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Corresponding author(s): Jude Canon and J. Russell Lipford

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Reporting Summary

Nature Research 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 Research policies, see Authors & Referees 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	B3 v3 (x-ray crystallography) EnVision Manager v1.13-1.14 (nucleotide exchange, viability, combination assays) Discovery Workbench v4.0 (p-ERK assays) ImageLab v4.1 and v5.2.1 (immunoblotting) Agilent RapidFire v4.0, MassHunter Workstation B.05.01 (mass spectrometry kinetic assay) nSolver v4.0 (NanoString) StudyDirector v3.1 (in vivo studies) BD FACSDiva v8.0.1(flow cytometry) Immunospot v2.6.1 (ELIspot) Analyst v1.6 (AMG 510-KRAS G12C conjugate detection, SILAC)
Data analysis	CCP4 Program Suite v6.4.0, HKL2000 v717, MolRep v11.2.08, Refmac5 v5.8.0073, Coot v0.7.2, PRODRG v050106.0517 (x-ray crystallography) Microsoft Excel for Office 365 (nucleotide exchange, viability, p-ERK, kinetic, ELIspot, cysteine proteomics, flow cytometry) GraphPad Prism v7.04 (nucleotide exchange, viability, p-ERK, kinetic, in vivo efficacy/survival, flow cytometry, NanoString, ELIspot, SILAC) MassHunter Qualitative Analysis B.07.00 (mass spectrometry kinetic assay) Chalice Analyzer v1.5.0.71 (combination synergy scores) SEQUEST (cysteine proteomics) nSolver v4.0 (NanoString) Mathematica v11.3 (SILAC) Immunospot v2.6.1 (ELIspot) BD FACSDiva v8.0.1, FlowJo software v10 (flow cytometry) Biostatistical Analysis R Shiny application v1.0.5 (in vivo PKPD studies)

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/reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research 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 list of figures that have associated raw data
- A description of any restrictions on data availability

The majority of data generated or analyzed during this study are included in this published article or available at the source data links. X-ray crystallographic coordinates and structure factor files have been deposited in the Protein Data Bank (PDB ID code: 6OIM). Other data that support the findings of this study are available from the corresponding authors. Qualified researchers may request data from Amgen clinical studies. Complete details are available here: http://www.amgen.com/datasharing.

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 in vivo PKPD studies, n=3/group were used. For efficacy studies, n=8-10 mice per group were used. Animal numbers for in vivo studies were selected using power analysis alpha 0.05 and 80% power such that a minimum change of 32-49% could be detected on the observed data scale. No sample size calculation was performed for in vitro studies.
Data exclusions	No data were excluded.
Replication	In vitro experiments were repeated the indicated number of times, with the exception of immunoblot experiments which were performed once. Synergy scores were determined from the aggregate of two 10x10 matrices for adherent monolayer combinations, but only one 6x10 matrix for spheroid combinations. In vivo PKPD dose response studies (MIA PaCa-2 T2, CT-26 KRAS p.G12C) were repeated with similar results at least twice. The combination of AMG 510 with anti-PD-1 in CT-26 KRAS p.G12C, as well as the tumor growth measurements of untreated CT-26 parental and CT-26 KRAS p.G12C tumors, were repeated twice with similar results. All other in vivo studies were performed once. Independent repeats and sample sizes, as well as statistical analyses and significance levels, are also indicated in the Figure legends or in the Statistics and Reproducibility section.
Randomization	Sample randomization is not relevant to the in vitro studies presented. For in vivo studies, animals were evenly distributed such that each group had a similar mean and SEM at the start of the study.
Blinding	Treatment groups for the in vivo combination studies were blinded to the investigator.

