Platform Trial Synopsis

Version and date

6.0, 13-Nov-2025

Sponsor and protocol number

University of Birmingham, RG_21-124

Title

A Global Study of Novel Agents in Paediatric and Adolescent Relapsed and Refractory B-cell Non-Hodgkin Lymphoma (Glo-BNHL)

Indication

Relapsed/Refractory (r/r) paediatric and adolescent mature B-cell non-Hodgkin Lymphoma (B-NHL)

Chief Investigator

Professor Amos Burke, Cancer Research UK Clinical Trials Unit (CRCTU), University of Birmingham

Contents

Co-Investigators

Treatment Arm I: Bispecific Antibody (BsAb)

- Treatment Arm Leads: Professor Sarah Alexander, BC Children's Hospital, Canada and Dr Simon Bomken, The Great North Children's Hospital, UK
- Early Career Investigators: Dr Charles Phillips, Children's Hospital of Philadelphia, USA, and Dr Charlotte Rigaud, Gustave Roussy, France

Treatment Arm II: Antibody-drug conjugate (ADC) with standard chemotherapy

- Treatment Arm Leads: Dr Auke Beishuizen, Princess Máxima Center, The Netherlands, and Dr Birte Wistinghausen, Children's National Hospital, USA
- Early Career Investigators: Dr Emma Seaford, University Hospitals Bristol and Weston NHS Foundation Trust, UK, and Dr James Ford, Primary Children's Hospital, USA

Treatment Arm III: Chimeric antigen receptor (CAR) T-cells

- Treatment Arm Leads: Prof Véronique Minard, Gustave Roussy, France, and Dr Joerg Kruger, The Hospital for Sick Children, Canada
- Early Career Investigators: Dr Keri Toner, Children's National Hospital, USA, and Dr Friederike Meyer-Wentrup, Princess Máxima Center, The Netherlands

Trials Unit

Cancer Research UK Clinical Trials Unit (CRCTU), University of Birmingham

Chief Investigator

Professor Amos Burke

CRCTU Lead Biostatistician and Co-investigator:

Professor Lucinda Billingham

CRCTU Team Leader:

Mrs Anna Lawson

Trial logistics

Planned number of centres

Total = 45 (Europe = 30; International = 15)

Planned number of patients

Annual recruitment: 30 patients (7 years)
Total recruitment: 210 patients

Duration of the trial

- Treatment period: Dependent on treatment arm
- Follow-up period: Minimum of 2 years from treatment completion
- Planned First Patient First Visit (FPFV): 2024
- Planned Last Patient In (LPI): 2031
- Planned Last patient Last Visit (LPLV): 2033
- Planned study end: 2034

Current open treatment arms:

- Treatment Arm I
- Treatment Arm II

Glossary of terms

- ADC - Antibody-Drug Conjugate
- ALT - Alanine aminotransferase
- ANC - Absolute neutrophil count
- AST - Aspartate aminotransferase
- B-NHL - B-cell non-Hodgkin Lymphoma
- BsAb - Bispecific Antibody
- CAR T-cells - Chimeric Antigen Receptor T-cells
- CAYA – Children, Adolescents and Young Adults
- CNS - Central nervous system
- CR - Complete response
- CRCTU - Cancer Research Clinical Trials Unit
- CT - Computerised tomography
- DLBCL - Diffuse Large B-Cell Lymphoma
- EFS - Event free survival time
- GFR - Glomerular filtration rate
- HSCT - Haematopoietic stem cell transplantation
- Modified R-ICE - Rituximab plus Ifosfamide, Carboplatin, Etoposide and Dexamethasone
- MRI - Magnetic resonance imaging
- NCI CTCAE - National Cancer Institute Common Terminology Criteria for Adverse Events
- NOS - Not Otherwise Specified
- OR - Objective response
- OS - Overall survival time
- PD - Progressive disease
- PFS - Progression free survival time
- PMLBL - primary mediastinal large B-cell lymphoma
- PR - Partial response
- SD - Stable disease
- ULN - Upper limit of normal

Primary objective (see the evaluation criteria below)

Treatment Arm I: Bispecific Antibody (BsAb)

Estimate the clinical efficacy of BsAb treatment in patients with r/r B-NHL in either first (only one prior line of therapy) or subsequent relapse (more than one prior line of therapy).

