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Reporting Summary

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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

- All experimental data was collected and stored according to The University of Texas MD Anderson Cancer Center intellectual property protection policy.
- Clinical data was obtained from review of electronic medical records.
- Human flow cytometry data was acquired on Aurora Spectral Flow Cytometer (Cytek) and murine flow cytometry data was acquired on Symphony A3 (BD Biosciences). Both were analyzed using FlowJo 10.8.1 software (BD Biosciences).
- Particle characteristics were collected using Malvern Panalytical's Zetasizer Ultra and NanoSight's NS300 nanoparticle tracking analysis.

Data analysis

Analysis was performed using standard protocols. No custom code was used for this study. Statistics were completed with R version 4.4.2 (2024-10-31) and GraphPad Prism v10.3 and v10.6. Flow cytometry data was analyzed with FlowJo 10.8.1 and FlowJo 10.10.0 (BD Biosciences). St.dev. were exported from ZS Xplorer.

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

Data generated in this study are available in the article and its supplementary files. Source data are also provided with this paper. All clinical data is de-identified to protect patient privacy.

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	Clinical data was collected retrospectively for all patients for whom data was available at our institution. Patients' self identified gender is presented as recorded in the electronic medical record.
Reporting on race, ethnicity, or other socially relevant groupings	Self-identified ethnicity (Caucasian, black, asian, hispanic/latino) was reported as recorded in the electronic medical record.
Population characteristics	University of Texas MD Anderson Cancer Center institutional review board approval was obtained. Healthy volunteers (>18yo) were recruited and provided informed consent for serum and blood analysis. Chart review for this study included three groups of patients: (a) patients with biopsy confirmed Stage III or Stage IV non-small cell lung cancer (NSCLC) between 1/2017 and 9/2022, (b) patients with melanoma treated with immune checkpoint blockade between 1/2019 and 12/2022, and (c) patients with any tumor histology with pathology results for PD-L1 from January 2020 to October 2023. Informed consent was waived due to the retrospective and de-identified nature of the data. The data collection cutoff was 9/1/2024; data analysis was performed from 9/1/2024 to 7/29/2025. Patient populations are described in detail in the manuscript and supplemental materials.
Recruitment	Healthy volunteers working in the Texas Medical Center and planning to obtain a COVID mRNA vaccine were recruited for the biomarker portion of this study. This group may be more likely to receive routine vaccinations compared to the general population.
Ethics oversight	This study was approved by the University of Texas MD Anderson 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	Retrospective clinical data included all available data points. Animal studies were completed with samples sizes based on previous studies from our group evaluating anti-tumor efficacy according to the University of Florida and University of Texas MD Anderson Cancer Center IACUC protocols.
Data exclusions	No data was excluded.
Replication	All clinical findings were replicated in at least two patient populations. Translational data presented in the manuscript included experiments performed in two independent laboratories. Major findings were validated in multiple tumor models. All attempts at replication were successful.
Randomization	Mice were randomly allocated to treatment arms described in each experiment once they reached the pre-determined tumor volume and/or designated time post tumor injection.
Blinding	Investigators were blinded to groups for tumor measurements but were not blinded during data 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
☒	☐ Plants

Methods

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

Antibodies

Antibodies used

The following antibodies were used for human samples:

Anti-CD14 (clone 63D3, BioLegend, catalog #367156); Anti-PD-1 (clone EH12.2H7, BioLegend, catalog #329920); Human TruStain FcX™ (BioLegend, catalog #422302); Anti-CD25 (clone BC96, BioLegend, catalog #302612); Anti-CD19 (clone HIB19, BioLegend, catalog #302274); Anti-CD8 (clone SK1, BioLegend, catalog #344766); Anti-PD-L1 (clone 29E.2A3, BioLegend, catalog #329738); Anti-CD16 (clone 3G8, BD Biosciences, catalog #612944); Anti-CD11c (clone B-ly6, BD Biosciences, catalog #741358); Anti-CD11b (clone M1/70, BD Biosciences, catalog #612977); Anti-CCR7 (CD197) (clone 3D12, BD Biosciences, catalog #741786); Anti-CD15 (clone 7C3.RMAB, BD Biosciences, catalog #568935); Anti-CD4 (clone L200, BD Biosciences, catalog #566148); Anti-HLA-DR (clone G46-6, BD Biosciences, catalog #563083); Anti-GITR (CD357) (clone V27-580, BD Biosciences, catalog #747664); Anti-CD127 (IL-7Rα) (clone hIL-7R-M21, BD Biosciences, catalog #563225); Anti-CD56 (clone NCAM16.2, BD Biosciences, catalog #563169); Anti-CD80 (clone L307.4, BD Biosciences, catalog #564159); Anti-Granzyme A (clone CB9, BD Biosciences, catalog #568661); Anti-Granzyme B (clone GB11, BD Biosciences, catalog #571117); Anti-CD86 (B7-2) (clone 2331 (FUN-1), BD Biosciences, catalog #755689); Anti-CD178 (FasL) (clone NOK-1, BD Biosciences, catalog #564261); Anti-CD33 (clone HIM3-4, BD Biosciences, catalog #758223); Anti-CD68 (clone Y1/82A, BD Biosciences, catalog #562111); Anti-CD45 (clone HI30, BD Biosciences, catalog #566961); Anti-CD3 (clone SK7, BD Biosciences, catalog #560176); Brilliant Stain Buffer Plus (BD Biosciences, catalog #566385); Anti-CD45RA (clone HI100, BD Biosciences, catalog #568712); Anti-CD69 (clone FN50, BD Biosciences, catalog #751501); Anti- PD-L1 (Clone MIH1, BD Biosciences, catalog #757550);

