Review

Targeting DLL3 in Small Cell Lung Cancer: Therapeutic Strategies and the Emerging Role of Tarlatamab

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Abstract: Historically, cancer treatment has been a continuous research achievement in the pharmaceutical sciences, yet significant challenges remain to be addressed. Among these challenges, high-grade neuroendocrine tumors, particularly malignancies such as small cell lung cancer (SCLC), have confronted persistent issues of recurrent relapse due to their rapid doubling time and high growth fraction. Conventional first-line platinum-based chemotherapy and immune checkpoint inhibitors provide only limited survival extension following initial response, with no distinct therapeutic options available after second-line treatment. These therapeutic limitations are associated with aberrant activation of signaling pathways related to the genetic and functional characteristics of SCLC, with Notch signal suppression and DLL3 overexpression being recognized as major molecular features. DLL3 is an inhibitory Notch ligand highly expressed in SCLC that is rarely expressed in normal tissues and appears selectively in tumor cells, making it an attractive therapeutic target. Recently, various therapeutic strategies targeting DLL3 have been developed, including antibody-drug conjugates, bispecific T cell engagers (BiTEs), and chimeric antigen receptor T cells. This review discusses the pathophysiology of SCLC and the role of DLL3, as well as the development process and clinical utility of DLL3-targeted immunotherapeutic strategies. Furthermore, we examine the latest research trends and developmental potential of BiTE-based immunotherapy centered on Tarlatamab among DLL3-targeted therapies.

Keywords: small cell lung cancer; notch signaling; delta-like ligand 3; targeted therapy; bispecific T cell engagers; tarlatamab

1. Introduction

Lung cancer is a major cause of cancer incidence and death worldwide, and it is often diagnosed at an incurable stage, although it is largely preventable [1]. Small cell lung cancer (SCLC), which accounts for approximately 13% of cases, is a poorly differentiated, aggressive tumor with a poor prognosis [2]. Although the incidence of SCLC has substantially declined due to a steady decrease in smoking over the past 20 years, it is still recognized as a significant threat in the medical field [3].

Platinum-based chemotherapy (PBC) for SCLC involves the administration of platinum-containing agents, such as cisplatin or carboplatin, which function by inducing cytotoxic damage to malignant cells through the targeting of DNA, inhibiting cell function, and ultimately inducing cell death [4]. It has long been used as the standard first-line treatment for SCLC. This regimen initially yields a median overall survival (OS) of 9–10 months. However, most patients eventually develop acquired resistance to cytotoxic agents as well as immune-based therapies following the initial response, resulting in rapid disease relapse [5]. This resistance stems from mechanisms such as reduced drug accumulation, increased detoxification, enhanced DNA repair, impaired apoptosis, and autophagy activation [6]. The treatment options for relapsed patients remain limited, and meaningful survival extension is difficult to achieve. Although single-agent second-line therapies, such as topotecan, lurbinectedin, and immune checkpoint inhibitors, are available, their tumor response rates are markedly lower than those observed with first-line regimens, reflecting the development of treatment resistance [7]. Furthermore, the reported median OS is approximately 4.7–6.9 months with topotecan and around 3.3 months with lurbinectedin, both notably shorter than those achieved with first-line regimens [8,9]. Currently, there are no

additional satisfactory treatment options for SCLC patients who are resistant to second-round therapy, highlighting the need for new treatment strategies.

Accordingly, innovative immunotherapies characterized by a significantly effective tumor response rate and low systemic side effects have also been actively studied recently. Bispecific T cell engagers (BiTE) are one such class; they are designed as bispecific antibodies that bind simultaneously to two different targets: one on T cells and the other on tumor cells. This mechanism brings T cells into close proximity with cancer cells, thereby promoting effective T cell-mediated cytotoxicity [10]. Tarlatamab-dlle (Tarlatamab, AMG 757) is the first BiTE therapy developed specifically to target SCLC. In this paper, we review Notch signaling and its target ligand DLL3 in SCLC, and discuss future perspectives on DLL3-targeted therapeutics, with particular focus on the oncologic application of Tarlatamab.

