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Original Article

The Clinical Impact of Capmatinib in the Treatment of Advanced Non–Small Cell Lung Cancer with *MET* Exon 14 Skipping Mutation or Gene Amplification

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Purpose Capmatinib, an oral MET kinase inhibitor, has demonstrated its efficacy against non–small cell lung cancer (NSCLC) with *MET* dysregulation. We investigated its clinical impact in advanced NSCLC with *MET* exon 14 skipping mutation (*MET*ex14) or gene amplification.

Materials and Methods Patients who participated in the screening of a phase II study of capmatinib for advanced NSCLC were enrolled in this study. *MET* gene copy number (GCN), protein expression, and *MET*ex14 were analyzed and the patients' clinical outcome were retrospectively reviewed.

Results A total of 72 patients were included in this analysis (group A: GCN ≥ 10 or *MET*ex14, n=14; group B: others, n=58). Among them, 13 patients were treated with capmatinib (group A, n=8; group B, n=5), and the overall response rate was 50% for group A, and 0% for group B. In all patients, the median overall survival (OS) was 20.2 months (95% confidence interval [CI], 6.9 to not applicable [NA]) for group A, and 11.3 months (95% CI, 8.2 to 20.3) for group B (p=0.457). However, within group A, median OS was 21.5 months (95% CI, 20.8 to NA) for capmatinib-treated, and 7.5 months (95% CI, 3.2 to NA) for capmatinib-untreated patients (p=0.025). Among all capmatinib-untreated patients (n=59), group A showed a trend towards worse OS to group B (median OS, 7.5 months vs. 11.3 months; p=0.123).

Conclusion Our data suggest that capmatinib is a new compelling treatment for NSCLC with *MET* GCN ≥ 10 or *MET*ex14 based on the improved survival within these patients.

Key words Non-small-cell lung carcinoma, c-MET, Capmatinib

Introduction

Patients diagnosed with advanced non-small cell lung cancer (NSCLC) generally have a very poor prognosis. The median overall survival of patients with unresectable disease is 10-13 months when treated with standard platinum-doublet chemotherapeutic regimens, and 22 months when immune checkpoint inhibitor is combined with cytotoxic chemotherapy [1-4]. Nevertheless, NSCLC treatment has been revolutionized by the discovery of oncogenic driver mutations and the development of matched selective and targeted inhibitors. For epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor therapy, survival outcomes have been significantly improved, and anaplastic lymphoma kinase (ALK) inhibitors demonstrate even better results in metastatic lung cancer patients harboring these targetable oncogenic molecular alterations [5,6]. Therefore, identifying driver mutations and developing matching selective inhibitors is a key strategy in the treatment of these specific subsets of lung cancer.

Mesenchymal-epithelial transition factor (MET) is a receptor tyrosine kinase that initiates multiple signaling cascades upon activation through binding of hepatocyte growth factor. Pathways activated by MET activation include mitogen-activated protein kinase, phosphoinositide 3-kinase/AKT-axis, signal transducer and activator of transcription, and nuclear factor-κB complex, which are all key signaling pathways in tumorigenesis [7]. Accordingly, MET dysregulation has been validated as an oncogenic driver in many types of malignancies, including NSCLC [8,9].

MET dysregulation is known to be caused by various mechanisms, including overexpression or genetic alteration. However, gene amplification or mutations that lead to functional activation of kinase activity are widely accepted indices for clinically defining MET dysregulations in patients with these molecular alterations, and have been associated with poor clinical prognosis and response to selective MET inhibition [10-13].

Previous studies have assessed *MET* amplification by utilizing gene copy number (GCN) in surgically resected NSCLC samples, and found that high GCN levels are associated with worse survival [10,11,14]. In addition, positive

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responses to MET inhibitors have been reported in patients with de novo *MET* amplification [15,16]. Mutations causing skipping of exon 14 (*MET*ex14) are another well-known mechanism of MET dysregulation. Exon 14 encodes the binding site for casitas B-lineage lymphoma, the E3 ubiquitin ligase that degrades MET [17]. Thus, mutations that result in deletion of exon 14 invariably enhance MET stability, causing signaling dysregulation. Exon 14-skipping mutations are also reported to be associated with poor clinical outcome in NSCLC [10,18]. Importantly, small molecule MET inhibitors have been shown to be effective in patients harboring these genetic mutations [12,13,19-22]. And recently, crizotinib has been demonstrated to be a potent therapeutic option in lung cancer patients with *MET*ex14 in a prospective clinical trial [23]. The incidence of MET dysregulation is relatively rare in newly diagnosed NSCLC, with *MET* amplification reportedly occurring in 2%-3% of newly diagnosed cases [11,24,25], and mutations leading to exon 14 skipping occurring in 3%-4% of NSCLCs [12,22,25,26]. Nevertheless, identifying lung cancer patients with MET dysregulation is a priority as novel therapeutic agents become available.

