Editorial

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'Tarlatamab's FDA approval: shaping the future of cancer therapy'

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Introduction

Small cell lung cancer (SCLC) is the most aggressive type of lung cancer, originating from neuroendocrine cells. It is notorious for its rapid proliferation due to its high vascularity, quickly metastasizing to other parts of the body such as the lungs, lymph nodes, liver, bones, brain, and adrenal glands. This stage with extensive metastasis is referred to as the extensive stage of SCLC (ES-SCLC), which accounts for ~15% of lung cancer cases, affecting 200 000 people worldwide annually[1]. About two-thirds of SCLC patients are diagnosed at the extensive stage[2]. Risk factors for SCLC include smoking, radiation exposure, environmental pollution, immunocompromised states, and a family history of lung cancer. Smokers, including those exposed to passive smoke, have a 15–30 times higher risk of developing lung cancer[3].

Clinical manifestations include coughing (with or without blood), shortness of breath, chest pain, fatigue, wheezing, hoarseness, loss of appetite, and significant weight loss. Initial diagnosis is based on imaging modalities, including CT scans, PET scans, and MRIs, with confirmation through fine-needle and core biopsies of the lung and surrounding thoracic region[4].

Recent advancements in treatment strategies for ES-SCLC have introduced Tarlatamab, marketed as Imdelltra. This bispecific T-cell engager (BiTE) binds delta-like ligand 3 and CD3[5]. Clinical trials have shown promising results, with Tarlatamab improving the prognosis and quality of life for individuals with this deadly disease.

Pathophysiology and mechanisms of ES-SCLC

The hostile nature of ES-SCLC is due to its rapidly dividing cancer cells and their dissemination to various organs. This is driven by different pathophysiological mechanisms and genetic mutations at the molecular level that enable the evasion of host immune responses. Different stimuli or genetic aberrations cause loss-of-function mutations in the TP53 and RB genes[6], leading to rapid proliferation and escape from cell death mechanisms. Immune checkpoint inhibition occurs due to the underexpression of the Major Histocompatibility Complex (MHC) and the inability to express antigens[7,8]. Delta-like ligand 3 (DLL3) is an inhibitory ligand of the Notch pathway present in growing neuroendocrine cells of the lung[9]. This molecular marker is overexpressed on the surface of neuroendocrine cancer cells in the lungs. Tarlatamab, a BiTE, binds to both DLL3 and CD3, resulting in T-cell-induced killing of cancer cells[10]. It provides a targeted immunotherapeutic response for patients previously treated with chemotherapy. This drug has brightened the future of people with ES-SCLC by offering adequate disease control, limiting progression, and enhancing survival. When it comes to SCLC treatment, Tarlatamab is definitely a major advancement, representing a novel therapeutic option for individuals with ES-SCLC.

Current treatment landscape

The current treatment landscape for small cell lung cancer (SCLC) revolves around chemotherapy, radiotherapy, immunotherapy, and smoking cessation for both management and prevention. In some cases, surgery can also be considered. Unlike non-small cell lung cancer (NSCLC), the systemic treatment of extensive-stage SCLC (ES-SCLC) has remained stagnant over the past few decades[11]. Only recently have several trials indicated that etoposide plus platinum (EP) could yield better results when combined with a PD-L1 inhibitor, such as atezolizumab or durvalumab[11,12]. Among these treatment options, chemotherapy is the most commonly used standard of care and the first line of treatment for SCLC due to its rapid metastasis. Platinum therapy combined with the nonplatinum agent etoposide is extensively employed due to its high efficacy[13]. The most frequently used platinum agents in SCLC are cisplatin and carboplatin, which are cytotoxic alkylating agents active throughout the cell cycle[13,14]. Although SCLC initially responds well to chemotherapy and radiation, relapse is nearly certain, and the effectiveness of subsequent lines of treatment diminishes as the cancer becomes more resistant.

Second-line therapy options for relapsed ES-SCLC include reconsideration with initial chemotherapy, CAV (cyclophosphamide, doxorubicin, and vincristine), irinotecan, lurbinectedin, and topotecan[15]. For platinum-sensitive patients who can tolerate it, retreatment with the initial platinum-based doublet chemotherapy can be considered, while progression within

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3 months of first-line chemotherapy may warrant CAV or IV topotecan, lurbinectedin, or irinotecan[15]. Subsequent lines of therapy often have lower efficacy, but some individuals may experience notable relief from symptoms[15].

