#EP1261

Phase 2A Open-Label Study Of MT-3724, A Novel CD20-Targeting Engineered Toxin Body, in Combination with Lenalidomide in Subjects with Relapsed or Refractory B-Cell Non-Hodgkin Lymphoma

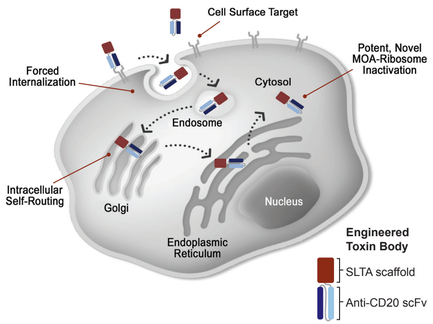
Jason Tache, DO[1]; Deborah A. Katz, MD[2]; Farrukh Awan, MD[3]; Amitabha Mazumder, MD[4]; Christine Burnett, PhD[5]; Thomas Strack, MD[5]; Tara Lehner, MS, PMP[5]; Roger Waltzman, MD, MBA[5]; Seung Lee, MD[6]

[1]BRCR Medical Center, Plantation, FL, USA; [2]Rush University Medical Center, Chicago, IL, USA; [3]UT Southwestern Medical Center, Dallas, TX, USA; [4]The Oncology Institute of Hope and Innovation, Glendale, CA, USA; [5]Molecular Templates, Inc., Jersey City, NJ, USA; [6]University of Maryland, Baltimore, MD, USA

Introduction

- Diffuse large B-cell lymphoma (DLBCL) is the most common histologic subtype of mature non-Hodgkin lymphoma (NHL), accounting for approximately 25% of NHL cases[1]
- Approximately one-third of all newly diagnosed patients with DLBCL are either refractory or relapsed (r/r) following initial response to therapy and represent a population with high unmet need for new therapeutic strategies to achieve or regain disease remission[2]
- CD20 is persistently and nearly ubiquitously expressed in B-cell malignancies, providing a strong rationale to develop compounds with novel mechanisms of action targeting CD20. However, as CD20 is non-internalizing, therapies to date have leveraged only cytotoxic mechanisms, such as antibody-dependent cellular cytotoxicity, which are vulnerable to resistance. Therapies that cause internalization of cytotoxic agents have not previously been developed.[3,4]
- 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**)[5,6]
- 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[7]
- MT-3724 represents a novel ETB modality comprised of an anti-CD20 single-chain variable fragment genetically fused to SLTA and is capable of both efficient internalization once bound to CD20 and the induction of potent direct cell killing via enzymatic ribosome inactivation (**Figure 1**)[5-7]

Figure 1. Internalization of MT-3724 into Target Cell



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

- MT-3724 has been shown to specifically bind and kill CD20+ human B-cells *in vitro* (IC_{50} <1 nM) and in CB17 SCID and PDX mice[5,7]
- Given the unique ability of MT-3724 to kill CD20+ cells by ribosomal inhibition, combining MT-3724 with standard cytotoxic chemotherapy and/or immunomodulatory agents may provide enhanced benefit in NHL treatment algorithms
  - Evaluation of lenalidomide (LEN) in combination with MT-3724 revealed a synergistic effect in CD20-positive Daudi cell lines[5]
- Based on these results and the known safety profile of MT-3724, LEN was chosen as a combination agent to maximize anti-tumor effects in subjects with B-cell NHL while minimizing overlapping toxicity risks

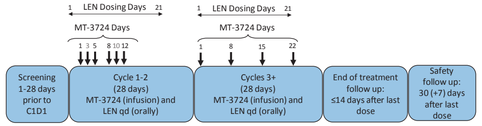
Objective

- To determine the safety, tolerability, and maximum tolerated dose (MTD) of MT-3724 in combination with LEN in subjects with r/r B-cell NHL

Study Design and Methods

- This multicenter, open-label, multiple-dose, Phase 2a, dose-escalation study of MT-3724 (NCT03645395) is being conducted in subjects with r/r B-cell NHL
- Secondary endpoints included pharmacokinetic (PK) and pharmacodynamic (PD) parameters, immunogenicity of MT-3724, and tumor response
- The study is being conducted in two parts (**Figure 2**)

Figure 2. Study Design[a]



For long-term follow-up, subjects from both parts of the study will be followed for 24 months for PFS and DOR until progressive disease, death, or lost to follow-up.
[a]A modification to the dosing schedule of MT-3724 is currently in development.
DOR, duration of tumor response; LEN, lenalidomide; PFS, progression-free survival; qd, once a day.

