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626.AGGRESSIVE LYMPHOMAS: PROSPECTIVE THERAPEUTIC TRIALS

A Potential Paradigm for the Robust and Systematic Prioritisation of Assets in Academic-Led, Multi-Industry Collaborative Trials in Rare Populations (Glo-BNHL)

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Overview

Given the rarity of children and adolescents with relapsed and refractory (r/r) B-cell Non-Hodgkin Lymphoma (B-NHL) and the large number of potential agents in development for adult mature B-cell malignancies, there is urgent need for prioritisation of agents as proposed by the ACCELERATE Paediatric Strategy Forum for medicinal development in paediatric B-NHL (Pearson 2019). The process developed for the global platform study Glo-BNHL (published separately) is described here.

Prioritisation process

Assets submitted for review by industry collaborators are prioritised under Confidentiality Disclosure Agreements by the Glo-BNHL Trial Steering Committee (TSC) comprising expert clinicians, statisticians and patient representatives. The assessment includes a quantitative element addressing each of the following areas, with greater weighting given to more relevant criteria such as paediatric-specific and clinical data.

- Target and scientific rationale
- Asset position within current prioritisation strategy*
- Pre-clinical data evaluating *in vitro* sensitivity, including the number, heterogeneity and relevance of cell lines tested and quality of the submitted elements of evidence
- Pre-clinical data evaluating *in vivo* activity of the asset including the number, type and relevance of models and quality of the elements of evidence submitted
- Clinical data regarding monotherapy efficacy in single arm and randomised trials, including the disease-type and therapeutic regimen studied
- Clinical data regarding combination efficacy (if studied)
- Clinical data regarding safety of the agent with regard to frequency, severity and modifiability of adverse events, including applicability to the paediatric population
- Feasibility of delivery in paediatrics, including formulation and dose-confirmation processes

**Classes of novel agents prioritised for inclusion at the initiation of the trial were: (1) Bispecific antibodies (2) antibody-drug conjugates (3) chimeric antigen receptor T-cell products. The TSC has committed to updating this list as the field evolves.* The assessment also includes a qualitative element incorporating expert opinion regarding relevance of the target, mechanism of action, and overall impression of the asset. These elements are combined to inform the final discussion before a decision is made.

A formal written response from the Sponsor and TSC Chair outlining the TSC decision on whether the asset has been prioritised for evaluation within Glo-BNHL, and associated rationale, is issued to the relevant industry partner (now also copied to the European Medicines Agency (EMA)) within 28 days of receipt of the asset information pack. A follow-up clarification meeting is offered. For prioritised assets, following agreement from the relevant industry partner, the process of formal inclusion in Glo-BNHL then begins.

Scope of assets reviewed

Between September 2020 and June 2023, information packs for 7 assets were submitted for review from 6 pharmaceutical companies. The assets spanned 5 classes of drugs: 3 bispecific antibodies, 1 antibody-drug conjugate, 1 chimeric antigen receptor T-cell product, 1 small molecule inhibitor and 1 immunomodulator. Formal responses were issued within a median of 20 days (mean 21.3 days) followed by a clarification meeting on 5 occasions.

Prioritised assets

Four of the 7 reviewed assets were prioritised for inclusion within Glo-BNHL. At time of planned opening only 2 of these assets are included. The other 2 assets are being investigated in industry-led competitive trials. A further asset was deemed to be of potential interest but insufficient data were available due to the early stage of development to reach a final conclusion (further review pending).

Non-prioritised assets

The rationale for non-prioritisation of assets included irrelevant target in paediatric B-NHL, insufficiently convincing mechanism of action, and lack of superiority over other agents within a non-prioritised class. The EMA has subsequently waived the obligation to submit the results of paediatric B-NHL studies for both non-prioritised assets reasoning they do not represent potential for significant therapeutic benefit.

Summary

The Glo-BNHL international platform trial prioritisation process represents a model for handling the challenge of development of multiple potential agents in very rare populations in the global arena.

Disclosures Gore: Amgen: Consultancy; Novartis: Consultancy; Roche: Consultancy. **Minard-Colin:** BMS: Consultancy; Adaptimmune Therapeutics plc: Consultancy; Roche: Consultancy; Aztra: Consultancy. **Bollard:** Cabaletta Bio, Catamaran Bio: Current equity holder in private company, Current equity holder in publicly-traded company, Current holder of stock options in a privately-held company, Membership on an entity's Board of Directors or advisory committees, Patents & Royalties: Patent applications in CAR-NKs; Roche: Consultancy. **Allen:** Sobi: Consultancy. **Auperin:** MSD France: Consultancy. **Burke:** Novartis: Consultancy.

