Case Report: iMDT Corner

Long-term survival after combination therapy with atezolizumab in a patient with small-cell lung cancer: a case report

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Background: Small-cell lung cancer (SCLC) is highly malignant. Despite being highly sensitive to initial chemotherapy and radiotherapy, the recurrence rate is high. Atezolizumab is the first immune checkpoint inhibitor (ICI) that has been proven to provide an overall survival (OS) benefit for extensive-stage SCLC (ES-SCLC), making ICIs in combination with chemotherapy the standard first-line treatment for ES-SCLC. However, the real-world treatment of SCLC is more complex, and multimodal therapy may be needed to achieve long-term patient survival. Few reports on later-line chemotherapy combined with immunotherapy have been published thus far. Moreover, there is limited data on the efficacy and safety of thoracic radiotherapy and radiotherapy for metastatic lesions after multiple lines of treatment have failed in ES-SCLC, and the value of small-molecule antiangiogenesis combined with immunotherapy also needs further exploration.

Case Description: A patient was diagnosed with mediastinal limited-stage SCLC (LS-SCLC) and experienced local progression following standard chemoradiotherapy and prophylactic cranial irradiation. Subsequently, the patient underwent second-line irinotecan chemotherapy, which resulted in severe hematological toxicity. Upon initiation of third-line therapy with anlotinib, the disease remained stable for 9 months. Unfortunately, imaging revealed the presence of a new lesion at the right lung apex. Nevertheless, there was renewed hope for survival when atezolizumab was introduced as part of the treatment regimen. Despite the later development of brain metastases and metastasis adjacent to the aortic arch, long-term survival was achieved through combination therapy involving immunotherapy, antiangiogenic therapy, and radiotherapy targeting the metastatic lesions. By March 2024, the OS had reached 70 months, with a duration of treatment with atezolizumab of 48 months, and only grade II hypothyroidism occurred during treatment, with no other immunotherapy-related adverse events being observed.

Conclusions: This case report suggests the potential efficacy and safety of integrating chemotherapy, immunotherapy, radiotherapy, and antiangiogenic therapy for the treatment of SCLC. Further clinical trials are warranted to validate the value of combining chemotherapy, immunotherapy, radiotherapy, and antiangiogenic therapy.

Keywords: Small-cell lung cancer (SCLC); radiotherapy; atezolizumab; long-term survival; case report

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Introduction

Small-cell lung cancer (SCLC) is a neuroendocrine tumor characterized by an aggressive nature, early metastasis, rapid proliferation, and a tendency toward drug resistance. Despite exhibiting high sensitivity to initial chemotherapy and radiotherapy, SCLC has a high recurrence rate. More than 90% of SCLC recurrences occur within two years, leaving limited treatment options for subsequent management, with most patients ultimately dying from recurrence or metastasis (1-5). Even in limited-stage SCLC (LS-SCLC), due to the high risk of disease recurrence and progression, the median overall survival (mOS) is less than 2 years (6).

The ALTER 1202 study yielded favorable efficacy and safety outcomes for anlotinib in patients with progressive or recurrent SCLC, with a median progression-free survival (mPFS) and mOS of 4.1 and 7.3 months, respectively (7). The IMpower133 study was the first clinical trial to demonstrate that combining atezolizumab with the etoposide and cisplatin (EP) chemotherapy regimen could provide an OS benefit for patients with extensive-stage SCLC (ES-SCLC), achieving an mPFS and mOS of 5.2 and 12.3 months, respectively (8). Consequently, it received approval as a first-line treatment option for ES-SCLC. In the context of frequent failures in immune checkpoint inhibitor (ICI) treatments for patients with SCLC (9-14), this has improved the first-line treatment landscape for ES-SCLC. Building on the findings from the CASPIAN (15), CAPSTONE-1 (16), ASTRUM-005 (17), EXTENTORCH (18), and RATIONALE-312 (19) trials, the array of immunotherapeutic drugs available for ES-SCLC has been further expanded. Moreover, recent evidence from a meta-analysis alleviates concerns regarding the safety of combining chemotherapy with ICIs. This analysis has demonstrated that the integration of PD-1/PD-L1 inhibitors into chemotherapy regimens not only maintains an excellent safety profile but also notably decreases mortality related to severe toxicities, offering a promising approach for ES-SCLC treatment (20). The ADRIATIC study further confirmed that consolidation immunotherapy following concurrent chemoradiotherapy brings dual benefits of PFS and OS for LS-SCLC, pioneering a new treatment paradigm for LS-SCLC (21).

However, the real-world scenario of SCLC is considerably more complex, and there is thus a substantial unmet need for treatment. Further improving survival and devising better treatment strategies requires ongoing investigation. Currently, there is limited data on the efficacy and safety of combining multicourse chest radiotherapy and metastatic lesion radiotherapy in addition to later-line immunochemotherapy in ES-SCLC; moreover, the value of different combinations of small-molecule antiangiogenesis and immunotherapy remains unclear. Here, we report a case of a patient with SCLC originating in the mediastinum, who after standard chemoradiotherapy and prophylactic cranial irradiation (PCI), experienced recurrence and metastasis but achieved long-term survival through the combination of immunotherapy, antiangiogenic therapy, and radiotherapy for metastatic lesions. We present this case in accordance with the CARE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-981/rc).

Highlight box

Key findings

- This case report describes the remarkable long-term survival of 70 months in a patient with limited stage small-cell lung cancer (LS-SCLC) following combination therapy with 48 months of atezolizumab treatment after recurrence and metastasis. The patient only experienced grade II hypothyroidism without other immune-related adverse events.

What is known and what is new?

- SCLC is recognized as a highly malignant disease with a high recurrence rate despite initial sensitivity to chemotherapy and radiotherapy. Atezolizumab, an immune checkpoint inhibitor (ICI), may provide an overall survival benefit for patients with extensive-stage SCLC (ES-SCLC).
- The novelty of this report lies in its documentation of long-term survival achieved through a multimodal therapy involving chemotherapy, immunotherapy, radiotherapy, and antiangiogenic therapy after multiple lines of treatment failed, which is an uncommon outcome in the current paradigm of SCLC treatment.

