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The Discovery of ARV-393, a potent, orally bioavailable BCL6-targeting PROTAC® for the treatment of NHL

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Arvinas, Inc., New Haven, CT

ARVINAS

Disclaimer

- I am both an employee and shareholder of Arvinas, Inc.

PROTAC® protein degraders combine the benefits of small molecules and gene-based knockdown technologies

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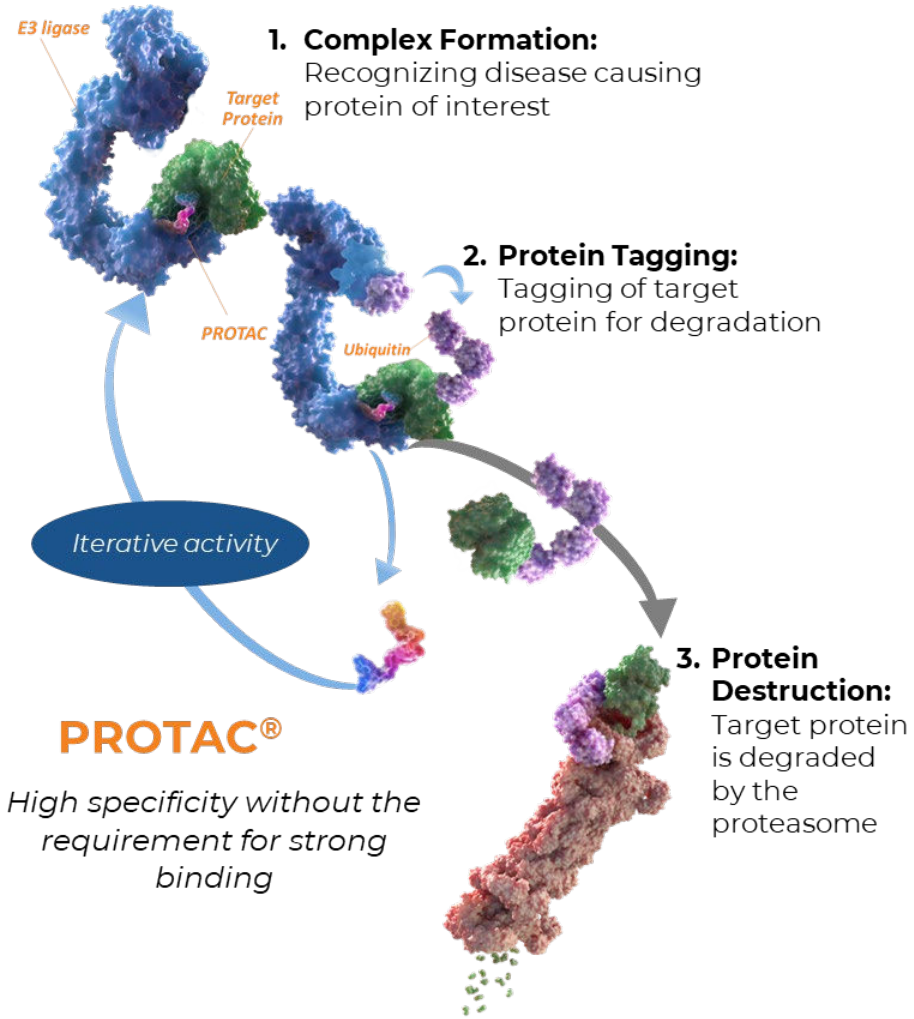

Arvinas' proteolysis-targeting chimera (PROTAC®) degraders have the potential to:

- Eliminate (rather than inhibit) disease-causing proteins' with enzymatic AND scaffolding functions
- Bind and degrade classically undruggable proteins
- Act iteratively (catalytically)
- Be administered orally and achieve broad tissue distribution, including across the blood-brain-barrier

Non-Hodgkins Lymphoma (NHL)

- NHL is a heterogenous disease that includes diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), angioimmunoblastic T-cell lymphomas (AITL), Burkitt lymphoma (BL)
- Worldwide, 544,000 new cases and 260,000 deaths were attributed to NHL in 2020[1]
  - In the US, there are approximately 80,000 new cases and 20,000 deaths per year[2,3]
- DLBCL is the most common sub-type of NHL, representing ~30% of all cases in the US[4]
  - Although outcomes vary by subtype, ~40% of patients with DLBCL ultimately relapse following standard front-line chemo-immunotherapy, [5-9]

[1]Sung et. al. *CA Cancer J Clin*. (2021), 71(3), 209 - 249; [2]Siegel et. al. *CA Cancer J Clin* (2023); [3]SEER:https://seer.cancer.gov/statfacts/html/nhl.html; [4]Freedman et. al. *UpToDate* (2024) Initial treatment of limited stage diffuse large B cell lymphoma; [5]Markanda & Kumar *Decision Resources* (2024); [6]Sehn et al. *J Hem Onc* (2020) 13(71); [7]Sehn & Salles *NEJM* (2021) 384(9) 842 - 858; [8]Coiffier et. al. *Blood* (2010), 116(12), 2040 - 2045; [9]Davies et. al. ASH (2022) ReMODL-B trial

BCL6 and NHL

- Structural rearrangements and mutations of *BCL6* result in its deregulation or overexpression and are sufficient to induce B-cell lymphoma[1]
- *BCL6* gene translocation occurs in ~40% of DLBCL and in 39% of FL cases that had transformed[2,3,4]
- Somatic mutation of the *BCL6* gene occurs in DLBCLs, BLs and FLs; increased BCL6 expression over normal levels is not necessarily required for oncogenesis[5]
- FL is largely incurable and can transform into a DLBCL-like cancer, with an annual risk of transformation of ~1-2%[6-7]
- An orally bioavailable BCL6 degrader has the potential to be a powerful tool to treat NHLs alongside, or in addition to standard of care (SOC) and new biological agents