The following antibodies were used for preclinical experiments:

T Cell Panel:
Anti-CD3 (clone 17A2, BD, catalog #740268); Anti-CD161 (clone PK136, BD, catalog #741233); Anti-CD127 (clone SB/199, BD, catalog #612841); Anti-CD4 (clone GK1.5, BioLegend, catalog #100428); Anti-PD1 (clone J43, BD, catalog #563059); Anti-CD25 (clone PC61, BioLegend, catalog #102051); Anti-CD44 (clone IM7, BioLegend, catalog #103016); Anti-KLRG1 (clone 2F1, BD, catalog #758385); Anti-CD69 (clone H1.2F3, BD, catalog #756896); Anti-CD62L (clone MEL-14, BD, catalog #569209); Anti-LAG-3 (clone C9B7W, BD, catalog #552380); Anti-TIM-3 (clone B8.2C12, BioLegend, catalog #134008); Anti-CD8A (clone 53-6.7, BD, catalog #557959); Live/Dead (Thermo, catalog #L10119)

Myeloid Panel:

Anti-CD45 (clone 30-F11, BD, catalog #564279); Anti-CD11c (clone N418, BD, catalog #750450); Anti-CD11c (clone N418, BD, catalog #570292); Anti-CD80 (clone 16-10A1, BD, catalog #612773); Anti-MHC-II (clone M5/114.15.2, BioLegend, catalog #107620); Anti-Ly6G (clone 1A8, BioLegend, catalog #127629); Anti-CD163 (clone S15049I, BioLegend, catalog #155325); Anti-Ly6C (clone HK1.4, BioLegend, catalog #128041); Anti- CD206 (clone C068C2, BioLegend, catalog #141710); Anti-CD86 (clone B7-2, BD, catalog #759079); Anti-F4/80 (clone T45-2342, BD, catalog #569223); Anti-CD11B (clone M1/70, BD, catalog #571473); Anti-PD-L1 (clone 485, Thermo, catalog #MA5-46763); Live/Dead (Thermo, catalog #L10119).

AIM Assay:

Anti-CD40L (clone SA047C3, BD, catalog #157006); Anti-CD25 (clone PC61, BioLegend, catalog #101920); Anti-CD69 (clone H1.2F3, BD, catalog #104514); Anti-CD3 (clone 17A2, BD, catalog #100216); Anti-CD8A (clone 53-6.7, BD, catalog #560182); Anti-CD4 (clone RM4-4, BioLegend, catalog #116008); Anti-4-1BB (clone 17B5, BioLegend, catalog #106106).

Immunofluorescence experiments were completed with the following antibodies:

Anti-CD274 (PD-L1) (clone 2B11D11, Proteintech, catalog #66248-1-Ig, dilution 1:100); Anti-SOX10 (clone SP267, Abcam, catalog #ab227680, dilution 1:200); Anti-CD3 (clone 145 2C11, BD, catalog #553057, dilution 1:100); Anti-CD8 (polyclonal, Invitrogen, catalog #PA5-81344, dilution 1:1000); Anti-PD1 (clone J121, eBioscience, catalog #14-2798-82, dilution 1:100); Goat anti-mouse AF488 (polyclonal, Invitrogen, catalog #A11001, dilution 1:1000); Goat anti-rabbit AF564 (polyclonal, Invitrogen, catalog #A11012, dilution 1:1000); Goat anti-hamster AF647 (polyclonal, Invitrogen, catalog #A78967, dilution 1:1000).

Validation	Validation was completed according to manufacturer recommendations, and prior publications. Antibodies were titrated to identify the concentration with the highest stain index in the cell population of interest

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s)	B16F0 and LLC cells were obtained from ATCC.
Authentication	No independent cell authentication was completed by our lab.
Mycoplasma contamination	Mycoplasma testing was performed routinely and cells were not contaminated with mycoplasma.
Commonly misidentified lines (See ICLAC register)	None

Animals and other research organisms

Policy information about studies involving animals; ARRIVE guidelines recommended for reporting animal research, and Sex and Gender in Research

Laboratory animals	4-9 week old C57Bl6 and RIGI-/- mice
Wild animals	No wild animals were used.
Reporting on sex	Sex was not evaluated as an independent variable in this study. Self-reported patient gender is included in the supplement.
Field-collected samples	This study did not include field-collected samples.
Ethics oversight	All experiments in this study were approved by the IACUC at MD Anderson and the University of Florida

