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ORIGINAL RESEARCH

A phase II study of tepotinib in patients with advanced solid cancers harboring *MET* exon 14 skipping mutations or amplification (KCSG AL19-17)

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Background: We evaluated the efficacy and safety of tepotinib in patients with various solid cancers harboring *MET* exon 14 skipping mutation (*MET*ex14*)* or *MET* gene amplification.

Patients and methods: A phase II, multicenter study was conducted in patients with advanced or metastatic solid cancers who progressed after standard treatment, harboring either *MET*ex14 or *MET* amplification detected in tissue-based next-generation sequencing (NGS). The primary endpoint was objective response rate (ORR). For exploratory analyses, we analyzed the gene profiles using plasma NGS test.

Results: Thirty-five patients were enrolled. The ORR was 57.6% for all patients, 52.2% for those with *MET*ex14, and 70% for those with *MET* amplification. Median progression-free survival (PFS) was 8 months [95% confidence interval (CI) 4.5-11.5 months] and median overall survival (OS) was 14 months (95% CI 7.8-20.2 months) in all patients. For patients with non-small-cell lung cancer with *MET*ex14, the median PFS was 9 months (95% CI 4.7-13.4 months) and the median OS was 17 months [95% CI not applicable (NA)-NA]. For patients with *MET* amplification, the median PFS was 7 months (95% CI 1.5-12.5 months) and the median OS was 10 months (95% CI 5.8-14.2 months). The ORR of patients with *MET* dysregulation detected by plasma NGS was 72.2%, whereas the ORR was 30% in those without detection. The most common adverse events were peripheral edema, asthenia, transaminase elevation, and anorexia, mostly grade 1 or 2.

Conclusions: Tepotinib demonstrated consistent antitumor activity in patients with *MET*ex14, and promising antitumor activity in various cancers with *MET* amplification. Detection of *MET* dysregulation by plasma NGS may predict the response to tepotinib.

Key words: tepotinib, *MET* exon 14 skipping mutation, *MET* amplification, solid tumor

INTRODUCTION

The role of c-mesenchymal epithelial transition factor (c-MET) signaling in tumorigenesis and treatment resistance in several cancers has been extensively investigated. The *MET* gene is located at 7q21-q31 on chromosome 7 and encodes a protein tyrosine kinase of the hepatocyte growth factor (HGF) receptor family.[1] The binding of MET to its sole ligand, HGF, leads to homodimerization and trans-phosphorylation of intracellular tyrosine residues, triggering the activation of multiple downstream oncogenic signaling

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pathways, such as phosphatidylinositol 3-kinase-Akt, mitogen-activated protein kinase, and Janus kinase/signal transducer and activator of transcription.[2]

Various types of *MET* aberrations have been reported to be associated with carcinogenesis in solid tumors; however, *MET* exon 14 skipping is currently the only established target in non-small-cell lung cancer (NSCLC). Overexpression or amplification of *MET* has been extensively investigated in clinical trials; however, with variable or disappointing results, only high *MET* amplification remains a potential biomarker.[3,4]

Several *MET* inhibitors, including multi-kinase *MET* inhibitors and antibodies against *MET* or *HGF* have been investigated in numerous preclinical and clinical trials.[5] Among these, two small-molecule *MET*-selective tyrosine kinase inhibitors (TKIs), tepotinib and capmatinib, have recently shown clinical benefits and manageable side-effects in patients with NSCLC harboring *MET* exon 14 skipping mutation (*MET*ex14).[6,7] Currently, these two drugs are approved by the Food and Drug Administration and recommended as standard treatments for NSCLC with *MET*ex14.[8]

However, data on the use of *MET* TKIs in other cancers with *MET*ex14 or *MET* amplification are limited. In Korea, the K-MASTER Cancer Precision Medicine Diagnosis and Treatment Enterprise (K-MASTER project) was launched in June 2017 as a nationwide precision medicine oncology clinical trial platform. Targetable gene alterations were screened using next-generation sequencing (NGS) tests in patients with advanced solid tumors and patients with detected targetable gene alterations were assigned to appropriate clinical trials.[9] As a biomarker-matched clinical trial of the K-MASTER study, this trial aimed to investigate the clinical efficacy of tepotinib, a selective *MET* TKI, in various solid cancers with *MET*ex14 or *MET* amplification detected using the NGS panel of the K-MASTER study or of each institution.

PATIENTS AND METHODS

Study design and patients' eligibility

This investigator-initiated, prospective, open-label trial was conducted at 25 Korean Cancer Study Group-affiliated hospitals in Korea. This was a biomarker-matched clinical trial of the K-MASTER study involving Korean patients. Patients $\geq$19 years of age with pathologically confirmed solid cancer who were intolerant to standard treatment or had progressive disease after prior standard treatment for advanced disease were eligible. All patients had to submit *MET*ex14 status or *MET* gene copy number (CN) alterations in the archival or fresh tumor tissue specimen identified by the SNUH FIRST Cancer Panel or K-MASTER Cancer Panel, which were used for screening in the K-MASTER study. The results of the local NGS panel from each institution were also acceptable. The NGS reports of all patients suspected of having *MET*ex14 or *MET* amplification were submitted to the molecular steering committee and reviewed before making decisions regarding eligibility. For *MET* amplification, CN of $\geq$6.0 using the NGS panel was allowed and eligible for this study.

