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A Phase 1, Open-Label, Dose-Escalation and Expansion, Multicenter Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of MT-0169 (TAK-169) in Patients with Relapsed or Refractory Multiple Myeloma and Non-Hodgkin Lymphoma

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Background

- Engineered toxin bodies (ETBs) are comprised of a proprietarily engineered form of de-immunized Shiga-like Toxin-I A1 subunit genetically fused to antibody-like binding domains[1].
- MT-0169 (formerly TAK-169) is a CD38-targeting next generation ETB with improved potency and reduced immunogenicity over MT-3724, a first-generation ETB targeting CD20[2], for hematological tumors (**Figure 1**).

Mechanism of Action of MT-0169

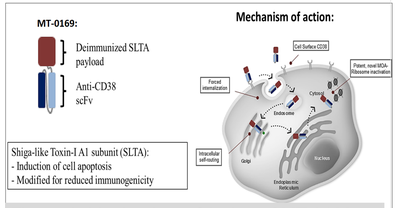

Figure 1: Mechanism of Action of MT-0169

MOA: mechanism of action, scFv: single-chain fragment variable.

- ETBs work through novel mechanisms of action and force internalization, self-routing through intracellular compartments to the cytosol, and inducing potent cell-kill via the enzymatic and permanent inactivation of ribosomes.
- This novel mechanism of action provides potential activity of MT-0169 in patients who are refractory to antibodies or other therapies.
- The cytotoxic activity of MT-0169 was found to be restricted to CD38+ cells, including multiple myeloma (MM), non-Hodgkin Lymphoma (NHL), and Natural Killer (NK) cells. MT-0169 was not found to be cytotoxic against T cells or B cells[3]

Activity of MT-0169 in Multiple Myeloma

- *In vitro*, MT-0169 retained potency against MM cells in the presence of daratumumab[4] **(Figure 2)**
  - H929 and Molp-8 cell viability is reduced to 0.04% and 0.4% with treatment of MT-0169, respectively.
  - When cells are pretreated with excess daratumumab, 90% or greater cytotoxic effect was retained for MT-0169.
  - Concurrent cell treatment resulted in a similar result, with MT-0169 retaining more than 80% efficacy when dosed with daratumumab, compared to MT-0169 treatment alone.
  - Daratumumab has minimal direct cell kill activity since the mechanism of action is mostly immune-mediated. In this experiment, there are no additional immune cells to elicit ADCC or ADCP and no human serum as a source of complement to elicit CDC
- The CD38 epitope recognized by MT-0169 is near but distinct from that of daratumumab[4], allowing for MT-0169 binding in the presence of daratumumab.
- Up-regulation of complement inhibitory proteins such as CD59 may lead to daratumumab resistance[5] . This may have contributed to the recent failure of daratumumab in a phase 2 trial of various subtypes of NHL[6] where high levels of CD59 were detected in a majority of patients at baseline.
- As with MT-3724, MT-0169 may not be subject to resistance mechanisms such as CD59 upregulation that exist for monoclonal antibodies in hematological malignancies

Figure 2: The Action of MT-0169 *In Vitro*

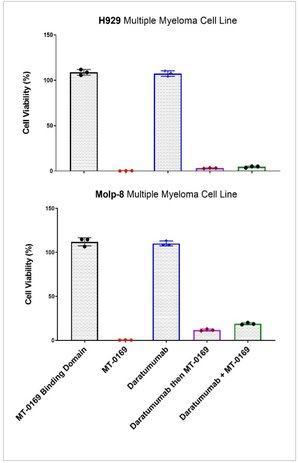

Figure 2: the effect on MM cell viability (CellTiter Glo Promega) after a 3-day treatment with 0.5 µg/mL MT-0169, either alone, after, or concurrent with treatment with excess daratumumab (200 µg/mL).

ADCC: Antibody dependent cellular cytotoxicity;
ADCP: Antibody dependent cellular;
CDC: Complement dependent cytotoxicity

Activity of MT-0169 in non-Hodgkin Lymphoma

- MT-0169 has shown greater *in vitro* potency than MT-3724 on various NHL cell lines, including Mino, REC-1, and Raji (**Figure 3**)
- MT-3724 showed clinical activity at exposures below the pre-clinical IC_{50} (<1 nM)[7] at doses as low as 5 µg/kg in heavily pre-treated patients with relapsed or refractory non-Hodgkin Lymphoma (RR NHL)

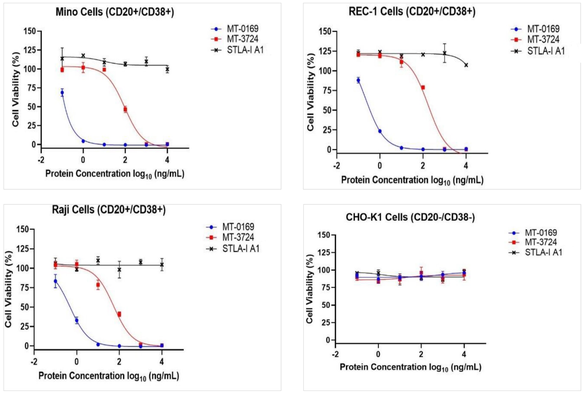

Figure 3: Evaluation of MT-0169, MT-3724, and SLTA-I A1 Cytotoxicity on non-Hodgkin Lymphoma (Mino, REC-1, Raji) and Control(CHO-K1) Cell Lines.

