

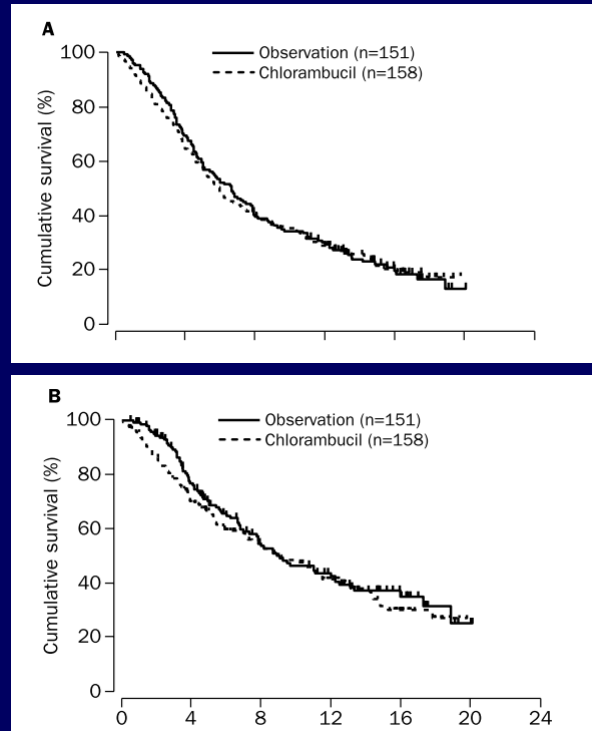
# Who, When, and How to Treat: The Paradox of Watching, Treatment and Retreatment of Indolent Lymphomas

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Lymphoma Research Foundation  
New York, NY

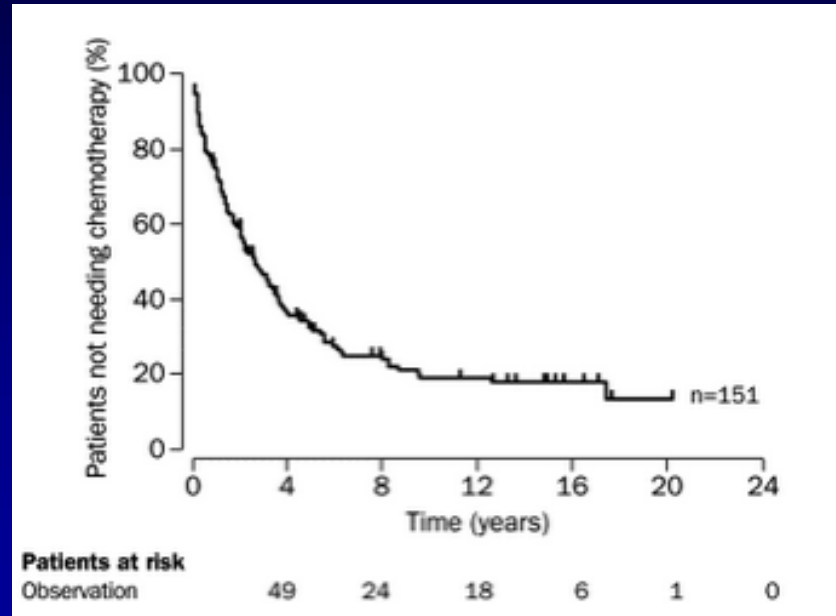
# Indications for Treatment of Advanced Follicular Lymphoma:GELF Criteria

- Maximum diameter  $> 7$  cm
- $\geq 3$  sites with a diameter of  $> 3$  cm
- Systemic symptoms
- “Substantial” spleen involvement
- Serious effusions
- Risk of local compression sx
- High numbers of circulating lymphoma cells
- Peripheral blood cytopenias

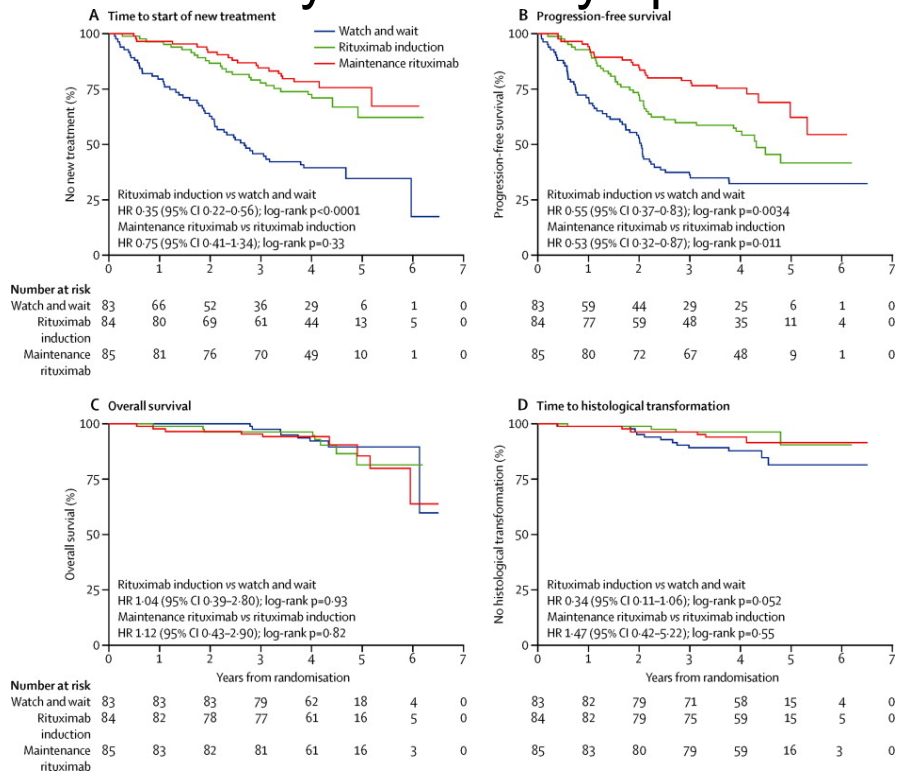
# Watch and Wait in FL:BNLI (n =309)



# Long-term Follow-up of FL



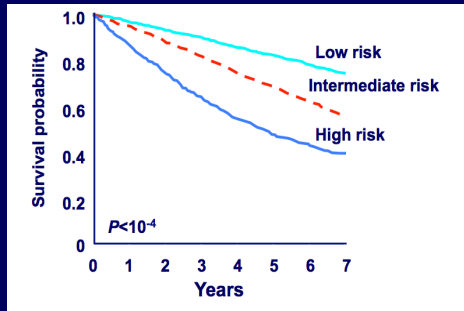
# Rituximab vs watch-and-wait in advanced-stage, asymptomatic, non-bulky follicular lymphoma



