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Pharmacokinetics and pharmacodynamics of Tarlatamab, DLL3-Targeted FDA-approved Bispecific T-Cell Engager

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Abstract

Small-cell lung cancer (SCLC) is a common aggressive cancer type, that exhibits overall lower rate of survival and poor prognosis. Treatment options of SCLC are limited including chemotherapy, radiotherapy, and surgery to dissect tumors. However, these therapies are not very effective in treating SCLCs, and no available therapies are in third-line or beyond. The notch signaling pathway plays a central role in regulating cell proliferation, survival, and maintenance. Notch signaling in SCLC is dysregulated and induces oncogenicity. DLL3 is a notch ligand whose expression is nominal in normal conditions and the DLL3 is overexpressed in SCLC which promotes tumor cell proliferation, migration, and invasiveness. Over 85% of human SCLC express elevated DLL3 on the cell surface. Therefore, targeting DLL3 is a promising therapeutic approach to treat SCLC. Bispecific T-cell engagers (BiTEs) molecule binds to DLL3 and CD3 simultaneously leading to T-cell activation and T-cell-induced tumor eradication. Tarlatamab is a half-life extended DLL3-targeted T-cell-engaging bispecific antibody (BsAb) that exhibited superior antitumor efficacy in the preclinical in vitro and in vivo model. Tarlatamab is the only DLL3-engaging BiTE molecule that was approved by the USFDA on May 16th, 2024 under the brand name Imdelltra (Amgen Inc). It showed higher clinical efficacy and the pharmacodynamic study reported that higher T-cell activation and IFN-γ elevation were mediated after the first dose of tarlatamab. Manageable safety profile with higher efficacy rate was reported in the clinical study. In this review, we present immune therapy, and pharmacokinetic and pharmacodynamic profiles of tarlatamab based on the clinical study reports.

Key words tarlatamab, BiTE, pharmacokinetic, pharmacodynamic, clinical study, T-cell

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Introduction

SCLC is a highly aggressive malignancy characterized by neuroendocrine differentiation, with an annual global incidence exceeding 150,000 cases [1, 2]. Patients with extensive-stage (ES) SCLC face a poor prognosis, exhibiting a 3-year survival rate of only 6% [3]. Recent advances in first-line therapy, combining platinum-etoposide chemotherapy with immune checkpoint inhibitors (atezolizumab or durvalumab) followed by maintenance immunotherapy, have demonstrated a ~30% reduction in mortality risk and modest survival benefits in a minority of ES-SCLC patients [3, 4]. Despite these advancements, therapeutic options remain severely constrained for relapsed SCLC. Topotecan, the most commonly prescribed second-line agent worldwide, offers suboptimal efficacy and significant toxicity [5, 6]. Lurbinectedin, granted accelerated FDA approval in 2020 based on a 35% objective response rate (ORR), represents the first new second-line therapy in two decades; however, subsequent randomized trials failed to confirm an overall survival (OS) advantage [7, 8]. Currently, no targeted or systemic treatments are approved for third-line management of recurrent SCLC [9].

A key factor limiting the efficacy of immune checkpoint blockade in most SCLC patients may be tumor-mediated downregulation of Major Histocompatibility Complex class I (MHC-I), which is essential for antigen presentation to $CD8^+$ cytotoxic T lymphocytes [10, 11]. While epigenetic approaches to restore MHC-I expression are under investigation, an alternative therapeutic strategy involves circumventing conventional antigen presentation pathways entirely using bispecific T-cell engagers (BiTEs). These engineered antibodies simultaneously bind tumor-specific surface antigens and CD3 on T cells, forcibly inducing immunological synapse formation, T-cell activation, and subsequent tumor cell lysis [12-16].