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
☐	☒ Animals and other organisms
☐	☒ Human research participants
☐	☒ Clinical data

Methods

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

Antibodies

Antibodies used	Immunoblot: all antibodies were used at 1:1,000 dilution unless otherwise indicated. phospho-EGF Receptor (Tyr1068) (D7A5) XP® Rabbit mAb Cell Signaling #3777; Lot 13

EGF Receptor (D38B1) XP® Rabbit mAb Cell Signaling #4267; Lot 11
Phospho-MEK1/2 (Ser217/221) Antibody Cell Signaling #9121; Lot 44
MEK1/2 Antibody Cell Signaling #9122; Lot 14
Phospho-S6 Ribosomal Protein (Ser235/236) (D57.2.2E) XP® Rabbit mAb Cell Signaling #4858; Lot 16
S6 Ribosomal Protein (5G10) Rabbit mAb Cell Signaling #2217; Lot 7
Phospho-Akt (Ser473) (D9E) XP® Rabbit mAb Cell Signaling #4060; Lot 19
Akt Antibody Cell Signaling #9272, Lot 27
Phospho-ERK1/ERK2 (Thr185, Tyr187) Polyclonal Antibody ThermoFisher #44-680G; Lot SB248818
p44/42 MAPK (Erk1/2) Antibody Cell Signaling #9102; Lot 26
Anti-Ras antibody [EPR3255] Abcam #ab108602; Lot GR117071-23
Cleaved Caspase-3 (Asp175) Antibody Cell Signaling #9661; Lot 45
Anti-β-Actin–Peroxidase Mouse mAb AC-15 Sigma #A3854; Lot 026M4820V; 1:20,000
Donkey Anti-rabbit IgG HRP GE Healthcare #NA934V; Lot 9677977; 1:5,000

Flow cytometry: all antibodies were used at 1:100 unless otherwise indicated.
PE Mouse anti-mouse H-2Dd (34-2-12, Biolegend #110608, Lot B256526)
PE Mouse anti-mouse H-2Kd (SF1-1.1, Biolegend #116608, Lot B244820)
PE Mouse anti-mouse H-2Ld/H-2Db (28-14-8, Biolegend #114507, Lot B240332)
BUV737 rat anti-mouse CD4 (RM4-5, BD Biosciences #564933, Lot 8164630)
BV421 rat anti-mouse CD8a (53-6.7, BD Biosciences #563898, Lot 7201962)
BUV737 rat anti-CD11b (M1/70, BD Biosciences #564443, Lot 7338572)
BV786 mouse anti-mouse CD45.2 (104, BD Biosciences #563686, Lot 8235903)
APC-H7 rat anti-mouse Ly-6G (1A8, BD Biosciences #565369, Lot 8121728)
BV711 hamster anti-mouse TCR B chain (H57-597, BD Biosciences #563135, Lot 7054698)
FITC rat anti-mouse CD24 (M1/69, ThermoFisher #11-0242-81, Lot 1937898)
APC hamster anti-mouse CD103 (2E7, ThermoFisher #17-1031-80, Lot 17-1031-80)
PE hamster anti-mouse CD279 (PD-1) (J43, ThermoFisher#12-9985-82, Lot 4329622)
APC/Cy7 rat anti-mouse CD90.2 (30-H12, Biolegend #105328, Lot B241601)
BV650 rat anti-mouse F4/80 (BM8, Biolegend #123149, Lot B256505)
BV711 rat anti-mouse Ly-6C (HK1.4, Biolegend #128037, Lot B247973)
BV510 rat anti-mouse I-A/I-E (MHCII) (M5/114.15.2, Biolegend #107635, Lot B263357)
APC rat anti-mouse CD8a (53-6.7, eBioscience #17-0081-82, Lot E07056-1635)
rat anti-mouse CD16/CD32 (2.4G2, BD Biosciences #553142, Lot 4198965)
FITC hamster anti-mouse TCR B chain (H57-597, BD Biosciences #553171, Lot 8351664)

