Can we cure follicular lymphoma?

Overview and role of early intervention

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No potential conflicts of interest

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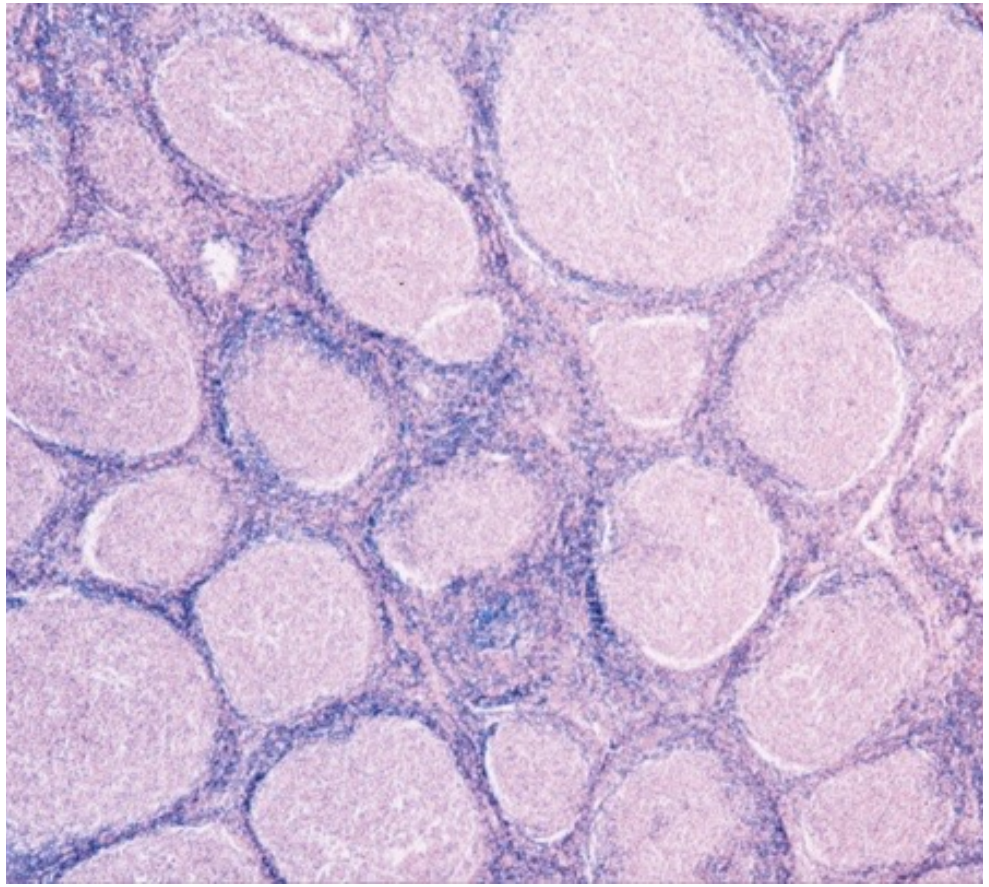
Key points: Follicular Lymphoma in 2025

For most patients with follicular lymphoma, outcomes are very favorable with our current therapeutic armamentarium.

Most patients with FL will probably not die from FL



Maddocks et al, *JCNI* 109: March 2017

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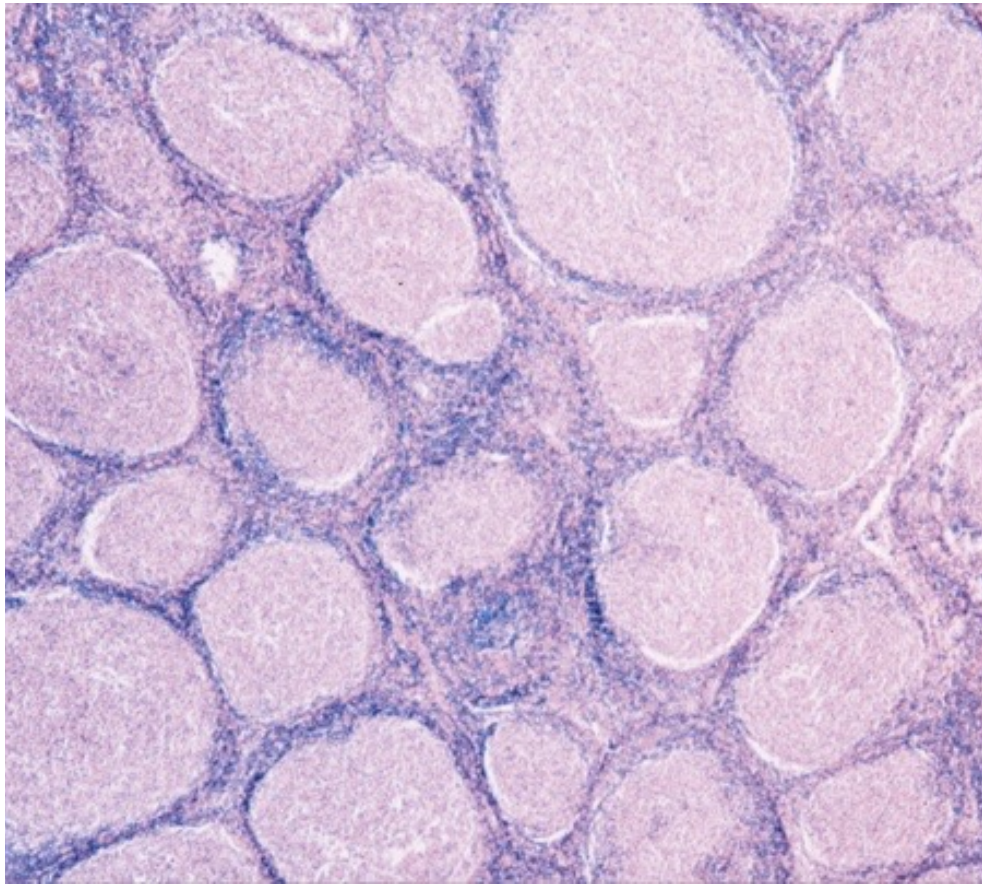

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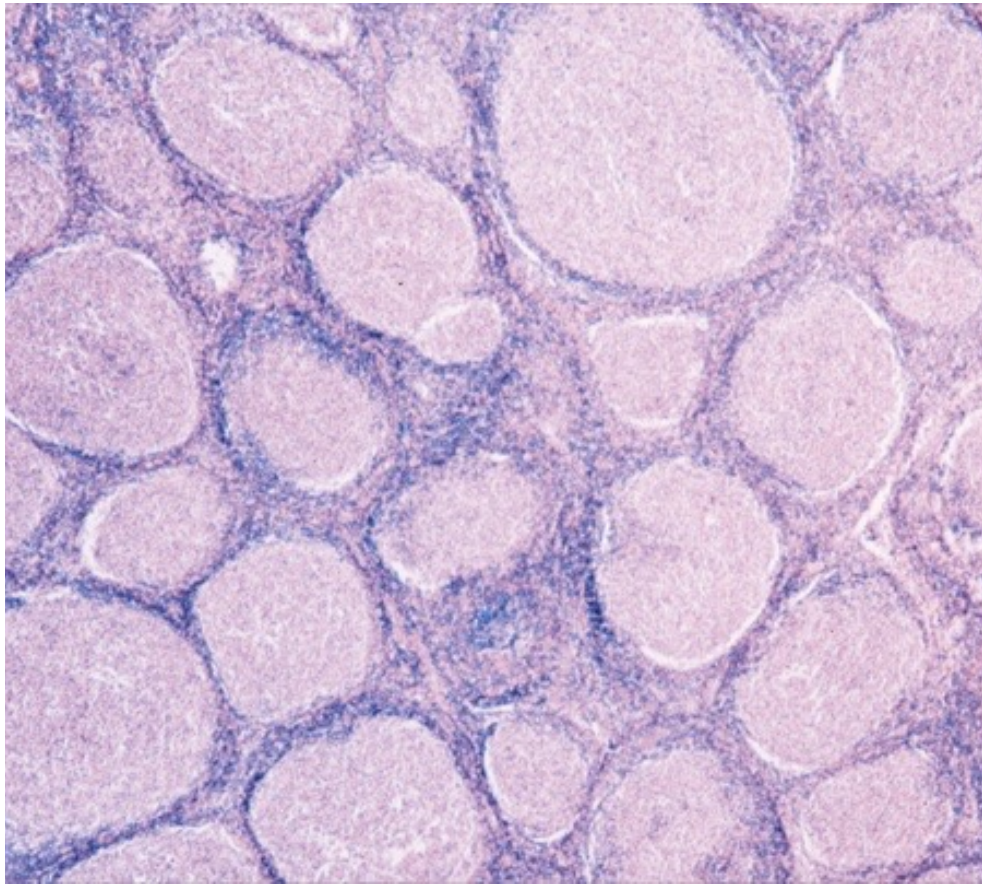
Advanced stage follicular lymphoma continues to be viewed by many as an incurable disease with standard therapies.



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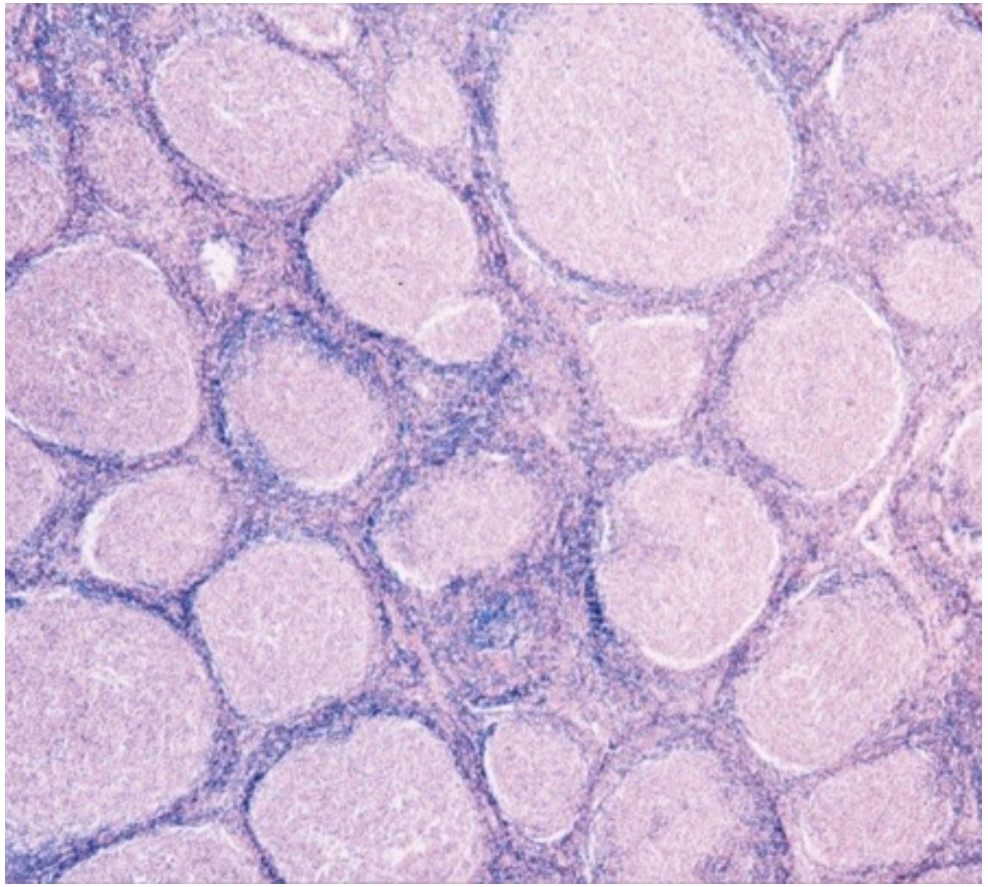
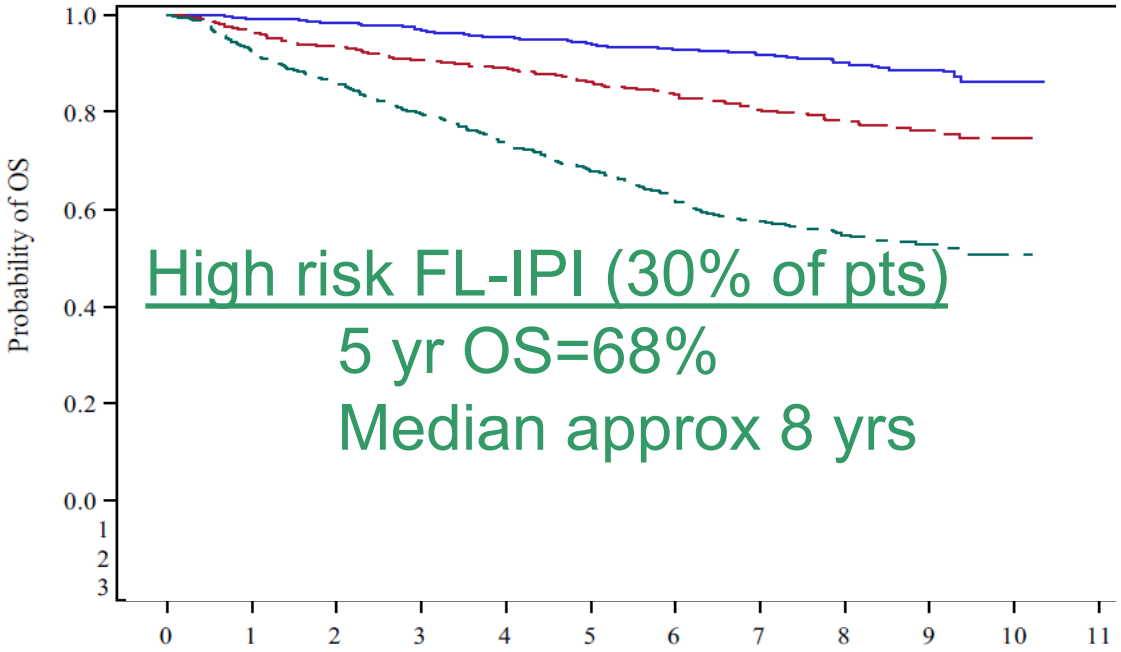
Is this still true?



