Case Report

Efficacy of osimertinib in a metastatic lung adenocarcinoma patient harboring somatic *EGFR* delL747_S752 and germline *BIM* deletion polymorphism: a case report and literature review

Wenyu Zheng, Niu Niu, Jialong Zeng, Xianni Ke, Shi Jin

Department of Medical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital & Shenzhen Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Shenzhen, China

Correspondence to: Shi Jin. Department of Medical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital & Shenzhen Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, 113 Baohe Road, Shenzhen, 518116, China. Email: catherine-jinshi@163.com.

Background: Epidermal growth factor receptor (*EGFR*) exon 19 deletion (19del) and the exon 21 L858R point mutation are the most established predictive factors for the efficacy of EGFR-tyrosine kinase inhibitor (TKI) in patients with non-small cell lung cancer (NSCLC). To date, more than 50 subtypes of *EGFR* 19dels have been documented in NSCLC. Evidence suggests that different subtypes of 19dels exhibit different survival outcomes to EGFR-TKI treatment. Whether patients harboring *EGFR* Leu747_Ser752 deletion (delL747_S752) as an uncommon subtype of 19dels benefit from EGFR-TKIs has not been investigated. *BIM* (B-cell chronic lymphocytic leukemia/lymphoma-like 1) deletion polymorphism is common in East Asian with *EGFR*-mutant NSCLC. Currently, the predictive role of *BIM* deletion polymorphism in patients with *EGFR*-mutant NSCLC treated with osimertinib remains debatable.

Case Description: A 34-year-old female patient was diagnosed with stage IV lung adenocarcinoma (LUAD) harboring somatic *EGFR* del L747_S752 and germline *BIM* deletion polymorphism in August 2018. She obtained benefit from the front-line treatment of osimertinib lasting for 8 months. After progression from osimertinib, the patient received bevacizumab combined with platinum-doublet chemotherapy, stereotactic radiosurgery plus osimertinib and crizotinib, anlotinib, and a programmed cell death-1 inhibitor sintilimab plus bevacizumab and docetaxel. She succumbed to her disease in June 2020 with an overall survival of 23 months.

Conclusions: Our work suggests that osimertinib might be a compromised treatment option for NSCLC patients with somatic *EGFR* delL747_S752 and germline *BIM* deletion polymorphism. Development of more effective regimens are needed for this small subset of NSCLCs.

Keywords: Lung adenocarcinoma (LUAD); osimertinib; *EGFR* delL747_S752; *BIM* deletion polymorphism; case report

Submitted Apr 14, 2022. Accepted for publication Aug 01, 2022.
doi: 10.21037/tcr-22-1050
View this article at: https://dx.doi.org/10.21037/tcr-22-1050

Introduction

Exon 19 deletion (19del) and the exon 21 L858R point mutation are the most established predictive factor for the efficacy of epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI) in patients with non-small cell lung cancer (NSCLC). *EGFR* 19dels comprise a heterogeneous group of genetic aberrations, including deletions, substitutions, and insertions. Different subtypes of 19dels exhibit heterogeneous response to EGFR-TKIs treatment. More than 50 subtypes of *EGFR* 19dels have been identified in NSCLC (1-7). delE746_A750 (65.9–72.3%), delL747_P753insS (6.1–8.1%) and delL747_

