

Tarlatamab in Small-Cell Lung Cancer: Clinical Validation of DLL3 as a Therapeutic Target

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How to cite this paper: Gutiérrez-Barros, G.A., Morales-Morales, M.V., Padilla, C.A.M., Reyes, S.M.M., Pérez, J.F.D., Cantor, L.E.V., Valencia, K.A.M., Caliz, E.J.D., Ricaurte, S.A.V. and Castillo, I.P. (2026) Tarlatamab in Small-Cell Lung Cancer: Clinical Validation of DLL3 as a Therapeutic Target. *Journal of Biosciences and Medicines*, 14, 154-170.

<https://doi.org/10.4236/jbm.2026.147014>

Received: May 8, 2026

Accepted: July 12, 2026

Published: July 15, 2026

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Abstract

Small-cell lung cancer (SCLC) remains a highly lethal malignancy, characterized by rapid proliferation, early dissemination, transcriptional plasticity, and frequent relapse after an initial response to systemic therapy. The incorporation of PD-L1 inhibitors into platinum-etoposide chemotherapy has modified the first-line standard for extensive-stage disease, although the absolute survival benefit remains limited and subsequent options continue to show restricted efficacy. Delta-like ligand 3 has emerged as a therapeutic target of particular interest because of its prevalent expression in small-cell lung cancer, its association with the neuroendocrine tumor program, and its limited expression in accessible normal tissues. Tarlatamab is a bispecific T-cell engager directed against DLL3 and CD3, designed to induce redirected T-cell cytotoxicity against DLL3-positive tumor cells, independently of conventional antigen presentation. The available clinical evidence in adults with extensive-stage SCLC progressing during or after platinum-based chemotherapy shows clinically relevant objective responses, prolonged duration of response, and survival benefit compared with investigator-selected standard chemotherapy. These findings position tarlatamab as the first anti-DLL3 strategy with robust clinical validation in this therapeutic setting, without implying automatic extrapolation to earlier lines of therapy, limited-stage disease, or populations not adequately represented in pivotal studies. Its safety profile is dominated by cytokine release syndrome and neurologic toxicity, including immune effector cell-associated neurotoxicity syndrome, events that are predominantly early and manageable under protocolized monitoring. Overall, tarlatamab represents a sub-

stantial modification of the treatment landscape for post-platinum extensive-stage SCLC and a platform with potential expansion toward earlier lines and combination strategies, currently under investigation.

Keywords

Small-Cell Lung Cancer, Tarlatamab, DLL3, Bispecific T-Cell Engager, Immunotherapy

1. Introduction

Small-cell lung cancer remains one of the thoracic malignancies with the highest disease-specific lethality, owing to its high proliferative fraction, short doubling time, early hematogenous dissemination, and rapid loss of therapeutic control after an initial response that is often intense but transient [1] [2]. Although it accounts for approximately 13% - 15% of lung cancers, its impact on mortality is disproportionate. Approximately 250,000 new cases and 200,000 deaths are estimated worldwide each year, while around 30,000 - 33,000 cases are reported annually in the United States. This burden is particularly relevant because 60% - 70% of patients are diagnosed with extensive-stage disease, a scenario in which long-term survival remains exceptional, and the natural history is still dominated by systemic relapse, early progression, and tumor-related death [3].

The clinical aggressiveness of SCLC reflects a complex and unstable molecular biology. The nearly universal functional loss of TP53 and RB1 constitutes its most characteristic genomic axis, accompanied by recurrent chromosomal alterations, oncogenic amplifications, epigenetic reprogramming, and dependence on neuroendocrine transcriptional circuits [4]. This architecture is compounded by marked intratumoral heterogeneity, with subpopulations regulated by ASCL1, NEUROD1, POU2F3, and inflammatory signatures, as well as transitions between neuroendocrine and non-neuroendocrine states mediated, among other mechanisms, by Notch signaling. This plasticity explains why initial sensitivity to cytotoxic agents rarely translates into sustained control: SCLC relapse represents the clinical manifestation of clonal persistence, transcriptional adaptation, and tumor selection under therapeutic pressure [5].

