8th POSTGRADUATE
Lymphoma
Conference

Follicular Lymphoma: What is the New Order?

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Grand Hotel Santa Lucia

President:
P.L. Zinzani

Disclosures of Bruce Cheson

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Abbvie			x				
Beigene			x		x		
Pharmacyclics			x				
Incyte					x	X	
Morphosys					x	X	
Regeneron						X	
Symbio						X	

Treatment As It Is Currently Done

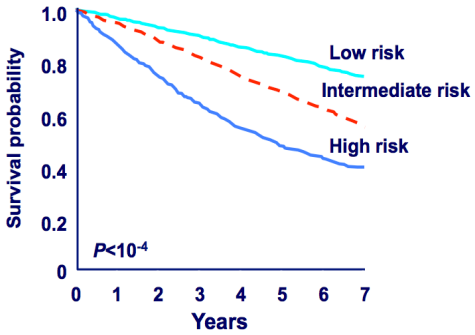
Indications for Treatment of Advanced Follicular Lymphoma:GELF Criteria

- Maximum diameter > 7 cm
- ≥ 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

Brice et al, JCO 15:1110, 1997

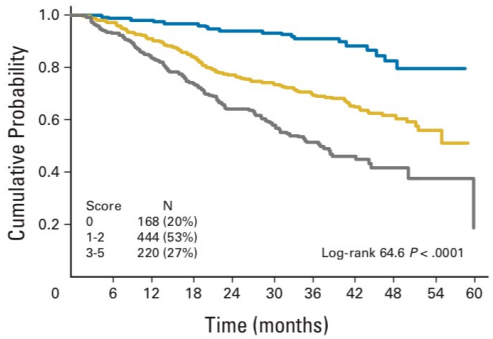
Prognostic Scoring Systems

FLIPI



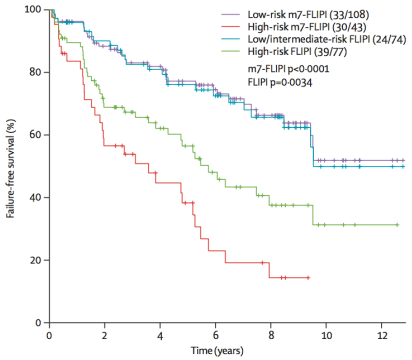
Nodes, LDH, Age, Stage, Hgb

F-2



β-2M, Hgb, Node size Age, BM

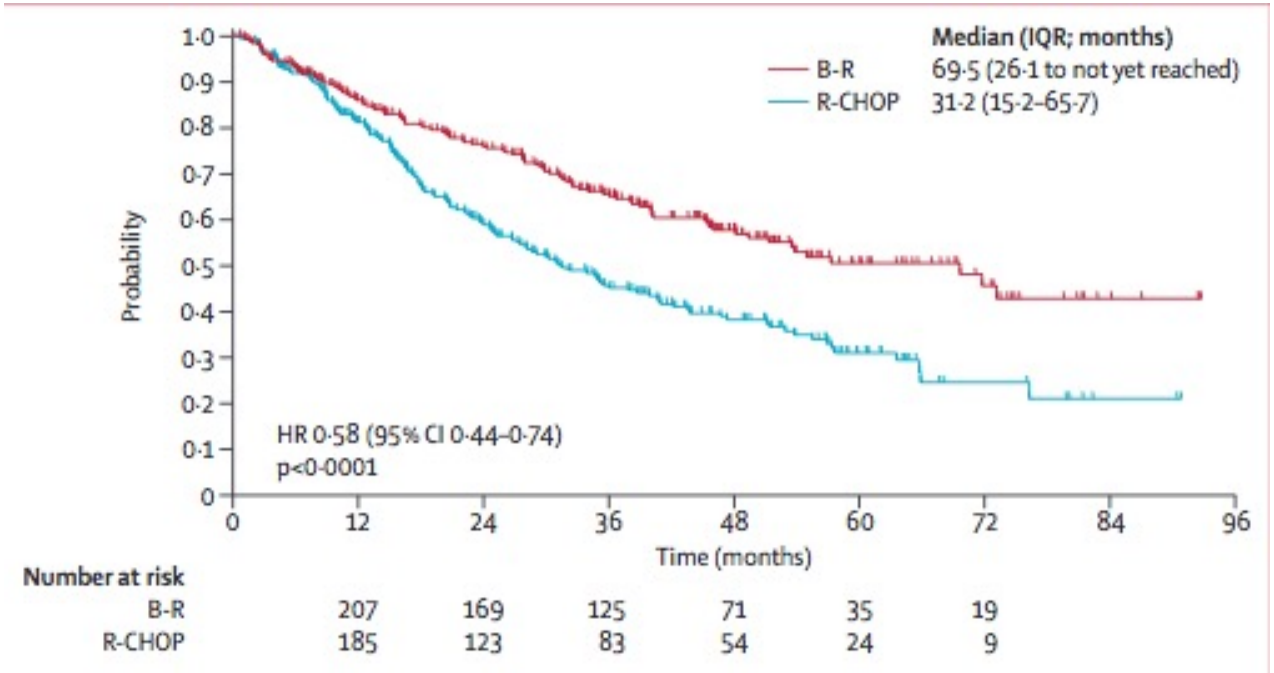
M7-FLIPI



Mutation of 7 genes, PS, F-2

But what do you do with the information??

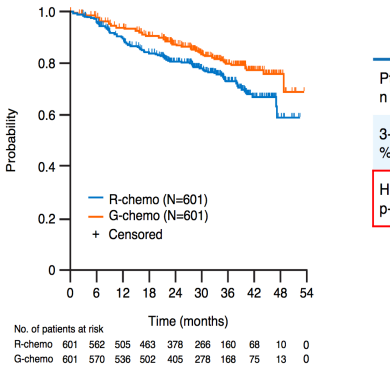
BR vs R-CHOP in Untreated iNHL



Rummel et al, Lancet 381:1203, 2013

GALLIUM Study: PFS and OS

INV-assessed PFS (FL; primary endpoint)



	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

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

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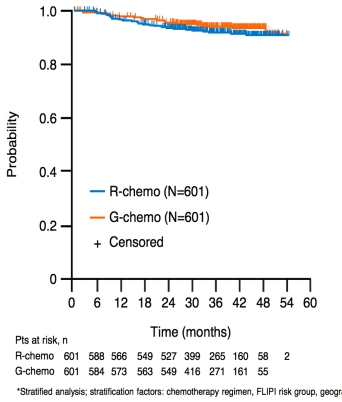
OS (FL)



	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

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

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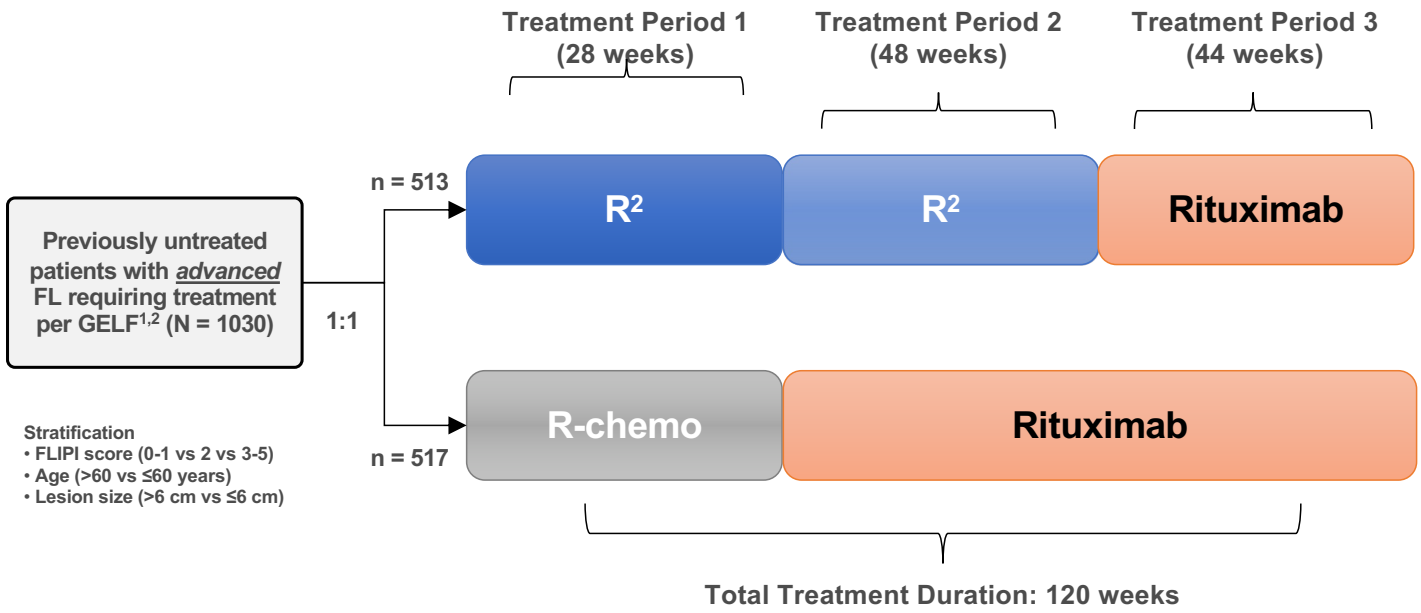
Marcus et al, NEJM 377:1331, 2017

RELEVANCE: Study Design



Co-primary endpoints per 1999 IWG criteria*

- CR/CRu at 120 weeks
- PFS (first interim analysis at ~50% of targeted events)