2. Notch Signal and DLL3 Interaction in SCLC

In SCLC, canonical homeostatic signaling pathways such as Notch are aberrantly regulated. This dysregulation is not restricted to SCLC but is also observed in various neuroendocrine tumors, in which cellular plasticity and differentiation are tightly governed by Notch activity [11]. A comprehensive understanding of Notch signaling in these malignancies is therefore critical for the rational development of targeted therapeutic strategies. This section summarizes the signaling process mediated by Notch receptor–ligand interactions and describes how the tumor-suppressive environment of SCLC is linked to Notch signaling. Furthermore, by examining the expression and intracellular function of DLL3—a Notch ligand—this section provides a foundation for understanding DLL3-targeted therapeutic approaches.

The Notch gene was first identified in 1917 through studies of a mutant phenotype characterized by "notched" wings in *Drosophila melanogaster* [12]. It was later molecularly isolated in 1983 and has since been the focus of extensive research over several decades in the fields of embryonic development, organogenesis, cell fate determination, and disease [13].

The Notch signaling pathway is an evolutionarily conserved developmental mechanism mediated by four receptors (Notch1–4) and five ligands (JAG1–2, DLL1–3) of the Delta/Serrate/Lag-2 family [14]. Signal transduction involves a series of complex steps, including glycosylation, proteolytic cleavage, receptor–ligand interaction, and engagement of downstream effectors [15]. Notch proteins are initially synthesized in the endoplasmic reticulum as single-chain precursors. After glycosylation—mainly at EGF-like repeat domains—the precursor is transported to the Golgi apparatus, where it is cleaved at the S1 site by a furin-like convertase. This yields a mature heterodimeric receptor, which is then trafficked to the cell surface. Upon ligand binding, the receptor undergoes sequential cleavage by ADAM10/17 at the S2 site, and by γ-secretase at the S3 site, releasing the Notch intracellular domain (NICD) into the cytoplasm. The NICD translocates to the nucleus and forms a transcriptional activator complex with CSL (CBF1/suppressor of hairless/Lag-1), mammalian mastermind-like proteins (MAML1–3), and co-activators [16]. This complex initiates a transcriptional cascade that regulates various downstream target genes. Among them, transcription factors of the hairy enhancer of split and hairy/enhancer-of-split related to YRPW motif families are particularly well-characterized (Figure 1a). The pathway is terminated by phosphorylation of the proline–glutamate–serine–threonine domain at the C-terminal region of the Notch receptor, which regulates NICD stability [17].

The role of Notch signaling in cancer was first recognized in 1991 with the identification of a chromosomal translocation involving the NOTCH1 locus in a patient with T cell acute lymphoblastic leukemia [18]. Since then, numerous studies have shown that Notch signaling may function either as an oncogene or a tumor suppressor, depending on the cellular context. In SCLC, Notch functions primarily as a tumor suppressor.

Neural and neuroendocrine differentiation in SCLC is partly regulated by the basic helix–loop–helix (bHLH) transcription factor human achaete-scute homologue-1 (hASH1). In this setting, Notch signaling acts as a key negative regulator of bHLH transcription factors, including hASH1, thereby modulating cellular differentiation. Additionally, Notch signaling selectively induces $p21^{waf1/cip1}$ and $p27^{kip1,}$ and significantly increases phosphorylation of ERK1 and ERK2. These combined effects contribute to G1 cell cycle arrest, ultimately inhibiting tumor cell proliferation in SCLC [19].

DLL3 is a member of the DSL family of Notch ligands that is selectively expressed on the surface of SCLC tumor cells. Unlike other DSL ligands that typically mediate trans-activation between adjacent cells, DLL3 is co-expressed with Notch receptors in the same cell and inhibits signaling in a cis manner [20,21]. This leads to reduced localization of the receptor at the cell surface and promotes degradation of full-length Notch receptors through the late endosome–lysosome pathway [22]. As previously mentioned, activation of Notch signaling suppresses NE differentiation in SCLC. In this context, DLL3-mediated silencing of Notch signaling and receptor degradation

appears to contribute to the promotion of NE tumorigenesis (Figure 1b). Accordingly, it is necessary to understand how DLL3 becomes overexpressed in SCLC and how this overexpression ultimately facilitates NE differentiation through suppression of Notch signaling.

