NUOVI ORIZZONTI TERAPEUTICI NEL MONDO DEI LINFOMI

Bologna 5 novembre 2018

Lenalidomide nel linfoma mantellare

Gli studi clinici

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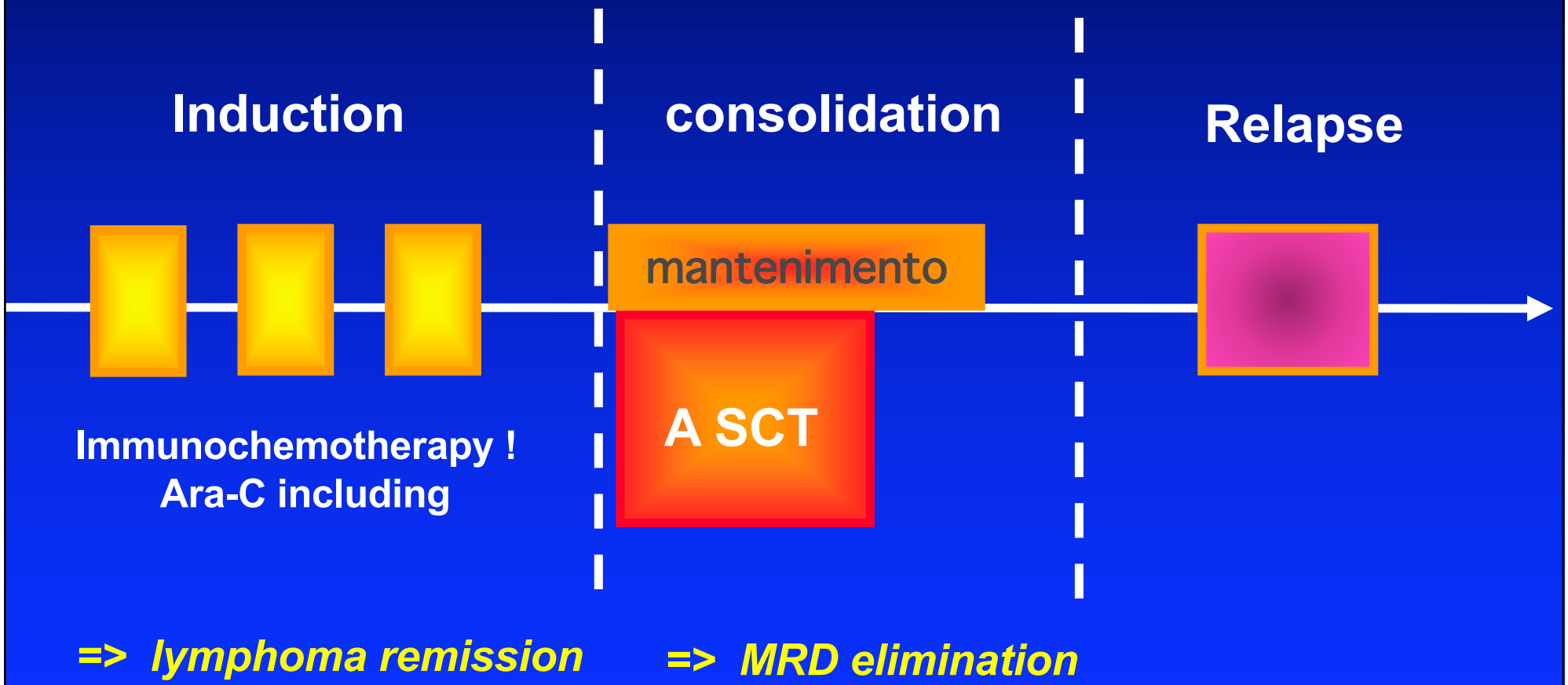
Mantle cell lymphoma (MCL)

- About 6% of non Hodgkin's lymphomas
- Predominantly elderly (>60), male patients
- Advanced Ann Arbor stage
- Extranodal involvement (bone marrow, gastrointestinal tract, liver, spleen)

The optimal strategy of MCL

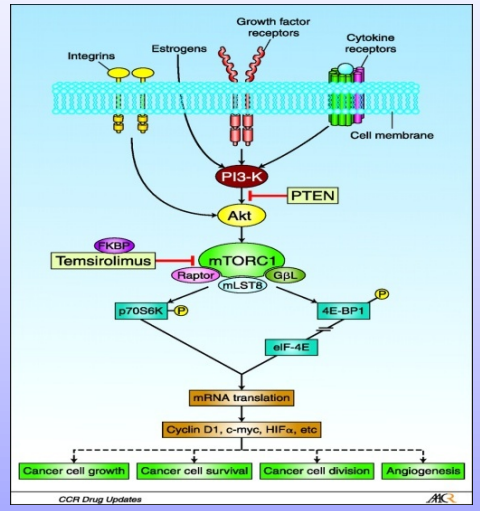


MCL: new options

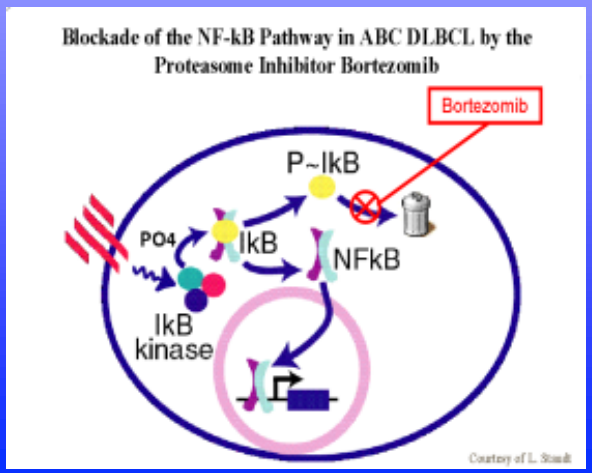
Signaling pathway inhibition

- Immunomodulators: lenalidomide
- Proteasome inhibitors: bortezomib
- mTOR inhibitors: everolimus, temsirolimus
- HDACs inhibitors: Abexinostat
- BCR inhibitors (BTKI: PCI-32765)
- Inhibitors of Syk in B-cell signaling pathway: tamatinib
- PI3K inhibitors: CAL-101
- Pro-apoptotic ABT-199 Bcl-2 family; AT-101 Bcl-2 family

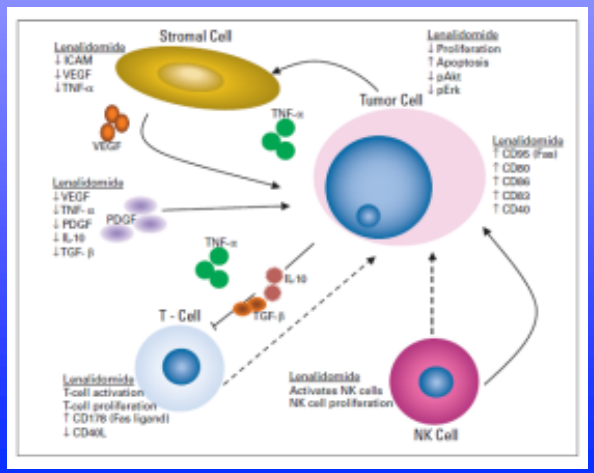
Temsirolimus



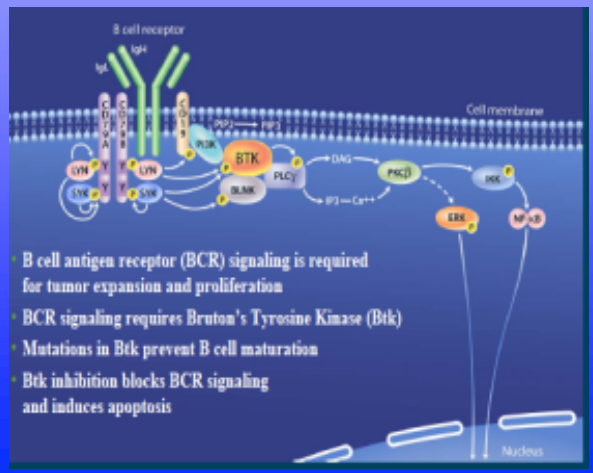
Bortezomib



Lenalidomide



BTKI Ibrutinib



R/R MCL
Single agent

Lenalidomide has been evaluated in patients with relapsed or refractory (R/R) mantle cell lymphoma (MCL) in

Phase II studies and a retrospective analysis as a single agent

Phase II and Phase I/II studies in combination with other agents (e.g., rituximab, dexamethasone, bortezomib, and thalidomide).

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JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

49 patients (15 MCL)

25 mg daily on Days 1-21 of each 28-day treatment cycle

Lenalidomide Monotherapy in Relapsed or Refractory Aggressive Non-Hodgkin's Lymphoma

Peter H. Wiernik, Izidore S. Lossos, Joseph M. Tuscano, Glen Justice, Julie M. Vose, Craig E. Cole, Wendy Lam, Kyle McBride, Kenton Wride, Dennis Pietronigro, Kenichi Takeshita, Annette Ervin-Haynes, Jerome B. Zeldis, and Thomas M. Habermann

ORR	**53%**
CR	**13%**
PR	**40%**
DoR	**6.2 mo**

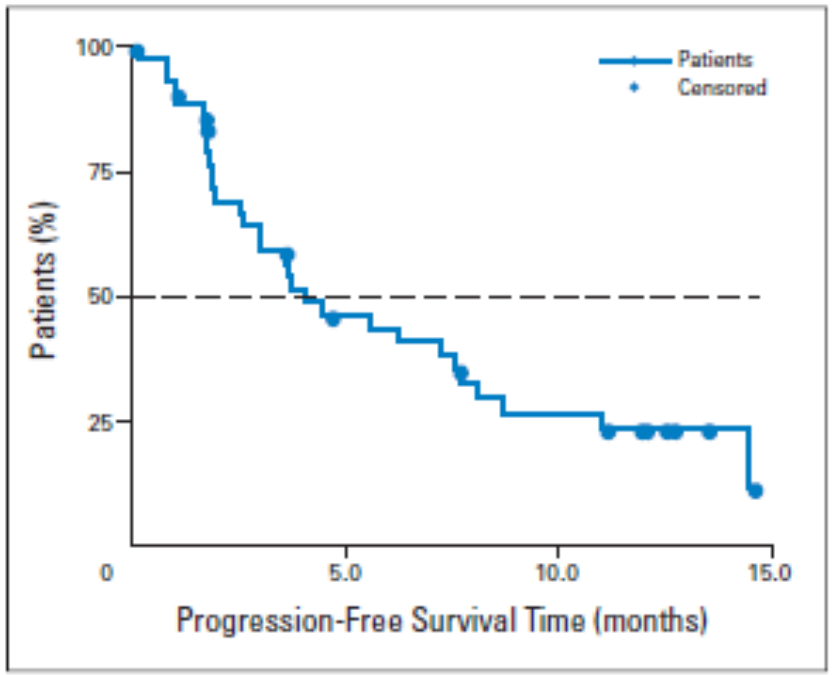


Fig 1. Kaplan-Meier plot of progression-free survival.

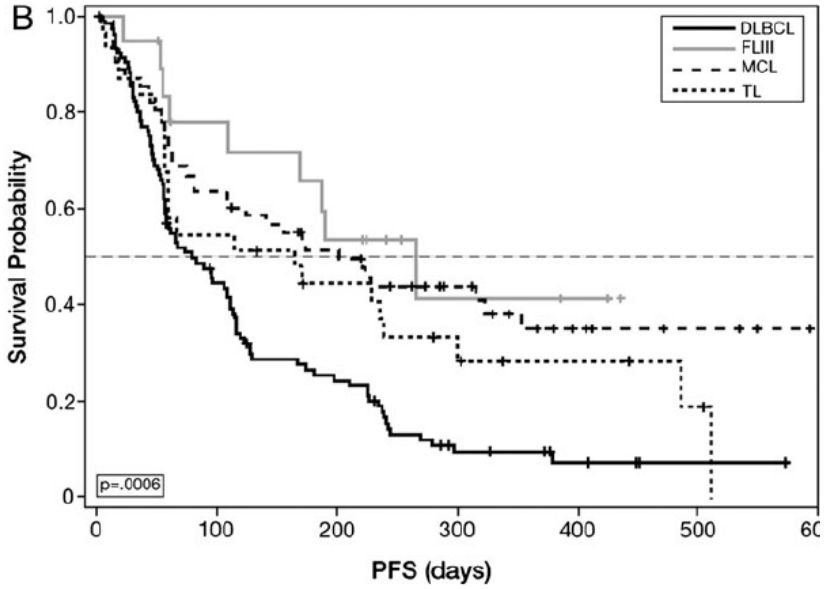
An international phase II trial of single-agent lenalidomide for relapsed or refractory aggressive B-cell non-Hodgkin's lymphoma

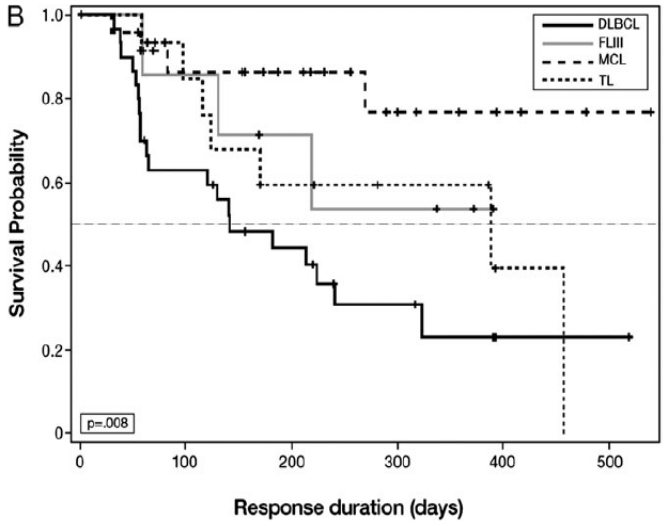
217 pts (57 MCL)

T. E. Witzig[1]*, J. M. Vose[2], P. L. Zinzani[3], C. B. Reeder[4], R. Buckstein[5], J. A. Polikoff[6], R. Bouabdallah[7], C. Haioun[8], H. Tilly[9], P. Guo[10], D. Pietronigro[10], A. L. Ervin-Haynes[10] & M. S. Czuczman[11]

[1]Department of Medicine, Division of Hematology, Mayo Clinic, Rochester; [2]Section of Hematology/Oncology, University of Nebraska, Omaha, USA; [3]Institute of Hematology and Oncology Seragnoli, University of Bologna, Bologna, Italy; [4]Department of Medicine, Division of Hematology, Mayo Clinic, Scottsdale, USA; [5]Department of Hematology, Sunnybrook Odette Cancer Center, Toronto, Canada; [6]Department of Hematology/Oncology, Kaiser Permanente Medical Group, San Diego, USA; [7]Department of Hematology, Institut Paoli Calmettes, Marseilles; [8]Department of Hôpital Henri Mondor-AP-HP, Créteil; [9]Department of Centre Henri Becquerel, Rouen, France; [10]Department of Celgene Corporation, Summit; [11]Department of Medicine, Lymphoma/Myeloma Service, Roswell Park Cancer Institute, Buffalo, USA

ORR	**42%**
CR	**21%**
PR	**21%**





Long-term follow-up of lenalidomide in relapsed/refractory mantle cell lymphoma: subset analysis of the NHL-003 study

P. L. Zinzani[1], J. M. Vose[2], M. S. Czuczman[3], C. B. Reeder[4], C. Haioun[5], J. Polikoff[6], H. Tilly[7], L. Zhang[8], K. Prandi[8], J. Li[8] & T. E. Witzig[9*]

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Outcomes	Central review	Investigator review
Response rates[a], *n* (%)		
ORR[b]	20 (35)	25 (44)
CR/CRu	7 (12)	12 (21)
PR	13 (23)	13 (23)
SD	25 (44)	13 (23)
PD	12 (21)	12 (21)
No response assessment/missing	0	7 (12)
Median TTFR[c], month (range)	1.9 (1.6–24.2)	1.9 (1.6–15.2)
Median DOR, month (95% CI)	16.3 (7.1-NR)	NR (15.4-NR)
Median DOR for CR/CRu, month (95% CI)	NR (9.7-NR)	NR (28.8-NR)
Median PFS, month (95% CI)	8.8 (5.5–23.0)	5.7 (2.7–10.7)
Median TTP, month (95% CI)	8.8 (5.5–23.0)	7.3 (3.6–17.2)

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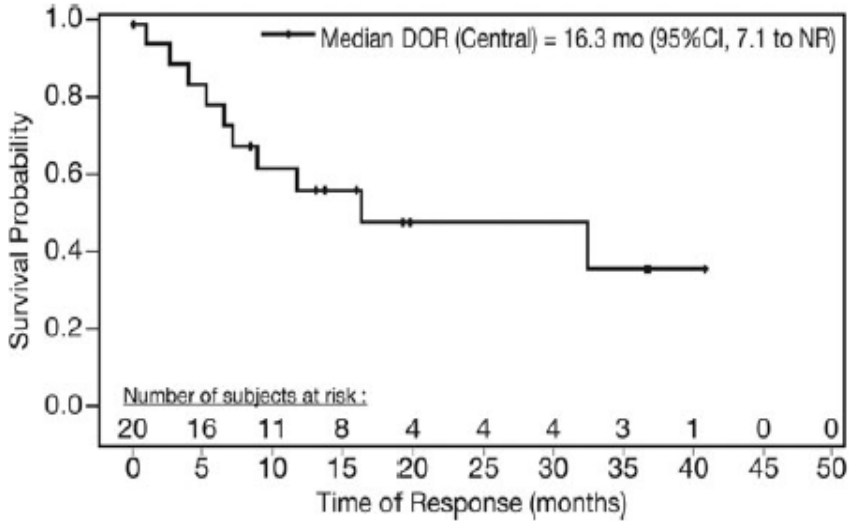

Figure 1. Median duration of response (DOR) of single-agent lenalidomide for responders with relapsed/refractory MCL (central review).

