Safety and Efficacy of Anti-CD20 Immunotoxin MT-3724 in Relapsed/ Refractory B-cell Non-Hodgkin Lymphoma (NHL) in a Phase 1 Study

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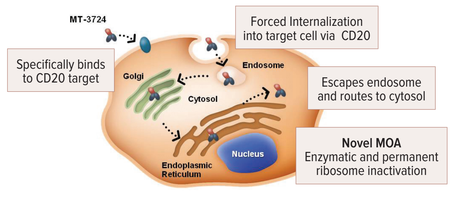
Introduction

- CD20 is a non-internalizing receptor expressed on B-cells and is central to B-cell malignances including DLBCL
- MT-3724 is an engineered toxin body (ETB) comprised of a single chain variable fragment (scFv) genetically fused to Shiga-like toxin A subunit (SLTA)
- MT-3724 binds CD20 and induces its own internalization; once internalized, MT-3724 destroys the cell through a novel mechanism of action: ribosomal inactivation
- In the MTD portion of the phase I study in heavily pre-treated NHL patients, MT-3724 exhibited good tolerability and promising efficacy, and the MTD was defined to be 75 mcg/kg; DLTs were observed at 100 mcg/kg consistent with capillary leak syndrome (CLS) that were non-life threatening and resolved upon cessation of dosing
- MT-3724 competes for binding of CD20 with RTX and showed no benefit in patients with high pre-existing serum levels of rituximab (RTX)

Figure 1. MT-3724 novel MOA – ribosome inactivation



- A phase Ib expansion study was initiated at 75 mcg/kg in R-R DLBCL with an exclusion criterion for patients with high pre-existing serum levels of RTX
- The first three patients enrolled in the phase Ib expansion study had high BMI (36-44) and body weights (97kg, 98kg, and 153kg); two of these patients required dose interruptions of two weeks and dose reduction to 50 mcg/kg due to grade 2 CLS which were deemed non-life threatening and resolved after the dose delay and reduction
- A new MTD was defined at 50 mcg/kg with a total per dose maximum of 6 mg
- Enrollment in the phase Ib expansion study was suspended by the sponsor in order to implement the redefined MTD of 50 mcg/kg based on high BMI and body weight subjects and the study was recently re-opened to enroll new patients
- The phase Ib expansion study continues to show good tolerability and promising activity in heavily pre-treated DLBCL patients

Objectives

Primary

- To determine the safety and tolerability, including the MTD, of MT-3724 in subjects with R-R CD20-positive NHL

Secondary

- To determine the PK, PD, immunogenicity, and tumor response profile of MT-3724 in subjects with R-R CD20-positive NHL

Exploratory

- To determine changes from baseline in humoral & cellular immune status of subjects during the treatment with MT-3724

Methods

Study Design

- The ongoing Phase 1/1b first-in-human, open label ascending dose study to evaluate the safety and tolerability (including MTD) of MT-3724 in patients with R-R CD20-positive DLBCL (NCT02361346)
- Part 1 – Dose Escalation (completed):
  - MT-3724 dose was escalated according to the 3+3 design based on ≤1 patient exhibiting DLT during Cycle 1 (28 days)
  - 6 sequential dose cohorts: 5, 10, 20, 50, 100 and 75 µg/kg/dose
- Part 2 – MTD Expansion (ongoing):
  - MTD of MT-3724 is being evaluated in up to 40 subjects with DLBCL who have serum RTX levels < 500 ng/mL before the start of treatment
- In both parts of the study, MT-3724 is administered via IV infusions over 1-4 hours on Day 1, 3, 5, 8, 10 and 12 of each treatment cycle for up to 5 cycles

Safety, Efficacy and PD

- Safety assessments included adverse events (NCI-CTCAE v.4.03), vital signs, ECG, physical examinations and laboratory test results at screening and in Cycles 1-5
- Radiological assessment of tumor response was performed by CT scans of all measurable tumor lesions, evaluated by the investigator according to the Cheson criteria at screening, at end of Cycle 1 (optional), Cycle 2, Cycle 4 and at the end of study visit (optional)
- Pharmacodynamic assessments (B-cell count, flow cytometry) were performed by serial plasma sampling in Cycles 1-5

