Phase I/Ib study of the novel CD20-targeted immunotoxin MT-3724 in relapsed/refractory non-Hodgkin's B-cell lymphoma

CT049

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Background

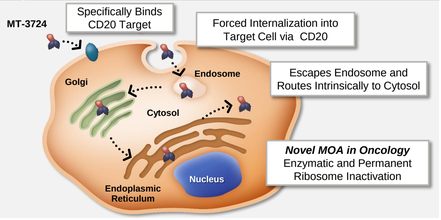
- In 2016 an estimated 72,580 new cases and 20,150 deaths attributable to non-Hodgkin's B-cell lymphoma (NHL) will occur in the US. (American Cancer Society. *Cancer Facts & Figures 2016*)
- Anti-CD20 monoclonal antibody (MAb) therapy is widely used for the treatment of NHL, but development of refractory disease to CD20 MAb(s) and chemotherapy regimens is common.
- There are several mechanisms by which disease may become refractory to CD20 Mab(s) including increased MAb catabolism, initial development or post-treatment selection of malignant cells with low-levels of surface CD20 expression, resistance to MAb effector mechanisms and/or impaired immune cell function. (Smith MR. *Rituximab: mechanisms of action and resistance 2003*).
- MT-3724 possesses a differentiated mechanism of action (MOA), enzymatic and irreversible ribosome inactivation, compared to currently available NHL therapies.
- MT-3724 is the first successful immunotoxin to bind and internalize against CD20 (a non-internalizing receptor).

Mechanism of Action

MT-3724's mechanism of action is differentiated from currently available oncology therapeutics

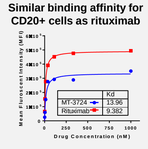
- MT-3724 inhibits protein translation by irreversibly and enzymatically inactivating ribosomes, leading to ribotoxic stress, caspase activation, and apoptosis.
- MT-3724 specifically targets and potently kills CD20 expressing cells, and demonstrates minimal cytotoxicity on cells that lack CD20 surface expression.

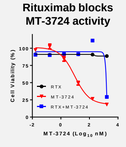
Figure 1. MT-3724 Novel MOA – Ribosome Inactivation

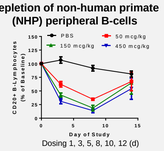


Preclinical Data Overview

Figure 2. MT-3724 Preclinical Activity







Dosing 1, 3, 5, 8, 10, 12 (d)

Serum half-life in NHP similar to other toxin drugs

Dose (mcg/kg)	$C_{max}D1$ (ng/mL)	$C_{max}D12$ (ng/mL)*	$T_{1/2}$ (hr)
50	1,260	0.1	1.17
150	4,010	16.8	1.83
450	14,300	55.7	1.86

*Reduced MT-3724 exposure at day 12 due to anti-drug antibody response

Methods

Phase I/Ib Study Design

- MT-3724 is being tested in a first-in-human (FIH), open label, dose escalation study (3 + 3 design).
- Sequential cohorts of 5, 10, 20, 50 and 100 mcg/kg/dose have been completed, and a 75 mcg/kg/dose cohort is currently enrolling.
- Eligible subjects who previously responded to a CD20 MAb containing therapy followed by relapse/recurrence of NHL or CLL receive 6 doses by IV infusion over the first 12 day of a 28 day cycle (first cycle).
- With continued safety, tolerability and lack of tumor progression, subjects may receive additional 6-dose cycles (21 day cycle) with tumor assessments after cycles 2 and 4.
- Dose escalation is based on < 33% dose limiting toxicities (DLTs) observed during the first 28 day cycle.

Patient Characteristics

- To date, 18 subjects have been enrolled in this Phase I/Ib study. Thirteen subjects (72%) had received more than four prior therapies.
- Lymphoma subtypes enrolled are follicular (n=8), diffuse large B-cell (n=8), and mantle cell (n=2). At the time of diagnosis 10 subjects (56%) had clinical stage III or IV disease.

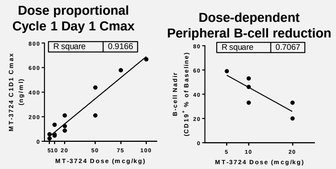
Table 1. Subject Baseline Characteristics

Characteristic	All doses (N = 18)
Median Age, years (range)	66 (34-78)
Sex, n (%)	
Male	8 (44%)
Female	10 (56%)
Prior Therapies, median (range)	4 (1-11)
<4, n (%)	5 (28%)
≥4, n (%)	13 (72%)
Years from diagnosis to treatment, median (range)	5 (1-13)
NHL Subtype, n (%)	
DLBCL	8 (44%)
FL	8 (44%)
MCL	2 (11%)
Clinical Stage, n (%)	
I-II	6 (33%)
III-IV	10 (56%)

Pharmacokinetics & Pharmacodynamics

- MT-3724 exposure demonstrates dose proportional increase.
- Increased levels of circulating B-cells (CD19+) resulted in lower MT-3724 serum half-life likely due to target (CD20) mediated clearance.
- High baseline rituximab (RTX) levels (≥1,000 ng/mL) correlated with lower baseline B-cells.
- MT-3724 serum half-life is (1-3 hr) comparable to other immunotoxins.
- Degree of reduction in peripheral B-cells appears to be dose-dependent.

