identification of subtype-specific molecular profiles and clinically meaningful biomarkers may contribute to novel targeted strategies. Indeed, recent genomic and proteomic data suggest that several putative targets in patients with SCLC representing subtype-specific vulnerabilities might exist (Figure 2C).[30,97,103] Among others, DLL3, a target of multiple SCLC therapeutics now in clinical development, is reported to be highly expressed in SCLC-A tumors.[6,92] Likewise, BCL-2 is also preferentially expressed in this subtype.[71,104,105] Histone demethylase LSD1 activity depends on the disruption of INSM1, which is linked to the NE subtypes SCLC-A and SCLC-N.[106] *MYC* amplification is frequently associated with SCLC-N, thus serving as a potential therapeutic target for this subtype.[69] Both arginine biosynthesis and increased AURKA activity are also specific features of this particular molecular subtype.[30,69,107] Regarding SCLC-P, CRISPR screening identified IGF-1R as a unique dependency in SCLC cells with high POU2F3 expression.[53] However, the most evident clinical implications have been linked with SCLC-I, given the elevated expression of genes associated with immune checkpoints and human leukocyte antigens in this subtype.[97,108,109] In support of this, the retrospective analysis of the phase 3 IMpower133 trial (ClinicalTrials.gov identifier NCT02763579), which assessed the addition of atezolizumab to EP, revealed that the highest benefit of the addition of immunotherapy can be seen in patients with SCLC-I.[19,97] Specifically, the median OS was approximately 8 months higher in patients with SCLC-I who received EP plus atezolizumab compared with those who received EP alone.[97]

PRECLINICAL MODELS FOR THE STUDY OF SCLC

Cell cultures and organoids

The scarcity of representative, surgically removed SCLC tissue samples urged the development of adequate preclinical models. Beginning in the 1970s (Figure 1) and continuing throughout the decades, a focus was laid on the establishment of SCLC cell lines from biopsies or pleural effusions for further in vitro research (Figure 3).[110,111] Currently, the pathologic signature of SCLC is frequently investigated using a comparative approach between cancer cell lines and human bronchial epithelial cells, such as hTERT and Cdk4 immortalized human bronchial epithelial cells.[112] However, as with any tumor entity, the study of cell lines comprises major limitations, such as the high chance of genetic transformations, frequent discrepancies between in vitro and in vivo drug efficacies, or the missing exposure to the microenvironment, especially the immune system.[113] Nevertheless, despite these disadvantages, human SCLC cell lines still represent an important resource for preclinical research. In contrast to other tumor types, such as colon or breast cancer, three-dimensional models that include organoids are rarely used in SCLC because of its extensive heterogeneity and complexity.[114,115]

In vivo models

Genetically engineered mouse models (GEMMs) bearing SCLC tumors were first designed using a double-gene (*TP53* and *RB1*) knockout (KO) approach.[116,117] In line with the aggressive potential of SCLC, corresponding GEMMs were frequently associated with vascular or lymphatic invasion as well as metastatic spread to the mediastinum or extrathoracic organs.[117] In addition to the SCLC double-KO mouse model, triple-KO mice harboring additional loss of *P130* or *PTEN* also exist.[118,119] Of note, triple-KO mice lacking *P130* are representative of the SCLC-A subtype.[118,120] In turn, *PTEN* triple-KO mice

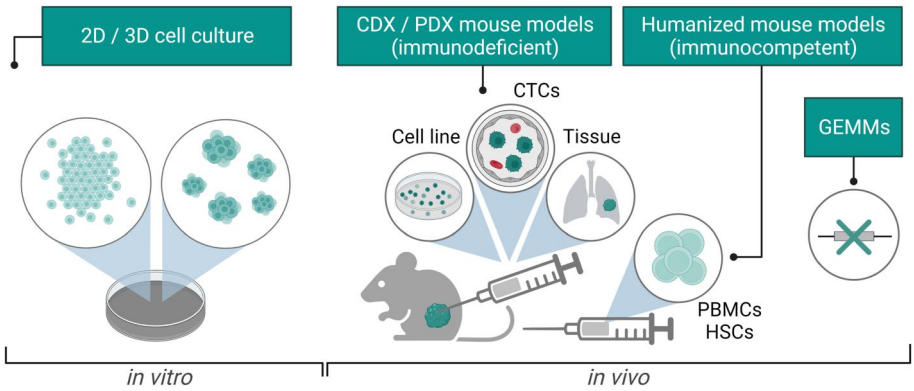

FIGURE 3 Frequently used in vitro and in vivo models of SCLC. 2D/3D indicates 2-dimensional/3-dimensional; CDX, cell line-derived xenograft; GEMMs, genetically engineered mouse models; HSCs, hematopoietic stem cells; PBMCs, peripheral blood mononuclear cells; PDX, patient-derived xenograft; SCLC, small cell lung cancer. Created with BioRender.com.

display variant features of SCLC but also characteristics from large cell NE carcinoma and NSCLC.[119] Importantly, GEMMs provide a faithful immunocompetent model for testing treatment efficacy and investigating the mechanism of action of immunotherapeutic agents.[121]

Mouse xenograft models (Figure 3) are defined by the engraftment of SCLC cell lines (cell line-derived xenografts), circulating tumor cells (CTCs), or tissue specimens (patient-derived xenografts) into immunodeficient mice and are common tools to investigate the efficacy of cytotoxic agents.[122] Although this experimental approach may provide information about the in vivo efficacy of cancer therapeutics, the results might be biased because of the lacking influence of the tumor microenvironment.[123] In addition, this preclinical model is usually not applicable to immunologic studies. These limitations are counterbalanced by the high feasibility of CTC-derived patient-derived xenografts because SCLC is one of the very few cancers in which engraftment of CTCs is actually possible and effective.[124]

One way of generating so-called humanized mice harboring major components of the human immune system is the engraftment of nude mice with human hematopoietic stem cells or peripheral blood mononuclear cells.[125] However, humanized mouse models are hampered by immunoglobulin switching, deficiency in T-cell development, and predominant affinity to the murine rather than the human major histocompatibility complex because of their education in the murine thymus.[125] Nevertheless, humanized animal models are powerful tools to investigate drug safety and efficacy, especially for immunotherapies in the presence of immunologic processes.

DIAGNOSIS, SCREENING, AND PREVENTION

Presentation and symptoms

SCLC occurs predominantly in the central airways and is typically associated with strong metastatic potential.[24] Given its explosive growth rate and aggressive nature, most patients with extensive-stage disease have some clinical manifestations. These signs and symptoms usually begin <12 weeks before presentation and depend on the localization and bulk of the primary tumor.[24] Local tumor growth explains the cough, dyspnea, and, eventually, the hemoptysis. In addition, intrathoracic tumor growth can also cause superior vena cava syndrome and upper body edema. Esophageal compression causes dysphagia, whereas compression of the recurrent laryngeal nerve leads to vocal cord paresis or hoarseness. Weight loss, fatigue, and neurologic disabilities are the results of extrapulmonary distant spread. The most common sites of metastasis include the brain, bones, liver, and adrenal glands.[126]

SCLC is the lung cancer subtype most often associated with paraneoplastic syndromes (PNSs). Indeed, approximately 10% of all patients with SCLC develop some kind of PNS throughout the course of their disease (Figure 4).[127,128] Endocrine PNSs (Figure 4) are caused by the ectopic production of biologically active hormones or peptides by the cancer cells themselves and include the syndrome of inappropriate antidiuretic hormone (ADH) secretion (SIADH) and ectopic Cushing syndrome.[127] The syndrome of inappropriate antidiuretic hormone secretion is the most common PNS in patients with SCLC and manifests as euvolemic, hypo-osmolar hyponatremia characterized by low serum osmolality and high urine osmolality, which is secondary to ectopic antidiuretic hormone production.[129] Clinically, this may present as headache, nausea, fatigue, and muscle cramps.[129] Meanwhile, the manifestation of ectopic Cushing syndrome results from the unregulated production of adrenocorticotropic hormone and includes hypokalemia, muscle weakness, acne, and peripheral edema.[130]

Neurologic PNSs (Figure 4) are immune-mediated consequences of SCLC tumors and are characterized by an autoantibody response against tumoral antigens.[129,131] The most commonly diagnosed neurologic PNS in SCLC is the Lambert–Eaton myasthenic syndrome, which features progressively worsening proximal muscle weakness and fatigue. It is caused by onconeural antibodies directed against voltage-gated calcium channels.[127,132] If the autonomic nervous system and cranial nerves are involved, symptoms such as dry mouth, constipation, ptosis, and respiratory weakness can also appear in Lambert–Eaton myasthenic syndrome.[127] Anti-Hu antibodies are

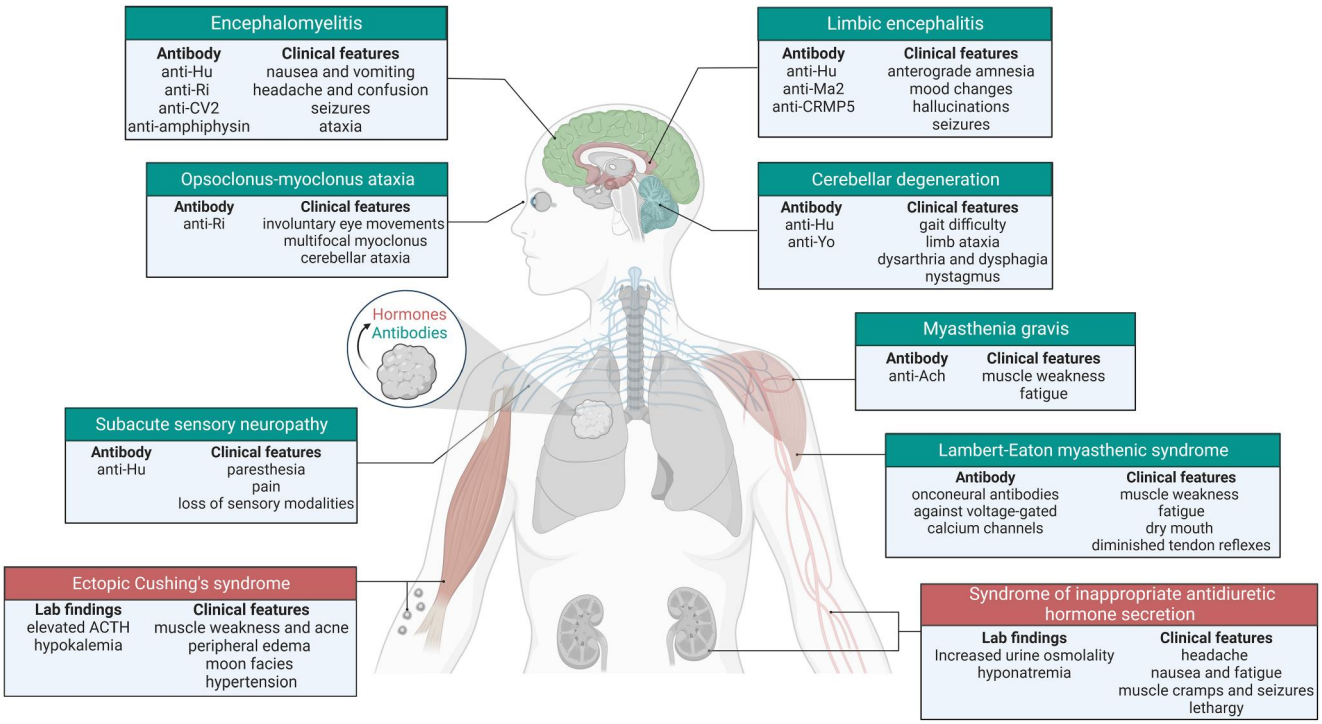

FIGURE 4 SCLC-associated PNSs and their clinical presentations. Orange indicates endocrine PNSs; cyan, neurologic PNSs. ACTH indicates adrenocorticotropic hormone; PNSs, paraneoplastic syndromes; SCLC, small cell lung cancer. Created with BioRender.com.

directed against RNA-associated neuronal proteins.[133] PNSs associated with the presence of anti-Hu antibodies occur in SCLC at a frequency of 1% and are characterized by inflammation and neuronal loss.[134] Among others, these include paraneoplastic encephalomyelitis, limbic encephalitis, and subacute sensory neuropathy, and their clinical manifestations vary according to the affected part of the nervous system (Figure 4).[127] For instance, limbic encephalitis is primarily characterized by mood and behavior changes with occasional seizures, whereas the specific symptoms in subacute sensory neuropathy include paresthesia and pain involving all limbs.[127,129] Importantly, in addition to anti-Hu antibodies, several other neural autoantibodies also contribute to the development of neurologic PNSs (Figure 4).[129,135]

Diagnostic work-up and diagnosis

Posteroanterior and lateral chest radiographs are usually the first imaging tests performed in patients with SCLC (Figure 5A).[136] However, chest radiographs are unremarkable in approximately 4% of patients with SCLC; and, in the absence of evident signs of invasiveness, chest radiography is frequently nonspecific.[137] Generally, tumors appear as hilar masses on chest radiographs, frequently accompanied by mediastinal widening caused by lymph node enlargement.[136] Whenever clinical and radiologic suspicion for lung cancer is raised by chest radiographs, a contrast-enhanced computed tomography (CT) scan of the chest (Figure 5A) and upper abdomen should also be performed for further evaluation. On CT scans, SCLC tumors are usually characterized as mass lesions with margins that are smooth, lobulated, or irregular and spiculated.[138] Necrosis and hemorrhage are both fairly common, as well as the bulky mediastinal nodes that conglomerate to form large masses.[138] Rarely, SCLC tumors can also appear as solitary pulmonary nodules.[138] Nevertheless, because of its frequent central localization, the primary tumor often cannot be visualized as a distinct entity because it merges with the nodal disease.[139] As the cornerstone of lung cancer imaging, CT scans play a pivotal role in determining the tumor's local invasiveness and its anatomic relationship to neighboring structures, such as vessels, the heart, pleura, chest wall, and esophagus.[140] This is of clinical importance because the evaluation of mediastinal involvement is crucial for correct staging. SCLC typically demonstrates intense uptake on fluorine-18 fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET)-CT scans, reflecting its high metabolic activity (Figure 5A).[86,141] Importantly, in addition to its diagnostic value concerning the primary tumor and distant metastases, ^{18}F-FDG PET-CT imaging might also help in estimating the prognosis. Indeed, higher maximum standardized uptake values can be observed more often in extensive-stage disease than in limited stage SCLC, and high metabolic tumor burden as well as high total lesion glycolysis are associated with a poor prognosis.[141–143] Because some SCLC tumors have high expression of somatostatin receptors, PET-CT imaging with gallium-68 dotatate, a positron emitter-labeled somatostatin analog, might also improve staging.[144]

Before treatment can commence, a firm tissue diagnosis of SCLC is required, even in patients with impaired lung function. Sampling methods (Figure 5B) are chosen by oncologists, surgeons, or

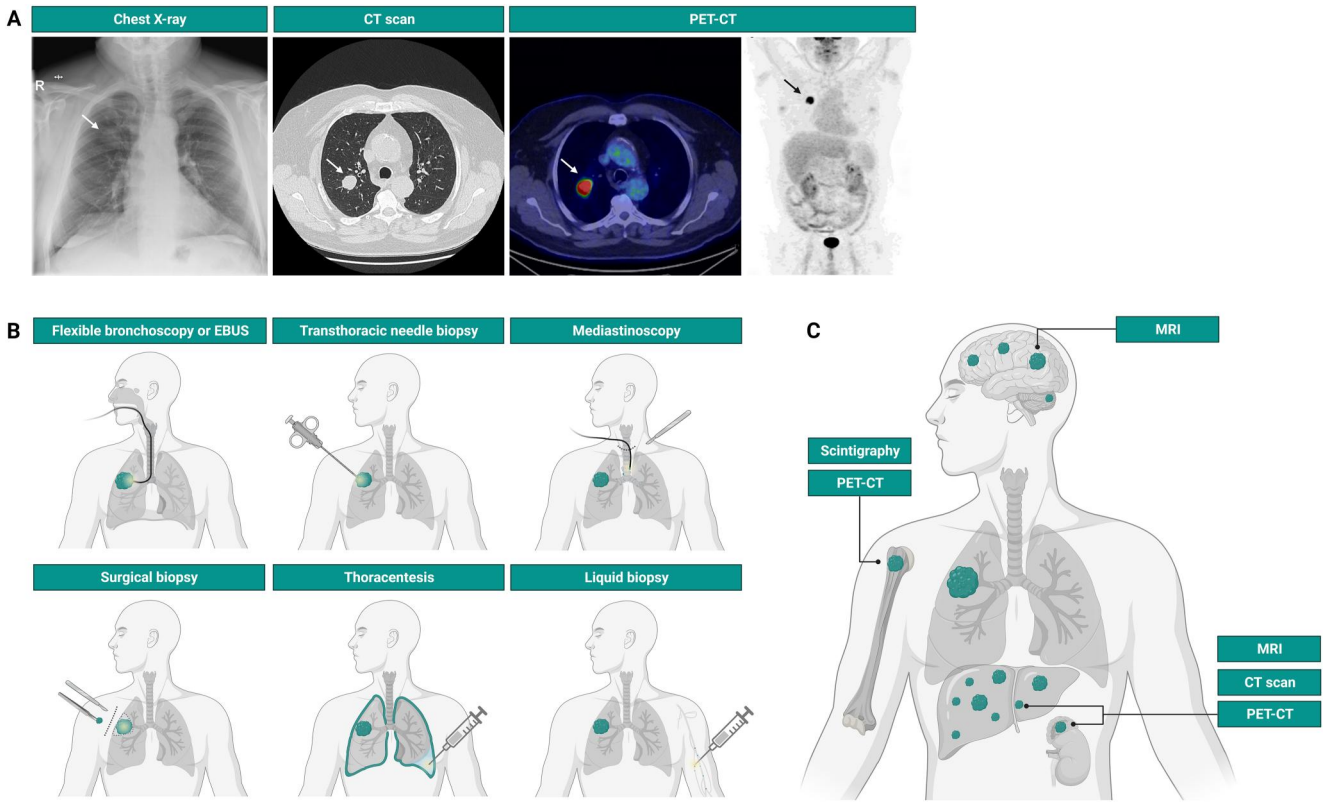

FIGURE 5 Diagnosis of SCLC and its distant metastases. (A) Imaging techniques for the primary tumor (indicated by arrows). (B) Schematic representations of the different techniques used to obtain tumor specimens. (C) Imaging techniques for the diagnosis of distant metastases. CT indicates computed tomography; EBUS, endobronchial ultrasound; MRI, magnetic resonance imaging; PET, positron emission tomography; SCLC, small cell lung cancer. Created with BioRender.com.

interventional radiologists primarily based on the tumor's anatomic localization. The decision must also take into account the likely stage of the disease and the overall performance status (PS) of the patient.[145] Generally, it is advised that the diagnosis of lung lesions be made by the most convenient and least invasive method available.[146] It is usually advisable to biopsy distant metastases because this allows simultaneous diagnosis of the tumor and confirmation of advanced tumor stage. Because many patients with SCLC have supraclavicular lymph node metastases, percutaneous ultrasound-guided biopsy can be the easiest way to get a sufficient amount of tissue.[147] Flexible bronchoscopy is usually recommended in patients with centrally located tumors.[148,149] Importantly, in addition to obtaining diagnostic tissue specimens using biopsy forceps, bronchoscopy with brushing or bronchoalveolar lavage can also contribute to the diagnosis with remarkable specificity.[150] Among the newer bronchoscopy-based technologies,[151] endobronchial ultrasound-guided transbronchial needle aspiration is preferably used for tumors with peribronchial localization and for enlarged mediastinal or hilar lymph nodes.[146,152] Another approach for mediastinal staging is mediastinoscopy (Figure 5B), which is performed under general anesthesia. However, endobronchial ultrasound-guided is a less invasive method with fewer complications and has higher diagnostic sensitivity than mediastinoscopy.[153] Therefore, whenever the lymph node station is reachable, endobronchial ultrasound-guided transbronchial needle aspiration should be considered as the procedure of choice for mediastinal staging.[154] When results of the bronchoscopy-based investigation are nondiagnostic, transthoracic needle biopsy (Figure 5B) can be applied, especially in peripheral lesions.[155] Transthoracic needle biopsy is usually performed using real-time CT visualization for improved yield and has a sensitivity exceeding 90%.[156,157] In rare cases when none of the previously elaborated methods are successful or feasible, thoracoscopy and surgical biopsy should be considered as the ultimate diagnostic approach.[158] Meanwhile, in patients with an accessible pleural effusion, thoracentesis is recommended to facilitate diagnosis.[155] Finally, given the high amount of circulating tumor DNA and CTCs in the bloodstream of patients who have SCLC, liquid biopsy also holds a potential diagnostic role, especially concerning monitoring disease progression.[159,160]

Radiologic diagnosis of distant metastases varies according to their anatomic localization (Figure 5C). However, except for brain metastases, PET-CT remains the imaging approach of choice in identifying extrathoracic metastases, especially bone and adrenal lesions.[161] Indeed, recent studies suggest that ^{18}F-FDG PET-CT is more sensitive than multidetector row CT scans, and even bone scintigraphy, for detecting osseous metastases in SCLC.[162] This is most likely because PET-CT scans also detect lytic lesions.[163] The traditional imaging method for the evaluation of brain metastases is contrast-enhanced magnetic resonance imaging (MRI).[164]

Depending on accessibility, distal metastatic sites can also be used for diagnostic tissue sampling.