For decades, systemic treatment for SCLC was based on the platinum-etoposide doublet, with high initial response rates but limited duration of benefit and historically short overall survival, particularly in extensive-stage disease. The incorporation of anti-PD-L1 immunotherapy into the first-line setting changed the therapeutic standard, although without reversing the general pattern of progression. In IMpower133, atezolizumab plus carboplatin-etoposide achieved a median overall survival of 12.3 months versus 10.3 months with chemotherapy alone. Similarly, CASPIAN showed a median overall survival of 13.0 months with durvalumab plus platinum-etoposide versus 10.3 months with chemotherapy. These results established a clinically relevant but quantitatively limited advance: they confirmed ac-

tivity of the PD-L1 axis, although insufficient to substantially modify the relapse biology of SCLC [6] [7].

Progressive disease remains the main area of fragility within the therapeutic algorithm. Once the benefit of platinum-based chemotherapy, with or without immunotherapy, has been exhausted, salvage options offer restricted activity, short response duration, and modest impact on overall survival. Topotecan, the historical second-line reference, retains a predominantly palliative role, with efficacy conditioned by prior platinum sensitivity and considerable hematologic toxicity [8]. Lurbinectedin provided a relevant signal of activity, with an objective response rate of 35.2% in previously treated disease, but it also failed to eliminate the transient nature of tumor control or definitively transform the prognosis of relapsed disease [9].

This therapeutic limitation is better understood by examining the immunologic interface of SCLC. Despite its association with heavy tobacco exposure and the resulting high mutational burden, the tumor frequently displays a functionally ineffective immune microenvironment, with defects in antigen presentation, variable density of lymphocytic infiltration, and restricted performance of checkpoint inhibitor-based strategies. In this context, delta-like ligand 3 acquired relevance as a neuroendocrine lineage target because of its prevalent expression in SCLC and its minimal representation in accessible normal tissues. Several series place its expression at approximately 75% - 96% of small-cell tumors, consolidating it as one of the most consistent surface targets in a disease historically poor in actionable targets. The importance of DLL3 lies not only in its prevalence, but also in the fact that it offers a relatively conserved biological vulnerability within an extraordinarily plastic tumor [10].

Tarlatamab arises directly from this biological and clinical rationale, since, as a bispecific T-cell engager directed against DLL3 and CD3, its development addresses an unresolved therapeutic need: to exploit a highly prevalent lineage target in order to induce redirected T-cell cytotoxicity in a disease with limited benefit from conventional salvage strategies. Its relevance depends on the convergence between the persistent lethal burden of SCLC, the still limited magnitude of benefit obtained with first-line chemoimmunotherapy, the insufficiency of traditional subsequent therapies, and the availability of a biologically plausible tumor target such as DLL3 [11] [12]. To avoid excessive extrapolation of clinical scope, this review uses “previously treated SCLC” as a general descriptor for populations exposed to prior systemic lines, whereas “relapsed or refractory SCLC” is reserved for early-phase or phase II studies involving patients treated with two or more previous lines, and “extensive-stage SCLC progressing during or after platinum-based chemotherapy” is used to precisely describe the setting of the most robust comparative and regulatory validation. Within this framework, the present article analyzes the post-platinum therapeutic crisis, the immunobiological basis of DLL3, the pharmacologic rationale for tarlatamab, and the consistency of the available clinical evidence, distinguishing between signal of activity, comparative confirmation, and expansion toward earlier lines that remains under evaluation.

2. Biological Basis of DLL3 in SCLC

Delta-like ligand 3 (DLL3) is an atypical ligand of the Notch pathway, with a predominantly inhibitory function, whose expression is increased in a broad proportion of pulmonary small-cell tumors. Unlike other Notch ligands, DLL3 does not primarily act as an activator of intercellular signaling, but rather as a negative modulator of the Notch axis, with direct implications for preservation of the neuroendocrine phenotype [13].

Nevertheless, DLL3 should not be interpreted as an absolutely static variable. Analyses of paired samples obtained before systemic treatment and after post-chemotherapy relapse show variations in expression intensity in a proportion of tumors, with increases or decreases depending on the case [14]. This observation is relevant from a translational perspective because it suggests that, although DLL3 retains value as a lineage marker, its antigenic density may be modified under therapeutic pressure. Therefore, DLL3 assessment in SCLC should consider not only tumor positivity, but also the molecular context, prior therapeutic exposure, and the possible selection of subclones with different expression levels.