What is the implication, and what should change now?

- The implications of this case are significant, suggesting that a comprehensive therapeutic approach integrating immunotherapy, chemotherapy, radiotherapy, and antiangiogenic therapy could be effective for treating SCLC. This case provides clinical evidence that may encourage a shift in treatment strategies for SCLC, supporting the consideration of multifaceted treatment plans to enhance patient survival and quality of life. Future clinical trials are warranted to validate this combined therapeutic strategy and explore its applicability across a broader patient population.

Case presentation

A 51-year-old male was admitted to the Fourth Hospital of Hebei Medical University on April 26, 2018, due to

"chest tightness and shortness of breath for two weeks". Physical examination showed no apparent abnormalities, and his Eastern Cooperative Oncology Group (ECOG) performance status was 1. He had a history of "old pulmonary tuberculosis" for over 30 years, no other underlying medical history, no smoking history, and no notable family history. A chest computed tomography (CT) scan indicated soft tissue masses in the 2R and 4R mediastinal areas but no abnormalities in either lung. Bronchoscopy revealed slight compression and narrowing of the trachea, patent openings of the bilateral lobe bronchi, and no obvious neoplasm. Endobronchial ultrasound-guided transbronchial needle aspiration suggested SCLC, and the immunohistochemical results were as follows: CD56, weak positive; chromogranin A, positive/negative; cytokeratin 7, positive; synaptophysin, positive; leukocyte common antigen, negative; P40, negative; thyroid transcription factor-1, negative; and proliferation cell nuclear antigen (Ki-67) proliferation index, 80%. Tumor markers were within normal limits. The patient refused a full-body positron emission tomography-CT scan. A gastroscopy was performed to rule out upper gastrointestinal tract lesions, but no significant abnormalities were found. Brain magnetic resonance imaging (MRI), abdominal CT, and bone scan did not reveal distant metastasis. According to the Veterans Administration Lung Study Group (VALG) staging system, the initial diagnosis was limited-stage SCLC in the mediastinum.

First-line treatment

On May 4, 2018, the patient began radiotherapy for lesions in the 2R and 4R mediastinal regions, with a prescribed dose of 60 Gy in 30 fractions at the planning target volume (PTV). The lung volume receiving ≥20 Gy (V20) was 23%, and the mean dose (Dmean) was 1,100 cGy. Concurrently, the patient received two cycles of an EP chemotherapy regimen (etoposide 100 mg d1–5 + cisplatin 40 mg d1–3 ivgtt, every 3 weeks) and tolerated the treatment well, experiencing only grade I radiation esophagitis. Following concurrent chemoradiotherapy, the patient underwent four cycles of EP consolidation chemotherapy and PCI (25 Gy in 10 fractions). Regular follow-up checks were conducted, and on December 12, 2018, a follow-up chest CT scan evaluated the therapeutic effect to be partial response (PR).

Second-line treatment

During a follow-up visit on February 26, 2019, a chest CT scan revealed an increase in the size of the lesion in the 2R region, with no significant changes in the 4R region, and a chest MRI suggested enlarged lymph nodes in the 2R region with high signal intensity on DWI sequences, indicating disease progression. The patient underwent UGT1A1 (UDP glucuronosyltransferase family 1 member A1) testing and was found to be heterozygous for UGT1A1*6 G/A and UGT1A1*28 6/7. On March 14, 2019, the patient began to receive two cycles of irinotecan chemotherapy with appropriate dose reduction, at a dosage of 120 mg on day 1 and 80 mg on day 8, administered intravenously every 3 weeks. After the second cycle, the patient developed grade IV neutropenia and refused further chemotherapy.

Third-line treatment

A follow-up chest CT evaluation on June 16, 2019, indicated stable disease (SD). Based on the ALTER 1202 phase II trial results (7), the treatment plan was adjusted on June 18, 2019, to 12 mg of anlotinib orally once daily before breakfast, continuously for 2 weeks, followed by 1 week off. During the treatment, due to grade II hand-foot syndrome, fatigue, and weight loss, the dose was reduced to 10 mg as maintenance therapy.

Fourth-line treatment

On March 11, 2020, a follow-up CT scan showed a new soft tissue mass at the right lung apex, and neuron-specific enolase (NSE) levels, which were previously within normal range, increased to 20.1 ng/mL. Abdominal CT, brain MRI, and bone scan showed no distant metastases. Based on the findings of the IMpower133 study (8), in February 2020, the National Medical Products Administration of China approved atezolizumab combined with chemotherapy for the first-line treatment of ES-SCLC. Consequently, on March 15, 2020, the patient commenced fourth-line treatment with the EC chemotherapy regimen (etoposide 100 mg d1–3 + carboplatin 500 mg d1 ivgtt, every 3 weeks) combined with atezolizumab (1,200 mg for two cycles). Concurrently, radiotherapy was administered to the right lung apex lesion, with a PTV prescription dose of 54 Gy in 30 fractions. The lung V20 was 4%, and the Dmean was 258 cGy. The patient tolerated the treatment well, experiencing only grade I radiation esophagitis. A follow-up chest CT on June 1, 2020, indicated the therapeutic effect to be PR. After two cycles of chemotherapy, the patient experienced grade IV neutropenia and thrombocytopenia

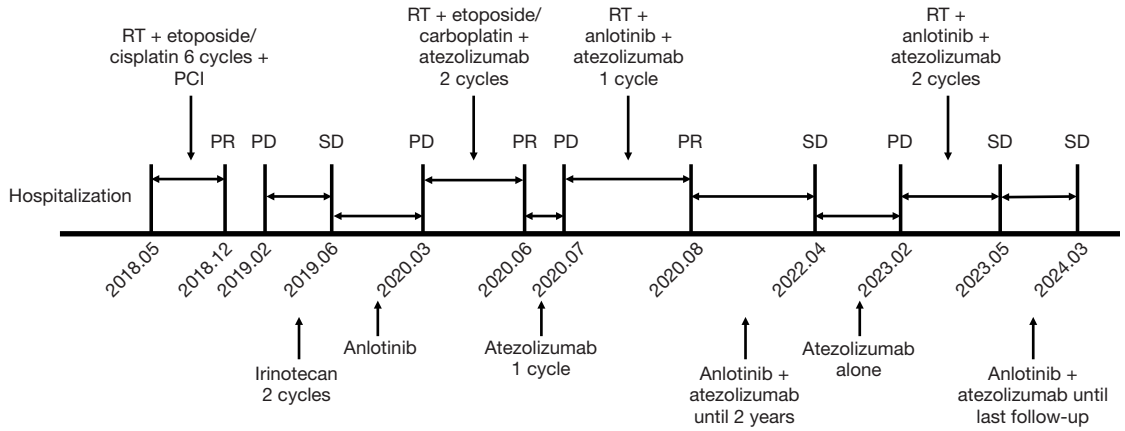

Figure 1 Timeline of the treatment process. RT, radiation therapy; PCI, prophylactic cranial irradiation; PR, partial response; PD, progressive disease; SD, stable disease.

