Linfoma follicolare all'esordio e pretrattato: un approccio chemo-free è possibile?

Caterina Patti

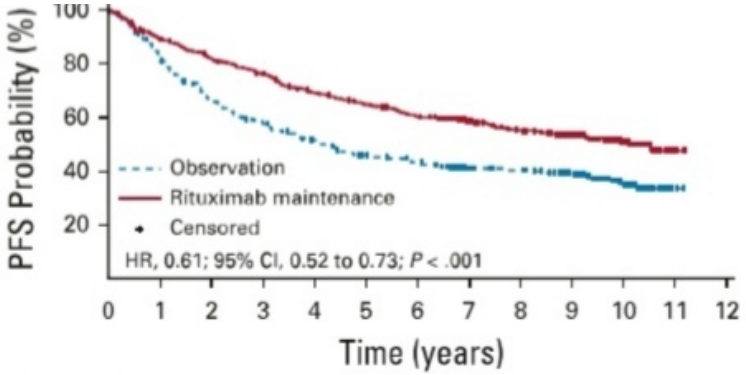
Ospedale Cervello Palermo

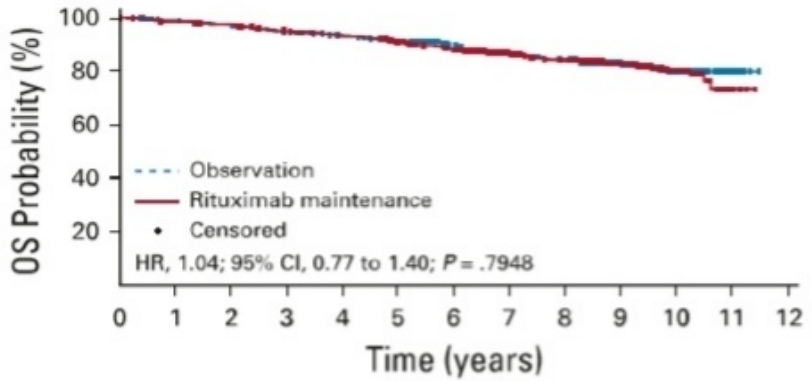
Financial disclosure

- **Advisory Board:** Abbvie, Roche, Jansenn,
- **Partecipazione a congressi/eventi formativi:** Roche, Takeda, Jansenn, Abbvie

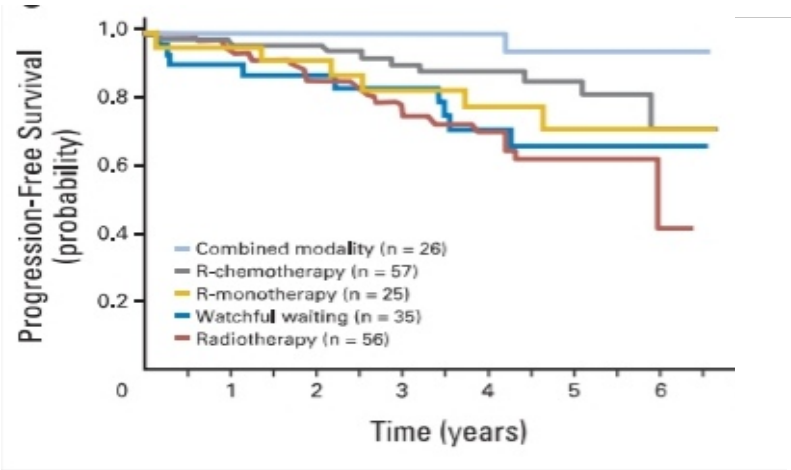
Follicular Lymphoma : Long - term Outcomes with Chemoimmunotherapy are Excellent for Most

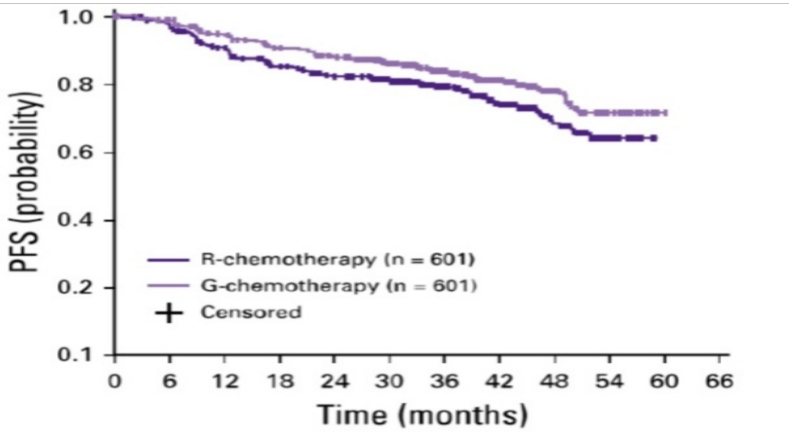
PRIMA





LymphoCare





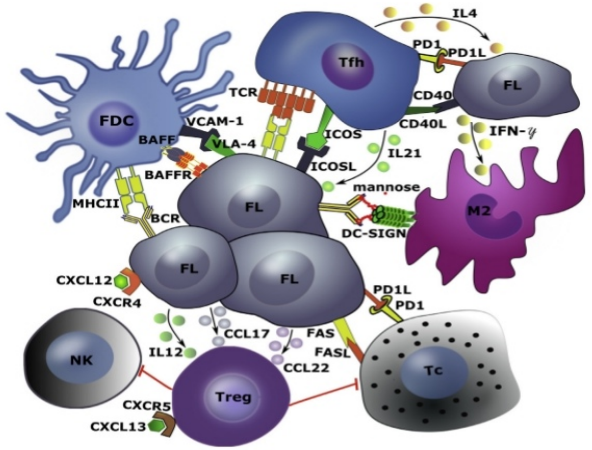
GALLIUM

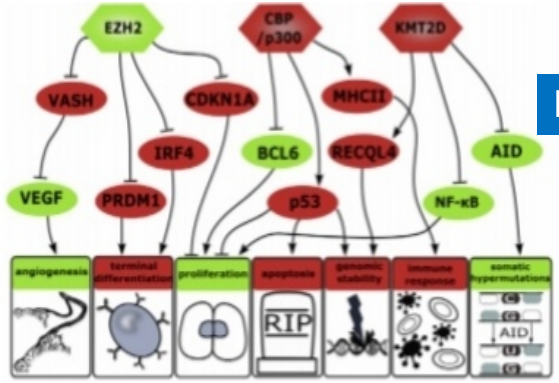
Bachy et al JCO 2019
Friedberg et al JCO 2012
Hiddmann et al JCO 2018

Follicular Lymphoma Biology Highlights Targets for Novel Therapies

Tumor immune microenvironment

- Imids
- Bispecific Abs
- Antibody-drug conjugates
- Chekpoint inhibitors
- Cart T-cells

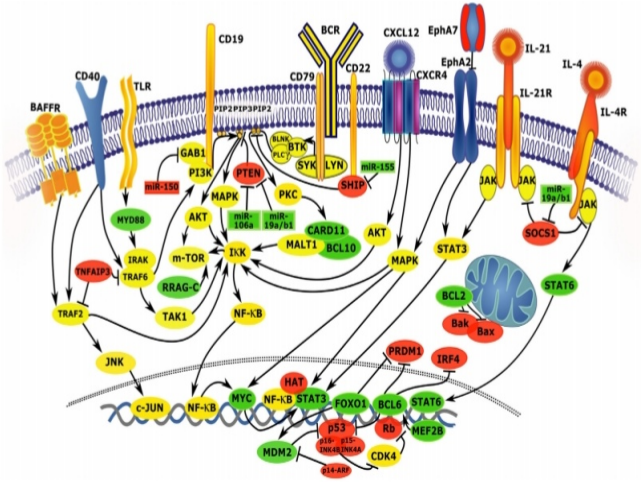




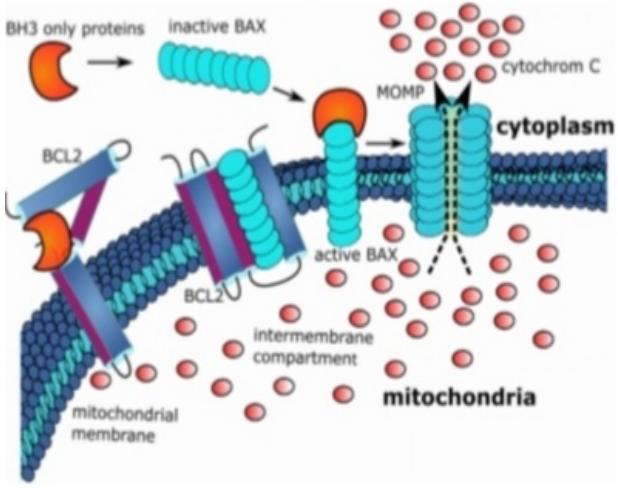
Epigenetic modification

EZH2 inhibitors

BCR and other cell surface signaling Pathway activation



BTK inhibitors
PI3 kinase inhibitors



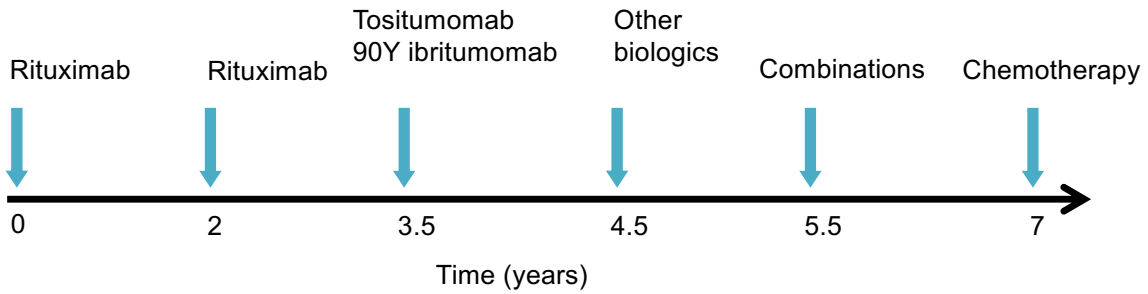
T (14 ;18) and BCL2 overexpression

Venetoclax

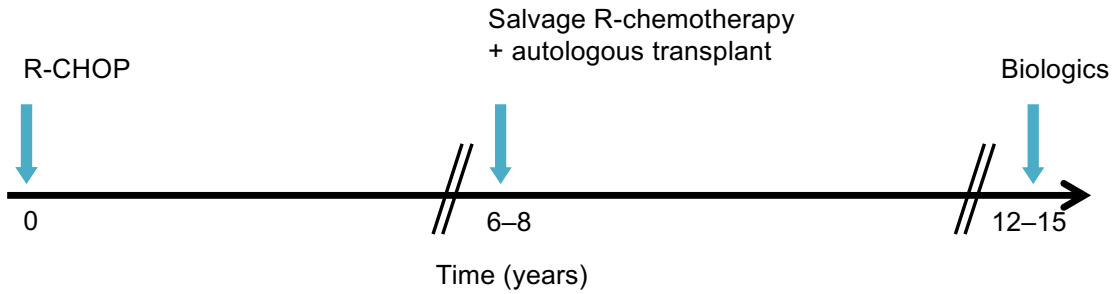
Devan et al Semin Oncol 2018

Different philosophies to treat FL

Avoid chemotherapy as long as possible



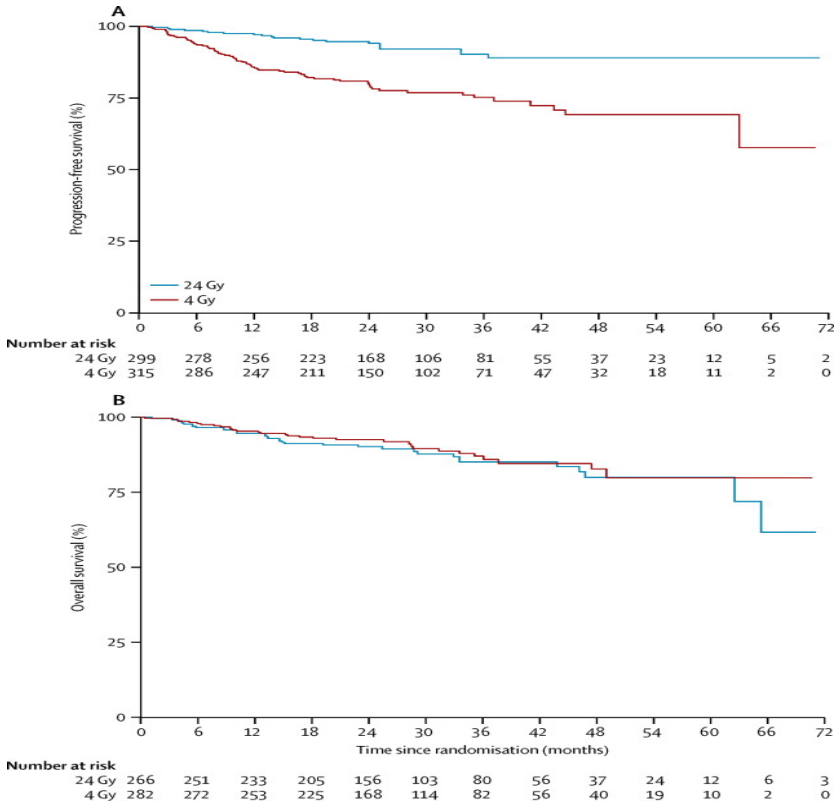
Try to reach a CR and have a long duration of CR



