



***BTN2A1-BRAF* fusion may be a novel mechanism of resistance to osimertinib in lung adenocarcinoma: a case report**

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Background: Non-small cell lung cancer (NSCLC) is one of the most common malignancies in the world. Osimertinib is a third-generation epidermal growth factor receptor tyrosine kinase inhibitor (*EGFR*-TKI) indicated for NSCLC that effectively targets sensitive epidermal growth factor receptor mutation and exon20 T790M. Despite initially impressive outcomes, acquired resistance (AR) develops rapidly, typically within 9–13 months, and the mechanisms of resistance are not fully understood. Over the past years, *EGFR*-TKI and programmed cell death-ligand 1 (PD-L1) inhibitors have been widely used to treat for patients with advanced lung adenocarcinoma.

Case Description: Herein we report a middle-aged female who suffered from lung adenocarcinoma based on the pathological diagnosis. Epidermal growth factor receptor exon 19 deletion was detected by next-generation sequencing (NGS). After the patient underwent a series of treatments, including osimertinib, *BTN2A1-BRAF* fusion was identified. After assessing PD-L1 expression by immunohistochemistry (IHC), the patient was switched to duvalizumab, a PD-L1 inhibitor, but no significant improvements were observed. NGS and IHC assays were conducted to analyze the biopsy and blood samples obtained during treatment.

Conclusions: This case substantiates that the acquisition of *BTN2A1-BRAF* fusion potentially serves as a mechanism of AR to osimertinib in NSCLC. Patients with sensitive epidermal growth factor receptor mutation derive minimal benefit from PD-L1 inhibitors irrespective of the degree of PD-L1 expression in the tumor tissue in IHC. Our case provides a new train of thought for treating this patient population.

Keywords: BRAF fusion; epidermal growth factor receptor tyrosine kinase inhibitors (*EGFR*-TKI); case report; programmed cell death-ligand 1 (PD-L1); non-small cell lung cancer (NSCLC)

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Introduction

Lung cancer is the main cause of cancer-related deaths worldwide. Non-small cell lung cancer (NSCLC) accounts for a significant portion of lung cancer cases (1). Epidermal growth factor receptor tyrosine kinase inhibitors (*EGFR*-TKIs) have attracted significant interest in recent years, given their ability to effectively prevent disease progression. Osimertinib is a third-generation *EGFR*-TKI that can target

exon20 T790M mutation. However, acquired resistance (AR) inevitably appears after 9–13 months of treatment. Although certain resistance mechanisms of third-generation *EGFR*-TKIs have been identified (such as C797S and *MET* amplification), many factors remain unknown, warranting exploration. Somatic mutations in *BRAF* genes occur in 3–8% of lung adenocarcinomas (2), and *BRAF* fusions account for 0.2% of NSCLCs (3). In our case, a new *BRAF* fusion, the

butyrophilin subfamily 2 member A1 (*BTN2A1*)-*BRAF* fusion, was detected using next-generation sequencing (NGS) after resistance to osimertinib, and the patient was switched to programmed cell death-ligand 1 (PD-L1) inhibitors (duvalizumab). We present the following case in accordance with the CARE reporting checklist (available at <https://tcr.amegroups.com/article/view/10.21037/tcr-22-2060/rc>).

Case presentation

A 53-year-old female who had never smoked was admitted to our hospital with a 2-month history of left-chest pain which worsened for 1 week. A computed tomography (CT) scan revealed space-occupying lesions in the left pulmonary hilum. Magnetic resonance imaging (MRI) showed a nodular abnormal signal intensity in the left frontal lobe, which was suspected to be a metastatic lesion. A biopsy sample obtained in the left-lobe of her lung by endobronchial ultrasonography (EBUS) was made into formalin-fixed paraffin-embedding (FFPE) tissue. The pathological diagnosis was NSCLC. Immunohistochemistry (IHC) staining was positive for TTF-1 but negative for P40 (Figure 1A). Finally, the patient was diagnosed with stage IIIc (T3N3Mx) lung adenocarcinoma. *EGFR* exon 19 deletion was detected in the tumor biopsy sample by 8-gene panel NGS (Burning Rock Dx, China). The patient first received monotherapy with gefitinib, and which

