Phase 1 Study to Evaluate Safety, Tolerability, Pharmacokinetics (PK), and Clinical Activity of the Antibody–Drug Conjugate (ADC) ARC-02 as Monotherapy and in Combination With Rituximab in Adults With B-Cell Non-Hodgkin Lymphoma (NHL)

Navid Hafez,[1] Eliza Hawkes,[2] Michael Gilbertson,[3] Tara Cochrane,[4] Katharine L. Lewis,[5,6] Sara Soukup,[7] Shinya Okamura,[7] Qing Xu,[7] Angela Hu,[7] Bernd Schlereth,[8] Vedran Radojcic,[7] Don Stevens,[9] Arvind Chaudry[10]

[1]START Los Angeles, Los Angeles, CA, USA; [2]Olivia Newton John Cancer Research Institute at Austin Health, Heidelberg, Australia; [3]Monash Health, Clayton, Australia; [4]Gold Coast University Hospital, Southport, Australia; [5]Department of Haematology, Sir Charles Gairdner Hospital, Nedlands, WA, Australia; [6]Linear Clinical Research, Nedlands, WA, Australia; [7]Taiho Oncology, Inc., Princeton, NJ, USA; [8]Araris Biotech AG, Au ZH, Switzerland; [9]Norton Cancer Institute, Louisville, KY, USA; [10]Summit Cancer Center, Spokane Valley, WA, USA

Introduction

- As many as 50% of individuals with B-cell non-Hodgkin lymphoma (NHL) may experience refractory or relapsed (R/R) disease, for which there are limited treatment options[1-3]
- Antibody–drug conjugates (ADC) are indicated for the treatment of aggressive high-grade lymphomas but are not approved for the treatment of other B-cell NHL subtypes. Toxicities induced by the unintended and premature release of the monomethyl auristatin E have limited the development of the anti-CD79b ADC polatuzumab-vedotin in other B-cell NHLs[4]
- ARC-02 is a novel anti-CD79b ADC developed using proprietary AraLinQ™ technology, which enhances ADC homogeneity and stability, offering improved on-target activity and enhanced safety
  - In preclinical studies, ARC-02 demonstrated a 16-fold higher therapeutic index over polatuzumab-vedotin (data on file). This was based on an up to 8-fold improvement in safety margin and potent cytotoxicity in NHL cell lines and xenograft models, with ARC-02 achieving comparable efficacy at 2-fold lower payload delivery.[5,6] Preclinical evidence also shows potential synergy between CD79b-targeted therapy and rituximab[7]

