

Lymphome B diffus à grandes cellules: évaluation et stratégie thérapeutique de première ligne en 2020

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Stratification sur l'IPI

	<60 ans	60 – 80 ans	>80ans
aaIPI = 0	LNH09-1B		SENIOR
aaIPI = 1	GAINED	REMARC	
aaIPI = 2-3			

< 60 ans aalPI 1-3

Prognosis value of Interim PET in DLBCL

Study	n	PET after...	2y-outcome PET-	2y-outcome PET+
Jerusalem 2000	28	median : 3 cycles	62 % (PFS)	0% (PFS)
Spaepen 2002	70	median : 3 cycles	85 % (PFS)	4% (PFS)
Kostakoglu 2002	30	1 cycle	85% (PFS)	< 15 % (PFS)
Haioun 2005	90	2 cycles	82 % (EFS)	43 % (EFS)
Mickaeel 2005	121	median : 2 cycles	87 % (PFS)	34 % (PFS)



LNH 2007-3B

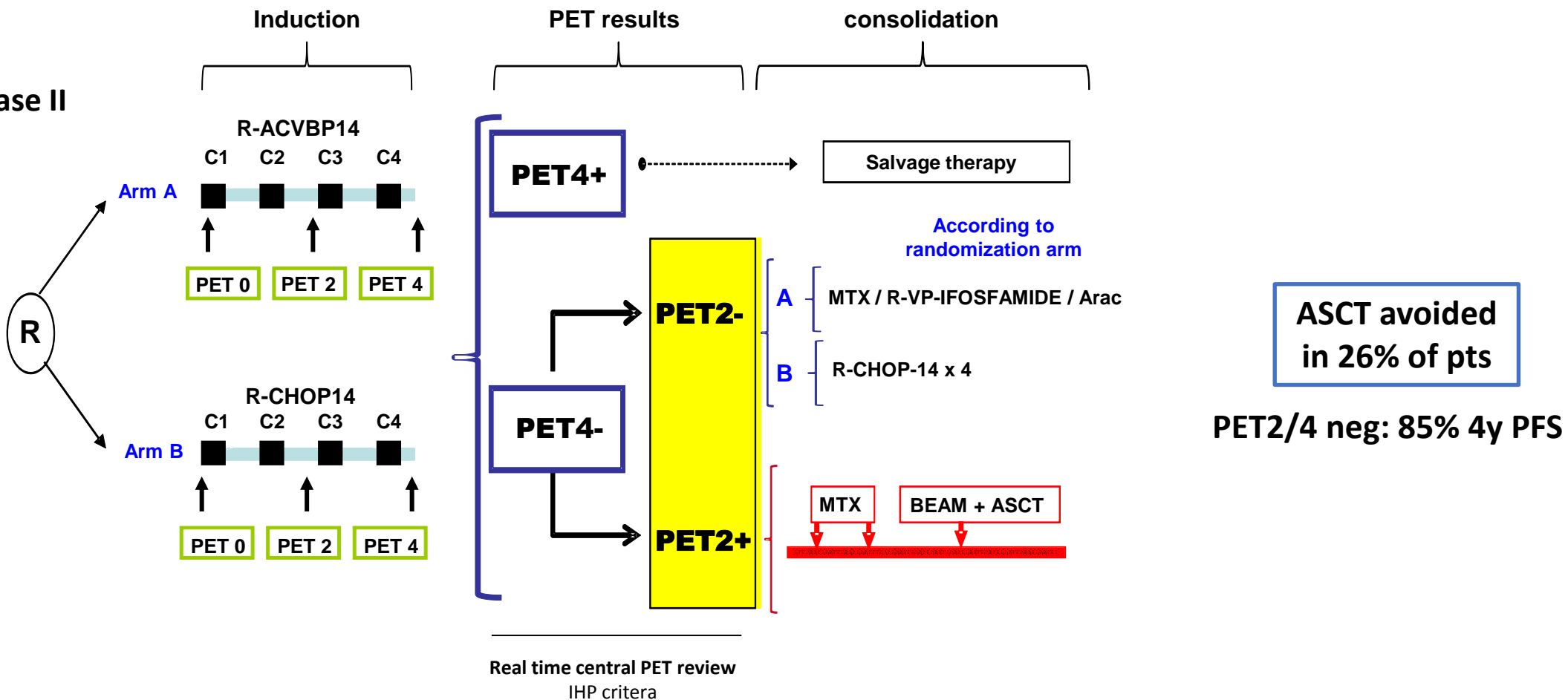
CLINICAL TRIALS AND OBSERVATIONS

FDG-PET–driven consolidation strategy in diffuse large B-cell lymphoma: final results of a randomized phase 2 study

R.-O. Casasnovas,¹ L. Ysebaert,² C. Thieblemont,³ E. Bachy,⁴ P. Feugier,⁵ A. Delmer,⁶ S. Tricot,⁷ J. Gabarre,⁸ M. Andre,⁹ C. Fruchart,¹⁰ N. Mounier,¹¹ R. Delarue,¹² M. Meignan,¹³ A. Berriolo-Riedinger,¹⁴ S. Bardet,¹⁵ J.-F. Emile,^{16,17} J.-P. Jais,¹⁸ C. Haioun,¹⁹ H. Tilly,²⁰ and F. Morschhauser²¹

