Lymphome Folliculaire
D'un ASH à un autre.....

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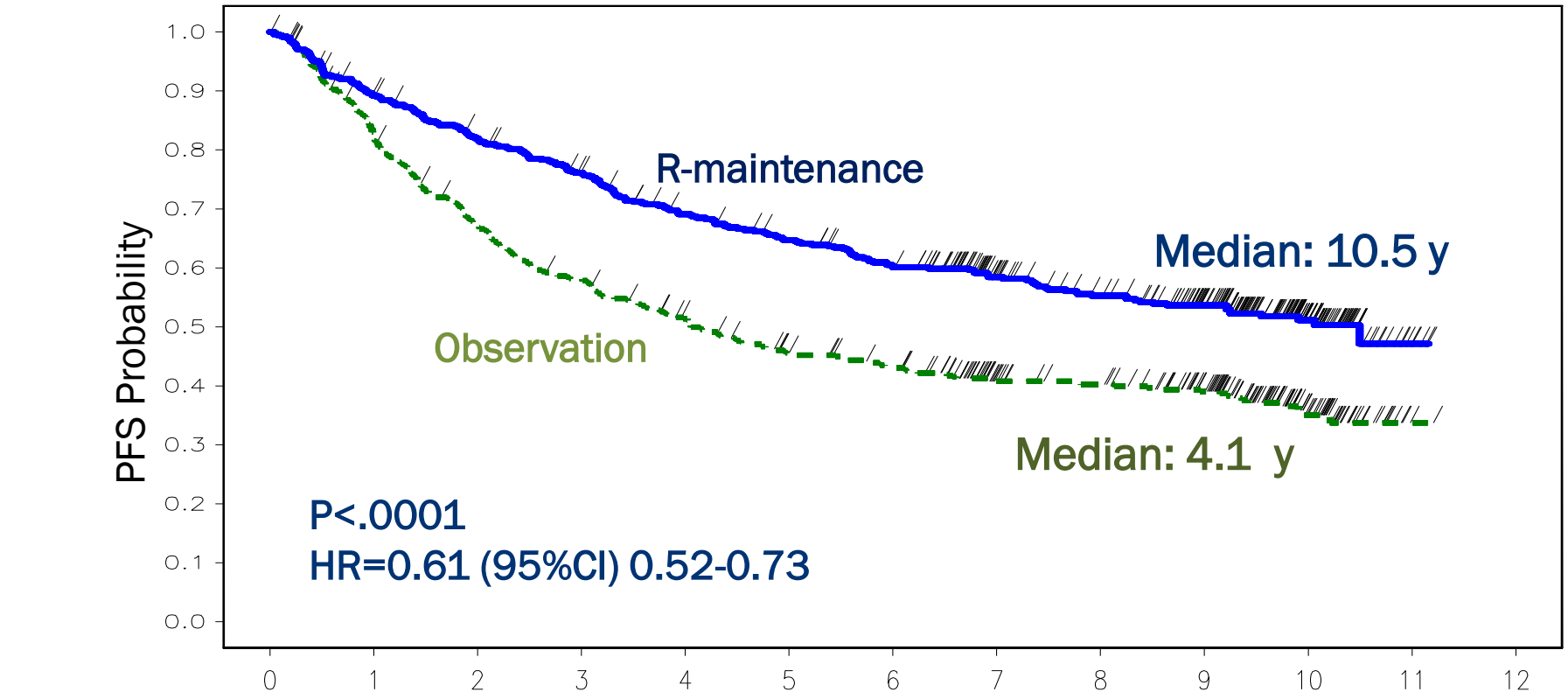
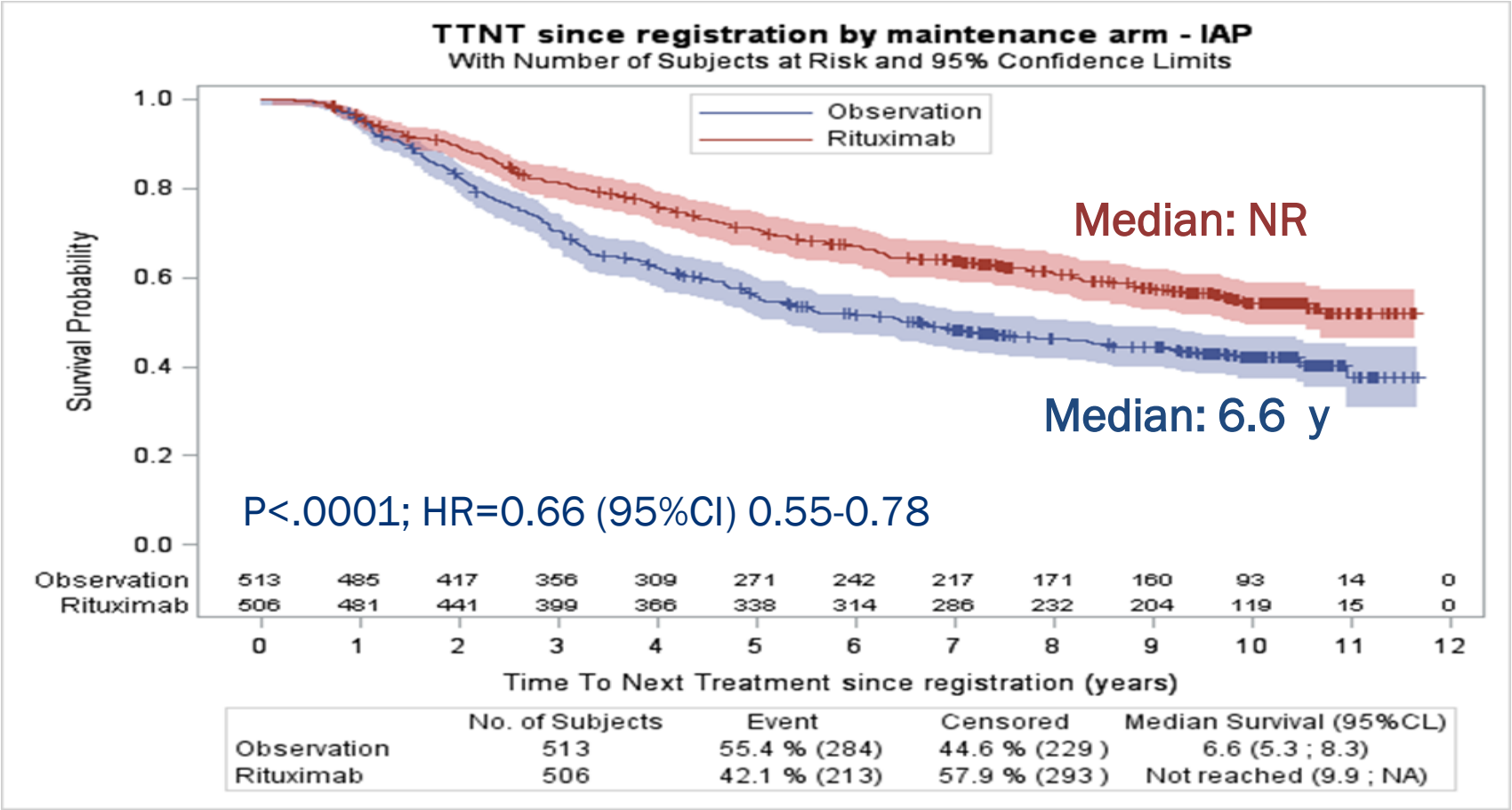
PRIMA: PFS From Randomization With Rituximab Maintenance vs Observation, 10 years FU from randomisation



No. left													
Observation	513	415	336	290	251	217	200	155	147	122	41	1	0
Rituximab	505	445	406	372	333	309	284	231	208	170	67	4	0

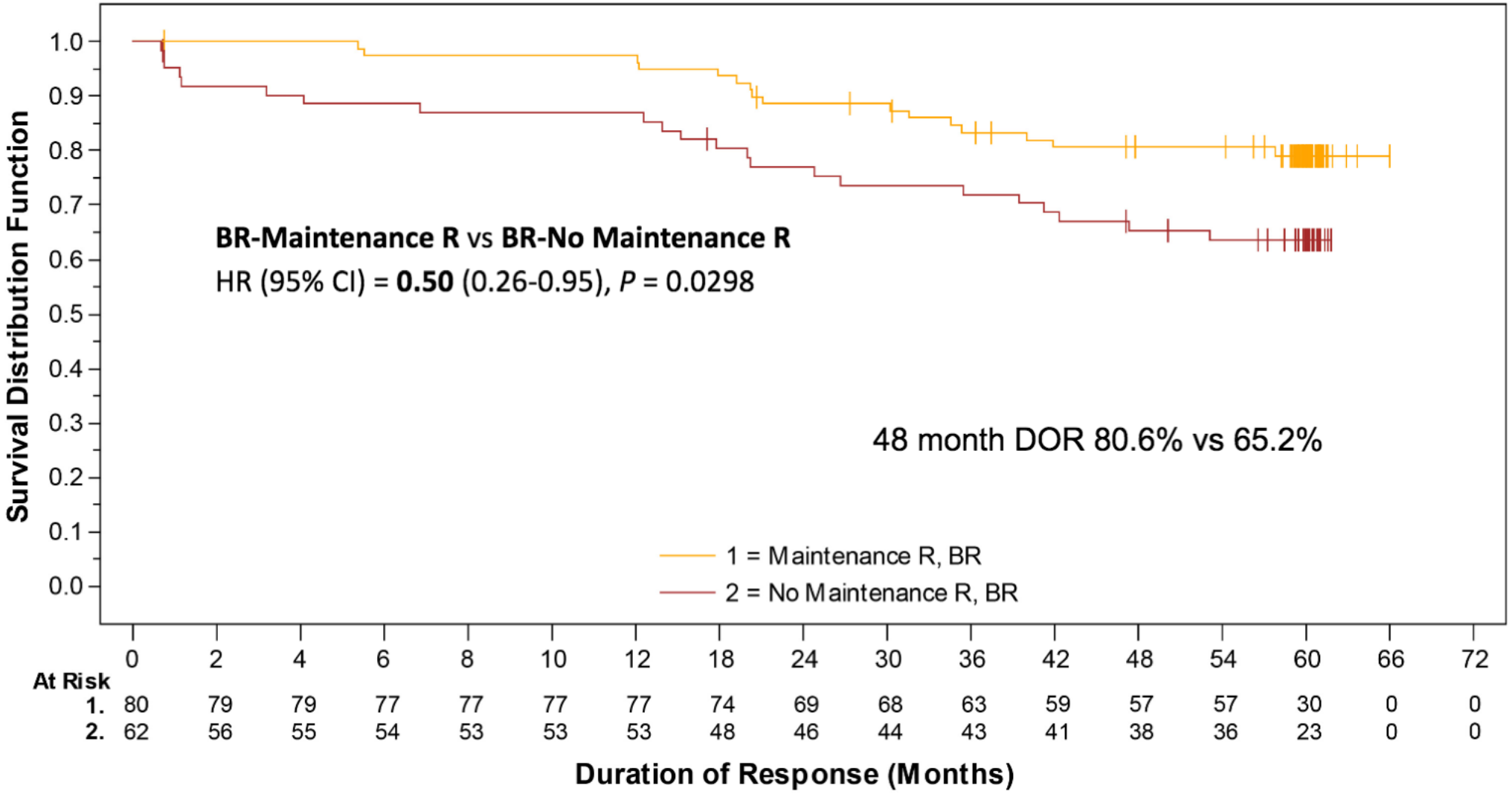
Salles G, et al. ASH. 2017.

