Capmatinib in MET exon 14-mutated non-small-cell lung cancer: final results from the open-label, phase 2 GEOMETRY mono-1 trial

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Capmatinib in *MET* exon 14-mutated non-small-cell lung cancer: final results from the open-label, phase 2 GEOMETRY mono-1 trial

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Summary

Background Capmatinib has previously shown activity in treatment-naive and previously treated patients with non-small-cell lung cancer (NSCLC) and a *MET* exon 14-skipping mutation (*MET*ex14). Here, we report the final outcomes from the phase 2 GEOMETRY mono-1 study with an aim to provide further evidence for the activity of capmatinib.

Methods In this non-randomised, multi-cohort, open-label, phase 2 trial conducted in 152 centres and hospitals in 25 countries, with patients treated in 95 centres in 20 countries, eligible patients (aged ≥18 years) with *MET*-dysregulated, EGFR wild-type, and ALK rearrangement-negative advanced NSCLC (stage IIIB/IV) and an Eastern Cooperative Oncology Group performance status of 0 or 1 were assigned to cohorts (1a, 1b, 2, 3, 4, 5a, 5b, 6 and 7) based on their *MET* status (*MET*ex14 or *MET* amplification) and previous therapy lines. Patients received capmatinib (400 mg orally twice daily) in 21-day treatment cycles. The primary endpoint was overall response rate by blinded independent central review per Response Evaluation Criteria in Solid Tumours version 1.1 and was performed on the full analysis set (all patients who received at least one dose of capmatinib). Previous reports of this study had published interim or primary data for cohorts 1–7. Here, we report the final clinical outcomes from all *MET*ex14 cohorts (4, 5b, 6, and 7) and safety from all study cohorts (1–7). The trial is registered with ClinicalTrials.gov, NCT02414139, and has been completed.

Findings Of 373 treated patients enrolled from June 11, 2015, to March 12, 2020, 160 (97 [61%] female) patients had *MET*ex14 NSCLC and were enrolled in four cohorts: 60 treatment-naive (cohorts 5b and 7) and 100 previously treated (cohorts 4 and 6). The overall median study follow-up was 46·4 months (IQR 41·8–65·4) for the treatment-naïve patients and 66·9 months (56·7–73·9) for previously treated patients, respectively. Overall responses were recorded in 41 (68%; 95% CI 55·0–79·7) of 60 treatment-naive patients and 44 (44%; 95% CI 34·1–54·3) of 100 previously treated patients. In all 373 treated patients, the most common treatment-related adverse events were peripheral oedema (n=174; 47%), nausea (n=130; 35%), increased blood creatinine (n=78; 21%), and vomiting (n=74; 20%). Grade 3–4 serious adverse events occurred in 164 (44%) patients, dyspnoea being the most common (18 patients [5%]). Treatment-related deaths occurred in four (1%) patients (one each of cardiac arrest, hepatitis, organising pneumonia, and pneumonitis). No new safety signals were reported.

Interpretation These long-term results support *MET*ex14 as a targetable oncogenic driver in NSCLC and add to the evidence supporting capmatinib as a targeted treatment option for treatment-naive and previously treated patients with *MET*ex14 NSCLC.

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Introduction

Genomic alterations resulting in *MET* exon 14-skipping mutation (*MET*ex14), *MET* gene amplifications, or protein overexpression lead to oncogenic activation of MET-mediated signalling.[1] Mutations within this pathway confer a poor prognosis for patients with non-small-cell lung cancer (NSCLC).[1,2] *MET*ex14 occurs in approximately 3–4% of patients with NSCLC and can be due to point mutations, insertions, or deletions, resulting in a spliced version of the MET receptor with higher stability and increased MET signalling.[2,3] *MET*ex14 can be detected using different methods, such as reverse transcription–polymerase chain reaction (RT-PCR) and next-generation sequencing using tissue-based or blood-based samples.[2] *MET* amplification, found in approximately 1–6% of patients diagnosed with NSCLC, can occur through polysomy and regional or focal amplification and can be detected through fluorescence in-situ hybridisation or next-generation sequencing.[4,5]

Capmatinib is an oral, highly potent, and selective MET inhibitor that can effectively inhibit in-vitro and in-vivo activity in various types of MET activation.[5] The clinical safety and activity of capmatinib were assessed

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Research in context

Evidence before this study

MET exon 14-skipping mutation (*MET*ex14) occurs in approximately 3–4% of patients with non-small-cell lung cancer (NSCLC). We searched PubMed from Jan 1, 2018, to Jun 30, 2024, with no restrictions on language, using the terms "MET inhibitor AND non-small-cell lung cancer" OR "METex14 AND non-small-cell lung cancer" OR "MET exon14 skipping AND non-small-cell lung cancer". We identified several MET inhibitors for which phase 2 data were available: capmatinib, tepotinib, savolitinib, vebreltinib, glumarontinib, and crizotinib. Overall, the results from some of these phase 2 studies and recent approvals of selective MET tyrosine kinase inhibitors, including capmatinib, have shown them to be highly effective with manageable safety profiles for patients with *MET*ex14 NSCLC. Additionally, the tissue-based FoundationOneCDx (F1CDx) and the FoundationOne Liquid CDx (F1LCDx) have been approved based on capmatinib data as companion diagnostic tests for the selection of patients with *MET*ex14 NSCLC in the USA and Japan. Considering the complexity of *MET*ex14 alterations and the sizeable evidence of acquired or emerging resistance to MET tyrosine kinase inhibitors, further investigations are warranted to better understand the genomic landscape and mechanisms underlying resistance to tyrosine kinase inhibitor therapy, as well as to explore prognostic and predictive biomarkers of treatment response or resistance to capmatinib.

Added value of this study

This current report of the final study data builds on and supports the clinically meaningful and highly effective outcomes of capmatinib treatment in treatment-naive and previously treated patients with *MET*ex14 NSCLC that is particularly pronounced in the first-line setting. Additionally, in a post-hoc analysis, intracranial lesion shrinkage with capmatinib was reported in patients with brain metastases with or without previous brain radiotherapy. Safety outcomes were consistent with those previously reported and comparable between previously treated and treatment-naive patients with *MET*ex14 NSCLC. Importantly, this study reports good concordance in the detection of *MET*ex14 between the tumour tissue-based RT-PCR clinical trial assay and the plasma-based F1LCDx (next-generation sequencing). Capmatinib clinical activity was similar in patients identified with *MET*ex14-positive NSCLC by F1LCDx and those identified by the clinical trial assay, supporting a broader adoption of liquid biopsy testing for identifying patients harbouring *MET*ex14 NSCLC. Exploratory biomarker analyses and correlation with clinical outcomes are also reported, providing further insights in the possible mechanism of intrinsic and acquired resistance in patients with *MET*ex14 NSCLC treated with capmatinib.

Implications of all the available evidence

Capmatinib continued to show substantial anti-tumour activity regardless of the treatment setting, supported by the durability of the observed responses and prolonged survival in patients with *MET*ex14 NSCLC. These patients are relatively elderly (compared with populations with other molecular drivers or lack of these drivers), frequently present with comorbidities and frailties in the context of their metastatic lung cancer and can be ineligible for or can have poor prognosis on standard therapies, including immunotherapies. This finding has considerable clinical relevance, as chemotherapy-based standard regimens might be less tolerable, and an effective oral targeted therapy offers a favourable treatment alternative with sustained quality of life. Capmatinib was found to be a safe treatment for patients with *MET*ex14 NSCLC, with notable clinical benefit particularly in treatment-naive setting, thus warranting its consideration as first-line therapy for this patient population. Comprehensive molecular profiling using next-generation sequencing in NSCLC is essential for identifying patients who might benefit from targeted therapy, as well as to the understanding of intrinsic or acquired mechanism of resistance as evidence for potential development of combination therapies. This study demonstrated an accurate and reliable detection of *MET*ex14 using blood plasma samples, further validating F1LCDx use as a companion diagnostic for capmatinib.

in the GEOMETRY mono-1 phase 2 study, which comprised of seven separate cohorts of patients with advanced NSCLC with either *MET*ex14 or *MET* amplification. In the GEOMETRY mono-1 study, the detection of *MET*ex14 for patient eligibility was determined using the RT-PCR-based clinical trial assay from tumour tissue biopsies, and was retrospectively confirmed using the next-generation sequencing-based FoundationOne CDx (F1CDx; Foundation Medicine, Cambridge, MA, USA)[5] and FoundationOne Liquid CDx (F1LCDx; Foundation Medicine), both approved as companion diagnostic tests for capmatinib in the USA and Japan.[6] Capmatinib has demonstrated clinically meaningful benefit in treatment-naive and previously treated patients with *MET*ex14 and advanced NSCLC. In patients with *MET* amplification and advanced NSCLC, capmatinib demonstrated modest activity primarily in cohort 1a (the cohort with the highest MET gene copy number ≥10); however, the overall response rate did not meet the prespecified threshold for significance.[5]

In this Article, we report the final results from 160 patients with *MET*ex14 NSCLC (treatment-naive patients in cohorts 5b and 7, and previously treated patients in cohorts 4 and 6) and safety outcomes from all 373 patients treated with capmatinib in the GEOMETRY mono-1 study. Additionally, clinical outcomes in patients who were retrospectively identified as having *MET*ex14 using the F1LCDx test are reported, along with exploratory biomarker analyses of patients with *MET*ex14 and in patients with *MET* amplification in correlation with their clinical outcome.