Other eligibility criteria included the presence of at least one measurable disease according to RECIST version 1.1; Eastern Cooperative Oncology Group performance status of 0-1; adequate organ functions including bone marrow, kidney, and liver; and life expectancy judged by the investigator for at least 3 months. Exclusion criteria were as follows: prior treatment with any agent targeting the *HGF/c-MET* pathway; prior epidermal growth factor receptor (*EGFR*) tyrosine kinase inhibitor treatment for *EGFR*-activating mutant NSCLC; patients who received local treatment within 4 weeks before the first administration of tepotinib (e.g. major surgery, radiation therapy, hepatic arterial embolization, transcatheter arterial chemoembolization, chemoembolization, radiofrequency ablation, percutaneous ethanol injection, or cryoablation) except for palliative radiotherapy which was completed at least 7 days before the first administration of tepotinib; patients with impaired cardiac function; pre-existing uncontrolled hypertension $>$150/90 mmHg despite adequate medical therapy; history of neoplasm other than current cancer; history of organ transplantation; known central nervous system or brain metastasis that is either symptomatic or untreated; clinically significant gastrointestinal bleeding; patients with a family history of long QT syndrome or taking any agent that is known to prolong QT/QTc interval or with a marked prolongation of QT/QTc interval; known human immunodeficiency virus infection; known or suspected drug hypersensitivity to any ingredients of tepotinib; female patients who were pregnant or lactating, or males and females of reproductive potential not willing or not able to employ a highly effective method of birth control/contraception; patients with concurrent treatment with anticancer therapy; previous anticancer treatment-related toxicities not recovered to baseline or grade 1 (except alopecia) before administration of tepotinib; and clinically significant third space fluid accumulation (despite the use of diuretics), e.g. uncontrolled pleural effusion or ascites and uncontrolled venous or arterial thromboembolism.

Treatment

Tepotinib was administered orally at 500 mg once daily without an off day until disease progression, occurrence of unacceptable toxicities, or withdrawal of consent. Each cycle lasted 21 days. Dose modifications or delays in the study drug administration were carried out based on the worst grade of toxicity according to the protocol. When grade 3 or 4 toxicities were observed, tepotinib treatment was discontinued until the toxicities resolved to grade 1 or lower. Tepotinib could be re-administered with one dose level reduction. The reduced dose was 250 mg once daily. When administration of the study medication was delayed, all evaluations, including tumor evaluation, adhered to the original schedule. When the administration of the study medication was either delayed for 3 weeks or more or the medication was discontinued because of toxicity, the patient was withdrawn from the study.

Plasma circulating tumor DNA sequencing

Serial plasma circulating tumor DNA (ctDNA) sequencing was planned for three occasions: before the administration of tepotinib initiation (baseline), after two cycles of treatment (T1), and at the time of disease progression (T2). A DNA NGS library was constructed using an c NGS DNA Library Prep Kit. Solution-based target enrichment was carried out at IMBdx, Inc. (Seoul, South Korea), using the AlphaLiquid® 100 target capture panel. The targeted gene panel included 118 cancer-related genes and was designed to cover all gene exons (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2024.103668). Captured DNA libraries were sequenced using the Illumina NovaSeq 6000 platform (Illumina, San Diego, CA) in 2 × 150 bp paired-end mode. All sequencing reads from the samples were generated in bcl format and demultiplexed into fastq files using the Burrows—Wheeler Aligner (BWA, version 0.7.17-r1188). Initial assessments were conducted based on fragment counts derived from both single-stranded consensus sequences (SSCS) and duplex consensus sequences (DCS) using fgbio tools (http://fulcrumgenomics.github.io/fgbio, accessed on 3 February 2022). The molecular depth (X) with an average sequencing depth of 56 603X was approximated by adding the SSCS and DCS counts within the coding sequence region. Subsequently, these assessments were scored using a machine learning model that differentiated genuine from spurious variants. Subsequently, they were annotated for functional effect prediction. We applied a cut-off for cfDNA mutations of variant allele frequency (VAF) $\geq$0.1% and altered the DCS count $\geq$4. A few unsatisfactory variants that showed high VAF at other time points were rescued. Unsatisfactory variants refer to mutations that did not meet the conditions of VAF $>$0.1% and DCS count $\geq$4 at a given time point. Somatic variants were distinguished from germline variants and clonal hematopoiesis of indeterminate potential variants (*ATM*, *CBL*, *CHEK2*, *IDH2*, *JAK2*, *MPL*, and *U2AF1*) in matched peripheral blood mononuclear cell samples.[10-12] To identify CN alterations, we used a pre-established sequencing depth profile of 50 healthy individuals, specifically targeting exonic regions covered by the panel as a reference. The log2 ratios were computed using a CN variation kit.[13] We characterized CN gains as instances where CN $\geq$ 4, in conjunction with applying statistical criteria that required *P* values to be $<$0.01.

