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Capmatinib in Japanese patients with *MET* exon 14 skipping–mutated or *MET*-amplified advanced NSCLC: GEOMETRY mono-1 study

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Abstract

MET mutations leading to exon 14 skipping (*MET*Δex14) are strong molecular drivers for non–small-cell lung cancer (NSCLC). Capmatinib is a highly potent, selective oral MET inhibitor that showed clinically meaningful efficacy and a manageable safety profile in a global phase II study (GEOMETRY mono-1, NCT02414139) in patients with advanced *MET*Δex14-mutated/*MET*-amplified NSCLC. We report results of preplanned analyses of 45 Japanese patients according to *MET* status (*MET*Δex14-mutated or *MET*-amplified) and line of therapy (first- [1L] or second-/third-line [2/3L]). The starting dose was 400 mg twice daily. The primary endpoint was the objective response rate (ORR) assessed by a blinded independent review committee. A key secondary endpoint was duration of response (DOR). Among *MET*Δex14-mutated patients, in the 1L group, one patient achieved partial response (DOR of 4.24 months) and the other had stable disease. In the 2/3L group, the ORR was 36.4% (95% confidence interval [CI] 10.9%-69.2%), median DOR was not evaluable, and progression-free survival was 4.70 months. One patient (2/3L group) showed partial resolution of brain lesions per independent neuroradiologist review. In *MET*-amplified patients with a *MET* gene copy number of ≥10, the ORR was 100% (2/2 patients) in the 1L group and 45.5% (5/11 patients) in the 2/3L group, with DOR of 8.2 and 8.3 months, respectively. Common treatment-related adverse events among the 45 Japanese patients were blood creatinine increased (53.3%), nausea (35.6%), and oedema peripheral (31.1%); most were grade 1/2 severity. In conclusion, capmatinib was effective and well tolerated by Japanese patients with *MET*Δex14/*MET*-amplified NSCLC, consistent with the overall population.

Abbreviations: AE, adverse event; AUC, area under the curve; BIRC, blinded independent review committee; CI, confidence interval; C_{max}, maximum concentration; CNS, central nervous system; CR, complete response; DCR, disease control rate; DOR, duration of response; GCN, gene copy number; HGF, hepatocyte growth factor; ILD, interstitial lung disease; *MET*Δex14, *MET* gene exon 14 skipping; NSCLC, non-small-cell lung cancer; ORR, overall response rate; PD, progressive disease; PFS, progression-free survival; PK, pharmacokinetic; PR, partial response; QTc, corrected QT; RTK, receptor tyrosine kinase; SD, stable disease; t_{max}, time to the maximum concentration; TTR, time to response.

Clinical trial registration: ClinicalTrials.gov (identifier NCT02414139).

KEYWORDS

capmatinib, MET receptor tyrosine kinase, non–small-cell lung cancer, response, safety

1 | INTRODUCTION

Non–small-cell lung cancer (NSCLC) is the most common type of lung cancer and is usually very serious, as about a third of patients present with advanced stage III or IV disease and have a very poor prognosis.[1,2] Accordingly, understanding the pathogenesis and identifying possible therapeutic targets has been a key focus of research. In the last few decades, receptor tyrosine kinases (RTKs) have been identified as potential therapeutic targets for NSCLC. One such RTK is the hepatocyte growth factor (HGF) receptor, also known as MET.[3] Dysregulation of the MET pathway may result from several mechanisms, including *MET* mutation,[4,5] *MET* gene amplification,[6-8] or overexpression of MET protein.[9,10] MET is thought to promote tumor cell proliferation, survival, invasion, and metastasis as well as tumor angiogenesis.[11] Recent studies have highlighted that mutations leading to *MET* gene exon 14 skipping (*MET*Δex14) are strong molecular drivers of NSCLC.[4,12] This is a rare alteration that occurs in approximately 2%-4% of patients with NSCLC, with a similar rate in Japanese and non-Japanese or Western populations, and is usually mutually exclusive with other molecular drivers.[4,13] *MET*Δex14 is also associated with impaired MET receptor degradation and enhanced oncogenic transformation due to increased levels of MET.[14,15] In some patients, this mutation is accompanied by *MET* amplification or increased gene copy number (GCN).[15-18] *MET*Δex14 is also associated with a poor prognosis of NSCLC,[4,5,13,19-23] and patients carrying this mutation typically show poor responses to standard therapies including immunotherapies in patients with high programmed death ligand-1 expression or a high tumor mutational burden.[4,5,22,24-28] Therefore, there is strong rationale for using MET inhibitors to treat *MET*Δex14-mutated NSCLC as well as *MET*-amplified NSCLC.[29-31]

Central nervous system (CNS) metastases are commonly seen in patients with NSCLC, particularly in those with the adenocarcinoma subtype. Among patients with an oncogenic driver (eg, *EGFR* mutation or *ALK* rearrangement), about 24% have brain metastases at the time of diagnosis of advanced disease.[32] In such patients, administration of tyrosine kinase inhibitors capable of penetrating the CNS, such as osimertinib, alectinib, and ceritinib, may help to control these metastases and might delay cranial radiotherapy.[33] Brain metastases are also present in about 35% of patients with *MET*Δex14 NSCLC at the time of metastatic NSCLC diagnosis.[34] Considering this frequency, the management of brain metastasis is an important aspect of the care of these patients.

