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ARV-393, a PROTAC BCL6 Degrader, Combined With the CD20×CD3 Bispecific Glofitamab in a Preclinical Model of HGBCL

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Objective

- To evaluate the preclinical combinability of the PROteolysis TArgeting Chimera (PROTAC) B-cell lymphoma 6 (BCL6) degrader ARV-393 with the CD20×CD3 bispecific antibody glofitamab in a humanized high-grade B-cell lymphoma (HGBCL) cell line-derived (CDX) model

Key Findings

- ARV-393 at a low dose (3 mg/kg) combined with glofitamab resulted in substantially greater tumor growth inhibition (TGI) with concomitant dosing (81%) and sequential (ARV-393 then glofitamab) dosing (91%) compared with single-agent ARV-393 (38%) or a sub-efficacious dose of glofitamab (36%)
- ARV-393 at a higher dose (6 mg/kg) in combination with glofitamab yielded deeper TGI of 106% with concomitant dosing and 107% with sequential dosing vs 99% TGI with single-agent ARV-393
- At the higher ARV-393 dose, an increase in tumor regressions was observed with concomitant (10/10 mice) and sequential dosing (7/8 mice) vs single-agent ARV-393 (5/11 mice) or glofitamab (0/11 mice)
- RNA sequencing and pathway biomarker analyses provided mechanistic insight into the observed synergistic activity and suggest that ARV-393 enhances CD20 expression, interferon (IFN) pathway activity, and antigen presentation, which likely collectively contribute to the observed combinatorial activity

Conclusions

- ARV-393 demonstrated combinatorial antitumor activity with glofitamab as evidenced by deeper TGI than single-agent ARV-393 or glofitamab and by an increase in tumor regressions with both concomitant and sequential dosing of the combination
- These findings suggest mechanistic synergy between BCL6 degradation with ARV-393 and T-cell engagement through a CD20-targeted bispecific antibody and support clinical investigation of the chemotherapy-free combination in patients with DLBCL

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Acknowledgments

This research was funded by Arvinas, Inc. Medical writing support was provided by Joanna Bloom of Arvinas Operations, Inc.

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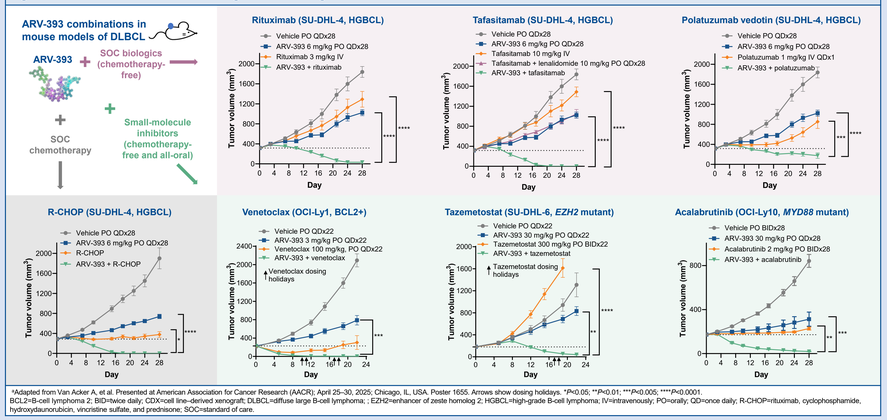
American Society of Hematology (ASH) Annual Meeting and Exposition
Orlando, FL, USA; December 6–9, 2025

