Case Report

Osimertinib in uncommon *EGFR* exon 21 L861R and *EGFR* exon 18 deletion-insertion mutant non-small cell lung cancer—case report

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Background: Tyrosine kinase inhibitors (TKIs) have changed the treatment landscape for patients with advanced non-small cell lung cancer (NSCLC) found to have oncogene-driven activating epidermal growth factor receptor (*EGFR*) mutations. Whilst there have been a handful of case reports of sensitivity to first-generation TKIs in *EGFR* L861R mutations, the efficacy of the third-generation TKI osimertinib in NSCLC patients with *EGFR* L861R and *EGFR* exon 18 deletion-insertion mutations is limited.

Case Description: We report two patients from our institution with uncommon *EGFR* mutations treated with first-line osimertinib. Our first patient, a 72-year-old male with metastatic lung adenocarcinoma was identified to harbour a rare *EGFR* L861R mutation and was commenced on osimertinib. After a follow-up period of 18 months, the patient is continuing to experience treatment benefit with imaging showing a good partial response. The second patient, a 60-year-old male also with metastatic lung adenocarcinoma and an *EGFR* exon 18 deletion-insertion mutation achieved a partial response for 6.6 months. Upon progression, he was commenced on carboplatin and pemetrexed chemotherapy however died from subsequent pneumonia. He had an overall survival (OS) from time of diagnosis of 7.6 months.

Conclusions: We demonstrate clinical efficacy of first-line osimertinib in the treatment of advanced NSCLC harbouring uncommon *EGFR* L861R and *EGFR* exon 18 deletion-insertion mutations. These results may be suggestive of the wider applicability of osimertinib in the treatment of uncommon *EGFR* mutant NSCLC.

Keywords: Uncommon epidermal growth factor receptor *EGFR* mutations (uncommon *EGFR* mutations); osimertinib; non-small cell lung cancer (NSCLC); case report

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Introduction

Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) have become the standard of care treatment for patients with *EGFR* mutant advanced non-small cell lung cancer (NSCLC). The common sensitising exon 19 deletion and L858R *EGFR* mutations account for the majority of *EGFR* mutant NSCLC diagnoses. Uncommon *EGFR* mutations are comprised of a highly heterogenous group with alterations within *EGFR* exons 18–21 (1). As next-generation sequencing (NGS) has become more increasingly utilised in the diagnoses of lung cancers, these uncommon *EGFR* mutations are being increasingly identified. Key studies, such as FLAURA which established osimertinib as first-line standard of care only included participants harbouring exon 19 deletion and L858R *EGFR* mutations (2). Both *EGFR* exon 21 L861R and *EGFR* exon 18 deletion-insertion are rare with an estimated prevalence of <1% and 0.3% respectively thus creating a challenge to determine whether these subtypes of *EGFR* mutations will respond to TKI therapy (3,4). There have been retrospective studies documenting benefit from osimertinib in subtypes of uncommon *EGFR* mutations and compound mutations, however there is limited published evidence of its efficacy in *EGFR* exon 21 L861R and *EGFR* exon 18 deletion-insertions (5,6). We present this article in accordance with the CARE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-788/rc).

Highlight box

Key findings

- These two case reports demonstrate the efficacy of osimertinib in epidermal growth factor receptor (*EGFR*) exon 21 L861R and *EGFR* exon 18 deletion-insertion mutant non-small cell lung cancer (NSCLC).

What is known and what is new?

- Osimertinib is widely accepted as the first-line treatment in patients with NSCLC harbouring common *EGFR* exon 19 deletion and L858R mutations.
- The efficacy of osimertinib in patients with uncommon *EGFR* mutations remains less well characterised, which presents a challenge to treating clinicians recommending tyrosine kinase therapy in this situation.

What is the implication, and what should change now?

- The case report provides further evidence of the efficacy of osimertinib for the treatment of uncommon *EGFR* mutations.

Case presentation

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki (as revised in 2013). Written informed consent for publication of this case report and accompanying images was not obtained from the patients or the relatives after all possible attempts were made and the article has been sufficiently anonymized to cause no harm to the patients or their family.

