Association between quality of response and outcomes in patients with newly diagnosed mantle cell lymphoma receiving VR-CAP versus R-CHOP in the phase 3 LYM-3002 study

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INTRODUCTION

- Mantle cell lymphoma (MCL) is an aggressive and generally incurable form of non-Hodgkin lymphoma (NHL) which accounts for approximately 5–6% of new NHL cases in the USA.[1,2]
  - Patients with MCL have a poor prognosis, with a median survival of 4–5 years.[3]
- For newly diagnosed MCL patients who are considered ineligible for intensive therapy and stem cell transplantation (SCT) (e.g. due to age, comorbidities), rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) is a standard of care.[4–6]
  - Complete response (CR) rates of up to 48% have been demonstrated with R-CHOP; however, progression-free survival (PFS) with R-CHOP is limited (median 16.6 months).[7]
- Based on the randomized, phase 3, LYM-3002 study (NCT00722137), which evaluated the efficacy and safety of bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone (VR-CAP) vs R-CHOP in newly diagnosed MCL patients considered ineligible for SCT, bortezomib has been approved for the treatment of newly diagnosed and relapsed MCL in both the USA and Europe.[8,9]
- Results from the primary analysis of LYM-3002 have been published previously[10] and are summarized in Table 1.
  - The study met its primary endpoint, demonstrating a 59% improvement in PFS by independent radiology review committee (IRC) assessment with VR-CAP vs R-CHOP (median 24.7 vs 14.4 months; hazard ratio [HR] 0.63; 95% confidence interval [CI] 0.50–0.79; P<0.001), and a 96% improvement in PFS by investigator assessment (median 30.7 vs 16.1 months; HR 0.51; CI 0.41–0.65; P<0.001).
  - Significant and clinically important improvements in secondary efficacy endpoints were also demonstrated with VR-CAP vs R-CHOP (Table 1).
  - The profile of adverse events (AEs) was as expected and AEs were manageable.
    - The most common grade ≥3 AEs were hematologic and included (VR-CAP vs R-CHOP): neutropenia (85% vs 67%), thrombocytopenia (57% vs 6%), and leukopenia (44% vs 29%).

Table 1. LYM-3002 study results (median follow-up 40 months; ITT population, N=487)[10]

	VR-CAP (n=243)	R-CHOP (n=244)	HR or OR§ (95% CI)	P-value
Median TTP, months				
By IRC	30.5	16.1	0.58 (0.45–0.74)	<0.001
By investigator	35.0	16.8	0.47 (0.36–0.60)	<0.001
Median TTNT, months	44.5	24.8	0.50 (0.38–0.65)	<0.001
OS				
Median duration, months	NR	56.3	0.80 (0.59–1.10)	0.173
At 4 years, %	64.4	53.9	–	–
CR*†¶ by IRC,				
Rate, %	53	42	1.29 (10.7–1.57)	0.007
Median duration‡, months	42.1	18.0	–	–
ORR* by IRC,				
Rate, %	92	89	1.03 (0.97–1.09)	n/s
Median duration¶¶, months	36.5	15.1	–	–

*n=229 (VR-CAP) and n=228 (R-CHOP); †Confirmed by evidence of BM clearance and LDH normalization; ‡CR rate defined as the proportion of patients achieving a CR or unconfirmed CR (CRu); §n=122 (VR-CAP) and n=95 (R-CHOP); ¶¶n=211 (VR-CAP) and n=204 (R-CHOP); §HR for TTP, TTNT, and OS; OR for response rates.
BM, bone marrow; ITT, intent-to-treat; LDH, lactate dehydrogenase; NR, not reached; n/s, not statistically significant; OR, odds ratio; OS, overall survival; TTNT, time to next treatment; TTP, time to progression.

