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COMMENTARY

Delta-like ligand 3: A promising target against small cell lung cancer

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Small cell lung cancer (SCLC) is a highly aggressive malignancy that primarily affects the elderly. SCLC frequently presents at an advanced stage and is characterized by rapid doubling time, a propensity for early distant metastasis, and transient responses to the current standard of care. The integration of immune checkpoint inhibitor therapy into first-line chemotherapy can only provide transformative benefit to a small subset of patients. Moreover, the second-line treatment options for advanced SCLC are still confined to chemotherapeutic agents, with a short duration of response and overall survival (OS) that rarely exceeds 8 months. Consequently, the development of clinically effective novel agents is an urgent need for SCLC.

Notch signaling is implicated in multiple oncogenic cellular processes in SCLC, such as cell proliferation, differentiation, chemoresistance, and modulation of the immune microenvironment. Delta-like ligand 3 (DLL3), a protein that inhibits Notch signaling, is typically localized intracellularly in normal cells but is abnormally expressed on the surface in 85%–94% of patients with SCLC, making it a potential tumor selective target in the treatment of SCLC.[1] Tarlatamab (formerly AMG575), a novel bispecific T cell engager (TCE), is the first DLL3-targeted immune therapy evaluated in a clinical trial. Tumor-intrinsic suppression of histocompatibility complex class I (MHC-I) might be an important contributor to poor immunogenicity of SCLC. The predominant advantage of TCE is MHC-I independent T-cell activation. Tarlatamab is designed to form a cytolytic synapse with dual affinity for DLL3 on tumor cells and CD3 on T cells, which allows for T-cell activation, transient cytokine production, and T-cell proliferation (Figure 1A). Previous phase 1 dose-exploration trial of tarlatamab in patients with heavily previously treated SCLC(DeLLphi-300) showed manageable safety profiles and promising preliminary efficacy over a broad range of doses. The maximum tolerated dose was not reached in the highest protocol-planned dose (100 mg every 2 weeks). Any-grade and grade ≥3 treatment-related adverse events occurred in 90.7% and 30.8% patients respectively. Confirmed objective response rate (ORR) was 23.4% with encouraging response durability.[2]

Myung-Ju Ahn et al.[3] presented the results of an international phase 2 trial (DeLLphi-301) evaluating the efficacy and safety of two different doses of tarlatamab (10-mg and 100-mg) in 200 patients with recurrent SCLC who had received a median of two lines of prior therapy, including those with brain metastases. Approximately 50% of the patients had refractory or resistant disease, with a chemotherapy-free interval of first-line platinum-based therapy of 6 months or less. The study found that tarlatamab, administered at a dose of 10-mg every 2 weeks, showed promising anti-tumor activity with an ORR of 40% and a median progression-free survival (PFS) of 4.9 months, which is comparable to standard first-line chemotherapy plus immune checkpoint inhibitor.[4,5] It is also notable that the response duration exceeded 9 months for 25% of the responders in 10-mg group. These results are encouraging, especially when compared to second-line chemotherapeutic agents such as lurbinectedin (ORR: 35%, median PFS: 3.9 months) and topotecan (ORR: 17%, median PFS: 3.5 months).[6] The safety profile of the 10-mg dose was acceptable, with the most common adverse events being cytokine-release syndrome (the incidence rate was 51%, including grade 3 in only

Xin Nie and Yu-meng Tian contributed equally to this work and should be considered co- first authors.