In SCLC, the biological relevance of DLL3 also derives from its integration into the transcriptional network dominated by achaete-scute homolog 1 (ASCL1), one of the main regulators of neuroendocrine identity. The relationship among ASCL1, DLL3, and Notch-HES1/HEY1 signaling forms a circuit in which Notch inhibition favors persistence of the neuroendocrine program, while DLL3 expression aligns with stabilization of that cellular state [15] [16].

The therapeutic importance of DLL3 also depends on its cellular localization pattern. In normal tissues, DLL3 shows low and predominantly intracellular expression, with localization in the Golgi apparatus and vesicular compartments. By contrast, in SCLC it may acquire aberrant surface expression, making this molecule an accessible target for directed therapeutic strategies [15] [16]. This topographic difference has direct translational implications: a protein associated with the neuroendocrine lineage, with limited exposure in accessible healthy tissues and redistribution toward the tumor-cell membrane, meets favorable conditions for the development of selective therapies.

The frequency of DLL3 expression reinforces its value as a target in SCLC. Available studies place its positivity in more than 80% of cases, with approximate ranges of 75% - 96% depending on the assay, cohort, and cutoff used [17]-[19]. Complementarily, studies using specific immunohistochemical assays and international cohorts have confirmed that DLL3 expression does not appear to be restricted to a narrow clinical subgroup defined by age, sex, stage, or number of prior lines of therapy [18] [19]. This broad distribution makes DLL3 a potentially applicable target across a substantial proportion of the clinical spectrum of SCLC.

DLL3 has also been linked to biological processes that exceed simple phenotypic characterization. Its overexpression has been associated with increased cell growth, greater migratory and invasive capacity, and modulation of programs related to phenotypic transition, particularly through Snail [20]. Complementarily,

regulation by the LIN28B/miR-518d-5p axis suggests involvement of DLL3 in proliferation, migration, and chemotherapy response in advanced SCLC [21]. These findings broaden its biological meaning: DLL3 does not function exclusively as a marker of neuroendocrine identity, but as a molecule integrated into circuits that may influence tumor progression, aggressiveness, and therapeutic adaptation.

Preclinical models provided an additional rationale for its therapeutic targeting. Saunders *et al.* demonstrated that an antibody-drug conjugate directed against DLL3 could eliminate tumor-initiating cells in models of high-grade pulmonary neuroendocrine neoplasms, consolidating the functional relevance of the target beyond its surface expression [22]. This observation has direct conceptual implications for the subsequent development of anti-DLL3 immunotherapeutic strategies: a prevalent target, accessible at the membrane, associated with the neuroendocrine program, and linked to compartments biologically relevant for tumor perpetuation provides a rational basis for cellular redirection through bispecific platforms.

Overall, the biological basis of DLL3 in SCLC rests on four convergent properties: integration into the neuroendocrine transcriptional program, negative regulatory function on the Notch pathway, differential tumor exposure relative to healthy tissues, and association with proliferation, migration, therapeutic response, and tumor-initiation potential. These features justify its consideration as a high-priority therapeutic target and explain why the development of tarlatamab is supported by a lineage vulnerability with consistent biological grounding.

3. DLL3 as a Practical Biomarker

Although DLL3 constitutes the biological foundation for the development of tarlatamab, its use in clinical practice should not yet be interpreted as that of a fully validated predictive biomarker. The available evidence supports DLL3 primarily as a therapeutic target associated with the neuroendocrine lineage of SCLC, rather than as a quantitative variable capable of precisely selecting patients with a higher probability of response. In practical terms, DLL3 positivity may vary according to the antibody used, the immunohistochemical platform, the type of specimen, the timing of tissue acquisition, prior treatment exposure, and the cutoff applied. This variability limits direct comparability across studies and explains why, to date, there is no universally accepted threshold of DLL3 expression that functions as a standardized predictive criterion [23].

