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Interim results of a phase 1 study of the novel engineered toxin body (MT-0169) TAK-169 in patients with relapsed or refractory multiple myeloma

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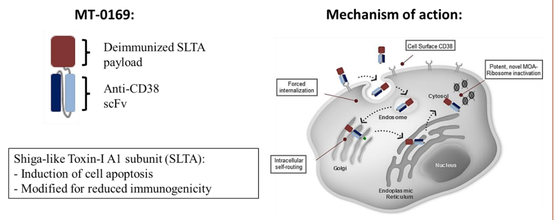
Background

- Engineered toxin bodies (ETBs) are composed of a proprietarily engineered and de-immunized Shiga-like Toxin-I A1 (SLTA) subunit genetically fused to an antibody-like binding domain
- ETBs can force receptor internalization, induce potent cell-kill via enzymatic and permanent inactivation of ribosomes, and may not be subject to resistance mechanisms of other therapeutics (**Figure 1**)

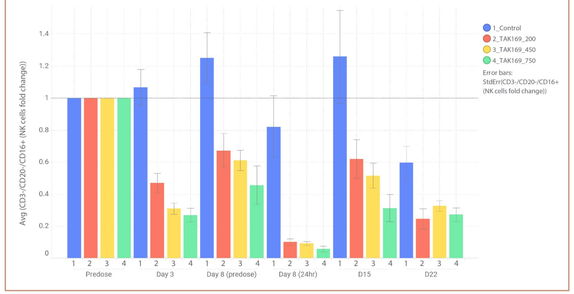
Figure 1. Mechanism of Action of MT-0169



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

- MT-0169 (formerly TAK-169) is a second-generation ETB targeting CD38 in hematologic malignancies including multiple myeloma (MM) and non-Hodgkin lymphoma (NHL)
- In a preclinical study, the cytotoxic activity of MT-0169 was found to be dependent on CD38 expression and preferential to MM and NHL cells; MT-0169 was found to be less cytotoxic against T cells, B cells, natural killer (NK) cells, and monocytes[1]
- In a non-human primate study, the largest reduction in D3-/CD20-/CD16+ NK-cells occurred on Day 8 24-hour post-dose (**Figure 2**)

Figure 2. D3-/CD20-/CD16+ NK Cell Measurements Over Time

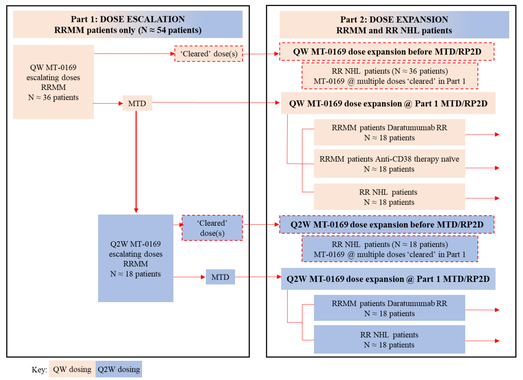


- One of the proposed mechanisms of daratumumab resistance is up-regulation of complement inhibitory proteins such as CD59;[2] since cell-killing effect of daratumumab is immune-mediated (specially complement dependent cytotoxicity - CDC), high levels of CD59 are believed to reduce the efficacy of daratumumab; this may have contributed to the recent failure of daratumumab in a phase 2 trial of various subtypes of NHL[3]
- By contrast, the mechanism of action of MT-0169 is targeted direct cell kill mediated by the SLTA; this means it is expected to work irrespective of the level of complement inhibitory proteins such as CD59

Methods

- This multicenter, open-label, phase 1a/b study is designed to evaluate the safety, tolerability, preliminary efficacy, pharmacokinetics, and pharmacodynamics of MT-0169 monotherapy in patients with relapsed or refractory MM (RRMM) or relapsed or refractory non-Hodgkin lymphoma (RR NHL) (NCT04017130)
- The study will consist of a dose escalation phase and an expansion phase (**Figure 3**)

Figure 3. Study Design



MTD, maximum tolerated dose; QW, once weekly; NHL, non-Hodgkin lymphoma; Q2W, once every 2 weeks; RP2D, recommended phase 2 dose; RR, relapsed or refractory; RRMM, relapsed or refractory multiple myeloma.

- The primary objective of the escalation phase (Part 1) is to evaluate the safety and tolerability of MT-0169 in patients with RRMM and establish the maximum tolerated dose/recommended phase 2 dose (MTD/RP2D)
- The primary objective of the expansion phase (Part 2) is to provide a preliminary evaluation of the clinical activity of MT-0169 monotherapy in patients with RRMM and RR NHL
- The starting dose of MT-0169 in Part 1 is 50 µg/kg IV once weekly (QW); subsequent planned dose levels are 100, 200, 335, 500, and 665 µg/kg and if necessary 1.25 × increases beyond 665 µg/kg; dose escalation will be guided by the modified toxicity probability interval (mTPI-2) method with over dose control
- Following determination of the QW MTD/RP2D, a second dose escalation cohort evaluating once every 2 weeks (Q2W) dosing of MT-0169 may be initiated; the planned starting dose level for Q2W administration will be the MTD/RP2D established for QW dosing with subsequent dose escalation by no more than 25% over the previously tolerated dose level
- Before QW or Q2W MTD/RP2D in Part 1, up to 6 patients with protocol specified subtypes of RR NHL may be treated as part of dose-expansion (Part 2) with the "cleared doses" (ie, a dose that is deemed sufficiently tolerable from Part 1)
- After each higher dose is cleared in patients with RRMM in Part 1 and previously lower doses are tolerated in RR NHL patients, an additional maximum 6 RR NHL patients will be treated with the higher dose
- 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
  - Previously, a CD20-targeting ETB, MT-3724, showed clinical activity at doses as low as 5 µg/kg in patients with RR NHL[4]
  - In addition, MT-0169 has shown greater *in vitro* potency than MT-3724 on various NHL cell lines, including Mino, REC-1, and Raji
  - Hence, provided that eligible patients are available, the planned starting dose of MT-0169 for the RR NHL patient cohort in this study will be 50 µg/kg

