

Lenalidomide for Lymphoma

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Goals

- Efficacy of lenalidomide in lymphoma in 2016
 - ▣ Mechanism of action
 - ▣ Single-agent studies in relapsed patients
 - ▣ Combinations
- Current FDA-approvals in lymphoma
 - ▣ Relapsed mantle cell lymphoma
- Current key trials to watch

Disclosure

- Mayo Clinic receives research support for clinical trials from Celgene, the manufacturer
- Celgene advisory board activities
 - ▣ No personal compensation
- ***In the US, single-agent lenalidomide is approved for relapsed MCL after 2 regimens (one of which contains bortezomib)***
 - ▣ ***Anything else I refer to today is “off-label”***

Mechanisms of Action

- No other approved drug for lymphoma has these unique mechanisms of action
 - ▣ Immunomodulatory agent
 - ▣ Direct anti-tumor activity
 - ▣ Anti-angiogenic
 - ▣ Immunostimulatory
 - Stimulates T-cell and NK cell cytotoxicity

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

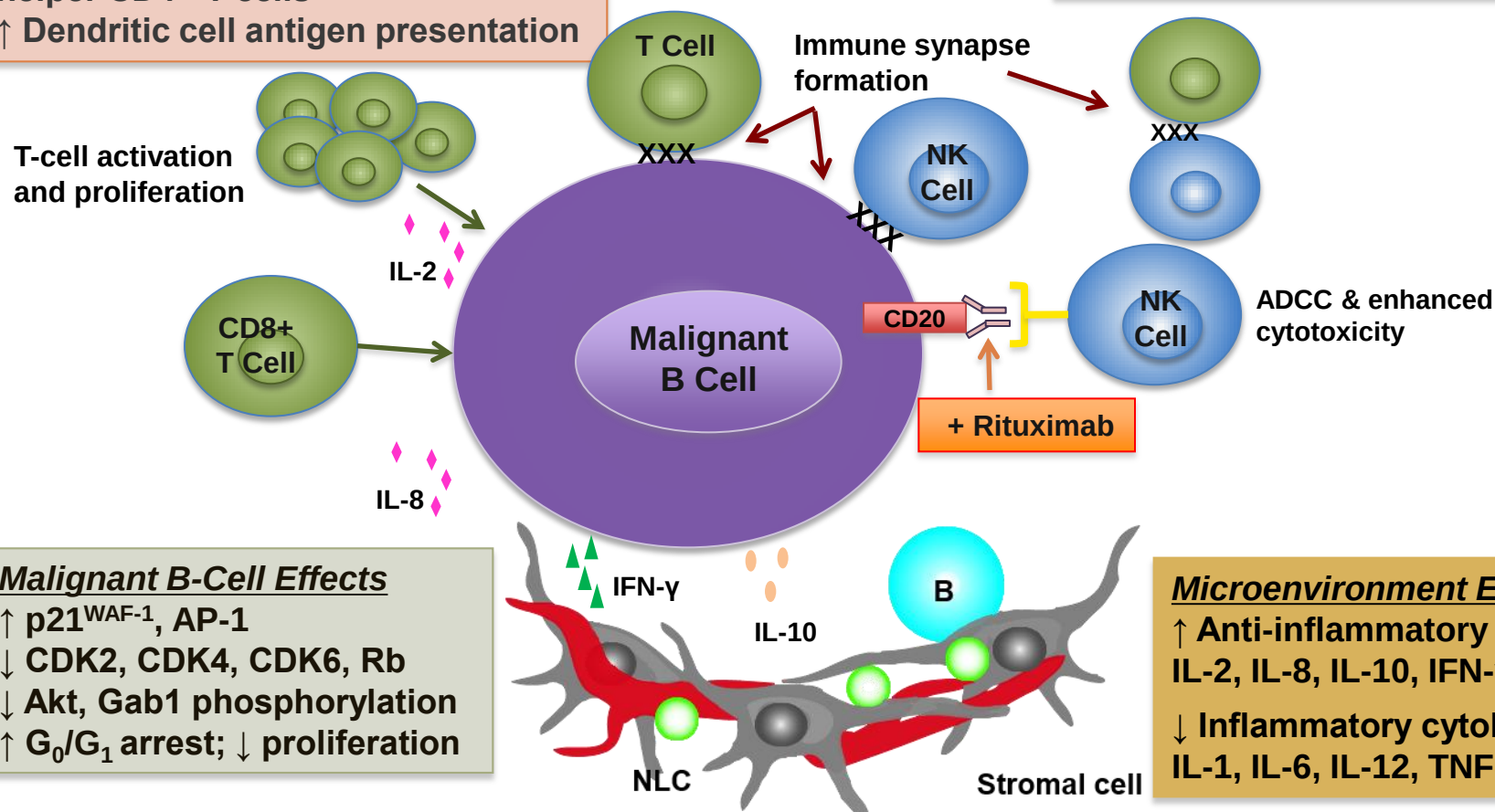
↑ Dendritic cell antigen presentation

NK-Cell Effects

↑ Number and activity of NK cells

↑ Enhanced ADCC

↑ Immune synapse formation and direct NK killing



Four IMiDs

- Thalidomide – no lymphoma approvals
 - ▣ Myeloma only
- Lenalidomide – relapsed MCL
- Pomalidomide – no lymphoma approvals
 - ▣ PCNSL trial ongoing
- CC-122 (investigational) – a nonphthalimide analog of thalidomide that retains binding to cereblon

Lenalidomide

- Is there evidence of single-agent activity in relapsed NHL?
- Study proposal to test this was approved March 2004
 - Trials NHL-001, 002, and 003
 - Lena 25 mg days 1-21 q 28 days

A comprehensive review of lenalidomide therapy for B-cell non-Hodgkin lymphoma

T. E. Witzig^{1*}, G. S. Nowakowski¹, T. M. Habermann¹, A. Goy², F. J. Hernandez-Ilizaliturri³, A. Chiappella⁴, U. Vitolo⁴, N. Fowler⁵ & M. S. Czuczman³

¹Department of Medicine, Division of Hematology, Mayo Clinic, Rochester; ²John Theurer Cancer Center at HUMC, Hackensack; ³Department of Medicine, Roswell Park Cancer Institute, Buffalo, USA; ⁴Department of Hematology, Città della Salute e della Scienza Hospital and University, Torino, Italy; ⁵Department of Lymphoma/Myeloma, University of Texas MD Anderson Cancer Center, Houston, USA

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Single –Agent Lenalidomide – 9 Years: 2004 - 13

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]	2009	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]	2008	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]	2011	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]	2013	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.

