#EP1220

Monotherapy Activity with the First CD20-Targeted Immunotoxin, MT-3724, in Subjects with Relapsed/Refractory (R/R) Diffuse Large B-Cell Lymphoma (DLBCL)

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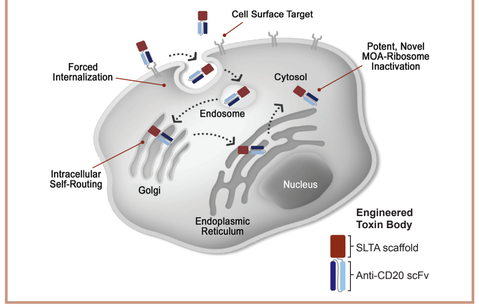
Background

- The near ubiquity and persistence of CD20 expression in B-cell malignancies provides a strong rationale for novel CD20-directed therapies[1]
- Engineered toxin bodies (ETBs) are a distinct class of targeted immunotoxins in development by Molecular Templates as anti-cancer therapeutics. ETBs have a novel mechanism of action that drives a potent and targeted response mediated by antibody-like binding, cellular internalization, and enzymatic ribosomal inhibition via the delivery of a Shiga-like toxin subunit A (SLTA) (**Figure 1**).[2] MT-3724 is comprised of an anti-CD20 single chain variable fragment genetically fused to SLTA with an approximate molecular weight of 110 kDa for the homodimer, and is being developed for the treatment of r/r DLBCL.

Figure 1. Internalization of MT-3724 and Ribosome Inactivation of Target Cell



MOA, mechanism of action; scFv, single-chain variable fragment; SLTA, Shiga-like toxin A.

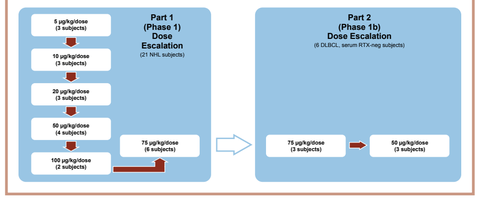
Objective

- Present safety and efficacy results from dose escalation to maximum tolerated dose (MTD) in B-cell non-Hodgkin lymphoma (NHL) subjects and dose expansion in DLBCL subjects

Methods

- This is a multi-center, open-label, multiple-dose, dose-escalation and dose-expansion study of MT-3724 (NCT02361346)
- The phase 1/1b portion of the study consists of Parts 1 and 2 (**Figure 2**):
  - Part 1: The MT-3724 dose was escalated in 21 subjects with B-cell NHL according to a 3+3 design based on ≤1 subject exhibiting dose-limiting toxicity (DLT) during Cycle 1 (28 days for first cycle, 21 days for subsequent cycles) in 6 sequential-dose cohorts (5, 10, 20, 50, 100, and 75 µg/kg/dose IV 3 times per week for the first two weeks of each cycle) for up to 5 cycles
  - Part 2: Safety and efficacy of MT-3724 were further evaluated in 6 serum rituximab-negative (RTX-neg) subjects with DLBCL; tumor response was assessed by the International Working Group Response Criteria for Clinical Trials[3]
    - For Parts 1 and 2: Retreatment under a separate extension protocol was considered for subjects who exhibited partial response (PR) or stable disease (SD) after completing 5 cycles (or 2 cycles after a complete response [CR])
- A phase 2 study is in progress

Figure 2. Study Schema



- Key eligibility criteria include:
  - B-cell NHL/chronic lymphocytic leukemia (CLL)
    - NHL: intermediate or high risk, as determined by International Prognostic Index (IPI)/Follicular Lymphoma International Prognostic Index (FLIPI); CLL: Rai Stage III/IV
    - DLBCL only in Part 2
  - Relapse after measurable response to at least one anti-CD20 containing regimen
  - Exhausted all approved therapies
  - Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0 to 2
  - Typical hematologic and chemistry parameters for a phase 1/2 trial
  - A minimum of 12-week washout is required after last course of RTX
    - In Part 1, all subjects' serum RTX levels were assessed but this was not part of eligibility
    - Following a mixed response in only 1 of 7 subjects with measurable serum RTX levels who were evaluable for response, Part 2 eligibility was amended to require a serum RTX-neg assessment at study entry

Results

- Twenty-seven subjects with B-cell NHL were enrolled; baseline characteristics are shown in **Table 1**
  - 21 in Part 1 (dose escalation) – completed
  - 6 in Part 2 (expansion cohort) – completed
- Median duration of treatment was 39 (5-362) days

Table 1. Baseline Characteristics

Characteristic	N=27
Sex	
F	17
M	10
Age (mean, range; years)	65 (34 – 78)
Body weight (mean, range; kg)	81 (51 – 154)
BMI (median, range; kg/m²)	29.1 (19 – 44.6)
ECOG performance status	
0	10
1	13
2	4
NHL type[a]	
DLBCL	16
Mixed DLBCL/FL	4[b]
FL	5
MCL	2
Prior NHL treatments (median, range)	4 (1 – 11)
Prior anti-CD20 treatments (median, range)	2 (1 – 9)
RTX level in serum	
<500 ng/mL	19[c]
≥500 ng/mL	8

[a]Although eligible for this study, no subject with CLL was enrolled. [b]One subject transformed from DLBCL to FL following auto-stem cell transplant (SCT) prior to study entry. [c]One subject did not require testing; >365 days since last RTX.
DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; NHL, non-Hodgkin lymphoma; RTX, rituximab.

