original reports

CNS Metastases in Patients With *MET* Exon 14–Altered Lung Cancers and Outcomes With Crizotinib

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abstract

PURPOSE Although *MET* exon 14 (*MET*ex14)–altered lung cancers were first identified more than a decade and a half ago, the frequency of CNS metastatic disease remains poorly defined. Furthermore, the seminal trial of crizotinib in these patients (PROFILE 1001) did not report patterns of CNS response or progression.

PATIENTS AND METHODS Patients with pathologically confirmed, advanced non–small-cell lung cancers (NSCLC) harboring a *MET*ex14 alteration by targeted DNA/RNA sequencing were studied. The incidence of brain metastases and the outcomes of MET inhibition with crizotinib were analyzed.

RESULTS Eighty-three patients with *MET*ex14-altered metastatic NSCLC were identified. The incidence of CNS metastases at diagnosis was 17% (95% CI, 10% to 27%). The lifetime incidence was 36% (95% CI, 26% to 47%); 83% of patients had parenchymal disease, and 17% had leptomeningeal disease. The probability of having brain metastasis at 1, 2, and 3 years was 24%, 35%, and 38%, respectively. Fifty-four patients received crizotinib. The median time to radiologic CNS progression was 5.8 months (range, 3.7-20.0 months). Patterns of crizotinib progression were as follows: intracranial only in 10% of patients, intracranial and extracranial in 12%, and extracranial only in 78%. In patients with brain metastases before treatment, the median time on crizotinib was 7.5 months (range, 7.2-11.7 months).

CONCLUSION CNS metastases, including leptomeningeal disease, occurred in more than a third of patients with *MET*ex14-altered lung cancers. In crizotinib-treated patients with or without CNS metastases, CNS failure was seen in less than a quarter of patients on progression.

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INTRODUCTION

MET exon 14 (*MET*ex14) alterations are oncogenic drivers that are found in 3%-4% of patients with non–small-cell lung cancers (NSCLCs).[1-3] Although CNS metastases are common (20%-50%) in metastatic lung cancers,[4] the frequency of brain metastases in *MET*ex14-altered lung cancers has not been reported. In addition, the PROFILE 1001 clinical trial of crizotinib that demonstrated an objective response rate (ORR) of 32% and a median progression-free survival of 7 months[5] only enrolled patients without active baseline brain metastases. The CNS outcomes and patterns of disease progression with crizotinib therapy have not been described.

PATIENTS AND METHODS

This study was approved by the Memorial Sloan Kettering Cancer Center (MSK; New York, NY) Institutional Review Board and conducted in accordance with US Common Rule and the Federalwide Assurance for the Protection of Human Subjects (FW00004998). Patients with *MET*ex14 alterations diagnosed between January 2014 and March 2018 at MSK were identified. Eligible patients had pathologically confirmed stage IV or recurrent metastatic NSCLC that harbored a *MET*ex14 alteration identified using next-generation sequencing of DNA (MSK-IMPACT/FoundationOne [Foundation Medicine, Cambridge, MA]) or RNA (anchored multiplex polymerase chain reaction; MSK-Solid Fusion Panel).[6-8] All patients had computed tomography or magnetic resonance imaging of the brain at the time of diagnosis of metastatic disease. Imaging after diagnosis was performed as per standard of care without predefined intervals; the 5 patients with known brain metastases who received crizotinib underwent CNS imaging approximately every 2-3 months, corresponding with their extracranial imaging.

A review of clinicopathologic characteristics and treatment history was performed. *MET* amplification, a concurrent alteration that occurs in a subset of *MET*ex14-altered lung cancers, was defined based on local assay cutoffs.[9] Patients treated with crizotinib were evaluated for systemic (extracranial and

ASSOCIATED CONTENT

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

In patients with *MET* exon 14–altered lung cancers, what is the frequency of CNS metastasis, and what are the CNS outcomes with the type Ia MET inhibitor crizotinib?

