Newly Diagnosed Advanced Stage Follicular Lymphoma and Future Landscapes

Laurie H. Sehn, MD, MPH

Chair, Lymphoma Tumour Group

BC Cancer Centre for Lymphoid Cancer

Vancouver, Canada

BC CANCER

Provincial Health Services Authority

a place of mind

THE UNIVERSITY OF BRITISH COLUMBIA

Disclosures

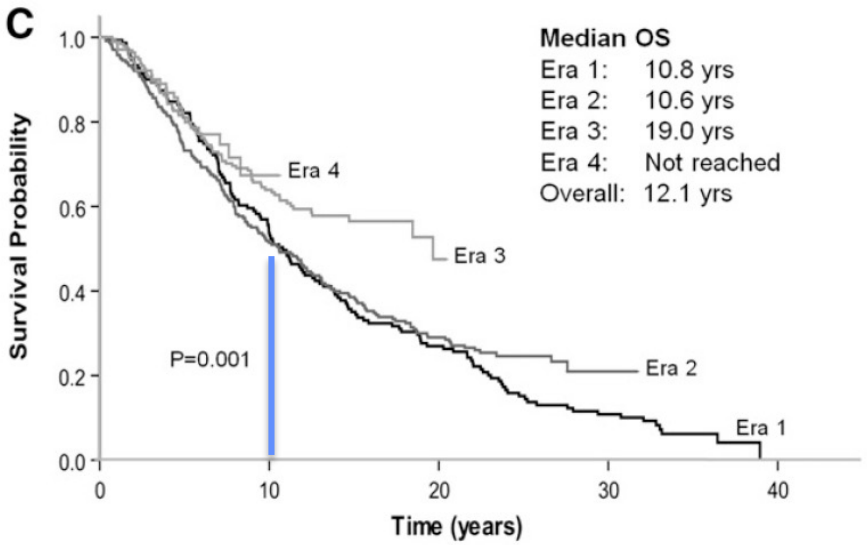
- **Consulting/Honoraria:** Roche/Genentech, Abbvie, Amgen, Apobiologix, Astra Zeneca, Acerta, Celgene, Kite/Gilead, Incyte, Janssen, Karyopharm, Lundbeck, Merck, Morphosys, Seagen, Teva, Takeda, TG Therapeutics, Verastem

- **Research funding:** Roche/Genentech, Teva

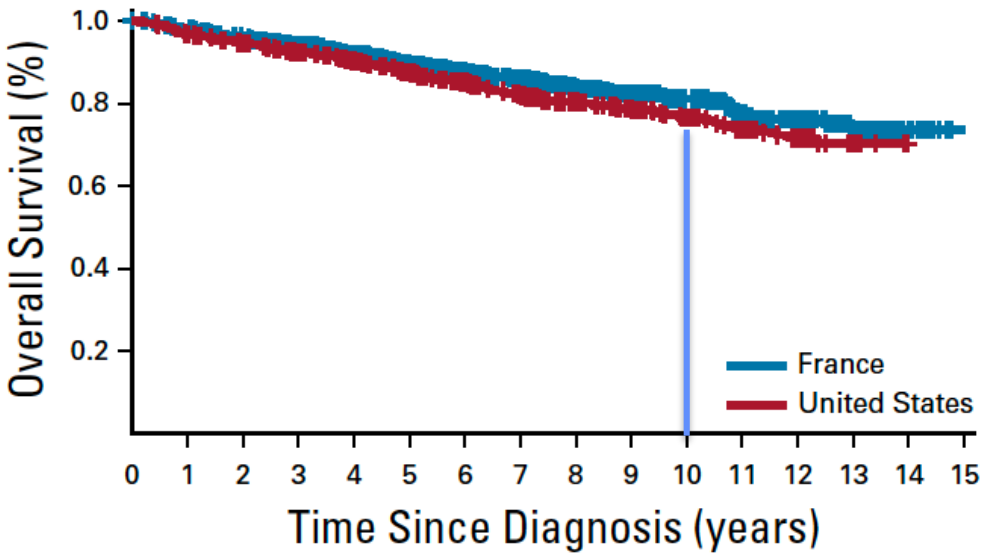
The Challenge of Follicular NHL

- Indolent behaviour and is responsive to many treatments, but remains incurable
- Most patients have a prolonged survival, but a subset exhibit a propensity to transformation or treatment-resistance that will affect their longevity
- Wide range of treatment options of varying intensity
- Goal is to control the disease, while maintaining quality of life

Outcomes have Improved Dramatically over the Decades



1986: 10-year OS ~54%



2015: 10-year OS ~80%

Tan, D et al Blood 2013; Sarkozy C, et al JCO 2018

What has improved?

- Overall lifespan
- Better diagnosis
- Better supportive care
- Better treatment
  - More effective chemotherapy
  - Introduction of anti-CD20 monoclonal antibodies
  - Novel agents
  - More and more options
- Improved outcomes following transformation

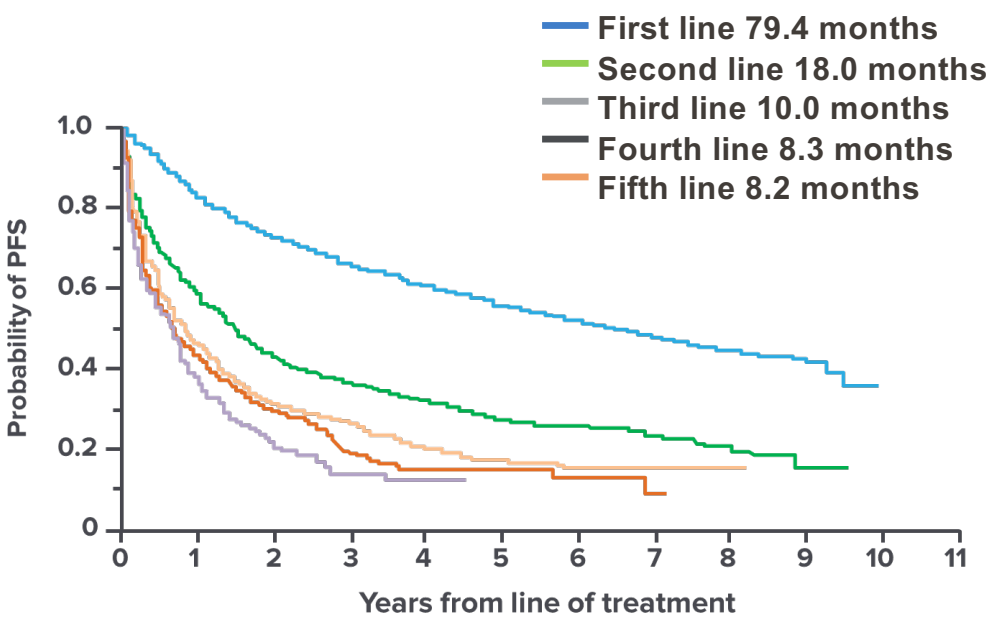
What will progress look like?

- No “chemotherapy”
  - Reduced toxicity
- More time without treatment
- Reduced risk of transformation
- Improved PFS
- Improved Disease-specific survival
- Improved OS
- Cure

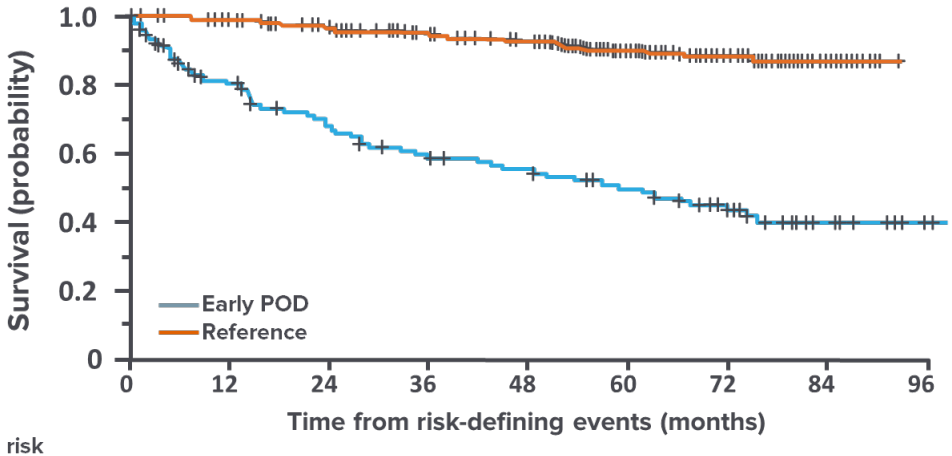
Outcomes According to Line of Therapy and POD24

National LymphoCare Study

PFS by Treatment Line[a]



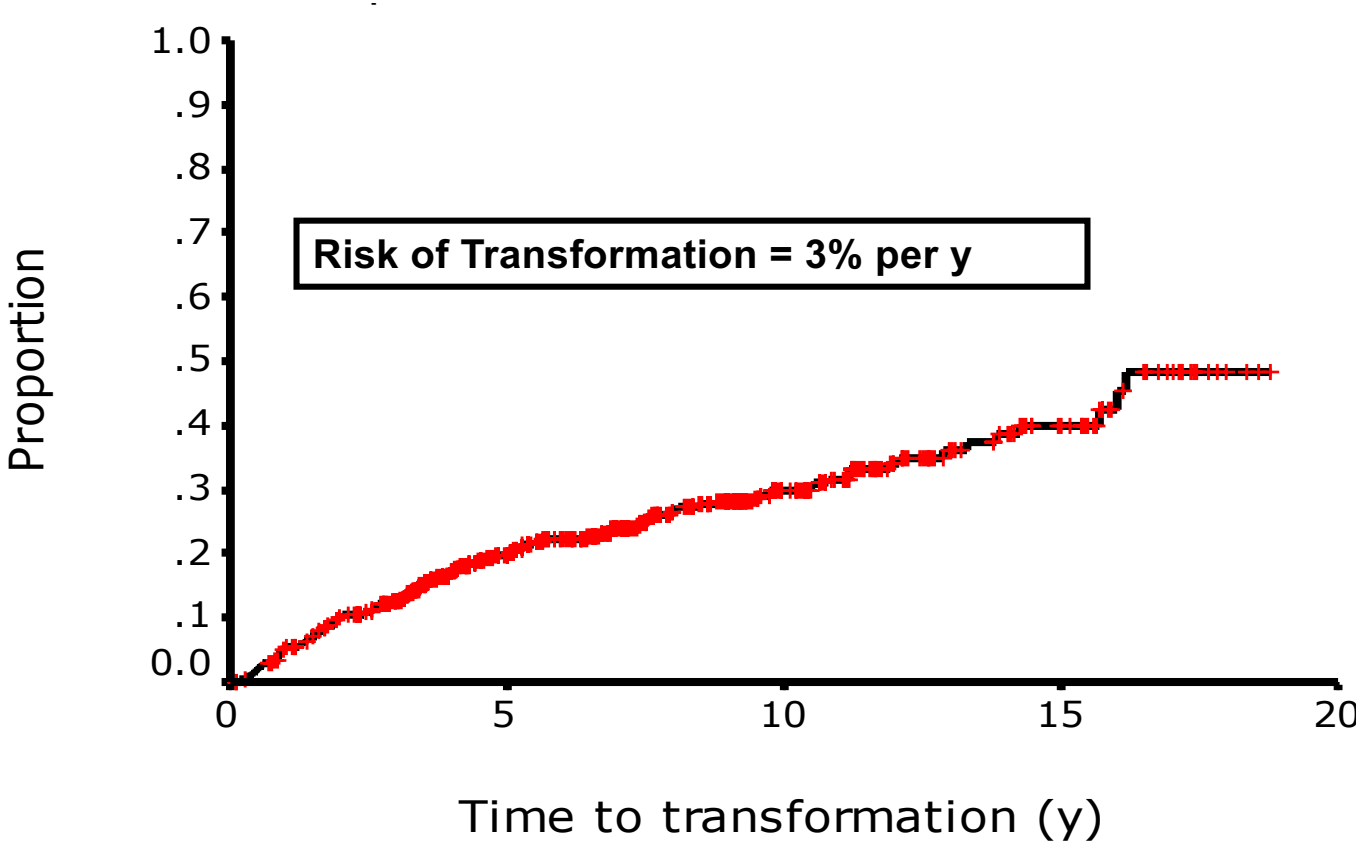
Survival With POD24 (progression < 24 months after initial therapy)[b]



