



# Unveiling the Uncommon: A Comprehensive Review and Case Report on Targeting Rare MET Fusions in NSCLC

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## ABSTRACT

Advancements in molecular diagnostics and targeted therapies have significantly transformed the management of non-small cell lung cancer (NSCLC). Rare mesenchymal-epithelial transition (MET) rearrangements, including novel fusions such as human leukocyte antigen (HLA)-DRB1-MET and HLA-DQB2-MET, represent actionable genetic alterations with critical therapeutic implications. This review synthesizes findings from multiple case reports to highlight the efficacy of MET tyrosine kinase inhibitors (TKIs) in MET-driven oncogenesis. A literature review of published case reports and studies on MET rearrangements in NSCLC was conducted. Data were analyzed to assess the clinical outcomes of patients treated with MET TKIs, such as crizotinib and tepotinib. Additionally, our case report demonstrates the utility of comprehensive next-generation sequencing (NGS) in identifying rare MET fusions and guiding personalized treatment strategies. Our case illustrates the potential of NGS to detect rare MET fusions, thereby enabling durable disease control with crizotinib. Comparative analyses indicate the necessity of individualized treatment approaches, particularly in cases with central nervous system involvement and a prior treatment history. The review further emphasizes that MET alterations are more frequently identified in never-smoking female patients, in whom driver mutation detection rates exceed 60%. Precision oncology plays a pivotal role in addressing rare MET rearrangements in NSCLC. Despite advancements, challenges persist in early identification, therapeutic sequencing, and access to advanced diagnostics. Collaborative efforts among researchers, clinicians, and policymakers are crucial to refining treatment strategies and improving patient outcomes.

**Keywords:** Non-small cell lung cancer; MET rearrangements; tyrosine kinase inhibitors; HLA-DRB1-MET fusion; precision oncology

## INTRODUCTION

Lung cancer is a leading cause of cancer-related mortality worldwide, responsible for approximately 1.8 million deaths annually. Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancer cases, with adenocarcinoma being the most common histologic subtype.<sup>1</sup> Advances in molecular profiling, particularly next-generation sequencing (NGS), have significantly reshaped the diagnostic and therapeutic landscape of NSCLC. The mesenchymal-epithelial transition (MET) proto-oncogene encodes a transmembrane receptor tyrosine kinase that plays a critical role in regulating cell growth, survival, and motility.<sup>2</sup> Among the actionable mutations, those alterations affecting

the MET proto-oncogene have garnered significant attention due to their oncogenic potential and therapeutic implications. Aberrations such as MET exon 14-skipping mutations, amplifications, and fusions result in constitutive activation of the MET signaling pathway, contributing to tumor progression.<sup>3</sup> MET fusions, although rare and accounting for approximately 0.5% of NSCLC cases, frequently involve novel partners such as human leukocyte antigen (HLA)-DRB1 and HLA-DQB2. These partners retain the MET kinase domain and drive oncogenesis through ligand-independent dimerization and activation.<sup>4</sup> Recent findings underscore the mounting importance of MET fusions in various malignancies, including NSCLC. These rare structural rearrangements have also been

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identified in other tumor types. A notable example is that of a pediatric glioblastoma patient with a MET fusion who achieved a partial response to the MET inhibitor crizotinib, demonstrating the potential of targeted therapies in addressing such oncogenic drivers. This underscores the critical need for further research into the therapeutic landscape of MET fusions, especially given the promising, albeit preliminary, outcomes seen in early clinical cases.<sup>5-7</sup> Aberrant MET activation has also been associated with cancer cell proliferation and angiogenesis across different tumor types. Adenosine triphosphate (ATP)-competitive tyrosine kinase inhibitors (TKIs) have demonstrated antitumor activity in NSCLC patients with MET alterations, particularly in cases with MET exon 14 skipping mutations. However, the therapeutic impact of MET TKIs on more complex structural rearrangements, such as MET fusions, remains poorly understood and warrants further investigation.<sup>8,9</sup> Crizotinib has demonstrated favourable response rate in the treatment of lung adenocarcinomas harboring MET gene alterations. Additionally, other MET-targeting agents, including cabozantinib, savolitinib, capmatinib, and tepotinib, have shown therapeutic potential in this context.<sup>10-12</sup> In this review, we analyse a range of cases reported in the literature and emphasise a unique case at Medipol University involving an HLA-DRB1-MET fusion. This case exemplifies the role of molecular diagnostics in guiding targeted therapy decisions. Additionally, we aim to contextualize this case within the broader spectrum of MET rearrangements to provide a comprehensive understanding of their therapeutic implications.