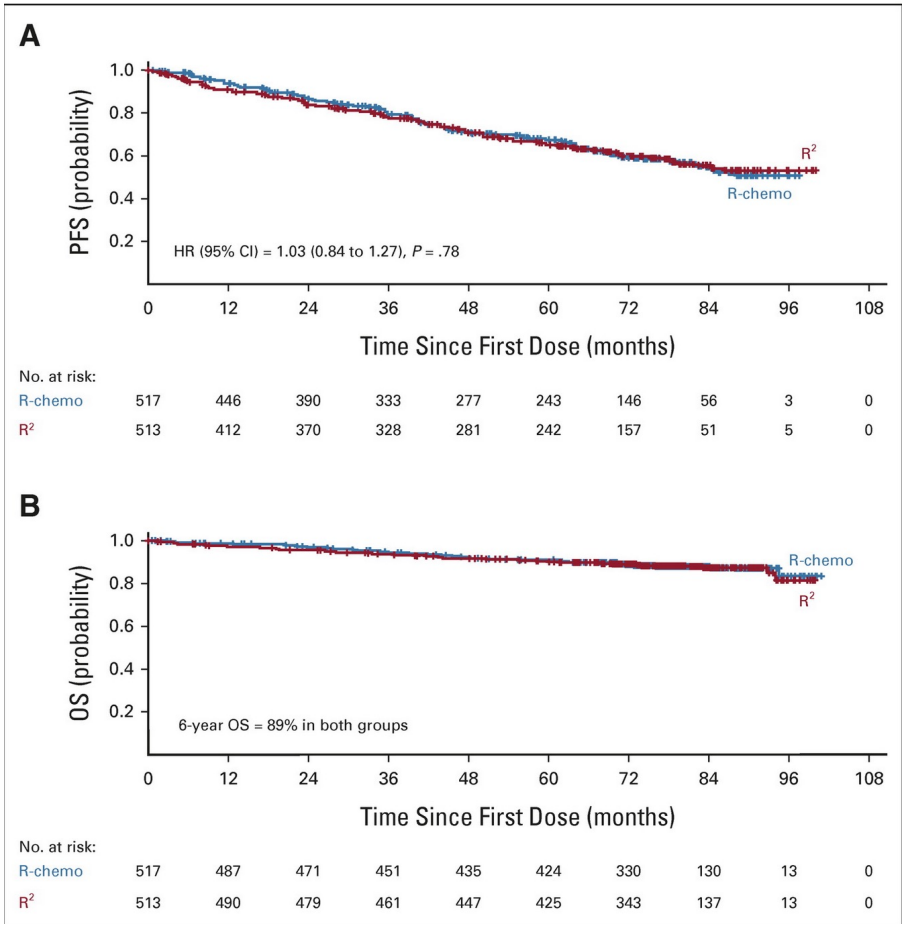
Dosing schedule

- **R²:** Lenalidomide 20 mg/d, d2-22/28 until CR/CRu at 6, 9, or 12 cycles, then 10 mg/d (total 18 cycles) and rituximab 375 mg/m²/wk c1 and d1 c2-6; continued in responders q8wk for 12 cycles
- **R-chemo:** 3 options (R-CHOP, R-B, R-CVP) plus 2 years rituximab maintenance
  - Included 72% R-CHOP, 23% R-B, and 5% R-CVP

Morschhauser et al, NEJM 379:934, 2018

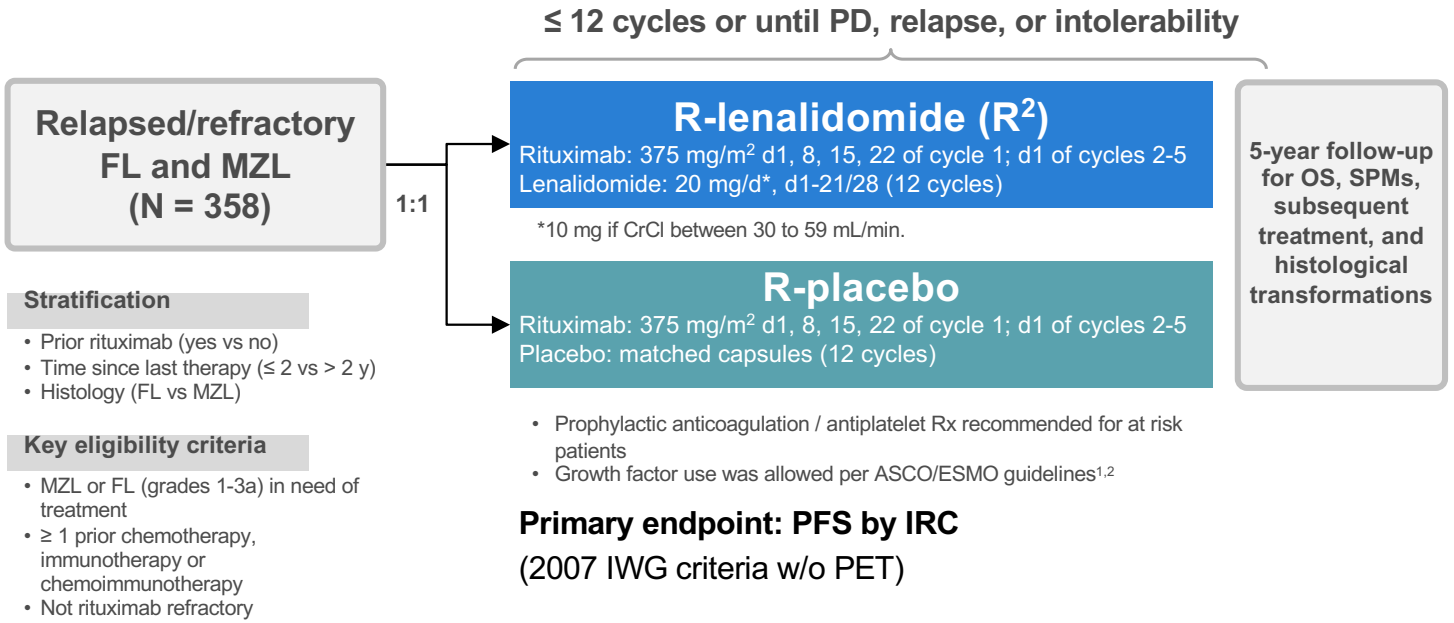
NCT01476787; NCT01650701; EUDRA 2011-002792-42. *Per central (IRC) review by 1999 IWG with CT.

6-Year Follow-up of RELEVANCE

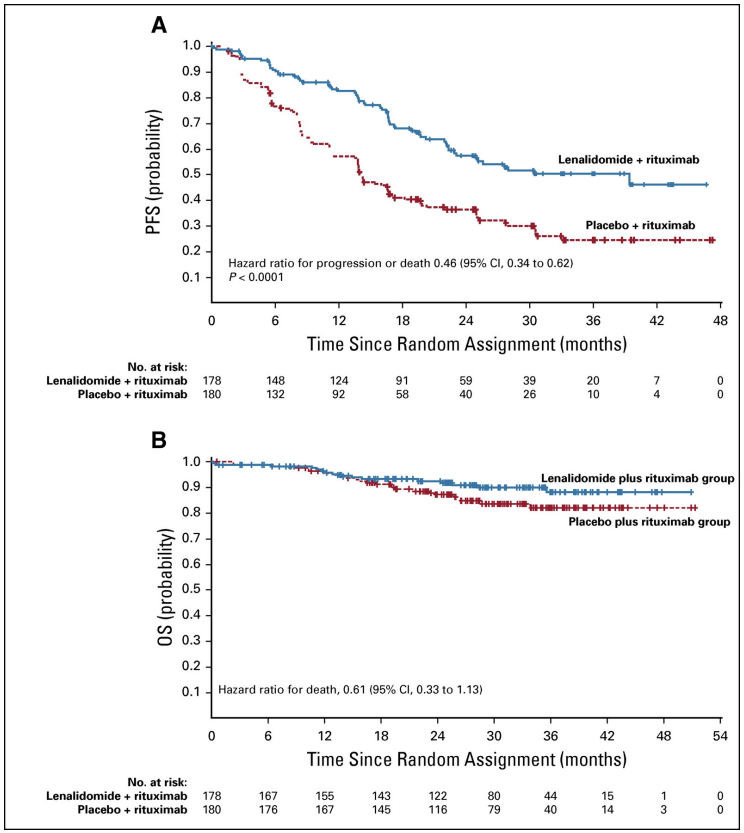


Morschhauser et al, JCO 40:3239, 2022

AUGMENT: Study Design: Randomized double blind phase III trial



PFS and OS From the AUGMENT Trial



Leonard, et al; *JCO* 2019 371188-1199.

