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- 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

- 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

- ARV-393 demonstrates synergistic antitumor activity, including complete regressions, in combination with SOC agents and select investigational SMLs 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 SMLs 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

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- 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

General PROTAC protein degrader is shown.
 BCL6-B-cell lymphoma 6; PROTAC=Proteolysis Targeting Chimera.

- 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

- The combination of ARV-393 with SOC biologics targeting CD19 (afasitamab), 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 afasitamab induced complete regressions in 10/10 mice (**Figure 4A**)
 - In contrast, afasitamab 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

- 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 1: ARV-393 inhibits tumor growth and improves body weight in a murine model of pancreatic cancer.

Top Left: Schematic of NHI cell. The diagram shows a cell with a nucleus containing ARV-393, a mitochondrion, and a Golgi apparatus. ARV-393 is shown inhibiting the cell cycle and promoting apoptosis. The cell is labeled 'NHI cell' and 'Pancreas'.

Top Right: Tumor Volume (mm³) Mean $\pm$ SEM. This line graph shows tumor volume over 28 days for various treatment groups. The groups are: IgG1 control (IV; days 1, 8, 15, 22), Vehicle (PO; QD $\times$ 28 days), ARV-393 (6 mg/kg PO; QD $\times$ 28 days), ARV-393 (30 mg/kg PO; QD $\times$ 28 days), Rituximab (3 mg/kg IV; days 1, 8, 15, 22), CHOP (30 mg/kg IV; day 1), R-CHOP, ARV-393 (6 mg/kg) + rituximab, ARV-393 (6 mg/kg) + CHOP, and ARV-393 (6 mg/kg) + R-CHOP. The graph shows that ARV-393 treatment significantly reduces tumor volume compared to control and vehicle groups, and that combination treatments with rituximab or CHOP further improve outcomes.

Middle Right: Body Weight (g) Mean $\pm$ SEM. This line graph shows body weight over 28 days for the same treatment groups. The graph indicates that ARV-393 treatment does not significantly affect body weight, suggesting it is well-tolerated.

Bottom: Change in Tumor Volume From Baseline (%). This bar graph shows the percentage change in tumor volume from baseline for the treatment groups. The groups are: IgG1 control, Vehicle, ARV-393 (6 mg/kg), ARV-393 (30 mg/kg), Rituximab, CHOP, R-CHOP, ARV-393 (6 mg/kg) + rituximab, ARV-393 (6 mg/kg) + CHOP, and ARV-393 (6 mg/kg) + R-CHOP. The graph shows that ARV-393 treatment significantly reduces tumor volume, and that combination treatments with rituximab or CHOP further improve outcomes.

ANOVA=analysis of variance; BCL6=B-cell lymphoma 6; BCR=B-cell receptor; CDX=cell line-derived xenograft; HGBCL=high-grade B-cell lymphoma; IgG1=immunoglobulin G1; IV=intravenously; NHL=non-Hodgkin lymphoma; PO=by mouth; QD=once daily; SEM=standard error of the mean; Ub=ubiquitin.

- ARV-393 rapidly degrades BCL6 in DLBCL cell lines (>90% degradation in 2 hours), and its iterative activity overcomes rapid BCL6 resynthesis (**Figure 2**); single-agent ARV-393 induced potent TGI, including regressions, in DLBCL patient-derived xenograft models⁵
- ARV-393 monotherapy is being evaluated in a phase 1 trial (NCT06393738) in patients with non-Hodgkin lymphoma, including DLBCL⁶
- Here, we explore the preclinical efficacy of ARV-393 in combination with SOC therapies and SMIs targeting complementary mechanistic pathways in DLBCL

(A) After ARV-393 washout, BCL6 levels nearly returned to baseline within 2 hours

hours post washout	BCL6 Levels (%)
0	100
2	~25
4	~75
6	~85
8	~90
10	~95
12	100

(B) ARV-393 rapidly degrades >90% of BCL6 within 2 hours, faster than the cell can resynthesize it

hours post washout	0h washout (%)	2h washout (%)	24h washout (%)
0	100	100	100
0.01	~95	~90	~90
0.1	~90	~80	~85
1	~85	~40	~75
2	~80	~20	~65
4	~75	~10	~55
6	~70	~5	~45
8	~65	~2	~35
10	~60	~1	~25
12	~55	~0	~15
14	~50	~0	~10
16	~45	~0	~8
18	~40	~0	~5
20	~35	~0	~3
22	~30	~0	~2
24	~25	~0	~1

