Trial in progress: QUINTESSENTIAL-2—a phase 3 study of arlocabtagene autoleucel versus standard of care in adult patients with relapsed and refractory multiple myeloma (RRMM) exposed to lenalidomide

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Introduction

- Despite advances in the management of multiple myeloma, most patients relapse,[1] highlighting the need for new drug classes to improve outcomes in RRMM
- Further, RRMM exposed to lenalidomide poses an additional challenge as the disease is less likely to respond to subsequent treatment[1,2]
- G protein-coupled receptor class C group 5 member D (GPRC5D) is a promising therapeutic target for MM as it is highly expressed on malignant plasma cells. Although also present on normal plasma cells and epithelial tissues (skin, hair follicles, tongue), GPRC5D shows minimal to no expression in other immune cells, bone marrow progenitors, and other healthy tissues. This restricted expression profile supports its potential for selective targeting in MM[3]
- Arlocabtagene autoleucel (arlo-cel; BMS-986393) is a GPRC5D-directed autologous chimeric antigen receptor (CAR) T-cell therapy that has been granted FDA Regenerative Medicine Advanced Therapy Designation for RRMM[4] (**Figure 1**)
- Arlo-cel has demonstrated safety and efficacy in patients with RRMM in a first-in-human phase 1 study[4,5]
  - Following a single infusion of arlo-cel (150 × 10^6 CAR T-cells) in those with 1-3 prior lines of therapy (LOT), overall response rate (ORR) and complete response rate (CRR) were 94% and 71%, respectively[6]
  - Among patients with ≥ 3 prior LOT treated with arlo-cel at doses of 75 x 10^6 and 150 x 10^6, ORR were 92% and 91%, respectively; CRR were 58% and 44%, respectively[7]
  - Based on the observed efficacy comparability and with the intent of optimizing benefit-risk for an early RRMM population, the dose on the phase 3 study was reduced to 75 x 10^6 CAR T-cells[7]

Figure 1. Mechanism of action of arlo-cel, a CAR T-cell therapy targeting GPRC5D[8,9]

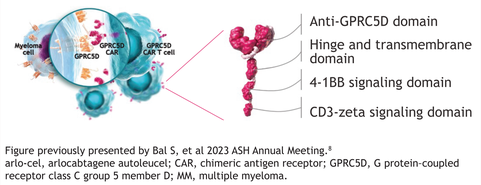
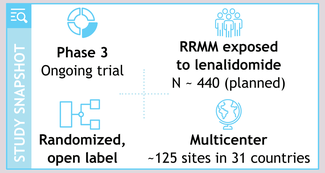
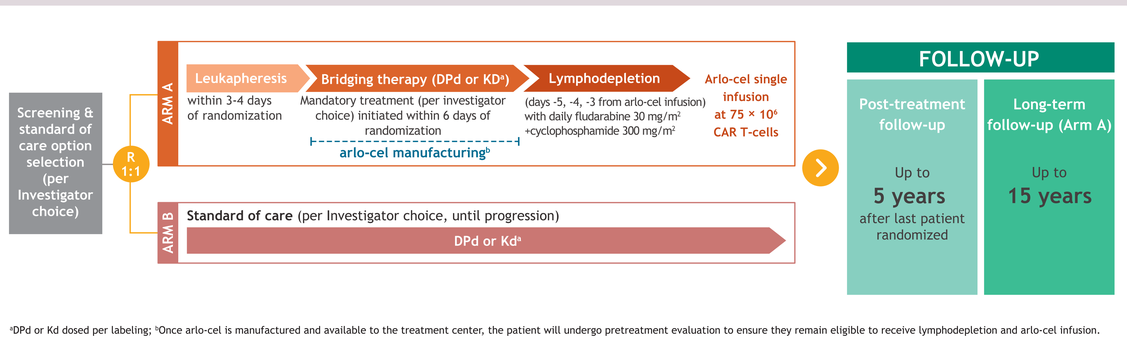


Figure previously presented by Bal S, et al 2023 ASH Annual Meeting.[8]
arlo-cel, arlocabtagene autoleucel; CAR, chimeric antigen receptor; GPRC5D, G protein-coupled receptor class C group 5 member D; MM, multiple myeloma.

Study design: QUINTESSENTIAL-2 (NCT06615479) is a randomized, open-label, multicenter, phase 3 confirmatory study comparing the efficacy and safety of arlo-cel vs standard of care (SOC) in adults with RRMM and prior lenalidomide exposure





[a]DPd or Kd dosed per labeling; [b]Once arlo-cel is manufactured and available to the treatment center, the patient will undergo pretreatment evaluation to ensure they remain eligible to receive lymphodepletion and arlo-cel infusion.

arlo-cel, arlocabtagene autoleucel; DPd, daratumumab, pomalidomide, and dexamethasone; GPRC5D, G protein-coupled receptor class C group 5 member D; Kd, carfilzomib and dexamethasone; R, randomization; RRMM, relapsed and refractory multiple myeloma.