Maximum Tolerated Dose

- Expansion cohort was open for enrollment at 5 sites: US (2), Canada (1) and Eastern Europe (2)
  - MT-3724 was not tolerated at 100 µg/kg/dose (DLTs: grade 3 pneumonia, grade 2 ileus)
- The MTD was initially defined at 75 µg/kg/dose
- The first 3 subjects treated in Part 2 at 75 µg/kg in the expansion cohort exhibited medically important adverse events (AEs) related to MT-3724
  - 2 subjects (both with BMI >35) had grade 2 capillary leak syndrome (CLS); both subjects started at 75 µg/kg (total dose of 11,573 µg/infusion and 7,207 µg/infusion, respectively), with this dose reduced to 50 µg/kg after C1D2 and C1D1, respectively
  - The third subject had a serious AE (SAE) of grade 3 edema
- The MTD was reduced to 50 µg/kg/dose, with an upper limit of 6000 µg/dose
- 3 subjects have now been treated in Part 2 at 50 µg/kg/dose with the upper limit of 6000 µg/dose

Safety

- The most common treatment-emergent AEs (TEAEs) of any grade were peripheral edema, fatigue, diarrhea and myalgia (**Table 2**)

Table 2. Treatment-Emergent Adverse Events Occurring in >15% Subjects

TEAE	N=27 n (%)	TEAE	N=27 n (%)
Peripheral edema	17 (63)	Hypotension	6 (22)
Fatigue	11 (41)	Anemia	5 (19)
Diarrhea	11 (41)	Stomatitis	5 (19)
Myalgia	11 (41)	Asthenia	5 (19)
Insomnia	8 (30)	Pneumonia	5 (19)
Nausea	7 (26)	Hypoalbuminemia	5 (19)
Pyrexia	7 (26)	Hypokalemia	5 (19)
Cough	7 (26)	Dyspnea	5 (19)
Arthralgia	6 (22)	Rash	5 (19)
Headache	6 (22)		

- 27 subjects had TEAEs with related causality, the most common were: peripheral edema (44%), myalgia (30%), fatigue (26%), nausea (26%), diarrhea (22%), pyrexia (22%), headache (19%), and stomatitis (19%)
- The most common related grade ≥3 TEAEs included neutropenia (including neutrophil count decrease) and myalgia (each 3/27 [11%])
- There were 9 related SAEs among 6 subjects (**Table 3**)

Table 3. Serious Adverse Events Attributable to MT-3724

Subject	SAE	Grade	Length of Hospitalization	Outcome	Subject Disposition
100 µg/kg					
14	Ileus[a]	2	9 days	Resolved	Withdrawn AE
	Muscle weakness	3	9 days	Resolved	
15	Pneumonia[a]	3	1 day	Resolved	Withdrawn AE
75 µg/kg					
19	Peripheral Edema	2	7 days	Ongoing	Withdrawn PD
23	Edema	3	14 days	Resolved	Withdrawn PD
	Pneumonia	3	14 days	Resolved	
20	Acute Kidney Injury (AKI)	4	12 days	Ongoing	Withdrawn AE (AKI)
	Viral Syndrome	2	3 days	Resolved	
50 µg/kg					
13	Worsening Hypertension	3	1 day	Resolved	Withdrawn AE

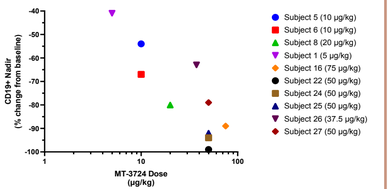
[a]Dose-limiting toxicity.

- Two of the subjects treated had prior CAR-T therapy and had no grade >1 AEs considered related to MT-3724
- One subject died on study from disease progression
- Overall, AEs expected to be related to MT-3724 due to reducing normal lymphocytes (eg, infections), or eliciting innate immune responses (eg, CLS, myalgia, arthralgia), were observed; however, no cases of grade >2 CLS were observed

Efficacy

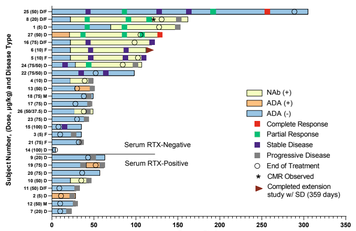
- The maximal reduction of B-cells (nadir) from 10 subjects who were serum RTX-neg at study initiation and with >10 (cells/µL) CD19+ peripheral B-cells at baseline are shown in **Figure 3**

Figure 3. Dose-Dependent Peripheral B-Cell Depletion by MT-3724 Dose (Maximal Change From Baseline)