From a regulatory and clinical-care perspective, tarlatamab administration is not currently conditioned on mandatory performance of a companion diagnostic test for DLL3. The approved indication is defined by the clinical context—adults with extensive-stage SCLC progressing during or after platinum-based chemotherapy—and not by a minimum value of DLL3 immunohistochemical expression. Therefore, in the current setting, DLL3 assessment may provide biological and translational information, but it should not be considered a universal require-

ment for initiating tarlatamab, nor should it replace clinical selection based on stage, prior platinum exposure, performance status, tumor burden, comorbidities, and institutional capacity to monitor early immune-mediated toxicity. This distinction is important: DLL3 confirms a therapeutic vulnerability associated with the neuroendocrine lineage, but it does not yet function as a validated predictive biomarker for defining indication, adjusting dose, or establishing individualized therapeutic sequencing [24].

4. Mechanism of Action and Pharmacologic Parameters of Tarlatamab

Tarlatamab is a bispecific T-cell engager designed to bind simultaneously to delta-like ligand 3 (DLL3) on the tumor cell and to cluster of differentiation 3 (CD3) on the T cell. This dual specificity induces physical proximity between both cellular compartments and enables activation of a cytotoxic response directed against DLL3-positive tumor cells. Its effector mechanism operates as a pharmacologically induced cytolytic synapse: DLL3/CD3 coupling triggers lymphocyte activation, transient cytokine release, and tumor lysis, with reduced dependence on classical antigen-processing and presentation pathways. This point is particularly relevant in SCLC, a neoplasm in which antigen-presentation defects and the limited efficacy of checkpoint inhibitors have historically restricted the magnitude of immunotherapeutic response [12] [25].

The preclinical potency of tarlatamab constituted the main foundation for its clinical transition. Giffin *et al.* demonstrated that AMG 757, the developmental designation of tarlatamab, induces T-cell-dependent cytotoxicity at low picomolar concentrations and retains activity against SCLC cell lines with very low surface DLL3 expression, below 1000 molecules per cell. The absence of effect on cells without DLL3 expression reinforced the functional specificity of the system. In orthotopic models and patient-derived xenografts, significant tumor regression was documented, including models with established pulmonary disease and liver metastases; moreover, toxicology studies in nonhuman primates showed adequate tolerability with repeated dosing. These findings defined a coherent translational profile, supported by biological potency, demonstrable antigen dependence, and an initial safety signal compatible with clinical evaluation [25].

From a pharmacologic standpoint, tarlatamab belongs to a generation of half-life-extended BiTE molecules developed to overcome a central limitation of conventional bispecific engagers: rapid systemic clearance and the need for continuous or very frequent exposure. Canonical formats lack an Fc domain and therefore do not benefit from neonatal Fc receptor-mediated recycling, which favors rapid clearance and has forced first-generation molecules into continuous-infusion schemes. By contrast, half-life-extended platforms incorporate modifications designed to prolong systemic exposure without compromising functional approximation between T cell and tumor cell. In tarlatamab, this optimization translates into exposure compatible with administration every two weeks, a decisive element

for its clinical development in patients with previously treated SCLC [26] [27].

Clinical pharmacokinetic analyses confirmed that this structural optimization translates into usable systemic behavior. In DeLLphi-300, tarlatamab showed an approximately proportional increase in exposure across the evaluated dose range, biphasic behavior after intravenous infusion, and half-life-extended characteristics compatible with biweekly administration. Complementarily, the integrated population analysis of DeLLphi-300 and DeLLphi-301 described tarlatamab pharmacokinetics using a two-compartment model with linear elimination, estimated a terminal half-life of approximately 11 days, and identified no clinically significant effects of age, sex, ethnicity, baseline renal or hepatic function, prior lines of therapy, baseline disease status, or immunogenicity on exposure that would justify systematic dose adjustment. The observed immunogenicity was low and showed no clinically relevant impact on exposure in the available analyses. This point is important because the serum persistence of a half-life-extended molecule could be compromised by antidrug antibodies; however, the available pharmacokinetic data suggest that the emergence of anti-tarlatamab antibodies does not substantially modify the exposure profile in the treated population. Overall, these findings support tarlatamab dosing based on a fixed regimen with an initial step-up dose, rather than individualized adjustments based on usual demographic or clinical characteristics [27] [28].

