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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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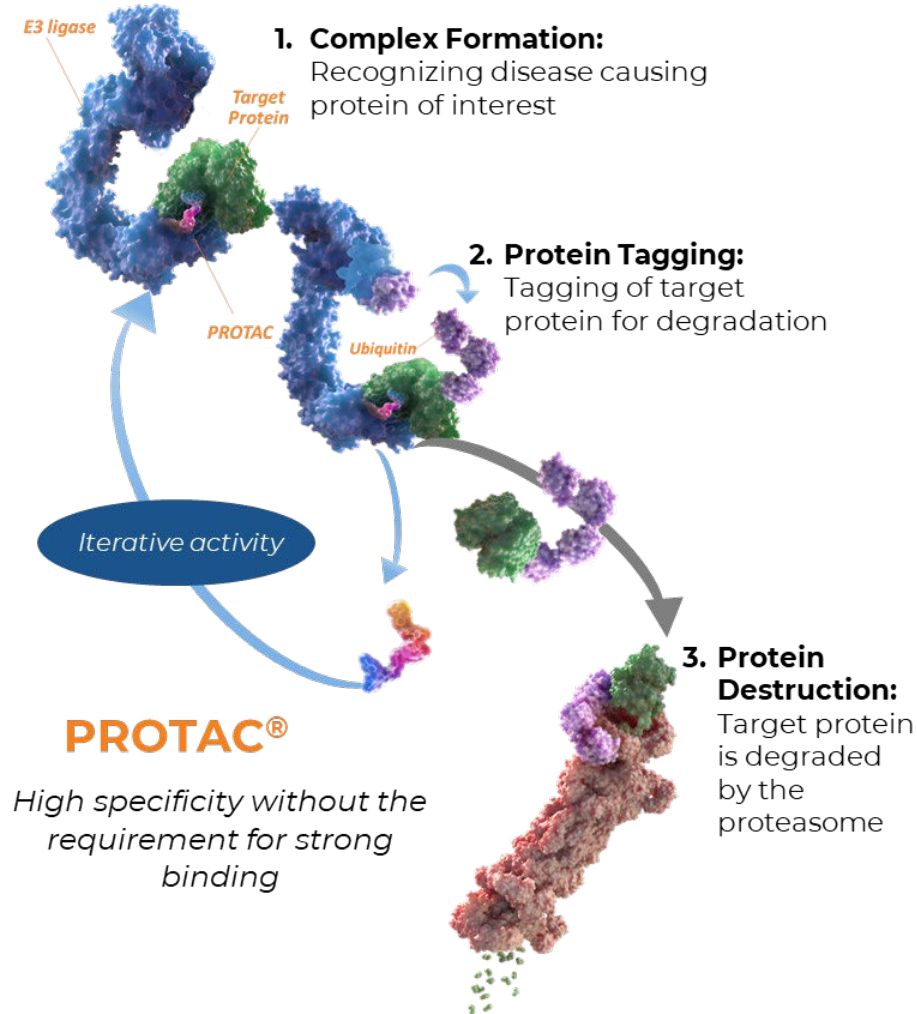
Arvinas, Inc., New Haven, CT



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



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 2020¹
 - 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 US⁴
 - Although outcomes vary by subtype, ~40% of patients with DLBCL ultimately relapse following standard front-line chemo-immunotherapy, ⁵⁻⁹

