Detailed characterization of combination treatment with MET inhibitor plus EGFR inhibitor in *EGFR*-mutant and *MET*-amplified non-small cell lung cancer

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Background: Detailed clinical data about combination treatment with MET inhibitor (METi) and EGFR inhibitor (EGFRi) is lacking in patients with *EGFR*-mutant, *MET*-amplified, and EGFRi-resistant non-small cell lung cancer (NSCLC). This study aimed to report longitudinal data on the efficacy and safety of this combination treatment.

Methods: We retrospectively analyzed 44 patients with advanced *EGFR*-mutant and *MET*-amplified NSCLC who were treated with any types of METi plus EGFRi after progression with EGFRi at the National Cancer Center Hospital. Longitudinal clinicogenomic data and plasma circulating tumor DNA (ctDNA) data were collected.

Results: The overall response rate was 74.4% and median progression-free survival (PFS) was 5.3 months [95% confidence interval (CI): 3.3–7.3]. Twenty-three patients (52.3%) required either or both treatment discontinuation due to adverse effects. The main cause of discontinuation was pneumonitis (69.2%). There was no significant difference in the PFS of patients with or without METi discontinuation [hazard ratio (HR), 0.93; 95% CI: 0.49–1.78; P=0.83]. Median clearance time of *MET* amplification in plasma ctDNA was measured as 63 days. Patients who stopped METi within 63 days of initiation showed poorer PFS compared to those who discontinued after (HR, 2.78; 95% CI: 1.00–7.75; P=0.050). Diverse resistance mechanisms including on-target mutations in *MET* (D1246H) and *EGFR* (C797S or T790M) were detected in 14 patients. One *MET* D1246H-mutant case and one *EGFR* C797S-mutant case responded to sitravatinib and amivantamab, respectively.

Conclusions: A combination of METi and EGFRi showed a promising anti-tumor effect in advanced *EGFR*-mutant and *MET*-amplified NSCLC. Pneumonitis was the main adverse effects leading to treatment discontinuation. Early discontinuation of METi negatively affected the survival outcomes.

Keywords: Non-small cell lung cancer (NSCLC); *EGFR* mutation; *MET* amplification; targeted therapy; circulating tumor DNA (ctDNA)

Introduction

Mesenchymal-epithelial transition factor (*MET*) gene amplification is a common mechanism of therapeutic resistance in *EGFR*-mutant non-small cell lung cancer (NSCLC) patients treated with EGFR inhibitors (EGFRi) (1,2). *MET* amplification was reported in 7–15% of these patients after progression with first-line osimertinib therapy and in 5–50% of patients after the failure of second-line osimertinib therapy (3). Thus, combination treatment with a MET inhibitor (METi) and an EGFRi has been proposed as a promising strategy to overcome *MET*-amplification-related resistance to EGFRi in *EGFR*-mutant NSCLC (4-6). The TATOON phase Ib study evaluated the efficacy and toxicity of a combination of savolitinib and osimertinib in 186 patients with advanced *EGFR*-mutant and *MET*-amplified NSCLC who developed progression on EGFRi treatment (4). In the TATOON study, the two-drug combination treatment showed promising efficacy with a tolerable toxicity profile. Interestingly, this phase I study showed a difference in the efficacy and toxicity outcomes depending on the dose of METi. In part B of that study, osimertinib 80 mg and savolitinib 600 mg daily resulted in a 66% response rate and 57% incidence of ≥ grade 3 adverse

effects, while in part D of the study, osimertinib 80 mg and savolitinib 300 mg daily resulted in a 23% response rate and 38% incidence of ≥ grade 3 adverse effects. Based on these results, the subsequent SAVANNAH phase 2 study has been evaluating 300 or 600 mg once-daily or 300 mg twice-daily dose of savolitinib in combination with osimertinib 80 mg. In addition, the currently ongoing SAFFRON phase 3 study aims to compare a 300 mg twice-daily dose of savolitinib plus osimertinib 80 mg with pemetrexed and carboplatin in the same patient subset. In addition, the INSIGHT phase 2 study tested tepotinib plus gefitinib in 122 patients with *EGFR*-mutant NSCLC who had acquired resistance to 1st line osimertinib due to *MET* amplification (7). Most recent final results of this study were that the combination regimen had high effectiveness with 43.9% of response rate and 5.4 months of progression-free survival (PFS) for this population.

In recent years, this dual EGFRi plus METi treatment has been making its way into clinical practice for patients with advanced *EGFR*-mutant and *MET*-amplified NSCLC. However, there is a lack of detailed clinical data to inform personalized treatment strategies for this distinct subset. For example, the intracranial response, true toxicity profile, drug discontinuation rate and its clinical impact, and post-treatment data including mechanisms of acquired resistance and response to corresponding subsequent therapy are not well characterized. Thus, in this observational study, we report longitudinal data for patients with *EGFR*-mutant and *MET*-amplified NSCLC who were treated with a combination of EGFRi plus METi. Our findings may provide valuable insights for treatment decision-making for these patients. We present this article in accordance with the STROBE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-273/rc).

Highlight box

Key findings
- A combination of MET-tyrosine kinase inhibitor (TKI) and EGFR-TKI showed a 74.4% of response rate and 5.3 months of progression-free survival (PFS) in advanced *EGFR*-mutant and *MET*-amplified non-small cell lung cancer (NSCLC).
- Median clearance time of *MET* amplification in plasma circulating tumor DNA (ctDNA) was measured as 63 days.
- Patients who stopped MET-TKI within 63 days of initiation showed poorer PFS.

What is known and what is new?
- A combination of MET-TKI and EGFR-TKI showed a promising anti-tumor effect in advanced *EGFR*-mutant and *MET*-amplified NSCLC.
- Early discontinuation of MET-TKI negatively affected the survival outcomes.

