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CAR T-cell therapy in small-cell lung cancer with a focus on DLL3-targeted approaches

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Abstract

Small-cell lung cancer (SCLC) remains a fast-growing, genomically plastic neuroendocrine cancer with poor survival despite chemo-immunotherapy. Converging biological and clinical evidence identifies delta-like ligand 3 (DLL3) as a lineage-linked target expressed in most SCLC with limited normal tissue expression, enabling selective T-cell-based strategies. This review synthesises the trajectory of DLL3-directed therapies, positioning chimeric antigen receptor (CAR) T cells within a broader T-cell engagement continuum that now includes a clinically validated DLL3 × CD3 engager. We integrate preclinical and early clinical data to articulate a design blueprint for DLL3-directed CAR T cell in solid tumours: binder affinity tuned for on-target specificity; second- and third-generation signalling to balance rapid cytolysis with persistence; and armouring modules, such as IL-7/CCL19 or IL-18, to counter hypoxia, poor trafficking and immune suppression in the SCLC tumour microenvironment. Using a representative next-generation DLL3-directed CAR T-cell platform as an example, we highlight the translational importance of shortened manufacturing that preserves T-cell stemness and may facilitate dose optimisation and improve treatment feasibility. We also set out a biomarker framework that links antigen density, longitudinal DLL3 assessment in tissue and liquid biopsies and pharmacodynamic tracking of expansion and persistence to patient selection and retreatment. Finally, we outline a pragmatic trial agenda that prioritises step-up dosing, built-in control features and rational combinations with radiotherapy or checkpoint blockade to mitigate toxicity and reduce antigen escape. Together, these engineering, biomarker and clinical design principles provide a framework for evaluating DLL3-directed CAR T-cell therapies in future clinical studies.

Keywords: *small-cell lung cancer, SCLC, DLL3, delta-like ligand 3, CAR T, chimeric antigen receptor T cells, tumour microenvironment*

Introduction

Small-cell lung cancer (SCLC) is a highly aggressive neuroendocrine malignancy, characterised by rapid doubling time, early dissemination and poor long-term survival [54]. SCLC accounts for ~12% of all lung cancers and as of 2022, global SCLC incidence remains high, International Agency for Research on Cancer estimated 267,965 new small-cell carcinoma cases worldwide in 2022 (180,063 men; 87,902 women), corresponding to 11.5% of male and 9.7% of female lung cancers globally [29]. In Australia, 12%–13% of new lung cancers are SCLC [50]. The majority of patients present with extensive-stage

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disease, with the current standard of care being platinum/etoposide chemotherapy and anti-PD-L1 immunotherapy. Unfortunately, despite some recent advances, therapeutic outcomes remain modest [42]. Although initial responses are common, most patients relapse rapidly, with a median overall survival of 12.3 months when using atezolizumab plus chemotherapy [19]. Given its poor prognosis and limited treatment options, SCLC remains a major focus of translational research [32]. In recent years, significant progress has been made in deciphering the biology of SCLC and in designing new treatment approaches, including novel drugs and refined radiotherapy protocols [48]. Among emerging strategies, chimeric antigen receptor (CAR) T-cell therapy is of particular interest. Although CAR T cells have demonstrated remarkable success in haematological malignancies [58], their application in solid tumours has been limited by tumour heterogeneity, immunosuppressive microenvironments and on-target/off-tumour toxicities [10]. Delta-like ligand 3 (DLL3), a Notch inhibitory ligand, has emerged as a promising target due to its high expression in SCLC (≥80% of cases) and limited presence in normal tissues [59]. Among DLL3-directed cell therapies for SCLC, development has progressed from the first-in-human T-cell therapy targeting DLL3, AMG 119, to newer constructs. This review summarises the preclinical and clinical advancements in DLL3-targeted CAR T-cell therapy for SCLC, with a focus on recent advances in next-generation DLL3-directed CAR T-cell therapies.