*Treatment As It Is  
Currently Done*

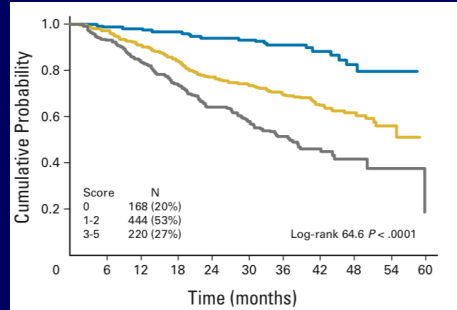
# Prognostic Scoring Systems

## FLIPI



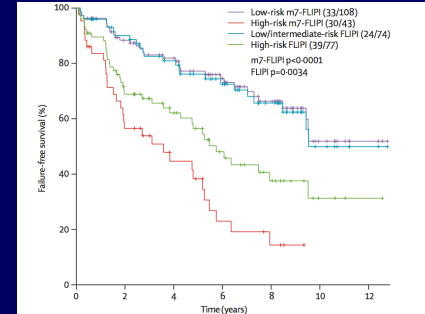
Nodes, LDH, Age,  
Stage, Hgb

## F-2



$\beta$ -2M, Hgb, Node size  
Age, BM

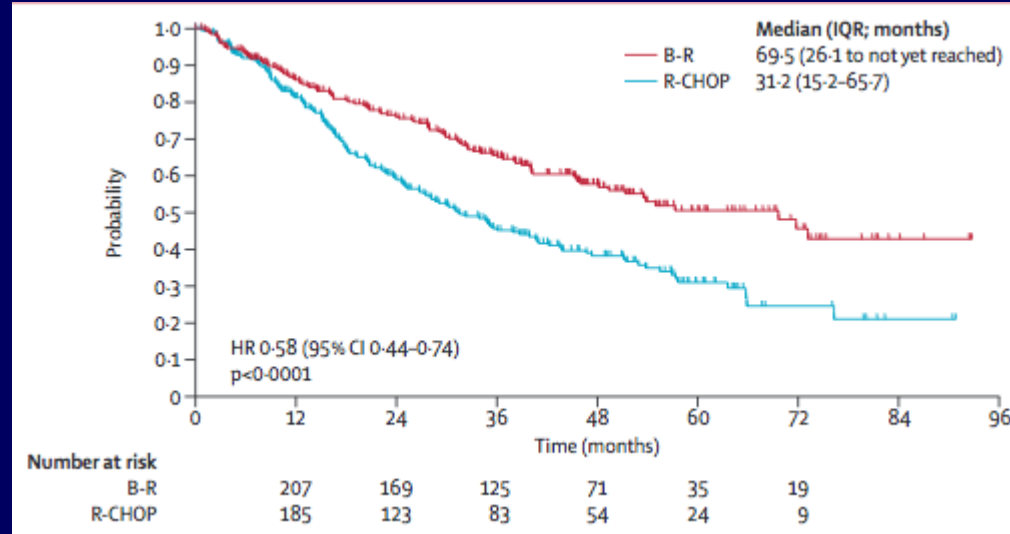
## M7-FLIPI



Mutation of 7 genes,  
PS, F-2

*But what do you do with the information??*

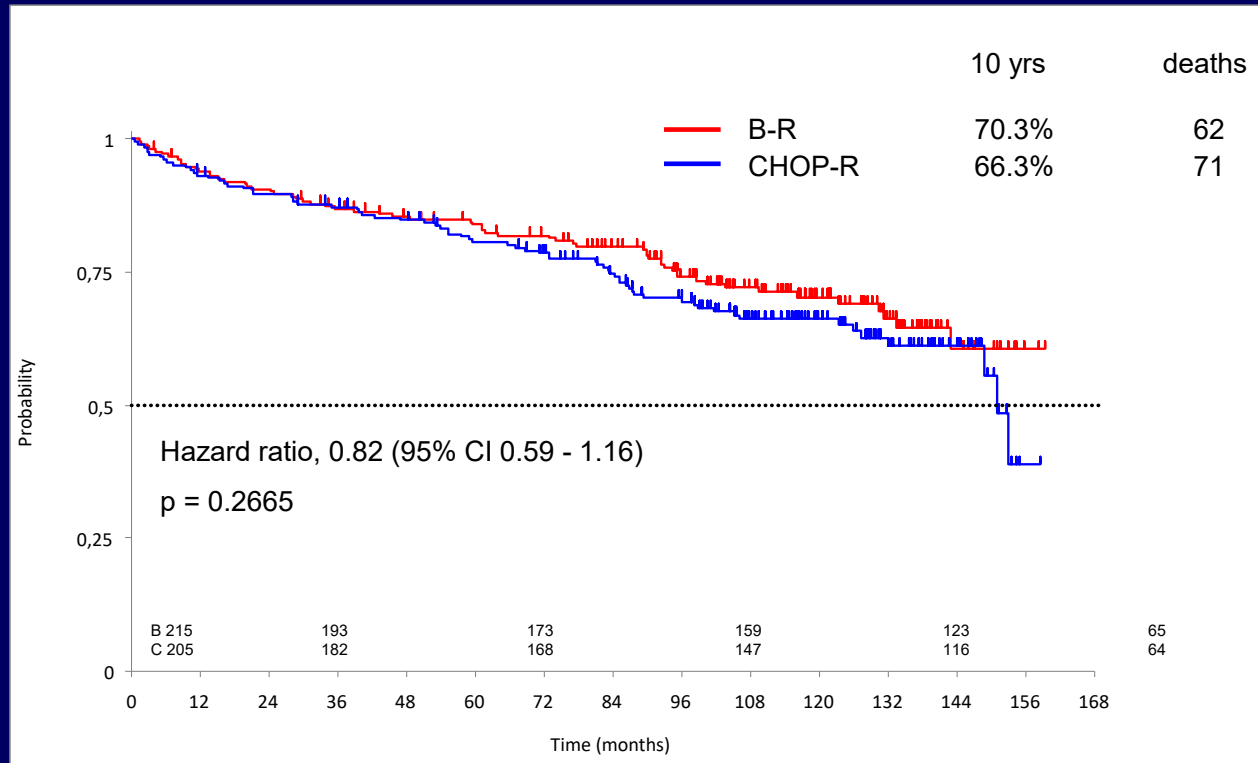
# BR vs R-CHOP in Untreated iNHL



Rummel et al, Lancet 381:1203, 2013

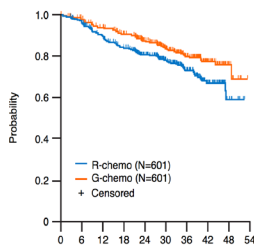


# Overall survival



# GALLIUM Study: PFS and OS

## INV-assessed PFS (FL; primary endpoint)



No. of patients at risk	
R-chemo	601 562 505 463 378 266 160 66 10 0
G-chemo	601 570 536 502 405 279 168 75 13 0

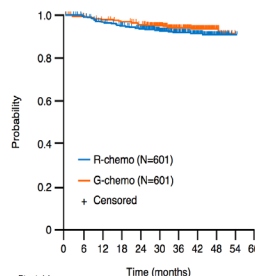
\*Stratified analysis; stratification factors: chemotherapy regimen, FLPII risk group, geographic region

	R-chemo, n=601	G-chemo, n=601
Pts with event, n (%)	144 (24.0)	101 (16.8)
3-yr PFS, % (95% CI)	73.3 (68.8, 77.2)	80.0 (75.9, 83.6)
HR (95% CI), p-value*	0.66 (0.51, 0.85), p=0.0012	

Median follow-up: 34.5 months

10

## OS (FL)



Pts at risk, n	
R-chemo	601 588 566 549 527 399 265 160 58 2
G-chemo	601 584 573 563 549 416 271 161 55

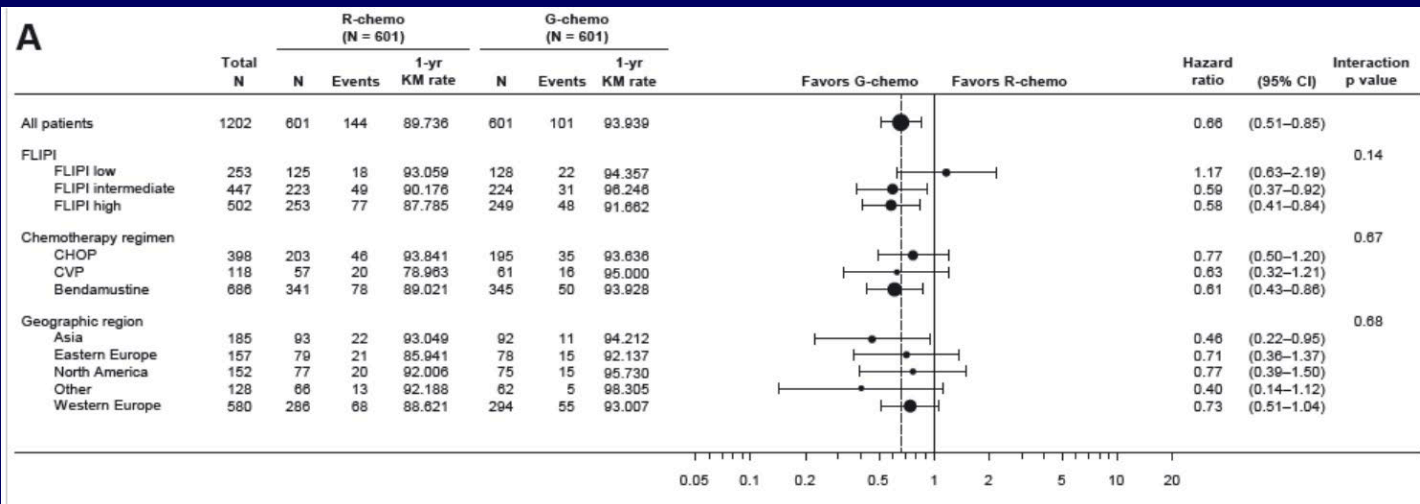
\*Stratified analysis; stratification factors: chemotherapy regimen, FLPII risk group, geographic region

	R-chemo, n=601	G-chemo, n=601
Pts with event, n (%)	46 (7.7)	35 (5.8)
3-yr OS, % (95% CI)	92.1 (89.5, 94.1)	94.0 (91.6, 95.7)
HR (95% CI), p-value*	0.75 (0.49, 1.17), p=0.21	

