nature portfolio

Peer Review File

Osimertinib with or without savolitinib as first-line treatment for MET-aberrant, EGFR-mutant NSCLC: randomized phase 2 trial (FLOWERS)

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This file contains all reviewer reports in order by version, followed by all author rebuttals in order by version.

Version 0:

Reviewer comments:

Reviewer #1

(Remarks to the Author)

Reviewer #2

(Remarks to the Author)
The Authors should be acknowledged for their original research manuscript "Osimertinib with or without savolitinib as first-line treatment for MET-aberrant, EGFR-mutant NSCLC (FLOWERS; CTONG2008): a randomized, multicenter, open-label, non-comparative, phase 2 trial".

This randomized, open-label, non-comparative phase II trial has addressed double oncogene addiction targeting in the first-line setting with very promising results. However, small sample size and trial design, which was descriptive only, with no statistical hypothesis undertaken, overall dampen the strength of the - notable - observed results. This represents an intrinsic feature of the clinical trial which cannot be amended or modified post-hoc.

No major comments or revisions.
Please check again uniformity of nomenclature (italicized gene names).

Reviewer #3

(Remarks to the Author)
This is randomized phase 2 study FLOWERS assessing osimertinib or osimertinib plus Savolitinib for patients with EGFR-mutant lung cancer and de novo MET amplification or overexpression. Primary endpoint was overall response rate with secondary endpoint of PFS and safety. In the monotherapy cohort 1 group the ORR was 60.9%, DCR 87%, mPFS 9.3mo and in the combination cohort 2, the ORR was 90.5%, DCR 95.2% and mPFS 19.6mo. 44 patients total, 23 in cohort 1, 21 in cohort 2.

This is an important study since MET signalling drives resistance to EGFR therapy, there is a solid rationale for assessing this combination as 1L treatment. The study was small and did not have a preconceived statistical plan. Further studies are needed to decide on whether this should be standard treatment. For feasibility, it is important to note how many patients were screened to enroll 44 patients.

Comments
• Introduction can also mention have MET amplification/overexpression is a common mechanisms of resistance to osimertinib so combination treatment upfront can be helpful in preventing MET directed resistance
• Is there any data as to how many patients with EGFR-mutant lung cancer were screened to identify 45 with de novo MET amp/overexpression? That is an important frequency that is not mentioned in the text.
• In the text I would specifically state how many patients had MET amplification vs overexpression and the overlap between the two.

• TP53 and RB1 alterations seem enriched in this population. Is there any association with MET, TP53 and RB1?
• Data cutoff date was 14 months ago with more than half of patients on treatment still. Can this data be updated? The efficacy data might have changed significantly with these additional possible events. The median follow up was very short. The maturity of the endpoints esp PFS was low.
• 2 patients had primary progressive disease on osimertinib and subsequent PR when switched to combination therapy- would like to know more about these patients in regards to continued response on osimertinib for how long? Also, any other risk factors that support primary progressive disease? The authors discuss one of the patients with primary progression in the discussion but do not mention the other- both should be discussed in more detail.
• The authors state that “dual-target therapy… improve convenience and reduces hospital and ambulatory care resources, line 209” The authors likely mean ORAL targeted therapy and so this should be clarified
• the authors discuss the relevant MET cutoffs for amplification and IHC, but do not relate the discussion to their criteria. Did the criteria change over time? Was it challenging to find patients? Do they have any suggestions for future studies in this space
• The authors enrolled only 44 patients and I believe the study stopped early due to challenges with enrollments. The discussion does not mention this at all and it is a critical point for the feasibility of this kind of combination treatment. It is clear that this is beneficial for patients with MET overexpression or MET amplification at baseline, but the challenge is these patients are challenging to find. Other methods to identify patients with MET dependence or “other drivers” is needed and the authors should discuss this in more detail in the discussion.
• Can the authors do a analysis to see if any of the Table 1 characteristics are unbalanced between the arms
• Figure S4 title is radiographic response in a typical patient in cohort 1; since this is primary progression would note this is an ATYPICAL patient and might just state in title that this is a patient with primary progression on osimertinib with response to the combination
• Table S2 displays the MET testing results. Can the authors provide how many patients with MET amplification have MET pos IHC and vice versa? Would like to know the overlap between the two biomarkers

Version 1:

Reviewer comments:

Reviewer #3

(Remarks to the Author)
The authors have thoroughly address my comments and the manuscript is stronger. I especially appreciate the updated data cut off for PFS.