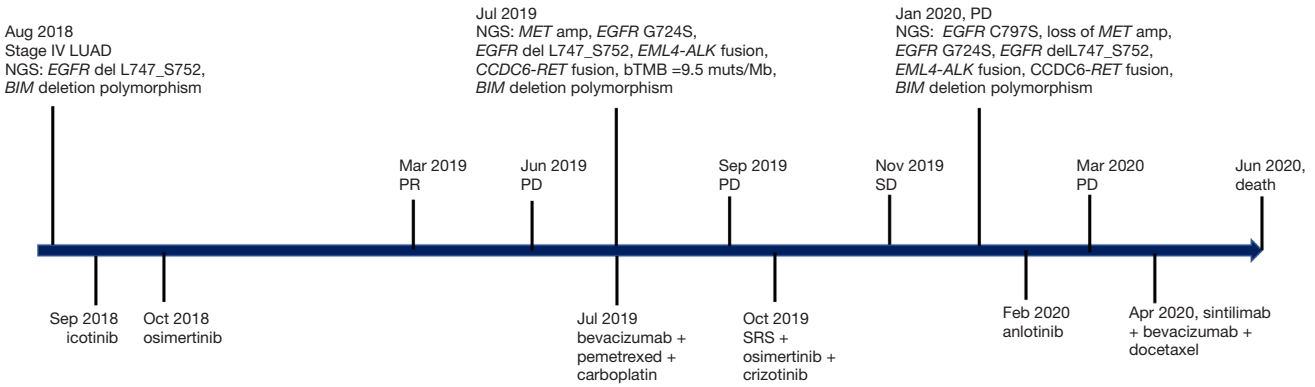

Figure 1 Timeline of the patient's clinical treatment course. LUAD, lung adenocarcinoma; NGS, next-generation sequencing; PR, partial response; SD, stable disease; PD, progressive disease; SRS, stereotactic radiosurgery; amp, amplification; muts/Mb, mutations/megabase; bTMB, blood tumor mutation burden.

T751 (5.8–7.7%) are the most frequent subtypes (2,4,5,7). Published literature have reported the associations between common subtypes of *EGFR* 19dels and survival outcomes in NSCLC patients who received EGFR-TKI therapy (1,2,4,5,7). However, the efficacy of EGFR-TKI in NSCLC patients harboring *EGFR* L747_S752 deletions (delL747_S752) as an uncommon subtype of 19dels remains elusive.

BIM, also known as B-cell chronic lymphocytic leukemia/lymphoma (Bcl-2)-like 11, encodes BCL2L11, which is a member of Bcl-2 protein family. *BIM* deletion polymorphism, resulting from the 2903-bp genomic deletion occurring in intron 2 of *BIM* gene, is commonly seen in East Asian and Hispanic patients with *EGFR*-mutant lung cancer with an incidence rate of 11.3–18.6% (8,9). Some studies reported that *BIM* deletion polymorphism predicted an unfavorable prognosis in *EGFR*-mutant NSCLC patients when treated with EGFR-TKIs (8,10-12), but other studies failed to find an association between the presence of *BIM* deletion polymorphism and the clinical outcome in these patients (13,14). Moreover, an array of studies have demonstrated that increased *BIM* at the RNA level enhances killing of NSCLC cells by the EGFR-TKIs, which contributes to the molecular mechanisms leading to tumor regression (15-18).

Here, we present a metastatic lung adenocarcinoma (LUAD) patient harboring *EGFR* delL747L_S752S and *BIM* deletion polymorphism who benefited from third-generation EGFR-TKI osimertinib with a progression-free survival (PFS) of 8 months. We present the following case in accordance with the CARE reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-1050/rc).

Case presentation

In August 2018, a 34-year-old female presented with fever at night and lower back pain. Ultrasound-guided biopsy of right supraclavicular lymph nodes revealed a metastatic carcinoma. She was diagnosed with stage IV LUAD with metastases to brain, bone, liver, right kidney gland, bilateral hilar lymph nodes, left and right supraclavicular lymph nodes, retroperitoneal lymph node and left external iliac lymph nodes. Plasma-based genotype was performed and revealed the presence of *EGFR* 19del (delL747_S752) with an allele frequency (AF) of 38.8% and *BIM* deletion polymorphism. The patient's treatment history is shown in *Figure 1*. She was initially given with icotinib combined with zoledronic acid. Her symptoms of lower back pain and fever were subsequently relieved. On October 20, 2018, the patient was switched to oral osimertinib based on the findings from FLAURA trial reported in January 2018 (19) that osimertinib demonstrates a longer progression-free survival than gefitinib/erlotinib in Asian patients with *EGFR*-mutant advanced NSCLC. In March 2019, the chest and abdominal computed tomography (CT) scans showed partial response (PR) (>50% reduction) in the primary lung tumor and metastatic liver tumor, and the magnetic resonance imaging (MRI) showed complete remission of the brain metastases (*Figure 2*). In June 2019, the chest and abdominal CT scans showed the presence of nodular mass in bilateral lungs, the enlarged primary lung tumor and a metastatic liver tumor (*Figure 2A*,*2B*). The brain MRI

