Health-Related Quality of Life of Naratuximab Emtasine + Rituximab (N+R) in Second Line and Heavily Pre-Treated Patients with Relapsed/Refractory (R/R) Diffuse Large B-Cell Lymphoma (DLBCL): An Analysis of the Functional Assessment of Cancer Therapy Lymphoma (FACT-LYM) Measure and Mapped EQ-5D Values from a Phase II Trial

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Objectives

Evaluate the impact of Naratuximab Emtasine + Rituximab (N+R) on the health-related quality of life (HRQoL) and patient reported tolerability of R/R DLBCL patients using the FACT-Lym questionnaire and derive patient EQ-5D utilities using mapping algorithms between the two instruments.

Methods

FACT-Lym was administered in a Phase II single-arm trial of N+R to patients in two cohorts, on weekly and every-3-week dosing schedules, prior to treatment and at each subsequent cycle. The FACT-Lym questionnaire includes the Functional Assessment of Cancer Therapy – General (FACT-G), along with the GP5 item, "I am bothered by side effects of treatment" ["Not at all" (0) – "Very much" (4)]. It also contains a lymphoma-specific subscale (LymS), which generates a score of 0-60, with higher scores indicating better HRQoL.

We pooled both cohorts to compare changes in the FACT-Lym from baseline to last HRQoL assessment up to and including end of treatment (EOT) between responders (complete/partial tumour response) and non-responders.

First, the un-adjusted change scores among the different subscales of the FACT-Lym questionnaire were estimated for responders from baseline to Cycle 6 and from baseline to EOT to allow an initial comparison with important differences reported in the literature for this questionnaire [1-3].

Second, empirical cumulative distribution function (eCDF) curves were generated, showing the cumulative percentage of the cohort having a given change or higher from baseline to EOT (Probability on Y axis, PRO change score on X axis). The curves were stratified by responder (CMR/CR, PMR/PR vs. NMR/SD, PMD/PD).

Then, a time to deterioration analysis was performed. We used the RCI (reliable change index) with 95% confidence interval [4, 5], and a "likely change index" (LCI) with 70% confidence interval [6], to define individual-level thresholds for deterioration. LCI = RCI but using critical value for the 70% confidence level (i.e., p-value of 0.30). The Kaplan Meier curves were stratified by responders vs. non responders and plotted for each dimension of the questionnaire

The first instance of decrease in PRO score from cycle 1 to post-baseline cycle that meets or exceeds the deterioration threshold counted as an event. Patients with no observed event were censored at final PRO assessment timepoint (including EOT assessment). Log-rank test used to determine if there was a significant difference between the two curves.

All input values for RCIs and LCIs were based on data from a sample larger than this study [2]

Finally, published equations [6] that map the FACT–G Physical, Emotional, and Functional well-being scales to the EQ-5D utility index were employed on the trial data. Different mapping algorithms reported were explored, based on either Ordinary Least Square (OLS) or censored least absolute deviations (CLAD) methods, using different dimensions of the FACT questionnaire as predictors. Most models demonstrated a low effect size and the model with the best effect size in OLS regressions was selected for our analysis (R^2 = 0.45).

Results

The assessment of score changes from baseline to last HRQoL assessment up to and including EOT, demonstrated that among responders, there was an improvement on the Lymphoma Subscale, TOI, and FACT-Lym Total score (***Table 1***). Both the RCI and LCI analyses demonstrated a very significant change, superior to the range observed in prior studies, for FACT-G, TOI, FACT-Lym and Total scores of the questionnaire (***Table 2***).

Table 1. Score change from Baseline to Cycle 6 and EOT among Responders

	Important Difference from lit [1-3]	Responder at baseline (mean, SD) (N=26)	Change to C6 (mean, SD), Responders (N=24)	Change to Last HRQoL[a] (mean, SD), Responders (N=26)
Physical Well-being	3-5	21.8 (5.7)	0.3 (5.5)	0.4 (4.7)
Social Well-being	3-5	21.5 (5.3)	-0.8 (5.0)	-1.0 (5.5)
Emotional Well-being	3-5	17.0 (4.3)	0.8 (3.4)	0.2 (3.7)
Functional Well-being	3-5	16.2 (5.7)	0.4 (5.3)	0.5 (5.2)
FACT-G	3-7	76.4 (14.8)	0.9 (13.2)	-0.1 (12.5)
Lymphoma Subscale	3-5	45.5 (9.5)	2.7 (6.6)	3.3 (6.3)
Trial Outcome Index	6-9	83.5 (17.2)	3.5 (14.5)	4.1 (13.0)
FACT-Lym Total	7-14	121.9 (21.9)	3.6 (18.1)	3.3 (16.9)

[a] Up to and including EOT

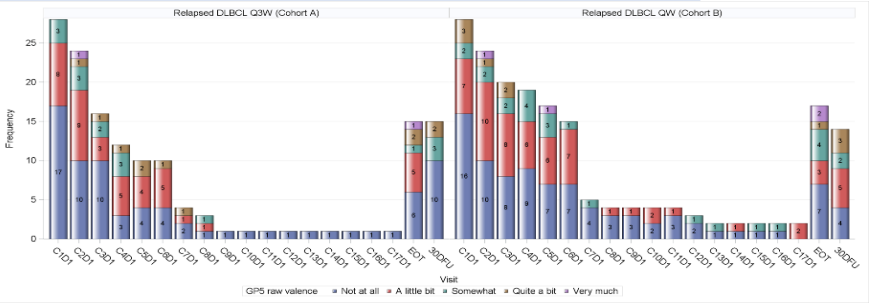
Table 2. RCI and LCI levels per FACT dimension