Patient A

A 72-year-old male with an ongoing heavy smoking history presented to Monash Health in July 2022 with a 1-month history of non-productive cough, chest tightness and dyspnoea. His medical history consisted of an ischaemic stroke in 2007 without any residual neurological deficits and hyperlipidaemia to which he was on aspirin and fenofibrate. A chest X-ray showed a left-sided pleural effusion that was aspirated revealing malignant cytology with immunohistochemistry demonstrating lung adenocarcinoma. A follow-up computed tomography (CT) showed an irregular spiculated mass in the left upper lobe. The patient was diagnosed with stage IV lung adenocarcinoma.

NGS was performed on DNA from patient tissue using Illumina TruSight Tumour 15 panel followed by massively parallel sequencing performed on an Illumina MiniSeq as shown in *Figure 1*. This detected an *EGFR* p.L861R mutation with concurrent *TP53* p.L194F mutation.

The patient was commenced on first-line treatment with osimertinib 80 mg daily from July 2022. His symptoms rapidly improved with treatment and at the time of the first assessment performed at 6 weeks (*Figure 2A*), there was a partial response in the left upper lobe malignancy and near complete resolution of his left-sided pleural effusion, confirmed using Response Evaluation Criteria in Solid Tumours 1.1 (RECIST 1.1). At 6 weeks (*Figure 2B*), there was further reduction of the primary left upper lobe lesion. His 6-month CT imaging as shown in *Figure 2C* shows an ongoing partial response. At his recent follow-up period of 18 months, the patient continues to experience treatment benefit. The patient's only adverse events reported from treatment are grade 1 acneiform rash and grade 1 mucositis.

