Follicular Lymphoma: When to Start Therapy and How to Decide the Optimal Treatment?

Nakhle Saba, MD

Associate Professor of Medicine

Tulane University

Annual New Orleans Summer Cancer Meeting

November 22, 2020

Disclosures

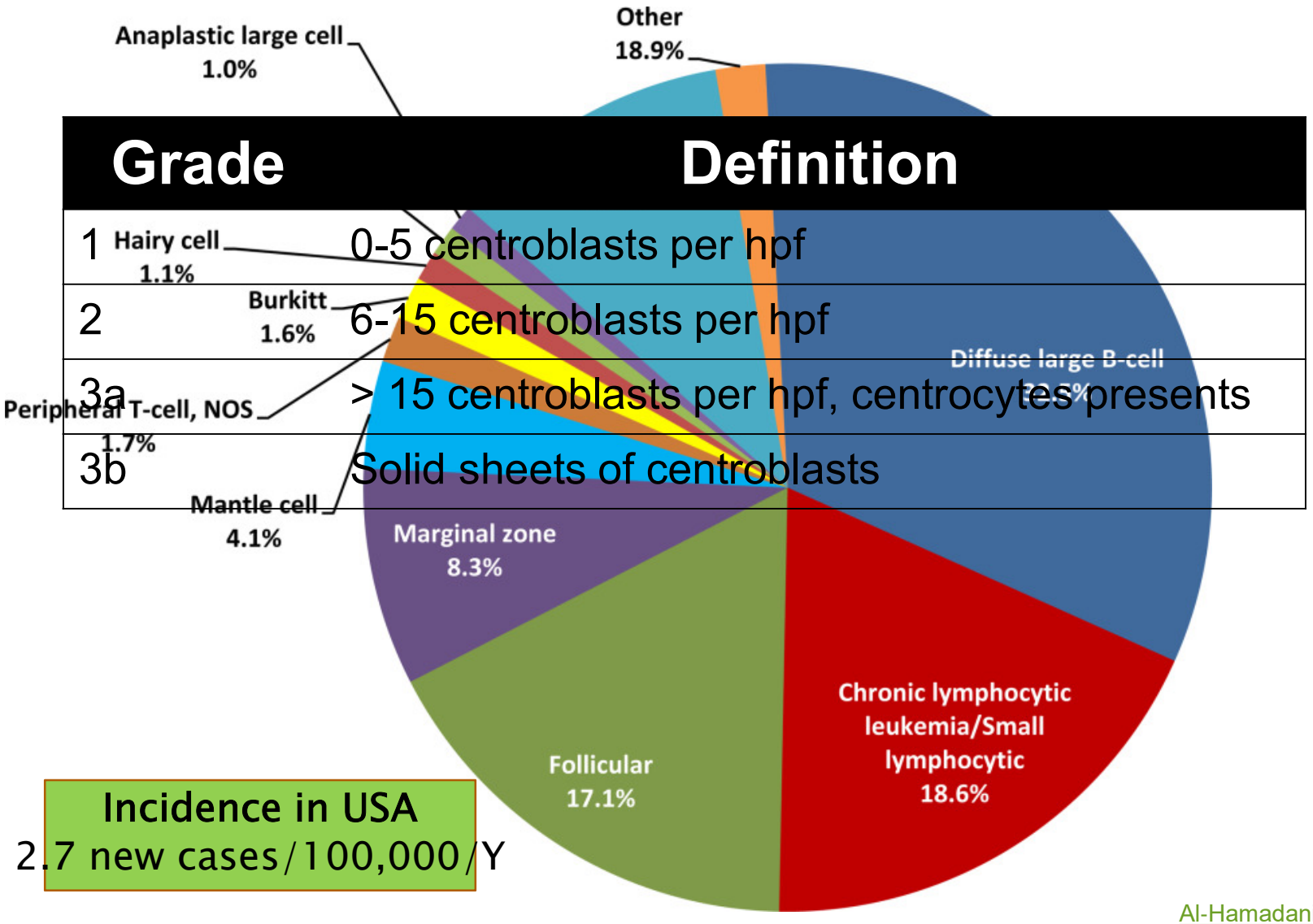
Advisory Board: Kite, Pharmacyclics, Janssen, AbbVie
Speakers Bureau: Pharmacyclics, Janssen, AbbVie
Consultancy: AbbVie

Agenda

- Introduction
- Risk Stratification – Stage, Grade, FLIPI
- Management of Stage I-II
- Management of Stage III-IV
- Role of maintenance therapy
- Role of PET-CT
- Approved novel therapies for relapsed disease
- Impact of COVID-19
- Treatment algorithms

FLSitatgee(1Amird Anbost)coomgradeNHL

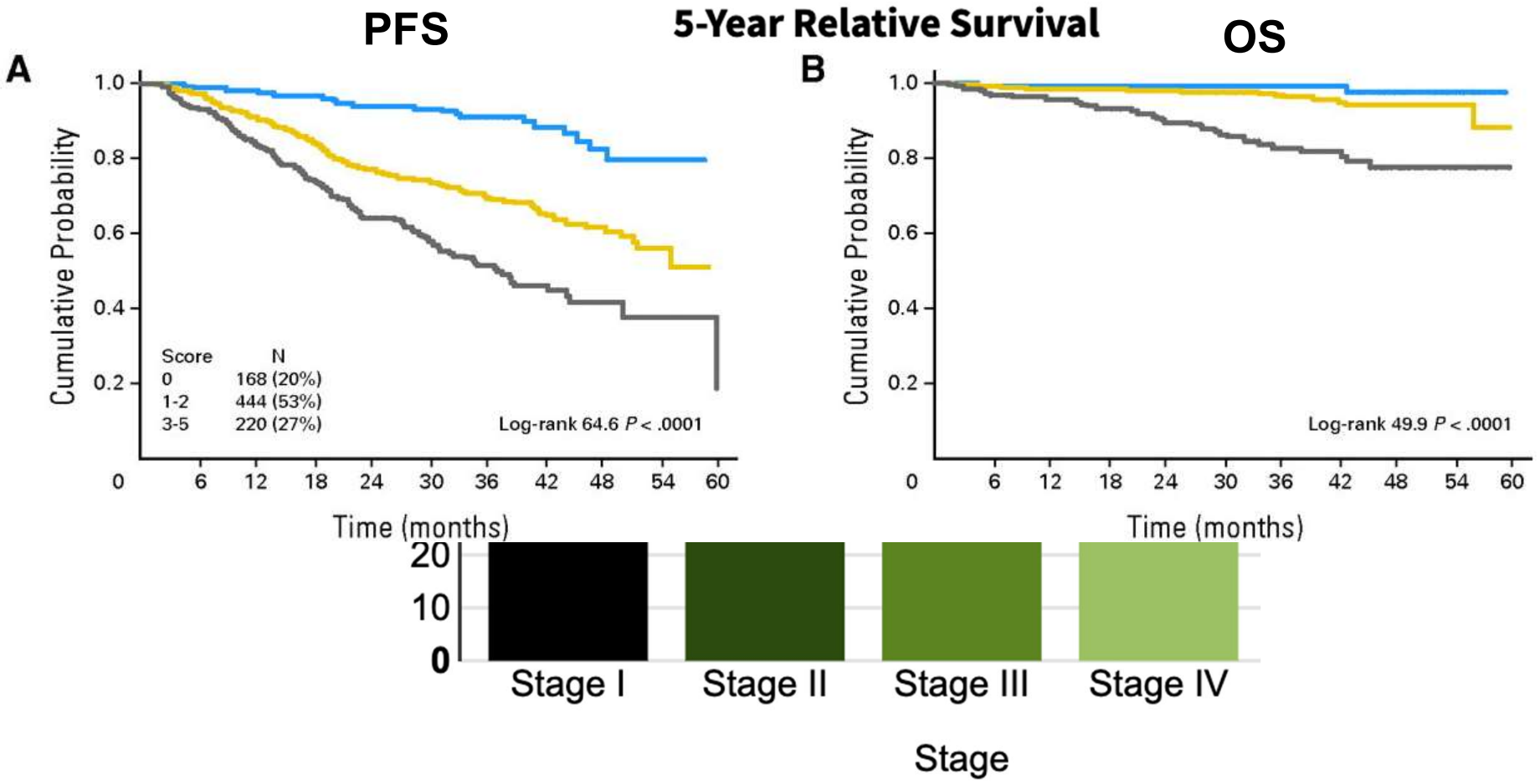
Grade	Definition
1	0-5 centroblasts per hpf
2	6-15 centroblasts per hpf
3a	> 15 centroblasts per hpf, centrocytes presents
3b	Solid sheets of centroblasts



Incidence in USA
2.7 new cases/100,000/Y

Al-Hamadani AJH 2015

Risk Stratification



Solal-Celigny et al. Blood 2004

SEER 21 2013–2017, All Races, Both Sexes

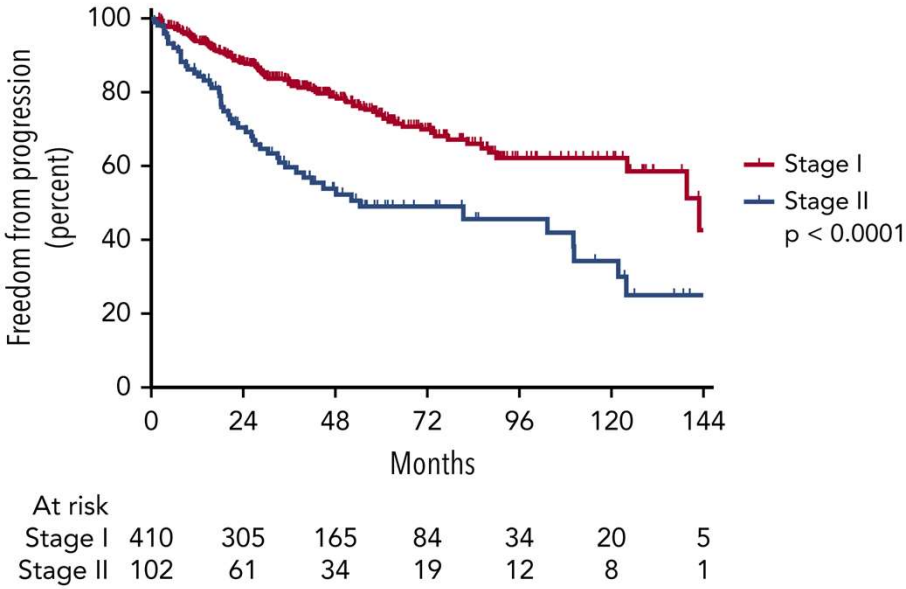
Federico et al. JCO 2009

Stage I-II

- Observation?
- RT alone?
- RT + Chemo-immunotherapy (CIT)?

