

Review

Transformation of NSCLC to SCLC: Insights into Molecular Alterations, Tumor Origin, and Therapeutic Advancements

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Simple Summary

Small-cell lung cancer (SCLC) is an aggressive neuroendocrine tumor characterized by limited treatment options and unfavorable survival outcomes. Recent studies indicate that certain non-small-cell lung cancers (NSCLC), especially those undergoing treatment with tyrosine kinase inhibitors or immunotherapy, may undergo transformation into SCLC as a means of developing acquired therapeutic resistance. Given the limitations of current treatment options, it is crucial to investigate the biological mechanisms underlying this transformation to facilitate the development of more effective therapies. Therefore, a deeper understanding of the molecular drivers that trigger this phenotypic switch is crucial for effective targeted therapeutic approaches.

Abstract

Small-cell lung cancer (SCLC) is a recalcitrant form of cancer, accounting for 15% of lung cancer cases worldwide. In recent years, the histological transformation from non-small-cell lung cancer (NSCLC) to SCLC has become a significant mechanism of acquired resistance, especially in patients undergoing treatment with tyrosine kinase inhibitors (TKIs) or immunotherapy. Although there is growing clinical understanding, the crucial biological mechanisms that drive this phenotypic switch are still not fully understood. Transformed SCLC (T-SCLC) seems to exhibit differences from de novo SCLC regarding molecular characteristics and tumor microenvironment, indicating unique evolutionary paths. While traditional chemotherapy has been the main treatment method after transformation, patient outcomes continue to be unsatisfactory, highlighting the necessity for a more profound mechanistic insight and the development of more effective treatments.

Keywords: transformed SCLC (T-SCLC); tyrosine kinase inhibitors (TKIs); immunotherapy; *EGFR* mutation



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1. Introduction

Lung cancer represents the most common type of malignant cancer and the primary cause of cancer-related deaths globally [1]. As reported by GLOBECAN 2022, lung cancer represented about 12.4% of all diagnosed cancers and 18.7% of deaths associated with cancer [1]. Lung cancer is categorized into two histological subtypes: NSCLC and SCLC [2,3]. According to the 2021 World Health Organization (WHO) Classification of

Thoracic Tumours, SCLC is currently classified within the broader category of pulmonary neuroendocrine neoplasms (NENs), together with typical carcinoid, atypical carcinoid, and large-cell neuroendocrine carcinoma (LCNEC). Nevertheless, the historical NSCLC–SCLC classification remains widely used in clinical practice [4]. NSCLC represents 80% of lung cancer cases and encompasses subtypes including lung adenocarcinoma (LUAD), lung squamous cell carcinoma (LUSC), and large-cell carcinoma (LCC) [2,5,6]. Although LUAD and LUSC are both classified as NSCLC, they are biologically distinct malignancies with different cells of origin, molecular characteristics, and clinical behavior. LUAD is thought to arise predominantly from alveolar epithelial cells and is frequently driven by oncogenic alterations involving *EGFR*, *KRAS*, *ALK*, *ROS1*, and *BRAF*, whereas LUSC is believed to originate primarily from basal cells of the bronchial epithelium and is more commonly characterized by alterations involving *TP53*, *CDKN2A*, *PIK3CA*, *FGFR1*, and *SOX2* [7,8]. Importantly, histologic transformation to SCLC has been reported predominantly in LUAD, particularly in *EGFR*-mutant tumors receiving targeted therapy. Conversely, SCLC represents approximately 15% of all lung cancer cases and is recognized as the most aggressive histological subtype of the disease [9]. LUAD originate from type II alveolar cells in the periphery of the lungs [10,11], while squamous cell carcinoma (SCC) develops from the squamous epithelial cells located at the airway epithelial cells at the center of the lungs [11,12]. SCLCs have been reported to have multiple origins primarily from pulmonary neuroendocrine cells (PNEC), as well as basal and club epithelial cells within the lung [13,14]. A small proportion of SCLCs have been identified to originate from tuft cells and AT2 cells, suggesting a potentially heterogeneous nature of SCLCs [13–15]. Patients with NSCLC often possess gene mutations including epidermal growth factor receptor (*EGFR*), Kirsten rat sarcoma viral oncogene homolog (*KRAS*), and anaplastic lymphoma kinase (*ALK*). In contrast, SCLC patients typically demonstrate the deletion of *TP53* and *RB1*, in addition to *MYC* amplification [13,16–18]. Individuals with early-stage NSCLC typically receive surgical resection, whereas those with advanced NSCLC could gain from chemotherapy, targeted therapy, and immunotherapy [2,19]. While SCLC demonstrates considerable sensitivity to initial chemotherapy and radiotherapy, platinum–etoposide-based chemotherapy, combined with immunotherapy, has been the standard treatment for patients with extensive-stage small-cell lung cancer (ES-SCLC) [9,17,20]. Nonetheless, the median survival rate rarely surpasses 1 year [21,22]. Recent studies have indicated the emergence of T-SCLC from NSCLC thereby increasing the clinical burden of lung cancer treatment [2,23,24]. Although histologic transformation occurs in approximately 3–14% of patients with *EGFR*-mutant NSCLC receiving *EGFR* tyrosine kinase inhibitors (*EGFR*-TKIs), the reported incidence varies among clinical cohorts and study designs and remains an important mechanism of acquired therapeutic resistance [25,26].

T-SCLCs expressed a combination of genetic and epigenetic variations, that include gene deletions, gene amplifications, and epigenetic modifications [2,27]. The first documented case of T-SCLC was reported in 2006, establishing histologic transformation as a clinically relevant mechanism of acquired therapeutic resistance [2,28]. The majority of studies indicate a loss of the *TP53* and *RB1* genes, which are associated with the transformed phenotype leading to the development of aggressive tumor types in patients, thereby reducing their survival period [2]. T-SCLC shares characteristics with SCLC, such as loss of *RB1*, elevated expression of neuroendocrine markers, reduced expression of *EGFR*, and increased sensitivity to inhibition of the B cell lymphoma 2 (*BCL-2*) family [2,27]. Nonetheless the tumor microenvironment in T-SCLCs and SCLCs exhibits significant differences [25]. Therapeutic options for T-SCLC are currently limited, resulting in a poor prognosis [25]. Increasing clinical evidence has identified T-SCLC as a notable mechanism of acquired therapeutic resistance in patients with *EGFR*-mutant NSCLC undergoing *EGFR*-TKI ther-

apy [25] Despite recent reviews summarizing the clinical characteristics and therapeutic aspects of NSCLC-to-SCLC transformation, significant knowledge gaps continue to exist concerning the integration of cellular origin, lineage plasticity, molecular and epigenetic mechanisms, as well as their therapeutic implications. The current study presents a framework that integrates these interconnected aspects and incorporates recent advancements in the molecular basis of histologic transformation and emerging therapeutic strategies. This review integrates mechanistic insights with clinical evidence to offer an updated perspective on the biological evolution and therapeutic management of transformed SCLC.

This review examines the molecular signatures linked to the transformation of NSCLC to SCLC, including therapy-induced transformations as reported in patient case studies. This highlights the necessity of elucidating the pathways and genes involved in this transformation to facilitate the development of effective therapeutic strategies. This article is structured as a narrative review. Relevant literature was identified through searches of PubMed, Scopus, and Web of Science using combinations of the terms “non-small cell lung cancer,” “small cell lung cancer,” “histologic transformation,” “lineage plasticity,” “neuroendocrine transformation,” “EGFR,” “RB1,” “TP53,” and “therapy resistance. Original research articles, clinical studies, genomic analyses, and pertinent review articles published in English were taken into account, focusing on studies and recent publications related to NSCLC-to-SCLC transformation. Figure 1 presents a graphical roadmap summarizing the overall organization of this review.

Basic Structure of Review

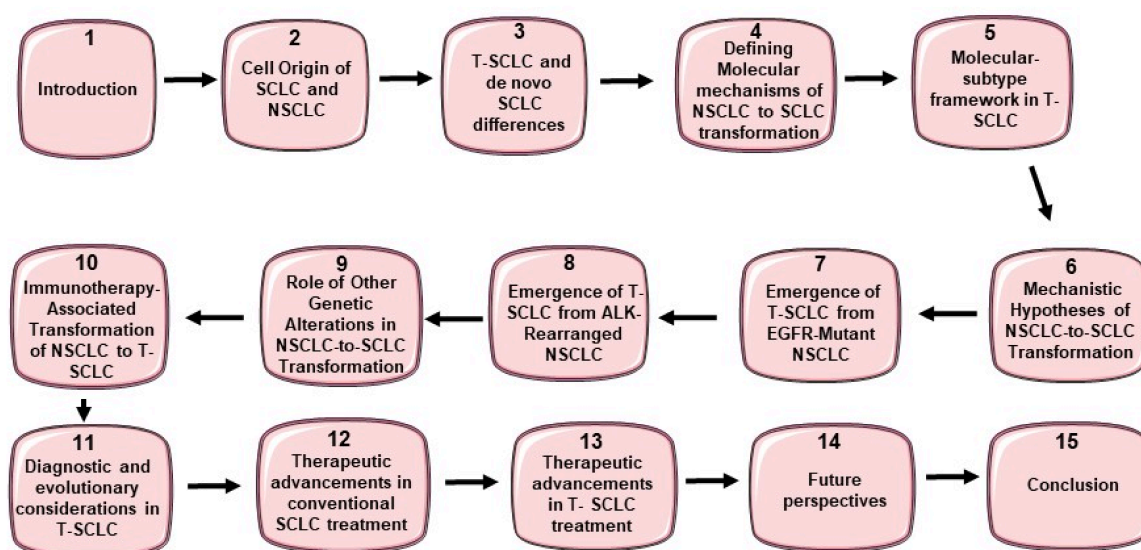


Figure 1. Overall structure of the review. Schematic overview illustrating the organization of the review, beginning with the biological basis and mechanisms of NSCLC-to-SCLC transformation, followed by discussions on clinical emergence, molecular alterations, therapeutic strategies, future perspectives, and concluding remarks.

