

**Title:**

Liquid biopsy-based detection of acquired MET resistance enables sequential targeted therapy in MET fusion-positive NSCLC

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**Abstract:**

Oncogenic alterations in MET represent therapeutically actionable driver alterations in non-small cell lung cancers (NSCLC). Among these, MET fusions are rare, occurring in approximately 0.1-0.3% of NSCLC. We report the case of a 52-year-old woman with metastatic, TTF1-positive lung adenocarcinoma harboring a KIF5B::MET fusion. After progression on chemotherapy and immunotherapy, she achieved a durable response lasting nearly five years on third-line treatment with the type Ia MET inhibitor crizotinib. At the time of suspected disease progression, two tissue re-biopsies were non-diagnostic due of insufficient tumor cell content. Circulating tumor DNA (ctDNA) analysis identified two newly acquired on-target resistance mutations within the MET kinase domain (L1213V and Y1248C) in addition to the known KIF5B::MET fusion. After re-evaluation by the institutional molecular tumor board, both alterations were considered mediators of resistance to type I MET inhibitors, with available data indicating preserved sensitivity to type II inhibitors. Based on these findings, the patient was switched to cabozantinib, a multikinase type II MET inhibitor, resulting in a radiographic disease stabilization

accompanied by a marked decline in tumor marker levels. This case illustrates the clinical utility of liquid biopsy for molecular resistance monitoring, particularly when tissue re-biopsy is not feasible, supports its integration into clinical decision-making, and underscores the therapeutic relevance of MET inhibitor class-switch strategies in MET fusion-positive disease.

#### Key points:

- MET fusions are rare but actionable oncogenic drivers in NSCLC
- Repeated molecular analyses, including ctDNA profiling, are critical to monitor molecular evolution
- On-target MET kinase domain alterations can confer resistance to type I MET inhibitors while retaining sensitivity to type II inhibitors

#### Introduction

Oncogenic alterations in MET, a receptor tyrosine kinase proto-oncogene, represent important and rare drivers of tumorigenesis. MET gene fusions have been identified across various tumor types with less than 0.4% of solid tumors harboring MET fusions [1, 2]. Within non-small cell lung cancer (NSCLC) MET fusions are detected in approximately 0.13% to 0.3% of cases whereas other MET alterations such as MET exon-14-skipping mutations (2–4%) or MET amplification (1–6%) are more common [1, 3].

No approved targeted treatment options exist for MET fusion-positive tumors, whereas MET inhibition is a standard of care for patients with MET exon-14-skipping mutations [4]. Currently approved MET inhibitors can broadly be classified into two types based on their binding mode to the MET kinase domain. Type I inhibitors interact with the active conformation of the MET kinase within the ATP binding pocket with type Ia agents, such as crizotinib, being relatively non-selective and also targeting ALK and ROS1, whereas type Ib agents, including capmatinib and tepotinib, display greater MET selectivity. In contrast type II inhibitors, such as cabozantinib, engage the inactive kinase conformation and are generally classified as multikinase agents with broader activity [3].

Despite initial clinical responses, resistance to MET inhibition is a major therapeutic challenge. On-target acquired resistance often arises through secondary mutations within the MET kinase domain [5-7], which reduce inhibitor binding affinity and compromise therapeutic efficacy. Off-target resistance mechanisms include activation of bypass pathways [8], further complicating long-term disease control. The diversity of resistance mechanisms necessitates both careful sequencing of therapies and ongoing molecular surveillance. Liquid biopsy has emerged as a minimally invasive approach for real-time detection of resistance mutations and longitudinal monitoring of clonal evolution during treatment. Circulating tumor DNA (ctDNA) analysis allows for dynamic assessment of emerging resistance, enabling timely adaptation of treatment strategies.

Because of its rarity, only limited data exist on the efficacy of MET inhibitors for MET fusion-positive NSCLC. Furthermore, data on acquired resistance mechanisms and optimal sequential MET inhibitor strategies in MET fusion-positive NSCLC remain extremely limited.