### Literature Search Strategy

A focused literature review was conducted to identify published case reports and case series describing MET gene rearrangements in NSCLC. The PubMed/MEDLINE and Scopus databases were searched for articles published from January 2010 to December 2024. The search strategy used combinations of the following keywords: "non-small cell lung cancer", "NSCLC", "MET fusion", "MET rearrangement", "HLA-DRB1-MET", "HLA-DQB2-MET", and "TKIs."

Articles were screened based on titles and abstracts, followed by full-text review when relevant. Studies were included if they reported clinical cases of NSCLC with confirmed *MET* gene rearrangements and provided molecular, therapeutic, and clinical outcome data. Reviews without original patient data, preclinical studies, and reports lacking sufficient clinical or molecular information were excluded. Reference lists of included articles were also manually reviewed to identify additional relevant publications.

### Clinical Cases and Therapeutic Insights

#### Tepotinib in HLA-DRB1-MET Fusion-positive NSCLC (Blanc-Durand et al.<sup>13</sup>)

A 41-year-old female patient diagnosed with stage IIIA NSCLC and subsequent brain metastases was found to harbor an *HLA-DRB1-MET* gene fusion. Initial treatment with cisplatin and vinblastine combined with radiotherapy resulted in a partial response, but the disease progressed within seven months, leading to brain, liver, and bone metastases. Molecular profiling identified the HLA-DRB1-MET fusion, and targeted therapy was initiated. Crizotinib was administered as first-line treatment, resulting in a complete response that lasted six months. However, disease progression occurred, manifesting as symptomatic cerebral metastases. Following disease progression, tepotinib was introduced as a second-line therapy. This resulted in a near-complete intracranial response and significant systemic disease control, which was maintained for nine months. Subsequently, cabozantinib was administered as the third-line therapy, further stabilizing the disease, preserving the patient's quality of life, and causing minimal adverse effects. This case underscores the significance of NGS in identifying actionable mutations and demonstrates the potential efficacy of tepotinib in managing NSCLC with central nervous system (CNS) involvement.<sup>13</sup>

#### Crizotinib in HLA-DRB1-MET Fusion-positive NSCLC (Davies et al.<sup>4</sup>)

A 74-year-old female patient, who had never smoked, had a history of stage I lung adenocarcinoma, which was treated with a wedge resection of the right lower lobe. Nine years later, a new left upper lobe mass was detected; following lobectomy, the tumor was confirmed as stage II lung adenocarcinoma. Initial testing of the second tumor sample revealed no epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) rearrangements. Adjuvant chemotherapy was declined by the patient. Eighteen months later, surveillance imaging revealed multiple new lung lesions and nodal involvement, and a biopsy confirmed adenocarcinoma, morphologically similar to previous samples, without ALK or ROS1 rearrangements. After four cycles of carboplatin-pemetrexed followed by maintenance pemetrexed, the disease remained stable, but progressed slowly after treatment cessation, which was due to fatigue. Subsequent NGS of a resected tumor specimen identified a novel HLA-DRB1-MET fusion with MET exon 15. Crizotinib was initiated off-label, as the patient's tumor was negative for other actionable mutations [EGFR, Kirsten rat sarcoma (KRAS), ALK, ROS1, rearranged during transfection]. Within

six weeks, the patient achieved a complete response, which was maintained for eight months with manageable side effects, including fatigue and mild hypokalemia. This case highlights the value of comprehensive NGS in uncovering rare actionable fusions, such as HLA-DRB1-MET, and demonstrates the efficacy of crizotinib as a targeted therapy for such patients.<sup>4</sup>

