Abstract: P1256

Title: ORAL ARV-393 IS A BCL6 DEGRADING PROTAC EFFICACIOUS AS MONOTHERAPY IN B-CELL LYMPHOMA PRECLINICAL CDX AND PDX MODELS

Abstract Type: Poster Presentation

Topic: Lymphoma biology & translational research

Background:

The B-cell lymphoma 6 (*BCL6*) gene is a well-known oncogenic driver of B-cell lymphomagenesis. The BCL6 protein functions as a transcriptional master regulator of germinal center development and has long been the focus of targeted therapy approaches, but historically has been considered undruggable. *BCL6* is often deregulated by chromosome translocation resulting in deregulation and overexpression, often occurring concurrently with a *MYC*- and/or *BCL2*-translocation giving rise to the most aggressive high-grade B-cell lymphomas also known as double- or triple-hit lymphomas. Point mutations in the 5'untranslated region of *BCL6* can also frequently occur and result in aberrant regulation of its transcriptional expression. These genomic abnormalities of *BCL6* have been found recurrently in diffuse large B-cell lymphoma (DLBCL), Burkitt's lymphoma, and follicular lymphoma, all germinal center derived subclasses of non-Hodgkin lymphoma (NHL). ARV-393 is an orally administered PROteolysis TArgeting Chimera (PROTAC) BCL6 degrader, a bifunctional small molecule consisting of a BCL6-binding moiety linked to a cereblon (E3-ligase)-binding moiety that induces degradation of BCL6 via the cellular ubiquitin proteasome system. ARV-393 has received Safe to Proceed to the clinic from the FDA and a Phase 1 trial in relapse/refractory NHL is planned to open in 2024.

Aims:

To develop an oral tablet-based treatment targeting the BCL6 protein, a known oncogenic driver of B-cell NHL.

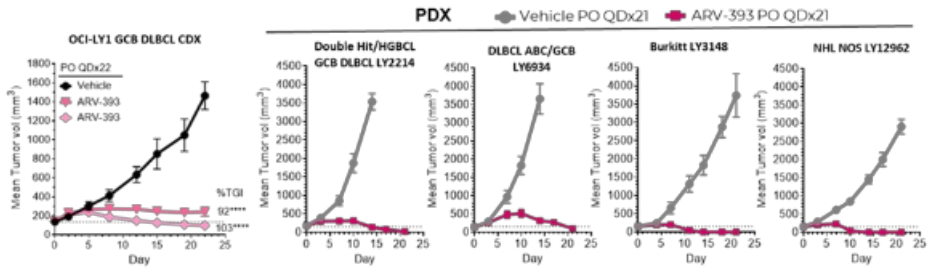
Methods:

We conducted a medicinal chemistry campaign employing biochemical binding and cell based high-throughput assays to identify potent BCL6 PROTAC degraders. The anti-proliferative activity of ARV-393 was evaluated in numerous DLBCL and Burkitt's lymphoma cell line models and its anti-tumor activity in a range of cell line-derived xenograft (CDX) and patient-derived xenograft (PDX) models.

Results:

ARV-393 demonstrated potent and near complete degradation of BCL6 resulting in significant antiproliferative activity in vitro. ARV-393 induced tumor stasis or regressions in-vivo across multiple CDX models. Similarly, in a study of more than 10 NHL PDX models, oral ARV-393 dosed daily for 21-days induced anti-tumor responses in BCL6-expressing lymphomas ranging from total tumor regressions to partial tumor growth inhibition (Figure 1).

Figure 1. Example tumor growth inhibition studies demonstrating the breadth of ARV-393 efficacy in CDX and PDX models



Summary/Conclusion: ARV-393 is an oral PROTAC BCL6 degrader that demonstrated potent anti-tumor

monotherapy activity in numerous preclinical models of NHL, indicating this molecule may provide a significant therapeutic benefit to NHL patients.

Keywords: Non-Hodgkin’s lymphoma, BCL6, Tumor model, DLBCL