The CAR T-cell continuum and beyond

CAR T-cell therapy, originally termed 'T-bodies', emerged from seminal work in 1987 by Yoshihisa Kuwana *et al* in Japan, who combined antibody-derived recognition domains with T-cell receptor (TCR) signalling elements [25]. Since then, the platform has advanced through five design "generations," from CD3ζ-only prototypes (as the sole intracellular signalling domain) to constructs incorporating costimulatory signalling and, more recently, cytokine and signalling-pathway modules [33]. An overview of the generational evolution of CAR T cells is provided in Table1.

First-generation CAR T cells fused a single-chain variable fragment (scFv) to the CD3ζ signalling motif alone. They could trigger cytotoxicity on contact but showed limited proliferation, cytokine production and *in vivo* persistence, so clinical activity was modest and short-lived [19,23,35]. Second-generation CARs added a single costimulatory domain, most commonly CD28 or 4-1BB, alongside CD3ζ [24]. This upgrade improved expansion and survival, boosted effector function and produced more durable remissions [44].

Third-generation CAR T cells incorporate two costimulatory domains, typically CD28 and 4-1BB, alongside CD3ζ to enhance both early effector function and longer-term persistence compared with second-generation constructs. Early clinical experience suggests this dual signalling can yield rapid tumour cytolysis (via CD28) while supporting durability (via 4-1BB), although definitive head-to-head trials remain limited [13,20,46].

Table 1. Generational evolution of CAR T-cell designs.

Generation	Key features	Rationale/notes
1st	scFv + CD3ζ only	Activation without co-stimulation; limited persistence
2nd	CD3 ζ + single co-stim (CD28 or 4-1BB)	Improved expansion, survival and durability
3rd	CD3 ζ + dual co-stim (CD28 and 4-1BB)	Blend rapid cytolysis (CD28) with persistence (4-1BB)
4th (Armoured/TRUCK)	Cytokine/agonist payload (e.g. IL-12, IL-18) released on activation	Inflame TME, recruit innate cells, overcome antigen-low disease
5th (Logic-gated)	Cytokine receptor domains, SynNotch, AND/OR/NOT gates, ON/OFF switches	Increase specificity, control toxicity, adapt to heterogeneous antigens

Fourth-generation 'armoured' CARs often termed TRUCKs (T cells redirected for antigen-unrestricted/universal cytokine-mediated killing) add an inducible payload cassette so that, upon antigen engagement, engineered T cells locally secrete cytokines (e.g. IL-12 or IL-18) or other immunomodulators (Figure 1). This aims to remodel hostile tumour microenvironments, recruit innate immunity and overcome antigen-low disease while limiting systemic exposure by restricting payload release to the tumour site [11,24].

In parallel, bispecific T-cell engager (BiTE) technology offers an 'off-the-shelf' approach that physically links CD3 on T cells to a tumour antigen, activating cytotoxicity independently of native TCR specificity [18]. The first-in-class CD19×CD3 BiTE, blinatumomab, clinically validated the platform in B-ALL and established characteristic toxicities such as cytokine release syndrome and neurotoxicity that are now managed with step-up dosing and supportive care [4,56]. More recently, FDA's accelerated approval of DLL3×CD3 BiTE tarlatamab (AMG 757; IMDELLTRA) for extensive-stage SCLC extends the milestones of T-cell-engaging therapies into a major solid tumour and underscores the potential complementarity of BiTEs and next-generation CARs as the field works to broaden antigen targets, deepen responses and mitigate toxicity [60].

