PO-010

Trial in Progress: Phase 1 Study of ARV-393, a PROteolysis TArgeting Chimera (PROTAC) B-Cell Lymphoma 6 Degrader, in Advanced Non-Hodgkin Lymphoma

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Objective

- This multicenter, first-in-human, phase 1 study (NCT06393738) is evaluating the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary antitumor activity of ARV-393 in patients with relapsed/refractory B-cell non-Hodgkin lymphoma (NHL) or nodal T-follicular helper cell lymphoma, angioimmunoblastic-type (nTFHL-AI), also known as angioimmunoblastic T-cell lymphoma (AITL)

References

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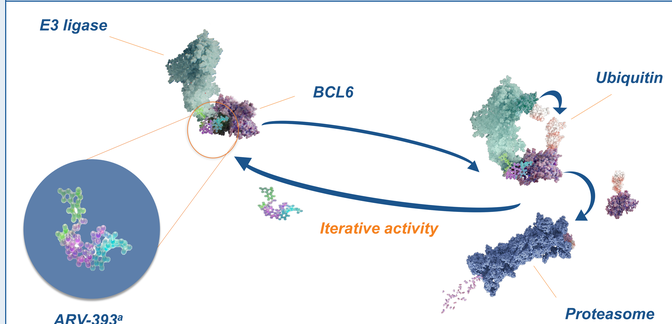
Background

- NHL represents a biologically and clinically diverse group of hematologic malignancies originating from B cells, T cells, and/or natural killer cells, with those of B-cell origin constituting approximately 80%–85% of all NHL cases[1]
- The B-cell lymphoma 6 (BCL6) transcription factor is a key oncogenic driver of B-cell lymphomagenesis, and deregulated BCL6 expression is a common feature of diffuse large B-cell lymphoma,[2-6] the most common type of NHL[1]
- BCL6 is also implicated in nTFHL-AI
  - BCL6 is a lineage-defining transcription factor of T follicular helper cells, thought to be the cell of origin for nTFHL-AI[7,8]
  - Human and murine nTFHL-AI tumor cells express BCL6, and its continued expression was required for tumor growth in a mouse model of nTFHL-AI[9]
- ARV-393 is an orally administered PROTAC BCL6 degrader that harnesses the ubiquitin-proteasome system to induce degradation of BCL6[10,11]
  - ARV-393 is a bifunctional molecule consisting of a BCL6-binding domain joined by a linker to an E3 ubiquitin ligase–binding domain
  - Formation of this trimer complex induces ubiquitination and subsequent degradation of BCL6 by the proteasome (**Figure 1**)

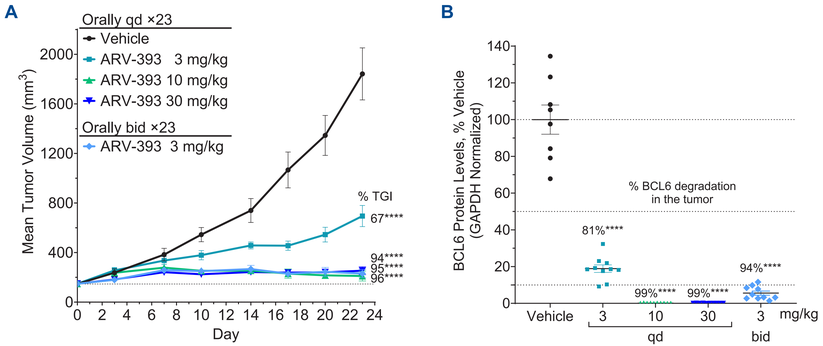
Figure 1: Mechanism of action of ARV-393



[a]General PROTAC protein degrader is shown.
BCL6=B-cell lymphoma 6; PROTAC=PROteolysis TArgeting Chimera.

