

# Follicular Lymphoma – Is there a standard first-line treatment?

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# Disclosures

- Consulting
  - Genentech/Roche, ADC Therapeutics, Abbvie, AstraZeneca, BeiGene, Celgene/BMS, Kite, Genmab, Lilly, GSK
- Research Funding
  - Genentech/Roche, Abbvie, AstraZeneca, BeiGene

# Follicular Lymphoma

- 2<sup>nd</sup> most common non-Hodgkin lymphoma in The United States
  - ~ 20,000 new cases/year
- Incidence increases with age
  - Median age 6<sup>th</sup> decade of life
- Prototype of “low grade” lymphomas
  - Indolent course with median survival 15+ yrs
  - Spontaneous remissions possible
  - Incurable?
  - Many patients may be “functionally cured”
- Risk of transformation over time **2-3% per year**

# FL Treatment Issues

- Cure is unlikely, so need different goals
  - Management, control, etc...
- Prognosis is quite good
  - Median OS exceeding 15 years
- Many effective treatment options
  - Can make decision making difficult
- Patient specific issues are important
  - Age, co-morbidities, coping style, FL risk-factors
- Don't want to overtreat, don't want to undertreat
  - Goldilocks principle

## How to assign “risk” to a newly diagnosed patient

1. FLIPI
  - Predicts OS
2. FLIPI 2
  - Predicts PFS to immunochemotherapy
3. M7 – FLIPI (mutations of 7 genes plus FLIPI)
  - Predicts FFS to R-CHOP
4. Gene Expression Profiling
  - Predicts PFS to R-CHOP

Turns out, none of these are very good at predicting who is likely to die from their FL

# Other Tools

- Tumor grade
  - 1-2, vs. 3a vs. 3b
  - Can help guide your treatment selection
  
- GELF criteria
  - Developed to identify appropriate W&W candidates
  - Can help guide the timing of treatment

# GELF Criteria

- 3 nodes greater than 3 cm
- Single node greater than 7 cm
- Compression or risk of compression of vital organ
- Significant serous effusions
- Cytopenias due to marrow infiltration
  - Hgb <10, ANC < 1.5, Plts < 100k
- Splenomegaly greater than 16 cm
- Elevated LDH or B2M

# A Way to Approach a Newly Diagnosed Patient

	Low Tumor Burden	High Tumor Burden
Symptoms absent	Watch & Wait vs. Single agent rituximab	R-chemo +/- MR vs. Watch & Wait
Symptoms present	Single agent rituximab vs. R-chemo	R-chemo +/- MR



# High Tumor Burden FL: Decisions to Make

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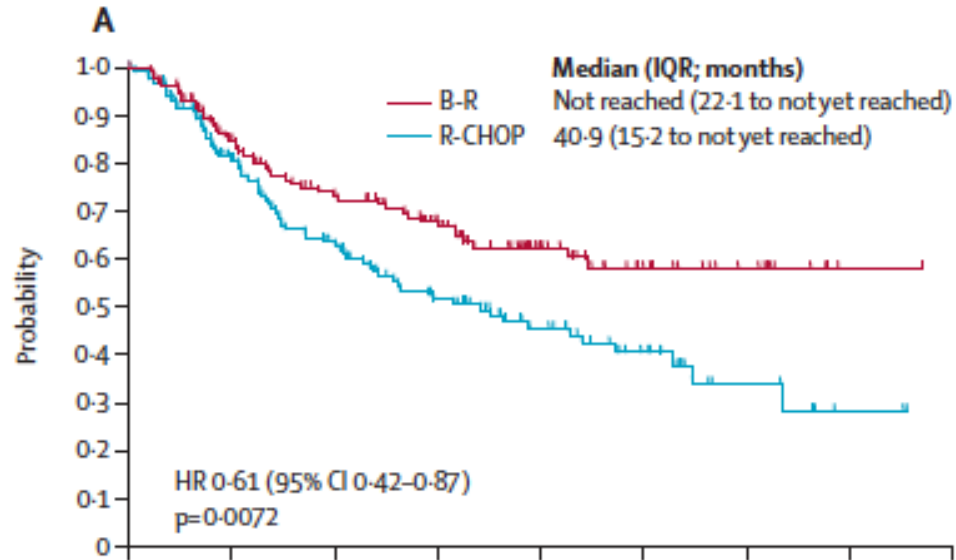
1. Which chemotherapy backbone?
2. Which MoAb?
3. Whether to use maintenance?

I typically use Bendamustine plus Rituximab with no maintenance but equally reasonable to choose