Treatment Arm II: Antibody-drug conjugate (ADC) with standard chemotherapy

Estimate the clinical efficacy of an ADC treatment with modified R-ICE chemotherapy in patients with r/r B-NHL in first (only one prior line of therapy) or subsequent relapse (more than one prior line of therapy).

Treatment Arm III: Chimeric antigen receptor (CAR) T-cells

Estimate the efficacy of CAR T-cell therapy in r/r B-NHL patients who have CAR T-cell product available.

Secondary objectives (see the evaluation criteria below)

- Assess the safety profile of the novel agent in children, adolescents, and young adults (CAYA)
- Confirm the pharmacokinetics of the novel agent at the recommended trial dose in CAYA where relevant
- Any other treatment arm specific objectives (e.g. assess the relevant pharmacodynamic markers for the novel agent). These will be detailed in the relevant treatment arm sections of the protocol

Primary outcome measures

Treatment Arm I: BsAb

Occurrence of an objective response (OR) i.e. Complete Response (CR) or Partial Response (PR) after 12 weeks of treatment assessed by Independent Central Review (according to International Paediatric Non-Hodgkin Lymphoma Response Criteria)

Treatment Arm II: ADC with standard chemotherapy

Occurrence of CR within a maximum of three cycles of treatment assessed by Independent Central Review (according to International Paediatric Non-Hodgkin Lymphoma Response Criteria)

Treatment Arm III: CAR T-cells

Occurrence of OR following CAR T-cell infusion

Secondary outcome measures

All treatment arms

- Event-free survival time (EFS)
- Progression-free survival time (PFS)
- Overall survival time (OS)
- Best overall response (BOR) during treatment
- Duration of response (DOR)

Treatment arm specific

- Occurrence of an objective response (OR), where relevant
- Occurrence of adverse events of special interest (AESI)
- Occurrence of treatment emergent adverse events (TEAEs), where relevant
- Pharmacokinetic profile of novel agent, where relevant
- Pharmacodynamic markers, where relevant

Study methodology

Prospective, non-randomised platform trial with a Bayesian design evaluating novel therapies in three parallel arms:

Treatment Arm I: BsAb

Population: CAYA with r*/r** B-NHL in first relapse (only one prior line of therapy) or subsequent relapse (more than one prior line of therapy), including those achieving insufficient response (partial response (PR), stable disease (SD) or progressive disease (PD)) to previous therapy, including a different arm of this study

Treatment arm II: ADC with standard chemotherapy

Population: CAYA with r*/r** B-NHL in first relapse (only one prior line of therapy) or subsequent relapse (more than one prior line of therapy), including those achieving insufficient response (PR, SD, or PD) to previous therapy, including a different arm of this study

Treatment arm III: CAR T-cells

Population CAYA with r*/r** B-NHL in first relapse (only one prior line of therapy), or subsequent relapse (more than one prior line of therapy), including those achieving insufficient response (PR, SD, or PD) to previous therapy, including a different arm of this study

Patients may be eligible to enter more than one treatment arm during the lifetime of the platform study. Please see the patient flow schema in Appendix 1 for further information.

***Relapsed disease**

- Patients with radiologically and/or histologically proven relapse after previous CR (refer to inclusion criteria for specific requirements)

****Refractory disease**

- Patients with primary refractory disease
- Patients with PR (biopsy proven), SD, or PD to previous therapy (refer to inclusion criteria for specific requirements)

Eligibility criteria

Each treatment arm will have additional specific inclusion and exclusion criteria.