Patient B

A 60-year-old never-smoker presented to Monash Health in

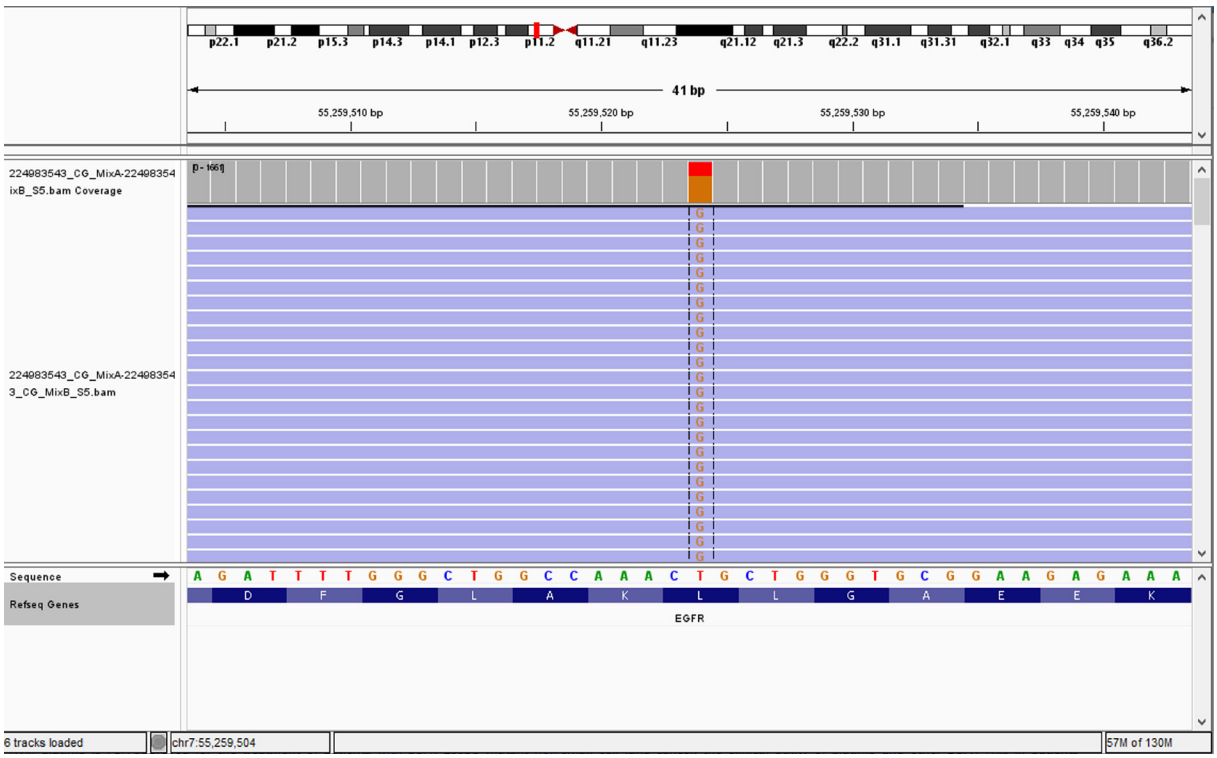

Figure 1 *EGFR* p.L861R mutation on chromosome 7 (chr7:55,259,504) identified by DNA-NGS with TruSight Tumour 15 panel. *EGFR*, epidermal growth factor receptor; NGS, next-generation sequencing.

April 2022 after weeks of worsening thoracic back pain. His past medical history consisted of nasopharyngeal carcinoma treated definitively with radiotherapy in 1995. A positron emission tomography (PET) scan showed a large left lower lobe lesion, bilateral hilar, mediastinal, cervical and axillary lymphadenopathy as well as metastasis to T8 vertebral body, right adrenal gland and gluteus muscle. An endoscopic biopsy revealed a mixed adeno-squamous NSCLC. NGS panel (similar platform as patient A's) revealed an *EGFR* exon 18 deletion-insertion (p.E709_T710) as shown in *Figure 3* and *TP53* mutation.

This patient was commenced on first-line osimertinib 80 mg daily from April 2022. He experienced an initial improvement in his pain, functional status, and marginal reduction in size of the left lower lobe primary and hilar lymph nodes at 6 weeks (stable disease by RECIST 1.1) when compared to baseline imaging as shown in *Figure 4A,4B*. At time of second assessment, there was interval metabolic progression in the left lower lobe lung primary as well as in local and distant nodes with an overall progression-free survival (PFS) of 6.6 months (*Figure 4C*). Subsequently, he was commenced on second-line carboplatin and pemetrexed chemotherapy and received one cycle prior to presenting to hospital with pneumonia and respiratory failure and died with an overall survival (OS) of 7.6 months since commencement of treatment.

Discussion

Here, we report the clinical activity of osimertinib in the treatment of two patients with advanced NSCLC harbouring uncommon *EGFR* mutations. Both these patients derived benefit from treatment with osimertinib. To the best of our knowledge, this is the first Australian report of the clinical effect of first-line osimertinib in patients carrying exon 21 L861R and exon 18 deletion-insertion *EGFR* mutations.

The varied incidence of uncommon *EGFR* mutant advanced NSCLC has meant that there is limited prospective clinical trial data that evaluates the efficacy of EGFR TKIs in patients harbouring uncommon *EGFR* mutations. Of these uncommon *EGFR* mutations, the most 'common' consist of substitution mutations G719X, S768I, L861Q and exon 20 insertions (5,7). Even amongst the uncommon