The definitive diagnosis of SCLC is established by histopathologic and/or cytopathologic examination. Notably, cytology is an especially reliable method in SCLC diagnosis because bronchial biopsies may contain crush artifacts and necrosis, hampering the definitive diagnosis.[165] Cytologic smears and cell blocks often show small blue cells (approximately 1.5 times the size of lymphocytes) with scant cytoplasm, loosely arranged or in a syncytial pattern.[165,166] Their oval or elongated nuclei are hyperchromatic, and nuclear molding is well developed.[165] Tumor cells usually have high mitotic activity. In addition, well preserved cells show a finely dispersed or *salt and pepper* chromatin pattern.[165,166] On hematoxylin and eosin-stained histopathologic slides, the small to medium-sized, round or fusiform tumor cells have scant cytoplasm, finely granular nuclear chromatin, and inconspicuous or absent nucleoli.[165] Necrosis and apoptosis of individual cells as well as the presence of crush artefacts are common.[4] Characteristic NE traits, including nested and trabecular growth patterns, rosettes, and peripheral palisading, are more obvious in surgical samples than in small biopsies.[167] In current practice, IHC assays are frequently performed when the hematoxylin and eosin–based diagnosis needs to be confirmed or when a differential diagnosis must be addressed.[165] SCLC tumors are usually positive for common NE markers, such as synaptophysin, chromogranin, CD56, or INSM1. Importantly, NE-differentiated SCLCs without extensive necrotic areas uniquely resemble pulmonary carcinoid tumors concerning both their NE marker expression and morphologic features.[168] In this context, the Ki67 labeling index is of diagnostic importance because it is considerably higher in SCLCs than in carcinoids.[165] Although it has not yet been implemented in the clinics, POU2F3 also may constitute a potential additional diagnostic marker for tumors that lack or exhibit minimal levels of standard NE markers and thus are negative for the aforementioned classical IHC markers.[96]

Differential diagnoses

SCLC has well defined diagnostic criteria, yet some other tumors tend to mimic its clinical, radiologic, and histologic features. The symptoms caused by local tumor growth and intrathoracic metastatic spread are the general clinical features of the majority of lung cancers, including NSCLC. PNSs are not exclusively specific either because they can also be associated with other NE tumors, although at a much lower percentage.[169] With regard to imaging, because of its central localization and mediastinal involvement, SCLC might appear similar to lymphomas or other mediastinal tumors.[138] From a pathologic point of view, SCLC should be distinguished from large cell NE carcinoma and carcinoid tumors, NSCLC, basaloid squamous cell carcinoma, and non-Hodgkin lymphoma.[4,165]

Screening

The US National Lung Screening Trial demonstrated that screening with low-dose CT reduced lung cancer mortality and resulted in a shift to earlier stage disease detection at diagnosis. However, these benefits were limited to NSCLC.[170] In the National Lung Screening Trial, a significant proportion of SCLC cases were interval cancers (diagnosed within 1 year after a negative screening), and only one third of all patients with SCLC were screen-detected.[171] In addition, the vast majority of these rare screen-detected individuals presented with advanced-stage disease.[171] Therefore, annual low-dose CT screening does not improve the survival or therapeutic outcome of SCLC.[172] However, because low-dose CT screening still identifies a considerable number of early stage NSCLC tumors (and a very small number of early stage SCLC tumors), screening should be applied in all individuals at risk according to evidence-based guidelines,[173] although its efficacy in SCLC lags far behind that observed in NSCLC.[171]

Notably, the fast progression and the high circulating tumor DNA burden in SCLC provide a rationale for conducting studies of liquid biopsy screening tests. Although multiple large-scale studies are evaluating the feasibility of blood-based screening tests for lung cancer (some with promising preliminary data),[174–176] these assays have not yet been translated into routine clinical practice.

Prevention

Considering the strong causal link between smoking and SCLC, avoidance of tobacco use is the most important way of preventing the disease.[177] Indeed, the risk of SCLC development decreases gradually after quitting smoking. In addition, quitters also tend to have improved survival in already developed, limited stage SCLC compared with continuing smokers.[177] The US Environmental Protection Agency recommends testing all homes below the third floor for radon and mitigation for homes with levels of 4 picocuries per liter or higher.[178] The European multidisciplinary RadoNorm Project aims to assure effective radiation protection through radon risk management and exposure normalization.[179] Carcinogenic air pollutants should also be avoided; although this risk factor is harder to elude on an individual level, clinicians should support relevant regulations that help prevent lung cancer.

STAGING OF SCLC

Principally, the therapeutic management of patients with SCLC (Figure 6) substantially differs according to the extent of tumoral spread and the patient's clinical condition (i.e., PS). In SCLC, tumor spread can be classified based on two staging approaches: (1) the tumor, node, metastasis (TNM) staging system, implemented by the

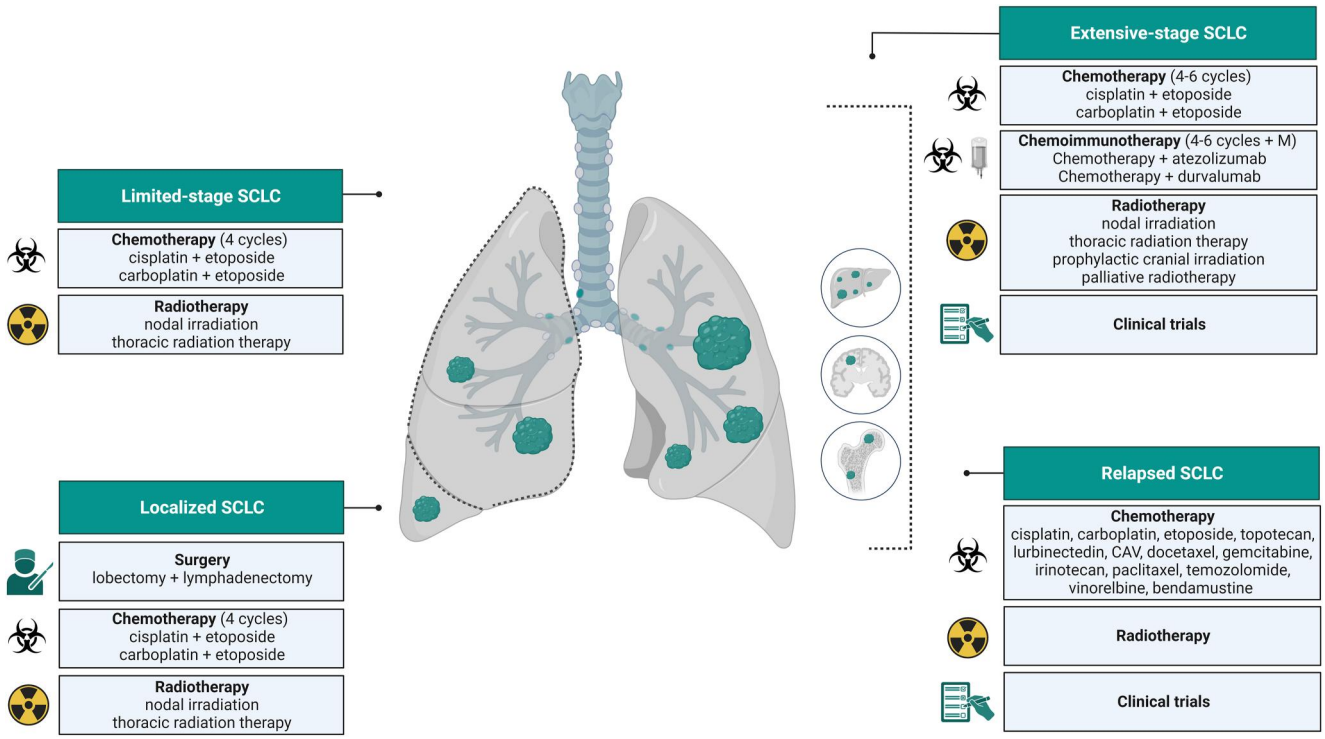

FIGURE 6 Therapeutic approaches in SCLC according to disease stage. CAV indicates cyclophosphamide, doxorubicin, and vincristine; M, maintenance; SCLC, small cell lung cancer. Created with BioRender.com.

American Joint Committee on Cancer (AJCC)[180] and updated by the International Association for the Study of Lung Cancer (IASLC),[181,182] and (2) the staging system of the Veterans Administration Lung Study Group (VALG).[183] The AJCC-IASLC TNM staging system has been developed over the past decades, allowing for a precise definition of tumor spread by containing detailed information about the size of the primary tumor as well as the extent of lymph node involvement and distant metastatic spread.[180–182] Although it has been continuously adapted at regular intervals, it should be noted that the AJCC-IASLC TNM staging system was primarily developed and validated with data originating from patients who had NSCLC. Meanwhile, the VALG staging system was specially adopted for patients who have SCLC to provide a simple staging approach for routine clinical practice by only distinguishing between limited stage and extensive-stage disease.[183] In this context, limited stage refers to localized disease affecting only one hemithorax that can be treated with a single radiation field.[183] Ipsilateral or supraclavicular lymph nodes—that can be included in the same radiation portal as the primary tumor—might also be affected.[183] Meanwhile, patients with both lungs affected or those with extrathoracic metastases are considered to have extensive-stage SCLC.[183] In an attempt to synchronize the two staging systems, the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology for SCLC generally refer to patients who have limited stage disease as those with stage I–III SCLC according to the AJCC-IASLC TNM staging system.[184] TNM stage IV is considered extensive-stage disease.[184] Currently, the VALG staging system is still the most frequently used approach in SCLC, although its prognostic capacity was shown to be significantly inferior compared with the AJCC-IASLC TNM staging system.[183,185] The overall condition of patients with SCLC both in clinical trials and in everyday clinical routine is standardly represented by calculating the Eastern Cooperative Oncology Group PS, which was published in 1982.[186]

THERAPEUTIC APPROACHES

Surgery

Surgical resection has been widely excluded from the therapeutic armamentarium of SCLC for decades mainly because of the somewhat disappointing outcomes of surgery-based randomized clinical trials from the 1970 and 1990s.[187,188] Still, in patients with very limited disease stage (T1–T2N0M0), lobectomy with mediastinal lymph node dissection followed by adjuvant chemotherapy has resulted in 3-year survival rates >50%.[189,190] Moreover, recent propensity-score-matched trials reported encouraging long-term survival rates for surgically managed patients who had even more advanced disease stage.[191,192] However, it has been widely demonstrated that durable long-term results after surgical resection can only be achieved if multicyclic, adjuvant, systemic chemotherapy is applied (Figure 6).[190,193] Specifically, in a study conducted on a large population-based cohort, treatment with adjuvant chemotherapy with or without radiotherapy, compared with no adjuvant therapy,

resulted in a significant increase of >12% in the 5-year survival rate.[193] This is even greater than the absolute benefit reported from postoperative chemotherapy in NSCLC, in which cisplatin-based chemotherapy increased the 5-year survival rate by 5.4%.[194] Accordingly, current practice guidelines recommend adjuvant chemotherapy for all patients who undergo lung resection because of T1–T2N0M0 SCLC.[184] Further strong predictors of durable long-term outcomes are anatomic lung resection (preferably lobectomy), sex (with a significant survival benefit for females), and pathologically confirmed complete tumor resection (R0 resection).[195–197] Here, the exact definition of R0 resection could be substantially complemented with negative results of assays for postoperative detection of circulating tumor cells or DNA in the near future.[198] Importantly, in case of nodal upstaging (N1 or N2) or incomplete surgical resection (i.e., R1), adjuvant chemotherapy should be complemented with thoracic radiotherapy.[199,200] In this setting, postoperative thoracic radiotherapy significantly decreases the 1-year, 2-year, and 3-year local recurrence rates in patients with nodal involvement (i.e., N1 and N2).[199] Postoperative prophylactic cranial irradiation (PCI) has been shown to significantly reduce the risk of brain metastasis and prolong OS in patients who undergo surgery for SCLC.[201,202] However, the overall risk for developing brain metastases in surgically resected patients who have early stage disease (especially stage I) is generally very low; therefore, active MRI surveillance might be equally effective.[203,204]

Altogether, the role of surgery in SCLC is still debatable.[200,205] Yet, after adequate staging, some patients with localized, very limited stage disease might indeed benefit from surgical removal of the primary tumor.[205,206] Accordingly, based on the contemporary NCCN guidelines, surgery should be applied to all individuals with clinical stage I–IIA (T1–T2N0M0) SCLC, and lobectomy supplemented with lymphadenectomy should always be followed by postoperative systemic therapy (Figure 6).[184]

Chemotherapy and radiotherapy

Systemic chemotherapy represents the backbone of therapeutic management across all stages of SCLC, and numerous cytostatic regimens have demonstrated activity in both upfront and subsequent lines of systemic therapy (Figure 6). Indeed, combinatory treatments of platinum-based, DNA-crosslinking agents (such as cisplatin or carboplatin) and topoisomerase inhibitors (such as etoposide or irinotecan) are currently the chemotherapeutic regimens of choice in patients with SCLC.[184,207,208] This combination is efficacious, and its application has been widely tested and is safe alone or in combination either with other systemic agents (e.g., immunotherapy) or treatment modalities (e.g., radiotherapy or surgery). However, given the heterogenous toxicity profile of these cytostatic agents, treatment should be personalized according to the general condition, comorbidity profile, and personal preferences of each patient. Cisplatin is more nephrotoxic and emetogenic but less myelotoxic than carboplatin.[209–211] Carboplatin-containing regimens are preferred in patients who are unfit for cisplatin-based chemotherapy (e.g., in elderly patients.[209]

The number of cycles differs according to disease stage. Generally, four cycles of cisplatin/carboplatin and etoposide are recommended for patients with limited stage SCLC, including those who underwent lung resection surgery (Figure 6).[184] Meanwhile, individuals with extensive-stage disease may receive up to six cycles of chemotherapy based on response and tolerability after four cycles (Figure 6).[184]

In addition to systemic chemotherapy, conformal radiotherapy also plays a pivotal role in the therapeutic management (Figure 6) of patients with SCLC as part of either definitive or palliative therapy.[184,212] Specifically, concurrent or sequential radiochemotherapy is part of the standard of care for patients with limited stage disease (up to N3, M0), whereas radiotherapy in those with extensive-stage SCLC mainly consists of consolidative thoracic radiation therapy or PCI after first-line treatment.[184] In addition, surgically treated patients with regional nodal involvement are also advised to undergo radiotherapy, either sequentially or concurrently with chemotherapy, as stated previously.[184]

Indeed, several studies suggest that chemotherapy supplemented with radiotherapy prolongs both OS and disease-free survival of patients with SCLC.[213,214] The manner of radiotherapy administration (i.e., sequential or concurrent, twice daily, or once daily) in limited stage disease should be individually adapted to clinicopathologic factors or practical reasons.[215–217] When feasible, patients with limited stage SCLC should be treated with concurrent chemoradiotherapy, and sequential treatment should be limited to patients with large tumor volumes or poor PS.[218] With regard to scheduling, neither the toxicity profiles nor the survival outcomes differ significantly between twice-daily and once-daily radiotherapy.[217] Therefore, given the shorter treatment time, twice-daily radiotherapy concurrently with chemotherapy might represent a more appealing approach.[217,219] However, the thumb rule is that radiation should be initiated as early as possible, and patients should be endorsed to quit smoking to further improve the prognosis and therapeutic efficacy.[220,221] Also, platinum-containing agents and etoposide in combination with radiotherapy should be preferred over other regimens because of clear superiority in efficacy and toxicity.[207,222,223] Regarding the role of PCI in patients who have limited stage disease treated only with systemic therapy, previous studies suggest that PCI reduces the risk of developing brain metastases in those who have good responses to initial therapy.[184,224,225] Notably, however, those past studies did not use active brain MRI follow-up in the control group. Consequently, the beneficial effects of PCI compared with active MRI surveillance alone warrants further investigation in this patient population.[226] Furthermore, if applied, the risk of treatment-related side effects and chronic neurologic sequelae, such as memory decline, should be minimized. Of note, modern PCI with hippocampal avoidance is similarly efficacious but can significantly reduce radiation-related cognitive or neurologic side effects.[227] Likewise, subsequent administration of neuroprotective drugs, such as memantine or donepezil,

might be beneficial. The use of these neuroprotectants was associated with fewer declines and modest improvements in cognitive functions in two randomized phase 3 trials, although the results were not statistically significant.[228,229]

In addition to its use in limited stage SCLC, radiotherapy can also be administered as part of consolidation therapy for residual tumor eradication in extensive-stage disease (Figure 6).[230] It should be noted, however, that radiotherapy in this patient population primarily offers delayed survival benefits: a large, phase 3, randomized controlled trial demonstrated that thoracic radiotherapy after chemotherapy did not significantly improve the survival outcomes at 1 year in patients with extensive-stage disease.[231] However, in that study, the 2-year OS was significantly improved, and PFS was also significantly greater in the thoracic radiotherapy group. In addition, the authors of that study reported an almost 50% reduction in intrathoracic recurrences.[231] Moreover, based on subsequent exploratory analyses, they concluded that the beneficial effects of consolidative radiotherapy are more evident in those with residual intrathoracic lesions after systemic therapy.[232] In light of this and other studies,[233,234] consolidative radiotherapy might be beneficial for selected patients with good clinical responses to systemic chemotherapy or chemoimmunotherapy, especially in those with low-bulk extrathoracic metastases and residual thoracic disease.[212,235]

Patients with extensive-stage SCLC who respond to initial chemotherapy and have a PS of 0–1 are often offered PCI.[224,236–238] Of note, the evidence supporting PCI is not as clear in elderly patients with a PS >2 and in those with preexisting neurologic conditions.[239] In addition, PCI warrants further validation in patients who have extensive-stage SCLC in the era of modern imaging. In this regard, a recent Japanese randomized trial showed that PCI is not associated with a clear survival benefit compared with strict MRI follow-up in patients who have extensive-stage SCLC.[240]

In light of the controversies on the role of surgery in SCLC, some studies suggest that concomitant thoracic radiochemotherapy is superior to surgical resection in patients who have limited stage, nonmetastatic (N0, M0) disease.[241] Therefore, stereotactic ablative radiotherapy is an appealing treatment approach for patients with limited stage disease in whom a decision was made not to pursue surgery and for those with a medically inoperable tumor. To date, the first reports concerning local tumor control and OS after stereotactic ablative radiotherapy in SCLC are promising.[242]

Immunotherapy

After decades without meaningful changes in the standard of care, 2019 produced a new landmark in the treatment of SCLC through US Food and Drug Administration (FDA) approval of the PD-L1 inhibitor atezolizumab in combination with first-line platinum doublet chemotherapy for patients with extensive-stage disease.[19,87,184] This approval was foreshadowed by the results of the IMpower133 randomized, phase 3 trial, in which the addition of atezolizumab (Figure 7) to first-line treatment resulted in a significant improvement of 0.9 and 2 months concerning the median PFS and OS, respectively.[19] In addition, both 1-year and 1.5-year survival rates were higher in patients who received atezolizumab compared with the placebo group.[243] The phase 3 CASPIAN study (ClinicalTrials.gov identifier NCT03043872) yielded results comparable to those observed in IMpower133, using a different PD-L1 inhibitor.[20] Here, in the planned interim analysis, durvalumab (Figure 7) in combination with chemotherapy significantly improved the median OS by

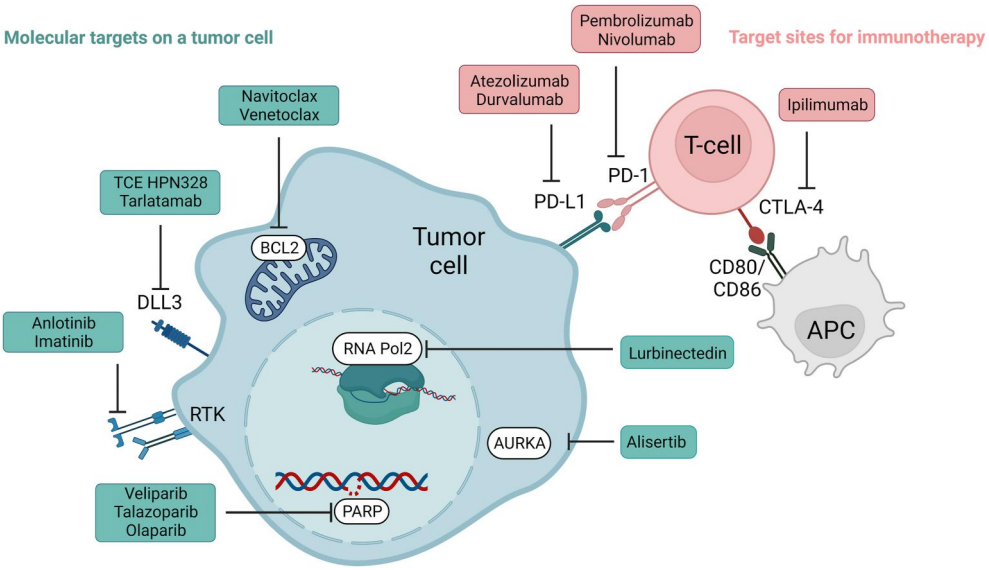

FIGURE 7 Areas of current therapeutic interest in SCLC. Schematic depiction of important molecular targets on a tumor cell (cyan), target sites for immunotherapy (orange), and the respective drugs. APC indicates antigen-presenting cell; RTK, receptor tyrosine kinase; SCLC, small cell lung cancer; TCE, T-cell engager. Created with BioRender.com.

