Future Directions in the Treatment of Follicular Lymphoma

Brad Kahl, MD

Professor of Medicine

SITEMAN CANCER CENTER
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BARNES-JEWISH Hospital
BJC HealthCare

Washington University in St. Louis
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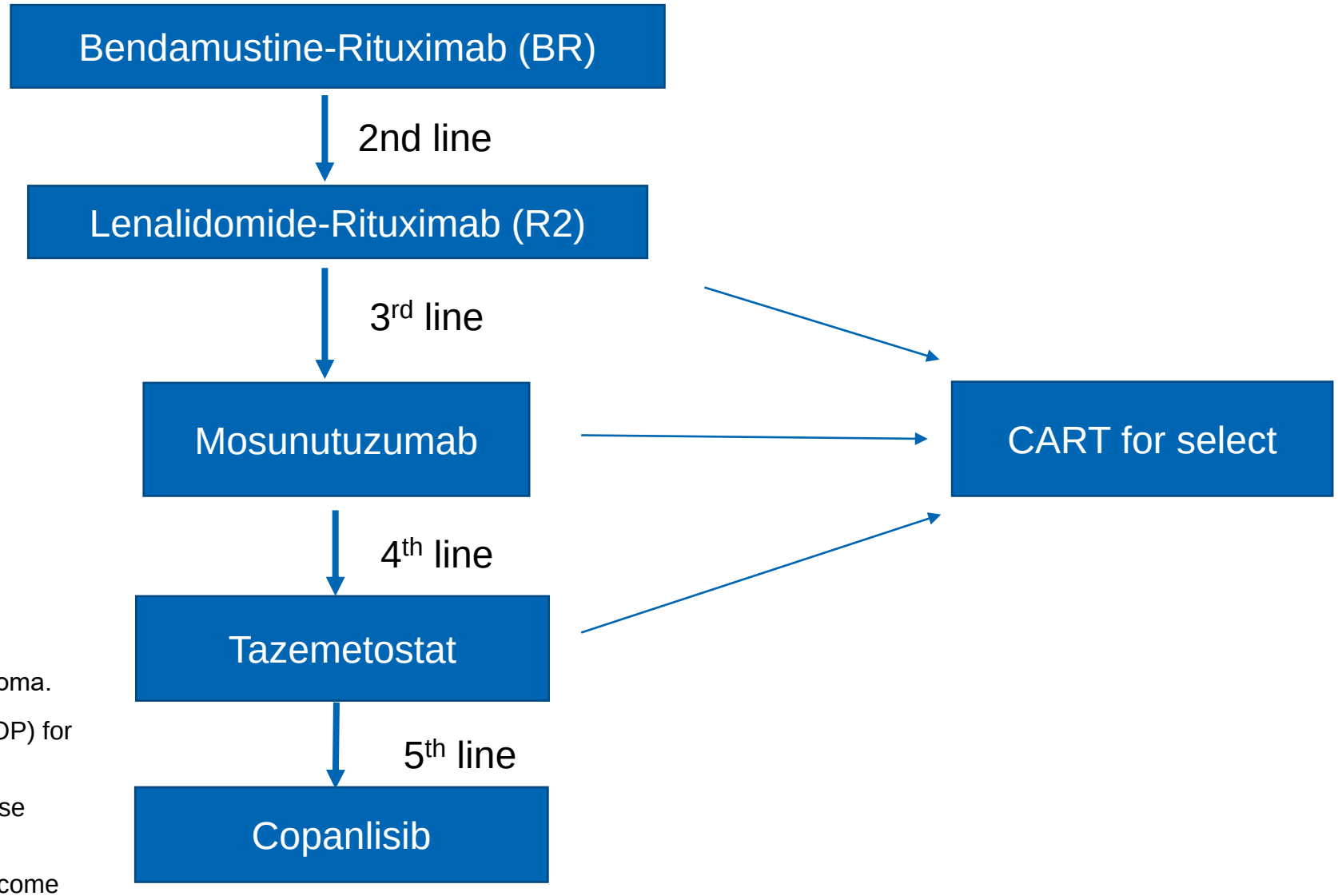
An approach to the Management of High Tumor Burden FL in 2023



- Paradigm applies to ”typical” follicular lymphoma.
- Allows one to save anthracycline (i.e. O-CHOP) for transformation events
- Emphasis on new agents. Can certainly re-use traditional agents.
- Anticipate this will change as new agents become available

Challenges in demonstrating improvement

1. Outcomes already quite good with 1st line treatment (see next slide)
    1. Long natural history of FL is good for patients, bad for drug development

2. Requires long term monitoring
    1. Not enough events in 1st few years to really declare ”winners”
    2. May need 5 -10 years of monitoring to really know
    3. Pharma generally not interested in these sorts of timelines
    4. Paucity of phase III trials since RELEVANCE and GALLIUM completed

3. Not agreement on best endpoints
    1. No argument that OS is most important, but almost impossible to show OS differences due to high activity of salvage therapies
    2. PFS is often used but can be “manipulated” with maintenance therapies
    3. If using maintenance therapies, need LTFU on toxicities and really need to factor in QOL, PROs, Cost, etc…

What does BR (or equivalent) achieve?

- Majority of patients appear to be still in 1st remission at 5 years
- StIL LTFU
  - just has TTNT (Rummel ASCO 2017)
- BRIGHT LTFU
  - 5 yr PFS ~ 70%
  - 5 yr PFS without MR ~60% (Flinn et al, JCO 2019)
- GALLIUM LTFU
  - 7 yr PFS 63% for O-chemo plus maintenance
  - 7 yr PFS 56% for R-chemo plus maintenance (in press)
- PRIMA LTFU
  - 10 yr PFS 51% with MR
  - 10 yr PFS 35% no MR (Bachy et al, JCO 2019)

What would “beating” BR look like?