Several anticancer monoclonal (mAbs) and bispecific antibodies (BsAbs) were approved by FDA in 2024 (**Table 1**). Tarlatamab is one of those BsAbs for solid tumors which has higher clinical efficacy. Tarlatamab is a first-in-class BiTE targeting delta-like ligand 3 (DLL3), a Notch pathway ligand overexpressed in SCLC, and the CD3ε subunit on T cells (**Figure 1**). Preclinical studies demonstrate that tarlatamab induces potent T-cell-mediated cytotoxicity against $DLL3^+$ SCLC cells in vitro and drives significant tumor regression in disseminated orthotopic SCLC models in vivo [17, 18]. As the inaugural DLL3-directed immunotherapeutic agent to enter clinical trials, tarlatamab represents a paradigm-shifting approach for overcoming SCLC's immune-evasion mechanisms. Tarlatamab, the first and exclusively DLL3-targeting bispecific T-cell engager (BiTE), elicits an immunotherapeutic response by directing the patient's immune system against DLL3-expressing neoplastic cells. The molecule operates via dual binding to CD3 on T lymphocytes and DLL3 on tumor cells, the latter being a surface protein overexpressed in 85–96% of small cell lung carcinoma (SCLC) cases while exhibiting minimal expression in normal tissues. Upon simultaneous engagement of both receptors, T-cell activation ensues, culminating in the formation of cytolytic synapses that mediate tumor cell lysis, thereby demonstrating potent oncolytic efficacy. In this review, we present the overview of tarlatamab [19-24]. Herein, we highlight the therapeutic response, efficacy, pharmacokinetic and pharmacodynamic analysis, mechanism of action, adverse effect, and ADME of Tarlatamab.

Tarlatamab: a precision immunotherapeutic for small cell lung carcinoma

The Notch signaling cascade serves as a critical modulator of neuroendocrine differentiation in small cell lung carcinoma (SCLC) [46, 47]. Notably, the inhibitory Notch ligand Delta-like protein 3 (DLL3) exhibits aberrant overexpression on the plasma membrane of approximately 85% of SCLC tumor cells, while demonstrating negligible expression in healthy tissues [48-51]. This tumor-restricted expression profile establishes DLL3 as a highly selective molecular target for therapeutic intervention [19, 52]. In vitro investigations utilizing SCLC model systems have demonstrated that DLL3 contributes to oncogenic

Table 1. Anti-tumor mAbs and BsAb approved by FDA in 2024.

Drug Name (Brand)	Target	Type	Clinical efficacy data	Approved indication	Manufacturer	Year
Epcoritamab (Epkinly) [25-27]	CD3 × CD20	Bispecific	ORR: 61% (CR: 38%) in R/R DLBCL (EPCORE NHL-1)	R/R DLBCL, Follicular Lymphoma	Genmab/ AbbVie	2024
Tarlatamab (Imdelltra)[28]	DLL3 × CD3	Bispecific	ORR: 40% (mDoR: 9.7 mos) in SCLC (DeLLphi-301)	SCLC (2L+)	Amgen	2024
Elranatamab (Elrexfio) [29-31]	BCMA × CD3	Bispecific	ORR: 58% (≥VGPR: 33%) in R/R MM (MagnetisMM-3)	R/R Multiple Myeloma	Pfizer	2024
Amivantamab (Rybrevant) [32, 33]	EGFR × c-MET	Bispecific	ORR: 37% (mPFS: 6.7 mos) in EGFR Exon20+ NSCLC (CHRYSALIS-2)	EGFR Exon20+ NSCLC	J&J	2024
Datopotamab deruxtecan (Dato-DXd) [34-37]	TROP2 (ADC)	ADC	PFS: 6.9 vs 4.9 mos (vs chemo) in HR+/HER2- BC (TROPION-Breast01)	HR+/HER2- BC, NSCLC	Daiichi Sankyo/ AstraZeneca	2024
Zolbetuximab (Vyloy)[38-41]	Claudin 18.2	mAb	mPFS: 8.2 vs 6.8 mos (vs placebo + chemo) in Gastric/ GEJ (SPOTLIGHT)	CLDN18.2+ Gastric/ GEJ	Astellas Pharma	2024
Pemigatinib (Pemazyre) + mAb[42-45]	FGFR1-3	TKI + mAb	ORR: 37% (mDoR: 8.1 mos) in FGFR2+ Cholangiocarcinoma (FIGHT-302)	Cholangiocarcinoma	Incyte	2024 (combo)