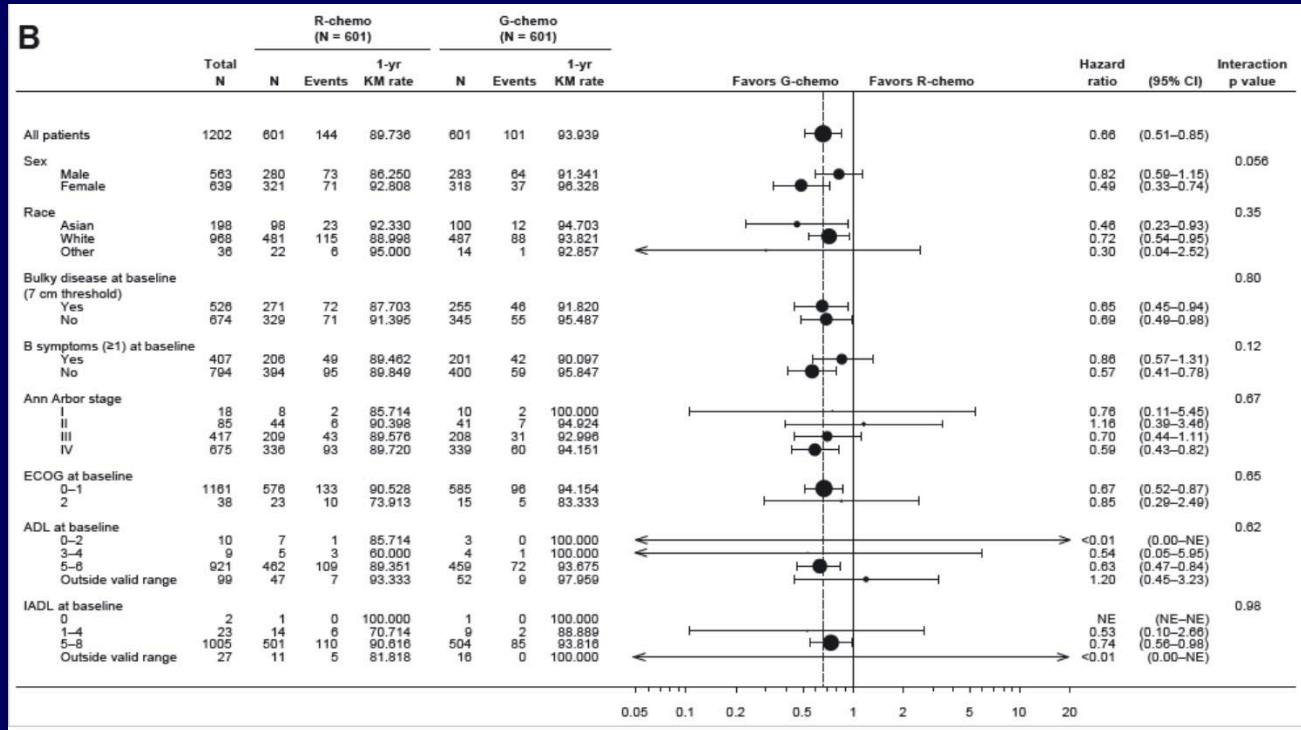
Median follow-up: 34.5 months

13

# Response by Stratification Factors

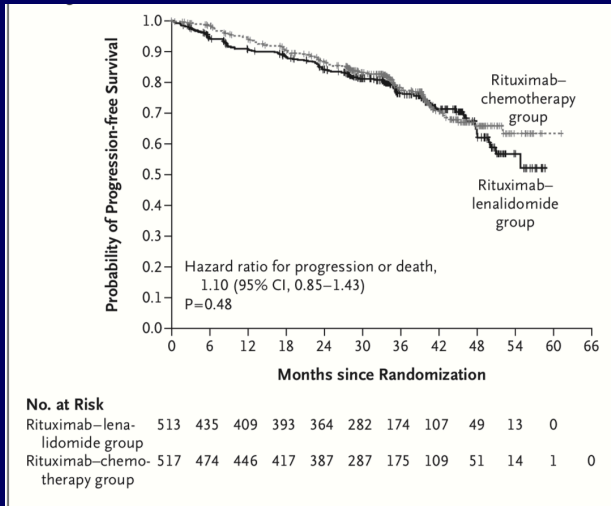


# GALLIUM Response By Baseline Features

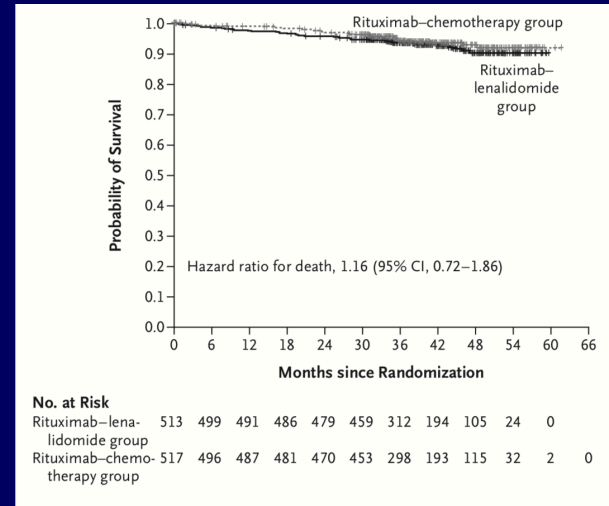


# RELEVANCE

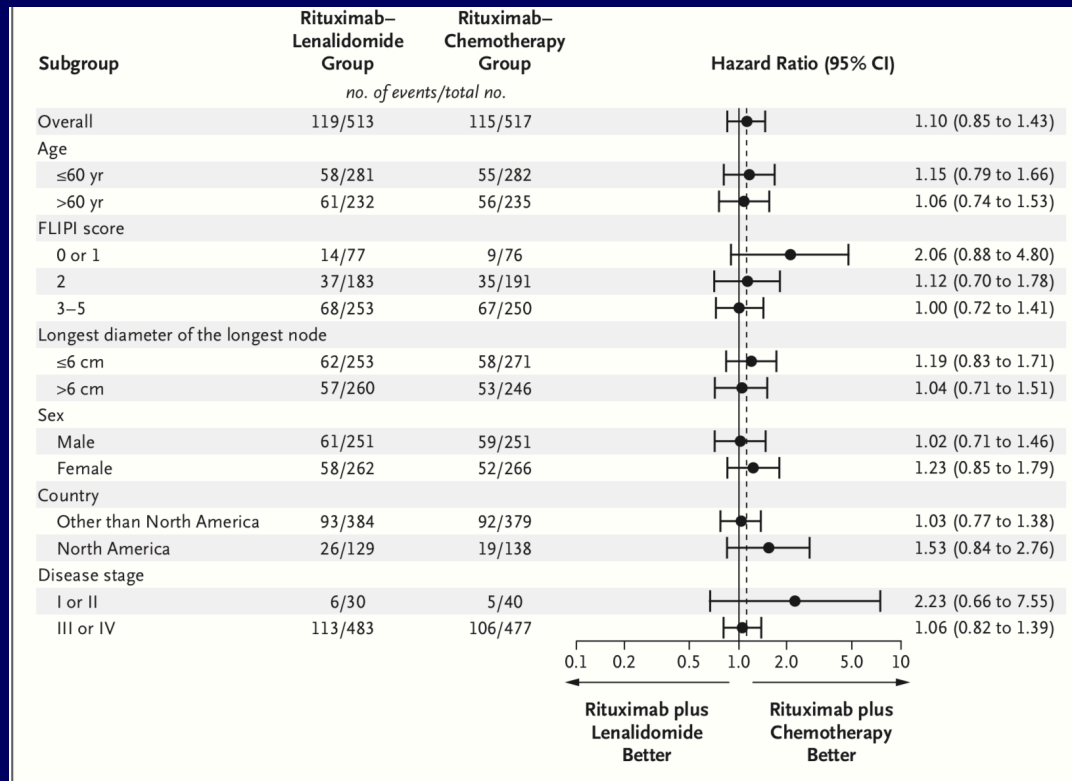
PFS



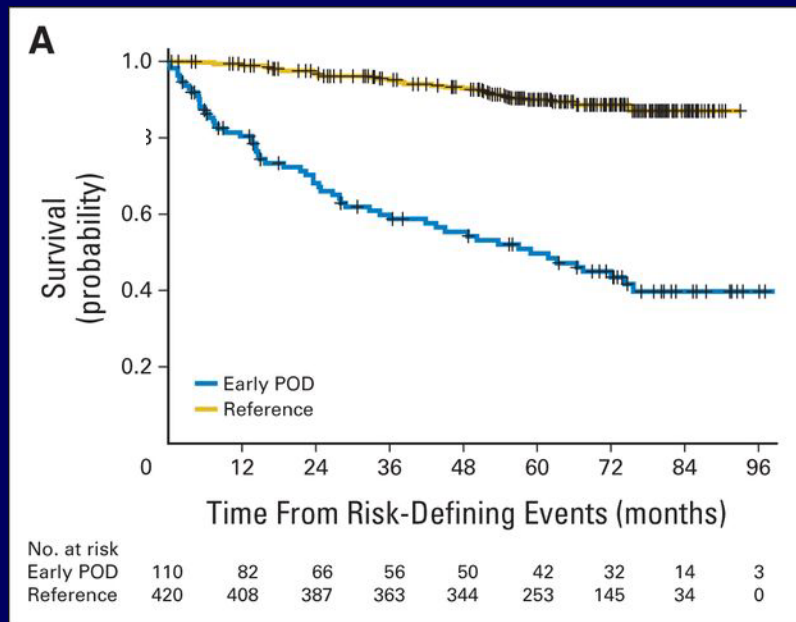
OS



# RELEVANCE: Clinical Features



# OS from a risk-defining event after diagnosis in FL patients who received R-CHOP in the National LymphoCare Study group.

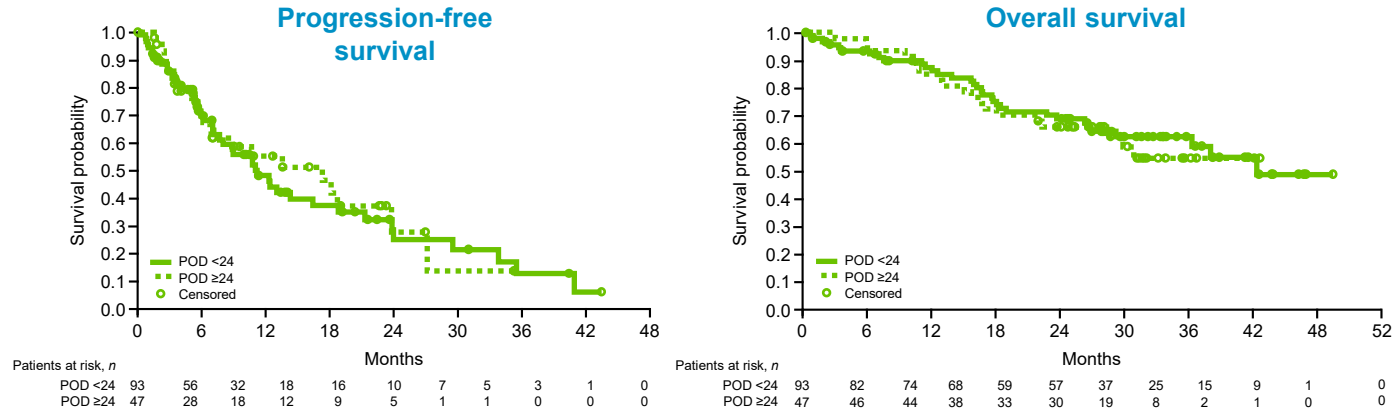


# Second Line Therapies in R/R FL

- NLCS involving 2736 pts
- 521 started 2<sup>nd</sup> line tx in <1 year
- 2<sup>nd</sup> line treatment selections in 991
  - XRT - 7.3%
  - Clinical trial - 6.3%
  - CIT – 36.1%
  - R monotherapy – 32.4%
  - Chemotherapy alone – 8.3%
  - RIT – 3%
  - BMT – 1.5%

