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ORIGINAL RESEARCH ARTICLE

Real-World Treatment Outcomes of MET Exon14 Skipping in Non-small Cell Lung Cancer: GFPC 03-18 Study

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Abstract

Background MET-targeted tyrosine kinase inhibitors (TKIs) demonstrated efficacy in advanced non-small cell lung cancer (aNSCLC) with *MET* exon14 skipping mutations (*MET*exon14); yet, data on the management of these patients in clinical practice is sparse.

Objective The aim of this study was to describe the management of *MET*exon14 aNSCLC patients.

Patients and Methods This real-life, retrospective study analyzed the management of *MET*exon14 aNSCLC. The primary endpoint was the median overall survival (mOS). Secondary endpoints were to assess investigator–progression-free survival (PFS) and mOS in different subgroups: patients treated with (a) crizotinib, regardless of treatment line; (b) anti-MET TKIs (crizotinib, tepotinib, capmatinib); and (c) immunotherapy.

Results A total of 118 patients were included between December 2015 and January 1, 2020 in 13 centers. Median age was 73 years, 62.7% were female, 83.9% had adenocarcinoma, 92.4% at stage IV, and 27% had more than three metastatic sites. The majority of the patients (106, 89.8%) received at least one systemic treatment; 73% received at least one anti-MET TKI: crizotinib (68.6%), tepotinib (16%), capmatinib (10%). Only 10% received two anti-MET TKIs in their treatment sequences. With a median follow-up of 16 months (95% CI 13.6–29.7), mOS was 27.1 months (95% CI 18–31.4). There was no significant difference between mOS of patients treated and never treated with crizotinib, 19.7 (95% CI 13.6–29.7) and 28 (95% CI 16.4–NR) months, respectively ($p = 0.16$); mOS of the TKI cohort and of the TKI-naïve patient cohort were 27.1 (95% CI 18–29.7) and 35.6 (95% CI 8.6–NR) months respectively, with no significant difference ($p = 0.7$).

Conclusions In this real-life study, there was no evidence of benefit in mOS with anti-MET TKIs.

Abbreviation

GFPC Groupe Français de Pneumo-Oncologie

Key Points

The majority patients with MET exon14 skipping mutation-positive advanced non-small cell lung cancer are elderly female non-smokers with adenocarcinomas.

Of the 106 analyzed patients, 73% received at least one anti-MET tyrosine kinase inhibitor (TKI) (crizotinib: 68.6%, tepotinib: 16%, capmatinib: 10%); 10% received two anti-MET TKIs in their treatment sequences.

In this real-life study, there was no evidence of benefit in median overall survival with anti-MET TKIs.

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1 Introduction

The *c-mesenchymal–epithelial transition proto-oncogene* (known as *c-MET*) encodes for a receptor tyrosine kinase expressed mainly by epithelial cells and which promotes tissue proliferation and regeneration [1]. Mutations in the *MET* gene associated with exon 14 skipping (*MET*exon14) occur in 3% of non-small cell lung cancers (NSCLC) [1, 2]. Exon 14 has an essential role in the regulation of MET; it encodes a juxta-membrane intracellular domain of MET which contains the tyrosine residue Y1003, the binding site of the Casitas B-lineage lymphoma (CBL) protein. In case of exon 14 skipping, part of the coding sequence of the receptor is deleted, and so CBL cannot bind and regulate ubiquitination and degradation of MET. This leads to a constitutive hyperactivity of the receptor [3–5]. *MET*exon14 comprises a large group of genetic alterations (point mutations, insertions, deletions, complex mutations) that determine different variants [6, 7]. Some of them do not affect the splicing sites and do not cause exon 14 skipping [8, 9]. This could explain the high variability of activity of anti-MET tyrosine kinase inhibitors (TKIs).

Knowledge of the clinical course of the disease is limited. Management of advanced *MET*exon14 NSCLC has evolved significantly in recent years, especially with the availability of anti-MET targeted therapies (crizotinib, capmatinib, and tepotinib) but also with the advent of immunotherapy [10–15]. MET TKIs are type I inhibitors and have potent and selective inhibitory activity against MET [15]. Crizotinib has data available in *MET*exon14 skipping NSCLC but is not approved in this setting. However, owing to its approval in advanced NSCLC (aNSCLC) with *ROS-1* or *ALK* gene fusions, crizotinib is often used in the clinic for patients with *MET*exon14 aNSCLC. In France, during the study inclusion period, crizotinib was accessible and the other anti-MET TKIs were only available within early access programs. The main objectives of this study were to describe the clinical characteristics and management of *MET*exon14 aNSCLC, and to assess efficacy of crizotinib and other anti-MET TKIs in a real-world setting.