What is the implication, and what should change now?
- A combination of MET-TKI and EGFR-TKI treatment needs to be maintained at least until the *MET*-amplified clones is cleared up.
- Plasma ctDNA might have to be monitored in conjunction with this combination treatment to verify the disappearance of the *MET*-amplified clone.

Methods

Patients and data collection

From the pharmacy disposition records, we identified 54 patients with NSCLC who were treated with any type of EGFRi plus METi at the National Cancer Center Hospital (Goyang, Republic of Korea) between May 2015 and April 2023. The inclusion criteria for this study were: (I) histologically or cytologically confirmed metastatic NSCLC; (II) drug-sensitive *EGFR* mutations; (III) previous use of EGFRi and (IV) *MET* amplification detected by MET-fluorescence in situ hybridization (FISH) [MET/

CEP7 ≥2 or *MET* gene copy number (GCN) ≥15 in >10% of tumor cells] (8) or next-generation sequencing (NGS) with plasma circulating tumor DNA (ctDNA) (FoundationOne Liquid CDx). Subsequently, the medical records and radiographic images of patients were reviewed to collect clinicopathologic data, genetic characteristics, adverse effects, details of dose modification, tumor response, and survival outcomes using a predesigned data format. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the institutional review board of the National Cancer Center (No. NCC 2016-0208). Informed consent was waived because of the retrospective nature of the study.

Treatment and tumor assessment

The drug type and the prescribed doses of EGFRi and METi were at the discretion of the treating physician. A 4-week treatment cycle was continued until the development of disease progression, intolerable toxicity, or patient refusal. Tumor response was assessed every 8 or 12 weeks by imaging studies. The imaging modalities including chest computed tomography (CT), abdominal CT, brain magnetic resonance imaging (MRI), bone scan, and positron emission tomography (PET) were performed according to the clinical needs. Thirty-three patients who were enrolled in prospective clinical studies (TATOON, SAVANNAH, and phase Ib/II capmatinib plus gefitinib study) received the treatment and tumor evaluation according to the protocol of the clinical study.

Tumor response was assessed in accordance with the guidelines established by the Response Evaluation Criteria in Solid Tumors 1.1 (RECIST 1.1) committee (9).

Droplet digital polymerase chain reaction (ddPCR) for ctDNA

Whole-blood samples were obtained from patients who provided written informed consent for translational research before the combination treatment with METi and EGFRi and at each response assessment. A QX200 Droplet Digital PCR system (BioRad, Hercules, CA, USA) was used for ddPCR as per the manufacturer's protocol. The TaqMan Probe mix was used to measure the *MET* GCN (MET copy number variation: FAM, #10031240; HEX, #10031243). After completion of the PCR, a droplet reader was used to read TaqMan Probe fluorescence in individual droplets using the QuantaSoft software.

Statistical analysis

An analysis of drug efficacy and adverse effects was performed for all patients who received at least one dose of EGFRi plus METi combination. Response rate was the percentage of patients whose best tumor response was complete response (CR) or partial response (PR). Pearson's Chi-squared test or Fisher's exact test was used to determine the relationship between categorical variables, where appropriate. PFS was assessed from the first day of treatment until the first documentation of disease progression or death, with censoring of patients who are lost to follow-up. Overall survival (OS) was measured from the first day of treatment until death or the most recent follow-up. Survival time was estimated using the Kaplan-Meier method and between-group differences in survival were assessed using the log-rank test. The standard Cox proportional hazards regression model was used to perform multivariate survival analysis. Two-tailed P values less than 0.05 were considered indicative of statistical significance.

Results

Patient characteristics

A total of 44 patients (mean age: 59 years; males: 56.8%) were included in this study (*Table 1*, Figure S1). The proportion of never smoker and adenocarcinoma histology were 38.6% and 93.2%, respectively. At the baseline, 22 (50.0%) patients had brain metastasis (BM) while 10 (22.7%) patients had pulmonary lymphangitic metastasis. *MET* amplification was diagnosed using FISH in 38 (86.4%) patients and by plasma ctDNA NGS in 6 (13.6%) patients. The median number of previous chemotherapy lines was 2 (range, 1–6). The EGFRi plus METi treatment was started after failure of 1st or 2nd generation EGFRi in 31 (70.5%) patients, and after failure of 3rd generation EGFRi in 13 (29.5%) patients. The following combination regimens were used in our cohort: osimertinib plus savolitinib (n=31); erlotinib plus crizotinib (n=5); osimertinib plus crizotinib (n=4); gefitinib plus capmatinib (n=2); gefitinib plus crizotinib (n=1); and afatinib plus crizotinib (n=1).

Adverse effects and drug discontinuation

The median number of treatment cycles administered in our cohort was 3 (range, 1–61). No drug-related death events occurred. Sixteen (36.4%) patients experienced severe grade 3 or 4 adverse effects, including hypersensitivity

Table 1 Characteristics of the study population

Characteristics	Subgroups	N (%)
Age	<65 years	35 (79.5)
	≥65 years	9 (20.5)
Sex	Male	25 (56.8)
	Female	19 (43.2)
Smoking	Never	17 (38.6)
	Ever	27 (61.4)
ECOG PS	0 or 1	36 (81.8)
	2	8 (18.2)
Histology	Adenocarcinoma	41 (93.2)
	Non-adenocarcinoma	3 (6.8)
EGFR mutation	Exon 19 deletion	25 (56.8)
	Exon 21 L858R	18 (40.9)
	Exon 18 G719X	1 (2.3)
Brain metastasis	Yes	22 (50.0)
	No	22 (50.0)
Lymphangitic metastasis	Yes	10 (22.7)
	No	34 (77.3)
Diagnostics for *MET* amplification	FISH test	38 (86.4)
	Plasma ctDNA NGS	6 (13.6)
Prior EGFR-TKI	1st or 2nd generation	31 (70.5)
	3rd generation	13 (29.5)
EGFR-TKI	1st or 2nd generation	9 (20.5)
	3rd generation	35 (79.5)
MET-TKI	Savolitinib	31 (70.5)
	Crizotinib	11 (25.0)
	Capmatinib	2 (4.5)

ECOG, Eastern Cooperative Oncology Group; PS, performance status; FISH, fluorescence in situ hybridization; ctDNA, circulating tumor DNA; NGS, next-generation sequencing; TKI, tyrosine kinase inhibitor.