Table 3. Treatment-related grade 3/4 adverse events (AEs) occurring in ≥5% of patients ($n = 57$)

Adverse event	All grade, *n* (%)	Grade 3/4, *n* (%)
Hematologic		
Neutropenia	30 (53)	26 (46)
Thrombocytopenia	25 (44)	17 (30)
Anemia	20 (35)	7 (12)
Nonhematologic		
Fatigue	22 (39)	5 (9)
Diarrhea	16 (28)	3 (5)
Dyspnea	9 (16)	3 (5)
Pleural effusion	7 (12)	4 (7)
Pain	3 (5)	3 (5)

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

134 patients

25 mg daily on Days 1-21 of each 28-day treatment cycle

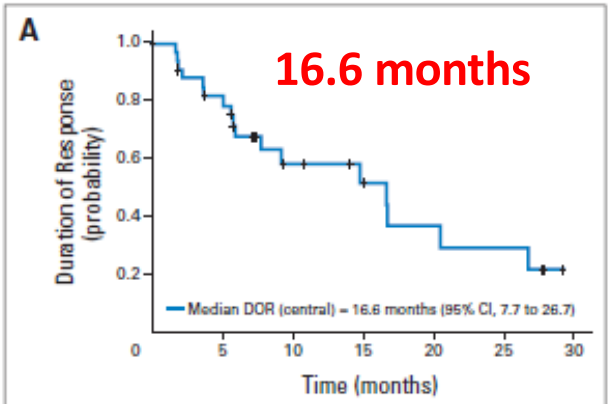
Single-Agent Lenalidomide in Patients With Mantle-Cell Lymphoma Who Relapsed or Progressed After or Were Refractory to Bortezomib: Phase II MCL-001 (EMERGE) Study

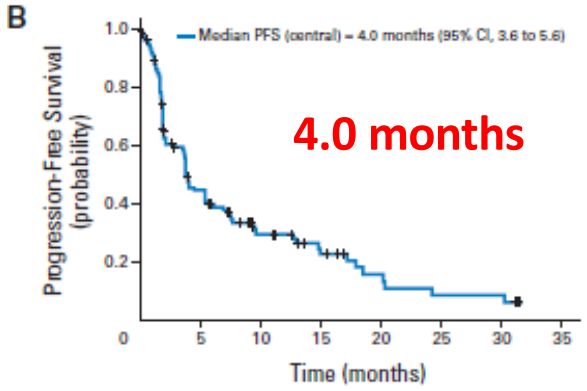
Andre Goy, Rajni Sinha, Michael E. Williams, Sevgi Kalayoglu Besisik, Johannes Drach, Radhakrishnan Ramchandren, Lei Zhang, Sherri Cicero, Tommy Fu, and Thomas E. Witzig

ORR 28%

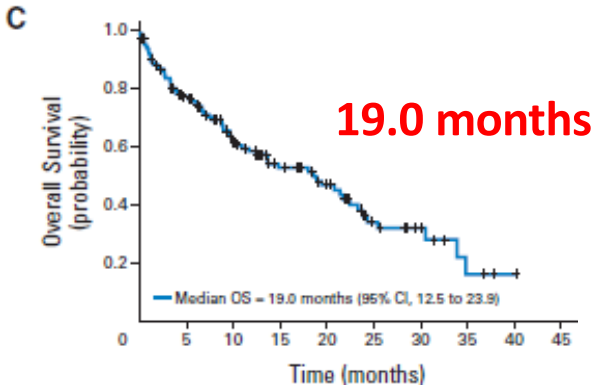
CR 7.5%

PR 20%





DoR 29.2 mo

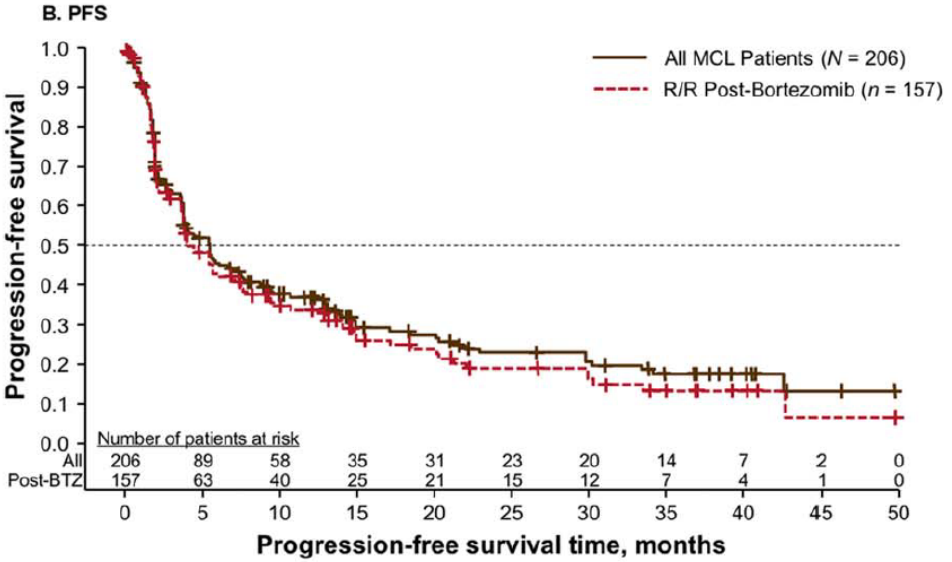


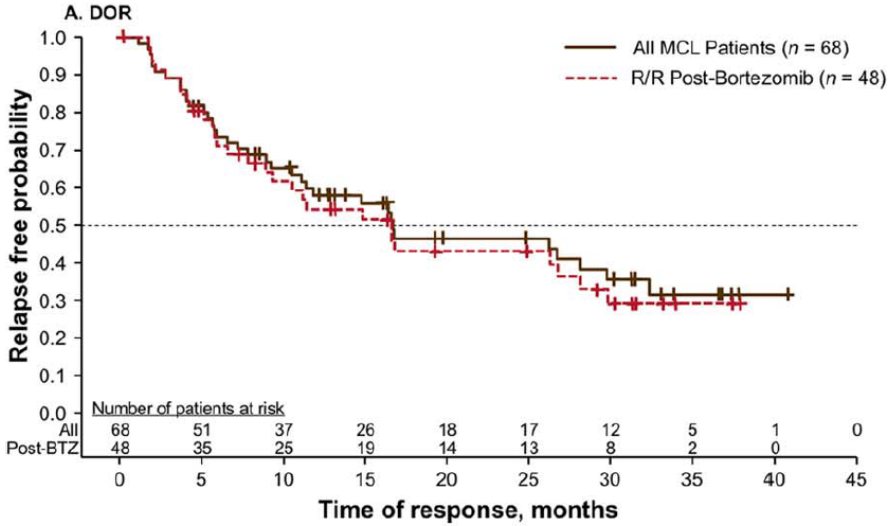
RESEARCH ARTICLE

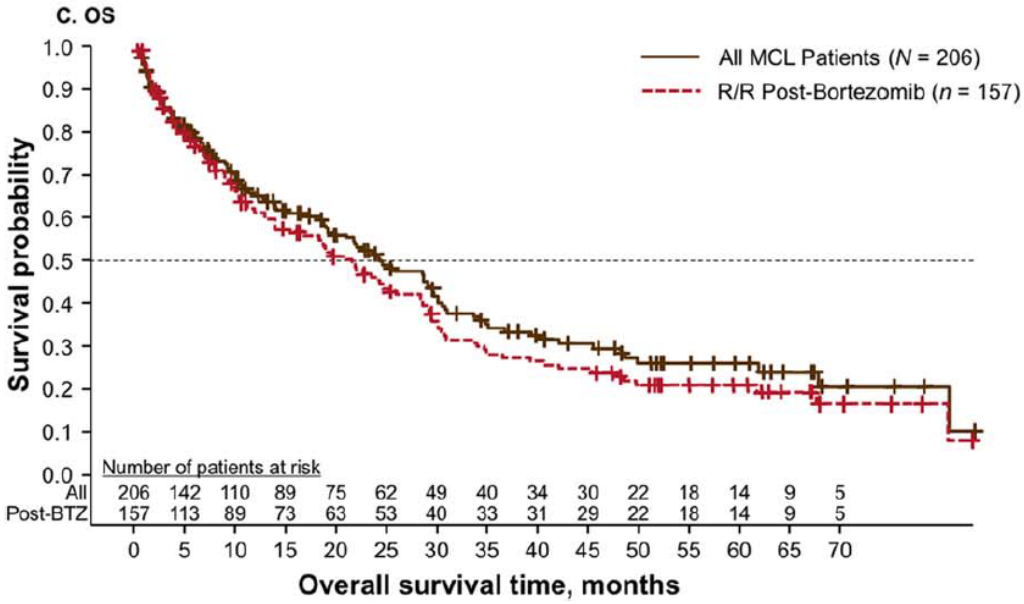
WILEY AJH

Long-term analysis of phase II studies of single-agent lenalidomide in relapsed/refractory mantle cell lymphoma

Thomas E. Witzig[1] | Pier Luigi Zinzani[2] | Thomas M. Habermann[1] | Joseph M. Tuscano[3] | Johannes Drach[4] | Radhakrishnan Ramchandren[5] | Sevgi Kalayoglu Besisik[6] | Kenichi Takeshita[7] | Marie-Laure Casadebaig Bravo[8] | Lei Zhang[7] | Tommy Fu[7] | Andre Goy[9]

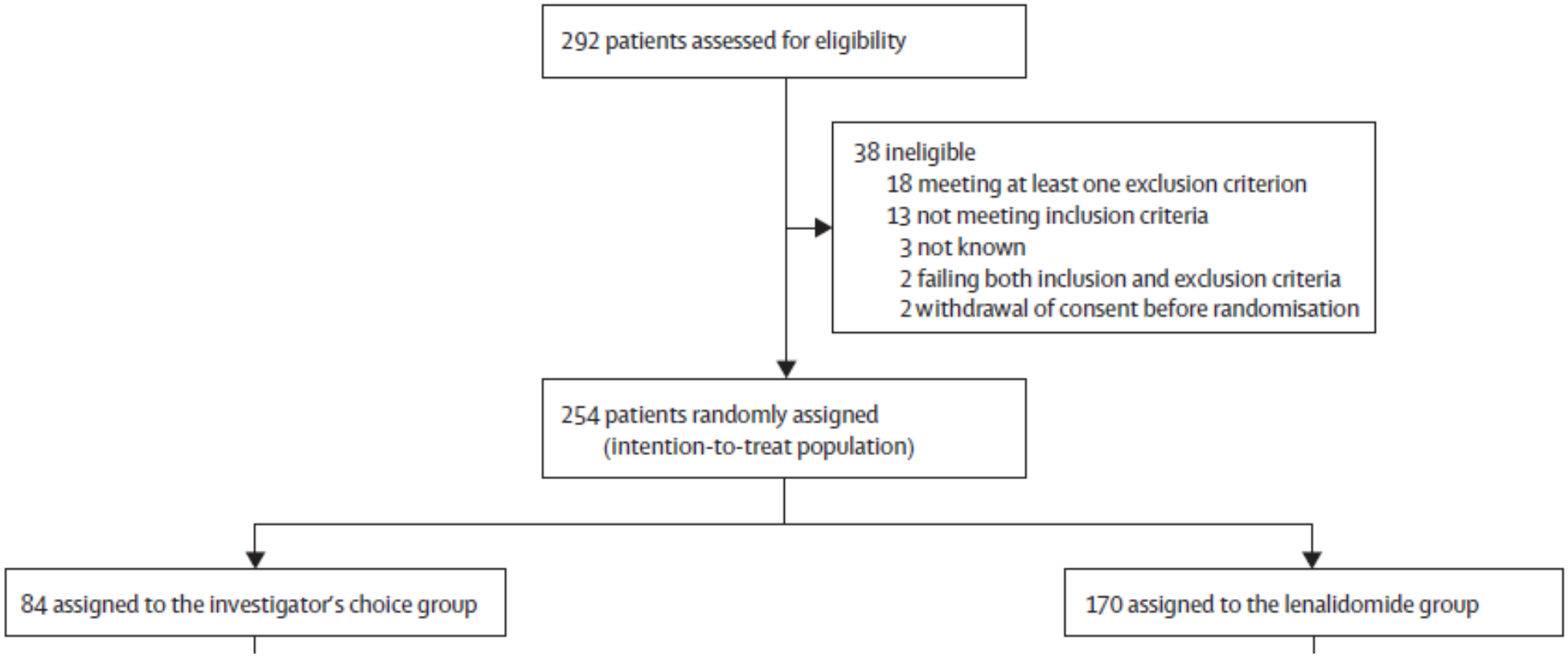






Lenalidomide versus investigator's choice in relapsed or refractory mantle cell lymphoma (MCL-002; SPRINT): a phase 2, randomised, multicentre trial

Marek Trněný, Thierry Lamy, Jan Walewski, David Belada, Jiri Mayer, John Radford, Wojciech Jurczak, Franck Morschhauser, Julia Alexeeva, Simon Rule, Boris Afanasyev, Kamil Kaplanov, Antoine Thyss, Alexej Kuzmin, Sergey Voloshin, Kazimierz Kuliczkowski, Agnieszka Giza, Noel Milpied, Caterina Stelitano, Reinhard Marks, Lorenz Trümper, Tsvetan Biyukov, Meera Patturajan, Marie-Laure Casadebaig Bravo, Luca Arcaini, on behalf of the SPRINT trial investigators and in collaboration with the European Mantle Cell Lymphoma Network



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ORR 40% vs. 11%; *P<.001; CR/CRu 5% vs. 0%; P =.04*