Methods

Study design and participants

This multicentre, open-label, non-randomised, multicohort, phase 2, GEOMETRY mono-1 study evaluated capmatinib in patients with advanced NSCLC with *MET*ex14 or *MET* amplification. The trial is registered with ClinicalTrials.gov, NCT02414139.The study was conducted in 152 centres and hospitals in 25 countries with patients treated in 95 centres and hospitals in 20 countries (the remaining sites are those with only patients who were prescreened or who were ineligble; appendix pp 43–50). Eligible patients were aged 18 years or older with advanced or metastatic (stage IIIB/IV), dysregulated *MET*, *EGFR* wild-type, and *ALK* rearrangement-negative NSCLC; an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1; at least one measurable lesion according to the Response Evaluation Criteria in Solid Tumours (RECIST), version 1.1, and included first-line and second-line or third-line patients. Patients with asymptomatic or neurologically stable brain metastasis were also allowed (full details are in the protocol). Cohorts (1a, 1b, 2, 3, 4, 5a, 5b, 6, and 7) were categorised based on their prior treatment and MET status (*MET* amplification and/or *MET* mutation). In our previous publications,[5,7] interim efficacy analyses led to the early closure of cohorts 1b, 2, and 3 (previously treated *MET*-amplified cohorts with gene copy number <10) due to futility. Primary efficacy analyses showed some activity in cohorts 1a and 5a (*MET*-amplified cohorts with gene copy number ≥10), but the primary objective was not met. The primary analysis of the *MET*ex14 cohorts (4, 5b, 6, and 7) has also been published previously.[5,7] The final analysis in this study included both first-line and second-line or third-line patients with *MET*ex14 NSCLC (cohorts 4, 5b, 6, and 7). The safety analysis included all patients (cohorts 1–7) treated with capmatinib. The flowchart of the study design is shown in the appendix (pp 9–10). The full clinical trial methodology has been previously published.[5] The final clinical data presented in this manuscript are as of May 16, 2023 (last patient last visit). Both the study protocol and statistical analysis plan can be accessed online.

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and the Good Clinical Practice guidelines of the International Council for Harmonisation. The initial study protocol and all subsequent amendments were reviewed and approved by the independent ethics committee or institutional review board for each centre. All patients provided written informed consent.

Procedures

Capmatinib (Novartis Pharma, Basel, Switzerland) was administered orally at the starting dose of 400 mg twice daily continuously in 21-day treatment cycles. A maximum of two dose reductions (to 300 mg twice daily, then 200 mg twice daily) were allowed. Treatment continued until patients had progressive disease as determined by the investigator and confirmed by blinded independent review committee; had unacceptable toxicity, per investigator or patient discretion; were lost to follow-up; or died. Treatment beyond progression was allowed for patients with ongoing clinical benefit according to investigator judgment.

Tumours were assessed per RECIST version 1.1 based on radiographical imaging done every 6 weeks (every two cycles). Data on gender and race or ethnicity was collected on the case report forms as allowed per local regulations.

All adverse events reported were graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.03. Safety was monitored at baseline, at every subsequent visit, or as clinically indicated.

See Online for appendix

Circulating tumour DNA (ctDNA) isolated from baseline blood plasma samples was analysed using the F1LCDx assay (Foundation Medicine, Cambridge, MA, USA), a 324-gene hybrid capture next-generation sequencing assay covering exonic regions and select intronic regions.

Blood plasma samples collected at disease progression, along with a subset of baseline blood plasma samples, were analysed using either the cell-free DNA (cfDNA) 1.0 or cfDNA 2.1 PanCancer assays (Novartis BioMedical Research; Foundation Medicine). The gene panels used with these assays contain either 566 or 579 cancer-relevant genes, respectively. The presence of genetic variants at baseline was evaluated using baseline samples sequenced with F1LCDx and fresh or archival tissue samples sequenced using F1CDx.[5] *MET* amplification presence and focality were determined through next-generation sequencing, using cfDNA isolated from patients enrolled in GEOMETRY mono-1 cohorts (cohorts 1a, 1b, 2, and 3).[5,8] Detailed information regarding the methods used for the additional biomarker analyses can be found in the appendix (pp 3–6).

Outcomes

The primary and secondary endpoints of the study have been detailed in the previous GEOMETRY mono-1 publication.[5] Briefly, the primary and key secondary endpoints were overall response rate and duration of response, respectively, as assessed by blinded independent review committee using RECIST version 1.1. Objective response rate was defined as the proportion of patients with a complete response or partial response. Duration of response was calculated as the time from the date of the first documented complete response or partial response per RECIST version 1.1 to the first documented progression or death due to any cause in patients with partial response or complete response. Other secondary endpoints were overall response rate and duration of response assessed by investigator; disease control rate (defined as a best overall response of complete response, partial response, or stable disease according to RECIST version 1.1), progression-free survival (defined as the time from the date of first dose of capmatinib to the date of the

For the **study protocol** see https://cdn.clinicaltrials.gov/large-docs/39/NCT02414139/Prot_000.pdf

For the **statistical analysis plan** see https://cdn.clinicaltrials.gov/large-docs/39/NCT02414139/SAP_001.pdf

first radiologically documented disease progression per RECIST 1.1 or death due to any cause), and time to response (defined as the time from start of study drug to first documented response for patients who had achieved a confirmed partial response or complete response) assessed by both blinded independent review committee and investigator per RECIST version 1.1; overall survival (defined as the time from the start date of study drug treatment to the date of death due to any cause); safety; and pharmacokinetics. The present analyses report the final outcome results from patients with *MET*ex14 NSCLC (cohorts 4, 5b, 6, and 7) and final cumulative safety data from all treated patients in the study.

As part of the prespecified exploratory endpoints, biomarker analyses were performed in patients with *MET*ex14 NSCLC to assess baseline genomic alterations in previously treated and treatment-naive patients and emerging mutations as potential mechanisms of acquired resistance. Response to capmatinib treatment was also analysed according to the expression of *MET* and *MET*-related or immune-related gene signatures and the clinical response to capmatinib, *PD-L1* gene expression in tumour tissue, and whether the presence of a *MET*ex14 was detected by F1LCDx or clinical trial assay. Full details on prespecified exploratory endpoints are in the appendix (pp 3–6).