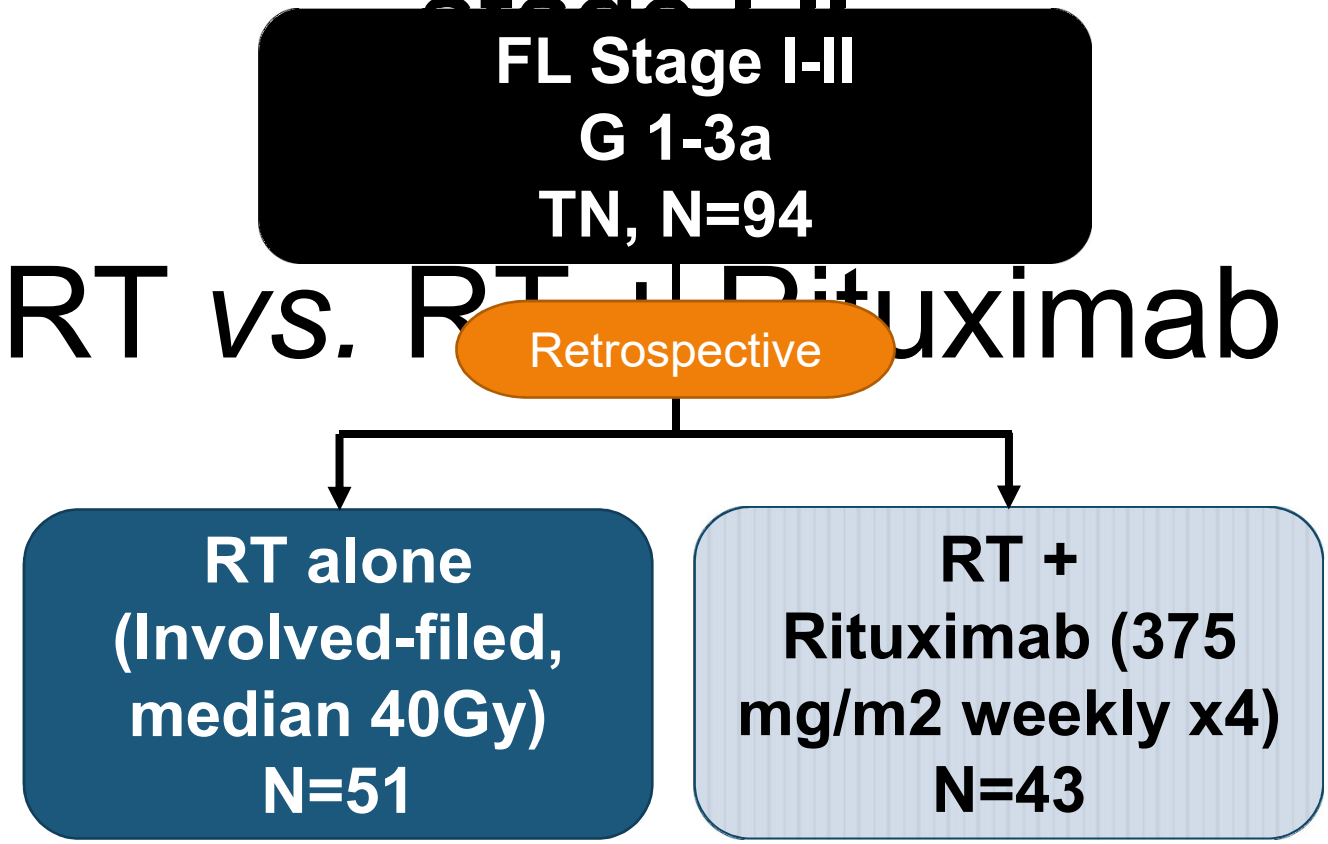
RT results in long term disease control in Stage I-II FL

- 512 patients (stage I: 410; 80.1%) – PET-CT
- Median follow-up was 52 months.
- Median RT dose was 30 Gy (range, 24-52 Gy).
- Common treatment volumes: IFRT (n = 256), ISRT (n = 144).



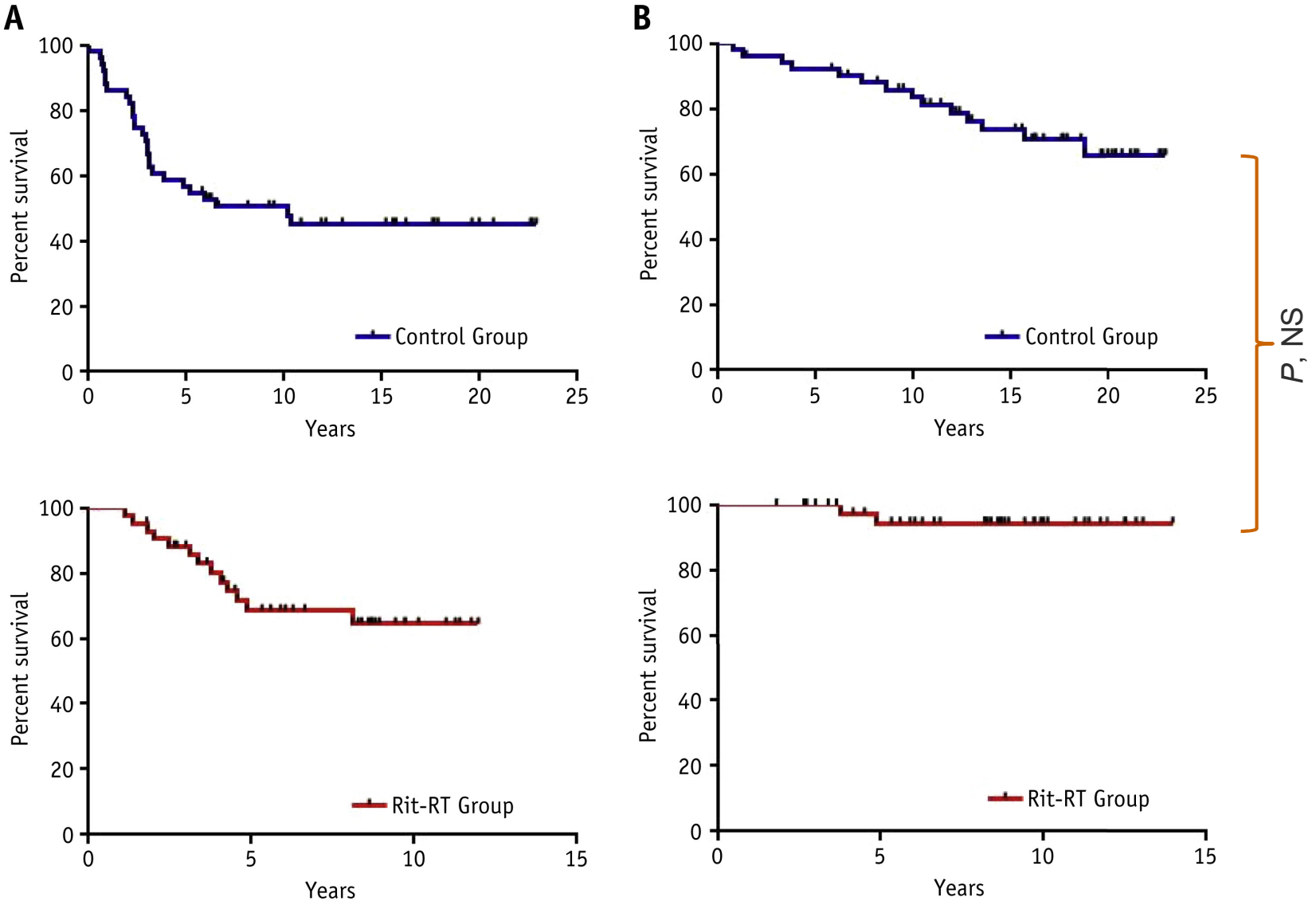
Bradyet al. BLOOD 2019

What if we add rituximab to RT in stage I-II



Ruella et al. Clinical Investigations 2015

When added to RT, Rituximab did not significantly improve outcomes



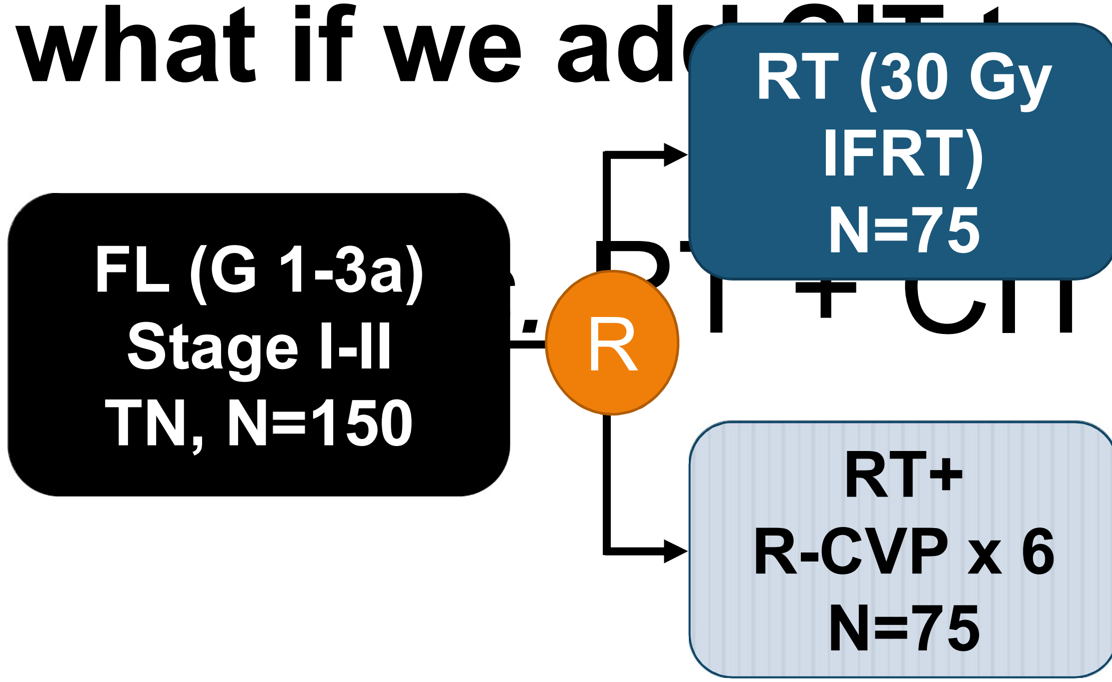
Ruella et al. Clinical Investigations 2015

TROG 99.03, prospective, randomized trial: RT vs. RT+R-CVP

Stage I-II

Rituximab did not add much to RT, what if we add CIT to RT

RT + CIT



Primary endpoints: PFS

Secondary endpoints include: OS, safety

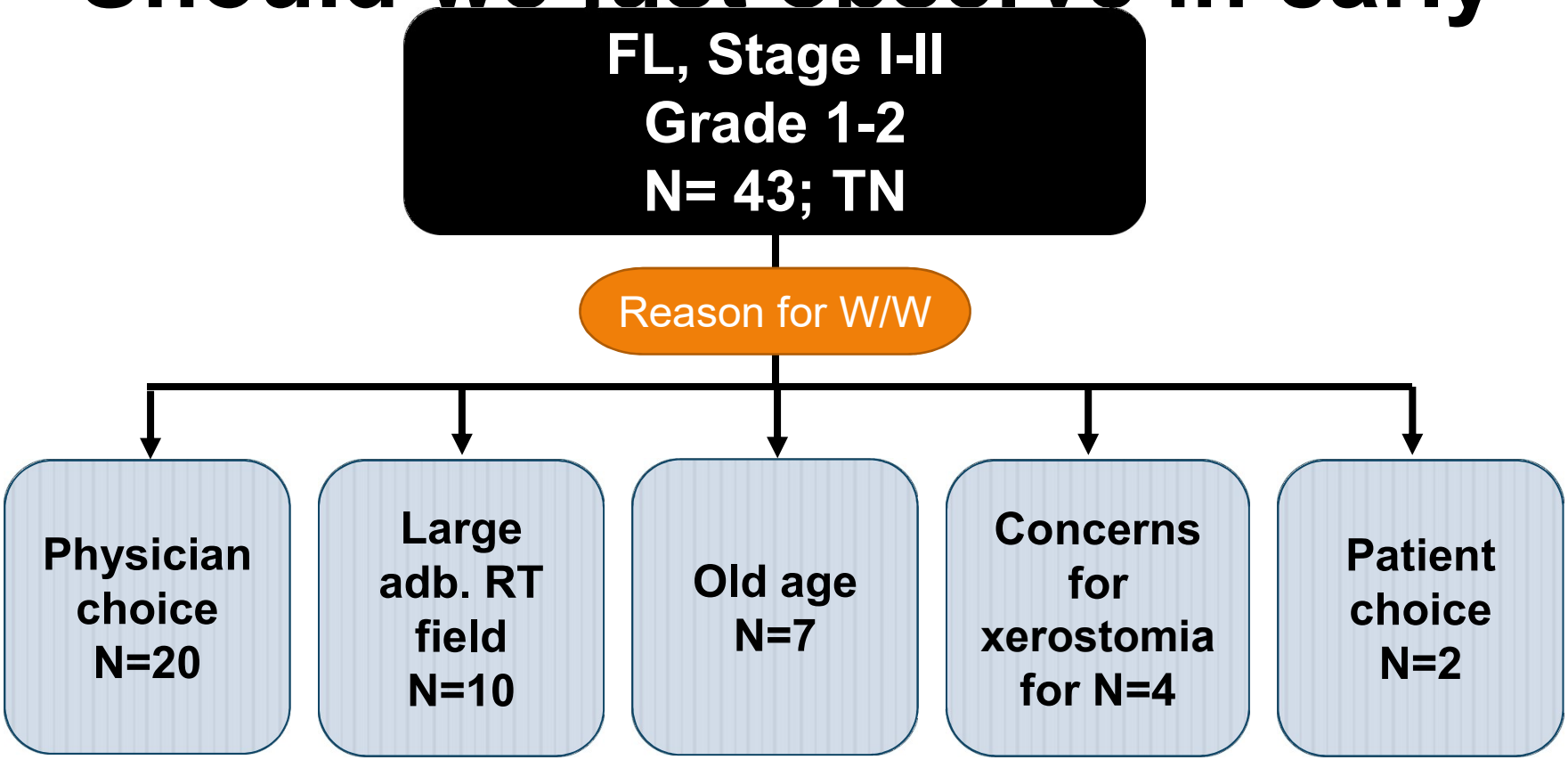
MacManus et al. JCO 2018

MSK Randomized trial: RT vs. RT + CHOP

- N =44, low/intermediate grade NHL.
- OS and PFS: No significant difference between the groups.