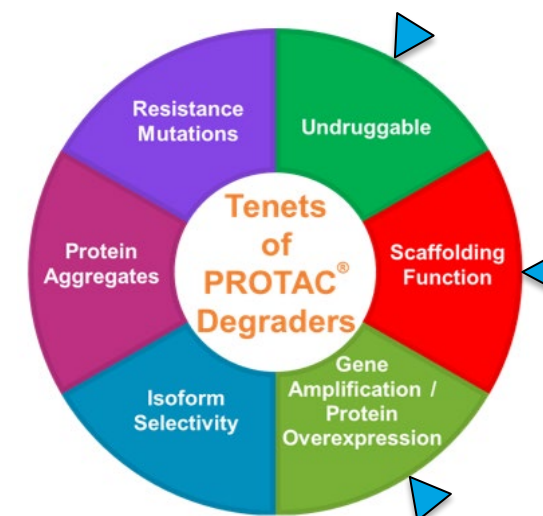
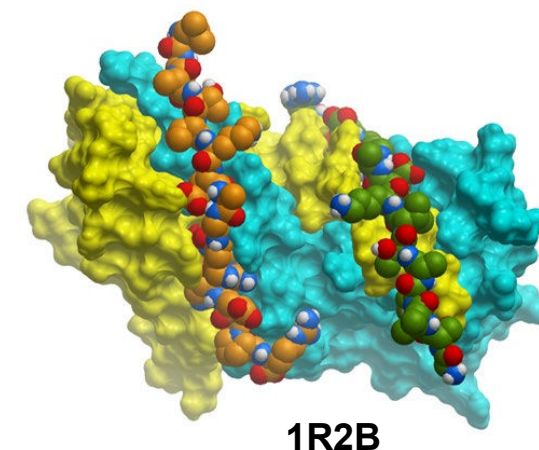
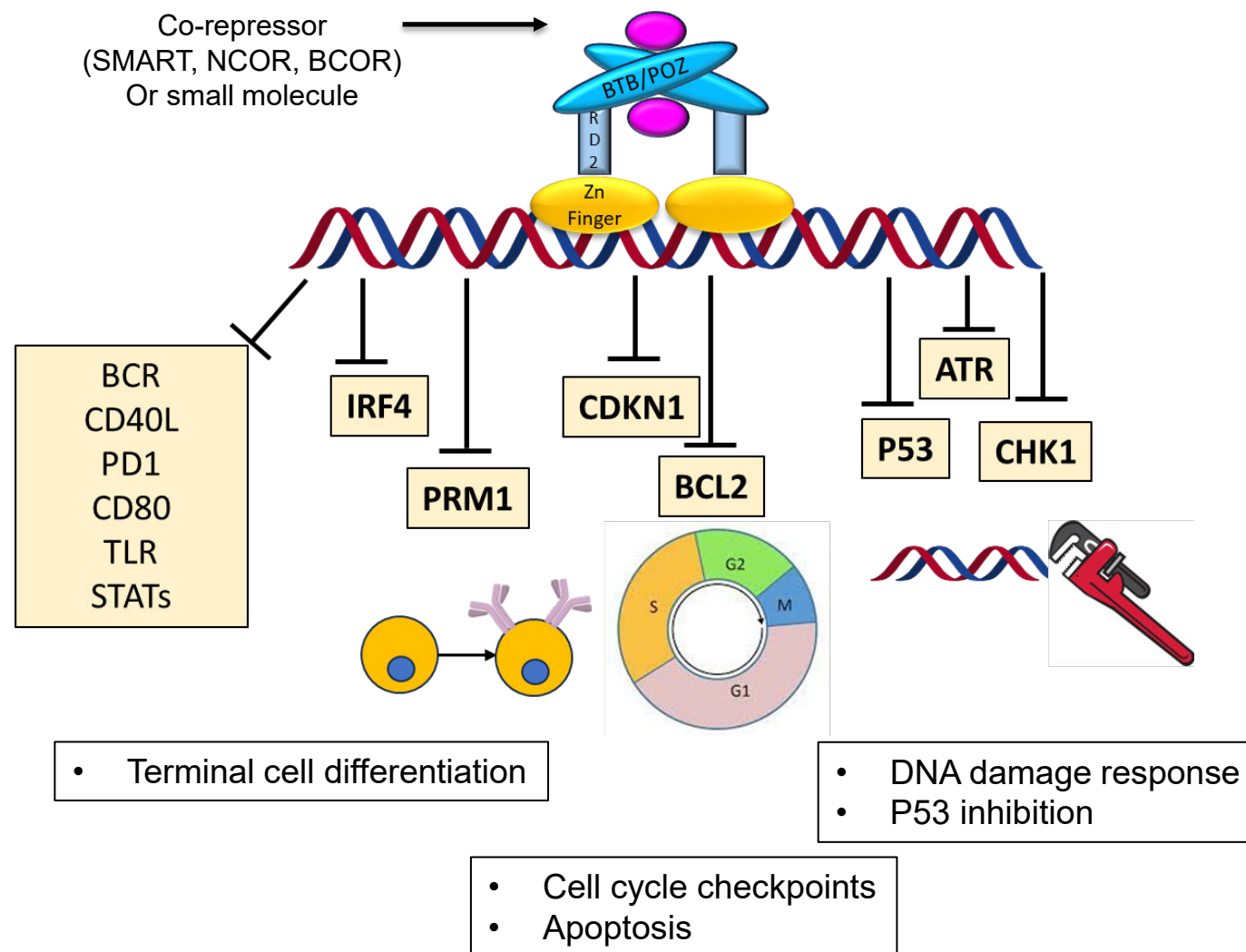
¹Sung et. al. *CA Cancer J Clin.* (2021), 71(3), 209 - 249; ²Siegel et. al. *CA Cancer J Clin* (2023); ³SEER:<https://seer.cancer.gov/statfacts/html/nhl.html>; ⁴Freedman et. al. *UpToDate* (2024) Initial treatment of limited stage diffuse large B cell lymphoma; ⁵Markanda & Kumar *Decision Resources* (2024); ⁶Sehn et al. *J Hem Onc* (2020) 13(71); ⁷Sehn & Salles *NEJM* (2021) 384(9) 842 - 858; ⁸Coiffier et. al. *Blood* (2010), 116(12), 2040 - 2045; ⁹Davies 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 lymphoma¹
- *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 oncogenesis⁵
- 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