PRIMA: Time To Next Treatment from randomisation



Salles G, et al. ASH. 2017.

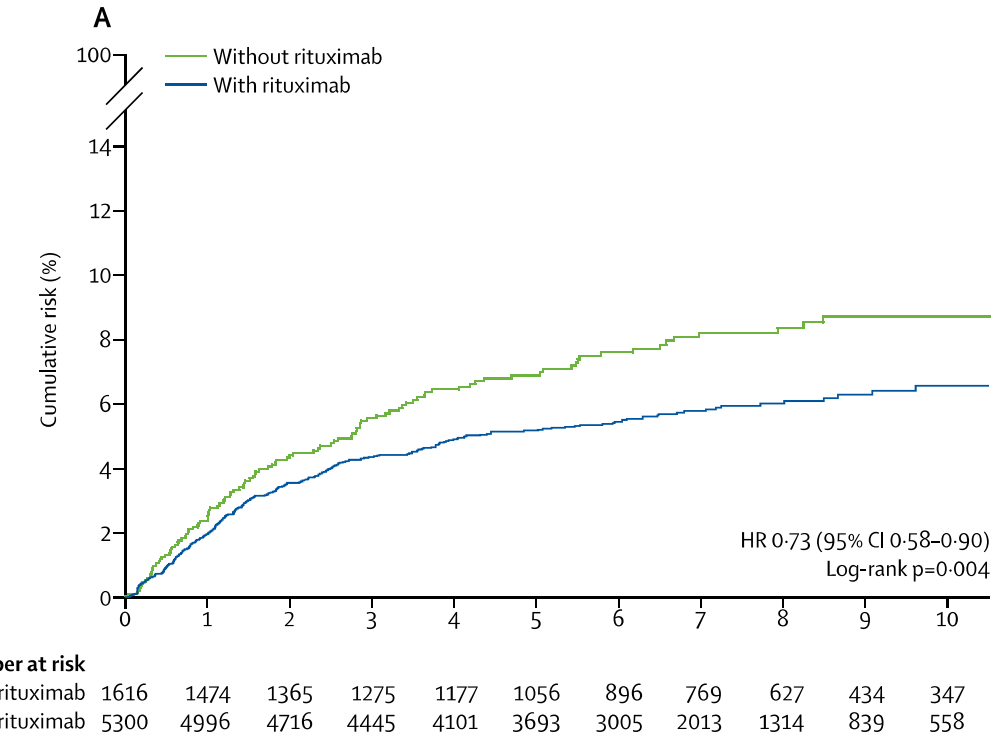
Duration of Response in FL*: BR



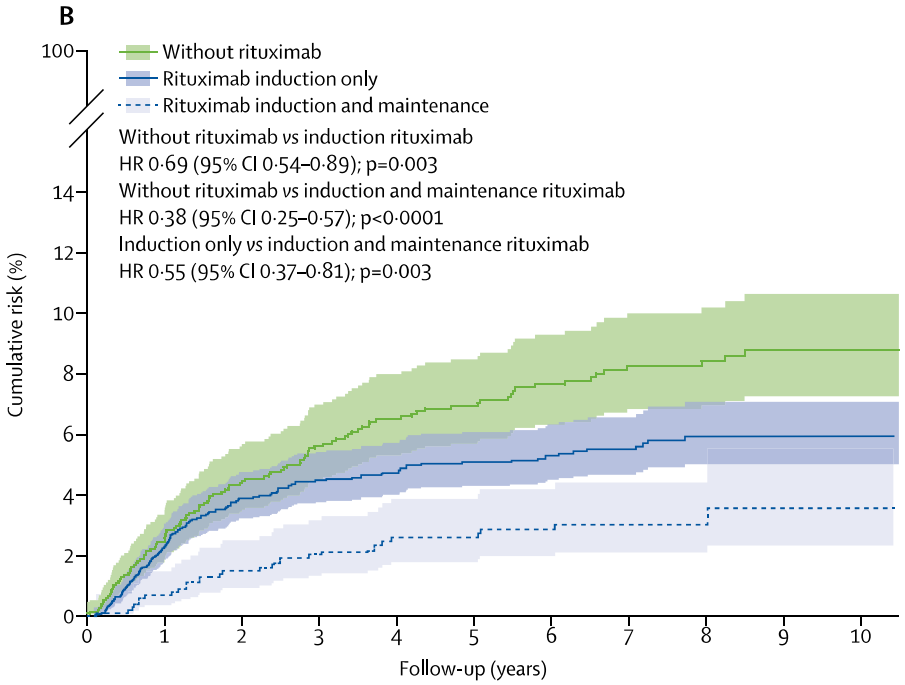
*FL patients with CR or PR.
B: bendamustine; CI: confidence interval; CR: complete response; FL: follicular lymphoma; HR: hazard ratio; PR: partial response; R: rituximab

Aristotle Study: Effect of Rituximab of HT risk and outcome

Risk of HT according to Rituximab use in 1L



Number at risk											
Without rituximab	1616	1474	1365	1275	1177	1056	896	769	627	434	347
With rituximab	5300	4996	4716	4445	4101	3693	3005	2013	1314	839	558

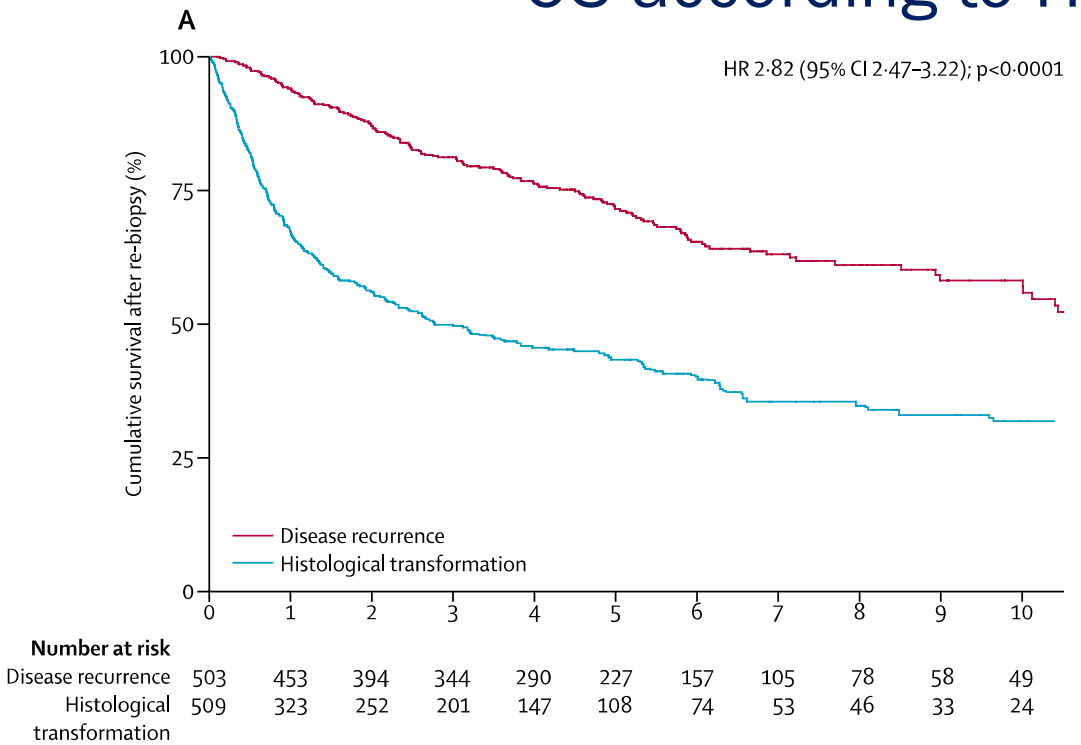


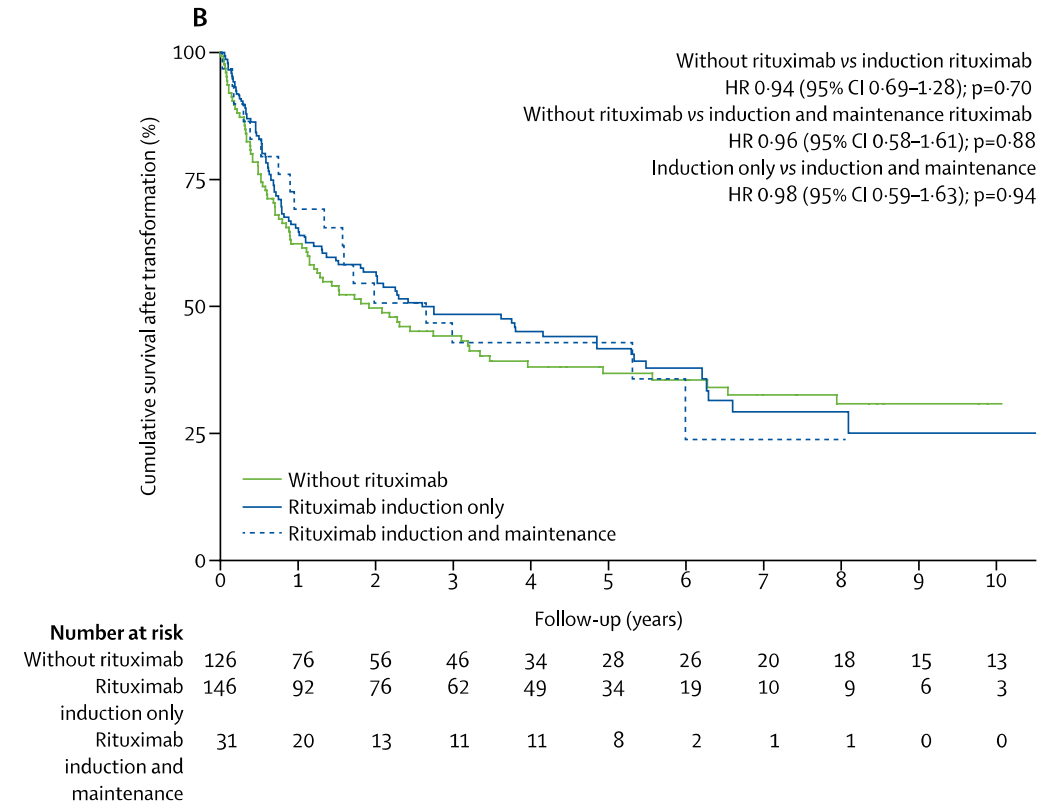
Number at risk											
Without rituximab	1616	1474	1365	1275	1177	1056	896	769	627	434	347
Rituximab induction only	2744	2549	2406	2293	2173	2018	1669	1119	723	494	348
Rituximab induction and maintenance	1022	1006	970	919	850	788	618	351	185	61	18

