

CASE REPORT

Durable response to durvalumab-based immunochemotherapy in small-cell lung carcinoma transformation from *EGFR*-mutant non-small cell lung cancer: A case report

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Abstract

Combined small-cell lung carcinoma (C-SCLC) is small-cell lung carcinoma (SCLC) with added non-small-cell morphology. We report a case of epidermal growth factor receptor (*EGFR*) mutation-positive C-SCLC in an 84-year-old patient with metastatic brain lesions who developed intrinsic resistance to osimertinib, a tyrosine kinase inhibitor (TKI). The patient was diagnosed with small-cell transformation of non-small-cell lung carcinoma (NSCLC) and received 6 cycles of dose-adjusted durvalumab with etoposide and carboplatin. In December 2021, the patient received the seventeenth cycle of maintenance durvalumab 19 months after diagnosis and showed continued treatment response and disease control. Comprehensive molecular profiling and repeated biopsies are recommended in NSCLC patients who progress on first-line *EGFR*-TKIs. Durvalumab in combination with chemotherapy appears to be beneficial for *EGFR* mutation-positive C-SCLC patients that are resistant to TKIs.

KEYWORDS

case reports, combined modality therapy, immunochemistry, immunotherapy, tumor biomarkers

INTRODUCTION

Small-cell lung carcinoma (SCLC) is a more aggressive form of lung cancer than non-small-cell lung carcinoma (NSCLC).¹ Approximately 3%–10% of patients with NSCLC and an epidermal growth factor receptor (*EGFR*) mutation may undergo transformation to SCLC.² Approximately 6% of transformation cases are combined small-cell lung carcinoma (C-SCLC), which involve SCLC and NSCLC components.² C-SCLC represents ~5%–10% of all SCLC cases,^{3,4} and conventional treatment options include surgery, radiotherapy, and chemotherapy.³ However, there are important prognostic and therapeutic differences between SCLC and C-SCLC owing to different cancer biologies.^{3,5} Treatment options for C-SCLC are limited, and patients with C-SCLC may have reduced sensitivity to chemotherapy with no optimal chemotherapeutic regimens available.^{3,6–8} This lack of knowledge applies especially to C-SCLC cases that involve an *EGFR* mutation.

Case report

An 84-year-old hypertensive ex-smoker with a history of tuberculosis presented with headache and blurred vision in August 2019 (Figure 1). Computed tomography (CT) of the thorax revealed a 2.36 cm diameter tumor in the left upper lobe of the lung. Magnetic resonance imaging (MRI) of the brain showed a focal lesion with a mixed cystic-solid component (2.9 × 2.9 × 2.5 cm) in the left superior temporal gyrus and a hyperintense lesion in the left occipital lobe. Adenocarcinoma was diagnosed with a CT guided-needle biopsy in July 2019. Initial staging determined that the patient had T2N0M1b stage IV cancer.⁹ Hotspot mutations were detected with fluorescent in situ hybridization and bidirectional standard sequencing. The tumor tested negative (<1%) for programmed death-ligand 1 (PD-L1), but harbored an *EGFR* exon 21-point mutation (L858R). Such mutations may account for around 25% of *EGFR* mutations in SCLC transformation cases.² Other sites of

metastasis were excluded by positron emission tomography-CT (PET-CT). Surgical intervention was avoided because of the patient's age and brain metastasis.

Instead, the patient received 50Gy stereotactic body radiation therapy (SBRT) in five alternate-day fractions at 80% isodose line (I.L.) for the primary lung tumor, and