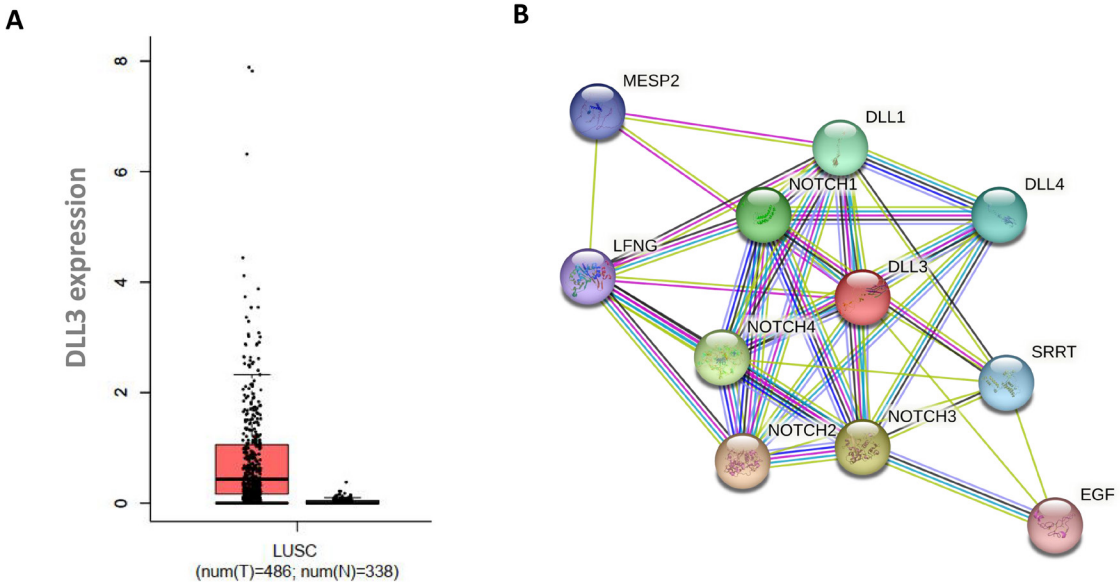

Figure 1. Notch signaling pathway. (A) Elevated DLL3 expression in Lung Squamous Cell Carcinoma (LUSC), Red bar represents DLL3 expression in LUSC tumor tissues and the black bar represents DLL3 expression in normal tissues; (B) DLL3 signaling, which is a central player of the Notch signaling pathway.

processes, including neoplastic proliferation, cellular motility, and metastatic invasion [51, 53]. Clinical validation of this target was achieved through the DLL3-directed antibody-drug conjugate rovalpituzumab tesirine, which exhibited measurable anti-tumor efficacy in SCLC patient cohorts [54]. Tarlatamab was evaluated by multiple clinical trials [55]. The DeLLphi-303 study represents a Phase 1b investigation examining tarlatamab's synergistic potential when combined with first-line standard-of-care regimens in extensive-stage small cell lung cancer (ES-SCLC). In the therapeutic landscape of relapsed SCLC, the randomized Phase 3 DeLLphi-304 trial is assessing the comparative efficacy of tarlatamab monotherapy versus conventional chemotherapy in the second-line setting [55]. Further advancing its clinical application, the DeLLphi-305 trial constitutes a Phase 3 randomized study evaluating tarlatamab plus durvalumab versus durvalumab monotherapy as first-line maintenance therapy for ES-SCLC. The DeLLphi-306 study represents a pivotal Phase 3 placebo-controlled investigation of tarlatamab as consolidation therapy following concurrent chemoradiation in limited-stage SCLC (LS-SCLC). Additionally, the DeLLpro-300 trial is exploring tarlatamab's therapeutic potential in neuroendocrine prostate cancer, encompassing both treatment-naïve and treatment-emergent disease phenotypes. These comprehensive clinical investigations aim to elucidate tarlatamab's therapeutic application across diverse treatment contexts and disease stages in neuroendocrine malignancies [55]. Tarlatamab exhibits a unique mechanism of action by concomitantly binding DLL3 on malignant cells and CD3ε on T lymphocytes, thereby facilitating immunological synapse formation and T-cell-mediated cytotoxicity independent of MHC recognition. Preclinical models demonstrate potency of the notch signaling cascade serves as a critical modulator of neuroendocrine differentiation in small cell lung carcinoma (SCLC) [46, 47]. Notably, the inhibitory notch ligand DLL3 exhibits aberrant overexpression on the plasma membrane of approximately 85% of SCLC tumor cells, while demonstrating negligible expression in healthy tissues [48-51]. This tumor-restricted expression profile establishes DLL3 as a highly selective molecular target for therapeutic intervention. In vitro investigations utilizing SCLC model systems have demonstrated that DLL3 contributes to oncogenic processes, including neoplastic proliferation, cellular motility, and metastatic invasion [51, 53]. Clinical validation of this target was achieved through the DLL3-directed antibody-drug conjugate rovalpituzumab tesirine, which exhibited measurable anti-tumor efficacy in SCLC patient cohorts [54, 55]. Preclinical models demonstrate potency of tarlatamab to induce tumor-selective lysis while sparing DLL3-negative healthy tissues. Clinical trials reveal durable objective responses (ORR: 40%) in relapsed/refractory SCLC, with a manageable safety profile dominated by cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity (ICANS), typically low-grade and mitigatable through step-up dosing protocols [28]. Pharmacodynamically, tarlatamab exhibits nonlinear pharmacokinetics attributable to target-mediated drug disposition (TMDD), with a terminal half-life supporting biweekly administration. Ongoing investigations explore its synergistic potential with PD-1/PD-L1 inhibitors and consolidation therapy post-chemoradiation [56, 57]. As the first FDA-approved DLL3-targeted agent, tarlatamab establishes a new precision immunotherapy paradigm for SCLC, addressing a critical unmet need in this aggressive malignancy with limited therapeutic options [28].

