Original Article

Exploring immunotherapy efficacy in non-small cell lung cancer patients with *BRAF* mutations: a case series and literature review

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Background: The use of immunotherapy in treatment of non-small cell lung cancer (NSCLC) patients with the *BRAF* gene mutations is an area of active research and is an item of clinical trials. While *BRAF* mutations are relatively infrequent in NSCLC patients, comprising approximately 1–3% of cases, the V600E substitution stands out as the most prevalent subtype of *BRAF* mutations. The presence of this mutation in cancer cells qualifies the patients for first-line therapy with BRAF and MEK inhibitors. This study aims to evaluate the efficacy of immunotherapy in NSCLC patients with BRAF mutations. We presented a series of seven NSCLC cases with *BRAF* mutations, four of whom received immunotherapy or chemoimmunotherapy.

Methods: We observed benefit from immunotherapy in all patients, but its duration depended on comorbidities and the presence of brain metastases. Utilization of the next generation sequencing (NGS) technique causes high detection frequency of BRAF mutations (4.7% of patients), although mutations other than V600E may predominate (4 out of 7 patients).

Results: In patients receiving immune checkpoint inhibitors (ICIs)-based therapy, the median progression-free survival (PFS) was 17 months from the start of immunotherapy, the overall objective response rate (ORR) was 50%, and disease control was achieved in all patients.

Conclusions: Immunotherapy can benefit NSCLC patients with BRAF mutations, though its efficacy is affected by comorbidities and brain metastases. The use of NGS enhances mutation detection, highlighting the need for personalized treatment approaches in NSCLC management. The varying responses to treatments among the patients emphasize the complexity of NSCLC management and the necessity for a personalized approach.

Keywords: Non-small cell lung cancer (NSCLC); *BRAF* mutation; immunotherapy; case series

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Introduction

The RAF proteins (ARAF, BRAF, CRAF) act as signal transmitters from membrane receptors for growth factors to transcription factors, regulating the proliferative activity of epithelial cells. In particular, the RAF proteins are the part of the mitogen activated protein kinase (MAPK) signaling pathway. RAF proteins have serine-threonine kinase activity (1).

Mutations in the *BRAF* gene result in constitutive kinase activity or in impaired kinase development. Therefore, these mutations are divided into three classes:

- Class I mutations occur at codon 600 (V600E, V600D, V600K, V600R, V600M) and they are associated with kinase activation, which does not require activation by KRAS and BRAF dimerization.
- Class II mutations occur at codons other than 600 (most often G464, G469, L597, K6001) and cause kinase activation independent of KRAS stimulation, but requiring BRAF dimerization;
- Class III mutation occurs in codons other than 600 and results in impaired kinase development, which requires KRAS stimulation and BRAF heterodimerization (e.g., with ARAF or CRAF) (2).

The most common mutation in the *BRAF* gene is V600E substitution, occurring in up to 50% of melanoma patients. The V600K mutation is presented in 10% of melanoma patients, while the remaining mutations are rare. Mutations in the *BRAF* gene are also found in 30–40% of patients with thyroid cancer, in 15% of patients with cholangiocarcinoma, in 10% of patients with colorectal cancer and in 3% of non-small cell lung cancer (NSCLC) patients. NSCLC patients with *BRAF* mutations are most often elderly, smokers (*BRAF* mutation may coexist with other driver mutations, resulting in a higher number of neoantigens) and have a diagnosis of adenocarcinoma. The V600E substitution occurs in less than 50% of NSCLC patients with *BRAF* mutations, and mutations in codon 594 are relatively common (3).

BRAF inhibitors in combination with MEK inhibitors (downstream signaling protein) have been used in the treatment of patients with mutations in the *BRAF* gene. BRAF inhibitors include vemurafenib (registration in melanoma patients), dabrafenib (registration in melanoma and NSCLC patients), and encorafenib (registration in melanoma and colorectal cancer patients). MEK inhibitors include cobimetinib, trametinib and binimetinib. Thus, therapy with BRAF and MEK inhibitors became one of the first agnostic therapies in oncology (4).