#### Crizotinib in HLA-DRB1-MET Fusion-positive NSCLC (Kunte and Stevenson<sup>14</sup>)

A 59-year-old woman with a history of stage IA lung adenocarcinoma underwent radiation therapy for recurrent pleural-based nodules. Despite treatment, disease control was not achieved. Molecular profiling with NGS identified a rare *HLA-DRB1-MET* gene fusion. Pembrolizumab monotherapy was initiated, resulting in disease stabilization for eight months before progression occurred. Subsequently, crizotinib was introduced based on the molecular findings, leading to a rapid and significant reduction in pleural lesions. A complete radiographic response was achieved within four months. Crizotinib was well tolerated, with only mild, manageable side effects, including fatigue and nausea. This case illustrates the clinical value of NGS in identifying rare MET fusions and substantiates the efficacy of crizotinib as a targeted therapy for patients with these actionable alterations.<sup>14</sup>

#### Tepotinib in HLA-DQB2-MET Fusion-positive NSCLC (Dias E Silva et al.<sup>15</sup>)

A 73-year-old female patient with advanced NSCLC (stage IVA) presented with a large left upper lobe mass, pleural effusion, and mediastinal lymph node involvement. Initial treatment with a combination of carboplatin, pemetrexed, and pembrolizumab resulted in temporary disease stabilization, but progression was noted following maintenance therapy. Molecular profiling via NGS identified a novel HLA-DQB2-MET fusion. Tepotinib, a selective MET inhibitor, was initiated at a dose of 450 mg daily. This treatment achieved significant tumor reduction and sustained disease control for over 12 months. Tepotinib was well tolerated, with no treatment-related adverse events reported.

These findings support the use of selective MET inhibitors, such as tepotinib, to manage rare MET fusion variants and emphasize the importance of comprehensive genomic testing in identifying actionable therapeutic targets.<sup>15</sup>

#### Sequential TKI Therapy in ALK-HLA-DRB1 Fusion-positive NSCLC (Gao et al.<sup>16</sup>)

A 48-year-old female patient with advanced NSCLC presented with bilateral pulmonary nodules and

mediastinal lymphadenopathy. Molecular profiling via NGS identified a rare ALK-HLA-DRB1 rearrangement that retains the kinase domain of ALK and drives oncogenesis. Crizotinib was administered as the patient's initial treatment, resulting in rapid clinical improvement and a substantial radiographic response. Disease control was maintained for six months. Due to economic constraints, the patient was transitioned to ceritinib, which further extended progression-free survival (PFS), resulting in 18 months of disease control. This case demonstrates the efficacy of sequential ALK TKI therapy in managing rare ALK rearrangements and highlights the critical role of precision oncology in improving outcomes for complex cases.<sup>16</sup>

#### Crizotinib in HLA-DRB1-MET Fusion-positive NSCLC: Our Experience

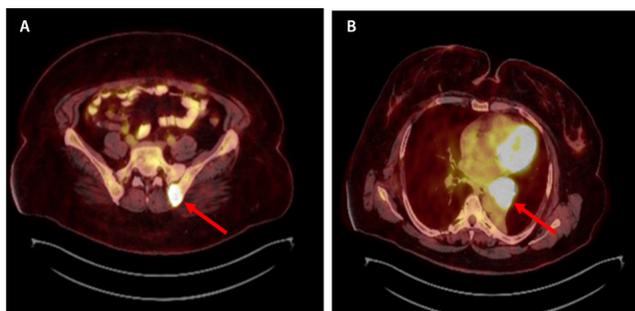
A 59-year-old female patient, a never-smoker, presented with complaints of persistent dry cough and mid-thoracic back pain lasting several weeks. She had no history of cancer and had only a diagnosis of hypertension, which was managed with amlodipine. No other chronic illness or ongoing medication use was reported. Her family history was negative for cancer or hereditary disorders, and she reported no significant psychosocial stressors. On physical examination, decreased breath sounds and dullness to percussion were noted in the left lower lung field. No cyanosis or digital clubbing was observed. Palpation of the thoracic spine revealed tenderness, particularly in the mid-thoracic region, suggesting skeletal involvement. No peripheral lymphadenopathy or hepatosplenomegaly were detected. The patient's performance status was Eastern Cooperative Oncology Group-1.

