Exposure-response of different dosing schedules of naratuximab emtansine in combination with rituximab in Non Hodgkin's lymphoma

Axel Facius(2), Marie-Claude Roubaudi-Fraschini(1), Antoine Attinger(1), Sandrine Micallef(1), Sandeepreddy Bommineni(1), Mariola Dymkowska(1), Gezim Lahu(2), Elisabeth Rouits(1)
(1)Debiopharm International SA, (2)thinkQ2

BACKGROUND

- **Naratuximab emtansine** (nara, Debio 1562, formerly IMGN529) is an antibody-drug conjugate (ADC) consisting of a humanized anti-CD37 monoclonal antibody, K7153A, conjugated via a thioether-based linker to the cytotoxic maytansinoid, DM1.
- **CD37**, a surface marker of B-lymphocytes, is highly expressed in Non-Hodgkin's Lymphoma (NHL), including diffuse large B-cell lymphoma (DLBCL)[1].
- In **preclinical NHL models**, nara showed strong antitumor activity that was further enhanced by the co-administration of rituximab (RTX). Nara internalization was 2- to 3-fold higher when combined with RTX[2].
- A **Phase 1** monotherapy study demonstrated a good safety profile and encouraging signs of clinical efficacy, with 22% overall response rate (ORR) in DLBCL patients (NCT0153471)[3].
- A **Phase 2** study evaluated the efficacy and safety of nara in combination with RTX in NHL patients (NCT02564744)[4]. Nara was administered in 3-week cycles at the dose of 0.7 mg/m^2 every 3 weeks (Q3W) or at 0.4/0.2/0.2 mg/m^2 weekly (QW) together with RTX 375 mg/m^2 once every 3 weeks.
- **PK disposition** of nara in monotherapy was initially explored in a population PK model (n=49) with data from the Phase 1 study. Further, nara PK in combination with RTX was evaluated in 98 patients. Additionally, pharmacokinetics/pharmacodynamics (**PK/PD**) and **exposure-response (E-R)** were explored in DLBCL patients for the two dosing schedules.

OBJECTIVE

- Here we report the E-R evaluation by population modeling approach of two different dosing schedules of nara when combined with RTX, based on Phase 2 safety and efficacy data. Moreover, an exploration of nara receptor occupancy (RO) on CD37-expressing peripheral blood mononuclear cells (PBMC) and the subsequent pharmacodynamic (PD) PBMC depleting effects of nara in combination with RTX is reported

METHODS

PK: A population PK model using Nonlinear Mixed Effects Modelling (NONMEM v7.3.0)[5] approach was initially developed for nara total ADC administered as a single agent, based on 49 patients (937 PK observations). As illustrated in figure 1 below, it is a one-compartment model with intravenous dosing and a dual elimination process consisting of a constant linear clearance (CL) and a concentration-dependent saturable clearance (K_M, V_{max}), using a Michaelis-Menten process.

The ADC elimination rate from plasma depends on the ADC concentration: $\frac{d}{dt}ADC(t) = \frac{-V_{max}}{K_M + ADC(t)/V} \cdot ADC(t)/V$

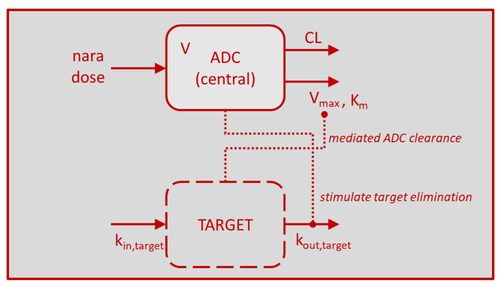

Figure 1: PK disposition model for nara

Amount of total ADC in mg ADC(central)
Volume of distribution V in L
Maximum elimination velocity V_{max} in mg/h
Michaelis-Menten constant K_M which is the concentration of ADC when the elimination velocity is at 50% of V_{max}

To adapt the model to the nara + RTX combo regimen (98 patients [n=69 Q3W; n=29 QW]; 2297 PK observations), an initial exploratory approach consisted in evaluating the impact of RTX as a covariate in the model.

PD: CD19+ B cell sub-populations of PBMCs were analyzed by flow cytometry to determine the extent of depletion induced by nara and RTX. The relationship between circulating levels of nara and cell depletion (CD19+ and CD3+) was evaluated graphically. The data from 15 and 14 patients entered this analysis for Q3W and QW regimen, respectively.
The fraction of the CD37 molecules occupied by nara in individual lymphocyte populations was determined. The % of receptor occupancy (RO) was assessed by flow cytometry on the CD3+ and CD56+ sub-populations.