2 Methods

2.1 Study Design and Patients

We conducted a retrospective, national and non-interventional study that included aNSCLC harboring *MET*exon14 mutations.

Eligible patients were at least 18 years old and had aNSCLC with locally determined *MET*exon14 mutation. Exclusion criteria were isolated amplification or overexpression of *MET* (without associated splicing mutation) and patient refusal to participate.

Patient data were obtained retrospectively from medical files and included demographics, ECOG performance status (PS), smoking status, occupational exposure, personal and family history, NSCLC characteristics (histology, TNM stage [16], number of metastatic sites at diagnosis, and locations), treatments performed, duration, and response to treatments. Patients were included consecutively in each center according to inclusion criteria without selection. Molecular genetic analysis reports from each center were also collected and recorded.

The primary endpoint was to evaluate the overall survival (OS) of a*MET* exon14 NSCLC. Secondary endpoints were to assess investigator–progression-free survival (PFS), objective response rate (ORR), disease control rates (DCR), and OS in different subgroups: patients treated with crizotinib regardless of treatment line, with an anti-MET TKI (crizotinib, tepotinib, capmatinib), and with immunotherapy.

2.2 Statistical Analysis

Clinico-pathological characteristics were described (numbers and frequencies for qualitative variables, median and extremes for quantitative variables) and then compared across groups by chi-2 and median tests. The Kaplan-Meier method was used to estimate OS and PFS for the entire cohort and the defined subgroups. OS was reported from the start of a line of therapy after advanced diagnosis until death, irrespective of subsequent therapy received across different lines of therapies. The Logrank test was used to compare survival by treatment category. Response to treatment was assessed locally by the investigator, according to RECIST 1.1 criteria in patients who have received at least 15 days of treatment. Statistical analyses were performed using SAS 9.4 software.

The study was conducted in accordance with the Declaration of Helsinki and was approved by the French Advisory Committee on Information Processing in Health Research (CCTIRS). Living patients were informed and gave their non-objection to participate in the study and for deceased patients, an exemption of information was obtained.

3 Results

A total of 118 patients with *MET*exon14 NSCLC were included in 13 centers between December 1, 2015, and January 1, 2020.

The median age was 73 (47–95) years, with a majority of women (62.2%) and never or former smokers (48.7%);

Table 1 Clinical and therapeutic characteristics of patients treated or not with crizotinib and anti-MET TKIs

	Total, $n = 106$ (%)	Crizotinib, $n = 55$ (%)	No crizotinib, $n = 51$ (%)	p-value	TKI, $n = 78$ (%)	No TKI, $n = 28$ (%)	p-value
Age, Median (min–max)	73 (47–95)	74 (47–90)	70 (49–89)	0.003	73 (47–90)	70.5 (49–89)	0.04
Sex (male)	39 (36.8)	20 (36.4)	19 (37.3)	0.92	27 (34.6)	12 (42.9)	0.44
Smoking							
Active/former	53 (50)	26 (48.1)	27 (55.1)	0.48	39 (50.0)	11 (39.3)	0.25
Non-smoking	53 (50)	28 (51.9)	22 (44.0)		36 (46.2)	17 (60.7)	
Adenocarcinoma	91 (85.4)	45 (81.8)	46 (90.2)	0.22	66 (84.6)	25 (89.3)	0.54
PS							
0–1	93 (87.8)	45 (81.2)	48 (94.1)	0.05	67 (85.9)	26 (92.9)	0.34
> 1	13 (12.2)	10 (18.2)	3 (5.9)		11 (14.1)	2 (7.1)	
Metastatic sites > 2	24 (22.6)	15 (27.8)	9 (18.8)	0.28	18 (23.1)	6 (21.4)	0.95
Platinum doublet	74 (69.8)	34 (618)	40 (78.4)	0.06	49 (62.8)	25 (89.3)	0.01
Immunotherapy	46 (43.4)	22 (40.0)	24 (47.1)	0.46	32 (41)	14 (50.0)	0.41

PS ECOG performance status, *TKI* tyrosine kinase inhibitor

performance status was preserved in a majority of patients at the time of diagnosis (82.2% with PS 0–1) (Table 1). The main histology was adenocarcinoma (83.9%), with stage IV disease in 109/118 (92.4%) cases; 29 (27%) patients had at least three metastatic sites. The main metastatic locations were bone (47/118, 40%), lymph nodes (45/118, 38%), pleura (40/118, 33.6%), and lung (39/118, 32.7%). At diagnosis, 25 (21.2%) patients had brain metastasis. PDL1 status was known for 79 (68.1%) patients and was positive (> 1%) in 58/79 (73%) cases. Within the limits of the study, only 14 *MET* co-amplifications were found (no routine search in France).

