VIA MEDICA

CASE REPORT

Paulina Terlecka[1, 2], Paweł Krawczyk[1], Anna Grenda[1], Izabela Chmielewska[1], Janusz Milanowski[1]

[1]Department of Pneumonology, Oncology, and Allergology, Medical University of Lublin, Poland
[2]Department of Endocrinology, Diabetology and Metabolic Diseases, Medical University of Lublin, Poland

Immunotherapy with pembrolizumab in a patient with advanced non-small-cell lung cancer with high PD-L1 expression and MET exon 14 splice site mutation

Address for correspondence:
Paulina Terlecka, MD
Department of Pneumology, Oncology, and Allergology, Medical University of Lublin
Jaczewskiego 8, 20–954 Lublin
tel. +48 81 724 42 93
e-mail: paulina.chwil@gmail.com

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ABSTRACT

Lung cancer is one of the major oncological problems in Poland. Pembrolizumab monotherapy can be applied as first-line treatment in patients with advanced non-small-cell lung cancer (NSCLC) with the expression of programmed death ligand 1 (PD-L1) in ≥ 50% of tumor cells. The article presents a case report of a female patient with advanced lung adenocarcinoma and high PD-L1 expression and an additional *MET* exon 14 skipping mutation. Despite the advanced stage of the disease, the patient benefited spectacularly from pembrolizumab administered following stereotactic radiotherapy for central nervous system (CNS) metastases. Partial remission followed by long-term stabilization of the disease was achieved. Unfortunately, the therapy was discontinued due to grade-3 pulmonary toxicity observed after 3 years of treatment. Despite the discontinuation of the pembrolizumab therapy, the disease has currently been stabilized and inflammatory changes have slowly resolved upon administration of corticosteroid.

Key words: non-small cell lung cancer, immunotherapy, splice site mutation, *MET* gene, PD-L1 expression

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Introduction

Pembrolizumab is a humanized monoclonal antibody directed against the programmed death 1 (PD-1) receptor on the surface of lymphocytes. Pembrolizumab monotherapy can be used as a first-line regimen in treatment-naive patients with advanced non-small-cell lung cancer (NSCLC) with programmed death ligand 1 (PD-L1) expression in ≥ 50% of tumor cells [1].

The abnormalities of the *MET* gene are rarely detected in NSCLC patients. Assessment of *MET* gene disorders is recommended in patients with non-squamous NSCLC in the case of exclusion of mutations in the *EGFR* (*epidermal growth factor receptor*) gene and rearrangement of the *ALK* (*anaplastic lymphoma kinase*) and *ROS1* genes or simultaneously with the examination of these genetic abnormalities when the next generation sequencing (NGS) is used. The most common *MET* abnormalities include amplification of the gene and the exon 14 splice site mutation. The presence of this abnormality is an indication for the use of MET tyrosine kinase inhibitors, i.e. tepotinib or capmatinib [2].

We present a case report of a female patient with lung adenocarcinoma, who initially presented with persistent low-grade fever after a respiratory tract infection. The chemoradiotherapy resulted in short-term remis-

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sion of the disease. When the disease disseminated, the patient developed neurological symptoms related to central nervous system (CNS) metastases. Despite the advanced stage of the disease, the patient benefited spectacularly from the immunotherapy administered following stereotactic radiotherapy of the CNS metastases, although we detected a *MET* exon 14 skipping mutation. The benefits from the immunotherapy continue despite the discontinuation of the pembrolizumab treatment.

Case report

A 69-year-old woman who had not smoked for 25 years was admitted to the Department of Pneumonology, Oncology, and Allergology in summer 2017 due to a persistent low-grade fever after a recent respiratory infection. The chest X-ray (CXR) examination showed a round shadow in the left lung. Therefore, the additional diagnostics included chest and abdominal cavity computed tomography (CT), which revealed the presence of a peripherally located, smooth-bordered, left upper lobe lesion measuring 40 × 35 × 42 mm and enlarged left hilar, mediastinal, and subcarinal lymph nodes. Apart from the lung, there were no lesions suggesting distant metastases. The disease stage was initially classified as IIIB (cT2aN3M0). The patient's status was good (grade 1 according to the WHO/ECOG performance status scale). Due to the suspicion of a proliferative process, bronchoscopy with endobronchial ultrasound-guided thin needle aspiration (EBUS-TBNA) was performed. Pathological examination revealed pulmonary adenocarcinoma. Molecular tests did not show any abnormalities in the *EGFR*, *ALK*, or *ROS1* genes; however, a very high level of PD-L1 expression on the malignant cells was detected (90% of cells expressing the molecule).

