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Combining *EGFR* and *MET* inhibition with crizotinib in *EGFR*-mutated lung adenocarcinoma harboring *MET* amplification: a brief report

AUTHORS

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INTRODUCTION

Epidermal growth factor receptor (*EGFR*) activating mutations are found in 10 to 15% of advanced non-squamous non-small cell lung carcinoma (NSCLC) for Caucasian patients and are associated with dramatic response to *EGFR* tyrosine kinase inhibitors (*EGFR* TKIs). All patients treated with 1st or 2nd generation *EGFR* TKIs experience disease progression due to secondary mutations (T790M mutation in exon 20 that confers sensitivity to third-generation *EGFR* TKI), phenotypic changes and activation of bypass signaling pathways¹⁻⁴. *MET* amplification is one of the bypass signaling pathways that promotes resistance to first-, second- and third-generation *EGFR* TKI, in approximately 5-20% of acquired resistances⁵⁻⁷. Preclinical data suggest that inhibition of both *EGFR* and *MET* is required to obtain tumor regression. Crizotinib is a potent *MET* inhibitor showing activity in NSCLC with *MET* amplification or *MET* exon 14 skipping mutations^{8,9}. Responses to dual *MET* and *EGFR* inhibition with a combination of crizotinib and *EGFR* TKI have been occasionally reported in patients with *EGFR* activating mutations and *MET* amplification¹⁰⁻¹⁸.

Herein, we report 5 patients' cases presenting with advanced lung adenocarcinoma harboring both *EGFR* mutation and *de novo* or acquired *MET* amplification treated in our institution with combination of a first- or third- generation *EGFR* TKI and crizotinib.

RESULTS

We report five cases of *EGFR*-mutated patients harboring *MET*-amplification which was defined as a *MET* copy number gain (CNG) ≥ 6 with *MET*/centromere ratio (*MET*/CEP7) ≥ 2 and was detected by immunohistochemistry (IHC) or Next-Generation Sequencing (NGS) and was confirmed by Fluorescent In Situ Hybridization in all patients. PD-L1 expression was assessed with Ventana SP263 antibody before initiation of combination TKIs.

Median age at the time of diagnosis was 51 years (range 36-66). All patients except one (#5) who was a former light smoker with 2.5 packs-year smoking history were non-smokers. All patients had stage IV adenocarcinoma, two depending on a L858R mutation in exon 21 and three on an exon 19 deletion. Clinical and biological characteristics are reported in Table A. Crizotinib was administrated at the dose of 250 mg twice daily, osimertinib was administrated at the dose of 80 mg once daily and erlotinib at the doses of 75, 100 or 150 mg once daily, based on the previous erlotinib dosage and according to the T790M status.

Abbreviations : CEP7= centromeric portion of chromosome 7 ; CN = copie number ; CNS = central nervous system ; CNG = copie number gain ; IHC = immunohistochemistry; MET = Mesenchymal-Epithelial Transition factor ; NGS = next-generation sequencing ; RNAseq = RNA sequencing ; TKI = tyrosine kinase inhibitor ; ORR = objective reponse rate

Patient #1 presented with metastatic (lung, mediastinal lymph nodes, pleural effusion without brain metastasis) lung adenocarcinoma with a *MET*-amplification associated to *EGFR* mutation L858R in exon 21 on lymph node core-needle biopsy at diagnosis (*MET* copy number (CN): 10.4; *MET*/centromere ratio: 2.1) and was treated with erlotinib. Restaging CT after 1 month demonstrated thoracic and mediastinal progressive disease (PD). No T790M was detected on ctDNA and lung biopsy. After 9 months of chemotherapy, erlotinib 150 mg once daily and crizotinib were initiated with response in some lung metastases but emergence of new pulmonary lesions. After disease progression under two subsequent lines of chemotherapy and nivolumab, patient #1 was rechallenged with erlotinib 100 mg once daily and crizotinib with partial response. After 5 months of treatment, the systematic brain MRI revealed 3 asymptomatic infracentimetric lesions without evidence of extra cerebral relapse. Brain metastases were treated with stereotactic radiotherapy and combination therapy is ongoing (Figure A).