Frederico M et al. Lancet Hematol. 2018; 5: 359-67

Aristotle Study: Effect of Rituximab of HT risk and outcome

OS according to HT and Rituximab use in 1L



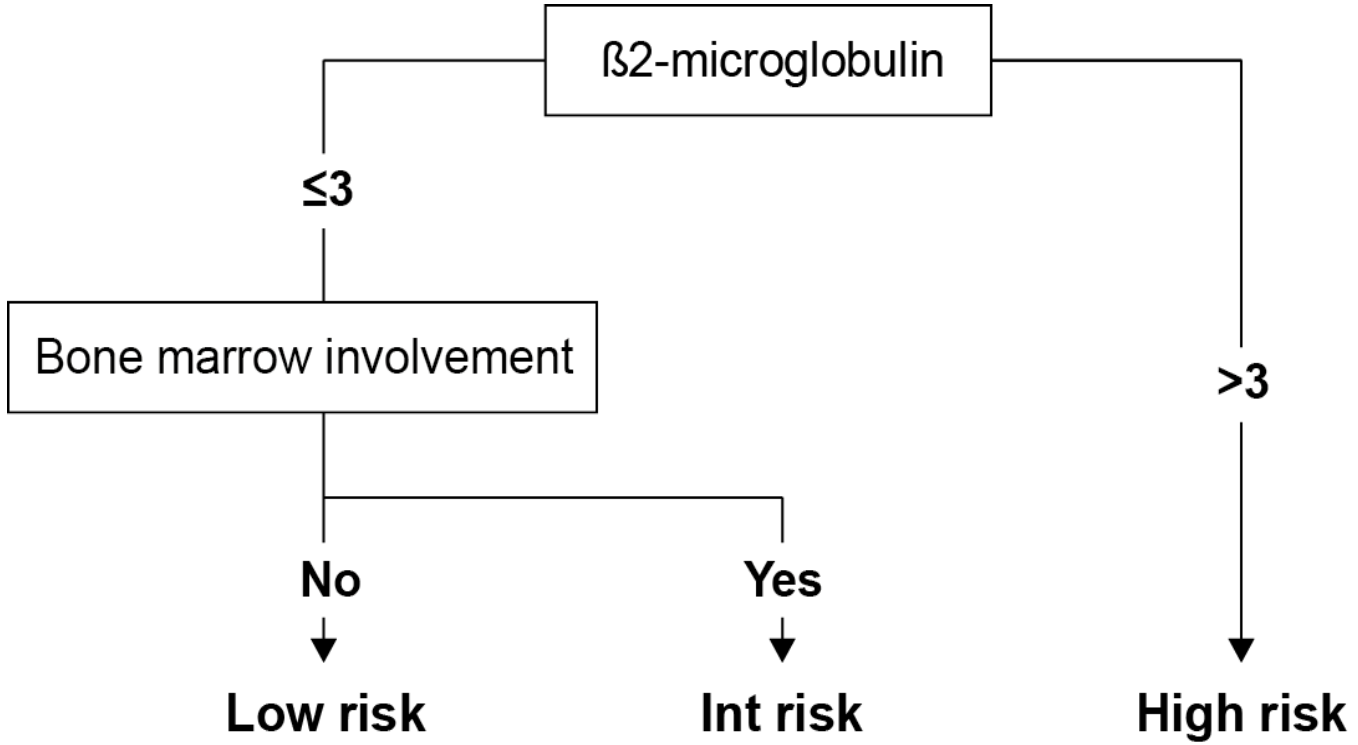


Frederico M et al. Lancet Hematol. 2018; 5: 359-67

Discovery and Validation of a Simplified Scoring System (the PRIMA-Prognostic Index) in *De Novo* Follicular Lymphoma Treated with Immunochemotherapy

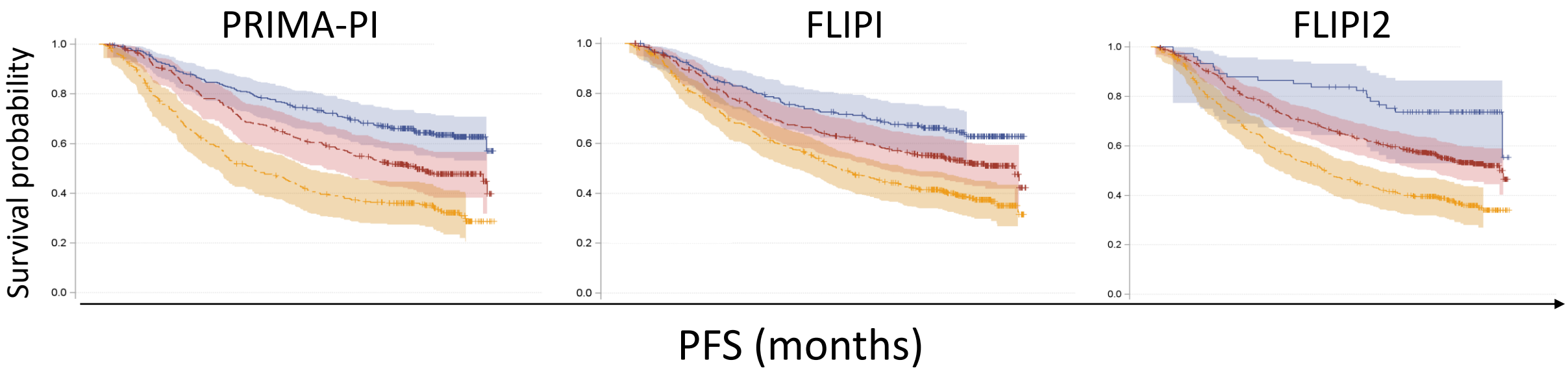
Emmanuel Bachy, Matthew J Maurer, Thomas M Habermann, Benedicte Gelas Dore, Delphine Maucort-Boulch, Jane Estell, E. Van Den Este, Reda Bouabdallah, Andrew L Feldman, Joan Bargay, Alain Jacques Delmer, Susan L Slager, Maria Gomes Silva, Olivier Fitoussi, David Belada, Herve Maisonneuve, Tanin Intragumtornchai, Stephen M. Ansell, Thierry Lamy, Peggy Dartigues-Cuillères, Brian K Link, John F Seymour, James R. Cerhan and Gilles Salles

PRIMA-prognostic index (PRIMA-PI)