The patient was qualified for sequential chemoradiotherapy, which started in September 2017. Imaging with CT performed after two cycles of combined cisplatin and vinorelbine chemotherapy showed partial response according to the RECIST 1.1 (Response Evaluation Criteria in Solid Tumors). The lesion in the upper lobe of the left lung was reduced to 24 × 25 mm. The mediastinal and hilar lymph nodes decreased to a maximum dimension of 14 mm in the long axis. Unfortunately, the positron emission tomography-computed tomography (PET-CT) examination performed after three chemotherapy cycles revealed the presence of a focal lesion with a moderate SUV (standardized uptake value) within the left suprarenal gland. The lesion had not been detected previously. Surgical consultation was conducted twice to qualify the patient for resection of the suprarenal gland. The patient was not qualified for surgery due to the probably benign nature of the lesion. After four chemotherapy cycles, the patient underwent radical radiotherapy at a dose of 62 Gy.

In May 2018, the patient presented with vertigo. Magnetic resonance imaging (MRI) of the brain revealed progression of the disease, inter alia three metastatic lesions in the central nervous system (CNS). The lesions were located in the right parietal region near the cerebellar falx, on the border of the pons and the right cerebellar peduncle, and in the right frontoparietal area (Fig. 1A–B). The patient was qualified for

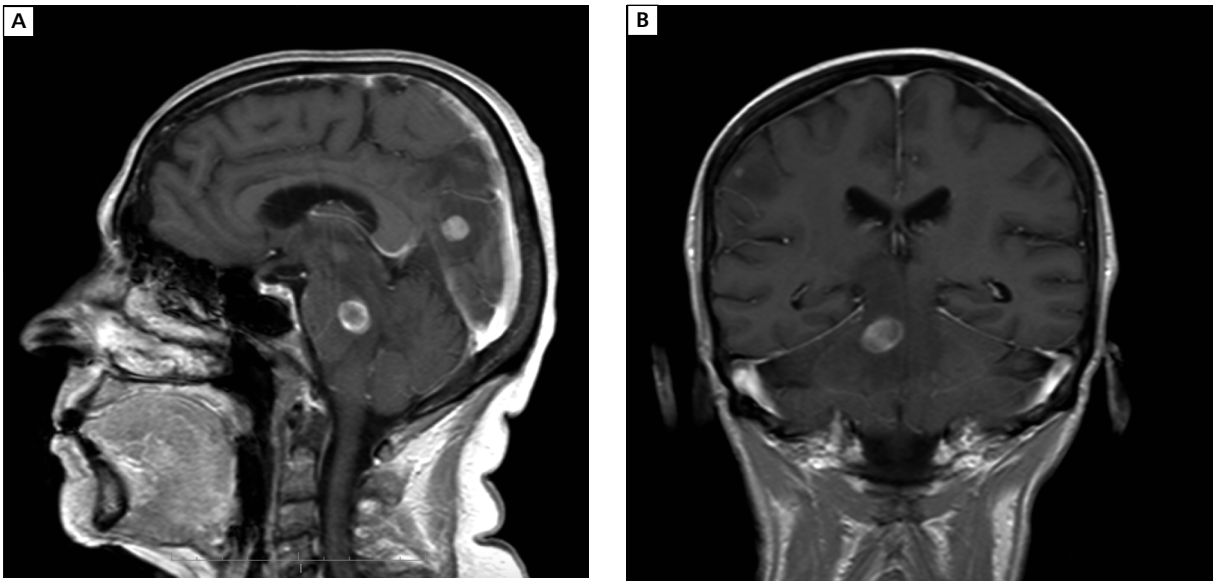

Figure 1. A. Magnetic resonance imaging of the brain in the sagittal projection showing metastatic lesions in the central nervous system located in the right parietal region near the cerebellar falx and on the border of the pons; **B.** Magnetic resonance imaging of the brain in the frontal projection showing metastatic lesions in the central nervous system located on the border of the pons and in the right frontoparietal area

