Successful re-challenge of dabrafenib-trametinib combination therapy in advanced *BRAF*^{V600E}-mutant non-small cell lung cancer after previous cytotoxic chemotherapy, targeted therapy, and immunotherapy: a case report

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Background: Patients with v-raf murine sarcoma viral oncogene homolog B1 (*BRAF*)^{V600E}-mutant non-small cell lung cancer (NSCLC) benefit from treatment with a combination of BRAF and mitogen-activated protein kinase (MEK) inhibitors, but resistance and disease progression develop in most patients. Pre-clinical studies and case studies of melanoma indicate that acquired resistance to BRAF inhibition may be reversible. However, studies on the effects of dabrafenib-trametinib (D/T) re-challenge for relapse in NSCLC are limited.

Case Description: A 58-year-old Chinese woman with a history of smoking and hypertension was diagnosed with stage IV B lung adenocarcinoma with metastasis. The targeted next-generation sequencing (NGS) of the patient's lung tumor biopsy tissues revealed the presence of a *BRAF*^{V600E} mutation with an allele frequency (AF) of 30.54%. The patient was treated with cytotoxic chemotherapy (the 1st line), D/T targeted therapy (the 2nd line), and immune checkpoint inhibitor monotherapy (pembrolizumab, the 3rd line), all of which achieved a partial response (PR) that lasted for a total of 8 months. The 2nd NGS analysis of the lung tissue specimens revealed the presence of a *BRAF*^{V600E} mutation (AF =18.41%) without mutations, which was potentially involved in the resistance to BRAF/MEK inhibition. At the 4th line, she subsequently re-challenged D/T, and achieved a 4th PR, lasting for 5 months. The 3rd NGS analysis revealed the retention of the *BRAF*^{V600E} mutation (AF =0.39%). Her treatment was switched to pembrolizumab (the 5th line), and the disease remained stable for another 6 months as of the last follow-up in November 2021. She didn't experience any adverse events throughout the treatment.

Conclusions: Our findings suggest that the re-challenge of D/T and immune checkpoint blockage therapies offer another therapeutic option for NSCLC patients with the *BRAF*^{V600E}-mutant who have received extensive prior treatments. In addition, our advanced NSCLC patient with the *BRAF*^{V600E}-mutant also derived long-term clinical benefits from initial chemotherapy, molecular-targeted therapy, and immunotherapy.

Keywords: Non-small cell lung cancer (NSCLC); D/T re-challenge; *BRAF*^{V600E}; immune checkpoint blockage (ICB); case report

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Introduction

The v-raf murine sarcoma viral oncogene homolog B1 (*BRAF*)^{V600E} (Val600Glu) mutation acts as an oncogene driver in patients with non-small cell lung cancer (NSCLC) and occurs in 1–2% of lung adenocarcinomas (1,2). Patients with *BRAF*^{V600E}-mutant NSCLC could benefit from treatment with BRAF inhibitor and mitogen-activated protein kinase (MEK) inhibitor combination therapy, but acquired resistance and disease progression develop in most of patients (2). Pre-clinical studies and case studies of melanoma indicate that acquired resistance to BRAF inhibition can be reversible (3,4). There is no dabrafenib-trametinib combination therapy (D/T) re-challenge case in an advanced *BRAF*^{V600E}-mutant NSCLC patient reported. In this article, we report the case in which a long-term partial response (PR) to D/T re-challenge in an advanced *BRAF*^{V600E}-mutant NSCLC patient was achieved after previous cytotoxic chemotherapy, targeted D/T therapy and immune checkpoint blockade (ICB) exposure. We present the following article in accordance with the CARE reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-3887/rc).

Case presentation

A 58-year-old Chinese woman with a history of smoking and hypertension was diagnosed with stage IV B lung adenocarcinoma with pleura, bilateral lungs, mediastinal lymph node, left cervical lymph node, and left adrenal metastasis. In September 2018, the 1st-line pemetrexed and carboplatin treatment led to the 1st PR based on the Response Evaluation Criteria in Solid Tumors version (RECIST) version 1.1 (see *Figure 1*). Some 4 months later, because of her kidney impairment, the chemotherapy was held.