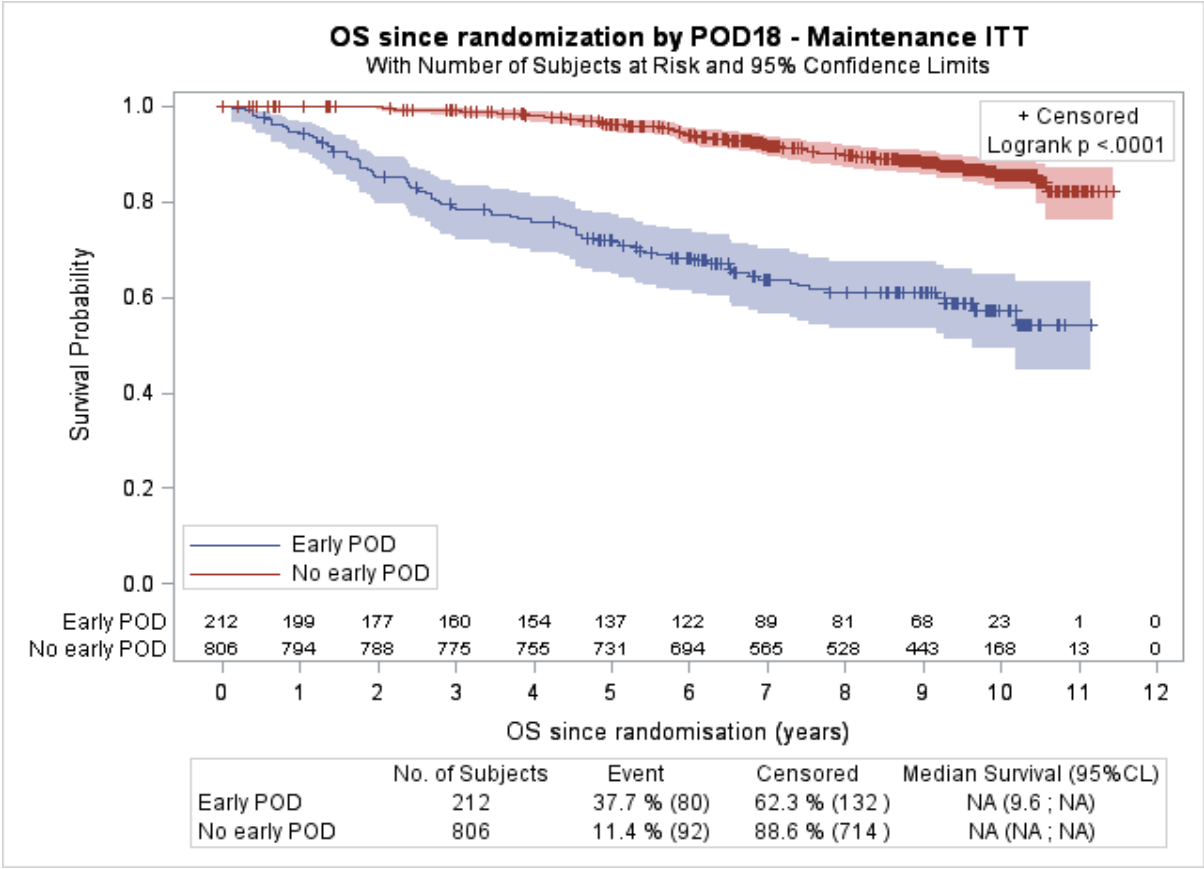


PRIMA-PI, FLIPI and FLIPI2 comparison

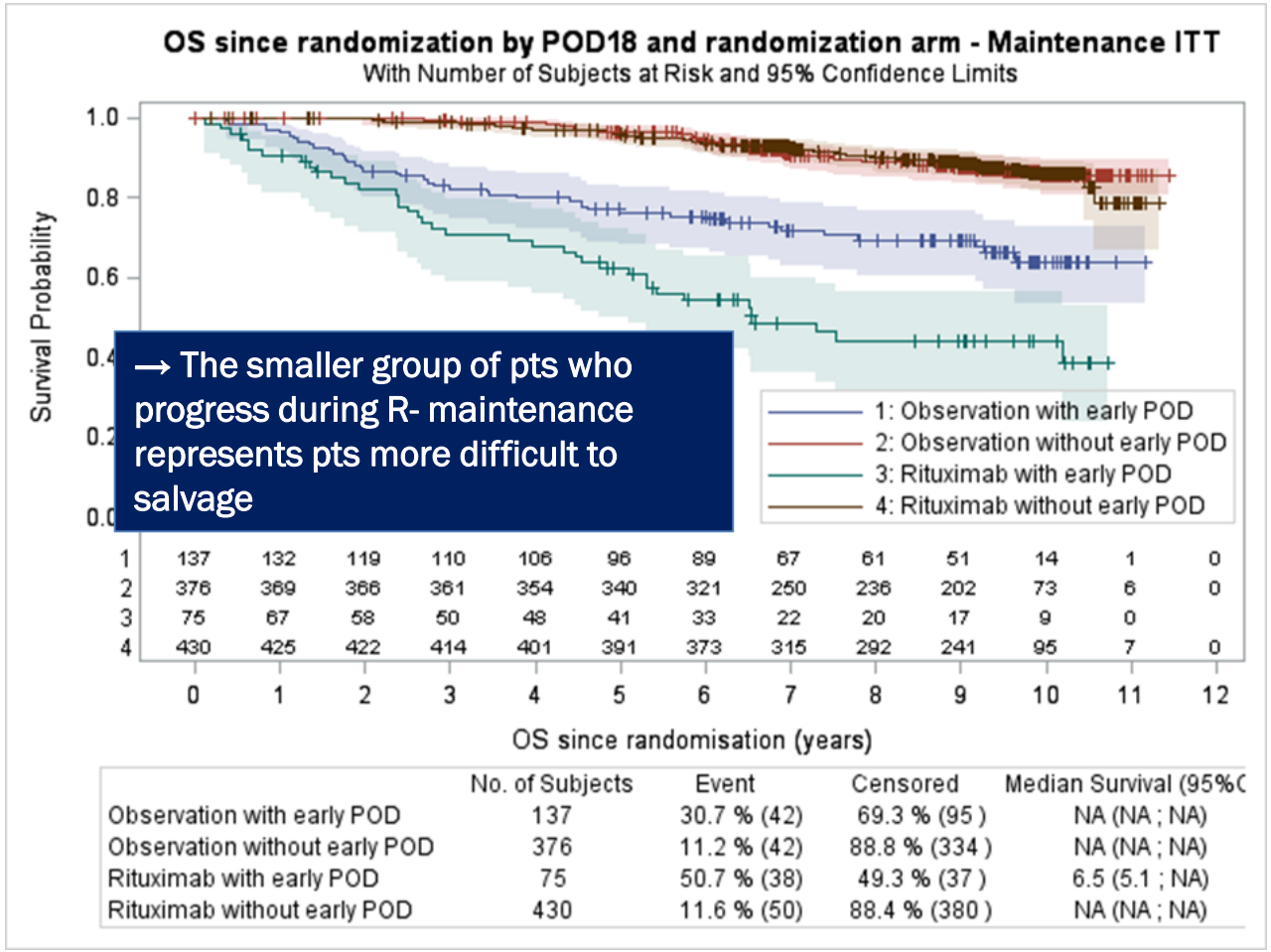
	PRIMA cohort					
	PRIMA-PI		FLIPI		FLIPI2	
	N (%)	5-year PFS % (95% CI)	N (%)	5-year PFS % (95% CI)	N (%)	5-year PFS % (95% CI)
Low	352 (34)	**69** (64-73)	238 (21)	**68** (62-74)	74 (7)	**75** (63-83)
Intermediate	346 (34)	**55** (49-60)	405 (36)	**58** (53-62)	619 (54)	**60** (56-63)
High	327 (32)	**37** (32-42)	487 (43)	**44** (38-48)	442 (39)	**41** (36-46)



POD24 in PRIMA study



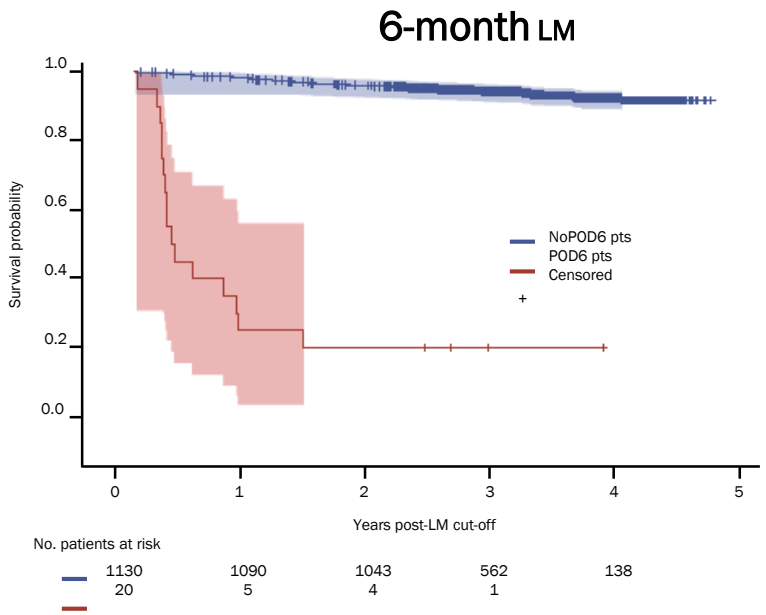
	No. of Subjects	Event	Censored	Median Survival (95%CL)
Early POD	212	37.7 % (80)	62.3 % (132)	NA (9.6 ; NA)
No early POD	806	11.4 % (92)	88.6 % (714)	NA (NA ; NA)

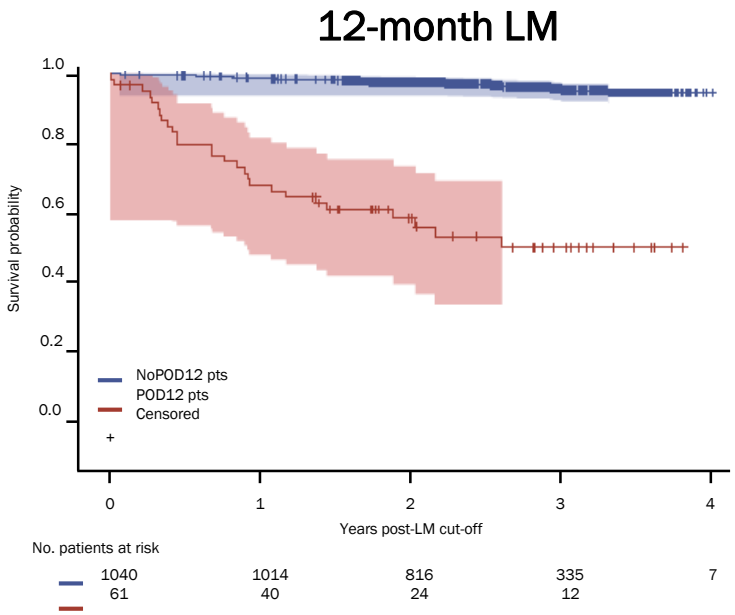


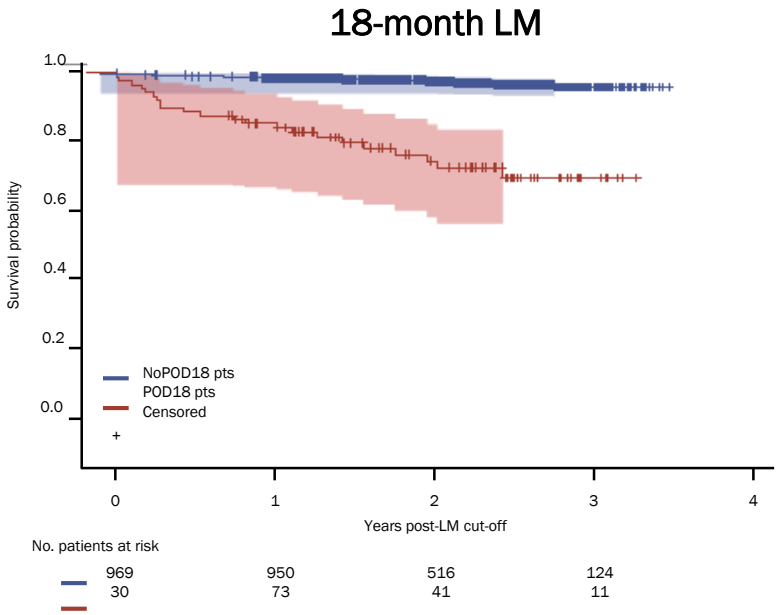
	No. of Subjects	Event	Censored	Median Survival (95%C
Observation with early POD	137	30.7 % (42)	69.3 % (95)	NA (NA ; NA)
Observation without early POD	376	11.2 % (42)	88.8 % (334)	NA (NA ; NA)
Rituximab with early POD	75	50.7 % (38)	49.3 % (37)	6.5 (5.1 ; NA)
Rituximab without early POD	430	11.6 % (50)	88.4 % (380)	NA (NA ; NA)

Salles G, *et al. ASH 2017*.