RATIONALE

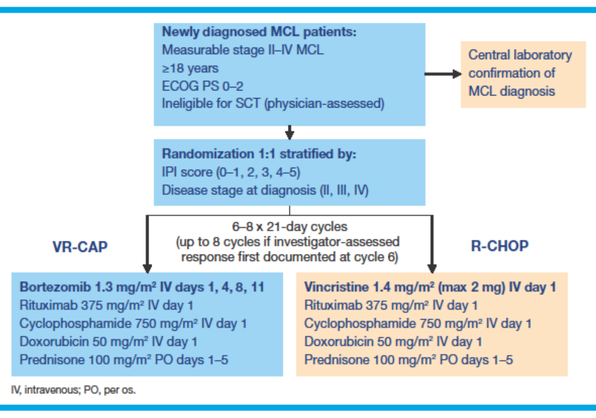
- This post-hoc analysis of the LYM-3002 study evaluated the association between the improved outcomes observed with VR-CAP vs R-CHOP and the quality of responses achieved.

METHODS

Study design and patient population

- Patients aged ≥18 years with newly diagnosed, measurable stage II–IV MCL, an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–2, and who were considered ineligible for SCT (as assessed by the treating physician), were eligible for enrollment in LYM-3002.
- Patients were randomized 1:1 (stratified by International Prognostic Index [IPI] score and disease stage) to receive 6–8 x 21-day cycles of VR-CAP or R-CHOP (Figure 1).

Figure 1. LYM-3002 study design



IV, intravenous; PO, per os.

Assessments

- Efficacy and response were assessed by blinded IRC review and investigator review, using modified International Workshop to Standardize Response Criteria for Non-Hodgkin's Lymphoma (IWRC) criteria.[11]
- Computed tomography scans were performed every 2 cycles (6 weeks) during treatment and every 6–8 weeks during follow-up (until progression, discontinuation, initiation of alternate therapy, or death).
- AEs were graded per National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE) v3.0.

Endpoints

- This post-hoc analysis assessed the following outcomes:
  - PFS
  - Duration of response (DOR)
  - TTNT.
- Outcomes were stratified by response category (CR/CRu and partial response [PR]) and Mantle Cell Lymphoma International Prognostic Index (MIPI) risk status.
  - A sensitivity analysis was also conducted looking at CR and CRu as individual categories.
- Depth of response was also evaluated by measuring the maximum reduction in lymph node measurement from baseline, expressed as the sum of the product of the diameter (SPD).
- In this analysis, response, DOR, and PFS were all based on IRC assessment.

Statistical analyses

- Time-to-event outcomes were estimated using Kaplan-Meier methodology, with stratified log-rank tests and Cox models (alpha=0.05, two-sided) used for inter-arm comparisons.
- The Cochran-Mantel-Haenszel Chi-squared test was used for response rate comparisons.

RESULTS

Patients

- Between May 2008 and December 2011, 487 (243 VR-CAP; 244 R-CHOP) patients from 128 centers in 28 countries were enrolled in LYM-3002.
  - 457 (229 VR-CAP; 228 R-CHOP) patients were response-evaluable, of whom 415 acheived either CR or PR and are included in the present analysis.
- In this overall population, patient demographic and baseline characteristics were generally well balanced between the two arms (Table 2).

Table 2. Patient demographics and baseline characteristics (ITT population, N=487)