In November 2018, targeted next-generation sequencing (NGS) was performed on lung tumor biopsy tissues from the patient using a 68-gene panel (Burning Rock Biotech, Guangzhou, China), and the presence of a *BRAF*^{V600E} mutation with an allele frequency (AF) 30.54% was identified. After a progression-free survival (PFS) of 8 months, the patient experienced clinical and radiological progressive disease (PD). In July 2019, the patient initiated the 2nd-line treatment with D/T combination therapy. Approximately 4 weeks after the initiation of D/T, computed tomography (CT) revealed the remarkable tumor shrinkage of the right lung mass (see *Figure 1*). The patient achieved the 2nd PR based on the RECIST. After 10 months of D/T treatment, a chest CT scan revealed a marked increase in tumor size that led to PD. From March to December 2020, the patient received immunotherapy with 11 cycles of a human monoclonal antibody against programmed cell death-1 (PD-1) pembrolizumab (Keytruda), and the patient achieved the 3rd PR that lasted until November 2012 when a CT scan showed the further progression of the disease in the lungs.

Based on a 520-gene panel (Burning Rock Biotech, Guangzhou, China), the 2nd NGS analysis of the lung tumor tissue revealed the presence of a *BRAF*^{V600E} mutation, a tumor mutational burden (TMB) of 6.98 mut/Mb. The programmed death-ligand 1 (PD-L1) tumor proportion score (TPS) was 80%. Other missense mutations with no clear functional role were detected. No mutation potentially involved in resistance to BRAF/MEK inhibition was detected. In December 2020, a D/T re-challenge was initiated. At the 4-week follow-up, a PR in the lungs, pleura, and lymph node was observed. The patient achieved the 4th PR that lasted for 5 months until May 2021, when the treatment was discontinued due to progression in the right lower lung, mediastinum, and lymph node. A 3rd NGS analysis was performed with her blood sample and revealed the retention of the *BRAF*^{V600E} mutation but with a declined abundance. Her treatment was switched to pembrolizumab (7 cycles), and her disease had remained stable for 6 months as of the last follow-up in November 2021.

All the procedures performed in this study were conducted 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 was obtained from the patient for the publication of this manuscript and any accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

In this article, we reported the case of an advanced NSCLC patient with the *BRAF*^{V600E}-mutantion, who derived 3 long-term survival benefits from cytotoxic chemotherapy, targeted therapy, and ICB therapy, and who also successfully re-challenged both the D/T treatment at the 4th line and the ICB treatment at the 5th line.

Our patient had a PFS of 5 months after the D/T re-challenge and obtained a PR on the lung, pleura, and lymph node. To date, 2 *BRAF*^{V600E}-mutant NSCLC cases treated