Background

- Despite significant progress made in the treatment of non-Hodgkin lymphoma (NHL) through advancements with immunochemotherapy, autologous stem cell transplantation, chimeric antigen receptor T-cell therapies, bispecific antibodies, and other targeted therapies, many patients ultimately experience disease progression or relapse[1–3]
- Thus, there is an unmet need for agents with novel mechanisms of action and combination strategies that can improve disease-free survival and overall survival without increasing toxicity
- BCL6 is a master transcriptional regulator that controls key processes during B-cell lymphomagenesis; deregulated BCL6, as a result of genomic aberrations of the *BCL6* gene or genes encoding factors that regulate BCL6, has been implicated as an oncogenic driver in NHL[4–6]
- ARV-393, a PROTAC BCL6 degrader, directly binds an E3 ubiquitin ligase and BCL6 to induce the ubiquitination of BCL6 and its subsequent proteasomal degradation[7]
- ARV-393 monotherapy is currently being evaluated in a phase 1 trial (NCT06393738) in patients with NHL, including diffuse large B-cell lymphoma (DLBCL)[8]
- ARV-393 demonstrated synergistic antitumor activity, including complete regressions, in combination with standard-of-care (SOC) agents and investigational small-molecule inhibitors in HGBCL and aggressive DLBCL CDX models (**Figure 1**)[9,10]

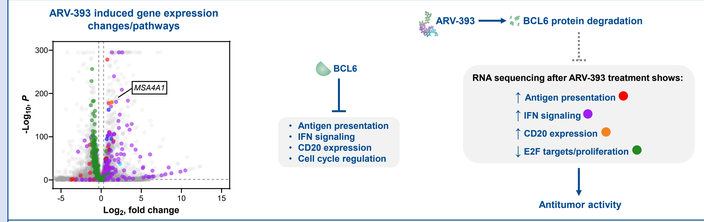
Figure 1: ARV-393 combined with SOC agents or investigational small-molecule inhibitors in CDX models of DLBCL[a]



[a]Adapted from Van Acker A, et al. Presented at American Association for Cancer Research (AACR); April 25–30, 2025; Chicago, IL, USA. Poster 1655. Arrows show dosing holidays. *P<0.05, **P<0.01, ***P<0.005, ****P<0.0001.
BCL2=B-cell lymphoma 2; BID=twice daily; CDX=cell line–derived xenograft; DLBCL=diffuse large B-cell lymphoma; ; EZH2=enhancer of zeste homolog 2; HGBCL=high-grade B-cell lymphoma; IV=intravenously; PO=orally; QD=once daily; R-CHOP=rituximab, cyclophosphamide, hydroxydaunorubicin, vincristine sulfate, and prednisone; SOC=standard of care.

- Two bispecific CD20-directed CD3 T-cell engagers, epcoritamab-bysp and glofitamab, recently received accelerated approval for late-line relapsed/refractory DLBCL and are emerging as new SOC agents[11–13]
- Emerging research suggests that the clinical benefit of CD20xCD3 bispecific antibody treatment is enhanced in tumors characterized by enrichment of immune-related gene sets, including IFN-γ and IFN-α response genes as compared to those with upregulation of cell cycling/proliferation gene sets[14,15]
- We previously demonstrated that treatment of lymphoma cells with ARV-393 induces CD20[9] immune-related gene sets (IFN-γ targets and IFN-α response genes) and reduced cell cycling/proliferation gene sets (**Figure 2**),[10] suggesting that ARV-393 may enhance the activity of CD20×CD3 bispecific antibodies

Figure 2: Gene expression changes with ARV-393 treatment and impact on pathways that potentially enhance the immune-mediated activity of a CD20×CD3 bispecific antibody[a]



[a]Adapted from Van Acker A, et al. Presented at European Hematology Association (EHA) June 12–15, 2025, Milan, Italy. Poster PF1000.
BCL6=B-cell lymphoma 6; E2F=early region 2 binding factor; IFN=interferon; *MSA4A1*=gene encoding CD20.

Results

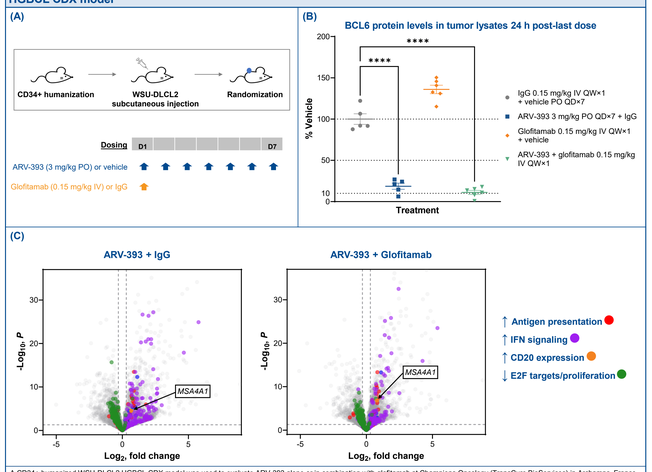
Target engagement and gene expression landscape following short-term treatment of ARV-393 alone or combined with glofitamab in a humanized WSU-DLCL2 HGBCL CDX model