yielded a good initial response. Space-occupying lesions in the left upper lobe of the lung regressed, and the area of inflammation in the surrounding pulmonary tissue decreased. MRI showed that the metastatic lesion in the left frontal lobe regressed. After 13 months, disease progression was observed with an enlarged irregular mass in the left lung lobe, several obstructive inflammation pneumonia, involvement of multiple lymph nodes, and left pleural effusion. A plasma circulating tumor DNA (ctDNA)-associated 9-gene panel (Anoroad, China) and droplet digital polymerase chain reaction (ddPCR) were performed to determine subsequent therapy. *TP53* p.K132R and *EGFR* exon20 T790M-negative were identified in addition to the previously identified *EGFR* exon 19 deletion by liquid biopsy analysis. Despite treatment with “bevacizumab plus carboplatin plus pemetrexed” for 4 cycles, disease progression was observed. The left upper lobe mass became larger and obstructive pneumonia was exacerbated. Small nodules in the right lung and left oblique lung fissure were observed. Some lymph nodes under the left clavicle, in the mediastinum and at the left hilum of the lung were enlarged and were suspected to be metastatic. Moreover, left pleural effusion was still present. Besides, the patient experienced toxic side effects of chemotherapy with an abnormally elevated γ -Glutamyl transpeptidase (76 U/L), treated with the hepatoprotective drug glutathione. Besides, the patient experience other adverse events, including vomiting, allergy and urinary retention. *EGFR* amplification, *MTOR* mutation, and *BRCA* mutation were identified in the tumor biopsy sample using a 56-gene panel (Burning Rock Dx), the sample was harvested from the tumor tissue in the left lung by pulmonary puncture guided by CT. Later, the patient received a single cycle of “bevacizumab plus sintilimab”. Simultaneously, the *EGFR* exon20 T790M mutation was identified by cell-free DNA (cfDNA) using a 9-gene panel (Anoroad, China). Based on the liquid biopsy results, bevacizumab and osimertinib were administrated. The patient responded well and was diagnosed with stable disease (SD). Follow-up CT scans demonstrated regression of the primary lung lesion, resolution of the pleural effusion; and atelectasis recovery to a certain extent. CT scans also showed regression of the lymph nodes and left pleural thickening. The oncologist decided to continue treatment with osimertinib. At seven months, disease progression was follow-up, with enlargement of the primary lung tumor. Significant left pleural effusion was observed, accompanied by pericardial effusion. Part of the pleural effusion was encapsulated, with atelectasis of the left lung adjacent to

Highlight box

Key findings

- *BTN2A1-BRAF* fusion serves as a mechanism of acquired resistance to osimertinib in NSCLC.

What is known and what is new?

- Osimertinib is a third-generation *EGFR*-TKI that targets *EGFR* sensitive mutation and exon20 T790M in NSCLC. Although some mechanisms of resistance to osimertinib have been documented, many remain unexplored, warranting further research.
- *BTN2A1-BRAF* fusion is a new mechanism of acquired resistance to osimertinib. Patients with *EGFR* sensitive mutation and *BTN2A1-BRAF* fusion derive little benefit from PD-L1 inhibitors.

What is the implication, and what should change now?

- Next-generation sequencing is indicated for NSCLC patients before treatment with *EGFR*-TKI to identify gene mutations when the disease status changes. It is highly recommended to adjust the treatment regimen for patients positive for *BTN2A1-BRAF* fusion when taking osimertinib.

