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Protocol for a multicentre, open-label, dose-escalation phase I/II study evaluating the tolerability, safety, efficacy and pharmacokinetics of repeated continuous intravenous PPMX-T003 in patients with aggressive natural killer cell leukaemia

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ABSTRACT

Introduction Aggressive natural killer cell leukaemia (ANKL) is a rare form of NK cell lymphoma with a very low incidence and poor prognosis. While multi-agent chemotherapy including L-asparaginase has been used to treat ANKL patients, they often cannot receive adequate chemotherapy at diagnosis due to liver dysfunction. PPMX-T003, a fully human monoclonal antibody targeting the transferrin receptor 1, shows promise in treating ANKL by helping patients recover from fulminant clinical conditions, potentially enabling a transition to chemotherapy. This study aimed to evaluate the tolerability, safety, efficacy, and pharmacokinetics of repeated continuous intravenous PPMX-T003 in patients with ANKL.

Methods and analysis This multicentre, open-label, dose-escalation phase I/II study will be conducted at nine hospitals in Japan. Patients diagnosed with ANKL (whether as a primary or recurrent disease) and exhibiting abnormal liver function or hepatomegaly due to the primary disease will be included. The primary endpoint is the tolerability and safety of repeated continuous intravenous administration of PPMX-T003 in the first course, based on adverse events and dose-limiting toxicities. PPMX-T003 will be administered as a continuous intravenous infusion every 24 hours for five consecutive days, followed by a 2-day break. Pretreatment will be provided to minimise the risk of infusion-related reactions. Initial doses of PPMX-T003 will be 0.5, 1.0 or 2.0 mg/kg, with subsequent dose increases determined by the Data and Safety Monitoring Committee. The sample size is set at seven participants, with enrolment increased to up to 12 participants if dose-limiting toxicities occur, based on feasibility due to the rarity of ANKL. Descriptive statistics will summarise data according to initial dose, and pharmacokinetic analysis will be conducted based on administered dose.

Ethics and dissemination This study was approved by the institutional review boards at participating hospitals. The results will be disseminated in peer-reviewed journals.

Trial registration number jRCT2061230008 (jRCT); NCT05863234 (ClinicalTrials.gov).

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Despite the extremely rare lymphoma subtype of aggressive natural killer cell leukaemia, the study employs a feasible design that allows for evaluation of the tolerability of PPMX-T003.
⇒ Prior to each dose escalation, the Data and Safety Monitoring Committee carefully assesses the accumulating safety data to ensure patient safety.
⇒ The uncontrolled study design makes it difficult to draw definitive conclusions regarding treatment effects.

INTRODUCTION

Aggressive natural killer cell leukaemia (ANKL) is a rare form of NK cell lymphoma, closely associated with Epstein Barr virus (EBV) infection.[1 2] The incidence of ANKL is very low, with only 13 cases reported in Japan in 2020 according to statistics from the Japanese Society of Haematology.[3] ANKL is relatively more common in younger patients and in Eastern Asia.[2] It is one of the haematological malignancies with the poorest prognosis, with a median survival of only a few months after diagnosis.[4]

Treatment of ANKL has not yet been established and is currently conducted with reference to treatment of extranodal NK/T-cell lymphoma, nasal type.[5] While there is a possibility of curing the disease through allogeneic haematopoietic stem cell transplantation, it is crucial for chemotherapy to be successful prior to that.[6 7] Multiagent chemotherapy including L-asparaginase,[8 9] such as SMILE (dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide), has been applied in patients with ANKL. However,

patients with ANKL often do not receive adequate chemotherapy at the time of diagnosis due to organ failure and bone marrow suppression, particularly liver dysfunction, which may even render chemotherapy impossible. Therefore, it is necessary to improve liver function and the overall condition of the patient to enable the implementation of chemotherapy.