Knowledge Generated

Brain metastasis and leptomeningeal disease were identified in about a third of patients with advanced *MET* exon 14–altered lung cancers. Intracranial response was observed with crizotinib therapy, and eventual CNS progression was seen in less than a quarter of cases.

Relevance

Given the frequency of CNS metastases in *MET* exon 14–altered lung cancers, serial CNS imaging should be performed in patients who receive systemic therapy on clinical trials or in practice. Long-term comparative data are needed on CNS responses to crizotinib relative to type Ib selective MET inhibitors.

intracranial) or intracranial-only ORR and time to treatment discontinuation (TTD) using RECIST version 1.1. TTD was measured from crizotinib initiation to discontinuation for any reason. Overall survival (OS) was measured from the date of diagnosis of metastatic disease to death. TTD and OS were evaluated using Kaplan-Meier estimates. The log-rank test was used to compare OS in patients with or without brain metastasis. The probability of CNS metastasis over time was evaluated using the cumulative incidence function. The risk of developing brain metastases on treatment was computed using kernel smoothing.

RESULTS

Patients

Of 3,841 patients with NSCLC who underwent prospective next-generation sequencing, 114 (3%) had *MET*ex14 alterations; 83 patients (73%) had metastatic disease and were eligible for analysis. Clinicopathologic features (Table 1) were consistent with historic cohorts of *MET*ex14-altered lung cancers.[1,3] Most (65%) had a 5′ splice donor site alteration. and a minority (7%) had concurrent *MET* amplification.[9] The median follow-up time from the date of diagnosis of metastatic disease was 3.3 years (range, 0.4-10.2 years).

CNS Metastases

The incidence of CNS metastases is shown in Figure 1. Eighty-three patients had CNS imaging at the time of diagnosis of metastatic disease. Of these patients, 17% (95% CI, 10% to 27%; 14 of 83 patients) had brain metastasis. This included 1 patient with leptomeningeal disease as well. An additional 19% of patients (95% CI, 11% to 29%; 16 of 83 patients) developed brain metastasis later in their disease course. In total, CNS metastases were identified in 36% of patients (95% CI, 10% to 27%; 30 of 83 patients) with *MET*ex14-altered lung cancers. Among these individuals, 83% (25 of 30 patients) had parenchymal metastases and 17% (5 of 30 patients) had leptomeningeal disease. Sixty-five percent of patients with CNS disease received CNS-directed therapy; 52% (17 of 30 patients) received radiation and 13% (4 of 30 patients) underwent surgery.

The probability of developing brain metastases at 1, 2, and 3 years was 24%, 35%, and 38%, respectively (Fig 2A). Compared with not having brain metastasis, having brain metastasis at 6, 12, and 24 months increased the risk of death by 2.61-, 2.73-, and 2.94-fold (Fig 2B). The survival of patients who had brain metastases at diagnosis (median OS, 26.7 months) compared with those who did not (median OS, 27.2 months) was similar (hazard ratio, 0.70; 95% CI, 0.28 to 1.75; $P = .3$; Data Supplement).

Crizotinib Outcomes

Fifty-four patients with advanced *MET*ex14-altered lung cancers received crizotinib. The median line of systemic therapy at which crizotinib was administered was 2 (range, 1-7 lines). The ORR with crizotinib in all patients was 31% (95% CI, 18% to 45%). The median TTD was 7.8 months (95% CI, 5.5 to 13.0 months). The median OS was 13.7 months (95% CI, 10.8 to 22.9 months). Therapies administered after crizotinib are summarized in the Data Supplement.

Forty of the 54 patients developed progressive disease on crizotinib (Fig 3). The rates of intracranial-only, intracranial and extracranial, and extracranial-only progression were 10% (4 of 40 patients), 12% (5 of 40 patients), and 78% (31 of 40 patients), respectively. In total, the rate of CNS progression on crizotinib was 22% (9 of 40 patients). The median time to radiologic CNS progression was 5.8 months (range, 3.7-20.0 months). Of these patients, 44% (4 of 9 patients) developed new leptomeningeal disease (the rest had parenchymal metastases only). The median time to death after the diagnosis of leptomeningeal disease was 6 weeks (range, 2-62 weeks).

