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ORIGINAL ARTICLE

Capmatinib in *MET* Exon 14–Mutated or *MET*-Amplified Non–Small-Cell Lung Cancer

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ABSTRACT

BACKGROUND

Among patients with non–small-cell lung cancer (NSCLC), *MET* exon 14 skipping mutations occur in 3 to 4% and *MET* amplifications occur in 1 to 6%. Capmatinib, a selective inhibitor of the *MET* receptor, has shown activity in cancer models with various types of *MET* activation.

METHODS

We conducted a multiple-cohort, phase 2 study evaluating capmatinib in patients with *MET*-dysregulated advanced NSCLC. Patients were assigned to cohorts on the basis of previous lines of therapy and *MET* status (*MET* exon 14 skipping mutation or *MET* amplification according to gene copy number in tumor tissue). Patients received capmatinib (400-mg tablet) twice daily. The primary end point was overall response (complete or partial response), and the key secondary end point was response duration; both end points were assessed by an independent review committee whose members were unaware of the cohort assignments.

RESULTS

A total of 364 patients were assigned to the cohorts. Among patients with NSCLC with a *MET* exon 14 skipping mutation, overall response was observed in 41% (95% confidence interval [CI], 29 to 53) of 69 patients who had received one or two lines of therapy previously and in 68% (95% CI, 48 to 84) of 28 patients who had not received treatment previously; the median duration of response was 9.7 months (95% CI, 5.6 to 13.0) and 12.6 months (95% CI, 5.6 to could not be estimated), respectively. Limited efficacy was observed in previously treated patients with *MET* amplification who had a gene copy number of less than 10 (overall response in 7 to 12% of patients). Among patients with *MET* amplification and a gene copy number of 10 or higher, overall response was observed in 29% (95% CI, 19 to 41) of previously treated patients and in 40% (95% CI, 16 to 68) of those who had not received treatment previously. The most frequently reported adverse events were peripheral edema (in 51%) and nausea (in 45%); these events were mostly of grade 1 or 2.

CONCLUSIONS

Capmatinib showed substantial antitumor activity in patients with advanced NSCLC with a *MET* exon 14 skipping mutation, particularly in those not treated previously. The efficacy in *MET*-amplified advanced NSCLC was higher in tumors with a high gene copy number than in those with a low gene copy number. Low-grade peripheral edema and nausea were the main toxic effects. (Funded by Novartis Pharmaceuticals; GEOMETRY mono-1 ClinicalTrials.gov number, NCT02414139.)

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ACTIVATION OF THE MET PATHWAY IS ASSOCIATED with many cancers and can be caused by overexpression, gene amplification, and *MET* exon 14 skipping mutations, which can result from point mutations or from insertions or deletions.¹⁻⁷ The shorter exon 14–spliced protein has increased stability, which increases MET signaling.⁸ *MET* exon 14 skipping mutations occur in approximately 3 to 4% of patients with non–small-cell lung cancer (NSCLC), typically in the absence of other driver mutations,^{3-5,7} and are associated with a poor prognosis.^{7,9} *MET* amplification occurs in 1 to 6% of patients with NSCLC.¹⁰⁻¹³ Historically, the lack of clear biomarkers has made it difficult to select patients who will benefit the most from targeting MET with MET-specific therapy. In patients with NSCLC, selection of treatment on the basis of MET overexpression has not shown significant benefit.¹⁴ However, *MET* exon 14 skipping mutations and high-level *MET* amplification have emerged as potential predictive biomarkers.^{4,6,15-18}

Capmatinib (INC280), a highly potent and selective inhibitor of the MET receptor, has shown in vitro and in vivo activity in cancer models with various types of MET activation.¹⁹⁻²¹ In addition, capmatinib crosses the blood–brain barrier.^{22,23} Preliminary clinical data showed low-grade toxic effects and a promising efficacy of capmatinib monotherapy in patients with MET-dysregulated NSCLC.^{17,24}

We report the results of the GEOMETRY mono-1 study, which investigated the activity of capmatinib in patients with advanced NSCLC with a *MET* exon 14 skipping mutation or *MET* amplification. The study included patients who had received treatment previously and patients who had not.

METHODS

PATIENTS AND STUDY DESIGN

We conducted a prospective, international, open-label, multiple-cohort, phase 2 study to evaluate the safety and efficacy of capmatinib in patients with advanced NSCLC with a *MET* exon 14 skipping mutation or *MET* amplification. Eligible patients were adults (≥ 18 years of age) with stage IIIB or IV NSCLC with any histologic features, without an activating epidermal growth factor receptor mutation or anaplastic lymphoma kinase fusion, and with at least one measurable lesion, defined according to the Response Evalu-

ation Criteria in Solid Tumors (RECIST), version 1.1. *MET* status was determined by a central laboratory (see the Supplementary Methods section in the Supplementary Appendix, available with the full text of this article at NEJM.org).

Patients were assigned to cohorts on the basis of *MET* status and previous lines of therapy. In cohorts of patients with a *MET* exon 14 skipping mutation, enrollment was allowed regardless of concurrent *MET* amplification; however, no concurrent *MET* exon 14 skipping mutation was permitted in cohorts of patients with *MET* amplification. The study included five cohorts (with cohorts 1 and 5 having subcohorts) for the assessment of efficacy on the basis of prespecified statistical hypotheses; two expansion cohorts (6 and 7) were added to generate supportive clinical evidence.

Patients with brain metastases who had had no increase in glucocorticoid dose within the 2 weeks before enrollment were eligible for enrollment if their condition was judged by the investigator to be neurologically stable. The complete eligibility criteria are provided in the protocol, available at NEJM.org. Oral capmatinib at a dose of 400 mg twice daily was administered under fasting conditions in cohorts 1 through 5 and was administered without fasting restrictions in cohorts 6 and 7.

STUDY END POINTS

The primary end point was overall response (complete or partial response), as assessed under blinded conditions by an independent review committee according to RECIST, version 1.1.²⁵ The key secondary end point was the duration of response, as assessed under blinded conditions by the independent review committee. Other secondary end points included investigator-assessed response and duration of response, investigator-evaluated and independent review committee–evaluated time to response, disease control (defined as a best overall response of complete response, partial response, or stable disease according to RECIST, version 1.1), progression-free survival, and the safety profile and pharmacokinetics of capmatinib.

An ad hoc blinded review (by an independent neuroradiologic review committee) involving patients with a *MET* exon 14 skipping mutation and brain metastases at baseline was conducted after reports of responses in the brain in some patients. Prespecified exploratory analyses of

baseline tumor-biopsy samples obtained from patients with NSCLC with a *MET* exon 14 skipping mutation were performed in order to determine the type of *MET* alteration leading to exon 14 skipping, the presence or absence of concurrent *MET* amplification, and a correlation between reverse-transcriptase–polymerase-chain-reaction (RT-PCR) analyses and next-generation sequencing with the use of the FoundationOne CDx panel (Foundation Medicine).

STUDY OVERSIGHT

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

The study was sponsored by Novartis Pharmaceuticals and was designed by the sponsor and the authors in conjunction with an independent steering committee. The sponsor conducted all the statistical analyses. All the authors agreed to submit the manuscript for publication and vouch for the accuracy of the data and for the adherence of the study to the protocol. The manuscript was developed with medical writing assistance, funded by the sponsor in accordance with Good Publication Practice guidelines (www.ismpp.org/gpp3).