Response to Tazemetostat by *EZH2* Mutation Status

	EZH2^{mut} (n=45)		*EZH2*^{WT} (n=54)	
	IRC-assessed	**Investigator-assessed**	**IRC-assessed**	**Investigator-assessed**
Objective response rate[*]	31 (69%; 53–82)	35 (78%; 63–89)	19 (35%; 23–49)	18 (33%; 21–48)
Overall disease control rate[†]	44 (98%)	45 (100%)	37 (69%)	34 (63%)
Best overall response				
Complete response	6 (13%)	4 (9%)	2 (4%)	3 (6%)
Partial response	25 (56%)	31 (69%)	17 (31%)	15 (28%)
Stable disease	13 (29%)	10 (22%)	18 (33%)	16 (30%)
Progressive disease	1 (2%)	0	12 (22%)	16 (30%)
Not estimable or unknown	0	0	5 (9%)	4 (7%)

Morschhauser et al Lancet Oncol 21:1433, 2021

Tazemetostat in R/R FL

	EZH2^{mut} (n=45)	*EZH2*^{WT} (n=54)
Age, years	62 (57–68)	61 (53–67)
Sex		
Male	19 (42%)	34 (63%)
Female	26 (58%)	20 (37%)
ECOG performance status		
0	21 (47%)	26 (48%)
1	24 (53%)	23 (43%)
2	0	4 (7%)
Missing	0	1 (2%)
Satisfied GELF criteria*		
Yes	31 (69%)	40 (74%)
No	14 (31%)	14 (26%)
Time from initial diagnosis, years	4·7 (1·7–6·4)	6·3 (3·4–9·0)
Histology		
Grade 1, 2, or 3a	42 (93%)	51 (94%)†
Grade 3b or transformed follicular lymphoma‡	3 (7%)	6 (11%)†
Previous lines of anticancer therapy§		
One	2 (4%)	1 (2%)
Two	22 (49%)	16 (30%)
Three	10 (22%)	11 (20%)
Four	4 (9%)	10 (19%)
Five or more	7 (16%)	16 (30%)
Median	2 (2–43)	3 (2–5)
Refractory to last regimen¶	22 (49%)	22 (41%)
Poor risk features		
Refractory to a rituximab-containing regimen‖	22 (49%)	32 (59%)
Double refractory**	9 (20%)	15 (28%)
Previous haematopoietic stem-cell transplant	4 (9%)	21 (39%)
Disease progression within 24 months of disease diagnosis in patients treated with first-line immunochemotherapy (POD24)	19 (42%)	32 (59%)

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

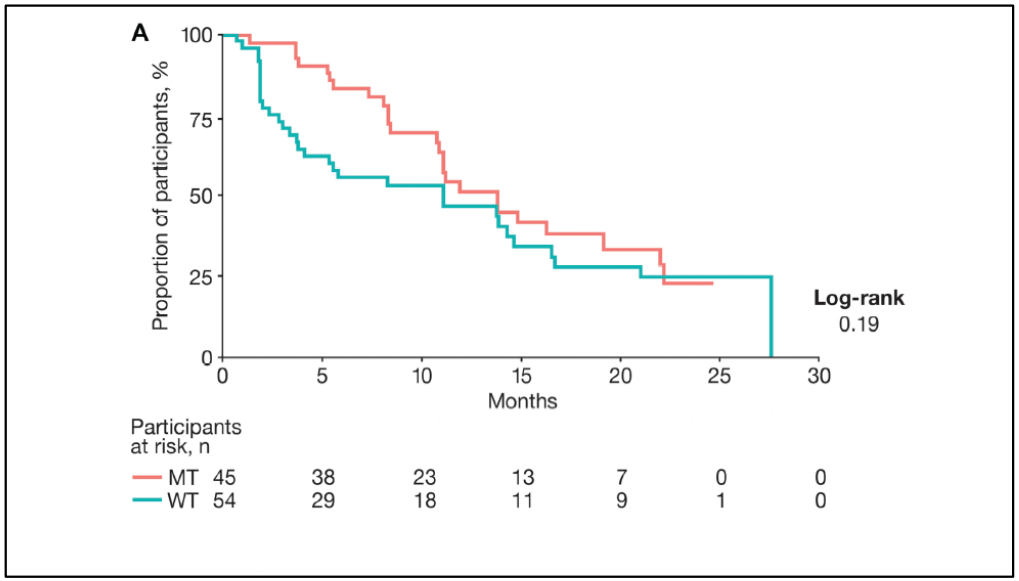
ORR By Mutation Status Before and After Matching

Population	Before matching ($n = 99$) (95% CI), %	After matching ($n = 56$) (95% CI), %
WT *EZH2*	35 (22–48)	50 (31–69)
MT *EZH2*	69 (55–83)	71 (54–88)

Abbreviations: CI: confidence interval; MT: mutant type, WT: wild type.

- Proudman DG, Gupta D, Nellesen D, et al, Cheson BD. Tazemetostat in relapsed/refractory follicular lymphoma: a propensity score–matched analysis of E7438-G000-101 trial outcomes. Oncotarget 2022;13:677-83.

PFS By Mutation Status Before and After Matching



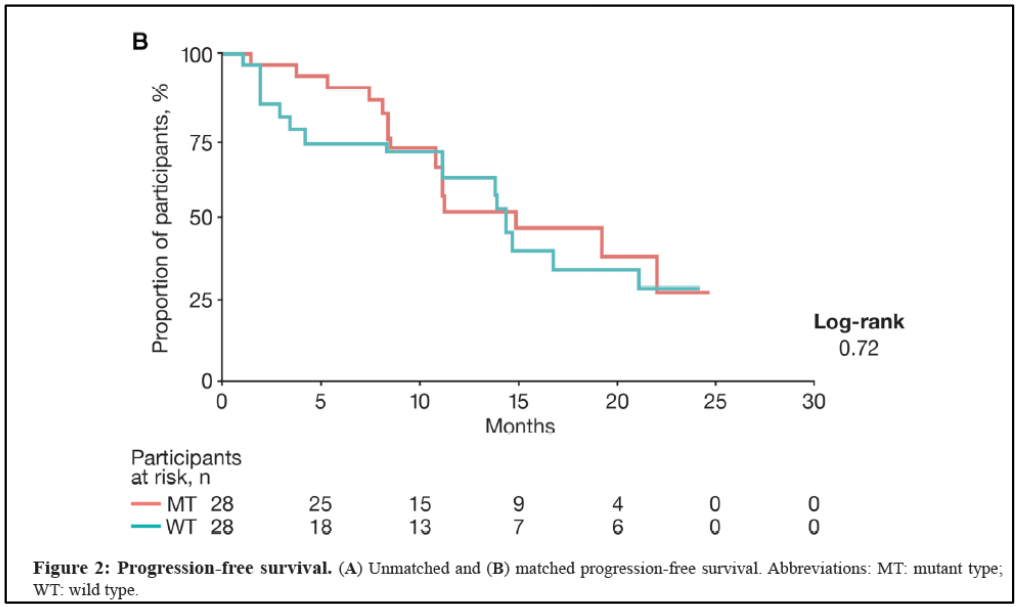


Figure 2: Progression-free survival. (A) Unmatched and (B) matched progression-free survival. Abbreviations: MT: mutant type; WT: wild type.

- Proudman DG, Gupta D, Nellesen D, et a, Cheson BD. Tazemetostat in relapsed/refractory follicular lymphoma: a propensity score–matched analysis of E7438-G000-101 trial outcomes. Oncotarget 2022;13:677-83.

ROSEWOOD: Study Design

Stratification by geographic region, number of prior lines, rituximab refractory status

Adults with grade 1-3a R/R FL previously treated with ≥2 prior regimens, including an anti-CD20 antibody and appropriate alkylator-based combination therapy; no prior BTK inhibitor; ECOG PS 0-2
(N = 217)

Zanubrutinib + Obinutuzumab*
(n = 145)

Obinutuzumab*
(n = 72)

Treated until disease progression or unacceptable toxicity†

*Zanubrutinib dosed at 160 mg PO BID. Obinutuzumab dosed at 1000 mg IV on Days 1, 8, and 15 of Cycle 1; Day 1 of cycles 2-6 and then Q8W up to a maximum of 20 doses. †Patients assigned to obinutuzumab with centrally confirmed PD or no response at 12 mo could crossover to receive combination therapy.

- **Primary endpoint:** ICR-assessed ORR according to Lugano classification
- **Key secondary endpoints:** investigator-assessed ORR, CR, DoR, PFS, OS, safety

Zinzani. ASCO 2022. Abstr 7510.

