VISITING PROFESSORS: Selection and Sequencing of Systemic Therapy in the Management of Follicular Lymphoma

An Interactive Grand Rounds Series

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Disclosures

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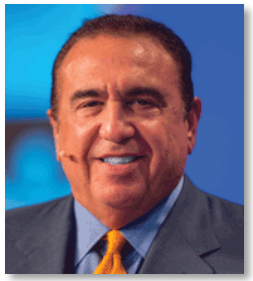

Project Chair
Neil Love, MD
Research To Practice
Miami, Florida

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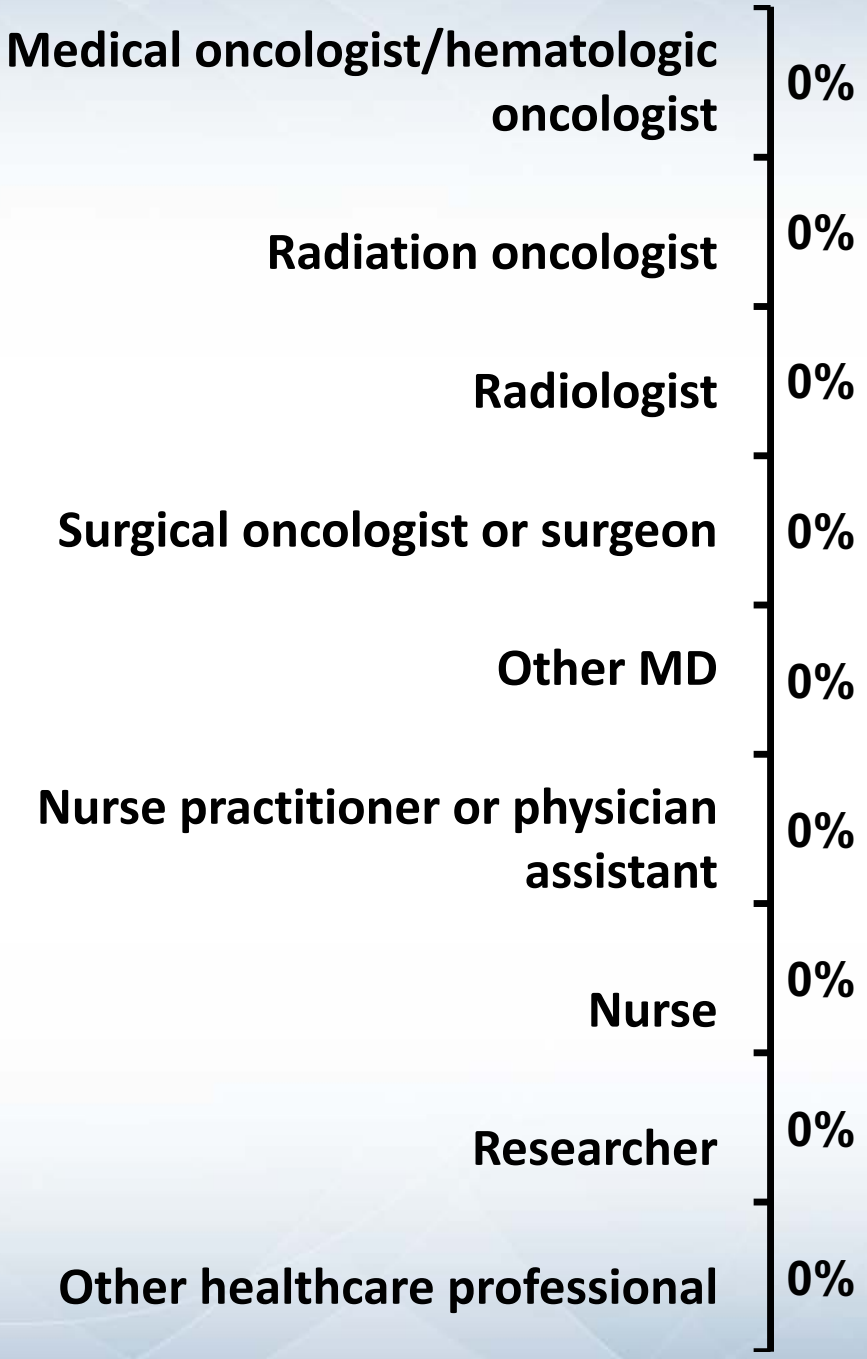
Which of the following best represents your clinical background?

1. Medical oncologist/hematologic oncologist
2. Radiation oncologist
3. Radiologist
4. Surgical oncologist or surgeon
5. Other MD
6. Nurse practitioner or physician assistant
7. Nurse
8. Researcher
9. Other healthcare professional



Selection and Sequencing of Systemic Therapy in the Management of Follicular Lymphoma (FL)

Module 1: Optimizing the Care of Patients with Newly Diagnosed FL

- Initiation of active therapy versus watchful waiting; indications for rituximab monotherapy
- Choice of systemic therapy for patients requiring treatment; impact of age, tumor bulk and symptomatology
- Clinical research data evaluating maintenance therapy; factors influencing its use
- Data for and clinical role of subcutaneous rituximab

Module 2: Management of Relapsed/Refractory (R/R) FL

- Factors affecting the sequencing of systemic therapy for R/R disease (eg, previous treatment received, remission duration, symptomatology)
- Integration of obinutuzumab in the R/R setting
- Role of lenalidomide/rituximab in the management of R/R FL
- Available clinical research data with the FDA-approved PI3K inhibitors

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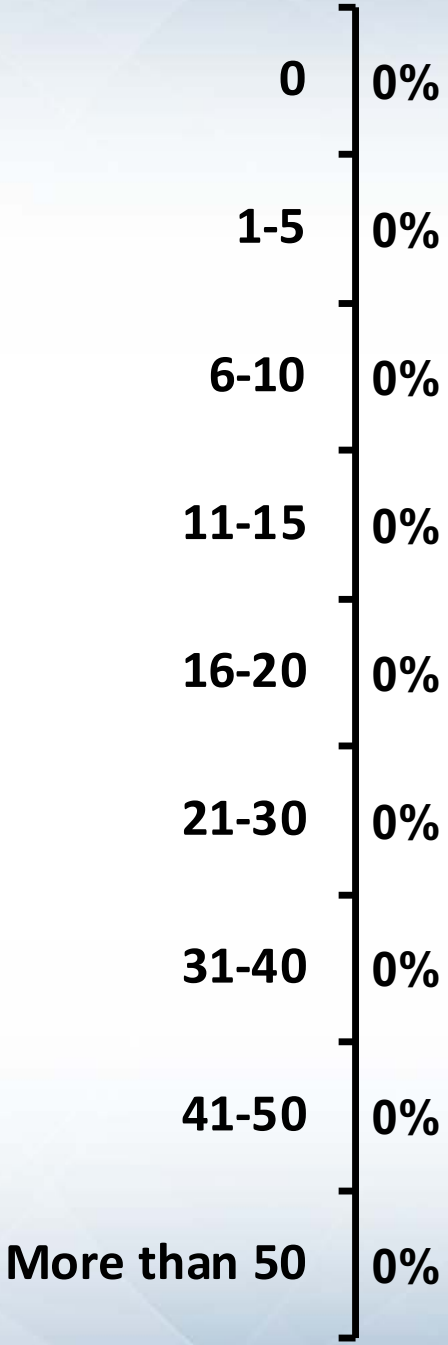
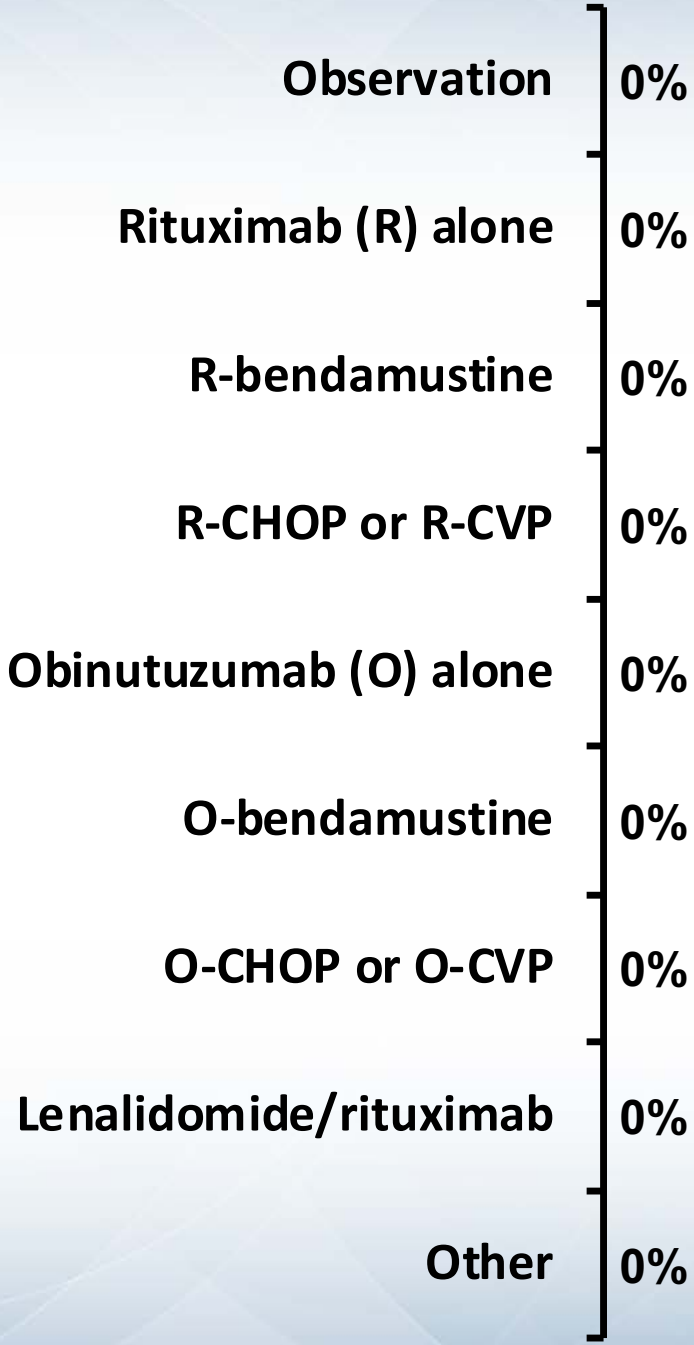
Approximately how many patients with follicular lymphoma are currently under your care?

1. 0
2. 1-5
3. 6-10
4. 11-15
5. 16-20
6. 21-30
7. 31-40
8. 41-50
9. More than 50



Regulatory and reimbursement issues aside, what would be your most likely initial treatment choice for a 60-year-old patient with newly diagnosed asymptomatic, low tumor-burden advanced-stage follicular lymphoma (FL)?

1. Observation
2. Rituximab (R) alone
3. R-bendamustine
4. R-CHOP or R-CVP
5. Obinutuzumab (O) alone
6. O-bendamustine
7. O-CHOP or O-CVP
8. Lenalidomide/rituximab
9. Other



Regulatory and reimbursement issues aside, what would be your most likely initial treatment choice, including maintenance, for a 60-year-old patient with newly diagnosed asymptomatic, low tumor-burden advanced-stage follicular lymphoma (FL)? What other options would you discuss with the patient?

	Treatment recommendation	Other options discussed
 BRUCE D CHESON, MD	Observation	None
 ANDREW M EVENS, DO, MSC	Observation	Rituximab alone
 CHRISTOPHER R FLOWERS, MD, MS	Observation	Rituximab alone
 NATHAN H FOWLER, MD	Observation	Rituximab alone
 ANN S LACASCE, MD, MMSC	Observation	Rituximab alone
 JOHN P LEONARD, MD	Observation	Rituximab alone; O-bendamustine; lenalidomide/rituximab; BR
 JULIE M VOSE, MD, MBA	Observation	Rituximab alone; BR
 ANDREW D ZELENETZ, MD, PHD	Observation	None

O = obinutuzumab; BR = bendamustine/rituximab

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In what clinical situations, if any, would you administer rituximab alone as up-front treatment for a patient with FL?

 BRUCE D CHESON, MD	Elderly, symptomatic, low to moderate tumor burden
 ANDREW M EVENS, DO, MSC	Low tumor burden and/or patient choice
 CHRISTOPHER R FLOWERS, MD, MS	Low tumor burden, symptomatic or asymptomatic who wants treatment
 NATHAN H FOWLER, MD	Patient not fit for or who does not want chemotherapy
 ANN S LACASCE, MD, MMSC	Nonbulky, asymptomatic progressive disease
 JOHN P LEONARD, MD	Low tumor burden, sufficient symptoms to prompt therapy
 JULIE M VOSE, MD, MBA	Elderly symptomatic patient with comorbidities
 ANDREW D ZELENETZ, MD, PHD	Elderly patient or patient refusing chemo; patient on observation w/ steady PD

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For a patient to whom you would administer rituximab alone as up-front treatment for FL, how long would you administer therapy?

 BRUCE D CHESON, MD	Weekly x 4
 ANDREW M EVENS, DO, MSC	Low tumor burden: Only induction; High tumor burden: Also as maintenance (x 2 y)
 CHRISTOPHER R FLOWERS, MD, MS	Weekly x 4
 NATHAN H FOWLER, MD	Weekly x 4
 ANN S LACASCE, MD, MMSC	Weekly x 4, repeat PET, if response then q2m x 4
 JOHN P LEONARD, MD	Weekly x 4
 JULIE M VOSE, MD, MBA	Weekly x 4 then q2m x 2 y
 ANDREW D ZELENETZ, MD, PHD	Weekly x 4

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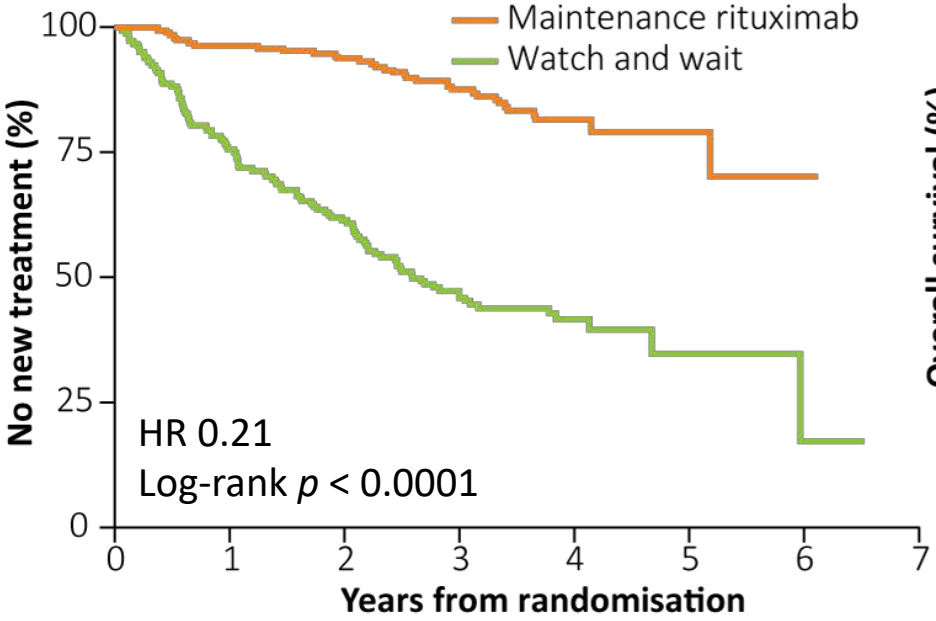
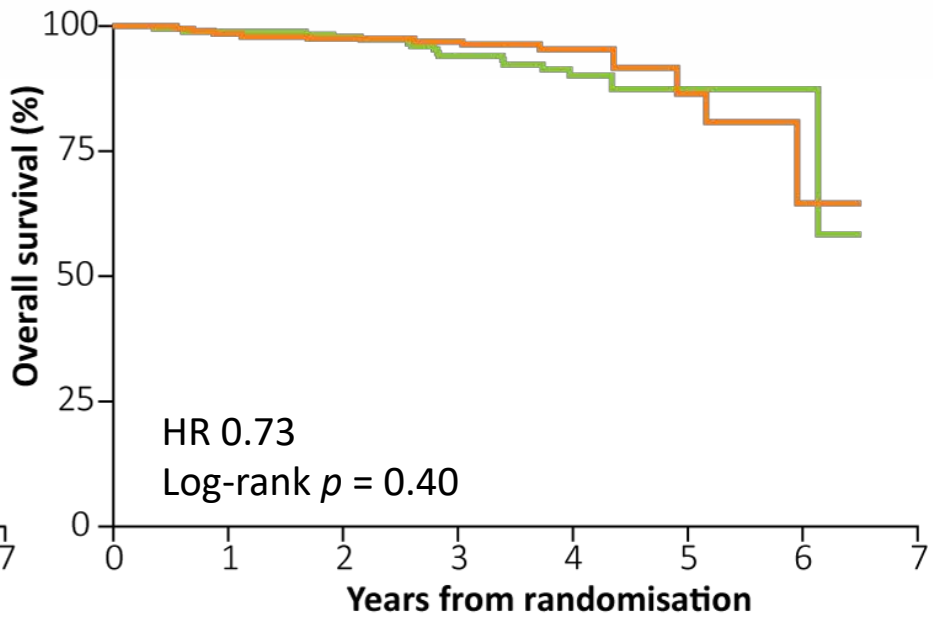
Rituximab Monotherapy Compared to Active Surveillance (Watch and Wait)

Time to start of new treatment



Overall survival



- Indication: Comorbidities not conducive to chemoimmunotherapy, low tumor burden and/or slowly progressing disease
- Schedule: Induction rituximab 375 mg/m^2 weekly for 4 weeks +/- maintenance rituximab q2m for 2 years

Ardeshna KM et al. *Lancet Oncol* 2014;15(4):424-35; NCCN Guidelines for B-Cell Lymphomas, v1.2019

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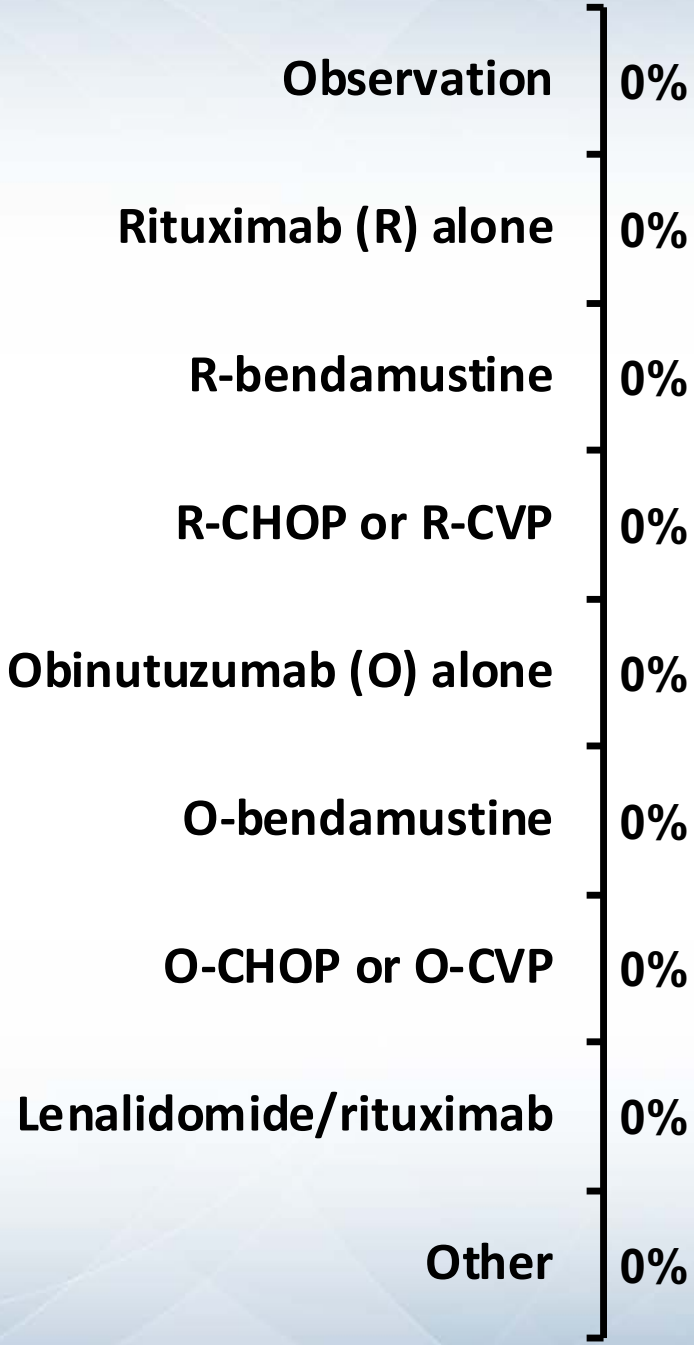
- Role of lenalidomide/rituximab in the management of R/R FL
- Available clinical research data with the FDA-approved PI3K inhibitors

Regulatory and reimbursement issues aside, what would be your most likely initial treatment choice for a 60-year-old patient with newly diagnosed symptomatic, high tumor-burden advanced-stage FL?

