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**

![Graph showing BCL6 ELISA for OCI-Ly1 in-vitro 24 hr](image)

- ARVN-71228 DC\textsubscript{50} 0.7 nM
- ARVN-129441 (E3-inactive ARVN-71228)
- ARVN-71228 + 30 μM 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-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

<table>
<thead>
<tr>
<th>Compound</th>
<th>DC&lt;sub&gt;50&lt;/sub&gt; (nM)</th>
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<tbody>
<tr>
<td>ARVN-71228</td>
<td>0.7 nM</td>
</tr>
<tr>
<td>BI-3802&lt;sup&gt;(5)&lt;/sup&gt; (A10174)</td>
<td>9.2 nM</td>
</tr>
<tr>
<td>ARVN-129441 (E3-inactive)</td>
<td>32 nM</td>
</tr>
<tr>
<td>CRUK CCT369260&lt;sup&gt;(7)&lt;/sup&gt; (A13085)</td>
<td>32 nM</td>
</tr>
<tr>
<td>AZ Cpd 15&lt;sup&gt;(6)&lt;/sup&gt; (A12399)</td>
<td>32 nM</td>
</tr>
<tr>
<td>ARVN-71228 + 30 μM E3-ligand competition</td>
<td>11.0 nM</td>
</tr>
<tr>
<td>BI-3802&lt;sup&gt;(5)&lt;/sup&gt; (A10174)</td>
<td>11.0 nM</td>
</tr>
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</tr>
</tbody>
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[Graphs showing BCL6 degradation and growth inhibition]
ARVN-71228 achieves tumor regressions in OCI-Ly1 CDX

Tumor volumes | ARVN-71228 efficacy
OCI-Ly1 / CB17SCID xenograft
PO QDx28

- Arm 1: Vehicle
- Arm 2: A71228-8 3mpk
- Arm 3: A71228-8 10mpk
- Arm 4: A71228-8 30mpk
- Arm 5: A71228-8 60mpk
- Arm 6: A71228-8 90mpk

* $p < 0.05$ (vs Veh, two-way ANOVA)
** $p < 0.0001$ (vs Veh, two-way ANOVA)

Body weights | ARVN-71228 efficacy
OCI-Ly1 / CB17SCID xenograft
PO QDx28

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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