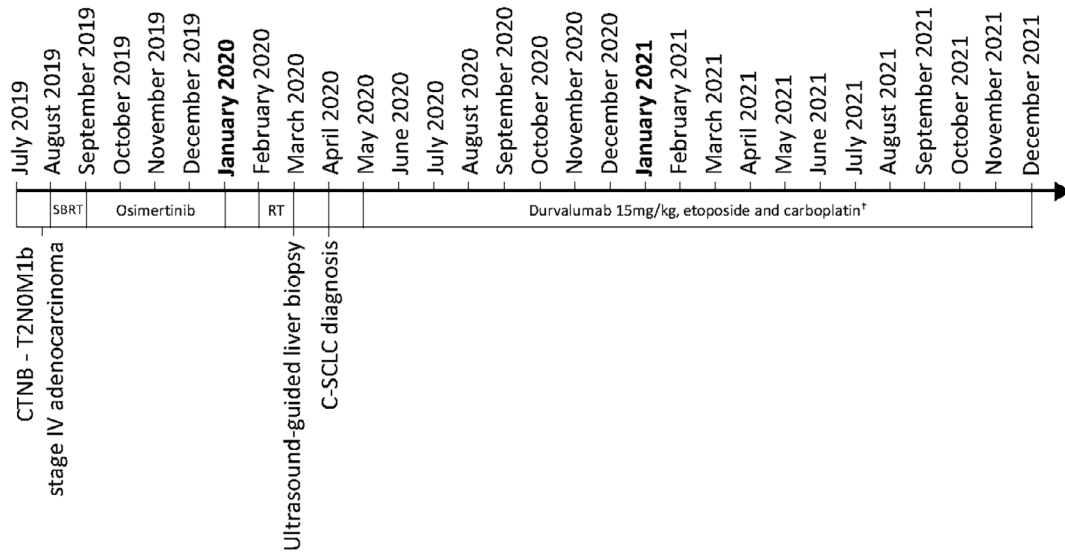


FIGURE 1 Collective treatment time course from patient presentation in August 2019 to December 2021. Etoposide and carboplatin both prescribed at 70% of the standard dose. Triple therapy was prescribed for 6 cycles, followed by maintenance durvalumab ongoing in December 2021. C-SCLC, combined small-cell lung carcinoma; CTNB, computed tomography-guided needle biopsy; RT, radiotherapy (whole brain); SBRT, stereotactic body radiation therapy

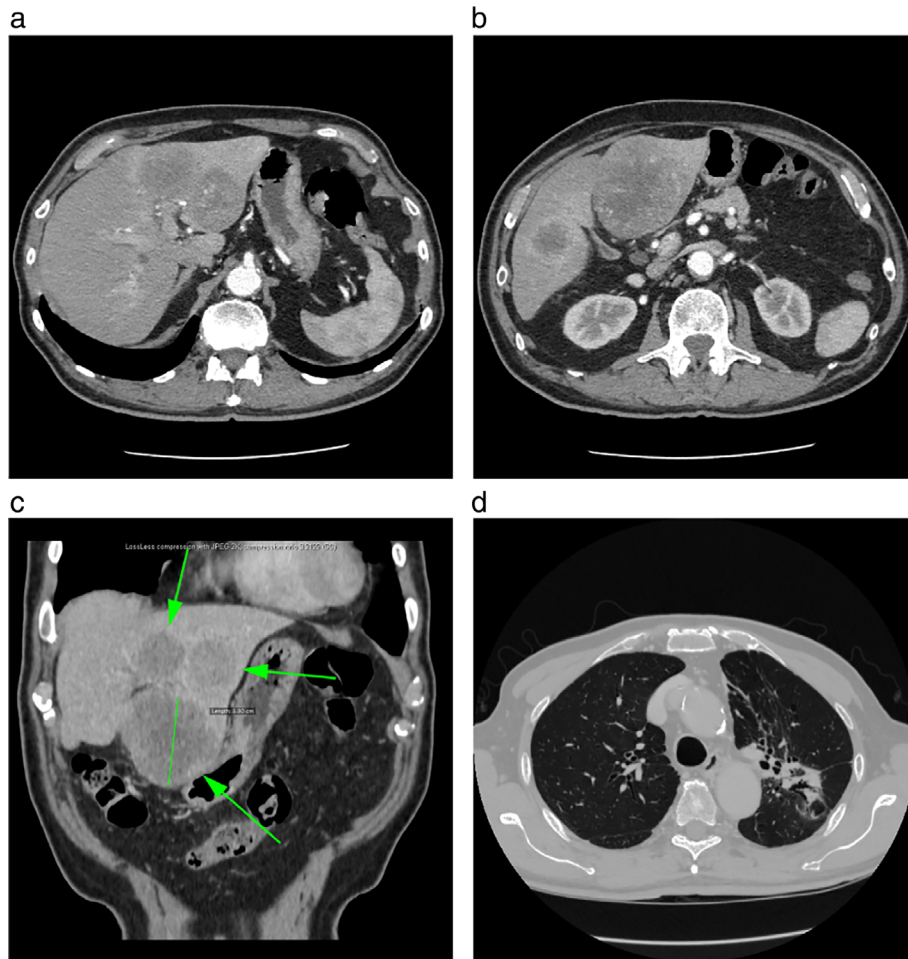


FIGURE 2 (a),(b),(c) Liver metastases demonstrated by computed tomography (CT) scan obtained in April 2020 before triple therapy and (d) lung scan demonstrated by CT, obtained in April 2020 post-radiotherapy