Dabrafenib and trametinib were approved in NSCLC patients based on phase II BRF113928 study (NCT01336634)—a multicenter, three-cohort, non-randomized, clinical trial. The study enrolled metastatic NSCLC patients with *BRAF* V600E mutation who were previously pretreated (chemotherapy) or treatment naïve (5). Currently, the most used first-line therapy in NSCLC patients without abnormalities in the *EGFR*, *ALK* and *ROS1* genes is immunotherapy or chemoimmunotherapy. There is no sufficient information on the effectiveness of BRAF and MEK inhibitors in the second-line treatment after failure of immunotherapy-based therapies in patients with the *BRAF* V600E mutation, because such patients were not recruited for the BRF113928 study (the study was active in 2014–2016). Recently, molecularly target therapies are also moving to the perioperative setting. Major pathological response to neoadjuvant therapy with dabrafenib and trametinib in patients with stage IIIA (cT1cN2M0) lung adenocarcinoma harboring *BRAF* V600E mutation was reported. Although it is a single experience, it suggests that double BRAF and MEK blockade may be a possible treatment option in potentially resectable NSCLC patients

Highlight box

Key findings

- The study provides a detailed examination of seven non-small lung cancer (NSCLC) patients with different *BRAF* mutations, showing the complexity and heterogeneity of this subset of lung cancer.
- In 4% of patients tested with next generation sequencing (NGS) *BRAF* mutation was present.
- In patients receiving immune checkpoint inhibitors (ICIs)-based therapy, the median progression-free survival (PFS) was 17 months from the start of immunotherapy, the overall objective response rate (ORR) was 50%, and disease control was achieved in all patients.

What is known and what is new?

- CommonV600E mutation was detected in only three patients and, in the remaining patients, mutations in codons other than 600 of the *BRAF* gene were showed.
- Programmed death ligand 1 (PD-L1) expression in study group is independent of *BRAF* mutation ranging from 0 to 80% of tumor cells.

What is the implication, and what should change now?

- The article highlights the challenges of managing advanced NSCLC with BRAF mutations, where approved targeted treatments are limited to second line.
- Future studies with larger cohorts are necessary to validate the role of immunotherapy as therapeutic option for NSCLC patients harboring *BRAF* mutations.

with mutation in *BRAF* gene (6).

We know that the presence of mutations in the *BRAF* gene affects the activity of the immune system and, thus, can influence on the effectiveness of immunotherapy with immune checkpoint inhibitors (ICIs). Therefore, the choice of first-line treatment in NSCLC patients with *BRAF* V600E mutation may be difficult. Whereas first-line immunotherapy or chemoimmunotherapy must be considered in patients with rare mutations in the *BRAF* gene (7-9). Presented series of case reports aims to demonstrate the efficacy and safety of immunotherapy and chemoimmunotherapy in advanced NSCLC patients with various *BRAF* gene mutations. We present this article in accordance with the AME Case Series reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-253/rc).

Methods

This was retrospective, non-interventional observational study included patients for whom we started performing next generation sequencing (NGS) from the year 2019 onwards. Study was performed in two lung cancer centers and included consecutive patients. The collected case descriptions represent all known cases of patients with *BRAF* gene mutations diagnosed or treated at Department of Clinical Oncology and Thoracic Surgery in Poznań and Department of Pneumonology, Oncology and Allergology at Medical University in Lublin. NGS testing was performed in 150 NSCLC patients who were diagnosed in two academic oncology centers in Poland. Frequent mutations in the *EGFR* gene and *ALK* gene rearrangements were excluded before NGS examination. DNA was isolated using QIAamp DNA FFPE Tissue Kit (Qiagen, Germany). RNA was isolated using RecoverAll Total Nucleic Acid Isolation Kit (Thermo Fisher Scientific, USA). Nucleic acids were isolated from formalin fixed paraffin embedded (FFPE) tumor tissue or metastatic lymph nodes. Quality and quantity of isolates were assessed by Qubit 4.0 (Invitrogen, USA). Library were manually performed using the Oncomine Focus Assay (Thermo Fisher Scientific, USA). NGS was performed on the S5 Ion Torrent platform using the Oncomine Focus Assay (Thermo Fisher Scientific, USA). Ion Reporter software was used to evaluate the identified genetic variants. NGS has been conducted in the archive tissue (biopsy) before progression during first line therapy to qualify the patients for the second-line treatment based on the Polish rescue program for access to unreimbursed drug technologies. NGS was also performed in some patients after radical surgery or in qualification to first-line treatment. Programmed death ligand 1 (PD-L1) was examined using SP 263 antibody clone on BenchmarkGX autostainer (Ventana). Retrospective data on treatment strategies and their effects were collected from patient medical records and clinical databases. This included details on the types of treatments administered, such as immunotherapy, chemotherapy, or targeted therapy, as well as information on treatment duration and response rates.