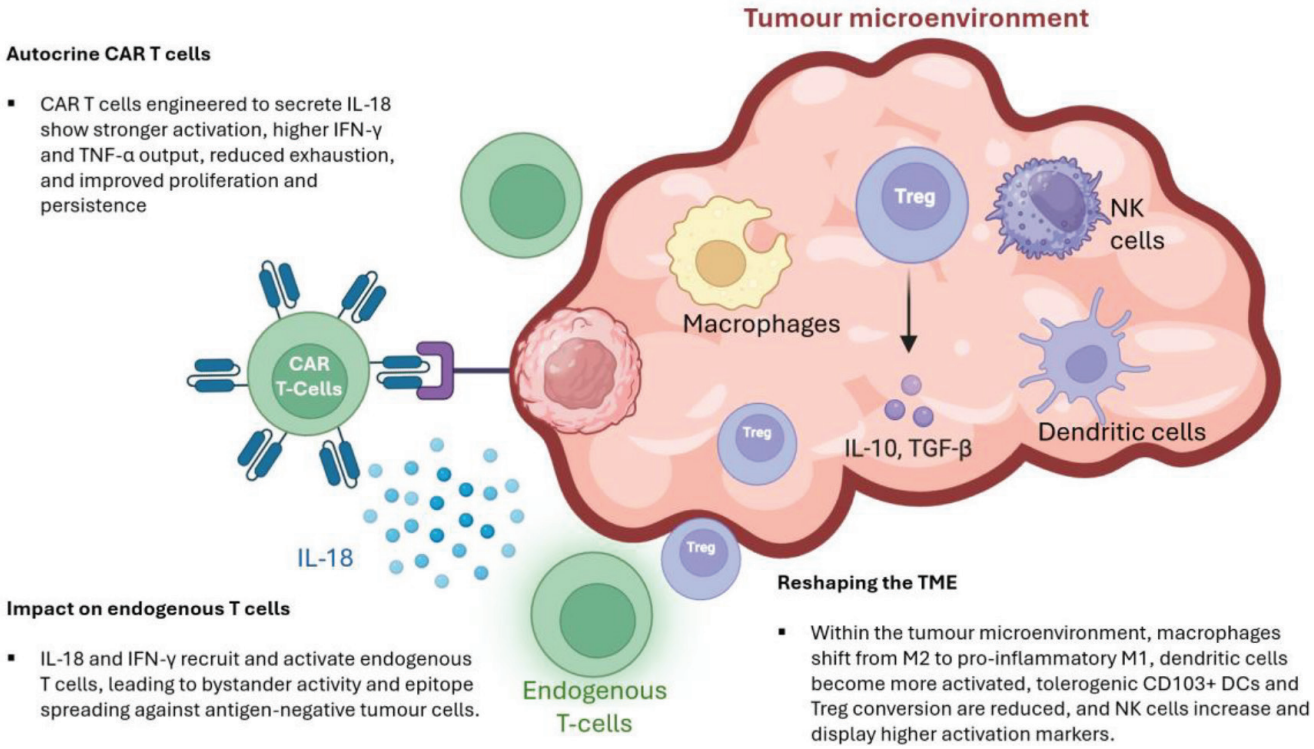


Figure 1. Mechanisms of tumour microenvironment remodelling by IL-18-secreting armoured CAR T cells. CAR T cells engineered to secrete the pro-inflammatory cytokine IL-18 operate through autocrine and paracrine mechanisms to enhance anti-tumour efficacy. In an autocrine loop, IL-18 binding to its receptor on the CAR T cell itself leads to stronger activation, enhanced production of IFN-γ and TNF-α, reduced exhaustion, and improved proliferation and persistence. Through paracrine signalling, the secreted IL-18 and IFN-γ recruit and activate endogenous T cells, enabling bystander killing of antigen-negative tumour cells through epitope spreading. Furthermore, this cytokine milieu reshapes the immunosuppressive TME by polarizing macrophages towards a pro-inflammatory M1 phenotype, enhancing DC activation, suppressing Treg function and boosting the activation and cytotoxicity of NK cells. IL-18 was selected as an illustrative example because it is one of the best-characterised armouring strategies in DLL3-directed CAR T-cell development and has demonstrated the ability to enhance T-cell persistence while simultaneously remodelling the tumour microenvironment, although several alternative cytokine and chemokine-based approaches are also under active investigation. *Adapted from and created based on mechanisms described in [54].*CAR, chimeric antigen receptor; IFN, interferon; TNF, tumour necrosis factor; IL, interleukin; Treg, regulatory T cell; NK, natural killer; DC, dendritic cell.