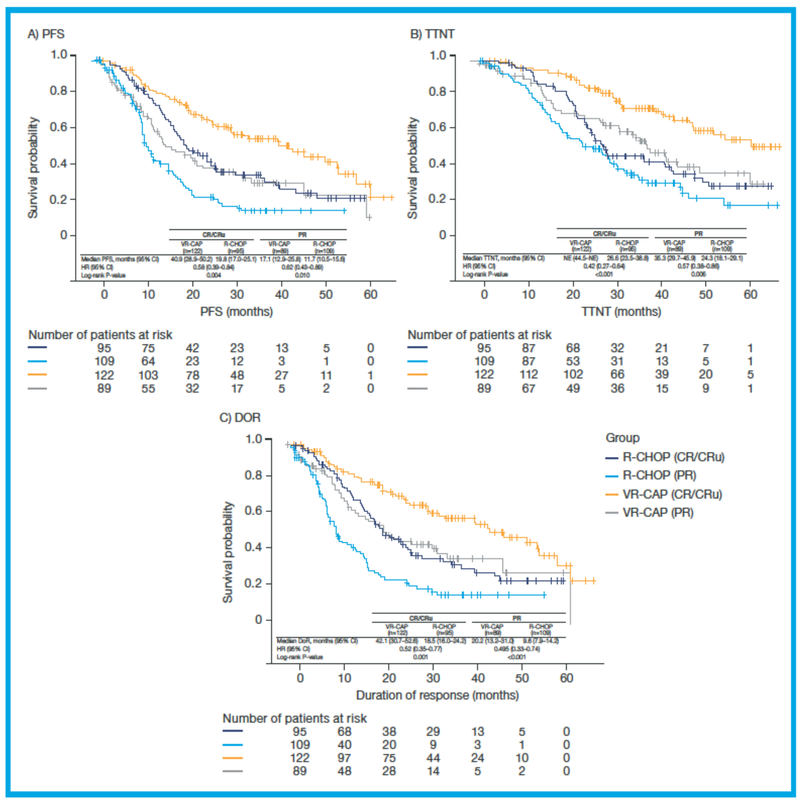
	VR-CAP (n=243)	R-CHOP (n=244)
Median age, years (range)	65 (26–88)	66 (34–82)
Male, n (%)	178 (73)	182 (75)
Race, n (%)		
White	151 (62)	172 (71)
Asian	88 (36)	68 (28)
Black/African American	3 (1)	0
Other	1 (<1)	4 (2)
Disease stage at diagnosis,* n (%)		
II / III / IV	12 (5) / 49 (20) / 182 (75)	16 (7) / 42 (17) / 186 (76)
ECOG PS, n (%)†		
0 / 1 / 2	111 (46) / 101 (42) / 31 (13)	85 (35) / 127 (52) / 31 (13)
IPI score (risk category), n (%)		
0–1 (low)	38 (16)	38 (16)
2 (low–intermediate)	75 (31)	71 (29)
3 (high–intermediate)	84 (35)	88 (36)
4–5 (high)	46 (19)	47 (19)
MIPI risk status, n (%)‡		
Low / intermediate / high	76 (31) / 96 (40) / 71 (29)	70 (29) / 93 (38) / 80 (33)
MIPIb risk status, n (%)‡		
Low / intermediate / high	23 (14) / 74 (45) / 66 (40)	23 (14) / 72 (44) / 69 (42)
Ki-67 status, n (%)¶		
Positive / negative	84 (52) / 79 (48)	82 (50) / 82 (50)
Elevated LDH, n (%)	88 (36)	86 (35)
Bone marrow involvement, n (%)	165 (68)	171 (70)

Source: Robak et al, 2015[10] and data on file.
*American Joint Committee on Cancer NHL disease staging system; †Data missing for n=1 in the R-CHOP arm (n=243 VR-CAP; n=243 R-CHOP); ‡Assessed in Ki-67-evaluable patients (n=163 VR-CAP; n=164 R-CHOP); ¶Based on a cut-off of 10% Ki-67 expression on an ordinal scale.
MIPIb, MIPI with biologic component.

