

Phase 1 Study of ARV-393, a PROTAC BCL6 Degradator, as Monotherapy in Patients With Advanced NHL or Combined With Glofitamab in Patients With DLBCL

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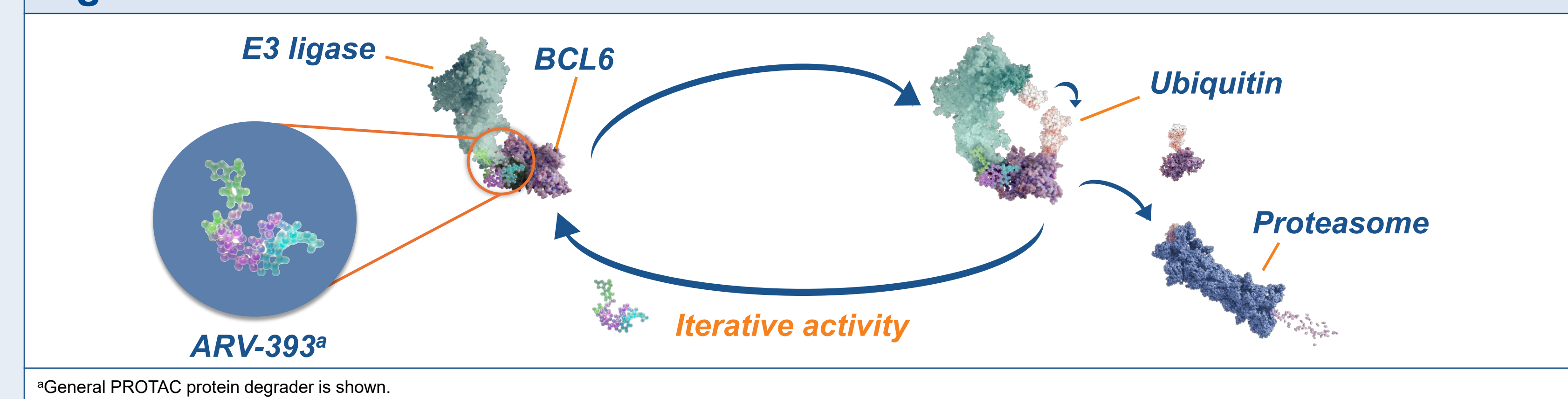
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Objective: This first-in-human, phase 1 dose escalation and optimization/expansion study is evaluating the safety, tolerability, PK, pharmacodynamics, and preliminary antitumor activity of ARV-393, an oral PROTAC BCL6 degrader, as monotherapy in R/R NHL or in combination with glofitamab in R/R DLBCL

Background

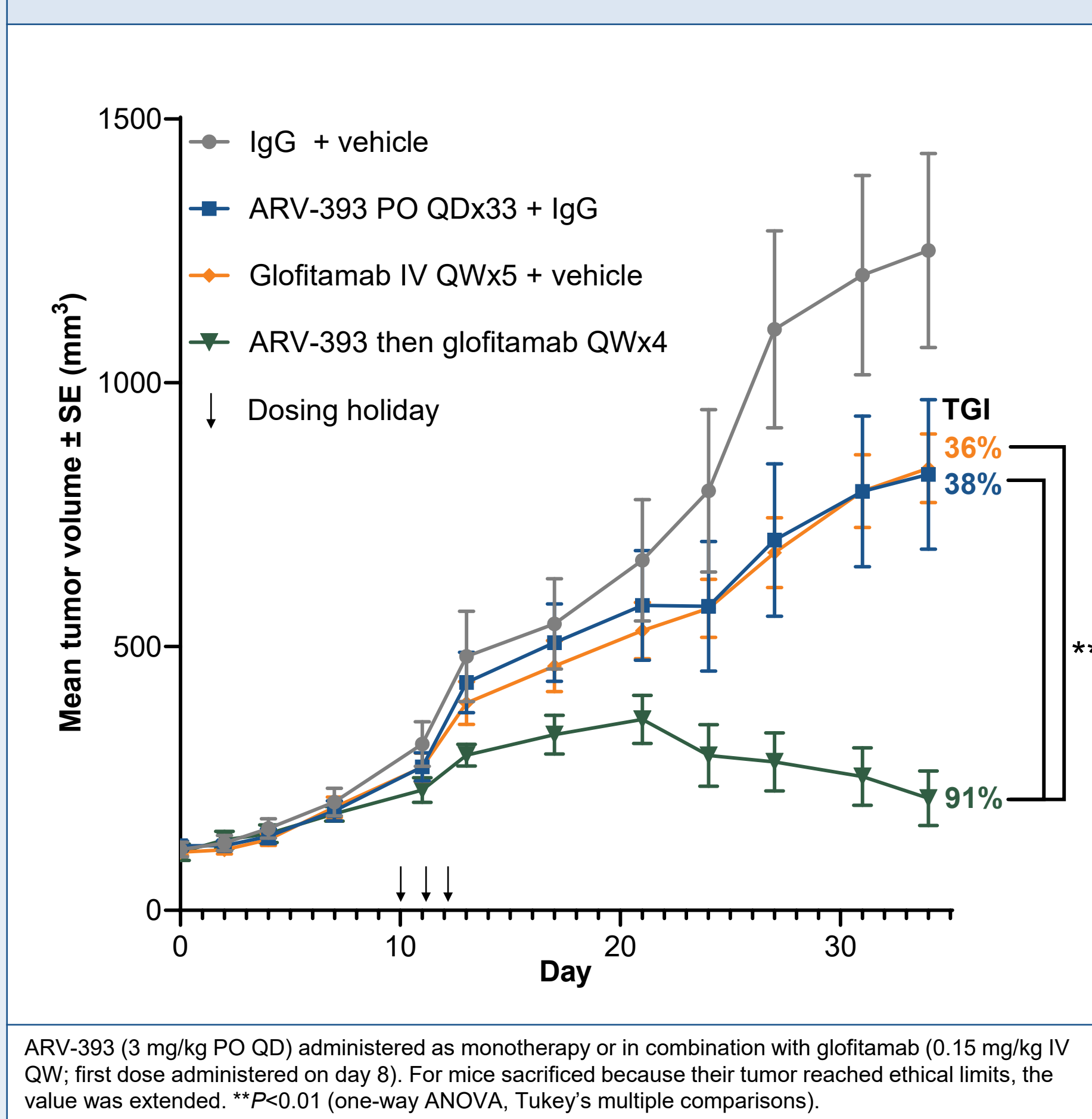
- Despite recent advancements in the treatment of NHL, many patients experience disease progression or relapse¹⁻³ and agents with novel mechanisms of action and combination strategies are needed to improve clinical outcomes
- BCL6 is a master transcriptional regulator of immune cells, particularly of germinal center B cells, and an established oncogenic driver in NHL⁴⁻⁶
- ARV-393 is an oral PROTAC BCL6 degrader that binds an E3 ubiquitin ligase and BCL6 to induce ubiquitination of BCL6 and its subsequent proteasomal degradation (Figure 1)⁷

