Potent and Orally Bioavailable BCL6 PROTAC® Degraders Demonstrate Efficacy in Pre-Clinical Models of Diffuse Large B-Cell Lymphoma (DLBCL)

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Disclosures

All authors are current employees of Arvinas and equity holders. SMG, DS, LD, JC, FG, XC, WZ, JH, LS and IT have divested Arvinas equity in the past 24 months.

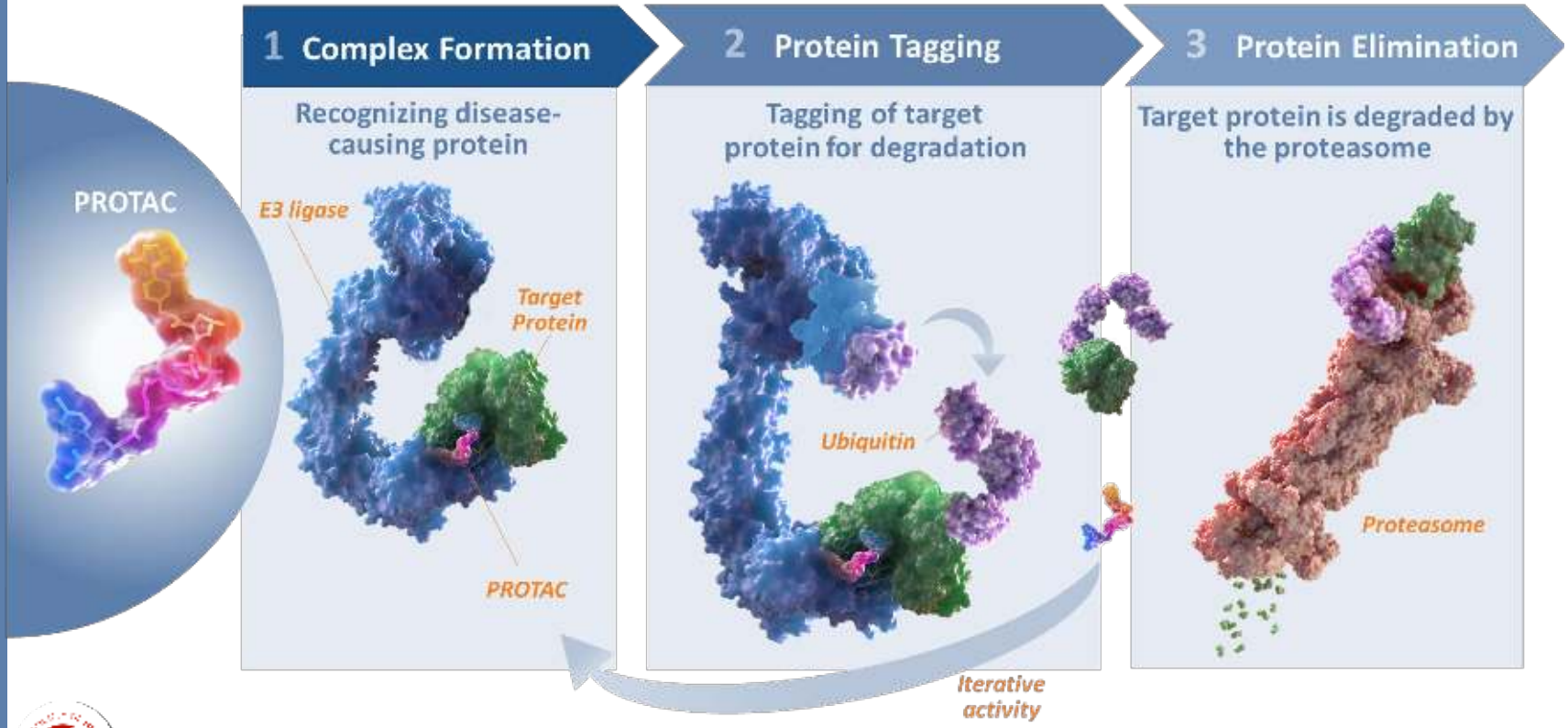
BCL6 is a driver of B-cell malignancies and a therapeutic target in DLBCL

BCL6 (*B-cell lymphoma 6 / BCL6 transcription repressor*)