No. at risk									
Early POD	110	82	66	56	50	42	32	14	3
Reference	420	408	387	363	344	253	145	34	0

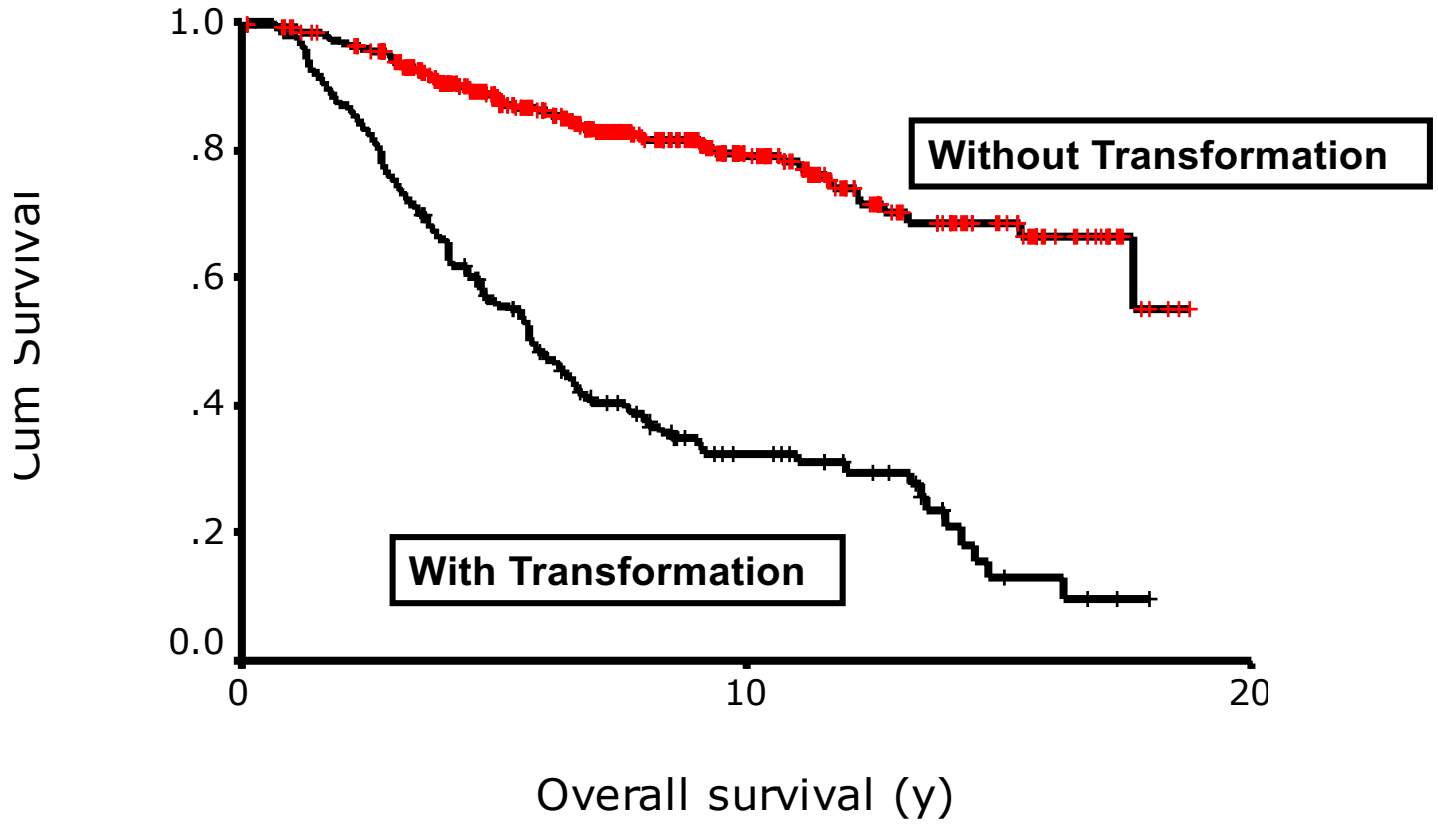
Link BK et al, Br J Haematol 2019; Casulo C, et al, J Clin Oncol. 2015