Figure 3. Exposure and B-Cell Depletion



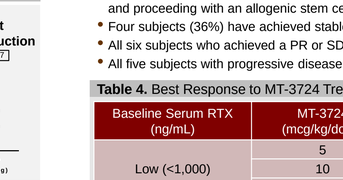


Table 2. Cycle 1 Day 1 Pharmacokinetic Parameters & Baseline Rituximab and B-Cell Levels

		MT-3724 (Cycle 1 Day 1)			Baseline		
Subject	Dose (mcg/kg)	Cmax (ng/mL)	$T_{1/2}$ (hr)	Cl (mL/hr/kg)	Last RTX (d)	RTX (ng/mL)	B-cells (cells/µL)
2006	20	124	3.00	40	35	1,958	9
2005	20	211	2.75	22	46	14,758	<1
1004	20	87	1.04	101	~545	<600	244
1005	50	211	2.62	46	185	1061	<1
4001	50	326	2.10	46	~225	<600	<1
4002	100	668	2.22	45	~1143	<600	88
4003	75	579	1.56	40	~882	<600	296

Safety

Adverse Events (AE)

- No treatment-related deaths have occurred.
- DLTs observed at 100 mcg/kg in two subjects.
- Three subjects are enrolled at 75 mcg/kg with one subject in this cohort who has completed cycle 1 with no DLTs.

Table 3. AE Summary as of 4/5/16 (N=16)

	All Grades		Grade 3 or 4	
	N	%	N	%
Pts with at least 1 AE	16	100%	8	50%
Total AE	99		13	
Adverse Events (Occurring in > 2 Subjects):				
Pain	10	10%		
Edema	8	8%		
Cough	6	6%		
Diarrhea	6	6%	1	8%
Fatigue	6	6%		
Nausea	6	6%		
Anemia	5	5%		
Constipation	4	4%		
Fever	4	4%		
Hypokalemia	4	4%		
Myalgia	4	4%	2*	15%
Anorexia	3	3%	1	8%
Blurred vision	3	3%		
Dizziness	3	3%		
Dyspnea	3	3%		
Headache	3	3%		
Hypoalbuminemia	3	3%		
Hypocalcemia	3	3%	1	8%
Hyponatremia	3	3%	1	8%
Insomnia	3	3%		
Neutropenia	3	3%	2*	15%
Thrombocytopenia	3	3%	3	23%
Weakness	3	3%	2**	15%

* Possibly treatment-related
** DLTs

Efficacy

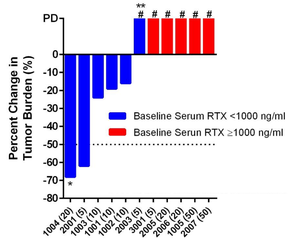
- Two (18%) subjects have achieved partial response (PR) with one subject demonstrating minimal residual disease (MRD) and proceeding with an allogenic stem cell transplant (ASCT).
- Four subjects (36%) have achieved stable disease (SD) or a mixed-response (MR).
- All six subjects who achieved a PR or SD had low baseline levels of serum RTX (<1,000 ng/mL).
- All five subjects with progressive disease (PD) had high baseline levels of serum RTX (≥1,000 ng/mL).

Table 4. Best Response to MT-3724 Treatment

Baseline Serum RTX (ng/mL)	MT-3724 (mcg/kg/dose)	Best Response to Treatment, N (subtype)			
		PR	SD	MR	PD
Low (<1,000)	5	1 (D)		1 (FL)	
	10		3 (2FL, D)		
	20	1 (D)			
High (≥1,000)	5				1 (D)
	20				2 (D)
	50				2 (D, MCL)
Total, N (%)		**2 (18%)**	**3 (27%)**	**1 (9%)**	**5 (45%)**

Subtypes: D = Diffuse Large B-cell Lymphoma; FL = Follicular Lymphoma; MCL = Mantle Cell Lymphoma

Figure 4. MT-3724 Tumor Shrinkage



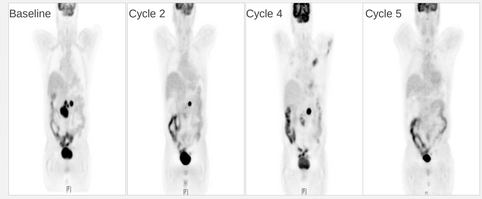
Legend and Notes:

* Response deepened to MRD with Subject proceeding to ASCT
** Mixed response with PD
\# PD with tumor assessment not available

- Subject 1001 completed 2 cycle, Subject 1002 completed 5 cycles, and Subject 1003 completed 5 cycles and is now enrolled in an extended access portion of the Phase I study
- Subjects 1004 and 2001 observed deepening response at cycle 5

Figure 5. Clinical Response in Subject at 5 mcg/kg of MT-3724 in Refractory Disease

- Subject diagnosed in 2009 with follicular lymphoma (stage 2); treated with bendamustine + rituximab and IFRT – PR achieved.
- Relapse in 2013 with high-grade follicular lymphoma (stage 3A) and treated with R-CHOP.
- Refractory to R-CHOP; biopsied and determined to be transformed DLBCL.
- Subject received 5 mcg/kg of MT-3724 for 5 cycles – PR achieved at cycle 2.



Conclusions

- **MT-3724 appears well tolerated up to 50 mcg/kg/dose over repeated cycles of treatment.**
- **Clinical activity in doses as low as 5 mcg/kg in a heavily pre-treated NHL population.**
- **Two responses observed in DLBCL – MOA may suit aggressive NHL subtypes.**
- **Maximum tolerated dose was exceeded at 100 mcg/kg.**
- **Recent anti-CD20 MAb exposure appears to block MT-3724 activity.**
- **Washout period extended to 12-week for prior anti-CD20 Mab and enrollment continues.**
- **Further studies in refractory and induction settings are planned for MT-3724.**

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