A Phase 1 First-In-Human Study of the Anti-CD38 Dimeric Fusion Protein TAK-169 for the Treatment of Patients with Relapsed or Refractory Multiple Myeloma who are Proteasome Inhibitor- and Immunomodulatory Drug-Refractory, Including Patients Relapsed/Refractory or Naïve to Daratumumab

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Background

- The range of therapeutic options for multiple myeloma (MM) has expanded greatly over the past 10 years.
- The transmembrane glycoprotein CD38 is highly expressed on MM cells; hence, CD38-targeting agents are of great interest and have demonstrated substantial efficacy in multiple treatment settings as a therapeutic approach in MM.[1, 2]
- Regimens incorporating the anti-CD38 monoclonal antibody daratumumab are emerging as new pillars of treatment for patients with relapsed/refractory MM (RRMM).[3]
  - Daratumumab-based therapy has demonstrated significantly improved efficacy outcomes in patients with RRMM.[4, 5]
- However, despite the increased availability of improved therapeutic options, MM remains generally incurable and typically follows a multiple relapsing course.
  - Thus, there remains a need for additional novel therapeutic approaches, particularly for patients who have relapsed following or are refractory to daratumumab-based therapy, when CD38 expression may be reduced.

TAK-169

- TAK-169 is a dimeric fusion protein of an anti-CD38 antibody single chain variable fragment fused to a modified Shiga-like toxin-A subunit (**Figure 1**).[6]
  - TAK-169 targets CD38 on myeloma cells and directly kills cells via enzymatic irreversible ribosomal destruction.
- TAK-169 has demonstrated potent, specific activity and direct cytotoxic activity to tumor cell lines, xenograft models, and MM patient samples (**Figure 2**).[6]

Figure 1. TAK-169 structure and mechanism of action

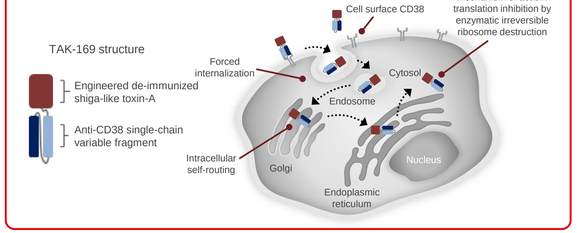
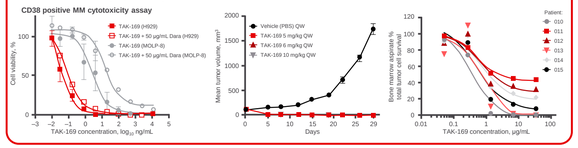


Figure 2. TAK-169 anti-myeloma activity[6]

In Vitro	In Vivo	Ex Vivo
• Cytotoxic activity demonstrated in MM cell lines with different expression levels of CD38 (e.g. H929 and MOLP-8). • Activity retained in the presence of daratumumab with modest shifts in EC_{50} at high daratumumab concentrations (10,000 nM).	• Activity across a broad range of MM mouse xenograft tumor models with a wide CD38 expression range when administered IV QW or Q2W. • Complete tumor regression in H929 human MM xenograft model with TAK-169 treatment.	• Cytotoxic activity demonstrated in bone marrow aspirates of MM patients. • Activity observed across a broad range of CD38 expression levels.



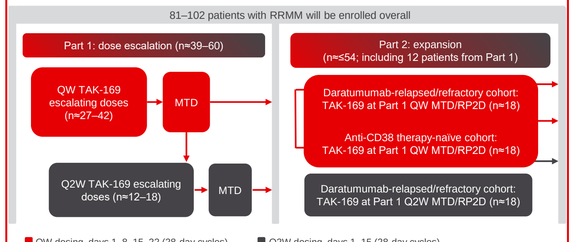
Rationale

- In contrast to daratumumab, TAK-169 might be an effective therapy in patients with RRMM, even in the daratumumab-resistant setting, given its efficacy in a broad range of CD38 expressing cells, recognition of a different CD38 epitope to daratumumab, and direct tumor cell killing activity, independent of patient's immune function status.
- Accordingly, this ongoing, first-in-human, phase 1, open-label, dose-escalation, multicenter study has been designed to evaluate the safety, tolerability, preliminary efficacy, PK, and PD of TAK-169 in patients with RRMM, including in daratumumab-resistant patients.

Study design

- This phase 1, multicenter study (NCT04017130) comprises dose-escalation (Part 1) and expansion (Part 2) (**Figure 3**).
  - In both parts, patients will be treated until progressive disease, unacceptable toxicity, or withdrawal.

