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ARVINAS

Oral ARV-393 is a BCL6 Degrading PROTAC® Efficacious as a Monotherapy in B-Cell Lymphoma Preclinical CDX and PDX Models

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Background

BCL6 (B-cell lymphoma 6) is a major oncogenic driver of B-cell malignancies. Chromosome translocations that result in promoter substitution or point mutations in the 5'UTR region of *BCL6,* lead to deregulation of *BCL6* expression in germinal center lymphomas[1-4]. These genomic aberrations result in perpetual or overexpression of BCL6 which is sufficient to induce and maintain lymphomagenesis[5,6].

PROTAC® protein degraders harness the ubiquitin-proteasome system to induce the degradation of disease-causing proteins[7].

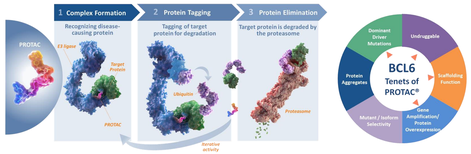

Figure 1. Mechanism of PROTAC® protein degradation and the ARVINAS Tenets of PROTAC® illustrating disease-causing mechanisms where a degradation approach could be advantageous; those most relevant to BCL6 are indicated.

Objective

Develop an orally bioavailable PROTAC degrader as a targeted therapy against the BCL6 transcription factor.

Key Findings

ARV-393:

- Is an orally bioavailable PROTAC BCL6 degrader that potently and rapidly degrades the BCL6 transcription factor;
- Inhibits the growth of diffuse large B-cell lymphoma (DLBCL) and Burkitt cell line models *in-vitro;*
- Demonstrates significant anti-tumor activity in:
  - DLBCL cell line-derived xenograft models (CDX);
  - Numerous Non-Hodgkin Lymphoma (NHL) **patient-derived xenograft (PDX)** models including GCB, ABC, GCB/ABC, BCL/NOS subtypes of DLBCL and Burkitt lymphoma.

Conclusions

ARV-393 is a potent orally bioavailable PROTAC BCL6 degrader demonstrating significant anti-tumor activity in numerous in-vivo DLBCL CDX and NHL PDX models as a monotherapy and could be an effective oral therapy for lymphoma patients.

ARV-393 Phase 1 study has opened in Relapsed/Refractory Non-Hodgkin Lymphoma (clinicaltrials.gov, NCT06393738) Trial in Progress abstract PB3043, EHA2024.

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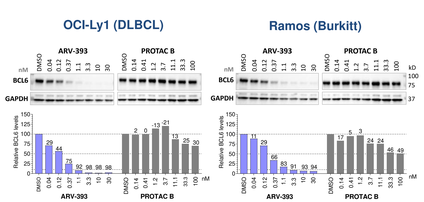
Results

ARV-393 potently and rapidly degrades BCL6 *in-vitro*



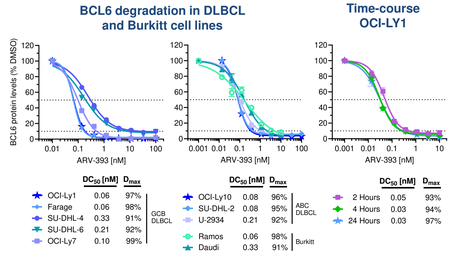


Figure 2. BCL6 degradation by ARV-393 in representative DLBCL and Burkitt lymphoma cell lines analyzed by western blot and semi-quantified by densitometry. GAPDH was used as a loading control to normalize BCL6 intensity. Percent degradation (change vs DMSO control) is indicated above bars in graph. The E3 ligase binding-inactive negative control analogue of ARV-393, PROTAC B, fails to degrade BCL6.

Figure 3. BCL6 protein levels quantified by ELISA in DLBCL cell lines OCI-Ly1, Farage, SU-DHL-4, SU-DHL-6, OCI-Ly7, OCI-Ly10, SU-DHL-2 and U-2932, and Burkitt cell lines Ramos and Daudi, following 24-hour treatment with ARV-393. Right, a BCL6 degradation time-course in OCI-Ly1. ARV-393 degrades >90% of BCL6 within 2 hours.