Early POD is associated with worst prognosis







OS at 2 years post-LM:
20% POD6 vs 95.8% noPOD6

OS at 2 years post-LM:
58.4% POD12 vs 97.6% noPOD12

OS at 2 years post-LM:
76.5% POD18 vs 97.8% noPOD18

Launonen A, *et al*. *ASH* 2017;

POD24 in GALLIUM study

	G + chemo (n=601)	R + chemo (n=601)
All PFS events at 24 months	**71 (12 %)**	**107 (18 %)**
All POD events at 24 months*	**57 (9 %)**	**98 (16 %)**
Deaths not due to PD†	14 (2 %)	9 (1 %)
2-year cumulative incidence of POD24 events accounting for non-PD deaths (95% CI)	0,10 (0,08 – 0,12)	0,17 (0,14 – 0,20)
Relative risk reduction for POD24 events, G-chemo vs R-chemo (Cox regression‡), % (95% CI)	**46,0 % (25,0 - 61,1)**	
Absolute risk of PFS24 events (in the 24 months after randomization), % (95% CI)	12,5 (10,1 – 15,6)	18,9 (15,9 – 22,4)
Relative risk reduction for PFS24 events, G-chemo vs R-chemo, % (95% CI)	**33,9 % (12,8 – 49,8)**	

At 24 months after randomization, the relative risk reduction for POD24 events with G-chemo relative to R-chemo was 46% (95% CI, 25.0–61.1%)

All 155 pts had PD; †at 24 months after randomization, deaths from any cause in all FL pts had occurred in 26 pts (G-chemo) and 38 pts (R-chemo); ‡cause-specific Cox regression, censoring for non-PD deaths and stratified by chemotherapy regimen and FLIPI group.

Launonen A, *et al. ASH* 2017;

How to predict POD24 (FLASH)?

- Unfavorable Factors

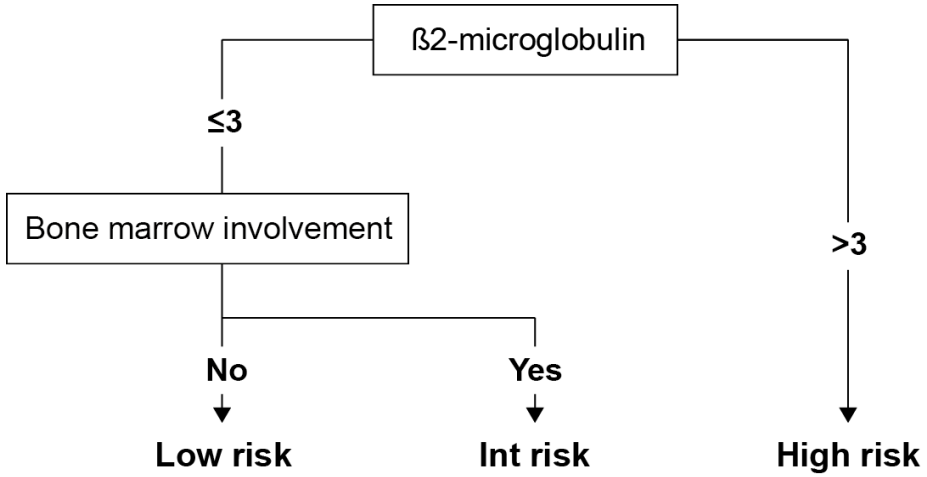
	OR (95% CI)	*P*
Male	1.30 (1.11-1.52)	0.0013
Performance status >3	1.59 (1.16-2.17)	0.0041
FLIPI High Risk (3-5)	2.94 (2.27-3.85)	< 0.0001
β2M >= 3	1.47 (1.25-1.75)	< 0.0001

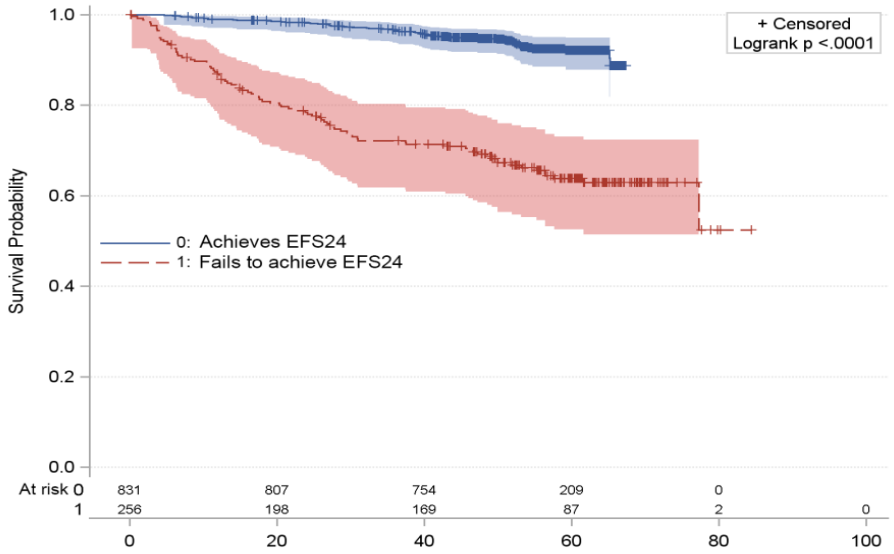
- Favorable Factors

	OR (95% CI)	*P*
Complete Response	0.439 (0.319-0.606	< 0.0001
Rituximab Exposed	0.494 (0.425-0.573)	< 0.0001
Anthracycline Exposed	0.567 (0.489-0.659)	< 0.0001

Casulo C, *et al. ASH 2017*

How to predict POD24 (PRIMA)?





	FLIPI, n (%)		Statistics	PRIMA-PI, n (%)		Statistics
	Achieved EFS24	Failed to achieve EFS24		Achieved EFS24	Failed to achieve EFS24	
Low	200 (84)	38 (16)	χ^2=22.27 Φ_c=0.14 P=1.36*10^{-5}	303 (86)	49 (14)	χ^2=55.48 Φ_c=0.23 P=1.41*10^{-12}
Intermediate	319 (79)	86 (21)		272 (79)	74 (21)	
High	337 (69)	150 (31)		203 (62)	124 (38)	

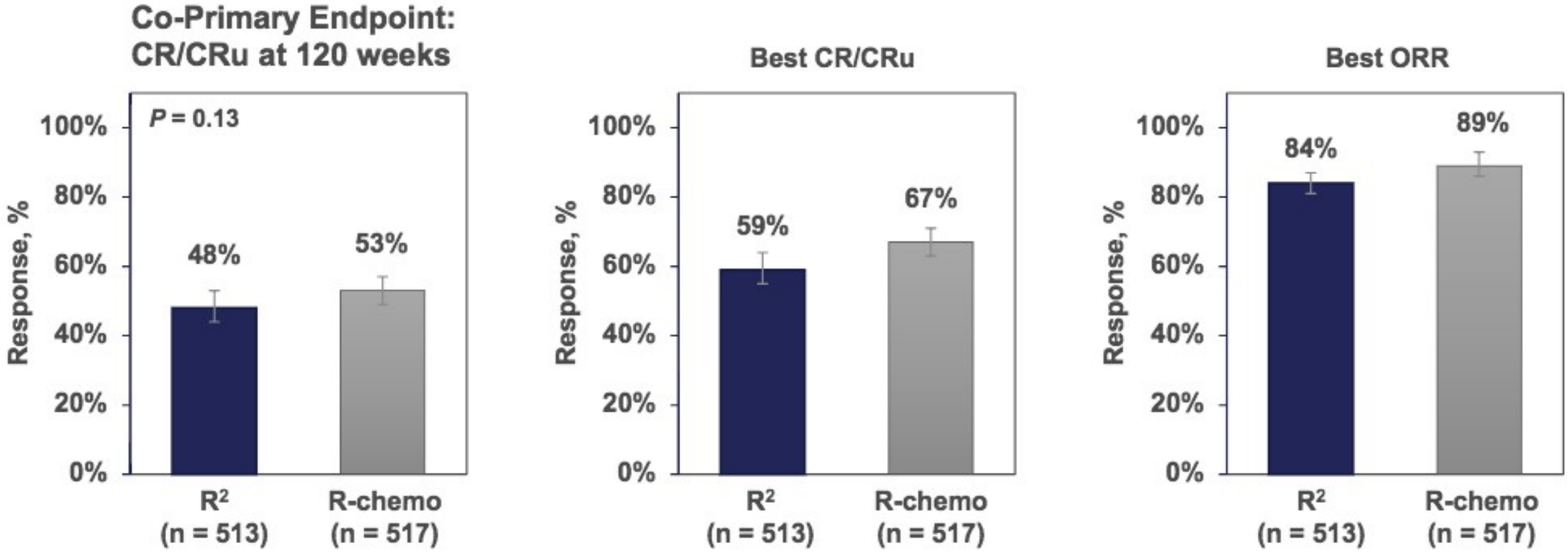
Bachy E , *et al. Blood 2018; 132: 49-58*.

RELEVANCE: PHASE III RANDOMIZED STUDY OF LENALIDOMIDE PLUS RITUXIMAB (R^2) VERSUS CHEMOTHERAPY PLUS RITUXIMAB, FOLLOWED BY RITUXIMAB MAINTENANCE, IN PATIENTS WITH PREVIOUSLY UNTREATED FOLLICULAR LYMPHOMA (FL)

Nathan H. Fowler, MD;[1*] Franck Morschhauser, MD[2*] (*co-primary authors); Pierre Feugier, MD;[3] Reda Bouabdallah, MD;[4] Hervé Tilly, MD;[5] M. Lia Palomba, MD;[6] Christophe Fruchart, MD;[7] Edward N. Libby, MD;[8] Rene-Olivier Casasnovas, MD;[9] Maria Gomes da Silva, MD, PhD;[10] Delphine Pranger, MD;[11] Pierre Zachée, MD;[12] Alejandro Martin Garcia-Sancho, MD, PhD;[13] Armando López Guillermo, MD;[14] Jean-François Larouche, MD;[15] Kiyoshi Ando, MD, PhD;[16] David Liu, MD, PhD;[17] Jianming Wang, PhD,[17] Luc Xerri, MD, PhD;[18] and Gilles A. Salles, MD, PhD;[19]
on behalf of the RELEVANCE Trial Investigators

[1]The University of Texas MD Anderson Cancer Center, Houston, TX; [2]University of Lille, CHU Lille, Lille, France; [3]Centre Hospitalier Universitaire Régional de Nancy, Service d'Hématologie, Vandoeuvre les Nancy, France; [4]Institut Paoli Calmettes, Marseille, France; [5]Centre Henri Becquerel, Rouen, France; [6]Memorial Sloan Kettering Cancer Center, New York, NY; [7]Institut d'Hématologie de Basse Normandie, Caen, France; [8]University of Washington, Seattle, WA; [9]CHU Le Bocage Service d'Hématologie Clinique, Dijon, France; [10]Instituto Português de Oncologia Lisboa Francisco Gentil (IPOLFG) Departamento de Hematologia, Lisboa, Portugal; [11]Grand Hôpital de Charleroi, Charleroi, Belgium; [12]ZNA Stuivenberg, Antwer, Belgium; [13]Hospital Universitario de Salamanca and IBSAL, CIBERONC, Salamanca, Spain; [14]Hospital Clinic de Barcelona, Barcelona, Spain; [15]CHU de Québec, Hôpital de l'Enfant-Jésus, Québec, Canada; [16]Tokai University Hospital, Kanagawa, Japan; [17]Celgene Corporation, Summit, NJ; [18]Departement de Bio-pathologie, Institut Paoli-Calmettes, Marseilles, France; [19]Hospices Civils de Lyon, Centre Hospitalier Lyon-Sud, University of Lyon, Pierre-Benite, France