Initial imaging included a thoracoabdominal computed tomography (CT) scan, which revealed a large mass in the left lung. A tru-cut biopsy of the pulmonary lesion confirmed the diagnosis of primary lung adenocarcinoma.

Further staging with positron emission tomography-CT imaging demonstrated a hypermetabolic hilar mass in the left lung, mediastinal lymphadenopathy, and multiple bone metastases, consistent with stage IV NSCLC (Figure 1).

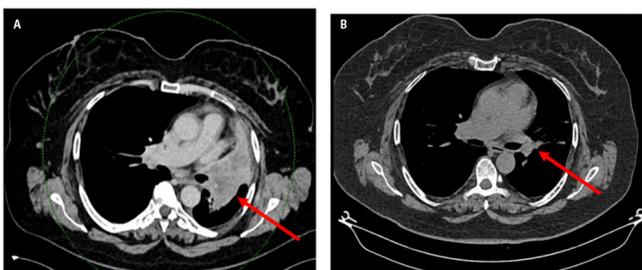
Molecular analysis showed that the tumor was negative for EGFR mutations and for *ALK* and *ROS1* gene rearrangements. However, programmed death-ligand 1 expression was positive, with a tumor proportion score of 40%, placing it in the 1-50% expression category.

Based on these findings, the patient was started on first-line chemoimmunotherapy comprising carboplatin, pemetrexed, and pembrolizumab. After four cycles, imaging revealed a partial response, and the regimen was modified



**FIGURE 1:** PET-CT at the time of diagnosis, A: Left iliac bone metastasis, B: Primary mass in the left lung.

*PET-CT: Positron emission tomography-computed tomography*



**FIGURE 2:** Thoracic computed tomography, (A) Before crizotinib: A right hilar mass (red arrow), likely representing a tumor or lymph node enlargement, causing partial compression of adjacent structures. (B) After crizotinib: Significant reduction in the size of the right hilar mass (red arrow), indicating a positive therapeutic response.

to maintenance pemetrexed and pembrolizumab, with carboplatin discontinued.

However, during the 11<sup>th</sup> cycle of pembrolizumab, radiological progression was noted in the primary lung lesion, suggesting acquired resistance (Figure 2A).

Given the patient's non-smoking status, female sex, and progression despite standard therapy, the presence of rare driver mutations was suspected. A comprehensive NGS panel was performed. The results identified CDKN2A underexpression and a HLA-DRB1-MET chromosomal rearrangement, which was considered actionable. No other driver mutations were detected. Microsatellite status was stable, and the tumor mutational burden was low (2.1 mutations/Mb).

In October 2024, the patient was started on crizotinib 250 mg twice daily based on the NGS results. Within two weeks of starting crizotinib, the patient reported marked symptomatic relief, including resolution of cough and back pain. No adverse effects or drug-related toxicities were noted. At the three-month follow-up, thoracic CT imaging demonstrated a substantial reduction in tumor size compared to baseline

(Figure 2B). The patient was completely asymptomatic, and treatment was well-tolerated. This robust response suggests the potential utility of crizotinib in MET-rearranged NSCLC, even in rare fusion types such as HLA-DRB1-MET.

A subsequent series of imaging tests confirmed a significant decrease in the size of the tumor and a stabilization of the metastatic disease. At the most recent follow-up, the patient continues to receive crizotinib with excellent tolerability and a sustained clinical and radiological response. There is no evidence of new metastatic lesions, and the patient maintains a high quality of life. Overall, this experience demonstrates the successful integration of chemotherapy, immunotherapy, and molecularly targeted therapy in the management of advanced NSCLC, highlighting the transformative impact of personalized medicine. Written informed consent was obtained from the patient for the publication of this case report and the accompanying clinical information. A comparative analysis of all cases is presented in the following table (Table 1).