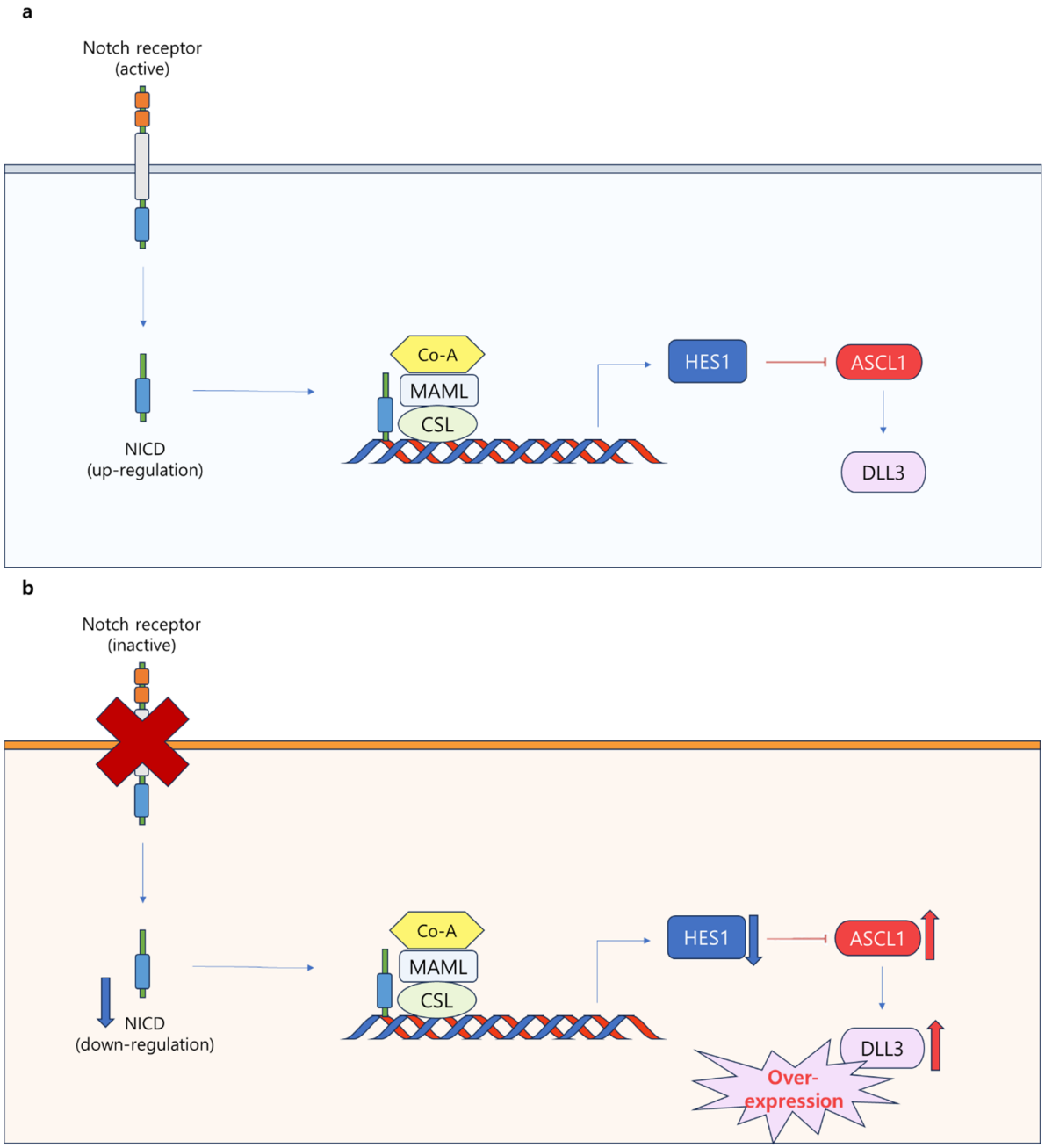

Figure 1. Notch signaling and DLL3 expression according to the intracellular environment. (**a**) In normal cells, Notch signaling is flexibly regulated between activation and inactivation states according to the surrounding microenvironment, maintaining balance. (**b**) In small cell lung cancer cells, unilateral Notch inhibition persists, leading to reduced NICD release into the cell and preventing NICD from reaching the nucleus, thereby suppressing transcriptional regulatory complex and HES1 expression. Consequently, DLL3 is overexpressed and presented on the cell surface. NICD, Notch intracellular domain; CSL, CBF1/suppressor of hairless/Lag1; MAML, mastermind-like, Co-A coactivator; HES1, Hairy and enhancer of split 1; ASCL1, Achaete-Scute homolog 1; DLL3, Delta-like ligand 3.

Primary SCLC is thought to arise through two principal mechanisms: biallelic mutations in TP53 and RB1, or aberrations in the Notch signaling pathway [23]. In vitro analysis of primary combined SCLC cases has revealed fractions harboring TP53 and RB1 mutations and delineated a signaling trajectory leading to the emergence of the small cell phenotype [24]. Ultimately, these molecular events establish a self-reinforcing loop of Notch cis-inhibition, driving sustained and unpredictable NE differentiation.

3. DLL3-Targeted Drugs

The marked overexpression of DLL3 on the surface of SCLC cells has introduced a novel paradigm in the development of targeted therapies for malignant tumors [25]. It is considered an attractive and selective therapeutic target due to its distinctly different expression patterns in tumor cells compared to normal cells [26]. Based on accumulating preclinical and clinical evidence, a variety of therapeutic approaches targeting DLL3 are currently being developed, including near-infrared