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CASE REPORT

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Optimizing treatment strategies for a MET exon 14 skipping mutation in non-small-cell lung cancer: a case report of sequential immunotherapy and targeted therapy and literature review

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ABSTRACT

The *MET* exon 14 skipping mutation is found in approximately 3–4% of non-small cell lung cancers (NSCLC). In 2020, the American Food and Drug Administration approved the first drug targeting this mutation. Capmatinib is a selective MET tyrosine kinase inhibitor. In the European Union, capmatinib is used when the patient needs further treatment after receiving immunotherapy or platinum-based chemotherapy, or both. In the described case, due to disease progression during treatment with pembrolizumab and then with platinum-based chemotherapy, next-generation sequencing was performed, which allowed for detection of the *MET* gene exon 14 skipping mutation. Targeted therapy with capmatinib was the only method of treatment resulting in a partial response to the disease and improvement of the patient's quality of life. This case indicates the importance of detailed molecular diagnosis and selection of the optimal method of treatment to prolong survival of the patient with advanced NSCLC. Due to promising results of research conducted so far, in the future, selective MET tyrosine kinase inhibitors — capmatinib and tepotinib — may become the new standard of first-line treatment in NSCLC patients with the *MET* exon 14 skipping mutation.

Key words: adenocarcinoma, capmatinib, *MET* proto-oncogene, MET exon 14 skipping mutation, non-small-cell lung cancer

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Introduction

Currently, the most common histological type of primary lung cancer (LC) is adenocarcinoma, and in recent years, there has been a steady increase in its incidence (especially in women). A characteristic feature of this type is early spread through the bloodstream; therefore, it is often detected at a metastatic stage, which is associated with poor prognosis [1, 2]. However, by using innovative diagnostic techniques, such as next-generation sequencing (NGS), targetable molecular changes can be found in approximately 50% of tumors, which significantly increases the chances of finding an effective targeted therapy and, consequently, prolonging patients' overall survival [3].

In this article, we will focus on one of the new molecular targets in the treatment of non-small-cell lung cancer (NSCLC) — the abnormal MET protein resulting from the *MET* exon 14 skipping mutation. The *MET* proto-oncogene encodes a receptor tyrosine kinase (RTK) for hepatocyte growth factor (HGF). Activation of this receptor by binding of its ligand stimulates downstream signaling pathways (MAPK, PI3K/AKT, STAT, and NF-κB) [4]. The MET pathway has an es-

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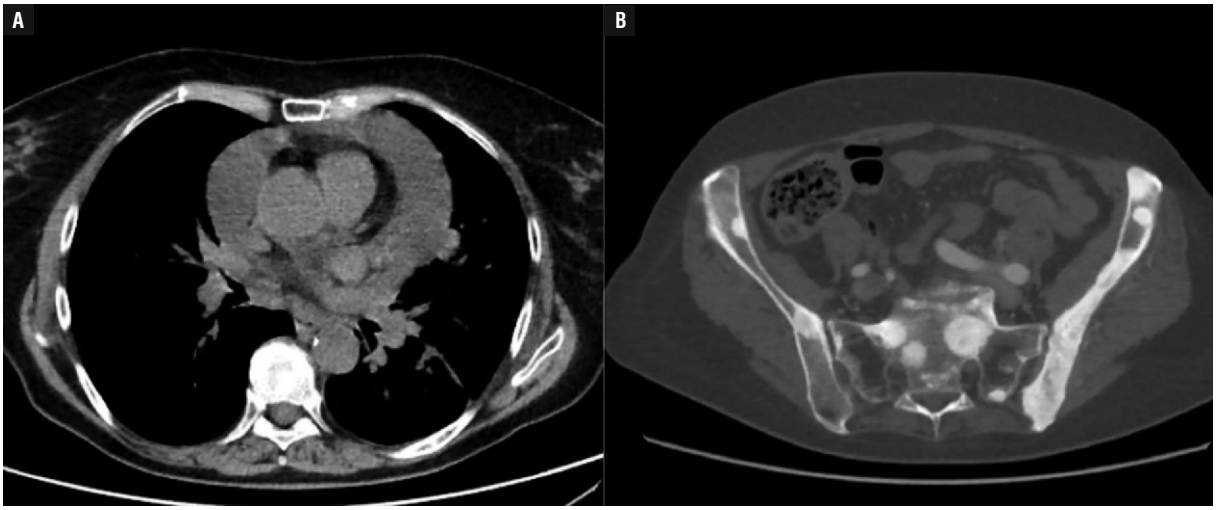

