Rome,
March 23-24 2017

VOI Donna Camilla Savelli Hotel

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Janssen			X				
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Celgene			X				
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Novartis			X				
Pharmacyclics			X				
Verastem			X				

Lenalidomide in Previously Treated Mantle Cell Lymphoma

March 26, 2017 pem9019@med.cornell.edu

Weill Cornell Medicine NewYork-Presbyterian

Efficacy of Lenalidomide in Relapsed Mantle Cell Lymphoma

- 134 patients were enrolled (EMERGE study).
- Prior bortezomib 100%
  - Refractory to bortezomib 60%
- Prior intensive therapy 33%
- Median age of 67 years and median of 4 prior therapies.
- The ORR was 28% (7.5% CR)
- Median DOR of 16.6 months.
- Median PFS was 4 months
- Median OS was 19.0 months.

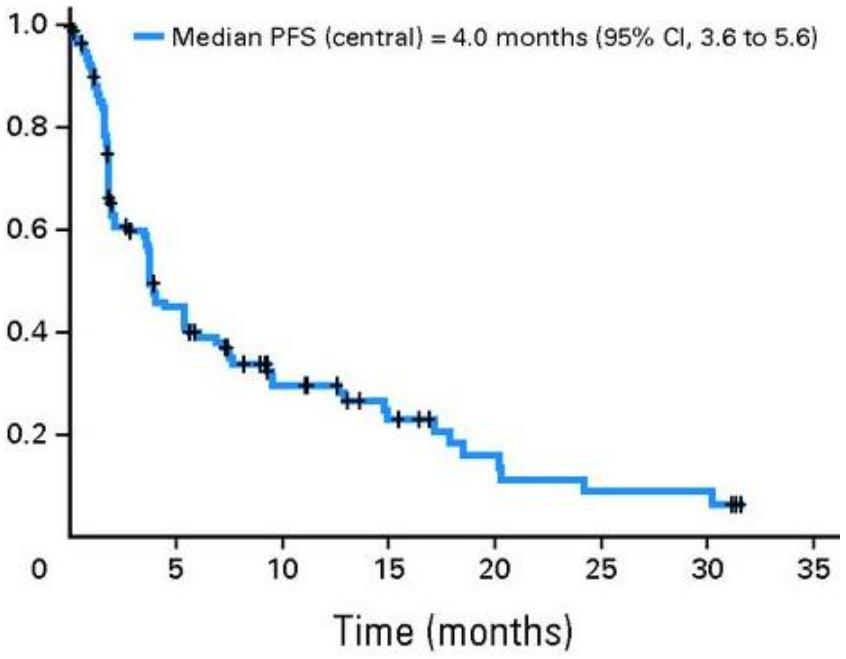


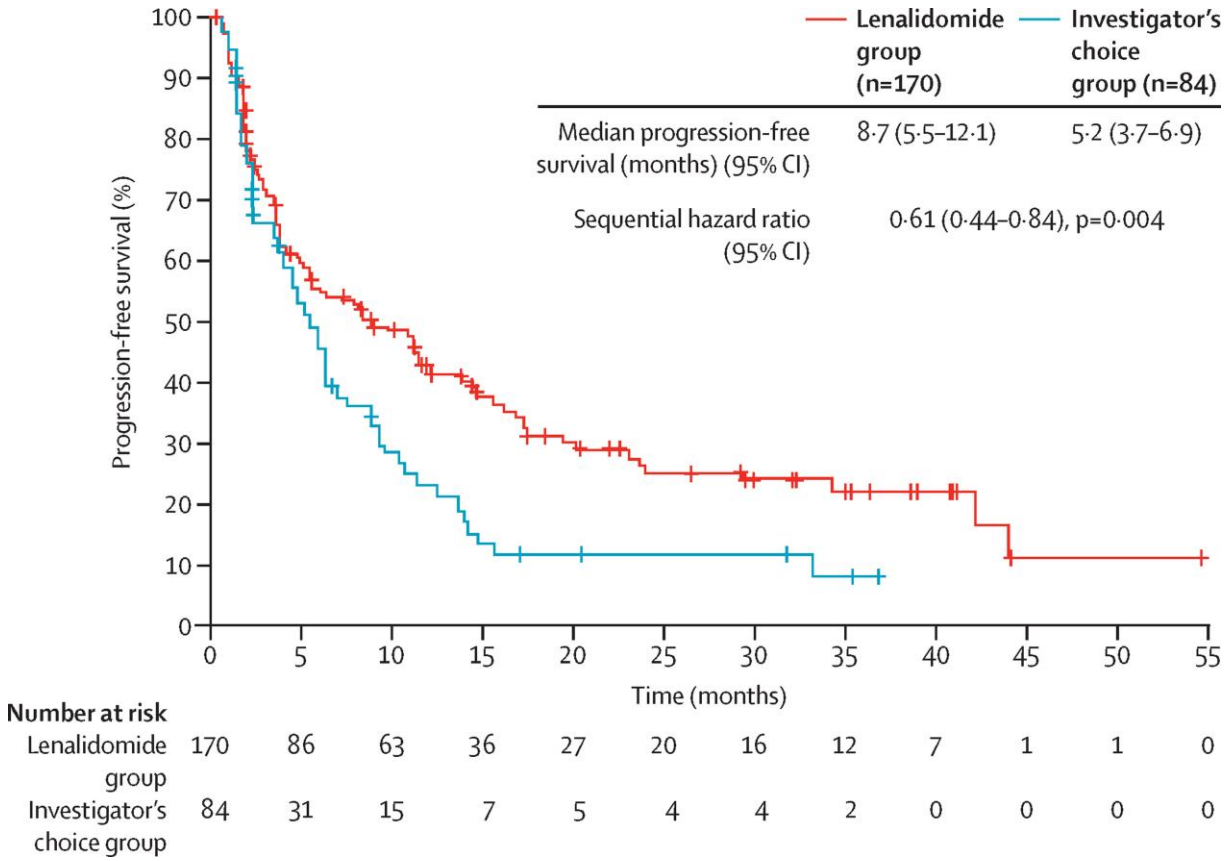
Table 4. All Treatment-Emergent AEs After Lenalidomide (regardless of attribution) in ≥ 10% of Patients With Relapsed/Refractory MCL (N = 134)

