Regimi di trattamento chemo-free nei linfomi non Hodgkin

Francesco Zaja, Udine

Is it possible to abrogate the chemo-immunotherapy in NHL?

- Old and new anti-CD20 MoAb
- Lenalidomide + other IMIDs
- Ibrutinib + other BTK inhibitors
- Idelalisib + other PI3K inhinibitors
- New non anti-CD20 MoAb
- Venetoclax
- Checkpoint inhibitors

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- Venetoclax
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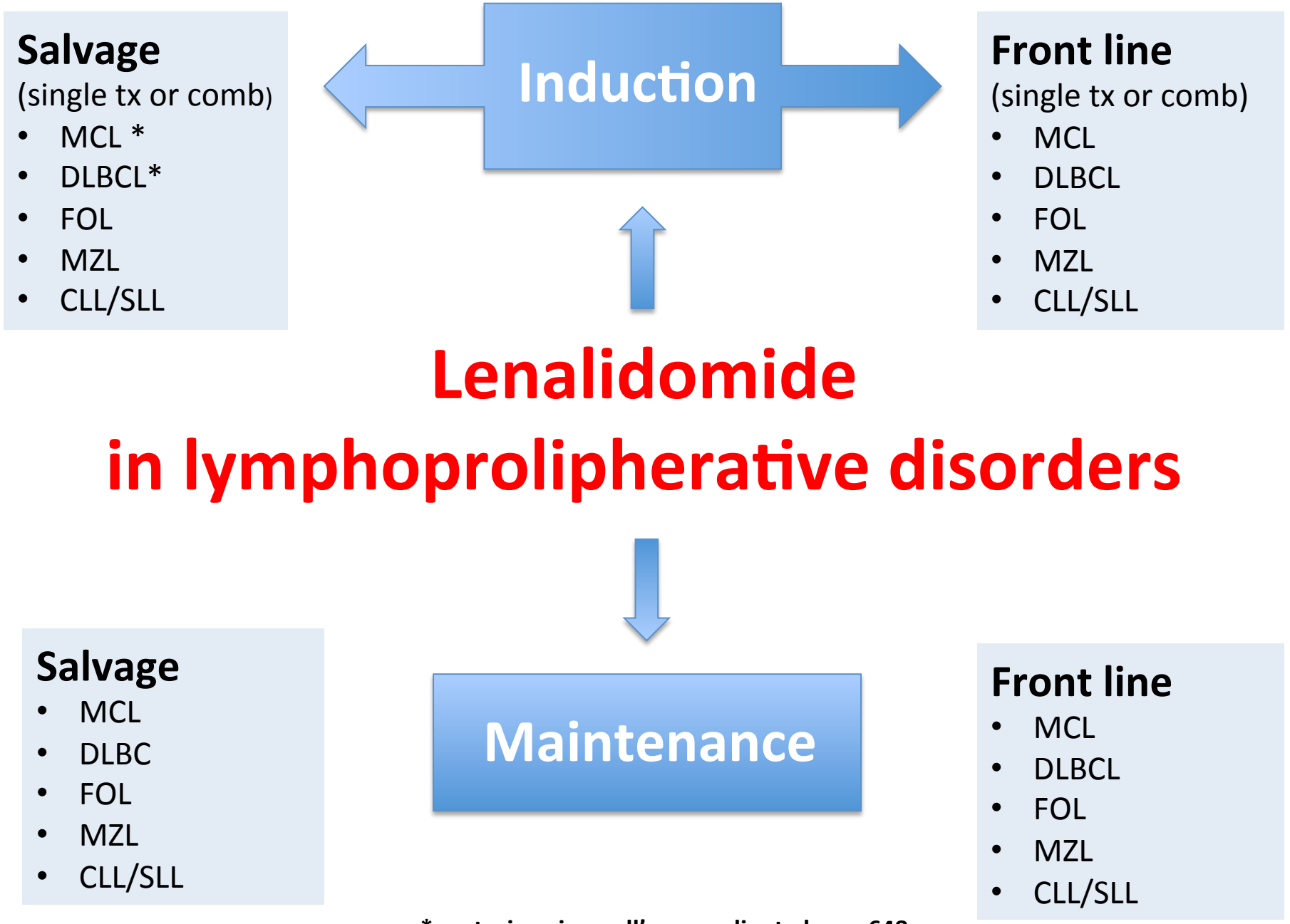
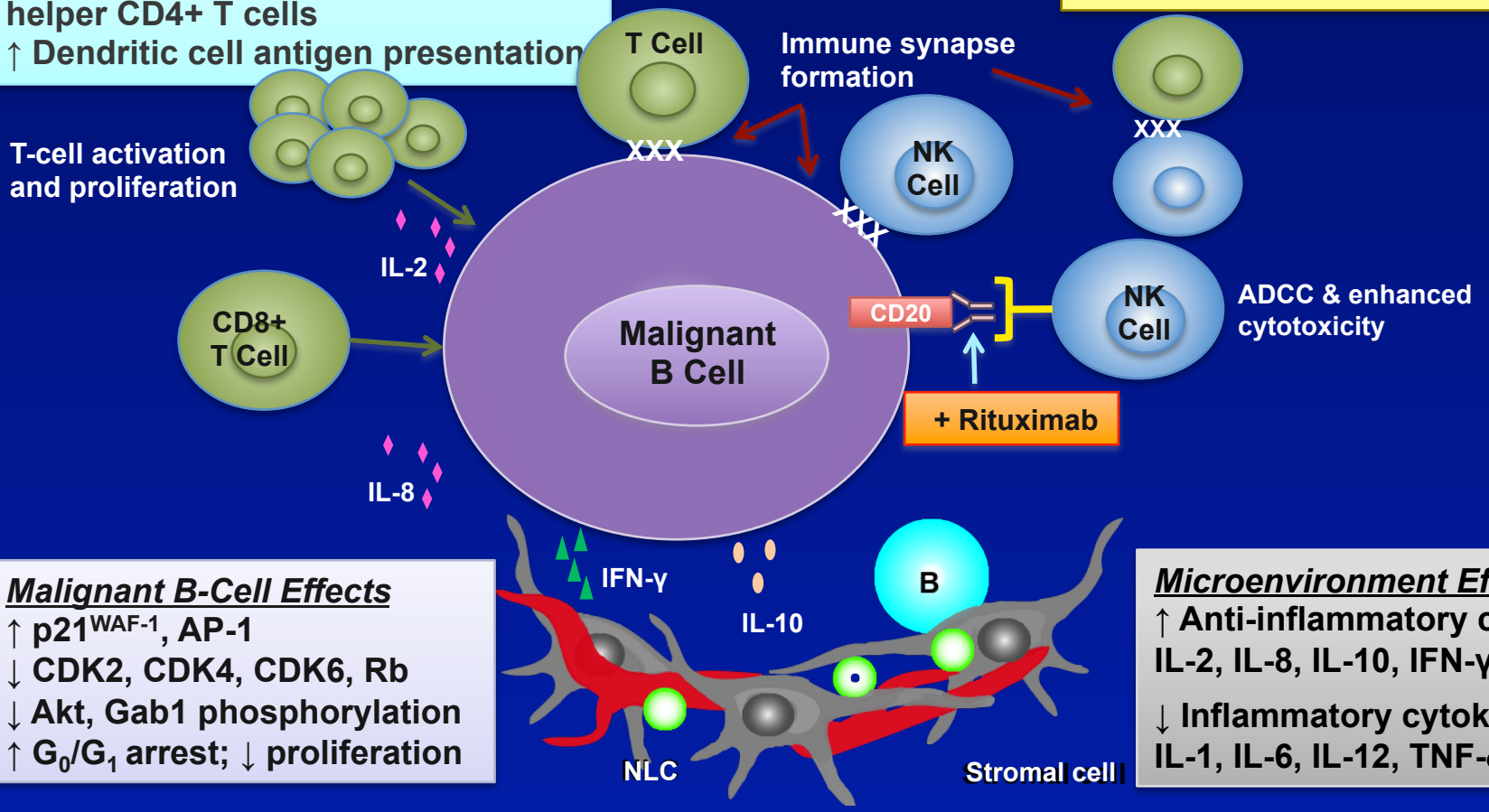
Lenalidomide


Salvage
(single tx or comb)
• MCL *
• DLBCL*
• FOL
• MZL
• CLL/SLL
Induction
Front line
(single tx or comb)
• MCL
• DLBCL
• FOL
• MZL
• CLL/SLL
Lenalidomide
in lymphoprolipherative disorders
Salvage
• MCL
• DLBC
• FOL
• MZL
• CLL/SLL
Maintenance
Front line
• MCL
• DLBCL
• FOL
• MZL
• CLL/SLL
*: autorizzazione all'uso mediante legge 648

Mechanisms of Action of Lenalidomide in Lymphoma Cells and the Nodal Microenvironment

T-Cell Effects
Activation and proliferation
↑ Immune synapse formation
↑ CD8+ T-effector cell activity
Stimulation of cytotoxic CD8+ and helper CD4+ T cells
↑ Dendritic cell antigen presentation

NK-Cell Effects
↑ Number and activity of NK cells
↑ Enhanced ADCC
↑ Immune synapse formation and direct NK killing



Malignant B-Cell Effects
↑ $p21^{WAF-1}$, AP-1
↓ CDK2, CDK4, CDK6, Rb
↓ Akt, Gab1 phosphorylation
↑ G_0/G_1 arrest; ↓ proliferation

Microenvironment Effects
↑ Anti-inflammatory cytokines: IL-2, IL-8, IL-10, IFN-γ, TNF-α
↓ Inflammatory cytokines: IL-1, IL-6, IL-12, TNF-α

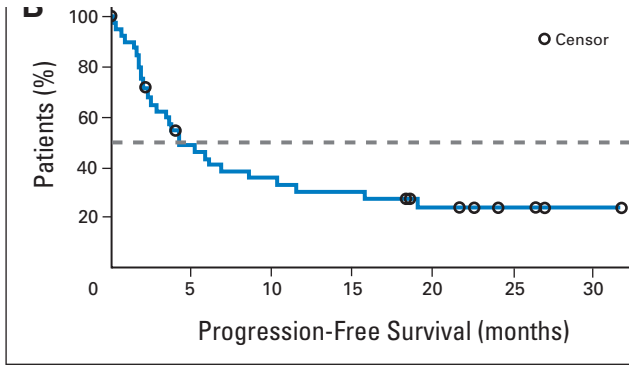
Gribben JG, et al. In press.

Lenalidomide Oral Monotherapy Produces Durable Responses in Relapsed or Refractory Indolent Non-Hodgkin's Lymphoma

Thomas E. Witzig, Peter H. Wiernik, Timothy Moore, Craig Reeder, Craig Cole, Glen Justice, Henry Kaplan, Michael Voralia, Dennis Pietronigro, Kenichi Takeshita, Annette Ervin-Haynes, Jerome B. Zeldis, and Julie M. Vose

Patients	43
Median age (years) Patients > 75 years	63 21%
FOL SLL MZL	51% 42% 7%
Refractory to last treatment Refractory to last chemotherapy Rituximab refractory	50% 42% 67%

ORR	**23%**
CR	**7%**
ORR • FOL • SLL	 27% 22%
Median PFS (mths)	**4.4**



JCO 2009

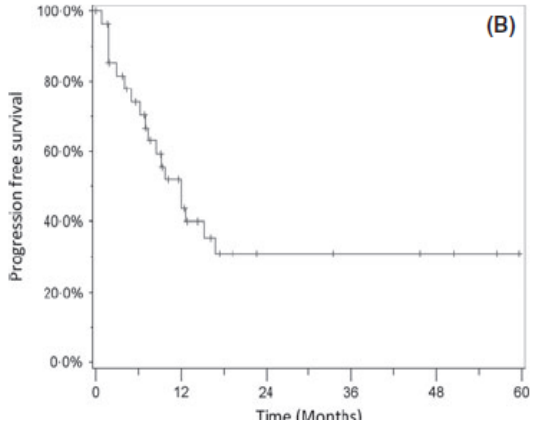
Lenalidomide plus rituximab can produce durable clinical responses in patients with relapsed or refractory, indolent non-Hodgkin lymphoma

Table I. Patient demographics and clinical characteristics.

Characteristics	*N*	%
Number of patients	30*	100·0
Gender		
Male	17	56·7
Female	13	43·3
Subtype		
Follicular lymphoma	22	73·3
Marginal zone lymphoma	3	10·0
SLL/CLL	3	10·0
Lymphoplasmacytic	1	3·3
Hodgkin lymphoma*	1	3·3
Median age (range), years	60·5	(45–91)
Stage III/IV NHL disease	30	100·0
Bone marrow involvement	7	24·1
Prior therapies, median (range), *n*	3	(1–11)
Prior rituximab	30	100·0
Refractory to rituximab	15	51·7

Table II. Response rates in patients with relapsed or refractory indolent NHL treated with lenalidomide plus rituximab.