DLL3 as a therapeutic target in SCLC

DLL3 is a membrane-bound notch ligand that is overexpressed in SCLC and other neuroendocrine tumours, with limited normal-tissue expression largely confined to the brain and pituitary, supporting a favourable therapeutic index [5,43]. Preclinical studies have demonstrated that DLL3-targeted therapies, including antibody–drug conjugates (ADCs) and BiTEs, exhibit potent anti-tumour activity [12,37]. The first targeted approach investigated was rovalpituzumab tesirine (Rova-T), an anti-DLL3 ADC, showed early promise but failed in phase III trials due to toxicity and limited efficacy [51]. Combination attempts to deepen and prolong responses included pairing Rova-T with PD-1 blockade, such as budigalimab, and with nivolumab with or without ipilimumab, but these did not rescue the programme [54]. Building on this experience, the field then pivoted to DLL3-directed T-cell engagement, the DLL3×CD3 bispecific tarlatamab received FDA's accelerated approval in May 2024 for ES-SCLC progressing after platinum therapy. The approval was based on a study showing a 40% objective response rate and median overall survival of about 14 months, with cytokine release syndrome and neurologic events as the key toxicities to manage [2]. Next-generation DLL3 engagers are broadening the field: the IgG-like DLL3/CD3 engager obrixtamig (BI 764532) has reported phase I activity across DLL3-positive SCLC and other NECs with manageable cytokine release syndrome (CRS) at step-up dosing and is now moving through expansion cohorts [55]. Similarly, the trispecific, half-life-extended DLL3 engager HPN328 (TriTAC/MK-6070) has shown early signals of efficacy in SCLC and other neuroendocrine malignancies, including neuroendocrine prostate cancer (NEPC), with ongoing dose-optimisation in phase I/II [6,34].

In addition to monotherapy, combination strategies involving the DLL3×CD3 bispecific T-cell engager tarlatamab are currently being explored in SCLC. In particular, ongoing clinical studies are evaluating tarlatamab in combination with pembrolizumab and other standard therapies. The rationale for combining tarlatamab with PD-1 blockade is that DLL3-directed T-cell activation may be further enhanced by reversal of T-cell exhaustion, potentially improving the depth and durability of anti-tumour responses. Although clinical data remain immature (ClinicalTrials.gov NCT06211036), these combination approaches may help overcome adaptive immune resistance mechanisms and further expand the role of DLL3-targeted immunotherapy in SCLC [2,37]

Collectively, the evidence establishes DLL3 as a viable SCLC target and motivates further development of cellular therapies, as summarised for key agents in Table 2. DJI136 is discussed throughout this review as an example of a next-generation DLL3-directed CAR T-cell platform.

Table 2. DLL3-targeted therapies for SCLC and related neuroendocrine cancers.

Modality	Agent	Sponsor	Setting/phase	Key outcome	Notable AEs	Status (2025)
ADC	Rova-T	AbbVie/ Stemcentrx (historic)	SCLC; phase III (terminated)	Early activity; phase III failed due to toxicity/limited efficacy	Serosal effusions, photosensitivity, thrombocytopenia	Discontinued
BiTE / T-cell engager	Tarlatamab (AMG 757; IMDELLTRA)	Amgen	ES-SCLC post-platinum; phase II/III	FDA accelerated approval (2025); ORR ~40%, median OS ~14 mo	CRS, neurologic events (managed with step-up dosing)	Approved (US); ongoing trials
IgG-like CD3xDLL3 engager	Obrixtamig (BI 764532)	Boehringer Ingelheim	DLL3+ SCLC/NECs; phase I/expansion	Early activity across SCLC/NECs; step-up dosing mitigates CRS	CRS (mostly low-grade with mitigation)	Active clinical development
Tri-specific/ extended half-life engager	HPN328 (MK-6070)	Harpoon/ Partnered	SCLC, NEPC; phase I/II	Signals of efficacy; dose optimisation ongoing	CRS, fatigue (reported)	Active clinical development
CAR T cell	AMG 119 (DLL3 CAR-T)	Amgen	R/R SCLC; phase I (first-in human)	Feasibility and pharmacology signals reported	CRS/neurologic events (monitoring)	Early clinical, discontinued
CAR T cell	DJI136 (DLL3 CAR-T)	Novartis	ES-SCLC; phase I/II (ongoing)	Design aims: enhanced persistence/ infiltration; shortened manufacturing	To be defined; DLTs monitored	Recruiting/ ongoing

DLL3 expression across SCLC molecular subtypes and implications for heterogeneity

SCLC is increasingly understood as a spectrum of molecular states defined by lineage transcriptional programmes, most commonly described by dominant regulators ASCL1 (SCLC-A), NEUROD1 (SCLC-N), POU2F3 (SCLC-P) and YAP1 (SCLC-Y), alongside immune-enriched or 'inflamed' phenotypes in some classifications ([3,17]. Across patient cohorts, these states can coexist within the same tumour and can shift under therapeutic pressure, highlighting biological plasticity as a core feature of SCLC [39].