Figure 1A–B. Computed tomography scans presenting pericardial effusion and bone metastasis at the time of diagnosis

sential role during embryogenesis, affecting the development of a diverse set of organs and systems. Beyond embryonic development, MET signaling is important for wound healing and tissue regeneration, especially liver regeneration [5]. However, increased MET RTK activity also causes pleiotropic effects in tumor cells, including survival, proliferation, metastasis, and drug resistance [6]. Furthermore, it has been demonstrated that tumor cells with the *MET* mutation are resistant to apoptosis [7, 8]. Excessive activation of the MET pathway in NSCLC patients results from high expression of this receptor caused by amplification of the *MET* gene, mutations in the tyrosine kinase domain of the *MET* gene, or mutations in the splice site in introns 13–14 or in exon 14 of the *MET* gene. Exon 14 of the *MET* gene encodes CBL tyrosine kinase binding domain and CBL acts as E3 ubiquitin ligase. Therefore, CBL-mediated MET protein degradation is impaired when exon 14 is skipped. No degradation of MET protein leads to the accumulation of MET RTK and activation of MET oncogenic signaling. The exon 14 skipping mutation is found in 3–4% of NSCLC patients (most often with an adenocarcinoma type), who usually have no other target mutation, and the finding is associated with poor prognosis [3, 9, 10].

In 2020, the American Food and Drug Administration (FDA) approved capmatinib, which is a new drug for the treatment of patients with metastatic NSCLC (mNSCLC) with the presence of the *MET* exon 14 skipping mutation. Capmatinib is a MET tyrosine kinase inhibitor (MET-TKI) [11, 12]. In 2022, the drug also gained the European Medicines Agency (EMA) approval. In comparison to other MET inhibitors (e.g. crizotinib), in *in vitro* assays, capmatinib was shown to be more potent and more selective for MET than for other kinases. Similar activity against MET is shown by tepotinib, which has also been registered by the FDA and EMA for the treatment of NSCLC patients with splicing mutations in the *MET* [12–14]. They prevent the activation of downstream effectors in the MET signaling pathway by blocking MET phosphorylation and, as a consequence, restrain tumor cell proliferation and migration [15]. In addition, capmatinib and tepotinib induce apoptosis in MET-dependent tumor cell lines [13].

We present a case report of a patient with mNSCLC and a rare *MET* exon 14 skipping mutation, in whom, after previous immunotherapy and chemotherapy, an innovative capmatinib targeted therapy was started.

Case report

In November 2021, a 70-year-old female patient with atrial fibrillation, hypertension, gout, and without smoking history was referred for diagnostics due to chronic cough. It turned out to be caused by pericardial effusion; therefore, pericardiocentesis was performed. To determine the reason for the accumulation of fluid in a pericardial cavity, computed tomography (CT) was performed. It showed an infiltrative lesion measuring 59 × 42 mm in the lower field of the left lung, lymphadenopathy of the right paratracheal nodes as well as right and left hilar nodes, sclerotic areas corresponding to bone metastases in the spine and left hip bone (Fig. 1). Adenocarcinoma (AC) of the lung was diagnosed in the pathological examination of the material from bronchoscopy with endobronchial ultrasound fine-needle aspiration (EBUS-FNA). Stage IV (T2bN2M1c) was confirmed according to the *Tumor,*