BLOOD, 14 SEPTEMBER 2017 • VOLUME 130, NUMBER 11

Randomized phase II
DLBCL: 18-60y
aaIPI=2-3





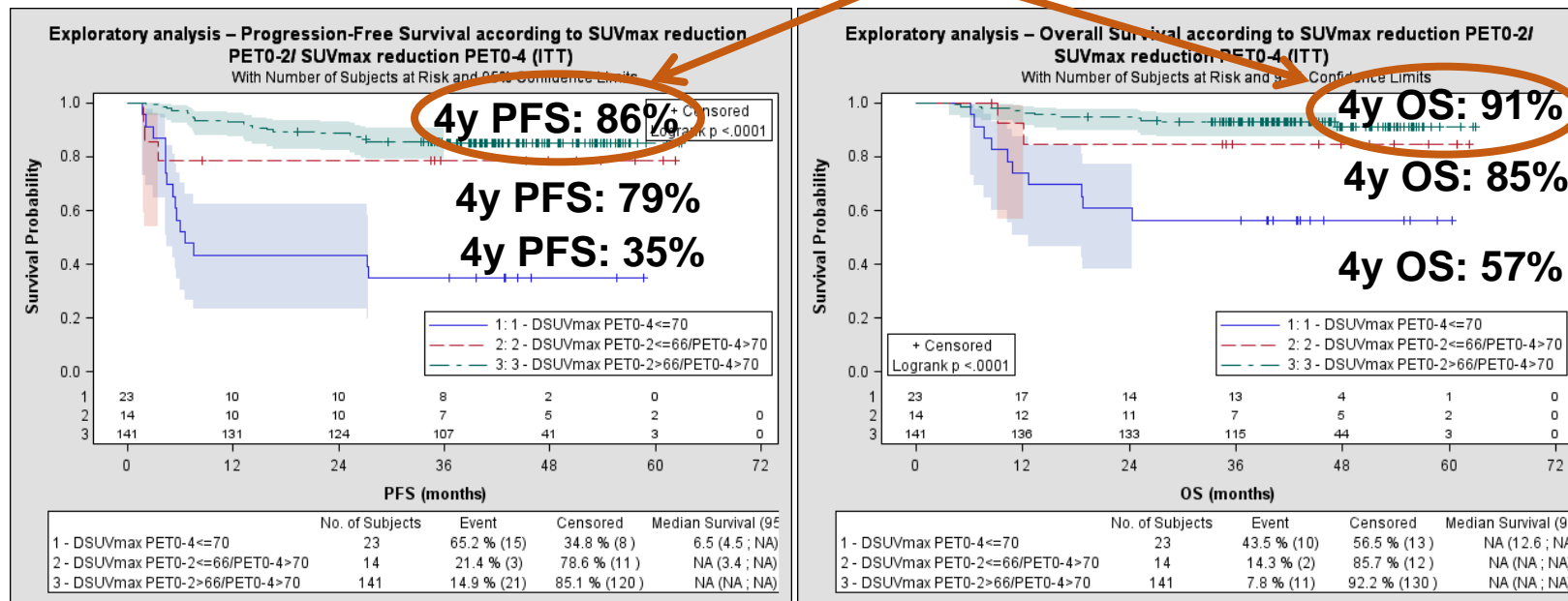
SUVmax reduction improves early prognosis value of interim positron emission tomography scans in diffuse large B-cell lymphoma

René-Olivier Casasnovas,¹ Michel Meignan,² Alina Berriolo-Riedinger,³ Stéphane Bardet,⁴ Anne Julian,⁵ Catherine Thieblemont,⁶ Pierre Vera,⁷ Serge Bologna,⁸ Josette Brière,⁶ Jean-Philippe Jais,⁹ Corinne Haioun,² Bertrand Coiffier,¹⁰ and Franck Morschhauser,¹¹ on behalf of the Groupe d'étude des lymphomes de l'adulte (GELA)

BLOOD, 7 JULY 2011 • VOLUME 118, NUMBER 1

37

80% of the whole population



Interim PET-driven strategy in de novo diffuse large B-cell lymphoma: do we trust the driver?

Steven Le Gouill¹⁻³ and René-Olivier Casasnovas^{4,5}

¹Department of Hematology, CHU de Nantes, University Hospital of Nantes, Nantes, France; ²Centre de Recherche en Cancérologie et Immunologie Nantes Angers, INSERM, Centre National de la Recherche Scientifique, Université de Nantes, Nantes, France; ³INSERM, University Hospital of Nantes, Nantes, France; ⁴Department of Hematology, CHU de Dijon, University Hospital of Dijon, Dijon, France; and ⁵INSERM, LNC UMR 1231, Dijon, France

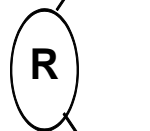


GAINED: Study design

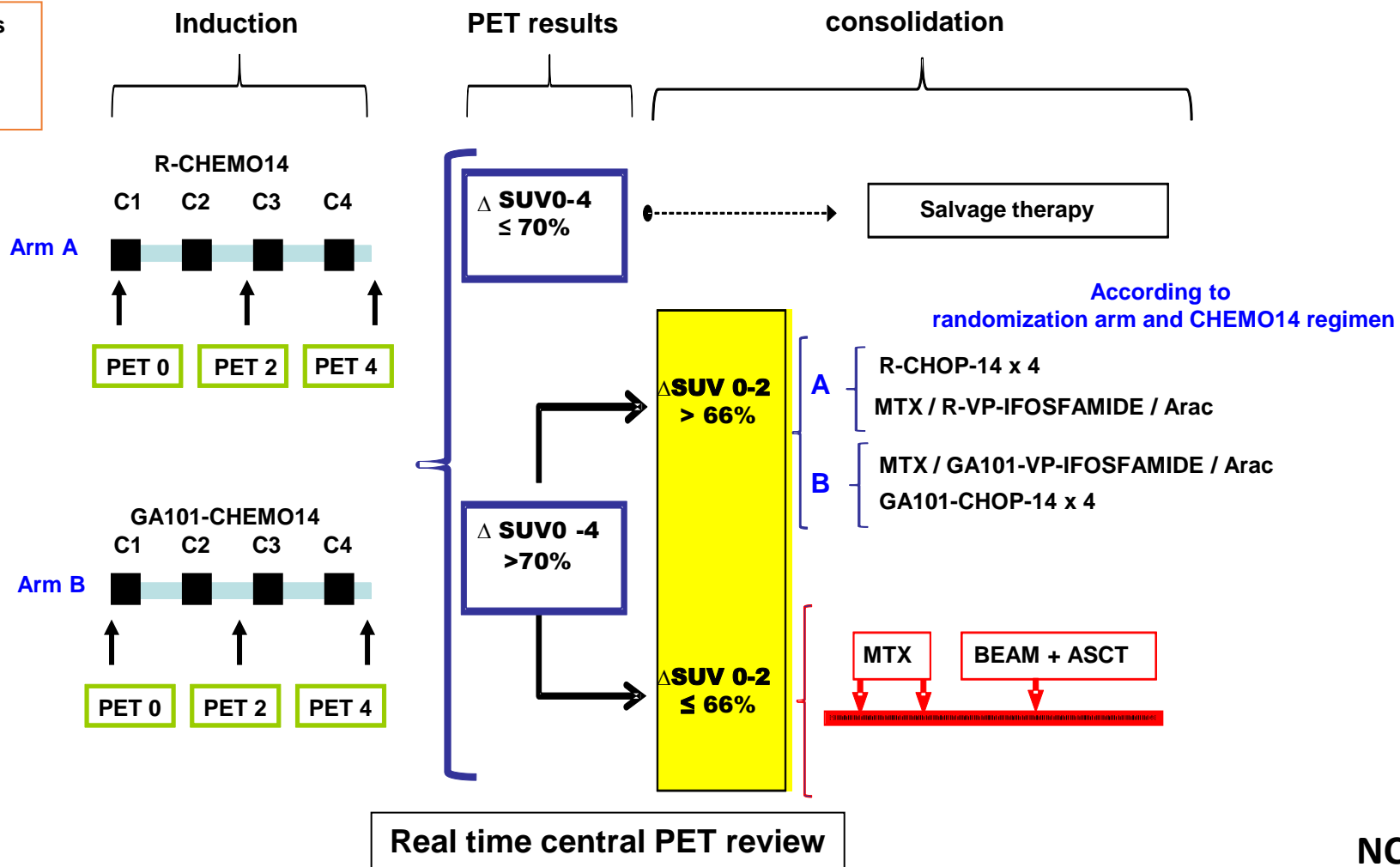
Previously untreated DLBCL: - Age: 18-60y
- aalPI = 1-3
- Baseline PET