- Bendamustine + Obinutuzumab
- R-CHOP
- O-CHOP

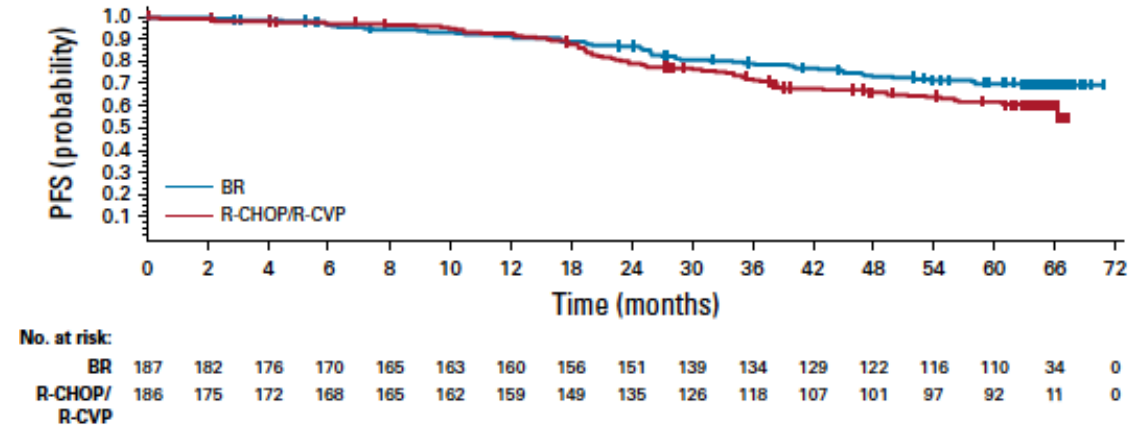
# BR vs. R-CHOP

StIL Trial: Median f/u 45 months



Rummel et al, Lancet 2013

BRIGTH Trial: Median f/u 65 months



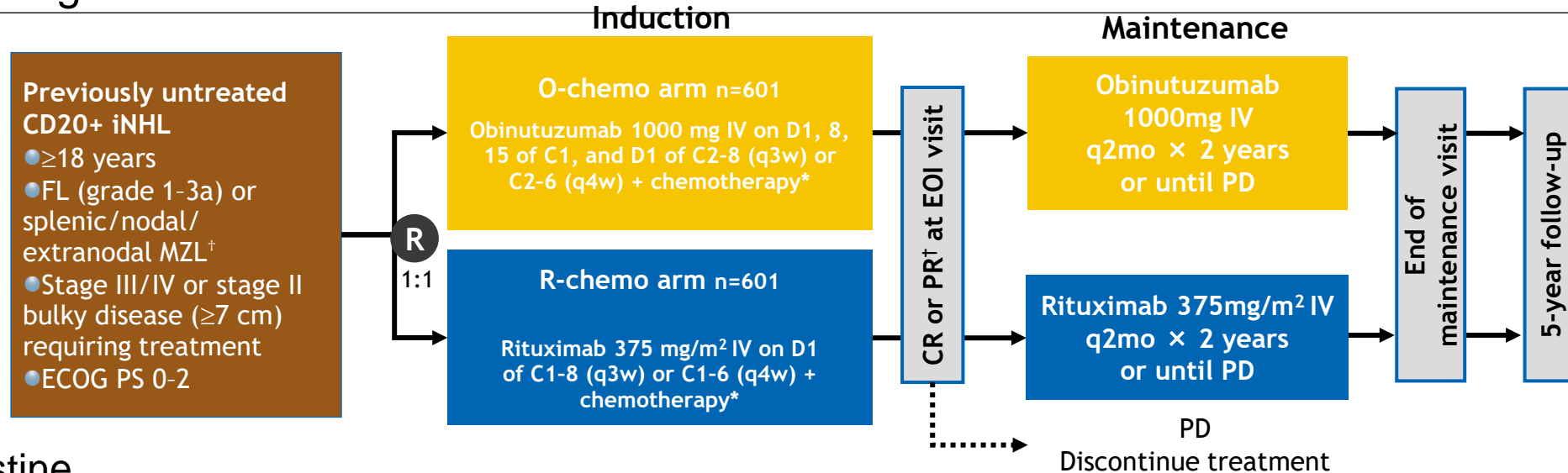
Flinn et al, JCO 2019

# Results not completely congruent

- BR better than R-CHOP in StIL
  - Much longer PFS
    - No maintenance rituximab administered
  - Less toxic in short term
- BR roughly equivalent to R-CHOP in BRIGHT
  - PFS not statistically better (trend towards better, certainly not worse)
    - About 50% of patients received maintenance rituximab
  - Toxicity tradeoff in short term.
- OS similar in both
- I have found bendamustine easier to deliver than CHOP in FL

# GALLIUM: A test of MoAbs

## Study Design

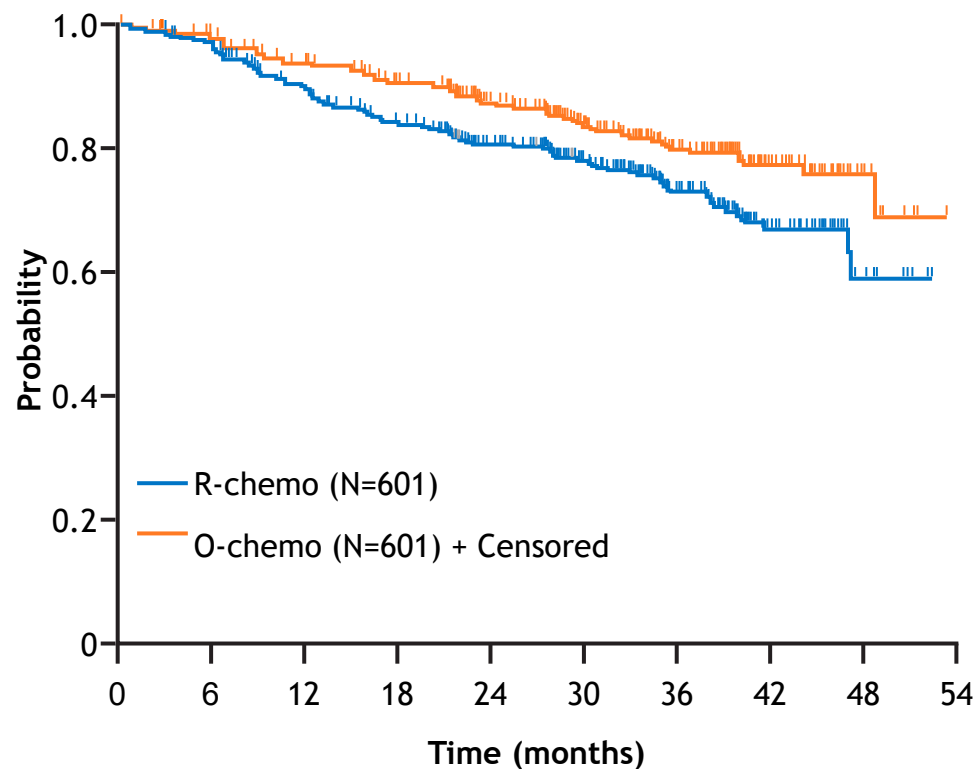


Bendamustine  
CHOP  
CVP

<b>Primary endpoint</b>	PFS <sup>‡</sup> by investigator in FL patients
<b>Secondary endpoints</b>	PFS <sup>‡</sup> by investigator in iNHL; PFS <sup>‡</sup> by IRC, ORR/CR <sup>‡</sup> at EOI by investigator and IRC (+/- FDG-PET), OS, EFS, DFS, DoR, TTNT, safety and PROs (FACT-Lym, EQ-5D) in iNHL and FL

# GALLIUM

Primary Endpoint: Investigator-Assessed PFS in FL



No. of patients at risk

R-chemo	601	562	505	463	378	266	160	68	10
G-chemo	601	570	536	502	405	278	168	75	13

PFS by investigator	O-chemo (n=601)	R-chemo (n=601)
Events, n (%)	101 (16.8)	144 (24.0)
3-year PFS, % (95% CI)	80.0 (75.9, 83.6)	73.3 (68.8, 77.2)
Median PFS, months (95% CI)	Not reached	Not reached
Stratified HR (95% CI), p-value	<b>0.66</b> (0.51, 0.85) <b>p=0.001</b>	

