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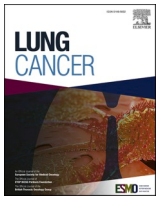

Research Paper

Capmatinib efficacy for *MET*ex14 non-small cell lung cancer patients: Results of the IFCT-2104 CAPMATU study

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ABSTRACT

Background: Capmatinib is a selective MET inhibitor with demonstrated efficacy in a phase II study of non-small cell lung cancer (NSCLC) patients harboring *MET*ex14 mutations. However, the real-world outcomes of capmatinib are largely unknown. From June 2019, the French Early Access Program (EAP) provided capmatinib to *MET*ex14 NSCLC patients who were ineligible for or for whom first-line standard therapies had failed.
Methods: IFCT-2104 CAPMATU was a multicenter study that included all *MET*ex14 NSCLC patients who received capmatinib as part of the EAP until August 2021. The primary endpoints were time to treatment failure (TTF), progression-free survival (PFS), overall survival (OS) and objective response rate (ORR).
Results: A total of 146 patients were included. The median age was 74.9 years, 56.6 % were never-smokers, and 32.4 % had brain metastases. The median TTF, median PFS and median OS from capmatinib initiation were 5.1 months (95 % CI 4.2–6.0), 4.8 months (95 % CI 4.0–6.0) and 10.4 months (95 % CI 8.3–13.2), respectively. Evaluation of the best response to capmatinib was available for 134 patients and resulted in an ORR of 55.3 % (95 % CI 46.8 %-63.6 %). The median PFS was 7.7 months for treatment-naïve patients and 6.0 and 4.1 months for patients who had received one or 2 + prior lines of treatment, respectively. For patients with brain

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metastases, the median PFS was 3.0 months. Capmatinib had a known and manageable safety profile, with grade 3 to 4 adverse events, mostly peripheral edema (8.2 %), occurring in 17.8 % of patients.
Conclusion: In this large real-world study of *MET*ex14 NSCLC patients, the efficacy of capmatinib was confirmed, with a manageable safety profile, even in patients with brain metastases and in those who received several lines of treatment. This study reinforces the key role of capmatinib for these patients.

1. Introduction

MET exon 14 skipping mutations (*MET*ex14) are observed in 2 to 4 % of non-small cell lung cancer (NSCLC) patients. They lead to MET receptor stabilization at the membrane and its activation, leading to oncogenic addiction [1]. Preclinical studies have shown that NSCLC patients with *MET*ex14 mutations are sensitive to MET inhibitors [2]. *MET*ex14 mutations define a distinct subtype of NSCLC patients with specific clinical features, including older age at diagnosis as well as a high proportion of women and never smokers. In addition, *MET*ex14 mutations appear to be associated with poor prognosis, though data are still scarce and do not distinguish between a potential adverse effect of the *MET*ex14 mutation and associated poor prognostic factors, particularly advanced age and sarcomatoid histology [3–5]. Finally, these patients appear to derive modest benefit from other standard treatments for NSCLC, including chemotherapy and immunotherapy [4,5].

Several targeted therapies can inhibit the HGF/MET pathways, including antibodies targeting MET or HGF and MET tyrosine kinase inhibitors (TKIs) [6]. The recent discovery of *MET*ex14 mutations has prompted evaluation of MET TKIs in these patients. MET TKIs are divided into type I and type II, binding to the active and inactive ATP binding pockets, respectively. Type I inhibitors are further subdivided into Ia and Ib depending on their interaction with the G1163 residue. Capmatinib is an oral, ATP-competitive, selective, and highly potent MET type 1b inhibitor that has shown activity in preclinical models characterized by MET dysregulation [7,8]. In the phase II GEOMETRY-mono1 study, capmatinib yielded an objective response rate (ORR) of 68 % and a median progression-free survival (PFS) of 12.4 months for treatment-naïve patients and an ORR of 41 % and a median PFS of 5.4 months for pretreated patients [9]. The safety profile was characterized by a 13 % rate of treatment-related serious adverse events, with a predominance of peripheral edema, nausea and vomiting [10]. Based on these data, capmatinib was approved in several countries or made available through compassionate use.

However, data to confirm these good results are still scarce, especially under real-world conditions, regarding patients less selected than those included in clinical trials. Here, we report the results of the French Cooperative Thoracic Intergroup (IFCT)-2104 CAPMATU study, a nationwide study of *MET*ex14 NSCLC patients who received at least one dose of capmatinib as part of the French expanded access program.

2. Methods

2.1. Study design and treatment

IFCT-2104 CAPMATU is a multicenter study including NSCLC patients who received at least one dose of capmatinib as part of the French Early Access Program (EAP) between 1st June 2019 and 31st August 2021. All physicians who had included at least one patient in the EAP were asked if they agreed to participate in the study. If accepted, all patients included by the investigator were then asked to participate.

In this EAP, capmatinib was given to patients with *MET*ex14 NSCLC who had already received or were ineligible for first-line therapy. Capmatinib was administered orally at the standard dosage of 400 mg twice daily. Dose modifications were based on available recommendations and decided at physicians' discretion. Capmatinib was discontinued in cases of disease progression, unacceptable toxicity, or patient or physician decision.

2.2. Study endpoints

The objective of the study was to evaluate the efficacy and safety of capmatinib in *MET*ex14 NSCLC patients who received capmatinib as part of the French EAP. The main endpoints were time to treatment failure (TTF), real-world PFS, overall survival (OS), ORR and safety. TTF was defined as the time between the first dose of treatment and cessation of treatment. Real-world PFS was defined as the time between the first dose of treatment and first disease progression or death, regardless of cause. OS was defined as the time between the first dose of treatment and any cause of death. Central nervous system (CNS) PFS was evaluated in patients with brain metastasis at capmatinib initiation. DCR was defined as the sum of the complete, partial and stable disease rates and ORR was defined as the best ORR. The date of disease progression was assessed by the local physician in charge of the patient; there was no central review of patients' CT-scans to assess treatment response.