photoimmunotherapy (NIR-PIT), antibody–drug conjugates (ADCs), BiTEs, and chimeric antigen receptor T cell (CAR-T) therapies (Table 1) [27]. The development of DLL3-targeted therapies is expected to overcome the therapeutic challenges inherent to SCLC, such as rapid doubling time and early metastasis, while also expanding the limited treatment options defined by existing standard regimens [28].

Table 1. Summary of DLL3-targeted therapeutic strategies in SLCL.

Strategy	Mechanism	Representative Agent(s)	Clinical Status	Key Outcomes	Limitations
NIR-PIT	Antibody–photoabsorber conjugate (mAb + IR700) → cell necrosis after NIR light exposure	Rovalpituzumab (DLL3 mAb) + IR700	Preclinical (in vitro, xenograft models)	Selective killing of DLL3$^+$ cells; tumor suppression/survival benefit in mice	Preclinical only; clinical translation pending
ADCs	mAb linked to cytotoxic payload via cleavable linker	Rovalpituzumab tesirine (Rova-T)	Phase I–III (terminated)	Early response benefit	High-grade TEAEs; no survival benefit → development discontinued
BiTEs	Bispecific antibody engaging CD3 on T cells & DLL3 on tumor cells → T cell cytotoxicity	Tarlatamab (AMG 757)	Phase I–III (FDA accelerated approval; confirmatory Phase III positive)	Median OS benefit in phase III vs. chemotherapy (13.6 vs. 8.3 months)	CRS/neurologic AEs; limited long-term/real-world data; IV infusion required
CAR-T	Autologous T cells engineered to express DLL3-specific CAR	AMG 119	Phase I (terminated)	Some complete responses; no uncontrollable TRAEs	Limited efficacy; Development discontinued

NIR-PIT, near-infrared photoimmunotherapy; ADCs, antibody–drug conjugates; BiTE, bispecific T cell engager; CAR-T, chimeric antigen receptor T cell; TEAE, treatment-emergent adverse event; CRS, cytokine release syndrome; AE, adverse effect; OS, overall survival; IV, intravenous.