and could not tolerate further chemotherapy and was thus switched to monotherapy with 1,200 mg of atezolizumab for one cycle.

Fifth-line treatment

On July 21, 2020, a follow-up brain MRI detected cranial metastatic lesions, with the therapeutic evaluation indicating progressive disease (PD). On July 27, 2020, radiotherapy was administered to the brain metastatic lesions with a dose of 27 Gy in 3 fractions, and one cycle of atezolizumab (1,200 mg) treatment was used concurrently. Due to persistent low platelet counts of (50–75)×10^9/L, the patient could not tolerate chemotherapy and was once again administered anlotinib (10 mg daily) for treatment in combination with atezolizumab. A follow-up MRI on August 19, 2020, indicated PR in the brain metastatic lesions. On April 5, 2022, two years after the start of immunotherapy, follow-up indicated SD, and the patient continued with atezolizumab monotherapy (1,200 mg) as maintenance therapy.

Sixth-line treatment

On February 25, 2023, a chest CT scan revealed a new soft tissue lesion adjacent to the aortic arch, which was considered to be new metastasis, with the therapeutic evaluation indicating PD. Radiotherapy for the metastatic lesion adjacent to the aortic arch began on February 28, 2023, with a PTV prescription dose of 50 Gy in 25 fractions. The lung V20 was 5%, and the Dmean was 405 cGy. Anlotinib 10 mg daily was resumed with atezolizumab as the sixth-line treatment. A follow-up chest CT on May 5, 2023, assessed the therapeutic effect as SD. The patient continued regular maintenance treatment with 1,200 mg of atezolizumab combined with anlotinib 10 mg daily, and the treatment was well tolerated. In December 2023, the patient developed grade II hypothyroidism and was treated with levothyroxine sodium tablets without other treatment-related side effects.

Summary of treatment process

The timeline for the treatment through five lines is outlined in *Figure 1*. The patient was initially diagnosed with limited-stage mediastinal SCLC, with the disease confined to the mediastinal lymph nodes in the 4R and 2R regions. After standard chemoradiotherapy and PCI, the patient experienced progression in the 2R region and the appearance of new lesions in the right lung apex, brain, and the aortic arch level. Due to clinical constraints and patient preferences, next-generation sequencing or a rebiopsy was not performed. Through a combination of immunotherapy, antiangiogenic therapy, and radiotherapy, the patient's condition is under control at the time of writing. Changes in the CT and MRI images of the lesion sites throughout the treatment process are depicted in *Figure 2*. Radiotherapy has been administered five times over the course of whole treatment, with three sessions targeting the chest area. The PTV and dosage distribution maps for each stage of chest lesion radiotherapy are shown in *Figure 3*. At the last follow-up on March 19, 2024, the patient's condition was stable, with an ECOG performance status of 1. The duration of atezolizumab treatment has now reached 48