	Treatment-naive patients with *MET*ex14 NSCLC			Previously treated patients with *MET*ex14 NSCLC			All patients with *MET*ex14 NSCLC
	Cohort 5b in the first-line setting (n=28)	Cohort 7 in the first-line setting (n=32)	All patients in the first-line setting (n=60)	Cohort 4 in the second-line or third-line setting (n=69)	Cohort 6 in the second-line setting (n=31)	All patients in the second-line or third-line setting (n=100)	All patients (n=160)
Age, years	72·4 (7·0)	73·3 (8·4)	72·9 (7·7)	71·0 (8·3)	69·0 (6·3)	70·4 (7·8)	71·3 (7·8)
Age category, years							
<65	3 (11%)	3 (9%)	6 (10%)	14 (20%)	4 (13%)	18 (18%)	24 (15%)
≥65 to <75	14 (50%)	15 (47%)	29 (48%)	31 (45%)	22 (71%)	53 (53%)	82 (51%)
≥75 to <85	10 (36%)	12 (38%)	22 (37%)	20 (29%)	5 (16%)	25 (25%)	47 (29%)
≥85	1 (4%)	2 (6%)	3 (5%)	4 (6%)	0	4 (4%)	7 (4%)
Sex							
Male	10 (36%)	9 (28%)	19 (32%)	29 (42%)	15 (48%)	44 (44%)	63 (39%)
Female	18 (64%)	23 (72%)	41 (68%)	40 (58%)	16 (52%)	56 (56%)	97 (61%)
Race							
Caucasian	24 (86%)	26 (81%)	50 (83%)	49 (71%)	24 (77%)	73 (73%)	123 (77%)
Asian	4 (14%)	3 (9%)	7 (12%)	19 (28%)	5 (16%)	24 (24%)	31 (19%)
Other*	0	3 (9%)	3 (5%)	1 (1%)	2 (6%)	3 (3%)	6 (4%)
ECOG performance status							
0	7 (25%)	7 (22%)	14 (23%)	16 (23%)	10 (32%)	26 (26%)	40 (25%)
≥1	21 (75%)	25 (78%)	46 (77%)	53 (77%)	21 (68%)	74 (74%)	120 (75%)
Smoking history							
Never smoked	18 (64%)	20 (63%)	38 (63%)	40 (58%)	19 (61%)	59 (59%)	97 (61%)
Former smoker	9 (32%)	11 (34%)	20 (33%)	27 (39%)	10 (32%)	37 (37%)	57 (36%)
Current smoker	1 (4%)	1 (3%)	2 (3%)	2 (3%)	2 (7%)	4 (4%)	6 (4%)
Histology							
Adenocarcinoma	25 (89%)	29 (91%)	54 (90%)	53 (77%)	25 (81%)	78 (78%)	132 (83%)
Squamous cell carcinoma	2 (7%)	1 (3%)	3 (5%)	6 (9%)	4 (13%)	10 (10%)	13 (8%)
Other†	1 (4%)	2 (6%)	3 (5%)	10 (14%)	2 (6%)	12 (12%)	15 (9%)
Patients with brain metastases	3 (11%)	6 (19%)	9 (15%)	10 (14%)	7 (23%)	17 (17%)	26 (16%)
Number of metastatic sites							
0	0	0	0	1 (1%)	0	1 (1%)	1 (1%)
1	3 (11%)	7 (22%)	10 (17%)	5 (7%)	1 (3%)	6 (6%)	16 (10%)
2	11 (39%)	6 (19%)	17 (28%)	10 (14%)	9 (29%)	19 (19%)	36 (23%)
3	3 (11%)	7 (22%)	10 (17%)	14 (20%)	7 (23%)	21 (21%)	31 (19%)
>3	11 (39%)	12 (38%)	23 (38%)	39 (57%)	14 (45%)	53 (53%)	76 (48%)
Lesion diameter at baseline by BIRC, mm	78·9 (42·46)	94·8 (47·16)	87·5 (45·41)	77·6 (48·03)	70·1 (44·43)	75·3 (46·88)	79·9 (46·56)

Data are mean (SD) or n (%). BIRC=blinded independent review committee. ECOG=Eastern Cooperative Oncology Group. *MET*ex14=*MET* exon 14-skipping mutation. NSCLC=non-small-cell lung cancer. *Includes Native American, Black, and other or unknown populations among other patient populations. †Other histology types included undifferentiated carcinoma, carcinosarcoma, large-cell carcinoma, and adenosquamous cell carcinoma among others.

Table 1: **Baseline characteristics of patients with *MET*ex14 NSCLC**

Statistical analysis

Each cohort was analysed separately for the primary analysis using the full analysis set (all patients who had received at least one dose of capmatinib). For previously treated patients (cohort 4), capmatinib was considered to have clinically relevant activity if an overall response rate of 35% or more (assessed by blinded independent review committee) was observed, with a lower boundary of the 95% CI exceeding 25%. For treatment-naive patients (cohorts 5b and 7), capmatinib was considered to have a clinically relevant activity if an overall response rate of 55% or more (assessed by blinded independent review committee) was observed with a lower boundary of the 95% CI exceeding 35%. Cohort 6 was intended to provide supportive analyses of capmatinib activity and safety in patients with either *MET*ex14 or *MET* amplification (≥10 gene copy number) who had received one previous therapy; therefore, no hypothesis was planned for this cohort. As each cohort was independent, no multiplicity adjustment was made. Patients with an unknown best overall response according to RECIST version 1.1, or with no assessment of data by blinded independent review committee, were considered non-responders. Categorical variables are presented as n (%) and continuous variables are presented as median (IQR) or mean (SD). Binomial proportions (response endpoints) are reported with an exact 95% CI calculated with the Clopper–Pearson method. For time-to-event analyses, estimated median (in months) with 95% CIs are reported using Brookmeyer and Crowley method. Patients were censored if they continued without an event, were lost to follow-up, withdrew consent, or had two or more missing or adequate tumour assessments no longer available (as relevant). Censoring was non-informative. Safety analyses were reported for all patients (cohorts 1–7) who had received at least one dose of capmatinib. Statistical analyses were done using SAS version 9.4. The statistical analysis of exploratory biomarker analyses can be found in the appendix (pp 5–6). A post-hoc retrospective medical review of the intracranial activity of capmatinib in patients with brain metastases at baseline is also presented (as of last patient last visit).

Role of the funding source

The funder of the study had a role in study design, data collection, data analysis, data interpretation, and writing of the report.

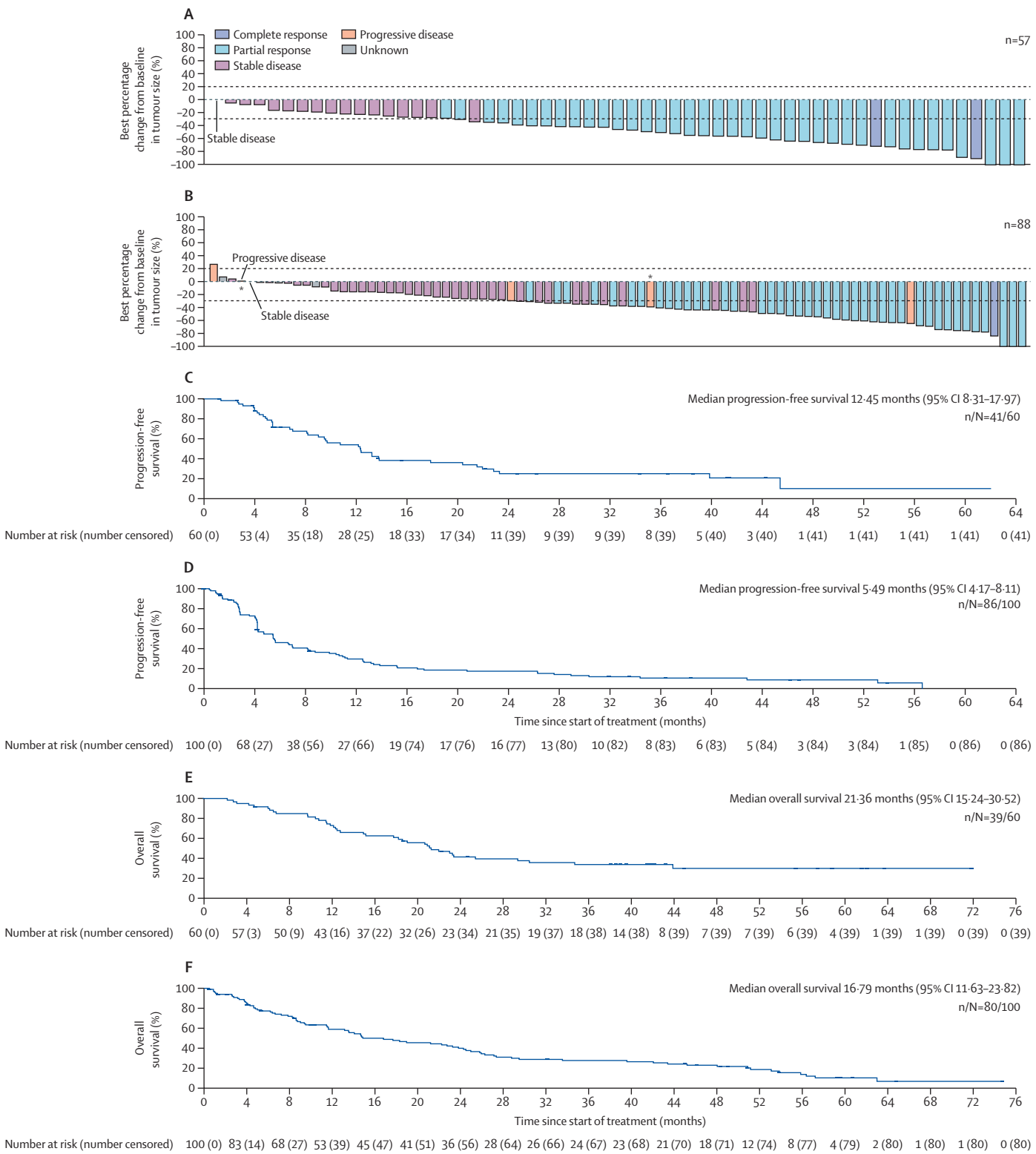
Results

Between June 11, 2015, and March 12, 2020, overall, 474 patients gave informed consent for participation in the

