

ARV-393, a PROteolysis Targeting Chimera (PROTAC) BCL6 Degradar, Combined With Biologics or Small-Molecule Inhibitors Induces Tumor Regressions in Diffuse Large B-Cell Lymphoma Models

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Objective

- To assess the activity of the PROTAC B-cell lymphoma 6 (BCL6) degrader, ARV-393, in combination with the standard of care (SOC) first-line chemotherapy regimen for diffuse large B-cell lymphoma (DLBCL), SOC biologics, or small-molecule inhibitors (SMIs) under clinical investigation in DLBCL xenograft models

Key Findings

- ARV-393 in combination with rituximab, cyclophosphamide, hydroxydaunorubicin, vincristine sulfate, and prednisone (R-CHOP), induced significantly greater tumor growth inhibition (TGI) compared with rituximab, CHOP, R-CHOP, or ARV-393 alone, with complete tumor regressions in all mice treated with the combination
- ARV-393 in combination with SOC biologics resulted in superior TGI compared with each agent alone, with complete tumor regressions observed in all mice treated with ARV-393 plus tafasitamab (anti-cluster of differentiation [CD]19) or rituximab (anti-CD20) and an increase in CD20 expression with ARV-393 alone
- ARV-393 in combination with investigational SMIs resulted in superior TGI compared with each agent alone, with tumor regressions observed in all mice treated with the combinations