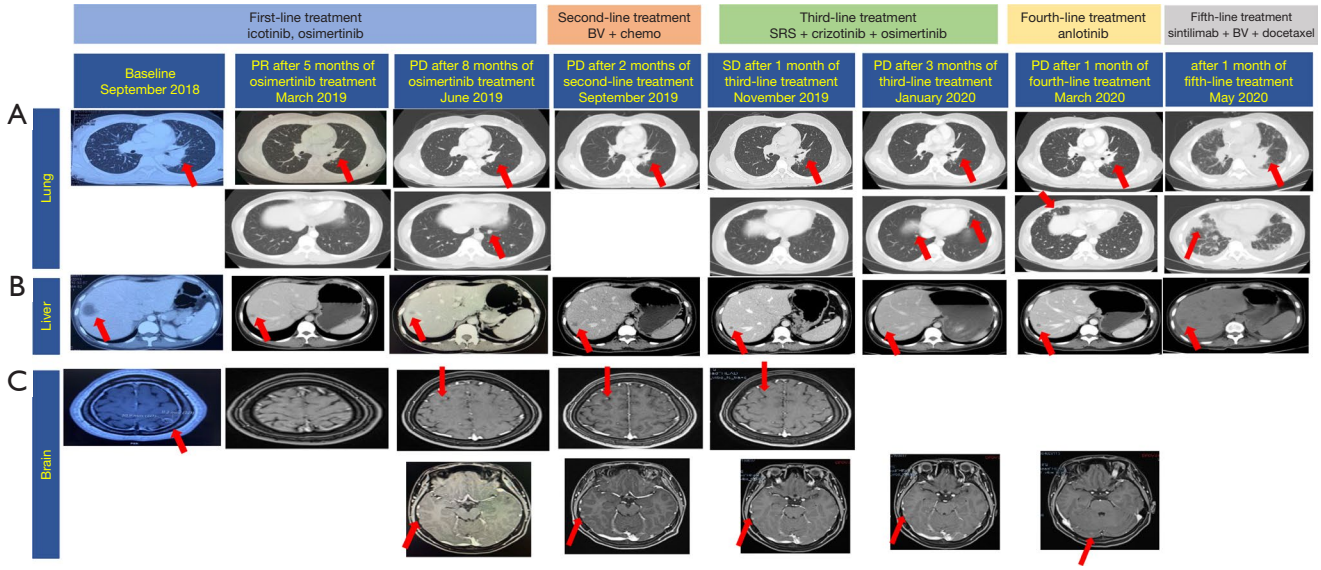

Figure 2 Computed tomography scans and magnetic resonance imaging of primary and metastatic tumors. (A) Chest CT scans; (B) Abdominal CT scans; (C) brain MRI. BV, bevacizumab; chemo, pemetrexed and carboplatin; CT, computed tomography; MRI, magnetic resonance imaging.

showed a newly developed lesion in the right frontal lobe with a diameter of 2 mm (*Figure 2C*). The assessment of tumor response was progressive disease (PD) with a PFS of 8 months (*Figure 1*). We also reviewed the previously reported clinical outcomes to EGFR-TKIs in NSCLC patients harboring different 19dels, which are summarized in *Table 1*.

The patient was treated with bevacizumab plus pemetrexed and carboplatin as second-line therapy on July 24, 2019. Meanwhile, next-generation sequencing (NGS) analysis using a panel covering 520 cancer-related genes (20) was performed on the plasma sample after failure of osimertinib treatment. The results revealed a blood tumor mutation burden (bTMB) of 9.5 mutations/Mb and the presence of new alterations, including *EGFR* G724S, *MET* amplification with a copy number of 4.0, *EML4-ALK* fusion and *CCDC6-RET* fusion. After three courses of the treatment, the brain MRI showed PD with newly developed metastases to the brain and enlarged tumor in right frontal lobe with a diameter of 4 mm (*Figure 2C*).