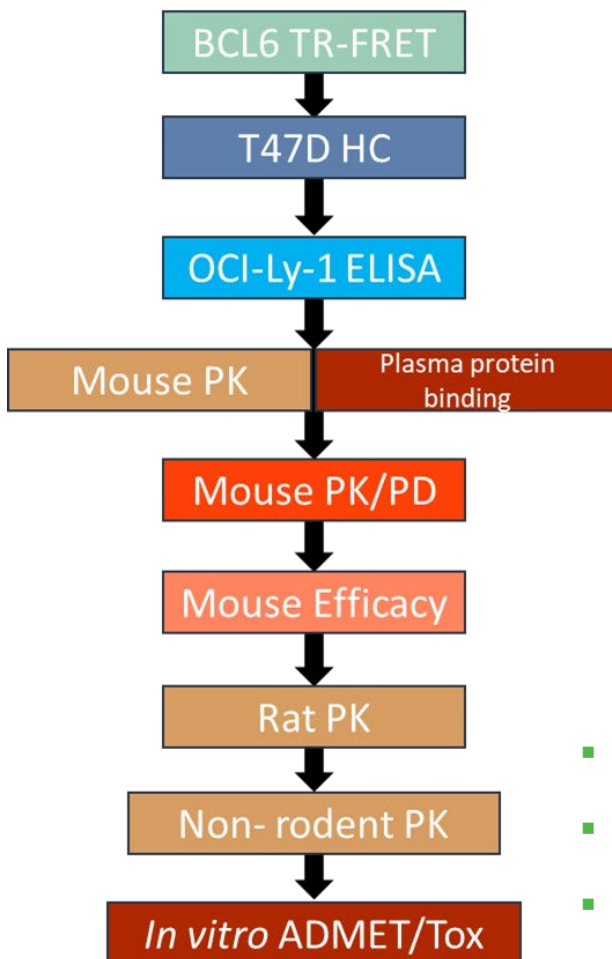
¹Cattoretti et. al. *Cancer Cell* (2005) 7, 445 – 455; ²Pasqualucci et. al., *Blood* (2003), 101(8) 2914 – 2923; ³Akasaka et. al. *Neoplasia* (2003), 102(4) 1443-1448; ⁴Vega and Medeiros *Arch Pathol Lab Med* (2003) 127(9), 1148-1160; ⁵Green et. al. *Nat Comm* (2014); 1857 - 1862; ⁶Batlevi et. al. *Blood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

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

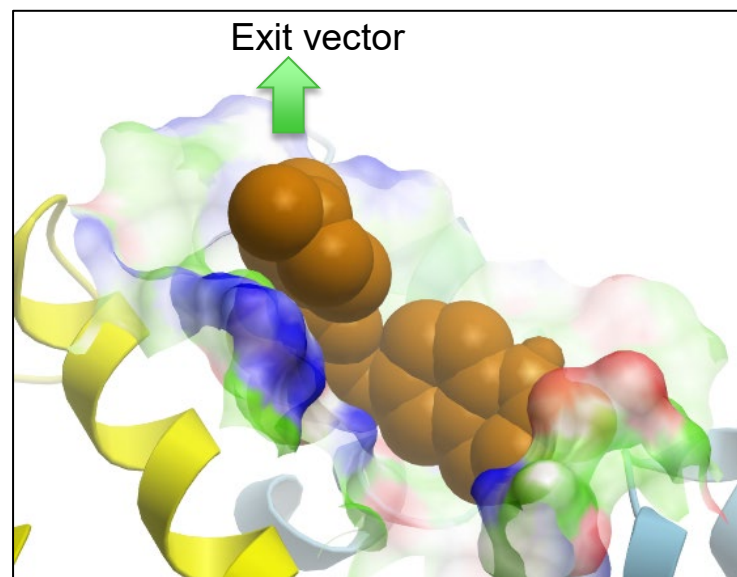


BCL6 degrader discovery at Arvinas

Assay Cascade



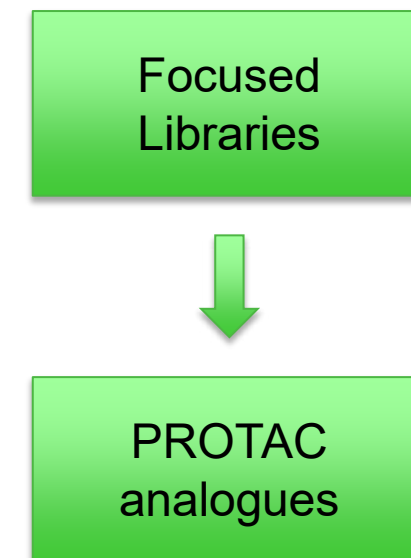
Structural Models



BCL6 homodimer models based on published co-crystal structures (5N21¹, 6EW8¹, 5MW6²)