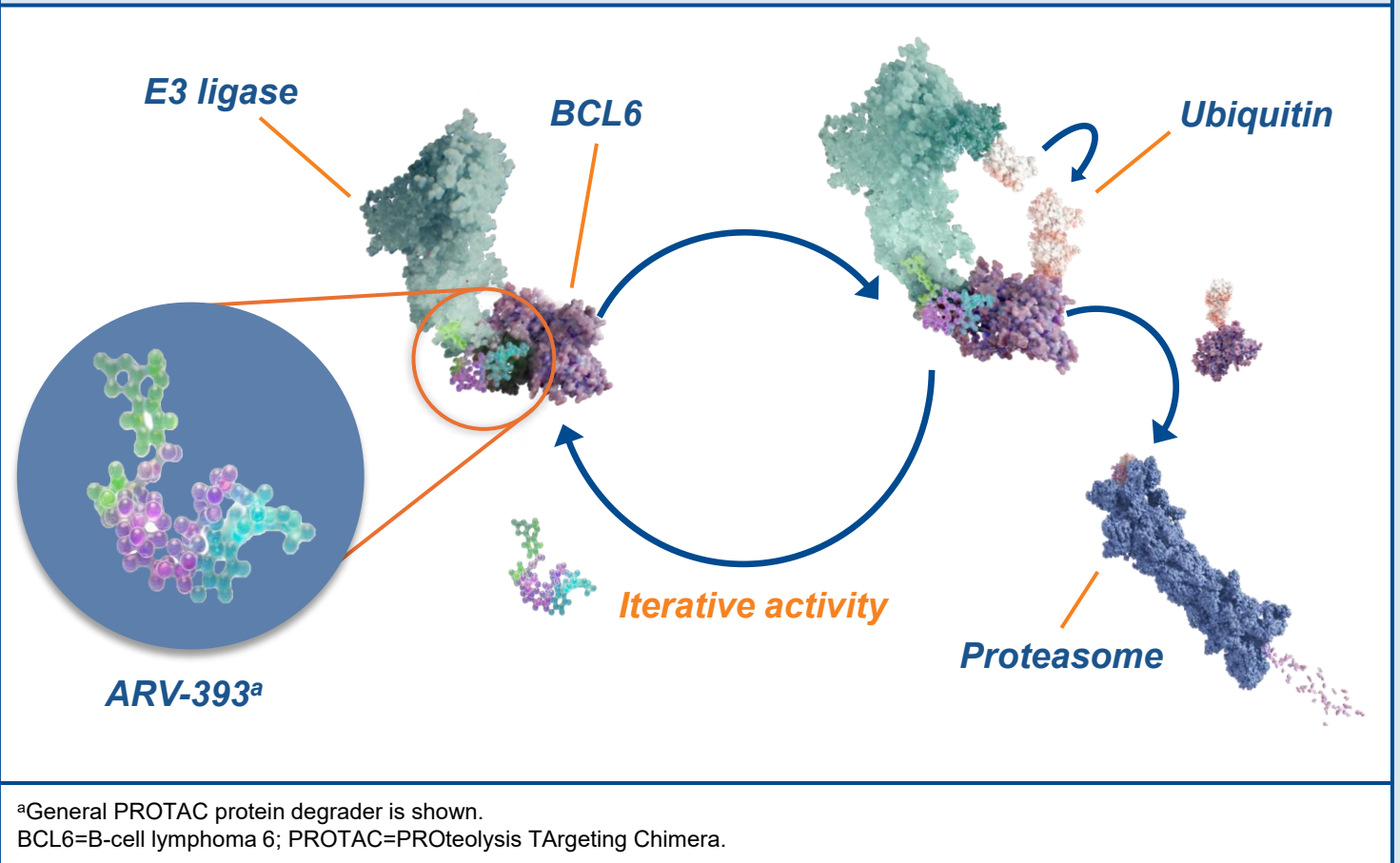
Conclusions

- ARV-393 demonstrates synergistic antitumor activity, including complete regressions, in combination with SOC agents and select investigational SMIs in high-grade B-cell lymphoma (HGBCL) and aggressive DLBCL models
- These findings support future clinical investigation of ARV-393 in combination with SOC chemotherapy, SOC biologics, and investigational SMIs in patients with DLBCL
 - Preliminary studies demonstrating that ARV-393 increases CD20 expression provide additional support for the exploration of combinations with CD20-targeted agents and in the context of low or loss of CD20 expression

Background

- BCL6 is a preclinically validated oncogenic driver of DLBCL historically considered to be undruggable¹⁻³
- Given the heterogeneity and multiple resistance mechanisms of DLBCL and that BCL6 regulates hundreds of genes linked to oncogenesis and resistance,¹ BCL6 degradation has the potential for broad drug combinability
- 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 (Figure 1)⁴

Figure 1: Mechanism of action of ARV-393



Methods

ARV-393 in Combination With R-CHOP

- A SU-DHL-4 cell line–derived xenograft (CDX) mouse model representing a HGBCL (with MYC, B-cell lymphoma 2 [BCL2], and BCL6 rearrangements) was used to evaluate ARV-393 in combination with rituximab, CHOP, and R-CHOP
 - ARV-393 6 mg/kg or 30 mg/kg was administered orally (PO) once daily (QD) for 28 days; rituximab 3 mg/kg was administered intravenously (IV) on days 1, 8, 15, and 22; CHOP (30:2.475:0.375:0.15 mg/kg) was given IV on day 1 (prednisone was given PO QD on days 1–5); and R-CHOP followed these same dosing methods. The ARV-393 6 mg/kg dose was used for combination studies
 - Control groups included mice that received an immunoglobulin G1 (IgG1) IV on days 1, 8, 15, and 22 or mice treated with the oral vehicle QD

ARV-393 in Combination With SOC Biologics

- Using the SU-DHL-4 CDX mouse model, ARV-393 was evaluated in combination with clinically relevant doses of SOC biologic therapies
 - ARV-393 6 mg/kg PO QD was administered alone or in combination with tafasitamab (anti-CD19 biologic), polatuzumab vedotin (anti-CD79b antibody-drug conjugate), or rituximab
 - Tafasitamab 10 mg/kg was administered IV on days 1, 4, 8, 15, and 22; polatuzumab vedotin 1 mg/kg was administered IV on day 1; and rituximab 3 mg/kg or 10 mg/kg was administered IV on days 1, 8, 15, and 22
 - Control groups included mice that received IgG1 IV on days 1, 8, 15, and 22; mice treated with the oral vehicle QD; and mice that received lenalidomide 10 mg/kg PO QD combined with tafasitamab

