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	eCRF from CRO Ospedale Pediatrico Bambin Gesu', a web based toolkit for data capture in clinical trials
Data analysis	Statistical analysis has been performed using MedCalc statistical software 12.7 (MedCalc Software bvba, Ostend, Belgium) and Jamovi version 2.3.28 (The Jamovi Project, retrieved from https://www.jamovi.org, Sydney, Australia).

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 study protocol is available as Supplementary Note in the Supplementary Information file. The clinical raw data are protected and are not available due to data privacy laws. The data that support the findings of this study are available from the corresponding author upon reasonable request (equivalent purposes to those for which the patients grant their consent to use the data). Data sharing requests will be considered on a case-by-case basis in a timely manner. Response to access requests will be provided within 4 weeks and data will be available for 6 months once access has been granted. Data will be provided anonymized, with no personal

identifiable data. Source data are provided with this paper.

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	Findings apply to both genders (as patients of both genders were included). Sex and gender were not considered in the study design. Sex was derived by census data; gender was self-reported by study participants. There was a complete correspondence between sex and gender among study patients (females:20; males:17). No consent has been obtained for sharing individual-level based data.
Reporting on race, ethnicity, or other socially relevant groupings	We collected information on race and ethnicity. Such variables were not used as proxies for other socially constructed/ relevant variables. Definitions (White, Black, Asian, Hispanic/Latino, Native American, Pacific Islander) were provided by the researchers based on census data. All the enrolled patients were classified as White.
Population characteristics	The median age of the patient population was 59 (31-78) years. Twenty patients (54%) were of female gender and thirty-one of them (84%) had a performance status of 0. Most patients had grade 2 or 3 well-differentiated tumors (76%). The Ki-67 index was comprised between 1% and 50%, with a median of 7%. Primary tumor sites included pancreas (12 patients), small bowel (n=10), lung (n=9), colon (n=2), unknown (n=2), stomach (n=1) and gallbladder (n=1). Ten patients had carcinoid syndrome. Homogeneous lesion uptake on 68Ga-DOTApeptide PET/CT was observed in 33/37 patients. The primary tumor had been resected in 17/37 patients before enrollment on the trial. Patients had received a median of two lines of prior systemic therapy; 33 received prior somatostatin analogs, 19 received prior 177Lu-based radioligand therapy, 5 had prior cytotoxic chemotherapy (including etoposide/cisplatin, mFOLFOX6 and cyclophosphamide/epirubicin/vincristine), 5 had prior everolimus, 1 had prior sunitinib, 1 received prior interferon-α, and 5 had prior investigational agents (including axitinib, lenvatinib and surufatinib). At study entry, 19/37 patients (51%) remained on somatostatin analogs.
Recruitment	Participants were recruited between June 2021 and July 2023 from three study sites (Istituto Nazionale Tumori, Naples, Italy; Policlinico di Bari, Bari, Italy; Policlinico di Palermo, Palermo, Italy). Eligibility criteria were applied as per the study protocol. All patients provided written informed consent prior to enrollment.
Ethics oversight	Ethics Committee of Istituto Pascale, Naples; Ethics Committee of Policlinico di Bari; Ethics Committee of Policlinico di Palermo

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	The primary endpoint of the trial was ORR. Secondary endpoints included PFS, OS, CBR, duration of response (DOR) per RECIST 1.1 as well as safety and tolerability of the combination in the patient population. The sample size calculation was based on the assumption that a true ORR of >50% would generate interest in a larger randomized study, whereas a response rate of <25% would not yield any further interest in this drug combination for this disease. The sample size was chosen based on a one-sided α level of 10% and a power of 90%. Taking into account a 15% drop-out rate, a final sample size of 35 patients was determined for the study.
Data exclusions	No data were excluded
Replication	ELISA assays were performed according to the manufacturer's instructions and included appropriate calibration curves. All measurements were conducted in technical triplicates. Experiments were repeated twice for all samples, with consistent results. Immunohistochemistry (IHC) analyses were conducted on independent patient samples using predefined staining procedures and scoring criteria; representative images in the manuscript show prevalent staining patterns
Randomization	Not applicable; this was a single-arm study
Blinding	Not applicable; this was an open-label study

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: Detailed in Supplementary Table 1

Validation: Clone MT3.1 @MGMT: KO validated for confirmed specificity by the manufacturer (https://www.abcam.com/en-us/products/primary-antibodies/mgmt-antibody-mt31-ab39253)
Clone D1C2 @c-MET: https://www.cellsignal.com/products/primary-antibodies/met-d1c2-rabbit-monoclonal-antibody/8198?srsltid=AfmBOoo89d1nHqhCgY1D2SxF8c-nNeuuQQTngNE3v13yEHtydAhsTg32
Clone C89E7 @AXL: https://www.cellsignal.com/products/primary-antibodies/axl-c89e7-rabbit-monoclonal-antibody/8661?srsltid=AfmBOoqWCi3Tl-QfTdvzXx85-YioRubBQeDIOu5-cgq0d7OS8oHAfhiZ
Clone D5B1 @VEGFR2: https://www.cellsignal.com/products/primary-antibodies/vegf-receptor-2-d5b1-rabbit-monoclonal-antibody/9698?srsltid=AfmBOor4ElvkMoPe0YJcWM8IjOmm3LBgw3fkMsxvLli9EMFpNJ620Hit
Positive controls for each antibody have been detailed in Supplementary Table 1

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: EudraCT Number: 2020-001898-78; NCT Number: NCT04893785

Study protocol: Attached to the submission (Supplementary Information)

Data collection: Detailed in the manuscript

Outcomes: Detailed in the manuscript

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.*