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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 doi:10.3324/haematol. 2016.152496

Received: August 25, 2016.

Accepted: February 7, 2017.

Pre-published: April 14, 2017.

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Supplementary materials (Web appendix)

Methods – overview of LYM-3002 study design

In brief, the LYM-3002 study enrolled patients with newly diagnosed, measurable stage II, III or IV mantle cell lymphoma (MCL) who were ineligible or not considered for stem cell transplantation by the treating physician. All patients were aged ≥18 years and had an Eastern Cooperative Oncology Group performance status of 0–2. The trial was conducted according to the provisions of the Declaration of Helsinki, Good Clinical Practice guidelines, and local regulatory requirements. The local ethics committee or institutional review board at each site approved the study protocol, and all patients provided written informed consent.

Patients were stratified according to their International Prognostic Index (IPI) score and disease stage at diagnosis, and then randomized in a 1:1 ratio to receive six 21-day cycles of VR-CAP or R-CHOP. Up to 8 cycles could be administered if a response was first documented at cycle 6. R-CHOP consisted of 375 mg/m^2 rituximab, 750 mg/m^2 cyclophosphamide, 50 mg/m^2 doxorubicin and 1.4 mg/m^2 vincristine (with maximum total dose of 2 mg), all given intravenously on day 1, plus 100 mg/m^2 oral prednisone given on days 1 to 5. VR-CAP comprised intravenous bortezomib given at 1.3 mg/m^2 on days 1, 4, 8 and 11, followed by rituximab (administered second on day 1) and cyclophosphamide, doxorubicin, and prednisone, as described above

Criteria for Response Categories

The response criteria used to assess efficacy are based on modified International workshop to Standardize Response Criteria (IWRC) for Non-Hodgkin's Lymphoma (1). Full criteria for each disease response category, complete response (CR), unconfirmed CR (CRu), partial response (PR), stable disease (SD), disease relapse and progression, are provided below.

Complete Response (CR) requires ALL of the following:

1. Complete disappearance of all detectable clinical and radiological evidence of disease and disease-related symptoms and normalization of biochemical abnormalities definitely assignable to lymphoma (e.g., lactate dehydrogenase [LDH]) if present before therapy.
2. All measurable lymph nodes and nodal masses must have regressed on computed tomography (CT) to normal size (≤1.5 cm in their greatest transverse diameter for nodes >1.5 cm before therapy).
3. Non-measurable and assessable nodes that were 1.1 to 1.5 cm in their greatest transverse diameter before treatment must have decreased to 1 cm in their greatest transverse diameter after treatment, or by more than 75% in the sum of the products of the greatest diameters (SPD), as visually estimated.
4. The spleen or liver, if considered enlarged due to involvement with lymphoma before therapy on the basis of a physical examination or CT scan, should not be palpable on physical examination and should be considered normal size by imaging studies. Similarly, other organs considered to be enlarged before therapy due to involvement by lymphoma such as kidneys, must have decreased in size.
5. If the bone marrow was involved by lymphoma, indeterminate or not adequately assessed during screening, an adequate aspirate and biopsy of the same site must be clear of lymphoma.
6. All extranodal sites of disease must have completely disappeared.

Unconfirmed Complete Response (CRu) requires:

That the first and fourth criteria for CR be satisfied, however:

- Any residual lymph node mass >1.5 cm in longest transverse dimension or extranodal site of disease (irrespective of size) must have regressed by more than 75% of the product of the longest perpendicular dimensions compared to the pre-treatment baseline.
- The bone marrow aspirate may be indeterminate (contain increased number or size of lymphoid aggregates without cytological or architectural atypia).

If there are residual masses, or there was no bone marrow/LDH confirmation in a patient who would otherwise be considered to have achieved a CR or CRu, the patient should be classified as a partial responder.

Partial Response (PR) requires ALL of the following:

- At least a 50% decrease in SPD of the measurable sites of disease.
- No increase should be observed in any site of disease that meet the criteria for relapsed or progressive disease.
- Non-measurable nodes and nodules must regress by ≥50% in their SPD or, for single non-measurable lesions, in the greatest transverse diameter, as visually estimated.
- Bone marrow assessment is irrelevant for determination of a PR if the sample was positive before treatment. However, patients who achieve a CR by the above criteria, but who have persistent morphologic bone marrow involvement will be considered partial responders. When the bone marrow was involved before therapy and a clinical CR was achieved, but with no bone marrow assessment after treatment, patients should be considered partial responders.
- No new sites of disease should be observed that meet the criteria for relapsed or progressive disease.

Stable disease (SD) is defined as the following:

A patient is considered to have SD when he or she fails to attain the criteria needed for a CR or PR, but does not fulfil those for progressive disease (see below).