One hundred and six (89.8%) patients received at least one systemic treatment and the median number of treatment lines was 2; 37 (35.1%) patients received three lines or more. The majority (74/106, 69.8%) received a treatment line with a platinum-based doublet (Table 2).

With a median follow-up time of 16.6 months (95% CI 14.5–20.4), median OS of the patients who received at least one systemic treatment was 27.1 months (95% CI 18–31.4).

The majority of the patients, 78 (73.6%), received at least one TKI targeting MET: crizotinib: 73 (68.6%), tepotinib: 17 (16%), capmatinib: 11 (10.3%), or cabozantinib: 2 (1.9%). Crizotinib was the sole TKI of the treatment sequence for 55/106 (51.9%) patients. Median duration of treatment (mDOT) was 5.2 months (95% CI 2.8–8). Median OS, ORR, and DCR of these patients was 19.7 months (95% CI 13.6–29.7), 50.8%, and 69.1%, respectively. Median OS of patients treated with a TKI other than crizotinib (23/106, 21.7%) was 27.2 months (95% CI 18–NR).

Compared with patients never treated with a MET TKI (28/106, 26.4%), those who received at least one TKI were significantly older and significantly less frequently treated with a platinum-based doublet (Table 1). There is no significant difference for OS between patients treated and never treated with a TKI—27.1 (95% CI 18–29.7) and 35.6 (95% CI 8.6–NR) months, respectively (Fig. 1).

In their therapeutic sequences, 45/106 (42.5%) patients received an anti-PD(L)1 therapy (Table 2). The mDOT was 2.3 months (95% CI 1.7–5.5), and ORR was 39.5%. Among patients receiving immunotherapy and never treated with anti-MET TKIs (28/106, 26.4%), the mDOT was 12.7 months (95% CI 1.8–23.9). Eight patients had a prolonged response of > 1 year, including three patients in response at 2, 2.5, and 4.5 years.

4 Discussion

Retrospective analysis of this large cohort of *MET*exon14 aNSCLC patients confirmed that this rare mutation has a particular clinical phenotype with a high rate of women, never-smokers, and adenocarcinomas. The prognosis of this real-life cohort does not seem to differ from that of patients without oncogenic mutations [17]. The majority of patients were exposed to the first-generation anti-MET TKI crizotinib, but there was no difference in median OS in this analysis between patients exposed to crizotinib and/or another anti-met TKI. The efficacy of crizotinib, with treatment duration of 5.2 months and ORR of 52.8%, is consistent with the literature [10–14]. In a French expanded access study, the ORR of crizotinib in 28 c-MET patients was 36%, with a median PFS and OS of 2.4 (95% CI 1.6–5.9) and 8.1 (95% CI 4.1–12.7) months, respectively [11]. In a phase II, prospective trial, ORR of the 10 patients with *c-MET* mutation or amplification, treated with crizotinib, was 20.0% (95% CI