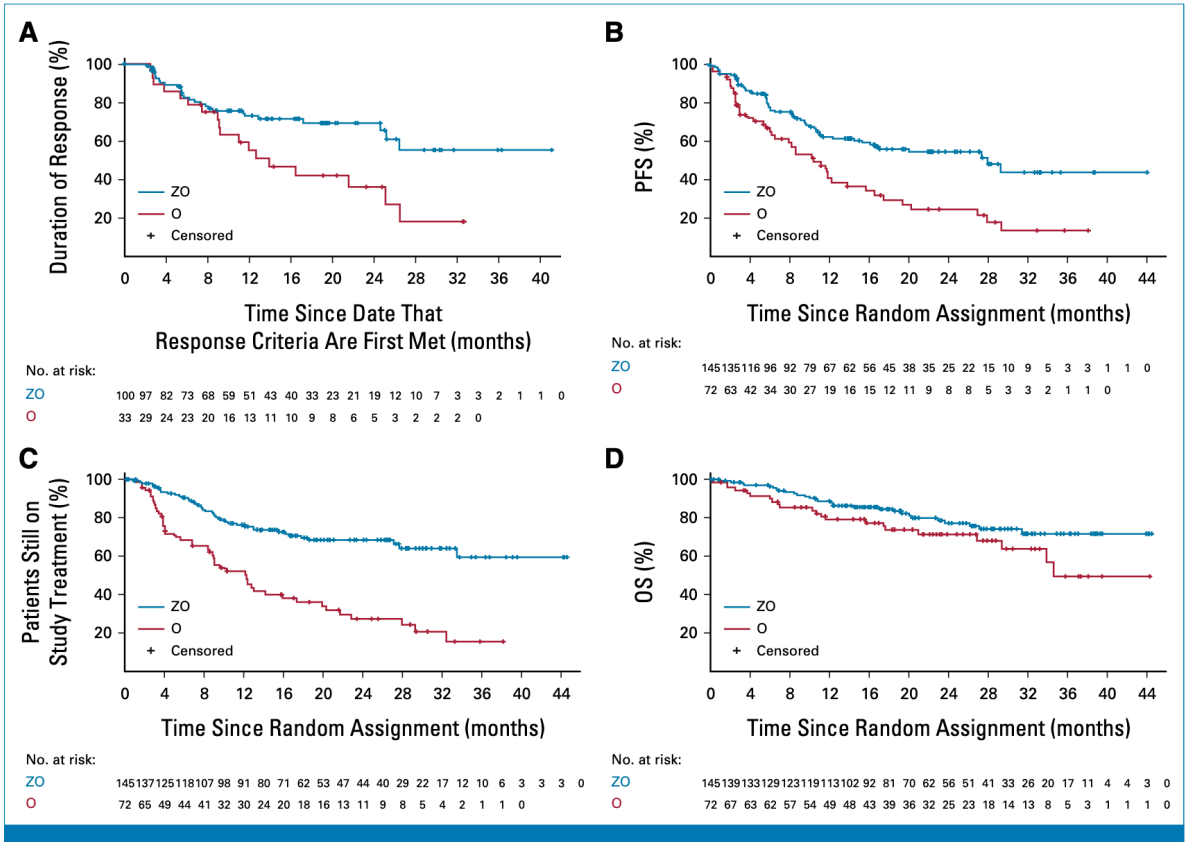
ROSEWOOD: Patient Outcomes

End Point	ZO (n = 145)	O (n = 72)	HR (95% CI)	Two-Sided *P* Value
ORR by ICR, % (95% CI)	69 (61 to 76)	46 (34 to 58)	—	.001
CR, No. (%)	57 (39)	14 (19)	—	.004
PR, No. (%)	43 (30)	19 (26)	—	—
DOR by ICR, months, median (95% CI)	NE (25.3 to NE)	14.0 (9.2 to 25.1)	—	—
18-month rate, %	69 (58 to 78)	42 (23 to 60)	—	—
Duration of CR by ICR, months, median (95% CI)	NE (26.5 to NE)	26.5 (2.7 to NE)	—	—
18-month rate, % (95% CI)	87 (74 to 94)	51 (21 to 75)	—	—
PFS by ICR, months, median (95% CI)	28.0 (16.1 to NE)	10.4 (6.5 to 13.8)	0.50 (0.33 to 0.75)	<.001
Median TTNT, months	NE (33.4 to NE)	12.2 (8.5 to 17.3)	0.34 (0.22 to 0.52)	<.001
Median OS, months (95% CI)	NE (NE to NE)	34.6 (29.3 to NE)	0.62 (0.35 to 1.07)	.085
24-month rate, % (95% CI)	77 (68 to 84)	71 (58 to 81)	—	—

Abbreviations: CR, complete response; DOR, duration of response; HR, hazard ratio; ICR, independent central review; NE, not estimable; O, obinutuzumab; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; TTNT, time to next treatment; ZO, zanubrutinib plus obinutuzumab.

Zinzani et al, JCO 41:5107, 2023

ROSEWOOD: Patient Outcomes



Zinzani et al, JCO 41:5107, 2023

Regulatory Approval Status in the US for CD20xCD3 Bispecific Abs for FL

- **Mosunetuzumab**
  - FDA approval for R/R follicular lymphoma, ≥ 3rd line, **12/22/2022**
- **Odronextamab**
  - FDA accepted application 09/29/2023
  - Target action date for FDA decision **03/31/2024**
- **Epcoritamab**
  - FL cohort of EPCORE NHL-1 trial "exceeded protocol pre-specified threshold for efficacy" ORR 82% (ASH 2023)
  - Will submit application to FDA in next 6-12 mo

CD20xCD3 Bispecifics for r/r FL Gr 1-3a

Agent	No. of pts	ORR %	CR %	Med DOCR mo	PFS mo	Ref
Glofitamab	44	71	48	NR	11.8	1, 2
Mosunetuzumab	90	**79**	**60**	**NR**	**24**	3, 4
Odronextamab	131	**82**	**75**	20.5	20.2	5, 6
Epcoritamab	10	90	50	NA	NR	7

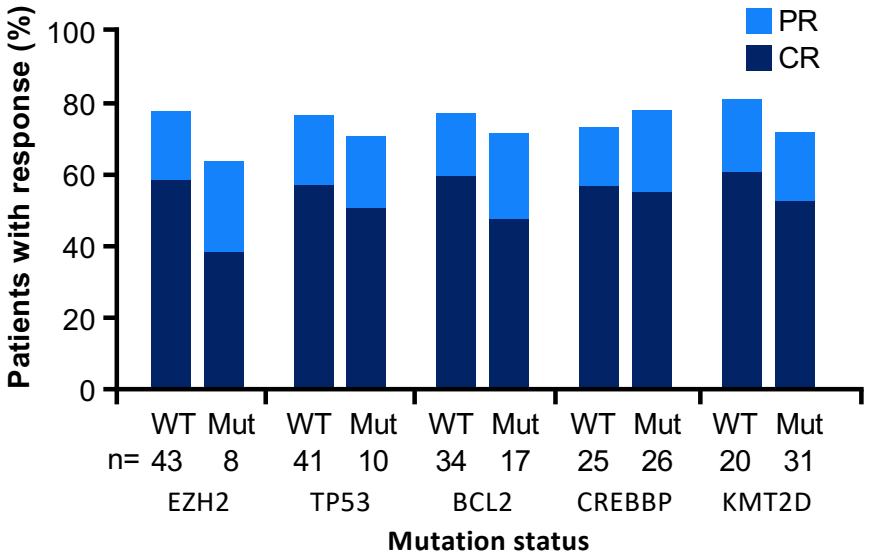
- **Responses including CRs occur early (median time ≤ 3 mo)**

- 1. Hutchings 2021: JCO 39:1959-1970; 2. Morschhauser et al, ASH 2021, 3. Budde Lancet Oncol 2022; 23:1055-1065 4. Bartlett ASH 2022; 5. Bannerji Lancet Haem 2022: 9: e327–39;23: 1055–65; 6. Taszner EHA 2023; 7. Hutchings Lancet 2021; 398: 1157–69

Mosun CR rates in high risk subsets

Risk factor	CR rate %
ALL	60%
POD24	57% (vs. 62%)
Bulky	61% (vs. 59%)
Refract to prior CD20	55% (vs. 79%)
Double refractory	50% (vs. 71%)
Refractory last line	52% (vs. 79%)

Response by mutation status

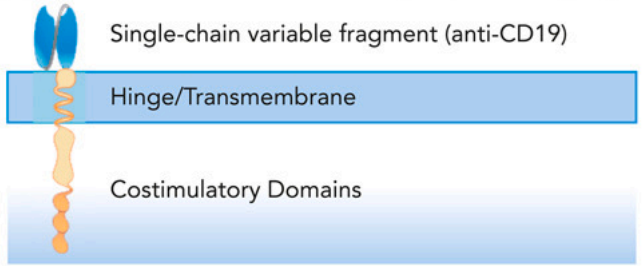


Bispecific Studies in Untreated Follicular Lymphoma

Bispecific	CT.Gov identifier	Design of study	Phase	Additional Agent(s)	Sponsor/Investigator
Mosunetuzumab (M)	NCT05207670	Subq M, Front-Line, low tumor burden FL (+other B-NHL)	2	-	Genentech
	NCT05169658	M +/- Pola + Obin in untreated FL	2	Pola, Obin	U of Washington
	NCT05410418	M + Polatuzumab for FL	2	Pola	Wash U
	NCT05994235	Taz and Mosun in Untreated FL	2	Tazemetostat	Cornell
Epcoritamab (E)	NCT05783609	R+E for First-Line FL	2	Rituximab	DFCI
	NCT06112847	Len+E for Untreated FL	2	Lenalidomide	City of Hope/NCI
	NCT06191744	ER^2 vs R^2 vs CIT First-Line FL	3	Rituximab, Len	Genmab

Three-year follow-up analysis of –cell in R/R indolent NHL(ZUMA-5)

Axi-cel: Autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy approved for R/R follicular lymphoma (FL)



ZUMA-5: Phase 2 study of axi-cel in R/R iNHL

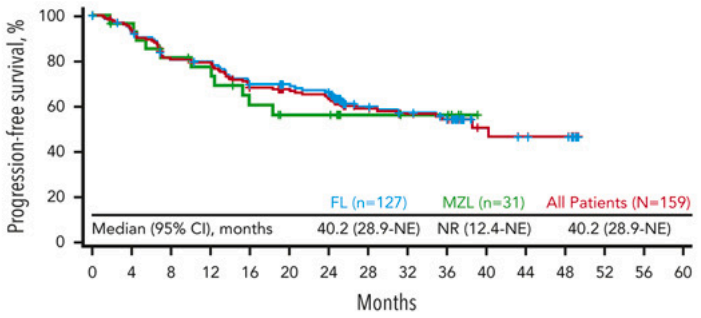
R/R iNHL (N=159)
- FL or marginal zone lymphoma (MZL)
- ≥2 prior lines of therapy

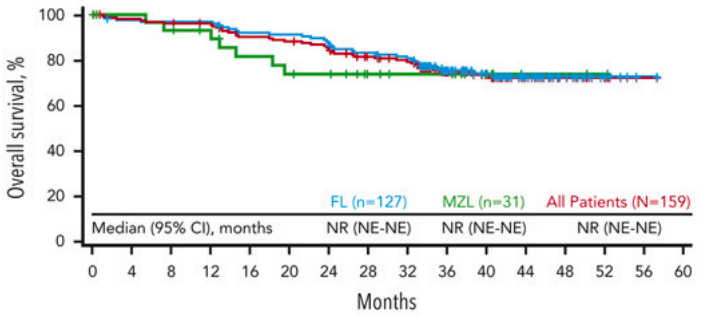
Axi-Cel Treatment

Leukapheresis → Lymphodepleting chemotherapy → CAR T-cell infusion

Key Long-Term Endpoints
- DOR, PFS, OS, TTNT
- Lymphoma-specific survival
- Safety
- Outcomes by prior bendamustine exposure and baseline tumor burden

