BRIEF REPORT

Combination of Lurbinectedin and Osimertinib for Treatment of *EGFR*-Mutated Transformed SCLC: A Brief Report

Aditi Singh, MBBS, MPH,[a,*] Arthi Sridhar, MBBS,[a] Aastha Poddar, MBBS,[b] Anastasios Dimou, MD,[a] Kaushal Parikh, MBBS,[a] Mohamed Shanshal, MD,[a] Anna Schwecke, APRN, CNP, MS,[a] Nicole Moffett, APRN, CNP, MSN,[a] Manish R. Patel, DO,[c] Aaron S. Mansfield, MD,[a] Konstantinos Leventakos, MD, PhD[a]

[a]*Department of Medical Oncology, Mayo Clinic, Rochester, Minnesota*
[b]*Department of Health Sciences Research, Mayo Clinic, College of Medicine, Rochester, Minnesota*
[c]*Division of Hematology, Oncology, and Transplantation, University of Minnesota Medical School, Minneapolis, Minnesota*

Received 11 November 2024; revised 28 January 2025; accepted 10 February 2025
Available online - 13 February 2025

ABSTRACT

Third-generation tyrosine kinase inhibitors are effective treatment of *EGFR*-mutated NSCLC. After an initial response, patients on this therapy ultimately develop resistance leading to disease progression. One of the resistance mechanisms is histological transformation to SCLC. There is no standard of care for the management of transformed SCLC. Given the rarity of transformed SCLC, it is important to study treatment options that are safe and effective for this disease. In this case series, three patients received treatment with lurbinectedin plus osimertinib after transformation to SCLC. In our limited experience, the combination was found to be safe.

Keywords: NSCLC; SCLC; EGFR; Osimertinib; Lurbinectedin; Tranformed SCLC; Drug resistance

Introduction

Osimertinib is a third-generation tyrosine kinase inhibitor (TKI), which forms an irreversible covalent bond with the cysteine-797 residue in the ATP binding site of EGFR and is a standard of care for the treatment of *EGFR*-mutant NSCLC.[1] After an initial good response, progression on TKIs is universal. Histological transformation (HT) is a mechanism of disease progression in NSCLC especially after treatment with TKI and is challenging to treat.[2] HT might be seen more frequently in the future owing to the increasing use of molecular testing and availability of more treatment options leading to longer overall survival. Therefore, it is pertinent to evaluate effective treatment modalities and their safety for the treatment of transformed SCLC (tSCLC). In this case series, we report our experience of using lurbinectedin with osimertinib for the treatment of tSCLC.

Materials and Methods

We identified three patients with *EGFR* mutation with either de-novo SCLC or tSCLC who received treatment with lurbinectedin plus osimertinib (LO). Clinical and laboratory data was extracted by retrospective chart review. Tumors were staged according to the American Joint Committee on Cancer Guidelines (version 8). Response assessment was done using the Response Evaluation Criteria in Solid Tumors, version 1.1. This study was approved by the Institutional Review Board of the Mayo Clinic (23-009882) and informed consent was waived.

***Corresponding author.**

Address for correspondence: Aditi Singh, MBBS, MPH, Department of Hematology Oncology, 1 Veterans Drive, Minneapolis, Minnesota. E-mail: aditisingh0215@gmail.com

Cite this article as: Singh A, Sridhar A, Poddar A, et al. Combination of lurbinectedin and osimertinib for treatment of EGFR-mutated transformed SCLC: a brief report. *JTO Clin Res Rep* 2025;6:100807

ISSN: 2666-3643

https://doi.org/10.1016/j.jtocrr.2025.100807

Results

All three patients were diagnosed at an advanced stage and had *EGFR* Exon 19 deletion (Table 1). One patient reported partial response to the LO (Fig. 1), and it was well-tolerated in all three cases. The dose reduction of Lurbinectedin was required in two cases owing to thrombocytopenia.