Statistical analysis

At first, we designed a basket study so that patients with all kinds of solid tumors with MET alterations could participate in this study. We planned this trial with two strata (NSCLC and other cancers) and planned a phased decision of number of patients in two strata by interim analysis using an adaptive Bayesian hierarchical model design. We assumed $\gamma = 0.55$ (the prior probability that the drug is active in any particular stratum) and $\lambda = 0.6$ (the probability that the activities are perfectly correlated across strata). The target response rate was assumed to be 60% (p_hi), and a rate of 20% (p_lo) or below was considered futile. We set the threshold posterior probability of activity as 0.8 for the two strata. Therefore, accrual to each stratum was planned to be curtailed following interim analysis if the posterior probability is below 0.2 after analysis of 30 patients. In addition, accrual to each stratum were planned to be continued if the posterior probability is between 0.2 and 0.8. In case the posterior probability is higher than 0.8 of each stratum, accrual to each stratum was supposed to discontinue regarding the result of this stratum as success. The prevalence of each stratum was assumed as same for NSCLC and other cancer types. This design yielded a true-positive rate of 0.99, false-negative rate of 0.01, true-negative rate of 0.96, false-positive rate of 0.04, and the probability of no false positives when all strata are negative: 0.96. Therefore, the expected minimal sample size of two strata was 30 and maximum sample size of two strata was 100.

However, two global prospective studies on capmatinib and tepotinib were reported and got accelerated approval by Food and Drug Administration. Moreover, the very low detection rate of METex14 and MET amplification caused slow accrual, therefore we re-planned the number of study participants and amended the protocol.

Therefore, we revised the statistical plan for the single-arm phase II study. Considering heavily pre-treated patients with any solid tumors who can be included in this study, we set the estimation of H0 = 0.2 and H1 = 0.4 with one-side type I error of 5% at 85% power and the target of the total number of participants as 35 patients.

The progression-free survival (PFS) was defined as the time from the date of the first dosing to the date of disease progression or death. The overall survival (OS) was defined from the date of the first dosing to the date of death. The probability of survival and the duration of response (DoR) were estimated with the Kaplan—Meier method. Comparisons of survival between the different groups were made with log-rank tests. All analyses were carried out with SPSS for Windows 21.0 (IBM Corporation, Armonk, NY). Data were analyzed in April 2023.

Endpoints and assessment

The primary endpoint was the objective response rate (ORR) as determined by the investigators in accordance with RECIST 1.1.[14] Secondary endpoints included PFS, DoR, OS, disease control rate (DCR), and toxicities. All patients were included in an intention-to-treat analysis. Non-assessable patients were excluded from the per-protocol analyses. The efficacy analysis was carried out on a per-protocol basis.

Response evaluations were carried out using RECIST 1.1 and carried out every 6 weeks until disease progression. Tumor assessment was carried out every 6 weeks in both arms. If disease progression was suspected due to symptomatic aggravation, an earlier image assessment was carried out based on each investigator's decision. Adverse events (AEs) were monitored and severity recorded according to the National Cancer Institute-Common Terminology Criteria for Adverse Events version 5.0, during the

treatment phase and for 28 days after the last dose of tepotinib.

Ethical consideration

This trial was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice Guidelines, and National Policies on Bioethics and Human Biological Specimens. This trial is registered at ClinicalTrials.gov (NCT04647838). The study protocol was approved by the institutional review board of each participating institution (IRB number of the Chungbuk National University Hospital: 2019-09-015-002). Written informed consent was obtained from all patients before participation.

RESULTS

Patient and disease characteristics

Thirty-five patients were enrolled in this study between March 2020 and March 2022. The baseline patient characteristics are shown in Table 1. Among these, 68.6% ($n = 24$) of patients had NSCLC and 31.4% ($n = 11$) of patients had other cancers, which included gastroesophageal cancer ($n = 2$), head and neck cancer ($n = 2$), glioblastoma multiforme ($n = 2$), breast cancer, colon cancer, melanoma, and cholangiocarcinoma. Two patients with lung adenocarcinoma had both *MET*ex14 and *MET* amplifications. These patients were allocated to the *MET*ex14 group for efficacy analysis. MET exon 14 skipping was observed almost exclusively in NSCLC ($n = 21$) but was also observed in other cancers ($n = 3$), including gastric, nasopharyngeal, and tonsillar cancers. The median number of lines of previous anticancer treatment was 1 (range 0-5). Fifteen patients (42.9%) in the study population were pre-treated with at least two previous systemic treatments before inclusion in this study.

Table 1. Baseline characteristics of study participants

Characteristics	All	*MET* exon 14 skipping mutation	*MET* amplification
No. of patients	35	24[a]	11
Age			
Median (range), years	70 (32-82)	74.5 (48-82)	56.0 (32-70)
≥65years, *n* (%)	19 (54.3)	18 (75.0)	1 (9.1)
Female, *n* (%)	18 (51.4)	14 (58.3)	4 (36.4)
ECOG performance status, *n* (%)			
0	8 (22.9)	5 (20.8)	3 (27.3)
1	27 (77.1)	19 (79.2)	8 (72.7)
Smoking history, *n* (%)			
Never smoked	20 (57.1)	16 (66.7)	4 (36.4)
Cigarette smoker	7 (20.0)	5 (20.8)	2 (18.2)
Current smoker	3 (8.6)	2 (8.3)	1 (9.1)
Unknown	5 (14.3)	1 (4.2)	4 (36.4)
Primary tumor, *n* (%)			
NSCLC	24 (68.6)	21 (87.5)	3 (27.3)
Others	11 (31.4)	3 (12.5)	8 (72.7)
Brain metastases at baseline, *n* (%)	4 (11.4)	4 (16.7)	0 (0.0)
Number of previous lines of anti-neoplastic therapy, *n* (%)			
0	2 (5.7)	2 (8.3)	0 (0.0)
1	17 (48.6)	14 (58.3)	3 (27.3)
2	8 (22.9)	4 (16.7)	4 (36.4)
≥3	7 (20.0)	4 (16.7)	3 (27.3)

ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small-cell lung cancer.
[a]Two NSCLC patients harboring both *MET*ex14 and *MET* amplification were included in this group.