Capmatinib (INC280) is a highly potent MET inhibitor that has been validated in preclinical research [27]. We participated in the phase 2 trial of capmatinib (GEOMETRY mono-1, NCT02414139) and screened locally advanced/metastatic NSCLC patients for eligibility [28]. The study was designed to evaluate the efficacy of MET inhibition in six different cohorts based on *MET* GCN levels or the presence of *MET*ex14. We tested these two profiles in addition to performing immunohistochemical (IHC) staining of MET for patients who participated in the screening.

In this retrospective study, we aimed to delineate the clinical characteristics and prognostic effect of MET dysregulation in advanced NSCLC by utilizing clinical data from patients who were screened for eligibility in the capmatinib trial. We also determined whether capmatinib affects the survival of patients with MET dysregulation, defined as either the presence of *MET*ex14 or GCN of at least 10 copies per cell.

Materials and Methods

1. Patients

Patients who were screened for eligibility for a phase 2 trial of capmatinib (INC280) at the National Cancer Center Hospital (Goyang, Korea) from December 2015 to January 2019 were included in this retrospective analysis (NCT02414139). All the patients were diagnosed with locally advanced (stage IIIB) or metastatic (stage IV) NSCLC, with no documented molecular alteration of *EGFR* or *ALK* genes. Data were mainly collected by review of electronic medical records. For patients enrolled in the trial, capmatinib was given at the dose of 400 mg twice a day in tablet formulation. Response to capmatinib was assessed by the Response Evaluation Criteria in Solid Tumors ver. 1.1.

2. Gene copy number

MET GCN was analyzed by fluorescence *in situ* hybridization (FISH) using the Vysis MET FISH kit (Abbott Molecular, Des Plaines, IL). In brief, 4-μm thick sections prepared from formalin-fixed paraffin-embedded (FFPE) tissue samples were deparaffinized, hybridized with probes targeting *MET*, and counterstained with 4′,6-diamidino-2-phenylindole (DAPI). At least 50 non-overlapping nuclei of tumor cells were selected using DAPI, and the average count of *MET* signals was determined for each specimen.

3. Detection of *MET* exon 14-skipping mutation

MET exon 14-skipping mutation was assessed by real-time quantitative polymerase chain reaction (RT-qPCR). RNA was extracted from FFPE samples, and cDNA was synthesized for use as the template. TaqMan probes spanning the exon 13 and 15 junction (Applied Biosystems, Foster City, CA) were used to detect exon 14 skipping in RT-qPCR.

4. IHC staining

All pathology slides were examined and reviewed by a board-certified pathologist with expertise in thoracic malignancies. IHC staining for MET (CONFIRM anti-Total c-MET (SP44), Ventana Medical Systems, Tucson, AZ) was performed on FFPE tissue sections using the Benchmark XT instrument (Ventana Medical Systems). Results were scored based on the intensity and proportion of the staining. Intensity was scored in a semiquantitative manner from 0 (absent) to 3 (strong). A proportion of the stained area was scored as either < 25%, 25%-50%, or ≥ 50%. By combining the intensity and proportion scales, IHC results were classified into three groups, modifying the previously reported scoring system [29,30]. High expression was defined as an intensity score greater than 3 and proportion ≥ 50%. An intermediate expression was defined as an intensity score of 2 and a proportion ≥ 50%, or an intensity score of 3 and a proportion between 25 and 50%. All other cases were classified as low expression.