2. Cell Origin of SCLC and NSCLC

Lung cancer is a heterogeneous disease broadly divided into NSCLC and SCLC. This biological divergence is reflected not only in their different genetic landscapes, but also their different cellular origins [29]. The “cell of origin” concept describes the normal cell type that first acquires oncogenic alterations and begins tumorigenesis, and mounting evidence shows that tumor phenotype is determined by the interaction between genetic

mutations and the cellular context in which they arise [30]. Early foundational studies proposed that lung cancers are initiated from region-specific epithelial stem/progenitor populations along the proximal–distal axis of the respiratory tract, such as basal cells in proximal airways, Clara (club) cells in bronchioles, alveolar type II (AT2) cells in distal alveoli, and specialized niches such as the bronchioalveolar duct junction (BADJ). Different potentials for self-renewal and differentiation among these epithelial populations provide a biological basis for tumor heterogeneity [31–33].

In NSCLC, which constitutes approximately 80% of lung cancers, multiple candidate cells of origin have been identified, reflecting its marked histological diversity [34]. Previous studies identified bronchioalveolar stem cells, located at the BADJ, as potential tumor-initiating cells that co-express CC10 and SPC and can undergo multilineage differentiation [35]. Oncogenic *KRAS* activation was able to induce BASC expansion and tumor formation, suggesting a mechanistic link between stem/progenitor activity and tumorigenesis [36]. However, subsequent lineage-tracing studies challenged the centrality of BASCs, showing that they may not function as primary stem cells in normal lung maintenance, thus raising questions about their definitive role in cancer initiation [37]. Moreover, recent evidence now support alveolar type II (AT2) cells as the principal cells of origin for lung adenocarcinoma, especially in *KRAS*-mutant models, where lineage-specific activation of oncogenes in AT2 cells results in robust tumor formation, while Clara cells mostly give rise to hyperplastic lesions that do not progress to malignancy [38,39]. However, recent studies have demonstrated that alveolar type I (AT1) cells can also initiate LUAD under specific oncogenic conditions through cellular plasticity and lineage reprogramming, further highlighting the heterogeneity of LUAD initiation [40]. In contrast, another major NSCLC subtype, squamous cell carcinoma (SCC), is strongly associated with basal cells of the proximal airway epithelium, which express KRT5, KRT14, and p63 and have multipotent differentiation capacity [34]. Experimental lineage tracing confirms that these basal progenitors are capable of self-renewal and producing luminal epithelial lineages, supporting their candidacy as cells of origin for SCC [41]. Thus, NSCLC develops from different epithelial progenitors, with tumor subtype determined by both anatomical location and genetic drivers.

For the SCLC, the traditional model identifies PNECs as the principal cells of origin. This notion is strongly supported by the pioneering work of the Berns lab, who used cell type-specific Adeno-Cre viruses driven by different promoters to inactivate *Trp53* and *Rb1* in distinct pulmonary epithelial populations. Their study demonstrated that PNECs represent the predominant cells of origin for SCLC [42]. These cells are located in neuroepithelial bodies (NEBs) within bronchiolar epithelium and express neuroendocrine markers consistent with the SCLC phenotype [43,44]. Loss of the tumor suppressor genes *TP53* and *RB1* in these compartments results in SCLC development in experimental models, consistent with a neuroendocrine lineage origin. However, PNECs seem to function as unipotent progenitors and not bona fide stem cells, which raises the question of whether they are solely responsible for tumor initiation. Other hypotheses propose that SCLC may originate from progenitor populations that are less differentiated, such as variant Clara cells or multipotent epithelial stem cells, which are able to undergo neuroendocrine differentiation during transformation. The finding of tumors exhibiting mixed features of SCLC and NSCLC further supports the notion of a common progenitor or a shared lineage hierarchy. Recently, a distinct molecular subtype of SCLC characterized by *POU2F3*-positive tuft cells has been identified. This finding suggests that tuft cells, which are a rare population of chemosensory epithelial cells in the airway, may serve as a potential cell of origin in specific genetic contexts [15]. These findings suggest that the cell of origin of

SCLC is more complex than initially considered and could involve both lineage-restricted and plastic progenitor populations [45,46].

Cancer stem cells (CSCs), which can self-renew, initiate tumors, and resist therapy, are a common feature of both NSCLC and SCLC. Studies have shown that CD133-positive cell populations in both tumor types can form tumor spheres in vitro and generate xenografts in vivo, while CD133-negative cells cannot do so. These CSCs are resistant to chemotherapy, partly due to the upregulation of ATP-binding cassette (ABC) transporters involved in drug efflux, and are enriched following treatment with agents such as cisplatin, suggesting a role in tumor recurrence and treatment failure. However, the exact identity and origin of CSCs in the lung epithelium are still obscure, and this gap in knowledge is critically important [47,48].

The conceptual framework of lung cancer origin has been significantly reshaped by some recent developments, with a focus on cellular plasticity, lineage reprogramming and tumor heterogeneity. Single-cell RNA sequencing and spatial transcriptomics in NSCLC have identified AT2 cells as important stem/progenitor cells capable of initiating adenocarcinoma but also indicate that club cells and basal cells can serve as alternative origins depending on mutational context (e.g., *KRAS*, *EGFR*, and *ALK*). Importantly, these studies show that tumor initiation is not restricted to a single lineage but is instead a spectrum of permissive epithelial states. Recent studies in SCLC have identified different molecular subtypes (e.g., *ASCL1*-, *NEUROD1*-, and *POU2F3*-driven tumors), suggesting either multiple cells of origin or dynamic lineage transitions during tumor evolution [49,50]. In addition, substantial clinical and experimental evidence indicates that NSCLC can trans-differentiate into SCLC under targeted therapy pressure, particularly in *EGFR*-mutant tumors. The retention of the original oncogenic driver mutations following transformation supports a common clonal origin and is consistent with lineage plasticity and epigenetic reprogramming, rather than providing direct evidence for a single common progenitor cell. Moreover, recent studies have also implicated transcriptional regulators and chromatin remodelling in promoting lineage switching, further strengthening the notion that cell identity in lung cancer is not static but rather dynamic [51–53]. Therapy-induced neuroendocrine lineage plasticity is not specific to lung cancer. Neuroendocrine transformation has been observed in prostate cancer, where treatment-induced neuroendocrine prostate cancer (NEPC) emerges as an adaptive response to therapeutic resistance. This indicates that lineage plasticity may be a widespread phenomenon among epithelial malignancies [54].

NSCLC and SCLC exhibit both convergence and divergence with respect to their cellular origins. NSCLC is a heterogeneous disease with various epithelial progenitor populations along the airway-alveolar axis. The tumor phenotype is mainly dictated by the cell of origin, with basal cells primarily leading to LUSC [55], alveolar epithelial cells to LUAD [40], and pulmonary neuroendocrine cells to SCLC [42], while genetic alterations additionally shape tumor behavior and evolution. SCLC is more genetically homogeneous, driven mainly by loss of *TP53* and *RB1* [14,56,57]. However, SCLC shows more phenotypic plasticity, being able to arise from a variety of epithelial cells and acquire neuroendocrine features by transcriptional reprogramming. The progression of NSCLC is tightly connected to the differentiation and regenerative capacity of the cell of origin. In contrast, SCLC is increasingly considered a disease driven by lineage plasticity and epigenetic remodelling. Both tumor types support the idea that cancer stem-like populations maintain tumor growth and mediate resistance, underlining the importance of targeting not only genetic drivers but also cellular hierarchies and plasticity [58,59].

3. Difference Between T-SCLC and De Novo SCLC

SCLC has traditionally been considered a primary neuroendocrine tumor arising de novo in the lung. However, recent advances in cancer biology have shown that a subset of NSCLCs, especially *EGFR*-mutant adenocarcinomas, can transform into SCLC during targeted therapy, resulting in the emergence of T-SCLC.

T-SCLC and de novo SCLC are biologically, molecularly and clinically distinct entities, although they both exhibit similar neuroendocrine characteristics. De novo SCLC arises as a primary neuroendocrine malignancy, whereas T-SCLC develops from pre-existing NSCLC during prolonged targeted therapy. This is a remarkable phenomenon of lineage plasticity in which tumor cells gradually change identity under therapeutic pressure to escape from drug-induced stress. T-SCLC denotes an adaptive evolutionary mechanism linked to therapeutic resistance, lineage plasticity and tumor survival [60]. Changes in signalling pathways, especially Notch signalling, further drive neuroendocrine differentiation and favour the transition to an SCLC phenotype under the selective pressure of *EGFR*-targeted therapies [61]. Experimental studies in mice have also shown that pulmonary neuroendocrine cells are the main cells of origin of classical SCLC. However, alveolar type II cells can also become SCLC-like tumors upon certain genetic alterations [42,62]. These findings support the idea that LUAD cells possess remarkable cellular plasticity and can directly transdifferentiate into T-SCLC during treatment resistance. More recent studies have implicated neuroendocrine transformation as an adaptive survival mechanism that allows tumor cells to evade targeted therapies and acquire aggressive clinical behaviour [63].

Both T-SCLC and de novo SCLC are characterized by aggressive growth, rapid metastasis, and initial response to platinum-based chemotherapy, although transformed tumors often follow a more complex and treatment-resistant clinical course. Patients with T-SCLC often have a shorter progression-free survival and a worse overall prognosis than patients with primary SCLC. Moreover, transformed tumors might have a different response to immunotherapy due to their distinct molecular background and previous treatment. Clinically, this distinction is of great importance. Rapid progression of *EGFR*-mutant NSCLC on targeted therapy should raise suspicion for histological transformation, highlighting the need for repeat biopsy and molecular reassessment. Thus, T-SCLC should be classified as a separate biological and clinical entity rather than just a subtype of conventional SCLC [60,64].

4. Defining Molecular Mechanisms of NSCLC-to-SCLC Transformation

SCLC is an aggressive malignancy characterized by unique molecular and transcriptional characteristics that distinguish it from NSCLC. Comprehending these changes is crucial for clarifying the mechanisms that drive SCLC transformation and therapeutic resistance. However, the molecular basis of SCLC transformation is still not well understood, with only a few mechanistic details currently available. Key molecular mechanisms are summarized in Figure 2 and discussed below.