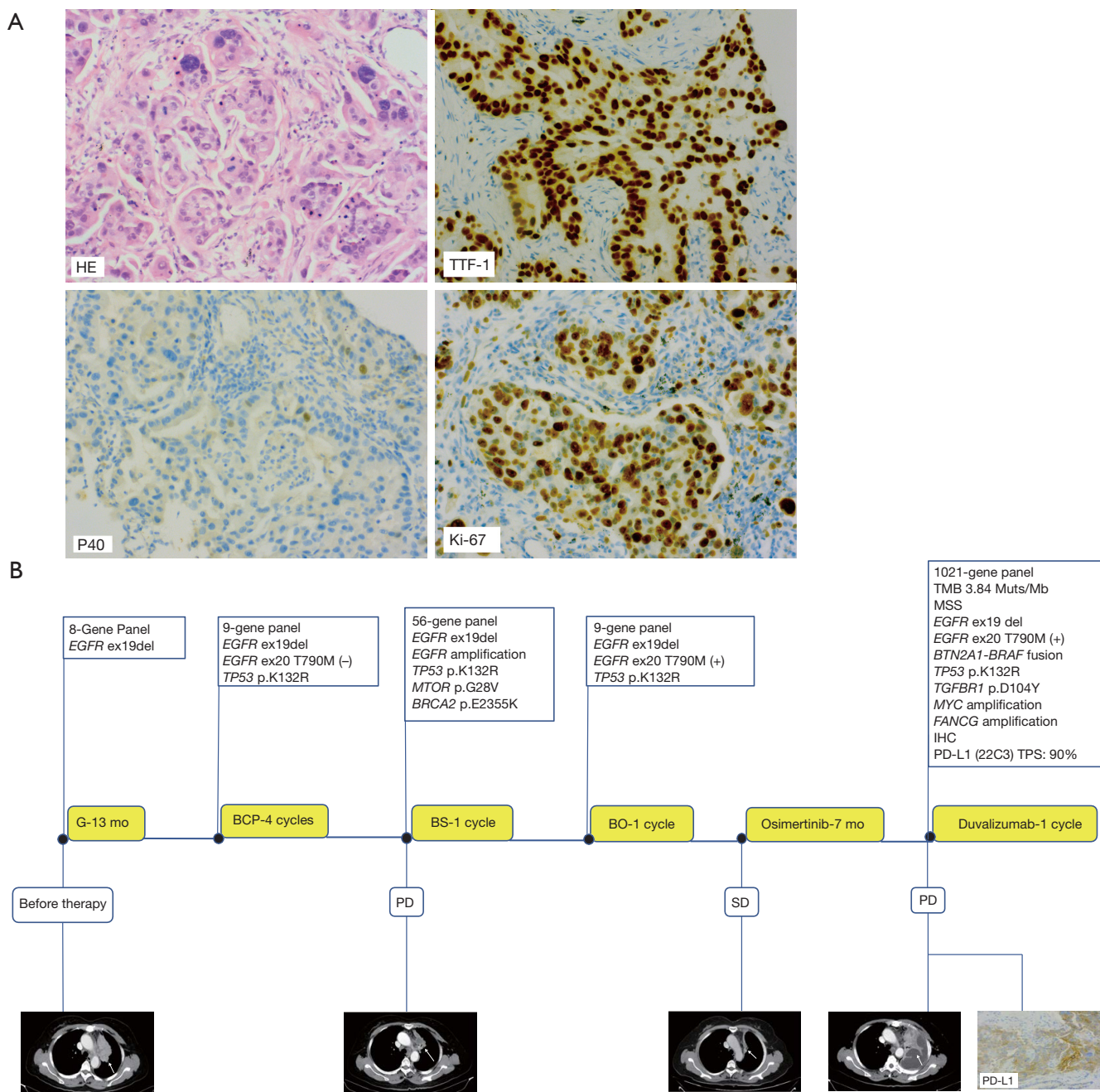


Figure 1 Evidence of diagnosis and clinical course of the patient. (A) The sample biopsy was positive for TTF-1 and negative for P40, with a high Ki-67 proliferation index (HE $\times 200$, TTF-1 $\times 200$, P40 $\times 200$, Ki-67 $\times 200$), suggesting lung adenocarcinoma. (B) CT of the chest (white arrows indicate lung adenocarcinoma in the left lobe) and drugs taken by the patient are illustrated on the time axis. The lung adenocarcinoma lesion regressed after taking bevacizumab and osimertinib for 1 cycle, but disease progression was observed after taking osimertinib for 7 months. PD-L1 staining was assessed through immunohistochemistry using the 22C3 PharmDx assay (Dako North America). PD-L1 ($\times 200$) was positive in 90% of tumor cells after progression with osimertinib and *BTN2A1-BRAF* fusion was detected by NGS. HE, hematoxylin and eosin; TTF-1, thyroid transcription factor-1; G, gefitinib; mo, month; BCP, bevacizumab + carboplatin + pemetrexed; BS, bevacizumab + sintilimab; BO, bevacizumab + osimertinib; PD, progressive disease; SD, stable disease; TMB, tumor mutational burden; MSS, microsatellite stability; IHC, immunohistochemistry; PD-L1, programmed cell death-ligand 1; TPS, tumor proportion score; NSCLC, non-small cell lung cancer; CT, computed tomography; NGS, next-generation sequencing.

the pleural effusion. Interestingly, we identified *BTN2A1-BRAF* fusion, a low tumor mutational burden (TMB; 3.84 Muts/Mb), and microsatellite stability (MSS), *TGFBR1* p.D104Y, *MYC* amplification and *FANCG* amplification in the following 1021 cancer-related genes (Geneplus, China) using FFPE tumor tissues obtained by EBUS. A high PD-L1 expression (tumor proportion score, TPS =90%) was found by IHC. Therefore, the patient was given duvalizumab; however, she passed away three months later. *Figure 1B* depicts the entire course of treatment. *Figure 2A,2B* illustrate the model of *BTN2A1-BRAF* fusion. *Table 1* shows the results of all tests conducted.