1. Observation
2. Rituximab (R) alone
3. R-bendamustine
4. R-CHOP or R-CVP
5. Obinutuzumab (O) alone
6. O-bendamustine
7. O-CHOP or O-CVP
8. Lenalidomide/rituximab
9. Other



Regulatory and reimbursement issues aside, what would be your most likely initial treatment choice, including maintenance, for a 60-year-old patient with newly diagnosed symptomatic, high tumor-burden advanced-stage FL? What other options would you discuss with the patient?

	Treatment recommendation	Other options discussed
 BRUCE D CHESON, MD	Lenalidomide/rituximab	BR
 ANDREW M EVENS, DO, MSC	O-bendamustine → O maintenance x 2 y	BR
 CHRISTOPHER R FLOWERS, MD, MS	BR → R maintenance x 2 y	O-bendamustine; O-CHOP; O-CVP; lenalidomide/rituximab
 NATHAN H FOWLER, MD	Lenalidomide/rituximab → R maintenance	BR
 ANN S LACASCE, MD, MMSC	BR → R maintenance x 2 y if PR	None
 JOHN P LEONARD, MD	BR	Lenalidomide/rituximab; R-CHOP; O-CHOP; O-bendamustine
 JULIE M VOSE, MD, MBA	BR → R maintenance x 2 y	R-CHOP; O-bendamustine
 ANDREW D ZELENETZ, MD, PHD	O-CVP → O maintenance x 2 y	R-CVP, R-CHOP; O-CHOP; lenalidomide/rituximab

BR = bendamustine/rituximab; O = obinutuzumab; R = rituximab

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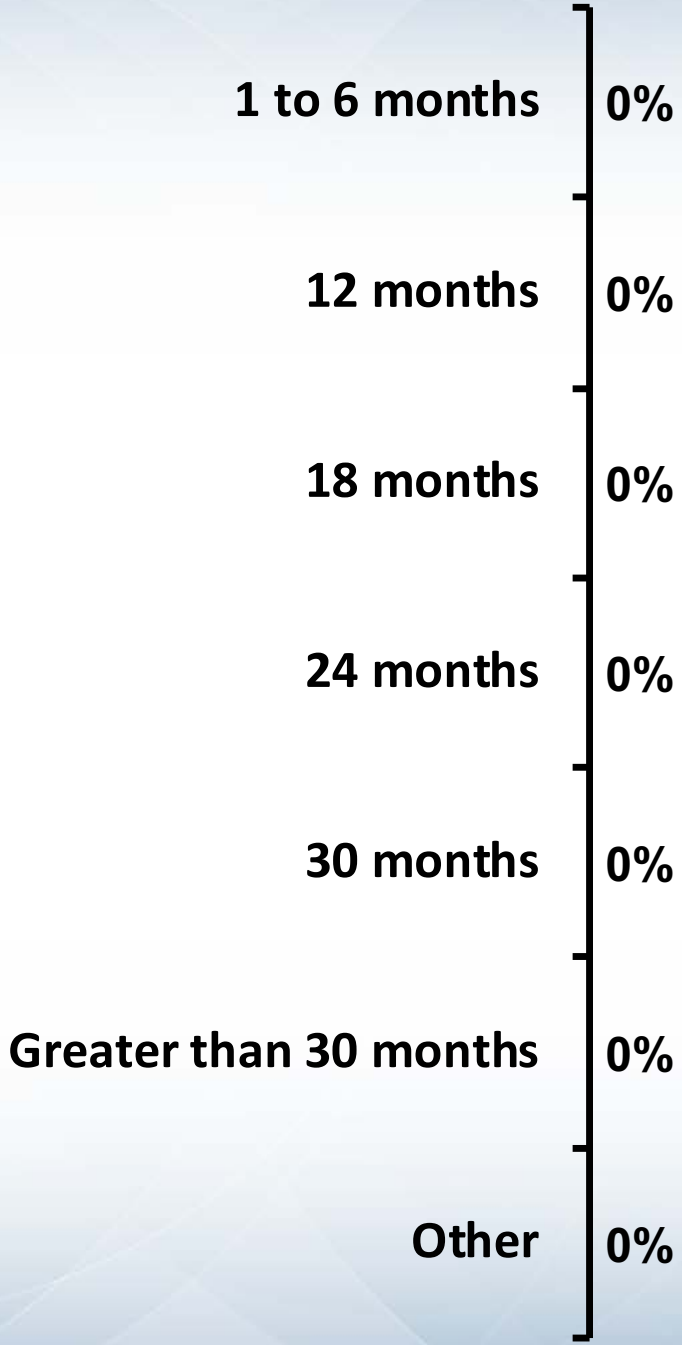
Regulatory and reimbursement issues aside, for a 60-year-old patient with newly diagnosed symptomatic, high tumor-burden advanced-stage FL, what would be the likely total duration of the treatment regimen (including maintenance therapy, if any) that you would generally recommend?

1. 1 to 6 months
2. 12 months
3. 18 months
4. 24 months
5. 30 months
6. Greater than 30 months
7. Other



Regulatory and reimbursement issues aside, for a 60-year-old patient with newly diagnosed symptomatic, high tumor-burden advanced-stage FL, what would be the likely total duration of the treatment regimen (including maintenance therapy, if any) that you would generally recommend?

 BRUCE D CHESON, MD	Len/ritux x 6 mo + len x 6 mo (no maintenance)
 ANDREW M EVENS, DO, MSC	O-bendamustine x 6 mo → O maintenance x 2 y
 CHRISTOPHER R FLOWERS, MD, MS	BR x 6 mo → R maintenance x 2 y
 NATHAN H FOWLER, MD	Len/ritux x 18 mo → R maintenance x 12 mo
 ANN S LACASCE, MD, MMSC	BR x 6 mo → R maintenance x 2 y if PR
 JOHN P LEONARD, MD	BR x 6 mo (no maintenance)
 JULIE M VOSE, MD, MBA	BR x 6 mo → R maintenance x 2 y
 ANDREW D ZELENETZ, MD, PHD	O-CVP x 6 mo → O maintenance x 2 y

Len/ritux = lenalidomide/rituximab; O = obinutuzumab; BR = bendamustine/rituximab

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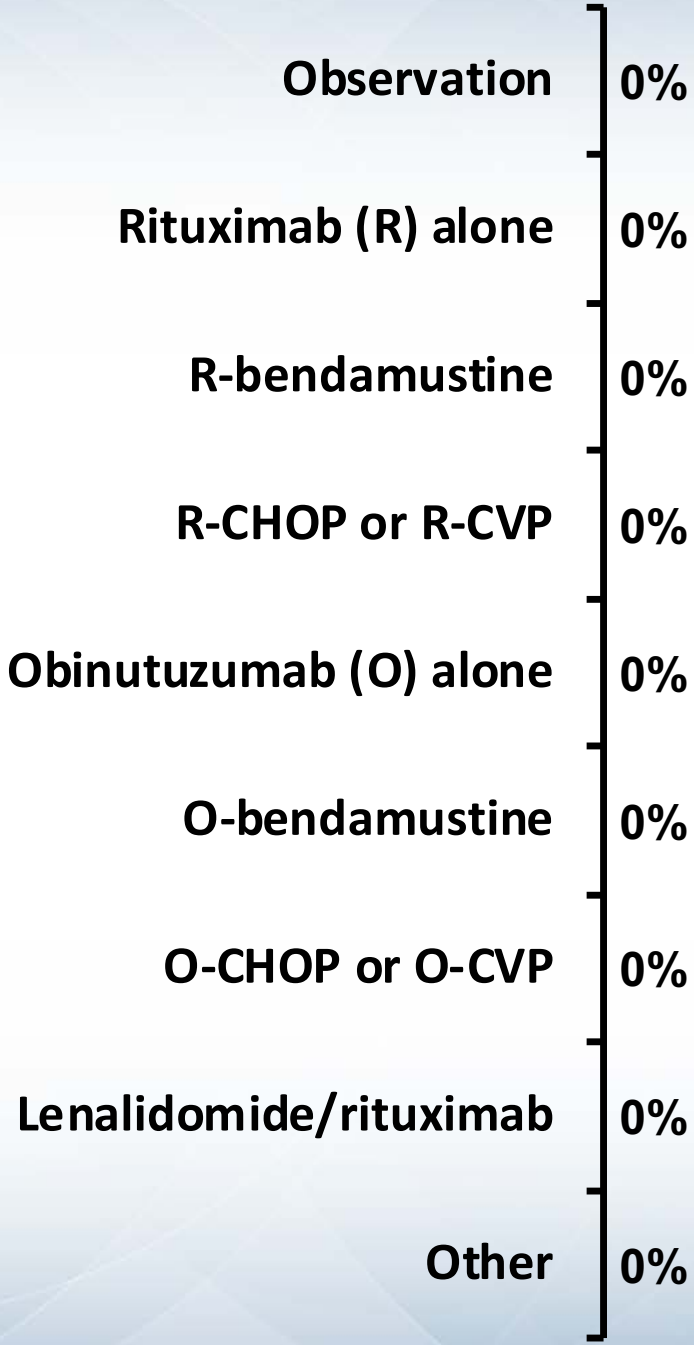
Regulatory and reimbursement issues aside, what would be your most likely initial treatment choice for an 80-year-old patient with newly diagnosed symptomatic, high tumor-burden advanced-stage FL?

1. Observation
2. Rituximab (R) alone
3. R-bendamustine
4. R-CHOP or R-CVP
5. Obinutuzumab (O) alone
6. O-bendamustine
7. O-CHOP or O-CVP
8. Lenalidomide/rituximab
9. Other



Regulatory and reimbursement issues aside, what would be your most likely initial treatment choice, including maintenance, for an 80-year-old patient with newly diagnosed symptomatic, high tumor-burden advanced-stage FL? What other options would you discuss with the patient?

	Treatment recommendation	Other options discussed
 BRUCE D CHESON, MD	Lenalidomide/rituximab	Rituximab alone; BR
 ANDREW M EVENS, DO, MSC	BR → R maintenance x 2 y	Lenalidomide/rituximab
 CHRISTOPHER R FLOWERS, MD, MS	BR → R maintenance x 2 y	O-bendamustine; O-CVP
 NATHAN H FOWLER, MD	Lenalidomide/rituximab → R maintenance	BR
 ANN S LACASCE, MD, MMSC	Lenalidomide/rituximab → R maintenance	Dose-reduced BR
 JOHN P LEONARD, MD	BR	Rituximab alone; O-bendamustine
 JULIE M VOSE, MD, MBA	BR → R maintenance x 2 y	Lenalidomide/rituximab
 ANDREW D ZELENETZ, MD, PHD	O-CVP → O maintenance x 2 y	R-CVP, R-CHOP; O-CHOP; lenalidomide/rituximab; R mono

BR = bendamustine/rituximab; R = rituximab; O = obinutuzumab

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Differences between Rituximab (Type I Antibody) and Obinutuzumab (Type II Antibody)

Increased direct cell death

Type II character…

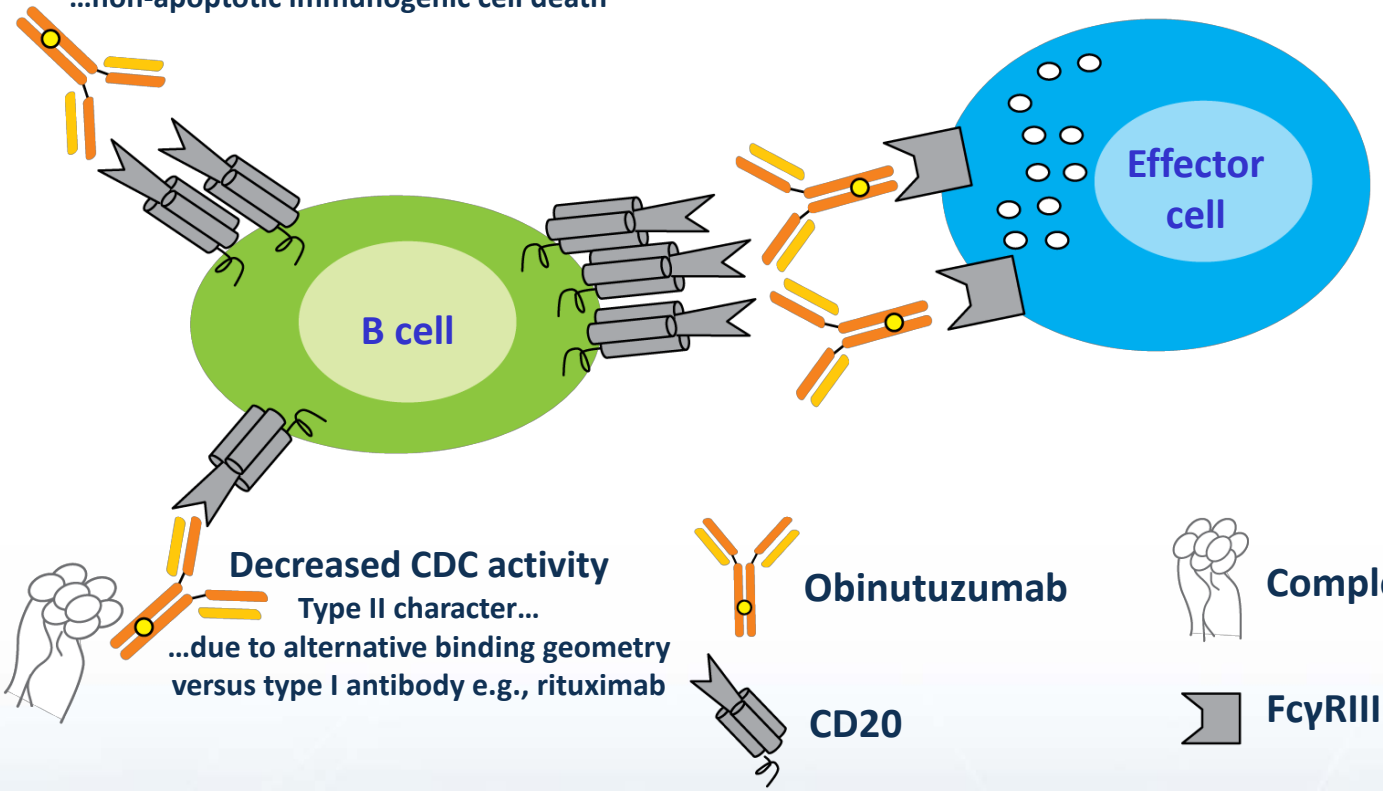
…due to alternative geometry (elbow-hinge modification) versus type I antibody e.g., rituximab

…non-apoptotic immunogenic cell death

Increased effector cell-mediated ADCC and ADCP

Increased affinity for FcγRIII receptors on immune effector cells…

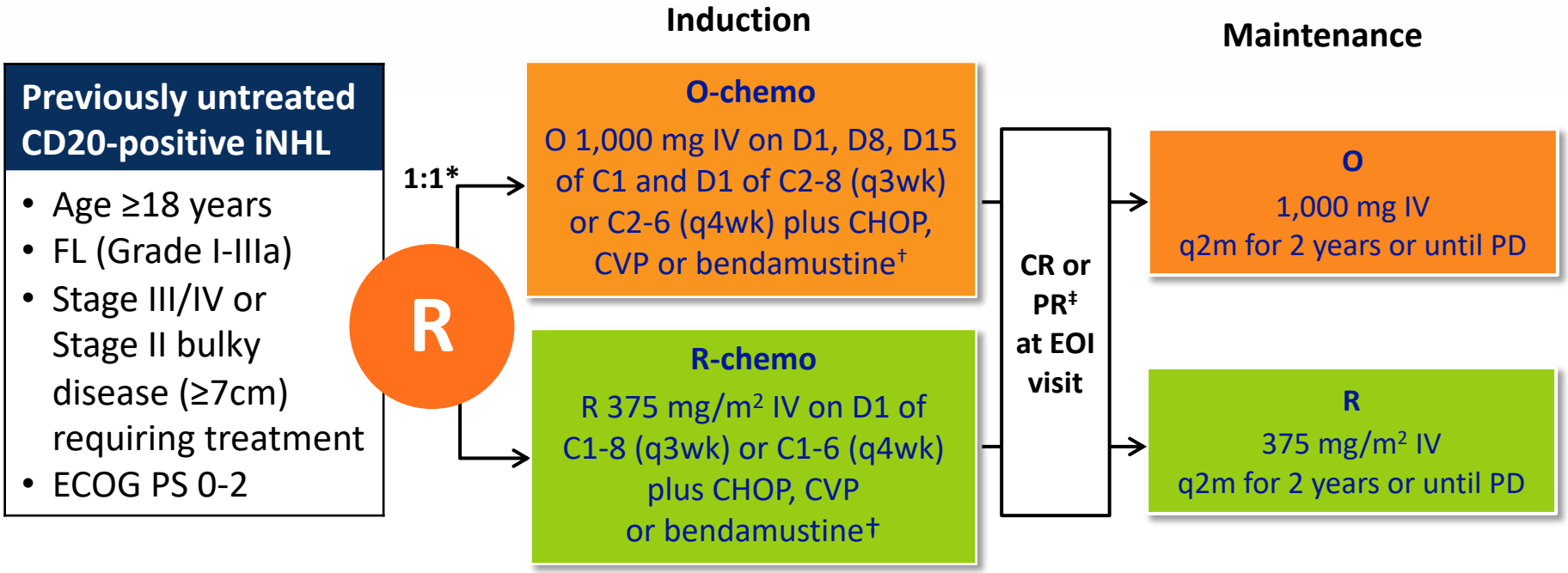
…due to glycoengineered Fc region



ADCC = antibody-dependent cell-mediated cytotoxicity; ADCP = antibody-dependent cellular phagocytosis; CDC = complement-dependent cytotoxicity

Tobinai K et al. *Adv Ther* 2017;34(2):324-56.