4.1. *TP53* and *RB1*

A complete loss of the *TP53* gene located on chromosome 17p, which encodes the p53 protein, is recognized as a defining characteristic of SCLC, present in approximately 98% of SCLC tumors [65,66]. In contrast to the findings for SCLCs, only 15–50% of NSCLCs exhibit *TP53* mutations [67,68]. *TP53* mutations encompass missense mutations affecting the protein coding region, as well as truncations and deletions, which contribute to the buildup of mutations associated with the aggressive characteristics of SCLC tumors [66,69]. Alterations in *TP73*, a member of the p53 family that plays a role in cell cycle regulation and apoptosis, have been observed in SCLC, in addition to *TP53* mutations. These alterations

may result in the loss of the compensatory function of the p73 protein in the absence of p53 [65,70,71]. The isoform p73 α 1 decreases cancer cell viability and upregulates the Notch pathway, leading to increased *NOTCH1* expression, as observed in mouse models [70,72,73]. A separate study highlights the functional diversity of COOH-terminal p73 variants pertaining to SCLC biology. The study identified that p73 α inhibited drug-induced apoptosis in SCLC cells, while p73 β promoted apoptosis. p73 α inhibited Bax activation, mitochondrial dysfunction, and caspase activation. Furthermore, p73 α demonstrated the capacity to diminish apoptosis triggered by the BH3-only protein PUMA (p53 up-regulated modulator of apoptosis) in SCLC cells [74]. Tang et al. investigated the functional interaction between mutant p53 and the NAD-dependent deacetylase sirtuin-3 (SIRT3) in human SCLC cells. SIRT3 induces the ubiquitination and proteasomal degradation of mutant p53, thereby facilitating apoptosis and necroptosis in SCLC cells [70,75]. Hubaux lab examined the functional role of enhancer of zeste homolog 2 (EZH2), a histone-lysine N-methyltransferase, in the biology of SCLC [70,76]. The impact of EZH2 silencing on the cell cycle and cell death was investigated by targeting EZH2 with shRNA. The data indicate that EZH2 inhibits apoptosis by downregulating the expression of pro-apoptotic factors, specifically p53 up-regulated modulator of apoptosis (PUMA) and BCL2 associated agonist of cell death (BAD). Additionally, EZH2 facilitates cell cycle progression by reducing the expression of the cell cycle inhibitor p21 [70,76].

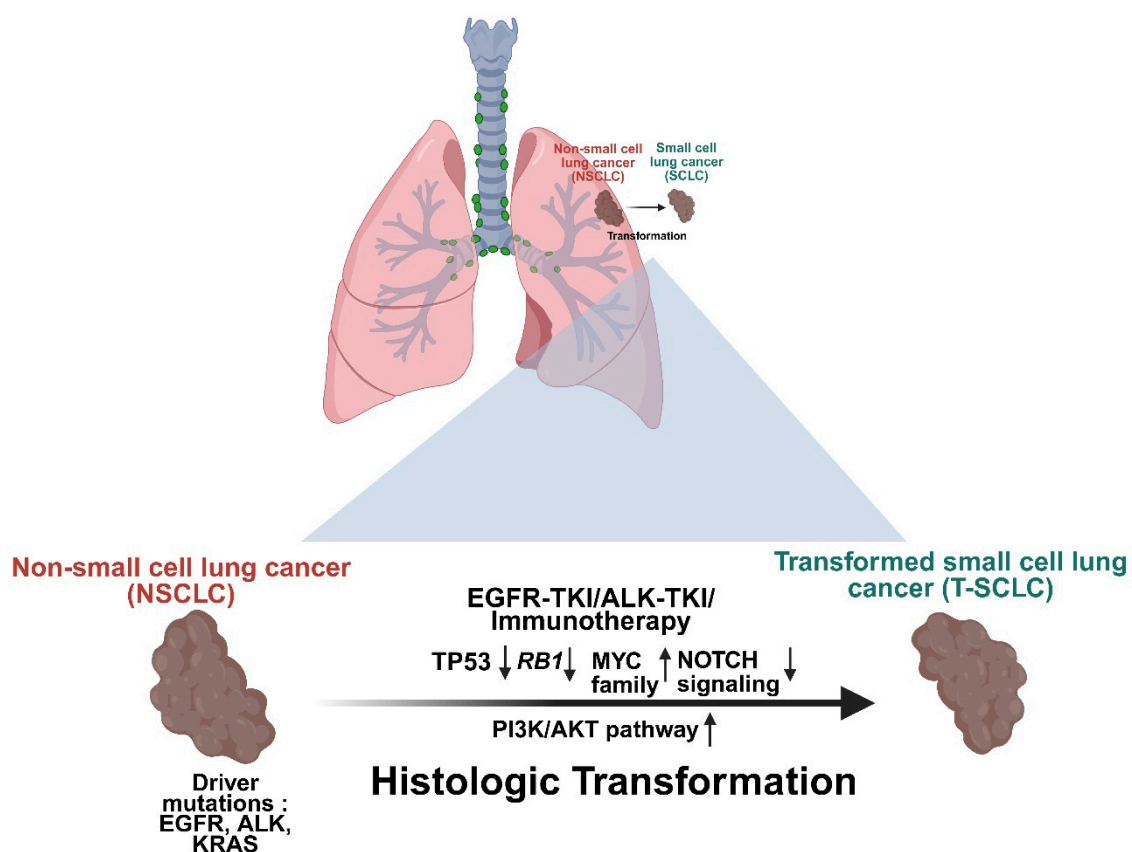


Figure 2. Schematic representation of histologic transformation from oncogene-driven NSCLC to T-SCLC under therapeutic pressure. The process is associated with major molecular alterations, including TP53 and RB1 loss, activation of the MYC family and PI3K/AKT signaling, and suppression of NOTCH signaling, ultimately leading to acquisition of the aggressive T-SCLC phenotype.

The tumor suppressor gene, *RB1* plays a crucial role in regulating the cell cycle by inhibiting the expression of cyclins and controlling the progression through the S phase [66]. The *RB1* gene is located on chromosome 13q14.2 and is among the most

frequently altered tumor suppressor genes in SCLC [77]. Alterations of *RB1* are among the most frequent genomic events in SCLC and occur through multiple mechanisms, including mutations, deletions, and copy-number alterations. *RB1* genomic alterations were identified in 73.5% of SCLC cases in a comprehensive genomic analysis [66]. In an independent study combining genomic analysis with immunohistochemistry, complete loss of RB1 protein expression was observed in 184 of 208 (88.5%) clinical SCLC samples [78]. The difference between the reported rates therefore reflects the distinct endpoints evaluated, as genomic profiling detects *RB1* alterations, whereas immunohistochemistry assesses loss of Rb protein expression. *RB1* mutations occur in a limited fraction of NSCLC cases; however, the majority of NSCLC tumor samples and cell lines maintain an intact *RB1* gene. This observation suggests that the loss of RB1 is more closely linked to SCLC and the transformation to SCLC [27]. The simultaneous loss of *RB1* and *TP53* indicates that NSCLC may be evolving into SCLC; however, further molecular alterations are necessary for full transformation [66,79]. Research on murine models with deleted *TP53* and *RB1* genes in the lungs confirmed the presence of SCLC in the mice, resembling human SCLC tumors [66,69].

In a cohort of 863 patients with *EGFR*-mutant lung cancer, 43 harboured concurrent *RB1* and *TP53* alterations. The overall histologic transformation rate to SCLC in the *EGFR*-mutant cohort was approximately 3%; however, among patients with concurrent *EGFR*, *RB1*, and *TP53* alterations, the transformation rate increased to approximately 18%, indicating that this molecular subgroup carries a substantially higher risk of SCLC transformation [80,81]. Another retrospective study found that *RB1* and *TP53* were the most commonly altered genes in cases where *EGFR*-mutant NSCLC transformed into SCLC, with mutation rates of 68% and 36%, respectively [82,83]. In another study, *RB1* loss was observed in all T-SCLC cases, while it was absent in tumors that remained as NSCLC [27,83]. Furthermore, patients carrying combined *EGFR*, *RB1*, and *TP53* mutations showed a higher likelihood of SCLC transformation compared to those with only *EGFR/TP53* mutations (with intact *RB1*) or *EGFR* mutations alone (with both *RB1* and *TP53* wild-type). Overall, these findings suggest that changes in *TP53* and *RB1* may significantly contribute to the process of SCLC transformation [81,83]. The loss of *RB1* may additionally facilitate the transformation to SCLC by enhancing the upregulation of epigenetic regulators and factors related to stem cell reprogramming in *EGFR*-mutant LUAD [83,84]. Furthermore, research indicates that the loss of *TP53* can aid in the transformation of alveolar type II cells, suggesting that the inactivation of *TP53* is significant in advancing SCLC transformation [42,83]. Nonetheless, research indicates that the relationship is not definitive.

The mechanisms of *RB1* and *TP53* in the SCLC transformation process are unclear. A previous study found that *RB1* mutation caused the release of E2F, leading to excessive cell proliferation and *TP53* inactivation, which caused dysregulation of the G1/S checkpoint and uncontrolled cell cycle progression. Co-mutation of *RB1* and *TP53* accelerated cell proliferation and promoted the phenotypic conversion of cells. In lung cancer, *RB1* mutations are associated with the acquisition of the neuroendocrine phenotype, whereas *TP53* mutation promotes cancer cell progression and metastasis. *EGFR/RB1/TP53* triple-mutant lung cancer exhibits a prevalence of whole-genome duplication (WGD) and AID/APOBEC hypermutation, which may occur before transformation and contribute to the process [80,81,85,86].