STATISTICAL ANALYSIS

Cohorts 1 through 5 were analyzed separately with independent statistical hypotheses. In the cohorts involving previously treated patients, on the basis of historical data,^{26,27} capmatinib was considered to have clinically relevant efficacy if a response was observed in at least 35% of the patients, with a lower boundary of the 95% confidence interval of more than 25%, as assessed by the independent review committee. For the cohorts involving patients who had not received treatment previously, capmatinib was considered to have clinically relevant efficacy if a response was observed in at least 55% of the patients, with a lower boundary of the 95% confidence interval of more than 35%, as assessed by the independent review committee.^{28,29}

No efficacy hypothesis was planned for cohort 6, which was intended to provide supportive analyses of efficacy and safety in patients who

had received one previous line of treatment for NSCLC with a *MET* exon 14 skipping mutation or *MET* amplification with a gene copy number of at least 10 in tumor tissue. The efficacy hypotheses for cohort 7 were the same as those used for the cohorts involving patients who had not received treatment previously.

All the tests were performed on the basis of the exact 95% confidence interval for response in each cohort, with the use of a one-sided alpha level of 0.025. No adjustment for multiplicity was made because each cohort was independent; therefore, the reported confidence intervals have not been adjusted for multiplicity.

An interim analysis for futility was planned to involve previously treated patients with NSCLC with a *MET* exon 14 skipping mutation or *MET* amplification when at least 28 patients (≥ 20 patients in cohort 3) had completed at least six cycles of treatment or had discontinued treatment. Small sample sizes precluded interim futility analyses in cohorts involving patients who had not received treatment previously, and no interim analysis was planned for cohort 6.

The primary analysis was to be performed when all treated patients in their respective cohort (if the study was not stopped for futility at the interim analysis) had completed at least six cycles of treatment or had discontinued treatment. Confirmed partial responses or complete responses that were reported before the receipt of any additional anticancer therapy were included in the calculation of response. Patients with a best overall response of “unknown” according to RECIST, version 1.1, or with no blinded assessment of data by the independent review committee were considered to not have had a response when the percentages of patients with a response were estimated (as a worst-case scenario). Multiple imputation analysis was also performed and is described in the Supplementary Appendix. The consistency in the treatment effect (response) was explored according to subgroup, including prespecified analyses (age, sex, race, and Eastern Cooperative Oncology Group performance-status score) and post hoc analyses (smoking status, histologic features, and receipt of previous immunotherapy).

Safety analyses included all the patients in cohorts 1 through 7 who had received at least one dose of capmatinib. The pharmacokinetics of capmatinib were characterized under fasting conditions in cohorts 1 through 5 and were

characterized without regard to food intake in cohorts 6 and 7.

The statistical analysis plan is provided with the study protocol. Additional details of the study end points and methods are described in the Supplementary Appendix.

RESULTS

PATIENTS

A total of 364 patients with advanced NSCLC were enrolled in the study (Fig. 1). Across cohorts 1 through 5, a total of 97 patients had a *MET* exon 14 skipping mutation and 210 had *MET* amplification. The characteristics of these patients at baseline are described in Table 1. Previously treated patients who were enrolled in cohorts 1 through 4 had received one or two lines of therapy previously (Table S1), and patients in cohorts 5a and 5b had not received treatment previously. The median age of the patients was slightly higher in cohorts involving patients with a *MET* exon 14 skipping mutation (71 years) than in most of the cohorts involving patients with *MET* amplification (60 to 70 years). Patients with a *MET* exon 14 skipping mutation were more likely to be women and were more likely to have never smoked than were patients with *MET* amplification.

Cohort 6 comprised 34 patients: 3 patients with *MET*-amplified NSCLC with a gene copy number of at least 10 and 31 patients with NSCLC with a *MET* exon 14 skipping mutation who had received one previous line of therapy (Table S2). As of the data-cutoff point (January 6, 2020), a total of 23 patients, all of whom had NSCLC with a *MET* exon 14 skipping mutation and had not received treatment previously, had been enrolled in cohort 7; no efficacy data were available for this cohort.

The cutoff date for the efficacy analyses was January 6, 2020, except in the three cohorts in which patients had a gene copy number of less than 10 (cohorts 1b, 2, and 3); these cohorts had been closed earlier for futility (cutoff date, April 15, 2019). The cutoff date for the safety analyses in all the cohorts was January 6, 2020.

EFFICACY

Advanced NSCLC with MET Exon 14 Skipping Mutation
Among patients with advanced NSCLC with a *MET* exon 14 skipping mutation, the primary end point of overall response, as assessed by the in-

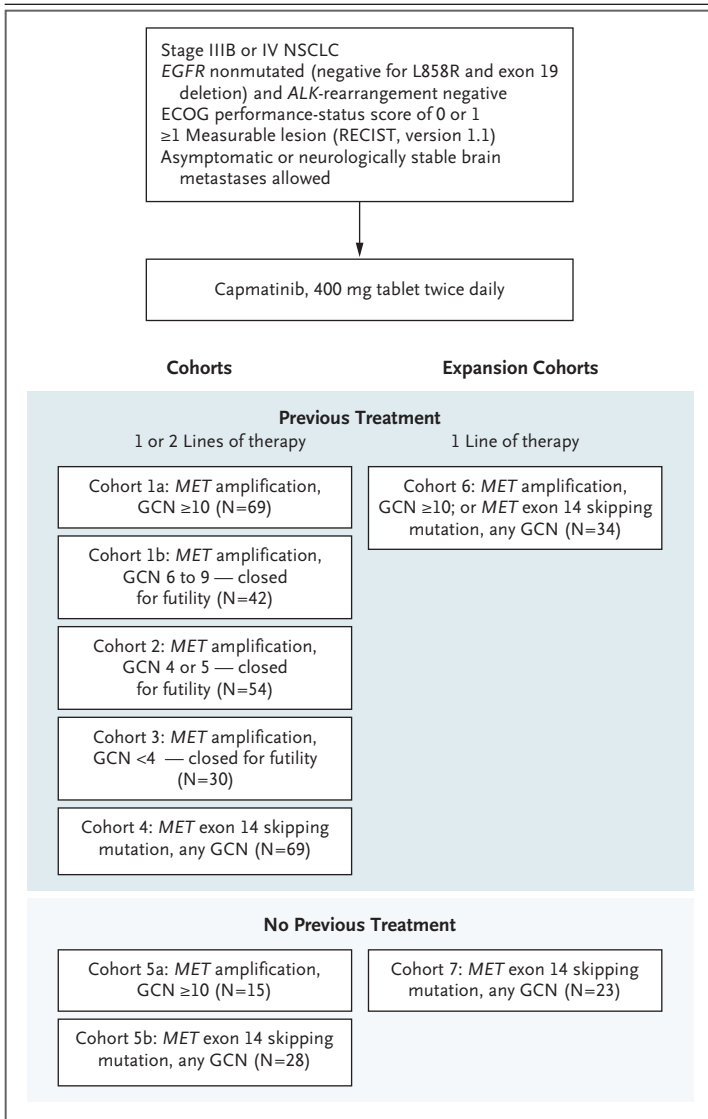
dependent review committee, was observed in 41% (95% confidence interval [CI], 29 to 53) of 69 previously treated patients and in 68% (95% CI, 48 to 84) of 28 patients who had not received treatment previously (Table 2 and Fig. 2A and Fig. S1). The median duration of response, as assessed by the independent review committee, was 9.7 months (95% CI, 5.6 to 13.0) among previously treated patients and 12.6 months (95% CI, 5.6 to could not be estimated) among patients who had not received treatment previously (Table 2).