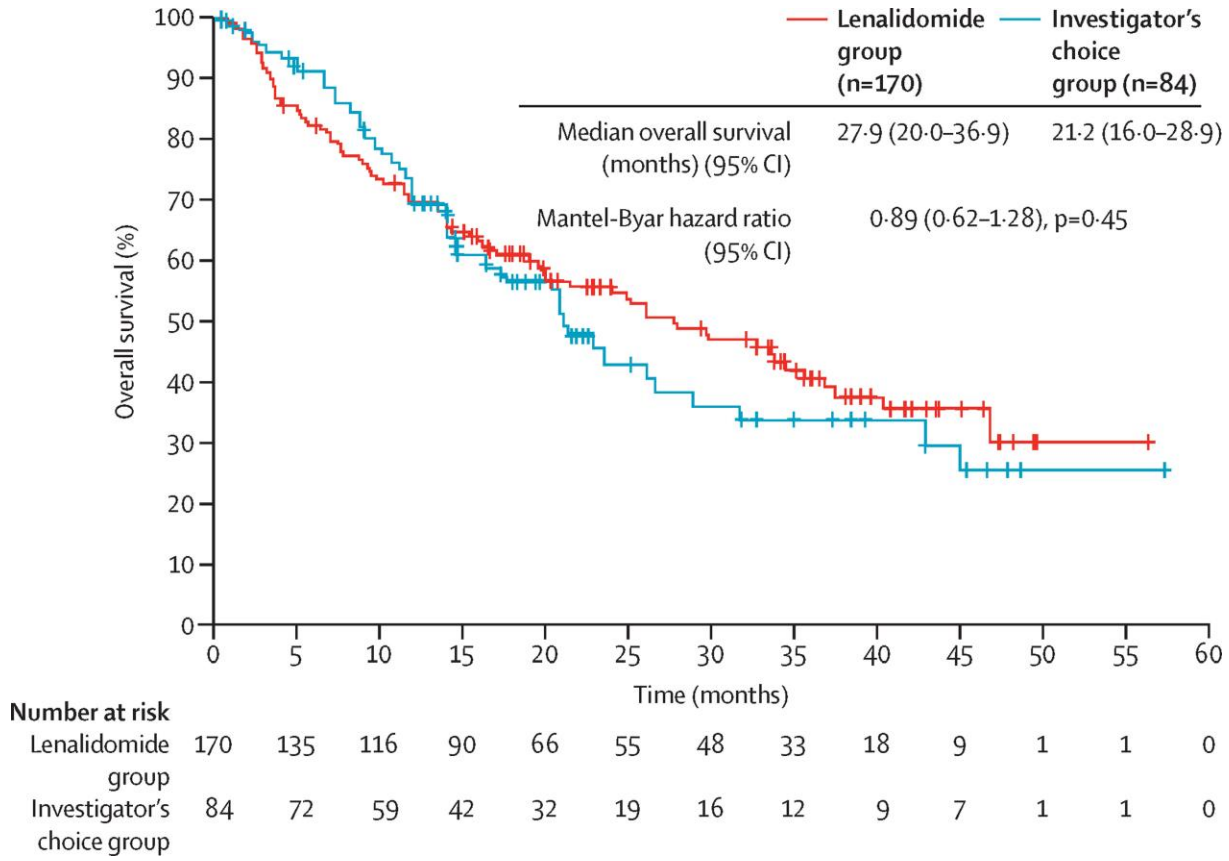
AE	Any Grade		Grade 3		Grade 4	
	No.	%	No.	%	No.	%
Patients with one or more AEs	132	99	47	35	41	31
Hematologic						
Neutropenia	65	49	26	19	32	24
Thrombocytopenia	48	36	23	17	14	10
Anemia	41	31	11	8	4	3
Leukopenia	20	15	7	5	2	1
Nonhematologic						
Fatigue	45	34	9	7	0	0
Diarrhea	42	31	8	6	0	0
Nausea	40	30	0	0	1	< 1
Cough	38	28	1	< 1	0	0
Pyrexia*	31	23	1	< 1	1	< 1
Rash	30	22	2	1	0	0
Dyspnea*	24	18	6	5	1	< 1
Pruritus	23	17	1	< 1	0	0
Constipation	21	16	1	< 1	0	0
Peripheral edema	21	16	0	0	0	0
Pneumoniat	19	14	10	8	0	0
Asthenia*	19	14	2	1	1	< 1
Decreased appetite	19	14	1	< 1	0	0
Back pain	18	13	2	1	0	0
Hypokalemia	17	13	2	1	1	< 1
Muscle spasms	17	13	1	< 1	0	0
Upper respiratory tract infection	17	13	0	0	0	0
Decreased weight	17	13	0	0	0	0
Vomiting	16	12	0	0	1	< 1

Abbreviations: AE, adverse event; MCL, mantle-cell lymphoma.
*Denotes one grade 5 event per AE.
†Two grade 5 pneumonia events.

Goy A et al. JCO 2013;31:3688-3695
Goy BJH 2015

SPRINT: Lenalidomide vs. IC
Better PFS, no difference in OS





Trneny et al. The Lancet Oncology **2016 17, 319-331**

Question: Does lenalidomide work after ibrutinib?

Figure 1. MCL-004 Study Design (NCT02341781)