Attributed to prof yf B. Coiffier

4 Gy versus 24 Gy radiotherapy for patients with indolent lymphoma (FORT): a randomised phase 3 non-inferiority trial

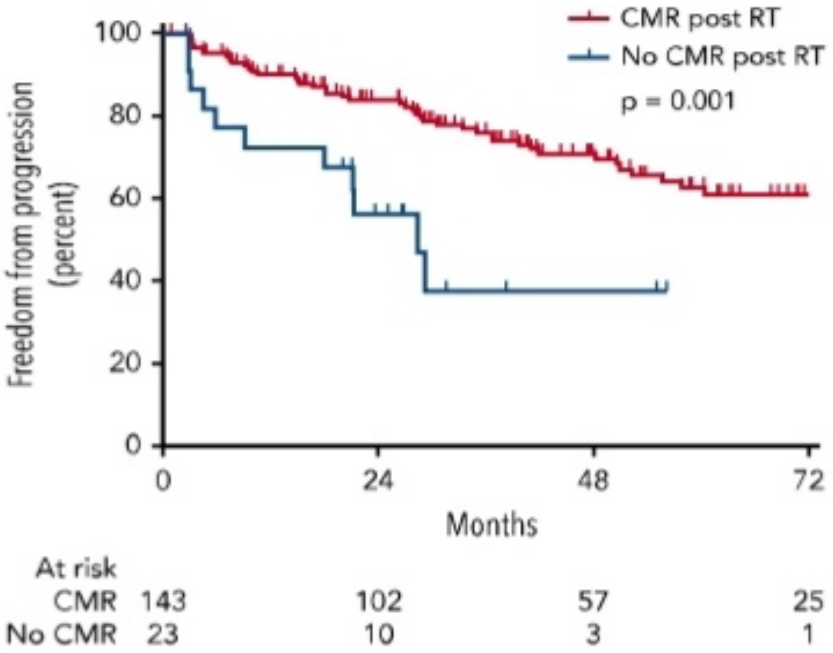
Peter J Hoskin, Amy A Kirkwood, Bilyana Popova, Paul Smith, Martin Robinson, Eve Gallop-Evans, Stewart Coltart, Timothy Illidge, Krishnaswamy Madhavan, Caroline Brammer, Patricia Diez, Andrew Jack, Isabel Syndikus

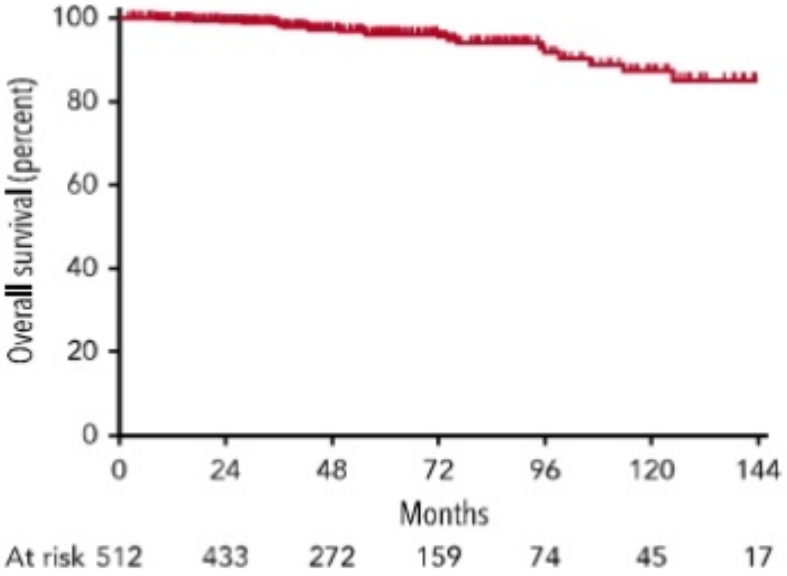


Patients receiving radical radiotherapy for early stage follicular lymphoma should receive 24 Gy. 4 Gy has, however, a potential role as a simpler, shorter, and more pragmatic schedule in patients being treated for local control in the palliative setting, in which durable response might be less important.

The Lancet Onclogy 2014

Radiotherapy for localized follicular lymphoma staged by 18F-FDG PET-CT: a collaborative study by ILROG

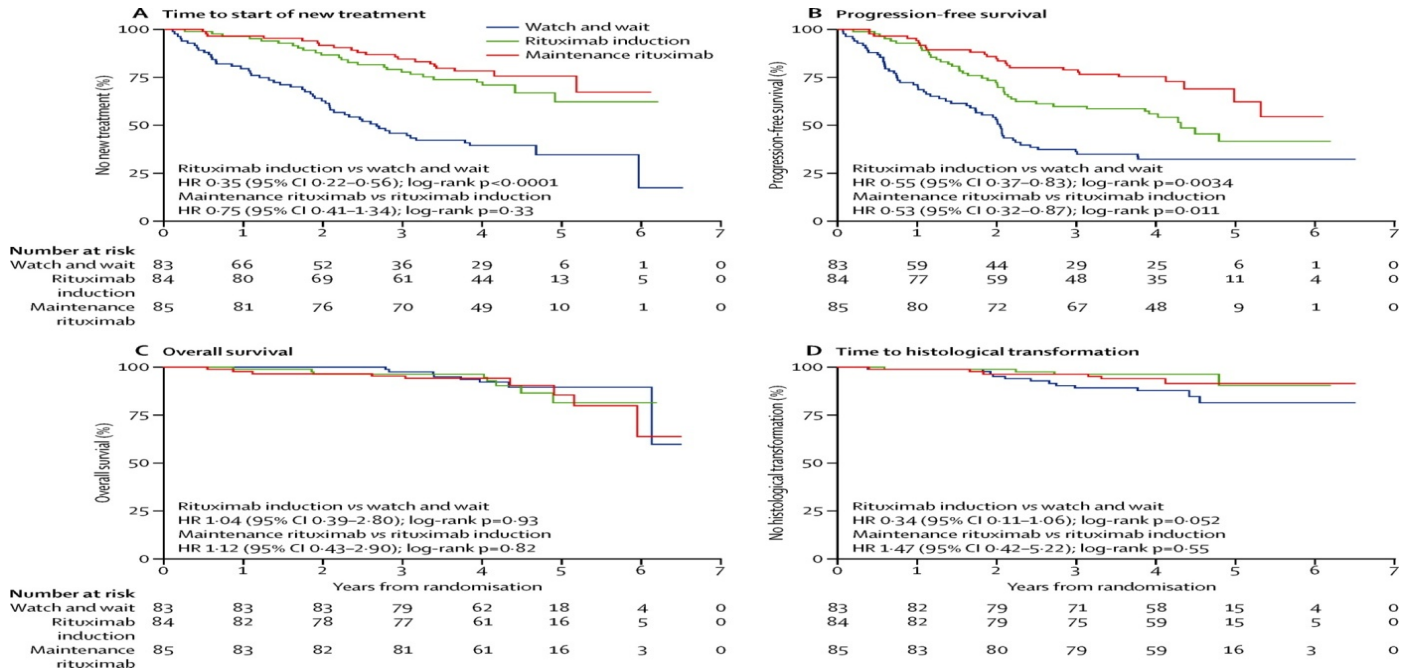




JL. Brady et al Blood. 2019;

Rituximab versus a watch-and-wait approach in patients with advanced-stage, asymptomatic, non-bulky follicular lymphoma: an open-label randomised phase 3 trial

Kirit M Ardeshna, Wendi Qian, Paul Smith, Nivette Braganca, Lisa Lowry, Pip Patrick, June Warden, Lindsey Stevens, Christopher F E Pocock, Fiona Miall, David Cunningham, John Davies, Andrew Jack, Richard Stephens, Jan Walewski, Burhan Ferhanoglu, Ken Bradstock, David C Linch



Lancet Oncol 2014

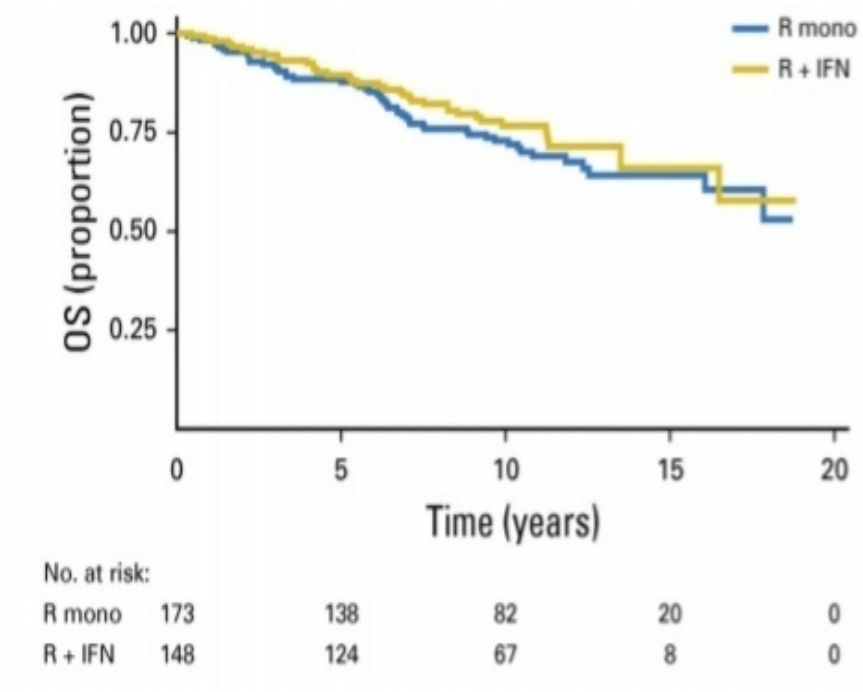
VOLUME 36 · NUMBER 33 · NOVEMBER 20, 2018

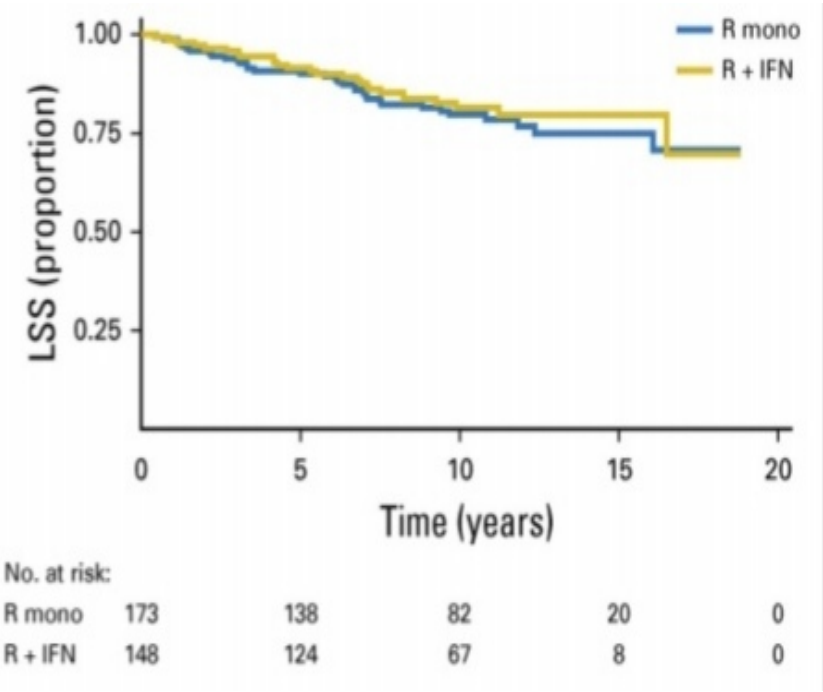
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Chemotherapy-Free Initial Treatment of Advanced Indolent Lymphoma Has Durable Effect With Low Toxicity: Results From Two Nordic Lymphoma Group Trials With More Than 10 Years of Follow-Up

Sandra Lockmer, Bjørn Østenstad, Hans Hagberg, Harald Holte, Ann-Sofie Johansson, Björn Engelbrekt Wahlin, Karin Fahl Wader, Chloé Beate Steen, Peter Meyer, Martin Maisenhølder, Karin Ekström Smedby, Peter Brown, and Eva Kimby





Watch and Wait in the Rituximab era

PRO:

- Delay acute and late toxicity
- Safely defer inization of systemic therapy by a median of 2-3 yrs
- Improve pts' QoL
- Reduced risk of cross-resistance to other therapy

Rituximab alone:

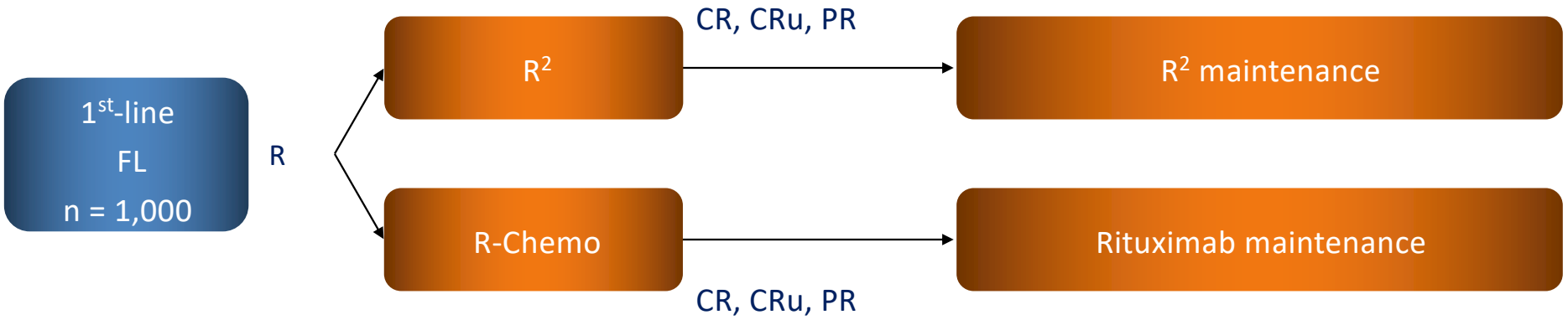
- Effective
- Low risk option (excellent safety profile)
- Well tolerated
- Can delay the time to first treatment
- Can avoid over-treatment in low tumor burden (cure?)
- Can improve the psycologic QoL by reducing anxiety and depression