On October 8, 2019, she received stereotactic radiosurgery (SRS) as the definitive local therapy and was subsequently challenged with osimertinib combined with crizotinib. In November, 2019, the chest and abdominal CT scans showed shrinkage of the metastatic liver tumor (*Figure 2B*). The treatment response assessment was stable disease (SD). She had loss of appetite during treatment of osimertinib plus crizotinib. In January 2020, the chest CT scans demonstrated PD with enlarged bilateral lung metastatic lesions and newly developed lesions in the lower lobe of the left lung (*Figure 2A,2C*). At PD, NGS analysis was performed on plasma sample. NGS results showed the presence of new alterations, *EGFR* C797S and loss of *MET* amplification. She was administered with anlotinib as a single agent in February 2020. After one month of the treatment, the chest CT and brain MRI revealed newly developed metastatic lesions in bilateral lungs and brain metastatic tumors (*Figure 2A,2C*). The assessment of the response to fourth-line treatment was PD. In April, 2020, she was treated with sintilimab plus bevacizumab and docetaxel. The patient underwent nausea, vomiting, and muscle pain. After two months of the treatment, she succumbed to her disease in June 2020.

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.

Table 1 Clinical outcomes of NSCLC patients harboring different deletions of *EGFR* exon 19 in previous and our studies

Publication	Year of publication	Clinical setting of EGFR-TKI treatment	*EGFR* 19dels	No. of patients	Median PFS or PFS in mo	P value
Chung *et al.* (5)	2012	First-line, second-line, third-line, or subsequent line gefitinib/erlotinib	Delta E746	219	9.8	0.665
			Delta E747	79	10.5	
			Non-LRE deletions	10	5.9 (6.6–20.8)	
			Delt751-i759insn	1	NA	
			Delt751-e758	1	NA	
			S752-i759	1	NA	
			Delr748-P753	1	6.6	
			Delr748-S752	1	20.8	
			Dels752-I759	1	3.3	
			Dels752-I759	1	2.7	
			Dels752-i759insn	1	5.9	
			Delt751-i759insd	1	4.9	
			Delt751-i759insn	1	4.8	
Lee *et al.* (1)	2013	First-line gefitinib/erlotinib	Delta E746	46	14.2	0.021
			Delta L747	16	6.5	
			Dell747_p753inss	10	6.5 (2.1–15.3)	0.021
			Dele746_A750	42	12.4	
			Mix insertions/substitution	12	22.3 (0.7–63)	
			Dell747_k754insankg	1	0.7	
			Dell747_a750insp	1	1.5	
			Delt751_i759insn	1	2.4	
			Dell747_a750insp	1	5.7	
			Dele746_t751insv	1	7.6	
			Delt751_i759inss	1	13.3	
			Dele746_t751insi	1	16.1	
			Dell747_a755insskg	1	18.3	
			Dele746_t751insva	1	22.3	
			Dell747_t751insp	1	40.6	
			Dele746_s752insv	1	43.1	
			Dele746_a750insap	1	63	
			Non-LRE deletions			
			Delta T751	1	13.3	
			Delta T751	1	NR	

Table 1 (*continued*)

Table 1 (*continued*)

Publication	Year of publication	Clinical setting of EGFR-TKI treatment	*EGFR* 19dels	No. of patients	Median PFS or PFS in mo	P value
Kaneda *et al.* (4)	2014	First-line, second-line or subsequent line gefitinib/erlotinib	Delta E746		11.7	0.022
			Delta E747		10.0	
			With ins/sub		10.0	0.024
			Without ins/sub		11.7	
Zhao *et al.* (2)	2020	First-line gefitinib/erlotinib	Delta E746	78	12.1	0.816
			Delta L747	15	10.6	
			Delta L747 with insertions	8	8.3	0.017
			Delta L747 without insertions	7	15.0	
			Dele746_A750	72	12.1	0.795
			Dele746_a750ins	6	10.0	
			Deletions with insertion	14	9.5	0.102
			Deletions without insertion	76	12.6	
Peng *et al.* (3)	2020	First-line gefitinib/erlotinib	Uncommon 19delins	93	19	0.0016
			Common19del (E746_A750)	93	13	
			Dell747_p753inss	23	18	0.58
			Dell747_a750insp	24	20	
Xu *et al.* (6)	2020	First-line gefitinib/erlotinib/icotinib	Delta E746	126	11.4	<0.001
			Delta L747	62	17.2	
			Delta T51 or S752	6	2.9	
Wang *et al.* (7)	2021	First-line gefitinib/erlotinib/icotinib	Del L747_T751delinsP	6	18.7	0.035
			Others	35	13.1	
Our work	2022	First-line osimertinib	DelL747_S752	1	8	