Capmatinib (INC280) is an oral, highly selective, potent, ATP competitive, reversible inhibitor of the MET RTK that blocks MET-dependent signaling and neoplastic activities in cell and animal models of NSCLC.[35-37] Several clinical studies, including a phase 1 study in Japan, indicated that capmatinib had a manageable safety profile and promising efficacy for the treatment of NSCLC or advanced solid tumors.[38,39] These studies were followed by a global phase 2 study, GEOMETRY mono-1, which evaluated the efficacy and safety of capmatinib in MET inhibitor–naïve patients with *MET*Δex14-mutated or *MET*-amplified NSCLC.[40] The study included 97 patients with *MET*Δex14-mutated NSCLC, of whom 28 received capmatinib as first-line therapy with an overall response rate (ORR) by blinded independent review committee (BIRC) of 68% (95% confidence interval [CI] 48%-84%). Confirmed complete response was observed in one of these patients. The other 69 patients received capmatinib as second-/third-line therapy, and their ORR by BIRC was 41% (95% CI 29%-53%), with tumor shrinkage of >90% in two patients. The median duration of response (DOR) in responders was 12.6 and 9.7 months in the first-line and second-/third-line groups, respectively. Among patients with *MET*-amplified NSCLC and a GCN of ≥10, the ORR for capmatinib was 40% (95% CI 16%-68%) as first-line therapy and 29% (95% CI 19%-41%) as second/third-line therapy, with median DOR of 7.5 and 8.3 months, respectively. These data suggest that capmatinib achieves clinically meaningful responses in patients with *MET*Δex14-mutated NSCLC and in patients with *MET*-amplified NSCLC, especially in those with a high GCN.

Here, we describe the results of preplanned analyses to investigate the efficacy of capmatinib according to *MET* status (*MET*Δex14-mutated or *MET*-amplified) and by line of therapy (first or second/third line) in Japanese patients enrolled in the GEOMETRY mono-1 study. We also evaluated the safety of capmatinib in the overall cohort of Japanese patients.

2 | METHODS

Further information about this study is available in the global study publication.[40] The study adhered to the Declaration of Helsinki and Good Clinical Practice and was registered on ClinicalTrials.gov (identifier NCT02414139).

2.1 | Patients, study design, and treatments

GEOMETRY mono-1 enrolled patients with *MET*Δex14-mutation–positive or *MET*-amplified, *EGFR* wild-type, *ALK*-negative NSCLC with a performance status of 0-1, ≥1 measurable lesion, if they were neurologically stable or had asymptomatic brain metastases.[40] Patients were divided into nine separate cohorts according to *MET* GCN and treatment history (Figure 1): cohort 1a, *MET* GCN ≥ 10 (no *MET* mutation); cohort 1b, *MET* GCN ≥ 6 to < 10 (no *MET* mutation); cohort 2, *MET* GCN ≥ 4 to < 6 (no *MET* mutation); cohort 3, *MET* GCN < 4 (no *MET* mutation); cohort 4, *MET* mutation regardless of GCN; cohort 5a, *MET* GCN ≥ 10 (no *MET* mutation); cohort 5b, *MET* mutation regardless of GCN; cohort 6, *MET* GCN ≥ 10 (no *MET* mutation) or *MET* mutation regardless of GCN; cohort 7, *MET* mutation regardless of GCN. Cohorts

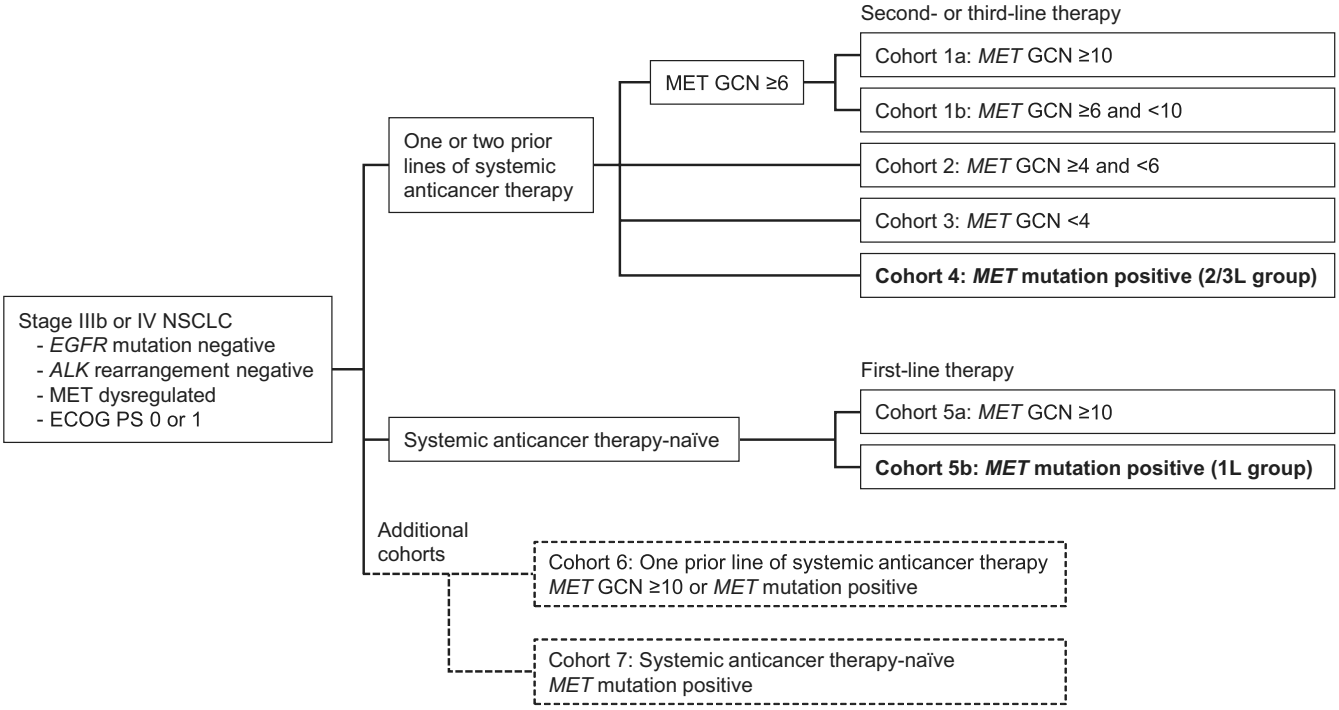


FIGURE 1 Study design. ECOG PS, Eastern Cooperative Oncology Group performance status; GCN, gene copy number; NSCLC, non–small-cell lung cancer

1-4 received capmatinib as second/third-line therapy, cohorts 5 and 7 as first-line therapy for advanced disease, and cohort 6 as second-line therapy. Cohorts 6 and 7 are not included in this report.