CONTRA:

- W & W data obtained in pre-R era
- R-based treatments largely improved prognosis of FL
- Pts demand differs from years ago
- Pts are currently aware of all treatment approaches

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

Franck Morschhauser, M.D., Ph.D., Nathan H. Fowler, M.D et al NEJM 2018

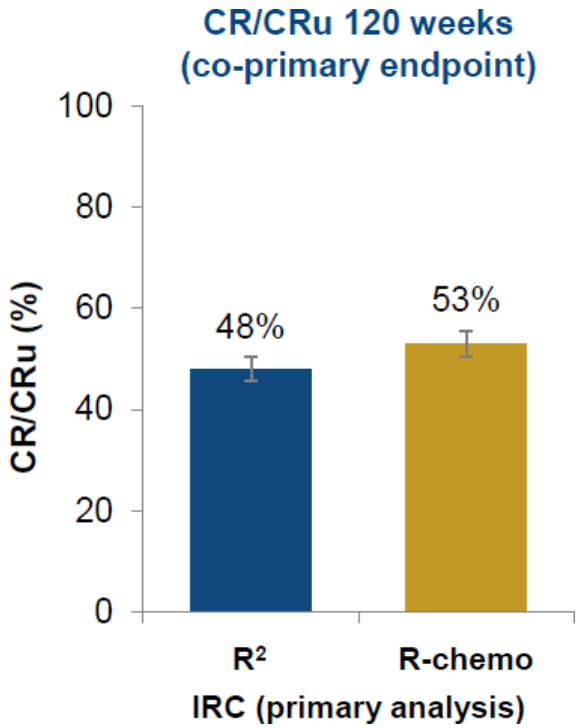
RELEVANCE: Dosing Schedule

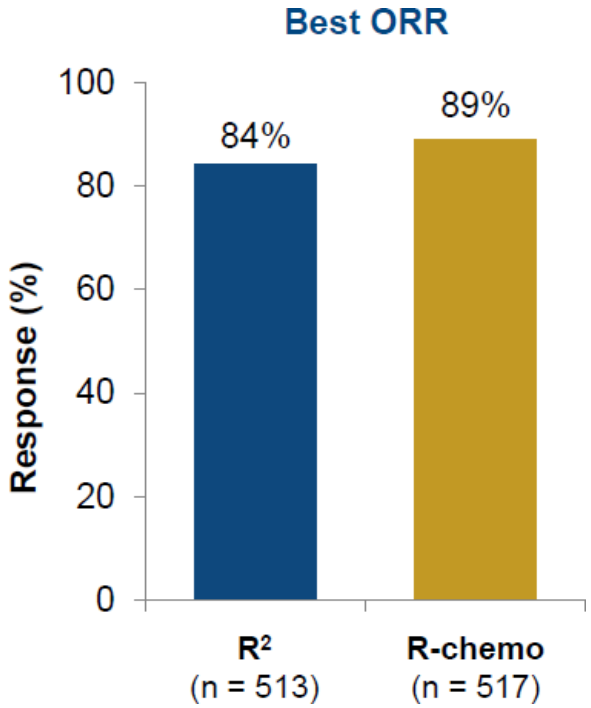
Treatment Period	R^2 Arm	R-Chemo Arm
1 (~6 months)	• Lenalidomide: 20 mg/d, d2-22/28 • Rituximab: 375 mg/m^2	Investigator/patient choice prior to randomization • R-CHOP (72%) • R-B (23%) • R-CVP (5%)
2 (~1 year)	• Lenalidomide: 20 or 10 mg/d per response at 6, 9, or 12 cycles • Rituximab: 375 mg/m^2	• Rituximab: 375 mg/m^2
3 (~1 year)	• Rituximab: 375 mg/m^2	• Rituximab: 375 mg/m^2

- **R^2:** Lenalidomide 20 mg/d, d2-22/28 until CR/CRu at 6, 9, or 12 cycles, then 10 mg/d (total 18 cycles); rituximab (R) 375 mg/m^2/wk cycle 1 and d1 cycles 2-6; continued in responders q8wk for 12 cycles
- **R-CHOP:** Q21d for 6 cycles: R 375 mg/m^2 IV d1, cyclophosphamide 750 mg/m^2 d1, doxorubicin 50 mg/m^2 IV d1, vincristine 1.4 mg/m^2 IV d1, prednisone 100 mg/d PO d1-5. Then R 375 mg/m^2 IV d1 q21d for 2 cycles
- **B. :** Q28d for 6 cycles: R 375 mg/m^2 IV d1, bendamustine 90 mg/m^2 IV d1-2
- **C.VP:** Q21d for 8 cycles: R 375 mg/m^2 IV d1, cyclophosphamide 750 mg/m^2 IV d1, vincristine 1.4 mg/m^2 IV d1, prednisone 40 mg/d PO d1-5
- **R maintenance:** In responders, R 375 mg/m^2 IV d1 of each cycle q8wk

F Morschhauser, et al NEJM 2018

R² vs R-Chemo as Initial Therapy: Similar Efficacy





→ 3-year DoR: 77% for R² versus 74% for R-chemo
Investigator results were consistent with IRC

IRC = independent review committee

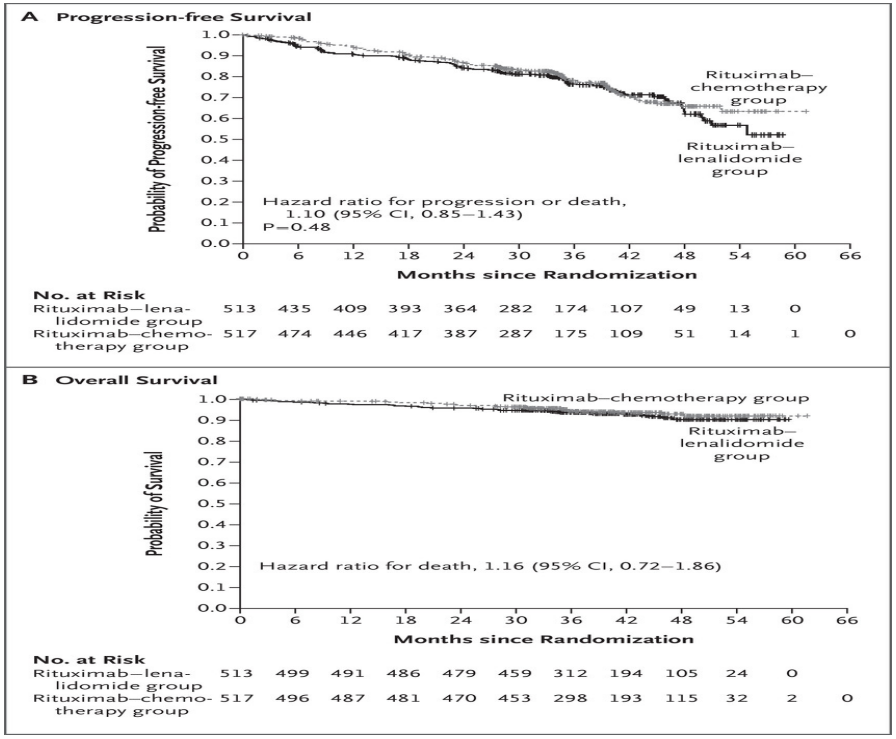
F Morschhauser, et al NEJM 2018

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

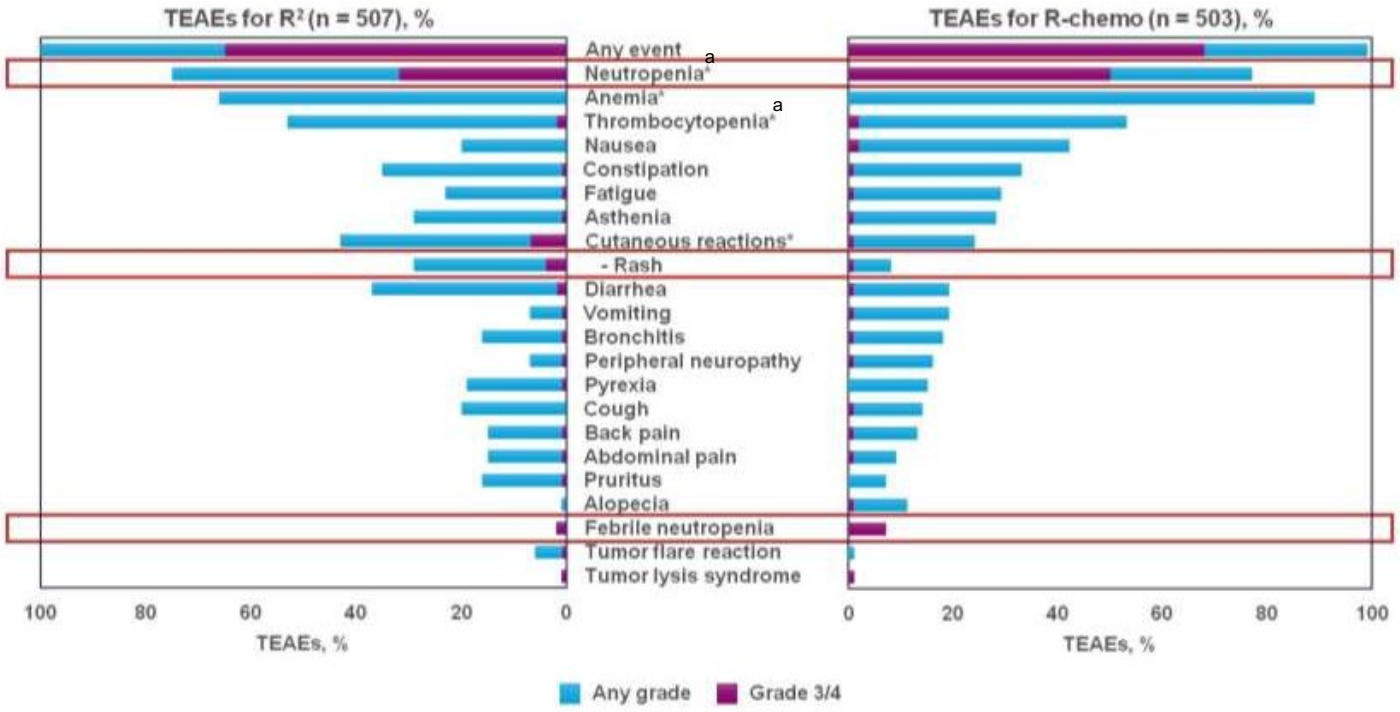
Rituximab plus Lenalidomide in Advanced Untreated Follicular Lymphoma

F. Morschhauser, N.H. Fowler, P. Feugier, R. Bouabdallah, H. Tilly, M.L. Palomba, C. Fruchart, E.N. Libby, R.-O. Casasnovas, I.W. Flinn, C. Haioun, H. Maisonneuve, L. Ysebaert, N.L. Bartlett, K. Bouabdallah, P. Brice, V. Ribrag, N. Daguindau, S. Le Gouill, G.M. Pica, A. Martin Garcia-Sancho, A. López-Guillermo, J.-F. Larouche, K. Ando, M. Gomes da Silva, M. André, P. Zachée, L.H. Sehn, K. Tobinai, G. Cartron, D. Liu, J. Wang, L. Xerri, and G.A. Salles, for the RELEVANCE Trial Investigators*



F Morschhauser, et al NEJM 2018

RELEVANCE:
Treatment-Emergent Adverse Events



[a]Hematologic adverse events were based on laboratory tests; all anemia events were grade 1. Cutaneous reactions included preferred terms From the system organ classes of skin and subcutaneous tissues disorders (including rash), gastrointestinal disorders, and general disorders, along with administration site conditions, infections/infestations, and reproductive system and breast disorder.
TEAEs = treatment-emergent adverse events.

Fowler et al, ASCO 2018.