Statistical analysis

Descriptive statistics: mean, median, minimum-maximum range and standard deviation (SD) of progression-free survival (PFS) were used to characterize the studied patients. Statistica 13.3 software (Tibco, USA) was used in the analyses.

Ethical statement

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and approved by the local Bioethics Committee at the Medical University of Lublin (No. KE-0254/160/2021). Written informed consent was obtained from the patients.

Results

BRAF mutations have been found in 7 patients (4.7% of the entire group of patients who underwent NGS testing). Three V600E mutations (42.9% of all *BRAF* mutations) and 4 mutations in other codons of the *BRAF* gene (57.1% of all *BRAF* mutations) were diagnosed. The study group consisted of 3 women and 4 men with a diagnosis of lung adenocarcinoma. The mean age of patients was 64.1 years.

In four cases, ICIs were part of the treatment strategy. Two patients received second-line immunotherapy, and two patients received first-line immunotherapy or chemoimmunotherapy. In patients receiving ICIs-based therapy, the median and mean of PFS from the start of immunotherapy were 17 and 19.5 months respectively (range, 5–39, SD +16.0) months. The overall objective response rate (ORR) was 50%, and disease control was achieved in all patients. The *BRAF* gene mutations were also found in two patients in early stage of disease who underwent lobectomy and one patient who were treated

Table 1 Characteristics of NSCLC patients with the *BRAF* gene mutations

No.	Gender	Age (years)	Histology type	Smoking history	*BRAF* gene mutations type	Co-alterations	PD-L1 expression	Treatment methods	Response to ICIs	PFS (months)
1	Female	59	AC	Unknown	V600E	*E542K* substitution in *PIK3CA*, amplification of *MED12* gen	5% of TC	Lobectomy	–	–
2	Male	65	AC	Non-smoker	V600E	–	30% of TC	1st line CTH and 2nd line nivolumab	SD	39
3	Male	69	AC	Smoker	D594G	–	80% of TC	1st line CTH and 2nd line atezolizumab	SD	26
4	Male	62	AC	Ex-smoker	V600E	–	<1% of TC	Palliative RTH and 1st line CTH	SD	18
5	Female	56	AC	Ex-smoker	N581S	–	80% of TC	1st line pembrolizumab	PR	5
6	Male	78	SCC	Smoker	D594G	*NF1*, *TP53*, *FANC* and *CDKN2A/B*	2% of TC	1st line pembrolizumab with CTH	PR	8
7	Female	60	AC	Unknown	G466V	–	10% of TC	Lobectomy	–	–

NSCLC, non-small cell lung cancer; PD-L1, programmed death ligand 1; ICIs, immune checkpoint inhibitors; PFS, progression free survival; AC, adenocarcinoma; TC, tumor cells; CTH, chemotherapy; RTH, radiotherapy; SD, stabilization of disease; PR, partial response; SCC, squamous cell carcinoma.

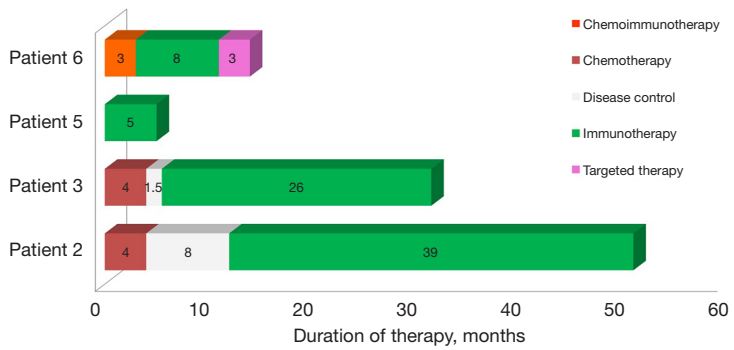

Figure 1 Duration of chemotherapy, immunotherapy, and molecularly targeted therapy in NSCLC patients with *BRAF* mutations. NSCLC, non-small cell lung cancer.

with palliative radiotherapy and first-line chemotherapy. Characteristic of the patients and treatment results are presented in *Table 1*. Comparative duration of chemotherapy, immunotherapy, and targeted therapy is presented in *Figure 1*.

