Case Report

ALK-tyrosine kinase inhibitor intrinsic resistance due to *de novo MET*-amplification in metastatic *ALK*-rearranged non-small cell lung cancer effectively treated by alectinib-crizotinib combination—case report

Edyta M. Urbanska[1]^, Morten Grauslund[2]^, Siv M. S. Berger[3]^, Junia C. Costa[3]^, Peter R. Koffeldt[2]^, Jens B. Sørensen[1,4]^, Eric Santoni-Rugiu[2,4]^

[1]Department of Oncology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark; [2]Department of Pathology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark; [3]Department of Radiology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark; [4]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

Contributions: (I) Conception and design: EM Urbanska, E Santoni-Rugiu; (II) Administrative support: None; (III) Provision of study materials or patients: E Santoni-Rugiu, EM Urbanska, M Grauslund, SMS Berger, JC Costa, PR Koffeldt; (IV) Collection and assembly of data: E Santoni-Rugiu, M Grauslund, SMS Berger, JC Costa, PR Koffeldt; (V) Data analysis and interpretation: EM Urbanska, M Grauslund, JB Sørensen, E Santoni-Rugiu; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Edyta M. Urbanska, MD, PhD. Department of Oncology, Rigshospitalet, Copenhagen University Hospital, Blegdamsvej 9, 2100 Copenhagen, Denmark. Email: edyta.maria.urbanska@regionh.dk; Eric Santoni-Rugiu, MD, PhD. Department of Pathology, Rigshospitalet, Copenhagen University Hospital, Blegdamsvej 9, 2100 Copenhagen, Denmark; Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark. Email: eric.santoni-rugiu.02@regionh.dk.

Background: Most patients with advanced anaplastic lymphoma kinase (*ALK*)-rearranged (*ALK*+) non-small cell lung cancer (NSCLC) experience prolonged response to second-generation (2G) ALK-tyrosine kinase inhibitors (TKIs). Herein, we present a case of metastatic *ALK*+ NSCLC rapidly progressing on first-line treatment due to *de novo* amplification of the mesenchymal-epithelial transition factor (*MET*) gene, which is a still elusive and underrecognized mechanism of primary resistance to ALK-TKIs.

Case Description: A 43-year-old, female diagnosed with T4N3M1c NSCLC harboring the echinoderm microtubule-associated protein-like 4 (*EML4*)-*ALK* fusion variant 1 (*EML4-ALK* v.1) and *TP53* co-mutation, displayed only mixed response after three months and highly symptomatic progression after 6 months of first-line brigatinib treatment. Immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) analysis on re-biopsies from a new liver metastasis revealed overexpression of MET receptor (3+ in 80% of tumor cells) and heterogeneously increased *MET* gene copy number (CN) in tumor cells, including 20% with *MET* clusters (corresponds to ≥15 gene copies, thus exact CN uncountable by FISH) and the other 80% with median *MET* CN of 8.3, both changes indicating high-level *MET*-amplification. DNA and RNA next-generation sequencing (NGS) displayed preserved *ALK* fusion and *TP53* co-mutation, but no additional genomic alterations, nor *MET*-amplification. Therefore, we retrospectively investigated the diagnostic biopsy from the primary tumor in the left lung with IHC and FISH revealing the presence of increased MET receptor expression (2+ in 100% of tumor cells) and *MET*-amplification (median *MET* CN of 6.1), which otherwise was not detected by NGS. Thus, given the well-documented efficacy of alectinib towards *EML4-ALK* v.1, combined second-line treatment with alectinib and the MET-TKI, crizotinib, was implemented resulting in very pronounced objective response, significantly improved quality of life, and no adverse events so far during the ongoing treatment (6 months).

^ ORCID: Edyta M. Urbanska, 0000-0002-4578-9346; Morten Grauslund, 0000-0001-6416-8660; Siv M. S. Berger, 0009-0006-2068-8203; Junia C. Costa, 0000-0001-8910-433X; Peter R. Koffeldt, 0009-0005-0193-650X; Jens B. Sørensen, 0000-0001-7780-0178; Eric Santoni-Rugiu, 0000-0002-2283-3535.

Conclusions: The combination of alectinib and crizotinib may be a feasible and effective treatment for *ALK*+ NSCLC with *de novo MET*-amplification. The latter may represent a mechanism of intrinsic ALK-TKI resistance and its recognition by FISH, in NGS-negative cases, may be considered before initiating first-line treatment. This recognition is clinically important as combined therapy with ALK-TKI and MET-inhibitor should be the preferred first-line treatment.