2.3. Eligibility criteria

The following main inclusion criteria were: (i) cytological or pathological diagnosis of NSCLC, (ii) stage IIIB or IV, (iii) age of 18 or older, (iv) presence of a *MET*ex14 mutation diagnosed based on a tumor sample and/or on liquid biopsy, and (v) treatment with at least one dose of capmatinib (regardless of the treatment line) as part of the French EAP initiated between June 1st, 2019, and August 31st. 2021, (vi) informed about the study and did not object for their data to be collected. The cutoff date was chosen to have a minimal 6-month follow-up. The exclusion criteria were as follows: (i) included in an ongoing clinical trial evaluating treatment with capmatinib, (ii) opposition to the collection of data, (iii) under curatorship or guardianship, (iv) a psychiatric history that hinders understanding of the information letter and (v) inability to collect data. As the study was designed to investigate the impact of capmatinib in NSCLC cancer patients in whom the *MET*ex14 mutation was the oncogenic driver and not a resistance mechanism, we excluded patients in whom the *MET* mutation was detected when there was already another oncogenic driver identified in a previous sample. Patients in whom coalterations were identified using the same sample as the *MET*ex14 mutation were included.

2.4. METex14 mutations

Detection of *MET*ex14 mutations was based on local tests performed by certified molecular testing laboratories. No central confirmation of the result was needed. Although there is no recommendation in France for using a specific test for detecting *MET*ex14 mutations, the vast majority of laboratories use Next-Generation Sequencing (NGS)-based techniques with DNA and/or RNA, as described below. *MET*ex14 mutations were further reviewed by a panel of molecular biologists and categorized as "standard" or "uncommon" mutations depending on their predicted effect on splicing. *MET*ex14 mutations were considered "standard" if (i) the skipping of exon 14 was confirmed by RNA sequencing, (ii) the mutation at the DNA level is known to induce exon 14 splicing, (iii) in silico prediction by the SPiP tool of effect on splicing is greater than 80 % or (iv) by expert agreement and probability of prediction by effect on splicing between 50–80 % in silico. *MET*ex14 mutations were considered "uncommon" in all other cases. If no data on the specific type of *MET*ex14 mutation were available, the mutation was considered "unclassified".

2.5. Data collected

All data were collected retrospectively from patient medical records for all patients in a single campaign per center. A dedicated and trained IFCT clinical research associate (CRA) was in charge of the collection of the data from electronic health records. Data included information about patient demographics and clinical characteristics, including sex, date of birth, smoking status, Eastern Cooperative Oncology Group (ECOG) performance status (PS), cancer stage, previous treatments, cancer histology, *MET* mutation status, techniques used for detection of *MET* mutations, presence of coalterations, capmatinib treatment (duration, best response and progression patterns), and drug safety profile. Regarding the safety profile, the following data were collected: treatment-related adverse events (TRAEs) of grade 3 or more during capmatinib treatment for all patients, dose reductions and their cause, temporary withdrawals of treatment and their cause and discontinuations of treatment and their causes.

2.6. Ethics approval and informed consent

As part of secondary data use, the present protocol was prepared in accordance with the compliance commitment to reference method MR-004 submitted to the CNIL (French National Commission for the protection of private data and rights). This research was registered in the Health Data Hub (HDH) public directory (https://www.health-data-hub.fr/projets) and in the clinicaltrials.gov database under ID NCT05154344. An information letter was given to living patients to obtain their nonobjection to collection of their medical data and to inform them of their rights in accordance with regulations, as per French law. Information pertaining to deceased patients may be subject to data processing, except if the concerned patient voiced refusal while still alive.

2.7. Statistical analysis

Categorical variables are expressed as frequencies and percentages. Quantitative variables are expressed as medians (range). The number of missing data (Nmiss) is also presented. The Kaplan–Meier method was used to estimate TTF, PFS and OS endpoints. The prognostic value of clinical or biological parameters was assessed using a univariate Cox regression model. A multivariate model was tested with all the variables of the univariate model, and a backward-type step-by-step selection was employed. A first sensitivity analysis was performed excluding patients with uncommon mutations. Another sensitivity analysis was carried out excluding patients with a coalteration (all coalterations and coalterations considered oncogenic drivers, i.e., involving *EGFR*, *KRAS*, *HER2*, *BRAF*, *ALK*, *ROS1* or *PiK3CA*). All analyses were performed using SAS® 9.4 software.