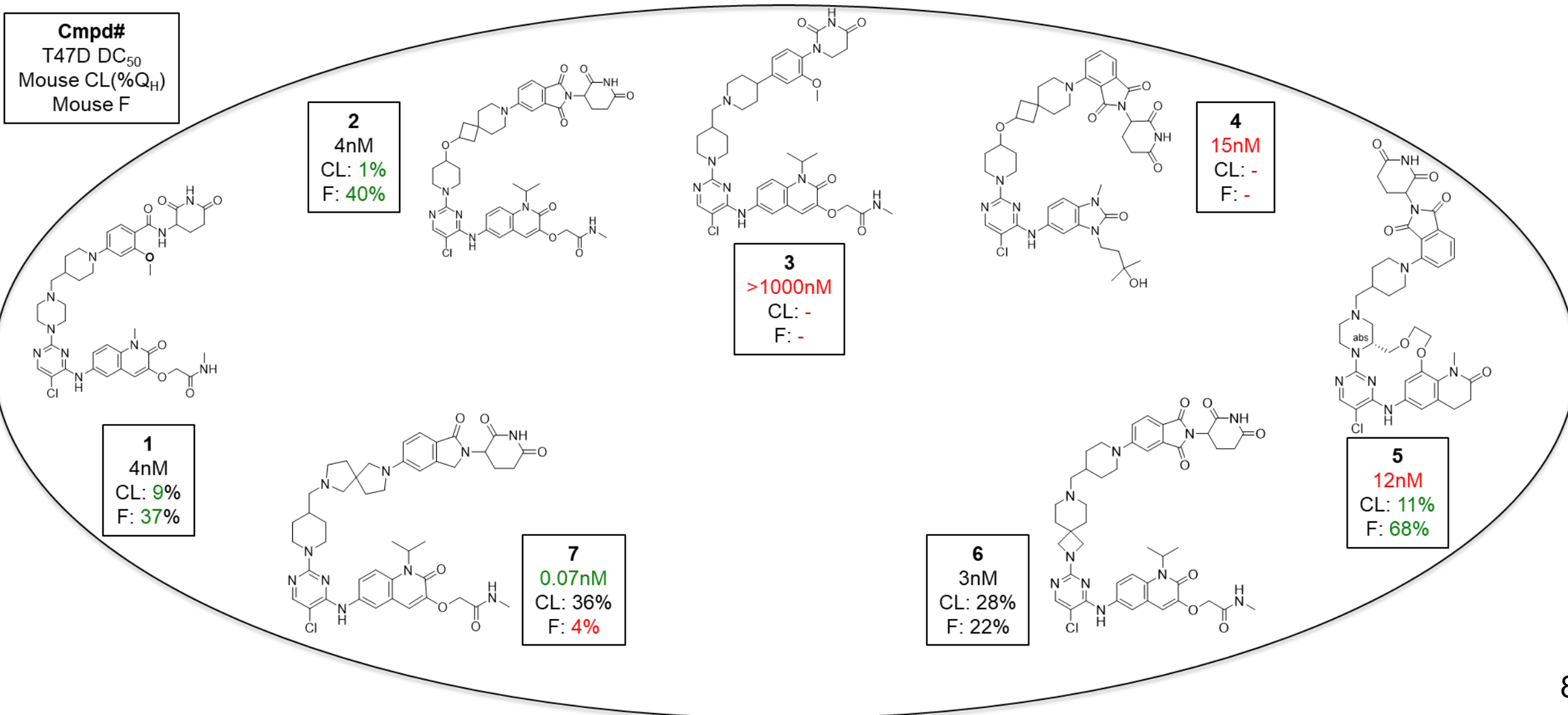
- T47D: High content assay (BCL6 expression, adherent cells, high-throughput)
- OCI-Ly-1: GCB DLBCL work horse cell line, ELISA format highly reproducible
- *In vitro* ADME permeability and metabolic stability assays not useful for triaging compounds for PK

Med Chem



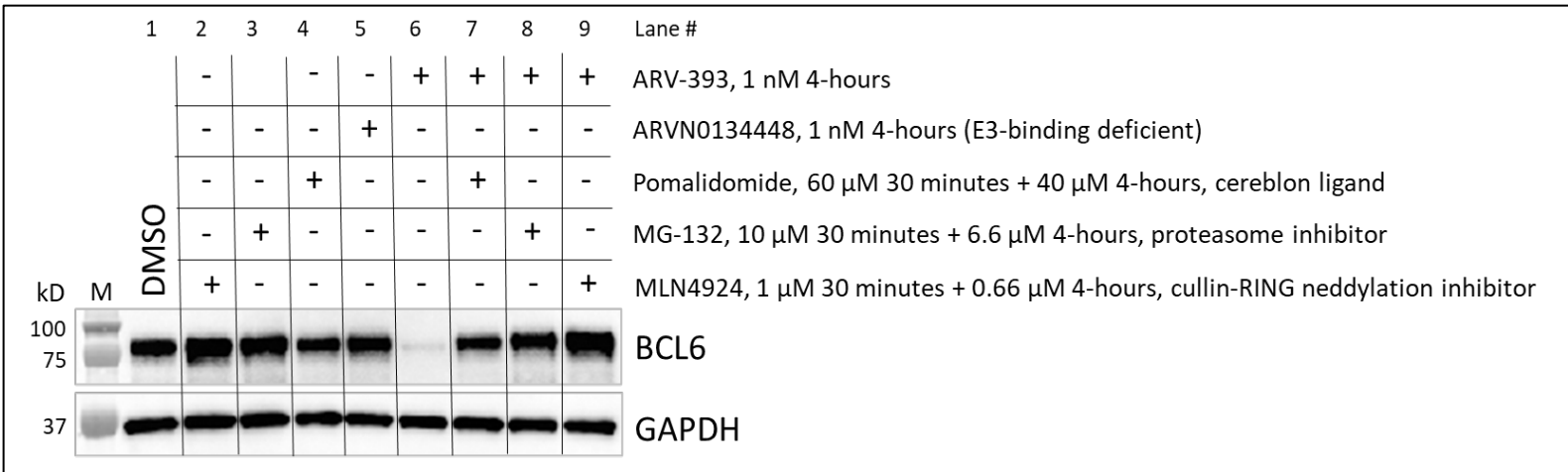
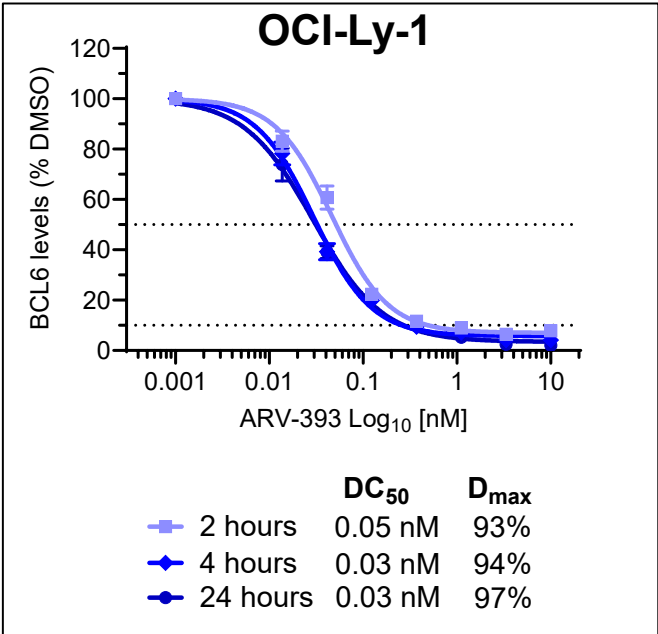
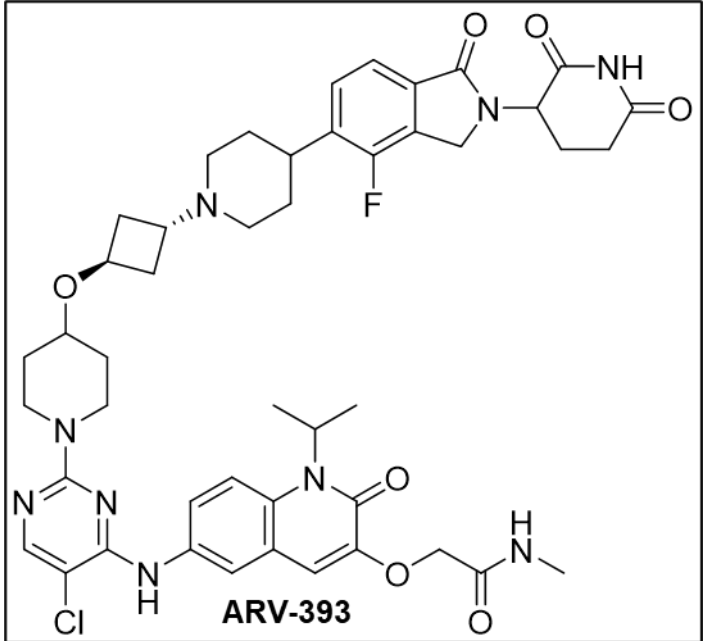
BCL6 PROTAC SAR waypoints