E-R: In a subset of DLBCL patients, a series of PK/PD models were developed to link various exposure parameters with either efficacy or safety response variables (n=76 for efficacy; n=80 for safety). Exposure parameters were based on the individual nara ADC PK parameter estimates obtained from the population PK analysis. These parameters were used to predict individual PK profiles for each treatment cycle. For each patient, cumulative AUC over each cycle (AUC_{cycle}), maximal concentration (C_{max}) and time above a threshold concentration were derived.

RESULTS

PK: The introduction of RTX as covariate in the monotherapy model was not sufficient to describe reasonably well the phase 2 data in combination. Therefore, a dedicated model for nara combined with RTX was developed. The combo model had two levels of nested random effects to characterize the between subject variability (BSV) and the residual variability (RV). BSV was based on a log-normal distribution of random effects. For RV, a mixed additive and proportional error was used. Because of the substantial amount of BLQ data, the M3 method was implemented[5].
An exploratory evaluation of covariates showed that V would be mildly decreased (-24%) in females and that larger tumour size at baseline would weakly increase maximal enzyme velocity (V_{max}). Furthermore, some subjects appeared to have a much faster non-linear elimination, independent from the baseline tumour size covariate. No additional appropriate covariate correlation could be found. Thus, the model estimated an anonymous covariate with 2 different V_{max}, *ie* «normal V_{max}» and «high V_{max}».
Table 1 shows parameters estimates of the final model. As illustrated in Figure 2, this model described reasonably well the observed nara ADC data for both QW and Q3W regimens.

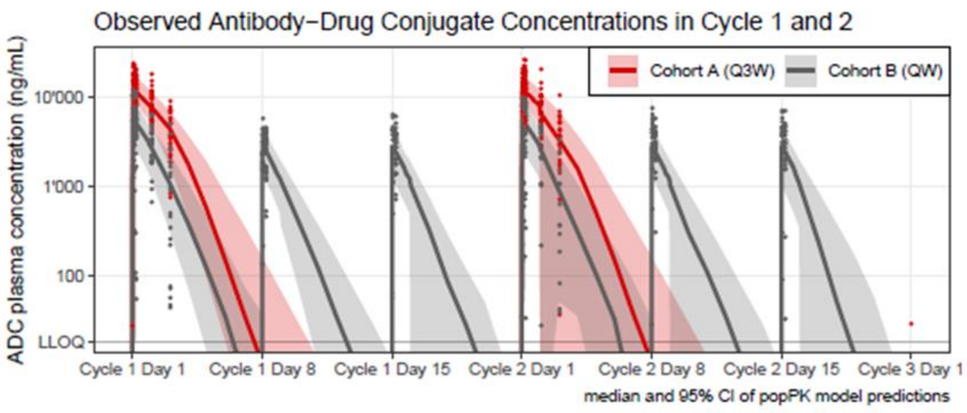

Figure 2: Observed nara ADC concentrations in cycle 1 and 2. Dots represent observed concentrations. Lines and shaded areas represent median model simulations and 95% model-predicted concentrations, respectively.

Parameter	Role	Estimate
V	Typical value (L)	5.03
	Gender effect for females (%)	-24
	BSV	0.0525
V_{max}	Typical value (mg/h)	1.83
	Tumor size at baseline effect (power exponent)	0.0635
	P (V_{max}=normal) (%)	93.1
	Ratio high/normal	9.72
	BSV	0.0718
K_M	Typical value (ng/mL)	26.2
Residual variability	Proportional error (%)	22.9
	Additive error (ng/mL)	1278

Table 1: Parameter estimates of the final PK model

PD: Receptor occupancy (RO) and pharmacodynamic effects of nara + RTX were analyzed in blood samples from 15 and 14 participants in Q3W (cohort A) and QW (cohort B) regimens, respectively. Maximum (100%) RO was observed on CD3+ (figure 3) and CD56+ (not shown) cells 2-4 h after nara end of infusion (EoI). In both cohorts, a profound and sustained B cell depletion was observed (figure 4). Because of the rapid CD19+ depletion, RO analysis on CD19+ B cells was not possible.