Long-Term Survival Outcomes





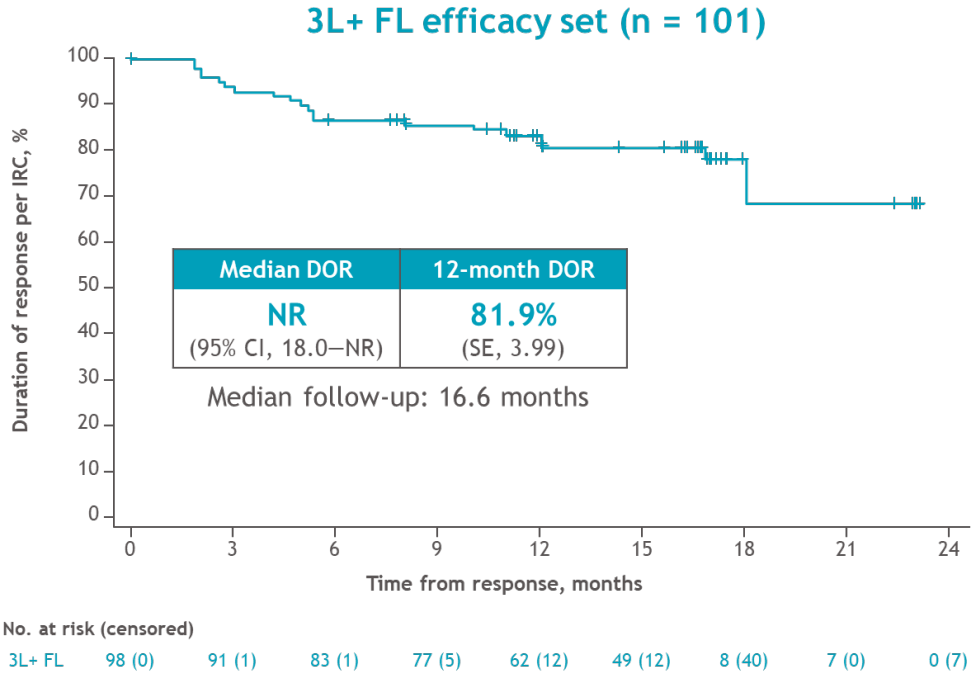
Neelapu SS, et al, Blood, 143:496, 2024

ZUMA-5 Outcomes by POD24 Status

Parameter (95% CI)	Follicular Lymphoma (n=78)[a]	
	With POD24 (n=49)	Without POD24 (n=29)
Median DOR, months	38.6 (14.5–NE)	NR (24.7–NE)
24-month rate, %	61.1 (44.3–74.3)	72.4 (50.2–85.9)
Median PFS, months	39.6 (13.1–NE)	NR (25.7–NE)
24-month rate, %	57.3 (41.2–70.4)	73.0 (51.1–86.2)
Median OS, months	NR (39.6–NE)	NR (NE–NE)
24-month rate, %	77.6 (63.1–86.9)	85.9 (66.7–94.5)

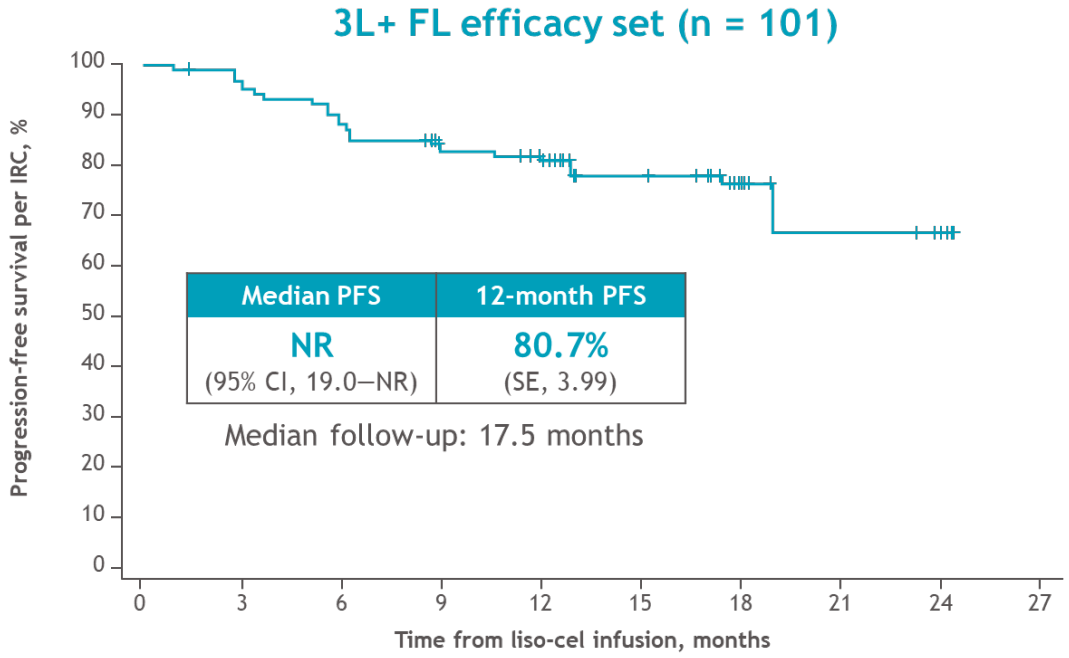
Neelapu ASH 2021

TRANSCEND-FL: DOR and PFS



No. at risk (censored)

3L+ FL	98 (0)	91 (1)	83 (1)	77 (5)	62 (12)	49 (12)	8 (40)	7 (0)	0 (7)



No. at risk (censored)

3L+ FL	101 (0)	96 (1)	89 (0)	78 (6)	72 (3)	50 (20)	19 (30)	7 (11)	2 (5)	0 (2)

Morschhauser et al ICML 2023

Treatment As It Could Be Done

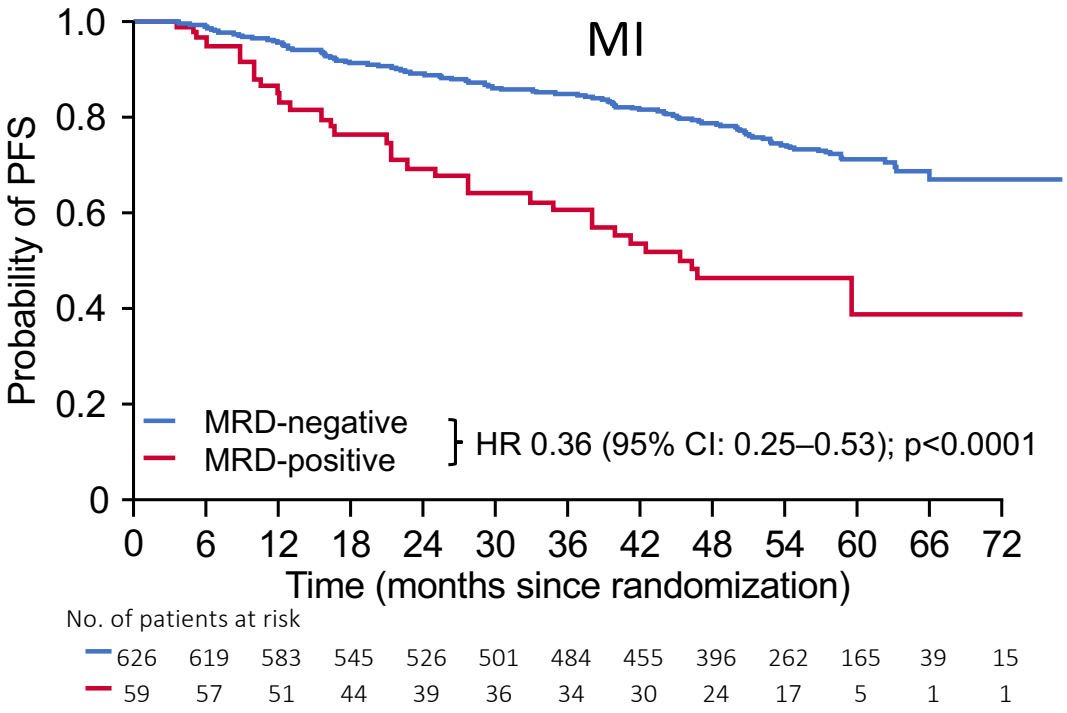
GALLIUM:Response rates at end of induction