- In preclinical studies, ARV-393 induced rapid and robust degradation (>90%) of BCL6 in NHL cell lines and demonstrated substantial tumor growth inhibition in xenograft models, supporting further investigation in patients with NHL (**Figure 2**)

Figure 2: A) Antitumor activity of ARV-393 in the OCI-Ly1 cell line xenograft model; B) BCL6 levels at takedown 24 hours post-dose[11]

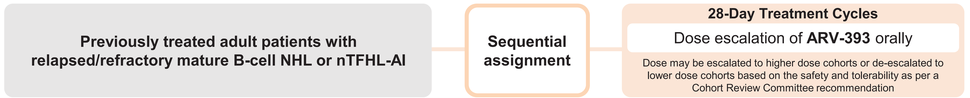


****P<0.0001 vs vehicle. ARV-393 administered for 23 consecutive days.
BCL6=B-cell lymphoma 6; bid ×23=twice daily for 23 days; GAPDH=glyceraldehyde 3-phosphate dehydrogenase; qd ×23=once daily for 23 days; TGI=tumor growth inhibition.

Study Design

- This open-label, first-in-human, phase 1 dose-escalation study in adult patients with relapsed/refractory NHL is evaluating the safety, tolerability, PK, PD, and preliminary antitumor activity of ARV-393 (**Figure 3**)
- Eligible patients have relapsed/refractory mature B-cell NHL and ≥2 prior systemic therapies, or histologically confirmed nTFHL-AI that has recurred or progressed following standard of care therapy (**Table 1**)
- Key outcome measures are shown in **Table 2**

Figure 3: Study schema



NHL=non-Hodgkin lymphoma; nTFHL-AI=nodal T-follicular helper cell lymphoma, angioimmunoblastic-type.

Table 1: Key eligibility criteria

Inclusion criteria	Exclusion criteria
• Adults aged ≥18 years • Relapsed/refractory mature B-cell NHL and ≥2 prior systemic therapies, or histologically confirmed nTFHL-AI that has recurred or progressed following institutional standard of care therapy • ≥1 measurable lesion at study entry • ECOG performance status of 0 or 1 • Freshly biopsied or archival tumor tissue available • Adequate organ function	• Active central nervous system involvement • Prior allogeneic stem cell transplant or solid organ transplantation • Autologous stem cell transplant ≤100 days and previous CAR T-cell therapy ≤60 days prior to cycle 1, day 1 of ARV-393 treatment • Significant acute or chronic medical illness, including hypereosinophilic syndrome, active interstitial lung disease or pneumonitis, or active or uncontrolled infection

CAR=chimeric antigen receptor; ECOG=Eastern Cooperative Oncology Group; NHL=non-Hodgkin lymphoma; nTFHL-AI=nodal T-follicular helper cell lymphoma, angioimmunoblastic-type.

Table 2: Key outcome measures

Primary objective	Primary endpoints
• Evaluate the safety and tolerability of ARV-393	• DLTs during cycle 1 • TEAEs including incidence, severity, seriousness, and relationship to study drug • Changes from baseline in vital signs, laboratory parameters, or ECG parameters • Grade 3/4 clinical laboratory abnormalities
Secondary objectives	**Secondary endpoints**
• Evaluate the PK profile of multiple ARV-393 doses	• Plasma concentration of study drug (AUC) • PK parameters of study drug (C_{max}, C_{min}, CL/F, T_{max}, and Vd/F)
• Assess preliminary antitumor activity of ARV-393	• ORR[a] by investigator assessment • CRR[b] by investigator assessment • DOR by investigator assessment

[a]The proportion of participants achieving a complete response or partial response according to the Lugano response criteria for NHL.[12]
[b]The proportion of participants achieving a complete response according to the Lugano response criteria for NHL.[12]
AUC=area under the plasma concentration time-curve; CL/F=clearance/bioavailability; C_{max}=maximum observed serum drug concentration; C_{min}=minimum observed serum drug concentration; CRR=complete response rate; DLT=dose-limiting toxicity; DOR=duration of response; ECG=electrocardiogram; ORR=objective response rate; PK=pharmacokinetic; TEAE=treatment-emergent adverse event; T_{max}=time taken to reach C_{max}; Vd/F=volume of distribution/bioavailability.

Study Status

- Enrollment is ongoing
- To view currently recruiting sites, please visit clinicaltrials.gov (NCT06393738)