CHEMO pre-planned for all pts according to center decision:
- ACVBP14
- CHOP14

Randomization 1:1 stratified according to aalPI 1 vs 2-3 and Chemo regimen



GA101: 1000mg by injection
D1-D8 cycles 1-2



NCT01659099

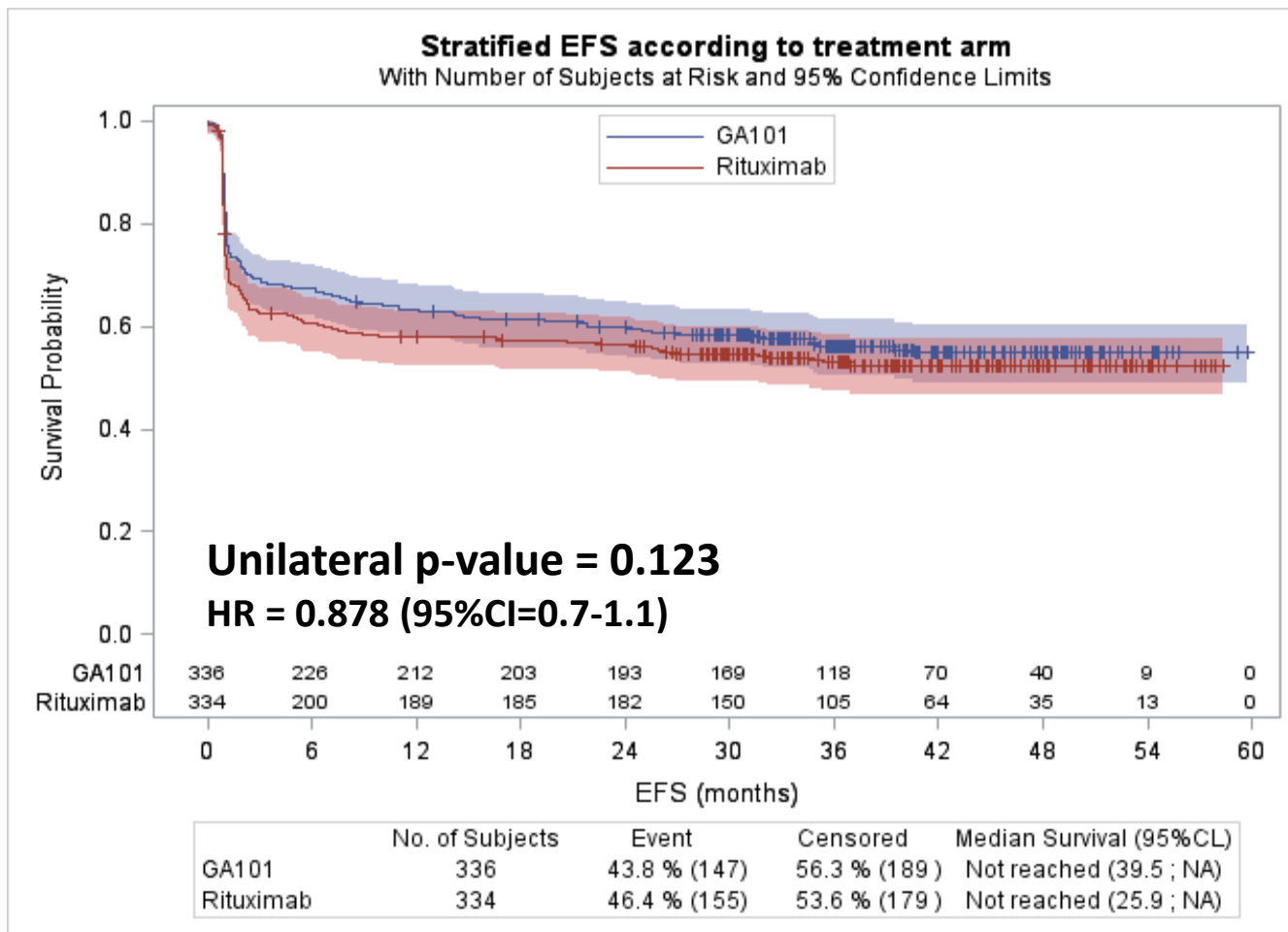


Concordance between planned and actually received consolidation treatment

		G-Chemo n = 292		R-Chemo n = 289	
		N	% of agreement	N	% of agreement
PET2-/PET4- n=401 (69%)	All	215		186	
	Chemotherapy	213	99	185	99
	High dose therapy + ASCT	1		0	
	Salvage therapy	1		1	
PET2+/PET4- n=77 (15%)	All	40		47	
	High dose therapy + ASCT	34	85	40	85
	Chemotherapy	4		4	
	Salvage therapy	2		3	
PET4+ n=93 (16%)	All	37		56	
	Salvage therapy	35	95	56	100
	High dose therapy + ASCT	0		0	
	Chemotherapy	2		0	



GAINED: EFS (Primary endpoint)