Table 2 Drug dose modification

Characteristics	Subgroups	N (%)
Dose reduction	EGFR-TKI	0/44 (0.0)
	MET-TKI	6/44 (13.6)
Drug discontinuation	Both drugs	13/44 (29.5)
	MET-TKI only	10/44 (22.7)
Cause of discontinuation of both drugs	Pneumonitis	9/13 (69.2)
	Hypersensitivity	2/13 (15.4)
	Mediastinitis	1/13 (7.7)
	Recurrent cellulitis	1/13 (7.7)
Cause of discontinuation of MET-TKI	Hypersensitivity	5/10 (50.0)
	Generalized pain	2/10 (20.0)
	Hepatitis	2/10 (20.0)
	Deep vein thrombosis	1/10 (10.0)
Discontinuation rate per drug	EGFR-TKI	
	• 1st or 2nd generation	4/9 (44.4)
	• 3rd generation	19/35 (54.3)
	MET-TKI	
	• Savolitinib	19/31 (61.3)
	• Crizotinib	3/11 (27.3)
	• Capmatinib	1/2 (50.0)

TKI, tyrosine kinase inhibitor.

(n=7), pneumonitis (n=2), hepatitis (n=2), cellulitis (n=2), nausea (n=1), generalized pain (n=1), and deep vein thrombosis (n=1). The number of patients who permanently discontinued any drug due to adverse effects was 23 (52.3%): both drugs (n=13, 29.5%); METi only (n=10, 22.7%), and EGFRi only (n=0, 0.0%) (*Table 2*). The median time from starting treatment to discontinuing both drugs or METi only was 84 days (range, 10–952 days) or 16 days (range, 8–117 days), respectively. The reasons for discontinuation of both drugs were pneumonitis (69.2%), hypersensitivity (15.4%), mediastinitis (7.7%), and recurrent cellulitis (7.7%). The reasons for discontinuation of only METi were hypersensitivity (50.0%), generalized pain (20.0%), hepatitis (20.0%), and deep vein thrombosis (10.0%). There was no significant difference in the discontinuation rate between 1st or 2nd generation EGFRi and 3rd generation EGFRi (44.4% *vs.* 54.3%). Among the three METis, the discontinuation rate of savolitinib was relatively higher than other METis (61.3% *vs.* 30.8%).

Among total patients, the incidence of pneumonitis was 25.0% (11/44): grade 2 (9/11, 81.8%), grade 3 (1/11, 9.1%), and grade 4 (1/11, 9.1%). The incidence and severity of pneumonitis according to the combination regimen of METi plus EGFRi were shown in Table S1. Crizotinib plus 1st or 2nd generation EGFRi had relatively higher incidence
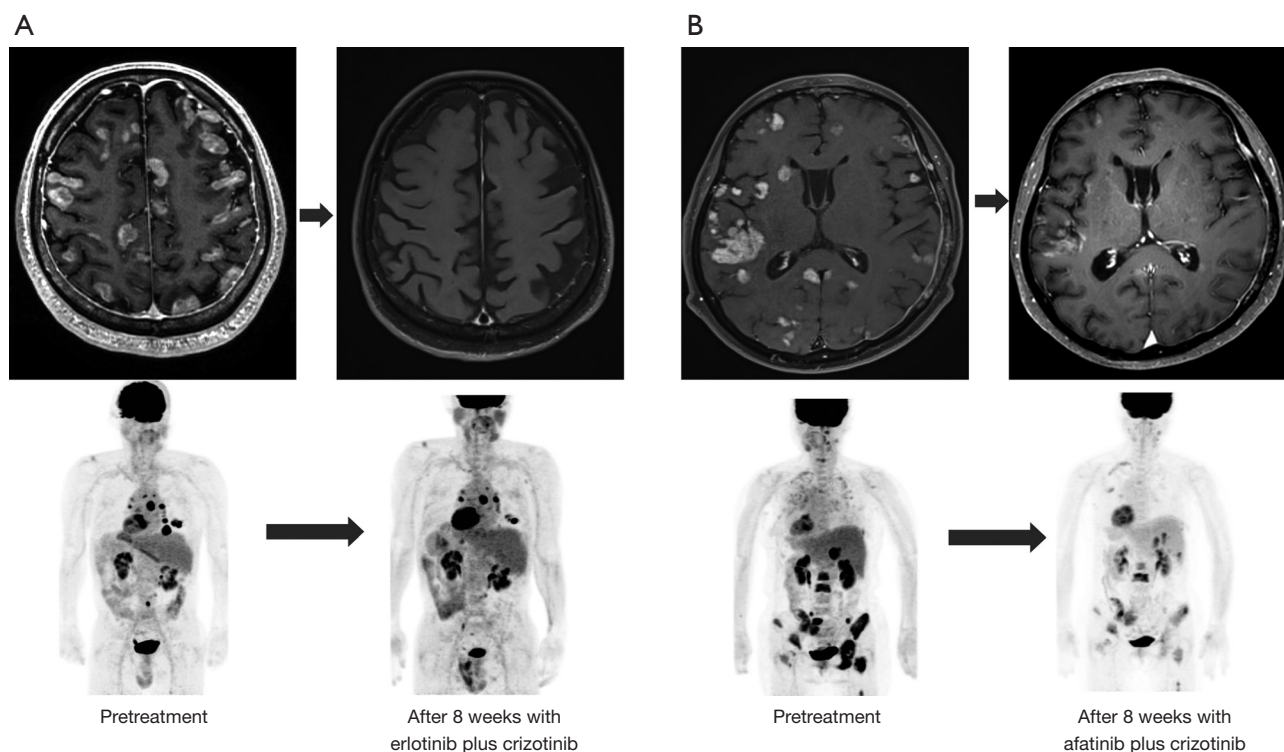
Figure 1 Cases with intracranial response to combination of MET inhibitor and EGFR inhibitor. (A) Radiologic response to erlotinib 150 mg plus crizotinib 250 mg daily in a 67-year-old man with stage IV *EGFR*-mutant and *MET*-amplified NSCLC resistant to osimertinib. Upper panel: brain MRI; lower panel: torso PET scan. (B) Radiologic response to afatinib 20 mg plus crizotinib 250 mg daily in a 59-year-old woman with stage IV *EGFR*-mutant and *MET*-amplified NSCLC resistant to osimertinib. Upper panel: brain MRI; lower panel: torso PET scan. MRI, magnetic resonance imaging; PET, positron emission tomography; NSCLC, non-small cell lung cancer.

