

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

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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



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1-3 pLOT.