Nature Communications

Osimertinib with or without savolitinib as first-line treatment for *MET*-aberrant, *EGFR*-mutant NSCLC (FLOWERS; CTONG2008): a randomized, multicenter, open-label, non-comparative, phase 2 trial

We would like to thank the editors and the reviewers for their detailed and thoughtful comments on our submission. In our resubmission, we have carefully considered all the points raised and revised the manuscript accordingly. A point-by-point response to all reviewer comments was provided. Specifically, in accordance with your request, we have included the additional ad-hoc follow-up analyses, including the addition of progression-free survival (PFS) and overall survival (OS) with a cutoff date of 11 Aug, 2025, as requested by Reviewer #3 (Comment 5). All changes in the revised manuscript were clearly marked using highlighted text. We appreciate the opportunity to revise and resubmit our work, and we look forward to your further consideration.

Reviewer #1:

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No comments.

Response:

We are grateful to the reviewer for his/her assessment of our work and his/her support in recommending the manuscript without additional revisions.

Reviewer #2:

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Comment 1:

The Authors should be acknowledged for their original research manuscript "Osimertinib with or without savolitinib as first-line treatment for *MET*-aberrant, *EGFR*-mutant NSCLC (FLOWERS; CTONG2008): a randomized, multicenter, open-label, non-comparative, phase 2 trial".

This randomized, open-label, non-comparative phase II trial has addressed double oncogene addiction targeting in the first-line setting with very promising results. However, small sample size and trial design, which was descriptive only, with no statistical hypothesis undertaken, overall dampen the strength of the - notable - observed results. This represents an intrinsic feature of the clinical trial which cannot be amended or modified post-hoc.

No major comments or revisions.

Please check again uniformity of nomenclature (italicized gene names).

Response:

We sincerely thank the reviewer for their supportive and encouraging comments regarding our study. As suggested, we have carefully reviewed the manuscript to ensure

uniformity of nomenclature, and all gene names are now consistently italicized (Lines 3, 7, 47, 67, 78, 83, 85, 122, 147, 148, 218, 221, 272, 280, 292, 521, 523).

Reviewer #3:

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This is randomized phase 2 study FLOWERS assessing osimertinib or osimertinib plus Savolitinib for patients with *EGFR*-mutant lung cancer and de novo *MET* amplification or overexpression. Primary endpoint was overall response rate with secondary endpoint of PFS and safety. In the monotherapy cohort 1 group the ORR was 60.9%, DCR 87%, mPFS 9.3mo and in the combination cohort 2, the ORR was 90.5%, DCR 95.2% and mPFS 19.6mo. 44 patients total, 23 in cohort 1, 21 in cohort 2.

This is an important study since *MET* signalling drives resistance to *EGFR* therapy, there is a solid rationale for assessing this combination as 1L treatment. The study was small and did not have a preconceived statistical plan. Further studies are needed to decide on whether this should be standard treatment. For feasibility, it is important to note how many patients were screened to enroll 44 patients.

Comment 1: Introduction can also mention have *MET* amplification/overexpression is a common mechanisms of resistance to osimertinib so combination treatment upfront can be helpful in preventing *MET* directed resistance.

Response:

We thank the reviewer for this suggestion. We have revised the Introduction (see *Lines 122-125*) to mention that *MET* amplification or overexpression is a mechanism of resistance to osimertinib, which provides a rationale for evaluating the combination therapy as a first-line treatment.

Revised text:

MET amplification or overexpression is a mechanism of resistance to osimertinib, providing a rationale for evaluating the combination of osimertinib with savolitinib as a first-line treatment to potentially reduce *MET*-driven resistance.

Comment 2: Is there any data as to how many patients with *EGFR*-mutant lung cancer were screened to identify 45 with de novo *MET* amp/overexpression? That is an important frequency that is not mentioned in the text.