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



Medicinal chemistry campaign identifies ARV-393

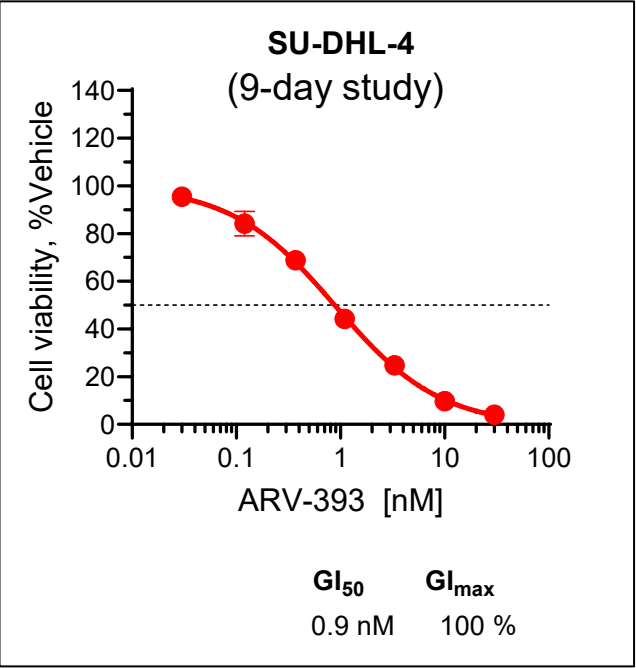
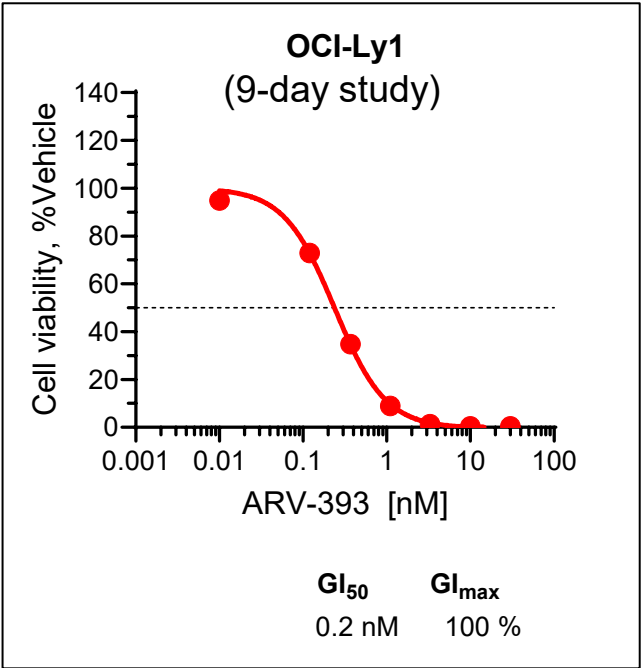
A potent, rapid, on-mechanism and orally bioavailable BCL6 PROTAC



