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<REVIEWER 1>

COMMENT #1

1. Intracranial Tumor Response:

Two cases with dramatic responses to brain metastases are presented. The manuscript states that the intracranial tumor response rate is 63.6%. Given the serious issue of brain metastases in EGFR-mutant lung cancer, could a more detailed analysis be provided? For example, are there common backgrounds or factors among patients who do or do not respond to the treatment?

REPLY #1

Thanks for your kind comment. We further analyzed the subgroup with brain metastasis. Consequently, we could found out crizotinib was numerically inferior to other specific MET inhibitors in terms of treating brain metastasis : response rate to brain metastasis, sarvonitinib (11/14, 78.6%), crizotinib (2/7, 28.6%), and capmatinib (1/1, 100%). Whether the BM was treated with local treatment before the combination treatment was not significant in response to the BM.

Supplementary Table 2. Characteristics of patients with brain metastasis

Characteristics		**BM-Responder** N (%)	**BM-Nonresponder** N (%)	***P***
Age	< 65 years	11 (78.6)	7 (87.5)	1.000
	≥ 65 years	3 (21.4)	1 (12.5)	
Sex	male	8 (57.1)	6 (75.0)	0.649
	female	6 (42.9)	2 (25.0)	
Smoking	never	6 (42.9)	2 (25.0)	0.649
	ever	8 (57.1)	6 (75.0)	
ECOG PS	0 or 1	12 (85.7)	6 (75.0)	0.602
	2	2 (14.3)	2 (25.0)	
Histology	adenocarcinoma	13 (92.9)	8 (100.0)	1.000
	non-adenocarcinoma	1 (7.1)	0 (0.0)	
EGFR mutation	exon 19 deletion	7 (50.0)	4 (50.0)	0.480

		exon 21 L858R	7 (50.0)	3 (37.5)	
		exon 18 G719X	0 (0.0)	1 (12.5)	
Previous treatment	BM	Radiotherapy	2 (14.3)	1 (12.5)	0.701
		Surgery + Radiotherapy	0 (0.0)	1 (12.5)	
		None	12 (85.7)	6 (75.0)	
Prior EGFR-TKI		1st or 2nd generation	9 (64.3)	6 (75.0)	1.000
		3rd generation	5 (35.7)	2 (25.0)	
EGFR-TKI		1st or 2nd generation	3 (21.4)	3 (37.5)	0.624
		3rd generation	11 (78.6)	5 (62.5)	
MET-TKI		savolitinib	11 (78.6)	3 (37.5)	0.052
		crizotinib	2 (14.3)	5 (62.5)	
		capmatinib	1 (7.1)	0 (0.0)	

Abbreviations: BM, brain metastasis; ECOG, Eastern Cooperative Group; PS, performance status. FISH, fluorescence in situ hybridization; EGFR-TKI, EGFR tyrosine kinase inhibitor; MET-TKI, MET tyrosine kinase inhibitor.

Changes in the text #1:

We have modified our text as advised (see Supplementary Table 2; Page 13, line 273-line 279)

COMMENT #2

1 Discussion on Intracranial Lesions:

The discussion on the results of intracranial lesions is insufficient. It would be beneficial to include further analysis, incorporating a literature review on why combination therapy is effective against intracranial lesions.

REPLY #2

Based on the reviewer's comment, we added the further analysis for intracranial lesion respose into the result and discussion part as follows:

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)

Changes in the text #2:

We have modified our text as advised (see Page 17, line 371 to Page 18, line 383)

COMMENT #3

ctDNA Analysis:
The analysis using ctDNA is highly intriguing but raises several questions. One of them is about the timing of blood sample collection. The manuscript mentions ddPCR analysis for MET gene amplification in nine patients receiving combination therapy. Was there a protocol for monitoring blood sample timing common to these patients? (e.g., blood samples before treatment, at specific weeks post-treatment, at PD or when side effects appeared)

REPLY #3

As addressed with the reviewer's comment, we have added the sentence about blood sampling to the result section as follows:

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.