Glo-BNHL inclusion criteria (applicable to all treatment arms):

- Histologically proven mature high-grade B-NHL classified according to either:
  - the 5th edition of the World Health Organisation (WHO) Classification of Haematolymphoid Tumours (WHO-HAEM5), 2022 (diffuse large B-cell lymphoma - not otherwise specified (DLBCL - NOS), high-grade B-cell lymphoma with MYC and BCL-2 rearrangements, primary mediastinal large B-cell lymphoma, Burkitt's lymphoma, and high-grade B-cell lymphoma - NOS) at initial diagnosis; or
  - the revised 4th edition of the WHO Classification of Tumours of Haematopoietic and Lymphoid Tissue, 2017 (diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma/leukaemia or Burkitt-like lymphoma with 11q aberration, primary mediastinal large B-cell lymphoma (PMLBL), high-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements and high-grade B-cell lymphoma - (NOS)) at initial diagnosis
- Radiologically and/or histologically proven B-NHL in first relapse (only one prior line of therapy) or subsequent relapse (more than one prior line of therapy) or refractory B-NHL. In the following circumstances biopsy is mandated:
  - Relapsed or refractory disease following previous targeted therapy; biopsy required to confirm continuing target positivity, confirmed by immunohistochemistry or flow cytometry
  - Relapsed disease occurring more than two years after previous therapy; biopsy required to confirm relapsed disease
  - Relapsed or refractory disease following previous therapy within the Glo-BNHL platform; biopsy required to confirm relapsed disease
  - Partial Response (PR) to previous therapy; biopsy required to confirm active residual disease
- Evaluable disease as per the Revised International Paediatric Non-Hodgkin Lymphoma Staging System, including:
  - at least one bi-dimensionally measurable nodal lesion >1.5 cm in its longest dimension;
  - or at least one bi-dimensionally measurable extra-nodal lesion > 1.0 cm in its longest dimension on computerised tomography (CT) or Magnetic Resonance Imaging (MRI);
  - or bone marrow involvement (≥25% involvement from bone marrow, if only site of disease. Any standard method of assessment is acceptable i.e. cytomorphology, flow cytometry and/or immunohistochemistry);
  - or, dependent on treatment arm, evaluable Central Nervous System (CNS) disease§ (evaluable by imaging or Cerebrospinal Fluid (CSF) analysis)
- Aged from birth to ≤25 years old at the time of trial entry
- Performance status ≥50 using Karnofsky or Lansky performance scores
- Life expectancy ≥8 weeks
- Adequate bone marrow function documented by:
  - Platelet count ≥50 x 109/L (no platelet transfusion therapy within seven days prior to treatment), unless bone marrow involvement ‡
  - Absolute neutrophil count (ANC) ≥0.75 x 109/L (no granulocyte colony stimulating factor within 2 days prior to treatment), unless bone marrow involvement ‡
- Documented negative pregnancy test for female patients of childbearing potential within seven days prior to trial entry
- Patients of reproductive potential must agree to use effective contraception whilst on trial treatment and for 12 months following treatment discontinuation
- Written informed consent given by patient and/or parents/legal representative

§ CNS only disease
Patients with CNS only disease may be eligible depending on the treatment arm. Please refer to the relevant treatment arm specific eligibility criteria.

‡ Bone marrow involvement
Patients who have ≥25% blasts in the bone marrow are considered to have bone marrow involvement. For these patients, requirements for bone marrow function do not apply.

Glo-BNHL exclusion criteria (applicable to all treatment arms):

- B-cell Acute Lymphoblastic Leukaemia (B-ALL)/B-cell Lymphoblastic Lymphoma (B-LBL)
- Patients with post-transplant lymphoproliferative disorder (PTLD)
- Patients with primary CNS lymphoma
- Patients within:
  - 90 days after an allogenic HSCT procedure
  - 45 days after an autologous HSCT procedure
  - 28 days of experiencing graft versus host disease (GvHD) requiring systemic therapy, and/or immunosuppressive treatment
  - 14 days of previous investigational treatment
  - 28 days of receiving craniospinal radiation, unless otherwise specified in the treatment arm specific eligibility criteria; or 14 days of any other radiation
  - For patients who have received any CAR T-cell therapy or other cellular therapies, see treatment arm specific eligibility criteria
- Patients who have ongoing acute toxicities from most recent lymphoma directed therapy (any toxicity ≥ grade 3 not otherwise defined in the exclusion criteria)
- Patients who have received any cytoreductive or other chemotherapy in the last 7 days prior to trial entry
- Patients with known DNA repair disorder or known primary immunodeficiency
- Patients who are pregnant or breastfeeding (exclusively or partially)
- Patients for whom non-compliance with treatment, trial procedures, or protocol follow up schedule is expected and all available resources to facilitate inclusion have been exhausted
- Uncontrolled concomitant infection. Severe infection (such as sepsis, pneumonia, etc.) should be clinically controlled at the time of trial entry.
- Known HIV positivity
- Hepatitis B carrier status, history of Hepatitis B Virus, or positive serology. A patient is considered as a Hepatitis B Virus carrier or to have (had) Hepatitis B Virus infection in case of:
  - Unimmunized and HBsAg and/or anti-HBs antibody and/or anti-HBc antibody positive, or
  - Immunized and HBsAg and/or anti-HBc antibody positive
- Live vaccine within 28 days prior to trial entry
- Known history of hypersensitivity to any of the treatments or excipients