Here, we focused on patients with *MET*Δex14-mutation–positive NSCLC, regardless of GCN, who received capmatinib as first-line (1L group; cohort 5b) or second-/third-line (2/3L group; cohort 4) therapy, and for patients with *MET*-amplified NSCLC according to GCN and line of therapy (1L: cohort 5a; 2/3L: cohorts 1a, 1b, 2, and 3). Safety data are reported for Japanese patients in all seven of these cohorts combined. Key exclusion criteria were prior treatment with crizotinib or another MET or HGF inhibitor, neurologically unstable brain metastases, or carcinomatous meningitis. All patients provided written informed consent. *MET*Δex14 status and *MET* GCN were assessed from formalin-fixed, paraffin-embedded human tissue at a central laboratory at enrollment by quantitative real-time RT-PCR and fluorescence in situ hybridization, respectively.[41] All patients were administered capmatinib 400 mg tablets twice daily in fasting conditions in 21-day cycles, except in cohorts 6 and 7 where capmatinib was administered regardless of fasting status. Treatment was continued until progressive disease (PD), as determined by the investigator and confirmed by the BIRC. Imaging scans were performed every 6 weeks/every 2 cycles, and included brain imaging for patients with brain metastasis at baseline.

2.2 | Study objectives and endpoints

The primary objective was to determine the antitumor activity of capmatinib in terms of the ORR determined by a BIRC according to RECIST 1.1. The key secondary objective was the BIRC-assessed DOR. Other secondary objectives included the BIRC-assessed time to response (TTR), disease control rate (DCR), and progression-free survival (PFS). ORR was defined as the proportion of responders with a best overall response of complete response (CR) or partial response (PR). DCR was defined as the proportion of patients with CR, PR, stable disease (SD), or non-CR/non-PD. DOR was calculated as the time from the first documented response of CR or PR to the first documented progression or death due to any cause in responders. TTR was calculated as the time from the first dose of capmatinib to the first documented response of CR or PR in responders. PFS was defined as the time from the first dose of capmatinib to progression or death due to any cause. Ad-hoc BIRC neuroradiologist review of patients with *MET*Δex14 and baseline brain metastases was conducted due to observed brain responses in some patients.

Safety was assessed in terms of adverse events (AEs), vital signs, laboratory test results, and electrocardiography. AEs of special interest included CNS toxicities, liver toxicities, pancreatitis, pneumonitis, corrected QT (QTc) interval prolongation, renal dysfunction, photosensitivity, drug-drug interactions with strong CYP3A4 inducers, and teratogenicity.

For pharmacokinetic (PK) analysis, the plasma concentration–time profiles of capmatinib, when administered in fasting conditions, were evaluated after the initial dose (cycle 1 day 1) and at steady state (cycle 1 day 15). The plasma concentrations of capmatinib were measured by liquid chromatography–tandem mass spectrometry methods with a lower limit of quantification of approximately 1.0 ng/mL. PK parameters (maximum concentration [C_{max}], time to maximum concentration [t_{max}], and the area under

TABLE 1 Characteristics of the overall Japanese cohort (*MET*Δex14-mutated/*MET*-amplified non–small-cell lung cancer [NSCLC]) and patients with *MET*Δex14-mutated NSCLC (1L and 2/3L groups)

	Overall Japanese cohort (n = 45)[a]	1L group (n = 2)[b]	2/3L group (n = 11)[c]
Sex, female/male, n			
Female	15 (33.3)	1 (50.0)	6 (54.5)
Male	30 (66.7)	1 (50.0)	5 (45.5)
Age, y	68.0 (38.0-82.0)	66.0 and 68.0	72.0 (60.0-82.0)
<65 y	15 (33.3)	0	3 (27.3)
≥65 to <75 y	25 (55.6)	2 (100.0)	5 (45.5)
≥75 to <85 y	5 (11.1)	0	3 (27.3)
ECOG PS			
0	21 (46.7)	2 (100.0)	3 (27.3)
1	24 (53.3)	0	8 (72.7)
Smoking history			
Never smoked	19 (42.2)	1 (50.0)	7 (63.6)
Ex-smoker	25 (55.6)	1 (50.0)	4 (36.4)
Current smoker	1 (2.2)	0	0
Histological type			
Adenocarcinoma	35 (77.8)	2 (100.0)	8 (72.7)
Undifferentiated carcinoma	2 (4.4)	0	0
Squamous cell carcinoma	3 (6.7)	0	0
Adenosquamous cell carcinoma	1 (2.2)	0	1 (9.1)
Other	4 (8.9)	0	2 (18.2)
Brain metastasis	9 (20.0)	0	1 (9.1)
Bone metastasis	17 (37.8)	0	7 (63.6)
Stage at study entry			
IIIB	2 (4.4)	0	1 (9.1)
IV	43 (95.6)	2 (100.0)	10 (90.9)
Prior therapies			
Surgery	14 (31.1)	–	4 (36.4)
Radiotherapy	16 (35.6)	–	4 (36.4)
Adjuvant chemotherapy	6 (13.3)	–	2 (18.2)
Neoadjuvant	1 (2.2)	–	0
Prior antineoplastic regimens	41 (91.1)	–	11 (100.0)
1 antineoplastic regimen	23 (51.1)	–	9 (81.8)
2 antineoplastic regimens	18 (40.0)	–	2 (18.2)
Platinum-based chemotherapy	36 (80.0)	–	8 (72.7)
Immune checkpoint inhibitor	8 (17.8)	–	4 (36.4)
Targeted therapy[d]	8 (17.8)	–	1 (9.1)

Note:: Data cutoff: April 15, 2019.

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status.

[a]All patients enrolled in Japan regardless of *MET* status. Values are reported as the n (%) of patients or median (range).