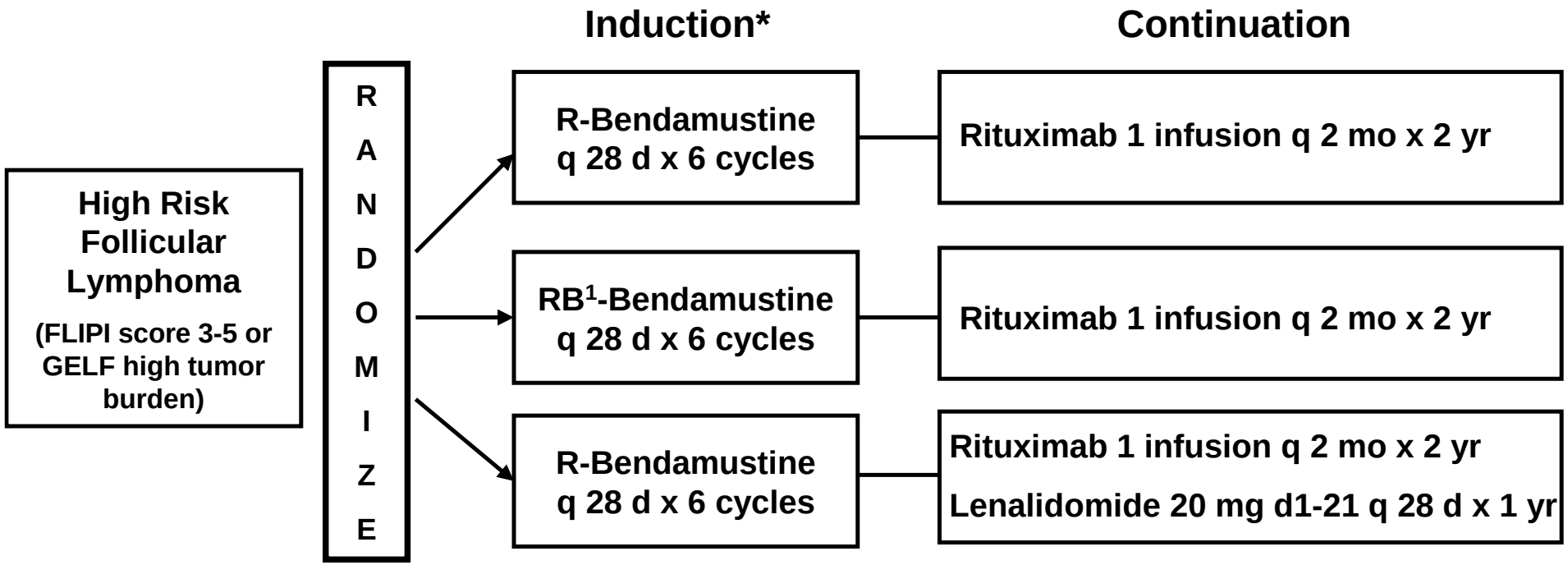
- Better PFS at 3-5 years - without increased toxicity
- Comparable PFS at 3-5 years with less toxicity
  - BR (with no maintenance) is WELL TOLERATED
- Could just focus on the 10-20% of progressions in 1st two years
  - No biomarkers to accurately identify high risk patients at diagnosis
  - Efforts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

Previous Strategies and Lessons Learned

1. Add to BR
   - BR plus X and R maintenance plus Z (E2408)
2. Replace R in BR
   - GALLIUM
3. Replace R in BR and add X
   - PrE0403
4. Risk adapt (personalize)
   - Foll 12
5. Move novel agent into front line
   - RELEVANCE

Untreated High Risk Follicular Lymphoma: E2408 Study Schema

BIONIC (Bortezomib Induction Or Novel Imid Continuation)



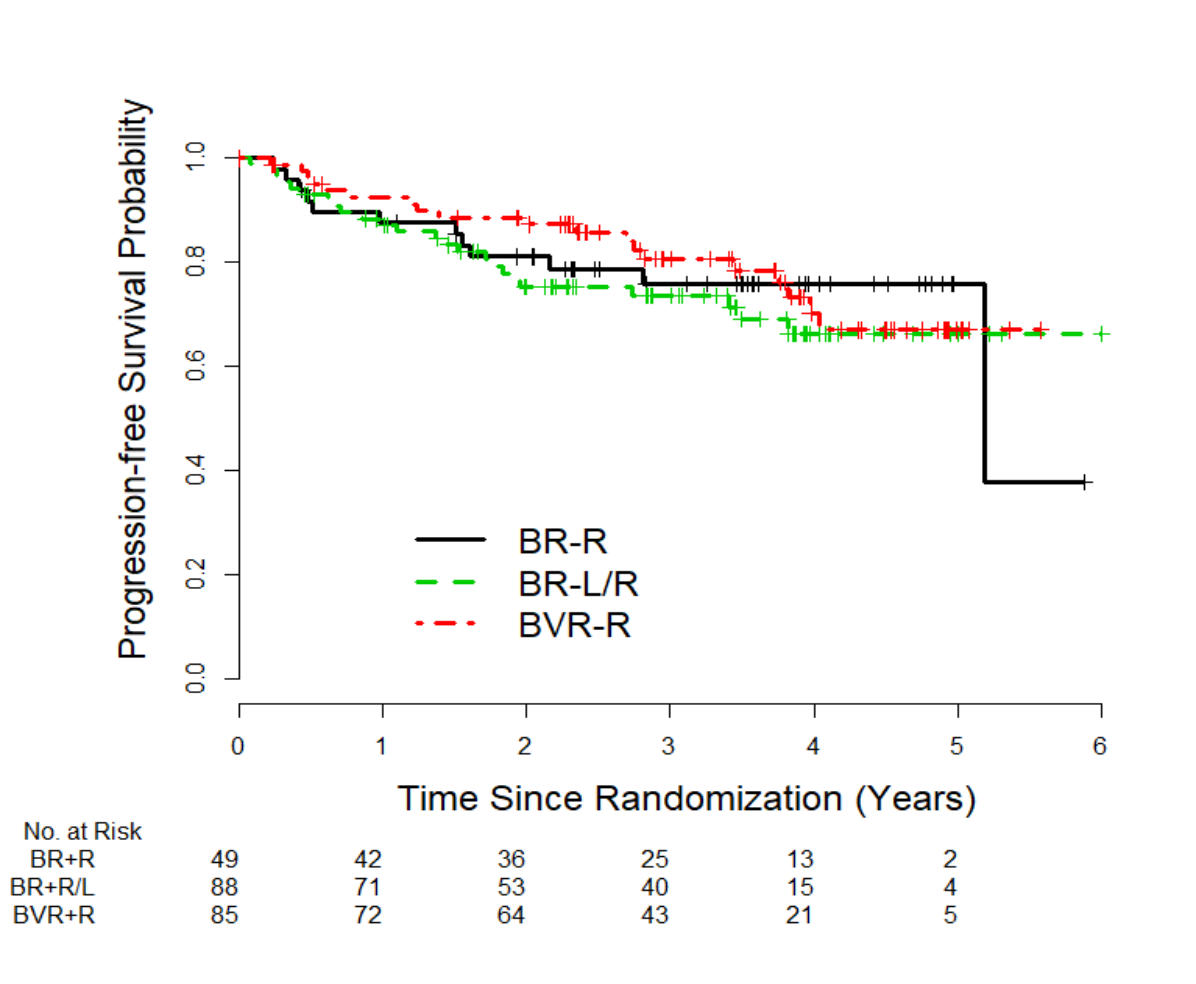
Initial target accrual: 250 patients (*n=236 evaluable*)