[1]Cattoretti et. al. *Cancer Cell* (2005) 7, 445 – 455;[2] Pasqualucci et. al., *Blood* (2003),101(8) 2914 – 2923; [3]Akasaka et. al. Neoplasia (2003), 102(4) 1443-1448; [4]Vega and Medeiros *Arch Pathol Lab Med* (2003) 127(9), 1148-1160; [5]Green et. al. *Nat Comm* (2014); 1857 - 1862; [6]Batlevi et. al. *Blood Can J* (2020) 10 (74); [7]Freedman, A. & Friedberg, J *UpToDate* (2024), Histologic transformation of follicular lymphoma

The BCL6 transcription repressor:
A key modulator of B-cell responses

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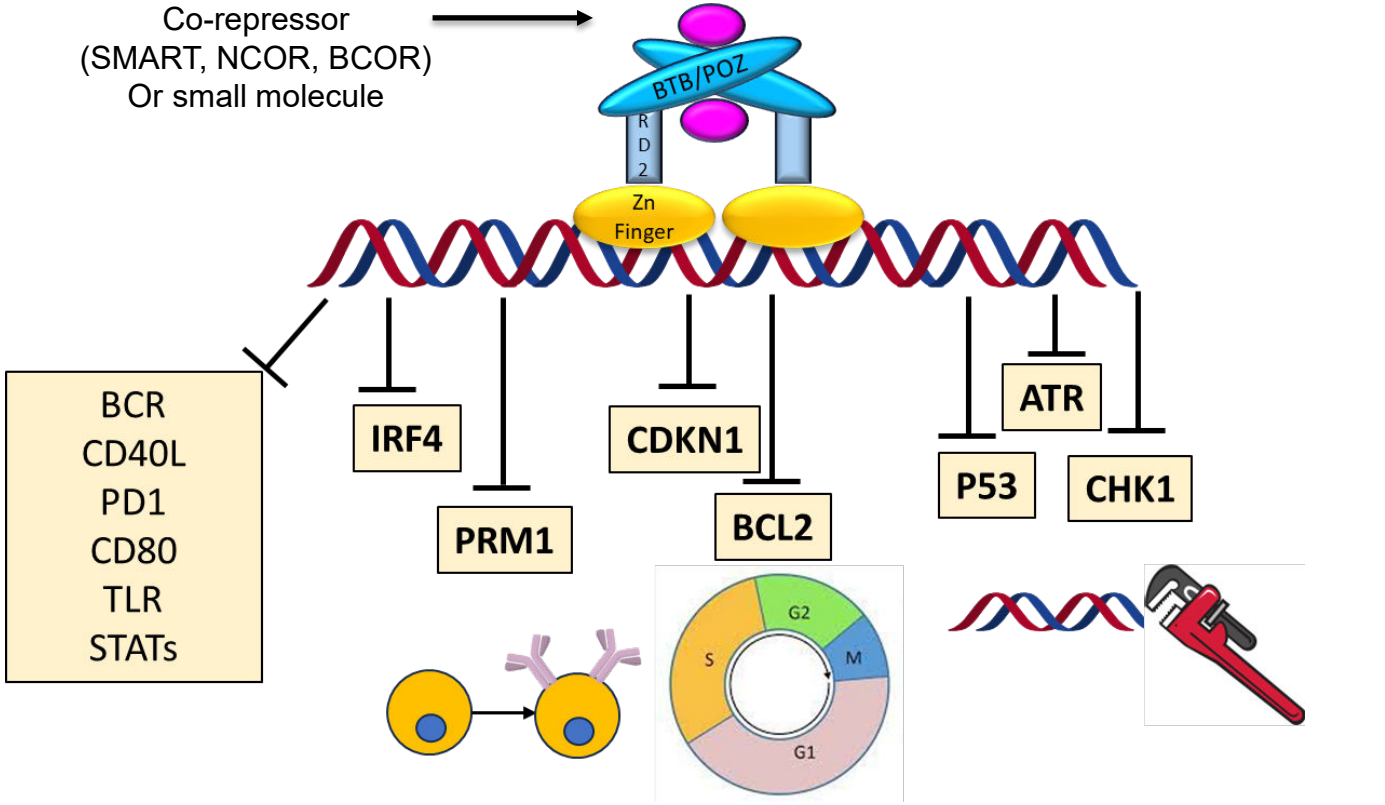
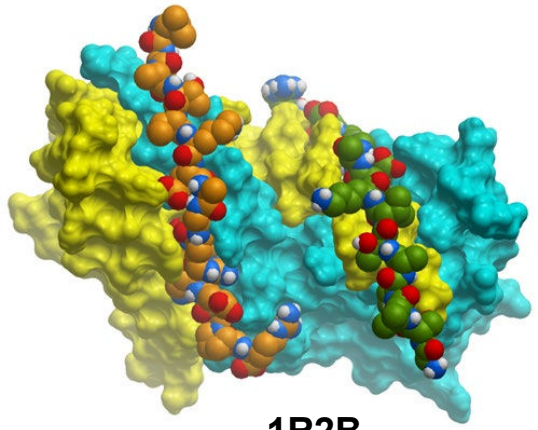