Case 1

A 59-year-old woman with a small tumor in the right lung was treated surgically with resection of middle right lobe in November 2019. Adenocarcinoma in stage IB, T2bN0M0 was diagnosed. Based on pathological results no adjuvant treatment was implemented at that time. In surgical specimen NGS was performed. The coexistence of V600E substitution in the *BRAF* gene and E542K substitution in the *PIK3CA* (phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha) gene was found. These variants were accompanied by amplification of *MED12*

(mediator complex subunit 12) gene. Patient was lost to follow up one year after surgery.

Case 2

A 65-years old male with a history of pulmonary embolism and ischemic stroke was diagnosed with stage IV, T3N2M1 adenocarcinoma in October 2020. First-line treatment included cisplatin and pemetrexed with a total of 5 cycles (4 cycles of platinum doublet and one cycle of pemetrexed maintenance monotherapy). Due to disease progression in October 2021 (PFS of 12 months), he received nivolumab. Partial response was observed in first computed tomography (CT) scans. Immunotherapy was very well tolerated. During treatment, NGS was performed to plan further treatment in case of progression. BRAF V600E mutation was diagnosed. The response to nivolumab is still maintained (39 months) and the patient does not require dabrafenib and trametinib therapy.

Case 3

A 69-years old male with a history of heavy smoking, Eastern Cooperative Oncology Group (ECOG) 1 was diagnosed with stage T3N2M1 lung adenocarcinoma in October 2019. First line treatment included cisplatin and pemetrexed with a total of 5 cycles (4 cycles of platinum doublet and one cycle of pemetrexed monotherapy). Due to disease progression in March 2020 (PFS of 5.5 months) he received atezolizumab. Partial response was observed, and immunotherapy was very well tolerated. He received total of 30 cycles immunotherapy until progression in May 2022 (PFS of 26 months). D594G substitution in the *BRAF* gene has been found in NGS examination. There is no approved therapy for patients with this rare mutation in the *BRA*F gene and, therefore, the patient did not receive molecularly targeted therapy. Following immunotherapy, he received dapotopamab-deruxtecan in clinical trial with good tolerance and partial response.

Case 4

A 60-year-old male patient was diagnosed with stage IIIB lung adenocarcinoma in March 2022. PD-L1 expression on tumor cells were negative. However, NGS test revealed *BRAF* V600E mutation. Due to multiple concomitant diseases [chronic obstructive pulmonary disease (COPD), diabetes mellitus, hypertension, dyslipidemia, cerebral venous thrombosis] and poor performance status ECOG 2, patient was treated with radiotherapy of the tumor and mediastinal lymph nodes with palliative intent. The patient's condition improved and chemotherapy with carboplatin and pemetrexed was possible. He received 4 cycles of chemotherapy with good tolerance. No disease progression has been observed in following CT scans (PFS of 18 months from the start of chemotherapy). The patient is being observed in the clinic as part of standard care, including imaging examination every 3 months. In case of progression, dabrafenib with trametinib will be a valuable therapeutic option.

Case 5

In a 56-year-old woman with a history of heavy smoking, frontal lobe brain metastasis was diagnosed in October 2021. The resected brain tumor revealed adenocarcinoma with primary origin from the lung. NGS performed in the resected brain tumor revealed N581S substitution in the *BRAF* gene. Due to high expression of PD-L1 (PD-L1 expression on 80% of tumor cells) patient was treated with pembrolizumab monotherapy in the first-line setting. Partial remission of lung lesions occurred. Unfortunately, after 5 months of treatment a new metastasis appeared in the brain occurred and pembrolizumab was discontinued. Patient died due to neurological symptomatic progression.