DLL3 expression is most consistently linked to neuroendocrine lineage programmes and is frequently enriched in ASCL1-high disease. In surgically resected SCLC, DLL3 protein expression correlates positively with ASCL1 expression, supporting a lineage-coupled model in which DLL3 marks neuroendocrine differentiation rather than a universally uniform tumour antigen [56]. Emerging subtype analyses further suggest that ASCL1-dominant tumours show higher DLL3 expression than NEUROD1-dominant tumours, while neuroendocrine-low states such as POU2F3-driven or YAP1-associated disease may show lower or absent DLL3 in a subset of cases [3].

This subtype-linked heterogeneity has practical implications for patient selection and for anticipating antigen escape. Baseline testing should therefore consider not only DLL3 positivity but also the underlying lineage state, using paired immunohistochemistry panels (e.g. DLL3 with ASCL1, NEUROD1, POU2F3 and YAP1) to contextualise antigen density and to identify patients most likely to benefit from DLL3-directed cellular therapy. Because subtype composition and DLL3 levels can vary between lesions and over time, longitudinal sampling using repeat tissue assessment where feasible and liquid-biopsy approaches where validated, may help guide selection and retreatment decisions and should be incorporated into correlative science in prospective trials [14,39].

Beyond baseline heterogeneity, therapeutic pressure may drive antigen escape through downregulation of DLL3 expression or transition towards alternative lineage states [2,37]. Similar mechanisms have been observed with other targeted therapies and cellular immunotherapies. Given the recognised plasticity of SCLC, transitions from neuroendocrine-high states towards neuroendocrine-low phenotypes may reduce DLL3 expression and compromise durable responses [16,39]. These observations provide a rationale for longitudinal monitoring of DLL3 expression and support future development of dual-targeting or logic-gated CAR T-cell approaches to reduce selective pressure on a single antigen [40].

DLL3 beyond SCLC

Although DLL3 has been most extensively studied in SCLC, its expression is not restricted to pulmonary neuroendocrine malignancies. High levels of DLL3 expression have also been reported in large-cell neuroendocrine carcinoma, NEPC and a subset of poorly differentiated gastroenteropancreatic and extrapulmonary neuroendocrine carcinomas [6,55]. In these tumours, DLL3 expression is frequently associated with neuroendocrine differentiation and aggressive clinical behaviour, proving its potential as a therapeutic target across multiple high-grade neuroendocrine malignancies [45].

The clinical development of DLL3-targeted therapies has increasingly reflected this broader relevance. Recent studies of tarlatamab, obrixtamig and HPN328 have expanded enrollment beyond SCLC to include patients with neuroendocrine carcinomas and NEPC, demonstrating preliminary evidence of activity across DLL3-expressing tumour types [1,55]. As a result, advances in DLL3-directed cellular therapies may have implications beyond SCLC and could provide a framework for treating a wider group of aggressive neuroendocrine cancers characterised by limited therapeutic options.

CAR T-cell therapy in SCLC: preclinical evidence

Notably, DLL3 is commonly expressed across disease stages and treatment lines, although expression can vary between lesions and over time with therapy [14]. DLL3-CAR-natural killer (NK) cells exhibited significant efficacy and robust tumour infiltration in SCLC subcutaneous xenograft models [28]. However, orthotopic models may better recapitulate the lung tumour microenvironment. Encouragingly, these findings have already translated to clinical testing, with a phase I trial investigating DLL3-CAR-NK cells in relapsed/refractory SCLC (NCT05507593). Similarly, AMG119, was a phase I study initiated by Amgen in 2018 which was based on DLL3-targeted CAR T cells that was suspended after early clinical evaluation, although detailed reasons for programme termination have not been publicly reported [36].