Efficacy

The efficacy population included subjects who met all the inclusion criteria and none of the exclusion criteria, received at least one dose of the investigational product, and underwent tumor response evaluation as per RECIST (Ver. 1.1) guidelines. Of all the included subjects, response evaluation was conducted in 33 assessable patients (23 in the *MET*ex14 arm and 10 in the *MET* amplification arm; Table 2). At a median follow-up of 19 months, the ORR was 57.6% for all patients, 52.1% for those with *MET*ex14, and 70% for those with *MET* amplification. The DCR was 90.9% in all patients (Table 2). The median DoR was 14.5 months [95% confidence interval (CI) 7.1-21.9 months] for all patients. The majority of patients (78.8%) experienced tumor shrinkage, and 94.7% of patients who showed partial response started this response within 5 months after starting treatment (Figure 1A and B).

Interestingly, for the *MET*ex14 group, a response was observed only in patients with NSCLC with an ORR of 60%, and no response was observed in other cancers. In contrast to the *MET*ex14 group, a response was observed in the *MET* amplification group, regardless of the primary cancer. However, the DoR of the *MET* amplification group was shorter than that in the *MET*ex14 group, with a mean of 5.8 months (95% CI 3.7-7.9 months) while the median DoR of the *MET*ex14 group was 14.5 months (95% CI 7.1-21.9 months).

The median PFS was 8.0 months (95% CI 4.5-11.5 months) and the median OS was 14.0 months (95% CI 7.8-20.2 months) in all efficacy populations (Table 2; Figure 1C and D). For the *MET*ex14 group, the median PFS was 9.0 months (95% CI 4.6-13.6 months), and the median OS was 17 months [95% CI not applicable (NA)-NA] (Table 2). In the patients with NSCLC with *MET*ex14, the median PFS was 9.0 months (95% CI 4.7-13.4 months), and the median OS was not reached (Supplementary Figure S1A and B, available at https://doi.org/10.1016/j.esmoop.2024.103668). For *MET* amplification, the median PFS was 7.0 months (95% CI 1.5-12.5 months) and the median OS was 10.0 months (95% CI 5.8-14.2 months) (Table 2). Among patients with *MET* amplification, those with gastric cancer with a gene copy number (GCN) of 18 showed the longest PFS of 19 months.

Toxicities

A total 35 patients were included in safety analyses. The median number of tepotinib cycles received was 9.0 cycles (range 1-44 cycles). The average dose intensity of tepotinib was 88.4% (with a standard deviation of 16.6%) and the median was 99.2% (range 47.7%-100%). Eleven patients (31.4%) experienced dose interruption, 12 (34.2%)

Table 2. Summary of tepotinib efficacy results

Response	All ($n = 33$)	*MET* exon14 skipping mutation		*MET* amplification	
		NSCLC ($n = 20$)	Other cancers ($n = 3$)	NSCLC ($n = 3$)	Other cancers[a] ($n = 7$)
Best response, *n* (%)					
Complete response	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Partial response	19 (57.6)	12 (60.0)	0 (0.0)	2 (66.7)	5 (71.4)
Stable disease	11 (33.3)	8 (40.0)	1 (33.3)	1 (33.3)	1 (14.3)
Progressive disease	3 (9.1)	0 (0.0)	2 (66.7)	0 (0.0)	1 (14.3)
Objective response[b], *n* (%)	19 (57.6)	12 (60.0)	0 (0.0)	2 (66.7)	5 (71.4)
Disease control[c], *n* (%)	30 (90.9)	20 (100.0)	1 (33.3)	3 (100.0)	6 (85.7)
Duration of response, months	14.5 (7.1-21.9)	14.5 (7.1-21.9)		5.8[d] (3.7-7.9)	
		14.5 (7.1-21.9)	NA	1.0 (NA)	7.0 (NA)
Progression-free survival, months (95% CI)	8.0 (4.5-11.5)	9.0 (1.6-13.6)		7.0 (1.5-12.5)	
Overall survival, months (95% CI)	14.0 (7.8-20.2)	17.0 (NA-NA)		10.0 (5.8-14.2)	

The data cut-off date was 28 February 2023.
CI, confidence interval; GBM, glioblastoma multiforme; NA, not applicable; NSCLC, non-small-cell lung cancer.
[a]Patients with colon cancer, gastric cancer, breast cancer, melanoma, or cholangiocarcinoma showed partial response. One patient with GBM showed stable disease and one patient with breast cancer showed progressive disease.
[b]Overall response was defined as a complete response or partial response.
[c]Disease control was defined as a complete response, partial response, stable disease, or non-complete response or non-progressive disease.
[d]Mean value (unable to calculate median).

experienced dose reduction, and 5 (14.2%) discontinued tepotinib due to AEs.