Marcus et al, NEJM 2017

# GALLIUM Conclusions

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- Is Obinutuzumab a better anti-CD20 MoAb than Rituximab?
  - Appears superior in CLL
  - Not better in DLBCL (see GOYA results)
- In Follicular Lymphoma
  - PFS better with O-chemo. No OS difference
- Are the positive results simply a function of giving more MoAb?
  - Obinutuzumab patients received approximately 35% more Ab
  - HR for progression reduced by approximately 35%
- Perfectly reasonable to choose obinutuzumab in frontline



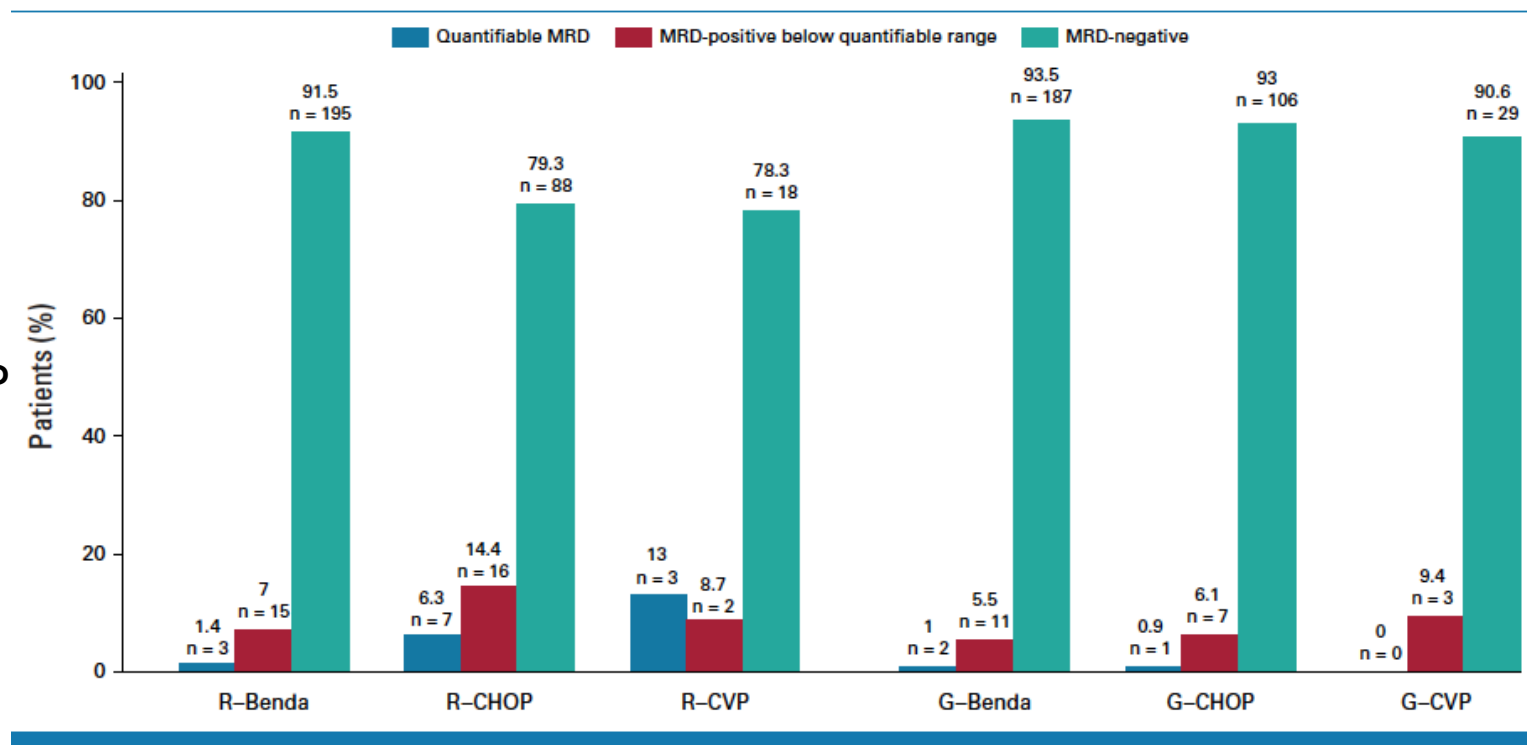
## Minimal Residual Disease Status Predicts Outcome in Patients With Previously Untreated Follicular Lymphoma: A Prospective Analysis of the Phase III GALLIUM Study

Christiane Pott, MD, PhD<sup>1</sup>; Vindi Jurinovic, PhD<sup>2,3</sup>; Judith Trotman, MBChB<sup>4</sup>; Britta Kehden, PhD<sup>1</sup>; Michael Unterhalt, MD, PhD<sup>2</sup>; Michael Herold, MD<sup>5</sup>; Richard van der Jagt, MD<sup>6</sup>; Ann Janssens, MD, PhD<sup>7</sup>; Michael Kneba, MD<sup>1</sup>; Jiri Mayer, MD, PhD<sup>8</sup>; Moya Young, MBBS, MRCP, FRCPath<sup>9</sup>; Christian Schmidt, MD<sup>2</sup>; Andrea Knapp, PhD<sup>10</sup>; Tina Nielsen, MD, PhD<sup>10</sup>; Helen Brown, MPhil<sup>11</sup>; Nathalie Spielwoy, PhD<sup>10</sup>; Chris Harbron, MPhil<sup>11</sup>; Alessia Bottos, PhD<sup>10</sup>; Kirsten Mundt, PhD<sup>10</sup>; Robert Marcus, MD<sup>12</sup>; Wolfgang Hiddemann, MD, PhD<sup>2</sup>; and Eva Hoster, PhD<sup>2,3</sup>

DOI <https://doi.org/10.1200/JCO.23.00838>

MRD results suggest:

1. Benda slightly better than CHOP
2. Obinutuzumab is an equalizer

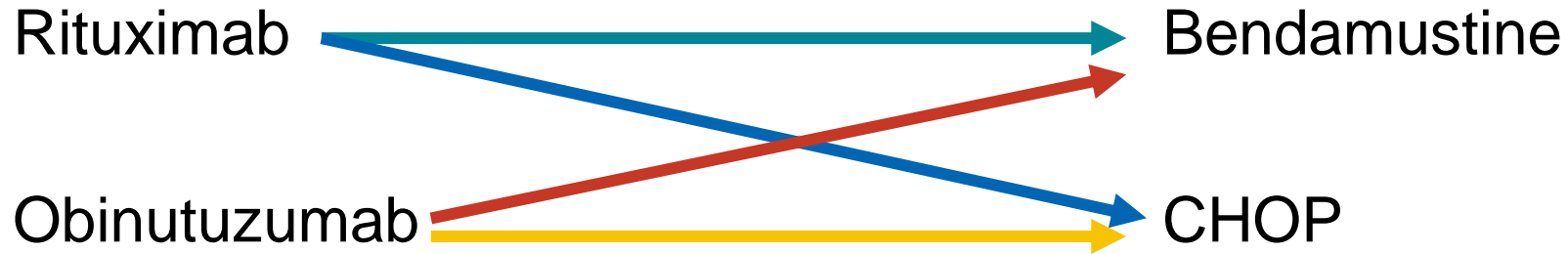


# The Decisions

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## PICK A MONOCLONAL ANTIBODY

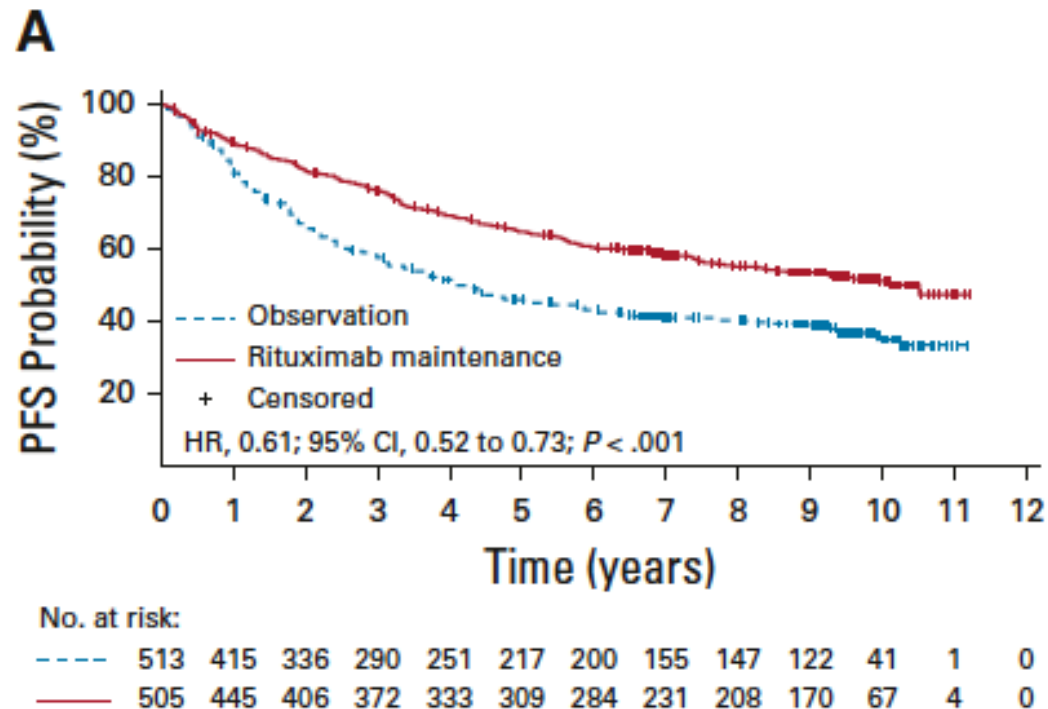
## PICK A CHEMOTHERAPY



Should you give maintenance MoAb therapy?



# Maintenance: PRIMA Long Term Follow Up



- Large PFS benefit after R-CHOP/R-CVP
- 20% absolute difference at 5-10 years
- Small benefit in time to next lymphoma therapy
- Slight increase in infections
- No OS benefit
- MR commonly utilized based upon PRIMA data

# Wisdom of maintenance? Toxicity Considerations from GALLIUM

## Fatal AE rate:

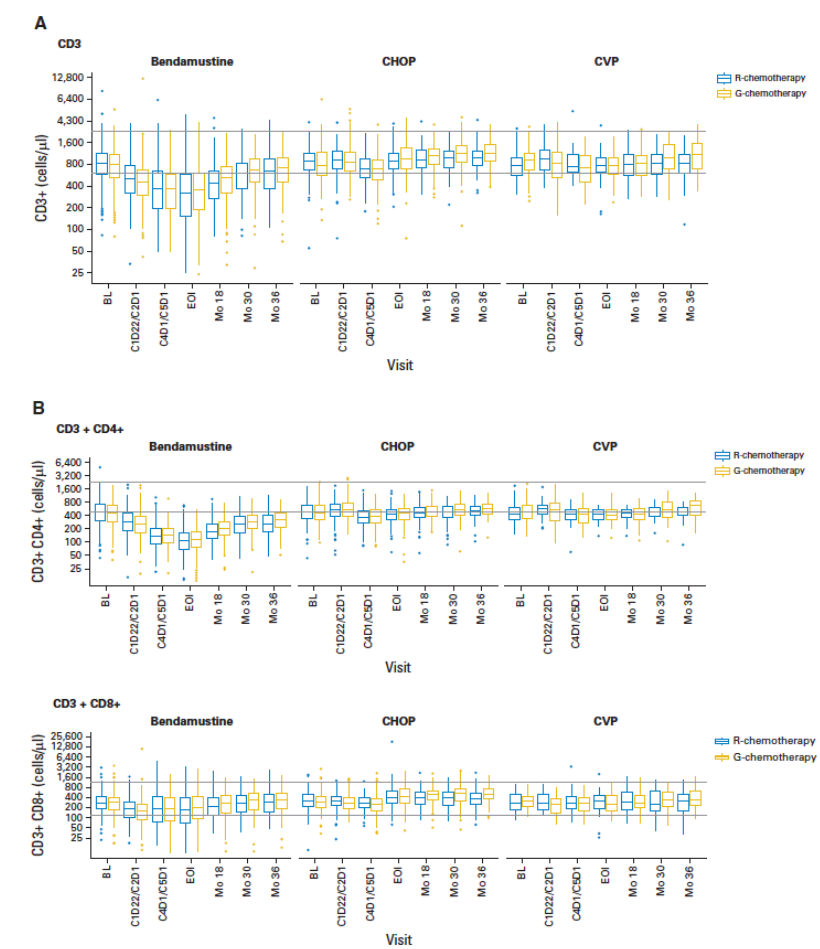
G-Benda: 6.8%

R-Benda: 5.1%

G-CHOP: 1.6%

R-CHOP: 2.5%

	G-chemo			R-chemo		
	Induction	Maintenance	Follow-up	Induction	Maintenance	Follow-up
<b>Benda</b>	3/338 (0.9%)	7/312 (2.2%)	10/270 (3.7%)	2/338 (0.6%)	8/305 (2.6%)	5/263 (1.9%)
<b>CHOP</b>	1/193 (0.5%)	2/179 (1.1%)	0/128 (0.0%)	0/203 (0.0%)	2/187 (1.1%)	2/143 (1.4%)
<b>CVP</b>	0/61 (0.0%)	1/57 (1.8%)	0/44 (0.0%)	1/56 (1.8%)	0/43 (0.0%)	0/45 (0.0%)



