CORSO TEORICO-PRATICO

PER LA GESTIONE OTTIMALE DEI PAZIENTI AFFETTI DA LINFOMA MANTELLARE, LINFOMA FOLLICOLARE E LEUCEMIA LINFATICA CRONICA

Torino, 21-22-23 maggio 2018

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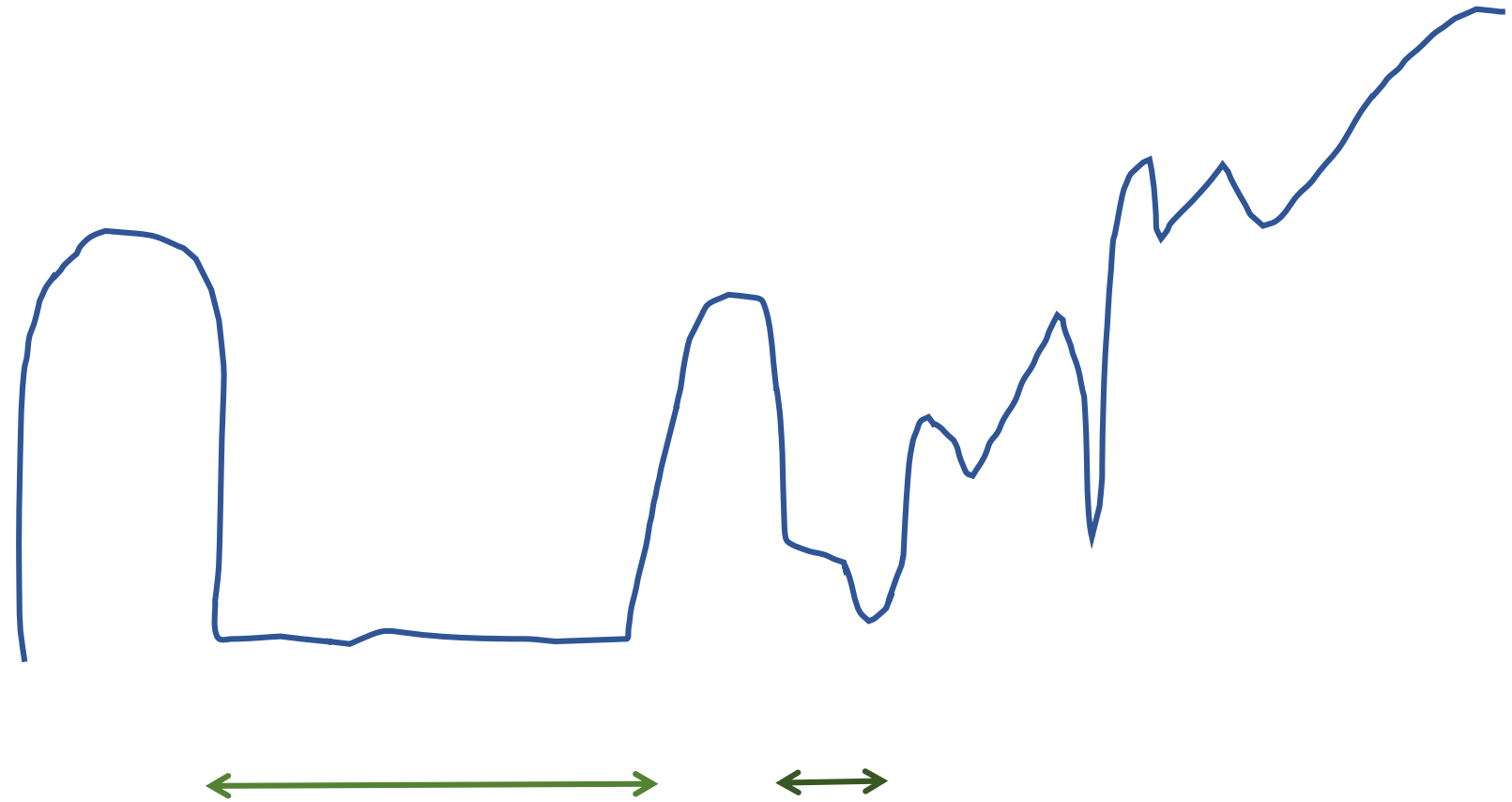
23 maggio, 2018

12.45 Linfoma Mantellare: il trattamento delle recidive e nuovi farmaci
Carlo Visco

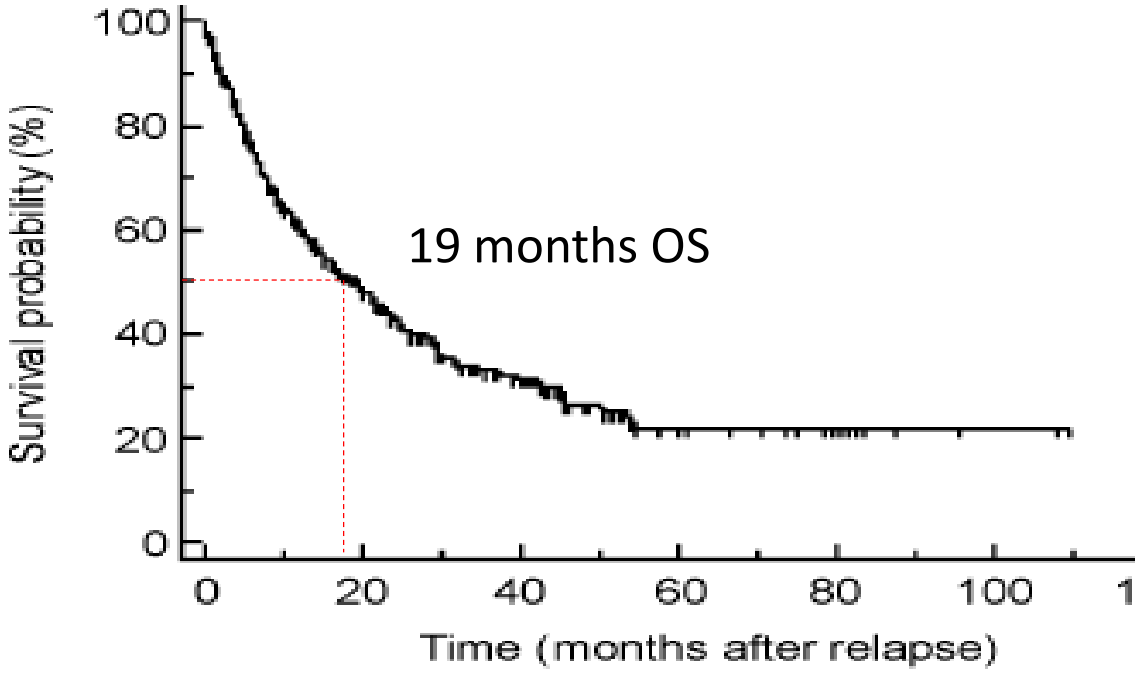
Mantle Cell Lymphoma

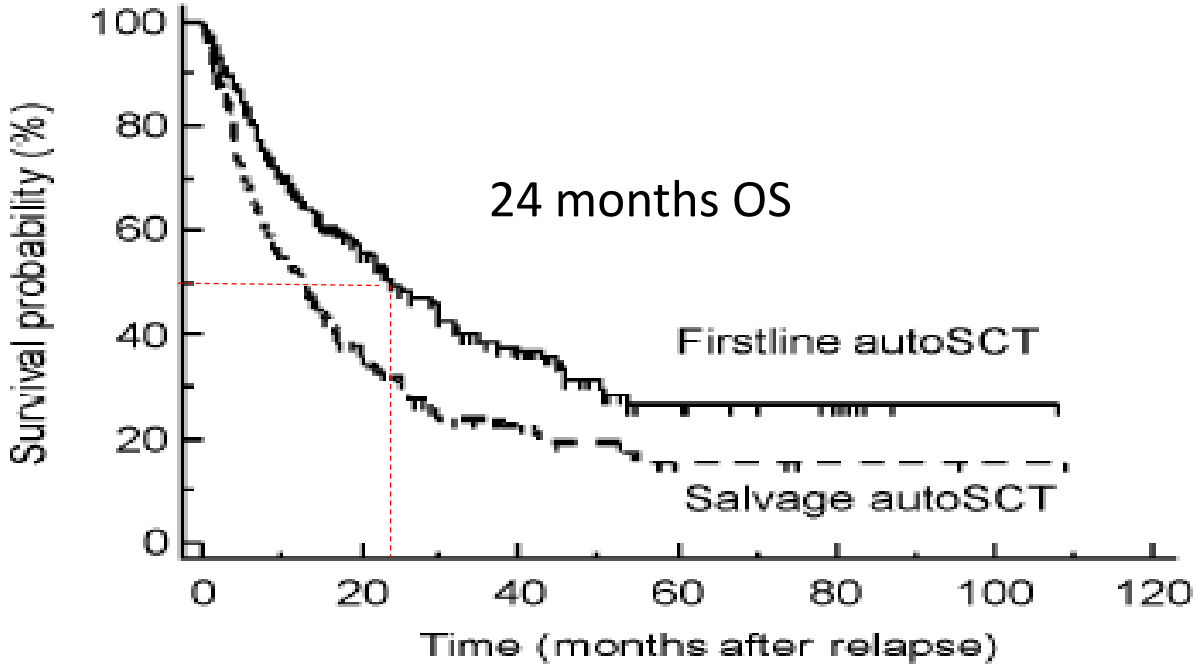
A *schizophrenic* disease



Patients relapsed after Auto transplant

EBMT registry 2000-2009 (n=360)

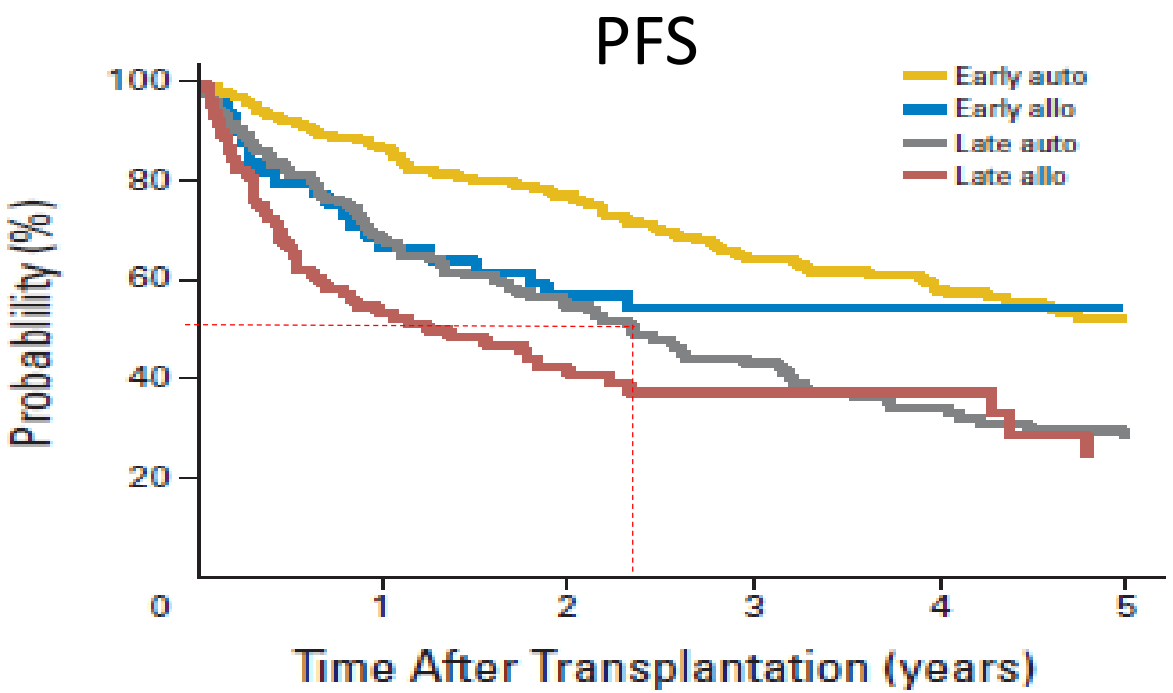




Dietrich S, Ann Oncol 2014

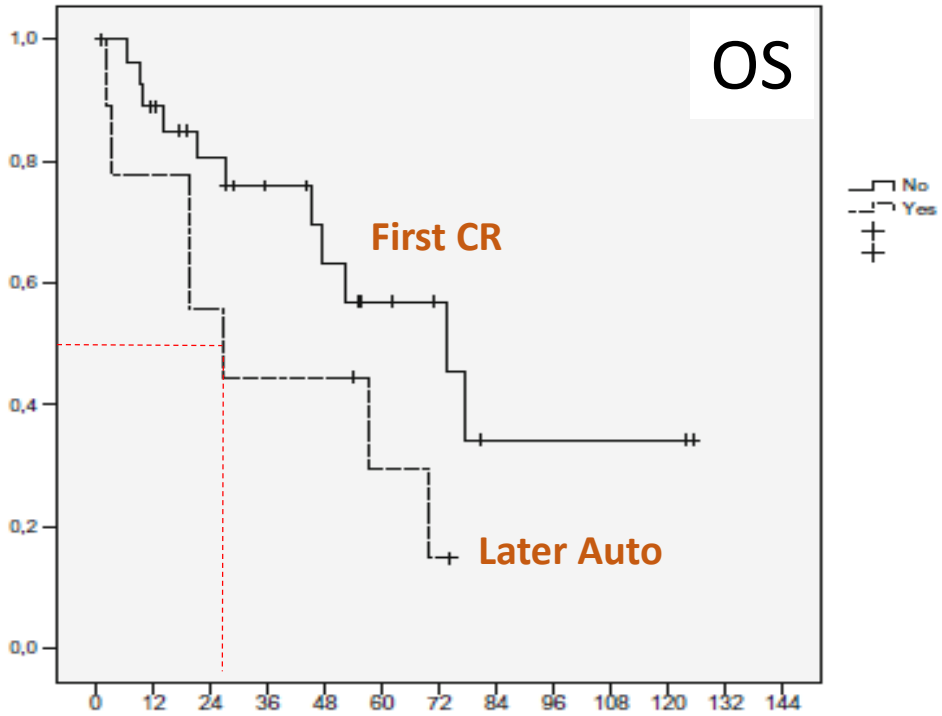
Patients receiving Auto transplant for Chemo-Sensitive MCL