Figure 1: Mechanism of action of ARV-393



- In preclinical studies, ARV-393 monotherapy induced potent TGI and tumor regressions across NHL CDX and PDX models, including models of DLBCL, transformed follicular lymphoma, and nTFHL-AI^{8,9}
- ARV-393 demonstrated synergistic antitumor activity, including complete regressions, in combination with SOC agents and investigational small-molecule inhibitors in HGBCL and aggressive DLBCL CDX models^{9,10}
- Glofitamab-gxbm, a bispecific CD20-directed CD3 T-cell engager, was granted accelerated approval in 2023 for the treatment of adults with R/R DLBCL or LBCL arising from follicular lymphoma, after ≥2 lines of systemic therapy¹¹
- In a humanized HGBCL CDX model, co-administration of ARV-393 and glofitamab demonstrated combinatorial antitumor activity, as evidenced by deeper TGI and increased tumor regressions compared with either agent alone (Figure 2)¹²
- These preclinical findings demonstrated single-agent ARV-393 antitumor activity across NHL subtypes and suggested mechanistic synergy with glofitamab, supporting clinical investigation of ARV-393 monotherapy in NHL and this chemotherapy-free combination in patients with DLBCL

Figure 2: TGI with ARV-393 ± glofitamab in a humanized CD34+ WSU-DLCL2 HGBCL CDX model¹²



Study Design

- This global, multicenter, open-label, first-in-human, phase 1 dose escalation and optimization/expansion study (NCT06393738; **Figure 3**) is evaluating ARV-393 as monotherapy in patients with R/R NHL or in combination with glofitamab in patients with R/R DLBCL (**Table 1**)
- ARV-393 will be administered PO QD in 28-day cycles alone or combined with IV glofitamab during 21-day cycles
- Primary and secondary outcome measures are listed in **Table 2**
- Approximately 255 patients will be enrolled across study cohorts

Table 1: Key eligibility criteria^a

Disease- and treatment-specific inclusion criteria	
ARV-393 monotherapy	ARV-393 + glofitamab
<ul style="list-style-type: none"> R/R mature B-cell NHL and ≥2 prior systemic therapies, or Histologically confirmed nTFHL-AI that recurred or progressed after ≥1 prior line of therapy 	<ul style="list-style-type: none"> R/R DLBCL, DLBCL NOS, or LBCL arising from follicular lymphoma^b and ≥2 prior lines of systemic therapy
General inclusion criteria	
<ul style="list-style-type: none"> Males and females aged ≥18 y ≥1 measurable nodal lesion >1.5 cm or extranodal lesion >1.0 cm ECOG performance status 0 or 1^c Adequate bone marrow, kidney, and liver function 	
Exclusion criteria	
<ul style="list-style-type: none"> Prior allogeneic stem cell transplant or solid organ transplantation Other active malignancy within 3 years, with certain exceptions Recent history of clinically important cerebrovascular or cardiac events, including myocarditis Active inflammatory GI disease or prior gastric resection 	