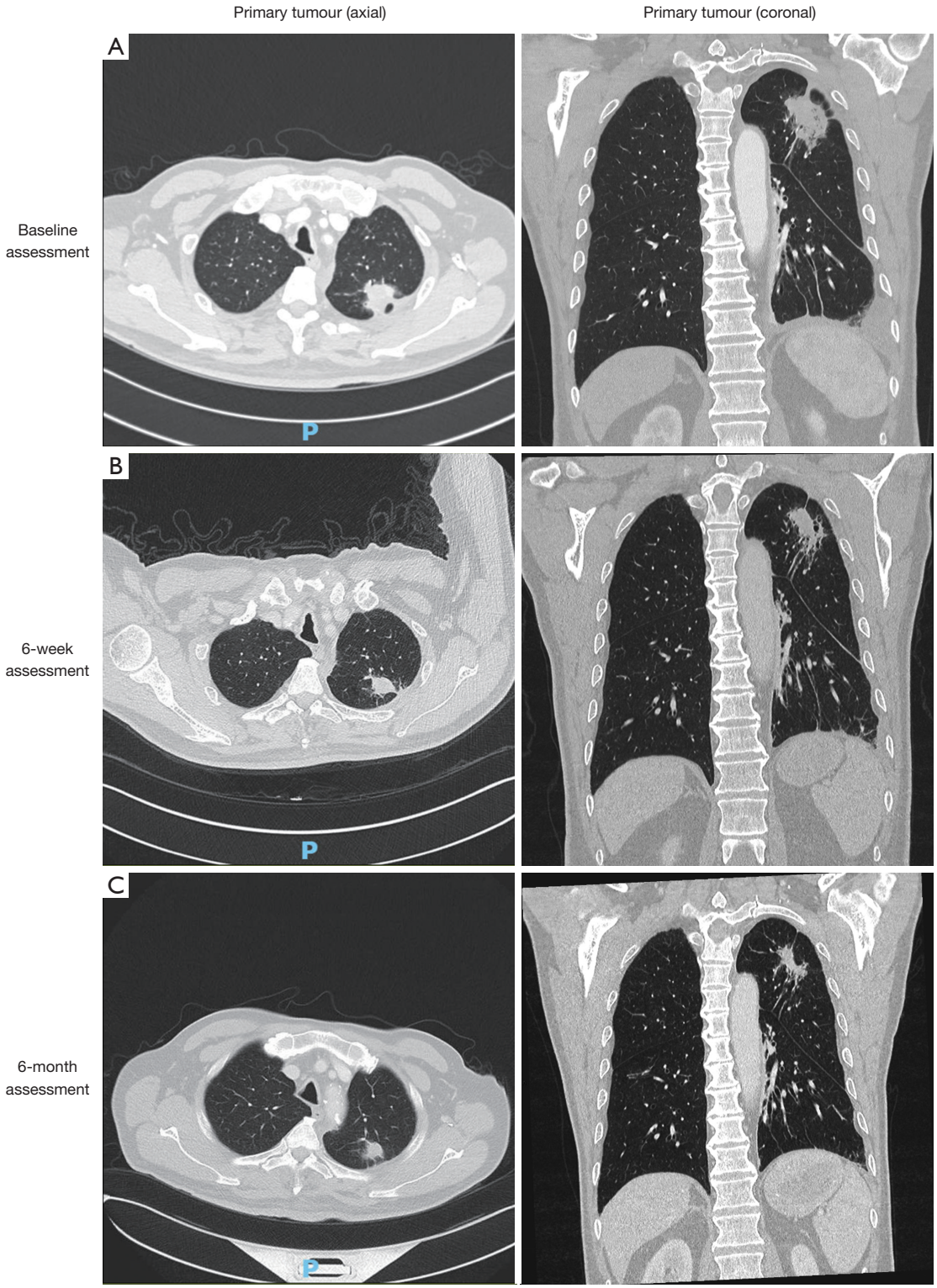

Figure 2 Chest CT scans. (A) Pre-treatment 3.6 cm primary left upper lobe lung cancer. (B) Response to treatment of the primary tumour (2.0 cm) at 6 weeks. (C) Further response of the primary tumour at 6 months (1.7 cm). CT, computed tomography.