Phase III GALLIUM Study: Design



* Chemotherapy regimen was chosen by site and received by all patients at that site

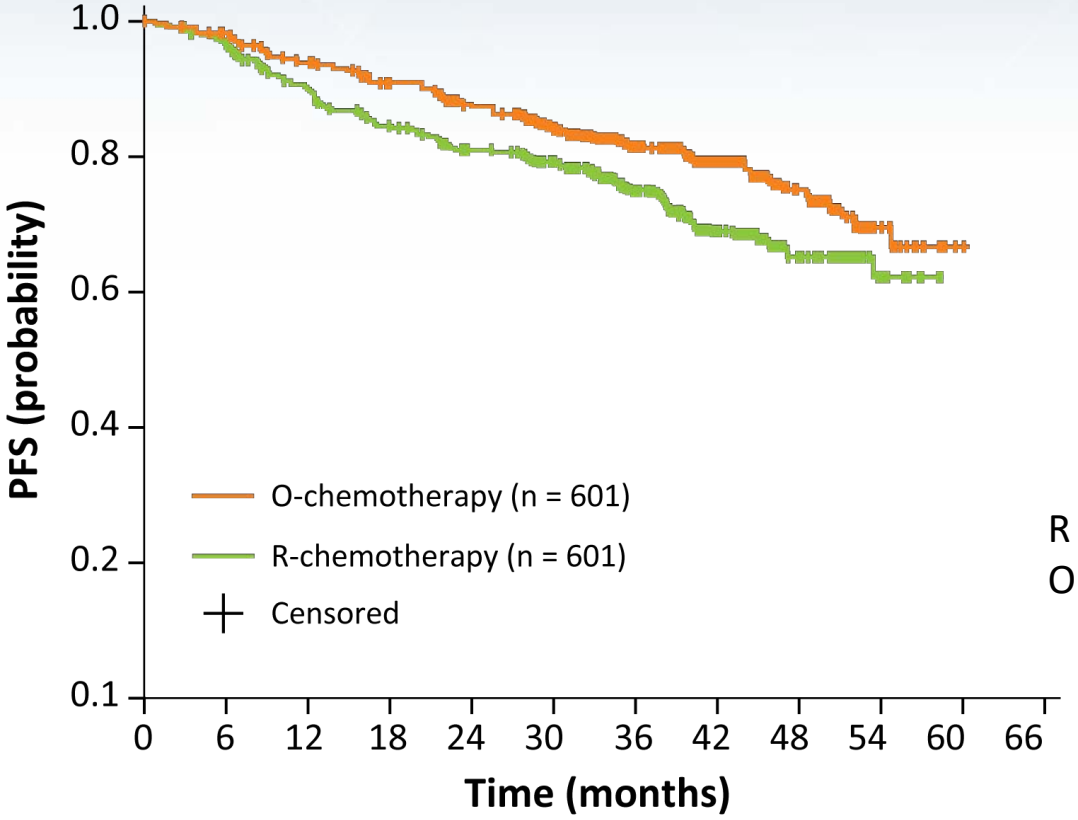
† CHOP q3wk × 6 cycles, CVP q3wk × 8 cycles, bendamustine q4wk × 6 cycles

‡ Patients with stable disease at EOI were followed for PD for up to 2 years

O = obinutuzumab; CVP = cyclophosphamide/vincristine/prednisone; R = rituximab

Marcus R et al. *Proc ASH* 2016;Abstract 6.

GALLIUM: PFS (Investigator Assessed)



R = rituximab
O = obinutuzumab

Estimated 3-year PFS (median follow-up: 41.1 months)	O-chemo	R-chemo	HR, *p*-value
All patients (n = 601, 601)	82%	75%	0.68, 0.0016
CHOP (n = 196, 203)	81%	76%	0.72, 0.13
CVP (n = 60, 57)	71%	64%	0.79, 0.46
Bendamustine (n = 345, 341)	84%	76%	0.63, 0.0062

Hiddemann W et al. *J Clin Oncol* 2018;36(23):2395-404.

GALLIUM: Select Adverse Events (AEs)

	O-chemo (n = 595)	R-chemo (n = 597)
Grade 3-5 AEs	75%	69%
Neutropenia	45%	38%
Infusion-related reactions	7%	4%
Thrombocytopenia	6%	3%
Grade 3-5 AEs of special interest		
Infections	20%	16%
Second neoplasms	5%	4%
Grade 5 (fatal) AEs	4%	4%

Hiddemann W et al. *J Clin Oncol* 2018;36(23):2395-404.

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GALLIUM: Tolerability of Maintenance Obinutuzumab Compared to Rituximab

Grade ≥3 AEs	Maintenance obinutuzumab (N = 548)	Maintenance rituximab (N = 535)
Neutropenia	16.4%	10.7%
Anemia	1.1%	0.2%
Pneumonia	2.6%	3.0%
Infusion-related reaction	0.5%	0.2%
Dyspnea	0.5%	0.4%
Hypertension	0.5%	0.4%

Marcus R et al. *NEJM* 2017;377(14):1331-44.

GALLIUM: Select Adverse Events by Chemotherapy Regimen

	Bendamustine (B)		CHOP		CVP	
	O + B (n = 338)	R + B (n = 338)	O + CHOP (n = 193)	R + CHOP (n = 203)	O + CVP (n = 61)	R + CVP (n = 56)
Grade 3-5 AEs	69%	67%	89%	74%	69%	54%
Neutropenia	30%	30%	71%	55%	46%	23%
Leukopenia	3%	4%	20%	17%	2%	2%
Infections	26%	20%	12%	12%	13%	13%
Second neoplasms	6%	4%	4%	3%	2%	4%
Grade 5 (fatal) AEs	6%	5%	2%	2%	2%	2%

- Study was not designed to compare chemotherapy backbones, leading to imbalances in patient baseline characteristics:
  - Bendamustine: older age, higher comorbidity index
  - CHOP: more bulky disease, high-risk FLIPI

Hiddemann W et al. *J Clin Oncol* 2018;36(23):2395-404.

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FDA Approval of Obinutuzumab for Previously Untreated Advanced Follicular Lymphoma

Press Release – November 16, 2017

"The US Food and Drug Administration approved obinutuzumab in combination with chemotherapy, followed by obinutuzumab alone in those who responded, for people with previously untreated advanced follicular lymphoma (stage II bulky, III or IV). The approval is based on results from the Phase III GALLIUM study, which showed superior progression-free survival (PFS) for patients who received this obinutuzumab-based regimen compared with those who received a rituximab-based regimen as an initial (first-line) therapy."

http://www.businesswire.com/news/home/20171116006149/en/FDA-Approves-Genentech%E2%80%99s-Gazyva-Previously-Untreated-Advanced

In what clinical situations, if any, you would administer the R-squared regimen of lenalidomide/rituximab as up-front treatment for a patient with FL?

When administering the R-squared regimen of lenalidomide/rituximab as up-front treatment for FL, what dose and schedule do you use?

	Clinical situation	Dose and schedule
 BRUCE D CHESON, MD	Anyone who needs treatment	Modified RELEVANCE regimen
 ANDREW M EVENS, DO, MSC	Older patient where BR not tolerated and/or patient choice	RELEVANCE regimen*
 CHRISTOPHER R FLOWERS, MD, MS	Patient with high tumor burden, wants to avoid chemotherapy and is comfortable with differences in treatment duration	RELEVANCE regimen*
 NATHAN H FOWLER, MD	All patients in whom transformation not suspected	RELEVANCE regimen*
 ANN S LACASCE, MD, MMSC	Patient who does not want IV chemo with too much tumor burden for rituximab, or a very elderly patient	RELEVANCE regimen*
 JOHN P LEONARD, MD	Patient who needs treatment and prefers the regimen	RELEVANCE regimen*
 JULIE M VOSE, MD, MBA	Elderly patient with symptomatic, nonbulky disease	Modified RELEVANCE regimen
 ANDREW D ZELENETZ, MD, PHD	Patient who wants to avoid chemotherapy	Modified RELEVANCE regimen

* RELEVANCE regimen: lenalidomide 20 mg/d, days 2-22 of 28 until CR/CRu at 6, 9 or 12 cycles, then 10 mg/d (total 18 cycles) and rituximab 375 mg/m^2, weekly cycle 1 and day 1 cycles 2-6; continued in responders q8wk for 12 cycles

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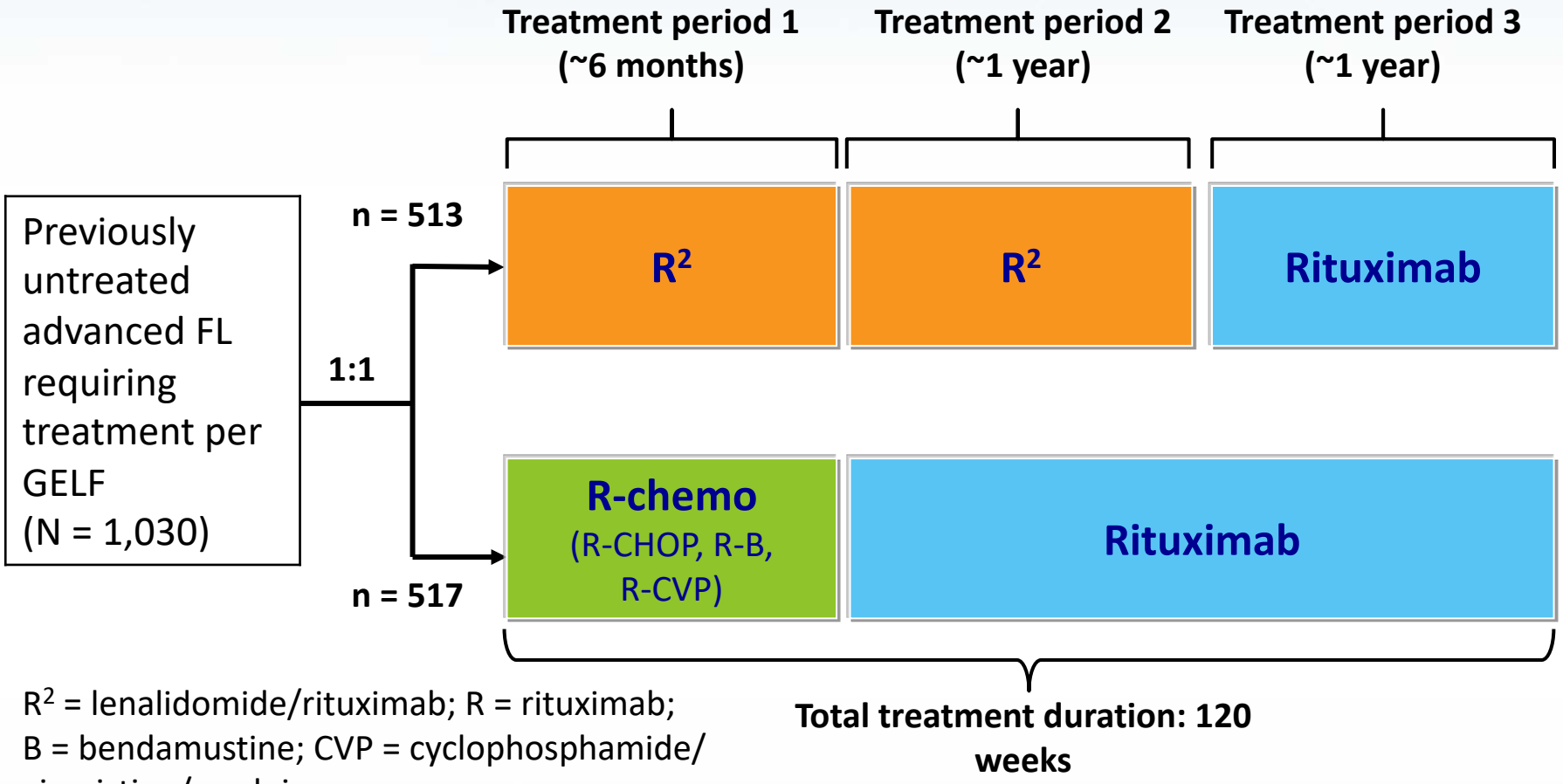
Based on current clinical trial data and your personal experience, how would you compare the global efficacy of lenalidomide/rituximab to that of BR when used as up-front therapy for FL?

How would you compare the global tolerability/toxicity of lenalidomide/rituximab to that of BR when used as up-front therapy for FL?

	Efficacy	Tolerability/toxicity
 BRUCE D CHESON, MD	About the same	Lenalidomide/rituximab has less toxicity
 ANDREW M EVENS, DO, MSC	BR is more efficacious	About the same
 CHRISTOPHER R FLOWERS, MD, MS	About the same	About the same
 NATHAN H FOWLER, MD	About the same	Lenalidomide/rituximab has less toxicity
 ANN S LACASCE, MD, MMSC	BR is more efficacious	About the same
 JOHN P LEONARD, MD	About the same	About the same
 JULIE M VOSE, MD, MBA	About the same	About the same
 ANDREW D ZELENETZ, MD, PHD	About the same	Toxicities are distinct

RELEVANCE: Phase III Trial Design



R^2 = lenalidomide/rituximab; R = rituximab; B = bendamustine; CVP = cyclophosphamide/vincristine/prednisone

Primary endpoints: CR/CRu at 120 weeks and PFS

Fowler NH et al. *Proc ASCO* 2018;Abstract 7500.

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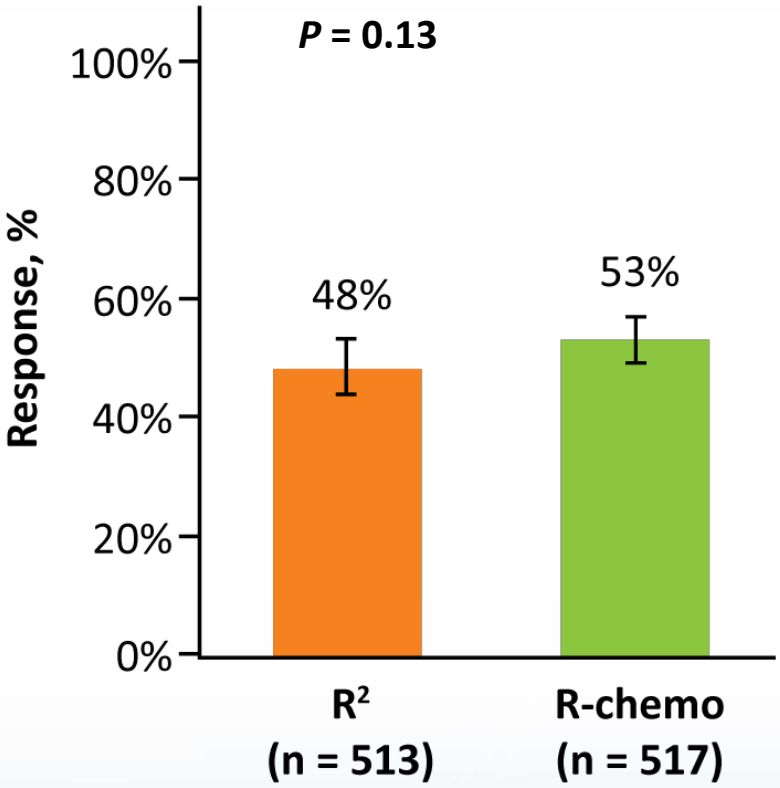
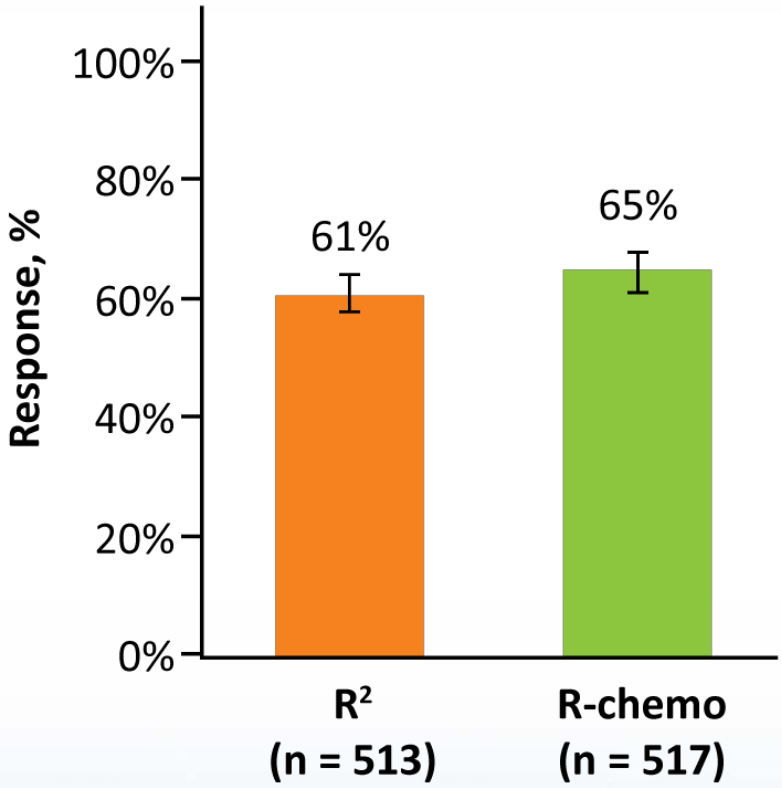
RELEVANCE: Response

Coprimary endpoint:
CR/CRu at 120 weeks



ORR at 120 weeks

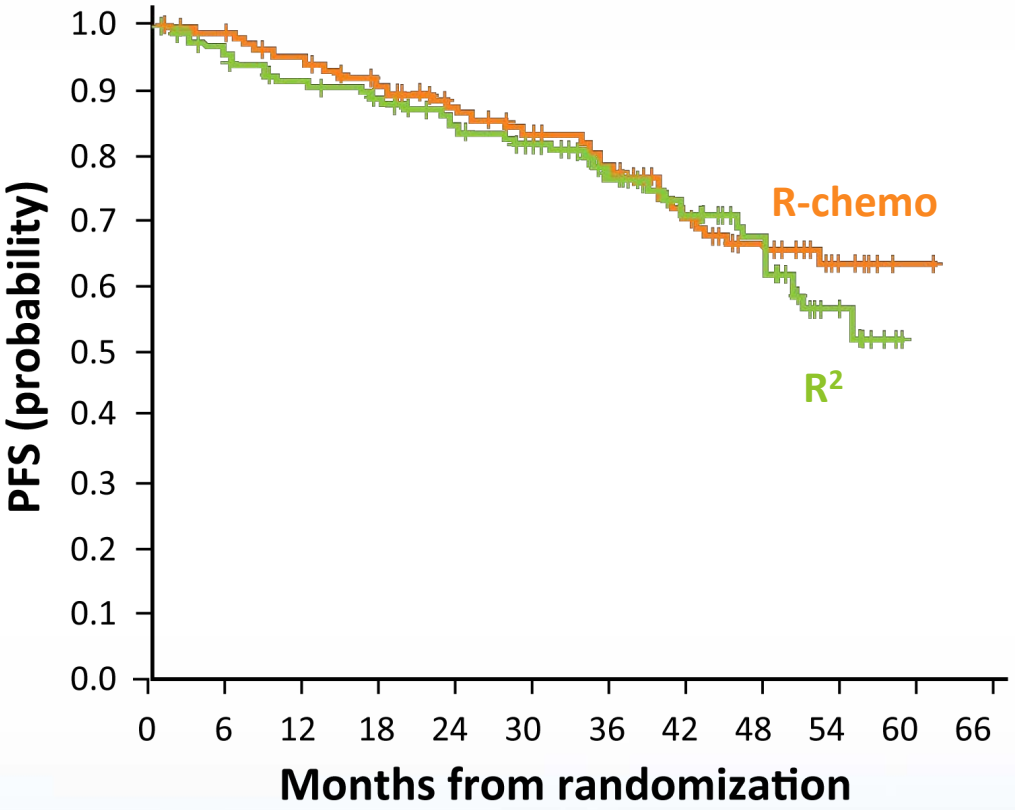


- 3-year duration of response = 77% (R^2) versus 74% (R-chemo)

Fowler NH et al. *Proc ASCO* 2018;Abstract 7500;
Morschhauser F et al. *N Engl J Med* 2018;379(10):934-47.