RELEVANCE:

Neutropenia and Related Complications

(Entire Treatment Period)

Patients, n (%)	R² (n=507)	R-Chemo (n=503)
Grade 3/4 neutropenia[a]	160 (32)	252 (50)
Grade 4 neutropenia	41 (8)	154 (31)
Nadir ANC <100/μL	5 (1)	32 (6)
Median time to onset of first grade 3/4 lab	3.7 months	0.6 months
Grade 3/4 infections associated with grade 3/4 neutropenia	10 (2)	20 (4)
Febrile neutropenia[a]	11 (2)	34 (7)
Febrile neutropenia requiring hospitalization	8 (2)	26 (5)
Infections requiring hospitalization	46 (9)	60 (12)
Received growth factors	117 (23)	340 (68)

→ Per protocol, patients in the R² arm had more frequent laboratory assessments than those in the R-chemo arm

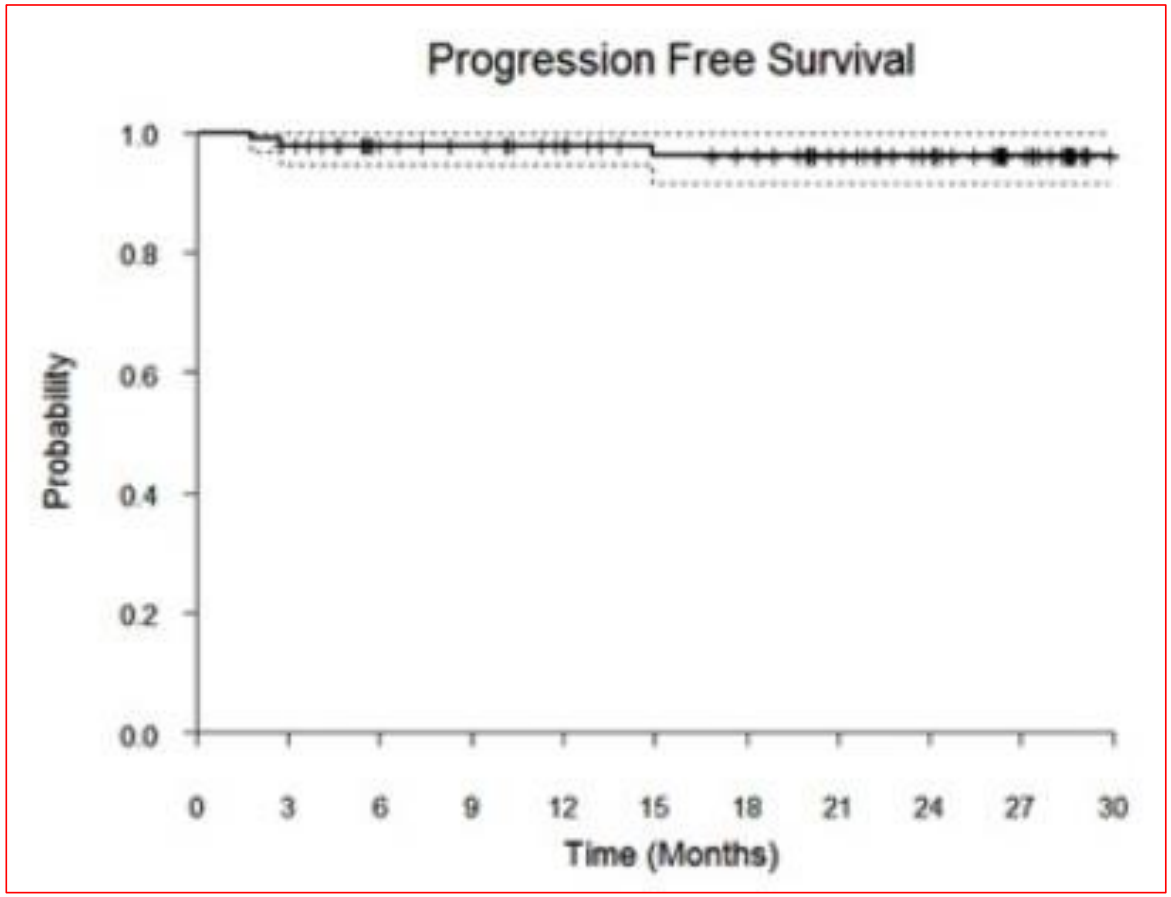
[a]Including 4 cases of febrile bone marrow aplasia (all in R-chemo arm).
ANC = absolute neutrophil count.
Fowler et al, 2018.

Obinotuzumab plus lenalidomide in untreated, high tumor burden FL: Study design

- A Phase II study enrolled patients with previously untreated, stage II, III, or IV, high tumor burden FL (grade 1, 2 or 3A).
- Patients received Obinotuzumab (O) on Days (D) 1, 8, and 15 of cycle 1, D1 of cycles 2-6, and D1 of even numbered cycles, cycle 8-30, and len (20 mg) on D1-21 of cycles 1-6.
- Patients with a CR after 6 cycles received a reduced dose of len (10 mg on D1-21) for cycles 7-18.
- Patients with a PR after 6 cycles continued to receive len at 20 mg for 3-6 cycles, or until CR; len was then reduced to 10 mg on D1-21 for the remainder of 18 cycles.
- The primary endpoint was PFS at 2 years (according to Lugano 2014 criteria).
- Secondary endpoints included: safety, CR, PR, ORR, and overall survival (OS).

Nastoupil L, et al. ASH 2019

Obinotuzumab plus lenalidomide in untreated, high tumor burden FL



- O-len was associated with 92% CR rates and 2-year PFS estimates in 90 previously untreated, high tumor burden FL.
- The toxicity profile of G-len was manageable in this patient population.

O-len may be an effective regimen for the treatment of previously untreated, high tumor burden FL.

Nastoupil L, et al. ASH 2019

Conclusion
Follicular Lymphoma first line

- A chemotherapy-free initial approach in follicular Lymphoma with low tumor burden is associated with an OS comparable with that found in other studies of first- line chemoimmunotherapy[1].
- Adverse effects are few for both the short and the long term[1]
- A substantial proportion of patients do not need chemotherapy even after a long follow-up time [1]
- A chemotherapy-free initial approach in follicular Lymphoma with high tumor burden is associated with a PFS and OS comparable with that found with first- line chemoimmunotherapy with a higher incidence of grade 3 or 4 neutropenia and febrile neutropenia of any grade with Rituximab plus chemotherapy and a higher incidence of grade 3 or 4 cutaneous reactions with Rituximab plus lenalidomide[2] , follow-up is still short
- Obinotuzumab-lenalidomide is actually the most promising chemo-free combination for the treatment of previously untreated, high tumor burden FL[3]

1)S.Lockmer JCO 2018
2)F. Morschhauser NEJM 2018
3) *Nastoupil L, et al. ASH 2019*

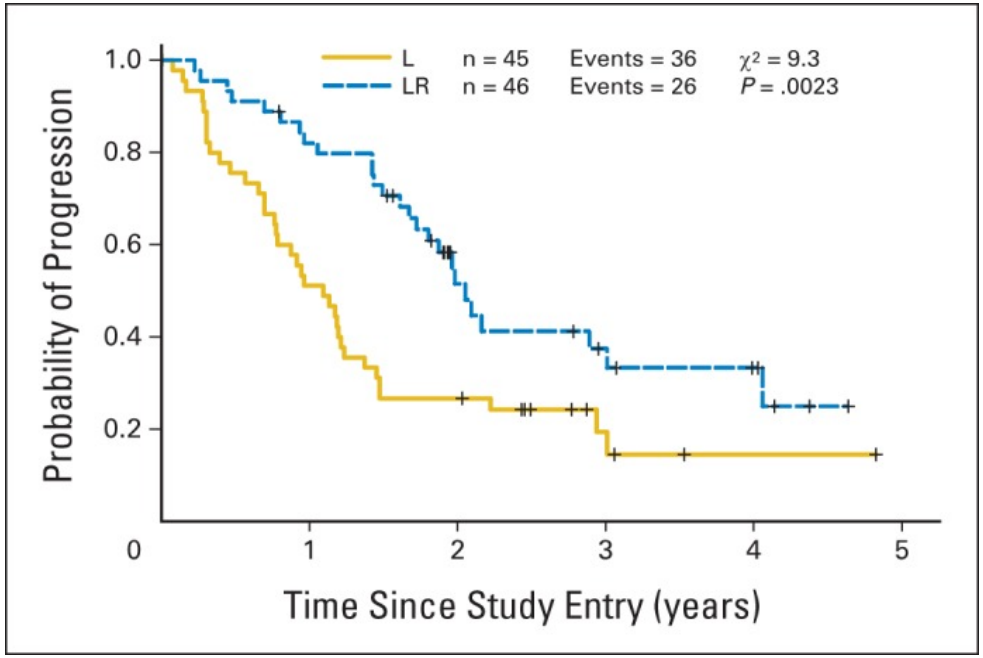
VOLUME 33 · NUMBER 31 · NOVEMBER 1 2015

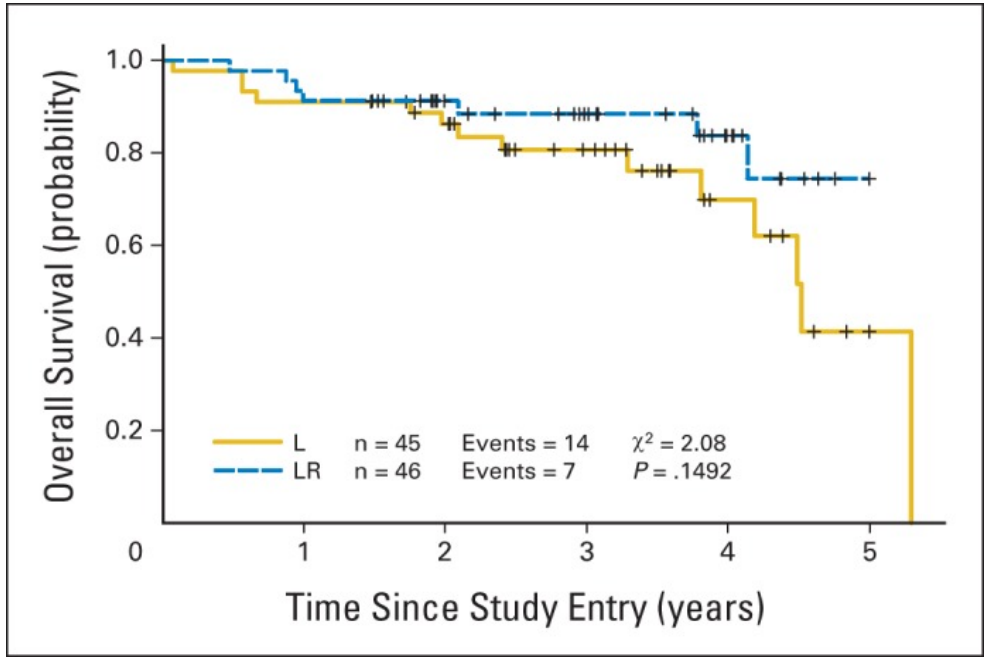
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

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

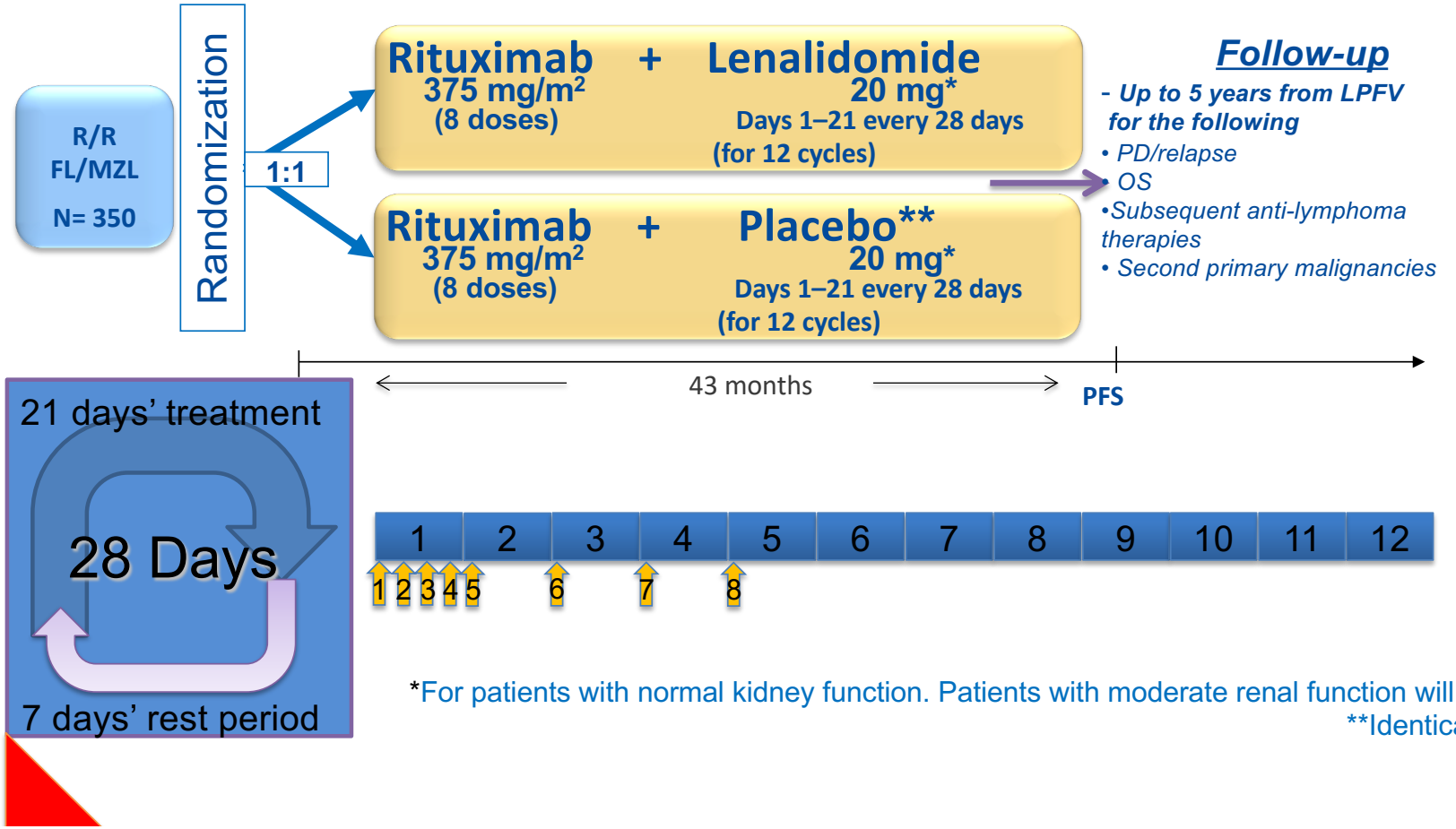
John P. Leonard, Sin-Ho Jung, Jeffrey Johnson, Brandelyn N. Pitcher, Nancy L. Bartlett, Kristie A. Blum, Myron Czuczman, Jeffrey K. Giguere, and Bruce D. Cheson





AUGMENT: Study Design

Objective is to compare the safety and efficacy of rituximab plus lenalidomide to rituximab plus placebo in subjects with relapsed/refractory indolent lymphoma