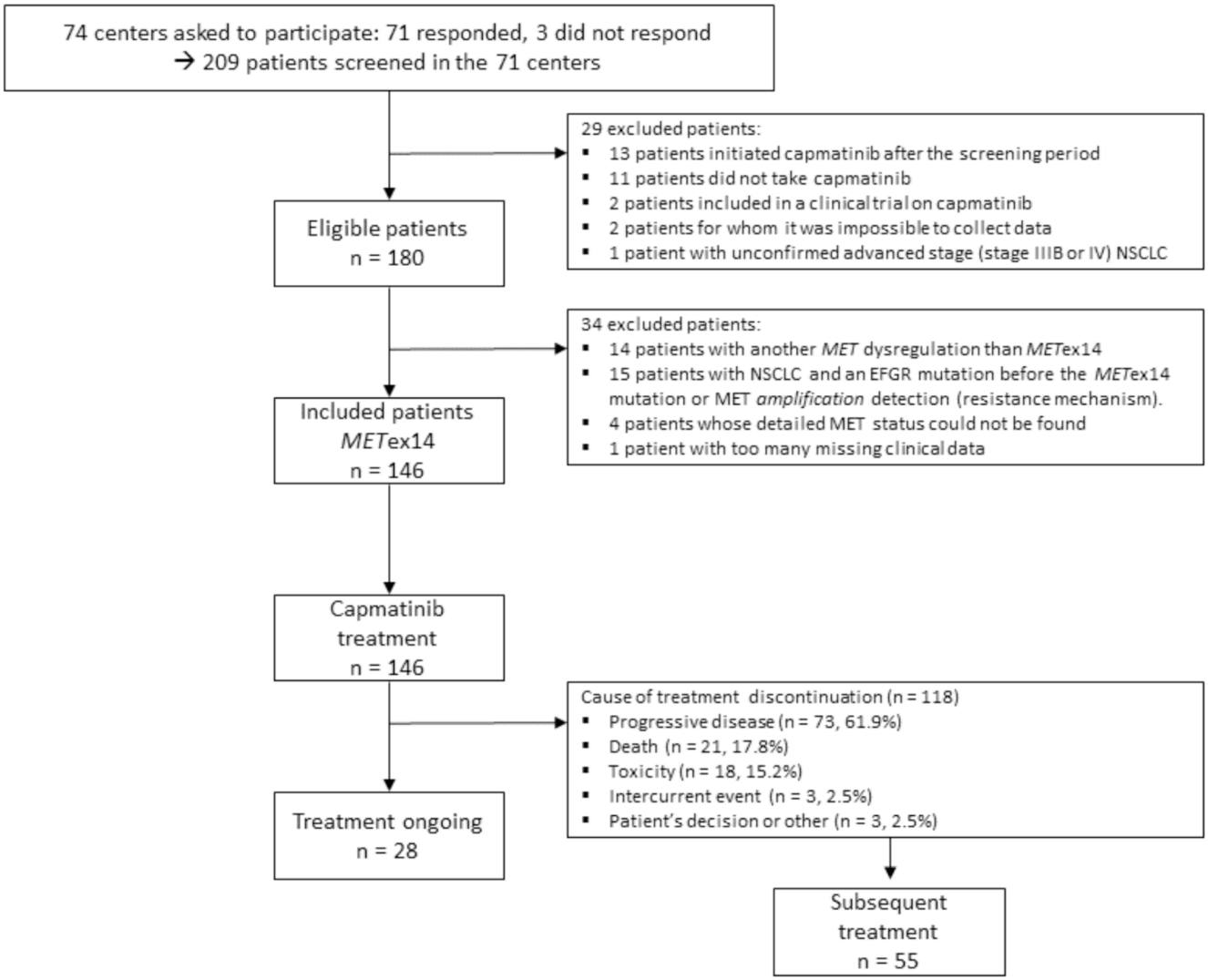

Fig. 1. Flow-chart of the study.

3. Results

3.1. Patient population

Among the 74 centers that requested the EAP for capmatinib, 71 agreed to participate, corresponding to 209 potential patients. The eligibility criteria were met for 180 patients, including 146 patients with a *MET*exon14 mutation (Fig. 1). Baseline characteristics at the time of capmatinib initiation of the 146 patients enrolled in the study are reported in Table 1. Most of these patients had adenocarcinoma. The median age was 74.9 years. There were 82 women (56.2 %), 82 never-smokers (56.6 %), 74 patients with ECOG PS 0/1 (66.7 %) and 47 patients with brain metastases (32.4 %). Among the 47 patients with brain metastases at capmatinib initiation, 24 had received previous local treatment. The most frequent sites of metastases were bones (52.7 %), pleura (35.6 %) and brain (32.2 %).

Data about the type of molecular testing were available for 145 patients (99.3 %). The testing method for *MET* mutations was next-generation sequencing (NGS) using DNA for 121 patients (83.4 %) and RNA sequencing for the others. One hundred patients were classified as carriers of a standard *MET*ex14 mutation, 15 patients had an uncommon *MET*ex14 mutation, and 31 patients had an unclassified mutation. The baseline characteristics of these subgroups are provided in Table 1 and the mutation list in Supplementary Table 1: we identified 100 patients with a *MET*ex14 standard mutation, 15 patients with a *MET*ex14 uncommon mutation and 31 patients with a *MET*ex14 unclassified mutation. *EGFR* and *KRAS* mutations were present in 4 (2.7 %) and 8 (5.5 %) patients, respectively; *ALK* and *ROS1* rearrangements were present in 1 (0.7 %) and 3 (2.1 %) patients, respectively. PD-L1 expression was $\geq$ 50 % in 63 patients (43.2 %), 1–49 % in 43 (29.5 %), and $<$ 1 % in 27 (18.5 %).

3.2. Efficacy

The median follow-up from capmatinib initiation was 13 months. The median TTF, median PFS and median OS from capmatinib initiation were 5.1 months (95 % CI 4.2–6.0), 4.8 months (95 % CI 4.0–6.0) and 10.4 months (95 % CI 8.3–13.2), respectively (Table 2 and Fig. 2). Evaluation of the best response to capmatinib was available for 134 patients and resulted in an ORR of 55.3 % (95 % CI 46.8 %-63.6 %) and a disease control rate (DCR) of 79.1 % (Table 2 **and** Supplementary Table 4). When capmatinib was continued beyond progression (n = 22), the mean duration of treatment was 2.5 months (range 1.0–10.5).

Globally, the efficacy of capmatinib differed depending on the *MET*ex14 mutation classification with a better PFS, TTF, OS and ORR with patients with a standard mutation compared to patients with an uncommon or unclassified mutation. Patients with a standard mutation had a median PFS of 5.9 months (95 % CI 4.8–7.7), whereas patients with an uncommon or unclassified mutation had a median PFS of 2.4 months (95 % CI 0.6–3.6) and 3.6 months (95 % CI 2.1–5) respectively (Table 2).

