nature portfolio

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Last updated by author(s): Jun 7, 2026

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	Microsoft Excel was used for data collection.
Data analysis	R version 4.5.0 and GraphPad Prism version 8.

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 study protocol is provided in the Supplementary Information file as the Supplementary Note 2. Individual participant data are not publicly available due to patient privacy considerations. However, deidentified individual participant data can be accessed upon reasonable request from the corresponding author Qingqing Cai for 10 years. All requests for data will be reviewed by the leading site Sun Yat-Sen University Cancer Center to verify if the request is subject to any intellectual property or confidentiality obligations. Requests for access to the patient-level data from this study can be submitted via email to caiqq@sysucc.org.cn with detailed proposal for approval. The remaining data are available within the Article, Supplementary Information, or Source Data file. Source data are provided with this paper.

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	There was no restriction on sex in the eligibility criteria. Sex was self-reported by participants at enrollment.
Reporting on race, ethnicity, or other socially relevant groupings	All patients enrolled were Han Chinese. No reporting on race, ethnicity, or other socially relevant groupings are applicable.
Population characteristics	Demographics and baseline characteristics of the 40 patients are summarized in table 1. The median age was 48 years (range 22-73). Twenty-one (53%) were male, 25 (63%) had stage III-IV disease, and 23 (58%) had refractory disease. Most patients had received P-GemOx-based regimens (Supplementary Table 1). The median number of prior systemic therapies was 1 (range 1-4). Five patients (13%) had undergone autologous stem cell transplantation (ASCT) and 21 (53%) had received previous anti-PD-1 therapy.
Recruitment	The trial was conducted at 16 centers across China (Supplementary Note 1). Patients aged 18-75 years with histologically confirmed ENKTL, R/R after at least one prior asparaginase-based therapy were eligible. Refractory disease was defined as failure to achieve a CR to asparaginase-based chemotherapy or disease progression within 6 months after the last asparaginase-containing regimen. Relapsed disease was defined as disease recurrence after achieving a CR to initial therapy and occurring beyond 6 months of the last regimen. Additional eligibility requirements included an ECOG PS between 0 and 2; adequate liver, renal, and bone-marrow function; a life expectancy of at least 3 months; and at least one measurable lesion according to the Lugano 2014 criteria.40 Key exclusion criteria included previous exposure to non-liposomal mitoxantrone at a cumulative dose of > 160 mg/m2, a cumulative doxorubicin dose of > 360 mg/m2, a diagnosis of aggressive natural killer cell leukemia, central nervous system involvement, and pregnancy or lactation. Full eligibility and exclusion criteria are described in the trial protocol (Supplementary Note 2). Patients were consecutively recruited at participating centers according to prespecified eligibility criteria. As this was a multicenter single-arm trial, some degree of selection bias toward patients with better performance status or organ function may be present, which could limit the generalizability of the findings.
Ethics oversight	This multicenter, single-arm, phase 1b/2 trial was approved by the institutional ethics committees of all participating centers (Ethics committee of Sun Yat-sen University Cancer Center; Ethics Committee of Beijing Tongren Hospital, Capital Medical University; Ethics committee of The First Affiliated Hospital, Zhejiang University School of Medicine; Ethics committee of Army Medical University Daping Hospital; Ethics committee of The First People's Hospital of Foshan; Ethics committee of Jiangxi Cancer Hospital; Ethics committee of The Second Hospital of Dalian Medical University; Ethics committee of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology; Ethics committee of The First Affiliated Hospital of Guangxi Medical University; Ethics committee of Fujian Cancer Hospital; Ethics committee of The Fifth Affiliated Hospital of Guangzhou Medical University; Ethics committee of Qilu Hospital of Shandong University; Ethics committee of Peking Union Medical College Hospital; Ethics committee of Fujian Medical University Union Hospital; Ethics committee of Fudan University Shanghai Cancer Center; and Ethics committee of Guangxi Medical University Cancer Hospital). This study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines. Written informed consent was obtained from all participants.