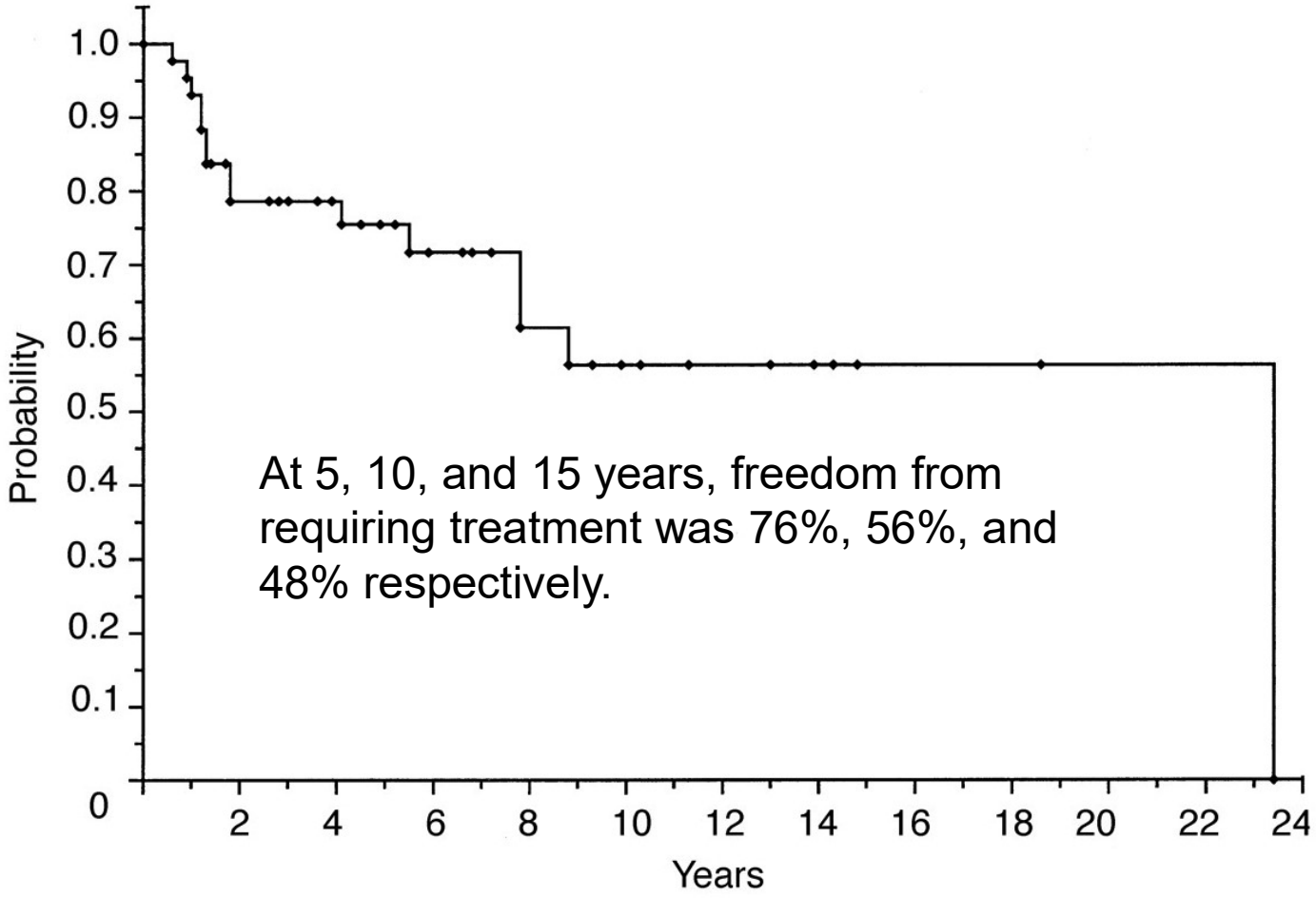
Yahalom et al. Cancer 1992

Stage I-II
Retrospective, watch and wait
Should we just observe in early



Advani et al. JCO 2002

PFS and OS comparable to historic control

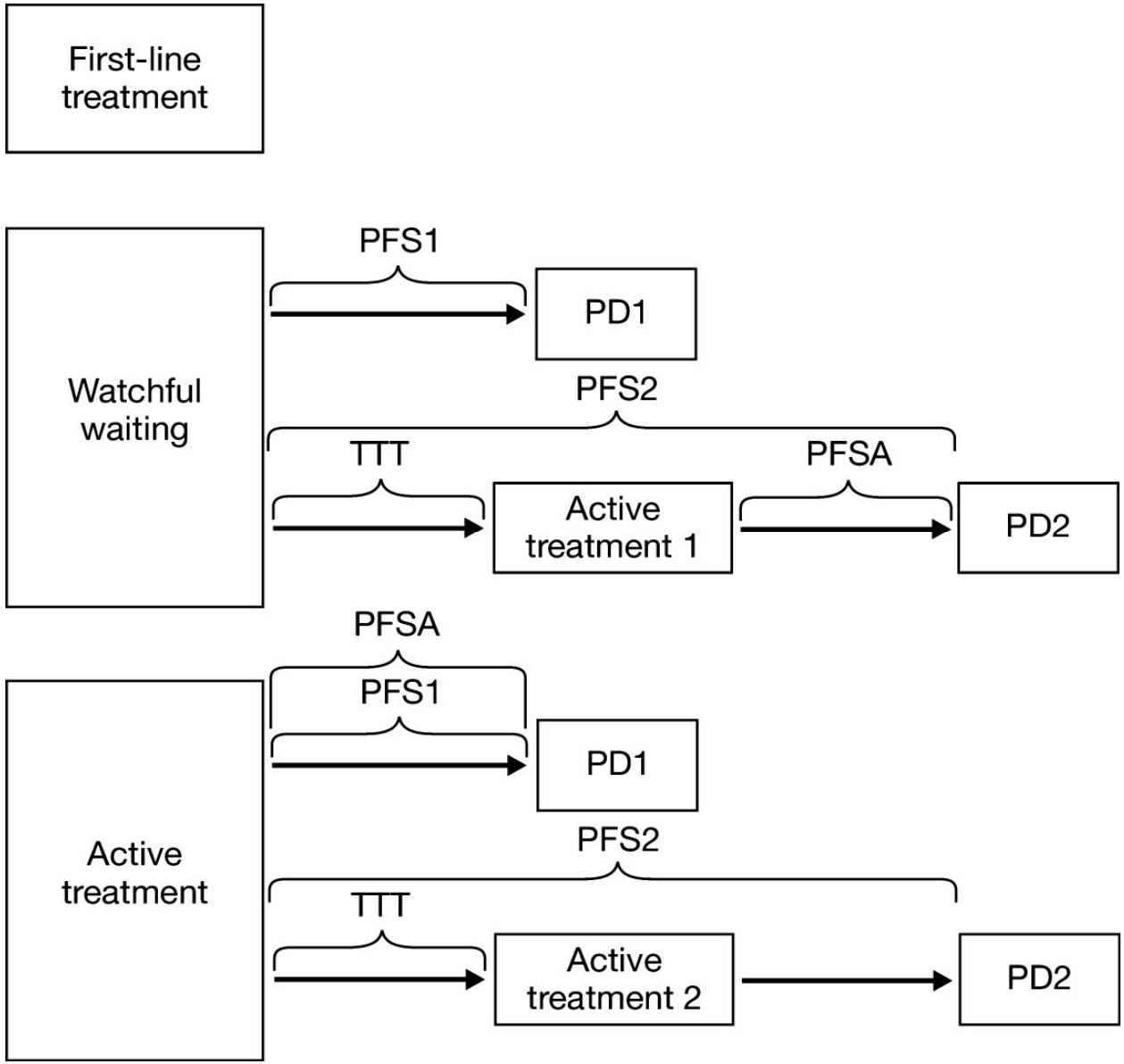


Advani et al. JCO 2002

Stage I-II

- RT: Long-term disease control in >90% of patients
  - 10-Y PFS: 40-59%
  - 10Y OS: 58-86%
- R+/-chemo could improve PFS but not OS
- ISRT (24-30 Gy) is preferred
- Observation in select cases
- Bulky (>7cm) stage I-II, and non-contiguous stage II: Treat as advanced stage

National LymphoCare Study:

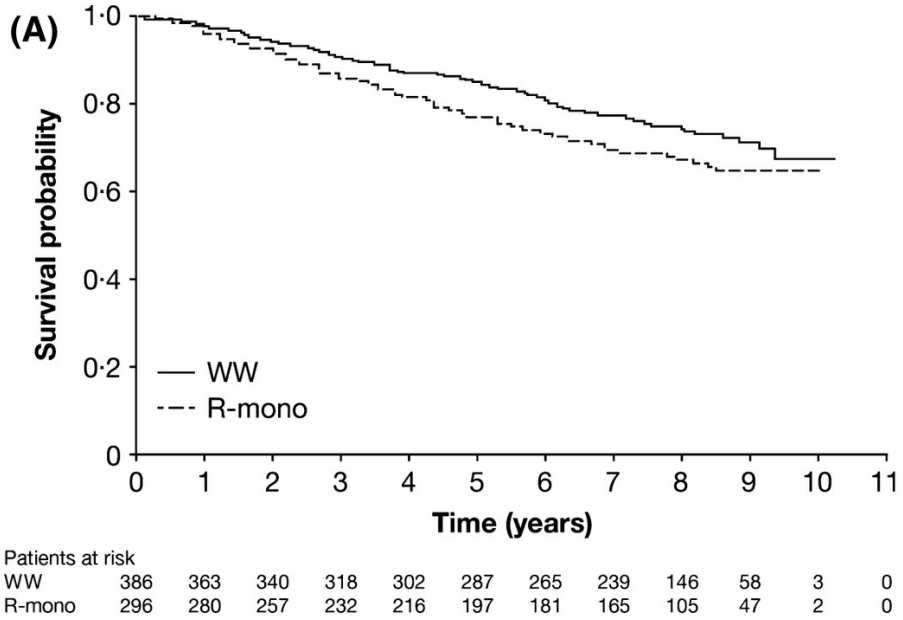


Secondary endpoints include: OS, EFS, DoR, safety

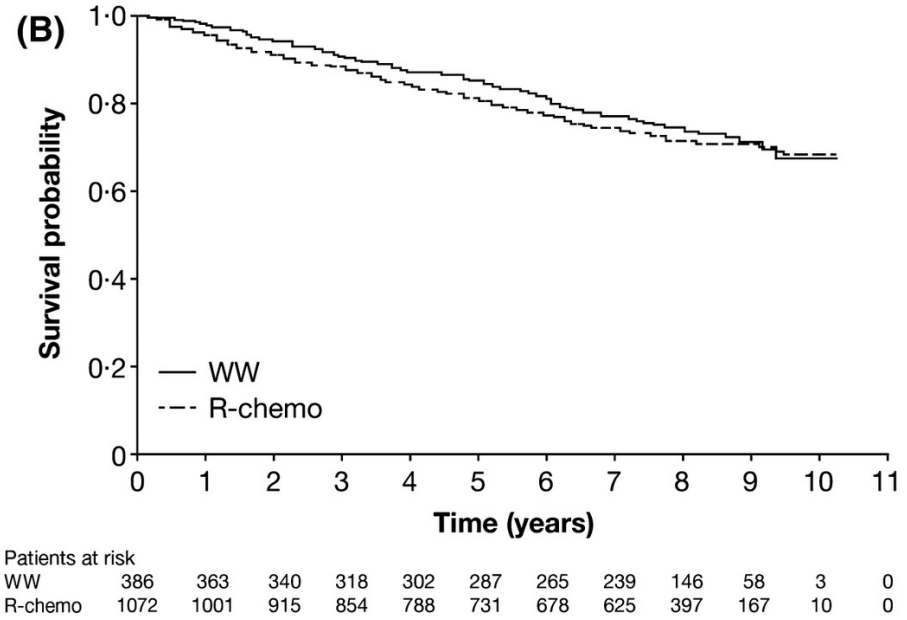
Nastoupil et al. BJH 2016

Early therapy has no benefit in PFS-2 nor in OS

OS



Patients at risk												
WW	386	363	340	318	302	287	265	239	146	58	3	0
R-mono	296	280	257	232	216	197	181	165	105	47	2	0



Patients at risk												
WW	386	363	340	318	302	287	265	239	146	58	3	0
R-chemo	1072	1001	915	854	788	731	678	625	397	167	10	0

Nastoupil et al. BJH 2016

Modified GELF* Criteria

Any of the following:

- Symptoms attributed to FL (such as B-symptoms)
- Threatened organ function
- Cytopenia secondary to FL
- Bulky disease (single mass >7 cm, or 3 masses > 3 cm)
- Symptomatic splenomegaly
- Steady progression over 6 months

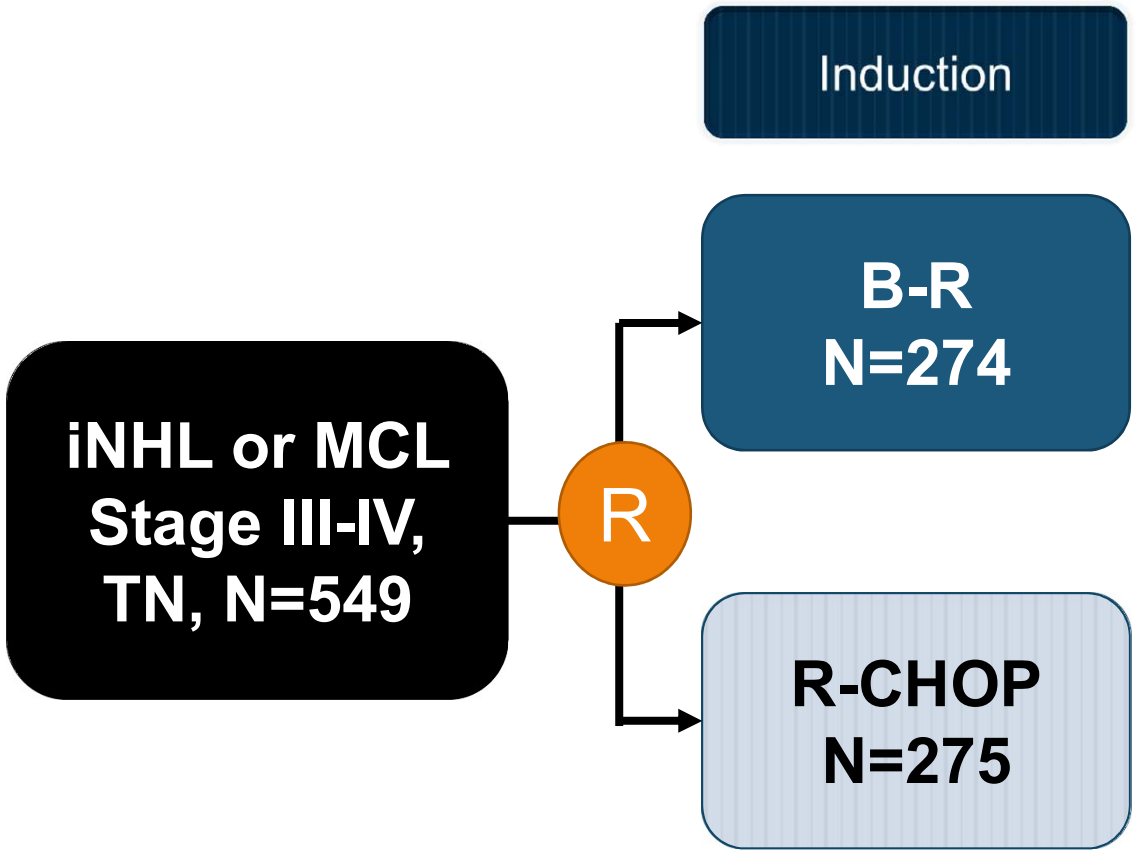
**Groupe d'étude des lymphomes folliculaires (GELF)*

Brice et al. JCO 1997

When indication are met, what to use?
R-CHOP/CVP or B-R?

StiL NHL1 study: B-R vs. R-CHOP

Open label, randomized, non-inferiority phase III



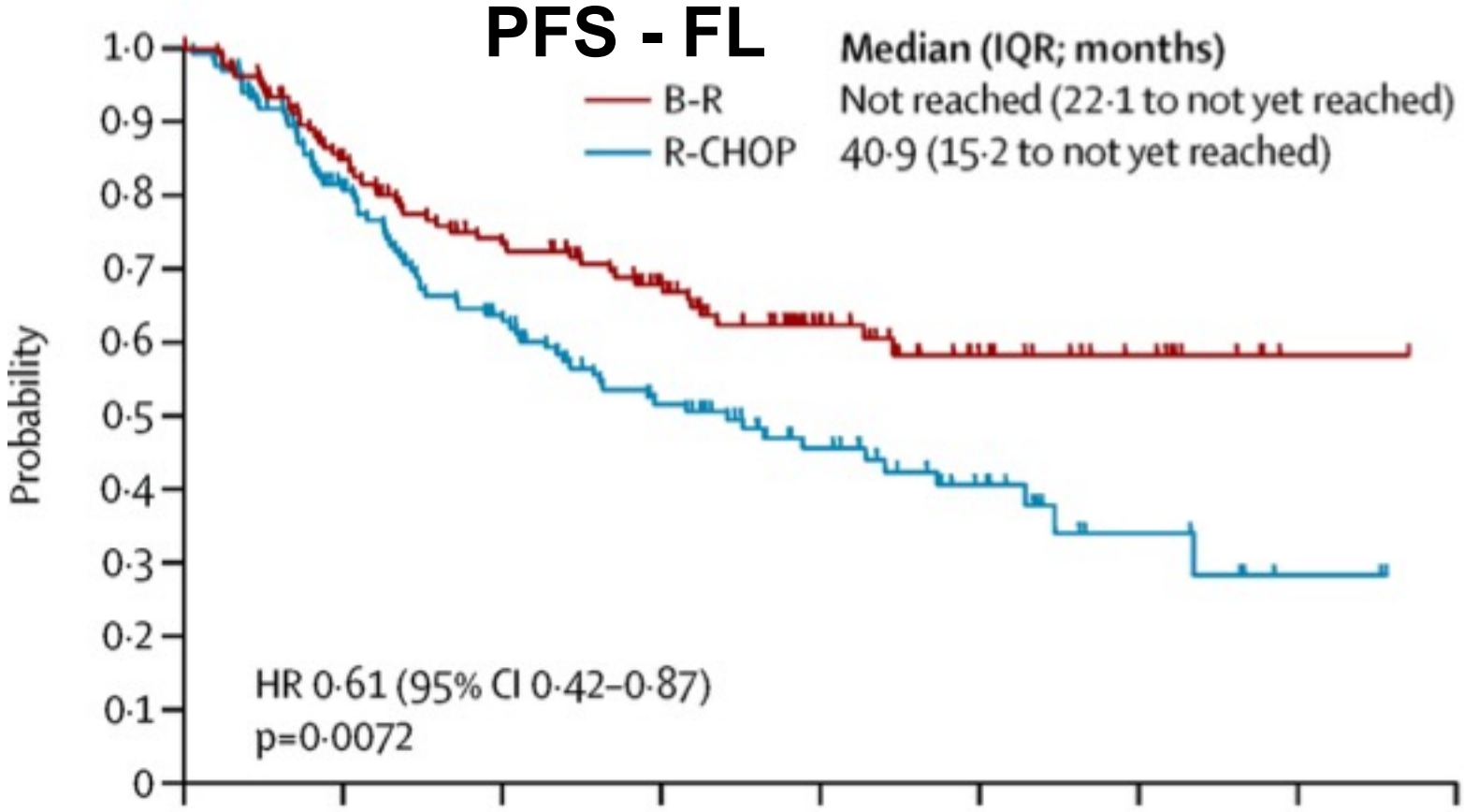
Histology	B-R	R-CHOP
FL	139 (53%)	140 (55%)
MCL	46 (18%)	48 (19%)
MZL	37 (14%)	30 (12%)
LPL	22 (8%)	19 (8%)
SLL	10 (4%)	11 (4%)
Other	7 (3%)	5 (2%)

Primary endpoints: PFS
Secondary endpoints: OS, ORR, CR, safety, TTNT

Rummel et al. THE LANCET 2013

StiL NHL1 study: B-R vs. R-CHOP

Open label, randomized, non-inferiority phase III



Rummel et al. THE LANCET 2013

Rummel et al. ASCO 2017 A#7501

StiL NHL1 study: B-R is less toxic than R-CHOP

	Grade 3-4	
	R-CHOP	B-R
Leucocytopenia	181 (72%)*	98 (37%)*
Neutropenia	173 (69%)*	77 (29%)*
Lymphocytopenia	106 (43%)	196 (74%)
Anaemia	12 (5%)	8 (3%)
Thrombocytopenia	16 (6%)	13 (5%)

