

Life Sciences Reporting Summary

Nature Research wishes to improve the reproducibility of the work that we publish. This form is intended for publication with all accepted life science papers and provides structure for consistency and transparency in reporting. Every life science submission will use this form; some list items might not apply to an individual manuscript, but all fields must be completed for clarity.

For further information on the points included in this form, see [Reporting Life Sciences Research](#). For further information on Nature Research policies, including our [data availability policy](#), see [Authors & Referees](#) and the [Editorial Policy Checklist](#).

► Experimental design

1. Sample size

Describe how sample size was determined.

No sample size calculation was performed.

The number of cell lines used in this study was determined by the availability of KRAS mutant (NSCLC) cell lines present in our laboratory. Given the consistency in the results across cell lines we believe our sample size was sufficient. For the xenograft experiments, the number of mice per group was determined based on previous experience with the cell lines used. The unpredictiveness of the effect of PTPN11 knockout or inhibition made it difficult to more accurately pre-calculate the sample size, but the actual extent of the effect was big enough to obtain significant differences and thus confirm the adequacy of the sample size. For PDX experiments, the number of mice per group was determined based on previous experience with the patient tumors used in the study. Also in this case the unpredictiveness of the effect of PTPN11 inhibition (alone or in combination with MEK inhibition) made it difficult to pre-calculate the sample size, but the extent of the actual effect made us confident that the sample size was sufficient.

2. Data exclusions

Describe any data exclusions.

No data was excluded from the analysis.

3. Replication

Describe whether the experimental findings were reliably reproduced.

All experiments were successfully reproduced (excluding occasional failures due to technical errors).

4. Randomization

Describe how samples/organisms/participants were allocated into experimental groups.

For xenograft experiments, when tumors reached a volume of approximately 200-250 mm³ mice were randomly assigned to a different treatment group (vehicle, AZD6244 or SHP099, depending on the experiment). Mice from different groups were co-allocated in the same cages. For subcutaneous PDX experiments, when tumors reached a volume of approximately 200-1000 mm³ (depending on the experiment) mice were randomly assigned to a different treatment group (vehicle, SHP099, AZD6244 or combination, depending on the experiment). Mice from different groups were co-allocated in the same cages. For orthotopic PDOX experiments, mice were randomly assigned to a different treatment group (vehicle or SHP099) one week after the implant. Mice of both groups were co-allocated in the same cages.

5. Blinding

Describe whether the investigators were blinded to group allocation during data collection and/or analysis.

Technicians and researchers were blinded to group allocation during data collection (tumor measurement).

Note: all studies involving animals and/or human research participants must disclose whether blinding and randomization were used.

6. Statistical parameters

For all figures and tables that use statistical methods, confirm that the following items are present in relevant figure legends (or in the Methods section if additional space is needed).

n/a Confirmed

- ☐ ☒ The exact sample size (n) for each experimental group/condition, given as a discrete number and unit of measurement (animals, litters, cultures, etc.)
- ☐ ☒ A description of how samples were collected, noting whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
- ☐ ☒ A statement indicating how many times each experiment was replicated
- ☐ ☒ The statistical test(s) used and whether they are one- or two-sided (note: only common tests should be described solely by name; more complex techniques should be described in the Methods section)
- ☒ ☐ A description of any assumptions or corrections, such as an adjustment for multiple comparisons
- ☐ ☒ The test results (e.g. P values) given as exact values whenever possible and with confidence intervals noted
- ☐ ☒ A clear description of statistics including central tendency (e.g. median, mean) and variation (e.g. standard deviation, interquartile range)
- ☐ ☒ Clearly defined error bars

See the web collection on [statistics for biologists](#) for further resources and guidance.

► Software

Policy information about [availability of computer code](#)

7. Software

Describe the software used to analyze the data in this study.

Analyses were performed either with Prism 6 software from GraphPad (San Diego, CA, USA) or with Microsoft Excel (version 14.7.2).

For manuscripts utilizing custom algorithms or software that are central to the paper but not yet described in the published literature, software must be made available to editors and reviewers upon request. We strongly encourage code deposition in a community repository (e.g. GitHub). *Nature Methods* [guidance for providing algorithms and software for publication](#) provides further information on this topic.

► Materials and reagents

Policy information about [availability of materials](#)

8. Materials availability

Indicate whether there are restrictions on availability of unique materials or if these materials are only available for distribution by a for-profit company.

No restrictions on materials availability.

9. Antibodies

Describe the antibodies used and how they were validated for use in the system under study (i.e. assay and species).

Antibodies against SHP2 (3752S) (Lot 2 Ref 07/2017), ERK 1/2 (137F5) (4695S) (Lot21 Ref 09/2017 and Ref 10/2017), p-RB (9308L) Ser807/811 (Lot12 Ref 01/2015), GAPDH (5174S) (D16H11) XP(R) (Lot 7 Ref 11/2017), STAT-1 (9172) (Lot 25 Ref 08/2017) and p-STAT-1 (Y701)(58D6) (9167) (Lot 18 Ref 10/2017) were purchased from Cell Signaling Technology.