[b]Received capmatinib as first-line therapy (cohort 5b).

[c]Received capmatinib as second-/third-line therapy (cohort 4).

[d]Includes bevacizumab, necitumumab, and pictilisib in combination with chemotherapy and/or immunotherapy.

the concentration-time curve [AUC]) were calculated by noncompartmental analysis.

2.3 | Statistical analyses

The preplanned analyses of the primary and secondary endpoints in these Japanese patients were performed in an exploratory manner. ORR and DCR are reported as the number and percent of patients with 95% CIs using the exact Clopper-Pearson method. The Kaplan-Meier method was used to analyze TTR, DOR, and PFS. Efficacy outcomes are reported for patients divided by *MET* status and treatment line separately. Safety data are reported as the number and percent of patients for all cohorts combined. Efficacy and safety analyses are provided for all Japanese patients who received at least one dose of capmatinib. SAS version 9.4 (SAS Institute) was used for analyses. PK parameters were derived using WinNonlin Pro (Version 5.0 or higher; Certara).

3 | RESULTS

3.1 | Patients

The cutoff dates of these analyses were April 15, 2019 (cohorts 1b, 2, and 3 with *MET* GCN < 10 were closed for futility) for efficacy and exposure (January 6, 2020 for efficacy in cohorts 1a and 5a), and September 18, 2019 for safety (all cohorts). As of September 18, 2019, 348 patients had been enrolled in GEOMETRY mono-1. Of these, 45 were enrolled in Japan. The characteristics of the overall Japanese population and the *MET*Δex14-mutated cohorts are summarized in Table 1. The characteristics of the *MET*-amplified cohorts are summarized in Table S1. Overall, there were 15 females and 30 males in the Japan safety cohort, with a median age of 68.0 years (range 38.0-82.0 years). Nineteen patients overall were never-smokers. Adenocarcinoma was the most common type of NSCLC. Brain metastases were observed in nine patients, of which eight had *MET*-amplified NSCLC (two in the 1L group) and one had *MET*Δex14-mutated NSCLC (1L group). Among 41 previously treated patients, 23 had received one prior antineoplastic regimen and 18 had received two prior antineoplastic regimens.

Characteristics of patients with *MET*Δex14-mutated NSCLC in the 1L and 2/3L groups are generally comparable with those of the overall Japanese cohort. Both patients in the 1L group had adenocarcinoma classified as stage IV, without evidence of brain metastases. The time since diagnosis to start of study treatment was 1.3 and 1.8 months. Both patients had four target lesions. Neither patient had undergone any prior treatment, including surgery or radiotherapy.

In the 2/3L group, eight patients had adenocarcinoma. The median time since diagnosis to study treatment was 10.9 months, and the median time since most recent relapse was 1.9 months. Nine had previously received one antineoplastic regimen, two had received two antineoplastic regimens, and four had received an immune checkpoint inhibitor prior to capmatinib.

The characteristics of patients with *MET*-amplified NSCLC were similar to those of the *MET*Δex14-mutated cohort and are reflective of disease and treatment histories (Table S1).

3.2 | Capmatinib exposure and follow-up

The disposition of patients is shown in Table 2. As of April 15, 2019, eight of 45 patients were still on treatment, while 37 had discontinued due to PD (28), an AE (eight), and at the patient's request (one). The median duration of exposure was 13.6 weeks (range 0.7-124.6 weeks). The median average daily dose was 772.5 mg (range 394.0-800.0 mg) with a median relative dose intensity of 91.4% (range 13.0%-100.0%).

Among patients with *MET*Δex14-mutated NSCLC, the median study follow-up in the 1L group (defined as the time from the start date of study drug to the cutoff date) was 15.4 months. Both patients had discontinued capmatinib due to PD in one and an AE in the other. The duration of treatment was 4.0 and 30.0 weeks (0.9 and 6.9 months, respectively) in the individual patients in the 1L group. Dose reductions due to AEs occurred in one patient, and capmatinib was interrupted due to AEs in both patients. The average daily dose in the individual patients was 766.7 and 788.3 mg, with relative dose intensities of 82.1% and 96.2%.

In the 2/3L group, the median study follow-up time was 19.7 months. Three patients were still receiving capmatinib, and the other eight patients had discontinued due to PD (five) or an AE (three). The median duration of treatment was 18.3 (range 3.1-79.7) weeks (4.2 [0.7-18.3] months). Dose reductions due to AEs occurred in eight of the 2/3L patients, and capmatinib was interrupted due to AEs in 10 patients. The median average daily dose of capmatinib was 753.1 mg (range 434.0-796.7 mg), and the median relative dose intensity was 74.4% (range 44.1%-96.5%).

3.3 | Efficacy

The responses to capmatinib, as assessed by the BIRC, are given in Table 3 for *MET*Δex14-mutated NSCLC.

Among *MET*Δex14-mutated NSCLC patients, PR was observed in one patient in the 1L group. In this patient, the lesion size decreased by 76.5% (Figure 2) and the DOR was 4.24 months (Figure S1). This patient was confirmed to have PD at 168 days (5.5 months) after starting capmatinib and subsequently died due to the study indication. The best response in the second patient in the 1L group was SD. The PFS in this patient was 131 days (4.3 months).