An overall summary of the AEs reported during this study is presented in Table 3. Any-grade AEs were reported in 32 (91.4%) patients and were grade 3 or higher in 18 (51.4%); the most frequently reported AE was peripheral edema (40.3%), with three patients (8.6%) experiencing grade 3. Other AEs occurred in ≥20% of the patients, followed by

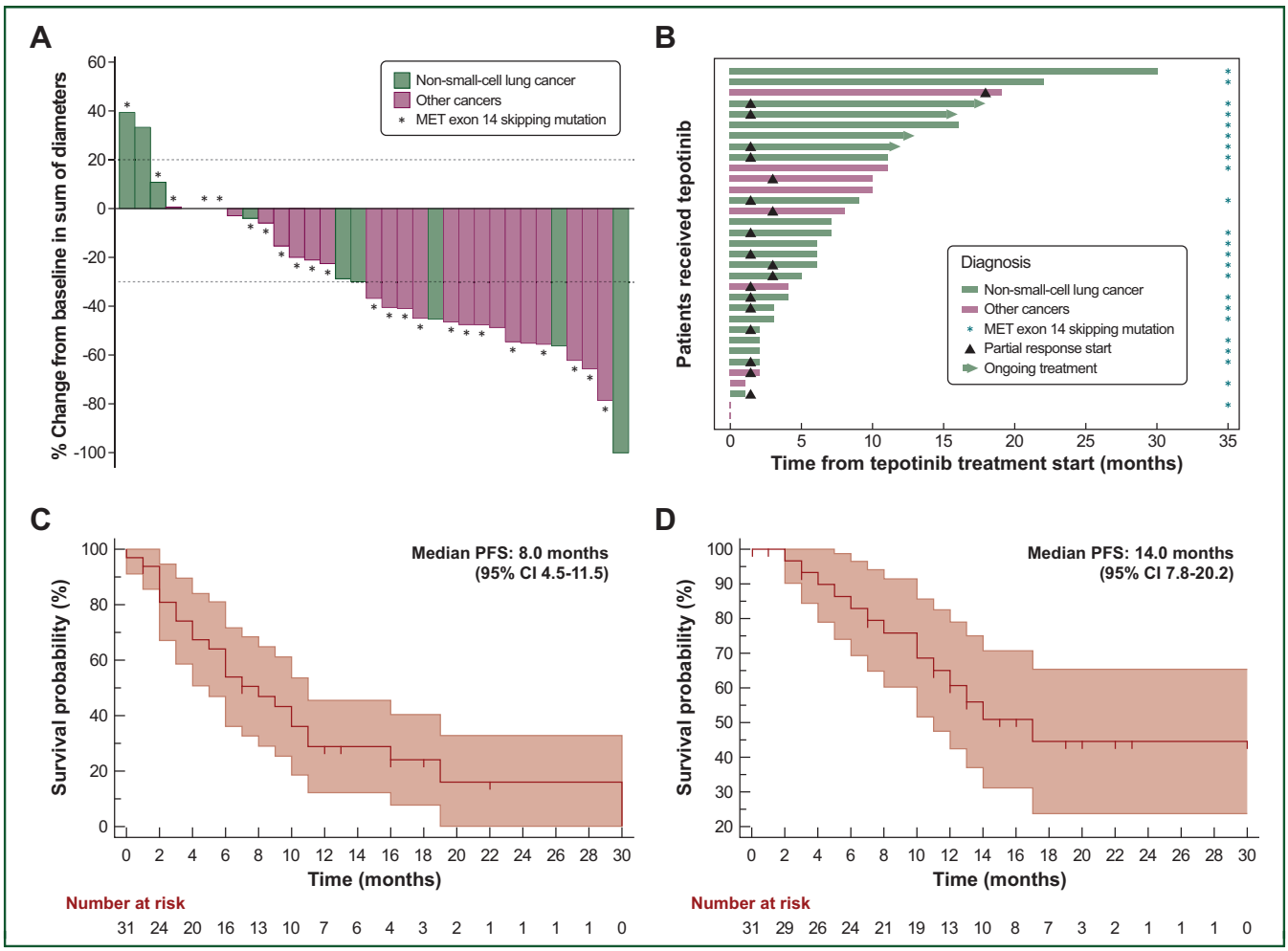

Figure 1. Response and survival of study participants. (A) Maximum change in tumor size from baseline in individual patients. (B) Swimmer's plot of treatment durations. (C) Progression-free survival in study patients. (D) Overall survival in study patients.
CI, confidence interval; NSCLC, non-small-cell lung cancer; OS, overall survival; PFS, progression-free survival.