Seventeen patients had other genetic alterations in addition to *MET*ex14 mutations, most of a time *MET*ex14 mutation was a resistance mechanism to the first mutation. In these patients, median TTF, PFS and OS were 3.7 months (95 % CI 1.8–11.1), 3.6 months (95 % CI 2.4–7.9) and 13.4 months (95 % CI 6.1-NR). ORR was 53.3 % (95 % CI 28.1 %-78.6 %). The median PFS was 5.0 months (95 % CI 4.0–6.2) for patients without associated driver oncogene alteration.

The median PFS and OS were 7.7 months (95 % CI 4.0-NR) and not reached (NR) (95 % CI 6.2-NR) in patients who had received no prior treatment (n = 23), 6.0 months (95 % CI 3.6–7.7) and 14.1 months (95 % CI 10.0-NR) in those who received one prior line of therapy (n = 56), and 4.1 months (95 % CI 2.5–5.1) and 6.8 months (95 % CI 5.4–10.0) in those who received two or more prior lines of therapy (n = 67) (Fig. 3**A** and Supplementary Fig. 1**A**). The median PFS for capmatinib was 2.6 months (95 % CI 2.1–4.6) in 46 patients who previously received

Table 1
Baseline characteristics.

Characteristics	*MET*ex14 N=146 (%)	*MET*ex14 standard mutation N=100 (%)	*MET*ex14 uncommon mutation N=15 (%)	*MET*ex14 unclassified mutation N=31 (%)
Sex				
Male	64 (43.8)	43 (43.0)	7 (46.7)	14 (45.2)
Female	82 (56.2)	57 (57.0)	8 (53.3)	17 (54.8)
Median age (years. range)	74.9 (31.5–91.4)	76.6 (47.5–91.4)	64.3 (48.3–76.4)	74.5 (31.5–89.5)
Smoking status				
Current or former smokers	63 (43.4)	38 (38.0)	11 (78.6)	14 (45.2)
Never smokers	82 (56.6)	62 (62.0)	3 (21.4)	17 (54.8)
Unknown	1	0	1	0
Initial stage				
I to IIIC	28 (19.4)	24 (24.5)	2 (13.3)	2 (6.5)
IVA and B	116 (80.6)	74 (75.5)	13 (86.7)	29 (93.5)
Unknown	2	2	0	0
Stage at capmatinib initiation				
IIIB/IIIC	2 (1.4)	2 (2.0)	0	0
IVA	46 (31.7)97	36 (36.0)	1 (6.7)	9 (30.0)
IVB	(66.9)	62 (62.0)	14 (93.3)	21 (70.0)
Unknown	1	0	0	1
Brain metastases at capmatinib initiation				
Yes	47 (32.4)	24 (24.0)	8 (53.3)	15 (50.0)
No	98 (67.6)	76 (76.0)	7 (46.7)	15 (50.0)
Unknown	1	0	0	1
Histology				
Adenocarcinoma	123 (84.2)	83 (83.0)	13 (86.7)	27 (87.1)
Squamous cell carcinoma	9 (6.2)	7 (7.0)	1 (6.7)	1 (3.2)
Sarcomatoid carcinoma	6 (4.1)	6 (6.0)	0	0
Other	8 (5.5)	4 (4.0)	1 (6.7)	3 (9.7)
PD-L1 expression				
$\geq$50 %	63 (43.2)	46 (46.0)	2 (13.3)	15 (48.4)
$\geq$1% and $<$ 50 %	43 (29.5)	28 (28.0)	6 (40)	9 (29.0)
$<$1%	27 (18.5)	15 (15.0)	6 (40)	6 (19.4)
Not done or undetermined	13 (8.9)	11 (11.0)	1 (6.7)	1 (3.2)
PS at capmatinib initiation				
0	18 (16.2)56	15 (18.8)	2 (20)	1 (4.8)
1	(50.5)	39 (48.7)	6 (60)	11 (52.4)
$\geq$2	37 (33.3)	26 (32.5)	2 (20)	9 (42.8)
Unknown	35	20	5	10
Previous lines of systemic therapy				
0	23 (15.8)	20 (20.0)	0	3 (9.6)
1	56 (38.4)	35 (35.0)	7 (46.7)	14 (45.2)
$\geq$2	67 (45.9)	45 (45.0)	8 (53.3)	14 (45.2)
Other genetic alterations				
EGFR mutated	4 (2.7)	0	2 (13.3)	2 (6.5)
KRAS mutated	8 (5.5)	4 (4.0)	3 (20.0)	1 (3.2)
HER2 mutated	1 (0.7)	0	1 (6.7)	0
ALK rearranged	1 (0.7)	1 (1.0)	0	0
ROS1 rearranged	3 (2.1)	3 (3.0)	0	0

Table 2
Capmatinib therapy clinical outcome in the entire cohort and according to *MET*ex14 mutations.