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

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	Study analysis was retrospective
Data collection	The data collection cutoff was 9/1/2024; data analysis and retrospective chart review were performed from 5/1/2024 to 9/1/2024.
Outcomes	For patients who received COVID-19 mRNA vaccination in both the NSCLC and melanoma datasets, overall survival was calculated as the time between the date of immunotherapy start closest to mRNA vaccination date, and the last follow-up date (for patients who are living) or date of death. For patients who did not receive COVID-19 mRNA vaccination, overall survival was calculated as the time between the initiation of their first ICI start and the date of death or last follow-up. For patients who received COVID mRNA vaccination in both datasets, progression-free survival was calculated as the time between the initiation of ICI closest to mRNA vaccination and the first incidence of either pathology-confirmed recurrence or imaging-confirmed progression, whichever occurred earlier, that was declared progression in their primary medical oncologist's clinical notes. For patients who did not receive COVID mRNA vaccination, progression-free survival was calculated as the time between their first ICI start date and clinician-confirmed progression as described in the text.

Plants

Seed stocks	N/A
Novel plant genotypes	N/A
Authentication	N/A

Flow Cytometry

Plots

Confirm that:

☒ The axis labels state the marker and fluorochrome used (e.g. CD4-FITC).

☒ The axis scales are clearly visible. Include numbers along axes only for bottom left plot of group (a 'group' is an analysis of identical markers).

☒ All plots are contour plots with outliers or pseudocolor plots.

☒ A numerical value for number of cells or percentage (with statistics) is provided.

Methodology

Sample preparation	For human samples, PBMCs were thawed in a 37°C water bath and immediately transferred into a 50 mL tube containing 9 mL of complete RPMI media (RPMI + 10% FBS) in a ratio of 1 part cells to 9 parts media. Cells were centrifuged at 400g for 10 minutes, and the supernatant was decanted. The cell pellet was resuspended in 1 mL of PBS, and incubated with live/dead marker (1 µL per 1000 µL of cell suspension, containing 1-10 million cells per mL) for 30 minutes at 4°C. After incubation, 3 mL of PBS + 2% FBS was added, and the cells were centrifuged again at 400g for 8 minutes and the supernatant was decanted. Cells were then pre-incubated with 5 µL of Human TruStain FcX™ (BioLegend, cat. 422302) per 100 µL of cell suspension for 5 minutes at room temperature. The cells were then washed with PBS and centrifuged at 400g for 6 minutes. After decanting the supernatant, 10 µL of Brilliant Buffer was added to each tube, and the mixture was allowed to sit for 5 minutes before addition of antibodies targeting extracellular markers and the cells were incubated for 20 minutes at room temperature in the dark. After incubation, the cells were washed and fixed in the dark for 45 minutes at 4°C with 500 µL of Fixation solution (BD). Cells were then permeabilized with 2 mL permeabilization buffer. Intracellular stains were added in permeabilization buffer, and the cells were incubated for approximately 40 minutes at room temperature. After incubation, cells were washed with permeabilization buffer and resuspended in 200 µL of PBS + 2% FBS. For murine samples, 1x10^6 cells from tumors or spleen were placed into 96 well v-bottom plates. Unless stated otherwise wash steps were done by centrifugation steps were performed at 500G for 5 minutes at 4C and resuspension of cells with 200uL of buffer with mixing done via pipetting. Cells were washed with cold PBS and stained with 100uL of live/dead stain (Thermo, cat. L10119) for 30 minutes at 4C. Live dead dye was quenched with 100uL of cold PBS and washed one time with cold FACs buffer (PBS with 2% FBS). Cells were centrifuged and resuspended with 10uL True stain FCX buffer (BioLegend, cat. 422302) diluted to 100ug/mL with FACs buffer for 10 minutes. 90uL of antibodies (Antibody table 1 and 2) and Brilliant Stain buffer (BD, cat. 563794) were added and incubated for 30 minutes at 4C. 100uL of FACs buffer was added to each well and washed 2 times with cold FACs buffer. Cells were fixed for 15 minutes with 100uL of Cytofix buffer (BD, cat. 554655) at 4C 100uL of PBS was added to each sample and cells were washed 2 times and stored in FACs buffer at 4C in the dark until analysis. Compensation was performed using Ultracomp eBeads (Thermo Fisher Scientific, cat. 01-2222-42) and ArC amine reactive compensation beads (Thermo Fisher Scientific, cat. A10346)
Instrument	Human samples: Cytek Aurora Spectral Flow Cytometer. Murine samples: BD Symphony A3.
Software	FlowJo v10.10.0
Cell population abundance	Studies were performed on PBMCs (human), splenocytes, (murine) and whole tumors (murine).
Gating strategy	FSC-A/SSC-A gates were used to select mononuclear cells. FSC-A/FSC-H gates were then used to gate single cells. Live cells were identified with a live dead marker. Fluorescence minus one controls were used to identify the positive and negative populations for each additional marker.

☒ Tick this box to confirm that a figure exemplifying the gating strategy is provided in the Supplementary Information.