Safety and efficacy of CD37-Targeting Naratuximab Emtansine plus Rituximab in Diffuse Large B-cell Lymphoma and Other Non-Hodgkin's B-cell Lymphomas – a Phase 2 Study

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BACKGROUND

- Non-Hodgkin's lymphoma (NHL) patients (pts) with relapsed/refractory (R/R) disease who are not candidates for stem cell transplant (SCT) have a poor prognosis
- The **medical need** for new treatments in this setting is even more crucial in diffuse large B-cell lymphoma (DLBCL), which is the most common aggressive NHL (40% of all NHL)
- **Naratuximab emtansine** (nara, Debio 1562, formerly IMGN529) is an antibody-drug conjugate (ADC) consisting of a humanized anti-CD37 antibody, K7153A, conjugated via a thioether-based linker to a cytotoxic maytansinoid, DM1
- CD37, a surface marker of B-lymphocytes, is highly expressed in NHL, including DLBCL[1]
- In preclinical NHL models, nara showed strong antitumor activity that was further enhanced by the co-administration of rituximab (RTX).[2] Nara internalization was 2 to 3-fold higher when combined with RTX
- A Phase 1 monotherapy study demonstrated a good safety profile and encouraging signs of clinical efficacy, with 22% overall response rate (ORR) in DLBCL pts (NCT0153471)[3]
- Here we report the results of an open-label Phase 2 clinical study to evaluate the safety and efficacy of nara, in combination with RTX, in pts with R/R DLBCL and other forms of NHL (NCT02564744)

METHODS

Study endpoints

- **Primary endpoints:** (1) number of pts with clinical responses (ORR) as assessed by the Lugano classification of response assessments, (2) treatment emergent adverse events (TEAEs), clinically significant changes in clinical laboratory tests, ECG and vital signs measurements
- **Secondary endpoints:** progression free survival (PFS), overall survival, time to response, duration of response (DoR) and pharmacokinetics (PK)
- **Exploratory endpoints include** CD37 receptor occupancy

Key eligibility criteria

- **For all pts:**
  - 1-6 prior treatment lines
  - ECOG performance status score of 0−2
  - CNS lymphomas excluded
  - Prior anti-CD37 targeting therapy excluded

Note: double/triple hit (i.e. with translocations in MYC + either BCL2 and/or BCL6), bulky disease and transformed lymphoma pts were not excluded. There was no limit on life expectancy

- **For pts in Part 1:**
  - Confirmed diagnosis of R/R NHL, including DLBCL, FL, MCL, MZL
  - Allogeneic SCT excluded
- **For pts in Part 2:**
  - Confirmed diagnosis of DLBCL
  - Pts with <8 weeks of response post last-line, and/or <24 weeks of response post first-line, were excluded
  - Ineligible for stem cell transplant (SCT)

Response assessment

- Baseline tumor assessment ≤28 days prior to treatment start
- Response was assessed by CT scan or PET-CT[4]

PK and pharmacodynamic assessments

- Blood samples were drawn for PK and pharmacodynamic assessments (see details in the result section)

Figure 1: Study design

Part 1		Part 2
Safety run-in	**Run-in expansion**	
R/R NHL: •DLBCL: N=9 •Other NHL: N=8 •Q3W	Cohort 1: •R/R DLBCL: N=8 •Q3W Cohort 2: •Other R/R NHL: N=12 •Q3W	Cohort A: •DLBCL: N=33 •Q3W Cohort B: •DLBCL: N=30 •QW

DLBCL: diffuse large B-cell lymphoma; NHL: non-Hodgkin's lymphoma; QW: 21-day cycles, nara on day 1, 0.4 mg/kg, and on days 8 and 15, 0.2 mg/kg, followed by rituximab 375 mg/m² on day 1; Q3W: 21-day cycles, nara on day 1, 0.7 mg/kg, followed by rituximab 375 mg/m²; R/R: relapsed/refractory