Combinations – R2

Lenalidomide/Rituximab =

Revlimid/Rituximab = R2

R2 + Bortezomib

R2CHOP

R2 + Bendamustine

See Table 2 Annals of Oncology 26:1667-77, 2015 for full summary

Combinations for Relapsed Lymphoma

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JOURNAL OF CLINICAL ONCOLOGY

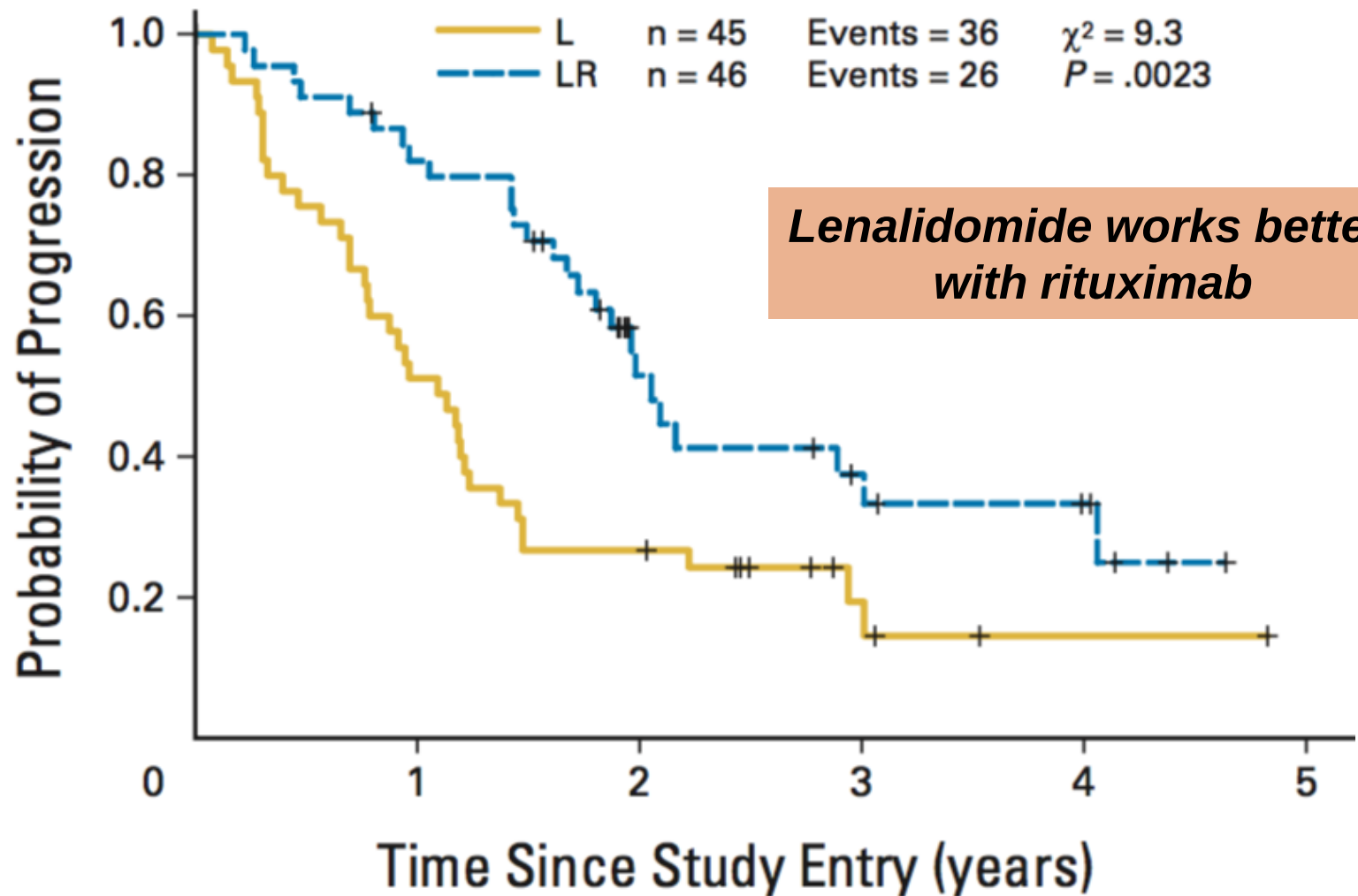
ORIGINAL REPORT

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

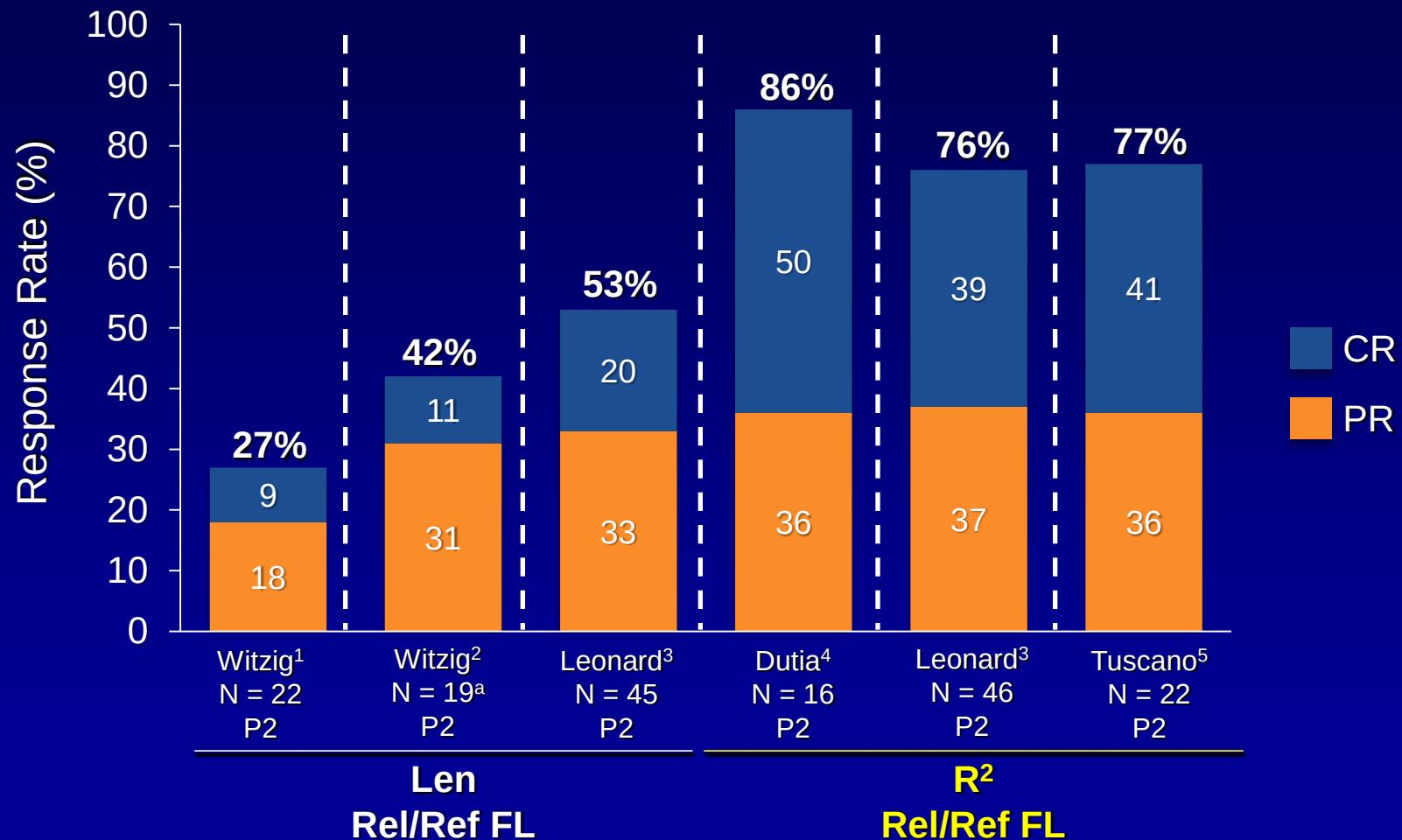
*John P. Leonard, Sin-Ho Jung, Jeffrey Johnson, Brandelyn N. Pitcher, Nancy L. Bartlett, Kristie A. Blum,
Myron Czuczman, Jeffrey K. Giguere, and Bruce D. Cheson*

J Clin Oncol 2015;33:3635-3640

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



Comparative Summary of Response Rates for Lenalidomide and R² in R/R Follicular Lymphoma



^aGrade 3 follicular lymphoma.