Although the specific reasons for discontinuation of AMG 119 have not been fully reported, the programme likely encountered challenges that are common to CAR T-cell therapy in solid tumours. Unlike haematological malignancies, CAR T-cell therapy in SCLC must overcome several well-recognised barriers, including an immunosuppressive tumour microenvironment, tumour heterogeneity and rapid disease progression. In addition, intratumoural heterogeneity and variability in DLL3 expression may reduce the effectiveness of single-antigen targeting strategies, while rapid disease progression and declining performance status can further complicate treatment delivery [5,8,9]. These challenges highlight the biological barriers that early DLL3-directed CAR T-cell programmes were required to overcome and provide important context for the development of next-generation approaches

Several features distinguish newer DLL3-directed CAR T-cell platforms from earlier approaches and may improve their therapeutic potential in SCLC. Advances in CAR design have focused on enhancing T-cell persistence, reducing exhaustion and improving activity within the immunosuppressive tumour microenvironment. In addition, newer strategies incorporate armoured constructs, chemokine-receptor engineering and biomarker-driven patient selection to address limitations associated with tumour trafficking and antigen heterogeneity [21,22,24,38]. Manufacturing innovations aimed at preserving less-differentiated T-cell populations may also improve product fitness and durability. While these developments provide a strong biological rationale for improved outcomes, their clinical benefit remains to be confirmed in ongoing studies [2,37].

[58] developed a second-generation anti-DLL3 CAR T-cell construct (CD28 or 4-1BB costimulatory domains) that demonstrated robust cytotoxicity against DLL3+ SCLC cell lines and xenografts [58]. However, a key hurdle was ensuring sufficient persistence and tumour infiltration. To enhance efficacy, strategies such as armoured CAR T cells (secreting IL-15 or PD-1 blockers) and combinatorial approaches with ICIs have been investigated [22]. These findings support continued clinical evaluation of DLL3-targeted CAR T-cell therapy to determine whether the encouraging preclinical activity translates into meaningful clinical benefit for patients with SCLC.

DJI136: a novel DLL3-targeted CAR T-cell therapy for SCLC

DJI136, an investigational CAR T-cell therapy designed to target DLL3, a validated tumour-associated antigen highly expressed in SCLC. DJI136 has been designed to enhance persistence, proliferation and tumour infiltration, addressing key limitations of earlier CAR T-cell therapies. Notably, this product exhibits high-affinity binding to DLL3, which may increase on-target/off-tumour toxicity risk and activation in antigen-low normal tissue, depending on epitope density and kinetics. DJI136 is also reported to use an accelerated manufacturing workflow, a strategy that is intended to preserve less-differentiated T-cell phenotypes and improve feasibility of delivery (shortened 'vein-to-door') compared with conventional autologous CAR T-cell manufacturing; the impact on product phenotype, scalability and cost requires confirmation with programme-specific manufacturing and release-characterisation data

Clinical evaluation and trial design

DJI136 is currently being evaluated in an ongoing first-in-human Phase I study incorporating dose escalation followed by expansion cohorts in patients with relapsed or refractory DLL3-positive SCLC. The primary objectives are to evaluate safety, determine the recommended dose and assess preliminary anti-tumour activity while incorporating pharmacodynamic biomarkers including CAR T-cell expansion and persistence (NCT07564401).

Toxicity management

Toxicity management may be particularly challenging in patients with relapsed or refractory SCLC, who frequently present with extensive metastatic disease, high tumour burden, prior thoracic radiotherapy and declining performance status. These factors may increase vulnerability to treatment-related complications and complicate attribution of symptoms during therapy. In addition, central nervous system metastases are common in SCLC and may increase the complexity of monitoring for and managing immune effector cell-associated neurotoxicity syndrome (ICANS), particularly where baseline neurological symptoms are already present [2,5,36,37].