In the 2/3L group, the best overall response was PR in four patients according to BIRC assessment, resulting in an ORR of 36.4% (95% CI 10.9%-69.2%). SD was achieved in a further five patients, resulting in a DCR of 81.8%. The median TTR and DOR were not evaluable (Table 3). Tumor shrinkage was observed in most patients, with

TABLE 2 Disposition of the overall Japanese cohort and of patients with *MET*Δex14-mutated non–small-cell lung cancer

	Overall Japanese cohort (n = 45)[a]	1L group (n = 2)[b]	2/3L group (n = 11)[c]
Treatment status			
Ongoing	8 (17.8)	0	3 (27.3)
Discontinuation from treatment phase	37 (82.2)	2 (100.0)	8 (72.7)
Entered post-treatment follow-up	15 (33.3)	1 (50.0)	5 (45.5)
Entered survival follow-up	22 (48.9)	1 (50.0)	3 (27.3)
Reason for discontinuation			
PD	28 (62.2)	1 (50.0)	5 (45.5)
Adverse event	8 (17.8)	1 (50.0)	3 (27.3)
Patient request	1 (2.2)	0	0
Post-treatment follow-up phase			
Entered survival follow-up	12 (26.7)	0	4 (36.4)
Discontinued from study	2 (4.4)	1 (50.0)	1 (9.1)
Reason for discontinuation			
PD	12 (26.7)	0	5 (45.5)
Physician decision	2 (4.4)	1 (50.0)	0

Note: Values are n (%) of patients. Data cutoff: April 15, 2019.

Abbreviation: PD, progressive disease.

[a]All patients enrolled in Japan.

[b]Received capmatinib as first-line therapy (cohort 5b).

[c]Received capmatinib as second-/third-line therapy (cohort 4).

a deep response of ~80% in a patient with PR (Figure 2). The DOR was over 10 months in two patients (Figure S1). The median PFS was 4.70 months (Figure 3). One male patient (60 years old) with multiple brain metastases and intracranial disease progression following radiotherapy and one cycle of carboplatin/paclitaxel showed a brain response to capmatinib, with partial resolution of brain lesions at a second post-baseline computed tomography scan taken 12 weeks after starting capmatinib per ad hoc independent neuroradiologist review. This patient was classified as SD, and his PFS was 127 days (4.2 months) (Figure S2).

Responses to treatment among patients with *MET*-amplified NSCLC are summarized by treatment line and GCN in Table S2. In cohort 5a (1L), which comprised two patients with a GCN ≥ 10, the best overall response was PR in both patients, with an ORR of 100.0% (95% CI 15.8-100.0). In the 2/3L groups, the ORRs were 45.5%, 0%, 10%, and 16.7%, and the DCRs were 81.8%, 100.0%, 50.0%, and 66.7%, in cohorts 1a (GCN ≥ 10, n = 11), 1b (GCN ≥ 6 to <10, n = 1), 2 (GCN ≥ 4 to <6, n = 10), and 3 (GCN < 4, n = 6), respectively. The median DOR was 8.2 months in the 1L group (cohort 5a), and 8.3 and 9.7 in the 2/3L groups (cohorts 1a and 2, respectively).

3.4 | Safety

Safety data are reported for all 45 patients who received at least one dose of capmatinib. At the cutoff date of September 18, 2019, all 45 patients had experienced at least one AE (Table 4). One patient died due to NSCLC; no other deaths were reported during the study period. The treatment-related, grade 3/4 serious AEs were acute kidney injury, cellulitis, decreased appetite, hepatic function abnormal, hyponatremia, interstitial lung disease (ILD), liver function test abnormal, malaise, platelet count decreased, and pneumonitis, which occurred in one patient each. Grade 3/4 vomiting, hepatic function abnormal, liver function test abnormal, and ILD led to treatment discontinuation in one patient each (all four patients had *MET*-amplified NSCLC) (Table S3). The most frequent treatment-related AEs and laboratory investigations are listed in Table 5, and most of these common events were of grade 1 or 2. AEs of special interest are summarized in Table S4. The CNS toxicities were vertigo in two (4.4%) patients, and dizziness, dysphonia, seizure, and tremor in one patient each (2.2%). The three patients with ILD and pneumonitis discontinued study treatment in accordance with the study protocol. All episodes of pneumonitis and ILD had recovered. There were no cases of QTc interval prolongation, photosensitivity, or teratogenicity.

A swimmer plot showing the duration of capmatinib and major AEs requiring dose adjustment or interruption in the 13 patients with *MET*Δex14-mutated NSCLC (1L or 2/3L) is presented in Figure 4. As illustrated in this figure, the patients were able to continue capmatinib dosing, with dose interruptions or dose reductions, as necessary, to manage AEs. Of three patients still on treatment (≥76 weeks after starting treatment), the daily doses

TABLE 3 Response to treatment according to the blinded independent review committee in patients with *MET*Δex14-mutated non–small-cell lung cancer

	1L group (n = 2)[a]	2/3L group (n = 11)[b]
Best overall response		
CR	0	0
PR	1 (50.0)	4 (36.4)
SD	1 (50.0)	5 (45.5)
Non-CR/non-PD	0	0
PD	0	1 (9.1)
Unknown	0	1 (9.1)
Overall response rate (CR + PR) [95% CI]	–	4 (36.4) [10.9-69.2]
Disease control rate (CR + PR + SD + non-CR/non-PD) [95% CI]	–	9 (81.8) [48.2-97.7]
Median TTR, months (95% CI)	–	NE (1.38–NE)
Probability estimate at 3 mo for TTR (95% CI)	–	36.4 (15.5-70.3)
Median DOR, months (95% CI)	–	NE (3.35–NE)
KM estimate of DOR rate at 3 mo (95% CI)	–	100.0 (NE–NE)
KM estimate of DOR rate at 12 mo (95% CI)	–	50.0 (5.8-84.5)

Note: Values are n (%) of patients or median (95% CI). Summary statistics are not shown for the 1L group. Data cutoff: April 15, 2019.

Abbreviations: CI, confidence interval; CR, complete response; DOR, duration of response; KM, Kaplan-Meier; mo, months; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease; TTR, time to response.

[a]Received capmatinib as first-line therapy (cohort 5b).

[b]Received capmatinib as second-/third-line therapy (cohort 4).

of capmatinib at their last follow-up were 400, 300, and 200 mg twice daily. Capmatinib was tolerated in Japanese *MET* mutation–positive NSCLC patients without safety concerns specific to Japanese patients.