NIR-PIT is an emerging cancer treatment that uses an antibody–photoabsorber conjugate (APC), composed of a tumor-specific monoclonal antibody and the photosensitizer IR700, a hydrophilic silica-phthalocyanine derivative. Once bound to target molecules on the cell membrane, APCs induce rapid necrotic cell death upon exposure to NIR light at 690 nm through membrane rupture. This approach has been shown to work with various antibodies, enabling selective therapy across multiple tumor types, and its safety and efficacy are currently being evaluated in international phase III trials, such as for recurrent head and neck squamous cell carcinoma (LUZERA-301, NCT03769506). In the case of SCLC, preclinical studies have been conducted using DLL3-targeted NIR-PIT. In vitro analyses confirmed DLL3 expression across SCLC cell lines and patient-derived specimens, and DLL3-specific NIR-PIT with rovalpituzumab selectively induced tumor cell death. In mouse xenograft models, this approach significantly suppressed tumor growth and prolonged survival, suggesting that DLL3-targeted NIR-PIT holds promise as a future therapeutic option for SCLC [29,30].

ADCs are single-molecule constructs that combine monoclonal antibodies with biologically active cytotoxic molecules (warheads) through cleavable chemical linkers and are considered a promising therapeutic strategy [31]. Rovalpituzumab tesirine (Rova-T) is the first ADC developed to target delta-like protein 3 (DLL3). It incorporates a pyrrolobenzodiazepine (PBD) dimer toxin conjugated to the DLL3-specific humanized monoclonal antibody SC16 via a valine–alanine dipeptide linker that is sensitive to lysosomal proteases [25,32]. This linker enables efficient release of the payload following cellular internalization, thereby inducing potent tumor cell death [33]. Initial studies of Rova-T showed favorable outcomes. In preclinical models, it demonstrated prolonged time to tumor progression, and early-phase clinical trials reported impressive response rates, confirming its potential therapeutic value [25,26]. However, treatment-emergent adverse events (TEAEs) of grade ≥3 were consistently observed in patients receiving Rova-T, with treatment discontinuation occurring in 10–19% of cases [34]. Furthermore, in the preplanned interim analyses of the TAHOE and MERU clinical trials, Rova-T did not demonstrate a survival benefit compared to placebo, ultimately leading to the termination of its clinical

development program [35,36]. Although the Rova-T program was discontinued [37], the favorable clinical endpoints observed throughout its evaluation provided important evidence supporting the therapeutic potential of ADCs and contributed to the advancement of subsequent drug development.

BiTEs are designed to bind both T cells and tumor cells simultaneously, thereby inducing T cell–mediated cytotoxicity. This approach offers a way to overcome common obstacles in cancer therapy, including tumor resistance and immune evasion [38,39]. Owing to these advantages, numerous BiTE-based therapies targeting DLL3 are currently under investigation. Further details on DLL3-specific BiTEs will be discussed in the following section.

Alongside ADCs and BiTEs, CAR-T therapy has recently gained attention as another promising approach for targeting DLL3 in SCLC. Although CAR-T therapies have shown remarkable efficacy in hematologic malignancies [40], their application in solid tumors has been limited by issues such as antigen specificity, T cell infiltration, and cellular persistence in the tumor microenvironment [41,42]. AMG 119, like Rova-T, is the first CAR-T therapy to be clinically evaluated for the treatment of SCLC [43]. It generates genetically modified T cells by introducing an auto-inactivating lentiviral vector into autologous T cells, enabling them to target DLL3-expressing tumor cells. In a phase 1 clinical trial, AMG 119 did not result in uncontrollable toxicity or TRAEs, and cases of complete remission (CR) accompanied by measurable tumor shrinkage were observed [44]. Similar to Rova-T, the clinical investigation of AMG 119 was also discontinued; however, it may serve as an early proof-of-concept supporting the potential applicability of CAR-T cell therapy in solid tumors such as SCLC.