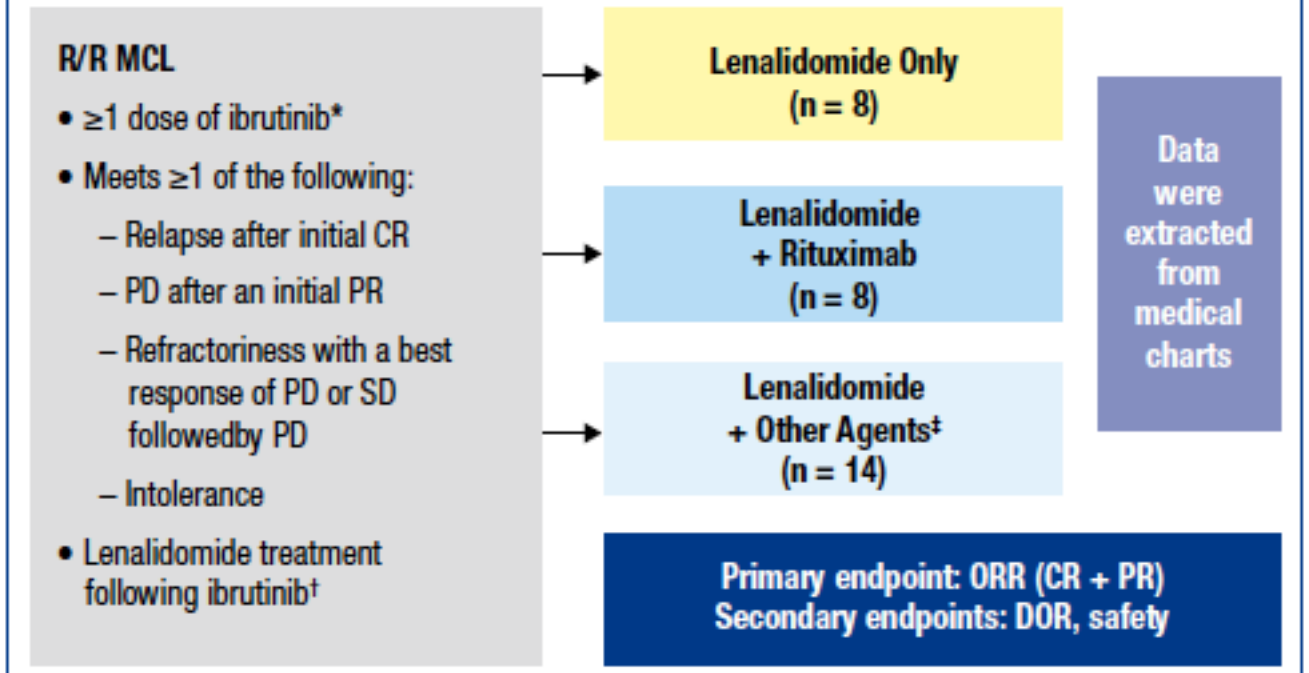


Table 2. MCL-004: Treatment History

Characteristic, n (%)	L (n = 8)	L+R (n = 8)	L+Others* (n = 14)	Overall (N = 30)
Median number of prior antilymphoma therapies (range)†	4.5 (3-7)	3 (2-4)	4 (3-6)	4 (2-7)
Ibrutinib status at study inclusion				
Relapse/PD	4 (50)	2 (25)	8 (57)	14 (47)
Refractory	1 (13)	6 (75)	5 (36)	12 (40)
Intolerant	2 (25)	0	1 (7)	3 (10)
Missing	1 (13)	0	0	1 (3)
Median duration of ibrutinib treatment, months (range)	6.9 (2.0-13.9)	3.7 (2.0-9.3)	4.3 (0.5-17.5)	4.5 (0.5-17.5)
Best response on ibrutinib				
CR	2 (25)	0	1 (17)	3 (10)
PR	3 (38)	2 (25)	8 (57)	13 (43)
SD	0	1 (13)	0	1 (3)
Relapse/PD	2 (25)	5 (63)	5 (36)	12 (40)
Unknown	1 (13)	0	0	1 (3)
Primary reason for ibrutinib discontinuation				
Lack of efficacy	5 (63)	8 (100)	13 (93)	26 (87)
Toxicity to ibrutinib	2 (25)	0	1 (7)	3 (10)
Physician/patient choice	1 (13)	0	0	1 (3)
Median time from end of last dose of ibrutinib to first dose of lenalidomide, weeks (range)	1.8 (0.4-7.4)	0.3 (0.1-21.7)	1.0 (0.1-16.8)	1.3 (0.1-21.7)

Wang, Martin, et al. ASH 2016

Answer: Lenalidomide works after ibrutinib, but not overwhelmingly well

But sufficient for EMA approval on 2/28/16

Table 3. MCL-004: Lenalidomide Treatment Exposure

	L (n = 8)	L+R (n = 8)	L+Others* (n = 14)	Overall (N = 30)
Median duration of lenalidomide treatment, weeks (range)	6.0 (0.4-11.9)	13.0 (0.9-37.9)	6.0 (1.4-44.0)	7.1 (0.4-44.0)
Median number of lenalidomide cycles (range)	2.0 (1.0-3.0)	2.0 (1.0-9.0)	1.5 (1.0-11.0)	2.0 (1.0-11.0)
Median duration of other therapy combined with lenalidomide, weeks (range)	NA	5.6 (0.1-28.9)	6.7 (2.6-55.1)	6.3 (0.1-55.1)

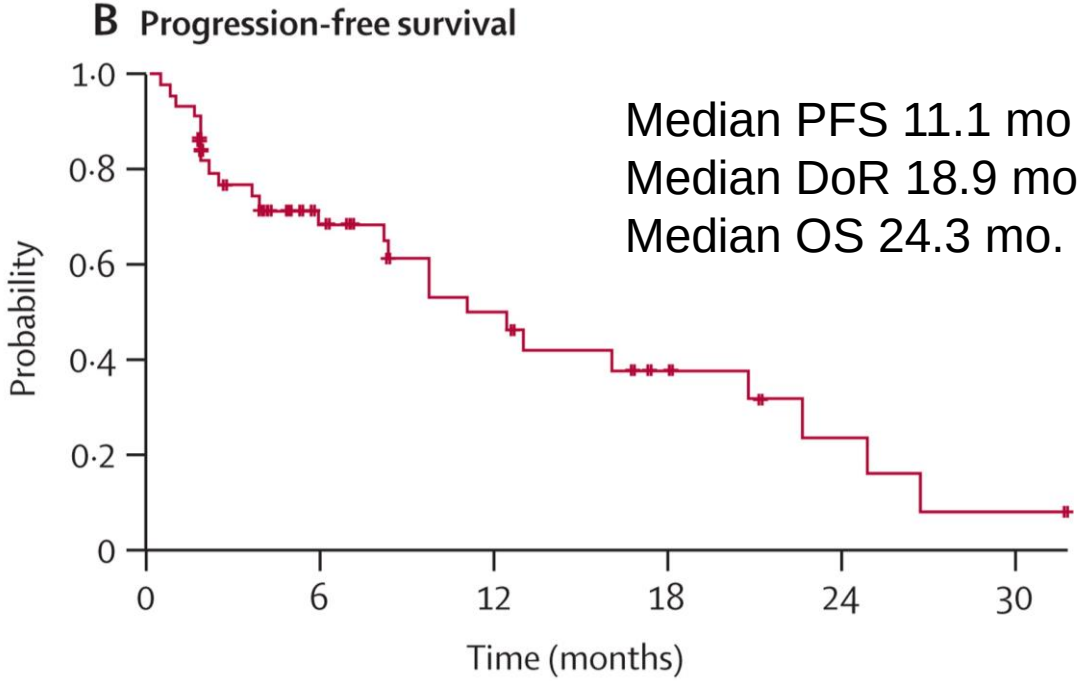
Table 4. MCL-004: Efficacy Outcomes With Lenalidomide-Based Therapy in Patients With MCL After Ibrutinib Failure or Intolerance

	L (n = 8)	L+R (n = 8)	L+Others* (n = 14)	Overall (N = 30)
Best response by investigator's assessment, n (%)				
ORR	1 (13)	2 (25)	5 (36)	8 (27)
95% CI	0.3%-53%	3%-65%	13%-65%	12%-46%
CR	0	1 (13)	3 (21)	4 (13)
PR	1 (13)	1 (13)	2 (14)	4 (13)
SD	0	1 (13)	0	1 (3)
Relapse/PD	4 (50)	2 (25)	6 (43)	12 (40)
Unknown	3 (38)	2 (25)	3 (21)	8 (27)
Missing	0	1 (13)	0	1 (3)