4.2. MYC

MYC family proteins are basic helix–loop–helix leucine zipper (bHLH-LZ) transcription factors that interact with the canonical E-box sequence (CACGTG) and modulate gene expression via heterodimerization with MAX [87,88]. The *MYC* gene serves as a principal

regulator of cell proliferation and survival pathways. Members of the *MYC* family exhibit highly conserved domains, which include a transactivation domain, a basic region for E-box DNA binding, *MYC* homology boxes (MBs), and a C-terminal helix–loop–helix leucine zipper (HLH-LZ) domain [89–95]. *MYC* has been linked with various resistance mechanisms pertaining to the transformation from NSCLC to SCLC, such as genomic instability, epigenetic reprogramming, and the acquisition of the *EGFR* T790M mutation [80,96]. Amplification of *MYC* proto-oncogenes, namely *MYC*, *MYCN*, and *MYCL*, occurs in roughly 20% of patient samples [13,97,98]. Voortman et al. found that 61.5% (8/13) of SCLC cell lines show significant copy number (CN) gains in *MYC* family genes, whereas CN gains ($\log_2$ ratio > 0.2) of at least one *MYC* family member were identified in 81.8% (27/33) of SCLC tumors. These findings suggest that changes in *MYC* family genes are significantly linked to the aggressiveness of SCLC [99]. Amplification of *MYC* leads to increased levels of the *MYC* protein, which triggers genes associated with cell cycle progression, resulting in enhanced cell proliferation and metabolism. *MYC* induces the transcription of *AURKA*, leading to the production of Aurora A kinase. This kinase is essential for the regulation of mitosis and the progression of SCLC tumors [13,100,101]. Reports suggest that the overexpression of *MYCL*, together with the loss of *TP53* and *RB1*, significantly reduces tumor latency. Additionally, the deletion of *MYCL* markedly inhibits tumor formation and results in a greater diversity of mixed and NSCLC morphologies, despite targeting neuroendocrine cells. The findings suggest that *MYCL* plays a role in SCLC differentiation alongside its function in promoting proliferation [79,88,102].

MYC amplification has often been noted in transformed SCLC and prostate neuroendocrine tumors, as well as in adenocarcinoma before transformation, indicating that *MYC* may play a significant role in the early stages of this process [83,103]. The T790M substitution, a prevalent resistance alteration that occurs after *EGFR*-TKI therapy, diminishes drug binding affinity by modifying the structure of the *EGFR* kinase domain [80,104]. Previous studies have suggested that *MYC* activation may aid in the development of this mutation during therapeutic resistance [80,96,105].

Research indicates that CDC7 facilitates the maintenance and accumulation of *MYC* protein, an oncogenic factor strongly linked with SCLC transformation [63,106,107]. In prostate cancer models, the inhibition of CDC7 resulted in the suppression of NE transformation; however, this effect was negated upon the introduction of a degradation-resistant *MYC* mutant, *MYCT58A*. These findings underscore *MYC* as a pivotal downstream target via which CDC7 facilitates NE plasticity and transformation [63,107].

4.3. PI3K/AKT Signalling Cascade

The phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT)/mTOR signaling pathway is often activated in SCLC and is closely associated with radioresistance. This pathway additionally influences glucose metabolism, potentially contributing to radioresistance by modifying cellular energy balance and metabolic activity [108]. A study that compared differentially expressed genes between LUAD and transformed SCLC revealed that crucial components of the PI3K/AKT pathway—specifically *PIK3CA*, *PIK3R1*, and *AKT3*—were found to be upregulated in transformed SCLC samples [83,109]. Furthermore, the *PTEN* M264I mutation, which impacts a negative regulator of PI3K signaling, is infrequently observed in NSCLC but was detected after histologic transformation. This indicates that changes in *PTEN* might also be linked to the transformation process [83,105]. AKT may also facilitate the NE phenotypic transition in non-tumoral lung cells [83,110]. Studies revealed that decreased *PTEN* expression during the transformation to SCLC is associated with the activation of the PI3K/AKT/mTOR pathway, which facilitates tumor progression and lineage transition [80,105,109–111]. Results from mouse models demonstrated that

the loss of *PTEN* accelerates the development of SCLC in conjunction with deficiencies in *RB1* and *TP53*. Additionally, analogous activation of the PI3K signaling pathway has been reported in transformed human tumors [80,82].

4.4. *ASCL1*

ASCL1 is a basic helix-loop-helix (bHLH) transcription factor typically found in fetal pulmonary neuroendocrine cells (PNECs) and is crucial for their differentiation [112,113]. *ASCL1* expression is essential for the survival of tumors reliant on it in SCLC [114]. Furthermore, its expression is closely linked to the classical morphological characteristics of SCLC [114–116]. The overexpression of *ASCL1* promotes the phosphorylation and inactivation of *RB1* protein, partially via the induction of cyclin-dependent kinase 5 (CDK5) [117]. The loss of *RB1* function can promote the proliferation of *TP53*-mutant cells and may facilitate tumor transformation [117]. Ectopic overexpression of *FOXN4* and *ASCL1* has been shown to decrease *EGFR* expression in *EGFR*-mutant LUAD cell lines, indicating that these factors may promote neuroendocrine transformation through the suppression of *EGFR* signalling [83,109].

4.5. *NOTCH*

The Notch signaling pathway serves as a crucial signal transduction mechanism that plays a significant role in cell proliferation, differentiation, and apoptosis [118]. Notch signalling influences stemness, exhibiting both pro-tumorigenic and tumor-suppressor roles in SCLC [14]. Notch inhibits neuroendocrine differentiation and is downregulated in the majority of SCLCs [117]. The early stages of transformation are characterized by decreased expression of Notch signaling components, such as receptors *NOTCH1*, *NOTCH2*, and *NOTCH3*, along with ligands *JAG2* and *DLL4* [83,109]. At the same time, differential gene expression analyses indicate elevated expression of *DLL3* and *HES6*, which are associated with Notch signalling inhibition during the transition to SCLC [83,109]. A previously reported investigation revealed distinct molecular alterations associated with histologic transformation, demonstrating a reduction in *NOTCH2* expression and an elevation in *ASCL1* expression in transformed SCLC relative to the original adenocarcinoma phenotype [61,80]. The inhibition of NOTCH signaling could enhance neuroendocrine lineage plasticity by allowing *ASCL1* to be derepressed. Increased levels of *ASCL1* subsequently trigger the activation of cyclin-dependent kinase 5 (CDK5), resulting in the phosphorylation and functional inactivation of *RB1* protein. In this respect, these molecular events enable uncontrolled proliferation of cells and play a role in the development of neuroendocrine traits linked to T-SCLC [80,117].

4.6. *YAP and TAZ*

SCLC cases exhibit minimal or absent expression of *YAP* and *TAZ*, with the exception of a small subset, specifically *YAP*-positive SCLC-Y tumors [63,119–124]. *YAP* expression is similarly diminished in T-SCLC patient samples, human cell lines, and xenograft models [63,109,119,125]. *YAP* inhibits neuroendocrine differentiation via the Notch/REST pathway [63,126–128]. The loss of *YAP/TAZ* may facilitate the transformation, although the underlying mechanism is not yet fully understood.

4.7. *EHMT2*

Recent studies have identified the histone methyltransferase *EHMT2* (G9a) as a significant epigenetic regulator in T-SCLC. *EHMT2* was significantly upregulated in T-SCLC cell lines and patient tumors [63,125]. *EHMT2* mechanistically activated WNT/ β -catenin signaling through the epigenetic suppression of *SFRP1*, which serves as a negative regulator of the pathway [63,125]. Inhibition of WNT/ β -catenin signaling notably reversed the neu-

roendocrine phenotype, underscoring the significance of the EHMT2–WNT/ β -catenin axis in SCLC transformation [63]. The recurrent molecular alterations associated with NSCLC-to-SCLC transformation and their proposed functional consequences are summarized in Table 1.

Table 1. Recurrent molecular alterations and their proposed roles in NSCLC-to-SCLC transformation.

Gene/Pathway	Change Associated with Transformation	Functional Consequences	References
<i>TP53</i>	(↓) Loss/inactivation in T-SCLC	Facilitate the transformation of alveolar type II cells, <i>TP53</i> mutation is also associated with tumor progression and metastasis.	[42,83,84]
<i>RB1</i>	(↓) Loss/inactivating mutations in T-SCLC	Upregulation of epigenetic regulators and stem-cell reprogramming factors in <i>EGFR</i> -mutant LUAD, associated with the acquisition of a neuroendocrine phenotype; the precise mechanism remains unclear.	[83,84]
MYC family	(↑) Amplification or upregulation in T-SCLC	Associated with genomic instability and epigenetic reprogramming and may facilitate neuroendocrine plasticity and transformation.	[63,83,103,107]
PI3K/AKT/mTOR	(↑) Activation and upregulation in T-SCLC	Decreased PTEN expression activates PI3K/AKT/mTOR signalling, thereby facilitating tumour progression and neuroendocrine lineage transition.	[80,83,105,109–111]
<i>ASCL1</i>	(↑) Increased <i>ASCL1</i> expression in T-SCLC	Promotes neuroendocrine differentiation through <i>EGFR</i> suppression and functional <i>RB1</i> inactivation	[83,109,117]
NOTCH	(↓) Reduced pathway activation in T-SCLC	Associated with <i>ASCL1</i> derepression and increased neuroendocrine lineage plasticity	[61,80,83,109,117]
YAP/TAZ	(↓) Reduced YAP expression in T-SCLC	May facilitate neuroendocrine differentiation through reduced Notch/REST-mediated inhibition; the precise contribution of YAP/TAZ to transformation remains unclear.	[63,109,119,125–128]
<i>EHMT2</i>	(↑) Increased expression in T-SCLC	Experimental evidence supports its involvement in epigenetic reprogramming through SFRP1 suppression and WNT/ β -catenin activation.	[63,125]

5. Molecular-Subtype Framework in T-SCLC

Comprehensive analyses of cancer cell lines, genetically engineered mouse models (GEMMs), patient-derived xenografts (PDXs), and primary human tumors have identified four principal transcription factor-defined subtypes based on the differential expression of achaete-scute homolog 1 (*ASCL1*; SCLC-A), neurogenic differentiation factor 1 (*NEUROD1*; SCLC-N), POU class 2 homeobox 3 (*POU2F3*; SCLC-P), and yes-associated protein 1 (*YAP1*; SCLC-Y) [120,121,129]. Recently, this classification has been refined to include an inflamed subtype (SCLC-I), which is characterized by low expression of lineage-defining transcription factors, enhanced antigen-presentation and immune-signaling activity. Additionally, another subtype has been identified that exhibits elevated expression of the

neuroendocrine transcription factor ATOH1 [9,14,120,130,131]. Growing evidence indicates that these molecular subtypes should be regarded as dynamic transcriptional cell states rather than static biological entities, given the reported intratumoral heterogeneity, marker co-expression, and treatment-associated subtype switching.