	Treatment-naive patients with *MET*ex14 NSCLC			Previously treated patients with *MET*ex14 NSCLC		
	Cohort 5b in the first-line setting (n=28)	Cohort 7 in the first-line setting (n=32)	All patients in the first-line setting (n=60)	Cohort 4 in the second-line or third-line setting (n=69)	Cohort 6 in the second-line setting (n=31)	All patients in the second-line or third-line setting (n=100)
Best overall response						
Complete response	2 (7%)	1 (3%)	3 (5%)	1 (1%)	0	1 (1%)
Partial response	17 (61%)	21 (66%)	38 (63%)	27 (39%)	16 (52%)	43 (43%)
Stable disease	7 (25%)	10 (31%)	17 (28%)	25 (36%)	11 (35%)	36 (36%)
Non-complete response or non-progressive disease	1 (4%)	0	1 (2%)	1 (1%)	1 (3%)	2 (2%)
Progressive disease	1 (4%)	0	1 (2%)	6 (9%)	0	6 (6%)
Not evaluable*	0	0	0	9 (13%)	3 (10%)	12 (12%)
Overall response rate (complete response + partial response)	19 (68%; 47·6–84·1)	22 (69%; 50·0–83·9)	41 (68%; 55·0–79·7)	28 (41%; 28·9–53·1)	16 (52%; 33·1–69·8)	44 (44%; 34·1–54·3)
Disease control rate (complete response + partial response + stable disease + non-complete response or non-progressive disease)	27 (96%; 81·7–99·9)	32 (100%; 89·1–100·0)	59 (98%; 91·1–100·0)	54 (78%; 66·7–87·3)	28 (90%; 74·2–98·0)	82 (82%; 73·1–89·0)
Duration of response						
Number of events	14/19 (74%)	13/22 (59%)	27/41 (66%)	25/28 (89%)	12/16 (75%)	37/44 (84%)
Median duration of response (95% CI), months	12·6 (5·6–38·7)	16·6 (8·3–NE)	16·6 (8·4–22·1)	9·7 (5·6–13·0)	9·1 (4·2–27·6)	9·7 (5·6–13·0)
Progression-free survival						
Number of events	20 (71%)	21 (66%)	41 (68%)	62 (90%)	24 (77%)	86 (86%)
Median progression-free survival (95% CI), months	12·4 (8·2–23·4)	12·5 (6·9–22·1)	12·5 (8·3–18·0)	5·4 (4·2–7·0)	6·9 (4·2–13·3)	5·5 (4·2–8·1)
Overall survival						
Number of events	18 (64%)	21 (66%)	39 (65%)	58 (84%)	22 (71%)	80 (80%)
Median overall survival (95% CI), months	20·8 (12·4–43·9)	21·4 (12·9–34·8)	21·4 (15·2–30·5)	13·6 (8·6–22·2)	26·0 (13·5–43·4)	16·8 (11·6–23·8)

Data are n (%), n (%; 95% CI), or n/N (%) unless otherwise stated. Values have been rounded off to one decimal digit. BIRC=blinded independent review committee. *MET*ex14=*MET* exon14-skipping mutation. NE=not estimable. NSCLC=non-small-cell lung cancer. *Unknown as per Response Evaluation Criteria in Solid Tumours version 1.1 (ie, not qualified for confirmed complete response or partial response and without stable disease after >6 weeks or progression within the first 12 weeks).

Table 2: **Key outcomes in patients with *MET*ex14 NSCLC per BIRC assessment**


A
Complete response
Partial response
Stable disease
Progressive disease
Unknown
n=57
Best percentage change from baseline in tumour size (%)
Stable disease
B
n=88
Progressive disease
Stable disease
C
Median progression-free survival 12·45 months (95% CI 8·31–17·97)
n/N=41/60
Progression-free survival (%)
Number at risk (number censored) 60 (0) 53 (4) 35 (18) 28 (25) 18 (33) 17 (34) 11 (39) 9 (39) 9 (39) 8 (39) 5 (40) 3 (40) 1 (41) 1 (41) 1 (41) 1 (41) 0 (41)
D
Median progression-free survival 5·49 months (95% CI 4·17–8·11)
n/N=86/100
Progression-free survival (%)
Time since start of treatment (months)
Number at risk (number censored) 100 (0) 68 (27) 38 (56) 27 (66) 19 (74) 17 (76) 16 (77) 13 (80) 10 (82) 8 (83) 6 (83) 5 (84) 3 (84) 3 (84) 1 (85) 0 (86) 0 (86)
E
Median overall survival 21·36 months (95% CI 15·24–30·52)
n/N=39/60
Overall survival (%)
Number at risk (number censored) 60 (0) 57 (3) 50 (9) 43 (16) 37 (22) 32 (26) 23 (34) 21 (35) 19 (37) 18 (38) 14 (38) 8 (39) 7 (39) 7 (39) 6 (39) 4 (39) 1 (39) 1 (39) 0 (39) 0 (39)
F
Median overall survival 16·79 months (95% CI 11·63–23·82)
n/N=80/100
Overall survival (%)
Time since start of treatment (months)
Number at risk (number censored) 100 (0) 83 (14) 68 (27) 53 (39) 45 (47) 41 (51) 36 (56) 28 (64) 26 (66) 24 (67) 23 (68) 21 (70) 18 (71) 12 (74) 8 (77) 4 (79) 2 (80) 1 (80) 1 (80) 0 (80)

main study. Of these, 373 patients (79%) received at least one dose of study treatment. Of the 373 treated patients, 160 patients had *MET*ex14 NSCLC (60 patients in the first-line setting and 100 patients in the second-line or third-line setting) and were recruited into four cohorts (cohorts 4, 5b, 6, and 7; appendix pp 9–10). Baseline characteristics of these patients are shown in table 1. Across all *MET*ex14 cohorts, mean age was 71·3 years (SD 7·8), 97 (61%) of 160 patients were female, and 136 (85%) of 160 patients were aged 65 years or older. No history of smoking was reported in 97 (61%) of the 160 patients. All patients have either discontinued study treatment, or have moved to receive capmatinib via alternative method of post-study drug supply as of May 16, 2023 (last patient last visit). The study is now closed. Progressive disease was the most common cause of treatment discontinuation (30 [50%] of 60 patients in the first-line setting and 63 [63%] of 100 patients in the second-line or third-line setting), followed by adverse events (14 [23%] of 60 patients in first-line setting and 20 [20%] of 100 patients in the second-line or third-line setting; appendix p 25). A list of subsequent anti-neoplastic therapies after study drug discontinuation is provided in the appendix (pp 41–42).

For the treatment-naive patients with *MET*ex14, the median study follow-up was 46·4 months (IQR 41·8–65·4) overall, and was 65·8 months (62·9–70·2) and 41·8 months (39·7–43·8) for cohorts 5b and 7, respectively. Cohort 7 enrolment started only after the recruitment completion in cohort 5b. For the previously treated patients with *MET*ex14, the median treatment follow-up was 66·9 months (IQR 56·7–73·9) overall, and was 71·5 months (66·9–76·1) and 51·4 months (49·4–56·4) for cohorts 4 and 6, respectively. Cohort 6 enrolment started only after the recruitment completion in cohort 4 (and in cohort 1a).