Maddocks et al, *JCNI* 109: March 2017

Follicular lymphoma is heterogeneous: Overall Survival by FLIPI Risk Group

- Age (>60)
- Ann Arbor stage (III-IV)
- Hb level (<120 g/L)
- Serum LDH(>ULN)
- Number of nodal sites (>4)



Nooka et al, *Ann Oncol*. 24:441-8, 2013

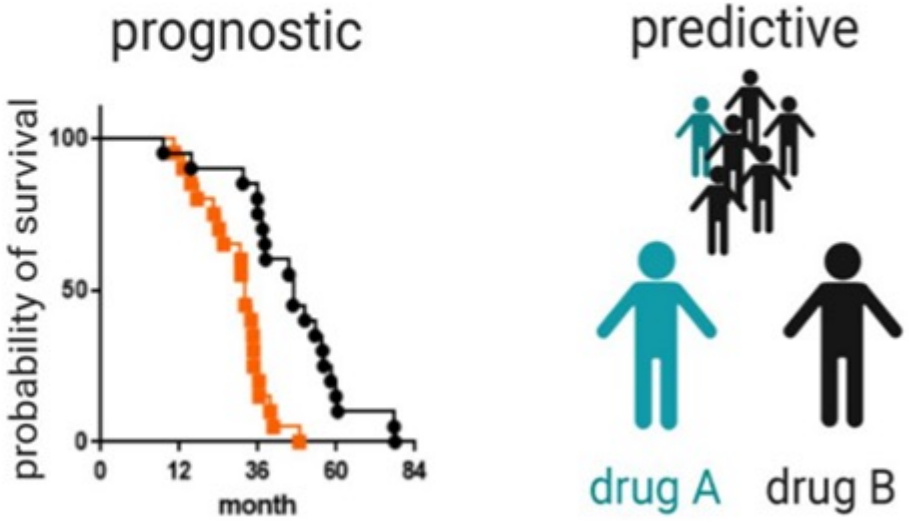
Prognostic indices in FL: Current status

Several recent prognostic indices incorporating gene expression and mutation analyses confirm biological heterogeneity of follicular lymphoma.

Low frequency clones at diagnosis often contribute to therapy resistance and transformation; these may not appear in routine genetic and molecular studies.

At present, none of these indices serve as predictive biomarkers for a precision medicine approach to therapy.

Biomarkers



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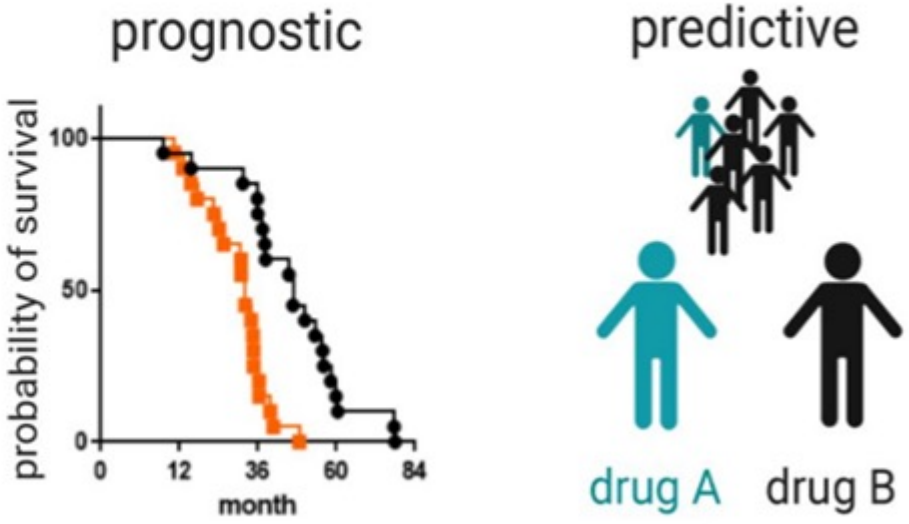
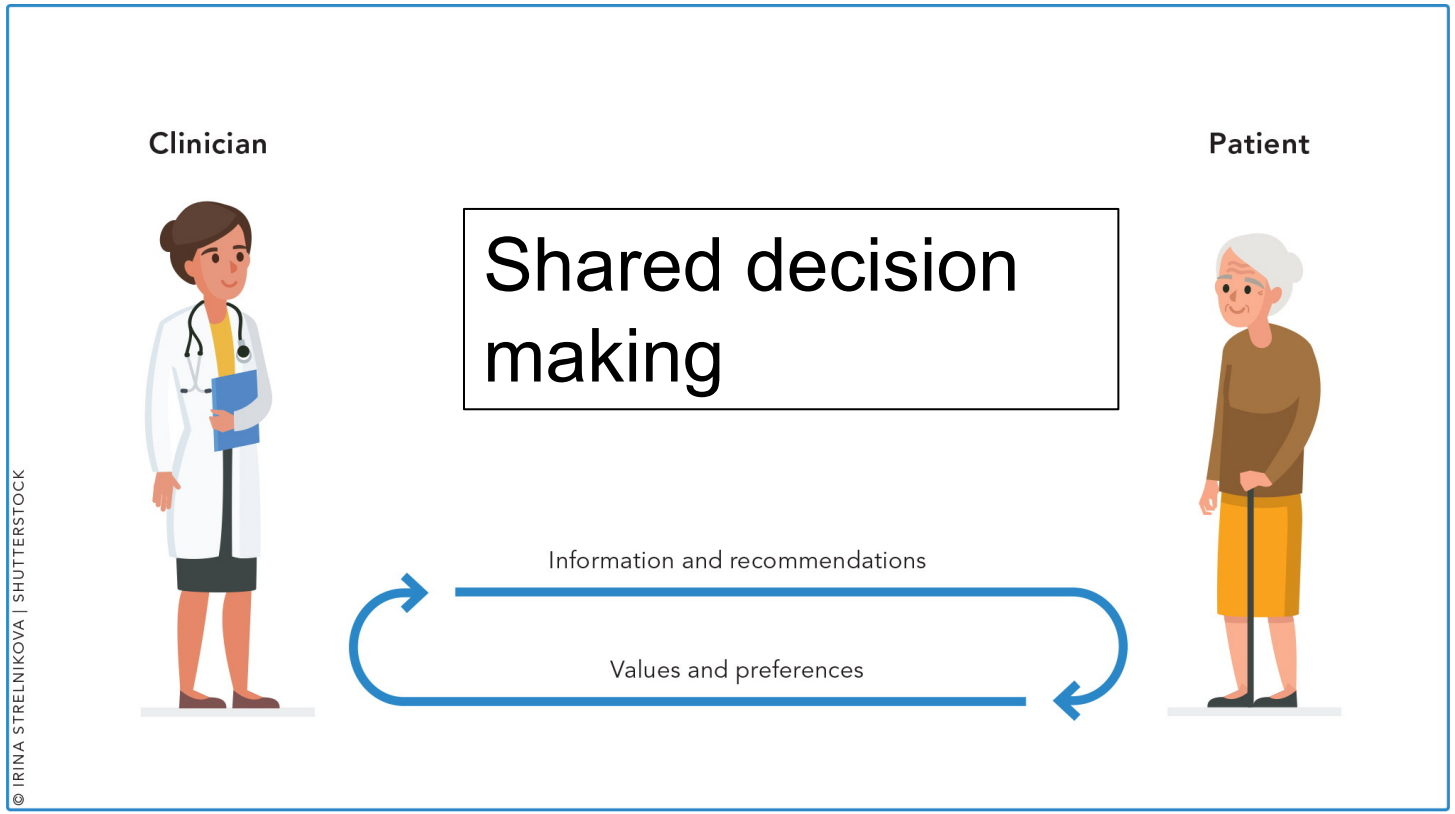
- The ability to analyze circulating tumor DNA may accelerate progress in this area in the future.

Biomarkers



Follicular lymphoma: What are goals of treatment?

- Change natural history of disease:
  - Decrease transformation
  - Improve survival
- "Remission":
  - Make patients feel better
  - *Active disease is often asymptomatic*
- Improve quality of life