Please scan this QR code to view previously presented ARV-393 preclinical data.⁴

(A) BCL6 protein levels quantified by Western blot in the DLBCL OCI-Ly1 cell line, following a 4-hour treatment with ARV-393 15 nM. Duplicate samples shown following ARV-393 washout and addition of ceramide ligand to block residual ARV-393. **(B)** BCL6 degradation time-course in OCI-Ly1 cells. BCL6-synthetic gene 6; DC=short-half maximal degradation concentration; DLBCL=diffuse large-B-cell lymphoma; D_{max}=maximum level of degradation; DMSO=dimethyl sulfoxide; GAPDH=glyceraldehyde-3-phosphate dehydrogenase.

(A) Tafasitamab (SU-DHL-4 model)

Legend for Tumor Volume and Body Weight:

- IgG1 control (IV; days 1, 4, 8, 15, 22)
- ▬ Vehicle (PO; QD × 28 days)
- ▲ ARV-393 (6 mg/kg PO; QD × 28 days)
- ◆ Tafasitamab (10 mg/kg IV; days 1, 4, 8, 15, 22)
- ◇ Tafasitamab + lenalidomide (10 mg/kg PO; QD × 28 days)
- ARV-393 + tafasitamab

Figure 10 Data Summary:

Day	IgG1 control (mm ³)	Vehicle (mm ³)	ARV-393 (mm ³)	Tafasitamab (mm ³)	Tafasitamab + lenalidomide (mm ³)	ARV-393 + tafasitamab (mm ³)
0	350	350	350	350	350	350
4	400	400	400	400	400	400
8	500	500	500	500	500	500
12	600	600	600	600	600	600
16	900	900	900	900	900	900
20	1300	1300	1300	1300	1300	1300
24	1600	1600	1600	1600	1600	1600
28	1800	1800	1800	1800	1800	1800

Figure 10 Inset: BCL6 Regulation in a B Cell

The inset diagram illustrates the regulation of BCL6 in a B cell. BCL6 is shown as a transcription factor that inhibits the expression of ARV-393. ARV-393 is shown as a protein that inhibits the expression of BCL6. The diagram also shows the expression of BCL6 and ARV-393 in a B cell, and the effect of BCL6 on B cell migration.

Figure 1: ARV-393 inhibits tumor growth and body weight loss in a murine model of metastatic melanoma.

Schematic of BCL6 Signaling Pathway: ARV-393 inhibits BCL6, which in turn inhibits the transcription of genes including *CD79b*. BCL6 also promotes the transcription of *CD79b*. The pathway involves BCL6, ARV-393, and the transcription of *CD79b*.

Tumor Volume (mm³) Mean $\pm$ SEM:

Day	Vehicle (PO; QD $\times$ 28 days)	ARV-393 (6 mg/kg PO; QD $\times$ 28 days)	Polatuzumab vedotin (1 mg/kg IV; day 1)	ARV-393 + polatuzumab vedotin
0	400	400	400	400
2	450	450	450	450
4	500	500	450	450
6	550	550	450	450
8	600	600	450	450
10	650	650	450	450
12	700	700	450	450
14	800	800	450	450
16	900	900	450	450
18	1000	1000	450	450
20	1100	1100	450	450
22	1200	1200	450	450
24	1300	1300	450	450
26	1400	1400	450	450
28	1500	1500	450	450

Body Weight (g) Mean $\pm$ SEM:

Day	Vehicle (PO; QD $\times$ 28 days)	ARV-393 (6 mg/kg PO; QD $\times$ 28 days)	Polatuzumab vedotin (1 mg/kg IV; day 1)	ARV-393 + polatuzumab vedotin
0	24.0	24.0	24.0	24.0
2	23.5	23.5	23.5	23.5
4	23.0	23.0	23.0	23.0
6	22.5	22.5	22.5	22.5
8	22.0	22.0	22.0	22.0
10	21.5	21.5	21.5	21.5
12	21.0	21.0	21.0	21.0
14	20.5	20.5	20.5	20.5
16	20.0	20.0	20.0	20.0
18	20.5	20.5	20.5	20.5
20	21.0	21.0	21.0	21.0
22	21.5	21.5	21.5	21.5
24	22.0	22.0	22.0	22.0
26	22.5	22.5	22.5	22.5
28	23.0	23.0	23.0	23.0

Change in Tumor Volume From Baseline (%):

Treatment	Change in Tumor Volume From Baseline (%)
lgS1 control	~800
Vehicle	~400
ARV-393	~200
Polatuzumab vedotin	~100
ARV-393 + polatuzumab vedotin	~-50

A

Tumor Volume (mm^3)
Mean $\pm$ SEM

Day

Legend:
 - IgG1 control (IV; days 1, 4, 8, 15, 22)
 - Vehicle (PO; OD + 28 days)
 - ARV-393 (6 mg/kg PO; OD + 28 days)
 - Rituximab (3 mg/kg IV; days 1, 8, 15, 22)
 - Rituximab (10 mg/kg IV; days 1, 8, 15, 22)
 - ARV-393 + rituximab (3 mg/kg)
 - ARV-393 + rituximab (10 mg/kg)

B

Body Weight (g)
Mean $\pm$ SEM

Day

C

Change In Tumor Volume From Baseline (%)

Legend:
 - IgG1 control
 - Vehicle
 - ARV-393
 - Rituximab 3 mg/kg
 - Rituximab 10 mg/kg
 - ARV-393 + rituximab 3 mg/kg
 - ARV-393 + rituximab 10 mg/kg

D

Schematic diagram illustrating the mechanism of action. ARV-393 binds to BCL6, leading to its ubiquitination and subsequent proteasomal degradation. The diagram shows BCL6 interacting with ARV-393, which is bound to E3 ubiquitin ligase complex (CUL1, UBR1, UBR2), resulting in BCL6 ubiquitination and degradation.

Study Design Schematic:

- Vehicle (n=393)
- ARV-393 (100 mg/kg, 24h) (n=393)

Protein Levels in Tumor Lysates 24 Hours After Last Dose

BCL6: The dot plot shows protein levels for Vehicle (black dots) and ARV-393 (blue dots). The Vehicle group has a mean level of approximately 100, while the ARV-393 group has a significantly lower mean level of approximately 50. The difference is statistically significant (***).

CD20: The dot plot shows protein levels for Vehicle (black dots) and ARV-393 (blue dots). The Vehicle group has a mean level of approximately 100, while the ARV-393 group has a significantly higher mean level of approximately 150. The difference is statistically significant (**).

Legend:

- Vehicle
- ARV-393

- 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

- 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 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 (Bcrn tyrosine kinase [BTK] SMI) or tazemetostat (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

(A) Acalabrutinib (OCI-Ly10 model)

The figure illustrates the efficacy of Acalabrutinib in the OCI-Ly10 model. The schematic shows Acalabrutinib inhibiting BTK, which in turn affects the BCL2 signaling pathway, leading to BCL2 degradation. The bar graph shows that Acalabrutinib treatment significantly reduces tumor volume compared to Vehicle and ARV-393. The line graphs show that Acalabrutinib treatment significantly reduces tumor volume and body weight over 28 days compared to Vehicle and ARV-393.

Legend:

- Vehicle (PO; BID × 28 days)
- ARV-393 (30 mg/kg PO; QD × 28 days)
- Acalabrutinib (2 mg/kg PO; BID × 28 days)
- ARV-393 + acalabrutinib

Graphs:

- Tumor Volume (mm³) Mean ± SEM:** Shows tumor volume over 28 days. Acalabrutinib treatment significantly reduces tumor volume compared to Vehicle and ARV-393.
- Change in Tumor Volume From Baseline (%):** Shows the percentage change in tumor volume from baseline. Acalabrutinib treatment significantly reduces tumor volume compared to Vehicle and ARV-393.
- Body Weight (g) Mean ± SEM:** Shows body weight over 28 days. Acalabrutinib treatment significantly reduces body weight compared to Vehicle and ARV-393.