	*MET*ex14 N=146 (%)	*MET*ex14 standard mutation (N=100)	*MET*ex14 uncommon mutation (N=15)	*MET*ex14 unclassified mutation (N=31)
Median TTF: months [95 % CI]	5.1 [4.2–6.0]	5.9 [5.0–7.8]	2.7 [0.6–3.7]	4.2 [2.6–6.4]
Median PFS: months [95 % CI]	4.8 [4.0–6.0]	5.9 [4.8–7.7]	2.4 [0.6–3.6]	3.6 [2.1–5.0]
Median OS: months [95 % CI]	10.4 [8.3–13.2]	11.2 [8.5–16.0]	8.5 [0.8-NR]	9.4 [5.5–12.0]
ORR: N (%) [95 % CI]	74 (55.2 %) [46.8 %-63.6 %]	56 (58.9 %) [49.1 % – 68.8 %]	4 (36.4 %) [7.9 % – 64.8 %]	14 (50.0 %) [31.5 % – 68.5 %]

crizotinib and 6.0 months (95 % CI 4.5–7.7) in the others (Fig. 3**B**); their median OS was 7.3 months (95 % CI 5.5–11.2) and 11.6 months (95 % CI 8.5–15.7), respectively (Supplementary Fig. 1**B**). In a multivariate analysis, we found no statistically significant difference in OS or PFS according to sex, age, PS, or presence of brain metastases (Supplementary Tables 2 and 3).

Among the 47 patients with brain metastases, the median PFS was 3.0 months (95 % CI 2.4–5.8) compared to 5.3 months 95 % (CI 4.5–7.7) for the 98 patients without brain metastases (Fig. 3**C**). The median CNS PFS for the 47 patients with brain metastases was 6.2 months (95 % CI 4.7–12.3). Evaluation of the best CNS response to capmatinib was available for 38 patients, with an ORR of 50 % (95 % CI 34.1–65.9) and DCR of 76.3 % (Supplementary Table 4).

The efficacy of capmatinib was similar for patients with ECOG PS 0–1, with a median PFS of 4.8 months (95 % CI 3.2–6.2), and patients with ECOG PS2 or more, with a median PFS of 4.4 months (95 % CI 2.4–5.9).

3.3. Patterns of progression and subsequent treatments

Among the 95 patients who experienced progression, the main sites of tumor progression were the lung in 45 patients (47.4 %), bones in 27 (28.4 %), mediastinal lymph nodes in 21 (22.1 %), pleura in 20 (21.1 %), liver in 13 (13.7 %) and brain in 12 (12.6 %) (Supplementary Table 5). After treatment with capmatinib, 55 patients received at least one subsequent systemic therapy, representing only 46.2 % of all patients who experienced progression on capmatinib. Immediate subsequent therapy was mainly chemotherapy in 23 patients (41.8 %), immunotherapy in 13 (23.6 %), chemo-immunotherapy in 4 (7.3 %), and crizotinib in 8 (14.5 %) (Supplementary Table 6). For these 55 patients, the median PFS of the first subsequent treatment was 2.1 months (95 % CI 1.6–3.6). Among these 55 patients, 8 patients received crizotinib after resistance to capmatinib. For these 8 patients, TTF, PFS and OS were 5.1 months (95 % CI 0.9–11.7), 3.7 months (95 % CI 0.9–11.7) and 11.2 months (95 % CI 2–16) respectively; ORR was 16.7 % (95 % CI 0 %-46.5 %).

3.4. Safety

Grade 3 to 5 TRAEs occurred in 26 patients (17.8 %) during capmatinib treatment (Table 3). The vast majority of them were grade 3, and no grade 5 was observed. The most common adverse events were peripheral edema (8.2 %), fatigue (2.1 %), and ALAT and ASAT increases (4.1 % and 3.4 %, respectively). Adverse events leading to treatment dose reduction occurred in 62/146 patients (42.5 %). Among the 118 patients who discontinued capmatinib, 18 (15.2 %) stopped the treatment because of adverse events (Fig. 1 and Table 3).

4. Discussion

In this study, which is the largest real-world study of capmatinib in *MET*ex14-mutated NSCLC patients thus far, we confirmed the efficacy of capmatinib, with a median PFS of 4.8 months and an ORR of 55 %. Moreover, we found that capmatinib was active even in patients with poor performance status and in those with brain metastases. We report for the first time the lower efficacy of capmatinib in patients who have been previously exposed to crizotinib. Finally, we observed a lower efficacy of capmatinib in patients harboring uncommon *MET*ex14 mutations.

The characteristics of the patients included in this study are typical of *MET*ex14 patients, i.e., elderly, never-smoker patients, with a high proportion of women and cases of adenocarcinoma. They also reflect the real-world design of the study. Compared to the Geometry mono-1 study, our patients were older, more of them had poor PS or brain metastases, and more of them had coalterations [10]. Nevertheless, the efficacy of capmatinib for pretreated patients was very similar in both studies, with a median PFS of approximately 5 months. The results regarding first-line treatment are much more different, which is expected because the patients in the French EAP could be treated as the first-line only if they were ineligible for standard first-line therapy [9]. Thus, the frailty of the population included in this study did not seem to hamper the efficacy of capmatinib. RECAP is another real-world multicenter study evaluating capmatinib in 81 *MET*ex14 NSCLC patients [11]. The ORR of capmatinib was 58 %, and the median PFS was 9.5 months. Differences in results from the present study may be due to differences in baseline patient characteristics. Taken together, the results suggest good translation of the results of the Geometry mono-1 study to routine practice.

This study also provides original data on capmatinib efficacy with regard to patients with brain metastases. With a CNS ORR of 50 %, capmatinib was found to be active on brain metastases. However, the median PFS was lower in patients with brain metastases than in those without. This result may be questionable and must be confirmed, as the CNS PFS in patients with brain metastases was rather good and the CNS did not appear to be a major site of relapse with capmatinib. Moreover, in a recent study involving 68 *MET*ex14 NSCLC patients with brain metastases treated with capmatinib in the first line or later, the CNS ORR was 87 %, and the median PFS was 14.1 months [12].