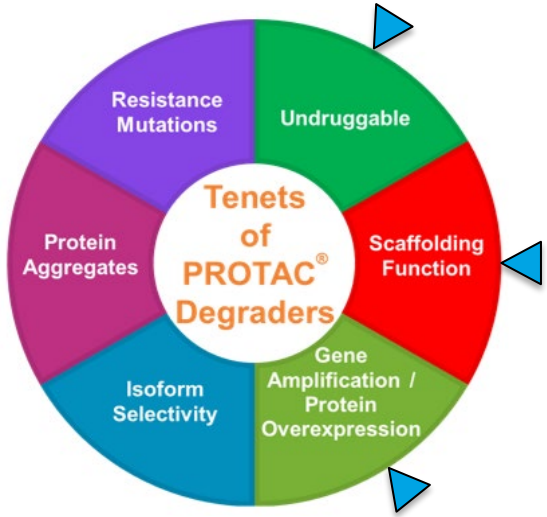
- Terminal cell differentiation

- DNA damage response
- P53 inhibition

- Cell cycle checkpoints
- Apoptosis



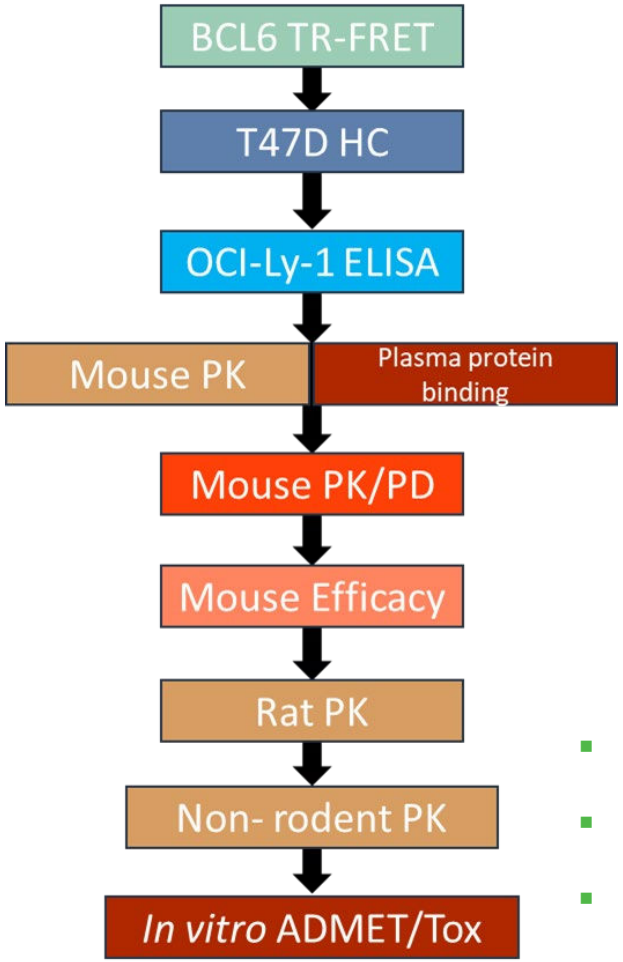
1R2B



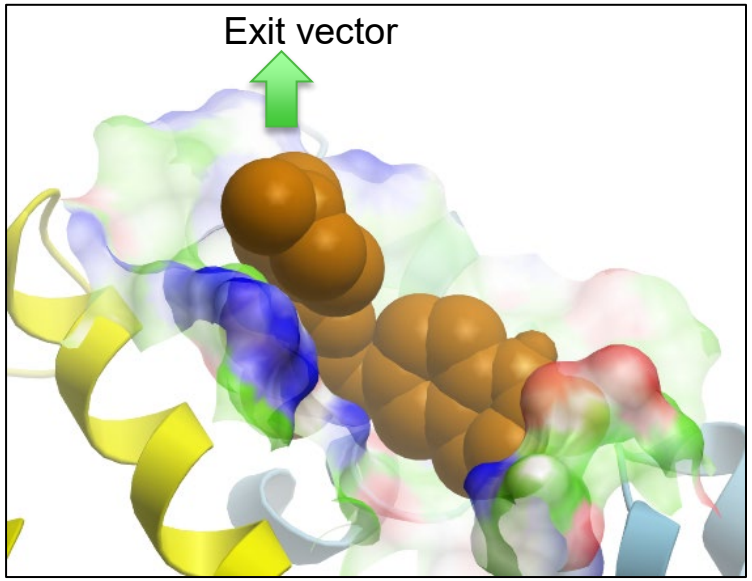
Adapted from Leeman-Neill & Bhagat *Expert Opin Ther Targets* (2017) 22(2), 143 – 152; 1R2B structure: Ahmad et. al. *Mol Cell* (2003) 12, 1551-1564;

BCL6 degrader discovery at Arvinas

Assay Cascade



Structural Models



BCL6 homodimer models based on published co-crystal structures (5N21[1], 6EW8[1], 5MW6[2])

Med Chem

Focused Libraries

↓

PROTAC analogues

- T47D: High content assay (BCL6 expression, adherent cells, high-throughput)
- OCI-Ly-1: GCB DLBCL work horse cell line, ELISA format highly reproducible
- *In vitro* ADME permeability and metabolic stability assays not useful for triaging compounds for PK

[1]McCoul et. al. J. Med Chem (2017), 60(10), 4386 – 4402; [2]Kerres et.al. Cell Reports (2017) 20(12), 2860-2875

BCL6 PROTAC SAR waypoints

High potency and oral exposure demonstrated to be possible with BCL6 PROTAC

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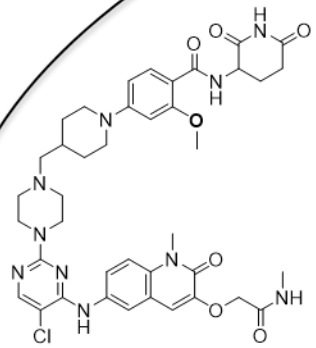
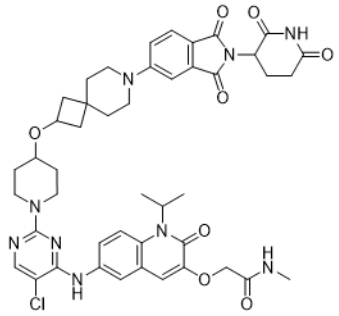
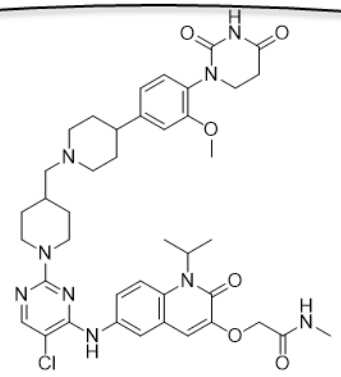
Cmpd#
T47D DC_{50}
Mouse CL(%Q_H)
Mouse F