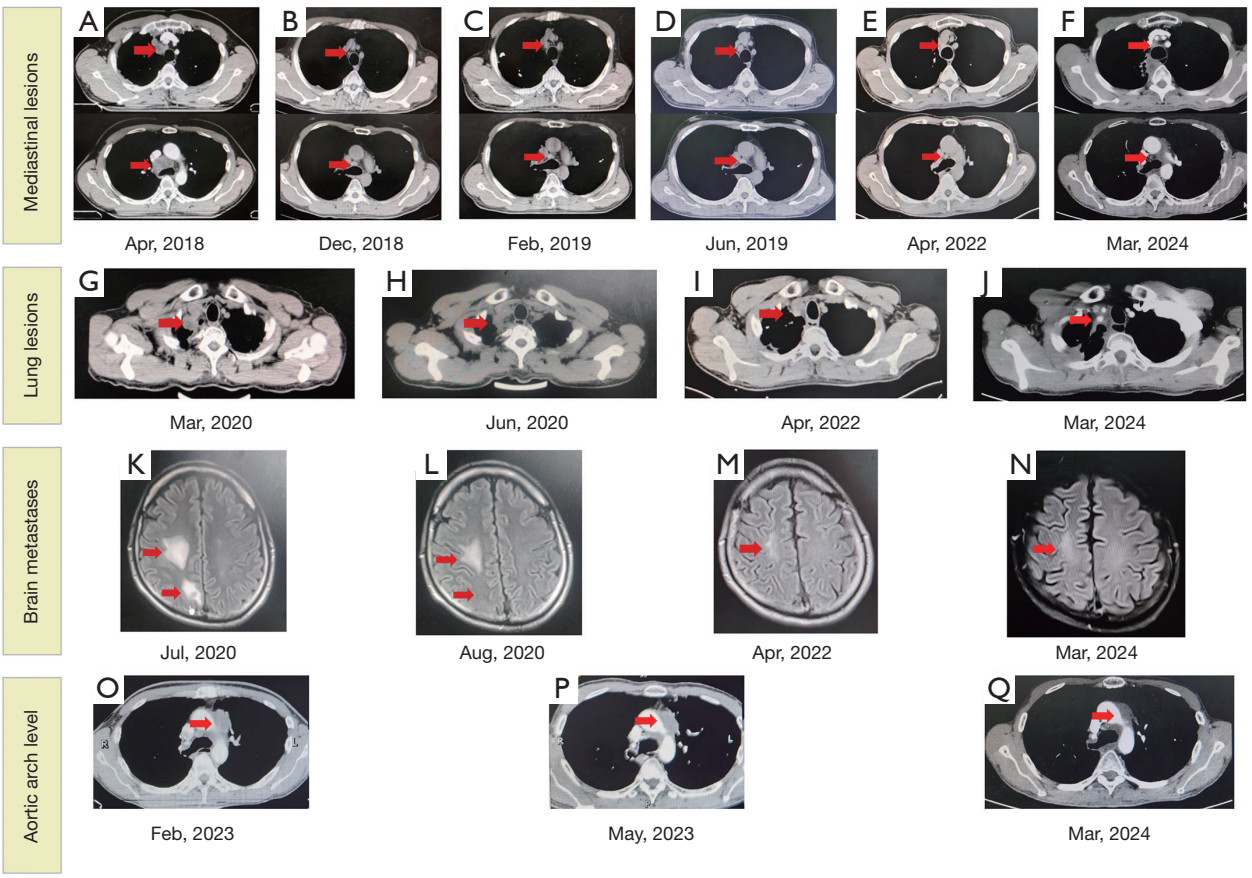

Figure 2 CT and brain MRI images during treatment. (A) Baseline mediastinal lesions in 2R and 4R. (B) Partial response in mediastinal 2R and 4R after first-line chemoradiotherapy. (C) Progressive disease in 2R and stable disease in 4R after first-line treatment during follow-up. (D) Stable disease in 2R and 4R after two cycles of second-line irinotecan chemotherapy. (E) Mediastinal lesions in 2R and 4R after 2 years of immunotherapy. (F) Mediastinal lesions in 2R and 4R at the last follow-up. (G) New lesion at the right lung apex. (H) Partial response in the right lung apex lesion after two cycles of chemotherapy and immunotherapy combined with radiotherapy. (I) Right lung apex lesion after 2 years of immunotherapy. (J) Right lung apex lesion at the last follow-up. (K) Newly detected brain metastatic lesions. (L) Partial response in brain metastatic lesions after SRS. (M) Brain metastatic lesions after 2 years of immunotherapy. (N) Brain metastatic lesions at the last follow-up. (O) New lesion adjacent to the aortic arch. (P) Stable disease in the lesion adjacent to the aortic arch after radiotherapy. (Q) Lesion adjacent to the aortic arch at the last follow-up. The arrows indicate the location of the tumor lesions. CT, computed tomography; MRI, magnetic resonance imaging; SRS, stereotactic radiosurgery.

months, with an OS of 70 months. The patient expressed satisfaction with his treatment experience and its efficacy. All procedures performed in this study were in accordance with the ethical standards of the Fourth Hospital of Hebei Medical University ethics committee and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for the publication of any potentially identifiable images or data included in this article. A copy of the written consent is available for review by the editorial office of this journal.

International Multidisciplinary Team (iMDT) discussion

Discussion among physicians from Fourth Hospital of Hebei Medical University

Department of Radiation Oncology

In this case, the patient initially presented with lesions in mediastinal 2R and 4R, which were confirmed as SCLC through biopsy findings. No pulmonary lesions were identified through imaging, suggesting occult mediastinal

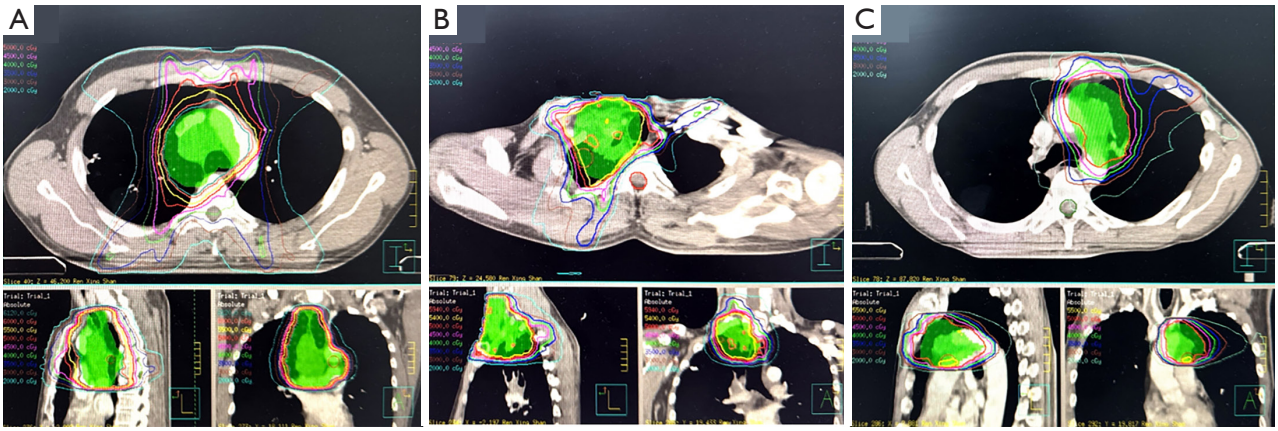

Figure 3 Planning target volume (green area) and dosage distribution maps for each stage of the chest lesion radiotherapy. (A) Mediastinal lesions in the 2R and 4R. (B) Right lung apex lesion. (C) Lesion adjacent to the aortic arch.

LS-SCLC. It is widely acknowledged that initiating treatment immediately after diagnosing LS-SCLC could be highlighted as a factor in prolonging OS and PFS. Despite receiving standard chemoradiotherapy and PCI timely, the patient soon experienced local progression. After a switch to second-line irinotecan chemotherapy, the lesions remained stable, but severe hematological toxicity occurred. The ALTER 1202 study (7) demonstrated that anlotinib provides benefits to OS and PFS for patients with recurrent SCLC as a third-line or later treatment when no other chemotherapy options are viable. Anlotinib successfully provided an additional 9 months of PFS in this case. Unfortunately, new lesions were detected at the right lung apex during this period, possibly indicating a primary lung cancer that had remained occult and was only identified through imaging during ineffective treatment phases. However, fortunately, based on findings of the IMpower133 study (8), atezolizumab was approved for use in combination with chemotherapy as a first-line treatment for ES-SCLC on February 13, 2020, by the National Medical Products Administration of China; this made it feasible for the patient to receive immunotherapy in timely and economical fashion. Ultimately, the patient achieved long-term survival of 70 months.

