(PB3736) PHASE 1 STUDY OF ARV-393, A PROTAC BCL6 DEGRADER, AS MONOTHERAPY IN PATIENTS WITH ADVANCED NON-HODGKIN LYMPHOMA (NHL) OR COMBINED WITH GLOFITAMAB IN PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL)

Topic: 19. Large B cell lymphomas - Clinical

Sarit Assouline*[1], Andrew Zelenetz[2], Jacob Haaber Christensen[3], Almudena Cascales Hernandez[4], Luis Malpica[5], Shalin Kothari[6], Dipenkumar Modi[7], Miguel Ángel Canales Albendea[8], Damian Cubillas[9], Alejandro Martín García-Sancho[10], Catherine Diefenbach[11], John Kuruvilla[12], Paolo F Caimi[13], Krish Patel[14], Sean Landrette[15], Eric Zhi[15], Yuanyuan Zhang[15], Roland Meier[15], Matthew Matasar[16], Martin Hutchings[17]

[1]McGill University, Montreal, Canada;[2]Memorial Sloan Kettering Cancer Center, New York, United States of America;[3]Odense University Hospital, Odense, Denmark;[4]Hospital Clínico Universitario Virgen De La Arrixaca, Murcia, Spain;[5]The University of Texas MD Anderson Cancer Center, Houston, United States of America;[6]Yale School of Medicine and Yale Cancer Center, New Haven, United States of America;[7]Karmanos Cancer Institute, Wayne State University, Detroit, United States of America;[8]Clínica Universidad de Navarra, Pamplona, Spain;[9]START Center for Cancer Research, Madrid, Spain;[10]Hospital Universitario de Salamanca, Salamanca, Spain;[11]Laura and Isaac Perlmutter Cancer Center, New York University Grossman School of Medicine, New York, United States of America;[12]Princess Margaret Cancer Centre, Toronto, Canada;[13]Cleveland Clinic, Cleveland, United States of America;[14]Sarah Cannon Research Institute, Nashville, United States of America;[15]Arvinas Operations, Inc., New Haven, United States of America;[16]Rutgers Cancer Institute of New Jersey, New Brunswick, United States of America;[17]Rigshospitalet and University of Copenhagen, Copenhagen, Denmark;

Background

Despite recent advancements in NHL therapies, many patients experience disease progression or relapse. Agents with novel mechanisms of action and combination strategies are needed to improve clinical outcomes. B-cell lymphoma 6 (BCL6) is a master transcriptional regulator of immune cells, particularly of germinal center B cells, and an established oncogenic driver in NHL. ARV-393 is an oral PROteolysis TArgeting Chimera (PROTAC) BCL6 degrader that binds an E3 ubiquitin ligase and BCL6 to induce ubiquitination of BCL6 and its subsequent proteasomal degradation. ARV-393 monotherapy potently inhibited tumor growth and induced tumor regressions across NHL cell-derived xenograft (CDX) and patient-derived xenograft models, including models of DLBCL, transformed follicular lymphoma, and nodal T-follicular helper cell lymphoma (nTFHL). Furthermore, administration of ARV-393 with a CD20×CD3 bispecific antibody, glofitamab, demonstrated combinatorial antitumor activity in a humanized high-grade B-cell lymphoma CDX model, inducing deeper tumor growth inhibition and increased tumor regressions vs either monotherapy. These preclinical findings demonstrated single-agent ARV-393 antitumor activity across NHL subtypes and suggested mechanistic synergy with glofitamab.

Aims

To clinically evaluate ARV-393 monotherapy in patients with NHL and ARV-393 in combination with glofitamab in patients with DLBCL, this global, multicenter, open-label, first-in-human, phase 1 dose escalation and optimization/expansion study (NCT06393738) is assessing the safety, tolerability, pharmacokinetics, pharmacodynamics, and preliminary antitumor activity of ARV-393 as monotherapy in relapsed or refractory (R/R) NHL or in combination with glofitamab in R/R DLBCL, with a primary objective of determining provisional doses for further exploration.

Methods

Patients eligible for ARV-393 monotherapy are adults with confirmed R/R B-cell NHL who previously received ≥2 lines of systemic therapy (including rituximab), or nTFHL who previously received standard of care therapy. Patients eligible for ARV-393 in combination with glofitamab are adults with pathologically confirmed R/R DLBCL, DLBCL not otherwise specified, or large B-cell lymphoma arising from follicular lymphoma who were treated with ≥2 prior lines of systemic therapy. ARV-393 will be administered orally once daily in 28-day cycles alone or in combination with intravenous glofitamab during 21-day cycles. Approximately 255 patients will be enrolled across study cohorts.

Results

As of January 2026, enrollment is ongoing.

Summary/Conclusion

This study will provide data on the tolerability and preliminary antitumor activity of the PROTAC BCL6 degrader ARV-393 administered as monotherapy or in a chemotherapy-free combination with glofitamab.