CIBMTR registry 1996-2007 (n=519)



Fenske CS, JCO 2013

GELTAMO registry 1990-2011 (n=227)



Garcia-Noblejas A, Ann Hematol 2017

Autologous Transplant in the relapsed setting (Auto2)

Evidence from the literature

- Very selected patients
- TRM (8%) significantly higher than Auto1
- Median PFS approximately 2 years
- No plateau in survival curves

Freedman AS, JCO 1998; Vandenberghe, BJH 2003
Tam CS, Blood 2009; Till BG, Leuk Lymph 2008;
Gopal AK, Blood 2002; Fenske CS, JCO 2013;
Garcia-Noblejas A, Ann Hematol 2017

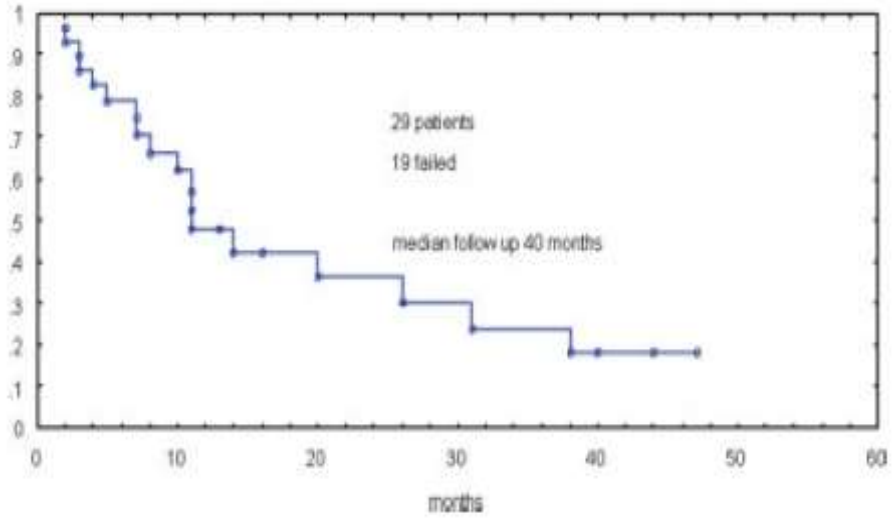
R-HyperCVAD+MTX-ARA-C in R/R MCL

Prospective phase 2 study

TABLE 1
Prior Therapies Used in 29 Patients With Relapsed or Refractory Mantle Cell Lymphoma

Therapy	No. of Patients
Median prior no. of regimens (range)	1 (1-5)
Doxorubicin-containing regimens	21
Fludarabine-containing regimens	5
Rituximab-containing regimens	18
Radiotherapy (excluding TBI)	9
Zevalin or Bexxar	2
Rituximab plus hyperCVAD alternating with rituximab plus methotrexate-cytarabine	4
Autologous stem cell transplantation or TBI	5

TBI indicates total body irradiation.



Wang M, Cancer 2008

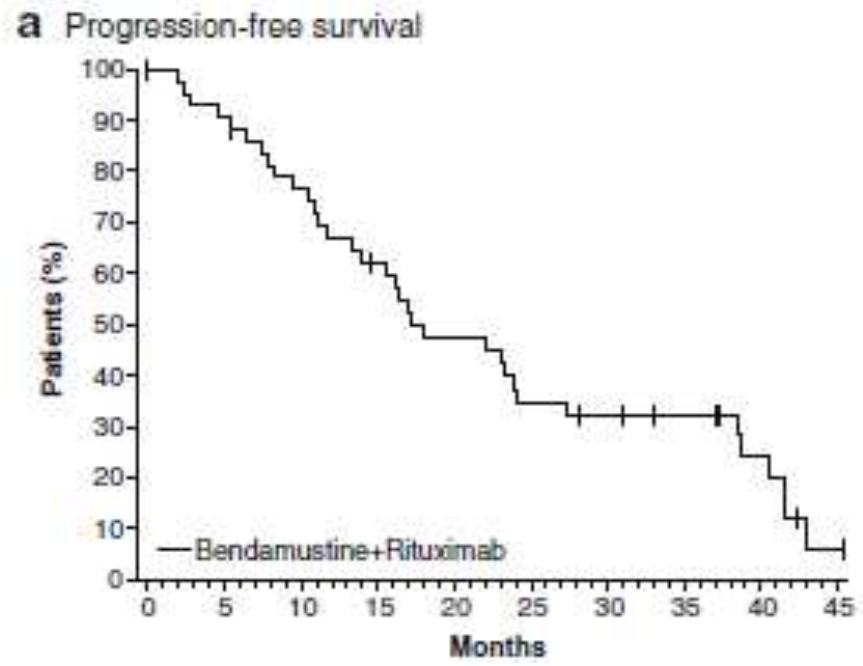
Bendamustine and Rituximab in R/R MCL

Phase 2 studies

Rummel JCO 2005: 16 patients, median age 63 (40-81 yrs)
OR 80% with 50% CR,
Median TTF 18 months

Robinson JCO 2008: 12 patients, median age 60 (45-84 yrs)
OR 92% with 42% CR,
Median TTF 21 months

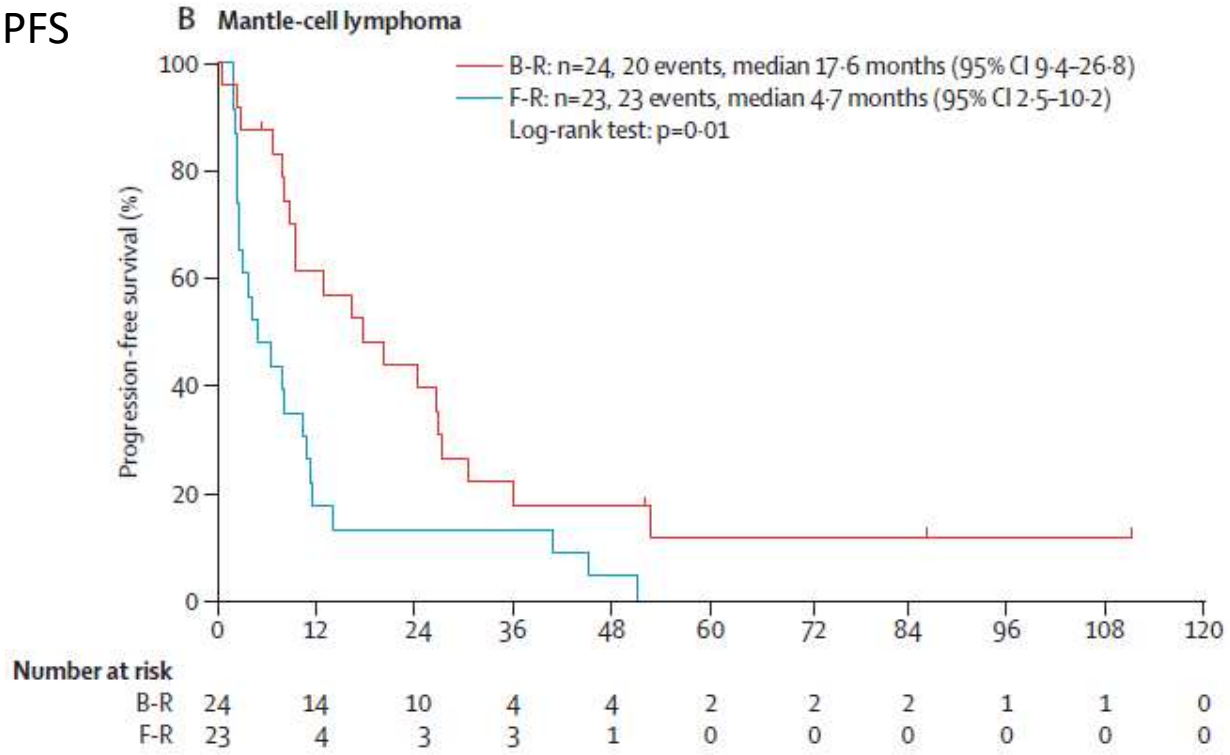
Czuczmann
Ann Hematol 2015: 45 patients, median age 70 (48-88 yrs)
Median prior Tx 2 (1-4)
ORR was 82% (40% CR)
Median PFS was 17 months



BR vs FR in patients with R/R indolent and MCL

Randomized phase 3 study

PFS



	Bendamustine plus rituximab (n=114)	Fludarabine plus rituximab (n=105)
Age		
Median (years)	68·5 (59·0–74·0)	66·4 (59·3–73·7)
Patients aged >70 years	43 (38%)	37 (35%)
Number of previous treatments		
Median	1 (1–2)	1 (1–2)
1	75 (66%)	54 (51%)
2	23 (20%)	34 (32%)
>2	16 (14%)	17 (16%)

Rummel et al, Lancet Oncol 2016

Bendamustine, Lenalidomide and Rituximab (R2-B)

MCL relapsed after a single previous treatment

Induction phase

R2-B* x 4 cycles

Consolidation phase

R2* x 2 cycles

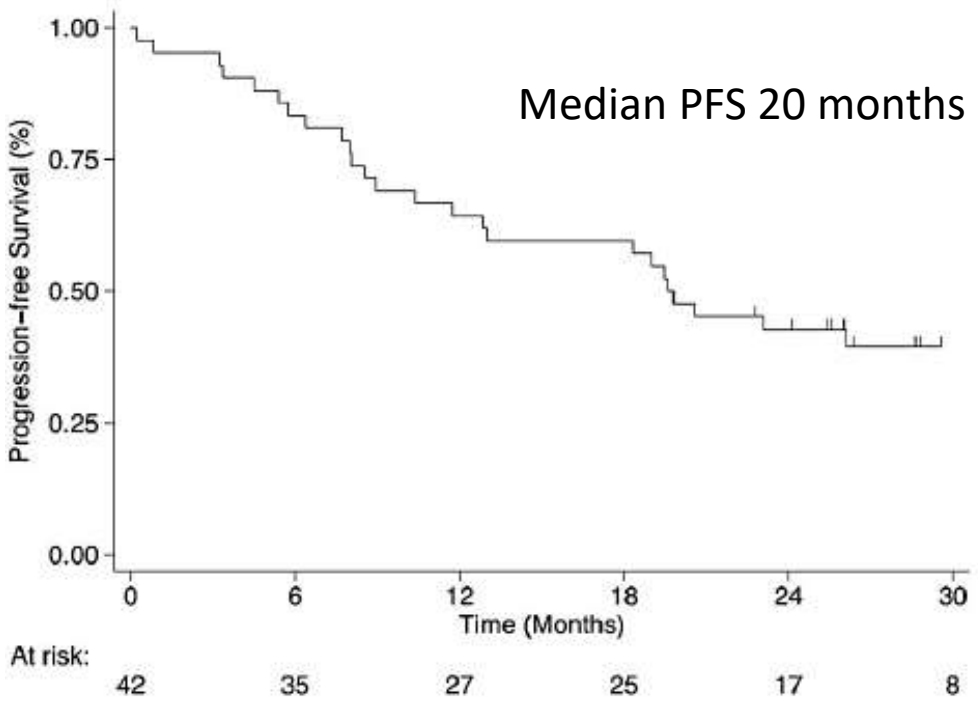
Maintenance phase

Lenalidomide* x 18 months

*Lenalidomide 10, 15, 15 mg/4 wks, respectively
Bendamustine 70 mg/m2

Patients	42
Median age, years (range)	70 (45-86)

	ORR (%)	CR (%)
End of Induction	88	44



Zaja F et al, Haematologica 2017

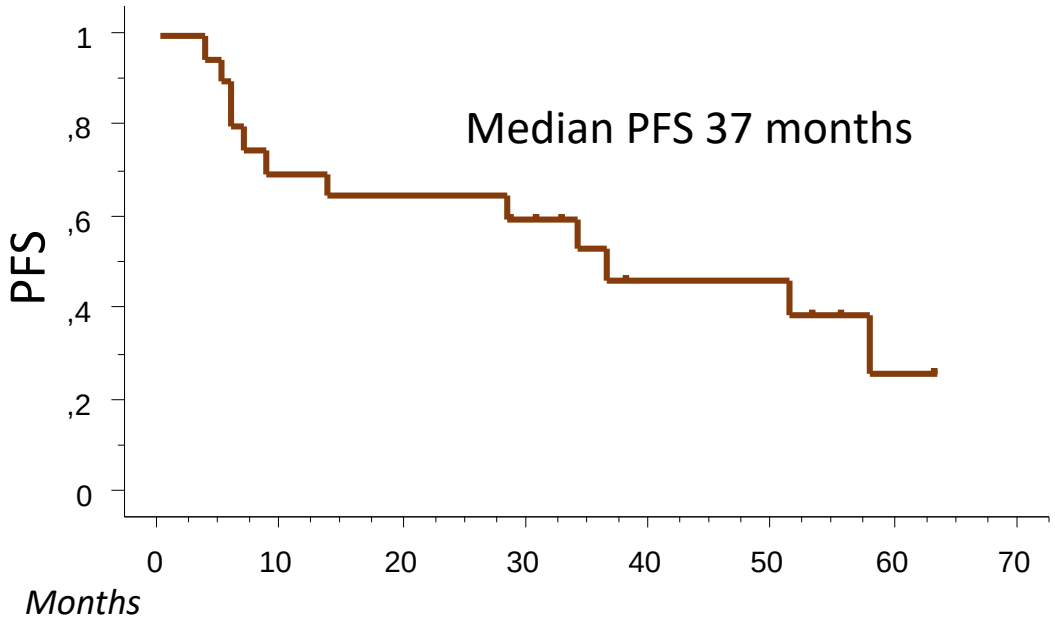
Bendamustine, Cytarabine and Rituximab (R-BAC)