2.7 months compared with the chemotherapy-alone group.[20,244] The FDA approved the use of durvalumab for extensive-stage SCLC in the first-line setting shortly thereafter.[245] Of note, the approximately 2-month extension of median survival seen in these studies may seem modest, yet median values do not tell the full story. Taking a glance at the tail of the survival curves, it becomes evident that the addition of immune checkpoint inhibitors to the platinum-based backbone leads to an approximate tripling of 3-year survival.[4,246] Currently, the NCCN SCLC panel recommends platinum-based chemotherapy plus etoposide plus atezolizumab or durvalumab as the preferred first-line systemic therapy option, followed by maintenance atezolizumab or durvalumab for patients with extensive-stage SCLC (Figure 6) based on the aforementioned clinical trials and FDA approval.[184] In contrast to chemotherapy alone, administration of PD-L1 inhibitors within the framework of chemoimmunotherapy is not terminated after four to six cycles, and maintenance immunotherapy is continued until progression.[184] This raises questions about the applicability of radiotherapy in this setting because the effects of both consolidative thoracic radiotherapy and PCI were primarily interpreted in chemotherapy-treated patients after termination of systemic therapy.[230] Current practice guidelines support the idea that consolidative thoracic radiotherapy can be applied both before and during maintenance immunotherapy.[184] There are no solid, evidence-based data on optimal sequencing or safety to date.[184] Recent studies, however, suggest that the combination of thoracic radiotherapy and immunotherapy exhibits a synergistic effect by upregulating major histocompatibility complex class I expression and promoting CD8-positive T-cell infiltration.[247] Further data on the benefit of thoracic radiotherapy in the context of chemoimmunotherapy will be delivered by the RAPTOR/NRG LU007 trial (ClinicalTrials.gov identifier NCT04402788).[248] To date, the benefit of PCI in patients with active tumor control achieved by immunotherapy maintenance is unclear.[230] For patients with limited stage disease, consolidative pembrolizumab had favorable tolerability and activity in a recent phase 1/2 trial.[249] Nevertheless, in the randomized phase 2 STIMULI trial (ClinicalTrials.gov identifier NCT02046733), consolidation combination immunotherapy did not improve PFS.[250] Given these mixed data, to date, immune checkpoint inhibitors are not part of the standard of care for limited stage SCLC. Ongoing clinical trials, such as the phase 3 ADRIATIC study (ClinicalTrials.gov identifierNCT03703297), will help to define the role of immunotherapy in this patient population.

Mechanisms of drug resistance and relapsed SCLC

In contrast to NSCLC, which has an intrinsic tendency for chemotherapy resistance, approximately 75%–80% of all untreated SCLCs are initially highly sensitive to DNA-damaging agents, with clinical response rates nearly double those observed in NSCLC.[7] However, the development of resistance is essentially inevitable, and response rates to second-line therapy are markedly reduced.[251] The EMT as well as the downregulation of Schlafen11 (*SLFN11*) expression by methylation has been historically implicated in the resistance to treatment for SCLC.[2,252,253] In addition, the occurrence of drug resistance might also be linked to DNA-related processes, such as promoting cellular DNA damage repair and preventing antitumor drugs from interacting with DNA.[254] One other mechanism might be that the various molecular and cellular fates adopted by SCLC provide reservoirs of cells with intrinsic resistance to treatment.[4] Regarding transcription factors, although YAP1 is not expressed to a sufficient extent in treatment-naive patients to define a distinct subtype, its elevated level is linked with platinum resistance. Accordingly, an intratumoral shift toward increased YAP1 expression may underlie platinum resistance.[81,89,97,255] Finally, suppression of apoptosis by *BCL2* expression and *TP53* mutations may also result in chemoresistance.[2]

Subsequent systemic therapy in SCLC (Figure 6) depends on the administered therapeutic agent in the first-line setting as well as the disease-free interval since termination of the initial therapy.[184] According to the contemporary NCCN guidelines, rechallenging with the original regimen or a similar platinum-based regimen is recommended if more than 6 months have elapsed (sensitive disease) from initial therapy to relapse and may be considered if there has been a disease-free interval of at least 3–6 months (refractory or resistant disease).[184] It should be noted that the European Society for Medical Oncology guidelines use cutoffs of ≥3 and <3 months to define sensitive and resistant SCLC, respectively.[256] If rechallenging is not feasible, the topoisomerase 1 inhibitor topotecan represents a therapeutic agent of choice as second-line therapy.[184] Topotecan can be administered orally or intravenously because its antitumor activity and tolerability are similar with either route.[257] Nevertheless, because oral topotecan offers a useful and compassionate treatment alternative for patients, many practicing oncologists prefer this option. Oral topotecan at 2.3 mg/m^2 or intravenous topotecan at 1.5 mg/m^2 (as a 30-minute infusion) should be administered on a daily basis for 5 days every 3 weeks.[257] Notably, in addition to yielding survival benefits similar to those obtained with the combination regimen of cyclophosphamide, doxorubicin, and vincristine, intravenous topotecan causes less grade 4 neutropenia and improves the symptoms of dyspnea, fatigue, hoarseness, and anorexia.[258] In certain circumstances (e.g., bone marrow deficiency), irinotecan can also be used as an alternative to topotecan in relapsed disease because of its less frequent dosing (i.e., weekly) and lower occurrence rates of myelosuppressive adverse events.[259,260] Recently, lurbinectedin, a synthetic derivative of the marine drug trabectedin (Figure 7) (a DNA-binding, alkylating agent that selectively inhibits RNA polymerase II transcription), also demonstrated activity against SCLC both as a single agent and in combination with doxorubicin.[261] This led to its accelerated FDA approval as second-line therapy after progression on platinum-based chemotherapy. Of note, in the subsequent phase 3 randomized ATLANTIS study (ClinicalTrials.gov identifier NCT02566993), lurbinectedin plus doxorubicin did not improve OS in patients who had relapsed SCLC compared with those in the control group.[262] Immune checkpoint inhibitors have also been evaluated in patients with relapsed SCLC. At first, the anti-PD1

monoclonal antibodies nivolumab and pembrolizumab were granted accelerated FDA approval for patients whose disease has progressed after platinum-based chemotherapy and at least one other prior line of systemic therapy. This was based on the encouraging response rates and durations of response seen in the CheckMate 032 (ClinicalTrials.gov identifier NCT01928394), KEYNOTE-158 (cohort G; ClinicalTrials.gov identifier NCT01928394), and KEYNOTE-028 (cohort C1; ClinicalTrials.gov identifier NCT02054806) trials.[263,264] However, subsequent confirmatory trials (CheckMate 451 [ClinicalTrials.gov identifier NCT02538666], CheckMate 331 [ClinicalTrials.gov identifier NCT02481830], and KEYNOTE-604 [ClinicalTrials.gov identifier NCT03066778]) in different treatment settings did not meet their primary end point.[265–267] Despite having manageable toxicity profiles and prolonging PFS, nivolumab and pembrolizumab failed to demonstrate a clear OS benefit. Because of the frail results from these later studies, the FDA and the manufacturers withdrew their indication of nivolumab and pembrolizumab for treating patients with SCLC.[268,269] Accordingly, to date, contemporary practice guidelines recommend neither of these immune checkpoint inhibitors in relapsed SCLC. Nevertheless, in some cases, their off-label and experimental use within the confines of a clinical trial can still be considered based on individualized considerations when no immunotherapeutics have been administered in previous lines. Radiotherapy, clinical trial enrollment, and other chemotherapeutic regimens (Figure 6) might also represent possible therapeutic approaches for refractory SCLC.

Predictive biomarkers and immune landscape

Cell line screening for biomarker candidates revealed that SLFN11 expression is strongly associated with sensitivity to a broad spectrum of DNA-damaging agents and inhibitors and thus might represent a promising predictor of sensitivity to chemotherapy.[7] Although this association has since been confirmed in various preclinical models, and high SLFN11 IHC expression was indeed associated with increased survival outcomes in patients treated with temozolomide plus veliparib (PARP-inhibitor) even in a phase 1 clinical trial, its use as a predictive biomarker is still not validated in the clinics.[270–272]

Both high TMB and microsatellite instability have shown promise as biomarkers of response to immune checkpoint blockage across cancer types.[273] In SCLC, however, because tumors are almost always associated with the chemical mutagenic effects of tobacco exposure and thus generally have a high clonal mutational load, establishing a clear predictive cutoff might be difficult.[87] Reflecting on this, the role of TMB as a predictive biomarker of SCLC response to immunotherapy is controversial. In the CheckMate 032 study, tumors in the highest tertile of TMB were more sensitive to nivolumab or to the combination of ipilimumab and nivolumab, as defined by the survival outcomes.[274] Yet subsequent analyses of the IMpower133 trial showed no evident association between blood-based TMB and responsiveness to atezolizumab.[243] Another potential biomarker of responsiveness to immune checkpoint blockage might be PD-L1 IHC expression, which is an approved biomarker in other solid tumors. Nevertheless, PD-L1 is scarcely expressed in SCLC, and its predictive value is rather contentious.[275] Neither the subsequent results of the CheckMate 032 study nor the outcomes of the exploratory analyses of the IMpower133 trial demonstrated a PD-L1–dependent treatment benefit in patients treated with nivolumab or atezolizumab, respectively.[243,263] In contrast, the combined PD-L1 expression on tumor and immune stromal cells might constitute a positive predictive biomarker in patients with SCLC who receive pembrolizumab.[87] Recently, the different SCLC molecular subtypes were also linked with distinct sensitivity profiles to immunotherapy. As discussed above, NE-low SCLCs, and specifically SCLC-I tumors, have a higher abundance of cytotoxic T cells, natural killer cells, and macrophages and higher expression of checkpoint molecules compared with NE-high SCLCs.[85,97] Indeed, the results of the IMpower133 trial support the idea that the addition of atezolizumab to standard-of-care chemotherapy is more beneficial in SCLC-I than in SCLC-A and SCLC-N.[19,97]

Insights into potential targeted therapy

Several targeted agents are being tested for the treatment of SCLC (Figure 7). Compared with other lung cancer subtypes and normal lung epithelial cells, SCLC cells show a high PARP expression profile and thus are sensitive to PARP inhibitors.[30,276] Moreover, PARP inhibitors have the potential to enhance the cytotoxic response to chemotherapy, immunotherapy, and ionizing radiation in SCLC.[276,277] The phase 2 Eastern Cooperative Oncology Group-American College of Radiology Imaging Network Cancer Research Group 2511 trial (ClinicalTrials.gov identifier NCT01642251) partly confirmed these preclinical suspicions by demonstrating a 1.4-month OS benefit in patients who received veliparib in combination with a cisplatin and etoposide doublet.[278] Nevertheless, because the results did not reach statistical significance, predictive biomarkers are required to maximize the clinical efficacy of PARP inhibitors. Here, an appealing biomarker might be the already mentioned SLFN11, which is strongly associated with veliparib efficacy.[272] Another valid concern regarding PARP inhibitors is their more-than-additive toxicity profile when administered together with cytotoxic chemotherapy. Indeed, early phase clinical trials revealed a higher frequency of hematologic toxicities in veliparib-treated patients.[278,279] Importantly, however, these adverse events were all clinically manageable and did not affect the delivery of standard chemotherapy.

DLL3, an inhibitory Notch pathway ligand, might also represent a potential therapeutic target in SCLC because it is frequently expressed on the surface of SCLC tumor cells.[280] After encouraging results from the first human phase 1 study,[281] the targeted agent rovalpituzumab tesirine (Rova-T) only produced modest antitumor activity in the subsequent phase 2 TRINITY study (ClinicalTrials.gov identifier NCT02674568).[282] Specifically, the objective response rates were 14.3% and 13.2% in DLL3-high and DLL3-positive patients, respectively.[282] Unfortunately, patients who received

treatment with Rova-T exhibited inferior OS and higher rates of toxicities in a recent phase 3 clinical trial compared with those who received the current standard second-line chemotherapy.[283] Because of this lack of survival benefit, the phase 3 TAHOE trial (ClincalTrials.gov identifier NCT03061812) was halted after the Independent Data Monitoring Committee recommended stopping enrollment.[280]

Given the elevated expression of BCL-2 in certain SCLC tumors, BCL-2 antagonists may constitute an attractive therapeutic option for treating these patients. Certainly, the recent addition of these prosurvival BCL-2 family inhibitors to the repertoire of targeted therapies revealed remarkable preclinical activity in SCLC tumors.[284] However, BCL-2 targeting by navitoclax showed only limited single-agent activity against advanced and recurrent SCLC in a phase 2 trial, because a partial response and stable disease were achieved in only one patient (2.6%) and eight patients (23%), respectively.[285] Importantly, there was dose-limiting thrombocytopenia in the study, which reached grade 3–4 in 41% of patients.[285] This may be caused in part by the nonselective nature of navitoclax because it targets both BCL-2 and BCL-xL, which leads to considerable toxicities. Venetoclax (an FDA-approved drug for hematologic malignancies), conversely, is a selective BCL-2 inhibitor that is well tolerated even in elderly patients with severe hematologic disease.[284] Moreover, the observation that venetoclax induces tumor regressions in mice bearing high BCL-2-expressing SCLC tumors also provides a strong rationale for assessing its clinical efficacy in a biomarker-selected SCLC population.[286]

Targeted drug screening revealed that SCLC with high MYC expression is vulnerable to AURK inhibition, which, combined with chemotherapy, strongly suppresses proliferation and tumor growth in vitro and in vivo.[287] A recently reported clinical trial demonstrated that the AURKA inhibitor alisertib plus paclitaxel produced improved PFS and OS compared with paclitaxel alone in patients with relapsed or refractory SCLC.[288] Although these survival benefits were not statistically significant, c-Myc expression proved to be a reliable predictor of responsiveness to alisertib.[288] Accordingly, patients with c-Myc-expressing tumors had significantly improved PFS in the alisertib/paclitaxel arm.[288] Finally, several preclinical studies have demonstrated that inhibitors against c-Kit receptor, EGFR, insulin-like growth factor receptor, and c-MET receptor tyrosine kinases might also be efficacious in SCLC. However, subsequent clinical trials to date have failed to demonstrate the superiority of these agents against the current standard of care.

SURVEILLANCE AND FOLLOW-UP

Given the high relapse rates in SCLC, regular CT scans (chest scans with or without abdominal/pelvic scans) are recommended to identify recurrence as early as possible and to offer salvage treatment if appropriate. The frequency of surveillance depends on the disease stage and elapsed time since the completion of initial or subsequent therapy.[184] Generally, follow-up visits are required every 2 to 3 months in the first 2 years and less frequently thereafter. Patients with extensive metastatic disease can be checked even more regularly. To allow the early treatment of potentially debilitating neurologic symptoms caused by brain metastases, it is important to scan for cranial lesions. Currently, brain MRI is the diagnostic approach of choice for the detection of cerebral metastases and should be performed regardless of the PCI status.[184] In certain cases, brain MRI can be substituted with a contrast-enhanced brain CT. The contemporary NCCN guidelines do not recommend PET-CT for routine follow-up.[184]

Another particularity of SCLC is that patients who survive >2 years after initial diagnosis have a significantly increased risk of developing a second primary tumor, including lung cancer.[289–291] Specifically, the relative risk of a second primary lung cancer in patients who have SCLC is 16.0 (95% CI, 8.4-27.0) compared with that in the general population.[291] This further emphasizes the role of smoking cessation (see the contemporary smoking cessation guideline in the report by Shields et al.[292]) because quitting smoking after successful therapy significantly decreases the risk of secondary malignancies.[289,291] Nevertheless, if a new pulmonary nodule develops after a longer period of stable disease, it should prompt evaluation for new primary lung cancer. However, most screening guidelines state that asymptomatic cancer survivors with a high risk of developing a second malignancy should be screened at the same intervals as the general population unless they have another independent risk factor.[290,293]

Finally, the management of long-term, treatment-related adverse effects, such as pulmonary fibrosis, cardiac complications, or polyneuropathy, also requires regular consulting.

ONGOING CLINICAL TRIALS

In addition to the extensive clinical studies of PD-(L)1 inhibition, other therapeutic approaches, such as targeting the T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibitory domains (TIGIT) are currently under investigation in patients with SCLC (Table 1). TIGIT is frequently co-expressed with PD-L1 on T cells or natural killer cells, likewise acting as a crucial modulator in T-cell–mediated immunity.[294] The corresponding randomized phase 3 clinical trial SKYSCRAPER-02 (ClinicalTrials.gov identifier NCT04256421) compared standard-of-care carboplatin/etoposide plus atezolizumab in addition to placebo or tiragolumab (anti-TIGIT inhibitor) in patients who had treatment-naive SCLC. Unfortunately, the preliminary data on tiragolumab in combination with chemoimmunotherapy, recently reported at the 2022 American Society of Clinical Oncology Annual Meeting, did not reveal clinical benefit.[295] Nevertheless, the combination was well tolerated, and no new safety signals were identified.[295]

Within the past years, research groups have focused on the efficacy of various targeted agents interfering with cell cycle, apoptosis, DNA-damage repair, epigenetic modifications, or angiogenesis. Currently, several phase 1/2 clinical trials elucidate the safety profile of PARP inhibitors other than veliparib, such as olaparib, rucaparib,

TABLE 1 Completed and ongoing clinical trials evaluating the safety and efficacy of immune checkpoint inhibitors in patients with small cell lung cancer.