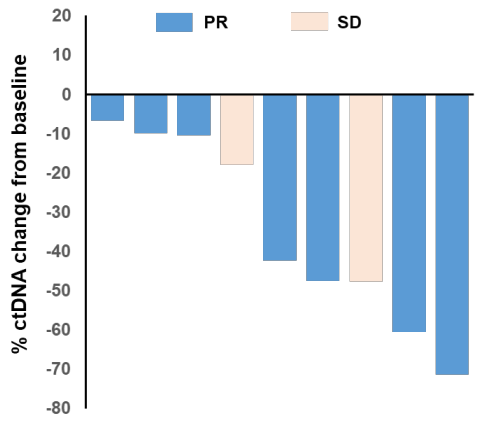
Changes in the text #3:

We have modified our text as advised (see Page 9, line 182-line 184)

COMMENT #4

Correlation between MET Gene Amplification Changes and Clinical Outcomes:
It is essential to provide a more detailed presentation of the correlation between changes in MET gene amplification and clinical outcomes. Can you provide figures or tables comparing the trends in MET gene amplification from blood monitoring of the nine patients with treatment efficacy? The goal is to understand whether the reduction in MET gene amplification contributes to treatment success.

REPLY #3



We showed the waterfall plot of best percentage change from baseline in MET ctDNA. All nine patients showed a reduction in MET ctDNA after the combination treatment regardless of tumor response. We could not observe any trend associated with turmor response dut to too small sample size.

Changes in the text #4:

We have no modification.

COMMENT #5

Comparison of Pre- and Post-treatment Blood Sample Results for ctDNA:

Regarding ctDNA, since there is a reference gene ratio, it suggests there are pre-treatment blood sample results. Can you compare the pre- and post-treatment ctDNA sample results to confirm the attenuation rate of the MET gene ratio? If possible, Was the rate of ctDNA reduction with treatment related to PFS or OS?

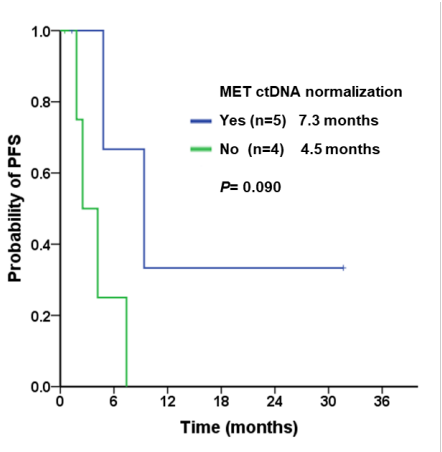
REPLY #5

We evaluated the association between the best percentage change from baseline in MET ctDNA and PFS or OS. The rate of ctDNA reduction was not associated with survivial outcomes.

PFS; HR= 0.997 (95% CI, 0.959-1.036), P= 0.870

OS; HR= 1.003 (95% CI, 0.973-1.034), P= 0.836

We further analyzed the median PFS according to MET ctDNA normalization in nine patients. As shown figure below, there was no signficiant difference in the median PFS between with or without MET ctDNA normalization. In previous other study (TATTON), early clearance of EGFR mutation at ctDNA analysis showed favorable prognosis (Hartmaier R.J et al. Cancer discovery Jan 2023). That finding was not repeated in our study. I think that's because the number of our study's subjects were too small to analysis. Additionally, it seems difficult to measure gene amplification at plasma ctDNA analysis as surrogate maker for tumor burden or minimal residual disease, compared to gene point mutation.



Changes in the text #5:

We have no modification.

COMMENT #6

P5 Line 188-190:

"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=9, 23.3%], and disease progression [PD] [n=1, 2.3%])". The total here adds up to 42, not 43. Is there a reason for this discrepancy? This issue is also present in the next paragraph with the 23 patients being 22. Does this relate to the statement, "One patient was still alive receiving the EGFRi plus METi combination," meaning they are too early in treatment to be evaluated or should be excluded from the analysis?

REPLY #6

Thanks for your comment on critical point. This is a typo error while updating raw data. One patients who the reviewer mentioned is a long user with 71 months of PFS and thus there was no case who is too early in treatment without tumor assessment. We corrected the number of stable disease from 9 to 10 and the number of brain metastasis from 23 to 22.

Changes in the text #6:

We have modified our text as advised (see Page 12, line 249; Page 12, line 22 and Table 1)

COMMENT #7

P6 Line 234:

The letter 'I' in EGFRI is capitalized. Please correct this.

REPLY #7

We have correted EGFRI into EGFRi.