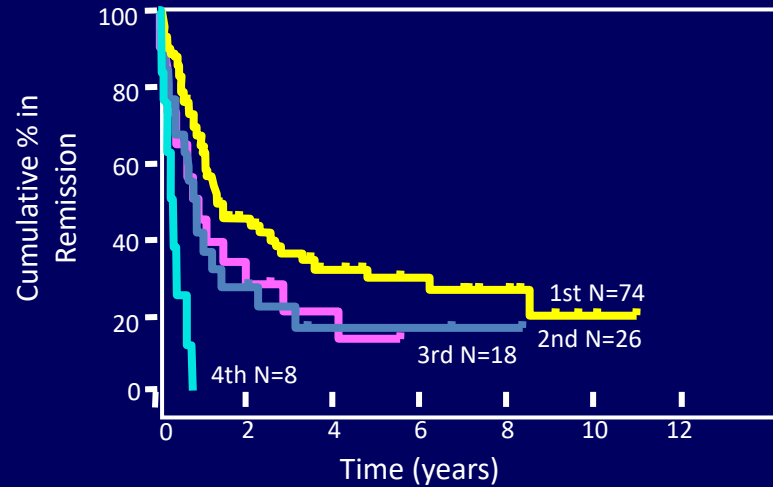


# Copanlisib: Progression-free survival and overall survival



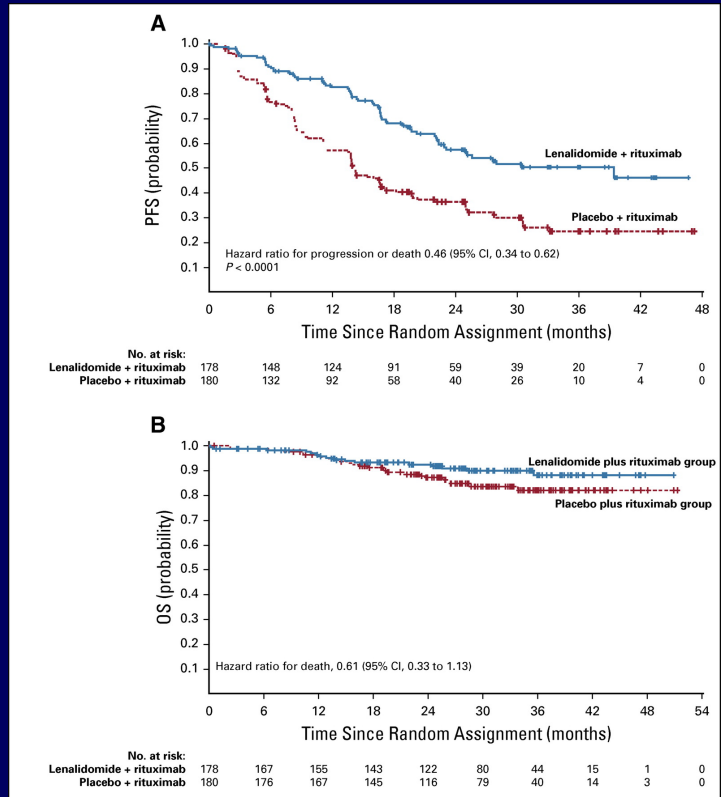
- Median PFS was 11.3 months (range 0-44.2 months) in the POD <24 group and 17.6 months (range 0-35.8 months) in the POD ≥24 group
- Median OS was 42.6 months (range 0.2-49.8 months) in the POD <24 group and had not yet been reached in the POD ≥24 group (range 3.0-43.0 months)

# Duration of Remission Following Relapse of Indolent NHLs



Gallagher et al. *J Clin Oncol.* 1986;4:1470-1480.

# PFS and OS From the AUGMENT Trial



# AUGMENT: PFS vs Prior Regimen

	Lenalidomide-Rituximab Group (n = 178)		Placebo-Rituximab Group (n = 180)	
	Last prior systemic antilymphoma regimen	Lenalidomide plus rituximab	Last prior systemic antilymphoma regimen	Placebo plus rituximab
Median progression-free survival, as assessed by IRC – months (95% CI)	32.4 (28.4-36.0)	39.4 (22.9-NR)	30.6 (26.4-36.2)	14.1 (11.4-16.7)

Courtesy of John Leonard

# AUGMENT by POD24 Status

	POD24 Yes/No	R <sup>2</sup>	R/Placebo	HR (95% CI)
Median PFS, mo (95% CI)	Yes	30.4 (16.8-NR)	13.8 (6.7-16.9)	0.41 (0.24-0.68)
	No	39.4 (22.9-NR)	13.9 (11.2-16.6)	0.43 (0.28-0.65)
Best ORR (CR), %	Yes	80 (30)	51 (18)	–
	No	80 (37)	58 (21)	–

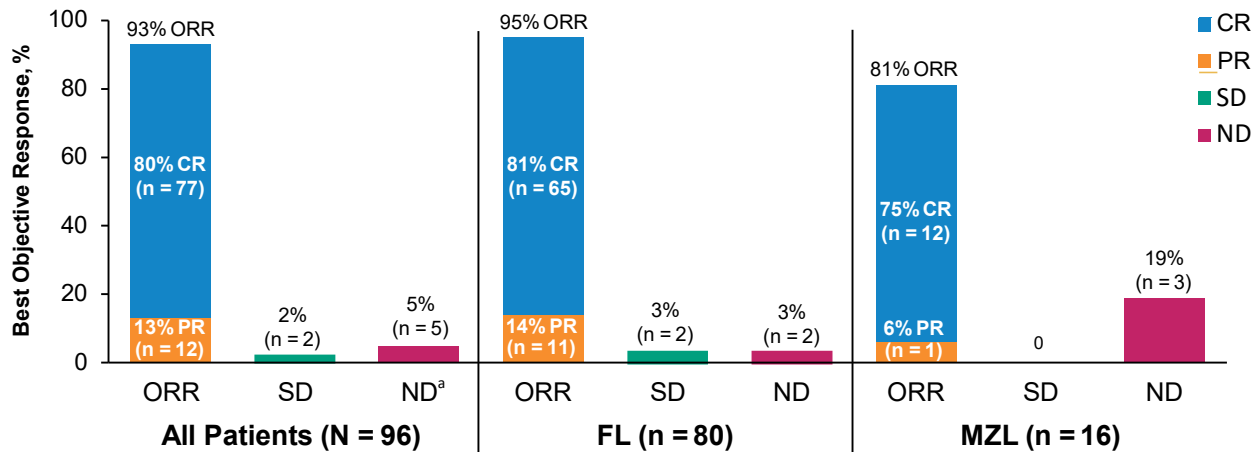
Courtesy John Leonard

# Targeted Agents for FL

Agent	Target
Obinutuzumab*/Ublituximab	CD20
Magrolimab	CD47
Ibrutinib, acalabrutinib	Btk
Idelalisib*, Copanlisib*, Duvelisib*, Umbralisib	PI3-K
Venetoclax Tazemetostat*	Bcl-2 EZH2
Lenalidomide/Rituximab*	Multiple
Nivolumab/Pembrolizumab	PD-1
Atezolizumab	PDL-1
CART-cell	CD19

\* FDA approved

## Overall ORR by IRRC Assessment Was 93% (95% CI, 86 – 97), and CR Rate Was 80% (95% CI, 71 – 88)

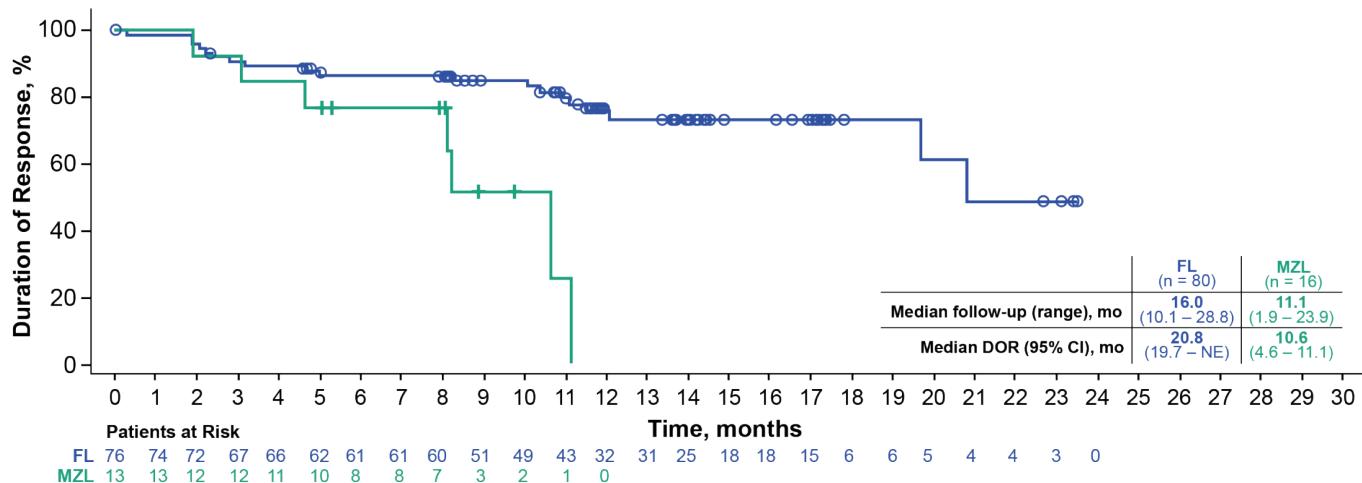


- The median time to first response was 1 month (range, 0.8 – 3.1)
- Of the 80 patients with FL, 10 (13%) had an initial response of PR at Week 4 and later converted to CR

The investigator-assessed ORR (N = 96) was 95%, with a CR rate of 80%.

<sup>a</sup> For the 5 patients reported as ND, 4 (1 with FL and 3 with MZL) had no disease at baseline and postbaseline assessments by IRRC; 1 patient with FL died prior to the first scheduled assessment. CR, complete response; FL, follicular lymphoma; IRRC, Independent Radiology Review Committee; MZL, marginal zone lymphoma; ND, undefined/not done; ORR, objective response rate; PR, partial response; SD, stable disease.

## Duration of Response

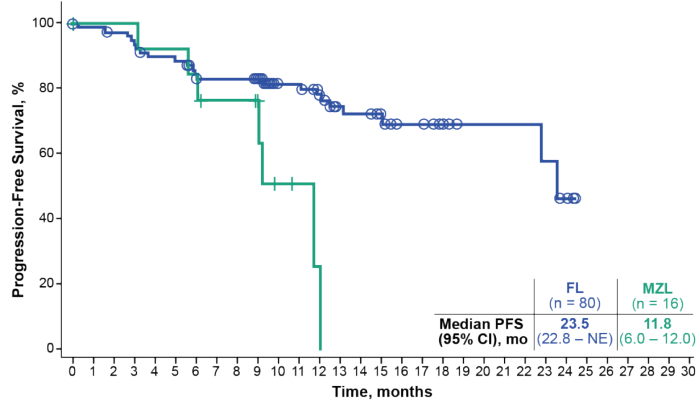


- With a median follow-up of 15.3 months, estimated median DOR in all patients was 20.8 months, and 68% of patients with FL had an ongoing response
  - Among patients with FL, responses were ongoing in 80% of patients with a CR and 18% of patients with a PR

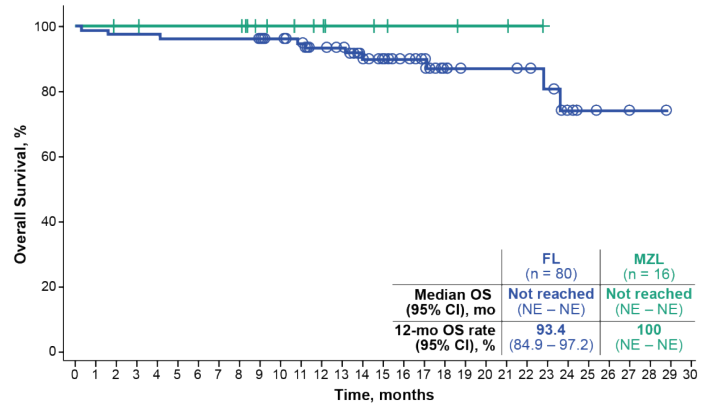
CR, complete response; DOR, duration of response; FL, follicular lymphoma; MZL, marginal zone lymphoma; NE, not estimable; PR, partial response.