Wang, Martin, et al. ASH 2016

Lenalidomide plus rituximab

	Phase 2 (n=44)*
Complete response	16 (36%)
Partial response	9 (20%)
Overall response	25 (57%)
Stable disease	10 (23%)
Progressive disease	9 (20%)
Response duration (months)	18·9 (17·0–NR)
Progression-free survival (months)	11·1 (8·3–24·9)
Overall survival (months)	24·3 (19·8–NR)
Time to first response (months)	2 (2–8)
Time to best response (months)	2 (2–12)
Follow-up time (months)	23·1 (15·6–54·2)

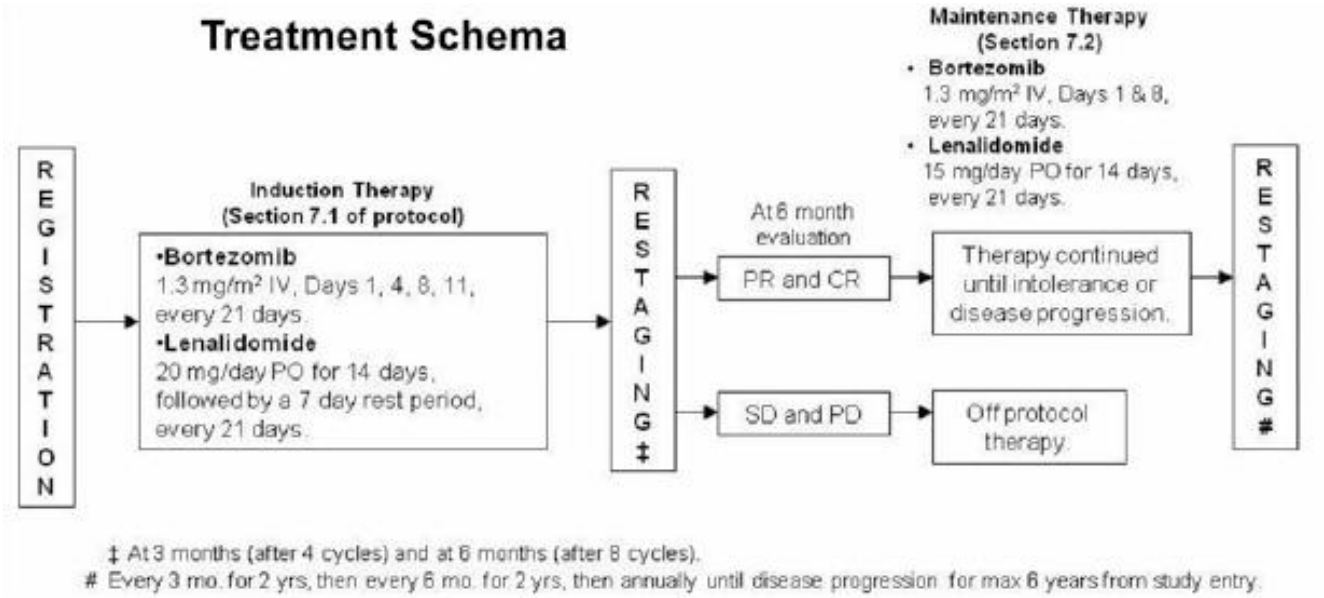


Median PFS 11.1 mo
Median DoR 18.9 mo
Median OS 24.3 mo.

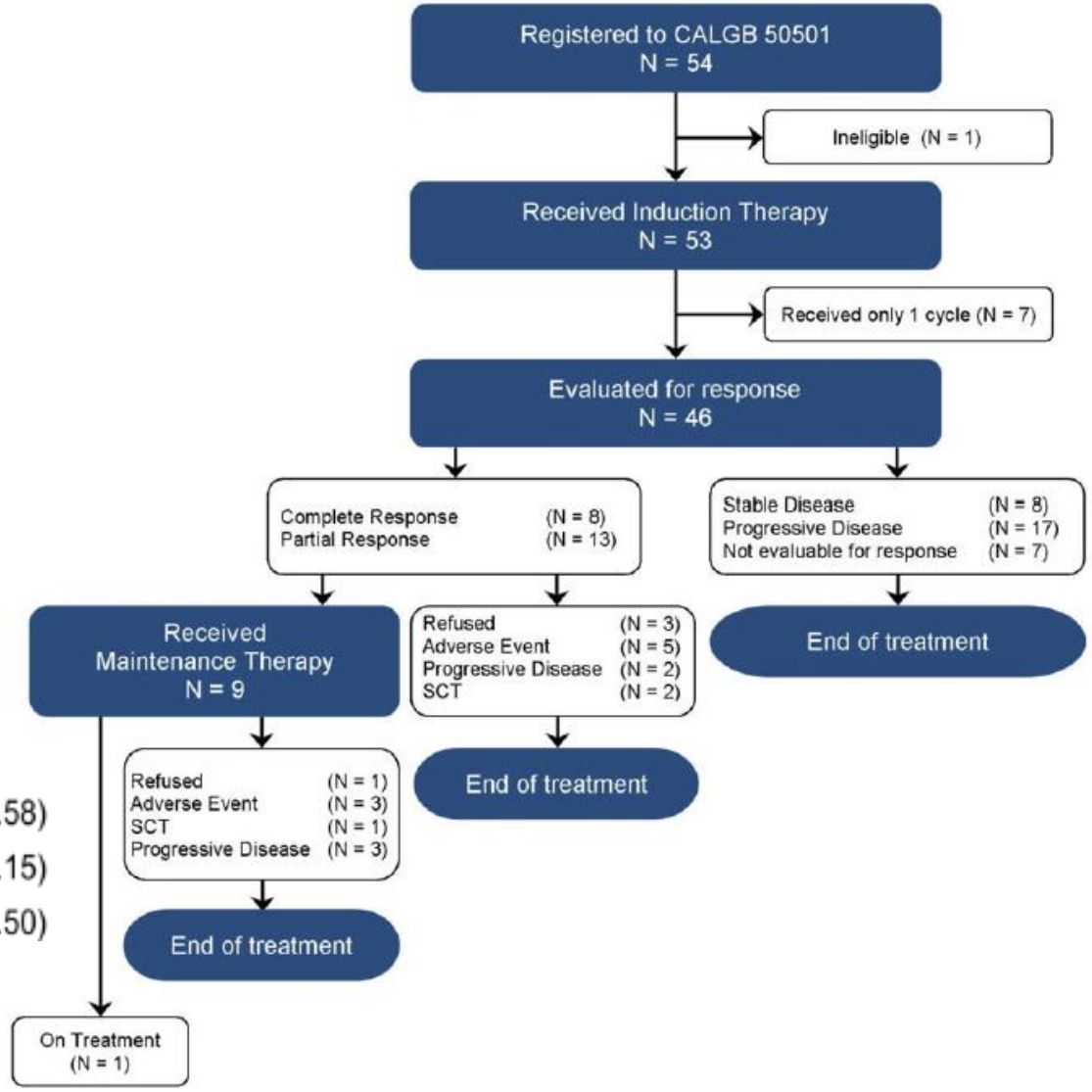
Prior R-hyperCVAD – 85%
Prior bortezomib – 27%
Prior ASCT - 11%
5/11 rituximab-refractory vs. 22/33 rituximab sensitive patients responded.