ARV-393 potently inhibits DLBCL and Burkitt cell growth *in-vitro*

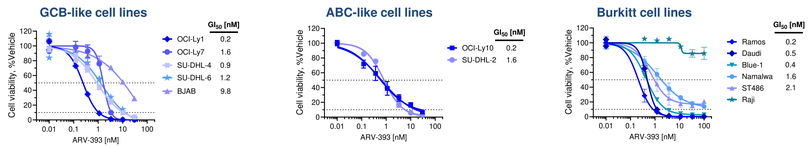


Figure 4. Growth inhibition of germinal center B-cell (GCB)- (left), activated B-cell (ABC)-like (middle) DLBCL, or right, Burkitt lymphoma cell line models by ARV-393. Cells were cultured in complete media using fetal bovine serum as recommended (ATCC). Cells were split, re-fed/dosed every 3 or 4 days for a total of 9- or 10-days for DLBCL lines, or for a total of 13 days for Burkitt lines. Cell viability was measured by CellTiter-Glo® Assay (Promega) and compared to vehicle (DMSO) controls. Curves are representative of 2-3 independent experiments per cell line.

ARV-393 induces dose-dependent tumor growth inhibition (TGI) correlating with BCL6 degradation in the OCI-Ly1 cell line xenograft model

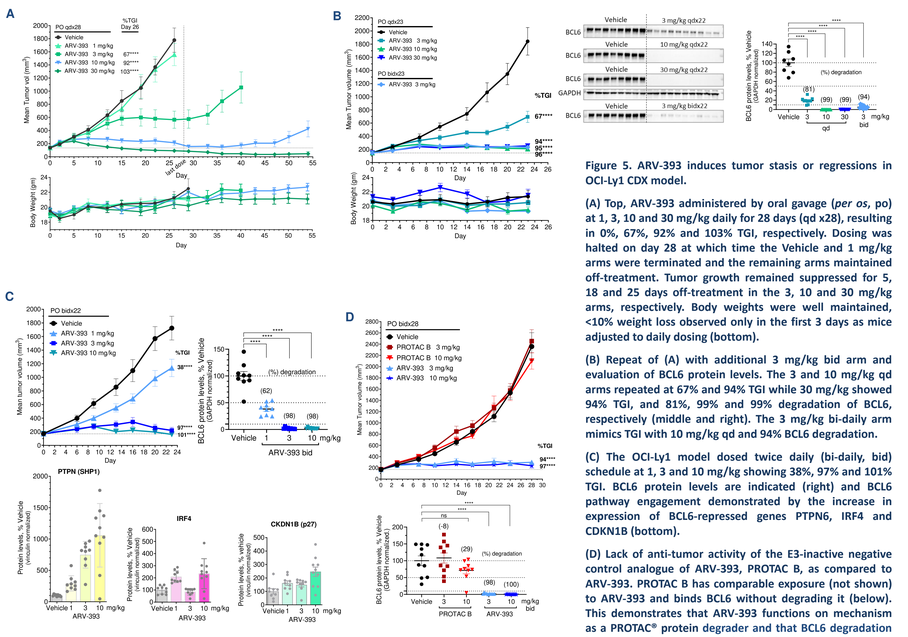


Figure 5. ARV-393 induces tumor stasis or regressions in OCI-Ly1 CDX model.

(A) Top, ARV-393 administered by oral gavage (*per os*, po) at 1, 3, 10 and 30 mg/kg daily for 28 days (qd x28), resulting in 0%, 67%, 92% and 103% TGI, respectively. Dosing was halted on day 28 at which time the Vehicle and 1 mg/kg arms were terminated and the remaining arms maintained off-treatment. Tumor growth remained suppressed for 5, 18 and 25 days off-treatment in the 3, 10 and 30 mg/kg arms, respectively. Body weights were well maintained, <10% weight loss observed only in the first 3 days as mice adjusted to daily dosing (bottom).

(B) Repeat of (A) with additional 3 mg/kg bid arm and evaluation of BCL6 protein levels. The 3 and 10 mg/kg qd arms repeated at 67% and 94% TGI while 30 mg/kg showed 94% TGI, and 81%, 99% and 99% degradation of BCL6, respectively (middle and right). The 3 mg/kg bi-daily arm mimics TGI with 10 mg/kg qd and 94% BCL6 degradation.