# Progression-Free Survival and Overall Survival



**Patients at Risk**  
 FL 80 78 76 74 69 68 63 61 59 49 49 43 34 33 26 18 18 15 6 6 6 5 3 0  
 MZL 16 13 13 13 12 11 8 8 7 3 2 1 0



**Patients at Risk**  
 FL 80 79 78 78 78 77 77 77 77 76 72 69 61 58 48 43 36 31 22 16 16 15 13 7 3 2 1 1 0  
 MZL 16 16 15 15 14 14 14 14 14 10 9 8 7 5 5 4 3 3 3 2 2 2 1 0

- With a median follow-up of 15.3 months, median PFS was 23.5 months (95% CI, 22.8 – NE) in all patients, and the median OS was not reached
  - The 12-month OS rate was 94.3% (95% CI, 86.8 – 97.6) for all patients

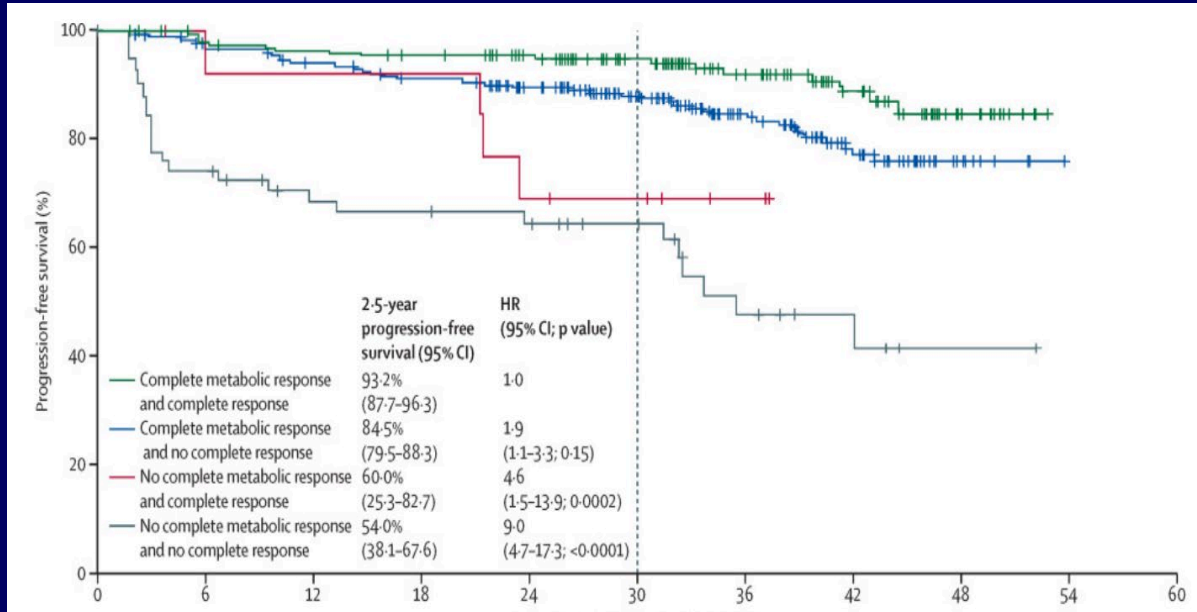
FL, follicular lymphoma; MZL, marginal zone lymphoma; NE, not estimable; OS, overall survival; PFS, progression-free survival.

*Treatment As It Could  
Be Done*

# Biomarkers and Outcome in FL

- Tumor biology-based
  - PET-CT
  - Gene expression signature
  - FOXP1
- Microenvironment
  - PET-CT
  - PD-L1
  - PD-L2
  - TIL (PD1+, GATA3+)
  - Macrophage content

# PFS by EOT PET: GALLIUM Study



# GALLIUM: Response rates at end of induction (FL)\*

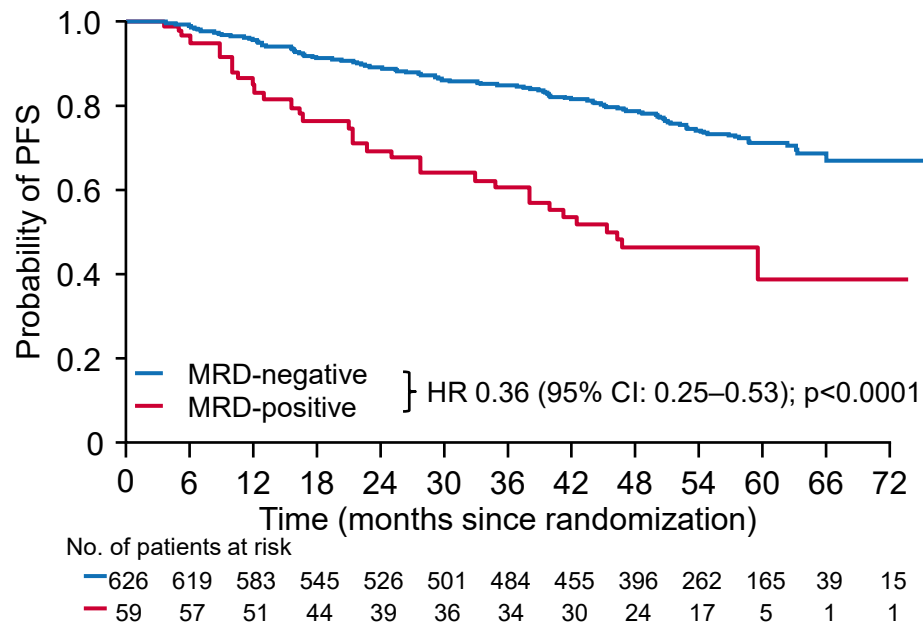
	<i>CT (by investigator)% (n); 95% CI</i>	
	<i>R-chemo, n=601</i>	<i>G-chemo, n=601</i>
<b>ORR</b>	<b>86.9% (522); 83.9, 89.5</b>	<b>88.5% (532); 85.7, 91.0</b>
<b>CR</b>	<b>23.8% (143); 20.4, 27.4</b>	<b>19.5% (117); 16.4, 22.9</b>
PR	63.1% (379)	69.1% (415)
SD	1.3% (8)	0.5% (3)
PD	4.0% (24)	2.3% (14)
Not evaluable / missing	3.5% (21) / 4.3% (26)	4.0% (24) / 4.7% (28)

\*INV-assessed using the Revised Response Criteria for Malignant Lymphoma (Cheson BD, et al. J Clin Oncol 2007)

INV: investigator

Marcus et al NEJM 377:1331, 2017

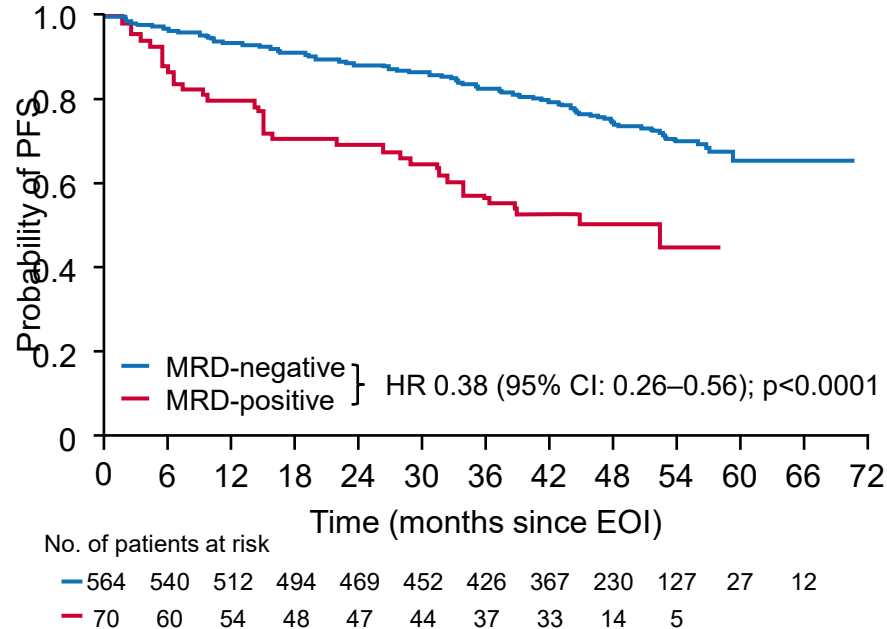
## PFS by MRD status at MI\*



- PFS was improved in patients who were MRD-negative
  - versus those who were MRD-positive

Data cut-off: 12 February 2018. \*Patients are excluded if they have missing MRD assessment at MI or their PFS event occurred prior to MRD assessment at MI. MI MRD results are only in PB, and therefore are less sensitive than BM. Results combine patients treated with both G and R.

