


Survival benefit of combinatorial osimertinib rechallenge and entrectinib in an EGFR-mutant NSCLC patient with acquired LMNA-NTRK1 fusion following osimertinib resistance

Jiao-Li Wang^{1,2,3,4} | Liu-sheng Wang¹ | Jun-qi Zhu³ | Jie Ren³ | Di Wang⁵ | Man Luo^{1,2} 

¹Department of Respiratory Medicine, Affiliated Hangzhou First People's Hospital, Zhejiang University School of Medicine, Hangzhou, China

²Department of Translation Medicine Center, Key Laboratory of Clinical Cancer Pharmacology and Toxicology Research of Zhejiang Province, Affiliated Hangzhou First People's Hospital, Zhejiang University School of Medicine, Hangzhou, China

³The Fourth Clinical Medical College of Zhejiang Chinese Medical University, Hangzhou, China

⁴Zhejiang University Cancer Centre, Hangzhou, China

⁵Department of Medical Nanjing, Geneseeq Technology Inc., Nanjing, China

Correspondence

Man Luo, Department of Respiratory Medicine, Affiliated Hangzhou First People's Hospital, Zhejiang University School of Medicine, #261 Huansha Road, Hangzhou, Zhejiang Province, China.
Email: luoman926@163.com

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Abstract

Acquired resistance to osimertinib is inevitable and heterogeneous despite its documented efficacy against EGFR-mutated non-small cell lung cancer (NSCLC). Subsequent therapeutic options assume the dominant form of the resistance mechanism; however, the more rare oncogenic driver, NTRK1 fusion, has also reportedly conferred osimertinib resistance. Nevertheless, clear-cut options when NSCLCs are driven by EGFR mutation and the subsequent NTRK fusion are lacking. This is a case of NSCLC wherein exon 19 deletion in EGFR (19del) and acquired LMNA-NTRK1 fusion were accompanied by the persistence of EGFR T790M. The patient underwent peritoneal metastasis after multiple targeted therapies: gefitinib, osimertinib, chemotherapy, and anlotinib plus docetaxel (in clinical trials). Osimertinib was subsequently re-administered with the NTRK fusion inhibitor entrectinib, resulting in remission of peritoneal metastases even after slow progression of pancreatic metastasis over the following 5 months. An extensive literature review to identify the efficacies of therapies for NTRK fusion as the means to acquired resistance to EGFR TKIs revealed that blocking both the EGFR mutation and the subsequent NTRK fusion can provide clinical benefits following EGFR TKIs resistance; however, the efficacy and safety of combination therapies must be further investigated. To precisely manage EGFR-mutated NSCLCs, it is also essential to identify the resistance mechanisms by repeating biopsies.

KEYWORDS

EGFR-TKI acquired resistance, non-small cell lung cancer (NSCLC), NTRK fusion, osimertinib rechallenge

INTRODUCTION

Lung cancer remains the leading cause of cancer-related death worldwide, accounting for 22% of all cancer deaths.¹ Overall survival and quality-of-life among those with non-small cell lung cancer (NSCLC) have significantly improved since the advent of molecular targeted therapies.² Tyrosine kinase inhibitors (TKIs) have been a therapeutic mainstay when these patients also have epidermal growth factor receptor (EGFR)-positive mutations. Osimertinib, a third-

generation EGFR-TKI, is the first-line therapy for advanced EGFR-mutated NSCLC, regardless of T790M mutation status.³ Nonetheless, the occurrence of acquired resistance invariably ensues and poses a great clinical challenge.⁴ To precisely plan management strategies, it is vitally important to identify the detailed phenotypic and genomic alterations by repeating biopsies and performing subsequent genomic testing.

As a transmembrane receptor tyrosine kinase, neurotrophic tropomyosin receptor kinase (NTRK) gene fusion

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has been identified as an oncogenic driver in NSCLC. The prevalence of NTRK gene fusion varies from 0.07% to 3.3%.⁵⁻⁷ A recent retrospective study enrolled 7395 Chinese with NSCLC finding that the NTRK rearrangement frequency was 0.59%, far less frequent than what is found with other gene fusions (e.g., ALK, RET, and ROS1).⁸ Currently, NTRK fusion is recognized as a mechanism of resistance to EGFR-TKIs in NSCLC.^{6,9-12} The NTRK inhibitors larotrectinib and entrectinib have been approved in the United States, Europe, and elsewhere for patients with NTRK gene fusion-positive solid tumours, including NSCLC¹³⁻¹⁵; therefore, the detection and diagnosis of NTRK gene fusion could provide clues for appropriate therapeutic strategies against NSCLC.