Inherent Risk of Transformation



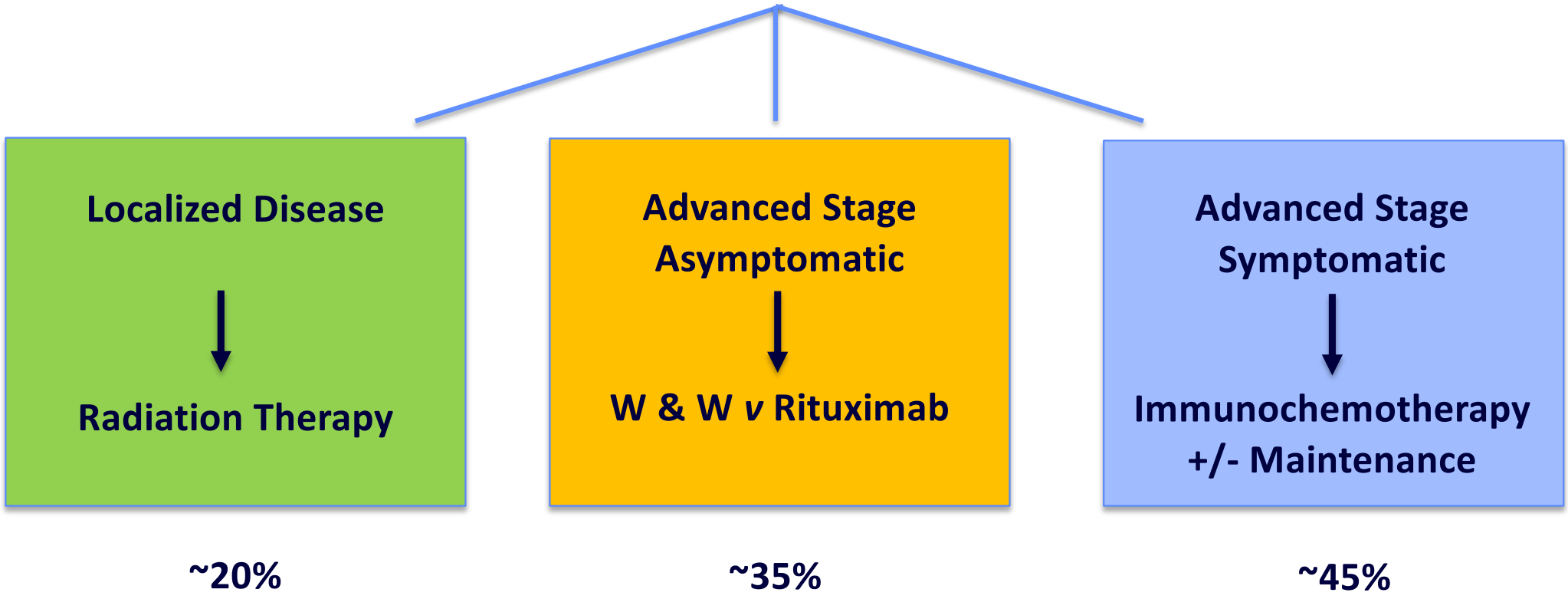
Al-Tourah A, et al JCO 2008

Transformation has Major Impact on OS

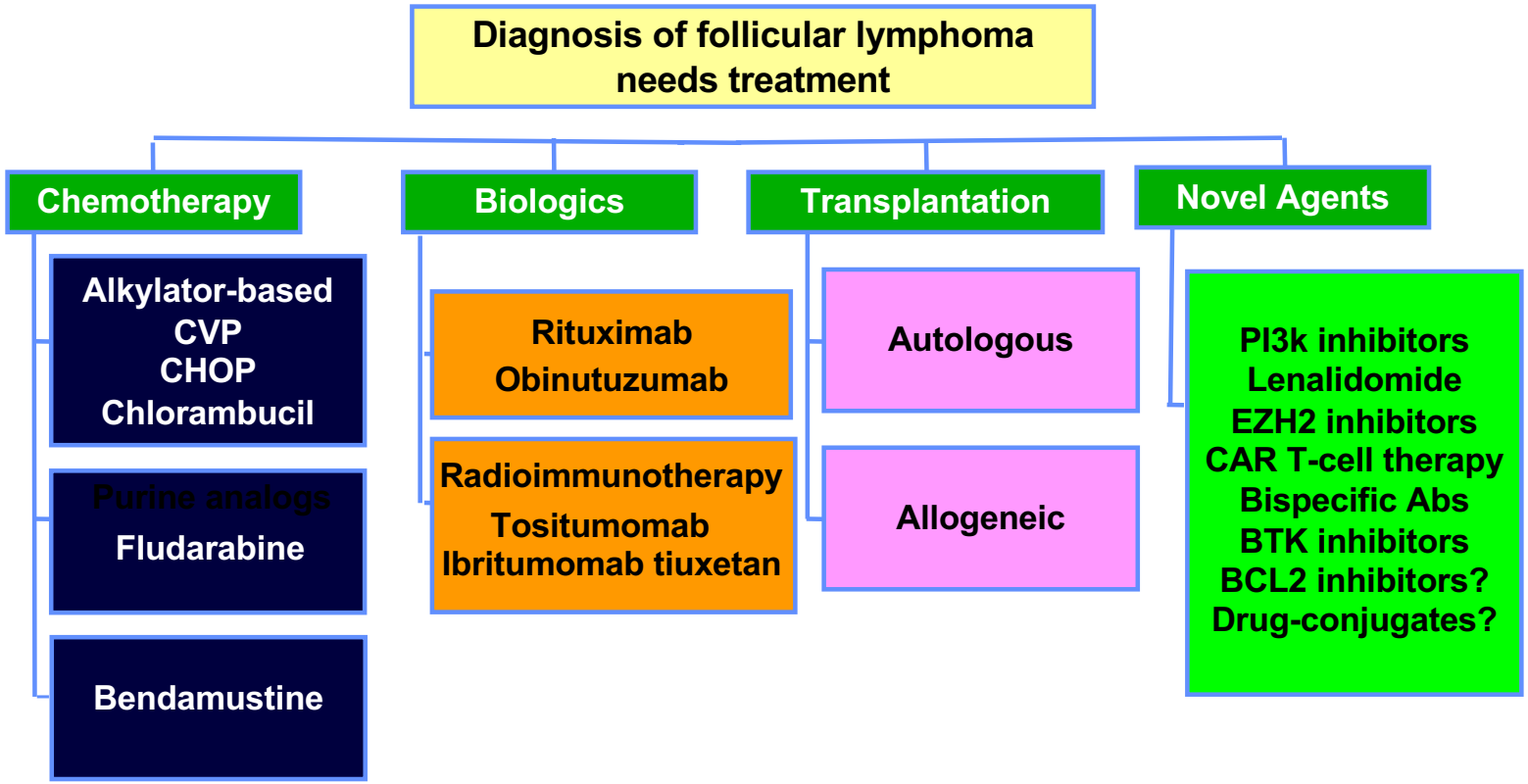


Al-Tourah A, et al JCO 2008

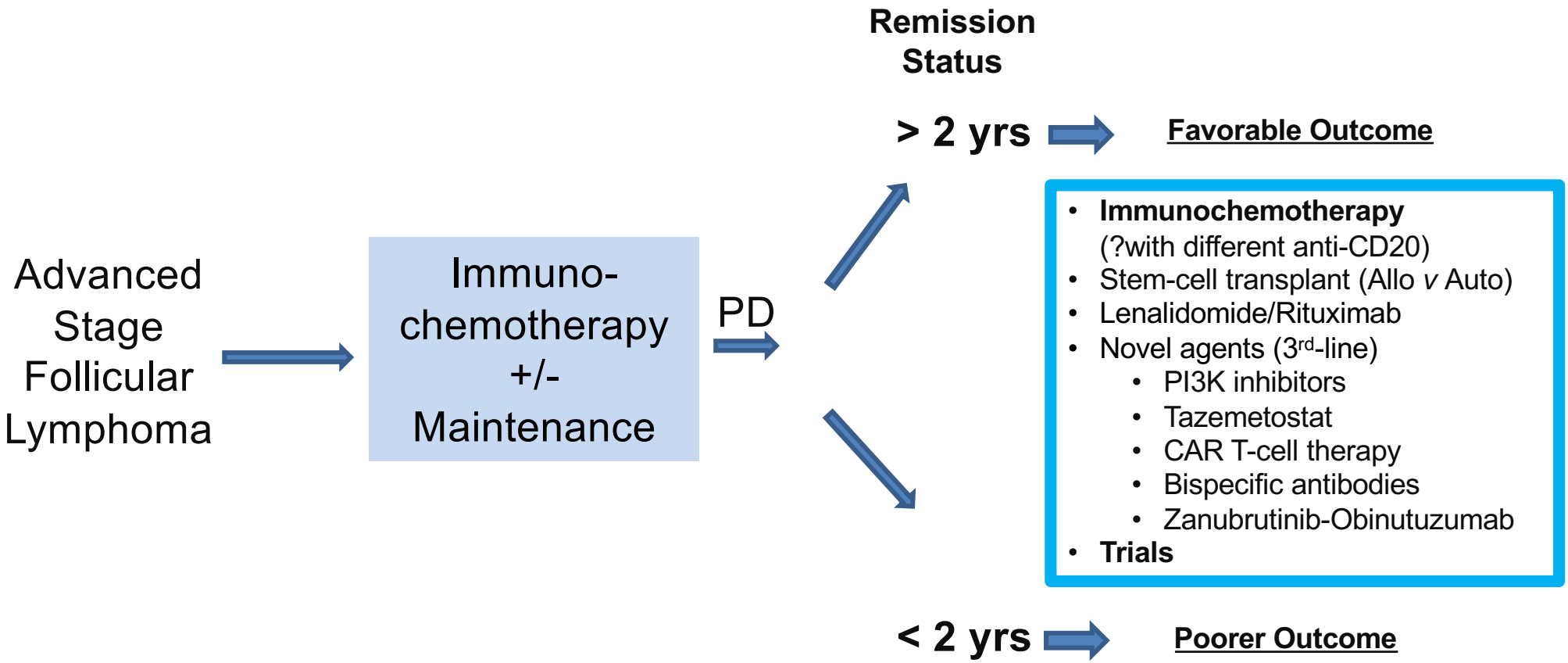
Follicular Lymphoma: Treatment Initiation



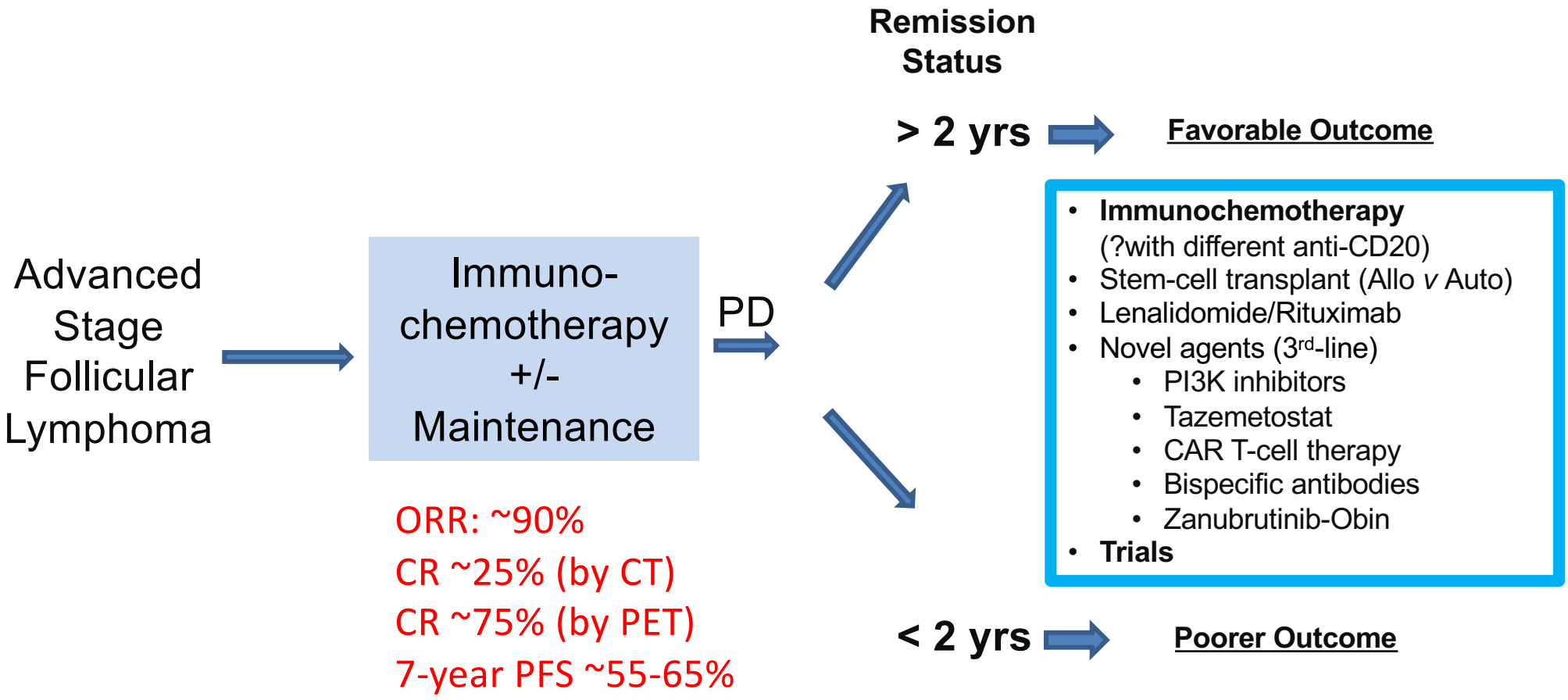
Treatment Options for Follicular Lymphoma



Treatment of Follicular Lymphoma



Treatment of Follicular Lymphoma

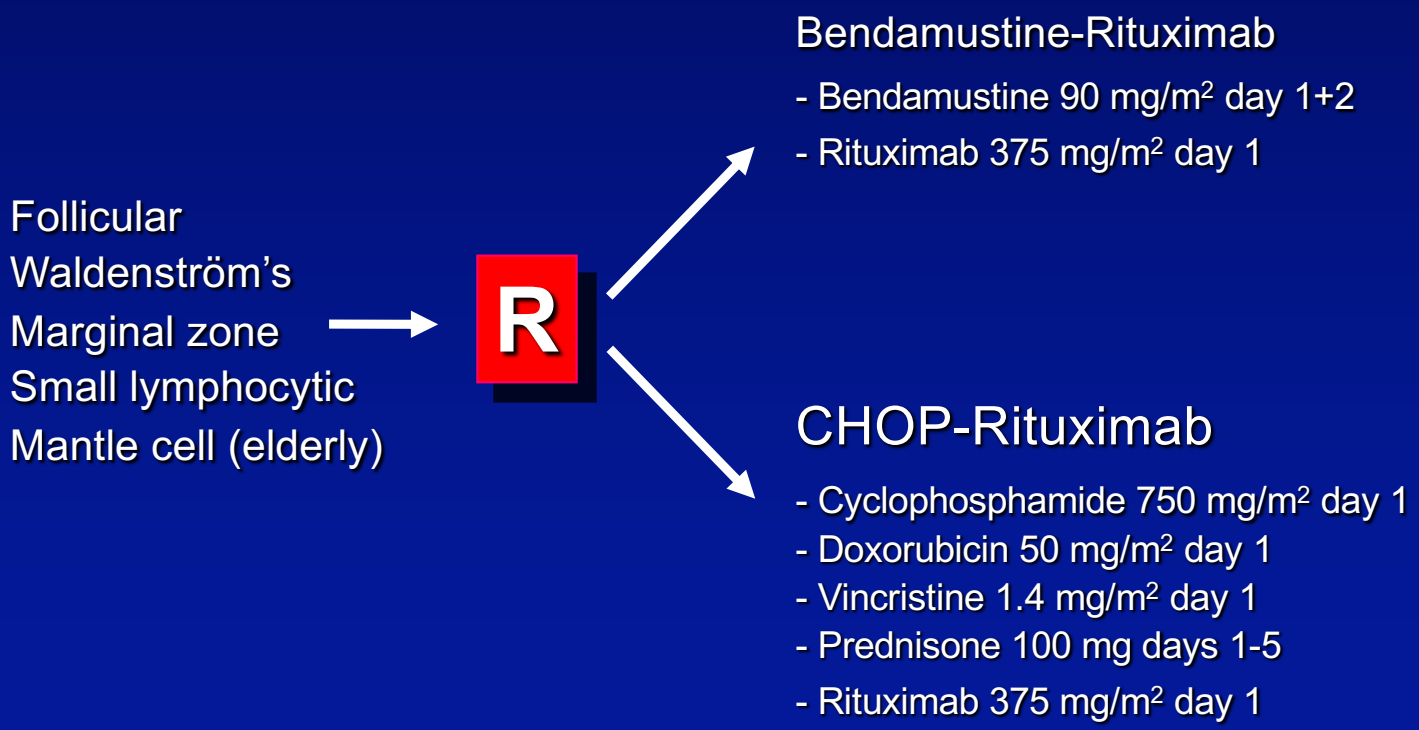


Randomized Trials of Rituximab and Chemotherapy in Untreated FL

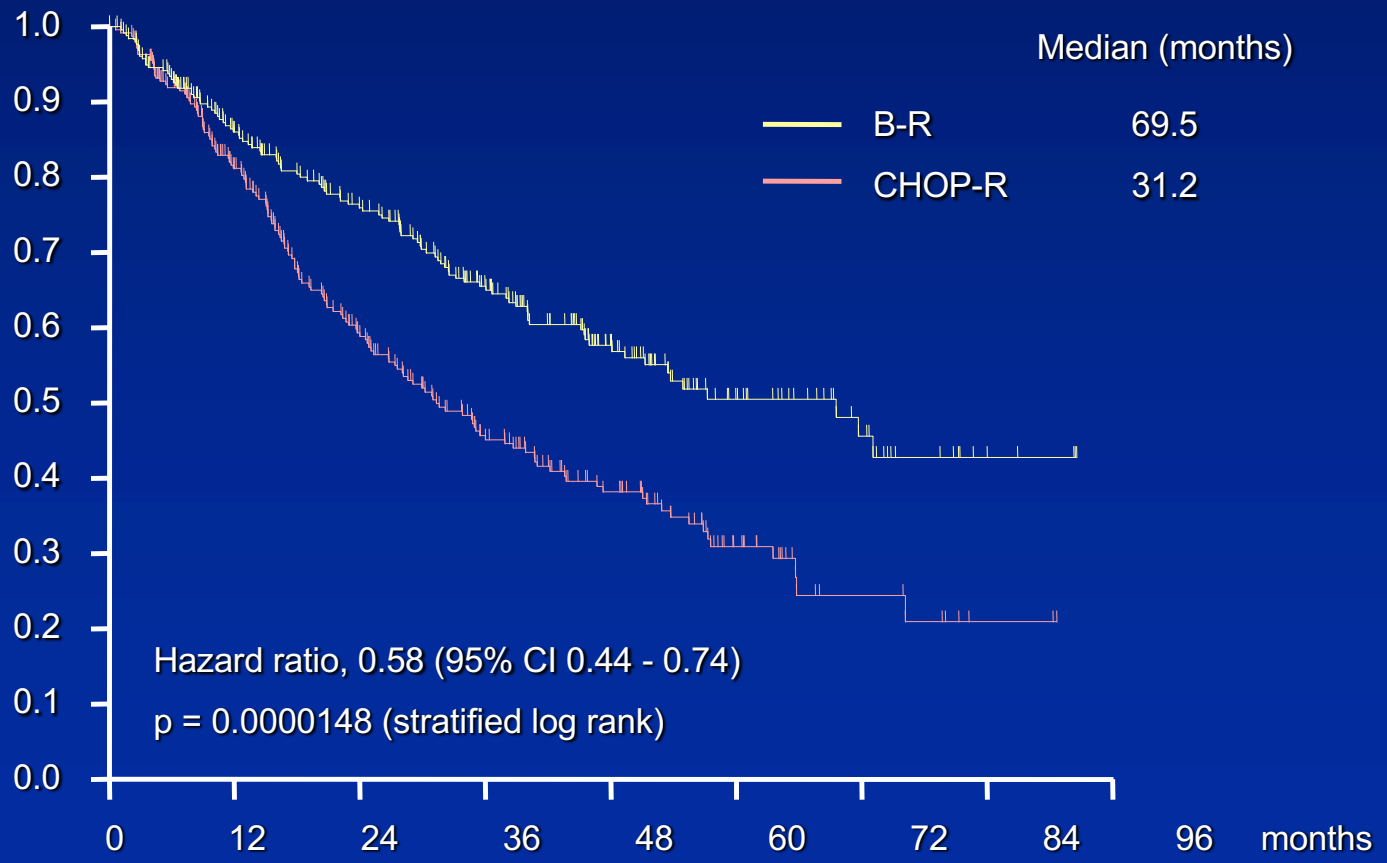
Trial	Patients	Treatment	Results
Marcus *J Clin Oncol 2008*	n = 321	CVP vs R-CVP	Improved TTP and OS
Hiddemann *Blood 2005*	n = 428	CHOP vs R-CHOP	Improved TTF and OS
Herold *J Clin Oncol 2007*	n = 201	MCP vs R-MCP	Improved EFS and OS
Salles, Foussard *Blood 2008*	n = 358	CHVP/IFN vs R-CHVP/IFN	Improved EFS and OS (high risk)