NK cell lymphomas have a unique property of proliferating along the hepatic sinusoids, and their proliferation has been found to be strongly dependent on the presence of transferrin.[10] Binding transferrin to the transferrin receptor 1 (TfR1) is crucial for iron intake in cell proliferation, and aggressive cancer cells, including ANKL cells, often exhibit high levels of TfR1 on their surfaces. PPMX-T003 is a fully human monoclonal antibody targeting TfR1, which competitively blocks the binding of transferrin to TfR1. A recent study using nonclinical patient-derived xenograft models demonstrated that the transferrin-TfR1 interaction is a potential therapeutic target in ANKL, and PPMX-T003 extended the survival period by depleting ANKL cells from the liver microenvironment.[10] Additionally, another study revealed that the influx of extracellular amino acids through LAT1 was the key environmental factor determining the iron dependency of ANKL cells, which may explain the high sensitivity to PPMX-T003 in the liver sinusoids, where abundant amino acids absorbed from the gut are present.[11] This mechanism is particularly promising for treating blood cancers such as ANKL. It is anticipated that early induction therapy with PPMX-T003 will facilitate recovery from fulminant clinical conditions in patients with ANKL, enabling a transition to chemotherapy.

Regarding clinical trials with PPMX-T003, a phase 1 study involving healthy volunteers who received single-dose intravenous infusions ranging from 0.008 mg/kg to 0.25 mg/kg was completed.[12] In this study, adverse events (AEs) occurred in half of the participants, including infusion-related reactions (IRRs) and expected decreases in blood cell levels. However, the drug showed an acceptable safety profile with no severe AEs (SAEs).[12] A separate phase 1 study was recently completed (28 June 2024) in patients with polycythemia vera, evaluating the safety and pharmacokinetics of a single intravenous dose of PPMX-T003, with doses up to 1.0 mg/kg (jRCT Trial ID jRCT2051210083 and ClinicalTrials.gov identifier NCT05074550). This study indicated that PPMX-T003 could potentially treat polycythaemia vera patients, supported by an acceptable safety profile with no SAEs and only mild AEs (eg, elevated CRP, lymphocytopenia) (unpublished data). The current multicentre, open-label, dose-escalation phase I/II study aims to assess the tolerability, safety, efficacy and pharmacokinetics of repeated continuous intravenous PPMX-T003 in patients with ANKL. Findings from this study will offer valuable insights for the further development of PPMX-T003.

METHODS AND ANALYSIS

Study design and setting

This multicentre, open-label, dose-escalation phase I/II study will be conducted at eight Japanese university hospitals (Tokai, Tohoku, Kyoto, Okayama, Kyushu, Hiroshima, Hokkaido and Nagoya University Hospitals) and Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital. Initially, the study was launched at seven university hospitals; two additional hospitals were included to facilitate patient enrolment. All the hospitals with experience in treating patients with ANKL. The study will take place in an inpatient setting. The overall planned interventions and assessments are shown in online supplemental table 1.

Objectives

The primary objective of this study was to assess the tolerability and safety of repeated, continuous intravenous PPMX-T003 in patients with ANKL by monitoring AEs. Secondary objectives included evaluating efficacy through improvements in hepatomegaly as measured by CT scans, determining patients' eligibility for chemotherapy in the treatment of ANKL and analysing pharmacokinetics.

Eligibility criteria

Participants who meet all inclusion criteria and none of the exclusion criteria will be eligible for enrolment. The investigators will provide an explanation based on the informed consent form (online supplemental data) to the participant or a surrogate and will obtain written informed consent to ensure their voluntary participation in the study before screening. The informed consent includes permission for the use of data and specimens collected in this trial for future research.

Inclusion criteria

- Patients aged 18 years or older and under 75 at the time of informed consent.
- Patients diagnosed with ANKL (whether as a primary or recurrent disease) based on diagnostic criteria developed in accordance with the WHO 4th edition (2017).[1]
- Patients with abnormal liver function or hepatomegaly due to the primary disease.
- Patients with an Eastern Cooperative Oncology Group performance status of 3 or less.
- For women of childbearing potential and men, patients who agree to use adequate contraception from the time of consent until 24 weeks after receiving the final dose.
- Patients who have provided written consent, either personally or through a surrogate, to participate in this clinical trial.