Responses to capmatinib were rapid, with the majority of patients (82% of the previously treated patients and 68% of those who had not received treatment previously) having a tumor response at the first tumor evaluation after the initiation of capmatinib therapy. Within the limitation of the small sample size of each subgroup, clinical benefit was noted across all the subgroups analyzed (Table S3).

In an analysis involving 73 patients (53 of whom had been previously treated and 20 of whom had not received treatment previously), a 99% concordance between next-generation sequencing and RT-PCR analyses was observed and there were no considerable differences in response to capmatinib according to the type of genetic alteration causing *MET* exon 14 skipping mutations or the co-occurrence of *MET* amplification (see the Supplementary Results section and Figs. S2, S3, and S4). The tumor mutational burden was low in patients with NSCLC with a *MET* exon 14 skipping mutation (Fig. S5).

The median progression-free survival, as assessed by the independent review committee, was 5.4 months (95% CI, 4.2 to 7.0) among previously treated patients and 12.4 months (95% CI, 8.2 to could not be estimated) among patients who had not received treatment previously (Figs. S6 and S7). Results according to investigator assessment were similar to those of the independent review committee (Table S4).

A total of 14 patients with NSCLC with a *MET* exon 14 skipping mutation had brain metastases at baseline, of whom 13 (10 patients who had been previously treated and 3 who had not received treatment previously) had data that could be evaluated by the independent neuroradiologic review committee. A total of 12 of the 13 patients had intracranial disease control according to neuroradiologic assessment. Seven patients had an intracranial response, including 4 who

**Figure 1. Study Design.**

Eligible patients with non–small-cell lung cancer (NSCLC) had to have an Eastern Cooperative Oncology Group (ECOG) performance-status score of 0 or 1 (on a scale from 0 [fully active] to 5 [death]; a score of 1 indicates that the patient is ambulatory but restricted from strenuous activity) and to have at least one measurable tumor, according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. Patients were assigned to cohorts on the basis of *MET* status (*MET* exon 14 skipping mutation or *MET* amplification, as measured by gene copy number [GCN]) and previous lines of therapy. Enrollment in cohorts with a *MET* exon 14 skipping mutation was allowed regardless of concurrent *MET* amplification, but no concurrent *MET* exon 14 skipping mutation was permitted in cohorts with *MET* amplification. Previously treated patients had received systemic antineoplastic therapy for advanced NSCLC. Enrollment in cohort 5a was stopped early because of slow enrollment. Each cohort of the study, except the expansion cohorts, enrolled patients in parallel. Enrollment in cohort 6 was to be initiated only on completion of enrollments in cohort 1a or cohort 4 and included only patients who had received one line of therapy previously. Cohort 7 was added in a protocol amendment (on February 28, 2019); enrollment was ongoing at the data-cutoff date (January 6, 2020). The expansion cohorts allowed further data collection in the specified patient populations. ALK denotes anaplastic lymphoma kinase, and EGFR epidermal growth factor receptor.

of therapy previously, were in line with the efficacy of capmatinib as observed in cohort 4 (which included previously treated patients with *MET* exon 14 skipping mutation). Among these 31 patients in cohort 6, an overall response was observed in 48% (95% CI, 30 to 67) (Table S6).

Advanced NSCLC with *MET* Amplification

Among patients with advanced NSCLC with *MET* amplification, the primary end point of overall response, as assessed by the independent review committee, was observed in 12% of those (95% CI, 4 to 26) who had tumor tissue with a gene copy number of 6 to 9, in 9% of those (95% CI, 3 to 20) who had tumor tissue with a gene copy number of 4 or 5, and in 7% of those (95% CI, 1 to 22) who had tumor tissue with a gene copy number of less than 4 (Table 2). Therefore, these cohorts were closed for futility at the interim analysis. The median progression-free survival, as assessed by the independent review committee, was as follows: among patients who had tumor tissue with a gene copy number of 6 to 9, the median progression-free survival was 2.7 months (95% CI, 1.4 to 3.1); among those who

had a complete response. (Computed tomographic scans in a patient with a response are shown in Fig. S8.) Three of the 7 patients who had a response had received brain radiotherapy previously. Intracranial responses were observed at the first assessment.

At time of the analyses, 63 previously treated patients (91%) and 23 patients who had not received treatment previously (82%) had discontinued treatment (Table S5). The primary reason for discontinuation was progressive disease (in 58% of the previously treated patients and in 46% of those who had not received treatment previously).

Results from the expansion cohort 6, which included 31 patients with NSCLC with *MET* exon 14 skipping mutation who had received one line

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	NSCLC with MET Exon 14 Skipping Mutation			NSCLC with MET Amplification				
	Cohort 4 (N=69)	Cohort 5b (N=28)	Cohort 1a (N=69)	Cohort 5a (N=15)	Cohort 1b (N=42)	Cohort 2 (N=54)	Cohort 3 (N=30)	
Age								
Median (range) — yr	71 (49–90)	71 (57–86)	61 (33–76)	70 (49–86)	60 (36–76)	64 (39–84)	63 (38–78)	
≥65 yr — no. (%)	55 (80)	25 (89)	28 (41)	10 (67)	13 (31)	24 (44)	14 (47)	
Female sex — no. (%)	40 (58)	18 (64)	15 (22)	4 (27)	21 (50)	15 (28)	11 (37)	
ECOG performance-status score — no. (%)†								
0	16 (23)	7 (25)	17 (25)	4 (27)	14 (33)	23 (43)	9 (30)	
≥1	53 (77)	21 (75)	52 (75)	11 (73)	28 (67)	31 (57)	21 (70)	
Smoking history — no. (%)								
Never smoked	40 (58)	18 (64)	5 (7)	2 (13)	7 (17)	11 (20)	7 (23)	
Former smoking	27 (39)	9 (32)	54 (78)	8 (53)	29 (69)	34 (63)	20 (67)	
Current smoking	2 (3)	1 (4)	10 (14)	5 (33)	6 (14)	9 (17)	3 (10)	
Histologic findings — no. (%)								
Adenocarcinoma	53 (77)	25 (89)	57 (83)	11 (73)	35 (83)	48 (89)	22 (73)	
Squamous-cell carcinoma	6 (9)	2 (7)	7 (10)	2 (13)	2 (5)	4 (7)	5 (17)	
Large-cell carcinoma	1 (1)	0	2 (3)	1 (7)	1 (2)	0	1 (3)	
Other	9 (13)	1 (4)	3 (4)	1 (7)	4 (10)	2 (4)	2 (7)	
Brain metastases at baseline — no. (%)‡	11 (16)	3 (11)	26 (38)	7 (47)	14 (33)	18 (33)	6 (20)	
No. of previous lines of antineoplastic therapy — no. (%)§								
1	51 (74)	NA	41 (59)	NA	27 (64)	28 (52)	9 (30)	
2	16 (23)	NA	27 (39)	NA	15 (36)	26 (48)	21 (70)	
3	2 (3)	NA	1 (1)	NA	0	0	0	

* Patients with non–small-cell lung cancer (NSCLC) with a MET exon 14 skipping mutation were assigned to study cohorts on the basis of receipt of previous treatment: cohort 4 included patients who had received treatment previously, and cohort 5b included those who had not received treatment previously. Patients with NSCLC with MET amplification were assigned to study cohorts on the basis of gene copy number (≥ 10 , 6 to 9, 4 or 5, or < 4) and receipt of previous treatment (yes or no); among patients with a gene copy number of at least 10, cohort 1a included previously treated patients and cohort 5a included patients who had not received treatment previously; cohort 1b included patients with a gene copy number of 6 to 9, cohort 2 those with a gene copy number of 4 or 5, and cohort 3 those with a gene copy number of less than 4. All the patients with a gene copy number of less than 10 had received treatment previously. The data-cutoff date was January 6, 2020. Percentages may not total 100 because of rounding. NA denotes not applicable.