Case 6

Lung squamous cell carcinoma was diagnosed in a 76-year-old male patient with history of heavy smoking. Metastasis of squamous cell carcinoma was also diagnosed in the kidney, and nephrectomy was performed in April 2021. An attempt to surgical removal of the lung tumor was also made, but due to invasion of the upper lobe withdraw patient from the procedure The patient had numerous comorbidities: post-myocardial infarction, myelodysplastic syndrome (MDS), goat and type 2 diabetes but remained in good performance status, ECOG 1. The patient was qualified for chemoimmunotherapy with carboplatin and paclitaxel in combination with pembrolizumab due to low expression of PD-L1 on tumor cells. In first assessment, partial regression was observed. However, in next routine CT scans after 9 cycles of pembrolizumab, progression of the disease in the pelvis and abdominal area was observed. To optimize treatment, NGS in the primary tissue material was performed with the presence of the D594G mutation

in the *BRAF* gene. Additionally, pathogenic variants in the *NF1* (neurofibromin 1), *TP53*, *FANC* (Fanconi anemia complementation group) and *CDKN2A/B* (cyclin dependent kinase inhibitor 2A/2B) genes were found in the NGS test performed by Foundation One. The procedure for expanded access to dabrafenib and trametinib was initiated due to exhaustion of therapeutic options for this patients, lack of registration of BRAF and MEK inhibitors for the patients with mutations in the *BRAF* gene other than V600E, and the coexistence of other genetic alterations (e.g., *NF1* mutation) that could activate the BRAF-MEK pathway. During treatment adverse events of anemia grade 3 (patient presented symptoms of MDS) and hyponatremia grade 3 were present. After 3 months of treatment with dabrafenib and trametinib, stable disease was present in tumor evaluation. However, patient discontinued treatment due to general health deterioration and he died shortly thereafter.

Case 7

A 60-year-old woman underwent lobectomy due to lung adenocarcinoma. Pathological examination allowed us to determine disease stage of IB and conduct NGS examination in which the pathogenic mutation G466V in the *BRAF* gene was detected. Due to stage IB after lobectomy no further treatment was required.

Discussion

The first reports on the immunosuppressive effect of *BRAF* gene mutations come from studies on melanoma cell lines and from melanoma patients. Constant activation of the MAPK pathway caused by mutations in the *BRAF* gene leads to the production of various immunosuppressive factors by neoplastic cells. Immunosuppressive cytokines produced by melanoma cells include IL-1 (interleukin-1), IL-10, VEGF (vascular endothelial growth factor) and IL-6. IL-1 induces expression of suppressive immune checkpoints: PD-L1 and PD-L2 on tumor associated fibroblasts (TAF). In turn, IL-10, VEGF and IL-6 could promote recruitment of immunosuppressive cells (myeloid-derived suppressor cells—MDSCs, regulator T cells—Treg) in the tumor microenvironment. Moreover, *BRAF* gene mutations cause internalization of MHC class I molecules from the surface of tumor cells, which reduces their ability to present tumor antigens (6,7). Moreover, the lack of STING impairs the MHC-I dependent antigen presentation. Blocked initiation of a type I interferon response leads to lack of expression of a set of interferon-stimulated genes (8).

In NSCLC patients, Li *et al.* performed nanostring RNA sequencing to evaluated tumor immune microenvironment (TIME) in 57 patients with different status of BRAF gene. Authors found that BRAF-mutated tumors (n=22) compared to tumors without BRAF mutations (n=35) had similar ratio of CD8-positive cells to Treg lymphocytes, levels of B lymphocytes and M2 macrophages as well as T cell-related gene expression (9). In contrast, the transcripts of genes related to effective immune cells (cytotoxic T cells, Th1 cells, NK cells, M1 macrophages) as well as immunosuppressors (such as Treg, mast cells, and neutrophils) were enriched in group of patients with BRAF mutation (10).

