Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Ruan J, Martin P, Shah B, et al. Lenalidomide plus rituximab as initial treatment for mantle-cell lymphoma. N Engl J Med 2015;373:1835-44. DOI: 10.1056/NEJMoa1505237

Supplementary Appendix

Supplement to: Ruan J, Martin P, Shah B, et al. Lenalidomide Plus Rituximab as Initial Treatment for Mantle Cell Lymphoma

Contents

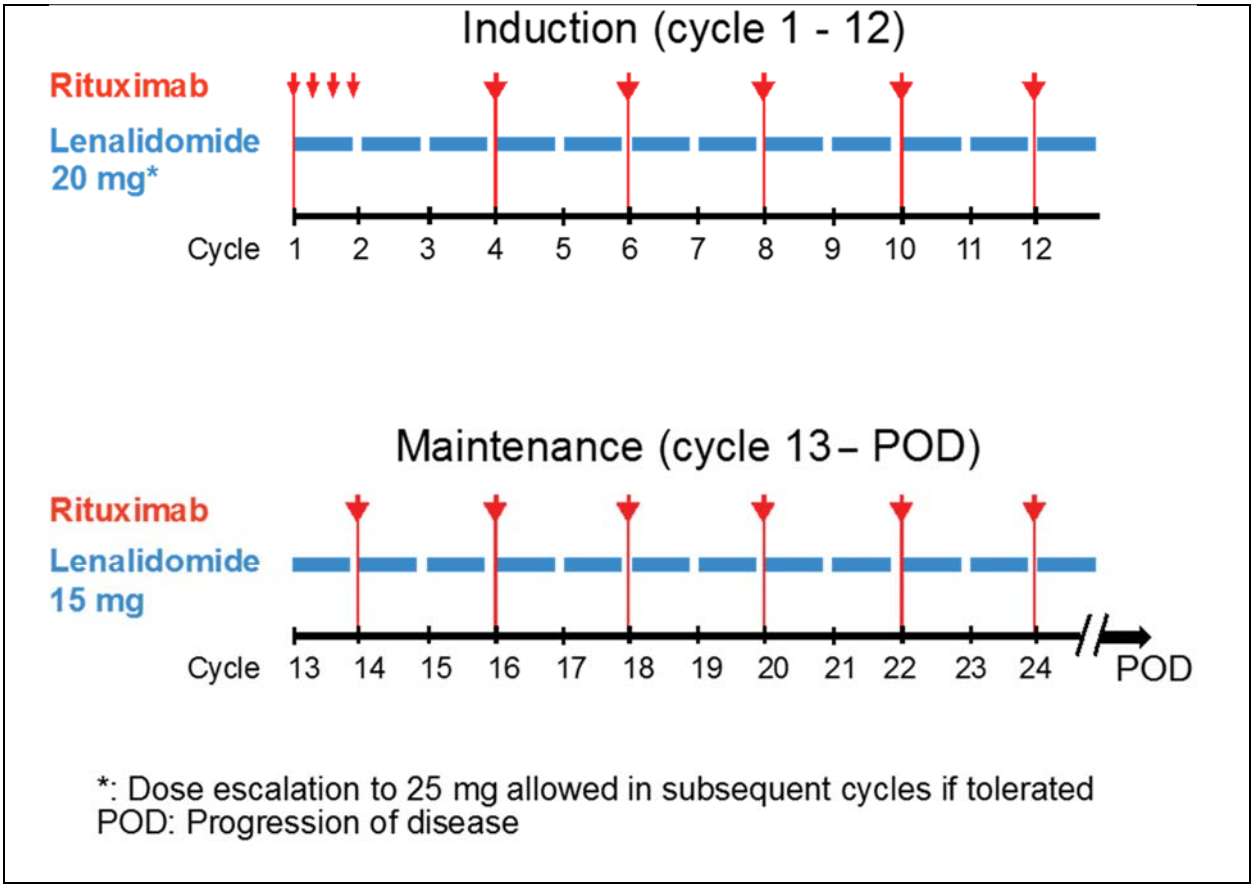

Figure S1. MCL lenalidomide plus rituximab treatment schedule. Treatment consisted of induction and maintenance phases. During induction, lenalidomide was administered at 20 mg daily on days 1-21 of a 28-day cycle for a total of 12 cycles, with dose escalation to 25 mg daily if tolerated. Standard dose rituximab was administered weekly x 4 during cycle 1, then once every other cycle, for a total of 9 doses. During maintenance, lenalidomide was administered at 15 mg daily on days 1-21 of a 28-day cycle, with rituximab maintenance once every other cycle until progression of disease.