† Eastern Cooperative Oncology Group (ECOG) performance-status scores are assessed on a scale from 0 (fully active) to 5 (death); a score of 1 indicates that the patient is ambulatory but restricted from strenuous activity. One patient in cohort 4, who had undergone randomization in error (protocol deviation), had an ECOG performance-status score of 2 (indicating that the patient was ambulatory and capable of self-care but unable to carry out any work activities).

‡ Among patients with NSCLC with a MET exon 14 skipping mutation, 12 were identified from their medical history and 2 were identified on the basis of the baseline computed tomographic scan.

§ The types of antineoplastic therapy that had been received by patients in the previously treated cohorts are shown in Table S1.

Table 2. Responses to Capmatinib Treatment, as Assessed by the Independent Review Committee.*

Response	NSCLC with MET Exon 14 Skipping Mutation			NSCLC with MET Amplification				
	Cohort 4 (N=69)	Cohort 5b (N=28)	Cohort 1a (N=69)	Cohort 5a (N=15)	Cohort 1b (N=42)	Cohort 2 (N=54)	Cohort 3 (N=30)	
Best response — no. (%)								
Complete response	0	1 (4)	1 (1)	0	0	0	0	
Partial response	28 (41)	18 (64)	19 (28)	6 (40)	5 (12)	5 (9)	2 (7)	
Stable disease	25 (36)	7 (25)	28 (41)	4 (27)	17 (40)	20 (37)	14 (47)	
Noncomplete response or nonprogressive disease	1 (1)	1 (4)	1 (1)	0	1 (2)	0	0	
Progressive disease	6 (9)	1 (4)	12 (17)	4 (27)	15 (36)	21 (39)	6 (20)	
Unknown or could not be evaluated	9 (13)	0	8 (12)	1 (7)	4 (10)	8 (15)	8 (27)	
Overall response†								
No. of patients with overall response	28	19	20	6	5	5	2	
Percent of patients (95% CI)	41 (29–53)	68 (48–84)	29 (19–41)	40 (16–68)	12 (4–26)	9 (3–20)	7 (1–22)	
Disease control‡								
No. of patients with disease control	54	27	49	10	23	25	16	
Percent of patients (95% CI)	78 (67–87)	96 (82–100)	71 (59–81)	67 (38–88)	55 (39–70)	46 (33–60)	53 (34–72)	
Duration of response								
No. of events/no. of patients with response	23/28	11/19	15/20	6/6	3/5	4/5	2/2	
Median duration of response (95% CI) — mo	9.7 (5.6–13.0)	12.6 (5.6–NE)	8.3 (4.2–15.4)	7.5 (2.6–14.3)	24.9 (2.7–24.9)	9.7 (4.2–NE)	4.2 (4.2–4.2)	
Progression-free survival								
Progression or death — no. of patients	60	17	58	15	34	50	22	
Median progression-free survival (95% CI) — mo	5.4 (4.2–7.0)	12.4 (8.2–NE)	4.1 (2.9–4.8)	4.2 (1.4–6.9)	2.7 (1.4–3.1)	2.7 (1.4–4.1)	3.6 (2.2–4.2)	

* The data-cutoff date was January 6, 2020, for cohorts 4, 5b, 1a, and 5a and April 15, 2019, for cohorts 1b, 2, and 3. Complete response required at least two determinations of complete response (according to the Response Evaluation Criteria in Solid Tumors, version 1.1) that were made at least 4 weeks apart before progression. Partial response required at least two determinations of partial response or better (not qualifying for complete response) that were made at least 4 weeks apart before progression. Stable disease required at least one assessment of stable disease or better (not qualifying for complete response) that was made more than 6 weeks after the start of capmatinib. A noncomplete response or nonprogressive disease was noted when neither complete response nor progressive disease was observed (for patients with nontarget lesions only at baseline). Progressive disease was noted when progression occurred 12 weeks or less after the start of capmatinib (and when the criteria for complete response, partial response, or stable disease were not met). Unknown status indicates all other cases (i.e., those not qualifying as a confirmed complete response or partial response and that did not involve stable disease after >6 weeks after the start of capmatinib or progression within the first 12 weeks of therapy). Percentages may not total 100 because of rounding. NE denotes could not be estimated.

† Overall response was defined as a complete response or partial response.

‡ Disease control was defined as a complete response, partial response, stable disease, or noncomplete response or nonprogressive disease.

had tumor tissue with a gene copy number of 4 or 5, it was 2.7 months (95% CI, 1.4 to 4.1); and among those who had tumor tissue with a gene copy number of less than 4, it was 3.6 months (95% CI, 2.2 to 4.2).

Capmatinib showed activity in patients who had tumor tissue with a gene copy number of at least 10; however, the overall response was lower than the prespecified threshold for clinically relevant activity. An overall response, as assessed by the independent review committee, was observed in 29% (95% CI, 19 to 41) of 69 previously treated patients and in 40% (95% CI, 16 to 68) of 15 patients who had not received treatment previously (Table 2 and Fig. 2B). With the limitation of small sample size in the subgroups involving patients who had not received treatment previously, the results regarding response appeared to be consistent across subgroups (Table S3).

The median duration of response was 8.3 months (95% CI, 4.2 to 15.4) among 20 previously treated patients and 7.5 months (95% CI, 2.6 to 14.3) among 6 patients who had not received treatment previously (Fig. 2D); the median progression-free survival was 4.1 months (95% CI, 2.9 to 4.8) and 4.2 months (95% CI, 1.4 to 6.9), respectively. The results according to investigator assessment were similar to those of the independent committee (Table S4).

Among patients who had NSCLC with *MET* amplification and tumor tissue with a gene copy number of at least 10, a total of 66 previously treated patients (96%; cohort 1a) and all 15 patients who had not received treatment previously (cohort 5a) had discontinued treatment as of the data-cutoff date (Table S5). Discontinuation was due primarily to progressive disease. Results regarding the 3 patients who had NSCLC with *MET* amplification and tumor tissue with a gene copy number of at least 10 who had been enrolled in cohort 6 are shown in Table S6.