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

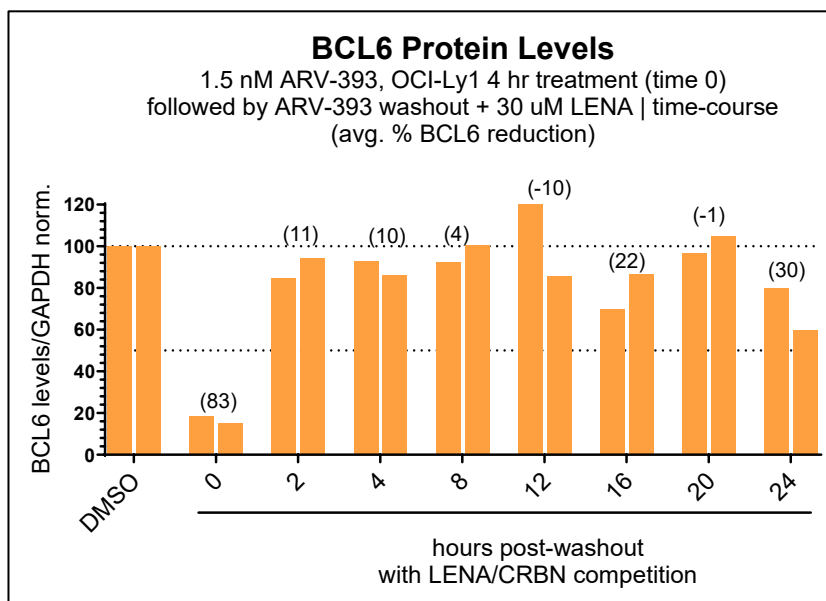
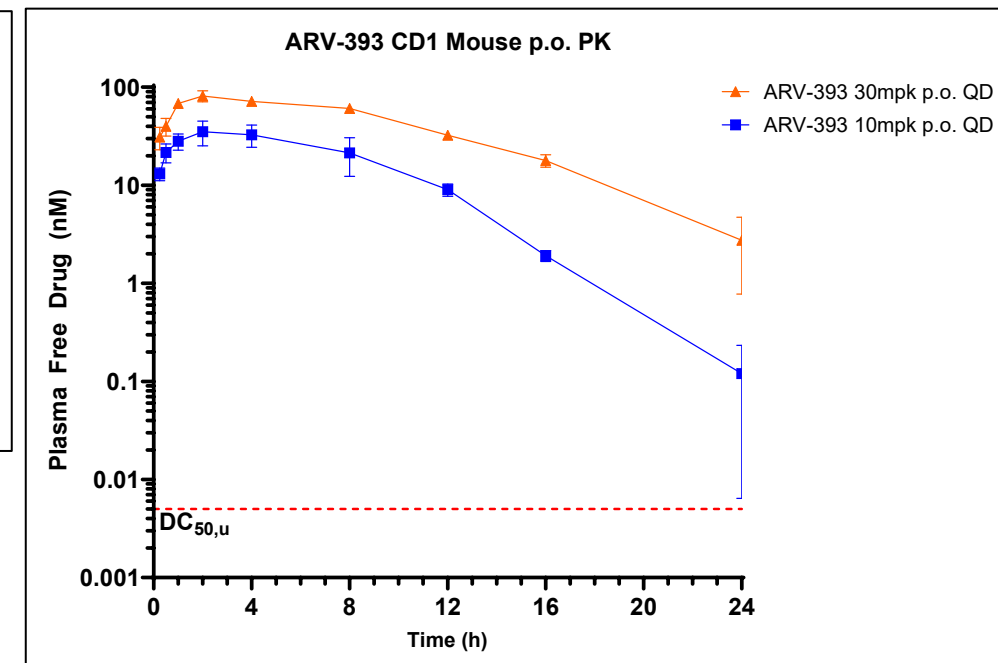
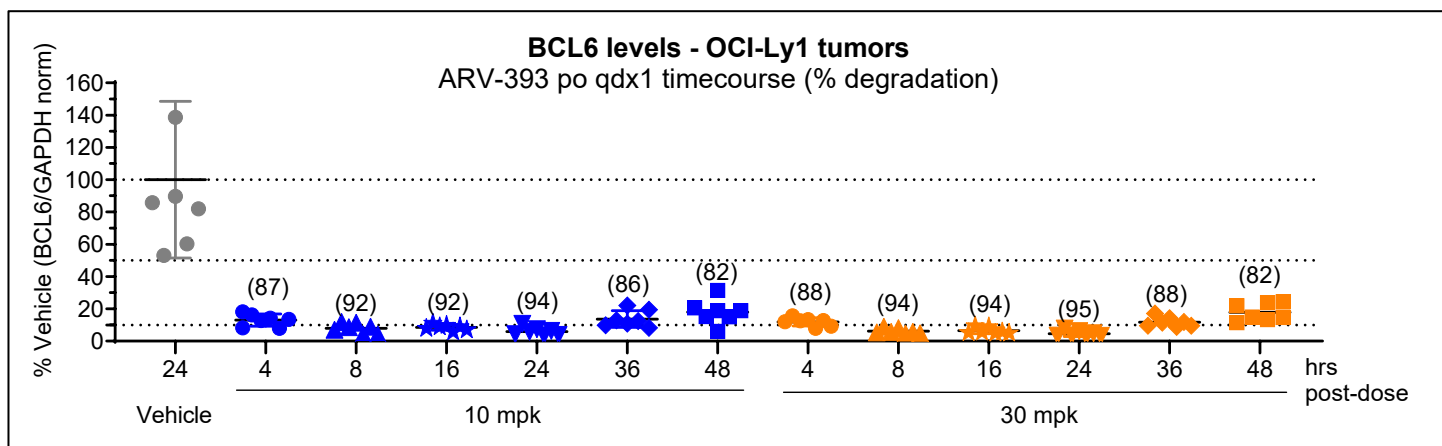