5. Statistical analyses

Statistical analyses were performed using R (ver. 3.5.1, R Foundation for Statistical Computing, Vienna, Austria). Descriptive statistics were reported as numbers and percentages of patients. Continuous variables were compared using a t test, or analysis of variance (ANOVA) test. Categorical variables were analyzed using the chi-square test or Fisher

Table 1. Clinical characteristics of patients

	Total (n=72)	Group A (GCN ≥ 10 or *MET*ex14) (n=14, 19.4%)	Group B (others) (n=58, 80.6%)	p-value
Age, mean (range, yr)	62.2 (32-79)	67.7 (57-79)	60.8 (32-79)	0.014
Sex				
Male	60 (83.3)	14 (100)	46 (79.3)	0.106
Female	12 (16.7)	0	12 (20.7)	
Histology				
Adenocarcinoma	58 (80.6)	13 (92.9)	45 (77.6)	0.663
Squamous cell carcinoma	10 (13.9)	1 (7.1)	9 (15.5)	
Other	4 (5.5)	0	4 (6.9)	
Smoking history				
Never	8 (11.1)	2 (14.3)	6 (10.3)	
Current or former	64 (88.9)	12 (85.7)	52 (89.7)	0.648
Pack years	36.2 (0.1-120.0)	30.2 (1.0-94.0)	37.5 (0.1-120.0)	0.380
Stage				
III	7 (9.7)	3 (21.4)	4 (6.9)	0.128
IV	65 (90.3)	11 (78.6)	54 (93.1)	
ECOG PS				
0	24 (33.3)	4 (28.6)	20 (34.5)	0.762
1	48 (66.7)	10 (71.4)	38 (65.5)	

Values are presented as mean (range) or number (%). ECOG PS, Eastern Cooperative Oncology Group performance status; GCN, gene copy number; *MET*ex14, *MET* exon 14 skipping mutation.

Table 2. Assessments of the MET status

	Total	Group A (GCN ≥ 10 or *MET*ex14)	Group B (others)
GCN	72	14	58
Mean (range)	5.9 (1.8-22.8)	11.9 (4.1-22.8)	4.5 (1.8-8.5)
GCN ≥ 10	10 (13.9)	10 (71.4)	0
GCN < 10	62 (86.1)	4 (28.6)	58 (100)
Exon 14 skipping mutation	64	12	52
Present	5 (7.8)	5 (41.7)	0
Absent	59 (92.2)	7 (58.3)	52 (100)
Immunohistochemistry[a]	66	13	53
High	32 (48.5)	8 (61.5)	24 (45.3)
Intermediate	17 (25.8)	1 (7.7)	16 (30.2)
Low	17 (25.8)	4 (30.8)	13 (24.5)

Values are presented as number (%) unless otherwise indicated. GCN, gene copy number; *MET*ex14, *MET* exon 14 skipping mutation.
[a]High: intensity 3+ and proportion > 50%; Intermediate: intensity 2+ and proportion > 50%, or intensity 3+ and proportion 25%-50%; Low: intensity 1+ or proportion < 25%.

exact test. Overall survival (OS) was determined from the date the patient was diagnosed of locally advanced or metastatic NSCLC to the date of death or last follow-up. Survival was analyzed with the Kaplan-Meier method and compared using a log-rank test, and multivariable analysis was performed with the Cox regression method. Statistical significance was defined as a two-sided p-value < 0.05.

Results

1. Clinical characteristics

A total of 72 patients who participated in the screening for a phase 2 capmatinib trial were enrolled in this study. Data cutoff was August 19, 2019, and the median follow-up period was 10.0 months (with a range of 1.0-68.6 months).

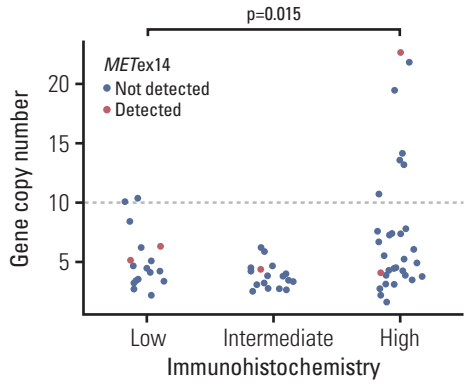

Fig. 1. Correlation of MET immunohistochemistry and gene copy numbers. Scatter plot of *MET* gene copy number values classified by immunohistochemistry staining results. A dotted line indicates the gene copy number threshold value of 10 copies per cell. Statistical analyses were performed using an ANOVA test. *MET*ex14, *MET* exon 14 skipping mutation.