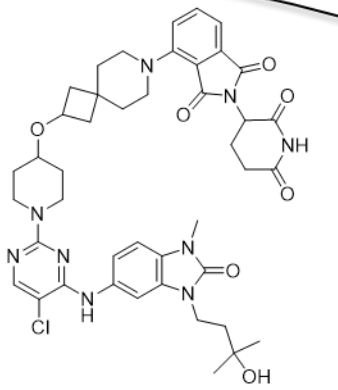
1
4nM
CL: 9%
F: 37%



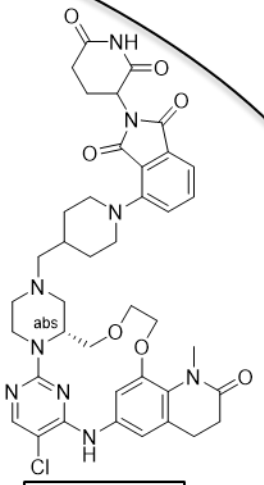
2
4nM
CL: 1%
F: 40%



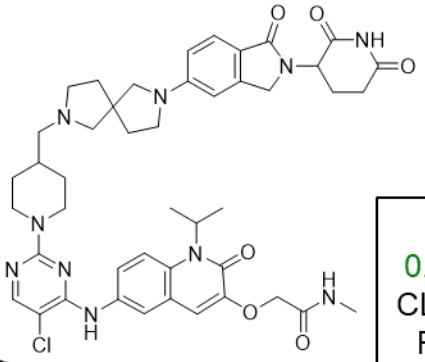
3
>1000nM
CL: -
F: -



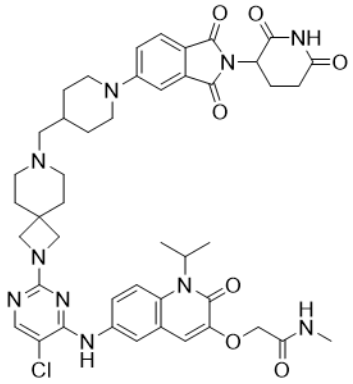
4
15nM
CL: -
F: -



5
12nM
CL: 11%
F: 68%



7
0.07nM
CL: 36%
F: 4%



6
3nM
CL: 28%
F: 22%

Medicinal chemistry campaign identifies ARV-393

A potent, rapid, on-mechanism and orally bioavailable BCL6 PROTAC

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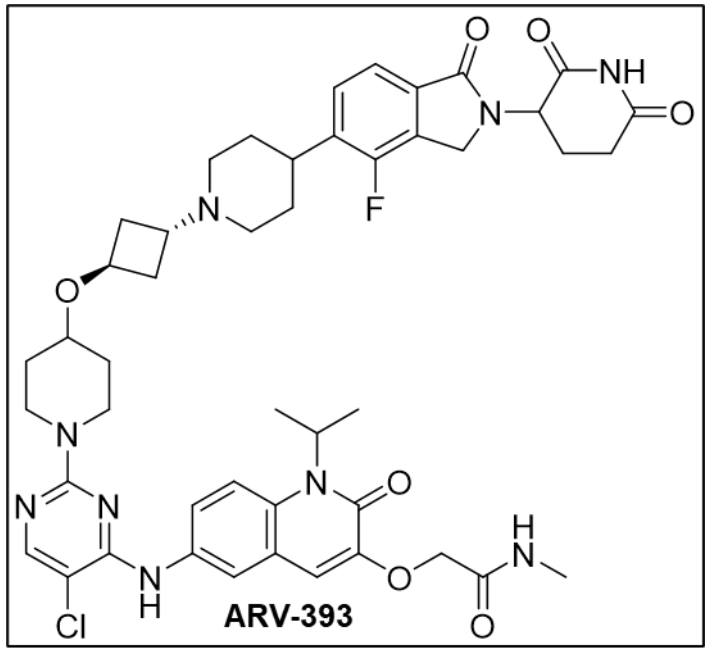