Keywords: *De novo MET*-amplification; intrinsic ALK-tyrosine kinase inhibitor resistance (intrinsic ALK-TKI resistance); *ALK*-rearranged non-small cell lung cancer (*ALK*-rearranged NSCLC); tyrosine kinase inhibitor combination (TKI combination); case report

Submitted May 20, 2024. Accepted for publication Jul 26, 2024. Published online Sep 26, 2024.
doi: 10.21037/tlcr-24-439
View this article at: https://dx.doi.org/10.21037/tlcr-24-439

Introduction

No guidelines for personalized diagnostics and treatment of intrinsic and acquired resistance mechanisms in oncogene addicted non-small cell lung cancer (NSCLC) are available. Due to the evolving nature and heterogeneity of this disease, such guidelines are hardly expected to cover the entire area of a complex variety of mechanisms. Both according to National Comprehensive Cancer Network (NCCN) guidelines version 8.2024 and in real-world setting, the next treatment choice for anaplastic lymphoma kinase (*ALK*)-rearranged (*ALK*+) NSCLC progressing with multiple lesions on second-generation (2G) ALK-tyrosine kinase inhibitors (TKI) is often a reflex switch to lorlatinib or chemotherapy despite the rationality for re-biopsy is broadly documented (1). For NSCLC patients with *ALK*-rearrangement and progressive disease on first-line crizotinib treatment, the switch to 2G or third-generation (3G) ALK-TKI may be reasonable to some extent, especially when no re-biopsies are available. The argument for such an approach is a frequently occurring on-target resistance represented by secondary *ALK* mutations sensitive to 2G and 3G ALK-TKIs, and often a need for inhibiting progression in the brain. However, when progression is observed on 2G ALK-TKIs a variety of off-target resistance mechanisms, both molecular and phenotypical, may be implicated (2-4). In epidermal growth factor receptor (*EGFR*)-mutant NSCLC progressing on osimertinib, amplification of the mesenchymal-epithelial transition factor (*MET*) gene is the most frequent off-target resistance mechanism, and disease control may be restored by a combination of EGFR- and MET-TKI (5-8). Similarly, acquired *MET*-amplification was recently described to occur in 10–22% of *ALK*+ NSCLC patients treated with ALK-TKIs, often as a heterogenous alteration (9). Currently no clinical trials exploring combinations of ALK- and MET-TKIs in NSCLC are registered (10). However, the rationale behind such a combination has been assessed in preclinical setting (11), and initial real-world attempts have been reported (12). In contrast, lack of response to ALK-TKIs within the first 3–6 months after treatment initiation is rare and suggests intrinsic resistance due to possible preexisting co-alterations interfering with the beneficial effect of these

Highlight box

Key findings

- *De novo* amplification of the mesenchymal-epithelial transition factor (*MET*) gene represents a druggable mechanism of intrinsic resistance to second-generation (2G) anaplastic lymphoma kinase (ALK)-tyrosine kinase inhibitors (TKIs) in *ALK*-rearranged non-small cell lung cancer (NSCLC).

What is known and what is new?

- Several mechanisms of acquired resistance to 2G ALK-TKIs are known, yet there is still limited knowledge regarding intrinsic resistance to these drugs.
- Our case illustrates that in *ALK*-rearranged NSCLC, *de novo MET*-amplification can be an off-target mechanism of intrinsic resistance to 2G ALK-TKIs, which may be counteracted by combining the 2G ALK-TKI with crizotinib (or another MET inhibitor).

What is the implication, and what should change now?

- In cases of lack of response to highly effective 2G ALK-TKIs, one should consider *de novo MET*-amplification as possible intrinsic resistance mechanism and test for it.
- Future studies will indicate whether upfront testing for *MET*-amplification by fluorescence in situ hybridization (FISH) should be performed before initiating treatment with 2G ALK-TKIs.
- Because of its heterogeneity, *de novo MET*-amplification is more likely to be detected by FISH than next-generation sequencing.

drugs. These *de novo* co-alterations are not fully uncovered, and it remains elusive whether *MET*-amplification might be one of them. Herein, we present a real-world case of *ALK*+ NSCLC with *de novo MET*-amplification rapidly progressing on a 2G ALK-TKI but responding to combined ALK- and MET-TKI treatment. To our knowledge, such a MET-mediated intrinsic resistance to 2G ALK-TKIs has not been reported before. Its occurrence indicates that assessing *MET*-amplification may be considered before initiating ALK-TKI treatment and that it is possible to effectively counteract this off-target mechanism of intrinsic ALK-TKI resistance using a combination of targeted TKIs. We present this case in accordance with the CARE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-439/rc).