Wang et al. Lancet Oncol 2012; 13: 716–23

CALGB 50501: Lenalidomide Plus Bortezomib
A Negative Trial



	6 Month	1 Year	2 Year	3 Year	Median
OS	0.77 (0.64,0.86)	0.68 (0.54,0.79)	0.50 (0.36,0.63)	0.43 (02.9,0.56)	2.17 (1.15,4.58)
PFS	0.51 (0.37,0.63)	0.40 (0.27,0.52)	0.28 (0.17,0.41)	0.18 (0.09,0.29)	0.58 (0.29,1.15)
EFS	0.35 (0.23,0.49)	0.25 (0.14,0.37)	0.15 (0.07,0.26)	0.11 (0.04,0.21)	0.36 (0.18,0.50)



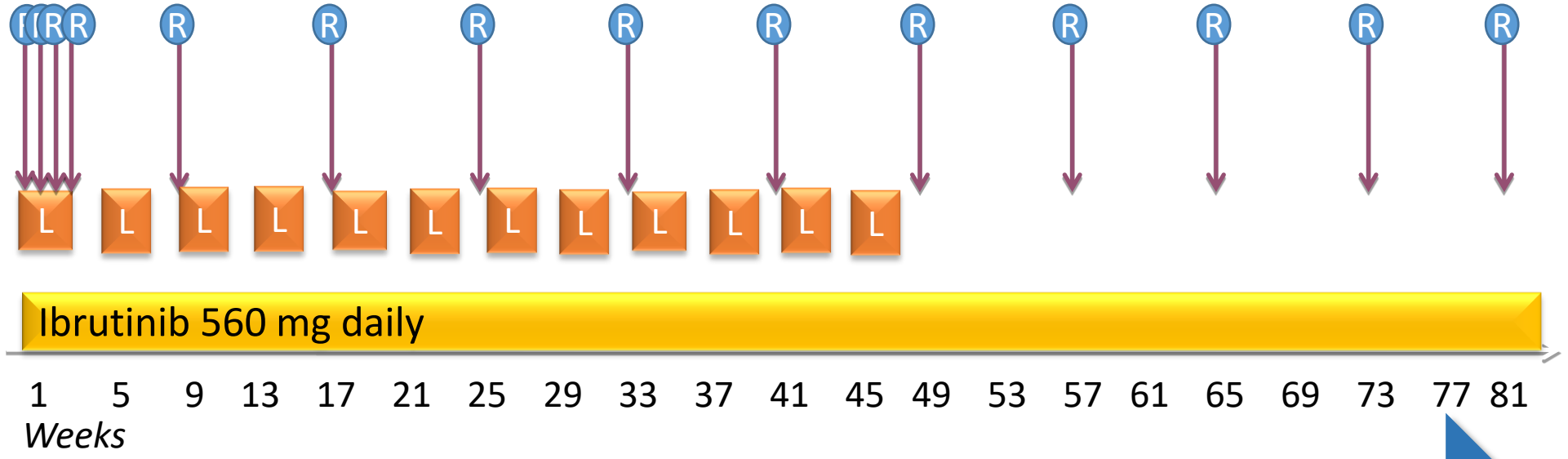
Morrison et al. Leuk & Lymphoma 2015

Bendamustine, Rituximab, Lenalidomide

	Doses	N	ORR/CR	Notes
Cheson	B 90mg/m^2 x 2 R 375 mg/m^2 x 1 L 20 mg x 21/28	20 All r/r MCL, n=1	35%/25%	Not worthy of further study
Hitz	B 70mg/m^2 x 2 R 375 mg/m^2 x 1 L 10 mg x 21/28	N=41 n=28 r/r MCL, n=1	61%/37% 55%/32%	14/41 completed 6 cycles 2 died with sudden death
Zaja	B 70mg/m^2 x 2 R 375 mg/m^2 x 1 L 10 mg x 14/28	N=42 All r/r All MCL	79%55%	Median PFS 20 mo. 71% G3-4 ANC

Cheson BJH 2015
Hitz et al. BJH 2016
Zaja et al. Haematologica 2017

Ibrutinib-Lenalidomide-Rituximab in Patients with Relapsed/Refractory Mantle Cell Lymphoma: First Results from the Nordic Lymphoma Group MCL6 (PHILEMON) Phase II Trial