FL=follicular lymphoma; CR=complete response; PR=partial response; R²=lenalidomide + rituximab; Rel/Ref=relapsed/refractory.

1. Witzig TE, et al. *J Clin Oncol.* 2009;27:5404-5409.

2. Witzig TE, et al. *Ann Oncol.* 2011;22:1622-1627.

3. Leonard JP, et al. *J Clin Oncol.* 2015 Aug 24. pii: JCO.2014.59.9258. [Epub ahead of print].

4. Dutia M, et al. *Ann Oncol.* 2011;22(suppl 4):iv183-iv189.

5. Tuscano JM, et al. *Br J Haematol.* 2014;165(3):375-381.



What About R2 for Upfront?

It Works

R²-Revlimid/Rituximab

18

- Upfront therapy; Phase II; Single-Institution
- ***Lenalidomide 20 mg days 1-21 q 28***
- ***Rituximab 375 mg/m² each cycle***
- 6 cycles; response assessment; optional 12 total
 - ▣ No rituximab maintenance
- 110 patients enrolled over 3 years (2008-11)
 - ▣ ***Follicular lymphoma – 50***
 - ▣ Marginal zone – 30
 - ▣ SLL - 30

R²-Revlimid/Rituximab

19

□ All patients

- ▣ ORR 90% (93/103 evaluable)
- ▣ CR 63% (65/103) and PR 27% (28/103)

□ Follicular patients

- ▣ ORR 98% (45/46 evaluable)
- ▣ CR 87% (40/46) and PR 11% (5/46)

R²-Revlimid/Rituximab

20



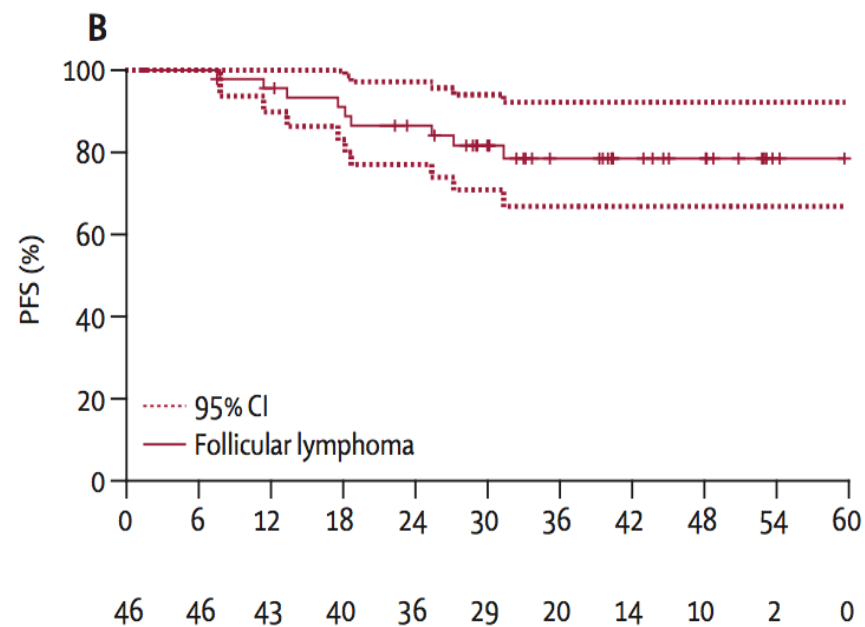
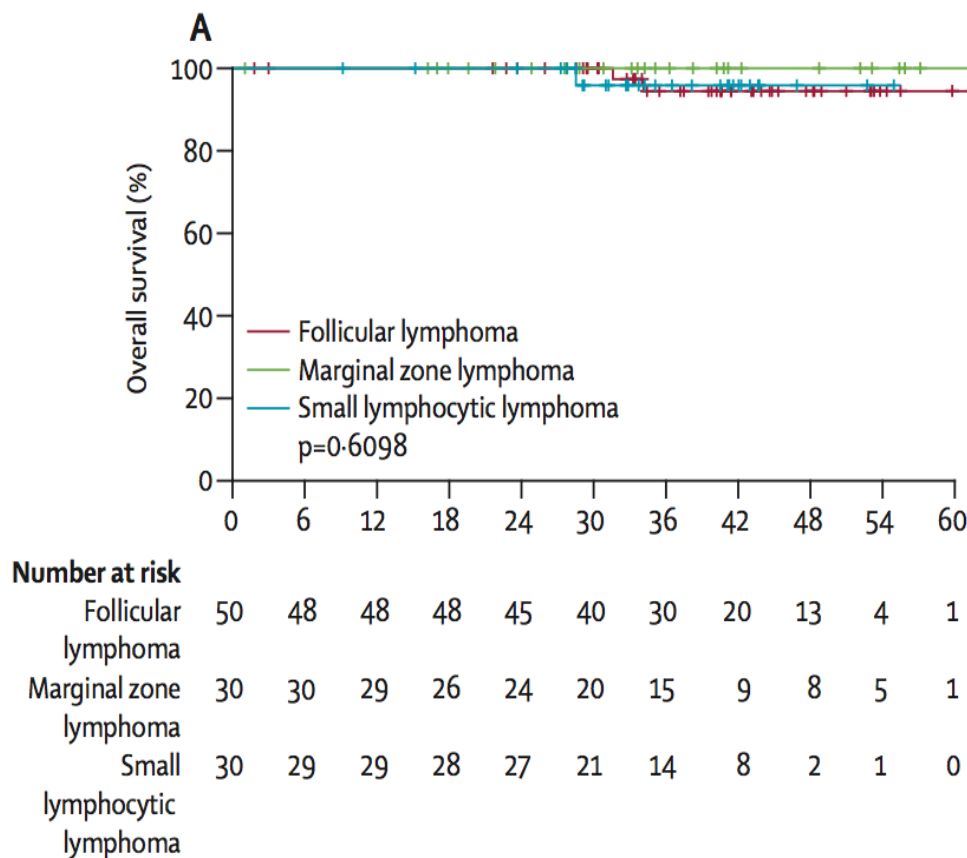
	Follicular lymphoma (n=50)	Marginal zone lymphoma (n=30)	Small lymphocytic lymphoma (n=30)
Age (years; median, range)	56 (35–84)	59 (36–77)	59 (34–76)
Sex, female	22 (44%)	18 (60%)	12 (40%)
Stage			
III	23 (46%)	9 (30%)	0
IV	27 (54%)	21 (70%)	30 (100%)
High tumour burden (as per GELF)	27 (54%)	13 (43%)	14 (47%)
FLIPI score			
0–1	11 (22%)	..	..
2	25 (50%)	..	..
3–5	14 (28%)	..	..

Data are number (%), unless otherwise indicated. GELF=Groupe d'Etudes des Lymphomes Folliculaires. FLIPI=Follicular Lymphoma International Prognostic Index.

