

ARV-393, a PROTAC BCL6 Degradator, 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-therapeutic 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

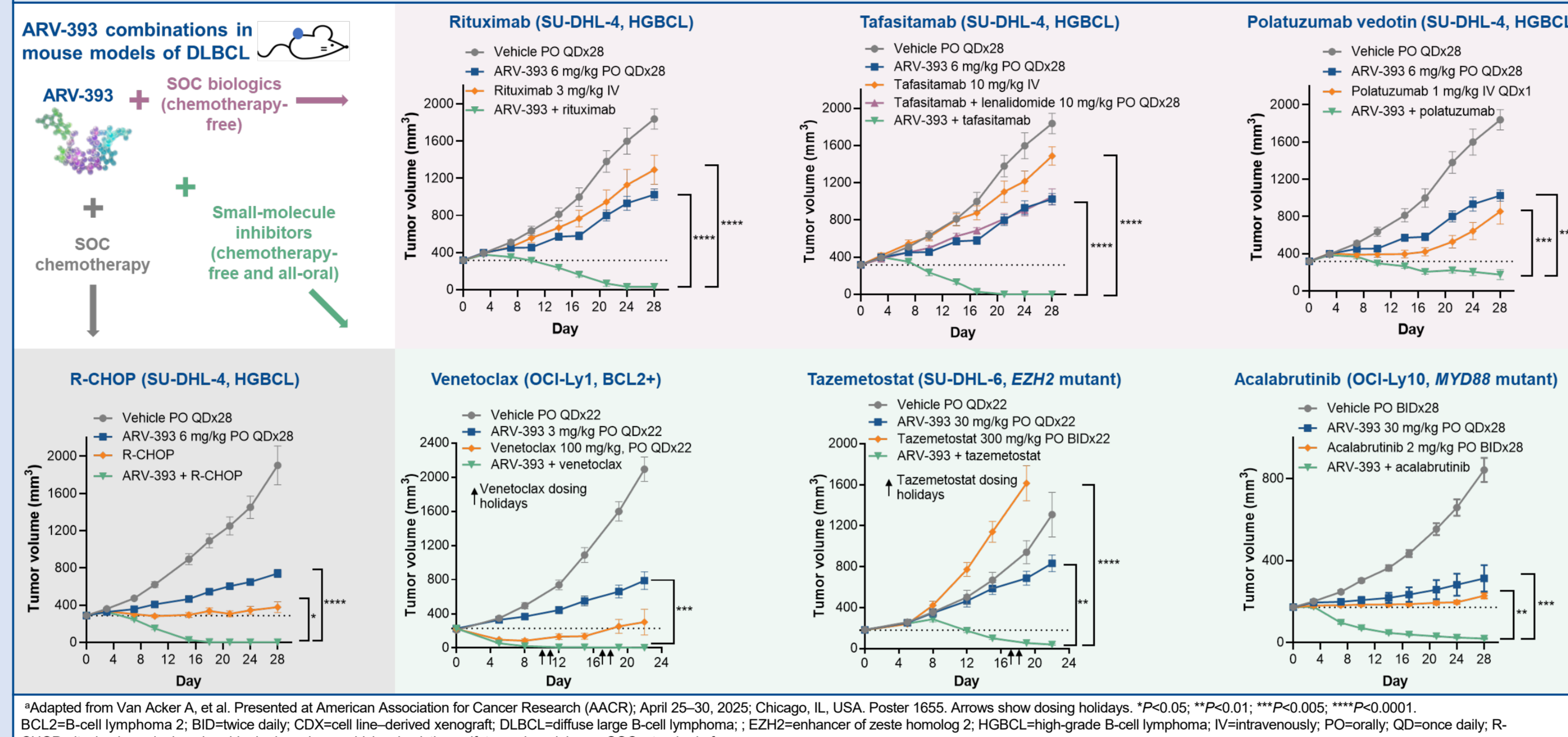
Conclusions

- 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 this chemotherapy-free combination in patients with DLBCL