Bendamustine-Rituximab (B-R) vs CHOP-R in Untreated Indolent Lymphoma

StiL NHL 1-2003



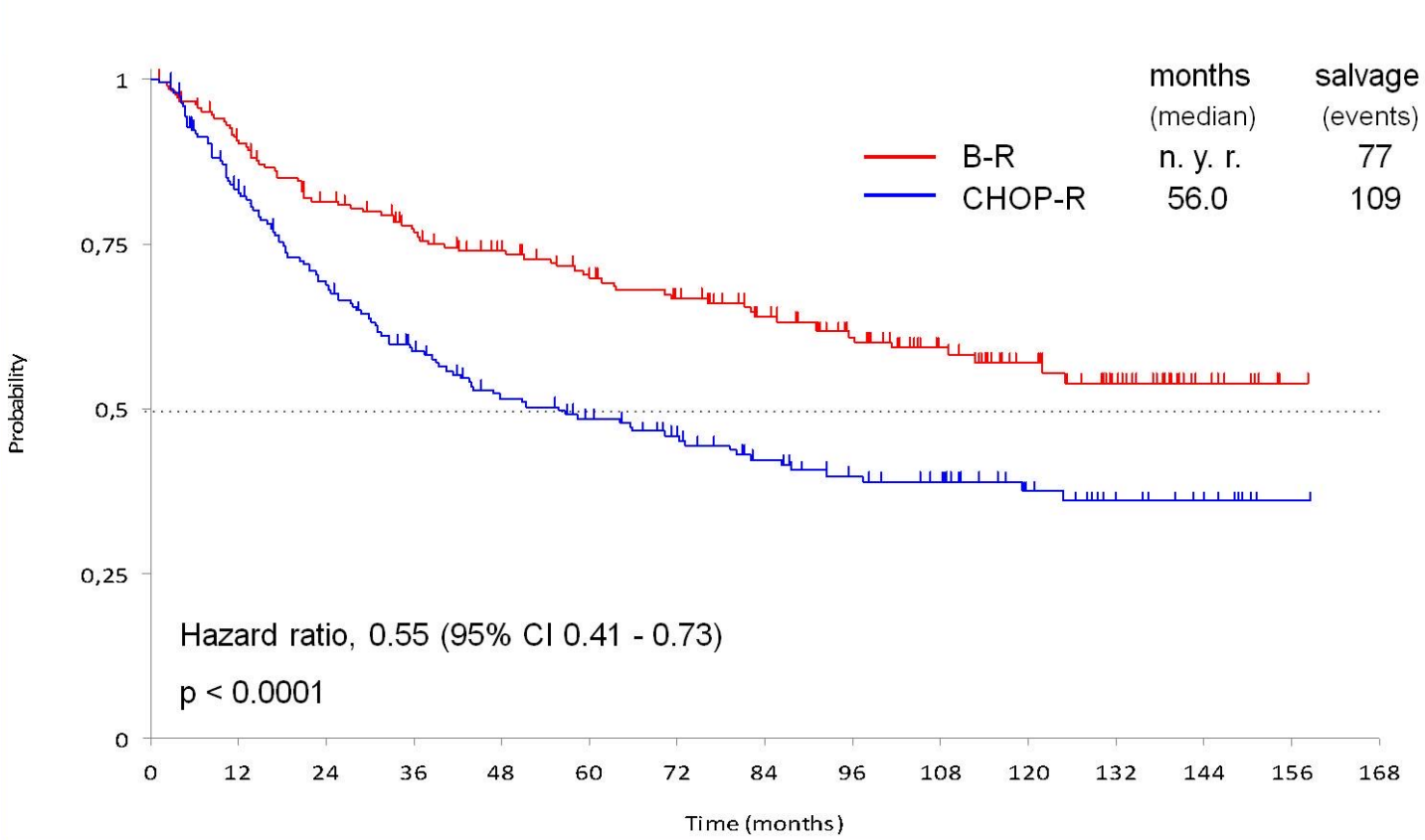
Bendamustine-Rituximab (B-R) vs CHOP-R
Progression-Free Survival



Rummel, M Lancet 2013

MJR

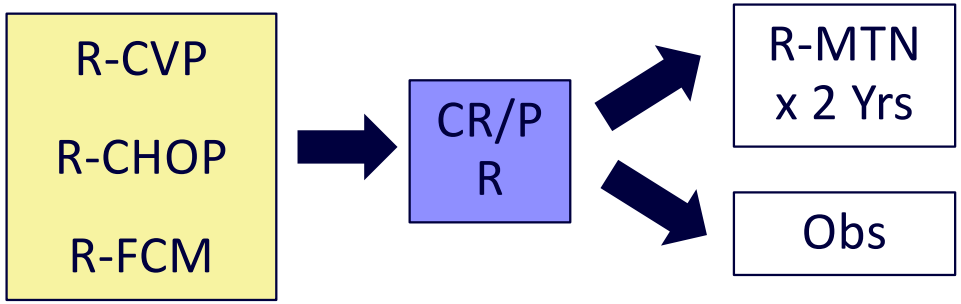
STIL-1: Nine Year Updated Results
Time-to-Next-Treatment

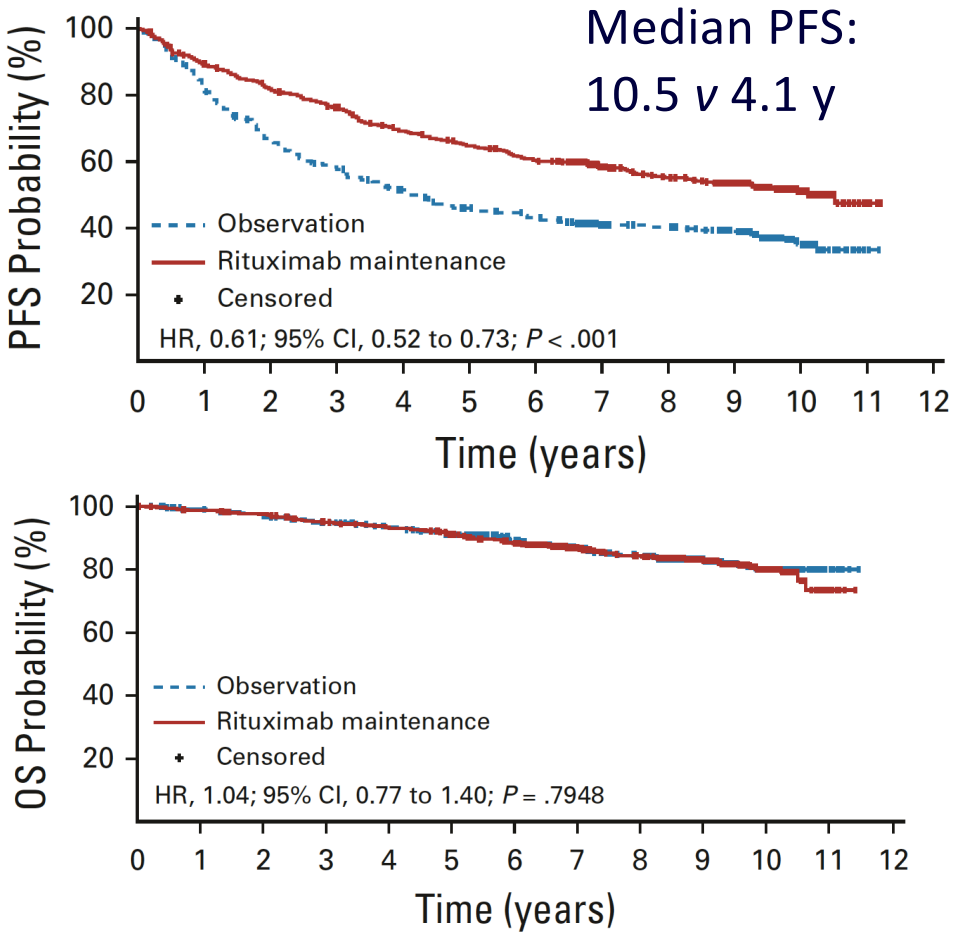


Rummel et al, ASCO 2016

*** No difference in OS or secondary malignancies**

PRIMA Trial: R-Maintenance after R-Chemo

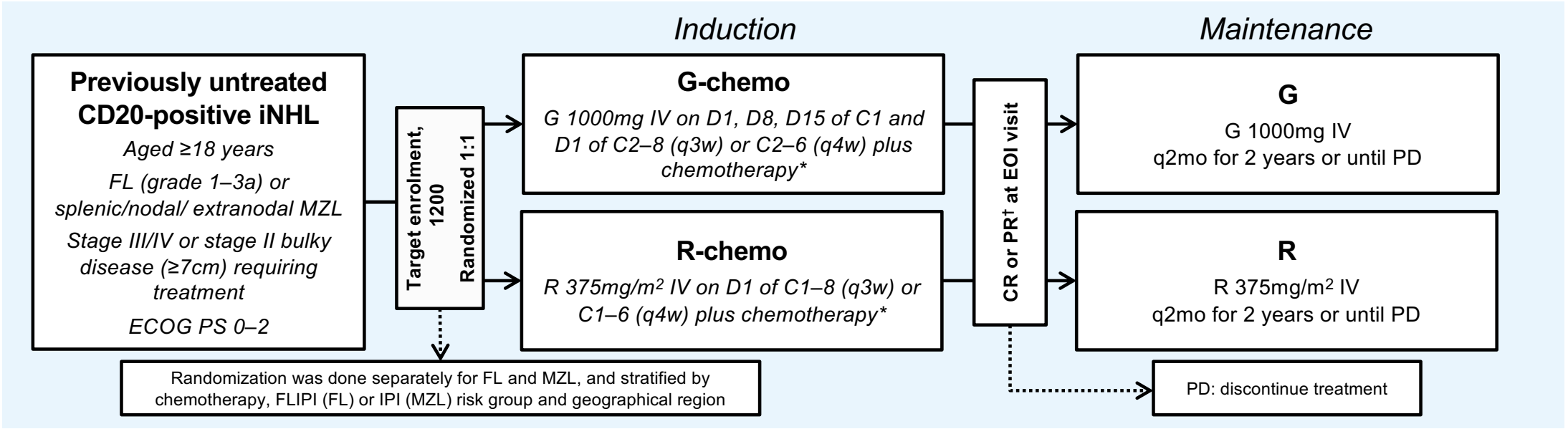




Bachy E et al, JCO 2019

Gallium Trial: R-Chemo *v* G-Chemo in Untreated FL

Global, open-label, randomized Phase 3 study in 1L iNHL patients



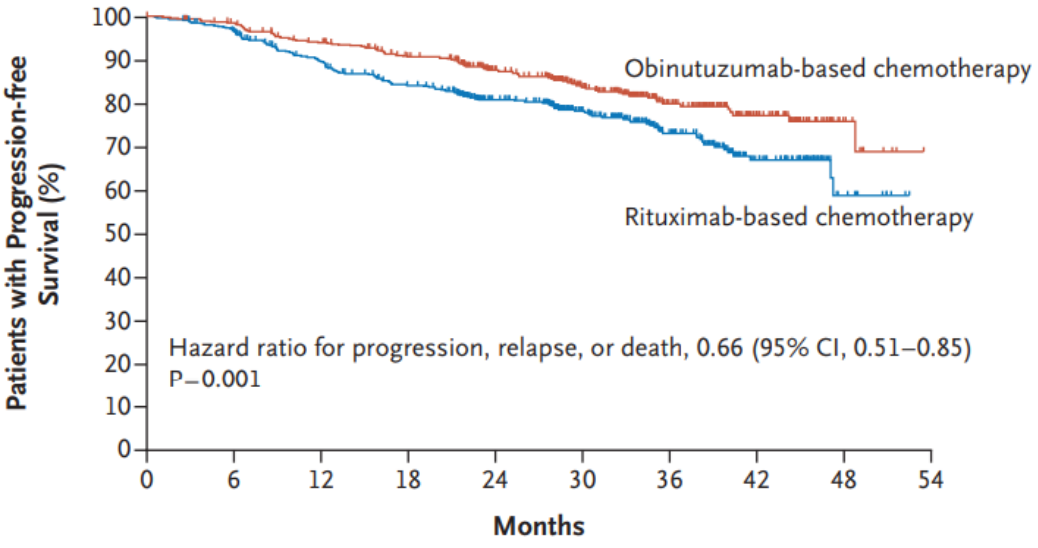
Choice of chemotherapy:

R-CHOP, R-CVP, or R-Bendamustine

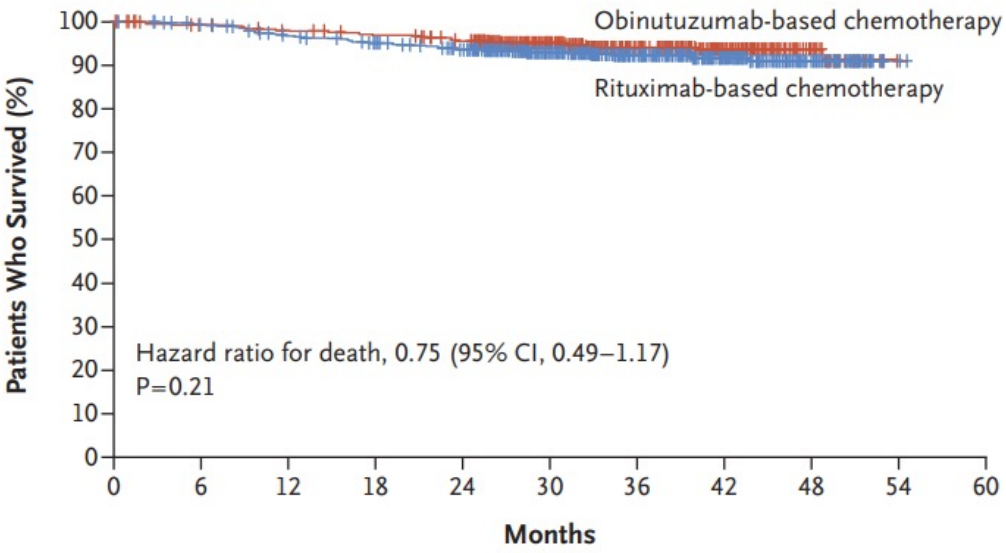
Marcus et al, NEJM 2017

Gallium Trial: Rituximab *v* Obinutuzumab

PFS



OS



- Obinutuzumab: ↑ IRRs and neutropenia
- Most benefit in intermed-high risk FLIPI

- **Median follow-up: 34.5 months**

Marcus et al, NEJM 2017;
Hiddemann et al, JCO 2018

Overview of safety

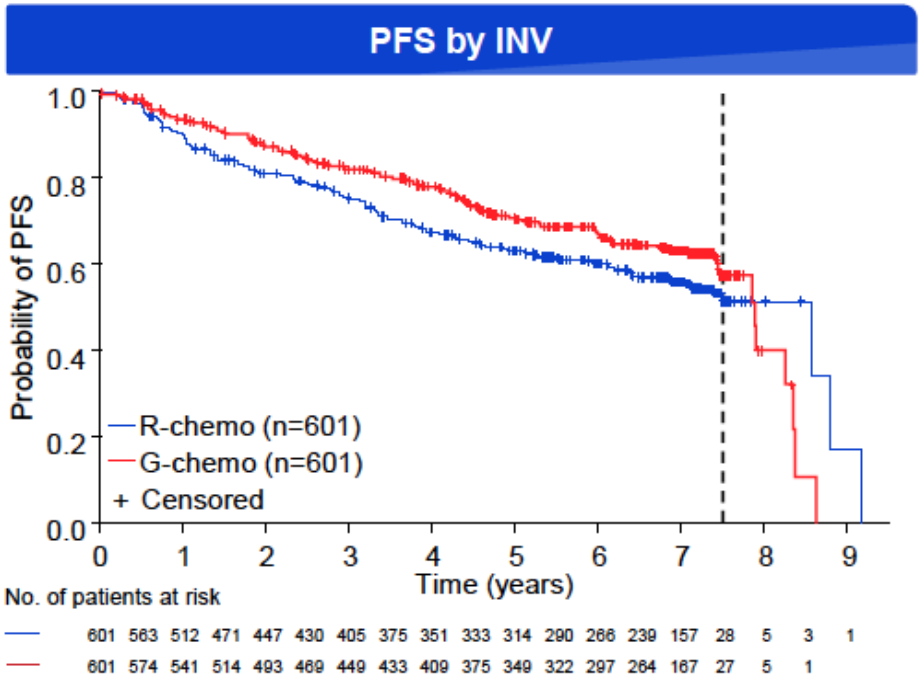
	R-benda (n=338)	G-benda (n=338)	R-CHOP (n=203)	G-CHOP (n=193)	R-CVP (n=56)	G-CVP (n=61)
Total number of patients with ≥1 event (AE/death)	331 (97.9%)	338 (100.0%)	201 (99.0%)	191 (99.0%)	56 (100.0%)	61 (100.0%)
Total number of deaths	37 (10.9%)	28 (8.3%)	9 (4.4%)	28 (8.3%)	6 (10.7%)	3 (4.9%)
Total number of Grade 3-5 AE	601	732	666	727	89	104
Total number of patients with ≥1:						
AE with fatal outcome	**16 (4.7%)**	**20 (5.9%)**	4 (2.0%)	3 (1.6%)	1 (1.8%)	1 (1.6%)
Grade 3–5 AE	228 (67.5%)	233 (68.9%)	**151 (74.4%)**	**171 (88.6%)**	30 (53.6%)	42 (68.9%)
Serious AE	160 (47.3%)	176 (52.1%)	67 (33.0%)	76 (39.4%)	19 (33.9%)	26 (42.6%)
AE leading to withdrawal from any treatment	48 (14.2%)	52 (15.4%)	31 (15.3%)	32 (16.6%)	9 (16.1%)	11 (18.0%)
AE leading to any dose reduction	46 (13.6%)	43 (12.7%)	38 (18.7%)	51 (26.4%)	11 (19.6%)	13 (21.3%)
AE leading to any dose interruption	194 (57.4%)	217 (64.2%)	114 (56.2%)	135 (69.9%)	29 (51.8%)	44 (72.1%)

- Study not designed or powered to compare differences between R-chemo and G-chemo within chemo groups

- Bendamustine: ↑ infections & fatal AEs?

Marcus et al, NEJM 2017;
Hiddemann et al, JCO 2018

PFS benefit was maintained with G- vs R-chemo after 8 years of follow-up



KM estimates became unreliable beyond 7.5 years, due to low numbers of patients at risk[1]

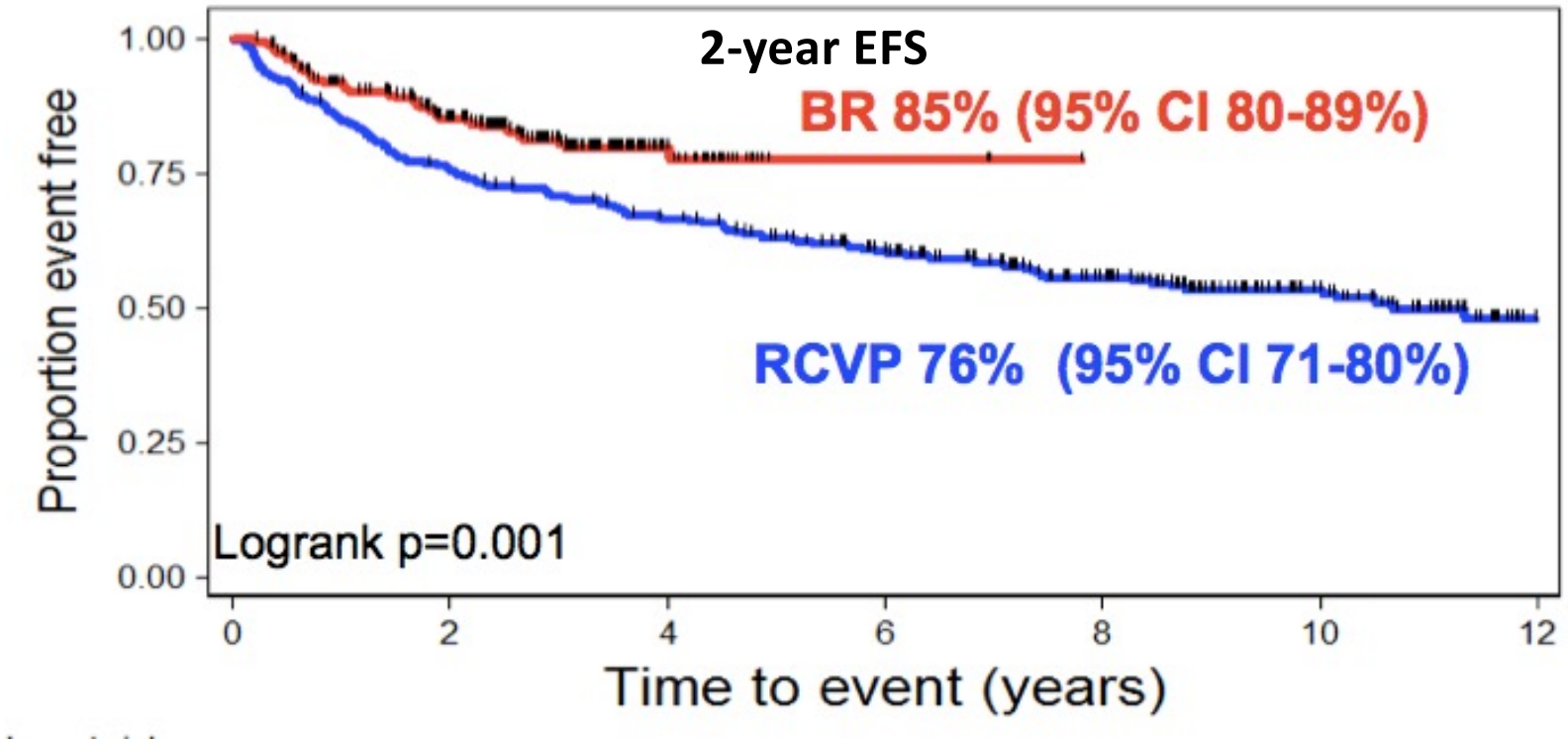
Median observation time: 7.9 (0.0–9.8) years

INV-assessed PFS	G-chemo (n=601)	R-chemo (n=601)
Patients with event, n (%)	206 (34.3)	244 (40.6)
7-year PFS, % (95% CI)	63.4 (59.0–67.4)	55.7 (51.3–59.9)
HR (95% CI)*	0.77 (0.64–0.93)	
P-value	0.006	

No new safety signals, ? higher grade ≥3 neutropenia and infection with Obinutuzumab