MCL relapsed after a single previous treatment

Treatment	Day 1	2	3	4
Rituximab 375 mg/m²	↓			
Bendamustine 70 mg/m²		↓	↓	
Ara-C 800 mg/m²		↓	↓	↓

	Patients	20
	Median age, years (range)	70 (51-82)

	ORR (%)	CR (%)
R/R	80	70



Visco C et al, JCO 2013

Published clinical trials investigating targeted approaches in R/R MCL

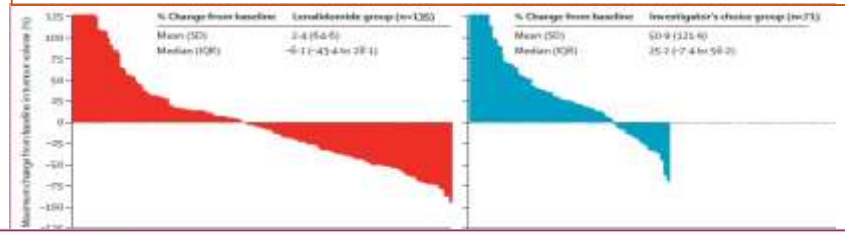
Author	Study features	Assessable patients	Therapeutic regimen	ORR% (CR%)	Median PFS (months)	Median OS (months)
Proteasome inhibitors						
Goy et al. [45]	Phase II	141	Bortezomib	33 (8)	6.7 (TTP)	23.5
mTOR inhibitors						
Hess et al. [42]	Phase III, randomised	54	Temsirolimus 175 mg/75 mg	22 (2)	4.8	12.8
		54	Temsirolimus 175 mg/25 mg	6 (0)	3.4	10.0
		53	Investigator's choice	2 (2)	1.9	9.7
Ansell et al. [43]	Phase II	69	Temsirolimus, rituximab	59 (19)	9.7	29.5
Hess et al. [44]	Phase II	32	Temsirolimus, BR	87 (8)	18	36.0
Immunomodulatory drugs						
Zinzani et al. [38]	Phase II	57	Lenalidomide	35 (12)	8.8	NR
Goy et al. [39]	Phase II	134	Lenalidomide	28 (8)	4	19.0
Trneny et al. [40]	Phase III	254	Lenalidomide	46 (11)	8,7	27.9
			Investigator's choice	23 (8)	5.2	21.2
Wang et al. [41]	Phase II	44	Lenalidomide, rituximab	57 (36)	11.1	24.3
Antibody-based approaches						
Wang et al. [47]	Phase II	32	^{90}Y-ibritumumab tiuxetan	31 (16)	6 (EFS)	21
Ferrero et al. [48]	Phase II	15+[a]	^{90}Y-ibritumumab tiuxetan	40 (20)	3.7	13.8
BCR signalling inhibitors						
Wang et al. [35]	Phase II	111	Ibrutinib	68 (21)	13.9	NR (1.5-year OS 58%)
Dreyling et al. [36]	Phase III	280	Ibrutinib versus temsirolimus	72 (26)	14.6	NR (68% at 1 year)
Wang et al. [37]	Phase II	50	Ibrutinib, rituximab	88 (44)	NR	NR
Kahl et al. [57]	Phase I	16	Idelalisib	62 (N/A)	3 (DOR)	N/A
BCL2 inhibitors						
Davids et al. [53]	Phase I	32 (8 MCL)	Venetoclax[b]	100 (0)	N/A	N/A

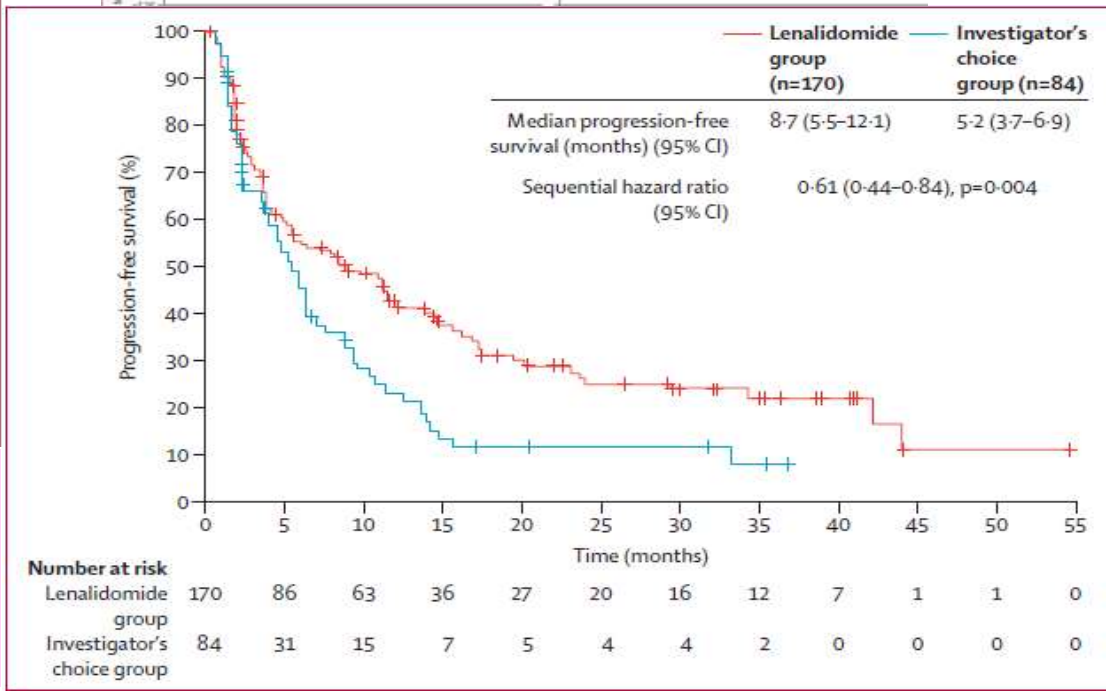
Lenalidomide vs investigator's choice in R/R MCL

Phase 2 randomized SPRINT trial

	Lenalidomide group (n=170)	Investigator's choice group (n=84)
Median age in years (range)	68·5 (44–88)	68·5 (49–87)
Age ≥65 years	115 (68%)	57 (68%)
Sex		
Male	123 (72%)	63 (75%)
Female	47 (28%)	21 (25%)
Mantle cell lymphoma stage at diagnosis		
I/II	13 (8%)	3 (4%)
III	30 (18%)	20 (24%)
IV	123 (72%)	59 (70%)
Missing	4 (2%)	2 (2%)
MIPI score at baseline		
Low	42 (25%)	21 (25%)
Intermediate	66 (39%)	37 (44%)
High	60 (35%)	25 (30%)
Missing	2 (1%)	1 (1%)
Ki-67 index >30%	31 (18%)	19 (23%)
Time from diagnosis to first dose‖		
<3 years	91 (54%)	44 (52%)
≥3 years	76 (45%)	39 (46%)
Median number of previous treatment regimens (IQR)	2 (1–3)	2 (1–3)

ORR 40% vs 11% (CR 5% vs 0%)





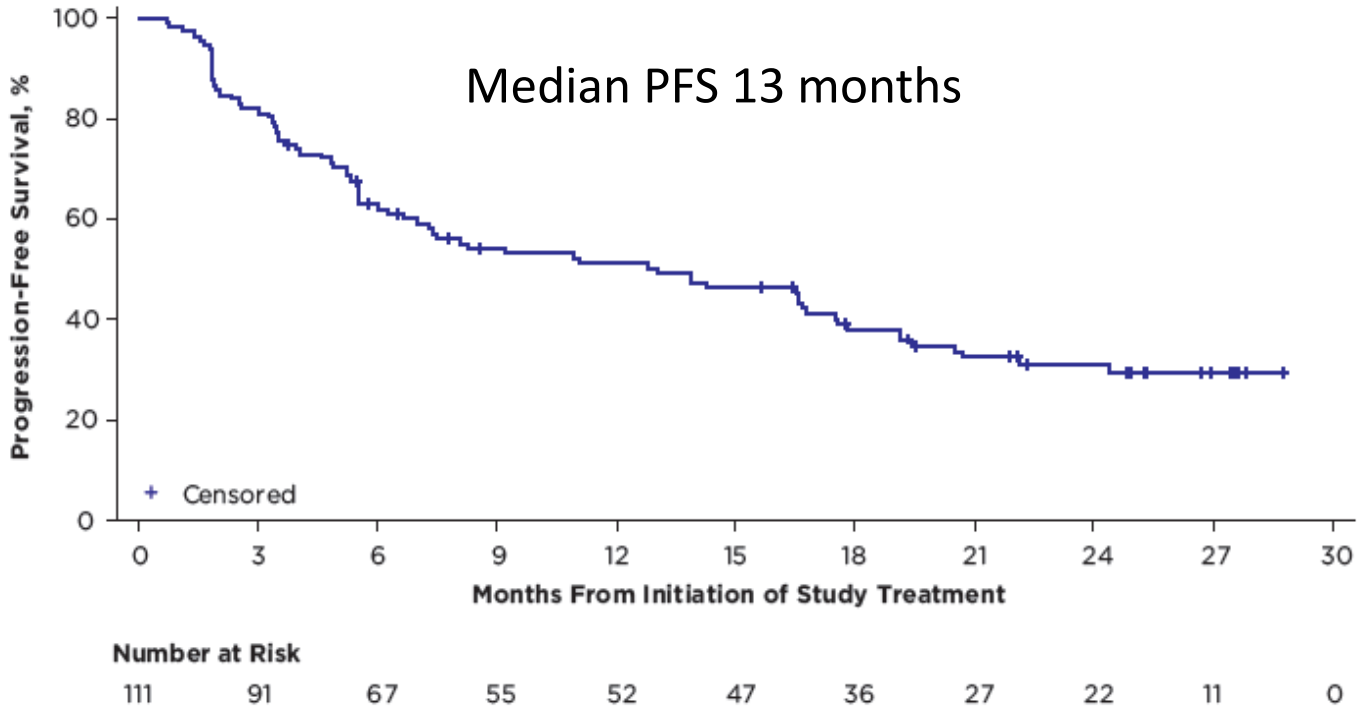
Trerny M et al, Lancet Oncol 2016

Single agent Ibrutinib in R/R MCL

Long-term follow-up: updated safety and efficacy results

111 pts, median 3 prior tx
Median f/u 27 months
Infection (78%, 28% gr ≥3)
Diarrhea (54%, 5% gr ≥3)
Bleeding (50.5%, 6% gr ≥3)
Atrial Fibrillation (11%, 6% gr 3)

ORR 67%, CR 23%



Wang ML et al, Blood 2015

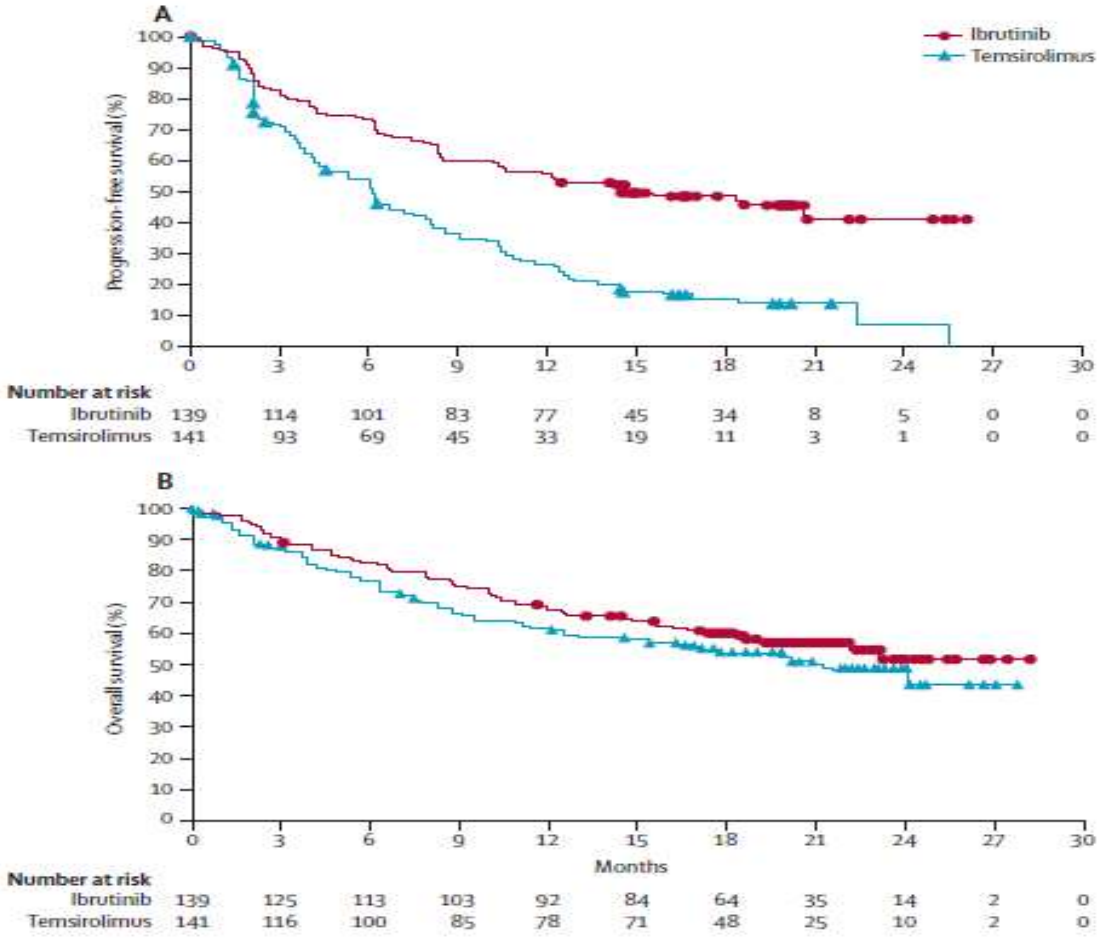
Ibrutinib versus Temsirolimus in R/R MCL

