Review Article
Running Title: Monoclonal Antibodies in Small Cell Lung Cancer
Received: October 9, 2025; Accepted: December 6, 2025

Monoclonal Antibodies in the Treatment of Small Cell Lung Cancer: A Review of Clinical Trials

Ali Asghar Hemmati, PhD, Soroush Alaei♦, PhD candidate

Department of Pharmacology, School of Pharmacy, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

♦Corresponding Author
Soroush Alaei, PhD candidate
Department of Pharmacology,
School of Pharmacy,
Ahvaz Jundishapur University of Medical Sciences,
Ahvaz, Iran
Email: Alaeisoroush@gmail.com

Abstract
Small cell lung cancer (SCLC) is an aggressive type of cancer with a relatively high mortality rate after diagnosis. It has been accepted for decades that platinum-based medicines, in addition to chest radiotherapy, can be used in limited-stage of SCLC. Currently, chemotherapy or combination immunotherapy are used for treatment. However, fully successful treatment may not to be attained due to the resistance and relapse that can occur. Several reports have demonstrated that the addition of anti-programmed death-ligand 1 (anti–PD-L1) immunotherapy or cytotoxic T-cell–associated antigen antibodies and increasing of delta-like ligand 3 antigens on SCLC tumor cells into chemotherapy could improve the survival rate of patients for few years. Monoclonal Antibodies, as a new and effective class of biopharmaceutical compounds, showed broad application prospects in the treatment of SCLC. Monoclonal antibodies that specifically target cancer cells and are attached to cytotoxic drugs, allowing for targeted killing of cancer cells while healthy tissues are not affected. In this review, we discussed the therapeutic efficacy and safety of MABs in SCLC. The latest agents of this group of drugs are described. Their efficacy and challenges are discussed and compared.

Keywords: Small Cell Lung Carcinoma, Immunotherapy, Monoclonal antibody

Introduction
Lung cancer has the second-highest mortality rate among malignancies, worldwide. Tobacco smoking, which contains nicotine, alkaloids, nitrosamines, and polycyclic aromatic hydrocarbons, has been demonstrated to be the leading cause of all types of lung cancer.[1] Small cell lung cancer (SCLC), named for the small microscopic appearance of the cancer cells, is a high-

grade, poor-prognosis neuroendocrine carcinoma and has the strongest epidemiological link to tobacco among all lung cancers. SCLC accounts for about 15% of lung cancer cases and has a high mortality rate (25%) compared with other common solid tumors. SCLC typically presents with respiratory symptoms, including cough, dyspnoea, or haemoptysis. Imaging usually shows a centrally located lung mass and often bulky thoracic lymph node involvement. The inactivation of two tumor suppressors, p53 and RB, is found in the vast majority of SCLC cases; this is distinct from the primary oncogenic drivers of many other solid tumors, notably non-small-cell lung cancers (NSCLC). Several studies have described the amplification of *MYC* family genes (*MYC*, *MYCL*, and *MYCN*) in a subset of SCLC tumors.[2,3]

SCLC is biologically and clinically distinct from other types of lung cancer. Therefore, therapeutic progress is very different from that seen in NSCLC. It has been accepted for decades that platinum-based medicines, in addition to chest radiotherapy, can be used in limited-stage SCLC. But when tumors spread from one lung to the other and to other organs called extensive-stage, platinum-based combinations that included etoposide provided superior survival. In order to improve the survival of patients with SCLC, the development of new drugs and treatment methods is essential. The etoposide plus platinum combination was standard therapy until 2019, when it was demonstrated that the addition of anti-programmed death-ligand 1 (anti–PD-L1) immunotherapy to chemotherapy could improve survival even in some patients up to 3 years.[4]

Recently, checkpoint inhibitors, for their anticancer effect by blocking a negative regulatory signal for T-cell activation from the tumor microenvironment, have been widely used for the treatment of different types of cancer. They include programmed cell death protein-1 (PD-1), programmed cell death ligand-1 (PD-L1), and cytotoxic T-cell–associated antigen (CTLA-4) antibodies. Also, the increasing expression of delta-like ligand 3 (DLL3) antigens on SCLC tumor cells has led pharmaceutical companies to develop anti-DLL3 monoclonal antibodies (MABs) for SCLC. In this review, we aimed to evaluate all clinical studies investigating monoclonal antibody-based therapies in SCLC. We included interventional human studies of any monoclonal antibody that has been approved or tested for SCLC with due attention to their regulatory approval status. Eligible studies comprised randomized controlled trials (RCTs) as well as non-randomized trials (including single-arm studies) that evaluated at least one monoclonal antibody in patients with limited-stage, extensive-stage, or relapsed SCLC, with no restriction on the time period of publication or conduct. A comprehensive literature search was performed using the Medline (PubMed), Web of Science, and Google Scholar databases.

Target Agents for PD-1 and PD-L1

PD-1 is a member of the CD28 family. It is an inhibitory receptor expressed on activated T cells, B cells, macrophages, natural killer cells, and regulatory T cells (Tregs). This receptor has two binding ligands, PD-L1 and PD-L2, which are expressed on T cells, B cells, macrophages, dendritic cells, and many other cells, including tumor cells. Binding of PD-1 to either ligand inhibits T cell activity, induces T cell tolerance, suppresses proliferation, and reduces the immune response of T cells. Tumors cause overstimulation of the PD-1/L1 signaling pathway.[5]

Adebrelimab

Adebrelimab, developed by Jiangsu Hengrui Pharmaceuticals, is a monoclonal antibody against PD-L1 that has been approved since 2023 in combination with chemotherapy by

the National Medical Products Administration (NMPA) of China as the first-line treatment for extensive-stage SCLC.[6]

In phase 3 clinical trial (CAPSTONE-1), 462 patients with extensive-stage SCLC randomly assigned (1:1) to Adebrelimab in combination with platinum compound + etoposide (P/E) group or P/E alone group, demonstrated 15.3 months median overall survival (OS) versus 12.8 months respectively.[7]

Atezolizumab

Atezolizumab, developed by the American biotechnology company Genentech, is a therapeutic anti-PD-L1 antibody, approved by the U.S. Food and Drug Administration (FDA), for the treatment of patients with metastatic urothelial carcinoma, NSCLC and the first approved monoclonal antibody for SCLC at March 2019. It works by blocking PD-1/PD-L1 interaction and preventing T cell tolerance.[8]

One of the first RCTs evaluating Atezolizumab in extensive-stage SCLC in comparison with standard chemotherapy (P/E) showed no significant difference in OS.[9] But in phase 3 clinical trial (IMpower133) when 403 patients with extensive-stage SCLC randomly received Atezolizumab added to P/E chemotherapy versus P/E alone, mean OS significantly increased from 10.3 to 12.3 months, although the objective response rate (ORR) decreased from 64.4% to 60.2%.[10] most obvious adverse effects reported in Atezolizumab group were 5-4% Immune-related hyper/hypothyroidism.[11]

Evaluation of OS in the long-term period showed the superiority of Atezolizumab and P/E combination again. In one study, patients who survived over 18 months were 34% in the combination group versus 20% in the P/E alone group.[12] In another study, from 202 patients in the P/E alone arm, none survived more than 34 months, but from 201 patients with Atezolizumab + P/E induction dose continued with Atezolizumab maintenance (every 3 weeks), at least 12 patients survived more than 59 months.[13]

Camrelizumab

Camrelizumab is a PD-1-blocking monoclonal antibody that prevents the binding of PD-1 on immune cells to PD-L1 expressed on tumor cells. Camrelizumab was developed by Jiangsu Hengrui Medicine Co. Ltd. It has been approved in China for several cancer types, including relapsed/refractory classical Hodgkin lymphoma, hepatocellular carcinoma, and others. However, it has only received Orphan Drug Designation (not full approval) from the U.S. FDA for advanced hepatocellular carcinoma.[14]