RESULTS

Table 1: Patient Baseline Characteristics (Safety Population)

Characteristic	DLBCL Q3W (N=50)	DLBCL QW (N=30)	Other NHL (N=20)
Median age (range), years	69 (29–88)	72 (33–84)	69 (59–83)
Male, n (%)	28 (56.0)	15 (50.0)	13 (65.0)
ECOG performance status			
0, n (%)	16 (32.0)	9 (30.0)	11 (55.0)
1, n (%)	24 (48.0)	18 (60.0)	8 (40.0)
2, n (%)	10 (20.0)	3 (10.0)	1 (5.0)
Bulky disease >7.5 cm, n (%)	13 (26.0)	4 (13.3)	2 (10.0)
Ann Arbor stage III/IV, n (%)	40 (80.0)	22 (73.3)	17 (85.0)
Extranodal involvement, n (%)	33 (66.0)	18 (60.0)	13 (65.0)
Bone marrow involvement, n (%)	6 (12.0)	5 (16.7)	7 (35.0)
IPI score 3–5 at enrollment, n (%)	23 (46.0)	14 (46.7)	Not defined
Median n of prior therapies (range)	2 (1–6)	1 (1–4)	2 (1–5)
1 prior line, n (%)	24 (48.0)	21 (70.0)	9 (45.0)
2 prior lines, n (%)	13 (26.0)	4 (13.3)	3 (15.0)
≥3 prior lines, n (%)	13 (26.0)	5 (16.7)	8 (40.0)
Primary refractory, n (%)*	9 (18.0)	1 (3.3)	4 (20.0)
Refractory to last treatment, n (%)*	20 (40.0)	4 (13.3)	7 (35.0)
Duration of response post last treatment <12 months, n (%)	34 (68.0)	12 (40.0)	8 (40.0)
Prior anti-CD20 therapy, n (%)	47 (94.0)	27 (90.0)	20 (100.0)
Transformed lymphoma, n (%)	11 (22.0)	4 (13.3)	1 (5.0)

ECOG: Eastern Cooperative Oncology Group; IPI: International Prognostic Index; safety population: all pts receiving at least one dose of nara + RTX; QW: weekly regimen; Q3W: 3-weekly regimen
*No response or progressive disease within 6 months of last dose of treatment

Table 2: Treatment Summary

	DLBCL Q3W (N=50)	DLBCL QW (N=30)	Other NHL (N=20)
Completed ≥6 cycles, n (%)	18 (36.0)	15 (50.0)	12 (60.0)
Median cycles, n (range)*	3 (1–38)	5.5 (1–30)	7 (1–52)
Discontinued study treatment:			
due to PD, n (%)	29 (58.0)	16 (53.3)	6 (30.0)
due to AE not leading to death, n (%)	3 (6.0)	0 (0.0)	3 (15.0)
due to AE leading to death, n (%)	1 (2.0)	1 (3.3)	0 (0.0)

AE: Adverse Event; PD: progressive disease; QW: weekly regimen; Q3W: 3-weekly regimen
* In the QW regimen, cycles were counted if the first dose was taken

PATIENT RECRUITMENT AND DISPOSITION

- 100 pts were dosed:
  - 80 DLBCL and 20 other B-NHL
- **At data cut-off (13 Jan 2021)** median follow-up was 2.8 months (95% CI: 1.4-5.4 months)
- Four pts were still on treatment; 55 died (9 AE, 31 progressive disease (PD), 15 other or unknown causes); 3 pts withdrew consent, 1 was lost to follow-up, 1 discontinued (investigator decision) 2 reason unknown
- Baseline characteristics are shown in **Table 1**
- Treatment duration and discontinuations are summarized in **Table 2**