No., number; NSCLC, non-small cell lung cancer; *EGFR*, epidermal growth factor receptor; PFS, progression-free survival; mo, month; delta E746, deletions starting from E746; delta L747, deletions starting from L747; ins/sub, insertions/substitutions; NR, the patient was still free from progression after taking EGFR-TKI for 2.4 months; TKI, tyrosine kinase inhibitor; NA, the PFS data of those patients was unavailable; delta T751, deletions starting at T751; Non-LRE, deletions not encompassing the entire amino acid string from L747 through E749; 19delins, exon 19 insertion-deletion variants; others, delL747_P753delinsS, L747_A750delinsP, and E746_S752delinsV.

Discussion

To the best of our knowledge, we reported for the first time that a metastatic LUAD patient with *EGFR* delL747_S752 and *BIM* deletion polymorphism received osimertinib treatment.

Several studies have reported the association between subgroup of 19dels and clinical outcomes to EGFR-TKI in NSCLC patients, but have obtained conflicting results. A prior study reported by Chung *et al.* (5) is the first to subcategorize *EGFR* 19dels into three groups, deletions starting on codon E746 (delta E746), deletions starting on codon L747 (delta L747), deletions not involving the entire amino acid string from L747 through E749 (Non-LRE deletions). Chung *et al.* (5) and Zhao *et al.* (2) found that subgroup of 19dels was not associated with PFS in

NSCLC patients treated with first-generation EGFR-TKIs. However, some studies demonstrated the presence of association between subgroup of 19dels and clinical outcome to EGFR-TKI in NSCLC patients. Lee *et al.* (1) revealed that delta L747 predicted a significantly shorter PFS compared to delta E746 (6.5 *vs.* 14.2 months) in NSCLC patients treated with first-generation EGFR-TKIs as first-line treatment. The similar results (10.0 *vs.* 11.7 months) were observed in a cohort of NSCLC patients treated with EGFR-TKIs as any line of first-generation EGFR-TKIs (4). In contrast, Xu et al (6) reported that delta L747 predicted a longer PFS than delta E746 (17.2 *vs.* 11.4 months). The controversial results may be attributed to several factors. Some studies (1-3,6) only included patients who were treated with EGFR-TKIs as fist-line setting, in contrast, others included patients using EGFR-TKIs as first-, second- or later-line treatment (4,5).

EGFR delL747_S752 is an uncommon subtype of 19dels, accounting for 0.6–3.6% of cases with *EGFR* 19dels (2,4,5). Due to its rarity, patients with this rare subtype are commonly pooled for investigating the clinical outcomes to EGFR-TKIs in NSCLCs. There are very few reports in the efficacy of EGFR-TKI against delL747_S752. The previous study (2) has demonstrated delta L747 with insertions (n=22) predicted a significantly shorter PFS than delta L747 without insertions (n=16) (8.3 *vs.* 15.0 months) in a cohort of 208 NSCLC patients treated with first-line EGFR-TKIs. Only one patient (6.25%, 1/16) harboring *EGFR* delL747_S752 was observed in delta L747 without insertions group (2). The true efficacy of EGFR-TKI in *EGFR* delL747_S752 patients could be masked by other patients. Evidence suggested that patients carrying *EGFR* delL747_S752 showed a good response (an objective response rate of 88.9%) to gefitinib or erlotinib in a small cohort (n=11) (5). In addition, a recent study shows subtypes of delta L747 with insertions impact on the efficacy of first-line EGFR-TKI that delL747_T751delinsP that predict a better prognosis (7). However, whether patients with *EGFR* delL747_S752 benefit from EGFR-TKIs has not been documented. In the present work, a metastatic LUAD patient harboring *EGFR* delL747_S752 and *BIM* deletion polymorphism obtained benefit from first-line osimertinib treatment with a PFS of 8 months. Moreover, *EGFR* G724S, *MET* amplification, *EML4-ALK* fusion and *CCDC6-RET* fusion were identified when she progressed from osimtertinib. These new alterations contributed to acquired resistance mechanisms to osimertinib treatment, which was consistent with a previous study indicating that *EGFR* G724S, *MET* amplification, *ALK* fusions and *RET* fusions were resistance mechanisms reported for osimertinib as first-line treatment (9,21).