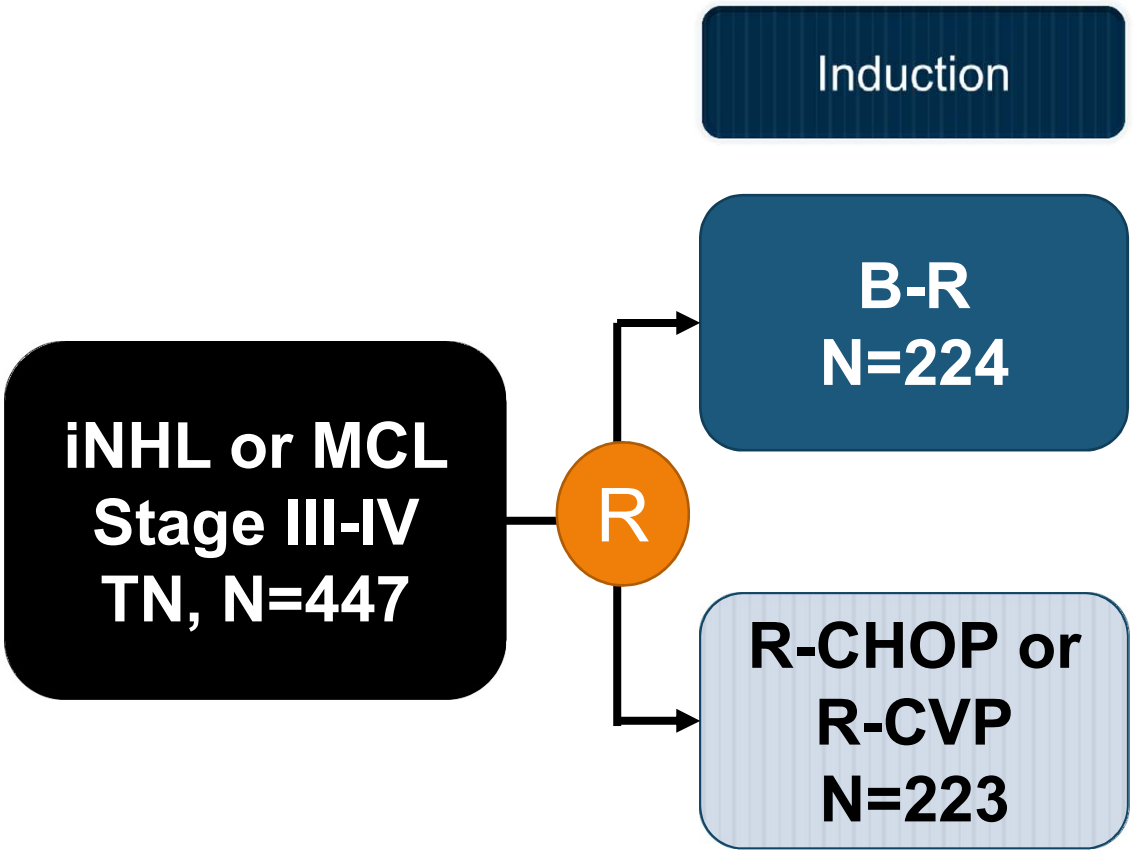
	B-R (n=261)	R-CHOP (n=253)	p value
Alopecia	0	245 (100%)*	<0·0001
Paresthesia	18 (7%)	73 (29%)	<0·0001
Stomatitis	16 (6%)	47 (19%)	<0·0001
Skin (erythema)	42 (16%)	23 (9%)	0·024
Skin (allergic reaction)	40 (15%)	15 (6%)	0·0006
Infectious episodes	96 (37%)	127 (50%)	0·0025
Sepsis	1 (<1%)	8 (3%)	0·019

Rummel et al. THE LANCET 2013

Rummel et al. ASCO 2017 A#7501

BRIGHT study: B-R vs. R-CHOP/R-CVP

Open label, randomized, non-inferiority phase III

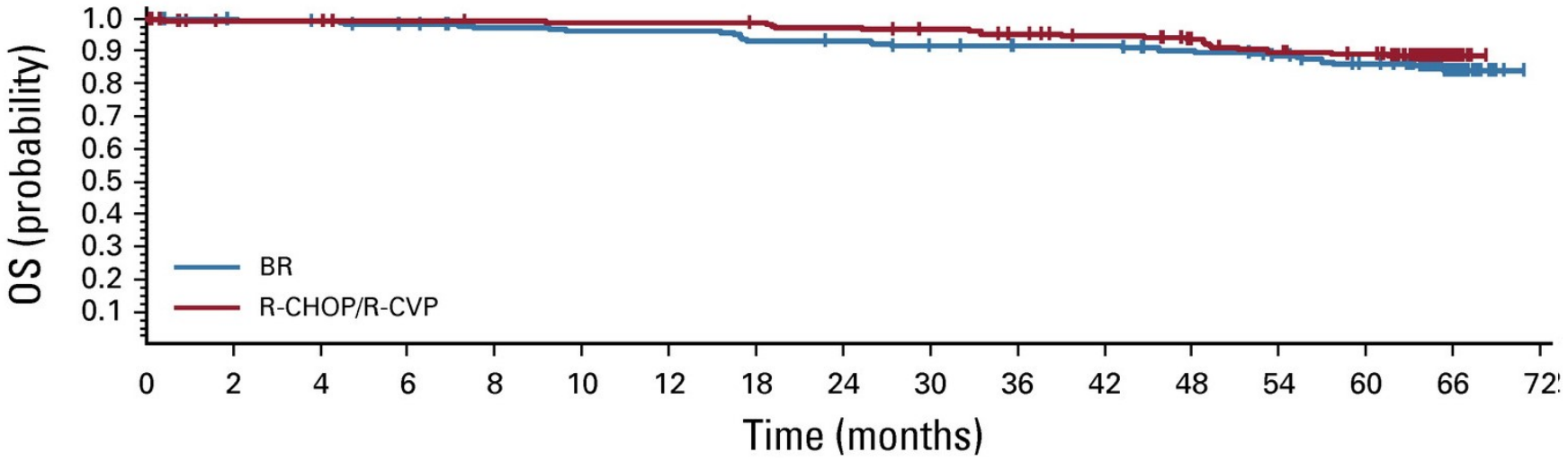


Histology	B-R	R-CHOP/R-CVP
FL	154 (69%)	160 (71%)
MCL	36 (16%)	38 (17%)
MZL	28 (12%)	18 (8%)
LPL	5 (2%)	6 (3%)
Other	1 (< 1%)	1 (< 1%)

Primary endpoints: CR
Secondary endpoints: ORR, OS, PFS, safety

Flinn et al. Blood 2014

BRIGHT study: B-R resulted in higher PFS and CR rates compared to R-CHOP/R-CVP



No. at risk:																	
BR	187	184	182	178	173	171	171	166	165	160	157	157	152	146	138	44	0
R-CHOP/ R-CVP	186	177	177	175	174	173	173	172	169	166	161	156	149	142	138	16	0

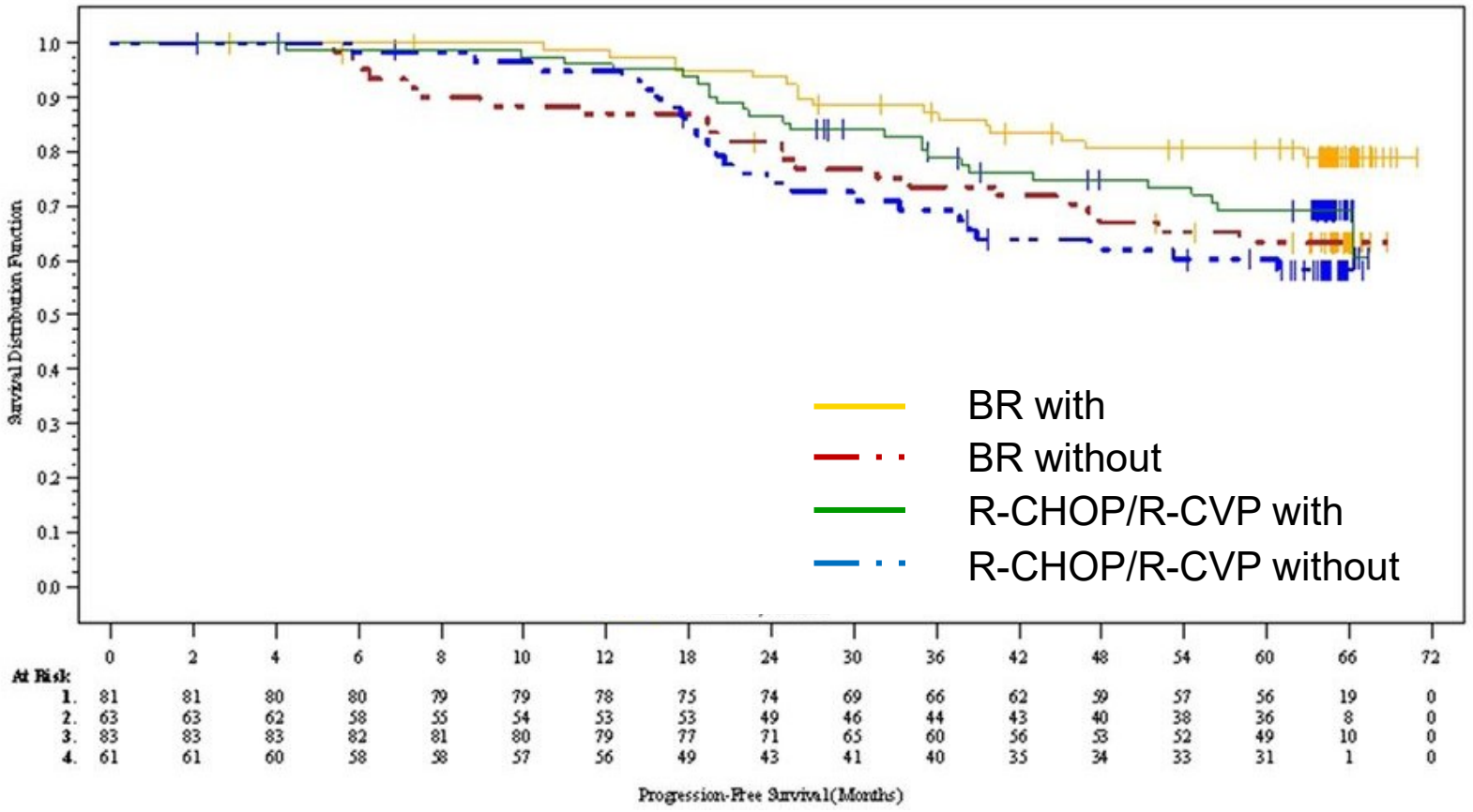
Flinn et al. JCO 2019

Flinn et al. Blood 2014

BRIGHT study: FL subset analysis, role of maintenance R

Figure. Progression-free survival by maintenance R in patients with follicular lymphoma.

OS tended to be better in patients assigned to maintenance R (BR treatment group, HR = 0.39 [95% CI 0.14-1.05], *P*= 0.0537; R-CHOP/R-CVP group, HR = 0.32 (0.10-1.05; *P*= 0.0481).