3.5 | Pharmacokinetics

The PK parameters (steady state) of capmatinib administered in fasting conditions on days 1 and 15 in cycle 1 are shown in Table S5 for Japanese patients. Following 400 mg twice daily, capmatinib exposure accumulated, and the AUC increased from 18 200 ng·h/mL on day 1 to 27 000 ng·h/mL on day 15 ($AUC_{0\text{-}12}$, geometric mean). The accumulation ratio was 1.41 and the maximum concentration on day 15 was 5920 ng/mL, which was reached rapidly by 1 hour after administration.

4 | DISCUSSION

GEOMETRY mono-1 investigated the safety and efficacy of capmatinib in patients with *MET*Δex14-mutated or *MET*-amplified advanced NSCLC and reported promising antitumor activities in these patients, particularly previously untreated patients and patients with a high *MET* GCN.[40] Furthermore, intracranial responses were observed in about half of patients with *MET*Δex14-mutated NSCLC and evaluable brain metastases at baseline.[40]

Here, we describe the results of subgroup analyses of Japanese patients enrolled in GEOMETRY mono-1 according to *MET* status. Among patients with *MET*Δex14-mutated NSCLC, the best overall response was PR in one patient and SD in the other in the 1L group. In the 2/3L group, the ORR was 36.4%. Almost all patients in both groups showed tumor shrinkage, with a deep response of ~80% in one patient in each group. Furthermore, an intracranial response was observed in the patient with brain metastases at enrollment. These findings confirm that capmatinib is effective (including brain) in Japanese patients with *MET*Δex14-mutated advanced NSCLC, and are consistent with the results observed in the overall study population.[40] In Japanese patients with *MET*-amplified NSCLC and a *MET* GCN ≥ 10, the ORR was 45.5% in the 2/3L group and 100.0% in the 1L group. These results are also consistent with those in the overall study population[40] and suggest that patients with *MET*-amplified NSCLC are also candidates for capmatinib therapy.

The results in these Japanese patients are notable considering the majority of patients were ≥ 65 years old with a median of 68 years, similar to the overall study population in which the median age was 71 years in the *MET*Δex14 cohorts and 60-70 years in the *MET*-amplified cohorts.[40] Patients with the *MET*Δex14 mutation are generally older than patients without this mutation[25] and patients with *EGFR*-mutant NSCLC.[22] Older patients may be more difficult to treat for a variety of reasons, including worse functional status, presence of comorbidities, and need for polypharmacy.[42] Because the current Japanese guidelines for NSCLC include "weak recommendations" for carboplatin-based combination therapy or a single cytotoxic agent for patients aged ≥ 75 years, standard platinum-based combination therapy is not necessarily a treatment option for older patients harboring *MET* mutations.[43] Therefore, targeted agents, including MET inhibitors, may be considered instead of conventional systemic multidrug therapies in older patients.[44]

We also evaluated the safety of capmatinib in the full cohort of 45 Japanese patients. Similar to the global population,[40] we found that the most common AEs were blood creatinine increased, nausea, and vomiting, most of which were of grade 1/2. These, and other AEs, including oedema peripheral, pneumonitis, and liver dysfunction, were manageable with dose reductions/interruptions or other additional treatments as deemed necessary. Most of the AEs were predictable, considering the known mechanism of action of capmatinib, including inhibition of creatinine transport, while gastrointestinal toxicities are also known side effects of MET inhibitors.

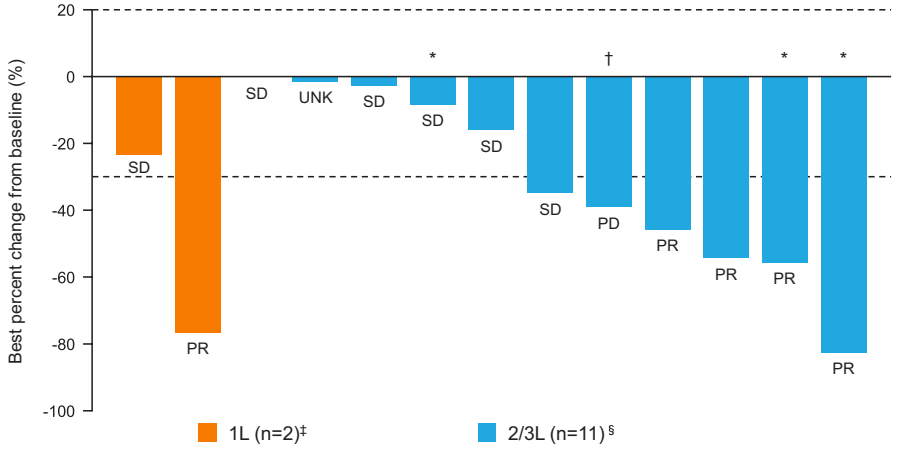
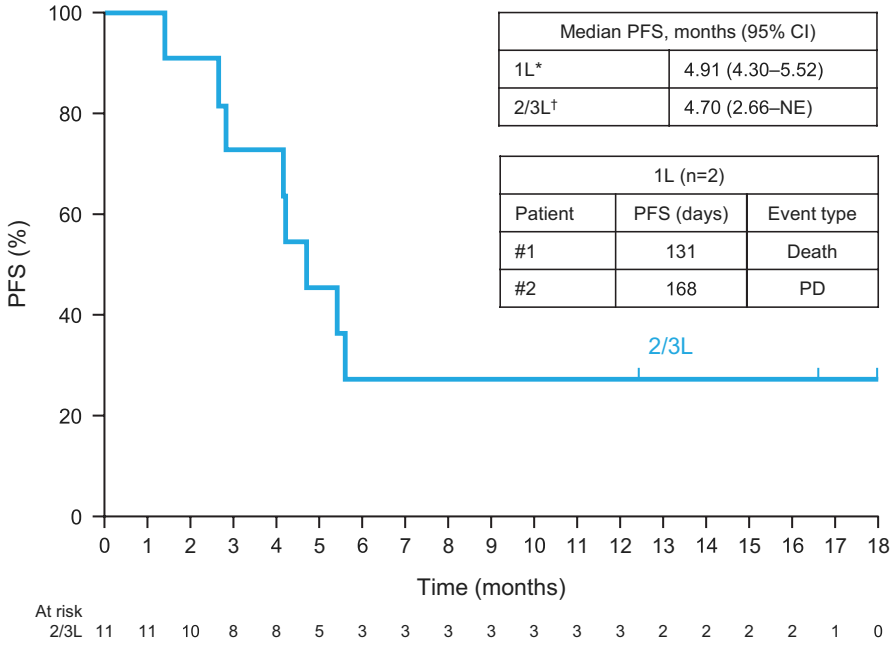