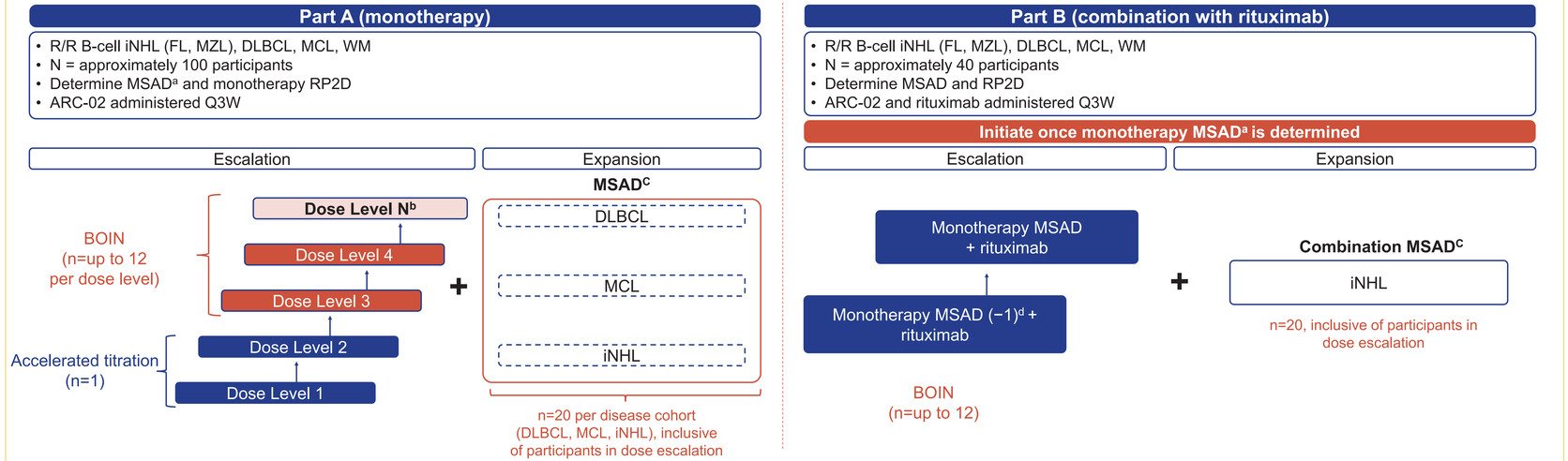
Study Design

- ARC-02-101 (NCT07691606) is a first-in-human open-label, dose-finding phase 1 study designed to evaluate the safety, tolerability, PK, pharmacodynamics, and preliminary clinical activity of ARC-02 alone and in combination with rituximab in adults with R/R B-cell NHL
- The study consists of Part A (ARC-02 monotherapy) and Part B (ARC-02 in combination with rituximab) (**Figure 1**). Both Part A and Part B include a dose escalation phase followed by a dose expansion phase. Commencement of Part B will be informed by findings from Part A dose escalation
- Approximately 140 participants are planned to be enrolled in both monotherapy and combination therapy cohorts in Part A and Part B
- In Part A (monotherapy), dose escalation follows accelerated titration design with single-participant cohorts used for the first 2 dose levels, before transitioning to a Bayesian Optimal Interval (BOIN) design. BOIN methodology will be used to estimate the maximum tolerated dose and is defined as the highest dose level with a dose-limiting toxicity (DLT) rate lower than the prespecified target toxicity rate of 25%. Approximately 100 participants will be enrolled in Part A (dose escalation will enroll up to 12 participants per dose level [approx. n=40] and dose expansion will enroll up to 20 participants per disease cohort (indolent NHL [iNHL], diffuse large B-cell NHL, mantle cell lymphoma; [approx. n=60])
- Part B (ARC-02 combination with rituximab) will initiate after the ARC-02 monotherapy maximum safely administered dose (MSAD) has been determined in Part A and will enroll approximately 40 participants
  - In the dose escalation portion, the starting dose (one dose level below the ARC-02 monotherapy MSAD) and the ARC-02 monotherapy MSAD dose will be evaluated
  - The dose expansion portion will enroll up to 20 participants with iNHL (follicular lymphoma and marginal zone lymphoma). Data from this cohort will inform the recommended phase 2 dose (RP2D) for ARC-02 in combination with rituximab. The Lugano criteria[8] will be used to assess response in participants with radiographically measurable disease

Study Status

- **Study start date:** June 22, 2026
- **Estimated study completion date:** December 2030
- As of August 26, 2026, two participants have been enrolled

Figure 1: Study design



aMSAD represents the maximum safely administered dose.
bDose levels above Dose Level 4 may be evaluated if supported when sufficient clinical data are available at the lower dose levels and after protocol amendment.
cIf results of expansion cohort justify further ARC-02 development, to support dose optimization, an additional lower dose level (per B-cell NHL type) may be expanded after protocol amendment.
d(−1) represents a dose level lower than the monotherapy MSAD.
BOIN, Bayesian Optimal Interval; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; iNHL, indolent non-Hodgkin lymphoma; MCL, mantle cell lymphoma; MSAD, maximum safely administered dose; MZL, marginal zone lymphoma; NHL, non-Hodgkin lymphoma; Q3W, every 3 weeks; RP2D, recommended phase 2 dose; R/R, relapsed/refractory; WM, Waldenstrom macroglobulinemia.

Participant Eligibility Criteria

Key inclusion criteria	Key exclusion criteria
• Aged ≥18 years	• Grade >1 neuropathy
• B-cell NHL with histology based on WHO criteria[9] and disease requiring treatment: - FL grades 1–3B - MZL - MCL - DLBCL - Other B-cell NHL	• Has any of the following medical conditions: - Active infection - Active ILD/pneumonitis or history of ILD/pneumonitis requiring treatment - Concurrent malignancy (progressing or requires treatment) - Active CNS lymphoma involvement requiring treatment - Cardiac event within 6 months prior to study entry - QTcF >470 ms
• Measurable disease, defined by Lugano classification	• Has received chemotherapy, radiotherapy, small molecule, investigational, and biologic agents (including CD79b-directed agents) within 28 days (or at least 5 half-lives, whichever is shorter), prior to the first dose of the study intervention
• Has received at least 2 prior lines of systemic therapies for B-cell NHL and is not eligible to receive additional standard of care therapies	• Use of any live or live-attenuated vaccine within 28 days before the first dose of the study intervention
• ECOG performance status of ≤2	• Use of immunosuppression for management of allogeneic HCT within 3 months prior to the first dose of the study intervention
• Adequate organ function	• CAR-T or autologous HCT within 100 days prior to the first dose of the study intervention
	• Ongoing toxicity from prior anticancer therapy that has not resolved[a]

[a]Resolved to grade ≤2 (neutropenia) or grade ≤1 (thrombocytopenia or nonhematologic toxicities, with the exception of alopecia).
CAR-T, chimeric antigen receptor T-cell; CNS, central nervous system; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; FL, follicular lymphoma; HCT, hematopoietic cell transplantation; ILD, interstitial lung disease; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; NHL, non-Hodgkin lymphoma; WHO, World Health Organization.

Endpoints

Endpoint	Dose escalation	Dose expansion
Primary	• Incidence of DLTs and TEAEs (including SAEs)	• ORR (investigator-assessed)
Secondary	• ORR (investigator-assessed)	• Number of participants with TEAEs and SAEs
	• TTR • DoR • PFS • PK parameters for acMMAE, total anti-CD79b antibody and free MMAE (C_{max}, $T_{½}$, AUC_{0-T}, and $AUC_{0-\infty}$) • Presence of ADA and nAb	

acMMAE, antibody-conjugated monomethyl auristatin E; ADA, antidrug antibody; AUC_{0-T}, area under the curve from time to last measurable concentration; $AUC_{0-\infty}$, area under the curve from time 0 to infinity; C_{max}, maximum serum concentration; DLT, dose-limiting toxicity; DoR, duration of response; MMAE, monomethyl auristatin E; nAb, neutralizing antibody; ORR, objective response rate; PFS, progression-free survival; PK, pharmacokinetics; SAE, serious adverse event; $T_{½}$, half-life; TEAE, treatment-emergent adverse event; TTR, time to response.

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