In this work, the patient with somatic *EGFR* del747_S752 and germline *BIM* deletion polymorphism was given with icotinib in September 2018 obtaining PR to icotinib, and switched to osimertinib based on the findings of FLAURA trial reported in January 2018. The updated data on FLAURA trial published in January 2020 has revealed no difference of overall survival was observed in osimertinib versus gefitinib/erlotinib group for the Asian patients (22). Upon the previous and our work, we cannot conclude that osimertinib is more effective than icotinib based on the presence of the germline *BIM* deletion. Further *in vitro*, *in vivo*, and clinical trials studies are warranted to investigate whether osimertinib is more effective than icotinib in lung cancers with germline *BIM* deletion.

A recent study has revealed that regimens starting with afatinib and subsequently switched to osimertinib suppressed tumor development more efficiently than the opposite combination for *EGFR* variants according to preclinical assessment (23). These findings suggest that afatinib followed by osimertinib might be an efficacious treatment regimen for NSCLC patients with somatic *EGFR* delL747_S752 and concurrent germline *BIM* deletion polymorphism and further clinical trials are warranted.

There are some limitations associated with our study. First, since this is a case report, large cohort studies or clinical trials are necessary to validate the efficacy of osimertinib for metastatic LUAD patients with *EGFR* delL747_S752 and *BIM* deletion polymorphism. Second, *BIM* expression at the RNA level reported to contribute to molecular mechanisms leading to tumor regression was not investigated for the patient.

In conclusion, our work revealed that an *EGFR* delL747_S752/*BIM* deletion polymorphism double-positive LUAD patient obtained a PFS of 8 months with osimertinib treatment. Our work suggests that osimertinib might be a compromised treatment option for NSCLC patients with *EGFR* delL747_S752 and *BIM* deletion polymorphism. Further studies are needed to develop the more effective regimen for this small subset of NSCLCs, such as afatinib followed by osimertinib.

Acknowledgments

Funding: This study was supported by the Project from the Shenzhen Science and Technology Program (Grant No. RCJC20200714114436049) and Cancer Hospital, Chinese

Academy of Medical Sciences, Shenzhen Center/Shenzhen Cancer Hospital Research Project (No. SZ2020ZD006).

Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-1050/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-1050/coif). SJ declares that this study was supported by the project from the Shenzhen Science and Technology Program (Grant No. RCJC20200714114436049) and Cancer Hospital, Chinese Academy of Medical Sciences, Shenzhen Center/Shenzhen Cancer Hospital Research Project (No. SZ2020ZD006). 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 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.

References

1. Lee VH, Tin VP, Choy TS, et al. Association of exon 19 and 21 EGFR mutation patterns with treatment outcome after first-line tyrosine kinase inhibitor in metastatic non-small-cell lung cancer. J Thorac Oncol 2013;8:1148-55.
2. Zhao C, Jiang T, Li J, et al. The impact of EGFR exon 19 deletion subtypes on clinical outcomes in non-small cell lung cancer. Transl Lung Cancer Res 2020;9:1149-58.
3. Peng X, Long X, Liu L, et al. Clinical impact of uncommon epidermal growth factor receptor exon 19 insertion-deletion variants on epidermal growth factor receptor-tyrosine kinase inhibitor efficacy in non-small-cell lung cancer. Eur J Cancer 2020;141:199-208.
4. Kaneda T, Hata A, Tomioka H, et al. Possible differential EGFR-TKI efficacy among exon 19 deletional locations in EGFR-mutant non-small cell lung cancer. Lung Cancer 2014;86:213-8.
5. Chung KP, Wu SG, Wu JY, et al. Clinical outcomes in non-small cell lung cancers harboring different exon 19 deletions in EGFR. Clin Cancer Res 2012;18:3470-7.
6. Xu H, Li W, Yang G, et al. Heterogeneous Response to First-Generation Tyrosine Kinase Inhibitors in Non-Small-Cell Lung Cancers with Different EGFR Exon 19 Mutations. Target Oncol 2020;15:357-64.
7. Wang Y, Zheng R, Hu P, et al. Patients harboring uncommon EGFR exon 19 deletion-insertion mutations respond well to first-generation EGFR inhibitors and osimeritinib upon acquisition of T790M. BMC Cancer 2021;21:1215.
8. Wakabayashi Y, Masuda T, Fujitaka K, et al. Clinical significance of BIM deletion polymorphism in chemoradiotherapy for non-small cell lung cancer. Cancer Sci 2021;112:369-79.
9. Zeng Y, Yu D, Tian W, et al. Resistance mechanisms to osimertinib and emerging therapeutic strategies in nonsmall cell lung cancer. Curr Opin Oncol 2022;34:54-65.
10. Isobe K, Hata Y, Tochigi N, et al. Clinical significance of BIM deletion polymorphism in non-small-cell lung cancer with epidermal growth factor receptor mutation. J Thorac Oncol 2014;9:483-7.
11. Zhao M, Zhang Y, Cai W, et al. The Bim deletion polymorphism clinical profile and its relation with tyrosine kinase inhibitor resistance in Chinese patients with non-small cell lung cancer. Cancer 2014;120:2299-307.
12. Ng KP, Hillmer AM, Chuah CT, et al. A common BIM deletion polymorphism mediates intrinsic resistance and inferior responses to tyrosine kinase inhibitors in cancer. Nat Med 2012;18:521-8.
13. Liu SY, Zhou JY, Li WF, et al. Concomitant genetic alterations having greater impact on the clinical benefit of EGFR-TKIs in EGFR-mutant advanced NSCLC than BIM deletion polymorphism. Clin Transl Med 2020;10:337-45.
14. Lee JY, Ku BM, Lim SH, et al. The BIM Deletion