Patient #2 was diagnosed with a metastatic (brain and lung) lung adenocarcinoma harboring an *EGFR* L858R mutation and was treated with erlotinib 150 mg once daily for 4 months. Lung rebiopsy at disease progression (lung, mediastinal lymph nodes and new bone lesions with stable brain metastases) did not detect T790M mutation but *MET*-amplification (CN: 12.6; *MET*/centromere ratio: 5.6). She then received a second-line chemotherapy with carboplatin and pemetrexed with thoracic and brain disease progression after 2 cycles of pemetrexed maintenance. She was treated with brain stereotactic radiotherapy for the two brain metastases and erlotinib 75 mg once daily and crizotinib were subsequently initiated with a dissociated response consisting in an improvement of carcinomatous lymphangitis and irradiated brain metastases but appearance of new lung nodules. ctDNA revealed T790M mutation and erlotinib was then replaced by osimertinib whereas crizotinib was continued. First disease evaluation at 3 months of treatment revealed partial response but the patient experienced rapid subsequent cerebral disease progression and died one month later.

Patient #3: lung adenocarcinoma was revealed by a single brain metastasis treated with stereotactic radiotherapy. An *EGFR* exon 19 deletion was found on the primary lung tumor biopsy. She experienced PD (supra-clavicular, jugular-carotid node) without detection of T790M mutation neither on supra-clavicular rebiopsy, nor on ctDNA after 6 months of gefitinib treatment. *MET*-amplification (CN: 6.4; *MET*/centromere ratio: 2.3) was detected after failure of a second line chemotherapy (carboplatin-paclitaxel-bevacizumab, maintenance with pemetrexed, then docetaxel 4 cycles) on a retrospective analysis of the previous supra-clavicular biopsy. Combination of erlotinib 75mg once daily and crizotinib was initiated leading to an almost complete response (Figure B.1). After almost one year of combination treatment, PET-scanner showed evidence of oligo-progression on the primary tumor without recurrence of the disease on other sites (bone metastases, mediastinal and supra-clavicular nodes) leading to propose local stereotactic radiotherapy with continuation of combination therapy. Five months later, she experienced progression disease with brain and liver metastases.

ctDNA revealed T790M mutation and erlotinib was replaced by osimertinib with continuation of crizotinib. PET-scanner and brain MRI performed 1 month later showed complete response. Treatment is ongoing.

Patient #4 was diagnosed with stage IVa lung adenocarcinoma depending on EGFR exon 19 deletion and was treated by gefitinib 250 mg once daily. After 17 months of treatment, she experienced cerebral and lung disease progression leading to give chemotherapy with cisplatin-pemetrexed-bevacizumab followed with pemetrexed-bevacizumab as maintenance treatment. An almost complete response was observed on brain metastases. After 18 months, she experienced a subsequent thoracic disease progression leading to gefitinib reintroduction then replaced by osimertinib based on ctDNA revealing a T790M mutation. Lung and mediastinal PD without brain disease progression occurred after 21 months of osimertinib with evidence of *MET*-amplification (CN: 12; ratio *MET*/centromere: 4.1) on lung rebiopsy. After failure of subsequent chemotherapy and immunotherapy with nivolumab, she received a combination of crizotinib and osimertinib leading to almost complete response after 1 month. After 7 months of treatment, disease progression (new brain metastases, lung carcinomatous lymphangitis and meningitis) was observed and patient died one month later.

Patient #5 was treated with gefitinib for a lung adenocarcinoma revealed by a single bone metastasis, with evidence of EGFR exon 19 deletion. She experienced bone and lung disease progression after 30 months of treatment with detection of a T790M mutation on bone biopsy. As osimertinib was not available yet, she received cisplatin-pemetrexed-bevacizumab and continuation chemotherapy with pemetrexed during 3 years. After rechallenge with gefitinib for a lung and mediastinal lymph nodes symptomatic progression, the patient subsequently received osimertinib with disease stabilization as best response and mediastinal lymph node progression at 4 months. Mediastinal lymph node cytology revealed exon 19 deletion, disappearance of T790M mutation but *MET*-amplification (CN: 8.1; *MET*/centromere ratio: 2.1) leading to addition of crizotinib to osimertinib with almost complete response lasting one year (Figure B.2). Systematic brain MRI then revealed two asymptomatic brain metastases without systemic disease progression. She was treated with stereotactic brain radiotherapy and combination therapy is ongoing.