ADVERSE EVENTS

The median duration of exposure to capmatinib varied across the cohorts, with values ranging from 6.6 weeks to 48.2 weeks (Table 3). Across all the cohorts (364 patients), the most commonly reported adverse events regardless of causality were peripheral edema, nausea, and vomiting, and adverse events of grade 3 or 4 regardless of causality were reported in 67% of the

patients (Table 3). The most common treatment-related adverse events (those occurring in $\geq 10\%$ of the patients) are listed in Table S7; the most frequent of these were peripheral edema, nausea, vomiting, and increased blood creatinine level. Treatment-related serious adverse events occurred in 48 of 364 patients (13%); the incidence was lower in cohorts 1b, 2, and 3, which had shorter durations of exposure to capmatinib (Table S7). Treatment-related adverse events leading to discontinuation of treatment occurred in 39 patients (11%); the results were generally consistent across the cohorts (Table S7). Treatment-related peripheral edema led to discontinuation in 6 patients (2%), with an event of grade 3 or 4 occurring in 2 patients (1%). In total, 83 patients (23%) had at least one adverse event (regardless of causality) that led to dose reduction.

Death from causes other than advanced NSCLC occurred during treatment in 13 patients (4%). The reported causes were atrial fibrillation, hepatitis, pneumonia, organizing pneumonia, bacterial pneumonia, pneumonitis, respiratory distress, sepsis, septic shock, sudden death, and assisted suicide (in 1 patient each) and cardiac arrest (in 2 patients). Only one death (from pneumonitis) was suspected to be related to capmatinib according to review by the investigator and according to medical review by Novartis Pharmaceuticals.

The safety results in cohorts 6 and 7 are shown in Tables S8 and S9. A lower incidence of gastrointestinal adverse events was observed when capmatinib was administered without fasting restrictions than when it was administered under fasting conditions (Table S10). Results regarding the pharmacokinetics of capmatinib are shown in Table S11.

DISCUSSION

We evaluated the clinical efficacy of the highly specific *MET* inhibitor capmatinib in patients with advanced NSCLC with a *MET* exon 14 skipping mutation or *MET* amplification. Capmatinib led to clinically meaningful antitumor activity in patients with NSCLC with a *MET* exon 14 skipping mutation who had not received treatment previously (overall response in 68% of the patients and disease control in 96%); the median duration of response was more than

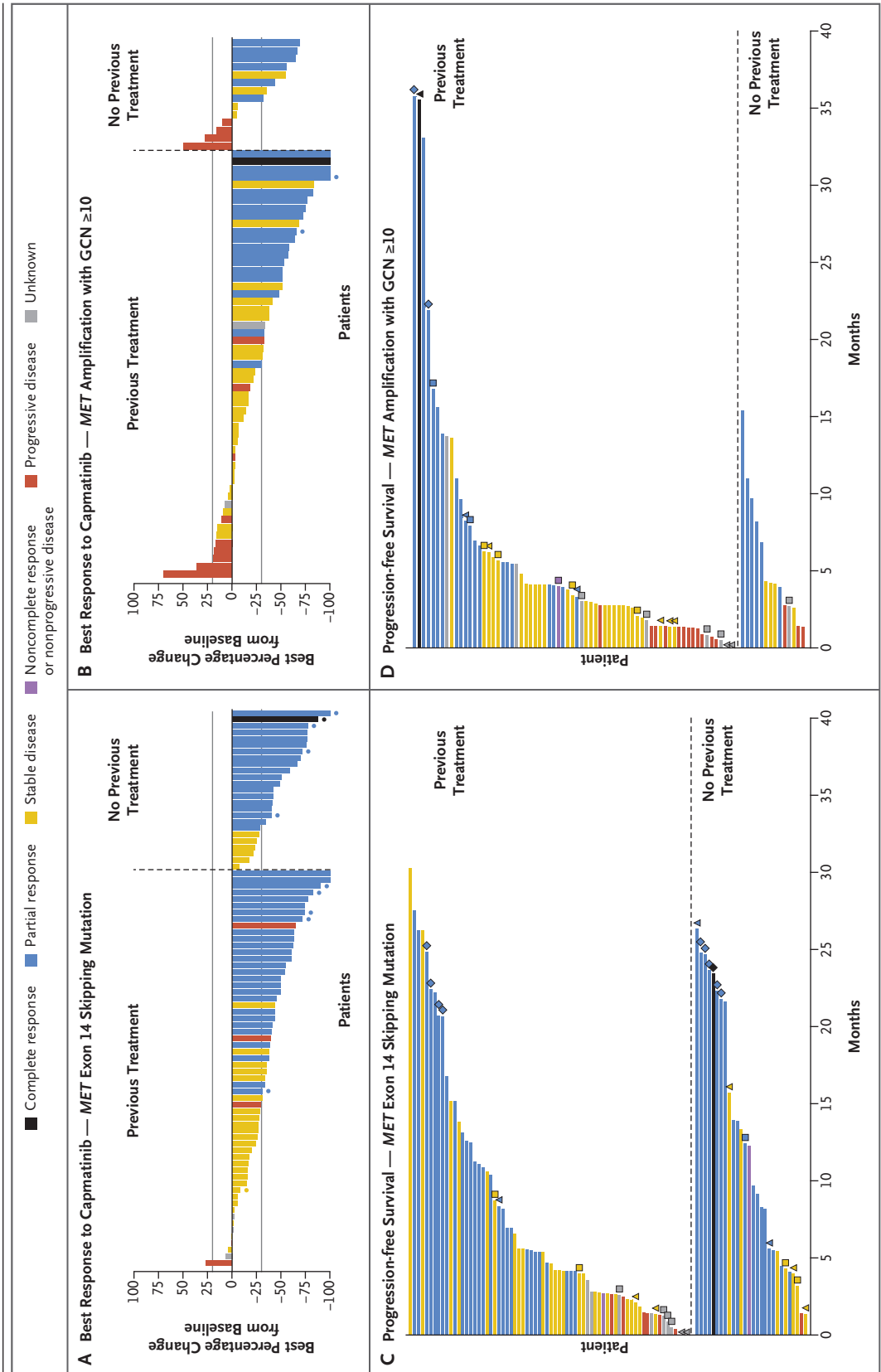


Figure 2 (facing page). Tumor Responses to Capmatinib.

Assessments were conducted by an independent review committee whose members were unaware of the cohort assignments. Panel A shows the best percentage change from baseline in the sum of the longest diameters in patients with NSCLC with a *MET* exon 14 skipping mutation who had measurable disease at baseline and at least one valid postbaseline assessment; the analysis included 60 previously treated patients and 26 patients who had not received treatment previously. The line at 20% corresponds to a change indicating progressive disease; the line at -30% corresponds to a change indicating a partial response. Circles at the end of the bars indicate patients receiving ongoing treatment. Panel B shows the best percentage change from baseline in the sum of the longest diameters in patients with *MET*-amplified NSCLC (tumor tissue with a gene copy number [GCN] ≥ 10) who had measurable disease at baseline and at least one valid postbaseline assessment; the analysis included 55 previously treated patients and 14 patients who had not received treatment previously. Panel C shows progression-free survival among patients with NSCLC with a *MET* exon 14 skipping mutation; the analysis included 69 previously treated patients and 28 patients who had not received treatment previously. Diamonds at the end of the bars indicate censored data because the patient was still followed for efficacy and had not had disease progression or died, triangles indicate censored data because the patient was no longer followed for efficacy and had not had disease progression or died, and squares indicate death. Patients with no symbol at the end of the bar had progressive disease at the data-cutoff date (January 6, 2020). Panel D shows progression-free survival among patients with *MET*-amplified NSCLC (tumor tissue with a GCN ≥ 10); the analysis included 69 previously treated patients and 15 patients who had not received treatment previously.