(C) The OCI-Ly1 model dosed twice daily (bi-daily, bid) schedule at 1, 3 and 10 mg/kg showing 38%, 97% and 101% TGI. BCL6 protein levels are indicated (right) and BCL6 pathway engagement demonstrated by the increase in expression of BCL6-repressed genes PTPN6, IRF4 and CDKN1B (bottom).

(D) Lack of anti-tumor activity of the E3-inactive negative control analogue of ARV-393, PROTAC B, as compared to ARV-393. PROTAC B has comparable exposure (not shown) to ARV-393 and binds BCL6 without degrading it (below). This demonstrates that ARV-393 functions on mechanism as a PROTAC® protein degrader and that BCL6 degradation is necessary for tumor growth inhibition.

ARV-393 demonstrates significant anti-tumor activity in DLBCL OCI-Ly7, SU-DHL-2 and HGBCL triple hit SU-DHL-4 models

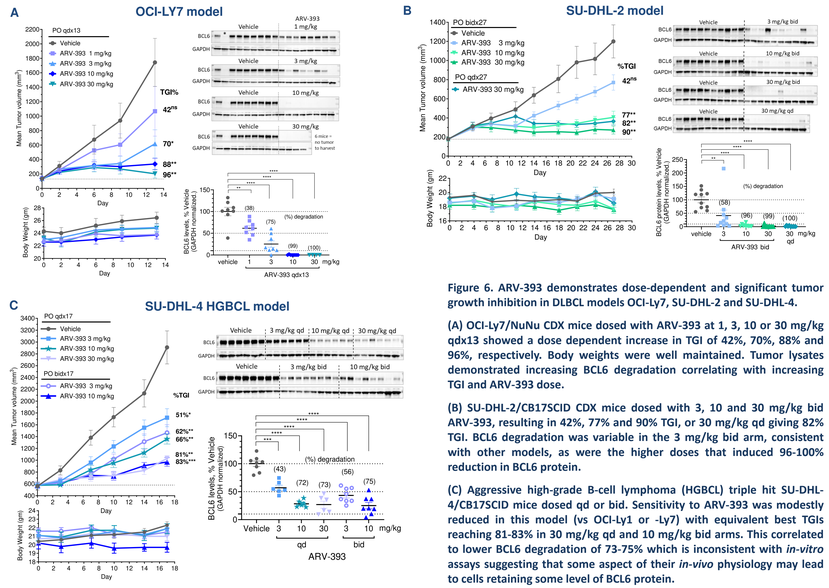


Figure 6. ARV-393 demonstrates dose-dependent and significant tumor growth inhibition in DLBCL models OCI-Ly7, SU-DHL-2 and SU-DHL-4.

(A) OCI-Ly7/NuNu CDX mice dosed with ARV-393 at 1, 3, 10 or 30 mg/kg qdx13 showed a dose dependent increase in TGI of 42%, 70%, 88% and 96%, respectively. Body weights were well maintained. Tumor lysates demonstrated increasing BCL6 degradation correlating with increasing TGI and ARV-393 dose.

(B) SU-DHL-2/CB17SCID CDX mice dosed with 3, 10 and 30 mg/kg bid ARV-393, resulting in 42%, 77% and 90% TGI, or 30 mg/kg qd giving 82% TGI. BCL6 degradation was variable in the 3 mg/kg bid arm, consistent with other models, as were the higher doses that induced 96-100% reduction in BCL6 protein.

(C) Aggressive high-grade B-cell lymphoma (HGBCL) triple hit SU-DHL-4/CB17SCID mice dosed qd or bid. Sensitivity to ARV-393 was modestly reduced in this model (vs OCI-Ly1 or -Ly7) with equivalent best TGIs reaching 81-83% in 30 mg/kg qd and 10 mg/kg bid arms. This correlated to lower BCL6 degradation of 73-75% which is inconsistent with *in-vitro* assays suggesting that some aspect of their *in-vivo* physiology may lead to cells retaining some level of BCL6 protein.