As with other CAR T-cell therapies, CRS and ICANS remain key safety concerns for DLL3-directed CAR T-cell approaches. Although early experience with DLL3-targeted cellular therapies remains limited, lessons from haematological malignancies suggest that careful patient selection, inpatient monitoring during peak CAR T-cell expansion and early intervention with corticosteroids and anti-cytokine therapies such as tocilizumab are likely to be important components of safe clinical implementation [5,56]. Furthermore, the low-level expression of DLL3 reported in selected normal tissues, including the brain and pituitary gland, highlights the importance of continued vigilance for potential off-tumour toxicities as these therapies advance through clinical development.

Beyond biological challenges, successful implementation of CAR T-cell therapy in SCLC will also depend on practical considerations. Autologous CAR T-cell manufacturing requires specialised infrastructure, is associated with substantial cost and may involve production times that are difficult to accommodate in a disease characterised by rapid clinical progression. Access to specialised treatment centres, the need for bridging therapy during manufacturing and careful patient selection based on performance status and disease burden are also likely to influence real-world applicability. Continued efforts to shorten manufacturing time and improve scalability may therefore be as important as advances in CAR design for successful clinical implementation [1,21].

The following strategies represent emerging approaches that aim to address current limitations of CAR T-cell therapy in solid tumours but remain largely preclinical or in early clinical development.

Challenges and future directions

It is important to distinguish between advances that have already demonstrated clinical activity and those that remain largely experimental. Clinical validation of DLL3-directed T-cell engagement has been established through the approval of tarlatamab and the ongoing clinical evaluation of DLL3-targeted cellular therapies. In contrast, many next-generation CAR T-cell engineering strategies, including logic-gated receptors, cytokine-armoured constructs, chemokine-receptor engineering and dual-targeting approaches, remain at the preclinical or early clinical stage. While these innovations may help overcome key barriers associated with solid tumours, their safety and efficacy in SCLC remain to be established [2,5,21,24,37,56].

DLL3 CAR T cell is biologically compelling but remains investigational and faces many of the same challenges that have limited CAR T-cell efficacy in solid tumours. While DLL3 is overexpressed in a majority of SCLC, its prevalence and intensity vary by cohort and assay, with real-world and systematic reviews reporting high overall positivity but only a subset achieving very high tumour-cell staining fractions – important for antigen density – dependent platforms [7,41]. Longitudinal assessment of DLL3 expression remains important because antigen expression may vary between lesions and evolve during treatment, as discussed above [14,21].

Off-tumour risks must be managed: Although available evidence suggests minimal cell-surface DLL3 expression in normal tissues, transcriptomic studies demonstrate detectable expression in selected regions of the central nervous system and pituitary gland. While no major off-tumour CNS toxicity signal has yet emerged from DLL3-targeting approaches, continued vigilance remains warranted, particularly in the setting of neuroinflammation, blood–brain barrier disruption or future cellular therapies capable of prolonged persistence [37,53] (Figure 2).

Beyond antigen biology, SCLC's hypoxic, T-cell-poor microenvironment impairs trafficking and function, a recognised barrier across solid tumours [1,8,9]. Several experimental strategies have been proposed to counter this, including 'armouring' CAR T cells to enhance persistence and infiltration (e.g. IL-7/CCL19 secretion or chemokine-receptor engineering such as CXCR1/2), and pairing with modalities that modulate hypoxia or inflame the tumour bed (e.g. radiotherapy or checkpoint blockade), all of which are supported by emerging preclinical/early-clinical data and recent consensus reviews [21,38]. If forthcoming trials demonstrate acceptable safety, durability and feasibility with biomarker-driven selection and correlative science, DLL3-directed CAR T-cell therapy could move to a new standard for relapsed or refractory SCLC. Ongoing clinical studies of next-generation DLL3-directed CAR T-cell products will determine whether these design innovations translate into improved patient outcomes.