		ORR		CR/CRu		PR		SD		PD	
	N	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%
Indolent NHL	27	20	74·1%	12	44·4%	8	29·6%	4	14·8%	3	11·1%
Age > 65 years	11	9	81·8%	5	45·5%	4	36·4%	2	18·2%	0	0·0%
Response according to histology											
Follicular lymphoma	22	17	77·3%	9	40·9%	8	36·4%	2	9·1%	3	13·6%
Marginal zone lymphoma	3	2	66·7%	2	66·7%	0	0·0%	1	33·3%	0	0·0%
SLL/CLL	2	1	50·0%	1	50·0%	0	0·0%	1	50·0%	0	0·0%
Response according to prior treatment											
Refractory to rituximab	13	8	61·5%	4	30·8%	4	30·8%	3	23·1%	2	15·4%
Heavily pretreated*	15	9	60·0%	6	40·0%	3	20·0%	3	20·0%	3	20·0%



Tuscano et al BJH 2014

Randomized Trial of Lenalidomide Alone Versus Lenalidomide Plus Rituximab in Patients With Recurrent Follicular Lymphoma: CALGB 50401 (Alliance)

- Lenalidomide 15 mg/d 21/28 days cycle 1, 20 mg/d 21/28 days cycle 2-12
- Rituximab 375 mg/m2 weekly x 4 +Lenalidomide 15 mg/d 21/28 days cycle 1, 20 mg/d 21/28 days cycle 2-12

	Lenalidomide	**Lenalidomide + RTX**
Patients	45	46
Median Age	63	64
FLIPI Low Intermediate High	33% 42% 25%	51% 29% 20%

Leonard et al JCO 2015

Table 4. Response Rate and Progression-Free Survival

Outcome	L Arm (n = 45)	LR Arm (n = 46)
Overall response		
No. of patients	24	35
%	53.3	76.1
95% CI*	37.9 to 68.3	61.2 to 87.4
Complete response		
No. of patients	9	18
%	20.0	39.1
95% CI	9.6 to 34.6	25.1 to 54.6
Partial response rate, %	33.3	37.0
Median TTP, years	1.1	2.0
2-Year TTP, %	27	52

Abbreviations: L, lenalidomide; LR, lenalidomide plus rituximab; TTP, time to progression.
*The 95% CIs are calculated using the Jennison-Turnbull method for the true overall response rate of each arm.

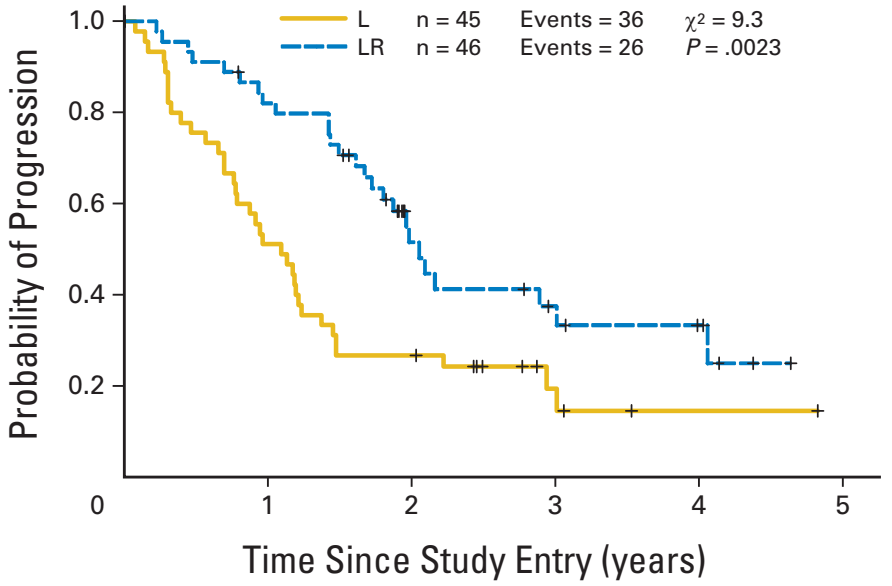


Fig 2. Kaplan-Meier curve for time to progression by treatment arm (arm B =

	Lenalidomide	**Lenalidomide + RTX**
Patients	Grade 3-4	Grade 3-4
Neutropenia	16%	20%
Infections with neutropenia	4%	2%
Thrombocytopenia	0	4%
Thrombosis	16%	5%

Leonard et al JCO 2015

Frontline Combination of Lenalidomide and Rituximab (R2) for FL: Clinical Response

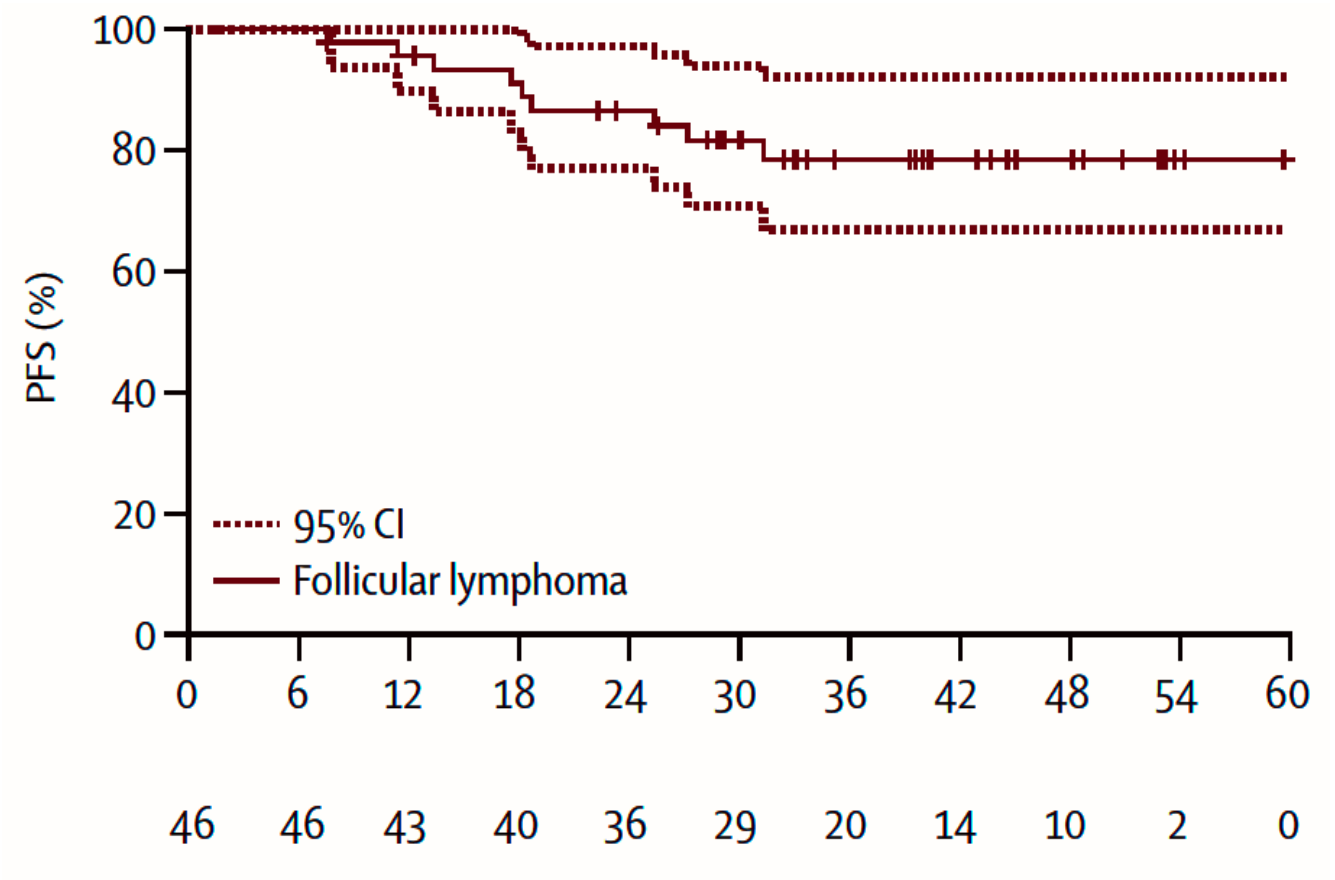
	SLL (N = 24)	Marginal (N = 24)*	Follicular (N = 45)*	All patients Eval (N = 93)	All patients ITT (N = 100)
ORR, n (%)	20 (83)	21 (88)	**44 (98)**	85 (91)	85 (85)
CR/Cru	6 (25)	16 (67)	**38 (85)**	60 (65)	60 (60)
PR	14 (59)	5 (21)	**6 (13)**	25 (27)	25 (25)
SD, n (%)	2 (8)	3 (13)	**1 (2)**	6 (6)	6 (6)
PD, n (%)	2 (8)	0	**0**	2 (2)	2 (2)

*7 patients inevaluable for response:

- 5 due to adverse event in cycle 1
- 1 due to non-compliance
- 1 due to withdrawal of consent

Fowler N, et al. Lancet Oncol 2014

Safety and activity of lenalidomide and rituximab in untreated indolent lymphoma: an open-label, phase 2 trial



Fowler NH et al, Lancet Oncol 2014; 15: 1311–18

Rituximab vs R2 in untreated Follicular Lymphoma Patients in Need of Therapy. First Analysis of Survival Endpoints of the Randomized Phase-2 Trial SAKK 35/10

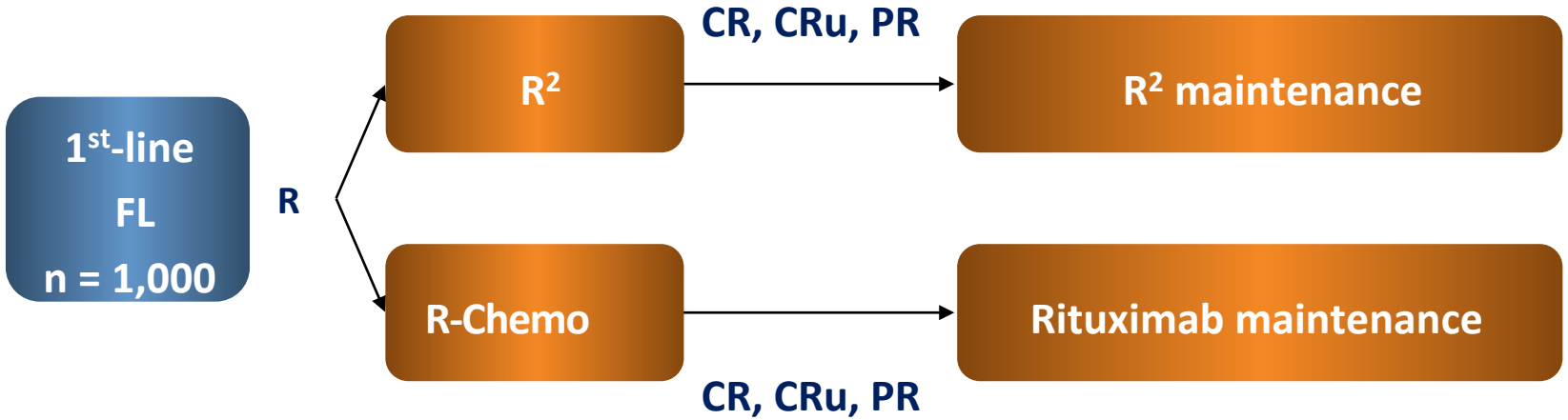
	Rituximab	R2	P
Patients	77	77	
Median age	63	61	
CR/Cru (%)	**36**	**61**	
Grade ≥3 Aes (%)	22	56	
Grade ≥3 neutropenia (%)	7	23	
Median PFS	**2.3 years**	**Not reached**	
CR30	**19%**	**42%**	**0.001**
TTNT	**2.1 years**	**Not reached**	**0.02**
3-year OS (%)	**92**	**93%**	

- Rituximab: 375mg/m^2 at week 1, 2, 3, 4, 12, 13, 14 and 15
- R2: rituximab (same schedule) plus lenalidomide (15 mg daily, from 14 days before the first until 14 days after the last rituximab administration).