Selection of the clinical regimen was not empirical, but derived from an integrated analysis of exposure, efficacy, and safety. Chen *et al.* demonstrated, using pooled data from DeLLphi-300 and DeLLphi-301, favorable exposure-response relationships for objective response rate, disease control rate, tumor reduction, progression-free survival, and overall survival. Efficacy approached a functional plateau at the exposures achieved by the 10 mg every-two-weeks regimen. Importantly, no clear relationship was identified between greater exposure and increased grade ≥ 3 events for cytokine release syndrome, neurologic toxicity, including immune effector cell-associated neurotoxicity syndrome, or overall treatment-related toxicity, although a superficial trend toward higher-grade neutropenia was observed at higher exposures. This pharmacologic information supports the 10 mg every-two-weeks regimen as a strategy with antitumor activity close to the expected maximum and without an evident parallel increase in the most relevant severe immunologic toxicities [29].

The integration of early pharmacodynamics and safety explains the need for an initial step-up dose. The first pharmacologic exposure induces activation of the T-cell compartment and transient cytokine release, a phenomenon that constitutes the biological basis of cytokine release syndrome and early neurologic surveillance. Therefore, the initial step-up administration should not be interpreted as a mere precautionary measure, but as a pharmacologic intervention intended to modulate the early effector peak while subsequently maintaining effective exposure; in this context, tarlatamab represents a platform in which antigen specificity, serum kinetics, temporally concentrated immune activation, and rational dose selection converge into a coherent therapeutic design for SCLC exposed to prior sys-

temic treatment, particularly in the post-platinum setting in which its clinical development was consolidated.

5. Clinical Results and Magnitude of Therapeutic Benefit

The clinical evidence for tarlatamab in previously treated SCLC can be organized into five complementary levels: early-phase signal of activity, phase II registration confirmation, maturation of follow-up, comparative validation versus standard chemotherapy, and experience in routine clinical practice. This structure allows the clinical development of the drug to be assessed in an integrated manner. Interpretation of tarlatamab should not be limited to objective response rate, but should incorporate duration of response, survival, intracranial activity, safety profile, and reproducibility of benefit in less selected populations.

Dowlati *et al.* demonstrated, through the DeLLphi-300 update, that the activity observed in the initial phase persisted with longer follow-up. In this phase I trial, which included 152 patients treated with clinically relevant doses of tarlatamab, the objective response rate was 25.0%, the median duration of response was 11.2 months, and the median overall survival reached 17.5 months. The subgroup treated with 10 mg every two weeks showed the results of greatest clinical interest, with an objective response rate of 35.3%, median duration of response of 14.9 months, and median overall survival of 20.3 months. In addition, 29.4% of patients maintained disease control for at least 52 weeks [30].

The intracranial assessment of DeLLphi-300 added a clinically relevant component. Using modified Response Assessment in Neuro-Oncology Brain Metastases criteria, a reduction of at least 30% in central nervous system lesions was documented in 62.5% of patients with a baseline brain lesion of at least 10 mm. This finding does not amount to definitive validation of independent intracranial efficacy, but it does constitute a relevant signal in an anatomic compartment of high importance for SCLC, given the frequency of brain metastases during the course of the disease.

Registration confirmation came from DeLLphi-301, a multicenter, open-label phase II study in patients with recurrent SCLC previously treated with two or more lines of therapy. Ahn *et al.* evaluated tarlatamab administered every two weeks at two dose levels, 10 mg and 100 mg, with the aim of defining antitumor activity and the benefit-risk relationship. In the 10 mg cohort, the confirmed objective response rate was 40%, compared with 32% in the 100 mg cohort. Median progression-free survival was 4.9 months with 10 mg and 3.9 months with 100 mg; estimated survival at 9 months was 68% and 66%, respectively. These data established that dose escalation did not translate into a proportional efficacy gain and consolidated the 10 mg every-two-weeks regimen as the most clinically relevant dose [31].

Subsequent maturation of DeLLphi-301 reinforced the consistency of the signal, although it must be interpreted with the appropriate follow-up reported in abstract form. In the extended follow-up, Sands *et al.* reported that the objective

response rate of the 10 mg regimen remained around 40%, with a disease control rate of 70%, median progression-free survival of 4.3 months, and median overall survival of 15.2 months [32]. Approximately one-quarter of patients maintained tumor control for at least 52 weeks. In the subgroup with baseline brain metastases, a reduction of at least 30% in central nervous system lesions was reported in a relevant proportion of evaluable patients, along with high intracranial control. These results support the existence of a subgroup with prolonged benefit, although the abstract format limits the methodological depth available for interpreting the exact magnitude of intracranial activity.