Kahl et al. ASH 2017A#484

BRIGHT study: B-R resulted in higher PFS and CR rates compared to R-CHOP/R-CVP

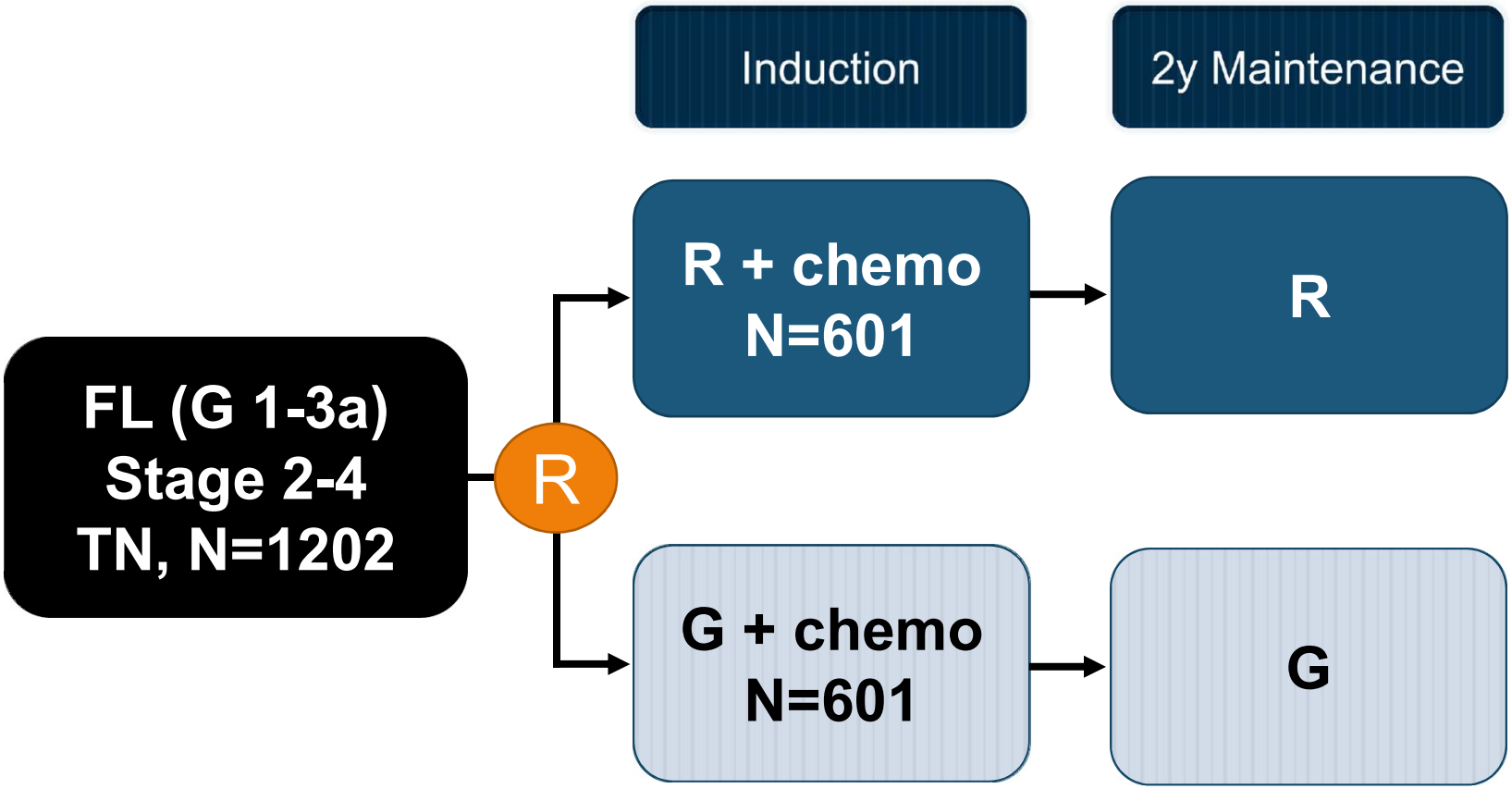
		ORR (%)	CR (%)
BRIGHT	B-R	97	31
	R-CHOP/ R-CVP	91	25
	P	0.01	.02
STiL	B-R	93	40
	R-CHOP/ R-CVP	91	30
	P	N.S.	.02

Flinn et al. Blood 2014

CIT:
Is G superior to R when combined with chemo?

R-chemo vs. G-chemo

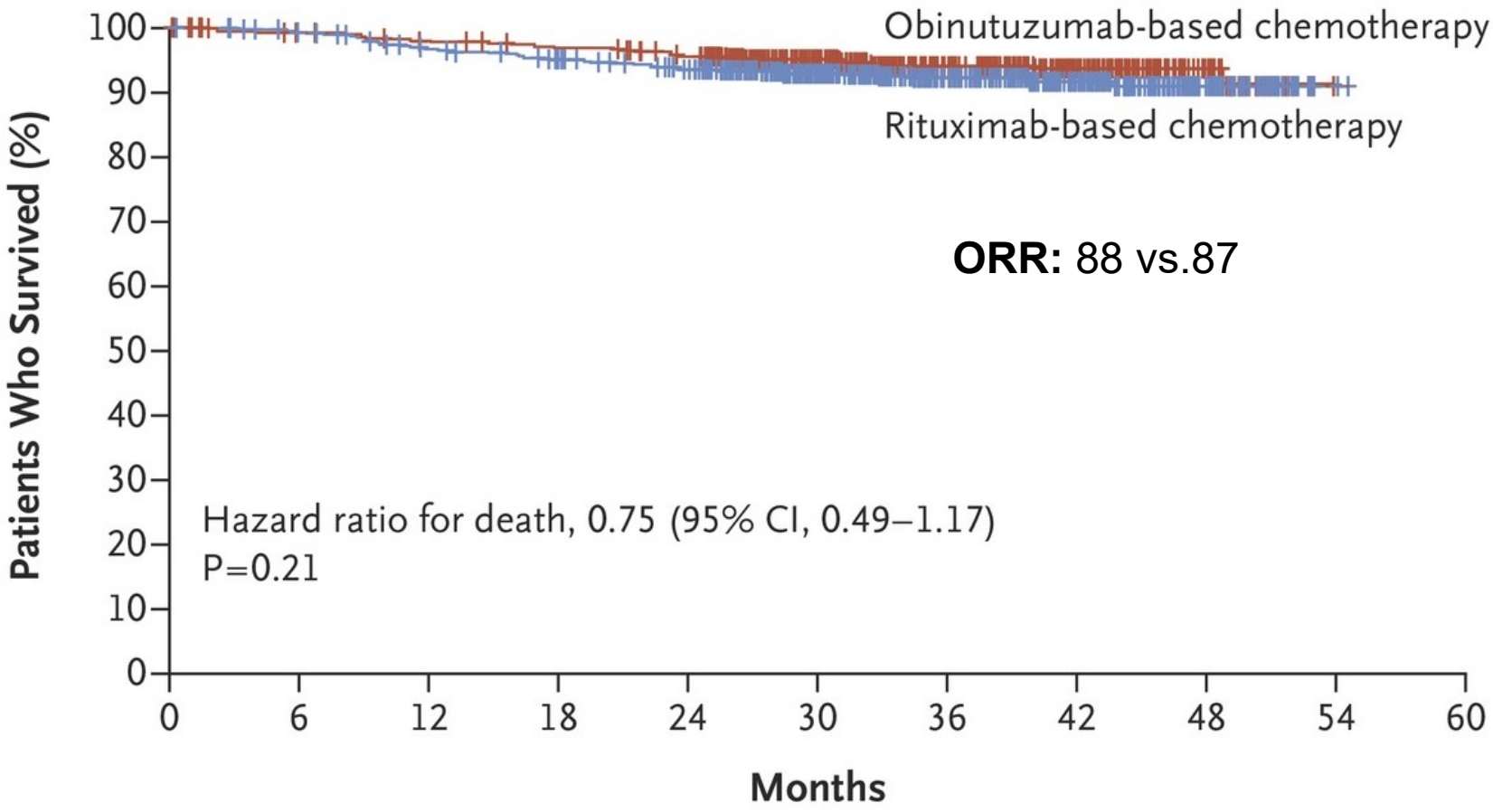
GALLIUM trial: R-chemo vs. G-chemo



Chemo: CHOP, Benda, CVP
Primary endpoints: PFS
Secondary endpoints include: OS, EFS, DoR, safety

Marcus et al. NEJM 2017

GALLIUM trial: R-chemo vs. G-chemo



ORR: 88 vs.87

Marcus et al. NEJM 2017

GALLIUM trial: R-chemo vs. G-chemo

Table 4. Adverse Events of Special Interest during Treatment, According to Prespecified Category, in the Safety Population.

Category	All Adverse Events		Adverse Events of Grade 3 to 5		Serious Adverse Events	
	Obinutuzumab Group (N=595)	Rituximab Group (N=597)	Obinutuzumab Group (N=595)	Rituximab Group (N=597)	Obinutuzumab Group (N=595)	Rituximab Group (N=597)
	number of patients (percent)					
Infection*	460 (77.3)	418 (70.0)	119 (20.0)	93 (15.6)	108 (18.2)	86 (14.4)
Neutropenia	301 (50.6)	269 (45.1)	273 (45.9)	236 (39.5)	50 (8.4)	44 (7.4)
Infusion-related event†						
Any event	406 (68.2)	349 (58.5)	74 (12.4)	40 (6.7)	33 (5.5)	14 (2.3)
Antibody-related event	353 (59.3)	292 (48.9)	63 (10.6)	30 (5.0)	28 (4.7)	12 (2.0)
Tumor lysis syndrome	6 (1.0)	3 (0.5)	6 (1.0)	3 (0.5)	3 (0.5)	1 (0.2)
Cardiac event‡	78 (13.1)	58 (9.7)	22 (3.7)	17 (2.8)	26 (4.4)	12 (2.0)
Thrombocytopenia	68 (11.4)	45 (7.5)	36 (6.1)	16 (2.7)	4 (0.7)	1 (0.2)

Bendamustine:

- Higher grade 3-5 infections and secondary cancers
- Higher non-relapse mortality: 6% G arm, 4% R arm, compared to 2% in CHOP/CVP + G or R.
- PJP and VZV prophylaxis are highly recommended.

Marcus et al. NEJM 2017

While the role of CIT is well established in FL, what about a “chemo-free” regimen with lenalidomide + rituximab?

R-chemo vs. R-Lenalidomide, Phase II

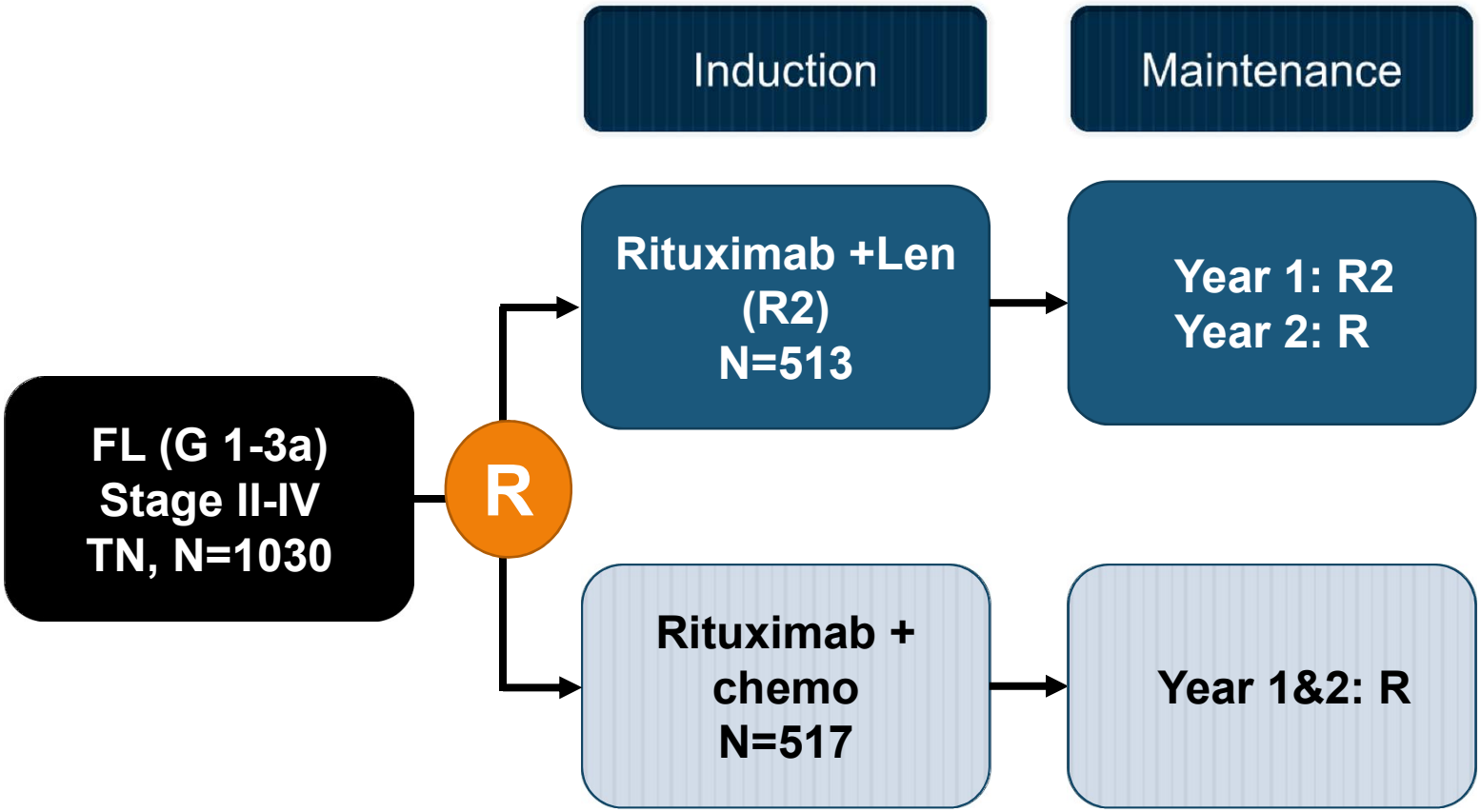
- ORR 95% to 98%
- 2-year PFS rates of 86% to 89%
- Phase III trial: Len-R (R^2) vs. R-chemo