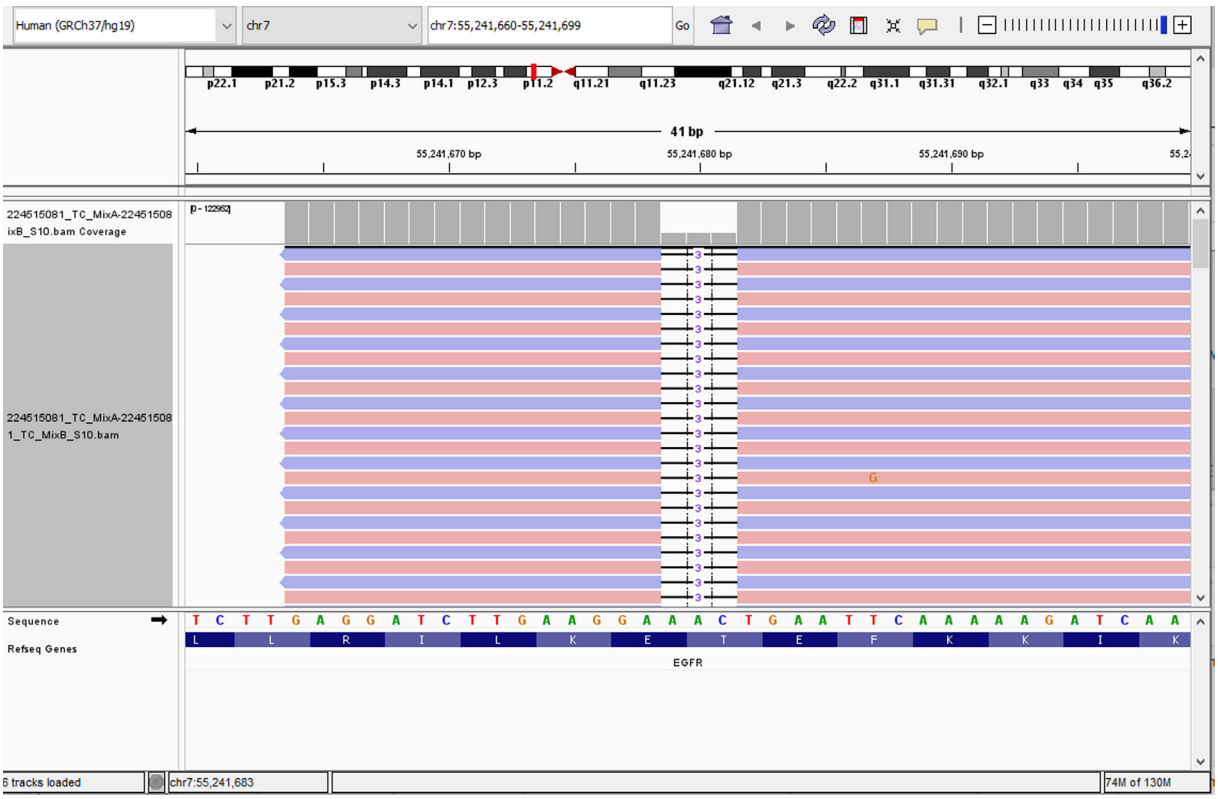

Figure 3 *EGFR* exon 18 deletion-insertion (p.E709_T710) on chromosome 7 (chr7:55,241,683) identified by DNA-NGS with TruSight Tumour 15 panel. *EGFR*, epidermal growth factor receptor; NGS, next-generation sequencing.

EGFR mutations there are different PFS patterns. The combined *post hoc* analysis of LUX-Lung 2, LUX-Lung 3, and LUX-Lung 6 trials demonstrated that NSCLC patients harbouring G719X mutations in *EGFR* exon 18 treated with afatinib had an objective response rate (ORR) of 77.8%, with a median PFS of 13.8 months (8). Similarly, in the same analysis, patients with L861Q mutations in *EGFR* exon 21 treated with afatinib had an ORR of 56% with a median PFS of 8.2 months and an OS of 17.1 months (8). Similarly, the rare S768I mutation in *EGFR* exon 20 has also been shown to have the longest PFS of 14.7 months. Recently, both a retrospective and prospective phase 2 non-randomised study (UNICORN) demonstrated clinical activity of osimertinib in uncommon *EGFR* mutations with an ORR of up to 66% (9,10). Despite this, none of the trials included patients with *EGFR* exon 18 deletion-insertion (p.E709_T710) which resulted in our decision to utilise osimertinib instead of afatinib based on its superior intracranial efficacy and favourable side effect profile.

Conversely, there is increasing evidence to suggest that EGFR TKIs are ineffective in NSCLC patients with *EGFR* exon 20 insertion mutations (11-13). The retrospective analysis by Wu *et al.* demonstrated a substantially poorer response rate in patients with *EGFR* exon 20 insertions treated with EGFR TKIs compared to *EGFR* exon 19 deletions and *EGFR* L858R substitutions with inferior ORR (0% *vs.* 47.5%, P=0.003), median PFS (1.4 *vs.* 5.0 months, P<0.001), and median OS (4.8 *vs.* 15.0 months, P=0.242) (14). This has led to *EGFR* exon 20 insertions to be categorised as a distinct entity separate from other *EGFR* mutations and has led to the development of *EGFR* exon 20 insertion inhibitors; mobocertinib and amivantamab which have demonstrated an improvement in PFS of 7.3 and 8.3 months, respectively (15,16).