Phase 3 randomized trial

	Ibrutinib (n=139)	Temsirolimus (n=141)	Total (n=280)
Age			
Median (IQR), years	67 (11)	68 (13)	68 (13)
≥65 years	86 (62%)	87 (62%)	173 (62%)
Previous lines of therapy			
Mean (SD)	2·1 (1·4)	2·2 (1·3)	2·2 (1·3)
Median (range)	2·0 (1–9)	2·0 (1–9)	2·0 (1–9)
1–2	95 (68%)	93 (66%)	188 (67%)
3–5	41 (29%)	45 (32%)	86 (31%)
>5	3 (2%)	3 (2%)	6 (2%)
Type of treatment indication			
Relapsed disease*	103 (74%)	94 (67%)	197 (70%)
Refractory disease†	36 (26%)	47 (33%)	83 (30%)

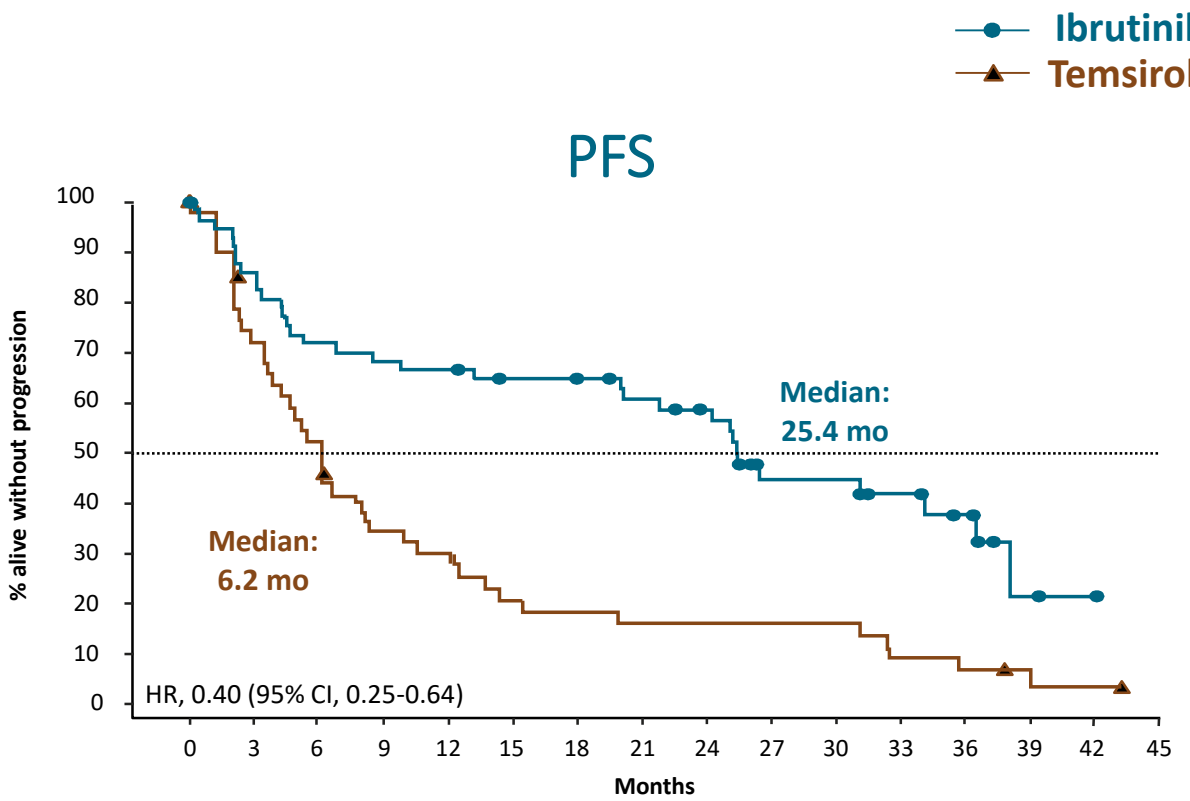
ORR	72%	40%	*p<0·0001*
CRR	19%	1%	

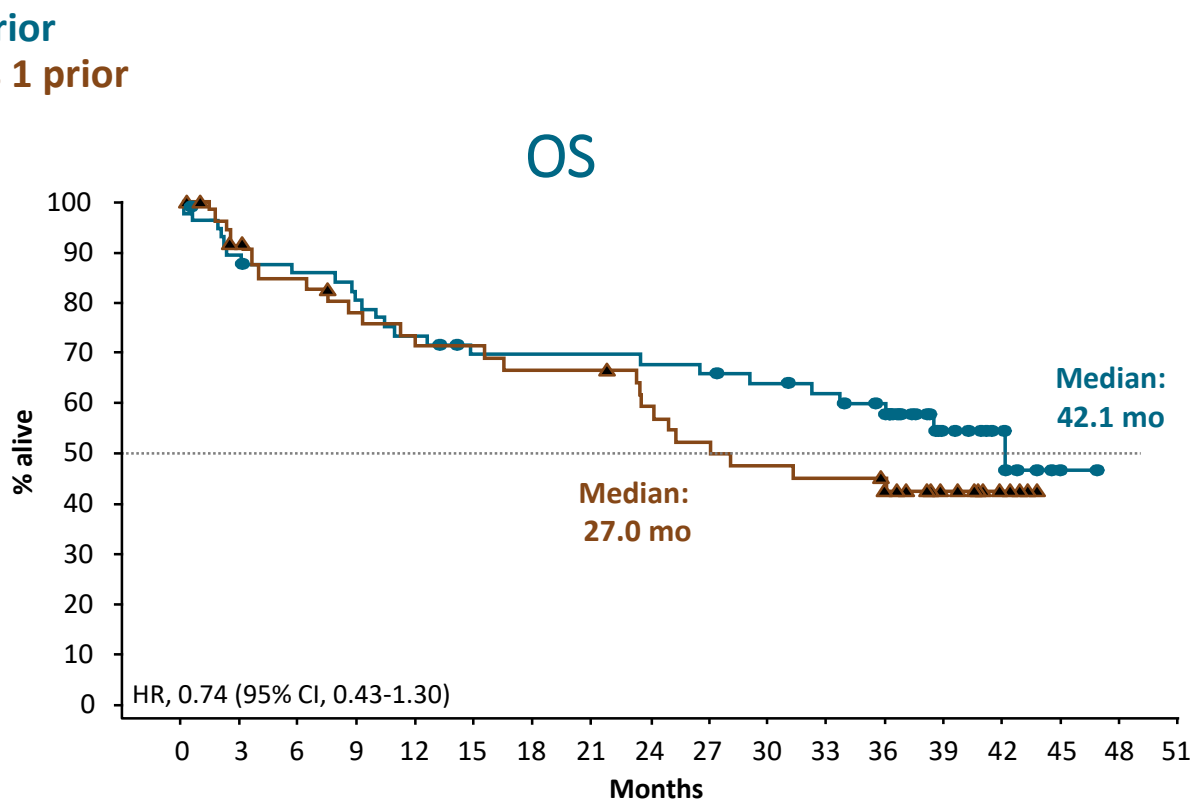
Median PFS 14.6 vs 6.2 months



Dreyling M et al, Lancet Oncol 2016

PFS and Overall Survival: Patients with 1 Prior Line





Patients at risk

Ibr 1 prior	57	49	41	39	38	34	33	30	27	15	15	11	8	2	1	0
Tem 1 prior	50	34	24	15	13	9	8	7	7	7	7	4	3	1	1	0

Patients at risk

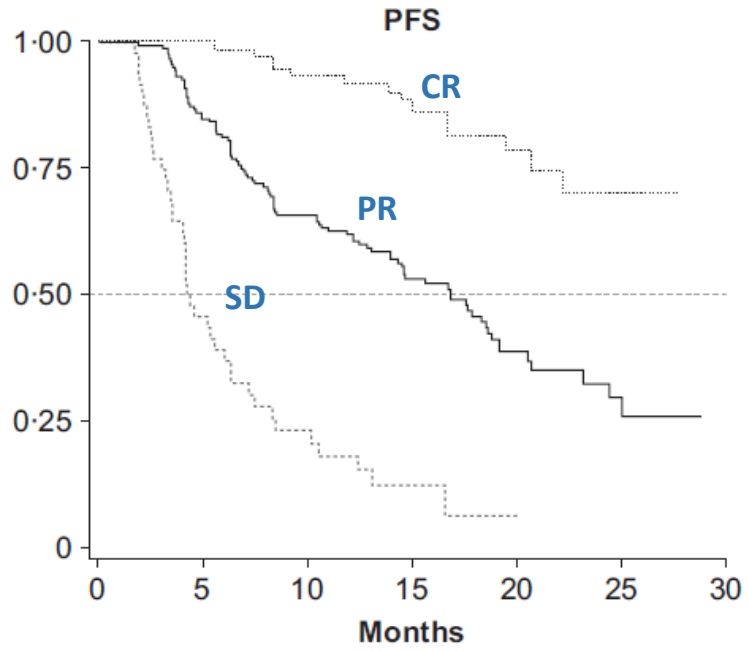
Ibr 1 prior	57	51	48	45	41	37	37	37	36	35	33	31	27	14	7	1	0	0
Tem 1 prior	50	42	38	34	31	31	29	29	25	22	20	19	16	11	4	0	0	0

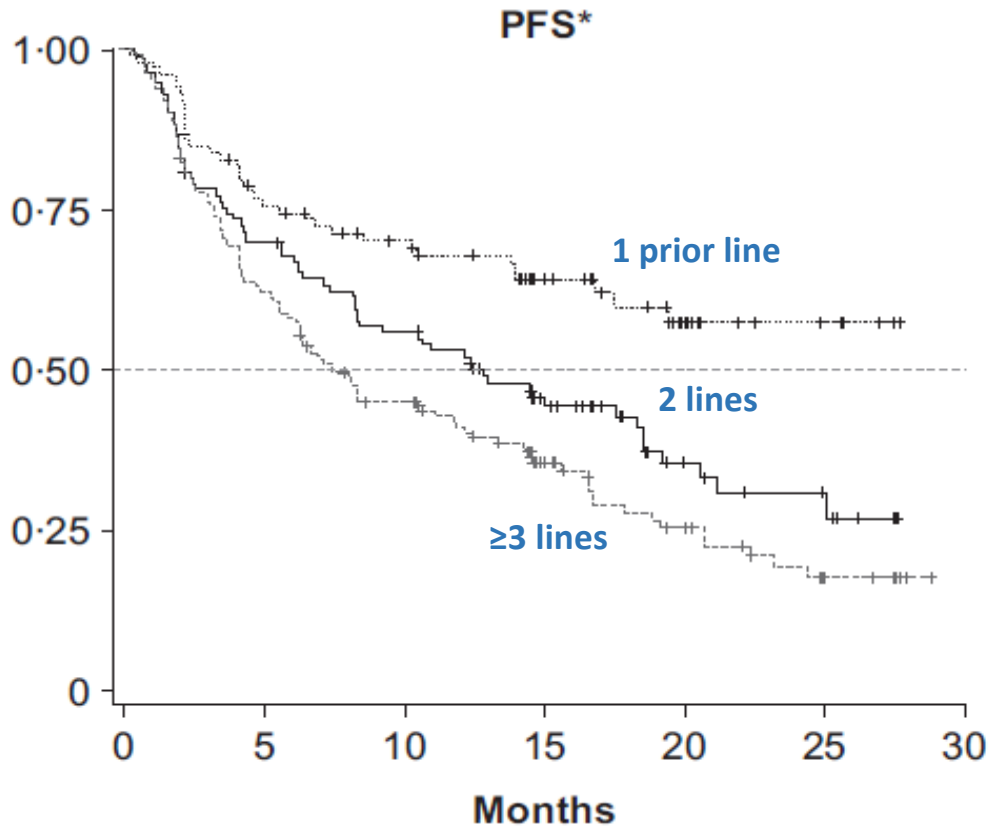
- In patients with only 1 prior line of therapy, median PFS was 4-fold longer and median OS was 15 months longer for ibrutinib than for temsirolimus

MCL3001 (RAY)

Median 3.5-Year Follow-up of Ibrutinib Treatment in Patients with R/R MCL: A Pooled Analysis of 370 patients