Results

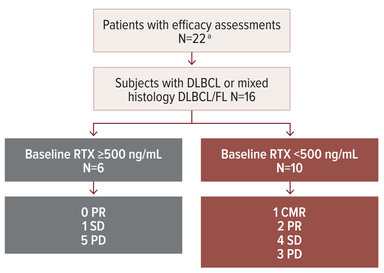
- As of May 2018, a total of 24 patients have been treated in the study of which 22 patients had efficacy assessments and the study is ongoing
  - 19 subjects (10 DLBCL, 3 mixed histology DLBCL/FL) in Part 1
  - 3 subjects (all DLBCL) in Part 2
- 2 patients did not have post-baseline efficacy assesment or did not qualify for efficacy assessment
- Median prior number of therapies was 5
- Serum RTX levels at screening were:
  - < 500 ng/mL in 15 subjects (8 DLBCL, 2 mixed histology DLBCL/FL)
  - ≥ 500 ng/mL in 7 subjects (5 DLBCL, 1 mixed histology DLBCL/FL)

Table 1. Subject baseline characteristics

Characteristics (n=24)		
Sex (n. %)	F	14 (58%)
	M	10 (42%)
Age (mean, range; years)		69 (34 – 78)
Body weight (mean, range; kg)		75 (51 – 154)
BMI (median, range; kg/m2)		29.1 (19- 44)
ECOG performance status (n)	0	11
	1	11
	2	2
NHL type (n)	DLBCL	15
	Mixed histology DLBCL/FL	3
	FL	4
	MCL	2
Prior NHL treatments (median, range)		5 (1 - 11)
Prior anti-CD20 treatments (median, range)		2 (1 – 9)
RTX level in serum (n)	<500 ng/mL	16
	≥500 ng/mL	8

Abbreviations: BMI – body mass index; ECOG – Eastern Cooperative Oncology Group; NHL – non-Hodgkin lymphoma; RTX – rituximab

Figure 2. DLBCL subtype, serum RTX levels at screen, and response



a 2 patients did not have post-baseline efficacy assessments

Efficacy

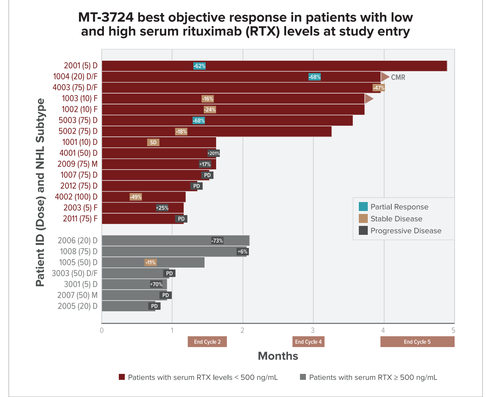
- PRs were reported in 3 patients treated at 5, 20 and 75 mcg/kg
  - All patients had serum RTX levels < 500 ng/mL at screening
  - 2 patients had DLBCL and one had mixed histology DLBCL/FL
  - 2 DLBCL patients had near-PRs of 49% and 47% reduction in tumor volumes
- SD were reported in 7 patients treated at 10 (3), 50 (1), 75 (2) and 100 mcg/kg
  - All but one patient had serum RTX level < 500 ng/mL at screening
  - 2 DLBCL patients with serum RTX levels < 500 ng/mL had near-PRs with tumor regression of 49% and 47%
  - 5 patients had DLBCL and one had mixed histology DLBCL/FL subtype

