

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

Martin Hutchings¹, Andrew Zelenetz², Jacob H Christensen³, Almudena Cascales Hernandez⁴, Sarit Assouline⁵, Luis E Malpica Castillo⁶, Shalin Kothari⁷, Dipenkumar Modi⁸, Miguel Angel Canales Albendea⁹, Damian Cubillas¹⁰, Alejandro Martin Garcia-Sancho¹¹, Catherine M Diefenbach¹², John Kuruvilla¹³, Paolo F Caimi¹⁴, Krish Patel¹⁵, Sean Landrette¹⁶, Eric Zhi¹⁶, Yuanyuan Zhang¹⁶, Roland Meier¹⁶, Mathew J Matasar¹⁷

¹Rigshospitalet and University of Copenhagen, Copenhagen, Denmark; ²Memorial Sloan Kettering Cancer Center, New York, NY, USA; ³Odense University Hospital, Odense, Denmark; ⁴Hospital Clínico Universitario Virgen de la Arrixaca, Murcia, Spain; ⁵McGill University, Montreal, QC, Canada; ⁶The University of Texas MD Anderson Cancer Center, Houston, TX, USA; ⁷Yale School of Medicine and Yale Cancer Center, New Haven, CT, USA; ⁸Karmanos Cancer Institute/Wayne State University, Detroit, MI, USA; ⁹Clínica Universidad de Navarra, Pamplona, Spain; ¹⁰START Center for Cancer Research, Madrid, Spain; ¹¹Hospital Universitario de Salamanca, Salamanca, Spain; ¹²Laura and Isaac Perlmutter Cancer Center, New York University Grossman School of Medicine, New York, NY, USA; ¹³Princess Margaret Cancer Centre, Toronto, ON, Canada; ¹⁴Cleveland Clinic, Cleveland, OH, USA; ¹⁵Sarah Cannon Research Institute, Nashville, TN, USA; ¹⁶Arvinas Operations, Inc., New Haven, CT, USA; ¹⁷Rutgers Cancer Institute of New Jersey, New Brunswick, NJ, USA

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

Contact

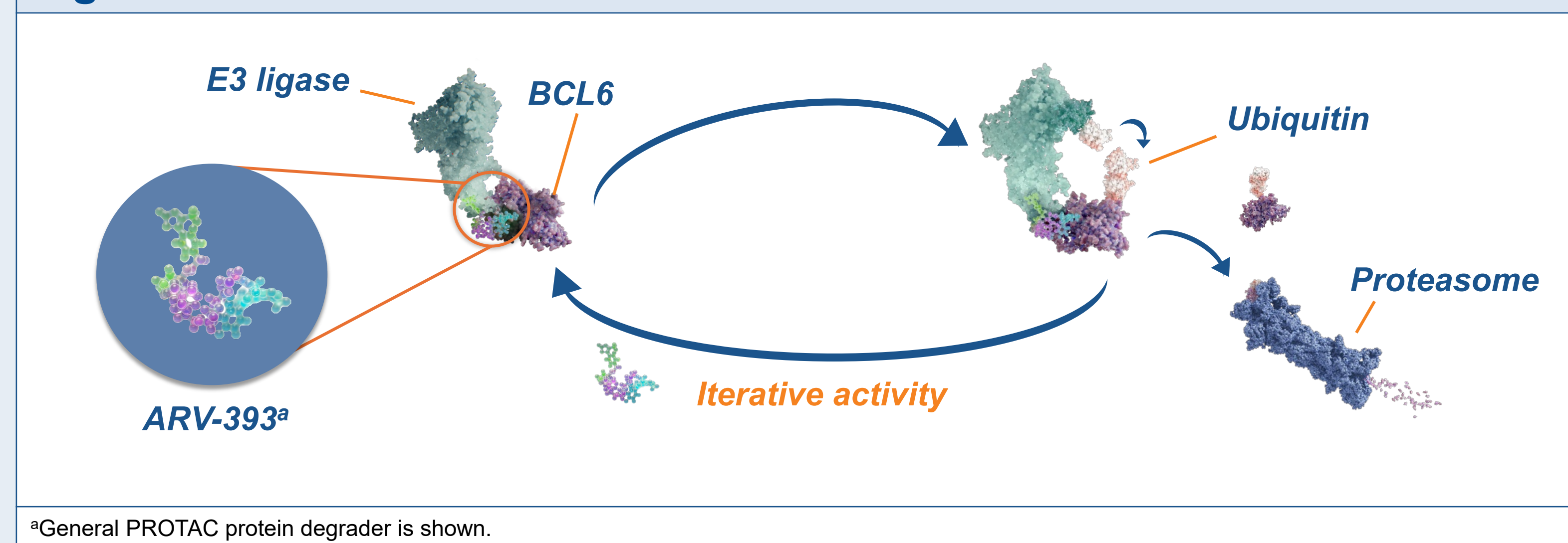
Martin Hutchings: Martin.Hutchings@region.dk