- Part 1 includes MT-3724 dose escalation according to the modified 3+3 design to identify the MTD of MT-3724 in combination with standard doses of LEN
  - The MTD will be defined as the highest MT-3724 dose that can be given in combination with LEN such that no more than 1 of 6 subjects experiences a dose-limiting toxicity (DLT)
    - DLTs were defined as a TEAE occurring after the start of infusion in Cycle 1 of Part 1 and were at least possibly related to MT-3724 as determined by the sponsor after consultation with the investigator. TEAEs that emerged at Cycle 2 or later could be declared a DLT after consultation with the investigator. TEAEs related to LEN were not considered a DLT unless they did not appear in or occurred at a worse severity than that described in the prescribing information.
  - The MT-3724 dose cannot exceed 50 µg/kg/dose (with a maximum total dose of 6000 µg), as this is the MTD for MT-3724 given as monotherapy
- Part 2 will confirm the safety and tolerability of MT-3724 + LEN in the MTD expansion cohort. MT-3724 at the MTD determined in Part 1 will be given in combination with LEN in up to 40 subjects with DLBCL; in addition, the PK, PD, immunogenicity and tumor response of MT-3724 + LEN will be evaluated in Part 2.

Treatment Schedule

- In Part 1, MT-3724 dose ranged from 10 to 25 µg/kg
- In Cycles 1 and 2, subjects received MT-3724 as an IV infusion over 1 hour on Days 1, 3, 5, 8, 10, and 12. In Cycle 3 and beyond, MT-3724 was administered weekly on Days 1, 8, 15, and 22 of each cycle
- In all cycles, LEN was administered orally on Days 1-21 of each 28-day cycle

Key Eligibility Requirements

- Eligible subjects were adults with histologically confirmed r/r B-cell NHL with measurable disease by Lugano classification for NHL. Subjects provided written, informed consent and had previously received all currently available approved therapies for NHL
- All subtypes of B-cell NHL were considered for Part 1; only histologically documented DLBCL was considered for Part 2
- Subjects were not eligible if they had received rituximab (within 84 days of treatment initiation), obinutuzumab (within 184 days), ofatumumab (within 88 days), or allogeneic hematopoietic stem cell transplant (within 180 days)
- Serum rituximab level must have been negative (<500 ng/mL) at screening

Analysis

- Data were summarized descriptively
- This analysis, conducted on 05 May 2020, was not a pre-specified data cut in the protocol. The data reported here have not been verified.

Results

- The analysis included 8 subjects (**Table 1**)

Table 1. Baseline Characteristics

Characteristic	MT-3724 + LEN (N=8)
Sex, n (%)	
Male	6 (75)
Age, years	
Mean (range)	66 (53 – 86)
Weight, kg	
Mean	88
Median (range)	86 (62 – 124)
BMI, kg/m²	
Mean	28.9
Median (range)	26.4 (22.5 – 39.1)
ECOG performance status, n	
0	4
1	4
2	0
NHL type, n	
Diffuse large B-cell lymphoma	3
Follicular lymphoma	3
Mantle cell lymphoma	1
Small lymphocytic lymphoma	1
Prior NHL treatments, n	
Mean	3
Median (range)	2 (1 – 6)
Prior anti-CD20 treatments, n	
Mean	1
Median (range)	1 (1 – 3)
At least 1 genetic abnormality, n (%)	6 (75)
t(11;14)(q13;q32) or cyclin D1 (BCL1, PRAD1, or CCND1) overexpression, n	1
IgH/BCL2 rearrangement or BCL2 overexpression, n	3
BCL-6 (ie, 3q27 rearrangement) overexpression, n	3
t(14;18)(q32;q21)	1

BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; NHL, non-Hodgkin lymphoma.

Dose-Limiting Toxicities

- Protocol DLT criteria included occurrence of any grade 2 or higher capillary leak syndrome (CLS), or any other qualifying events, in Cycle 1
- Two subjects treated in Cohort 2 (25 µg/kg/dose) experienced a DLT of grade 2 capillary leak syndrome, 1 subject was hospitalized and therefore met seriousness criteria. One subject was initially evaluated for a DLT due to grade 2 fatigue; hypoalbuminemia, peripheral edema, and myalgia were subsequently reported, resulting in the identification of capillary leak syndrome in this subject.

Safety

- Treatment-emergent adverse events (TEAEs) occurred in 7 (88%) subjects (**Table 2**)

Table 2. Safety Summary

	n (%)
Non-serious TEAE	
All-cause	7 (88)
MT-3724 related	6 (75)
Serious TEAE	
All-cause	3 (38)
MT-3724 related[a]	2 (25)
Subjects with TEAE that led to treatment modification due to TEAE	
Dose interrupted	1 (13)
Dose reduction	2 (25)
Permanent discontinuation	0
Death	
Deaths	0
MT-3724 related	0

[a]One subject had grade 3 pneumonia; another subject with grade 2 CLS was hospitalized.
CLS, capillary leak syndrome; TEAE, treatment-emergent adverse event.
Relatedness was investigator assessed.