Background

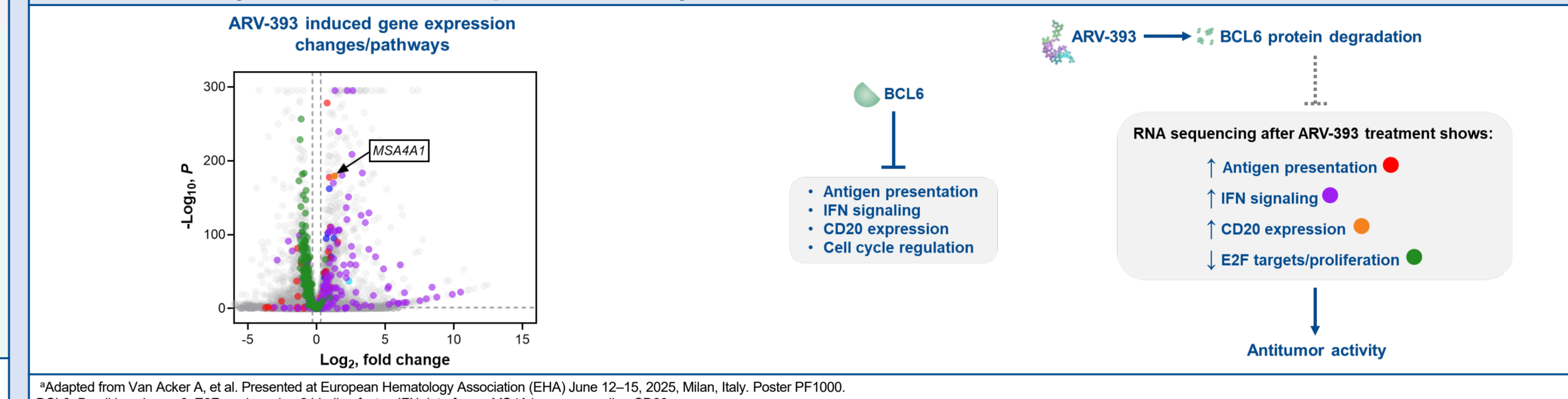
- Despite significant progress made in the treatment of non-Hodgkin lymphoma (NHL) through advancements with immunotherapy, autologous stem cell transplantation, chimeric antigen receptor T-cell therapies, bispecific antibodies, and other targeted therapies, many patients ultimately experience disease progression or relapse¹⁻³
- 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 NHL⁴⁻⁶
- ARV-393, a PROTAC BCL6 degrader, directly binds an E3 ubiquitin ligase and BCL6 to induce the ubiquitination of BCL6 and its subsequent proteasomal degradation⁷
- 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 DLBCL⁹



- 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 agents¹¹⁻¹³
- Emerging research suggests that the clinical benefit of CD20×CD3 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 CD20⁹ 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 antibody⁹



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 lines¹⁶
 - 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