SAFETY

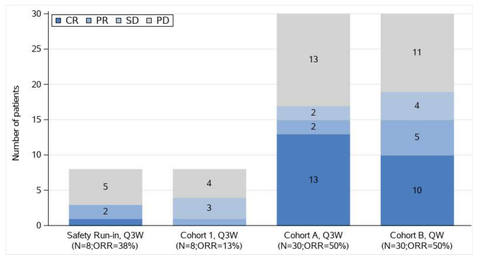
- The most common grade ≥3 TEAEs and most common serious AEs of any grade, are presented in **Table 3**
- Only very few grade ≥3 TEAEs, known to be linked with free DM1,[5-6] were reported: 3 (3%) liver events (1 toxic hepatitis, 1 GGT increased, 1 ALP increased) with sequelae, and 2 (2%) cases of non-serious neuropathy (1 motor and 1 sensory)
- Two COVID-19 cases were reported in pts on treatment, including 1 of the pneumonia cases in **Table 3**. One of the COVID-19 cases was fatal
- Ten pts (10%) experienced fatal SAEs, including 2 events considered as possibly related to Debio 1562 by the investigators (1 pneumonitis and 1 left ventricular failure in a pt with a pre-existing cardiac medical history)

Table 3: TEAE Review (Safety Population)

	All (N=100)	DLBCL Q3W (N=50)	DLBCL QW (N=30)
Pts with at least 1 grade ≥3 TEAE, n (%)	81 (81.0)	43 (86.0)	25 (83.3)
Grade 3–4 TEAE, ≥10% of all pts, n (%)			
Neutropenia*	54 (54.0)	27 (54.0)	17 (56.7)
Leukopenia*	19 (19.0)	8 (16.0)	8 (26.7)
Lymphopenia*	17 (17.0)	10 (20.0)	4 (13.3)
Thrombocytopenia*	12 (12.0)	4 (8.0)	5 (16.7)
Grade 5 TEAE	10 (10.0)	5 (10.0)	2 (6.7)
SAE occurring in ≥3 pts			
Pneumonia and/or Lung Infection	5 (5.0)	2 (4.0)	2 (6.7)
Febrile neutropenia	4 (4.0)	3 (6.0)	0 (0.0)
General physical health deterioration	3 (3.0)	3 (6.0)	0 (0.0)
TEAE leading to nara + RTX discontinuation, n (%)**	8 (8.0)	4 (8.0)	1 (3.3)
TEAE leading to nara dose reduction, n (%)	6 (6.0)	3 (6.0)	0 (0.0)

TEAE: treatment emergent adverse event: from first dose till 30 days after last dose; Pts: patients; SAE: serious adverse event
*All cytopenias refer to the cytopenia term and/or the corresponding term of cell count decreased
** Per protocol, when nara was discontinued, patients had to discontinue also rituximab

Figure 2: Best Overall Response in DLBCL*

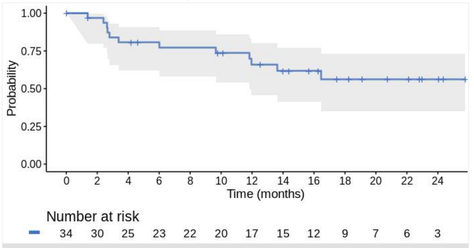


*Efficacy evaluable population; CR: complete remission; PR: partial remission; SD: stable disease; PD: progressive disease; QW: weekly regimen; Q3W: 3-weekly regimen; ORR: overall response rate