stereotactic radiosurgery using a linear accelerator for brain metastases at 16Gy and 74% I.L for the temporal lobe and 22Gy at 77% I.L for the occipital lobe. The patient was prescribed osimertinib, a third generation *EGFR*-tyrosine kinase inhibitor (TKI), following radiotherapy in September 2019.

Treatments and observations

Nine weeks post-SBRT, in January 2020, a chest X-ray showed that the primary lung tumor size was compatible with post-radiotherapy changes. An MRI indicated the brain tumor had shrunk from 3.5 to 1.9 cm. New lesions in the right frontal (8.2×5.6 mm) and left occipital lobe (5.1×6.2 mm) suggested intrinsic resistance to osimertinib. In February 2020, the patient received whole brain radiation therapy, which was generally well-tolerated, with mild nausea during the first few days of treatment (Figure 1).

The patient was subsequently screened for inclusion in a clinical trial, and baseline CT and MRI found multiple hypovascular lesions in both liver lobes (up to 2.7 cm in segment III). An ultrasound-guided liver biopsy in March 2020 showed both small-cell and non-small-cell carcinoma components. In April 2020, the patient was diagnosed with

EGFR mutation-positive lung adenocarcinoma with small-cell transformation (CT images in Figure 2). The patient was excluded from the clinical trial because of the mixed histology. Cells were found to be focally positive for synaptophysin, CK8/18, TFF-1, and CDX2 via immunostaining.

In May 2020, treatment began with dose-adjusted triple therapy comprising durvalumab (a PD-L1 inhibitor) 15 mg/kg, etoposide, and carboplatin (at 70% of the standard doses) every 3 weeks.¹⁰ The reduced durvalumab dose was modified from the CASPIAN¹¹ and PACIFIC trial regimen⁴ because of the patient's age. Triple therapy was well-tolerated, with weight loss in the first week, but no other systemic symptoms. No adverse event-related dose adjustments were required, and the patient's weight remained stable afterward.

A CT of the thorax and upper abdomen in July 2020 after 3 cycles of triple therapy showed dramatic shrinkage of the bilobed liver mass from $7.1 \times 6.4 \times 5.8$ to $2.6 \times 1.8 \times 2.2$ cm, with no new lesions (Figure 3). Carcinoembryonic antigen levels declined from 37.4 ng/mL at baseline to 5.8 ng/mL at final follow-up. In January 2021, PET-CT showed a reduction in liver metastases size to 0.6 cm diameter and a reduction in metabolic activity to a maximum standardized uptake value (SUVmax) of 2.7. MRI indicated that most brain metastases had disappeared. By