Tolerance of the addition of crizotinib to EGFR TKI was quite good, without emergence of unexpected toxicities. No significant prolongation of QTc was observed on systematic ECG. Adverse events observed were rash, transaminase elevation, nausea, edema, visual disorders and diarrhea. Most of them were grade 1 or 2 and crizotinib dose was only reduced to 200 mg twice daily for patient #4 due to nausea.

DISCUSSION

In vitro, *MET* amplification results in the activation of *PI3K/AKT* downstream pathway through *EGFR*-independent phosphorylation of *ERBB3*, occurring also in the presence of *EGFR*-TKI,

reinforcing the rationale for a concomitant inhibition in the EGFR mutation landscape¹⁹. Its occurrence varies from 3% at diagnosis to at least 15 to 20% at progression under osimertinib first-line, probably underestimated due to evaluation of resistance mechanisms based on circulating tumor DNA in FLAURA and AURA3 trials^{6,7}.

Identification of biomarkers remains the cornerstone to predict the efficacy of targeted therapies; however the definition of *MET* amplification is heterogeneous across the different studies. In some trials, *MET*-amplification is defined only as *MET* copy number gain (CNG), evaluating the copy number of gene per nucleus and potentially identifying polysomy. Others take into consideration the ratio of *MET* gene to centromeric portion of chromosome 7 (CEP7), which detect “true amplification” but the cut-off used for this ratio is not standardized. The interpretation is all the more difficult as polysomy and amplification can coexist on the same tumor. *MET*-amplification is probably more a subclonal event, and a special attention is required with next-generation sequencing results, which reflects circulating tumor DNA as a part of a tumor at a non-cellular level, which makes interpretation difficult.

In our cohort, *MET*-amplification was defined by *MET* CNG ≥ 6 and ratio *MET*/CEP7 ≥ 2 , as often defined in previous studies as high-level of *MET*-amplification. We only associated crizotinib with EGFR TKIs as it is the only routinely available MET-inhibitor in France. Herein, combining crizotinib with first- or third-generation EGFR TKI, according to T790M status, demonstrated encouraging results with three almost complete responses, one objective complete response and importantly durable responses. Interestingly, two patients were rechallenged with osimertinib + crizotinib directly after failure under combination of 1st generation EGFR-TKI and crizotinib due to emergence of T790M resistance mutation, producing a new objective response suggesting that tumor was still depending on this oncogenic pathway. However, central nervous system (CNS) was a frequent site of relapse under combination therapy probably due to the lower intracranial penetration of crizotinib; association of EGFR TKIs with selective MET-inhibitors with high CNS activity should be promising.

Studies evaluating the association of EGFR and different MET-inhibitors in treatment-naïve patients or in the context of resistance are ongoing, showing promising results. A phase Ib/II study evaluated gefitinib associated with capmatinib in EGFR-mutated patients with acquired resistance to EGFR-TKI and MET-dysregulation defined as *MET* amplification (ratio ≥ 2 and/or GCN ≥ 5) and/or MET overexpression (IHC 2+ or 3+). Objective response rate (ORR) in the overall population was 27%. Responses better correlated with GNC (ORR of 32% for IHC 3+ and 47% in patients with GCN ≥ 6)²⁰. Tepotinib, a potent selective MET-TKI demonstrated significant median progression free survival (PFS) and overall survival (OS) improvement (16.6 vs 4.2 months and 37.3 vs 13.1 months respectively) compared with chemotherapy in *MET* amplified (ratio ≥ 2 GCN ≥ 5) *EGFR*-mutated patients at acquired resistance to gefitinib. Three patients with *MET* amplification are still receiving