Case presentation

A 43-year-old female without comorbidities, never smoker, in performance status (PS) 2, was diagnosed with T4N2M1c (*Figure 1*, A1-E1) NSCLC of adenocarcinoma histological type that was immunohistochemically positive for CK7 and TTF-1 (data not shown). The tumor tissue harbored the echinoderm microtubule-associated protein-like 4 (*EML4*)-*ALK* fusion variant1 (v.1) and *TP53* mutation c.733G>A, p.G245S, which were identified by RNA- and DNA-next-generation sequencing (NGS) (Oncomine Comprehensive Assay v.3, ThermoFisher Scientific, Roskilde, Denmark), respectively. The patient was initially treated with first-line brigatinib, 180 mg once a day (QD), according to the national reimbursement agreement for ALK-TKIs in Denmark. Due to multiple metastases to bones, kidneys and skeletal muscles, the patient was heavily affected by pain, rest dyspnea, dizziness, and fatigue. The baseline assessment of circulating free DNA (cfDNA) in plasma by NGS (Oncomine Lung cfDNA Assay, ThermoFisher Scientific) displayed the *TP53* mutation [variant allele frequency (VAF) 6.05%]. The first computerized tomography (CT) evaluation after 3 months of treatment with brigatinib revealed limited clinical improvement, and a modest mixed response according to RECIST version 1.1 criteria, as new lytic metastases in the skeleton appeared alongside sclerosing lesions (*Figure 1*, C2-D2), a pericardial exudate and a semisolid infiltrate in the left lung progressed, while the primary tumor in the left upper lobe (*Figure 1*, A2), mediastinal lymph nodes (data not shown) and metastases in the kidneys were diminished (*Figure 1*, B2). Newly sampled cfDNA showed persistent *TP53* mutation (VAF 1.53%). After 6 months of brigatinib treatment, despite further decrease of the primary lung tumor and renal metastases (*Figure 1*, A3-B3), the disease further progressed with the increased size of a skeletal metastasis with a prominent soft tissue component in the right scapula (*Figure 1*, C3-D3) and a new metastasis in the liver (*Figure 1*, E3). Given the increasing skeletal pain the patient received higher doses of analgesics and palliative radiation therapy against the metastatic conglomerate in the right scapula. A tumor re-biopsy was taken from the new hepatic metastasis, which exhibited maintained adenocarcinoma histology without any phenotypic transformation (*Figure 2A*). Immunohistochemistry (IHC) showed maintained expression of ALK fusion protein in tumor cells as well (*Figure 2B*). Accordingly, NGS analysis (Oncomine Dx Express Test, ThermoFisher Scientific) of DNA and RNA isolated from the re-biopsy displayed persistence of the original *EML4-ALK* fusion and *TP53* mutation, but no additional variants or copy number (CN) variations. However, supplementary IHC displayed overexpression of MET receptor protein in the metastatic tumor cells (stain intensity 3+ in 80% of tumor cells) (*Figure 2C*). Consistent with this finding, fluorescence in situ hybridization (FISH) analysis with the ZytoLight® SPEC *MET/CEN* 7 dual color probe (Zytovision GmbH, AH Diagnostics A/S, Tilst, Denmark), revealed heterogenous high-level *MET*-amplification. Indeed, 20% of tumor cells appeared with *MET* gene clusters, which by convention is considered as representing ≥15 gene copies, given that the exact CN is uncountable by FISH when so many signals are clustered together (5,13,14), whereas the other 80% revealed median *MET* CN of 8.3 (*Figure 2D*,*2E*). Thus, to elucidate whether the *MET*-amplification was acquired or had been already present at baseline, we retrospectively investigated the diagnostic biopsy from the primary adenocarcinoma in the left lung (*Figure 3A*) by IHC and FISH. We observed that, concomitant to positive ALK immunostaining (*Figure 3B*), there was increased MET receptor expression (2+ in 100% of tumor cells) and a median *MET* gene CN of 6.1, which fulfills previously reported criteria for high-level *MET*-amplification (5,13,14) (*Figure 3C*,*3D*). Collectively, these results revealed that the *MET*-amplification was a *de novo* alteration already present at baseline and with apparent further *MET* CN increase at progression.

Thus, based on reported real-world experience (5,9,11,12) second-line therapy with combination of alectinib and crizotinib was initiated, both in reduced doses, i.e., alectinib 300 mg twice a day (BID) and crizotinib 200 mg BID. The switch to another 2G ALK-TKI, alectinib, instead of continuing brigatinib, was justified by the better efficacy of