PK/PD: The relationship between PK disposition and PD data was explored graphically. Data suggested a trend between circulating levels of nara (time-matched ADC concentrations, figure 5 and GeoMean AUC_{cycle}, figure 6) and the extent of CD19+ B-cell depletion, whereas CD3+ T cell levels remained unchanged irrespective of the concentration.

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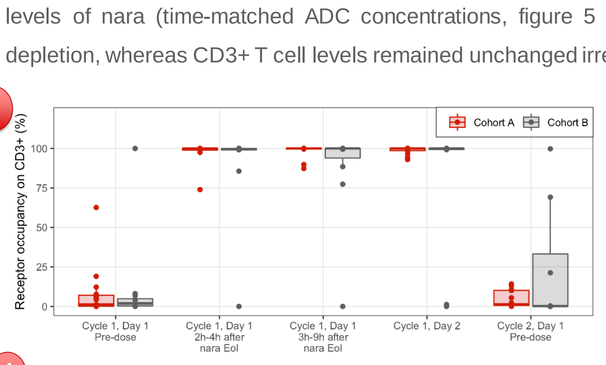

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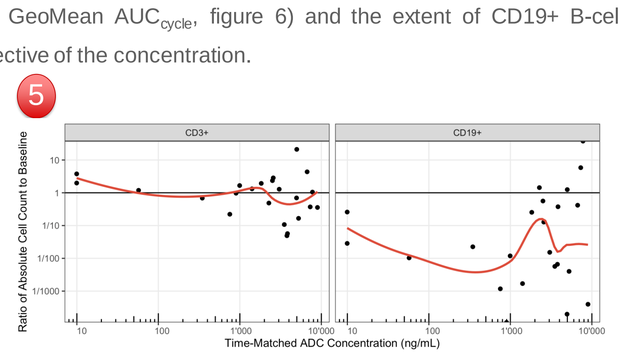

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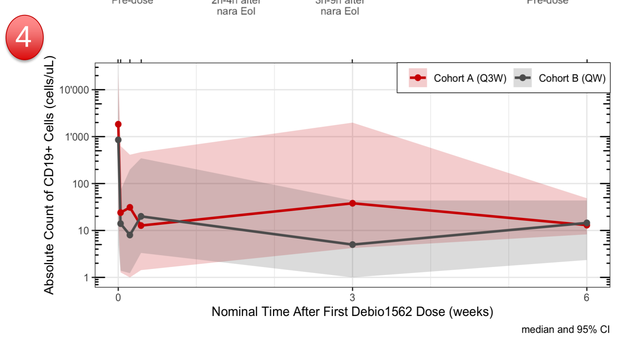

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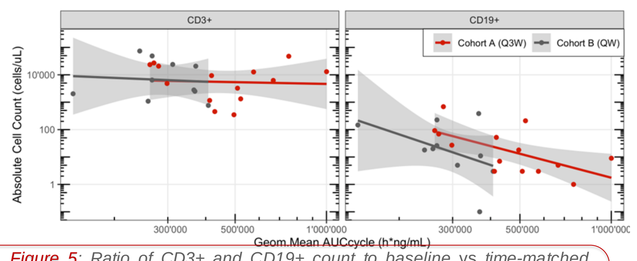

Figure 3: RO on CD3+ at cycle 1 and cycle 2. Dots are observed individual receptor occupancy levels
Figure 4: Absolute count of CD19+ vs time after first nara dose. Solid lines and dots are median observed counts of CD19+ cells. Shaded areas are 95% prediction intervals of observed counts of CD19+ cells.
Figure 5: Ratio of CD3+ and CD19+ count to baseline vs time-matched ADC concentration. Dots are observed individual absolute cell count
Figure 6: Absolute cell count vs AUC_{cycle}. Dots are observed individual absolute cell counts. Solid lines are linear regression. Shaded areas are 95%CI of the linear regression.

E-R: Finally, relationships between PK disposition and efficacy and safety endpoints were explored. The endpoints and number of evaluable patients for these Exposure-Response explorations are listed in table 2.