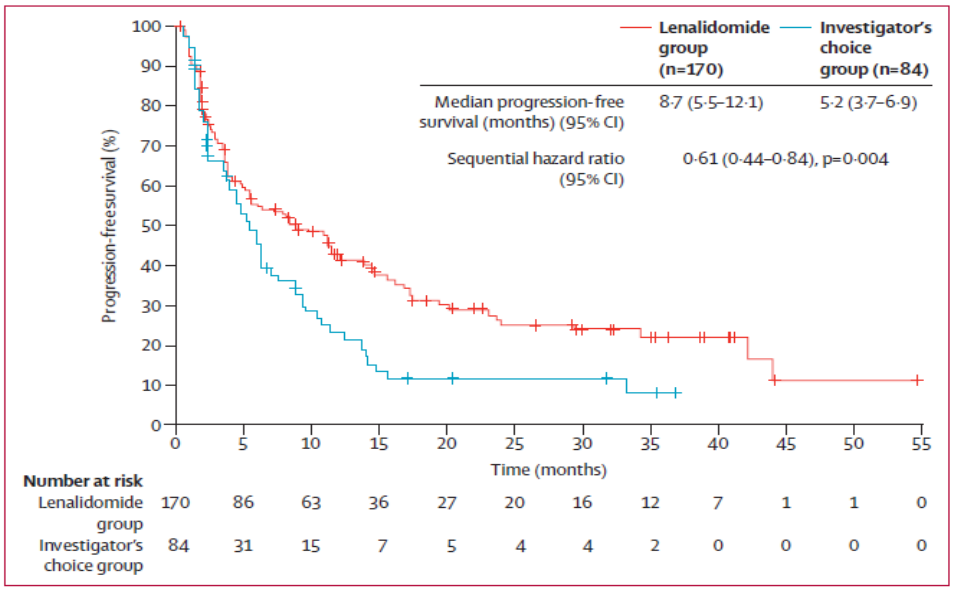


Figure 2: Progression-free survival with lenalidomide compared with investigator's choice in relapsed or refractory mantle cell lymphoma (central review)

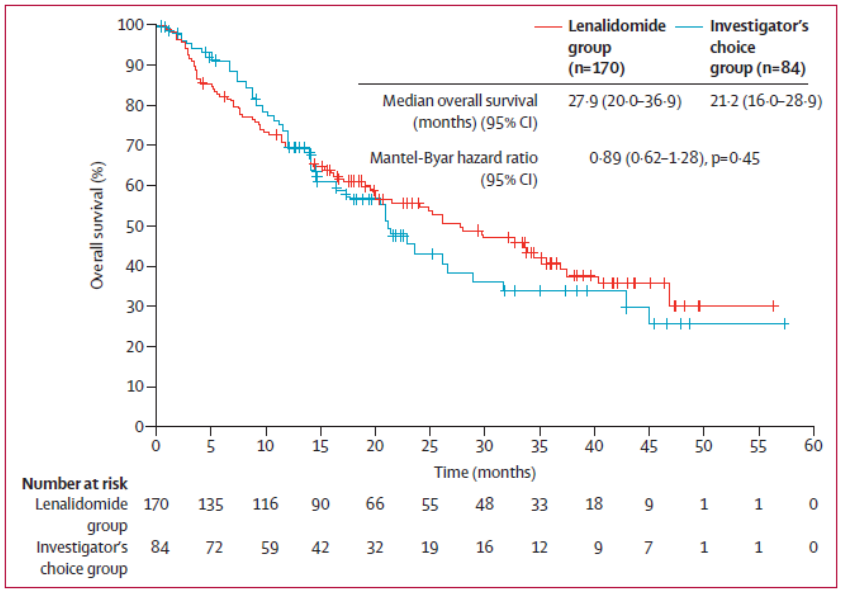
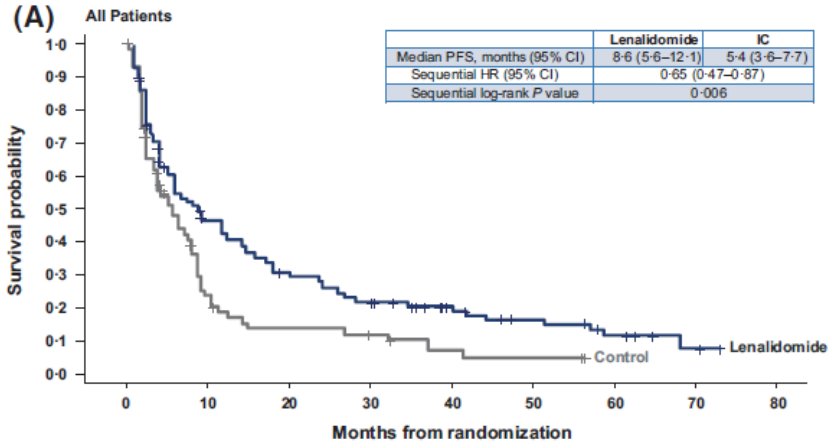
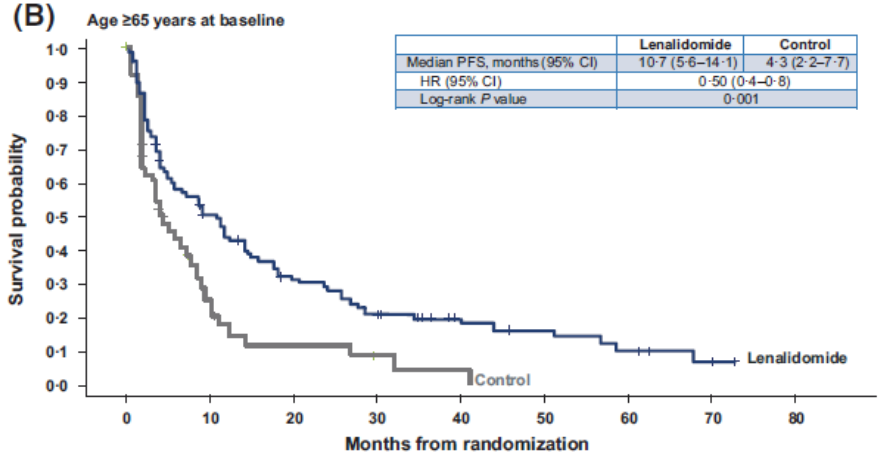


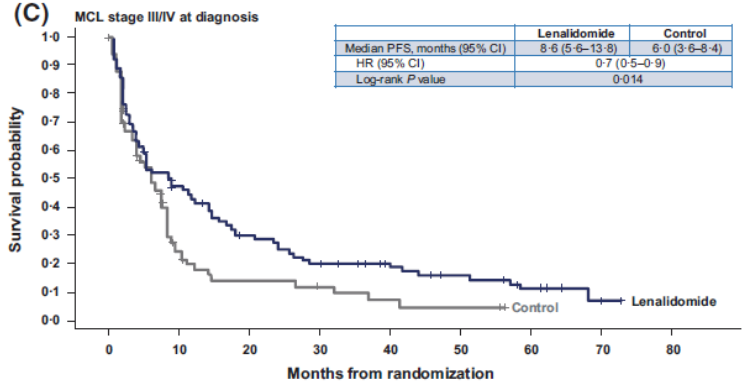
Figure 4: Overall survival with lenalidomide compared with investigator's choice in relapsed or refractory mantle cell lymphoma (central review)

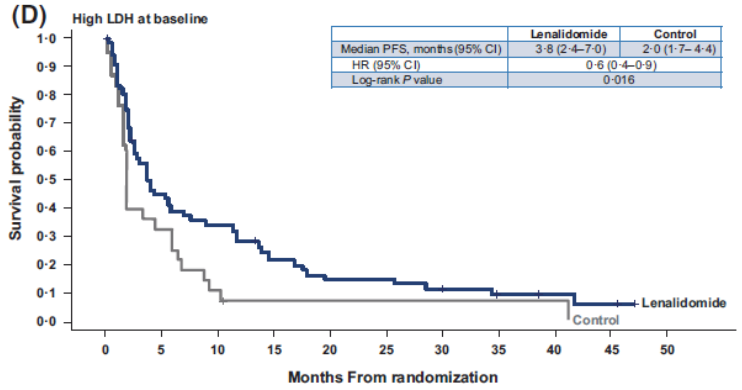
bjh research paper

Prospective subgroup analyses of the randomized MCL-002 (SPRINT) study: lenalidomide *versus* investigator's choice in relapsed or refractory mantle cell lymphoma





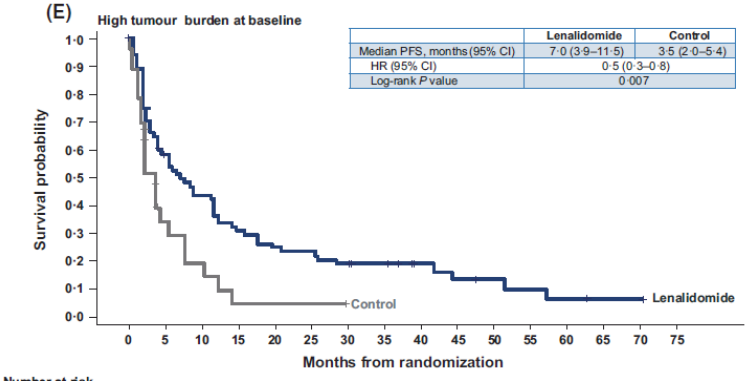




Prospective subgroup analyses of the randomized MCL-002 (SPRINT) study: lenalidomide *versus* investigator's choice in relapsed or refractory mantle cell lymphoma

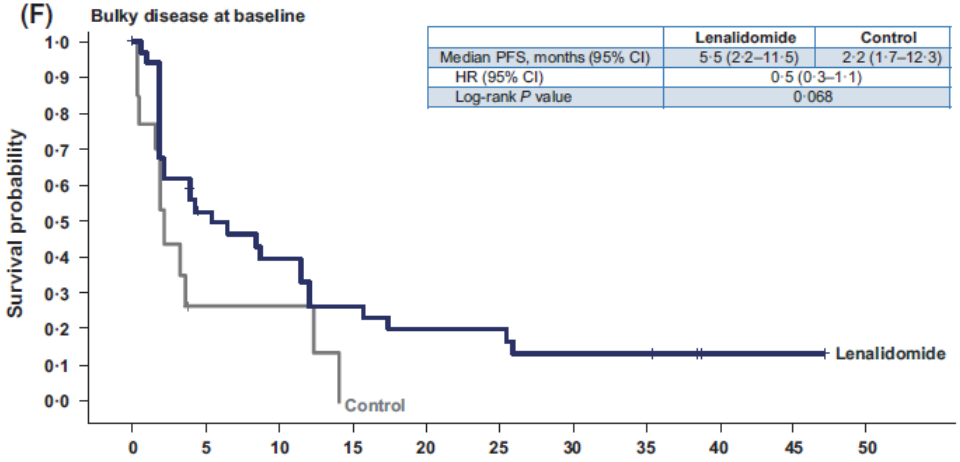
(E) High tumour burden at baseline

	Lenalidomide	Control
Median PFS, months (95% CI)	7·0 (3·9–11·5)	3·5 (2·0–5·4)
HR (95% CI)	0·5 (0·3–0·8)	
Log-rank *P* value	0·007	



(F) Bulky disease at baseline

	Lenalidomide	Control
Median PFS, months (95% CI)	5·5 (2·2–11·5)	2·2 (1·7–12·3)
HR (95% CI)	0·5 (0·3–1·1)	
Log-rank *P* value	0·068	



(G) Refractory patients

	Lenalidomide	Control
Median PFS, months (95% CI)	6·1 (3·5–13·8)	1·9 (1·3–4·3)
HR (95% CI)	0·3 (0·2–0·6)	
Log-rank *P* value	<0·001	

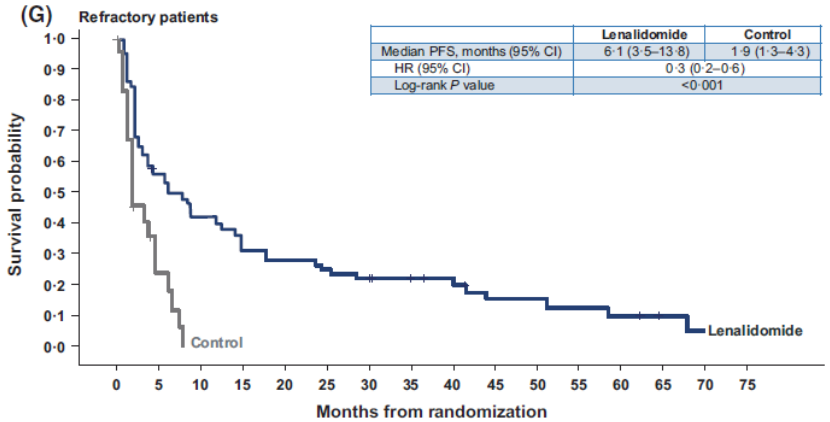


Table I. Univariate and multivariate analyses by Cox Regression on PFS by investigator assessment.*

Baseline variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Treatment (lenalidomide *versus* IC)	0·65 (0·48–0·87)	0·005	0·42 (0·28–0·62)	<0·001
MIPI-based characteristics				
MIPI score at diagnosis (high *versus* low/intermediate)†	1·57 (1·12–2·20)	0·009	—	—
MIPI score at baseline (high *versus* low/intermediate)†	2·11 (1·57–2·83)	<0·001	1·51 (1·00–2·27)	0·052
Age, years (≥65 vs. <65)	1·02 (0·75–1·38)	0·919	—	—
ECOG PS (2 vs. 0–1)	1·46 (0·99–2·16)	0·053	—	—
LDH (high *versus* low/normal)‡	2·00 (1·49–2·67)	<0·001	2·02 (1·35–3·01)	<0·001
WBC (≥10 × 10^9/l vs. <10 × 10^9/l)	1·55 (1·08–2·21)	0·017	—	—
Other patient characteristics				
Sex (female *versus* male)	0·86 (0·62–1·18)	0·348	—	—
MCL stage at diagnosis (III/IV *versus* I/II)	0·81 (0·46–1·42)	0·461	—	—
Tumour burden (low *versus* high)§	0·81 (0·60–1·08)	0·155	—	—
Bulky disease (yes *versus* no)¶	1·40 (0·98–2·01)	0·063	1·57 (1·01–2·43)	0·045
Bone marrow assessment (negative *versus* indeterminate/positive)**	0·72 (0·44–1·20)	0·206	—	—
Renal function (normal *versus* moderate/severe insufficiency)††	0·60 (0·43–0·84)	0·003	—	—
Prior treatment history				
Time from MCL diagnosis to first dose (≥3 *versus* <3 years)	0·85 (0·64–1·14)	0·280	—	—
Number of prior systemic antilymphoma therapies (≥3 *versus* <3)	1·51 (1·11–2·06)	0·009	1·75 (1·19–2·58)	0·005
Disease status to last prior therapy (relapsed‡‡ *versus* refractory)	0·77 (0·58–1·03)	0·075	—	—
Time from last prior therapy to first dose (≥6 vs. <6 months)	0·74 (0·55–0·98)	0·034	0·68 (0·47–0·97)	0·032
Time since last rituximab to first dose (≥230 vs. <230 days)	0·79 (0·59–1·07)	0·127	—	—
Prior HDT (yes *versus* no)§§	0·98 (0·68–1·42)	0·930	—	—
Prior SCT (yes *versus* no)	0·96 (0·66–1·39)	0·837	—	—

Table 1. Clinical efficacy of single-agent lenalidomide in relapsed/refractory NHL

Study	Patients/subset	*n*	Median age, years/prior therapies, *n*	ORR (%)	CR/CRu (%)	Median DOR, months (95% CI)	Median PFS, months (95% CI)
NHL-001 [24]	All patients	43	63/3	23	7	>16.5 (15.5–NR)	4.4 (2.5–10.4)
	FL grade 1/2	22	–	27	9		
	SLL	18	–	22	6		
NHL-002 [25, 26]	All patients	49	65/4	35	12	6.2 (range, 0–12.8)	4.0 (range, 0–14.5)
	DLBCL	26	–	19	12	–	–
	MCL	15	66/4	53	20	13.7 (4.0-NR)	5.6 (2.6–18.2)
	FL grade 3	5	–	60	20	–	–
NHL-003 [27, 28]	All patients	217	66/3	35	13	10.6 (7.0–NR)	3.7 (2.7–5.1)
	DLBCL	108	–	28	7	4.6	2.7
	MCL	57	68/3	35	12	16.3 (7.1–NR)	8.8 (5.5–23.0)
	TL	33	–	45	21	12.8	5.4
	FL grade 3	19	–	42	11	NR	8.9
MCL-001 [29]	MCL	134	67/4	28	7.5	16.6 (7.7–26.7)	4.0 (3.6–5.6)
Pooled analyses [30–32]	MCL	206	67/4	32	10	16.6 (9.2–32.4)	5.4 (3.7–6.7)
	DLBCL	134	66/3	26	9	6.0	–
Lenalidomide lower dose [33]	MCL	26	66/3	31	8	22.2 (0–53.6)	3.9 (0–11.1)

CR, complete response; CRu, unconfirmed CR; DLBCL, diffuse large B-cell lymphoma; DOR, duration of response; FL, follicular lymphoma; MCL, mantle cell lymphoma; NHL, non-Hodgkin lymphoma; NR, not reached; ORR, objective response rate; PFS, progression-free survival; SLL, small lymphocytic lymphoma; TL, transformed large B-cell lymphoma.