In the phase 2 trial, participants were enrolled through various cohorts based on different GCN cutoff values and the presence of *MET*ex14. Nevertheless, to scrutinize the clinical impact of MET dysregulation, study participants were divided into two groups based on the GCN cutoff level of 10 and the presence of *MET*ex14. Fourteen patients were classified as group A (GCN ≥ 10, or *MET*ex14), and the other 58 patients as group B (Table 1, S1 Fig.). The majority of patients were male and had a history of adenocarcinoma histology and smoking. Patients in group A were significantly older than group B, with a mean age of 67.7 and 60.8 years, respectively (p=0.014). Although the difference was not statistically significant, all the patients in group A were male (Table 1).

2. Correlation of MET assessments

We analyzed MET status using GCN, *MET*ex14, and IHC. These data were available in 72, 64, and 66 patients, respectively (Table 2). Among patients in group A, 10 had high GCN levels (GCN ≥ 10), and five had *MET*ex14. These two alterations occurred simultaneously in one patient (S2 Fig.).

IHC for MET protein expression is a feasible assay that might reflect the level of *MET* amplification. Therefore, we sought whether MET IHC results have correlation with GCN values or *MET*ex14 mutations. Patients with high protein expression had significantly higher GCN values (ANOVA, p=0.015), and were also enriched for *MET*-amplified subjects (GCN ≥ 10). However, *MET*ex14 did not show a correlation with IHC. Among the five patients with *MET*ex14, two showed low expression, one showed intermediate, and two showed high expression results in IHC (Fig. 1).

3. Responses to capmatinib

For the capmatinib clinical trial (NCT02414139), patients were enrolled through six cohorts with varying degrees of *MET* GCN levels and treatment histories. Thirteen patients in our study population were enrolled in the trial, and of these, eight patients were classified as group A and five were group B (S3 Table, S1 Fig.). All 13 patients were male. Three patients had stage 3B cancer, and 10 patients had stage 4. Among the patients in group A, five patients had high GCN, two had *MET*ex14, and one patient had alterations in both GCN and *MET*ex14.

Capmatinib responses were different between the two groups. For patients in group A, the objective response rate (ORR) was 50%, with four partial responses (PR), one stable disease (SD), and three progressive diseases. Median duration of response was 16.1 months (range, 5.3 to 36.4 months). However, there was no PR in group B. Only one patient showed SD (Table 3).

4. Prognostic impact of MET dysregulation

In order to assess the prognostic impact of MET dysregulation in advanced NSCLC, we compared OS between the two groups of our study population. The median OS was 20.2 months (95% confidence interval [CI], 6.9 to not applicable [NA]) for patients in group A, and 11.3 months (95% CI,

Table 3. Best overall response to capmatinib

	Total (n=13)	Group A (GCN ≥ 10 or *MET*ex14) (n=8, 61.5%)	Group B (others) (n=5, 38.5%)
Best response, n (%)			
Complete remission	0	0	0
Partial response	4 (30.8)	4 (50.0)	0
Stable disease	2 (15.4)	1 (12.5)	1 (20.0)
Progressive disease	7 (53.8)	3 (37.5)	4 (80.0)
Overall response rate (%)	30.8	50.0	0

GCN, gene copy number; *MET*ex14, *MET* exon 14 skipping mutation.