- Following 7 days of ARV-393 treatment (alone or co-administered with glofitamab on day 1; **Figure 3A**), BCL6 protein levels were reduced by 81% and 89%, respectively (**Figure 3B**)
- RNA sequencing revealed enrichment of early region 2 binding factor (E2F) targets among genes significantly downregulated by ARV-393 and IFN response signaling and antigen presentation among genes significantly upregulated by ARV-393 in vivo (**Figure 3C**), mirroring the changes previously observed in vitro (**Figure 2**)[10] and suggesting that ARV-393–mediated degradation of BCL6:
  - Inhibits tumor cell cycle progression (by decreasing E2F pathway activity), consistent with previous data demonstrating a G0/G1 cell cycle block induced by PROTAC-mediated BCL6 degradation in lymphoma cell lines[16]
  - Promotes IFN signaling and antigen presentation mechanisms that are predicted to enhance the activity of a CD20×CD3 bispecific antibody

TGI, target engagement, and immune cell dynamics following treatment with ARV-393 or glofitamab in a humanized WSU-DLCL2 HGBCL CDX model

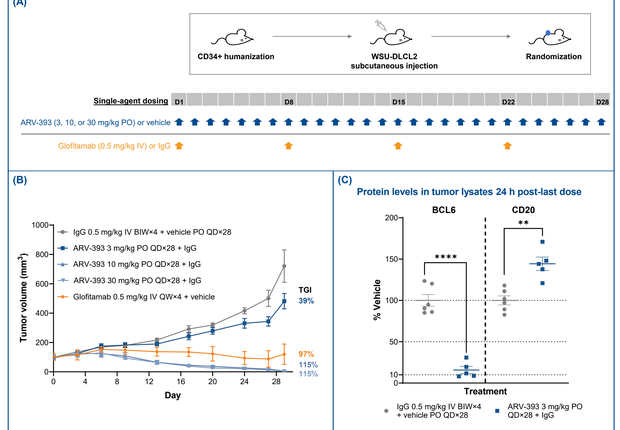
- Oral once-daily (PO QD) dosing of ARV-393 3 mg/kg, 10 mg/kg or 30 mg/kg (**Figure 4A**) induced TGIs of 39%, 115%, and 115%, respectively, compared with 97% for 0.5 mg/kg weekly intravenous (IV) glofitamab dosing (**Figure 4B**)
- Significant BCL6 protein reduction was observed with 3 mg/kg ARV-393 (**Figure 4C;** tumors for other ARV-393 dose levels were too small for analysis)
- Significant induction of the glofitamab target CD20 was also seen with 3 mg/kg ARV-393 treatment (**Figure 4C**)
- CD19+ B cell numbers were depleted with glofitamab treatment but were not significantly changed with ARV-393 treatment at any dose level (**Figure 4D**)
- CD3+ T cell numbers were not significantly affected by ARV-393 or glofitamab after 28 days of dosing (**Figure 4D**)

Figure 3: Short-term treatment with ARV-393 alone or in combination with glofitamab in a humanized WSU-DLCL2 HGBCL CDX model