Hiddemann et al, JCO 2018

Significant and prolonged T cell depletion after bendamustine

# Wisdom of maintenance MoAb

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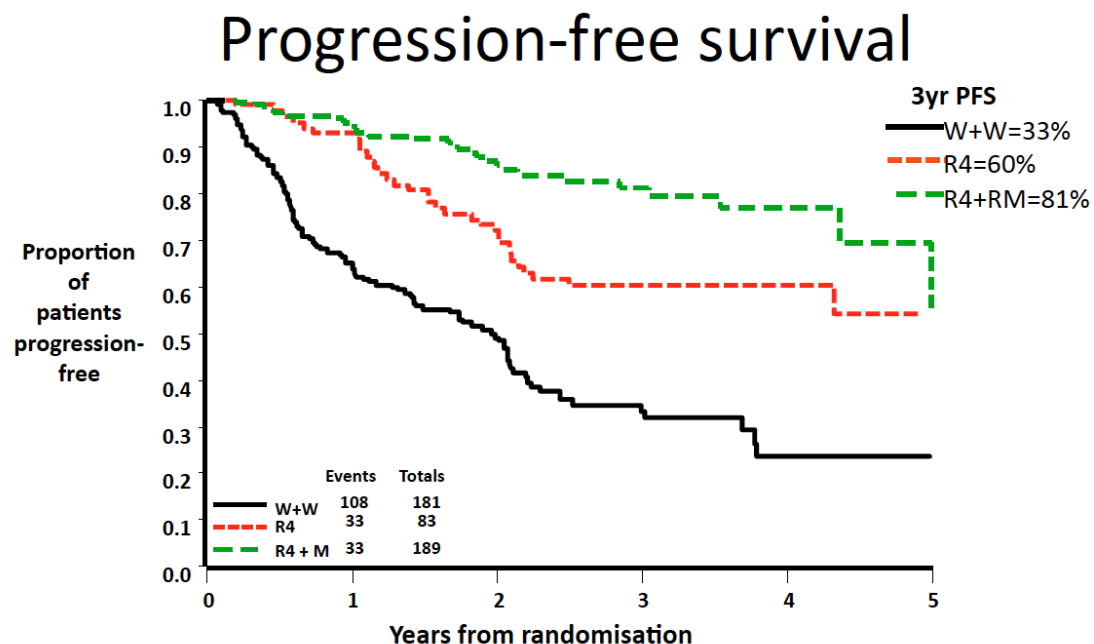
- Prolongs PFS, No impact on OS
- Prolonged B cell depletion was surprisingly low risk, until COVID pandemic
  - We learned (the hard way) the risk with new pathogens
  - Higher mortality from COVID
  - Harder to vaccinate
- Risk/benefit ratio may favor “no maintenance” particularly if using bendamustine
  - Prolonged B cell depletion combined with prolonged T cell depletion
- I am not recommending maintenance at this time

## When is single agent rituximab appropriate?

	Low Tumor Burden	High Tumor Burden
Symptoms absent	Watch/Wait vs. single agent rituximab	R-chemo +/- MR vs. Watch/Wait
Symptoms present	Single agent rituximab vs. R-chemo	R-chemo +/- MR

# When is it OK to administer single agent rituximab?

## UK TRIAL OF R VS WATCH AND WAIT



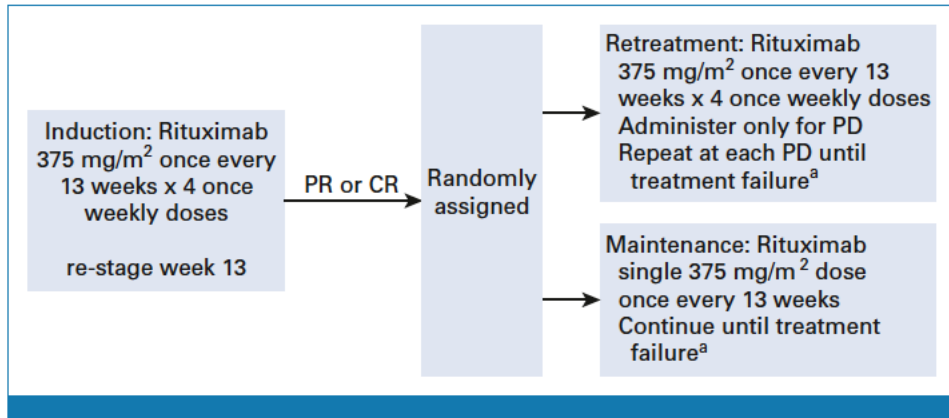
Ardeshtna et al, Lancet Oncology 2014

## Some guidelines

- Rituximab works best in low tumor burden FL
  - Loses efficacy when nodes > 5 cm
  - Loses efficacy if LDH elevated
- Consider when:
  - Patient elderly, frail, with co-morbidities
  - Patient struggles to cope with W&W
- RESORT trial showed effective to use re-treatment strategy vs. maintenance