Herein, we report a patient with NSCLC, EGFR 19del, and the T790M mutation. Prognosis was poor after metastasis to the peritoneum following EGFR-TKI treatment with gefitinib and, subsequently, osimertinib. Platinum-based chemotherapy and treatment with both anlotinib and docetaxel in clinical trials were recommended following osimertinib resistance. Progression of peritoneal metastasis was observed after 14 months, leaving limited options for treatment. Rechallenge with osimertinib, combined with entrectinib, was the chosen therapy once LMNA-NTRK1 fusion emerged as a resistance mechanism. Notably, Osimertinib-based combination therapy induced the remission of peritoneal metastases although pancreatic metastasis occurred, and the disease slowly progressed over the following 5 months.

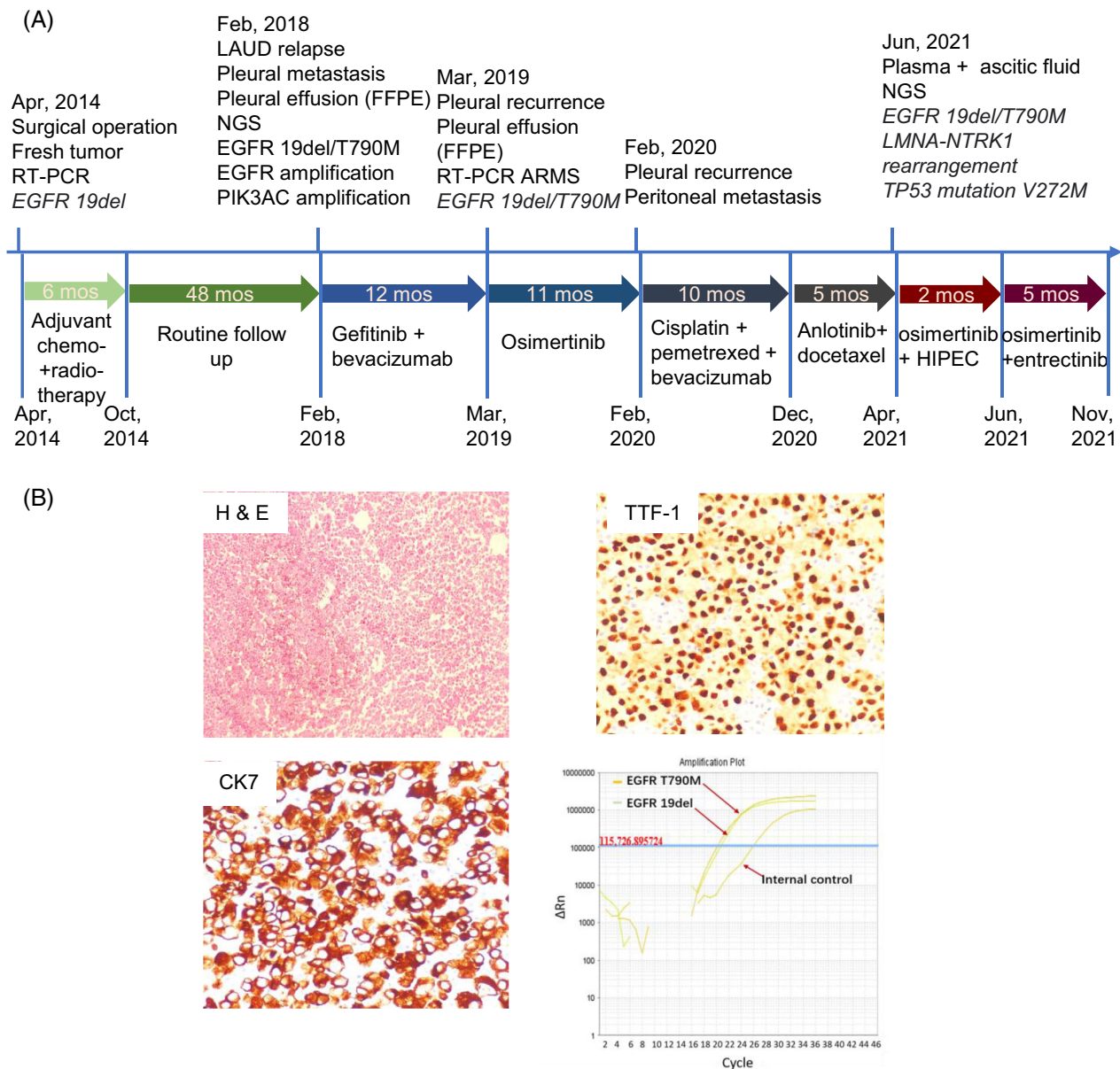


FIGURE 1 Summary of disease course, therapies, and molecular findings. (A) Timer shaft of gene testing and treatment measurement. (B) Pathological and RT-PCR examination of the pleural effusion specimen. IHC showed CK7 (+), Napsin a (+). RT-PCR amplification plot showed co-occurrence of EGFR 19del and T790M mutation. FFPE, formalin-fixed paraffin-embedded; HIPEC, hyperthermic intraperitoneal chemotherapy; LAUD, lung adenocarcinoma; mos, months

CASE REPORT

A 50-year-old Chinese man without a history of smoking was diagnosed with adenocarcinoma of the right lung

(pT2aN2M0, stage IIIA). He received a right middle lobectomy in March 2014 at a tertiary university hospital. Amplification-refractory mutation system polymerase chain reaction of the tumour sample revealed the EGFR 19del



FIGURE 2 CT scan of the primary lung adenocarcinoma at treatment milestones. CT, computed tomography; mos, months; mo, month; PD, progressive disease; SD, stable disease