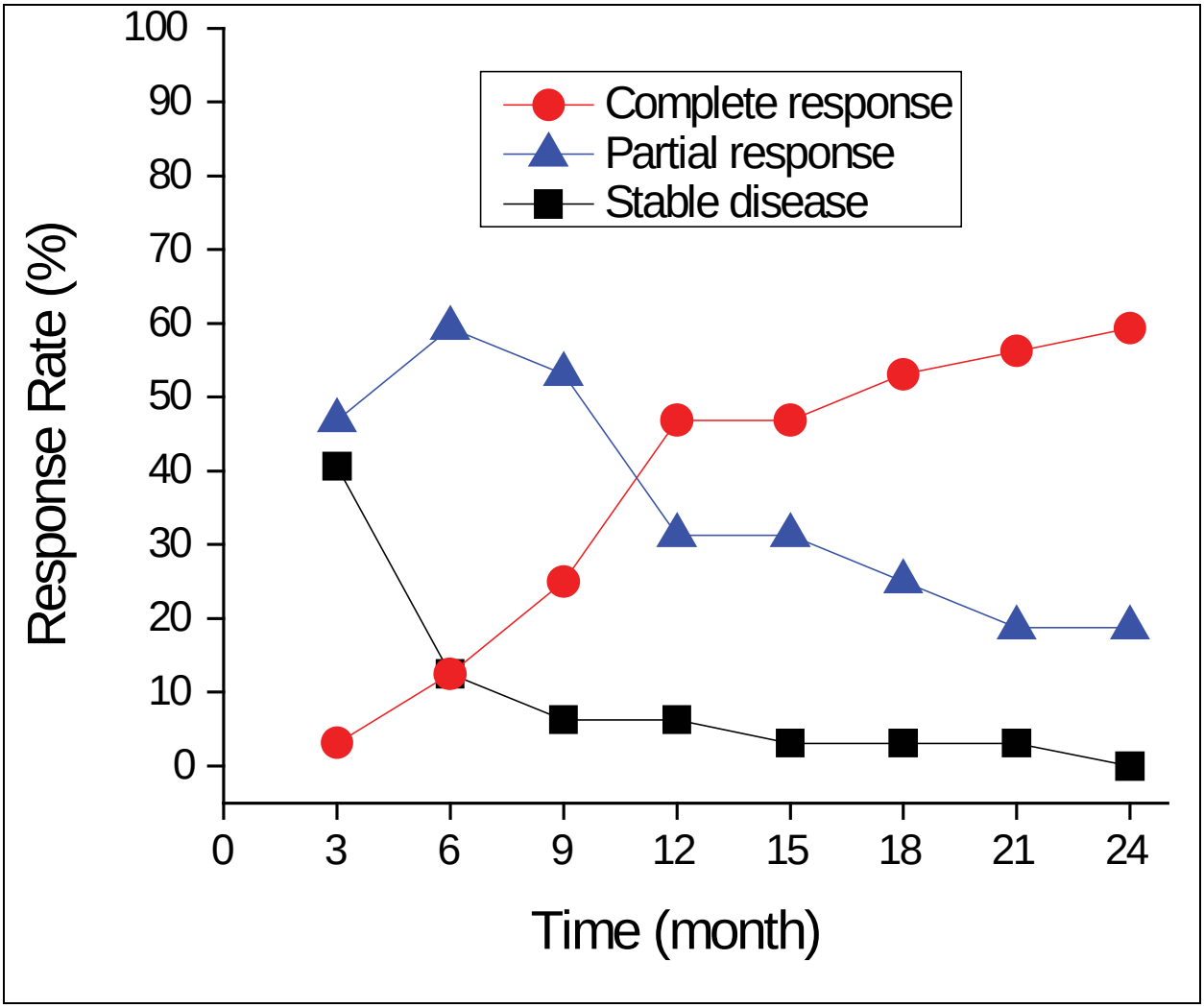

Figure S2. MCL lenalidomide plus rituximab treatment response curves. Response curves over time for 24 months, including complete response (red solid circle), partial response (blue solid triangle), and stable disease (black solid square), were plotted for the first 32 patients who have had at least 24 months of follow-up on study.