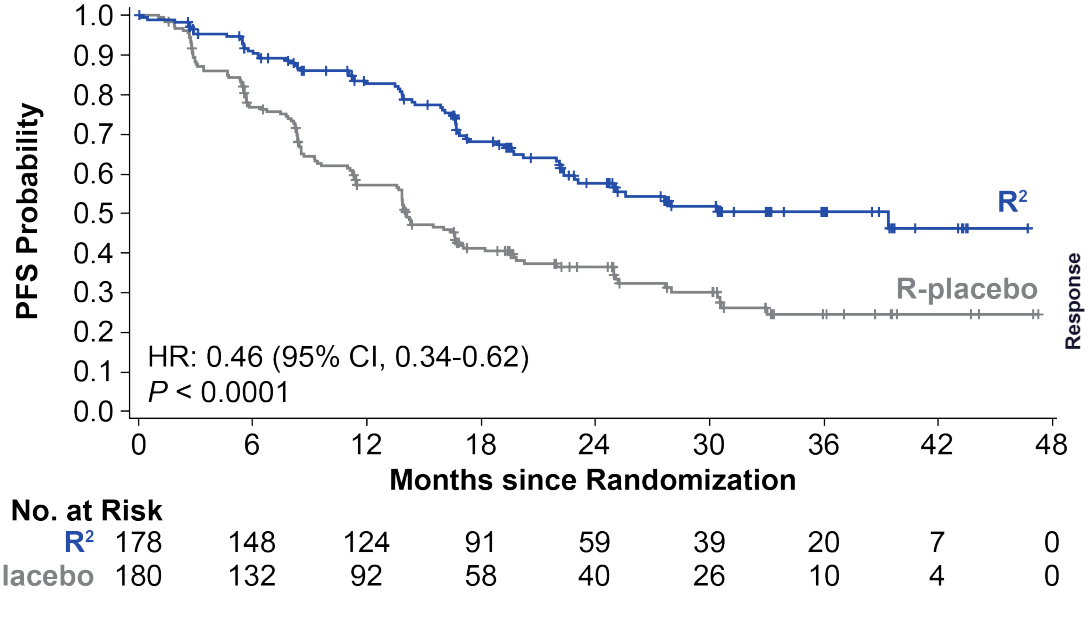


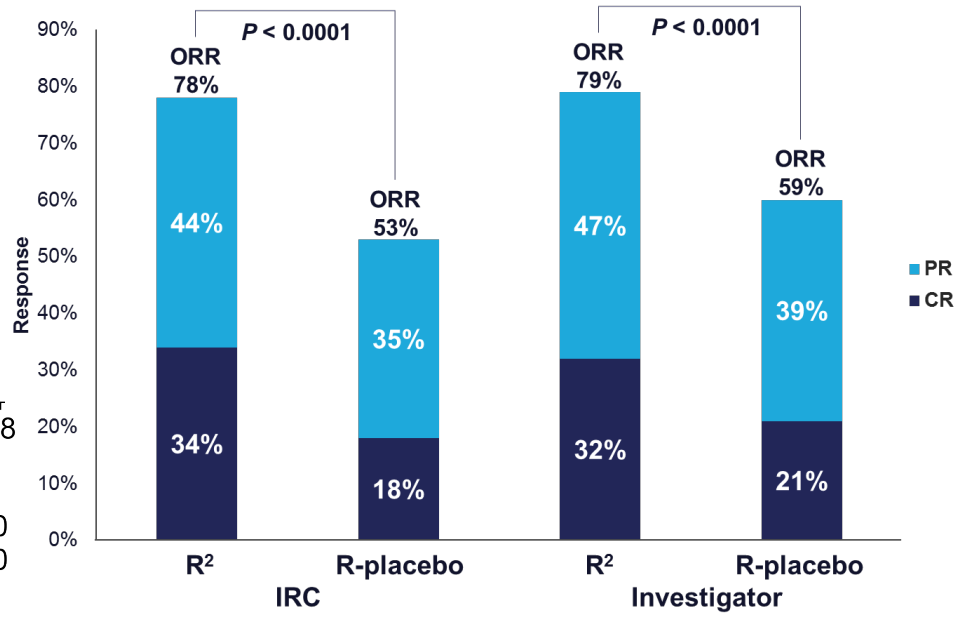
*For patients with normal kidney function. Patients with moderate renal function will start at 10 mg

**Identically matched capsule

AUGMENT Primary Efficacy Results (ITT)

- At a median follow-up of 28.3 mo, the primary endpoint of superior PFS was met for R^2 over R-placebo (median PFS: 39.4 vs 14.1 mo, respectively; $P < 0.0001$)[1]
- ORR and CR were significantly improved for R^2 vs R-placebo

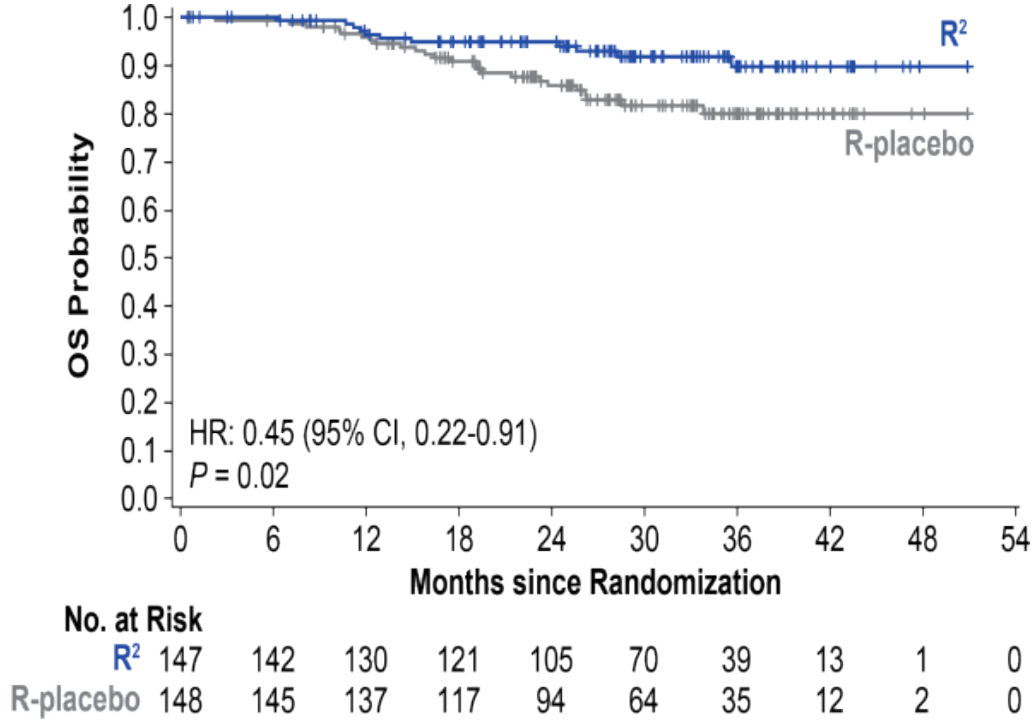




1. Leonard et al. *J Clin Oncol.* 2019

AUGMENT

Overall Survival in Patients With FL (Prespecified Subgroup Analysis)



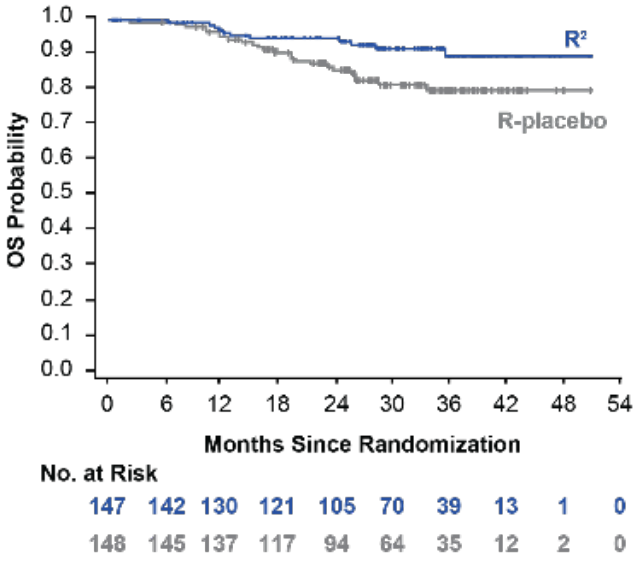
- 35 total deaths (R^2 = 11, R- placebo = 24)
- 2-year OS for R^2 = 95%
- 2-year OS for R-placebo =86%

Median follow-up: 28.3 months

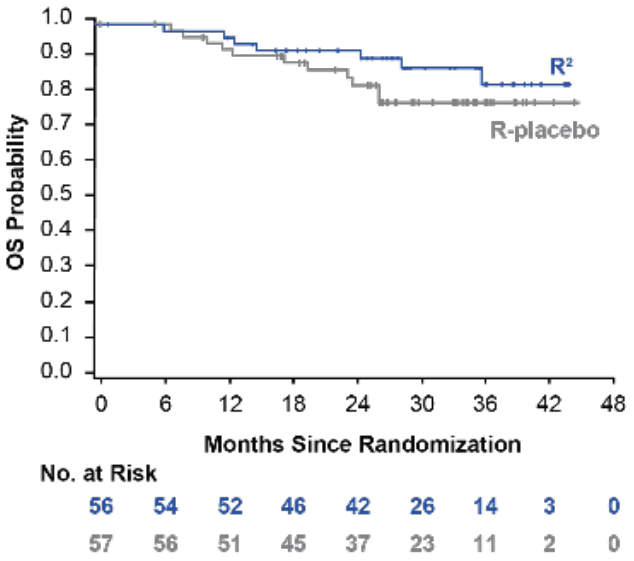
J.P. Leonard J of Clin Onc 2019

AUGMENT POD24 ANALYSES: OS for All FL Patients and by POD24 Status

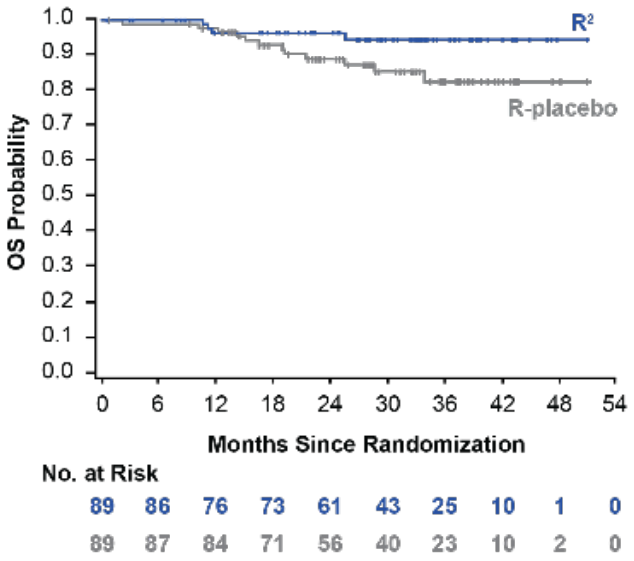
All FL Patients (*P* = 0.02)



POD24 Patients



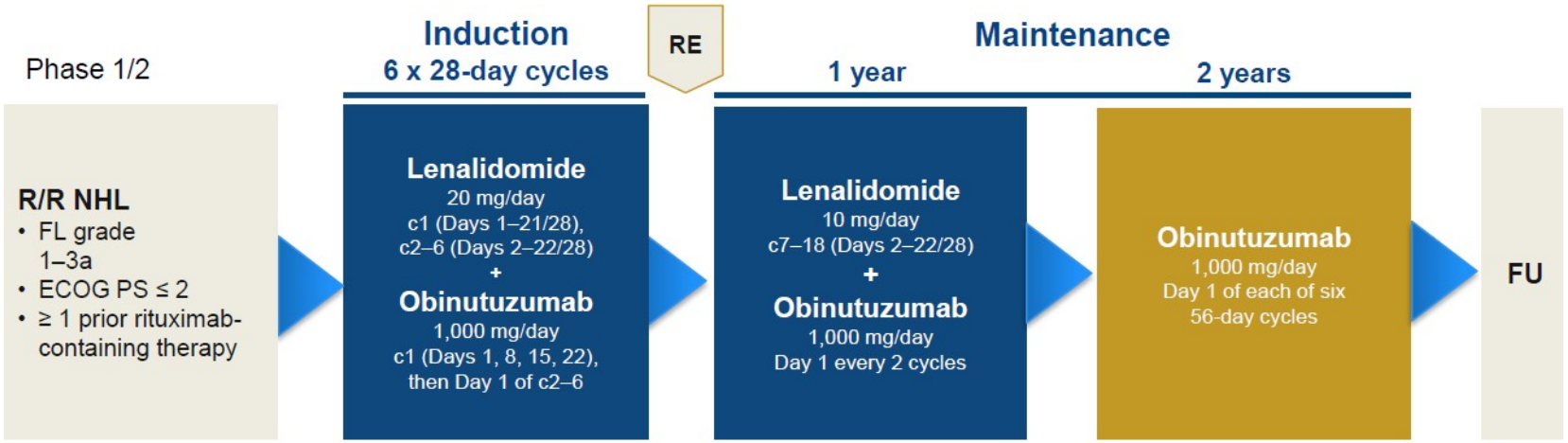
No POD24 Patients



- At a median follow-up time of 28.6 mo (range, 0.5-50.9), median OS was not reached in all patients or according to POD24 status

J.P. Leonard J of Clin Onc 2019

GALEN: Obinutuzumab/Lenalidomide in R/R FL



- **Primary endpoint:** ORR at end of induction by IWG criteria (Cheson 1999)
- **Secondary endpoints:** response rates according to Cheson 2007, PFS, RD, OS, safety (AEs, SPM)
- **Exploratory:** response and outcome according to POD24 vs POD > 24 mo, refractory status (no response or PD within 6 months of last rituximab-containing regimen), number of prior regimens, bulk

RE = response evaluation; FU = follow-up; AE = adverse event; RD = response duration; SPM = second primary malignancies; POD = progression of disease.