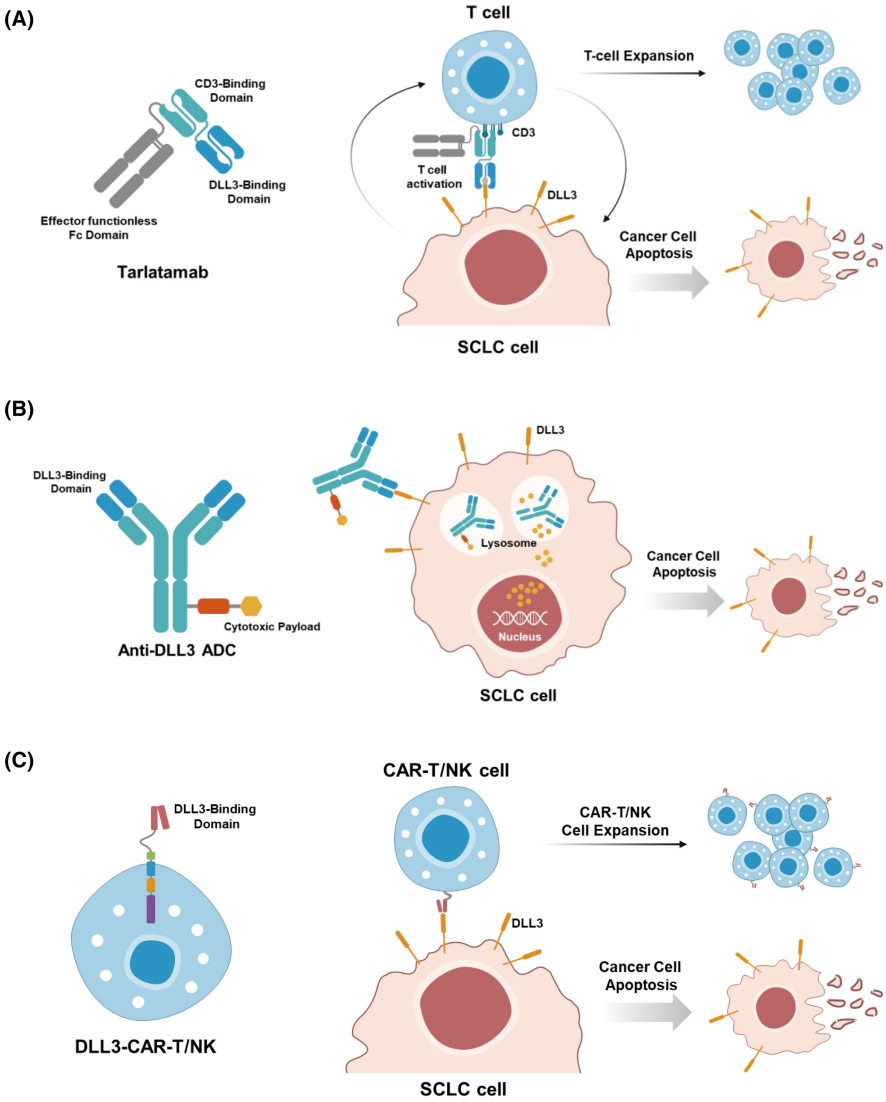

FIGURE 1 Novel strategies for targeting DLL3 in SCLC. (A) Tarlatamab induces tumor cytolysis and T cell proliferation by linking DLL3 on tumor cells and CD3 on T cells. (B)DLL3-targeting ADC consist of an anti-DLL3 monoclonal antibody linked to a cytotoxic agent. Upon binding to DLL3-positive tumor and endocytosis, the ADC releases its toxic payload within lysosomes to induce tumor cell apoptosis and lysis. (C) DLL3-specific CAR therapy involves the expression of a CAR that recognizes DLL3, redirecting immune cells to attack DLL3-positive tumor cells, resulting in tumor elimination. ADC, antibody-drug conjugate; CAR, chimeric antigen receptor; DLL3, Delta-like ligand 3; SCLC, small cell lung cancer.

1% of the patients), decreased appetite (29%), and pyrexia (35%). Only 3% of patients discontinued tarlatamab due to treatment-related adverse events. Therefore, the 10-mg dose was selected for subsequent tarlatamab trials for its better benefit-to-risk profile than the 100-mg dose. Currently, phase 1 and phase 2 clinical trials have confirmed that tarlatamab, via its distinctive bispecific T cell antibody structure, exhibits promising anti-tumor activity by fostering targeted immune responses and enhancing T cell proliferation. However, this trial also had some limitations, including the exclusion of patients with poor performance status and the need for investigation in a more diverse population. The ongoing phase 3 DeLLphi-304 trial is comparing tarlatamab with standard care in patients with previously treated extensive-stage SCLC to explore further safety and efficacy profiles. Besides, whether DLL3 expression can translate into enhanced clinical benefit remains to be further investigated. Additionally, the predictive value of novel immune-related biomarkers and SCLC subtypes based on the expression levels of transcription factors ASCL1, NeuroD1, YAP1, and POU2F3 should be further explored.[7]

Apart from tarlatamab, several other DLL3-targeted TCEs candidates, such as BI764532, HPN328, QLS31904, and ZG006, have entered clinical trial phases, and some have shown preliminary evidence of efficacy. In addition to bispecific/trispecific TCEs immunotherapy, other DLL3-targeted therapies for the treatment of SCLC have been explored, including antibody-drug conjugates (ADCs) and chimeric antigen receptor (CAR) therapies (Figure 1B,C). Rovalpituzumab tesirine (Rova-T), a DLL3-targeting ADC consisting of a humanized monoclonal antibody (SC16) and a

TABLE 1 Ongoing clinical trials of DLL3-targeting therapies for SCLC.