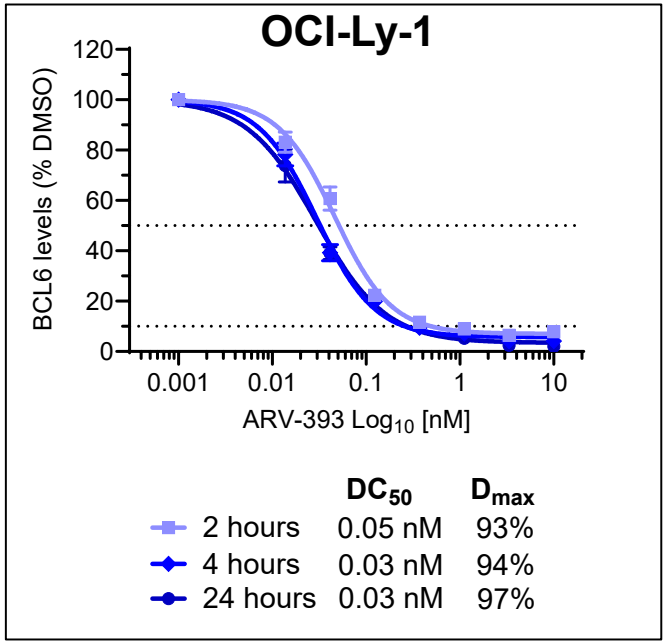

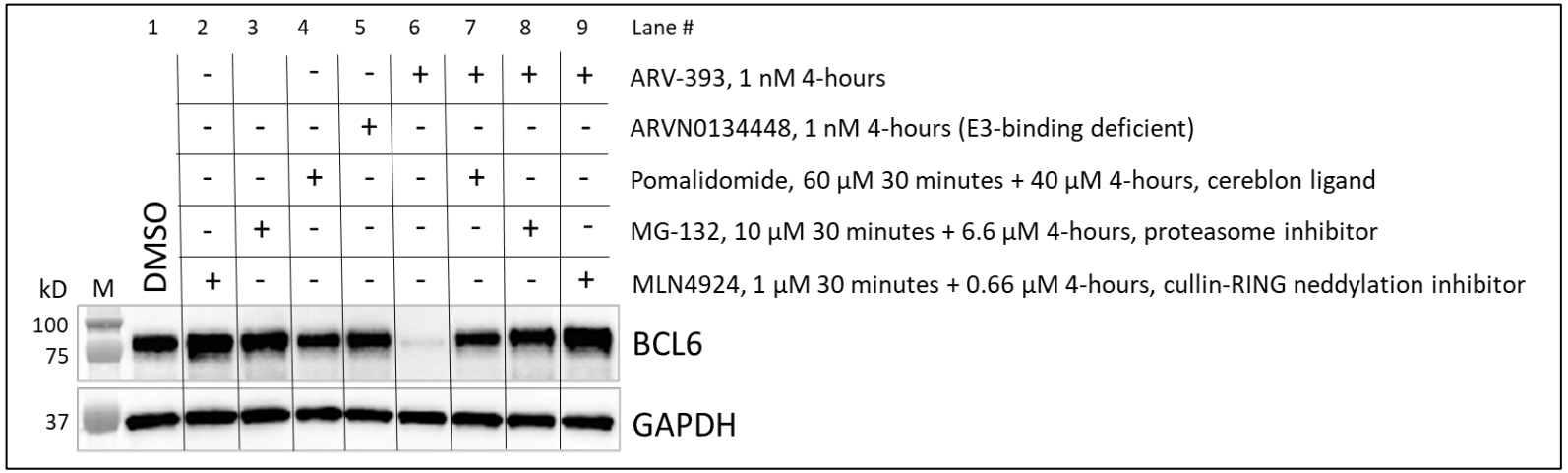

Species	CL (%Q_H)	Bioav. (F%)
Mouse	18%	>100%
rat	47%	29%
dog	16%	18%
cyno	26%	21%

CL = plasma clearance

ARV-393 has broad antiproliferative activity *in-vitro* against numerous NHL cell lines

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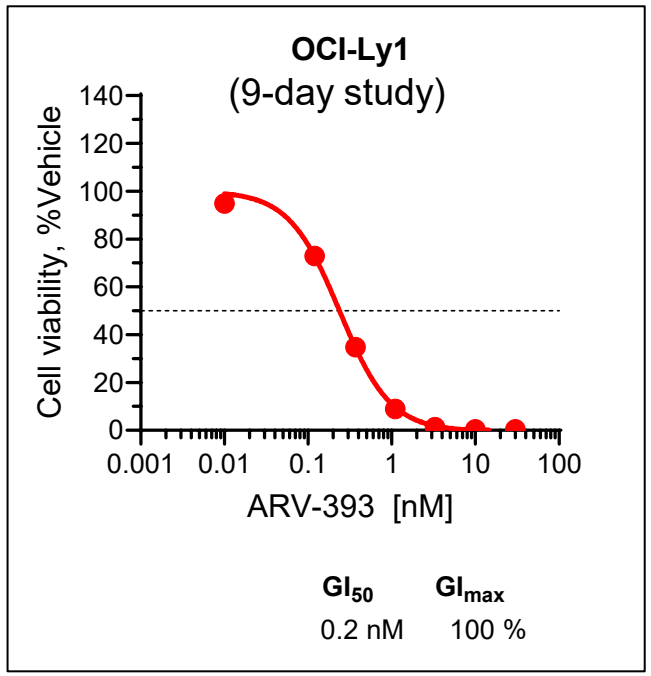

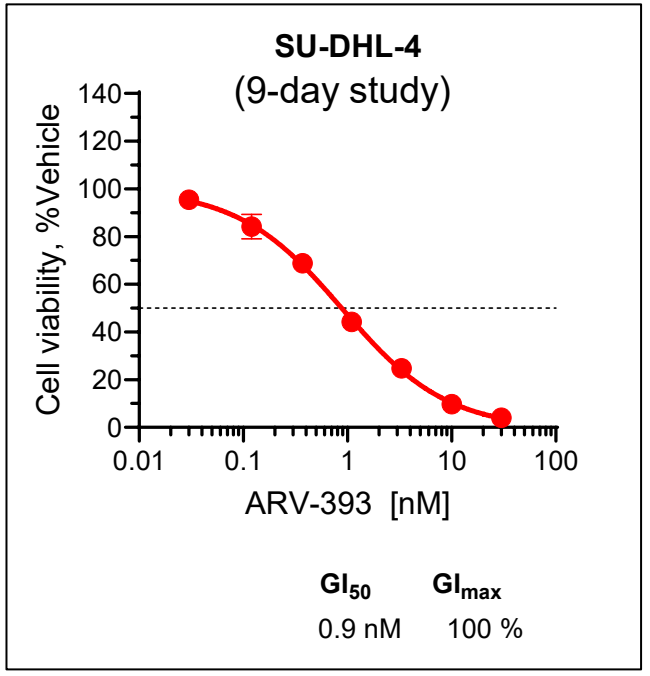

Cell line	Subtype	DC_{50} (nM)	D_{Max}	9-Day GI_{50} (nM)
OCI-LY1	GCB	0.03	97%	0.2
OCI-LY7	GCB	0.10	97%	1.2
OCI-LY10	ABC	0.11	95%	0.4
SU-DHL-2	ABC	0.07	95%	0.2
SU-DHL-4	GCB	0.16	95%	0.9
SU-DHL-6	GCB	0.14	96%	0.9
Daudi	BL	0.15	99%	2.9
Ramos	BL	0.09	100%	0.4