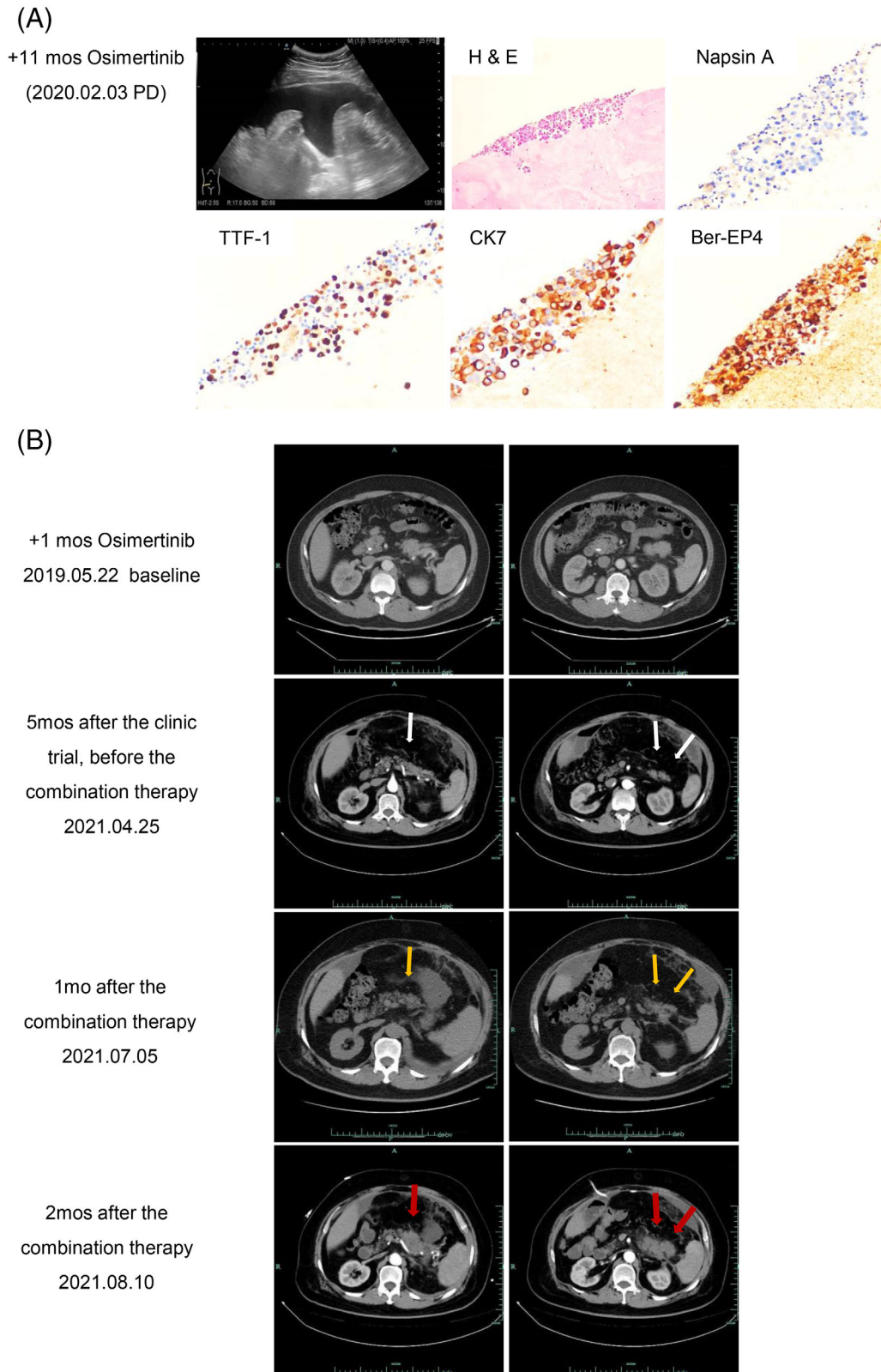


FIGURE 3 The progression of peritoneal and pancreatic metastasis. (A) Pathological examination of the ascitic fluid specimen. IHC showed CK7(+), Napsin a (+), TTF-1(+), Ber-EP4 (+), and Moc31(+). (B) Abdominal CT scan before and after 1 month and 2 months of the combination therapy of osimertinib and entrectinib. CT, computed tomography

(Figure 1A). Treatment was then sequential pemetrexed plus cisplatin for 4 cycles with adjuvant radiotherapy, and follow-up was performed every 6 months thereafter. The patient was referred to our hospital because of increasing dyspnea on 14 February 2018. Chest computed tomography showed bilateral pleural effusion (PE; Figure 2), and pleural fluid cytology revealed recurrent metastatic lung adenocarcinoma (Figure 1B) stage IIIB (pT4N2M0) without measurable lesions in the lung field. The DNA-based next-generation sequencing test was performed on formalin-fixed paraffin-embedded (FFPE) PE samples. The amplifications of EGFR (MAF, 6.87%) and PIK3AC (MAF, 6.06%) were found, and the EGFR 19del (MAF, 45.54%) with the co-existence of T790M mutation (MAF, 14.38%) were confirmed (Figure 1A). Osimertinib was suggested first, but the patient choose gefitinib instead because of economic reasons. Gefitinib was started at 250 mg/d on 25 February 2018. Regular follow-up showed distinct resolution of the PE; however, his recovery could not be defined as either

complete remission or partial remission because of the absence of measurable primary lung lesions. After 12 months of this first-line therapy, the patient developed recurrent PE, confirmed by verifying the concurrent EGFR 19del and T790M mutations using the amplification refractory mutation system (ARMS; Figure 1B). Osimertinib (80 mg/d) was prescribed on March 10, 2019, and progression-free survival (PFS) was achieved for 11 months.

