



Activity of osimertinib in a patient with stage IV non-small cell lung cancer harboring *HER2* exon 19, p.L755P mutation: case report

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Background: Recurrent in-frame insertions within exon 20 causing duplication of amino acids Tyrosine-Valine-Methionine-Alanine (YVMA) represent 80% of all *HER2* alterations in non-small cell lung cancer (NSCLC). *HER2* tyrosine kinase inhibitors (TKI), anti-*HER2* monoclonal antibodies and *HER2* directed antibody-drug conjugates have been evaluated in patients with *HER2* mutated NSCLC. Limited data are available regarding the activity of these agents in exon 19 alterations. Osimertinib, a 3rd generation EGFR-TKI, has been found in pre-clinical studies to decrease growth of NSCLC with *HER2* exon 19 aberrations.

Case Description: A 68-year-old female with a past medical history of type 2 diabetes and minimal smoking was diagnosed with stage IV NSCLC. Next generation sequencing on tumor tissue demonstrated an ERBB2 exon 19 c.2262_2264delinsTCC, p.(L755P) mutation. After five lines of treatment that included chemotherapy, chemoimmunotherapy and investigational agents the patient's disease was progressing. At this time her functional status remained good, therefore clinical trials were explored however, none were available. Based on findings from pre-clinical studies, the patient was commenced on osimertinib 80 mg OD and achieved a partial response (PR) according to RESIST criteria both intra- and extracranially.

Conclusions: This is the first report to our knowledge to demonstrate activity of osimertinib in a patient with NSCLC harboring *HER2* exon 19, p.L755P mutation resulting in intra- and extracranial response. In the future, osimertinib could become a targeted treatment for patients harboring exon19 ERBB2 point mutations.

Keywords: Case report; non-small cell lung cancer (NSCLC); *HER2*; osimertinib; ERBB2 exon 19 p.L755P mutation

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Introduction

Erb-B2 receptor tyrosine kinase 2 (ERBB2) is a member of the ErbB tyrosine receptor family, that also includes EGFR, ERBB3, and ERBB4. ERBB2 dimerizes either

with itself or other ErbB members, causing activation of downstream signaling through two major pathways, the PI3K-AKT and MEK-ERK pathways, which induce cell proliferation and migration (1,2). *HER2* dysregulation in

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non-small cell lung cancer (NSCLC) may arise as a result of protein overexpression, caused by gene amplification and/or aberrations in regulatory regions, or alternatively by the acquisition of gain of function coding mutations. ERBB2 gene amplification often emerges as a mechanism of acquired resistance to treatment, whereas somatic alterations usually represent oncogenic driver events (3-5).

Clinical trials combining anti-HER2 monoclonal antibodies with chemotherapy in NSCLC, aimed at targeting HER2 protein overexpression, have yielded disappointing results, which is in contrary to the success of these agents in breast and gastric cancer with HER2 protein overexpression (6).

The incidence of *HER2* mutations in NSCLC is 2–4% (7), and have been associated with female sex, younger age, light or never smoking history, higher incidence of brain metastasis and worse prognosis (8,9). Therefore, HER2 targeting represents an urgent clinical need in NSCLC. Recurrent in-frame insertions within exon 20 causing duplication of amino acids YVMA represent 80% of all *HER2* alterations in NSCLC. Tyrosine kinase inhibitors (TKIs) such as poziotinib, pyrotinib and antibody-drug conjugates (ADC) like trastuzumab deruxtecan (T-DXd), have shown promising results in early phase clinical trials in NSCLC harboring *HER2* aberrations (10–13). Currently there is no phase III clinical data available to guide treatment in this population and the activity of these agents in patients with ERBB2 exon

19 c.2262_2264delinsTCC, p.(L755P) mutation is limited. Osimertinib, a 3rd generation TKI that irreversibly and specifically targets both sensitizing and resistant T790M-mutated EGFRs, has been found to inhibit HER2 in pre-clinical studies (2,3). We present the following case in accordance with the CARE reporting checklist (available at <https://tcr.amegroups.com/article/view/10.21037/tcr-22-596/rc>).

Case presentation

A 68-year-old Caucasian female with a past medical history of type 2 insulin dependent diabetes and a 3-pack-year smoking history (quit smoking in 1971) was diagnosed with adenocarcinoma of the lung (right lower lobe primary) in October 2016 via CT guided core needle biopsy. Immunohistochemical testing showed that the tumor was strongly positive for TTF-1 and CK7. At diagnosis her disease TNM staging was T3N3M1b according to AJCC 8th edition as she had metastatic disease to right hilar nodes, bilateral mediastinal nodes, and celiac axis nodes. Molecular testing showed that FISH for ALK and ROS was negative. PD-L1 tumor proportion score was <1% (22C3 assay). A 50 gene custom panel was performed using Ampliseq-based next generation sequencing on a NextSeq 550 (Illumina Inc., San Diego, CA, USA) and showed ERBB2 exon 19 mutation, c.2262_2264delGTTinsTCC, causing leucine to proline substitution at codon 755 (p.L755P). No other driver alterations were identified, including EGFR mutations. The timeline of this patient's cancer treatment journey is portrayed in *Figure 1*.