Comparative validation of therapeutic benefit came from DeLLphi-304, a randomized, open-label phase III trial in patients with extensive-stage SCLC whose disease had progressed during or after platinum-based chemotherapy. In this study, tarlatamab was compared with investigator-selected standard chemotherapy—topotecan, lurbinectedin, or amrubicin—so the control group reflected active salvage options, although with inherent therapeutic heterogeneity. Median overall survival was 13.6 months with tarlatamab versus 8.3 months with chemotherapy, with a hazard ratio for death of 0.60; in addition, tarlatamab showed significant benefit in progression-free survival and patient-reported outcomes related to dyspnea and cough, along with a lower incidence of grade 3 or higher adverse events than chemotherapy [33]. The relevance of DeLLphi-304 is decisive for the post-platinum setting because the benefit was no longer supported only by historical comparisons or early-phase signals, but was demonstrated against an active comparator in a randomized trial, although subgroup interpretation and extrapolation to nonrepresented populations must remain cautious.

The magnitude of benefit in DeLLphi-304 is also relevant from the perspective of the therapeutic algorithm. Superiority in overall survival versus investigator-selected standard chemotherapy positions tarlatamab as an option with confirmed clinical impact after progression on platinum. Nevertheless, interpretation of subgroups, including patients with brain metastases, should remain prudent when there is no specific stratification designed to formally demonstrate intracranial efficacy. Therefore, current evidence supports a robust systemic benefit and consistent signals of activity in the central nervous system, but does not replace the need for prospective analyses specifically oriented toward intracranial disease.

Routine clinical-practice data add a complementary level of analysis, especially because they allow observation of tarlatamab performance in patients less selected than those included in pivotal studies. Bolte *et al.* retrospectively evaluated a cohort in which 40.9% of patients had brain metastases, 63.8% had liver metastases, and 81.8% would not have met the eligibility criteria for DeLLphi-301; after a median follow-up of 6.7 months, the objective response rate in patients with SCLC was 42.9%, supporting the external plausibility of the activity observed in trials, although without replacing randomized evidence or allowing definitive inferences of comparative efficacy [34]. The same series also showed a potentially more complex toxicity profile, with cytokine release syndrome in 72.7% of patients and immune effector cell-associated neurotoxicity syndrome in 40.9%, events that were

more frequent and severe in the presence of untreated brain metastases. These findings do not contradict the pivotal-trial results, but they underscore that real-world implementation of tarlatamab requires careful clinical selection, structured early surveillance, and particular caution in patients with active intracranial disease, high metastatic burden, or lower functional reserve.

The integration of tarlatamab into post-platinum SCLC should be interpreted within a resistance biology dominated by cellular plasticity, lineage heterogeneity, and immune evasion, since SCLC is not a uniform transcriptional entity but rather a spectrum of molecular states defined by ASCL1, NEUROD1, POU2F3, and YAP1, with relevant differences in DLL3 expression, neuroendocrine dependence, antigen presentation, and tumor microenvironment composition. In this framework, neuroendocrine phenotypes such as SCLC-A and part of SCLC-N tend to express DLL3 and could be more vulnerable to anti-DLL3 strategies, whereas transition toward non-neuroendocrine states, emergence of hybrid phenotypes under therapeutic pressure, lymphocytic exclusion, loss of MHC class I, and consolidation of an immunosuppressive microenvironment may limit the duration of benefit. Although tarlatamab offers a mechanistic advantage by redirecting T cells against DLL3-positive tumor cells without relying on classical antigen presentation, its positioning relative to lurbinectedin, topotecan, or platinum rechallenge should be individualized according to prior platinum sensitivity, pace of progression, tumor burden, performance status, hematologic reserve, and institutional capacity to monitor early immune-mediated toxicity; therefore, the optimal sequence should still be considered open and susceptible to refinement through molecular subtyping, immune profiling, and dynamic biomarkers of resistance [35].