Table 3. Summary of adverse events during study period

Adverse events	Safety population ($n = 35$)			
	All grade	Grade 1 or 2	Grade 3	Grade 4-5
Any adverse events, *n* (%)	32 (91.4)	28 (80.0)	16 (45.7)	2 (5.7)
Nausea	6 (17.1)	6 (17.1)	0	0
Vomiting	3 (8.6)	3 (8.6)	0	0
Anorexia	8 (22.9)	8 (22.9)	0	0
Constipation	4 (11.4)	4 (11.4)	0	0
Diarrhea	7 (20.0)	6 (17.1)	1 (2.9)	0
Dyspepsia	7 (20.0)	7 (20.0)	0	0
Abdominal pain	6 (17.1)	5 (14.3)	1 (2.9)	0
Oral mucositis	4 (11.4)	3 (8.6)	1 (2.9)	0
Dyspnea	3 (8.6)	3 (8.6)	0	0
Myalgia	2 (5.7)	2 (5.7)	0	0
Arthralgia	3 (8.6)	3 (8.6)	0	0
Asthenia, fatigue	10 (28.6)	9 (25.7)	1 (2.9)	0
Itching	6 (17.1)	6 (17.1)	0	0
Rash	7 (20.0)	7 (20.0)	0	0
Hand-foot syndrome	3 (8.6)	2 (5.7)	1 (2.9)	0
Nail change	1 (2.9)	1 (2.9)	0	0
Hyperkeratosis	3 (8.6)	3 (8.6)	0	0
Alopecia	2 (5.7)	2 (5.7)	0	0
Sweating	3 (8.6)	3 (8.6)	0	0
Rhinorrhea	1 (2.9)	1 (2.9)	0	0
Generalized edema	5 (14.3)	4 (11.4)	1 (2.9)	0
Peripheral edema	14 (40.0)	11 (31.4)	3 (8.6)	0
Pleural effusion	3 (8.6)	2 (5.7)	1 (2.9)	0
Pneumonitis	3 (8.6)	2 (5.7)	1 (2.9)	0
Pneumonia	7 (20.0)	2 (5.7)	3 (8.6)	2 (5.7)
Urinary tract infection	3 (8.6)	3 (8.6)	0	0
Laboratory abnormalities				
Creatinine elevation	4 (11.4)	4 (11.4)	0	0
Amylase/lipase elevation	4 (11.4)	4 (11.4)	0	0
Hypoalbuminemia	6 (17.1)	5 (14.3)	1 (2.9)	0
Anemia	4 (11.4)	3 (8.6)	1 (2.9)	0
Thrombocytopenia	1 (2.9)	1 (2.9)	0	0
Neutropenia	2 (5.7)	0	2 (5.7)	0
Transaminase elevation	8 (22.9)	8 (22.9)	0	0

fatigue (28.6%), elevated transaminase (22.9%), anorexia (22.9%), diarrhea (20.0%), dyspepsia (20.0%), and pneumonia (20.0%) mostly of grades 1 and 2 (22.9%). For serious adverse events (SAEs), seven SAEs were considered to be treatment related. Generalized edema (5.7%), pleural effusion (2.9%), pneumonia (2.9%), interstitial pneumonitis (2.9%), enteritis (2.9%), and oral mucositis (2.9%) grade 3 were reported as treatment-related SAEs.

Two patients experienced pneumonia after starting tepotinib treatment, and one died due to pneumonia. However, the investigators concluded that the tepotinib treatment was not associated with this AE. Common AEs leading to dose reduction were peripheral edema, diarrhea, pneumonitis, transaminase elevation, pleural effusion, and hand-foot syndrome.

Genomic analysis

Plasma ctDNA NGS testing at baseline was conducted in 28 patients. Among them, *MET*ex14 or *MET* amplification was detected in 18 patients. The sensitivity of plasma NGS testing for *MET*ex14 was 63% and that for *MET* amplification was 60%. Amplification of *MET* was detected in six patients, including one patient with both *MET* amplification and *MET*ex14. During the baseline plasma NGS, *MET*ex14 was detected in 13 patients. Among them, one patient had *MET*ex14 in plasma NGS, whereas *MET* amplification was detected in tissue NGS. In the baseline plasma NGS, the most frequently identified mutation, other than *MET*, was *TP53* (18/28, 64.3%). Mutations in *PIK3CA*, *ATM*, and *MYCN* were also identified. All patients showed microsatellite stability and the median blood tumor mutational burden was 3.15 mut/Mb (Figure 2).

Interestingly, there was a difference in ORR between the MET alteration-detected and non-detected groups in baseline plasma NGS. The ORR of 18 patients with *MET*ex14 or *MET* amplification detected by baseline plasma NGS was 72.2%, whereas that of 10 patients without *MET* dysregulation was 30%.

Co-mutations of *TP53* in tissue or blood NGS tests at baseline were found in 21 patients (60.0%). The ORR of patients with co-mutations on *TP53* was not inferior at 57.9%; however, the patients with *TP53* mutation demonstrated a trend of poor outcomes in terms of median PFS and OS. The median PFS in patients with *TP53* was 6.0 months whereas the median PFS in patients without *TP53* mutation was 11 months ($P = 0.057$). The median OS of patients with *TP53* mutations was 12 months, whereas that of patients without *TP53* mutations was not reached ($P = 0.061$).