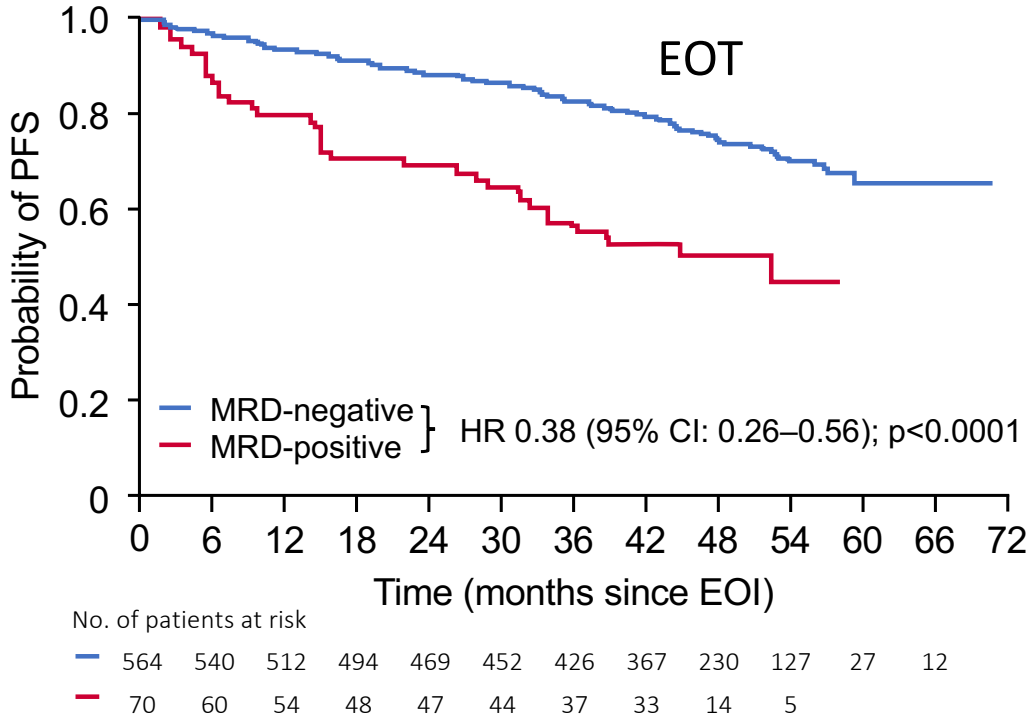
	CT (by investigator) % (n); 95% CI	
	R-chemo, n=601	***G-chemo, n=601***
ORR	**86.9% (522); 83.9, 89.5**	**88.5% (532); 85.7, 91.0**
CR	**23.8% (143); 20.4, 27.4**	**19.5% (117); 16.4, 22.9**
PR	63.1% (379)	69.1% (415)
SD	1.3% (8)	0.5% (3)
PD	4.0% (24)	2.3% (14)
Not evaluable / missing	3.5% (21) / 4.3%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

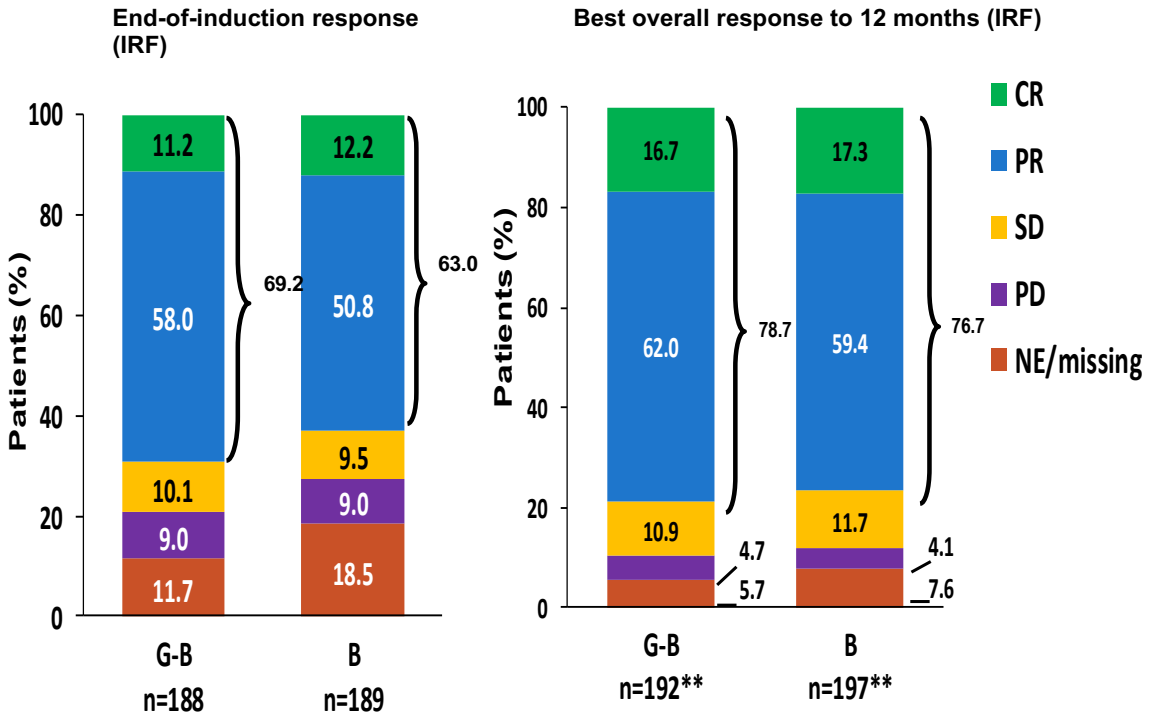
Marcus et al NEJM 377:1331, 2017

PFS by MRD status





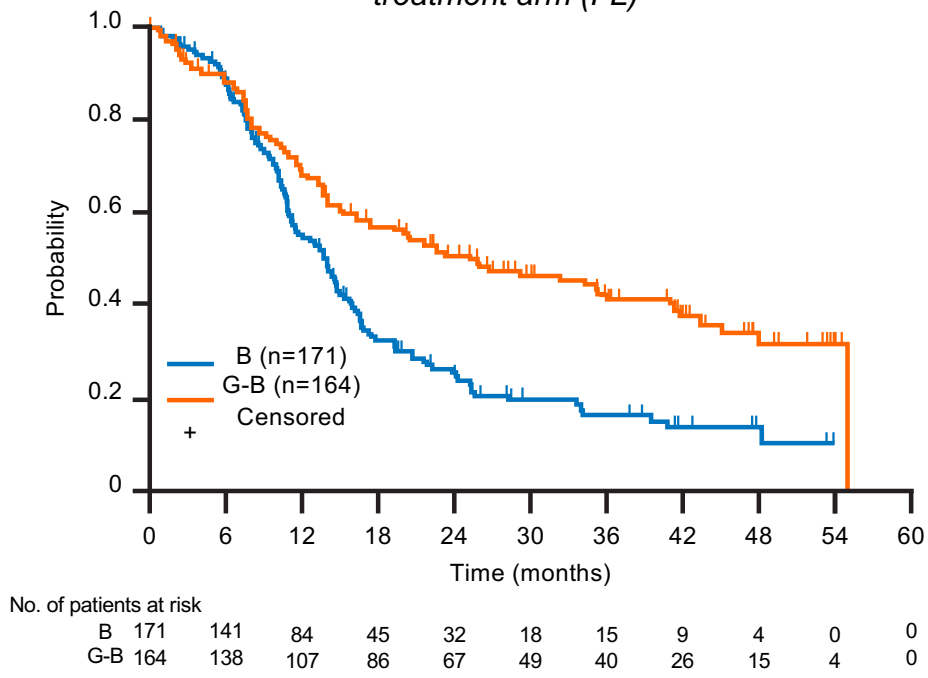
GADOLIN: Response to Therapy



Cheson et al, JCO 36:2259,2018

INV-assessed PFS in the FL population

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



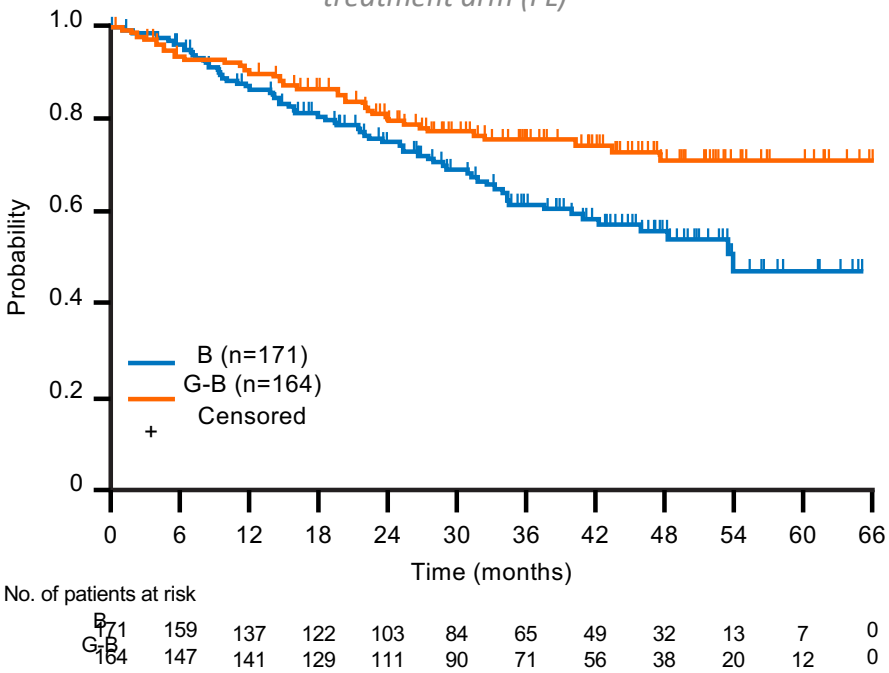
	G-B, n=164	*B, n=171*
Pts with event, n (%)	93 (56.7)	125 (73.1)
Median PFS (95% CI), mo	25.3 (17.4, 36.0)	14.0 (11.3, 15.3)
HR (95% CI), p-value*	0.52 (0.39, 0.69), p<0.0001	