Case 1

A 45-year-old former smoker with a 10-pack-year smoking history and no specific medical or family history presented with headache and tongue deviation. Magnetic resonance imaging of the brain with/without contrast showed brain metastasis. A computed tomography scan found a left upper lobe mass and mediastinal and hilar lymphadenopathy. Positron emission tomography-computed tomography scan revealed additional hepatic, adrenal, osseous, intramuscular, and subcutaneous metastases. A lymph node biopsy revealed neoplastic cells positive for synaptophysin, chromogranin, TTF 1, CK-7, and Ki-67 higher than 95% are consistent with SCLC. He received whole-brain radiation therapy for the brain lesions. He was treated upfront with etoposide, carboplatin, and atezolizumab (ECA). After four cycles, he was found to have disease progression. He was then treated with lurbinectedin in the second-line setting. Molecular testing was performed at this time using liquid biopsy and it revealed *EGFR* exon 19 deletion. Osimertinib was added to his treatment 19 days after his first cycle of lurbinectedin. He developed thrombocytopenia with a platelet count of 81,000 requiring a two-week delay of cycle 2 of lurbinectedin. He achieved a partial response after two cycles of Lurbinectedin. The dose of lurbinectedin was reduced to 2 mg/m^2 from cycle two onwards for anticipated thrombocytopenia. He completed seven cycles of LO. He tolerated the treatment well. Though his previously seen disease resolved, he developed new bone lesions, subcarinal adenopathy, and pancreatic lesions. Molecular testing using liquid biopsy reported the persistence of his *EGFR* mutation. He was sequentially treated with docetaxel plus osimertinib, B7H3 T-cell engager as part of a phase 1 clinical trial without osimertinib, topotecan plus osimertinib, temozolomide plus osimertinib before ultimately transitioning to hospice (Fig. 2).

Case 2

A 31-year-old female nonsmoker with no specific medical and family history presented with right upper quadrant abdominal discomfort and right shoulder pain. Imaging revealed a right upper lobe mass and right pleural and chest wall metastasis. Pathology revealed adenocarcinoma of the lung. Molecular testing revealed

Table 1. Clinical Characteristics of the Patients

Case	Age (y)	Race	PS	Type of Initial Testing	Mutations Identified	Type of Testing After Transformation	Mutations Identified	Number of Lurbinectedin Cycles	Best Response
Case 1	45	White	0	NGS (Blood)	*EGFR E746_A750del* (Exon 19 deletion), *HRAS G12S*, *TP53 D228fs*, *EGFR* amplification	NA	NA	7	PR
Case 2	31	Asian Taiwanese	0	Single-gene testing	*EGFR E746_A750del* (Exon 19 deletion)	NGS (Blood)	*EGFR E746_A750del* (Exon 19 deletion), *EGFR* amplification, *TP53 S241fs*, *CCNE1* amplification, *RB1* slice site SNV	7	PD
Case 3	53	White	0	NGS (Tissue)	*EGFR E746_A750del* (Exon 19 deletion), *TP53 c.841G>T (p.D281Y)*	NGS (Tissue)	*EGFR E746_A750del* (Exon 19 deletion), *TP53 c.841G>T (p.D281Y)*, *RB* loss exons 3-27, *AKT2* amplification, *CCNE1* amplification	3	PD

NA, not applicable; NGS, next-generation sequencing; PD, progressive disease; PR, partial response; PS, performance status.

