

ORIGINAL ARTICLE

Tepotinib in Non–Small-Cell Lung Cancer with *MET* Exon 14 Skipping Mutations

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ABSTRACT

BACKGROUND

A splice-site mutation that results in a loss of transcription of exon 14 in the oncogenic driver *MET* occurs in 3 to 4% of patients with non–small-cell lung cancer (NSCLC). We evaluated the efficacy and safety of tepotinib, a highly selective *MET* inhibitor, in this patient population.

METHODS

In this open-label, phase 2 study, we administered tepotinib (at a dose of 500 mg) once daily in patients with advanced or metastatic NSCLC with a confirmed *MET* exon 14 skipping mutation. The primary end point was the objective response by independent review among patients who had undergone at least 9 months of follow-up. The response was also analyzed according to whether the presence of a *MET* exon 14 skipping mutation was detected on liquid biopsy or tissue biopsy.

RESULTS

As of January 1, 2020, a total of 152 patients had received tepotinib, and 99 patients had been followed for at least 9 months. The response rate by independent review was 46% (95% confidence interval [CI], 36 to 57), with a median duration of response of 11.1 months (95% CI, 7.2 to could not be estimated) in the combined-biopsy group. The response rate was 48% (95% CI, 36 to 61) among 66 patients in the liquid-biopsy group and 50% (95% CI, 37 to 63) among 60 patients in the tissue-biopsy group; 27 patients had positive results according to both methods. The investigator-assessed response rate was 56% (95% CI, 45 to 66) and was similar regardless of the previous therapy received for advanced or metastatic disease. Adverse events of grade 3 or higher that were considered by investigators to be related to tepotinib therapy were reported in 28% of the patients, including peripheral edema in 7%. Adverse events led to permanent discontinuation of tepotinib in 11% of the patients. A molecular response, as measured in circulating free DNA, was observed in 67% of the patients with matched liquid-biopsy samples at baseline and during treatment.

CONCLUSIONS

Among patients with advanced NSCLC with a confirmed *MET* exon 14 skipping mutation, the use of tepotinib was associated with a partial response in approximately half the patients. Peripheral edema was the main toxic effect of grade 3 or higher. (Funded by Merck [Darmstadt, Germany]; VISION ClinicalTrials.gov number, NCT02864992.)

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THE *MET* PROTO-ONCOGENE ENCODES A receptor tyrosine kinase, and binding to its ligand (hepatocyte growth factor [HGF]) induces downstream signaling through the RAS–RAF and phosphoinositide 3-kinase (PI3K) pathways. Aberrant *MET* signaling drives tumor growth through increased cell proliferation, survival, invasion, and metastasis. *MET* dysregulation through splice-site alterations that cause a loss of transcription of exon 14 in *MET* can result from point mutations, insertions or deletions, or large-scale whole-exon deletions. These alterations spatially disrupt distinct splicing sites at the acceptor or donor site flanking *MET* exon 14. As a result of *MET* exon 14 skipping mutations, the *MET* juxtamembrane domain, which contains a binding site for Y1003 CBL (an E3 ubiquitin ligase), is deleted; this leads to impaired *MET* ubiquitination, decreased *MET* turnover, and increased signaling.^{1,2}

Such *MET* alterations are primary oncogenic drivers that occur in 3 to 4% of patients with non–small-cell lung cancer (NSCLC)^{2–5} and can be detected in liquid-biopsy or tissue-biopsy samples. These tumors typically do not contain other known oncogenic drivers.^{2,3} Unlike patients with other oncogene-driven forms of NSCLC (e.g., ALK, EGFR, and ROS1), patients with *MET* exon 14 skipping mutations are typically 70 years of age or older.^{6,7}

Many tyrosine kinase inhibitors compete with ATP to block the phosphotransferase activity of their targets. Several ATP-competitive, small-molecule tyrosine kinase inhibitors targeting *MET* are being evaluated for the treatment of patients with NSCLC who have *MET* exon 14 skipping mutations. These drugs include nonselective type 1a inhibitors (e.g., crizotinib) and selective type 1b inhibitors (e.g., tepotinib, savolitinib, and capmatinib).^{8,9} Tepotinib is a once-daily, highly selective oral *MET* inhibitor^{10,11} that has shown promising clinical activity in patients with *MET*-driven tumors.^{11–14} We conducted the multicohort, open-label, phase 2 VISION study to evaluate the efficacy and side-effect profile of tepotinib in patients with advanced NSCLC with *MET* alterations. Here, we report the results in patients with *MET* exon 14 skipping mutations.

METHODS

STUDY DESIGN AND OVERSIGHT

The ongoing VISION study is being conducted at more than 130 sites in 11 countries. Patients

with *MET* exon 14 skipping mutations were enrolled in cohort A and those with *MET*-amplified disease (but without *MET* exon 14 skipping mutations) in cohort B; cohort C is currently enrolling patients with *MET* exon 14 skipping mutations for confirmatory analysis of the results in cohort A (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). The study aims to assess the antitumor activity and side-effect profile of 500 mg of tepotinib given orally once daily until disease progression, consent withdrawal, or adverse events leading to discontinuation. In this article, we report the results for cohort A, which has completed recruitment. All the patients provided written informed consent for participation in the study.