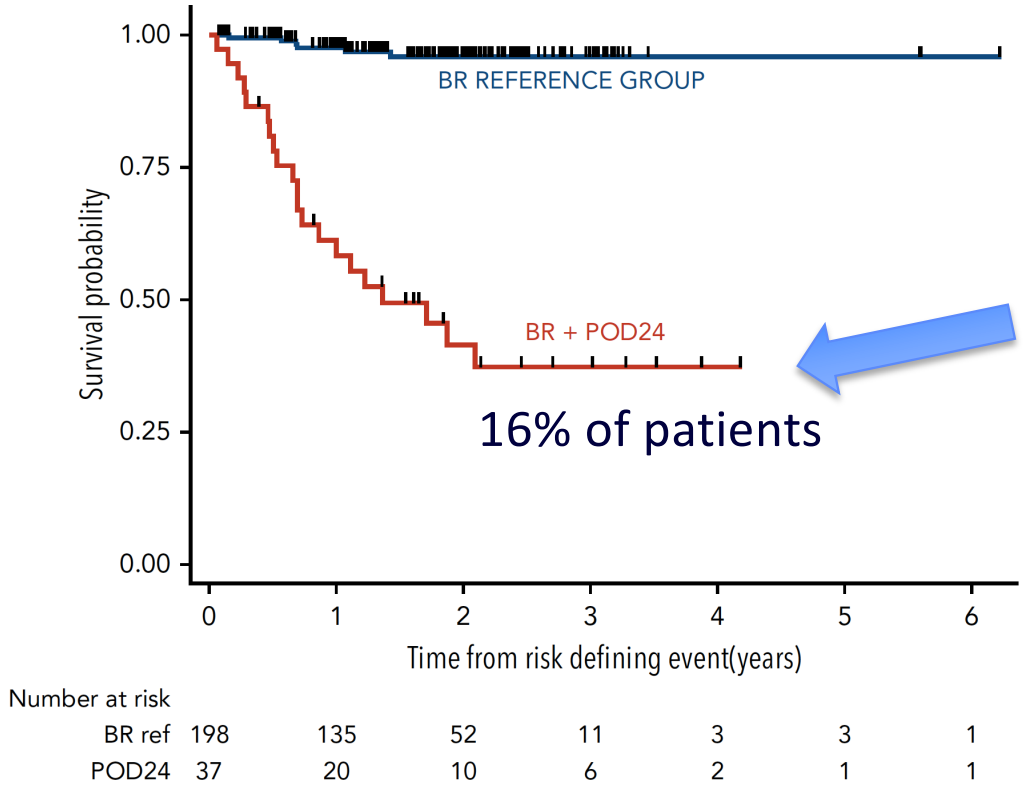
Townsend et al, EHA 2022

Outcomes in BC Since Adopting BR as Frontline Therapy



Freeman C, et al ASH 2018

Early Progression after BR is Associated with High Rate of Transformation



84% of patients

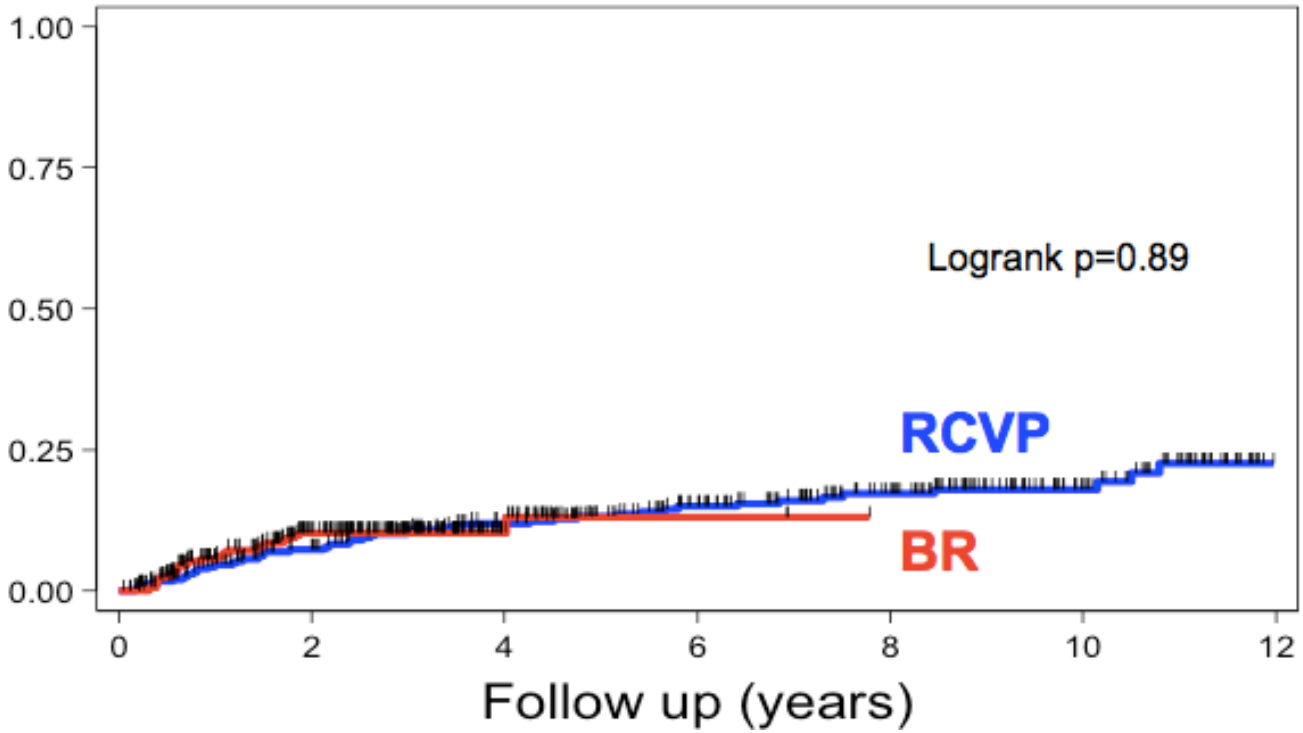
76% Transformed

4% of FL = POD24 without Transformation

2-year post-transformation OS: 40%

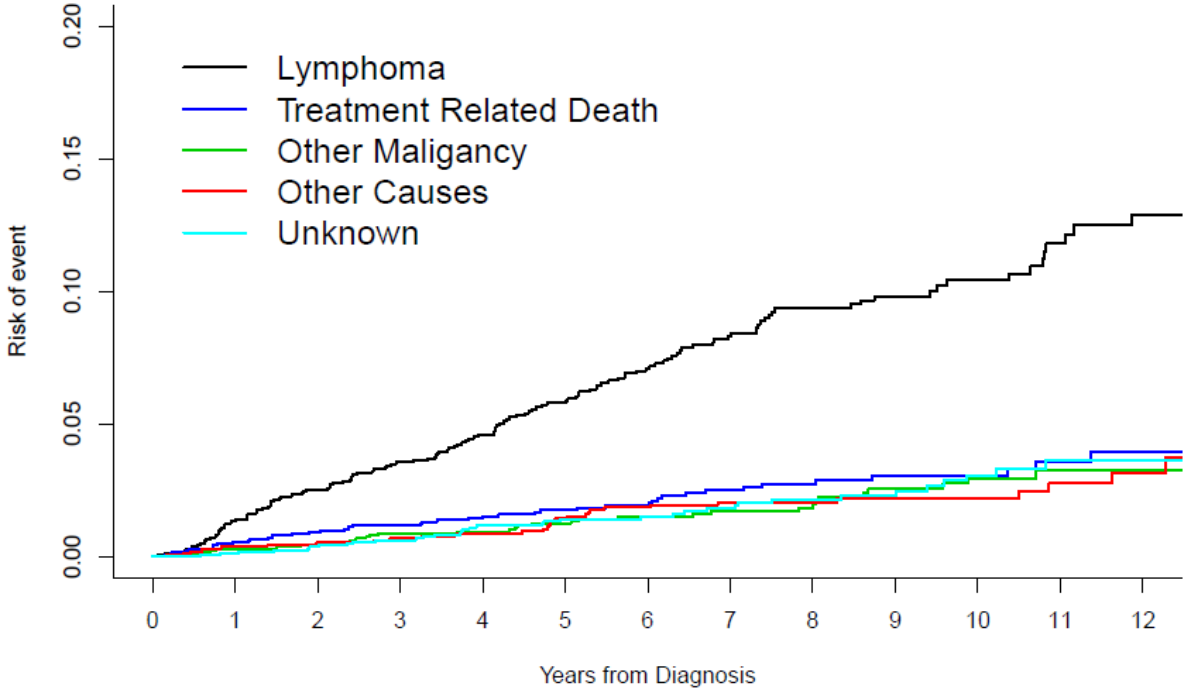
Freeman C et al, Blood 2019

Cumulative Incidence of Transformation over Time



Freeman C, et al ASH 2018

Causes of Death in FL in Rituximab Era



Lymphoma + treatment-related toxicity was primary cause of death in:

- POD24
- Transformed
- FLIPI 3-5

Sarkozy C, et al JCO 2018

Six-Year Results from the Phase 3 RELEVANCE Study: Similar Outcomes for Previously Untreated FL Receiving Lenalidomide Plus Rituximab (R^2) versus R-Chemotherapy Followed by R Maintenance

Figure 1. RELEVANCE Study Design

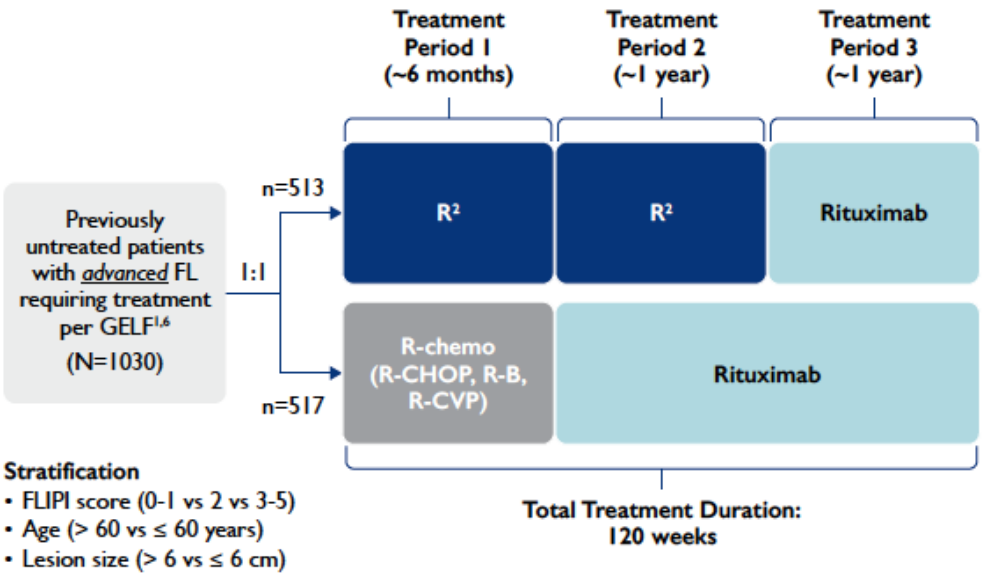


Figure 3: Progression-Free Survival by IRC, FDA Censoring Rules

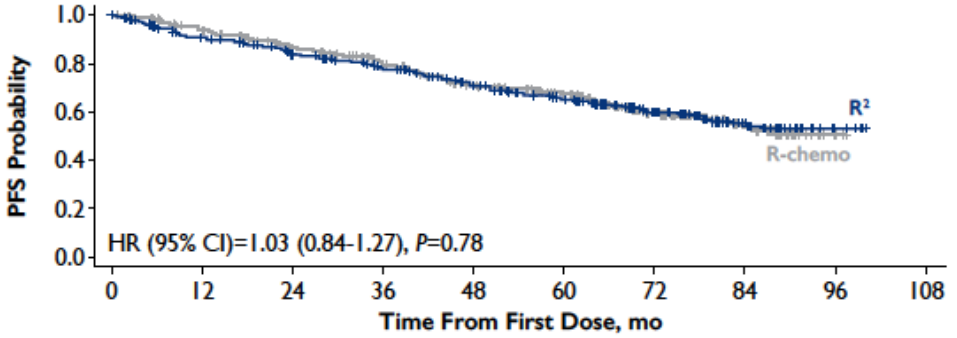
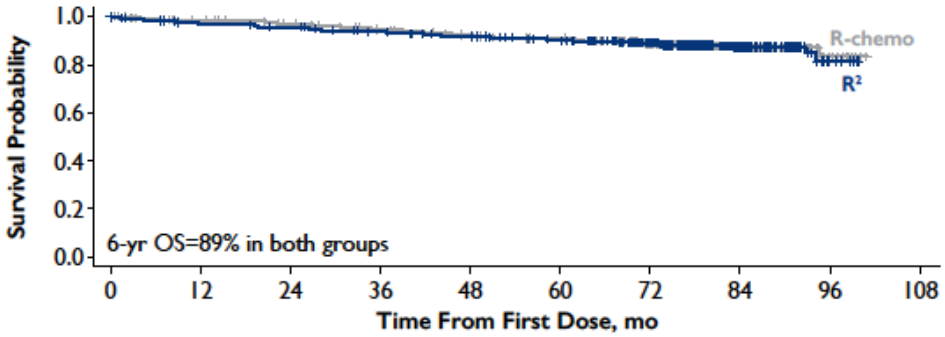