Unfortunately, a CT scan on February 3, 2020 (Figure 2) indicated progressive disease (PD) with increasing PE. In addition, the evaluation of newly discovered ascitic fluid was consistent with adenocarcinoma (Figure 3A). Treatment was subsequently changed to cisplatin/pemetrexed combined with bevacizumab for 4 cycles starting on 26 February 2020 followed by pemetrexed/bevacizumab maintenance therapy. The disease was stabilized for approximately 10 months using subsequent chemotherapy until malignant PE and ascites recurred. Because the disease progressed without having had an objective response to previous therapies, the

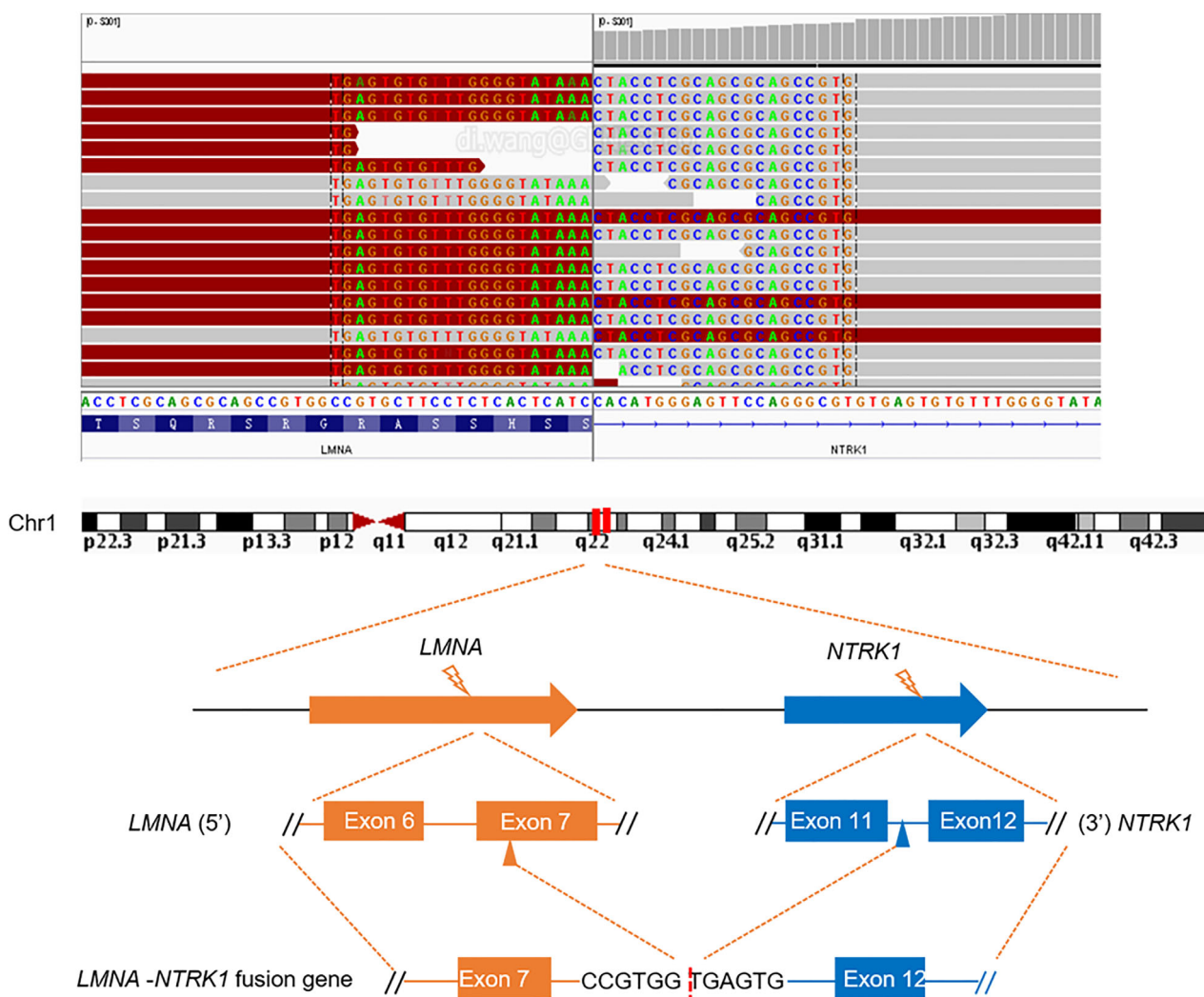


FIGURE 4 Identification of LMNA-NTRK1 rearrangement. (A) Next-generation sequencing test reads in the two LMNA and NTRK1 fusion breakpoints in chromosome 1 were visualized by integrated genomics viewer (IGV). The exact breakpoints are shown in the figure. (B) A scheme showing the fused exons of the LMNA-NTRK1 rearrangement