The study was performed in accordance with the principles of the Declaration of Helsinki, the Good Clinical Practice guidelines of the International Council on Harmonisation, local laws, and applicable regulatory requirements. The study was designed and funded by Merck (Darmstadt, Germany), and representatives of the sponsor were responsible for the collection and analysis of the data. The first author had full access to the data, and all the authors were involved in the data analysis and manuscript preparation and vouch for the completeness and accuracy of the data and the adherence of the study to the protocol, which is available at NEJM.org. Editorial support, including cowriting of the first draft of the manuscript with the first author, was provided by a medical writer employed by Syneos Health with funding from the sponsor.

PATIENTS

Patients were 18 years of age or older with histologically or cytologically confirmed, locally advanced or metastatic NSCLC with *MET* exon 14 skipping mutations. All the patients had measurable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, and a performance status of 0 or 1 on the Eastern Cooperative Oncology Group scale (which ranges from 0 to 5, with higher scores indicating greater disability). In addition, all the patients had negative results on local testing for the presence of *EGFR* mutations or *ALK* rearrangements. Prospective testing of *MET* exon 14 skipping mutations was performed centrally on circulating free DNA (cfDNA) obtained from plasma (liquid biopsy) with the use of next-generation sequencing panel Guardant360 (which includes 73 genes) or by

evaluating RNA obtained from fresh or archival (formalin-fixed, paraffin-embedded) tumor-biopsy tissue with the use of the Oncomine Focus Assay (which includes 52 genes); dual testing by the two biopsy methods was not a requirement for enrollment. (Details regarding testing are provided in the Supplementary Appendix.) Japanese patients could be enrolled on the basis of the criteria of LC-SCRUM (Lung Cancer Genomic Screening Project for Individualized Medicine).¹⁵ Patients could have received up to two courses of previous treatment for advanced or metastatic disease. Patients with brain metastases whose condition was neurologically stable and whose glucocorticoid dose was being tapered were eligible to participate, as were patients with untreated asymptomatic brain metastases measuring 1 cm or less in the longest diameter. Additional details regarding the enrollment criteria, including permitted concomitant medications, are provided in the protocol.

STUDY END POINTS AND ASSESSMENTS

The primary end point was a confirmed objective response (defined as a complete or partial response) as determined according to RECIST, version 1.1, on the basis of an assessment by an independent review committee. Secondary end points were the investigator-assessed objective response, duration of response, progression-free survival, and overall survival. To assess patient-reported outcomes, we used the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Lung Cancer Modules 13 and 30 (EORTC QLQ-LC13 and EORTC QLQ-C30) and the EuroQol Group 5-Dimension 5-Level questionnaire (EQ-5D-5L). The EORTC QLQ-C30 is a 30-item questionnaire consisting of five multiple-item functional subscales, three multiple-item symptom scales, a subscale of global health status and quality of life, and six single-item symptom scales assessing other cancer-related symptoms. The EORTC QLQ-LC13 is a 13-item lung cancer-specific supplement to the EORTC QLQ-C30. On the two EORTC scales, responses to all items are converted to a scale of 0 to 100 with a standard scoring algorithm. On the functionality scales and scales for global health status and quality of life, higher scores indicate a better level of functioning and quality of life. On the EQ-5D-5L questionnaire, scores on the visual-analogue health scale range from 0 to 100 and scores on the descriptive health

index range from 0 to 1, with higher scores indicating a better quality of life. Adverse events were assessed with the use of the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.

Blood samples for exploratory biomarker cfDNA analyses were obtained at baseline, at weeks 6 and 12, and at the end of treatment and were tested with the use of next-generation sequencing panel Guardant360. We defined a molecular cfDNA response to tepotinib as either a complete response (100% depletion of *MET* exon 14 alterations in cfDNA, indicating no detection of the *MET* exon 14 variant) or a deep response (>75% but <100% depletion).¹⁶

STATISTICAL ANALYSIS

No statistical comparisons were conducted; data were analyzed in a descriptive manner. According to the protocol, the primary efficacy analysis was conducted when the target enrollment population of at least 60 patients in both the liquid-biopsy and tissue-biopsy subgroups had undergone at least 9 months of follow-up (efficacy population). Three analysis groups were defined to independently assess findings in the liquid-biopsy group, the tissue-biopsy group, and the combined group (either biopsy method). In each primary-analysis group, the trial aimed to show an objective response rate of 40 to 50% and a lower limit of the corresponding two-sided exact Clopper–Pearson 95% confidence interval of at least 20% across all lines of therapy. We used Kaplan–Meier methods to analyze the duration of response, progression-free survival, and overall survival. The safety population included all the patients who had enrolled in the study and received at least one dose of tepotinib. Patients could be evaluated for an objective response if they had undergone at least two post-baseline assessments or had discontinued participation for any reason. The data cutoff for the analyses reported here was January 1, 2020.