1 year. Although these efficacy results need confirmation in a larger population, the results are similar to those reported with effective, established targeted therapies for NSCLC.³⁰⁻³² Expansion cohort 7 (which includes patients with NSCLC with a *MET* exon 14 skipping mutation who had not received treatment previously) is ongoing.

Lower efficacy was observed among patients with NSCLC with a *MET* exon 14 skipping mutation who had previously received one or two lines of therapy, with an overall response observed in 41% of the patients (and in 48% of patients who had received one previous line of therapy [cohort 6]) and disease control in 78%; the median duration of response was 9.7 months. Nonetheless, these values are higher than those reported for current second- or third-line therapies in patients with advanced NSCLC.³³⁻³⁸

In findings that were consistent with evidence that has suggested that the level of gene amplification may dictate whether *MET* amplification acts as an oncogenic driver in NSCLC,³⁹ capmatinib showed limited activity in patients who had *MET*-amplified NSCLC and tumor tissue with a gene copy number of less than 10. The frequent coexistence of other known drivers at lower or moderate levels of *MET* amplification might argue against a true driver function in this context, as compared with high-level *MET* amplification, in which co-occurring drivers are rare.⁴⁰ In cohorts involving patients with *MET* amplification with a gene copy number of at least 10 in tumor tissue, an overall response was observed in 29% of previously treated patients and in 40% of patients who had not received treatment previously; however, the results were lower than the prespecified threshold for significance.

Our results and those from previous trials confirm that *MET* exon 14 skipping mutations constitute a valid biomarker for the selection of patients for *MET*-directed treatment. Crizotinib therapy led to a response in 32% of patients with advanced NSCLC with a *MET* exon 14 skipping mutation,¹⁸ and recent results have shown that tepotinib therapy led to a response in 46% of patients.⁴¹ Savolitinib has also shown activity in this NSCLC subgroup.⁴²

Patients who have tumors with a *MET* exon 14 skipping mutation have a poor prognosis with standard therapies, including immunotherapies.⁴³⁻⁴⁵ The efficacy of capmatinib is noteworthy because these patients are generally elderly^{3,5} and are thus more challenging to treat owing to a greater risk of toxic effects from first-line multi-drug regimens.

Among the patients with NSCLC with a *MET* exon 14 skipping mutation in our study, the difference in response between previously treated patients and patients who had not received treatment previously remains unexplained, although it is important to consider the limited number of patients and the overlapping 95% confidence intervals. An overall decline in health during longer durations of disease, as well as the evolution of resistant clones during first-line therapy, might contribute to this observation. On the basis of available data, the antitumor activity and the duration of response that we observed seemed to be independent of the type of *MET*

Table 3. Adverse Events, According to Grade, Regardless of Causality, and Exposure to Capmatinib.*

Variable	NSCLC with MET Exon 14 Skipping Mutation				NSCLC with MET Amplification												All Cohorts (N=364)	
	Cohort 4 (N=69)		Cohort 5b (N=28)		Cohort 1a (N=69)		Cohort 5a (N=15)		Cohort 1b (N=42)		Cohort 2 (N=54)		Cohort 3 (N=30)		Total	Grade 3 or 4		
	Total	Grade 3 or 4	Total	Grade 3 or 4	Total	Grade 3 or 4	Total	Grade 3 or 4	Total	Grade 3 or 4	Total	Grade 3 or 4	Total	Grade 3 or 4				
Adverse events																		
Any event — no. (%)	68 (99)	52 (75)	28 (100)	21 (75)	67 (97)	48 (70)	15 (100)	10 (67)	42 (100)	27 (64)	54 (100)	35 (65)	28 (93)	22 (73)	355 (98)	244 (67)		
Most common events — no. (%) †																		
Peripheral edema	37 (54)	10 (14)	21 (75)	3 (11)	34 (49)	5 (7)	11 (73)	3 (20)	18 (43)	3 (7)	24 (44)	3 (6)	11 (37)	1 (3)	186 (51)	33 (9)		
Nausea ‡	32 (46)	0	13 (46)	0	32 (46)	5 (7)	9 (60)	0	17 (40)	3 (7)	24 (44)	0	15 (50)	0	163 (45)	9 (2)		
Vomiting ‡	18 (26)	0	7 (25)	0	24 (35)	5 (7)	4 (27)	1 (7)	16 (38)	1 (2)	12 (22)	0	9 (30)	1 (3)	102 (28)	9 (2)		
Blood creatinine increased	23 (33)	0	10 (36)	0	16 (23)	0	3 (20)	0	8 (19)	0	14 (26)	0	5 (17)	0	89 (24)	0		
Dyspnea	19 (28)	7 (10)	6 (21)	2 (7)	13 (19)	4 (6)	5 (33)	0	16 (38)	5 (12)	14 (26)	4 (7)	7 (23)	1 (3)	84 (23)	24 (7)		
Fatigue	18 (26)	6 (9)	4 (14)	1 (4)	11 (16)	1 (1)	2 (13)	1 (7)	10 (24)	2 (5)	16 (30)	2 (4)	6 (20)	3 (10)	80 (22)	16 (4)		
Decreased appetite ‡	15 (22)	1 (1)	8 (29)	0	15 (22)	1 (1)	4 (27)	0	7 (17)	0	12 (22)	1 (2)	8 (27)	0	76 (21)	3 (1)		
Constipation	10 (14)	2 (3)	4 (14)	0	16 (23)	0	6 (40)	0	9 (21)	0	10 (19)	0	7 (23)	1 (3)	66 (18)	3 (1)		
Diarrhea	12 (17)	0	5 (18)	0	19 (28)	1 (1)	4 (27)	1 (7)	6 (14)	0	7 (13)	0	8 (27)	0	64 (18)	2 (1)		
Cough	10 (14)	1 (1)	7 (25)	0	9 (13)	1 (1)	2 (13)	0	9 (21)	0	9 (17)	0	5 (17)	0	58 (16)	2 (1)		
Back pain	11 (16)	2 (3)	4 (14)	0	8 (12)	0	2 (13)	0	7 (17)	0	10 (19)	1 (2)	2 (7)	0	54 (15)	3 (1)		
Pyrexia	9 (13)	1 (1)	2 (7)	0	10 (14)	0	3 (20)	0	8 (19)	0	8 (15)	0	5 (17)	0	50 (14)	3 (1)		
ALT increased	8 (12)	6 (9)	4 (14)	2 (7)	12 (17)	7 (10)	5 (33)	2 (13)	4 (10)	1 (2)	5 (9)	2 (4)	3 (10)	0	48 (13)	23 (6)		
Asthenia	6 (9)	3 (4)	4 (14)	2 (7)	6 (9)	3 (4)	2 (13)	1 (7)	8 (19)	0	11 (20)	3 (6)	3 (10)	1 (3)	42 (12)	13 (4)		
Pneumonia	7 (10)	4 (6)	2 (7)	0	12 (17)	3 (4)	1 (7)	0	7 (17)	3 (7)	3 (6)	3 (6)	3 (10)	1 (3)	39 (11)	17 (5)		
Weight loss	9 (13)	0	3 (11)	0	7 (10)	1 (1)	3 (20)	0	4 (10)	0	2 (4)	1 (2)	4 (13)	0	36 (10)	2 (1)		
Noncardiac chest pain	5 (7)	1 (1)	1 (4)	0	10 (14)	2 (3)	3 (20)	0	5 (12)	1 (2)	7 (13)	0	1 (3)	0	35 (10)	4 (1)		