Therefore, it is assumed that the use of BRAF and MEK inhibitors in patients with the *BRAF* V600 mutation restores the activity of the immune system through an increase in the presentation of tumor antigens, a decrease in the expression of suppressive immune checkpoints, a decrease in tumor infiltration by Treg lymphocytes and MDSCs, and an increase in tumor infiltration by CD8-positive cells and natural killer cells. The use of immunotherapy after therapy with BRAF and MEK inhibitors may turn out to be more effective than using this method of treatment in the first line of therapy (6,7). Based on melanoma phase III randomized trial, DREAMseq (Doublet, Randomized Evaluation in Advanced Melanoma Sequencing), compared the efficacy and toxicity of nivolumab/ipilimumab followed by dabrafenib/trametinib to the converse sequence, the toxicity difference was insignificant between the treatment arms (11).

Zhang *et al.* analyzed ICIs efficacy in NSCLC patients with *BRAF* gene mutations collected form cBioPortal. 27 patients with *BRAF* mutations and 323 patients with wild type (wt) *BRAF* gene were included in the survival analysis. The authors found no effect of the *BRAF* mutations presence on the expression of PD-L1 on cancer cells. Tumor mutation burden (TMB) was higher in patients with mutations than in those with wt *BRAF* gene. They did not observe differences in overall survival (OS) among patients with and without *BRAF* gene mutations. However, the median OS was significantly longer in patients with non-V600E mutations than in patients with V600E substitution (12).

On the other hand, Dudnik *et al.* found that *BRAF* mutant NSCLC is associated with high level of PD-L1 expression, low/intermediate TMB and microsatellite-stable status. ICIs have favorable activity both in patients with

V600E and non-V600E mutation (13).

There is a documented case of a patient with NSCLC harboring a rare *BRAF* E501Q mutation, who had prolonged response to immunotherapy combined with chemotherapy in Vietnam. The patient was diagnosed with metastatic PD-L1-negative lung adenocarcinoma and received pembrolizumab plus chemotherapy as first-line treatment (14). On the opposite, there is a series of cases giving more overview on treatments strategies in patients with *BRAF* mutation and high PD-L1 expression. Four of the five patients with high PD-L1 expression on tumor cells received pembrolizumab. Of them, one patient experienced a partial response, but two patients experienced progressive disease and one patient was not evaluable (15).

Li *et al.* examined effectiveness of ICIs monotherapy or combined therapies in 59 NSCLC patients with *BRAF* mutations and 358 NSCLC patients without these mutations. There were no significant differences in PD-L1 expression between these two groups. The median OS was 18.5 months for patients with wt *BRAF* gene and 26.0 months for *BRAF*-mutated patients (HR =0.85, P=0.47). The median PFS was the same in both groups at 8.4 months. 45.8% and 33.0% of patients responded to treatment, respectively. The type of treatment (monotherapy *vs.* combined treatment in subgroups with and without mutations) and the type of *BRAF* mutation (V600E *vs.* non-V600E) had no effect on OS, PFS and ORR (9).

Wang *et al.* studied the effectiveness of different therapies in a total of 34 NSCLC patients with *BRAF* mutations. The median PFS for the whole cohort was 5.8 months and ORR was 24%. Patients who were treated with ICIs combined with chemotherapy reported a median PFS of 12.6 months and an ORR of 44%. Those who were treated with non-ICIs therapy had a median PFS of 5.3 months and an ORR of 14%. Patients had better clinical benefits form first line chemoimmunotherapy. In this group of patients, the median PFS was 18.5 months and ORR was 56% (16).

Maziers *et al.* conducted a retrospective study (IMMUNOTARGET registry) in NSCLC patients receiving ICIs monotherapy in second and subsequent lines who had at least one oncogenic driver alterations. The authors included 43 patients with *BRAF* gene mutations. Partial remission (PR) and disease control occurred in 25% and 54% of patients, median OS was 13.6 months, and median PFS was 3.1 months. The results of ICIs treatment in patients with *BRAF* mutations were better than in patients with actionable driver alterations in *EGFR*, *ALK*, *ROS1* or *RET* genes. However, the effectiveness of ICIs in *BRAF*-mutated patients was compared to the effect of immunotherapy in NSCLC patients with abnormalities in *KRAS*, *MET* and HER2 genes, where there were long-term responders were more frequent (17).

