nature portfolio

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Reporting Summary

Nature Portfolio wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Portfolio policies, see our Editorial Policies and the Editorial Policy Checklist.

Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed	
☐	☒	The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒	A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☒	☐	The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☒	☐	A description of all covariates tested
☒	☐	A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒	A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☒	☐	For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐	For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐	For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☐	☒	Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	Clinical data was collected via Agile EDC system.
Data analysis	Statistical analysis of clinical data were performed using SAS version 9.4.

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy

The full clinical dataset generated in this study is not publicly available. All requests for clinical data will be reviewed by the Guangdong Provincial People's Hospital to verify whether the request is subjected to any confidentiality obligations. Requests for additional clinical data should be emailed to the corresponding author with detailed proposals for approval. Individual patient-level raw data containing identifiable patient information cannot be shared. Source data are provided with this paper. The ctDNA data generated in this study have been uploaded to the Genome Sequence Archive database (https://ngdc.cncb.ac.cn/gsa-human/), an approved public repository (accession code: HRA014210). The remaining data are available within the Article, Supplementary Information or Source Data file.

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	Biologic sex was reported by the participants; on the intake survey, they were asked, "What was your sex assigned at birth?" The options provided were female and male. The median age was 58 years (range, 29 to 74), with 52.3% male and 47.7% female participants.
Reporting on race, ethnicity, or other socially relevant groupings	Race, ethnicity or other socially relevant groupings were not used in our reporting.
Population characteristics	The covariate-relevant population characteristics of the human research participants, including age, sex, ECOG PS score, Smoking history, Histologic subtype, Clinical stage, Brain Metastasis, EGFR mutation and MET aberrant are described in Table 1.
Recruitment	This trial is a phase 2, open-label, randomized, two-arm, multicenter, interventional study (NCT05163249). The study enrolled participants aged 18 years or older with de novo MET amplifications and/or overexpression, EGFR-mutant, histologically or cytologically confirmed locally advanced or metastatic NSCLC who had not received any systemic anti-cancer therapy at first line. All participants had measurable disease based on computed tomography (CT) or magnetic resonance imaging (MRI) in accordance with the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 guidelines and an Eastern Cooperative Oncology Group (ECOG) or World Health Organization (WHO) performance status of 0 to 1. Adequate liver function was required at screening. MET overexpression was defined as an IHC score of 3+ in at least 75% of tumor cells, based on our previously published study and subsequent research findings. MET amplification was assessed by FISH with a MET GCN of ≥5, or MET/ centromere-enriched protein 7 (CEP7) ratio of ≥2, or by NGS of tumor tissue, with ≥20% of tumor cells sequenced at a depth of ≥200x showing a copy number of ≥5. The complete set of inclusion and exclusion criteria is listed in the supplementary appendix.
Ethics oversight	The trial protocol and amendments were approved by independent ethics committees or institutional review boards at each participating center. (10 research centers: Guangdong Provincial People's Hospital, The First People's Hospital Foshan, Sichuan Cancer Hospital & Institute, Beijing Cancer Hospital, Dongguan People's Hospital, The First Affiliated Hospital of Sun Yat-Sen University, Chongqing University Cancer Hospital, The First Affiliated Hospital of Guangzhou Medical University, Zhejiang Cancer Hospital, The Affiliated Panyu Central Hospital of Guangzhou Medical University)

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	Based on expected ORRs of 44% for osimertinib monotherapy and 65% for the combination, 22 subjects in each cohort, assuming a 10% drop out rate will yield the specified precision using the Clopper-Pearson's exact method.
Data exclusions	No data was excluded.
Replication	Not applicable because each participant is a different individual in this phase 2 study.
Randomization	Eligible participants were randomized in a 1:1 ratio to receive either osimertinib monotherapy (Cohort 1; 80 mg orally once daily) or combination therapy with osimertinib (80 mg orally once daily) plus savolitinib (300 mg orally twice daily) (Cohort 2).
Blinding	This trial is open-label, so it's not blinded.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☐	☒ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Clinical data

Policy information about clinical studies

All manuscripts should comply with the ICMJE guidelines for publication of clinical research and a completed CONSORT checklist must be included with all submissions.

Clinical trial registration	ClinicalTrials.gov registration: NCT05163249.
Study protocol	The study protocol is provided in the supplemental information.
Data collection	Patients with MET amplification and/or overexpression who met the definition of study requirment identified by prospective tumor tissue testing (FISH, NGS, or IHC) were referred to participate in this study. A total of 45 participants with de novo MET amplification and/or overexpression, EGFR-mutant advanced NSCLC were screened for inclusion and 44 participants were randomized across 10 research centers between May 22, 2021, and February 5, 2024. Baseline, demographic, treatment, efficacy, follow-up, and other relevant data were collected at each center during each patient's visits and entered into a central database.
Outcomes	The primary endpoint was the confirmed ORR assessed by investigators. Key secondary endpoints included PFS, duration of response (DoR), disease control rate (DCR), OS, 12-month OS rate, and safety. Definitions for secondary endpoints are provided in the SAP (in Supplementary). The median duration of treatment was 7.6 months (range, 0.7 to 22.5) in Cohort 1 and 6.6 months (range, 1.7 to 19.6) in Cohort 2, respectively. The median follow-up period was 7.8 months (range, 2.8 to 23.8) in Cohort 1 and 8.5 months (range, 3.7 to 18.7) in Cohort 2, respectively. The confirmed ORR was 60.9% (95% CI: 38.5 – 80.3) in Cohort 1 and 90.5% (95% CI: 69.6 - 98.8) in Cohort 2, respectively. The DCR was 87.0% (95% CI: 66.4 - 97.2) in Cohort 1 and 95.2% (95% CI: 76.2 - 99.9) in Cohort 2. The median DoR was 8.4 months (range, 6.6-NE) in Cohort 1 and 18.6 months (95% CI: NR-NE) in Cohort 2. The investigator-assessed median PFS was 9.3 months (95% CI: 7.4-NE) in Cohort 1 and 19.6 months (95% CI: 10.2-NR) in Cohort 2. At 6 months, PFS rates were 82.1% (95% CI: 66.2-98.0) for Cohort 1 and 87.3% (95% CI: 70.2-98.9) for Cohort 2. At 12 months, the PFS rate was 49.0% (95% CI: 20.4-77.6) in Cohort 1, compared to 65.5% (95% CI: 35.5-95.4) in Cohort 2. Grade 3 or higher TEAEs occurred in 6 participants (26.1%) in Cohort 1, compared to 15 participants (71.4%) in Cohort 2. Grade 3 or higher TRAEs occurred in 2 participants (8.7%) in Cohort 1, compared to 12 participants (57.1%) in Cohort 2.

Plants

Seed stocks	*Report on the source of all seed stocks or other plant material used. If applicable, state the seed stock centre and catalogue number. If plant specimens were collected from the field, describe the collection location, date and sampling procedures.*
Novel plant genotypes	*Describe the methods by which all novel plant genotypes were produced. This includes those generated by transgenic approaches, gene editing, chemical/radiation-based mutagenesis and hybridization. For transgenic lines, describe the transformation method, the number of independent lines analyzed and the generation upon which experiments were performed. For gene-edited lines, describe the editor used, the endogenous sequence targeted for editing, the targeting guide RNA sequence (if applicable) and how the editor was applied.*
Authentication	*Describe any authentication procedures for each seed stock used or novel genotype generated. Describe any experiments used to assess the effect of a mutation and, where applicable, how potential secondary effects (e.g. second site T-DNA insertions, mosiacism, off-target gene editing) were examined.*