4. Tarlatamab

4.1. BiTE Molecules: Mechanism and Challenges

BiTE molecules are antibody constructs possessing two binding domains. The binding domains are single-chain variable fragment regions of monoclonal antibodies, with one specific for T cell CD3 and the other for target cancer cell surface molecules such as CD19, CD33, or DLL3 [45]. This is a characteristic shared by all BiTE molecules, and the binding of these two domains positions T cells in close proximity to tumor cells, forming malignant cell lysis synapses and inducing polyclonal T cell responses [46]. Target cell lysis occurs in the absence of major histocompatibility complex (MHC) class I/peptide antigen recognition and co-stimulation [47,48]. This demonstrates that molecular interactions between target cells and T cells are not essential for synapse formation and BiTE activity, suggesting that BiTE function is not affected by representative immune evasion mechanisms of tumor cells in vivo, such as downregulation of MHC class I expression. Additionally, BiTE possesses various pharmacological advantages, including high potency in inducing biological responses [49], prevention of nonspecific effector cell activation, and enhanced T cell accessibility based on its small antibody format.

Due to these characteristics, BiTE molecules have demonstrated remarkable clinical efficacy in hematologic malignancies, particularly in the treatment of acute leukemias and lymphomas targeting CD19 or CD33 [50,51]. Based on these successful experiences, various attempts to apply BiTE technology to solid tumors are being actively pursued. However, the immunosuppressive tumor microenvironment of solid tumors, antigen heterogeneity, and selectivity of target expression represent challenges that must be overcome to enhance BiTE therapeutic efficiency [52]. Furthermore, BiTE molecules require continuous intravenous infusion due to their relatively short half-life resulting from their small molecular size [39]. This may be accompanied by risks of cytokine release syndrome (CRS) and other adverse effects (AEs) due to immune cell hyperactivation. These pharmacological and immunological burdens lead to difficulties in ensuring therapeutic continuity and safety during clinical development, contributing to the limited approval of BiTE-class drugs to date despite their promising therapeutic potential.

4.2. Tarlatamab: Preclinical Development

To overcome the limitations of BiTE molecules, various structural and functional improvements are being pursued, including Fc domain attachment for half-life extension and miniaturization strategies (e.g., nanobody-Nb) to enhance tumor specificity and strengthen tumor tissue penetration [53,54]. Sophisticated approaches to drug delivery methods and immune toxicity control are also being investigated concurrently. Along with these technological advances, BiTE is emerging as a more promising therapeutic option for solid tumors with distinct overexpression of tumor-specific antigens, particularly malignancies such as SCLC characterized by abnormal cell surface expression of DLL3 [55]. Tarlatamab represents a prime example of this development, being the first BiTE-class therapeutic targeting DLL3 and representing a significant advancement in expanding the clinical applicability of BiTE to solid tumors in the SCLC field, where existing therapeutic options have clear limitations.

As previously mentioned, DLL3 is expressed on the cell surface of SCLC and large cell neuroendocrine carcinoma but does not occur in healthy tissues. Based on this in vivo signaling mechanism, Tarlatamab was

evaluated for its efficacy in various humanized SCLC xenograft models and patient-derived xenograft models during the early preclinical development stage, demonstrating rapid T cell-induced responses and potent tumor suppressive activity regardless of DLL3 expression levels in the subjects. Notably, non-human primate toxicity studies confirmed that major immune-related toxicities due to T cell activation were relatively mild and recoverable. Additionally, half-life extension technology was applied to compensate for the pharmacokinetic disadvantages of bispecific antibodies, securing in vivo stability, and the maintenance of sustained tumor suppressive effects without immune cell depletion or T cell exhaustion following repeated administration was also presented as a major characteristic of Tarlatamab's preclinical achievements [56].

4.3. Tarlatamab: Clinical Trials and FDA Approval

Encouraged by preclinical findings, Tarlatamab advanced into clinical trials to evaluate the pharmacological therapeutic effects of Tarlatamab in SCLC patients with disease progression following repeated PBC. In the Phase I clinical trial DeLLphi-300 (NCT03319940), a total of 107 patients participated in dose-finding and expansion cohort analyses. More than 70% of the enrolled patients had previously received second-line or higher treatments, 25% were platinum-refractory, and 50% had prior experience with PD-1/PD-L1 inhibitors. Major adverse events included CRS and mild neurological symptoms, but most were manageable at grade 1–2 levels. The objective response rate (ORR) was 23.4%, including 2 CR and 23 partial responses (PR) according to RECIST 1.1 criteria, where CR is defined as the complete disappearance of tumors and PR as a reduction in tumor size of 30% or more [57]. The median duration of response was 12.3 months, the median progression-free survival (PFS) was 3.7 months, and the median OS was 13.2 months, confirming meaningful clinical responses in a patient population with limited options following palliative treatment failure [58].