Response:

Thank you for your comment. Patients with *MET* amplification and/or overexpression who met the definition of study requirement identified by prospective tumor tissue testing (FISH, NGS, IHC) were referred to participate in this study. A corresponding clarification has been included in the Results section (*Lines 133-136*). However, systematic screening data across all participating centers were not collected in a standardized manner and therefore we cannot provide the precise number of patients screened. We will make efforts to collect the relevant data in subsequent research.

Revised text:
Patients with *MET* amplification and/or overexpression who met the definition of study requirement identified by prospective tumor tissue testing (fluorescence in situ hybridization [FISH], next-generation sequencing [NGS], or immunohistochemistry [IHC]) were referred to participate in this study.

Comment 3: In the text I would specifically state how many patients had *MET* amplification vs overexpression and the overlap between the two.
Response:
We thank the reviewer for this helpful suggestion. We have now clarified in the Results section (*Lines 146-148*) the number of patients with *MET* amplification, the number with MET overexpression, and the degree of overlap between these two groups. Specifically, 6 patients had *MET* amplification, 36 patients had MET overexpression, and 2 patients had both alterations.
Revised text:
In addition, 36 patients (81.8%) had MET overexpression, 6 patients (13.6%) had *MET* amplification, and 2 patients (4.5%) had both *MET* amplification and overexpression.

Comment 4: *TP53* and *RB1* alterations seem enriched in this population. Is there any association with *MET*, *TP53* and *RB1*?
Response:
We thank the reviewer for this important observation. In our analysis, we reported all detected baseline ctDNA variants, which may appear higher than studies restricted to pathogenic variants only. For comparability, we have re-tabulated pathogenic variants and provided a comparison between FLOWERS with first-line *EGFR*-mutant trials not enriched for *MET*-aberrant. As expected by design, FLOWERS was enriched for de novo *MET*-aberrant, *MET* amplification occurred in 13.6% in FLOWERS vs 1.2% in FLAURA2 and 0.3% in MARIPOSA.

Table. Baseline pathogenic variants in FLOWERS vs. other first-line *EGFR*m NSCLC trials

Variants, n (%)	FLOWERS (n = 44)	FLAURA2 (n = 167)[1]	MARIPOSA (n = 636)[2]
MET amplification	10 (22.7)	2 (1.2)	2 (0.3)
TP53	18 (40.1)	62 (37.1)	293 (46.1)
RB1	3 (6.8)	6 (3.6)	22 (3.5)

1. Yang, J.C., et al., MA12.03 FLAURA2: Resistance, and Impact of Baseline TP53 Alterations in Patients Treated With 1L Osimertinib ± Platinum-Pemetrexed. Journal of Thoracic Oncology, 2024. 19(10): p. S101–S102.
2. Felip, E. et al. Amivantamab plus lazertinib versus osimertinib in first-line *EGFR*-mutant advanced

non-small-cell lung cancer with biomarkers of high-risk disease: a secondary analysis from MARIPOSA. Annals of Oncology 35, 805–816 (2024).

Despite the *MET*-aberrant enrichment, the frequencies of *TP53* (40.9%) and *RB1* (6.8%) in the FLOWERS study were comparable to those reported in first-line *EGFR*-mutant trials without such enrichment. Specifically, no statistically significant differences (Fisher's exact test) were observed when compared with FLAURA2 (*TP53* 37.1%, p = 0.727; *RB1* 3.6%, p = 0.399) or MARIPOSA (*TP53* 46.1%, p = 0.535; *RB1* 3.5%, p = 0.215). These findings indicate that enrichment for *MET* aberrations in FLOWERS did not lead to concomitant enrichment of *TP53* or *RB1* alterations.

Comment 5: Data cutoff date was 14 months ago with more than half of patients on treatment still. Can this data be updated? The efficacy data might have changed significantly with these additional possible events. The median follow up was very short. The maturity of the endpoints esp PFS was low.