Witzig et al. Ann Oncol 2015

R/R MCL
Combination therapy

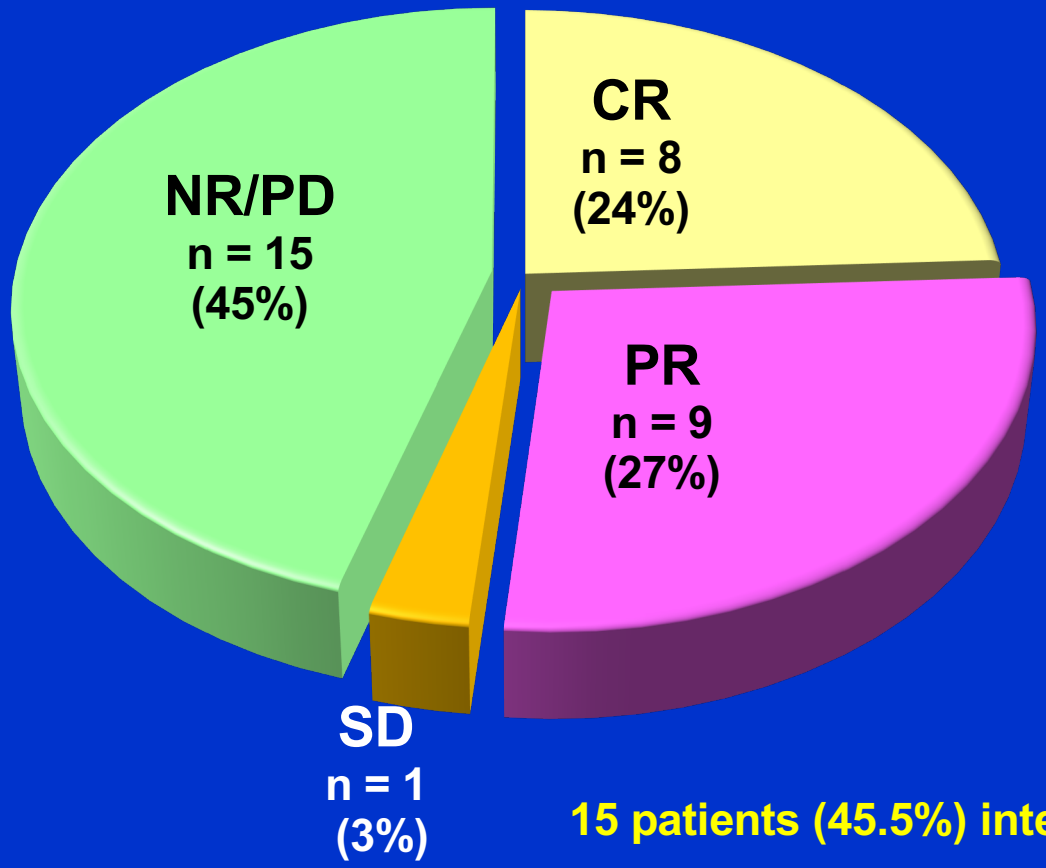
MCL: Len-Dex

Characteristic, n (%)	N = 33
Males	21 (64)
Histology: Classic	30 (91)
: Blastoid	3 (9)
Median age, years (range)	68 (21–80)
Median number of prior therapies, n (range)	3 (1–7)
Lines of prior therapy:	
2	10 (30)
3	10 (30)
> 3	13 (39)
Prior autologous SCT	12 (36)
Prior bortezomib	8 (24)
Response to last therapy	
CR	12 (36)
PR	9 (27)
SD	2 (6)
NR/PD	10 (30)

NR, no response; PD, progressive disease.

Zaja et al Haemaologica 2012

Response to Lenalidomide plus Dexamethasone after Therapy Completion

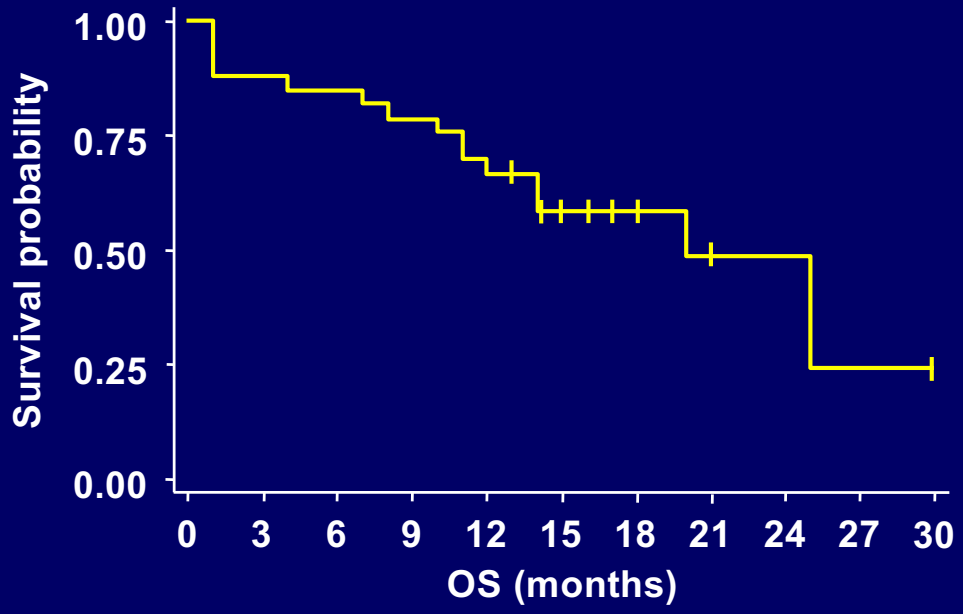


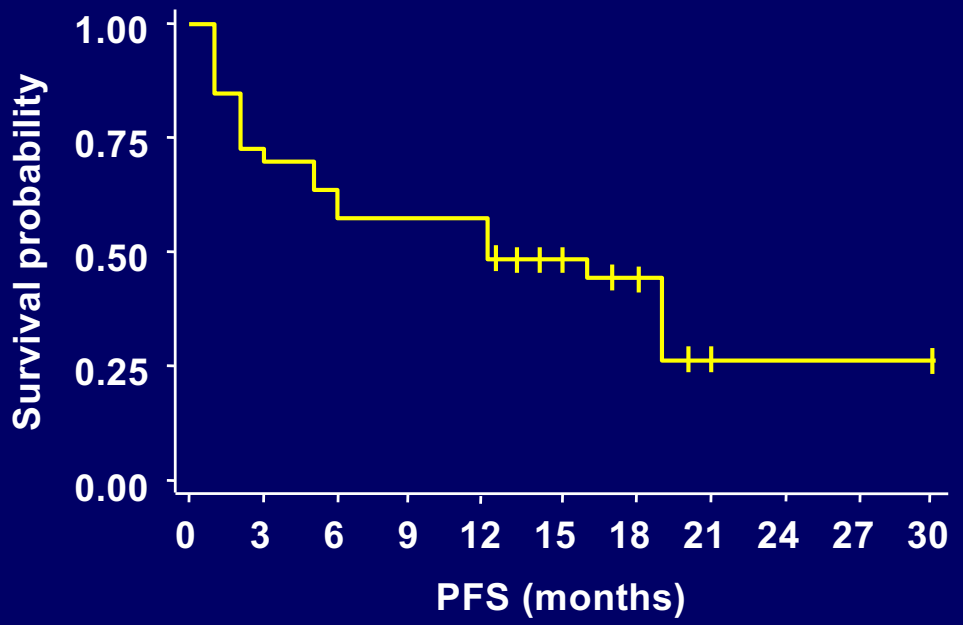
ORR: 52%

15 patients (45.5%) interrupted therapeutic program

Zaja et al Haematologica 2012

PFS and OS Following Lenalidomide plus Dexamethasone in Patients with Relapsed/Refractory MCL (N = 33)





Median follow-up: 16 months

Median OS: 20 months

Median DoR: 18 months

Median follow-up: 16 months

Median PFS: 12 months

Zaja et al Haematologica 2012

Lenalidomide with Rituximab in R/R MCL: phase1/2 study

- **Phase I**
  - **Lenalidomide:**
    10–25 mg on days 1–21 of every 28-day cycle
  - **Rituximab**
    375 mg/m^2 once weekly for 4 weeks during cycle 1
- **Phase II**
  - **Rituximab and lenalidomide at the maximum tolerated dose**
- **Treatment continued until progression or major adverse event**

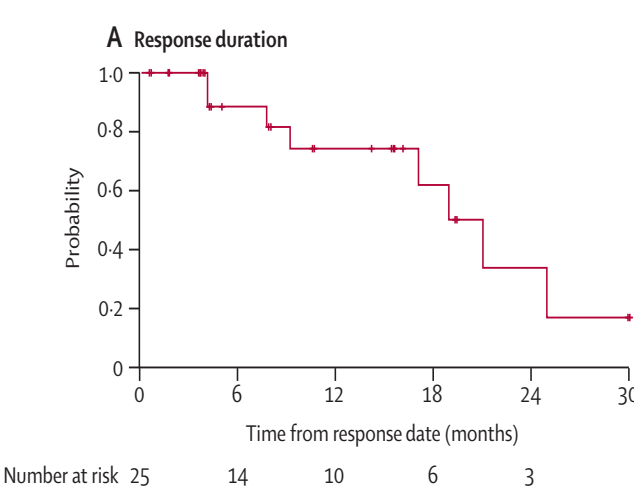
- **Lenalidomide dosage levels: 10 mg (n = 3)**
  15 mg (n = 3)
  20 mg (n = 6)
  25 mg (n = 2)
- **2 patients experienced a DLT (in cycle 1) at 25 mg dosage level:**
  1. **Grade 3 hypercalcemia, hyperuricemia, and elevation of creatinine**
  2. **Grade 4 non-neutropenic fever, hypotension, and sepsis**

The MTD of lenalidomide was 20 mg daily on days 1–21 of every 28-day cycle

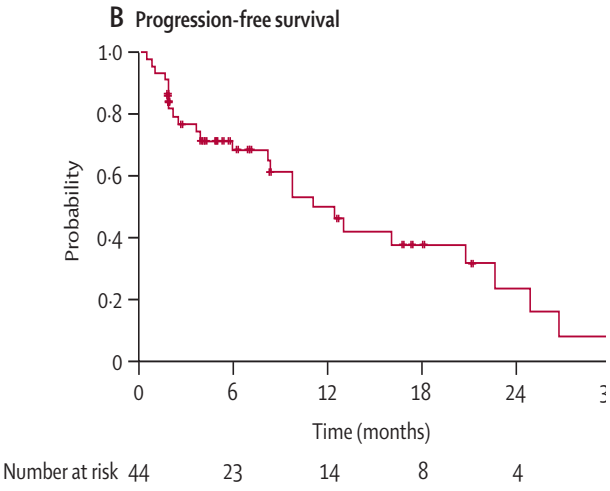
Wang et al, Lancet Oncology 2012

Lenalidomide with Rituximab in R/R MCL: phase 2

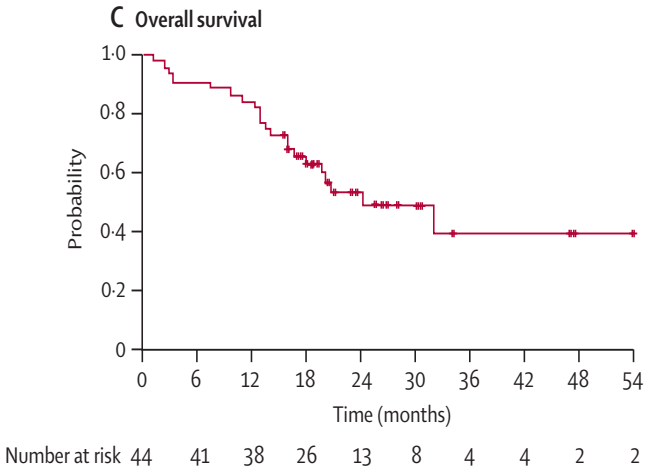
Response	N* 44 (%)
Overall response	25 (57)
Complete response	16 (36)
Partial response	9 (20)
Stable disease	10 (23)
Progressive disease	9 (20)



Median RD 18.9 months



Median PFS 11.1 months



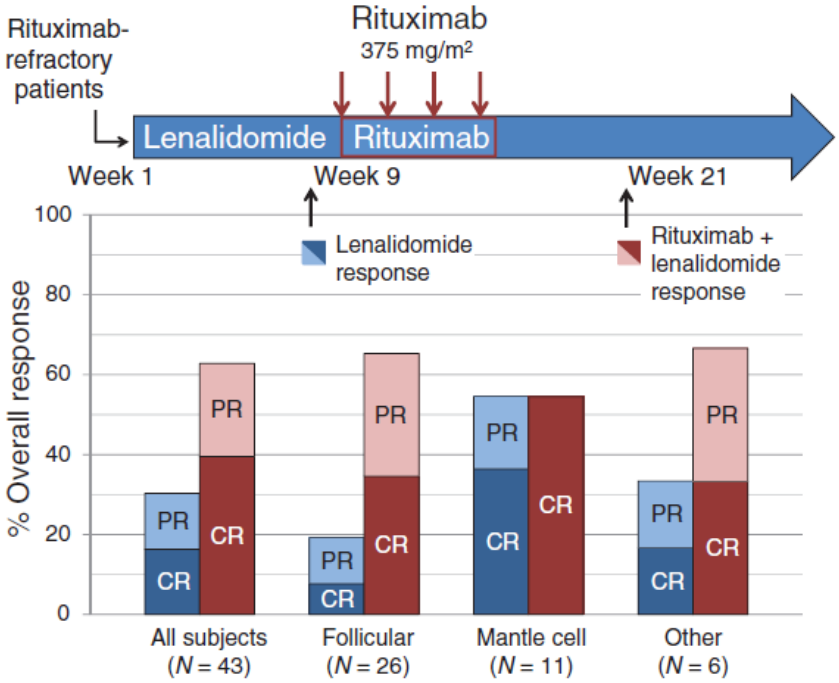
Median OS 24.3 months

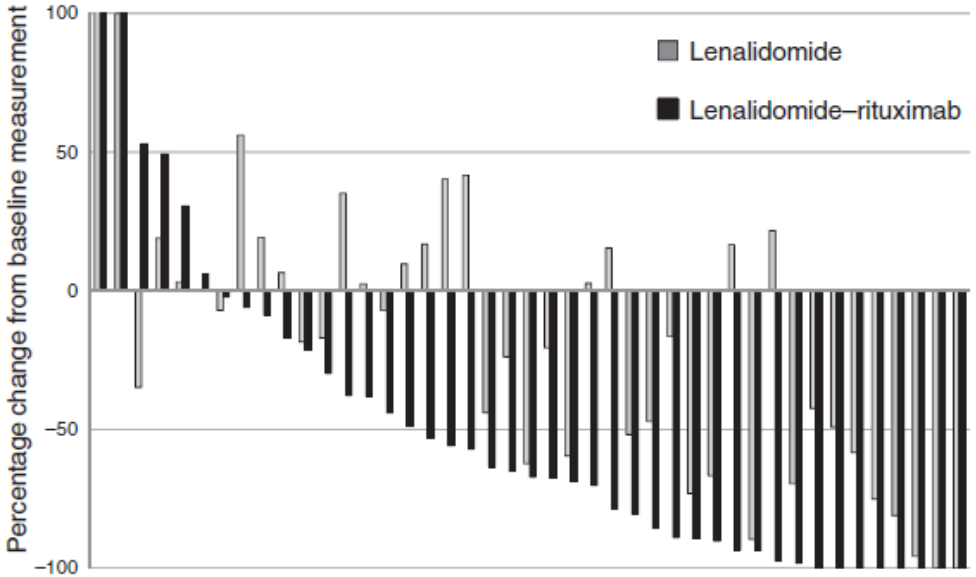
Wang et al, Lancet Oncology 2012

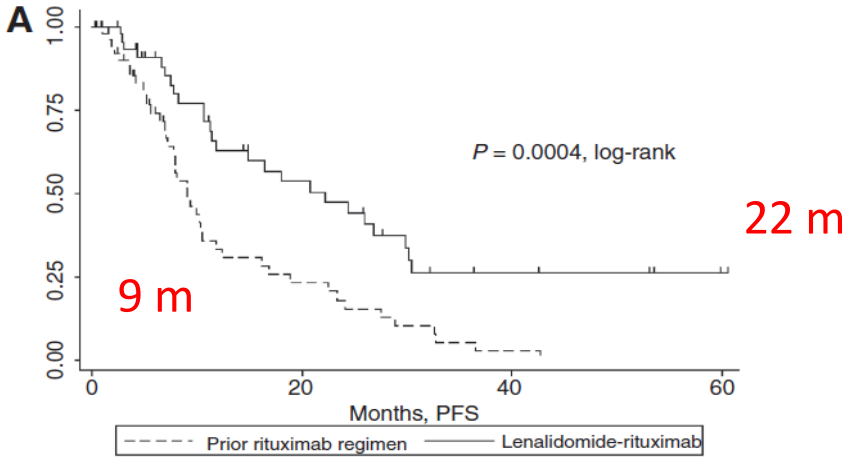
Combination of Lenalidomide and Rituximab Overcomes Rituximab Resistance in Patients with Indolent B-cell and Mantle Cell Lymphomas