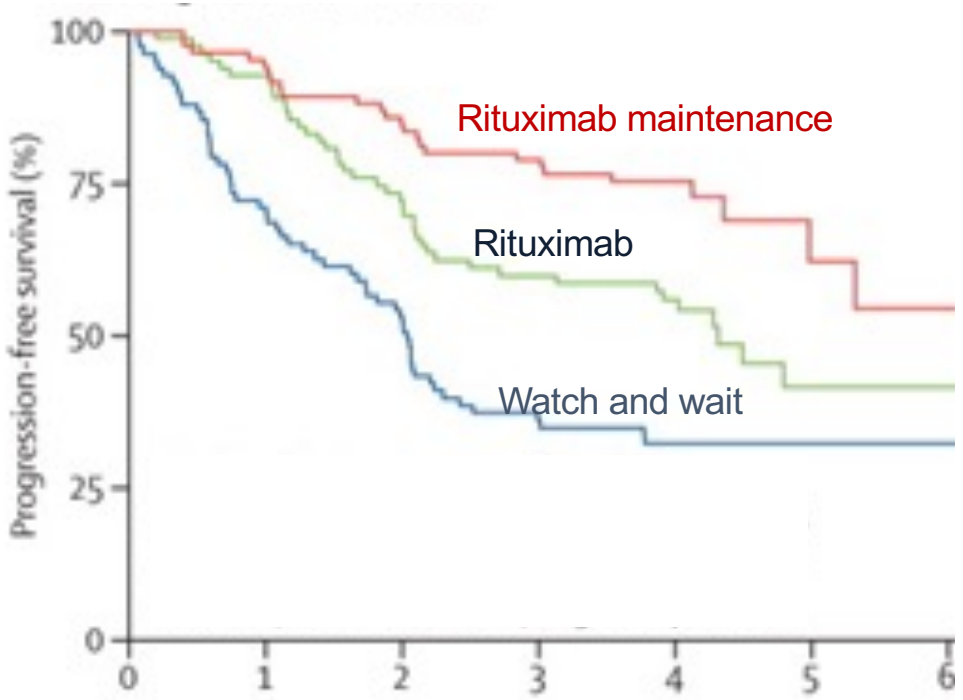
Low tumor burden FL

“Watch and wait” vs. rituximab: PFS

Randomized trial

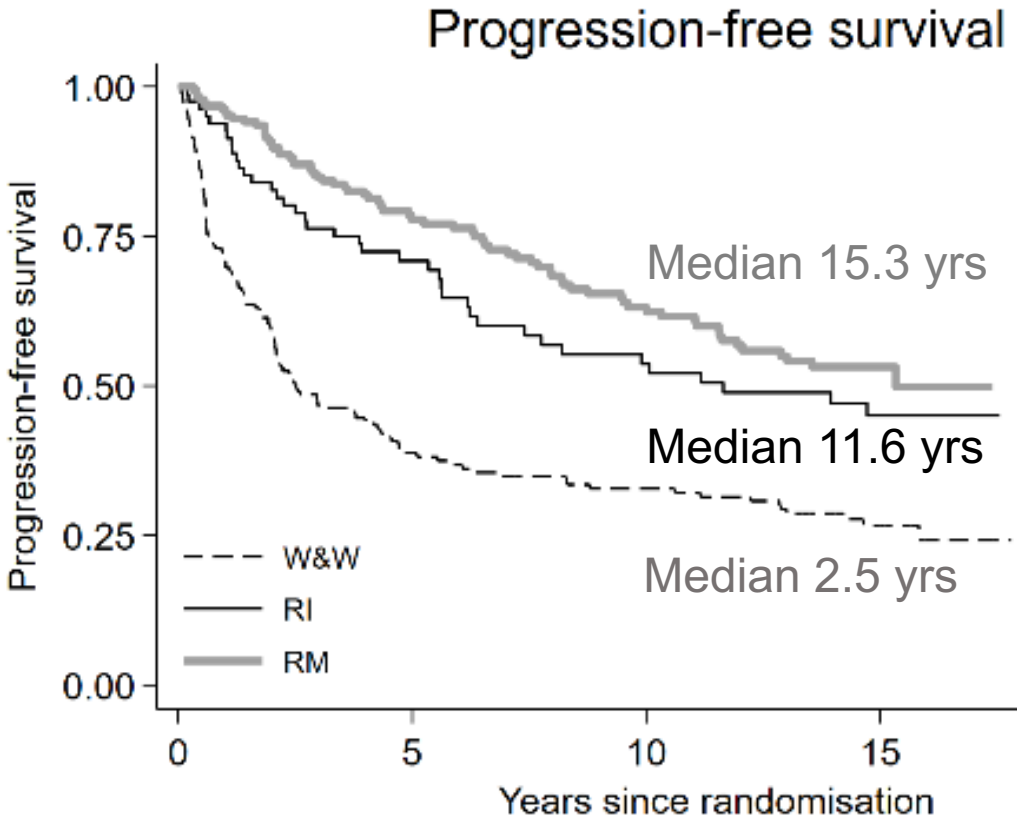
Median follow up:
3-4 years

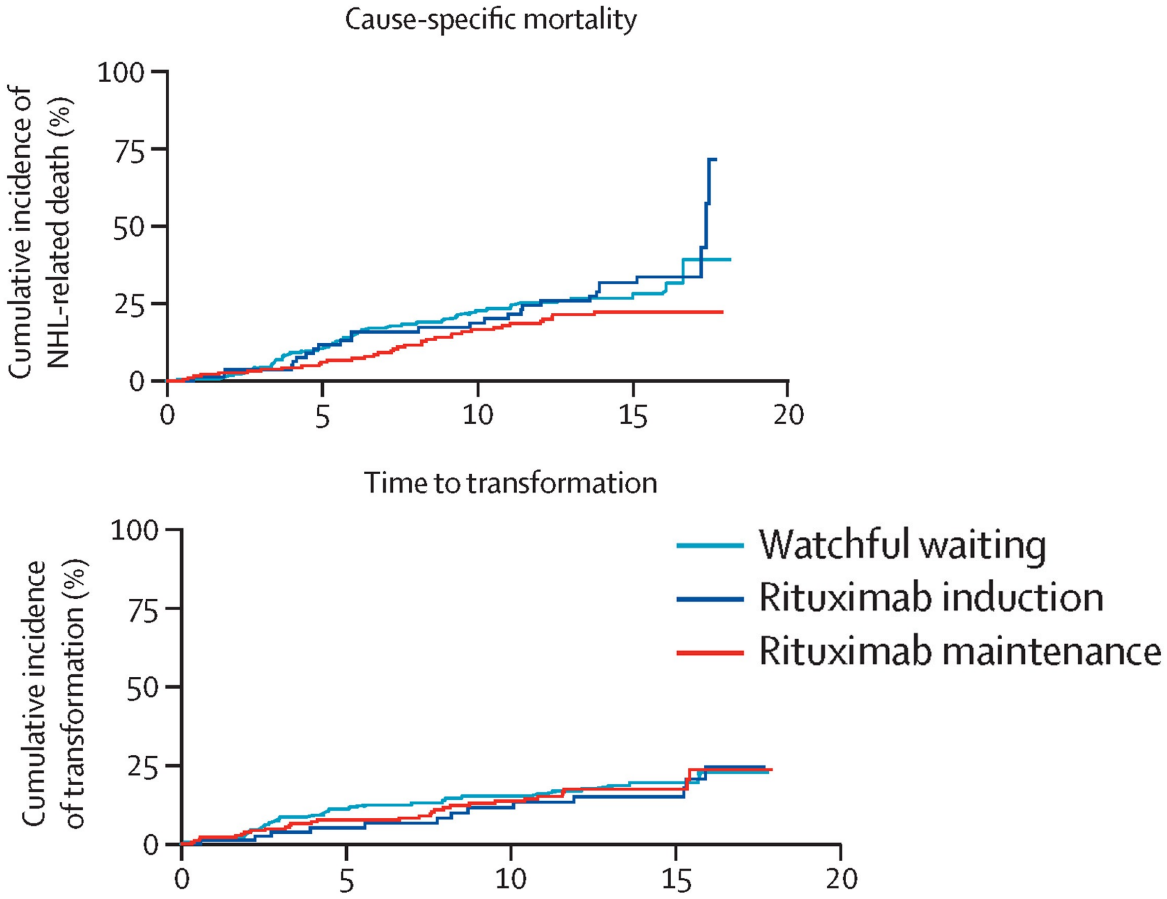
Rituximab alone arm
early closure



Ardeshna et al *Lancet Oncology* 15:424 2014

“Watch and wait” vs. rituximab: Long-term outcomes





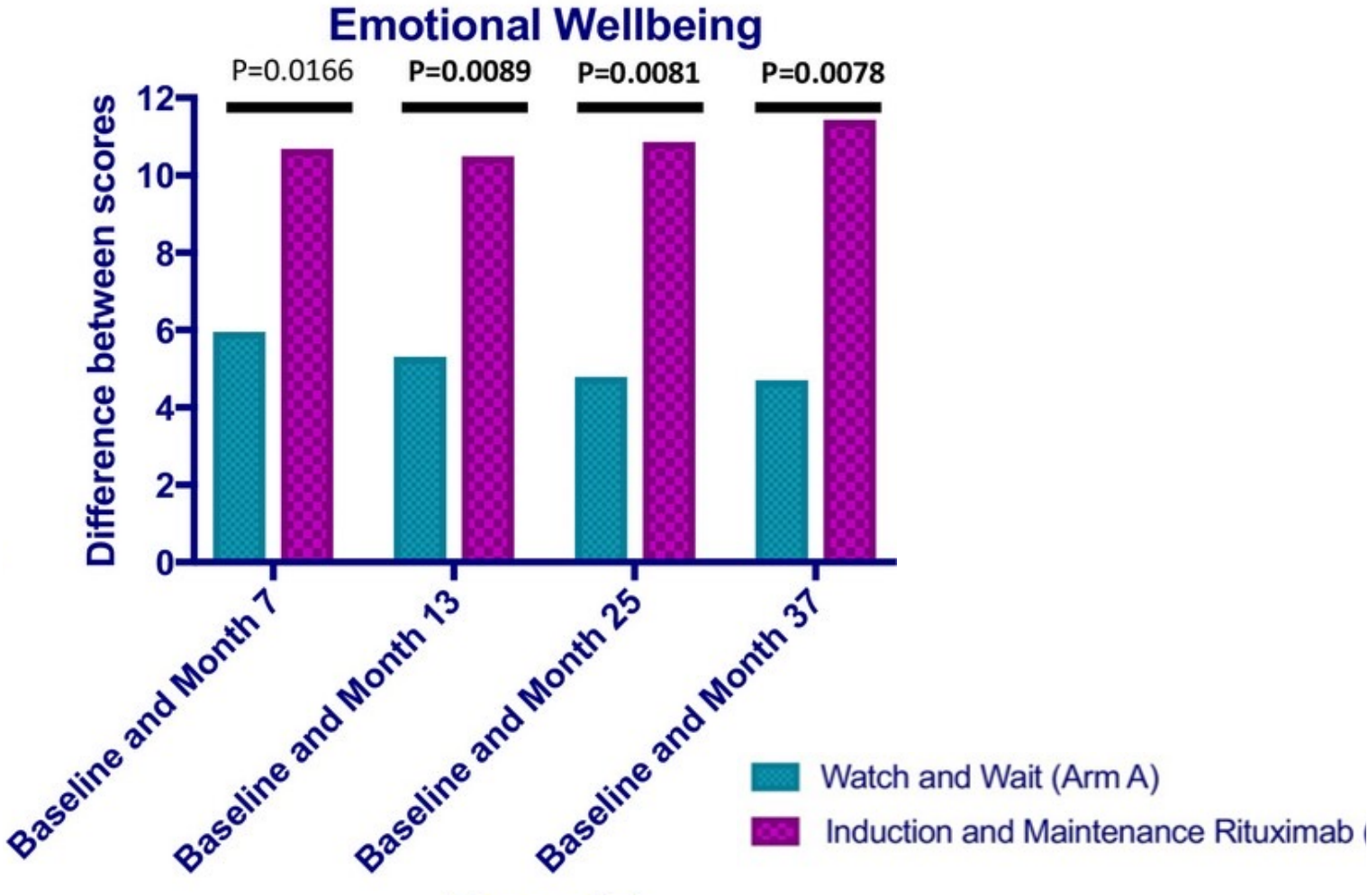
Northend et al *Lancet Haematology* 12:E335-45 2025

“Watch and wait” vs. rituximab: Quality of life comparison

Watchful-waiting patients were significantly more likely to avoid thinking about their illness and were more likely to attach unpleasant connotations to clinic visits.

These results demonstrate improved QoL scores in the induction and maintenance rituximab arm,

Rituximab was not detrimental to QoL and resulted in an improved QoL in some domains.



“Watch and wait” vs. rituximab: Conclusions

Rate of high-grade transformation low (16%) and no difference between arms

34% of patients in watchful waiting group had not started treatment at 15 years

Low rates of high-grade toxicities associated with rituximab

Northend et al *Lancet Haematology* 12:E335-45 2025

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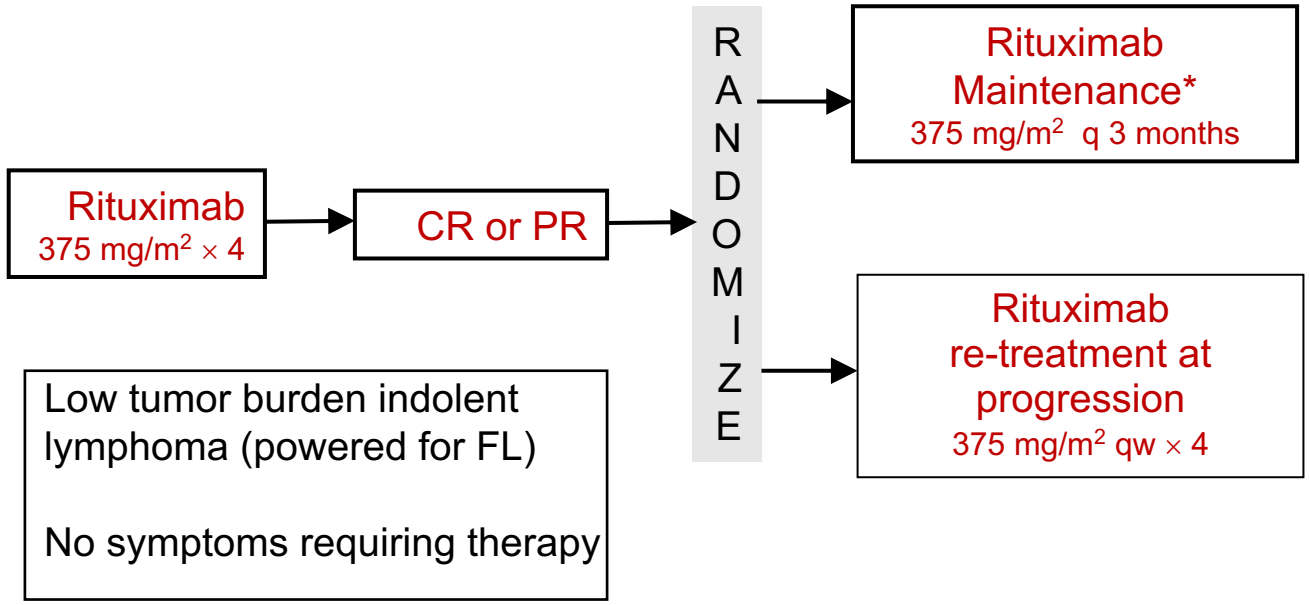
Low rates of high-grade toxicities associated with rituximab

“*Early rituximab monotherapy substantially delays the need for new treatment…confirming value for patients who seek to avoid or defer treatment with chemotherapy”.*

Northend et al *Lancet Haematology* 12:E335-45 2025

RESORT trial schema

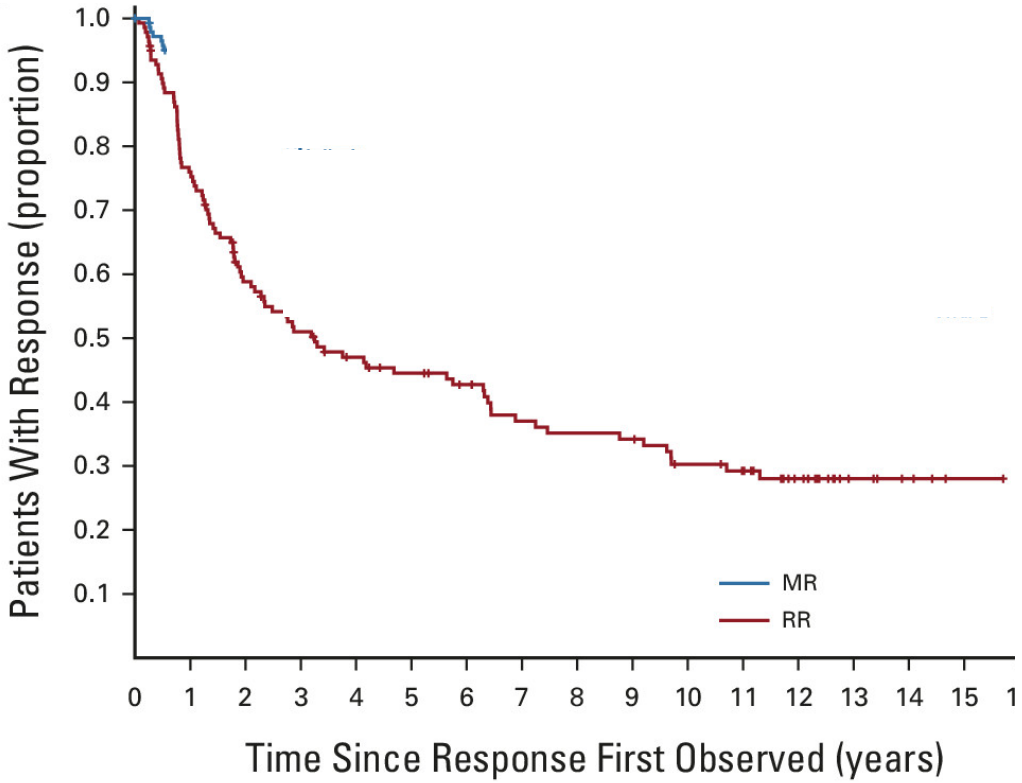


Kahl et al, *J Clin Oncol* 32:3096-102, 2014

RESORT long-term follow-up: Duration of Response to single agent rituximab

	5 years	7 years	10 years
RR*	45%	37%	30%

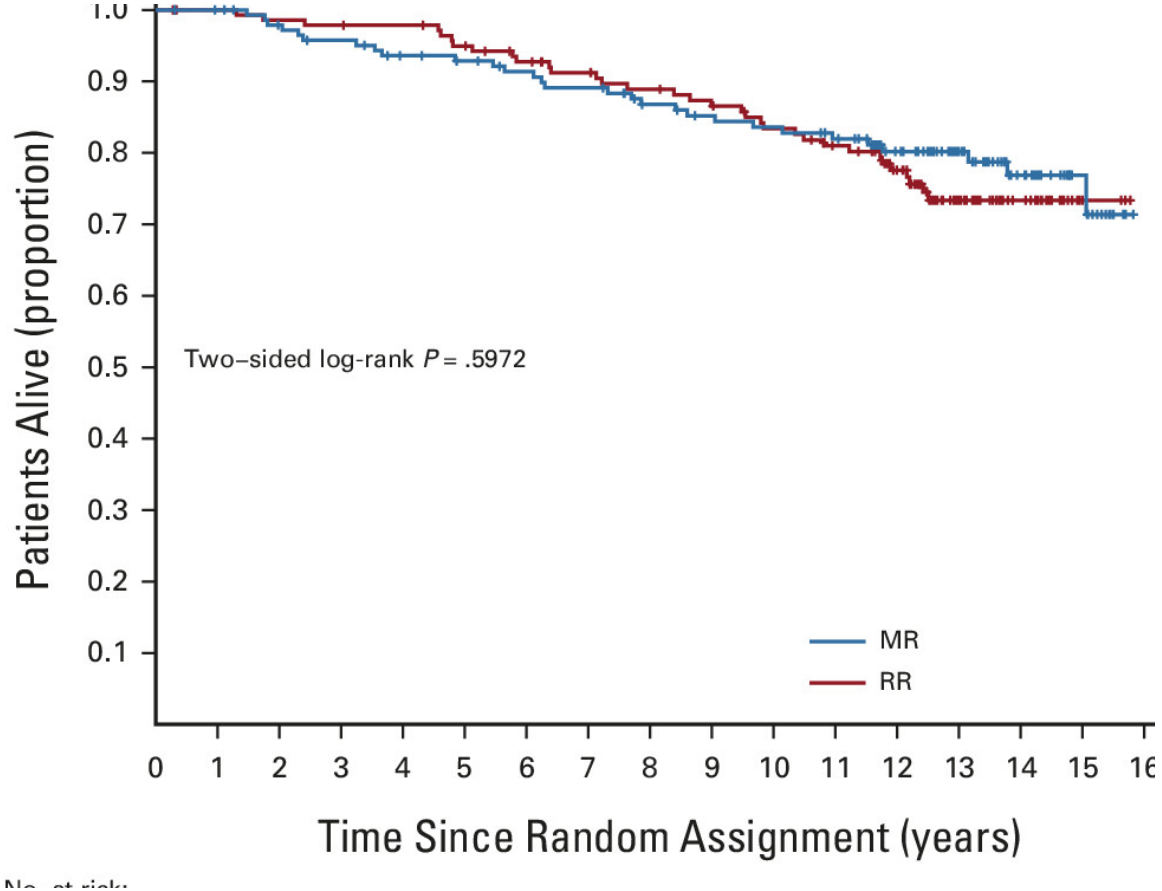
Median follow up 12.1 years



Median DOR for induction R: 3.2 years

Kahl et al., *JCO* 42:774-8, 2024

RESORT long-term follow-up: Overall Survival/Transformation/2nd Cancer



OS at 10 yrs: 83% vs. 84%

Transformation risk:

- 6 RR vs. 2 MR (per final analysis)
- possibly under reported

2nd malignancies:

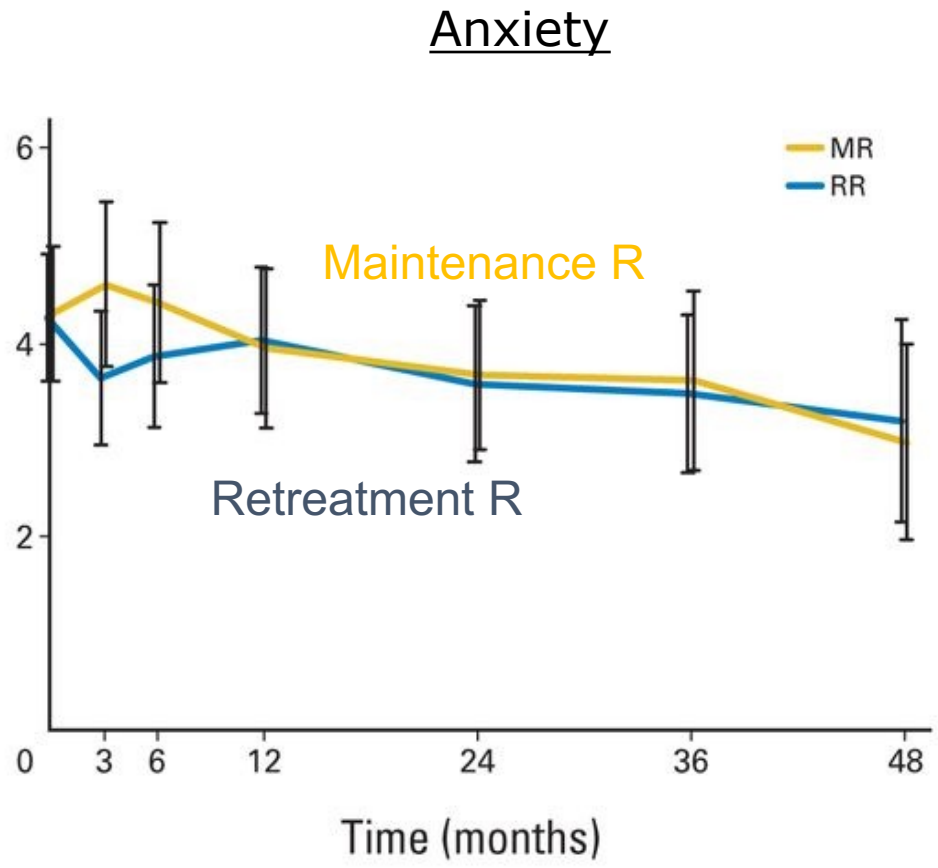
- 19 on RR
- 17 on MR

Kahl et al., *JCO* 42:774-8, 2024

RESORT: QoL maintenance vs. retreatment rituximab

Illness-related anxiety was comparable between treatment arms at all time points (P > .05) and significantly decreased over time on both arms.

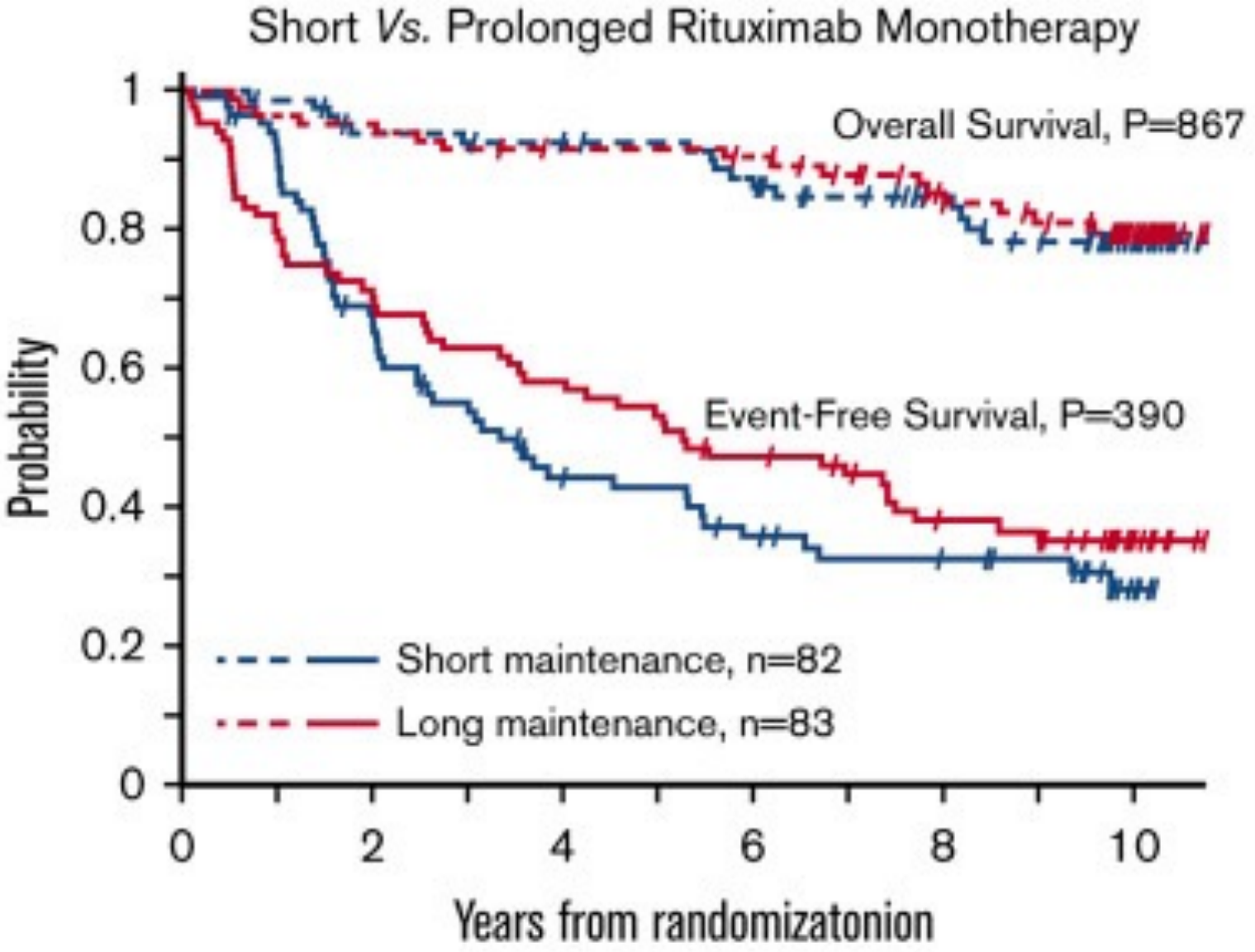
HRQoL scores were relatively stable and did not change significantly from baseline for both arms.



Wagner et al, *JCO* 33:740-8 2015

SAKK 35/03 Randomized Trial of Follicular Lymphoma

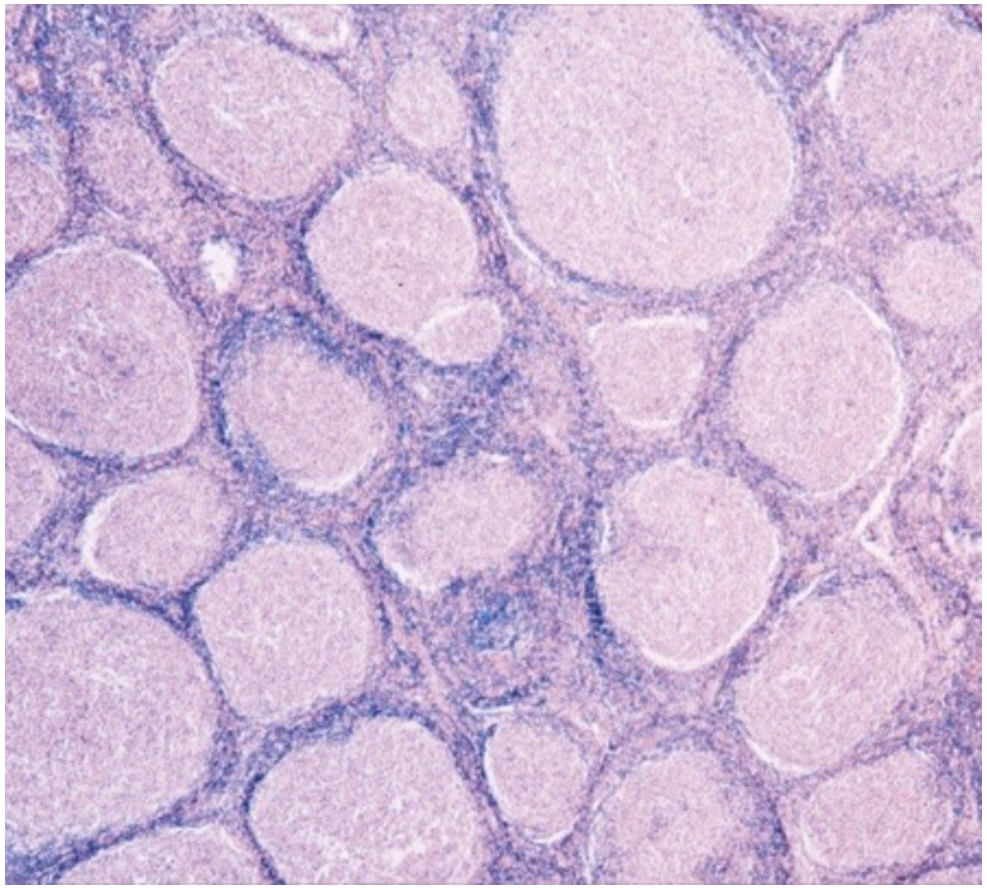
- 165 patients, achieving at least a partial response after4 weekly infusions of single-agent rituximab
- Randomized to maintenance rituximab every 2 months, either on a short-term (4 doses) or long-term (up to 5 years) schedule
- After a median follow-up of 10 yrs:
  - No significant differences in EFS or OS
  - 10-yr overall survival >80%, in symptomatic treatment-naïve patients, irrespective of treatmtnt duration
  - Over 1/3 of responders never needed additional treatment



Moccia et al., *Blood Adv* 4:5951-7, 2020

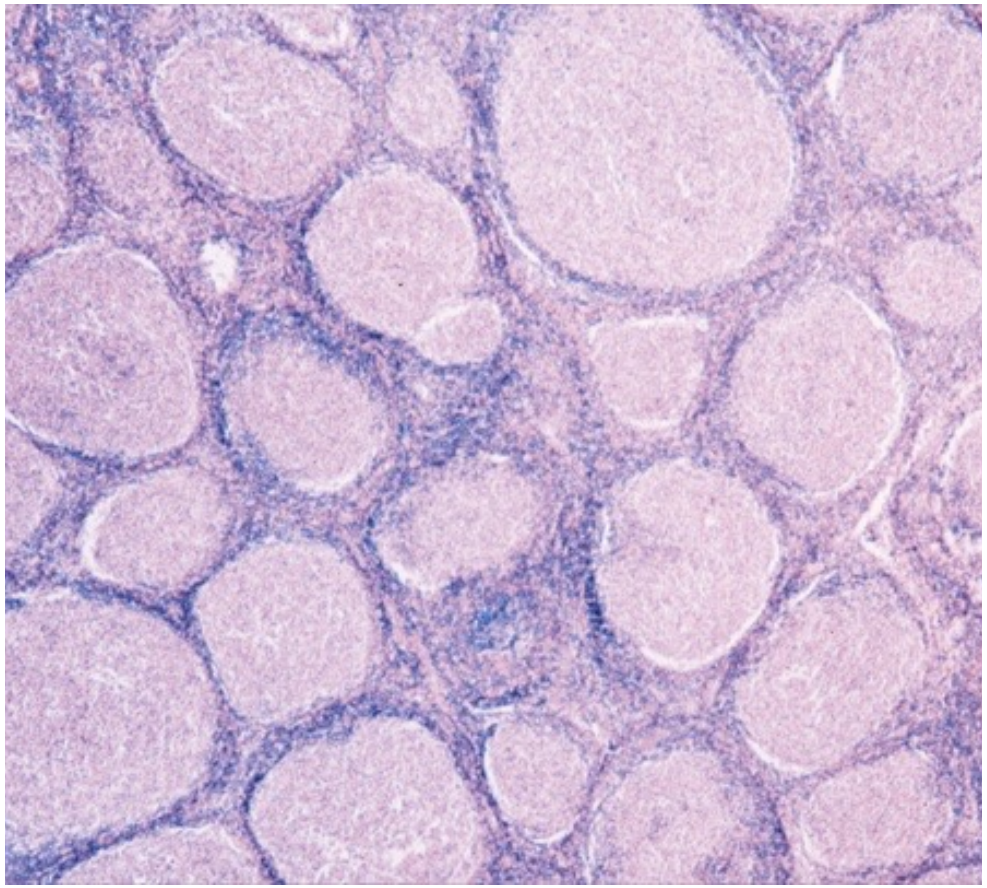
Conclusions: Low tumor burden FL

- Overall survival in recent datasets better compared with historical trials.
- No survival benefit or decreased transformation risk demonstrated with early intervention.
- Many patients who receive limited rituximab dosing have prolonged remissions and improved quality of life.