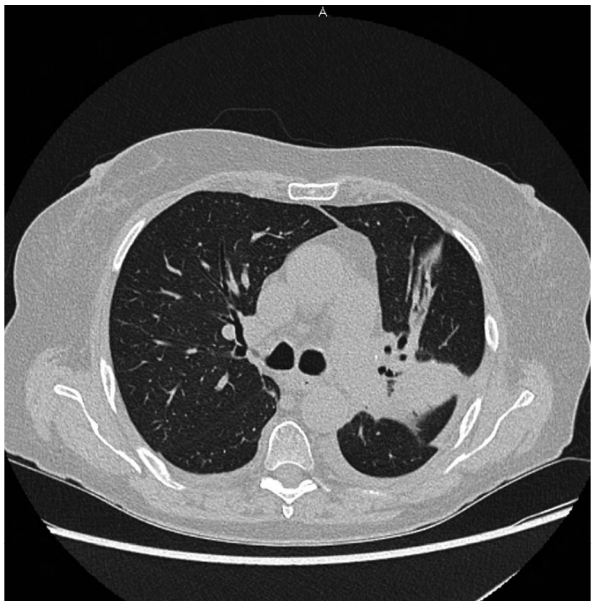

Figure 2. High-resolution chest computed tomography) showing the presence of lesions that could represent pseudoprogression, inflammatory lesions, or radiotherapy-induced perihilar infiltrative lesions on the left side

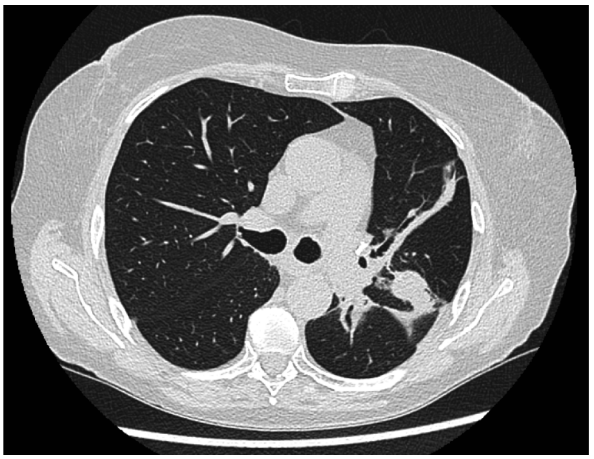

Figure 3. High-resolution chest computed tomography of the lung showing regression of the lesions and partial remission of the primary lesion

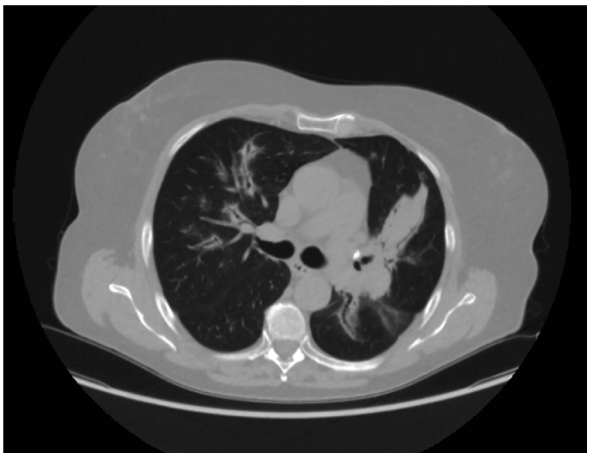

Figure 4. High-resolution chest computed tomography of the lung performed in February 2021, showing an untypical image of intense thickening of bronchial walls and peribronchial infiltrations in the lower lobes of both lungs and a 30 mm area of consolidation in the 5th segment of the right lung

stereotactic radiotherapy of the CNS metastases, which was performed in May 2018.

Given the radical aim of chemoradiotherapy applied in 2017, in June 2018 the patient was qualified for first-line pembrolizumab monotherapy at a dose of 200 mg every three weeks. Due to the good tolerance of the treatment, it was decided to increase the dose of pembrolizumab to 400 mg scheduled every six weeks in September 2019. Three days after the first administration of pembrolizumab in a higher dose, the patient was admitted to the hospital due to an episode of fever, general weakness, severe joint pain, and a moderate dry cough. The symptoms resolved quickly after appropriate treatment. Due to the above-described complications, a chest CT was performed. It showed the presence of lesions suggesting pseudoprogression, inflammatory lesions, or radiotherapy-induced perihilar infiltrative lesions on the left lung (Fig. 2). Pembrolizumab treatment was discontinued, and a control CT scan revealed regression of the new lesions and partial remission of the tumor and metastatic lymph nodes (Fig. 3). Immunotherapy was continued despite the high risk of intensification of the side effects. Gradual regression of malignant lesions was revealed. The patient reported feeling well throughout the treatment period. Imaging examinations of the CNS showed no recurrence or new metastases. A three-year progression-free survival (PFS) was achieved with the patient's well-being and high quality of life.