RESULTS

PATIENTS

From September 13, 2016, through January 1, 2020, a total of 6708 patients were prescreened for *MET* alterations; 169 patients with *MET* exon 14 skipping mutations were subsequently screened for inclusion (Fig. S2). Of these patients, 152 were treated with tepotinib (safety population), and

Table 1. Characteristics of the Patients at Baseline (Efficacy Population).*

Characteristic	Liquid Biopsy (N=66)	Tissue Biopsy (N=60)	Combined Biopsy (N=99)
Median age (range) — yr	74 (49–88)	74 (41–94)	74 (41–94)
Sex — no. (%)			
Male	32 (48)	39 (65)	54 (55)
Female	34 (52)	21 (35)	45 (45)
Race — no. (%)†			
Asian	11 (17)	15 (25)	21 (21)
White	52 (79)	44 (73)	74 (75)
Smoking history — no. (%)‡			
Yes	28 (42)	30 (50)	46 (46)
No	34 (52)	22 (37)	45 (45)
ECOG performance-status score — no. (%)§			
0	14 (21)	16 (27)	22 (22)
1	52 (79)	44 (73)	77 (78)
Histologic subtype — no. (%)¶			
Adenocarcinoma	58 (88)	56 (93)	89 (90)
Squamous	6 (9)	3 (5)	7 (7)
Sarcomatoid	1 (2)	0	1 (1)
Previous courses of therapy for advanced or metastatic disease — no. (%)			
0	29 (44)	27 (45)	43 (43)
1	22 (33)	19 (32)	33 (33)
≥2	15 (23)	14 (23)	23 (23)
Brain metastases as identified by independent review — no. (%)	9 (14)	3 (5)	11 (11)

* Among the 99 patients who were included in the primary efficacy population (combined-biopsy group), the presence of a *MET* exon 14 skipping mutation was determined on liquid biopsy (in 66 patients) or on tissue biopsy (in 60 patients); 27 patients had positive results according to both methods. An additional patient was enrolled in the study but was not included in the efficacy population since she did not have confirmed non-small-cell lung cancer (NSCLC) with a *MET* exon 14 skipping mutation; this patient (who was 82 years of age, was white, had a history as a smoker, and had a score of 0 on the Eastern Cooperative Oncology Group [ECOG] performance-status scale) had squamous-cell lung cancer and had received one previous line of therapy. Percentages may not total 100 because of rounding.

† Race was determined by the investigators and was unknown or missing in 4 patients.

‡ Smoking history was unknown or missing in 8 patients.

§ Scores on the ECOG performance-status scale range from 0 (no disability) to 5 (death).

¶ One patient in the liquid-biopsy group had adenosquamous carcinoma, and 1 patient in the tissue-biopsy group had NSCLC not otherwise specified.

|| Brain metastases were nontarget lesions; there were no patients with target lesions in the brain.

99 had at least 9 months of follow-up (efficacy population; combined-biopsy group). The liquid-biopsy group included 66 patients, and the tissue-biopsy group included 60 patients; 27 patients had positive results according to both methods.

The median age of the patients in the efficacy population was 74 years; 46% of the patients had a history of smoking, and almost all (97%) had metastatic disease at study entry (Table 1). (Data for the safety population are provided in Table

S1.) The characteristics of the patients were similar among the three biopsy groups. Overall, only 3 patients had tumors with sarcomatoid features on histologic analysis, a characteristic that has been associated with the presence of *MET* exon 14 skipping mutations.⁶ Of the 99 patients, 56 had undergone previous treatment (including immunotherapy in 26); their response to previous therapy is shown in Table S2. The median duration of tepotinib treatment was 6.9

months (range, <0.1 to 36.7). The median follow-up in the efficacy population was 17.4 months; the median follow-up in the safety population was 11.8 months (range, 0.3 to 37.1).

EFFICACY

Among the 99 patients in the efficacy population, the objective response rate was 46% (95% confidence interval [CI], 36 to 57), according to independent review. All the responses were partial; no patients had a complete response. The response rate was consistent in the two biopsy groups: 48% (95% CI, 36 to 61) in the liquid-biopsy group and 50% (95% CI, 37 to 63) in the tissue-biopsy group (Fig. 1 and Table S3). The response rates were similar regardless of baseline characteristics and the number of lines of previous therapies (Fig. S3).

The response rate according to investigator assessment was 56% (95% CI, 45 to 66) in the efficacy population. The investigators found that 2 patients had a complete response and 53 patients had a partial response; the response rate was 56% (95% CI, 43 to 68) in the liquid-biopsy group and 62% (95% CI, 48 to 74) in the tissue-biopsy group. Tumor shrinkage was observed in most patients: 89% by independent review (Fig. 1) and 88% as assessed by investigators (Fig. S4A). Responses were rapid, with onset usually within 6 weeks after the initiation of treatment (Fig. S4B and S4C). Results were similar among the 146 patients who were enrolled in the study but may have had less than 9 months of follow-up (Table S4).

The median duration of response by independent review was 11.1 months (95% CI, 7.2 to could not be estimated) in the combined-biopsy group, 9.9 months (95% CI, 7.2 to could not be estimated) in the liquid-biopsy group, and 15.7 months (95% CI, 9.7 to could not be estimated) in the tissue-biopsy group (Fig. S5). The results according to investigator assessment were similar. The median duration of progression-free survival by independent review was 8.5 months (95% CI, 6.7 to 11.0) in the combined-biopsy group, 8.5 months (95% CI, 5.1 to 11.0) in the liquid-biopsy group, and 11.0 months (95% CI, 5.7 to 17.1) in the tissue-biopsy group (Fig. 2), with similar results according to investigator assessment (Fig. S6). At the time of data cutoff, 27 of 77 patients (35%) who had discontinued tepotinib received subsequent treatment (Table S5). The median duration of overall survival was 17.1

months (95% CI, 12.0 to 26.8) according to data that were not mature (Fig. S7).