Outcomes stratified by response category

- Time-to-event outcomes by response category (CR/CRu and PR) are shown in Figure 2.
- PFS was longer with VR-CAP versus R-CHOP in patients achieving CR/CRu (median 40.9 vs 19.8 months, respectively) and in those achieving PR (median 17.1 vs 11.7 months, respectively) (Figure 2A).
- TTNT was also longer with VR-CAP versus R-CHOP in patients achieving CR/CRu (median not evaluable [NE] vs 26.6 months, respectively) and PR (median 35.3 vs 24.3 months, respectively) (Figure 2B).
- In the VR-CAP arm, DOR was 42.1 months in patients achieving CR/CRu and 20.2 months in those achieving PR; in the R-CHOP arm, corresponding DOR were 18.5 and 9.6 months, respectively (Figure 2C).
- Notably, results across all time-to-event outcomes in patients receiving VR-CAP who achieved PR were similar to those seen in patients receiving R-CHOP who achieved CR/CRu.
- Median times to overall response (VR-CAP: 42 days, R-CHOP: 47 days) and to CR (VR-CAP: 82 days, R-CHOP: 84 days) were a little shorter in the VR-CAP arm than in the R-CHOP arm.

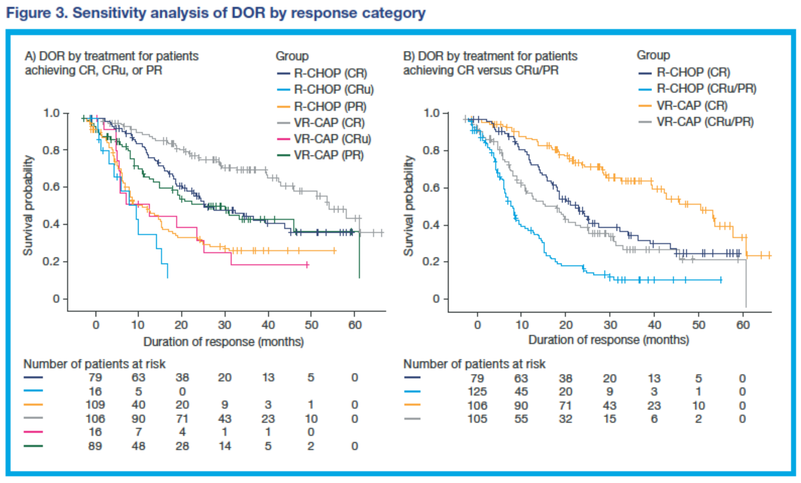
Figure 2. Time-to-event outcomes (VR-CAP vs R-CHOP) by response category



Outcomes stratified by response category: sensitivity analysis

- A sensitivity analysis of long-term outcomes, which considered CR and CRu separately, indicated that results in patients achieving CRu were closer to those reported in patients achieving PR than to those in patients achieving CR (Figure 3). As such, it may be more clinically relevant to group CRu with PR than with CR.

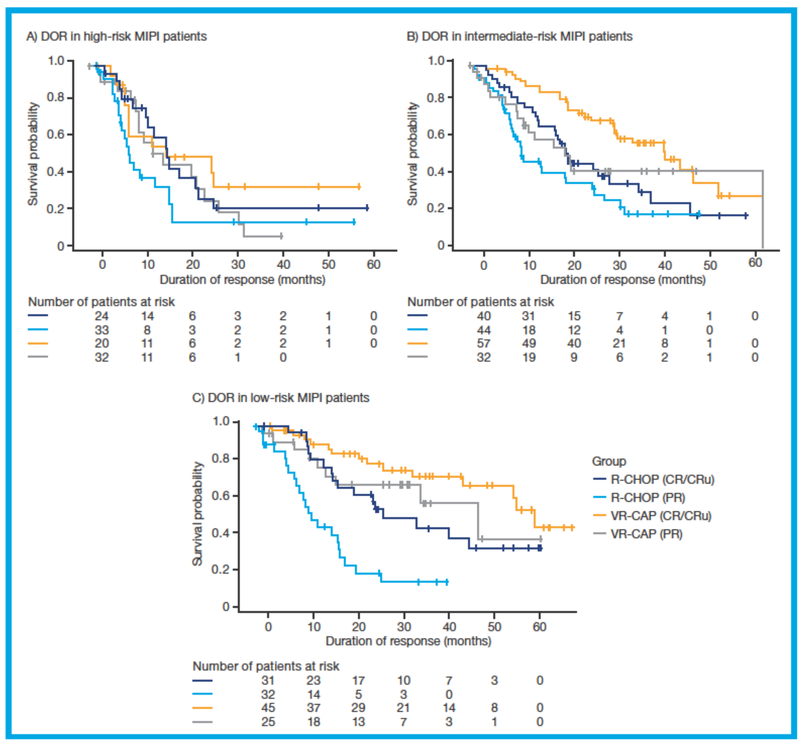
Figure 3. Sensitivity analysis of DOR by response category