RELEVANCE: Interim PFS by Independent Review Committee

Coprimary endpoint: Interim PFS (~50% events)



	R² (n = 513)	R-chemo (n = 517)
3-year PFS	77%	78%
HR	1.10	
p-value	0.48	

- **At median follow-up of 37.9 mo, interim PFS was similar in both arms**
- 3-y OS (immature in ITT) = 94% (R^2) vs 94% (R-chemo); HR = 1.16

Fowler NH et al. *Proc ASCO* 2018;Abstract 7500.

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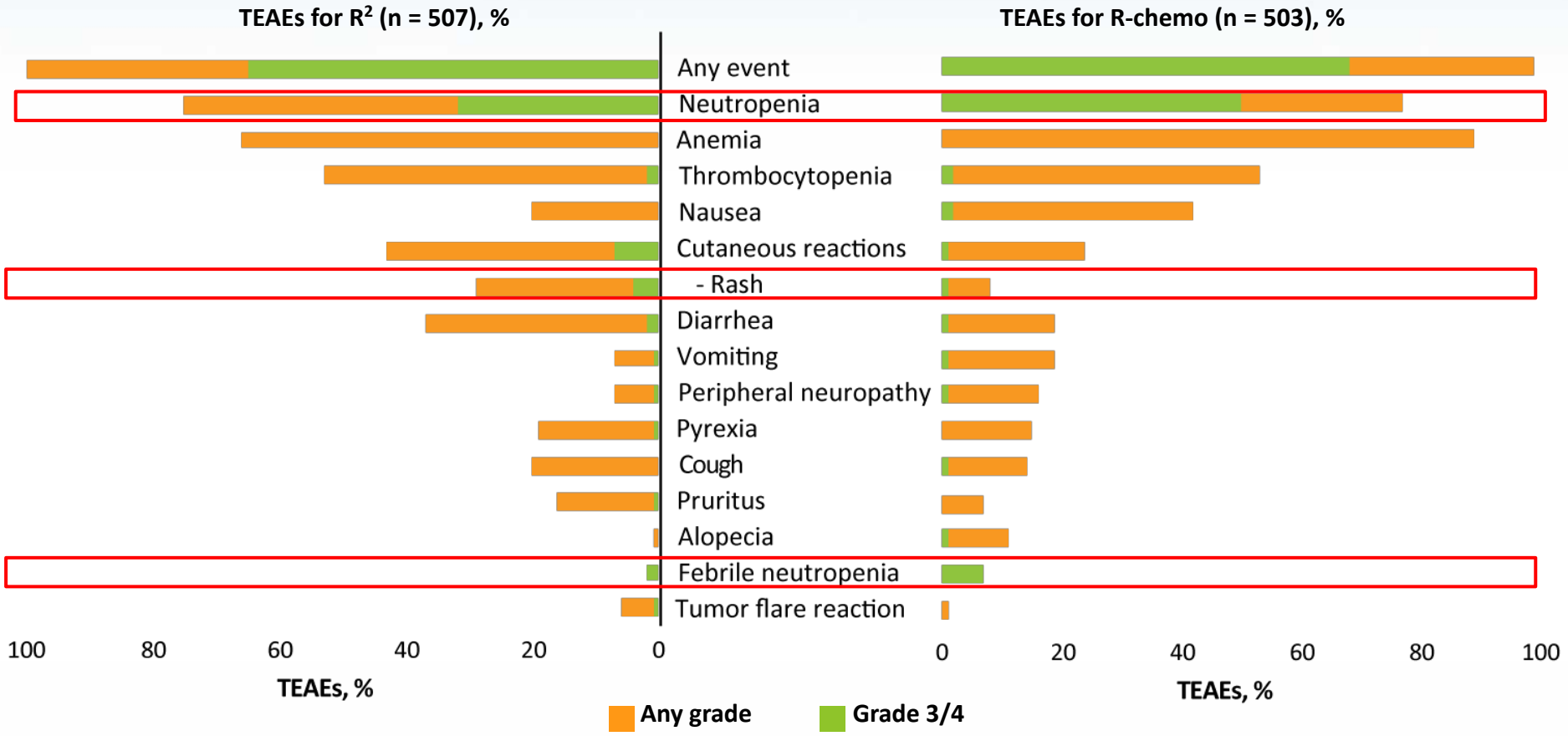
RELEVANCE: Select Treatment-Emergent AEs (TEAEs)



- Early discontinuation of trial treatment: 11% with R^2 versus 3% with R-chemo
- Second primary cancers: 7% with R^2 versus 10% with R-chemo

Fowler NH et al. *Proc ASCO* 2018;Abstract 7500;
Morschhauser F et al. *N Engl J Med* 2018;379(10):934-47.

Selection and Sequencing of Systemic Therapy in the Management of Follicular Lymphoma (FL)

Module 1: Optimizing the Care of Patients with Newly Diagnosed FL

- Initiation of active therapy versus watchful waiting; indications for rituximab monotherapy
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- Role of lenalidomide/rituximab in the management of R/R FL
- Available clinical research data with the FDA-approved PI3K inhibitors

Guidelines on Rituximab Maintenance

- **NCCN Guidelines**[1]
  - "Patients with CR or PR to first-line therapy **can either be observed or can be treated** with optional consolidation or extended therapy."
- **UpToDate**[2]
  - "Maintenance improves PFS, but has not improved OS. Even though maintenance is designed to have a low toxicity profile, **a decision regarding its use in an individual patient** must take into consideration both the **potential benefit** from attaining a deeper response and the likelihood that this patient will **tolerate the prolonged therapy**."
- **ESMO**[3]
  - **Recommend maintenance rituximab** for patients with high tumor burden in CR or PR to front-line rituximab-based therapy.

[1] NCCN Guidelines for B-Cell Lymphomas, v1.2019; [2] UpToDate "Initial treatment of advanced stage (III/IV) follicular lymphoma," v37.0; [3] Dreyling M et al. *Ann Oncol* 2016;27(Suppl 5):v83-90.

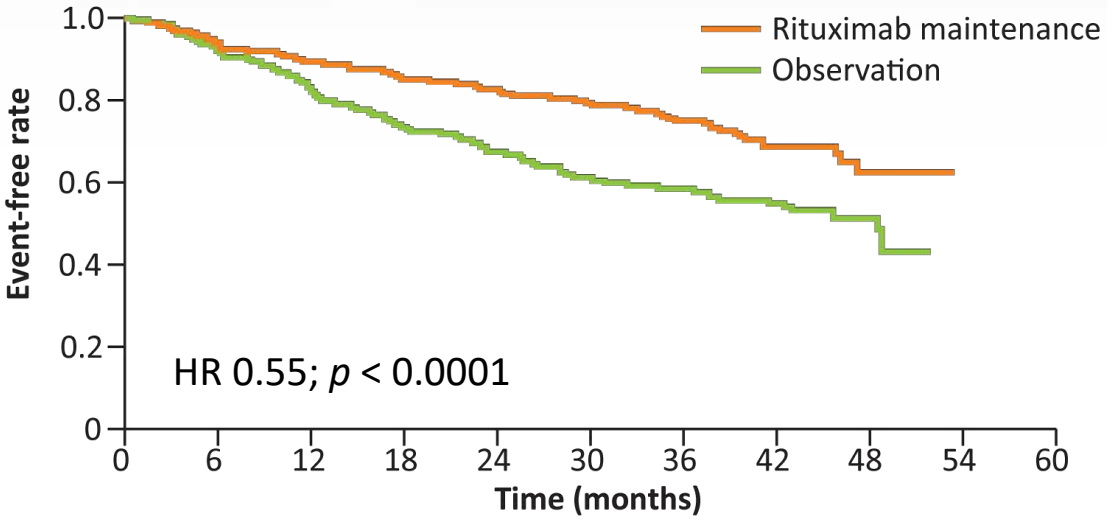
Approaches to Maintenance Therapy

Study	Maintenance schedule
EORTC-20981[1]	Rituximab 375 mg/m^2 IV q12wk x 8
SAKK 35/03[2]	Rituximab 375 mg/m^2 IV q8wk x 4
Hainsworth et al[3]	Rituximab 375 mg/m^2 IV weekly x 4 every 6 months x 4
PRIMA[4]	Rituximab 375 mg/m^2 IV q8wk x 12
RESORT[5]	Rituximab 375 mg/m^2 IV q13wk until treatment failure
GALLIUM[6]	Obinutuzumab 1,000 mg q8wk x 12

[1] van Oers MHJ et al. *J Clin Oncol* 2011;28(17):2853-8; [2] Taverna C et al. *J Clin Oncol* 2016;34(5):495-500. [3] Hainsworth JD et al. *J Clin Oncol* 2002;20(20):4261-7; [4] Salles G et al. *Lancet* 2011;377(9759):42-51; [5] Kahl BS et al. *J Clin Oncol* 2014;32(28):3096-102. [6] Marcus R et al. *NEJM* 2017;377(14):1331-44.

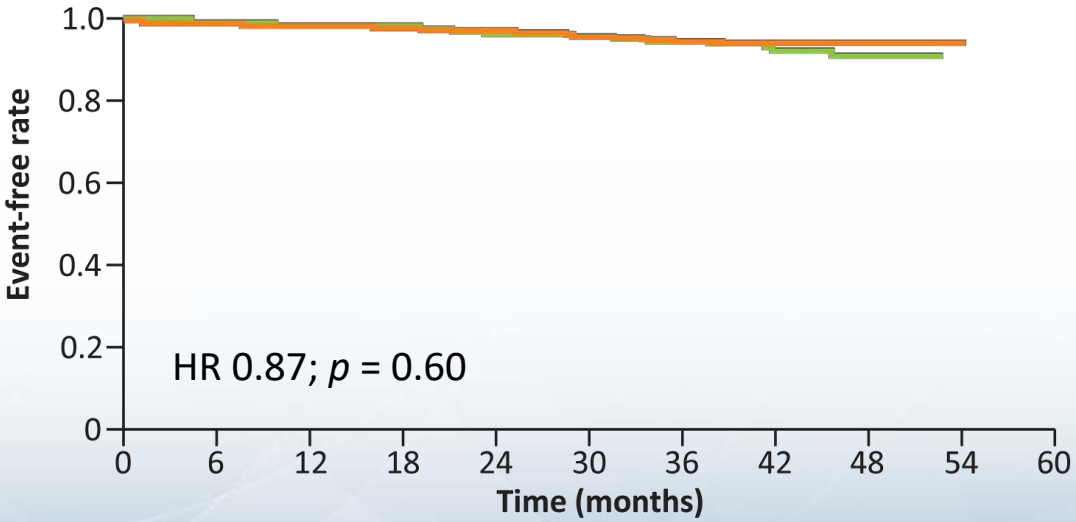
PRIMA Trial: Maintenance Rituximab for 2 Years or Observation After Induction Chemotherapy

Progression-Free Survival[1]



10-year PFS[2]:
R maintenance: 51%
Observation: 35%

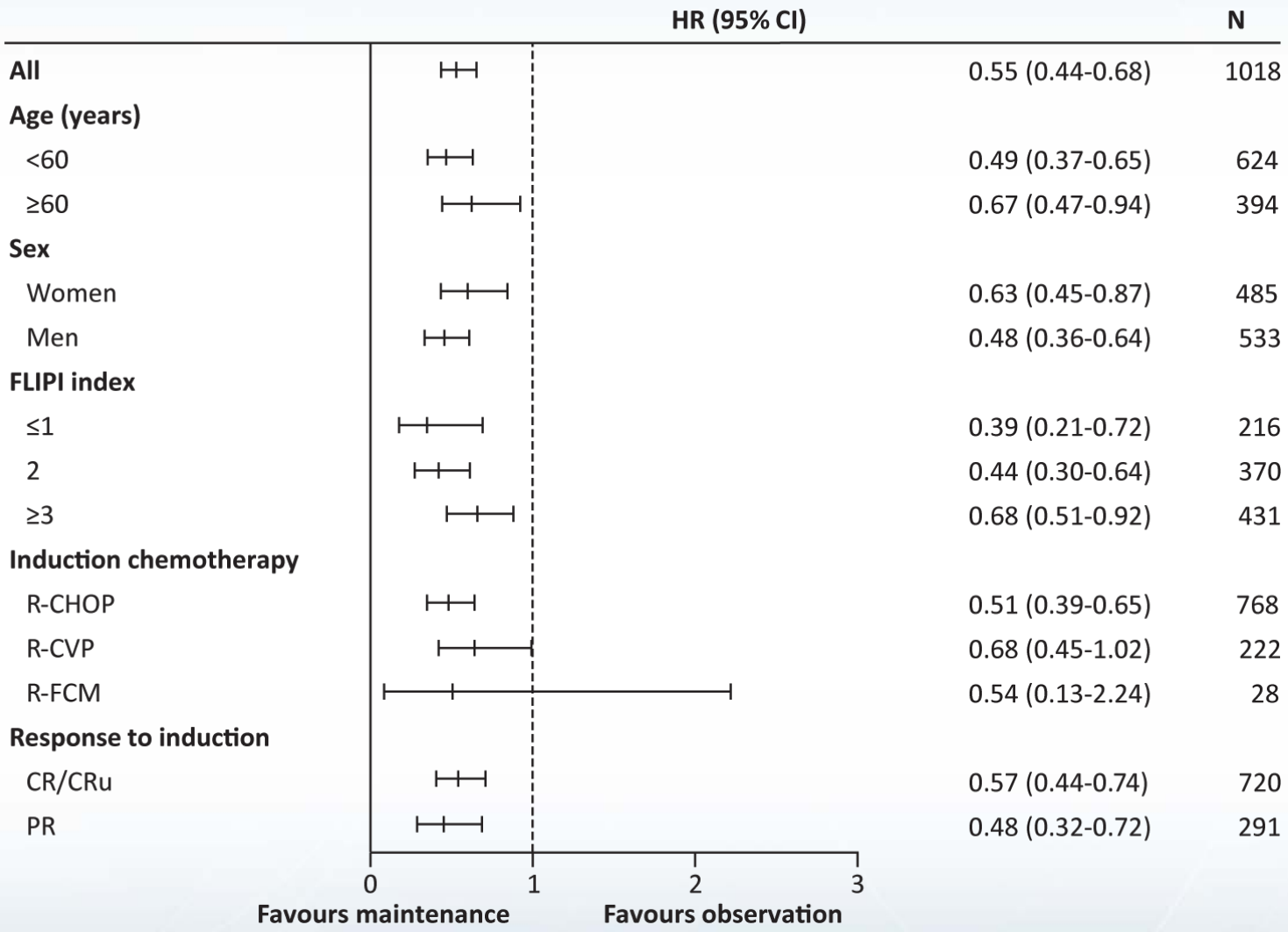
Overall Survival[1]



10-year OS[2]:
R maintenance: 80%
Observation: 80%

[1] Salles G et al. *Lancet* 2011;377(9759):42-51; [2] Salles G et al. *Proc ASH* 2017;Abstract 486.

PRIMA: Subgroup Analysis of PFS



Salles G et al. *Lancet* 2011;377(9759):42-51.

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PRIMA: Tolerability

Adverse events	Observation (N = 508)		Maintenance rituximab (N = 501)	
	Grade 3/4	Leading to treatment discontinuation	Grade 3/4	Leading to treatment discontinuation
All adverse events	84 (17%)	8 (2%)	121 (24%)	19 (4%)
Neoplasia	17 (3%)	6 (1%)	20 (4%)	5 (1%)
Neutropenia	5 (1%)	0	18 (4%)	0
Febrile neutropenia	2 (<1%)	0	1 (<1%)	1 (<1%)
Infections	5 (1%)	0	22 (4%)	4 (1%)
CNS disorders	13 (3%)	0	10 (2%)	0
Cardiac disorders	5 (1%)	0	11 (2%)	1 (<1%)

Salles G et al. *Lancet* 2011;377(9759):42-51.