Translational research studies

There will be prospective sample collection for an embedded biological study and further biological studies may be added throughout the lifetime of the platform.

Further details are supplied in the full study protocol.

Evaluation during treatment and follow-up

Response will be measured in accordance with the International Paediatric Non-Hodgkin Lymphoma Response Criteria.

Patients will be followed up for a minimum of two years after completion of treatment. Data on outcomes, events and any further treatment given will be collected.

Patients enrolled on to Treatment Arm III (CAR T-cells) may undergo longer term follow up in accordance with regulatory requirements.

Statistical methodology and sample size determination

The trial will use a Bayesian approach to estimation and decision-making in each treatment arm.

The primary outcome measure for each arm is a binary variable representing treatment success and therefore, the statistical analysis plan will be a simple beta-binomial conjugate analysis combining the observed trial data with a minimally-informative prior distribution. The posterior probability distribution will be used to:

(i) estimate the true success rate with 95% credible intervals to indicate the level of uncertainty and

(ii) determine the probability that the true success rate is greater than a clinically relevant critical target rate thereby enabling a GO/No GO decision.

Secondary outcome measures analysed by CRCTU will use a Bayesian approach that will generate estimates and 95% credible intervals for each outcome based on the observed data and minimally informative prior distributions.

The target sample size for the initial stage of the trial is at least 15 patients in each treatment arm (or sub-group) and is sufficient to provide initial robust decision-making. Should a treatment arm be declared worthy of further consideration based on the transition analysis of 15 patients, then there will be an option to expand the cohort to a larger number to provide evidence to support a marketing authorisation application. The expansion stage is provisionally planned to recruit a further 15 evaluable patients, after which a confirmatory analysis will take place including all evaluable patients from the initial and expansion stages.

Interim analyses to allow early stopping for futility are planned throughout both stages of the trial. At these stopping points, the predicted probability of success will be calculated given the current observed data and the clinically relevant target response rates. Success during the initial and expansion stages is a GO decision at the transition and confirmatory analyses respectively.

GO decision criteria at the transition analysis is a probability of at least 0.8 that the true response rate is above the target response rate, while the GO decision criteria at the confirmatory analysis is a probability of at least 0.95 that the true response rate is above the target response rate.

Operating characteristics for each of the open treatment arms are summarised below.

Treatment Arm I: BsAb

Sub-group A: For patients with first relapse (only one prior line of therapy) or refractory disease, the clinically meaningful target OR rate is 40%.
With 15 patients, the trial would have <0.05 probability of an incorrect GO decision for any true OR rate ≤30% and >0.8 probability of a correct GO decision for any true OR rate ≥61%. A GO decision at the transition analysis would require an observed OR rate of at least 8/15 patients (Bayesian estimate 53%).
With at least 30 patients, the trial would have <0.05 probability of an incorrect GO decision for any true OR rate ≤41% and >0.8 probability of a correct GO decision for any true OR rate ≥65%. A GO decision at the confirmatory analysis would require an observed OR rate of at least 17/30 patients (Bayesian estimate 56%).

Sub-group B: For patients with subsequent relapse (more than one prior line of therapy), the clinically meaningful target OR rate is 10%.

With 15 patients, the trial would have <0.05 probability of an incorrect GO decision for any true OR rate ≤5% and >0.8 probability of a correct GO decision for any true OR rate ≥27%. A GO decision at the transition analysis would require an observed OR rate of at least 3/15 patients (Bayesian estimate 22%).