Morschhauser et al, Lancet Haematol 2019.

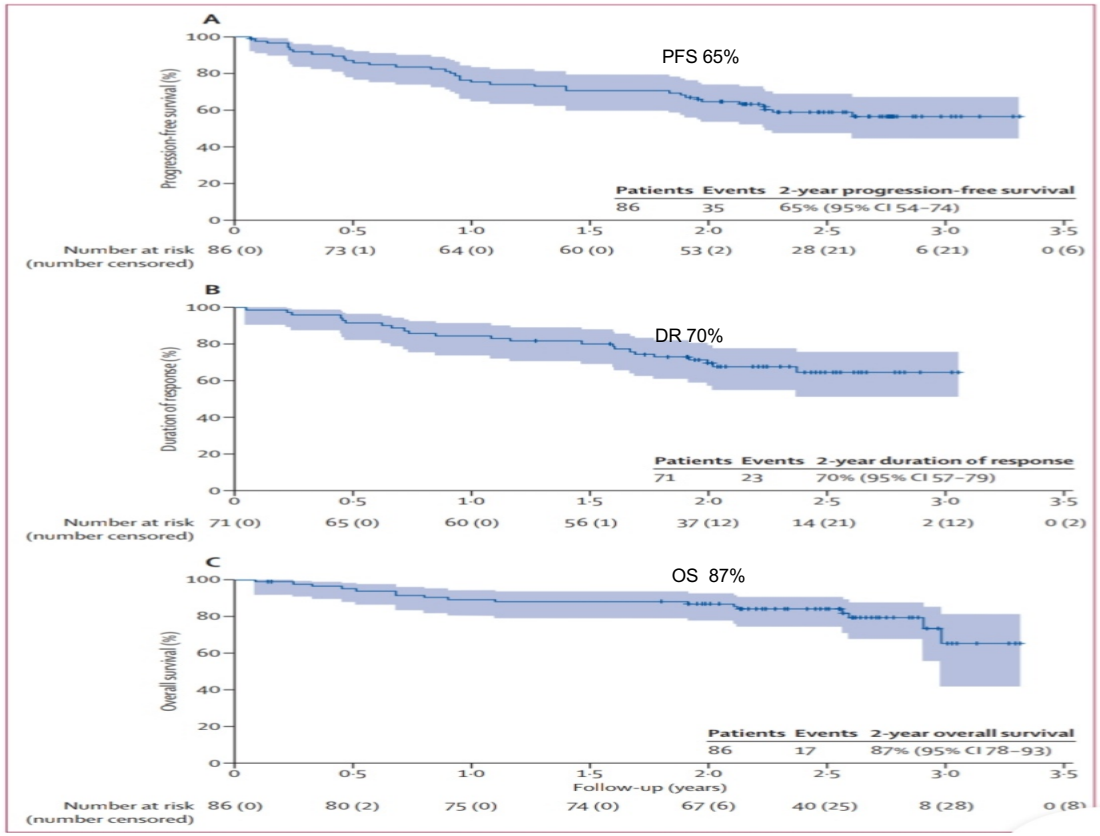
GALEN: Response

Response rates at the end of induction

Response evaluation		All patients (N = 86)	Early relapse patients[a] (n = 24)	Refractory patients (n = 23)
IWG 1999	**ORR, %** (95% CI)	**80.2** (70.2–88.0)	**70.8** (48.9–87.4)	**60.9** (38.5–80.3)
	CR/CRu, % (95% CI)	**39.5** (29.1–50.6)	**33.3** (15.6–55.3)	**34.8** (16.4–57.3)
IWG 2007	**ORR, %** (95% CI)	**74.4** (63.8–83.2)	**66.7** (44.7–84.4)	**56.5** (34.5–76.8)
	CR, % (95% CI)	**44.2** (33.5–55.3)	**54.2** (32.8–74.4)	**30.4** (13.2–52.9)

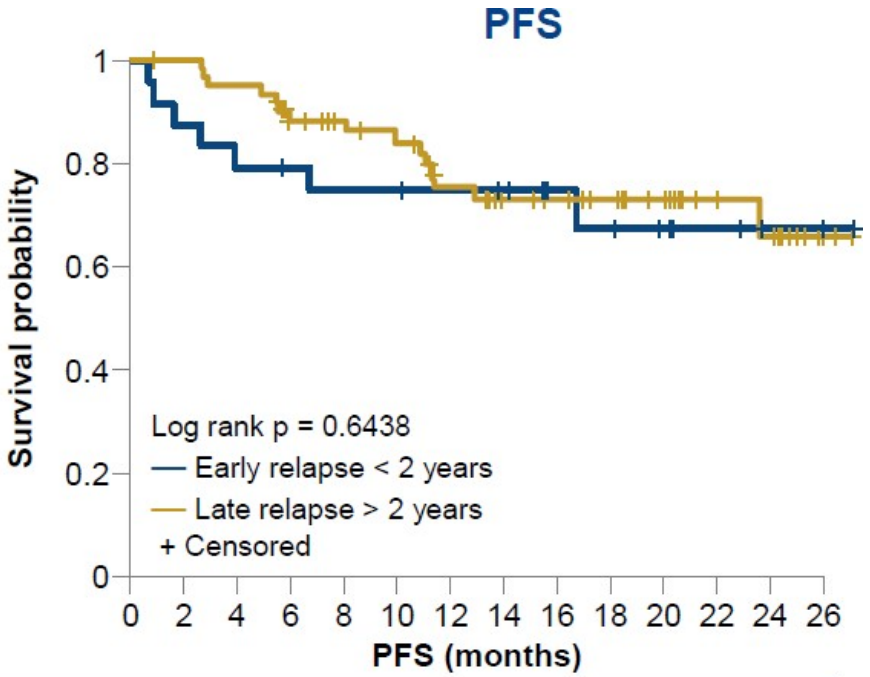
Morschhauser et al Lancet Haematol 2019.

Obinutuzumab combined with lenalidomide for relapsed or refractory follicular B-cell lymphoma (GALEN): a multicentre, single-arm, phase 2 study



F Morschhauser et al , Lancet Haematol 2019

GALEN: Progression-Free Survival



	POD24 (n = 24)	POD > 24 m (n = 62)	All patients (N = 86)
1 y PFS, % (95% CI)	74.8 (52.2–87.8)	75.3 (60.9–85.0)	75.5 (64.2–83.7)

Median follow-up: 18.1 month

Morschhauser et al Lancet Haematol 2019

GALEN: Toxicity

Non-haematological AEs	Any grade (%)	Grade ≥ 3 (%)
Infections	62.5	6.8
Asthenia	52.3	2.3
Constipation	30.7	0
Muscle spasms	30.7	0
Diarrhoea	25.0	0
Nausea	20.5	0
Cough	20.5	0

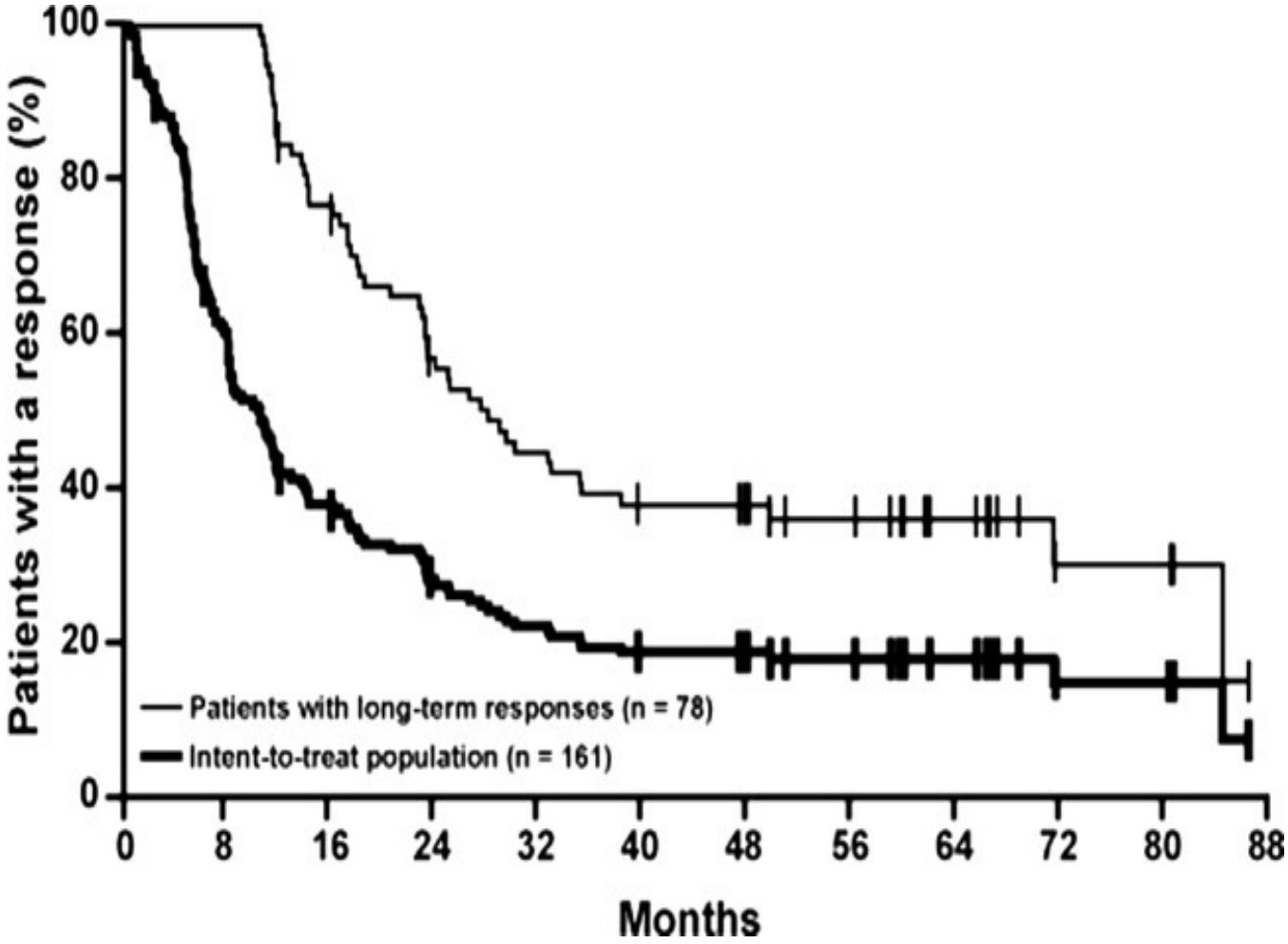
- Haematological AEs: neutropenia (grade ≥ 3 in 28.4% patients), thrombocytopenia (11.4% grade ≥ 3), anaemia, and lymphopenia
- Febrile neutropenia: 3.4%
- Infusion-related reaction: 14.8%

Morschhauser et al,Lancet Haematol 2019.

Long-Term Responses in Patients With Recurring or Refractory B-Cell Non-Hodgkin Lymphoma Treated With Yttrium 90 Ibritumomab Tiuxetan

Durations of Response in Patients With Long-Term Responses

	All histologies n = 78	Follicular lymphoma n = 59 ,
Duration of follow-up median (range)	49.8 m (12.7–88.9)	54.9 m (12.7–88.9)
Patients with CR/CRu	65%	64%
Duration of response, median (range)		
All patients	28.1 m (10.5–86.61)	29.4 m (10.5–86.61)
Patients with CR/CRu	29.4 m (10.8–86.61)	29.8 m (11.2–86.61)
Patients with ongoing responses*	62.0 m (48–871)	60.3 m (48–871)
Time to progression, median (range)		
All patients	29.3 m (12.1–87.81)	30.9 m (12.1–87.81)
Patients with CR/CRu	30.9 m (12.1–87.81)	31.1 m (12.1–87.81)



Thomas E. Witzige et sl, Cancer. 2007

Targeting PI3 Kinase in r/r Follicular Lymphoma

Trial	Drug	PI3K isoform	Disease	N	ORR	CR	DOR	PFS	Key Toxicities
Gopal et al	Idelalisib	delta	FL	72	57 %	6 %	12.5m	11m	Diarrhea Pneumonitis, LFT abnormalities
Dreylin et al	Copanlisib	Alpha delta	All FL MZL LPL	142 104 23 6	59 % 59 % 70 % 17%	12 %	22.6m	11.2m	Transiet Hyperglycemia And hypertension; less immune-mediated side effects
Finn et al	Duvelisib	Gamma delta	All FL MZL	129 83 18	47,3 % 42,2 % 38,8%	1.6 %	10m	9.5m	Diarrhea; cough; neutropenia; fewer LFT abnormalities