***1:2:2 randomization**

[1]Bortezomib (1.3mg/m^2 days 1, 4, 8, 11: initially IV, then SQ)

ECOG-ACRIN cancer research group
Reshaping the future of patient care

Progression-free survival (PFS)



3-year PFS*:

BR-R 76%
(95% CI: 64-90%)

BVR-R 81%
(95% CI:72-91%)

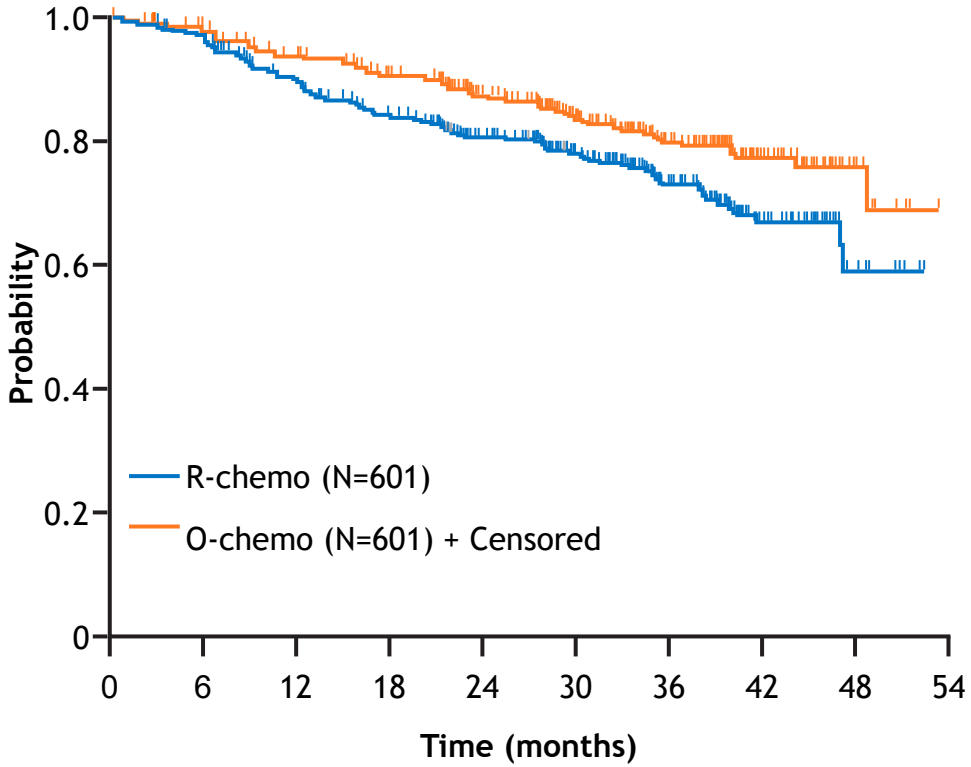
BR-LR 74%
(95% CI: 64-84%)

P=0.49

** Note: only first 250 enrolled patients (N=222 evaluable) included here*

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	**0.66** (0.51, 0.85) **p=0.001**	

Marcus et al, NEJM 2017

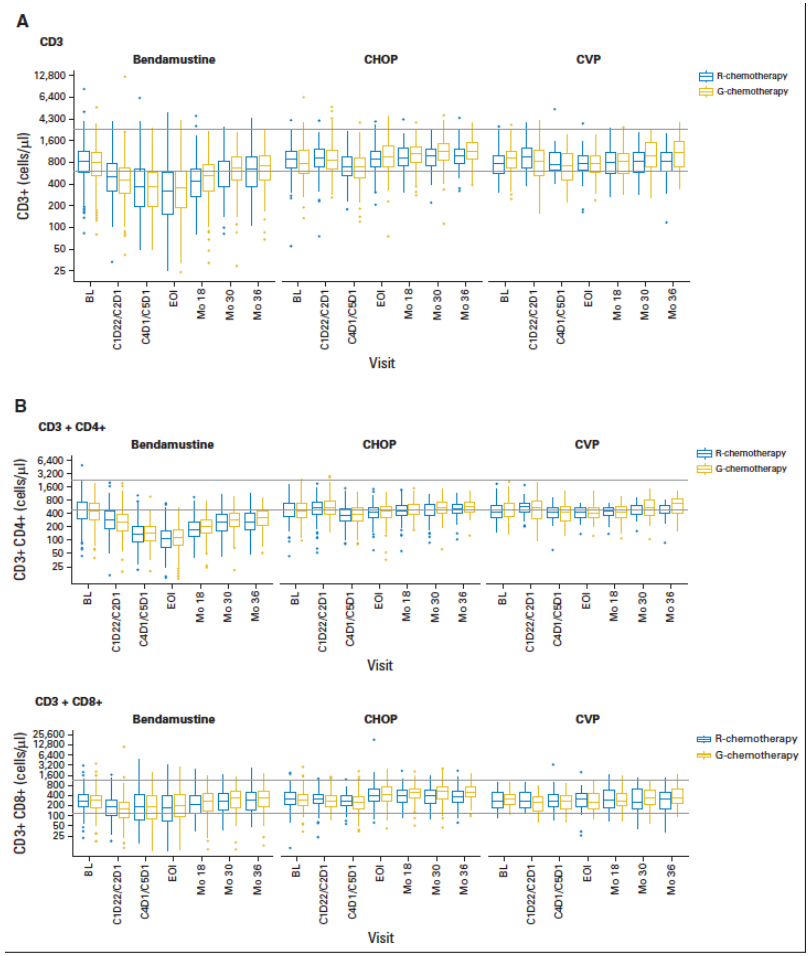
Wisdom of maintenance? Toxicity Considerations from GALLIUM

