Editorial Commentary

Tarlatamab: the promising immunotherapy on its way from the lab to the clinic

Daolin Tang, Rui Kang

Department of Surgery, UT Southwestern Medical Center, Dallas, TX, USA

Correspondence to: Daolin Tang; Rui Kang. Department of Surgery, UT Southwestern Medical Center, Dallas, TX 75390, USA.

Email: daolin.tang@utsouthwestern.edu; rui.kang@utsouthwestern.edu.

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Small cell lung cancer (SCLC) is a highly aggressive type of lung cancer that typically originates in the bronchi, which are the breathing tubes located in the central area of the chest. It accounts for about 10–15% of all lung cancer cases and tends to spread quickly to other parts of the body (lung, the brain, liver, adrenal glands, and bone) (1). The 5-year survival rate for SCLC is less than 7%, making it one of the deadliest forms of lung cancer (2). Patients with SCLC typically experience respiratory symptoms, such as coughing, difficulty breathing, and coughing up blood. Due to its aggressive nature, most patients are diagnosed with advanced or metastatic disease (3).

For many years, the standard treatment for newly diagnosed metastatic SCLC has been a combination of a platinum-based chemotherapy (cisplatin or carboplatin) and etoposide (1). While recent randomized phase III studies have shown that adding an immune checkpoint inhibitor, such as atezolizumab or durvalumab, to first-line chemotherapy can provide benefits for some patients with extensive-stage SCLC, most patients do not experience long-lasting benefits from this approach (4,5). Therefore, identifying the characteristics of tumors and hosts that are associated with a response to immunotherapy and developing additional anticancer strategies, especially in the second-line setting and beyond, is essential to improve outcomes for SCLC patients. A recent global multi-institutional phase 1 study led by Paz-Ares found that tarlatamab, a novel bispecific T cell engager (BiTE), has a manageable safety profile and provides encouraging response durability in patients with recurrent SCLC who have previously received platinum-based regimens and anti-programmed cell death 1 (PD-1)/programmed cell death ligand 1 (PD-L1) antibodies (6).

A BiTE is a type of immunotherapy that has shown great promise in treating different types of cancer, including Kirsten rat sarcoma viral oncogene homolog (KRAS)-driven tumors (7). The fundamental concept behind BiTEs is to create an antibody that can bind to both a T cell and a cancer cell simultaneously, bringing the T cell close to the cancer cell and enabling it to recognize and attack it. BiTEs are designed to be very specific, allowing them to target cancer cells while leaving healthy cells unharmed (8). One promising BiTE is tarlatamab, also known as AMG 757 (9). This drug works by binding to delta-like ligand 3 (DLL3) on tumor cells and cluster of differentiation 3 (CD3) on T cells, which triggers T cell-dependent antitumor immunity (*Figure 1*). DLL3 is an inhibitory Notch ligand that is highly expressed in SCLC and other neuroendocrine tumors, but it is minimally expressed in normal tissues (10,11). As a result, DLL3 is being explored as a potential therapeutic target in SCLC (12).

In a previous preclinical study conducted by Paul E. Hughes' group, potent and specific killing of SCLC cell lines by AMG 757 with very low DLL3 expression (<1,000 molecules per cell) was observed (9). AMG 757 was also found to effectively engage human T cells when