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

Cheson et al, JCO 36:2259,2018

OS in the FL population

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



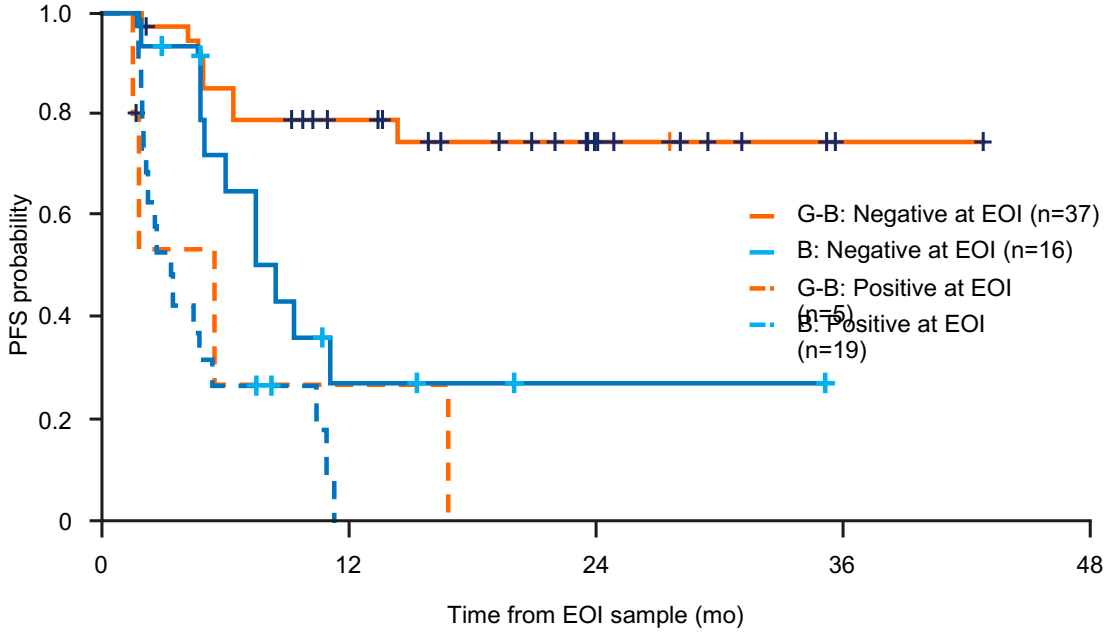
	G-B, n=164	*B, n=171*
Pts with event, n (%)	39 (23.8)	64 (37.4)
Median OS (95% CI), mo	NR (NR, NR)	53.9 (40.9, NR)
HR (95% CI), p-value*	0.58 (0.39, 0.86), p=0.0061	

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 withPFS in the FL population[1]

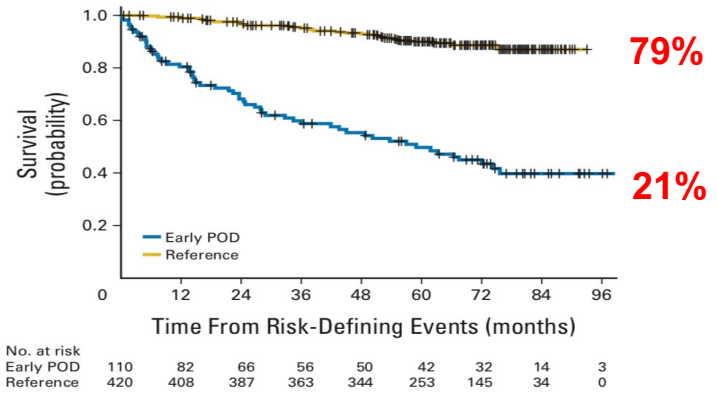
Kaplan-Meier plot of PFS by MRD status at EOI and by treatment arm in the FL population



- 1. Pott C, et al. Blood 2015;126:3978

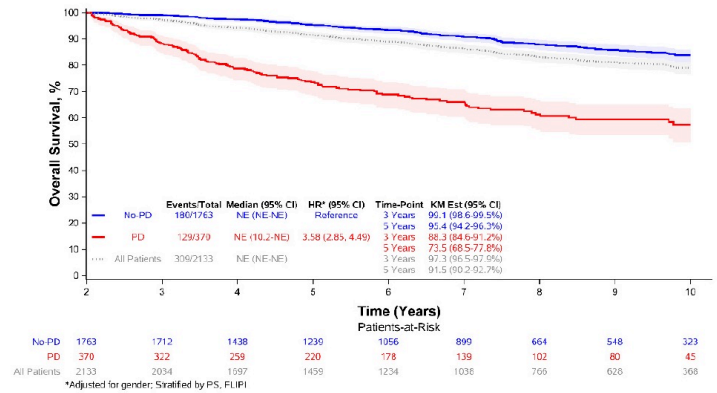
Treatment As It Will Be Done

Early Relapsing FL after Chemoimmunotherapy Identifies Patients with Inferior Overall Survival



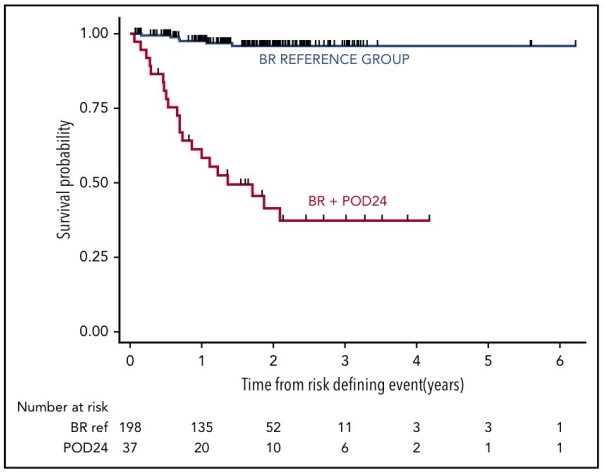
79%

21%



83%

17%

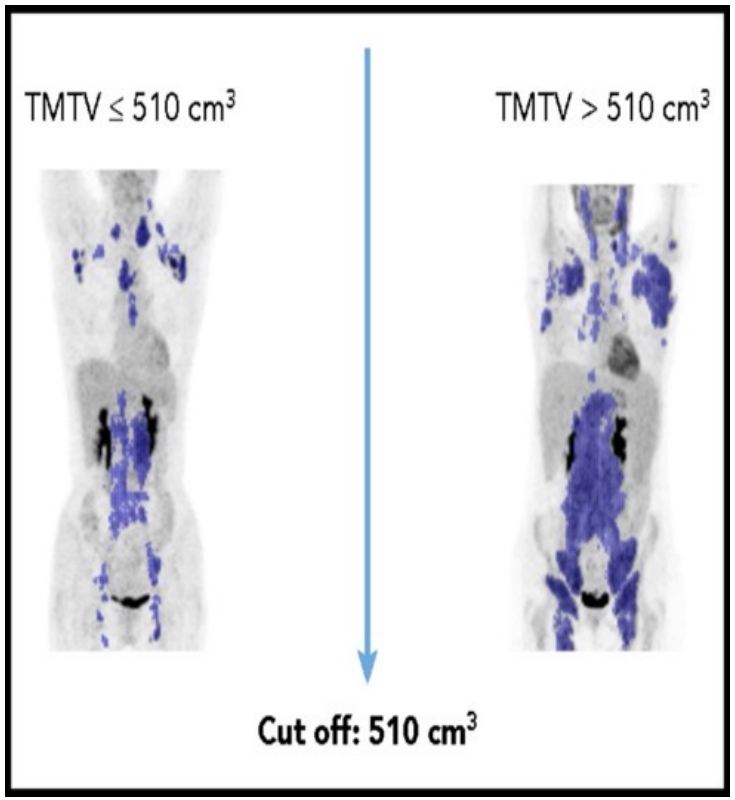


87%

13%

Casulo et al JCO 2015;33:2516; Casulo et al Blood 2022; 139:1684; Freeman et al Blood 2019;134:761