RELEVANCE: RESPONSE BY IRC (ITT)

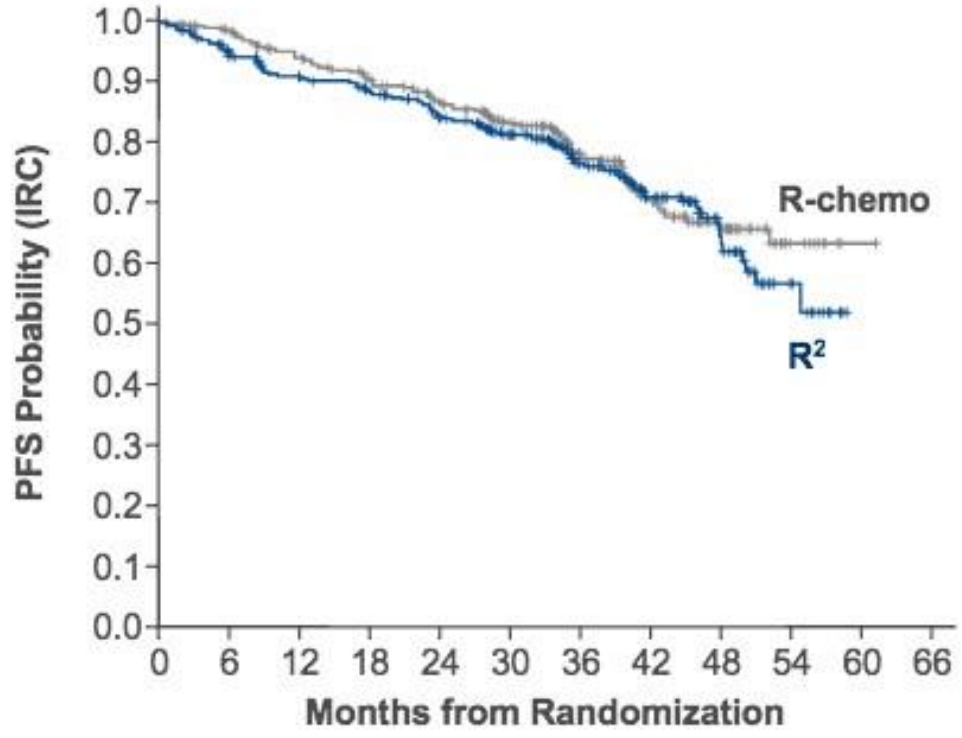


- 3-year DOR was 77% for R² vs 74% R-chemo (IRC)
- Investigator results were consistent with IRC

Data cut-off 31May2017.

RELEVANCE: INTERIM PFS BY IRC

Co-Primary Endpoint: Interim PFS (~50% events)



Number of Patients at Risk

R²	513	435	409	393	364	282	174	107	49	13	0	
R-chemo	517	474	446	417	387	287	175	109	51	14	1	0

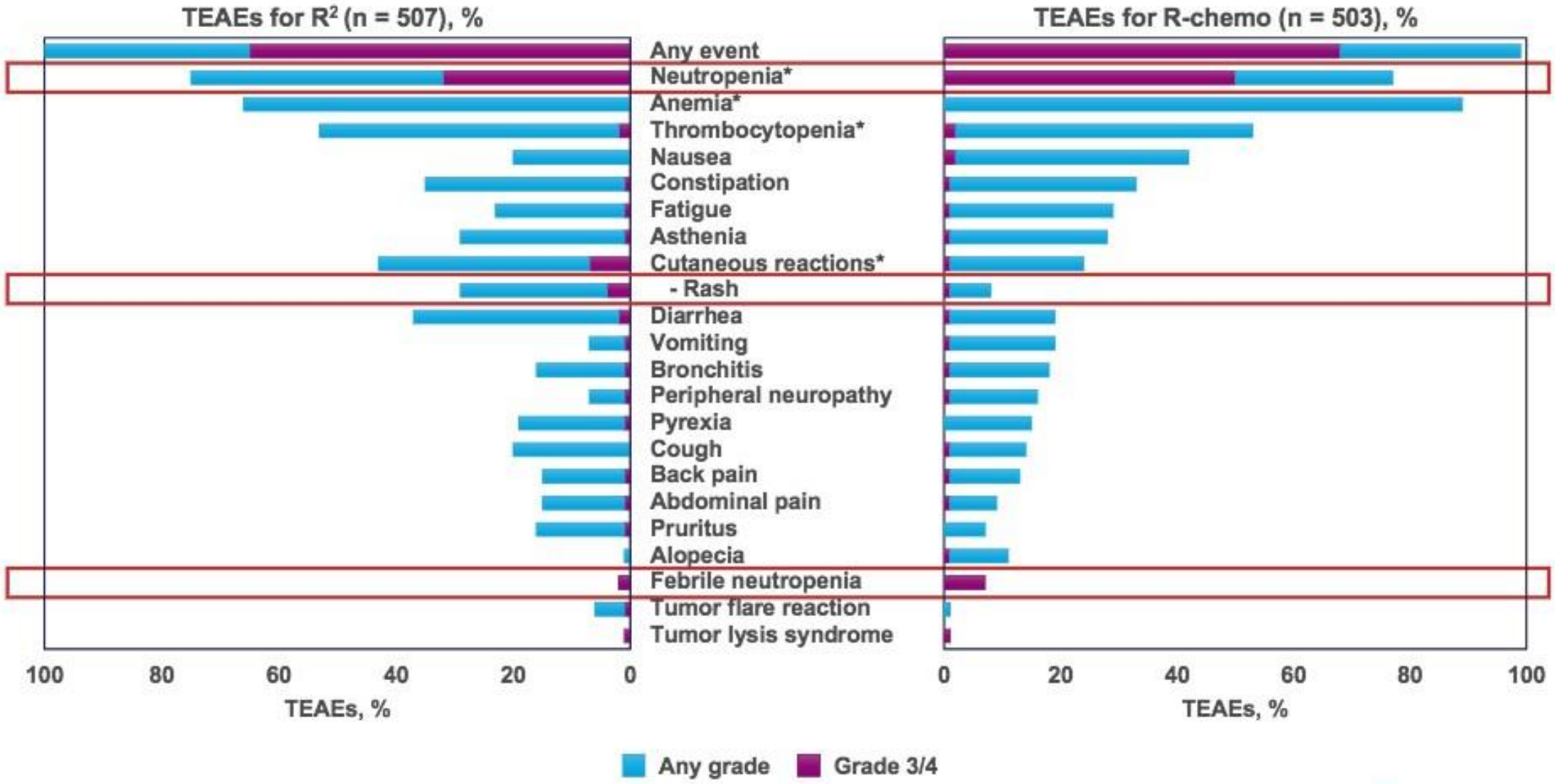
	R² (n = 513)	R-chemo (n = 517)
Events, n (%)	119 (23)	111 (21)
3-year PFS (95% CI)	77% (72%-80%)	78% (74%-82%)
HR (95% CI)	1.10 (0.85-1.43)	
P value	0.48	

- At a median follow-up of 37.9 months, interim PFS was similar in both arms

Data cut-off 31May2017.

RELEVANCE

RELEVANCE: TREATMENT-EMERGENT ADVERSE EVENTS

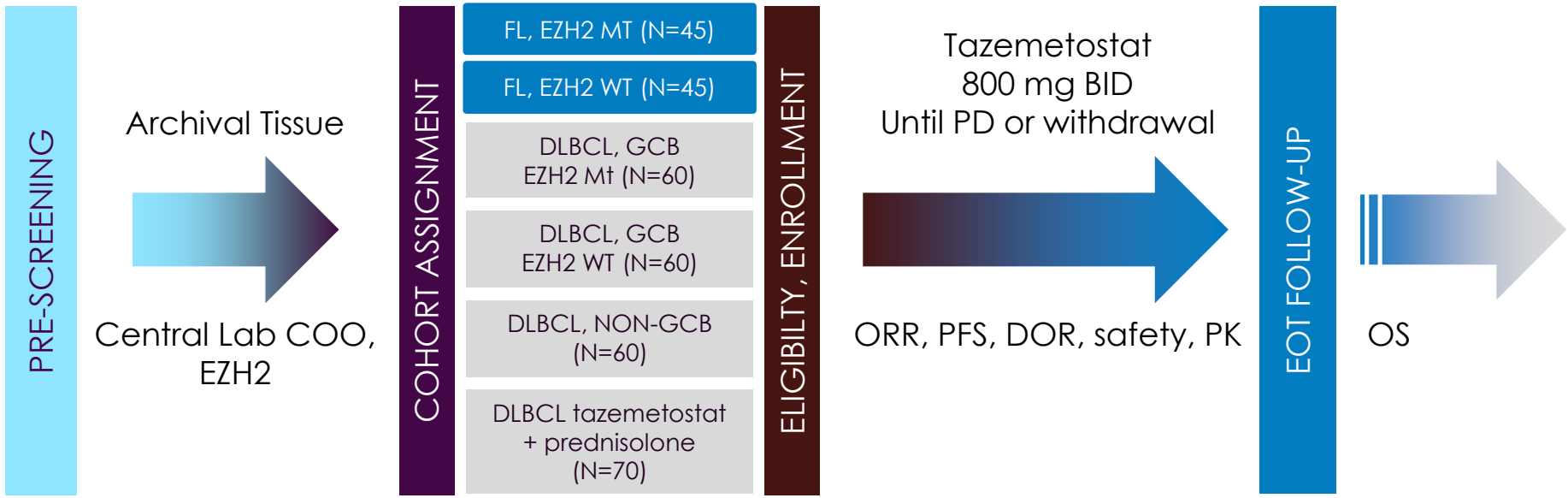


Data cut-off 31May2017. Includes any-grade TEAEs (≥15%) and select AEs of interest as assessed per NCI CTCAE v4.03.
*Hematologic AEs were based on laboratory tests; all anemia events were grade 1. Cutaneous reactions included preferred terms from skin and subcutaneous tissue disorders (including rash), gastrointestinal disorders, general disorders and administration site conditions, infections and infestations, and reproductive system and breast disorders.