In February 2021, chest CT showed a very untypical image of intense thickening of bronchial walls and peribronchial thickenings in the lower lobes of both lungs and a 30 mm area of consolidation in the 5th segment of the right lung. The infiltrative lesion in the left lung cavity increased to 24 mm, and the area of the hilar consolidation increased to 45 × 22 mm (Fig. 4). Imaging of the chest showed four nodules in the apex of the right lung with a maximum size of up to 10 mm and two nodules in segment 6th of the left lung with a maximum size of 7 mm. The patient initially reported weakness, which she linked to the administration of the COVID-19 vaccine (Comirnaty). Subsequently, the patient reported dyspnea. The immunotherapy was discontinued in March 2021, after 33 months of treatment, due to suspected progression. Bronchoscopy was performed to confirm the nature of the infiltrative

and peribronchial lesions. No neoplastic cells were found in the collected material — pathology showed intense inflammatory lesions in the bronchial mucosa.

Given the clinical image, several additional genetic analyses were carried out. We conducted next-generation sequencing (NGS) examination using the Ion Torrent technology on the S5 sequencer (Thermo Fisher Scientific, Waltham, USA). We performed a simultaneous analysis of DNA and RNA isolated from tumor tissue from formalin-fixed paraffin-embedded (FFPE) block. DNA isolation was performed using the QIAamp DNA FFPE Tissue Kit (Qiagen, Hilden, Germany). RNA isolation was performed using the RecoverAll Total Nucleic Acid Isolation Kit for FFPE (Thermo Fisher Scientific, Waltham, USA). Sequencing was performed using the Oncomine Focus Assay (Thermo Fisher Scientific, Waltham, USA) allowing targeted sequencing and analysis of mutations, SNV (single nucleotide variation), and CNV (copy number variation) changes, as well as gene fusions in 52 genes related to the pathology of solid tumors. The NGS study showed the presence of a pathogenic skipping mutation in the *MET* gene, in the region of introns 13-15, which resulted in the deletion of exon 14 in the transcript. The mutation in the ClinVar or Varsome databases has a pathogenic status and is associated with the risk of osteofibrous dysplasia [3]. To confirm the NGS result, we conducted the RT-qPCR (reverse transcriptase-quantitative PCR) test using the Lung Cancer RNA Panel kit (EntroGen, Inc., Woodland Hills, Canada), which enables simultaneous assessment of the occurrence of *ALK*, *ROS1*, and *RET* gene fusions, as well as *MET* exon 14 skipping mutations in mRNA. The test result was positive for the *MET* skipping mutation and negative for the other targets.

The thorough analysis of the radiological image and histology, as well as a good response to corticosteroids, suggested that the lesions described above were unrelated to disease progression but were associated with another complication of the immunotherapy. Therefore, the patient did not receive pembrolizumab or any other systemic treatment and is now under close observation. Follow-up imaging studies revealed continuous regression of the inflammatory lesions in the lungs (Fig. 5). The persistent effectiveness of the pembrolizumab immunotherapy despite therapy discontinuation was demonstrated. Imaging of the brain performed in August 2021 showed no disease progression. Due to the concomitant *MET* gene abnormality, the patient may benefit from the treatment with MET inhibitors. However, given the stabilization of the disease, there are no indications for the administration of the next line of therapy. The patient is in a good general condition and her post-diagnosis survival time is now 4.5 years (January 2022).

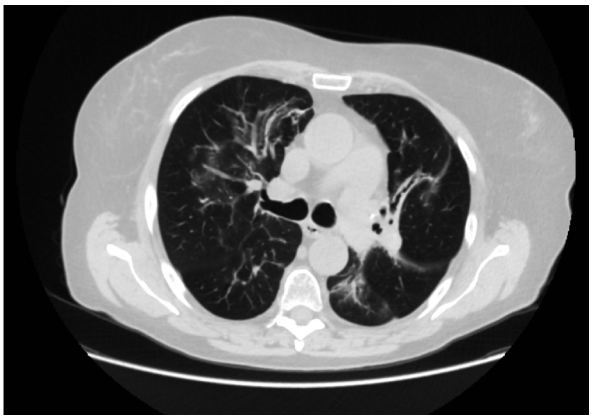

Figure 5. High-resolution chest computed tomography performed in December 2021 showing continuous regression of the inflammatory lesions in the lungs