Unfortunately, there is no RCT with placebo control evaluating the efficacy and safety of Camrelizumab. However, some non-randomized or single-arm clinical trials have administered Camrelizumab in combination with other common treatments, and the results are promising. Camrelizumab with common chemotherapy for induction, followed by maintenance Camrelizumab plus Apatinib in patients with extensive-stage SCLC, increased median OS up to 15.38 months.[15] In another single-arm study with the same treatments, median OS was 17.3 months.[16]

Durvalumab

Durvalumab, developed by MedImmune/AstraZeneca company is another monoclonal antibody that blocks the interaction between PD-L1 and T cells, enhancing T-cell responses against cancer. This immune checkpoint inhibitor has been approved for many cancers, including NSCLC, biliary tract cancer, hepatocellular carcinoma, and from December 2024 for SCLC.[17]

In phase 3 clinical trial (CASPIAN), the addition of durvalumab to P/E standard chemotherapy significantly increased OS in patients with extensive-stage SCLC compared with placebo plus P/E, from 10.5

to 12.9 months. ORR also increased from 58% to 68%.[18] Promising results were also reported in limited-stage SCLC: the addition of Durvalumab to P/E and maintenance therapy improved OS up to 55.9 months versus 33.4 months in the chemotherapy-alone group.[19,20]

Nivolumab

Nivolumab is another PD-1-blocking monoclonal antibody developed and manufactured by Bristol Myers Squibb. It has FDA approval for many cancers such as NSCLC and others as listed in Table 1. [21]

There are few RCTs evaluating Nivolumab efficacy and safety in SCLC patients. Most studies are single-arm or combined with other drugs and cannot demonstrate the exact effect of Nivolumab. One RCT of Nivolumab in relapsed SCLC compared with common chemotherapy showed no significant OS difference. The most common adverse effects of Nivolumab reported were asthenia, fatigue, and decreased appetite, although these were more prevalent in the chemotherapy group.[22] In phase II clinical trial (ECOG-ACRIN), evaluating Nivolumab in combination with P/E and Nivolumab maintenance versus P/E and observation in 144 patients with extensive-stage SCLC, OS was 11.2 months in the Nivolumab group versus 8.1 months in the observation group. However, ORR was 77% for the Nivolumab group versus 80% for the observation group.[23]

Pembrolizumab

Pembrolizumab is another anti-PD-1 monoclonal antibody developed by Merck & Co incorporated. Pembrolizumab has been approved by the U.S. FDA for various indications as listed in Table 1. Because of its strong efficacy across a wide range of malignancies, researchers have been eager to evaluate Pembrolizumab in SCLC.[24]

A combination of Pembrolizumab plus P/E compared with P/E alone in extensive-stage SCLC showed modest but significant OS improvement, from 9.7 to 10.8 months. ORR was 70.6% in the Pembrolizumab plus P/E group and 61.8% in the placebo plus P/E group.[25] Studies of Pembrolizumab in limited-stage and relapsed SCLC are few and mostly uncontrolled. Some useful single-arm studies reported that adding Pembrolizumab to paclitaxel in relapsed SCLC resulted in 9.1 months OS, [26] while adding Pembrolizumab to chemoradiotherapy in limited-stage SCLC yielded OS of 39.5 months.[27] The most common adverse effects were asthenia and fatigue.[28]

Serplulimab

Serplulimab, developed by Henlius, is a recombinant humanized anti-PD-1 antibody. It works by binding to PD-1 on T cells, blocking interaction with PD-1/PD-L1. As mentioned in Table 2 Serplulimab was approved by the Medicines and Healthcare products Regulatory Agency (MHRA) in the United Kingdom in June 2025 and the European Commission (EC) in February 2025 for extensive-stage of SCLC. By preventing immunosuppression mediated by the PD-1 pathway, it allows the immune system to better destroy cancer cells.[29]

In phase 3 clinical trial (ASTRUM-005), Serplulimab combined with P/E for first-line treatment of extensive-stage SCLC resulted in 15.8 months OS versus 11.1 months in the P/E alone group. ORR was 80.2% in the Serplulimab group compared with 70.4% in the P/E group.[30] Although ASTRUM-005 was a standard RCT, there are no other independent studies to confirm these results, and reliable data remain limited.

Tislelizumab

Tislelizumab, developed by BeiGene, is another monoclonal antibody that specifically targets PD-1 on T cells. Its unique feature is minimized binding to FcγR receptors on macrophages, which may help prevent antibody-dependent phagocytosis and improve efficacy. Tislelizumab has been approved by the U.S. FDA for esophageal

squamous cell carcinoma (ESCC) and gastroesophageal adenocarcinoma, and by the EC for SCLC since May 2025.[31]

In Phase 3 Clinical Trial (RATIONALE-312), 457 Patients with extensive-stage SCLC randomly assigned. Patients who treated with Tislelizumab plus P/E had 15.5 months OS versus 13.5 months in the P/E alone group. Confirmed ORR was 68% in the Tislelizumab group versus 62% in the P/E alone group.[32]

Toripalimab

Toripalimab, developed by Junshi Biosciences, is another PD-1 inhibitor. The U.S. FDA approved Toripalimab for nasopharyngeal carcinoma in combination with chemotherapy as a first-line treatment, and it is also approved in the EU for ESCC.[33]

In phase 2 clinical trial, patients with limited-stage SCLC receiving Toripalimab plus P/E plus radiotherapy versus P/E plus radiotherapy alone had 24-month OS of 82.7% versus 59.1%, and ORR of 78.0% versus 73.1%.[34] In phase 3 clinical trial (EXTENTORCH), patients with extensive-stage SCLC treated with Toripalimab plus P/E compared with P/E alone had 14.6 months OS versus 13.3 months in the P/E group ($P = 0.03$).[35]

Target Agents for CTLA-4

CTLA-4 is known as an "immune checkpoint," preventing T-cells from becoming hyperactive and attacking other cells. As demonstrated in Figure 1, this mechanism is facilitated by the attachment of the CD80/86 surface antigen to the antigen-presenting cell. Agents blocking CTLA-4 allow T-cells to recognize and attack cancer cells more effectively. Targeting CTLA-4, a protein found on the surface of T-cells, is a cancer immunotherapy strategy that aims to boost the body's immune response against cancer.[36]

Ipilimumab

Ipilimumab, developed by Bristol-Myers Squibb, is a CTLA-4 blocker and as listed in Table 1 approved by the FDA for the treatment of several cancers.[37]

Two RCTs evaluating Ipilimumab in extensive-stage SCLC in combination with chemotherapy versus chemotherapy alone.

In phase 2 clinical trial, median OS was 9.1 versus 9.9 months and ORR was 33% versus 49% respectively.[38] Despite negative results, phase 3 trial was conducted. It also failed to demonstrate a statistically significant improvement.[39]

Tremelimumab

Tremelimumab is another CTLA-4-blocking monoclonal antibody developed by AstraZeneca and licensed from Pfizer. It was approved by the U.S. FDA for unresectable hepatocellular carcinoma and also in combination with durvalumab for NSCLC.[40]

Unfortunately, no RCTs have revealed individual results for Tremelimumab in SCLC. However, its combination with durvalumab has shown promising results for relapsed SCLC, a severe and poor-prognosis stage, which will be discussed in the combination therapy section.

Also, treatment with durvalumab for relapsed SCLC, has been studied in combination with Tremelimumab, with or without radiotherapy. OS was 5.7 months and 2.8 months, respectively, but the difference was not significant ($P = 0.3$).[41]

Target Agents for DLL3

DLL3 is a protein highly expressed on the surface of many tumor cells but less so in normal tissues. MABs targeting DLL3 are a promising area of cancer therapy research, particularly for SCLC and other neuroendocrine tumors. Some treatment strategies using DLL3 targeting are based on antibody-drug conjugates (ADCs), where the antibody serves as a carrier to deliver toxin (drug) to tumor cells.[42] Most DLL3-targeted agents are new and not yet approved, but the recent approval of Tarlatamab in SCLC has raised hopes for a treatment revolution.