Figure 1: ARV-393 inhibits RBLA degradation and tumor growth.

Schematic of RBLA Degradation: The diagram shows a cell with a nucleus containing DNA. A red box labeled 'ARV-393' is shown inhibiting the process. A green box labeled 'RBLA' is shown being degraded by a 'Protease' (indicated by a red 'X' over the protease). The degradation of RBLA leads to 'RBLA degradation' (indicated by a red 'X' over the RBLA). The process is also labeled 'ARV-393' and 'RBLA'.

Change in Tumor Volume From Baseline (%)

Treatment	Change in Tumor Volume From Baseline (%)
Vehicle	~1200
ARV-393	~400
Venetoclax	~700
ARV-393 + venetoclax	~100

Tumor Volume (mm³)

Day	ARV393 (3 mg/kg PO, QD × 22 days)	Venetoclax (100 mg/kg PO, QD × 22 days)	ARV393 + venetoclax
0	~200	~200	~200
4	~400	~150	~150
8	~500	~100	~100
12	~1000	~400	~100
16	~1600	~500	~100
20	~2100	~600	~100
22	~2200	~700	~100

Body Weight (g)

Day	ARV393 (3 mg/kg PO, QD × 22 days)	Venetoclax (100 mg/kg PO, QD × 22 days)	ARV393 + venetoclax
0	~20	~20	~20
4	~20	~20	~20
8	~20	~20	~20
12	~20	~20	~20
16	~20	~20	~20
20	~20	~20	~20
22	~20	~20	~20

Figure 1: ARV-393 inhibits BCL-9-mediated transcriptional activation of cyclin D1.

Schematic of BCL-9 Complex: The BCL-9 complex (BCL9, ARV393, E3, and BCL9 degradation) is shown in the cytoplasm, interacting with the TCF4 transcription factor in the nucleus. The complex is involved in the transcriptional activation of cyclin D1, which promotes cell cycle progression.

Tumor Volume Change (Bar Graph): The bar graph shows the change in tumor volume from baseline (%) for various treatment groups. The groups are: Vehicle (black bars), ARV-393 (green bars), Tazemetostat (blue bars), and ARV-393 + tazemetostat (purple bars). The ARV-393 group shows a significant reduction in tumor volume compared to the Vehicle group.

Tumor Volume (mm³) (Line Graph): The line graph shows the tumor volume (mm³) over 24 days for the same treatment groups. The ARV-393 group shows a significant reduction in tumor volume compared to the Vehicle group.

Body Weight (g) (Line Graph): The line graph shows the body weight (g) over 24 days for the same treatment groups. All groups maintain similar body weights, indicating that the treatments do not cause significant weight loss.

Protein Levels in Tumor Lysates 24 Hours After Last Dose

Mean tumor volume over time, animal body weight over time, and waterfall plot of individual tumor volume change from baseline to final measurement (day 28 or 22) for ARV-393 in combination with (A) acalabrutinib (BTK SMN) in an ABC OCI-Ly10 (MYD88-mutant) CDX mouse model; (B) venetoclax (BCL2 SM) in a BCL2+ OCI-Ly1 CDX mouse model; (C) and (D) tazemetostat (EZH2 SM) in an EZH2-mutant SU-DHL-6 CDX mouse model. Tumor lysate levels of EZH2, MYC, BCL2, and BCL6 proteins in vehicle, ARV-393-, tazemetostat-, or ARV-393 + tazemetostat-treated mice 24 hours after the last dose are shown. (E) Body weight was measured twice weekly during the study.

* $P < 0.01$; ** $P < 0.005$; *** $P < 0.001$ (one-way ANOVA, Tukey's multiple-comparisons).
 ABC=activated B-cell; ABC=analysis of variance; BCL2=cell lymphoma 2; BCL6=B-cell lymphoma 6; BTK=Bruton tyrosine kinase; CDX=cell-line-derived xenograft; EZH2=enhancer of zeste homolog 2; NHL=non-Hodgkin lymphoma; PO=body weight; OD=once daily; SEM=standard error of the mean; SM=small-molecule inhibitor; Ub=ubiquitin.