R-chemo: 2y-EFS = 56.6%; 4y-EFS = 52.4%

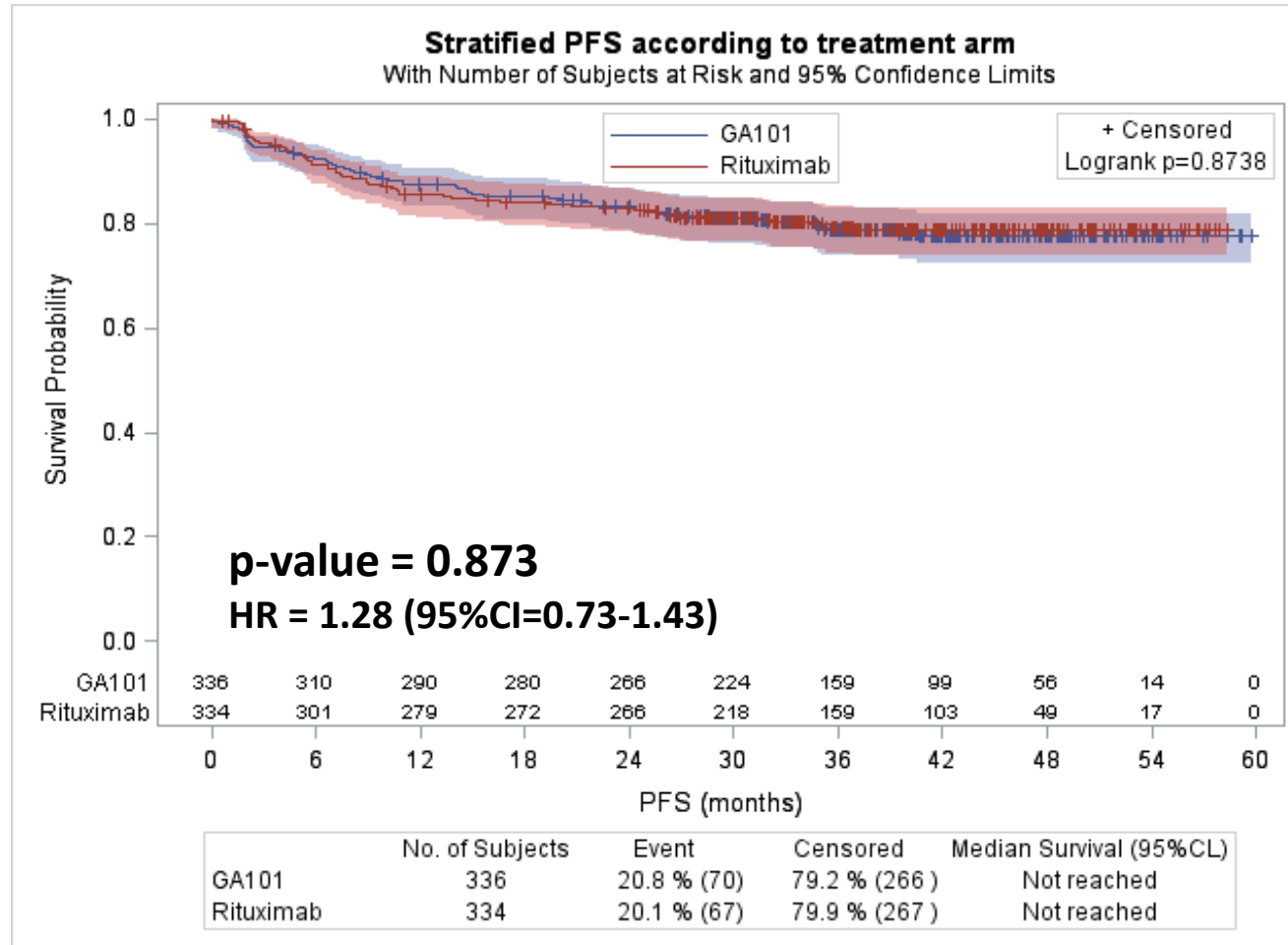
G-chemo: 2y-EFS = 59.8%; 4y-EFS = 54.8%

Median follow up = 36.7 months

Stopping date december 31 2017

*Testing the superiority of the experimental arm

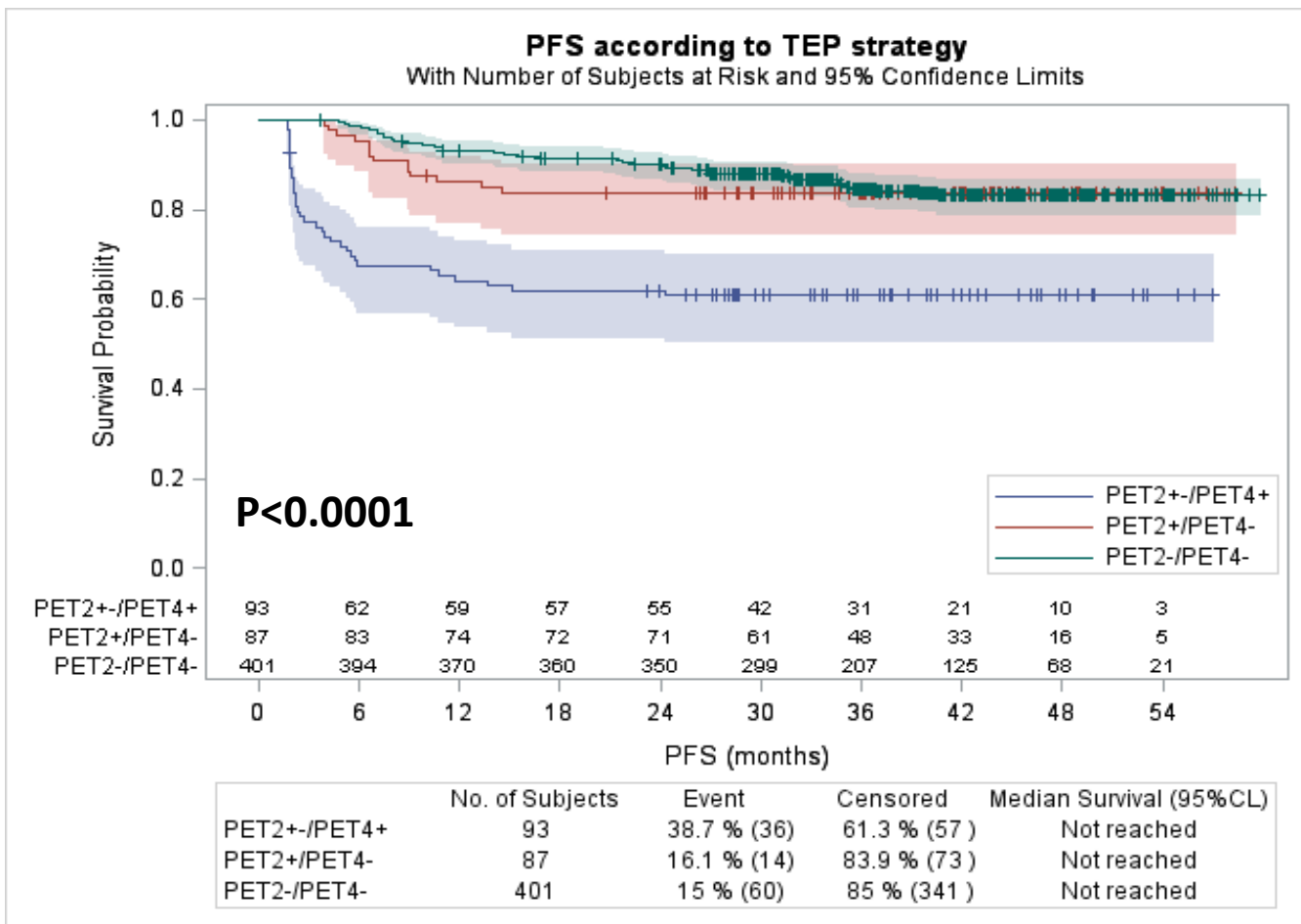
GAINED: PFS according to the randomization arm