Progressive Disease (after PR/SD) or Relapsed Disease (after CR/CRu)

Progressive or relapsed disease requires any 1 of the following:

1. A) ≥50% increase from nadir in the SPD of all measurable sites of disease at the time that progressive or relapsed disease is identified and the absolute change in at least 1 dimension is ≥0.5 cm for at least 1 lesion; or B) ≥50% increase in the long axis of any measurable site of disease at the time that progressive or relapsed disease is identified and the absolute change in the long axis is ≥0.5 cm.
2. A) ≥50% increase from nadir in the SPD of all non-measurable sites of disease (excluding truly assessable disease), as visually estimated, and the absolute change in at least 1 dimension is ≥0.5 cm for at least 1 non-measured lesion as estimated visually; or B) ≥50% increase in the long axis of any non-measurable site of disease (excluding truly assessable disease), and the absolute change in the long axis is ≥0.5 cm, as estimated visually.
3. ≥50% increase from nadir in any truly assessable site of disease, as visually estimated.
4. Appearance of any new lymph node site of disease that measures >1.5 cm in long axis and >1.0 cm in short axis, any new unequivocal extranodal site of disease (irrespective of size), or unequivocal evidence of a new site of assessable disease (for example effusions, ascites, masses with indistinct borders, new involvement of the bone marrow).
5. Appearance of a new organ enlargement or unequivocal increase of an organ enlargement that was present since baseline.

Measurable extranodal disease should be assessed in a manner similar to that for nodal disease. For these recommendations, the spleen is considered nodal disease. Disease that is only assessable (e.g., pleural effusions, bone lesions) will be recorded as no change, increased, decreased, or new, unless, while an abnormality is still noted by imaging studies or physical examination, it is found to be histologically negative.

When the patient is recorded to have an event of progressive disease (PD), a repeat CT scan to confirm PD must be undertaken at least 30 days after the scan that was used to determine PD. In the event a patient starts subsequent anti-lymphoma treatment, it is strongly recommended that this repeat CT scan be performed before the patient starts treatment. The repeat CT scan must be done using intravenous and oral contrast and must be of the neck, chest, abdomen and pelvis. If the patient is intolerant of intravenous contrast agents, the scan may be performed with only oral contrast.

Death and events of progression constitute PFS, the primary endpoint for this study; it is therefore important that instances of PD, death or study discontinuation be reported to the sponsor as soon as possible. A PD fax form provided by the sponsor together with documentation of PD (e.g., CT scan report) must be sent to the sponsor's medical representation within 24 hours of the event.

Reference

1. Cheson BD, Pfistner B, Juweid ME, et al.: Revised response criteria for malignant lymphoma. J Clin Oncol 25:579-586, 2007

Supplementary Table S1. Patients achieving a SPD nadir of 0 by MIPI risk score (lesions absent or 'too small to measure' by CT scan)

Patients, n/N (%)	VR-CAP		R-CHOP	
	SPD nadir 0	**SPD nadir 0+**	**SPD nadir 0**	**SPD nadir 0+**
Patients with low-risk MIPI				
CR/CRu	34/45 (76)	11/45 (24)	20/31 (65)	11/31 (35)
CR	31/39 (79)	8/39 (21)	20/28 (71)	8/28 (29)
CRu	3/6 (50)	3/6 (50)	0/3 (0)	3/3 (100)
PR	15/24 (63)	9/24 (37)	3/31 (10)	28/31 (90)
Patients with intermediate-risk MIPI				
CR/CRu	44/57 (77)	13/57 (23)	25/37 (68)	12/37 (32)
CR	43/52 (83)	9/52 (17)	23/31 (74)	8/31 (26)
CRu	1/5 (20)	4/5 (80)	2/6 (33)	4/6 (67)
PR	16/31 (52)	15/31 (48)	15/44 (34)	29/44 (66)
Patients with high-risk MIPI				
CR/CRu	9/19 (47)	10/19(53)	9/24 (38)	15/24 (62)
CR	9/14 (64)	5/14 (36)	9/17 (53)	8/17 (47)
CRu	0/5 (0)	5/5 (100)	0/7 (0)	7/7 (100)
PR	11/32 (34)	21/32 (66)	12/33 (36)	21/33 (64)

Response evaluable population: VR-CAP: n=229; R-CHOP: n=229

SPD nadir calculated based on the up to 10 measureable lesions identified at baseline