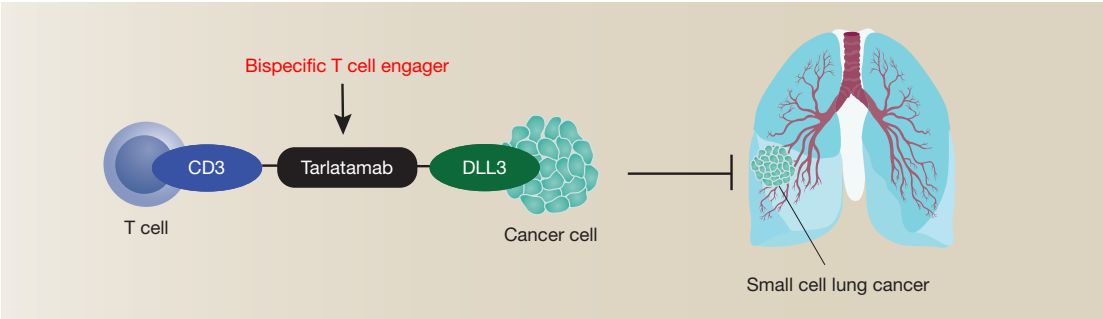

Figure 1 Mechanism of tarlatamab-mediated tumor suppression in SCLC. Tarlatamab, also known as AMG 757, is a BiTE. By binding to DLL3 on tumor cells and CD3 on T cells, tarlatamab enables the recruitment and activation of T cells, which in turn leads to the destruction of tumor cells. This mechanism of action makes tarlatamab a promising therapeutic option for the treatment of SCLC. CD3, cluster of differentiation 3; DLL3, delta-like ligand 3; SCLC, small cell lung cancer; BiTE, bispecific T cell engager.

systemically administered, induce T-cell activation, and redirect T cells to kill tumor cells, resulting in significant tumor regression and complete responses in patient derived xenograft models of SCLC, as well as in orthotopic models of established primary lung SCLC and metastatic liver lesions. Furthermore, a 1-month repeat dose nonhuman primate toxicology study revealed that AMG 757 was well tolerated at a dose of 4.5 mg/kg, which provided exposure levels exceeding the mean *in vitro* cell effective concentration 50% (EC50) values. No AMG 757-related adverse findings were observed in animal. Overall, these preclinical studies indicate that AMG 757 may be a viable option for targeting DLL3-expressing SCLC tumors in the clinical setting.

The current clinical trials conducted by Paz-Ares *et al.* were sponsored by Amgen Inc. (6). A total of 107 patients were enrolled in the trial, and DLL3 expression (≥1%) was detected in 94% of the evaluable patients. Participants received tarlatamab intravenously every 2 weeks at doses ranging from 0.003 to 100 mg. Patients whose tumors improved received step dosing. The mean terminal elimination half-life of tarlatamab was found to be 5.7 days. Tarlatamab was discontinued in 4 (3.7%) patients, and 25 patients showed a confirmed response (23.4%), including 2 with a complete response. The median duration of response was 12.3 months, and the longest duration of response observed was 14.9 months. However, the drug also showed some toxicity, and 90.7% of the patients experienced side effects. The most common side effects were cytokine release syndrome in 56 patients (52.3%), pyrexia in 43 patients (40.2%), and constipation in 33 patients (30.8%). Cytokine release syndrome is an inflammatory syndrome caused by an aggressive immune response, which was generally grade 1 in this trial. Treatment-related grade 3 adverse events occurred in 33 patients (30.8%), and grade 5 adverse event was reported in one patient (1%). The disease control rate was found to be 51.4%. The median progression-free survival and overall survival were 3.7 and 13.2 months, respectively. As expected, the treatment with tarlatamab resulted in increased T cell infiltration and activation in tumor samples with interferon gamma production.

In summary, this phase 1 human trial demonstrated that tarlatamab as a first-in-class DLL3-targeted BiTE is reasonably effective and has manageable levels of toxicity. The treatment was well-durable in SCLC patients who responded to the drug. However, to better understand the long-term response and potential side effects of tarlatamab, more multicenter evidence is needed, either as monotherapy or in combination therapy. In normal tissues, DLL3 expression is generally high not only in brain tissue but also in the pituitary gland and testis. Further monitoring of the functional effects of tarlatamab on these tissues is required. Successful patient recruitment is a major challenge in conducting clinical trials, and further monitoring of the relationship between underlying disease and response to tarlatamab in SCLC patients could help better define patient stratification of the trial population. Finally, effective biomarkers for clinical evaluation of tarlatamab drug and antitumor immune response are still lacking. Understanding the mechanisms of drug-induced cell death, including tarlatamab, and drug resistance is an important task in basic cancer research (13).

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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