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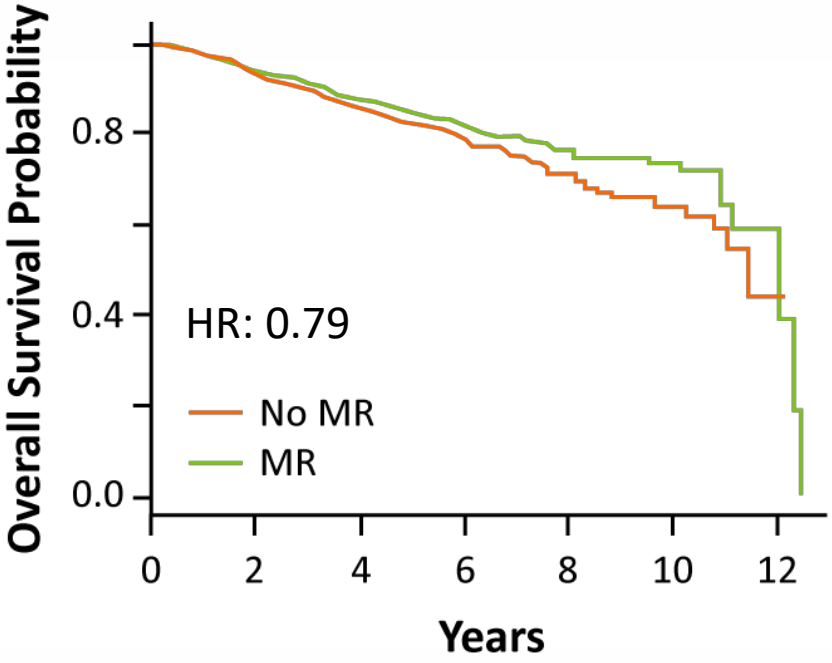
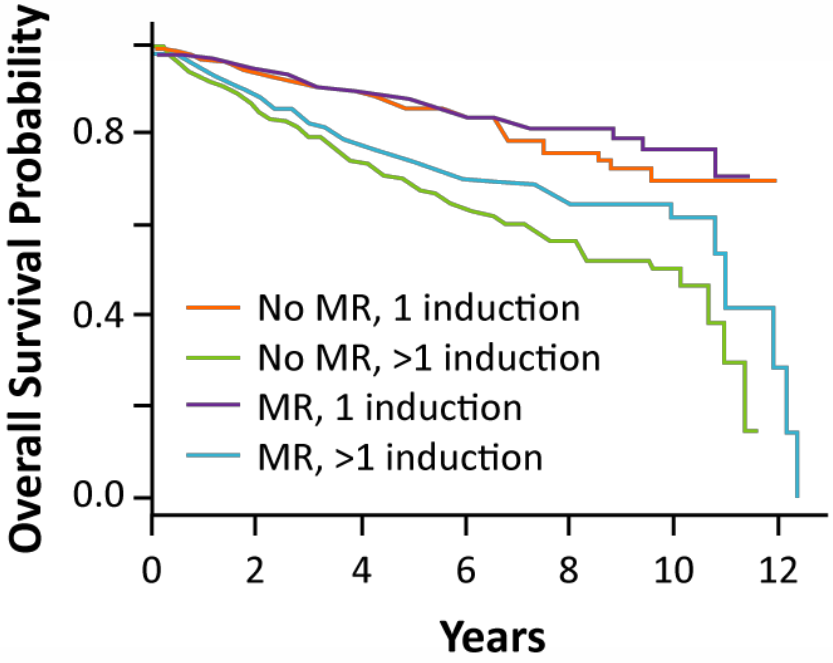
Meta-Analysis of 7 Trials of Maintenance Rituximab: Overall Survival

Overall Survival (All Trials)



Overall Survival By Line of Therapy



	First line	Second or later line
No rituximab induction	HR = 0.71; *p* = 0.15	HR = 0.69; *p* = 0.075
Induction with rituximab	HR = 1.049; *p* = 0.78	HR = 0.70; *p* = 0.035

Vidal L et al. *Eur J Cancer* 2017;76:216-25.

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Selection and Sequencing of Systemic Therapy in the Management of Follicular Lymphoma (FL)

Module 1: Optimizing the Care of Patients with Newly Diagnosed FL

- Initiation of active therapy versus watchful waiting; indications for rituximab monotherapy
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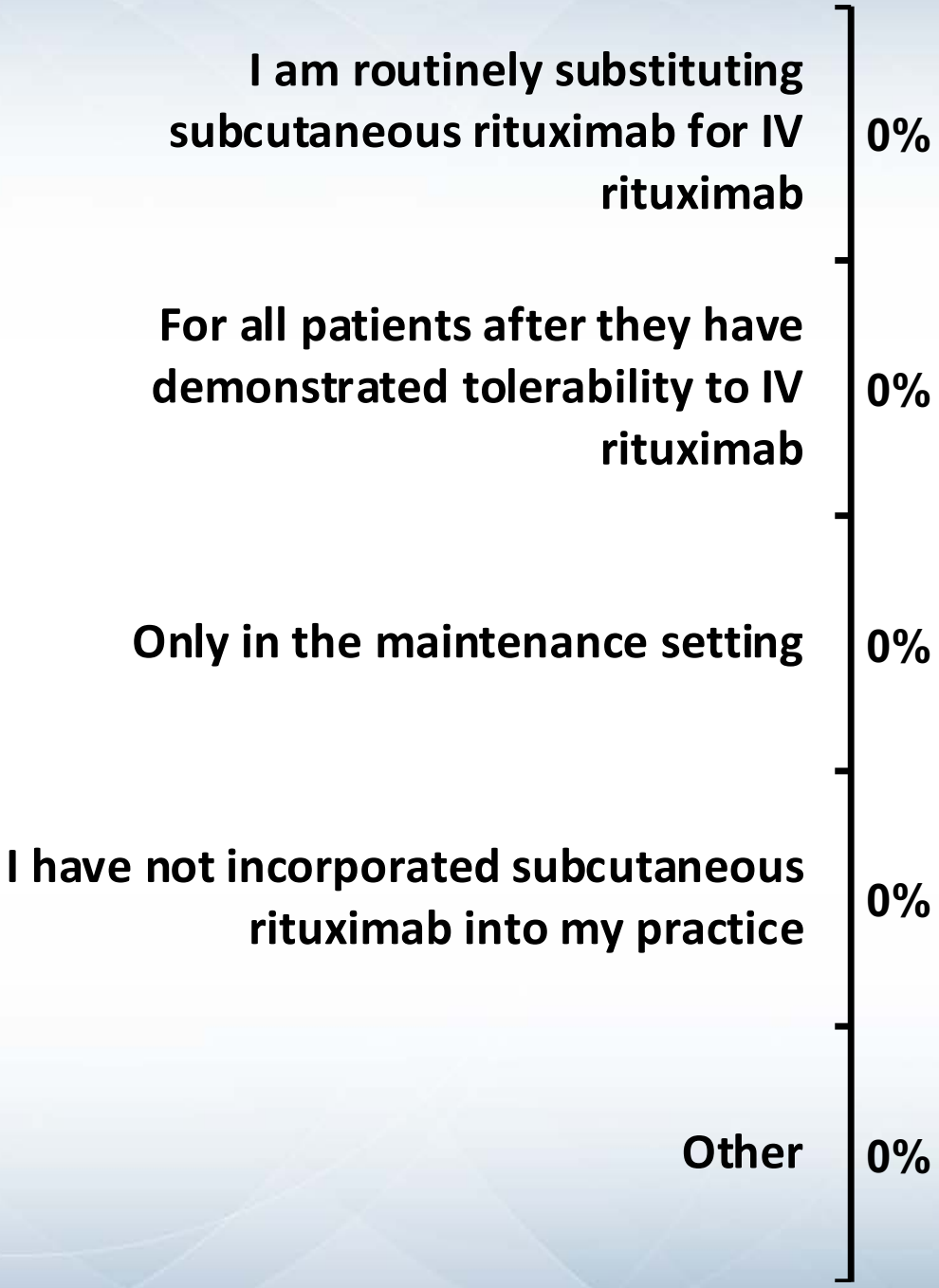
- Available clinical research data with the FDA-approved PI3K inhibitors

In general, how, if at all, have you incorporated subcutaneous rituximab into your management of FL?

1. I am routinely substituting subcutaneous rituximab for IV rituximab
2. For all patients after they have demonstrated tolerability to IV rituximab
3. Only in the maintenance setting
4. I have not incorporated subcutaneous rituximab into my practice
5. Other



In general, how, if at all, have you incorporated subcutaneous rituximab into your management of FL?

 BRUCE D CHESON, MD	I routinely substitute subcutaneous rituximab for IV rituximab
 ANDREW M EVENS, DO, MSC	Only in the maintenance setting
 CHRISTOPHER R FLOWERS, MD, MS	All interested patients with demonstrated tolerability to IV rituximab
 NATHAN H FOWLER, MD	Only in the maintenance setting
 ANN S LACASCE, MD, MMSC	I offer to all patients. Some are enthusiastic, others are not
 JOHN P LEONARD, MD	I routinely substitute subcutaneous rituximab for IV rituximab
 JULIE M VOSE, MD, MBA	All patients with demonstrated tolerability to IV rituximab
 ANDREW D ZELENETZ, MD, PHD	All patients with demonstrated tolerability to IV rituximab

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SABRINA: A Phase III Study of Subcutaneous versus IV Rituximab for First-Line FL

	IV rituximab (n = 205)	SubQ rituximab (n = 205)
Overall response	84.9%	84.4%
Complete response	32.2%	32.2%
PFS*	HR = 0.84	
EFS*	HR = 0.91	
OS*	HR = 0.81	

* At a median follow-up of 37 months, no significant difference between groups

	IV rituximab (n = 210)	SubQ rituximab (n = 197)
Serious AEs	34%	37%
Grade ≥3 AEs	55%	56%
Administration-related reaction	35%	48%

Davies A et al. *Lancet Haematol* 2017;4(6):e272-82.

FDA Approves Rituximab/Hyaluronidase Combination for Treatment of FL, DLBCL and CLL

Press Release – June 22, 2017

- The approval provides patients a subcutaneous route of rituximab administration that shortens the administration time to 5 to 7 minutes as compared to intravenous infusion that can take several hours. This new product also provides for flat dosing (1,400 mg rituximab and 23,400 units hyaluronidase human for FL and DLBCL, and 1,600 mg rituximab and 26,800 units hyaluronidase human for CLL)
- The approval specifies that the combination is indicated for the following indications for which rituximab was previously approved:
  - R/R FL
  - Previously untreated FL, in combination with first-line chemotherapy and as single-agent maintenance therapy for responding patients
  - Nonprogressing (including stable disease) FL after first-line CVP

https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm564235.htm

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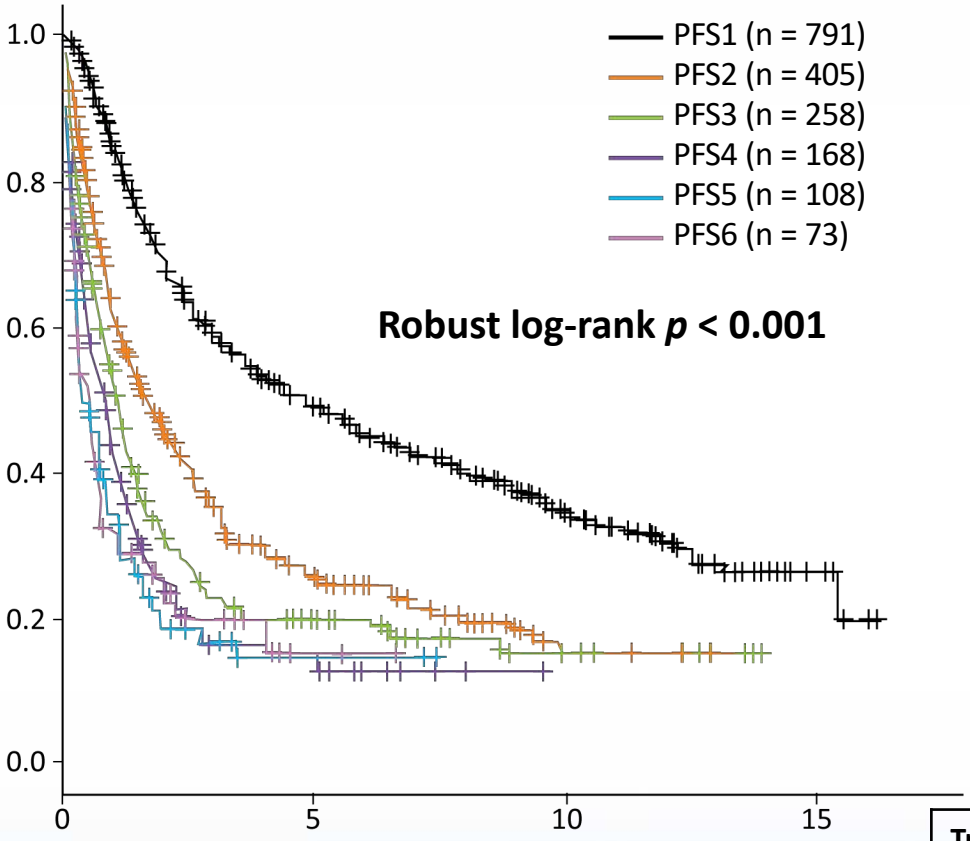
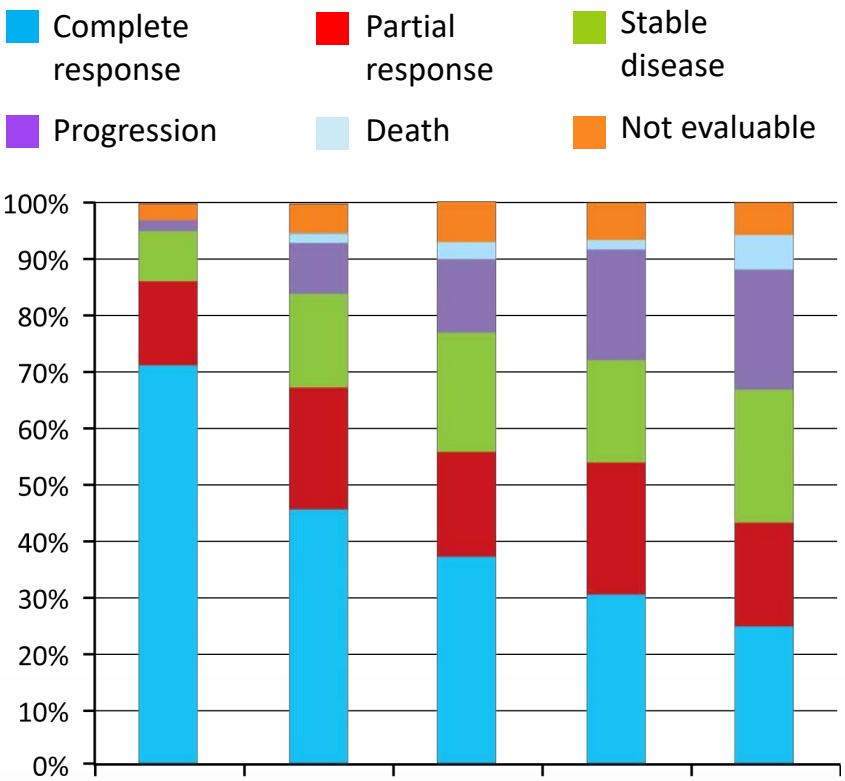
Decreasing PFS and Response with Subsequent Lines of Therapy

PFS by line of treatment



Clinical response based on lines of treatment



Treatment	1	2	3	4	5
N =	791	406	258	168	108

Alperovich A et al. *Proc ASH* 2016;Abstract 2955.

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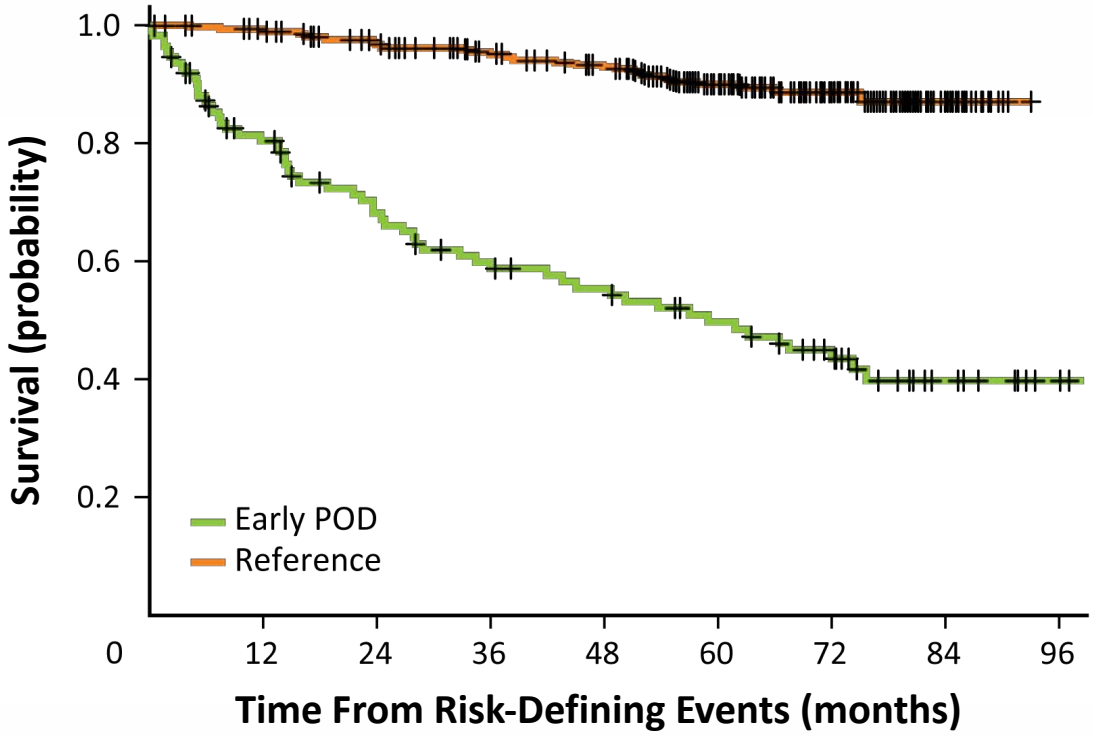
National LymphoCare Study: Relapse within 24 Months Associated with Decreased Overall Survival



- Analysis of 588 patients who received first-line R-CHOP on the National LymphoCare Study
- 19% of patients experienced relapse within 24 months of diagnosis; associated with significantly reduced OS (HR = 7.17)

Casulo C et al. *J Clin Oncol* 2015;33(23):2516-22.

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Regulatory and reimbursement issues aside, what is your usual second-line therapy for a 60-year-old patient with FL who achieves a complete remission to BR (no maintenance) but then experiences symptomatic disease relapse after ≤2 years?

What would you recommend if the patient were 80 years old?