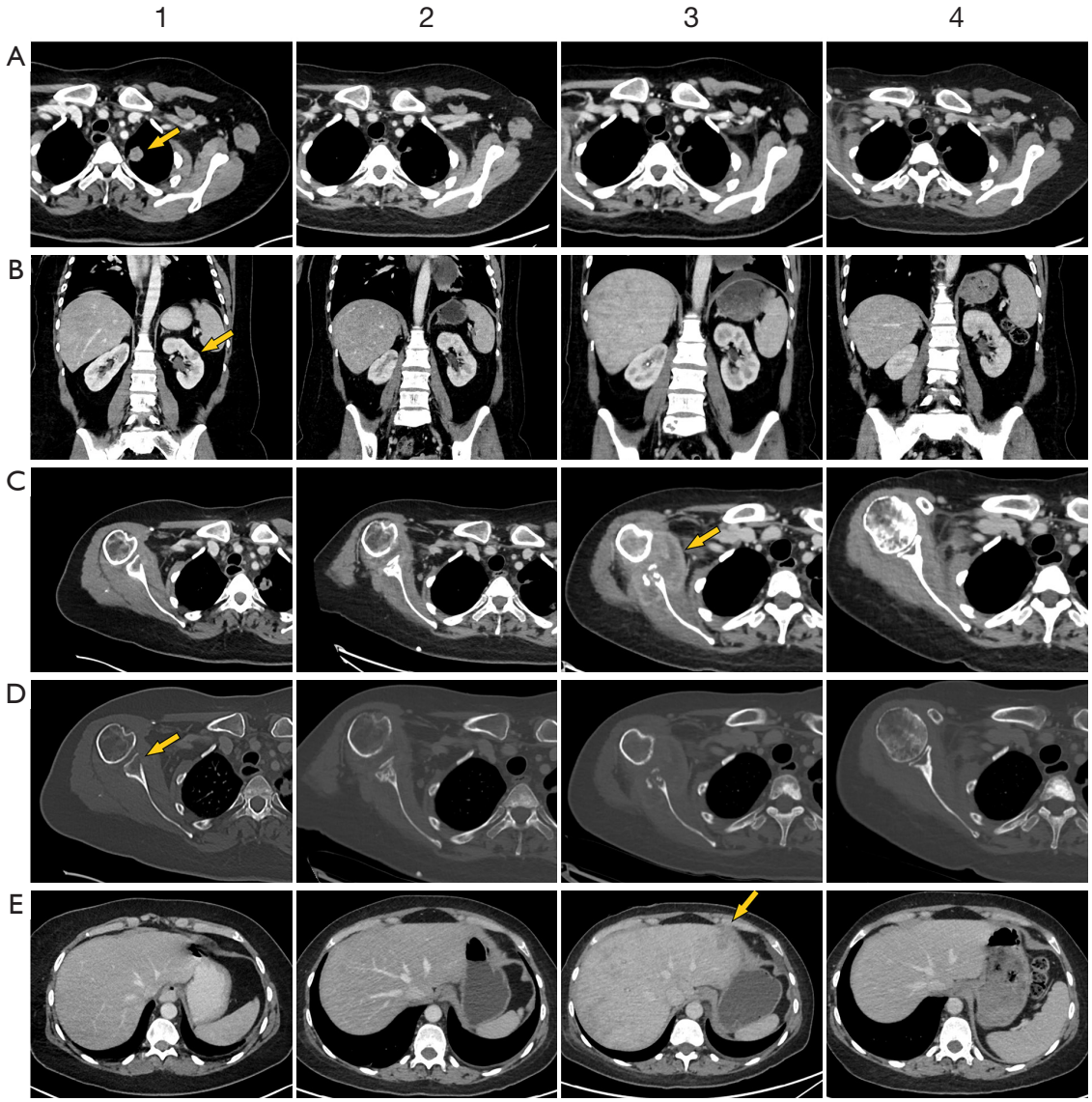

Figure 1 Chronological radiographical evaluation by contrast-enhanced CT images. Column 1 represents the baseline scan, column 2 the 1st assessment after 3 months, column 3 the 2nd assessment at 6 months, and column 4 the 3rd assessment at 12 months after baseline. Row A-E represents malignant lesions. (A) The primary tumor (NSCLC) located medially in the left lung upper lobe measured 2 cm at baseline (A1; arrow). It responded to initial treatment with brigatinib decreasing in size to approximately 1 cm and was stationary on all subsequent scans (A2-A4). (B) Metastasis in the left renal cortex at baseline measuring approximately 1.5 cm (B1; arrow). It responded completely to initial treatment and was found only as a cicatricial lesion on all following scans (B2-B4). Soft tissue window CT (C) and bone window CT (D): one of the multiple skeletal metastases at baseline was localized in the humerus and right scapula, with pathological fracture but without visible soft tissue component (C1/D1; arrow). This metastasis progressed and developed a small soft tissue component involving the glenohumeral joint visible on follow-up scan 3 months after baseline (C2/D2). The following scan 6 months after baseline showed marked progression of the soft tissue component involving the joint and muscles (C3; arrow) and bone metastasis in the humerus and right scapula (D3). These metastatic lesions were treated with radiotherapy. The soft tissue component was no longer visible on the following scan 12 months after baseline, and the fractures were increasingly sclerotic as a sign of healing (C4/D4). (E) CT scans of the liver. No liver metastases were identified at baseline or 1st follow-up after 3 months (E1/E2). At the 2nd follow-up after 6 months of treatment with brigatinib, a metastasis in the cranial part of the left liver lobe was detected, measuring approximately 2.6 cm (E3; arrow). After 6 months of combined treatment with alectinib and crizotinib, the metastasis was no longer visible (E4). CT, computerized tomography; NSCLC, non-small cell lung cancer.