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

Fatal AE rate:

G-Benda: 6.8%
R-Benda: 5.1%
G-CHOP: 1.6%
R-CHOP: 2.5%

Hiddemann et al, JCO 2018



Significant and prolonged T cell depletion after bendamustine

PrE0403 Study Schema

N=56

REGISTRATION

Induction[3]

Cycle 1-6:
Obinutuzumab[1] 1000 mg IV d1 +
Bendamustine 90 mg/m^2 IV d1, 2
every 28 days

Cycle 2-6:
Venetoclax[2] 800 mg PO daily
days 1-10 of each
28 day cycle

PR or SD

Complete Response

Maintenance[4]

Obinutuzumab 1000 mg IV
every 2 months x 12 cycles

Venetoclax 800 mg PO daily
days 1-28
every 28 days x 24 cycles

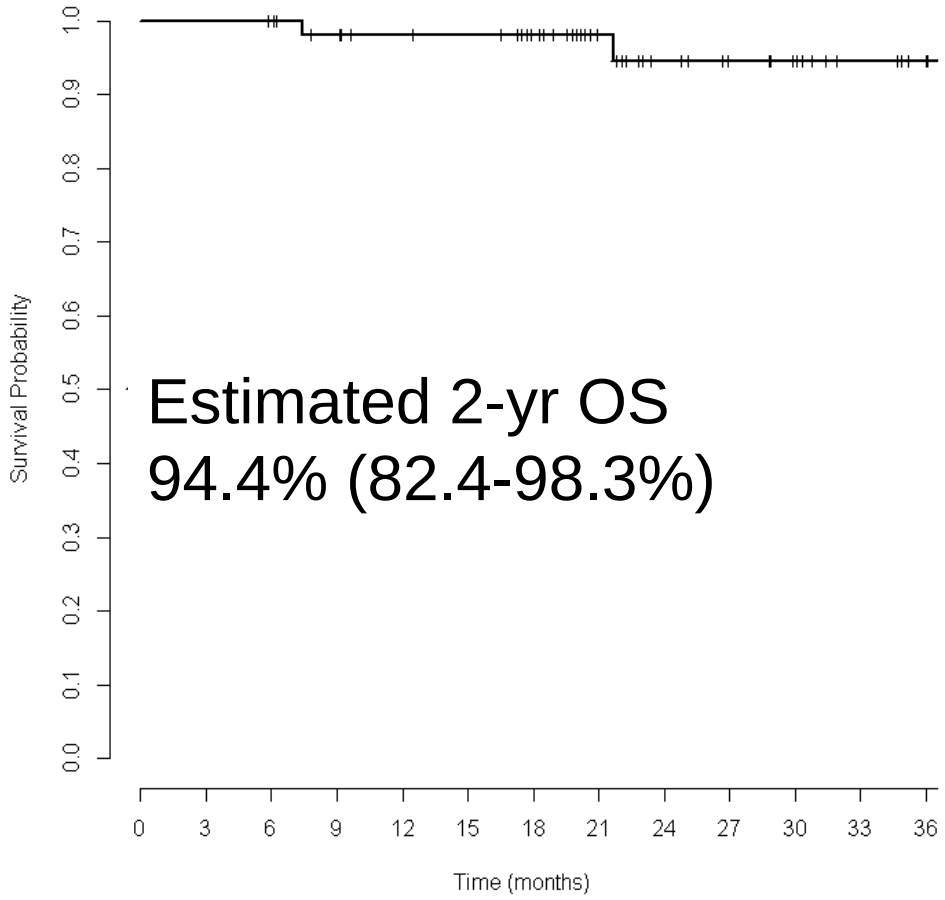
Obinutuzumab 1000 mg IV
every 2 months x 12 cycles

[1] Cycle 1 only: obinutuzumab 100 mg IV day 1 and 900 mg on day 2 followed by day 8 and day 15, 1000 mg IV.
[2] Due to high rate of laboratory TLS in first 21 patients, study was amended to start venetoclax at Cycle 2 through 6 only
[3] Growth Factor was required during induction cycles
[4] Patients move on to the maintenance phase begins 8-12 weeks after induction. Maintenance for 2 years after induction.