Challenges in the treatment of ES-SCLC, such as relapse, acquired resistance, and toxicity, highlight the need for new, effective therapeutic strategies to improve health outcomes and increase survival rates. Emerging therapies under investigation include poly ADP-ribose polymerase (PARP) inhibitors, vascular endothelial growth factor (VEGF) inhibitors, and delta-like ligand 3 (DLL3) targeting strategies[15].

Table 1 provides a summary of current treatments for small-cell lung cancer.

Imdelltra (tarlatamab-dlle): mechanism of action

IMDELLTRA, an injectable drug, also known as Tarlatamab-dlle, is a half-life extended bispecific DLL3-directed CD3 T cell engager designed to target and eradicate cancer cells by leveraging the body's defense system. The FDA granted accelerated approval to this drug for the treatment of ES-SCLC with disease progression on or after platinum-based chemotherapy on 16 May 2024[16]. Tarlatamab (AMG 757) binds DLL3 on cancer cells and CD3 on T cells simultaneously, resulting in T-cell-mediated tumor lysis. In SCLC, the notch signaling pathway is a regulator of neuroendocrine differentiation[17]. Delta-like ligand 3 (DLL3), a notch signaling ligand, helps control the growth, division, and metastatic progression of SCLC cells and other neuroendocrine cells. Numerous investigations have demonstrated the aberrant expression of DLL3 on the surface of SCLC cells, with minimal expression in normal tissues, making it a potent therapeutic drug[18]. It also specifically targets CD3, a component of the T cell receptor complex on T cells, which are crucial mediators in the immune response.

Down-regulation of MHC class 1 is a common immune escape mechanism, even though programmed cell death inhibitors are part of the standard-of-care chemotherapeutic regimen for ES-SCLC[7]. Instead of depending on the presentation of MHC class 1 antigen, Tarlatamab binds both DLL3 and CD3, bringing T cells in close proximity to small-cell lung cancer cells. This forms a cytolytic synapse, leading to cancer cell lysis[19,20]. As a result of its mode of action, AMG 757 is particularly advantageous in the treatment of small-cell lung cancer.

Efficacy and safety profile

Tarlatamab, the first drug developed from this new therapeutic class, received FDA approval after phase 1 and 2 clinical trials. The phase 1 and 2 clinical trials were named DeLLphi-300 and DeLLphi-301, respectively. Participants had to be 18 years of age or older with a histologically confirmed diagnosis of SCLC that was refractory or recurrent after a median of two prior lines of therapy, including a platinum-based treatment regimen or another line of therapy such as a PD-L1 inhibitor.

During the phase 1 trial, 107 individuals were assigned tarlatamab in dose exploration (0.003 to 100 mg; in 73 patients) and expansion (100 mg; in 34 patients) cohorts[10]. The dose was administered every 2 weeks intravenously and continued until the SCLC worsened, intolerable side effects appeared, or the patient withdrew consent. The median follow-up was 8.7 months[9]. Treatment-emergent adverse effects were experienced by all patients, but serious ones occurred in only 51% of the patients[10]. Adverse effects of interest included cytokine release syndrome (52%), neurologic events (50%), such as immune effector cel l-associated neurotoxicity syndrome (ICANS), and neutropenia (16%). Other adverse effects included pyrexia (37%), nausea (20%), dysgeusia (22%), fatigue (22%), decreased appetite (13%), vomiting (12%), anemia (11%), asthenia (11%), neu tropenia (11%), headache (10%), decreased WBCs (8%), decreased lymphocyte count (8%), confusional state (6%), hyponatremia (6%), maculopapular rash (4%), pneumonitis (4%), lymphopenia (3%), encephalopathy (3%), and hyperten sion (3%). In the course of this trial, the median time until disease progression was 3.7 months (95% CI: 2.1–5.4), and the median duration of survival was 13.2 months (95% CI: 10.5 to not reached)[10].

In this phase 2 trial, the antitumor activity and safety were examined by injecting Tarlatamab intravenously every 2 weeks at doses of 10 mg or 100 mg[21]. The trial was divided into three parts: dose comparison, expansion of promising doses, and

Table 1

Overview of treatment modalities in small cell lung cancer.