Test	Overall	Q3W	QW
Responder	34/76 (44.7%)	19/46 (41.3%)	15/30 (50.0%)
Leukopenia	16/80 (20.0%)	8/50 (16.0%)	8/30 (26.7%)
Lymphopenia	14/80 (17.5%)	10/50 (20.0%)	4/30 (13.3%)
Neutropenia	44/80 (55.0%)	27/50 (54.0%)	17/30 (56.7%)
Thrombocytopenia	9/80 (11.2%)	4/50 (8.0%)	5/30 (16.7%)

Table 2: Number of evaluable patients for the E-R exploration. Number of patients/all patients (percent) for all response parameters, overall and by treatment schedule (0.7 mg/kg Q3W and 0.4/0.2/0.2 mg/kg QW

AUC_{cycle} was tested as the most relevant "Exposure" parameter to evaluate E-R for efficacy. A significant relationship between AUC_{cycle} and "Response" (expressed as responders, *i.e.* subjects with either a partial or a complete response) was identified for the QW regimen (*p=0.021*) but not for the Q3W regimen (*p=0.888*), as shown in Figure 7.

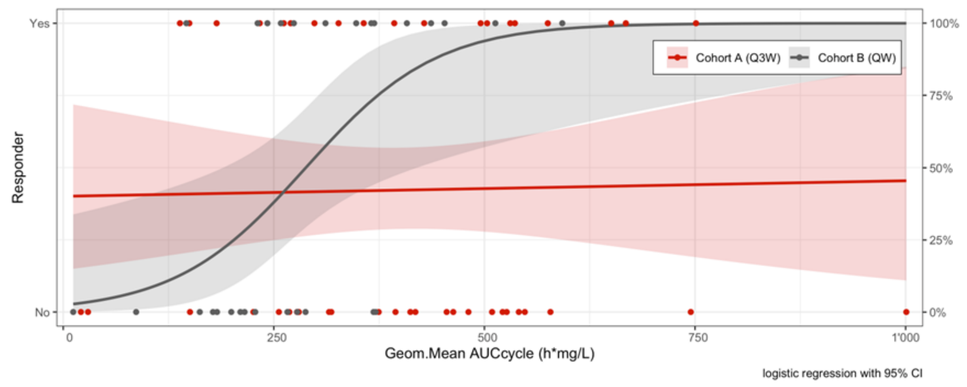

Figure 7: E-R relationship evaluated as logistic regression of observed individual BOR (Yes=complete or partial response; No=stable or progressive disease) vs AUC_{cycle} (AUC over a 3-week cycle). "Exposure" = geometric mean AUC_{cycle}; Response = Individual BOR. Solid line = logistic regression; shaded area = 95% CI of the logistic regression.

For E-R related to safety, data (not shown) suggested that for both QW and Q3W regimens, if a concentration threshold of 2000 ng/mL is reached during 10% of time of a 3-week cycle, there is a 50% risk of severe neutropenia.

ACKNOWLEDGEMENTS

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REFERENCES

[1]**Deckert J** *et al.*, Blood 2013; [2]**Hicks SW** *et al.*, Neoplasia 2017; [3]**Stathis A** et al., Invest new Drugs 2018; [4]**Levy M** *et al.*, ICML 2021; [5]**Beal SL** *et al.*, NONMEM User's Guides (1989-2017)

DISCUSSION AND CONCLUSIONS

As anticipated for an ADC, PK disposition of nara is characterized by a non-linear elimination. This non-linear process is substantially different when combined with rituximab. This might be attributed to the increased CD37 internalization process observed *in vitro* when nara is combined with anti-CD20 such as rituximab[4]. Development of anti-drug antibodies may explain, at least in part, the characterization of an accelerated V_{max} in a limited number of patients. However, further exploration is warranted provided the early onset of this observation.

When combined with rituximab every 3 weeks, both the QW and Q3W dosing regimens of nara are driving a profound and sustained CD19+ B cell depletion, evidencing the combined biological activity of nara and rituximab. The contribution of nara is further supported by a trend observed graphically between nara exposure and the extent of CD19+ B cell depletion.

In the population of patients evaluated, an E-R relationship analyses suggested that the risk of neutropenia may be increased when nara concentrations > 2000 ng/mL for both Q3W and QW regimens. In addition, increased nara exposure (expressed as AUC_{cycle}) was correlated with increased BOR in the QW regimen.

PK/PD and E-R relationships described herein support the clinical benefit of nara observed in this DLBCL and other NHL patient populations[1].

CONTACT

Debiopharm International S.A.,
Lausanne, Switzerland.
www.debiopharm.com
elisabeth.rouits@debiopharm.com

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