Table 1: Baseline clinical characteristics of patients with indolent non-Hodgkin lymphomas

R²-Revlimid/Rituximab

21



NCT01476787- RELEVANCE

22

Arms

Experimental: Lenalidomide + Rituximab

- Lenalidomide dose 20-mg on days 2-22 every 28 days for 6 cycles, if CR then 10-mg on days 2-22 every 28 days for 12 cycles. PR after 6 cycles, continue 20 mg for 3~6 cycles and then 10 mg on days 2-22 every 28-day cycles for up to 18 cycles.
- Rituximab, 375 mg/m² on days 1, 8, 15 and 22 of cycle 1, day 1 of cycles 2 to 6; 8 weeks later responding patients continue with 375 mg/m² rituximab every 8 weeks for 12 cycles.

Active Comparator: Control

- ONE of the following: Rituximab-CHOP, Rituximab-CVP, Rituximab-Bendamustine. 7 to 8 weeks later responding patients will continue with 375 mg/m² rituximab every 8 weeks for 12 cycles.



R2 Upfront for Mantle Cell

- Best response rates for single-agent Lena in relapsed disease were in MCL
- R2 was effective in upfront for FL (2014)
- R2 for MCL upfront

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.

R2 for Upfront MCL

□ Induction

- ▣ Lenalidomide 20 mg days 1-21 q28 x 12
- ▣ Rituximab 375 mg/m² x 9

□ Maintenance

- ▣ Lenalidomide 15 mg days 1-21 q 28
- ▣ Rituximab 375 mg/m² q 2 months

□ Duration of treatment was 36 months

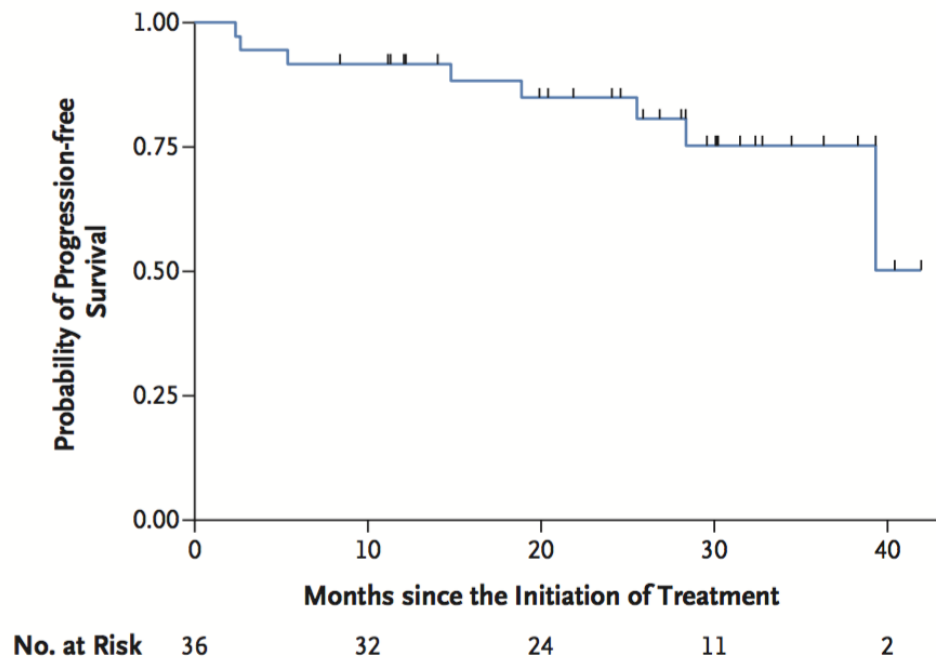
R2 for Upfront MCL

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

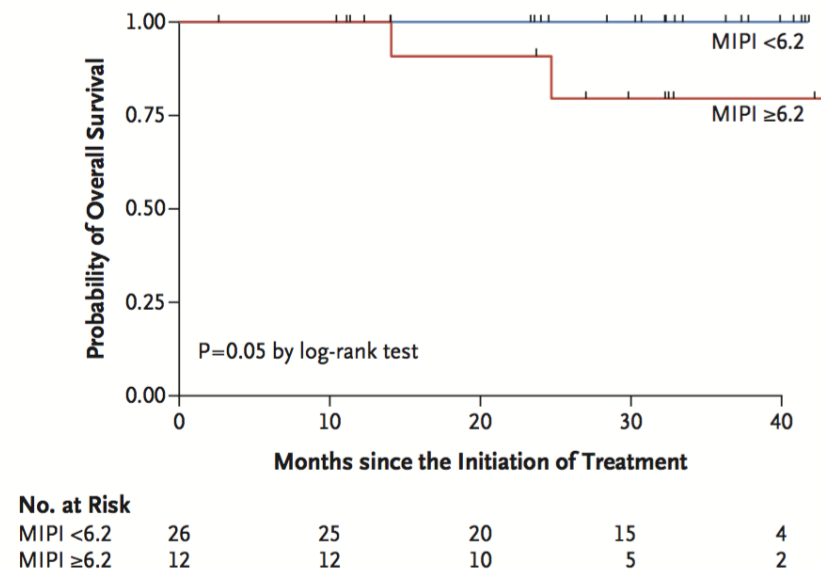
Response	Patients <i>no.</i>	Intention-to-Treat Population (N = 38) %	Patients Who Could Be Evaluated (N = 36)
Overall response	33	87	92
Complete response*	23	61	64
Partial response	10	26	28
Stable disease	1	3	3
Progressive disease†	2	5	6
Could not be evaluated‡	2	5	

Ruan J et al N Engl J Med 2015;373:1835-44

A Progression-free Survival



B Overall Survival According to MIPI Score



Ruan J et al N Engl J Med 2015;373:1835-44

Is R2 Maintenance Better?

- Rituximab maintenance is *a standard* of care after induction R-chemotherapy
- E2408 is testing whether R2 maintenance is better than R alone for FL
- E1411 is testing whether R2 maintenance is better than R alone for MCL

ECOG 2408 Follicular Lymphoma

Eastern Cooperative
Oncology Group

E2408

Evens, ASCO 2016

Schema

High Risk
Follicular Lymphoma
(FLIPI 1 score 3-5
OR
GELF high tumor burden)