- The most common TEAEs were fatigue and peripheral edema (**Table 3**)

Table 3. Summary of TEAEs (All Causality)

	10 µg/kg TIW (n=3)	20 µg/kg TIW[a] (n=1)	25 µg/kg TIW (n=4)	Total (N=8)
Fatigue	1	0	3	4
Peripheral edema	0	0	4	4
Myalgia	0	0	3	3
Anemia	0	0	2	2
Chest discomfort	0	0	2	2
Constipation	2	0	0	2
Hypoalbuminemia	0	0	2	2
Hypokalemia	2	0	0	2
Pain in extremity	0	0	2	2

[a]One subject was enrolled in an interim cohort at 20 µg/kg because of DLTs observed in the 25 µg/kg cohort.
TIW, three-times weekly.

- Treatment-related TEAEs occurred in 6 (75%) subjects. Treatment-related TEAEs occurring in ≥2 subjects included hypokalemia (n=2), fatigue (n=2), and peripheral edema (n=2)
- Treatment-related TEAEs ≥grade 3 included hypokalemia (n=2), anemia (n=1), leukopenia (n=1), neutropenia (n=1), and thrombocytopenia (n=1)
- Five serious adverse events (SAEs) occurred in 3 subjects (**Table 4**)

Table 4. Summary of SAEs (All Causality)

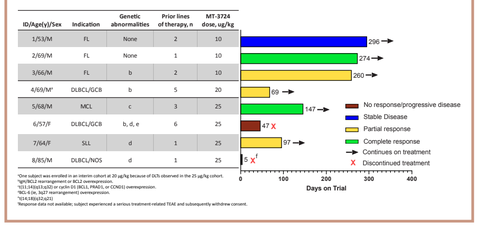
Subject	SAE	Grade	MT-3724 Related
10 µg/kg TIW			
3	Atrial fibrillation	3	No[a]
25 µg/kg TIW			
6	Anemia	3	Yes
	Capillary leak syndrome[b]	2	Yes
	Neutropenia	4	Yes
8	Pneumonia	3	Yes[a]

[a]The SAE in Subject 3 was not a DLT as it occurred in Cycle 9, outside the DLT assessment period, and also because it was assessed as unrelated to study drug; the SAE in Subject 8 was not a DLT because Subject 8 was given the incorrect dose (25 instead of 20 µg/kg) and was therefore not evaluable for DLTs.
[b]Another instance of CLS did not meet criteria for seriousness.
CLS, capillary leak syndrome; DLT, dose-limiting toxicity; SAE, serious adverse event; TIW, three times weekly.

Efficacy

- Among 8 subjects, 7 of whom had response data available, two subjects had complete responses (CRs), three subjects had partial responses (PRs), one subject had stable disease, and one had progressive disease (**Figure 3**)

Figure 3. Summary of Best Response and Time on Study



*One subject was enrolled in an interim cohort at 20 µg/kg because of DLTs observed in the 25 µg/kg cohort.
†IgH/BCL2 rearrangement or BCL2 overexpression.
‡t(11;14)(q13;q32) or cyclin D1 (BCL1, PRAD1, or CCND1) overexpression.
§BCL-6 (ie, 3q27 rearrangement) overexpression.
¶t(14;18)(q32;q21)
#Response data not available; subject experienced a serious treatment-related TEAE and subsequently withdrew consent.

DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; GCB, germinal center B-cell; MCL, mantle cell lymphoma; NOS, not otherwise specified; SLL, small lymphocytic lymphoma; TEAE, treatment-emergent adverse event.

CONCLUSIONS

- In this unplanned interim analysis of a Phase 2a study of MT-3724+LEN in subjects with r/r B-cell NHL, grade 2 capillary leak syndrome occurred at doses lower than expected. Therefore, a new schedule of therapy with LEN is under development for this study, in which MT-3724 will be administered twice weekly, rather than three times per week.
- The preliminary response data were encouraging: among 7 evaluable subjects, there were two CRs and three PRs.

REFERENCES

1. Teras LR, et al. *CA Cancer J Clin.* 2016;66(6):443-59.
2. Friedberg JW. *Hematology Am Soc Hematol Educ Program.* 2011;2011:498-505.
3. Marshall MJE, et al. *Front Immunol.* 2017;8:1245.
4. Torka P, et al. *Curr Hematol Malig Rep.* 2019;14(5):426-38.
5. Robinson GL, et al. *Cancer Res.* 2016;76(14 suppl):1483.
6. Rajagopalan S, et al. *Cancer REs.* 2016;76(14 suppl):595.
7. Huang S, et al. *Blood Cancer J.* 2018;8(3):33.

ACKNOWLEDGMENTS

The study was sponsored by Molecular Templates, Inc. Funding to support the development of this poster was provided by Molecular Templates to MedVal Scientific Information Services, LLC, Princeton, NJ.

DISCLOSURES

CB: Employment: Molecular Templates. **GG:** Consultant: Molecular Templates; Equity ownership: Abbott, AbbVie. **TS:** Employment: Molecular Templates. **TL:** Consultant: Molecular Templates. **JPH:** Employment and Equity Ownership: Molecular Templates. **JT:** No relevant disclosures.

Presented at the 25th European Hematological Association (EHA) Annual Meeting, June 11-21, 2020, Virtual Edition

The study was sponsored by Molecular Templates, Inc.