Kimby et al ASH 2016

RELEVANCE: Phase 3 Study Design (Rituximab and LEnalidomide Versus ANy ChEmotherapy, FL-001)

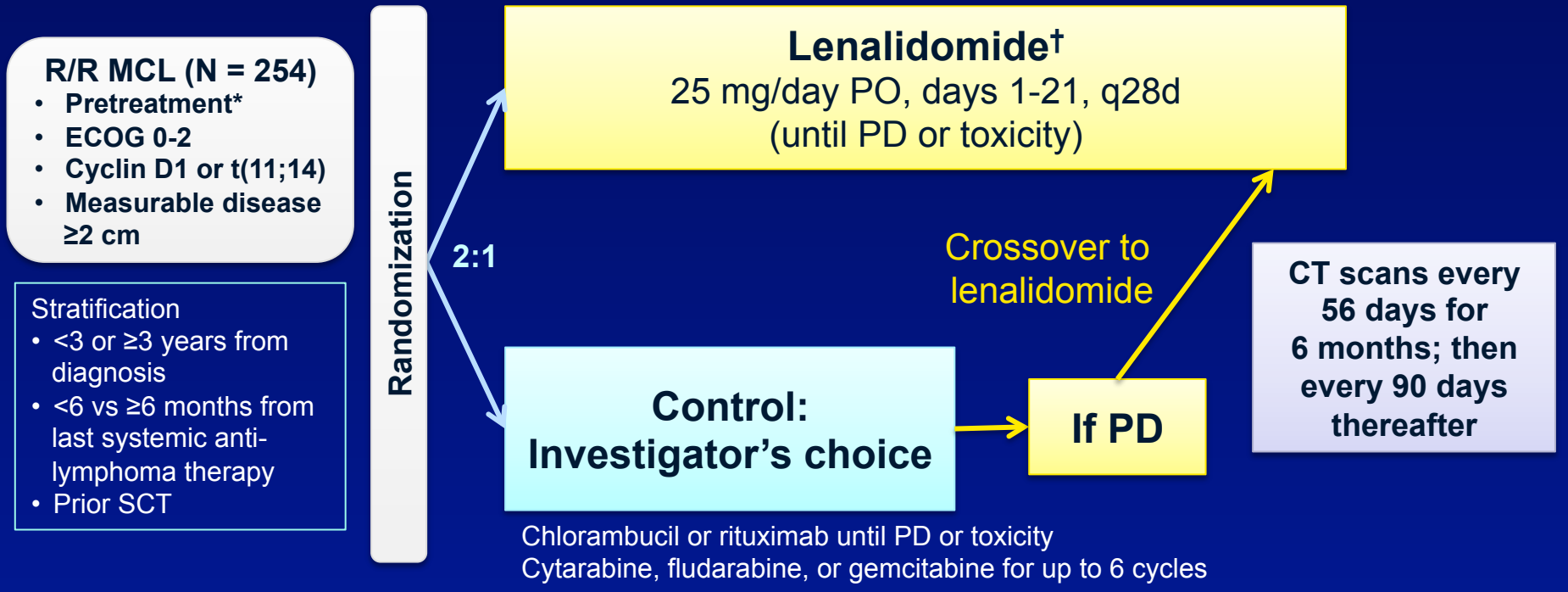
International, multi-centre, randomized study (Frank Morchhauser, Nathan Fowler)



- R-Chemo
  - investigator choice of R-CHOP, R-CVP, R-B
- Lenalidomide 20 mg x 6 cycles, if CR then 10 mg
- Co-primary end-points
  - surrogate end-point: CR/CRu rate at 1.5 years
  - PFS

NCT01476787. Available from: http://clinicaltrials.gov. Accessed March 2012.

MCL-002 (SPRINT): Phase II European Multicenter, Open-Label Study (5/2009-3/2013)



Primary endpoint: PFS (per independent central review)
Secondary endpoints: ORR, DOR, TTR, OS, and safety

Courtesy of Marek Trněný, Lancet Oncology 2016

MCL-002: Efficacy (ITT)*

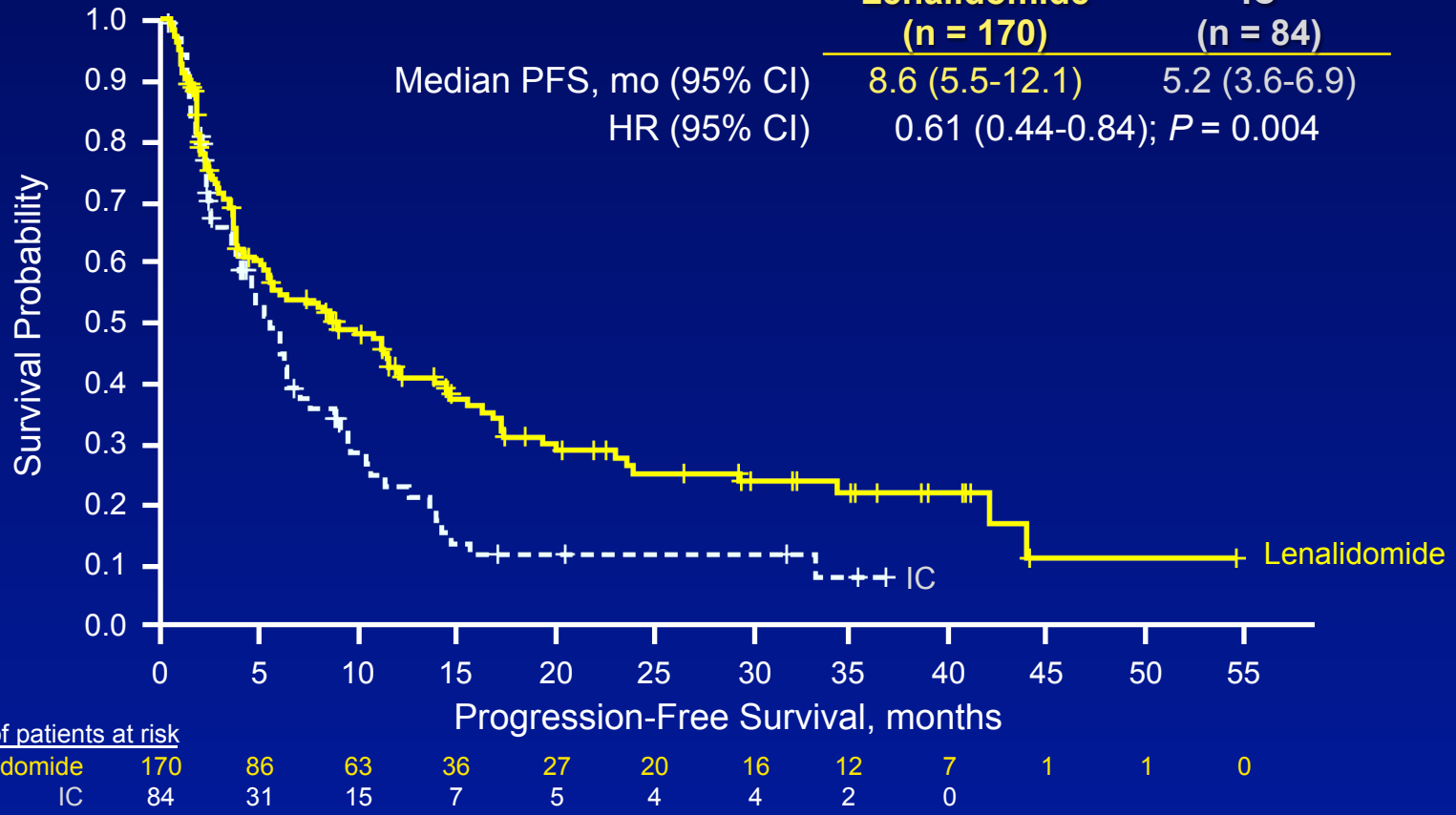
Efficacy, n (%)†	Lenalidomide (n = 170)	IC (n = 84)	*P* value
ORR	68 (**40**)	9 (**11**)	<0.001
CR/CRu	8 (**5**)	**0**	0.043
PR	60 (**35**)	9 (**11**)	–
PD	34 (**20**)	26 (**31**)	–
Median DOR, months (95% CI)	16.0 (9.5-20.0)	10.4 (8.4-18.6)	0.42

- For 39 patients who crossed over from IC to lenalidomide, best responses included 2 (5%) CR, 4 (10%) PR, 3 (8%) SD†

Courtesy of Marek Trněný, Lancet Oncology 2016

MCL-002: Progression-Free Survival (ITT)*

	Lenalidomide (n = 170)	IC (n = 84)
Median PFS, mo (95% CI)	8.6 (5.5-12.1)	5.2 (3.6-6.9)
HR (95% CI)	0.61 (0.44-0.84); *P* = 0.004	



Number of patients at risk

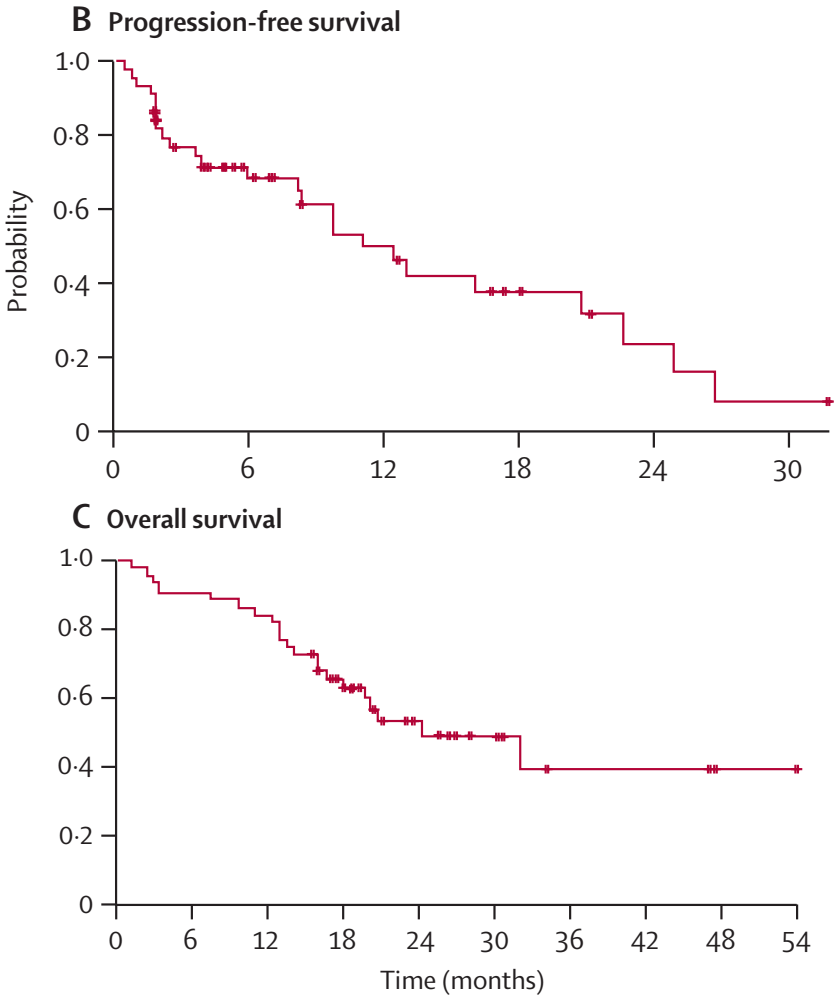
Lenalidomide	170	86	63	36	27	20	16	12	7	1	1	0
IC	84	31	15	7	5	4	4	2	0			

- Lenalidomide vs IC showed a 39% reduction in the risk of PD or death, reflected as an estimated improvement in median PFS of 3.4 months

*Data cut-off March 7, 2014.

Lenalidomide in combination with rituximab for patients with relapsed or refractory mantle-cell lymphoma: a phase 1/2 clinical trial

Response	%
ORR	**57**
CR	**36**
PR	20
SD	23
PD	20
Median RD (months)	18.9
Median PFS (months)	11.1



Wang et al. Lancet Oncol 2012

Lenalidomide salvage therapy in MCL

	Lenalidomide (Treny et al. Lancet Oncology 2016)	**Len Dex** (Zaja et al. Haematol 2012)	**Len RTX** (Wang et al. Lancet Oncol 2012)	**R2B** (Zaja et al. ICML 2015)
ORR	40%	52%	57%	79%
CR	5%	24%	36%	55%
Median PFS (months)	8.6	12	11	24

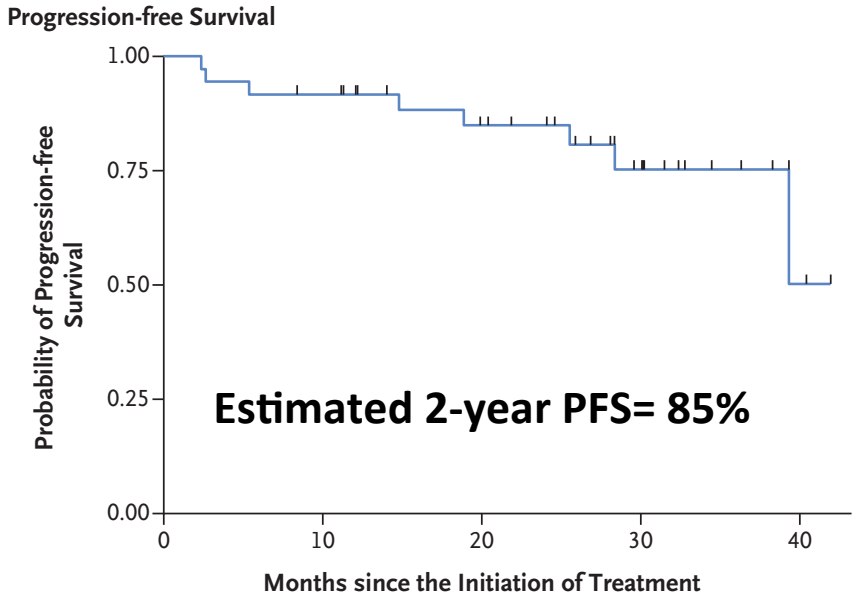
Lenalidomide plus Rituximab as Initial Treatment for Mantle-Cell Lymphoma

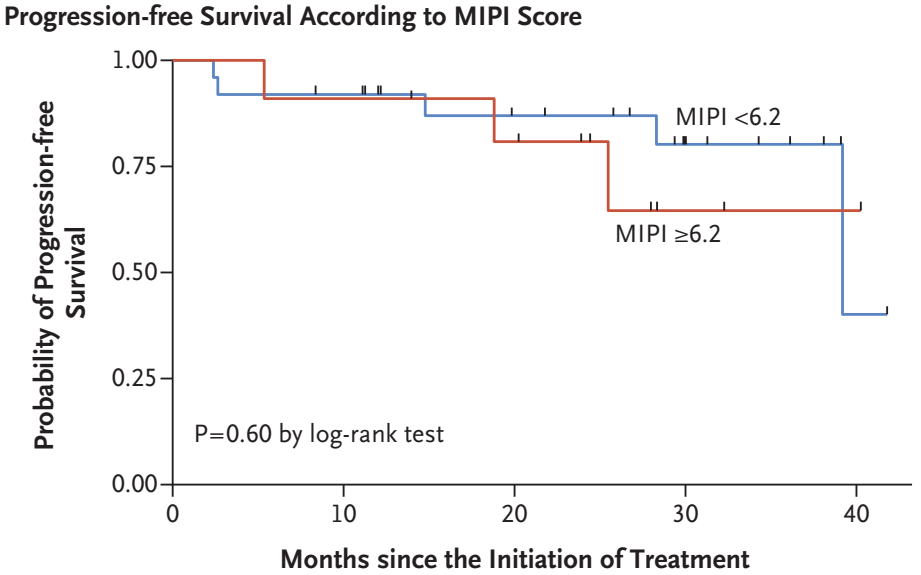
Jia Ruan, M.D., Ph.D., Peter Martin, M.D., Bijal Shah, M.D., Stephen J. Schuster, M.D., Sonali M. Smith, M.D., Richard R. Furman, M.D., Paul Christos, Dr.P.H., Amelyn Rodriguez, R.N., Jakub Svoboda, M.D., Jessica Lewis, P.A., Orel Katz, P.A., Morton Coleman, M.D., and John P. Leonard, M.D.