From the American Association for Cancer Research (AACR) Project Genomics Evidence Neoplasia Information Exchange (GENIE), an international pan-cancer registry of real-world data, *EGFR* exon 21 L861R substitutions are found in approximately 0.03% of cases (17). Previous case reports have shown activity of earlier generation TKIs in

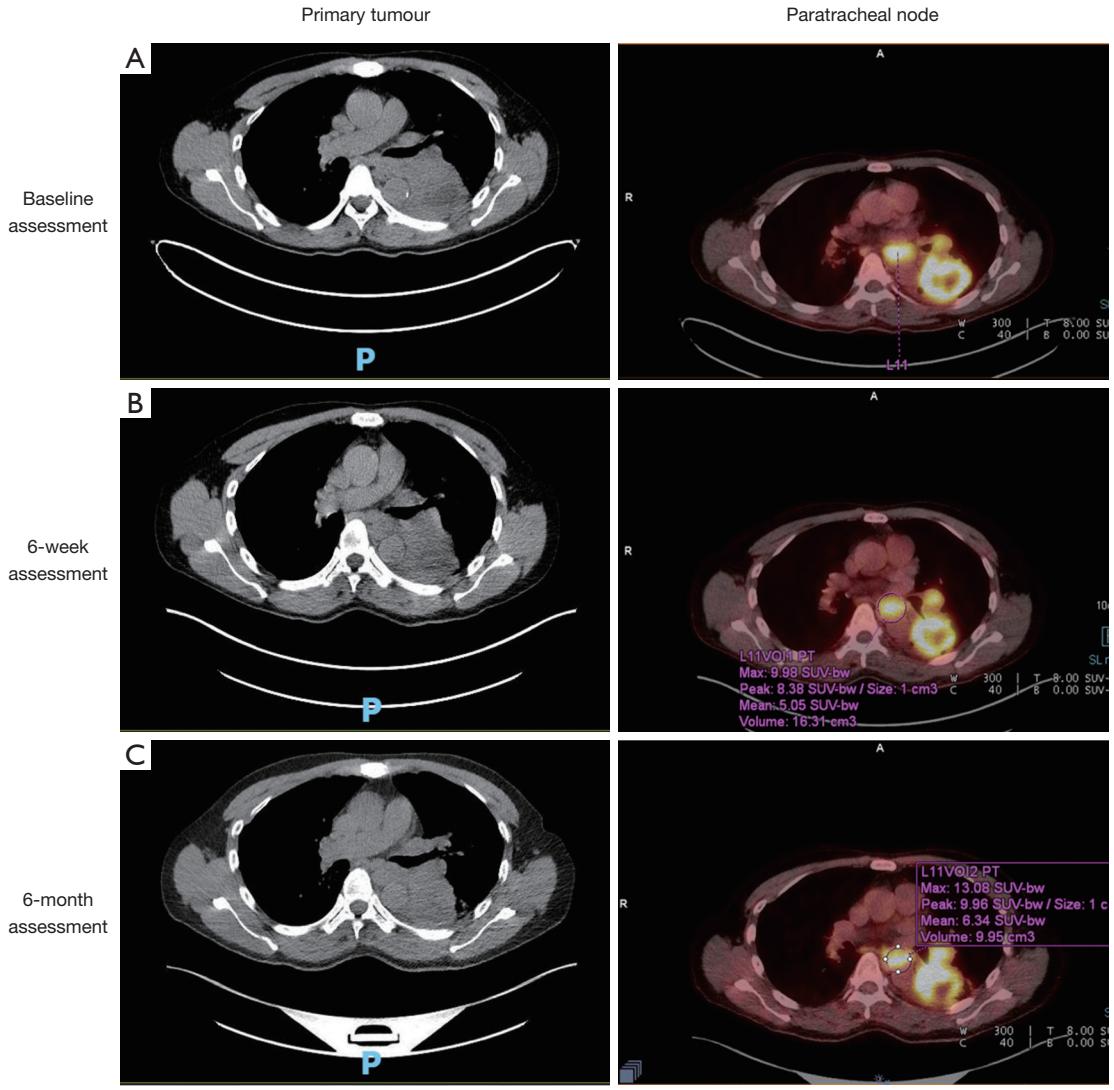

Figure 4 Chest CT and PET scan. (A) Pre-treatment 6.4 cm primary left lower lobe lung cancer and hilar lymphadenopathy. (B) Marginal reduction in size of the left lower lobe tumour (6.2 cm) and FDG-avidity in the hilar lymphadenopathy at 6 weeks. (C) No change in size of the primary tumour at 6 months with increasing FDG-avidity in the hilar lymphadenopathy and new paratracheal nodal metastases (not shown). SUV, standardized uptake value; CT, computed tomography; PET, positron emission tomography; FDG, fluorodeoxyglucose.

the treatment of *EGFR* L861R mutant NSCLC. In one report, an 84-year-old with *EGFR* L861R mutant NSCLC obtained a partial response with second-line afatinib and bevacizumab (18). Similarly in a case series, a 34-year-old female never smoker who was initially treated with cisplatin, gemcitabine and bevacizumab with partial response was subsequently commenced on erlotinib however experienced disease progression after 2 months (19). Another patient found to have an L861R and R831C *EGFR* germline co-mutation was treated with gefitinib and derived a partial response (20). In a retrospective series, Ji *et al.* identified one patient with an L861R and V774M mutation that derived stable disease with osimertinib (5).

There is little evidence regarding the efficacy of third-generation osimertinib in patients with *EGFR* L861R and *EGFR* exon 18 deletion-insertion mutations. Our case report highlights the ongoing benefit of osimertinib in patient A with *EGFR* L861R mutation at the follow-up period of 18 months whilst patient B with *EGFR* exon 18 deletion-insertion mutation achieved a PFS of 6.6 months.

We hypothesise that the reason patient B experienced a relatively short PFS was due to the mixed adenosquamous histology which has been shown to confer a poorer prognosis (21). Of note, both patients co-exhibited *TP53* mutations which have been shown in recent literature to be associated with a poorer prognosis and reduced response to EGFR TKI therapy (22-25). Our study is limited as it is a case report and