#### Patient story

A 52-year-old Caucasian woman with a 5 pack-year smoking history, who had stopped smoking 20 years prior, was referred to the precision oncology unit at Charité-Universitätsmedizin Berlin in Y1M2 (one year and two months) after initial diagnosis (**Fig. 1**) of a TTF1-positive lung adenocarcinoma and pulmonary, adrenal, and osseous metastases (stage IVB, AJCC 8<sup>th</sup> edition). At the time of initial diagnosis (Y0M0), immunohistochemistry showed a PD-L1 combined positive score of 0. Targeted next-generation sequencing (NGS) revealed a tumor cell content of 30% and identified a KIF5B::MET in-frame fusion (K24::M15) as the primary oncogenic driver. Co-occurring alterations included SMAD4 Q256L (c.767A>T) with allele frequency (AF) of 4.5% and TP53 P72R (c.215C>G) with AF of 30%, likely a common germline polymorphism (**Tab. 1**). The patient received first-line treatment with cisplatin and pemetrexed, followed by pemetrexed maintenance with stable disease as best response. After disease progression in Y1M0 a second-line treatment with nivolumab was initiated, and the case was discussed in our molecular tumor board (Y1M2). In view of the KIF5B::MET fusion, off-label treatment with

crizotinib was recommended, which was started in Y1M7 after progression under nivolumab. Treatment-related visual disturbances, nausea, constipation, fatigue, and heartburn necessitated dose reduction to 200 mg once daily. A durable radiographic response was observed, with a maximum tumor reduction of 31% achieved in Y3M5, fulfilling criteria for partial remission according to RECIST 1.1 [9], and disease control was maintained for nearly five years under crizotinib treatment (**Fig. 1A**). This was accompanied by a marked decline in serum carcinoembryonic antigen (CEA) levels from 81.6 ng/mL in Y1M7 prior to crizotinib to a nadir of 18.5 ng/mL in Y2M9 (**Fig. 1B**) and preservation of excellent quality of life. In Y4M6 computed tomography demonstrated a mixed response, characterized by a slowly enlarging tumor-atelectasis complex in the right lower lobe and the emergence of new satellite nodules not amenable to local therapy, while adrenal and osseous metastases remained stable (**Fig. 1A**). Repeat tissue sampling was attempted. Bronchoscopy with endobronchial ultrasound-guided transbronchial needle aspiration and a CT-guided lung biopsy did not yield sufficient tumor tissue for molecular analyses. Given good tolerance and indolent disease kinetics, crizotinib was continued until radiographic multifocal pulmonary progression was documented in Y6M6.

### **Molecular tumor board**

Given past repeated non-diagnostic biopsies, a plasma-based ctDNA approach was chosen. In Y6M8, a liquid biopsy confirmed persistence of the activating KIF5B::MET fusion and additionally identified two newly acquired on-target resistance mutations within the MET kinase domain: MET L1213V (c.3637C>G) with an AF of 0.38% and MET Y1248C (c.3743A>G) with an AF of 0.12% (**Tab. 1**). Both MET mutations have been described as contributing mediators of resistance to type I MET inhibitors. The concomitant presence of both mutations was consistent with clinical resistance to crizotinib and supported the rationale for a switch to cabozantinib [3, 12, 13]. Additionally, the liquid biopsy identified a variant of unknown significance in FGFR1 c.1977+1G>A with AF of 0.23%, predicted to alter splicing within the kinase domain (**Tab. 1**). However, no established clinical or functional relevance of this variant has been reported to date. No alterations in KRAS, BRAF, or EGFR were detected, arguing against off-target resistance mechanisms. After multidisciplinary discussion in the institutional molecular tumor board, off-label treatment with the type II MET inhibitor cabozantinib was recommended.

### **Patient update**

An early imaging assessment in Y6M11 demonstrated disease stabilization with regression of the pulmonary lesions and stability of the adrenal and osseous metastases (**Fig. 1A**). In parallel, a decrease in serum CEA levels was observed, declining from 190 ng/mL in Y6M8 to 63.7 ng/mL in Y7M1 under cabozantinib treatment (**Fig. 1B**). At a later follow-up (Y7M5), imaging demonstrated overall stable disease, with a slight increase in pulmonary satellite metastases, a stable primary tumor, and regressing adrenal metastases. Correspondingly, the CEA level showed a modest increase to 93.1 ng/mL at Y7M6. In the context of ongoing clinical benefit, treatment with cabozantinib was continued.