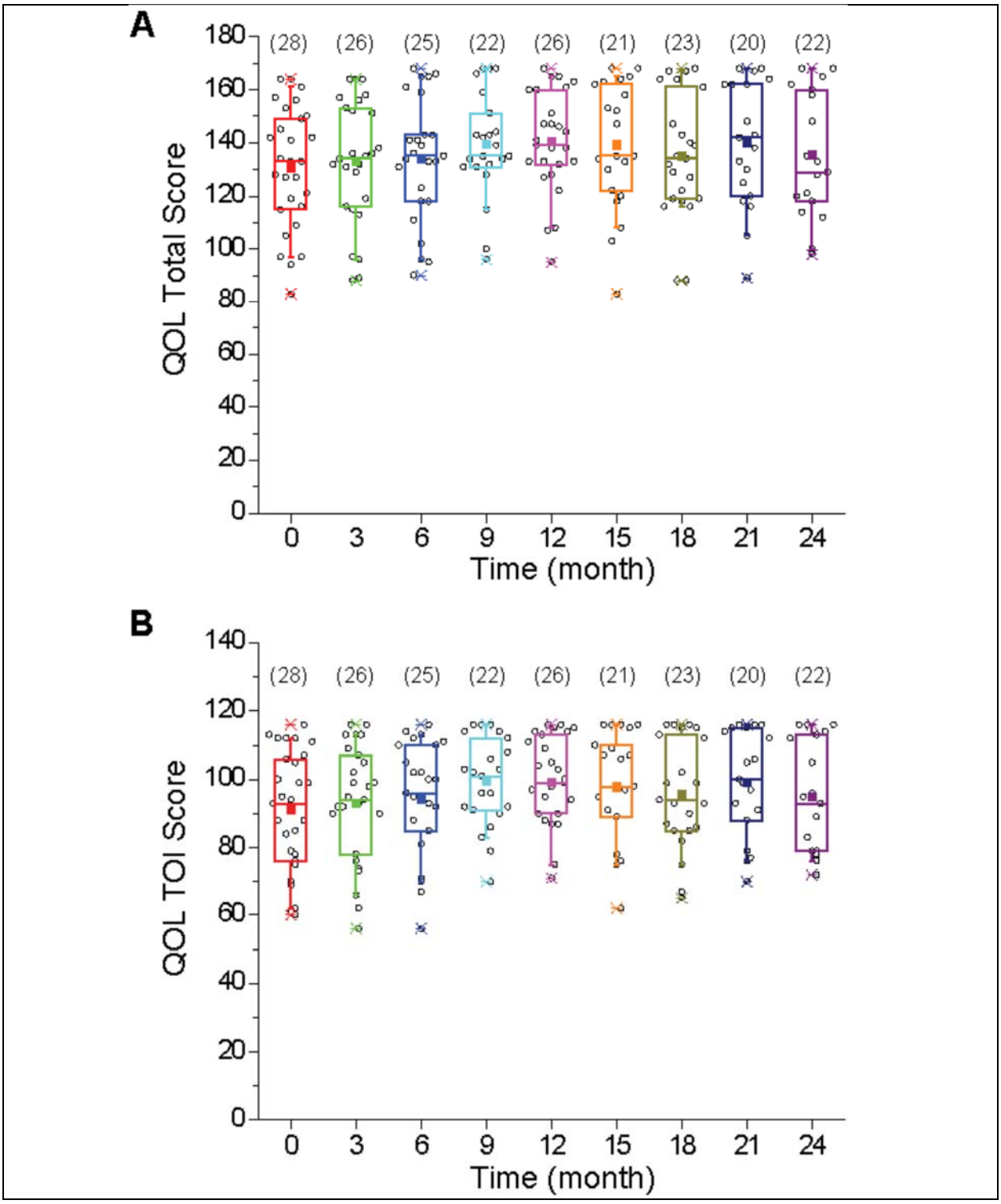

Figure S3. Health-related Quality-of-Life measurement over time. The box and whisker plots of the FACT-LYM total score (range 0-168) and modified trial outcome index (TOI, range 0-116), measured at baseline, every 3 months until month 24 for the first 32 patients on study, delineated the impact of therapy on HRQoL. The numbers of the completed questionnaires at each time points were marked on the graph in parentheses.

Table S1. Severe Adverse Events			
Study Phase	Age (year)	Severe Adverse Event	Relatedness
Induction	74	Skin squamous cell Carcinoma, left hand	Possible
Induction	60	Shortness of breath / Dyspnea	Possible
Induction	68	Cough / hypothyroidism	Possible
Induction	86	Pneumonia	Probable
Induction	70	Rash	Probable
Induction	66	Serum Sickness	Probable
Induction	66	Serum sickness	Possible
Induction	52	Tumor flare / serum sickness	Probable
Induction	66	Tumor flare	Possible
Induction	74	Tumor flare	Possible
Induction	66	Tumor flare	Probable
Induction	81	Ventricular fibrillation / neutropenic fever	Possible
Induction	57	Non-neutropenic fever	Possible
Induction	80	Non-neutropenic fever / transfusion reaction	Unlikely
Induction	56	Vertigo	Unlikely
Induction	68	Non-neutropenic fever	Unrelated
Induction	68	Atrial fibrillation	Unrelated
Induction	69	Blood bilirubin increased	Unrelated
Maintenance	62	Skin Squamous cell carcinoma in situ	Possible
Maintenance	75	Skin squamous cell carcinoma, right forehead & jaw	Possible
Maintenance	60	Skin basal cell carcinoma	Unlikely
Maintenance	69	Pancreatic cancer	Possible
Maintenance	86	Melanoma in situ	Unlikely
Maintenance	86	Merkel cell carcinoma	Unlikely
Maintenance	70	Fever	Possible
Maintenance	67	Cholecystitis / cholangitis / neutropenic fever	Possible
Maintenance	84	Pneumonia	Possible
Maintenance	84	Gastroenteritis	Possible
Maintenance	70	West Nile virus encephalitis	Unlikely
Maintenance	84	Syncope	Unlikely
Maintenance	84	Left femoral neck fracture	Unrelated
Maintenance	54	Car accident	Unrelated
Maintenance	60	Cholecystitis	Unrelated