In the 60 treatment-naive patients with *MET*ex14 NSCLC, the overall response rate by blinded independent review committee was 68% (41 patients; 95% CI 55·0–79·7), with a complete response in three patients and a partial response in 38 patients. In the 100 previously treated patients, the overall response rate was 44% (44 patients; 95% CI 34·1–54·3), with a complete response in one patient and a partial response in 43 patients. Objective response rate was higher in patients in the second-line setting (cohort 6) compared with that in patients in the second-line or third-line setting (cohort 4; table 2).

Median follow-up time for duration of response was 11·1 months (IQR 5·6–23·5) for cohort 5b, 11·1 months (5·5–32·5) for cohort 7, 9·7 months (4·2–17·3) for cohort 4, and 9·1 months (4·9–27·2) for cohort 6. The observed responses were durable in both treatment-naive patients and pretreated patients (table 2). Most responses per blinded independent review committee assessment occurred early within 2 months of initiating treatment, regardless of treatment lines (data not shown).

Most treatment-naive (cohorts 5b and 7) and previously treated (cohorts 4 and 6) patients had tumour shrinkage in response to capmatinib treatment (figure 1A, B). In treatment-naive patients, median progression-free survival and median overall survival for cohort 7 were consistent with those for cohort 5b (table 2; figure 1). In previously treated patients, the median progression-free survival in patients in the second-line setting (cohort 6) was comparable to that in patients in the second-line and third-line setting in cohort 4; however, median overall survival was prolonged in cohort 6 compared with that in cohort 4 (table 2).

The results by investigator assessment broadly aligned with the assessments made by blinded independent review committee (appendix p 26).

A post-hoc medical review evaluating the intracranial shrinkage of brain lesions in patients with *MET*ex14 NSCLC and brain metastases at baseline was done using blinded independent review committee neuroradiological assessments. Among the 160 patients with *MET*ex14 NSCLC, 16 (57%) of 28 evaluable patients (including 13 who received previous intracranial radiotherapy and 15 who did not) had intracranial complete responses or partial responses (including nine complete responses: eight in the second-line or third-line setting and one in the first-line setting). The duration of overall intracranial complete response was maintained for more than 6 months in five patients and was less than 6 months in the other four patients with complete response. In patients with no previous intracranial radiotherapy, ten (67%) of 15 evaluable patients showed intracranial complete responses or partial responses (including five complete responses: all in the second-line or third-line setting). The duration of overall intracranial complete response was maintained for more than 6 months in two patients and was less than 6 months in the other three responders.

Median duration of exposure to capmatinib was 34·9 weeks (IQR 13·0–80·6) in all patients with *MET*ex14 NSCLC, and in all patients the median duration of exposure was 17·9 weeks (7·0–45·1). Adverse events were reported in 367 (98%) of 373 patients across all cohorts, including patients with *MET*ex14 and *MET* amplification. Grade 3–4 adverse events were reported in 263 (71%) patients (tables 3, 4). Treatment-related adverse events were reported in 324 (87%) patients.

Figure 1: **Activity outcomes for treatment-naive patients and previously treated patients with *MET*ex14 NSCLC**

Tumour shrinkage for treatment-naive patients in first-line cohorts 5b and 7 (A) and previously treated patients in second-line or third-line cohorts 4 and 6 (B). Dashed line at 20% corresponds to a change indicating progressive disease; the dashed line at −30% corresponds to a change indicating a partial response. Kaplan–Meier estimates of progression-free survival per BIRC assessment in first-line cohorts 5b and 7 (C) and in previously treated patients in second-line or third-line cohorts 4 and 6 (D). Kaplan–Meier estimates of overall survival in first-line cohorts 5b and 7 (E) and in previously treated patients in second-line or third-line cohorts 4 and 6 (F). Dots on graphs C–F represents censoring times. *Percentage change in target lesion available but contradicted by overall lesion response=progressive disease or unknown. A post-baseline assessment with unknown response for target lesion or unknown overall lesion response was considered invalid, so one patient with complete response was not displayed on the figure. BIRC=blinded independent review committee. *MET*ex14=*MET* exon 14-skipping mutation. NSCLC=non-small-cell lung cancer.

Treatment-related grade 3–4 adverse events were reported in 153 (41%) patients. Fatal serious adverse events occurred in 12 (3%) patients, of which four (1%) were treatment-related fatal serious adverse events. Adverse events irrespective of study drug effects that led to treatment discontinuation occurred in 68 (18%) patients, and 46 (12%) patients discontinued treatment due to treatment-related adverse events. Overall, the most common treatment-related adverse events were peripheral oedema (n=174; 47%), nausea (n=130; 35%), increased blood creatinine (n=78; 21%), and vomiting (n=74; 20%; further details are provided in the appendix [p 27]). Serious adverse events of any grade occurred in 202 (54%) patients, and 164 (44%) patients had grade 3–4 serious adverse events, of which dyspnoea was the most common (in 18 [5%] patients). Only 52 (14%) patients had serious adverse events suspected to be treatment-related, of which 37 (10%) were grade 3–4. Treatment-related serious adverse events included vomiting (n=6; 2%), nausea (n=5; 1%), and peripheral oedema (n=4; 1%).

Of the 63 (17%) on-treatment deaths (on treatment or within 30 days of the last dose), 14 (4%) were attributed to causes other than the underlying NSCLC, four (1%) of which were assessed as treatment-related (cardiac arrest,

	Treatment-naive patients with *MET*ex14 NSCLC (n=60)			Previously treated patients with *MET*ex14 NSCLC (n=100)			All patients with *MET*ex14 NSCLC (n=160)			All patients (n=373)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
All adverse events	12 (20%)	34 (57%)	13 (22%)	28 (28%)	61 (61%)	10 (10%)	40 (25%)	95 (59%)	23 (14%)	104 (28%)	215 (58%)	48 (13%)
Treatment-related adverse events	21 (35%)	28 (47%)	7 (12%)	39 (39%)	45 (45%)	5 (5%)	60 (38%)	73 (46%)	12 (8%)	171 (46%)	133 (36%)	20 (5%)
All serious adverse events	6 (10%)	17 (28%)	8 (13%)	10 (10%)	37 (37%)	5 (5%)	16 (10%)	54 (34%)	13 (8%)	38 (10%)	131 (35%)	33 (9%)
Treatment-related serious adverse events	1 (2%)	4 (7%)	3 (5%)	4 (4%)	13 (13%)	2 (2%)	5 (3%)	17 (11%)	5 (3%)	15 (4%)	27 (7%)	10 (3%)
Fatal serious adverse events	0	0	3 (5%)	0	2 (2%)	1 (1%)	0	2 (1%)	4 (3%)	0	4 (1%)	8 (2%)
Treatment-related fatal serious adverse events	0	0	0	0	2 (2%)	0	0	2 (1%)	0	0	2 (1%)	2 (1%)
Adverse events leading to discontinuation	3 (5%)	7 (12%)	5 (8%)	7 (7%)	9 (9%)	3 (3%)	10 (6%)	16 (10%)	8 (5%)	25 (7%)	31 (8%)	12 (3%)
Treatment-related adverse events leading to discontinuation	3 (5%)	5 (8%)	2 (3%)	5 (5%)	7 (7%)	2 (2%)	8 (5%)	12 (8%)	4 (3%)	20 (5%)	21 (6%)	5 (1%)
Adverse events leading to dose adjustment or interruption	12 (20%)	29 (48%)	4 (7%)	15 (15%)	46 (46%)	3 (3%)	27 (17%)	75 (47%)	7 (4%)	69 (18%)	150 (40%)	15 (4%)
Treatment-related adverse events leading to dose adjustment or interruption	12 (20%)	26 (43%)	3 (5%)	13 (13%)	37 (37%)	3 (3%)	25 (16%)	63 (39%)	6 (4%)	61 (16%)	111 (30%)	9 (2%)

GEOMETRY mono-1 study uses Common Terminology Criteria for Adverse Events version 4.03 criteria for adverse event grading where grade 5 category is not in scope, and therefore not collected as such. MedDRA version 26·0 was used. *MET*ex14=*MET* exon 14-skipping mutation. NSCLC=non-small-cell lung cancer.