Elise A. Chong, Tahamtan Ahmadi, Nicole A. Aqui, Jakub Svoboda, Sunita D. Nasta, Anthony R. Mato, Kristy M. Walsh, and Stephen J. Schuster

Clinical Cancer Research







Clin Cancer Res; 21(8) April 15, 2015

Original Article

Combined Lenalidomide, Low-Dose Dexamethasone, and Rituximab Achieves Durable Responses in Rituximab-Resistant Indolent and Mantle Cell Lymphomas

Tahamtan Ahmadi, MD, PhD[1]; Elise A. Chong, MD[1]; Amanda Gordon, BSN, CRNP[1]; Nicole A. Aqui, MD[1]; Sunita D. Nasta, MD[1]; Jakub Svoboda, MD[1]; Anthony R. Mato, MD, MSCE[2]; and Stephen J. Schuster, MD[1]

48 pts **12 MCL**

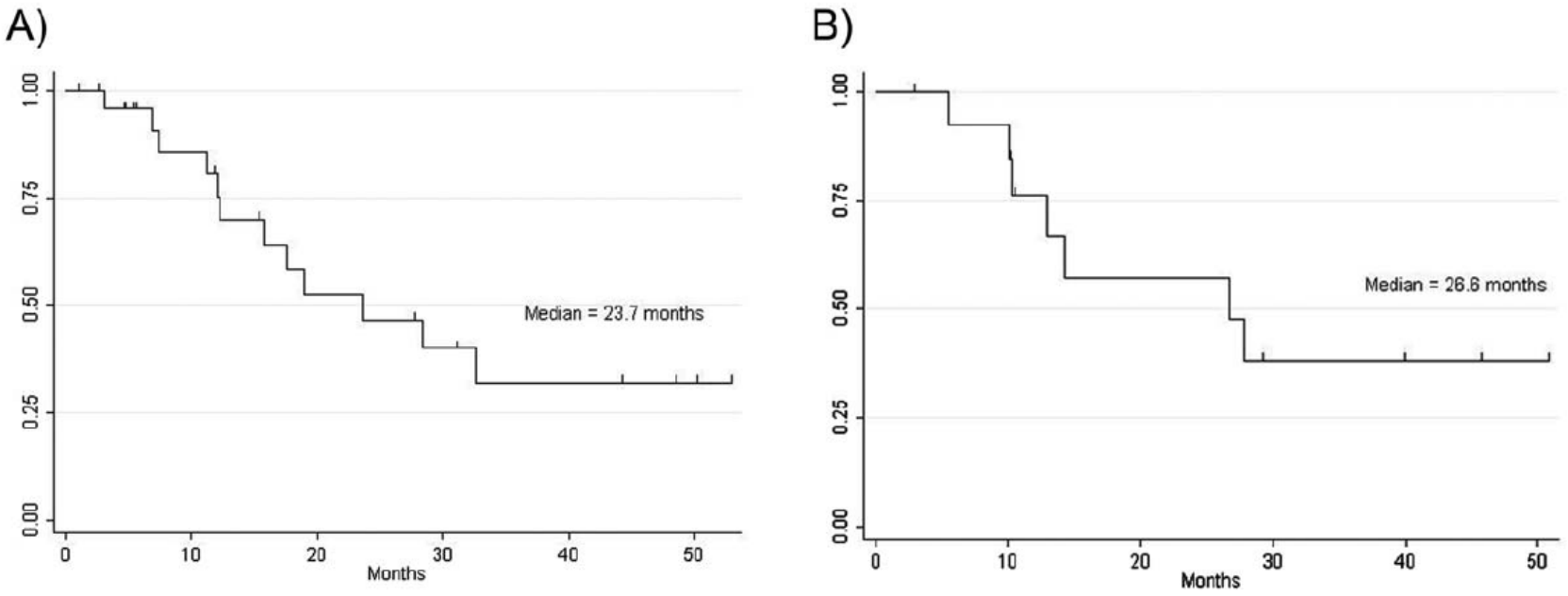


Figure 2. Progression-free survival and response duration are illustrated. (A) This Kaplan-Meier curve illustrates progression-free survival for all enrolled patients (n = 27). (B) This Kaplan-Meier curve illustrates response duration (or time to progression as defined by Davis et al[17]) for all responding patients measured from the first observation of response (CR, CRu, or PR) after either part I or part II of treatment until progression (n = 14).

Bendamustine, Lenalidomide and Rituximab (R2-B) combination as a second-line therapy for first relapsed-refractory MCL: a phase II study

PRINCIPAL INVESTIGATOR

Francesco Zaja, Udine

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FONDAZIONE FIL ITALIANA LINFOMI

R2B: TRIAL DESIGN

Induction phase

R2-B x 2 cycles

Benda 70 mg/mq x 2
Lena 10 mg day 1 to 14

↓ CR, PR, SD

R2-B x 2 cycles

↓ CR, PR

Consolidation phase

Lena 15 mg day 1 to 21

R2 x 2 cycles

↓ CR, PR

Lena 15 mg day 1 to 21

Maintenance phase

↓

Lenalidomide x 18 months

Baseline

Month 4

Month 6

Month 24

R2B: patients characteristics at study enrollment (2)

Patients		42
Median age, years (range)		**70 (45-86)**
Male/Female		31/11 (74%)
Blastoid variant		1 (2%)
Ki-67 (19 patients) (in the original biopsy)	≤ 10% > 10% ≤ 30% > 30%	2 (10%) 6 (32%) 11 (58%)
B symptoms		6 (14%)
WHO PS:	0-1 2	40 (95%) 2 (5%)
Ann Arbor stage:	I-II III IV	3 (7%) 7 (17%) 32 (76%)
Bone marrow involvement		18 (43%)
MIPI:	low intermediate high	18 (43%) 11 (26%) 13 (31%)

R2B: patients characteristics (2)

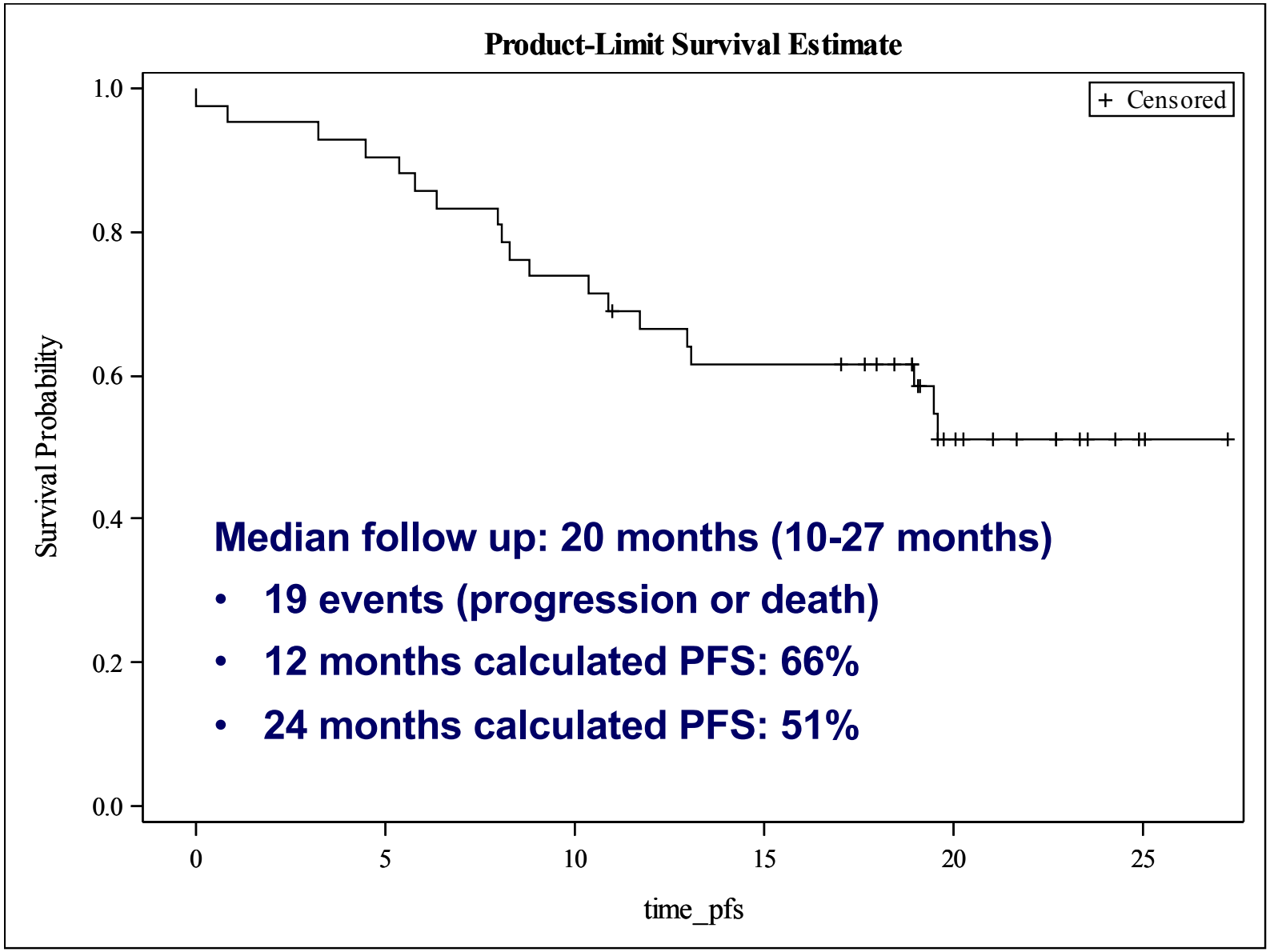
Previous 1^ tx:	
R-CHOP (like) + R-VNCOP	27 (64%)
R-CVP	2 (5%)
R-ARA-C based therapy	11 (26%)
R-FC	2 (5%)
Autologous-SCT (front line)	10 (24%)

Response to first line therapy	**Patients**
CR	30 (71%)
PR	8 (19%)
ORR	38(90%
SD	2 (5%)
PD	2 (5%)

Response duration to first line therapy	**Patients** (not known 1 case)
Primary refractory	4 (10%)
< 12 months	11 (26%)
> 12 < 24 months	12 (29%)
> 24 months	14 (33%)

Median duration of response of the first line therapy: **19 months** (range: 1.6-85 months)

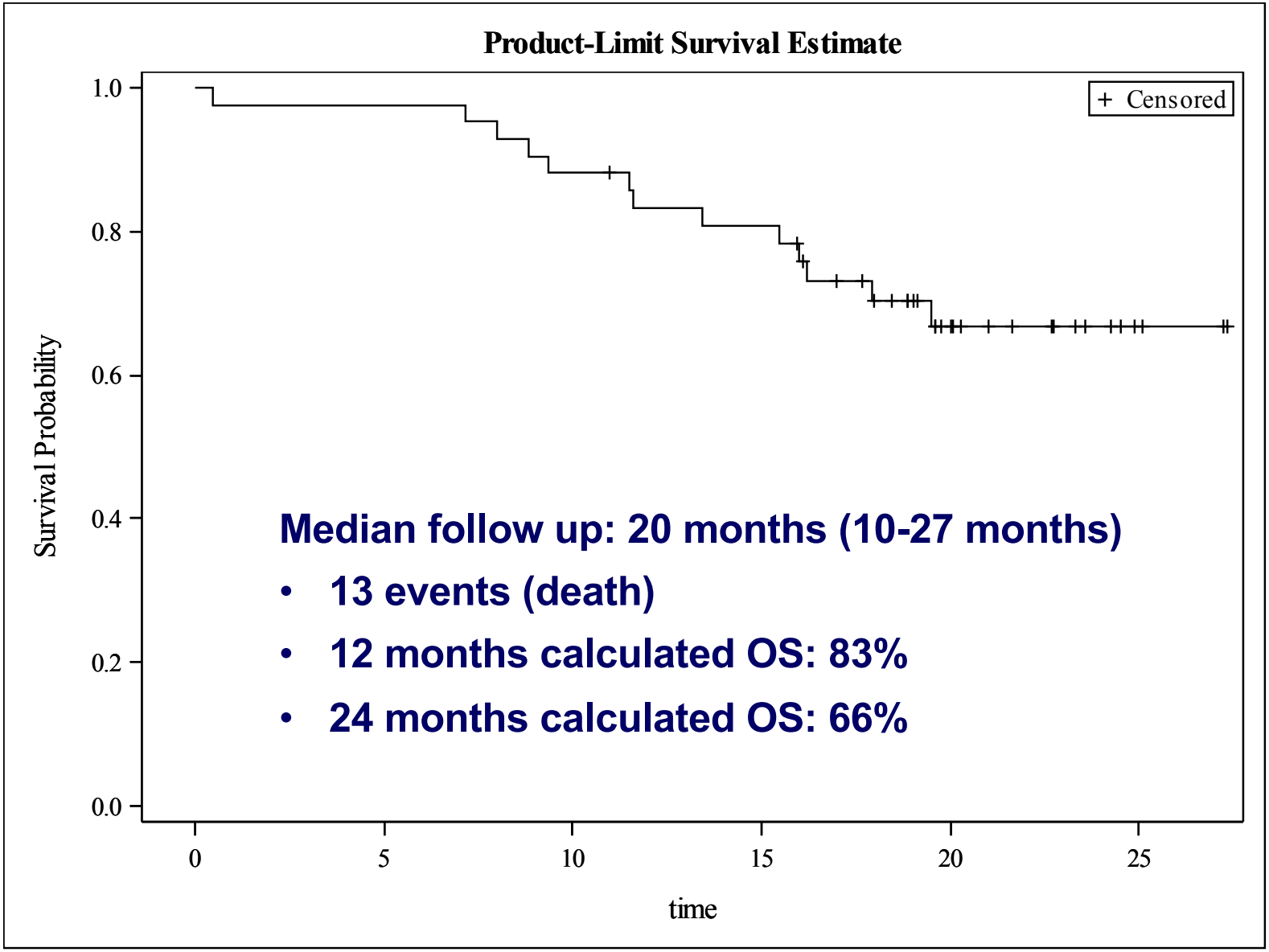
R2B: progression free survival



Median follow up: 20 months (10-27 months)