treatment with tepotinib for more than 27 months²¹. Savolitinib, another highly potent and selective MET-inhibitor, was also assessed in association with osimertinib in the TATTON Phase Ib study in patients with evidence of acquired resistance to EGFR TKI and *MET*-alteration defined as following: IHC 3+ on $\geq 50\%$ of cells or FISH+ (ratio ≥ 2 GCN ≥ 5) or NGS ($\geq 20\%$ tumor cells, $\geq 200\times$ sequencing depth of coverage and ≥ 5 copies over tumor ploidy). Patients enrolled in cohort B received osimertinib 80 mg and savolitinib 600 mg daily and were divided in 3 groups: patients previously treated with third generation TKI (B1); not previously treated with third generation TKI and T790M negative (B2) or T790M positive (B3). Patients in cohort D had the same characteristics than in cohort B2 but received savolitinib 300 mg daily. Median PFS were 7.6 and 9.1 months with ORR of 48 and 64% in cohorts B and D, respectively²². In these studies, the combination of a MET-inhibitor and an EGFR TKI was well tolerated with a low rate of additional toxicities. SAVANNAH (NCT03778229), a single arm phase II study of osimertinib combined with savolitinib for patients who experienced progression after prior osimertinib is ongoing.

Associating MET-inhibitors to the standard EGFR-inhibition in patients progressing with a *MET*-amplification seems to be a valid therapeutic option based on a strong preclinical rationale, showing minimal and acceptable overlapping toxicity and leading to deep and prolonged responses^{20,23,24}. Low CNS crizotinib penetration is a clear limitation and new potent MET-inhibitors with a better CNS penetration are needed^{25,26}. This underscores the need for rebiopsy even after acquired resistance to osimertinib, notably when given in frontline, as MET inhibition in addition to EGFR inhibition can achieve durable disease control.

DISCLOSURE

The authors Aubanel M., Doublet L., Neidhardt EM., declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The authors Swalduz A., Perol M., Avrillon V., Mastroianni B., declare the following financial interests/personal relationships which may be considered as potential competing interests:

- Swalduz A.: advisory boards for Roche, Bristol-Myers Squibb, Takeda, Lilly, Pfizer and lectures for Roche, AstraZeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, Pfizer, Takeda
- Perol M.: advisory boards for Roche, Genentech, Eli Lilly, Pfizer, Boehringer-Ingelheim, Clovis Oncology, MSD, Bristol-Myers Squibb, Novartis, Pierre Fabre, AstraZeneca, Takeda. Institutional grants for Roche, AstraZeneca, Chugai, Takeda and lectures for Eli Lilly, Roche, AstraZeneca, Pfizer, Amgen, Boehringer-Ingelheim, Bristol-Myers Squibb, Takeda, Chugai

- Avrillon V.: congress and boards financing MSD, Bristol-Myers Squibb, Roche, AstraZeneca
- Mastroianni B.: Roche, Astrazeneca

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Figure A: Treatment sequence and patient's outcomes

Arrows indicate patients who had an ongoing response at the time of the last evaluation. The symbol † indicates that patient is dead. The symbol ▲ indicates PR, * indicates brain PD and brain radiotherapy and ** thoracic PD and thoracic radiotherapy