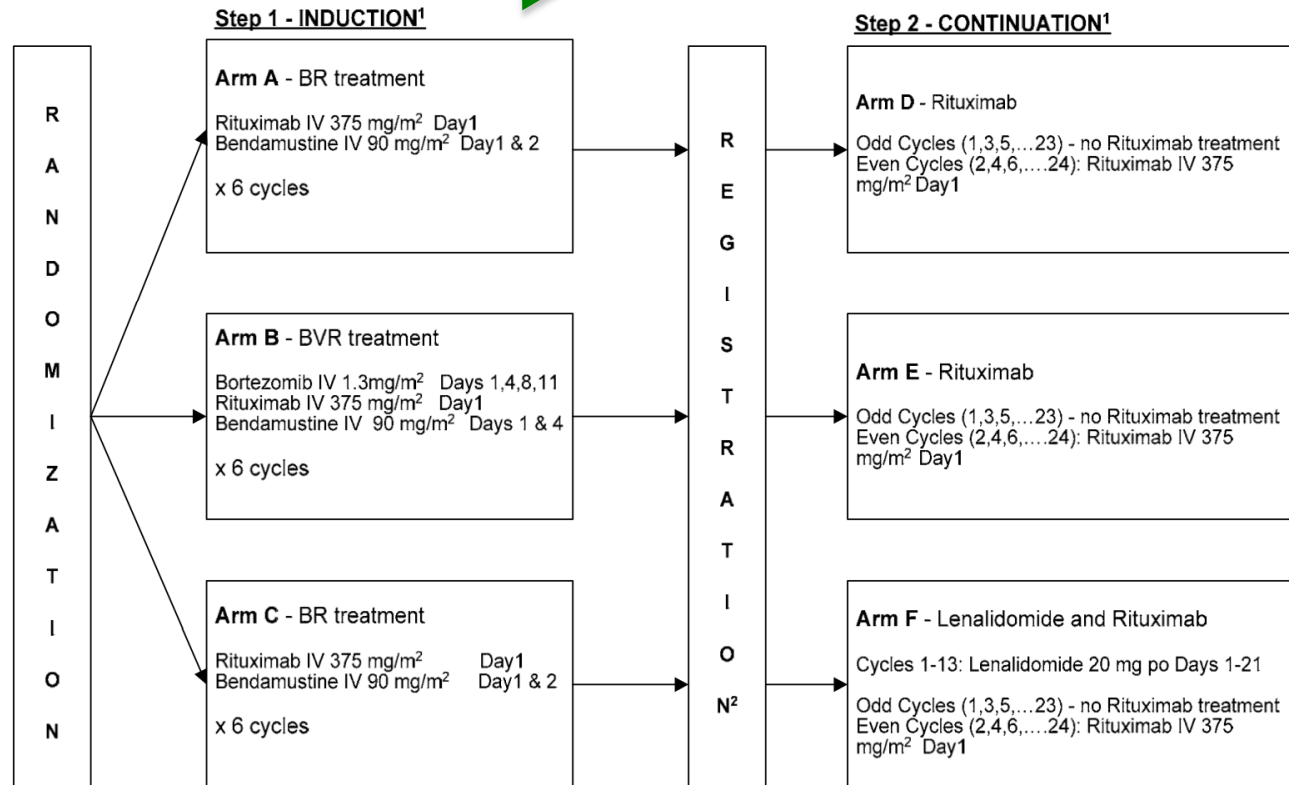
Stratification

1. FLIPI 1 STATUS

- Score 1-2*
- Score 3
- Score 4-5

2. GELF Criteria

- Low tumor burden**
- High tumor burden



Accrual goal = 250 total patients
Cycle length is 28 days (4 weeks)

*Requires High tumor burden per GELF criteria (see section 3)

** Requires FLIPI Status of 3 or higher (per FLIPI 1 criteria)

Enrollment complete

ECOG1411 Mantle Cell NHL

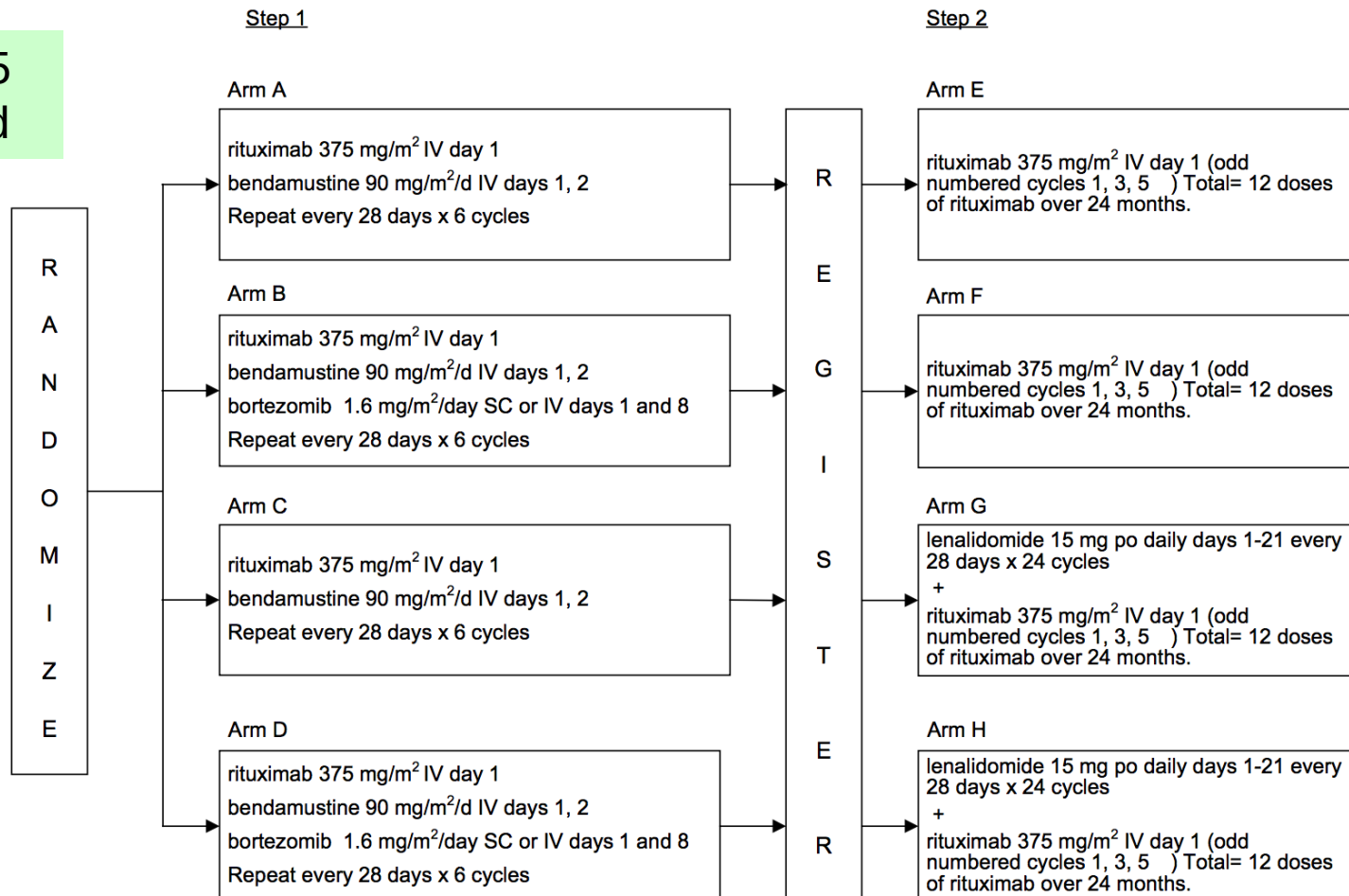
336/375
accrued

Stratify:
MIPI risk score¹

- low
- intermediate
- high

Age

- < 60
- = 60



Strategies in Large Cell Lymphoma

- Combined with RCHOP = R2CHOP
- Maintenance

ORIGINAL ARTICLE

Lenalidomide can be safely combined with R-CHOP (R2CHOP) in the initial chemotherapy for aggressive B-cell lymphomas: phase I study

GS Nowakowski¹, B LaPlant², TM Habermann¹, CE Rivera³, WR Macon⁴, DJ Inwards¹, IN Micallef¹, PB Johnston¹, LF Porrata¹, SM Ansell¹, RR Klebig¹, CB Reeder⁵ and TE Witzig¹

¹Division of Hematology, Mayo Clinic, Rochester, MN, USA; ²Division of Biomedical Statistics and Informatics, Mayo Clinic, Rochester, MN, USA; ³Division of Hematology-Oncology, Mayo Clinic, Jacksonville, FL, USA; ⁴Division of Anatomic Pathology, Mayo Clinic, Rochester, MN, USA and ⁵Division of Hematology-Oncology, Mayo Clinic, Scottsdale, AZ, USA