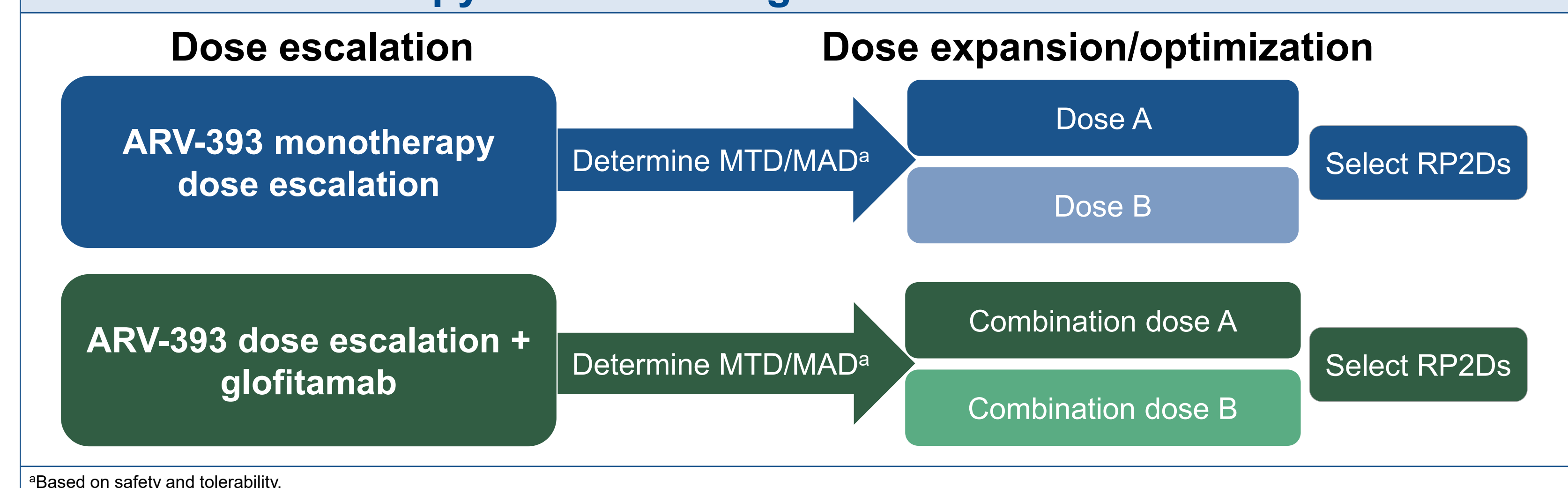
^aThis is not the complete list of inclusion/exclusion criteria. ^bAccording to criteria of The International Consensus Classification of Mature Lymphoid Neoplasms. ^cECOG performance status of 2 is allowed for participants with secondary CNS lymphoma in a backfill cohort of the monotherapy dose escalation.

Table 2: Outcome measures

Primary	<ul style="list-style-type: none"> DLTs during the first 28 days TEAEs, including incidence, severity, seriousness, and relationship to study intervention Changes from baseline in vital signs, ECGs, and laboratory parameters Incidence of grade 3 and grade 4 clinical laboratory abnormalities
Secondary	<ul style="list-style-type: none"> PK parameters for ARV-393 as monotherapy and in combination with glofitamab Preliminary antitumor activity (ORR, CR rate, DOR)^a

^aBased on investigator assessment using the 2014 Lugano criteria for NHL¹⁴ and the International PCNSL Collaborative Group Criteria for CNS lymphoma,¹⁵ if applicable.

Figure 3: Dose escalation and expansion/optimization phase 1 study of ARV-393 monotherapy or ARV-393 + glofitamab



Abbreviations

ANOVA=analysis of variance; BCL6=B-cell lymphoma 6; CDX=cell-line derived xenograft; CNS=central nervous system; CR=complete response; DLBCL=diffuse large B-cell lymphoma; DLT=dose-limiting toxicity; DOR=duration of response; ECOG=Eastern Cooperative Oncology Group; ECG=electrocardiogram; GI=gastrointestinal; HGBCL=high-grade B-cell lymphoma; IgG=immunoglobulin; IV=intravenously; LBCL=large B-cell lymphoma; MAD=maximally administered dose; MTD=maximum tolerated dose; NHL=non-Hodgkin lymphoma; NOS=not otherwise specified; nTFHL-AI=nodal T-follicular helper cell lymphoma, angioimmunoblastic type; ORR=objective response rate; PDX=patient-derived xenograft; PK=pharmacokinetic; PO=orally; PROTAC=PROteolysis TArgeting Chimera; QD=once daily; QW=once weekly; R/R=relapsed or refractory; RP2D=recommended phase 2 dose; SOC=standard of care; TEAE=treatment-emergent adverse event; TGI=tumor growth inhibition

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- This poster was previously presented at the American Association for Cancer Research (AACR) Annual Meeting; San Diego, CA; 2026

Study Status

- Enrollment is currently ongoing in monotherapy and combination cohorts
- To view currently recruiting sites, visit clinicaltrials.gov (NCT06393738)



Scan to view the clinicaltrials.gov webpage for this study