Among the 11 patients with brain metastases (all of which were nontarget tumors [i.e., did not qualify to be defined as target lesions according to RECIST]), the response rate by independent review was 55% (95% CI, 23 to 83), with a median duration of response of 9.5 months (95% CI, 6.6 to could not be estimated). Among these patients, the median duration of progression-free survival was 10.9 months (95% CI, 8.0 to could not be estimated).

Completion rates for the EORTC QLQ-C30, EORTC QLQ-LC13, and EQ-5D-5L were more than 88% up to week 12. Mean changes from baseline in cough, as part of the EORTC QLQ-LC13 symptom score, exceeded the predefined minimally important difference (10 points), which indicated a reduction in symptoms; symptoms of dyspnea and chest pain showed stability (Fig S8A). Scores for global functioning showed stability in the patients' reported quality of life over time on the EORTC QLQ-C30 scale (Fig. S8B) and the EQ-5D-5L (data not shown).

SAFETY

Among the 152 patients in the safety population, adverse events of any cause were reported in 98% during treatment (Table S6). Adverse events that were considered by the investigators to be related to tepotinib were reported in 89% of the patients. Such events were of grade 3 or higher in 28% of the patients, including grade 3 in 25% and grade 4 in 2% (Table 2). The most common of these adverse events of grade 3 or higher was peripheral edema (in 7%). Increased levels of amylase and lipase were common but were mild to moderate in severity; such increases were asymptomatic and not accompanied by symptoms of pancreatitis. For the most common adverse events of any grade, the median time until onset ranged from 3 to 11 weeks after the initiation of tepotinib; for events of grade 3 or higher, the interval was 10 to 27 weeks.

Serious adverse events that were considered to be related to tepotinib were reported in 15% of the patients (Table S7). Treatment-related adverse events led to a dose reduction in 33% of the patients and to permanent discontinuation in 11%; such reductions or discontinuations were related mainly to peripheral edema, pleural effusion, or dyspnea (Table S8). Peripheral edema was the most common treatment-related adverse event

and led to a dose reduction in 16% of the patients and a dose interruption in 18%; permanent discontinuation was uncommon (5%). A total of 21 patients had adverse events leading to death while they were receiving tepotinib; one death of a 79-year-old patient with respiratory failure and dyspnea, secondary to interstitial lung disease, was considered by investigators to be related to tepotinib.

BIOMARKER FINDINGS IN THE LIQUID-BIOPSY GROUP

The baseline results of cfDNA molecular profiling of liquid-biopsy samples were available for 62 patients (Fig. 3). *MET* exon 14 mutations were diverse; most involved the splice acceptor site (68%), followed by the splice donor site (31%); 1 patient had a whole-exon deletion. Fifty percent of the mutations were indels, and 50% were