	1 prior line (n 99)	>1 prior line (n 271)
OR	77.8%	66.8%
CR	36.4%	22.9%



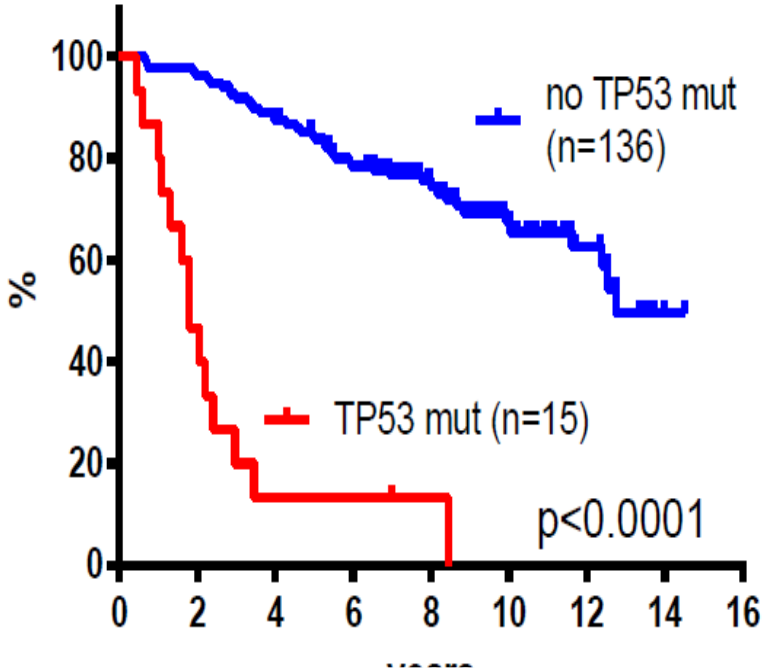


Rule et al, BJH 2017

PFS according to *TP53* mutation

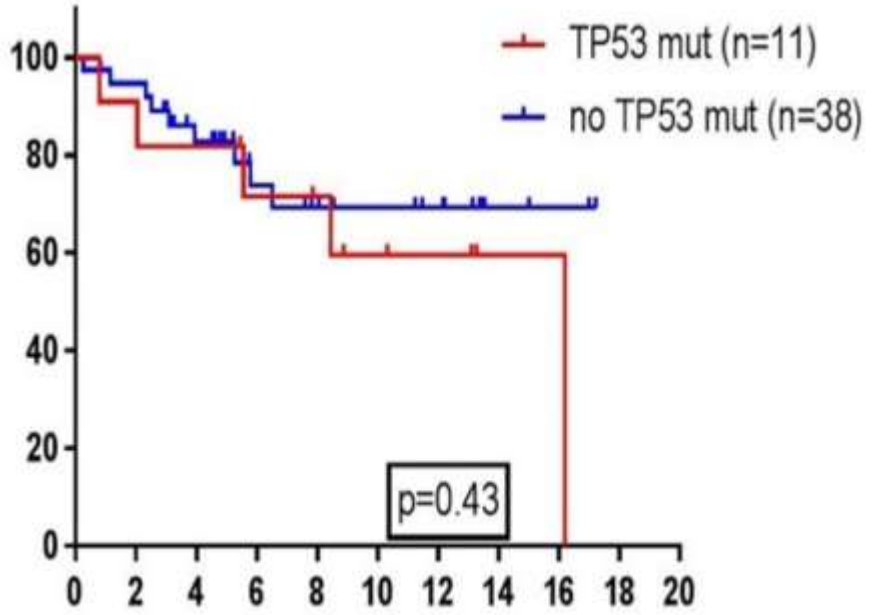
STANDARD R-CT

NORDIC MCL2/3



IBRUTINIB-LENA-R

NORDIC MCL6 PHILEMON



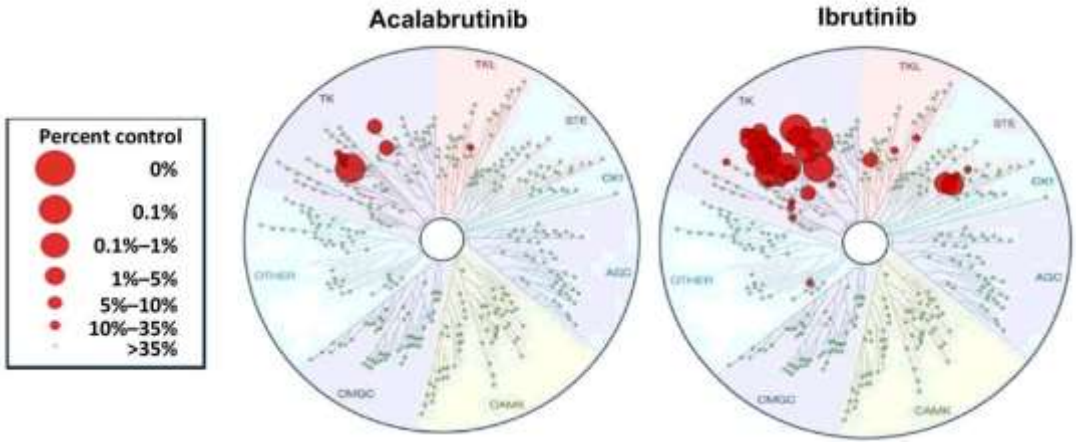
	n	%
ATM	12	24
KMT2D	8	16
CCND1	4	8
TP53	11	22

Jerkeman M et al, ASH 2016, Abstr 148
Eskelund C et al, ASH 2016, Abstr 1095

Efficacy and Safety of Acalabrutinib Monotherapy in Patients with Relapsed/Refractory Mantle Cell Lymphoma in the Phase 2 ACE-LY-004 Study

ABSTR 155: Wang et al.

- Acalabrutinib is more selective for BTK with less off-target kinase inhibition compared to Ibrutinib



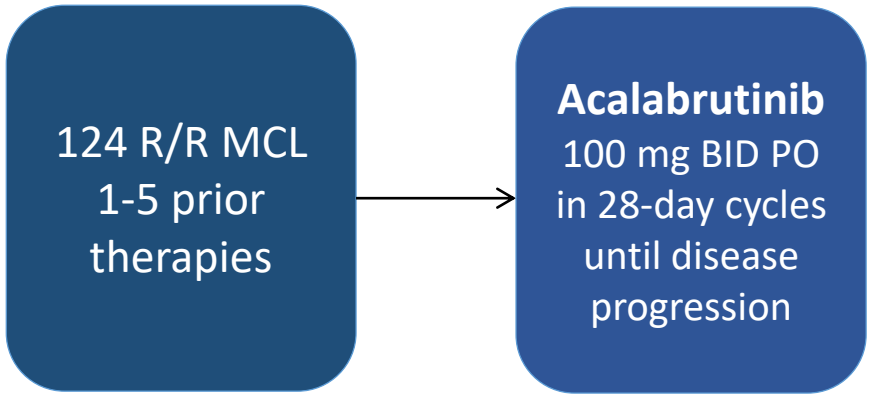
Kinase Inhibition
Average IC_{50} (nM)

Kinase	Acalabrutinib	Ibrutinib
BTK	5.1	1.5
TEC	126.0	10.0
ITK	>1000	4.9
BMX	46.0	0.8
TXK	368.0	2.0
EGFR	>1000	5.3
ERBB2	~1000	6.4
ERBB4	16	3.4
BLK	>1000	0.1
JAK3	>1000	32

Efficacy and Safety of Acalabrutinib Monotherapy in Patients with Relapsed/Refractory Mantle Cell Lymphoma in the Phase 2 ACE-LY-004 Study

ABSTR 155: Wang et al.

- Enrollment in 40 sites across 10 countries



Primary Endpoint: ORR
by investigator assessment
based on Lugano Classification

Inclusion criteria:

- Confirmed R/R MCL
- ECOG ≤ 2
- Age ≥ 18

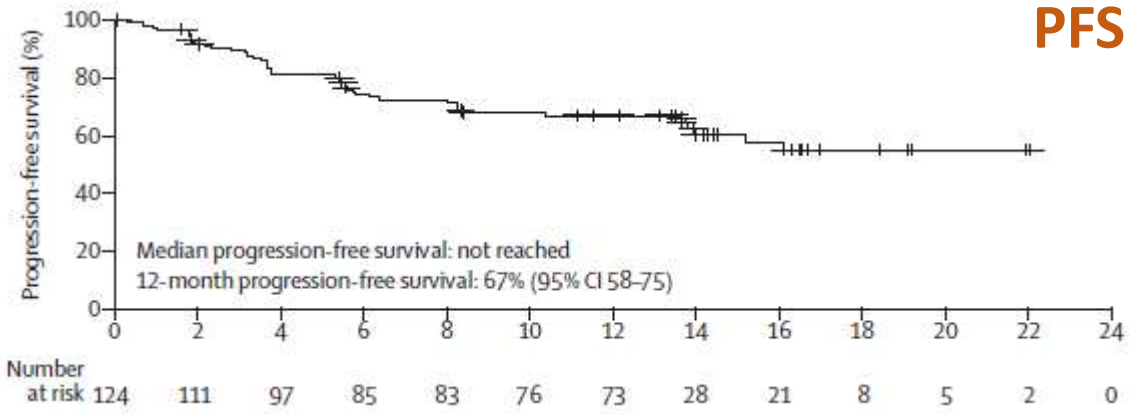
Exclusion criteria:

- Use of Warfarin
- Previous BTK-inhibitor
- Cardiovascular disease (arrhythmia, congestive heart failure, recent IMA, QTc>480 ms)

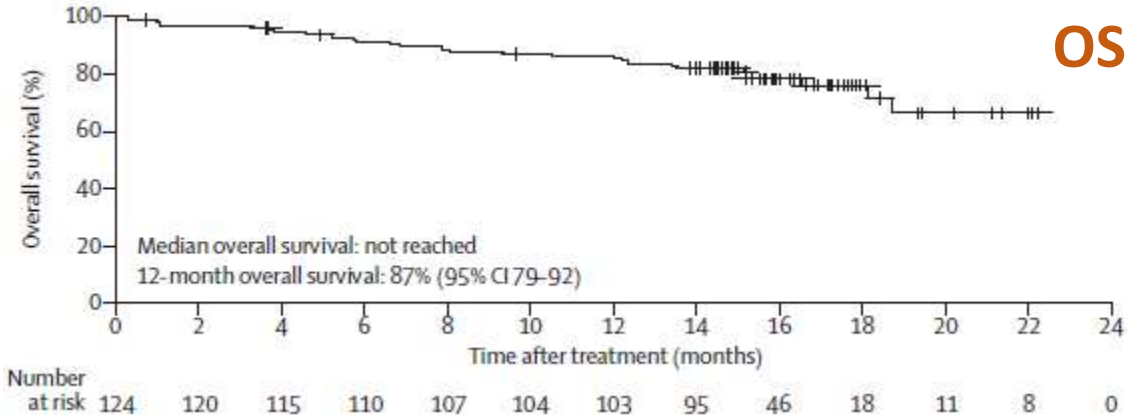
Efficacy and Safety of Acalabrutinib Monotherapy in Patients with Relapsed/Refractory Mantle Cell Lymphoma in the Phase 2 ACE-LY-004 Study

ABSTR 155: Wang et al.

PFS



OS



Conclusions

- Acalabrutinib demonstrated remarkable efficacy and different safety profile compared to Ibrutinib
- ORR 81%, CRR 40%
- There were few discontinuations (6%)
- No AF observed and bleeding grade 3-4 was low (1%)

A Phase 1 Study of Venetoclax (ABT-199)

First-in-Human Study of Venetoclax in Patients With R/R NHL

Characteristic, n (%)		All N=106	MCL n=28	FL n=29	DLBCL n=41 [a]	Other [b] n=8
Age, years	Median (range)	66 (25–86)	72 (35–85)	64 (46–75)	67 (25–86)	63 (56–73)
Prior therapies	Median (range)	3 (1–10)	3 (1–7)	3 (1–10)	3 (1–8)	4 (2–6)
	Rituximab-refractory	33 (31)	8 (29)	8 (28)	16 (39)	1 (33)
Bulky nodes	>5 cm	49 (48)	16 (59)	8 (29)	22 (54)	3 (38)
	>10 cm	14 (14)	3 (11)	2 (7)	8 (20)	1 (13)
LDH	> Upper Limit of Normal	45 (44)	7 (27)	10 (35)	27 (68)	1 (13)

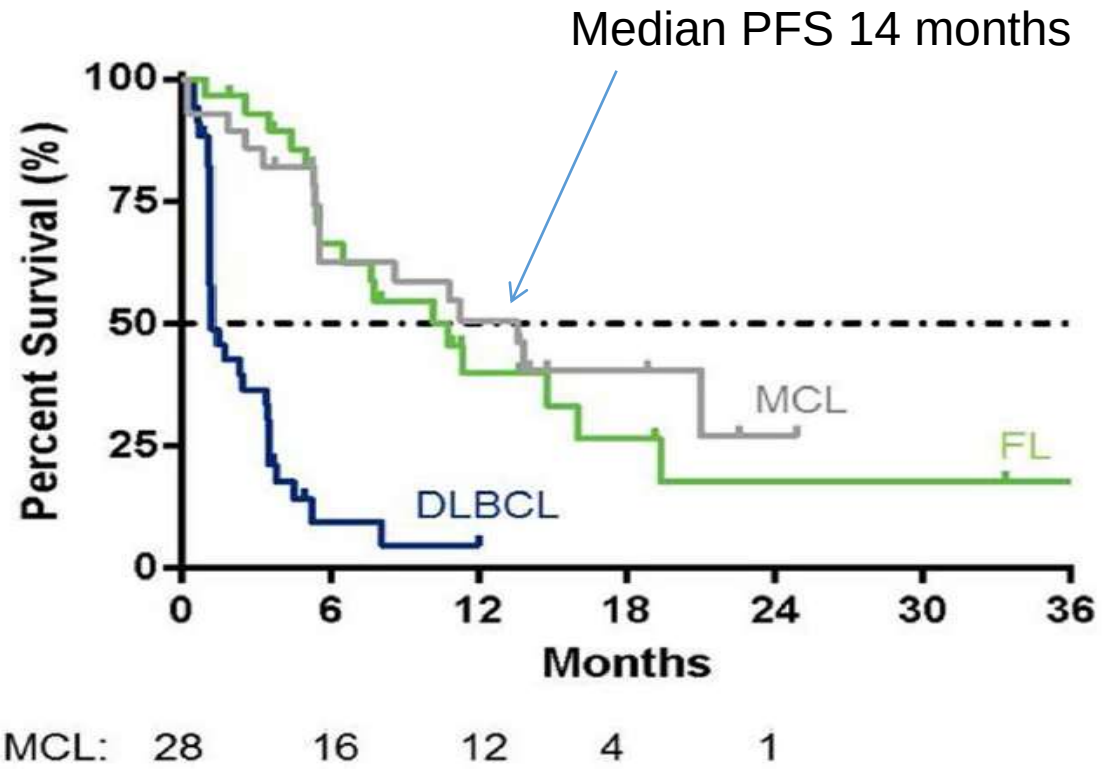
[a] Includes 7 patients DLBCL-Richter's transformation
[b] Includes n=4 WM, n=3 MZL, n=1 MM