Only 5 of the 54 patients had known brain metastasis before the initiation of crizotinib. A partial response was observed in 1 patient, stable disease in 3 patients, and progressive

TABLE 1. Baseline Characteristics

Characteristic	No. of Patients (%; N = 83)[a]
Median age, years (range)	72 (44-88)
Sex	
Female	47 (57)
Male	36 (43)
Cigarette smoking	
Never	39 (47)
Former or current	44 (53)
Median pack-years, range	15 (0.25-64)
Histology	
Adenocarcinoma	59 (71)
Sarcomatoid carcinoma	14 (17)
Squamous cell	4 (5)
Adenosquamous	4 (5)
NSCLC-NOS[b]	2 (2)
Median lines of systemic therapy, No. (range)	2 (0-7)
MET exon 14 splice site alteration	
5′ splice donor site	54 (65)
3′ splice acceptor site	20 (24)
Unknown (RNA sequencing performed)	9 (11)
Concurrent *MET* amplification	
Yes	6 (7)
No	70 (84)
Unknown (RNA sequencing performed)	7 (9)

NOTE. The clinicopathologic features of 83 patients with advanced *MET* exon 14–altered lung cancer are summarized. All patients were evaluable for baseline CNS metastases using imaging performed at the diagnosis of metastatic disease.
Abbreviation: NSCLC-NOS, non–small-cell lung cancer not otherwise specified.
[a]Values are numbers and percentages unless otherwise noted.
[b]Poorly differentiated carcinoma (n = 1) and mixed histology (n = 1).

disease in the remaining patient (Data Supplement). The median TTD was 7.5 months (range, 7.2-11.7 months). Of the 5 patients with preexisting brain metastasis, 3 had RECIST-measurable intracranial disease. The best intracranial response was a partial response in 1 patient and stable disease in the remaining 2 patients.

DISCUSSION

We report the largest evaluation of the incidence of CNS metastasis in patients with *MET*ex14-altered lung cancers to date. CNS metastases at the time of diagnosis were observed in 17% of patients, and 19% developed CNS metastases during the course of their disease. Importantly, a substantial proportion of patients with *MET*ex14-altered lung cancers were found to have leptomeningeal disease, many of whom died quickly thereafter. The 36% lifetime incidence of CNS metastases observed in *MET*ex14-altered lung cancers was comparable to that of *KRAS*-mutant lung cancers (32%) and less than that seen in *EGFR*-mutant (47%), *HER2*-mutant (47%), and *RET* fusion–positive (46%) lung cancers (Data Supplement).[10]

MET kinase inhibition with crizotinib was effective in this series. Both overall and intracranial responses were achieved. The median time to crizotinib discontinuation (7.5 months) and time to CNS progression (5.8 months) were meaningful. These outcomes highlight the utility of crizotinib in patients with CNS metastases and complement the published activity of the drug in PROFILE 1001.[5] Crizotinib is widely available, has a well-recognized safety profile, and is currently listed in the National Comprehensive Cancer Network guidelines as a therapy for patients with advanced *MET*ex14-altered lung cancers.

In *ALK* fusion–positive lung cancers, CNS outcomes with crizotinib are poorer than those with other tyrosine kinase inhibitors (TKIs; ie, alectinib or brigatinib), and approximately half of patients have intracranial progression on crizotinib.[11,12] A similar rate of intracranial progression on crizotinib was seen in a small cohort of patients with *ROS1* fusion–positive NSCLC. The rate of intracranial progression on crizotinib was 22% in this series of patients with *MET*ex14-altered lung cancers. Although this rate seems lower compared with that observed in *ALK* fusion– and *ROS1* fusion–positive lung cancers, the observed rate may