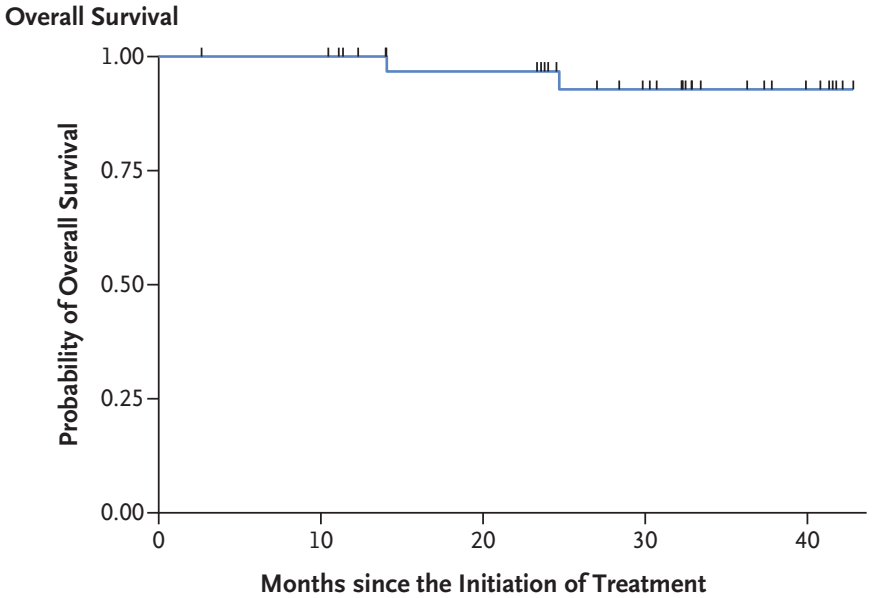
Patients	38
Males/Females	71/29 %
Median age (range)	**65 (42-86)**
ECOG 0-1	37 (97%)
Ann Arbor stage III-IV	38 (100%)
Elevated LDH	15 (39%)
MIPI LOW/INT/HIGH	**34/34/32 %**
Ki-67 > 30%	8 (21%)

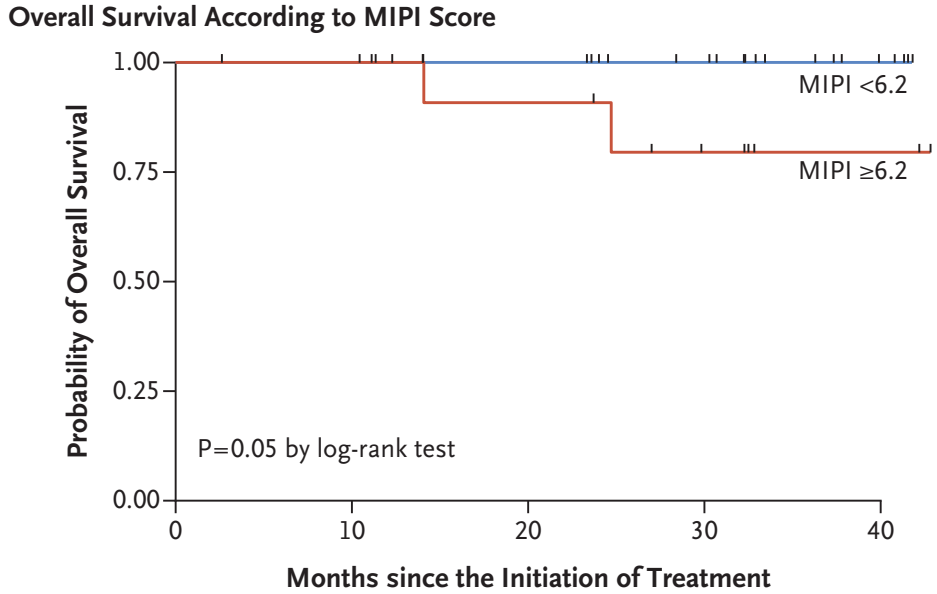
Response	**%**
ORR	**87**
CR	**61**
PR	26
SD	3
PD	5
Not evaluable	5

NEJM 2015





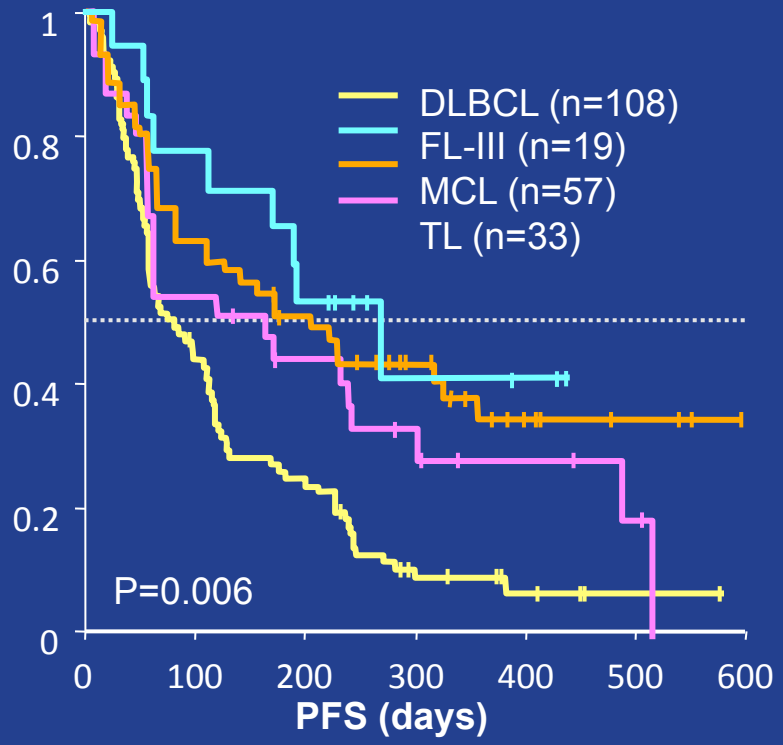




Ruan et al. NEJM 2015

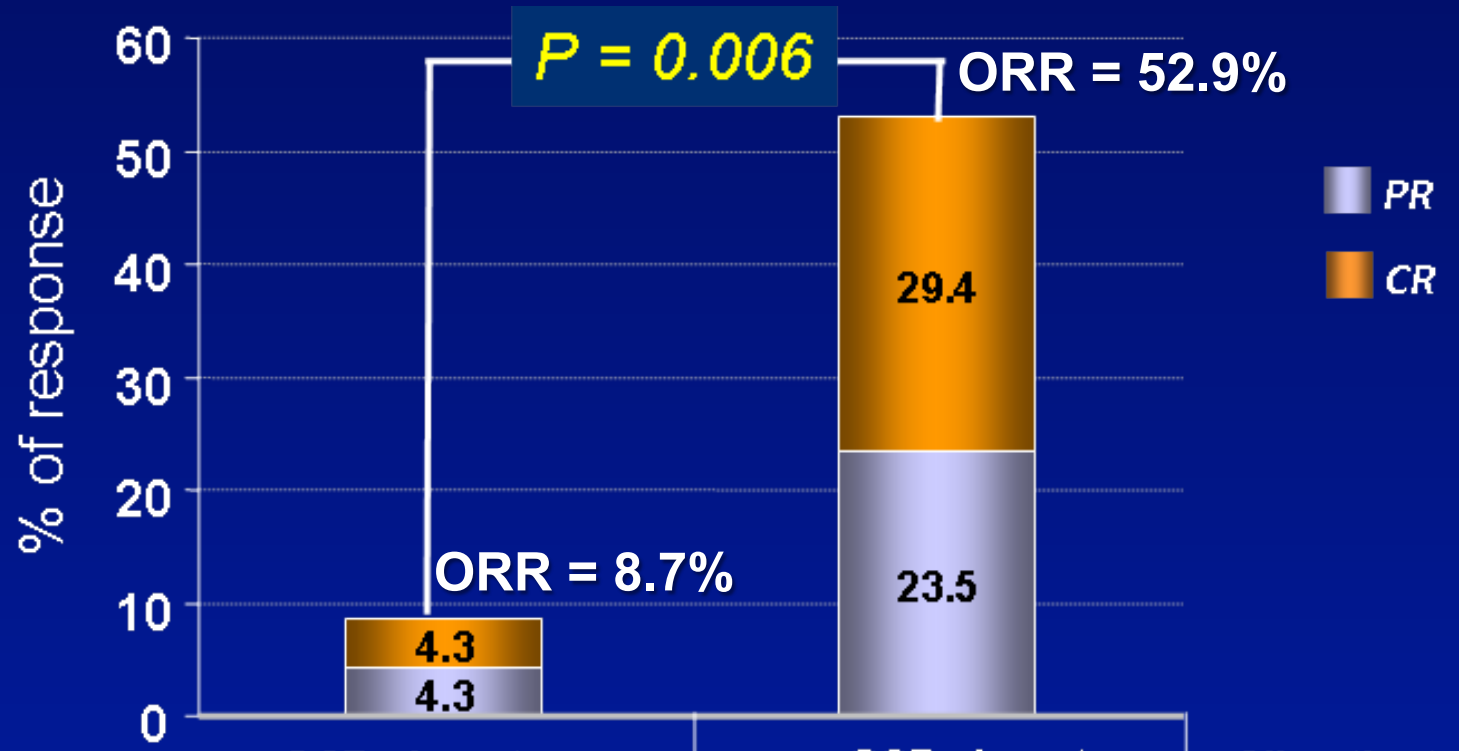
Lenalidomide in DLBCL

Author	N.	ORR	CR/Cru	Median PFS (months)	Median DOR (months)
Wiernik 2008	26	19%	15%	2-3	
Witzig 2011	108	28%	7%	2.7	4.6
REVEAL 2013	77	43%	18%	3.5	



Witzig et al 2011

Responses and PFS in Lenalidomide-treated Rel/Ref GCB vs. Non-GCB DLBCL Patients (N = 40)



	GCB phenotype (N=23)	non-GCB phenotype (N=17)	All patients (N = 40)
Median PFS, months (95% CI)	1.7 (0.25–3.14)	6.23 (2.87–9.6)	2.56 (0.92–4.21)

CI, confidence interval.

Hernandez-Ilizaliturri FJ, et al. J Clin Oncol. 28:7s, 2010:[abstract 8038]

A Phase II LYSA Study of Obinutuzumab + Lenalidomide (GALEN) for R/R Aggressive B-Cell Lymphoma Aggressive Lymphoma (DLBCL and Other)

- **LEN 20** on days 1-21 of a 28-day cycle cycles 1 to 6
- **GA 101** 1000mg on days 8, 15, and 22 of cycle 1 and at D1 of cycles 2 to 6

Responding pts then received GALEN consolidation/maintenance

DLBCL =77; MCL=13, other =1

median age was 70 (range, 48–84)

median number of prior systemic therapies was 2 (range, 1–9) 11

		DLBCL (n=71)	MCL (n=13)	All (n=85)
IWG 1999	ORR*, % (95%CI)	35.2 (24.2-47.5)	46.2 (13.9-68.4)	36.5 (26.3-47.6)
	CR/CRu*, % (95%CI)	16.9 (9.0-27.6)	15.4 (1.9-45.4)	16.5 (9.3-26.1)
	Best ORR**, % (95%CI)	43.7 (31.9-55.9)	46.2 (19.2-74.8)	43.5 (32.8-54.7)
IWG 2007	ORR*, % (95%CI)	29.6 (19.3-41.6)	38.5 (13.9-68.4)	30.6 (21.0-41.5)
	CR*, % (95%CI)	15.5 (8.0-26.0)	23.1 (5.0-53.8)	16.5 (9.3-26.1)
	Best ORR**, % (95%CI)	45.1 (33.2-57.3)	53.8 (25.1-80.8)	45.9 (35.0-57.4)
Median OS, months (95% CI)		10.6 (6.5-NR)	16.2 (12.4-NR)	13.0 (7.0-NR)

