GLO-BNHL

A Global Study of Novel Agents in Paediatric and Adolescent Relapsed and Refractory B-cell non-Hodgkin Lymphoma

TRIAL DESIGN

Glo-BNHL is an adaptive prospective early phase international multicentre platform clinical trial designed to evaluate the safety and efficacy of novel agents for the treatment of children, adolescents and young adults with relapsed and/or refractory B-cell non-Hodgkin Lymphoma (r/r B-NHL).

Novel agents will be prioritised for inclusion in the platform according to an overarching prioritisation list and a robust systematic scientific assessment, performed by the international Trial Steering Committee (TSC). The platform consists of three parallel treatment arms, each one investigating a different novel agent in a group of patients. The platform allows the testing of a pipeline of novel agents in each treatment arm sequentially. Patients in the platform may be enrolled into any of the available treatment arms for which they are eligible. The classes of novel agents prioritised for inclusion at the initiation of the trial are:

- Treatment Arm I: bispecific antibody (BsAb)
- Treatment Arm II: antibody-drug conjugate (ADC) with standard chemotherapy
- Treatment Arm III: chimeric antigen receptor (CAR) T-cells

The platform trial has an adaptive Bayesian design that facilitates efficient GO/NoGO decisions relevant to the target population enrolled in each treatment arm. The Bayesian approach estimates the probability that a novel agent is clinically effective and enables decision-making even with small numbers of patients. It can also incorporate prior knowledge, thereby maximising the utility of all available data in this rare population. It allows continuous evaluation of any novel agent as the sample size increases and the discontinuation of an agent, if the observed trial data demonstrate a high probability that the novel agent is ineffective at any time, allowing the next agent in the pipeline to be introduced. If the prioritisation of classes of novel agents by the Trial Steering Committee (TSC) changes, treatment arms can be amended to reflect this.

OBJECTIVES

Primary Objectives

- Treatment Arm I: 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: ADC with standard chemotherapy: Estimate the clinical efficacy of ADC treatment with modified R-ICE (rituximab, ifosfamide, carboplatin, etoposide and dexamethasone) 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: CAR T-cells: Estimate the efficacy of CAR T-cell therapy in r/r BNHL patients who have CAR T-cell product available

Secondary Objectives

- Assess the safety profile of the novel agent in children, adolescents and young adults

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- Confirm the pharmacokinetics of the novel agent at the recommended trial dose in children, adolescents and young adults, 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.

OUTCOME MEASURES

Primary Outcome Measures

- Treatment Arm I: BsAb: Occurrence of an objective response ((OR) i.e. Complete Response (CR) or Partial Response (PR) as their best response (timeframe dependent on the asset under investigation) assessed according to International Paediatric Non-Hodgkin Lymphoma Response Criteria)
- Treatment Arm II: ADC with standard chemotherapy: Occurrence of CR following a maximum of three cycles of treatment
- Treatment Arm III: CAR T-cells: Occurrence of OR following CAR T-cell infusion

Secondary Outcome Measures

- Event-free survival time (EFS)
- Overall survival time (OS)
- Incidence and severity of adverse events defined by the National Cancer Institute Common Terminology Criteria for Adverse Events
- Pharmacokinetic profile of novel agent, where relevant
- Pharmacodynamics markers, where relevant

PATIENT POPULATION

Treatment arm	Population
I: BsAB	Children, adolescents and young adults with relapsed*/refractory** 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 ADC with standard chemotherapy to progress to HSCT or those without available CAR T-cells
II: ADC with standard chemotherapy	Children, adolescents and young adults with relapsed*/refractory** B-NHL in first relapse (only one prior line of therapy) or subsequent (more than one prior line of therapy relapse), including those achieving insufficient response PR, SD or PD) to BsAb therapy to progress to HSCT or those without available CAR T-cells
III: CAR T-cells	Children, adolescents and young adults with relapsed*/refractory** B-NHL who have had insufficient response (PR, SD, PD to prior therapy to progress to HSCT) and have CAR T-cell product available
* Late relapsed disease For patients who relapse more than one year after their last treatment, a biopsy is recommended to confirm the relapse diagnosis. If relapse occurs after two years after the last treatment, a biopsy is mandated (see exclusion criteria). ** Refractory disease The following patients are considered to have refractory disease and can be included in this trial: Patients who do not achieve PR or CR with last therapy Patients with partial response to last relapse therapy (biopsy proven), with no evidence of progression.	