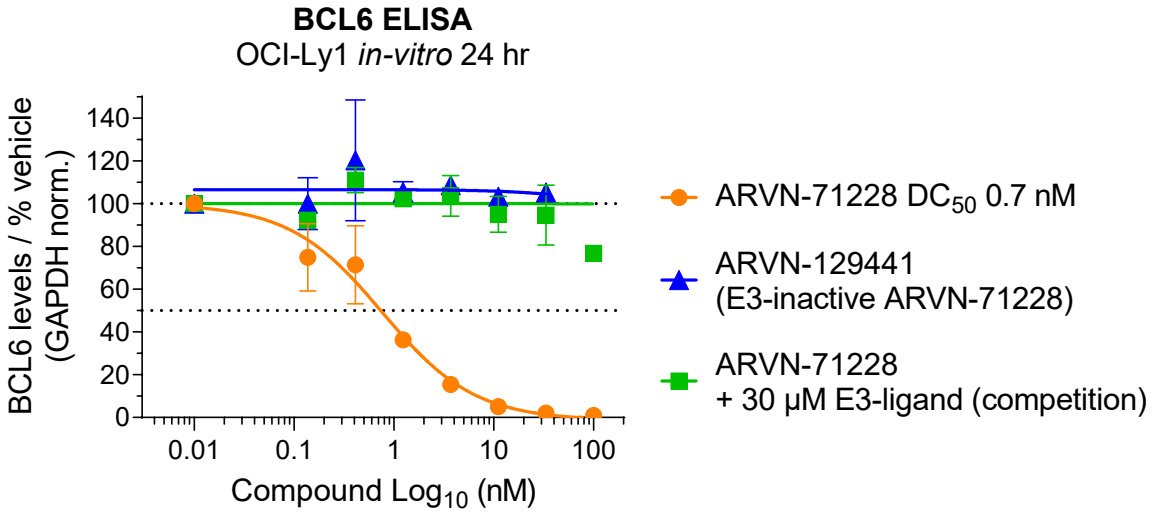
- regulates the transcription of numerous target genes as a transcriptional repressor and master regulator of germinal center formation, B-cell development, and other cellular processes such as cell cycle and DNA damage response
- has been shown to be a key molecular driver of diffuse large B-cell lymphoma (DLBCL) via somatic mutation resulting in overexpression or the deregulated expression of BCL6
- facilitates a permissive environment for mutation acquisition and aberrant cell proliferation

*We have developed specific, potent and **orally bioavailable BCL6 PROteolysis TArgeting Chimera (PROTAC®) degraders** that are efficacious in multiple pre-clinical DLBCL models.*

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



PROTAC® degraders demonstrate potent, on-mechanism degradation of BCL6 *in-vitro*



- BCL6 levels following 24 hr ARVN-71228 treatment and blocked with E3-ligand competition

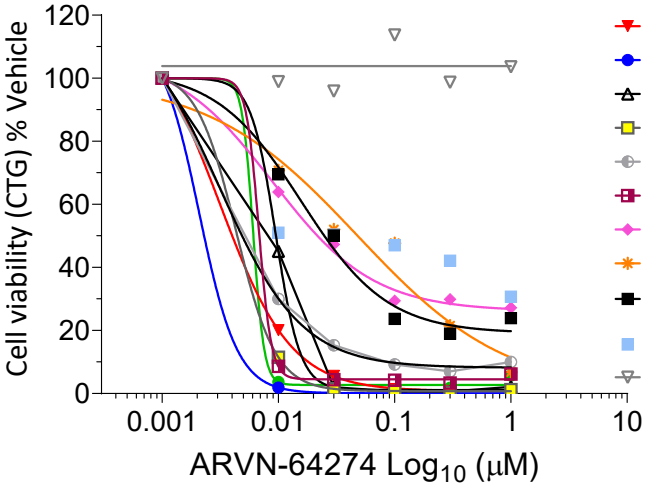
PROTAC®-mediated degradation of BCL6 inhibits the proliferation of numerous DLBCL cell lines

- Proliferation of DLBCL cell lines is inhibited in germinal center B cell (GCB) and activated B-cell (ABC, see poster) subtypes as a result of BCL6 degradation with early stage BCL6 PROTAC® degraders

