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	No software used for data collection
Data analysis	Pharmacokinetic analysis used Phoenix v8.1, Certara. Pharmacodynamic graphs produced by GraphPad Prism v10.4.1

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 anonymized derived data from this study that underly the results will be made available upon consideration of a reasonable scientific proposal by the sponsoring institutions. Requests are to be sent to the corresponding author.

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	The sex of patients in the study is reported in Table 1.
Reporting on race, ethnicity, or other socially relevant groupings	The ethnicity of patients in this trial is reported in Table 1
Population characteristics	The age of patients in the trial is reported in Table 1
Recruitment	Patients were recruited by referral to oncology phase I centers by oncologists or GPs. No bias that would influence analysis expected.
Ethics oversight	The trial was conducted as per the principles of the declaration of Helsinki. The protocol was reviewed and allowed to proceed by the Medicines and Healthcare products Regulatory Agency (MHRA) UK. The protocol was also reviewed by the National research and ethics committee REC/LO/1473. EudraCT number 2017-001035-39, NCT03875820.

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	For dose escalation the sample per cohort was determined by the 3+3 dose escalation design. For expansions the cohort sizes of 10-20 were not based on formal power calculations. However, it was estimated that with 80 patients in total in the expansion cohorts, the probability of seeing 0 responses was <0.1% if the true response rate was 20%, and the probability of seeing 2 or more responses was 99.9%. The 80% confidence interval if the response rate was 10% was [6.4%; 16.0%], the 80% confidence interval if the response rate was 20% was [14.3%; 26.4%], and the 80% confidence interval if the response rate was 30% was [23.7%; 37.5%].
Data exclusions	All patients who received at least one dose of drug was evaluable for evaluation of toxicity which was the primary endpoint of the study. Patients who consented but did not receive a dose of drug were not included for assessment for the primary endpoint.
Replication	This is a dose escalation study with expansion arms which has described a dose/schedule for the combination demonstrated proof of concept clinical activity in certain subtypes of cancer. Future trials will be done to confirm/replicate these studies but this is out of scope for the current study.
Randomization	This is dose escalation study with expansions in different disease types. There are no control arm and patients can not be randomized in this trial design.
Blinding	This is a phase I study with expansions in different tumour types. It is not possible to blind patients or researchers as there is no control arm and there are ethical reasons not to blind patients or researchers as there is a risk of toxicity being evaluated in oncology phase I trials.

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

Antibodies

Antibodies used: Phosphorylation of cytoplasmic FAK was assessed by immunohistochemistry. Primary antibody used was p-FAK (Tyr397) antibody clone D20B1 (Catalogue number 8556) Cell signaling technologies Leiden Netherlands 1:50 dilution for 1 hr. Detection was with EnVision Flex high PH kit rabbit Kit (catalogue number K800021-2, Dako, Agilent Technologies)

Validation: The antibodies were validated by exposing lung cancer cell line pellets to x10 GI50 of defactinib for 24 hrs

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: (NCT03875820NCT03875820/EudraCT number 2017-001035-39)

Study protocol: Has been uploaded

Data collection: The trial opened to recruitment in December 2017 and the cut off for data collection for this manuscript was June 2023. The trial recruited across three centers, The Royal Marsden Hospital NHS Foundation Trust, London, Christie NHS Foundation Trust, Manchester and The Freeman Hospital, Newcastle.

Outcomes: The primary objectives of the study were to propose a recommended dose for phase 2 evaluation by determining the maximum tolerated dose and to assess the safety and toxicity profile of the combination of avutometinib and defactinib. The primary endpoint was to determine a dose at which no more than one patient out of six at a dose level experience highly probable or probable drug related dose limiting toxicities. The toxicity was described by National Cancer Institute (NCI) common toxicity criteria for adverse events (CTCAE) Version 4.0. The secondary endpoints in the study were to characterize the pharmacokinetic profiles of avutometinib and defactinib in combination. Pharmacokinetic sampling was conducted on the day of avutometinib dosing the second or third week of dosing i.e. in cycle 1 between day 8-21. Samples were collected at pre-dose, 30 minutes, 1 hr, 2 hr, 4 hr, 8 hr, 12 hr, 24 hr and 48 hr. The plasma concentrations of Avutometinib and Defactinib were obtained by liquid chromatography-mass spectrometry (LC-MS). Pharmacokinetic parameters such as maximum plasma concentration (Cmax), terminal half-life (t1/2) and area under the plasma concentration versus time curve (AUC) were calculated using non-compartmental analysis (Phoenix v8.1, Certara).

Plants

Seed stocks: N/A

Novel plant genotypes: N/A

Authentication: N/A

Magnetic resonance imaging

Experimental design

Design type: Routine standard of care imaging for RECIST measurement of tumour in cancer used in some cases.

Design specifications: CT and MRI scans were allowed for use in the protocol to measure disease as per RECIST, which are criteria used in clinical s for cancer.

Behavioral performance measures: N/A

Acquisition

Imaging type(s): As per standard of care in the National Health Service, not a research measure.

Field strength: As per standard of care in the National Health Service, not a research measure.

Sequence & imaging parameters: As per standard of care in the National Health Service, not a research measure.

Area of acquisition: Abdomen/pelvis and brain where appropriate as a substitute for CT scans

Diffusion MRI ☐ Used ☒ Not used

Preprocessing

Preprocessing software: As per standard of care in the National Health Service, not a research measure.

Normalization: As per standard of care in the National Health Service, not a research measure.

Normalization template: As per standard of care in the National Health Service, not a research measure.

Noise and artifact removal: As per standard of care in the National Health Service, not a research measure.

Volume censoring: As per standard of care in the National Health Service, not a research measure.

Statistical modeling & inference

Model type and settings: As per standard of care in the National Health Service, not a research measure.

Effect(s) tested: As per standard of care in the National Health Service, not a research measure.

Specify type of analysis: ☐ Whole brain ☒ ROI-based ☐ Both

Anatomical location(s): Depends on where the tumour was at start of study for individual patients.

Statistic type for inference: As per standard of care in the National Health Service, not a research measure.

(See Eklund et al. 2016)

Correction: As per standard of care in the National Health Service, not a research measure.

Models & analysis

n/a	Involved in the study
☒	☐ Functional and/or effective connectivity
☒	☐ Graph analysis
☒	☐ Multivariate modeling or predictive analysis