Table 2. Summary efficacy in all NHL subtypes

Tumor response	N=22			
	Serum RTX level ≥ 500 ng/mL (N=7)		Serum RTX level < 500 ng/mL (N=15)	
	DLBCL [a] N=6	FL/MCL N=1	DLBCL [a] N=10	FL/MCL N=5
CMR	0	0	1	0
PR	0	0	2	0
SD	1	0	4 [b]	2
PD	5	1	3 [c]	3
Mean RTX:MT-3724 ratio (range)	41:1 (6:1 to 117:1)		1:1 (0.1:1 to ^2:1) [d]	

Abbreviations: N – number of patients per treatment group; CMR – complete metabolic response; PR – partial response; SD – stable disease; PD – progressive disease
a DLBCL and mixed histology DLBCL/FL
b One DLT patient in the 100 mcg/kg DLT cohort had a near PR (49% tumor reduction) efficacy assessment after two doses; a second SD patient had a near PR (47% tumor reduction)
c One patient had quantifiable RTX levels greater than the undetectable levels of MT-3724 in the 5 mcg/kg dose cohort
d Calculated for those patients with quantifiable levels of RTX < 500 ng/mL

Figure 3. Time on study and best response



D = DLBCL, D/F = Mixed histology DLBCL, F = Follicular, M = MCL
2 patients did not have post-baseline efficacy assessments
Patient 1004 achieved a complete metabolic response and went onto to stem cell transplant
Patient 1003 went onto extended access protocol

Table 3. Summary of efficacy in DLBCL patients with RTX serum levels < 500 ng/mL

Best tumor response (ORR)	DLBCL [a] (N=10)
CMR	1
PR	2
SD	4 [b]
PD	3 [c]
ORR	30% (1 CMR, 2 PR)
DCR	70% (1 CMR, 2 PR, 4 SD)
Serum RTX:MT-3724 Ratio mean (range)	0.5:1 (0.1:1 to 0.8:1) [d]

Abbreviations: N – number of patients per treatment group; CMR – complete metabolic response; PR – partial response; SD – stable disease; PD – progressive disease; ORR –objective response rate; DCR – disease control rate
a DLBCL and mixed histology DLBCL/FL
b One DLT patients in the 100 mcg/kg DLT cohort had a near PR (49%) and efficacy assessment after one dose; a second SD patient had a near PR (48%)
c One patient had quantifiable RTX levels greater than the undetectable levels of MT-3724 in the 5 mcg/kg dose cohort
d Calculated for those patients with quantifiable levels of RTX < 500 ng/mL

Safety

Table 4. Overall TEAE summary

	All patients n (%)
Number of subjects	24 (100)
Any TEAE	24 (100)
Drug related TEAE	23 (96)
Serious TEAE	13 (54)
Drug related serious TEAE	5 (21)
TEAE led to dose delay or reduction	1 (4) [a]
TEAE led to drug withdrawal	8 (33)
TEAE with fatal outcome	1 (4) [b]

a Reductions due to cytokine release syndrome, capillary leak syndrome; delays/interruptions due to gastric hemorrhage, acute coronary syndrome, thrombocytopenia, fatigue, dehydration, edema, viral syndrome
b Death due to progressive disease and unrelated to MT-3724

Table 5. TEAEs of any grade occurring in >20% of subjects

	All subjects n (%)		All subjects n (%)
Number of subjects	24 (100)	Pyrexia	6 (25)
Edema peripheral	15 (62)	Headache	6 (25)
Myalgia	11 (46)	Stomatitis	5 (21)
Fatigue	11 (46)	Hypotension	5 (21)
Diarrhea	11 (46)	Dyspnea	5 (21)
Insomnia	8 (33)	Asthenia	5 (21)
Nausea	7 (29)	Arthralgia	5 (21)
Cough	7 (29)	Anemia	5 (21)

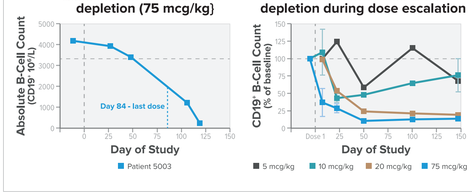
Table 6. Grade ≥3 TEAEs occurring in >1 subject (>4%)