Study name	Study phase	Mechanism of action	Agent	Outcomes
IMpower133 (NCT02763579)	1/3	PD-L1 inhibitor	Atezolizumab	Safety, well tolerated
				ORR, 60.2% vs. 64.4%
				PFS, 5.2 vs. 4.3 months (p = .02)
				OS, 12.3 vs. 10.3 months (p = .007)
CASPIAN (NCT03043872)	3	PD-L1 inhibitor	Durvalumab	Safety, well tolerated
				ORR, 79% vs. 70%
				PFS, 5.1 vs. 5.4 months (p = NS)
				OS, 13.0 vs. 10.3 months (p = .004)
KEYNOTE-604 (NCT03066778)	3	PD-1 inhibitor	Pembrolizumab	Safety, well tolerated
				ORR, 70.6% vs. 61.8%
				12-month PFS, 13.6% vs. 3.1% (p = .0023)
				24-month OS, 22.5% vs. 11.2% (p = .0164)
NCT01450761	3	CTLA-4 inhibitor	Ipilimumab	Safety, well tolerated
				ORR, 62% vs. 62%
				PFS, 4.6 vs. 4.4 months (p = .016)
				OS, 11.0 vs. 10.9 months (p = .377)
CheckMate 331 (NCT02481830)	3	PD-1 inhibitor	Nivolumab	Safety, well tolerated
				ORR, 14% vs. 16%
				PFS, 1.4 vs. 3.8 months
				OS, 7.5 vs. 8.4 months
CheckMate 451 (NCT02538666)	3	PD-1 and CTLA-4 inhibitors	Nivolumab plus ipilimumab	Primary end points not met
SKYSCRAPER-02 (NCT04256421)	3	TIGIT	Tiragolumab	Primary end points not met
ADRIATIC (NCT03703297)	3	PD-L1 and CTLA-4 inhibitors	Durvalumab plus tremelimumab	Ongoing
REACTION	2	PD-1 inhibitor	Pembrolizumab	Safety, well tolerated
				ORR, 61%
				PFS, 4.7 vs. 5.4 months
				OS, 12.3 vs. 10.4 months
NCT02359019	2	PD-1 inhibitor	Pembrolizumab	Safety, well tolerated
				ORR, 11.1%
				PFS, 1.4 months
				OS, 9.6 months
KEYNOTE-158 (NCT02628067)	2	PD-1 inhibitor	Pembrolizumab	Safety, well tolerated
				ORR, 18.7%
				PFS, 2.0 months
				OS, 9.1 months
BIOLUMA (NCT03083691)[a]	2	PD-1 and CTLA-4 inhibitors	Nivolumab plus ipilimumab	Safety, high toxicity rates
				ORR, 38.8%

(Continues)

TABLE 1 (Continued)

Study name	Study phase	Mechanism of action	Agent	Outcomes
CheckMate 032 (NCT01928394)	1/2	PD-1 and CTLA-4 inhibitors	Nivolumab plus ipilimumab/ nivolumab	Safety, manageable safety profile ORR, 21.9% vs. 11.6% PFS, 1.5 vs. 1.4 months OS, 4.7 vs. 5.7 months
NCT02261220	1/2	PD-L1 and CTLA-4 inhibitors	Durvalumab plus tremelimumab	Safety, well tolerated ORR, 13.3% PFS, 1.8 months OS, 7.9 months
KEYNOTE-028 (NCT02054806)	1b	PD-1 inhibitor	Pembrolizumab	Safety, well tolerated ORR, 33.3% PFS, 1.9 months OS, 9.7 months

Abbreviations: CTLA-4, cytotoxic T-lymphocyte–associated protein 4; NCT, ClinicalTrials.gov identifier; NS, not significant; ORR, objective response rate; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PFS, progression-free survival; TIGIT, T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibitory domains.

[a]Only patients with high tumor mutation burden were included.

or talazoparib (Table 2).[296] Interim analysis concerning the efficacy of rucaparib plus nivolumab in a frontline setting showed clinical benefit in 56% of patients and a median PFS of 7.4 months from the time of diagnosis. Notably, the patient with the longest active treatment was approaching 16 months of therapy at the time of reporting.[297]

As mentioned above, Rova-T produced a survival benefit neither in the phase 2 TRINITY trial nor in the phase 3 TAHOE trial. Nevertheless, DLL3 remains an intriguing target for multiple alternative therapeutic strategies, including bispecific and trispecific T-cell engagers (TCEs), and chimeric antigen receptor (CAR) T-cell therapy. Bi-specific TCEs bind to DLL3 and cells of the immune system (such as CD3-positive T cells) simultaneously, thus leading to T-cell–mediated tumor lysis.[298] Meanwhile, trispecific agents are designed to also bind to albumin for half-life extension.[299] In this context, two independent phase 1 studies and a phase 1/2 clinical trial are currently investigating the safety, tolerability, and preliminary efficacy of DLL3 targeting in SCLC (Table 2).[298–300] Encouragingly, preliminary data on the bispecific, DLL3-targeted TCE tarlatamab (AMG 757) revealed a manageable safety profile and a median duration of response of 12.3 months among confirmed responders in heavily pretreated patients with SCLC.[298] Likewise, HPN328, a trispecific DLL3-targeting TCE, also proved to be well tolerated and clinically active in patients with SCLC and other NE cancers.[299] With regard to CAR T-cell therapy, AMG 119 is an adoptive cellular therapy targeting DLL3 and redirecting cytotoxic T-cell specificity to DLL3-positive cells. In addition to inhibiting tumor growth in SCLC xenograft models, AMG 119 was recently associated with a manageable safety profile and promising antitumor activity in a phase 1 study (Table 2).[301]

Another approach is cell cycle checkpoint inhibition, including AURK or CDK4/DCK6 targeting. Currently, two ongoing phase 2 and 3 clinical trials focus on the efficacy and safety profiles of AZD2811 (AURKB inhibitor) or trilaciclib (CDK4/6 inhibitor) in patients with advanced SCLC (Table 2). To date, the first-in-class agent trilaciclib is solely administered to reduce chemotherapy-induced bone marrow suppression in patients with SCLC because it maintains hematopoietic stem cells and progenitor cells in G1 arrest and protects them from the damaging effects of chemotherapy.[302] Indeed, the addition of trilaciclib to standard-of-care chemotherapy resulted in increased tolerability of cytotoxic agents in a recent phase 2 trial, as demonstrated by myelopreservation across multiple hematopoietic lineages.[302] In early 2021, this was shortly followed by the FDA approval of rilaciclib as a myeloprotective agent in patients who had SCLC treated with EP-containing or topotecan-containing regimens.

It is to be highlighted that SCLC has been historically associated with increased vascularization, which furthermore correlates with prognosis. Although the first phase 2 trial (SALUTE; ClinicalTrials.gov identifier NCT00403403) investigating the efficacy of bevacizumab in previously untreated patients with extensive-stage SCLC did not result in an improvement in OS,[303] it is hypothesized that the addition of bevacizumab to the chemoimmunotherapy backbone might improve the efficacy of immune checkpoint inhibitors. The ongoing CeLEBrATE trial (ClinicalTrials.gov identifier NCT04730999) is an open-label, multicenter, phase 2 study designed to assess the efficacy and safety of the combination of carboplatin/etoposide/atezolizumab plus bevacizumab in patients with treatment-naive SCLC.[304] Similarly, antiangiogenic agents, such as anlotinib, apatinib, or cediranib,

TABLE 2 Completed and ongoing clinical trials evaluating the safety and efficacy of targeted therapies in patients with small cell lung cancer.

Study name	Study phase	Mechanism of action	Agent	Outcomes
DNA damage repair				
NCT02454972	2	RNA-polymerase II inhibitor	Lurbinectedin	ORR, 35.2%
				PFS, 3.5 months
				OS, 9.3 months
NCT01638546	2	PARP inhibitor	Veliparib	ORR, 39% vs. 14% ($p = .016$)
				PFS, 3.8 vs. 2.0 months ($p = .39$)
				OS, 8.2 vs. 7.0 months ($p = .50$)
ECOG-ACRIN 2511 (NCT01642251)	2	PARP inhibitor	Veliparib	ORR, 71.9% vs. 65.6% ($p = .57$)
				PFS, 6.1 vs. 5.5 months ($p = .06$)
				OS, 10.3 vs. 8.9 months ($p = .17$)
NCT02289690	1/2	PARP inhibitor	Veliparib	Safety, well tolerated
NCT01286987	1	PARP inhibitor	Talazoparib	Safety, well tolerated
NCT04334941	2	PARP inhibitor	Talazoparib	Ongoing
NCT03672773	2	PARP inhibitor	Talazoparib	Ongoing
NCT03958045	2	PARP inhibitor	Rucaparib	Recruiting
NCT04728230	1/2	PARP inhibitor	Olaparib	Recruiting
NCT03923270	1	PARP inhibitor	Olaparib	Recruiting
Neuroendocrine differentiation				
TAHOE (NCT03061812)	3	DLL3-targeted antibody-drug conjugate	Rova-T	Primary end points not met
TRINITY (NCT02674568)	2	DLL3-targeted antibody-drug conjugate	Rova-T	Primary end points not met
NCT04471727	1/2	DLL3/CD3 trispecific T-cell engager	HPN328	Well tolerated
				Clinically active
NCT03319940	1	DLL3/CD3 bispecific T-cell engager	Tarlatamab (AMG 757)	Manageable safety profile
				ORR, 24.0%
				Median duration of response, 12.3 months[a]
NCT04429087	I	DLL3/CD3 bispecific T-cell engager	BI 764532	Ongoing
NCT03392064	I	DLL3/chimeric antigen receptor T-cell (CAR-T) therapy	AMG 119	Well tolerated
				Promising antitumor activity
Angiogenesis				
ALTER1202 (NCT03059797)	2	Tyrosine kinase inhibitor	Anlotinib	PFS, 4.1 vs. 0.7 months ($p < .0001$)
				OS, 7.3 vs. 4.9 months ($p = .029$)
NCT00154388	2	Tyrosine kinase inhibitor	Imatinib	Primary end points not met
SALUTE (NCT00403403)	2	VEGF inhibitor	Bevacizumab	ORR, 58% vs. 48%
				PFS, 5.5 vs. 4.4 months
				OS, 9.4 vs. 10.9 months
CeLEBrATE (NCT04730999)	2	VEGF inhibitor	Bevacizumab	Ongoing

(Continues)

TABLE 2 (Continued)

Study name	Study phase	Mechanism of action	Agent	Outcomes
NCT01533181	2	IGF-R1 inhibitor	Linsitinib	Primary end points not met
NCT00869752	1	IGF-R1 inhibitor	Dalotuzumab	Safety, well tolerated
Cell cycle checkpoints				
NCT02038647	2	AURKA inhibitor	Alisertib	ORR, 22% vs. 18% ($p = .406$)
				PFS, 3.32 vs. 2.17 months ($p = .113$)
				OS, 6.86 vs. 5.58 months ($p = .714$)
TAZMAN (NCT04745689)	2	AURKB inhibitor	AZD2811	Ongoing
NCT04902885	3	CDK4/CDK6	Trilaciclib	Recruiting
Apoptosis				
NCT03366103	1/2	BCL-2/mTOR inhibitor	Navitoclax/ vistusertib	Terminated
NCT00521144	1/2	BCL-2, BCL-XL, and MCL1 inhibitor	Obatoclax mesylate	Primary end points not met
NCT00042978	2	BCL-2 antisense oligonucleotide	Oblimersen sodium	Primary end points not met

Abbreviations: AURKA, aurora kinase A; DLL3, delta-like protein 3; ECOG-ACRIN, Eastern Cooperative Oncology Group-American College of Radiology Imaging Network Cancer Research Group; IGF-R1, insulin-like growth factor 1 receptor; NCT, ClinicalTrials.gov identifier; ORR, objective response rate; OS, overall survival; PARP, poly(ADP-ribose) polymerase; PFS, progression-free survival; Rova-T, rovalpituzumab tersirine; VEGF, vascular endothelial growth factor.

[a]Among responders.

are also under investigation as potential frontline or maintenance treatment options for patients with advanced SCLC.[305]

Actively recruiting clinical trials sponsored by the National Institutes of Health are summarized in Table 3.

FUTURE DIRECTIONS: SUBTYPE-SPECIFIC DIAGNOSTIC AND THERAPEUTIC APPROACHES

The implementation of targeted therapies to date has failed in SCLC, and the success of immunotherapy in NSCLC has not yet been entirely reflected in this malignancy. This lack of a breakthrough in the therapeutic armamentarium of SCLC is mainly because of its high tumoral plasticity and the nonselected patient groups upon clinical trial enrollment. Accordingly, stratifying patients by their dominant molecular subtypes and specific protein-level alterations may contribute to the development of novel targeted strategies in this hard-to-treat disease.

Because surgery is seldom performed in SCLC and small biopsies often fail to mirror the expression profile of the entire tumor, the diagnosis of molecular states might be a challenging notion, especially in clinical settings. The analysis of blood-based tumor components, such as circulating tumor cells, cell-free tumor DNA, and tumor-derived extracellular vesicles, could provide alternative opportunities to monitor the molecular phenotypes throughout the disease and to assess biomarkers of treatment response and prognosis.[87] Recently, two independent, cell-free tumor DNA-based classifiers were reported to be able to distinguish between SCLC subtypes based on methylation profiling.[306,307] Importantly, despite the different teaching and training approaches, both were able to correctly identify SCLC subtypes with an accuracy of >90%. Because certain tumor-associated proteins are of diagnostic importance, in-depth proteomic profiling might also offer new insights into subtype-specific biomarkers. In total, 367 subtype-specific proteins were identified recently by mass spectrometry-based proteomics that were differentially expressed in a given subtype compared with all other subtypes.[103] Considering that the cell pellet and culture media were analyzed separately, the results can also be interpreted as potential tissue-based and blood-based biomarkers. However, that study[103] was conducted on SCLC cell lines; therefore, the clinical utility and applicability of these proteins warrant further validation using human tissue and blood samples.

The unique vulnerability profiles of each SCLC subtype may provide a future framework for choosing the most effective therapy. This is especially relevant because, in contrast to NSCLC, SCLC usually shows loss of tumor suppressors as a main genetic feature, resulting in much more limited possibilities to target oncogenic drivers. Given the direct transcriptional interaction of ASCL1 with DLL3 in Notch-inactive tumor cells, the SCLC-A subtype is expected to be sensitive to DLL3 inhibition.[92,308] In addition, as mentioned above, SCLC-A is highly dependent on both BCL-2 and INSM1 levels.[6,97] Therefore, BCL-2 inhibitors might represent potential subtype-specific therapeutic agents

TABLE 3 Actively recruiting clinical trials sponsored by the National Institutes of Health.

Study name	Study phase	Mechanism of action	Therapeutic agent	Disease stage	Start of enrollment
NCT05353439	Phase 1	EZH2 inhibition	Tazemetostat plus topotecan and pembrolizumab	Recurrent SCLC	May 12, 2022
NCT03811002	Phase 2/3	PD-L1 inhibition	Atezolizumab plus chemoradiation	LS SCLC	May 28, 2019
NCT03554473	Phase 1/2	Bifunctional anti-PD-L1/TGFβ trap	M7824 plus topotecan or temozolomide	Relapsed SCLC	September 11, 2018
NCT04155034	Phase 3	Radiation therapy	MRI /prophylactic cranial irradiation	LS/ES SCLC	January 10, 2020
NCT04402788 (RAPTOR trial)	Phase 2/3	Radiation therapy	Atezolizumab alone or plus radiation	ES SCLC	August 17, 2020
NCT04560972	Phase 1	PP2A inhibition	LB-100 plus carboplatin, etoposide, and atezolizumab	Treatment-naive ES SCLC	May 28, 2021
NCT04826341	Phase 1/2	Anti–Trop-2 antibody-drug conjugate	Sacituzumab govitecan plus berzosertib	SCLC	September 20, 2021
NCT04728230 (PRIO trial)	Phase 1/2	PARP inhibition	Olaparib and durvalumab with carboplatin, etoposide, and/or radiation therapy	ES SCLC	January 5, 2021
NCT05450965	Phase 2	PLK1 inhibitor	Onvansertib	Relapsed SCLC	July 19, 2022
NCT04538378	Phase 2	PARP inhibition	Olaparib plus durvalumab	Transformed SCLC	July 7, 2021
NCT04516070	Phase 2	Stereotactic radiosurgery	Stereotactic radiosurgery	SCLC plus brain metastasis	August 28, 2020
NCT02769962	Phase 1/2	Cyclodextrin linked to camptothecin	EP0057 plus olaparib	Relapsed/refractory SCLC	May 9, 2016
NCT04514497	Phase 1	ATR inhibition	BAY 1895344 plus chemotherapy	SCLC	February 11, 2021
NCT05191797	Phase 1/2	LSD1 inhibition	Bomedemstat plus maintenance immunotherapy	ES SCLC	April 11, 2022
NCT05244239	Phase 1	Radiation therapy	Palliative radiotherapy plus lurbinectedin	ES SCLC	July 27, 2022
NCT01737502	Phase 1/2	mTOR inhibition/inhibition of redox enzymes	Sirolimus and auranofin	ES/recurrent SCLC	November 29, 2012
NCT04804644	Phase 3	Radiation therapy	High-dose radiation	ES/recurrent SCLC	March 24, 2021
NCT04514484	Phase 1	Multiple tyrosine kinase receptor inhibition	Cabozantinib and nivolumab	Advanced/recurrent/metastatic SCLC	November 4, 2020
NCT04140526	Phase 1/2	Anti–CTLA-4 monoclonal antibody	ONC-392 alone or plus pembrolizumab	SCLC	September 16, 2020
NCT04491942	Phase 1	ATR inhibition	BAY 1895344 plus chemotherapy	SCLC	February 1, 2021
NCT03735095	Phase 1/2	Photodynamic therapy	Porfimer sodium	SCLC	February 12, 2020

Abbreviations: ATR, ataxia telangiectasia and Rad3; CTLA-4, cytotoxic T-lymphocyte–associated protein 4; ES, extensive-stage; EZH2, enhancer of zeste 2 polycomb-repressive complex 2 subunit; LS, limited stage; LSD1, lysine-specific demethylase 1; mTOR, mammalian target of rapamycin; NCT, ClinicalTrials.gov identifier; PARP, poly(ADP-ribose) polymerase; PD-L1, programmed death-ligand 1; PLK1, polo-like kinase 1; PP2A, protein phosphatase 2A; SCLC, small cell lung cancer; TGFβ, transforming growth factor beta.

for this subset of SCLC, just like the LSD1 inhibitors, which disrupt the interaction between LSD1 and the transcriptional repressor INSM1 and thus inhibit the expression of NE-associated genes, such as ASCL1.[106] CREBBP is an acetyltransferase that mediates chromatin accessibility and acts as a potent tumor suppressor in SCLC.[309] Because SCLC-A is frequently associated with CREBBP inactivation,

and *Crebbp*-deleted tumors are widely sensitive to histone deacetylase inhibition, histone deacetylase inhibitors like pracinostat or tinostamustine might open new avenues of treatment in ASCL1-defined tumors.[309] Finally, inhibition of the SOX2 oncogene by hedgehog signal cascade inhibitors (sonidegib or vismodegib) might also represent an appealing targeted therapeutic approach in SCLC-A given the high expression of SOX2 in this subtype.[67]

With regard to SCLC-N, this subtype is often associated with MYC amplification, which serves as a potential target for specific MYC inhibitors (e.g., MYCi361) that engage MYC inside the cells, disrupt MYC/MAX dimers, and impair MYC-driven gene expression.[310] In addition, because of the increased arginine biosynthesis and AURKA activity, NEUROD1-driven tumors are suspected to be sensitive to arginine depletion caused by pegylated arginine deaminase (ADI-PEG 20) and AURKA inhibition (e.g., alisertib).[69,107] SCLC-N exhibits selective tropism for the oncolytic Seneca Valley virus. Therefore, with appropriate biomarker-guided patient selection, the Seneca Valley virus may have selective efficacy either as single-agent therapy or in combination with immunotherapy. In this context, the NEUROD1-to-ASCL1 ratio may function as a predictive biomarker.[95]

Recent CRISPR screens revealed that POU2F3-driven tumors possess vulnerability to IGF-1R deficiency provoked by IGF-1R inhibitors like dalotuzumab.[53] Moreover, PARP inhibitors like veliparib as well as nucleoside analogs are also anticipated to be most effective in SCLC-P. However, SLFN11 expression, known as a predictive biomarker for PARP-inhibition efficacy, does not seem to correlate with the expression of subtype-defining markers.[30,97]

The SCLC-I subtype is preferentially linked to immune blockade targeting the PD-1/PD-L1 axis because these tumors are associated with an inflamed, *immune oasis* phenotype and high expression of immune-checkpoint markers.[97,101,311] Notably, retrospective data analysis of the IMpower133 trial has already confirmed that the beneficial effects of incorporating immunotherapy into the EP backbone were more pronounced in patients with SCLC-I.[97] This provides a rationale for the use of immunotherapeutic agents in this particular subtype. SCLC cell lines with high YAP1 expression show high sensitivity to mTOR, PLK, and CDK4/CDK6 inhibitors.[30]

CONCLUSION

SCLC remains a rare but highly aggressive and nearly universally fatal malignancy that is typified by genomic instability and early metastatic spread. Although the clinical armamentarium for patients with SCLC has changed minimally over several decades, we have witnessed an accelerating pace of biologic insights into the disease in recent years. Presented here is a comprehensive review of multimodal clinical approaches in SCLC, with a special focus on illuminating how the underlying pathobiology that drives this disease and the recent advancements in the field of SCLC research can be exploited in the clinic. In very early stage disease, surgical resection within the framework of multimodal treatment improves survival outcomes. Nevertheless, patients are typically diagnosed with a more advanced disease stage, when platinum-based chemotherapy supplemented with immunotherapy represents the therapeutic approach of choice. The role of radiotherapy with concomitant systemic therapy is also well established in the management of patients with SCLC. Although these therapeutic approaches are indeed efficacious at the beginning, most patients demonstrate rapid acquired resistance, highlighting the clear need to improve the effectiveness and expand the scope of current therapeutic strategies. The impressive preclinical advances during the past decade and the worldwide resurgence of profiling studies have converged on a new model of the SCLC classification scheme. This emerging knowledge of SCLC molecular subtypes and the related genomic alterations have the potential to lead to the implementation of subtype-specific therapeutic approaches, with the goal of improving patient care for this once-enigmatic cancer.