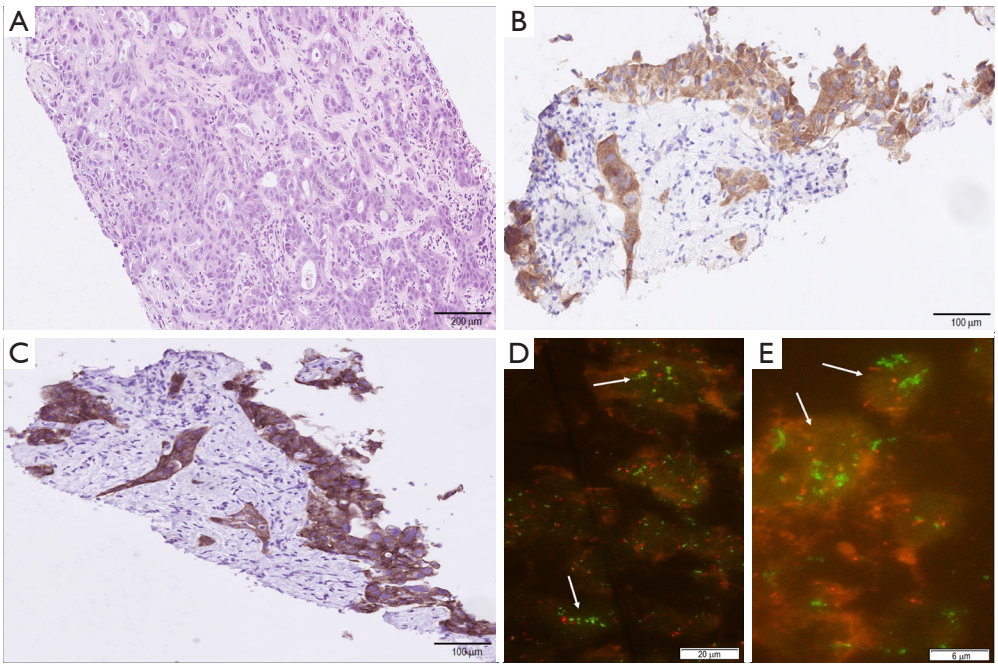

Figure 2 Biopsy from new liver metastasis at tumor progression. (A) The metastatic tumor tissue exhibited maintained adenocarcinoma histology without phenotypic transformation (conventional H&E stain; scale bar, 200 µm). (B) IHC performed on serial section showed that tumor cells had preserved expression of the ALK fusion protein (scale bar, 100 µm). (C) Additional immunostaining showed overexpression of MET receptor (3+ intensity) (scale bar, 100 µm). (D) Accordingly, FISH analysis revealed *MET* gene amplification (green signals) with 20% of cells containing *MET* gene clusters (arrows), respectively (scale bar, 20 µm). (E) A close-up of two tumor cell nuclei with *MET* clusters (arrows) is shown (scale bar, 6 µm). H&E, hematoxylin and eosin; IHC, immunohistochemistry; *ALK*, anaplastic lymphoma kinase; *MET*, mesenchymal-epithelial transition factor; FISH, fluorescence in situ hybridization.

Alectinib against *EML4-ALK* v.1. (15,16). To ensure that the patient would benefit from this combination, CT scanning of the chest and abdomen was performed already 6 weeks after initiating this treatment and showed pronounced shrinkage of the metastasis in the liver and either decrease or no change in other tumor lesions (data not shown). The patient was able to markedly reduce the doses of analgesics, experienced significant improvement of symptoms and tolerated the treatment well. The next CT scan of the chest and abdomen after 6 months of combination treatment (i.e., 12 months after baseline) demonstrated disappearance of the hepatic metastasis and no change in other lesions (*Figure 1*, A4-E4). Since the patient's PS significantly improved, the doses of both TKIs were increased to exploit the potential of this combination. Alectinib dose was increased to 450 mg BID and crizotinib dose to 250 mg BID. The follow-up after 4 weeks of increased dosage did not reveal any adverse events. The patient's good quality of life has been maintained for 6 months so far. The summarized course of the ongoing treatment is presented in *Figure 4*. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

Our case revealed a unique and targetable molecular configuration in the form of *EML4-ALK* fusion v.1 co-existing with *de novo MET*-amplification. Previous work has shown that acquired *MET*-amplification is one of the most common mechanisms of resistance to 2G ALK-TKIs in *ALK*+ NSCLC patients (9,11,12). However, there is limited data regarding *de novo MET*-amplification in these patients. To the best of our knowledge, only one case of *ALK*+