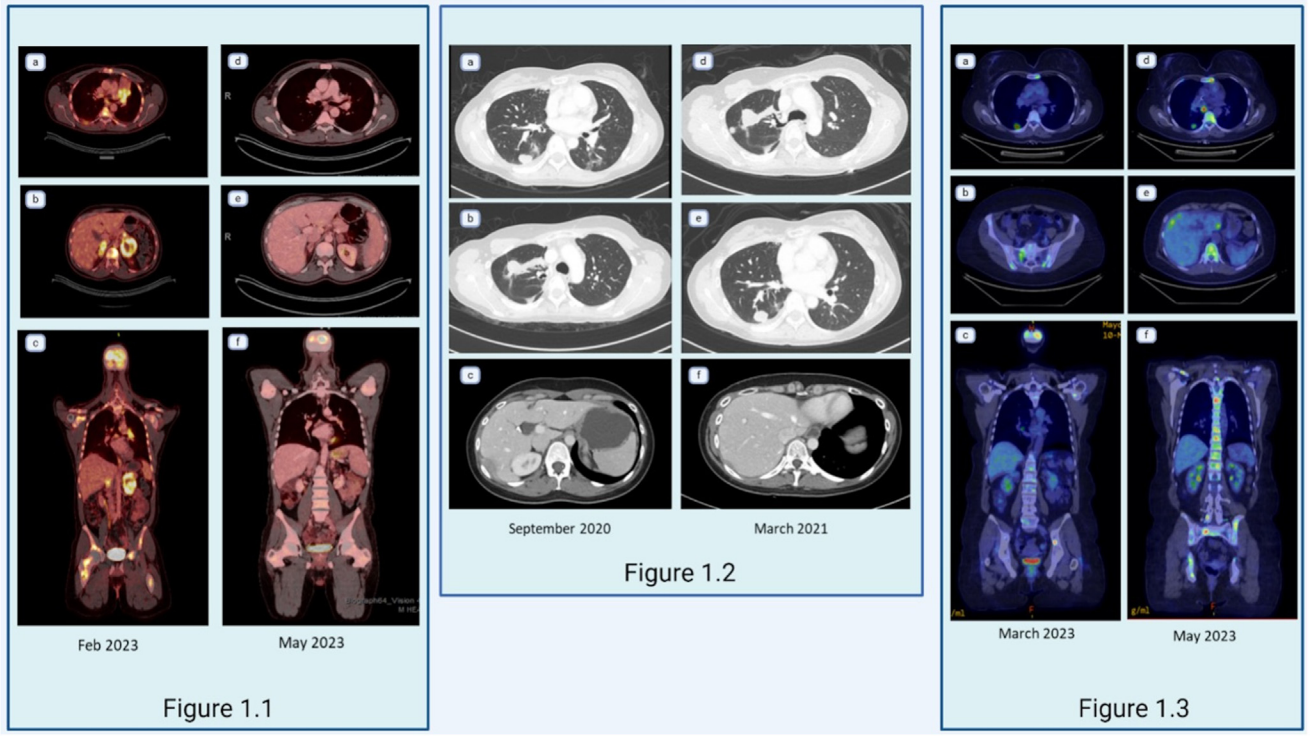

Figure 1. Response to LO. LO, lurbinectedin plus osimertinib. **Figure 1.1.** (*A-C*) PET-CT scan showing disease progression after carboplatin/etoposide/atezolizumab with increasing metabolic activity of thoracic lymph nodes, adrenal gland lesions, and lesion in the left hepatic lobe with development of additional lesions in the right hepatic lobe, lesion in the pancreatic body/tail, and innumerable additional osseous lesion. (*D-F*) Significant improvement in the progressive disease after two cycles of LO. LO, lurbinectedin plus osimertinib; PET-CT, positron emission tomography-computed tomography. **Figure 1.2.** (*A-C*) A CT scan shows disease progression after carboplatin/etoposide/atezolizumab with new pulmonary nodules and a mass centered in the right abdominal wall indenting the right lobe of the liver. (*C-F*) A CT scan shows improvement in peri-hepatic metastatic disease but a progression of metastatic disease in the thorax. CT, computed tomography. **Figure 1.3.** (*A-C*) PET-CT scan shows progressive disease on carboplatin/etoposide/atezolizumab with osseous and pulmonary lesions. (*D-F*) Shows disease progression on LO with worsening osseous and pulmonary lesions. LO, lurbinectedin plus osimertinib; PET-CT, positron emission tomography-computed tomography.