Rovalpituzumab Tesirine

Rovalpituzumab tesirine (Rova-T) was originally developed by Stemcentrx and later acquired by AbbVie. Rova-T is a DLL3-targeted ADC consisting of a humanized DLL3-specific monoclonal antibody that conjugate to Tesirine, a toxic DNA crosslinking agent of pyrrolobenzodiazepine class. ADC is internalized, releasing a cytotoxic pyrrolobenzodiazepine dimer, leading to DNA damage and cell death. Although Rova-T has undergone several clinical trials in various cancers, it has not received approval to date.[43]

In Phase 3 clinical trial (MERU), 748 patients with extensive-stage SCLC previously treated with P/E chemotherapy, randomized in a 1:1 ratio received Rova-T as maintenance therapy or placebo. OS in the Rova-T group was 8.5 months versus 9.8 months in the placebo group. Pleural effusion, decreased appetite, peripheral edema, photosensitivity reaction, fatigue, nausea, and dyspnoea were more frequently observed in the Rova-T group.[43]

Tarlatamab

Tarlatamab is a bispecific T-cell engager therapy developed by Amgen company is the newest immunotherapy approved by the U.S. FDA in May 2024 for extensive-stage SCLC after platinum-based chemotherapy. Tarlatamab selectively attaches to DLL3 on tumor cells and CD3 on T cells, inducing apoptosis of tumor cells.[44]

Several single-arm clinical trials in relapsed SCLC have shown surprisingly improved OS. One study reported a median OS of 13.2 months,[45] while another reported 17.5 months .[46] These results have encouraged researchers to explore this therapy further in both extensive- and limited-stage patients. After promising results in phase 1 and 2, open-label phase 3 RCT comparing Tarlatamab versus common chemotherapy (topotecan, amrubicin, etc.) in extensive-stage SCLC reported median OS of 13.6 months versus 8.3 months, respectively ($P <$ 0.001). Most adverse effects reported by Tarlatamab group that were uncommon in chemotherapy alone group were Cytokine release syndrome, Dysgeusia, Pyrexia, Decreased appetite, Hyponatremia and Headache.[47]

Target agents for Vascular Endothelial Growth Factor A (VEGF-A)

VEGF-A is a key factor in angiogenesis, essential for the development of new blood vessels. Target agents for VEGF-A directly inhibit or modulate VEGF-A activity, thereby interfering with angiogenesis, which is crucial for tumor growth and metastasis.[48]

Bevacizumab

Bevacizumab, one of the VEGF-A inhibitors, was developed by Genentech and has U.S. FDA approval for a wide range of cancers as listed in Table 1.[49]

Among studies of bevacizumab in SCLC, only a few RCTs with placebo controls exist. In one RCT, addition of bevacizumab to P/E treatment showed no OS improvement in extensive-stage SCLC compared with P/E alone. OS was 9.4 months in the bevacizumab group versus 10.8 months in the P/E group, with ORR of 58% and 48%, respectively.[50] In phase II–III clinical trial (IFCT-0802), bevacizumab combined with chemotherapy showed 11.1 months OS versus 13.3 months in the chemotherapy-alone group.[51]

Sacituzumab Govitecan

Sacituzumab Govitecan is an ADC developed by Immunomedics and approved by the U.S. FDA for metastatic triple-negative breast cancer and urothelial cancer. Sacituzumab targets Trop-2, a protein overexpressed in many cancers. Upon binding, the ADC is internalized, and the conjugated payload, Govitecan (a topoisomerase inhibitor), induces DNA damage and cell death.[52]

There are no standard RCTs for Sacituzumab Govitecan in SCLC patients, but some single-arm studies show promising results. Patients

with relapsed SCLC and extensive-stage SCLC treated with Sacituzumab Govitecan monotherapy had OS of 7.5 months and 13.6 months, respectively.[53,54]

CTLA-4 and PD-1 Blocking Combination

Some studies have combined agents targeting two independent T-cell inactivation pathways. Nivolumab (PD-1 blocker) plus ipilimumab (CTLA-4 blocker) in relapsed SCLC compared with nivolumab alone showed OS of 4.7 months and ORR of 21.9% in the combination group versus 5.7 months OS and 11.6% ORR in the nivolumab-only group.[55] In another study, nivolumab plus ipilimumab versus placebo in extensive-stage SCLC resulted in OS of 9.2 and 9.6 months, respectively.[56] Even in limited-stage SCLC, nivolumab plus ipilimumab with continued nivolumab maintenance versus chemotherapy and observation (no maintenance) showed no significant OS difference.[57]

CTLA-4 and PD-1 Blocking Plus DLL3-Targeted Antibody Drug Conjugate Combination

In another study, extensive-stage SCLC patients received Rova-T plus nivolumab (Group 1) or Rova-T plus nivolumab plus ipilimumab (Group 2). OS was 7.4 months versus 11 months, and ORR was 27.6% versus 36.4% in Group 1 and Group 2, respectively.[58]

Agents Rely on Biomarkers

Numerous studies have been conducted to evaluate the efficacy of MABs depending on the level of expression of specific biomarkers in patients. All remarkable data are shown in Table 3. In the CASPIAN phase 3 trial, patients with extensive-stage SCLC with high levels of T cells who received durvalumab plus Tremelimumab plus P/E had an OS of 30.8 months, compared with 10 months in patients with low levels of T cells. In the durvalumab plus P/E group, patients with high levels of T cells had an OS of 15.8 months versus 11.5 months in low-level T cell patients. Similar results were observed for patients with high CD8A expression/CD8 cell compared with those with low expression.[59]

Also, patients with high levels of major histocompatibility complex (MHC) who received durvalumab plus Tremelimumab and P/E had 23.5 months OS versus 10.4 months in low-level MHC patients. In the durvalumab plus P/E group, patients with high levels of MHC had 17.3 months OS versus 11.3 months in low-level MHC patients. Patients with high levels of antigen processing and presentation machinery (APM) in the durvalumab plus Tremelimumab and P/E group had 25.9 months OS versus 10 months in low-level APM patients. In the Durvalumab plus P/E group, patients with high levels of APM had 14.6 months OS versus 11.5 months in low-level APM patients.[59]

In the durvalumab plus Tremelimumab and P/E group, median OS was 22.8 versus 10.4 months in patients with high versus low expression of CTLA-4. Also, OS was 28.4 versus 10.4 months in patients with high versus low expression of FOXP3 (forkhead box P3). In contrast, expression of these genes did not impact OS in the Durvalumab plus P/E group.[59]

In the TRINITY study, 339 patients with relapsed SCLC were divided into DLL3-positive and DLL3-high groups according to immunohistochemistry assay for Rova-T monotherapy. OS for all, positive, and high patients was 5.6, 5.8, and 5.7 months, and ORR was 12.4%, 13.2%, and 14.3%, respectively ($P > 0.05$).[60] In another smaller-scale study, 29 Japanese patients with relapsed SCLC were divided into DLL3-high and non-high groups for Rova-T monotherapy. Median OS in DLL3-high, non-high, and all patients was 7.4, 5.1, and 5.8 months, respectively.[61]

In the CheckMate 451 study, patients with extensive-stage SCLC with no progression

after at least four cycles of first-line chemotherapy received maintenance therapy. Patients with high levels of tumor mutational burden (TMB) in the nivolumab plus ipilimumab group had 13.5 months OS versus 13.2 months in the nivolumab-only group and 9.5 months in the placebo group. Patients with low-level TMB in the nivolumab plus ipilimumab group had 7.8 months OS versus 10.1 months in the nivolumab-only group and 10 months in the placebo group.[56]