Cell line	Subtype	DC ₅₀ (nM)	D _{Max}	9-Day GI ₅₀ (nM)
OCI-LY1	GCB	0.03	97%	0.2
OCI-LY7	GCB	0.10	97%	1.2
OCI-LY10	ABC	0.11	95%	0.4
SU-DHL-2	ABC	0.07	95%	0.2
SU-DHL-4	GCB	0.16	95%	0.9
SU-DHL-6	GCB	0.14	96%	0.9
Daudi	BL	0.15	99%	2.9
Ramos	BL	0.09	100%	0.4

- 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 resistant¹ cell line

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

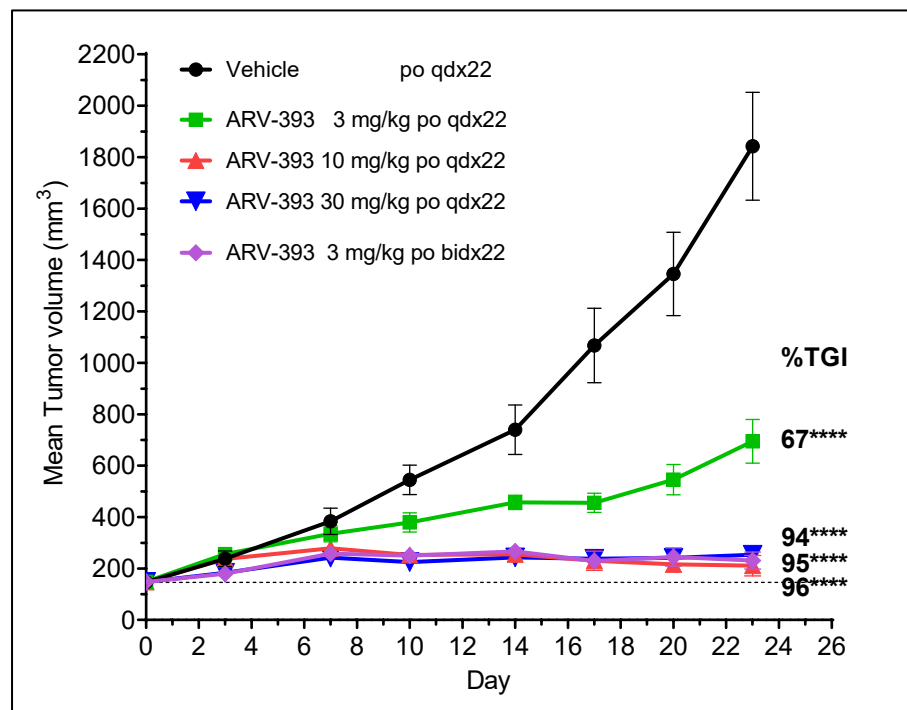
ARV-393 induces ~90% BCL6 degradation *in-vivo* 4-hours after oral dosing



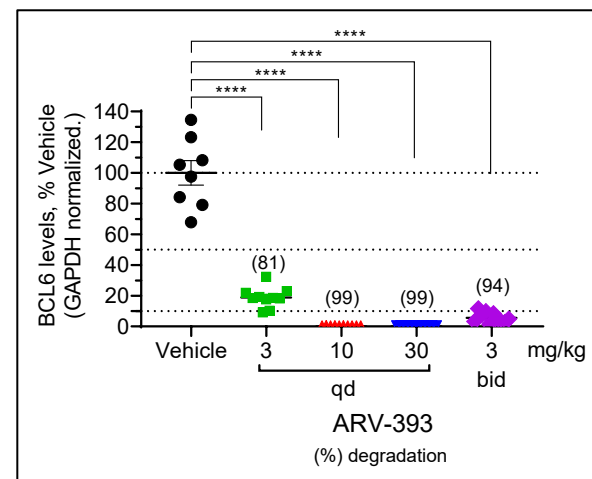
- Sustained knockdown of BCL6 achieved beyond 24hrs with single oral 10mpk dose
- Exposure well in excess of OCI-Ly-1 DC_{50} corrected for assay media binding ($DC_{50,u}$)
- Washout experiment shows that sustained plasma/tumor exposure required to maintain low BCL6 levels as it is rapidly resynthesized