Antibodies against PTPN11 (SHPTP2) (C-18) (sc-280) (Lot E2014), p-ERK1/2 (E-4) (sc-7383) (Lot#D2117), ERK1 (C-16) (sc-93) (Lot#NA), ERK2 (C-14) (sc-154), (Lot#H1312) and HSP90 (H-114) (sc-7947) (Lot#C2615) were purchased from Santa Cruz Biotechnology.

P-PTPN11 (p-SHP2) (Y542) (ab62322) (Lot GR59852-18) was obtained from Abcam.

Anti-CRAF antibody was purchased from BD Biosciences (#610152) (Lot 2125525).

Anti-RAS antibody (#1862335, Lot #S1259698 and Lot#SE244788) was obtained from Thermo Fisher Scientific as included in the Active Ras Pulldown and Detection Kit (#16117).

RAS10 (05-516) anti-RAS antibody was purchased from Millipore (Lot#NA).

Where possible, the antibodies were validated for western blot by using knockout cells as negative controls (as PTPN11 knockouts and RAS knockouts).

All antibodies were used at 1:1000 dilution for western blot studies, except Anti-Ras Thermo Scientific (1:200).

10. Eukaryotic cell lines

a. State the source of each eukaryotic cell line used.

All the human cell lines used in this study (H2122, H23, H358, H2030, H1944, A549, SW1116, LoVo, HCT116, SW480, SW1463, MiaPaCa2, Panc10.05) were purchased from American Type Culture Collection (ATCC). The reconstituted Rasless MEFs (WT, G13D, G12C, G12D, G12V, Q61R) were obtained from the NCI RAS Initiative (NIH) under an MTA agreement.

b. Describe the method of cell line authentication used.

None of the cell lines used have been authenticated.

c. Report whether the cell lines were tested for mycoplasma contamination.

All the cell lines were tested negative for mycoplasma contamination.

d. If any of the cell lines used are listed in the database of commonly misidentified cell lines maintained by [ICLAC](#), provide a scientific rationale for their use.

No commonly misidentified cell lines were used.

► Animals and human research participants

Policy information about [studies involving animals](#); when reporting animal research, follow the [ARRIVE guidelines](#)

11. Description of research animals

Provide details on animals and/or animal-derived materials used in the study.

For xenograft experiments, 8-weeks old female CD1 or NODSCID (depending on the experiment, as reported in the manuscript) mice were used. PDX experiments were performed using 6 weeks old male Crl:NU-Foxn1nu mice. PDOX experiments were performed using 6 weeks old female Crl:NU-Foxn1nu mice.

Policy information about [studies involving human research participants](#)

12. Description of human research participants

Describe the covariate-relevant population characteristics of the human research participants.

PDX2: female, 75y, never smoker, papillary adenocarcinoma, KRASG12D-mutant, pT1apN0, surgical resection, no additional treatment. Further information available at Nature Medicine: doi:10.1038/nm.4041.
 PDX3: female, 53y, former smoker, 20 pack/year, lung adenocarcinoma, KRASG12R-mutant, mets in the lung, spinal bones, soft tissue and right adrenal gland, treatment 1 carboplatin and paclitaxel with disease progression. Further information available at Nature Medicine: doi:10.1038/nm.4041.
 PDX4: Male, 50y, Caucasian, former smoker, 15 packs/year; diagnosed 11/12/2015, Lung adenocarcinoma TTF1+, EGFR/KRAS/BRAF WT; ALK/ROS1 not rearranged, Oncomine WT, T3N3M1c at diagnosis, stage IV, mets in brain, bone, adrenal, retroperitoneal lymph nodes, treatment 1 whole brain RT with complete response to WBRT, treatment 2 CBDCA+ paclitaxel +atezolizumab and maintenance with atezo (clinical trial) with stable disease, treatment 3 CBDCA+PEMETREXED with stable disease, treatment 4 Bone palliative RT, death 26-02-2018, survived 26,6 months, PDX generated 26-02-2017, tumor resistant to chemo plus anti-PD-L1.
 PDX5: female, 48y, caucasian, never smoker, diagnosed 17-12-2015, Lung adenocarcinoma, EGFR/KRAS/BRAF WT; ALK/ROS1 not rearranged, Oncomine not performed, T2aN2M1a at diagnosis, stage IV, pleural involvement, treatment 1 CDDP+ Pemetrexed and pemetrexed maintenance with partial response, treatment 2 Nivolumab with progression, treatment 3 Docetaxel with stable disease, death 21-08-2017, Tumor resistant to chemo and anti-PD1.