A CD34+ humanized WSU-DLCL2 HGBCL CDX model was used to evaluate ARV-393 alone or in combination with glofitamab at Champions Oncology (TransCure BioServices) in Archamps, France. Tumors were collected 24 h after the last ARV-393 or vehicle dose and snap frozen. Transcriptional changes (relative to vehicle control) were evaluated for differential expression.
(**A**) Experimental design and dosing schema. (**B**) BCL6 protein levels in tumor lysates 24 h post-last dose as determined by western blot. **** P<0.0001 (one-way ANOVA, Tukey's multiple comparisons). (**C**) Volcano plots depicting genes that were significantly induced or repressed by ARV-393 alone (left panel) or combined with glofitamab (right panel) as compared to vehicle 24 h post-last dose. Log2 fold change equal to ±0.2 are marked as dashed vertical lines; adjusted *P* value equal to 0.05 is marked as dashed horizontal line.
ANOVA=analysis of variance; BCL6=B-cell lymphoma 6; CDX=cell line–derived xenograft; E2F=early region 2 binding factor; HGBCL=high-grade B-cell lymphoma; IFN=interferon; IgG=immunoglobulin G; IV=intravenously; *MSA4A1*=gene encoding CD20; PO=orally; QD=once daily; QW=once weekly.

Figure 4: Treatment with ARV-393 or glofitamab in a humanized WSU-DLCL2 HGBCL CDX model