## DISCUSSION

The present report highlights the potential of personalized therapy in advanced-stage NSCLC, particularly in cases harboring rare gene fusions such as HLA-DRB1-MET. As the fourth reported instance of an *HLA-DRB1-MET* gene rearrangement in the extant literature, this case underscores the importance of comprehensive molecular profiling, including NGS, in identifying actionable mutations and guiding tailored treatment strategies. HLA-DRB1-MET rearrangements, which are rare driver mutations in lung adenocarcinoma, are detected using comprehensive molecular profiling. In this instance, crizotinib was initiated following disease progression on chemo-immunotherapy, leading to significant disease control. The patient remains on crizotinib therapy with ongoing clinical and radiological stability, demonstrating the sustained efficacy of this targeted approach. Five months after treatment initiation, the patient remained progression-free with a sustained partial response and a PFS of 5 months (ongoing).

Although prospective data for MET fusions remain limited to small series and case reports, outcomes from larger MET-driven NSCLC cohorts provide clinically useful benchmarks for MET inhibition. In the long-term follow-up of the phase 2 VISION trial evaluating tepotinib in MET exon 14-skipping NSCLC, objective response rates (ORR) were approximately 51-56% across lines of therapy, and responses were durable (median duration of response approximately 18-21 months in the overall population), supporting sustained clinical benefit in appropriately selected patients with MET-altered disease.<sup>3,17</sup>

TABLE 1: Comparative analysis of cases.

Case	Age gender	Smoking status	Molecular findings	Treatment	Response	Current status	PFS/disease control duration
Crizotinib in HLA-DRB1-MET fusion-positive NSCLC Davies et al. <sup>4</sup>	74 Female	Never-smoker	HLA-DRB1-MET fusion	-Pemetrexed plus Carboplatin (1 <sup>st</sup> line) -Crizotinib (2 <sup>nd</sup> line)	Complete radiographic response within 6 weeks, maintained for 8 months	Stable with manageable side effects (fatigue, mild hypokalemia)	Crizotinib PFS: 8 mo.
Tepotinib in HLA-DRB1-MET fusion-positive NSCLC Blanc-Durand et al. <sup>13</sup>	41 Female	Never-smoker	HLA-DRB1-MET fusion	-Crizotinib (1 <sup>st</sup> line) -Tepotinib (2 <sup>nd</sup> line) -Cabozantinib (3 <sup>rd</sup> line)	Complete intracranial response to tepotinib, sustained control for 9 months	Stable with good tolerance to treatment	Crizotinib PFS: 6 mo. Tepotinib PFS: 9 mo. Cabozantinib PFS: NR
Crizotinib in HLA-DRB1-MET fusion-positive NSCLC Kunte and Stevenson <sup>14</sup>	59 Female	Never-smoker	HLA-DRB1-MET fusion	-Curative RT (1 <sup>st</sup> line) -Pembrolizumab (2 <sup>nd</sup> line) -Crizotinib (3 <sup>rd</sup> line)	Complete radiographic response within 4 months	Stable with mild side effects (fatigue, nausea)	Crizotinib PFS: at least 4 months (Ongoing at last follow-up)
Tepotinib in HLA-DQB2-MET fusion-positive NSCLC Dias e Silva et al. <sup>15</sup>	73 Female	Never-smoker	HLA-DQB2::MET fusion	-Pemetrexed plus Carboplatin plus Pembrolizumab (1 <sup>st</sup> line) -Tepotinib (2 <sup>nd</sup> line)	Sustained disease control for over 12 months	Stable, no treatment-related adverse events	Tepotinib PFS: 12 mo.
Sequential TKI therapy in ALK-HLA-DRB1 fusion-positive NSCLC Gao et al. <sup>16</sup>	48 Female	Never-smoker	ALK-HLA-DRB1 fusion	-Crizotinib (1 <sup>st</sup> line) -Ceritinib (2 <sup>nd</sup> line)	24 months progression-free survival (crizotinib plus ceritinib)	Stable after sequential TKI therapy	Crizotinib PFS: 6 mo Ceritinib PFS: 18 mo.
Crizotinib in HLA-DRB1-MET fusion-positive NSCLC: Our experience	59 Female	Never-smoker	HLA-DRB1-MET fusion	-Pemetrexed plus Carboplatin plus Pembrolizumab (1 <sup>st</sup> line) -Crizotinib (2 <sup>nd</sup> line)	Significant tumor regression and symptomatic relief	Ongoing treatment with sustained good response	Crizotinib PFS: At least 8 months (ongoing at last follow-up)

TKI: Tyrosine kinase inhibitor; PFS: Progression-free survival; NR: Not reached; RT: Radiotherapy; NSCLC: Non small cell lung cancer; HLA: Human leukocyte antigen; MET: Mesenchymal-epithelial transition.