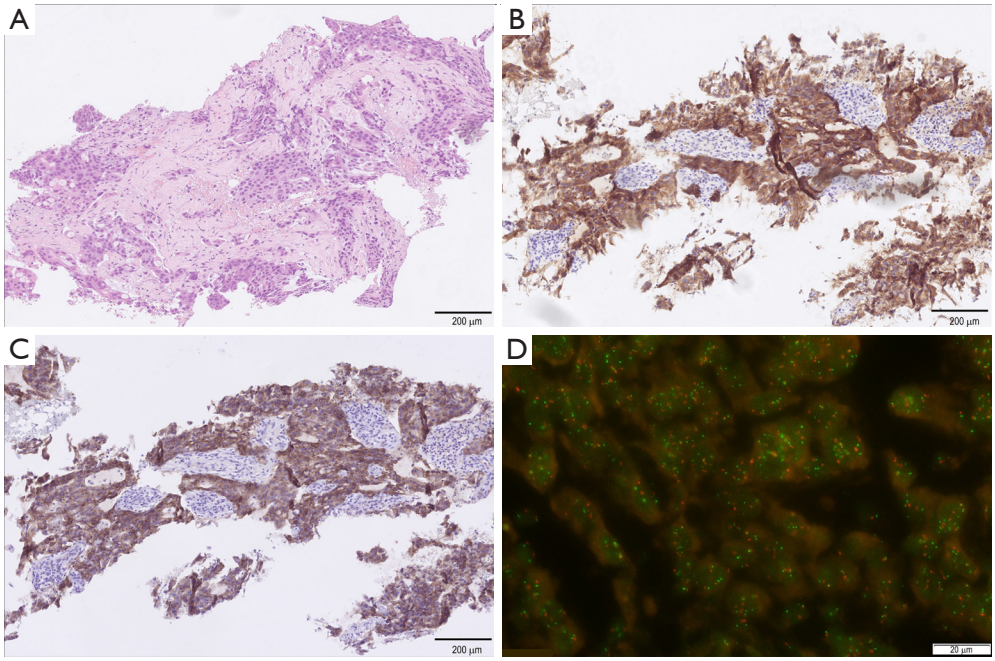

Figure 3 Retrospective characterization of diagnostic needle biopsy from the primary tumor in the left upper lung lobe. (A) Histological image of the pulmonary adenocarcinoma observed in the biopsy (conventional H&E stain; scale bar, 200 µm). (B) Immunostaining on serial section of the biopsy displaying the tumor cells with positive expression of ALK fusion protein (scale bar, 200 µm). (C) Immunostaining on serial section of the biopsy showing moderately increased (2+ intensity) MET receptor expression (scale bar, 200 µm). (D) FISH analyses showed *MET* gene amplification (green signals) in tumor cells (scale bar, 20 µm). H&E, hematoxylin and eosin; *ALK*, anaplastic lymphoma kinase; *MET*, mesenchymal-epithelial transition factor; FISH, fluorescence in situ hybridization.

NSCLC concomitantly harboring *MET*-amplification has previously been reported and treated with only crizotinib for a brief period of time (17). Instead, our case describes *de novo MET*-amplification as mechanism of intrinsic resistance to 2G ALK-TKIs. As opposed to widely explored mechanisms of acquired resistance in NSCLC patients with *ALK*-rearrangement (18,19), little is known about *de novo* co-existing alterations, which may have impact on primary response to ALK-TKIs. *De novo* mutations in the *ALK* kinase domain capable of conferring resistance to crizotinib and 2G ALK-TKIs were reported in <3% of cases (20). Furthermore, a case of *MYC*-amplification as intrinsic mechanism of resistance to Crizotinib was reported (21). Certain non-*EML4* fusion partners may also impair the response to ALK-TKIs (22). Rare *de novo* double *ALK*-fusions have displayed discrepant response to ALK-TKIs, so that some of them represent another form of intrinsic resistance (23). Co-existence of the non-canonical *KLC1-ALK* fusion and *MET*-amplification was reported in the above-mentioned case with marginal response to crizotinib (17). Additionally, patients treated with crizotinib, who harbored deletion polymorphism of the Bcl-2-like protein 11, BIM, which is required for TKI-induced apoptosis of cancer cells, had reduced progression-free survival (PFS) and lower objective response rate (ORR) (24). Baseline *KRAS* co-mutations or *CDKN2A*-deletion were also reported as potential mechanisms of intrinsic resistance to ALK-TKIs (25,26). Additional reasons for reduced objective response to first-line ALK-TKIs could reflect discrepancy between the diagnostic methods used to identify *ALK*-fusions (27). In our patient the *de novo MET*-amplification conferred intrinsic resistance to a 2G ALK-TKI, but it was neither revealed by NGS analysis on the diagnostic biopsy nor on the tumor re-biopsy at progression. This reflects the possible discordance between NGS and FISH as diagnostic methods, given the frequent heterogenous and subclonal nature of *MET*-amplification in NSCLC (5,9,28-31). This heterogeneity may indeed cause NGS, where bulky DNA of a tissue sample is analyzed, to miss *MET*-amplification, which otherwise may be detected by FISH, in which *MET*-amplified cells can be identified and quantified by microscopy. Thus, in keeping with our standard procedures