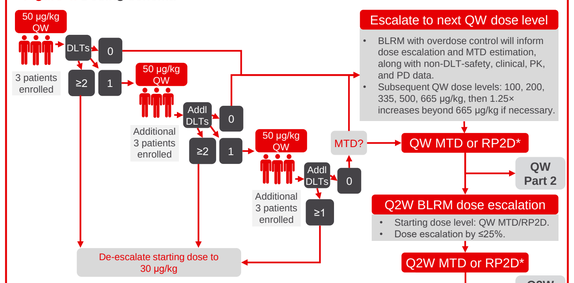
Figure 3. NCT04017130 study design



Part 1: dose escalation

- Dose escalation will start at 50 µg/kg TAK-169 QW and then proceed as shown in **Figure 4**, according to the number of DLTs observed in cycle 1 of therapy. DLTs definitions are provided in **Table 1**.
- Following evaluation of the 50 µg/kg dose, subsequent dose escalation and MTD determination will be informed by Bayesian Logistical Regression Model (BLRM) with overdose control, along with consideration of other available non-DLT-safety, clinical, PK, and PD data.

Figure 4. Dosing schema



*A recommended dose below the MTD may be identified for assessment in Part 2 on the basis of review of available safety, efficacy, PK, and PD data from Part 1 of the study.

Table 1. Definition of DLTs

Hematologic DLTs	Nonhematologic DLTs
• Any grade ≥4 hematologic TEAEs occurring during cycle 1, with the following exceptions: – Hematologic AEs clearly due to extraneous causes – Grade 4 lymphopenia – Grade 4 neutropenia (ANC <500 cells/mm^3) lasting <7 consecutive days. • Febrile neutropenia of any grade and duration. • Grade ≥3 thrombocytopenia with clinically meaningful bleeding. • Grade 4 thrombocytopenia of any duration. • Grade ≥3 capillary leak syndrome. • Grade ≥3 hemolysis clearly unrelated to the underlying disease (e.g. negative direct Coombs test).	• Any grade ≥3 nonhematologic TEAEs occurring during cycle 1, with the following exceptions: – Nonhematologic AEs clearly due to extraneous causes – Asymptomatic laboratory changes (other than renal and hepatic laboratory values and grade 4 lipase/amylase levels) successfully reversible (grade 4 → grade ≤2; grade 3 → grade ≤1 or baseline) within 72 hours – Grade 3 nausea/vomiting manageable with antiemetics – Grade 3 fatigue lasting <72 hours – Grade 3 elevation of ALT or AST that resolves to grade ≤1 or baseline within 7 days – Grade 3 infusion-related reaction that responds to symptomatic treatment (e.g. antihistamines, NSAIDs, narcotics, IV fluids), without recurrence of grade 3 symptoms.

Part 2: expansion

- Following investigator and sponsor review of the observed safety, PK, PD, and efficacy data from Part 1 of the study, Part 2 (the expansion portion of the study) may be opened.
  - The TAK-169 dose for the QW daratumumab-relapsed/refractory and anti-CD38 therapy-naïve expansion cohorts will be the MTD/RP2D of QW administration determined in Part 1.
  - The TAK-169 dose for the Q2W daratumumab-relapsed/refractory expansion cohort will be the MTD/RP2D of Q2W administration determined in Part 1.
  - A recommended dose below the MTD may be identified for assessment in Part 2 on the basis of review of available safety, efficacy, PK, and PD data from Part 1 of the study.
- In the absence of DLT, the dose that will be administered in Part 2 will be based upon a comprehensive review of available data from Part 1 of the study.

Patient eligibility criteria

Key inclusion criteria	Key exclusion criteria
• Aged ≥18 years. • Confirmed diagnosis of MM, with measurable disease: – Serum M-protein ≥500 mg/dL on SPEP – Urine M-protein ≥200 mg/24 hours on UPEP – Abnormal serum FLC ratio and FLC level ≥10 mg/dL. • Failed/intolerant/not candidates for available treatments for RRMM. • Prior therapy: – Refractory to ≥1 PI and ≥1 IMiD and (Part 1 only) to ≥1 steroid – Received ≥3 prior lines of therapy or ≥2 prior lines of therapy if 1 of those lines included a combination of PI and IMiD – Prior treatment with an anti-CD38 therapy (including daratumumab*) permitted, except in the anti-CD38 therapy naive expansion cohort in Part 2. • ECOG PS 0 or 1. • Adequate hematologic, renal, and hepatic function. **Part 2 only:** • Relapsed/refractory to daratumumab* OR • No prior treatment with daratumumab or any other anti-CD38 therapy.	• Clinical signs of CNS involvement of MM. • History of documented significant pleural or pericardial effusions. • History of hypersensitivity or serious toxic reactions to kanamycin or other aminoglycosides. • Prior allogeneic SCT or organ transplant. • Use of systemic corticosteroids at a dose of >10 mg/day of prednisone or equivalent. • Grade ≥3 sensory or motor neuropathy. • Not recovered (grade ≤1 or baseline) from adverse reactions to prior myeloma treatment (excluding alopecia). • Received a final dose of any of the following treatments/procedures before the first dose of TAK-169: – Myeloma-specific therapy, including PIs and IMiDs within 14 days – Anti-CD38 therapy within 90 days – Corticosteroid therapy for myeloma within 7 days – Radiation therapy for localized bone lesions within 14 days – Major surgery within 30 days – Autologous SCT within 90 days – Investigational therapy within 30 days. • POEMS, solitary plasmacytoma, amyloidosis, Waldenström macroglobulinemia, monoclonal gammopathy of unknown significance, smoldering myeloma or IgM myeloma.