Table 1. Glo-BNHL prioritisation: systematic scoring tool

Domain	Evidence	Considerations	Outcome	Quality	Weight
Target and scientific rationale	- Primary target +/- pathway - Mechanism-of-action	Scientific rationale for target, evidence of dependence in paediatric B-NHL	-	-	-
Prioritisation	Asset position within current prioritisation strategy	-	1 = currently prioritised MoA class 0.5 = not currently prioritised class but scientific rationale worthy of further study 0.1 = non-prioritised class and not deemed adequately relevant at current timepoint	N/A	1
Pre-clinical in vitro	In vitro sensitivity to asset - IC50 observed after 72 hours*	- Type of cell lines tested: established or patient-derived - Number of cell lines (target/control) tested - Relevance of concentration range tested - Validation of biological efficacy (e.g. effects on apoptosis, proliferation, cell cycle, migration, gene or protein expression)	1 = IC50 <500nM or ≤ clinically relevant concentration 0.6 = IC50 = 500 - 1500nM 0.2 = IC50 >1500 nM 0 = No activity (IC50 > 10uM)	1 = >2 cell lines representing the heterogeneity of paediatric B-NHL; plus validation 0.5 = 2-5 cell lines covering disease relevant to paediatric B-NHL; plus validation 0.2 = <2 cell lines relevant to paediatric B-NHL and/or lack of control and/or lack of validation	0.4
Pre-clinical in vivo	In vivo activity of asset - in vivo tumour response	- Number of models used - Type of models used: xenograft/PDX/GEMM - Dosing schedule used - Measurement of pharmacodynamic markers in tumour (e.g. target inhibition, pathway modulation, biologic effect) and/or phenotypic response - Efficacy-PK-PD relationships**	1 = Response comparable to CR/PR 0.6 = Response comparable to SD 0.2 = Very minor response (between SD and PD, slight TGI) 0 = No activity or clear PD, growth comparable to control	1 = ≥ 2 xenograft models or 1 transgenic mouse model with appropriate control; treatment with clinically relevant dose; validation 0.6 = 1 xenograft model with appropriate control; treatment with clinically relevant dose; validation 0.2 = 1 xenograft model OR use of supra-clinical dose levels; no appropriate control or validation	0.8
Clinical Single arm monotherapy	Efficacy - Response rate (best response seen)	- Disease type studied - Therapeutic regimen and applicability to paediatric population	1 = ≥70% CR 0.8 = ≥70% ORR (CR+PR) 0.6 = 20-70% ORR (CR+PR) 0.4 = <20% ORR (CR+PR) 0.2 = stable disease only 0 = progressive disease only	1 = childhood BL or DLBCL 0.9 = adult BL or DLBCL 0.4 = other disease types with same target 0.2 = other cancer types	1
Clinical Single arm combination	Efficacy - Response rate (best response seen)	- Disease type studied - Therapeutic regimen and applicability to paediatric population	1 = ≥70% CR 0.8 = ≥70% ORR (CR+PR) 0.6 = 20-70% ORR (CR+PR) 0.4 = <20% ORR (CR+PR) 0.2 = stable disease only 0 = progressive disease only	1 = childhood BL or DLBCL 0.9 = adult BL or DLBCL 0.4 = other disease types with same target 0.2 = other cancer types	1
Clinical Randomised trial	Efficacy - Progression-free survival - Overall survival	- Disease type studied - Therapeutic regimen and applicability to paediatric population	1 = met objectives of trial with regard to efficacy outcomes 0 = did not meet objectives of trial	1 = childhood BL or DLBCL 0.9 = adult BL or DLBCL 0.4 = other disease types with same target 0.2 = other cancer types	1
Safety profile Single agent	Toxicity profile***	- Frequency of adverse events (AEs) - Severity of AEs - Extent modifiable - Relevance of population studied to paediatric patients with r/r B-NHL - Therapeutic regimen and applicability to paediatric population	0.6 = <20% grade 3-4 non-haematological toxicities 0.4 = 20-50% patients grade III-IV non-haematological toxicity 0.2 = >50% patients grade III-IV non-haematological toxicities 0.1 = >80% patients grade III-IV non-haematological toxicity or 1 grade V adverse reaction 0 = >1 grade V adverse reaction PLUS 0.4 = <20% grade IV haem toxicity 0.3 = 20-50% grade IV haem toxicity 0.2 = >50% grade IV haem toxicity 0.1 = >80% grade IV haem toxicity	1 = ≥50 paediatric patients 0.9 = ≥100 adults with aggressive B-NHL 0.6 = ≥100 adults with any disease or ≥20 paediatric patients 0.4 = ≥50 adults with any disease 0.2 = <50 adults with any disease	1
Safety Combination	Any SUSARs and details				
Feasibility in paediatrics		- Formulation - Likelihood uncomplicated dose-confirmation process	1 = Paediatric specific formulation developed or not necessary 0.8 = paediatric specific formulation in progress, adult formulation easily administered to majority of children 0.7 = no paediatric specific formulation planned currently, adult formulation easily administered to majority of children 0.5 = paediatric specific formulation in progress, adult formulation not easily administered to majority of children 0.2 = no paediatric specific formulation planned currently, adult formulation will limit dosing or administration to children	1 = clear recommendations for paediatric dosing or PK equivalence studies conducted 0.5 = no paediatric-specific information available, no anticipated challenges 0.2 = known PK differences that will make paediatric dose-finding challenging	0.9
Overall impression	Interesting asset that will fit into Platform at the current time	Interesting asset worthy of further development but does not fit into Platform at the current time	Asset not showing adequate activity in field of paediatric B-NHL to merit further study currently		

*Where IC₅₀ is an inappropriate method of evaluation an alternative preclinical package will be considered. Where in vitro work is not appropriate then score zero and total scores will be adjusted accordingly;
 **Assess single agent activity unless the mechanism-of-action of a drug is solely dependent on another agents (e.g. is asset a prodrug) in which case the combination should be assessed;
 ***Plus any anticipated paediatric-specific safety concerns (short- or long-term), any pre-clinical juvenile toxicity data available, any data on neurotoxicity, autoimmune issues, second malignancies or pre-malignant lesions

Figure 1

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