Survival

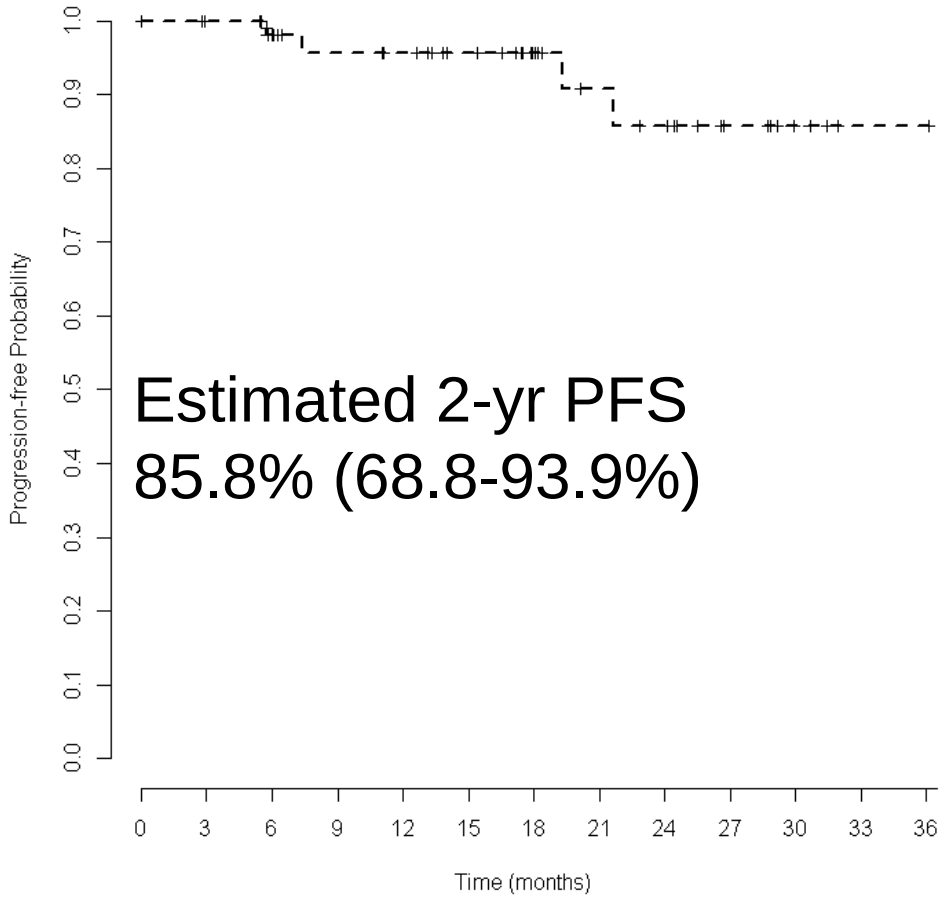
Median Follow up 20.9 months

Overall Survival



Estimated 2-yr OS
94.4% (82.4-98.3%)

Progression Free Survival



Estimated 2-yr PFS
85.8% (68.8-93.9%)

Treatment Emergent AEs of Interest

- Grade 5 CMV encephalitis as well as PJP pneumonia after C6 of induction
- Grade 3 PJP pneumonia after 3rd maintenance obinutuzumab
  - On Bactrim prophylaxis for 6 months
- Grade 4 BK virus nephropathy leading to ESRD and chronic hemodialysis after 6th maintenance obinutuzumab
- Grade 5 myocarditis after 8th dose maintenance obinutuzumab
  - Suspected—not proven—to be viral in etiology

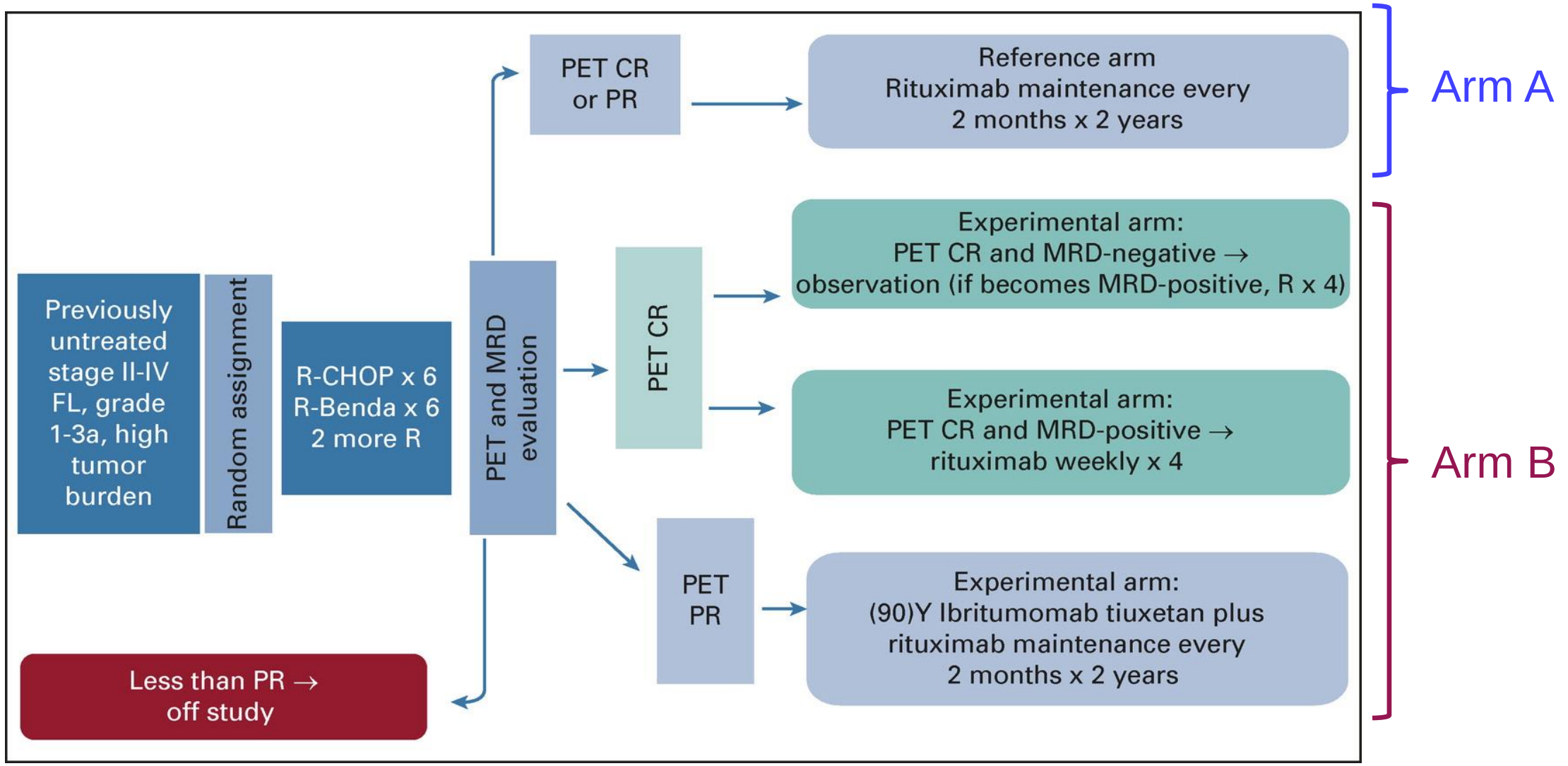
Lessons Learned

- E2408
  1. Not easy to improve on baseline BR plus R
  2. May need an agent with more activity in FL than bortezomib
  3. R2 after BR disappointing. Perhaps poor T cell health after benda diminishes lenalidomide impact.

