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☐ Initial submission ☐ Revised version ☒ Final submission

Life Sciences Reporting Summary

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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.

Sample sizes choice applicable to mouse xenograft models study (Fig. 5): Sample sizes were chosen based on the historical data of the variability of tumor growth and treatment response observed in the MM.1S xenograft model at Pharmaron.

2. Data exclusions

Describe any data exclusions.

Data exclusion in crystallographic datasets (outlier reflection rejection) was carried out automatically as implemented in the program Xia2 using pre-established criteria.

3. Replication

Describe whether the experimental findings were reliably reproduced.

Every experiment was replicated at least twice with near-identical results. Biophysical measurements were repeated with different samples / days / and every time in technical triplicate. Many experiments were replicated not only internally, but also in two different labs.

4. Randomization

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

Based on the tumour volumes on the first day of treatment, MM.1S xenograft tumour bearing mice were randomly assigned to treatment groups such that each treatment group or time point/treatment group (efficacy or PD -study, respectively) had the same average tumour volume.

5. Blinding

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

The data presented did not require the use of blinding.

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.	See the methods section for details. Xia2, Phaser, Coot, Refmac, Pymol, Molecular Operating Environment (MOE), Biacore T200 Evaluation Software, FluoChem FC2, Microsoft Excel, Graphpad Prism, MaxQuant, ActivityBase.

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.	FT671 and FT827 are available from FORMA Therapeutics under appropriate Material Transfer Agreements. All other material are available upon reasonable request to the corresponding authors.

9. Antibodies

Describe the antibodies used and how they were validated for use in the system under study (i.e. assay and species).	Cell line studies: anti-HA (12CA5, Roche, #11583816001), anti-USP7 (Enzo #PW0540), anti-p53 (DO1, Santa Cruz), anti-MDM2 (IF2, Calbiochem), anti-p21 (F-5, Santa Cruz), anti-USP7 (Abcam, ab4080), anti-N-Myc (Cell Signaling Technology, #9405), anti-DNMT1 (D63A6, XP® Rabbit mAb Cell Signaling Technology, #5032), anti-UHRF1 (H-8, Santa Cruz sc-373750), Vinculin (E1E9V, XP® Rabbit mAb #13901), and anti-b-actin (Abcam #ab8227, Abcam #ab6276, Sigma #A2266). Mouse xenograft studies: Anti-p53 (Santa Cruz sc-126), anti-b-Actin (Cell Signaling Technology #4970), anti-p21 (Cell Signaling Technology #2946). HRP-conjugated anti-rabbit (Cell Signaling Technology #7074), HRP-conjugated anti-mouse (Cell Signaling Technology #7076), IRdye 800CW Goat anti-Rabbit (#925-32211, Li-COR), Goat anti-Mouse (#925-332210, Li-COR). All antibodies were validated by the supplier for human samples, and were checked in the lab by Western Blotting on cell lysate and by comparing to the manufacturer's or in-house results.

10. Eukaryotic cell lines

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

MM.1S cells were acquired from ATCC (Manassas, VA, CRL-2974) and their identity was authenticated using STR analysis. HCT116 cells were acquired from ATCC (ATCC-CCL-247, October 2016). IMR-32 were acquired from Sigma (cat. number 86041809, January 2016). MCF7 were acquired from ATCC (HTB-22). U2OS were acquired from ATCC (HTB-96, authenticated in March 2017). HCT116, MCF7 and U2OS cells were authenticated frequently.

b. Describe the method of cell line authentication used.

Authentication was done using STR analysis.

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

All cell lines are frequently tested for mycoplasma contamination. Cell lines used in this study were verified to be mycoplasma negative before undertaking any experiments with them.

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 cells were used. All cells displayed homogeneous characteristic morphology.

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.

Studies used 6-8 week old female NOD SCID mice (Vital River Laboratory Animal Technology Co, Beijing, China) which were irradiated (200 rads) with a Co60 irradiator source 24 h prior to subcutaneous inoculation of tumor xenografts. All animal experiments were performed at Pharmaron (Beijing, China). All the animal experiments were performed according to guidelines approved by the Institutional Animal Care and Use Committee (IACUC) of Pharmaron (Beijing, China) following the guidance of the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC).

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.

not applicable.