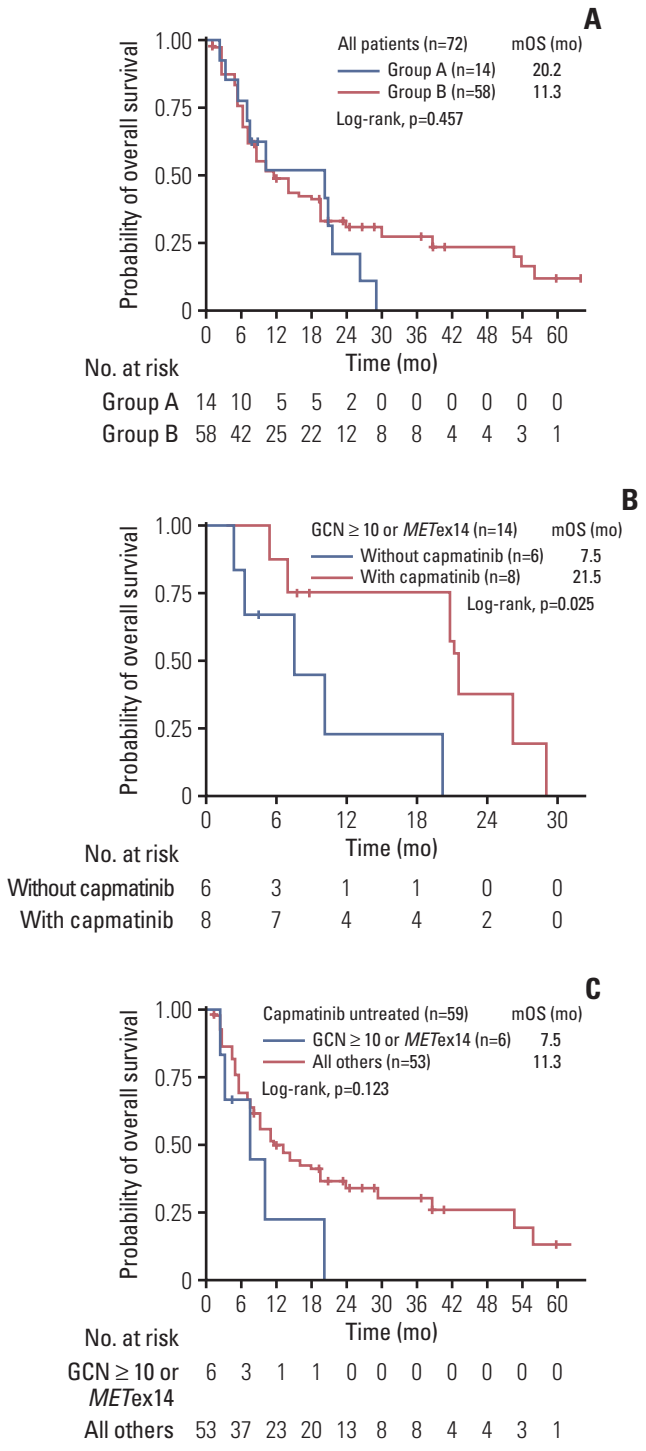

Fig. 2. Kaplan-Meier plots for overall survival. Kaplan-Meier plots for overall survival in all study patients (n=72) stratified by study groups (log-rank test, p=0.457) (A), patients with *MET* gene copy number (GCN) ≥ 10 or *MET* exon 14 skipping mutation (*MET*ex14) (n=14) stratified by capmatinib treatment (log-rank test, p=0.025) (B), and patients untreated with capmatinib (n=59) stratified by *MET* GCN levels (GCN > 10) and the presence of *MET*-ex14 (log-rank test, p=0.123) (C). mOS, median overall survival.

8.2 to 20.3) for group B. Although survival time was greater in group A, this difference was not statistically significant (log-rank test, p=0.457) (Fig. 2A). Because eight out of 14 patients in group A were enrolled in the capmatinib trial, we compared the OS according to capmatinib treatment among group A patients. The clinical characteristics of these patients, including histologic subtype, smoking history, clinical stage, and Eastern Cooperative Oncology Group performance status, were similar between the two subgroups (Table 4). Capmatinib was given as first-line therapy in one patient, and second-line therapy in seven patients. Patients who were not enrolled in the trial were treated with standard cytotoxic chemotherapy regimens. The median OS was 21.5 months (95% CI, 20.8 to NA) for patients treated with capmatinib, and 7.5 months (95% CI, 3.2 to NA) for patients without capmatinib (log-rank test, p=0.025) (Fig. 2B).

As capmatinib was beneficial to patients with GCN ≥ 10 and *MET*ex14, we investigated whether it would have led to a survival benefit in patients with lower GCN values. However, capmatinib treatment did not significantly prolong the OS of patients in subgroups with GCN values higher than 4 or 6 (S4A and S4B Fig.). Likewise, we also attempted to see whether IHC high expression could be a predictive biomarker for capmatinib treatment, but the OS also did not significantly differ within this subgroup (S4C Fig.).

To corroborate whether capmatinib treatment is a predictive biomarker for better clinical outcome in NSCLC patients with GCN ≥ 10 or *MET*ex14, we analyzed various clinical characteristics that are known to be associated with survival. In multivariable analyses, capmatinib treatment was the only factor associated with better clinical outcome (hazard ratio, 0.09; 95% CI, 0.01 to 0.73) (S5 Table).