R-chemo: 2y-PFS = 83%; 4y-PFS = 78.8%

G-chemo: 2y-PFS = 83.2%; 4y-PFS = 77.5%

PFS according to the PET driven strategy

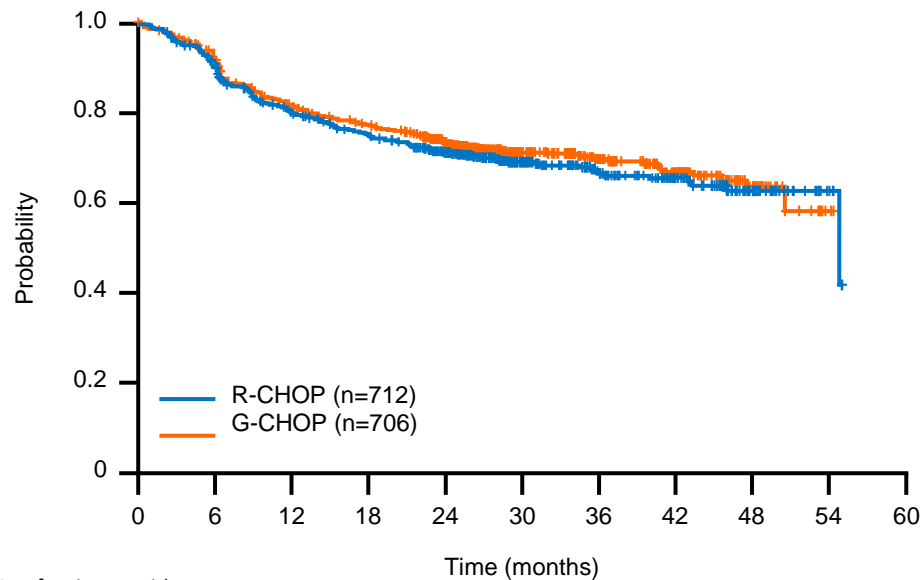


Compared to **PET2-/PET4-** pts (**3y-PFS = 84.6%**):

- **PET2+/PET4-** pts: **3y-PFS = 83.9%**; HR = 1.11; p < 0.71

- **PET2+/-/PET4+** pts: **3y-PFS = 60.9%**; HR = 3.56; p < 0.0001

GOYA: Investigator-assessed PFS (primary endpoint)

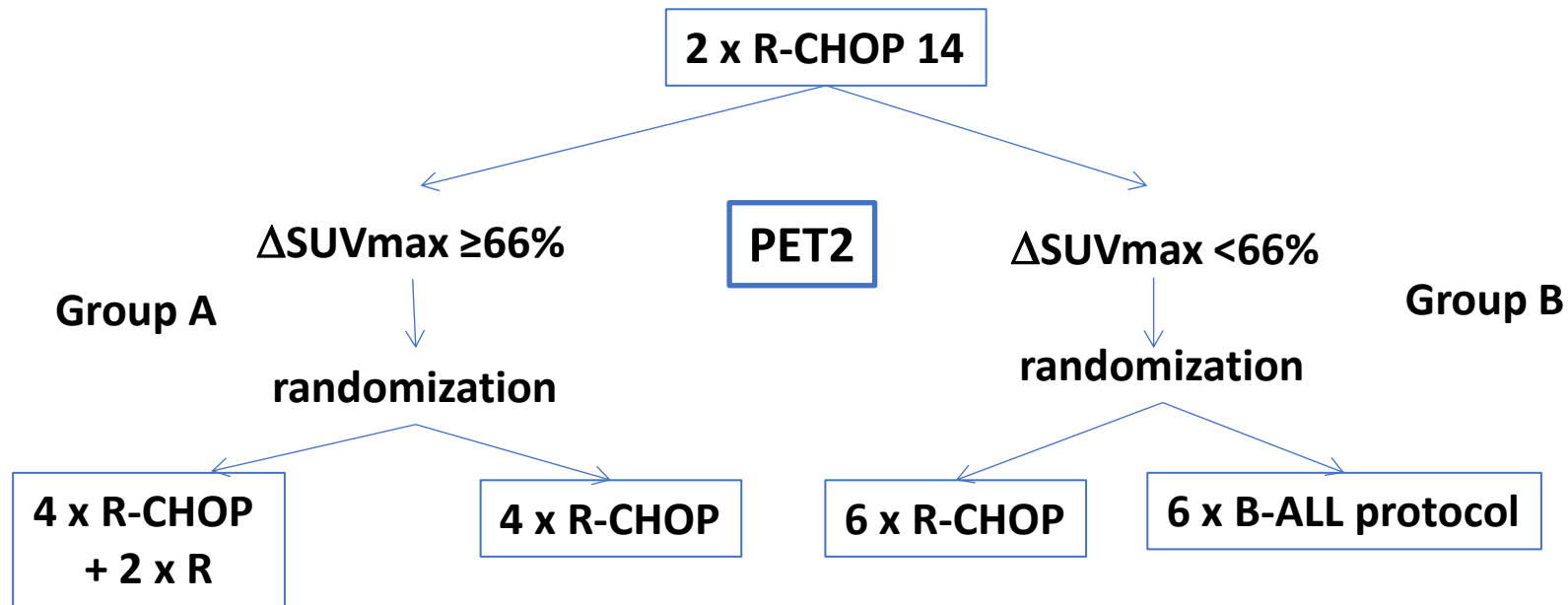


No. of patients at risk		Time (months)									
		0	6	12	18	24	30	36	42	48	54
R-CHOP	712	616	527	488	413	227	142	96	41	6	
G-CHOP	706	622	540	502	425	240	158	102	39	2	