RELEVANCE

TAZEMETOSTAT PHASE 2 NHL STUDY DESIGN

- Global, multi-center, open-label study in 6 cohorts of patients with R/R FL or DLBCL
  - Patients prospectively assigned to cohorts according to *EZH2* mutational status
    - **cobas®** *EZH2* Mutation Test (in development, Roche Molecular Systems)
  - ≥2 prior therapies
- Primary endpoint: objective response rate (ORR)
  - Secondary efficacy endpoints: progression-free survival (PFS), duration of response (DOR), safety and tolerability
  - Objective response assessed by IWG-NHL criteria (Cheson 2007)
    - Restaging every 8 weeks for 6 cycles, then every 12 weeks thereafter

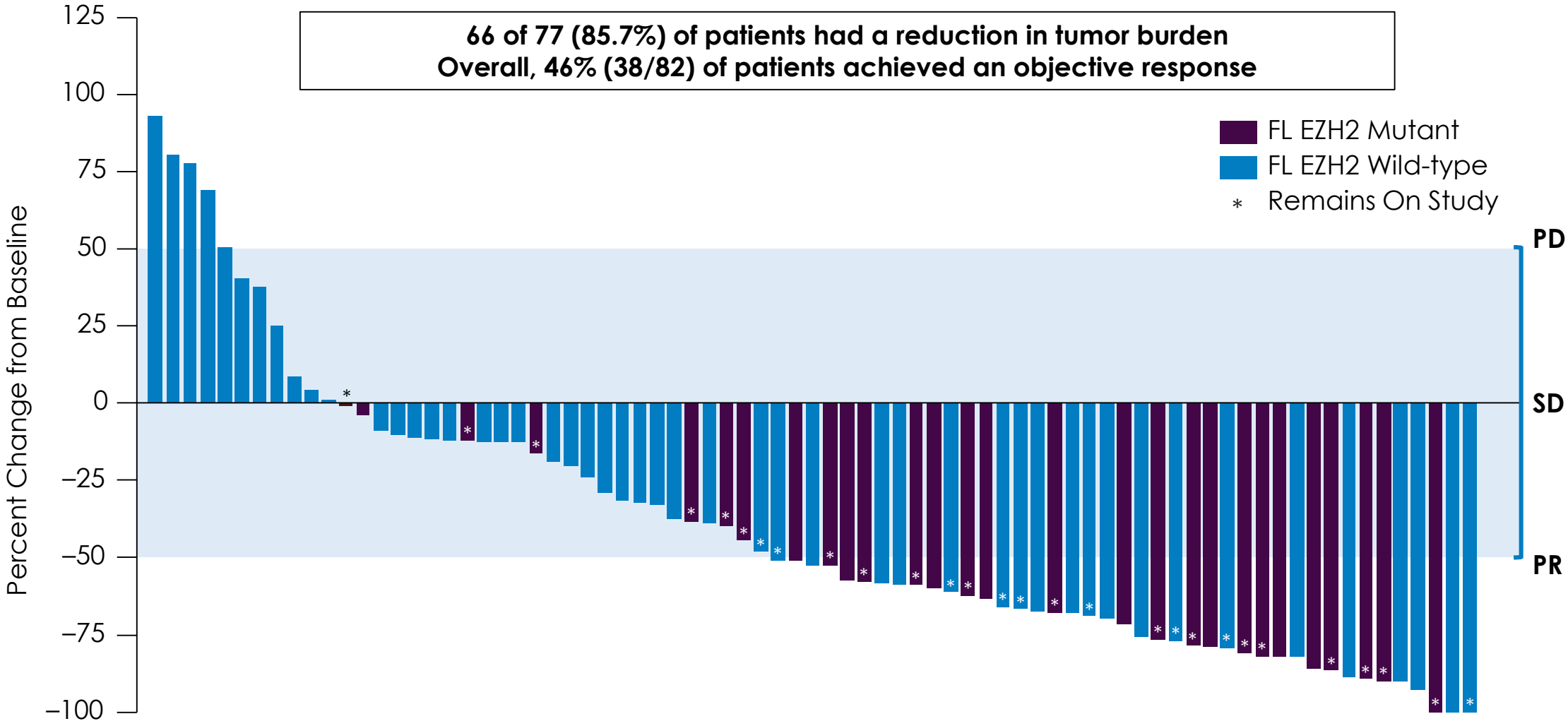


ACTIVITY AND DURABILITY OBSERVED ACROSS BOTH COHORTS

Best Response	FL EZH2 MT (n=28)	FL EZH2 WT (n=54)
Objective response rate (CR + PR), n (%)	**20 (71)**	**18 (33)**
95% CI[1]	51-87%	21-47%
Best response, n(%)		
Complete response (CR)	3 (11)	3 (6)
Partial response (PR)	17 (61)	15 (28)
Stable disease (SD)	8 (29)	17 (31)
Study drug ongoing	6 (21)	1 (2)
Progressive disease (PD)	0	17 (31)
No data/unknown (UNK)	0	2 (4)
Median time to first response[2,3], weeks	11.9	15.9
Median duration of response[2,3], weeks	32.3+	76.0+
Patients with ongoing response[3,4], n (%)	11 (55)	10 (56)
Median progression-free survival[3,4], weeks	48.6+	29.9
Median progression-free survival (responders)[3,4], weeks	48.6+	84.3+

Data as of 01 May 2018. Ongoing patients with best response of 'No Data, Unknown' are not included in this table. Patients that discontinued due to clinical or radiological progression without a valid response assessment are included in PD. [1] By Clopper-Pearson exact confidence interval. [2] Calculated with Kaplan-Meier analysis. [3] Not including time from Rollover study EZH-501. [4] Includes discontinued patients with response ongoing at time of discontinuation. +, Cohort median not yet reached.

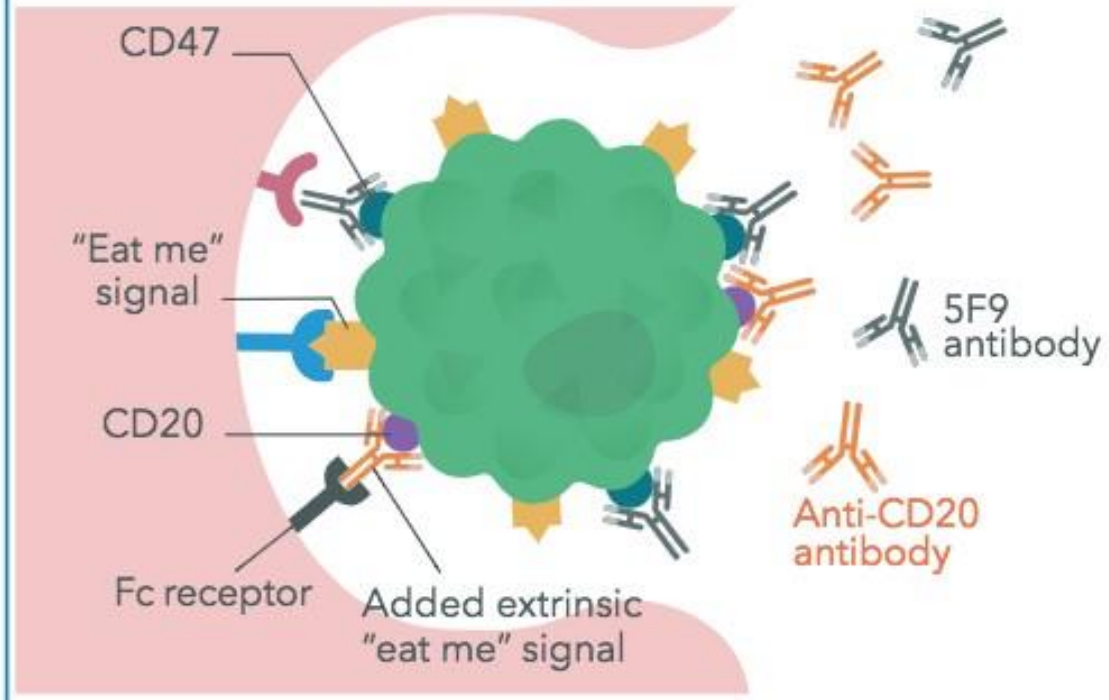
TUMOR CHANGE FROM BASELINE FOR FL PATIENTS

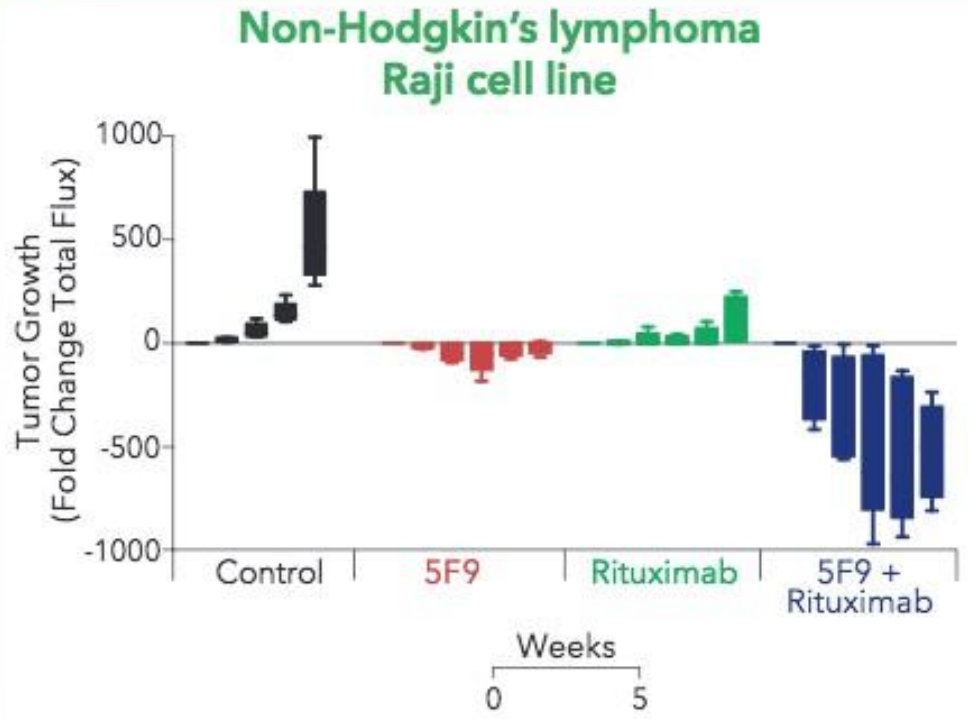


Data as of 01 May 2018. Plot does not include tumor measurements or status from Rollover study EZH-501. Five wild-type FL EZH2 patients are not present as they do not have post-baseline scans. Per Cheson 2007, percent change of sum of target nodal lesion SPD and target extranodal lesion SPD.