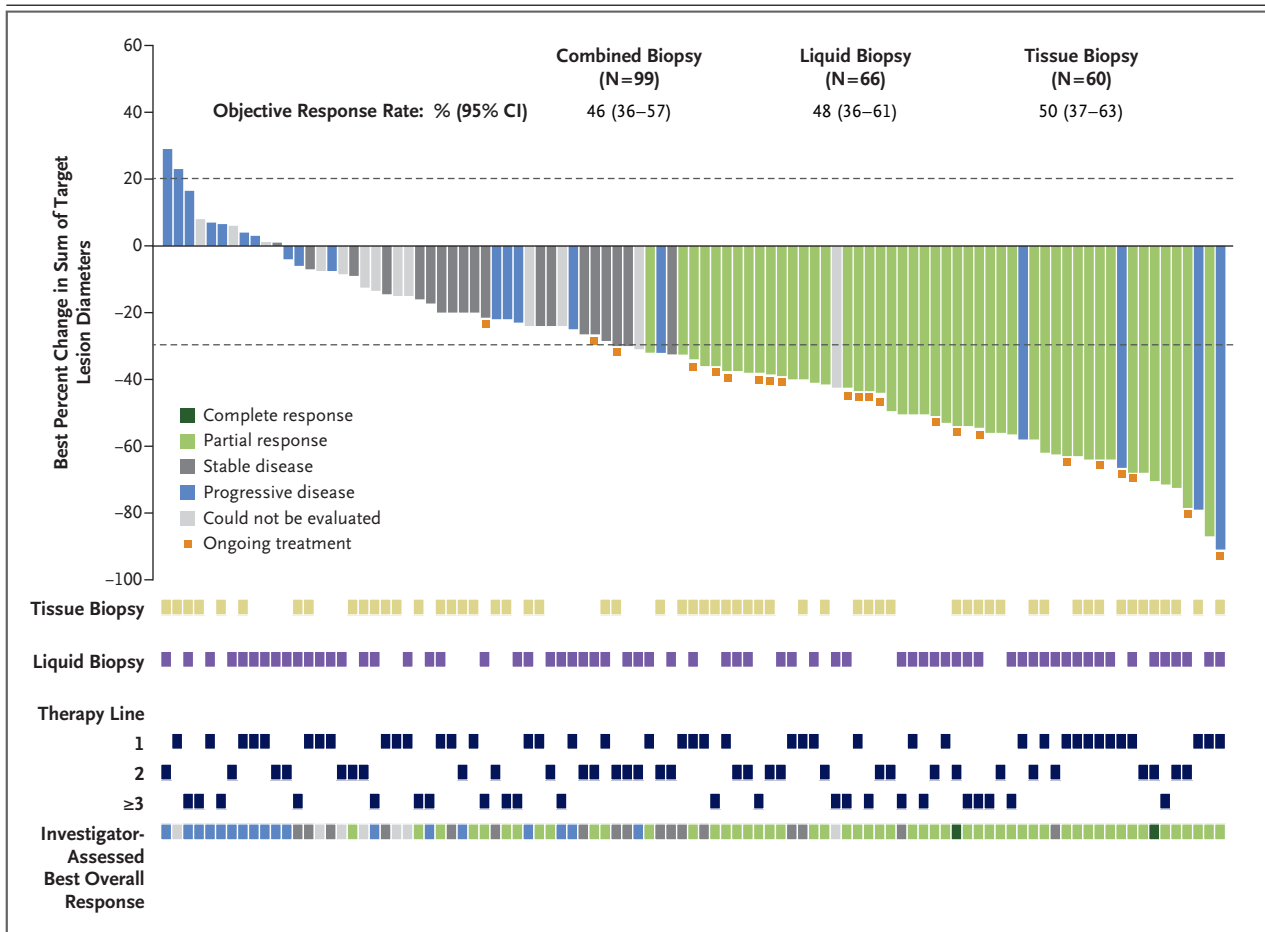


Figure 1. Response Rate and Change from Baseline in Tumor Burden.

At the top of the graph, the objective response rate among the 99 patients in the efficacy population (combined-biopsy group) is shown, according to whether the *MET* exon 14 skipping mutation was detected by liquid biopsy or tissue biopsy; 27 patients had positive results according to both methods. The waterfall plot shows the change in the sum of the longest diameters of lesions from baseline to the best post-baseline assessment by independent reviewers. Data for 2 patients are not shown, since baseline or on-treatment measurements were not available. Four patients who had a decrease of more than 30% in the sum of target lesions on independent review were classified as having progressive disease as the best response because of the growth of new lesions. These 4 patients all had a partial response to therapy, according to investigator assessment. At the time of data cutoff, treatment was ongoing in 2 of the 4 patients (17.3 months and 11.8 months); another patient discontinued treatment after 16.2 months because of an adverse event, and 1 patient discontinued treatment for other reasons after 5.4 months and no additional imaging was performed. The gold and purple boxes show whether the *MET* exon 14 skipping mutation was detected by tissue biopsy or liquid biopsy, and the boxes below show the number of previous lines of therapy that each patient received. The best overall response as assessed by investigators is shown at the bottom of the figure.

point mutations. No association was noted between the location or type of the *MET* exon 14 alteration and outcome. *TP53* mutations were identified in 48% of the patients. Other concomitant alterations were mutations in *NF1* and amplifications in *EGFR* (10% of patients with each mutation). Concomitant *MET* amplification was detected in 5 patients (8%), 4 of whom had a reduction in tumor size of more than 60%. According to independent review, no response was seen in patients with activating point mutations in *PI3KCA* (3%), *KRAS* (2%), and *NRAS* (2%) or with inactivating mutations in *PTEN* (3%) at baseline.

Matched baseline and on-treatment biomarker profiles from liquid-biopsy samples were available for 51 patients. Of these patients, 34 (67%) had a molecular cfDNA response. Of the 34 patients, 27 patients had a complete molecular cfDNA response and 7 had a deep molecular cfDNA response (Fig. 4). Among the patients with a molecular cfDNA response, 24 (71%) had a radiographic response according to independent review. Six patients had stable disease, resulting in a disease control rate of 88% (30 of 34 patients). Four patients who had a decrease in the cfDNA level did not have a corresponding clinical response. In 10 patients, an increase from baseline in the frequency of the variant causing

MET exon 14 skipping was observed; 1 of these patients (10%) had a response.

DISCUSSION

In the VISION trial, we found that tepotinib had durable antitumor activity in patients with advanced NSCLC with *MET* exon 14 skipping mutations, as detected on next-generation sequencing in samples obtained by either tissue or liquid biopsy. The response rate was 46 to 50% by independent review and 56 to 62% by investigator assessment. The onset of response was mostly within 6 weeks after the initiation of therapy, with a median duration of response as long as 15.7 months in one biopsy group. Outcomes were similar in the two biopsy categories.

These results compare favorably with results from other studies of investigational *MET* inhibitors involving patients with NSCLC who had *MET* exon 14 skipping mutations. In the PROFILE 1001 trial of crizotinib involving 65 patients, the response rate as assessed by investigators was 32% (95% CI, 21 to 45), with a median duration of progression-free survival of 7.3 months (95% CI, 5.4 to 9.1).¹⁷ In the GEOMETRY mono-1 phase 2 trial of capmatinib, the response rate by independent review was 41% (95% CI, 29 to 53),