	<i>R-CHOP,</i> <i>n=712</i>	<i>G-CHOP,</i> <i>n=706</i>
Pts with event, n (%)	215 (30.2)	201 (28.5)
1-yr PFS, %	79.8	81.6
2-yr PFS, %	71.3	73.4
3-yr PFS, %	66.9	69.6
HR (95% CI), p-value*	0.92 (0.76–1.11) p=0.3868	

Median follow-up: 29 months

PET Guided Therapy of Aggressive Lymphomas – (PETAL Trial)



1072 pts 18-80 y with aggressive lymphoma

853 pts evaluables (83 (10%) T-NHL)

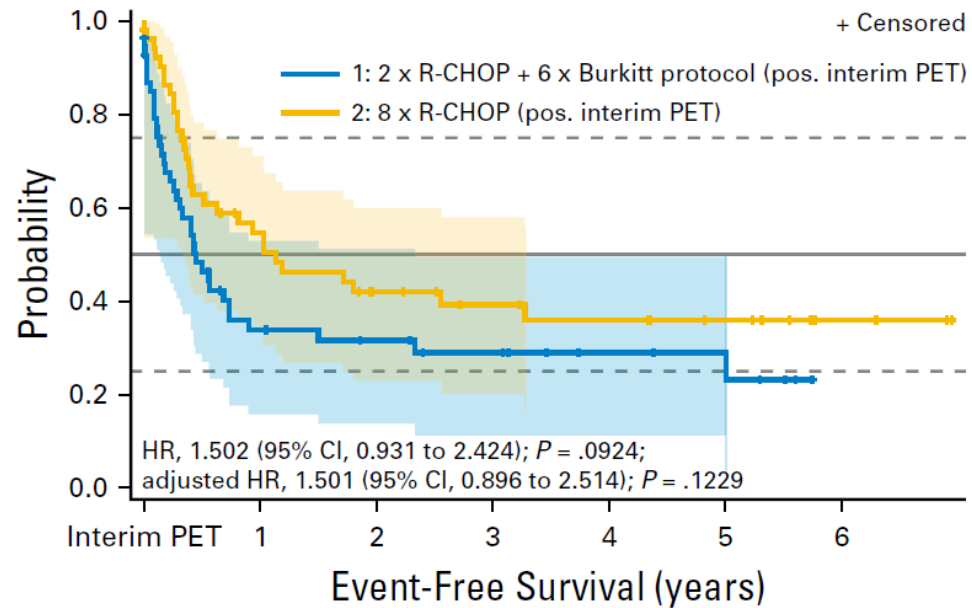
83% of B lymphoma = DLBCL

Follow Up 33 months