- Gallium and PrE0403
  1. Obinutuzumab does not combine as well with bendamustine
  2. Maintenance obinunuzumab after BO probably unwise from risk benefit standpoint
  3. Venetoclax may have improved efficacy, but unacceptable risk

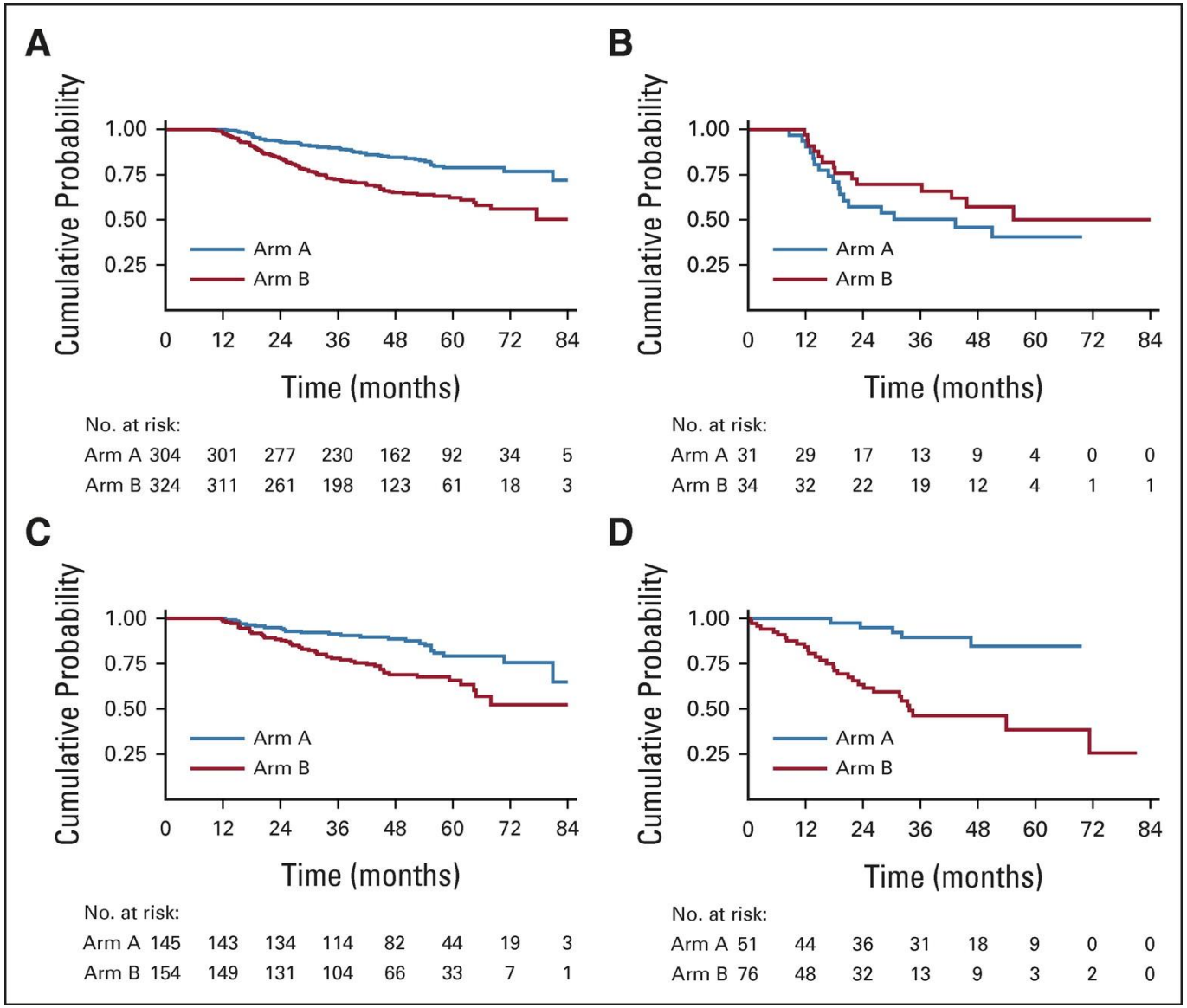
- Still unclear regarding risk of MR after BR, we did not see same worrisome safety signals in E2408, but in COVID era, I no longer recommend MR in FL

Response-adapted therapy: FOLL 12



Luminari S et al. J Clin Oncol 2022 40729-739.

Response-adapted therapy: FOLL 12



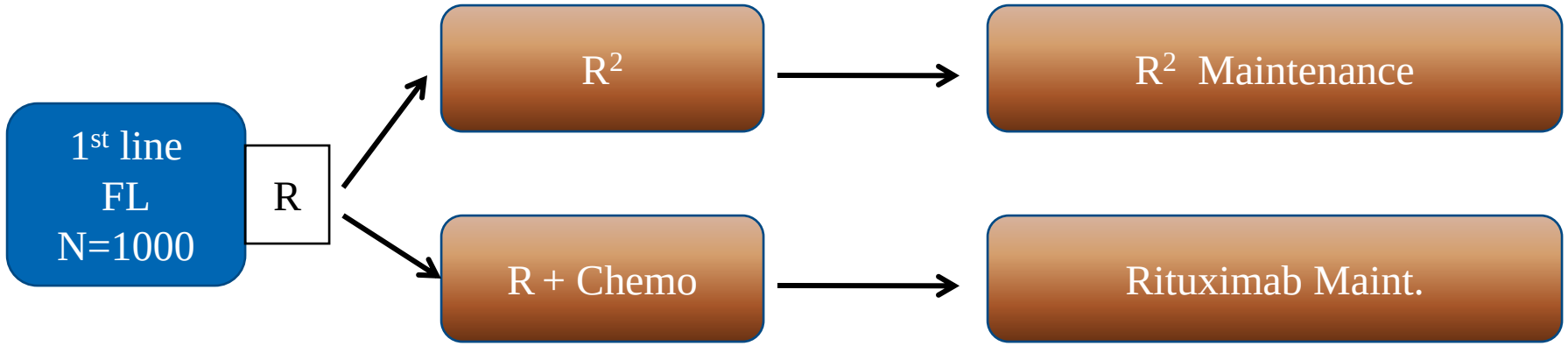
PFS for patients in CR/PR after EOI with reviewed PET and MRD:
(A) EOT PET–,
(B) EOT PET+,
(C) EOT PET- MRD -
(D) EOT PET- MRD +

Arm A, reference arm

Luminari S et al. J Clin Oncol 2022 40729-739.