Response:

We thank the reviewer for this important suggestion. In our clinical trial protocol, only two analyses were pre-specified: the primary analysis focused on the primary endpoint of ORR, which was completed after all patients had two efficacy assessments, and the second analysis focused on PFS, with a cutoff of approximately 40-month post-enrollment of the last patient based on a target PFS data maturity of 80%. Therefore, additional data updates were not planned in the original study design. Nevertheless, in response to the reviewer's comment, we have conducted ad-hoc analysis for PFS with a cutoff date of 11 Aug, 2025. The median follow-up time was 22.4 months (95% CI, 19.9–24.9). The updated median PFS was 11.2 (4.0-18.4) months in cohort 1 and 22.6 (13.1-32.1) months in cohort 2, with maturity of 73.9% and 52.4%, respectively. The data maturity for OS was 25%.

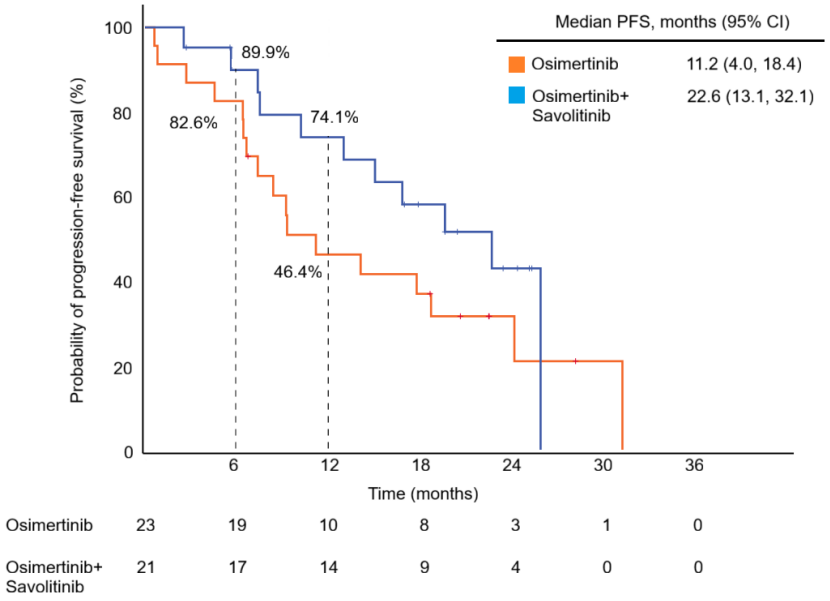

Figure. Kaplan-Meier curves for progression-free survival.

Comment 6: 2 patients had primary progressive disease on osimertinib and subsequent PR when switched to combination therapy- would like to know more about these patients in regards to continued response on osimertinib for how long? Also, any other risk factors that support primary progressive disease? The authors discuss one of the patients with primary progression in the discussion but do not mention the other- both should be discussed in more detail.

Response:

Thank you for your valuable comment. We agree that it is necessary to provide further clarification regarding the two patients who experienced primary progressive disease (PD) during osimertinib monotherapy and subsequently achieved partial response (PR) after transitioning to combination therapy. We have added in the Discussion section (*Lines 218-230*)

Patient #01023: A 62-year-old male (ECOG PS 1) with stage IVB adenocarcinoma of the right lower lung lobe (cT4N3M1c), with multiple metastases involving the lungs, brain, bones, liver, and eyes. Biomarkers: *MET* IHC 3+ (95%), PD-L1 80%, *EGFR* exon 19 deletion (+) and *MET* CN by NGS (3.4). Randomly assigned to Cohort 1, the patient experienced PD at the first efficacy assessment (week 4). He subsequently crossed over to Cohort 2 and achieved PR, but discontinued after 3 months due to a threefold elevation in grade 3 ALT. On subsequent self-administered dual-targeted therapy, PFS2 was 11.4 months.

Patient #01019: A 54-year-old male (ECOG PS 1) with stage IVA adenocarcinoma of

the right lower lung lobe (cT1cN2M1a, pleural metastasis). Biomarkers: MET IHC 3+ (95%), *EGFR* exon 19 deletion (+), and PD-L1 20%. Randomly assigned to Cohort 1, the patient achieved SD (−28%) with a PFS of 6.4 months. After progression, he crossed over to Cohort 2 and remained PR for more than 1 year at the data cutoff date.

We have revised the Discussion sections to include both cases in detail, highlighting their baseline characteristics, initial responses, and outcomes following crossover to combination therapy.