Patients who achieved prolonged PFS following first-line therapy tend to have extended OS. Moreover, those who exhibit prolonged efficacy after rechallenge during sensitive relapse also benefit in terms of OS (22). The patient experienced disease progression only four months after the initial treatment, indicating a refractory relapse, and encountered severe myelosuppression during the second-line therapy, which portends a potentially unfavorable prognosis. In cases of refractory relapse, patients who achieve durable efficacy with amrubicin (AMR) are similarly associated with an extension of OS (23). However, we cannot predict which of the limited later-line treatment options will be more effective. Therefore, we need to explore more treatment plans with proven efficacy.

As early as 2011, immunotherapy emerged as a potential therapeutic to treat SCLC. CTLA-4 inhibitors combined with chemotherapy were among the first to provide survival benefits in ES-SCLC. Unfortunately, a study did not significantly extend OS or PFS (9). Subsequent research involving PD-1 inhibitors also encountered setbacks, with patients not experiencing survival benefits from these treatment plans (10-14). In 2018, the results of the IMpower133 study (8) were published in *The New England Journal of Medicine*, marking the first clinical study to confirm that immunotherapy could provide OS benefits to patients with ES-SCLC. Subsequent reports from the CASPIAN (15), CAPSTONE-1 (16), ASTRUM-005 (17), EXTENTORCH (18), and RATIONALE-312 (19) studies further enriched the armamentarium of drug options available for the immunotherapeutic treatment of ES-SCLC.

Although the introduction of immunotherapeutic agents has revitalized the treatment landscape for SCLC, a notoriously difficult-to-treat cancer, the complexities of treatment in the real world are considerable. In this case, the patient experienced brain metastases and a metastatic lesion adjacent to the aortic arch during immunotherapy. However, the combination of immunotherapy,

antiangiogenic therapy, and radiotherapy for metastatic lesions has resulted in a remarkable long-term survival of over 5 years for the patient, which was inconceivable in the era preceding immunotherapy. Nevertheless, it is crucial not to underestimate the significant contributions that can be made by antiangiogenic therapy and radiotherapy. A multimodal treatment approach may yield more sustained effects for complex and hard-to-treat cancers such as SCLC.

Thoracic consolidative radiotherapy in the chemotherapy era for ES-SCLC could confer survival benefits to patients (24,25). In the era of immunotherapy, radiotherapy can enhance antigen presentation, promote T-cell infiltration, and modulate the immune microenvironment. When used with ICIs, it can enhance the immune response and improve therapeutic efficacy (26-30). However, reports on combined immunotherapy and radiotherapy in ES-SCLC are rare. In a single-arm phase II trial, low-dose radiation therapy (LDRT) (15 Gy/5 f) was combined with atezolizumab plus chemotherapy as first-line therapy for ES-SCLC in the MATCH trial (NCT04622228). This study confirmed that the combination of LDRT and chemoimmunotherapy was both safe and effective for treating ES-SCLC. The overall response rate (ORR) was 87.5% in 56 patients. The median PFS was 6.9 months (31). A multicenter single-arm phase II study added a significant fraction of thoracic radiotherapy (30–45 Gy/3 Gy) to first-line immunochemotherapy for ES-SCLC, with allowance for PCI and radiotherapy for metastatic lesions during the maintenance phase of immunotherapy, which demonstrated good tolerability and clinical efficacy (32). Two retrospective studies showed that patients with ES-SCLC receiving immunochemotherapy combined with thoracic consolidative radiotherapy experienced good safety and significant survival benefits (33,34). In our case, the patient underwent five sessions of radiotherapy targeting the mediastinal lesions, the whole brain, the right lung apex lesion, the brain metastatic lesions, and a lesion adjacent to the aortic arch, which played a crucial role in the patient's long-term survival. Future strategies combining radiotherapy and immunotherapy in ES-SCLC require further exploration through prospective randomized controlled studies to validate and refine these approaches.

The ALTER1202 study (7) confirmed the efficacy of anlotinib in treating patients with progressive or recurrent SCLC. In our case, the patient exhibited intolerance to second-line chemotherapy and achieved a PFS of 9 months with single-agent anlotinib. Anlotinib was then combined with atezolizumab to maintain long-term disease stability. As of this writing, anlotinib combined with atezolizumab remains the maintenance therapy. Although the combination of anlotinib and atezolizumab used in this case is not an approved therapy for SCLC. Anlotinib not only inhibits tumor angiogenesis, growth, and migration but also improves the tumor immune microenvironment, thereby synergistically exerting antitumor activity with immunotherapy (35). The ETER701 study (36) represents the first attempt to combine small-molecule multitargeted antivascular drugs with immunotherapy and chemotherapy for SCLC treatment. Preliminary results demonstrated a mPFS of 6.9 months and an mOS of 19.3 months, confirming the feasibility of combining immunochemotherapy with multitargeted antivascular drugs. We anticipate that future clinical trials investigating antiangiogenesis combined with immunotherapy will yield further promising outcomes.

SCLC demonstrates substantial intratumoral subtype heterogeneity characterized by highly plastic transcriptional states, indicating that the initially dominant subtype can shift during disease progression and in association with resistance to therapy. Exploration of molecular subtypes could facilitate the development of more durable and effective treatments for patients with SCLC. Notably, approximately half of the patients receiving PD-1/PD-L1 inhibitors experienced extended OS, supporting recent findings on genetic subtypes in SCLC (37-40). A study indicates that PARP inhibitors and platinum-based agents show efficacy in SCLC expressing SLFN11 (37). Additionally, inflamed subtypes characterized by low expression of ASCL1, NEUROD1, and FOU2F3 may respond well to ICIs (38). There is also evidence of a subtype shift from ASCL1 to inflamed following platinum-doublet therapy (38). Furthermore, ASCL1-positive subtypes may respond to DLL3 and BCL2 inhibitors (39,40).

Another interesting point is that the patient's NSE was only elevated at the time of the fourth-line treatment, and there was an inverse correlation between serum NSE levels and OS (41-43), which may be a potential factor contributing to the long time survival.