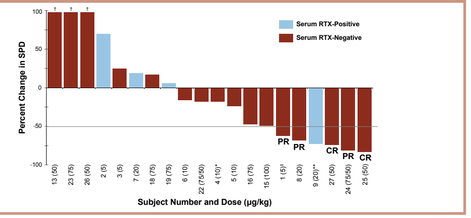
- In total, 25 subjects were evaluable for efficacy, including 19 subjects with DLBCL or mixed DLBCL/follicular lymphoma (FL); 2 subjects were not evaluable for efficacy (**Figure 4**)
- Of the 13 serum RTX-neg DLBCL or mixed DLBCL/FL subjects, 5 (38% objective response rate) responded across the range of 5 to 50 µg/kg/dose (**Figure 5**); **of subjects with RTX-neg DLBCL who received the MTD of 50 µg/kg/dose, 3 of 5 responded**
  - Of the 5 responses, 2 were CRs and 3 were PRs, including Subject 8 with composite DLBCL/FL post-autologous stem cell transplantation (post-SCT) who had a complete metabolic response of a large mesenteric mass and proceeded to allogeneic SCT
  - Among the 5 responders, 2 subjects with CR discontinued (subject decision) due to reasons unrelated to safety events, and durations of response were 169 and 90 days; 3 subjects with PR discontinued after disease progression, and durations of response were 107, 120, and 75 days
    - Of the responders, median age was 61 (50-76) yrs, and median number of prior lines of NHL therapy received was 3 (1-8)
  - Three serum RTX-neg subjects with DLBCL or mixed DLBCL/FL had SD, including two with 49% and 47% reductions in index tumor lesions (**Figure 5**)
- Of all 25 subjects evaluated for efficacy, 13 developed anti-drug antibodies (ADAs) or neutralizing antibodies (NAbs); ADAs/NAbs were observed in 4 of 5 subjects who showed a response, and in 3 of 5 subjects with SD; some subjects even had improvements in response following development of ADAs and NAbs (**Figure 4**)
- Three of the 4 subjects with detectable baseline serum RTX levels who were evaluable for response did not benefit from MT-3724; the fourth subject experienced a decrease in index lesions but an increase in non-target lesions as well as new lesions (**Figure 5**)

Figure 4. Objective Response, Development of ADAs/NAbs and Time on Study



On the y-axis, numbers in parentheses are the dose(s) (µg/kg) each subject received.
Subjects 14 and 20 did not have a response assessment; subject 14 left the study due to a dose-limiting toxicity; subject 20 left study due to an adverse event.
Subject 6 entered the extension study after a 3-month break, and the subject left the study with SD.
Subject 8 completed 1 cycle of the extension study and went on to receive allogeneic SCT post-study.
Subject 24 dose reduced from 75 to 50 µg/kg after 1 dose; subject 22 dose reduced from 75 to 50 µg/kg after 2 doses.
ADA, anti-drug antibody; CMR, complete metabolic response (best response was PR with CMR observed in the largest lesion); CR, complete response; D, diffuse large B-cell lymphoma; F, follicular lymphoma; M, mantle cell lymphoma; NAb, neutralizing antibody; PD, progressive disease; PR, partial response; RTX, rituximab; SD, stable disease.

Figure 5. Percent Change of Target Lesions



One serum RTX-positive subject (subject number 10) had incomplete evaluation of index lesions following Cycle 1 but an apparent increase of 11% in SPD and subsequently died during Cycle 2 due to progressive disease. In addition, 6 subjects did not have tumor response assessed radiographically (3 RTX-positive [subject numbers 11, 12, 20; 2 discontinued for clinical progression and one discontinued for AE, respectively] and 3 RTX-negative [subject numbers 17, 21, 14; 2 discontinued for clinical progression and one discontinued for AE, respectively]).
†Subjects 13, 23 and 26 had % change in SPD >100%, as follows: 201%, 182% and 304%, respectively.
*PD: Progression of non-target lesions.
**PD: 73% reduction in target lesions post Cycle 2 but substantial increase in non-target lesions and new lesions detected.
‡PR: Best response 62% reduction in target lesions. Progression at end of study due to progression of non-target lesions.
CR, complete response; PR, partial response; RTX, rituximab; SPD, sum of the product of the diameters.

CONCLUSIONS

- MT-3724 is the first CD20-targeted immunotoxin to enter clinical trials
- Safety events were mostly mild to moderate, and DLTs were indicative of innate immune response
- A tolerable dose schedule for phase 2 has been identified: 50 µg/kg/dose up to a maximum of 6000 µg/dose infused over 1 hour on Days 1, 3, 5, 8, 10, and 12 of a 21-day cycle
- A 38% objective response rate has been observed with monotherapy in a heavily pretreated, serum RTX-neg DLBCL or mixed DLBCL/FL population; **of the subjects with RTX-neg DLBCL who received the MTD, 3 of 5 responded**
- The development of ADAs did not preclude benefit of MT-3724, consistent with what has been seen with other immunotoxins like denileukin diftitox and tagraxofusp-erzs
- The phase 2 portion of the study is ongoing, with sites open and actively enrolling globally
- MT-3724 is also being studied in combination with lenalidomide (NCT03645395) and gemcitabine/oxaliplatin (NCT03488251)

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DISCLOSURE

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