How this framework applies to T-SCLC is not yet completely understood. Hwang et al. conducted a subtype analysis of 18 EGFR-TKI-transformed SCLC cases utilizing immunohistochemistry. Their findings indicated that SCLC-N (NEUROD1-high) was the most prevalent subtype at 50.0%, followed by SCLC-TN (triple-negative; lacking predominant expression of ASCL1, NEUROD1, POU2F3, or YAP1) at 27.8%, and SCLC-A (ASCL1-high) at 22.2%. No tumors were identified as SCLC-P (POU2F3-high) or SCLC-Y (YAP1-high). Patients with the SCLC-A subtype demonstrated a longer interval to histologic transformation and improved overall survival compared to those with SCLC-N or SCLC-TN. This suggests that molecular subtype may affect the biological behavior and clinical progression of transformed disease [132].

In contrast, Chiang et al. examined an immunohistochemical cohort that included both de novo small-cell lung cancer (SCLC) and 10 cases of EGFR-mutant transformed SCLC. In the overall cohort, SCLC-A was the predominant subtype, accounting for 55.2%, followed by SCLC-N at 26.9% and SCLC-P at 9.0%. No tumors exhibited predominant SCLC-Y expression. Notably, 41.8% of tumors co-expressed multiple subtype markers, and around 50% of the paired longitudinal samples demonstrated subtype switching after disease progression, underscoring the dynamic characteristics of SCLC transcriptional programs [133]. Future studies are needed to better understand the evolution of T-SCLC and evaluate whether molecular subtypes can be used to guide personalized treatment.

6. Mechanistic Hypotheses of NSCLC-to-SCLC Transformation

The transformation from NSCLC to SCLC presents a significant challenge in the clinical field, as the latter is characterized by its more aggressive and metastatic behavior. The molecular features that drive the transformation of NSCLC to SCLC are intricate and varied, demonstrating the diversity and adaptability of lung cancer cells at the levels of genomic, transcriptomic, and cellular communication [2,83,134]. The clinical features linked to transdifferentiation provide preliminary insights into the origin and behavior of the transformed cells. Numerous case reports have outlined patterns including prior treatment history, patients' smoking status, the frequency of transformation, the usual time to transformation, and survival outcomes following its occurrence [19]. Several hypotheses have been proposed to explain the transformation of NSCLC into SCLC (Figure 3).

The common progenitor cell hypothesis proposes that both NSCLC and SCLC originate from a shared multipotent stem cell, with their final phenotype shaped by variations in the surrounding microenvironment and the underlying signaling pathways [135]. In accordance with this, next-generation sequencing of sequential biopsies from a patient with T-SCLC, who was initially diagnosed with lung adenocarcinoma carrying an *EGFR* exon 19 deletion, consistently revealed both the *TP53* C176S mutation and the *EGFR* exon 19 deletion in tumor tissue and circulating blood samples, supporting a common clonal origin [136].

Another hypothesis proposes that NSCLC cells may transform into SCLC due to genetic and epigenetic reprogramming induced by therapy. These changes may involve alterations in DNA methylation patterns, modifications of histones, and extensive changes in gene expression [2,81,137]. In the presence of therapeutic stress or various environmental factors, oncogenic signaling pathways can become activated, while the functions of tumor suppressors may be reduced, leading NSCLC cells to develop characteristics similar to those of SCLC [2,138]. Niederst et al. noted that T-SCLC closely mimics classical SCLC, exhibiting characteristics such as loss of *RB1*, heightened expression of neuroendocrine

markers, decreased *EGFR* expression, and increased sensitivity to inhibitors that target the BCL-2 family [2,27]. Furthermore, mutations in activation-induced cytidine deaminase (AID) were observed to occur more frequently in T-SCLC patients who did not have *EGFR*, *RB1*, or *TP53* mutations, in contrast to those without histologic transformation [2,86]. A multi-omic analysis of lung cancer indicates a novel mechanism whereby tumor transformation may be driven by methylation-associated transcriptional reprogramming, especially in cells with *TP53* and *RB1* loss [2,109]. T-SCLC derivatives are identified as a distinct subtype of SCLC, with a proposed origin from the transformation of tuft cells. The research indicated heightened expression of genes linked to the polycomb repressive complex 2 (PRC2) and the activation of the PI3K/AKT and Notch signaling pathways [2,62]. Collectively, the available evidence indicates that the transformation from NSCLC to SCLC is mainly influenced by lineage plasticity, which involves a coordinated interplay of genetic, epigenetic, and transcriptional reprogramming, rather than being the result of a singular molecular event. Nonetheless, the specific impact of individual molecular events, such as *TP53*/*RB1* loss, epigenetic remodeling, and therapy-induced selective pressure, is not fully explained, and it is still being explored whether these alterations are adequate to independently trigger transformation. Furthermore, a significant portion of the existing evidence comes from retrospective clinical cohorts, case reports, and experimental models, while prospective longitudinal studies and functional validation are still lacking. Future research incorporating serial biopsies, single-cell multi-omics, and functional validation will be crucial for elucidating the sequence of molecular events that drive histologic transformation.

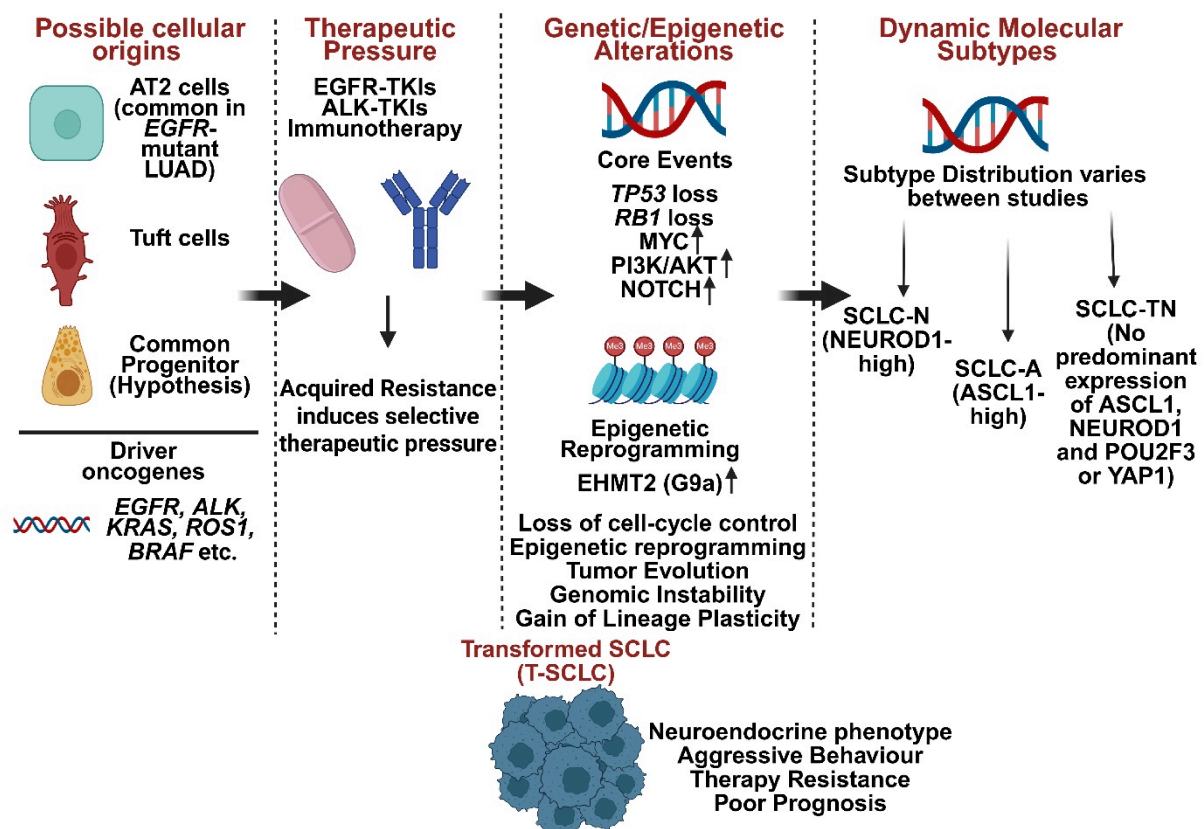


Figure 3. Proposed molecular framework underlying NSCLC-to-T-SCLC transformation. Under therapeutic pressure, genetically altered NSCLC undergoes epigenetic reprogramming and lineage plasticity driven by recurrent molecular alterations, including *TP53* and *RB1* loss, activation of the *MYC* family, *PI3K/AKT* signaling, and *EHMT2* (*G9a*), together with suppression of *NOTCH* signaling. Current evidence suggests multiple potential cellular origins and dynamic molecular subtype states, while the precise cellular origin of T-SCLC remains unresolved.

7. Emergence of T-SCLC from EGFR-Mutant NSCLC

KRAS mutations represent the most common oncogenic driver alterations in NSCLC globally. However, *EGFR* mutations are the predominant driver alterations in lung adenocarcinoma among never-smokers and East Asian patients, accounting for nearly 50% of cases in these populations [7,139]. This includes exon 19 deletions (ex19del), exon 21 point mutations (L858R), and exon 20 mutations (T790M) [2,140]. Patients with *EGFR*-mutant NSCLC receiving *EGFR* tyrosine kinase inhibitors (*EGFR*-TKIs) undergo histologic transformation to SCLC as a mechanism of acquired therapeutic resistance, although the reported incidence varies among clinical cohorts and study designs. Histologic transformation typically occurs after prolonged *EGFR*-TKI treatment, with a median time to transformation of approximately 17.8 months [19,26]. The histological transformation of lung cancer was initially reported in 2006 in a 45-year-old female non-smoker patient with *EGFR* exon 19-mutant NSCLC who developed acquired resistance to gefitinib and subsequently received erlotinib before histologic transformation to SCLC was confirmed by repeat biopsy [28,141]. Since the initial observation, numerous case reports have reported the transformation of *EGFR*-mutant adenocarcinomas into SCLC as a resistance mechanism to *EGFR*-targeted therapies. The small-cell lung cancer phenotype in all the observed case studies was confirmed through characteristic morphology and positive immunohistochemical staining for neuroendocrine markers, including synaptophysin, chromogranin, and NCAM [28,142–149]. In *EGFR*-mutant NSCLC, this transformation is linked to various other genetic changes, such as the loss of *RB1*, mutations in *TP53*, *PIK3CA*, *BRAF*, *WNK1*, *ETV1*, as well as *SPP1* upregulation and *REST* inactivation [27,85,86,141,142,149–151]. *EGFR* tyrosine kinase inhibitors (TKIs) in NSCLC induce apoptosis partially through the promotion of pro-caspase 8 dimerization, resulting in enhanced cleavage of PARP [152]. Furthermore, these agents have demonstrated the ability to increase PARP1 expression in NSCLC cell lines [153]. A significant increase of approximately 4.24-fold in cleaved PARP fragments has been detected in transformed SCLC. This finding indicates that TKI-induced apoptotic signaling may be associated, at least partially, with the process of histologic transformation [154].