A comparison of the present case with that reported by Kunte and Stevenson<sup>14</sup> reveals notable distinctions. While both cases involved crizotinib administration following immunotherapy, Kunte and Stevenson<sup>14</sup> administered it after disease progression on pembrolizumab monotherapy. In contrast, crizotinib was employed in the present case after progression on a chemo-immunotherapy combination. In a similar vein, Davies et al.<sup>4</sup> reported a dramatic and rapid response to crizotinib in the absence of prior systemic treatments. Conversely, the progression-driven use of crizotinib for this patient exemplifies a more complex treatment trajectory and underscores the need to integrate targeted therapies into a comprehensive therapeutic framework. By comparison, Blanc-Durand et al.<sup>13</sup> demonstrated the efficacy of tepotinib in a case

involving CNS metastases, in which the choice of therapy was influenced by the drug's ability to penetrate the blood-brain barrier. The absence of CNS involvement in this case enabled crizotinib to achieve effective disease control, emphasizing the need to tailor therapy to individual clinical profiles. Another comparison involves the report by Dias E Silva et al.<sup>15</sup>, in which tepotinib was employed following progression on prior systemic treatments. Both cases underscore the critical role of comprehensive genomic analysis in identifying rare fusions. However, the absence of CNS metastases in this instance simplified management and enabled a straightforward treatment strategy. In contrast, the sequential use of crizotinib and ceritinib, as described by Gao et al.<sup>16</sup>, involved crizotinib monotherapy, which was sufficient to achieve durable disease control.

From a biological perspective, MET fusions, such as HLA-DRB1-MET, act as oncogenic drivers by activating hepatocyte growth factor receptor (HGFR)-mediated signaling. Fusion events involving MET's exon 15 preserve the kinase domain, leading to constitutive activation and disruption of regulatory regions. Mechanistically, MET fusion proteins can promote ligand-independent receptor activation and downstream signaling through pathways such as MAPK/ERK and PI3K/AKT, reinforcing oncogenic dependence on MET. In addition to DNA-based detection, RNA-based assays can improve sensitivity for identifying expressed fusion transcripts and defining fusion breakpoints, which is particularly relevant when rare partners or complex rearrangements are present.<sup>18,19</sup> These advances have been instrumental in detecting such rearrangements. These assays facilitate the concurrent evaluation of multiple genes, thereby enabling precise therapeutic decisions, particularly in cases where conventional testing might miss rare alterations.<sup>20</sup> The efficacy and safety of targeted therapies, such as crizotinib and tepotinib, have been demonstrated in numerous cases, with improvements in patient outcomes and quality of life. Crizotinib's established activity against MET exon 14-skipping mutations and rare fusions has been attributed to its inhibition of HGFR-mediated signaling. Other MET inhibitors, such as capmatinib, have emerged as promising alternatives, particularly in cases involving CNS metastases or resistance to first-line MET inhibitors.<sup>21,22</sup>

Consistent with this, the Phase 2 GEOMETRY mono-1 study of capmatinib in MET exon 14-skipping NSCLC reported clinically meaningful activity in both treatment-naïve and previously treated populations: ORR of approximately 68% and 41%, respectively, and median PFS of approximately 12 months and 5 months, respectively. These data support the broader concept that dependence on the MET pathway can translate into substantial radiographic responses and meaningful disease control in patients treated with MET-selective TKIs.<sup>23,24</sup>

Beyond de novo MET-altered tumors, MET activation is also a key mechanism of acquired resistance. In the insight 2 phase 2 trial in patients with EGFR-mutant NSCLC and MET amplification after progression on first-line osimertinib, tepotinib plus osimertinib achieved an ORR of 50%, with a median duration of response of 8.5 months, median PFS of 5.6 months, and median OS of 17.8 months, illustrating how MET-directed therapy is increasingly incorporated into rational combination strategies when MET drives resistance.<sup>25</sup>