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

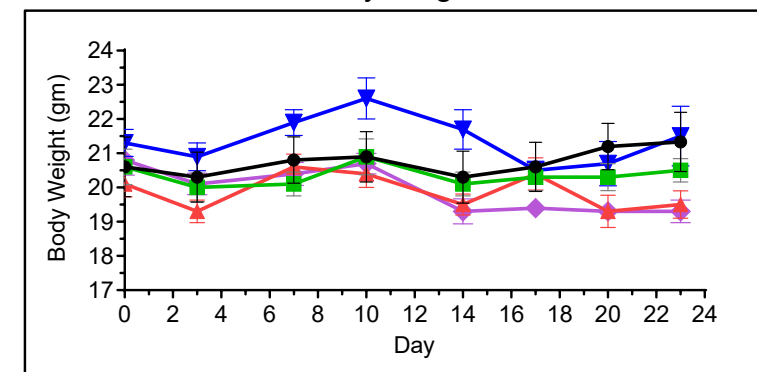
OCI-Ly-1 / CB17 SCID Xenograft



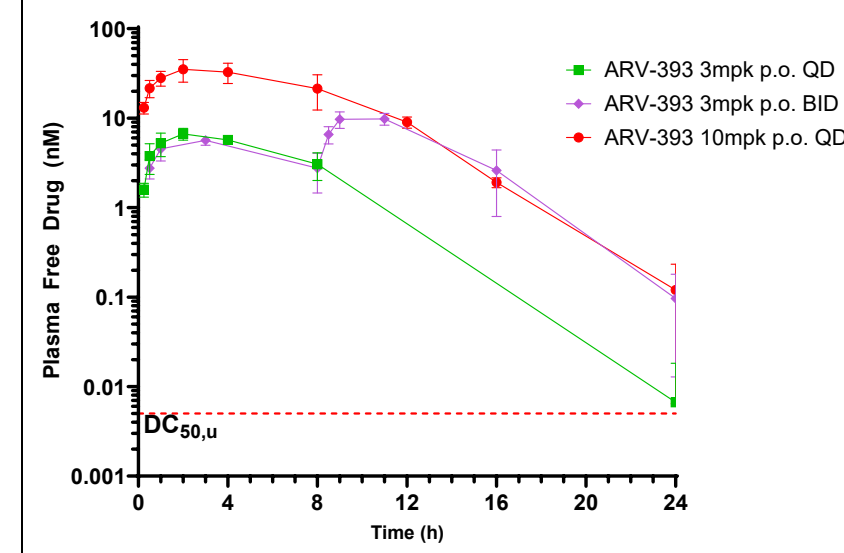
BCL6 levels at takedown 24hrs post dose



Body weights



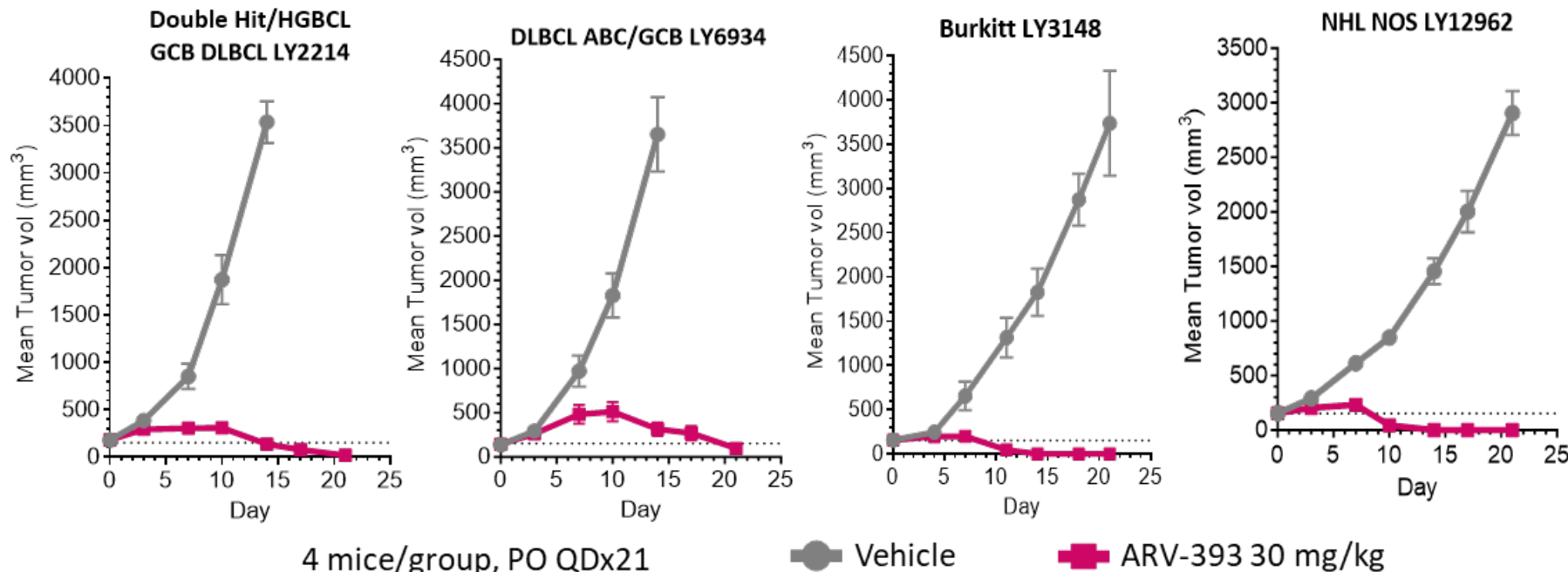
ARV-393 3mpk QD / BID & 10mpk QD



- 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

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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