Adverse drug reactions

Tarlatamab exhibits a clinically significant risk of CRS, with potential for severe or fatal manifestations. Accumulative clinical data demonstrate a CRS incidence rate of 55% across treated patients, stratified by severity as follows: Grade 1 (34%), Grade 2

(19%), Grade 3 (1.1%), and Grade 4 (0.5%). Notably, recurrent CRS events were observed in 24% of the patient cohort, with majority being Grade 1 (18%) and minority Grade 2 (6%) in severity [58].

Tarlatamab exerts potentially severe neurotoxicity, encompassing immune effector cell-associated neurotoxicity syndrome (ICANS). Pooled safety analyses revealed neurologic adverse events in 47% of treated patients, with 10% representing Grade 3 severity. The predominant manifestations included cephalgia (14%), peripheral neuropathy (7%), vertigo (7%), sleep initiation/maintenance disorder (6%), myasthenia (3.7%), acute confusional state (2.1%), transient loss of consciousness (1.6%), and generalized neurotoxicity (1.1%) [58].

Tarlatamab induces cytopenic events, neutropenia, thrombocytopenia, and anemia. Clinical safety data revealed, Neutrophil count reduction occurred in 12% of treated patients (6% Grade 3/4), with median onset of severe neutropenia at 29.5 days (range: 2-213). Thrombocytopenia manifested in 33% of cases (3.2% Grade 3/4), exhibiting a median latency of 50 days for severe presentations (range: 3-420). Hemoglobin decline was observed in 58% of recipients (5% Grade 3/4). Febrile neutropenia incidence was 0.5% [58].

Tarlatamab exerts potential hepatotoxic effects, as evidenced by pooled safety analyses, Alanine aminotransferase (ALT) elevations manifested in 42% of treated patients (2.1% Grade 3/4). Aspartate aminotransferase (AST) increases occurred in 44% of cases (3.2% Grade 3/4). Hyperbilirubinemia developed in 15% of recipients (1.6% Grade 3/4), severe Type I hypersensitivity reactions, characterized by immune-mediated manifestations including rash, and bronchospasm. Tarlatamab also may exert harmful effects to the fetus when administered to a pregnant woman [58].