an *EGFR* exon 19 deletion. She was treated with erlotinib and achieved a partial response. She developed oligoprogressive disease in the chest within six months for which she received stereotactic body radiation therapy. She experienced disease progression in nine months. Repeat molecular profiling revealed a T790M *EGFR* mutation and persistent exon 19 deletion. She was transitioned to osimertinib and experienced a partial response. Upon progression, a biopsy revealed SCLC. She was treated with ECA but experienced disease progression after four cycles. She was then treated with 11 cycles of docetaxel plus osimertinib but developed progressive disease after 15 months. She was then treated with LO. She developed oligoprogressive disease in her chest for which she received stereotactic body radiation therapy and LO was continued. She developed common terminology criteria for adverse events (CTCAE) grade 1 leukopenia and neutropenia with cycle 7 requiring dose reduction. She also experienced CTCAE grade 1 nausea and vomiting with LO. She was treated with one cycle of amivantamab post-progression after which she was transitioned to hospice (Fig. 2).

Case 3

A 53-year-old female nonsmoker with no specific medical history presented with facial tingling, headache, and vision disturbances. Brain magnetic resonance imaging revealed a temporal bone and left cerebral peduncle metastatic disease. Additional imaging revealed a right lower lobe mass, right hilar lymphadenopathy, and osseous metastases. Pathology revealed adenocarcinoma of the lung. A tissue molecular test revealed an *EGFR* exon 19 deletion. She was started on Osimertinib and achieved a partial response for three months. A biopsy of a new lesion revealed SCLC. She was treated with four cycles of ECA and two cycles of carboplatin and etoposide but experienced disease progression right after. She was then treated with Docetaxel and osimertinib and had a progression of disease after three cycles. She was switched to