Several issues concerning the diagnosis and treatment of this patient are discussed below

Optimal combination regimens

With first-line immunochemotherapy demonstrating unprecedented survival benefits for extensive-stage small cell lung cancer (ES-SCLC), what are the best drug

combination strategies in clinical practice to maximize patient benefit?

Expert opinion 1: Dr. Yusuke Inoue

Currently, there are two regimens available in clinical practice for patients with ES-SCLC: (I) carboplatin and etoposide and atezolizumab followed by maintenance atezolizumab, (II) and cisplatin/carboplatin and etoposide and durvalumab followed by maintenance durvalumab. There are a couple of differences in the pivotal trials that led to the approval of these regimens. First, in the phase III CASPIAN trial which compared first-line durvalumab in combination with platinum plus etoposide with platinum plus etoposide alone, the 3-year OS update data with a median follow-up of 39.4 months showed that OS was significantly improved in the durvalumab plus cisplatin/carboplatin and etoposide arm compared with the cisplatin/carboplatin and etoposide arm [hazard ratio (HR), 0.71; 95% confidence interval (CI): 0.60–0.86] (44). In the update analysis of the IMpower133 trial, the efficacy and safety of first-line atezolizumab combined with carboplatin and etoposide was confirmed with a shorter median survival follow-up of 22.9 months (45). Although a recent follow-up analysis of patients who transitioned from IMpower133 to IMbrella A extension study demonstrated the 4- and 5-year OS outcomes for patients receiving first-line atezolizumab combined with carboplatin and etoposide, this analysis lacked a control arm and patient numbers involved in the long-term survival analysis were limited (46). In terms of study design, the IMpower133 was a double-blind, randomized, placebo-controlled trial, whereas the CASPIAN was an open-label trial. These differences need to be recognized when interpreting and comparing the results of the two trials. Lastly, maintenance durvalumab is given every four weeks, while maintenance atezolizumab is given every three weeks. In clinical practice, some patients may prefer durvalumab because of less frequent hospital visit, but some physicians and patients may prefer atezolizumab for more close monitoring of this highly aggressive disease.

Value of different strategies of consolidative and metastatic site radiotherapy

In the context of first-line immunochemotherapy for ES-SCLC, what is the value of different strategies of consolidative thoracic radiotherapy and radiotherapy for metastatic sites?

Expert opinion 1: Dr. Yusuke Inoue

It remains unknown whether the addition of consolidative thoracic radiotherapy to immunochemotherapy can improve patient outcomes in ES-SCLC. As reviewed elsewhere (47), trials are investigating this question in different ways. One strategy is consolidative thoracic radiotherapy with maintenance immunotherapy after the completion of immunochemotherapy. For example, the phase II/III RAPTOR trial (NCT04402788) is comparing the effect of adding radiation therapy (QD on days 1–5 during weeks 1–5 only) to the usual maintenance atezolizumab versus atezolizumab alone in patients with ES-SCLC who have already received atezolizumab plus chemotherapy. Another strategy is first-line induction thoracic radiotherapy in combination with immunochemotherapy. The phase III TRIPLEX trial (NCT05223647) is investigating whether there is a synergistic or additive effect of concurrent thoracic radiotherapy (30 Gy/10 fractions) in patients with ES-SCLC receiving carboplatin, etoposide, and durvalumab. These studies along with others investigating the efficacy and safety of different modes of thoracic radiotherapy, including low-dose radiotherapy and stereotactic body radiotherapy, might change the treatment landscape of ES-SCLC. With regard to radiation therapy for oligometastasis in ES-SCLC, its impact on patient outcome remains unclear and warrants further investigation in the immunotherapy era. It would be an important topic considering the high frequencies of synchronous oligometastasis (21.0%) and oligoprogression (53.2%), which were defined as five or fewer lesions in two or fewer organs, revealed by a retrospective study of 265 patients with ES-SCLC (48).

Optimal combination of antiangiogenic drugs and immunotherapy

What is the optimal combination model for antiangiogenic drugs and immunotherapy in ES-SCLC?

Expert opinion 1: Dr. Yusuke Inoue

The adjunction of anti-angiogenic therapy has not demonstrated a significant improvement in survival outcomes in patients with ES-SCLC receiving first-line chemotherapy (49,50). However, anti-angiogenesis could augment the efficacy of PD-L1 blockade therapy including in SCLC (51). Indeed, the phase III ETER701 trial showed that benmelstobart (a novel PD-L1 inhibitor) plus anlotinib and standard chemotherapy significantly improved OS in treatment-naïve patients with ES-SCLC compared with chemotherapy (HR, 0.61; 95% CI: 0.47–0.79), while anlotinib plus chemotherapy did not. The phase II CeLEBrATE trial is investigating the efficacy of

atezolizumab, bevacizumab, carboplatin, and etoposide in patients with ES-SCLC (52). It is interesting to see whether the combination of atezolizumab and bevacizumab plus chemotherapy shows promise in ES-SCLC as observed in patients with non-small cell lung cancer (NSCLC) harboring *EGFR/ALK* genetic alterations in whom ICIs have shown limited efficacy (53,54). In the movement towards precision medicine in oncology, more than ten bispecific antibodies have been approved globally, with many others being in development. Notably, in the HARMONi-2 phase III trial, first-line ivonescimab (a bispecific antibody targeting PD-1 and VEGF) showed a striking improvement of PFS compared with pembrolizumab in advanced PD-L1-positive NSCLC patients without *EGFR/ALK* alterations across subgroups including PD-L1 expression status and histology (55). In SCLC, a phase II study (NCT06478043) is investigating the efficacy and safety of ivonescimab combined with irinotecan liposome in patients with ES-SCLC who failed first-line platinum-based chemotherapy with ICIs. Bispecific antibodies targeting PD-(L)1 and VEGF will also be worth to be tested in the first-line setting. With several types of antiangiogenic agents such as multi-target small molecules, more specific small molecules, monoclonal antibodies, and bispecific antibodies being available, continuous efforts are needed to reveal the most optimal strategy of combined antiangiogenic therapy and immunotherapy for ES-SCLC.