The concurrent loss of *RB1* along with mutations in *TP53* in NSCLC undergoing *EGFR* TKI treatment have been identified as significant determinants of SCLC transformation [27,86,141]. Niederst et al. found that loss of *RB1* occurred in the majority of tumor cells from patients with T-SCLC who had *EGFR*-mutant NSCLC resistant to *EGFR*-TKIs, while this alteration was infrequently observed in patients who did not experience transformation [27]. Other studies indicate that SCLC transformation is rare in *EGFR*-mutant NSCLC unless there is a pre-existing deletion of both *RB1* and *TP53*, implying that these mutations may be critical prerequisites for the transformation process [81]. The loss of *RB1* is recognized to facilitate lineage plasticity. *RB1* loss in prostate cancer promotes neuroendocrine transformation through the upregulation of critical regulators, including *SOX2* and *EZH2*. A similar process is believed to play a role in the conversion of *EGFR*-mutant NSCLC to SCLC [155]. Furthermore, report indicates a higher incidence of the apolipoprotein B mRNA-editing enzyme (APOBEC) mutational profile in patients with transformed small-cell lung cancer (SCLC) originating from *EGFR*/*RB1*/*TP53*-mutant NSCLC relative to those without transformation, implying the involvement of additional molecular events in this phenomenon [81,86].

Amplification or overexpression of *MYC* has also been observed in T-SCLC tissues originating from *EGFR*-mutant NSCLC [81,86]. The loss of *PTEN* has been noted in transformed cases, even though it is less frequently seen in non-transformed NSCLC [105]. Reports indicate that adenocarcinoma can transform into SCLC even in the absence of *EGFR* driver mutations in the original tumors, implying that this phenomenon may occur regardless of *EGFR* mutational status [146,149]. The notion is additionally strengthened by

a previous case study from 1986—prior to the identification of *EGFR* mutations—which indicated that approximately 5% of patients originally diagnosed with NSCLC transitioned to SCLC upon relapse after developing resistance to standard chemotherapy or radiotherapy [149,156]. Nonetheless, the specific mechanisms driving transformation from NSCLC to SCLC are yet to be explored.

8. Emergence of T-SCLC from ALK-Rearranged NSCLC

The transition of SCLC from NSCLC is not restricted to individuals with *EGFR* mutations. Transformation has also been reported in ALK-rearranged tumors, particularly after treatment with ALK inhibitors including crizotinib, ceritinib, and alectinib [2,157–160]. Resistance to ALK-targeted therapies may develop via multiple mechanisms, including ALK amplification, secondary mutations like G1202R, epithelial-to-mesenchymal transition (EMT), and transformation from NSCLC to SCLC [161–163]. Alterations in essential tumor suppressor genes such as *RB1* and *TP53* are considered pivotal in driving resistance and facilitating histologic transformation [2,163]. Research indicates that patients with ALK-rearranged tumors who also demonstrate inactivation of *RB1*, *TP53*, *PTEN*, or *NOTCH1* have a greater propensity for transformation from NSCLC to SCLC [2,164,165]. A case of ALK-TKI-induced transformation of NSCLC to SCLC was documented in a 52-year-old male patient with *EML4-ALK* fusion (V3 variant), *KRAS* G12D mutation, *TP53* mutation, *RB1* mutation, and *PIK3CA* mutation [166]. Transformation from NSCLC to SCLC has been identified in ALK-rearranged cases without alterations in *RB1* or *TP53*, indicating that these modifications are not always necessary for transformation [2,167].

9. Role of Other Genetic Alterations in NSCLC-to-SCLC Transformation

A case report described advanced LUAD carrying an *EGFR* exon 19 deletion and a concurrent *BRCA2* mutation that subsequently transformed into SCLC. After several unsuccessful treatment attempts, the disease progressed and was histologically confirmed to have transformed into a SCLC phenotype [19,168]. Mutations in *PIK3CA* have been identified in T-SCLC, with variants including E726K and E545K found in liquid biopsy samples [169]. Studies indicate that early and concurrent alterations in *PIK3CA* and *PTEN* occur in SCLC cell lines [19,170]. A study of patients who developed transformed SCLC during erlotinib therapy identified a *KRAS* p.G12C mutation in peripheral blood samples after histologic transformation [2,171].

Furthermore, various transcription factors, including *FOXP4*, *ONECUT2*, and *POU3F2*, have been associated with T-SCLC [19,109]. Additionally, *FOXP4*, in conjunction with *ASCL1*, a promoter of neuroendocrine differentiation, has been linked to a notably aggressive subtype of neuroendocrine lung adenocarcinoma characterized by unfavorable clinical outcomes [19,172,173]. Research on T-SCLC samples has uncovered aberrant activation of genes and pathways involved in cell cycle regulation, DNA repair mechanisms, and WNT signaling pathways, indicating their potential involvement in tumor progression and resistance to therapy [2].

The PI3K/AKT/mTOR pathway plays a crucial role in tumor transformation and the emergence of resistance to chemotherapy [19,26]. AKT has been demonstrated to facilitate the transition to a neuroendocrine (NE) phenotype in lung cells [110]. Research using xenograft models derived from patients with *EGFR*-mutant tumors indicates that inhibition of the PI3K/AKT pathway may reduce tumor growth and delay neuroendocrine transformation [19,109]. An investigation of a T-SCLC patient with *ROS1* fusion undergoing *ROS1*-TKIs demonstrated that the histological transition to SCLC from NSCLC resulted in resistance to *ROS1*-TKIs. NGS analysis identified gene alterations in *RB1* and *TP53* from

autopsy tissue samples while the *ROS1* G2032R resistance mutation was no longer detected after transformation [2,174].

10. Immunotherapy-Associated Transformation of NSCLC to T-SCLC

In addition to targeted therapies, immunotherapy has become a prevalent treatment option for advanced NSCLC. Like EGFR-TKIs, certain patients receiving immune checkpoint inhibitors (ICIs) undergo transformation from NSCLC to SCLC, which is regarded as a mechanism by which tumors acquire resistance to immunotherapy [175–178]. Numerous studies have documented *TP53* mutations in pre-transformation tumor samples from patients who subsequently developed transformed SCLC following treatment with PD-1 inhibitors [24,176]. A case report detailed a patient with *KRAS*-mutant lung adenocarcinoma who developed SCLC after nivolumab therapy. Notably, post-transformation next-generation sequencing (NGS) analysis indicated the absence of the original *KRAS* G12C driver mutation [179]. Instances of SCLC transformation after PD-1 inhibitor therapy are infrequent, with the majority of existing evidence derived from limited studies. Most patients were men (11 out of 15), with a mean age of approximately 69 years, and nearly all participants reported a history of smoking. The original tumor types comprised adenocarcinoma, squamous cell carcinoma, and, in certain instances, squamous tumors exhibiting neuroendocrine characteristics. Patients received treatment with immune checkpoint inhibitors, including nivolumab, pembrolizumab, and sintilimab. Treatment responses exhibited variability, including partial response, stable disease, and disease progression. The duration from the commencement of immunotherapy to the identification of SCLC transformation exhibited considerable variability, ranging from 4 weeks to nearly 3 years. Upon identification of transformation, patients were generally treated according to established SCLC treatment protocols. Outcomes were suboptimal; of the 11 cases with survival data, 9 patients died [180]. A recent study indicates that nivolumab, an anti-programmed death-1 (PD-1) antibody, causes inhibition of the PD-1/programmed death ligand-1 (PD-L1) may be associated with the transformation of NSCLC into SCLC. While the precise mechanism remains unclear, previous findings offer some evidence for this hypothesis [178]. Overall, these reports indicate that immune checkpoint inhibitors show limited effectiveness in transformed SCLC, highlighting the necessity for predictive biomarkers and combination strategies.

11. Diagnostic and Evolutionary Considerations in T-SCLC

11.1. Diagnostic Considerations and Re-Biopsy

Histologic transformation from NSCLC to SCLC cannot be reliably established by radiographic findings or plasma genotyping alone and requires histopathological confirmation by tissue biopsy. Therefore, repeat biopsy should be strongly considered in patients with acquired resistance to EGFR-targeted therapy, particularly when the clinical course is atypical or transformation is suspected, as accurate histologic diagnosis is essential for selecting appropriate subsequent treatment. Whenever feasible, biopsy should be obtained from the most actively progressing and safely accessible lesion, as different metastatic sites may exhibit distinct histologic features reflecting intratumoral heterogeneity [26,181].

Histopathological evaluation of repeat biopsy is the most reliable method for confirming the transformation of NSCLC to SCLC. Evidence indicates that transformed tumors maintain the original *EGFR* driver mutation while developing neuroendocrine characteristics, exhibiting heightened expression of neuroendocrine markers and alterations in the RB pathway. This supports the notion of a shared clonal origin rather than the emergence of an independent primary tumor. Comparison of the repeat biopsy with the original adenocarcinoma specimen, including morphology, neuroendocrine marker expression,

RB protein status, and retention of the founding driver alteration, can establish clonal continuity and confirm histologic transformation [27,182].