ACKNOWLEDGMENTS

Balazs Dome and Zsolt Megyesfalvi were supported by funding from the Hungarian National Research, Development, and Innovation Office (KH130356 to Balazs Dome; 2020-1.1.6-JÖVŐ, TKP2021-EGA-33, and FK-143751 to Balazs Dome and Zsolt Megyesfalvi). Balazs Dome was also supported by the Austrian Science Fund (FWF I3522, FWF I3977, and I4677). Zsolt Megyesfalvi was supported by the New National Excellence Program of the Ministry for Innovation and Technology of Hungary (UNKP-20-3 and UNKP-21-3) and by the Hungarian Respiratory Society (MPA #2020). Zsolt Megyesfalvi is also the recipient of an International Association for the Study of Lung Cancer/International Lung Cancer Foundation Young Investigator Grant (2022). Karin Schelch was supported by the Austrian Science Fund (FWF No. T 1062-B33) and the City of Vienna Fund for Innovative Interdisciplinary Cancer Research. Karin Schelch is also the recipient of an International Association for the Study of Lung Cancer Early Career Education Award (2021). Carl M. Gay is the recipient of an American Society of Clinical Oncology Young Investigator Award, a Cancer Research Prevention Institute of Texas Early Clinical Investigator Award, and a LUNGevity Foundation Career Development Award.

CONFLICT OF INTEREST STATEMENT

Fred R. Hirsch reports participation on scientific advisory boards for Bristol-Myers Squibb (BMS), AstraZeneca, Sanofi, Novartis, Merck & Company Inc., Regeneron Pharmaceuticals, Blueprint, G1 Therapeutics, Merus, Genentech, Amgen, Novocure, NextCure, Nectin Therapeutics, OncoCyte, and Daiichi Sankyo Company, outside the submitted work. Carl M. Gay reports personal fees from AstraZeneca, BeiGene USA Inc., BMS, G1 Therapeutics, Jazz Pharmaceuticals, and Monte Rosa Therapeutics outside the submitted work. Paul A. Bunn Jr is a member of a Data Monitoring Committee at Merck & Company Inc. and BMS; a member of the Board of Directors of Verastem Inc.; and reports personal fees from BeiGene Ltd., CStone, Ascentage, Viecure, Imidex, Eli Lilly & Company, and Genentech outside the submitted work. Simon Heeke reports consulting fees from AstraZeneca, Boehringer Ingelheim, Nucleix, and Qiagen outside the submitted work. Helmut Prosch reports speakers'

honoraria from AstraZeneca, BMS, Boehringer Ingelheim, Janssen, Merck Sharp & Dohme, Novartis, Roche/Intermune, Sanofi, Siemens Healthcare, and Takeda; and research support from AstraZeneca, Boehringer, Siemens, and EU4Health outside the submitted work. Konrad Hoetzenecker reports personal fees from Medtronic outside the submitted work. Robert Pirker reports speakers' fees and honoraria for advisory board service from AstraZeneca, Eli Lilly & Company, and Merck Serono outside the submitted work. Lauren A. Byers reports grants and personal fees from AstraZeneca, AbbVie, and GenMab; and personal fees from Alethia Biotherapeutics Inc., Amgen, Arrowhead Pharmaceuticals, BeiGene Ltd., BMS, Chugai Pharmaceutical Company Ltd., Daiichi Sankyo Company, Genentech Inc., Jazz Pharmaceuticals, Merck Sharp & Dohme, PharmaMar, and Puma Biotechnology outside the submitted work. The remaining authors declared no conflicts of interest.

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REFERENCES

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. *CA Cancer J Clin*. 2022;72(1):7-33. doi:10.3322/caac.21708
2. 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(12):725-737. doi:10.1038/nrc.2017.87
3. George J, Lim JS, Jang SJ, et al. Comprehensive genomic profiles of small cell lung cancer. *Nature*. 2015;524(7563):47-53. doi:10.1038/nature14664
4. Rudin CM, Brambilla E, Faivre-Finn C, Sage J. Small-cell lung cancer. *Nat Rev Dis Primers*. 2021;7(1):3. doi:10.1038/s41572-020-00235-0
5. Jordan EJ, Kim HR, Arcila ME, et al. Prospective comprehensive molecular characterization of lung adenocarcinomas for efficient patient matching to approved and emerging therapies. *Cancer Discov*. 2017;7(6):596-609. doi:10.1158/2159-8290.cd-16-1337
6. Rudin CM, Poirier JT, Byers LA, et al. Molecular subtypes of small cell lung cancer: a synthesis of human and mouse model data. *Nat Rev Cancer*. 2019;19(5):289-297. doi:10.1038/s41568-019-0133-9
7. Drapkin BJ, Rudin CM. Advances in small-cell lung cancer (SCLC) translational research. *Cold Spring Harb Perspect Med*. 2021;11(4):a038240. doi:10.1101/cshperspect.a038240
8. Barnard WG. The nature of the "oat-celled sarcoma" of the mediastinum. *J Pathol Bacteriol*. 1926;29(3):241-244. doi:10.1002/path.1700290304
9. Azzopardi JG. Oat-cell carcinoma of the bronchus. *J Pathol Bacteriol*. 1959;78(2):513-519. doi:10.1002/path.1700780218
10. Haddadin S, Perry MC. History of small-cell lung cancer. *Clin Lung Cancer*. 2011;12(2):87-93. doi:10.1016/j.cllc.2011.03.002
11. Matthews MJ, Kanhouwa S, Pickren J, Robinette D. Frequency of residual and metastatic tumor in patients undergoing curative surgical resection for lung cancer. *Cancer Chemother Rep 3*. 1973;4:63-67.
12. Skarlos DV, Samantas E, Kosmidis P, et al. Randomized comparison of etoposide-cisplatin vs. etoposide-carboplatin and irradiation in small-cell lung cancer. A Hellenic Co-operative Oncology Group study. *Ann Oncol*. 1994;5(7):601-607. doi:10.1093/oxfordjournals.annonc.a058931
13. Karim SM, Zekri J. Chemotherapy for small cell lung cancer: a comprehensive review. *Oncol Rev*. 2012;6(1):e4. doi:10.4081/oncol.2012.e4
14. Rudin CM, Poirier JT. Small-cell lung cancer in 2016: shining light on novel targets and therapies. *Nat Rev Clin Oncol*. 2017;14(2):75-76. doi:10.1038/nrclinonc.2016.203
15. Evans WK, Shepherd FA, Feld R, Osoba D, Dang P, Deboer G. VP-16 and cisplatin as first-line therapy for small-cell lung cancer. *J Clin Oncol*. 1985;3(11):1471-1477. doi:10.1200/jco.1985.3.11.1471
16. Hirsch FR, Hansen HH, Hansen M, et al. The superiority of combination chemotherapy including etoposide based on in vivo cell cycle analysis in the treatment of extensive small-cell lung cancer: a randomized trial of 288 consecutive patients. *J Clin Oncol*. 1987;5(4):585-591. doi:10.1200/jco.1987.5.4.585
17. Paul A.Bunn Jr, Greco FA, Einhorn L. Cyclophosphamide, doxorubicin, and etoposide as first-line therapy in the treatment of small-cell lung cancer. *Semin Oncol*. 1986;13:45-53.
18. Ragavan M, Das M. Systemic therapy of extensive stage small cell lung cancer in the era of immunotherapy. *Curr Treat Options Oncol*. 2020;21(8):64. doi:10.1007/s11864-020-00762-8
19. 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(23):2220-2229. doi:10.1056/nejmoa1809064
20. Paz-Ares L, Dvorkin M, Chen Y, et al. Durvalumab plus platinum-etoposide versus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial. *Lancet*. 2019;394(10212):1929-1939. doi:10.1016/s0140-6736(19)32222-6
21. Bray F, Ferlay J, Laversanne M, et al. Cancer Incidence in Five Continents: inclusion criteria, highlights from volume X and the global status of cancer registration. *Int J Cancer*. 2015;137(9):2060-2071. doi:10.1002/ijc.29670
22. Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. *CA Cancer J Clin*. 2023;73(1):17-48. doi:10.3322/caac.21763
23. Huang R, Wei Y, Hung RJ, et al. Associated links among smoking, chronic obstructive pulmonary disease, and small cell lung cancer: a pooled analysis in the International Lung Cancer Consortium. *EBioMedicine*. 2015;2(11):1677-1685. doi:10.1016/j.ebiom.2015.09.031
24. Basumallik N, Agarwal M. *Small Cell Lung Cancer*. StatPearls Publishing LLC; 2022.
25. Ragavan M, Patel MI. The evolving landscape of sex-based differences in lung cancer: a distinct disease in women. *Eur Respir Rev*. 2022;31(163):210100. doi:10.1183/16000617.0100-2021
26. Torre LA, Siegel RL, Jemal A. Lung cancer statistics. *Adv Exp Med Biol*. 2016;893:1-19.
27. Zhou K, Shi H, Chen R, et al. Association of race, socioeconomic factors, and treatment characteristics with overall survival in patients with limited-stage small cell lung cancer. *JAMA Netw Open*. 2021;4(1):e2032276. doi:10.1001/jamanetworkopen.2020.32276
28. American Lung Association. *Tobacco Use in Racial and Ethnic Populations*. American Lung Association; 2022. <zaq;12>Accessed December 7, 2022. https://www.lung.org/quit-smoking/smoking-facts/impact-of-tobacco-use/tobacco-use-racial-and-ethnic
29. Stram DO, Park SL, Haiman CA, et al. Racial/ethnic differences in lung cancer incidence in the Multiethnic Cohort Study: an update. *J Natl Cancer Inst*. 2019;111(8):811-819. doi:10.1093/jnci/djy206
30. Schwendenwein A, Megyesfalvi Z, Barany N, et al. Molecular profiles of small cell lung cancer subtypes: therapeutic implications. *Mol Ther Oncolytics*. 2021;20:470-483. doi:10.1016/j.omto.2021.02.004
31. Wang S, Tang J, Sun T, et al. Survival changes in patients with small cell lung cancer and disparities between different sexes, socioeconomic statuses and ages. *Sci Rep*. 2017;7(1):1339. doi:10.1038/s41598-017-01571-0
32. Siegel DA, Fedewa SA, Henley SJ, Pollack LA, Jemal A. Proportion of never smokers among men and women with lung cancer in 7 US states. *JAMA Oncol*. 2021;7(2):302-304. doi:10.1001/jamaoncol.2020.6362
33. Khuder SA. Effect of cigarette smoking on major histological types of lung cancer: a meta-analysis. *Lung Cancer*. 2001;31(2-3):139-148. doi:10.1016/s0169-5002(00)00181-1

34. Kim CH, Lee YC, Hung RJ, et al. Exposure to secondhand tobacco smoke and lung cancer by histological type: a pooled analysis of the International Lung Cancer Consortium (ILCCO). *Int J Cancer*. 2014;135(8):1918-1930. doi:10.1002/ijc.28835
35. Sun JM, Choi YL, Ji JH, et al. Small-cell lung cancer detection in never-smokers: clinical characteristics and multigene mutation profiling using targeted next-generation sequencing. *Ann Oncol*. 2015;26(1):161-166. doi:10.1093/annonc/mdu504
36. Liu X, Jiang T, Li W, et al. Characterization of never-smoking and its association with clinical outcomes in Chinese patients with small-cell lung cancer. *Lung Cancer*. 2018;115:109-115. doi:10.1016/j.lungcan.2017.11.022
37. Hecht SS. Lung carcinogenesis by tobacco smoke. *Int J Cancer*. 2012;131(12):2724-2732. doi:10.1002/ijc.27816
38. Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health. *How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease: A Report of the Surgeon General*. Centers for Disease Control and Prevention (US); 2010.
39. Van Duuren BL, Goldschmidt BM. Cocarcinogenic and tumor-promoting agents in tobacco carcinogenesis. *J Natl Cancer Inst*. 1976;56(6):1237-1242. doi:10.1093/jnci/56.6.1237
40. Liu T, Zhang L, Joo D, Sun SC. NF-κB signaling in inflammation. *Signal Transduct Targeted Ther*. 2017;2(1):17023. doi:10.1038/sigtrans.2017.23
41. Smith CJ, Perfetti TA, King JA. Perspectives on pulmonary inflammation and lung cancer risk in cigarette smokers. *Inhal Toxicol*. 2006;18(9):667-677. doi:10.1080/08958370600742821
42. Wong KK, Jacks T, Dranoff G. NF-κB fans the flames of lung carcinogenesis. *Cancer Prev Res*. 2010;3(4):403-405. doi:10.1158/1940-6207.capr-10-0042
43. Liu J, Chen SJ, Hsu SW, et al. MARCKS cooperates with NKAP to activate NF-kB signaling in smoke-related lung cancer. *Theranostics*. 2021;11(9):4122-4136. doi:10.7150/thno.53558
44. Thomas A, Mian I, Tlemsani C, et al. Clinical and genomic characteristics of small cell lung cancer in never smokers: results from a retrospective multicenter cohort study. *Chest*. 2020;158(4):1723-1733. doi:10.1016/j.chest.2020.04.068
45. Torres-Durán M, Curiel-García MT, Ruano-Ravina A, et al. Small-cell lung cancer in never-smokers. *ESMO Open*. 2021;6(2):100059. doi:10.1016/j.esmoop.2021.100059
46. Rodríguez-Martínez Á, Torres-Durán M, Barros-Dios JM, Ruano-Ravina A. Residential radon and small cell lung cancer. a systematic review. *Cancer Lett*. 2018;426:57-62. doi:10.1016/j.canlet.2018.04.003
47. Hystad P, Demers PA, Johnson KC, Carpiano RM, Brauer M. Long-term residential exposure to air pollution and lung cancer risk. *Epidemiology*. 2013;24(5):762-772. doi:10.1097/ede.0b013e3182949ae7
48. Lamichhane DK, Kim HC, Choi CM, et al. Lung cancer risk and residential exposure to air pollution: a Korean population-based case-control study. *Yonsei Med J*. 2017;58(6):1111-1118. doi:10.3349/ymj.2017.58.6.1111
49. Wang J, Liu Q, Yuan S, et al. Genetic predisposition to lung cancer: comprehensive literature integration, meta-analysis, and multiple evidence assessment of candidate-gene association studies. *Sci Rep*. 2017;7(1):8371. doi:10.1038/s41598-017-07737-0
50. Harbour JW, Lai SL, Whang-Peng J, Gazdar AF, Minna JD, Kaye FJ. Abnormalities in structure and expression of the human retinoblastoma gene in SCLC. *Science*. 1988;241(4863):353-357. doi:10.1126/science.2838909
51. Takahashi T, Nau MM, Chiba I, et al. p53: a frequent target for genetic abnormalities in lung cancer. *Science*. 1989;246(4929):491-494. doi:10.1126/science.2554494
52. Sutherland KD, Proost N, Brouns I, Adriaensen D, Song JY, Berns A. Cell of origin of small cell lung cancer: inactivation of Trp53 and Rb1 in distinct cell types of adult mouse lung. *Cancer Cell*. 2011;19(6):754-764. doi:10.1016/j.ccr.2011.04.019
53. 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(13-14):915-928. doi:10.1101/gad.314815.118
54. Chen HJ, Poran A, Unni AM, et al. Generation of pulmonary neuroendocrine cells and SCLC-like tumors from human embryonic stem cells. *J Exp Med*. 2019;216(3):674-687. doi:10.1084/jem.20181155
55. Quintanal-Villalonga Á, Chan JM, Yu HA, et al. Lineage plasticity in cancer: a shared pathway of therapeutic resistance. *Nat Rev Clin Oncol*. 2020;17(6):360-371. doi:10.1038/s41571-020-0340-z
56. Niederst MJ, Sequist LV, Poirier JT, et al. RB loss in resistant EGFR mutant lung adenocarcinomas that transform to small-cell lung cancer. *Nat Commun*. 2015;6(1):6377. doi:10.1038/ncomms7377
57. Gazeu A, Aubert M, Pissaloux D, et al. Small-cell lung cancer transformation as a mechanism of resistance to pralsetinib in RET-rearranged lung adenocarcinoma: a case report. *Clin Lung Cancer*. 2023;24(1):72-75. doi:10.1016/j.cllc.2022.10.005
58. Offin M, Chan JM, Tenet M, et al. Concurrent RB1 and TP53 alterations define a subset of EGFR-mutant lung cancers at risk for histologic transformation and inferior clinical outcomes. *J Thorac Oncol*. 2019;14(10):1784-1793. doi:10.1016/j.jtho.2019.06.002
59. Oser MG, Niederst MJ, Sequist LV, Engelman JA. Transformation from non-small-cell lung cancer to small-cell lung cancer: molecular drivers and cells of origin. *Lancet Oncol*. 2015;16(4):e165-e172. doi:10.1016/s1470-2045(14)71180-5
60. Piper-Vallillo AJ, Sequist LV, Piotrowska Z. Emerging treatment paradigms for EGFR-mutant lung cancers progressing on osimertinib: a review. *J Clin Oncol*. 2020;38(25):2926-2936. doi:10.1200/jco.19.03123
61. Marcoux N, Gettinger SN, O'Kane G, et al. EGFR-mutant adenocarcinomas that transform to small-cell lung cancer and other neuroendocrine carcinomas: clinical outcomes. *J Clin Oncol*. 2019;37(4):278-285. doi:10.1200/jco.18.01585
62. Ferrer L, Giaj Levra M, Brevet M, et al. A brief report of transformation from NSCLC to SCLC: molecular and therapeutic characteristics. *J Thorac Oncol*. 2019;14(1):130-134. doi:10.1016/j.jtho.2018.08.2028
63. Balla A, Khan F, Hampel KJ, Aisner DL, Sidiropoulos N. Small-cell transformation of ALK-rearranged non-small-cell adenocarcinoma of the lung. *Cold Spring Harb Mol Case Stud*. 2018;4(2):a002394. doi:10.1101/mcs.a002394
64. Ahmed T, Vial MR, Ost D, Stewart J, Hasan MA, Grosu HB. Non-small cell lung cancer transdifferentiation into small cell lung cancer: a case series. *Lung Cancer*. 2018;122:220-223. doi:10.1016/j.lungcan.2018.06.024
65. Puca L, Vlachostergios PJ, Beltran H. Neuroendocrine differentiation in prostate cancer: emerging biology, models, and therapies. *Cold Spring Harb Perspect Med*. 2019;9(2):a030593. doi:10.1101/cshperspect.a030593
66. Peifer M, Fernández-Cuesta L, Sos ML, et al. Integrative genome analyses identify key somatic driver mutations of small-cell lung cancer. *Nat Genet*. 2012;44(10):1104-1110. doi:10.1038/ng.2396
67. Rudin CM, Durinck S, Stawiski EW, et al. Comprehensive genomic analysis identifies SOX2 as a frequently amplified gene in small-cell lung cancer. *Nat Genet*. 2012;44(10):1111-1116. doi:10.1038/ng.2405
68. Romero OA, Torres-Diz M, Pros E, et al. MAX inactivation in small cell lung cancer disrupts MYC-SWI/SNF programs and is synthetic lethal with BRG1. *Cancer Discov*. 2014;4(3):292-303. doi:10.1158/2159-8290.cd-13-0799
69. 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(2):270-285. doi:10.1016/j.ccell.2016.12.005
70. 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(5). doi:10.1126/sciadv.abc2578
71. Augustyn A, Borromeo M, Wang T, et al. ASCL1 is a lineage oncogene providing therapeutic targets for high-grade neuroendocrine lung cancers. *Proc Natl Acad Sci U S A*. 2014;111(41):14788-14793. doi:10.1073/pnas.1410419111
72. Meder L, König K, Ozretić L, et al. NOTCH, ASCL1, p53 and RB alterations define an alternative pathway driving neuroendocrine and small cell lung carcinomas. *Int J Cancer*. 2016;138(4):927-938. doi:10.1002/ijc.29835
73. Lim JS, Ibaseta A, Fischer MM, et al. Intratumoural heterogeneity generated by Notch signalling promotes small-cell lung cancer. *Nature*. 2017;545(7654):360-364. doi:10.1038/nature22323
74. Bensch KG, Corrin B, Pariente R, Spencer H. Oat-cell carcinoma of the lung. Its origin and relationship to bronchial carcinoid. *Cancer*. 1968;22(6):1163-1172. doi:10.1002/1097-0142(196811)22:6<1163::aid-cncr2820220612>3.0.co;2-l
75. 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;45:2913-2923.
76. Berniker AV, Abdulrahman AA, Teytelboym OM, Galindo LM, Mackey JE. Extrapulmonary small cell carcinoma: imaging features with radiologic-pathologic correlation. *Radiographics*. 2015;35(1):152-163. doi:10.1148/rg.351140050
77. Gazdar AF, Carney DN, Nau MM, Minna JD. Characterization of variant subclasses of cell lines derived from small cell lung cancer having distinctive biochemical, morphological, and growth properties. *Cancer Res*. 1985;45:2924-2930.
78. Denny SK, Yang D, Chuang CH, et al. Nfib promotes metastasis through a widespread increase in chromatin accessibility. *Cell*. 2016;166(2):328-342. doi:10.1016/j.cell.2016.05.052
79. Semenova EA, Kwon MC, Monkhorst K, et al. Transcription factor NFIB is a driver of small cell lung cancer progression in mice and marks metastatic disease in patients. *Cell Rep*. 2016;16(3):631-643. doi:10.1016/j.celrep.2016.06.020
80. Ko J, Winslow MM, Sage J. Mechanisms of small cell lung cancer metastasis. *EMBO Mol Med*. 2021;13(1):e13122. doi:10.15252/emmm.202013122
81. Wu Q, Guo J, Liu Y, et al. YAP drives fate conversion and chemoresistance of small cell lung cancer. *Sci Adv*. 2021;7(40):eabg1850. doi:10.1126/sciadv.abg1850
82. Yang D, Qu F, Cai H, et al. Axon-like protrusions promote small cell lung cancer migration and metastasis. *Elife*. 2019;8:e50616. doi:10.7554/elife.50616
83. 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(1):32-49. doi:10.21037/tlcr.2018.02.02
84. Lohinai Z, Megyesfalvi Z, Suda K, et al. Comparative expression analysis in small cell lung carcinoma reveals neuroendocrine pattern change in primary tumor versus lymph node metastases. *Transl Lung Cancer Res*. 2019;8(6):938-950. doi:10.21037/tlcr.2019.11.30
85. 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(9):1947-1965. doi:10.1002/1878-0261.12741
86. Park H, Tseng SC, Sholl LM, Hatabu H, Awad MM, Nishino M. Molecular characterization and therapeutic approaches to small cell lung cancer: imaging implications. *Radiology*. 2022;305(3):512-525. doi:10.1148/radiol.220585
87. Poirier JT, George J, Owonikoko TK, et al. New approaches to SCLC therapy: from the laboratory to the clinic. *J Thorac Oncol*. 2020;15(4):520-540. doi:10.1016/j.jtho.2020.01.016
88. 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(12):1823-1835. doi:10.1016/j.jtho.2020.09.009
89. Megyesfalvi Z, Barany N, Lantos A, et al. Expression patterns and prognostic relevance of subtype-specific transcription factors in surgically resected small-cell lung cancer: an international multicenter study. *J Pathol*. 2022;257(5):674-686. doi:10.1002/path.5922
90. Handa T, Hayashi T, Ura A, et al. Comparison of ASCL1, NEUROD1, and POU2F3 expression in surgically resected specimens, paired tissue microarrays, and lymph node metastases in small cell lung carcinoma. *Histopathology*. 2023;82(6):860-869. doi:10.1111/his.14872
91. Qi J, Zhang J, Liu N, Zhao L, Xu B. Prognostic implications of molecular subtypes in primary small cell lung cancer and their correlation with cancer immunity. *Front Oncol*. 2022;12:779276. doi:10.3389/fonc.2022.779276
92. Furuta M, Sakakibara-Konishi J, Kikuchi H, et al. Analysis of DLL3 and ASCL1 in surgically resected small cell lung cancer (HOT1702). *Oncologist*. 2019;24(11):e1172-e1179. doi:10.1634/theoncologist.2018-0676
93. Kosari F, Ida CM, Aubry MC, et al. ASCL1 and RET expression defines a clinically relevant subgroup of lung adenocarcinoma characterized by neuroendocrine differentiation. *Oncogene*. 2014;33(29):3776-3783. doi:10.1038/onc.2013.359
94. Wooten DJ, Groves SM, Tyson DR, et al. Systems-level network modeling of small cell lung cancer subtypes identifies master regulators and destabilizers. *PLoS Comput Biol*. 2019;15(10):e1007343. doi:10.1371/journal.pcbi.1007343
95. Poirier JT, Dobromilskaya I, Moriarty WF, Peacock CD, Hann CL, Rudin CM. Selective tropism of Seneca Valley virus for variant subtype small cell lung cancer. *J Natl Cancer Inst*. 2013;105(14):1059-1065. doi:10.1093/jnci/djt130
96. Baine MK, Febres-Aldana CA, Chang JC, et al. POU2F3 in SCLC: clinicopathologic and genomic analysis with a focus on its diagnostic utility in neuroendocrine-low SCLC. *J Thorac Oncol*. 2022;17(9):1109-1121. doi:10.1016/j.jtho.2022.06.004
97. 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(3):346-360.e7. doi:10.1016/j.ccell.2020.12.014
98. Caeser R, Egger JV, Chavan S, et al. Genomic and transcriptomic analysis of a library of small cell lung cancer patient-derived xenografts. *Nat Commun*. 2022;13(1):2144. doi:10.1038/s41467-022-29794-4
99. 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(4):437-451. doi:10.1038/s43018-020-0046-2
100. 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(5):1259-1272. doi:10.1016/j.celrep.2016.06.081
101. 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(3):464-476. doi:10.1016/j.jtho.2020.11.006
102. 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(4):423-436. doi:10.1038/s43018-019-0020-z