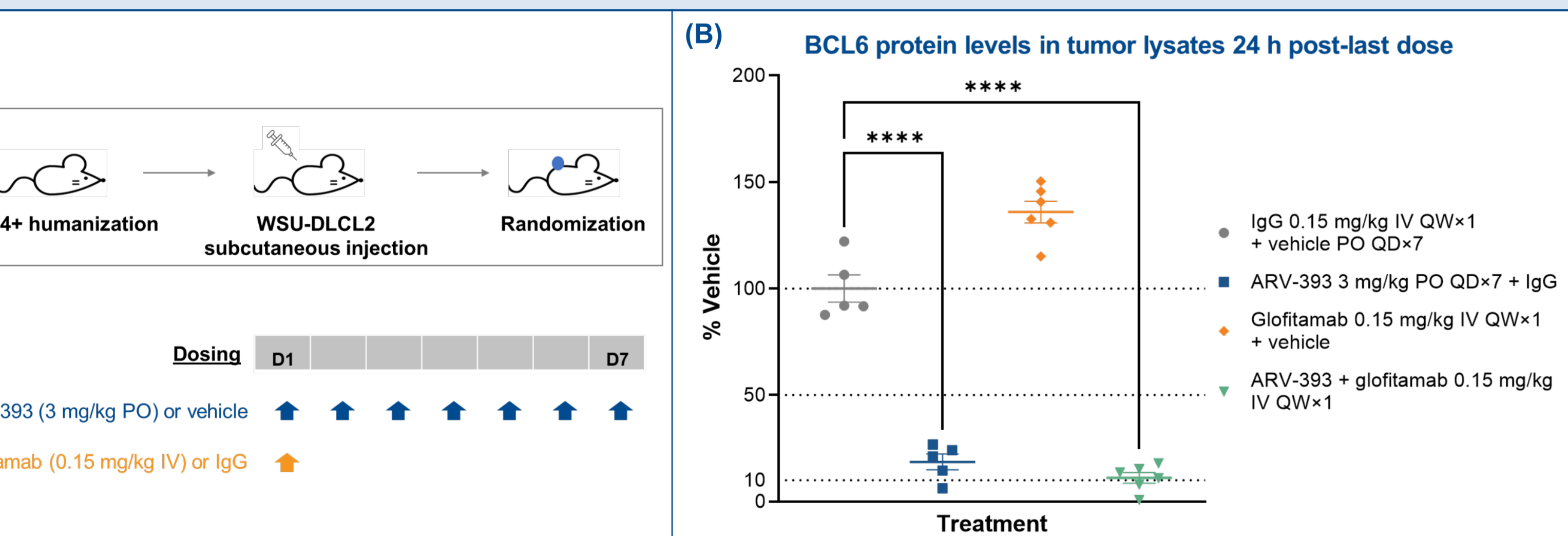


Figure 4: Treatment with ARV-393 or glofitamab in a humanized WSU-DLCL2 HGBCL CDX model