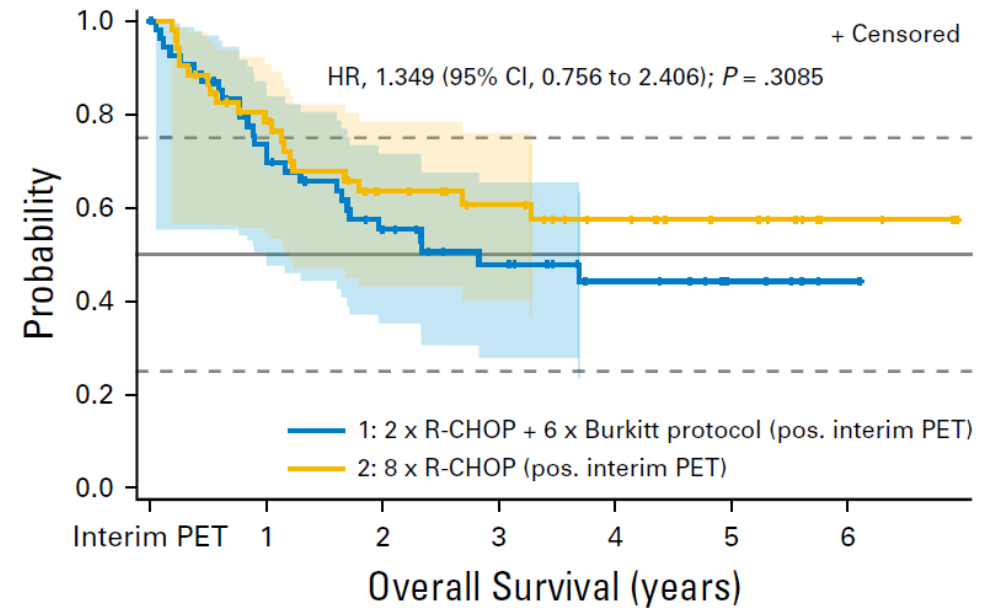
Main objective: increase 2y-TTF

- Group A: from 80% to 90%
- Group B: from 30% to 40%

PETAL: PET2+ patients

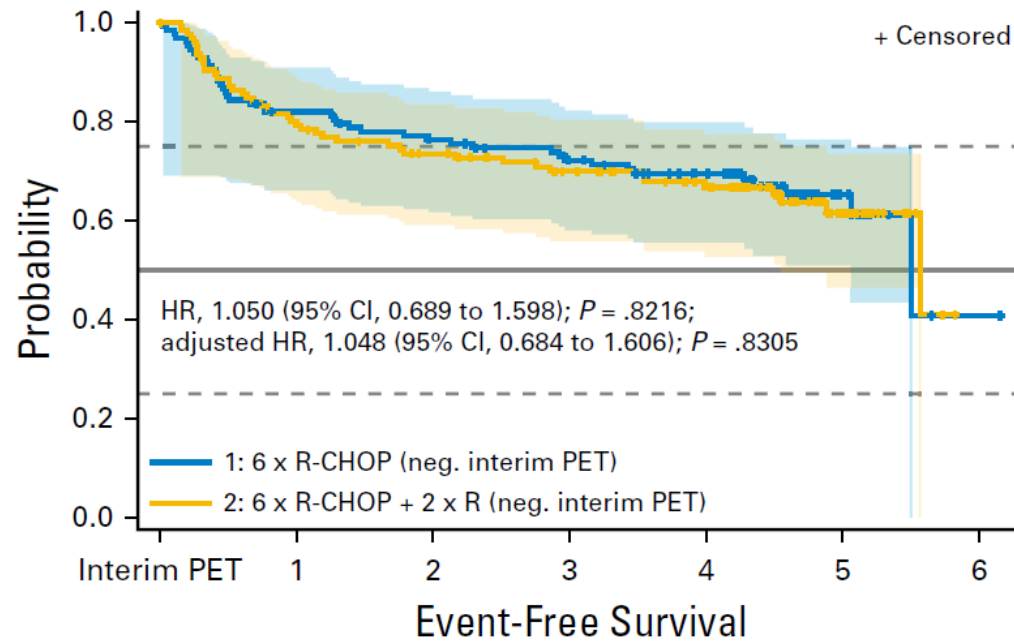


No. at risk		1	2	3	4	5	6
1	56	16	13	10	6	5	0
2	52	26	17	13	11	8	3

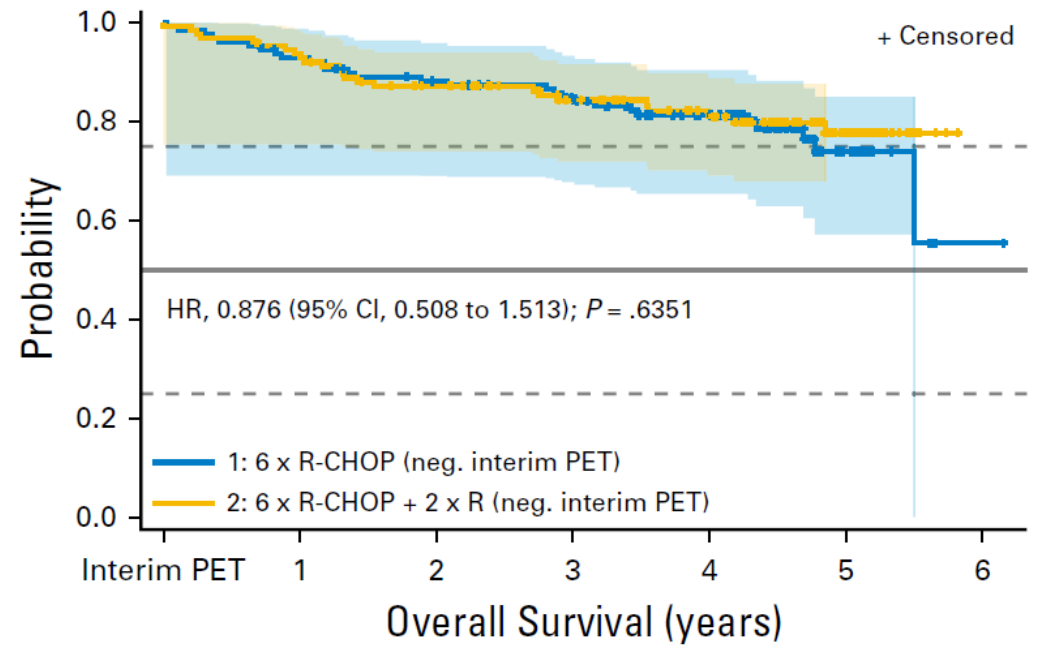


No. at risk		1	2	3	4	5	6
1	56	37	25	18	10	5	1
2	52	38	25	20	14	9	3

PETAL: PET2- patients

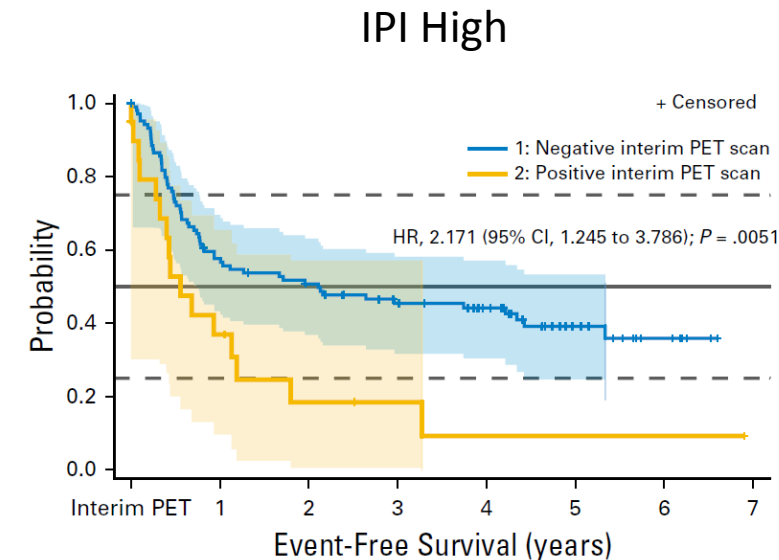
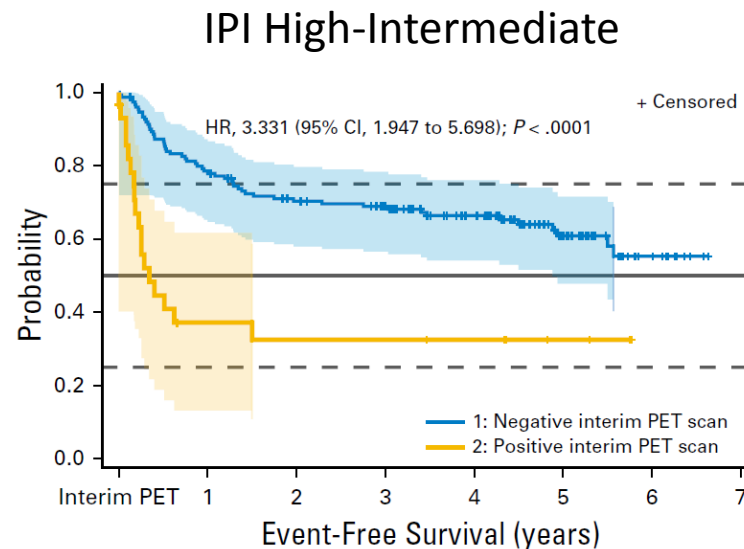