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 relatives of 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 of *BTN2A1* being a fusion partner for *BRAF* and the clinical course of an NSCLC patient with *BTN2A1-BRAF* fusion. During therapy, *BTN2A1-BRAF* fusion was detected only after disease progression with osimertinib; therefore, we hypothesize that *BTN2A1-BRAF* fusion is another possible mechanism of AR to osimertinib. After *EGFR* T790M mutation, the following mutations were observed, including *BTN2A1-BRAF* fusion, *TP53* p.K132R, *TGFBR1* p.D104y, *MYC* amplification and *FANCG* amplification in addition to *EGFR* exon 19 deletion in the final 1021 panel by NGS. According to Le *et al.* (4) resistance mechanisms to osimertinib in patients with *EGFR* T790M include *EGFR* reactivation or bypass pathway. In our case, the acquisition of *BTN2A1-BRAF* fusion was observed. We hypothesize that *BTN2A1-BRAF* fusion may be the mechanism that leads to resistance to osimertinib. Schoenfeld *et al.* (5) found that *TRIM24-BRAF* fusion was acquired after disease progression following treatment with first-line osimertinib in NSCLC, while genomic alterations associated with *BRAF* fusion after later-line osimertinib were *AGK-BRAF* and *MRPS33-BRAF*. Both *AGK-BRAF* and *MRPS33-BRAF* were observed in patients with *EGFR* T790M loss. Inconsistent with the literature, in our case, *BTN2A1-BRAF* fusion was acquired in a patient who still harbored the *EGFR* T790M

mutation after disease progression with osimertinib.

BRAF fusion genes differ in the position of the breakpoints within *BRAF*, which occur in introns (6). In this case, the breakpoint of *BTN2A1-BRAF* fusion occurred at intron 6 of the *BTN2A1* gene and intron 9 of the *BRAF* gene (*Figure 2*). This structure led to oncogene overexpression due to the absence of the auto-inhibition domain in conserved region 1 (CR1) (7), located on the 5' gene of *BRAF*. A promoter regulates oncogene expression in the 5' gene derived from the fusion partner (8). Many experiments indicated that *BRAF* fusion could interfere with the *RAS-RAF-MAPK* pathway and compromise the efficacy of osimertinib (9,10). Vojnic *et al.* validated that *AGK-BRAF* and *PJA2-BRAF* fusions were mechanisms of AR to osimertinib and demonstrated that the combination of osimertinib and trametinib (*MEK* inhibitor) effectively inhibited the growth of *BRAF*-fusion-positive cell lines (11). Wang *et al.* reported a successful case of trametinib response in a patient with primary *LIMD1-BRAF* fusion, with progression-free survival (PFS) of 7.4 months (12). Overall, *BTN2A1-BRAF* fusion may be an underlying resistance mechanism to osimertinib.

In our case, the patient harbored exon 19 deletion, a sensitive *EGFR* mutation in NSCLC. Peng *et al.* argued that *BRAF* fusion was more likely to occur in patients with *EGFR* exon 19 deletion than those with non-exon 19 deletion mutations, such as exon 21 L858R and *EGFR* amplification (13). Schrock *et al.* reported ten NSCLC cases with *BRAF* fusion, including six with exon 21 L858R and four with exon 19 deletion (14). However, it remains unclear which baseline sensitizing mutation (exon 19 deletion or exon 21 L858R) is more frequently retained with *BRAF* fusion.

In this case, the patient first took gefitinib for 13 months. Despite a good initial response, disease progression was eventually observed, which prompted switching to osimertinib. However, growing evidence suggests that osimertinib yields a longer PFS and overall survival (OS) (15), and better response for patients with central nervous system (CNS) metastases than gefitinib (16). However, there was no significant difference in PFS and OS among Asian patients (16), and the beneficial effect of osimertinib in this patient population is not sustained.