ARV-393 in Combination With SMIs

- ARV-393 was evaluated in combination with SMIs in HGBCL or aggressive activated B-cell (ABC) DLBCL CDX models
 - ARV-393 30 mg/kg PO QD was administered alone or in combination with acalabrutinib (BTK tyrosine kinase [BTK] SMI) or tazemetostat (enhancer of zeste homolog 2 [EZH2] SMI); ARV-393 3 mg/kg PO QD was administered alone or in combination with venetoclax (BCL2 SMI)
 - Acalabrutinib 2 mg/kg PO was administered twice daily (BID) to mice bearing the ABC OCI-Ly10 MYD88-positive CDX, venetoclax 100 mg/kg PO QD to mice bearing the BCL2-positive OCI-Ly1 CDX, and tazemetostat 300 mg/kg PO BID to mice bearing the EZH2-mutant SU-DHL-6 HGBCL CDX
 - One group of mice from each model received the oral vehicle QD

Results

ARV-393 in Combination With R-CHOP

- The combination of ARV-393 with rituximab, CHOP, or R-CHOP (the first-line SOC therapy for DLBCL) all resulted in tumor regressions; ARV-393 combined with R-CHOP induced complete regressions and had significantly higher TGI compared with rituximab, CHOP, R-CHOP, or ARV-393 alone (Figure 3)
 - ARV-393 induced complete regressions in 4/10 mice when combined with rituximab, in 6/10 mice when combined with CHOP, and in 10/10 mice when combined with R-CHOP
 - Body weights were maintained with monotherapy and combination treatments

ARV-393 in Combination With SOC Biologics

- The combination of ARV-393 with SOC biologics targeting CD19 (tafasitamab), CD79b (polatuzumab vedotin), or CD20 (rituximab) resulted in tumor regressions and demonstrated significantly stronger TGI compared with either agent alone (Figure 4)
 - ARV-393 combined with tafasitamab induced complete regressions in 10/10 mice (Figure 4A)
 - In contrast, tafasitamab combined with lenalidomide resulted in 55% TGI
 - ARV-393 combined with polatuzumab vedotin induced complete regressions in 4/10 mice (Figure 4B)
 - ARV-393 combined with rituximab 3 mg/kg or 10 mg/kg induced complete regressions in 9/10 and 9/9 mice, respectively; of note, ARV-393 monotherapy resulted in a significant increase in CD20 expression compared with vehicle (Figure 4C)
 - Body weights were maintained with monotherapy and combination treatments

ARV-393 in Combination With SMIs

- The combination of ARV-393 with SMIs of BTK (acalabrutinib), BCL2 (venetoclax), or EZH2 (tazemetostat) demonstrated strong TGI, including tumor regressions in all mice (Figure 5)
 - ARV-393 combined with acalabrutinib showed significantly stronger TGI than either agent alone (Figure 5A)
 - ARV-393 combined with venetoclax demonstrated significantly stronger TGI compared with ARV-393 alone, whereas venetoclax monotherapy resulted in rebound of tumor growth and progressive disease (Figure 5B)
 - ARV-393 combined with tazemetostat showed significantly stronger TGI than either ARV-393 or tazemetostat monotherapy (Figure 5C), consistent with literature reports showing that BCL6 and EZH2 play cooperative roles in lymphomagenesis⁷
 - In this model, MYC, EZH2, and BCL2 protein levels were increased by 56%, 66%, and 12%, respectively, with ARV-393 alone vs vehicle, but were decreased by 75%, 80%, and 96%, respectively, with ARV-393 plus tazemetostat vs vehicle, demonstrating a synergistic reduction in proteins known to drive lymphoma cell growth
 - BCL6 degradation was greater with ARV-393 combined with tazemetostat vs ARV-393 alone (87% vs 65%)
 - Body weights were maintained with monotherapy and combination treatments, with dosing holidays implemented in the venetoclax and tazemetostat combinations

Figure 3: ARV-393 in combination with R-CHOP (SU-DHL-4 model)