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

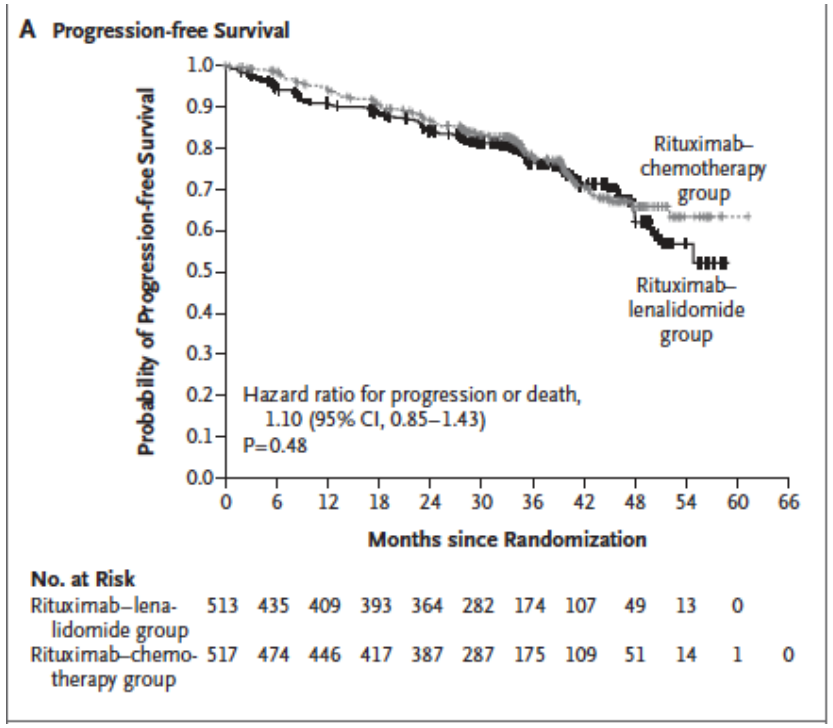


Table 3. Adverse Events during the Treatment Period in the Safety Population.

Adverse Event	Rituximab–Lenalidomide Group (N=507)		Rituximab–Chemotherapy Group (N=503)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients (percent)			
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)

Morschauser et al, NEJM 2018

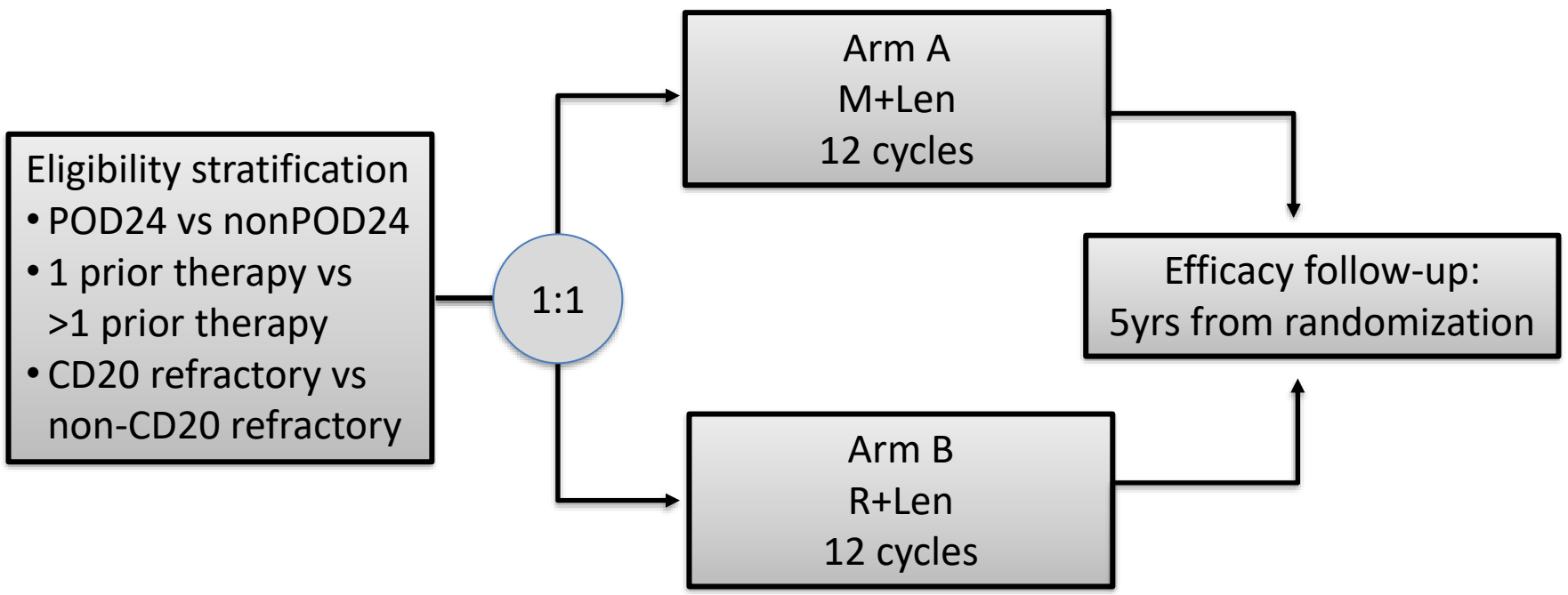
Lessons Learned

- Foll 12 Study
  1. Strategies using maintenance/consolidation selectively in poor responders will not be superior to broad use of MR since MR works best in good responders.
  2. We actually saw this in E2496!
  3. If reference arm does not contain MR, this strategy might work.

- 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.