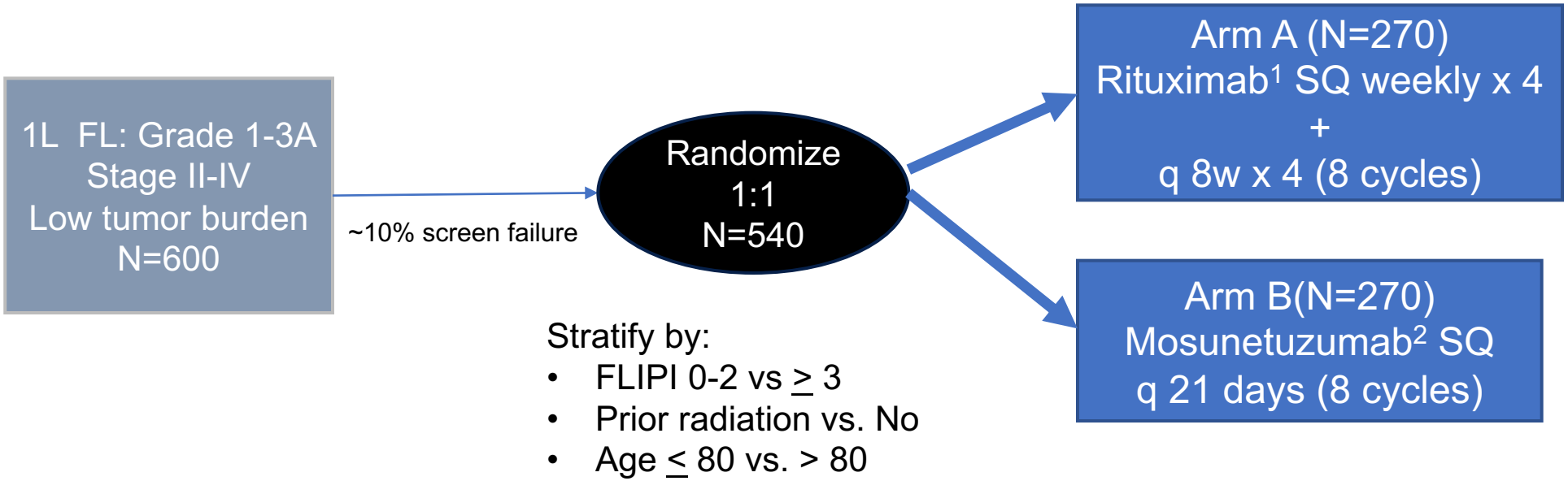


Conclusions: Low tumor burden FL

- Overall survival in recent datasets better compared with historical trials.
- No survival benefit or decreased transformation risk demonstrated with early intervention.
- Many patients who receive limited rituximab dosing have prolonged remissions and improved quality of life.
- Definition of optimal management strategy benefit complex; should be individualized:
  - Remission may not be optimal surrogate for clinical benefit
  - Cost: physical, financial, emotional
  - Treatment-free intervals, ? Some cures ?



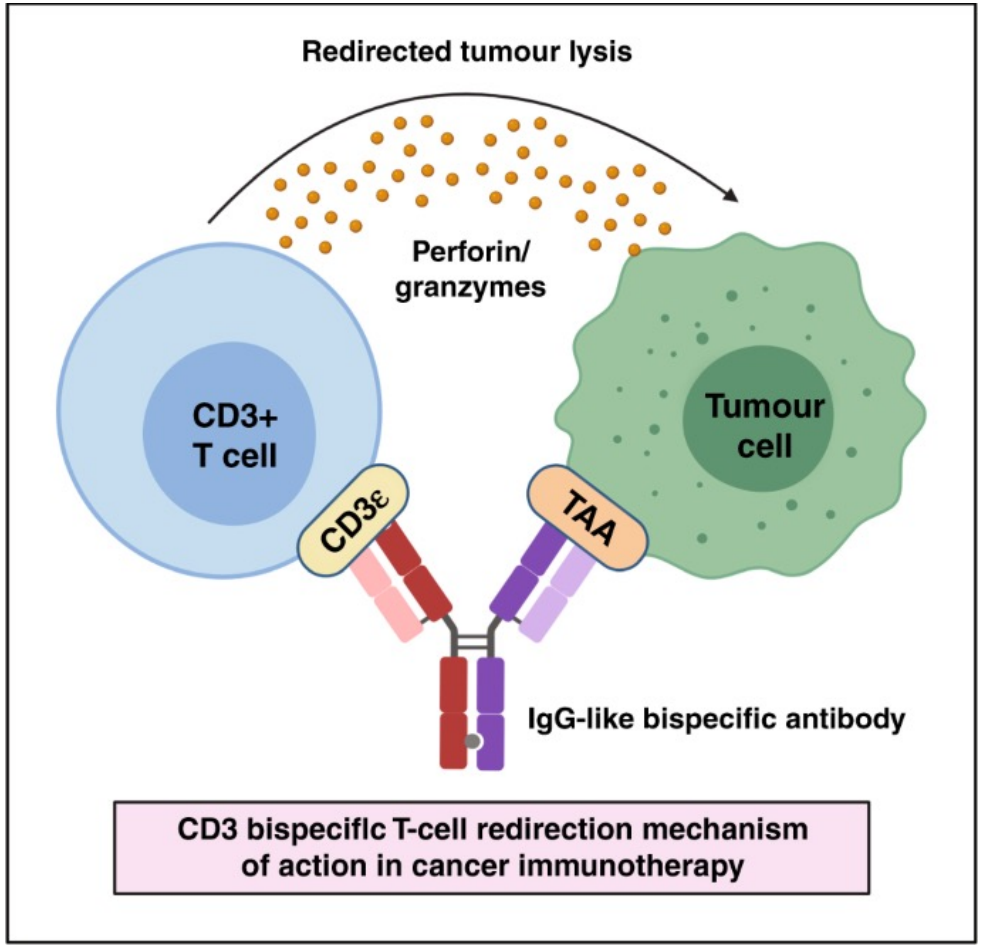
S2308: Newly diagnosed, low tumor burden FL



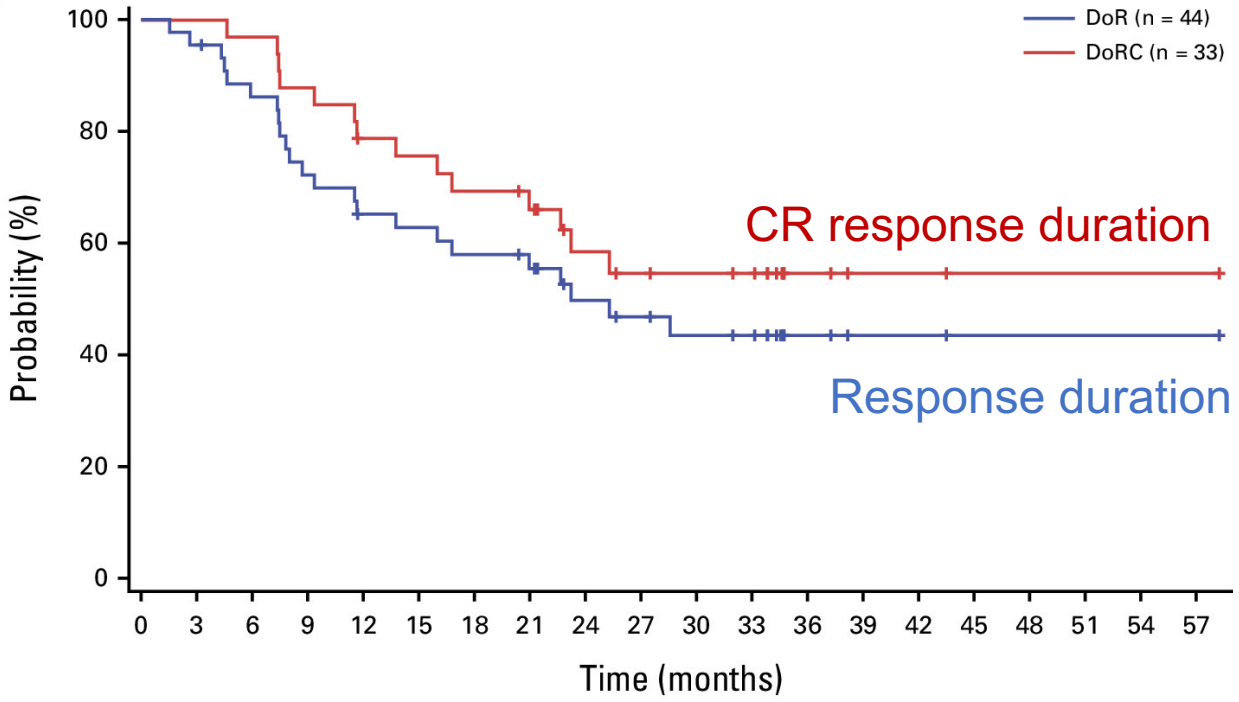
Stratify by:

- FLIPI 0-2 vs $\leq$ 3
- Prior radiation vs. No
- Age $\leq$ 80 vs. > 80

Mosunetuzumab: Durable responses in R/R FL



CD3 bispecific T-cell redirection mechanism of action in cancer immunotherapy



Median follow-up: 3.5 years

Budde et al., *JCO* 42: 2250-58, 2024

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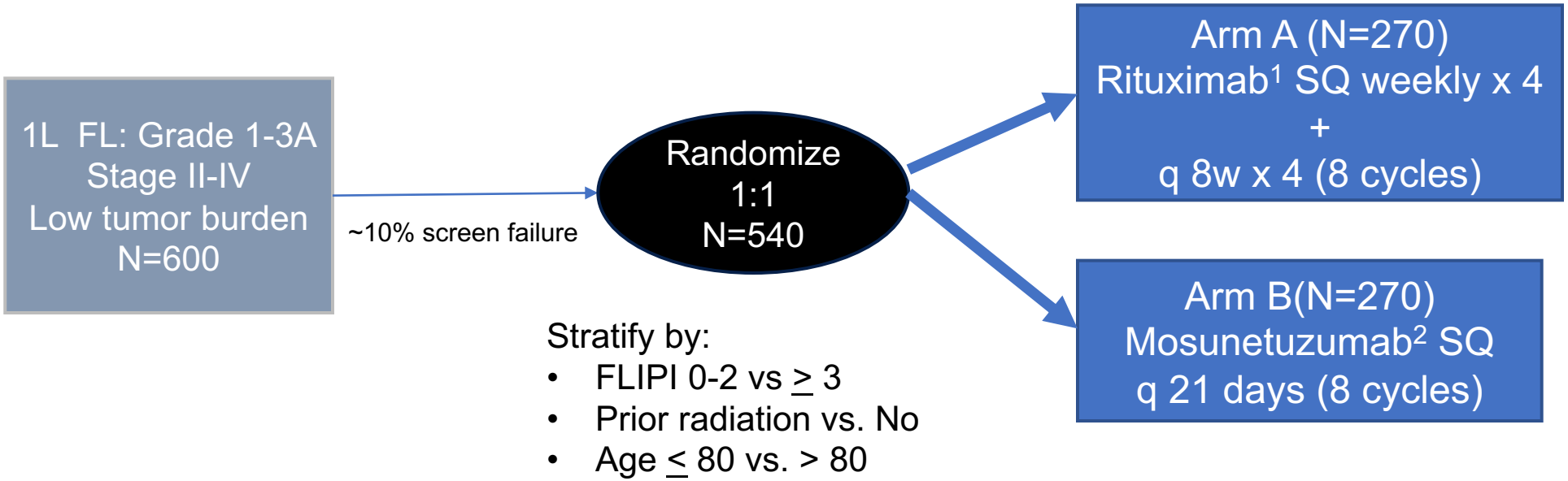
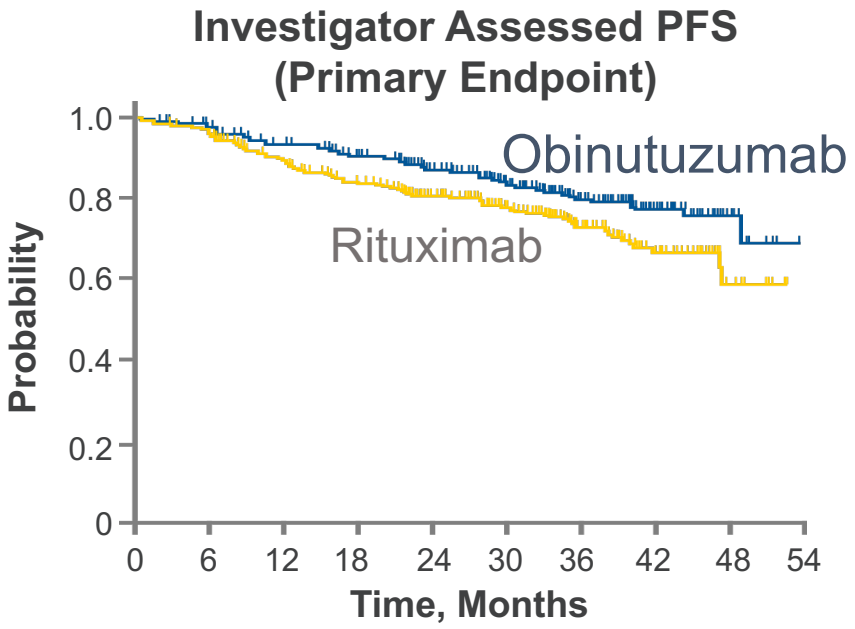


Will this be a curative approach for some patients?