we did not attempt a re-biopsy in patient B or use circulating tumour DNA (ctDNA) analysis at time of disease progression as he needed to promptly commence second-line chemotherapy. It remains unknown whether the common resistance mechanisms to osimertinib such as C797S mutations, MET amplification, activation of RAS-MAPK or RAS-PI3K pathways were responsible for disease relapse (26). Recent phase 3 trials MARIPOSA and FLAURA 2 have demonstrated an improved median PFS with upfront treatment intensification using EGFR TKI-combination therapy compared with EGFR TKI monotherapy alone in patients with common *EGFR* mutations and further study is required to understand if this can be translated to patients with uncommon *EGFR* mutations (27,28).

Conclusions

In conclusion, there is a paucity of data for treatment in patients with uncommon *EGFR* mutations. Our case report further adds to the growing body of literature demonstrating the activity of osimertinib in uncommon *EGFR* mutant NSCLC. Given uncommon *EGFR* mutations show variable sensitivity to treatment, this further highlights the importance of molecular tumour boards to assist in clinical decision making to ensure that these patients are not inadvertently excluded from being treated with EGFR TKIs. Further research is needed to ascertain whether EGFR TKI combination therapies can be utilised in the treatment of uncommon *EGFR* mutations.

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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-23-788/rc

Peer Review File: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-788/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-788/coif). S.A. reports speaker fees from Merck-Sharpe & Dohme, Astra Zeneca, Roche, Bristol-Myers Squibb; travel support from Astra Zeneca, Roche, Merck-Sharpe & Dohme; non-financial aid from Astra Zeneca, Pfizer; and Advisory Boards of Boehringer Ingelheim, Roche. The other 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 institutional and/or national research committee(s) and with the Declaration of Helsinki (as revised in 2013). Written informed consent for publication of this case report and accompanying images was not obtained from the patients or the relatives after all possible attempts were made and the article has been sufficiently anonymized to cause no harm to the patients or their family.

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