Changes in the text #7:

We have modified our text as advised (see Page 14, line 301)

<REVIEWER 2>

COMMENT #1

In the section "Predictors of PFS," the author states that only lymphangitic metastasis was involved in PFS. Was there no difference in PFS in patients with brain metastases when treated with drugs with poor blood-brain barrier permeability and nonspecific MET inhibition, such as crizotinib, versus specific type I MET inhibitors like tepotinib and type II MET inhibitors like savolitinib? Similar to the results of the FLAURA2 Clinical Trials, 1,2 did the clinical results show that the combination was effective in reducing CNS metastasis? This point is of great interest to the reader and needs to be addressed.

REPLY #1

Thanks for your valuable comment as well as references. We totally agreed with the reviewer. Thus, we had added the possibility that combination therapy may further be effective against intracranial lesions in the discussion section as follows:
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)

Changes in the text #1

We have modified our text as advised (see Page 17, line 371 to Page 18, line 383)

<REVIEWER 3>

COMMENT #1

Study Design and Patient Population: The retrospective, single-center design and the inclusion of patients from prospective clinical trials introduce significant biases that may limit the generalizability of the findings. The authors should explicitly acknowledge these limitations and thoroughly discuss their potential impact on the study results.

The inclusion of both clinical trial patients and real-world patients introduces a potential bias in the evaluation of efficacy data, as these two groups may differ in baseline characteristics and management. It is essential for the authors to clearly delineate these groups in the CONSORT diagram and to provide a rationale for their combined analysis in the text.

Furthermore, the heterogeneity of the patient population, particularly the diverse treatment regimens and prior lines of therapy, makes it challenging to draw definitive conclusions about the efficacy and safety of specific METi/EGFRi combinations.

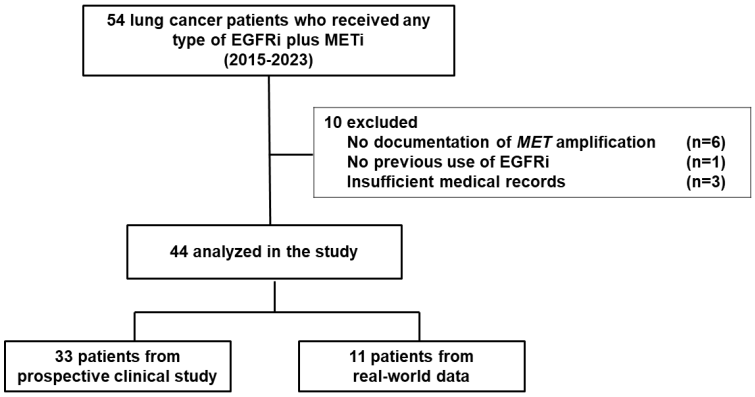
A figure illustrating the duration of response for each patient according to the specific combination used could provide more clinically relevant insights.

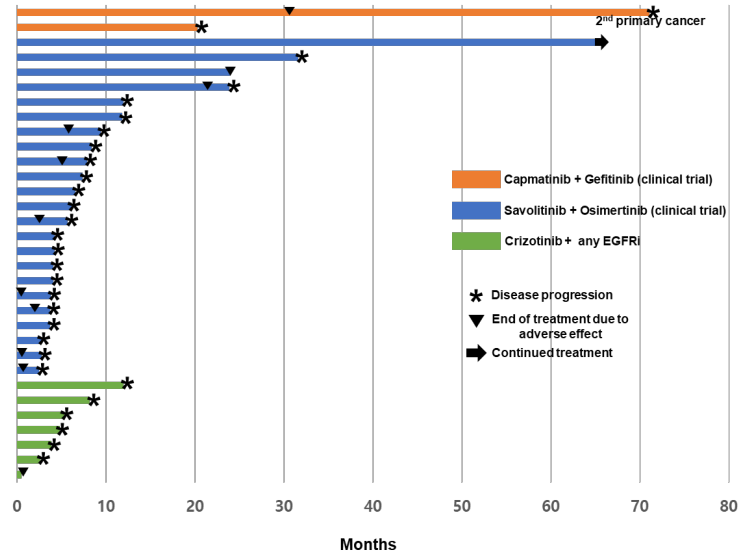
REPLY #1

Thanks for your valuable comment. We totally agreed with the reviewer. Thus, we already had described the significant limitation of this study in terms of significant heterogeneity (chemotherapy regimen, dose, and administration schedule) and this limitation could have affected outcomes because the adverse drug effect and efficacy can vary depending on the type of drug or dose. Especially, we had added that two clinical trials had different safety profiles. However, according to the reviewer's comment, we further have described the limitation that the inclusion of both clinical trial patients and real-world patients introduces a potential bias in the evaluation of efficacy data, as these two groups may differ in baseline characteristics and management. In addition, the CONSORT diagram and a rational for the combined analysis have been added. We had newly provided a figure for the reponse duration for each paeints as follows:

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 admini stration 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 th e 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.4,7 In the TATTON study with EGFR mutation-positive, MET-amplified, and EGFR-TKI-failed NSCLC, the patient treated by savolitinib 600mg and osimertinib 80 mg showed 57% of grade ≥3 adverse event and 28% of savolitinib treatment discontinuation, but they had a 48% response rat e 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 ad verse event, 13.0% of treatment discontinuation due to adverse effects, 29% response rate and 5.5 mo nths PFS. ***Despite these limitations, this retrospective study was conducted to provide physician treat***

ing this rare and poor patient population with more detailed and longitudinal data beyond the effic acy and safety of clinical trials.





Changes in the text #1

We have modified our text as advised (see Supplementary Figure 1 and 2; Page 21, line 453-Pase 22, line 477)

COMMENT #2

Resistance Mechanisms and EGFR TKI Generation: It is unclear whether MET amplification was the sole resistance mechanism identified in the cohort. Given the use of first- and second-generation EGFR TKIs in some patients, it is plausible that other mechanisms, such as the EGFR T790M mutation, may have been present. This could potentially bias the efficacy results, particularly with osimertinib-based combinations. The authors should clarify the distribution of resistance mechanisms in the study population and discuss the potential impact of EGFR T790M and other resistance mechanisms on the observed outcomes.

REPLY #2

To address the reviewer's comment, we added the status of EGFR T790M mutations of 23 patients who were treated with the combination treatment of 3rd generation EGFRi plus METi after progression to 1st or 2nd generation EGFRi. In addition, we further evaluated the efficacy of combination with 3rd generation EGFRi/METi according to EGFR T790M mutation status was concurrently detected in 2 patients, not detected in 15 patients, and not evaluated in 6 patients. *EGFR* T790M mutation was concurrently detected in 2 patients, not detected in 15 patients, and not evaluated in 6 patients. In this patient subgroup, there was no significant difference in PFS between with or without EGFR T790M mutation (6.1 months vs. 7.4 months, HR=1.90; 95% CI, 0.38–9.46; *P*= 0.434). On the other hand, a tatal of 7 patients who were treated with the combination treatment of non-3rd generation EGFRi plus METi after progression to 1st or 2nd generation EGFRi had the tumor without *EGFR* T790M mutation. When the EGFRi type was compared in 22 T790M-negative group who were treated with the combination treatment of EGFRi plus METi after progression to 1st or 2nd generation EGFRi, there was no significant difference in PFS between the 3rd G vs non-3rd G EGFRi groups (7.4 months vs. 8.2 months, HR= 1.36, 95% CI 0.37-4.92, *P*= 0.643).

In addition, we added the this finding in the discussion section as follows:

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.

Changes in the text #2

We have modified our text as advised (see Page 14, line 290-line 296; Page 22, line 472- line 477)

COMMENT #3

Adverse Events: The high rate of treatment discontinuation due to adverse events, primarily pneumonitis, raises concerns about the safety and tolerability of combination therapies. The authors should provide a more detailed analysis of the incidence and severity of pneumonitis, stratified by the specific METi/EGFRi combinations used. Additionally, detailed information regarding the initiation of combination therapy (e.g., concomitant vs. sequential) and dosing schedules should be provided to better understand the factors contributing to toxicity.

REPLY #3

To address the reviewer's comment, we analyzed the incidence and severity of pneumonitis, stratified by the specific METi/EGFRi combinations used. All patients had the same initial dosing schedule and started to concurrently receive METi and EGFRi. Thus, dosing schedule did not affect the incidence of pneumonitis.

Supplementary Table 1. Incidence of pneumonitis according to combination regimen

Combination regimen	Overall grade (%)	Grade 3-4 (%)
Savolitinib+Osimertinib	6/31 (19.4%)	0/31 (0.0%)
Capmatinib+Gefitinib	0/2 (0.0%)	0/2 (0.0%)

Crizotinib+Osimertinib	1/4 (25.0%)	0/4 (0.0%)
Crizotinib+1/2G EGFR-TKI	4/7 (57.1%)	2/7 (28.6%)

Abbreviations: 1/2 G EGFR-TKI, 1st or 2nd generation EGFR tyrosine kinase inhibitor.