Exclusion criteria

- Patients eligible to receive chemotherapy as treatment for ANKL.
- Patients whose screening tests reveal abnormalities unrelated to ANKL and who are deemed unsuitable

for study participation by the investigator or others based on factors such as physical examination, standard 12-lead ECG, chest X-ray, haematology, blood chemistry, urinalysis and immunological tests.
- Patients treated with other investigational drugs or unapproved therapies within 16 weeks prior to enrolment
- Patients who, at the time of screening, tested positive for hepatitis B virus surface antigen, hepatitis B virus core antibody, hepatitis B virus surface antibody (HBsAb), hepatitis C virus (HCV) antibody, HIV antibody/antigen and syphilis serological response. Exceptions include those with HBsAb positive with a vaccination history, HBsAb positive but HBV–DNA negative and HCV antibody positive but HCV–RNA negative. Monthly hepatitis virus testing should be conducted throughout the administration period to ensure safety.
- Pregnant and lactating female patients.
- Other patients deemed unsuitable for study participation by the investigator or others.

Endpoints

The primary endpoint is the tolerability and safety of repeated continuous intravenous administration of PPMX-T003 during the first course, assessed by AEs and dose-limiting toxicities (DLTs). Secondary endpoints include: (1) tolerability and safety (including DLT evaluation after the second course), (2) efficacy (change in liver size measured by the product of maximum long and short diameters on CT scans, as assessed by the investigator), (3) improvement in liver function based on the model for end-stage liver disease (MELD or MELD-Na) score, (4) 6-month survival rate after study entry, (5) proportion of participants transitioning to chemotherapy, (6) pharmacokinetics and (7) anti-drug antibody (ADA) production. Additionally, the percentage of tumour cells in bone marrow nucleated cells and EBV–DNA copy number will be evaluated.

Dose-limiting toxicity (DLT)

DLTs are any of the following toxicities occurring during each 7-day course, as assessed by the investigator to be related to PPMX-T003. Toxicity grading is based on the National Cancer Institute Common Terminology Criteria for AE (CTCAE) V.5.0.
- Grade≥3 non-haematologic toxicities.
- Grade≥4 haematologic toxicities.
- AEs that require dose interruption of PPMX-T003 drug during each course.
- Anaemia or thrombocytopenia that requires transfusion.
- Any other toxicity considered DLTs in the opinion of the investigators.

Given the severity of ANKL and the pharmacological effects of PPMX-T003, manageable DLTs such as those requiring transfusion or associated with tumour lysis syndrome are considered tolerable.

Treatment and pretreatment

The PPMX-T003 will be administered as a continuous intravenous infusion over 1 hour (with a 5-minute margin). The drug will be given every 24 hours for 5 consecutive days, followed by a 2-day break. This cycle will be repeated for subsequent courses. Administration of PPMX-T003 will be directly confirmed by the investigators and/or other study staff.

Due to the occurrence of mild to moderate IRRs in participants receiving 0.16 mg/kg and 0.25 mg/kg of PPMX-T003 in healthy volunteers,[12] premedication with acetaminophen, diphenhydramine hydrochloride and dexamethasone sodium phosphate will be administered to minimise the risk of IRR.

Rationale for study design

In this clinical trial, no placebo control group will be used. The reasons for this decision are as follows:
- ANKL is an extremely rare disease, with only about 10 to 20 new cases occurring annually in Japan. While this clinical trial plans to involve six participating institutions, the expected annual enrolment is likely to be limited to just two or three cases. Establishing a placebo control group would lead to an impractically long trial duration, making it unfeasible.
- While no established treatment exists for ANKL, previous studies have shown that even with the best available treatments, the median survival period is only about 2 months.[4] Thus, if this clinical trial demonstrates a median survival period longer than 2 months, PPMX-T003 treatment could be deemed effective. Furthermore, historical data from participating institutions could serve as a comparative benchmark.
- Given that ANKL is a very rare disease, treatment options should be provided on ethical grounds, making a placebo control group potentially unjustifiable.