Gerecitano et al, JCO 2017

A Phase 1 Study of Venetoclax (ABT-199)

Response to Venetoclax Monotherapy and PFS in MCL patients

Best Objective Response, n (%)	All N=106	MCL n=28
Overall Response	**47 (44)**	**21 (75)**
CR	14 (13)	6 (21)
PR	33 (31)	15 (54)
SD	32 (30)	5 (18)
PD	23 (22)	1 (4)

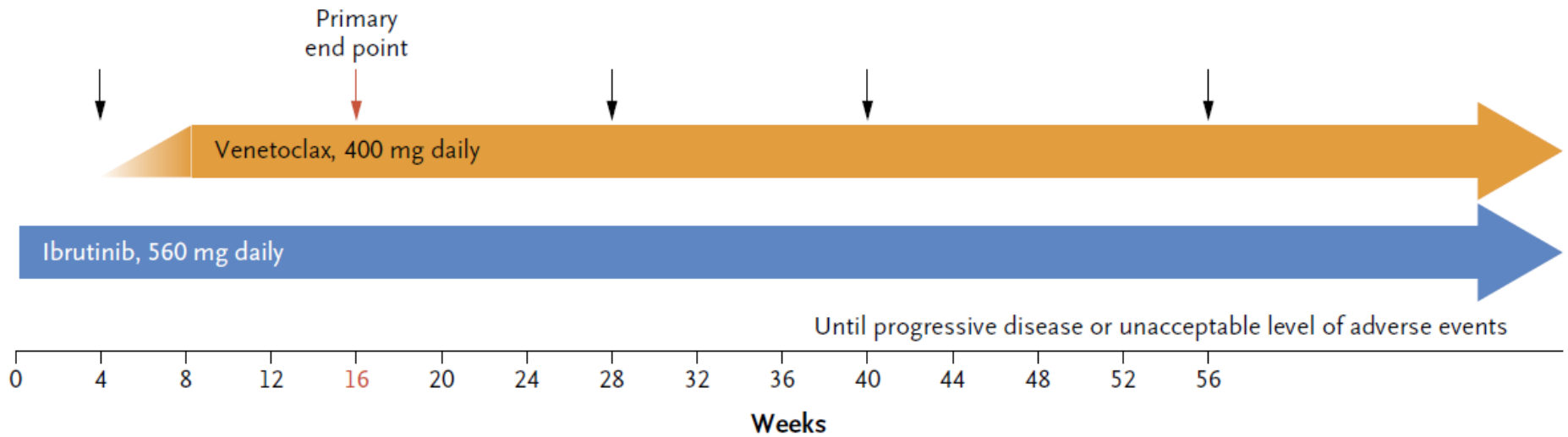


Gerecitano et al, JCO 2017

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ibrutinib plus Venetoclax for the Treatment of Mantle-Cell Lymphoma



Tam CS et al, NEJM 2018

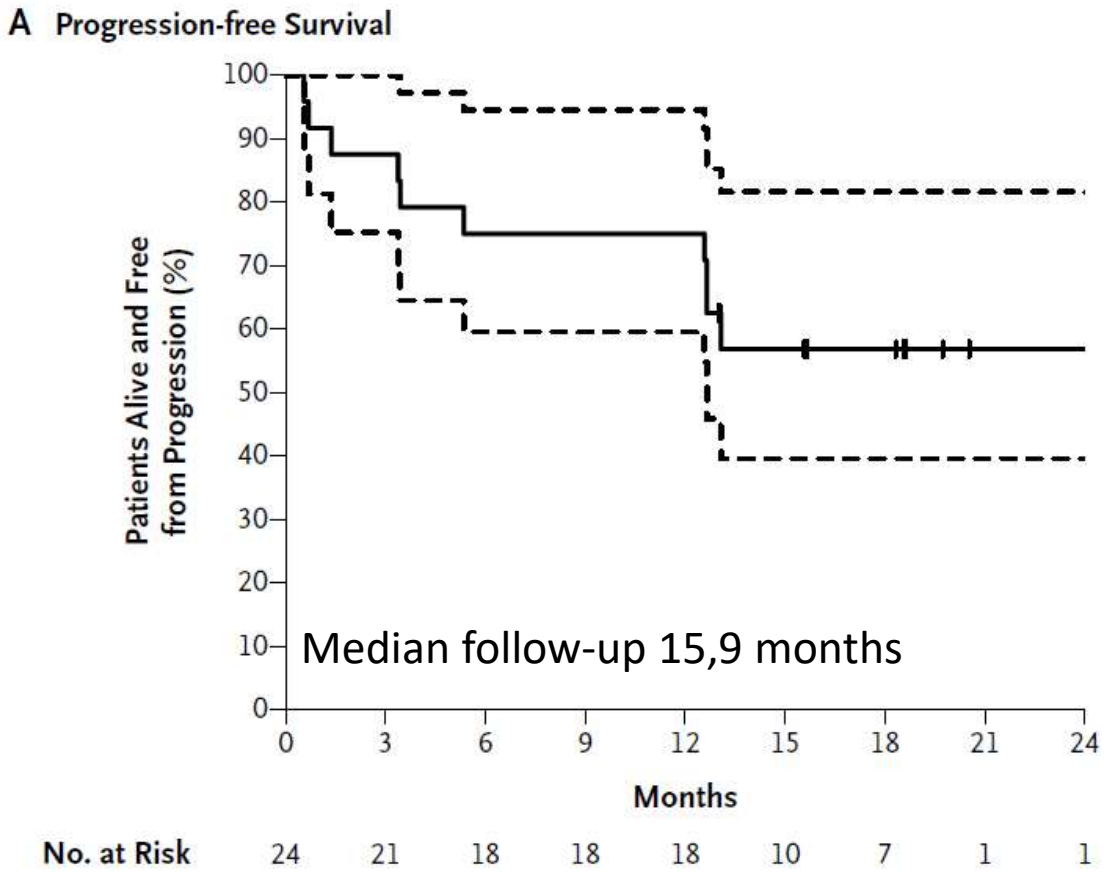
Patients characteristics (n=24)

Characteristic	Value
Median age (range) — yr	68 (47–81)
Sex — no. (%)	
Female	3 (12)
Male	21 (88)
Previous treatment for mantle-cell lymphoma — no. (%)	
Yes	23 (96)
No†	1 (4)
No. of previous therapies among patients who had received therapy — median (range)‡	2 (1–6)
Previous therapy — no./total no. (%)‡	
Autologous transplantation	7/23 (30)
Rituximab	23/23 (100)
Anthracycline	21/23 (91)
High-dose cytarabine	11/23 (48)
Bendamustine	4/23 (17)
Blastic or pleomorphic mantle-cell lymphoma — no./total no. (%)	1/21 (5)
Ki-67 ≥30% — no./total no. (%)	9/21 (43)
TP53 status — no. (%)	
Mutated with deletion	4 (17)
Mutated without deletion	7 (29)
Deletion without mutation	1 (4)

Tam CS et al, NEJM 2018

Response, PFS, toxicity

	CT-scan	PET
Response at wk 16	**N (%)**	**N (%)**
CR	10 (42)	15 (62)
PR	4 (17)	2 (8)
PD	3 (12)	4 (17)

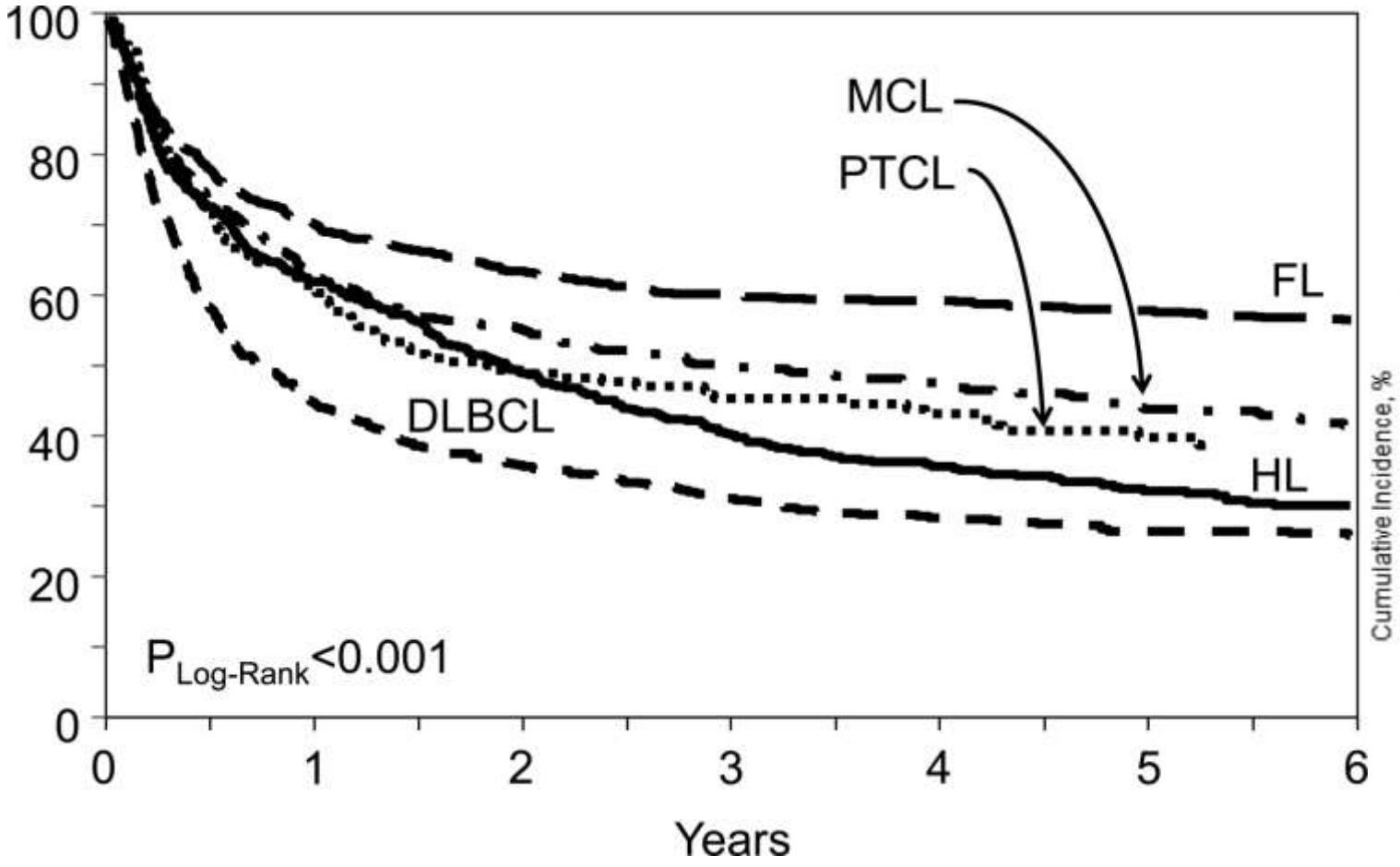


The most common toxic effects were gastrointestinal
diarrhea in 83% (gr 1 in 38%, 2 in 33%, 3 in 12%),
typically transient, lasting a median of 2 weeks
nausea or vomiting in 71%
gastroesophageal reflux in 38%
fatigue in 75%
bleeding, bruising in 54%
musculoskeletal or connective-tissue pain in 50%
soft-tissue infection in 42%
neutropenia in 33%
lower respiratory tract infection in 33%.
With the exception of neutropenia, these events were predominantly of grade 1 or 2 in severity.