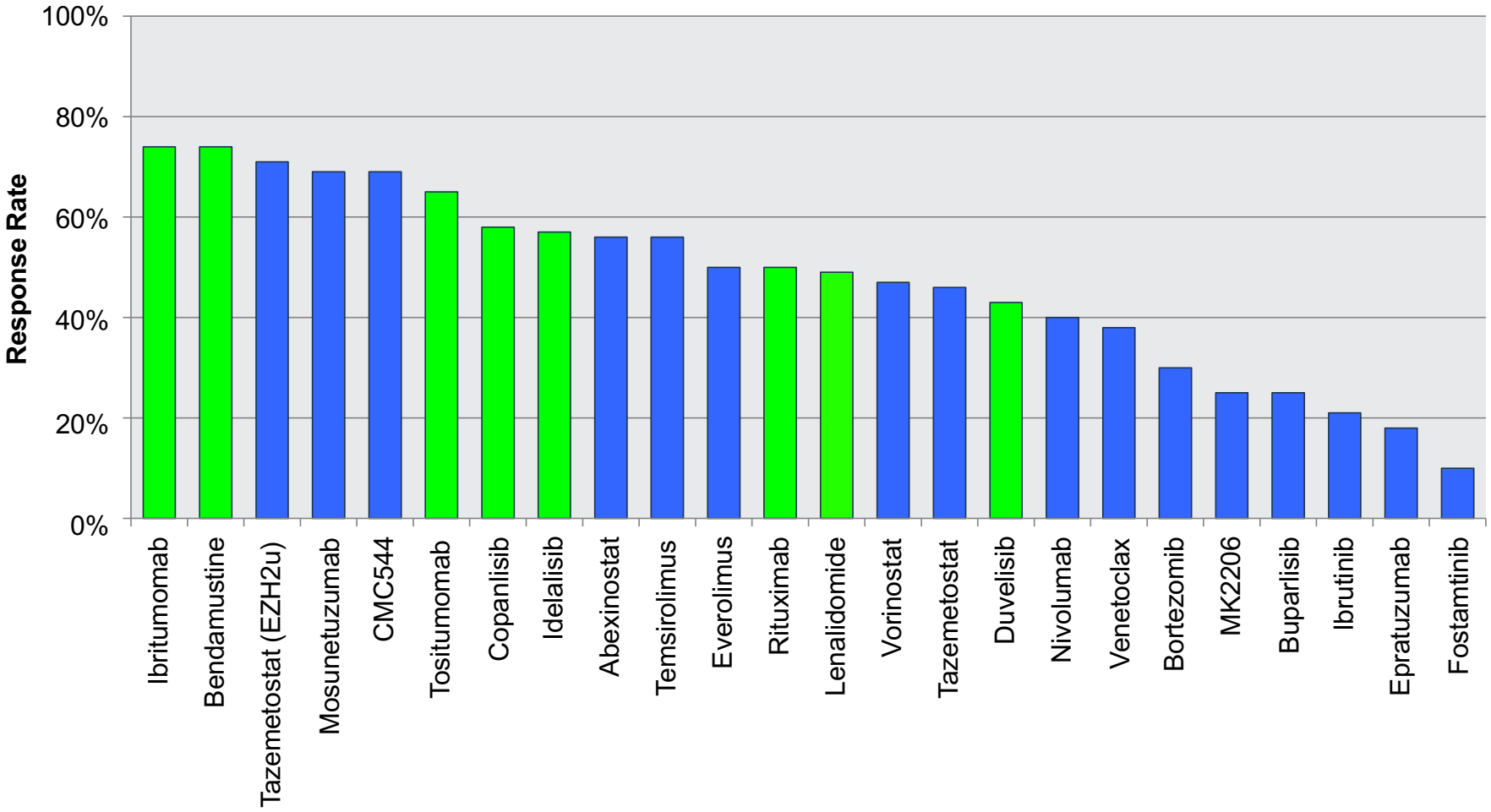
Gopal AK et al. NEJM 2014;370:1008
Dreyling M et al. JCO 2017;35:3898
Finn IW et al. JCO 2019;37:912

Novel Drugs in Follicular Lymphoma

Drug category	Drug name	Target	Mecanism of action	Stage of clinical developement	Reference numbers
Anti CD20	Ofatumumab Obinutuzumab	CD20	ADCC/CDC	Phase 2-3 Phase 2-3	7,8 11,12,13
Other cell surface-directed mAb	Epratuzumab Lumiliximab Inotuzumab Galiximab Polatuzumab Blinatumumab	CD22 CD23 CD80 CD79b CD19/CD3	ADCC/CDC Engages CD3 T-cell killing of CD19 B-cell tumor cells	Phase 1 Phase 1 Phase 1 Phase 1 Phase 1 Phase 1	14-15 14 16 17 18 47
Drugs targeting oncogeneic pathways	Idelalisib Duvelisib TGR1202 Copanlisib	PI3Kδ PI3Kγ-δ PI3Kδ PI3Kα-δ	BCR pathway inhibition	Phase 2 Phase 2-3 Phase 1 Phase 2	22 26 24
	Ibrutinib	BTK	BCR pathway inhibition	Phase 1/1b	29
	ABT263 ABT199	BCL2	Reversing inhibition of apoptosis	Phase 1 Phase 1	31 32
	Vorinostat Temsirolimus Everolimus	mTOR	Histone deacetylase inhibition	Phase 2 Phase 2-3 Phase 1,3	34 33 35
Immunomodulatory drugs (IMiD)	Lenalidomide		Modulation of the lymphoma microenvironment Enhanced anti-lymphoma immune response	Phase 2-3	38-41
	Nivolumab Pidilizumab Epratuzumab	PD1 PD1 PDL1	Inhibition of T-cell response blunting	Phase 1 Phase 2 Phase 1	45 46
Chimeric antigen receptor (CAR)-modified T cells	CAR-T cell	Anti-CD19	Chimeric antigen receptor (CAR)-modified T cells	Phase 1	49-51

Anastasia A.et al. Mediterr J Hematol Infect Dis 2016

Single-Agent Activity on Relapsed Follicular Lymphoma



Younes, 2019.

Conclusions

In the modern era, the median OS of FL is approaching 20 years but FL remain an incurable disease .
With less toxic and more precise tratment it is likely that more patients will enjoy long- term disease control

Treatment options of newly diagnosed advanced-stage FL include multiple immunochemotherapy regimens +/- anti-CD20 maintenance but Lenalidomide/rituximab , chemotherapy-free regimen is as effective as standard immunochemotherapy regimens in advanced stage FL and is actually the most promising chemo-free combination in follicular lymphoma

Drugs approved for relapsed/refractory FL by FDA include three PI3K inhibitors and lenalidomide plus rituximab and we hope to have them all soon available

A pletora of new targeted drugs have shown activity in FL and more are in earlier stages of development but will be soon widely available to make an **chemo-free approach feasible .**

These new therapies present different safety profile from that of the classical Immunochemotherapy regimens and the follow-up is still short especially in the front-line setting


Grazie per l’attenzione

Idelalisib Monotherapy: Adverse Events

Adverse Event	Any Grade n (%)	Grade ≥3 n (%)
Diarrhea	54 (43)	16 (13)
Nausea	37 (30)	2 (2)
Fatigue	37 (30)	2 (2)
Cough	36 (29)	0
Pyrexia	35 (28)	2 (2)
Decreased appetite	22 (18)	1 (1)
Dyspnea	22 (18)	4 (3)
Abdominal pain	20 (16)	3 (2)
Vomiting	19 (15)	3 (2)

Adverse Event	Any Grade n (%)	Grade ≥3 n (%)
Upper respiratory tract infection	18 (14)	0
Decreased weight	17 (14)	0
Rash	16 (13)	2 (2)
Asthenia	14 (11)	3 (2)
Night sweats	14 (11)	0
Pneumonia	14 (11)	9 (7)
Peripheral edema	13 (10)	3 (2)
Headache	13 (10)	1 (1)

Gopal et al NEJ M , 2014.

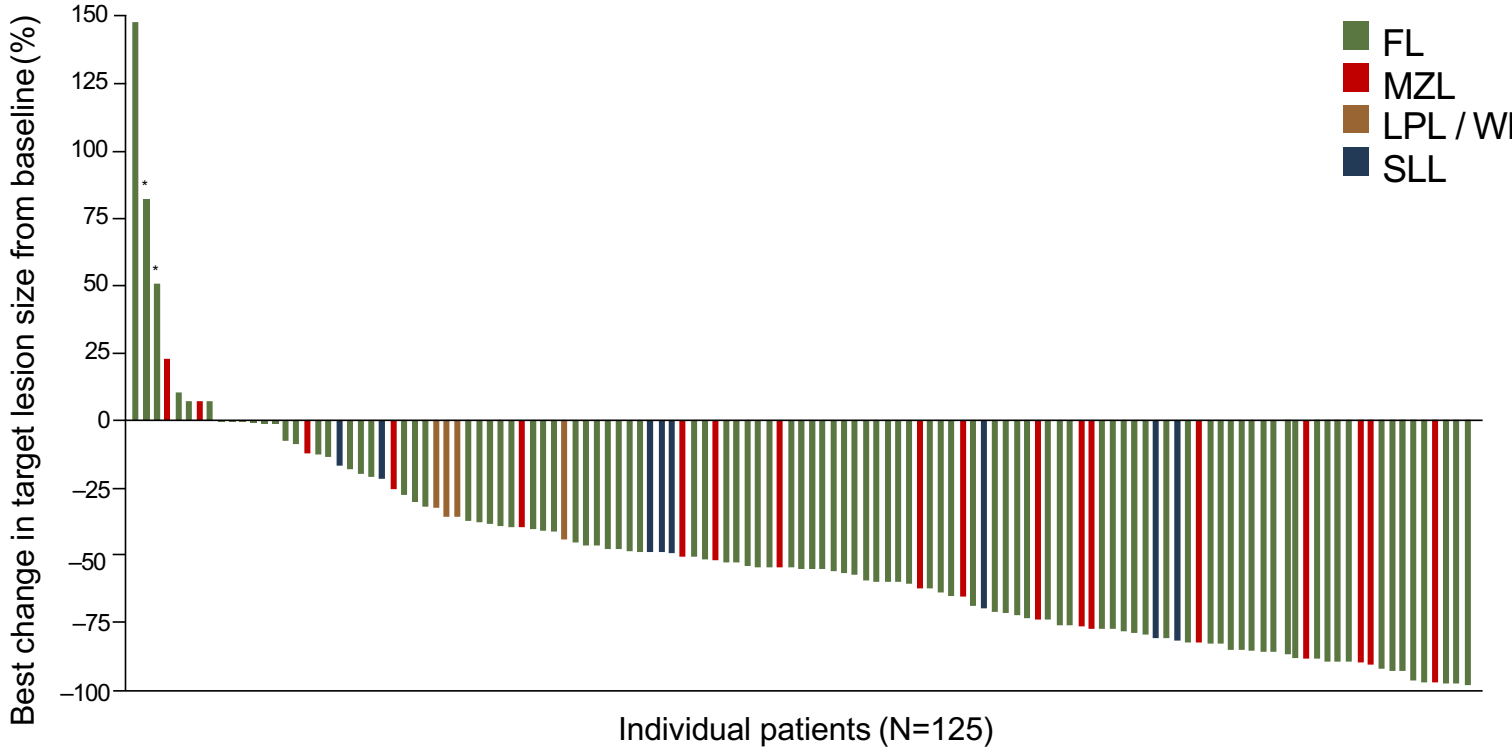
CHRONOS-1: Trial Design

- Patients with indolent B-cell NHL (N=142)
  - FL (104 Pts), MZL, SLL, WM
  - Relapsed/refractory to ≥2 prior lines of treatment
    - Rituximab plus an alkylating agent/regimen
- Copanlisib 60 mg via 1-hour IV on days 1, 8, and 15 on a 28-day cycle
  - Until progression or unacceptable toxicity
- Primary end point: ORR after ≥4 cycles
  - Secondary end points: DOR, PFS, OS

Dreyling et al, JCO 2017.

CHRONOS-1

Copanlisib for Relapsed/Refractory Indolent B-Cell Lymphoma



59% ORR

12 % RC

Median TR days 53

Median duration of response 22.ms

Median PFS 11 ms

Median OS not yet reached

Dreyling et al, JCO 2017.

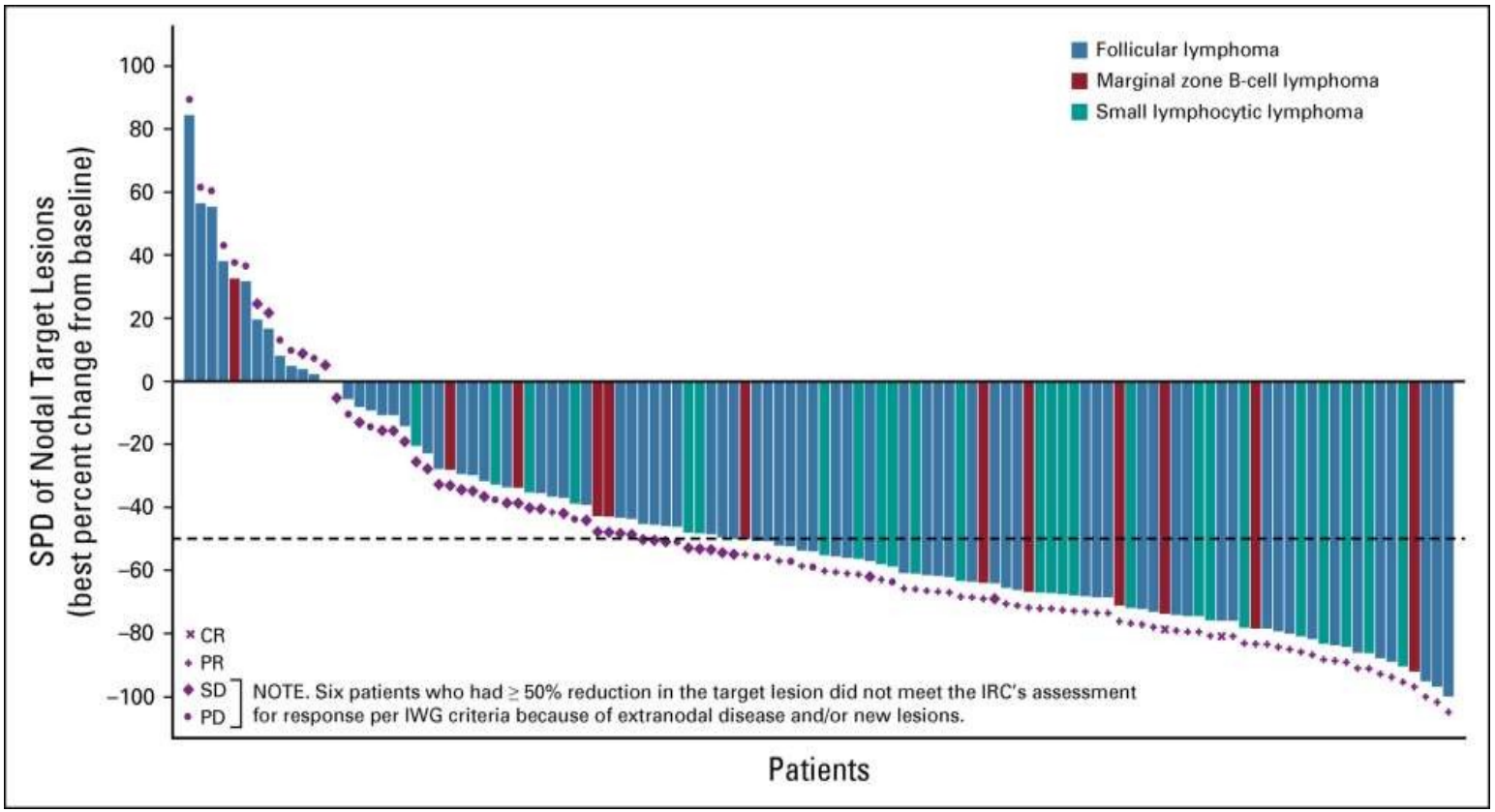
CHRONOS-1: Copanlisib Safety

Most Common TRAEs	All Grades	Grade 3	Grade 4
Transient hyperglycemia	50.0%	33.1%	7.0%
Transient hypertension	29.6%	23.9%	-
Neutropenia	28.9%	9.2%	14.8%
Diarrhea	35.2%	8.5%	-
Pneumonitis	6.3%	1.4%	-

→ TRAEs led to dose reductions in 25.4% and interruptions in 50.7%

Dreyling et al, JCO 2017.