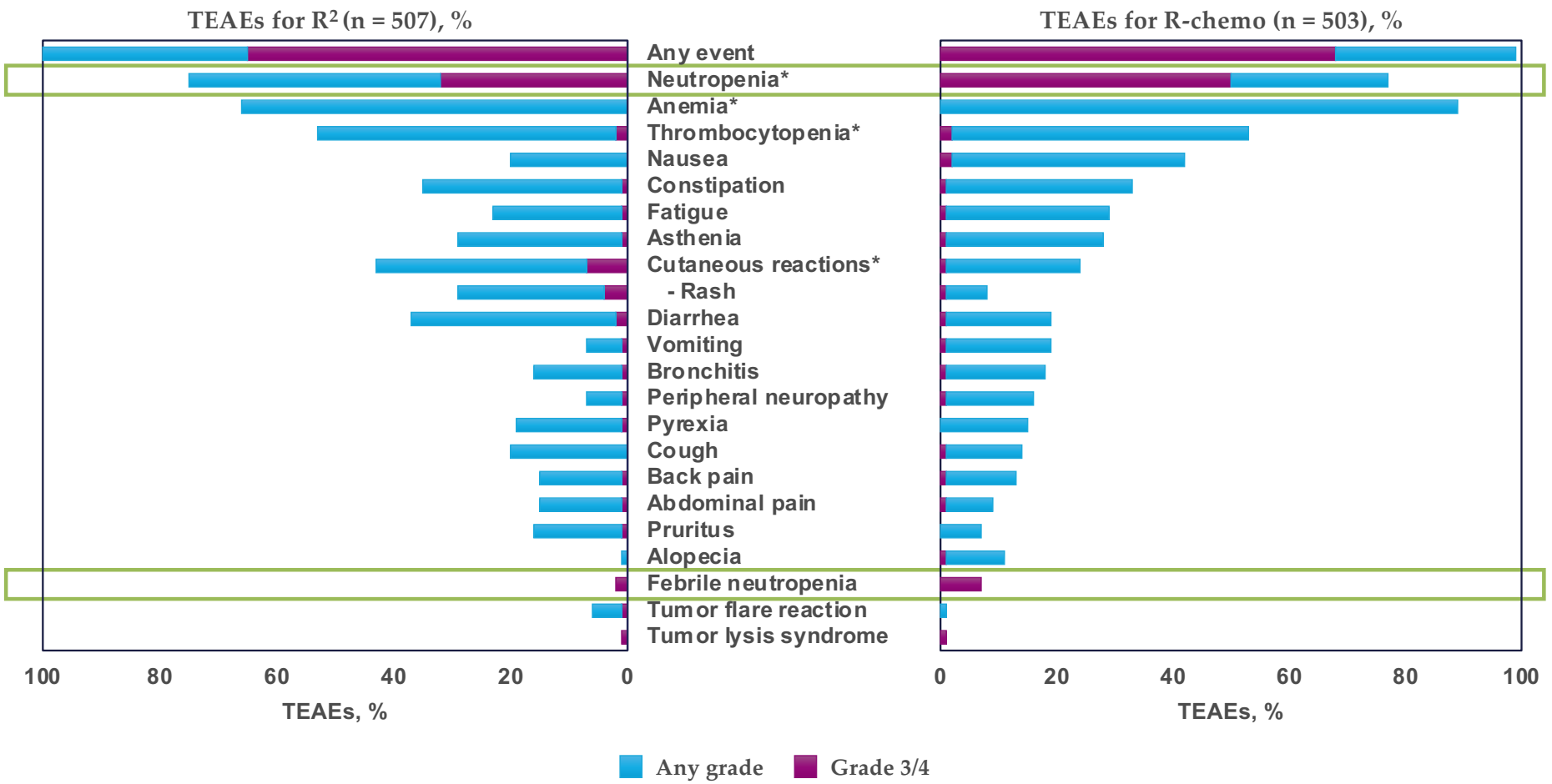
Figure 6: Overall Survival



- More patients died from lymphoma in R^2 arm
- No difference in transformation rate

Morschhauser F, et al JCO 2022

Relevance: Treatment Emergent Adverse Events



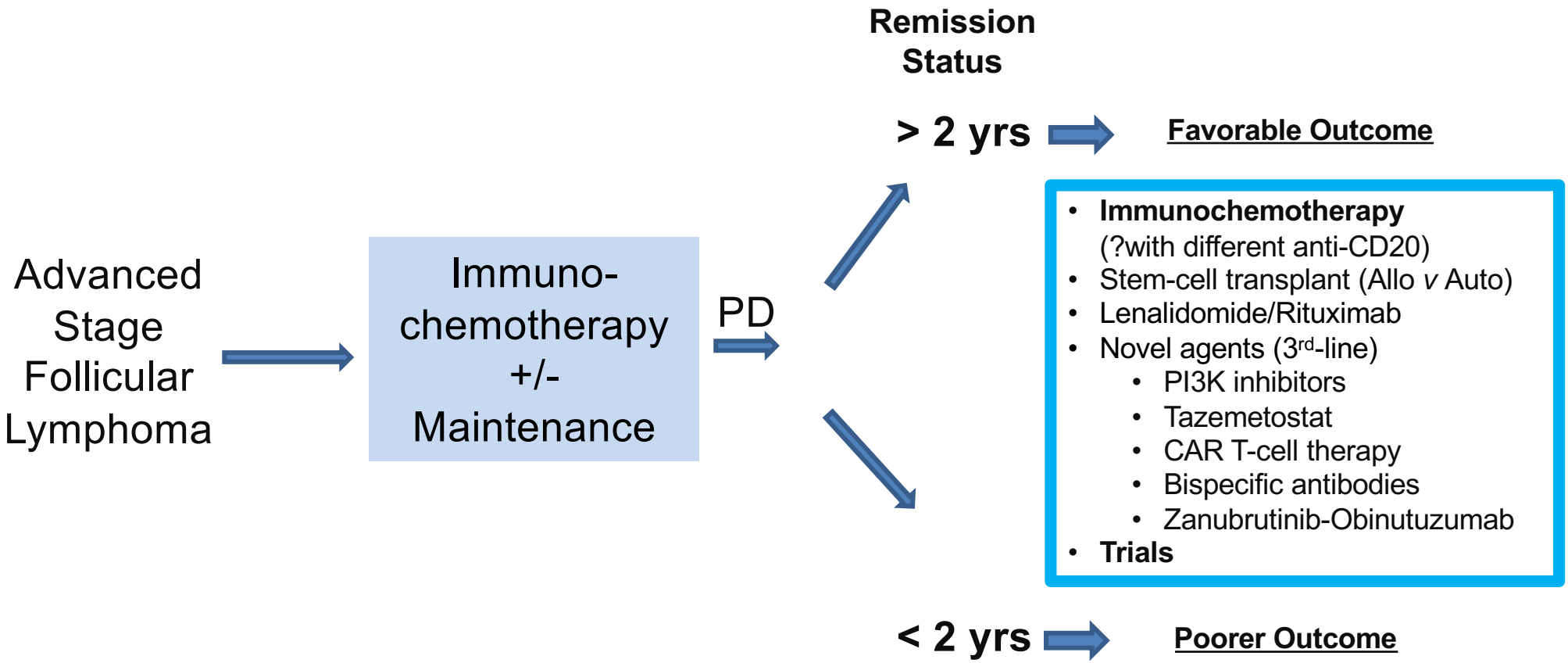
Morschhauser F, et al JCO 2022

Relevance: Discontinuation Rate

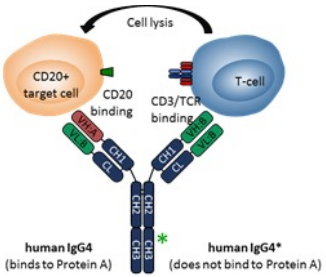
Reasons for Discontinuation, n (%)	R^2 (n = 507)	R-chemo (n = 503)
All discontinuations	157 (31)	146 (29)
Progression	64 (13)	71 (14)
Toxicity	43 (8)	16 (3)
Insufficient response*	15 (3)	3 (1)
Concurrent illness	12 (2)	9 (2)
Voluntary discontinuation/ consent withdrawal	11 (2)	18 (4)
Major protocol violation	1 (< 1)	6 (1)
Death	0	1 (< 1)
Other†	11 (2)	22 (4)

Morschhauser F, et al JCO 2022

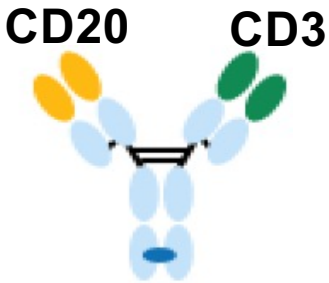
Treatment of Follicular Lymphoma



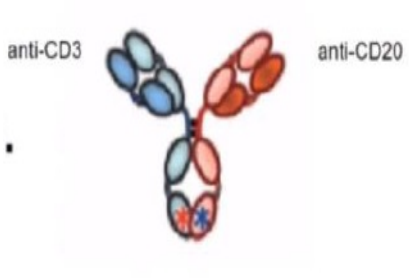
CD20/CD3 Bispecific Antibodies in B-cell lymphomas



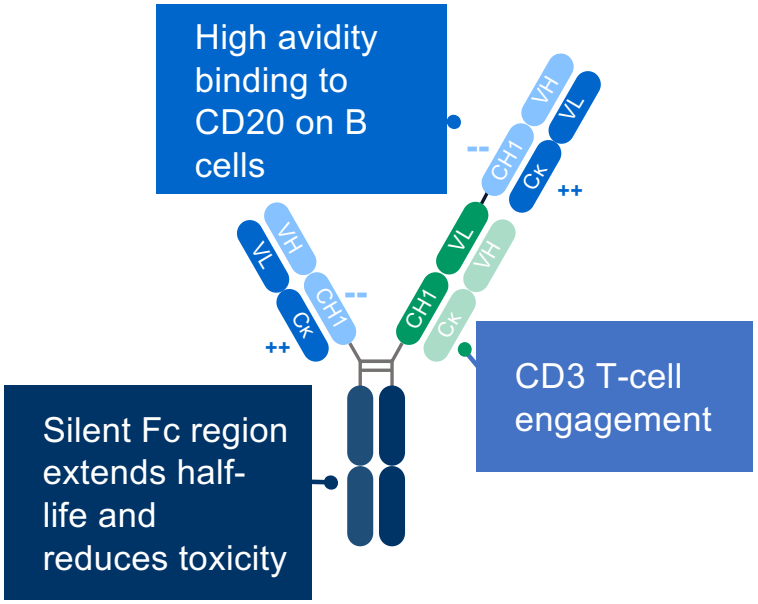
Odronextamab
(IV)
(REGN1979)
IgG4



Mosunetuzumab
(IV/SC)