- **19 events (progression or death)**
- **12 months calculated PFS: 66%**
- **24 months calculated PFS: 51%**

R2B: overall survival



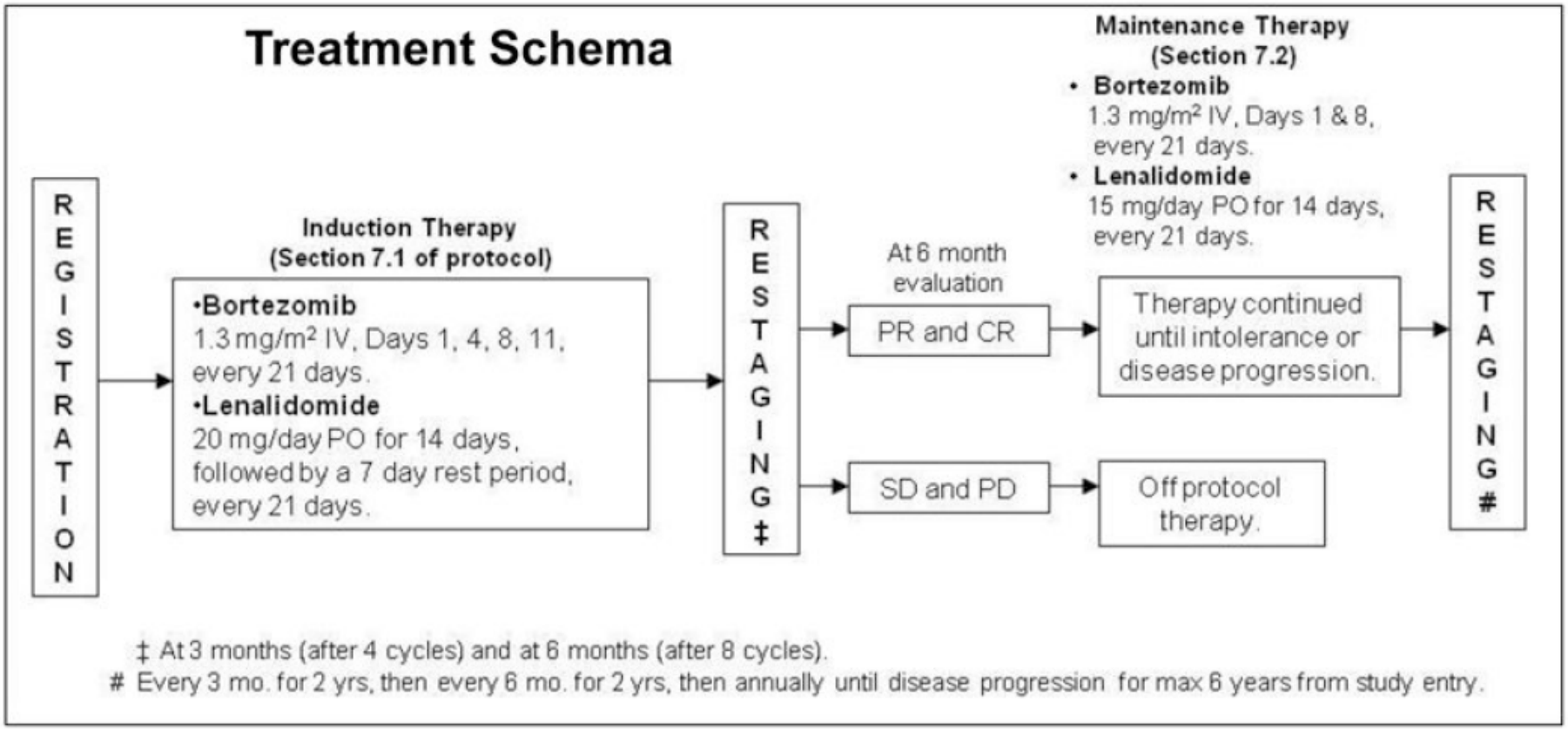
Median follow up: 20 months (10-27 months)

- **13 events (death)**
- **12 months calculated OS: 83%**
- **24 months calculated OS: 66%**

Leuk Lymphoma. 2015 April ; 56(4): 958–964. doi:10.3109/10428194.2014.938333.

Therapy with bortezomib plus lenalidomide for relapsed/ refractory mantle cell lymphoma: Final results of a phase II trial (CALGB 50501)

Vicki A. Morrison[1], **Sin-Ho Jung**[2], **Jeffrey Johnson**[2], **Ann LaCasce**[3], **Kristie A. Blum**[4], **Nancy L. Bartlett**[5], **Brandelyn N. Pitcher**[2], and **Bruce D. Cheson**[6]



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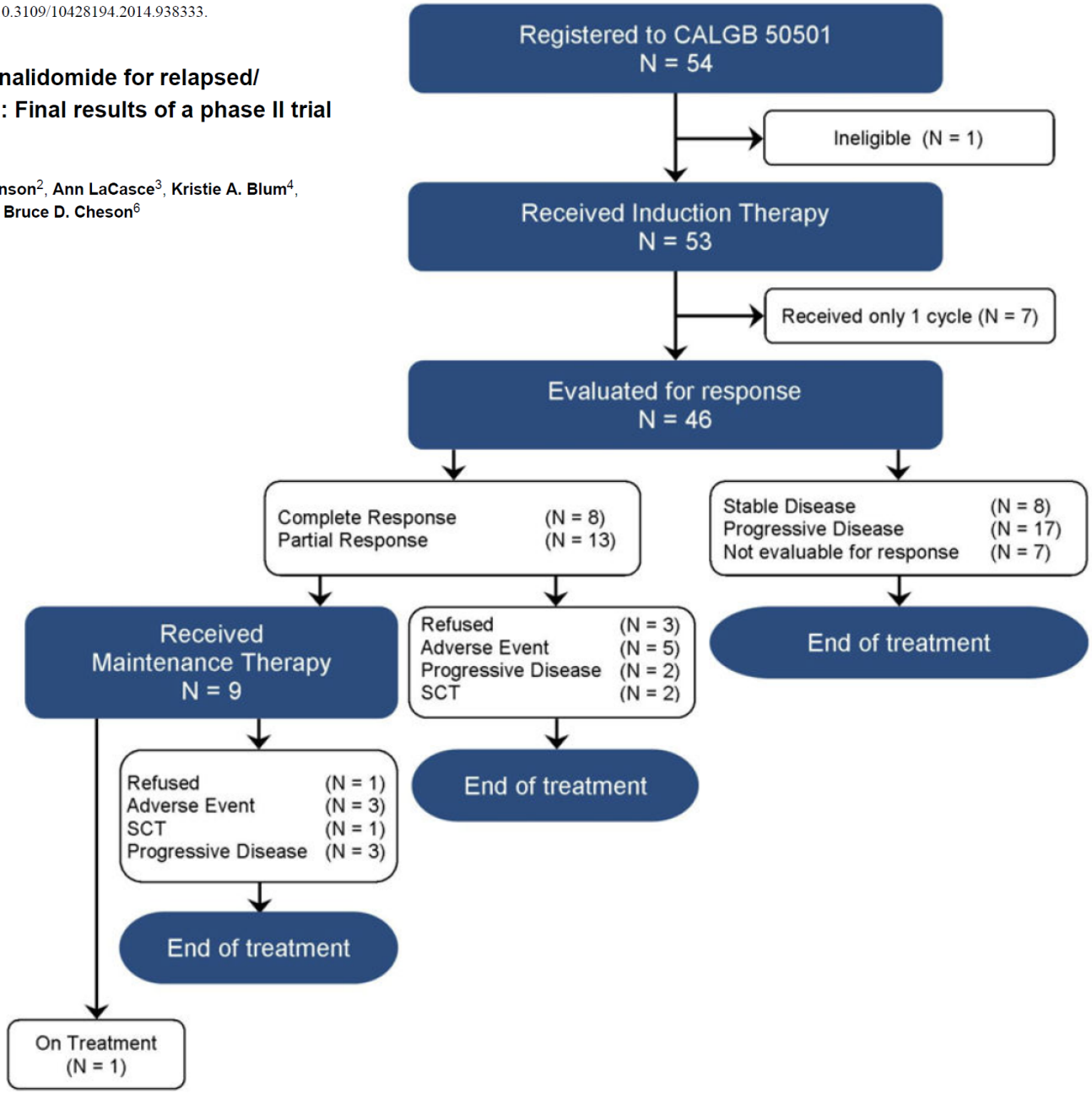
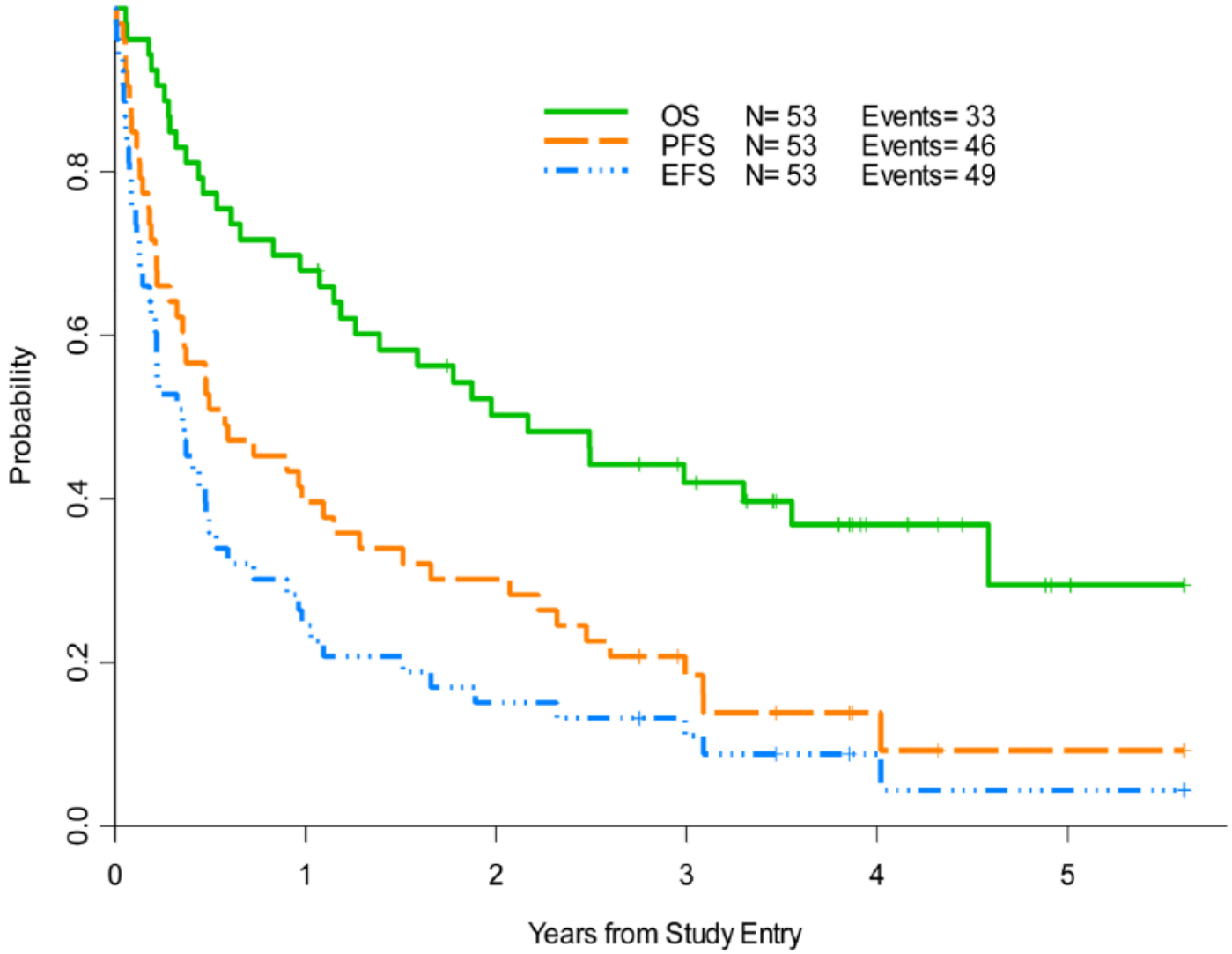


Figure 2. CONSORT Diagram: CALGB 50501



	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)

Ibrutinib, lenalidomide, and rituximab in relapsed or refractory mantle cell lymphoma (PHILEMON): a multicentre, open-label, single-arm, phase 2 trial

Mats Jerkeman, Christian Winther Eskelund, Martin Hutchings, Riikka Räty, Karin Fahl Wader, Anna Laurell, Helle Toldbod, Lone Bredo Pedersen, Carsten Utoft Niemann, Christina Dahl, Hanne Kuitunen, Christian H Geisler, Kirsten Grønbæk, Arne Kolstad

	All patients (n=50)
Age (years)	69 (45–85)
Sex	
Female	14 (28%)
Male	36 (72%)
ECOG performance status score 0–1	45 (90%)
MIPI score	
Low risk (<5·7)	8 (16%)
Intermediate risk (5·7–6·1)	15 (30%)
High risk (>6·2)	23 (46%)
Missing	4 (8%)
Ann Arbor stage IV disease	42 (84%)
Bone marrow involvement	34 (68%)
Refractory disease	8 (16%)
Number of previous therapies	2 (1–7)
Previous therapy	
Autologous stem-cell transplantation	21 (42%)
Allogeneic stem-cell transplantation	3 (6%)
Ibrutinib	4 (8%)
Lenalidomide	1 (2%)

Data are n (%) or median (range). ECOG=Eastern Cooperative Oncology Group. MIPI=Mantle Cell Lymphoma International Prognostic Index.

Table 1: **Patient and disease characteristics**

	All patients (n=50)	*TP53* unmutated (n=38)	*TP53* mutated (n=11)
Overall response	38 (76%, 63–86)	30 (79%, 64–89)	8 (73%, 43–90)
Complete remission	28 (56%, 42–69)	21 (55%, 40–70)	7 (64%, 35–85)
Partial remission	10 (20%, 11–33)	9 (24%, 13–39)	1 (9%, 2–38)
Stable disease	1 (2%, 0–1)	1 (3%, 0–14)	0 (0%, 0–0)
Progressive disease	5 (10%, 4–21)	3 (8%, 3–21)	2 (18%, 5–48)
Not evaluable*	6 (12%, 6–24)	4 (11%, 4–24)	1 (9%, 2–38)

Data are n (%, 95% CI). *Six patients were not evaluable because of withdrawal of consent (n=3) or treatment discontinuation because of treatment-related toxicity before response evaluation (n=3). One patient was not evaluable for *TP53* mutation status for technical reasons.