Tam CS et al, NEJM 2018

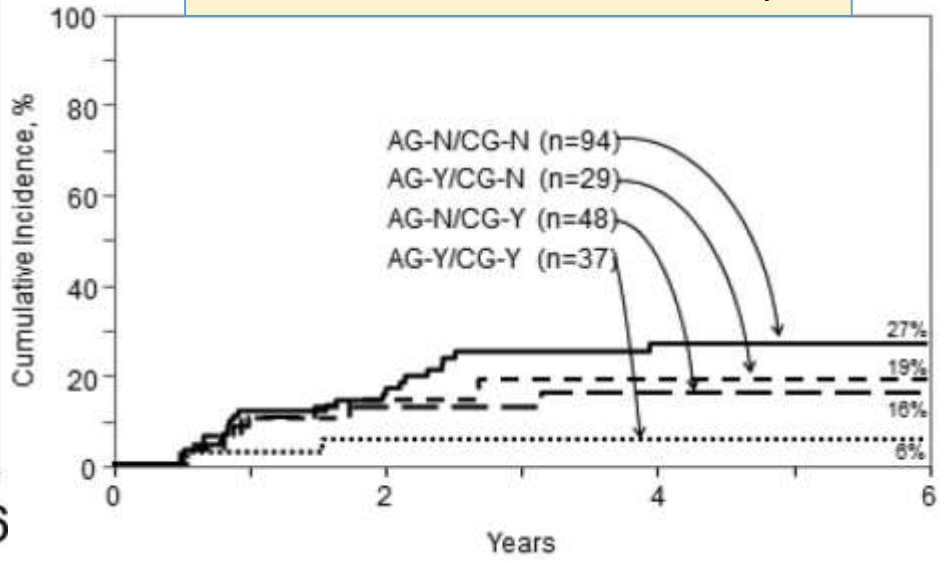
Allogeneic transplant in different lymphoma subtypes

CIBMTR registry 1997-2009 (n=2611)



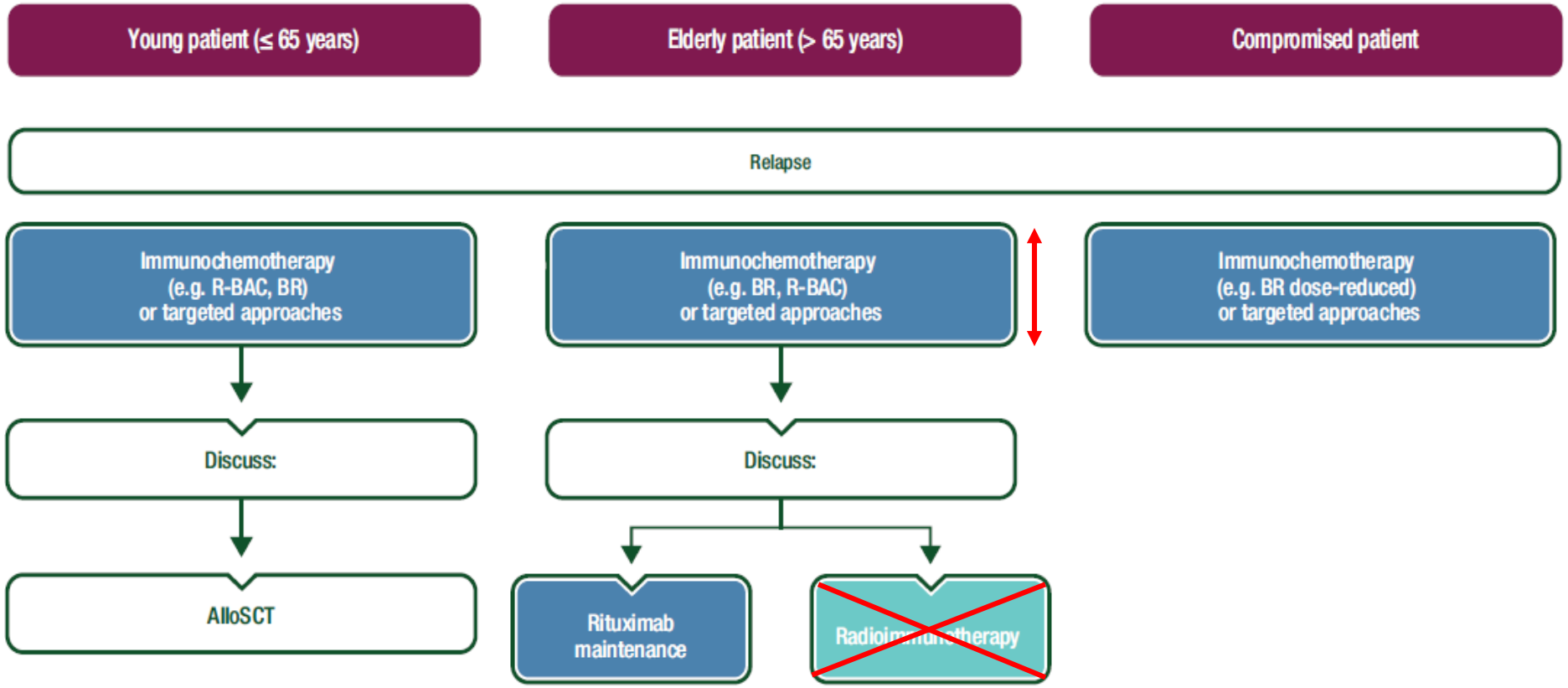
RIC-Allo

Cumulative incidence of relapse



Urbano-Ispizua A, Biol BMT 2015

ESMO GUIDELINES 2017: AT RELAPSE



Dreyling M, et al. Ann Oncol 2017

Thank you for your attention

Allogeneic non-myeloablative SCT

Retrospective series and phase II studies

Registry data

TRM 30-50% and 2-years OS 30-46%.

Kiss TL, BMT 2005; Dietrich S, Ann Oncol 2014

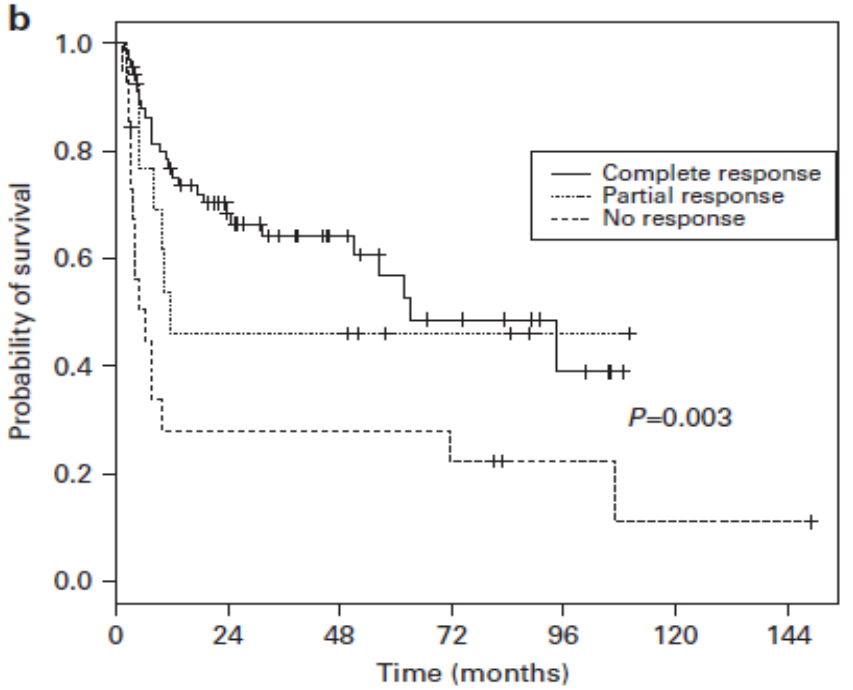
Centers of excellence more encouraging

TRM 20-25%, 2-years OS 45-65%

Plateau in survival curves*

Maris MB, Blood 2004; Khouri IF, JCO 2003; Corradini P, Leukemia 2007;
Cook G, BiolBMT 2010; LeGouill, Ann Oncol 2012; Fenske CS, JCO 2013
Kasamon YL, JCO 2015

Characteristics	*1 month TRM (%)*	*3 months TRM (%)*	*1 year TRM*
HLA			
Identical sibling	0	5.5	22
Matched unrelated	0	6	35
Mismatched unrelated	5	14	24

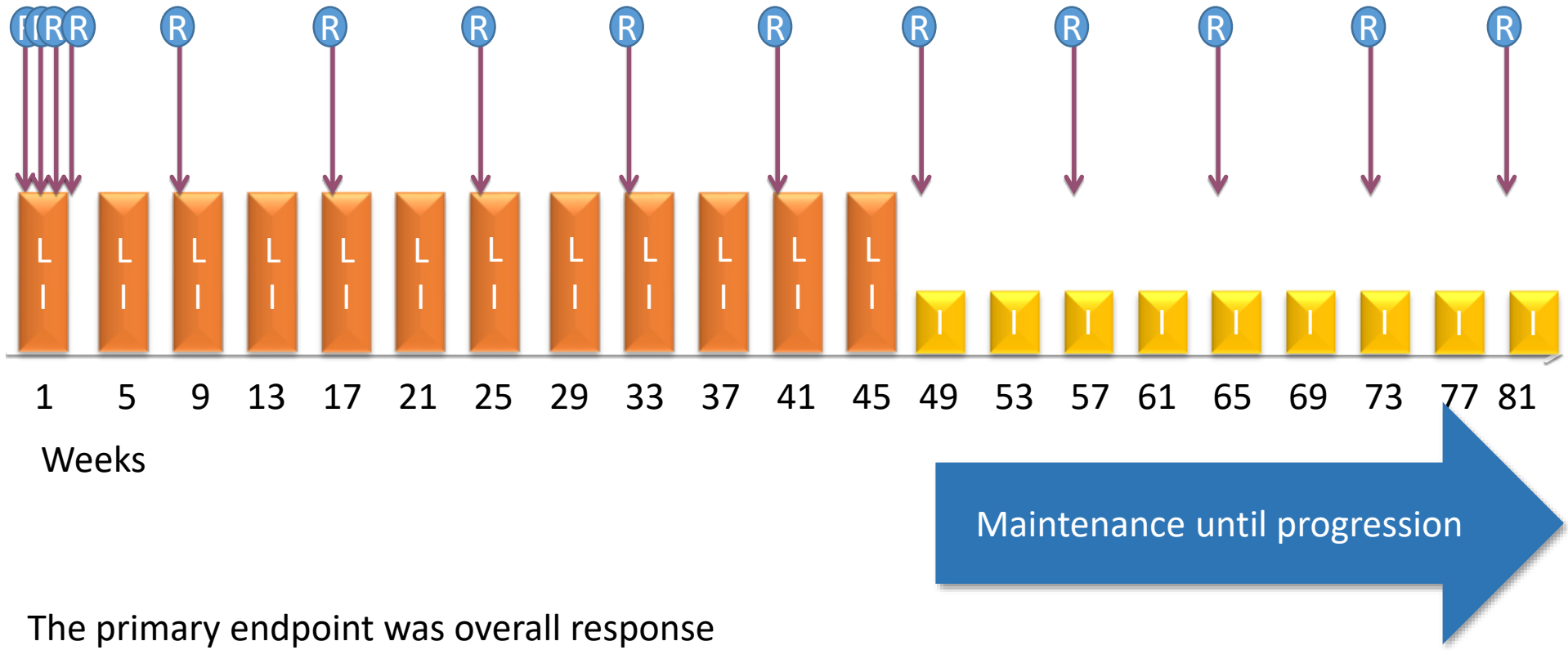


*Tessoulin B, BMT 2016

NLG-MCL6 (PHILEMON)

Ibrutinib+Lenalidomide+Rituximab

PHase II study



The primary endpoint was overall response

Courtesy of M Jerkemann

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

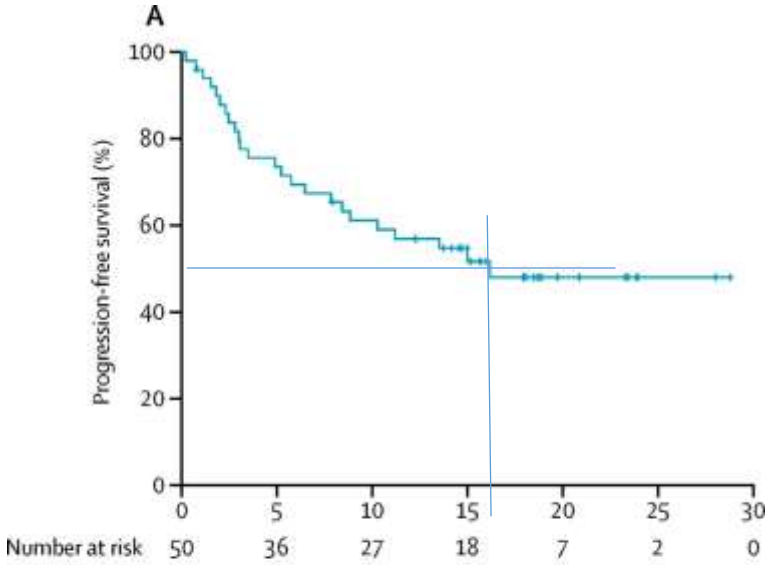
50 patients included in 12 months

Median age (years)	70	46-85
Male gender	36	72%
Median lines of therapy	1.5	(1-7)
Previous autologous SCT	21	42%
Previous allogeneic SCT	3	6%
Previous ibrutinib	4	8%
Previous lenalidomide	1	2%
MIPI High Risk	24	48%

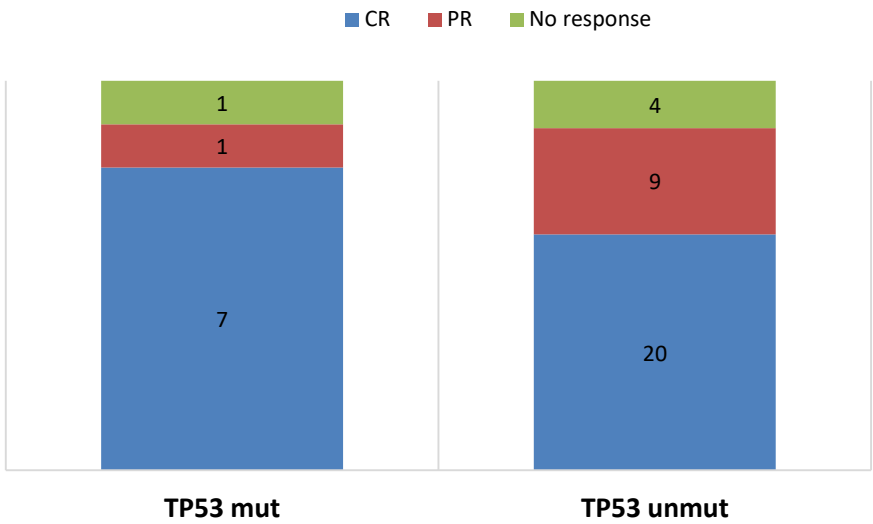
	All patients		**Single ibrutinib** Wang *NEJM 2013*
	N=50	%	N=111 (%)
ORR	***38***	***76***	***68***
CR	28	56	21
PR	10	20	47
NR/PD	12	24	20