DISCUSSION

In this study, tepotinib showed favorable efficacy in patients with advanced solid cancer with *MET*ex14 or *MET* amplification, as identified by tissue NGS. The response rate determined by investigator assessment was 57.6% for all patients, the median PFS was 8.0 months, and the median OS was 14 months. Even though patients with diverse primary cancers were included and 42.9% of the patients in this study population were heavily pre-treated with at least two previous systemic treatments before inclusion in this study, the overall results on clinical efficacy were comparable to those of global prospective clinical trials.[6,7,15]

In this study, the ORR and median PFS with tepotinib in patients with NSCLC with *MET*ex14 were 60% and 9.0 months, respectively. In the VISION study, a prospective global phase II study that investigated the efficacy of tepotinib in patients with NSCLC with *MET*ex14, the ORR was 56%, and the median PFS was 8.5 months, according to investigator assessment.[6] Additionally, analyses of 15 Japanese patients from the VISION study demonstrated an ORR of 60.0% and a median PFS of 11.0 months, respectively [95% CI 1.4-not evaluable (NE)]. In the GEOMETRY mono-1 study, the ORR of capmatinib was 68% and PFS was 12.4 months in patients with NSCLC harboring *MET*ex14 who had not received treatment previously. The ORR was 41% and the PFS was 5.4 months in patients with *MET*ex14 who were previously treated.[7] In a phase II study of savolitinib, the ORR was 53.2% and the median PFS was 6.9 months in Chinese patients with NSCLC with *MET*ex14.[15]

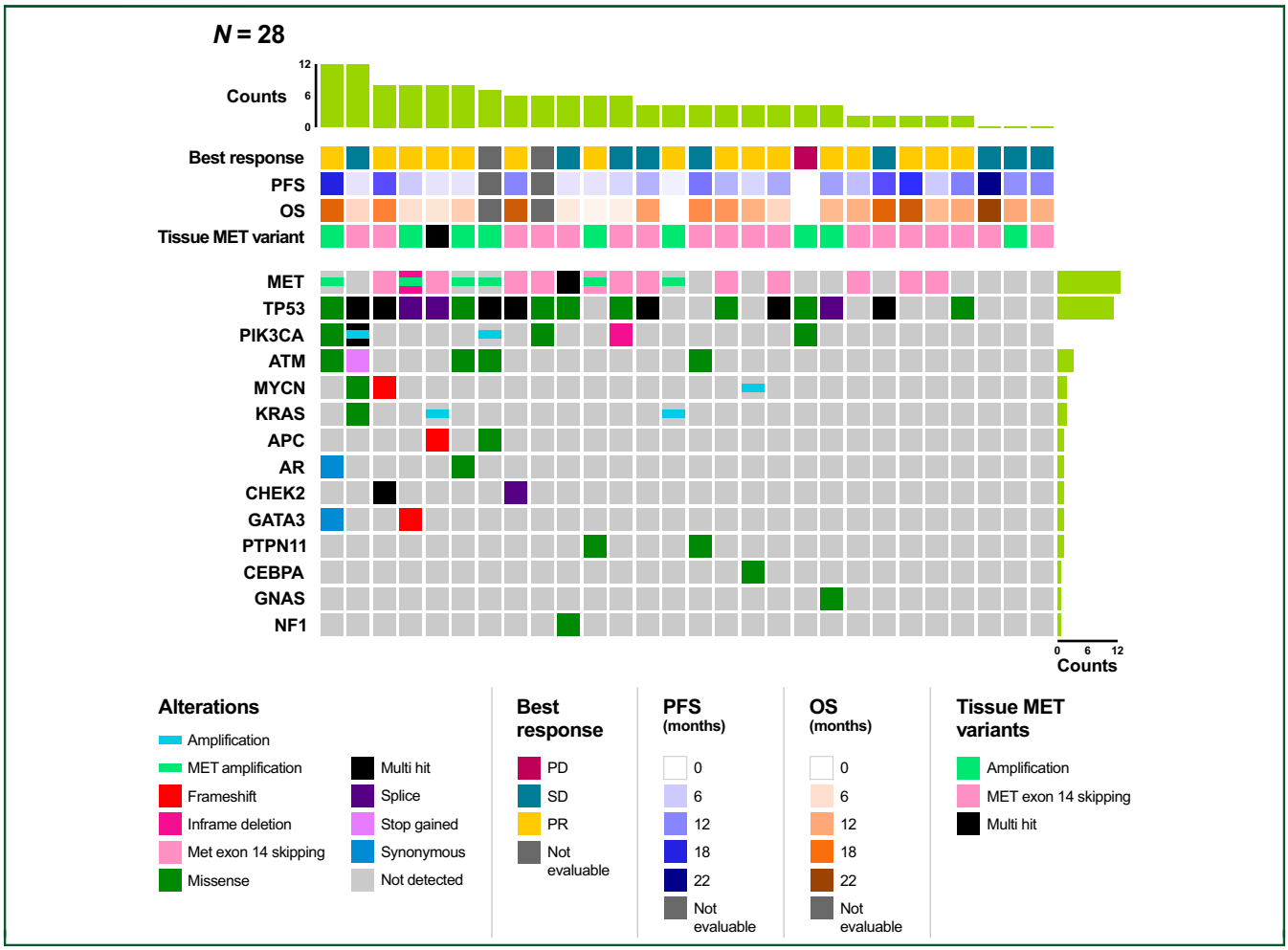

Figure 2. Baseline molecular profiles of plasma NGS test and response to treatment.
NGS, next-generation sequencing; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