Macroscopic tumor burden on PET scan

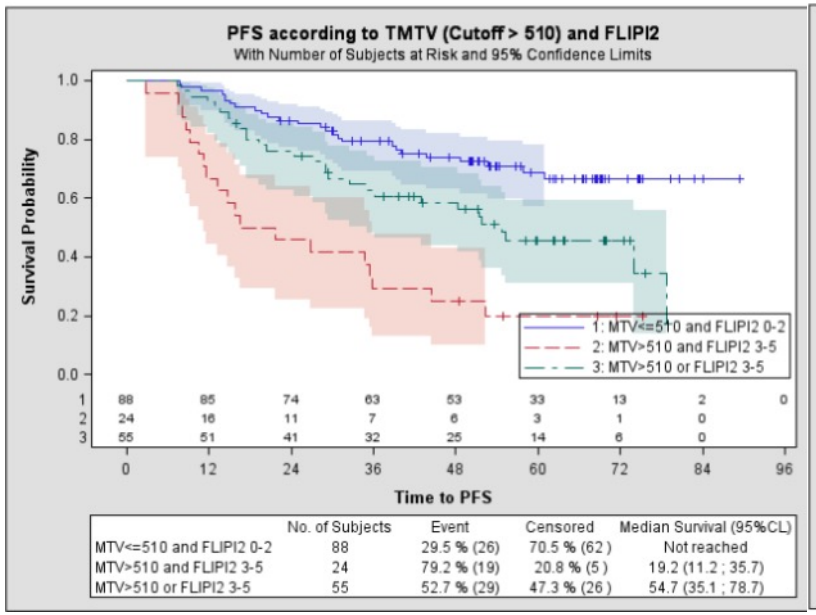


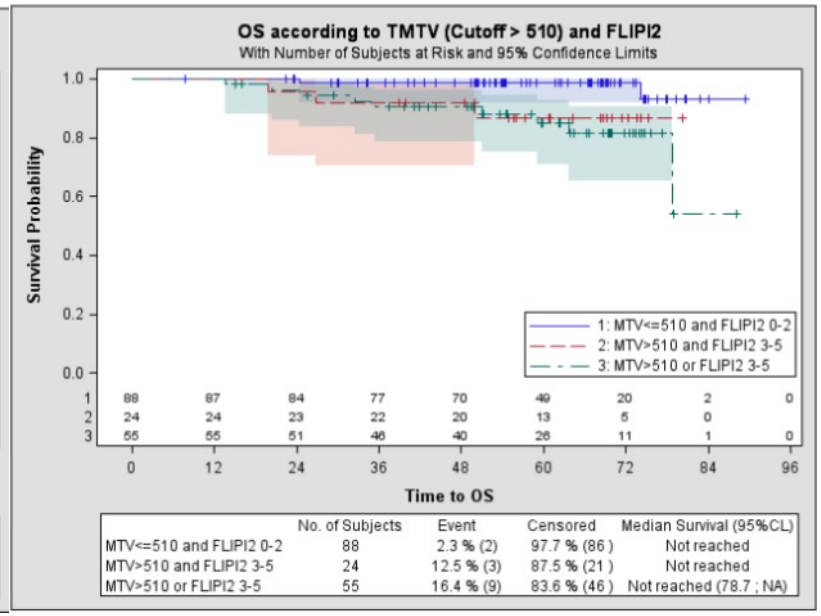
Courtesy, Michel Meignan

TMTV : Total metabolic tumor volume

TMTV = sum total of all metabolically active lesions.

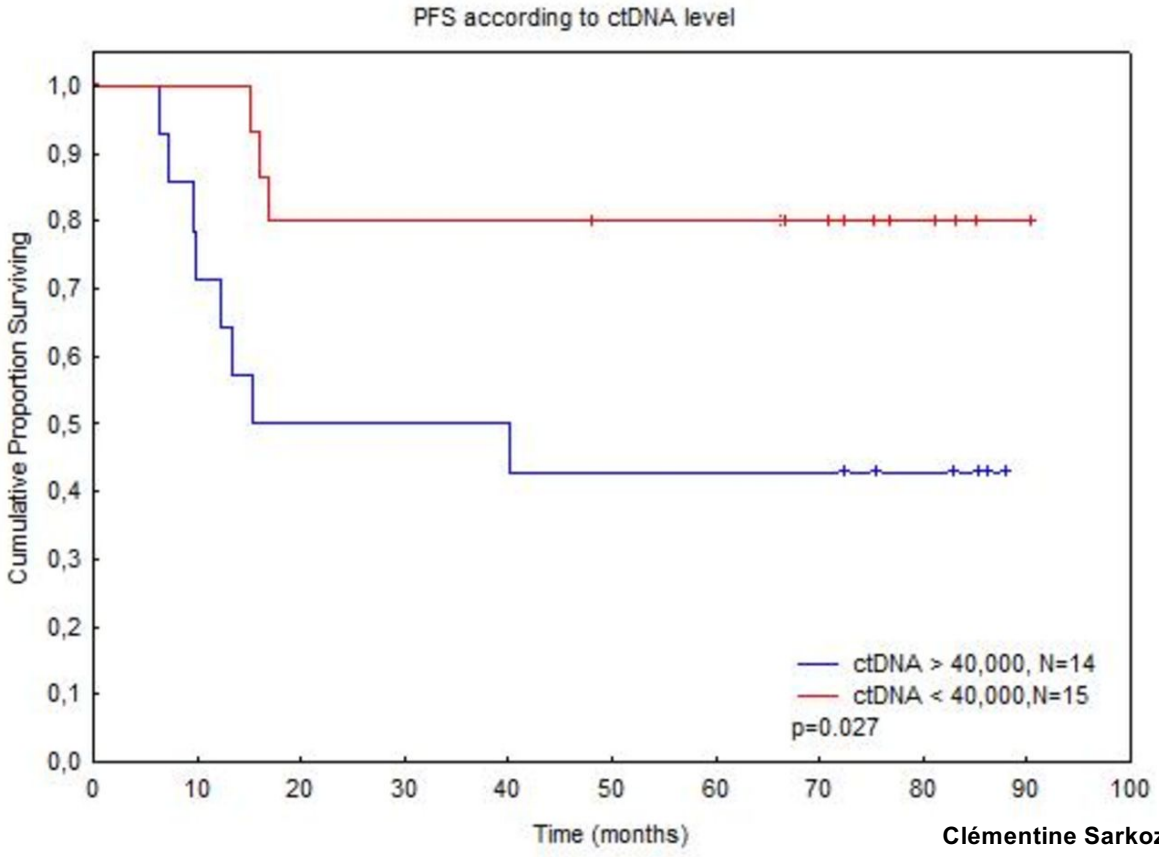
Pre-Treatment TMTV in FL





Meignan et al, JCO, 34:3618, 2016

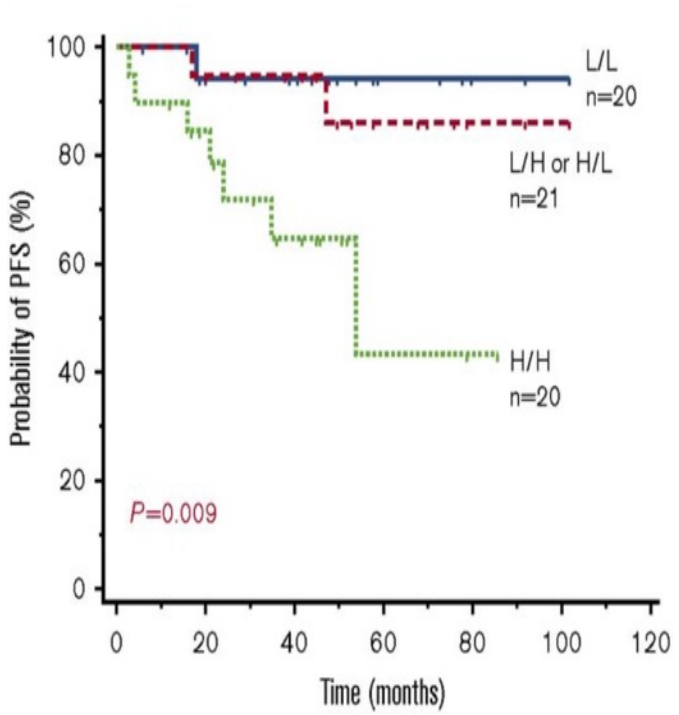
PFS of FL according to the level of pre-tx circulating tumor DNA (Clonoseq)



Clémentine Sarkozy et al. Blood 2015;126:2675

Pretreatment TMTV + ctDNA

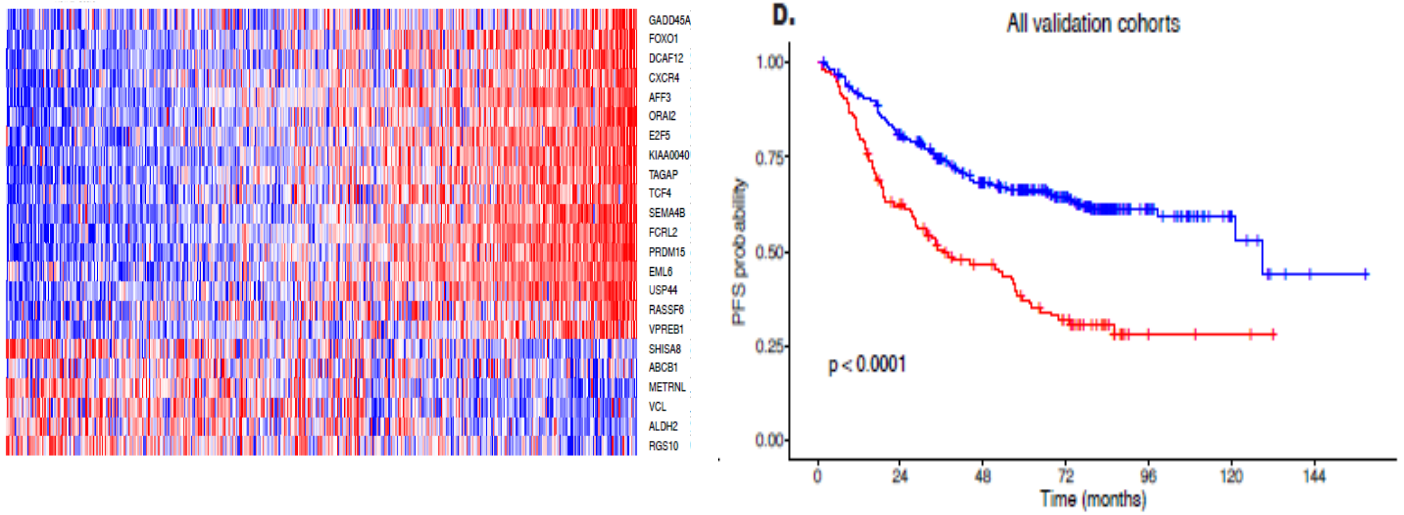
- Tumor burden assessment in two clinical cohorts with FL diagnosed between 2007 and 2014.
- High TMTV defined as TMTV > 510cm^3
- High ctDNA defined as >2550 Eqg/mL (equivalent genome per mililiter)
- L/L versus H/H 4 year PFS 96% vs 73%.



Delfau-Larue et al Blood advances 2018

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 abstr 413)
- GEP biological stratification using a simple digital expression test



- (Huet et al., Lancet Oncology, 19:549, 2018)

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
  - Novel agents in lieu of CIT (where available)
  - Increase the *cure* of follicular lymphoma