American Association for Cancer Research (AACR) Annual Meeting San Diego, CA, April 17–22, 2026

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
- 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-gxblm, 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 1: Mechanism of action of ARV-393



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

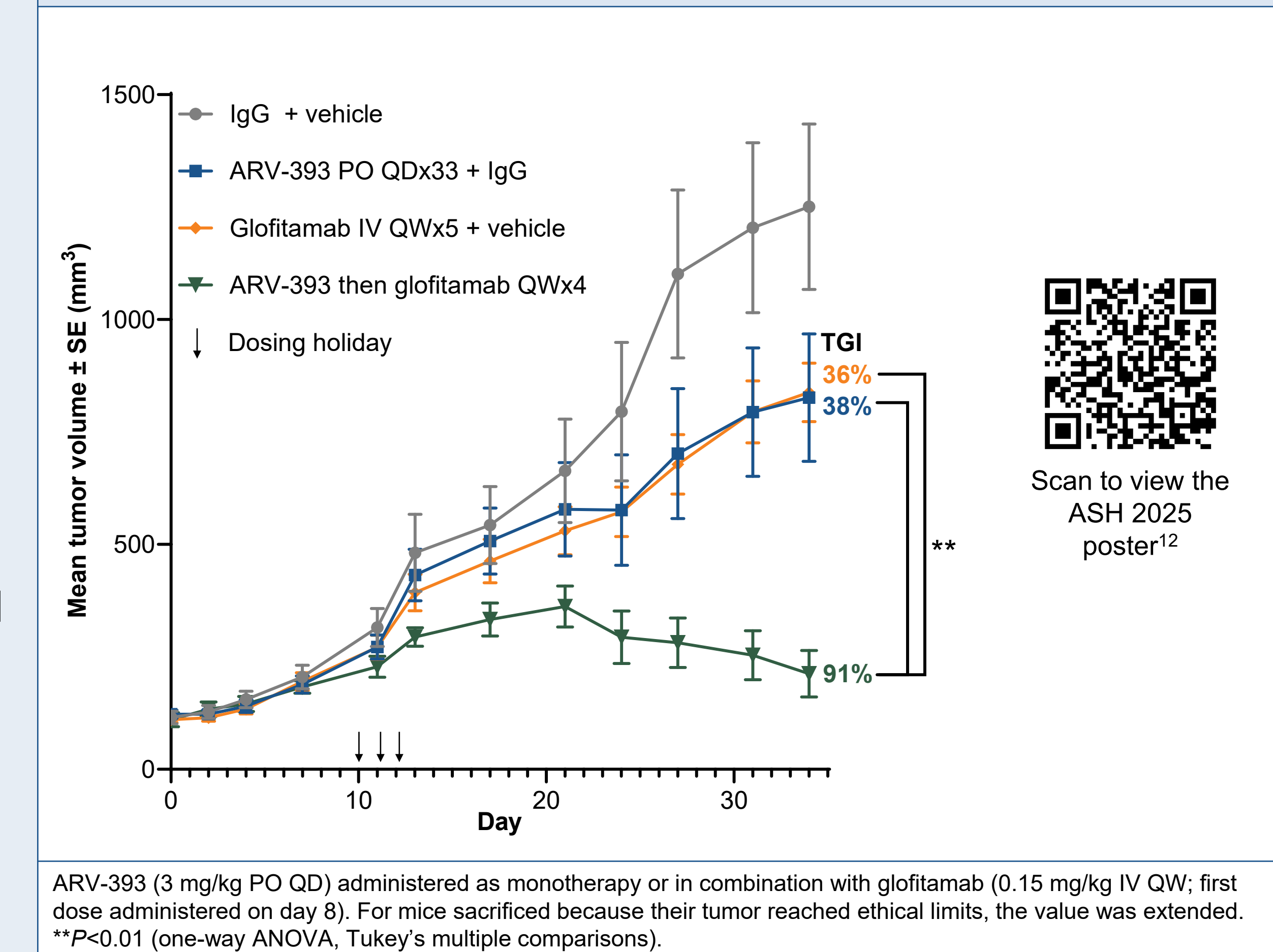
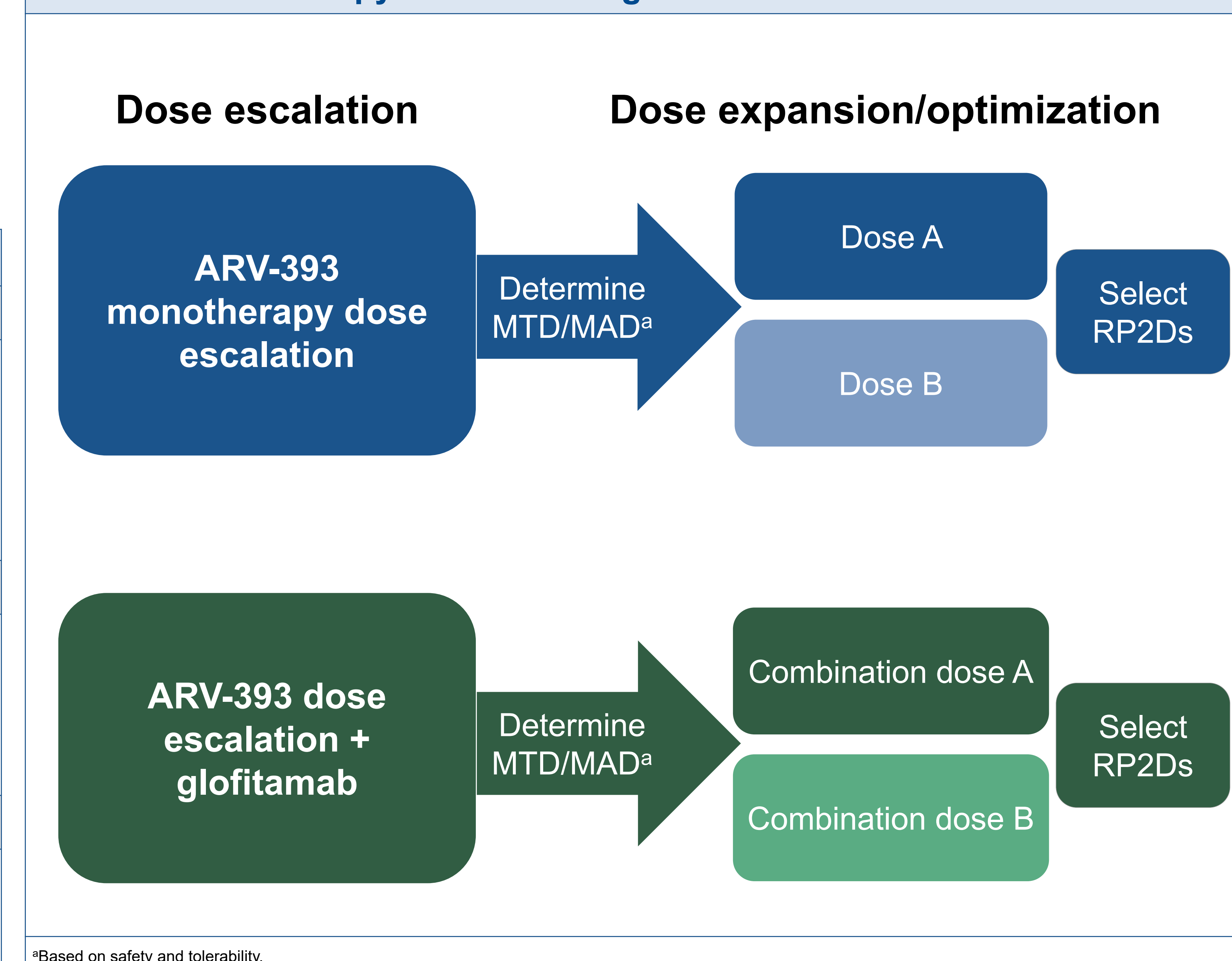