FIGURE 2 Waterfall plot showing the best percent change in lesion size according to best overall response (blinded independent review committee assessment) in patients with *MET*Δex14-mutated non-small-cell lung cancer. Data cutoff: April 15, 2019. *Patients still on treatment. †Percent change in target lesion available, but contradicted by overall lesion response = PD or UNK. ‡Received capmatinib as first-line therapy (cohort 5b). §Received capmatinib as second-/third-line therapy (cohort 4). PD, progressive disease; PR, partial response; SD, stable disease; UNK, unknown

FIGURE 3 Kaplan-Meier plots of progression-free survival (PFS) for the 2/3L group according to blinded independent review committee assessment in patients with *MET*Δex14-mutated non-small-cell lung cancer. The PFS times are reported for both patients in the 1L group. Data cutoff: April 15, 2019. *Received capmatinib as first-line therapy (cohort 5b). †Received capmatinib as second-/third-line therapy (cohort 4). CI, confidence interval; NE, not evaluable



Median PFS, months (95% CI)	
1L*	4.91 (4.30–5.52)
2/3L†	4.70 (2.66–NE)

1L (n=2)		
Patient	PFS (days)	Event type
#1	131	Death
#2	168	PD

Some prior studies have evaluated capmatinib in NSCLC, including in patients with *EGFR*-mutated, *MET*-dysregulated NSCLC[38] and in Japanese patients with advanced solid tumors (including lung cancer in 15/44 patients).[39] The latter study was a Japanese phase 1 study and primarily focused on the maximum tolerated dose and/or highest studied dose of capmatinib determined to be safe as a single agent. Although the maximum tolerated dose was not identified, the highest studied dose to be safe was declared to be 400 mg twice daily in a tablet formulation.

Capmatinib is extensively metabolized by CYP3A4 and aldehyde oxidase. The PK parameters in Japanese patients were similar to those of non-Japanese patients in this study (data not shown). Exposure following 400 mg twice daily showed a moderate accumulation of 1.41-fold, which was close to the overall study result of 1.39-fold, suggesting the effective half-life of capmatinib is 6.54 hours. Furthermore, no obvious PK differences were observed in the Japanese phase 1 study[39] and in an international phase 1 study of patients with c-MET–dependent advanced solid tumors.[45]

Some limitations of this study warrant mention, including the relatively small sample size and nonrandomized design. Therefore, larger studies may be necessary to verify the efficacy and safety of capmatinib in Japanese patients with *MET*Δex14-mutated or *MET*-amplified NSCLC, although this may not be feasible, especially as first-line therapy, owing to the rarity of this mutation. Furthermore, the Japanese 1L groups of patients with *MET*Δex14-mutated or *MET*-amplified NSCLC (ie cohorts 5a and 5b) each comprised two patients. Thus, further studies are needed to confirm the robust efficacy data for capmatinib as first-line therapy. Data from cohorts 6 and 7 will

TABLE 4 Adverse events (AEs) (safety analysis set) in the overall Japanese cohort

	All patients (n = 45)
Any AE	45 (100.0)
Any grade 3/4 AE	33 (73.3)
Any treatment-related AE	44 (97.8)
Any grade 3/4 treatment-related AE	25 (55.6)
Deaths[a]	1 (2.2)
Any serious AE	22 (48.9)
Any grade 3/4 serious AE	18 (40.0)
Any treatment-related serious AE	12 (26.7)
Any treatment-related grade 3/4 serious AE	9 (20.0)
AEs leading to permanent discontinuation	8 (17.8)
Grade 3/4 AEs leading to permanent discontinuation	4 (8.9)
AEs requiring dose adjustment/interruption	30 (66.7)
Grade 3/4 AEs requiring dose adjustment/interruption	22 (48.9)

Note: Values are n (%) of patients. Data cutoff: September 18, 2019.
[a]Considered related to non–small-cell lung cancer, there were no deaths related to serious AEs.

provide further insight into the efficacy and safety of capmatinib in *MET*Δex14-mutated (any GCN) or *MET*-amplified (GCN ≥ 10) NSCLC.

In conclusion, the results of this study suggest that capmatinib is effective and well tolerated as first- or second/third-line therapy in Japanese patients with *MET*Δex14-mutated or *MET*-amplified (GCN ≥ 10) advanced NSCLC. These results in Japanese patients are also consistent with those observed in the overall study population.