Interestingly, in some cases, immune checkpoint inhibitors plus chemotherapy can benefit patients with metastatic, non-squamous *EGFR*-sensitive mutation NSCLC (17). Given that duvalizumab is often used as a third-line or later treatment for advanced NSCLC, and the TPS of this patient's PD-L1 was high (TPS =90%), the

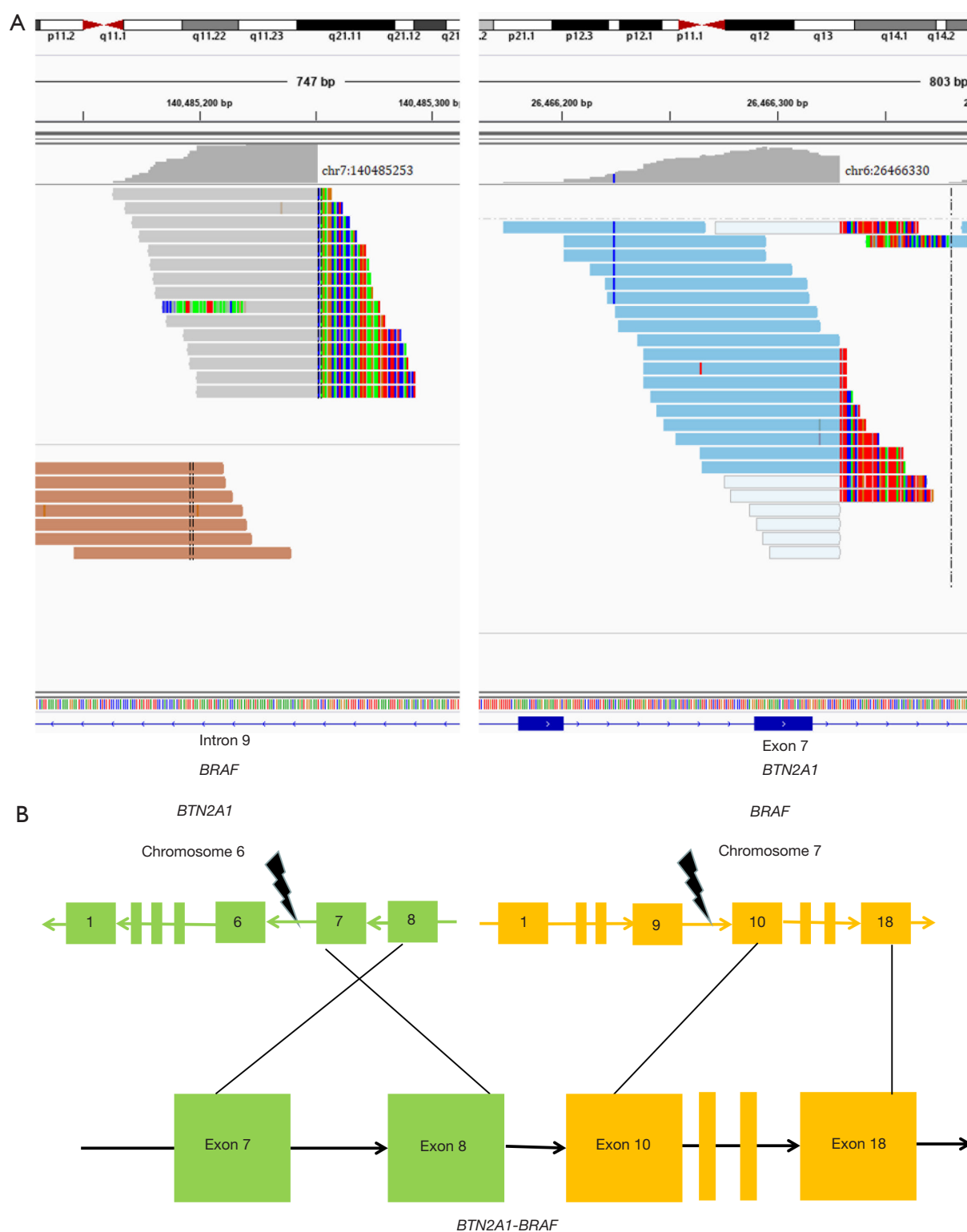


Figure 2 Evidence of *BTN2A1-BRAF* fusion. (A) The Integrative Genomics Viewer snapshot of *BTN2A1-BRAF*. (B) Schematic representation of *BTN2A1-BRAF* fusion structure. Arrows represent the direction of transcription.