Interestingly, the efficacy of capmatinib was maintained in patients with poor PS, who represented one-third of the overall population. This is in agreement with previous studies showing that targeted therapies can be active even in fragile patients, contrary to what is observed with immunotherapy or chemotherapy [13]. Due to their fragility, these patients may not be amenable to other treatments. Indeed, half of the patients who received capmatinib in this study did not receive further treatment at progression. In another observational study, only 23 patients received a second-line treatment of 52 patients treated with first-line therapy [14]. Moreover, the efficacy of capmatinib was maintened in patients with co-mutations too, with a TTF and PFS slightly worse but an equivalent or even better OS and ORR than the total cohort.

In our cohort, capmatinib efficacy decreased as the number of previous lines increased. This is in agreement with results from Geometry mono-1, which showed a median PFS of 10.8–12.4 months in treatment-naïve patients and 5.4–6.9 months in pretreated patients [9]. However, the same trend was not expected in our study since patients treated first-line were ineligible for any other treatment, suggesting the presence of poor prognostic factors. Moreover, we report for the first time the efficacy of capmatinib in patients previously treated with crizotinib,

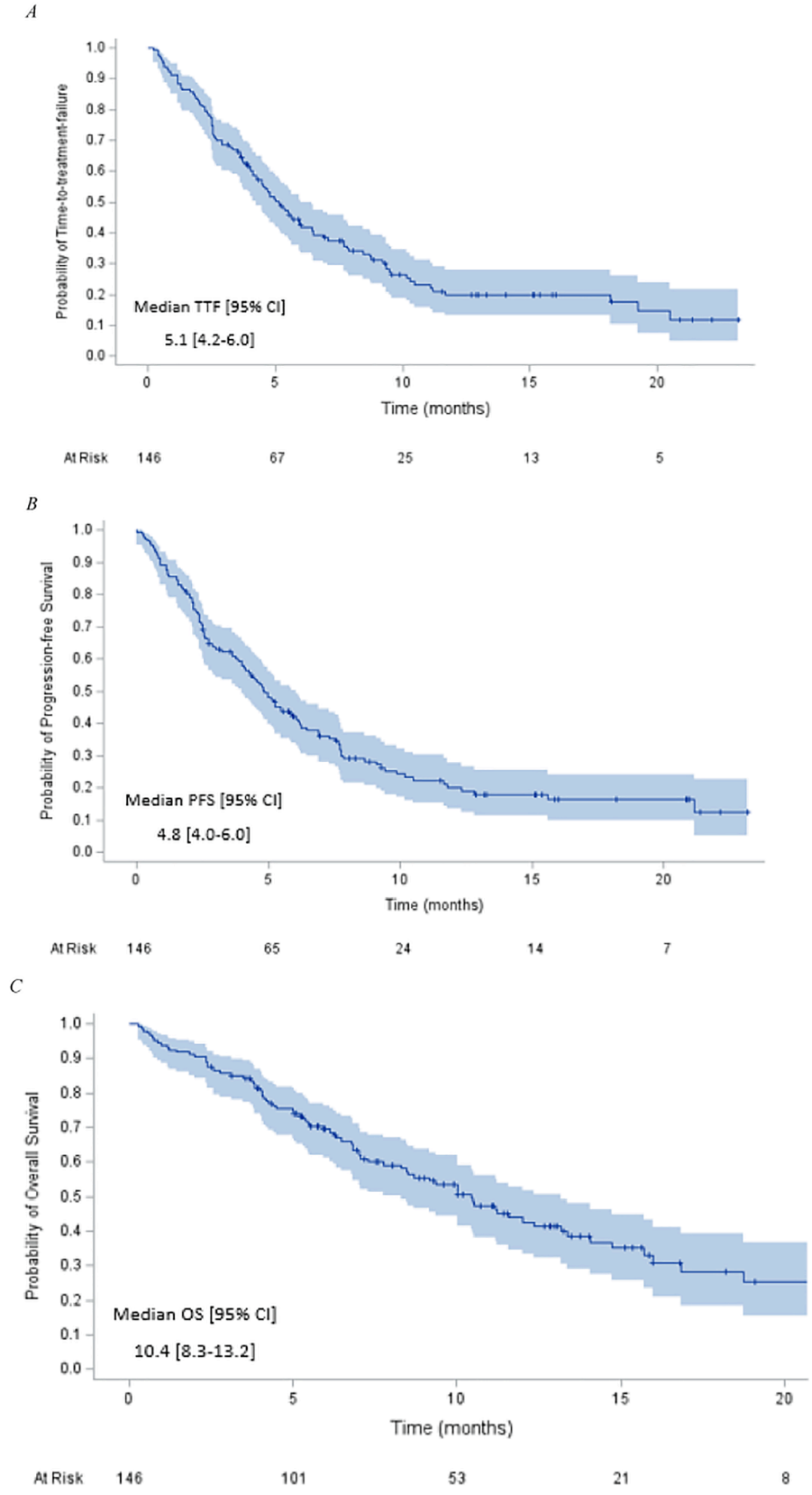

Fig. 2. TTF (2A), PFS (2B) and OS (2C) in the global cohort. No color needed.