SPD 0: defined as SPD nadir of 0 for all measureable lesions

SPD 0+: defined as SPD nadir of >0

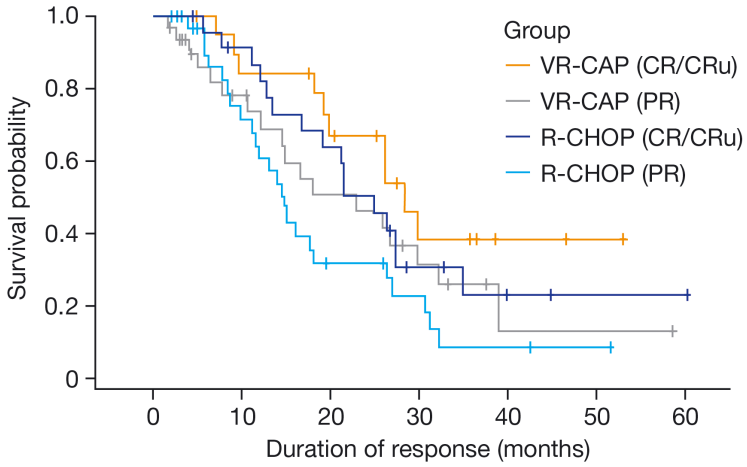
CR, complete response; CRu, unconfirmed complete response; PR, partial response. R-CHOP, rituximab plus cyclophosphamide-doxorubicin-vincristine-prednisone; SPD, sum of the product of the diameters; VR-CAP, bortezomib plus rituximab-cyclophosphamide-doxorubicin-prednisone.

Supplementary Figure Legends

Supplementary Figure S1. Time to next anti-lymphoma therapy according to MIPI risk status

Supplementary Figure S2. Duration of response according to MIPI risk status. A) High-risk, B) intermediate-risk and C) low-risk

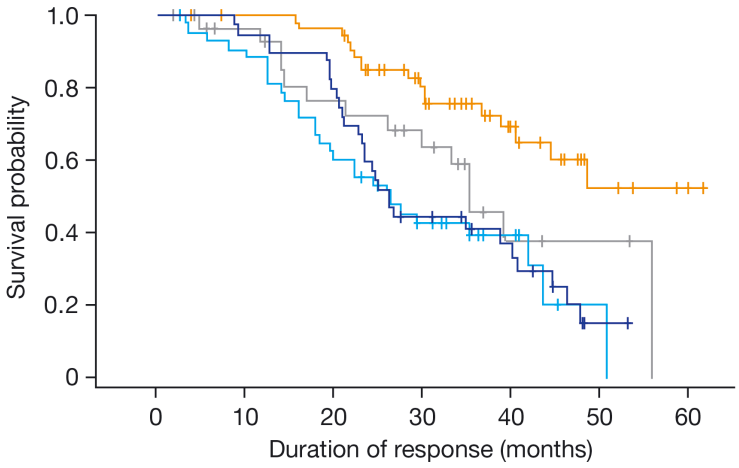
A) High-risk patients



Number of patients at risk

VR-CAP (CR/CRu)	20	16	12	5	2	1	0
VR-CAP (PR)	32	19	11	6	1	1	0
R-CHOP (CR/CRu)	24	20	14	5	2	1	1
R-CHOP (PR)	33	20	8	5	2	1	0

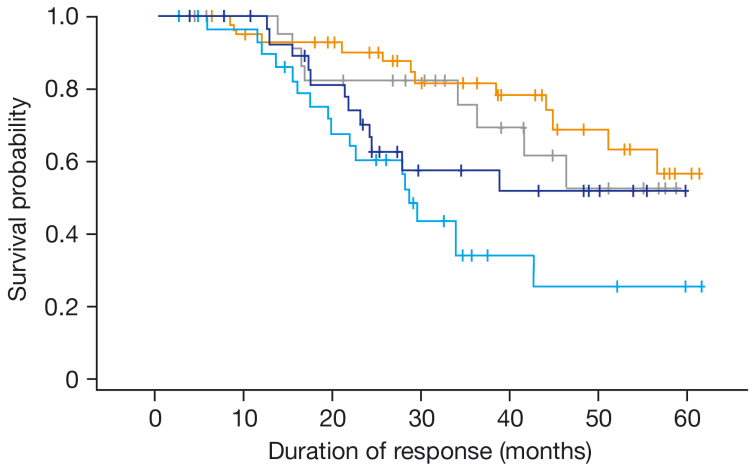
B) Intermediate-risk patients



Number of patients at risk

VR-CAP (CR/CRu)	57	55	53	34	18	6	2
VR-CAP (PR)	32	26	19	14	4	2	0
R-CHOP (CR/CRu)	40	38	32	16	10	1	0
R-CHOP (PR)	44	39	26	16	7	1	0