6. Toxicity, Monitoring, and Therapeutic Projection

Tarlatamab toxicity is defined mainly by two immune-mediated entities: cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). Both reflect acute immune activation induced by the functional coupling between the T cell and the delta-like ligand 3 (DLL3)-positive tumor cell, and they constitute the risk axis that conditions initial administration, structured surveillance, and the design of specific care models. In the DeLLphi-301 safety analysis, CRS was frequent but mostly low grade and concentrated during the first cycle; events were managed primarily with supportive measures, including antipyretics, intravenous hydration, and glucocorticoids, while the use of tocilizumab, high-flow oxygen, or vasopressors was infrequent. ICANS and other associated neurologic events occurred in a minority of patients, predominantly at grades 1 - 2. The clinical importance of these data lies in their temporal pattern: the risk is most intense during the step-up dosing period and tends to decrease in subsequent cycles, allowing anticipatory surveillance proportional to the timing of exposure [36].

CRS corresponds to a systemic inflammatory syndrome triggered by acute release of proinflammatory mediators after immune activation, whereas ICANS

comprises a spectrum of neurologic manifestations associated with immune effector cells. The clinical grading of both events should be standardized using the criteria of the American Society for Transplantation and Cellular Therapy (ASTCT). In this classification, CRS is graded on the basis of fever, hypotension, and hypoxemia, whereas ICANS requires structured assessment of mental status, level of consciousness, motor findings, seizures, and signs of intracranial hypertension or cerebral edema. Adoption of this classification homogenizes event interpretation, avoids overestimation derived from isolated constitutional symptoms, and enables comparison of toxicity across different immunotherapeutic platforms [37].

From a regulatory standpoint, tarlatamab received accelerated approval from the Food and Drug Administration on May 16, 2024, for adults with extensive-stage SCLC progressing during or after platinum-based chemotherapy, an indication initially supported by objective response rate and duration of response in previously treated disease. Subsequently, on November 19, 2025, the FDA converted this indication to traditional approval after verification of clinical benefit in DeLLphi-304, a randomized phase III trial that compared tarlatamab with investigator-selected standard chemotherapy and demonstrated a median overall survival of 13.6 months versus 8.3 months, with a hazard ratio for death of 0.60. This precision is relevant because it delimits the approved clinical scope to post-platinum extensive-stage SCLC, not to all contexts of previously treated SCLC, and because the current regulatory information maintains the need for administration by trained teams and structured monitoring during the first exposures owing to the risk of cytokine release syndrome and neurologic toxicity, including ICANS.

Accumulated experience has allowed exploration of less intensive observation models in selected contexts. Chiang *et al.* evaluated, in a phase I DeLLphi-300 substudy, the safety of 6 - 8-hour outpatient monitoring after cycle 1 doses compared with 48-hour inpatient monitoring. In the outpatient group, 60% experienced tarlatamab-related CRS, all events occurred during cycle 1 and were grade 1 - 2, and the median time to resolution was 3 days, similar to that observed in the inpatient group. This finding does not authorize indiscriminate de-intensification. Its correct interpretation is operational: reduced observation time may be considered only when adequate infrastructure, careful patient selection, prespecified visits, rapid access to hospital evaluation, and precise patient and caregiver education are available [24] [38].

The early pathophysiology of tarlatamab-associated CRS has begun to be characterized, although the evidence remains limited. In an exploratory series of three patients with advanced SCLC, Imakita *et al.* described elevations of interleukin 6, interleukin-1 receptor antagonist, interleukin 10, and granulocyte colony-stimulating factor during initial CRS episodes, whereas monokine induced by interferon- γ and interferon- γ -induced protein 10 persisted as prominent signals during recurrences. These findings are insufficient to define clinical biomarkers or therapeutic algorithms, but they suggest that tarlatamab-associated CRS may not be dominated exclusively by the IL-6 axis. Therefore, response to tocilizumab may

be sufficient in a relevant proportion of cases, although inflammatory interpretation should remain individualized and guided by clinical evolution [39].