She was started on 1st line platinum-based doublet therapy with carboplatin and paclitaxel with an investigational agent through a clinical trial. After induction therapy she received pemetrexed switch-maintenance therapy. Her disease metastasized to the brain while receiving maintenance pemetrexed. She subsequently underwent whole-brain radiation with 30 Gy/10 fx and received 2nd line treatment with pembrolizumab and an investigational immunomodulatory agent as part of a clinical trial. However, she developed progression within two months.

She then started afatinib based on phase II data in patients with NSCLC and *HER2* mutation, however, this was discontinued within a week due to grade 4 diarrhea.

After this, she received gemcitabine-vinorelbine combination resulting in stable intra- and extracranial disease for nine months. At which time there was disease

Highlight box

Key findings

- We present a case of a 68-year-old female with stage IV NSCLC harboring a ERBB2 exon 19 c.2262_2264delinsTCC, p.(L755P) mutation treated with osimertinib, resulting in intra- and extracranial response.

What is known and what is new?

- Osimertinib, a 3rd generation EGFR-TKI has been found in pre-clinical studies, both *in vitro* and *in vivo*, to have activity against various *HER2* exon 19 aberrations, including *HER2* exon 19, p.L755P mutations.
- Here we demonstrate for the first time in humans, that osimertinib was an effective and well tolerated treatment in a patient with stage IV NSCLC harboring *HER2* exon 19, p.L755P mutation.

What is the implication, and what should change now?

- The efficacy of osimertinib against *HER2* exon 19, p.L755P mutations and other *HER2* exon 19 aberrations should be tested in clinical trials to determine its efficacy as a potential *HER2* targeted treatment for patients harboring these mutations.

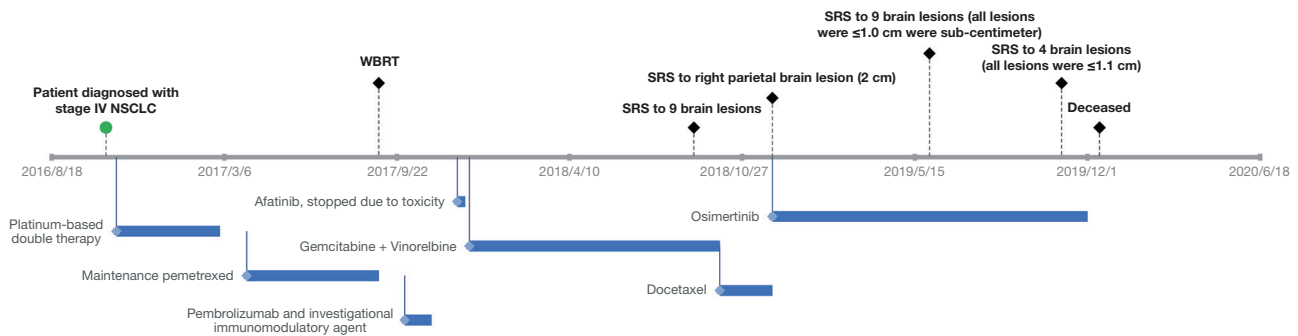


Figure 1 Timeline of the patient's cancer treatment. NSCLC, non-small cell lung cancer; WBRT, whole brain radiation therapy; SRS, stereotactic radiosurgery.

progression in the primary lung lesion and brain. She underwent stereotactic radiosurgery (SRS) to brain lesions and started on docetaxel.

After three cycles, imaging showed multiple new brain lesions and she received SRS to the largest lesion only. At this time the patient was still fit for treatment. Therefore, clinical trials with anti-Her2 therapy were considered however she either did not qualify for available trials due to eligibility criteria or open slots were not available when enrollment was needed.