The *MET*ex14 mutation in solid tumors other than NSCLC is rarely observed, and there have been several reports suggesting the *in vitro* activity of MET inhibitors.[4,16-19] However, the clinical effects of *MET* inhibitors in these patients have rarely been reported. Three patients with extrapulmonary malignancies, each with gastric, nasopharyngeal, and tonsillar cancers, with *MET*ex14 were included in this study. Interestingly, all three patients showed no response to tepotinib, and the disease progressed rapidly. Although the number of patients was notably small, these findings render the therapeutic role of tepotinib questionable for cancers other than NSCLC. Our study also revealed the clinical effect of tepotinib on several cancers with *MET* amplification. In our study, 31.4% of all included patients had *MET* amplification with a GCN of at least 6. Particularly, among patients with NSCLC with *MET* amplification, patients with treatment resistance-related *MET* amplification after other TKI treatments were not included. For the efficacy of *MET* TKI in NSCLC with *MET* amplification, various results have been reported. In a study where the efficacy of crizotinib was evaluated in *MET*-amplified NSCLC, the response rate was 40.0% with *MET* GCN $\geq$6 in tissue NGS testing.[20] Capmatinib shows a poor response in *MET*-amplified NSCLC. In the GEOMETRY mono-1 study, the ORR of capmatinib was 29% in previously treated patients and 40% in treatment-naïve patients with a MET GCN of at least 10 and 40% in treatment-naïve patients. For Cohort 1b with *MET* GCN 6-9, the response was decreased at 12% and the PFS was 2.7 months; therefore, it was closed after the interim analysis in the study.[7] Tepotinib demonstrated an ORR of 41.7% for patients with NSCLC with *MET* amplification in liquid biopsy (GCN $\geq$2.5) and 71.4% (5/7) for treatment-naïve patients. However, PFS was only 4.2 months (95% CI 1.4 months-NE).[21] In our study, a relatively high ORR of $\sim$70% was observed for NSCLC and other cancers with *MET* amplification ($n = 10$). Among these, two out of three patients with NSCLC showed partial response; however, consistent with previous reports, the DoR or PFS was notably short. In contrast, patients with other cancers with *MET* amplification showed a similar ORR (5/7) with a PFS of 8 months, which could be considered favorable given the extensive prior treatment. In our study, the patient with gastric cancer with *MET* amplification of GCN 18 showed a long PFS of 18 months. Considering *MET* amplification as a potential treatment target for gastric cancer, further investigations into the development of *MET* TKIs,

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particularly for *MET*-amplified gastric cancer, are anticipated.[22,23]

For study enrollment, only tissue-based NGS test results were included. However, we planned to test blood-based NGS from the start of the study treatment and follow it sequentially to investigate gene alterations related to treatment response or resistance. In the baseline testing, targetable *MET* alterations were detected in 18 of the 28 patients (64.3%) in baseline plasma NGS. In addition, our study revealed that patients with *MET* alterations detected using plasma NGS at baseline showed a profoundly better response rate than those without such detection. Similar to other studies that have reported the potential role of monitoring *EGFR* mutations or anaplastic lymphoma kinase (ALK) alterations in ctDNA as predictors of treatment response, we suggest that the detection of plasma *MET* alterations could be used as a predictor of response to tepotinib.[24-26]

In this study, concomitant TP53 mutations with *MET* alterations showed a trend toward poor PFS and OS in patients treated with tepotinib. Several studies have reported that concurrent *TP53* mutations are associated with short treatment duration and OS in patients with *EGFR* or *ALK* mutations who were treated with TKIs.[27-29] Although the number of patients in this trial was limited, this finding suggests the universal nature of concurrent TP53 mutations as negative regulators of targeted therapy.

The safety profiles of tepotinib in our study were comparable to those of previous clinical trials, and AEs were mostly grade 1 or 2. In this study, the most common treatment-related AE was edema, including peripheral and generalized edema, in 54.3% of the population, and 11.5% of the patients experienced grade 3.

Our study has some limitations. We terminated the study earlier than planned because of the low *MET* detection rates in NGS testing and other competitive clinical trials of new *MET* TKIs conducted at several institutions. Therefore, the efficacy of tepotinib in small populations, such as other cancer groups or *MET* amplification groups, needs to be evaluated in large-sized trials. However, this study has the strength of evaluating the response and safety of tepotinib in Korean patients with cancer, regardless of cancer type or in patients with cancer harboring *MET*ex14 or *MET* amplification. Notably, this study offers novelty by presenting the first report of clinical outcomes with tepotinib in cancers other than NSCLC harboring METex14. In addition, we elucidated the potential role of *MET* alterations in plasma NGS as a method to detect *MET*ex14 or *MET* amplification in patients with cancer, as well as a potential predictor of therapeutic response.

In conclusion, we confirmed the efficacy and safety of tepotinib for patients with various solid cancers harboring *MET*ex14 or *MET* amplifications whose disease progressed during prior standard treatment. However, this anti-*MET*ex14 effect was not confirmed for tumors other than NSCLC. Tepotinib also showed promising activity against various cancers with *MET* amplification. Further clinical studies of the efficacy of targeted *MET* amplification are required to validate the efficacy of tepotinib.

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