of pneumonitis compared to other regimens.

Intracranial tumor response

As of the data cutoff date (June 1, 2023), 36 (81.8%) disease progression and 38 (86.4%) death events occurred over a median follow-up of 65.2 months [95% confidence interval (CI): 0.0–139.8]. One patient was still alive receiving the EGFRi plus METi combination.

The response evaluation was available for 43 patients. The overall response rate was 74.4% [CR (n=1, 2.3%), PR (n=31, 72.1%), stable disease (SD) (n=10, 23.3%), and disease progression (n=1, 2.3%)] (Figure S2). Among 22 patients with BM, intracranial tumor response rate was 63.6%; SD (n=8) and PR (n=14). *Figure 1* illustrates two patients in whom multiple BM showed prompt and dramatic response to the EGFRi plus METi combination. The first patient was a 67-year-old man with stage IV lung adenocarcinoma with *EGFR* 19 deletion mutation

(*Figure 1A*). Secondary *MET* amplification was identified in his lung tumor tissue after progression to second-line osimertinib treatment. At the time of progression, he had dysdiadochokinesia and speech fluency disorder; brain MRI showed multiple lobulated necrotic lesions in both cerebral hemispheres, cerebellum, and left thalamus. Thus, he was prescribed erlotinib 150 mg plus crizotinib 250 mg daily. After 8 weeks, almost all brain lesions had completely resolved and his neurologic symptoms were much improved. Moreover, there was significant regression of his lung and bone metastases. His tumor response was maintained for 5.3 months. The second patient was a 59-year-old woman with stage IV lung adenocarcinoma who developed acquired resistance to second-line osimertinib treatment (*Figure 1B*). She had multifocal nodular or necrotic lesions in both cerebral hemispheres and cerebellum with localized leptomeningeal enhancement in the right Sylvian fissure as well as multiple bone, liver, and right adrenal gland metastases. At the time of progression, *EGFR* 19 deletion

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and T790M mutation and *MET* amplification were detected in her plasma ctDNA NGS test (Guardant360®). Thus, she was prescribed afatinib 20 mg and crizotinib 250 mg daily. After two cycles, multiple BM and leptomeningeal carcinomatosis were considerably attenuated along with remarkable improvement in dysarthria. Extracranial metastatic lesions were also much improved. Her tumor response was maintained for 3.9 months. Further analysis of clinicopathologic factors related to BM response showed the previous history of local treatment for BM and EGFRi type was not significantly associated with the BM response (Table S2). However, METi type was associated with the BM response (P=0.052). Crizotinib was numerically inferior to other specific MET inhibitors in terms of treating BM: the response rate to BM, savolitinib (11/14, 78.6%), crizotinib (2/7, 28.6%), and capmatinib (1/1, 100%) (P=0.052).

Predictors of PFS

The median PFS in our cohort was 5.3 months (95% CI: 3.3–7.3) and the median OS was 13.4 months (95% CI: 10.2–16.6) (Figure S3A,S3B). We further analyzed the clinicopathologic factors related to survival outcomes after treatment with EGFRi plus METi combination. In the univariate analysis of PFS, only lymphangitic metastasis was associated with PFS [hazard ratio (HR), 2.46; 95% CI: 0.14–5.34; P=0.02] (Table S3). The potential factors related to METi efficacy such as MET/CEP7 ratio on FISH test, METi type, and METi discontinuation were not significant predictors of PFS. In addition, the potential factors related to EGFRi efficacy such as *EGFR* mutation type, history of EGFRi therapy and its response, and EGFRi type were not related to the risk of disease progression. Among 23 patients who were treated with the combination treatment of 3rd generation EGFRi plus METi after progression to 1st or 2nd generation EGFRi, *EGFR* T790M mutation was simultaneously detected in 2 patients, not detected in 15 patients, and not evaluated in 6 patients. In this patient population, there was no significant difference in PFS between the tumors with or without *EGFR* T790M mutation (HR, 1.90; 95% CI: 0.38–9.46; P=0.43). The presence of lymphangitic metastasis remained significant even in the multivariate PFS analysis accounting for MET/CEP7 ratio, prior EGFRi therapy, and current METi type. Patients with lymphangitic metastasis showed a significantly shorter median PFS compared to those without lymphangitic metastasis (3.8 *vs.* 6.1 months, P=0.03) (Figure S3C,S3D).

In the univariate analysis of OS, prior EGFRi treatment type and current METi treatment type were associated with the risk of death from the combination treatment (Table S4). However, no independent predictors of OS were identified in multivariate analysis.