103. Szeitz B, Megyesfalvi Z, Woldmar N, et al. In-depth proteomic analysis reveals unique subtype-specific signatures in human small-cell lung cancer. *Clin Transl Med*. 2022;12(9):e1060. doi:10.1002/ctm2.1060
104. 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(48):5869-5878. doi:10.1038/onc.2015.38
105. Valko Z, Megyesfalvi Z, Schwendenwein A, et al. Dual targeting of BCL-2 and MCL-1 in the presence of BAX breaks venetoclax resistance in human small cell lung cancer. *Br J Cancer*. Published online March 14, 2023. doi:10.1038/s41416-023-02219-9
106. Takagi S, Ishikawa Y, Mizutani A, et al. LSD1 inhibitor T-3775440 inhibits SCLC cell proliferation by disrupting LSD1 interactions with SNAG domain proteins INSM1 and GFI1B. *Cancer Res*. 2017;77(17):4652-4662. doi:10.1158/0008-5472.can-16-3502
107. 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(16):5107-5121. doi:10.1158/1078-0432.ccr-18-4140
108. McColl K, Wildey G, Sakre N, et al. Reciprocal expression of INSM1 and YAP1 defines subgroups in small cell lung cancer. *Oncotarget*. 2017;8(43):73745-73756. doi:10.18632/oncotarget.20572
109. Horie M, Saito A, Ohshima M, Suzuki HI, Nagase T. YAP and TAZ modulate cell phenotype in a subset of small cell lung cancer. *Cancer Sci*. 2016;107(12):1755-1766. doi:10.1111/cas.13078
110. Oboshi S, Tsugawa S, Seido T, Shimosato Y, Koide T. A new floating cell line derived from human pulmonary carcinoma of oat cell type. *Gan*. 1971;62:505-514.
111. Ohara H, Okamoto T. A new in vitro cell line established from human oat cell carcinoma of the lung. *Cancer Res*. 1977;37:3088-3095.
112. Ramirez RD, Sheridan S, Girard L, et al. Immortalization of human bronchial epithelial cells in the absence of viral oncoproteins. *Cancer Res*. 2004;64(24):9027-9034. doi:10.1158/0008-5472.can-04-3703
113. Gazdar AF, Girard L, Lockwood WW, Lam WL, Minna JD. Lung cancer cell lines as tools for biomedical discovery and research. *J Natl Cancer Inst*. 2010;102(17):1310-1321. doi:10.1093/jnci/djq279
114. Sato T, Stange DE, Ferrante M, et al. Long-term expansion of epithelial organoids from human colon, adenoma, adenocarcinoma, and Barrett's epithelium. *Gastroenterology*. 2011;141(5):1762-1772. doi:10.1053/j.gastro.2011.07.050
115. Rossi R, De Angelis ML, Xhelili E, et al. Lung cancer organoids: the rough path to personalized medicine. *Cancers (Basel)*. 2022;14(15):3703. doi:10.3390/cancers14153703
116. Berns A, Barbacid M. Mouse models of cancer. *Mol Oncol*. 2013;7(2):143-145. doi:10.1016/j.molonc.2013.02.014
117. Gazdar AF, Savage TK, Johnson JE, et al. The comparative pathology of genetically engineered mouse models for neuroendocrine carcinomas of the lung. *J Thorac Oncol*. 2015;10(4):553-564. doi:10.1097/jto.0000000000000459
118. Schaffer BE, Park KS, Yiu G, et al. Loss of p130 accelerates tumor development in a mouse model for human small-cell lung carcinoma. *Cancer Res*. 2010;70(10):3877-3883. doi:10.1158/0008-5472.can-09-4228
119. McFadden DG, Papagiannakopoulos T, Taylor-Weiner A, et al. Genetic and clonal dissection of murine small cell lung carcinoma progression by genome sequencing. *Cell*. 2014;156(6):1298-1311. doi:10.1016/j.cell.2014.02.031
120. Meuwissen R, Linn SC, Linnoila RI, Zevenhoven J, Mooi WJ, Berns A. Induction of small cell lung cancer by somatic inactivation of both Trp53 and Rb1 in a conditional mouse model. *Cancer Cell*. 2003;4(3):181-189. doi:10.1016/s1535-6108(03)00220-4
121. Nguyen EM, Taniguchi H, Chan JM, et al. Targeting lysine-specific demethylase 1 rescues major histocompatibility complex class I antigen presentation and overcomes programmed death-ligand 1 blockade resistance in SCLC. *J Thorac Oncol*. 2022;17(8):1014-1031. doi:10.1016/j.jtho.2022.05.014
122. Daniel VC, Marchionni L, Hierman JS, et al. A primary xenograft model of small-cell lung cancer reveals irreversible changes in gene expression imposed by culture in vitro. *Cancer Res*. 2009;69(8):3364-3373. doi:10.1158/0008-5472.can-08-4210
123. Frese KK, Tuveson DA. Maximizing mouse cancer models. *Nat Rev Cancer*. 2007;7(9):645-658. doi:10.1038/nrc2192
124. Drapkin BJ, George J, Christensen CL, et al. Genomic and Functional fidelity of small cell lung cancer patient-derived xenografts. *Cancer Discov*. 2018;8(5):600-615. doi:10.1158/2159-8290.cd-17-0935
125. Fujiwara S. Humanized mice: a brief overview on their diverse applications in biomedical research. *J Cell Physiol*. 2018;233(4):2889-2901. doi:10.1002/jcp.26022
126. Megyesfalvi Z, Tallosy B, Pipek O, et al. The landscape of small cell lung cancer metastases: organ specificity and timing. *Thorac Cancer*. 2021;12(6):914-923. doi:10.1111/1759-7714.13854
127. Gandhi L, Johnson BE. Paraneoplastic syndromes associated with small cell lung cancer. *J Natl Compr Cancer Netw*. 2006;4(6):631-638. doi:10.6004/jnccn.2006.0052
128. Iams WT, Shiuan E, Meador CB, et al. Improved prognosis and increased tumor-infiltrating lymphocytes in patients who have SCLC with neurologic paraneoplastic syndromes. *J Thorac Oncol*. 2019;14(11):1970-1981. doi:10.1016/j.jtho.2019.05.042
129. Soomro Z, Youssef M, Yust-Katz S, Jalali A, Patel AJ, Mandel J. Paraneoplastic syndromes in small cell lung cancer. *J Thorac Dis*. 2020;12(10):6253-6263. doi:10.21037/jtd.2020.03.88
130. Anwar A, Jafri F, Ashraf S, Jafri MAS, Fanucchi M. Paraneoplastic syndromes in lung cancer and their management. *Ann Transl Med*. 2019;7(15):359. doi:10.21037/atm.2019.04.86
131. Binks S, Uy C, Honnorat J, Irani SR. Paraneoplastic neurological syndromes: a practical approach to diagnosis and management. *Pract Neurol*. 2022;22(1):19-31. doi:10.1136/practneurol-2021-003073
132. Lennon VA, Kryzer TJ, Griesmann GE, et al. Calcium-channel antibodies in the Lambert–Eaton syndrome and other paraneoplastic syndromes. *N Engl J Med*. 1995;332(22):1467-1474. doi:10.1056/nejm199506013322203
133. Winkler AS, Dean A, Hu M, Gregson N, Chaudhuri KR. Phenotypic and neuropathologic heterogeneity of anti-Hu antibody-related paraneoplastic syndrome presenting with progressive dysautonomia: report of two cases. *Clin Auton Res*. 2001;11(2):115-118. doi:10.1007/bf02322055
134. Dalmau J, Furneaux HM, Cordon-Cardo C, Posner JB. The expression of the Hu (paraneoplastic encephalomyelitis/sensory neuronopathy) antigen in human normal and tumor tissues. *Am J Pathol*. 1992;141:881-886.
135. Mutoh T, Tachi M, Yano S, Mihara T, Yamamoto H. Impairment of Trk-neurotrophin receptor by the serum of a patient with subacute sensory neuropathy. *Arch Neurol*. 2005;62(10):1612-1615. doi:10.1001/archneur.62.10.1612
136. Panunzio A, Sartori P. Lung cancer and radiological imaging. *Curr Radiopharm*. 2020;13(3):238-242. doi:10.2174/1874471013666200523161849
137. Gridelli C, Rossi A, Carbone DP, et al. Non-small-cell lung cancer. *Nat Rev Dis Primers*. 2015;1:15009. doi:10.1038/nrdp.2015.9
138. Danaher L, Niknejad M, El-Feky M. Small cell lung cancer. Accessed December 7, 2022. Radiopaedia.org<zaq;13>
139. Purandare NC, Rangarajan V. Imaging of lung cancer: implications on staging and management. *Indian J Radiol Imaging*. 2015;25(02):109-120. doi:10.4103/0971-3026.155831
140. Kalemkerian GP. Staging and imaging of small cell lung cancer. *Cancer Imaging*. 2012;11(1):253-258. doi:10.1102/1470-7330.2011.0036

141. Martucci F, Pascale M, Valli MC, et al. Impact of (18)F-FDG PET/CT in staging patients with small cell lung cancer: a systematic review and meta-analysis. *Front Med*. 2019;6:336. doi:10.3389/fmed.2019.00336
142. van der Leest C, Smit EF, Baas J, et al. SUVmax during 18FDG-PET scanning in small cell lung cancer: similar information as in non-small cell lung cancer? *Lung Cancer*. 2012;76(1):67-71. doi:10.1016/j.lungcan.2011.09.007
143. Zer A, Domachevsky L, Rapson Y, et al. The role of 18F-FDG PET/CT on staging and prognosis in patients with small cell lung cancer. *Eur Radiol*. 2016;26(9):3155-3161. doi:10.1007/s00330-015-4132-2
144. Lapa C, Hänscheid H, Wild V, et al. Somatostatin receptor expression in small cell lung cancer as a prognostic marker and a target for peptide receptor radionuclide therapy. *Oncotarget*. 2016;7(15):20033-20040. doi:10.18632/oncotarget.7706
145. Yung RC. Tissue diagnosis of suspected lung cancer: selecting between bronchoscopy, transthoracic needle aspiration, and resectional biopsy. *Respir Care Clin*. 2003;9(1):51-76. doi:10.1016/s1078-5337(02)00083-7
146. Rivera MP, Mehta AC, Wahidi MM. Establishing the diagnosis of lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2013;143(5 suppl):e142S-e165S. doi:10.1378/chest.12-2353
147. van Overhagen H, Brakel K, Heijenbrok MW, et al. Metastases in supraclavicular lymph nodes in lung cancer: assessment with palpation, US, and CT. *Radiology*. 2004;232(1):75-80. doi:10.1148/radiol.2321030663
148. El-Bayoumi E, Silvestri GA. Bronchoscopy for the diagnosis and staging of lung cancer. *Semin Respir Crit Care Med*. 2008;29(3):261-270. doi:10.1055/s-2008-1076746
149. Prosch H, Strasser G, Sonka C, et al. Cervical ultrasound (US) and US-guided lymph node biopsy as a routine procedure for staging of lung cancer. *Ultraschall Med*. 2007;28(06):598-603. doi:10.1055/s-2007-963215
150. Chen CC, Bai CH, Lee KY, Chou YT, Pan ST, Wang YH. Evaluation of the diagnostic accuracy of bronchial brushing cytology in lung cancer: a meta-analysis. *Cancer Cytopathol*. 2021;129(9):739-749. doi:10.1002/cncy.22436
151. Chandrika S, Yarmus L. Recent developments in advanced diagnostic bronchoscopy. *Eur Respir Rev*. 2020;29(157):190184. doi:10.1183/16000617.0184-2019
152. Sehgal IS, Agarwal R, Dhooria S, Prasad KT, Aggarwal AN. Role of EBUS TBNA in staging of lung cancer: a clinician's perspective. *J Cytol*. 2019;36(1):61-64. doi:10.4103/joc.joc_172_18
153. Um SW, Kim HK, Jung SH, et al. Endobronchial ultrasound versus mediastinoscopy for mediastinal nodal staging of non-small-cell lung cancer. *J Thorac Oncol*. 2015;10(2):331-337. doi:10.1097/jto.0000000000000388
154. Detterbeck FC, Lewis SZ, Diekemper R, Addrizzo-Harris D, Alberts WM. Executive summary: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2013;143(5 suppl):7S-37S. doi:10.1378/chest.12-2377
155. Rivera MP, Mehta AC. Initial diagnosis of lung cancer: ACCP evidence-based clinical practice guidelines (2nd edition). *Chest*. 2007;132(3 suppl):131S-148S. doi:10.1378/chest.07-1357
156. Lee KH, Lim KY, Suh YJ, et al. Diagnostic accuracy of percutaneous transthoracic needle lung biopsies: a multicenter study. *Korean J Radiol*. 2019;20(8):1300-1310. doi:10.3348/kjr.2019.0189
157. Borelli C, Vergara D, Simeone A, et al. CT-guided transthoracic biopsy of pulmonary lesions: diagnostic versus nondiagnostic results. *Diagnostics (Basel)*. 2022;12(2):359. doi:10.3390/diagnostics12020359
158. Sihoe ADL, Hiranandani R, Wong H, Yeung ESL. Operating on a suspicious lung mass without a preoperative tissue diagnosis: pros and cons. *Eur J Cardiothorac Surg*. 2013;44(2):231-237. doi:10.1093/ejcts/ezs671
159. Pizzutilo EG, Pedrani M, Amatu A, et al. Liquid biopsy for small cell lung cancer either de novo or transformed: systematic review of different applications and meta-analysis. *Cancers (Basel)*. 2021;13(9):2265. doi:10.3390/cancers13092265
160. Mohan S, Foy V, Ayub M, et al. Profiling of circulating free DNA using targeted and genome-wide sequencing in patients with SCLC. *J Thorac Oncol*. 2020;15(2):216-230. doi:10.1016/j.jtho.2019.10.007
161. Farsad M. FDG PET/CT in the staging of lung cancer. *Curr Radiopharm*. 2020;13(3):195-203. doi:10.2174/1874471013666191223153755
162. Treadwell JR, Mitchell MD, Tsou A, Torigian D, Aggarwal C, Schoelles KM. *AHRQ Comparative Effectiveness Reviews. Imaging for the Pretreatment Staging of Small Cell Lung Cancer*. Agency for Healthcare Research and Quality (US); 2016.
163. Santos JC, Abreu MH, Santos MS, et al. Bone scintigraphy and PET-CT: a necessary alliance for bone metastasis detection in breast cancer [abstract]? *J Clin Oncol*. 2020;38(15 suppl):e13070. doi:10.1200/jco.2020.38.15_suppl.e13070
164. Tong E, McCullagh KL, Iv M. Advanced imaging of brain metastases: from augmenting visualization and improving diagnosis to evaluating treatment response. *Front Neurol*. 2020;11:270. doi:10.3389/fneur.2020.00270
165. Raso MG, Bota-Rabassedas N, Wistuba II. Pathology and classification of SCLC. *Cancers (Basel)*. 2021;13(4):820. doi:10.3390/cancers13040820
166. Sturgis CD, Nassar DL, D'Antonio JA, Raab SS. Cytologic features useful for distinguishing small cell from non-small cell carcinoma in bronchial brush and wash specimens. *Am J Clin Pathol*. 2000;114(2):197-202. doi:10.1309/8mqg-6xek-3x9l-a9xu
167. Nicholson SA, Beasley MB, Brambilla E, et al. Small cell lung carcinoma (SCLC): a clinicopathologic study of 100 cases with surgical specimens. *Am J Surg Pathol*. 2002;26(9):1184-1197. doi:10.1097/00000478-200209000-00009
168. Fisseler-Eckhoff A, Demes M. Neuroendocrine tumors of the lung. *Cancers (Basel)*. 2012;4(3):777-798. doi:10.3390/cancers4030777
169. Kaltsas G, Androulakis II, de Herder WW, Grossman AB. Paraneoplastic syndromes secondary to neuroendocrine tumours. *Endocr Relat Cancer*. 2010;17(3):R173-R193. doi:10.1677/erc-10-0024
170. National Lung Screening Trial Research Team; Aberle DR, Adams AM, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med*. 2011:365:395-409. doi:10.1056/NEJMoa1102873
171. Thomas A, Pattanayak P, Szabo E, Pinsky P. Characteristics and outcomes of small cell lung cancer detected by CT screening. *Chest*. 2018;154(6):1284-1290. doi:10.1016/j.chest.2018.07.029
172. Silva M, Galeone C, Sverzellati N, et al. Screening with low-dose computed tomography does not improve survival of small cell lung cancer. *J Thorac Oncol*. 2016;11(2):187-193. doi:10.1016/j.jtho.2015.10.014
173. Wender R, Fontham ET, Barrera E Jr, et al. American Cancer Society lung cancer screening guidelines. *CA Cancer J Clin*. 2013;63(2):107-117. doi:10.3322/caac.21172
174. Mathios D, Johansen JS, Cristiano S, et al. Detection and characterization of lung cancer using cell-free DNA fragmentomes. *Nat Commun*. 2021;12(1):5060. doi:10.1038/s41467-021-24994-w
175. Delfi Diagnostics. *Delfi Diagnostics Initiates 15,000-Patient Prospective Lung Cancer Screening Trial*. Delfi Diagnostics; 2022. Accessed December 7, 2022. https://www.prnewswire.com/news-releases/delfi-diagnostics-initiates-15-000-patient-prospective-lung-cancer-screening-trial-301542248.html
176. Grail. *Grail Announces Final Results From the PATHFINDER Multi-Cancer Early Detection Screening Study at ESMO Congress 2022*.