Immunohistochemistry:
Rat anti-human CD3 (mouse CD3 cross-reactive) (CD3-12, Bio-Rad #MCA1477, Lot 7708); 1:1,000
Rabbit anti-mouse CD8a (D4W2Z, Cell Signaling Technology #98941, Lot 0712017); 1:500
Rabbit anti-human Ki67 (mouse Ki67 cross-reactive) (SP6, Sigma-Aldrich #275R-1, Lot 45305); 1:500
Rat IgG isotype negative control (Jackson Immunoresearch Labs #012-000-003, Lot 68714); 2 mcg/mL
Rabbit IgG isotype negative control (Jackson Immunoresearch Labs #011-000-003, Lot 132409); 2 mcg/mL
HRP-anti-rat-IgG (Biocare Medical #BRR4016L, Lot 100317); undiluted
HRP-anti-rabbit-IgG (Dako #K4003, Lot 10147964); undiluted

Validation

All antibodies were validated by the manufacturer. Please refer to the manufacturers' websites with the catalog information listed above.

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)

The following cell lines were purchased from American Type Culture Collection (ATCC): MIA PaCa-2, NCI-H1373, NCI-H2030, NCI-H2122, SW1463, SW1573, UM-UC-3, Calu-1, NCI-H1792, NCI-H23, NCI-H358, SW837, AsPC-1, A-427, LS 174T, SW480, A549, NCI-H1355, HCC-827, COLO-205. KM12 and NCI-H3122 were obtained from the Amgen internal cell bank, originally sourced from the National Cancer Institute.

MIA PaCa-2 T2 and SW480-1AC cells were generated by passaging MIA PaCa-2 and SW480 cells, respectively, in mice.

CT-26 KRAS p.G12C cells were generated from the murine CT-26 colorectal line (ATCC) using CRISPR technology to replace both KRAS p.G12D alleles with p.G12C (ThermoFisher Scientific).

Authentication

Cell lines were authenticated by short tandem repeat (STR) profiling or were used immediately after purchase from ATCC.

Mycoplasma contamination

All cell lines used for in vivo studies were confirmed to be negative for mycoplasma contamination.

Commonly misidentified lines
(See ICLAC register)

No commonly misidentified cell lines were used.

Animals and other organisms

Policy information about studies involving animals; ARRIVE guidelines recommended for reporting animal research

Laboratory animals

BALB/c or athymic nude mice, all female, all 6-12 weeks of age.

Wild animals	Studies did not involve wild animals.
Field-collected samples	Studies did not involve samples collected in the field.
Ethics oversight	All animal experimental protocols were approved by the Amgen Animal Care and Use Committee and were conducted in accordance with the guidelines set by the Association for Assessment and Accreditation of Laboratory Animal Care.

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

Human research participants

Policy information about studies involving human research participants

Population characteristics	See clinicaltrials.gov NCT03600883. Key inclusion criteria: age ≥18; documented locally-advanced or metastatic KRASG12C; measurable or evaluable disease; ECOG ≤2; life expectancy >3 months (mo). Key exclusion criteria: active brain metastases; myocardial infarction within 6 mo.
Recruitment	Patients were recruited at clinical study sites based on the presence of the KRAS p.G12C mutation in their tumor by standard genotype testing.
Ethics oversight	Clinical trial NCT03600883 was conducted in compliance with all relevant ethical regulations. The protocol was approved by the institutional review boards (IRB)/independent ethics committees (IEC) of all clinical study sites.

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	NCT03600883
Study protocol	Study is ongoing; clinical trial information is available on clinicaltrials.gov
Data collection	This multicenter, open-label, 1st in human, phase 1 study (NCT03600883) evaluates safety, tolerability, PK/pharmacodynamics (PK/PD), and efficacy of AMG 510 in patients (pts) with KRASG12C advanced solid tumors. Primary endpoint: safety [eg, adverse events (AEs); dose limiting toxicities (DLT)]; key secondary endpoints: PK, ORR (overall response rate)[assessed every 6 weeks (wks)] and PFS (progression free survival). Key inclusion criteria: age ≥18; documented locally-advanced or metastatic KRASG12C; measurable or evaluable disease; ECOG ≤2; life expectancy >3 months (mo). Key exclusion criteria: active brain metastases; myocardial infarction within 6 mo. Sequential dose escalation cohorts are enrolled to evaluate safety, tolerability, PK/PD and to find the maximum tolerated dose (MTD). After identifying the MTD, 60 pts with advanced KRASG12C STs can enroll. Daily oral AMG 510 is given until disease progression (PD), intolerance, or consent withdrawal. Clinical data presented in this manuscript was collected at participating clinical sites from September 2018 through June 2019.
Outcomes	The endpoints described in this manuscript were based on RECIST 1.1 criteria for clinical responses.

