A Phase I Study of the Anti-CD79b THIOMAB™ Antibody Drug Conjugate DCDS0780A in Patients with Relapsed or Refractory B-Cell Non-Hodgkin's Lymphoma

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BACKGROUND

- CD79b is expressed on a majority of B cell-derived malignancies, including nearly all non-Hodgkin's lymphoma (NHL) and chronic lymphocytic leukemia (CLL)[1]
- Indolent B-cell malignancies remain incurable, as do approximately a third of aggressive NHLs, despite improvements in clinical outcomes of NHL patients with treatments such as rituximab
- DCDS0780A is a THIOMAB™ antibody drug conjugate (TDC) consisting of the potent anti-mitotic agent, monomethyl auristatin E (MMAE), conjugated to a humanized IgG_1 anti human CD79b monoclonal antibody via a protease labile linker
- The DCDS0780A TDC encompasses THIOMAB™ antibody technology[2] that allows an essentially homogeneous product from the conjugation of 2 drugs per antibody to engineered cysteine residues

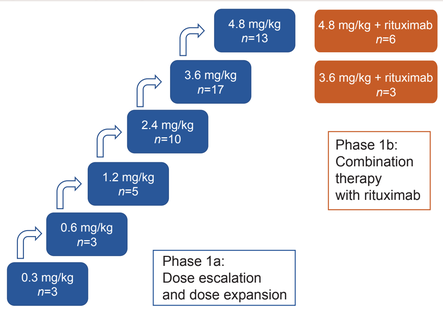
OBJECTIVES

- To assess the safety, tolerability, pharmacokinetics (PK), maximum tolerated dose (MTD), and dose limiting toxicities (DLT) of DCDS0780A alone and in combination with rituximab in patients with relapsed/refractory B-NHL
- To determine the recommended Phase II dose (RP2D) and biologic activity of DCDS0780A alone and in combination with rituximab in the same patients population

METHODS

- Patients with histologically confirmed B-cell NHL that had relapsed after or failed to respond to at least one prior treatment regimen and for which no suitable curative or higher priority therapy existed were enrolled
- Patients received DCDS0780A (0.3–4.8 mg/kg) intravenously every 21 days until disease progression or unacceptable toxicity in a standard 3+3 design (Figure 1)
- DLT were assessed in Cycle 1. Additional patients were enrolled at clinically active doses following confirmation of tolerability in order to further evaluate safety and efficacy based on Lugano Classification[3]
- The protocol was approved by Institutional Review Boards prior to patient recruitment and was conducted in accordance with ICH E6 Guidelines; written informed consent was obtained for all patients prior to performing study-related procedures in accordance with federal and institutional guidelines
- The study was registered on ClinicalTrials.gov (NCT02453087)

Figure 1. Study Design.



RESULTS

Patient characteristics

- As of the data cutoff date of 19 Sep, 2017, 60 patients were enrolled (Table 1)

Table 1. Patient Demographics and Baseline Characteristics.

	DCDS0780A monotherapy (*n*=51)	DCDS0780A + rituximab (*n*=9)
Age year, median (range)	67 (32–86)	71 (44–82)
Sex, *n* (%)		
Males	29 (57)	3 (33)
Baseline ECOG PS, *n* (%)		
0	8 (16)	0
1	43 (84)	9 (100)
Type of malignancy		
DLBCL	33 (65)	8 (89)
FL	12 (24)	0
MZL	4 (8)	1 (11)
MCL	2 (4)	0
Duration of malignancy prior to study (days), median (range)	840 (41–4823)	1123 (331–3633)
No. prior systemic therapies, median	3	3
Prior rituximab therapy, *n* (%)	51 (100)	9 (100)
Autologous stem cell transplantation, *n* (%)	3 (6)	3 (33)

DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MZL, marginal zone lymphoma; MCL, mantle cell lymphoma