- Potent BCL6 degradation gives potent *in vitro* antiproliferation activity in GCB, ABC and BL cell lines
  - SU-DHL-4 is a triple hit, high grade BCL and R-CHOP resistant[1] cell line

[1]Hicks et. al. *Neoplasia* (2017) 19, 661 – 671; GCB: Germinal Center B-Cell; ABC: Activated B-Cell; FL = Follicular lymphoma

ARV-393 induces ~90% BCL6 degradation *in-vivo* 4-hours after oral dosing

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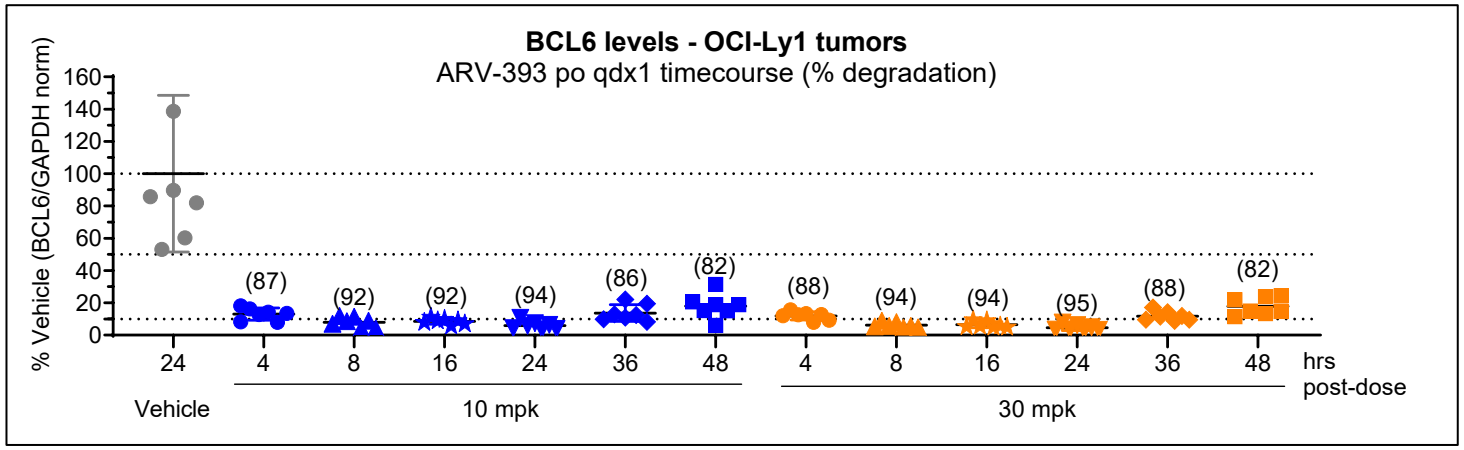