High tumor burden follicular lymphoma

GALLIUM Obinutuzumab/chemo vs Rituximab/chemo Followed by Maintenance



Median follow-up, 34.5 months

Curves separate early

2-year PFS:

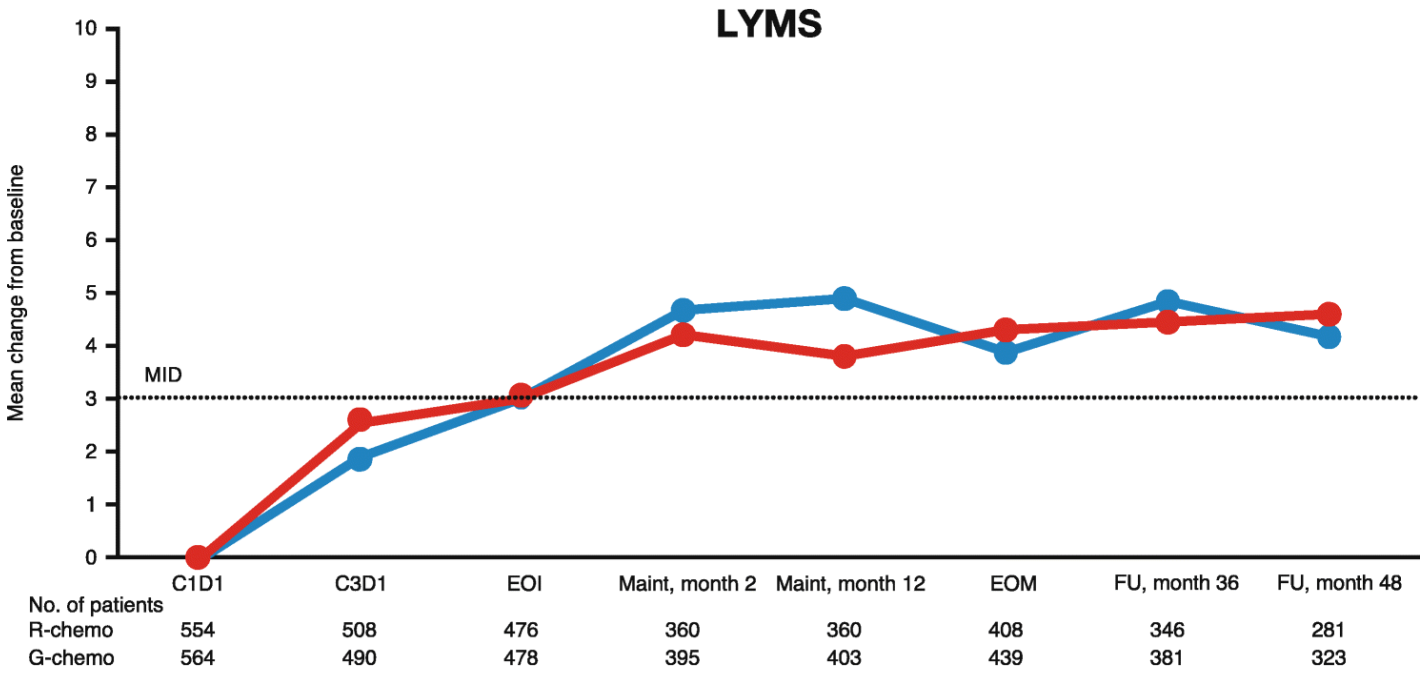
Rituximab 81%

Obinutuzumab 88%

	n	Events, n (%)	3-Year PFS (95% CI), %	Stratified HR[a] (95% CI), *P* Value
G-CT	601	101 (16.8)	80.0 (75.9-83.6)	0.66 (0.51-0.85), 0.0012
R-CT	601	144 (24.0)	73.3 (68.8-77.2)	

Marcus RE, et al. *NEJM* 377:1331 2017

GALLIUM QoL analysis: Immunochemotherapy reduces lymphoma-related symptoms

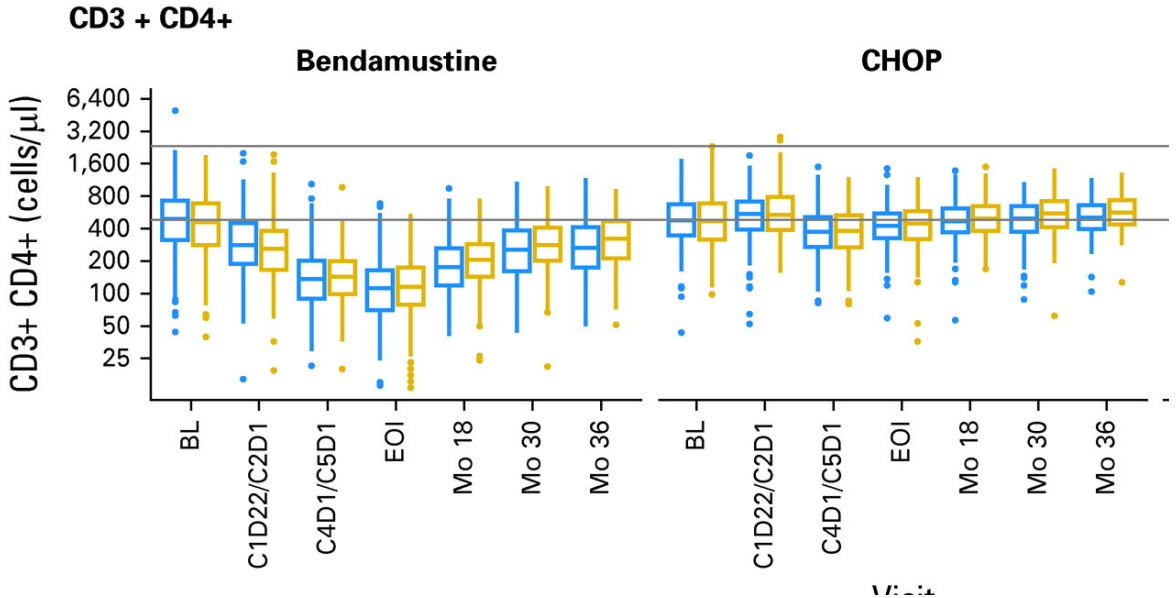


Davies et al., *Ann Hematology* 99:2837-46 2020

GALLIUM Obinutuzumab/chemo vs rituximab/chemo

- Highest response rates observed with bendamustine chemotherapy.
- Increased deaths observed in remission during maintenance following bendamustine with both rituximab and obinutuzumab.
- Questions role of maintenance in this setting.

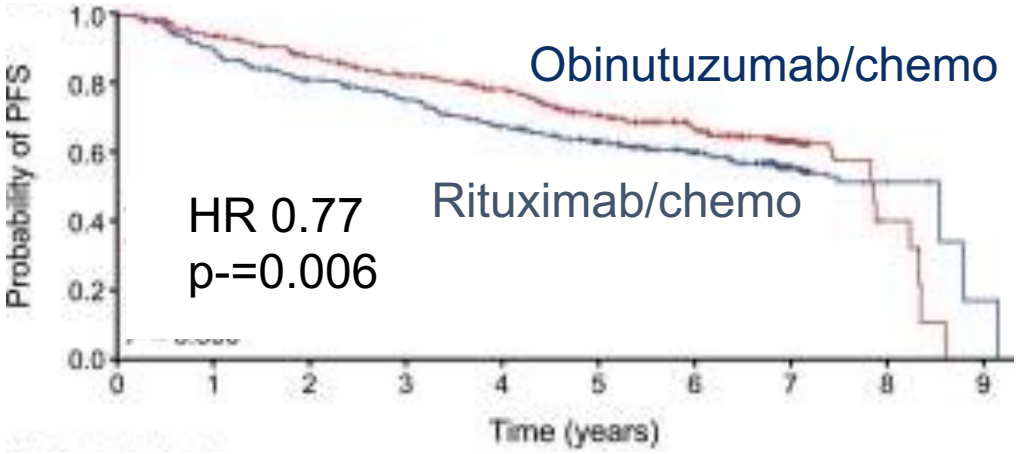
CD4 positive T cell counts over time:
Bendamustine vs. CHOP



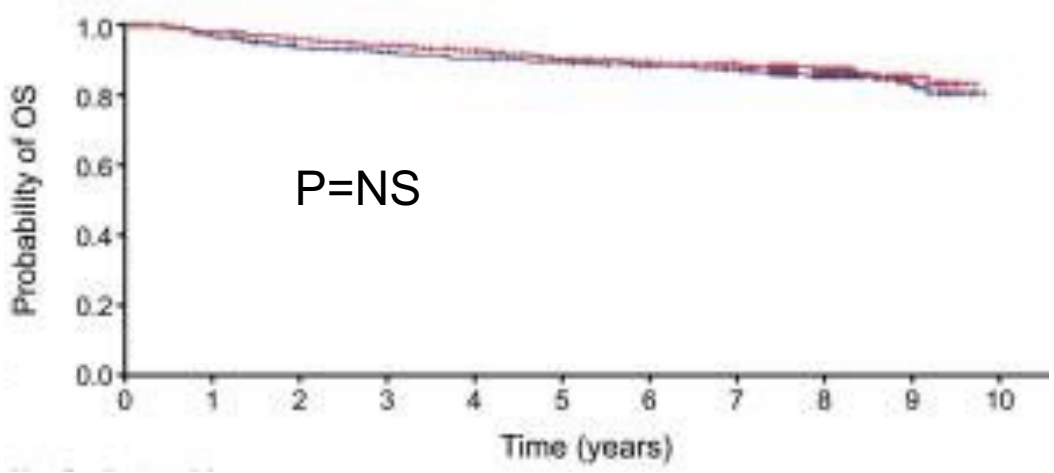
Hiddeman et al., *JCO* 36:2395-2404, 2018
Friedberg, *JCO* 36:2363-65, 2018

GALLIUM Long-term follow-up

Progression-Free Survival

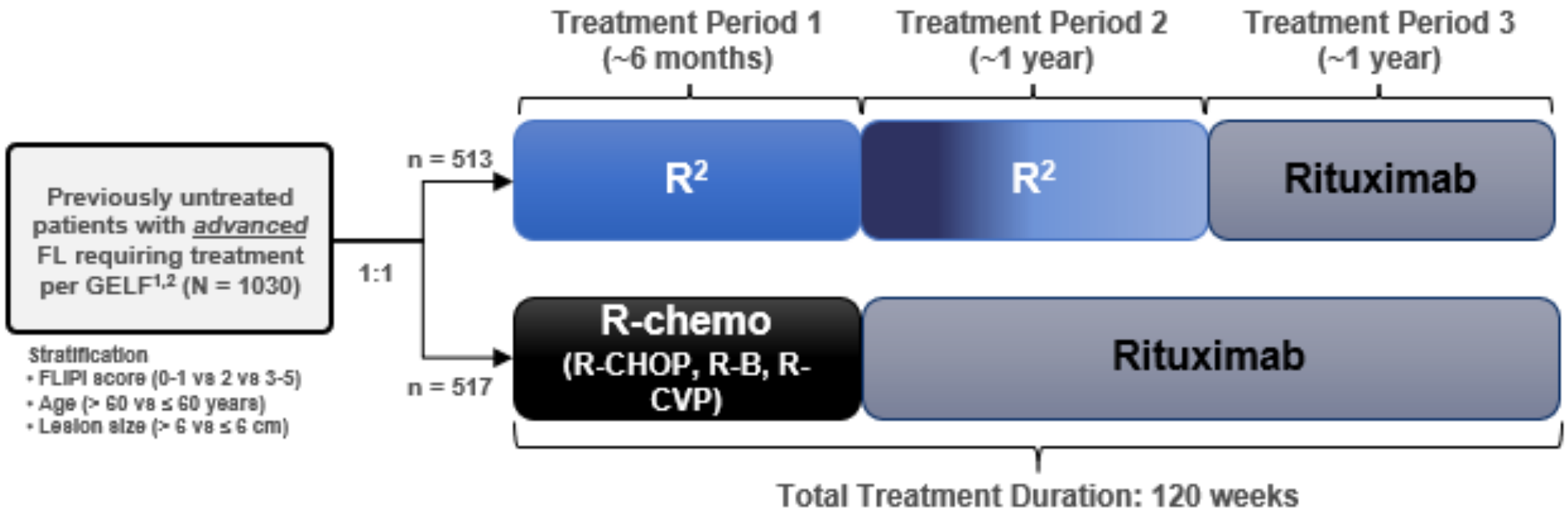


Overall Survival



Townsend et al., *HemaSphere,* 7:e919 2023

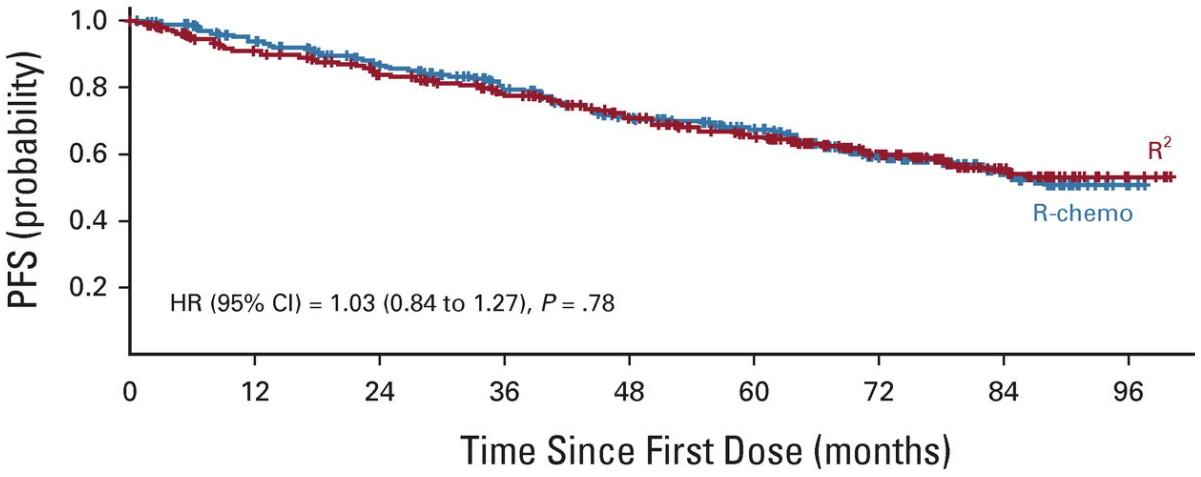
RELEVANCE: Study Design: R2 vs. R-chemo



Morschhauser et al., *NEJM* 379:934-47 2018

RELEVANCE: Long-term outcomes (6-year follow-up)

Progression-Free Survival



Median age 59 years

40% bulky disease > 7cm

28% elevated LDH

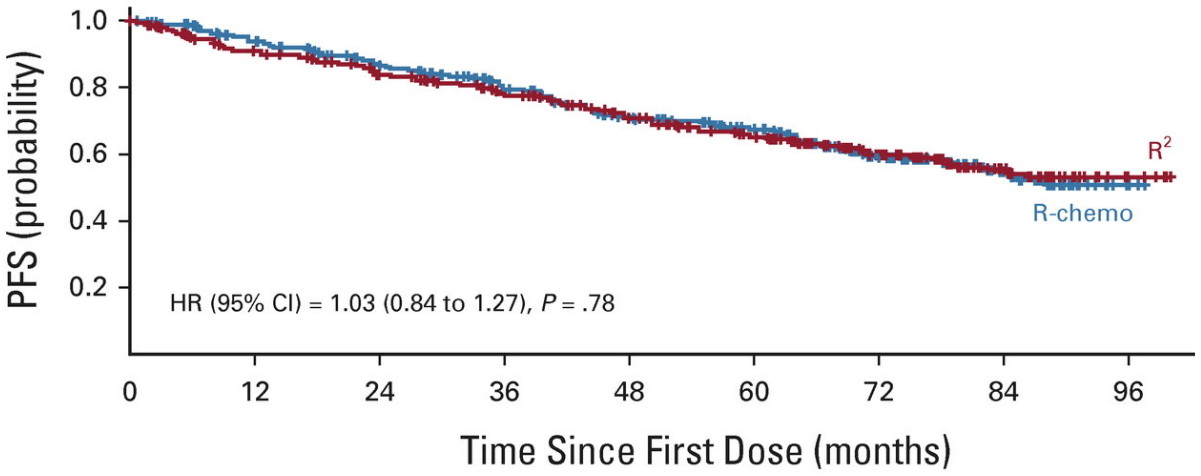
51% elevated beta-2 macroglobulin

49% high risk FL-IPI

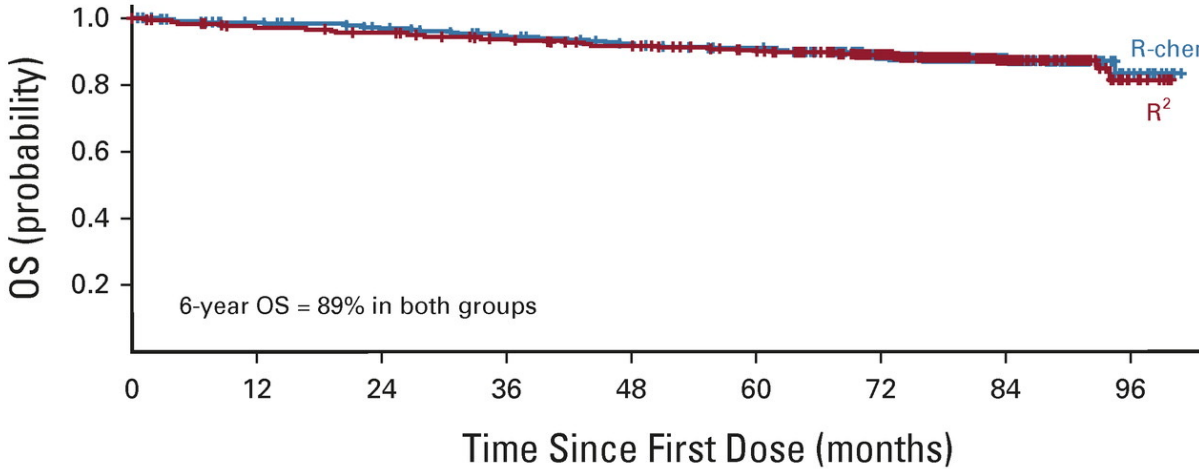
Morschhauser et al., *J Clin Oncol* 40:3239 2022