Safety

- Adverse event (AE) profiles were similar between DCDS0780A monotherapy at ≥ 2.4 mg/kg and DCDS0780A + rituximab
- Grade ≥ 3 AEs in ≥ 2 patients included neutropenia (22%), hypercalcemia (5%), thrombocytopenia (5%), and white blood cell count decreased (5%)
- One DLT of Grade 4 systemic inflammatory response syndrome (SIRS) occurred in patient dosed at 2.4 mg/kg (monotherapy)
- Nine patients discontinued treatment due to AE, including ocular events in 5 (corneal deposits in 2; corneal opacity, keratitis, and blurred vision in 1 each), and hypoxic-ischemic encephalopathy, hypercalcemia, muscular weakness, and acute respiratory distress syndrome (*n*=1 each)
- Two deaths with single agent DCDS0780A were reported within 30 days of last treatment, one due to anoxic encephalopathy following SIRS and another due to progressive disease

Figure 2. All Adverse Events vs. Related Adverse Events with ≥ 15% Incidences for Doses ≥ 2.4 mg/kg in Phase 1a Cohorts.

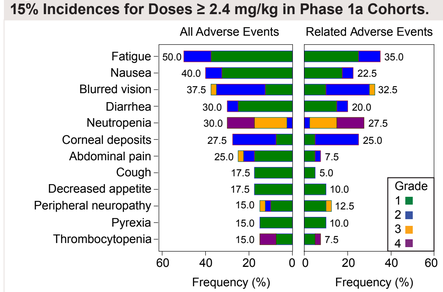
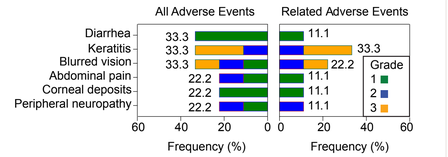


Figure 3. All Adverse Events vs. Related Adverse Events with ≥ 15% Incidences for Doses ≥ 2.4 mg/kg in Phase 1b Cohorts.



- Ocular events related to study drug consisted of blurry vision due to corneal deposits/keratitis at dose levels of ≥ 2.4 mg/kg ± rituximab
- Ocular findings and symptoms improved or resolved with dose or drug discontinuation; out of 19 patients who continued to receive study drug, 3 had recurrence of ocular toxicity after initial ocular event

Table 2. Ocular Toxicity Related to Study Drug at ≥ 2.4 mg/kg.

	DCDS0780A monotherapy (*n*=40)	DCDS0780A + rituximab (*n*=9)
Patient with ocular toxicity, *n* (%) [a]	16 (40)	5 (56)
Keratitis/corneal deposit, *n* (%)		
All grades	14 (35)	4 (44)
Grade 1-2	14 (35)	2 (22)
Grade 3	0	2 (22)
Median time to onset (days)	58	50
Patients with dose reduction due to any ocular toxicity, *n* (%)	4 (10)	3 (33)
Study discontinuation due to any ocular toxicity, *n* (%)	1 (3)	0

[a] Includes blurry vision, keratitis, punctate keratitis, and corneal deposits.

- The protocol-specified MTD was not formally reached; however, 4.8 mg/kg DCDS0780A was determined to be the RP2D based on the overall safety and tolerability profile at that dose
- All dose reductions occurred at dose levels ≥ 2.4 mg/kg DCDS0780A

Table 3. Dose and Schedule Modifications.

Dose Modification	DCDS0780A monotherapy (*n*=51)	DCDS0780A + rituximab (*n*=9)
Number of doses received, median (range)	4 (1–19)	4 (2–6)
Dose reductions, *n* (%)	7 (14)	3 (33)

At data cutoff, 18 out of 60 patients remained on study therapy, including 11 patients on monotherapy and 7 on combination therapy

Pharmacokinetics

- Exposures (AUC, C_{max}) of the antibody-conjugated MMAE (acMMAE) and total antibody analytes increased with an increase in dose
- Clearance values for acMMAE and total antibody analytes were similar at clinical doses tested (0.3–3.6 mg/kg), with evidence of linear PK at doses ≥ 1.2 mg/kg
- Unconjugated MMAE exposures were low and demonstrated formation rate-limited kinetics

Clinical Activity

- Majority of responses occurred at doses ≥ 2.4 mg/kg; 4 patients currently on therapy have not yet undergone response assessment
- Of 44 response-evaluable patients at doses ≥ 2.4 mg/kg, 25 (57%) experienced an objective response; 16 responders were still on study at data cutoff
- Of the 25 responders, 16 remain on study; 3 responders have had disease progression and 1 has died

Figure 4. Best Percent Change from Baseline in Sum of Product Diameter (SPD) in Safety-Evaluable Subjects.