ARV-393 induces tumor regressions in the majority of BCL6-expressing NHL patient derived xenograft (PDX) models

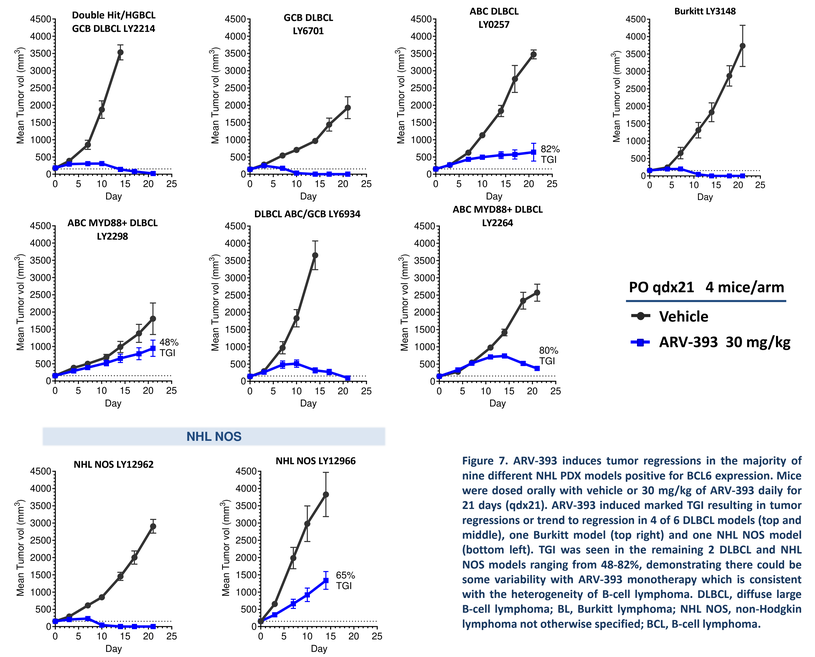


Figure 7. ARV-393 induces tumor regressions in the majority of nine different NHL PDX models positive for BCL6 expression. Mice were dosed orally with vehicle or 30 mg/kg of ARV-393 daily for 21 days (qdx21). ARV-393 induced marked TGI resulting in tumor regressions or trend to regression in 4 of 6 DLBCL models (top and middle), one Burkitt model (top right) and one NHL NOS model (bottom left). TGI was seen in the remaining 2 DLBCL and NHL NOS models ranging from 48-82%, demonstrating there could be some variability with ARV-393 monotherapy which is consistent with the heterogeneity of B-cell lymphoma. DLBCL, diffuse large B-cell lymphoma; BL, Burkitt lymphoma; NHL NOS, non-Hodgkin lymphoma not otherwise specified; BCL, B-cell lymphoma.

In-vivo methods

Female CB17-SCID mice were implanted subcutaneously with OCI-Ly1, SU-DHL-2 or SU-DHL-4 and NuNu females with OCI-Ly7 cells (10^7/100 µl/mouse). ARV-393 was formulated in a 40% HPBCD, pH 3.0 citrate buffer vehicle and dosed by oral gavage (*per os*, PO) to evaluate tumor growth inhibition (TGI). Mice were dosed once daily (qd) or twice daily (bidaily, bid), 8-10 mice/arm. Tumors were harvested 16-hours post-last dose and protein levels determined by traditional western blot and densitometry analyses to plot relative changes. Tumor volumes were calculated using (width² x length)/2, measured twice weekly and statistical significances vs vehicle determined by 2-way ANOVA analysis (p = <0.05*, <0.01, <0.001***, <0.0001****; ns, not significant). Studies were conducted at Arvinas in the vivarium facility of North East Life Sciences, New Haven, CT, following Institutional Animal Care & Use Committee (IACUC) regulations and approved procedures.**

References

1. Basso & Dalla-Favera. Immunol Reviews 2012, v247, p172-183. **2.** Pasqualucci *et.al.*, Blood 2003;101 (8). **3.** Lossos *et.al.*, Leukemia 2002,16, p1857. **4.** Szereday *et.al.*, Am J Path 2000 156 (3). **5.** Cattoretti *et.al.* Cancer Cell 2005, v7, p445. **6.** Green *et.al.* Nat Comm 2014, v5, p3904. **7.** Békés *et.al.* Nat Rev 2022, v21, p181.