EFFICACY

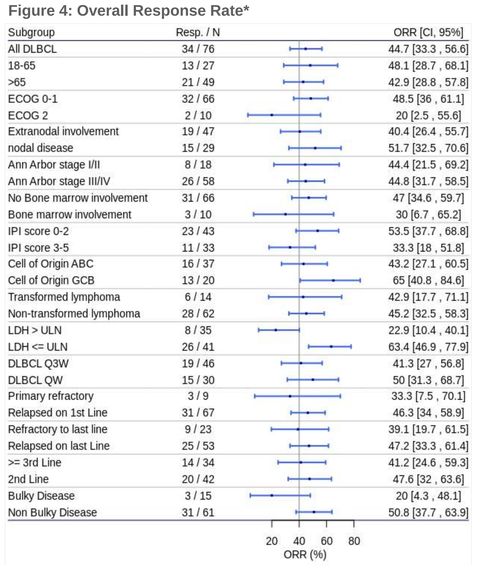
- **Efficacy is reported only in DLBCL pts**
- Of the 80 DLBCL pts dosed, 76 were part of the efficacy evaluable population (both a baseline tumor assessment and a post-baseline tumor assessment or an assessment of clinical PD). All efficacy analyses are reported in the efficacy evaluable population, unless noted otherwise
- The ORR in all cohorts combined was 44.7% (95% CI: 33.3-56.6), with 31.6% CR (95% CI: 21.4-43.3). ORR per cohort is shown in **Figure 2**
- Of the 32 pts with best overall response of PD, 10 were clinical PD with no radiological confirmation (1 in safety run in, 2 in Cohort 1, 3 in Cohort A and 4 in Cohort B). In addition, 1 pt in Cohort 1 and 1 pt in Cohort B achieved a short period of SD before a clinical PD
- The per protocol (PP) set is composed of pts in the efficacy evaluable set, excluding pts with no PP baseline tumor assessment. This led to the exclusion (from PP set) of 4 DLBCL pts with baseline tumor assessments 36-51 days prior to first dose: 1 pt in Cohort 1, 2 in cohort A and 1 in cohort B. In the PP set (N=72), the ORR was 47.2% (95% CI: 35.3-59.3), with CR in 33.3% (95% CI: 22.7-45.4) [Cohort A: ORR: 53.6% (95% CI: 33.9-72.5), CR: 46.4% (95% CI: 27.5-66.1); Cohort B: ORR: 51.7% (95% CI: 32.5-70.6), CR: 34.5% (95% CI: 17.9-54.3)]
- Overall median DOR (mDoR) was not reached (**Figure 3**). The 95% CI was 12.0-NA months, with a median duration of follow-up of 15 months (95% CI 9-18 months). 77% of pts had a DoR >9 months; 66% were still responding at 12 months
- The mPFS was 2.8 months (95% CI 1.5-7.3 months); the median duration of follow-up was 2.8 months (range: 1.4-5.4) [Cohort A: mPFS: 5.1 months (95% CI: 1.4-NA); Cohort B: mPFS: 4.6 months (95% CI: 1.4-13.4)]
- ORR in relevant subgroups is shown in **Figure 4**
- In heavily pre-treated (≥2 prior systemic cancer therapies) not primary refractory pts, who received the Q3W regimen, (19 pts), ORR was 42.1% (95% CI: 20.3-66.5) and CR was 31.6% (95% CI: 12.6-56.6). mDoR was NA in these pts (95% CI 11.8-NA)

Figure 3: Duration of Response in DLBCL*



*Efficacy evaluable population

Figure 4: Overall Response Rate*



*By main baseline characteristics (efficacy evaluable DLBCL population). Cell of origin was performed by mRNA expression using HTG's EdgeSeq DLBCL assay. CI: confidence interval; ORR: overall response rate; QW: weekly regimen; Q3W: 3-weekly regimen; ABC: activated B-cell; GCB: Germinal center B-cell

PHARMACOKINETICS

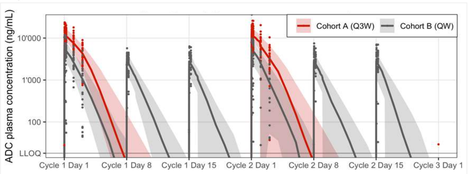
- Nara PK was assessed during treatment in Cohort A (Q3W) and Cohort B (QW) **(Figure 5).** Maximal concentrations (C_{max}) are in agreement with the dose levels administered
- As expected, Q3W resulted in a higher C_{max}, while concentration levels were better sustained with the QW regimen
- PK of DM1 and RTX was also assessed:
  - Plasma C_{max} of DM1 and catabolites ranged between 0.1-3.5 µmol/L, indicative of acceptable systemic release of the cytotoxic moieties[7]
  - RTX levels in circulating plasma in both study regimens were similar to those previously reported for RTX[8]