With at least 30 patients, the trial would have <0.05 probability of an incorrect GO decision for any true OR rate ≤9% and >0.8 probability of a correct GO decision for any true OR rate ≥29%. A GO decision at the confirmatory analysis would require an observed OR rate of at least 6/30 patients (Bayesian estimate 21%).

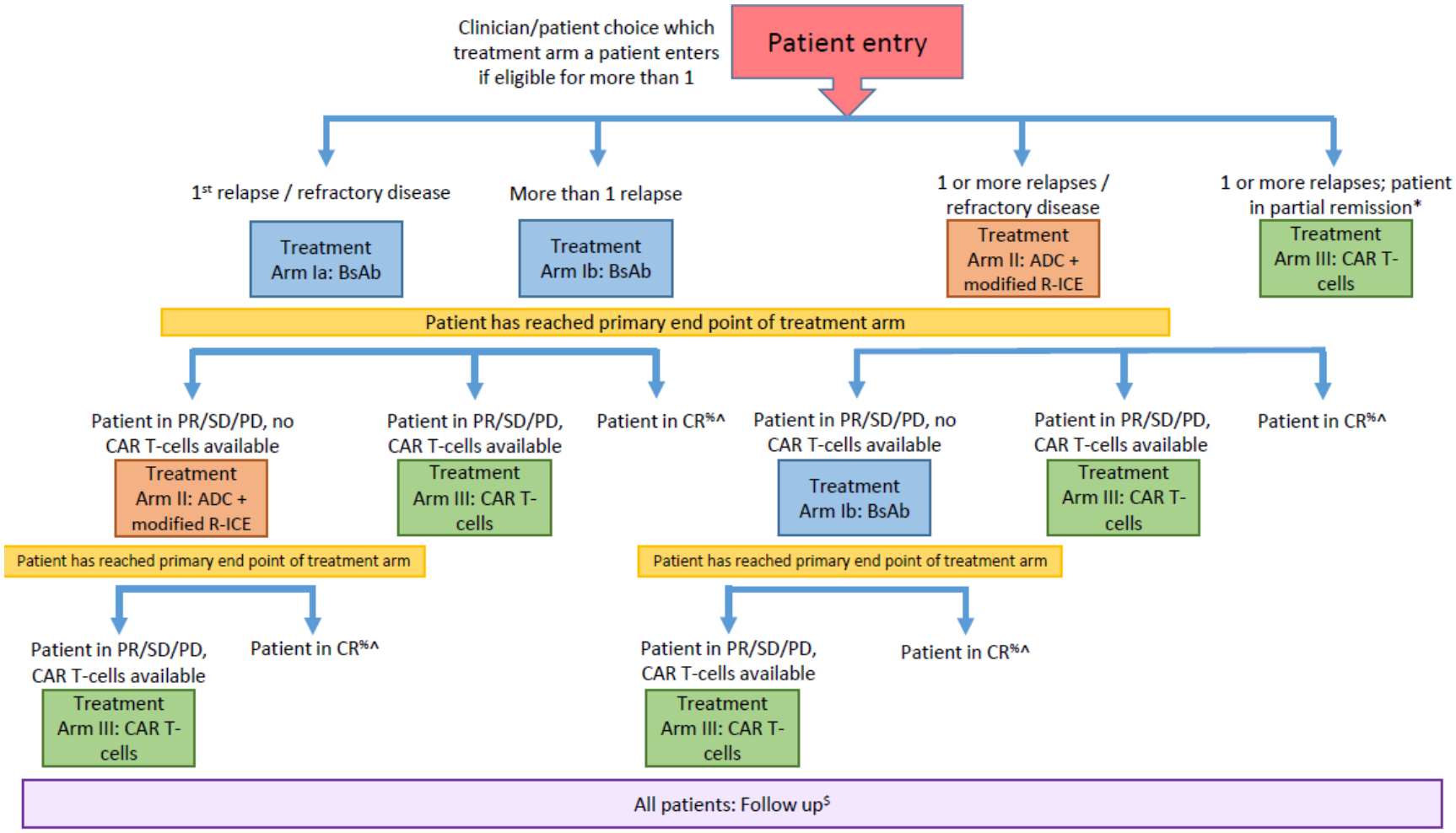
Treatment arm II: ADC with standard chemotherapy

The clinically meaningful target CR rate is 20%.