*Response at the end of induction

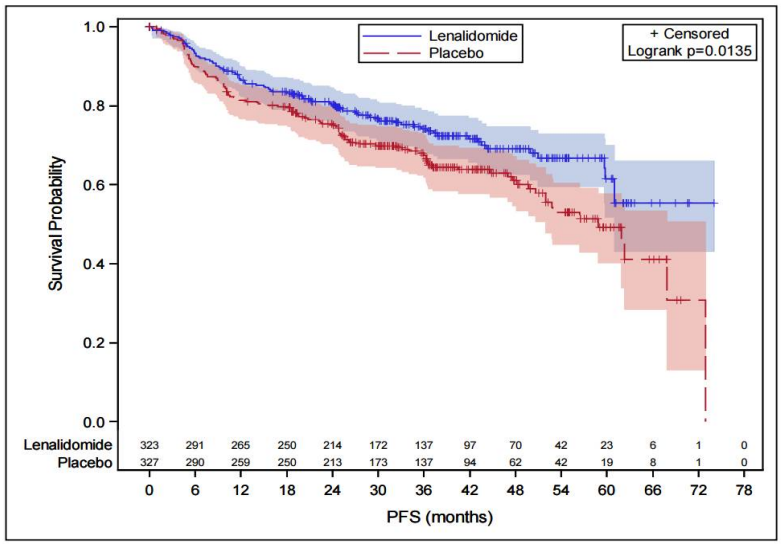
** Best response during induction phase

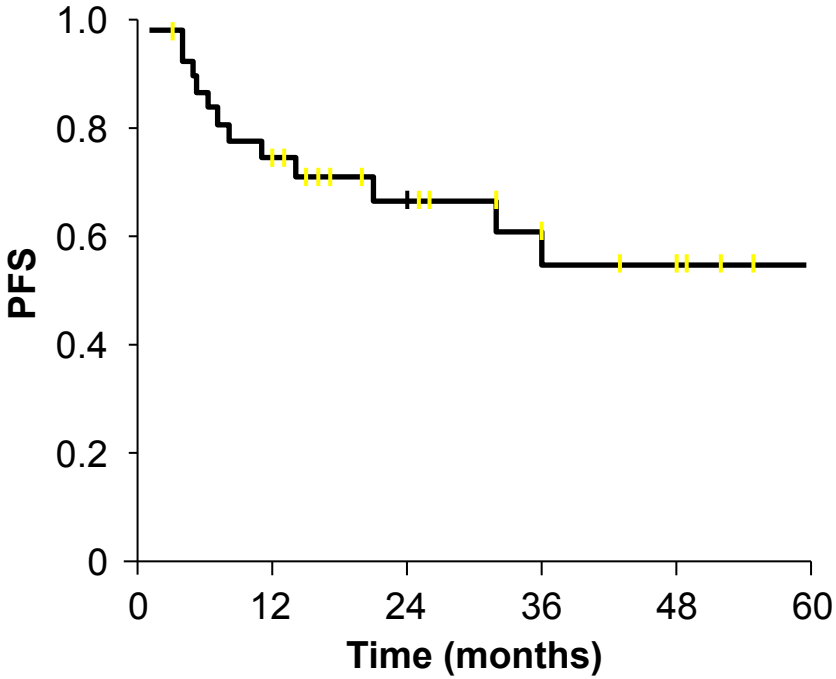
CI, confidence interval; NR, not reached

Morschhauser et al ASH 2016

First Analysis of an International Double-Blind Randomized Phase III Study of Lenalidomide Maintenance in Elderly Patients with DLBCL Treated with R-CHOP in First Line, the Remarc Study from Lysa

Lenalidomide Maintenance Significantly Improves Survival in R/R DLBCL Not Eligible for ASCT





Thieblemont et al ASH 2016; Ferreri et al ASH 2016

R2 1L nei DLBCL fragili

FIL

PI: dr. Gini

Lenalidomide ± Rituximab in NHL

	FL/Indolent		MCL		DLBCL	
	R/R	**1L**	**R/R**	**1L**	**R/R**	**1L**
Lenalidomide	**ORR:** 20% **CR**: <10% **mPFS:** 4		**ORR:** 40% **CR:** 5% **mPFS**: 9		**ORR:** 30% **CR:** 10% **mPFS:** 3	
Rituximab + Lenalidomide (R2)	**ORR:** 75% **CR:** 40% **mPFS:** 24	**ORR:** 90% **CR:** 60% **mPFS:** NR	**ORR**: 57% **CR:** 36% **mPFS:** 11	**ORR:** 87% **CR:** 61 % **mPFS:** NR	**ORR:** 30% **CR:** 15% mPFS:	

Ibrutinib

VOLUME 31 · NUMBER 1 · JANUARY 1 2013

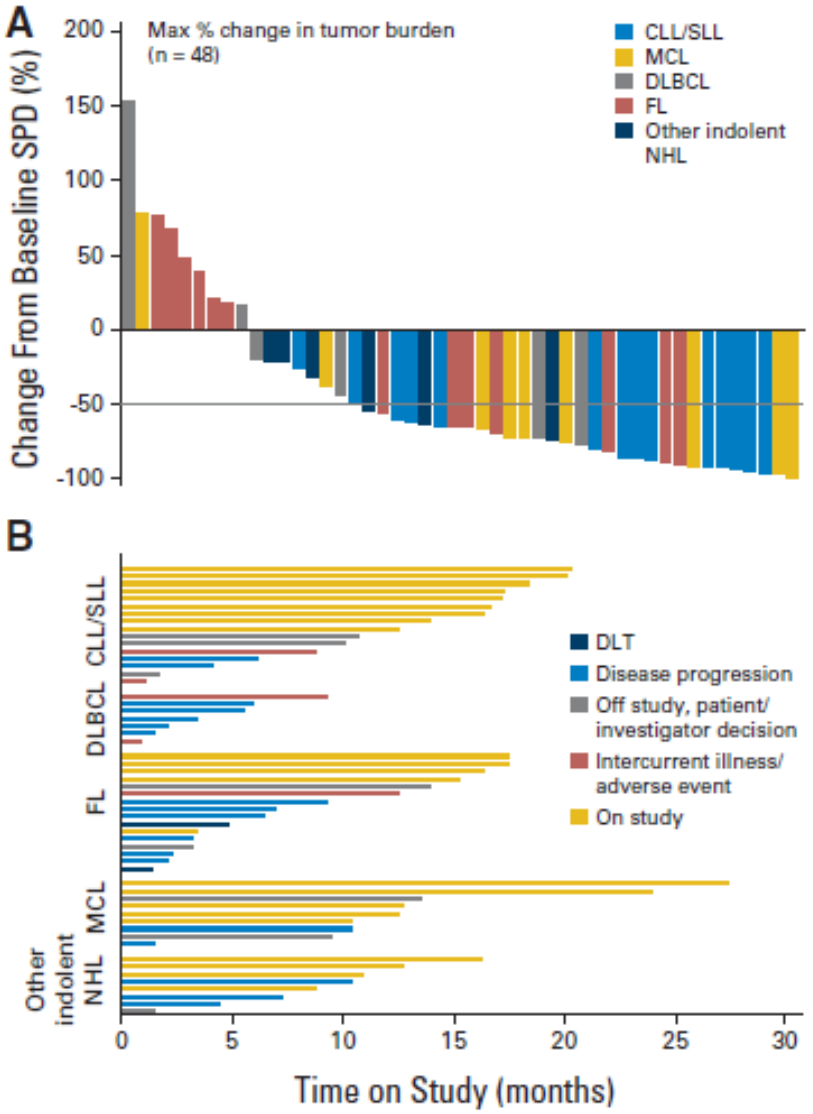
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Bruton Tyrosine Kinase Inhibitor Ibrutinib (PCI-32765) Has Significant Activity in Patients With Relapsed/Refractory B-Cell Malignancies

Ranjana H. Advani, Joseph J. Buggy, Jeff P. Sharman, Sonali M. Smith, Thomas E. Boyd, Barbara Grant, Kathryn S. Kolibaba, Richard R. Furman, Sara Rodriguez, Betty Y. Chang, Juthamas Sukbuntherng, Raquel Izumi, Ahmed Hamdy, Eric Hedrick, and Nathan H. Fowler

ORR in 50 pts= 60%
CR = 16%
Median PFS = 14 mths

	CR+PR rate
CLL/SLL	79%
MCL	77%
DLBCL	28%
FL	38%
Other indolent NHL	



Advani RH et al. J Clin Oncol 2013

The NEW ENGLAND JOURNAL of MEDICINE

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Targeting BTK with Ibrutinib in Relapsed or Refractory Mantle-Cell Lymphoma

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ABSTRACT

BACKGROUND

Bruton's tyrosine kinase (BTK) is a mediator of the B-cell–receptor signaling pathway implicated in the pathogenesis of B-cell cancers. In a phase 1 study, ibrutinib, a BTK inhibitor, showed antitumor activity in several types of non-Hodgkin's lymphoma, including mantle-cell lymphoma.

METHODS

In this phase 2 study, we investigated oral ibrutinib, at a daily dose of 560 mg, in 111 patients with relapsed or refractory mantle-cell lymphoma. Patients were enrolled into two groups: those who had previously received at least 2 cycles of bortezomib therapy and those who had received less than 2 complete cycles of bortezomib or had received no prior bortezomib therapy. The primary end point was the overall response rate. Secondary end points were duration of response, progression-free survival, overall survival, and safety.

RESULTS

The median age was 68 years, and 86% of patients had intermediate-risk or high-risk mantle-cell lymphoma according to clinical prognostic factors. Patients had received a median of three prior therapies. The most common treatment-related adverse events were mild or moderate diarrhea, fatigue, and nausea. Grade 3 or higher hematologic events were infrequent and included neutropenia (in 16% of patients), thrombocytopenia (in 11%), and anemia (in 10%). A response rate of 68% (75 patients) was observed, with a complete response rate of 21% and a partial response rate of 47%; prior treatment with bortezomib had no effect on the response rate. With an estimated median follow-up of 15.3 months, the estimated median response duration was 17.5 months (95% confidence interval [CI], 15.8 to not reached), the estimated median progression-free survival was 13.9 months (95% CI, 7.0 to not reached), and the median overall survival was not reached. The estimated rate of overall survival was 58% at 18 months.

CONCLUSIONS

Ibrutinib shows durable single-agent efficacy in relapsed or refractory mantle-cell lymphoma. (Funded by Pharmacyclics and others; ClinicalTrials.gov number, NCT01236391.)

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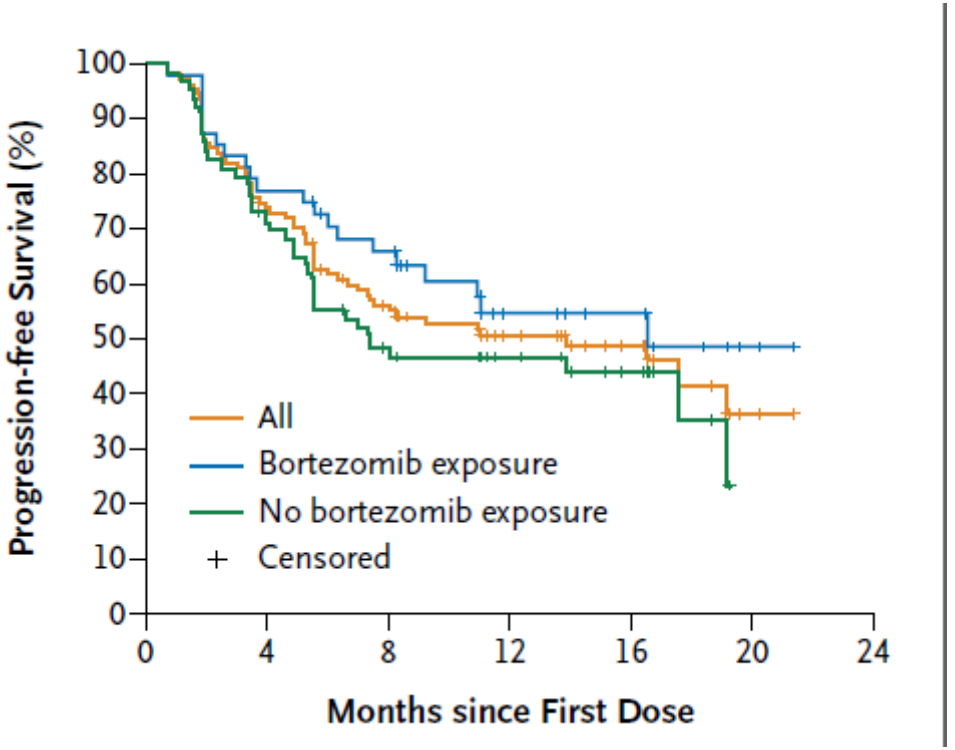
- **ORR: 67%**
- **CR: 22.5%**
- Median time to response: 1.9 months
- Median time to CR:5.5 months
- Median duration of response: 17.5 months
- Estimated median follow-up: 26.7 months
- **Median PFS: 13 months**
- Median OS: 22.5 months
- **24-month Kaplan-Meier PFS: 31%**
- 24-month Kaplan-Meier OS: 47%