Outcomes stratified by MIPI risk status

- Within the CR/CRu and PR response categories, prolongation of time-to-event outcomes (PFS, DOR, and TTNT) with VR-CAP vs R-CHOP were more pronounced in low- and intermediate-risk MIPI patients.
  - Treatment effect was less apparent in patients with high-risk MIPI scores.
- DOR according to MIPI risk status by response category is shown in Figure 4; similar curves were observed for PFS and TTNT (not shown).

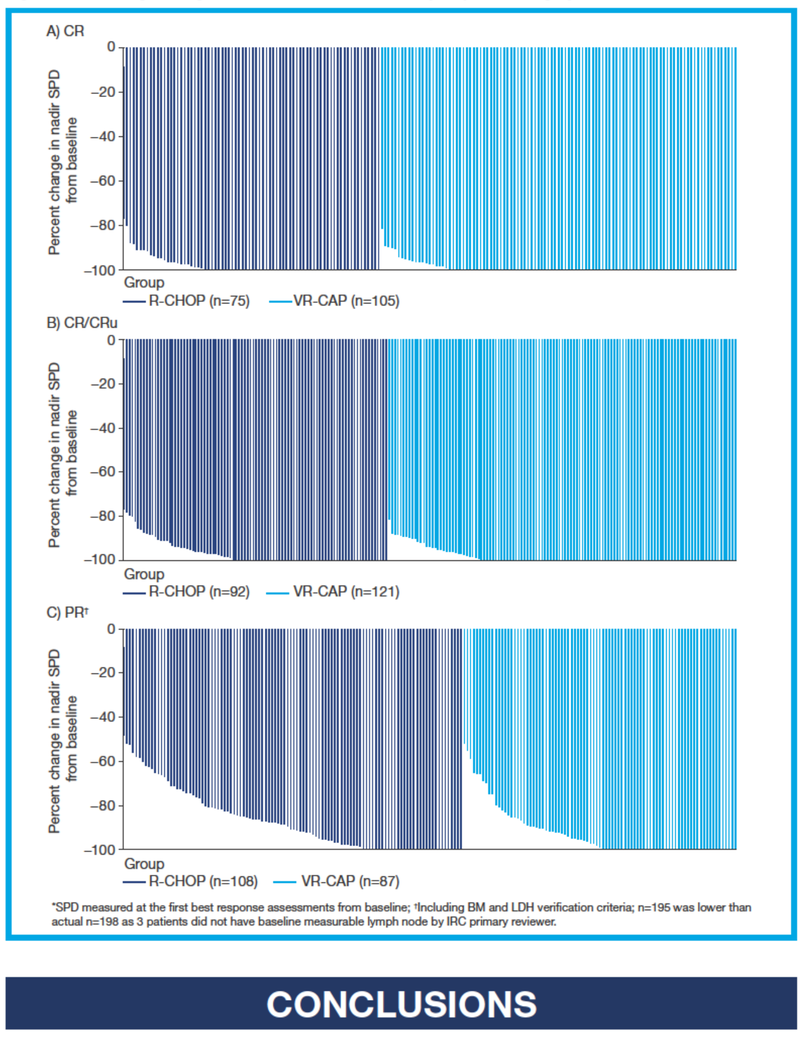
Figure 4. DOR according to MIPI risk status