With 15 patients, the trial would have <0.05 probability of an incorrect GO decision for any true CR rate ≤14% and >0.8 probability of a correct GO decision for any true CR rate ≥41%. A GO decision at the transition analysis would require an observed CR rate of at least 5/15 patients (Bayesian estimate 35%)

With at least 30 patients, the trial would have <0.05 probability of an incorrect GO decision for any true CR rate ≤20% and >0.8 probability of a correct GO decision for any true CR rate ≥43%. A GO decision at the confirmatory analysis would require an observed CR rate of at least 10/30 patients (Bayesian estimate 34%).

Appendix 1 – Patient flow diagram



*Dependent on agent in treatment arm – specified in protocol

$Continue to follow up patient and report any subsequent treatment data

%Patient may stay on treatment – as defined in protocol

^Patients in CR may receive HSCT and will continue to be followed up

Acronyms:

ADC = Antibody-Drug Conjugates
BsAb = Bispecific Antibodies
CAR T-cells = Chimeric Antigen Receptor T-cells
CR = Complete response
HSCT = Haematopoietic Stem Cell Transplant
Modified R-ICE = Rituximab plus Ifosfamide, Carboplatin, Etoposide and Dexamethasone
PD = Progressive disease
PR = Partial response
SD = Stable disease

Glo-BNHL Patient Flow Schema V2.0_02-Jun-2023

Patient flow through the Glo-BNHL platform

Acronyms

- ADC = Antibody-Drug Conjugates
- BsAb = Bispecific Antibodies
- CAR T-cells = Chimeric Antigen Receptor T-cells
- CR = Complete response
- HSCT = Haematopoietic Stem Cell Transplant
- Modified R-ICE = Rituximab plus Ifosfamide, Carboplatin, Etoposide and Dexamethasone
- PD = Progressive disease
- PR = Partial response
- SD = Stable disease

It is clinician/parent choice which treatment arm a patient enters, if they are eligible for more than one.

Patient Entry - Treatment Arm I: BsAb (TAI)

At entry, if a patient is in first relapse or refractory disease, they may be eligible for TAIa. If the patient has had more than one relapse, they may be eligible for TAIb. When the patient reaches the primary end point for TAIa/TAIb, subsequent treatment will be guided by the patient's disease status.

- If they have PR, SD, PD or no CAR T-cells available, they may be eligible for Treatment Arm II: ADC + modified R-ICE (TAII). When the patient reaches the primary end point for TAII, subsequent treatment will be guided by the patient's disease status.
  - If they have PR, SD, PD and have CAR T-cells available, they may be eligible for Treatment Arm III: CAR T-cells (TAIII).
  - If they have a CR, they may stay on treatment as defined in the protocol or receive HSCT and continue to be followed up.
- If they have PR, SD, PD and have CAR T-cells available, they may be eligible for TAIII.
- If they have a CR, they may stay on treatment as defined in the protocol or receive HSCT and continue to be followed up.

Patient Entry - Treatment Arm II: ADC + modified R-ICE (TAII)

At entry, if a patient has had one or more relapses or refractory disease, they may be eligible for TAII. When the patient reaches the primary end point for TAII, subsequent treatment will be guided by the patient's disease status.

- If they have PR, SD, PD or no CAR T-cells available, they may be eligible for TAIb. When the patient reaches the primary end point for TAIb, subsequent treatment will be guided by the patient's disease status.
  - If they have PR, SD, PD and have CAR T-cells available, they may be eligible for TAIII.
  - If they have CR, they may stay on treatment as defined in the protocol or receive HSCT and continue to be followed up.
- If they have PR, SD, PD and have CAR T-cells available, they may be eligible for TAIII.
- If they have a CR, they may stay on treatment as defined in the protocol or receive HSCT and continue to be followed up.

Patient Entry - Treatment Arm III: CAR T-cells (TAIII)

At entry, if a patient has had one or more relapses or is in PR, they may be eligible for TAIII.

After completing trial treatment, all patients will continue to be followed up and any subsequent treatment data should be reported.