Wang et al. ASH 2014

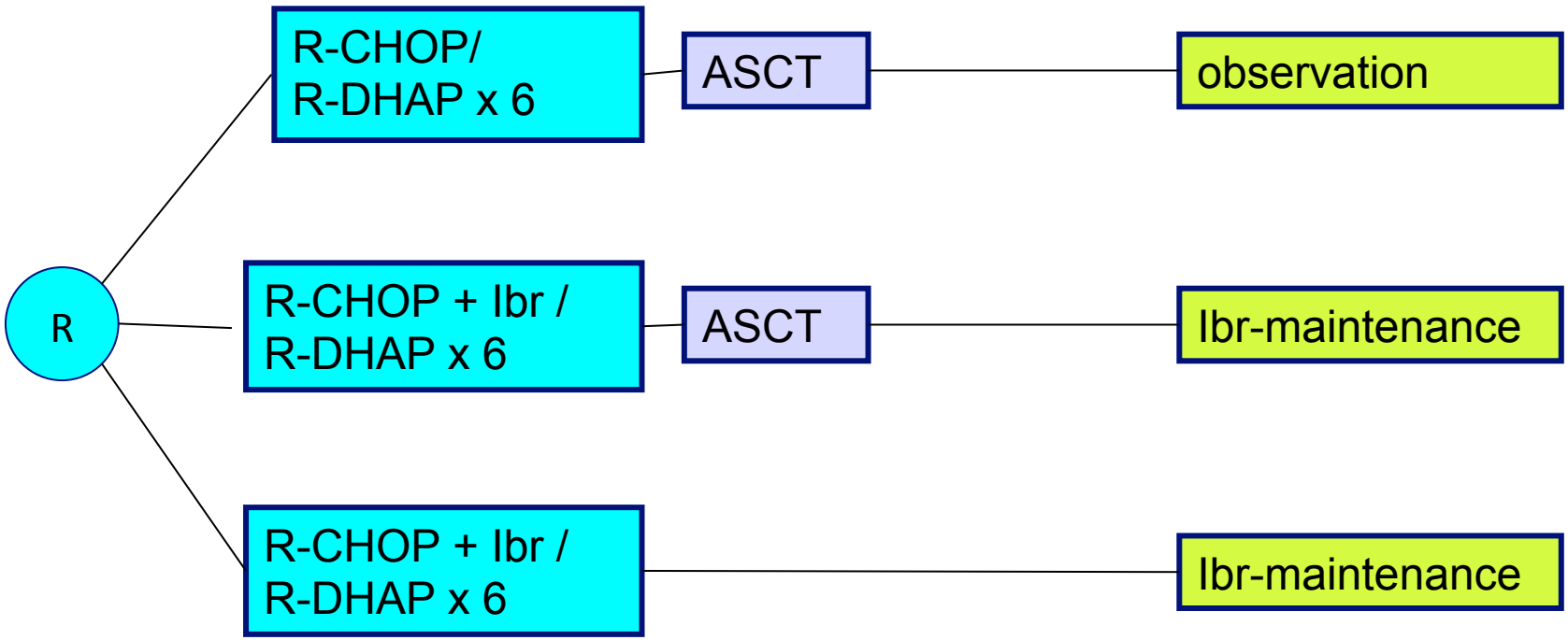
Ibrutinib + Rituximab in relapsed MCL

	ALL	Ki-67 < 50%	Ki-67 ≥ 50%	Ibrutinib NEJM 2014
Patients	45	33	12	111
ORR	87%	100%	50%	67%
CR	38%	48%	8%	22.5%
DR	NR	NR	NR	17 months
PFS	NR	NR	NR	13 months

Wang et al. ASH 2014

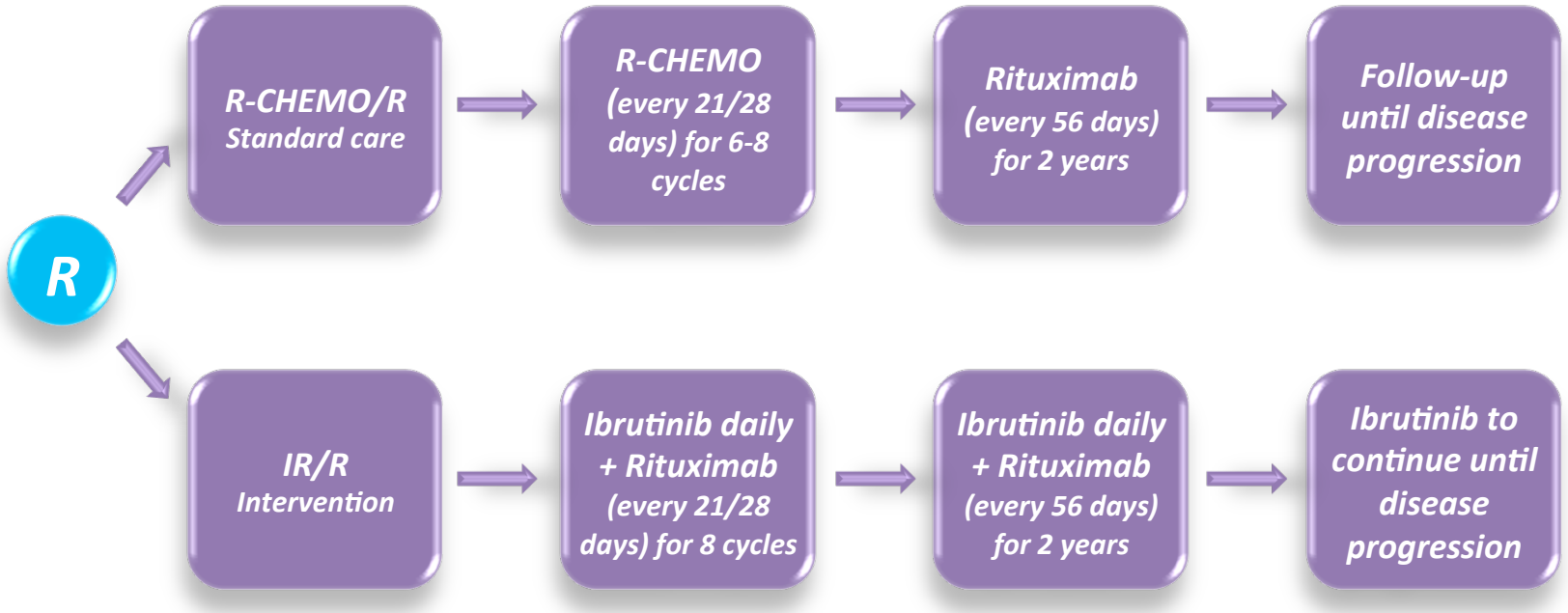
TRIANGLE Phase III Trial

MCL, 18 to 65 years old



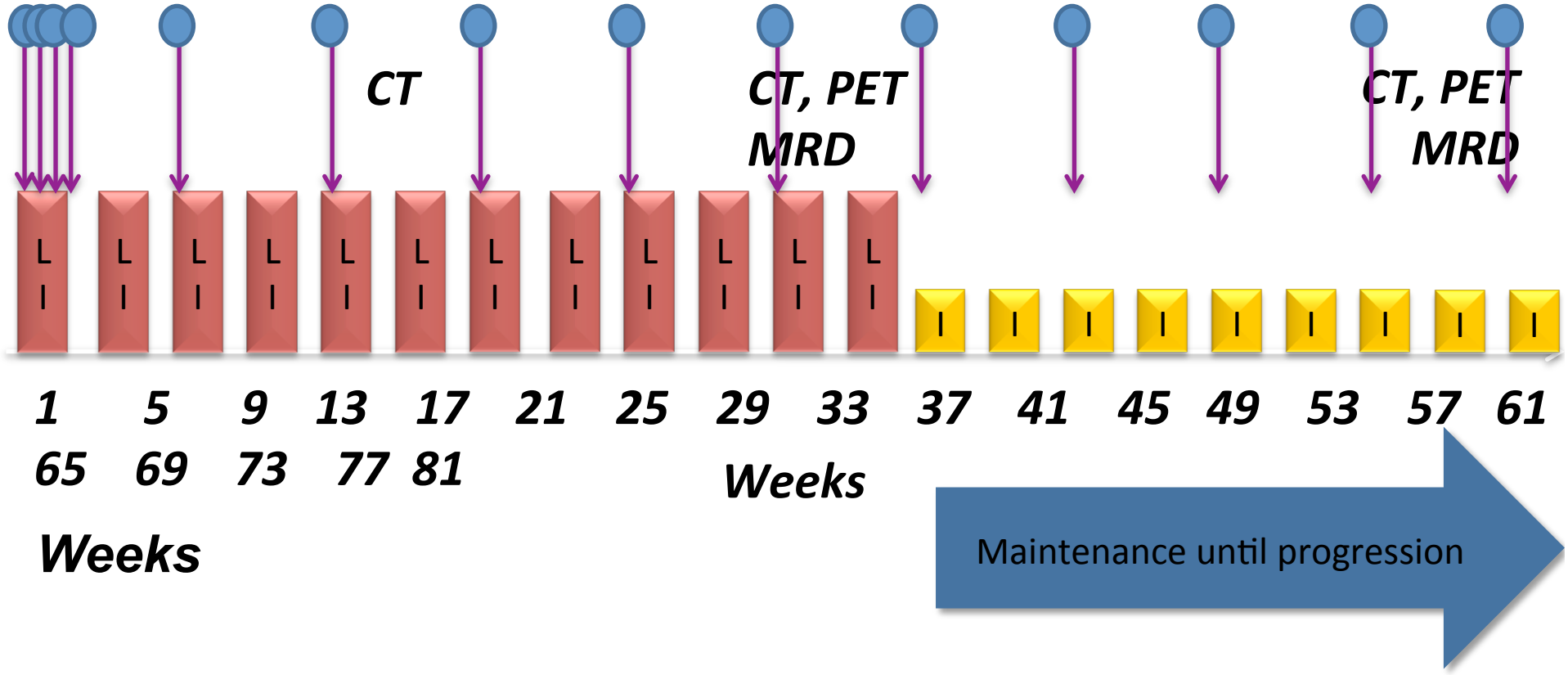
on behalf of European MCL Network

ENRICH – NCRI multicentre Randomised open label phase II/III trial of Rituximab & Ibrutinib vs Rituximab & CHemotherapy in Elderly mantle cell lymphoma

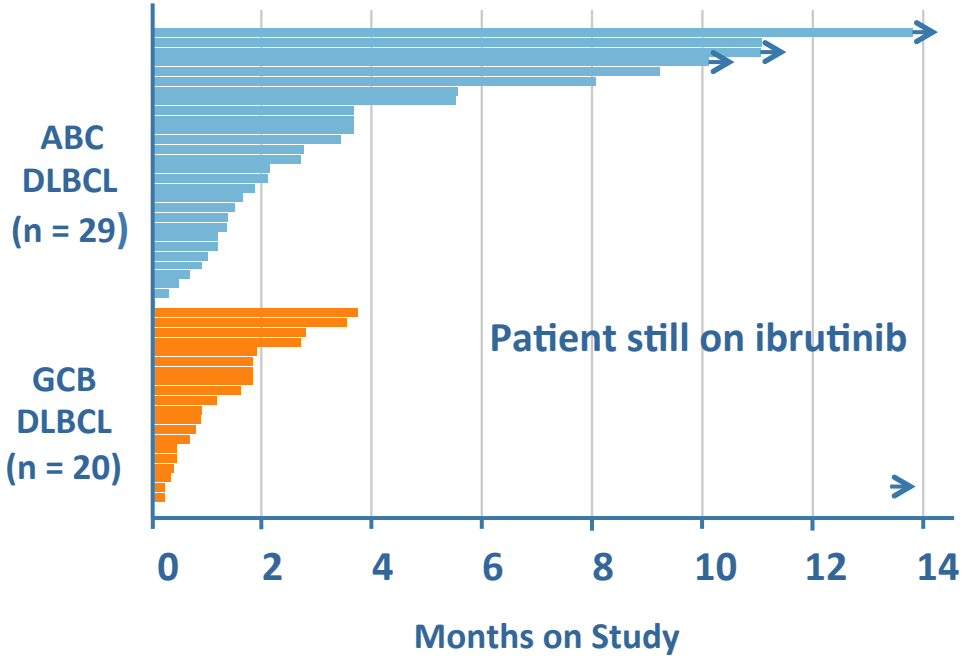


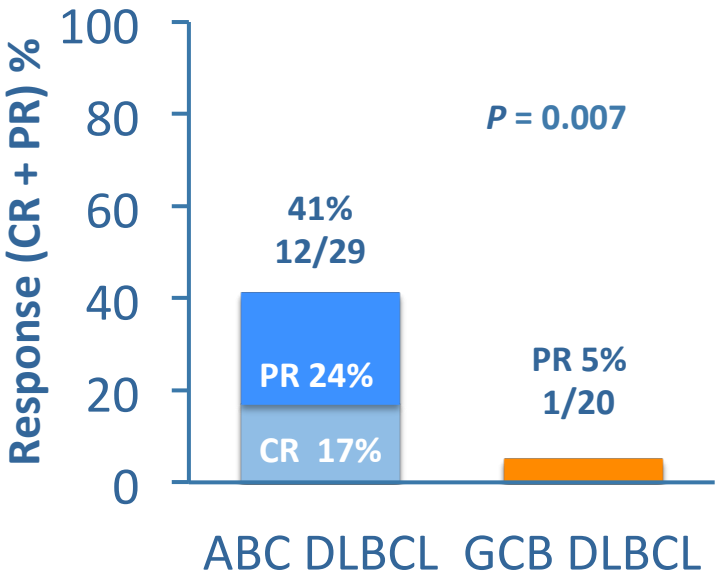
R/R MCL: NLG-MCL6 (PHILEMON)

Phase I-II, 60 patients



Ibrutinib Has Preferential Activity in the Activated B Cell-like (ABC) Subtype of Relapsed/Refractory (R/R) DLBCL: Phase 2





- Ibrutinib activity will be restricted to ABC DLBCL
- Ibrutinib activity will be dependent on pathogenetic events within the BCR pathway

Wilson et al, ASH 2012

Phase 1b/2 Study of Ibrutinib in Combination With Lenalidomide and Rituximab in Patients with R/R DLBCL

Goy et al ASH 2016

Single-Agent Ibrutinib in R/R CNS DLBCL

Drug concentrations in CSF are higher at steady state (day 29) and meaningful CSF concentrations are reached.