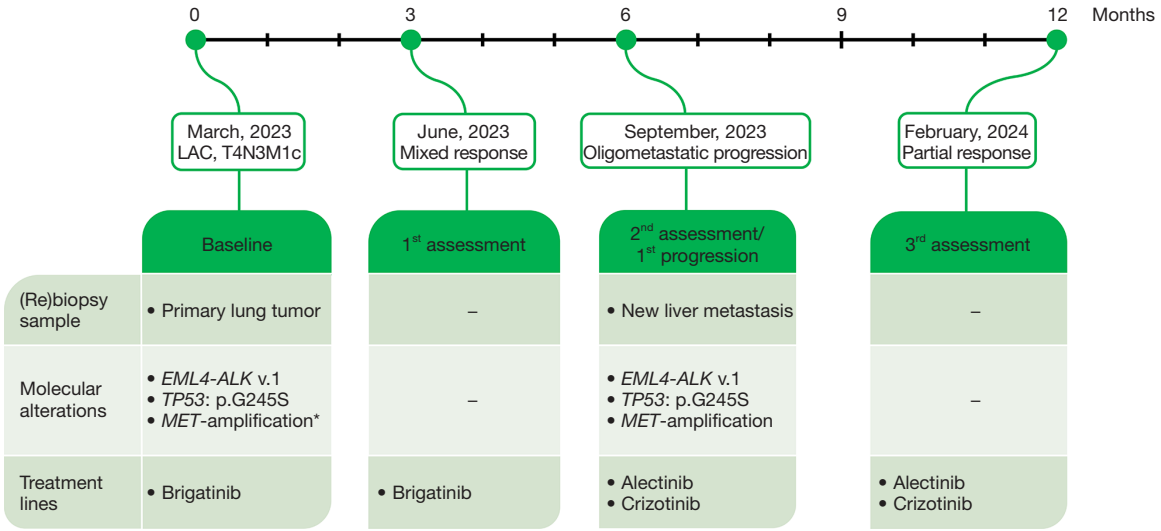

Figure 4 Time course of the treatment in months after diagnosis and treatment initiation of the patient's LAC (baseline). Sites biopsied at baseline and 1st progression are shown together with corresponding identified genomic alterations. The drugs used for treating the patient and the clinical and radiographic assessments are also displayed. *, *de novo MET*-amplification was detected in the initial diagnostic biopsy from the primary lung tumor by retrospective IHC and FISH analysis (but not by NGS) after identifying *MET*-amplification in the hepatic metastasis at progression on brigatinib. LAC, lung adenocarcinoma; *EML4-ALK* v.1, *EML4-ALK* fusion variant 1; *EML4*, echinoderm microtubule-associated protein-like 4; *ALK*, anaplastic lymphoma kinase; *MET*, mesenchymal-epithelial transition factor; IHC, immunohistochemistry; FISH, fluorescence in situ hybridization; NGS, next-generation sequencing.

for tumor re-biopsies (5), we performed MET-IHC and -FISH analyses on the hepatic metastasis and detected heterogenous high-level *MET*-amplification resulting in MET receptor overexpression, which can be considered as a mechanism of resistance to 2G ALK-TKI (9,11,12). Yet, the tumor progression had occurred rapidly, raising the question whether the *MET*-amplification could have already been present at baseline before Brigatinib treatment. We addressed the question by retrospective IHC and FISH analysis of the original diagnostic biopsy and thereby we revealed that the patient's NSCLC was already *MET*-amplified at baseline, even though with lower *MET* gene CN. This confirmed the higher sensitivity of FISH in detecting this genomic alteration (5,9,24,28-31).

Additionally, our case shows that combining a 2G ALK-TKI with crizotinib may be clinically effective in counteracting MET-driven intrinsic resistance. Interestingly, the mixed response to brigatinib observed at the first and second assessment with maintained reduction of both the primary lung tumor and the metastasis in the left kidney, but progression in the right humerus/scapula and finally a new liver metastasis, illustrates the fact that *ALK*+ NSCLC can be a heterogenous disease. The primary lung tumor did show a partial response to brigatinib, despite the *de novo MET*-amplification that we retrospectively detected. This might suggest that in the primary tumor clones driven by *ALK*-rearrangement were dominating at baseline. On the other hand, tumor cells in the re-biopsy at progression showed significantly higher level of *MET*-amplification as compared to those at baseline, indicating that they had become less sensitive to monotherapy with ALK-TKI because of the co-occurrence of ALK- and MET-driven clones. This notion is in accordance with previous observations of spatial heterogeneity of acquired *MET*-amplification (9). Yet, our case revealed that *MET*-amplification may also be temporally heterogeneous, occurring already at baseline but increasing in CN at progression. Furthermore, rapidly progressing disease observed 6 months after initiating the therapy is rather unexpected, considering the significant efficacy of brigatinib, with median PFS (mPFS) of 24.0 months reported in the ALTA-1L study (16). Other co-alterations like mutations in *TP53* gene are often (>80%) associated with *MET*-amplified *ALK*-rearranged tumors (9). In our case, the *TP53* p.G245S mutation was detected in the diagnostic biopsy and in the repeated cfDNA samples