Timing of METi discontinuation

Serial monitoring of *MET* amplification in ctDNA isolated from plasma was available for nine patients who continued the combination treatment without interruption of METi. At the baseline, the median value of MET to reference gene ratio was 1.85 (range, 1.00–3.30). The median time to the normalization of ctDNA MET ratio (1.00) from the initiation of the combination treatment was estimated using Kaplan-Meier curve (*Figure 2A*). The median time elapsed from the initiation of combination treatment to ctDNA *MET* gene normalization was 63 days (95% CI: 39–not available). We divided the 23 patients in whom METi treatment was withheld due to adverse effects into two subgroups based on the median ctDNA MET normalization time. Patients who stopped METi before 63 days from the start of combination treatment (n=14) had a significantly inferior outcome compared with those who discontinued METi after ≥63 days (n=9) [PFS: HR, 2.78, 95% CI: 1.00–7.75, P=0.050; OS: HR, 2.71, 95% CI: 1.02–7.16, P=0.045] (*Figure 2B,2C*).

On the other hand, continuation of EGFRi even after withholding METi was not associated with survival outcomes (with *vs.* without EGFRi maintenance; PFS: HR, 2.06; 95% CI: 0.73–5.80, P=0.17; OS: HR, 0.95, 95% CI: 0.39–2.33, P=0.92).

Acquired resistance and subsequent treatment

Table 3 lists the details of 14 (31.8%) patients for whom the mechanism of resistance to EGFRi and METi combination was detected via genomic and histologic comparison between pretreatment and posttreatment samples. Secondary *MET* mutation (*MET* D1246H) was detected in 1 (7.1%) patient who received osimertinib and savolitinib for 11.8 months. This patient was administered a trial of a multi-receptor-tyrosine-kinase-targeting MET inhibitor (sitravatinib) and showed a PR with 40% tumor shrinkage. On the other hand, secondary *EGFR* mutation was detected in seven patients (50%): C797S (n=2) and T790M (n=5). In one patient who acquired *EGFR* C797S mutation after osimertinib and savolitinib treatment for 4 months,
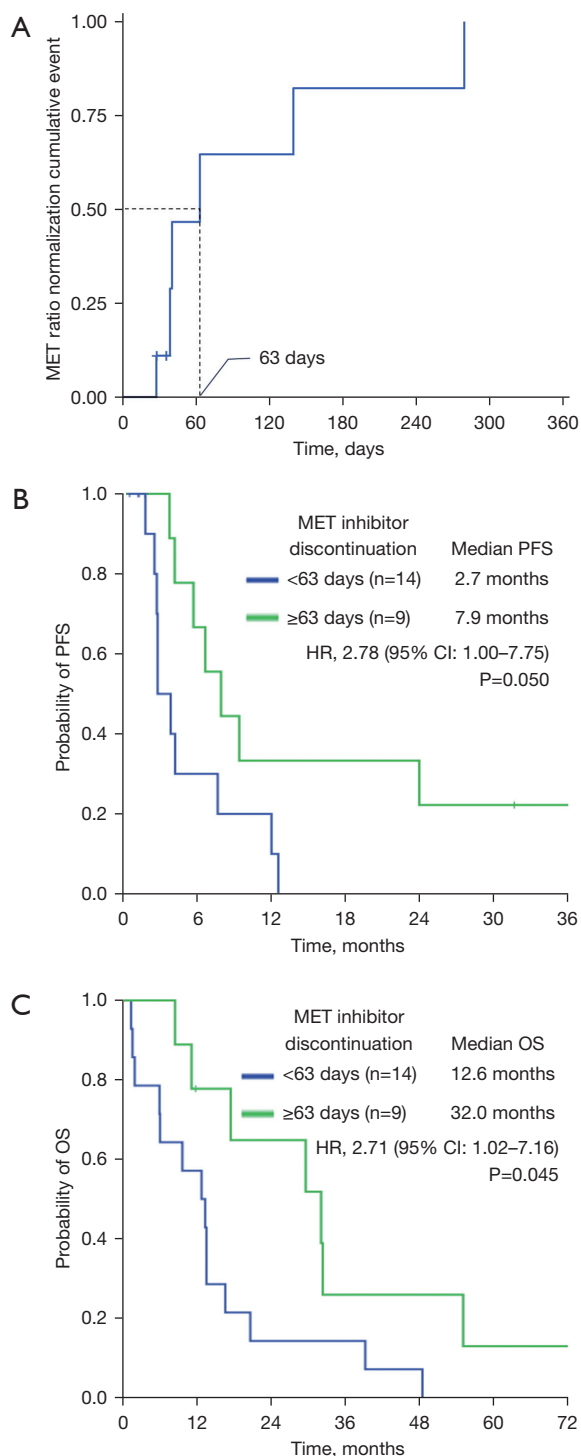
Figure 2 Effect of the timing of discontinuation of MET inhibitor on survival. Kaplan-Meier curves: (A) estimated median *MET* amplification ctDNA clearance time; PFS (B) and OS (C) according to the timing of discontinuing MET inhibitor. CI, confidence interval; HR, hazard ratio; PFS, progression-free survival; OS, overall survival; ctDNA, circulating tumor DNA.

amivantamab, an EGFR-MET bispecific antibody, was used as subsequent therapy; this patient showed a PR with 38% tumor shrinkage. *EGFR* T790M mutation developed in four patients who received 1st- or 2nd-generation EGFRi plus METi and one patient who stopped osimertinib plus savolitinib due to pneumonitis before the disease progression. All five patients with *EGFR* T790M-mutant tumors received osimertinib with or without METi after the failure of initial EGFRi plus METi treatment. Three patients showed clinical benefit from osimertinib: PR (n=2); SD (n=1). The two non-responders to osimertinib included one patient whose tumor showed histologic transformation to squamous cell carcinoma and one patient whose tumor still had high *MET* amplification along with *EGFR* T790M mutation. After osimertinib failure, the patient with both *EGFR* T790M mutation and histologic transformation to squamous cell carcinoma as acquired resistance was treated with atezolizumab, bevacizumab, carboplatin, and paclitaxel (ABCP) and showed a PR with 52% tumor shrinkage. Secondary bypass resistance mechanisms included *KRAS* amplification, *MAP2K1* mutation and *FGFR3* amplification, *CDK4* and *FGFR1* amplification, *CCND1* amplification, and *RB1* mutation.