Revised text:

Notably, one patient in the osimertinib monotherapy cohort (62-year-old male, ECOG PS 1, stage IVB adenocarcinoma, cT4N3M1c, with extensive metastases; biomarkers: MET IHC 3+ [95%], PD-L1 [80%], *EGFR* exon 19 deletion [+], *MET* CN by NGS [3.4]) experienced disease progression within the first four weeks, which was subsequently confirmed as MET overexpression (100% 3+). Following the study protocol, this patient transitioned to combination therapy and achieved PR (Figure S4). The patient discontinued study treatment after 3 months due to a threefold elevation in grade 3 ALT, but on subsequent self-administered dual-targeted therapy, achieved a PFS of 11.4 months. Another patient in the osimertinib monotherapy cohort (54-year-old male, ECOG PS 1, stage IVA adenocarcinoma, cT1cN2M1a, with pleural metastasis; biomarkers: MET IHC 3+ [95%], *EGFR* exon 19 deletion [+], PD-L1 20%) achieved SD (−28%) with a PFS of 6.4 months. After progression, he crossed over to cohort 2 and remained in PR for more than 1 year at the data cutoff date.

Comment 7: The authors state that "dual-target therapy… improve convenience and reduces hospital and ambulatory care resources, line 209" The authors likely mean ORAL targeted therapy and so this should be clarified.

Response:

We thank the reviewer for this helpful clarification. Our intention was indeed to emphasize the convenience of oral targeted therapy compared with intravenous regimens. We have revised the text accordingly in the Discussion (*Lines 214*).

Revised text:

Additionally, oral dual-targeted therapy provides psychological benefits, improves daily life convenience, and reduces the utilization of hospital and ambulatory care resources.

Comment 8: The authors discuss the relevant *MET* cutoffs for amplification and IHC, but do not relate the discussion to their criteria. Did the criteria change over time? Was it challenging to find patients? Do they have any suggestions for future studies in this space.

Response:

We appreciate the reviewer's insightful comment. The eligibility criteria for *MET* amplification and IHC positivity were predefined in the study protocol and remained

unchanged throughout the trial. As the reviewer points out, there is currently no universally accepted standard for defining *MET* amplification or overexpression. The prevalence of *de novo MET* amplification and/or MET overexpression in *EGFRm* treatment-naïve advanced NSCLC patients is low based on previous literature reported, the patient identification is challenging. We have revised the Discussion (*Lines 254–261*) to clarify how our trial criteria relate to the broader debate on *MET* cutoffs and to emphasize the need for harmonized definitions in future studies.

Revised text:

These findings highlight the value of precise patient selection and treatment strategies to improve outcomes in advanced NSCLC patients with *EGFR* mutations and de novo *MET* amplification and/or overexpression, signifying a potential benefit for this NSCLC subtype. In summary, the establishment of standardized *MET* testing criteria, coupled with refined biomarker strategies, will be critical for improving patient selection and ensuring the reproducibility and clinical applicability of such combination regimens in subsequent studies.

Comment 9: The authors enrolled only 44 patients and I believe the study stopped early due to challenges with enrollments. The discussion does not mention this at all and it is a critical point for the feasibility of this kind of combination treatment. It is clear that this is beneficial for patients with MET overexpression or *MET* amplification at baseline, but the challenge is these patients are challenging to find. Other methods to identify patients with *MET* dependence or "other drivers" is needed and the authors should discuss this in more detail in the discussion.

Response:

We thank the reviewer for this comment. In our study, enrollment was completed after reaching the target sample size pre-specified in the study protocol (44 patients), rather than being terminated early. We acknowledge these enrollment challenges and emphasize that future studies will require not only harmonized *MET* testing criteria but also the integration of broader biomarker strategies to more effectively identify patients with *MET* dependence or alternative oncogenic drivers. We have revised the discussion accordingly to address these important considerations (*Lines 258-261*).

Comment 10: Can the authors do a analysis to see if any of the Table 1 characteristics are unbalanced between the arms.