Table S2. Outcome Following Disease Progression									
Subject	Age at Relapse (year)	MIPI Risk	Best Response	Study Duration (month)	Rebiopsy Ki67	Suspect Blastoid Transformation	Subsequent Therapy	Survival Status	OS (month)
1	69	High	PD	6	N/A	No	BVR, ibrutinib	Alive	42+
2	58	Low	PD	3	N/A	No	BR, autoSCT	Alive	41+
3	66	Intermediate	SD	3	N/A	No	BR	Alive	23+
4	88	High	CR	18	N/A	No	Palliation	Deceased	24
5	54	Low	PR	14	15-20%	No	Local radiation	Alive	23+
6	66	High	PR	25	N/A	No	Ibrutinib	Alive	32+
7	72	Intermediate	PR	28	20%	No	Ibrutinib+palbociclib	Alive	32+
8	45	Low	CR	39	5%	No	Ibrutinib+palbociclib	Alive	40+
Abbreviations: BVR – bendamustine, bortezomib, and rituximab; autoSCT – autologous stem cell transplant.									

Mantle Cell Lymphoma International Prognostic Index (MIPI) (Hoster, 2008)
MIPI score = [0.03535 x age (years)]
+ [0.6978 (if ECOG >1)]
+ [1.367 x $\log_{10}$(LDH/ULN)]
+ [0.9393 x $\log_{10}$(WBC count per 10^{-6} L)]

MIPI Score	**Risk Group**
< 5.7	Low risk
≥ 5.7 and < 6.2	Intermediate risk
≥ 6.2	High risk

International Prognostic Index (IPI) (NEJM, 1993)
One point is assigned for each of the following risk factors:

- Age greater than 60 years
- Stage III or IV disease
- Elevated serum LDH
- Eastern Cooperative Oncology Group performance status of 2, 3, or 4
- More than 1 extranodal site

IPI Score	**Risk Group**
0 - 1	Low risk
2	Low-intermediate risk
3	High-intermediate risk
4 - 5	High risk

Lymphoma Response Criteria (Cheson, 2007)				
Response	**Definition**	**Nodal Masses**	**Spleen, Liver**	**Bone Marrow**
CR	Disappearance of all evidence of disease	1) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative 2) Variably FDG-avid or PET-negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; IHC negative if indeterminate by morphology
PR	Regression of measurable disease and no new sites	≥ 50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes 1) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site 2) Variably FDG-avid or PET negative; regression on CT	≥ 50% decrease in SPD or nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR or PD	1) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET 2) Variably FDG-avid or PET negative; no change in size of previous lesions on CT		
PD	Any new lesion or increase by ≥ 50% of previously involved sites from nadir	Appearance of a new lesion(s) > 1.5 cm in any axis, ≥ 50% increase in SPD of more than one node, or ≥ 50% increase in longest diameter of a previously identified node > 1 cm in short axis; lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy	> 50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement
Abbreviations: CR, complete remission; PR, partial remission; SD, stable disease; PD, progressive disease; FDG, [^{18}F]fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography; SPD, sum of the product of the diameters; IHC, immunohistochemistry.				

References

Hoster E, Dreyling M, Klapper W, et al. A New Prognostic Index (MIPI) for Patients with Advanced-stage Mantle Cell Lymphoma. Blood. 2008;111:558-65.

A Predictive Model for Aggressive Non-Hodgkin's Lymphoma. The International Non-Hodgkin's Lymphoma Prognostic Factor Project. New England Journal of Medicine 1993;329:987-94

Cheson BD, Pfistner B, Juweid ME, et al. Revised Response Criteria for Malignant Lymphoma. Journal of Clinical Oncology. 2007:25:579-86.