Grail; 2022. Accessed December 7, 2022. https://grail.com/press-releases/grail-announces-final-results-from-the-pathfinder-multi-cancer-early-detection-screening-study-at-esmo-congress-2022/
177. Parsons A, Daley A, Begh R, Aveyard P. Influence of smoking cessation after diagnosis of early stage lung cancer on prognosis: systematic review of observational studies with meta-analysis. *BMJ*. 2010;340(1):b5569. doi:10.1136/bmj.b5569
178. US Environmental Protection Agency (EPA). *A Citizen's Guide to Radon. The Guide to Protecting Yourself and Your Family from Radon*. EPA; 2016.
179. Mc Laughlin JP, Gutierrez-Villanueva JL, Perko T. Suggestions for improvements in national radon control strategies of member states which were developed as a requirement of EU Directive 2013/59 EURATOM. *Int J Environ Res Publ Health*. 2022;19(7):3805. doi:10.3390/ijerph19073805
180. Amin MB, Greene FL, Edge SB, et al. The eighth edition AJCC Cancer Staging Manual: continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. *CA Cancer J Clin*. 2017;67(2):93-99. doi:10.3322/caac.21388
181. Lim W, Ridge CA, Nicholson AG, Mirsadraee S. The 8th lung cancer TNM classification and clinical staging system: review of the changes and clinical implications. *Quant Imaging Med Surg*. 2018;8(7):709-718. doi:10.21037/qims.2018.08.02
182. Nicholson AG, Chansky K, Crowley J, et al. The International Association for the Study of Lung Cancer Lung Cancer Staging Project: proposals for the revision of the clinical and pathologic staging of small cell lung cancer in the forthcoming eighth edition of the TNM classification for lung cancer. *J Thorac Oncol*. 2016;11(3):300-311. doi:10.1016/j.jtho.2015.10.008
183. Micke P, Faldum A, Metz T, et al. Staging small cell lung cancer: Veterans Administration Lung Study Group versus International Association for the Study of Lung Cancer—what limits limited disease? *Lung Cancer*. 2002;37(3):271-276. doi:10.1016/s0169-5002(02)00072-7
184. Ganti AKP, Loo BW, Bassetti M, et al. Small Cell Lung Cancer, Version 2.2022, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Cancer Netw*. 2021;19(12):1441-1464. doi:10.6004/jnccn.2021.0058
185. Williams R, Eskandari N, Kendall A. Staging of small cell lung cancer (SCLC): comparison of two criteria by survival analysis [abstract]. *J Clin Oncol*. 2006;24(18 suppl):17030. doi:10.1200/jco.2006.24.18_suppl.17030
186. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol*. 1982;5(6):649-655. doi:10.1097/00000421-198212000-00014
187. Fox W, Scadding JG. Medical Research Council comparative trial of surgery and radiotherapy for primary treatment of small-celled or oat-celled carcinoma of bronchus. Ten-year follow-up. *Lancet*. 1973;2(7820):63-65. doi:10.1016/s0140-6736(73)93260-1
188. Lad T, Piantadosi S, Thomas P, Payne D, Ruckdeschel J, Giaccone G. A prospective randomized trial to determine the benefit of surgical resection of residual disease following response of small cell lung cancer to combination chemotherapy. *Chest*. 1994;106(6 suppl):320S-323S. doi:10.1378/chest.106.6.320s
189. Shepherd FA, Ginsberg RJ, Feld R, Evans WK, Johansen E. Surgical treatment for limited small-cell lung cancer. The University of Toronto Lung Oncology Group experience. *J Thorac Cardiovasc Surg*. 1991;101(3):385-393. doi:10.1016/s0022-5223(19)36720-0
190. Tsuchiya R, Suzuki K, Ichinose Y, et al. Phase II trial of postoperative adjuvant cisplatin and etoposide in patients with completely resected stage I–IIIa small cell lung cancer: the Japan Clinical Oncology Lung Cancer Study Group Trial (JCOG9101). *J Thorac Cardiovasc Surg*. 2005;129(5):977-983. doi:10.1016/j.jtcvs.2004.05.030
191. Liu T, Chen Z, Dang J, Li G. The role of surgery in stage I to III small cell lung cancer: a systematic review and meta-analysis. *PLoS One*. 2018;13(12):e0210001. doi:10.1371/journal.pone.0210001
192. Combs SE, Hancock JG, Boffa DJ, Decker RH, Detterbeck FC, Kim AW. Bolstering the case for lobectomy in stages I, II, and IIIA small-cell lung cancer using the National Cancer Data Base. *J Thorac Oncol*. 2015;10(2):316-323. doi:10.1097/jto.0000000000000402
193. Yang CFJ, Chan DY, Speicher PJ, et al. Role of adjuvant therapy in a population-based cohort of patients with early-stage small-cell lung cancer. *J Clin Oncol*. 2016;34(10):1057-1064. doi:10.1200/jco.2015.63.8171
194. Pignon JP, Tribodet H, Scagliotti GV, et al. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. *J Clin Oncol*. 2008;26(21):3552-3559. doi:10.1200/jco.2007.13.9030
195. Rami-Porta R, Wittekind C, Goldstraw P. Complete resection in lung cancer surgery: proposed definition. *Lung Cancer*. 2005;49(1):25-33. doi:10.1016/j.lungcan.2005.01.001
196. Edwards JG, Chansky K, Van Schil P, et al. The IASLC Lung Cancer Staging Project: analysis of resection margin status and proposals for residual tumor descriptors for non–small cell lung cancer. *J Thorac Oncol*. 2020;15(3):344-359. doi:10.1016/j.jtho.2019.10.019
197. Varlotto JM, Recht A, Flickinger JC, Medford-Davis LN, Dyer AM, DeCamp MM. Lobectomy leads to optimal survival in early-stage small cell lung cancer: a retrospective analysis. *J Thorac Cardiovasc Surg*. 2011;142(3):538-546. doi:10.1016/j.jtcvs.2010.11.062
198. Rami-Porta R, Wittekind C, Goldstraw P. Complete resection in lung cancer surgery: from definition to validation and beyond. *J Thorac Oncol*. 2020;15(12):1815-1818. doi:10.1016/j.jtho.2020.09.006
199. Zhang S, Sun X, Sun L, Xiong Z, Ma J, Han C. Benefits of postoperative thoracic radiotherapy for small cell lung cancer subdivided by lymph node stage: a systematic review and meta-analysis. *J Thorac Dis*. 2017;9(5):1257-1264. doi:10.21037/jtd.2017.03.174
200. Schreiber D, Rineer J, Weedon J, et al. Survival outcomes with the use of surgery in limited-stage small cell lung cancer: should its role be re-evaluated? *Cancer*. 2010;116(5):1350-1357. doi:10.1002/cncr.24853
201. Xu J, Yang H, Fu X, et al. Prophylactic cranial irradiation for patients with surgically resected small cell lung cancer. *J Thorac Oncol*. 2017;12(2):347-353. doi:10.1016/j.jtho.2016.09.133
202. Bischof M, Debus J, Herfarth K, et al. Surgery and chemotherapy for small cell lung cancer in stages I–II with or without radiotherapy. *Strahlenther Onkol*. 2007;183(12):679-684. doi:10.1007/s00066-007-1740-z
203. Yang Y, Zhang D, Zhou X, et al. Prophylactic cranial irradiation in resected small cell lung cancer: a systematic review with meta-analysis. *J Cancer*. 2018;9(2):433-439. doi:10.7150/jca.21465
204. Rusthoven CG, Kavanagh BD. Prophylactic cranial irradiation (PCI) versus active MRI surveillance for small cell lung cancer: the case for equipoise. *J Thorac Oncol*. 2017;12:1746-1754. doi:10.1016/j.jtho.2017.08.016
205. Hoda MA, Klikovits T, Klepetko W. Controversies in oncology: surgery for small cell lung cancer? It's time to rethink the case. *ESMO Open*. 2018;3:e000366. doi:10.1136/esmoopen-2018-000366
206. Zhang C, Li C, Shang X, Lin J, Wang H. Surgery as a potential treatment option for patients with stage III small-cell lung cancer: a propensity score matching analysis. *Front Oncol*. 2019;9:1339. doi:10.3389/fonc.2019.01339
207. Mascaux C, Paesmans M, Berghmans T, et al. A systematic review of the role of etoposide and cisplatin in the chemotherapy of small cell lung cancer with methodology assessment and meta-analysis. *Lung Cancer*. 2000;30(1):23-36. doi:10.1016/s0169-5002(00)00127-6
208. Fink TH, Huber RM, Heigener DF, et al. Topotecan/cisplatin compared with cisplatin/etoposide as first-line treatment for patients with extensive disease small-cell lung cancer: final results of

a randomized phase III trial. *J Thorac Oncol*. 2012;7(9):1432-1439. doi:10.1097/jto.0b013e318260de75
209. Hatfield LA, Huskamp HA, Lamont EB. Survival and toxicity after cisplatin plus etoposide versus carboplatin plus etoposide for extensive-stage small-cell lung cancer in elderly patients. *J Oncol Pract*. 2016;12(7):666-673. doi:10.1200/jop.2016.012492
210. Bishop JF, Raghavan D, Stuart-Harris R, et al. Carboplatin (CBDCA, JM-8) and VP-16-213 in previously untreated patients with small-cell lung cancer. *J Clin Oncol*. 1987;5(10):1574-1578. doi:10.1200/jco.1987.5.10.1574
211. Rossi A, Di Maio M, Chiodini P, et al. Carboplatin- or cisplatin-based chemotherapy in first-line treatment of small-cell lung cancer: the COCIS meta-analysis of individual patient data. *J Clin Oncol*. 2012;30(14):1692-1698. doi:10.1200/jco.2011.40.4905
212. Daly ME, Ismaila N, Decker RH, et al. Radiation therapy for small-cell lung cancer: ASCO guideline endorsement of an ASTRO guideline. *J Clin Oncol*. 2021;39(8):931-939. doi:10.1200/jco.20.03364
213. Bunn PA Jr, Lichter AS, Makuch RW, et al. Chemotherapy alone or chemotherapy with chest radiation therapy in limited stage small cell lung cancer. A prospective, randomized trial. *Ann Intern Med*. 1987;106(5):655-662. doi:10.7326/0003-4819-106-5-655
214. Corso CD, Rutter CE, Park HS, et al. Role of chemoradiotherapy in elderly patients with limited-stage small-cell lung Cancer. *J Clin Oncol*. 2015;33(36):4240-4246. doi:10.1200/jco.2015.62.4270
215. Christodoulou M, Blackhall F, Mistry H, et al. Compliance and outcome of elderly patients treated in the concurrent once-daily versus twice-daily radiotherapy (CONVERT) trial. *J Thorac Oncol*. 2019;14(1):63-71. doi:10.1016/j.jtho.2018.09.027
216. Turrisi AT 3rd, Kim K, Blum R, et al. Twice-daily compared with once-daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide. *N Engl J Med*. 1999;340(4):265-271. doi:10.1056/nejm199901283400403
217. Faivre-Finn C, Snee M, Ashcroft L, et al. Concurrent once-daily versus twice-daily chemoradiotherapy in patients with limited-stage small-cell lung cancer (CONVERT): an open-label, phase 3, randomised, superiority trial. *Lancet Oncol*. 2017;18(8):1116-1125. doi:10.1016/s1470-2045(17)30318-2
218. Glatzer M, Schmid S, Radovic M, Früh M, Putora PM. The role of radiation therapy in the management of small cell lung cancer. *Breathe (Sheff)*. 2017;13(4):e87-e94. doi:10.1183/20734735.009617
219. Levy A, Le Péchoux C, Faivre-Finn C. Twice-daily chemo-radiotherapy in limited-stage small-cell lung cancer. *Lancet Oncol*. 2021;22(6):e220. doi:10.1016/s1470-2045(21)00255-2
220. Murray N, Coy P, Pater JL, et al. Importance of timing for thoracic irradiation in the combined modality treatment of limited-stage small-cell lung cancer. The National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol*. 1993;11(2):336-344. doi:10.1200/jco.1993.11.2.336
221. Spiro SG, James LE, Rudd RM, et al. Early compared with late radiotherapy in combined modality treatment for limited disease small-cell lung cancer: a London Lung Cancer Group multicenter randomized clinical trial and meta-analysis. *J Clin Oncol*. 2006;24:3823-3830. doi:10.1200/jco.2005.05.3181
222. Pujol JL, Carestia L, Daurès JP. Is there a case for cisplatin in the treatment of small-cell lung cancer? A meta-analysis of randomized trials of a cisplatin-containing regimen versus a regimen without this alkylating agent. *Br J Cancer*. 2000;83(1):8-15. doi:10.1054/bjoc.2000.1164
223. Sundstrøm S, Bremnes RM, Kaasa S, et al. Cisplatin and etoposide regimen is superior to cyclophosphamide, epirubicin, and vincristine regimen in small-cell lung cancer: results from a randomized phase III trial with 5 years' follow-up. *J Clin Oncol*. 2002;20(24):4665-4672. doi:10.1200/jco.2002.12.111
224. Aupérin A, Arriagada R, Pignon JP, et al. Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. Prophylactic Cranial Irradiation Overview Collaborative Group. *N Engl J Med*. 1999;341(7):476-484. doi:10.1056/nejm199908123410703
225. Scotti V, Meattini I, Franzese C, et al. Radiotherapy timing in the treatment of limited-stage small cell lung cancer: the impact of thoracic and brain irradiation on survival. *Tumori*. 2014;100(3):289-295. doi:10.1177/1578.17206
226. Farris MK, Wheless WH, Hughes RT, et al. Limited-stage small cell lung cancer: is prophylactic cranial irradiation necessary? *Pract Radiat Oncol*. 2019;9(6):e599-e607. doi:10.1016/j.prro.2019.06.014
227. Rodríguez de Dios N, Couñago F, Murcia-Mejía M, et al. Randomized phase III trial of prophylactic cranial irradiation with or without hippocampal avoidance for small-cell lung cancer (PREMER): a GICOR-GOECP-SEOR study. *J Clin Oncol*. 2021;39(28):3118-3127. doi:10.1200/jco.21.00639
228. Brown PD, Pugh S, Laack NN, et al. Memantine for the prevention of cognitive dysfunction in patients receiving whole-brain radiotherapy: a randomized, double-blind, placebo-controlled trial. *Neuro Oncol*. 2013;15(10):1429-1437. doi:10.1093/neuonc/not114
229. Rapp SR, Case LD, Peiffer A, et al. Donepezil for irradiated brain tumor survivors: a phase III randomized placebo-controlled clinical trial. *J Clin Oncol*. 2015;33(15):1653-1659. doi:10.1200/jco.2014.58.4508
230. Berta J, Rózsás A, Megyesfalvi Z, Ostoros G, Döme B. Thoracic irradiation as consolidation therapy in patients with extensive-stage small cell lung cancer. *Curr Opin Oncol*. 2023;35(1):54-60. doi:10.1097/cco.0000000000000911
231. Slotman BJ, van Tinteren H, Praag JO, et al. Use of thoracic radiotherapy for extensive stage small-cell lung cancer: a phase 3 randomised controlled trial. *Lancet*. 2015;385(9962):36-42. doi:10.1016/s0140-6736(14)61085-0
232. Slotman BJ, van Tinteren H, Praag JO, et al. Radiotherapy for extensive stage small-cell lung cancer—authors' reply. *Lancet*. 2015;385(9975):1292-1293. doi:10.1016/s0140-6736(15)60679-1
233. Jeremic B, Shibamoto Y, Nikolic N, et al. Role of radiation therapy in the combined-modality treatment of patients with extensive disease small-cell lung cancer: a randomized study. *J Clin Oncol*. 1999;17(7):2092-2099. doi:10.1200/jco.1999.17.7.2092
234. Yee D, Butts C, Reiman A, et al. Clinical trial of post-chemotherapy consolidation thoracic radiotherapy for extensive-stage small cell lung cancer. *Radiother Oncol*. 2012;102(2):234-238. doi:10.1016/j.radonc.2011.08.042
235. Tian Y, Ma J, Jing X, et al. Radiation therapy for extensive-stage small-cell lung cancer in the era of immunotherapy. *Cancer Lett*. 2022;541:215719. doi:10.1016/j.canlet.2022.215719
236. Meert AP, Paesmans M, Berghmans T, et al. Prophylactic cranial irradiation in small cell lung cancer: a systematic review of the literature with meta-analysis. *BMC Cancer*. 2001;1:5. doi:10.1186/1471-2407-1-5
237. Arriagada R, Le Chevalier T, Rivière A, et al. Patterns of failure after prophylactic cranial irradiation in small-cell lung cancer: analysis of 505 randomized patients. *Ann Oncol*. 2002;13(5):748-754. doi:10.1093/annonc/mdf123
238. Slotman B, Faivre-Finn C, Kramer G, et al. Prophylactic cranial irradiation in extensive small-cell lung cancer. *N Engl J Med*. 2007;357(7):664-672. doi:10.1056/nejmoa071780
239. Eaton BR, Kim S, Marcus DM, et al. Effect of prophylactic cranial irradiation on survival in elderly patients with limited-stage small cell lung cancer. *Cancer*. 2013;119(21):3753-3760. doi:10.1002/cncr.28267
240. Takahashi T, Yamanaka T, Seto T, et al. Prophylactic cranial irradiation versus observation in patients with extensive-disease small-cell

lung cancer: a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol*. 2017;18(5):663-671. doi:10.1016/s1470-2045(17)30230-9