Lenalidomide-RCHOP (R2CHOP)

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- Untreated DLBCL eligible for RCHOP
- Standard RCHOP-21 x 6 cycles
- Lenalidomide d1-10 q 21
- Three dose levels tested:
 - ▣ 15 mg
 - ▣ 20 mg
 - ▣ **25 mg (250 mg/cycle)**
- All patients received prophylactic Neulasta d2
- All patients received Aspirin 81 mg daily

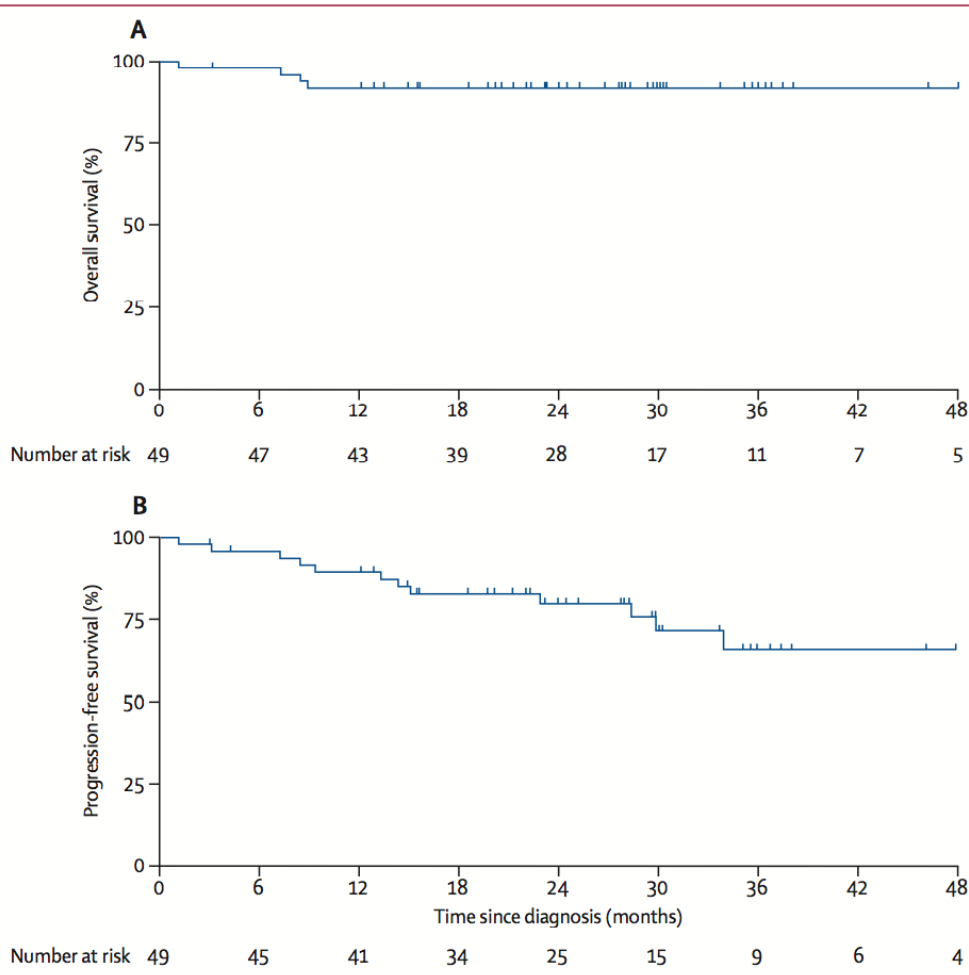


Lenalidomide plus R-CHOP21 in elderly patients with untreated diffuse large B-cell lymphoma: results of the REAL07 open-label, multicentre, phase 2 trial

Umberto Vitolo, Annalisa Chiappella, Silvia Franceschetti, Angelo Michele Carella, Ileana Baldi, Giorgio Inghirami, Michele Spina, Vincenzo Pavone, Marco Ladetto, Anna Marina Liberati, Anna Lia Molinari, Pierluigi Zinzani, Flavia Salvi, Pier Paolo Fattori, Alfonso Zaccaria, Martin Dreyling, Barbara Botto, Alessia Castellino, Angela Congiu, Marcello Gaudiano, Manuela Zanni, Giovannino Ciccone, Gianluca Gaidano, Giuseppe Rossi, on behalf of the Fondazione Italiana Linfomi

Outcome of R2CHOP (Italian)