Also, patients with a PD-L1 combined positive score (CPS) > 1% in the Nivolumab plus Ipilimumab group had 11.9 months OS versus 14.1 months in the Nivolumab group and 13.9 months in the placebo group. Patients with low CPS < 1% in the Nivolumab plus Ipilimumab group had 8.6 months OS versus 9.4 months in the Nivolumab group and 6.1 months in the placebo group.[56]

In the IMpower133 study, patients with extensive-stage SCLC received Atezolizumab plus P/E in comparison with placebo. They were evaluated for the role of TMB and neutrophil-to-lymphocyte ratio (NLR) in response. Patients in the Atezolizumab plus P/E group with TMB ≥ 10 and NLR < median had 18.33 months OS versus 12.53 months (P = 0.001) in the placebo group. Also, patients in the Atezolizumab plus P/E group with TMB < 10 and NLR ≥ median had 7.67 months OS versus 7.3 months in the placebo group.[62]

Conclusion

The use of MABs as add-on therapy in the treatment of SCLC has marked a significant shift in the therapeutic landscape, particularly for extensive-stage disease. The integration of anti-PD-1/PD-L1 therapies, such as Atezolizumab, Durvalumab, and Serplulimab, into standard platinum-etoposide regimens has demonstrated significant but modest improvements in OS, with studies reporting increases of about two months in comparison with common chemotherapy regimens in various randomized clinical trials. It seems that the PD-1/PD-L1 checkpoint has a significant but not a key role in SCLC pathology.

Similarly, the emergence of DLL3-targeted therapies, notably Tarlatamab, has shown remarkable promise, particularly in relapsed SCLC, with median OS increasing by more than five months in comparison with standard chemotherapy. There is a necessity for future studies to confirm the superiority of DLL3 inhibitors over other antibody pathways such as PD-1/PD-L1, and also combination therapy to ensure we use the maximum capacity of these pathways.

However, the variable efficacy of other agents, such as Ipilimumab and Bevacizumab, underscores the complexity of SCLC's biology, where not all MABs yield consistent survival benefits. These findings highlight the critical role of immune checkpoint inhibitors and targeted therapies in reshaping SCLC management, offering new hope for a disease historically plagued by poor prognosis.

Despite these advancements, challenges persist in optimizing monoclonal antibody therapies for SCLC. The limited efficacy of CTLA-4 inhibitors, like Ipilimumab and Tremelimumab, either alone or in combination, suggests that not all immune checkpoint pathways are equally effective in SCLC's immunosuppressive tumor microenvironment. Furthermore, the lack of robust RCTs for some agents, such as Camrelizumab and Sacituzumab Govitecan, limits definitive conclusions about their efficacy.

Biomarker-driven approaches show that high levels of T cells, CD8A, MHC, APM, CTLA4, and FoxP3 in patients result in greater efficacy of Durvalumab and Tremelimumab, alone and in combination. According to the mechanism of action of

Tremelimumab, a high level of CTLA4 is a logical predictor of greater efficacy due to CTLA4 blockade by Tremelimumab. However, other biomarkers have no direct connection with the known mechanisms of these drugs. There is a necessity for further investigation to find true connections between medications and biomarkers, and to avoid imposing unnecessary cost and time on patients who show no efficacy to these treatments.

While the therapeutic targeting of DLL3 has proven clinically viable, it is crucial to distinguish its established role as a lineage marker from its unresolved role as a predictive biomarker of response. DLL3 is a robust lineage marker for tumors of neuroendocrine origin, including SCLC, owing to its high and specific expression on the cell surface of these malignancies and its near absence in most normal adult tissues. This oncofetal pattern makes it an ideal target for directed therapies, like Tarlatamab. However, as our data and prior trials with Rova-T demonstrate, high DLL3 expression alone is an insufficient predictor of which patients will derive significant benefit. This suggests that therapeutic efficacy is governed by additional factors beyond target presence, such as tumor microenvironment interactions, drug payload mechanisms, and intrinsic tumor resistance pathways. Consequently, future trial designs must move beyond the binary assessment of a lineage marker and integrate multimodal biomarker strategies. These should aim to elucidate the complex mechanisms of action and resistance, potentially combining DLL3 quantification with assessments of immune contexture, target density, and downstream signaling pathways to identify the patients most likely to respond to DLL3-directed therapies.

Also, high levels of TMB and low levels of NLR show greater efficacy in patients treated with Atezolizumab. This can guide us in setting biomarker conditions for patients who can significantly increase their survival with this drug.

Looking forward, the future of monoclonal antibody therapies in SCLC lies in leveraging biomarker-driven precision medicine and innovative combination strategies. The success of Tarlatamab as a bispecific T-cell engager highlights the potential of novel mechanisms, such as DLL3-targeted therapies, to address relapsed and refractory cases. Ongoing research should prioritize large-scale, randomized trials to validate the efficacy of promising agents like Camrelizumab and Sacituzumab-Govitecan, while exploring combinations of PD-1/PD-L1 inhibitors with DLL3- or VEGF-A-targeted therapies to overcome resistance mechanisms. Additionally, integrating advanced genomic and proteomic profiling could enhance the identification of patients most likely to benefit from specific therapies, moving SCLC treatment toward a more personalized paradigm. Collaborative efforts between researchers, clinicians, and pharmaceutical companies will be essential to address current gaps, such as the limited data on long-term outcomes and optimal maintenance strategies.

In conclusion, MABs have ushered in a new era of hope for SCLC patients. While agents such as Atezolizumab, Durvalumab, and Tarlatamab show clear survival benefits, the variability in other therapies and challenges in biomarker reliability highlight the need for continued innovation. By embracing precision medicine, novel therapeutic combinations, and rigorous clinical trial designs, the oncology community can further unlock the potential of MABs to transform SCLC from a historically intractable disease into a more manageable disease, ultimately improving survival and quality of life for patients worldwide.

Funding

Not applicable.

Acknowledgements
Not applicable.

Authors' Contributions
A.A.H: Reviewing the manuscript, research guide, drafting and writing a part of the article; S.A: Study design, data gathering, writing the original draft, diagrams and figures preparation. All authors read and approved the final manuscript version and agreed with all parts of the work in ensuring that any queries about the accuracy or integrity of any component of the work are appropriately investigated and handled.

Conflict of Interest
None declared.

References

1. Puri S, Kaur G, Piplani H, Sanyal SN, Vaish V. Imatinib modulates pro-inflammatory microenvironment with angiostatic effects in experimental lung carcinogenesis. *Inflammopharmacology.* 2020;28(1):231-52. doi: 10.1007/s10787-019-00656-8. PMID: 31676982.
2. Rudin CM, Brambilla E, Faivre-Finn C, Sage J. Small-cell lung cancer. *Nat Rev Dis Primers.* 2021;7(1):3. doi: 10.1038/s41572-020-00235-0. PMID: 33446664; PMCID: PMC8177722.
3. Soliman M. PET/CT as a prognostic factor for small cell lung cancer. *Middle East J Cancer.* 2023;14(3):436-42. doi:10.30476/mejc.2022.94538.1729.
4. Megyesfalvi Z, Gay CM, Popper H, Pirker R, Ostoros G, Heeke S, et al. Clinical insights into small cell lung cancer: Tumor heterogeneity, diagnosis, therapy, and future directions. *CA Cancer J Clin.* 2023;73(6):620-52. doi: 10.3322/caac.21785. PMID: 37329269.
5. Makuku R, Khalili N, Razi S, Keshavarz-Fathi M, Rezaei N. Current and future perspectives of PD-1/PDL-1 blockade in cancer immunotherapy. *J Immunol Res.* 2021;2021:6661406. doi: 10.1155/2021/6661406. PMID: 33681388; PMCID: PMC7925068.
6. Yang H, Yang L, Liu Y, Wang L. Adebrelimab in small cell lung cancer: From current advances to emerging combination strategy and challenge. *Biologics.* 2025;19:365-77. doi: 10.2147/BTT.S500470. PMID: 40475251; PMCID: PMC12138384.
7. Wang J, Zhou C, Yao W, Wang Q, Min X, Chen G, et al. Adebrelimab or placebo plus carboplatin and etoposide as first-line treatment for extensive-stage small-cell lung cancer (CAPSTONE-1): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol.* 2022;23(6):739-47. doi: 10.1016/S1470-2045(22)00224-8. PMID: 35576956.
8. Zhang F, Qi X, Wang X, Wei D, Wu J, Feng L, et al. Structural basis of the therapeutic anti-PD-L1 antibody atezolizumab. *Oncotarget.* 2017;8(52):90215-24. doi: 10.18632/oncotarget.21652. PMID: 29163822; PMCID: PMC5685743.
9. Pujol JL, Greillier L, Audigier-Valette C, Moro-Sibilot D, Uwer L, Hureaux J, et al. A randomized non-comparative phase II study of anti-programmed cell death-ligand 1 atezolizumab or chemotherapy as second-line therapy in patients with small cell lung cancer: Results from the IFCT-1603 trial. *J Thorac Oncol.* 2019;14(5):903-13. doi: 10.1016/j.jtho.2019.01.008. PMID: 30664989.
10. Horn L, Mansfield AS, Szczęsna A, Havel L, Krzakowski M, Hochmair MJ, et al. First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. *N Engl J Med.* 2018;379(23):2220-9. doi: 10.1056/NEJMoa1809064. PMID: 30280641.