Efficacy of tarlatamab

The confirmed objective response rate (ORR) was 23.4% (95% CI: 15.7-32.5), comprising two complete responses and 23 partial responses as assessed. It was reported that the maximal tumor burden reduction from baseline in evaluable patients (n=94), with a disease control rate of 51.4% (95% CI: 41.5-61.2) [28]. Dose-response analysis revealed detectable activity at the 0.3 mg dose level, with enhanced efficacy observed at doses ≥3 mg. Radiographic assessment demonstrated ≥30% reduction in target lesion burden in 36.4% of cases (n=39) [28]. Among responders, the median time to response was 1.8 months (range: 1.2-7.4), with a median duration of response (DOR) of 12.3 months (95% CI: 6.6-14.9). At data cutoff, 44% of responders (n=11) maintained ongoing responses, with the maximum DOR reaching 14.9 months. Survival analysis yielded median progression-free survival (PFS) of 3.7 months (95% CI: 2.1-5.4) and median overall survival (OS) of 13.2 months (95% CI: 10.5-not estimable). Disease progression occurred in 77 patients, including intracranial progression in 10.4% (n=8). Subsequent therapies were administered to 26.2% (n=28) of the cohort. Post hoc analysis suggests potential predictive value of DLL3 expression thresholds for patient stratification, with clinical benefit observed across multiple expression levels [28].

Prior investigations by Hughes et al. demonstrated that tarlatamab exhibited potent cytotoxic activity against SCLC cell lines, even those with minimal DLL3 expression (<1,000 surface molecules/cell). Mechanistic studies revealed that systemic administration of tarlatamab induced robust T-cell activation and mediated targeted tumor cell lysis through immune synapse formation [20]. This activity translated to significant antitumor efficacy across multiple in vivo models, including complete regression in patient-derived xenografts (PDXs) of SCLC, orthotopic primary lung tumors, and metastatic hepatic lesions. Toxicology assessments showed favorable safety profiles at doses up to 4.5 mg/kg, which achieved systemic exposures surpassing the mean in vitro EC50 for T-cell engagement. Notably, no drug-related adverse effects were observed in these preclinical safety studies. Collectively, these findings support the clinical study of tarlatamab as a promising immunotherapeutic strategy for DLL3-expressing SCLC, with demonstrated efficacy at low antigen density and an acceptable preclinical safety window [20, 59].

In another clinical study was conducted by University of Virginia. The efficacy analysis cohort comprised exclusively of SCLC patients receiving tarlatamab, with exclusion of the atypical carcinoid case included in safety evaluations. Median therapy duration was 8 weeks (range: 1-35) with three median treatment. Treatment persistence: 22.7% (n=5) remained on therapy at data cutoff, including one patient continuing post-progression following stereotactic radiosurgery (SRS) [60]. Therapeutic outcomes demonstrated, ORR was 42.9% and rapid response kinetics was 88.8% of responses (n=8) manifested within 6 weeks of initiation Disease progression or mortality was 66.6% (n=14) during follow-up. Exploratory biomarker analysis (n=18) suggested: LDH reduction post-cycle 1 correlated with enhanced disease control probability (stable disease/partial response; OR=9, p=0.12) Median progression-free survival (mPFS): 2.7 months [60].

Pharmacokinetic analysis

The pharmacokinetic profile of tarlatamab was characterized through noncompartmental analysis performed on the pharmacokinetic evaluable population, defined as subjects receiving at least one dose with measurable drug concentrations. Pharmacokinetic parameters including maximum observed serum concentration (Cmax) following intravenous administration, area under the concentration-time curve from 0 to 336 hours post-dose (AUC336h), systemic clearance (CL), steady-state volume of distribution (Vss), terminal elimination half-life (t½), and pre-dose trough concentrations (Ctrough) [61]. The analysis incorporated actual administered doses and precise sampling times, with concentrations below the lower limit of quantification (0.0203 ng/mL) imputed as zero prior to analysis. Subjects requiring dose reductions were excluded from pharmacokinetic parameter calculations at the target dose level to maintain data integrity [61]. Pharmacokinetic parameters are shown in **Table 2**.