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 in vitro studies, cells were non-enzymatically detached from the wells, washed with staining buffer (PBS/0.5% BSA), and then incubated with PE-conjugated H-2Dd, H-2Kd, or H-2Ld antibodies (BioLegend) for 30 minutes on ice. After washing, cells were resuspended in staining buffer containing SYTOX Blue Dead Cell Stain (Life Technologies), and then analyzed by flow cytometry. For co-cultures, CellTrace Violet-labeled CD8+ T cells from spleens of OT-I transgenic mice were combined with bone marrow-derived dendritic cells (BMDCs) in 96-well plates with or without further AMG 510 or MEKi treatment. Co-cultures were incubated for three days at 37°C. Cell division was assessed by flow cytometry by measuring CTV dilution in TCRβ+ CD8α+ cells. For in vivo studies, tumors were harvested, weighed, minced, and placed in Liberase TL (0.2 mg/ml; Roche) and DNase I (20 µg/ml; Ambion). Tumor cell suspensions were then homogenized using a gentle MACS Dissociator (Miltenyi Biotech) and incubated

at 37°C for 15 minutes on a MACSmix Tube Rotator (Miltenyi Biotech). Cells were then treated with 0.02% EDTA (Sigma) and heat-inactivated FBS (ThermoFisher Scientific) and filtered to remove clumps. After centrifugation, the cell pellets were resuspended in LIVE/DEAD Fixable Blue Dead Cell Stain (ThermoFisher Scientific) for 30 minutes. Cell surface staining was performed with the indicated antibodies (see Antibodies section above) before fixation and permeabilization of the cells (Intracellular Fixation & Permeabilization Buffer Set, eBiosciences) for intracellular staining. CountBright™ Absolute Counting Beads (ThermoFisher Scientific) were added to each sample before analysis on an LSR II flow cytometer (BD Biosciences). All analyses were performed with FlowJo software v10 (FlowJo). Absolute cell counts were determined by normalizing cell numbers to beads recorded, divided by the volume of tumor aliquot analyzed and the mass of the tumor.

Instrument

In vitro samples were run on a BD LSRFortessa. In vivo samples were run on a LSR II flow cytometer (BD Biosciences).

Software

All analyses were performed with either BD FACSDiva or FlowJo software v10.

Cell population abundance

Describe the abundance of the relevant cell populations within post-sort fractions, providing details on the purity of the samples and how it was determined.

Gating strategy

For in vitro experiments, FSC-H/FSC-A gate was used to identify single cells and eliminate doublets from the analysis. FSC/SSC gate (P1) was used to gate on the population of CT-26 KRAS p.G12C cells. Cells from P1 were displayed on a histogram and SYTOX Blue negative cells were gated on to identify live cells. The mean fluorescent intensity (MFI) of MHC class I antigen expression was measured on these live cells.

For co-culture experiments, lymphocytes were first gated using FSC/SCC. Live cells were then gated using 7AAD viability dye, followed by exclusion of doublets using SSC-A/SSC-H. CD8+ T cells were then gated using fluorescently labeled antibodies. Finally, CellTrace Violet dye incorporation was assessed on the CD8+ T cells.

For in vivo experiments, cells were gated first in intact cells using FSC/SCC. Cells were then gated on live cells using the viability dye, followed by cell type-specific gating using fluorescently labeled antibodies.

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