Clinical response was seen in 75% of CNS lymphoma patients.

A combination arm will assess the adverse events of ibrutinib in combination with high-dose methotrexate chemotherapy.

Grommes et al ASH 2016

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ibrutinib in Previously Treated Waldenström's Macroglobulinemia

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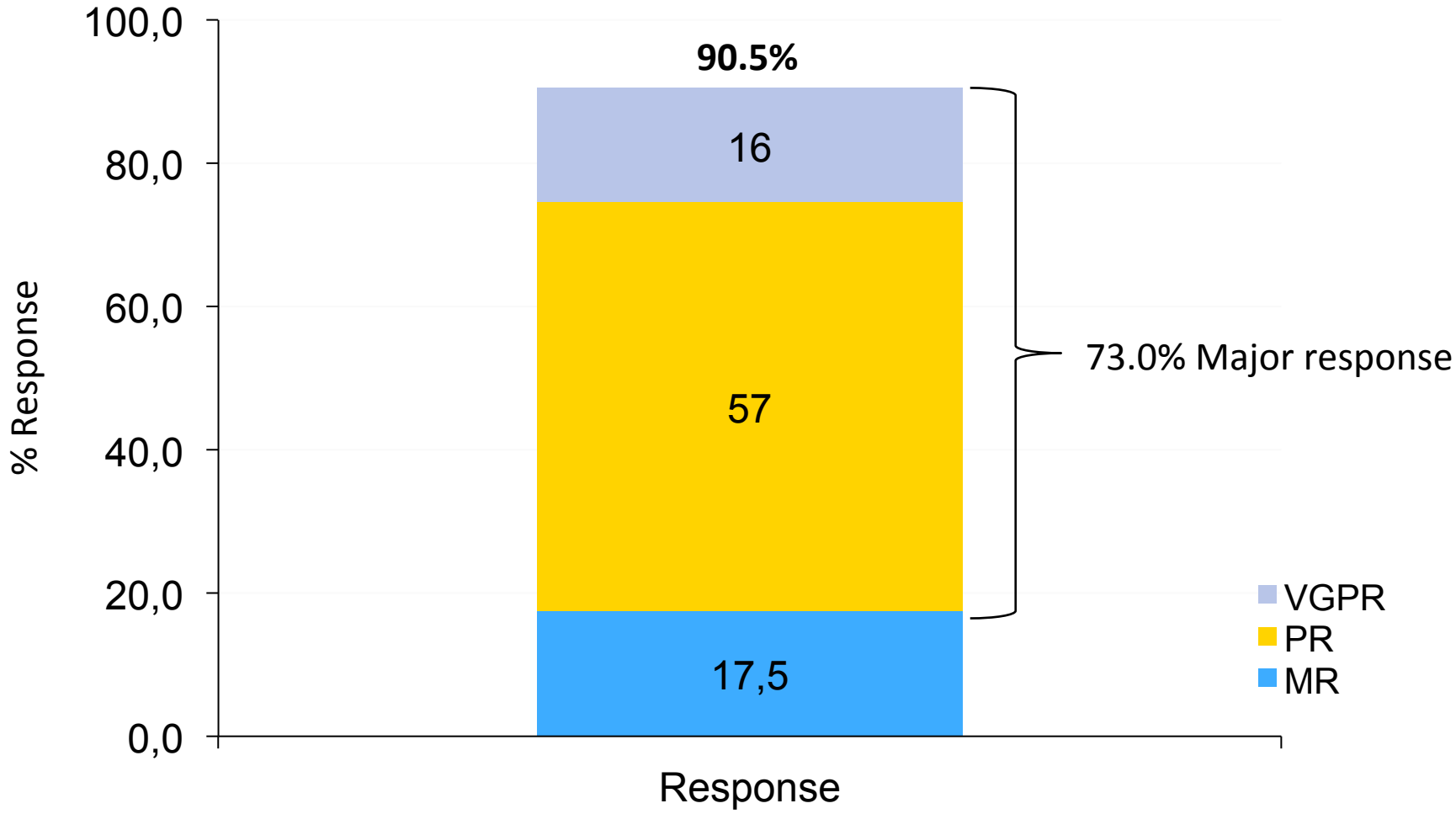
Results: response

Median times to at least MR and PR were 4 weeks and 8 weeks, respectively



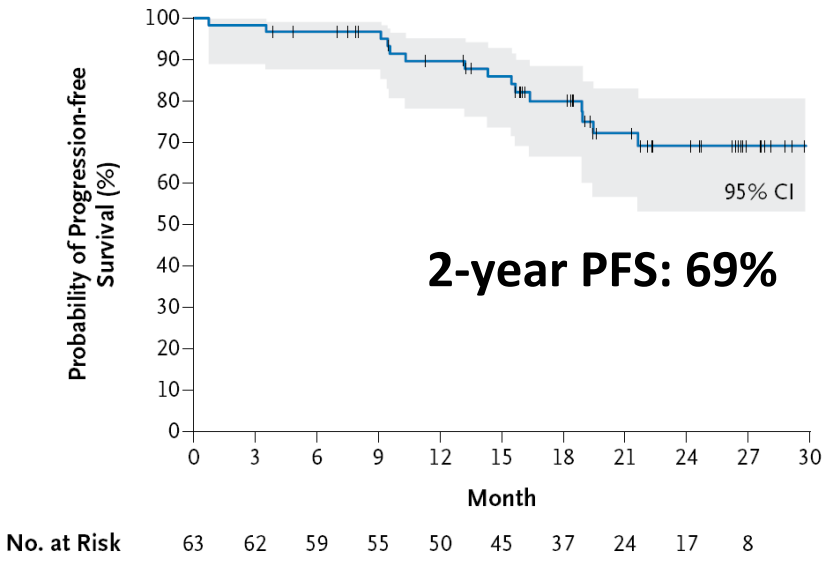
Treon SP et al. N Engl J Med 2015;372:1430-1440

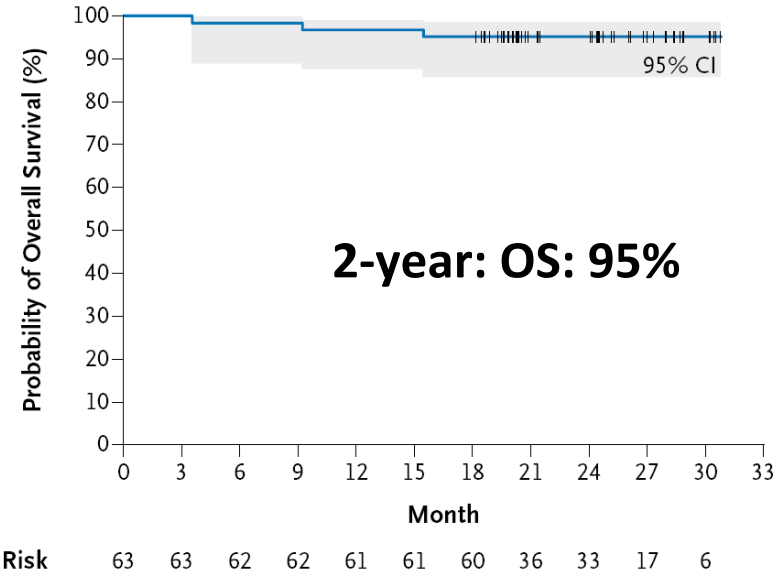
Responses to Ibrutinib according to MYD88 and CXCR4 mutation status

	$MYD88^{L265P}$ $CXCR4^{WT}$	$MYD88^{L265P}$ $CXCR4^{WHIM}$	$MYD88^{WT}$ $CXCR4^{WT}$	P value
Patients	36	21	5	
ORR	100%	86%	60%	<0.05
Major RR	92%	62%	0%	<0.001

Treon SP et al. N Engl J Med 2015;372:1430-1440

Progression-Free Survival and Overall Survival





Treatment-related toxic effects of grade 2 or higher included:

- neutropenia (22% of the patients)
- thrombocytopenia (14%)
- bleeding (in 6%)
- atrial fibrillation (5%)

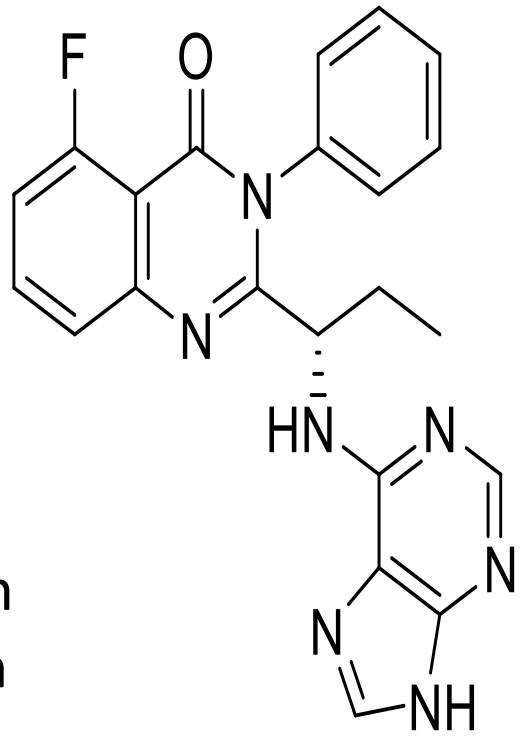
Treon SP et al. N Engl J Med 2015;372:1430-1440

Idelalisib

Idelalisib is a first-in-class, oral, selective PI3Kδ inhibitor

Idelalisib provides a direct and indirect action on malignant B cells to:

- Reduce proliferation
- Induce apoptosis
- Inhibit homing and retention of B cells in the protective microenvironments (lymph nodes and bone marrow)[1–3]



1. Idelalisib SmPC (Aug 2015; available at www.ema.europa.eu).
2. Lannutti BJ, *et al. Blood* 2011; 117:591–594
3. Hoellenriegel J, *et al. Blood* 2011; 118:3603–3612.
Figure adapted from Somoza JR, *et al. J Biol Chem* 2015; 290:8439–8446.

Linfomi follicolari:
Indicazioni terapeutiche di Idelalisib

Idelalisib è indicato in monoterapia per il trattamento di linfoma follicolare refrattario a due precedenti linee di trattamento comprensive di rituximab e alchilanti

Dosaggio raccomandato di Idelalisib: 150 mg 2 volte al giorno

Eligible patients were double-refractory FL to both rituximab and an alkylating agent

Key eligibility criteria	
Refractory iNHL (FL, SLL, MZL, LPL ± WM)	• **Defined as less than PR on therapy, or progression within 6 months of completion of therapy** • **Refractory to BOTH rituximab and an alkylating agent**
Radiographically measurable disease	• Presence of ≥1 lymph nodes with perpendicular dimensions measuring ≥2.0 × ≥1.0 cm
Organ function	• Neutrophils ≥1.0 × 10^9/L, Hg ≥80 g/L, platelets ≥50 × 10^9/L • Serum transaminases ≤2.5 × ULN, bilirubin ≤1.5 × ULN • Serum creatinine <1.5 × ULN
Performance status	• Karnofsky score ≥60 (ECOG performance status 0–2)

Hg: haemoglobin; LPL: lymphoplasmacytic lymphoma;
MZL: marginal zone lymphoma; SLL: small lymphocytic lymphoma;
ULN: upper limit of normal; WM: Waldenström's macroglobulinaemia

Gopal AK, *et al. N Engl J Med* 2014; 370:1008–1018.

