

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

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Introduction/Objectives: Naratuximab emtansine (nara) is an antibody-drug conjugate (ADC) comprised of a humanized anti-CD37 monoclonal antibody conjugated to the cytotoxic compound maytansinoid DM1. A phase 2 study (NCT02564744) evaluated the efficacy and safety of nara in combination with rituximab in NHL patients¹. Nara was administered as 3-week cycles at the dose of 0.7 mg/m² every 3 weeks (Q3W) or at 0.4/0.2/0.2 mg/m² weekly (QW) together with rituximab 375 mg/m² once every 3 weeks. PK disposition of nara in combination with rituximab was evaluated in 98 patients. Additionally, PK/PD and exposure-response (E-R) were explored in DLBCL patients (n=29 and n=76, respectively) for the two dosing schedules.

Methods: A population PK model using Nonlinear Mixed Effects Modelling (NONMEM v7.3.0)² was developed for nara total ADC based on data from 98 patients treated in combination with rituximab. This model was derived from a model previously developed for nara ~~total~~ ADC administered as single agent⁴. It was a one-compartment model with intravenous dosing and non-linear elimination using a Michaelis-Menten process (simplified target-mediated drug disposition process). In parallel, the relationships between nara exposure and CD19+ B cell depletion as well as receptor occupancy (RO) on CD3+ T cells were evaluated graphically. Finally, a series of exposure parameters (period of time with nara concentration above a threshold; C_{max} ; AUC) were correlated with response parameters (neutro-, leuko-, lympho- or thrombocytopenia for safety; and best overall response (BOR) for efficacy) using logistic regression. Optimal thresholds were selected based on three goodness-of-fit parameters.

Results: PK: Simple covariate addition to the single-agent model did not permit to fit adequately the observations and specific PK model parameters had to be defined for nara in combination with rituximab. The typical parameters of the final model were V=5L (volume of distribution); V_{max} =1.83 mg/h and K_M =26.2 ng/mL (Michaelis-Menten parameters for the non-linear elimination). An accelerated V_{max} (~x10) was observed in 6 out of the 98 patients included in the analysis, as early as the first cycle.

PK/PD: Because maximal (100%) RO was reached at the end of the nara infusion for both regimens, no E-R assessment was performed for RO. A trend between nara plasma exposure (mean AUC_{cycle}) and the extent of CD19+ B cell depletion was graphically observed whereas for other lymphocyte populations (CD45+, CD3+, CD4+, CD8+) no relationship with nara was observed.

E-R: Time with nara concentration > 2000 ng/mL triggered an increased risk of neutropenia in Q3W and QW dosing regimens. In both regimens, a positive relationship (but not significant, $p=0.135$) between time with nara concentration > 1500 ng/mL and BOR was found. Interestingly, a significant relationship was identified between nara AUC_{cycle} and BOR for the QW regimen ($p=0.021$) but not for the Q3W regimen ($p=0.888$).

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 may evidence, at least in part, the increased CD37 internalization process observed *in vitro* when nara is combined with anti-CD20 such as rituximab⁴. 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, 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 appeared strongly correlated with increased BOR in the QW regimen.

PK/PD and E-R relationships described herein are supporting the clinical benefit of nara observed in this DLBCL and other NHL population of patients¹.

References: ¹Levy MY, *et al.* ICML 2021. Safety and efficacy of CD37-targeting naratuximab emtansine plus rituximab in DLBCL and other NHL – a phase 2 study.

²Beal SL, Sheiner LB, Boeckmann AJ and Bauer RJ, 2014, NONMEM User's Guides. (1989-2014) Icon Development Solutions, Ellicott City, MD, USA

³Stathis A, *et al.* Invest New Drugs. 2018 Oct;36(5):869-876. Safety, tolerability, and preliminary activity of IMG529, a CD37-targeted antibody-drug conjugate, in patients with relapsed or refractory B-cell non-Hodgkin lymphoma: a dose-escalation, phase I study.

⁴Hicks SW, *et al.* Neoplasia 2017 Sep;19(9):661-671. The antitumor activity of IMG529, a CD37 targeting antibody drug conjugate, is potentiated by rituximab in non Hodgkin lymphoma models.