Flower et al. Lancet Oncol 2014

Martin et al. Ann Oncol 2017

RELEVANCE trial: R^2 vs. R-chemo:

A superiority trial



Chemo: CHOP, Benda, CVP
Primary endpoints: CR/CRu at 120W, PFS
Secondary endpoints include: OS, TTT, MRD, EFS

Morschhauser et al. NEJM 2018

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)

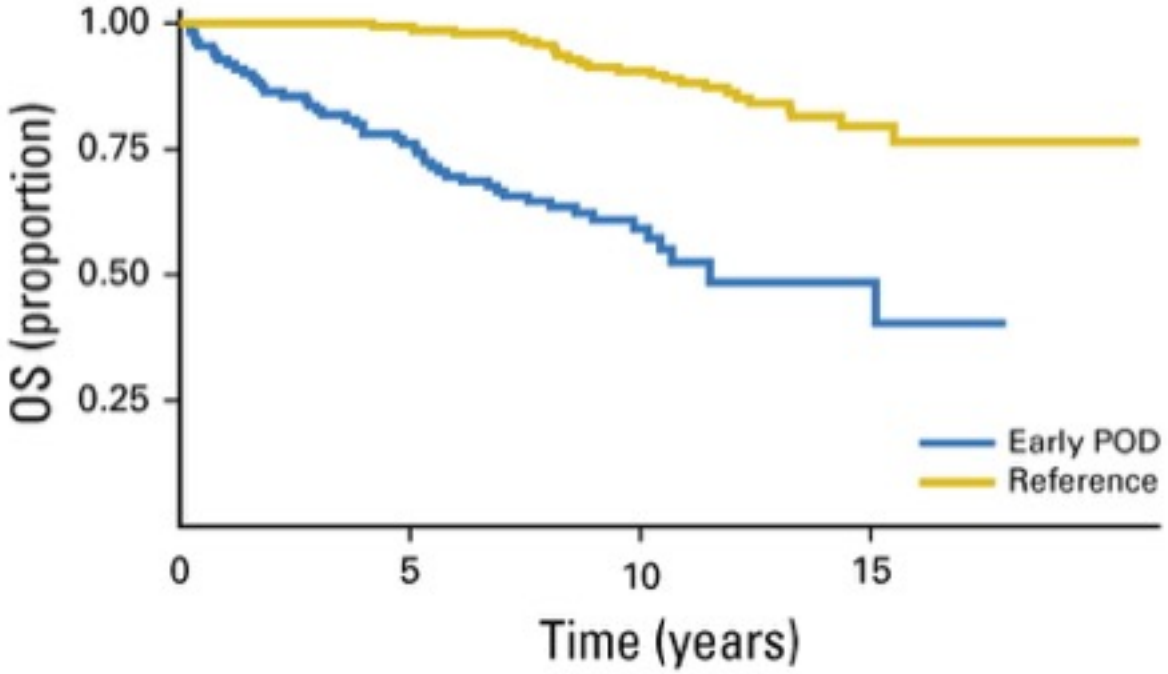
Morschhauser et al. NEJM 2018

Does sustained follow-up single agent rituximab prolong PFS?

- 321 TN patients (84% FL) requiring therapy
- 88% stage III-IV
- 41% of FL had poor FLIPI score
- All patients received one or two cycles of four weekly infusions of rituximab 375 mg/m^2

Lockmer et al. JCO 2018

POD ≤ 24 months predicts OS



No. at risk:				
Early POD	110	82	33	6
Reference	147	141	118	34

Lockmer et al. JCO 2018

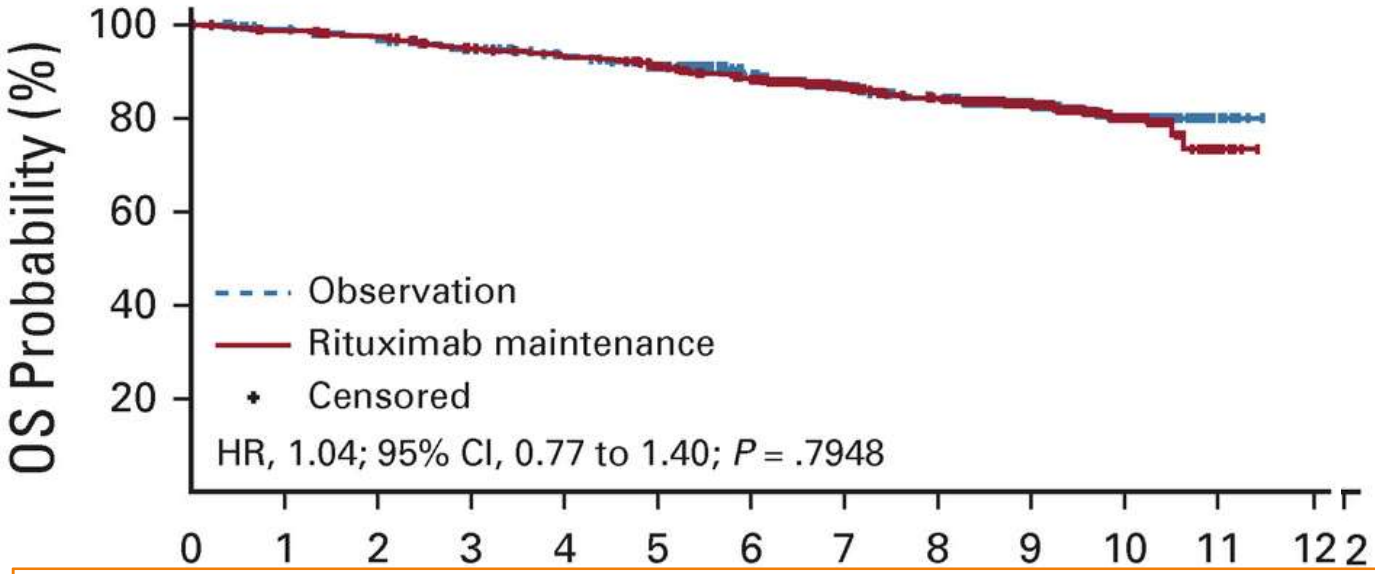
As a single agent:

Rituximab could be a good option for patients with low disease burden and low FLIPI.

Role in maintenance therapy?

- After CIT
- After R induction

PRIMA trial: Phase III R maintenance vs. observation following response to CIT



Rituximab maintenance arm:

- Higher rate of grade 3 to 4 AEs (24.4% *v* 16.9%) and serious AEs (21.2% *v* 13.4%)
- Higher rates of G3-4 cytopenias (5.2% *v* 1.6%) and infections (4.4% *v* 1.0%)

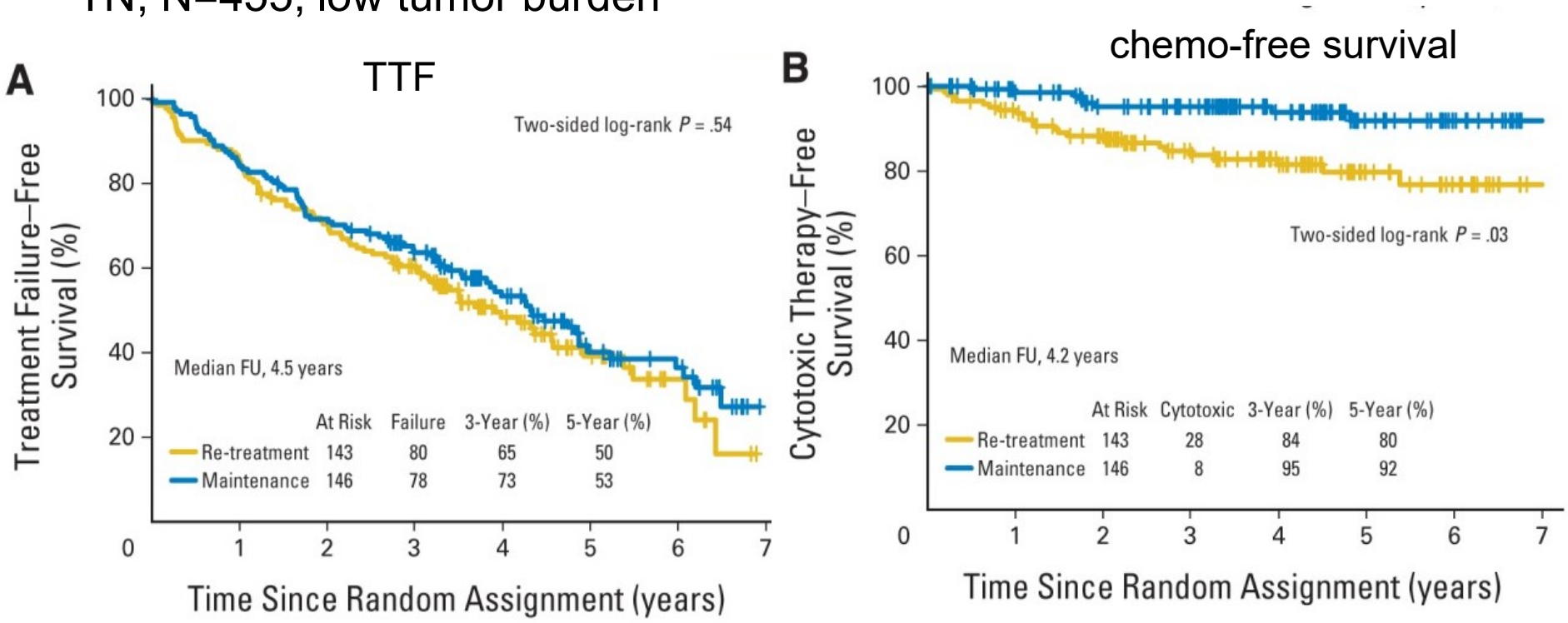
Primary endpoints: investigator-assessed PFS.
Secondary endpoints include: TTNLT, TTNCT, OS, and transformation rate at relapse.