Dose escalation

In this study, the initial dose and subsequent dose escalation for the next participants will be determined with careful assessment of tolerability based on all available results obtained up to that point. However, if sufficient information for making such decisions is available without the need to wait for all treatment courses of the previous participants to be completed, enrolment will continue without interruption. In any case, when increasing the dose for the same patient, approval from the Data and Safety Monitoring Committee (DSMC) will be required. To ensure the safety of the participants, as far as possible, and to maintain the integrity of the clinical trial, a DSMC, consisting of three members independent of this trial, has been established to assess ongoing trial data and provide appropriate advice and recommendations to the coordinating investigator based on the findings.

For the first two patients, the starting dose is 0.5 mg/kg (low-dose group), increasing sequentially to 1.0 mg/kg and 2.0 mg/kg with each course. If a patient cannot tolerate doses of 1.0 mg/kg or higher, the dose may be

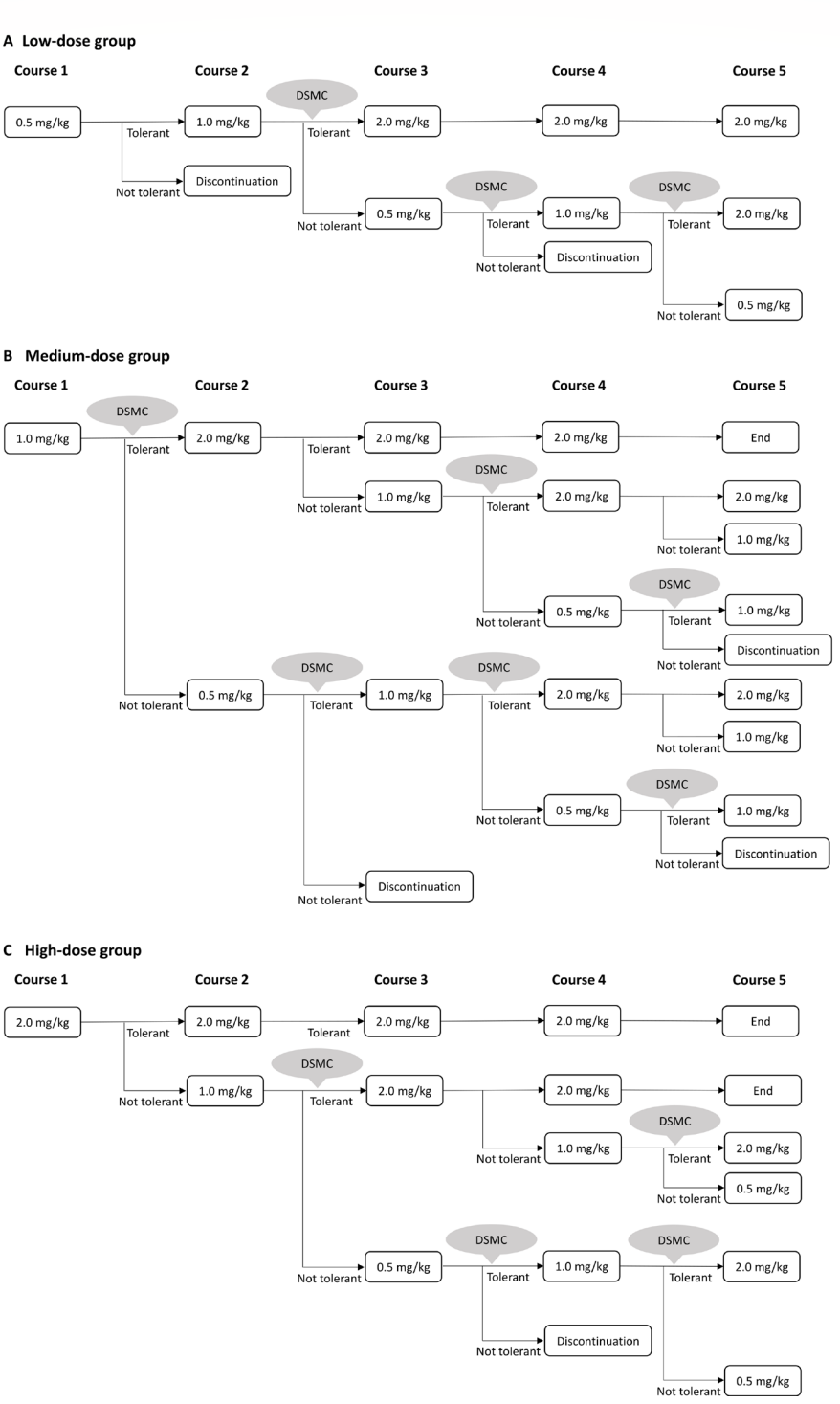

Figure 1 Schema of dose escalation for (A) low-dose, (B) medium-dose and (C) high-dose groups. DSMC, Data and Safety Monitoring Committee.