Response:

Thank you for your insightful comment. We would like to clarify that patients were randomized using a stratified approach based on smoking status and *EGFR* mutation status. As outlined in the study design, the analyses were descriptive only, and no statistical hypothesis testing was undertaken. Nevertheless, we performed statistical

tests to evaluate the distribution of baseline characteristics between the two groups and the results showed that no imbalance was observed between the two groups.

Table. Baseline demographics and clinical characteristics of the patients.

Characteristic	Cohort 1 (*n* = 23)	Cohort 2 (*n* = 21)	Total (*n* = 44)	*P*
Age, median (range), years	62.0 (40.0–74.0)	56.0 (29.0–72.0)	58.0 (29.0–74.0)	0.249
Sex				0.232
Male	14 (60.9)	9 (42.9)	23 (52.3)	
Female	9 (39.1)	12 (57.1)	21 (47.7)	
ECOG PS score				0.403
0	2 (8.7)	4 (19.0)	6 (13.6)	
1	21 (91.3)	17 (81.0)	38 (86.4)	
Smoking history				1.000
Never Smoked	15 (65.2)	14 (66.7)	29 (65.9)	
Former Smoker	7 (30.4)	7 (33.3)	14 (31.8)	
Currently Smoking	1 (4.3)	0 (0.0)	1 (2.3)	
Histological subtype				0.733
Adenocarcinoma	22 (95.7)	20 (95.2)	42 (95.5)	
Adenosquamous Carcinoma	0 (0.0)	1 (4.8)	1 (2.3)	
Squamous Cell Carcinoma	1 (4.3)	0 (0.0)	1 (2.3)	
Clinical stage				0.222
IIIB	0 (0.0)	2 (9.5)	2 (4.5)	
IV	23 (100.0)	19 (90.5)	42 (95.5)	
Brain Metastasis				0.222
No	15 (65.2)	14 (66.7)	29 (65.9)	
Yes	8 (34.8)	5 (23.8)	13 (29.6)	
Unknown	0 (0.0)	2 (9.5)	2 (4.5)	
EGFR mutation				0.898
19 DEL	11 (47.8)	9 (42.9)	20 (45.5)	
L858R[a]	10 (43.5)	9 (42.9)	19 (43.2)	
19 DEL + L858R	0 (0.0)	1 (4.8)	1 (2.3)	
L858R + uncommon[b]	0 (0.0)	1 (4.8)	1 (2.3)	
Only uncommon[c]	2 (8.7)	1 (4.8)	3 (6.9)	
MET aberrant				0.649
MET OE	20 (87.0)	16 (76.2)	36 (81.8)	
MET Amp	2 (8.7)	4 (19.0)	6 (13.6)	

Characteristic	Cohort 1 (*n* = 23)	Cohort 2 (*n* = 21)	Total (*n* = 44)	*P*
MET Amp & OE	1 (4.3)	1 (4.8)	2 (4.5)	

Comment 11: Figure S4 title is radiographic response in a typical patient in cohort 1; since this is primary progression would note this is an ATYPICAL patient and might just state in title that this is a patient with primary progression on osimertinib with response to the combination.

Response:

We thank the reviewer for this helpful suggestion. We have revised the title of Figure S4 to clarify that this patient experienced primary progression on osimertinib and subsequently responded to combination therapy. The updated figure title now reads: "Radiographic response in a patient with primary resistance on osimertinib achieving response to combination therapy."

Comment 12: Table S2 displays the *MET* testing results. Can the authors provide how many patients with *MET* amplification have MET pos IHC and vice versa? Would like to know the overlap between the two biomarkers.

Response:

We thank the reviewer for this insightful comment. We have now analyzed the overlap between *MET* amplification and MET positive IHC among the enrolled patients. Specifically, 2 patients with *MET* amplification also had MET positive IHC. This information has been added to the Results section (*Lines 146-148*).

Revised text:

In addition, 36 patients (81.8%) had MET overexpression, 6 patients (13.6%) had *MET* amplification, and 2 patients (4.5%) had both *MET* amplification and overexpression.

We tried our best to improve the manuscript and made some changes in the manuscript. We sincerely appreciate the time and effort that the reviewers have invested in evaluating our manuscript. We are eager to receive any additional feedback or suggestions that may further enhance our work.