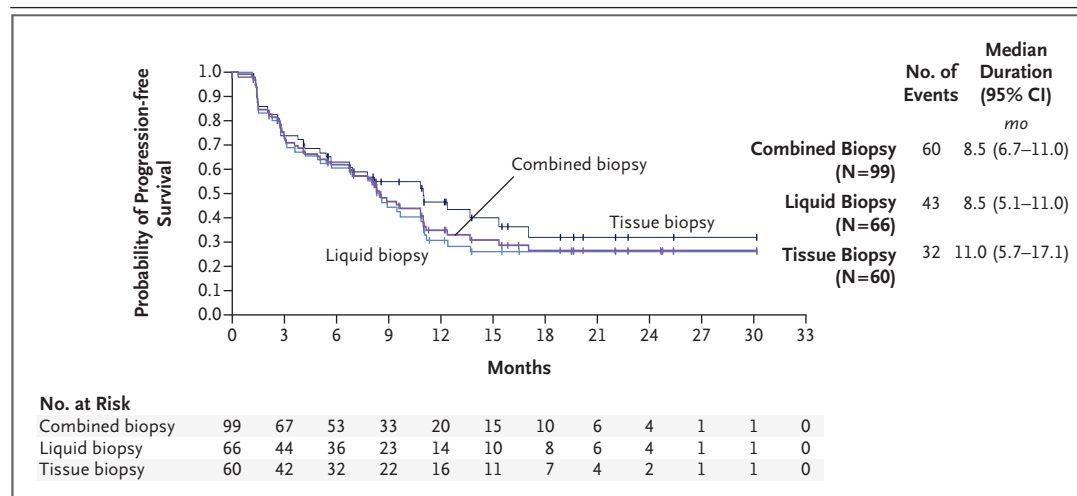


Figure 2. Progression-free Survival, According to Biopsy Group.

Shown are Kaplan–Meier estimates of progression-free survival among patients who underwent liquid biopsy or tissue biopsy; 27 patients underwent both biopsy methods. The duration of progression-free survival was defined as the time from the first administration of tepotinib to the date of the first documentation of progressive disease or death from any cause within 84 days after the last tumor assessment, whichever occurred first. Of the 60 events in the combined group, 36 events were progressive disease and 24 events were death.

Table 2. Adverse Events (Safety Population).*

Adverse Events	Safety Population (N = 152)			
	All Grades	Grade 1 or 2	Grade 3	Grade 4
	<i>number of patients (percent)</i>			
Any adverse event†	135 (89)	93 (61)	38 (25)	3 (2)
Peripheral edema	96 (63)	85 (56)	11 (7)	0
Nausea	39 (26)	38 (25)	1 (1)	0
Diarrhea	33 (22)	32 (21)	1 (1)	0
Blood creatinine increased	27 (18)	26 (17)	1 (1)	0
Hypoalbuminemia	24 (16)	21 (14)	3 (2)	0
Amylase increased	17 (11)	13 (9)	3 (2)	1 (1)
Lipase increased	13 (9)	9 (6)	4 (3)	0
Asthenia	12 (8)	11 (7)	1 (1)	0
Decreased appetite	12 (8)	11 (7)	1 (1)	0
Pleural effusion	12 (8)	8 (5)	4 (3)	0
Alopecia	12 (8)	12 (8)	0	0
Fatigue	11 (7)	10 (7)	1 (1)	0
Alanine aminotransferase increased	11 (7)	7 (5)	3 (2)	1 (1)
Aspartate aminotransferase increased	10 (7)	7 (5)	2 (1)	1 (1)
Vomiting	9 (6)	9 (6)	0	0
General edema	9 (6)	5 (3)	4 (3)	0
Upper abdominal pain	8 (5)	8 (5)	0	0

* Listed are the highest grades of adverse events that were considered by the investigator to be related to tepotinib and that were reported in at least 5% of the patients.

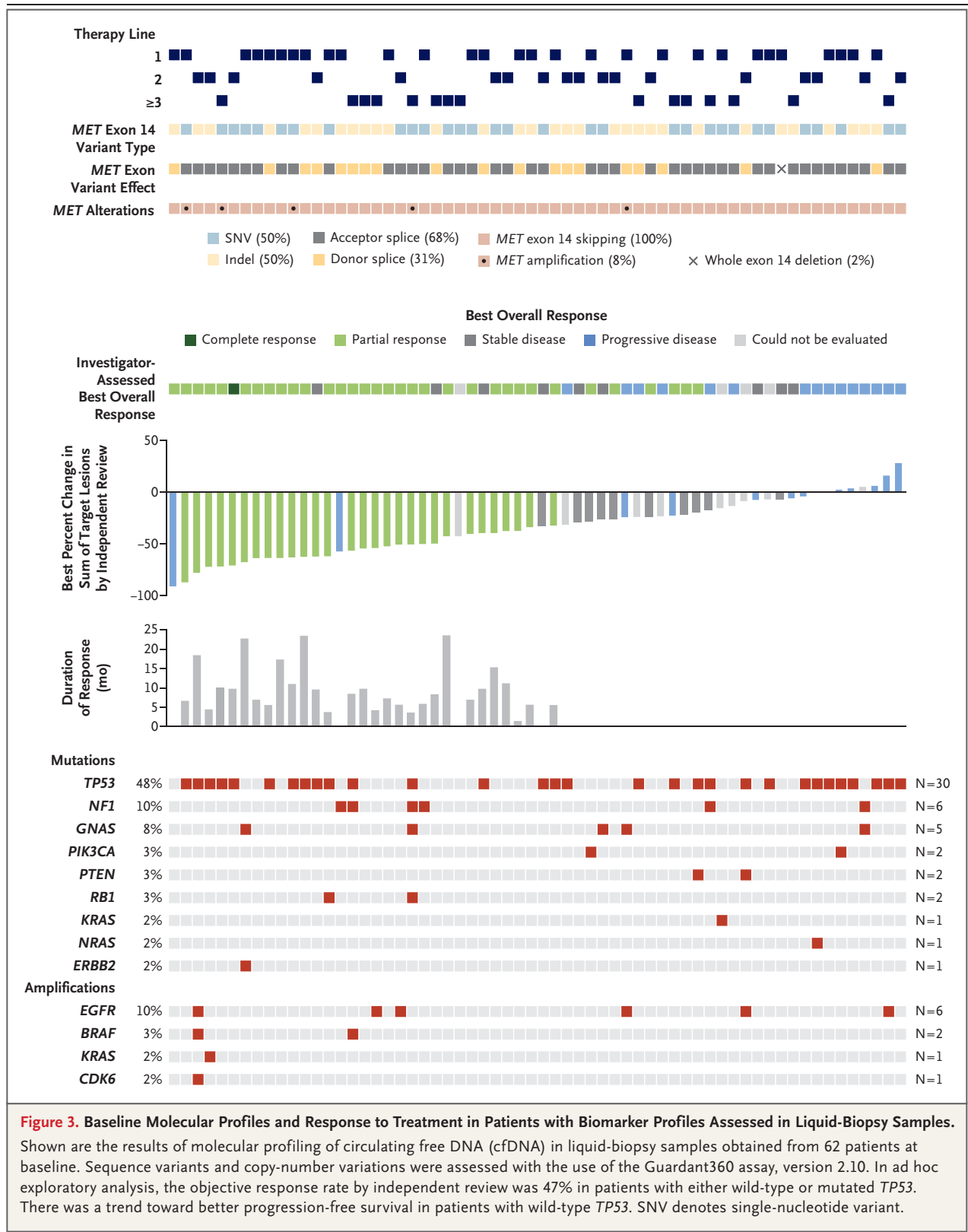
† The incidence of adverse events of any grade was similar in 39 patients who had received previous immunotherapy and in 113 patients who did not receive such therapy. There were few reports of pneumonitis of any grade in the study, but this adverse event occurred only in patients who had not received previous immunotherapy. One patient had a combination of respiratory failure and dyspnea related to interstitial lung disease that was reported as a grade 5 adverse event.