11. Nishio M, Sugawara S, Atagi S, Akamatsu H, Sakai H, Okamoto I, et al. Subgroup analysis of Japanese patients in a phase III study of atezolizumab in extensive-stage small-cell lung cancer (IMpower133). *Clin Lung Cancer.* 2019;20(6):469-76.e1. doi: 10.1016/j.cllc.2019.07.005. PMID: 31466854.
12. Liu SV, Mok TS, Nabet BY, Mansfield AS, De Boer R, Losonczy G, et al. Clinical and molecular characterization of long-term survivors with extensive-stage small cell lung cancer treated with first-line atezolizumab plus carboplatin and etoposide. *Lung Cancer.* 2023;186:107418. doi: 10.1016/j.lungcan.2023.107418. PMID: 37931445.
13. Reck M, Dziadziuszko R, Sugawara S, Kao S, Hochmair M, Huemer F, et al. Five-year survival in patients with extensive-stage small cell lung cancer treated with atezolizumab in the Phase III IMpower133 study and the Phase III IMbrella A extension study. *Lung Cancer.* 2024;196:107924. doi: 10.1016/j.lungcan.2024.107924. PMID: 39306923.
14. Chen Z, Lu X, Koral K. The clinical application of camrelizumab on advanced hepatocellular carcinoma. *Expert Rev Gastroenterol Hepatol.* 2020;14(11):1017-24. doi: 10.1080/17474124.2020.1807939. PMID: 32762583.
15. Zhao Y, Zhang M, Liu J, Pu H, Li Y, Li X, et al. Camrelizumab combined with chemotherapy followed by maintenance camrelizumab and apatinib as first-line therapy for extensive-stage small cell lung cancer: A phase II, single-arm, exploratory study [abstract]. *J Clin Oncol.* 2024;42(16_suppl): e20107. doi: 10.1200/JCO.2024.42.16_suppl.e20107
16. Liu M, Qiu G, Guan W, Xie X, Lin X, Xie Z, et al. Induction chemotherapy followed by camrelizumab plus apatinib and chemotherapy as first-line treatment for extensive-stage small-cell lung cancer: a multicenter, single-arm trial. *Signal Transduct Target Ther.* 2025;10(1):65. doi: 10.1038/s41392-025-02153-7. PMID: 39962074; PMCID: PMC11833049.
17. Carter PJ, Lazar GA. Next generation antibody drugs: pursuit of the 'high-hanging fruit'. *Nat Rev Drug Discov.* 2018;17(3):197-223. doi: 10.1038/nrd.2017.227. PMID: 29192287.
18. Goldman JW, Dvorkin M, Chen Y, Reinmuth N, Hotta K, Trukhin D, et al. Durvalumab, with or without tremelimumab, plus platinum–etoposide versus platinum–etoposide alone in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): updated results from a randomised, controlled, open-label, phase 3 trial. *Lancet Oncol.* 2021;22(1):51-65. doi: 10.1016/S1470-2045(20)30539-8. PMID: 33285097.
19. Park S, Noh JM, Choi Y-L, Chi SA, Kim K, Jung HA, et al. Durvalumab with chemoradiotherapy for limited-stage small-cell lung cancer. *Eur J Cancer.* 2022;169:42-53. doi: 10.1016/j.ejca.2022.03.034. PMID: 35500460.
20. Cheng Y, Spigel DR, Cho BC, Laktionov KK, Fang J, Chen Y, et al. Durvalumab after chemoradiotherapy in limited-stage small-cell lung cancer. *N Engl J Med.* 2024;391(14):1313-27. doi: 10.1056/NEJMoa2404873. PMID: 39268857.
21. Xu JX, Maher VE, Zhang L, Tang S, Sridhara R, Ibrahim A, et al. FDA approval summary: Nivolumab in advanced renal cell carcinoma after anti-angiogenic therapy and exploratory

predictive biomarker analysis. *Oncologist.* 2017;22(3):311-7. doi: 10.1634/theoncologist.2016-0476. PMID: 28232599; PMCID: PMC5344649.

22. Spigel DR, Vicente D, Ciuleanu TE, Gettinger S, Peters S, Horn L, et al. Second-line nivolumab in relapsed small-cell lung cancer: CheckMate 331☆. *Ann Oncol.* 2021;32(5):631-41. doi: 10.1016/j.annonc.2021.01.071. PMID: 33539946.
23. Leal TA, Wang Y, Dowlati A, Chay CH, Chen Y, Mohindra AR, et al. Randomized phase II clinical trial of cisplatin/carboplatin and etoposide (PE) alone or in combination with nivolumab as frontline therapy for extensive-stage small cell lung cancer (ES-SCLC): ECOG-ACRIN EA5161. *Cancer.* 2025;131(12):e35938. doi: 10.1002/cncr.35938. PMID: 40526078; PMCID: PMC12276847.
24. Poole RM. Pembrolizumab: first global approval. *Drugs.* 2014;74(16):1973-81. doi: 10.1007/s40265-014-0314-5. PMID: 25331768.
25. Rudin CM, Awad MM, Navarro A, Gottfried M, Peters S, Csőszi T, et al. Pembrolizumab or placebo plus etoposide and platinum as first-line therapy for extensive-stage small-cell lung cancer: Randomized, double-blind, phase III KEYNOTE-604 study. *J Clin Oncol.* 2020;38(21):2369-79. doi: 10.1200/JCO.20.00793. PMID: 32468956; PMCID: PMC7474472.
26. Kim YJ, Keam B, Ock CY, Song S, Kim M, Kim SH, et al. A phase II study of pembrolizumab and paclitaxel in patients with relapsed or refractory small-cell lung cancer. *Lung Cancer.* 2019;136:122-8. doi: 10.1016/j.lungcan.2019.08.031. PMID: 31494530.
27. Welsh JW, Heymach JV, Chen D, Verma V, Cushman TR, Hess KR, et al. Phase I trial of pembrolizumab and radiation therapy after induction chemotherapy for extensive-stage small cell lung cancer. *J Thorac Oncol.* 2020;15(2):266-73. doi: 10.1016/j.jtho.2019.10.001. PMID: 31605794.
28. Ott PA, Elez E, Hiret S, Kim D-W, Morosky A, Saraf S, et al. Pembrolizumab in patients with extensive-stage small-cell lung cancer: results from the phase Ib KEYNOTE-028 study. *J Clin Oncol.* 2017;35(34):3823-9. doi: 10.1200/JCO.2017.72.5069. PMID: 28813164.
29. Zhang Y, Wei R, Song G, Yang X, Zhang M, Liu W, et al. Insights into the mechanisms of serplulimab: a distinctive anti-PD-1 monoclonal antibody, in combination with a TIGIT or LAG3 inhibitor in preclinical tumor immunotherapy studies. *MAbs.* 2024;16(1):2419838. doi: 10.1080/19420862.2024.2419838. PMID: 39497266; PMCID: PMC11540081.
30. Cheng Y, Han L, Wu L, Chen J, Sun H, Wen G, et al. Effect of first-line serplulimab vs placebo added to chemotherapy on survival in patients with extensive-stage small cell lung cancer: The ASTRUM-005 randomized clinical trial. *JAMA.* 2022;328(12):1223-32. doi: 10.1001/jama.2022.16464. PMID: 36166026; PMCID: PMC9516323.
31. Lee A, Keam SJ. Tislelizumab: First approval. *Drugs.* 2020;80(6):617-24. doi: 10.1007/s40265-020-01286-z. PMID: 32185681.
32. Cheng Y, Fan Y, Zhao Y, Huang D, Li X, Zhang P, et al. Tislelizumab plus platinum and etoposide versus placebo plus platinum and etoposide as first-line treatment for extensive-stage SCLC (RATIONALE-312): A Multicenter,