After progression while on the combination treatment, 31 (70.5%) patients underwent subsequent chemotherapy. The median number of subsequent chemotherapy regimens was 2 (range, 1–6). *Figure 3* displays all types of chemotherapy regimens administered to all patients after showing progression while on EGFRi plus METi combination. The most frequently used regimen was anti-PD(L)1 inhibitor (n=12) and 1st- or 2nd-generation EGFRi (n=12). Among these regimens, the regimens that included paclitaxel and platinum, such as ABCP, showed a trend of higher response rates compared to other regimens. It seems that immune checkpoint inhibitor, retreatment with 1st- or 2nd-generation EGFRi, and pemetrexed had little effect on the tumors resistant to EGFRi plus METi combination.

Discussion

To the best of our knowledge, this is the first study to present longitudinal data about patients with *EGFR*-mutant and *MET* amplified lung cancer treated with EGFRi plus METi combination, including the efficacy, safety profile, acquired resistance mechanism, and subsequent treatment. This study suggests that the strategy of combining EGFRi and METi was highly effective for secondary *MET*-amplified *EGFR*-mutant lung cancer patients because it

Table 3 Putative mechanisms of resistance to EGFR-TKI and MET-TKI combination treatments

ID	Age (years)/ sex	Prior EGFR-TKI	Current regimen	Drug discontinuation due to adverse effect (time)	Response (PFS)	Progression site	Mechanism of acquired resistance	MET amplification after progression (test)	Subsequent treatment (response)
1	75/M	Olmutinib	Osimertinib 80 mg QD + savolitinib 600 mg QD	None	PR (11.8 m)	Lung, bone	MET D1246H	–	Sitravatinib (PR)
2	55/M	Afatinib	Osimertinib 80 mg QD + savolitinib 600 mg QD	None	PR (4.2 m)	Brain	EGFR C797S	Negative (FISH)	Amivantamab (PR)
3	59/F	Osimertinib	Osimertinib 80 mg QD + crizotinib 250 mg QD	None	PR (12.0 m)	Lung, liver, bone	EGFR C797S	–	–
4	53/M	Erlotinib	Gefitinib 250 mg QD + capmatinib 400 mg BID	None	PR (20.3 m)	Lung	EGFR T790M	–	Osimertinib (PR)
5	58/M	Dacomitinib	Erlotinib 100 mg QD + crizotinib 250 mg BID	None	PR (8.2 m)	Brain, mediastinal lymph node	EGFR T790M	Positive (FISH)	Osimertinib (PD)
6	58/F	Osimertinib	Afatinib 20 mg QD + crizotinib 250 mg QD	None	PR (3.9 m)	Lung, liver, brain	EGFR T790M	–	Osimertinib + crizotinib (SD)
7	60/F	Erlotinib	Osimertinib 80 mg QD + savolitinib 300 mg QD	Both drugs (8 cycles)	PR (7.9 m)	Lung	EGFR T790M	Negative (FISH)	Osimertinib (PR)
8	61/M	Afatinib	Erlotinib 100 mg QD + crizotinib 250 mg BID	None	PR (2.6 m)	Bone	EGFR T790M and SQCC transformation	Positive (FISH)	Osimertinib + crizotinib (PD)
9	55/M	Erlotinib	Osimertinib 80 mg QD + savolitinib 300 mg QD	Savolitinib (1 cycle)	PR (3.8 m)	Lung	MAP2K1 E203K and FGFR3 amplification	–	PCb (PD)
10	57/F	Gefitinib	Osimertinib 80 mg QD + savolitinib 600 mg QD	None	SD (18.6 m)	Lung, brain	KRAS amplification	Negative (FISH)	Afatinib (PD)
11	41/F	Gefitinib	Osimertinib 80 mg QD + savolitinib 600 mg QD	Savolitinib (1 cycle)	PR (2.8 m)	Pericardial effusion	EGFR wild type	Negative (FISH)	GCb (PD)
12	60/M	Osimertinib	Osimertinib 80 mg QD + crizotinib 250 mg QD	None	SD (1.8 m)	Lung	CDK4 amplification and FGFR1 amplification	Negative (FISH)	Trametinib (PD)
13	69/F	Erlotinib	Osimertinib 80 mg QD + savolitinib 600 mg QD	None	PR (4.1 m)	Soft tissue	CCND1 amplification	Positive (FISH)	IP (PD)
14	58/M	Erlotinib	Osimertinib 80 mg QD + savolitinib 600 mg QD	Savolitinib (1 cycle)	SD (2.7 m)	Pleura	RB1 R320*	Positive (NGS)	Amivantamab (PR)