	Min – Max from Lit	RCI [a]	LCI [b]
Physical Well-being (PWB)	3 - 5 pts	5 pts	3 pts
Social Well-being (SWB)	3 – 5 pts	5 pts	3 pts
Emotional Well-being (EWB)	3 – 5 pts	5pts	3 pts
Functional Well-being (FWB)	3 – 5 pts	6pts	3 pts
FACT-G	3 – 7 pts	14 pts	8 pts
Lymphoma Subscale	3 – 5 pts	10 pts	6 pts
Trial Outcome Index	6 – 9 pts	13 pts	7 pts
FACT-Lym Total	7 – 14 pts	18 pts	10 pts

[a] *Based on 95% confidence;* [b] *Based on 70% confidence / RCI, LCI values based on Hlubocky et al. [2]*

Analysing the GP5 item, "*I am bothered by side effects of treatment*" of the questionnaire, it is demonstrated (***Figure 1***) that N+R was very well tolerated by patients both on the Every 3 weeks (A) and Weekly (B) administration cohorts, with the vast majority of patients reporting not at all or minimal bother from side effects. At EOT, only 1 (9%) responder and 4 (19%) non-responders reported high side effect bother ("very much"/"quite a bit") on the GP5 item.

Figure 1. GP5 item "I am bothered by side effects of treatment" – Responses per cycle and by cohort



In ***Figure 2*** (eCDF curves), it is shown that at the individual level by last HRQL assessment (up to and including EOT), 31% (8/26) of responders vs. 12% (3/26) of non-responders had improvement at the individual level of ≥6 points on the LymS (p=0.17). For the FACT-Lym Trial Outcome Index (TOI: FACT-G physical and functional well-being + Lyms), 38% (10/26) of responders vs. 8% (2/26) of non-responders had a significant improvement of ≥7 points (p=0.02). Finally, on the Fact-Lym Total score, 35% (9/26) of responders vs. 4% (1/26) of non-responders had a significant improvement of ≥10 points (p=0.01). In the time to deterioration analysis (***Figure 3***), Responders had a significantly lower probability of deterioration on the LymS, TOI and Total Score across the trial follow-up (p<0.001).

Figure 2. eCDF for Lymphoma subscale, TOI and FACT-Lym

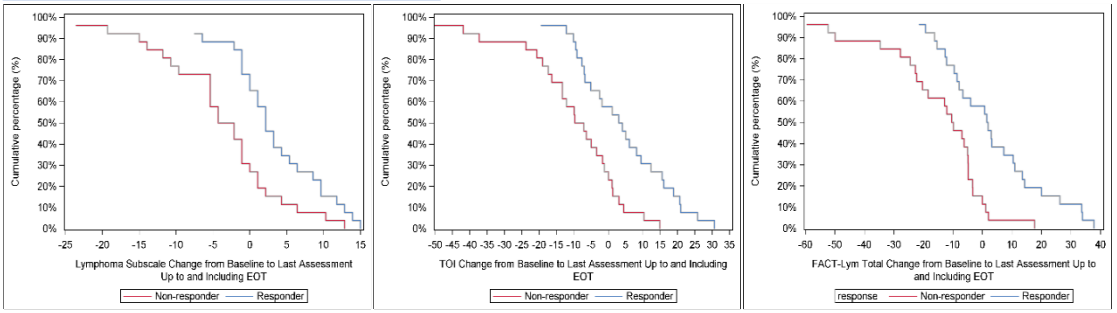
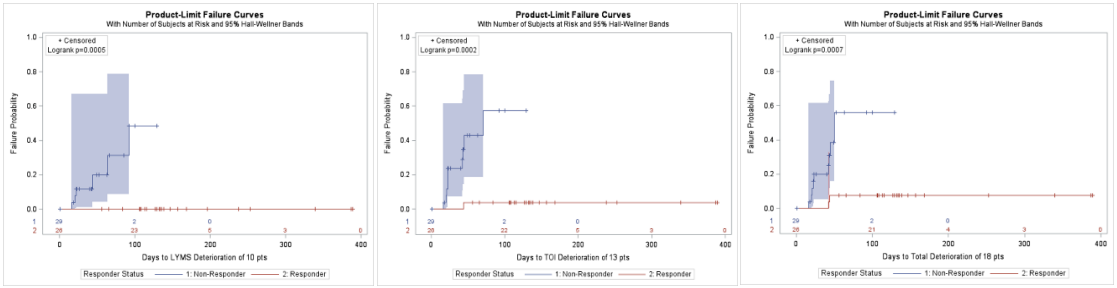


Figure 3. Time to deterioration curves for LYM, TOI and Total score



The overall EQ-5D mapped utility for the entire cohort was 0.74 (CI: 0.45 – 0.90) with 0% on either ceiling or floor values and a very smooth distribution across the 25th and 75th percentiles. This value is very much aligned with other EQ-5D utility values reported in the literature in similar treatment line cohorts in this disease area, treated with latest innovative combination therapies.

At baseline, the mean estimated EQ-5D utility index scores for responders vs. non-responders were 0.78 vs. 0.73, while at EOT these were 0.77 vs. 0.67, demonstrating that responders had a very similar if not superior quality of life compared to similar patients in other studies and they also maintained their quality of life along the treatment pathway.

Conclusions

The rigorous analysis of the PRO data demonstrated that N+R responders were more likely to improve and less likely to decline in their HRQL. At the same time, side effect bother was not increased for N+R responders. The use of the GP5 item in a Phase II clinical study to examine side effect bother is an innovative assessment of patient-reported tolerability of cancer therapy in a safety setting. The mapped EQ-5D value as well as the comparability of improvement from the literature also demonstrated that N+R combination performs equally well if not better in terms of quality of life, to other similar therapies in this disease area. These values are strong signals of N+R efficacy and favourable tolerability.

References

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