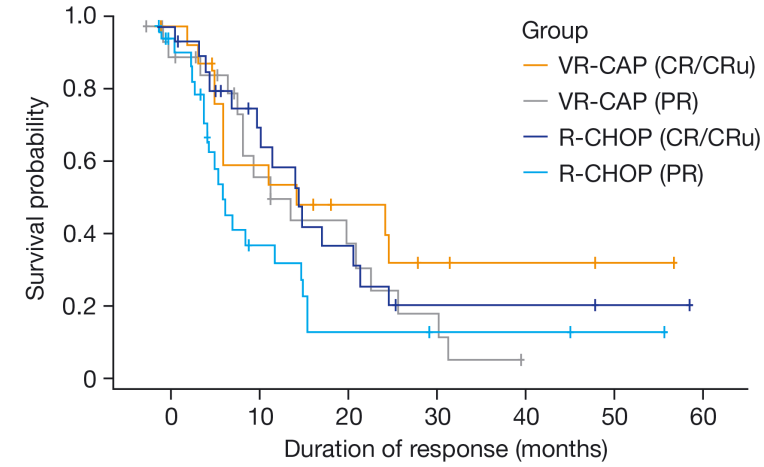
C) Low-risk patients



Number of patients at risk

VR-CAP (CR/CRu)	45	41	37	27	19	13	3
VR-CAP (PR)	25	23	19	16	10	6	0
R-CHOP (CR/CRu)	31	29	22	11	9	5	0
R-CHOP (PR)	32	28	19	10	4	3	1

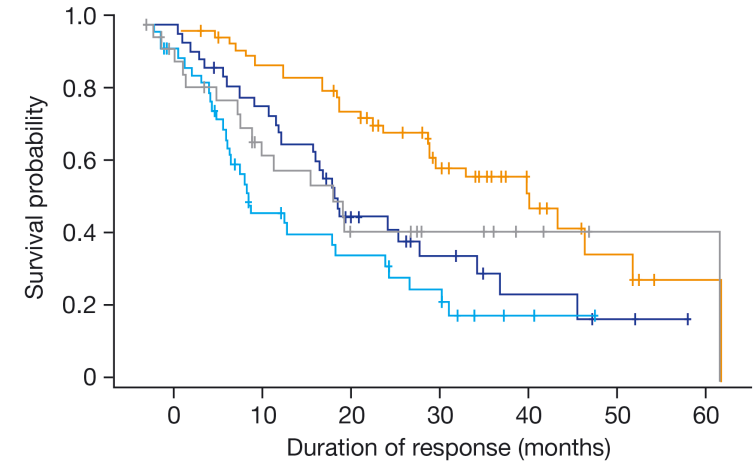
A) Duration of response in high-risk MIPI patients



Number of patients at risk

VR-CAP (CR/CRu)	20	11	6	2	2	1	0
VR-CAP (PR)	32	11	6	1	0		
R-CHOP (CR/CRu)	24	14	6	3	2	1	0
R-CHOP (PR)	33	8	3	2	2	1	0

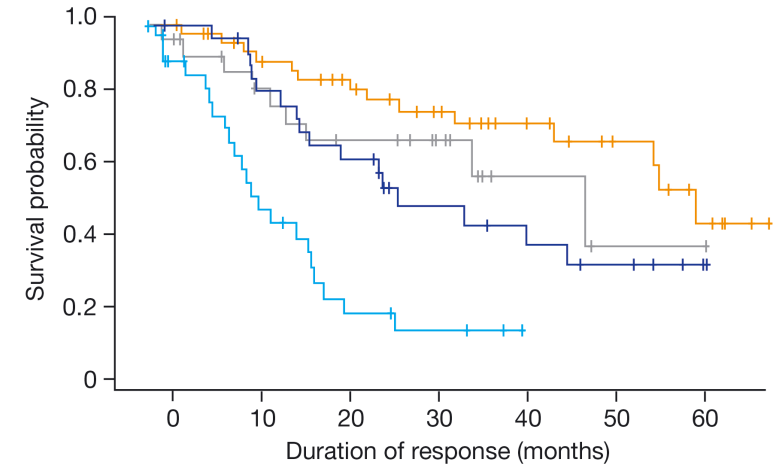
B) Duration of response in intermediate-risk MIPI patients



Number of patients at risk

VR-CAP (CR/CRu)	57	49	40	21	8	1	0
VR-CAP (PR)	32	19	9	6	2	1	0
R-CHOP (CR/CRu)	40	31	15	7	4	1	0
R-CHOP (PR)	44	18	12	4	1	0	

C) Duration of response in low-risk MIPI patients



Number of patients at risk

VR-CAP (CR/CRu)	45	37	29	21	14	8	0
VR-CAP (PR)	25	18	13	7	3	1	0
R-CHOP (CR/CRu)	31	23	17	10	7	3	0
R-CHOP (PR)	32	14	5	3	0		