Liquid biopsy is best viewed as a complement rather than a substitute for repeat biopsy. Serial circulating tumor DNA (ctDNA) can reveal persistence of the founding *EGFR* mutation, emergence of *RB1/TP53* or PI3K-pathway alterations, changes in copy number, and shifts in clonal abundance before or during clinical progression. It is particularly useful when tissue is unsafe to obtain and for longitudinal monitoring across multiple disease sites. However, ctDNA does not show morphology and cannot by itself distinguish true SCLC transformation from genomic evolution within NSCLC; a suspicious plasma pattern should prompt tissue confirmation whenever feasible [183,184]. Emerging cell-free DNA methylation and fragmentation approaches may eventually support non-invasive SCLC detection and subtype assignment, but their role in diagnosing T-SCLC remains investigational [183].

11.2. Predictive Biomarkers and Clonal Evolution

Baseline co-inactivation of *RB1* and *TP53* remains the most reproducible risk signal for transformation, but it is neither necessary nor sufficient. Beyond this pair, no biomarker has been prospectively validated for routine prediction. Candidate features include whole-genome doubling, APOBEC-associated hypermutation, PI3K-pathway alterations. These findings are biologically plausible, but most arise from small retrospective series, paired samples or experimental model systems and should be described as risk-enriching features rather than clinically validated predictive biomarkers [86,184,185].

Temporal data also argue against a single universal evolutionary route. Retention of the founding *EGFR* mutation in the original adenocarcinoma and the transformed SCLC supports a shared clonal origin. Whole-genome analysis has shown that, in some patients, the future SCLC lineage diverged early from a common ancestor before the first *EGFR*-TKI exposure, consistent with branched evolution and subsequent treatment-driven selection [86]. In other patients, serial biopsies appear to show a more linear sequence, with progressive acquisition or enrichment of *RB1/TP53* loss, PI3K-pathway activation or neuroendocrine programmes during therapy [184].

12. Therapeutic Advancements in Conventional SCLC Treatment

Therapeutic strategies for SCLC and T-SCLC have evolved considerably through the incorporation of immunotherapy, newer cytotoxic agents, and immune-engaging approaches. However, the distinct evolutionary origin and molecular characteristics of T-SCLC complicate the direct application of treatment paradigms developed for de novo SCLC [13,186].

Neuroendocrine transformation is well established as a mechanism of acquired resistance to targeted therapies in lung cancer. Some NSCLC tumors, under the selective pressure of prolonged exposure to *EGFR*-TKIs or other targeted agents, undergo histologic and transcriptional reprogramming into a SCLC phenotype while still often harboring the original oncogenic driver mutation. This is a case of adaptive lineage switching, a process that is not governed by simple clonal selection but by molecular reconfiguration [52,187]. Simultaneous loss of *TP53* and *RB1* is hallmark genomic event to promote transformation at genomic level. *RB1* inactivation alters cell cycle control and chromatin structure, and loss of *TP53* induces genomic instability and survival during therapeutic stress. Such changes create an epigenetic landscape that is permissive for neuroendocrine differentiation [188,189]. Recent studies have highlighted the importance of chromatin modifiers such as *EZH2* and *EHMT2*, activation of lineage-defining transcription factors such as *ASCL1* and *NEUROD1*, and altered DNA-damage response pathways such as *CDC7* and *XPO1* signalling [190–192]. Platinum-based chemotherapy, typically including cisplatin or carboplatin in conjunction

with etoposide, continues to be the usual first-line treatment for extensive-stage SCLC, with significant initial response rates but offering only marginal long-term survival advantages [25]. A significant recent development has been the incorporation of immune checkpoint inhibitors that target the PD-L1 pathway (e.g., atezolizumab and durvalumab) into first-line therapy [193]. Crucial clinical trials, like IMpower133 and CASPIAN, have demonstrated that including these medicines into platinum–etoposide chemotherapy significantly enhances overall survival compared to chemotherapy alone, thereby establishing chemo-immunotherapy as the prevailing standard of care. Furthermore, the continuation of immunotherapy enhances disease control following induction and signifies a paradigm shift in the management of SCLC towards immunomodulation [25].

The approval of lurbinectedin in 2020 was a significant advancement, demonstrating improved response rates and reduced toxicity relative to conventional treatments such as topotecan. Lurbinectedin functions by inhibiting oncogenic transcription and inducing apoptosis in neoplastic cells. The efficacy of this treatment in recurrent SCLC has been validated by real-world and clinical research; nevertheless, outcomes remain suboptimal in severely pretreated populations [194]. The recent discovery of bispecific T-cell engagers, particularly tarlatamab, has garnered significant attention. Tarlatamab targets DLL3, a protein exclusively expressed in SCLC cells, redirecting cytotoxic T lymphocytes to tumor cells. It has shown substantial enhancements in response rates and overall survival in relapsed scenarios, as evidenced by the DeLLphi-301 and DeLLphi-304 studies [195,196]. The data indicate that DLL3-targeted treatments constitute a promising novel therapy class in SCLC. Concurrently, measures for combination and maintenance have been investigated to enhance response durability. Research on combinations, such as lurbinectedin in conjunction with immunotherapy (e.g., atezolizumab), has shown promising enhancements in progression-free and overall survival relative to monotherapy [197]. Furthermore, anti-angiogenic medicines like VEGF inhibitors, including anlotinib, are undergoing assessment in conjunction with immunotherapy, reflecting a broader trend to address both tumor-intrinsic pathways and the tumor microenvironment. These multimodal solutions underscore the growing intricacy of managing SCLC and the necessity for cohesive therapeutic approaches [198,199].

13. Therapeutic Advancements in T-SCLC Treatment

The therapeutic environment of T-SCLC presents other complications. T-SCLC is a histological transformation of NSCLC rather than a de novo occurrence of SCLC, typically preserving the initial oncogenic driver mutation while acquiring changes such as the deletion of *TP53* and *RB1*. In the clinic, T-SCLC is managed using conventional SCLC protocols, such as platinum-etoposide chemotherapy; nevertheless, results are frequently inferior, and the efficacy of immunotherapy seems less reliable. Notably, in certain instances, T-SCLC may maintain a degree of sensitivity to targeted therapy directed at the initial driver mutation, including EGFR inhibitors. This has prompted the exploration of combinatorial treatments, encompassing targeted therapy in conjunction with chemotherapy or other drugs (Table 2) [63,141,200]. The recognition that transformed tumors frequently retain the original driver mutation (e.g., *EGFR* exon 19 deletion) has led to the exploration of dual-targeted strategies. Clinical studies imply that the use of EGFR inhibitors coupled with platinum-etoposide chemotherapy may extend progression-free survival compared to chemotherapy alone in specific individuals, indicating that the initial oncogenic dependence may not be fully eradicated post-transformation. Translational studies utilizing patient-derived xenograft (PDX) models of *EGFR*-mutant NSCLC with SCLC transformation have shown that physiologically informed drug selection may enhance results. The use of chemotherapy alongside *EGFR*-TKIs as an initial treatment following SCLC transformation

may improve progression-free survival for patients, although it does not appear to enhance overall survival. In a study, patients with T-SCLC from *EGFR* mutant adenocarcinoma who received first-line chemotherapy in combination with *EGFR*-TKIs demonstrated a marginally higher response rate than those treated with chemotherapy alone (43.8% vs. 37.5%). The combined approach led to a notably extended median progression-free survival (5.2 vs. 3.0 months). Nonetheless, there was no significant difference in overall survival noted between the two treatment groups [201]. In another study involving 27 patients with *EGFR* mutant adenocarcinoma (67% with *EGFR* exon 19 deletion) who had transformed to T-SCLC demonstrated that treatment with chemotherapy combined with immunotherapy resulted in the highest response rate (80.0%) and the longest median progression-free survival (PFS) of 11.3 months. In comparison, chemotherapy plus *EGFR*-TKIs yielded a response rate of 44.4% and a median PFS of 7.2 months, while chemotherapy alone resulted in lower outcomes, with a response rate of 16.7% and a PFS of 3.7 months. No statistically significant differences in progression-free survival or overall survival were observed among the treatment groups [202]. Clinical trials, such as NCT03567642, are assessing EP chemotherapy following osimertinib treatment in T-SCLC patients with *EGFR*, *RB1*, and *TP53* mutations. Patients with transformed small-cell lung cancer exhibited superior responses to EP chemotherapy in comparison to those with de novo small-cell lung cancer [203]. ABT-263, an orally administered BCL-2 family inhibitor, has shown significant therapeutic efficacy in transformed small-cell lung cancer (SCLC) by promoting apoptosis in *EGFR*-mutant tumor cells [27].

Table 2. Summary of clinical evidence for systemic therapies after histologic transformation from NSCLC to transformed small-cell lung cancer (T-SCLC).

Sl. No.	Study Design	T-SCLC Population (N)	Treatment Setting/Line	Intervention and Comparator	Standardised Outcomes	Interpretation	Reference
1	Retrospective cohort	29 patients in total; first post-transformation treatment evaluable in 24 patients: chemotherapy plus <i>EGFR</i> -TKI, <i>n</i> = 16; chemotherapy alone, <i>n</i> = 8	First systemic treatment following histologically confirmed transformation	Chemotherapy plus <i>EGFR</i> -TKI versus chemotherapy alone	ORR: 43.8% versus 37.5%; median PFS: 5.2 versus 3.0 months, <i>p</i> = 0.014; median OS after transformation: 14.8 versus 13.0 months, <i>p</i> = 0.474	Concurrent <i>EGFR</i> -TKI treatment was associated with significantly longer PFS, but not OS. Interpretation is limited by the non-randomised design and small treatment subgroups.	[201]
2	Multicentre retrospective cohort	27 patients: chemotherapy, <i>n</i> = 12; chemotherapy plus <i>EGFR</i> -TKI, <i>n</i> = 10; chemotherapy plus immunotherapy, <i>n</i> = 5	Subsequent systemic treatment following progression on first-line <i>EGFR</i> -TKI and pathological confirmation of T-SCLC	Chemotherapy alone versus chemotherapy plus <i>EGFR</i> -TKI versus chemotherapy plus immunotherapy	ORR: 16.7% versus 44.4% versus 80.0%; DCR: 41.7% versus 88.9% versus 100%; median PFS: 3.7 versus 7.2 versus 11.3 months; no statistically significant differences in PFS or OS among the groups	Combination regimens demonstrated numerically higher response and disease-control rates. However, the study was underpowered, and survival differences were not statistically significant.	[202]
3	Multicentre retrospective cohort with a small treatment subgroup	Post-transformation anlotinib-treated subgroup; the denominator was reported as a small cohort in the source study	Post-transformation therapy; treatment line was not uniform	Anlotinib-containing treatment; no clearly defined comparator	ORR: 66.7%; median PFS: 6.2 months	Anlotinib-containing therapy demonstrated potential activity. However, the small subgroup size and heterogeneous treatment setting substantially limit interpretation.	[82]

Table 2. Cont.