36

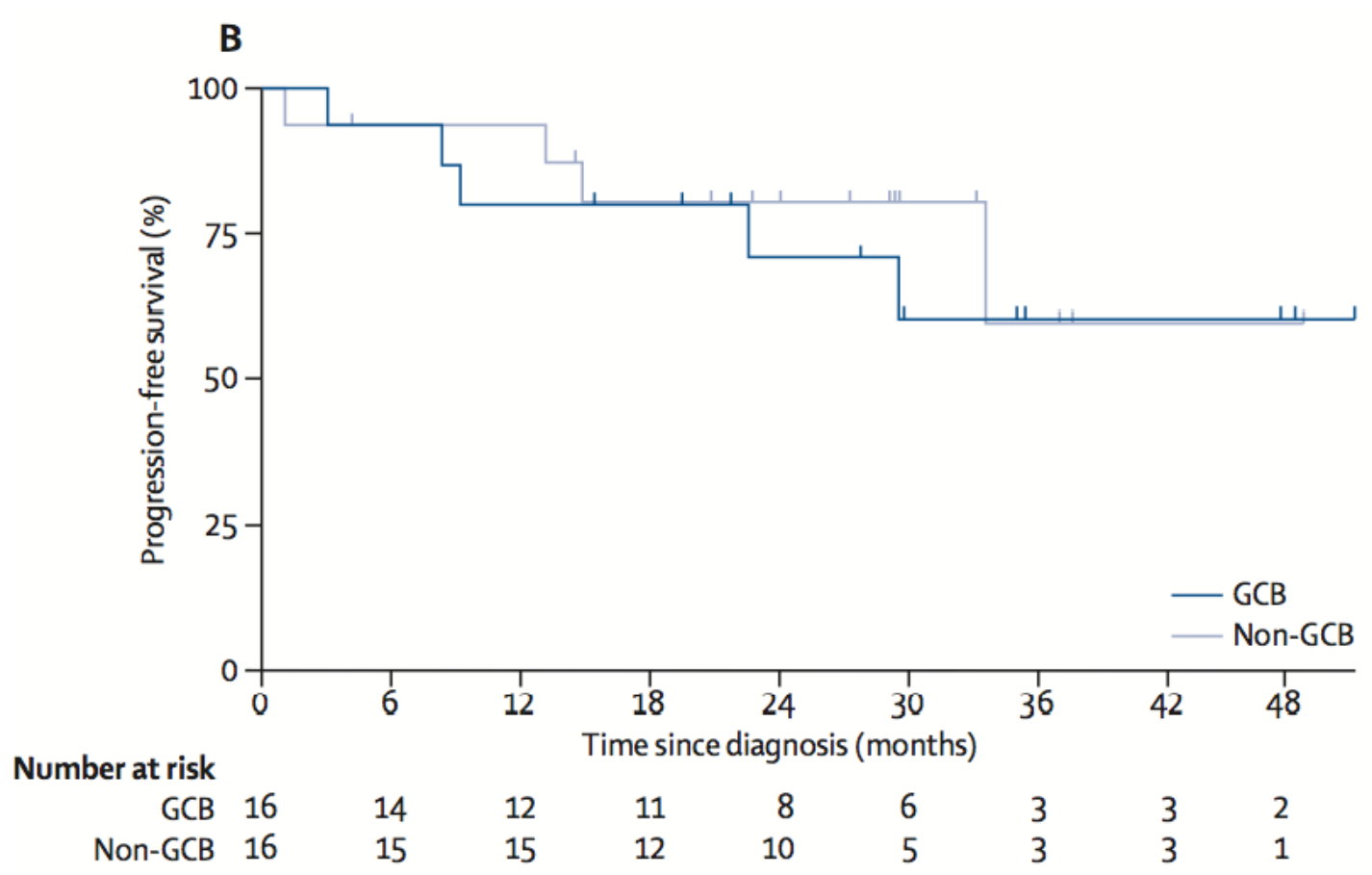


- R2CHOP-13 centers in Italy
- DLBCL and FL 3b
- GCB vs non-GCB IHC (Hans)
- Standard RCHOP x 6
- **Revlimid 15 mg d1-14 q 21 (210 mg/cycle)**
- 49 patients
- 92% (45/49) ORR
- 86% functional CR

Figure 2: Kaplan-Meier curves of (A) overall survival and (B) progression-free survival
Lines indicate censoring.

GCB vs non-GCB

37



Lancet Oncol. 2014;15(7):730-7.

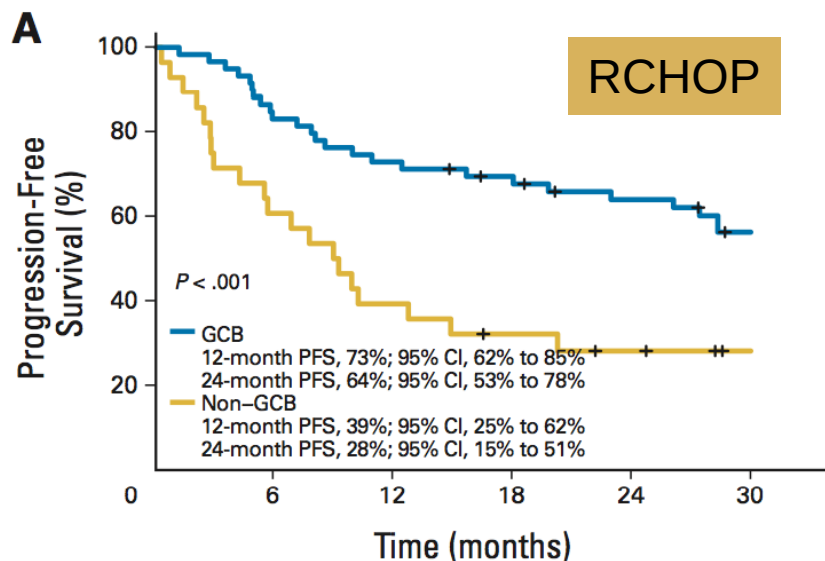
R2CHOP for Non-GCB Type DLBCL

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

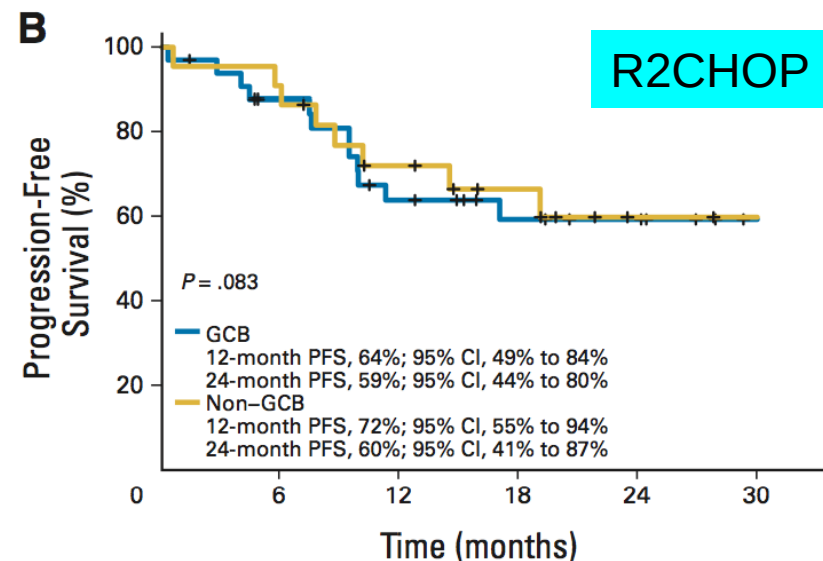
Lenalidomide Combined With R-CHOP Overcomes Negative Prognostic Impact of Non–Germinal Center B-Cell Phenotype in Newly Diagnosed Diffuse Large B-Cell Lymphoma: A Phase II Study

Grzegorz S. Nowakowski, Betsy LaPlant, William R. Macon, Craig B. Reeder, James M. Foran, Garth D. Nelson, Carrie A. Thompson, Candido E. Rivera, David J. Inwards, Ivana N. Micallef, Patrick B. Johnston, Luis F. Porrata, Stephen M. Ansell, Thomas M. Habermann, and Thomas E. Witzig



