3. RELAPSED/REFRACTORY MULTIPLE MYELOMA

TRIAL IN PROGRESS: QUINTESSENTIAL-2 – A PHASE 3 STUDY OF ARLOCABTAGENE AUTOLEUCEL VS. STANDARD OF CARE IN ADULT PATIENTS WITH RELAPSED AND REFRACTORY MULTIPLE MYELOMA EXPOSED TO LENALIDOMIDE

E. Lebel[1], A. Abdulgawad[2], S. Bramanti[3], G. Garate[4], P. J. Ho[5], M. Keränen[6], Y. Cohen[7], M. Vase[8], A. Khot[9], I. Kristensen[10], R. Leblanc[11], C. Lee[12], W. Legiec[13], H. Magen[14], M. -V. Mateos[15], D. Oh[16], L. Pour[17], N. Schutz[18], A. Spyridonidis[19], K. Weisel[20], J. Zaucha[21], S. Larson[22], A. Varshavsky-Yanovsky[23], K. Grazioli[24], D. Basudhar[24], H. Hu[24], Y. Meng[24], L. Eldjerou[24], S. Bal[25], S. Harrison[9], R. Popat[26], M. Raab[27], P. Rodriguez-Otero[28]

[1]Hadassah Medical Center, Jerusalem, Israel; [2]Christie NHS Foundation Trust, Manchester, UK; [3]IRCCS Istituto Clinico Humanitas, Rozzano, Italy; [4]Hospital Aleman, Buenos Aires, Argentina; [5]Royal Prince Alfred Hospital and University of Sydney, Camperdown, Australia; [6]Helsinki University Hospital, Finland; [7]Tel Aviv Sourasky Medical Center and Faculty of Medical and Health Sciences, Tel Aviv University, Israel; [8]Aarhus Universitetshospital, Midtjylland, Denmark; [9]Peter MacCallum Cancer Centre, Royal Melbourne Hospital and University of Melbourne, Victoria, Australia; [10]Odense Universitetshospital, Denmark; [11]Hematology-Oncology and Cell Therapy University Institute, Hôpital Maisonneuve-Rosemont Research Center, Université de Montréal, Quebec, Canada; [12]Royal Adelaide Hospital, Australia; [13]St. John of Dukla Oncology Center of Lublin Land,Poland; [14]Department of Hematology, Chaim Sheba Medical Center, Ramat-Gan, Faculty of Medicine, Tel Aviv University, Israel; [15]Hospital Universitario de Salamanca, Spain; [16]Monash Health and Monash University, Clayton, Victoria, Australia; [17]Masaryk University and University Hospital Brno, Czech Republic; [18]Hospital Italiano de Buenos Aires, Argentina; [19]University Hospital of Patras, Greece; [20]University Medical Center Hamburg-Eppendorf, Germany; [21]Medical University of Gdańsk and University Clinical Center, Poland; [22]UCLA Medical Center, Los Angeles, USA; [23]Fox Chase Cancer Center Temple Health, Philadelphia, USA; [24]Bristol Myers Squibb, Princeton, USA; [25]University of Alabama at Birmingham, USA; [26]University College London Hospital, UK; [27]Universitaetsklinikum Heidelberg, Germany; [28]Clinica Universidad de Navarra, Pamplona, Spain

Introduction. Despite advances in multiple myeloma (MM) treatment, most patients (pts) will relapse, highlighting the need for new drug classes in relapsed/refractory (RRMM). Further, with the extensive use of lenalidomide (LEN), an immunomodulatory drug (IMiD), in frontline and maintenance therapies, lenalidomide-refractoriness has become increasingly common and poses an additional challenge as the disease is less likely to respond to subsequent treatment. G protein-coupled receptor class C group 5 member D (GPRC5D) is a promising therapeutic target for MM as the receptor is highly expressed on malignant plasma cells; it has little to no expression on non-plasma cell immune populations and limited expression on other tissues. Arlocabtagene autoleucel (arlo-cel) is a GPRC5D-directed autologous chimeric antigen receptor (CAR) T-cell therapy that has demonstrated safety and efficacy in pts with RRMM in a first-in-human phase 1 study. Overall response rate (ORR) was 94% and 91% in pts with 1-3 and ≥3 prior lines of therapy (pLOT), respectively, following a single arlo-cel infusion of 150×10^6 CAR T-cells; ORR was 92% in pts with ≥3 pLOT following an infusion of 75×10^6 CAR T-cells. These phase 1 study outcomes support further development of arlo-cel in clinical trials.

Methods. QUINTESSENTIAL-2 (NCT06615479) is a randomized, open-label, multicenter, phase 3 confirmatory study comparing the efficacy and safety of arlo-cel versus standard of care (SOC) in adults with RRMM and prior LEN exposure. Key inclusion criteria were age ≥18 years, confirmed diagnosis of MM as per International Myeloma Working Group (IMWG) criteria, 1-3 pLOT (may include a proteasome inhibitor, IMiD, anti-CD38 antibody, and BCMA-targeted therapy), be exposed to lenalidomide (with ≥2 consecutive cycles, unless progressive disease [PD] was the best response to LEN-containing treatment or if there was LEN intolerance or unacceptable toxicity), have measurable disease, and ECOG performance status 0 or 1. Pts who received prior GPRC5D-targeted therapy are excluded. Eligible pts will be randomized 1:1 to two arms. Arm A includes leukapheresis within 3-4 days of randomization, mandatory bridging therapy within 6 days of randomization with DPd (daratumumab, pomalidomide, dexamethasone) or Kd (carfilzomib, dexamethasone) per investigator choice and lymphodepleting chemotherapy prior to a single arlo-cel infusion. Arm B includes SOC of DPd or Kd per investigator choice, dosed per labeling, until PD. Primary endpoints are progression-free survival and minimal residual disease (MRD) negativity in complete response (CR). Key secondary endpoints include overall survival and ORR. Other endpoints include safety, MRD-negative status, CR rate, time to response, duration of response, pharmacokinetics, and pt-reported outcomes. Pts will be followed for ≤5 years after the last pt is randomized, and with a long-term follow-up study (≤15 years post-infusion) for pts receiving arlo-cel.

Results. This trial in progress is expected to enroll 440 pts at ~125 sites globally. The first pt was enrolled in March 2025.

Conclusion. This phase 3 study will compare the efficacy and safety of arlo-cel vs SOC in adult pts with RRMM after 1-3 pLOT.