TABLE 1 Reported responses in lung cancer with NTRK fusion as acquired EGFR-TKI-resistance

Case no	Age	Sex	Pathology	Stage	Baseline (EGFR) blood/tissue	Pre-osi progression	Concurrent alterations	NTRK1- fusion blood/tissue MAF	Post-osi progression	Response
1. (Helman et al., 2018) ²⁶	NA	F	NSCLC	IV	G719C and S768I tissue	Rociletinib 8mos (T790M+)	PIK3CA amplification MYC amplification EGFR FGFR1 Amplification NFI Indel SMAD4 Q446fs CTNNB1 D32N	TPM3-NTRK1 plasma (0.14/10%)	Rociletinib	PD in 1 month
2. (Xia et al., 2019) ⁶	63	F	adenoCA	IV	del19 (746_751) T790M + plasma	Gefitinib 12mos, afatinib 3mos, osimertinib 15mos (T790M+)	EGFR C797S (14%) del 19 (MAF:37%) T790M (MAF:22%) EGFR amplification	LMNA-NTRK1 plasma (0.5%)	Crizotinib + osimertinib	PD in 9 month
3. (Wang et al., 2019) ²⁷	51	F	adenoCA	IV	None	Chemotherapy gefitinib Nedaplatin pemetrexed	None	IRF2BP2-NTRK1 fresh tumor (32.4%) pleural effusion (1.19%)	Crizotinib	SD for 16months
4. (Lin et al., 2021) ²⁸	68	F	adenoCA	IV	L858R plasma 42.87%	erlotinib 4mos osimertinib 6mos (T790M+)	NA	NOTCH2-NTRK1 Pleural effusion (24.85%)	larotrectinib + osimertinib	PD in 3 months
5. (Song et al., 2021) ²⁹	NA	NA	adenoCA	IV	L858R FFPE	Pemetrexed + nedaplatin (SD 2 mos) erlotinib (PR)16 mos osimertinib (PR 17 mos)	NA	TPR-NTRK1 plasma	Osimertinib + ensartinib	PR SD for 2 months, PD in 5 months
6.	NA	NA	adenoCA	IV	del19 (746_750) FFPE	Gefitinib 24mos osimertinib 6mos (T790M+) paclitaxel pemBrolizumab	NA	46 (SPATA46)-NTRK1 plasma	Ensartinib + icotinib	Durable response

Abbreviations: adenoCA, adenocarcinoma; NA, not applicable; NSCLC, none small-cell lung cancer; PD, progressive disease; PR, partial response; SD, stable disease.

patient was referred to a clinical trial of anlotinib (12 mg, QD from day 1 to 14 of a 21-day cycle) combined with docetaxel (60 mg/m², q3w, up to 4 cycles) on 16 December 2020.

Disease recurred with massive ascites 5 months after the third-line treatment. Abdominal CT revealed peritoneal metastases (Figure 3B). The next-generation sequencing test (425-gene panel; Nanjing Geneseeq Technology, Jiangsu, China) on the ascitic fluid to evaluate all possible druggable and driver mutations. Apart from the EGFR 19del (MAF, 34.2%), the T790M mutation (MAF, 12.1%), and a TP53 mutation (MAF, 50%), the LMNA-NTRK1 fusion (MAF, 9.4%; Figure 4) was detected. The MAF of LMNA-NTRK1, EGFR 19del, and T790M in its matched plasma sample were 0.6%, 0.5%, and 0.3%, respectively. Osimertinib was re-administered on 10 April 2021 together with 3 rounds of hyperthermic intraperitoneal chemotherapy after a multidisciplinary team discussion. We further proposed that this NTRK1 fusion gene could be partially responsible for resistance to osimertinib in this patient, given the temporal relationship between the emergence of NTRK1 fusion and previous EGFR TKI therapy. Because pan-TRK inhibitors became available in mainland China 2 months later, the therapy was changed to combination of osimertinib and entrectinib (600 mg/d). Disease slowly progressed with pancreatic metastasis in the following 5 months (Figure 3B) while peritoneal and pleural infiltration remained stable. The patient declined further cancer-related treatments due to their poor performance, and he died 1 month later.

