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Life Sciences Reporting Summary

Nature Research wishes to improve the reproducibility of the work we publish. This form is published with all life science papers and is intended to promote consistency and transparency in reporting. All life sciences submissions use this form; while some list items might not apply to an individual manuscript, 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.

For in vivo experiments each arm was designed to contain at least 6 tumors which we estimated to provide 90% power to detect a 20% difference in growth rate at p-value < 0.05.

2. Data exclusions

Describe any data exclusions.

We performed exome sequencing of the acquired resistant cell lines and did not ind any significant recurrent mutation. Hence we are not showing the data, but we mention this in our manuscript.

3. Replication

Describe whether the experimental findings were reliably reproduced.

Biological replications are as indicated in figure legends. All attempts at replication were successful.

4. Randomization

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

Animals were randomized at the start of treatment. In figure 4b some animals in the combination arm had significantly larger tumors at the start of treatment. This bias does not impact the interpretation of the experiment.

5. Blinding

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

Mitotic errors and IHC scoring were performed in a blinded manner to avoid observation bias.

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 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 summary of the descriptive 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.	Statistical analyses for this study were performed using GraphPad Prism 6 (version 6.0g). IHC profiler plug-in Fiji Image J (version 2.0.0-rc-43/1.51p). FlowJo was version 10.2.

For all studies, we encourage code deposition in a community repository (e.g. GitHub). Authors must make computer code available to editors and reviewers upon request. The *Nature Methods* guidance for providing algorithms and software for publication may be useful for any submission.

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.	All material are available from standard available sources and cell lines available upon reasonable request.

9. Antibodies

Describe the antibodies used and how they were validated for use in the system under study (i.e. assay and species).	Antibodies for pEGFR (Y1068; 3777, D7A5, 1:500), pERK1/2 (T202/Y204; 4370, D13.14.4E, 1:1000), ERK1/2 (9102, 1:1000), pAKT (S473; 4060, D9E, 1:1000), AKT (9272, 1:1000), PARP (5625, D64E10, 1:1000), pAURKA (T288; 3079, C39D5, 1:250), AURKA (4718, 1G4, 1:500), pan-pphospho AURKA/B/C (T288/T232/T198, 2914, D13A11, 1:500) pRb (S780; 9307, 1:1000), BIM (2933, C34C5, 1:500), pBIM (S69; 4585, D7E11, 1:300), BAX (5023, D2E11, 1:1000), Vimentin (5741, D21H3, 1:1000), p-p65 (S536; 3033, 93H1, 1:500), p65 (8242, D14E12, 1:1000), CD44 (3570, 156-3C11, 1:1000), Histone H3 (9715, 1:1000) were purchased from Cell Signaling Technology; TPX2 (HPA005487, 1:250) and pan total AURKA/B/C (HPA002636, 1:1000) were purchased from Sigma; EGFR (SC-03, 1:1000), NEDD9 (sc-33657, 14A11, 1:200), AJUBA (sc-398008, B-3, 1:100), PAK1 (sc-166174, D-8, 1:500), CD24 (sc-19585, SN3, 1:300), CD133 (sc-30219, M-286, 1:1000), B-tubulin (sc-9104, H-235, 1:500), p53 (sc-126, DO-1, 1:500) were purchased from Santa Cruz biotechnology and FZR1/CDH1 (ab3242, 1:50) from Abcam and V5 tag (46-0705, R960-25, 1:100) from Thermofisher. All antibodies have been previously published with citations available from the vendor and were validated for use via western blot indicating a protein band of the expected size.

10. Eukaryotic cell lines

a. State the source of each eukaryotic cell line used.	H1975, HCC827, and HCC4006 were from the American Type Culture Collection (ATCC). PC9 cells were a gift from Dr. F. Koizumi (National Cancer Center Research Institute and Shien-Lab, Tokyo, Japan).
b. Describe the method of cell line authentication used.	Cell line identity was confirmed by short-tandem repeat analysis (Genetica)
c. Report whether the cell lines were tested for mycoplasma contamination.	All cell lines used in this study tested negative for mycoplasma before their use.
d. If any of the cell lines used in the paper 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 in this study.

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.	Female C.B-17 SCID mice were purchased from Taconic for both xenograft and PDX experiments and were between 4 and 8 weeks of age at the start of the experiment.

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.	All patients were diagnosed with EGFR-mutant lung adenocarcinoma and treated with the indicated EGFR TKI. Analysis was blind to age and gender.