RELEVANCE: Long-term outcomes (6-year follow-up)

Progression-Free Survival

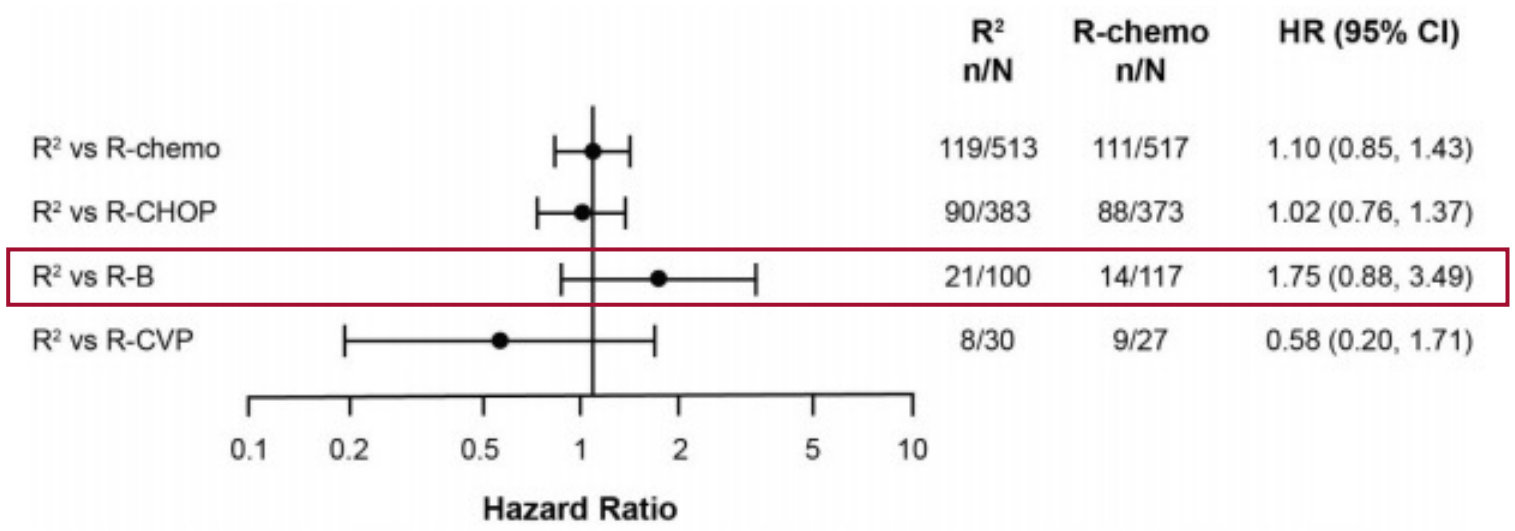


Overall Survival



Morschhauser et al., *J Clin Oncol* 40:3239 2022

RELEVANCE: Hazard ratios (not randomized)



Morschhauser et al., *NEJM* 379:934-47 2018

RELEVANCE: Adverse events

Percentage of patients with grade 3 or 4 adverse events was similar between two groups (65% R2 vs. 68% Rchemo). Deaths were 1% in each group.

Withdrawals from treatment:

43 patients in R2

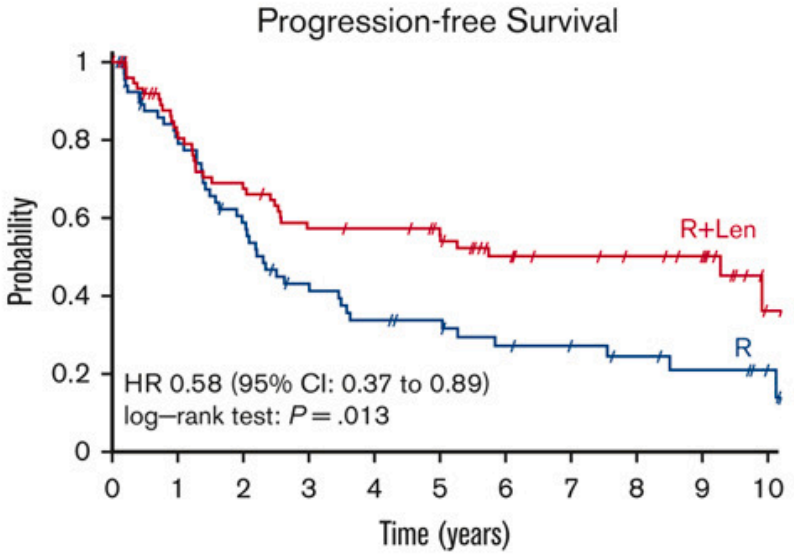
16 patients in Rchemo

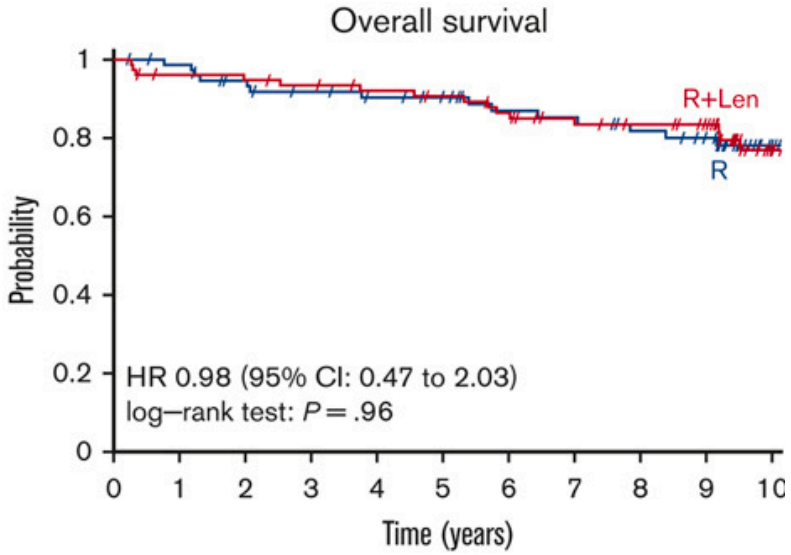
Rituximab vs. rituximab/lenalidomide: median follow-up 9.5 years

Rituximab-lenalidomide:

longer duration of response
progression-free survival
time to next treatment

<u>Over 60% of RL responders remained in first CR at 10 years</u>.



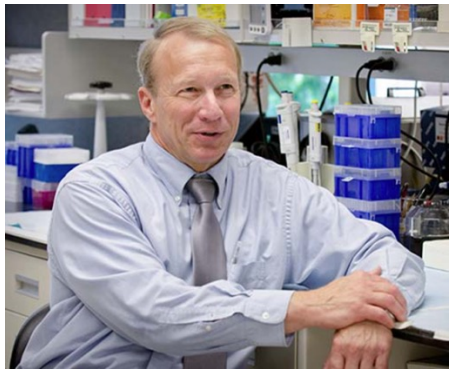


SWOG S0016 Trial

Untreated Advanced Stage FL

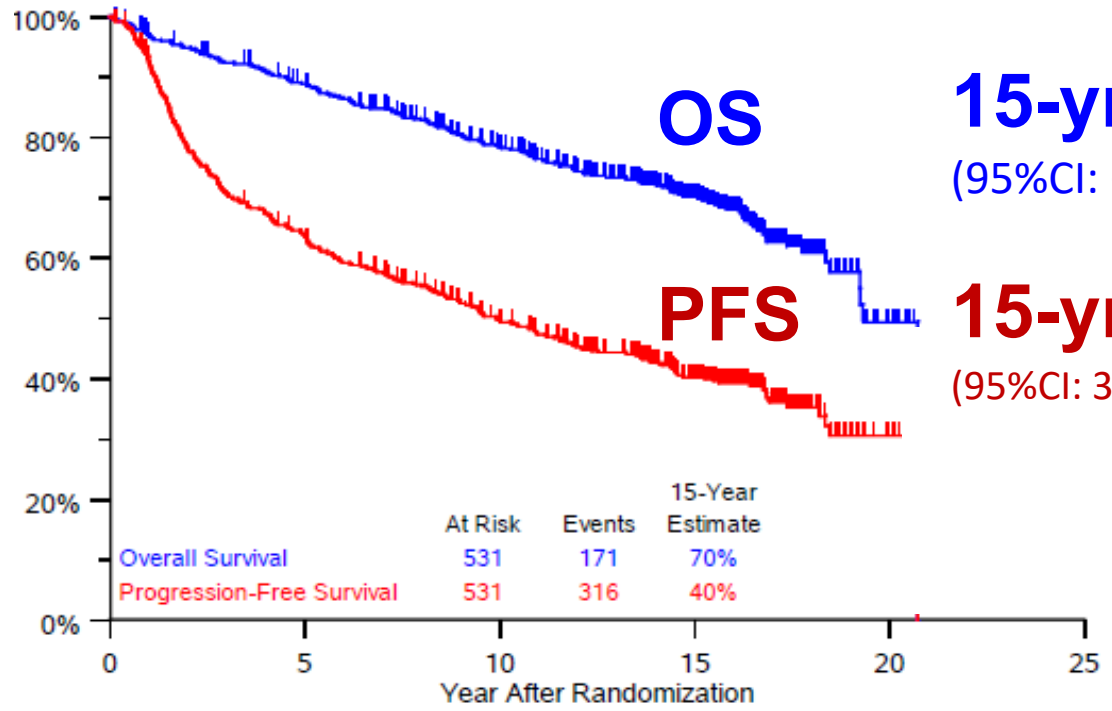
CHOP x 6 + Rituximab	CHOP x 6 + ^{131}I-Tositumomab

- Stratification Factor: β2M Level (Elevated or Not)
- Treatment did NOT include maintenance therapy
- Primary Endpoint: PFS



Press et al., *J Clin Oncol* 31: 314-20, 2013
Shadman et al. *J Clin Oncol* 36:697-703, 2018

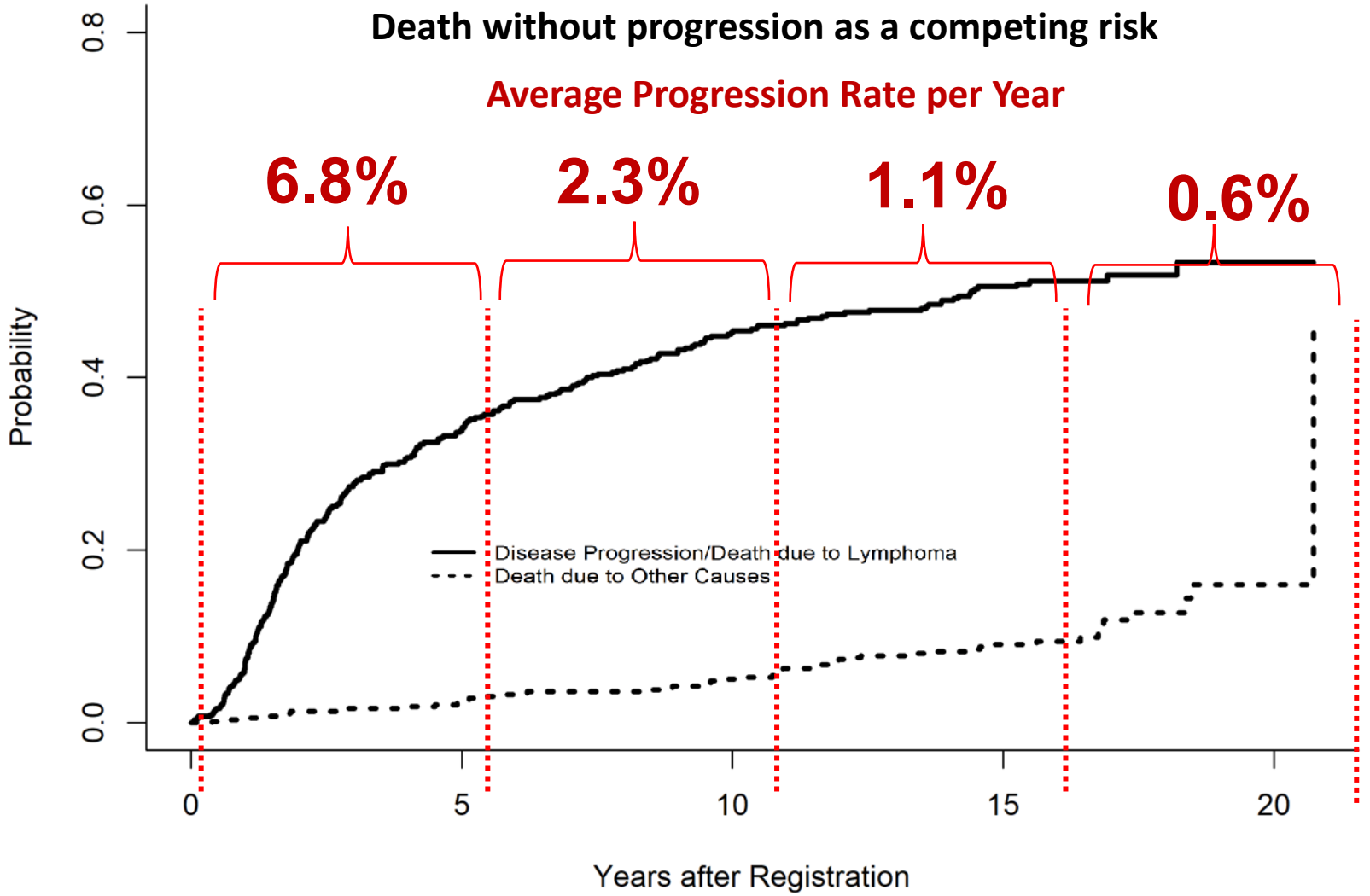
S0016 Entire Cohort Median follow-up 15.5 years