Table 2: **Maximal responses to treatment in all patients and according to presence of *TP53* mutation**

Ibrutinib, lenalidomide, and rituximab in relapsed or refractory mantle cell lymphoma (PHILEMON): a multicentre, open-label, single-arm, phase 2 trial

Mats Jerkeman, Christian Winther Eskelund, Martin Hutchings, Riikka Räty, Karin Fahl Wader, Anna Laurell, Helle Toldbod, Lone Bredo Pedersen, Carsten Utoft Niemann, Christina Dahl, Hanne Kuitunen, Christian H Geisler, Kirsten Grønbæk, Arne Kolstad

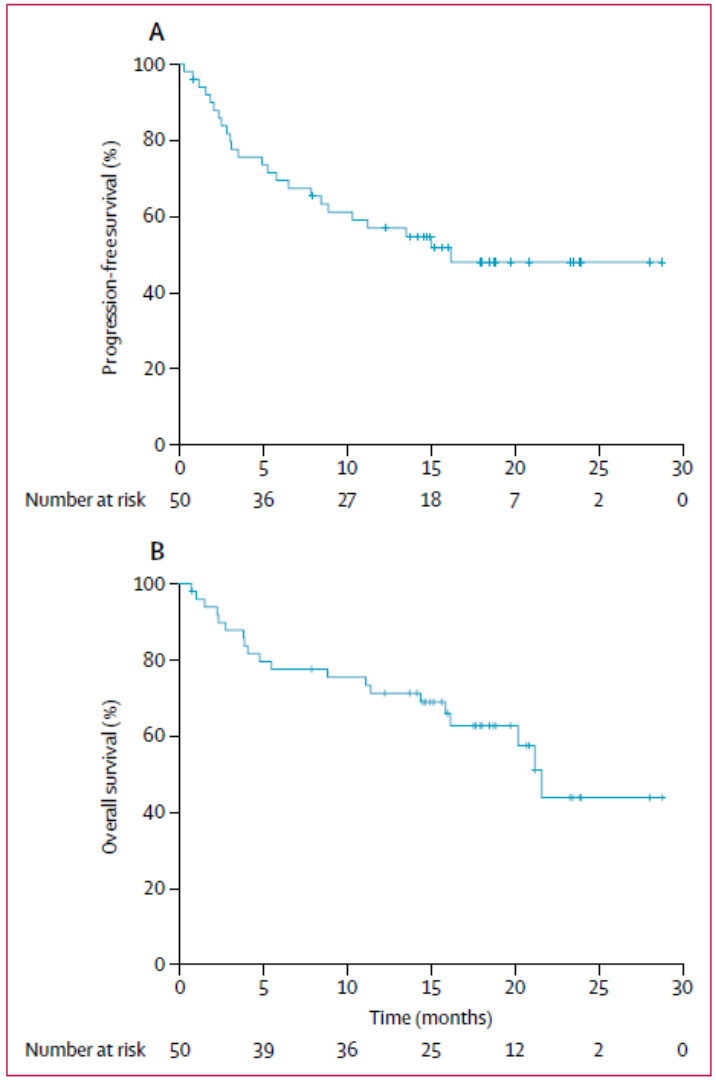


Figure 2: **Progression-free survival (A) and overall survival (B)**

	Grade 1–2*	Grade 3	Grade 4	Grade 5
Haematological adverse events				
Thrombocytopenia	8 (16%)	4 (8%)	2 (4%)	0 (0%)
Anaemia	8 (16%)	1 (2%)	0 (0%)	0 (0%)
Neutropenia	NR	13 (26%)	6 (12%)	0 (0%)
Non-haematological adverse events				
Gastrointestinal	34 (68%)	5 (10%)	1 (2%)	0 (0%)
Infections	18 (36%)	9 (18%)	2 (4%)	2 (4%)
Cutaneous	28 (56%)	7 (14%)	0 (0%)	0 (0%)
Fatigue	28 (56%)	1 (2%)	0 (0%)	0 (0%)
Muscle cramps	15 (30%)	3 (6%)	0 (0%)	0 (0%)
Respiratory	19 (38%)	1 (2%)	1 (2%)	0 (0%)
Neurological	19 (38%)	1 (2%)	0 (0%)	1 (2%)
Ocular	13 (26%)	0 (0%)	0 (0%)	0 (0%)
Psychiatric	6 (12%)	0 (0%)	0 (0%)	0 (0%)
Vascular	11 (22%)	5 (10%)	0 (0%)	0 (0%)
Renal	7 (14%)	0 (0%)	0 (0%)	0 (0%)
Atrial fibrillation	NR	1 (2%)	0 (0%)	0 (0%)

Data are n (%). The denominator is 50. NR=not reported. *For grade 1–2 events, only those occurring in ≥10% of patients are reported.

Table 4: **Treatment-emergent adverse events**

	6 months		12 months		18 months		24 months	
	Bone marrow (n=28)	Peripheral blood (n=27)	Bone marrow (n=19)	Peripheral blood (n=19)	Bone marrow (n=11)	Peripheral blood (n=12)	Bone marrow (n=5)	Peripheral blood (n=5)
Negative	12	15	13	11	3	6	3	4
Positive	16	12	6	8	8	6	2	1
Molecular remission (%)	43%	56%	68%	58%	27%	50%	60%	80%

Table 3: **Molecular remission in peripheral blood and bone marrow at 6, 12, 18, and 24 months**

Lancet Haematol. 2017 April ; 4(4): e176–e182. doi:10.1016/S2352-3026(17)30028-5.

Safety and Tolerability of Idelalisib, Lenalidomide, and Rituximab in Relapsed and Refractory Lymphoma: Alliance A051201 and A051202 Phase I Trials

Sonali M. Smith, MD[1], **Brandelyn N. Pitcher, MS**[2], **Sin-Ho Jung, PhD**[2], **Nancy L. Bartlett, MD**[3], **Nina Wagner-Johnston, MD**[3], **Steven I. Park, MD**[4], **Kristy L. Richards, MD**[4], **Amanda F. Cashen, MD**[3], **Anthony Jaslowski, MD**[5], **Scott E. Smith, MD, PhD**[6], **Bruce D. Cheson, MD**[7], **Eric Hsi, MD**[8], and **John P. Leonard, MD**[9]

Interpretation—The combination of idelalisib, lenalidomide and rituximab in these trials is excessively toxic, and these trials serve as cautionary notes as new combinations are proposed. Off-target effects, drug-drug interactions, and emerging toxicities should be carefully evaluated when investigating biologic agents in combination and should never be done outside of a clinical trial setting.

FRONT LINE

ORIGINAL ARTICLE

Lenalidomide plus Rituximab as Initial Treatment for Mantle-Cell Lymphoma

Jia Ruan, M.D., Ph.D., Peter Martin, M.D., Bijal Shah, M.D., Stephen J. Schuster, M.D., Sonali M. Smith, M.D., Richard R. Furman, M.D., Paul Christos, Dr.P.H., Amelyn Rodriguez, R.N., Jakub Svoboda, M.D., Jessica Lewis, P.A., Orel Katz, P.A., Morton Coleman, M.D., and John P. Leonard, M.D.

Table 2. Rates of Best Response at the Median Follow-up of 30 Months.

Response	Patients	Intention-to-Treat Population (N=38)	Patients Who Could Be Evaluated (N=36)
	no.	%	
Overall response	33	87	92
Complete response*	23	61	64
Partial response	10	26	28
Stable disease	1	3	3
Progressive disease†	2	5	6
Could not be evaluated‡	2	5	

ORIGINAL ARTICLE

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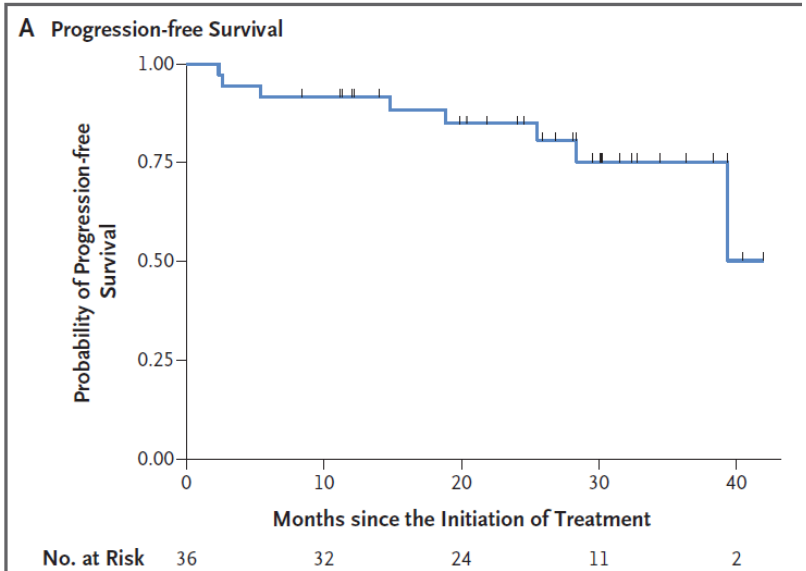


Table 3. Survival and Follow-up Data.

Variable	Value
Median progression-free survival	Not reached
2-Yr progression-free survival — % of patients (95% CI)	85 (67–94)
2-Yr overall survival — % of patients (95% CI)	97 (79–99)
Follow-up time — mo	
Median	30
Range	10–42
Time to partial response — mo	
Median	3
Range	3–13
Time to complete response — mo*	
Median	11
Range	3–22

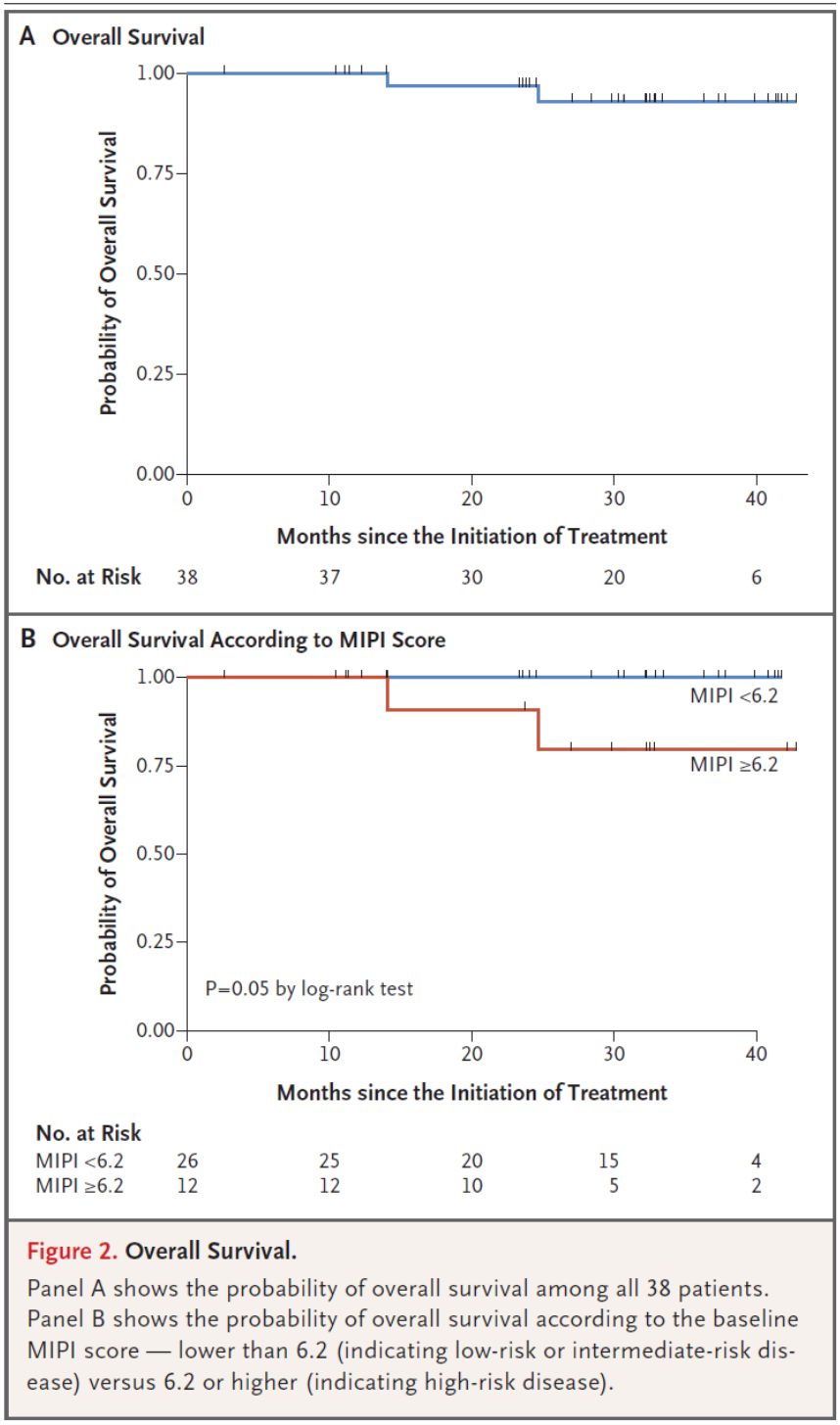


Figure 2. Overall Survival.

Panel A shows the probability of overall survival among all 38 patients. Panel B shows the probability of overall survival according to the baseline MIPI score — lower than 6.2 (indicating low-risk or intermediate-risk disease) versus 6.2 or higher (indicating high-risk disease).

Blood First Edition Paper, prepublished online September 4, 2018; DOI 10.1182/blood-2018-07-859769

Five-year Follow-up of Lenalidomide Plus Rituximab as Initial Treatment for Mantle Cell Lymphoma

[1]Jia Ruan, M.D., Ph.D., [1]Peter Martin, M.D., [2]Paul Christos, Ph.D., M.P.H., [1]Leandro Cerchietti, M.D., [3]Wayne Tam, M.D., Ph.D., [4]Bijal Shah, M.D., [5]Stephen J. Schuster, M.D., [1]Amelyn Rodriguez, R.N., [1]David Hyman, [1]Maria Nieves Calvo-Vidal, Ph.D., [6]Sonali M. Smith, M.D., [4]Jakub Svoboda, M.D., [1]Richard R. Furman, M.D., [1]Morton Coleman, M.D., [1]John P. Leonard, M.D.