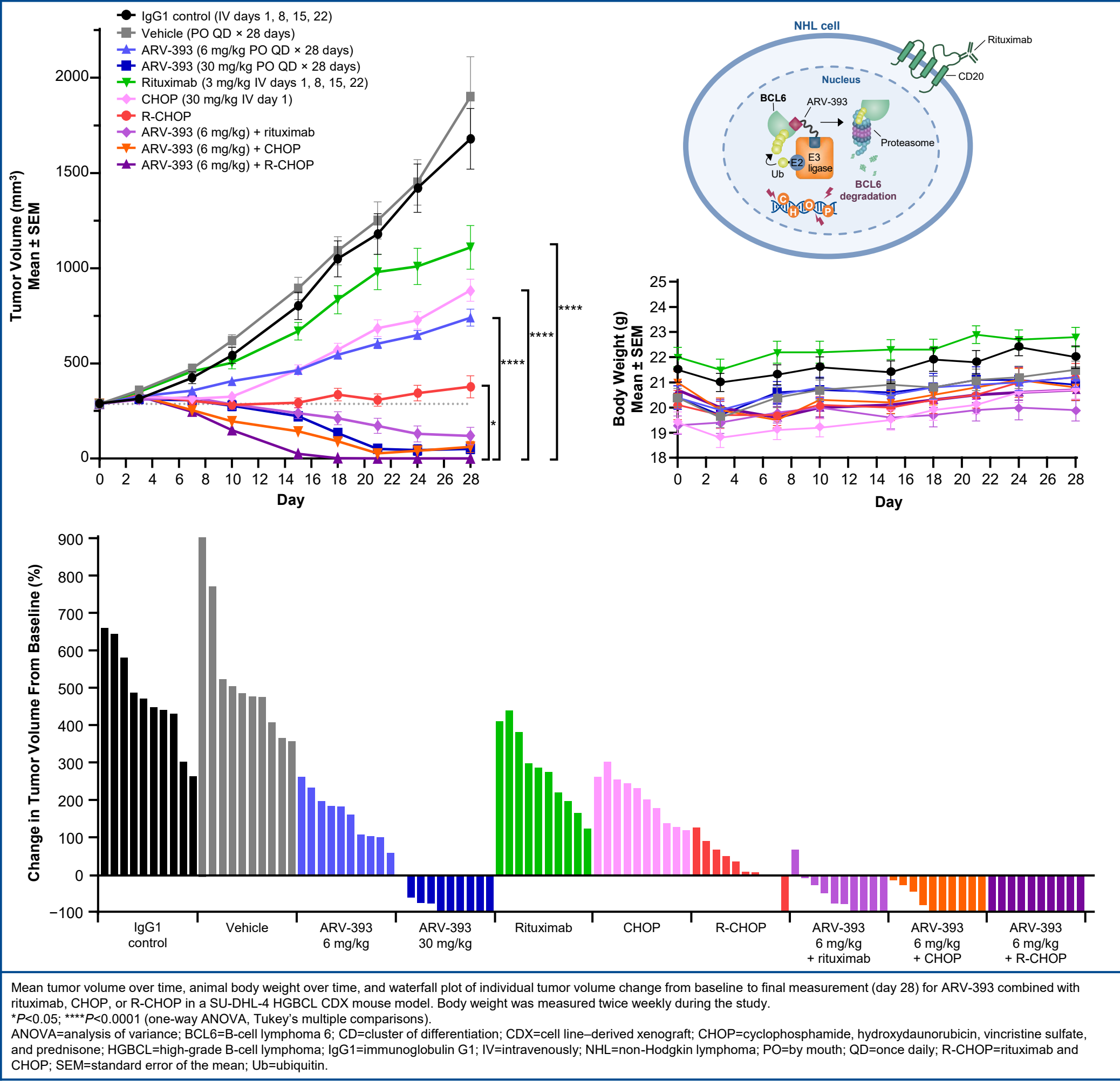
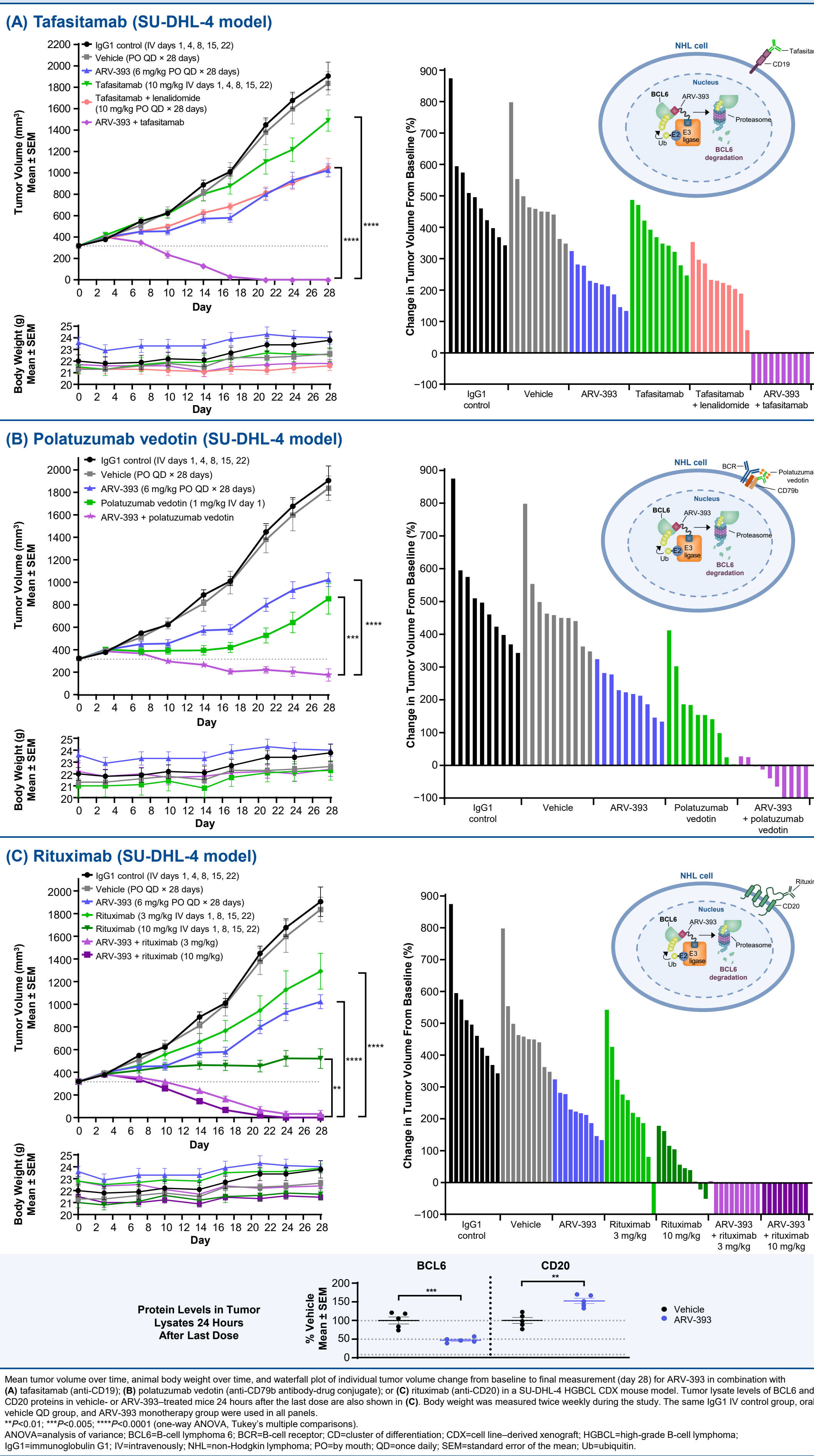


Figure 4: ARV-393 in combination with (A) tafasitamab, (B) polatuzumab vedotin, or (C) rituximab



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Disclosure

All authors are employees and shareholders of Arvinas Operations, Inc. Anna Van Acker, Dan Sherman, Sean Landrette, and Sheryl M Gough also hold patents with Arvinas Operations, Inc.

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