The regulatory review broadens understanding of risk beyond CRS and ICANS. Liu *et al.* described, in the FDA approval summary, that the most frequent adverse reactions included CRS, fatigue, pyrexia, dysgeusia, decreased appetite, musculoskeletal pain, constipation, anemia, and nausea; in addition, safety issues considered priorities included CRS, neurologic toxicity with ICANS, hepatotoxicity, infections, cytopenias, and hypersensitivity. Therefore, although CRS and ICANS structure early surveillance, monitoring should not be limited to them: clinical evaluation should retain a broad view that includes cytopenias, infections, hepatic abnormalities, hypersensitivity, and neurologic toxicity not limited to ICANS, especially in patients with extensive prior therapeutic exposure, accumulated comorbidity, or reduced organ reserve [40].

The therapeutic projection of tarlatamab rests on a dual condition: confirmed clinical benefit in post-platinum extensive-stage SCLC and immune-mediated toxicity that is potentially protocolizable when trained teams, early monitoring, and clear intervention pathways are available. In the combination setting, Paulson *et al.* evaluated tarlatamab together with programmed death-ligand 1 (PD-L1) inhibitors as first-line maintenance after chemoimmunotherapy in extensive-stage SCLC within DeLLphi-303, a multicenter, nonrandomized phase 1b study whose signal of activity and manageable safety provides a rational basis for confirmatory research, but should not be interpreted as definitive evidence of first-line efficacy or as an automatic extension of the approved indication [41].

In the confirmatory setting, DeLLphi-305 is evaluating tarlatamab plus durvalumab as first-line maintenance in extensive-stage SCLC, whereas DeLLphi-306 is examining tarlatamab versus placebo after chemoradiotherapy in limited-stage disease. The logic of these strategies is clear: if the greatest value of tarlatamab lies in T-cell cytotoxicity redirected against a lineage target, its impact could be greater in settings of lower tumor burden, less functional deterioration, and lower baseline inflammatory complexity. This hypothesis, however, must be considered prospective. Ongoing studies should not be presented as evidence of efficacy, but as formal evaluation of a biologically plausible strategy [42] [43].

Despite the consistency of the clinical signal, interpretation of tarlatamab must acknowledge several uncertainties that remain relevant. The initial studies supporting the drug's activity were open-label and noncomparative, which limited their ability to estimate relative benefit versus other salvage alternatives; in addition, part of the extended follow-up information comes from abstract communications, with less methodological granularity than a full publication. DeLLphi-304 largely corrected this limitation by demonstrating superiority over standard chemotherapy in a randomized trial, although the control arm included heterogeneous options—topotecan, lurbinectedin, or amrubicin—which should be considered when interpreting indirect comparisons with specific regimens. Finally, evidence remains less robust in patients with untreated brain metastases, symptomatic in-

tracranial disease, poor performance status, or high clinical frailty, groups in which the relationship among efficacy, neurologic toxicity, and feasibility of monitoring requires prospective data and more mature real-world experience.

7. Conclusions

Tarlatamab represents the first robust clinical validation of DLL3 as a therapeutic target in extensive-stage SCLC progressing during or after platinum-based chemotherapy. Its relevance transcends the induction of objective responses, as the observed benefit integrates duration of response, prolonged tumor control, and survival superiority over investigator-selected standard chemotherapy within a disease historically characterized by early relapse, biological plasticity, and limited efficacy of salvage strategies.

This advance must be interpreted within a precise clinical balance. T-cell redirection against DLL3 offers a therapeutic pathway mechanistically distinct from chemotherapy and checkpoint inhibition, but it requires early recognition and structured management of immune-mediated toxicities, particularly cytokine release syndrome and neurologic toxicity, including immune effector cell-associated neurotoxicity syndrome. Safe implementation of tarlatamab will therefore depend on care protocols capable of integrating patient selection, initial monitoring, patient education, and timely access to supportive interventions.

Overall, tarlatamab should not be considered merely a new option for post-platinum extensive-stage SCLC, but rather a clinical proof that DLL3 can be exploited as a lineage vulnerability through T-cell redirection. Its consolidation redefines the therapeutic value of DLL3 in this specific setting and opens a rational platform for evaluating strategies in earlier lines, lower-tumor-burden contexts, and immunotherapeutic combinations, although these applications must remain differentiated from the currently validated indication until prospective confirmatory results become available. The immediate challenge will be to translate this benefit into real-world practice without losing the rigor of surveillance required by a cellular-redirection immunotherapy.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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