# Global Study of Novel Agents in Paediatric and Adolescent Relapsed and Refractory B-NHL

## Background

The Glo-BNHL trial has been developed as a direct output of the 2nd ACCELERATE Paediatric Strategy Forum [1]. Following this forum an International Working Group was formed to address the following specific goals:

- To identify which of the many potential new drugs would have the optimal probability of improving rates of cure in paediatric patients with chemo-resistant B-cell malignancies
- To design and execute scientifically sound studies in a very small international population of children with relapsed mature B-cell malignancies

Several challenges had to be overcome including too many potential assets of interest to be evaluated in a rare paediatric population (estimated 50-70 patients with relapsed/refractory B- cell Non-Hodgkin Lymphoma (B-NHL) per year globally). International collaboration and a platform-trial infrastructure were recognised as requirements and have led to the development of the Glo-BNHL trial.

## Overview

Glo-BNHL is an international academic-led early phase clinical trial designed to efficiently assess multiple prioritised novel agents in paediatric patients with relapsed and refractory B-NHL. It is sponsored by the University of Birmingham and managed by the Cancer Research UK Clinical Trials Unit (CRCTU) in Birmingham.

CRCTU is one of the largest cancer trials units in the UK and has the expertise to manage international clinical trials of Investigational Medicinal Products. Core-funded by Cancer Research UK, it is a fully registered UK Clinical Research Collaboration (UKCRC) Clinical Trials Unit and a member of the National Cancer Research Institute (NCRI) Clinical Trials Unit Group. The University of Birmingham has previously been independently reviewed and approved to act as the European Sponsor for the Innovative Therapies for Children with Cancer (ITCC) consortium multi-country early phase clinical trials in children with cancer.

This global trial will open in multiple sites across Europe, North America and Australasia. Using a well-established hub and spoke management model the CRCTU will arrange Coordinating Centre Agreements with a National Co-ordinating Centre (NCC) in each country that will be responsible for regulatory submissions and management of the study within that country. As Sponsor and lead trial coordinating centre, the University of Birmingham and CRCTU will retain oversight of the conduct of the NCCs.

The trial will be run in compliance with national and international regulatory requirements and in accordance with the University and CRCTU's quality management system and associated standard operating procedures. The conduct of the trial and the data generated will meet International Conference on Harmonisation Good Clinical Practice (ICH GCP) standards to facilitate regulatory submissions.

## Prioritisation

Prioritisation of potential agents for inclusion in the Glo-BNHL trial is a key element of the platform given the rarity of relapsed B-NHL in the paediatric population and the number of potential assets.

The primary class prioritisation was delivered through the multi-stakeholder ACCELERATE Paediatric Strategy Forum. The published consensus was that the following three classes of agents held the greatest potential for benefit in paediatric relapsed and refractory B-NHL, based on their mechanism-of-action [1]:

- T-cell engagers (Bi-specific antibodies)
- Antibody-drug conjugates (excluding those carrying a vinca alkaloid-like drug)
- Chimeric antigen receptor (CAR) T-cells

In addition, it was felt that new trials using cell signalling inhibitors should not commence until the final results of the SPARKLE trial [2] were known. An iterative 'living prioritisation' approach has been adopted as part of the Glo-BNHL Platform to ensure this overarching mechanism-of-action prioritisation list is up to date. Members of the Trial Steering Committee (TSC) have committed to conducting this re-prioritisation on a regular basis (every 18 months to 2 years) with earlier review if a significant change in the treatment landscape becomes apparent.

Specific agents within the three classes noted above will currently be prioritised for entry into the Glo-BNHL trial, however consideration will be given to any proposed novel agent. Potential assets will be assessed by the TSC using a robust scientific systematic approach comprising pre-defined scoring criteria. The TSC includes voting members (Independent Chair, Chief Investigator, Sponsor Representative, globally-representative academic clinicians, statisticians and parent representatives) and non-voting trial management group representatives. The TSC are bound by the TSC Charter and a Confidentiality Agreement with the University of Birmingham.

### Submission of Asset Information

Information regarding a potential asset for consideration for inclusion in the trial should be submitted electronically to the trial mailbox: Glo-BNHL@trials.bham.ac.uk.

This documentation should include a completed summary sheet (Appendix 1 of this pack) and additional detailed information (in any suitable format) covering the following information:

- Primary target, mechanism-of-action and scientific rationale for the target
- Pre-clinical data
    - Details of cell lines and models used
    - Concentration range tested and relation to human dosing
    - Observed responses and validation
- Clinical data
    - Safety data in adults including severity and frequency of Adverse Events, ability to support/modify toxicity and details of population in whom tested
    - Efficacy data in adults including details of tumour types, population, dosing regimens, study design and end-points
    - Any early safety/efficacy data in paediatrics if available (any disease)
- Feasibility in paediatrics
    - Plans for development of paediatric formulation (if applicable)
    - Pharmacokinetic studies or modelling supporting starting dose decision in children (if available)

Members of the TSC will review the information pack. A decision regarding inclusion in the trial will be reached during offline review of the documentation and a TSC teleconference. Every reasonable effort will be made for all TSC members to be present however the minimum attendees required for the TSC to be quorate for decision-making has been defined in the approved CRCTU Charter as "at least 7 members, including the statistician, one trial management group member and three clinicians (including the Chair, unless otherwise agreed)". Additionally a teleconference will be offered between the relevant Industry partner and the Sponsor/Chief Investigator to allow for questions and clarifications prior to a final decision being reached.

The TSC have committed to returning the final decision regarding inclusion of the asset in the Glo-BNHL trial within 4 weeks of receipt of the information pack. The prioritisation decision will be returned in writing alongside a detailed summary of the rationale to facilitate subsequent interaction with the relevant regulatory bodies.

## Trials Office Contact Details

Glo-BNHL Trials Office
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1. Pearson ADJ, Scobie N, Norga K, et al. ACCELERATE and European Medicine Agency Paediatric Strategy Forum for medicinal product development for mature B-cell malignancies in children. *Eur J Cancer* 2019; **110**: 74-85
2. Burke GAA, Beishuizen A, Bhojwani D, et al. Ibrutinib plus CIT for R/R mature B-NHL in children (SPARKLE trial): initial safety, pharmacokinetics, and efficacy. *Leukemia* 2020

## APPENDIX 1: Summary of Proposed Asset

| | |
|---|---|
| **Proper Name** | |
| **Proprietary Name** | |
| **Proposer / Contact** | |
| **Manufacturer** | |

**Regulatory Requirements**

| | *Please tick* | | | |
|---|---|---|---|---|
| Do you have an approved Paediatric Investigation Plan (PIP)? | No | ☐ | Yes | ☐ |
| Do you have an agreed Paediatric Study Plan (PSP)? | No | ☐ | Yes | ☐ |

- If yes, please attach the approved document(s)
- If no, please describe the current stage of development including any submission timelines

**Clinical Trial Design**

| | *Please tick* |
|---|---|
| Do you foresee any difficulties with the current protocol (*see Trial Synopsis*) in relation to your proposed asset? | No ☐ Yes ☐ |

- If yes, please detail these on a separate sheet and submit alongside asset information

**Statistical Trial Design**

| | *Please tick* |
|---|---|
| Do you anticipate assessment of your asset requiring a change to the planned outcome measures (*see Trial Synopsis*)? | No ☐ Yes ☐ |

- If yes, please detail these on a separate sheet

**Please return this completed form alongside the detailed potential asset information to Glo-BNHL@trials.bham.ac.uk**