Conclusions

The treatment decisions in this case closely followed the evidence-based forefront of SCLC management, including findings from clinical trials, which have contributed to the long-term survival of the patient. This case report suggests the potential efficacy and safety of integrating chemotherapy, immunotherapy, radiotherapy, and antiangiogenic therapy for the treatment of SCLC. Further clinical trials are warranted to validate the value of combining chemotherapy, immunotherapy, radiotherapy, and antiangiogenic therapy.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-981/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-981/coif). The authors have no conflicts of interest to declare.

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. All procedures performed in this study were in accordance with the ethical standards of the Fourth Hospital of Hebei Medical University ethics committee and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for the publication of any potentially identifiable images or data included in this article. A copy of the written consent is available for review by the editorial office of this journal.

References

1. Ganti AKP, Loo BW, Bassetti M, et al. Small Cell Lung Cancer, Version 2.2022, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2021;19:1441-64.
2. Assi HA, Padda SK. Latest advances in management of small cell lung cancer and other neuroendocrine tumors of the lung. Cancer Treat Res Commun 2020;23:100167.
3. Gong J, Salgia R. Managing Patients With Relapsed Small-Cell Lung Cancer. J Oncol Pract 2018;14:359-66.

4. Karacz CM, Yan J, Zhu H, et al. Timing, Sites, and Correlates of Lung Cancer Recurrence. Clin Lung Cancer 2020;21:127-135.e3.
5. Rudin CM, Brambilla E, Faivre-Finn C, et al. Small-cell lung cancer. Nat Rev Dis Primers 2021;7:3.
6. Das M, Padda SK, Weiss J, et al. Advances in Treatment of Recurrent Small Cell Lung Cancer (SCLC): Insights for Optimizing Patient Outcomes from an Expert Roundtable Discussion. Adv Ther 2021;38:5431-51.
7. Cheng Y, Wang Q, Li K, et al. Anlotinib vs placebo as third- or further-line treatment for patients with small cell lung cancer: a randomised, double-blind, placebo-controlled Phase 2 study. Br J Cancer 2021;125:366-71.
8. Horn L, Mansfield AS, Szczęsna A, et al. First-Line Atezolizumab plus Chemotherapy in Extensive-Stage Small-Cell Lung Cancer. N Engl J Med 2018;379:2220-9.
9. Reck M, Luft A, Szczesna A, 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;34:3740-8.
10. Antonia SJ, López-Martin JA, Bendell J, et al. Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): a multicentre, open-label, phase 1/2 trial. Lancet Oncol 2016;17:883-95.
11. Ready NE, Ott PA, Hellmann MD, 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;15:426-35.
12. Owonikoko TK, Park K, Govindan R, et al. Nivolumab and Ipilimumab as Maintenance Therapy in Extensive-Disease Small-Cell Lung Cancer: CheckMate 451. J Clin Oncol 2021;39:1349-59.
13. Spigel DR, Vicente D, Ciuleanu TE, et al. Second-line nivolumab in relapsed small-cell lung cancer: CheckMate 331(☆). Ann Oncol 2021;32:631-41.
14. Rudin CM, Awad MM, Navarro A, 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;38:2369-79.
15. Paz-Ares L, Dvorkin M, Chen Y, et al. Durvalumab plus platinum-etoposide versus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial. Lancet 2019;394:1929-39.
16. Wang J, Zhou C, Yao W, 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;23:739-47.
17. Cheng Y, Han L, Wu L, 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;328:1223-32.
18. Cheng Y, Liu Y, Zhang W, et al. LBA93 EXTENTORCH: A randomized, phase III trial of toripalimab versus placebo, in combination with chemotherapy as a first-line therapy for patients with extensive stage small cell lung cancer (ES-SCLC). Ann Oncol 2023;34:S1334.
19. Cheng Y, Fan Y, Zhao Y, 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;19:1073-85.
20. Moraes FCA, Lôbo AOM, Sano VKT, et al. Treatment-related Adverse Events, Including Fatal Toxicities, in Patients With Extensive-stage Small-cell Lung Cancer Receiving Adjuvant Programmed Cell Death 1/Programmed Cell Death Ligand 1 Inhibitors: A Meta-analysis and Trial Sequential Analysis of Randomized Controlled Trials. Clin Oncol (R Coll Radiol) 2024;36:e408-19.
21. Cheng Y, Spigel DR, Cho BC, et al. Durvalumab after Chemoradiotherapy in Limited-Stage Small-Cell Lung Cancer. N Engl J Med 2024;391:1313-27.
22. Tendler S, Zhan Y, Pettersson A, et al. Treatment patterns and survival outcomes for small-cell lung cancer patients - a Swedish single center cohort study. Acta Oncol 2020;59:388-94.
23. Takahara Y, Tanaka T, Ishige Y, et al. Influencing factors of efficacy and long-term use of amrubicin in patients with small cell lung cancer. Thorac Cancer 2023;14:1286-93.
24. Jeremic B, Shibamoto Y, Nikolic N, et al. Role of radiation therapy in the combined-modality treatment of patients with extensive disease small-cell lung cancer: A randomized study. J Clin Oncol 1999;17:2092-9.
25. Slotman BJ, van Tinteren H, Praag JO, et al. Use of thoracic radiotherapy for extensive stage small-cell lung cancer: a phase 3 randomised controlled trial. Lancet 2015;385:36-42.
26. Demaria S, Coleman CN, Formenti SC. Radiotherapy: Changing the Game in Immunotherapy. Trends Cancer 2016;2:286-94.