MT-0169 was >100-fold more potent than MT-3724 on Raji BL cells, and >750-fold more potent on REC-1 and Mino MCL cell-lines

Trial Objectives and Design

- Primary objectives:
  - Part 1: to evaluate the safety and tolerability of MT-0169 monotherapy in patients with RRMM, and establish the maximum tolerated dose/recommended phase 2 dose (MTD/RP2D)
  - Part 2: to provide a preliminary evaluation of the clinical activity of MT-0169 monotherapy in patients with RR MM and RR NHL

Trial Design

- Open-label, Dose-escalation and Expansion, multicenter study (Clinicaltrials.gov identifier: NCT04017130) (**Figure 4**)
- Dose escalation will be done for once weekly and, if found necessary, for once every 2 weeks dosing cohorts
- If initiated, the RRMM expansion cohorts (Part 2) will be treated with MTD and will evaluate daratumumab-relapsed or refractory cohorts (QW or Q2W) and an anti-CD38 therapy-naïve cohort (QW)
- Before QW or Q2W MTD/RP2D in Part 1, up to 6 patients with CD38+ NHL may be treated as part of dose-expansion (Part 2) with each doses deemed sufficiently tolerable from Part 1
- After MTD/RP2D (QW or Q2W) is available from Part 1, up to 18 additional RR NHL patients may be treated at the MTD/RP2D
- A modified toxicity probability interval (mTPI-2) with overdose control will be used to guide the dose escalation decisions and MTD estimation
- Prior treatment with an anti-CD38 therapy (including daratumumab) is permitted except for patients enrolled in the anti-CD38-therapy naïve expansion cohort

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- Dose escalation phase (Part 1): RRMM patients ≥18 years old, refractory to at least 1 PI, 1 IMiD, and 1 steroid will be enrolled
- Dose expansion phase (Part 2), RRMM and RR NHL patients ≥18 years old will be enrolled, including:
  - RRMM patients refractory or intolerant to ≥ 1 PI and ≥ 1 IMiD, and have received ≥3 prior lines of therapy or ≥2 prior lines of therapy if 1 of those lines included a combination of PI and IMiD
  - RR NHL patients with CD38 expression whose disease has progressed, are intolerant to, or are not a candidate for available therapies

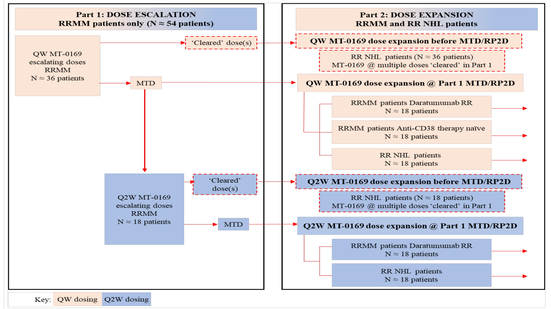

Figure 4: Study Design of MT-0169-001

IMiD: immunomodulatory drug, NHL: Non-Hodgkin lymphoma, MTD: maximum tolerated dose, PI: proteasome inhibitor, QW: once weekly, Q2W: once every two weeks, RP2D: recommended phase 2 dose, RR: relapsed or refractory, RRMM: relapsed or refractory multiple myeloma.

- MT-0169 will be administered by IV infusion once weekly (QW) on Days 1, 8, 15, and 22 of each 28-day cycle
- Dose escalation will start with 50 µg/kg, which is predicted to result in a C_{max} range of 2.92-4.78 nM in comparison to the predicted similar C_{max} *in vitro* MM cell killing data obtained from patient bone marrow aspirate assays, which resulted in an EC_{50} of 5nM.
- Subsequent planned MT-0169 dose levels are 100, 200, 335, 500, 665 µg/kg, and if necessary, 25% increases beyond 665 µg/kg
- Patients will continue treatment with MT-0169 until they experience progressive disease, unacceptable toxicity, or withdraw for other reasons.

Study Status

- Recruiting at three US sites; additional US sites are expected to open in Q4 2021.
- Dose escalation is ongoing

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