TKI, tyrosine kinase inhibitor; M, male; F, female; QD, once daily; BID, twice daily; PFS, progression-free survival; PR, partial response; SD, stable disease; m, months; SQCC, squamous cell carcinoma; FISH, fluorescence in situ hybridization; NGS, next-generation sequencing; PD, progressive disease; PCb, paclitaxel plus carboplatin; GCb, gemcitabine plus carboplatin; IP, irinotecan plus cisplatin.
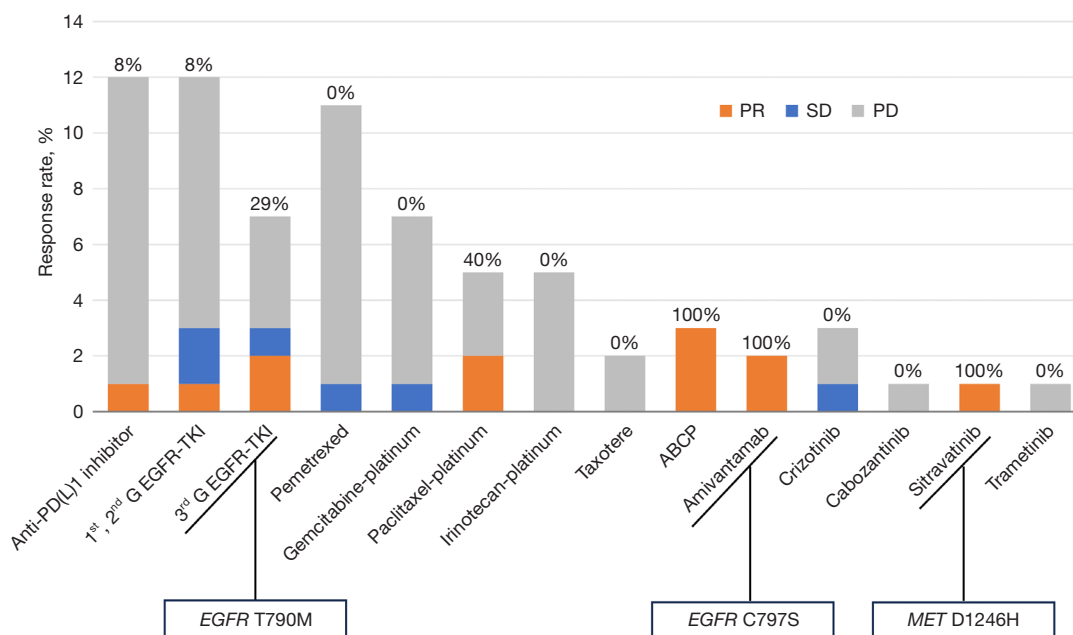
Figure 3 Tumor response per regimen which was used after progression with a combination of MET inhibitor and EGFR inhibitor. PR, partial response; SD, stable disease; PD, progressive disease; TKI, tyrosine kinase inhibitor; G, generation; ABCP, atezolizumab-bevacizumab-carboplatin-paclitaxel.

resulted in a prompt and dramatic tumor response with rapid symptom relief. This combination treatment provided a survival gain of approximately 1 year to previously-treated lung cancer patients with poor prognosis.

Interestingly, this study demonstrated substantial tumor response was observed in intracranial lesion as well as extracranial lesions. 1st or 2nd generation EGFRi is generally considered to be inferior to 3rd generation EGFRi in terms of the central nervous system (CNS) penetration activity (10). Crizotinib also is known to have poor penetration ability into the blood-brain barrier (11). However, two cases of this study having bulky brain metastases with or without leptomeningeal disease showed the remarkable response to the combination treatment with a 1st- or 2nd-generation EGFRi and half dose of crizotinib. Although the specific METi was numerically better in the response to BM than the nonspecific METi, these cases raise the possibility that two-drug combination strategy may have a synergistic effect against intracranial lesions. Most recently, the FLAURA2 clinical study supported this finding that the addition of chemotherapy to osimertinib improved survival outcomes compared to osimertinib monotherapy in patients with the CNS metastasis (12,13).

Nevertheless, in this study, 52.3% of patients had to

discontinue both EGFRi and METi or METi alone due to drug-related adverse effects. The discontinuation rate in our study seems to be higher than that in a previous clinical trial (14). The primary cause of drug discontinuation due to adverse effects was pneumonitis for both drugs or hypersensitivity for METi alone, which can lead to a fatal and life-threatening event. Concurrent administration of two drugs may be the ideal way to overcome acquiring bypass resistance mechanisms such as *MET* amplification in patients treated with targeted therapy. However, in case of overlapping adverse effects of the two drugs, it is challenging to assess the effectiveness of this concurrent treatment. Thus, we further evaluated the survival impact of discontinuing METi due to adverse effects. Unexpectedly, this study found no significant difference in the survival outcomes between patients who discontinued METi due to adverse effects and those who did not. Several case series have presented the effect of METi monotherapy in the same patient subsets with *EGFR*-mutant and secondary *MET*-amplified lung cancer (15-20). Among these reports, van Veggel *et al.* demonstrated that *MET* amplification in tumors disappeared even after short treatment with METi and suggested that *MET*-amplified cells might be minor clones among the whole EGFRi-resistant cells (17). These

previous findings might explain why the patients who had to receive short-term METi treatment owing to toxicities did not have worse survival compared to those who received long-term METi treatment in this study.

If transient use of METi could successfully eradicate METi-sensitive subclones, it might reduce the duration of concurrent administration of EGFRi and METi. Thus, we sought to determine the time required to clear METi-sensitive cells, utilizing serial plasma ctDNA data. Recent studies have demonstrated that the blood ctDNA test is a useful tool to identify minimal residual disease, which has been proposed as a surrogate biomarker to predict postoperative recurrence after curative surgery in early-staged solid cancers (21-23). In this study, the estimated time required for the disappearance of *MET* amplification in plasma ctDNA was 63 days from starting the combination treatment. This plasma *MET* amplification clearance time is shorter than the time required for the development of severe adverse effects leading to the discontinuation of both drugs (84 days). Additionally, patients who discontinued METi after 63 days of treatment showed significantly longer survival outcomes than those who discontinued METi before 63 days. Thus, it is recommended that plasma ctDNA should be monitored in conjunction with this treatment to monitor treatment response and potentially guide therapeutic decisions in this patient population.