	AGE 60	AGE 80
 BRUCE D CHESON, MD	Lenalidomide/rituximab	Lenalidomide/rituximab
 ANDREW M EVENS, DO, MSC	O-bendamustine	Lenalidomide/rituximab
 CHRISTOPHER R FLOWERS, MD, MS	R-CHOP	Lenalidomide/rituximab
 NATHAN H FOWLER, MD	Lenalidomide/rituximab	Lenalidomide/rituximab
 ANN S LACASCE, MD, MMSC	Chemotherapy → autologous transplant	Lenalidomide/rituximab
 JOHN P LEONARD, MD	Lenalidomide/rituximab	Lenalidomide/rituximab
 JULIE M VOSE, MD, MBA	Chemotherapy → autologous transplant	Lenalidomide/rituximab
 ANDREW D ZELENETZ, MD, PHD	O-CHOP or O-lenalidomide or chemotherapy → transplant	O-lenalidomide or idelalisib or duvelisib

BR = bendamustine/rituximab; O = obinutuzumab

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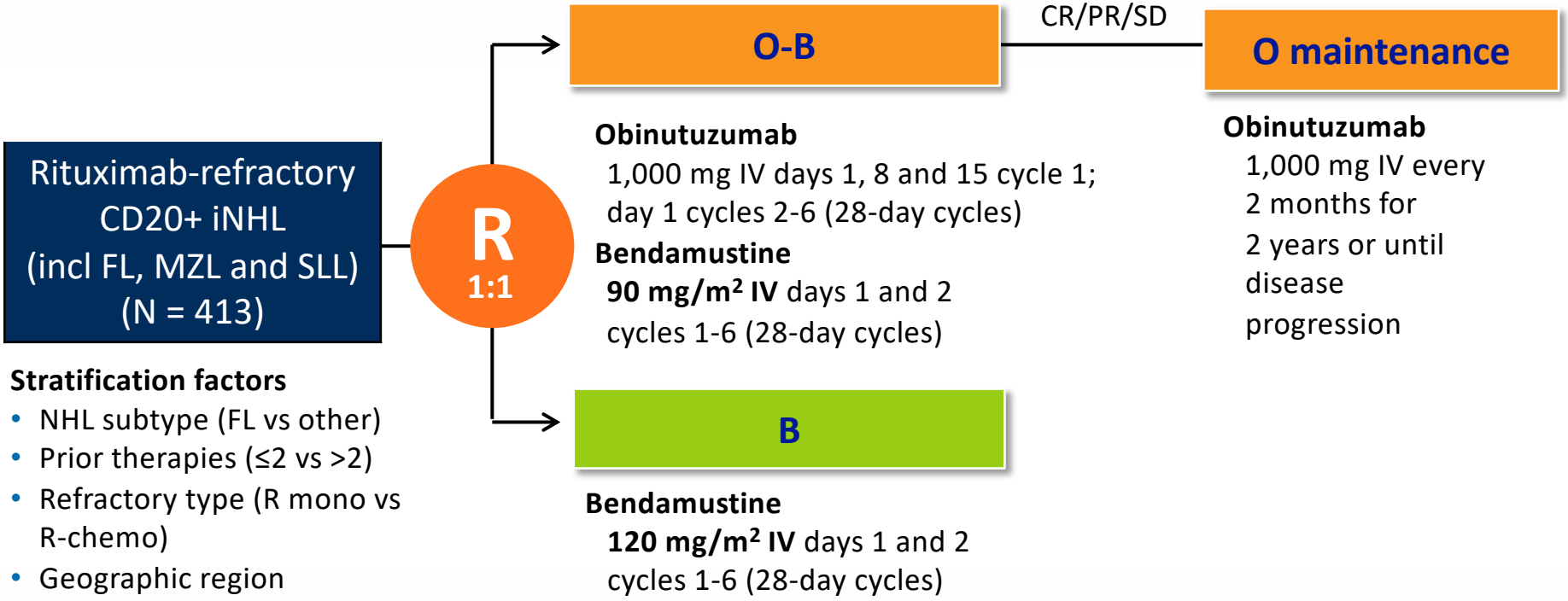
GADOLIN Study Design (NCT01059630)



- International, randomized, open-label study
- Response monitored by CT scan postinduction, then every 3 months for 2 years, then every 6 months

iNHL = indolent non-Hodgkin lymphoma; O = obinutuzumab; B = bendamustine

Sehn LH et al. *Proc ASCO* 2015;Abstract LBA8502.

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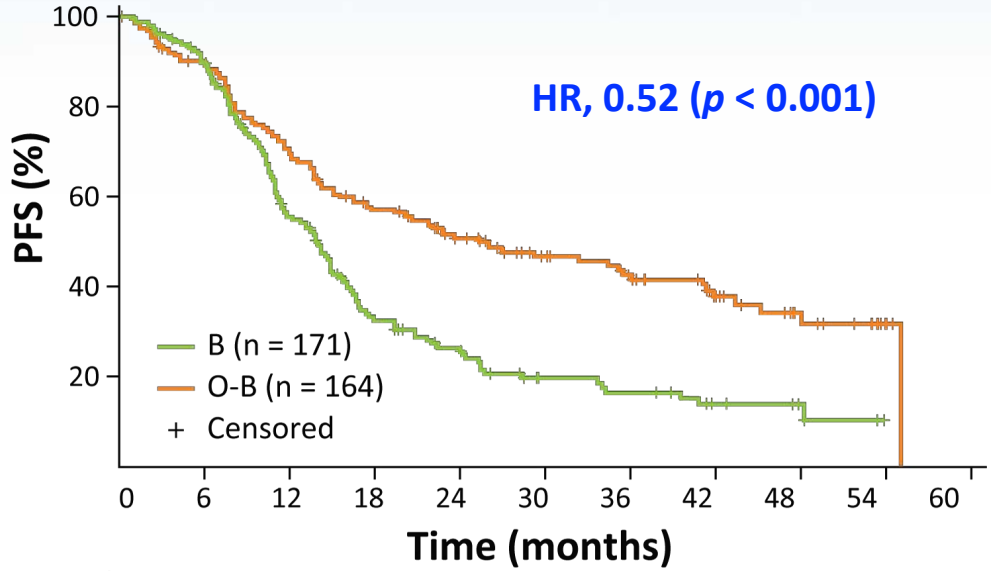
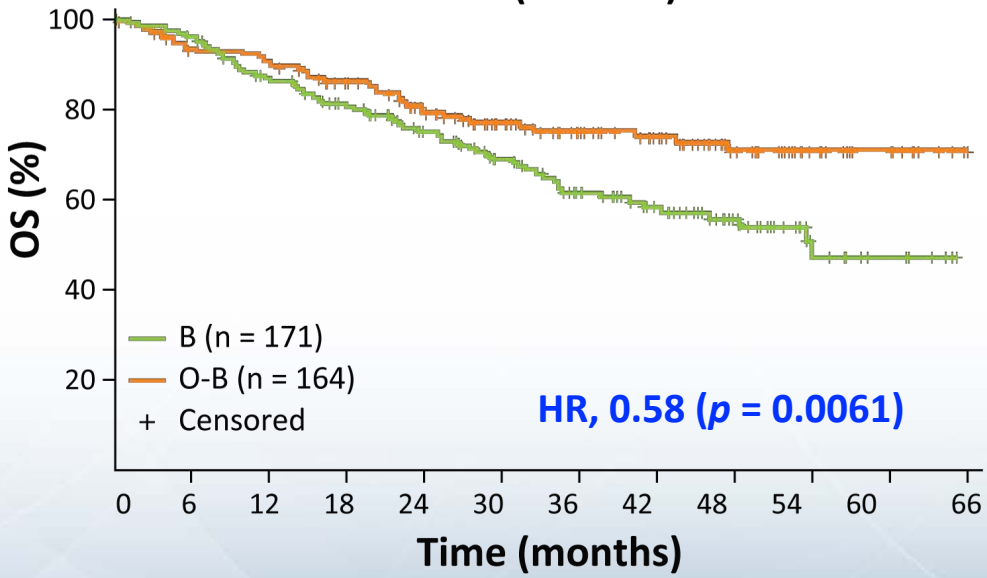
GADOLIN Subgroup Analysis: Obinutuzumab/Bendamustine with Maintenance Obinutuzumab for Rituximab-Refractory FL





Cheson BD et al. *J Clin Oncol* 2018;36(22):2259-66.

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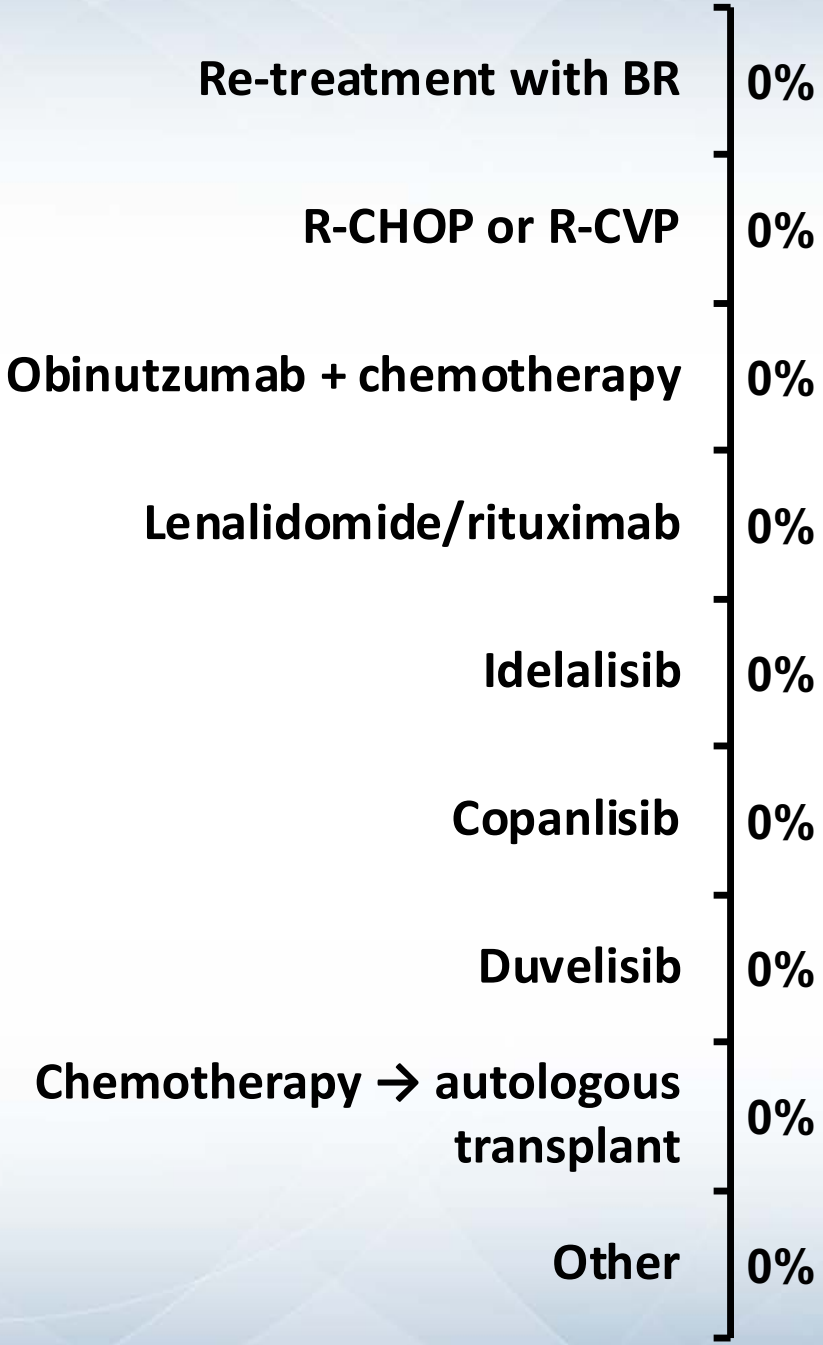
Regulatory and reimbursement issues aside, what is your usual second-line therapy for a 60-year-old patient with FL who achieves a complete remission to BR (no maintenance) but then experiences symptomatic disease relapse after 3 years?

1. Re-treatment with BR
2. R-CHOP or R-CVP
3. Obinutzumab + chemotherapy
4. Lenalidomide/rituximab
5. Idelalisib
6. Copanlisib
7. Duvelisib
8. Chemotherapy → autologous transplant
9. Other



Regulatory and reimbursement issues aside, what is your usual second-line therapy for a 60-year-old patient with FL who achieves a complete remission to BR (no maintenance) but then experiences symptomatic disease relapse after 3 years?

What would you recommend if the patient were 80 years old?

	Age 60	Age 80
 BRUCE D CHESON, MD	Lenalidomide/rituximab	Lenalidomide/rituximab
 ANDREW M EVENS, DO, MSC	Re-treatment with BR	Consider rituximab alone
 CHRISTOPHER R FLOWERS, MD, MS	R-CHOP	Lenalidomide/rituximab
 NATHAN H FOWLER, MD	Lenalidomide/rituximab	Lenalidomide/rituximab
 ANN S LACASCE, MD, MMSC	Lenalidomide/rituximab	Lenalidomide/rituximab
 JOHN P LEONARD, MD	Lenalidomide/rituximab	Rituximab alone
 JULIE M VOSE, MD, MBA	R-CHOP	Lenalidomide/rituximab
 ANDREW D ZELENETZ, MD, PHD	O-CVP or O-CHOP	O-CVP or O-CHOP

BR = bendamustine/rituximab; O = obinutuzumab

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Regulatory and reimbursement issues aside, what is your usual second-line therapy for a 60-year-old patient with FL who achieves a complete remission to BR followed by 2 years of maintenance rituximab but then experiences symptomatic disease relapse after 3 years?

What would you recommend if the patient were 80 years old?

	Age 60	Age 80
 BRUCE D CHESON, MD	Lenalidomide/rituximab	Lenalidomide/rituximab
 ANDREW M EVENS, DO, MSC	O-CHOP	Lenalidomide/rituximab
 CHRISTOPHER R FLOWERS, MD, MS	Lenalidomide/rituximab	Lenalidomide/rituximab
 NATHAN H FOWLER, MD	Lenalidomide/rituximab	Lenalidomide/rituximab
 ANN S LACASCE, MD, MMSC	Lenalidomide/rituximab	Lenalidomide/rituximab
 JOHN P LEONARD, MD	Lenalidomide/rituximab	Lenalidomide/rituximab
 JULIE M VOSE, MD, MBA	R-CHOP	Lenalidomide/rituximab
 ANDREW D ZELENETZ, MD, PHD	O-CVP or O-CHOP	O-CVP or O-CHOP

O = obinutuzumab

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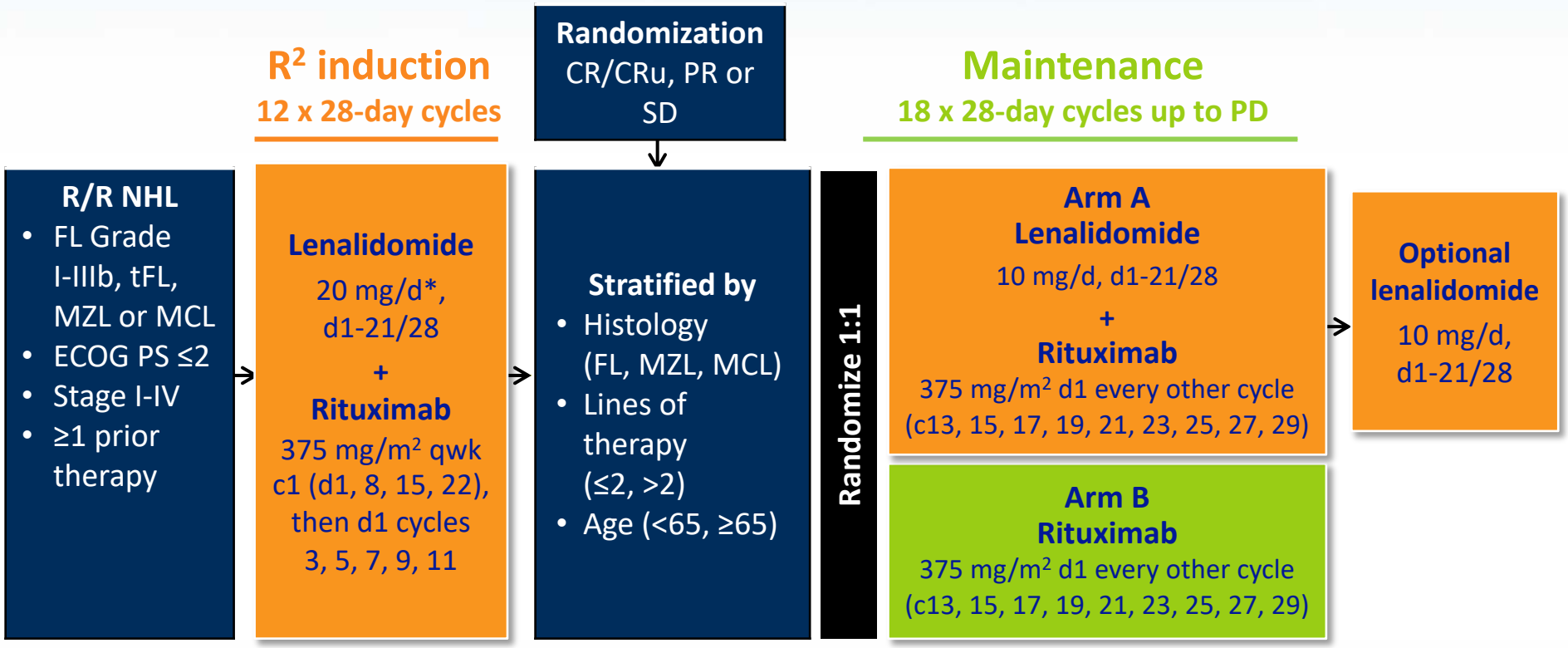
MAGNIFY Study Design



Primary endpoint: PFS (maintenance; 2-sided test $\alpha = 0.05$ and HR = 0.67)†
Secondary endpoints: OS, IOR, ORR, CR, DOR, DOCR, TTNLT, TTHT, safety
Exploratory subgroup analysis: Efficacy and safety by histology and QoL

* Lenalidomide administered at 10 mg if creatine was ≥30 to <60 mL/min
† Assessed per CT/MRI and 1999 IWG criteria with modifications to include extranodal disease

Andorsky DJ et al. *Proc ASCO* 2017;Abstract 7502.

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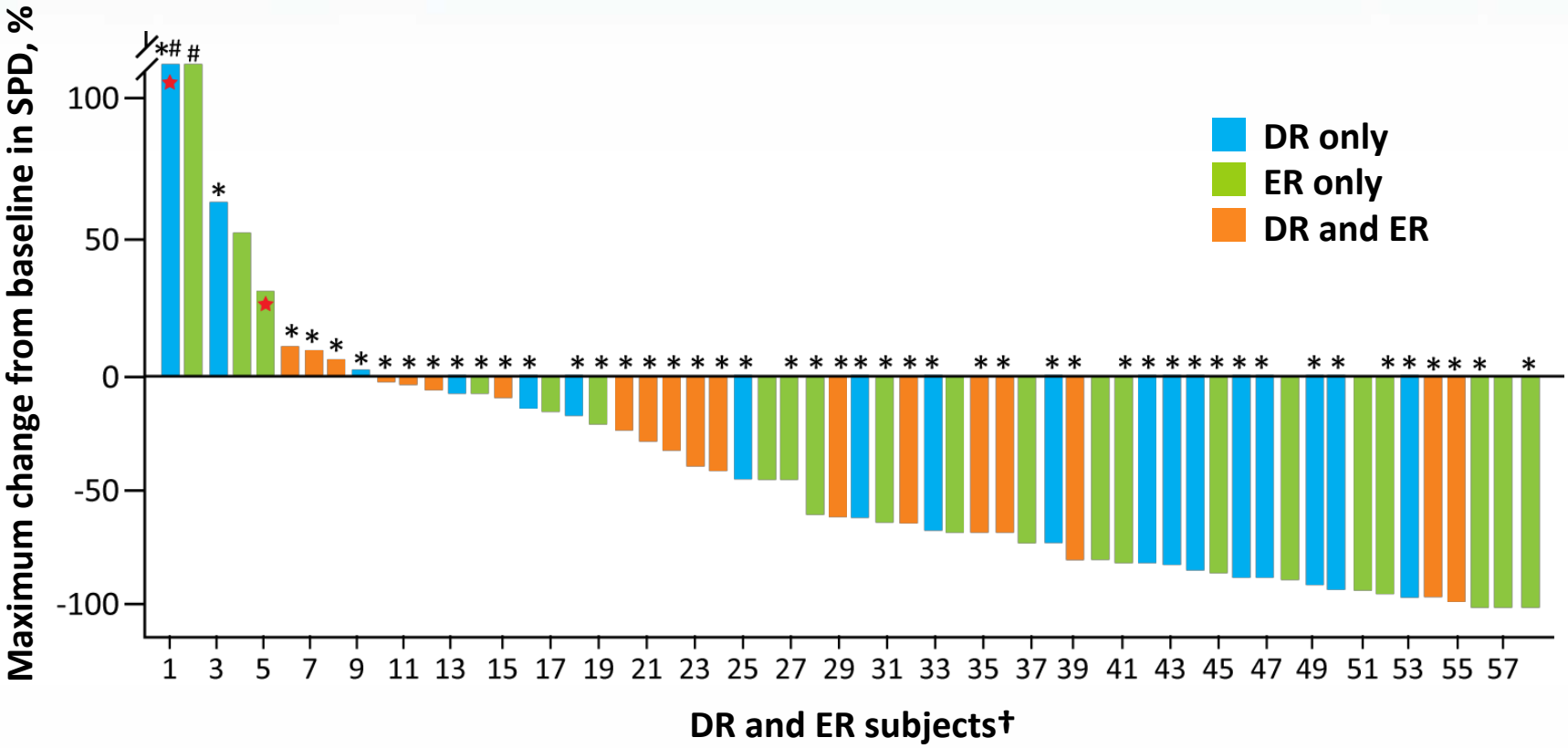
MAGNIFY Subgroup Analysis: R^2 Induction and Maintenance in Double-Refractory (DR) or Early Relapsed (ER) FL



* Patients with rituximab-refractory disease

★ Patients with transformed FL

Change in size of the target lesion falls outside the scale of this figure

† Includes patients with both baseline and postbaseline SPD assessment

Andorsky DJ et al. *Proc ASCO* 2017;Abstract 7502.