- In patients with RRMM after 1-3 prior LOT treated with arlo-cel (N=31)[6]:
  - Treatment-emergent adverse events (TEAEs) were predominantly hematologic. No grade ≥ 3 infections were reported
  - Treatment-related AEs (TRAEs):
    - Cytokine-release syndrome (CRS) was the most common TRAE; all events of CRS and immune effector cell–associated neurotoxicity (ICANS) were grade ≤ 2 and resolved
    - Other select neurotoxicities occurred in 2 patients: one experienced grade 2 ataxia and gait disturbance (ongoing), and one patient had grade 1 gait disturbance (resolved) and grade 1 dysarthria (ongoing)
    - On-target/off-tumor toxicities (skin, oral/dysgeusia, and nail disorders) were observed in 55% of patients; all events were grade ≤ 2 and did not require intervention in most cases
    - One patient experienced grade 1 weight loss that resolved without intervention

Objective

- To present the design of the phase 3 QUINTESSENTIAL-2 study, evaluating arlo-cel versus standard of care in patients with RRMM and prior exposure to lenalidomide

Population

- Adult patients who have received 1-3 prior LOT and have been exposed to lenalidomide (**Figure 2**)
  - Prior B-cell maturation antigen-directed therapy is permitted in a limited number of patients

Figure 2. Key eligibility criteria

INCLUSION CRITERIA
- Men and women ≥ 18 years of age
- Documented diagnosis of MM per IMWG criteria
- Received 1-3 prior LOT[a] including prior exposure to lenalidomide with ≥ 2 consecutive cycles, unless PD was the best response to lenalidomide-containing treatment or if there was lenalidomide intolerance or unacceptable toxicity
- Measurable disease
- ECOG performance status 0 or 1
- Documented disease progression during or after their last anti-myeloma regimen

EXCLUSION CRITERIA
- Active or history of central nervous system involvement with MM
- Solitary plasmacytomas or non-secretory myeloma without other evidence of measurable disease
- Need for urgent treatment due to rapidly progressing MM
- Active systemic fungal, bacterial, viral, or other infection despite appropriate anti-infective treatment at time of leukapheresis
- Received any prior GPRC5D-directed therapy or other prior MM treatment without the required washout prior to leukapheresis

[a]May include a proteasome inhibitor, immunomodulatory drug, anti-CD38 monoclonal antibody, and in a limited number of patients, B-cell maturation antigen-directed therapy; must have undergone ≥ 2 consecutive cycles of treatment for each LOT (except for CAR T-cell therapy), unless PD was the best response to the regimen or in the event of unacceptable toxicity. CAR, chimeric antigen receptor; ECOG, Eastern Cooperative Oncology Group; GPRC5D, G protein-coupled receptor class C group 5 member D; IMWG, International Myeloma Working Group; LOT, lines of therapy; MM, multiple myeloma; PD, progressive disease.

Study endpoints

- Study endpoints are detailed in **Figure 3**

Figure 3. Study endpoints

DUAL PRIMARY ENDPOINTS
- **Progression-free survival (PFS)[a]**
- **Minimal residual disease (MRD) negativity in complete response (CR)[b]**

KEY SECONDARY
- Overall survival (OS)
- Overall response rate (ORR)[a]

OTHER ENDPOINTS
- Safety and tolerability[c]
- CR rate[a]
- Time to response (TTR)[a,d]
- Duration of response (DOR)[e]
- MRD-negative status
- Pharmacokinetics
- Patient-reported quality of life outcomes (EORTC QLQ-C30 and -MY20)

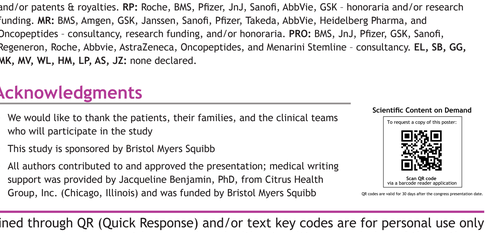
[a]Based on the IMWG Uniform Response Criteria for MM as assessed by an IRC (or death due to any cause for PFS); [b]Defined as MRD negativity at 10^{-5} sensitivity level and with CR/stringent CR, per IMWG criteria as assessed by IRC; [c]Based on incidence and severity of AEs, AEs of special interest, serious AEs, and laboratory results; [d]Defined as time from randomization to first documentation of partial response or better; [e]Defined as time from first documentation of partial response or better to first documentation of progressive disease or death from any cause, whichever occurs first.
AE, adverse event; C30, Core30; EORTC QLQ, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; IMWG, International Myeloma Working Group; IRC, independent review committee; MM, multiple myeloma; MY20, multiple myeloma module.

Enrollment

- The study is currently recruiting and is expected to enroll 440 patients across ~125 sites (**Figure 4**)

Figure 4. Planned enrollment

QUINTESSENTIAL-2
- **Study start date (first patient first visit):** March 12, 2025
- **Estimated primary analysis completion date:** December 30, 2027
- **Estimated study completion date:** June 22, 2032
- **Estimated enrollment:** 440



Approximately 125 sites in 31 countries

Study information as of October 2025.

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Disclosures

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