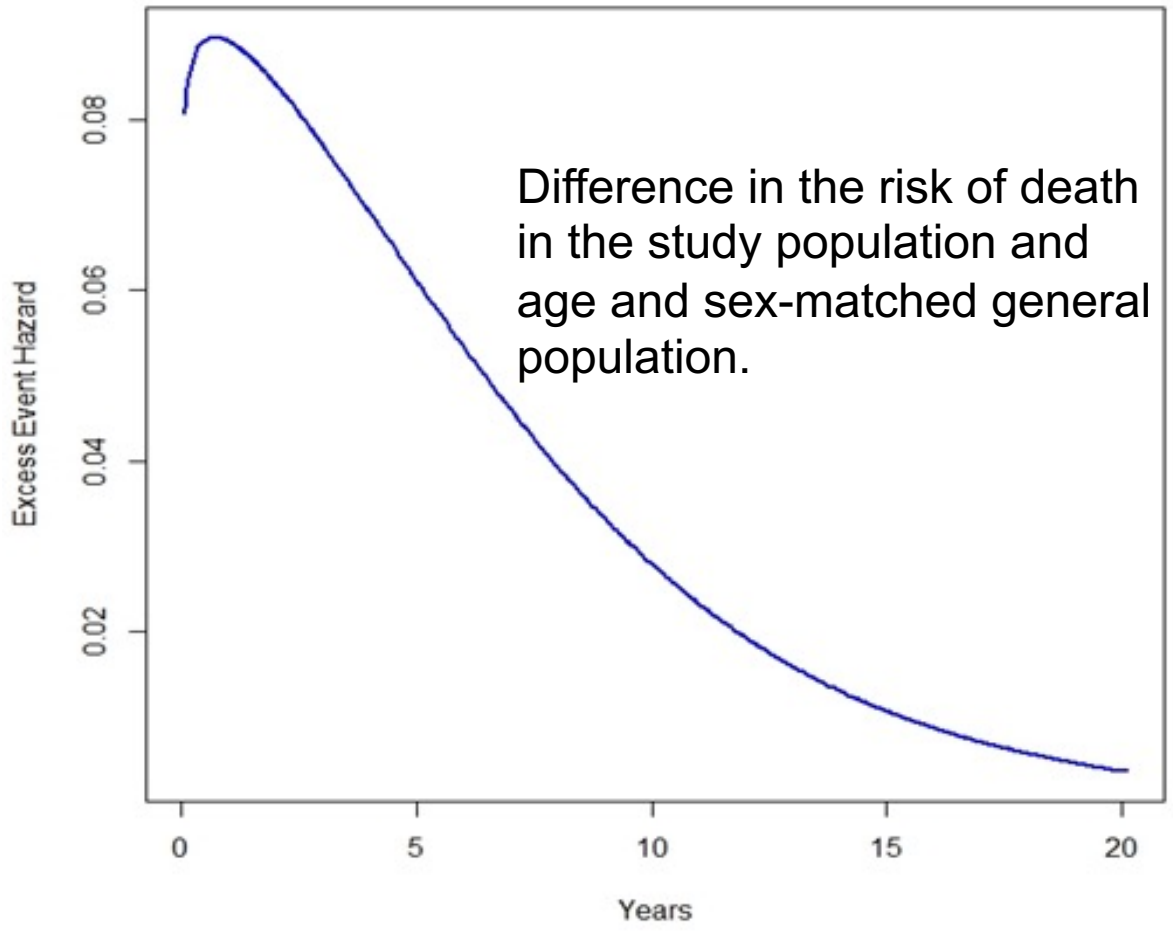
15-yr OS: 70%
(95%CI: 65.9%, 74.1%)

15-yr PFS: 40%
(95%CI: 36.0%, 44.7%)

Cumulative Incidence of Progression/Death: S0016



Excess Hazard Curve: compared with age-matched controls



Advanced stage follicular lymphoma is curable

Cure Rate Estimates		
	Cure Estimate	95% CI (%)
Overall	**47%**	**41-54**
FLIPI Score		
Low (0-1)	52%	40-65
Intermediate (2)	42%	38-60
High (3-5)	36%	26-48
B2M		
Low	58%	49-67
High	37%	28-47

MRD highly predictive of outcome in S0016

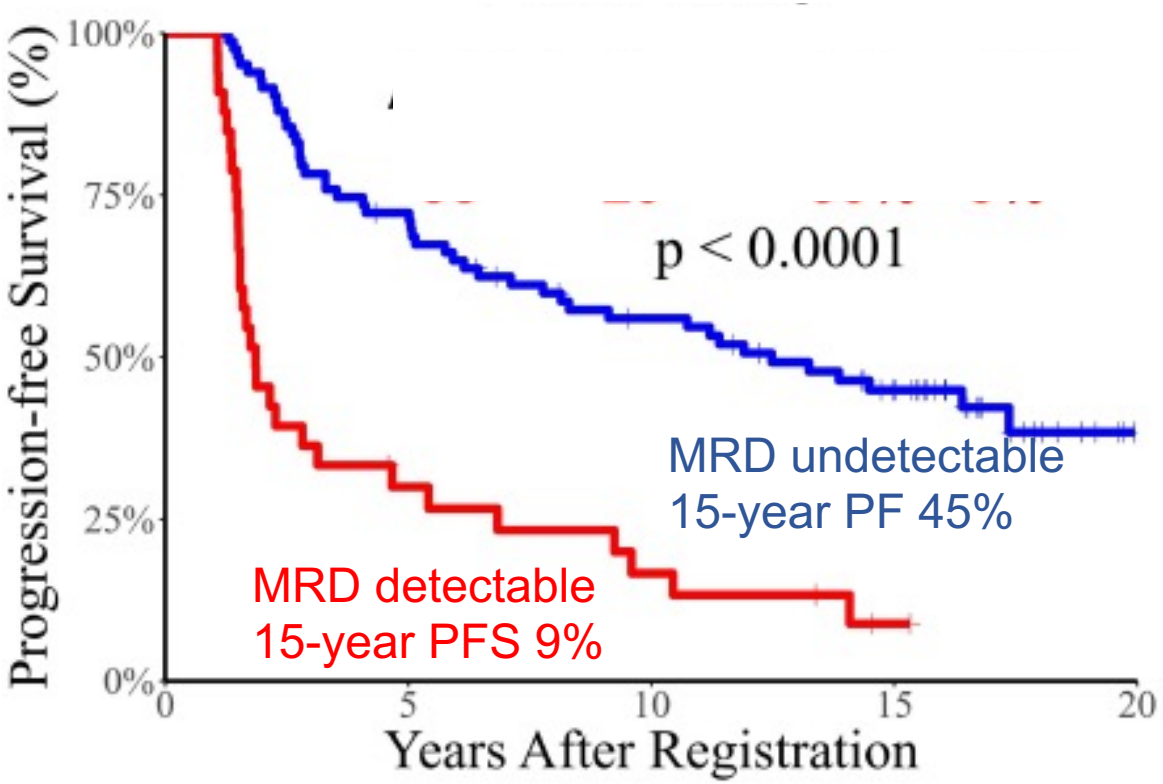
ClonoSeq assay; N=163 analyzed
N=36 no trackable clone
N=11 follow-up samples inadequate

MRD undetectable: 72%
MRD detectable: 28%

10- and 15-year PFS improved with MRD undetectable

Almost no patients who had detectable MRD remained progression-free

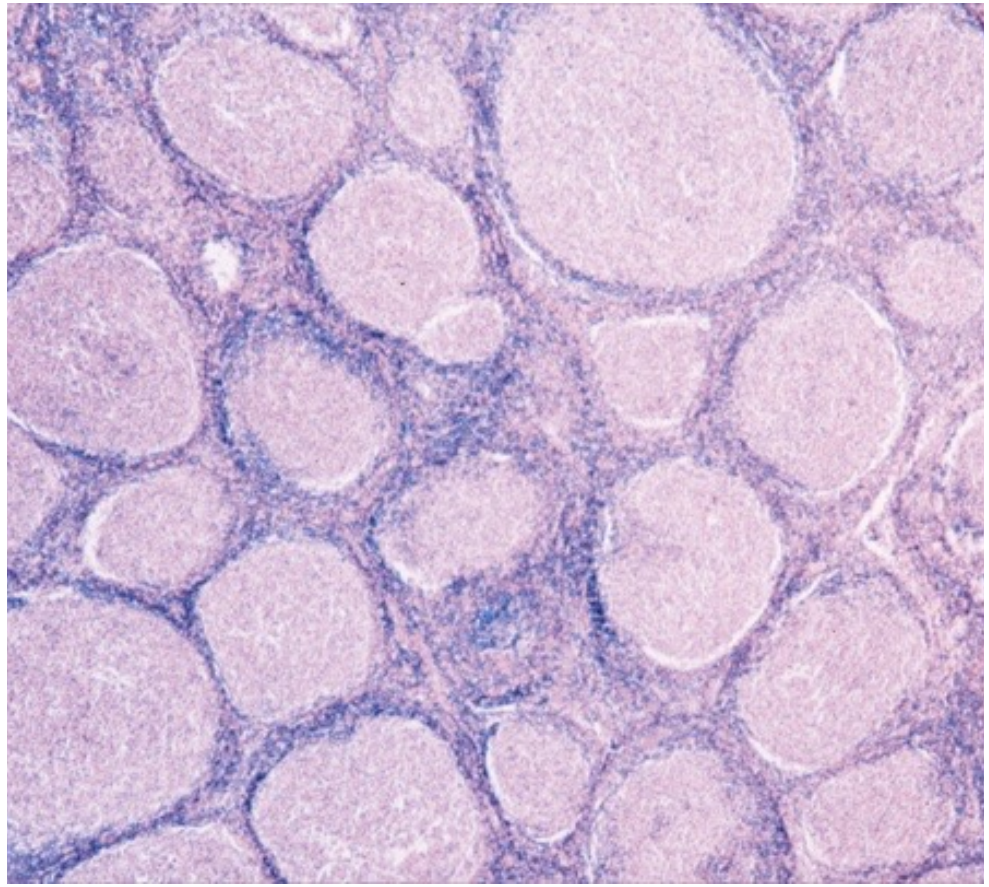
Potentially powerful prognostic biomarker



Danilov et al. *Haematologica* in press 2025

Conclusions: High tumor burden FL

- Long-term follow-up of studies demonstrate a subset of patients with durable EFS, suggesting possible cure.
- Chemoimmunotherapy should remain the standard
- My current approach:
  - Younger patients
    - Asymptomatic: BR
    - Symptomatic: R-CHOP; consider O-CHOP
  - Older patients: BR (dose modified)
  - Grade III FL: R-CHOP or O-CHOP
  - Antibody maintenance (PFS benefit without OS benefit)
    - Individualized; rarely give



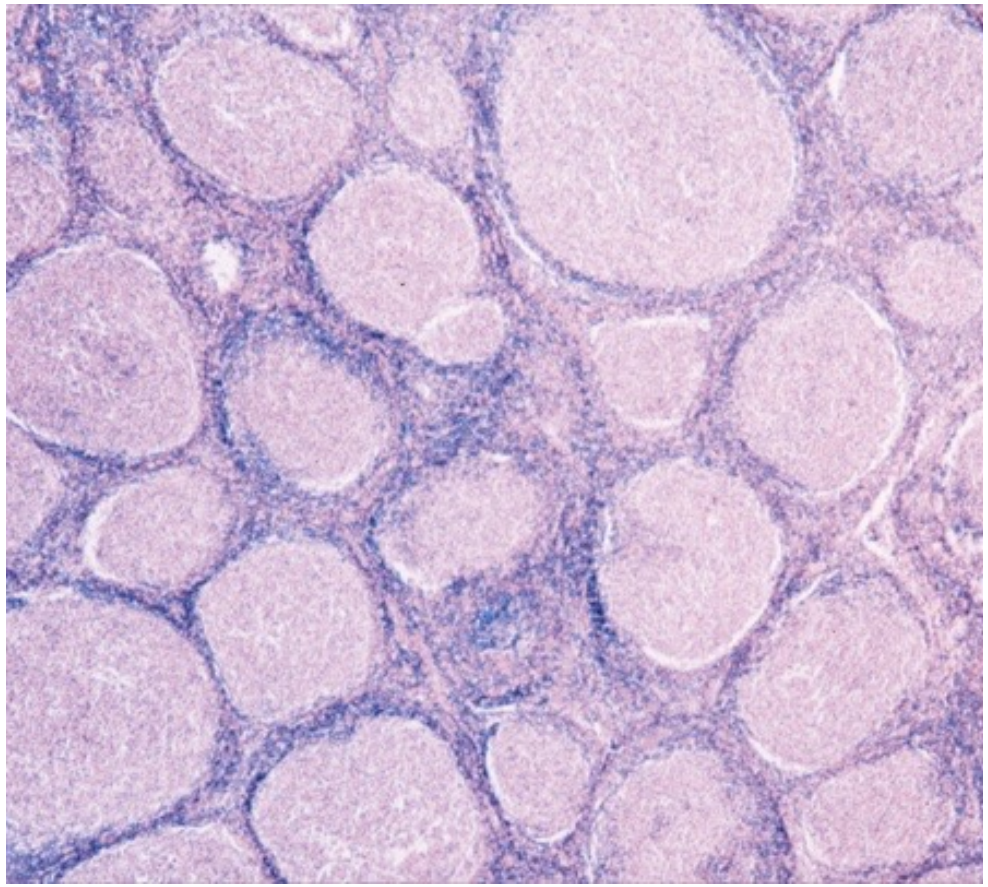
Ongoing phase 3 studies in advanced stage FL

MorningLyte: Monsunetuzumab + Lenalidomide vs. Chemo + antiCD20 (N=790)

Olympia2: Odronextamab vs. R-chemo (N=733)

Some final thoughts on moving forward in follicular lymphoma

- We are achieving cure in a subset of patients.
- Therapy at relapse can be highly effective; how important is PFS in FL?
- Low toxicity therapies which result in long-term PFS remain an important goal of frontline treatment.
- Can we define molecular subsets for rational therapeutic targeting and a precision approach to treatment?



Thank you!