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 Supplementary Table 1. Crizotinib plus 1st or 2nd generation EGFRi had relatively higher incidence of pneumonitis compared to other regimens.

Changes in the text #3

We have modified our text as advised (see Supplementary Table 1; Page 12, line 238-line 242).

COMMENT #4

Data Interpretation and Discussion: The interpretation of the study findings should be more cautious, given the limitations of the study design and the small sample size. The authors should avoid making definitive conclusions about the optimal duration of METi therapy based on the limited data on plasma ctDNA MET amplification clearance. Nevertheless, the analysis of plasma ctDNA to assess MET amplification clearance offers a valuable proof-of-concept for using liquid biopsies to monitor treatment response and potentially guide therapeutic decisions in this patient population.

The discussion should also include a more comprehensive comparison with existing literature, highlighting the similarities and differences in study design, patient population, and treatment outcomes. The lack of a significant difference in PFS based on EGFR TKI generation is unexpected and warrants further discussion. This finding contradicts some data in the literature and may be due to the limited sample size or other confounding factors, which should be explored in the discussion.

REPLY #4

To address the reviewer's comment, we removed the phrases related to the optimal duration of METi therapy in the discussion section and only emphasized the potential role of ctDNA monitoring as follows:

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.

And, in the discussion section, we added more detailed data of two published prospective clinical trials (TATTON and Capmatinib plus Iressa study) as follows:

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.4,7 In the TATTON study with EGFR mutation-positive, MET-amplified, and EGFR-TKI-failed NSCLC, the patient treated by savolitinib 600mg 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.

Thanks for your comment about the lack of a significant difference in PFS based on EGFR TKI generation. Based on previous clinical trials, a subgroup of patients for whom EGFRi type may have significant impact on the overall efficacy with combination treatment, are those who received non-3rd G EGFRi plus METi for T790M-positive tumor after progression to non-3rd G EGFRi. In this study, the number of those patients (n=2) was too small to affect the efficacy of combination treatment and thus, the EGFRi type was not associated with PFS.

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.

Changes in the text #4

We have modified our text as advised (see Page 19, line 416- line 418; Page 21, line 458- Page 22, line 468).

COMMENT #5

Statistical Analysis: The authors should clarify the statistical methods used for survival analysis, including the specific type of Cox proportional hazards model and the handling of censored data.

REPLY #5

To address the reviewer's comment, we descibred the specific type of Cox proportional hazards model and the handling of censored data in the method section as follows:

The standard Cox proportional hazards regression model was used to perform multivariate survival analysis.

with censoring of patients who are lost to follow-up.

Changes in the text #5

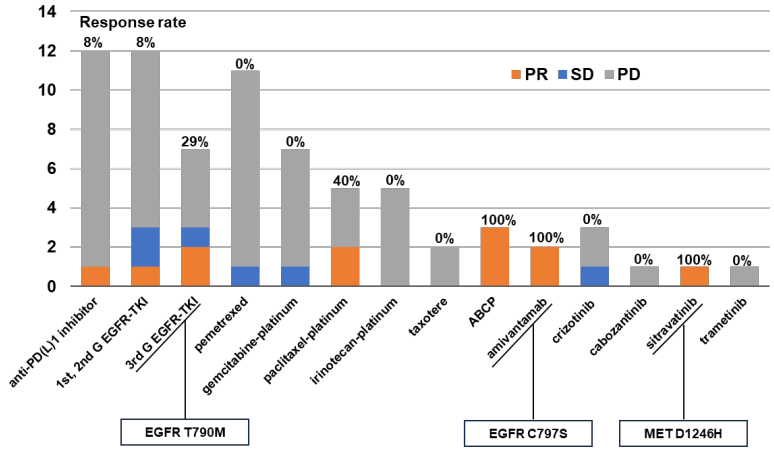
We have modified our text as advised (see Page 10, line 198; Page 10, line 202).

COMMENT #6

Figure Presentation: Figure 3 would be more informative if the specific resistance mechanisms were included alongside the chemotherapy regimens.

REPLY #6

To address the reviewer's comment, we added the specific resistance mechanisms related successful subsequent targeted therapy in Figure 3.



Changes in the text #6

We have modified our text as advised (see Figure 3).