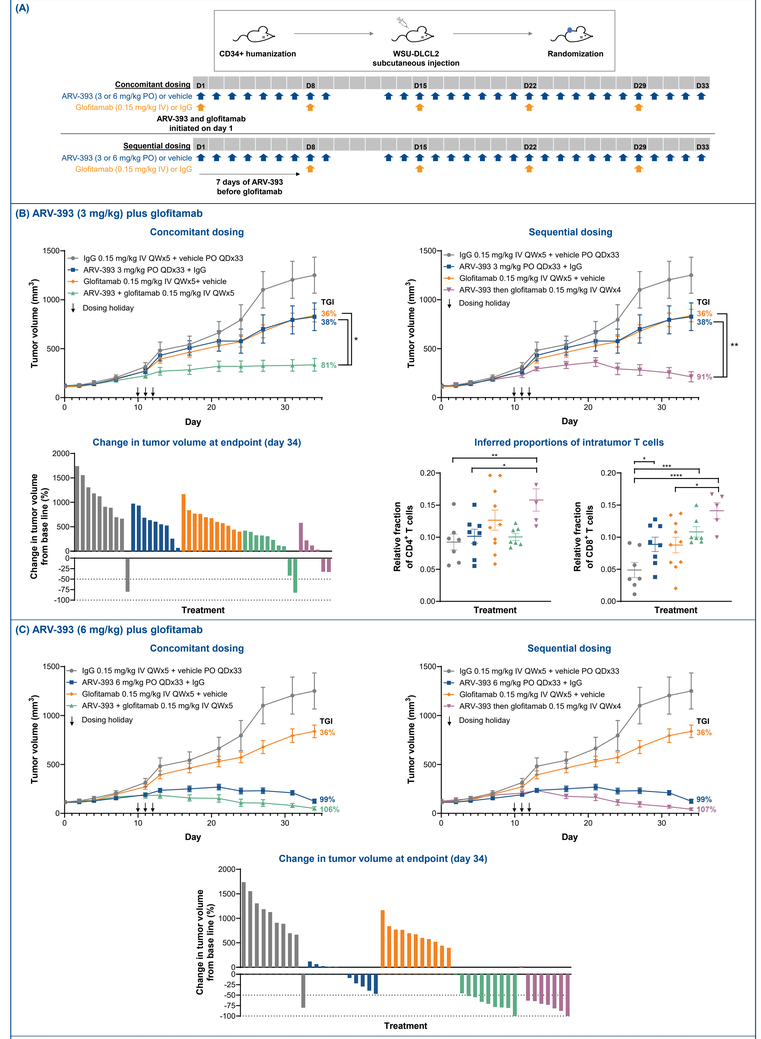


A CD34+ humanized WSU-DLCL2 HGBCL CDX model was used to evaluate ARV-393 or glofitamab at Champions Oncology (TransCure BioServices) in Archamps, France. Tumors were collected 24 h after the last ARV-393 or vehicle dose and snap frozen. Whole blood was collected 24 h after the last ARV-393 or vehicle dose and directly processed for flow cytometry.
(**A**) Experimental design and dosing schema. (**B**) Mean tumor volume over time with single-agent dosing of ARV-393 or glofitamab. (**C**) BCL6 and CD20 protein levels in tumor lysates 24 h post-last dose as determined by western blot. **P<0.01, ****P<0.0001 (unpaired *t*-test). (**D**) CD19+ B cells/mL (left panel) and CD3+ T cells/mL (right panel) as determined by flow cytometry in peripheral blood 24 h post-last dose. **P<0.01 (one-way ANOVA, Tukey's multiple comparisons).
ANOVA=analysis of variance; BCL6=B-cell lymphoma 6; BIW=every other week; CDX=cell line–derived xenograft; HGBCL=high-grade B-cell lymphoma; IgG=immunoglobulin G; IV=intravenously; PO=orally; QD=once daily; QW=once weekly; TGI=tumor growth inhibition.

TGI and changes in tumor volume following concomitant or sequential treatment with ARV-393 and glofitamab in a humanized WSU-DLCL2 HGBCL CDX model

- Concomitant (initiating ARV-393 [3 or 6 mg/kg] and glofitamab [0.15 mg/kg] treatment together) and sequential dosing (initiating glofitamab [0.15 mg/kg] after 7 days of ARV-393 [3 or 6 mg/kg] dosing) were both evaluated to determine if sequencing could enhance TGI (**Figure 5A**)
- ARV-393 at a low dose (3 mg/kg) combined with glofitamab resulted in significantly greater TGI with concomitant dosing (81%) and sequential dosing (91%) compared with single-agent ARV-393 (38%) or glofitamab (36%; **Figure 5B**)
  - Immune cell deconvolution analysis revealed that the highest inferred proportions of intratumor CD8+ T cells were in the combination groups, which was consistent with TGI
- ARV-393 at a higher dose (6 mg/kg) combined with glofitamab yielded deeper TGI of 106% with concomitant dosing and 107% with sequential dosing vs 99% TGI with single-agent ARV-393 (**Figure 5C**)
  - An increase in tumor regressions was observed with concomitant dosing (10/10 mice) and sequential dosing (7/8 mice) vs single-agent ARV-393 (5/11 mice) or glofitamab (0/11 mice)

Figure 5: Concomitant or sequential dosing of ARV-393 and glofitamab in a humanized WSU-DLCL2 HGBCL CDX model



A CD34+ humanized WSU-DLCL2 HGBCL CDX model was used to evaluate concomitant or sequential dosing of ARV-393 and glofitamab at Champions Oncology (TransCure BioServices) in Archamps, France. Tumors were collected 24 h after the last ARV-393 or vehicle dose and snap frozen. (**A**) Experimental design and dosing schema. (**B**) ARV-393 (3 mg/kg) in combination with glofitamab. (**C**) ARV-393 (6 mg/kg) in combination with glofitamab. (**B** and **C** upper panels) Mean tumor volume over time with concomitant dosing (upper left) or sequential dosing (upper right) of ARV-393 and glofitamab. Arrows indicate dosing holidays. For mice sacrificed because their tumor reached ethical limits, the value was extended. *P<0.05, **P<0.01 (one-way ANOVA, Tukey's multiple comparisons). (**B** lower left panel and **C** lower panel) Waterfall plot of individual tumor volume changes from baseline to final measurement. (**B** lower right panel) Immune cell deconvolution of RNA sequencing data using iSort™ (CiberMed) was performed to determine inferred immune cell proportions in available tumors at sacrifice (day 29–34). *P≤0.05, **P≤0.01, ***P≤0.001, ****P≤0.0001 (relative immune cell fractions within range (0,1) were fitted with beta regression, pairwise contrasts between group estimated marginal means were tested using Wald *z*-tests, and *P* values were adjusted for multiple comparisons using Tukey's method).
ANOVA=analysis of variance; CDX=cell line–derived xenograft; HGBCL=high-grade B-cell lymphoma; IgG=immunoglobulin G; IV=intravenously; PO=orally; QD=once daily; QW=once weekly; TGI=tumor growth inhibition.