Trial in progress: a phase 1 study to evaluate the safety and preliminary efficacy of arlocabtagene autoleucel, a GPRC5D-targeted chimeric antigen receptor T cell therapy, in combination with mezigdomide in patients with relapsed/refractory multiple myeloma

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Objective

- To describe arm B of the phase 1 CA088-1005 study, which aims to determine safety, tolerability, and recommended phase 2 dose (RP2D) of arlo-cel plus MEZI in patients with RRMM

Conclusions

- Arlo-cel has previous demonstrated a high ORR and manageable safety profile in a phase 1 trial in patients with RRMM; combining arlo-cel treatment with other novel therapies with differing MoAs may improve patient outcomes
- CA088-1005 is a multicenter, open-label, phase 1 study to determine the safety, tolerability, and RP2D of arlo-cel plus other novel therapies, including MEZI, in patients with RRMM
- Enrollment began in February 2024 and is ongoing in the United States and Canada

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Introduction

- Multiple myeloma (MM) is a chronic hematologic malignancy characterized by clonal proliferation of malignant plasma cells and high clinical and molecular heterogeneity
- Treatment advances have improved survival for patients with MM, with median overall survival from first progression rising from 36 months to 52 months between 2004 and 2019,[1] and a 5-year relative survival of ~ 60% between 2015 and 2021[2]
- Despite treatment advances, MM remains an incurable disease that becomes relapsed/refractory (RR) to current treatments[3]
- Given the heterogeneity of the disease and frequent relapses, the choice of treatment is challenging[1]
  - Numerous novel combination regimens have demonstrated clinical benefit for patients across first-, second-, and later-line settings, extending treatment options throughout the disease course[3]
  - Still, there remains an unmet need for novel therapies that better address individual patient needs and improve outcomes beyond the current treatment options[3]
- Arlocabtagene autoleucel (arlo-cel; BMS-986393) is a chimeric antigen receptor (CAR) T cell therapy that targets the orphan transmembrane G protein-coupled receptor class C, group 5, member D (GPRC5D), which is expressed by malignant plasma cells in patients with MM (**Figure 1**)
  - In a phase 1, first-in-human clinical trial (CC-95266-MM-001; NCT04674813) in patients with RRMM who received ≥ 3 prior lines of therapy, arlo-cel demonstrated encouraging preliminary efficacy results with an acceptable safety profile[4-6]
    - Among patients who received 75 × 10^6 or 150 × 10^6 cells, the overall response rates (ORRs) were 92% and 91%, respectively, with complete response (CR) rates of 58% and 44%, respectively[5]
    - Cytokine release syndrome was the most common treatment-emergent adverse event (TEAE), occurring in 75% and 88% of patients in the 75 × 10^6 and 150 × 10^6 dose cohorts, respectively; all TEAEs were grade 1/2 and resolved[5]

Figure 1. Mechanism of action (MoA) of arlo-cel

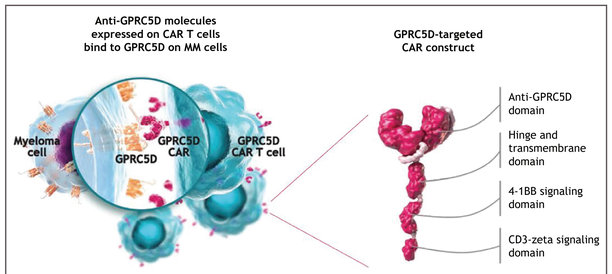
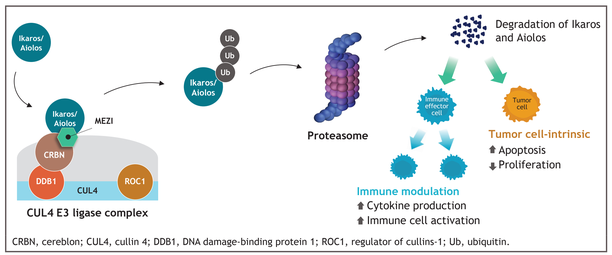


Figure previously presented by Patel K, et al 2025 IMS Annual Meeting[7]

- To potentially increase efficacy by improving T-cell function, the CA088-1005 (NCT06121843) study is evaluating arlo-cel in combination with other treatments
- Mezigdomide (MEZI) is an oral CELMoD™ agent optimized for maximal Ikaros/Aiolos degradation, leading to increased MM cell apoptosis and immunostimulatory effects[8-9] (**Figure 2**)
  - MEZI may enhance arlo-cel efficacy via added cytotoxicity or synergistic T cell stimulation, leading to potentially greater durability of response

Figure 2. MoA of MEZI



CRBN, cereblon; CUL4, cullin 4; DDB1, DNA damage-binding protein 1; ROC1, regulator of cullins-1; Ub, ubiquitin.

Methods

Study design

- Patients will be assigned to one of multiple treatment arms to evaluate arlo-cel in combination with various compounds; here, we focus on arm B (arlo-cel plus MEZI)
- The study design is presented in **Figure 3** and treatment periods are described in **Figure 4**

Figure 3. Study design (NCT06121843)

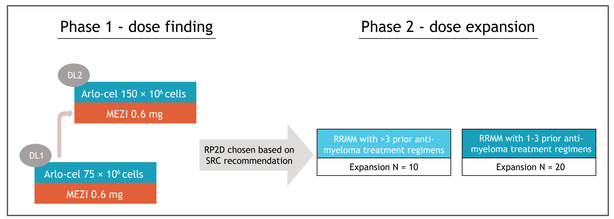
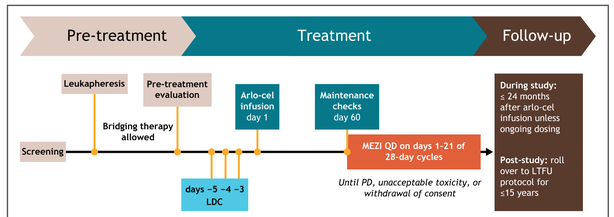


Figure 4. Study treatment periods



C, cycle; LTFU, long term follow up; LDC, lymphodepleting chemotherapy; QD, once daily.