DYNAMO: Duvelisib (IPI-145) for Refractory iNHL



42% ORR

1.6 % RC

Median TR days ?

Median duration of response 10 ms

Median PFS 9.5 ms

Flinn et al, JCO 2019.

DYNAMO: Adverse Events

Adverse Event	Any Grade n (%)	Grade ≥3 n (%)
Diarrhea	63 (48.8)	19 (14.7)
Nausea	38 (29.5)	2 (1.6)
Neutropenia	37 (28.7)	32 (24.8)
Fatigue	36 (27.9)	6 (4.7)
Cough	35 (27.1)	0
Anemia	34 (26.4)	19 (14.7)
Pyrexia	32 (24.8)	0
Rash	24 (18.6)	6 (4.7)
Thrombocytopenia	24 (18.6)	15 (11.6)
Vomiting	24 (18.6)	5 (3.9)
Decreased appetite	19 (14.7)	1 (0.8)
Headache	20 (15.5)	0
Peripheral edema	22 (17.1)	3 (2.3)

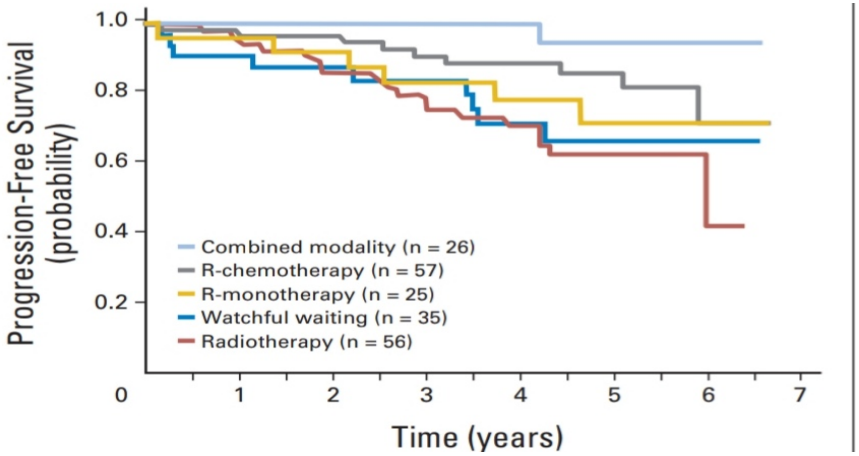
Adverse Event	Any Grade n (%)	Grade ≥3 n (%)
ALT increased	18 (14.0)	7 (5.4)
Back pain	17 (13.2)	1 (0.8)
Arthralgia	19 (14.7)	0
Abdominal pain	19 (14.7)	2 (1.6)
Hypokalemia	17 (13.2)	4 (3.1)
Constipation	15 (11.6)	0
Asthenia	15 (11.6)	3 (2.3)
AST increased	13 (10.1)	4 (3.1)
Night sweats	13 (10.1)	0
Febrile neutropenia	12 (9.3)	12 (9.3)
Lipase increased	12 (9.3)	9 (7.0)
Pneumonia	10 (7.8)	7 (5.4)
Colitis	10 (7.8)	7 (5.4)

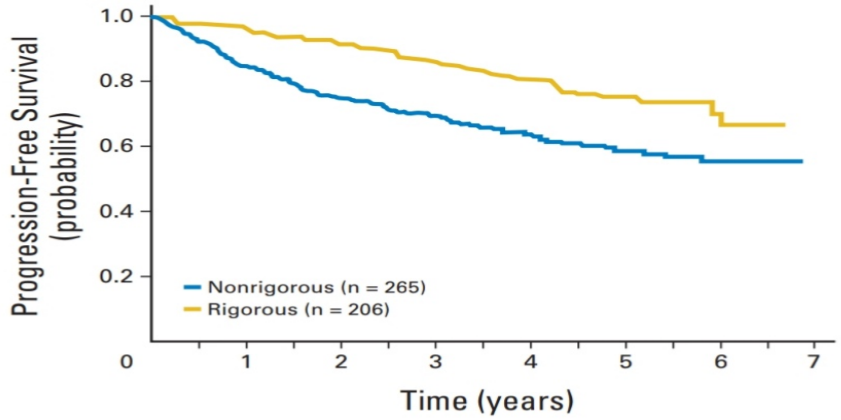
Flinn et al, JCO 2019.

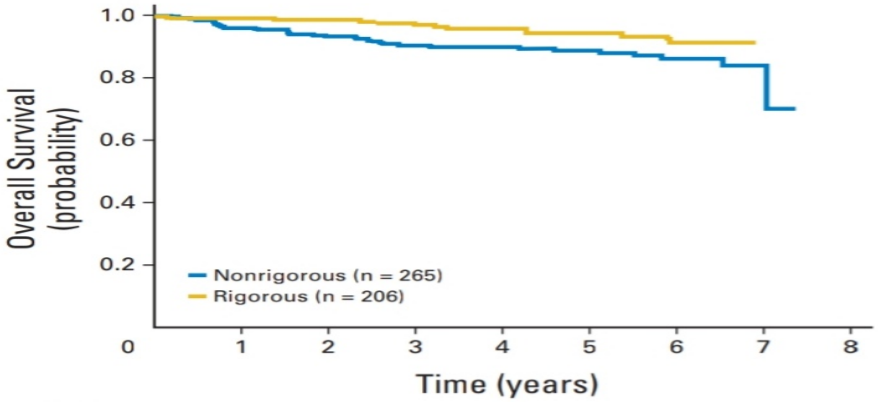
VOLUME 30 · NUMBER 27 · SEPTEMBER 20 2012
JOURNAL OF CLINICAL ONCOLOGY
ORIGINAL REPORT

Effectiveness of First-Line Management Strategies for Stage I Follicular Lymphoma: Analysis of the National LymphoCare Study

Jonathan W. Friedberg, Michelle Byrtek, Brian K. Link, Christopher Flowers, Michael Taylor, John Hainsworth, James R. Cerhan, Andrew D. Zelenetz, Janie Hirata, and Thomas P. Miller







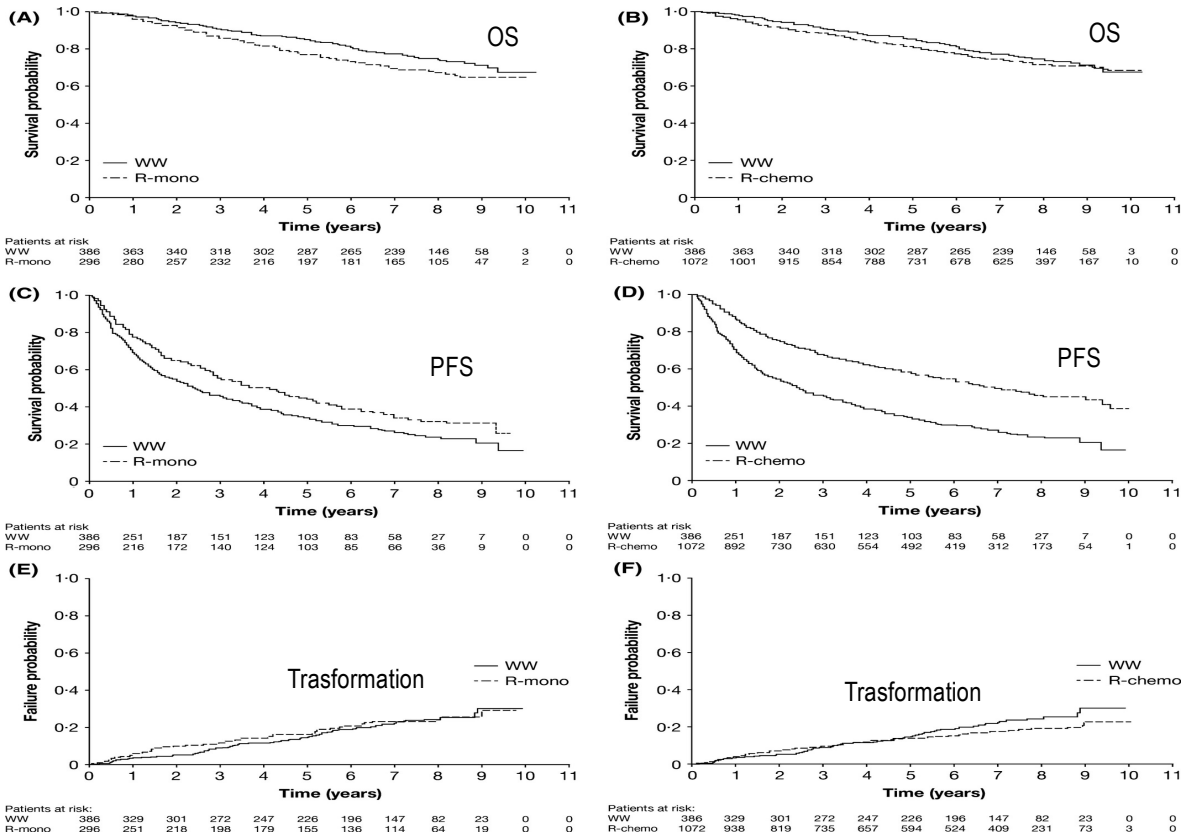
No. at risk

Nonrigorous	265	259	248	236	226	217	202	194	185	160	128	105	75	44	1	0
Rigorous	206	204	202	196	187	178	172	165	141	105	68	34	9	0		

bjh research paper

Outcomes following watchful waiting for stage II–IV follicular lymphoma patients in the modern era

Nastoupil LJ1, Sinha R2, Byrtek M3, Ziemiecki R4, Zhou X4, Taylor M3, Friedberg JW5, Link BK6, Cerhan JR7, Dawson K3, Flowers CR8.



Br J Haematol. 2016

NHL Treatment: Relapsed/Refractory FL

Second-line and later therapy

- Chemoimmunotherapy as listed under first-line therapy (not previously used)
- Rituximab
- Lenalidomide ±
- rituximab Ibritumomab
- tiuxetan PI3K inhibitors
  - Idelalisib (R/R after 2 prior therapies)
  - Copanlisib (R/R after 2 prior therapies)
  - Duvelisib (R/R after 2 prior therapies)
- Second-line therapy options typically used for aggressive B-cell NHL/DLBCL without regard to transplant eligibility

Consolidation or extended dosing (optional)

- Rituximab maintenance
- Obinutuzumab maintenance (rituximab refractory)
- HDT plus autologous SCT
- Allogeneic SCT for selected patients

R/R = relapsed/refractory; HDT = high-dose therapy; SCT = stem cell transplantation.
NCCN, 2019.

Terapie *chemofree* ≠ *toxicity free*

I LINEA

Farmaci	PFS	ORR	TOX extraematologica ≥3	TOX ematologica ≥3
R-Lenalidomide[1]	77% 3aa	61%	-	Neutropenia 32%
Ibrutinib[2]	92% 18mesi	100%	FA 7%; Ipertensione arteriosa 13%	Neutropenia 7%

II LINEA

Farmaci	PFS	ORR	TOX extraematologica ≥3	TOX ematologica ≥3
R-Lenalidomide[3]	39.4 mesi	79%	-	Neutropenia 50%
Ibrutinib[4]	69% 2aa	91%	FA 5%; Sanguinamento 3%	Neutropenia 22% Trombocitopenia 14%
Idelalisib[5]	11 mesi	57%	Diarrea 13%; ALT elev. 13%	Neutropenia 27%
Copanlisib[6]	11 mesi	59%	Iperglicemia 41%; Ipertensione 24%	Neutropenia 24%
Duvelisib[7]	9.5 mesi	42%	Polmoniti 16%; Diarrea 15%	Neutropenia 25%; Anemia 15% Trombocitopenia 12%

1 Relevance NEJM 2018; 3 Treon et al JCO 2018; 3 Augment JCO 2019; 4 Treon et al NEJM 2015; 5 Gopal et al NEJM 2014;

6 Dreyling et al JCO 2017; 7 Dynamo JCO 2019