Some data from literature point out that patients with BRAF non-V600E (ORR 34%) mutations respond slightly better to immunotherapy than patients with BRAF V600E mutation (ORR 20%) (18). This might be due to more frequent co-existence with other mutations and higher TMB in non-V600E subgroup (19). The largest group of NSCLC patients with mutations in the *BRAF* gene was observed by Murciano-Goroff *et al.* Clinical and genomic data were collected for 5,945 patients. Authors identified 29 patients with class I mutations, 59 patients with class II or III mutations and 39 patients with variants of unknown significance (VUS) in the *BRAF* gene. TMB was higher in patients with class II or III mutations than in patients with class I mutations. ORR in patients treated with ICIs was 9% among patients with V600E mutation and 26% among patients with class II or III mutations. The median time on treatment in both groups was 1.9 months. Nine patients were treated with ICIs for 2 years or longer (two with class I mutations, two with class II or III mutations and five with VUS in the *BRAF* gene) (20).

In melanoma, BRAF mutant patients achieve long-term outcomes with immunotherapy, and also the sequence of treatments matters, with more favorable clinical outcomes with upfront ICI followed by targeted therapy, which is certainly a paradox in contrast with BRAF mutant NSCLC. The clinical findings reported in this small group of BRAF mutant NSCLC patients treated with ICI are similar to the overall results attained with ICI in the overall population of BRAF mutant melanoma patients. Hence, a major understanding of the reasons for this unexpected finding of such long PFS in this small, identified group of BRAF mutant NSCLC patients warrants in-depth explanation. The study provides a detailed examination of seven NSCLC patients with different *BRAF* mutations, showing the complexity and heterogeneity of this subset of lung cancer. In patients received ICIs, the median PFS and ORR offer a glimpse into the therapeutic outcomes for this cohort. Two patients were lost to follow up shortly after surgery. In other two patients with the V600E and D594G mutations in the *BRAF* gene, who were treated with ICIs in second-line monotherapy, disease stabilization lasting several months was achieved. These patients had no serious comorbidities or metastases affecting the prognosis. However, in two patients with the N581S and D594 mutations, who

received immunotherapy in the first line of treatment (as monotherapy or in combination with chemotherapy), despite initial response to therapy, progression occurred early and fast. These patients had poor prognostic factors. The first one had MDS, which worsens the function of the immune system, and the second one had metastases to the central nervous system, worsening the prognosis. Moreover, in our group of patients, mutations in the *BRAF* gene were common (over 4% of patients), which was related to the use of the NGS technique to detect common and rare genetic alterations. Therefore, we detected the V600E mutation in only three patients and, in the remaining patients, mutations in codons other than 600 of the *BRAF* gene were present. The expression of PD-L1 varied among tumor cells with mutations in the BRAF gene, ranging from 0% to 80%.

Conclusions

The study provides valuable clinical insights into the efficacy of immunotherapy and chemoimmunotherapy in NSCLC patients with BRAF mutations, offering a detailed analysis of seven cases and highlighting the potential benefits of personalized treatment approaches facilitated by NGS technology. However, the retrospective design and limited sample size of the study may introduce biases and limit the generalizability of the findings, while the absence of a control group hinders the ability to make direct comparisons with alternative treatment modalities. The lack of evaluation regarding immunotherapy side effects limits the comprehensive understanding of treatment outcomes and potential risks associated with therapy.

The sequence of first line immunotherapy and targeted therapy in *BRAF*-mutated patients is justified, although the effectiveness is varied and could be influenced by the specific type of *BRAF* mutation and co-existing genetic alterations. However, data for sequence of treatment is still scarce. The cases highlight the challenges of managing advanced NSCLC with *BRAF* mutations, where approved targeted treatments are limited to second-line therapy. The study underscores the complexities of treating NSCLC patients with BRAF mutations, indicating the need for further research to validate the efficacy of immunotherapy in this subset.

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Footnote

Reporting Checklist: The authors have completed the AME Case Series reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-253/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-253/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. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and approved by the local Bioethics Committee at the Medical University of Lublin (No. KE-0254/160/2021). The consent of the bioethics committee was provided by Medical University of Lublin as the main contractor of scientific project, all other sites were mentioned in the document. Written informed consent was obtained from the patients.

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