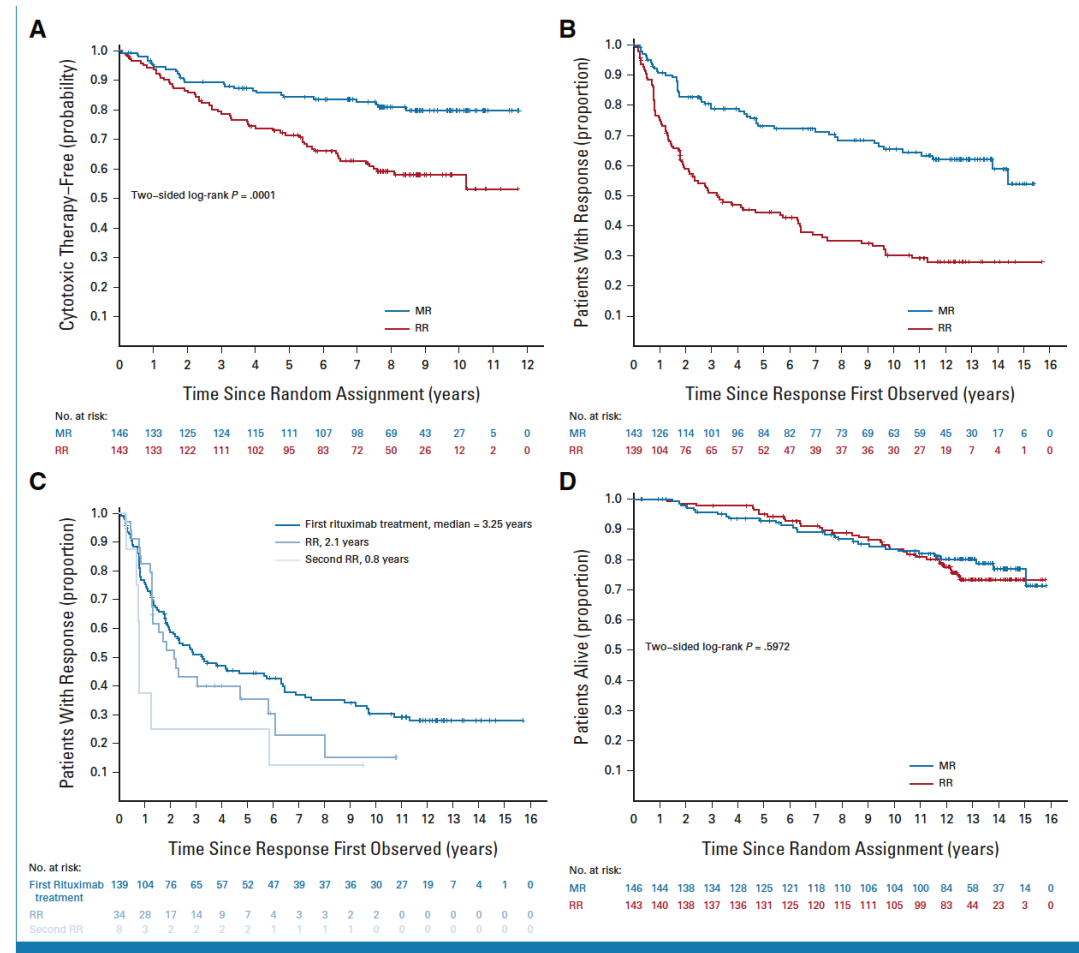
Kahl...Williams et al, JCO 2014 & 2024

# RESORT: Long Term Follow Up

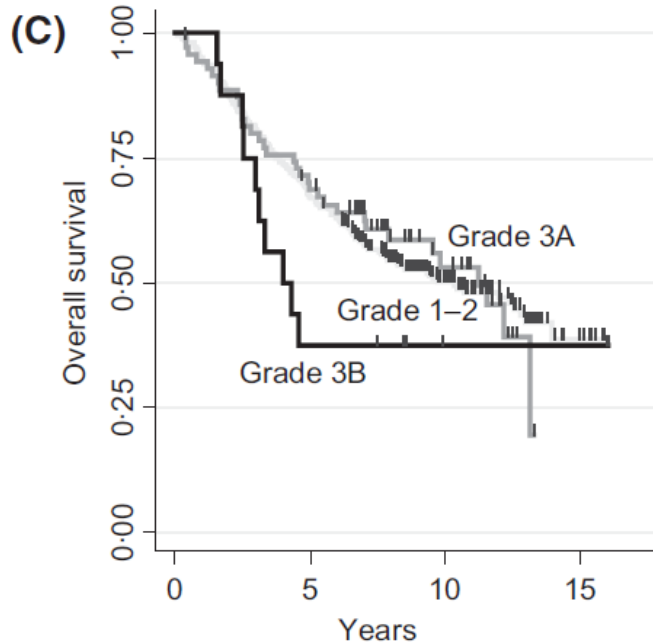


**FIG 1.** RESORT treatment schema. <sup>a</sup>Treatment failure definition: (1) no response to retreatment or PD within 26 weeks of last rituximab dose, (2) initiation of alternative treatment, and (3) inability to complete the planned rituximab treatment. CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

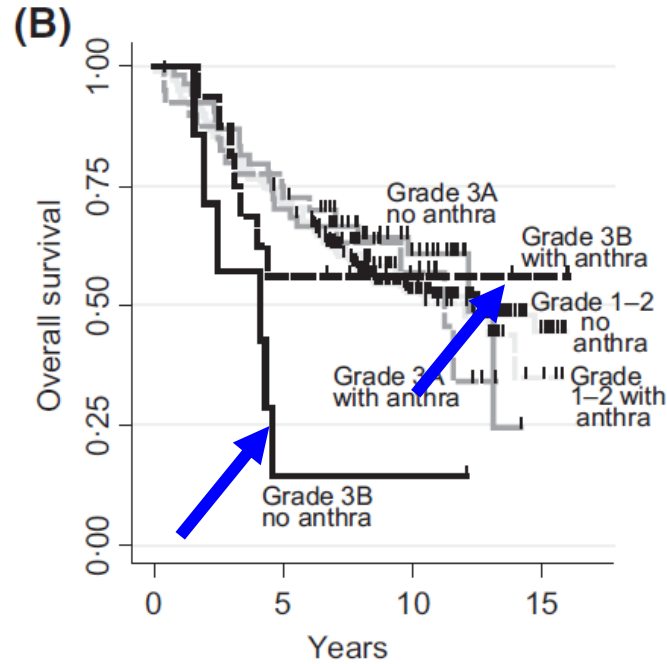
Kahl...Williams et al, JCO 2014 & 2024



# Special Situations: FL3A: prognosis is similar to FL1-2. FL3B better managed like DLBCL



No. of patients at risk				
	0	5	10	15
Grade 1-2	279	186	81	8
Grade 3A	70	49	20	0
Grade 3B	16	7	3	1



No. of patients at risk				
	0	5	10	15
1-2 no A.	243	173	81	13
1-2 w. A.	102	73	28	4
3A no A.	54	39	18	0
3A w. A.	40	30	10	0
3B no A.	7	1	1	0
3B w. A.	16	10	4	2

Favor anthracycline-based therapy when:

- Grade 3B
- Aggressive Presentation
  - High SUV on PET
  - High LDH
  - High Ki67
  - Bony destruction
  - Large effusions
  - Any concern for occult transformation

# What would “beating” BR/R-CHOP look like?

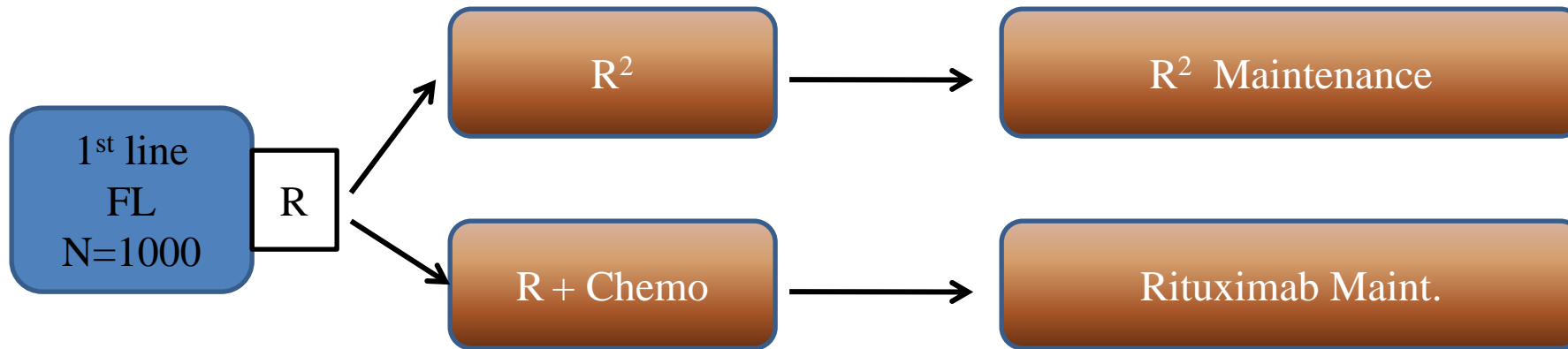
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- Better PFS at 3-5 years - without increased toxicity
- Comparable PFS at 3-5 years with less toxicity
  - BR (with no maintenance) is WELL TOLERATED
- Could just focus on the 10-20% of progressions in 1<sup>st</sup> two years
  - No biomarkers to accurately identify high risk patients at diagnosis
  - Efforts such of POD24 PI were not precise enough



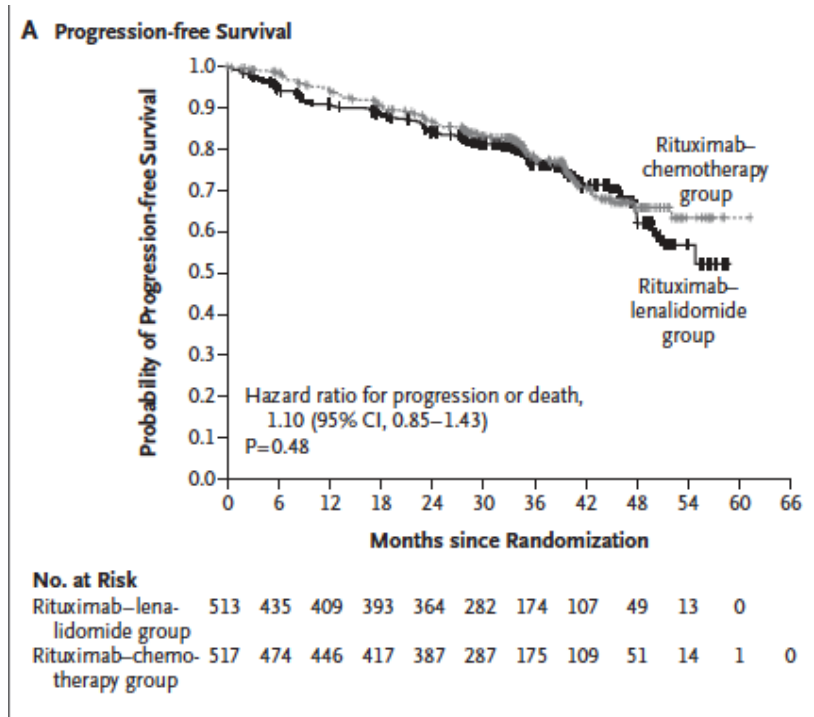
# Novel Approaches to Frontline: RELEVANCE Study Design

(Rituximab and LEnalidomide versus Any ChEmotherapy)



- R+Chemo:
  - Investigator's choice of R-CHOP, R-CVP, BR
- Lenalidomide 20mg for 6 cycles, then 10mg if CR
- GELA + Selected North American Sites

# RELEVANCE Results



**Table 3. Adverse Events during the Treatment Period in the Safety Population.**

Adverse Event	Rituximab–Lenalidomide Group (N=507)		Rituximab–Chemotherapy Group (N=503)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	<i>number of patients (percent)</i>			
Neutropenia*	381 (75)	160 (32)	386 (77)	252 (50)
Anemia*	333 (66)	0	446 (89)	0
Thrombocytopenia*	268 (53)	11 (2)	266 (53)	8 (2)
Cutaneous reactions†	220 (43)	36 (7)	120 (24)	5 (1)
Diarrhea	187 (37)	10 (2)	95 (19)	6 (1)
Constipation	178 (35)	1 (<1)	167 (33)	5 (1)
Rash	146 (29)	20 (4)	39 (8)	1 (<1)
Fatigue	115 (23)	1 (<1)	147 (29)	4 (<1)
Nausea	100 (20)	0	209 (42)	8 (2)
Abdominal pain	78 (15)	4 (<1)	46 (9)	4 (<1)
Myalgia	73 (14)	0	29 (6)	1 (<1)
Arthralgia	71 (14)	3 (<1)	70 (14)	1 (<1)
Peripheral edema	69 (14)	0	47 (9)	1 (<1)
Muscle spasms	68 (13)	0	21 (4)	0
Infusion-related reaction	66 (13)	7 (1)	56 (11)	1 (<1)
Upper respiratory tract infection	47 (9)	0	55 (11)	0
Vomiting	34 (7)	2 (<1)	94 (19)	7 (1)
Peripheral neuropathy	35 (7)	1 (<1)	79 (16)	3 (<1)
Tumor flare reaction	30 (6)	7 (1)	1 (<1)	0
Leukopenia	21 (4)	8 (2)	48 (10)	30 (6)
Febrile neutropenia	11 (2)	11 (2)	34 (7)	33 (7)
Tumor lysis syndrome	7 (1)	6 (1)	5 (1)	3 (<1)
Alopecia	5 (1)	0	45 (9)	3 (<1)

Morschauer et al, NEJM 2018

# Lessons Learned

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- **RELEVANCE**
  1. It is hard to beat BR (or equivalent)
  2. If RELEVANCE had been designed as a non-inferiority study and achieved frontline approval for R2, the results still would not truly have moved the needle in frontline FL
- We are going to need better drugs, predictive biomarkers, or both
  1. Currently no predictive biomarkers except EZH2 mutation - tazemetostat
  2. Better drugs? Maybe Bi-specific MoAb will pan out.
  3. Companies suddenly interested in frontline FL again.