Phase III of R2 vs Mosun/Len in R/R FL



- Group sequential design, interim analysis when ≈70% of planned PFS events have occurred in the ITT population
- 400 patients globally

- M+Len: Mosun 1mg C1D2, 2mg C1D8, 30 mg C1D15 then D1 C2-12; Len D1-21 on C2-12
- R+Len: Rituxan 375mg/m^2 C1 D1,8,15,22 then D1 every other cycles (C3,5,7,11); Len D1-21 on C1-12

Frontline phase III concept (pharma)

- R2 plus bispecific X vs. R-chemo plus maintenance
  - Bispecific given for 2.5 years
- Could be very active.
- I worry about prolonged, profound B cell depletion.
- Wish was more time limited.

A Phase II Study Evaluating the Efficacy of Mosunetuzumab in Combination with Polatuzumab Vedotin in Untreated Follicular Lymphoma

David A. Russler-Germain, MD/PhD

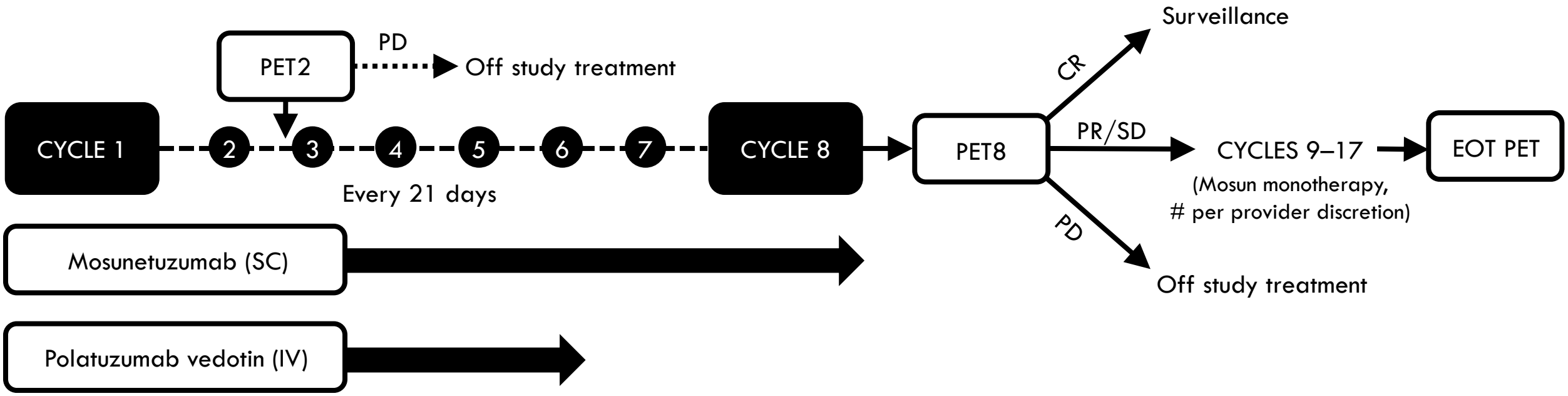
Nancy L. Bartlett, MD

Department of Medicine

Division of Oncology

Study Design

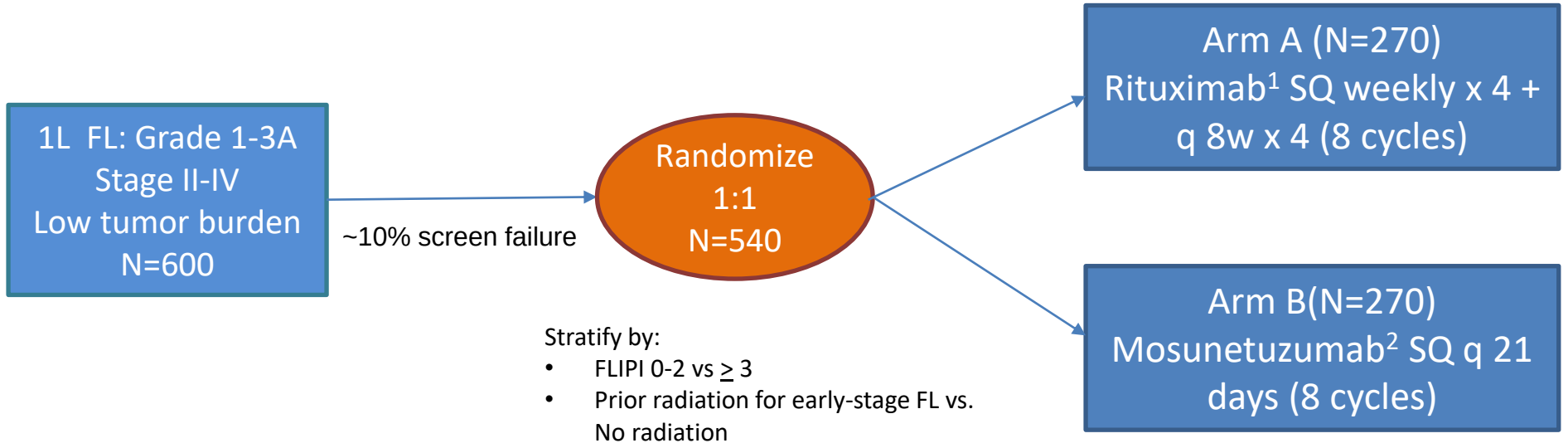
- Single-arm, open-label phase 2 clinical trial



What about Low Tumor Burden FL

- Patients often managed with a watch and wait strategy
- Single agent rituximab reasonable to offer
- Now have 10 year follow up from RESORT and UK Trial
  - Rituximab x 4 doses: 45% progression free at 5 years
  - Rituximab x 4 plus SAKK dosing: 55% progression free at 5 years
  - Over 1/3 progression free at 10 years

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



[1] First dose of Rituximab to be administered IV
[2] Mosunetuzumab ramp up in cycle 1

Primary endpoint: 5 year PFS

Conclusions: 1st Line FL

- Will be difficult to show improvement in frontline FL
- BR (without maintenance) is safe and very effective
  - BR is hard to combine with however
- I would prefer to avoid long maintenance strategies as the way to improve PFS
  - CLL model may not apply here. Different risk/benefit calculation.
- The next frontier of testing appears to be bi-specifics
  - I would prefer time limited exposures
- Any new regimen should not increase risk to patients

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