Table 2 Durations of treatment and responses according to lines of treatment

	Chemotherapy	Immunotherapy	Crizotinib	Other TKI
	First line			
	n = 69 (%)	*n* = 12 (%)	*n* = 15 (%)	*n* = 12 (%)
Duration of treatment, median, 95% CI (mo)	2.8 (2.1–3.8)	1.9 (0–2.8)	2.4 (1.4–6.5)	9.1 (2.2–15.2)
Response, *n* (%)				
Complete response	3 (4)	0	0	1 (8)
Partial response	26 (39)	4 (33)	7 (47)	7 (60)
Stable disease	20 (29)	0	1 (6)	2 (16)
Progressive disease	16 (24)	7 (58)	7 (47)	1 (8)
Non evaluable	4 (6)	1 (9)	0	1 (8)
	Second line			
	n = 13 (%)	*n* = 23 (%)	*n* = 30 (%)	*n* = 11 (%)
Duration of treatment, median, 95% CI (mo)	2.5 (1.6–3.7)	4.2 (2–7)	4.6 (1.2–5.1)	5.8 (1.3–7.5)
Response, *n* (%)				
Complete response	1 (8)	5 (23)	0	1 (9)
Partial response	2 (16)	7 (33)	15 (50)	6 (55)
Stable disease	6 (46)	4 (20)	3 (11)	1 (9)
Progressive disease	2 (16)	5 (23)	7 (23)	2 (18)
Non evaluable	2 (16)	2 (9)	5 (16)	1 (9)
	Third line			
	n = 11 (%)	*n* = 14 (%)	*n* = 5 (%)	*n* = 9 (%)
Duration of treatment, median, 95% CI (mo)	5.4 (0.3–10.5)	1.5 (0.7–4)	13.3 (3.7–23)	1.5 (0.6–2.7)
Response, *n* (%)				
Complete response	0	1 (8)	0	0
Partial response	5 (46)	1 (8)	2 (40)	2 (22)
Stable disease	1 (9)	3 (21)	2 (40)	4 (44)
Progressive disease	1 (9)	6 (42)	0	2 (22)
Non evaluable	4 (36	3 (21)	1 (20)	1 (12)
	Fourth line			
	n = 4 (%)	*n* = 1 (%)	*n* = 5 (%)	*n* = 1 (%)
Duration of treatment, median, 95% CI (mo)	3.4 (0.6–4.6)	0 (NR–NR)	7.3 (1.4–25.3)	1.5
Response, *n* (%)				
Complete response				
Partial response	2 (50)	0	3 (60)	0
Stable disease	0	0	1 (20)	0
Progressive disease	1 (25)	1 (100)	0	0
Non evaluable	1 (25)	0	1 (20)	1 (100)

CI confidence interval, *mo* months, *NR* not reported, *TKI* tyrosine kinase inhibitor

0.4–71.8) with a median PFS of 2.6 months (2.2–3.0) [13]. Median DOT, 5.2 (95% CI 2.8–8) months in our analysis, was superior to the PFS found in these prospective clinical trials, but the benefit of crizotinib was assessed by the investigator, with the option of continuing the treatment after progression, depending on the clinical benefit. Similarly, the results for patients exposed to a TKI other than crizotinib ($n = 23$) are in line with the literature. In a phase II trial, tepotinib showed an ORR of 44% and median PFS of 8.5 months in predominantly PS 0–1, pre-treated patients (56%) [12]. Capmatinib, also in a phase II trial, showed an ORR of 41% and a median PFS of 5.4 months, again in pretreated patients. In treatment-naive patients, the ORR of capmatinib was 68% (95% CI 48–84), with a median PFS of 9.7 months [14]. In a retrospective, international, multicenter analysis of 81 *c-MET* mutated NSCLC patients treated with capmatinib in an early access program between March 2019 and December 2021, the ORR was 68% (95% CI 50–82) in treatment-naïve, and 50% (95% CI 35–65) in pretreated patients, with a median PFS of 10.6 months (95% CI 5.5–15.7) in first line