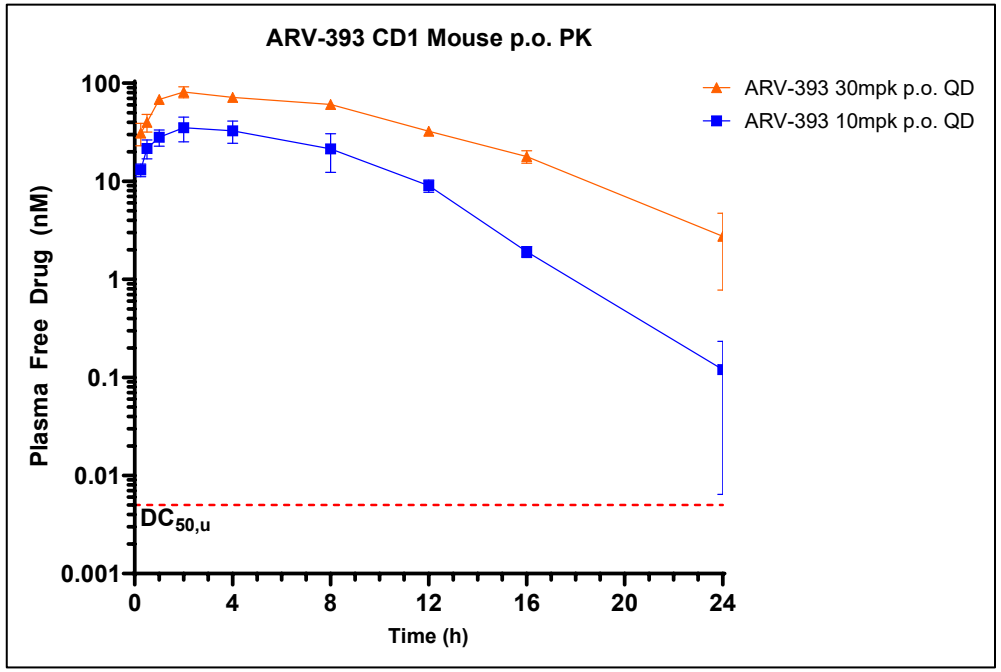

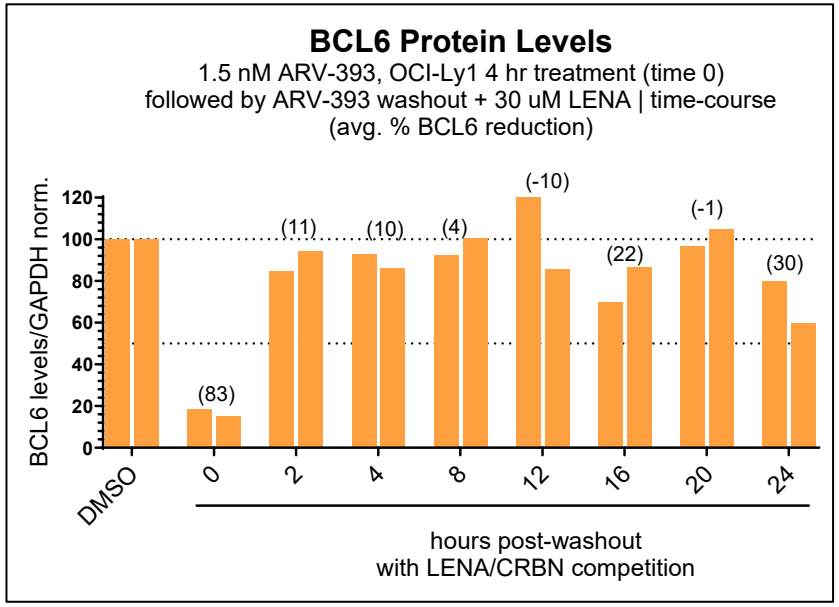

- Sustained knockdown of BCL6 achieved beyond 24hrs with single oral 10mpk dose
- Exposure well in excess of OCI-Ly-1 DC_{50} corrected for assay media binding ($DC_{50,u}$)
- Washout experiment shows that sustained plasma/tumor exposure required to maintain low BCL6 levels as it is rapidly resynthesized

ARV-393 is well tolerated and displays single agent anti-tumor activity in NHL xenograft models

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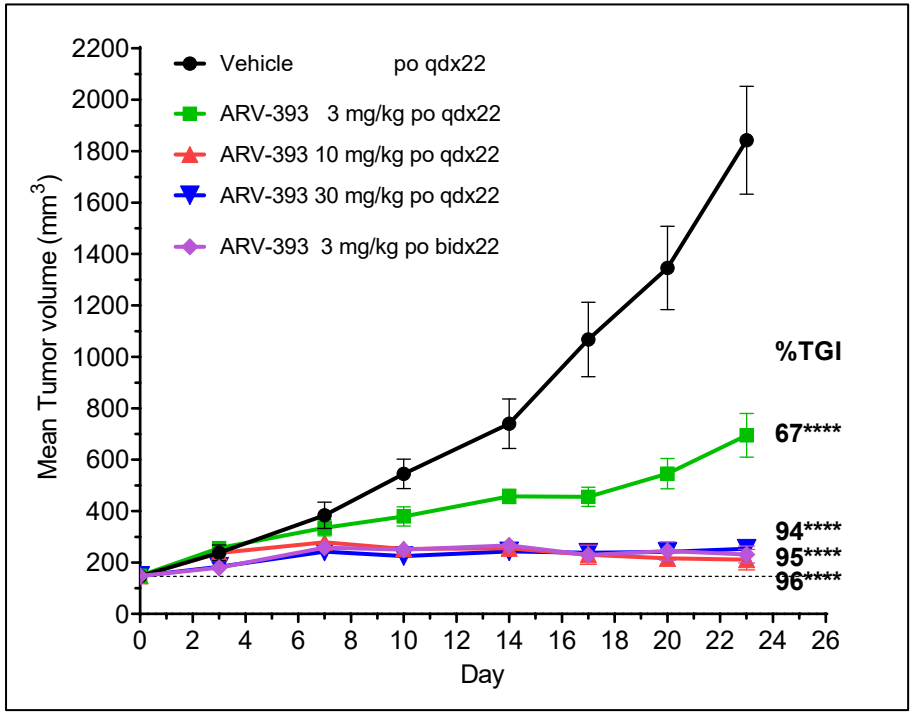
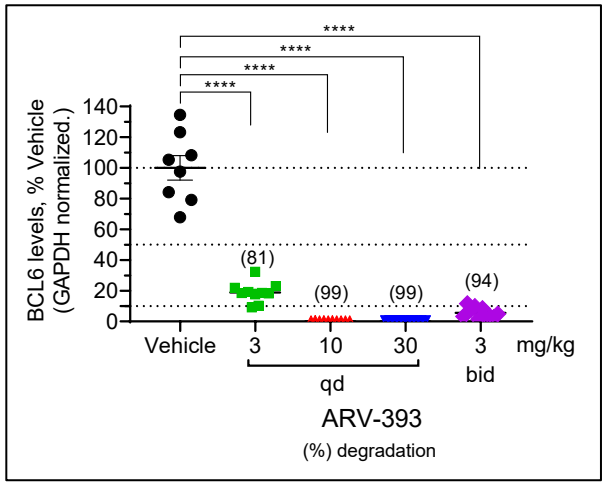
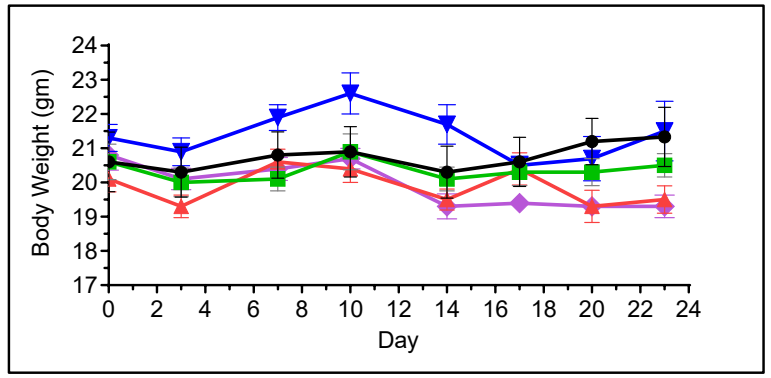
OCI-Ly-1 / CB17 SCID Xenograft

