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Life Sciences Reporting Summary

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Please do not complete any field with "not applicable" or n/a. Refer to the help text for what text to use if an item is not relevant to your study.
For final submission: please carefully check your responses for accuracy; you will not be able to make changes later.

Experimental design

1. Sample size

Describe how sample size was determined.

Sample sizes in in vivo experiments were determined based on pilot and preliminary experiments as well as what was reported in the literature

2. Data exclusions

Describe any data exclusions.

Mice (<5%) were excluded from statistical analysis if sacrificed due to health reasons unrelated to tumor volume end point

3. Replication

Describe the measures taken to verify the reproducibility of the experimental findings.

All attempts at replication were successful through repeated experiments.

4. Randomization

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

Mouse in in vivo studies were randomized and allocated into experimental groups by independent technician

5. Blinding

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

Investigators were not blinded during animal experiments as all treatment groups were clearly labeled with corresponding inhibitors or vehicle.

Note: all in vivo studies must report how sample size was determined and 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 *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☐	☒ A description of any assumptions or corrections, such as an adjustment for multiple comparisons
☐	☒ Test values indicating whether an effect is present *Provide confidence intervals or give results of significance tests (e.g. P values) as exact values whenever appropriate and with effect sizes 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 in all relevant figure captions (with explicit mention of central tendency and variation)

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.	Microsoft Office statistical tools and GraphPad Prism 7 software were used to analyze data. Online Sequence Logo analysis software from Phosphosite.org and BLASTP software from the online BLAST search engine was used for peptide optimization for mass spectrometry.

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 third party.	SHP099 is a proprietary tool SHP2 inhibitor that was developed by Novartis Institutes for BioMedical Research, Inc (NIBR) and was obtained via an MTA. Gastric PDX cell line (CAT12) can be obtained from D. Catenacci upon request. All other materials were purchased from commercial vendors.

9. Antibodies

Describe the antibodies used and how they were validated for use in the system under study (i.e. assay and species).	Primary antibodies for Western blotting were phospho ERK1/2 T202/Y204 (#4370-Rabbit; 1:500), total ERK1/2 (#4695-Mouse; 1:1000), phospho-AKT Ser473 (#4060-Rabbit; 1:500), total AKT (#9272-Rabbit; 1:1000), phospho-HER3 Y1222 (#4784-Rabbit; 1:500), total HER3 (#4754-Rabbit; 1:1000), phospho-IGF1Rβ Y1135 (#2918-Rabbit; 1:1000), total IGF1Rβ (#3027-Rabbit; 1:1000) and SOS1 (#5890-Rabbit; 1:500) were purchased from Cell Signaling Technologies. Primary SOS2 (#PAS-35070-Rabbit; 1:500) antibody was purchased from Pierce Protein Biology/Thermo Fisher Scientific. Primary KRAS (Ras10 clone)(#17-218-mouse; 1:1000) and KRAS (#F234-sc30-mouse; 1:1000) antibody was purchased from Milipore and Santa Cruz Biotechnology respectively. Primary antibodies to HRAS (C20: sc-520-Rabbit; 1:1000) and NRAS (F155: sc-31-Rabbit; 1:1000) were purchased from Santa Cruz Biotechnology. Anti-β actin antibody (sc-74-mouse; 1:20000) was purchased from Sigma-Aldrich. SOS1 (#5890-Rabbit) from Cell Signaling Technologies was also used for immunofluorescent staining. All antibodies were validated by manufacturers as noted on data sheets specifying species cross-reactivity and antibody validation was performed by western blot.

10. Eukaryotic cell lines

a. State the source of each eukaryotic cell line used.	IM95, YCC1, HUG1N, KE39, SNU1 and GSU were gifts from Dana-Farber Cancer Institute and Belfer Institute and purchased from commercial sources. CAT12 is a patient-derived xenograft line that was established at the University of Chicago
b. Describe the method of cell line authentication used.	None of the cell lines have been authenticated.
c. Report whether the cell lines were tested for mycoplasma contamination.	All cell lines were tested routinely tested for mycoplasma contamination and were tested negative.
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 all relevant details on animals and/or animal-derived materials used in the study.	Research animals used for inhibitor efficacy in vivo studies were female NOD.CB17-Prkdcscid/J mice (6-8 weeks old) obtained from Jackson Laboratories. Mouse gastric organoids were derived from gastric epithelium of Trp53flox/flox;KrasLSL-G12D/+ in C57BL/6J background (3-4 month old) adult female mice that were obtained from Dr. Kwok-kin Wong's laboratory at Dana-Farber Cancer Institute

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.	Study did not use human research participants

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Flow Cytometry Reporting Summary

Form fields will expand as needed. Please do not leave fields blank.

Data presentation

For all flow cytometry data, confirm that:

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

☒ 2. 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).

☐ 3. All plots are contour plots with outliers or pseudocolor plots.

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

Methodological details

5. Describe the sample preparation.	Cells from gastric cancer cell lines were washed twice in cold PBS, resuspended and stained using BD Pharmingen FITC Annexin V Apoptosis Detection kit (BD Biosciences) according to manufacturer's instructions
6. Identify the instrument used for data collection.	BD LSRFortessa
7. Describe the software used to collect and analyze the flow cytometry data.	BD FACS DIVA software
8. Describe the abundance of the relevant cell populations within post-sort fractions.	The abundance of cells undergoing early apoptosis, late apoptosis and necrosis were determined based on cell type, culture and treatment conditions
9. Describe the gating strategy used.	Gating strategy was based on FITC Annexin V and Propidium Iodide (PI) positive staining: 1) Cells undergoing apoptosis were FITC Annexin V high and PI low; 2) Necrotic cells were FITC Annexin V high and PI high and 3) Viable cells were FITC Annexin V low and PI low

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