Serious adverse event — no. (%)	36 (52)	30 (43)	14 (50)	12 (43)	42 (61)	36 (52)	9 (60)	5 (33)	21 (50)	19 (45)	30 (56)	22 (41)	15 (50)	13 (43)	184 (51)	152 (42)
Event leading to dis- continuation — no. (%)	14 (20)	8 (12)	6 (21)	5 (18)	11 (16)	8 (12)	3 (20)	2 (13)	5 (12)	5 (12)	8 (15)	1 (2)	5 (17)	2 (7)	56 (15)	35 (10)
Exposure																
Median duration—wk	22.1	48.2			17.6	15.3			11.8	8.8			6.6		15.3	
Range—wk	0.4– 136.0	4.0– 117.4			0.9– 201.0	3.1– 61.1			1.0– 215.0	0.6– 195.0			1.6– 73.0		0.4– 215.0	

* The data-cutoff date was January 6, 2020. The overall analysis included all patients from cohorts 1 through 7 who received at least one dose of capmatinib. ALT denotes alanine aminotransferase.

† The most common adverse events were those reported in more than 20% of the patients in any cohort.

‡ Capmatinib was administered under fasting conditions; food restriction was removed in cohorts 6 (34 patients) and 7 (23 patients). Safety data for cohorts 6 and 7 are shown in Tables S8 and S9, and safety data for cohorts with fasting restrictions, as compared with those without fasting restrictions, are shown in Table S10.

mutation leading to *MET* exon 14 skipping and independent of the co-occurrence of *MET* amplification — findings that suggest that off-target resistance mechanisms may play a role. Molecular characterization of larger cohorts involving patients with tumors with a *MET* exon 14 skipping mutation might elucidate such mechanisms. These observations support the need for broad molecular profiling before the decision point regarding first-line therapy. The high concordance of detection of *MET* exon 14 skipping mutations by both RT-PCR testing and next-generation sequencing is particularly important, given the need to test for an increasing number of therapeutically relevant genetic alterations in patients with advanced NSCLC with limited tumor material.

Brain metastases may develop in up to 20 to 40% of patients with stage IV NSCLC,⁴⁶ and the incidence among patients with NSCLC with a *MET* exon 14 skipping mutation is similar⁴⁷; the percentage of patients with brain metastases among patients with a *MET* exon 14 skipping mutation in this study was 11 to 23% (Table 1 and Table S2). The activity of capmatinib in the brain was encouraging; responses were observed in 7 of 13 patients with NSCLC with a *MET* exon 14 skipping mutation, including complete resolution of brain metastases in 4 patients. A total of 3 of the 7 patients with a response had received radiotherapy previously, which could have contributed to responses in brain metastases. Given the importance of central nervous system control to maintain best disease response and quality of life, confirmation of these preliminary findings in larger populations of patients will be important.

Our study confirmed the known safety profile of capmatinib.¹⁷ The majority of adverse events were of grade 1 or 2, were predictable, and were reversible with dose adjustments. The most frequently reported adverse events related to capmatinib treatment were peripheral edema, nausea, vomiting, and increased blood creatinine level. Peripheral edema and gastrointestinal toxic effects are known side effects of *MET* inhibitors. The reversible increase in the creatinine level was probably due to inhibition of renal transporters multidrug and toxic extrusion protein 1 and 2-K (*MATE1* and *MATE2-K*), because capmatinib is an inhibitor of these transporters (unpublished data). Approximately 10 to 40% of

the serum creatinine is cleared by means of active tubular secretion by renal transporters such as MATE and organic anion transporter, in addition to renal glomerular filtration.⁴⁸

Capmatinib therapy showed efficacy in patients with NSCLC with a *MET* exon 14 skipping mutation. These results and the safety profile, involving mainly low-grade and reversible adverse events, suggest that capmatinib may be a new therapeutic option in patients with advanced NSCLC with a *MET* exon 14 skipping mutation.

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APPENDIX

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REFERENCES

- Comoglio PM, Trusolino L, Boccaccio C. Known and novel roles of the *MET* oncogene in cancer: a coherent approach to targeted therapy. *Nat Rev Cancer* 2018;18:341-58.
- Koch JP, Aebbersold DM, Zimmer Y, Medová M. *MET* targeting: time for a rematch. *Oncogene* 2020;39:2845-62.
- Awad MM, Oxnard GR, Jackman DM, et al. *MET* exon 14 mutations in non-small-cell lung cancer are associated with advanced age and stage-dependent *MET* genomic amplification and c-Met overexpression. *J Clin Oncol* 2016;34:721-30.
- Frampton GM, Ali SM, Rosenzweig M, et al. Activation of *MET* via diverse exon 14 splicing alterations occurs in multiple tumor types and confers clinical sensitivity to *MET* inhibitors. *Cancer Discov* 2015;5:850-9.
- Schrock AB, Frampton GM, Suh J, et al. Characterization of 298 patients with lung cancer harboring *MET* exon 14 skipping alterations. *J Thorac Oncol* 2016;11:1493-502.
- Paik PK, Drilon A, Fan P-D, et al. Response to *MET* inhibitors in patients with stage IV lung adenocarcinomas harboring *MET* mutations causing exon 14 skipping. *Cancer Discov* 2015;5:842-9.
- Tong JH, Yeung SF, Chan AWH, et al. *MET* amplification and exon 14 splice site mutation define unique molecular subgroups of non-small cell lung carcinoma with poor prognosis. *Clin Cancer Res* 2016;22:3048-56.
- Reungwetwattana T, Liang Y, Zhu V, Ou SI. The race to target *MET* exon 14 skipping alterations in non-small cell lung cancer: the why, the how, the who, the unknown, and the inevitable. *Lung Cancer* 2017;103:27-37.
- Yeung SF, Tong JHM, Law PPW, et al. Profiling of oncogenic driver events in lung adenocarcinoma revealed *MET* mutation as independent prognostic factor. *J Thorac Oncol* 2015;10:1292-300.
- Onozato R, Kosaka T, Kuwano H, Sekido Y, Yatabe Y, Mitsudomi T. Activation of *MET* by gene amplification or by splice mutations deleting the juxtamembrane domain in primary resected lung cancers. *J Thorac Oncol* 2009;4:5-11.
- Okuda K, Sasaki H, Yukiue H, Yano M, Fujii Y. *Met* gene copy number predicts the prognosis for completely resected non-small cell lung cancer. *Cancer Sci* 2008;99:2280-5.
- Cappuzzo F, Marchetti A, Skokan M, et al. Increased *MET* gene copy number