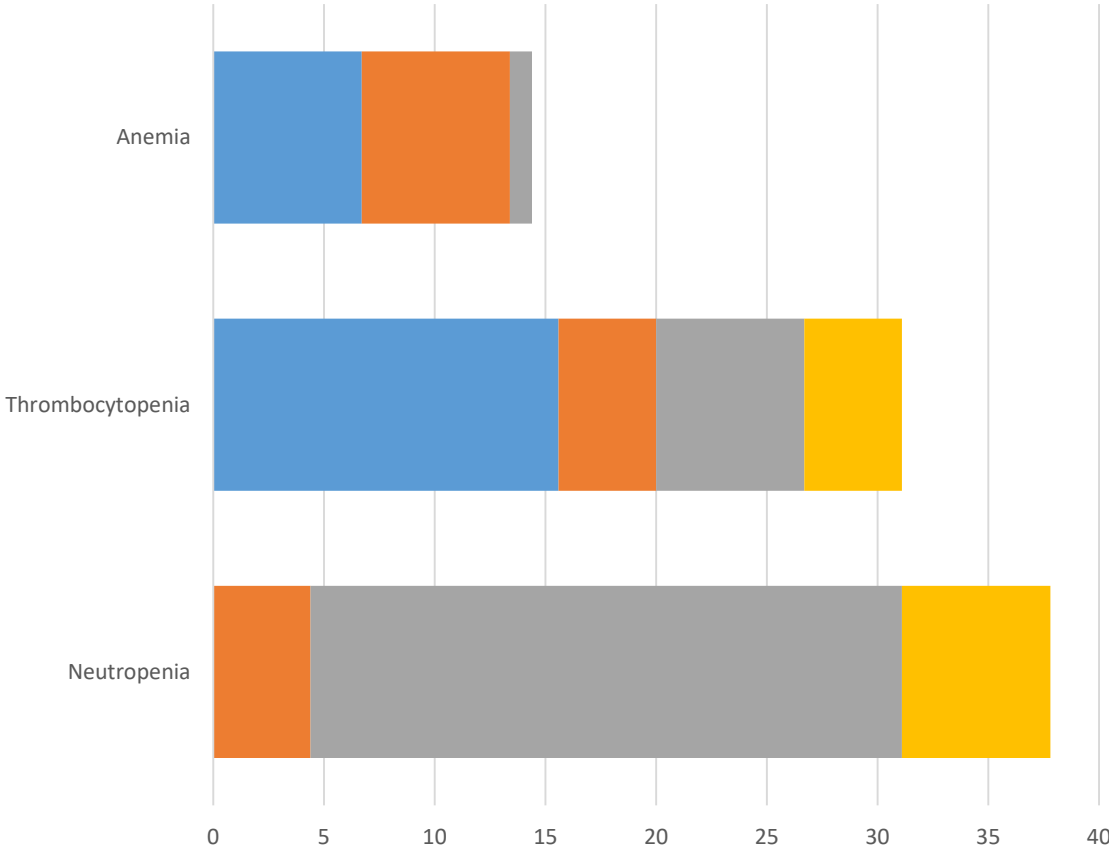


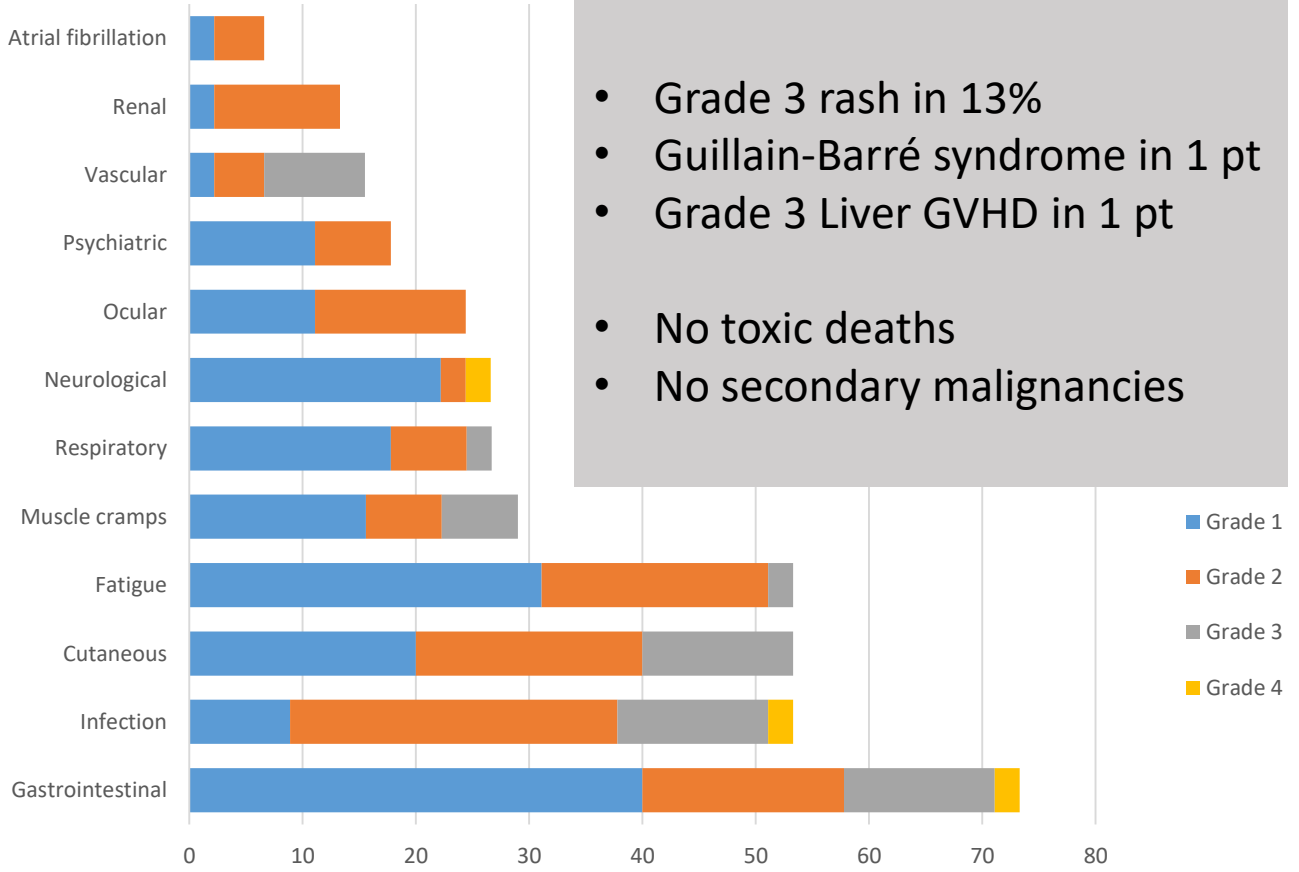
- R2 induction schedule adapted from Ruan et al, NEJM 2015
- Len 15 mg d 1-21, 28 days cycle, up to 12 months
- Eligible: R/R MCL, ≥1 rituximab regimen, no age limit
- Primary endpoint: ORR
- Aim: to improve ORR in R/R MCL, compared to single agent ibrutinib

Maintenance until progression

Jerkman et al. ASH 2016

AEs (359 cycles)





- Atrial fibrillation in 3 pts (6 %)
- Creatinine elevation in 11%

- Grade 3 rash in 13%
- Guillain-Barré syndrome in 1 pt
- Grade 3 Liver GVHD in 1 pt