reduced. If 0.5 mg/kg is not tolerated, the study treatment will be discontinued. Treatment will continue for up to five courses (figure 1A). Investigators will decide whether to reduce or discontinue the dose.

For the third patient, the DSMC will determine the starting dose based on all data obtained from the first two patients. If the committee cannot confirm tolerability, the next two patients will not receive an increased dose and will instead be given 0.5 mg/kg.

If the DSMC confirms tolerability at a dose of 1.0 mg/kg in the low-dose group, the next patient will begin at 1.0 mg/kg (medium-dose group) and increase to 2.0 mg/kg in the subsequent course. If a DLT is observed at 2.0 mg/kg in the low-dose group before escalating to 2.0 mg/kg in the medium-dose group, the dose will not be increased, and the committee will determine if further dose escalation is feasible. Patients unable to tolerate doses of 1.0 mg/kg or higher may have their doses

reduced. If tolerability cannot be established at 0.5 mg/kg after reduction, study treatment will be discontinued. Treatment can continue for up to four courses, but if the dose is reduced during a course, a fifth course will be administered within a total dose of 40 mg/kg (figure 1B). Investigators will make decisions regarding dose reduction or discontinuation. If a DLT is observed at 1.0 mg/kg, the next two patients will also begin treatment at 1.0 mg/kg.

All data from the medium-dose group will be evaluated by the DSMC. If the committee determines that tolerability cannot be confirmed, the study will be terminated. If tolerability is confirmed at 1.0 mg/kg in the medium-dose group, the next patient will start at 2.0 mg/kg (high-dose group), after confirming tolerability at 2.0 mg/kg in the medium-dose group. If tolerability cannot be confirmed in any course, the dose will be reduced to 1.0 mg/kg. If tolerability cannot be confirmed at 1.0 mg/kg, the dose will be further reduced to 0.5 mg/kg. If tolerability is confirmed at both 0.5 mg/kg and 1.0 mg/kg, the dose will be increased by one step. Administration will continue for up to four courses at 2.0 mg/kg, and if the dose is reduced during the course, a fifth course will be administered within a total dose of 40 mg/kg (figure 1C). Investigators will make the decision to reduce or discontinue the dose.

When the total dose after the fourth course reaches 40 mg/kg (high-dose group), or when the fourth course is 2 mg/kg and the total dose after the fourth course point reaches 35 mg/kg (medium- or high-dose group). In these scenarios, administering an additional 2 mg/kg in the fifth course would result in the total dose exceeding 40 mg/kg, and therefore, the dosing schedule excludes the fifth course in such cases.

Rationale for dose setting

PPMX-T003 has been tolerable up to 0.64 mg/kg in phase 1 studies involving patients with polycythaemia vera (unpublished data). While the tolerability of PPMX-T003 doses above 1.0 mg/kg remains unconfirmed, the estimated exposure at doses up to 2.0 mg/kg falls below the exposure levels observed in toxicity studies conducted on cynomolgus monkeys (no observable adverse effect level: 30 mg/kg).

This study employs an intra-subject ascending dose method to administer doses expected to demonstrate efficacy in all patients, given the high severity of ANKL. This approach is necessary due to the significant individual variability in PPMX-T003's pharmacological effects observed in non-clinical patient-derived xenograft models.

Risk benefit assessment

In this clinical trial, the protocol is designed to minimise risks to participants, although health benefits from administering PPMX-T003 cannot be guaranteed. Participants will be monitored for AEs and followed up appropriately until recovery is confirmed. The trial includes a dose escalation procedure, with each participant observed in an inpatient setting throughout. Safety reviews by the DSMC will be conducted as needed.