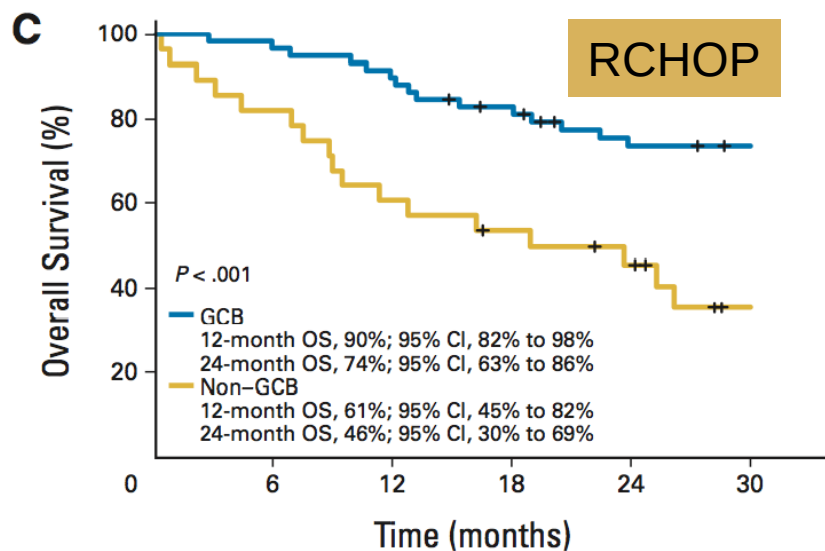
No. at risk

GCB	59	49	43	39	34	28
Non-GCB	28	17	11	8	6	3



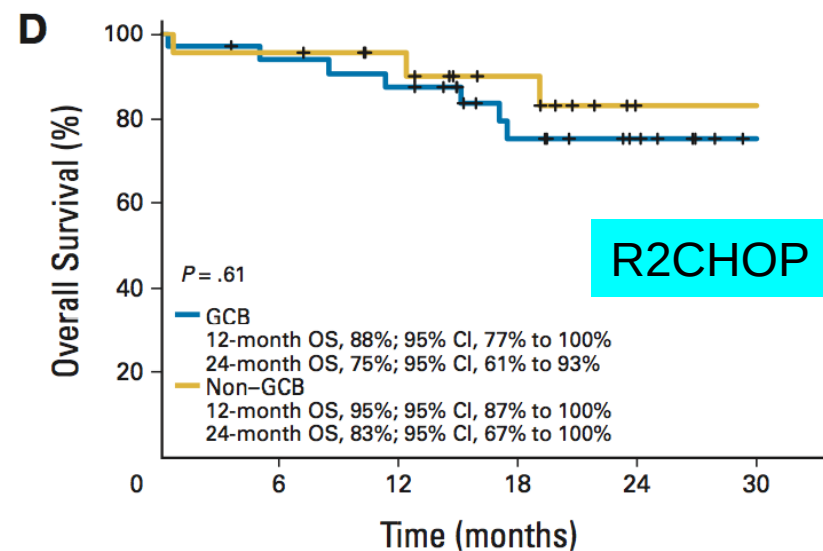
No. at risk

GCB	33	26	18	13	11	6
Non-GCB	22	20	14	10	5	4



No. at risk

GCB	59	57	53	47	39	37
Non-GCB	28	23	17	14	11	5



No. at risk

GCB	33	30	27	18	13	7
Non-GCB	22	21	18	13	6	6

Current Studies in R2CHOP

R2CHOP vs RCHOP

- E1412 – GCB and ABC by Nanostring
- ROBUST – ABC only by Nanostring
- ***These two trials will settle the issue regarding R2CHOP as induction for DLBCL that are non-GCB***

Some information on GCB

Maintenance After RCHOP

- Maintenance Lenalidomide after successful RCHOP
- No drugs approved in that space after RCHOP

REMARC Study Design

Induction

N = 621 (actual was 650)

Diagnosis

All Patients

R-CHOP
(6-8 cycles)

CR/PR
(3 mths)

S
D
/
P
D

Study
Withdrawal

Register

Maintenance

Lenalidomide
25mg / day
21/28 days for 2 yrs

Placebo
21/28 days for 2 yrs

R
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N

Register

Patient Population

- Front-line DLBCL (CD20+)
- 60-80 years
- Age Adjusted IPI ≥ 1

Primary endpoint: PFS (hypothesis: $\alpha=5\%$; power=80%; HR=1.55); (21 mths improvement in mPFS; 59.8 mths vs. 38.6 mths placebo)

Secondary endpoints: OS, EFS, ORR/CR, % conversion from PR to CR, QoL, PFS2, safety

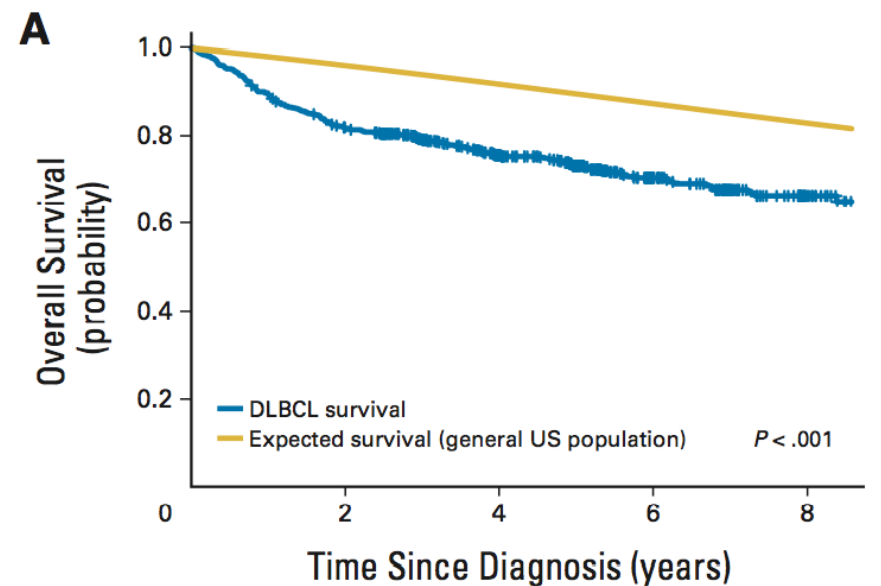
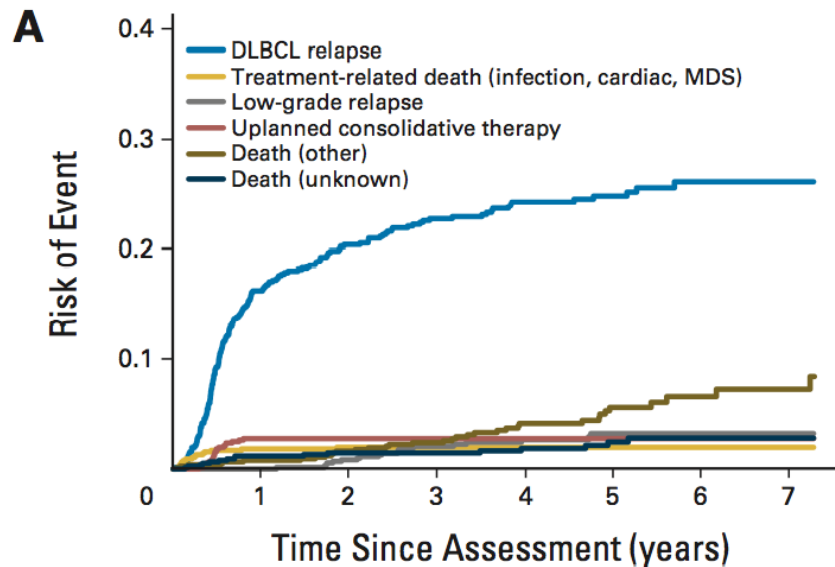
Event-Free Survival at 24 Months Is a Robust End Point for Disease-Related Outcome in Diffuse Large B-Cell Lymphoma Treated With Immunochemotherapy

Matthew J. Maurer, Hervé Ghesquières, Jean-Philippe Jais, Thomas E. Witzig, Corinne Haioun, Carrie A. Thompson, Richard Delarue, Ivana N. Micallef, Frédéric Peyrade, William R. Macon, Thierry Jo Molina, Nicolas Ketterer, Sergei I. Syrbu, Olivier Fitoussi, Paul J. Kurtin, Cristine Allmer, Emmanuelle Nicolas-Virelizier, Susan L. Slager, Thomas M. Habermann, Brian K. Link, Gilles Salles, Hervé Tilly, and James R. Cerhan

Iowa/Mayo Lymphoma SPORE J Clin Oncol. 2014;32(10):1066-73

43 Validated in GELA

Cause of Death



***Iowa/Mayo Lymphoma SPORE J Clin Oncol. 2014;32(10):1066-73
Validated in GELA***

Role of Maintenance in DLBCL

- REMARC will settle that issue but...
- What if R2CHOP wins upfront? Do you still need the two years?
- Will another trial be needed?

Lenalidomide Summary

- Single agent activity in many types of relapsed NHL
 - ▣ Highest activity in relapsed mantle cell lymphoma
 - Only FDA-approved indication in lymphoma
- Combinations with rituximab are superior to single-agent lenalidomide both upfront as R2 and for relapsed follicular lymphoma
- R2CHOP is safe and effective for DLBCL with a preference to ABC type DLBCL; however, randomized studies are in progress to provide the definitive answer.