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DISCLOSURE

Takashi Seto has received remuneration (≥1 million yen per year) from Precision Medicine Asia (as an employee); lecture fees, honoraria, or other fees (≥500 000 yen per year) from AstraZeneca, Chugai Pharmaceutical, Eli Lilly Japan, MSD, Pfizer Japan, and Taiho Pharmaceutical; and research funds (≥1 million yen per year) from AbbVie, AstraZeneca, Chugai Pharmaceutical, Daiichi Sankyo, Eli Lilly Japan, Kissei Pharmaceutical, LOXO Oncology, MSD, Nippon Boehringer Ingelheim, Novartis Pharma, Pfizer Japan, and Takeda Pharmaceutical. Shunichi Sugawara has received lecture fees, honoraria, or other fees (≥500 000 yen per year) from AstraZeneca, Chugai Pharmaceutical, MSD, Ono Pharmaceutical, Bristol-Myers Squibb, and Nippon Boehringer Ingelheim. Makoto Nishio has received lecture fees, honoraria, or other fees (≥500 000 yen per year) from Ono Pharmaceutical, Bristol-Myers Squibb, Pfizer, Chugai Pharmaceutical, Eli Lilly, Taiho Pharmaceutical, AstraZeneca, Boehringer Ingelheim, MSD, Novartis, Daiichi Sankyo Healthcare, Taiho Pharmaceutical, and Merck Serono; and research funds (≥1 million yen per year) from Novartis Pharma, Ono Pharmaceutical, Chugai Pharmaceutical, Bristol-Myers Squibb, Taiho Pharmaceutical, Eli Lilly, AstraZeneca, Pfizer, and Astellas. Keisuke Aoe has received lecture fees, honoraria, or other fees (≥500 000 yen per year) from Ono Pharmaceutical; and research funds (≥1 million yen per year) from MSD, AstraZeneca, Ono Pharmaceutical, Kissei, Eli Lilly, Novartis Pharma, Pfizer, and Bristol-Myers Squibb. Toyoaki Hida has received lecture fees, honoraria, or other fees (≥500 000 yen per year) from AstraZeneca; and research funds (≥1 million yen per year) from Novartis Pharma, AstraZeneca, Pfizer, Servier, and Janssen. Kadoaki Ohashi has received research funds (≥1 million yen per year)

TABLE 5 Treatment-related adverse events (AEs) in at least three patients in the overall Japanese cohort (safety analysis set, n = 45)

	Any grade	Grade 3/4
Any treatment-related AE	44 (97.8)	25 (55.6)
Nausea	16 (35.6)	0
Oedema peripheral	14 (31.1)	3 (6.7)
Vomiting	12 (26.7)	1 (2.2)
Decreased appetite	10 (22.2)	2 (4.4)
Diarrhoea	8 (17.8)	1 (2.2)
Pyrexia	7 (15.6)	0
Constipation	5 (11.1)	1 (2.2)
Rash	5 (11.1)	0
Fatigue	4 (8.9)	0
Hypoalbuminaemia	4 (8.9)	0
Dry skin	4 (8.9)	0
Anaemia	3 (6.7)	1 (2.2)
Malaise	3 (6.7)	1 (2.2)
Cellulitis	3 (6.7)	1 (2.2)
Headache	3 (6.7)	0
Investigations		
Blood creatinine increased	24 (53.3)	0
Amylase increased	8 (17.8)	2 (4.4)
Platelet count decreased	8 (17.8)	2 (4.4)
Lipase increased	6 (13.3)	3 (6.7)
ALT increased	6 (13.3)	2 (4.4)
AST increased	6 (13.3)	2 (4.4)
Neutrophil count decreased	5 (11.1)	3 (6.7)
WBC count decreased	4 (8.9)	1 (2.2)
Blood ALP increased	4 (8.9)	0
γGT increased	3 (6.7)	1 (2.2)

Note: Values are n (%) of patients.
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; WBC, white blood cell; γGT, γ-glutamyltransferase.

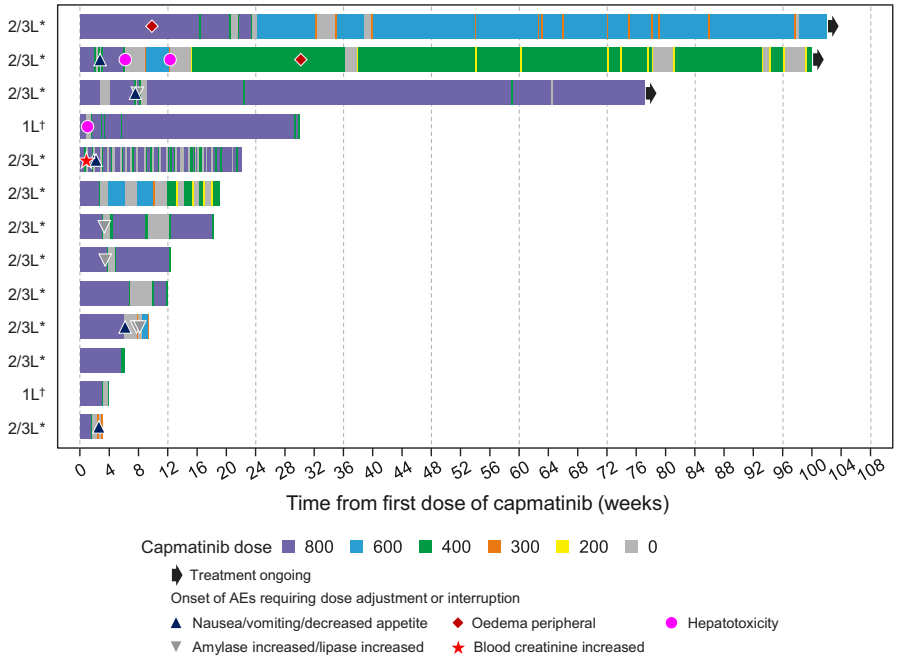

FIGURE 4 Swimmer plot showing duration of capmatinib administration and timing of common adverse events (AEs) according to treatment line in 13 patients with *MET*Δex14-mutated non–small-cell lung cancer. Data cutoff: September 18, 2019. *Received capmatinib as second-/third-line therapy (cohort 4). †Received capmatinib as first-line therapy (cohort 5b)

from Novartis Pharma. Sanae Moizumi, Satoshi Nomura, and Takeshi Tajima are employees of Novartis Pharma (remuneration of ≥ 1 million yen per year).

DATA AVAILABILITY STATEMENT

Novartis is committed to sharing with qualified external researchers access to patient-level data and supporting clinical documents from eligible studies. These requests are reviewed and approved by an independent review panel on the basis of scientific merit. All data provided is anonymized to respect the privacy of patients who have participated in the trial in line with applicable laws and regulations. This trial data availability is according to the criteria and process described on www.clinicalstudydatarequest.com.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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