Epcoritamab
(SC)
Duobody
GEN3013

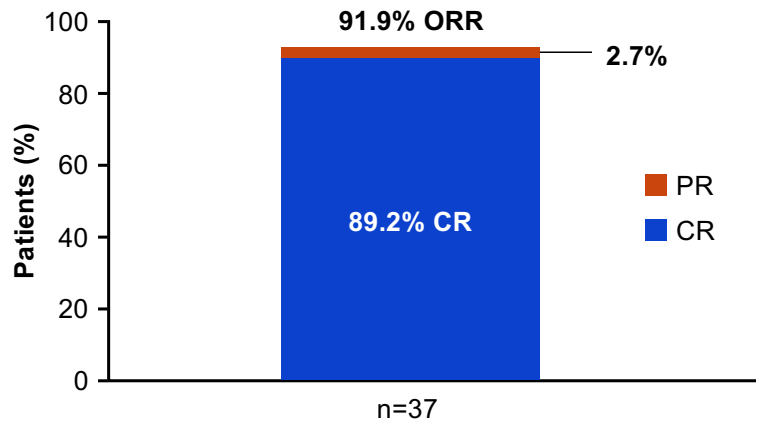


Glofitamab (IV)
CD20-TCB

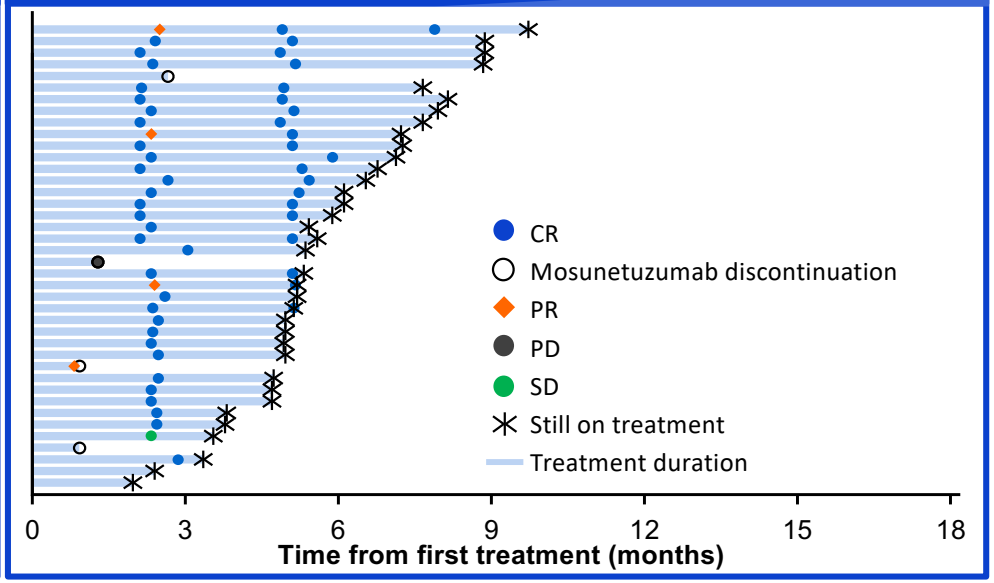
Mosunetuzumab + Lenalidomide in UntreatedFL

- Median duration of follow-up: 5.2 months (range: 1–10); most patients (95%) had 3–9 months of follow-up at CCOD

Best overall response*



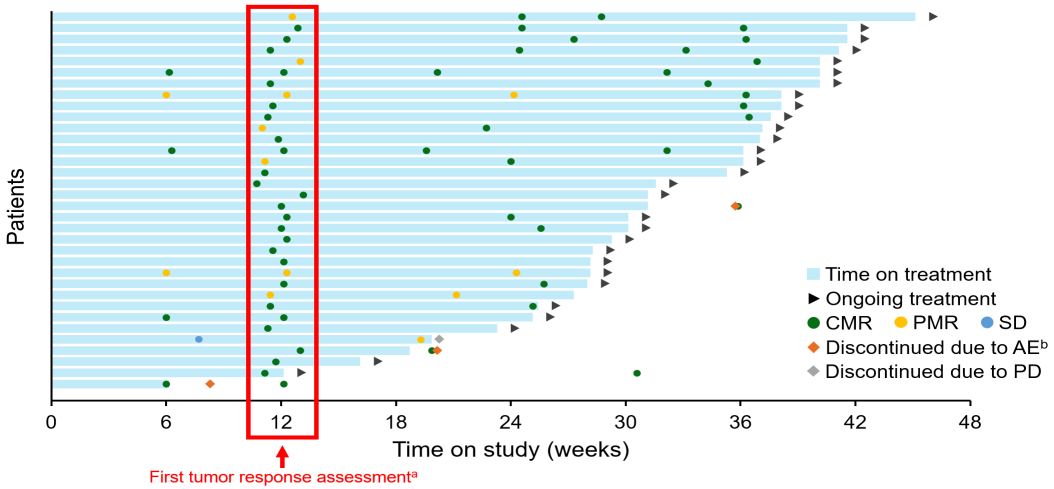
Response timing and duration†

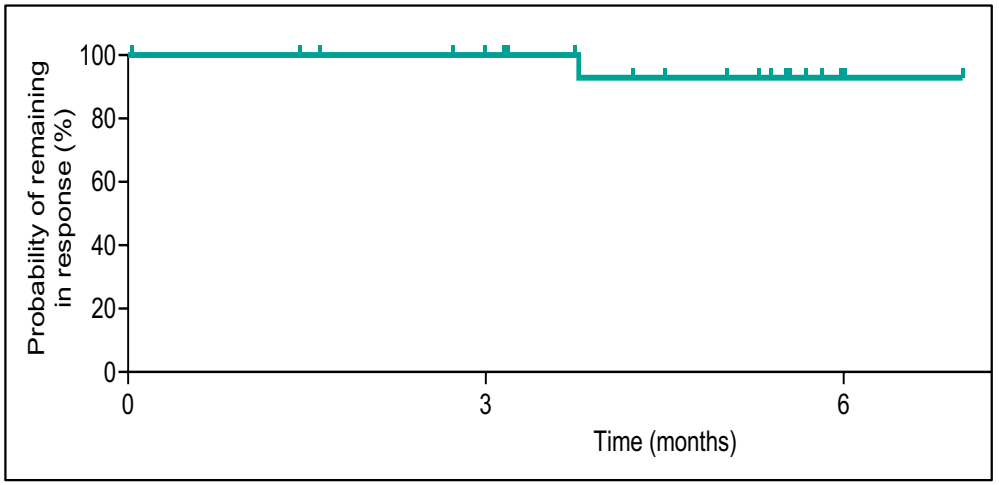


ORR and CR rates were high. All patients who responded were still in response at the CCOD

Morschhauser et al, ASH 2023

Epcoritamab + R^2 in Untreated FL





ORR 94%; CR 86%

CRS 39% G1; 15% G2

Falchi, L et al ASH 2022

Randomized Phase 3 Trials in FL

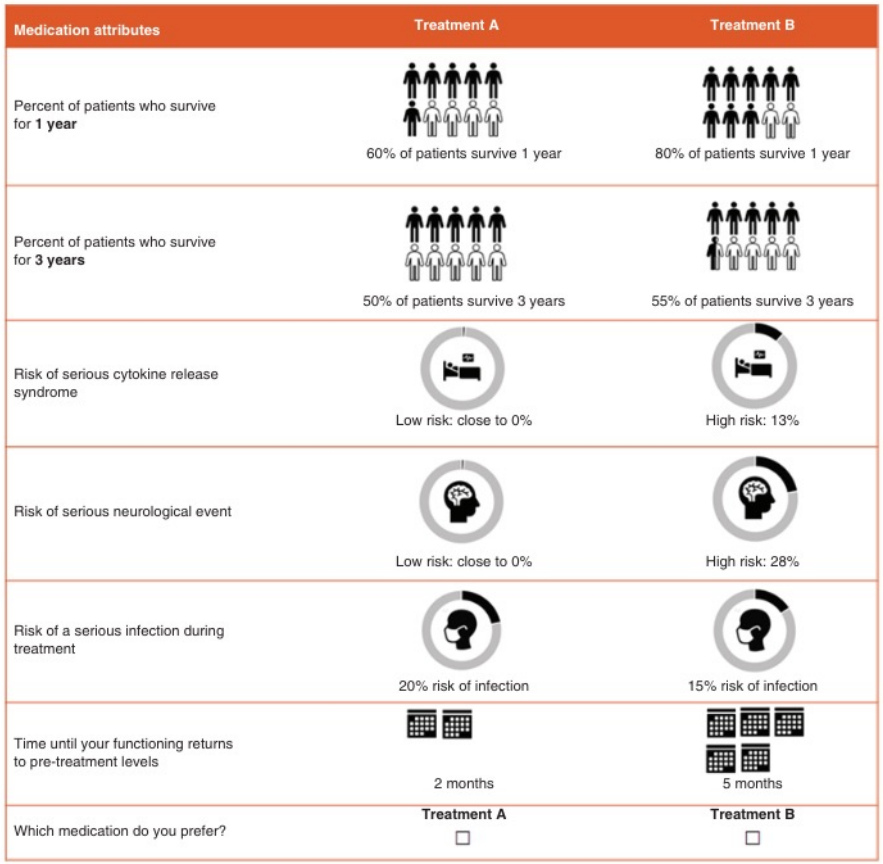
	Trial	Sponsor	N	Setting	Agent	Primary Endpoint	Key Secondary Endpoints
NCT06191744	EPCORE-FL2	AbbVie	900	Untreated	EpcorR2 vs CIT vs R2	CR30	PFS, OS, MRD, CR, EFS, DOR, TTNT, QOL (EORTC, FACT)
NCT06097364	OLYMPIA-2	Regeneron	733	Untreated	Odro-chemo vs R-chemo	CR30	PFS, EFS, OS, DOR, TTNT, QOL (EORTC, FACT)
NCT06284122	MorningLyte	LYSARC	790	Untreated	Mosun/len vs CIT	PFS	ORR, CMR, POD24, EFS, TTNLT, DOR, QOL (EORTC, FACT)
NCT06091254	OLYMPIA-1	Regeneron	478	Untreated	odro vs r-chemo	CR30	PFS, EFS, OS, DOR, TTNT, QOL (EORTC, FACT)
NCT06313996	TRANSFORM-FL	BMS	300	R/R	Liso-cel vs CIT/R2	PFS	CR, OS, OR, DOR, EFS, TTNLT, PFS2, QOL (EORTC)
NCT06149286	OLYMPIA-5	Regeneron	470	R/R	Odro-len vs R2	PFS	ORR, DOR, CR, OS, EFS, QOL (EORTC,FACT)
NCT05888493	LEDA	Novartis	108	R/R	tisa-gen vs (R2/R-CHOP)	PFS	CR, ORR, OS, TTNT, DOR,
NCT04224493	SYMPHONY-1	Epizyme	540	R/R	taz/R2 vs R2	PFS	ORR, DOR, OS, ECOG PS
NCT04712097	Celestimo	Roche	474	R/R	mosun/len vs R2	PFS	CR, ORR, OS, DOR, DOCR, QOL (EORTC, FACT), TTLT
NCT05371093	ZUMA-22	Kite	230	R/R	axi-cel vs CIT/R2	PFS	OS, CR, ORR, DOR, DOCR, TTNT, QOL (EORTC, NHL-LD20, EQ-5D)
NCT05100862	MAHOGANY	BeiGene	750	R/R	zan/O vs R2	PFS	DOR, ORR, CR, TTNLT, OS, QOL (EORTC)
NCT05409066	EPCORE-FL1	AbbVie	500	R/R	EpcorR2 vs R2	PFS	CR, OS, MRD
NCT04680052	InMIND	Incyte	654	R/R	tafa-len vs R2	PFS	CR, MRD, OS, CR, ORR, DOR, QOL

Slide courtesy M. Maurer

Measuring Quality of Life and Understanding Patient Preferences are Paramount

Evaluating Patient Preferences

- Patients are presented various scenarios and asked to pick a preferred treatment
- Attributes are pre-selected based on relevance to therapy
- Analysis can infer patient priorities and tradeoffs between choices



Medication attributes	Treatment A	Treatment B
Percent of patients who survive for **1 year**	60% of patients survive 1 year	80% of patients survive 1 year
Percent of patients who survive for **3 years**	50% of patients survive 3 years	55% of patients survive 3 years
Risk of serious cytokine release syndrome	Low risk: close to 0%	High risk: 13%
Risk of serious neurological event	Low risk: close to 0%	High risk: 28%
Risk of a serious infection during treatment	20% risk of infection	15% risk of infection
Time until your functioning returns to pre-treatment levels	2 months	5 months
Which medication do you prefer?	**Treatment A** ☐	**Treatment B** ☐

Birch et al, Future Oncology 2022

Goals for the Future

- Improve outcomes, especially for high-risk patients
- Reduce toxicity, especially for elderly, and decrease long-term complications
- Achieve “cure”
- Prevent transformation
- Identify biomarkers for risk stratification and treatment selection
- Consider patient preferences