*90 day washout period required for patients previously treated with daratumumab.

Study outcomes

PRIMARY OBJECTIVES

Part 1
- To evaluate the safety and tolerability of TAK-169 monotherapy in patients with RRMM, and establish the MTD/RP2D.

Part 2
- To provide a preliminary evaluation of the clinical activity of TAK-169 monotherapy in patients with RRMM.

SECONDARY OBJECTIVES

Part 1
- To characterize the PK of TAK-169.
- To conduct a preliminary evaluation of the anti-tumor activity of TAK-169 monotherapy in patients with RRMM.
- To assess the immunogenicity of TAK-169 by evaluating the immunogenicity status (ADA incidence) in patient serum.

Part 2
- To further evaluate safety at the MTD/RP2D.
- To further evaluate the clinical efficacy (DOR and time to event), PK, and immunogenicity of TAK-169.

EXPLORATORY OBJECTIVES

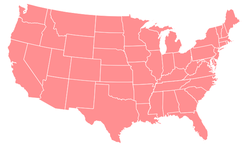
Overall
- To characterize the PD profile of TAK-169 in blood and bone marrow.
- To determine the impact of TAK-169 on depth of response by assessing frequency of MRD negativity in blood and marrow at CR, and monitoring changes in circulating cell free DNA during treatment and at relapse.
- To evaluate ORR and PFS in patients with high-risk cytogenetics (del17, t(4;14), t(14;16), and/or amp1q).
- To evaluate the impact of patient baseline immune system and microbiome makeup on TAK-169 efficacy and safety.
- To explore the impact of TAK-169 on the immune system (including cytokines and chemokines) during treatment and at relapse and correlation with efficacy and safety.
- To evaluate the relationship of baseline molecular characteristics of the tumor (such as protein and mRNA expression) with the efficacy and safety of TAK-169.

Assessments

- Patients will be assessed for disease response according to the IMWG response criteria for MM.[7]
- Response assessments will occur every cycle until progressive disease, unacceptable toxicity, withdrawal of consent, death, or termination of the study by the sponsor.
  - Serum and urine response assessments will be performed no later than the first day of every treatment cycle.
  - One bone marrow assessment has to occur to document CR.
- Patients who discontinue due to progressive disease will have a follow-up every 12 weeks and patients who discontinue for other reasons will continue PFS follow-up every 4 weeks.
- Toxicity will be evaluated through 30 days after last dose of the study drug and AEs will be graded according to the NCI CTCAE (version 5.0).

Current study status

- Study start date: October 28, 2019
- Planned enrollment locations: United States



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Abbreviations

ADA, anti-drug antibody; AE, adverse event; ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; CD38, cluster of differentiation 38; CNS, central nervous system; CR, complete response; DLT, dose-limiting toxicity; DOR, duration of response; EC_{50}, half maximal effective concentration; ECOG PS, Eastern Cooperative Oncology Group performance status; FLC, free light chain; IgM, immunoglobulin M; IMiD, immunomodulatory imide drug; IMWG, International Myeloma Working Group; IV, intravenous; MRD, minimal residual disease; MTD, maximum tolerated dose; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; NSAIDs, non-steroidal anti-inflammatory drugs; ORR, overall response rate; PBS, phosphate-buffered saline; PD, pharmacodynamic(s); PFS, progression-free survival; PI, proteasome inhibitor; PK, pharmacokinetic(s); POEMS, polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin; QW, once weekly; Q2W, once every 2 weeks; RP2D, recommended phase 2 dose; SCT, stem cell transplant; SPEP, serum protein electrophoresis; TEAEs, treatment-emergent adverse events; UPEP, urine protein electrophoresis.

Disclosures

The study is sponsored by Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited.

SKK: provides consultancy for and receives research funding from Abbvie, Celgene and Janssen, and receives research funding from Takeda. **RFC:** provides consultancy for Takeda and KaryoPharm. **OL:** has membership on the Board of Directors or advisory committees for Adaptive, Abbvie, Sanofi, Karyopharm, Amgen, Celgene, Janssen, and Takeda, reports honoraria from Amgen, Celgene, Janssen and Takeda, and IDMC membership for Merck and Theradex. **SA:** provides consultancy for Celgene, Amgen, Janssen, Takeda; receives research funding from Amgen, Pharmacyclics, Cellectar, Janssen. **JPH**, **RW:** employment with and owns equity in Molecular Templates, Inc. **EKW:** employment with Molecular Templates, Inc. **JL**, **YZ**, **ARL**, **ABD**, **MH**, **DM**, **ML**, **SO**, **RJL**, **JN**, **AV:** employment with Millennium Pharmaceuticals, Inc., Cambridge, MA, USA, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited.

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