In this study, on-target secondary mutations were identified as the most common mechanism of acquired resistance to the EGFRi plus METi combination treatment. Firstly, *EGFR* T790M or C797S mutation are well-known mechanisms of acquired resistance to EGFRi (3,24,25). Currently, novel 4th-generation EGFRis, such as BDTX-1535 and BLU-945, are being actively developed to treat *EGFR* C797S-mutant tumors (26). In our cohort, the patient with *EGFR* C797S mutation showed a good response to amivantamab, which has been evaluated in combination with lazertinib in the osimertinib-failed patients with *EGFR*-mutant NSCLC (CHRISALI-2 study) (27). This new drug may be effective in targeting both EGFR and MET signaling pathways. Another patient whose tumor had *MET* amplification and *RB1* mutation without *EGFR* C797S mutation after progression on osimertinib plus savolitinib demonstrated a good response to amivantamab. On the other hand, previous case studies have reported *MET* D1246H mutation as a mechanism of acquired resistance to EGFRi plus METi combination treatment (28,29). In this study, the patient who acquired *MET* D1246H

mutation after progression on osimertinib plus savolitinib was treated with sitravatinib alone and showed substantial tumor shrinkage. Recent studies have demonstrated the effectiveness of type II MET inhibitors against tumors acquiring resistance to type I MET inhibitors by secondary *MET* mutations (30,31). These studies suggest that tumors that acquire resistance to EGFRi and METi due to on-target secondary mutations may potentially be treated with another targeted therapy. Thus, attempts to identify the resistance mechanisms, including re-biopsy and comprehensive genetic analysis, should be continued even in patients who show progression after EGFRi plus METi combination treatment.

Among subsequent treatments including nontargeted therapy, pemetrexed and immune checkpoint inhibitors were the most frequently used but showed limited benefit after EGFRi plus METi combination treatment. The most effective cytotoxic therapy seems to be the regimen including paclitaxel and platinum [PR: 5 of 8 (62.5%)]. Especially, the patients treated with the ABCP regimen showed a promising response [PR: 3 of 3 (100%)] compared to the other chemotherapy regimens. In the IMPOWER 150 study, the ABCP regimen conferred a significant survival benefit in the subgroup of patients with *EGFR* mutation who are unlikely to benefit from immune checkpoint inhibitor therapy (32). Although the mechanism of the therapeutic effect of the ABCP regimen in *EGFR*-mutant tumors remains unknown, this study showed that this regimen can be effective even in heavily-treated patients with *EGFR*-mutant tumors.

The main limitations of this study should be considered while interpreting the results. First, there was significant heterogeneity in terms of patient characteristics, chemotherapy regimen, dose, and administration schedule. In particular, including both clinical trial patients and real-world patients could introduce potential bias into the evaluation of efficacy and safety data because the two groups' baseline characteristics and management may be different. Actually, two clinical studies about METi and EGFRi combination treatment into which some patients of this study were originally enrolled, showed the difference in the following (4,5). In the TATTON study with *EGFR* mutation-positive, *MET*-amplified, and EGFR-TKI-failed NSCLC, the patient treated by savolitinib 600 mg and osimertinib 80 mg showed 57% of grade ≥3 adverse event and 28% of savolitinib treatment discontinuation, but they had a 48% response rate and a PFS of 7.6 months (4).

In contrast, the phase Ib/II study of capmatinib plus gefitinib in patients with *EGFR*-mutated, *MET*-amplified or overexpressing NSCLC after progression to EGFRi, demonstrated 29.0% of grade ≥3 adverse event, 13.0% of treatment discontinuation due to adverse effects, 29% response rate and 5.5 months PFS (5). Despite these limitations, this retrospective study was conducted to provide physician treating this rare and poor patient population with more detailed and longitudinal data beyond the efficacy and safety of clinical trials. Second, the results of statistical analyses should be interpreted with caution due to the small sample size. For example, based on previous clinical trials, a subgroup of patients in whom EGFRi type may have significant impact on the overall efficacy with combination treatment, are those who received non-3rd-generation EGFRi plus METi for T790M-positive tumor after progression to non-3rd-generation EGFRi (4,33). However, in this study, the number of those patients (n=2) was too small to affect the clinical outcomes of combination treatment and thus, the EGFRi type was not significantly associated with median PFS. In addition, the plasma *MET* amplification clearance time was determined using data from only nine patients because this analysis was performed only for patients who continued both EGFRi and METi until disease progression. In addition, the number of patients was two small to compare the tumor response according to subsequent therapy regimens. Although secondary *MET*-amplified and *EGFR*-mutant lung cancer population is rather rare, a prospective study with a larger sample size is required to reassess these important findings.

Conclusions

The EGFRi plus METi combination therapy showed a remarkable response leading to rapid tumor-associated symptom relief in the EGFRi-treated patients with advanced *EGFR*-mutant and *MET*-amplified NSCLC. However, the occurrence of severe toxicity requiring drug continuation, such as pneumonitis, was relatively common with this combination regimen. Early discontinuation of METi negatively affected the survival outcomes. A variety of mechanisms of acquired resistance to the two drugs were detected after disease progression while receiving the combination treatment. Active surveillance to identify resistance mechanisms may help improve survival after the failure of the EGFRi plus METi combination.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-273/rc

Data Sharing Statement: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-273/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-273/coif). Y.L. received consulting fees from Roche, Merck, Yuhan, and Bayer. J.Y.H. received research grants from Roche, ONO, Pfizer and Takeda; consulting fee from Astra Zeneca, BMS, Eli Lilly, Merck, Novartis, Pfizer, Abion, Jints Bio; and honoraria for lecture from Astra Zeneca, BMS, Merck, Takeda and Novartis. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the institutional review board of the National Cancer Center (No. NCC 2016-0208). Informed consent was waived because of the retrospective nature of the study.

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