Written informed consent was obtained from the patient for publication of this report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

DISCUSSION

Osimertinib resistance is irreversible despite its documented efficacy in first- and second-line settings.^{16,17} Once osimertinib resistance occurs, no further clear-cut therapeutic options are available following platinum-based chemotherapy and locally ablative therapy. In this report of lung adenocarcinoma, LMNA-NTRK1 rearranged fusion emerged as resistance mechanism after treatment with osimertinib. A further diagnosis of peritoneal metastasis indicated a poor prognosis and unlikely survival. After treatments with sequential EGFR-TKI, platinum-based chemotherapy, and anlotinib plus docetaxel (clinical trial) failed, entrectinib was administered to the patient in combination with osimertinib. This combination therapy showed survival benefit. Meanwhile, the abdominal CT scan before and after the combination therapy indicated remission in peritoneal metastases.

Rechallenge with osimertinib has been described as an optional treatment for patients with acquired resistance following prior osimertinib therapy.^{18–23} Metro et al.²¹ documented the success of osimertinib rechallenge against EGFR T790M-positive NSCLC in a patient who progressed after

sequenced osimertinib and chemotherapy. A study that included 15 people with EGFRm NSCLC rechallenged with osimertinib after interval therapy, showing a response rate of 33% and a median progression-free survival (PFS) of 4.1 months.²³ Recently, Fuchs et al.¹⁹ described a case series of six patients with EGFRm NSCLC resistant to erlotinib, finding that the median duration of treatment was 5.0 months, and the median overall survival (OS) was 45.0 months. In addition, the combination of osimertinib rechallenge and bevacizumab showed benefits and resulted in significantly longer PFS and OS compared to chemotherapy plus bevacizumab in patients with acquired resistance to osimertinib.¹⁸ Comparatively, our patient received chemotherapy intervention and was then directed to clinical trials after osimertinib resistance. Moreover, serial next-generation sequencing testing showed EGFR T790M persistence, and rechallenge with osimertinib at a dosage of 80 mg once daily showed clinical benefits with the addition of entrectinib. This finding suggests that osimertinib re-administration is an optional treatment following standard treatments for NSCLC that lead to acquired resistance to EGFR TKIs.

Multiple mechanisms contribute to the acquired resistance to EGFR-TKIs, specifically gefitinib and osimertinib, in patients with NSCLC.²⁴ The extremely rare NTRK fusion, which carries a poor prognostic factor for EGFR-mutated NSCLC, has been recognized as a mechanism of resistance to EGFR TKIs.⁹ Potential resistance mechanism was identified as TPM3-NTRK1 fusion in paired pre- and post-EGFR TKI-treated samples, according to a large-scale survey of 3505 EGFR-mutant NSCLC samples.¹² Consistent with this result, NTRK1+ fusions emerged after treatment with EGFR-TKIs in another large-scale study of 21,155 cases of lung cancer among Chinese, suggesting it is also a mechanism of resistance to EGFR TKIs.⁶ Accumulating evidence^{11,25,26} indicates that NTRK fusion can function as an EGFR-TKI resistance mechanism, rendering NTRK inhibitors optional treatments when EGFR-TKI resistance emerges via NTRK fusion. However, NTRK fusion is mutually exclusive of other canonical mutations, limiting the clinical outcome data, given the rarity of NTRK-positive NSCLC. Furthermore, NTRK-targeted therapy results in a differential response in NSCLC.