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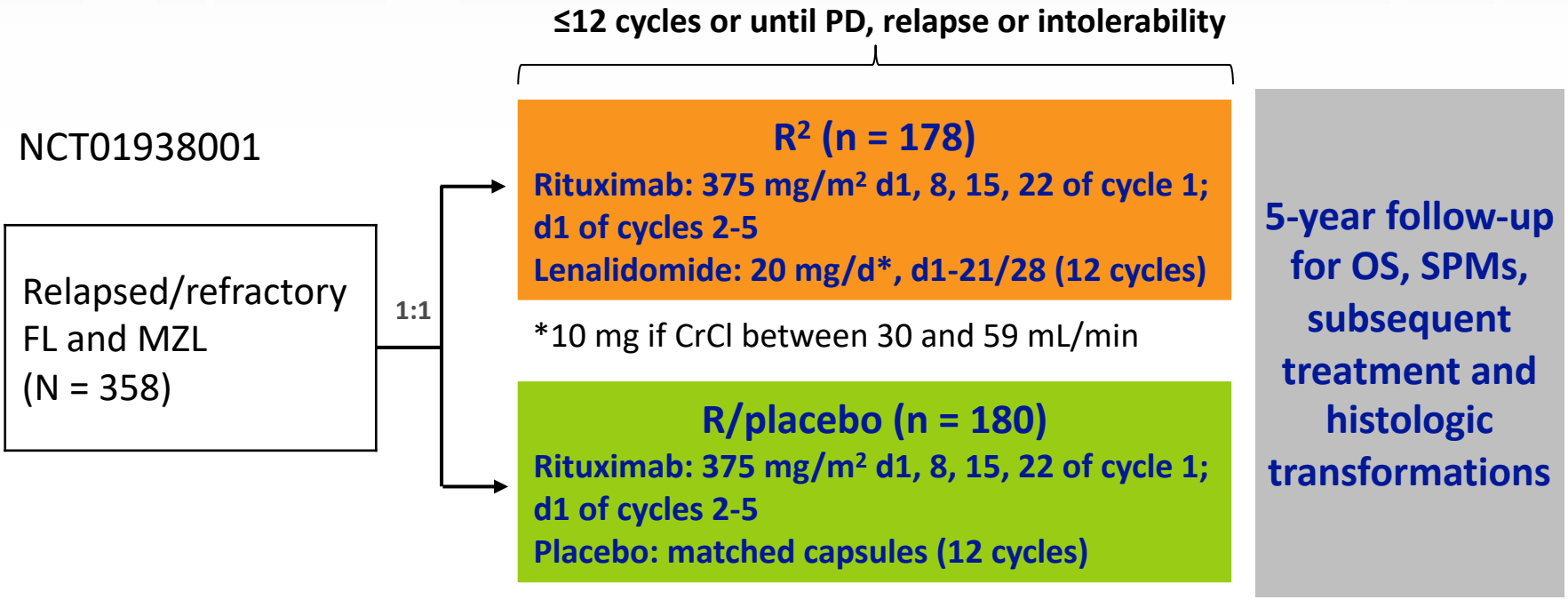
AUGMENT: A Randomized, Double-Blind Phase III Trial



- Prophylactic anticoagulation/antiplatelet Rx recommended for patients at risk
- Growth factor use was allowed per ASCO/ESMO guidelines[1,2]

Primary endpoint: PFS by IRC (2007 IWG criteria w/o PET)

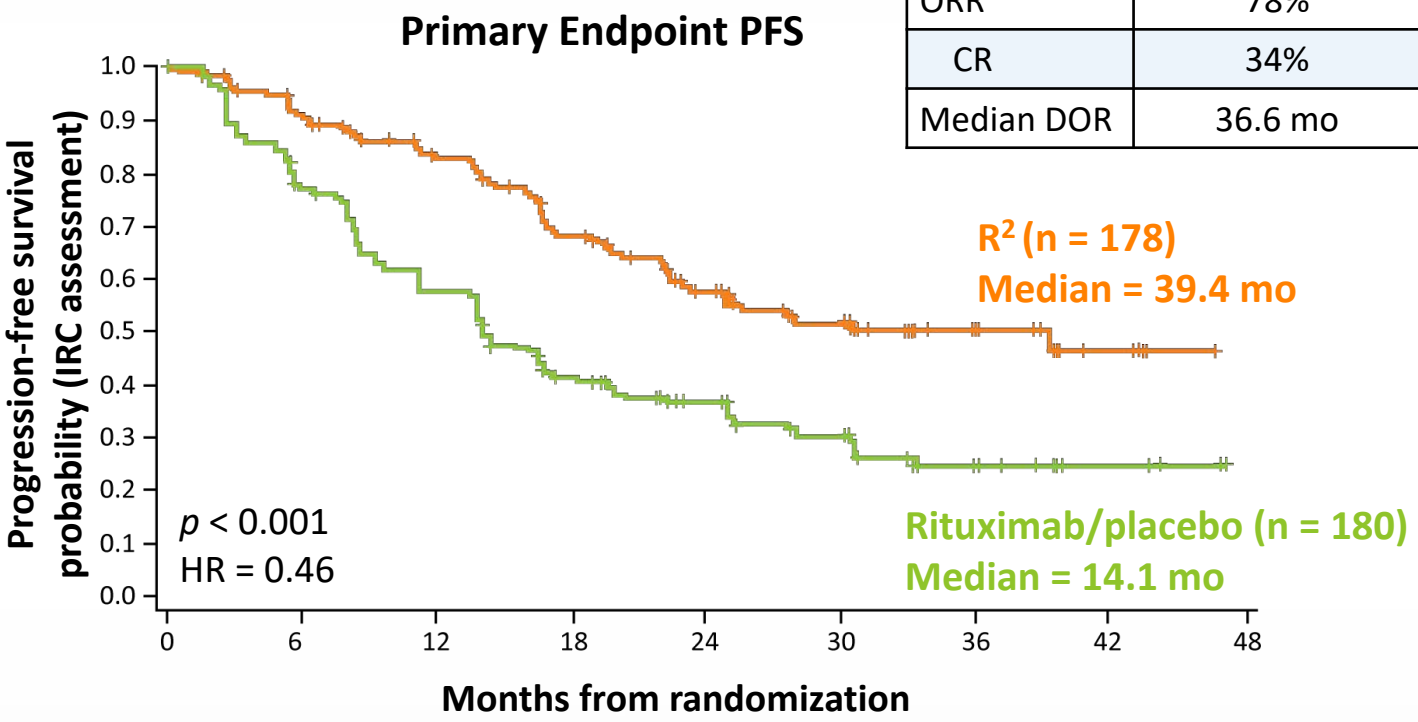
[1] Crawford J et al. *Ann Oncol* 2010;21(Suppl 5):248-51. [2] Smith TJ et al. *J Clin Oncol* 2015;33:3199-212.

Leonard JP et al. *J Clin Oncol* 2019;[Epub ahead of print]; *Proc ASH* 2018;Abstract 445.

AUGMENT: R² versus Rituximab/Placebo for R/R FL or Marginal Zone Lymphoma

By IRC	R² (n = 178)	R/placebo (n = 180)
ORR*	78%	53%
CR	34%	18%
Median DOR	36.6 mo	21.7 mo

* $p < 0.001$



- Grade 3 or 4 treatment-emergent adverse events: 69% with R² versus 32% with R/placebo
  - Neutropenia: 50% with R² versus 13% with R/placebo
  - Leukopenia: 7% with R² versus 2% with R/placebo

Leonard JP et al. *J Clin Oncol* 2019;[Epub ahead of print].

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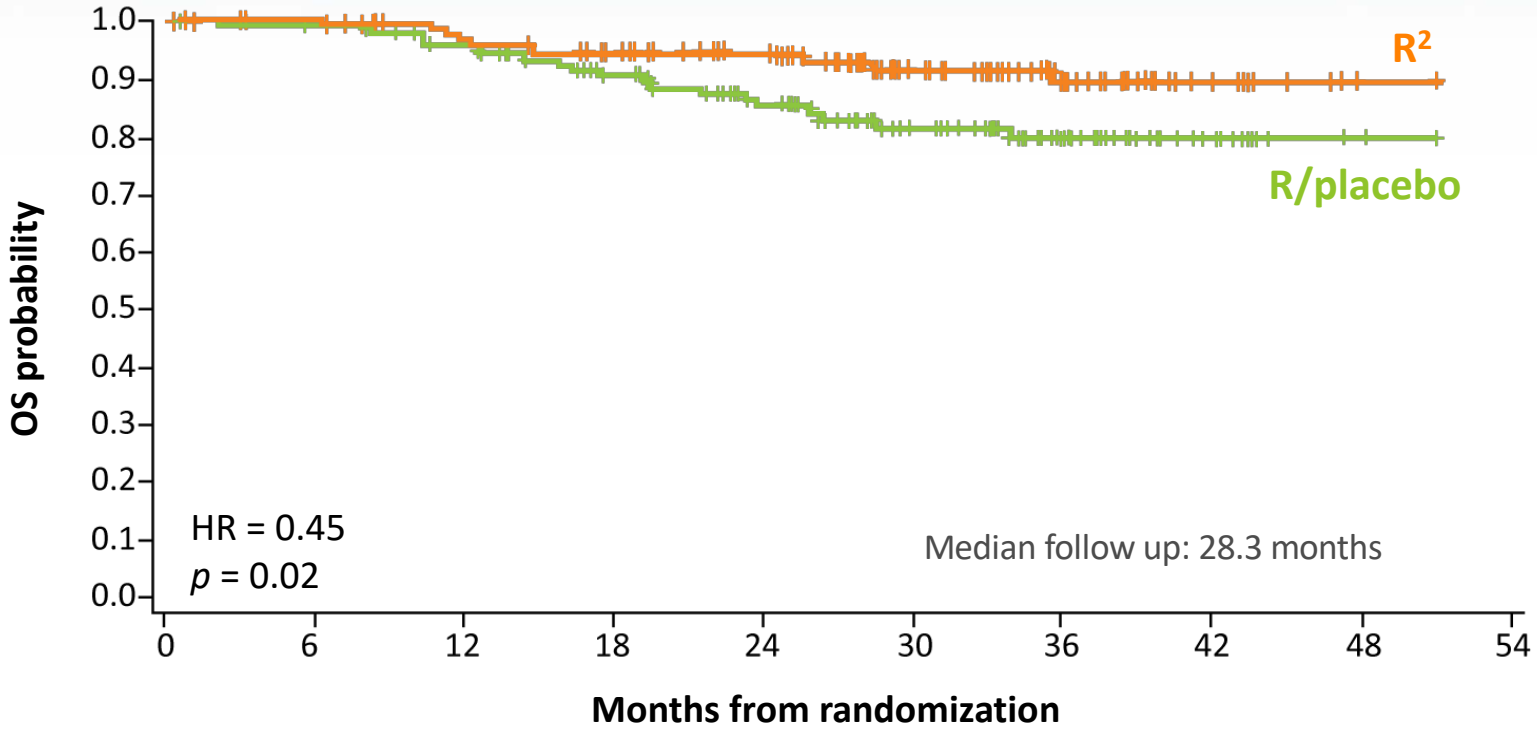
AUGMENT: Overall Survival for Patients with FL (Prespecified Subgroup Analysis)



R²	147	142	130	121	105	70	39	13	1	0
R-placebo	148	145	137	117	94	64	35	12	2	0

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

Leonard JP et al. *J Clin Oncol* 2019;[Epub ahead of print].

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FDA Approval of Lenalidomide for Follicular and Marginal Zone Lymphoma

Press Release – May 28, 2019

"The Food and Drug Administration approved lenalidomide in combination with a rituximab product for previously treated follicular lymphoma (FL) and previously treated marginal zone lymphoma (MZL). Approval was based on two clinical trials: AUGMENT (NCT01938001) and MAGNIFY (NCT01996865)….

The prescribing information includes a Boxed Warning alerting health care professionals and patients about the risk of embryo-fetal toxicity, hematologic toxicity, and venous and arterial thromboembolism which may be life-threatening or fatal.

The recommended lenalidomide dose for FL or MZL is 20 mg once daily orally on days 1-21 of repeated 28-day cycles for up to 12 cycles."

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-lenalidomide-follicular-and-marginal-zone-lymphoma

When administering the R-squared regimen of lenalidomide/rituximab for relapsed/refractory FL, what dose and schedule do you use?

 BRUCE D CHESON, MD	Ritux weekly x 4 cycle 1, then monthly for cycles 2-6; len 20 mg/d days 1-21 q28d to 12 mo
 ANDREW M EVENS, DO, MSC	AUGMENT regimen*
 CHRISTOPHER R FLOWERS, MD, MS	AUGMENT regimen*
 NATHAN H FOWLER, MD	Ritux monthly; len 20 mg d1-21 for 6 cycles
 ANN S LACASCE, MD, MMSC	AUGMENT regimen*
 JOHN P LEONARD, MD	AUGMENT regimen*
 JULIE M VOSE, MD, MBA	Ritux weekly x 4 cycle 1, then monthly x 6; len 10-15 mg days 1-21 q28d
 ANDREW D ZELENETZ, MD, PHD	Ritux monthly x 6 cycles (then q2m in months 7-12 if <CR); len 20 mg/d days 1-21 q28d

*AUGMENT regimen: Lenalidomide PO 20 mg/day (d), d1-21/28 for 12 cycles; rituximab IV 375 mg/m^2 weekly in cycle 1 and d1 of cycles 2-5.

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Selection and Sequencing of Systemic Therapy in the Management of Follicular Lymphoma (FL)

Module 1: Optimizing the Care of Patients with Newly Diagnosed FL

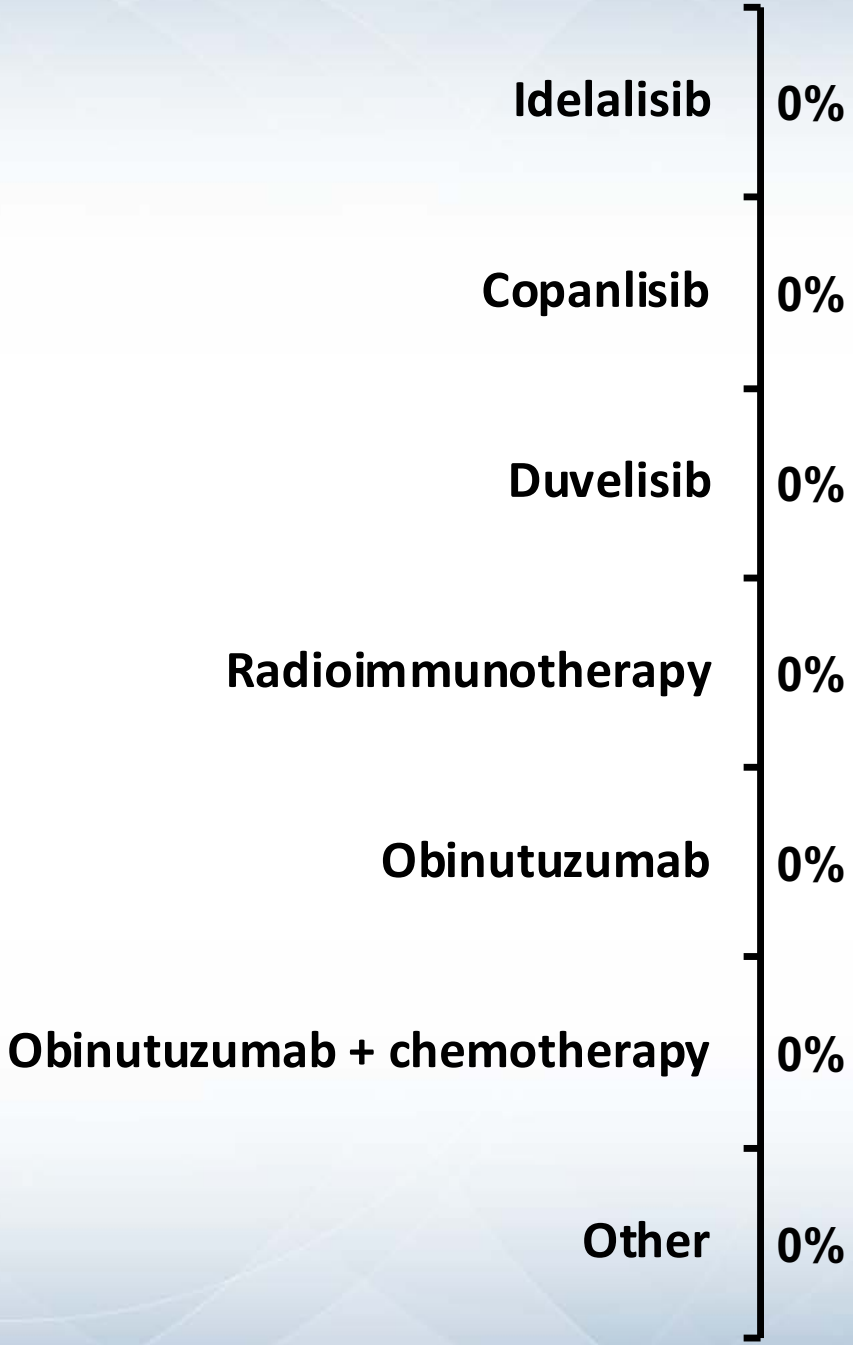
- Initiation of active therapy versus watchful waiting; indications for rituximab monotherapy
- Choice of systemic therapy for patients requiring treatment; impact of age, tumor bulk and symptomatology
- Clinical research data evaluating maintenance therapy; factors influencing its use
- Data for and clinical role of subcutaneous rituximab

Module 2: Management of Relapsed/Refractory (R/R) FL

- Factors affecting the sequencing of systemic therapy for R/R disease (eg, previous treatment received, remission duration, symptomatology)
- Integration of obinutuzumab in the R/R setting
- Role of lenalidomide/rituximab in the management of R/R FL
- Available clinical research data with the FDA-approved PI3K inhibitors

In general, what treatment would you recommend for an 80-year-old patient with FL who responds to BR followed by 2 years of maintenance rituximab and then lenalidomide/ rituximab on relapse but subsequently develops disease progression?