Discussion

The case report presented here is unique for two reasons. The first reason is the 9-month persistence of the response to immunotherapy after discontinuation of the pembrolizumab treatment caused by grade 3 pulmonary toxicity according to the Common Terminology Criteria for Adverse Events (CTCAE) v. 2.0. classification. Interestingly, pneumotoxicity appeared 3 years after the initiation of treatment. The second reason is the effectiveness of this immunotherapy in a patient with a rare mutation in the *MET* gene, that theoretically does not favor the effectiveness of immunotherapy.

The optimal duration of immunotherapy in cancer patients is unknown. Immunotherapy in clinical trials was used for up to 2 years or more in responding patients. However, it is observed that benefits from immunotherapy may persist after therapy discontinuation, regardless of the reason. Anti-PD-1 antibodies bind to the PD-1 receptor on circulating T lymphocytes for 3 months after a single dose of treatment [4]. Moreover, the effectiveness of immunotherapy is triggered by a persistent adaptive immune response through the activity of memory T cells that may be present for months [5]. In melanoma patients treated with pembrolizumab in clinical trials, a 2-year disease-free survival rate was reported in 67 of 105 complete responders who discontinued pembrolizumab and were observed without any anticancer therapy [6]. Similarly, long-lasting responses persisting despite treatment discontinuation have been reported in NSCLC patients treated with immunotherapy [7].

The CheckMate-153 clinical trial prospectively addressed the question about the optimal duration of immunotherapy [8]. Patients with pretreated advanced NSCLC with nivolumab efficacy after 1 year were randomized to two groups: the continuous nivolumab group *vs.* the observation group that resumed nivolumab

retreatment at disease progression. Patients treated with nivolumab continuously had a significantly longer PFS and insignificantly longer overall survival (OS) than the ones who discontinued immunotherapy [hazard ratio (HR) = 0.42 and HR = 0.63, respectively for PFS and OS]. These results suggested that treatment duration in patients who were benefiting from immunotherapy should last longer than 1 year [9].

Mesenchymal epithelial transition (*MET*) receptor alterations, including the *MET* exon 14 skipping mutation, are oncogenic in NSCLC and may induce patients' sensitivity to targeted therapy. The *MET* exon 14 skipping mutation is one of the rare molecular disorders observed in NSCLC patients. It usually occurs in elderly non-smoking females (over 75 years of age). It is considerably more frequent in patients with adenocarcinoma than in patients with squamous-cell carcinoma. The prevalence of splice site mutations in the *MET* gene is estimated at approximately 4–4.5% of NSCLC patients [10].

Tepotinib or capmatinib therapy should be the first-line treatment in NSCLC patients with *MET* exon 14 mutations. Certain efficacy of crizotinib, cabozantinib, and glesatinib in such patients has been also demonstrated [2]. Unfortunately, these drugs are not reimbursed in Poland and there is no routine testing for mutations in the *MET* gene. Therefore, NSCLC patients with this genetic abnormality most often receive first-line chemotherapy, chemoimmunotherapy, or immunotherapy, depending on the presence of comorbidities and PD-L1 expression on the tumor cells.

The presence of genetic driver abnormalities is usually associated with the low sensitivity of NSCLC patients to immunotherapy with anti-PD-1 or anti-PD-L1 antibodies. As shown by Gainor JF et al. [11], only 3.6% of NSCLC patients with *EGFR* gene mutations or *ALK* gene rearrangements responded to second-line immunotherapy, in contrast to 23.3% of patients without these genetic abnormalities. The median PFS in patients with *EGFR* gene mutations or *ALK* gene rearrangements receiving immunotherapy was only 2.1 months [11]. These observations were confirmed by clinical trials in which atezolizumab (e.g., OAK trial), nivolumab (CheckMate 057 trial), and pembrolizumab (KEYNOTE-010 trial) were used as second-line treatment. These studies involved 8–14% of NSCLC patients with *EGFR* gene mutations. The risk of death in the patients receiving the immunotherapy was higher or similar to patients receiving second-line chemotherapy (HR = 1.24, 1.18, and 0.88, respectively) [12–14]. As explained by the authors, single genetic driver abnormalities are associated with a low tumor mutation burden (TMB) and a low number of neoantigens. In turn, a small number of tumor-specific antigens results in low immunogenicity of the tumor, which is invisible to immune cells.