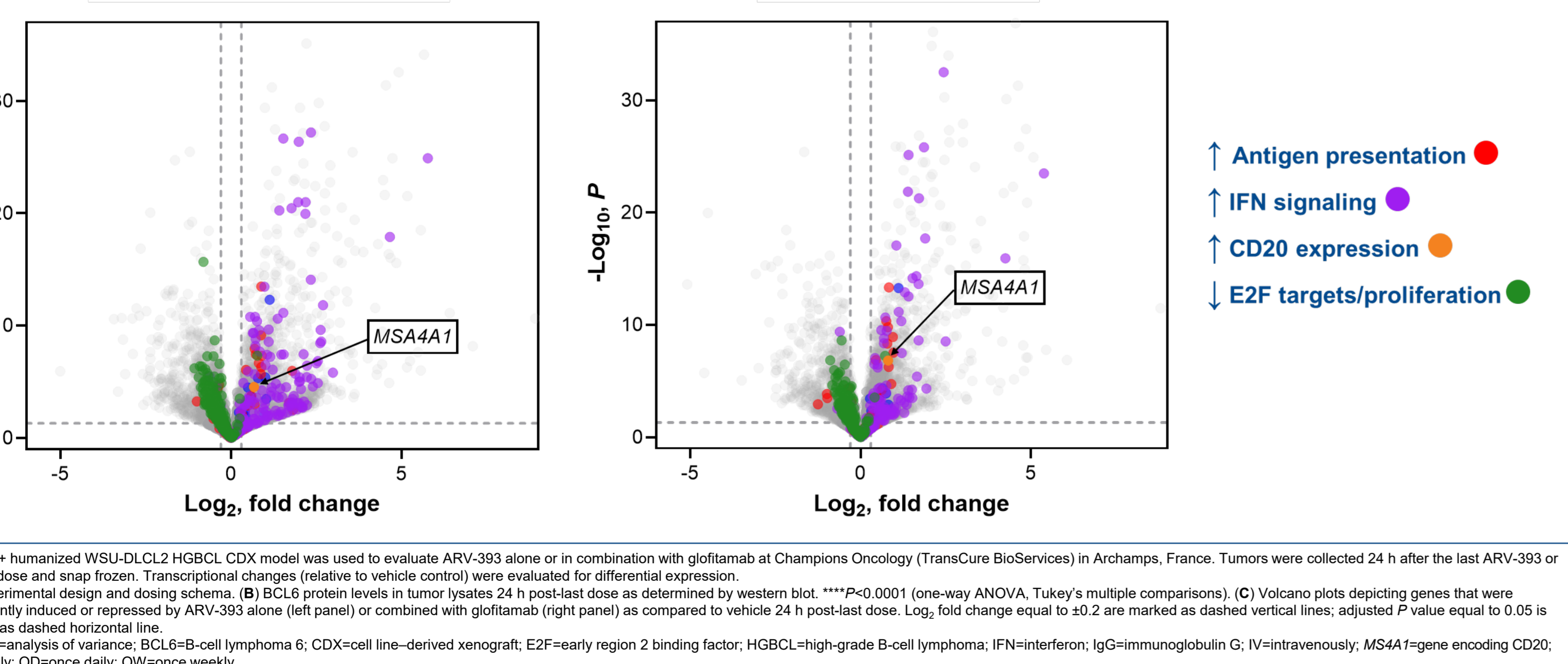
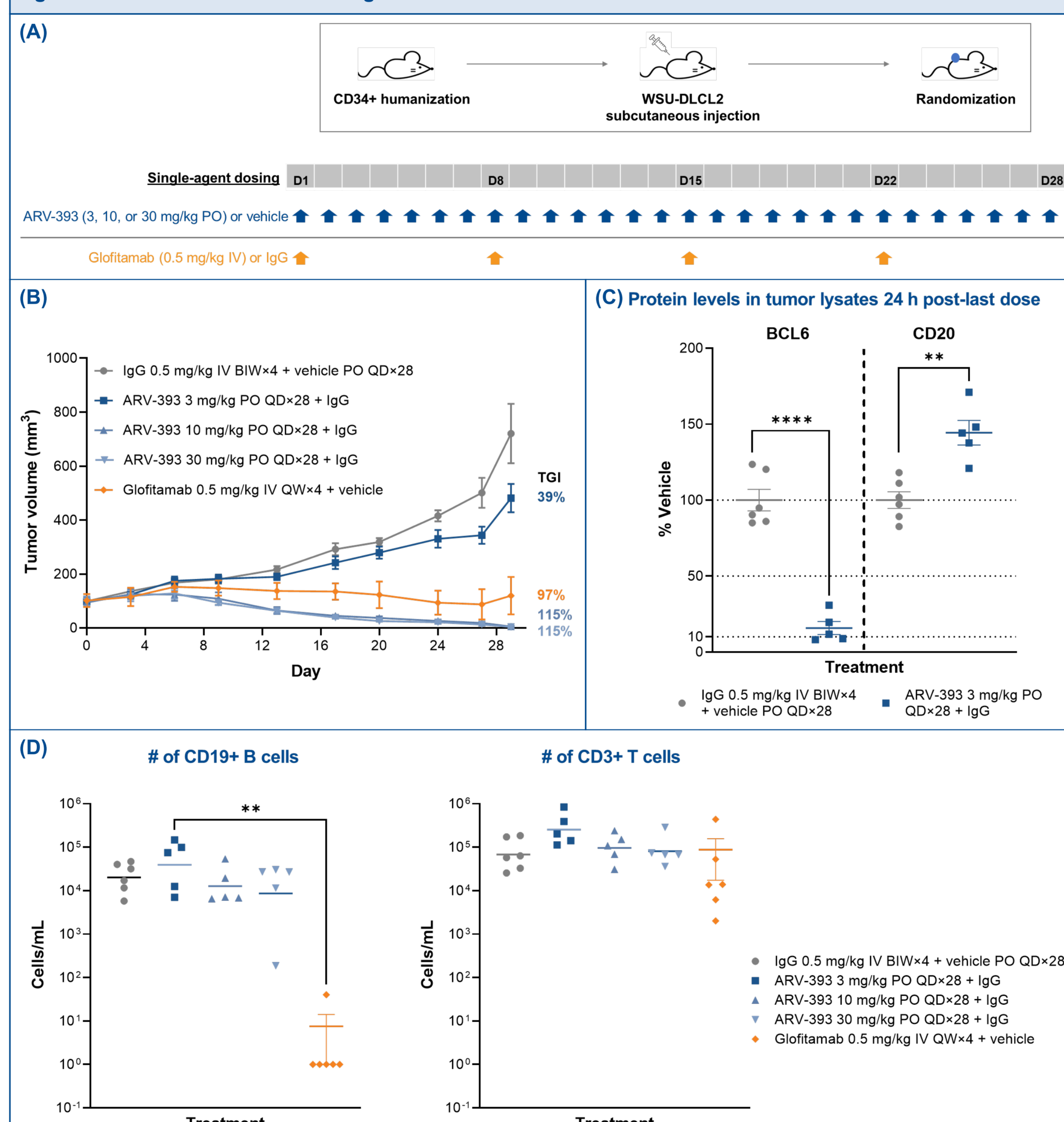