Treatment modality	Characteristics
Chemotherapy	- First-line treatment due to rapid metastasis. - Platinum-based (cisplatin or carboplatin) combined with etoposide. - High initial efficacy and commonly used standard of care. - Initially responsive, but relapse is nearly certain. - Subsequent lines of treatment have diminishing effectiveness due to acquired resistance. - Treatment toxicity is a significant concern
Radiotherapy	- Used in combination with chemotherapy, especially for localized disease control and symptomatic relief. - Particularly effective for brain metastases
Immunotherapy	- Recent trials suggest benefit when PD-L1 inhibitors (e.g. atezolizumab, durvalumab) are added to chemotherapy for extensive-stage SCLC (ES-SCLC). - Challenges include identifying responsive patients and managing immune-related adverse events
Surgery	- Considered in limited cases, often in combination with other therapies. - Not commonly performed due to high likelihood of metastasis at diagnosis
Second-line therapies	- Options for relapsed ES-SCLC include reconsideration with initial chemotherapy, CAV, irinotecan, lurbinectedin, and topotecan. - Subsequent lines of therapy have lower efficacy; some patients may experience symptom relief
Emerging therapies	- Investigational strategies include PARP inhibitors, VEGF inhibitors, and DLL3 targeting strategies. - Aim to overcome resistance and improve health outcomes. - Clinical trials are ongoing to validate efficacy and safety

Table 2

Summary of clinical trials DeLLphi-300 and DeLLphi-301.

Trial name	Trial phase	Participants	Dosage	Route of administration	Median follow-up (months)	Median disease progression free survival (months)	Median overall survival (months)	Overall survival at 9 months (%)	Adverse effects of interest (%)
DeLLphi-300	1	107	0.003–100 mg	Intravenous	8.7	3.7 months (95% CI: 2.1–5.4)	13.2 months (95% CI: 10.5 to not reached)	—	CRS (52%), Neurological Events (70%), Neutropenia (16%)
DeLLphi-301	2	220	10mg or 100 mg	Intravenous	10.6 months in the 10 mg group and 10.3 months in the 100 mg group	4.9 months (95% CI: 2.9–6.7) in the 10 mg group and 3.9 months (95% CI: 2.6–4.4) in the 100 mg group	14.3 in the 10 mg group.	68% in the 10 mg group, while 66% in the 100 mg group	CRS (51 and 61%), decreased appetite (29 and 44%), pyrexia (35 and 33%), and ICANS (8 and 28%)

reducing hospital monitoring postinfusion for cycle 1 from 2 days to 1 day. The median follow-up was 10.6 months for the 10 mg group and 10.3 months for the 100 mg group. The median pro gression-free survival was 4.9 months (95% CI: 2.9–6.7) for the 10 mg group and 3.9 months (95% CI: 2.6–4.4) for the 100 mg group. At 9 months, the overall survival was 68% in the 10 mg group and 66% in the 100 mg group[20]. Antitumor activity was observed in 40% (97.5% CI: 29–52) of the 10 mg group and 32% (97.5% CI: 21–44) of the 100 mg group[21]. The median overall survival was determined to be 14.3 months. The majority of adverse effects in both groups included CRS (51 and 61%), reduced appetite (29 and 44%), fever (35 and 33%), constipation (27 and 25%), and anemia (26 and 25%), respectively[21]. ICANS occurred in 8% of the 10 mg group and in 28% of the 100 mg group[21]. Patients with ICANS demonstrated confusion, com promised attention, and motor abnormalities such as tremors and weakness. CRS, the most common adverse effect, was treated with corticosteroids, IV hydration, acetaminophen, and tocilizu mab in a few patients. Common symptoms of CRS in the phase 2 trial included pyrexia (97% of patients), decreased BP (20%), and decreased O_2 saturation (17%)[21].

Table 2 summarizes crucial information from both trials for better understanding of the safety and efficacy profile.

Conclusion

Treatment for extensive-stage small cell lung cancer (ES-SCLC) has advanced significantly with the introduction of Tarlatamab (IMDELLTRA). As a bispecific T-cell engager, it binds to CD3 on T cells and DLL3 on cancer cells, enabling the immune system to combat the tumor. Clinical trials such as DeLLphi-300 and DeLLphi-301 have demonstrated its ability to extend survival and enhance the quality of life for patients who have exhausted other treatment options. Despite manageable side effects like neurotoxicity and cytokine release syndrome, Tarlatamab presents a promising therapeutic alternative that has the potential to revolutionize the standard of care for ES-SCLC. Further studies and clinical testing are required to fully determine its efficacy and safety profile.

Disparities in the availability of gene therapy and diagnostic tests underscore the necessity for more equitable and widespread access to cutting-edge cancer treatments. Global campaigns and partnerships should focus on increasing access to these treatments and enhancing diagnostic infrastructure in underprivileged areas to address this issue.

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Consent

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