27. Huang AC, Postow MA, Orlowski RJ, et al. T-cell invigoration to tumour burden ratio associated with anti-PD-1 response. Nature 2017;545:60-5.
28. Demaria S, Golden EB, Formenti SC. Role of Local Radiation Therapy in Cancer Immunotherapy. JAMA Oncol 2015;1:1325-32.
29. Mondini M, Levy A, Meziani L, et al. Radiotherapy-immunotherapy combinations - perspectives and challenges. Mol Oncol 2020;14:1529-37.
30. Kang K, Wu Y, Yao Z, et al. Tackling the current dilemma of immunotherapy in extensive-stage small cell lung cancer: A promising strategy of combining with radiotherapy. Cancer Lett 2023;565:216239.
31. Wang H, Yao Z, Kang K, et al. Preclinical study and phase II trial of adapting low-dose radiotherapy to immunotherapy in small cell lung cancer. Med 2024;5:1237-1254.e9.
32. Liu C, Zeng L, Deng C, et al. Hypofractionated radiotherapy with immunochemotherapy for extensive-stage small-cell lung cancer. Front Immunol 2023;14:1175960.
33. Li L, Yang D, Min Y, et al. First-line atezolizumab/durvalumab plus platinum-etoposide combined with radiotherapy in extensive-stage small-cell lung cancer. BMC Cancer 2023;23:318.
34. Yao Y, Li B, Song R, et al. Efficacy and safety of thoracic radiotherapy in extensive-stage small-cell lung cancer patients receiving first-line immunotherapy plus chemotherapy: a propensity score matched multicentre retrospective analysis. Radiat Oncol 2024;19:25.
35. Su Y, Luo B, Lu Y, et al. Anlotinib Induces a T Cell-Inflamed Tumor Microenvironment by Facilitating Vessel Normalization and Enhances the Efficacy of PD-1 Checkpoint Blockade in Neuroblastoma. Clin Cancer Res 2022;28:793-809.
36. Cheng Y, Yang R, Chen J, et al. OA01.03 Benmelstobart with Anlotinib plus Chemotherapy as First-line Therapy for ES-SCLC: A Randomized Double-blind, Phase III Trial. J Thorac Oncol 2023;18:S44.
37. Pietanza MC, Waqar SN, Krug LM, et al. Randomized, Double-Blind, Phase II Study of Temozolomide in Combination With Either Veliparib or Placebo in Patients With Relapsed-Sensitive or Refractory Small-Cell Lung Cancer. J Clin Oncol 2018;36:2386-94.
38. Gay CM, Stewart CA, Park EM, et al. Patterns of transcription factor programs and immune pathway activation define four major subtypes of SCLC with distinct therapeutic vulnerabilities. Cancer Cell 2021;39:346-360.e7.
39. Saunders LR, Bankovich AJ, Anderson WC, et al. A DLL3-targeted antibody-drug conjugate eradicates high-grade pulmonary neuroendocrine tumor-initiating cells in vivo. Sci Transl Med 2015;7:302ra136.
40. Dammert MA, Brägelmann J, Olsen RR, et al. MYC paralog-dependent apoptotic priming orchestrates a spectrum of vulnerabilities in small cell lung cancer. Nat Commun 2019;10:3485.
41. Tian Z, Liang C, Zhang Z, et al. Prognostic value of neuron-specific enolase for small cell lung cancer: a systematic review and meta-analysis. World J Surg Oncol 2020;18:116.
42. Wang C, Jin S, Xu S, et al. The combination of pretreatment prognostic nutritional index and neuron-specific enolase enhances prognosis predicting value of small cell lung cancer. Clin Respir J 2021;15:264-71.
43. Zhou M, Wang Z, Yao Y, et al. Neuron-specific enolase and response to initial therapy are important prognostic factors in patients with small cell lung cancer. Clin Transl Oncol 2017;19:865-73.
44. Paz-Ares L, Chen Y, Reinmuth N, et al. Durvalumab, with or without tremelimumab, plus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer: 3-year overall survival update from CASPIAN. ESMO Open 2022;7:100408.
45. Liu SV, Reck M, Mansfield AS, et al. Updated Overall Survival and PD-L1 Subgroup Analysis of Patients With Extensive-Stage Small-Cell Lung Cancer Treated With Atezolizumab, Carboplatin, and Etoposide (IMpower133). J Clin Oncol 2021;39:619-30.
46. Reck M, Dziadziuszko R, Sugawara S, 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.
47. Zhang S, Cheng Y. Immunotherapy for extensive-stage small-cell lung cancer: current landscape and future perspectives. Front Oncol 2023;13:1142081.
48. Hashimoto K, Morinaga D, Asahina H, et al. Synchronous Oligometastasis and Oligoprogression as a Prognostic Marker in Patients With Extensive-Stage SCLC Treated With a Combination of Immune-Checkpoint Inhibitor and Chemotherapy (HOT2301). JTO Clin Res Rep 2024;5:100715.
49. Pujol JL, Lavole A, Quoix E, 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;26:908-14.
50. Tiseo M, Boni L, Ambrosio F, et al. Italian, Multicenter, Phase III, Randomized Study of Cisplatin Plus Etoposide With or Without Bevacizumab as First-Line Treatment in Extensive-Disease Small-Cell Lung Cancer: The GOIRC-AIFA FARM6PMFJM Trial. J Clin Oncol 2017;35:1281-7.
51. Meder L, Schuldt P, Thelen M, et al. Combined VEGF and PD-L1 Blockade Displays Synergistic Treatment Effects in an Autochthonous Mouse Model of Small Cell Lung Cancer. Cancer Res 2018;78:4270-81.
52. Rihawi K, Lamberti G, Riccardi F, et al. 1994P Carboplatin, etoposide, bevacizumab, and atezolizumab in patients with extensive-stage SCLC – GOIRC-01-2019 CeLEBrATE ML41241 trial. Ann Oncol 2023;34:S1063-4.
53. Socinski MA, Jotte RM, Cappuzzo F, et al. Atezolizumab for First-Line Treatment of Metastatic Nonsquamous NSCLC. N Engl J Med 2018;378:2288-301.
54. Park S, Kim TM, Han JY, et al. Phase III, Randomized Study of Atezolizumab Plus Bevacizumab and Chemotherapy in Patients With EGFR- or ALK-Mutated Non-Small-Cell Lung Cancer (ATTLAS, KCSG-LU19-04). J Clin Oncol 2024;42:1241-51. Erratum in: J Clin Oncol 2024;42:2725.
55. Zhou C, Chen J, Wu L, et al. PL02.04 Phase 3 Study of Ivonescimab (AK112) vs. Pembrolizumab as First-line Treatment for PD-L1-positive Advanced NSCLC: Primary Analysis of HARMONi-2. J Thorac Oncol 2024;19:S1.

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