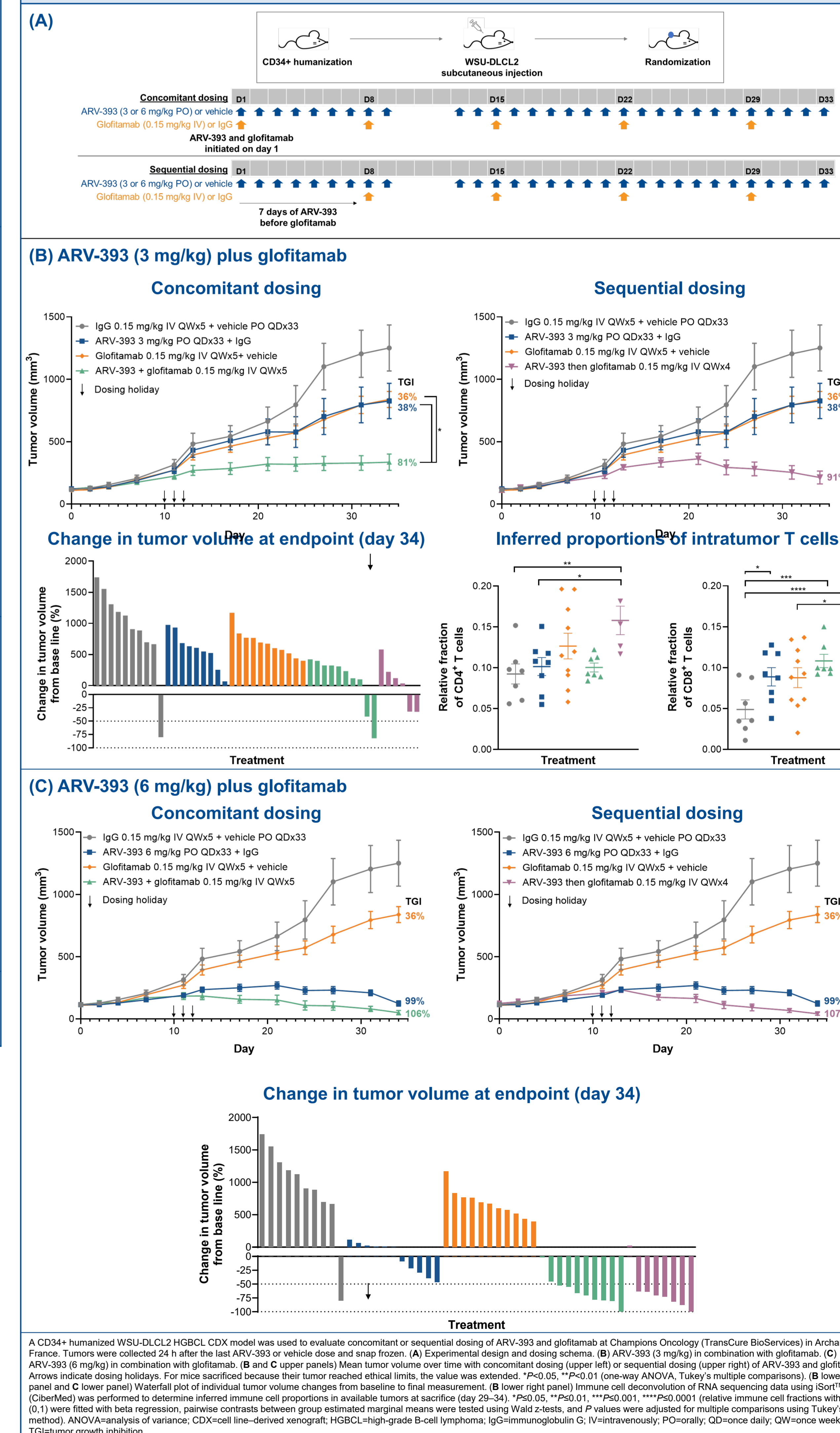
Figure 4: Treatment with ARV-393 or glofitamab in a humanized WSU-DLCL2 HGBCL CDX model



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



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