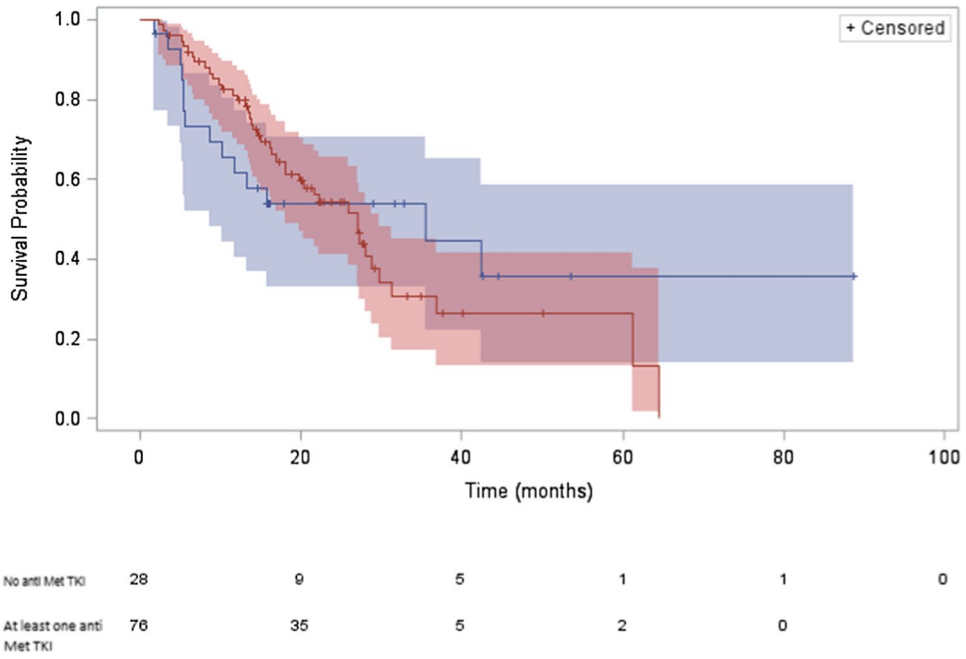

Fig. 1 Overall survival of patients treated with an anti-MET tyrosine kinase inhibitor (TKI) (red), and patients who did not receive an anti-MET TKI (blue)

and 9.1 months (95% CI 3.1–15.1) in pretreated patients. After a median follow-up of 11.0 months, the median OS was 18.2 months [18].

Despite this, we did not find any significant difference in survival between patients exposed or not to a TKI. However, patients exposed to crizotinib were significantly older, had a poorer general condition and less frequently received a platinum doublet. These poor prognosis factors could explain this lack of difference in OS. In contrast, Awad et al. showed a significant difference in median OS between patients exposed to anti-MET TKI or not (24.6 vs 8.1 months, respectively) [19]. But in this study, none of the non-TKI cohort patients were exposed to immunotherapy. Although classically immunotherapy had low activity in patients with a *MET*exon14 mutation [20], recent data, as in our study, show subgroups of *MET*exon14 mutated patients who may have a very good and durable response [21, 22]. ORR and median PFS duration with crizotinib and other anti-MET TKIs remain lower compared with TKIs targeting EGFR and ALK alterations, which appear to have a higher oncogenic addiction [22–26].

A recent international analysis, including 70 patients managed in six oncology sites [27], found clinicopathologic characteristics close to our results. Only 6 (8.6%) patients had a concomitant MET amplification. These patients are less exposed to anti-MET TKIs than those in our cohort. They have a worse prognosis, with a median OS of 12.0 months (95% CI 6.8–19.2) from the start of first-line therapy ($n = 52$), and 11.7 months (95% CI 6.0–32.9) from the start of second-line therapy. In another recent report, the real-world response rate to MET inhibitors was 45%, and time to treatment discontinuation was 4.4 months [28].

Our study has some limitations; we do not have detailed data on comorbidities or adverse events and we are not able to assess intracranial response and PFS. At least, certain molecular biology data, such as the association of *MET* amplification (not routinely sought in France) may also be a confounding factor, either because their association may be considered to have a poor prognosis, or because they also allow for anti-MET TKI activity [29–32]. In addition, there was no standardized method for patient follow-up and no independent review of responses. Access to TKIs also varied between centers, with some being able to benefit from clinical trials.

5 Conclusion

This study does not show a significant improvement in survival in patients exposed to an anti-MET TKI but the result should be interpreted with caution as patients were generally exposed late to these targeted therapies and the populations of exposed and unexposed patients are not easily comparable. Furthermore, we found, as reported recently in the literature, that a subgroup of patients had a prolonged benefit from immunotherapy treatment.

Declarations

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Conflicts of Interest/Competing Interests Hélène Babey, Philippe Jamme, Hubert Curcio, Jean Baptiste Assié, Remi Veillon, Hélène Doubre, Maurice Pérol, Florian Guisier, Eric Huchot, Chantal Decroisette, Lionel Falchero, Romain Corre, Alexis Cortot, Christos Chouaid, and Renaud Descourt declare that they have no conflicts of interest that might be relevant to the contents of this manuscript.

Ethics Approval, Consent to Participate This study was conducted in accordance with the Declaration of Helsinki and was approved by the French Advisory Committee on Information Processing in Health Research (CCTIRS). Living patients were informed and gave their non-objection to participate in the study, and for deceased patients, an exemption of information was obtained.

Data Availability The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Code Availability Not applicable.

Author Contributions HB, CC, and HC conceived, designed the study, and wrote the paper. JBA, RV, HD, MP, FG, RH, CD, LF, AMC, MA, and AC revised the paper for important intellectual content. All authors read and approved the final manuscript.

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