during the 6 months of treatment with brigatinib. *TP53* co-mutations were in the ALTA-L1 study demonstrated to maintain a strong prognostic trend toward worse PFS in the multivariate analysis both for patients treated with crizotinib and brigatinib (16). Concordantly, recently published retrospective data demonstrated a reduced response to alectinib in *ALK*+ NSCLC patients with co-existing alterations. The mPFS for patients with *ALK*+ NSCLC harboring *TP53* co-mutations was 30.4 months, significantly shorter than that of patients with tumors without co-alterations, whose mPFS was not mature (32). Therefore, co-existing *TP53* mutation may still represent a risk for reduced effectiveness of the combination treatment with alectinib and crizotinib in our patient, as it also was demonstrated for *EGFR*-mutated NSCLC with acquired *MET*-amplification (5,33). Furthermore, due to maintained *EML4-ALK* fusion in the re-biopsy, continuous treatment with an ALK-TKI was still needed. However, brigatinib was discontinued and replaced by alectinib. This treatment decision was based on the exploratory analysis in ALTA-L1 and ALEX studies. In the ALTA-1L study, ORR of brigatinib was 84% for *EML4-ALK* v.1, and 91% for *EML4-ALK* v.3 (16). Instead, the ALEX study showed that the ORR of alectinib for *EML4-ALK* v.1 was 90%, and for *EML4-ALK* v.3 was 68% (15). Shorter *EML4-ALK* fusion variants (v.3, v.5) and baseline *TP53* co-mutations were also linked to shorter OS in a Chinese population (34).

Additional real-world data and future clinical studies may help elucidate whether it is of cost-benefit to test upfront *ALK*+ NSCLC patients for potential mechanisms of intrinsic resistance such as *de novo MET*-amplification as this may concern only a minority of these patients. Furthermore, the possibility of detecting *MET*-amplification and other co-alterations in plasma cfDNA from ALK+ NSCLC patients may help monitor their response to therapy (35). In any case, the awareness of *de novo* ALK-TKI resistance is needed to explain early progression and better match the personalized-based treatment approach.

Conclusions

We report a case of intrinsic resistance to a 2G ALK-TKI due to *de novo MET*-amplification, which therefore is one of the co-alterations to consider at early progression on 2G ALK-TKIs. The revision of the diagnostic biopsy by MET-IHC and MET-FISH and performing a re-biopsy at progression on the 2G ALK-TKI were decisive for guiding the treatment in our patient. Even if it is often heterogenous, *MET*-amplification may drive the primary resistance and represents a druggable target for further treatment choice. Thus, MET-FISH may be needed to identify *de novo MET*-amplification in cases undetected by NGS. It is important to exclude this co-alteration due to the risk of treatment failure on ALK-TKI alone. The combination of alectinib and crizotinib has provided significant clinical benefit to our patient, and no adverse events have been observed so far. The treatment is ongoing, and we are awaiting the results of the long-term outcome. Further clinical studies of combining ALK-TKI with a more potent MET-TKI are needed for optimizing this approach.

Acknowledgments

We are very grateful to Camilla C. Mortensen and Svetlana Teplaia for their excellent technical assistance.
Funding: None.

Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-439/rc

Peer Review File: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-439/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-439/coif). E.M.U. reports research grants from AstraZeneca and Merck; speaker fees from Amgen, AstraZeneca, Janssen and Novartis; travel support related to participation in international scientific meeting from AstraZeneca and Roche; payment for participation in Advisory Board from AstraZeneca, Pfizer, Roche and Takeda. M.G. reports speaker fees from Amgen, AstraZeneca, Boehringer Ingelheim and ThermoFisher Scientific, and received research grants from Merck and Roche. J.B.S. received consulting fees from AstraZeneca, Bristol-Myers Squibb, Merck, Janssen, Roche; received honoraria for lectures from Bristol-Myers Squibb, Janssen; received support for attending meetings and/or travel from AstraZeneca, Janssen, Merck; and received payment for participation in Advisory Board from AstraZeneca, Bristol-Myers Squibb, Genmab, Janssen, Merck, Roche. E.S.R. received research grants

from Sanofi and Takeda; reports honoraria for lectures from Amgen, AstraZeneca, Bayer, Bristol-Myers Squibb, Roche, Takeda; and received payment for participation in Advisory Board from Roche and Takeda. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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Cite this article as: Urbanska EM, Grauslund M, Berger SMS, Costa JC, Koffeldt PR, Sørensen JB, Santoni-Rugiu E. ALK-tyrosine kinase inhibitor intrinsic resistance due to *de novo MET*-amplification in metastatic *ALK*-rearranged non-small cell lung cancer effectively treated by alectinib-crizotinib combination—case report. Transl Lung Cancer Res 2024;13(9):2453-2462. doi: 10.21037/tlcr-24-439