Nagano *et al.* had recently showed that among various TKIs, osimertinib had the best efficacy against the *HER2* exon 19, p.L755P mutation (2). The authors demonstrated that the IC₅₀ of osimertinib for the *HER2* exon 19, p.L755P mutation was 23.8 nmol/L and low-dose osimertinib (8 mg/kg) could inhibit the growth of tumors with this mutation. Additionally, osimertinib was known to penetrate the blood brain barrier which was important since the main site of the patient's disease progression was in the brain. Based on the findings from Nagano *et al.* osimertinib was commenced at a dose of 80 mg OD. Osimertinib was provided by Astrazeneca via patient assistance program at no cost to the patient. To maximize chances of intracranial disease control the dose of osimertinib was increased after two weeks of treatment to 160/80 mg alternating days and QTc monitored. The patient achieved a confirmed partial response (PR) to osimertinib intra- and extracranially according to RECIST criteria (Figures 2,3). Four months after starting osimertinib the patient was admitted with grade 3 fatigue and grade 2 transaminitis. It was thought that this could either have been related to osimertinib or other medications she was taking at that time (doxycycline). Osimertinib was withheld for two weeks with resolution of symptoms and dose was restarted at 160/80 mg alternating

days. After six months on treatment with osimertinib, there was evidence of disease progression in the brain and nine small lesions were treated with SRS. Extracranial disease was stable at this time. Osimertinib dose was increased to 160 mg OD for another four months, after which the patient had further CNS progression with development of lethargy and disorientation, ultimately leading to death.

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 Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

To our knowledge, this is the first report to show osimertinib activity in a patient with NSCLC harboring *HER2* exon 19, p.L755P mutation resulting in intra- and extracranial response. The patient lived for a total of 11-month after starting osimertinib. As well as being effective, osimertinib at alternating 160/80 mg daily dose was also well tolerated. This is an important observation considering toxicity concerns with some of the other *HER2*-targeting drugs. In the coming years, osimertinib could become a *HER2* mutant targeted therapy for patients harboring exon 19 *ERBB2* point mutations.

In a pre-clinical study using animal models, Liu *et al.* presented that osimertinib had antitumor efficacy against multiple *HER2* aberrations in NSCLC, either as a single agent or in combination with JQ1, a BET inhibitor (3). Subsequently, Nagano *et al.* showed using both *in vitro* cell

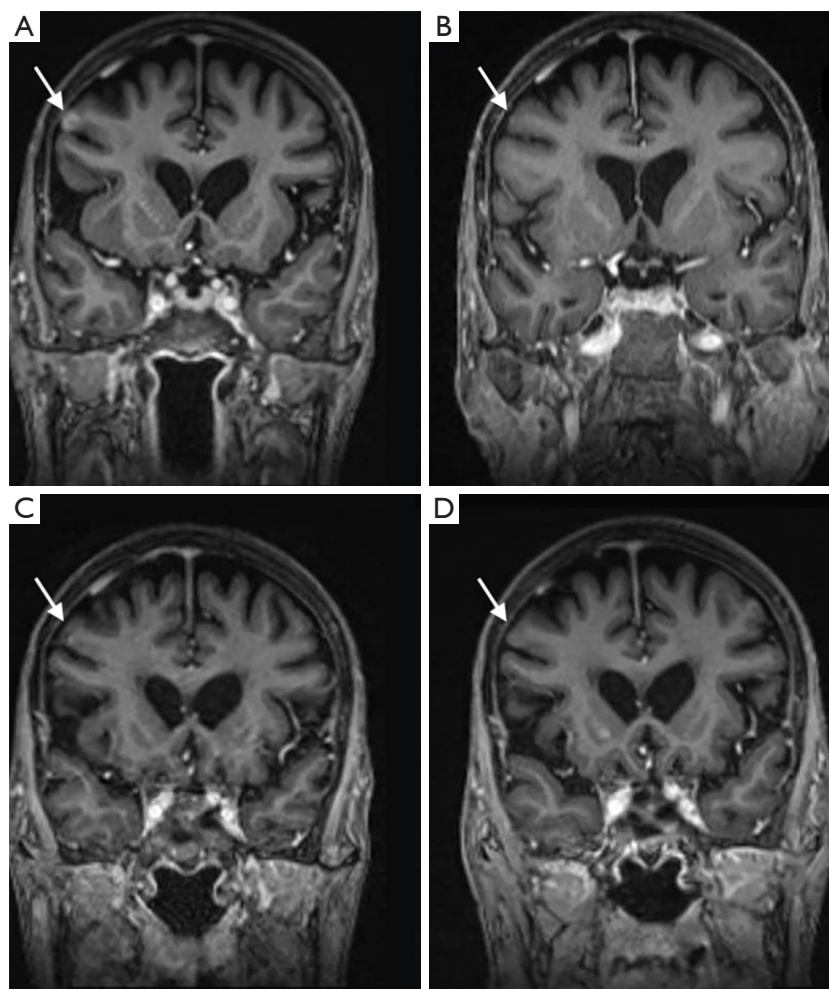


Figure 2 Serial magnetic resonance imaging shows ongoing response in the right frontal metastasis (arrows), which had not been irradiated before. (A) Jan 2019; Baseline before starting osimertinib, (B) March 2019; 2 months after starting osimertinib, (C) April 2019; 3 months after starting osimertinib, (D) June 2019; 5 months after starting osimertinib.