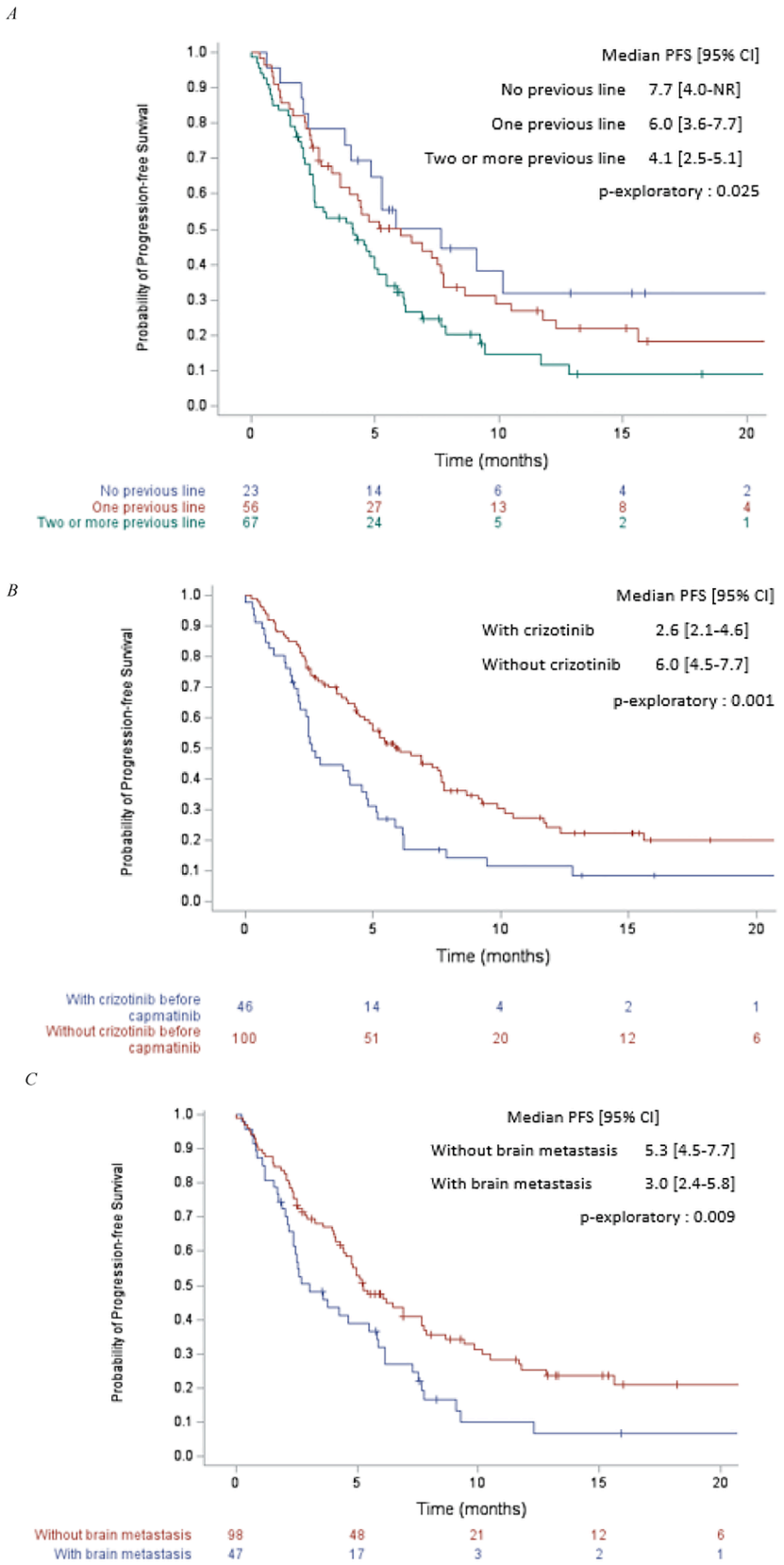

Fig. 3. PFS in subgroups: PFS according to previous lines (crizotinib, chemotherapy +/- immunotherapy) (3A), PFS according to exposure to crizotinib (3B), PFS according to the presence of brain metastases (3C). Color printing preferred.

Table 3
Capmatinib treatment adaptation, therapy clinical outcome after capmatinib discontinuation and serious adverse events in patients treated with capmatinib (reported in more than 1% of patients).

Characteristics			*MET*ex14 N=146 (%)	
Number of patients with dose adaptation			62 (42.5)	
Reason for dose adaptation (n = 102 adaptations)				
Toxicity			91 (89.2)	
Intercurrent event			8 (7.9)	
Disease progression			3 (2.9)	
Number of patients with transient withdrawal			52 (35.6)	
Reason for transient withdrawal (n = 85 withdrawals)				
Toxicity			75 (88.2)	
Intercurrent event			8 (9.4)	
Disease progression			1 (1.2)	
Patient's decision			1 (1.2)	
Adverse events	Any grade	Grade 3	Grade 4	Grade 5
Any adverse event	26 (17.8)	25 (17.1)	1 (0.7)	0
Peripheral edema	12 (8.2)	12 (8.2)	0	0
Fatigue	3 (2.1)	3 (2.1)	0	0
ALAT increased	6 (4.1)	5 (3.4)	1 (0.7)	0
ASAT increased	5 (3.4)	4 (2.7)	1 (0.7)	0

another *MET* TKI. We found poor efficacy of capmatinib in this setting. Although we lack data on the mechanisms of resistance in this study, it has been previously shown that resistance to *MET* inhibitors in *MET*-addicted models involves either mutations in the kinase domain of MET or activation of bypass pathways. In both cases, type I *MET* TKIs were not able to overcome this resistance, which may explain why capmatinib is not active following crizotinib failure [15]. Type II *MET* TKIs, on the other hand, may be active for MET kinase domain mutations.

This study also provides a unique opportunity to investigate the impact of capmatinib on uncommon *MET*ex14 mutations. Indeed, only a small number of centers use RNA-based techniques for direct detection of exon 14 skipping. In general, detection of a mutation within or close to splice sites of exon 14 using DNA-based techniques may be subject to interpretation with respect to its impact on exon 14 skipping. We identified 15 patients for whom the *MET*ex14 mutation was considered uncommon by a panel of experts. Interestingly, the PFS in these 15 patients was low, suggesting that the identified mutations are not responsible for oncogene addiction. These results suggest that RNA confirmation of exon 14 skipping should be performed when the functional consequences of a DNA mutation in exon 14 splice sites are unclear.