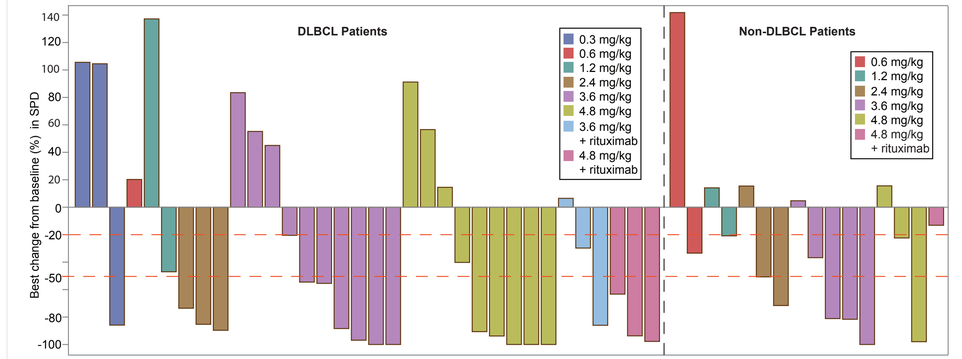
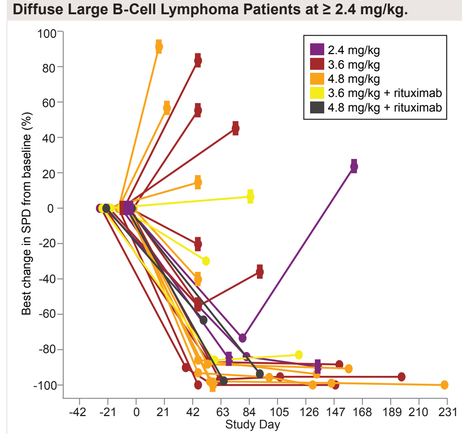


Table 4. Summary of Best Overall Response Rate in Efficacy-Evaluable Patients[a].

	DCDS0780A ≥ 2.4 mg/kg	DCDS0780A + rituximab[b]	All patients
ALL HISTOLOGIES	***n*=37**	***n*=7**	***N*=44**
Responders, *n* (%)	19 (51)	6 (85)	25 (57)
Complete response	12 (32)	4 (57)	16 (36)
Partial response	7 (19)	2 (28)	9 (20)
DLBCL PATIENTS	***n*=24**	***n*=6**	***N*=30**
Responders, *n* (%)	13 (54)	5 (84)	18 (60)
Complete response	9 (38)	4 (66)	13 (43)
Partial response	4 (17)	1 (16)	5 (17)

[a] Response assessment per Lugano Classification[3]
[b] Includes 3.6 and 4.8 mg/kg DCDS0780A dose levels + rituximab.

Figure 5. Percent Change from Baseline in SPD by Time for Diffuse Large B-Cell Lymphoma Patients at ≥ 2.4 mg/kg.



CONCLUSIONS

- Initial results indicate that DCDS0780A administered every 3 weeks at doses up to 4.8 mg/kg was tolerated in the majority of patients
- Ocular toxicity was frequent but reversible with dose reductions or withdrawal of drug
- The anti-tumor activity of DCDS0780A was encouraging in this Phase I study; patients receiving a dose of ≥ 2.4 mg/kg had 57% responders in the efficacy-evaluable patient population, including complete responses in 36% of these patients
- Response rate was 60% in the DLBCL patient subgroup, including complete response in 43% of DLBCL patients
- This study suggests that antibody drug conjugates targeting CD79b are an effective strategy for treating B-NHL

REFERENCES

1. Polson et al., Blood 2007;110:616–23.
2. Junutula et al., Nat Biotechnol 2008; 26:925–32.
3. Cheson et al., J Clin Oncol 2014; 32:3059–68.

DISCLOSURES

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