Polymorphism and its Clinical Implication in Patients with EGFR-Mutant Non-Small-Cell Lung Cancer Treated with EGFR Tyrosine Kinase Inhibitors. J Thorac Oncol 2015;10:903-9.
15. Costa DB, Halmos B, Kumar A, et al. BIM mediates EGFR tyrosine kinase inhibitor-induced apoptosis in lung cancers with oncogenic EGFR mutations. PLoS Med 2007;4:1669-79; discussion 80.
16. Cragg MS, Kuroda J, Puthalakath H, et al. Gefitinib-induced killing of NSCLC cell lines expressing mutant EGFR requires BIM and can be enhanced by BH3 mimetics. PLoS Med 2007;4:1681-89; discussion 90.
17. Gong Y, Somwar R, Politi K, et al. Induction of BIM is essential for apoptosis triggered by EGFR kinase inhibitors in mutant EGFR-dependent lung adenocarcinomas. PLoS Med 2007;4:e294.
18. Faber AC, Corcoran RB, Ebi H, et al. BIM expression in treatment-naive cancers predicts responsiveness to kinase inhibitors. Cancer Discov 2011;1:352-65.
19. Soria JC, Ohe Y, Vansteenkiste J, et al. Osimertinib in Untreated EGFR-Mutated Advanced Non-Small-Cell Lung Cancer. N Engl J Med 2018;378:113-25.
20. Wang M, Chen X, Dai Y, et al. Concordance Study of a 520-Gene Next-Generation Sequencing-Based Genomic Profiling Assay of Tissue and Plasma Samples. Mol Diagn Ther 2022.
21. Shaikh M, Shinde Y, Pawara R, et al. Emerging Approaches to Overcome Acquired Drug Resistance Obstacles to Osimertinib in Non-Small-Cell Lung Cancer. J Med Chem 2022;65:1008-46.
22. Ramalingam SS, Vansteenkiste J, Planchard D, et al. Overall Survival with Osimertinib in Untreated, EGFR-Mutated Advanced NSCLC. N Engl J Med 2020;382:41-50.
23. Ikeuchi H, Hirose T, Ikegami M, et al. Preclinical assessment of combination therapy of EGFR tyrosine kinase inhibitors in a highly heterogeneous tumor model. Oncogene 2022;41:2470-9.

Cite this article as: Zheng W, Niu N, Zeng J, Ke X, Jin S. Efficacy of osimertinib in a metastatic lung adenocarcinoma patient harboring somatic *EGFR* delL747_S752 and germline *BIM* deletion polymorphism: a case report and literature review. Transl Cancer Res 2022;11(10):3895-3902. doi: 10.21037/tcr-22-1050