Bachy et al. JCO 2019

E4402 Study, RESORT (Rituximab Extended Schedule or Re-Treatment Trial):

R maintenance vs. Retreatment

TN, N=455, low tumor burden



Primary endpoints: TTF

Secondary endpoints include: time to first cytotoxic therapy, toxicity

Kahl et al. JCO 2014

PET-CT

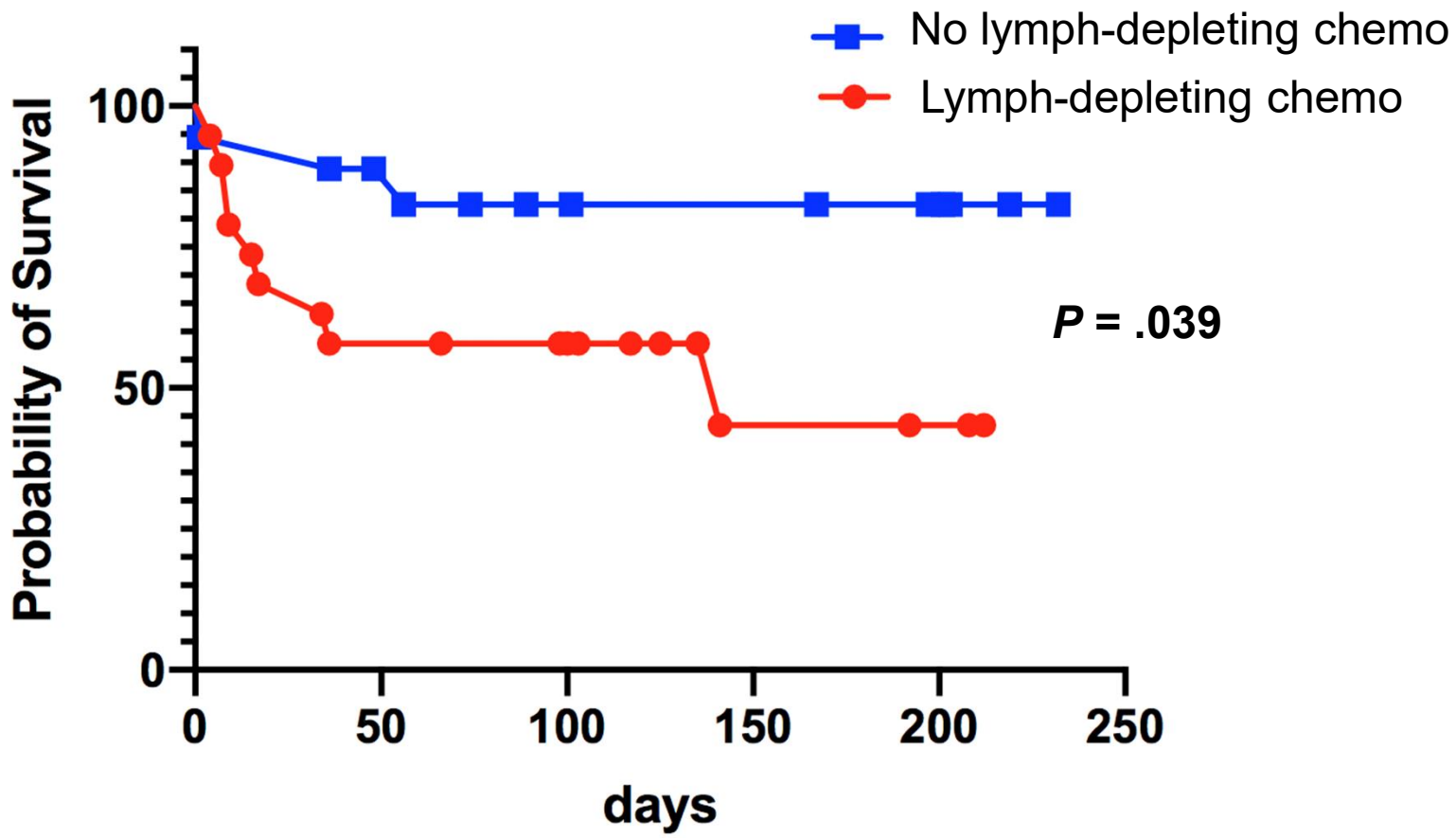
- More accurate than CT scans alone: sensitivity (94%–98%) and specificity (88%–100%) for PET/CT.
- Useful in identifying occult sites of disease.
- Useful in detecting histologic transformation of FL to DLBCL.
- End-of-treatment PET/CT scan is now considered a standard.
- Little data exist on the potential role of follow-up surveillance imaging.

Novel agents approved in R/R FL

Agent	Trial design	N	ORR (CR) %	mPFS	G 3-4 toxicity (>10%)
Idelalisib (PI3K-δ)	II single arm	72	56 (14)	11 m	• Neutropenia (27%) • ALT increase (13%) • Diarrhea (13%)
Copanlisib (PI3K-$\alpha\delta$)	II (CHRONOS-1)	104	59 (14)	11 m	• Neutropenia (24%), • Hyperglycemia (41%) • Hypertension (24%) • Pneumonia (15%)
Duvelisib (PI3K-$\delta\gamma$)	II (DYNAMO)	83	42 (1)	9.5 m	• Neutropenia (25%) • Anemia (15%) • Plt decreased (12%) • Diarrhea (15%)
Tazemetostat (EZH2)	II	99 (45 EZH2 ^{mut})	Mut: 69 (13) WT: 31 (4)	13.8 m 11.1 m	• Neutropenia (3%) • Plt decreased (3%) • Anemia (2%)

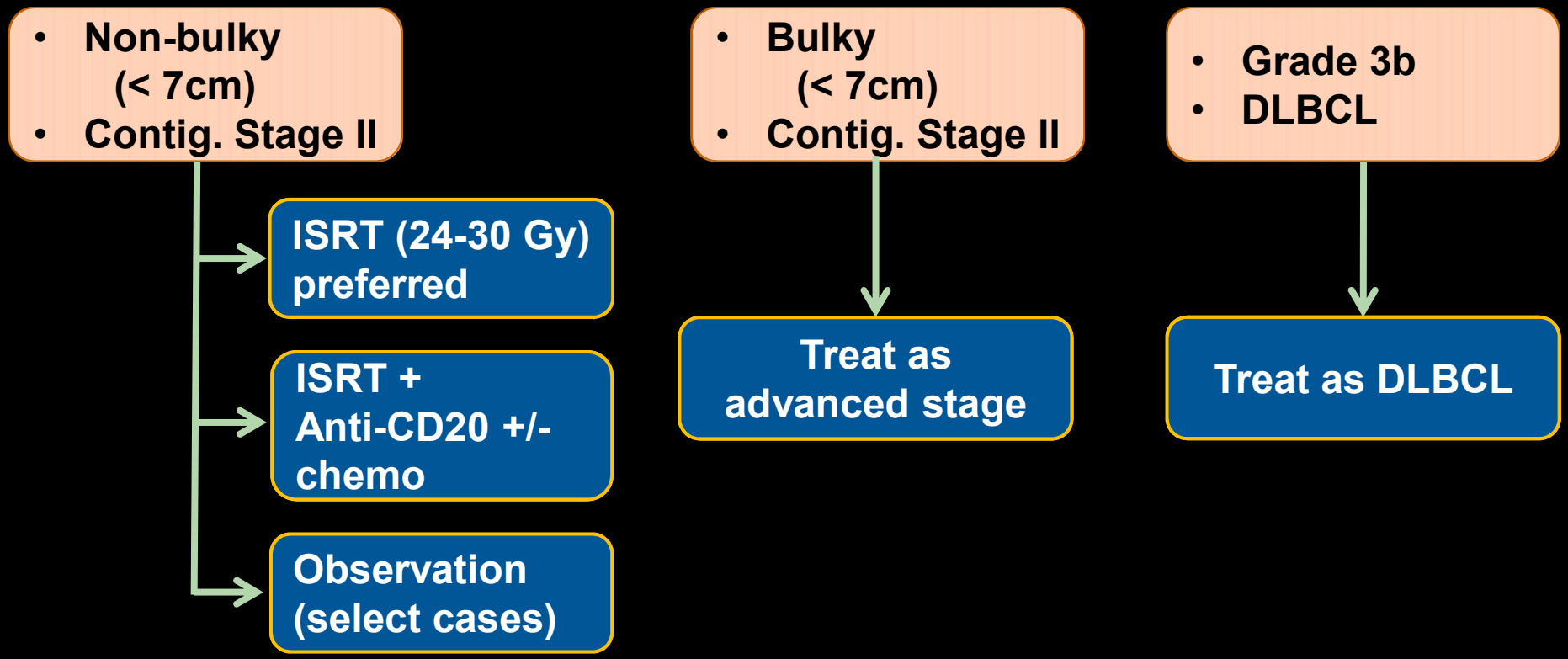
Salles et al. Haematologica 2017; Dreyling et al. JCO 2017; Flinn et al. JCO 2019; Morschhauser et al. The Lancet Oncol 2020.

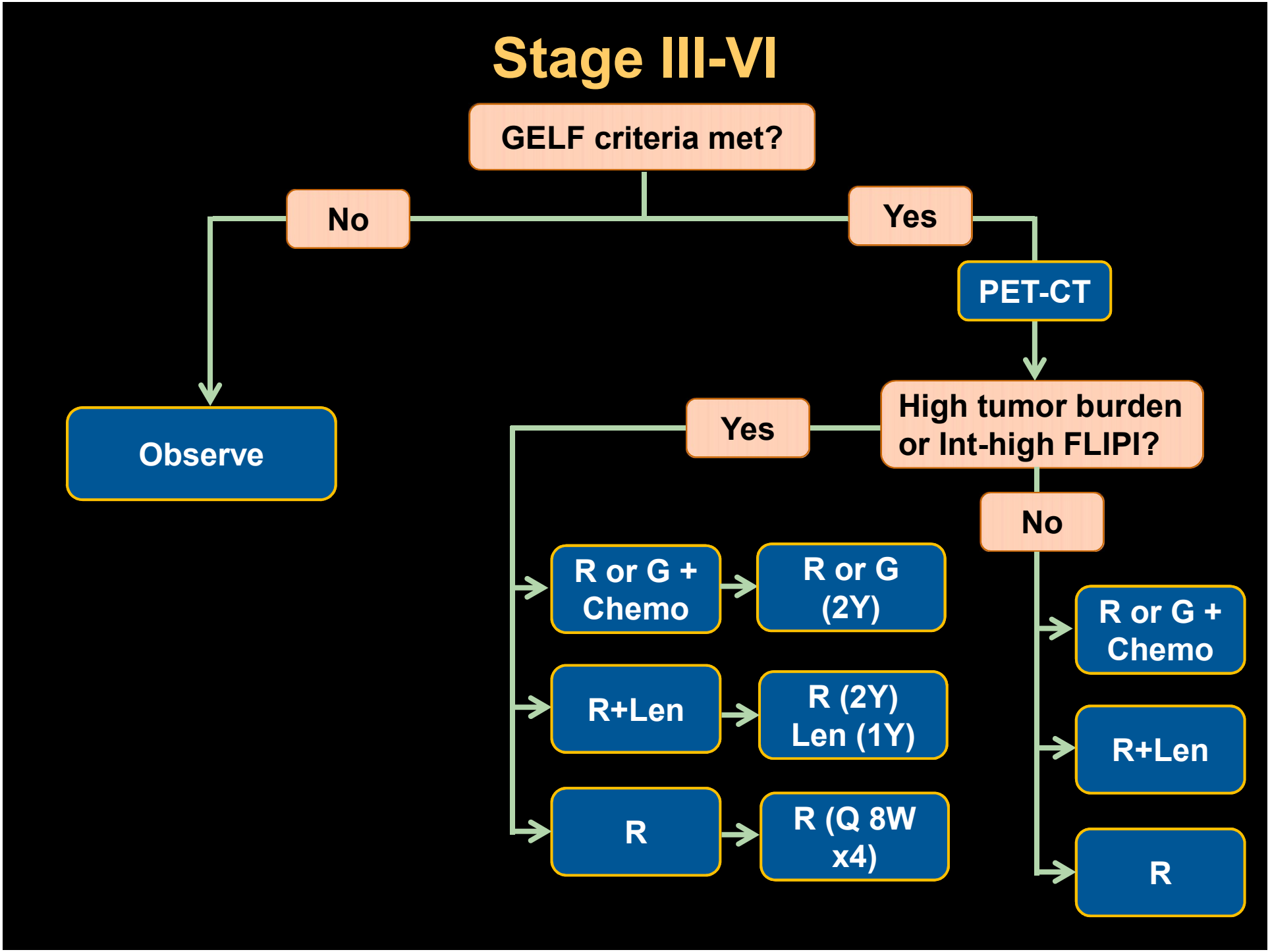
COVID-19 and Hematological malignancies



Niu… Saba. ASH 2020, A#313

Stage I-II


• Non-bulky (< 7cm)
• Contig. Stage II
ISRT (24-30 Gy) preferred
ISRT + Anti-CD20 +/- chemo
Observation (select cases)
• Bulky (< 7cm)
• Contig. Stage II
Treat as advanced stage
• Grade 3b
• DLBCL
Treat as DLBCL


Stage III-VI
GELF criteria met?
No
Yes
Observe
PET-CT
High tumor burden or Int-high FLIPI?
Yes
No
R or G + Chemo
R or G (2Y)
R+Len
R (2Y) Len (1Y)
R
R (Q 8W x4)
R or G + Chemo
R+Len
R

Thank you

nsaba@tulane.edu
Clinic: 504-988-6460
Cell: 423-946-1366