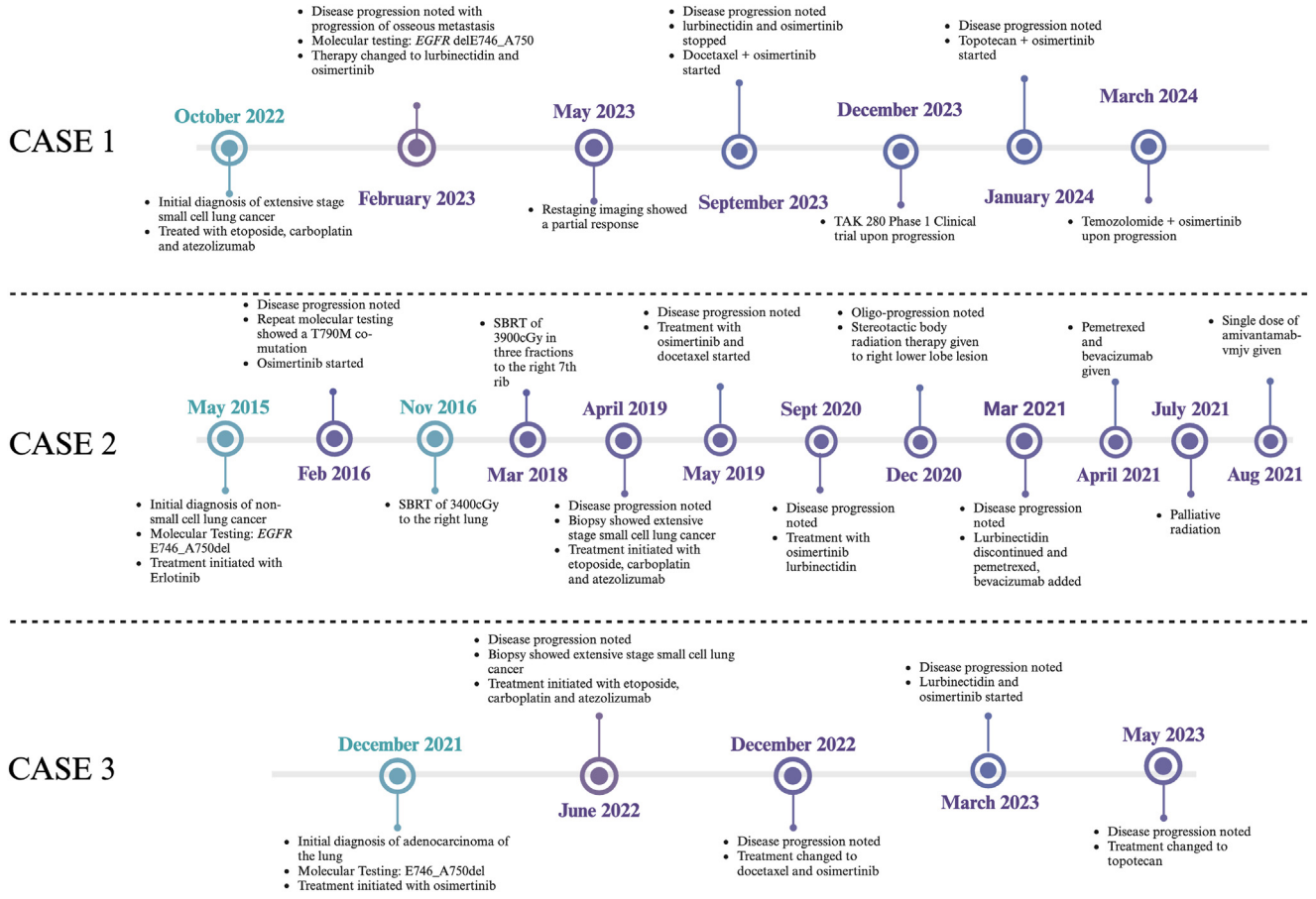

Figure 2. Treatment timeline. SBRT, stereotactic body radiation therapy.

LO and given pegfilgastrim owing to anticipated additive myelotoxicity and a previous history of grade 4 neutropenia. She also experienced CTCAE grade 1 nausea and vomiting and developed grade 2 thrombocytopenia after three cycles of LO. She experienced progressive disease after three cycles. She received one cycle of topotecan after which she was transitioned to hospice (Fig. 2).

Discussion

Increased frequency of repeat biopsy and molecular testing at the time of disease progression in *EGFR* mutated NSCLC has led to improved understanding of mechanisms of therapeutic resistance. HT to SCLC is one of the mechanisms of resistance to TKI in *EGFR*-mutated lung adenocarcinoma and can be seen in 2% to 15% of NSCLC cases.[3,4] Patients with concurrent *TP53* and *RB1* alterations are at increased risk for transformation but acquisition of these mutations alone is not responsible for transformation.[5] Frequent loss of the 3-p chromosome arm, upregulation of WNT/β-catenin, PI3K/AKT, and NOTCH signaling pathway are often seen in tSCLC.[6]

Most patients are treated with a standard SCLC regimen that includes platinum and etoposide.[7] A transient robust response to platinum-based therapy is seen. Immune checkpoint inhibitors can be added to chemotherapy regimens but single-agent PD-1 or PD-L1 inhibitors alone or in combination with CTLA-4 inhibitors have not shown significant efficacy.[8] Data is lacking regarding later line treatment of tSCLC. Lurbinectedin is an FDA-approved second-line neoplastic agent for de-novo SCLC.[9] There is preclinical data regarding the efficacy of lurbinectedin with or without osimertinib in transformed patient xenograft–derived SCLC models. In this study, the combination treatment led to the suppression of genes in the NOTCH, NF-kB, or PI3K/AKT pathways. Tumor volume reduction of more than 80% was noted with the combination.[10]

We aimed to see the efficacy and tolerance of this combination in clinical practice. Although LO only led to a significant response in one out of three cases, the combination was tolerable, and two of the three patients received seven cycles of combination therapy suggesting some clinical benefit. The progression-free survival noted with LO in our first case is better than the median progression-free survival reported with lurbinectedin alone, especially in patients with CNS disease.[11] Lurbinectedin is associated with a high rate of hematologic

adverse events, but it has been safely combined with other therapeutic agents.[12] In our study, the safety profile of the lurbinectedin and osimertinib combination was predictable. All three patients experienced myelotoxicity but none of them experienced any grade 3 or higher toxicity. In one of the cases, the combination was used with growth factor support owing to a previous history of high-degree myelotoxicity. Mild nausea, vomiting, and fatigue were other side effects reported with this combination. Though this is a limited sample size, the observed toxicity could be attributed to lurbinectedin alone suggesting there is no added toxicity using the combination. There is no consensus on the continuation of targeted therapy after HT. Nevertheless, we believe that continuation of TKI should be considered for patients who are fit with good bone marrow reserve. It can be hypothesized that subclones of adenocarcinoma that are sensitive to EGFR TKI are still present after HT.[13]