ARVN-64274

Representative Growth Inhibition Curves

GCB DLBCL lines | Day 9 or 10

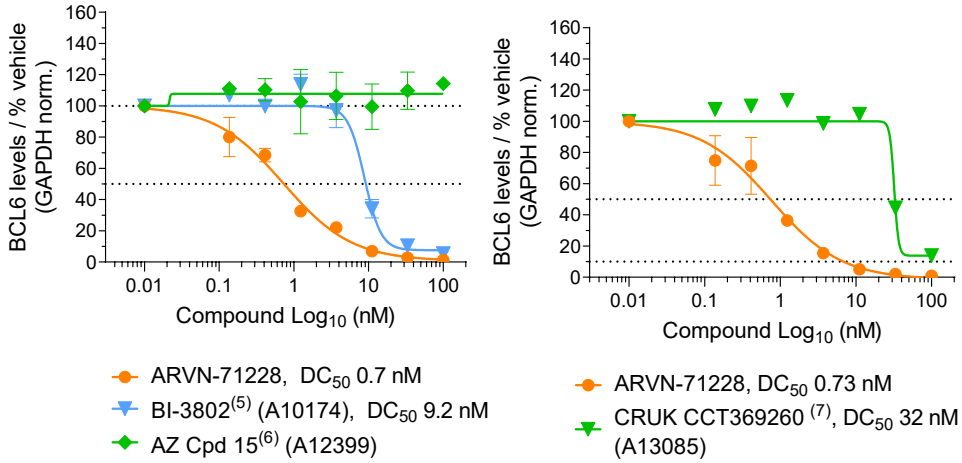


	GI_{50} (nM)	GI_{max} (%)
Farage	6	98
SUDHL6	3	100
SUDHL-5	2	100
OCI-Ly7	9	98
OCI-Ly1	4	99
Karpas 422	3	91
Pfeiffer	6	96
SUDHL-10	9	73
SUDHL-4*	48	93
OCI-Ly19$^{BCL6\ lo}$	16	80
MHHPREB1		
Toledo		

ARVN-71228 demonstrates superior activity to literature BCL6 degraders in OCI-Ly1 cell line