Figure 3: Dose escalation and expansion/optimization phase 1 study of ARV-393 monotherapy or ARV-393 + glofitamab



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

References

- Kanwal B. *Cureus*. 2021;13:e16307.
- Ngu H, et al. *Am Soc Clin Oncol Educ Book*. 2022;42:1-14.
- Skarbnik AZ and Patel K. *Front Oncol*. 2023;13:1120358.
- Basso K and Dalla-Favera R. *Immunol Rev*. 2012; 247:172-83.
- Yang H and Green MR. *Front Cell Dev Biol*. 2019;7:272.
- Hatzi K and Melnick A. *Trends Mol Med*. 2014;20:343-52.
- Sherman D, et al. Presented at AACR; April 5–10, 2024; San Diego, CA, USA. Abstract ND-05.
- Gough S, et al. Poster presented at EHA; June 13–16, 2024; Madrid, Spain. Poster P1256.
- Van Acker A, et al. Presented at European Hematology Association (EHA) Jun 12-15, 2025, Milan, Italy. Poster PF1000.
- Van Acker A, et al. Presented at American Association for Cancer Research (AACR); Apr 25–30, 2025; Chicago, IL, USA. Poster 1655.
- Columvi (glofitamab-gxblm) prescribing information. Genentech, Inc.; 2023.
- Van Acker A, et al. Presented at American Hematology Society (ASH) Dec 6–9, 2025, Orlando, FL. Poster 1520.
- Campo E, et al. *Blood*. 2022;140(11):1229-53.
- Cheson BD, et al. *J Clin Oncol*. 2014;32(27):3059-67.
- Abrey LE, et al. *J Clin Oncol*. 2005;23(22):5034-43.

Acknowledgments

This research was funded by Arvinas, Inc. Medical writing support was provided by Lela Creutz of Arvinas Operations, Inc.