- No toxic deaths
- No secondary malignancies

%

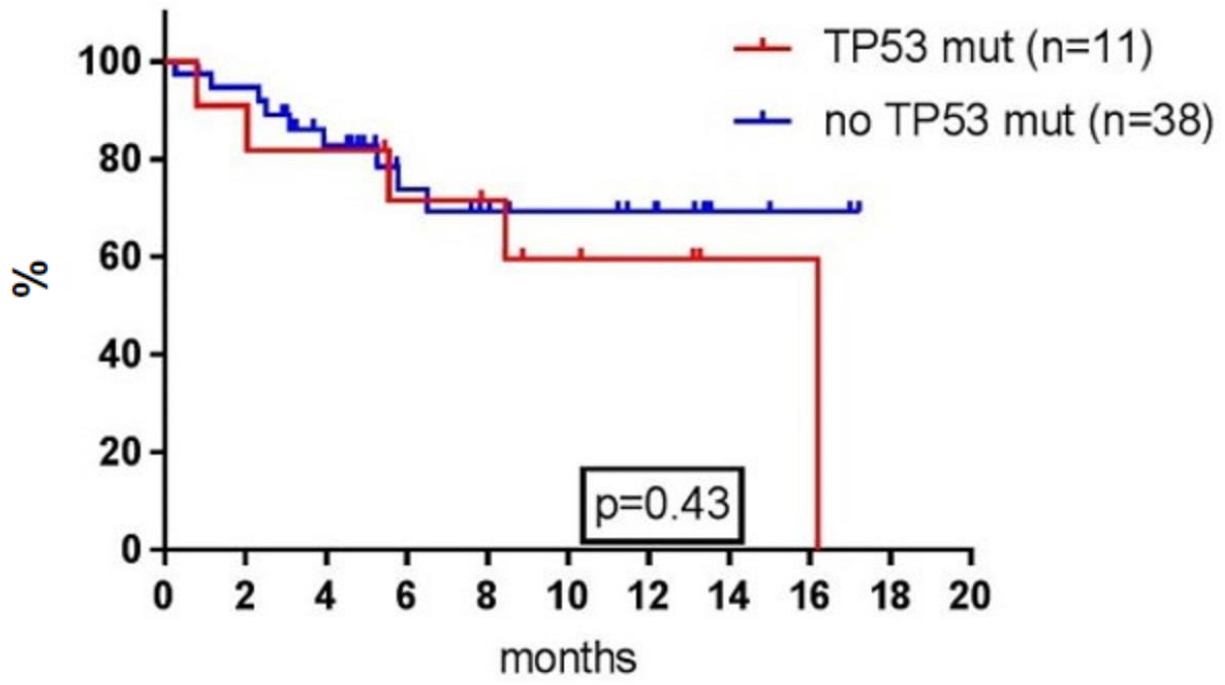
Response

	All patients		**No previous ibrutinib**		**Previous ibrutinib**		**Single ibrutinib Wang NEJM 2013**
	N=42	%	N=39	%	N=3	%	N=111
ORR	***37***	***88***	***35***	***90***	***2***	***67***	***68***
CR	27	64	27	69	0	0	21
PR	10	24	8	21	2	67	47
No response	5	12	4	10	1	33	20

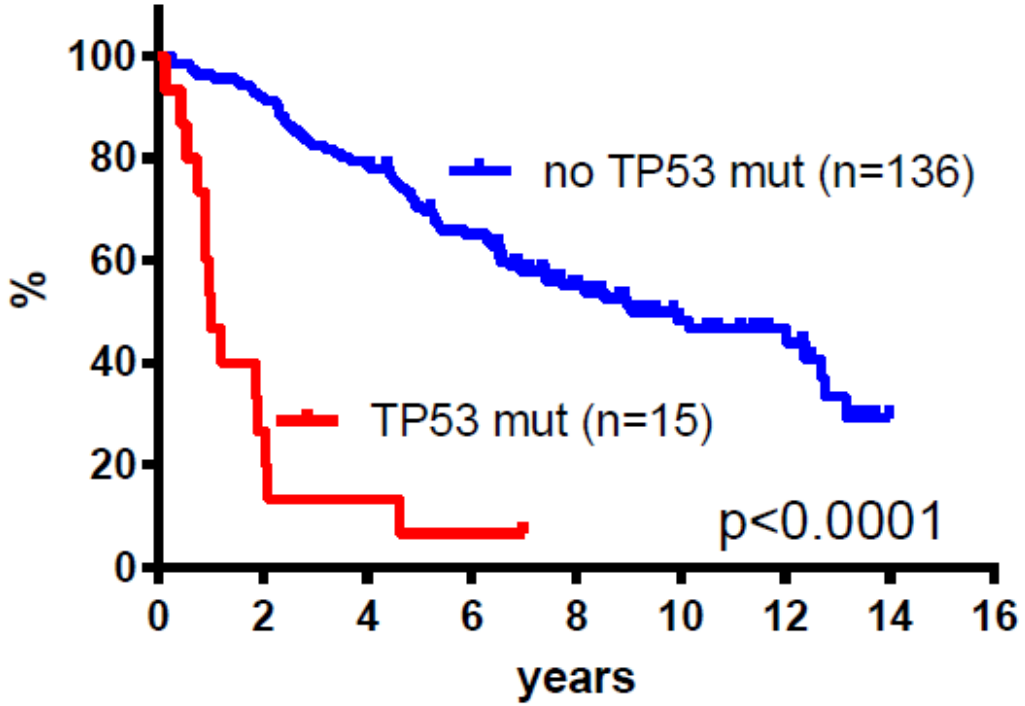
- PET-CT performed to confirm a CR, or at the time of maximal tumor reduction.
- 8 patients not evaluable