with a median duration of progression-free survival of 5.4 months (95% CI, 4.2 to 7.0) among 69 patients with pretreated disease; among 28 patients who had not received previous treatment, the response rate was 68% (95% CI, 48 to 84), with a median duration of progression-free survival of 9.7 months (95% CI, 5.5 to 13.9) and activity seen in patients with brain metastases.¹⁸ Confirmatory phase 2 data for capmatinib in the first-line setting are pending.

Outcomes with currently available therapies are typically poor in patients with NSCLC with *MET* mutations associated with exon 14 skipping, who are generally older (median age, 74 years) than patients who have more common and treatable molecular alterations.¹⁹⁻²¹ In patients lacking driver mutations, first-line immunotherapy with

or without chemotherapy has emerged as a new standard of care.²²⁻²⁵ The relative paucity of data from elderly patients in these studies warrants judicious use of these regimens in this population.²⁶ With regard to the interaction between *MET* exon 14 skipping mutations and the efficacy of immunotherapy, retrospective data suggest that the clinical activity of immune checkpoint inhibition is attenuated in this molecular subgroup (response rate, 16 to 17%), regardless of the expression of programmed death ligand 1.^{27,28}

In our trial, the patients' quality of life was maintained during receipt of tepotinib; symptoms of dyspnea were stable, whereas cough symptoms were reduced. The adverse-event profile reported here was similar to those in previous studies of tepotinib, with a low frequency of treatment dis-