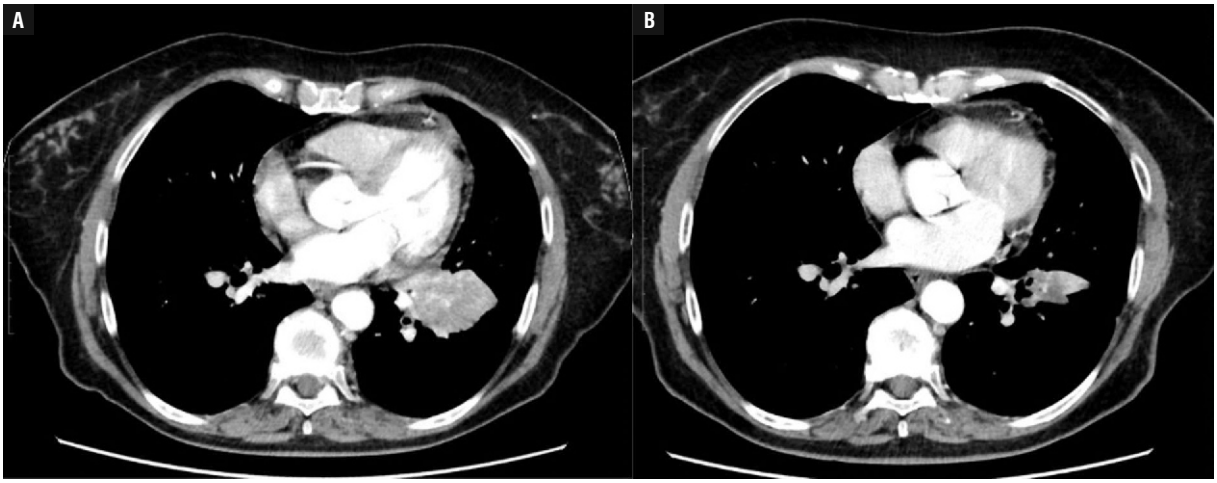

Figure 2A–B. Computed tomography scans presenting partial response after 6 months of effective treatment with capmatinib

Nodes, and Metastases (TNM) classification. Single-gene molecular tests performed at that time did not reveal any driver mutations that would allow administration of reimbursed targeted treatment. Genetic alterations in the *EGFR* (epidermal growth factor receptor) gene and rearrangements of the *ALK* (anaplastic lymphoma kinase) and *ROS1* genes were excluded. Expression of programmed death protein ligand-1 (PD-L1) was present in 80% of the tumor cells; therefore, monotherapy with pembrolizumab was initiated.

Due to tumor adherence to the pericardium, in February 2022, pericardial effusion reappeared, but it was successfully decompressed. Unfortunately, after three cycles of immunotherapy, disease progression was revealed. Computed tomography performed at the end of March, showed, in comparison to the previous examination, enlargement (by 3–5 mm) of the primary lesion that was adjacent to the pericardium with the wider base and connected with the pleura. Some liquid (up to 10 mm) in the left pleural cavity was visible. Moreover, satellite pulmonary nodules were found. An irregular change with a diameter of 24 mm in the liver, suspected metastasis, was also visible. In addition, there was significant progression of osteosclerotic skeletal lesions. Therefore, the treatment was changed to chemotherapy in the form of cisplatin and pemetrexed. As the subsequent cycles of chemotherapy were administered, a slight reduction of the primary lesion and amount of fluid in the pericardium was noticed. Nevertheless, CT performed in August 2022 (after 4 cycles of chemotherapy) showed progression in the number and size of osteosclerotic skeletal lesions, accompanied by severe pain in the affected bones.

Due to the unsatisfactory response to the treatment, the archive tissue sample was diagnosed by next-generation sequencing (NGS) to find targetable molecular changes. The *MET* exon 14 skipping mutation was detected. Treatment with capmatinib was initiated under the expanded access program (EAP). After six months of targeted therapy, CT scans confirmed a partial response (Fig. 2). The patient did not require pericardiocentesis. The skeletal pain diminished completely without local treatment. The patient has continued oral treatment for 9 months with very good tolerance, and no adverse effects have been noted so far.

Discussion

It should be remembered that in the case of metastatic NSCLC, a key influence on the patient's prognosis is not only the patient's health condition or disease stage but also the optimal method of treatment. In AC patients, it is crucial to look for molecular changes that enable targeted therapy. A single test may help to find common genetic alterations. However, only NGS can reveal rare molecular abnormalities. Evaluation of *MET* gene mutations is suggested in NSCLC patients after excluding mutations in the *EGFR* gene and rearrangements in the *ALK* and *ROS1* genes [16].

American Food and Drug Administration approval of two MET tyrosine kinase inhibitors — campatinib in 2020 and tepotinib in 2021 — for the treatment of metastatic NSCLC patients with the *MET* exon 14 skipping mutation opened a completely new chapter in molecularly targeted NSCLC therapy. The evidence of capmatinib efficacy and safety comes from a prospective, multicenter, multiple-cohort, phase II clinical trial — GEOMETRY mono-1. Eligible patients were adults (≥ 18 years of age) with stage IIIB or IV NSCLC with any