Conclusion

In conclusion, LO was tolerable and had few adverse effects in the three patients presented. This combination therapy can be a promising treatment for individuals with tSCLC for which larger preferably prospective studies are required. Growth factor support can be considered on a case-by-case basis on the basis of the history of myelotoxicity with previously used agents and baseline low blood cell count.

CRediT Authorship contribution Statement

Aditi Singh: Conceptualization, Design, Provision of study materials or patients, Data collection and assembly, Data analysis and interpretation, Writing - original draft, Final approval.

Arthi Sridhar: Provision of study materials or patients, Data collection and assembly, Data analysis and interpretation, Writing - original draft, Final approval.

Aastha Poddar: Provision of study materials or patients, Data collection and assembly, Data analysis and interpretation, Writing - original draft, Final approval.

Anastasios Dimou: Provision of study materials or patients, Data collection and assembly, Data analysis and interpretation, Writing - original draft, Final approval.

Kaushal Parikh: Provision of study materials or patients, Data collection and assembly, Data analysis and interpretation, Writing - original draft, Final approval.

Mohamed Shanshal: Provision of study materials or patients, Data collection and assembly, Data analysis and interpretation, Writing - original draft, Final approval.

Anna Schwecke: Provision of study materials or patients, Data collection and assembly, Data analysis and interpretation, Writing - original draft, Final approval.

Nicole Moffett: Provision of study materials or patients, Data collection and assembly, Data analysis and interpretation, Writing - original draft, Final approval.

Manish R. Patel: Provision of study materials or patients, Data collection and assembly, Data analysis and interpretation, Writing - original draft, Final approval.

Aaron S. Mansfield: Provision of study materials or patients, Data collection and assembly, Data analysis and interpretation, Writing - original draft, Final approval.

Konstantinos Leventakos: Conceptualization, Design, Provision of study materials or patients, Data collection and assembly, Data analysis and interpretation, Writing - original draft, Final approval.

Disclosure

Dr. Dimou reports grants from the Department of Defense, A Breath of Hope, The Mathy Family Development fund; support for attending meetings and/or travel from IASLC, honoraria from MultiMedia Medical LLC; consulting fees from TP Therapeutics, Guardant Health, Chromacode, AnHeart Therapeutics, and Rigel Pharmaceuticals. Dr. Parikh reports consulting fees from Jazz Pharmaceuticals, Guardant Health, Regeneron, Rigel Pharmaceuticals, AstraZeneca; honoraria from MJH Life Sciences, Dava Oncology Intellisphere, Clinical Education Alliance; support for attending meetings and/or travel from DAVA Oncology. Ms. Schwecke reports royalties or licenses from InveniQA, honoraria from APPOS, and UMOEN; and participation on a data safety monitoring board or advisory board for the Mayo Clinic. Ms. Moffett reports honoraria from APPOS. Dr. Patel reports grants from AstraZeneca. Dr. Mansfield reports grants from Novartis, Verily; consulting fees from Rising Tide, TRIPTYCH Health Partners—expert think tank; honoraria from Janssen, BeiGene, Chugai Pharmaceutical Co Ltd (Roche), Ideology Health LLC (formerly Health Media), AXIS Medical Education Inc, Johnson &amp, Johnson Global Services, Intellisphere LLC, Answers in CME, Ideology Health (formerly Nexus Health Media); participation on a data safety monitoring board or advisory board for Abbvie, AstraZeneca, Bristol Myers Squibb, Genentech/Roche, Janssen, Takeda, Sanofi Genzyme, Gilead, support for attending meetings and/or travel Shanghai Roche; leadership or fiduciary role with mesothelioma applied research foundation, friends of Patan hospital; and other financial or non-financial roles in Genentech, Janssen, Johnson & Johnson Global Services, Bristol Meyers Squibb. Dr. Leventakos reports grants from AstraZeneca, Mirati Therapeutics; consulting fees from Amgen, Boehringer Ingelheim Pharmaceuticals, Daiichi Sankyo, Janssen Biotech, Novartis; honoraria from MJH Life Sciences, AstraZeneca Interdisciplinary Corporation, OncLive State of the Summit, MD Outlook,