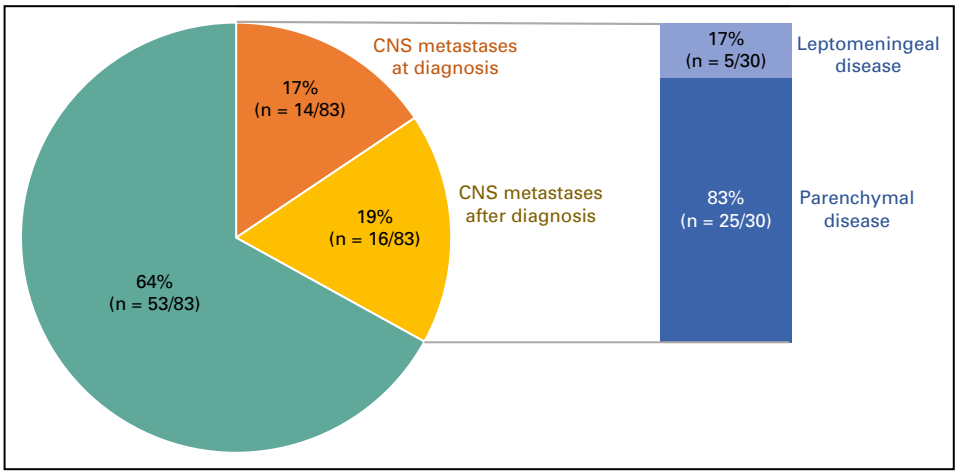

FIG 1. Brain metastases frequency. The frequency of CNS metastases at the diagnosis of metastatic disease or acquired during the course of treatment are depicted in 83 patients with advanced disease. The rates of parenchymal metastases and leptomeningeal disease are also shown.