Jerkeman M et al, Lancet Haematol 2018

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



	n	%
ATM	12	24
KMT2D	8	16
CCND1	4	8
TP53	11	22
BIRC3	1	2
WHSC1	2	4
NOTCH1	0	0
NOTCH2	0	0



Median follow-up 17.8 months

Jerkeman M et al, Lancet Haematol 2018

Effectiveness of Lenalidomide in Patients with MCL Who Relapsed/Progressed after or Were Refractory/Intolerant to Ibrutinib: The MCL-004 Study

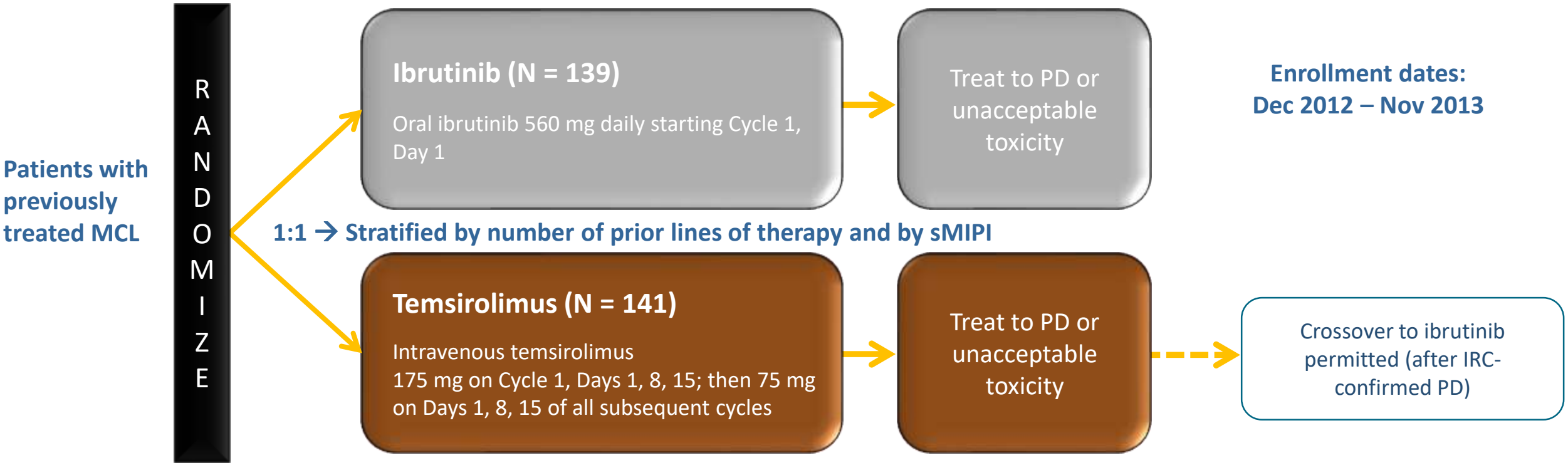
Wang M et al, USA, **ABSTR 1786**

BACKGROUND: A recent retrospective series of 114 patients who had failed ibrutinib showed very short median overall survival of 2.9 months after ibrutinib cessation (*Martin et al. Blood 2015*).

INCLUSION CRITERIA: Patients were either relapsed/progressed (50%), refractory (40%), or intolerant (10%) to ibrutinib.

RESULTS:

- 30 patients enrolled, that received a median of 2 cycles (range, 1-11) of lenalidomide-based treatment
- ORR was 27%, CR was 13%.
- Median duration of response (DOR) was 18 weeks (95% CI, 2.9-25+).
- No new safety signals for lenalidomide were identified.



Enrollment dates:
Dec 2012 – Nov 2013

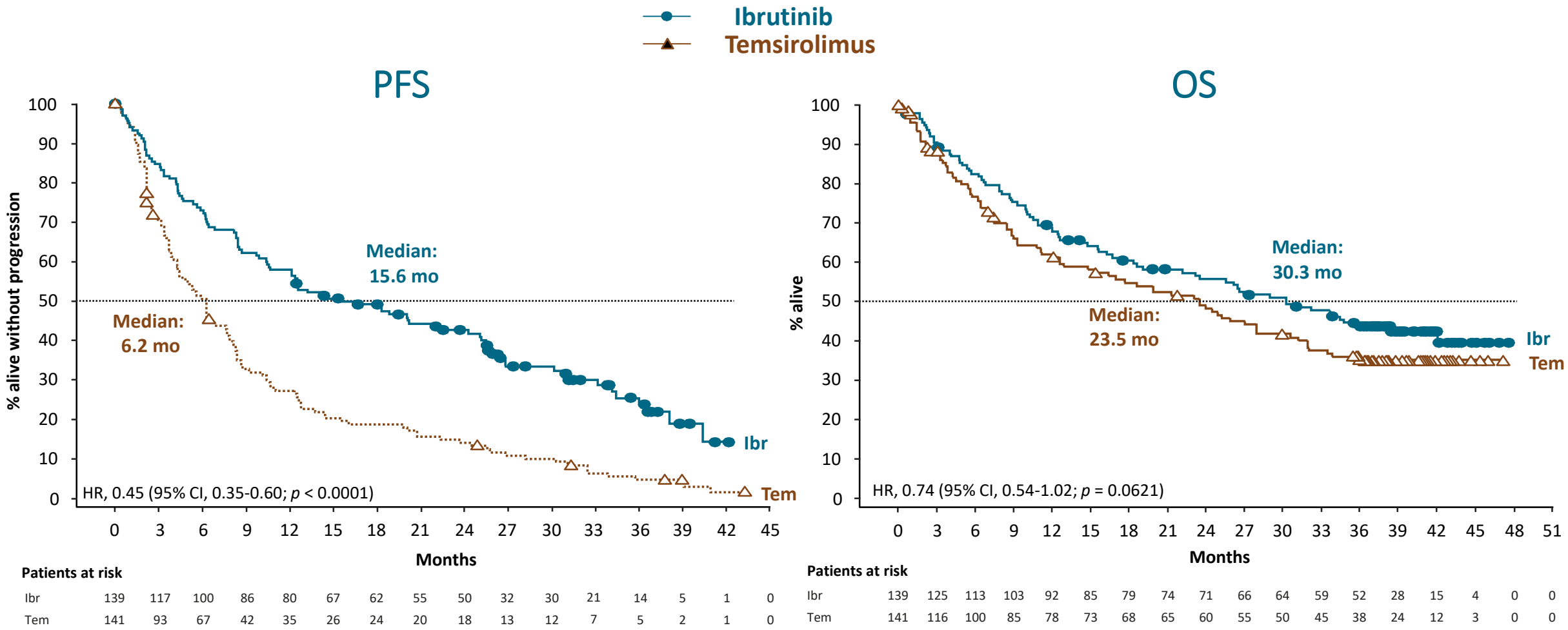
Primary end point:

- IRC-assessed PFS
- PFS was investigator-assessed beyond the primary analysis

Secondary end points included:

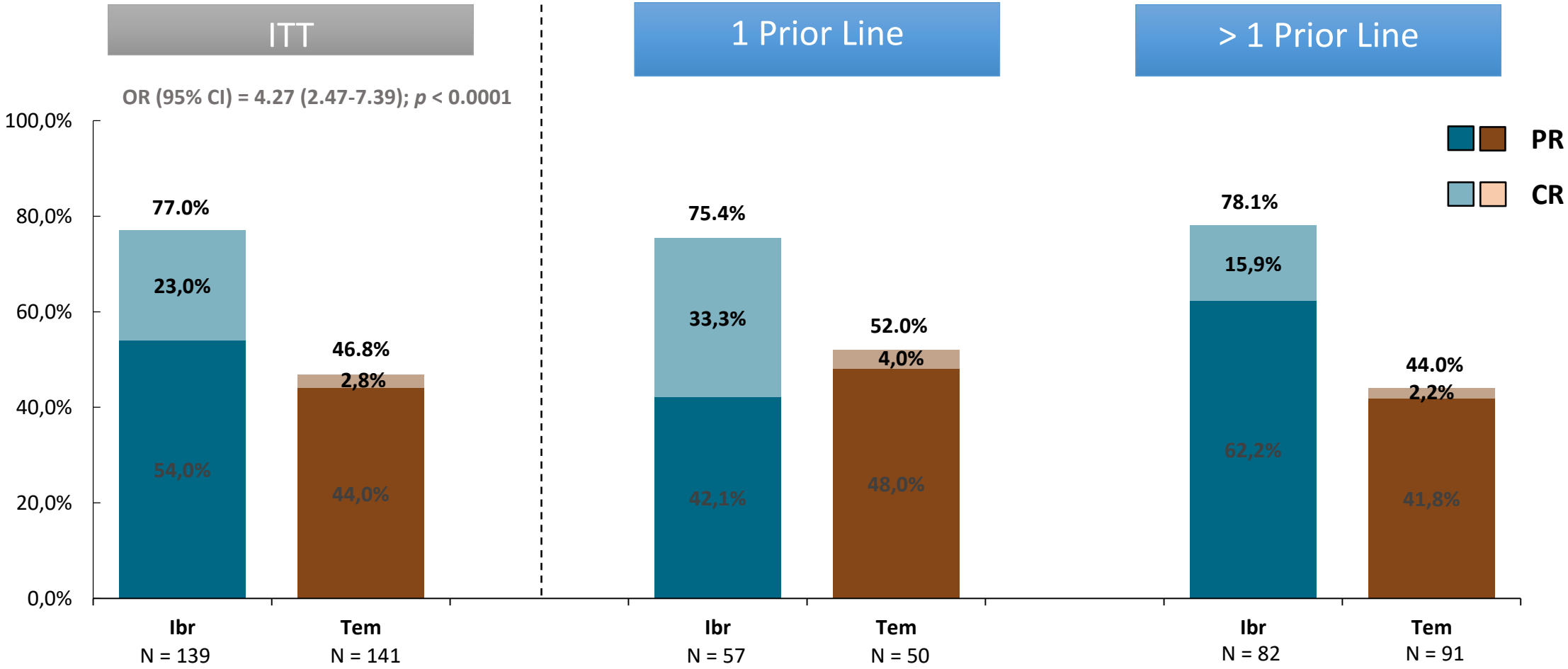
- IRC-assessed ORR (CR + PR)
- Overall survival
- Duration of response
- Time to next treatment
- Safety
- Patient-reported outcomes

MCL3001 (RAY)



- With median follow up of 38.7 months, significant PFS benefit and strong trend toward OS benefit for ibrutinib versus temsirolimus

MCL3001 (RAY)



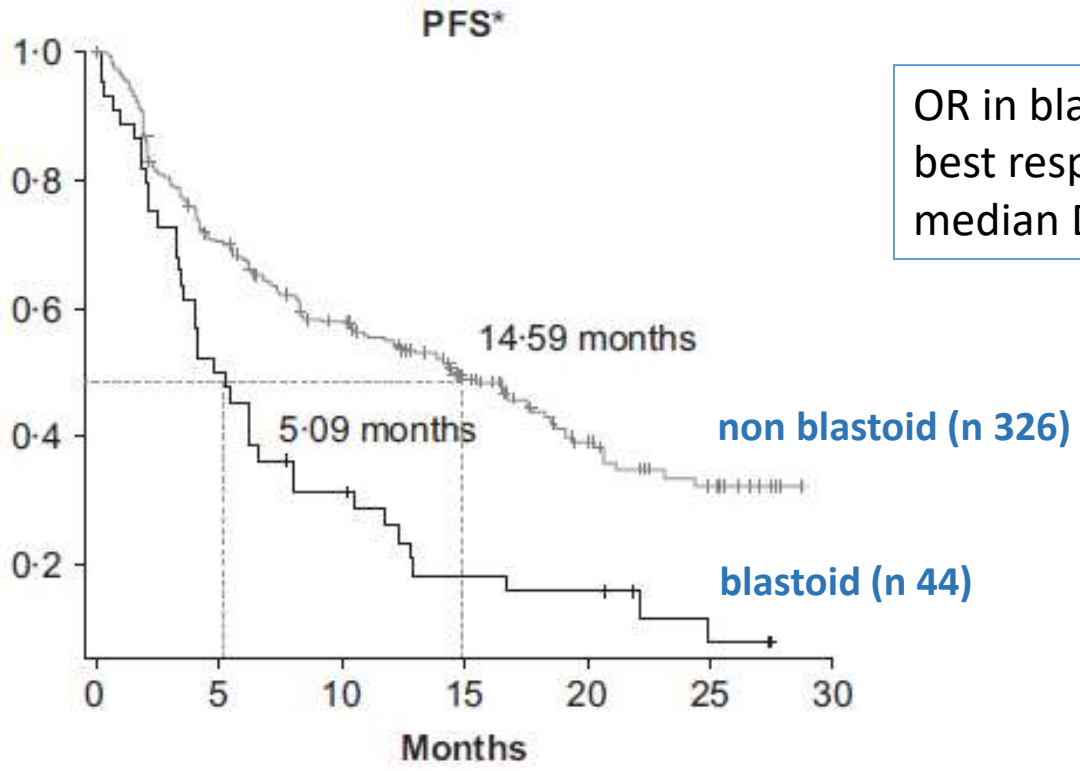
- CR rate for ibrutinib doubled when used in patients with 1 prior line versus > 1 prior line
- Median duration of response: 23.1 months for ibrutinib versus 6.3 months for temsirolimus

MCL3001 (RAY)

Median 3.5-Year Follow-up of Ibrutinib Treatment in Patients with R/R MCL: A Pooled Analysis

ABSTR 151; Rule et al.

Response rates and PFS in the pooled analysis of 370 patients



OR in blastoids was 50%,
best response within 2-3 months,
median DOR 8.5 months