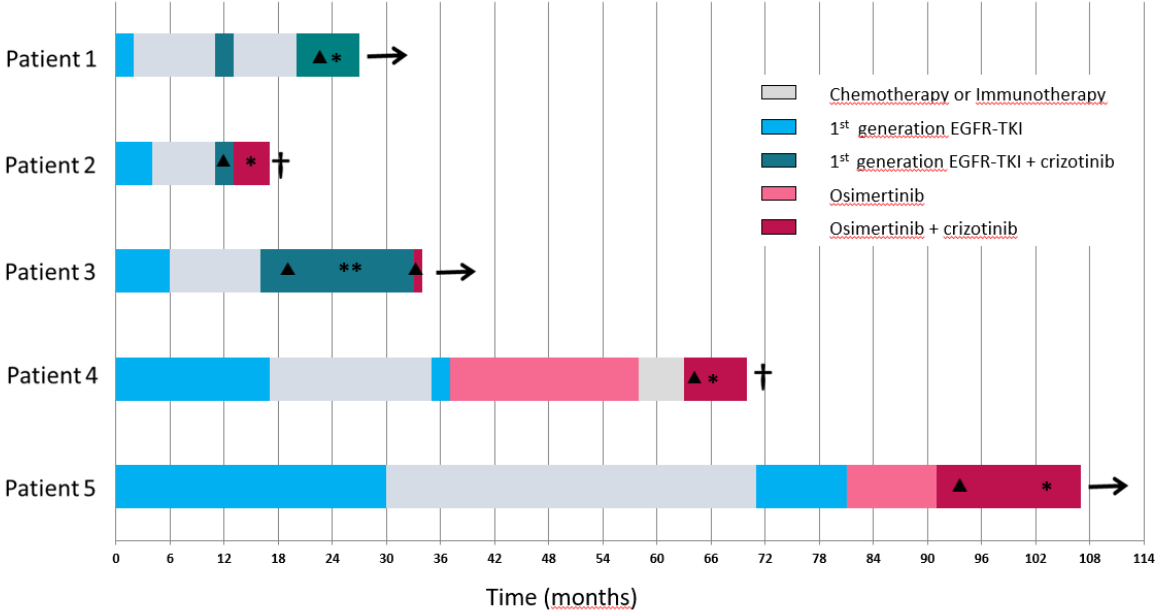
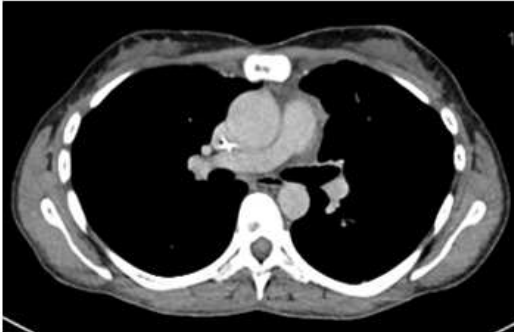


Figure B: Ct-scan response 4 months after crizotinib + erlotinib initiation in patient #3 (1) and #5 (2)

1



2

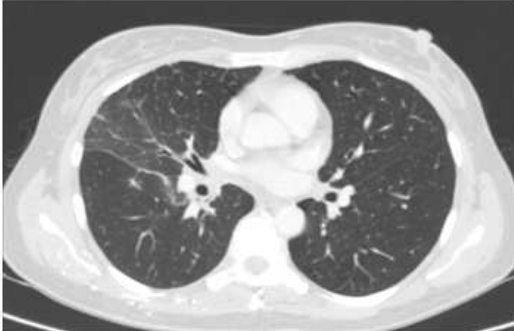
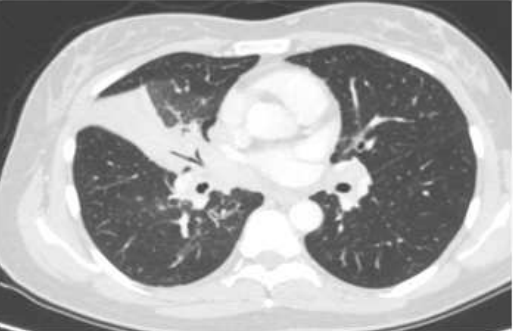


Table A: Patient characteristics and outcomes under combination therapy

M: Male; F: Female; ADC: adenocarcinoma; DR: dissociated response; PR: partial response; PD: progression disease; CR: complete response; RT: radiotherapy; Best CNS response (-): no brain mets; (+): ongoing treatment