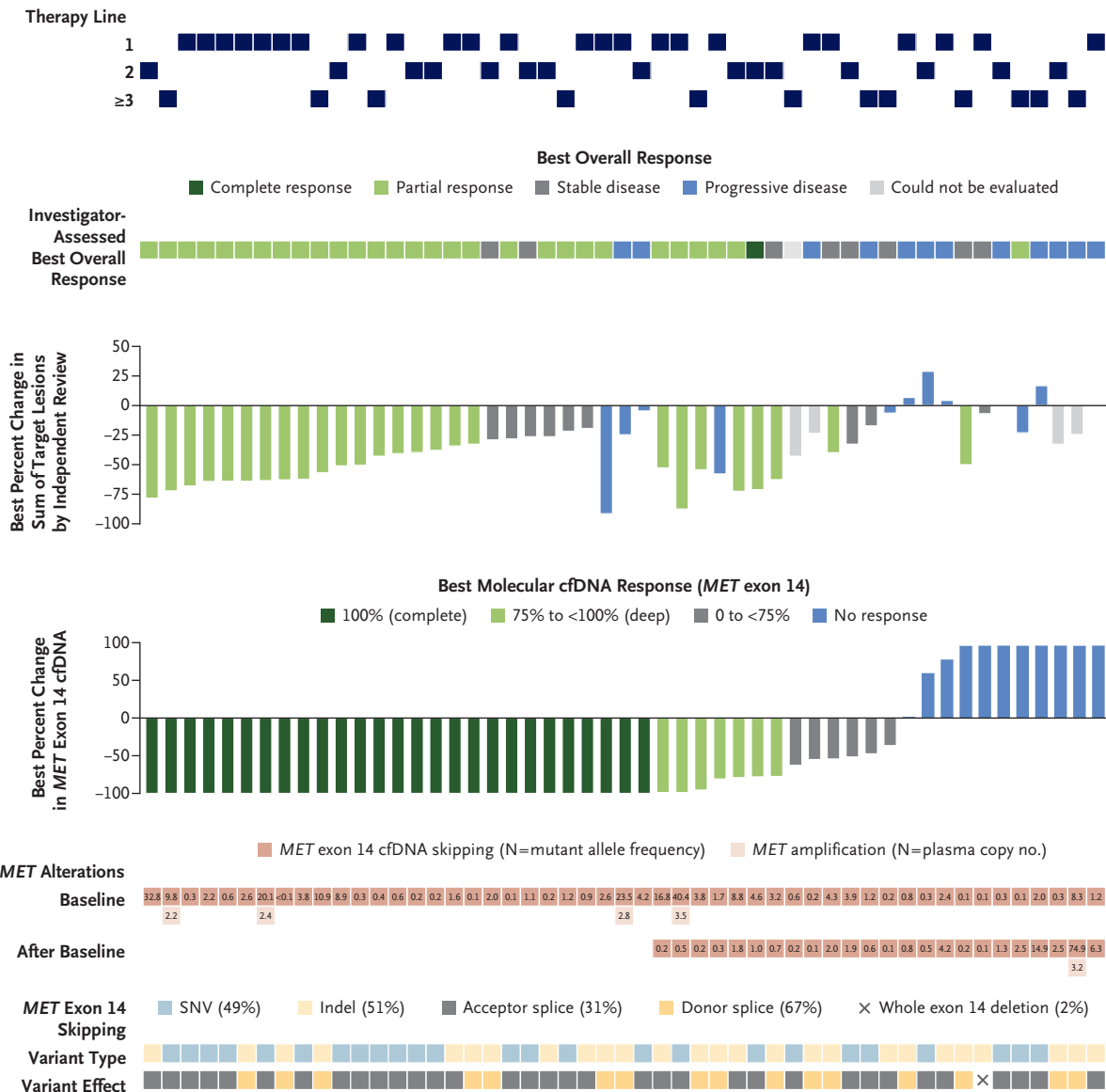


Figure 4. Best Response to Treatment and Molecular Response in Patients with Matched Baseline and On-Treatment Liquid-Biopsy Samples.

Matched baseline and on-treatment biomarker profiles from liquid-biopsy samples were available for 51 patients. Of these patients, 17 had a best molecular clearance of less than 75% of cfDNA. The clinical response as determined by independent review was a partial response in 2 patients, stable disease in 4 patients, and progressive disease in 6 patients; 5 patients could not be evaluated. Four patients had a molecular cfDNA response but were classified as having progressive disease by independent review. Of these patients, 2 had growth in new lesions: 1 had no other baseline alterations, and the other had a co-occurring *NF1* mutation. The other 2 patients had new lesions at progression: 1 had co-occurring amplifications in *EGFR* and a *GNAS* mutation, and the other had a *TP53* mutation. Shown at the bottom of the figure are the detected *MET* alterations at baseline and during treatment and the type of alteration that led to the *MET* exon 14 skipping. Numbers for *MET* exon 14 skipping represent the mutant allele frequencies, and numbers for *MET* amplification indicate plasma copy numbers. At the time of data cutoff, biomarker analyses from samples obtained at the time of disease progression were immature, with data available for only a few patients; however, one patient had a *MET* Y1230H mutation detected at the time of progression.

continuation.¹¹ Peripheral edema, the most commonly reported adverse event, has also been observed with other agents targeting the MET or HGF pathway and may be managed with limb elevation, compression stockings, reduction of dietary salt intake, and possibly the use of diuretics.^{29,30} Proactive monitoring for peripheral edema is recommended and can be managed with temporary discontinuation of tepotinib or dose reduction.

The convenience of using liquid biopsy as a diagnostic tool also allowed us to obtain longitudinal on-treatment biomarker data, which showed a high concordance between the molecular cfDNA response and clinical response on the basis of RECIST tumor measurement. The clinical progression of cancers in 4 patients who had decreased levels of cfDNA during treatment is unexplained. Although the use of the molecular cfDNA response is not yet part of standard practice in the management of solid tumors, as it is in some hematologic cancers, correlations between changes in the cfDNA level and tumor response have been reported in several cancer types, including lung cancer.¹⁶ Baseline cfDNA analysis provided valuable insight into the mutational profiles of patients with MET exon 14 skipping mutations. In agreement with the results of previous studies,^{2,3,31} we found that the patients in our study had very few co-occurring oncogenic drivers. Our data suggest that potential mechanisms of primary resistance to tepotinib may involve the RAS–RAF and PI3K–AKT pathways, which have previously been associated with resistance to MET inhibitors.^{8,31–33} As for acquired resistance mechanisms to tepotinib, a thorough examination of this question will need to wait until additional disease progression events occur and associated biomarker data become available. Acquired resistance mechanisms that have been reported with other MET inhibitors include amplification and mutations in KRAS and other RAS–MAPK pathway components.^{31,34,35} Secondary MET mutations (e.g., Y1230X), as reported here in one patient, have also been identified as acquired resistance mechanisms in both in vitro models³⁶ and clinical case reports.^{37–40}

In conclusion, the VISION study showed that the selective MET inhibitor tepotinib had durable

clinical activity in patients with NSCLC with MET mutations associated with exon 14 skipping. Results from this study have led to regulatory approval of tepotinib and its companion diagnostic assay for the detection of MET alterations (ArcherMET CDx) in March 2020 in Japan. These findings validate MET exon 14 skipping mutations as bona fide therapeutic targets and underscore the importance of routine testing for these MET alterations by means of liquid or tissue biopsy.

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APPENDIX

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