Pharmacodynamic analysis

The pharmacodynamic effects following a single tarlatamab infusion were characterized by transient CRS, evidenced by dose-dependent elevations in proinflammatory cytokines (IL-2, IL-6, IL-8, IL-10, IFN-γ) at doses ≥0.3 mg. Cytokine kinetics demonstrated peak concentrations approximately 24 hours post-administration during Cycle 1 (Day 1 at 1 mg dose), with levels returning to baseline prior to subsequent dosing (Cycle 1 Day 8). Pharmacokinetic and pharmacodynamic analyses revealed no clinically remarkable exposure-efficacy correlations across the therapeutic range (10–100 mg, representing 10-fold the maximum approved dose). However, a positive exposure-safety relationship was identified, with higher tarlatamab concentrations correlating with increased incidence of hematologic toxicity (neutropenia) and neurological adverse events, including immune effector cell-associated neurotoxicity syndrome (ICANS). These findings suggest that while cytokine-mediated effects are transient and dose-dependent, the risk of dose-limiting toxicities escalates with systemic drug exposure.

Tarlatamab construct integrating an immunoglobulin G crystallizable fragment (Fc) domain with an anti-DLL3 × anti-CD3 BiTE (bispecific T-cell engager) scaffold. The inclusion of an engineered, effector-function-silent Fc domain confers

Table 2. Pharmacokinetic parameters of tarlatamab [61].

Parameter	Value (Mean ± SD or Geometric Mean [%CV])	Notes
Bioavailability	Not applicable (IV administration)	Administered intravenously.
Volume of Distribution (Vd)	~5.2-6.8 L	Suggests limited distribution beyond plasma.
Clearance (CL)	~0.64 L/day	Non-linear clearance at lower doses; linear at higher doses.
Half-life (t½)	~5.8 days	Supports every 2- or 4-week dosing regimens.
C_{max}	Dose-dependent	Increases proportionally with dose (e.g., 1 mg/kg to 100 mg/kg).
T_{max}	End of infusion	Immediate peak post-IV administration.
Area Under Curve (AUC)	Dose-proportional	Non-linear PK at low doses; linear at therapeutic doses (>10 mg/kg).
Immunogenicity	~10–20% ADA incidence	Anti-drug antibodies may affect exposure in a subset of patients.

prolonged serum persistence, enabling reduced dosing frequency [62]. Tarlatamab exhibits high-affinity binding to human DLL3 [equilibrium dissociation constant (K) = 0.64 nM] and CD3 (K = 14.9 nM), demonstrating potent in vitro cytotoxicity against DLL3-positive small cell lung carcinoma (SCLC) cell lines—even those with low antigen density (<1000 molecules/cell)—as well as DLL3-expressing prostate adenocarcinoma models [63].

Mechanistically, tarlatamab activates CD3 T lymphocytes, stimulating proinflammatory cytokine secretion and eliciting T-cell-mediated lysis of SCLC cells, DLL3 prostate cancer cells in vitro, and small-cell/neuroendocrine (SCNC) prostate cancer patient-derived xenograft (PDX) cells ex vivo. Notably, in vitro assays revealed rapid, target-dependent cytotoxicity against DLL3-expressing tumors, with minimal off-target effects on DLL3-negative bystander cells. Tarlatamab demonstrated comparable cytotoxic efficacy against both treatment-naïve and chemoresistant small cell lung carcinoma (SCLC) cell lines, indicating its therapeutic potential for relapsed/refractory disease. Synergistic enhancement of tumor cell killing was observed when tarlatamab was co-administered with platinum-based chemotherapeutics, etoposide, or combination regimens. Mechanistically, tarlatamab upregulated programmed death-ligand 1 (PD-L1) expression on SCLC cells, which potentiated the cytotoxic effects when combined with PD-1/PD-L1 axis inhibitors in vitro [64]. These findings support the clinical investigation of tarlatamab as a combination therapeutic with existing standard-of-care (SOC) regimens for SCLC management [62].

Mechanism of action

BiTE molecules represent a novel class of bispecific antibody constructs engineered with dual antigen-binding domains: one targeting tumor-associated antigens (e.g., B-cell maturation antigen [BCMA], CD19, or delta-like ligand 3 [DLL3]), and the other specifically binding CD3ε, a constitutive component of the T-cell receptor (TCR) complex [65]. These molecules are composed of two distinct single-chain variable fragments (scFvs) derived from monoclonal antibodies, interconnected by a flexible polypeptide linker. The tumor-targeting scFv domain can be customized to recognize diverse tumor surface markers, enabling rapid deployment of off-the-shelf immunotherapies against multiple malignancies while permitting repeated administration [66]. In contrast, the CD3-binding scFv remains invariant, ensuring universal T-cell engagement [67, 68]. Upon simultaneous binding to both a tumor cell and a cytotoxic T lymphocyte, BiTE molecules induce T-cell activation, clonal expansion, and enhanced effector cell proliferation, thereby amplifying the therapeutic potency of this immunotherapeutic approach through increased tumor-specific cytolytic activity [69].