Targeted Oncology; participation on a data safety monitoring board or advisory board for AstraZeneca, Jazz Pharmaceuticals, Mirati Therapeutics, Regeneron, Targeted Oncology, Janssen, and Takeda. The remaining authors declare no conflict of interest.

References

1. Soria JC, Ohe Y, Vansteenkiste J, et al. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. *N Engl J Med*. 2018;378:113–125.
2. Leonetti A, Sharma S, Minari R, Perego P, Giovannetti E, Tiseo M. Resistance mechanisms to osimertinib in EGFR-mutated non-small cell lung cancer. *Br J Cancer*. 2019;121:725–737.
3. Sato Y, Saito G, Fujimoto D. Histologic transformation in lung cancer: when one door shuts, another opens. *Ther Adv Med Oncol*. 2022;14:17588359221130503.
4. Rivera-Concepcion J, Lo YC, Uprety D, Adjei AA, Ernani V, Leventakos K. A challenging case of stage IV EGFR-mutant lung cancer with histologic transformation and multiple resistance mechanisms. Current Problems in Cancer. *Case Rep*. 2024;13:100284.
5. Offin M, Chan JM, Tenet M, et al. Concurrent RB1 and TP53 alterations define a subset of EGFR-mutant lung cancers at risk for histologic transformation and inferior clinical outcomes. *J Thorac Oncol*. 2019;14:1784–1793.
6. Quintanal-Villalonga A, Taniguchi H, Zhan YA, et al. Multiomic analysis of lung tumors defines pathways activated in neuroendocrine transformation. *Cancer Discov*. 2021;11:3028–3047.
7. Marcoux N, Gettinger SN, O'Kane G, et al. EGFR-mutant adenocarcinomas that transform to small-cell lung cancer and other neuroendocrine carcinomas: clinical outcomes. *J Clin Oncol*. 2019;37:278–285.
8. Zhang CY, Sun H, Su JW, et al. A potential treatment option for transformed small-cell lung cancer on PD-L1 inhibitor-based combination therapy improved survival. *Lung Cancer*. 2023;175:68–78.
9. Trigo J, Subbiah V, Besse B, et al. Lurbinectedin as second-line treatment for patients with small-cell lung cancer: a single-arm, open-label, phase 2 basket trial. *Lancet Oncol*. 2020;21:645–654.
10. Chakraborty S, Coleman C, Manoj P, et al. De novo and histologically transformed small-cell lung cancer is sensitive to lurbinectedin treatment through the modulation of EMT and NOTCH signaling pathways. *Clin Cancer Res*. 2023;29:3526–3540.
11. Desai A, Smith CJ, Ashara Y, et al. Real-world outcomes with lurbinectedin in second-line setting and beyond for extensive stage small cell lung cancer. *Clin Lung Cancer*. 2023;24:689–695.e1.
12. Aix SP, Ciuleanu TE, Navarro A, et al. Combination lurbinectedin and doxorubicin versus physician's choice of chemotherapy in patients with relapsed small-cell lung cancer (Atlantis): a multicentre, randomised, open-label, phase 3 trial. *Lancet Respir Med*. 2023;11:74–86.
13. Ding L, Raphael BJ, Chen F, Wendl MC. Advances for studying clonal evolution in cancer. *Cancer Lett*. 2013;340:212–219.