Table 1. Comparison of MET-targeting therapies

Drug	Trial and phase	Study group	ORR	DoR	PFS	OS	Most common adverse events
Capmatinib	Phase II GEOMETRY NCT 02414139	97 NSCLC patients with *MET* exon 14 skipping mutation: 69 previously treated and 28 treatment-naïve	41% (95% CI 29–53) in pretreated and 68% (95% CI 48–84) in treatment-naïve	9.7 months (95% CI 5.6–13.0) in pretreated and 12.6 months (95% CI 5.6–NR) in treatment-naïve	5.4 months (95% CI 4.2–7.0) in pretreated and 12.4 months (95% CI 8.2–NR) in treatment-naïve	–	Peripheral edema (41.6% of patients), nausea (33.2%), elevated serum creatinine (19.5%), vomiting (18.9%)
Tepotinib	Phase II VISION NCT 02864992	152 NSCLC patients with *MET* exon 14 skipping mutation	46% (95% CI 36–57)	11.1 months (95% CI 7.2–NR)	8.5 months	17.1 months	Peripheral edema (65.6% of patients), nausea (30.2%), hypoalbuminemia (28.5%), diarrhea (27.8%), elevated serum creatinine (27.1%)

CI — confidence interval; DoR — duration of response; NR — not reported; NSCLC — non-small-cell lung cancer; ORR — overall response rate; OS — overall survival; PFS —progression-free survival

histologic features, without *EGFR* or *ALK* abnormalities, and with at least one measurable lesion, defined according to the Response Evaluation Criteria in Solid Tumors (RECIST 1.1). A total of 97 NSCLC patients with the *MET* exon 14 skipping mutation were recruited, including 69 previously treated and 28 treatment-naïve patients. They received capmatinib in a 400 mg oral dose twice daily. The primary endpoint was the overall response rate (ORR), and the key secondary endpoint was the duration of response (DoR). Additional secondary endpoints included (1) investigator-assessed response and duration of response, (2) investigator-evaluated and independent review committee-evaluated time to response, disease control, progression-free survival, and (3) the safety profile and pharmacokinetics of capmatinib.

The ORR was observed in 41% [95% confidence interval (CI) from 29 to 53] of previously treated patients and in 68% (95% CI 48–84) of treatment-naïve patients. The median DoR was 9.7 months (95% CI 5.6–13.0) and 12.6 months (95% CI 5.6–not reached), and median progression-free survival was 5.4 months (95% CI 4.2–7.0) and 12.4 months (95% CI 8.2–not reached) in the previously treated and treatment-naïve cohorts, respectively. Responses to therapy were rapid. The majority of patients (82% of the previously treated patients and 68% of treatment-naïve patients) had a response at the first evaluation after the initiation of capmatinib therapy. The most frequently reported adverse events were peripheral edema (41.6% of patients) and nausea (33.2%) These events were mostly of first- or second-grade severity (Tab. 1) [17].

Tepotinib is another MET tyrosine kinase inhibitor, which, by disrupting MET signal transduction pathways, induces apoptosis in tumor cells overexpressing this receptor. The efficacy of tepotinib was demonstrated in the open-label, phase II, multicenter VISION clinical trial that enrolled 152 patients with advanced or metastatic NSCLC with the *MET* exon 14 skipping mutation. Patients received oral tepotinib 500 mg once daily until disease progression or unacceptable toxicity. The primary endpoint was the ORR rate assessed by an independent review committee (IRC) in patients who had undergone at least 9 months of follow-up. The authors reported that tepotinib was associated with a partial response in approximately half of the patients, with an ORR of 46% (95% CI 36–57) according to the IRC review and 56% (95% CI 45–66) by investigator assessment. Median DoR was 11.1 months (95% CI 7.2–not reached). Progression-free survival (PFS) and overall survival (OS) were 8.5 and 17.1 months, respectively. Adverse events of grade 3 or higher were reported in 28% of the patients (Tab. 1) [18].

The favorable results of these trials made capmatinib and tepotinib the first two FDA and EMA-approved targeted therapies for lung cancer with *MET* proto-oncogene mutation. According to the European Society for Medical Oncology (ESMO) guidelines, capmatinib or tepotinib can be recommended following prior treatment with immunotherapy and/or platinum-based chemotherapy in patients with the *MET* exon 14 skipping mutation-positive metastatic NSCLC [19]. Whereas, both agents are preferred as first-line monotherapy options in the same indication according to the Na-

tional Comprehensive Cancer Network (NCCN) [20]. Recommended starting dose of capmatinib is 400 mg twice daily. Tablets can be taken with or without food. Dosing can be modified to manage adverse reactions, but therapy should be discontinued in patients who are unable to tolerate 200 mg twice daily. For tepotinib, the proposed dosing regimen is 450 mg once daily [21].