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	Dose-escalation phase followed the standard 3 + 3 design to enrol 6-12 patients. Sample size requirement in the dose-expansion phase was estimated based on the following assumptions: 1) complete response rate of 28% for Lipo-MIT monotherapy, and estimated target complete response rate of 50% for Lipo-MIT plus tislelizumab; 2) one-side α of 0.05 and 80% power; 3) 10% dropout rate. The calculation yielded 36 patients.
Data exclusions	No data were excluded.
Replication	Replication was not applicable as this was a clinical trial with unique patient samples.
Randomization	Randomization was not applicable as this is a single-arm, open-label, phase 1b/2 clinical trial.
Blinding	Blinding was not applicable as this is a single-arm, open-label, phase 1b/2 clinical trial.

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
[ ]	[x] Antibodies
[x]	[ ] Eukaryotic cell lines
[x]	[ ] Palaeontology and archaeology
[x]	[ ] Animals and other organisms
[ ]	[x] Clinical data
[x]	[ ] Dual use research of concern
[x]	[ ] Plants

Methods

n/a	Involved in the study
[x]	[ ] ChIP-seq
[x]	[ ] Flow cytometry
[x]	[ ] MRI-based neuroimaging

Antibodies

Antibodies used

Antibody (mIHC):
Anti-CD56 (Cell Signaling Technology, Cat #3576, 1:200);
Anti-PD-1 (Proteintech, Cat #66220-1-Ig, 1:6000);
Anti-PD-L1 (Cell Signaling Technology, Cat #13684, 1:400);
Anti-CD8 (Cell Signaling Technology, Cat #70306, 1:400);
HRP-conjugated anti-mouse and rabbit secondary antibody (Panovue, Cat #10013001050) , provided as a 1x ready-to-use solution and used according to the manufacturer's instructions;

Validation

All antibodies have been validated by the manufacturer, as indicated in the references provided:
Anti-CD56 antibody: https://www.cellsignal.cn/products/primary-antibodies/ncam1-cd56-123c3-mouse-monoclonal-antibody/3576
Anti-PD-1 antibody: https://www.ptgcn.com/products/PD-1-CD279-Antibody-66220-1-Ig.htm
Anti-PD-L1 antibody: https://www.cellsignal.cn/products/primary-antibodies/pd-l1-e1l3n-rabbit-monoclonal-antibody/13684
Anti-CD8 antibody: https://www.cellsignal.cn/products/primary-antibodies/cd8-alpha-c8-144b-mouse-monoclonal-antibody/70306
HRP-conjugated anti-mouse and rabbit secondary antibody: https://u5mpootmgx.jiandaoyun.com/dash/611cc8d79bbb8a0008295ad3

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 trial is registered with ClinicalTrials.gov, NCT05464433 (https://clinicaltrials.gov/study/NCT05464433; first posted on July 19, 2022).

Study protocol

The study protocol is provided in the Supplementary Information file as the Supplementary Note 2.

Data collection

Data were collected using Microsoft Excel at 16 participating centers in China. Data collection started with enrollment of the first patient, and follow-up continued until the data cutoff date of August 31, 2025.

Outcomes

The primary endpoint of the dose-escalation phase was DLTs, which in turn were assessed to determine the RP2D of Lipo-MIT when given in combination with tislelizumab. The primary efficacy endpoint of the dose-expansion phase was the best complete response rate. The secondary outcomes included the objective response rate, disease control rate, progression-free survival, overall survival, disease-free survival, duration of response, and safety. Exploratory post-hoc analyses were conducted to identify factors associated with treatment response and survival outcomes (including clinical variables, circulating EBV DNA copy number, and immune cell components in the tumour microenvironment)

Plants

Seed stocks	Not applicable.
Novel plant genotypes	Not applicable.
Authentication	Not applicable.