Patients were heavily pretreated and refractory to rituximab and an alkylating agent

Prior therapy exposure[1,2]	Patients (N=125)
Median (range) prior regimens, n	**4** (2–12)
Prior therapy, n (%)	
Rituximab	**125 (100)**
Alkylating agent	**125 (100)**
R + alkylating agent	114 (91)
Bendamustine	81 (65)
Anthracycline	79 (63)
Purine analogue	42 (34)
Stem cell transplantation	14 (11)
Median time from last regimen to study entry, months	3.9

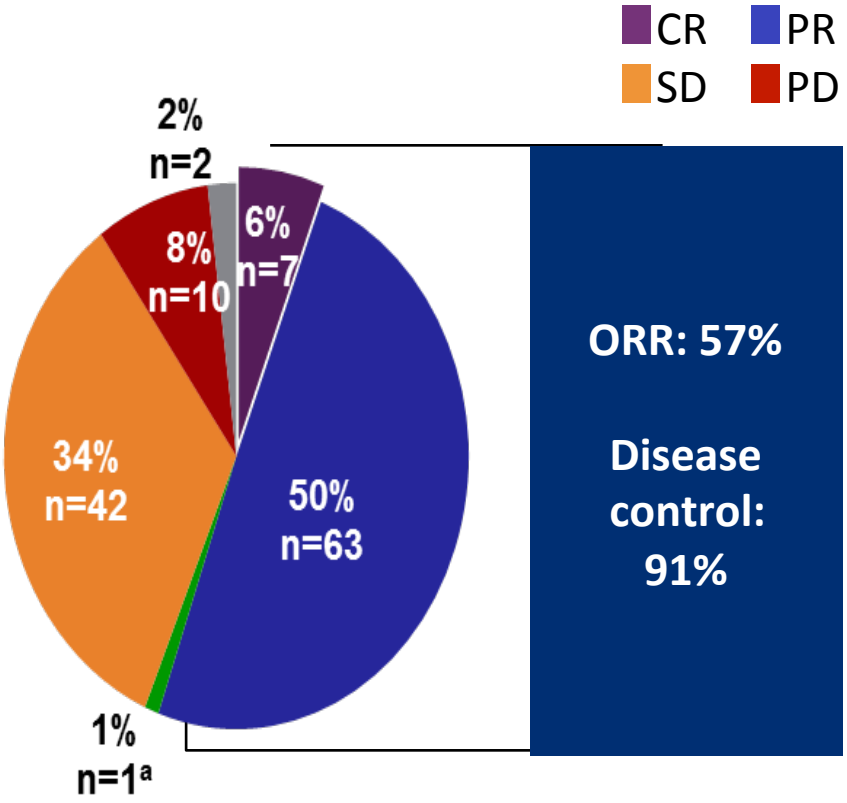
Prior therapy refractoriness, n/n (%)[1,2]	Patients (N=125)
Rituximab	**125/125 (100)**
Alkylating agent	**124/125 (99)[a]**
R + alkylating agent	**108/114 (95)**
R-CVP	29/36 (81)
R-bendamustine	47/60 (78)
Bendamustine	61/81 (75)
R-CHOP	40/56 (71)
Refractory to ≥ 2 regimens	99/125 (79)
Refractory to last regimen	**112/125 (90)**

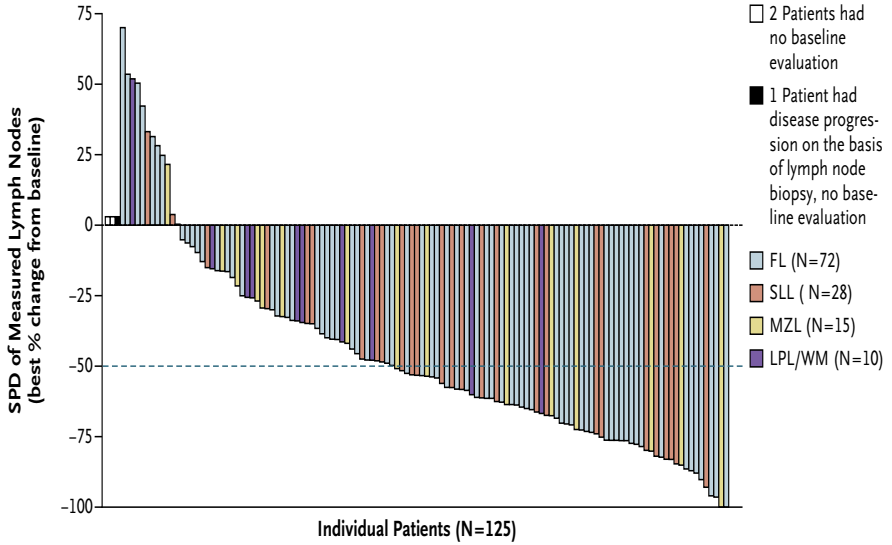
[a] Refractoriness to two cycles required to meet eligibility criteria but one patient received only one cycle, with no response after that cycle

1. Gopal AK, *et al*. *N Engl J Med* 2014; 370:1008–1018.
2. Gopal AK, *et al*. ASH 2013 (Abstract 85; oral).

ORR results for the overall study population
Primary endpoint

Median time to response: 1.9 months



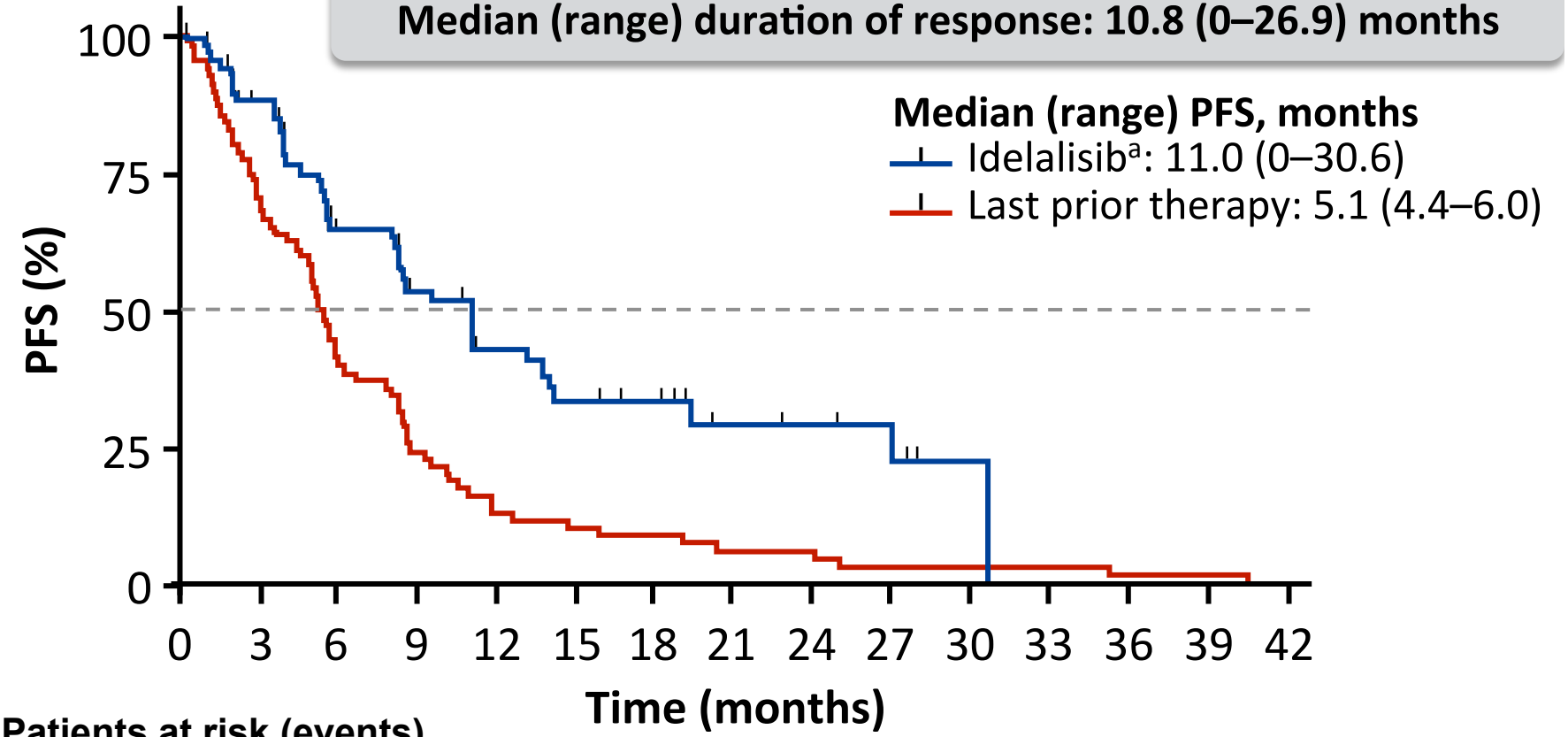


Disease control = CR + PR + SD
[a] LPL/WM patient

Gopal AK, *et al*. *N Engl J Med* 2014; 370:1008–1018.

Idelalisib delays progression compared with last prior therapy in patients with FL

Median (range) duration of response: 10.8 (0–26.9) months



Patients at risk (events)

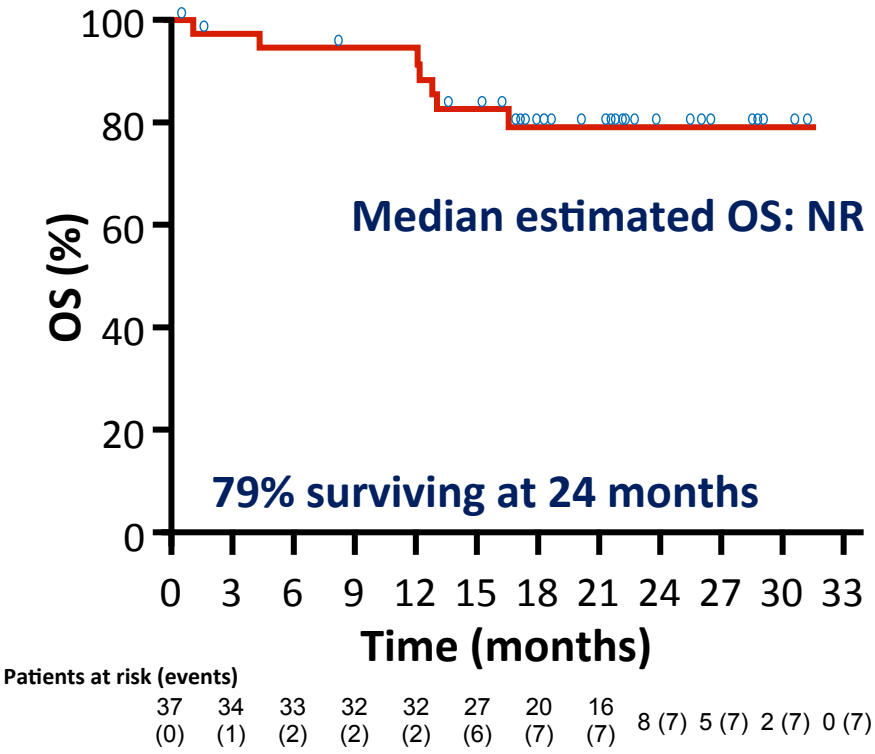
Idelalisib	72 (0)	55 (8)	35 (22)	26 (28)	18 (33)	14 (37)	11 (37)	6 (38)	5 (38)	3 (39)	1 (39)	0 (40)	0 (40)	0 (40)	0 (40)
Last prior therapy	72 (0)	50 (22)	28 (43)	17 (54)	9 (62)	7 (64)	6 (65)	4 (67)	4 (67)	2 (69)	2 (69)	2 (69)	1 (70)	1 (70)	0 (71)

[a] Long-term follow-up (June 2014 cut-off)

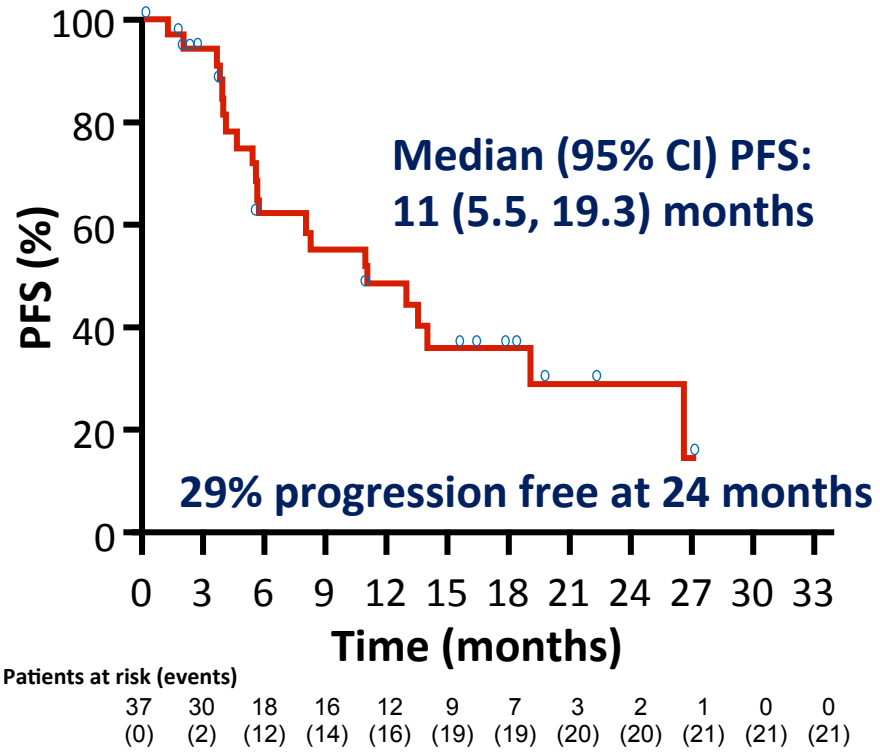
Salles GA, *et al.* ASCO 2015 (Abstract 8529; poster).

Idelalisib effective in patients with FL who relapsed‡ within 24 months first-line chemoimmunotherapy

OS in high-risk FL subgroup



PFS in high-risk FL subgroup



ORR: 57% (PR 43% and CR 14%)
Median duration of response: 11.8 months (95% CI=3.8, NE)

Gopal AK, *et al.* ASH 2015 (Abstract 2744; poster).

Safety profile

Lenalidomide	Ibrutinib	Idelalisib
Neutrop-grade ≥3: 20-50%	Atrial Fibrillation: 5-10%	Diarrhea grade ≥3: 13%
Infections	Bleeding grade > 2: 3-13%	Pneumonitis grade ≥2: 2%
Thrombo-embolism	Diarrhea grade > 2: 2-7%	AST-ALT grade ≥3: 13%
	Infections: 8-10%	Neutrop. grade ≥3: 27%

Verso un nuovo algoritmo di terapia dei LNH ?