SAMPLE SIZE

The initial target sample size is 15 evaluable patients in each treatment arm or relevant sub-group. Data will be reviewed by an independent Data Monitoring Committee (DMC) at regular intervals in recruitment to each treatment arm. Should the observed trial results for the initial 15 evaluable patients be sufficiently promising to deliver a GO decision, and further data is required (for example, to further confirm safety or efficacy), then an expansion cohort to recruit up to a further 15 evaluable patients will be considered. At this point, advice may be sought from the relevent regulatory agencies to ascertain the requirements for the expansion cohort. Data from the initial 15 patients will be combined with the data from the expansion cohort to provide data for the confirmatory analysis. It is anticipated this will be up to a maximum of 30 patients. Data will continue to be reviewed at regular intervals to allow efficacy and futility decisions to continue.

MAIN ELIGIBILITY CRITERIA

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

- Histologically proven mature B-NHL (Diffuse Large B-Cell Lymphoma (DLBCL), Burkitt Lymphoma/Leukemia or atypical Burkitt/Burkitt-like lymphoma, primary mediastinal large B-cell lymphoma (PMLBL), and mature B-NHL/Not Otherwise Specified (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. (Note: relapses following prior targeted therapy must have continuing target positivity, confirmed by an established method).
- If relapse occurs more than two years after previous therapy, a biopsy must be performed
- Evaluable disease as per the International Paediatric non-Hodgkin Lymphoma Response Criteria, 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 evaluable Central Nervous System (CNS) only disease (evaluable by imaging or Cerebrospinal Fluid (CSF) analysis)
- Age ≥6 months and <25 years old at the time of trial entry
- Performance status ≥50 using Karnofsky or Lansky performance scores
- Life expectancy of ≥8 weeks
- Adequate bone marrow function documented by:
    - Platelet count ≥50x 10^9/L (no platelet transfusion therapy within seven days prior to treatment) unless bone marrow involvement‡
    - Absolute neutrophil count (ANC) ≥ 0.75 x 10^9/L (no granulocyte colony stimulating factor within 2 days prior to treatment) unless bone marrow involvement‡
- Adequate hepatic function documented by:
    - Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) ≤5 x upper limit of normal (ULN)
    - Total bilirubin ≤1.5 X ULN
        - Patients with known Gilbert syndrome will be excluded if the total bilirubin value is >4 x ULN for the local general population
- Documented negative pregnancy test for female patients of childbearing potential within seven days prior to trial entry (see Appendix 1 for details)
- Patients of childbearing potential must agree to use effective contraception whilst on trial treatment and for 12 months following treatment discontinuation (see Appendix 1 for details)
- Written informed consent given by patient and/or parents/legal representative

†Refractory disease

The following patients are considered to have refractory disease and can be included in this trial:

- Patients with who do not achieve PR or CR with last therapy
- Patients with partial response to last therapy (biopsy proven), with no evidence of progression

‡ Bone marrow involvement

Patients who have ≥ 25% blasts in the bone marrow are considered to have bone marrow involvement. Requirements for bone marrow function do not apply to these patients.

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

- B-cell Acute Lymphoblastic Leukaemia (B-ALL)/B-cell Lymphoblastic Lymphoma (B-LBL)
- Patients within 90 days of an allogenic HSCT procedure
- Patients within 45 days of an autologous HSCT procedure
- Patients who have experienced graft versus host disease (GvHD) requiring therapy, and/or immunosuppressive treatment

- Patients within 42 days of any CAR T-cell therapy or other cellular therapies
- Patients who are pregnant or breastfeeding (exclusively or partially)
- Patients who cannot regularly be followed up in accordance with the protocol due to psychological, social, geographical or other issues
- Patients for whom non-compliance with treatment or trial procedures is expected
- Uncontrolled concomitant infection. Severe infection (such as sepsis, pneumonia, etc.) should be clinically controlled at the time of trial entry
- Known positive HIV serology
- Hepatitis B carrier status, history of Hepatitis B Virus or positive serology. A patient is considered as Hepatitis B Virus carrier or to have (had) Hepatitis B Virus infection in case of:
    - HBsAg positive
- Previous investigational treatment within 14 days prior to trial entry
- Live vaccine within 28 days prior to trial entry
- Known history of hypersensitivity to any of the treatments or excipients

SUB-STUDIES

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

TRIAL DURATION

Assuming 30 patients are recruited per year across all treatment arms, recruitment over seven years will allow for the sequential assessment of several agents and the potential inclusion of expansion cohorts for any agent showing promise. Patients will be followed up for a minimum of two years following trial entry.

TRIALS OFFICE CONTACT DETAILS

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OVERALL TRIAL SCHEMA