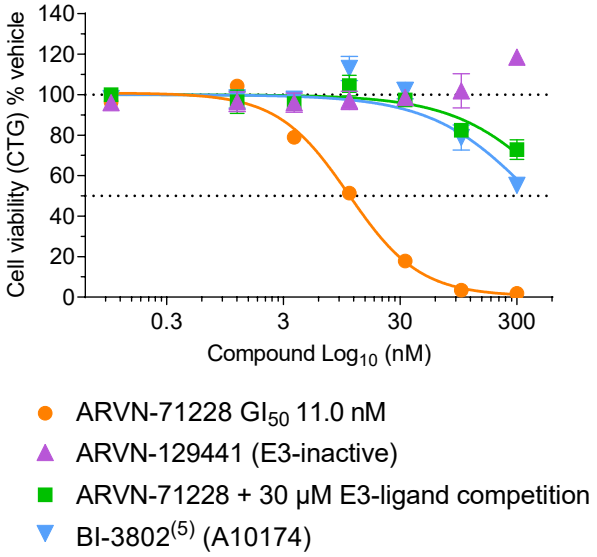
In-vitro BCL6 degradation

OCI-Ly1 24 hr, ELISA

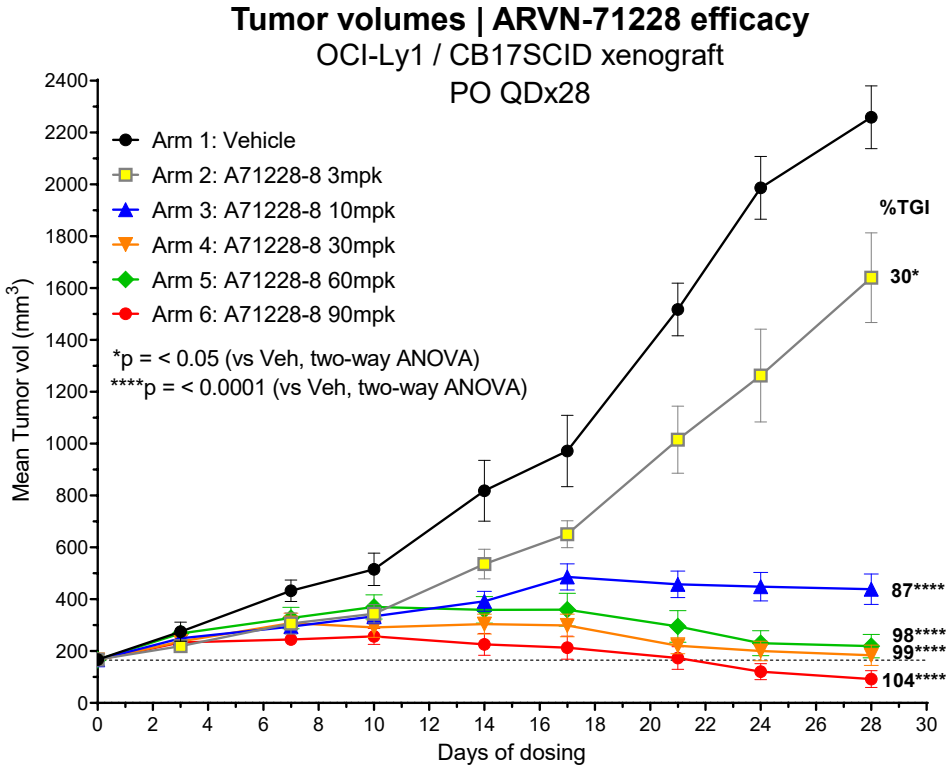


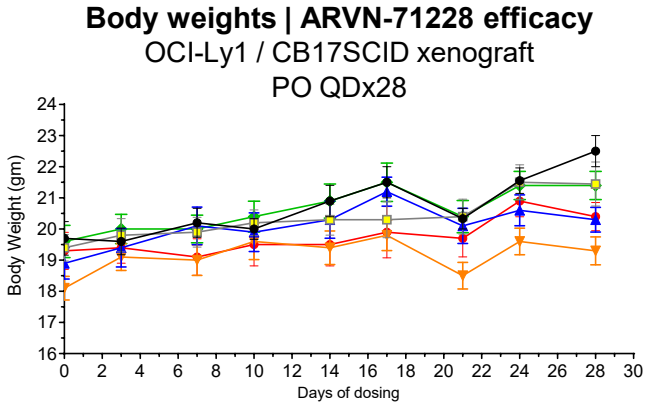
In-vitro growth inhibition

OCI-Ly1, 9-day study



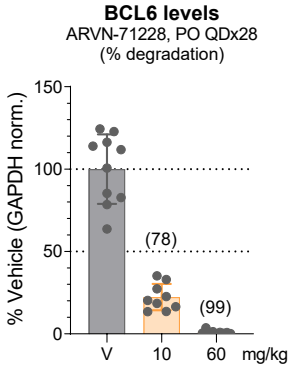
ARVN-71228 achieves tumor regressions in OCI-Ly1 CDX

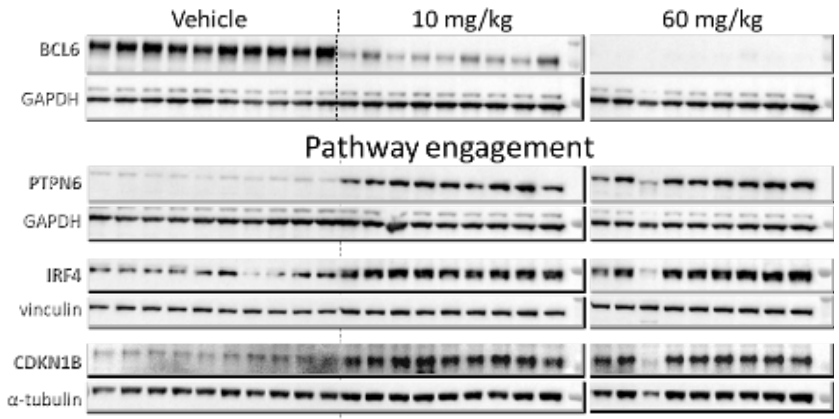




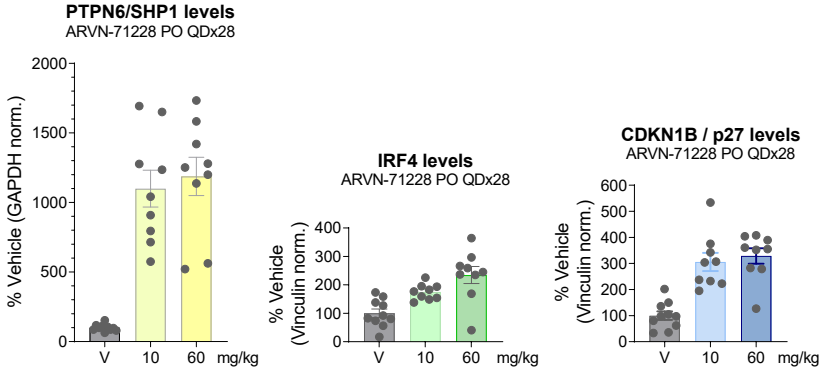
BCL6 is reduced in OCI-Ly1 tumors and show BCL6-pathway engagement

- Western blots (right) show 78% and 99% BCL6 reduction at 10 and 60 mg/kg arms, respectively.





- BCL6 degradation leads to the de-repression of BCL6 target genes PTPN6/SHP1, IRF4 and CDKN1B.



In Summary

- BCL6 PROTAC® degraders demonstrate potent, on mechanism degradation of BCL6 and growth inhibition of numerous DLBCL cell lines
- Orally administered ARVN-71228 shows tumor regressions and a dose-responsive degradation of BCL6 in an OCI-Ly1 DLBCL xenograft model

Acknowledgments