### **Discussion**

Management of NSCLC harboring MET fusions remains challenging due to the rarity of these alterations and the limited evidence. Nonetheless, MET inhibitors have demonstrated substantial clinical benefit in this molecular subset. As reviewed recently, clinical experience from case reports and series indicates that MET fusions are actionable with several MET-TKIs. Crizotinib is the most frequently reported agent, with 22 treated patients achieving high response rates, including complete and partial remissions, across first-line and later-line settings [14]. The patient we describe achieved a sustained radiographic response of nearly five years under crizotinib, which, to our knowledge, represents the longest response to MET inhibition in the context of a MET fusion so far reported. This is especially noteworthy, considering the pretreatment history of the patient. Cabozantinib has been used in four cases of MET fusion-positive solid tumors, once as first-line therapy in salivary gland carcinoma patient leading to partial remission [15]; in three further cases it was used as later line therapy after progress under prior treatment with MET inhibitors, with stable disease, partial response for three months and progressive disease as best response respectively [5, 16, 17]. Other agents, such as tepotinib and capmatinib,

have also demonstrated clinical efficacy in MET fusion-positive patients, further supporting the activity of MET-TKIs in this rare subset [14].

A central problem is the emergence of acquired resistance, which frequently limits the durability of response. Acquired resistance to MET inhibitors can occur through various genomic alterations, including on-target point mutations and copy-number variations of the MET gene, as well as off-target alterations in bypass signaling pathways [8]. Studies have identified specific mutations, such as Y1230H, D1228H, D1228N and D1246N that confer significant resistance under MET inhibition in the context of MET exon-14-skipping mutations and amplifications [6, 7, 12, 18, 19], but data on acquired resistance in the setting of MET fusions remain very limited [5, 8]. In this context, liquid biopsy has emerged as a particularly valuable tool. Analysis of ctDNA allows dynamic and minimally invasive monitoring of molecular evolution during treatment and facilitates the timely detection of resistance mechanisms, especially when repeated tumor biopsies are not feasible. It should be noted that ctDNA analysis has inherent limitations, including reduced sensitivity for the detection of resistance mechanisms such as MET amplification compared to tissue-based methods.

In the present case, multiple tissue biopsy attempts failed, yet liquid biopsy successfully identified both the primary KIF5B::MET fusion and the acquired resistance mutations. Our case highlights the detection of the MET resistance mutations L1213V and Y1248C emerging in the context of acquired resistance to crizotinib in a MET fusion-driven tumor. Specifically, the Y1248C substitution represents a well-characterized on-target mutation that confers resistance to both type Ia and type Ib MET inhibitors, which bind the active kinase conformation, while retaining sensitivity to type II inhibitors such as cabozantinib [10, 11]. In contrast, alterations at L1213 have been described as resistance mutations affecting the inactive kinase conformation targeted by type II inhibitors [11]. Consistent with this, the L1213V mutation exhibits a broader resistance profile, with preclinical data suggesting reduced sensitivity to both type Ia and, to a lesser extent, type II MET inhibitors, possibly retaining sensitivity to type Ib inhibitors e.g. tepotinib and capmatinib [11,12]. In general, resistance mutations to type I MET inhibitors retain sensitivity to type II inhibitors, and vice versa, reflecting their distinct conformational binding modes [12]. However, the co-occurrence of Y1248C and L1213V complicates therapeutic decision-making regarding subsequent MET inhibitor selection and may confer a heterogeneous resistance profile with only partial restoration of drug sensitivity under class-switch treatment, potentially explaining the observed disease stabilization rather than tumor regression with cabozantinib. Longer-term follow-up, including additional imaging and tumor marker assessments under cabozantinib, would be important to further evaluate the durability of disease control. Sequential ctDNA analyses during cabozantinib treatment were not available in this case. Such analyses would have been informative to assess clonal dynamics, including potential clearance of Y1248C and persistence or expansion of L1213V.

Following molecular tumor board recommendation, the patient was switched to cabozantinib, a multikinase inhibitor that functions as a type II MET inhibitor. This class-switch strategy exploits fundamental differences in MET kinase binding modes, as type II inhibitors engage the inactive kinase conformation and a distinct binding pocket. Such an approach may allow continued target inhibition in the presence of activation-loop resistance mutations, such as Y1248C, that impair binding of type I MET inhibitors. Under cabozantinib treatment, clinically meaningful disease stabilization with radiographic regression and decrease in CEA was achieved. These findings underscore the therapeutic potential of leveraging alternative binding modes to overcome structurally mediated on-target resistance mechanisms.