Next, we compared OS among patients untreated with capmatinib (n=59) to determine whether MET dysregulation, defined as GCN ≥ 10 or *MET*ex14, was indeed associated with poor clinical outcome. The median OS for patients in group B and untreated with capmatinib (n=53) was 11.3 months (95% CI, 7.9 to 29.4), similar to the result for all patients in the whole group B patients. Since the median OS for group A patients untreated with capmatinib was 7.5 months (Fig. 2B), we observed a tendency towards poorer clinical outcome in advanced NSCLC patients harboring *MET* amplification or activating mutation (log-rank test, p=0.123) (Fig. 2C).

Discussion

In this study, we retrospectively analyzed the clinical characteristics and prognosis of advanced NSCLC patients screened for enrollment in a phase 2 trial of capmatinib, a

Table 4. Clinical characteristics of patients with c-MET GCN ≥ 10 or *MET*ex14

	Total (n=14)	Capmatinib (–) (n=6, 42.9%)	Capmatinib (+) (n=8, 57.1%)	p-value
Age (yr)	69.5 (57-79)	68.0 (57-74)	70.0 (57-79)	0.559
Sex				
Male	14 (100)	6 (100)	8 (100)	> 0.99
Female	0	0	0	
Histology				
Adenocarcinoma	13 (92.9)	6 (100)	7 (87.5)	> 0.99
Squamous cell carcinoma	1 (7.1)	0	1 (12.5)	
Other	0	0	0	
Smoking history				
Current or former	12 (85.7)	5 (83.3)	7 (87.5)	> 0.99
Never	2 (14.3)	1 (16.7)	1 (12.5)	
Stage				
III	3 (21.4)	1 (16.7)	2 (25.0)	> 0.99
IV	11 (78.6)	5 (83.3)	6 (75.0)	
ECOG PS				
0	4 (28.6)	2 (33.3)	2 (25.0)	> 0.99
1	10 (71.4)	4 (66.7)	6 (75.0)	
First-line treatment				
Platinum-doublet[a)]	13 (92.9)	6 (100)	7 (87.5)	
Capmatinib	1 (7.1)	0	1 (12.5)	
Second-line treatment				
Platinum-doublet[a)]	3 (21.4)	2 (33.3)	1 (12.5)	
Pemetrexed	1 (7.1)	1 (16.7)	0	
Capmatinib	7 (50.0)	0	7 (87.5)	

Values are presented as median (range) or number (%). ECOG PS, Eastern Cooperative Oncology Group performance status; GCN, gene copy number; *MET*ex14, *MET* exon 14 skipping mutation. [a)]Platinum-doublet regimens include pemetrexed+platinum, gemcitabine+platinum, or taxane+platinum.

potent and selective MET inhibitor [28]. These patients had no *EGFR* or *ALK* mutations, reflecting the population treated with platinum-doublets as standard therapy. The median OS of patients without *MET*ex14 and GCN < 10 was 11.3 months, which is consistent with results of previous landmark studies [1,2]. OS of all patients in group A (GCN ≥ 10 or *MET*ex14) was comparable to group B (GCN < 10 without *MET*ex14). However, considering that ORR of capmatinib was 50% among group A patients, we subdivided this group based on capmatinib treatment. In group A patients untreated with capmatinib, the median OS was 7.5 months, indicating that MET dysregulation defined by GCN ≥ 10 or the presence of *MET*ex14 may cause worse clinical outcome in locally advanced or metastatic NSCLC. However, the median OS was significantly longer in patients treated with capmatinib, and was independent of other clinical factors that could affect survival. These results imply that MET inhibition could be a compelling treatment option for appropriately selected patients. The definition of MET dysregulation is still controversial, and there is no established consensus. This is largely due to a lack of studies examining subgroups of patients that best respond to selective MET inhibition. Although defining *MET*ex14 is relatively clear using RT-qPCR or next generation sequencing, the definition *MET* amplification varies according to the study. Many researchers have used GCN values with a threshold of 3 or 5 copies per cell [31]. These previous studies used a cutoff value that split the prognosis of their study cohort, rather than a robust, scientifically determined value that would assure true activation of MET signaling [28]. However, in order to scrutinize the clinical impact of MET dysregulation in advanced NSCLC, we applied the highest cutoff value (GCN 10) to enrich for patients with the strongest MET activity [22].