REFERENCES

1. Deckert J *et al.*, Blood 2013;122:3500-10. **2.** Hicks SW *et al.*, Neoplasia 2017;19(9):661–71. **3.** Stathis A *et al.*, Invest New Drugs 2018;36(5):869-76. **4.** Cheson B *et al.*, J Clin Oncol 2014;32:3059-67. **5.** Cobert AM *et al.*, Ther Adv Drug Safety 2020;11:1-8. **6.** Kowalczyk L *et al.*, Breast Care 2017;12:401-8. **7.** Li C *et al.*, Clin Pharmacokinet 2017;56:1069-80. **8.** Candelaria M *et al.*, Cancer Chemother Pharmacol 2018;81(3):515-27. **9.** Liang M *et al.*, Cytometry Part B 2016;90B:117-127

ABSTRACT #244

Figure 5: Nara PK

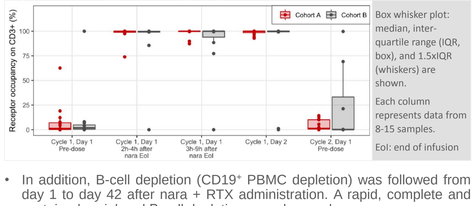


Antibody drug conjugate (ADC) plasma concentration profiles over cycles 1 and 2. ADC was quantified in human plasma using a bridging ligand-binding ELISA assay. On Day 1, 5 PK samples were collected between pre-dose and 9 hours post nara infusion. Individual dots: observed concentrations; lines and shaded areas: median and 95% CI of population PK model predictions

TARGET EXPRESSION AND PHARMACODYNAMICS

- CD37 and CD20 expression were assessed by IHC in pretreatment tumor samples. CD37 was assessed in 74 DLBCL samples (not present in 67 samples [90.5%]). CD20 was assessed in 75 DLBCL samples and was found to be present in 72 (96%). These high expression frequencies are in line with previous reports[1] and in most pts expression levels were high
- Receptor occupancy (RO, nara binding on CD37) was obtained using flow cytometry[9] on CD3⁺ PBMCs. A rapid and maximal (100%) RO was observed 2 hrs and 24 hrs after nara administration in both cohorts **(Figure 6)**. At day 21, RO was back to basal level

Figure 6: Receptor Occupancy



Box whisker plot: median, inter-quartile range (IQR, box), and 1.5xIQR (whiskers) are shown.
Each column represents data from 8-15 samples.
EoI: end of infusion

- In addition, B-cell depletion (CD19⁺ PBMC depletion) was followed from day 1 to day 42 after nara + RTX administration. A rapid, complete and sustained peripheral B-cell depletion was observed.

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CONCLUSIONS

- The safety profile of nara + RTX was tolerable and manageable with mainly hematological AEs, as expected for B-cell depleting therapies
  - Only 8 patients (8%) discontinued nara + RTX treatment due to an AE
  - Very few cases of liver enzyme elevations or neuropathy were recorded
- Both Q3W and QW regimens led to full CD37 target engagement
- The combination of nara + RTX resulted in 44.7% ORR and 31.6% CRR in efficacy-evaluable DLBCL patients
  - In both cohorts A (Q3W) and B (QW), ORR was 50%; CRR was 43.3% in cohort A and 33.3% in cohort B
  - Median Duration of Response (DoR) was not reached; 66% of responders had a DoR >12 months
- Nara + RTX could represent a new treatment option for patients with relapsed/refractory DLBCL, including heavily pre-treated patients

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