PFS according to *TP53* mutation

NORDIC MCL6 PHILEMON

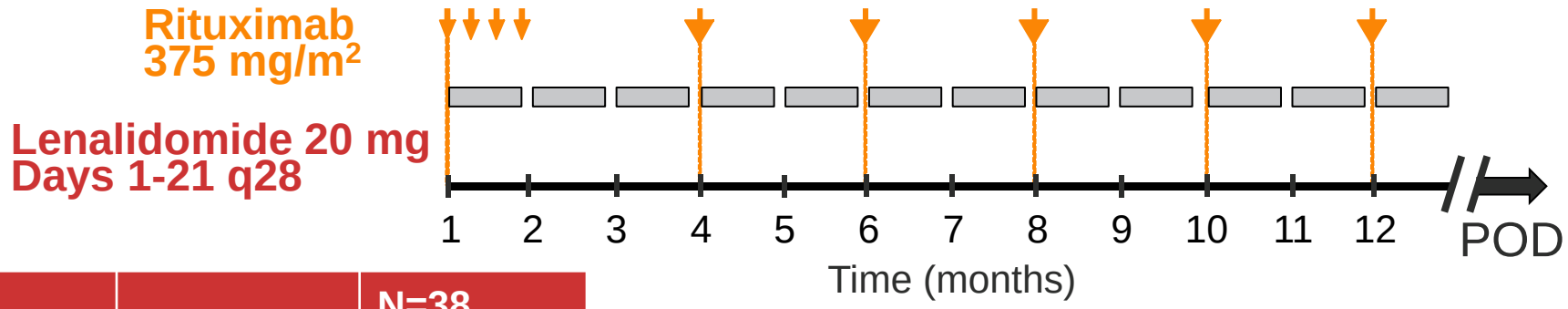


NORDIC MCL2/3

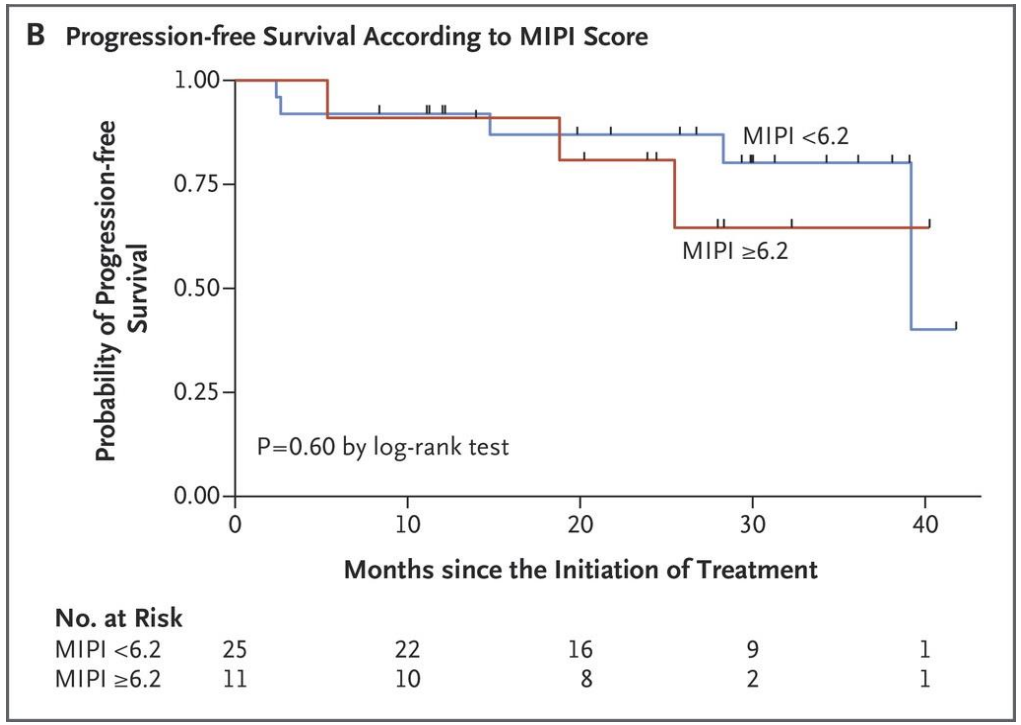


Eskelund C et al, ASH 2016
Abstract 1095, Dec 5, 17:00, Room 5AB

Frontline Lenalidomide Rituximab Appears Promising



		N=38
Age	65 years	42-86 y
MIPI	Low	13
	Int	13
	High	12
Ki67	<30%	26
	>30%	8
RR	CR	61%
	PR	26%
	SD	3%
	PD	5%



Ruan J et al. N Engl J Med 2015;373:1835-1844.

Progression following non-traditional regimens may have unique outcomes

- 8 patients progressed
  - 3 with primary refractory disease, 5 with responders (2 CR, 3 PR)
  - 4 had re-biopsy with no significant change in Ki67
  - 7 responded to subsequent therapy

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.

Ruan J et al. N Engl J Med 2015;373:1835-1844.

Non-traditional regimens have unique side effect profiles

Figure S3. QOL by FACT-Lym

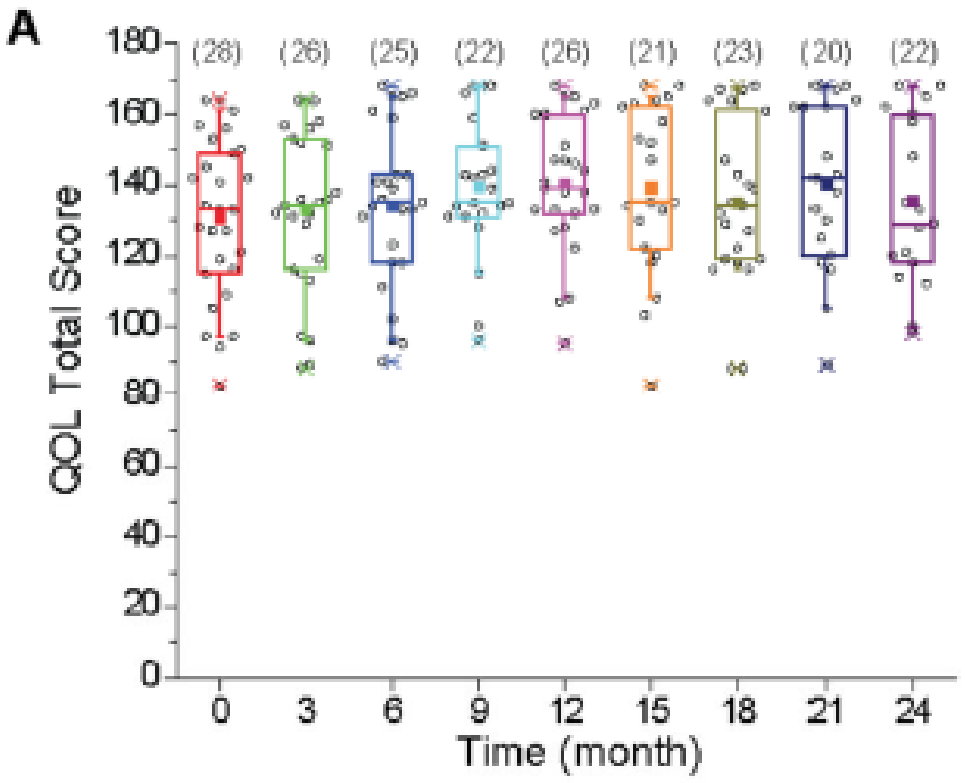


Table S3. Hospitalization*

	Induction		Maintenance	
Admission Diagnosis	**No.**	**Percentage**	**No.**	**Percentage**
Tumor flare	4	10.5%	0	0
Serum sickness	3	7.9%	0	0
Non-neutropenic fever	2	5.2%	1	2.6%
Infusion reaction	1	2.6%	0	0
Pneumonia	1	2.6%	2	5.2%
Dyspnea	1	3%	0	0
Hypothyroidism	1	2.6%	0	0
Neutropenic fever	0	0	2	5.2%
Total	13	34.2%	5	13.2%

* Only hospitalizations possibly related to treatment were included.

Ruan J et al. N Engl J Med 2015;373:1835-1844.

Conclusions

- Lenalidomide has clear activity in MCL but it's utility post-ibrutinib is limited.
- Lenalidomide-based combinations (e.g., lenalidomide + ibrutinib) might have a role in some patients.
- Lenalidomide/rituximab may have a role in previously untreated patients.
- Lenalidomide/rituximab is associated with immune mediated adverse events as well as cytopenias, both of which may limit utility in some patient populations.