We therefore conducted an extensive literature review to identify the efficacy of therapies targeting NTRK fusion as the mechanism of AR to EGFR TKIs. Results are summarized in Table 1. One patient with acquired TPM3-NTRK1 fusion with coexisting EGFR G719C-S768I, NF1 F1397fs, CTNBN1 D32N, and SMAD4 Q446fs mutations did not respond to treatment with the third-generation EGFR-TKI rociletinib.²⁶ Another benefited from crizotinib monotherapy against IRF2BP2-NRTRK1 NSCLC, achieving stable disease after 16 months of therapy with crizotinib. However, in this case, gene fusion likely acted as a potent oncogenic driver instead of a resistance mutation after treatment with gefitinib.²⁷ Xia H et al.⁶ reported a case in which EGFR T790M, EGFR C797S, and LMNA-NTRK1 fusion were

detected after osimertinib resistance occurred, but the disease responded to a combination of crizotinib and osimertinib even though the patient showed continual slow disease progression for 9 months. On the other hand, one patient who received erlotinib followed by osimertinib showed stable disease for only 2 months once osimertinib rechallenge was combined with larotrectinib as a NOTCH2-NTRK1 fusion inhibitor.²⁸ In a recent study²⁹ of two EGFR-positive cases with NTRK1 fusions as the cause of AR, one patient with the EGFR p.L858R mutation underwent multiple lines of chemotherapy and targeted therapy, including erlotinib and osimertinib, until developing progressive disease (PD). Subsequently, combinatorial therapy with osimertinib and ensartinib was administered when the TPR-NTRK1 rearrangement was discovered, resulting in SD for 2 months and PD after 5 months. One other patient received gefitinib and subsequent osimertinib until disease progression, then responded poorly to combinatorial chemo- and immunotherapy. Subsequent NGS testing of the plasma revealed SPATA46-NTRK1 fusion and the initial EGFR exon 19 deletion mutation. A durable response was observed with both the primary and metastatic lesion regressions under ensartinib and icotinib combination therapy. Collectively, the combination therapy targeting EGFR and acquired fusion has reportedly shown clinical benefits in some cases; however, it is associated with increased costs and potential adverse effects. Unfortunately, detailed safety information on the indexed patients was unavailable. Dual TKIs, such as osimertinib plus ALK TKIs were reported tolerable with mild gastrointestinal toxicity and rash.^{30–33} The two currently available NTRK inhibitors, larotrectinib and entrectinib, were generally well tolerated with a manageable safety-efficacy profile based on initial and updated analyses.^{34–36} For entrectinib, the most frequent serious adverse reactions were lung infection, dyspnoea, pleural effusion, cognitive impairment, and fractures. Dose modifications should be considered to manage adverse drug reactions, such as nervous system disorders and cardiac disorders.³⁷ Adverse events of larotrectinib were predominantly Grade 1–2. Grade 3 events were reported in two NSCLC patients, including myalgia, hypersensitivity, and weight increase.³⁸ Thus, further investigations are required regarding the efficacy and safety of the combination therapy of EGFR TKIs and NTRK inhibitors in more NSCLC cases going forward.

Acquired resistance is a constantly evolving process under the pressure of highly selective and potent inhibitors. Novel mechanisms of resistance that have thus far been uncovered encompass primarily complex resistance mutations and bypass track mechanisms. In our case, the TP53 mutation V272M (MAF, 50%) within the DNA-binding domain, confirmed as a negative factor for PFS and OS in EGFR-mutated NSCLC treated with EGFR-TKIs,^{39,40} could have potentially affected our patient's response.

In conclusion, this literature review together with this case report suggests that the combination therapy against the driver of the EGFR mutation and the druggable bypass NTRK fusion could provide clinical benefits and render this

a therapeutic option for patients acquiring resistance to EGFR TKIs. However, the outcomes of individual therapies depend on the dominant form of the resistance mechanism, and the effects of combinatorial inhibition of NTRK fusion and the driver EGFR mutation remain to be confirmed by the accumulation of additional case series and further research. Identification of resistance mechanisms using serial next-generation sequencing on tumour biopsies or cfDNA is crucial for the management of EGFR-mutated NSCLCs.

AUTHOR CONTRIBUTIONS

Jiao-Li Wang wrote the main manuscript, interpreted the data and submitted the manuscript. Liu-sheng Wang, Jun-qi Zhu, Jie Ren, and Di Wang collected the data and prepared the figures and tables. Man Luo contributed to the interpretation of data and wrote and revised the article critically. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST

None declared

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

The authors declare that appropriate written informed consent was obtained for the publication of this manuscript and accompanying images.

ORCID

Man Luo  <https://orcid.org/0000-0003-2393-102X>

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