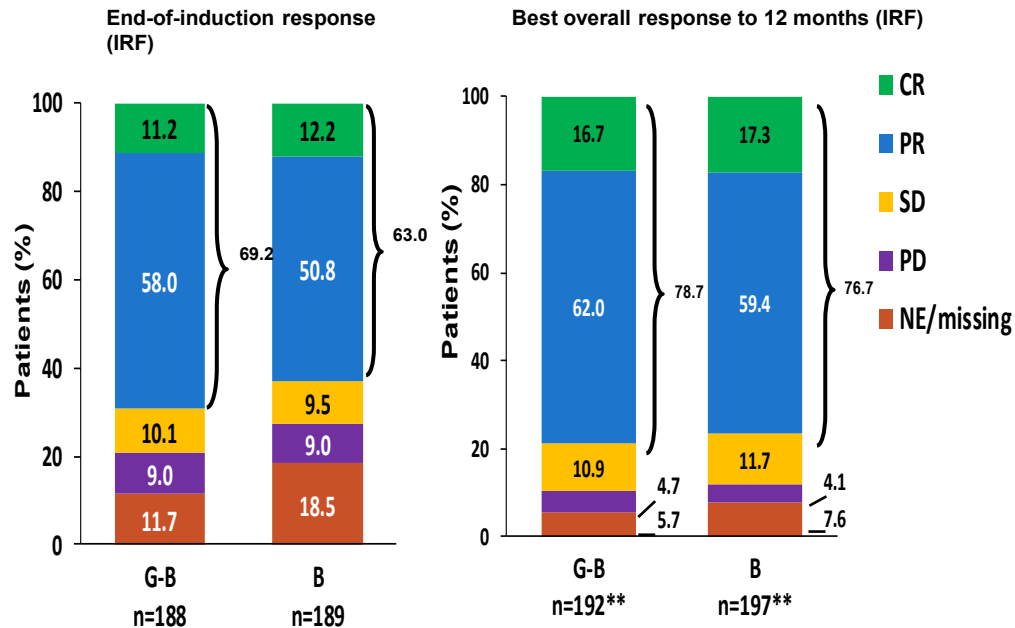
## PFS by MRD status at EOI\*



- PFS was improved in patients who were MRD-negative
  - versus those who were MRD-positive

\*Combined results for all patients treated with G and R.

# GADOLIN: Response to therapy



- 19 patients still in induction (G-B, n=6; B, n=13)\*

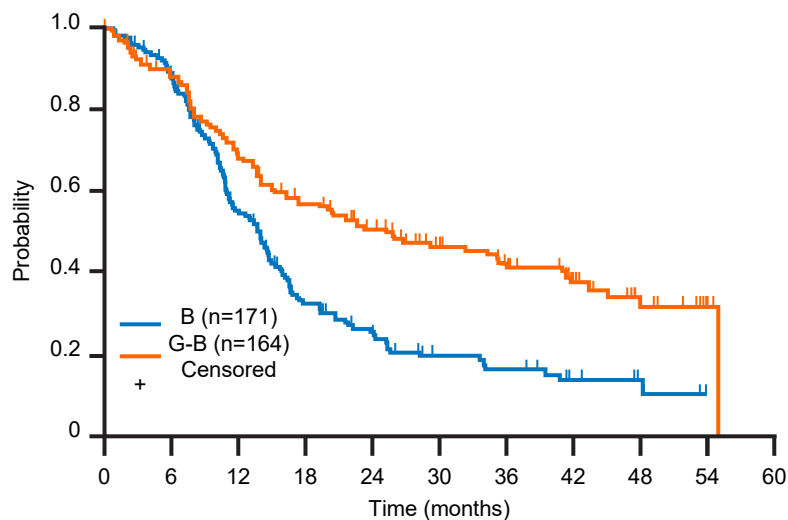
\* Patients ongoing in induction therapy are excluded from analysis. Patients with end of induction response assessment performed >60 days after last induction dose shown as missing.

\*\* Best overall response excludes ongoing patients who have not yet reached the first response assessment.  
IRF, independent radiology facility



# INV-assessed PFS in the FL population

Kaplan-Meier plot of INV-assessed PFS by treatment arm (FL)



No. of patients at risk

Time (months)	0	6	12	18	24	30	36	42	48	54	60
B (n=171)	171	141	84	45	32	18	15	9	4	0	0
G-B (n=164)	164	138	107	86	67	49	40	26	15	4	0

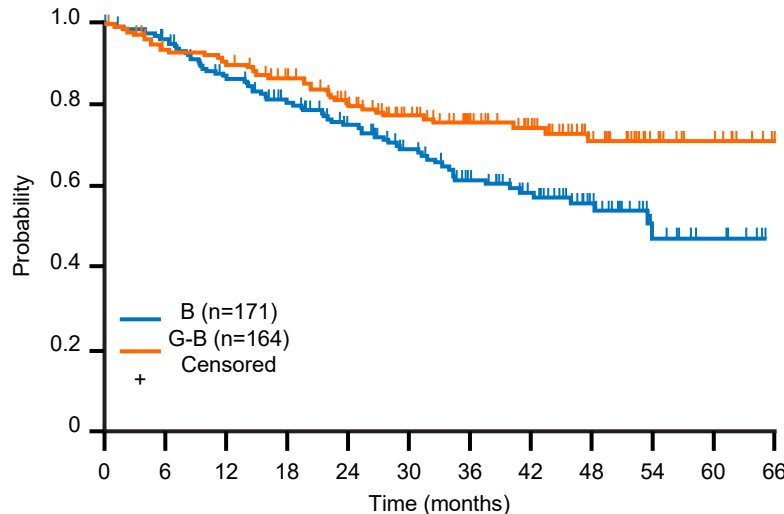
	G-B, n=164	B, n=171
Pts with event, n (%)	93 (56.7)	125 (73.1)
Median PFS (95% CI), mo	25.3 (17.4, 36.0)	14.0 (11.3, 15.3)
HR (95% CI), p-value*	0.52 (0.39, 0.69), p<0.0001	

Median follow-up (FL): 31.2 months  
(vs 21.1 months in primary analysis)

\*Stratified analysis; stratification factors: prior therapies, refractory type, geographical region

# OS in the FL population

Kaplan-Meier plot of OS by treatment arm (FL)



No. of patients at risk

Time (months)	0	6	12	18	24	30	36	42	48	54	60	66
B (n=171)	171	159	137	122	103	84	65	49	32	13	7	0
G-B (n=164)	164	147	141	129	111	90	71	56	38	20	12	0

NR, not reached

\*Stratified analysis; stratification factors: prior therapies, refractory type, geographical region

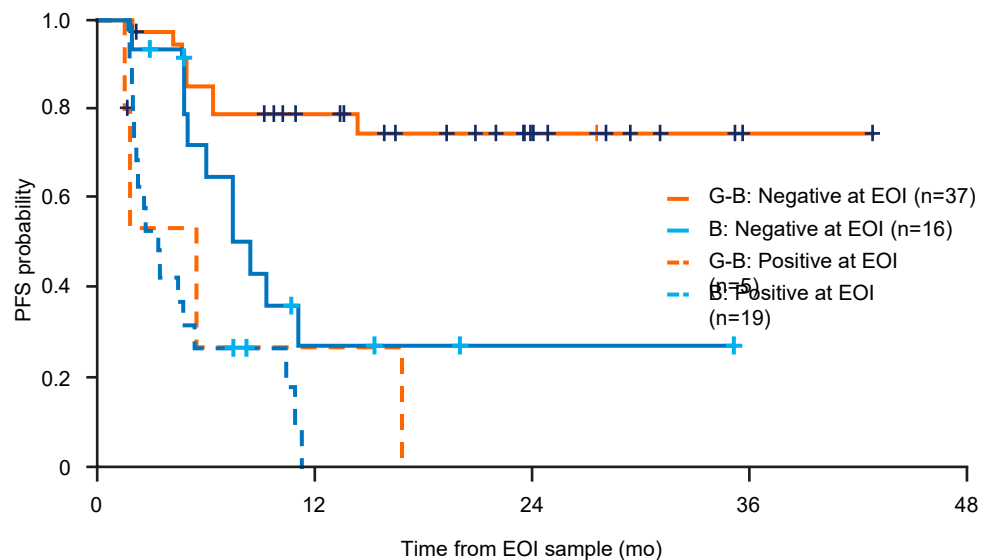
	G-B, n=164	B, n=171
Pts with event, n (%)	39 (23.8)	64 (37.4)
Median OS (95% CI), mo	NR (NR, NR)	53.9 (40.9, NR)
HR (95% CI), p-value*	0.58 (0.39, 0.86), p=0.0061	

Median follow-up (FL): 31.2 months  
(vs 21.1 months in primary analysis)