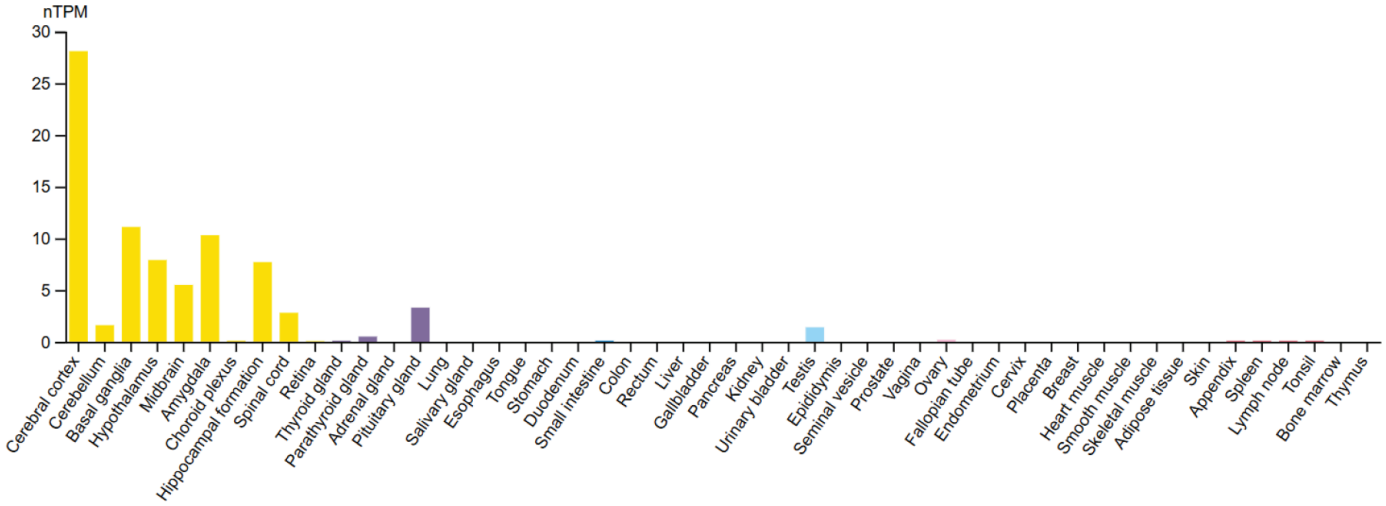


Figure 2. DLL3 expression in normal human tissues (consensus dataset). Normalized transcript levels (nTPM) of DLL3 are shown across various tissues. DLL3 transcript levels are highest in regions of the brain (e.g. cerebral cortex and amygdala) and detectable in the pituitary gland, indicating potential off-tumour expression [47].

Limitations of current evidence

Interpretation of the current literature is limited by the scarcity of mature clinical data. Most evidence supporting DLL3-directed CAR T-cell therapy derives from preclinical models, conference abstracts or early-phase studies with limited patient numbers and short follow-up. Consequently, key questions regarding durability of response, optimal patient selection, long-term toxicity, manufacturing feasibility and comparative effectiveness remain unresolved.

Conclusion

SCLC has a poor prognosis with few durable treatment options, yet DLL3 has emerged as a tractable lineage target across most tumours with limited normal-tissue expression. Clinical experience with Rova-T clarified the limits of ADCs in this setting, whereas the approval of tarlatamab confirms that DLL3-directed T-cell engagement can deliver meaningful activity in a common solid tumour. Preclinical and early clinical data now position DLL3-CAR approaches, including DJI136 and the first-in-human AMG 119 program, as credible next steps to deepen and prolong responses.

Realising this potential will depend on careful target management and engineering. Biomarker-guided patient selection and longitudinal assessment of DLL3 expression may help optimise treatment strategies and identify patients most likely to benefit from DLL3-directed cellular therapies. Safety will depend on affinity optimisation and delivery within established CAR T-cell safety pathways, including lymphodepleting chemotherapy. Close inpatient monitoring during the early post-infusion expansion and protocolised CRS and ICANS grading and management (with timely use of tocilizumab and corticosteroids when indicated) will further improve the safety. Overcoming microenvironmental barriers will likely require a combination of cellular engineering and rational combination strategies, as discussed above. Continued advances in CAR engineering are expected to further improve efficacy while reducing toxicity, although these approaches remain investigational.

If forthcoming trials can couple robust manufacturing and feasible delivery with biomarker-driven selection and rich correlative science, DLL3-directed CAR T-cell therapy could become an important addition to the therapeutic landscape for relapsed or refractory SCLC and provide a template for targeting other neuroendocrine malignancies.

Conflicts of interest

The authors declared no conflicts of interest.

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