Table 3: **Summary of adverse events**

	Treatment-naive patients with *MET*ex14 NSCLC (n=60)			Previously treated patients with *MET*ex14 NSCLC (n=100)			All patients with *MET*ex14 NSCLC (n=160)			All patients (n=373)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Total	12 (20%)	34 (57%)	13 (22%)	28 (28%)	61 (61%)	10 (10%)	40 (25%)	95 (59%)	23 (14%)	104 (28%)	215 (58%)	48 (13%)
Peripheral oedema	34 (57%)	10 (17%)	0	44 (44%)	17 (17%)	0	78 (49%)	27 (17%)	0	162 (43%)	42 (11%)	0
Nausea	28 (47%)	0	0	43 (43%)	1 (1%)	0	71 (44%)	1 (1%)	0	162 (43%)	9 (2%)	0
Vomiting	13 (22%)	1 (2%)	0	27 (27%)	0	0	40 (25%)	1 (1%)	0	98 (26%)	9 (2%)	0
Blood creatinine increased	21 (35%)	1 (2%)	0	34 (34%)	0	0	55 (34%)	1 (1%)	0	102 (27%)	1 (<1%)	0
Dyspnoea	8 (13%)	4 (7%)	0	19 (19%)	7 (7%)	0	27 (17%)	11 (7%)	0	69 (18%)	24 (6%)	2 (1%)
Fatigue	8 (13%)	2 (3%)	0	24 (24%)	6 (6%)	0	32 (20%)	8 (5%)	0	69 (18%)	17 (5%)	0
Decreased appetite	13 (22%)	1 (2%)	0	20 (20%)	1 (1%)	0	33 (21%)	2 (1%)	0	77 (21%)	4 (1%)	0
Alanine aminotransferase increased	2 (3%)	5 (8%)	0	8 (8%)	6 (6%)	2 (2%)	10 (6%)	11 (7%)	2 (1%)	27 (7%)	23 (6%)	3 (1%)
Lipase increased	6 (10%)	3 (5%)	3 (5%)	1 (1%)	7 (7%)	2 (2%)	7 (4%)	10 (6%)	5 (3%)	12 (3%)	20 (5%)	5 (1%)

Adverse events occurring in ≥20% patients for grade 1–2 , and in ≥5% patients for grades 3 and 4, regardless of causality. GEOMETRY mono-1 study uses Common Terminology Criteria for Adverse Events version 4.03 criteria for adverse event grading where grade 5 category is not in scope, and therefore not collected as such. MedDRA version 26·0 was used. *MET*ex14=*MET* exon 14-skipping mutation. NSCLC=non-small-cell lung cancer.

Table 4: **Most common adverse events**

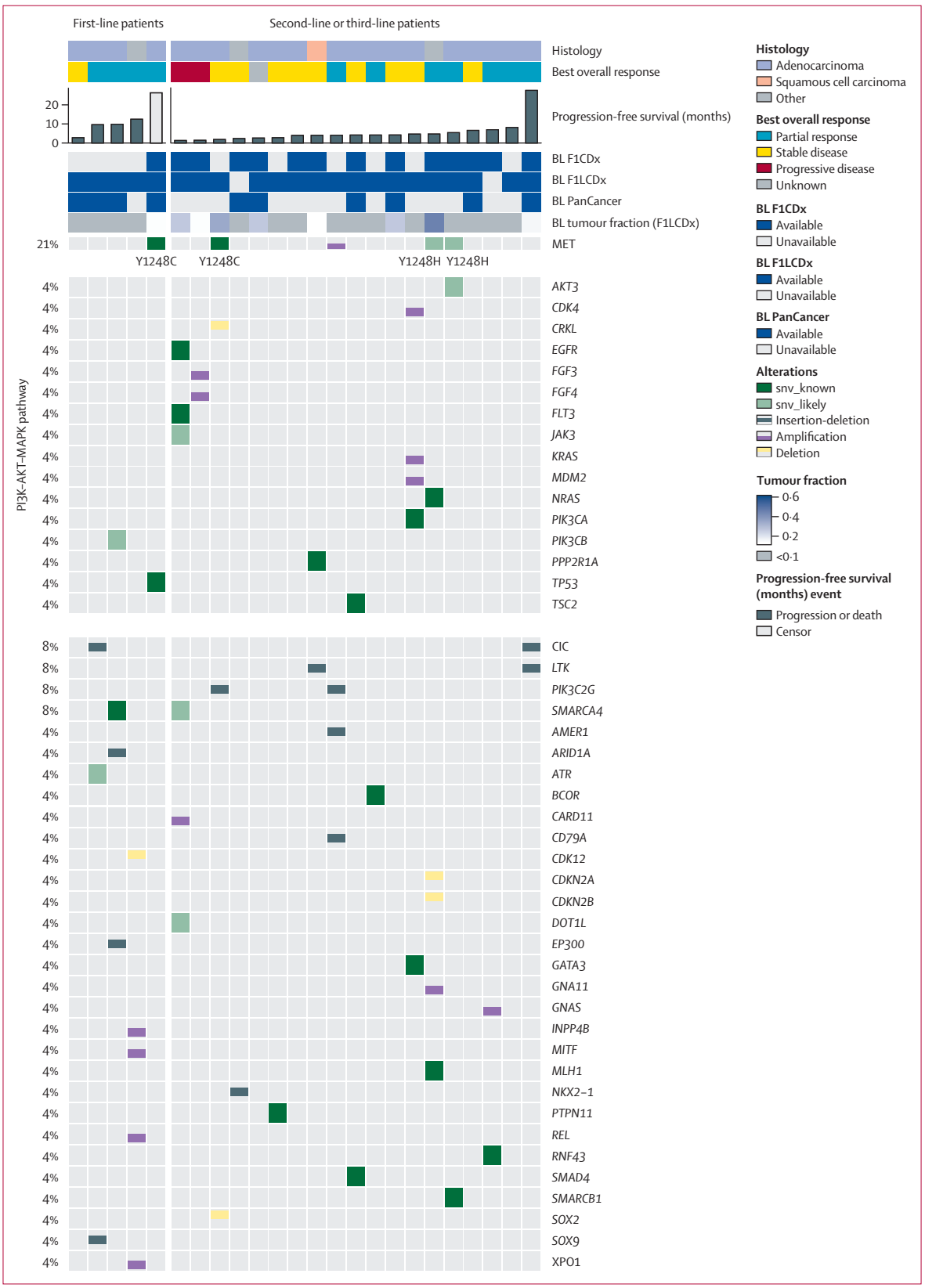


***Figure 2*: Emerging genetic variants at disease progression**
Oncoprint showing heterogenous genetic alterations in response to treatment limited to patients with a *MET*ex14 variant detected at baseline in plasma or tissue samples and an end-of-treatment sample with sufficient power to detect mutations (n=24). From top to bottom, the coloured bars indicate histology and best overall response (BIRC, Response Evaluation Criteria in Solid Tumours version 1.1). BIRC=blinded independent review committee. SNV=single-nucleotide variant. *MET*ex14=*MET* exon 14-skipping mutation.

hepatitis, organising pneumonia, and pneumonitis; appendix p 28).

F1LCDx results were compared with clinical trial assay results using baseline *MET*ex14-positive and *MET*ex14-negative samples to determine the level of concordance for the detection of *MET*ex14 in plasma versus tissue. *MET*ex14 was successfully detected in plasma in 90 of 134 patients with a positive percent agreement of 67·2% (95% CI 58·5–75·0; appendix pp 7–8, 29). A relatively low number (14 [6%] of 234 patients) of plasma samples produced an invalid *MET*ex14 result. Most samples with *MET*ex14 not detected in plasma had low tumour fraction in the plasma (tumour fraction <0·1), reflecting low tumour shedding (appendix p 30).

Baseline characteristics and clinical outcomes were generally comparable between patients identified as *MET*ex14 positive by F1LCDx in plasma and those by clinical trial assay in tumour tissue samples (appendix pp 31–33).

Activity was also analysed according to whether ctDNA was detectable at baseline by F1LCDx irrespective of *MET*ex14 status (appendix pp 7–8, 11). Overall survival was shorter in patients in the second-line or third-line setting with ctDNA detected by F1LCDx at baseline (n=26) than in those with ctDNA that was not detectable at baseline (n=57); no difference in overall survival was observed in patients in the first-line setting with ctDNA detected (n=10) versus not detected (n=42) by F1LCDx (appendix p 11). Patients with or without ctDNA detected at baseline had similar progression-free survival in both the first-line and second-line or third-line setting (appendix p 11). The baseline genomic landscape, analysed by F1CDx and F1LCDx, was heterogeneous, with the most frequent alterations appearing in *TP53*, in both tissue and plasma samples, in approximately half of the patients. In tissue samples, the most common co-occurring mutations after *TP53* were *MDM2* and *CDK4* amplifications, as well as *CDKN2A/B* and *MTAP* deletions (appendix pp 12–13). Amplifications and deletions were detected less frequently in plasma samples than in tissue samples (appendix pp 12–13).