double-blind, placebo-controlled, randomized, phase 3 clinical trial. *J Thorac Oncol.* 2024;19(7):1073-85. doi: 10.1016/j.jtho.2024.03.008. PMID: 38460751.
33. Keam SJ. Toripalimab: First global approval. *Drugs.* 2019;79(5):573-8. doi: 10.1007/s40265-019-01076-2. PMID: 30805896.
34. Zhang P, Liu F, Wang D, Zheng S, Guo J, Zou Y, et al. A randomized phase II study of toripalimab consolidation or observation after concurrent chemoradiotherapy in limited-stage small cell lung cancer [abstract]. *J Clin Oncol.* 2024;42(16_suppl):8098. doi: 10.1200/JCO.2024.42.16_suppl.8098.
35. Cheng Y, Zhang W, Wu L, Zhou C, Wang D, Xia B, et al. Toripalimab plus chemotherapy as a first-line therapy for extensive-stage small cell lung cancer: The phase 3 EXTENTORCH randomized clinical trial. *JAMA Oncol.* 2025;11(1):16-25. doi: 10.1001/jamaoncol.2024.5019. PMID: 39541202; PMCID: PMC11565370.
36. Wang SD, Li HY, Li BH, Xie T, Zhu T, Sun LL, et al. The role of CTLA-4 and PD-1 in anti-tumor immune response and their potential efficacy against osteosarcoma. *Int Immunopharmacol.* 2016;38:81-9. doi: 10.1016/j.intimp.2016.05.016. PMID: 27258185.
37. Wang J, Yuan R, Song W, Sun J, Liu D, Li Z. PD-1, PD-L1 (B7-H1) and tumor-site immune modulation therapy: The historical perspective. *J Hematol Oncol.* 2017;10(1):34. doi: 10.1186/s13045-017-0403-5. PMID: 28122590; PMCID: PMC5267378.
38. Reck M, Bondarenko I, Luft A, Serwatowski P, Barlesi F, Chacko R, et al. Ipilimumab in combination with paclitaxel and carboplatin as first-line therapy in extensive-disease-small-cell lung cancer: results from a randomized, double-blind, multicenter phase 2 trial. *Ann Oncol.* 2013;24(1):75-83. doi: 10.1093/annonc/mds213. PMID: 22858559.
39. Reck M, Luft A, Szczesna A, Havel L, Kim SW, Akerley W, et al. Phase III randomized trial of Ipilimumab plus etoposide and platinum versus placebo plus etoposide and platinum in extensive-stage small-cell lung cancer. *J Clin Oncol.* 2016;34(31):3740-8. doi: 10.1200/JCO.2016.67.6601. Erratum in: *J Clin Oncol.* 2019;37(34):3327. doi: 10.1200/JCO.19.02803. PMID: 27458307.
40. Keam SJ. Tremelimumab: First approval. *Drugs.* 2023;83(1):93-102. doi: 10.1007/s40265-022-01827-8. PMID: 36571670.
41. Pakkala S, Higgins K, Chen Z, Sica G, Steuer C, Zhang C, et al. Durvalumab and tremelimumab with or without stereotactic body radiation therapy in relapsed small cell lung cancer: a randomized phase II study. *J Immunother Cancer.* 2020;8(2):e001302. doi: 10.1136/jitc-2020-001302. PMID: 33428583; PMCID: PMC7754662.
42. Wang H, Zheng T, Xu D, Sun C, Huang D, Liu X. Targeting DLL3: Innovative strategies for tumor treatment. *Pharmaceutics.* 2025;17(4):520. doi: 10.3390/pharmaceutics17040520. PMID: 40284515; PMCID: PMC12030079.
43. Johnson ML, Zvirbule Z, Laktionov K, Helland A, Cho BC, Gutierrez V, et al. Rovalpituzumab tesirine as a maintenance therapy after first-line platinum-based chemotherapy in patients with extensive-stage-SCLC: Results from the phase 3 MERU study. *J Thorac Oncol.* 2021;16(9):1570-81. doi: 10.1016/j.jtho.2021.03.012. PMID: 33823285.

44. Dhillon S. Tarlatamab: First approval. *Drugs*. 2024;84(8):995-1003. doi: 10.1007/s40265-024-02070-z. PMID: 39023700.
45. Hummel HD, Champiat S, Olmedo Garcia ME, Boyer M, He K, Steeghs N, et al. Tarlatamab in previously treated small cell lung cancer (SCLC): DeLLphi-300 phase I study long-term outcomes and intracranial activity [abstract]. *ESMO Open*. 2024;9(S3). doi: 10.1016/j.esmoop.2024.102768.
46. Paz-Ares L, Champiat S, Lai WV, Izumi H, Govindan R, Boyer M, et al. Tarlatamab, a first-in-class DLL3-targeted bispecific T-cell engager, in recurrent small-cell lung cancer: An open-label, phase I study. *J Clin Oncol*. 2023;41(16):2893-903. doi: 10.1200/JCO.22.02823. PMID: 36689692; PMCID: PMC10414718.
47. Mountzios G, Sun L, Cho BC, Demirci U, Baka S, Gümüş M, et al. Tarlatamab in small-cell lung cancer after platinum-based chemotherapy. *N Engl J Med*. 2025;393(4):349-61. doi: 10.1056/NEJMoa2502099. PMID: 40454646.
48. Narayanan S, Srinivas S. Incorporating VEGF-targeted therapy in advanced urothelial cancer. *Ther Adv Med Oncol*. 2017;9(1):33-45. doi: 10.1177/1758834016667179. PMID: 28203296; PMCID: PMC5298449.
49. Gille H, Hülsmeyer M, Trentmann S, Matschiner G, Christian HJ, Meyer T, et al. Functional characterization of a VEGF-A-targeting Anticalin, prototype of a novel therapeutic human protein class. *Angiogenesis*. 2016;19(1):79-94. doi: 10.1007/s10456-015-9490-5. PMID: 26650228.
50. Spigel DR, Townley PM, Waterhouse DM, Fang L, Adiguzel I, Huang JE, et al. Randomized phase II study of bevacizumab in combination with chemotherapy in previously untreated extensive-stage small-cell lung cancer: results from the SALUTE trial. *J Clin Oncol*. 2011;29(16):2215-22. doi: 10.1200/JCO.2010.29.3423. PMID: 21502556.
51. Pujol JL, Lavole A, Quoix E, Molinier O, Souquet PJ, Barlesi F, et al. Randomized phase II-III study of bevacizumab in combination with chemotherapy in previously untreated extensive small-cell lung cancer: results from the IFCT-0802 trial†. *Ann Oncol*. 2015;26(5):908-14. doi: 10.1093/annonc/mdv065. PMID: 25688059.
52. Syed YY. Sacituzumab Govitecan: First approval. *Drugs*. 2020;80(10):1019-25. doi: 10.1007/s40265-020-01337-5. PMID: 32529410; PMCID: PMC7288263.
53. Gray JE, Heist RS, Starodub AN, Camidge DR, Kio EA, Masters GA, et al. Therapy of small cell lung cancer (SCLC) with a topoisomerase-I-inhibiting antibody-drug conjugate (ADC) targeting trop-2, sacituzumab govitecan. *Clin Cancer Res*. 2017;23(19):5711-9. doi: 10.1158/1078-0432.CCR-17-0933. PMID: 28679770.
54. Dowlati A, Chiang AC, Cervantes A, Babu S, Hamilton E, Wong SF, et al. Phase 2 open-label study of sacituzumab govitecan as second-line therapy in patients with extensive-stage SCLC: Results from TROPiCS-03. *J Thorac Oncol*. 2025;20(6):799-808. doi: 10.1016/j.jtho.2024.12.028. PMID: 39755168.
55. Ready NE, Ott PA, Hellmann MD, Zugazagoitia J, Hann CL, de Braud F, et al. Nivolumab monotherapy and nivolumab plus ipilimumab in recurrent small cell lung cancer: Results from the CheckMate 032 randomized cohort. *J Thorac Oncol*. 2020;15(3):426-35. doi:

10.1016/j.jtho.2019.10.004. PMID: 31629915.
56. Owonikoko TK, Park K, Govindan R, Ready N, Reck M, Peters S, et al. Nivolumab and ipilimumab as maintenance therapy in extensive-disease small-cell lung cancer: CheckMate 451. *J Clin Oncol.* 2021;39(12):1349-59. doi: 10.1200/JCO.20.02212. PMID: 33683919; PMCID: PMC8078251.
57. Peters S, Pujol JL, Dafni U, Dómine M, Popat S, Reck M, et al. Consolidation nivolumab and ipilimumab versus observation in limited-disease small-cell lung cancer after chemo-radiotherapy - results from the randomised phase II ETOP/IFCT 4-12 STIMULI trial. *Ann Oncol.* 2022;33(1):67-79. doi: 10.1016/j.annonc.2021.09.011. PMID: 34562610.
58. Malhotra J, Nikolinakos P, Leal T, Lehman J, Morgensztern D, Patel JD, et al. A phase 1-2 study of rovalpituzumab tesirine in combination with nivolumab plus or minus ipilimumab in patients with previously treated extensive-stage SCLC. *J Thorac Oncol.* 2021;16(9):1559-69. doi: 10.1016/j.jtho.2021.02.022. PMID: 33652156.
59. Xie M, Vuko M, Rodriguez-Canales J, Zimmermann J, Schick M, O'Brien C, et al. Molecular classification and biomarkers of outcome with immunotherapy in extensive-stage small-cell lung cancer: analyses of the CASPIAN phase 3 study. *Mol Cancer.* 2024;23(1):115. doi: 10.1186/s12943-024-02014-x. PMID: 38811992; PMCID: PMC11137956.
60. Morgensztern D, Besse B, Greillier L, Santana-Davila R, Ready N, Hann CL, et al. Efficacy and safety of rovalpituzumab tesirine in third-line and beyond patients with DLL3-expressing, relapsed/refractory small-cell lung cancer: Results from the phase II TRINITY study. *Clin Cancer Res.* 2019;25(23):6958-66. doi: 10.1158/1078-0432.CCR-19-1133. PMID: 31506387; PMCID: PMC7105795.
61. Udagawa H, Akamatsu H, Tanaka K, Takeda M, Kanda S, Kirita K, et al. Phase I safety and pharmacokinetics study of rovalpituzumab tesirine in Japanese patients with advanced, recurrent small cell lung cancer. *Lung Cancer.* 2019;135:145-50. doi: 10.1016/j.lungcan.2019.07.025. PMID: 31446987.
62. Zhang C, Huo Y, Shang X, Zhang T, Tang N, Wang H. Tumor mutational burden adjusted by neutrophil-to-lymphocyte ratio serves as a potential biomarker for atezolizumab-treated patients with extensive stage small cell lung cancer. *Respir Res.* 2024;25(1):253. doi: 10.1186/s12931-024-02885-0. PMID: 38902698; PMCID: PMC11191253.
63. The Medicines and Healthcare products Regulatory Agency (MHRA). Tarlatamab approved to treat adult patients with small cell lung cancer. London: GOV.UK; 2024 Dec 31 [cited 2026 Jun 9]. Available from: https://www.gov.uk/government/news/tarlatamab-approved-to-treat-adult-patients-with-small-cell-lung-cancer

Table 1. Monoclonal antibodies used for SCLC clinical trials and other FDA approvals

Name	U.S. FDA approval	RCT for SCLC	Mechanism
Adebrelimab	SCLC*	CAPSTONE-1 IFCT-1603	PD-L1 blocking
Atezolizumab	SCLC, NSCLC, Urothelial carcinoma	IMpower133 IMbrella	PD-L1 blocking
Bevacizumab	NSCLC, Cervical cancer, Ovarian cancer, Colorectal cancer, Glioblastoma, Hepatocellular carcinoma, Renal cell carcinoma	SALUTE IFCT-0802	VEGF-A blocking
Camrelizumab	-	PASSION	PD-1 blocking
Durvalumab	NSCLC, SCLC, MIBC, Biliary tract cancer, Hepatocellular carcinoma	CASPIAN	PD-L1 blocking
Ipilimumab	NSCLC, Melanoma, Esophageal cancer, Colorectal cancer, Hepatocellular carcinoma, Renal cell carcinoma, MPM	M. Reck et al. 2012 M. Reck et al. 2016	CTLA-4 blocking
Nivolumab	NSCLC, Colorectal cancer, Gastroesophageal cancer, Hepatocellular, carcinoma, Melanoma, Renal cell carcinoma, Urothelial carcinoma, Hodgkin lymphoma, Head and neck cancer	ECOG-ACRIN CheckMate 331	PD-1 blocking
Pembrolizumab	NSCLC, Cervical cancer, Gastroesophageal cancer, Head and neck cancer, Hepatocellular carcinoma, Melanoma, Renal cell carcinoma, Urothelial carcinoma, Breast cancer, Endometrial carcinoma, Hodgkin lymphoma, Merkel cell carcinoma, PMBCL, cSCC	KEYNOTE-604	PD-1 blocking
Rovalpituzumab-Tesirine	-	MERU	DLL3 blocking
Sacituzumab-govitecan	Breast cancer, Urothelial carcinoma	-	
Serplulimab	SCLC*	ASTRUM-005	PD-1 blocking
Tarlatamab	SCLC	DeLLphi-300 DeLLphi-306	DLL3 blocking

Tislelizumab	SCLC*, ESCC, Gastroesophageal-adenocarcinoma	RATIONALE-312	PD-1 blocking
Toripalimab	Nasopharyngeal carcinoma	EXTENTORCH	PD-1 blocking
Tremelimumab	NSCLC, Hepatocellular carcinoma	CASPIAN	CTLA-4 blocking

U.S. FDA: United States Food and Drug Administration; RCT: Randomized controlled trials; SCLC: Small-cell lung cancer; NSCLC: Non-small cell lung cancer; MIBC: Muscle invasive bladder cancer; MPM: Malignant pleural mesothelioma; PMBCL: Primary mediastinal B-cell lymphoma; cSCC: Cutaneous squamous cell carcinoma; ESCC: Esophageal squamous cell carcinoma; PD-L1: Programmed cell death ligand 1; VEGF-A: Vascular endothelial growth factor A; PD-1: Programmed cell death 1; CTLA-4: Cytotoxic T-lymphocyte-associated antigen 4; DLL3: Delta-like ligand 3; *Approved institutions other than US. FDA