The safety profile of capmatinib was in line with expectations, with a high rate of peripheral edema among grade 3 or 4 adverse events. Grade 1–2 side effects were not reported in this retrospective study due to a possible heterogeneity in reporting these effects in patient files depending on the center. Dose reduction occurred in 42 % of patients, but there were few permanent discontinuations of treatment for toxicity (15.2 %). Although management of peripheral edema can be challenging, particularly in cases of grade 3 or higher edema, the overall safety profile of capmatinib appeared to be manageable.

This study has several limitations. Its retrospective nature may have led to missing data, though involvement of CRA collecting data directly from source files helped to limit this bias. Furthermore, the "real-word" nature of the study led to use endpoints that are not exactly comparable to those used in prospective studies. Comparison with the results of the Geometry mono-1 study should therefore be made with caution. Analysis of toxicity must also be carried out with caution, as toxicity is generally underestimated in retrospective studies. Finally, the small number of patients within subgroups prevented any definitive conclusion.

Other MET inhibitors are currently available or in development including MET TKIs, monoclonal antibodies and antibody-drug conjugates (ADCs) [16]. Tepotinib, a MET-specific TKI, was evaluated in the phase II open-label VISION study in 152 patients. The long-term follow-up of the study reported an ORR of 51.4 %, median PFS 11.2 months and median OS 19.6 months [17]. Savolitinib is another MET-specific TKI that has been evaluated in a phase II study including a high proportion of patients with sarcomatoid carcinomas. ORR was 47.1 % and median PFS was 6.9 months [18]. Amivantamab, an EGFR/MET bispecific antibody with immune cell-directing activity, was evaluated in the phase 1 CHRYSALIS study and demonstrated antitumor activity in 36 *MET*ex14 NSCLC patients: ORR was 33.3 % in the overall population; 50 % in treatment-naïve patients and 21.1 % in patients with prior MET inhibitors [19]. Telisotuzumab-Vedotin is an ADC targeting MET that has been evaluated in NSCLC patients with MET overexpression with encouraging results but there are no data so far on its activity in METex14 patients [20].

5. Conclusion

In conclusion, this study confirms the efficacy and good tolerance of capmatinib by patients with lung cancer and *MET*ex14 mutations, even in a real-world, i.e., more fragile, population. These results reinforce the role of capmatinib as key treatment for patients with *MET*ex14 NSCLC.

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CRediT authorship contribution statement

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: M. Ferreira: Financial Interests, Personal, Other, Travel, Accommodations, Expenses: AstraZeneca, BMS. A. Swalduz: Financial Interests, Personal, Other, honoraria: AstraZeneca, Janssen, Roche, Amgen, BMS; Financial Interests, Personal, Advisory Role: AstraZeneca, Janssen, Roche, Amgen, BMS, Pfizer, Lilly. P. du Rusquec: Financial Interests, Personal, Other, Travel, Accommodations: Roche, Pfizer, Sandoz, Daiichi Sankyo, Merck, Novartis, Lilly, Amgen, Eisai, BMS, Takeda, AstraZeneca, Janssen, Sanofi. Advisory Role: Sanofi, Takeda. A.C. Toffart: Financial Interests, Personal, Advisory Role: AstraZeneca, MSD, BMS, Roche, Amgen, Takeda, Jannsen. J. Raimbourg: Financial Interests, Personal, Other, Travel, Accommodations, Expenses: BMS. V. Gounant: Financial Interests, Personal, Advisory Role: BMS, AstraZeneca, Takeda; Financial Interests, Personal, Other, Travel, Accommodations, Expenses: Sanofi, Pfizer. S. Couraud: Financial Interests, Personal, Other, honoraria: Amgen, AstraZeneca, BMS, MSD, Roche, Sanofi, Fabentech, Boehringer Ingelheim, Takeda; Financial Interests, Institutional, Research Grant: Amgen, AstraZeneca, BMS, MSD, Roche, Sanofi, Chugai, Novartis, Pfizer, Sysmex, Cellgene, Takeda, Janssen; Financial Interests, Personal, Other, Travel, Accommodations, Expenses: AstraZeneca, Roche, Takeda. M. Wislez: Financial Interests, Personal, Advisory Role: AstraZeneca, MSD, Amgen, BMS, Roche; Financial Interests, Personal, Speaker's Bureau: AstraZeneca, MSD, Amgen, BMS, Roche; Financial Interests, Institutional, Funding, research funding: AstraZeneca; Financial Interests, Personal, Other, Travel, Accommodations, Expenses: AstraZeneca, MSD, Amgen, BMS, Roche. C. Descarpentries reports personal fees and nonfinancial support from AstraZeneca, personal fees and nonfinancial support from Novartis Pharma SAS, nonfinancial support from Roche SAS, nonfinancial support from Boehringer Ingelheim france, nonfinancial support from Pfizer, outside the submitted work; G. Herbreteau reports personal fees and nonfinancial support from Pierre Fabre Oncology. V. Westeel: Financial Interests, Personal, Other, Honoraria: AstraZeneca, BMS, Amgen, Roche; Financial Interests, Personal, Advisory Role: MSD, Takeda; Financial Interests, Personal, Speaker's Bureau: BMS, AstraZeneca, Roche, MSD, Pfizer, Amgen; Financial Interests, Personal, Other, Travel, Accommodations, Expenses: BMS, AstraZeneca, Sanofi. A. B. Cortot: Financial Interests, Personal, Other, Consulting fees: Roche Novartis; Financial Interests, Personal, Other, Honoraria: Novartis Pfizer Takeda Roche; Financial Interests, Personal, Advisory Board: Roche Novartis Pfizer Takeda. All other authors have declared no conflicts of interest.

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Appendix A. Supplementary data

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