Mutations in the MAPK pathway and in *MET* parallel signalling pathway genes conferred worse prognosis in terms of progression-free survival. No notable differences were observed regarding overall survival (appendix p 34).

Blood plasma samples were collected at the time of disease progression and analysed to assess emerging mutations as possible mechanisms of resistance to capmatinib treatment. Several *MET* kinase domain mutations in D1246H and Y1248C/H, along with one instance of *MET* amplification, were observed. Most of these mutations were identified in patients with partial response as best overall response (five of six patients). One of these five patients with partial response, who had a *D1246H* variant, is not shown in figure 2 due to the absence of a baseline sample. Other emerging mutations were heterogenous, but in ten (42%) of 24 patients with sufficient ctDNA in both baseline and disease progression samples, emerging variants were observed in PI3K–AKT–MAPK pathway genes (figure 2). Additional mutations in PI3K–AKT–MAPK pathway genes were identified in five patients when including samples with lower ctDNA shed at disease progression, but no additional on-target mutations were observed (appendix pp 14–16).

Pretreatment tumour biopsies from 109 of the 160 enrolled patients with *MET*ex14 (41 patients in the first-line setting and 68 patients in the second-line or third-line setting) were successfully profiled using RNAseq. Baseline characteristics and disease history of patients with valid RNAseq results were similar to those in all patients (appendix p 35). In patients with *MET*ex14, higher *MET* expression and higher MET pathway expression were observed in those with response to capmatinib (figure 3); the higher MET pathway expression in responders versus non-responders was particularly noticeable in patients in the first-line setting, whereas *MET* expression was numerically higher in both the first-line setting and in the second-line or third-line setting (appendix pp 18–20), although this difference was not statistically significant.

Patients with high *MET* expression or high MET pathway expression had numerically longer median progression-free survival and overall survival than those with low MET or MET pathway expression (appendix p 17). These differences were not due to variations in baseline gene expression between cohorts, as baseline *MET*, MET pathway, and *PD-L1* gene expression were similar between patients in the first-line setting and in the second-line or third-line setting (appendix p 21). No difference in overall response rate or progression-free survival was observed in patients receiving capmatinib in the first-line setting and in the second-line or third-line

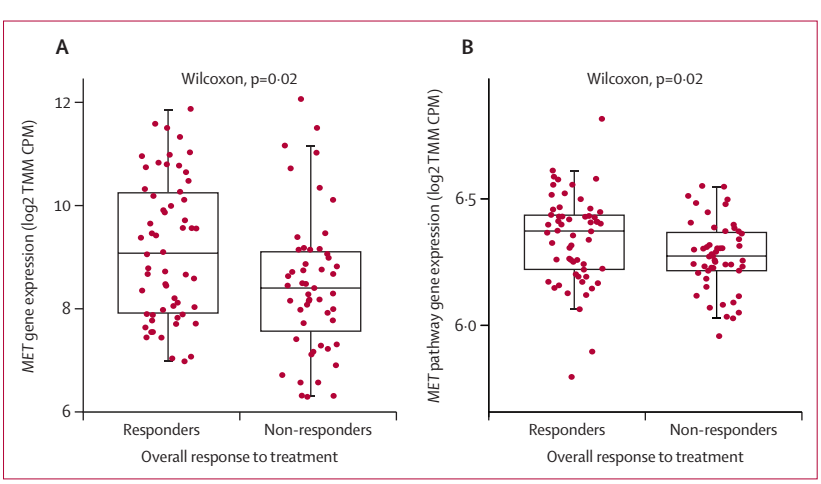


Figure 3: ***MET*** **gene expression (A) and MET pathway gene expression (B) in capmatinib responders and non-responders**

Patients were allocated into high expression and low expression groups based on the median *MET* gene expression or median MET pathway gene expression (*ACTA1, CRK, CRKL, DOCK1, ELK1, FOS, GAB1, GRB2, HGF, HRAS, ITGB1, JUN, MAP2K1, MAP2K2, MAP4K1, MAPK1, MAPK3, MAPK8, MET, PAK1, PIK3CA, PIK3CG, PIK3R1, PTEN, PTK2B, PTPN11, RAF1, RAP1A, RAP1B, RAPGEF1, RASA1, SOS1,* and *STAT3*) across all *MET* exon 14-skipping mutation non-small-cell lung cancer cohorts. CPM=counts per million reads. TMM=trimmed mean of the m-values.

setting based on *PD-L1* gene expression (appendix pp 22–23). Longer overall survival was observed in patients with high *PD-L1*-expressing NSCLC than in those with low *PD-L1* gene expression in both the first-line setting and in the second-line or third-line setting, although this difference was not statistically significant (appendix p 23).

Through an unbiased gene expression signature analysis, cell proliferation and interferon-γ emerged as gene expression signatures associated with tumour response (data not shown). However the gene expression signature did not predict tumour response after accounting for differences in *MET* expression and type of previous therapy exposure (appendix p 36). *MET* gene expression was the only independent RNA pattern that was significantly and independently associated with capmatinib response.

Results for biomarker analyses conducted in patients with different levels of *MET* amplification are shown in the appendix (pp 7–8, 24, 37–40)

Discussion

Herein, we report the final activity and safety results from the GEOMETRY mono-1 study in treatment-naive and in previously treated patients with *MET*ex14 NSCLC. An overall response rate of 68% in treatment-naive patients was one of the highest overall response rates reported thus far with MET tyrosine kinase inhibitors.[9–12] Previously treated patients also benefited from capmatinib treatment, with an overall response rate of 41% in the second-line or third-line setting and 52% in the second-line setting. Long-term survival benefit with capmatinib (represented by clinically meaningful median progression-free survival and median overall survival) was observed in both treatment-naive patients and previously treated patients.

In a post-hoc retrospective medical review based on central neuroradiological assessment of brain lesions, promising intracranial anti-tumour activity with capmatinib was observed in patients with brain metastases at baseline (including those without previous intracranial radiation), indicating the clinical benefit derived from capmatinib treatment in this patient population. The safety of capmatinib remains unchanged with long-term exposure, showing a consistent, manageable, and predictable safety profile in patients with advanced *MET*-mutated and *MET*-amplified NSCLC, irrespective of the treatment setting. With the caveat of a small sample size, safety data in patients with brain metastases at baseline in a previous study[13] was similar to the overall safety data in the present study.

The DNA-based F1LCDx assay showed high concordance in detecting *MET*ex14-positive patients in the plasma samples compared to those with the RNA-based clinical trial assay used for patient recruitment testing in tissue samples. The clinical outcomes in patients treated with capmatinib were generally comparable between patients who had *MET*ex14-positive NSCLC identified by F1LCDx in plasma and by clinical trial assay in tumour tissue samples. The findings support the use of a blood-based F1LCDx assay to aid clinicians in identifying patients with *MET*ex14 NSCLC who might be eligible for treatment with capmatinib, as well as offering a more convenient and less invasive approach for biomarker analysis. However, a *MET*ex14-negative liquid biopsy result does not preclude a *MET*ex14-positive result by tissue biopsy, underlining the importance of tissue testing for negative liquid biopsy results.