In conclusion, this case highlights several important aspects of precision oncology in MET fusion-positive NSCLC. It underscores the need for early comprehensive molecular profiling in order to identify rare oncogenic drivers that benefit from targeted therapy over chemotherapy and demonstrates the feasibility and efficacy of MET inhibition in this rare molecular subset. It further underscores the critical role of repeated molecular analyses, including liquid biopsy, for real-time detection of resistance mutations and supports the routine integration of ctDNA profiling into the management of MET-driven NSCLC. In this case, the primary clinical utility of ctDNA analysis was the identification of resistance mutations after repeated non-diagnostic tissue biopsies, rather than longitudinal monitoring. Finally, it highlights the value of a MET inhibitor class switch in overcoming on-target resistance to type I MET inhibitors in the context of a MET fusion.

## Methods

The patient consented to the publication of this report. This study was approved by the Institutional Ethics Committee of Charité-Universitätsmedizin Berlin (EA 1/152/10). Handling of patient data was performed in accordance with the Declaration of Helsinki. Clinical data, treatments, adverse events, and radiographic assessments were extracted from the patient's electronic medical record. Treatment decisions were discussed within an institutional molecular tumor board. Formalin-fixed, paraffin-embedded tumor tissue obtained at initial diagnosis underwent targeted NGS using the Ion AmpliSeq™ Colon and Lung Cancer Research Panel v2 and the Ion AmpliSeq™ Custom Lung Fusion Panel (Thermo Fisher Scientific, Waltham, MA, USA). CtDNA was analyzed using the Agilent HS2 Lung Liquid assay (Agilent Technologies, Santa Clara, CA, USA). All MET variants were annotated based on the reference transcript NM\_001127500; accordingly, L1213V and Y1248C correspond to L1195V and Y1230C, respectively, in the alternative transcript NM\_000245.5. Serial disease evaluations were performed by contrast-enhanced computed tomography at clinically indicated intervals.

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#### Author contributions

S.R., P.K. and D.T.R. wrote the main manuscript text. S.R. prepared the figures and tables. L.H., M.M. and T.G. performed the molecular analyses. J.L. performed the radiological assessments. M.J., M.M., T.G., M.B., L.V., C.-E.O., M.K., U.Kei. and D.T.R. discussed the case in the molecular tumor board. K.K., D.P.M., U.Kel., N.F. provided resources and supervised patient management. P.K. and D.T.R. treated the patient. All authors reviewed, revised and approved the final manuscript.

#### Competing interests

P.K. has received consultant and/or speaker fees from Johnson & Johnson, AbbVie, Amgen, Pfizer, Astra Zeneca, Sanofi, Roche, Stemline, Novartis. D.T.R. has received consultant and/or speaker fees from Bayer, Eli Lilly, Bristol-Myers Squibb, Johnson & Johnson, Roche, and Bei-Gene; travel support from Bayer and Johnson & Johnson; and research funding from SeaGen. All other authors have declared no conflicts of interest.

#### Funding Statement

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. This work was supported by the German national Network Genomic Medicine (nNGM) Lung Cancer.