Tarlatamab, binds with DLL3 on the tumor cell surface, and CD3 on T-cells simultaneously leading to form immune synapse resulting cytotoxic T-cell-mediated tumor cell eradication [17]. In vitro studies demonstrate that tarlatamab mediates robust T-cell activation upon engagement with DLL3-positive SCLC cell lines, culminating in targeted tumor cell lysis through granzyme/perforin-mediated cytotoxicity (**Figure 2**). This antitumor activity translates to significant in vivo efficacy, with tarlatamab inducing substantial tumor regression in disseminated orthotopic SCLC models that recapitulate human disease progression. As the first DLL3-directed immunotherapeutic agent to enter clinical evaluation, tarlatamab represents a novel therapeutic strategy for SCLC, a malignancy historically refractory to conventional treatments [18].

The notch signaling cascade serves as a master regulator of developmental ontogeny, including pulmonary neuroendocrine cell differentiation [70]. DLL3, a transmembrane notch pathway antagonist, exhibits strict intracellular localization in healthy adult tissues, primarily restricted to Golgi compartments [59, 71]. This inhibitory ligand represents a direct transcriptional target of achaete-scute homolog 1 (ASCL1), a basic helix-loop-helix transcription factor that drives neuroendocrine proliferation and is fundamentally implicated in small cell lung carcinoma tumorigenesis [72-74]. In ASCL1-positive SCLC, DLL3 undergoes profound overexpression coupled with aberrant cell surface translocation, creating a tumor-specific epitope that presents an ideal therapeutic target for precision oncology approaches [48, 75, 76].

Absorption, distribution, metabolism, and elimination (ADME) of tarlatamab

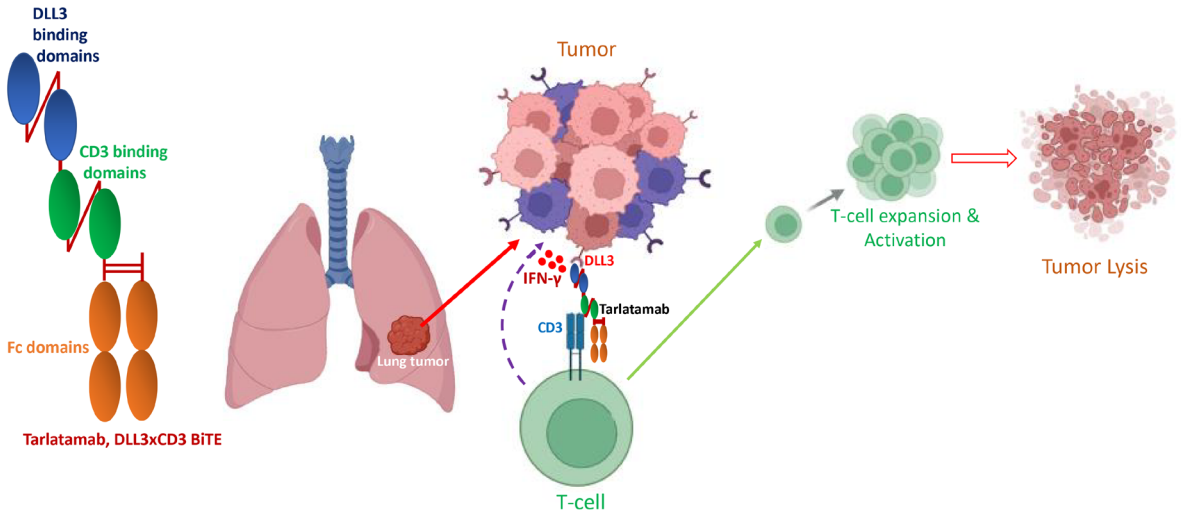

Figure 2. Schematic diagram of Tarlatamab, and its T-cell-mediated mechanism of tumor lysis. Tarlatamab comprised DLL3 and CD3 binding domains. It binds with T-cells through CD3 binding domains and targets DLL3 through DLL3 binding domains simultaneously. As a result, activated T-cells are redirected to the DLL3-overexpressed tumor cells leading to potential actions of tumor lysis.