1. Idelalisib
2. Copanlisib
3. Duvelisib
4. Radioimmunotherapy
5. Obinutuzumab
6. Obinutuzumab + chemotherapy
7. Other



In general, what treatment would you recommend for a 60-year-old patient with FL who responds to BR followed by 2 years of maintenance rituximab and then lenalidomide/rituximab on relapse but subsequently develops disease progression?

What would you recommend if the patient were 80 years old?

	Age 60	Age 80
 BRUCE D CHESON, MD	Copanlisib	Copanlisib
 ANDREW M EVENS, DO, MSC	Radioimmunotherapy	Radioimmunotherapy
 CHRISTOPHER R FLOWERS, MD, MS	Idelalisib	Idelalisib
 NATHAN H FOWLER, MD	Idelalisib	Obinutuzumab
 ANN S LACASCE, MD, MMSC	Chemotherapy → autologous transplant	Duvelisib
 JOHN P LEONARD, MD	Idelalisib	Idelalisib
 JULIE M VOSE, MD, MBA	Chemotherapy → autologous transplant	Duvelisib
 ANDREW D ZELENETZ, MD, PHD	Idelalisib or duvelisib	Idelalisib or duvelisib

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Based on current clinical trial data and your personal experience, how would you compare the global efficacy of idelalisib, copanlisib and duvelisib in FL?

How would you compare the global tolerability/toxicity of idelalisib, copanlisib and duvelisib in FL?

	Efficacy	Tolerability/toxicity
 BRUCE D CHESON, MD	Idelalisib and copanlisib are similar, duvelisib is less active	Copanlisib has less toxicity
 ANDREW M EVENS, DO, MSC	About the same	Duvelisib has less toxicity
 CHRISTOPHER R FLOWERS, MD, MS	About the same	About the same*
 NATHAN H FOWLER, MD	About the same	Copanlisib has less toxicity
 ANN S LACASCE, MD, MMSC	About the same	Duvelisib has less toxicity
 JOHN P LEONARD, MD	About the same	Duvelisib has less toxicity
 JULIE M VOSE, MD, MBA	About the same	Not enough data to determine
 ANDREW D ZELENETZ, MD, PHD	About the same	Toxicities are distinct

*Copanlisib has unique toxicity of hyperglycemia and HTN and requires IV infusion

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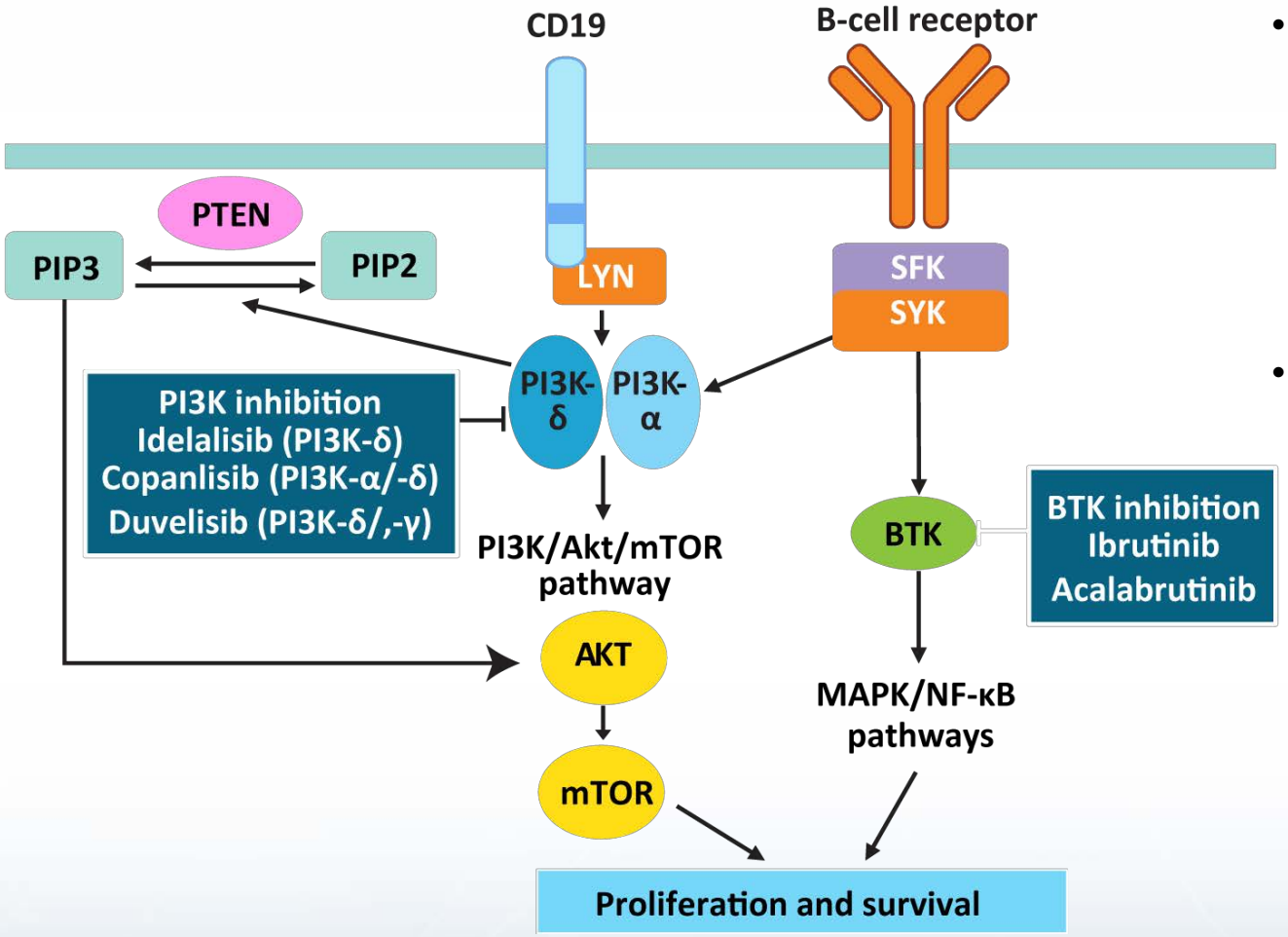
Targetable Signaling Pathways in B-Cell Lymphoma



- The B-cell receptor (BCR) and phosphoinositide 3-kinase (PI3K) signaling pathways play a key role in the proliferation and survival of indolent B-cell lymphomas
- Targeted inhibition of BCR/PI3K signaling has emerged as a therapeutic strategy for relapsed/refractory indolent B-cell lymphoma

Adapted from Zinzani PL et al. *Proc ESMO* 2018;Abstract 1006O.

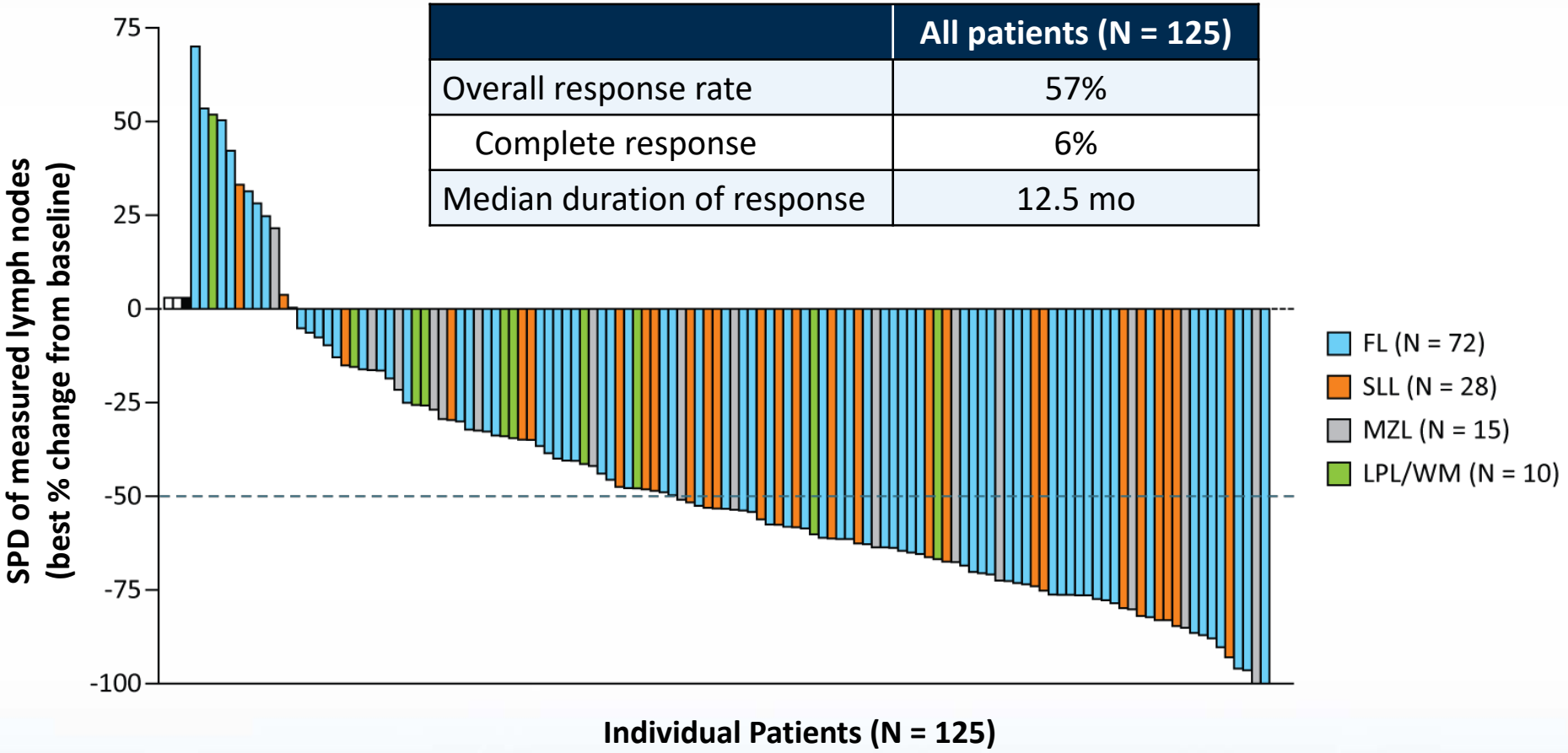
Approved PI3K Inhibitors for FL: Indication and Dosing

	Idelalisib[1]	Copanlisib[2]	Duvelisib[3]
Mechanism of action	Selective PI3Kδ inhibitor	Dual inhibitor of PI3Kδ,α	Dual inhibitor of PI3Kδ,γ
Indication	Relapsed FL after at least 2 prior systemic therapies	Relapsed FL after at least 2 prior systemic therapies	R/R FL after at least 2 prior systemic therapies
Dosing	150 mg orally, twice daily	60 mg as a 1-hour IV infusion weekly (3 weeks on, 1 week off)	25 mg orally, twice daily

[1] Gopal AK et al. *N Engl J Med* 2014;370(11):1008-18; Idelalisib package insert, January 2018.
[2] Dreyling M et al. *J Clin Oncol* 2017;35(35):3898-905; Copanlisib package insert, September 2017.
[3] Flinn IW et al. *J Clin Oncol* 2019;[Epub ahead of print]; Zinzani PL et al. *Proc EHA* 2017;Abstract S777; Duvelisib package insert, September 2018.

A Phase II Study of Idelalisib in R/R Indolent B-Cell Lymphoma

	All patients (N = 125)
Overall response rate	57%
Complete response	6%
Median duration of response	12.5 mo



FL = follicular lymphoma; SLL = small lymphocytic lymphoma; MZL = marginal zone lymphoma; LPL/WM = lymphoplasmacytic lymphoma/Waldenström macroglobulinemia

Gopal AK et al. *NEJM* 2014;370(11):1008-18; Idelalisib package insert, January 2018.

A Phase II Study of Idelalisib in R/R Indolent B-Cell Lymphoma

Select adverse events (N = 125)	All grades	Grade 3/4
Any adverse event	82%	54%
Neutropenia	56%	27%
Increased ALT	47%	13%
Diarrhea	43%	13%
Increased AST	35%	8%
Anemia	28%	2%
Rash	13%	2%

Gopal AK et al. *NEJM* 2014;370(11):1008-18; Idelalisib package insert, January 2018.

The hyperglycemia associated with copanlisib generally occurs during or immediately after the infusion.

 BRUCE D CHESON, MD	Agree
 ANDREW M EVENS, DO, MSC	Agree
 CHRISTOPHER R FLOWERS, MD, MS	Agree
 NATHAN H FOWLER, MD	Agree
 ANN S LACASCE, MD, MMSC	Agree
 JOHN P LEONARD, MD	Agree
 JULIE M VOSE, MD, MBA	Not enough experience to comment
 ANDREW D ZELENETZ, MD, PHD	Agree

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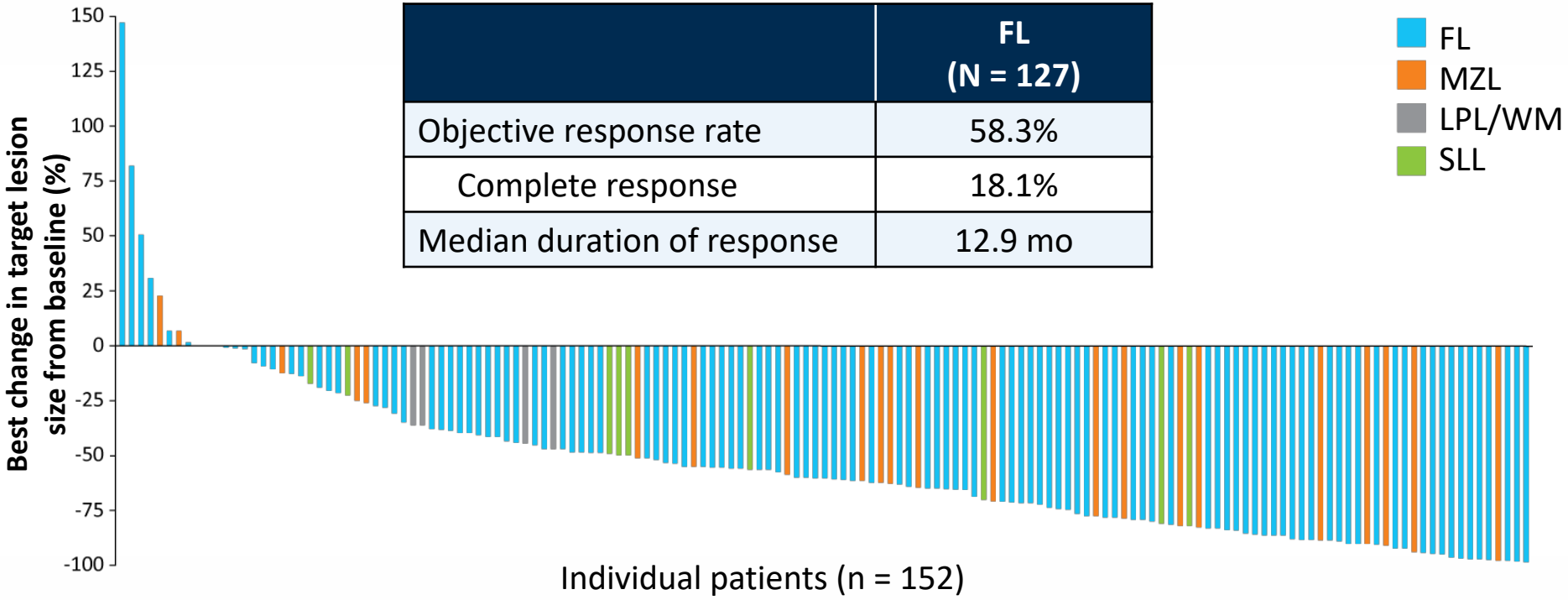
Combined Analysis of Phase I and II Studies of Copanlisib in R/R Indolent B-Cell Lymphoma

	FL (N = 127)
Objective response rate	58.3%
Complete response	18.1%
Median duration of response	12.9 mo



FL = follicular lymphoma; MZL = marginal zone lymphoma; LPL/WM = lymphoplasmacytic lymphoma/Waldenström macroglobulinemia; SLL = small lymphocytic lymphoma

Zinzani PL et al. *Proc ESMO* 2018;Abstract 1006O.

Combined Analysis of Phase I and II Studies of Copanlisib in R/R Indolent B-Cell Lymphoma

Select adverse events (n = 168)	All grades	Grade 3/4
Any adverse event	99%	84%
Hyperglycemia	52%	38%
Diarrhea	37%	7%
Hypertension	35%	28%
Neutropenia	29%	23%
Pneumonia	11%	9%

Zinzani PL et al. *Proc ESMO* 2018;Abstract 1006O.

Efficacy of Copanlisib in Patients with FL with Early Relapse (<24 months)

Response	Copanlisib (n = 102)	
	POD <24 mo (n = 68)	POD >24 mo (n = 34)
Objective response	60.3%	58.8%
Complete response	22.1%	17.7%
Partial response	38.2%	41.2%
Median duration of response	14.9 mo	14.1 mo
Median PFS	11.3 mo	17.6 mo

POD = progression of disease

Santoro A et al. *Proc ASH* 2018;Abstract 395.

DYNAMO: A Phase II Study of Duvelisib for Double-Refractory Indolent NHL

- Of 129 patients with indolent NHL on study, 83 patients with FL received duvelisib

Response in patients with FL (by IRC)	Duvelisib (n = 83)
ORR CR PR	42.2% 1.2% 41%
Select Grade ≥3 adverse events	n = 129
Neutropenia	24.8%
Diarrhea	14.7%
Anemia	14.7%
Thrombocytopenia	11.6%

For all treated patients (N = 129):

- ORR = 47.3%
- Median time to response = 1.87 months
- Median DoR = 10 months
- Median PFS = 9.5 months
- Median OS = 28.9 months

Flinn IW et al. *J Clin Oncol* 2019;[Epub ahead of print].

To obtain feedback from one of the expert steering committee members, please submit any questions or cases related to the topics discussed today at the Grand Rounds Follicular Lymphoma Submission Portal: www.ResearchToPractice.com/Meetings/GrandRoundsFL2019/Questions

Dr Neil Love and Research To Practice will contact you directly with their input.

To view the slides please visit
www.ResearchToPractice.com/Meetings/Slides

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VISITING PROFESSORS: Selection and Sequencing of Systemic Therapy in the Management of Follicular Lymphoma

An Interactive Grand Rounds Series

John P Leonard, MD
Richard T Silver Distinguished Professor of Hematology
and Medical Oncology
Associate Dean for Clinical Research
Weill Cornell Medical College
New York, New York

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