ID	Sex	Smoking status	Histology EGFR mutation	MET amplification (copy / ratio)	T790M mutation	PD-L1 status	Crizotinib associated-TKI	Line of treatment	Best response	Best CNS response	CNS progression	Duration of response	Toxicity
1	M	-	ADC L858R	10,4/2,1	No No	60%	Erlotinib 150 mg Erlotinib 100mg	3 rd 7 th	DR PR	- -	No Yes	1,5 months 3 months (+)	Hyperthyroidism grade 1 Oedema grade 1 Rash grade 1
2	F	-	ADC L858R	12,6/5,6	No Yes	100%	Erlotinib 75mg Osimertinib 80mg	3 rd 4 th	DR DR	PR (RT) PD	No Yes	2 months 4 months (death)	No toxicity
3	F	-	ADC Del19	6,4/2,3	No Yes	100%	Erlotinib 75mg Osimertinib 80mg	4 th 5 th	PR CR	- CR	Yes No	17 months 1 months (+)	Diarrhea grade 1 Paronychia grade 1 Rash grade 2 Visual disturbance grade 1 Diarrhea grade 2 Oedema grade 1
4	F	-	ADC Del19	12/4,1	Yes	100%	Osimertinib 80mg	8 th	PR	SD	Yes	6 months (death)	Diarrhea grade 1 Nausea grade 2 Vomiting grade 1
5	F	+	ADC Del19	8,1/2,1	Yes	5%	Osimertinib 80mg	5 th	PR	-	Yes	12 months (+)	Diarrhea grade 2 Nausea grade 1 Oedema grade 1 Visual disturbance grade 1

FIGURE A

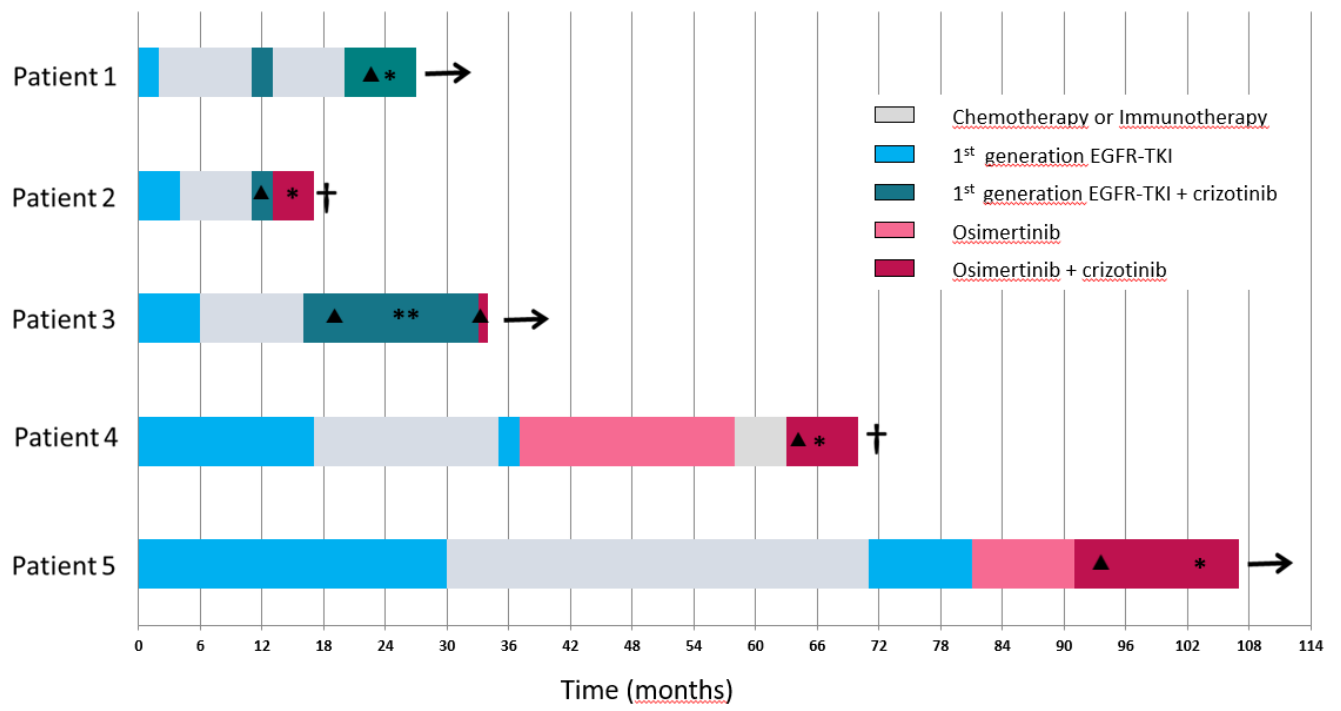


FIGURE B

1



2