Results

- At the data cut-off in June 2021, 4 MM patients with a median age of 70 years were enrolled at the initial MT-0169 dose level of 50 µg/kg
- All 4 patients were heavily pretreated with at least 5 previous lines of therapy
- The median duration on study treatment was 4 weeks (range 2 to 8 weeks)
- All patients have discontinued the study, 3 due to progressive disease and 1 due to a treatment-emergent adverse event (TEAE)
- The TEAE leading to discontinuation was asymptomatic grade 2 reversible myocarditis diagnosed by cardiac magnetic resonance imaging (MRI) and grade 3 hs-troponin elevation in the absence of clinical ischemia, ECG, or echocardiographic abnormalities; comparative baselines were not available for either the cardiac MRI or hs-troponin levels
- No other cardiac TEAEs have been observed with any other patient
- All other related TEAEs were either grade 1 or 2 events

Pharmacokinetics

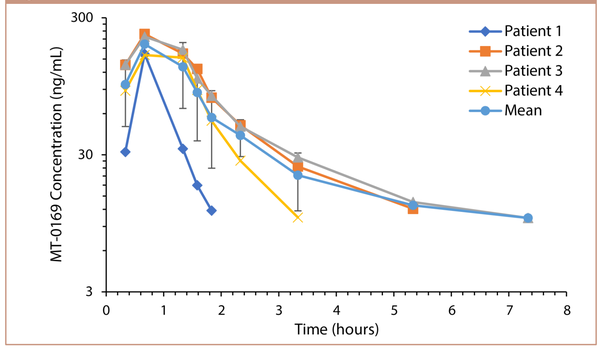
- All patients had quantifiable drug concentrations on Cycle 1 Day 1 (lower limit of quantification=10 ng/mL)
- The geometric mean elimination half-life was calculated as approximately 1 hour (**Table 1; Figure 4**)
- The geometric mean of C_{max} in the 4 patients was 1.73 nM (190 ng/mL)
  - Previously, an EC_{50} of 0.035 nM (median maximal lysis: 89%; range 45%-100%) was observed in a flow cytometry-based cell-lysis study of primary MM cells (purified mononuclear cells) derived from bone marrow samples of patients with newly diagnosed and RRMM (including daratumumab refractory); the cytotoxic activity of MT-0169 was mainly restricted to MM cells - except for limited lysis of NK cells (median maximal lysis: 18%) and monocytes (median maximal lysis: 21%), no other non-malignant hematopoietic cells were lysed[1]
  - EC_{50} of 5 nM was observed in MM cell-killing assays using patient bone marrow aspirates

Table 1. Pharmacokinetic Data Summary of MT-0169

	C_{max} (ng/mL)	AUC_{inf} (h*ng/mL)	$t_{1/2}$ (h)
N	4	4	4
Geomean	190	278	0.956
%CV	19%	47%	85%
Min, Max	160, 228	132, 455	0.311, 2.84

AUC, area under curve; C_{max}, concentration maximum; CV, coefficient of variation; geomean, geometric mean; $t_{1/2}$, half-life.

Figure 4. MT-0169 Concentration Over Time



Results (cont.)

Pharmacodynamics

- Number of NK cells in peripheral blood for the 4 patients was reduced by a maximum of 56%, 85%, 88%, and 92% after the first dose (**Figure 5**)
- The patient with 56% reduction in NK cells had the lowest NK cell count at baseline, along with a low percentage of CD38+ NK cells and had been treated with daratumumab in 3 regimens of prior therapy

Figure 5. NK Cells Percentage Change vs. Time

Red arrows represent when MT-0169 dosing occurred relative to measurements of CD56+CD16+ NK-cells. Except for the post-dose measurements of NK cells after C1D1 all other measurements were done pre-dose on the corresponding day.
C1D1, Cycle 1, Day 1; NK, natural killer.

Conclusions/Implications

- These data demonstrate that, at 50 mcg/kg, MT-0169 was engaging its target CD38, leading to robust NK-cell reductions
- A substantial pharmacodynamic effect, larger than what was observed in preclinical studies,[1] was demonstrated at this early stage of dosing; further data are needed to assess preliminary efficacy of MT-0169
- To date with MT-0169 there has been no evidence of capillary leak syndrome, an adverse event associated with first-generation ETB, MT-3724
- Additional tests, including baseline, pre-dose and post-dose high-sensitivity cardiac troponin T, and baseline cardiac MRI, were added to the protocol to extend cardiac safety monitoring
- Dose escalation is ongoing
- Due to the unique mechanism of action, MT-0169 has the potential to be used after other CD38 targeting agents

References

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