5F9 Synergizes with Rituximab to Induce Remissions in NHL Patient-Derived Xenograft Models

- Extrinsic "eat me" signals provided by rituximab through the Fc receptor enhances 5F9 activity via antibody-dependent cellular phagocytosis
- CD47 blockade takes the foot off the brakes, while rituximab puts the foot on the accelerator, leading to maximal tumor phagocytosis



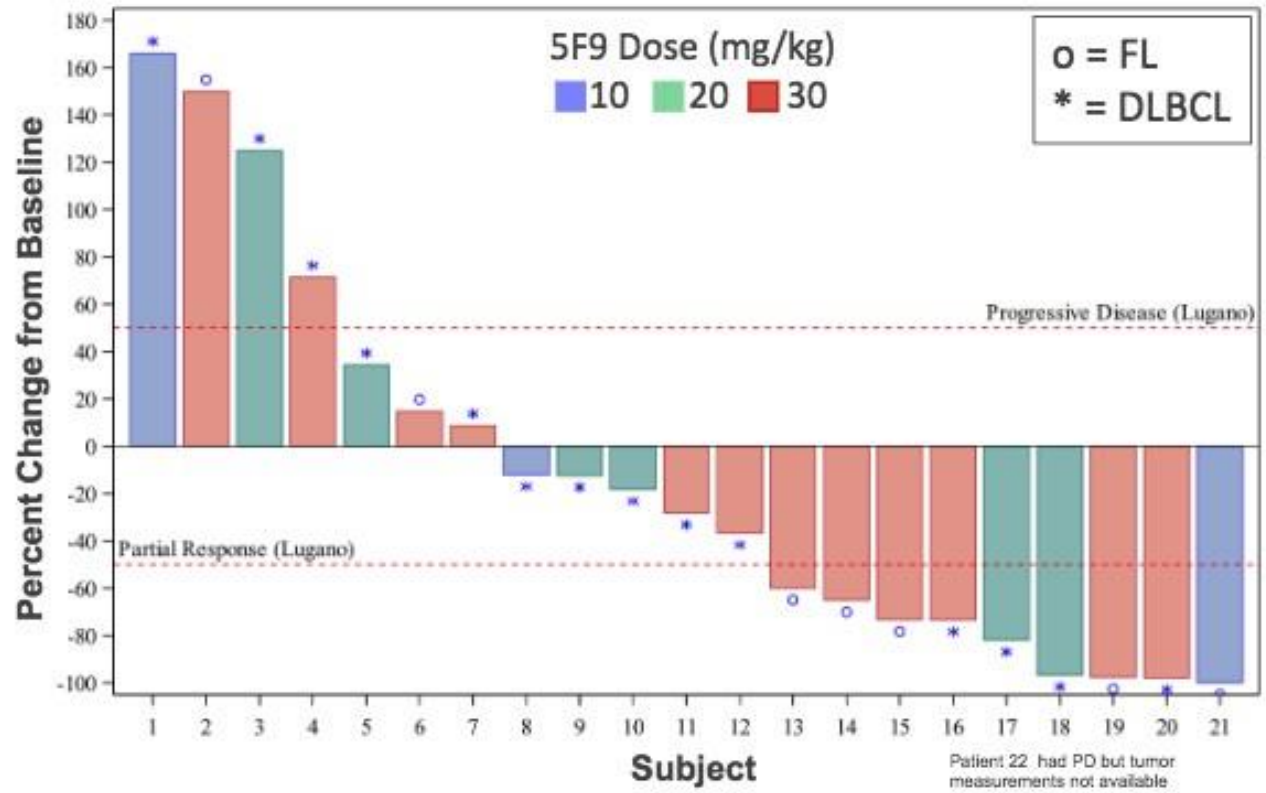


Liu et al., PLoS One 2015
Chao et al., Cell 2010

Anti-tumor Activity is Observed with 5F9 and Rituximab in Relapsed or Refractory NHL

	Phase 1b		
Response	All patients n=22	DLBCL n=15	Follicular Lymphoma n=7
Objective Response Rate (ORR)	11 (50%)	6 (40%)	5 (71%)
Partial Response (PR)	3 (14%)	1 (7%)	2 (29%)
Complete Response (CR)	8 (36%)	5 (33%)	3 (43%)
Disease control rate (CR+PR+SD)	14 (64%)	9 (60%)	5 (71%)

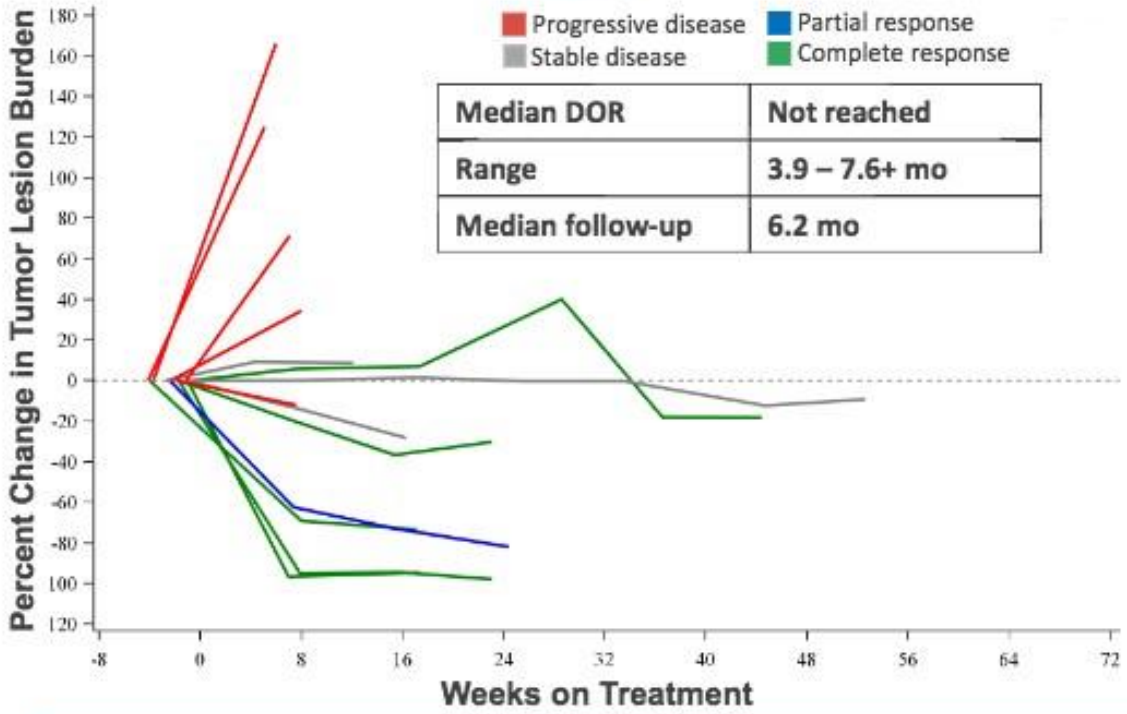
Data cutoff April 2018



- The objective response rate across all patients is 50% according to Lugano criteria
- Multiple CRs have been observed in both DLBCL and FL Phase 1b populations
- Efficacy is observed in rituximab-refractory patients

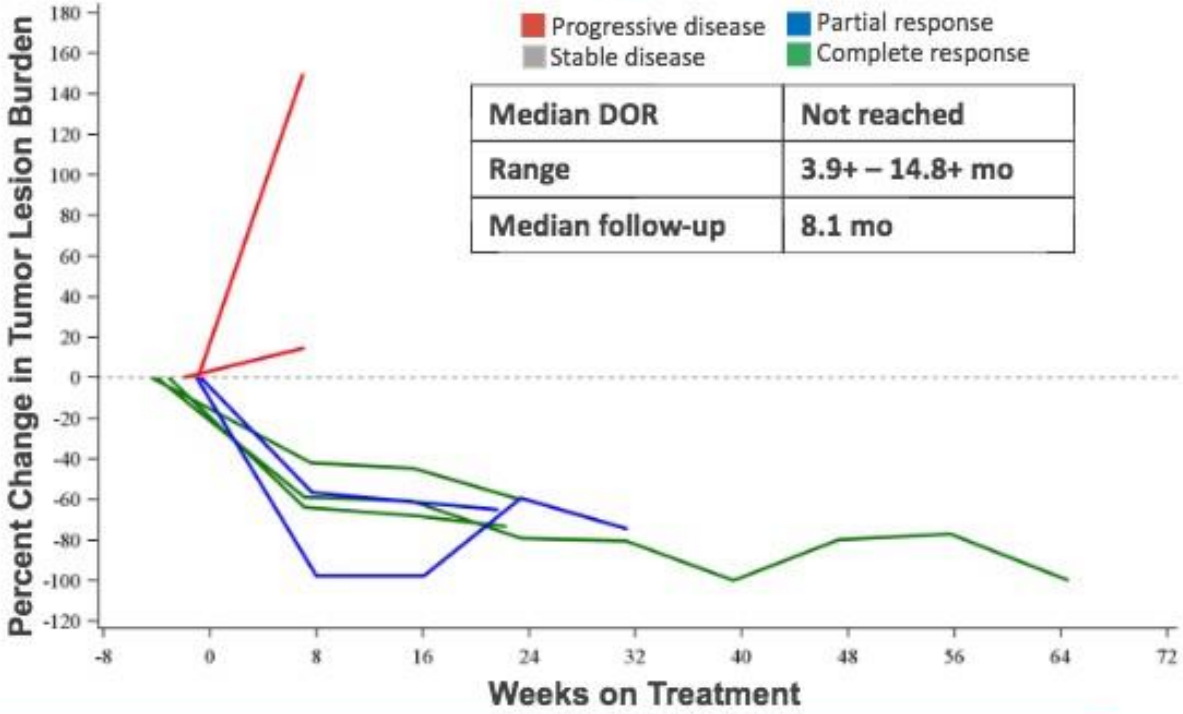
Durable Responses Observed in Phase 1b DLBCL and FL Patients

DLBCL



Median DOR	Not reached
Range	3.9 – 7.6+ mo
Median follow-up	6.2 mo

FL



Median DOR	Not reached
Range	3.9+ – 14.8+ mo
Median follow-up	8.1 mo

- Median time to response is rapid, within the first two months
- At a median follow-up > 6 months, only 1/11 responding patients has progressed
- Two DLBCL patients had improvement in response over time: SD to CR and PR to CR, both ongoing
- Median duration of response not reached, with longest patient in CR for > 14 months