- CA088-1005 is a multicenter (United States and Canada), open-label, phase 1 study; arm B of this study is being conducted in two parts:
  - In part 1 (dose finding), patients will receive LDC followed by arlo-cel by intravenous infusion on day 1 at a dose of either 75 × 10^6 cells (dose level [DL] 1) or 150 × 10^6 cells (DL 2); starting as early as day 60 after arlo-cel infusion, patients will then receive 0.6 mg oral MEZI administered once daily on days 1-21 of 28-day cycles
    - Patients will be observed for dose-limiting toxicities (DLTs) during the DLT evaluation period, which begins on the first day the patient is exposed to the assigned combination therapy and ends 28 days later
    - Patients will continue to receive arlo-cel plus MEZI in 28-day cycles until progressive disease (PD), unacceptable toxicity (defined as adverse events [AEs] that require discontinuation of combination therapy), or withdrawal of consent
    - Dose escalation and de-escalation decisions will be guided by the Bayesian optimal interval (BOIN) design
    - Upon completion of part 1, preliminary estimation of the RP2D will be performed using a BOIN algorithm based on the incidence rate of DLTs across all doses and the cumulative safety, efficacy, and pharmacokinetic (PK) and pharmacodynamic data
  - In part 2 (dose expansion), the safety and efficacy of arlo-cel plus MEZI at the selected RP2D will be further evaluated
    - Initially, 10 patients who received ≥ 3 prior anti-myeloma treatment regimens will be evaluated
    - Following review of the initial 10 patients, ~20 patients with 1-3 prior anti-myeloma treatment regimens will be accrued
  - All patients will complete a follow-up period after the end of the treatment period, and all patients who discontinue treatment for reasons other than PD, initiation of new anti-myeloma therapy, or withdrawal of consent will be assessed for myeloma response approximately every 3 months until PD, death, initiation of new anti-cancer therapies, or 24 months after arlo-cel therapy, whichever occurs first
  - All patients will undergo LTFU for lentiviral vector safety, long-term toxicity, disease status, anti-myeloma treatment, and survival until the end of combination therapy dosing or 24 months after arlo-cel infusion, whichever is longer, with patients then rolling over to a separate LTFU study for up to 15 years after arlo-cel infusion
- Eligible patients are ≥ 18 years of age with RRMM; key eligibility criteria are shown in **Table 1**
- Primary and secondary objectives and endpoints of the study are shown in **Table 2**
- Enrollment began in February 2024 and is ongoing

Table 1. Key eligibility criteria

Inclusion criteria	Exclusion criteria
• ≥ 18 years of age • Diagnosis of RRMM • Patients in part 1 and the first 10 patients in part 2: ≥ 3 prior anti-myeloma treatment regimens (including an IMiD® agent, PI, anti-CD38 mAb, and if eligible, ASCT) • Part 2: all additional patients must have received between 1 and 3 prior anti-myeloma treatment regimens (including an IMiD agent and PI) • ECOG PS score ≤ 1 • Measurable disease by local laboratory	• Central nervous system involvement of MM • Active or history of plasma cell leukemia, Waldenström macroglobulinemia, POEMS syndrome, or clinically significant amyloidosis • History of another primary malignancy, unless the patient has been in remission for over 2 years; exceptions include select non-invasive malignancies (ie, basal or squamous carcinoma of the skin) • Prior treatment with MEZI • Concurrent administration of PPIs, including within 14 days prior to initiating MEZI • Concurrent administration of strong CYP3A modulators within 14 days of initiating MEZI

ASCT, autologous stem cell transplant; CYP, cytochrome P450; ECOG PS, Eastern Cooperative Oncology Group performance status; IMiD, immunomodulatory drug; mAb, monoclonal antibody; PI, proteasome inhibitor; POEMS, polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, skin changes; PPI, proton-pump inhibitors.

Table 2. Study endpoints

Primary	
Objective	**Endpoints**
• To determine the safety and tolerability of arlo-cel in combination with MEZI	• Type, frequency, and severity of AEs, SAEs, AESI, and AEs leading to discontinuation and death
• To define the RP2D of MEZI in combination with arlo-cel	• Establish RP2D
Secondary	
Objective	**Endpoints**
• To evaluate the preliminary efficacy of arlo-cel in combination with MEZI	• ORR (≥ PR), CR (proportion of patients with sCR or CR), ≥ VGPR (proportion of patients achieving sCR, CR, or VGPR)
• To evaluate PK (cellular kinetics) of arlo-cel in combination with MEZI	• Estimated C_{max}, t_{max}, $AUC_{(0\text{-}28d)}$, and other relevant PK parameters of arlo-cel CAR T cells in the peripheral blood
Exploratory	
Objective	**Endpoints**
• To evaluate depth of response	• MRD
• To measure myeloma antigen expression	• BCMA and GPRC5D expression on plasma cells

AESI, AE of special interest; $AUC_{(0\text{-}28d)}$, area under the plasma concentration-time curve from time 0 to 28 days; BCMA, B-cell maturation antigen; C_{max}, maximum observed concentration; MRD, minimal residual disease; SAE, serious AE; sCR, stringent CR; t_{max}, time of maximum observed concentration; VGPR, very good partial response.

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