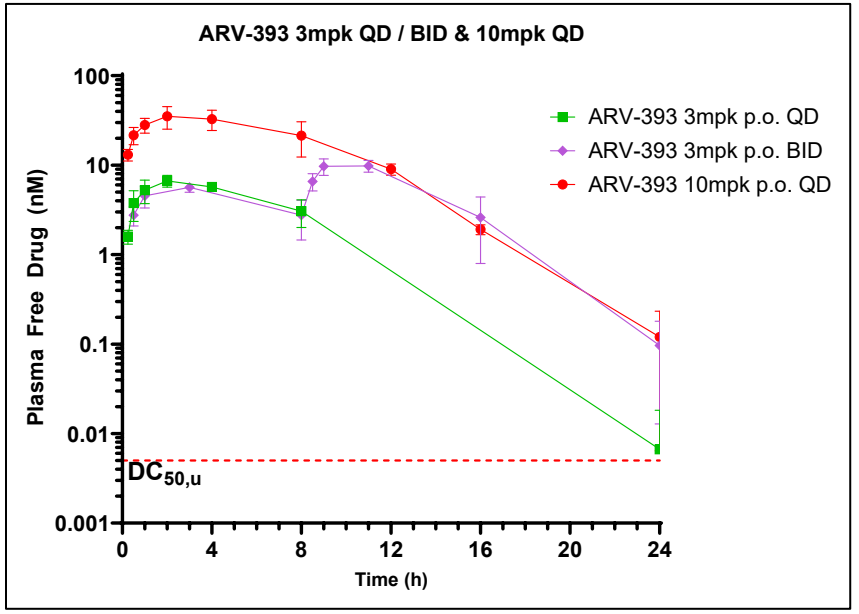


BCL6 levels at takedown 24hrs post dose



Body weights





- Significant TGI observed in multiple cell line-derived xenograft models

ARV-393 drives tumor regressions in patient-derived xenograft (PDX) models of multiple subtypes of NHL

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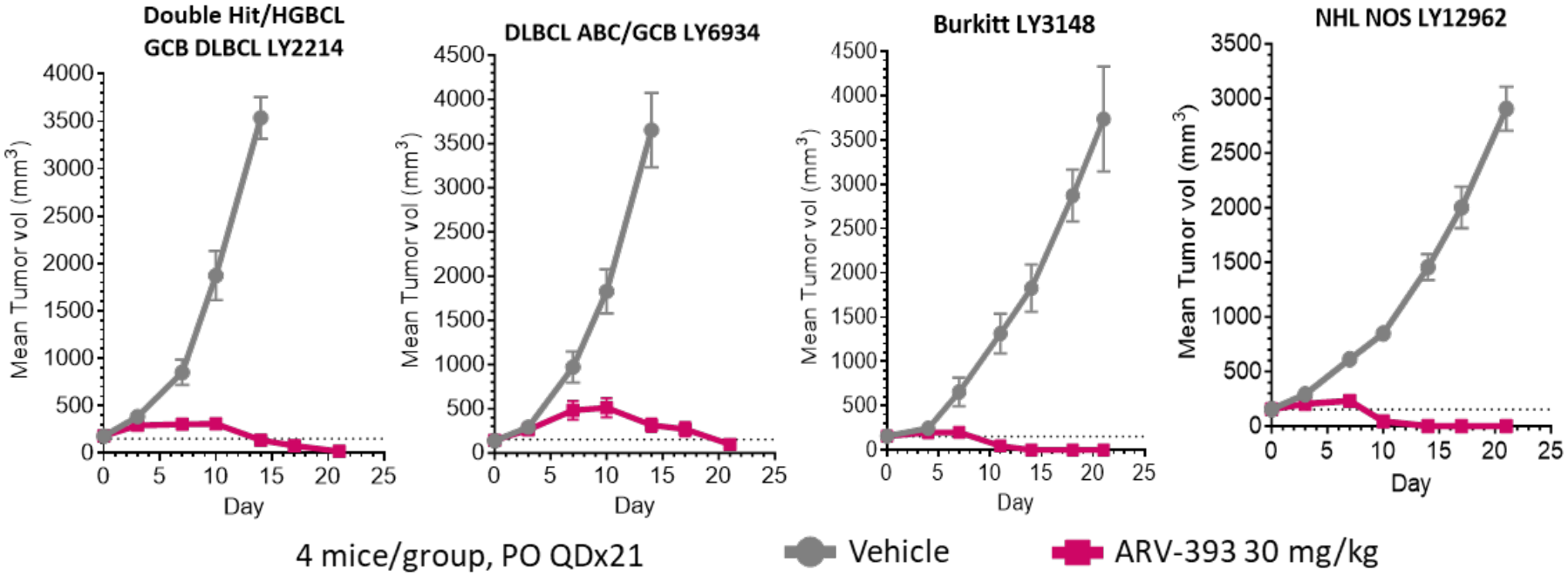
Breadth of efficacy beyond DLBCL demonstrated in multiple patient-derived xenograft (PDX) models with no body weight loss[a]



[a] Body weights not shown

NHL, non-Hodgkin's lymphoma; NOS, not otherwise specified; DLBCL, diffuse large B-cell lymphoma; HGBCL, high grade B-cell lymphoma; GCB, germinal center B-cell; ABC, activated B-cell.

Summary

- A medicinal chemistry effort identified ARV-393, a highly potent, orally bioavailable PROTAC® BCL6 degrader
- ARV-393 induces rapid and sustained BCL6 degradation *in vitro* and *in vivo,* leading to single agent efficacy against multiple NHL tumor xenograft models including those derived from patients
- ARV-393 was designated “safe to proceed” to the clinic by FDA in late 2023 with FIH trials to begin in 1H 2024

Acknowledgements

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