For the evaluation of DLTs during the first course, in the low- and medium-dose groups, if no DLTs are observed among the initially planned two participants, tolerability will be considered confirmed. If a DLT occurs in one of the initial participants at these dose levels, dose escalation will be held until tolerability is confirmed in three participants, including additional participants (ie, three out of four). If DLTs are observed in two or more of the four participants and the DSMC determines that tolerability is not acceptable, the study will be terminated. In the high-dose group, if no DLTs are observed among the initially planned three participants, tolerability will also be considered confirmed. If a DLT is observed in one of the three participants, an additional participant will be enrolled, and tolerability will be considered confirmed only if three out of the four participants are deemed to have tolerated the dose. If DLTs are observed in two or more of the four participants and the DSMC concludes that tolerability is not acceptable, the study will be terminated.

The DLT evaluation from the second course onward for each participant will be aggregated across all treatment groups and summarised by dose level and cumulative dose. If two cases of treatment discontinuation or unfavourable DLTs occur at a given dose level or cumulative dose (or three cases when the denominator is seven or more), enrolment will be held. The DSMC will then discuss the appropriateness of DLT evaluation, the feasibility of continuing the trial, and the tolerability of the treatment, and will provide recommendations to the investigators.

Safety

Safety assessments will include monitoring and recording all AEs, including all grades according to CTCAE V.5.0, and SAEs; laboratory tests for haematology, blood chemistry and urine values; regular vital sign checks and ECGs; and physical examinations. In the event of any trial-related injury, appropriate medical care and compensation will be provided. The sponsor has obtained clinical trial insurance to cover such events.

Adverse events (AEs)

An AE is any untoward medical occurrence in a participant receiving PPMX-T003. It is important to note that an AE may not necessarily be related to the drug.

Severe adverse events (SAEs)

An SAE is any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening (ie, the participant was at immediate risk of death from the AE when it occurred; this does not include an event that might have caused death if it had been more severe).

- Requires inpatient hospitalisation or prolongation of existing hospitalisation.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect (in the child of a participant who was exposed to PPMX-T003).
- Other important medical events, including IRR, anaemia and tumour lysis syndrome.

A TEAE is defined as an AE that emerges during treatment (from the first dose of PPMX-T003 until the end or discontinuation of the PPMX-T003 administration period).

Pharmacokinetics and anti-drug antibody (ADA)

Blood samples for pharmacokinetic analysis will be collected at the end of infusion, 4 and 8 hour (and if possible, 12 hours) after infusion on day 1, and before dosing from days 2 to 5, as well as at the end of infusion on days 2 and 5. In courses 2 and 3 (and course 4 for the low-dose group), blood samples will be collected before dosing on day 1 and at the end of infusion on days 1 and 5. In the final course, blood samples will be collected before dosing and at the end of infusion on day 1, and at the end of infusion, 4, 8 and 24 hours after infusion on day 5.

Blood samples for ADA analyses will be collected at the following times: before the first dose in course 1, on day 7 of the final course or when discontinuing the study, at discharge, 26 weeks after the initial PPMX-T003 dose and at the end of the follow-up period.

Data collection and management

Data collection will be conducted using a validated electronic case report form (eCRF). The investigators and other study staff involved in the preparation of the eCRF will receive training on the use of the system prior to completing the eCRF. Participants will be assigned unique identification codes and identified only by these codes in the eCRF. Investigators and other study staff will take appropriate precautions to protect participant confidentiality.

Case data entry, modification and tracking will be performed using a validated and secure electronic data capture system, based on source documents maintained by the principal and sub-investigators. Data management activities, including monitoring, query generation and resolution, and validation checks, will be conducted to ensure data integrity. Detailed procedures for data management will be described in a separate Data Management Plan.

Participants will be followed for a 26-week observation period after the first dose of the investigational drug. For participants who drop out during the study, follow-up will continue to the extent possible to collect information such as AEs and survival status. If an onsite visit is not feasible, relevant information may be obtained via telephone contact or written documentation from the referral medical institution.