Despite meaningful initial responses, both on-target and off-target resistance mechanisms can limit the durability of MET TKI benefit. On-target resistance may arise through secondary MET kinase-domain mutations (commonly involving residues such as D1228 and Y1230) that reduce binding of type I MET

inhibitors; other mutations (e.g., solvent-front alterations) can differentially affect sensitivity across MET inhibitors and may inform switching strategies. Off-target (bypass) resistance has been linked to activation of parallel signaling networks—such as ERBB-family signaling and reactivation of downstream PI3K/AKT or RAS/MAPK pathways—and to genomic events such as KRAS pathway alterations. These resistance patterns underscore the rationale for repeat molecular testing at progression and for tailoring subsequent therapy (switching MET inhibitor class, combination approaches, or clinical trial enrollment) based on the emergent mechanism.<sup>18,26,27</sup> The rarity of MET rearrangements, which occur in approximately 0.5% of lung adenocarcinomas, underscores the importance of advanced diagnostic tools. Techniques combining RNA and DNA analysis are expanding the scope of detectable alterations, enabling broader applications of precision oncology. This case aligns with global evidence supporting the integration of targeted therapies following standard treatments, showcasing the nuanced strategies required to manage NSCLC with rare MET rearrangements.

## CONCLUSION

This review synthesizes evidence from a variety of case reports, emphasizing the transformative impact of molecularly targeted therapies in NSCLC with MET rearrangements. While significant progress has been made in understanding and treating these rare alterations, challenges persist in their early identification, standardized management, and access to advanced diagnostics and therapies. Addressing these challenges will require coordinated efforts in research, healthcare policy, and patient advocacy. The efficacy of MET TKIs, particularly in cases involving novel fusions such as HLA-DRB1-MET and HLA-DQB2-MET, underscores the potential of precision oncology to deliver highly personalized and effective treatments. The case study presented here further illustrates the importance of a multidisciplinary approach combining advanced diagnostics with innovative therapies. This case provides further evidence supporting the efficacy of crizotinib in achieving durable disease control in patients with HLA-DRB1-MET fusions and is consistent with global evidence supporting targeted therapy. Furthermore, comparative analyses of involving tepotinib and sequential TKI therapies underscore the necessity to customize treatment strategies based on individual clinical profiles, including CNS involvement and prior therapies. For instance, the efficacy of tepotinib in patients with CNS metastases and the sequential use of TKIs to overcome resistance highlight the complexities inherent in the management of MET-altered NSCLC. Notably, among never-smoking female patients with NSCLC,

the detection rate of driver mutations can be as high as 60%, underscoring the critical importance of comprehensive NGS profiling in this subgroup. Such advanced molecular diagnostics are pivotal in guiding precise therapeutic decisions and have a significant impact on survival outcomes. Consequently, the integration of comprehensive NGS into the diagnostic workup of these patients should be prioritized to ensure optimal clinical management and to improve overall survival. As our understanding of MET rearrangements progresses, so too will the strategies to optimize outcomes and improve the quality of life for affected patients. Continued innovation and collaboration among researchers, clinicians, and industry stakeholders are essential to ensure that emerging therapies reach the patients who need them most. In conclusion, these findings contribute to the growing body of evidence that MET TKIs are effective treatments for NSCLC with MET rearrangements. The adaptive integration of molecular profiling and personalized therapy offers new hope for improved patient outcomes. Future research should aim to optimize therapeutic sequencing, explore the efficacy of emerging MET inhibitors, and further elucidate the mechanisms underlying MET-driven oncogenesis, thereby enhancing the precision and efficacy of cancer care.

### Ethics

**Informed Consent:** Written informed consent was obtained from the patient for the publication of this case report and the accompanying clinical information.

### Footnotes

### Authorship Contributions

Surgical and Medical Practices: H.M., J.H., B.K., Concept: H.M., B.K., M.H.Y., Ö.F.Ö., Design: H.M., E.S., M.H.Y., Ö.F.Ö., Data Collection or Processing: H.M., J.H., Analysis or Interpretation: H.M., M.H.Y., Literature Search: H.M., E.S., E.E.D., Writing: H.M., Ö.F.Ö.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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