	Dose (mcg/kg), n(%)						
	All subjects	5	10	20	50	75	100
Number of subjects	24 (100)	3 (100)	3 (100)	3 (100)	4 (100)	9 (100)	2 (100)
Myalgia	4 (17)	0 (0)	0 (0)	0 (0)	0 (0)	2 (22)	2 (100)
Renal failure acute	3 (12)	1 (33)	0 (0)	0 (0)	1 (25)	1 (11)	0 (0)
Anaemia	3 (12)	1 (33)	0 (0)	0 (0)	1 (25)	1 (11)	0 (0)
Thrombocytopenia	2 (8)	0 (0)	0 (0)	1 (33)	1 (25)	0 (0)	0 (0)
Pneumonia	2 ( )	0 (0)	0 (0)	0 (0)	0 (0)	1 (11)	1 (50)
Neutropenia	2 (8)	1 (33)	0 (0)	0 (0)	1 (25)	0 (0)	0 (0)
Muscular weakness	2 (8)	0 (0)	0 (0)	0 (0)	1 (25)	0 (0)	1 (50)
Lymphocyte count decreased	2 (8)	0 (0)	0 (0)	0 (0)	1 (25)	0 (0)	1 (50)
Fatigue	2 (8)	0 (0)	0 (0)	0 (0)	0 (0)	2 (22)	0 (0)

TEAE incidence is ranked based on the incidence in all subjects (n=24);
The incidence in each dose group is presented for the corresponding TEAE.

PK and PD

Figure 4. Patient 5003 CD19+ B-cell depletion at 75 mcg/kg



Patient 5003 narrative:
- DLBCL; PR best response; PD at end of study
- High body weight (95 kg) patient; initial dose at 75 mcg/kg and reduced to 50 mcg/kg after dose 1 of cycle 2 for remainder of study
- At study entry, CD19+ B-cell count was 4205 (normal range 55-558) which is 7.5x upper limit of normal (ULN)
- During study, flow cytometry showed 1/3 of CD19+ B-cells were CD20 negative with 2/3 low to dim CD20 expression
- 94% reduction in B-cell count during treatment with MT-3724
- Possible CLL or B-cell lymphocytosis at the time of progression with lymphoproliferative disorder phenotype confirmed by flow cytometry

Table 7. Pharmacokinetics

MT-3724 dose group (mcg/kg)	C_{max} ng/mL	t_{max} h	AUClast h*ng/mL	$t_{1/2}$ h
5 (n = 2)	41 (NC)	2.08 (NC)	102 (NC)	NR
10 (n = 3)	79 (62%)	2.39 (21%)	242 (151%)	NR
20 (n = 3)	141 (47%)	2.08 (NC)	382 (74%)	2.26 (47%)
50 (n = 4)	362 (38%)	2.25 (13%)	1140 (34%)	2.48 (10%)
75 (n = 8)	578 (84%)	2.08 (8%)	1530 (110%)	1.68 (41%)
100 (n = 2)	848 (NC)	2.08 (NC)	2550 (NC)	2.95 (NC)

Geometric mean (CV%) for all parameters except $t_{1/2}$, where median (CV%) is provided.
NR = Not reported
NC = Not calculated

Conclusions

- **MT-3724 as monotherapy showed encouraging preliminary activity in heavily pretreated patients with R-R DLBCL (median prior therapies of 5) with poor prognosis and a median age of 69 who may not be candidates for CAR-T therapy**
- **Patients with high circulating levels of RTX at study entry showed poor response to MT-3724 due to competitive inhibition and blocking of CD20 receptor by RTX**
- **The preliminary objective response rate in DLBCL patients, with low serum RTX levels at study entry, was 30% with a disease control rate of 70% where two stable disease patients had tumor reductions of 47% and 49%**
- **MT-3724 was well tolerated and a redefined MTD of 50 mcg/kg with a maximum per dose maximum of 6 mg was implemented based on experience with patients with high body weight**
- **Accrual and follow-up of patients is ongoing**