Audits will be conducted by an auditor appointed by the coordinating investigator. The frequency, methods and scope of audits will be defined in the audit plan, and audits will be conducted independently of the coordinating investigator and site investigators. Corrective actions will be taken as necessary based on the audit findings.

Sample size

The number of participants was not determined through formal statistical hypothesis testing. Due to the extreme rarity of ANKL, the sample size is seven participants based on feasibility. However, if DLTs occur, additional participants may be enrolled to further evaluate tolerability. In the most extensive scenario, it is anticipated that two additional participants may be enrolled in both the low- and medium-dose groups, and one additional participant in the high-dose group. As a result, the total number of enrolled participants may reach up to twelve.

Statistical analysis

Continuous and categorical data will be summarised using descriptive statistics based on initial dose. The percentage calculations will use the number of participants relevant to each analysis as the denominator. Unless stated otherwise, baseline data will be the last available data collected prior to the first administration. The primary evaluation of DLT will be based on the initial dose during the first course. DLTs in subsequent courses will be assessed separately by dose level and cumulative dose. Safety evaluations will be summarised by dose level and cumulative dose during the treatment period. Efficacy (change in liver size measured by the product of maximum long and short diameters on CT scans and proportion of participants transitioning to chemotherapy) will be evaluated at the end of PPMX-T003. The pharmacokinetic analysis group will include all participants who received PPMX-T003 and had measurable PPMX-T003 concentrations, analysed according to the administered dose. Demographic information will be summarised for the safety analysis group. Medical history, concurrent medications and concurrent therapies will be listed individually for each participant.

End of the trial

Termination or suspension of the clinical trial

The clinical trial will be terminated or suspended if any of the following conditions make it difficult to continue:

- No efficacy for ANKL is observed in the first three participants who have received PPMX-T003.
- DLTs are observed in two participants per dose group.
- The DSMC decides to terminate the trial.
- Any other reasons (eg, the investigator decides to terminate the study due to significant or persistent non-compliance with the study protocol)

Discontinuation criteria for individual participants

Participants may withdraw from this clinical trial at any time of their own accord. The investigator may also decide to discontinue a participant's participation for

safety, behavioural or operational reasons. Administration of PPMX-T003 will be halted, for instance, if the investigator determines it necessary due to a DLT or an AE that impacts treatment.

Replacement of participants

If a DLT occurs in each dose group, additional participants may be added: two in the low and medium-dose groups and one in the high-dose group. Furthermore, if a participant withdraws from the trial for reasons unrelated to DLT (such as withdrawal of consent) during the first treatment course (receiving fewer than three doses of PPMX-T003), they are considered ineligible for DLT evaluation and can be replaced by another participant.

Trial status

The study is actively recruiting participants according to protocol version 3.2, dated 4 December 2024. Recruitment began on 1 April 2023, with the first participant enrolled on 21 September 2023. The study is expected to conclude by 31 March 2026.

Patient and public involvement statement

Patients and public were not involved in the design, conduct or reporting of this study.

Ethics and dissemination

This study received approval from the relevant institutional review boards (Hiroshima University hospital Institutional Review Board (approval number: 50046), Institutional Review Board of Tohoku University Hospital (approval number: 233006), Tokai University Hospital Institutional Review Board (approval number: 22–4002), Kyoto University Hospital Institutional Review Board (approval number: K099), Institutional Review Board of Okayama University Hospital (approval number: M20230208), Kyushu University Hospital Institutional Review Board (approval number: 2023304) and Hokkaido University Hospital Institutional Review Board (approval number: R5-7)). Additionally, this study will receive approval from the relevant institutional review boards in Nagoya University Hospital and Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital before enrolment in these hospitals. It will be conducted in line with the Declaration of Helsinki and Good Clinical Practice principles. The study protocol is registered with jRCT (Trial ID: jRCT2061230008) and ClinicalTrials.gov (identifier: NCT05863234). If significant protocol amendments are necessary, the investigators will discuss them and report them to the institutional review boards for approval. Findings will be published in peer-reviewed journals. The study team will follow the International Committee of Medical Journal Editors guidelines on authorship.

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