The basis for FDA accelerated approval of Tarlatamab can be found in the subsequently conducted Phase II DeLLphi-301 study (NCT05060016). This trial, involving a total of 222 SCLC patients who had relapsed or shown resistance following one or more standard therapies, was conducted in three main parts. In Part 1 (dose selection), 88 patients each received intravenous injections of either 10 mg or 100 mg doses of Tarlatamab until disease progression. All patients participating in the clinical trial received 1 mg of Tarlatamab on day 1 of cycle 1, target doses on days 8 and 15, and subsequently received treatment every 2 weeks in 28-day cycles. In Part 2 (dose expansion), 100 patients received the selected dose of 10 mg, combining the 88 patients who received 10 mg in Part 1 with an additional 12 patients. Part 3 evaluated the safety of shortening Tarlatamab's adverse event monitoring from 48 h to 24 h post-infusion. As a follow-up study to preclinical and Phase I clinical trials, the reconfirmation of efficacy and safety results showed an ORR of 40%, PFS of 4.9 months, and OS of 14.3 months. The incidence of grade 3 or higher treatment-related severe adverse events was very favorable, with CRS at 1% and ICANS at 0%, showing an excellent safety profile. Furthermore, shortening the inpatient monitoring period for Tarlatamab from 48 h to 24 h did not worsen safety outcomes [59,60]. Through these successive clinical trials, Tarlatamab continuously demonstrated objective survival extension effects, and based on these results, the FDA decided on accelerated approval of Tarlatamab for adult patients with extensive-stage small cell lung cancer (ES-SCLC) who had disease progression during or after PBC.

In the phase III DeLLphi-304 trial (NCT05740566), Tarlatamab significantly improved overall survival compared with chemotherapy (median 13.6 vs. 8.3 months; HR 0.60, $p < 0.001$). It also demonstrated superior progression-free survival, symptom control, and a lower incidence of grade ≥3 adverse events, further consolidating its role in the treatment of SCLC [61]. The positive results of the confirmatory phase III DeLLphi-304 trial consolidate the role of Tarlatamab in SCLC treatment and may enable its transition from accelerated to full regulatory approval.

5. Conclusions

The tumor-specific expression of DLL3 has opened new avenues for targeted therapy in the persistent therapeutic challenges of SCLC and other NETs, as evidenced by the sequential clinical achievements of multiple DLL3-targeting agents currently undergoing clinical evaluation. Among various technological platforms targeting DLL3, BiTEs represent a therapeutic strategy that demonstrates the potential to expand immunotherapeutic possibilities in solid tumors, particularly SCLC. This approach has shown encouraging preliminary efficacy and safety profiles in early-phase clinical studies involving patients with relapsed and refractory small cell lung cancer, with Tarlatamab serving as a representative success case. However, objective comparative metrics against existing standard anticancer therapies remain insufficient, and continued evaluation of drug response heterogeneity, management of immune-related adverse events, and long-term treatment durability is required. Future research is anticipated to focus on the refinement of clinical trial design to address these issues, alongside the development of

biomarkers for patient selection. Despite confronting several unresolved challenges, DLL3-targeting therapeutic strategies present novel possibilities for immune-based treatments, and their potential is expected to become increasingly evident through continued mechanistic research and clinical validation.

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Abbreviations

SLCL, Small cell lung cancer; PBC, Platinum-based chemotherapy; OS, overall survival; BiTE, Bispecific T cell engagers; NCID, Notch intracellular domain; NIR-PIT, Near-infrared photoimmunotherapy; ADCs, Antibody–drug conjugates; CAR-T, Chimeric antigen receptor T cell; APC, Antibody–photoabsorber conjugate; TEAEs, Treatment-emergent adverse events; CR, Complete remission; MHC, Major histocompatibility complex; CRS, Cytokine release syndrome; AEs, Adverse effects; ORR, Objective response rate; PR, Partial response

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