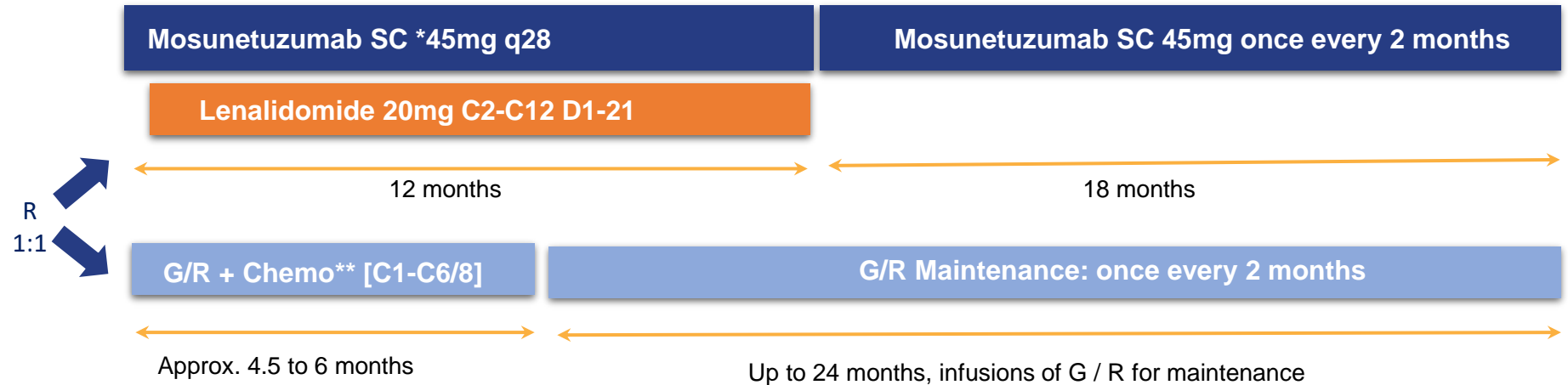
# MorningLyte Study Design

## Eligibility

- Symptomatic 1L FL
- FLIPI 2-5
- N = 790

## Stratification

- FLIPI 2 versus 3-5
- Diameter of the largest lesion (<6 vs. ≥6 cm)



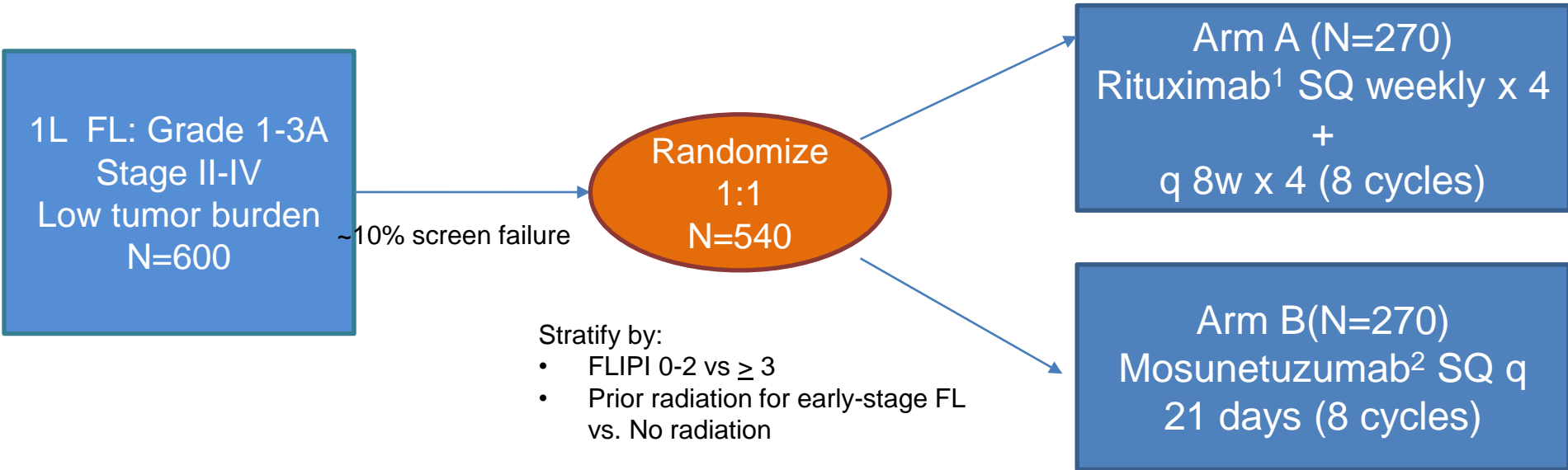
## Superiority Study:

- HR = 0.65
- Primary EP: PFS (IRC)
- Secondary EP: ORR, POD24, PFS by Inv, EFS, TTNT, DOR, OS, Safety, QOL, etc.
- Exploratory EP: Biomarkers

\*Step up dosing for CRS mitigation during C1: D1 5mg, D8 45mg, D15 45mg

\*\* CHOP or Bendamustine; mAb+chemo regimen → dealers choice

# S2308: Randomized Phase III Study of Mosunetuzumab vs. Rituximab for Low Tumor Burden Follicular Lymphoma



<sup>1</sup> First dose of Rituximab to be administered IV  
<sup>2</sup> Mosunetuzumab ramp up in cycle 1

Primary endpoint: 5 year PFS

# Future of 1<sup>st</sup> Line FL

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- Will be difficult to show improvement in frontline FL
- BR/BO (without maintenance) is safe and very effective
- R-CHOP/R-CVP is safe and effective (maintenance optional)
- The next frontier of testing appears to be bi-specifics
  - I would prefer time limited exposures



[www.siteman.wustl.edu](http://www.siteman.wustl.edu)