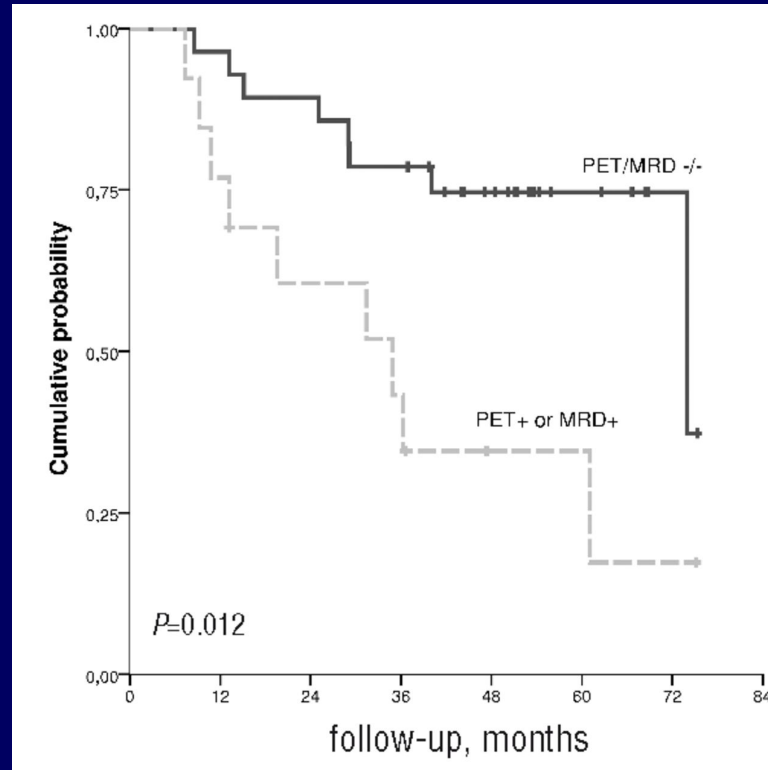
Cheson et al, JCO 36:2259,2018

# MRD status at EOI and association with PFS in the FL population<sup>1</sup>

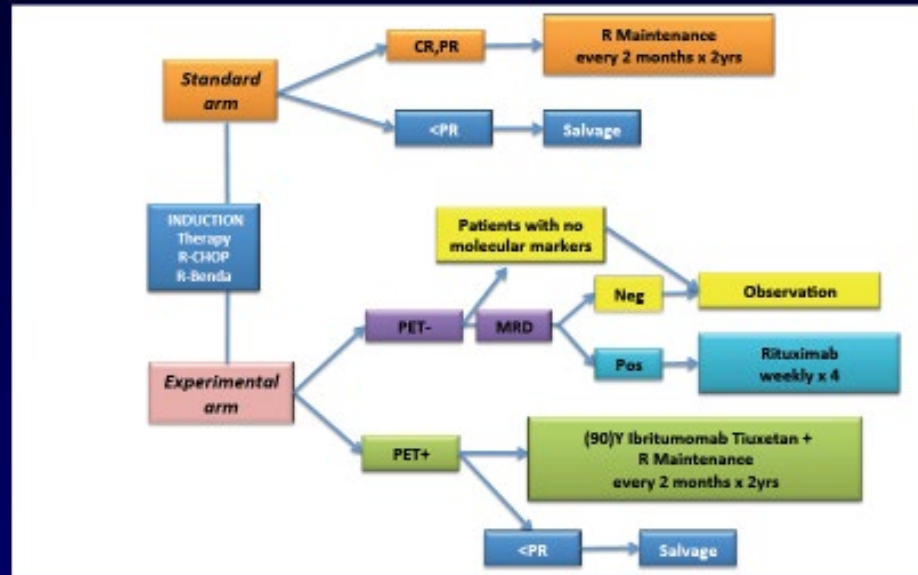
*Kaplan-Meier plot of PFS by MRD status at EOI and by treatment arm in the FL population*



# PFS in FOLLO5 according to combination of PET and MRD results.

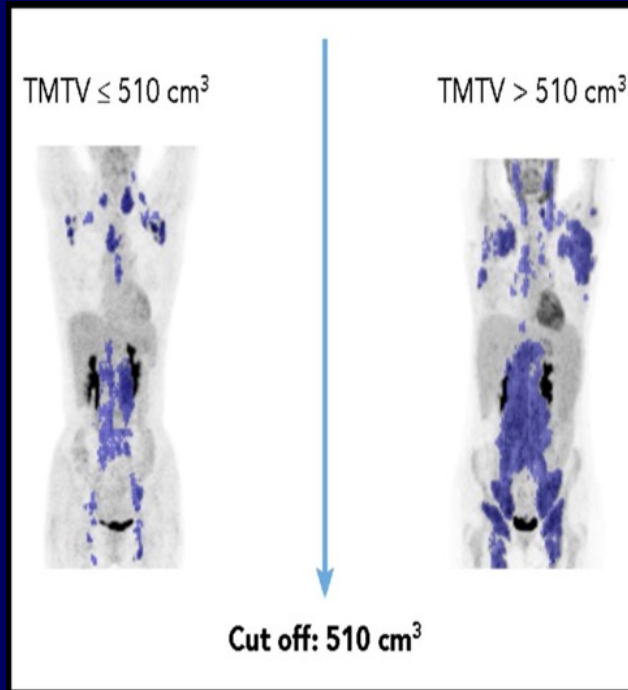


# Risk Adapted Strategies:FOLLO-12



*Treatment As It Will Be  
Done*

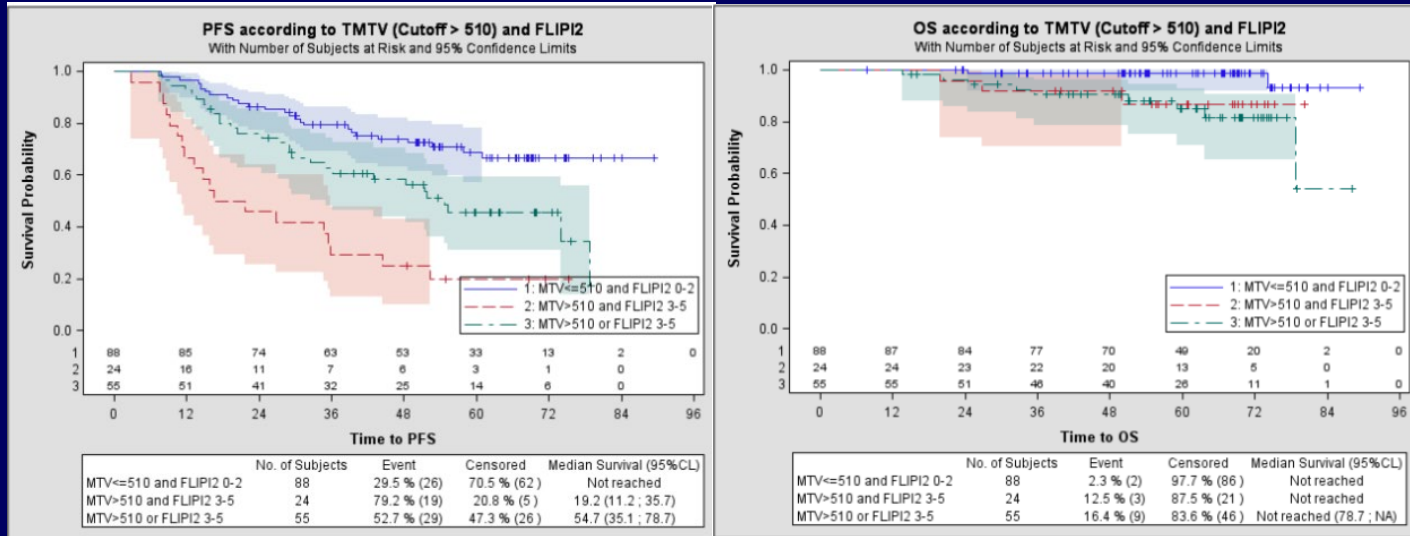
# Macroscopic tumor burden on PET scan



TMTV : Total metabolic tumor volume

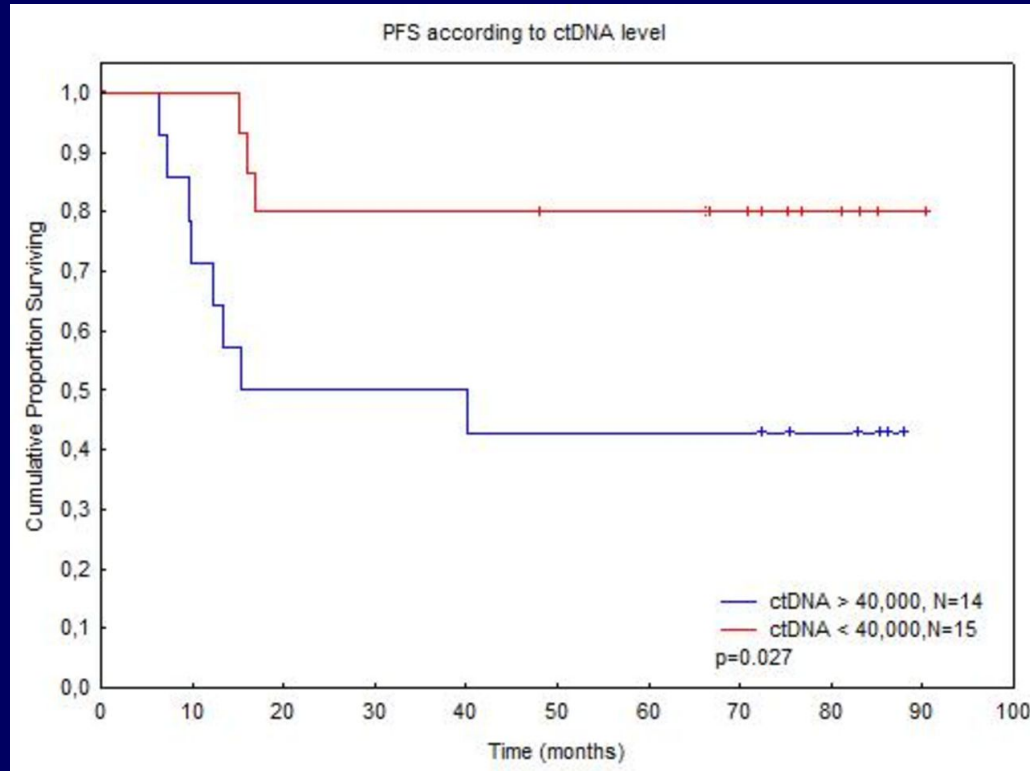
TMTV = sum total of all metabolically active lesions.