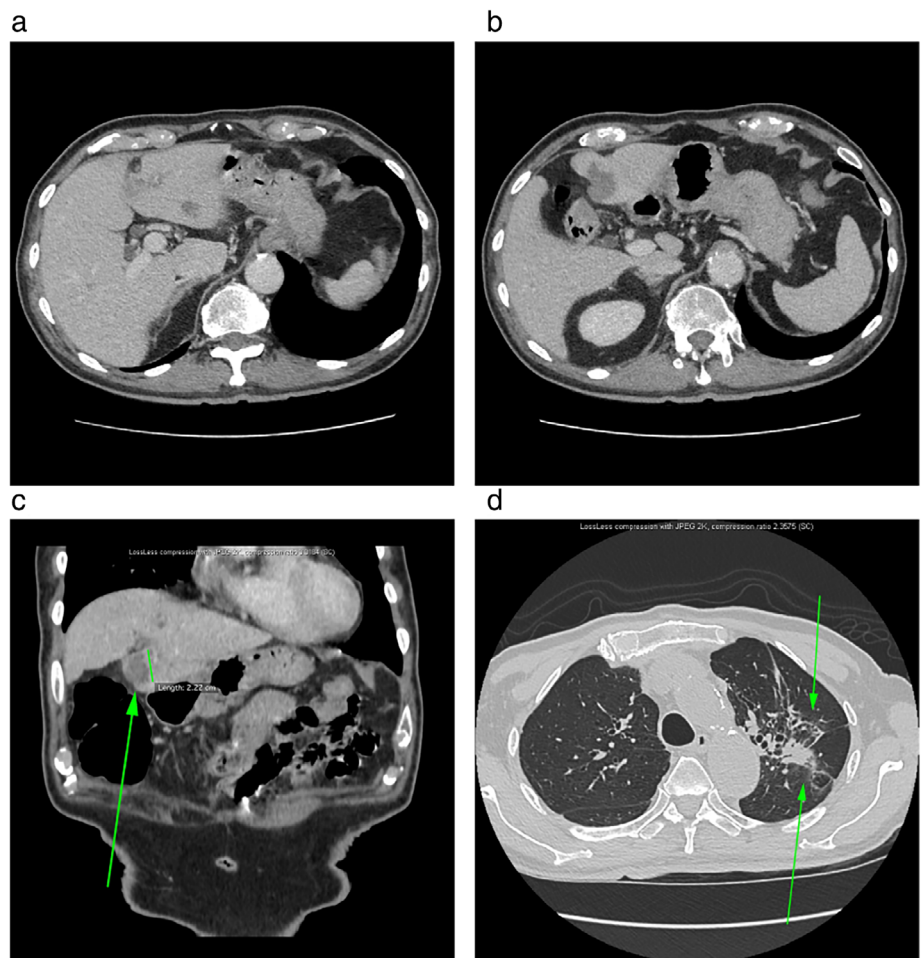


FIGURE 3 (a) Liver metastases demonstrated by computed tomography (CT) scan obtained in July 2020 after 3 cycles of triple therapy. (b) Liver metastases demonstrated by CT scan obtained in July 2020 after 3 cycles of triple therapy. (c) Liver metastases demonstrated by CT scan obtained in July 2020 after 3 cycles of triple therapy. (d) Lung scan demonstrated by CT scan obtained in July 2020 post-radiotherapy

