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Reporting Summary

Nature Portfolio 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 Portfolio policies, see our Editorial Policies 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	No software was used for data collection.
Data analysis	SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA) and R software version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria). The code used for this study is publicly available on Github.

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 and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio 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 description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy

The raw sequence data used in this study are available in the Genome Sequence Archive (Genomics, Proteomics & Bioinformatics 2021) in National Genomics Data Center (Nucleic Acids Res 2022), China National Center for Bioinformation/Beijing Institute of Genomics, Chinese Academy of Sciences database under accession code HRA009542. To respect participant confidentiality, the study clinical data are not publicly available. Individual de-identified clinical data can be made available for academic purposes upon request and approval by the study management committee and subject to appropriate data transfer agreements. Request should be

directed to the corresponding authors Kun Wang (wang-kun@vip.sina.com) and Baocai Xing (xingbaocai88@sina.com). Requests for data access will be processed within 4 weeks, and access will be granted for a month. The remaining data are available within the Article, Supplementary Information or Source Data file.

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	Self-reported sex of participants was collected and listed in Table 1. Gender was not collected.
Reporting on race, ethnicity, or other socially relevant groupings	Race, ethnicity or any other socially relevant groupings were not used in our manuscript.
Population characteristics	Characteristics of the participants including age, body mass index, smoking history, drinking history and so on are shown in Table 1. Fifty-five participants were enrolled. The mean age of the participants was 60.3±6.93 years, 80.0% of the participants were male, 39 (70.9%) had hepatitis B, one (1.8%) had hepatitis C, and 35 (63.6%) had liver cirrhosis. Fifty-one (92.7%) participants were in BCLC stage C, and 53 (96.4%) had Child-Pugh A liver function. Twenty-eight (50.9%) participants had extrahepatic metastases.
Recruitment	Patients meeting all inclusion and exclusion criteria of the study were screened at Peking University Cancer Hospital & Institute and Harbin Medical University Cancer Hospital. No other specific recruiting procedures were used to enroll patients.
Ethics oversight	This study was approved by the Institutional Ethical Review Board Committee of Beijing Cancer Hospital and Institute (Beijing, China) (approval number 2020YJZ37). This trial was conducted in accordance with the Declaration of Helsinki and Good Clinical Practices.

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

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	The ORR in historical controls was about 20%, and the ORR in this study was estimated at 40%. Considering a one-sided α of 0.025 and β of 0.15, 53 participants were required in this study (six of them were in the safety run-in period). Finally, 55 participants were enrolled in this study.
Data exclusions	No data was excluded for analyses.
Replication	The findings are not be able to replicate as these were results from a single clinical trial.
Randomization	This open-lable phase-2 clinical trial is a single-arm study, so the randomization is not relevant to our study.
Blinding	AS an open-lable study, there was no blinding.

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 and archaeology
☒	☐ Animals and other organisms
☐	☒ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

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

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	This study was registered at ClinicalTrials.gov. Clinical trial number is NCT04542837.
Study protocol	A copy of the study protocol will be submitted along with the manuscript.
Data collection	Patients with advanced hepatocellular carcinoma were enrolled at Peking University Cancer Hospital & Institute and Harbin Medical University Cancer Hospital in China. Seventy-three patients were screened and 55 participants were enrolled.
Outcomes	The primary endpoints were safety, tolerability, DLT, and objective response rate (ORR) judged by the investigators according to RECIST v1.1. The secondary endpoints were ORR assessed by the investigators based on modified RECIST (mRECIST) and immune-modified RECIST (imRECIST), duration of response (DOR), disease control rate (DCR), time to response (TTR), and progression-free survival (PFS) assessed by the investigators based on RECIST v1.1, mRECIST, and imRECIST, OS, and 12-month OS rate. Tumor assessment at baseline and follow-up based on computed tomography (CT) or magnetic resonance imaging (MRI) was conducted once every 6 (±1) weeks in the first year and then once every 12 (±1) weeks thereafter. Tumor response was assessed by the investigators based on the RECIST v1.1, mRECIST, and imRECIST criteria. For participants in the safety run-in period, safety was assessed once every week. DLT was recorded and graded based on CTCAE 5.0. During the subsequent treatment period, a follow-up visit was conducted before each administration of KN046. The safety assessment included vital signs, height, weight, physical examination, ECOG PS score, laboratory tests (blood routine, blood biochemistry, coagulation function, urine routine, stool routine, thyroid function, and blood/urine pregnancy test), and 12-lead electrocardiogram. AEs were followed until 30 days after the last administration of the study drug or initiation of a new antitumor therapy. Serious AEs (SAEs) and treatment-related AEs (TRAEs) were followed up to 90 days after the last administration. SAEs suspected to be related to KN046 were recorded regardless of the time of occurrence and time interval from discontinuing KN046 treatment.

Plants

Seed stocks	*Report on the source of all seed stocks or other plant material used. If applicable, state the seed stock centre and catalogue number. If plant specimens were collected from the field, describe the collection location, date and sampling procedures.*
Novel plant genotypes	*Describe the methods by which all novel plant genotypes were produced. This includes those generated by transgenic approaches, gene editing, chemical/radiation-based mutagenesis and hybridization. For transgenic lines, describe the transformation method, the number of independent lines analyzed and the generation upon which experiments were performed. For gene-edited lines, describe the editor used, the endogenous sequence targeted for editing, the targeting guide RNA sequence (if applicable) and how the editor was applied.*
Authentication	*Describe any authentication procedures for each seed stock used or novel genotype generated. Describe any experiments used to assess the effect of a mutation and, where applicable, how potential secondary effects (e.g. second site T-DNA insertions, mosiacism, off-target gene editing) were examined.*