# Pre-Treatment TMTV in FL



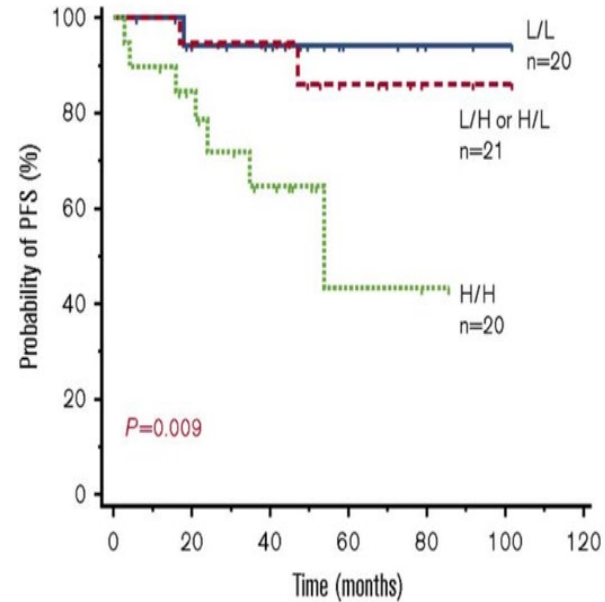


# PFS of FL according to the level of pre-tx circulating tumor DNA (Clonoseq)



# Pretreatment TMTV + ctDNA

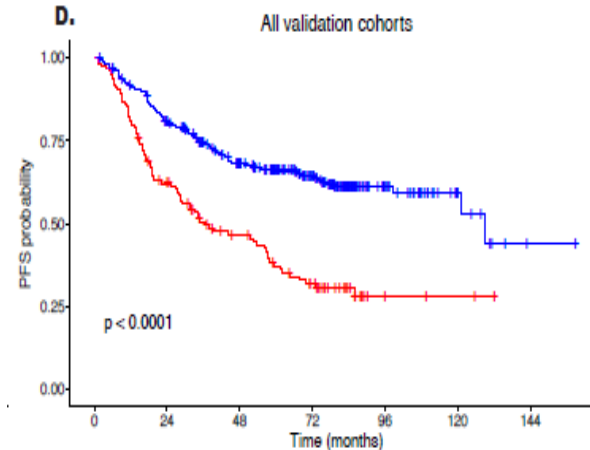
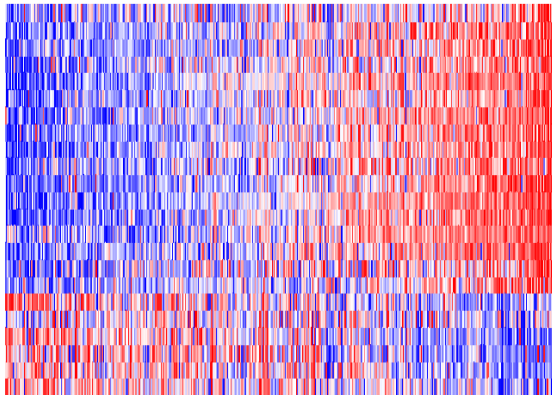
- Tumor burden assessment in two clinical cohorts with FL diagnosed between 2007 and 2014.
- High TMTV defined as  $TMTV > 510\text{cm}^3$
- High ctDNA defined as  $>2550\text{Eqg/mL}$  (equivalent genome per milliliter)
- L/L versus H/H 4 year PFS  $\text{शुद्ध vs पड़प}$ .



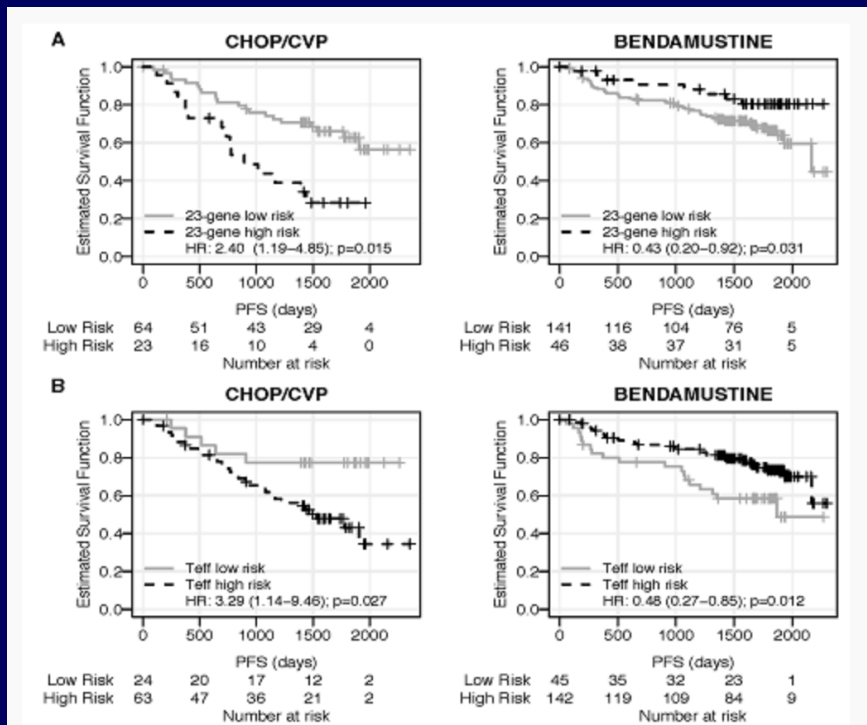
# Perspectives

To better personalize treatments in pts with follicular lymphoma, we need to better characterize upfront those with a high risk of treatment failure:

- new clinical index based on b2M and BM (Bachy et al., ASH 2018 abstract 413)
- GEP biological stratification using a simple digital expression test (Huet et al., Lancet Oncology, 19:549, 2018<sup>1</sup>)

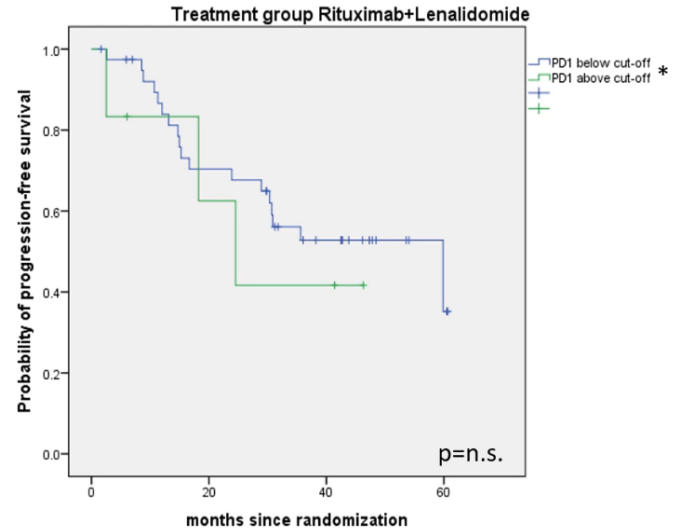
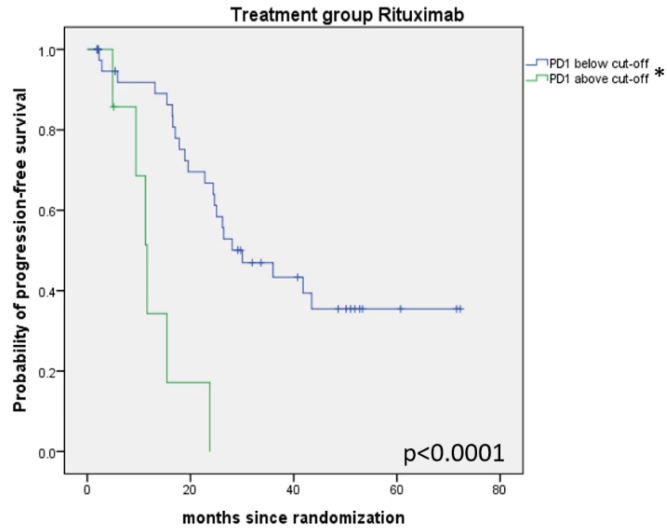


# PFS in GALLIUM By Gene Signatures



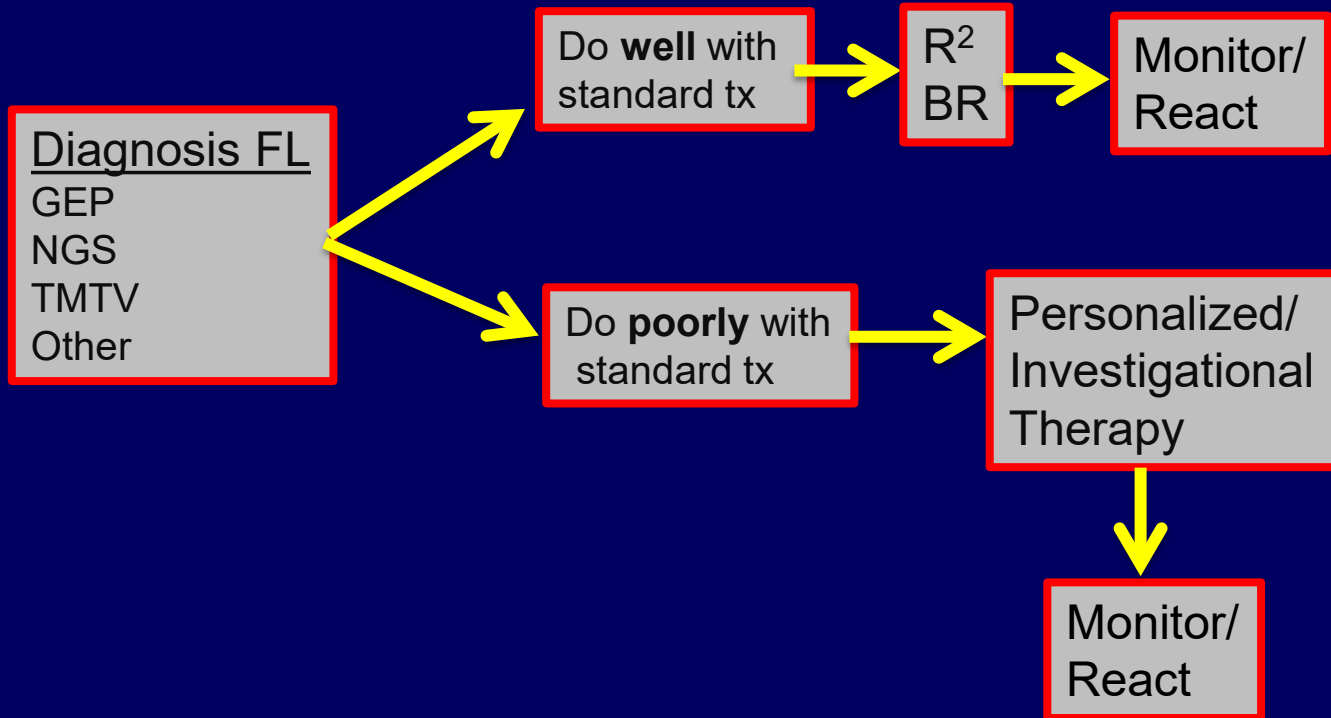
# SAKK35/10 Study

## Lenalidomide overcomes the prognostic importance of PD1<sup>+</sup> TIL



\*825 cells/mm<sup>2</sup>

# Future Treatment Strategy: Anticipatory Risk-Adaptation



# Potential Therapies for Risk-Adapted Therapy in FL

- $R^2$
- Tazemetostat
- Venetoclax
- Tafasitamab
- CART-cell
- TBD

# Conclusions

- Treatment the way we do it now - *Empiric*
- Treatment as we could do it now – *Reactive*
  - Posttreatment PET-CT
  - Interim MRD
  - Posttreatment MRD +/- PET
- Treatment as it will be done – *Proactive*
  - Pretreatment patient/tumor biology
  - Adaptive approach
  - Increase the *cure* of follicular/LG lymphoma