In the phase 2 trial of capmatinib, study subjects were recruited into various cohorts based on GCN and *MET*ex14. The cutoff values of GCN for cohort entry were 4, 6, or 10. A recent biomarker analysis from the phase 1 trial of capmatinib showed that patients with *MET* GCN ≥ 6 showed

a high response rate (ORR 47%, 7 out of 15) [32]. Yet, in the phase 2 GEOMETRY mono-1 trial, capmatinib showed substantial antitumor activity in patients with *MET*ex14 or GCN ≥ 10 [28]. Overall response for patients with *MET*ex14 was 41% for second- or third-line therapy, and 68% for first-line therapy. And in patients with GCN ≥ 10, overall response was 29% for second- or third-line therapy, and 40% for first-line therapy. In this study, only one patient was treated with capmatinib as first-line; thus, it is difficult to compare the efficacy according to the presence of prior therapy. Response rates were lower in patients with *MET* GCN levels below 10, and these cohorts were closed at the interim analysis. Results from our analyses are in line with these data which supports that capmatinib should be indicated for patients with *MET*ex14 or GCN ≥ 10.

Of note, high *MET* GCN and *MET*ex14 activity was concurrently observed in one patient (1 out of 5 with *MET*ex14). This observation is in line with a previous study that detected concurrent *MET* amplification in 15%-20% of patients with *MET*ex14 [22,26]. Since the majority of patients with *MET* amplification or activating mutations had only one of these alterations, both GCN levels and mutational status of *MET* should be tested to determine whether patients would benefit from selective MET inhibition.

Immunohistochemical staining was not considered for enrollment in this study, but is widely used in clinics due to its feasibility. In addition, protein expression levels reflected in IHC results may be correlated with amount of gene amplification. Hence, we examined whether IHC was correlated with GCN levels, and found that *MET*-amplified patients were enriched in patients with positive IHC results. This finding was consistent with previous reports demonstrating that high IHC scores correlated with *MET* gene amplification measured by the FISH technique [24,32,33]. However, IHC did not seem to correlate with *MET*ex14, as only two out of five patients with the mutation had positive IHC results. Additionally, IHC was not a good predictive biomarker for response to capmatinib in our data (S4C Fig.), and also in the analysis of the phase 1 trial [32]. Therefore, IHC alone cannot be employed as a single screening tool for MET dysregulation, and additional gene amplification or mutational profiles must be performed for accurate molecular assessment.

Notably, *MET*ex14 mutations are reported to be relatively frequent in pulmonary sarcomatoid carcinoma (PSC) which is a rare but highly aggressive subtype of NSCLC. Sequencing results have revealed that it ranges from 13.6% to 31.8% in PSC, varying from study to study, but still higher than adenocarcinoma or squamous cell carcinoma [10,34,35]. None of our patients with *MET*ex14 were PSC, but this may be because there were only five patients in our cohort. Since *MET*ex14 is a druggable oncogenic mutation, efforts to search potential candidates are especially required in these patients.

This study has several limitations such as the retrospective nature and the small number of patients. Nevertheless, our key findings are in line with the results from the prospective multi-cohort phase 2 trial (GEOMETRY mono-1), and strengthens its conclusion [28]. Also, this is the first report demonstrating that in patients with *MET* GCN ≥ 10 and *MET*ex14, treatment with capmatinib led to an improved OS compared to those that were treated only with standard chemotherapy.

In conclusion, in this study, we showed that patients with *MET* GCN ≥ 10 or *MET*ex14 tend to show worse clinical outcome in locally advanced or metastatic NSCLC. Nevertheless, MET inhibitors could be a compelling treatment option for carefully selected patients. Although the definition of MET dysregulation is still controversial, stringent criteria could be used to refine the target population that would benefit the most from selective MET inhibition.

Electronic Supplementary Material

Supplementary materials are available at Cancer Research and Treatment website (https://www.e-crt.org).

Ethical Statement

This study was approved by the Institutional Review Board (IRB) of the National Cancer Center (IRB number; NCC2019-0074). All patients provided written consent for participating in the screening for the phase 2 trial of capmatinib (NCT02414139) and providing their data for GEOMETRY study.

Author Contributions

Conceived and designed the analysis: Choi W, Han JY.
Collected the data: Choi W, Park SY, Lee Y, Lim KY, Lee GK, Han JY.
Contributed data or analysis tools: Park SY, Lee Y, Lim KY, Park M, Han JY.
Performed the analysis: Choi W, Han JY.
Wrote the paper: Choi W, Han JY.

Conflicts of Interest

Conflict of interest relevant to this article was not reported.

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