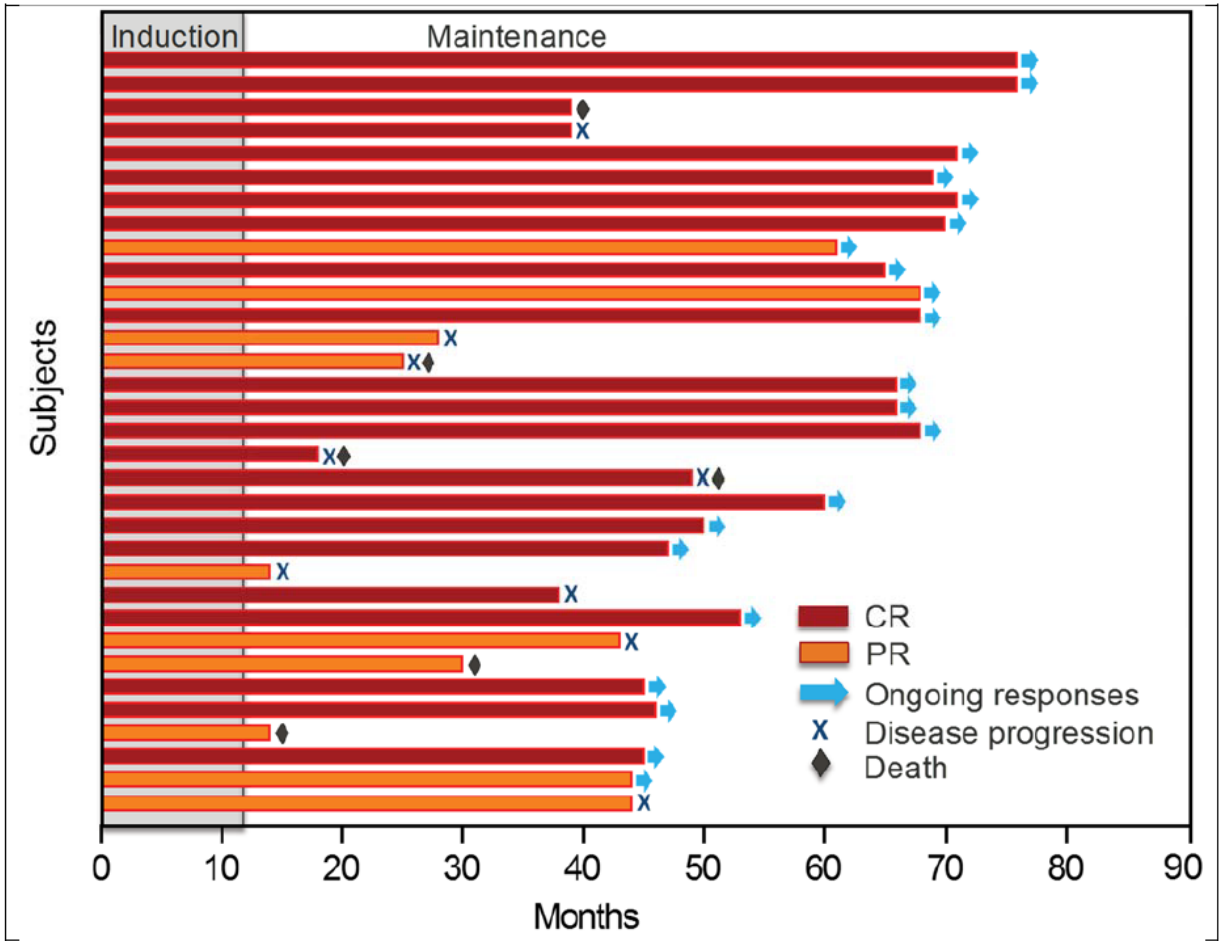
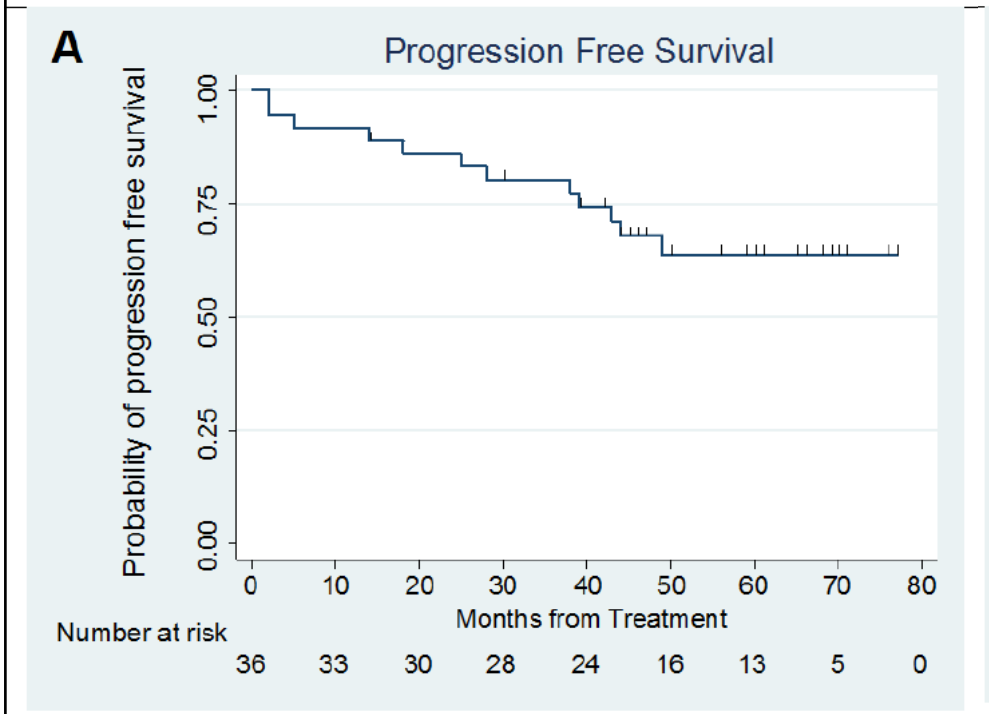
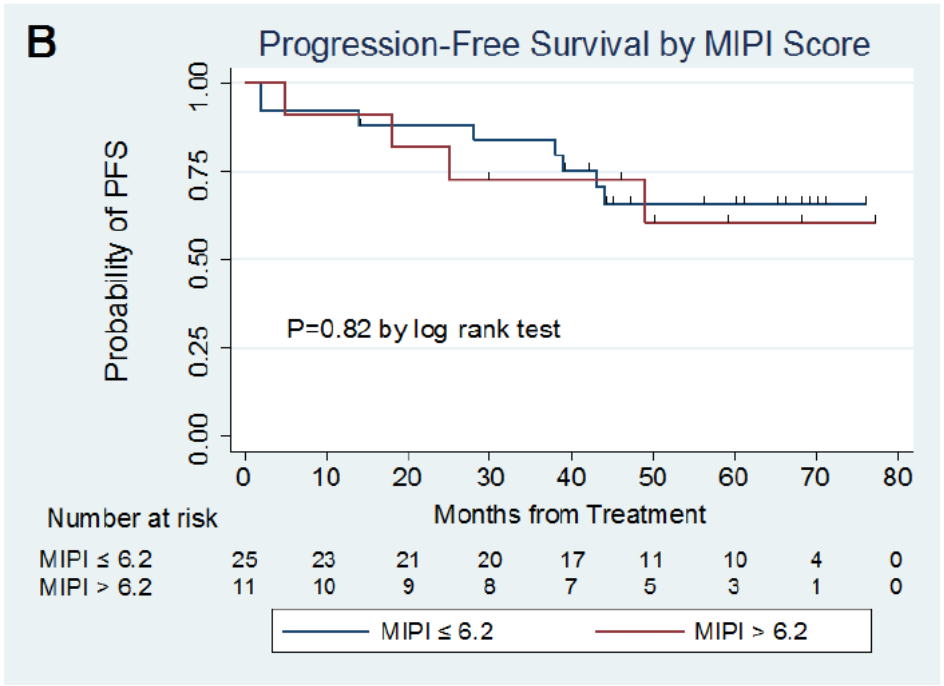
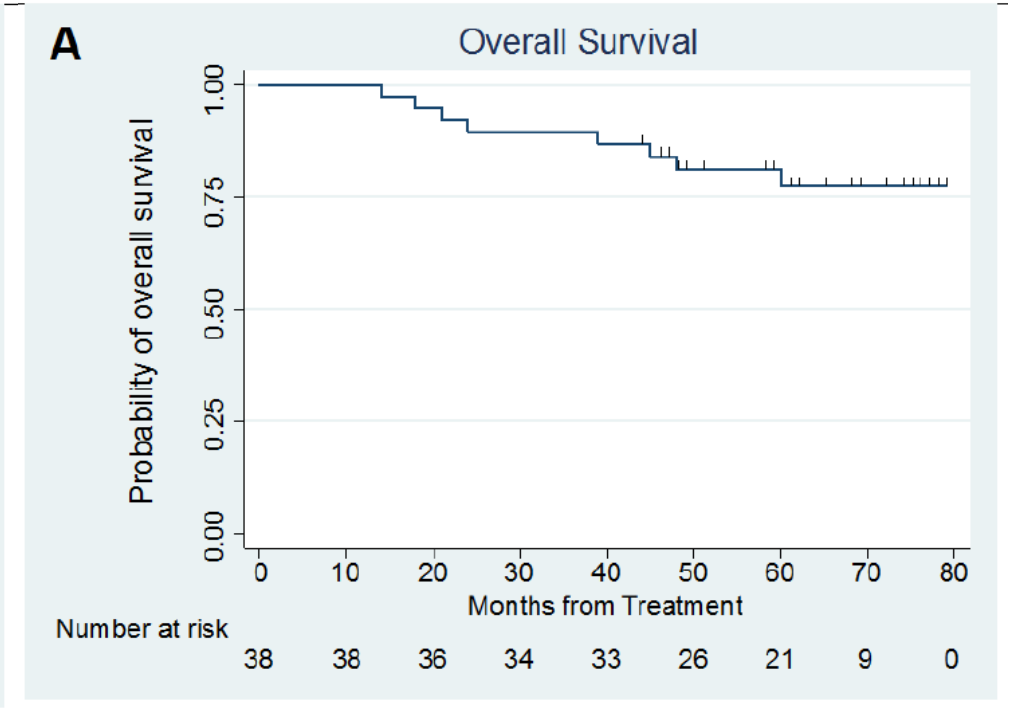
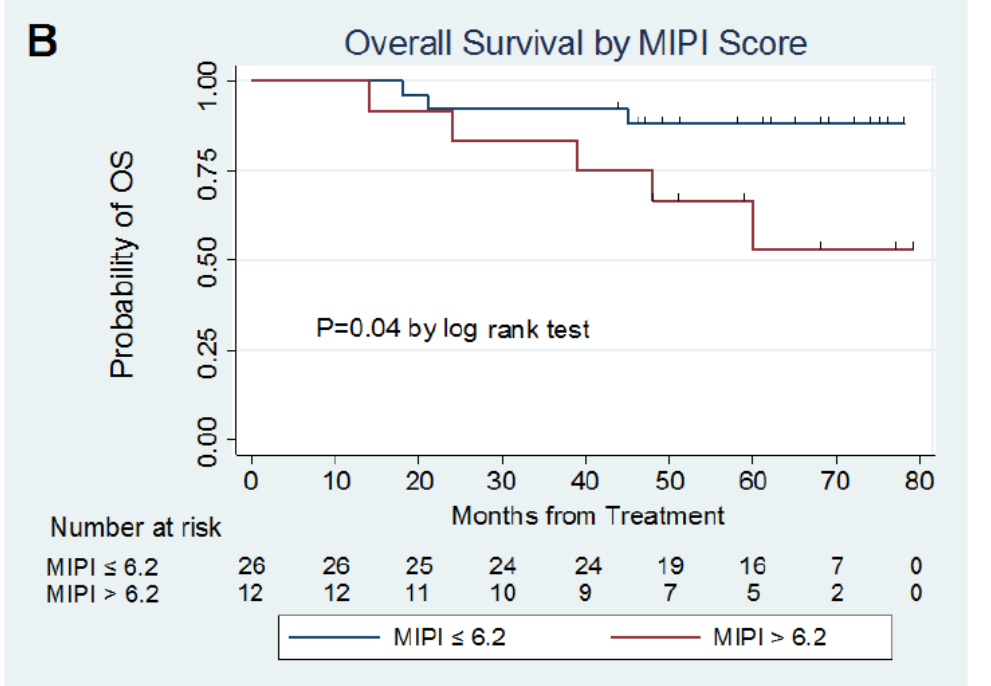


Figure 2. Swimmer's plot of response duration.


A
Progression Free Survival
Probability of progression free survival
0.00
0.25
0.50
0.75
1.00
0
10
20
30
40
50
60
70
80
Months from Treatment
Number at risk
36 33 30 28 24 16 13 5 0


B
Progression-Free Survival by MIPI Score
Probability of PFS
0.00
0.25
0.50
0.75
1.00
P=0.82 by log rank test
0
10
20
30
40
50
60
70
80
Months from Treatment
Number at risk
MIPI ≤ 6.2 25 23 21 20 17 11 10 4 0
MIPI > 6.2 11 10 9 8 7 5 3 1 0
MIPI ≤ 6.2
MIPI > 6.2


A
Overall Survival
Probability of overall survival
0.00
0.25
0.50
0.75
1.00
0
10
20
30
40
50
60
70
80
Months from Treatment
Number at risk
38 38 36 34 33 26 21 9 0


B
Overall Survival by MIPI Score
Probability of OS
0.00
0.25
0.50
0.75
1.00
P=0.04 by log rank test
0
10
20
30
40
50
60
70
80
Months from Treatment
Number at risk
MIPI ≤ 6.2 26 26 25 24 24 19 16 7 0
MIPI > 6.2 12 12 11 10 9 7 5 2 0
MIPI ≤ 6.2
MIPI > 6.2

Lenalidomide-bendamustine-rituximab in patients older than 65 years with untreated mantle cell lymphoma

Alexandra Albertsson-Lindblad,[1] Arne Kolstad,[2] Anna Laurell,[3] Riikka Räty,[4] Kirsten Grønbæk,[5] Jan Sundberg,[1] Lone Bredo Pedersen,[5] Elisabeth Ralfkiær,[6] Marja-Liisa Karjalainen-Lindsberg,[7] Christer Sundström,[8] Mats Ehinger,[9] Christian Geisler,[5] and Mats Jerkeman[1]

Table 3. Response rates and MRD according to CT scan and bone marrow examination

CT	3 mo	6 mo	1.5 mo after completed therapy
ORR (%)	88.0	80.0	64.0
CR/CRU	24 (48%)	32 (64%)	31 (62%)
PR	20	8	1
PD	1	3	8
Not evaluated*	5	7	10
Total	50	50	50
MRD-negativity	**3 mo**	**6 mo**	**12 mo**
BM	18 (50%)	18 (56%)	16 (64%)
PB	23 (61%)	21 (68%)	19 (80%)
Evaluated BM/PB	36/38	32/31	25/24
MRD-negativity (based on intention to treat)	**3 mo**	**6 mo**	**12 mo**
BM	18 (36%)	18 (36%)	16 (32%)
PB	23 (46%)	21 (42%)	19 (38%)
Total	50	50	50

(*Blood*. 2016;128(14):1814-1820)

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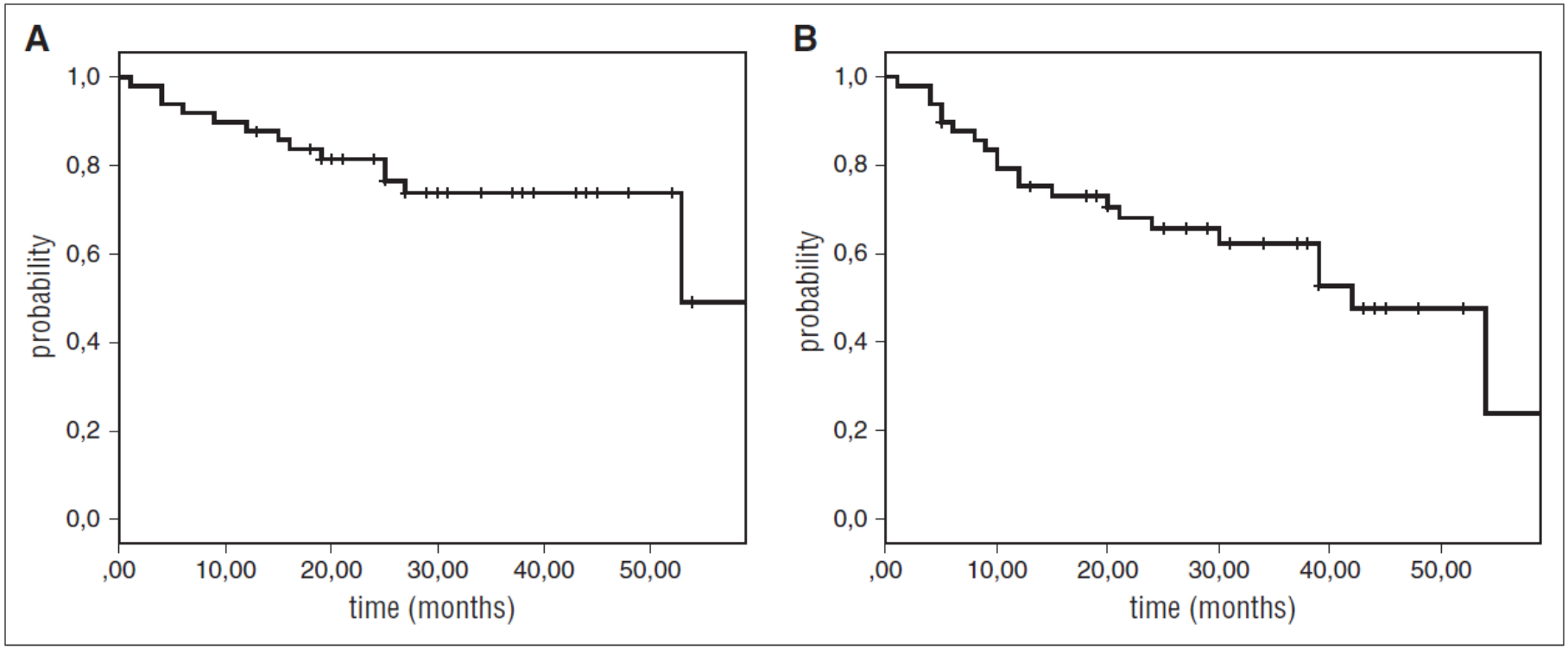

Figure 1. Overall survival and progression-free survival of patients enrolled in NLG/MCL2 (Lena-Berit) at a median follow-up time of 31 (13-59) months. (A) Overall survival; (B) progression-free survival.

(*Blood*. 2016;128(14):1814-1820)

Conclusions

- Relapsed disease is a challenging task that requires an individualized approach
- No standard therapy
- A list of biologic agents that target tumor cells and microenvironment
- Combination of these drugs seems feasible
- Promising results in first line treatment
- Hoping for chemo-free