#### Data availability statement

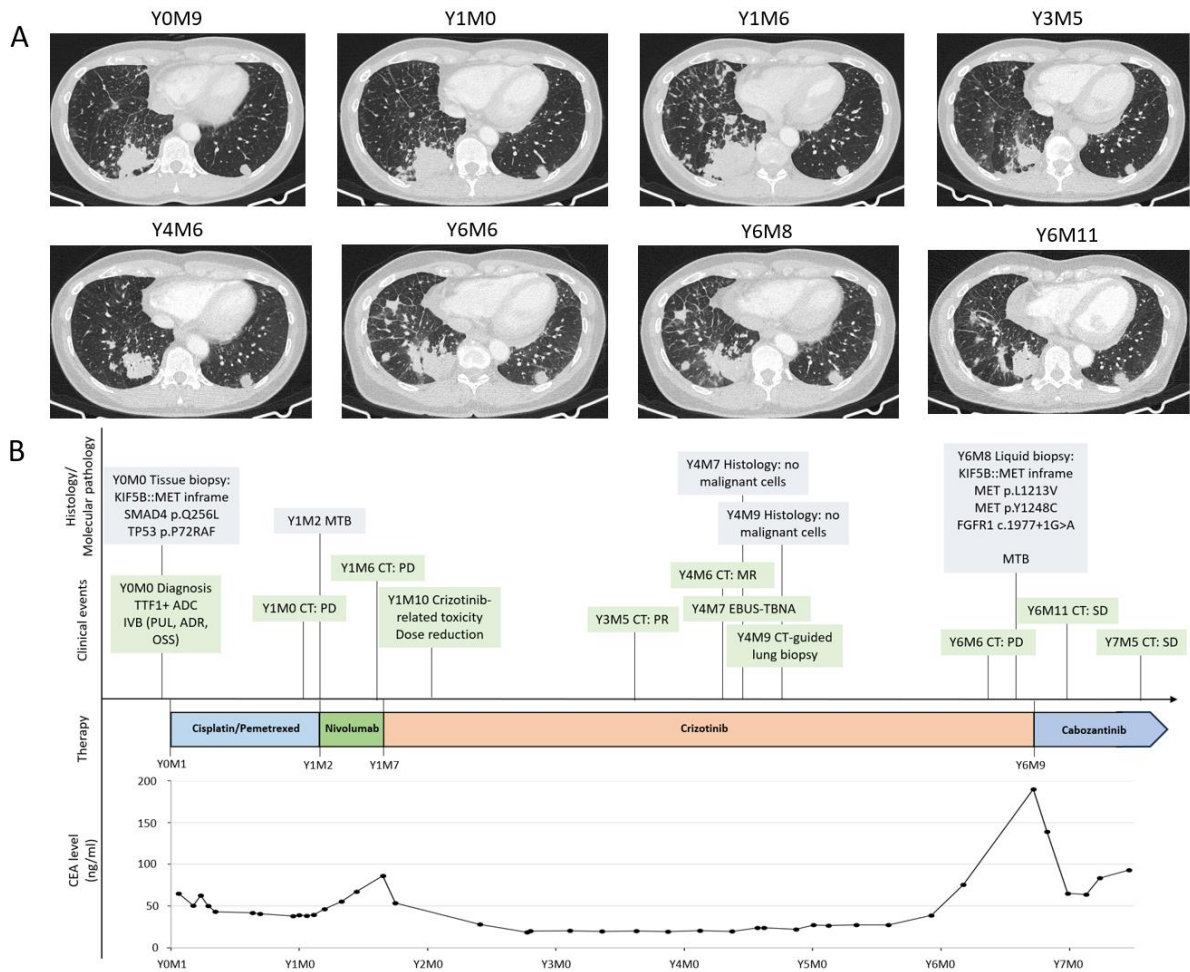
The data supporting the findings of this study are included within the article and its supplementary materials. Additional clinical or molecular data are available from the corresponding author upon reasonable request

#### Tables

Sample	Technology	Assay	Findings
<b>Tissue biopsy Y0M0</b>	NGS	Ion AmpliSeq™ Colon and Lung Cancer Research Panel v2/Custom Lung Fusion Panel (Thermo Fisher Scientific, Waltham, MA, USA)	TCC 30% KIF5B::MET (K24::M15) in-frame SMAD4 c.767A>T p.Q256L (exon 6) AF 4.5% TP53 c.215C>G p.P72R (exon 4) AF 30%
<b>Liquid biopsy Y6M8</b>	NGS	Agilent HS2 Lung Liquid assay (Agilent Technologies, Santa Clara, CA, USA)	KIF5B::MET (K24::M15) in-frame MET c.3637C>G p.L1213V (exon 18) AF 0.38 % MET c.3743A>G p.Y1248C (exon 19) AF 0.12% FGFR1 c.1977+1G>A AF 0.23%

**Tab. 1:** Results of genomic characterization. NGS, next-generation sequencing; TCC, tumor cell content. MET variants were annotated according to transcript NM\_001127500 (L1213V and Y1248C correspond to L1195V and Y1230C in the alternative transcript NM\_000245.5, respectively).

#### Figures



**Fig. 1:** Course of disease. **(A)** Representative CT scans, **(B)** Systemic treatment, molecular testing and longitudinal CEA levels. Abbreviations: MTB, molecular tumor board; CEA, carcinoembryonic antigen; YxMy, time since initial diagnosis expressed as years (Y) and months (M), with Y0M0 corresponding to the date of initial diagnosis.