The genomic landscape analysis before capmatinib treatment, through either ctDNA or tissue-based analysis, provided valuable insights into the mutational profiles of patients with *MET*ex14 NSCLC. Mutations in MAPK, MET parallel, or PI3K pathways have been shown previously to limit activity of MET inhibitors.[14,15] Additionally, emergence of mutations in genes belonging to the PI3K–AKT–MAPK pathways associated with drug resistance suggests that combination therapies targeting these pathways might be beneficial and, therefore, warrant further validation and investigation. Five of the six patients who presented with on-target *MET* mutations at disease progression initially had a partial response as the best response to capmatinib and later progressed, possibly reflecting a mechanism of acquired resistance due to these mutations.[16] *MET* mutations at D1246 and Y1248 (also known as D1228 and Y1230) have been previously reported to occur at the time of disease progression and are known to confer acquired resistance to type I MET inhibitors in vitro, such as capmatinib.[16,17] Indeed, MET tyrosine kinase inhibitors can be classified into different types depending on the MET region interacting with the tyrosine kinase inhibitor. Type I and type II MET inhibitors are ATP competitive inhibitors that bind to the ATP-binding pocket in its active (type I) and inactive (type II) states, respectively, whereas type III inhibitors represent allosteric MET inhibitors.[18] Different mutation patterns offer mechanisms of resistance specific to the different types of MET inhibitors (type I *vs* type II) and have been described in vitro.[17] Moreover, patients with activating aberrations of the *MET* gene and resistance to type I inhibitors after an initial response might respond to type II inhibitors.[19]

A recent large-scale analysis showed that gene expression of *MET*, *PD-L1*, and gene expression signature associated with IFN-γ and T-cell inflammation were significantly higher in the *MET*ex14 versus *MET* wild-type NSCLC.[20] Whole transcriptome analysis of *MET*ex14 baseline tumour samples allowed for an examination of *MET*, *PD-L1*, and MET pathway gene expression in addition to an unbiased gene expression signature analysis, leading to the observation of better overall response rate in patients with high *MET* or MET pathway gene expression, regardless of line of therapy, and numerically longer progression-free survival and overall survival, particularly in patients in the first-line setting. These observed differences in response by line of therapy might be attributed to the presence of escape mechanisms emerging from changes in the tumour

microenvironment, caused by pressure from previous therapies, which are not present in the first-line setting, where *MET*ex14 remains the singular driver and MET inhibition is potentially more effective.

Focal *MET* amplification is associated with a relatively high *MET* gene copy number and might be a predictor of benefit from MET inhibiton.[21] Consistent with this evidence, in the exploratory analyses conducted in the amplification cohorts, higher overall response rate was observed in patients with focal *MET* amplification. *MET* gene expression was numerically higher in patient samples with focal versus non-focal *MET* amplification, although this analysis could be performed only on a small number of patients. These data further support that patients with high *MET* gene expression might respond better to capmatinib.

Considering that the *MET*ex14 NSCLC population tends to express higher PD-L1 than the non-*MET*ex14 population and that the *MET*ex14 NSCLC population does not seem to respond well to immunotherapy,[22] we evaluated if PD-L1 expression would impact response to capmatinib. Our results showed that *PD-L1* gene expression had no association with response to capmatinib in either first-line or second-line or third-line patient samples. This result might have implications in decisions made between targeted MET inhibitors and immunotherapy, considering that patients respond to capmatinib regardless of *PD-L1* expression.

The limitations of the exploratory biomarker analyses include comparisons across multiple cfDNA assay types. The fraction of tumour DNA in cfDNA sequencing is typically much lower than that in tumour tissue sequencing; therefore, some variants present in patients' tumours might not be detected by this method. Differences in characteristics or response for patients with next generation sequencing data versus those without were not formally compared in this analysis. With a relatively small sample size, these results should be validated in a larger study. Finally, biomarker analyses conducted on tissue were predominantly conducted on archival biopsies and might not accurately represent the tumour tissue at the start of treatment, especially in patients in the second-line or third-line setting, for which biopsies collected before the previous line of treatment might have been analysed.

In conclusion, the final GEOMETRY mono-1 data provide further long-term evidence of the previously observed compelling activity of capmatinib as first-line and second-line or third-line treatment options for patients with *MET*ex14 NSCLC. Although the data presented are from a phase 2 non-randomised study, results from a phase 3 randomised trial of capmatinib versus docetaxel (albeit limited due to the small sample size) and real-world evidence reports provide supporting evidence for the robustness of capmatinib activity.[23–27] Although some difference in response rates between first-line and later-line settings in GEOMETRY mono-1 study is acknowledged, the overall trend is in line with observations from other MET inhibitors in patients harbouring *MET*ex14 NSCLC, as well as with other targeted therapy in patients with NSCLC with molecular drivers.[9,11,28,29] Evolution of tumour heterogeneity and its complex microenvironment following previous therapy might be contributing factors for the different activity in treatment-naive patients versus later line setting. A review of long-term safety data of capmatinib demonstrated a consistent safety profile that was manageable and predictable across all the cohorts, irrespective of previous treatments.

The biomarker findings add to the evidence of the clinical benefit, supporting the broader adoption of liquid biopsy testing for identifying patients with *MET*ex14 NSCLC who do not have adequate tumour samples for biomarker testing or are ineligible for invasive tissue biopsy.

Contributors

JW, MH, J-YH, NR, and P-JS contributed to data collection, data interpretation, data investigation, and reviewed the manuscript; EFS contributed to data investigation, writing the original draft, and reviewed and edited the manuscript; SVO contributed to data collection and reviewed the manuscript; JV was a clinical trial investigator and contributed to data collection, data interpretation, and manuscript review. MN, MdJ, WA, and EBG contributed to data collection, data interpretation, and data investigation, and reviewed the manuscript; HJMG contributed to data interpretation and data investigation, and reviewed the manuscript; DSWT contributed to data collection, data interpretation, and data investigation, and reviewed the manuscript; TS contributed to data collection, data interpretation, and data investigation, and reviewed the manuscript; GMF contributed to conceptualisation and methodology, and reviewed and edited the manuscript; AR contributed to conceptualisation, data curation, formal analysis, methodology, project administration, and supervision, and reviewed and edited the manuscript; MC contributed to conceptualisation, data curation, formal analysis, data investigation, methodology, supervision, validation, and data visualisation, wrote the original draft, and reviewed and edited the manuscript; SLM contributed to data curation, formal analysis, methodology, and writing the original draft, and reviewed and edited the manuscript; AY contributed to formal analysis, methodology, project administration, resources, supervision, validation, visualisation, and data review; AB contributed to biomarker data analysis and interpretation, writing the original draft, and reviewed and edited the manuscript; CB contributed to conceptualisation, biomarker formal analysis, supervision, validation, data visualisation, writing the original draft, and reviewed and edited the manuscript; YY contributed to formal analysis and reviewed and edited the manuscript; LJ contributed to biomarker formal analysis, and data visualisation, and reviewed and edited the manuscript; LF contributed to biomarker formal analysis, data investigation, software, and data visualisation, wrote the original draft, and reviewed and edited the manuscript; RSH contributed to conceptualisation, data curation, and data investigation, and reviewed and edited the manuscript. JW, EBG, and RSH accessed and verified the underlying data reported in the manuscript. All authors confirm that they had full access to all the data in the manuscript and accept responsibility to submit for publication.

Declaration of interests

JW reports research grant support (to their institution) from Bristol Myers Squibb, Janssen Pharmaceutica, Novartis, and Pfizer; and consulting fees or honoraria for lectures and for attending meetings from Amgen, AstraZeneca, Bayer, Blueprint, Bristol Myers Squibb, Boehringer-Ingelheim, Chugai, Daiichi Sankyo, Janssen, Lilly, Loxo, Merck, Mirati, MSD, Novartis, Nuvalent, Pfizer, Pierre Fabre, Roche, Seattle Genetics, Takeda, and Turning Point. MH declares personal honoraria for lectures and presentations from Boehringer Ingelheim, AstraZeneca, Takeda, Amgen, MSD, and Roche. J-YH reports research grants from Pfizer, Takeda, and ONO; consulting fees or honoraria for lectures and presentations from AstraZeneca, Jassen, Amgen, Oncobix, Daiichi Sankyo, Merck, Norvatis, Abion, Takeda, Pfizer, and Yuhan; participation in data safety monitoring board for AstraZeneca, Jassen; and a leadership role for

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Data sharing

Novartis is committed to sharing with qualified external researchers, access to patient-level data, and supporting clinical documents (protocol and statistical analysis plan) from eligible studies after publication. These requests are reviewed and approved by an independent review panel based on the scientific merit. All data provided are anonymised 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. The authors declare that all relevant aggregate biomarker data supporting the findings of this study are available within the Article and its supplementary information files. In accordance with the Health Insurance Portability and Accountability Act, we do not have institutional review board approval or patient consent to share individualised patient genomic data, which contains potentially identifying or sensitive patient information and cannot be reported in a public data repository. Novartis and its partner Foundation Medicine are committed to collaborative data analysis and has well established and widely used mechanisms by which qualified researchers can query our core genomic database of >500 000 de-identified sequenced cancers. More information and mechanisms for biomarker data access can be obtained by contacting the corresponding author or the Foundation Medicine Data Governance Council (data.governance.council@foundationmedicine.com).

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