Depth of response (SPD)

- Within each response category, the reduction in lymph node measurement was more pronounced in VR-CAP vs R-CHOP patients, with more VR-CAP patients achieving an SPD nadir of 0 vs R-CHOP (Figure 5).
  - In the CR response category (VR-CAP [n=105] vs R-CHOP [n=76]), 79% vs 68% of patients, respectively, achieved a nadir SPD of 0 (Figure 5A).
  - In the CR/CRu response category (VR-CAP [n=121] vs R-CHOP [n=92]), 72% vs 59% of patients, respectively, achieved a nadir SPD of 0 (Figure 5B).
  - In the PR response category (VR-CAP [n=87] vs R-CHOP [n=108]), 48% vs 28% of patients, respectively, achieved a nadir SPD of 0 (Figure 5C).

Figure 5. Percentage change in nadir SPD* from baseline by response category



*SPD measured at the first best response assessments from baseline; †Including BM and LDH verification criteria; n=195 was lower than actual n=198 as 3 patients did not have baseline measurable lymph node by IRC primary reviewer.

CONCLUSIONS

- Results for this post-hoc analysis suggest a greater duration and quality of response in patients receiving VR-CAP versus those receiving R-CHOP, both overall and when stratified by response category.
  - This effect was mainly evident in low- and intermediate-risk MIPI patients.
- Improvements in PFS and TTNT in the VR-CAP arm appeared to be driven by the duration of response rather than the overall response rate.
- As shown by the greater achievement of an SPD nadir of 0 in patients receiving VR-CAP, a deeper radiologic response within each response category was achieved versus R-CHOP.
- Long-term outcomes differed substantially when considering CRu in combination with CR patients versus analysis of CR alone, thus the relevance of the CRu category in relation to long-term outcomes is questionable. Based on our analysis, we believe grouping this category with PR may be more appropriate and may therefore have more clinical relevance.

REFERENCES

1. Herrmann A, et al. J Clin Oncol 2009;27:511–8.
2. Williams ME. Hematology Am Soc Hematol Educ Program 2013;2013:568–74.
3. Vose JM. Am J Hematol 2013;88:1082–8.
4. Dreyling M, et al. Ann Oncol 2014;25(Suppl_3):83–92.
5. McKay P, et al. Br J Haematol 2012;159:405–26.
6. National Cancer Institute. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Non-Hodgkin's Lymphomas. Version 5.2014.
7. Howard OM, et al. J Clin Oncol 2002;20:1288–94.
8. Millennium Pharmaceuticals Inc.: VELCADE® (bortezomib) prescribing information. October 2012, Revision 15. Available at: http://www.velcade.com/files/pdfs/velcade_prescribing_information.pdf. Accessed May 2015.
9. Committee for Medicinal Products for Human Use (CHMP): Summary of positive opinion (post-authorisation): Velcade® (bortezomib). Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000539/smops/Positive/human_smop_000767.jsp&mid=WC0b01ac058001d127&source=homeMedSearch&category=human. Accessed May 2015.
10. Robak T, et al. N Engl J Med 2015;372:944–53.
11. Cheson BD, et al. J Clin Oncol 2007;25:579–86.

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DISCLOSURES

TR: Grants (Janssen); **NS:** Grants (Roche and GlaxoSmithKline); **JD:** Honoraria (Janssen); **JM:** Grants and personal fees (Janssen and Roche); **RO:** Grants (Janssen); **LP:** Employment (Janssen); **BR:** Employment (Janssen), equity ownership (Johnson & Johnson); **HVdV:** Employment (Millennium Pharmaceuticals, Inc. and Janssen), equity ownership (Johnson & Johnson); **FC:** Consultancy (Novartis and Takeda), research funding (Roche, Pfizer and Mundipharma); **GV, HH, OS, HP, JP:** No disclosures.

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