Table 1 Findings of gene sequencing during treatment

Time of sampling	Method	Sample	Gene	Mutation style	Frequency or CN
Before using <i>EGFR</i> -TKI	8-gene panel NGS	FFPE	<i>EGFR</i>	Exon 19 deletion	14.85%
After using gefitinib	ddPCR	cfDNA (liquid biopsy)	<i>EGFR</i>	Exon 20 T790M (–)	–
	9-gene panel NGS	cfDNA (liquid biopsy)	<i>EGFR</i>	Exon 19 deletion	1.6%
			<i>TP53</i>	p.K132R	0.64%
After using bevacizumab + carboplatin + pemetrexed	56-gene panel NGS	FFPE	<i>EGFR</i>	Exon 19 deletion	26.02%
			<i>TP53</i>	p.K132R	51.12%
			<i>EGFR</i>	Amplification	CN =15.48
			<i>mTOR</i>	p.G28V	62.79%
			<i>BRCA2</i>	p.E2355K	70.17%
After using bevacizumab + sindilimab	9-gene panel NGS	cfDNA (liquid biopsy)	<i>EGFR</i>	Exon 19 deletion	8.2%
				Exon 20 T790M (+)	11.6%
			<i>TP53</i>	p.K132R	1.7%
After using osimertinib	1021-gene panel NGS	FFPE+ blood	TMB	–	3.84 Muts/Mb
			MSI	MSS	–
			<i>EGFR</i>	Exon19 deletion	30.8%
				Exon 20 T790M (+)	14.1%
			<i>BRAF</i>	<i>BTN2A1-BRAF</i> fusion	9.1%
			<i>TP53</i>	p.K132R	30%
			<i>TGFB1</i>	p.D104Y	12.8%
			<i>MYC</i>	Amplification	CN =7.4
			<i>FANCG</i>	Amplification	CN =6.8
	IHC	FFPE	PD-L1	PD-L1 (+)	90%

CN, copy number; *EGFR*-TKI, epidermal growth factor receptor tyrosine kinase inhibitor; NGS, next generation sequencing; FFPE, formaldehyde fixed paraffin embedded; ddPCR, droplet digital polymerase chain reaction; cfDNA, cell free DNA; TMB, tumor mutational burden; MSI, microsatellite instability; MSS, microsatellite stability; IHC, immunohistochemistry; PD-L1, programmed cell death-ligand 1.

patient was switched to a PD-L1 inhibitor (duvalizumab) after experiencing disease progression with osimertinib. However, the efficacy of duvalizumab in this patient was below par. The patient derived minimal benefit from PD-L1 inhibitors, consistent with reports that patients with *EGFR* driver mutation-positive lung adenocarcinoma have a negative response to immune checkpoint therapy. Yu *et al.* (18) reported that *EGFR* exon 19 deletion induces anergic dendritic cells to repress antitumor immunity through exosomes. There is a rich literature available substantiating that patients with *EGFR* driver mutation have a low expression of PD-L1 (19,20). Interestingly, in this case, the expression of PD-L1 was more than 90%,

which may be attributed to individual heterogeneity.

Importantly, this report provides hitherto undocumented evidence of the role of *BTN2A1-BRAF* in fusion inducing AR to osimertinib. Indeed, the emergence of *BRAF* fusion may impact the efficacy of osimertinib. Besides, immune checkpoint inhibitors are not recommended for patients with *EGFR* driver mutations. Our case emphasizes the need for clinicians to conduct a more comprehensive analysis before treatment selection. *BRAF* inhibitors and/or *MEK* inhibitors or triple combinations with *ERK* inhibitors should be considered to overcome resistance to *BTN2A1-BRAF*.

There were some limitations in this case report. For

instance, we did not carry out preclinical experiments, and more radiological evaluations should have been performed after each different treatment. Overall, monotherapy with PD-L1 inhibitors is not indicated according to the TPS of PD-L1 expression, regardless of the mutation of *EGFR* and other genes.

Conclusions

BTN2A1-BRAF fusion may be a mechanism of resistance to osimertinib, and patients with *EGFR* driver mutation derive minimal benefit from PD-L1 inhibitors in NSCLC.

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Footnote

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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 relatives of 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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