- negatively affects survival of surgically resected non-small-cell lung cancer patients. *J Clin Oncol* 2009;27:1667-74.
13. Schildhaus HU, Schultheis AM, Rüschoff J, et al. MET amplification status in therapy-naïve adeno- and squamous cell carcinomas of the lung. *Clin Cancer Res* 2015;21:907-15.
14. Spigel DR, Edelman MJ, O'Byrne K, et al. Results from the phase III randomized trial of onartuzumab plus erlotinib versus erlotinib in previously treated stage IIIB or IV non-small-cell lung cancer: METLung. *J Clin Oncol* 2017;35:412-20.
15. Jenkins RW, Oxnard GR, Elkin S, Sullivan EK, Carter JL, Barbie DA. Response to crizotinib in a patient with lung adenocarcinoma harboring a MET splice site mutation. *Clin Lung Cancer* 2015;16(5):e101-e104.
16. Waqar SN, Morgensztern D, Sehn J. MET mutation associated with responsiveness to crizotinib. *J Thorac Oncol* 2015;10(5):e29-e31.
17. Schuler M, Berardi R, Lim W-T, et al. Molecular correlates of response to capmatinib in advanced non-small-cell lung cancer: clinical and biomarker results from a phase I trial. *Ann Oncol* 2020;31:789-97.
18. Drilon A, Clark JW, Weiss J, et al. Antitumor activity of crizotinib in lung cancers harboring a MET exon 14 alteration. *Nat Med* 2020;26:47-51.
19. Liu X, Wang Q, Yang G, et al. A novel kinase inhibitor, INCB28060, blocks c-MET-dependent signaling, neoplastic activities, and cross-talk with EGFR and HER-3. *Clin Cancer Res* 2011;17:7127-38.
20. Baltschukat S, Engstler BS, Huang A, et al. Capmatinib (INC280) is active against models of non-small cell lung cancer and other cancer types with defined mechanisms of MET activation. *Clin Cancer Res* 2019;25:3164-75.
21. Wolf J, Seto T, Han J-Y, et al. Capmatinib in METΔex14-mutated advanced non-small cell lung cancer (NSCLC): efficacy data from the phase II GEOMETRY mono-1 study. *J Clin Oncol*. 2019;37:15 Suppl:9004. abstract.
22. Heist RS, Seto T, Han J-Y, et al. Capmatinib (INC280) in METΔex14-mutated advanced non-small cell lung cancer (NSCLC): efficacy data from the phase 2 GEOMETRY mono-1 study. *Neuro Oncol* 2019;21:vi56. abstract.
23. Shih K, Falchook GS, Becker K, et al. A phase Ib study evaluating the c-MET inhibitor INC280 in combination with bevacizumab in glioblastoma multiforme (GBM) patients. *Neuro Oncol* 2016;18: Suppl 6:vi11-vi12. abstract
24. Wu Y-L, Zhang L, Kim D-W, et al. Phase Ib/II study of capmatinib (INC280) plus gefitinib after failure of epidermal growth factor receptor (EGFR) inhibitor therapy in patients with EGFR-mutated, MET factor-dysregulated non-small-cell lung cancer. *J Clin Oncol* 2018;36:3101-9.
25. Eisenhauer EA, Therasse P, Bogaerts J, et al. New Response Evaluation Criteria in Solid Tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009;45:228-47.
26. de Marinis F, Grossi F. Clinical evidence for second- and third-line treatment options in advanced non-small cell lung cancer. *Oncologist* 2008;13:Suppl 1: 14-20.
27. Weiss JM, Stinchcombe TE. Second-line therapy for advanced NSCLC. *Oncologist* 2013;18:947-53.
28. Zhou C, Wu Y-L, Chen G, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. *Lancet Oncol* 2011;12:735-42.
29. Scagliotti GV, Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naïve patients with advanced-stage non-small-cell lung cancer. *J Clin Oncol* 2008;26:3543-51.
30. Mok TS, Wu Y-L, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med* 2009;361:947-57.
31. Solomon BJ, Mok T, Kim D-W, et al. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. *N Engl J Med* 2014;371:2167-77.
32. Shaw AT, Ou S-HI, Bang Y-J, et al. Crizotinib in ROS1-rearranged non-small-cell lung cancer. *N Engl J Med* 2014;371:1963-71.
33. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al. Erlotinib in previously treated non-small-cell lung cancer. *N Engl J Med* 2005;353:123-32.
34. Garon EB, Ciuleanu T-E, Arrieta O, et al. Ramucicromab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial. *Lancet* 2014;384:665-73.
35. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. *N Engl J Med* 2015;373:123-35.
36. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. *N Engl J Med* 2015;373:1627-39.
37. Rittmeyer A, Barlesi F, Waterkamp D, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. *Lancet* 2017;389:255-65.
38. Herbst RS, Baas P, Kim D-W, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet* 2016;387:1540-50.
39. Camidge DR, Otterson GA, Clark JW, et al. Crizotinib in patients (pts) with MET-amplified non-small cell lung cancer (NSCLC): updated safety and efficacy findings from a phase 1 trial. *J Clin Oncol* 2018;36:Suppl:36. abstract.
40. Noonan SA, Berry L, Lu X, et al. Identifying the appropriate FISH criteria for defining MET copy number-driven lung adenocarcinoma through oncogene overlap analysis. *J Thorac Oncol* 2016;11:1293-304.
41. Paik PK, Felip E, Veillon R, et al. Tepotinib in non-small-cell lung cancer with MET exon 14 skipping mutations. *N Engl J Med* 2020;383:931-43.
42. Lu S. Phase II study of savolitinib in patients (pts) with pulmonary sarcomatoid carcinoma (PSC) and other types of non-small cell lung cancer (NSCLC) harboring MET exon 14 skipping mutations (METex14+). Presented at the 2020 American Society of Clinical Oncology Annual Meeting, Chicago, May 29–31, 2020. abstract.
43. Wolf J, Baik C, Heist RS, et al. Natural history, treatment (tx) patterns, and outcomes in MET dysregulated non-small cell lung cancer (NSCLC) patients (pts). Presented at the EORTC-NCI-AACR Molecular Targets and Cancer Therapeutics, Dublin, November 13–16, 2018. abstract (<https://stanfordhealthcare.org/publications/507/507112.html>).
44. Sabari JK, Leonardi GC, Shu CA, et al. PD-L1 expression, tumor mutational burden, and response to immunotherapy in patients with MET exon 14 altered lung cancers. *Ann Oncol* 2018;29:2085-91.
45. Reis H, Metznermacher M, Goetz M, et al. MET expression in advanced non-small-cell lung cancer: effect on clinical outcomes of chemotherapy, targeted therapy, and immunotherapy. *Clin Lung Cancer* 2018;19(4):e441-e463.
46. Ali A, Goffin JR, Arnold A, Ellis PM. Survival of patients with non-small-cell lung cancer after a diagnosis of brain metastases. *Curr Oncol* 2013;20(4):e300-e306.
47. Awad MM, Leonardi GC, Kravets S, et al. Impact of MET inhibitors on survival among patients with non-small cell lung cancer harboring MET exon 14 mutations: a retrospective analysis. *Lung Cancer* 2019;133:96-102.
48. Lepist E-I, Zhang X, Hao J, et al. Contribution of the organic anion transporter OAT2 to the renal active tubular secretion of creatinine and mechanism for serum creatinine elevations caused by cobicicistat. *Kidney Int* 2014;86:350-7.

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