lines and *in vivo* animal models that *HER2* variants at L755 were more sensitive to osimertinib compared to other TKIs, interestingly it was not effective against common exon 20 alterations (2). Because of the homology between *HER2* and *EGFR* it has been speculated that the covalent binding site for osimertinib may be C805 (analogous Cys797 to *EGFR*) of human *HER2* (3). No clinical trials have tested the efficacy of osimertinib in *HER2* alterations.

Various other TKIs have been tested in NSCLC with *HER2* alterations. Results from a multicenter, phase II trial looking at patients with *HER2* exon 20 mutation treated with poziotinib after prior therapies (n=90) reported that the objective response rate (ORR) was 28% (10). We could not find any data regarding its activity in NSCLC

with *HER2* exon 19, p.L755P alteration. Pyrotinib has been found to produce an ORR of 30% in *HER2*-mutant NSCLC (n=60). This study included 4 patients with exon 19, p.L755P mutation of which 1 patient achieved a PR (11).

Ado-Trastuzumab emtansine, an ADC, demonstrated an ORR of 44% in 18 patients with *HER2* mutant NSCLC (12). However, patients with exon 19 p.L755P did not respond (n=2). T-Dxd, another ADC, was evaluated in a phase II trial in patients with NSCLC harboring *HER2* mutations (n=91). In this study, ORR was 55% and overall survival 17.8 months, 2 patients had an exon 19, p.L755P mutation. Their best responses were PR and stable disease, respectively (13). Toxicity concerns regarding fatal interstitial lung disease were noted in this trial.

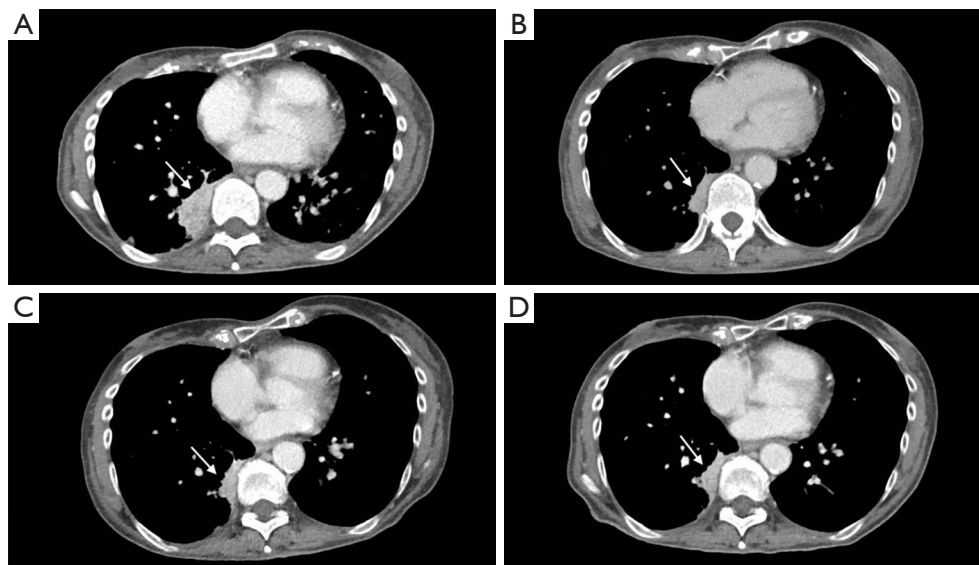


Figure 3 Serial computer tomography imaging of the chest, showing ongoing response in the right lower lobe lung primary (arrows). (A) Jan 2019; 1 baseline before starting osimertinib, (B) April 2019; 3 months after starting Osimertinib, (C) June 2019; 5 months after starting osimertinib, (D) Sept 2019; 8 months after starting osimertinib.

Conclusions

Osimertinib, a 3rd generation EGFR-TKI, was effective and well tolerated in a patient with stage IV NSCLC harboring ERBB2 exon 19 c.2262_2264delinsTCC, p.(L755P) mutation, including response of intracranial metastases. Future research is required to illustrate the differential effects of targeted therapies in NSCLC harboring various types of *HER2* alterations to select an optimal therapy.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at <https://tldr.amegroups.com/article/view/10.21037/tlcr-22-596/rc>

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://tldr.amegroups.com/article/view/10.21037/tlcr-22-596/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 institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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