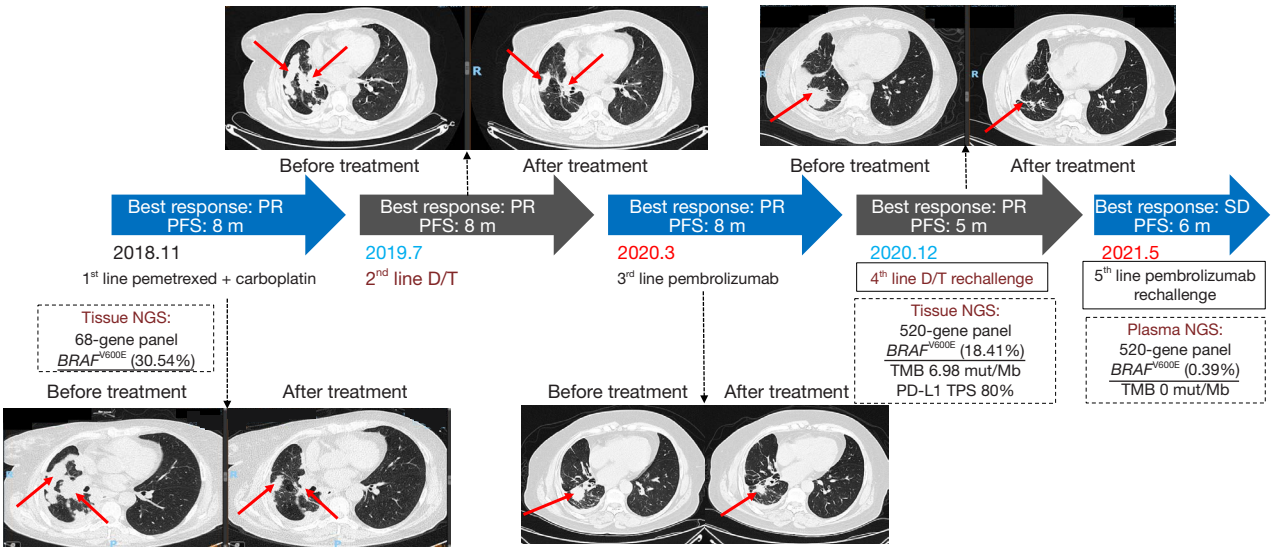

Figure 1 Timeline of the patient's treatment history and representative CT images. Red arrow: tumor lesions. CT, computed tomography; PFS, progression-free survival; PR, partial response; NGS, next-generation sequencing; D/T, dabrafenib-trametinib; mut, mutation; SD, stable disease; TMB, tumor mutational burden; TPS, tumor proportion score; R, right; P, posterior; m, month.

with D/T re-challenge have been reported. In one of these cases, the patient was re-challenged with D/T combination, but after a short stable disease (SD) (of 2 months), the patient passed away following the rapid progression of disease (5). The other *BRAF*^{V600E}-NSCLC patient successfully re-challenged D/T combination therapy after the failure of chemotherapy and achieved a PR for 6 months (6). In advanced *BRAF*^{V600E}-mutant melanoma, a re-challenge with D/T could induce a complete response or PR in patients who have developed PD while undergoing upfront D/T treatment (3,4). A study has reported on patients who have received alternative treatments, such as ICBs (PD-1 and cytotoxic T-lymphocyte-associated protein 4 inhibitors), after failure due to the continuous use of D/T, and of D/T re-challenge being used after the failure of ICBs (3). The mechanism of D/T re-challenge is still unclear. A study of metastatic melanoma has reported that acquired resistance to D/T may be reversible in a "drug-free" environment (3). In this study, the ICB therapy may have created a "drug holiday", and reduced the number of heterogeneous tumor cells previously treated with D/T, resulting in patients regaining their sensitivity to D/T therapy.

This patient harbored a TMB of 6.98 (intermediate) and PD-L1 TPS of 80%, and experienced prolonged disease stabilizations in 2 courses of immunotherapy (7). Our advanced *BRAF*^{V600E}-mutant NSCLC case is consistent with a previous report demonstrating that ICB therapy provides superior benefits (8). This may be attributed to the high TMB status and the high expression level of PD-L1 in *BRAF*^{V600E}-mutant NSCLC tumors. Conversely, other targetable oncogene alterations [e.g., epidermal growth factor receptor (*EGFR*) and human epidermal growth factor receptor 2 (*HER2*) mutations], and oncogenic fusions, including anaplastic lymphoma kinase (*ALK*), c-ros oncogene 1 (*ROS1*), rearranged during transfection (*RET*), and c-MET proto-oncogene (*MET*) of NSCLC with high TMB and PD-L1 expression still derive limited benefits from immunotherapy. Immunotherapy has been reported to have remarkable clinical benefits in *BRAF*^{V600E}-NSCLC patients. In a small cohort study, 3/4 *BRAF*^{V600E}-mutant NSCLC patients experienced prolonged disease stabilizations from immunotherapy (5). In another cohort study (n=26), the response rate was 26%, and the median PFS and overall survival were 5.3 and 22.5 months, respectively (9).

Conclusions

There are very limited therapeutic options for patients with advanced *BRAF*^{V600E}-mutated NSCLC who progress when treated with D/T and ICB therapies in clinical settings. The re-challenge of D/T and ICB could offer an option for

such patients who have received extensive prior treatments. In addition, *BRAF*^{V600E}-mutant NSCLC patients also derive long-term clinical benefits from initial chemotherapy, molecular-targeted therapy, and immunotherapy.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-3887/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-3887/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 Declaration of Helsinki (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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