Table 2. Monoclonal antibodies which approved for SCLC by an authorization medicine organization

Name	Approval for SCLC
Atezolizumab	❖ Approved by US. FDA in combination with carboplatin and etoposide, for the first-line treatment of adult patients with extensive-stage SCLC on March 2019. ❖ Approved by the EC for the initial treatment of extensive-stage SCLC on September 2019.
Adebrelimab	❖ Approved in combination with chemotherapy by the NMPA of China as the first-line treatment for extensive-stage SCLC on 2023.
Tarlatamab	❖ Approved by US. FDA for extensive-stage SCLC with disease progression on or after platinum-based chemotherapy on May 2024. ❖ Conditional approved by MHRA of UK for extensive-stage SCLC after progression on two or more therapies, including platinum-based chemotherapy on December 2024.[63]
Durvalumab	❖ Approved by US. FDA for adults with limited-stage SCLC whose disease has not progressed following P/E chemotherapy on December 2024. ❖ Approved by EC as monotherapy to treat adults with limited-stage SCLC on March 2025.
Tislelizumab	❖ Approved by EC in combination with etoposide and platinum chemotherapy, as a first-line treatment for adult patients with extensive-stage SCLC on May 2025.
Serplulimab	❖ Approved by MHRA for patients with extensive-stage SCLC on June 2025. ❖ Approved by EC in combination with chemotherapy for the frontline treatment of adult patients with extensive-stage SCLC on February 2025.

US. FDA: United States Food and Drug Administration; EC: European Commission; NMPA: National Medical Products Administration; MHRA: Medicines and Healthcare products Regulatory Agency; SCLC: Small-cell lung cancer

Table 3. Clinical outcomes of biomarker-based RCTs in SCLC

Study	Disease stage	Regimen	Biomarker	Median OS (months)
CASPIAN	Extensive-stage	Dur + Tre + P/E	High level T cell	30.8
			Low level T cell	10
CASPIAN	Extensive-stage	Dur + P/E	High level T cell	15.8
			Low level T cell	11.5
CASPIAN	Extensive-stage	Dur + Tre + P/E	High level MHC	23.5
			Low level MHC	10.4
CASPIAN	Extensive-stage	Dur + P/E	High level MHC	17.3
			Low level MHC	11.3
CASPIAN	Extensive-stage	Dur + Tre + P/E	High level APM	23.9
			Low level APM	10
CASPIAN	Extensive-stage	Dur + Tre + P/E	High level CTLA-4	22.8
			Low level CTLA-4	10.4
CASPIAN	Extensive-stage	Dur + Tre + P/E	High level FOXP3	28.4
			High level FOXP3	10.4
TRINITY	relapsed		All	5.6
		Rova-T	DLL3-positive	5.7
			DLL3-high	5.8
CheckMate 451	Extensive-stage	Nivo + Ipili	High level TMB	13.5
			Low level TMB	7.8
CheckMate 451	Extensive-stage	Nivo	High level TMB	13.2
			Low level TMB	10.1
CheckMate 451	Extensive-stage	Nivo + Ipili	PD-L1 (CPS) > 1%	11.9
			PD-L1 (CPS) < 1%	7.6
CheckMate 451	Extensive-stage	Nivo	PD-L1 (CPS) > 1%	14.1
			PD-L1 (CPS) < 1%	9.4
IMpower133	Extensive-stage	Atezo + P/E	TMB ≥ 10 & NLR < median	18.33

IMpower133	Extensive-stage	TMB < 10 & NLR ≥ median	7.67

SCLC: Small-cell lung cancer; Dur: Durvalumab; Tre: Tremelimumab; P/E: Platinum-based drug/ Etoposide; Rova-T: Rovalpituzumab Tesirine; Nivo: Nivolumab; Ipili: Ipilimumab; Atezo: Atezolizumab; MHC: Major histocompatibility complex; APM: Antigen processing and presentation machinery; CTLA-4: Cytotoxic T-cell–associated antigen; FOXP3: Forkhead box P3; TMB: Tumor mutational burden; CPS: Combined positive score; NLR: Neutrophil-to-lymphocyte ratio

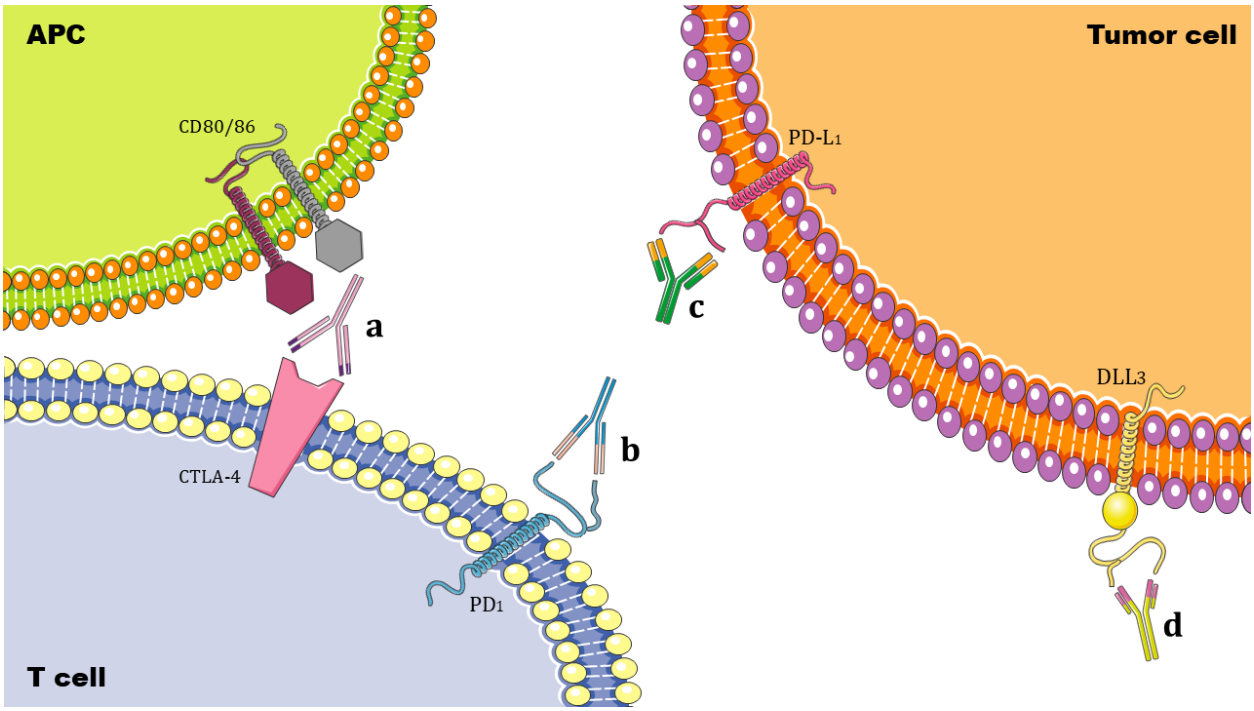

Figure 1. A graphical overview illustrating the mechanism of monoclonal antibodies that used as a treatment candidate in SCLC clinical trials: a. Target agents for CTLA-4. b. Target agents for PD-1. c. Target agents for PD-L1. d. Target agents for DLL3.

APC: Antigen presenting cell; CD80: Cluster of differentiation 80; CTLA-4: Cytotoxic T-lymphocyte-associated protein 4; DLL3: Delta-like canonical Notch ligand 3; PD1: Programmed cell death protein 1; PD-L1: Programmed cell death ligand 1