Sl. No.	Study Design	T-SCLC Population (N)	Treatment Setting/Line	Intervention and Comparator	Standardised Outcomes	Interpretation	Reference
4	Case report	One patient with EGFR-mutant NSCLC transformed into extensive-stage SCLC	Treatment following histological transformation after previous exposure to EGFR-TKI therapy	Serplulimab-based immunochemotherapy; no comparator	PFS after transformation: 6 months; cohort-level ORR and OS were not applicable	This single-patient observation suggests possible activity of serplulimab-based immunochemotherapy but cannot establish comparative efficacy or generalisability.	[204]
5	Retrospective cohort	T-SCLC cohort; PD-L1 inhibitor-based treatment group, $n = 11$, including eight responders	Post-transformation systemic therapy	PD-L1 inhibitor plus chemotherapy, with or without bevacizumab, versus non-immunotherapy treatment	ORR in the immunotherapy group: 73% (8/11); median PFS: 5.1 versus 4.1 months; median post-transformation OS: 20.2 versus 7.9 months, $p < 0.01$	The improvement in post-transformation OS was clinically notable. Nevertheless, retrospective treatment selection, small sample size and potential confounding introduce substantial bias.	[205]
6	Multicentre retrospective series	67 patients in the overall transformed cohort; taxane-treated subgroup, $n = 8$	Taxane treatment following T-SCLC transformation, generally after platinum-etoposide or other previous systemic therapy	Taxane chemotherapy, including paclitaxel or nab-paclitaxel; no randomised comparator	ORR: 50% (4/8); median PFS: 2.7 months	Taxanes demonstrated antitumour activity in a small and previously treated subgroup. The absence of a randomised comparator and the limited sample size restrict firm conclusions.	[26]

Abbreviations: CT, chemotherapy; DCR, disease-control rate; EGFR-TKI, epidermal growth factor receptor tyrosine kinase inhibitor; NSCLC, non-small-cell lung cancer; ORR, objective response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; SCLC, small-cell lung cancer; T-SCLC, transformed small-cell lung cancer.

Nonetheless, the management of T-SCLC predominantly relies on conventional protocols for SCLC. Recent studies indicate that outcomes may be enhanced with the implementation of customized solutions in this biologically intricate condition. The foundation of therapy is the combination of cisplatin or carboplatin doublets with etoposide, frequently integrated with radiation or paclitaxel-based chemotherapy [25]. These regimens may elicit initial responses; however, their persistence is constrained, underscoring the aggressive biology of altered illness.

Recent clinical studies reveal a potential synergistic advantage of anti-angiogenic and immunotherapeutic drugs. Combinations like anlotinib and oral etoposide have demonstrated improved antitumor activity in preclinical and early clinical contexts, reinforcing the need for targeting angiogenesis in conjunction with cytotoxic chemotherapy in transformed disease [206,207]. Anlotinib, a multi-targeted tyrosine kinase inhibitor exhibiting anti-angiogenic properties, has demonstrated notable efficacy in T-SCLC, with an objective response rate (ORR) of 66.7%, a median PFS of 6.2 months, and enhanced overall survival (OS) in specific cohorts [25,82,201]. The findings underscore the therapeutic potential of targeting tumor vascularization alongside cytotoxic treatment. Similarly, serplulimab-based immunochemotherapy demonstrated a clinically significant advantage, with median PFS prolonged to around 6 months compared to hitherto reported PFS of less than 4 months [26,204]. Serplulimab is a monoclonal antibody targeting PD-1, which revitalizes fatigued T cells and reinstates antitumor immune surveillance, enabling the immune system to re-engage altered neuroendocrine tumor cells [204]. In patients with PD-L1-positive T-SCLC, treatment with atezolizumab combined with platinum-etoposide chemotherapy, with or without bevacizumab, was associated with improved clinical outcomes. The combination therapy produced an overall response rate of 73% and extended the median overall survival to 20.2 months, compared with 7.9 months in patients receiving

chemotherapy alone [205]. The PARP inhibitor olaparib, known for its antitumor efficacy in SCLC, is under investigation in conjunction with durvalumab for patients with *EGFR*-mutant T-SCLC in the phase II trial NCT04538378. Alisertib, an AURKA inhibitor aimed at *RB1*-deficient T-SCLC cells, is being studied in conjunction with osimertinib in patients with *EGFR*-mutant LUAD-associated T-SCLC (NCT04085315) [208].

Case-based statistics further substantiate the justification for dual targeted interventions. A patient with an *EGFR* exon 19 deletion undergoing combination therapy with erlotinib, cisplatin, and etoposide had a progression-free survival of 8 months, surpassing that of those treated just with cisplatin and etoposide [209]. This observation indicates that remaining oncogenic drivers may be therapeutically targetable even in cases of histologic transition. These findings highlight the significance of comprehending the molecular pathways behind the transition from *EGFR*-mutant NSCLC to T-SCLC as essential for optimizing treatment targets. An enhanced mechanistic comprehension of lineage plasticity, immune evasion, and angiogenic signalling may enable more reasonable combination methods and signal a more tailored therapy approach for patients with this very aggressive illness [141,200].

Taxane-based chemotherapy has also been explored in cases of T-SCLC. Marcoux et al. found that patients with *EGFR*-mutant transformed SCLC who received first-line paclitaxel exhibited a response rate of approximately 50% and a median progression-free survival of 2.7 months. This outcome was more favorable than the response rates usually reported for de novo SCLC, which typically range from 20% to 30% [26].

Although there is a similar dependence on platinum-based chemotherapy, SCLC and T-SCLC are fundamentally different in biological origin, evolutionary course, and therapeutic behaviour. De novo SCLC is characterized by initial chemosensitivity followed by rapid relapse, while T-SCLC emerges through adaptive lineage reprogramming of previously treated oncogene-driven tumors and is often compounded by resistance. Novel agents such as lurbinectedin and DLL3-targeted therapies have improved outcomes in relapsed SCLC, but the precise role in T-SCLC is not yet clearly defined. The dual biology of T-SCLC, with the retention of oncogenic drivers and the acquisition of neuroendocrine features, underscores the importance of integrated treatment strategies against both components [210,211].

14. Future Perspectives

SCLC transformation represents a mechanism of resistance to *EGFR*-TKI therapy and correlates with unfavorable clinical outcomes. This process is associated with changes in *RB1* and *TP53*, as well as dysregulation of pathways related to Notch, MYC, and PI3K/AKT signalling [63]. Despite recent advances, numerous facets of SCLC transformation remain inadequately understood, including its underlying mechanisms and effective treatment strategies. Recent findings indicate that the transformation to SCLC may happen more often in *EGFR* wild-type NSCLC than was previously acknowledged, possibly surpassing its occurrence in *EGFR*-mutant tumors [63,185,212]. The mechanisms driving SCLC transformation are diverse and not yet completely understood. Some alterations, such as *SMAD4* mutations [26,185,213], are found exclusively in a subset of patients, indicating their limited universal relevance. Nonetheless, various molecular events may eventually align with a limited number of fundamental pathways that facilitate SCLC transformation. Inactivation of *RB1* and *TP53* may make NSCLC more susceptible to transforming into SCLC; however, it is probable that further signals are necessary to trigger this process [63]. Factors like therapeutic stress, tumor microenvironment, and cell of origin may determine why only specific tumors undergo transformation. Advancements in NGS and WES have enhanced our comprehension of the molecular foundation of transformed SCLC (T-SCLC), uncovering tumor heterogeneity and possible therapeutic targets [2]. While numerous

promising treatment strategies have been developed, additional clinical validation and mechanistic studies are necessary to enhance therapy and patient outcomes [80].

15. Conclusions

Although immunotherapy, novel cytotoxic agents, and emerging targeted approaches have expanded the therapeutic landscape, durable disease control remains difficult, particularly in T-SCLC because of its molecular heterogeneity and adaptive evolution [2]. Moreover the incidence of T-SCLC is likely underestimated due to the lack of routine repeat biopsies in many patients. A better understanding of the molecular mechanisms behind SCLC transformation is crucial for developing more personalized therapeutic strategies and identifying new therapeutic targets. Despite considerable progress, several critical questions remain unanswered, including whether T-SCLC arises predominantly through transdifferentiation of pre-existing NSCLC cells or from a common progenitor population, the sequence of molecular events that drive lineage plasticity, and the identification of biomarkers that can predict histologic transformation prior to clinical progression. Addressing these challenges is crucial for enhancing early diagnosis and formulating more effective therapeutic strategies. Future initiatives should emphasize on precision medicine tactics that integrate molecular subtyping, target lineage plasticity, and identify combination medicines to surmount resistance mechanisms. Further translational research and enrolment into biomarker-directed clinical trials will be essential to improving outcomes in these highly aggressive malignancies. Numerous recent reviews have provided valuable but largely complementary perspectives on NSCLC-to-SCLC transformation. Yang and Fan discussed its biological mechanisms and clinical relevance [2]; Wang et al., examined clonal evolution and lineage reprogramming in EGFR-mutant lung adenocarcinoma [52]; Joshi et al., highlighted neuroendocrine transformation as an important mechanism of resistance to targeted lung-cancer therapies [63]; and Dai et al., reviewed the molecular mechanisms, predictive biomarkers, and clinical management of transformed SCLC [200]. The present review offers a broader, integrated biological-to-clinical perspective by linking cell of origin and lineage plasticity with molecular and epigenetic alterations, dynamic molecular-subtype states, diagnostic surveillance, and the available evidence on post-transformation therapeutic strategies in T-SCLC.

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