Tarlatamab is delivered through intravenous infusion, ensuring rapid and complete systemic bioavailability. The peak serum concentration (Tmax) is attained immediately upon completion of the 1-hour intravenous administration. Steady-state volume of distribution exhibits a geometric mean (CV%) of 8.6 L (18.3%) [77]. While the specific metabolic fate of tarlatamab remains unelucidated, it is anticipated to undergo proteolytic catabolism, consistent with other biologic agents, yielding low-molecular-weight peptides and constituent amino acids. Pharmacokinetic analyses revealed a systemic clearance rate (inter-subject CV%) of 0.65 L/day (44%), with a median terminal elimination half-life (range) of approximately 11.2 days (4.3–26.5) in small cell lung cancer (SCLC) patients [77].

Resistance to tarlatamab

To investigate the molecular basis of acquired resistance to tarlatamab in the patient cohort, transcriptional profiling was performed by Ahn et al. using the nCounter PanCancer Pathways assay, following the absence of detectable genomic alterations and unsuccessful RNA sequencing attempts. While small-cell lung cancer (SCLC) subtyping traditionally relies on whole-transcriptome sequencing [78], comparative analysis between targeted gene panels and bulk RNA-seq data presents inherent limitations. To address this, a condensed SCLC subtype-specific gene signature was developed, derived from the original classification framework [78]. Subtype-exclusive genes were defined based on stringent expression criteria: genes exhibiting expression levels equal to or exceeding those of canonical subtype markers (ASCL1, NEUROD1, or POU2F3) in their respective subtypes.

Given prior evidence implicating notch signaling in SCLC pathogenesis and DLL3 regulation [79], transcriptional changes in this pathway were evaluated in pre- and post-tarlatamab tumors. When compared to the four reference cell lines, post-treatment tumors demonstrated upregulation of notch family genes and downregulation of DELTA-like ligands. This shift toward a notch-receptive phenotype, consistent with lateral inhibition dynamics, supports the hypothesis that tarlatamab resistance may arise through notch-mediated suppression of DLL3 [80]. A sharp differential expression among the four SCLC subtypes was observed through the adapted nCounter assay for molecular subtyping; however, comprehensive validation of these transcriptional changes following tarlatamab treatment may require RNA sequencing of the entire transcriptome across large clinical cohorts. The development of a clinically feasible and robust SCLC subtyping methodology would facilitate broader investigations into the influence of molecular subtypes on tarlatamab therapeutic efficacy. Findings from such studies are anticipated to optimize tarlatamab responsiveness and inform the development of novel strategies to circumvent resistance mechanisms [81].

Conclusions

Tarlatamab, is an FDA-approved novel T-cell-engaging BiTE molecule that targets DLL3 overexpressing tumor cells. SCLC is highly aggressive cancer type, which highly expresses DLL3. SCLC is characterized by higher metastasis and poor prognosis, and limited therapeutic options. In the preclinical study tarlatamab showed potent anti-tumor efficacy. Tarlatamab exhibited high response rates in SCLC in the phase II clinical trial with higher safety profile and limited severe toxicity. Besides, it has extended half-life to decrease dosing frequency. However, tarlatamab has some severe adverse reactions such as CRS, which can be manageable. Additionally, DLL3 loss or T-cell dysfunction may limit long-term efficacy. Accumulative clinical reports demonstrate that tarlatamab is a promising therapeutic agent for treating SCLC.

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Ethics approval

No applicable.

Data availability

The data will be available upon request.

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Authors' contribution

Ahmed Attia Ahmed Abdelmoaty and contributed to draft, critical revision of the article, table making, figure drawing and final submission. Ahmed Gamal Badran draw the figures and revised the manuscript.

Competing interests

The authors declare no competing interests.

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