

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 (<i>n</i>) 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 <i>Only common tests should be described solely by name; describe more complex techniques in the Methods section.</i>
☐	☒ 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. <i>F</i> , <i>t</i> , <i>r</i>) with confidence intervals, effect sizes, degrees of freedom and <i>P</i> value noted <i>Give P values as exact values whenever suitable.</i>
☒	☐ 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 <i>d</i> , Pearson's <i>r</i>), 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 was used for data collection.
Data analysis	All statistical analyses were conducted in R v4.2.3. The following R packages were used in the data analysis: ggplot2 v3.5.2, dplyr 1.1.4, survival v3.8.3, survminer v0.5.1, glmnet v4.1.10, statnet v2019.6, network v1.19.0, networkD3 v0.4.1, and pROC v1.19.0.1. Bulk RNA deconvolution was performed using EcoTyper (Luca et al., Cell 2021), with the code available at https://github.com/digitalcytometry/ecotyper . Immune signatures were calculated using the IOBR R package v0.99.0 (https://github.com/IOBR/IOBR). The ICI foundation model COMPASS was applied using code available at https://github.com/mims-harvard/COMPASS . All other codes that support the findings of this study are available upon reasonable request as part of a scientific collaboration with adherence to standards of good scientific practice.

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 ORIEN ICI RNAseq and clinical dataset, which was previously generated, is available under restricted access through a closed instance of cBioPortal; access requests can be submitted via the affiliated institutional ORIEN Program Managers (OPMs) (<https://researchdatarequest.orienavatar.com>), or by contacting ResearchDataRequest@AsterInsights.com. The E1609 datasets analyzed in this study will be made available in the National Clinical Trials Network / NCI Community Oncology Research Program (NCTN/NCORP) Data Archive (<https://nctn-data-archive.nci.nih.gov>; RRID: SCR_014708). The harmonized melanoma ICI dataset is available at <https://github.com/ParkerICI/MORRISON-1-public>. The multi-stage fine-tuned COMPASS model used in this study is available at <https://www.immuno-compass.com/download/> under the name "Pembro Model". All other data supporting the findings of this study are available within the Article, the Supplementary Information, or the Source Data file. Source Data are provided with this paper for all figures and supplementary figures.

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	No analyses conducted were stratified on sex or gender. All patient characteristics are summarized in Table 1.
Reporting on race, ethnicity, or other socially relevant groupings	No analyses conducted were stratified on race, ethnicity or other socially relevant grouping. All patient characteristics are summarized in Table 1.
Population characteristics	This study is based on existing retrospective cohorts and publicly available datasets, no new patient recruitment was performed. The patient characteristics of the main cohort analyzed (ORIEN-ICI cohort) are summarized in Table 1.
Recruitment	This research does not involve patient recruitment but relies solely on secondary analyses. All data are derived from retrospective cohorts or publicly available resources, with patient recruitment details reported in the original studies.
Ethics oversight	This research incorporated a retrospective examination of clinical data and gene expression profiles from consenting patients collected through the Total Cancer Care (TCC) Protocol (NCT03977402) and Avatar project conducted within the Oncology Research Information Exchange Network (ORIEN), which includes 18 collaborating cancer centers participating in TCC. Subjects participating in TCC provided written informed consent to allow the use of their tumor and blood biospecimens for genomic and transcriptomic analyses and corresponding clinical data as part of the standard clinical practice to manage their disease. The study was conducted in accordance with the ethical standards of the Declaration of Helsinki, along with approval by the Institutional Review Board (IRB) at each participating institution (Advara IRB # Pro00014441).

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](https://www.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 ORIEN Avatar cohort in our study consisted of 14,997 individuals, of whom 1,610 patients were treated with ICIs and constituted our target population. The final predictive model includes 160 ICI-treated melanoma patients. The analyses are based on observational data, thus effect size was not conducted. The E1609 dataset consisted of 700 patients with a focus on the 456 patients treated with ipilimumab. The external harmonized melanoma ICI dataset consisted of 442 RNAseq, we focus on three subcohorts in cutaneous melanoma with available survival data, (Gide et al. n=72, VA et al, n=39, Liu et al, n=115).
Data exclusions	In the ORIEN Avatar cohort, only patients treated with immune checkpoint inhibitors (ICIs) were included, restricted to those receiving Ipilimumab, Nivolumab, Dostarlimab, Pembrolizumab, Avelumab, Atezolizumab, Cemiplimab, or Durvalumab. In the internal validation cohort (E1609 trial), only patients treated with Ipilimumab were included, with all other treatment arms excluded. In the external harmonized melanoma validation cohort, only ICI-treated patients were included, specifically those who received anti-CTLA-4 or anti-PD-1 therapy.

Replication	This is an observational study; no replicated experiments were conducted. Nevertheless, all analyses are fully reproducible, and the codes have been carefully validated to ensure reproducibility.
Randomization	All data were obtained from retrospective cohorts or pubic resources; randomization is not applicable to this study
Blinding	All data were obtained from retrospective cohorts or pubic resources; bliding is not applicable to this 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

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	This study involved only secondary analyses of retrospective cohorts or existing clinical trial data. The main cohort was derived from the ORIEN Avatar study (NCT03977402), which included 14,997 patients overall, of whom 1,610 received immune checkpoint inhibitors and constituted our analysis population. For external validation, we used the ECOG-ACRIN E1609 cohort (NCT01274338), a randomized phase III trial in resected high-risk melanoma.
Study protocol	This study is a secondary analysis of existing retrospective cohorts. The main cohort was derived from the ORIEN Avatar program (NCT03977402), which is governed by the original Total Cancer Care (TCC, NCT03977402) protocol and also managed under agreements with Aster Insights. ORIEN Avatar is a multi-institutional collaboration across leading U.S. cancer centers that integrates longitudinal clinical data with comprehensive molecular profiling, including whole-exome sequencing, RNA sequencing, and germline sequencing. For external validation, we analyzed data generated in ECOG-ACRIN E1609 trial (NCT01274338), a phase III double-blinded randomized controlled study in resected high-risk melanoma that compared overall and relapse-free survival between ipilimumab (3 mg/kg or 10 mg/kg) and high-dose interferon. Detailed eligibility criteria and trial procedures are published elsewhere.
Data collection	This study is a secondary analysis of existing retrospective cohorts. The main analytic population was derived from the ORIEN Avatar program (NCT03977402), which is based on the Total Cancer Care (TCC) protocol. From the July 2023 dataset freeze, we identified 1,610 patients treated with immune checkpoint inhibitors (Ipilimumab, Nivolumab, Dostarlimab, Pembrolizumab, Avelumab, Atezolizumab, Cemiplimab, and Durvalumab) with matched tumor molecular data, including RNA sequencing and whole-exome sequencing. For external validation, we incorporated the gene expression and clinical data from ECOG-ACRIN E1609 trial (NCT01274338), a phase III randomized study in resected high-risk melanoma, as well as a publicly available harmonized melanoma ICI dataset published in https://github.com/ParkerICI/MORRISON-1-public .
Outcomes	The primary outcome of this study was overall survival (OS), defined from the initiation of ICI medication. We also evaluated real-world progression-free survival (rwPFS) as a secondary outcome. Progression events in rwPFS were defined as: annotated progression/recurrence in clinical records, annotation of therapy stopped due to progression, identification of new metastases, or death, with right censorship at date of last contact for patients without a progression event.

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, mosaicism, off-target gene editing) were examined.