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	N/A
Data analysis	N/A

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 molecular datasets presented in this article are not readily available because they are derived from commercial testing. This data can be made available under a fully executed data use agreement. Requests to access this data should be directed to Reagan Barnett. For the clinical data, requests for access to this data should be made to Pedro Barata.

Human research participants

Policy information about studies involving human research participants and Sex and Gender in Research.

Reporting on sex and gender	N/A
Population characteristics	Covariates, such as lines of previous therapies, location of metastases, type of prior therapy, MSI/MMR status, etc, were reported in Table 1. Kaplan-Meier curves also took MSI status into account.
Recruitment	N/A
Ethics oversight	IRB-approval was obtained at University Hospitals (STUDY20230043) and local IRBs at participating sites, according to the Declaration of Helsinki. The generation of de-identified data sets by Guardant Health for research purposes was approved by the Advarra Institutional Review Board.

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 clinical sample size was determined by retrospective collection of available patients/samples meeting the predetermined criteria. Given the rarity of IO use in these cancer types, we believe this sample size is sufficient for initial analyses.
Data exclusions	Patients with a TMB <10 mut/Mb were excluded unless otherwise noted. Triple negative breast cancer patients were also excluded from the clinical cohort, since that population is known to respond to IO therapy, and therefore isn't a cold tumor.
Replication	Since this was a specified cohort, there were not replicated experiments conducted.
Randomization	Covariates, such as lines of previous therapies, location of metastases, type of prior therapy, MSI/MMR status, etc, were reported in Table 1. Kaplan-Meier curves also took MSI status into account. The samples were not randomized.
Blinding	Blinding was not possible since this was a retrospective analysis.

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

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	N/A
Study protocol	Clinical outcomes were collected retrospectively from collaborators. Please contact Pedro Barata with any questions about the protocol. Appropriate IRB approvals were obtained and detailed in the manuscript.
Data collection	Metastatic breast, ovarian, pancreatic, or prostate cancer patients with a Guardant360 test between 10/2020-12/2022 with a blood TMB ≥10mut/Mb who had also received IO therapy were eligible to be included in the study. The clinical data was collected by the collaborating partner representing the institution.
Outcomes	The primary endpoint was PFS, stratified by blood TMB score.