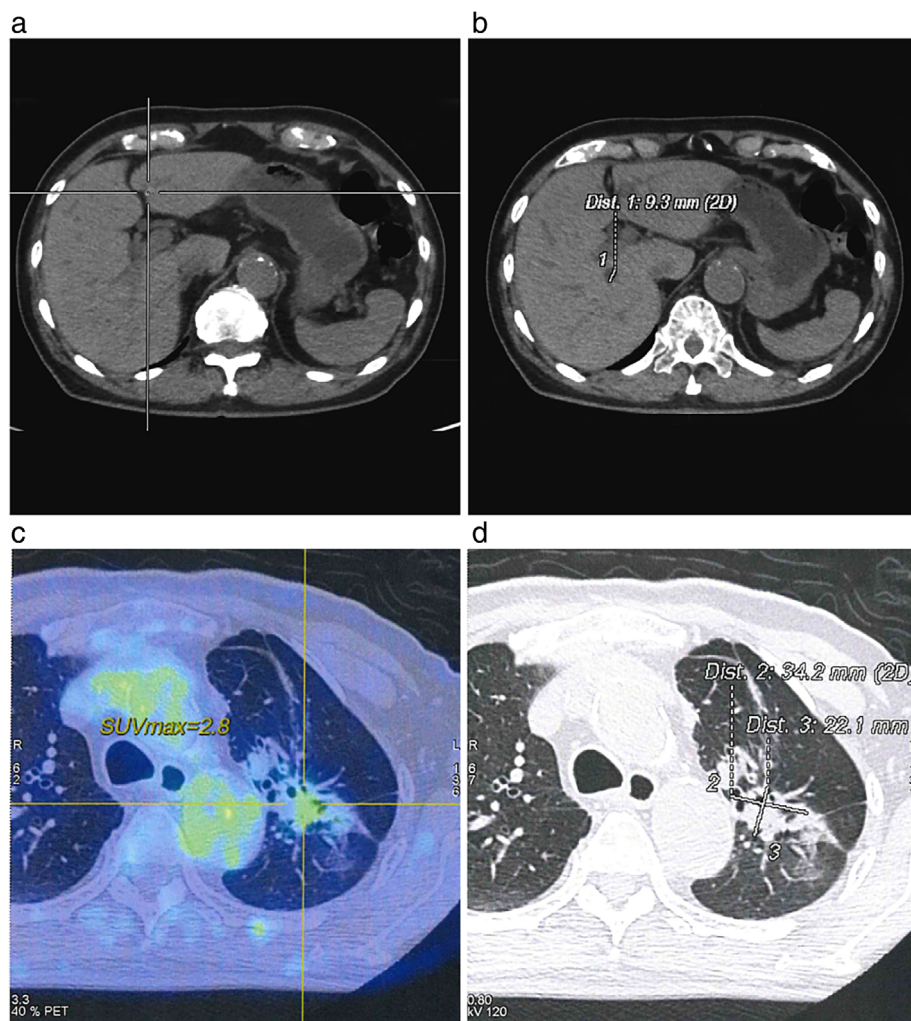


FIGURE 4 (a),(b) Liver by computed tomography (CT) scan, and (c) lung by 2-[fluorine-18] fluoro-2-deoxy-D-glucose positron emission tomography, and (d) by CT scan, all obtained in December 2021 on seventeenth cycle of maintenance durvalumab

December 2021, 19 months from diagnosis, the patient had received 6 cycles of triple therapy and was receiving the seventeenth cycle of maintenance durvalumab. PET-CT showed almost complete response in the liver with no 18F-fluorodeoxyglucose avid metastasis. There was a fibrotic scar ($3.4 \times 2.2 \times 4.5$ cm) in the left upper lung lobe with SUVmax of 2.8 that showed minimal, stable changes post-radiotherapy (Figure 4).

DISCUSSION

Clinical trial data suggested that ~5%–10% of patients with *EGFR* mutation-positive lung adenocarcinoma have primary resistance to *EGFR*-TKIs.^{12–14} Histological transformation of *EGFR*-mutant adenocarcinoma to SCLC, reported in 14% of cases within a case series,⁷ was likely the cause of progression on osimertinib seen in this case study. The time to osimertinib resistance was short, at around 4 months in this case. This case exemplifies the importance of undertaking additional molecular testing and repeated biopsies within 6 months of starting first-line *EGFR*-TKIs to detect possible histological transformation. Next-generation sequencing is

recommended to detect mutations that promote intrinsic resistance to TKIs, such as *HER2*, *PIK3CA* mutations, and *MET* amplification when determining optimal second-line treatment.¹²

Effective treatment options for C-SCLC have been limited. Chemotherapy and radiotherapy appear to be less sensitive in patients with C-SCLC than “pure” SCLC because of inherent differences in tumor biology.^{3,7} For example, Men et al.⁸ Found no significant difference between C-SCLC patients who received platinum-based chemotherapy versus those who did not (with a median 3-year overall survival [OS] of 37.7% and 35.4%, respectively). Furthermore, metastasis was the most common cause of treatment failure in 84% of patients that received chemotherapy.⁸

In recent years, two immunotherapy agents were approved as first-line treatments for extensive-stage (ES) SCLC.^{11,15,16} Atezolizumab with carboplatin and etoposide has been associated with a significant improvement in median OS for patients with ES-SCLC (12.3 months vs. 10.3 months in chemotherapy alone group).¹⁵ The CASPIAN study also showed a significant improvement in median OS in ES-SCLC patients receiving

durvalumab and platinum–etoposide (13.0 months) compared with platinum–etoposide alone (10.3 months; HR, 0.73, 95% CI, 0.59–0.91; $p = 0.0047$) in first-line setting.¹¹

Given the aggressive nature of C-SCLC, the addition of immunotherapy to chemotherapy may exert better disease control than chemotherapy alone. A durable response from durvalumab-based immuno-chemotherapy of up to 19 months (as of December 2021) was observed in this elderly patient, whereas previous studies have indicated a median OS of only 9 months with platinum-based chemotherapy alone in patients with *EGFR* mutated NSCLC that transformed to SCLC.⁶

Given the paucity of data and limited effective treatment options available for C-SCLC that has transformed from *EGFR* mutation positive NSCLC, this case report provides valuable information that suggests immunotherapy treatments such as durvalumab may result in considerable improvements to patient outcomes when combined with chemotherapy. Further research will confirm the value of immunochemotherapy in these patients.

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CONFLICT OF INTEREST

The author declares no conflict of interest.

DATA AVAILABILITY STATEMENT

No data sets were generated or analyzed for inclusion in this report.

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