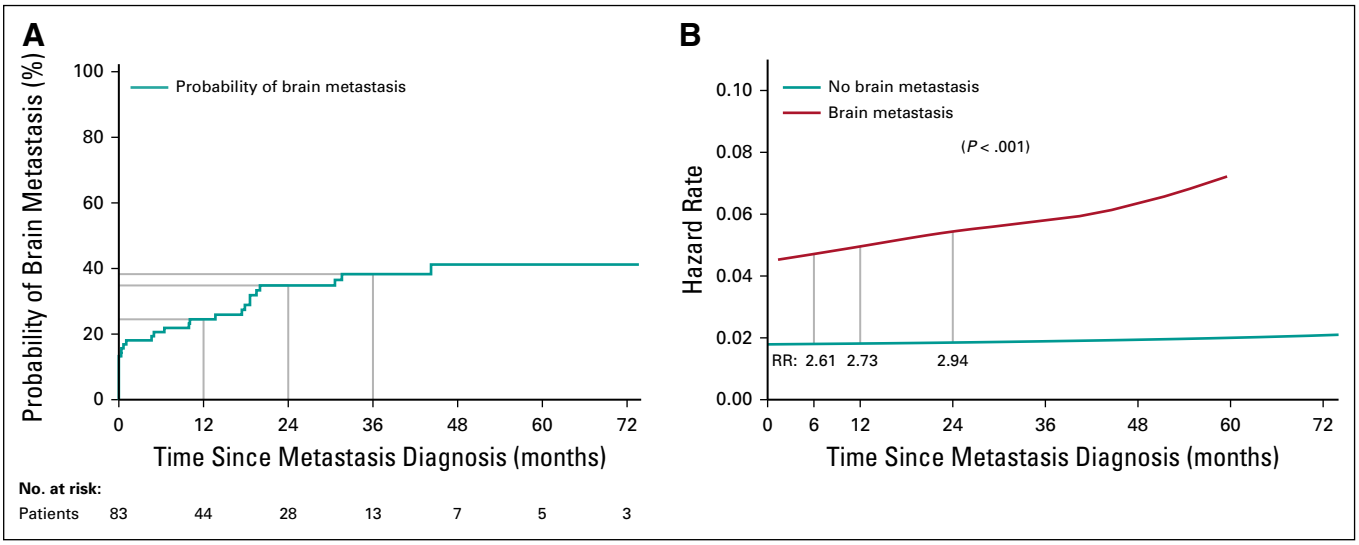

FIG 2. Cumulative brain metastases incidence and death. (A) The cumulative incidence function of the probability of developing brain metastasis in the 83 patients with *MET* exon 14–altered metastatic lung cancers is shown. The probabilities at 12, 24, and 36 months are 24%, 35%, and 38%, respectively. (B) Hazard functions of patients with *MET* exon 14–altered metastatic lung cancers who do and do not have brain metastases are depicted. The lines represent the likelihood a patient will experience death as a function of time depending on the presence of brain metastasis at baseline. The risk ratio (RR) comparing the 2 groups at a specific time is calculated by the division of hazard rates at that time point. Compared with not having brain metastasis, having brain metastasis at 6, 12, and 24 months increases the risk of death by 2.61-, 2.73-, and 2.94-fold, respectively.

be secondary to subclinical intracranial progression in asymptomatic patients who did not undergo CNS imaging after crizotinib progression, and the true frequency may be higher.

It is important to recognize that the true incidence of CNS metastases in *MET*ex14-altered lung cancers may have been underestimated in this series given that imaging was performed per standard of care without predefined intervals. Thus, it is critical that systemic therapy trials require CNS imaging before therapy initiation and serially even in patients without baseline CNS disease. This will allow more careful characterization of the frequency of CNS metastases and the profile of treatment response.

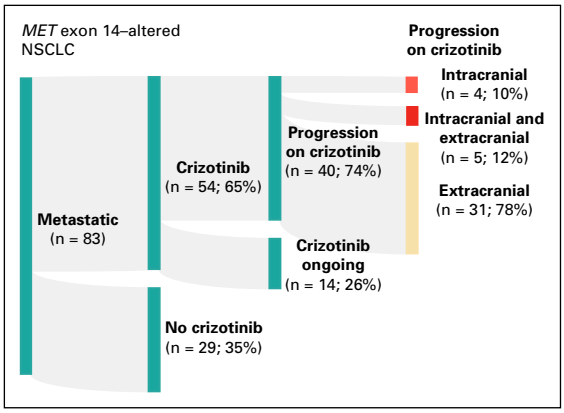

FIG 3. Crizotinib progression patterns. An alluvial plot of patients with *MET* exon 14–altered non–small-cell lung cancer (NSCLC) including 54 patients who were treated with crizotinib is shown. Patterns of disease progression including intracranial-only progression, intracranial and extracranial progression, and extracranial-only progression are depicted.

Next-generation MET-directed therapies, many of which are selective type Ib MET TKIs, are either approved or currently under study in the clinic. These include capmatinib,[13] tepotinib,[14] savolitinib,[15] glumetinib (ClinicalTrials.gov identifier: NCT04270591), and APL-101 (ClinicalTrials.gov identifier: NCT03175224). Preliminary data from the GEOMETRY phase II study of capmatinib showed that intracranial response was achieved in 7 (54%) of 13 patients, a rate higher than that observed with crizotinib in this series.[13] Intracranial responses were also observed in a phase II trial of savolitinib.[15] The VISION phase II study of tepotinib had 11 patients with brain metastases; however, intracranial response could not be determined because none of these patients had measurable intracranial disease.[14] Capmatinib and tepotinib have been granted accelerated approval and breakthrough designation, respectively, by the US Food and Drug Administration (FDA) for the treatment of *MET*ex14-altered lung cancers. Additional response data and long-term outcomes will elucidate the relative activity of these agents compared with crizotinib.

In conclusion, brain metastases and leptomeningeal disease occur in one third of *MET*ex14-altered lung cancers at diagnosis and during the course of therapy. This series demonstrates that crizotinib can achieve disease control in patients with *MET*ex14-altered lung cancers and intracranial metastases. However, selective MET inhibitors such as the FDA-approved type Ib inhibitor capmatinib may provide better intracranial disease control.

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