In addition to the ongoing search for new molecularly targeted therapies, another important issue is to determine the place of immune checkpoint inhibitors (ICIs) in the treatment of NSCLC patients with driver alterations. The efficacy of immunotherapy in patients with *MET* gene mutations remains unknown. Yoshimura et al. assessed the correlation between *MET* amplification, gene copy number gains, and MET expression with the efficacy of nivolumab monotherapy in patients with advanced NSCLC. No significant differences in both PFS and OS were observed between NSCLC patients with and without *MET* gene amplification. The ORR in patients with high and intermediate numbers of *MET* gene copies (50.0% for both) was significantly higher than those without increased *MET* gene copy number (17.6%), yet survival outcomes for both PFS and OS did not improve. This study showed that an increase in the *MET* gene copy number was not associated with greater efficacy of nivolumab in patients with NSCLC [22].

Mazieres et al. [23] conducted a retrospective study in patients receiving ICI monotherapy for advanced NSCLC with at least one oncogenic driver alteration. One of the analyzed subgroups included patients with *MET* amplification or exon 14 skipping mutation (n = 36). Programmed death protein ligand-1 expression was found in 90% of them. In this group, PFS was 3.4 months and the ORR was 16%. Progressive disease (PD) was observed in 51% of patients, which was a relatively low proportion, compared to other driver alterations subgroups [23]. A similar study was conducted by Guisier et al. [24], who obtained the following results: the subgroup of patients with *MET* mutations (n = 30) achieved an ORR of 35.7% and PFS of 4.9 months. These outcomes were better than in other studies, but the authors emphasized the possible impact of high PD-L1 expression status and comparably low number of treatment lines received before immunotherapy in a great percentage of patients [24]. Sabari et al. [25] researched the response to ICIs in a group of 24 NSCLC patients with the *MET* exon 14 skipping mutation. They reported an ORR of 17% and PFS of 1.9 months [25, 26].

A case from our department described by Terlecka et al. [27] indicates that sometimes the PD-1 blockade can be effective in *MET*-altered NSCLC, even despite an advanced stage of the disease. It concerned a patient with metastatic AC with high PD-L1 expression and *MET* exon 14 skipping mutation. Treatment with pembrolizumab was initiated after stereotactic radiotherapy for central nervous system (CNS) metastases. Partial remission was achieved, which was followed by long-term stabilization [27].

To sum up, clinical efficacy of ICIs in NSCLC with *MET* mutation is rather modest. However, it can be effective in some cases and further research is warranted to establish the place of immunotherapy in treatment regimens for patients with *MET*-altered NSCLC.

Conclusions

In conclusion, capmatinib and tepotinib paved the way for personalized molecularly targeted therapy for patients with rare *MET* gene alteration (*MET* exon 14 skipping mutation). Therapeutic management of patients with advanced NSCLC is often based on various methods of treatment. In the case of our patient, due to her resistance to immunotherapy and chemotherapy and lack of targeted alterations in the *EGFR*, *ALK,* and *ROS1* genes, therapeutic possibilities were extremely limited. Performance of the NGS turned out to be crucial. Detection of the uncommon mutation in the *MET* gene made it possible for us to use of capmatinib, which was effective in inhibiting disease progression. The presented case indicates that there is a need for detailed molecular diagnosis in NSCLC (AC in particular). Further research should aim to continue to identify new molecular targets in NSCLC, while clinicians implement targeted treatment as early as possible. Moreover, it is important to determine the place of immunotherapy in the treatment of NSCLC patients with driver alterations. It is needed to demonstrate the efficacy of selective MET tyrosine kinase inhibitors — capmatinib and tepotinib — in the first-line setting in NSCLC, not only in patients who have exhausted other treatment options.

Article Information and Declarations

Ethics statement

Article have been conducted according to the principles stated in the Declaration of Helsinki.

Author contributions

M.G.: conceptualization, investigation, writing — original draft; P.Kozieł: investigation, writing — original draft; I.C.: conceptualization, methodology, investigation, writing — original draft and review and editing; A.G.: methodology, writing — review and editing; P.Krawczyk: conceptualization, methodology, writing — review and editing; J.M.: writing — review and editing

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Conflict of interest
Authors declare no conflict of interests.

Supplementary material
None.

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