However, the situation in patients with splice site mutations in the *MET* gene is different. Spigel D et al. [15] assessed tumor burden mutation (TMB — mutations/Mb) using comprehensive genomic profiling (CGP). The top quartile of the number of somatic mutations in lung cancer patients was classified as high TMB. The mean number of somatic mutations in NSCLC patients with *MET* gene mutations was 6.2, which was almost twice as high as in patients with *EGFR* gene mutations and *ALK* gene rearrangements (4.5 and 3.1, respectively). About 10% of patients with *MET* mutations had a high value of TMB (more than 10 mutations/Mb) in comparison with 8% of patients with high TMB in the group with *EGFR* gene mutations and 4% of such patients in the group with *ALK* gene rearrangements. Moreover, almost half of NSCLC patients with splice site mutations in the *MET* gene had a moderate number of somatic mutations (elevated compared to an average TMB of 7.3) [15].

Sabari et al. [16] identified 111 patients with mutations in exon 14 of the *MET* gene. In this group, there were 41% of patients with high PD-L1 expression (≥ 50% of tumor cells with PD-L1 expression). The absence of PD-L1 expression was diagnosed in 37% of patients with *MET* gene alterations. The median TMB in patients with *MET* gene mutations was lower than that of unselected NSCLC patients in both independently evaluated cohorts: 3.8 *vs.* 5.7 mutations/Mb (n = 78 *vs.* n = 1769, cohort A) and 7.3 *vs.* 11.8 mutations/Mb (n = 62 *vs.* n = 1100, cohort B) [16]. In a study conducted by Maziers J et al., PD-L1 expression was found in 90% of patients with mutations or amplification of the *MET* gene [17].

The presented data showed that patients with *MET* exon 14 mutations usually exhibit high PD-L1 expression and quite high TMB. Therefore, the use of immunotherapy in these patients is justified in the second-line setting following the inability to use MET inhibitors. Patients with various genetic driver abnormalities were involved in the IMMUNOTARGET study, including 36 patients with mutations in exon 14 of the *MET* gene or with amplification of this gene. Most of the patients received second- or third-line immunotherapy. Disease control through immunotherapy was achieved in 50% of patients with *MET* splice site mutations, and partial response was observed in 15% of the patients. For comparison, disease control was achieved in 32–33% of patients with *EGFR* gene mutations and *ALK* gene rearrangements, and response to the treatment was observed in only 12% of patients with *EGFR* mutations and none of the patients with *ALK* gene rearrangements. The median PFS was 3.4 months, which was the longest time compared to that in patients with other genetic driver alterations (*EGFR*, *BRAF*, and *KRAS* gene mutations, *ALK*, *ROS1*, and *RET* gene rearrangements, and *HER2* gene ampli-

fication). Furthermore, the achievement of therapeutic response and long PFS depended mainly on the PD-L1 expression on tumor cells, which was frequently detected in patients with *MET* gene mutations. The median OS in patients with splice site mutations in the *MET* gene was 18.4 months, which is comparable to the median OS in patients without genetic abnormalities [17]. In a study conducted by Sabari et al. [16], the objective response rate to immunotherapy was 17% in NSCLC patients with *MET* exon 14 mutations, and their median PFS was 1.9 months (the number of response-evaluable patients was 24). The responses were not enriched in tumors with PD-L1 expression on ≥ 50% of tumor cells or with high TMB [16].

The present observations and findings reported by other authors confirm that pembrolizumab may be highly effective in NSCLC patients with the *MET* exon 14 skipping mutation, especially in the case of high PD-L1 expression on tumor cells [16–18]. These observations justify undertaking clinical trials based on the use of a combination of immunotherapy and therapy with MET tyrosine kinase inhibitors. A clinical trial (NCT03647488), which compared the efficacy of a second-line spartalizumab and capmatinib combination treatment *vs.* docetaxel, was conducted in NSCLC patients without a *MET* gene status assessment. The trial was unsuccessful as 55% of the patients had early disease progression and 28% had serious side effects of the therapy. However, only patients with advanced NSCLC with *MET* exon 14 skipping mutations are eligible for the ongoing trial NCT04323437. Although the results of this trial are still incomplete, the data reported in the present study encourage optimism.

Conflict of interest

Authors declare no conflict of interest.

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