Agent	Mechanism	Trial identifier	Indications	Comparison	Sponsor
Tarlatamab (DeLLphi-304)	DLL3/CD3 bi-specific antibody	NCT05740566 Phase III	Second-line therapy for relapsed SCLC (Chinese population included)	Standard of care	Amgen
Tarlatamab	DLL3/CD3 bi-specific antibody	NCT06064500 Phase IIIb	Advanced SCLC failed at least 2 lines of systemic therapy	Single arm	Amgen
Tarlatamab +AMG 404	DLL3/CD3 bi-specific antibody +PD-1 inhibitor	NCT04885998 Phase Ib	Advanced SCLC failed at least 1 line of systemic therapy	Single arm	Amgen
Tarlatamab +Carboplatin+ Etoposide	DLL3/CD3 bi-specific antibody	NCT05361395 Phase Ib	First-line therapy for advanced SCLC	Single arm	Amgen
BI764532	DLL3/CD3 bi-specific antibody	NCT04429087 Phase I	Advanced SCLC and other NEC	Single arm	Boehringer Ingelheim
BI764532	DLL3/CD3 bi-specific antibody	NCT05882058 Phase II	Relapsed/refractory SCLC or NEC	Single arm	Boehringer Ingelheim
BI 764532+ Ezabenlimab	DLL3/CD3 bi-specific antibody + PD-1 inhibitor	NCT05879978 Phase I	Advanced SCLC and other NEC	Single arm	Boehringer Ingelheim
QLS31904	DLL3/CD3 bi-specific antibody	CTR20221779 Phase I	Advanced solid tumors (SCLC included)	Single arm	Qilu Pharmaceutical
PT217	DLL3/CD47 bi-specific antibody	NCT05652686 Phase I	Refractory cancers (SCLC included) failed at least 1 line of systemic therapy	Single arm	Phanes Therapeutics
ZG006	Tri-specific antibody targeting two different DLL3 epitopes and CD3	NCT05978284 Phase I/II	Relapsed/refractory SCLC or NEC	Single arm	Zejing Pharmaceutical
HPN328+ atezolizumab	Tri-specific antibody targeting DLL3, CD3 and human serum albumin	NCT04471727 Phase I/II	Advanced SCLC failed at least of 1 line of systemic therapy	Single arm	Harpoon Therapeutics
RO7616789	Tri-specific antibody targeting DLL3, CD3 and CD137	NCT05619744 Phase I	Advanced SCLC or NEC relapsed after at least 1 line of systemic therapy	Single arm	Hoffmann-La Roche
LB2102	DLL3-targeted chimeric antigen receptor T-cells	NCT05680922 Phase I	Advanced SCLC failed at least 1 line of systemic therapy	Single arm	Legend Biotech USA Inc
DLL3-CAR-NK cells	Anti-DLL3-transduced NK cells	NCT05507593 Phase I	Advanced SCLC relapsed after at least 1 line of systemic therapy	Single arm	Tian jin Medical University Cancer Institute and Hospital

Abbreviations: NEC, neuroendocrine carcinomas; NK, natural killer; SCLC, small cell lung cancer.

pyrrolobenzodiazepine dimer toxin, revealed impressive efficacy in a phase 1 exploratory study for refractory SCLC.[8] However, both phase 3 studies, TAHOE (Rova-T vs. topotecan as second-line therapy) and MERU (Rova-T as maintenance therapy after first-line therapy vs. placebo), were terminated early due to their failure to meet the prespecified interim survival endpoints.[9,10] The failure of the Rova-T trials highlights the risks associated with directly skipping from phase 1 to phase 3 trials. Differences in the enrolled populations and the absence of a control group may have led investigators to overestimate the efficacy of Rova-T. Moreover, the possibility that Rova-T may not be a suitable ADC drug also contributed to the failure of the trials. Additional studies are necessary to assess the efficacy and safety profiles of DLL3-targeted ADCs with improved pharmacological properties. The success of CAR T-cell therapies for hematological malignancies has sparked interest in evaluating their efficacy in solid tumors. Currently, several CAR T-cell therapies and CAR natural killer therapies are in development or being investigated in phase 1 trials. A summary of ongoing DLL3-targeting clinical trials is provided in Table 1. It is noteworthy that several domestically developed DLL3-targeting novel agents are also under investigation in clinical trials. The identification of markers for response and toxicity, the improvement of

adverse event management, and the exploration of combinations with other treatment strategies are important areas of development for DLL3-targeting therapies.

In summary, SCLC remains a challenging disease to treat, particularly when it becomes refractory. A deeper understanding of SCLC biology and molecular landscape is the key factor in creating novel therapeutic methods. The aberrantly expressed on the surface of over 85% of SCLC cells makes DLL3 an extremely compelling novel therapeutic target. Despite the numerous challenges, the emerging data on DLL3-targeting agents provide renewed treatment strategies for patients with refractory SCLC.

AUTHOR CONTRIBUTIONS

Xin Nie: Conceptualization, writing—original draft preparation. Yu-meng Tian: Writing—figure and table preparation. Yue Yuan: Writing—reviewing and editing. Lin Li: Conceptualization, supervision, writing—reviewing and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no competing interests.

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