241. Yang CJ, Chan DY, Shah SA, et al. Long-term survival after surgery compared with concurrent chemoradiation for node-negative small cell lung cancer. *Ann Surg*. 2018;268(6):1105-1112. doi:10.1097/sla.0000000000002287
242. Videtic GM, Stephans KL, Woody NM, et al. Stereotactic body radiation therapy-based treatment model for stage I medically inoperable small cell lung cancer. *Pract Radiat Oncol*. 2013;3(4):301-306. doi:10.1016/j.prro.2012.10.003
243. Liu SV, Reck M, Mansfield AS, et al. Updated overall survival and PD-L1 subgroup analysis of patients with extensive-stage small-cell lung cancer treated with atezolizumab, carboplatin, and etoposide (IMpower133). *J Clin Oncol*. 2021;39(6):619-630. doi:10.1200/jco.20.01055
244. Goldman JW, Dvorkin M, Chen Y, et al. Durvalumab, with or without tremelimumab, plus platinum-etoposide versus platinum-etoposide alone in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): updated results from a randomised, controlled, open-label, phase 3 trial. *Lancet Oncol*. 2021;22(1):51-65. doi:10.1016/s1470-2045(20)30539-8
245. Mathieu L, Shah S, Pai-Scherf L, et al. FDA approval summary: atezolizumab and durvalumab in combination with platinum-based chemotherapy in extensive stage small cell lung cancer. *Oncologist*. 2021;26(5):433-438. doi:10.1002/onco.13752
246. Paz-Ares L, Chen Y, Reinmuth N, et al. Durvalumab, with or without tremelimumab, plus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer: 3-year overall survival update from CASPIAN. *ESMO Open*. 2022;7(2):100408. doi:10.1016/j.esmoop.2022.100408
247. Donlon NE, Power R, Hayes C, Reynolds JV, Lysaght J. Radiotherapy, immunotherapy, and the tumour microenvironment: turning an immunosuppressive milieu into a therapeutic opportunity. *Cancer Lett*. 2021;502:84-96. doi:10.1016/j.canlet.2020.12.045
248. Diamond BH, Verma N, Shukla UC, Park HS, Koffer PP. Consolidative thoracic radiation therapy after first-line chemotherapy and immunotherapy in extensive-stage small cell lung cancer: a multi-institutional case series. *Adv Radiat Oncol*. 2022;7(2):100883. doi:10.1016/j.adro.2021.100883
249. Welsh JW, Heymach JV, Guo C, et al. Phase 1/2 trial of pembrolizumab and concurrent chemoradiation therapy for limited-stage SCLC. *J Thorac Oncol*. 2020;15(12):1919-1927. doi:10.1016/j.jtho.2020.08.022
250. Peters S, Pujol JL, Dafni U, et al. Consolidation nivolumab and ipilimumab versus observation in limited-disease small-cell lung cancer after chemo-radiotherapy—results from the randomised phase II ETOP/IFCT 4–12 STIMULI trial. *Ann Oncol*. 2022;33(1):67-79. doi:10.1016/j.annonc.2021.09.011
251. Owonikoko TK, Behera M, Chen Z, et al. A systematic analysis of efficacy of second-line chemotherapy in sensitive and refractory small-cell lung cancer. *J Thorac Oncol*. 2012;7(5):866-872. doi:10.1097/jto.0b013e31824c7f4b
252. 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(2):286-299. doi:10.1016/j.ccell.2017.01.006
253. Cañadas I, Rojo F, Taus Á, et al. Targeting epithelial-to-mesenchymal transition with Met inhibitors reverts chemoresistance in small cell lung cancer. *Clin Cancer Res*. 2014;20(4):938-950. doi:10.1158/1078-0432.ccr-13-1330
254. Chen P, Kuang P, Wang L, et al. Mechanisms of drugs-resistance in small cell lung cancer: DNA-related, RNA-related, apoptosis-related, drug accumulation and metabolism procedure. *Transl Lung Cancer Res*. 2020;9(3):768-786. doi:10.21037/tlcr-19-547
255. Song Y, Sun Y, Lei Y, Yang K, Tang R. YAP1 promotes multidrug resistance of small cell lung cancer by CD74-related signaling pathways. *Cancer Med*. 2020;9(1):259-268. doi:10.1002/cam4.2668
256. Dingemans AC, Früh M, Ardizzoni A, et al. Small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up(☆). *Ann Oncol*. 2021;32(7):839-853. doi:10.1016/j.annonc.2021.03.207
257. Eckardt JR, von Pawel J, Pujol J-L, et al. Phase III study of oral compared with intravenous topotecan as second-line therapy in small-cell lung cancer. *J Clin Oncol*. 2007;25(15):2086-2092. doi:10.1200/jco.2006.08.3998
258. von Pawel J, Schiller JH, Shepherd FA, et al. Topotecan versus cyclophosphamide, doxorubicin, and vincristine for the treatment of recurrent small-cell lung cancer. *J Clin Oncol*. 1999;17(2):658-667. doi:10.1200/jco.1999.17.2.658
259. Das M, Padda SK, Weiss J, Owonikoko TK. Advances in treatment of recurrent small cell lung cancer (SCLC): insights for optimizing patient outcomes from an expert roundtable discussion. *Adv Ther*. 2021;38(11):5431-5451. doi:10.1007/s12325-021-01909-1
260. Kondo R, Watanabe S, Shoji S, et al. A phase II study of irinotecan for patients with previously treated small-cell lung cancer. *Oncology*. 2018;94(4):223-232. doi:10.1159/000486622
261. Trigo J, Subbiah V, Besse B, et al. Lurbinectedin as second-line treatment for patients with small-cell lung cancer: a single-arm, open-label, phase 2 basket trial. *Lancet Oncol*. 2020;21(5):645-654. doi:10.1016/s1470-2045(20)30068-1
262. Aix SP, Ciuleanu TE, Navarro A, et al. Combination lurbinectedin and doxorubicin versus physician's choice of chemotherapy in patients with relapsed small-cell lung cancer (ATLANTIS): a multicentre, randomised, open-label, phase 3 trial. *Lancet Respir Med*. 2023;11(1):74-86. doi:10.1016/s2213-2600(22)00309-5
263. 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(3):426-435. doi:10.1016/j.jtho.2019.10.004
264. 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(4):618-627. doi:10.1016/j.jtho.2019.12.109
265. Owonikoko TK, Park K, Govindan R, et al. Nivolumab and ipilimumab as maintenance therapy in extensive-disease small-cell lung cancer: CheckMate 451. *J Clin Oncol*. 2021;39(12):1349-1359. doi:10.1200/jco.20.02212
266. Spigel DR, Vicente D, Ciuleanu TE, et al. Second-line nivolumab in relapsed small-cell lung cancer: CheckMate 331(☆). *Ann Oncol*. 2021;32(5):631-641. doi:10.1016/j.annonc.2021.01.071
267. Rudin CM, Awad MM, Navarro A, et al. Pembrolizumab or placebo plus etoposide and platinum as first-line therapy for extensive-stage small-cell lung cancer: randomized, double-blind, phase III KEYNOTE-604 study. *J Clin Oncol*. 2020;38(21):2369-2379. doi:10.1200/jco.20.00793
268. American Society of Clinical Oncology (ASCO). Nivolumab Indication in Small Cell Lung Cancer Withdrawn in U.S. Market. ASCO; 2021.
269. American Society of Clinical Oncology (ASCO). Pembrolizumab's Indication in Small Cell Lung Cancer Is Withdrawn. ASCO; 2021.
270. Coleman N, Zhang B, Byers LA, Yap TA. The role of Schlafen 11 (SLFN11) as a predictive biomarker for targeting the DNA damage response. *Br J Cancer*. 2021;124(5):857-859. doi:10.1038/s41416-020-01202-y
271. Kundu K, Cardnell RJ, Zhang B, et al. SLFN11 biomarker status predicts response to lurbinectedin as a single agent and in

combination with ATR inhibition in small cell lung cancer. *Transl Lung Cancer Res*. 2021;10(11):4095-4105. doi:10.21037/tlcr-21-437

272. Pietanza MC, Waqar SN, Krug LM, et al. Randomized, double-blind, phase II study of temozolomide in combination with either veliparib or placebo in patients with relapsed-sensitive or refractory small-cell lung cancer. *J Clin Oncol*. 2018;36(23):2386-2394. doi:10.1200/jco.2018.77.7672
273. Goodman AM, Kato S, Bazhenova L, et al. Tumor mutational burden as an independent predictor of response to immunotherapy in diverse cancers. *Mol Cancer Ther*. 2017;16(11):2598-2608. doi:10.1158/1535-7163.mct-17-0386
274. Hellmann MD, Callahan MK, Awad MM, et al. Tumor mutational burden and efficacy of nivolumab monotherapy and in combination with ipilimumab in small-cell lung cancer. *Cancer Cell*. 2018;33(5):853-861.e854. doi:10.1016/j.ccell.2018.04.001
275. Yu H, Batenchuk C, Badzio A, et al. PD-L1 expression by two complementary diagnostic assays and mRNA in situ hybridization in small cell lung cancer. *J Thorac Oncol*. 2017;12(1):110-120. doi:10.1016/j.jtho.2016.09.002
276. Byers LA, Wang J, Nilsson MB, et al. Proteomic profiling identifies dysregulated pathways in small cell lung cancer and novel therapeutic targets including PARP1. *Cancer Discov*. 2012;2(9):798-811. doi:10.1158/2159-8290.cd-12-0112
277. Calabrese CR, Almassy R, Barton S, et al. Anticancer chemosensitization and radiosensitization by the novel poly(ADP-ribose) polymerase-1 inhibitor AG14361. *J Natl Cancer Inst*. 2004;96(1):56-67. doi:10.1093/jnci/djh005
278. Owonikoko TK, Dahlberg SE, Sica GL, et al. Randomized phase II trial of cisplatin and etoposide in combination with veliparib or placebo for extensive-stage small-cell lung cancer: ECOG-ACRIN 2511 study. *J Clin Oncol*. 2019;37(3):222-229. doi:10.1200/jco.18.00264
279. Owonikoko TK, Dahlberg SE, Khan SA, et al. A phase 1 safety study of veliparib combined with cisplatin and etoposide in extensive stage small cell lung cancer: a trial of the ECOG-ACRIN Cancer Research Group (E2511). *Lung Cancer*. 2015;89:66-70. doi:10.1016/j.lungcan.2015.04.015
280. Owen DH, Giffin MJ, Bailis JM, Smit MAD, Carbone DP, He K. DLL3: an emerging target in small cell lung cancer. *J Hematol Oncol*. 2019;12(1):61. doi:10.1186/s13045-019-0745-2
281. Rudin CM, Pietanza MC, Bauer TM, et al. Rovalpituzumab tesirine, a DLL3-targeted antibody-drug conjugate, in recurrent small-cell lung cancer: a first-in-human, first-in-class, open-label, phase 1 study. *Lancet Oncol*. 2017;18:42-51. doi:10.1016/s1470-2045(16)30565-4
282. Morgensztern D, Besse B, Greillier L, et al. Efficacy and safety of rovalpituzumab 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(23):6958-6966. doi:10.1158/1078-0432.ccr-19-1133
283. Blackhall F, Jao K, Greillier L, et al. Efficacy and safety of rovalpituzumab tesirine compared with topotecan as second-line therapy in DLL3-high SCLC: results from the phase 3 TAHOE study. *J Thorac Oncol*. 2021;16(9):1547-1558. doi:10.1016/j.jtho.2021.02.009
284. Lochmann TL, Bouck YM, Faber AC. BCL-2 inhibition is a promising therapeutic strategy for small cell lung cancer. *Oncoscience*. 2018;5(7-8):218-219. doi:10.18632/oncoscience.455
285. Rudin CM, Hann CL, Garon EB, et al. Phase II study of single-agent navitoclax (ABT-263) and biomarker correlates in patients with relapsed small cell lung cancer. *Clin Cancer Res*. 2012;18(11):3163-3169. doi:10.1158/1078-0432.ccr-11-3090
286. Lochmann TL, Floros KV, Naseri M, et al. Venetoclax is effective in small-cell lung cancers with high BCL-2 expression. *Clin Cancer Res*. 2018;24(2):360-369. doi:10.1158/1078-0432.ccr-17-1606
287. Taniguchi H, Sen T, Rudin CM. Targeted therapies and biomarkers in small cell lung cancer. *Front Oncol*. 2020;10:741. doi:10.3389/fonc.2020.00741
288. 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(2):274-287. doi:10.1016/j.jtho.2019.10.013
289. Kawahara M, Ushijima S, Kamimori T, et al. Second primary tumours in more than 2-year disease-free survivors of small-cell lung cancer in Japan: the role of smoking cessation. *Br J Cancer*. 1998;78(3):409-412. doi:10.1038/bjc.1998.507
290. Kono M, Allen PK, Lin SH, et al. Incidence of second malignancy after successful treatment of limited-stage small-cell lung cancer and its effects on survival. *J Thorac Oncol*. 2017;12(11):1696-1703. doi:10.1016/j.jtho.2017.07.030
291. Richardson GE, Tucker MA, Venzon DJ, et al. Smoking cessation after successful treatment of small-cell lung cancer is associated with fewer smoking-related second primary cancers. *Ann Intern Med*. 1993;119(5):383-390. doi:10.7326/0003-4819-119-5-199309010-00006
292. Shields PG, Bierut L, Arenberg D, et al. Smoking Cessation, Version 3.2022, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Cancer Netw*. 2023;21(3):297-322. doi:10.6004/jnccn.2023.0013
293. American Society of Clinical Oncology (ASCO). Surveillance for Recurrence and Second Cancers: Guidelines and Caveats; ASCO; 2016.
294. Chauvin JM, Zarour HM. TIGIT in cancer immunotherapy. *J Immunother Cancer*. 2020;8(2):e000957. doi:10.1136/jitc-2020-000957
295. Rudin CM, Liu SV, Lu S, et al. SKYSCRAPER-02: primary results of a phase III, randomized, double-blind, placebo-controlled study of atezolizumab (atezo) + carboplatin + etoposide (CE) with or without tiragolumab (tira) in patients (pts) with untreated extensive-stage small cell lung cancer (ES-SCLC) [abstract]. *J Clin Oncol*. 2022;40(17 suppl):LBA8507. doi:10.1200/jco.2022.40.17_suppl.lba8507
296. Mulroy MC, Cummings AL, Mendenhall MA, et al. Circulating tumor DNA (ctDNA) mutations may predict treatment response in extensive-stage small cell lung cancer (ES-SCLC) treated with talazoparib and temozolomide (TMZ) [abstract]. *J Clin Oncol*. 2021;39(15 suppl):8564. doi:10.1200/jco.2021.39.15_suppl.8564
297. Chauhan A, Kolesar J, Yan D, et al. OA07.03 A phase II study of frontline rucaparib + nivolumab in platinum sensitive ES SCLC: interim analysis [abstract]. *J Thorac Oncol*. 2021;16(10):S859. doi:10.1016/j.jtho.2021.08.056
298. Borghaei H, Paz-Ares L, Johnson M, et al. OA12.05 Phase 1 updated exploration and first expansion data for DLL3-targeted T-cell engager tarlatamab in small cell lung cancer [abstract]. *J Thorac Oncol*. 2022;17(9 suppl):S33. doi:10.1016/j.jtho.2022.07.062
299. Johnson ML, Dy GK, Mamdani H, et al. Interim results of an ongoing phase 1/2a study of HPN328, a tri-specific, half-life extended, DLL3-targeting, T-cell engager, in patients with small cell lung cancer and other neuroendocrine cancers [abstract]. *J Clin Oncol*. 2022;40(16 suppl):8566. doi:10.1200/jco.2022.40.16_suppl.8566
300. Wermke M, Felip E, Gambardella V, et al. Phase I trial of the DLL3/CD3 bispecific T-cell engager BI 764532 in DLL3-positive small-cell lung cancer and neuroendocrine carcinomas. *Future Oncol*. 2022;18(24):2639-2649. doi:10.2217/fon-2022-0196
301. Byers L, Heymach J, Gibbons D, et al. 697 A phase 1 study of AMG 119, a DLL3-targeting, chimeric antigen receptor (CAR) T cell therapy, in relapsed/refractory small cell lung cancer (SCLC) [abstract]. *J Immunother Cancer*. 2022;10:A728.
302. Weiss JM, Csoszi T, Maglakelidze M, et al. Myelopreservation with the CDK4/6 inhibitor trilaciclib in patients with small-cell lung cancer receiving first-line chemotherapy: a phase Ib/randomized phase II trial. *Ann Oncol*. 2019;30(10):1613-1621. doi:10.1093/annonc/mdz278

303. Spigel DR, Townley PM, Waterhouse DM, et al. Randomized phase II study of bevacizumab in combination with chemotherapy in previously untreated extensive-stage small-cell lung cancer: results from the SALUTE trial. *J Clin Oncol*. 2011;29(16):2215-2222. doi:10.1200/jco.2010.29.3423
304. Andrini E, Lamberti G, Mazzoni F, et al. A phase II, open-label, single-arm trial of carboplatin plus etoposide with bevacizumab and atezolizumab in patients with extended-stage small-cell lung cancer (CeLEBrATE study): background, design and rationale. *Future Oncol*. 2022;18(7):771-779. doi:10.2217/fon-2021-1027
305. Meijer JJ, Leonetti A, Airò G, et al. Small cell lung cancer: novel treatments beyond immunotherapy. *Semin Cancer Biol*. 2022;86:376-385. doi:10.1016/j.semcancer.2022.05.004
306. Chemi F, Pearce SP, Clipson A, et al. cfDNA methylome profiling for detection and subtyping of small cell lung cancers. *Nat Cancer*. 2022;3(10):1260-1270. doi:10.1038/s43018-022-00415-9
307. Heeke S, Gay CM, Estecio MR, et al. MA01.03 Exploiting DNA methylation for classification of SCLC subtypes from liquid biopsies using a robust machine learning approach [abstract]. *J Thorac Oncol*. 2022;17(9 suppl):S43. doi:10.1016/j.jtho.2022.07.076
308. Kim DW, Kim KC, Kim KB, Dunn CT, Park KS. Transcriptional deregulation underlying the pathogenesis of small cell lung cancer. *Transl Lung Cancer Res*. 2018;7(1):4-20. doi:10.21037/tlcr.2017.10.07
309. Jia D, Augert A, Kim DW, et al. Crebbp loss drives small cell lung cancer and increases sensitivity to HDAC inhibition. *Cancer Discov*. 2018;8(11):1422-1437. doi:10.1158/2159-8290.cd-18-0385
310. Llombart V, Mansour MR. Therapeutic targeting of "undruggable" MYC. *EBioMedicine*. 2022;75:103756. doi:10.1016/j.ebiom.2021.103756
311. Shibata M, Ham K, Hoque MO. A time for YAP1: tumorigenesis, immunosuppression and targeted therapy. *Int J Cancer*. 2018;143(9):2133-2144. doi:10.1002/ijc.31561
312. Green RA, Humphrey E, Close H, Patno ME. Alkylating agents in bronchogenic carcinoma. *Am J Med*. 1969;46(4):516-525. doi:10.1016/0002-9343(69)90071-0
313. Miller AB, Fox W, Tall R. Five-year follow-up of the Medical Research Council comparative trial of surgery and radiotherapy for the primary treatment of small-celled or oat-celled carcinoma of the bronchus. *Lancet*. 1969;2(7619):501-505. doi:10.1016/s0140-6736(69)90212-8
314. Bishop JF. Carboplatin/etoposide in small cell lung cancer. *Oncology*. 1992;49(suppl 1):11-17. discussion 17-18. doi:10.1159/000227105
315. Borges M, Linnoila RI, van de Velde HJ, et al. An achaete-scute homologue essential for neuroendocrine differentiation in the lung. *Nature*. 1997;386(6627):852-855. doi:10.1038/386852a0
316. Kularatne BY, Lorigan P, Browne S, Suvarna SK, Smith MO, Lawry J. Monitoring tumour cells in the peripheral blood of small cell lung cancer patients. *Cytometry*. 2002;50(3):160-167. doi:10.1002/cyto.10071

How to cite this article: Megyesfalvi Z, Gay CM, Popper H, et al. Clinical insights into small cell lung cancer: tumor heterogeneity, diagnosis, therapy, and future directions. *CA Cancer J Clin*. 2023;73(6):620-652. doi:10.3322/caac.21785