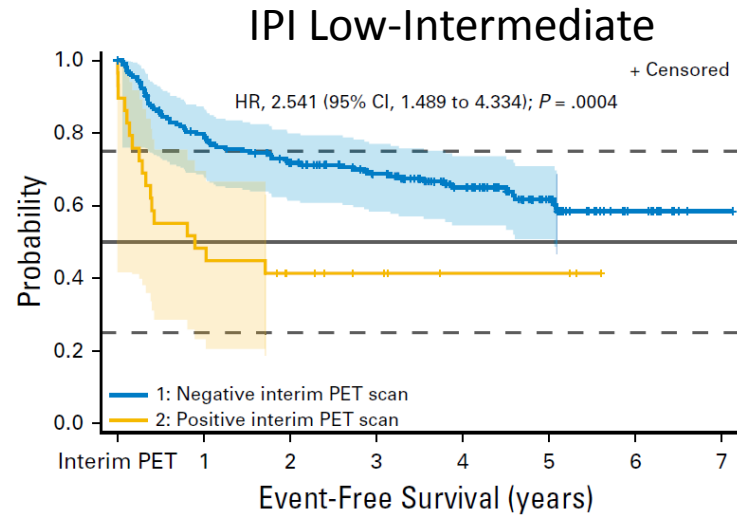
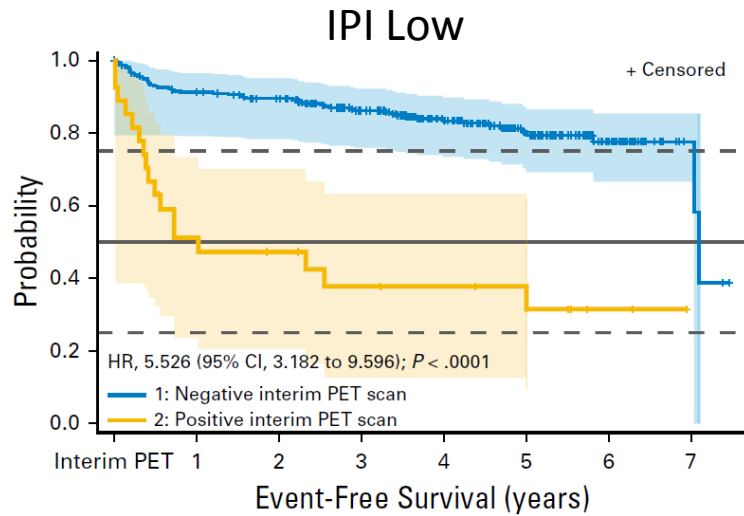


No. at risk		Interim PET	1	2	3	4	5	6
1	129	103	93	83	69	19	1	
2	126	99	88	73	59	22	0	



No. at risk		Interim PET	1	2	3	4	5	6
1	129	118	108	99	78	22	1	
2	126	117	104	86	69	29	0	

PETAL: EFS by IPI according to PET2 result



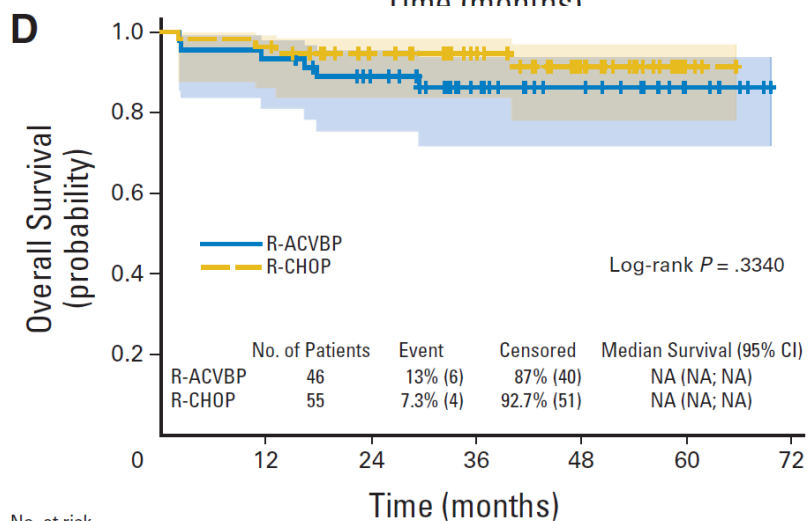
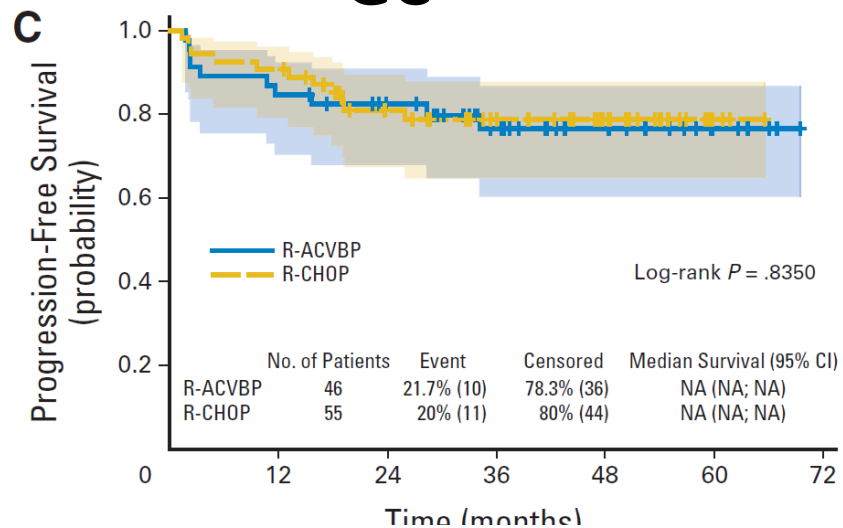
Δ SUVmax cutoff 66%
12.5% positive PET2

Median FU = 44 months



La chimiothérapie: R-CHOP / R-ACVBP

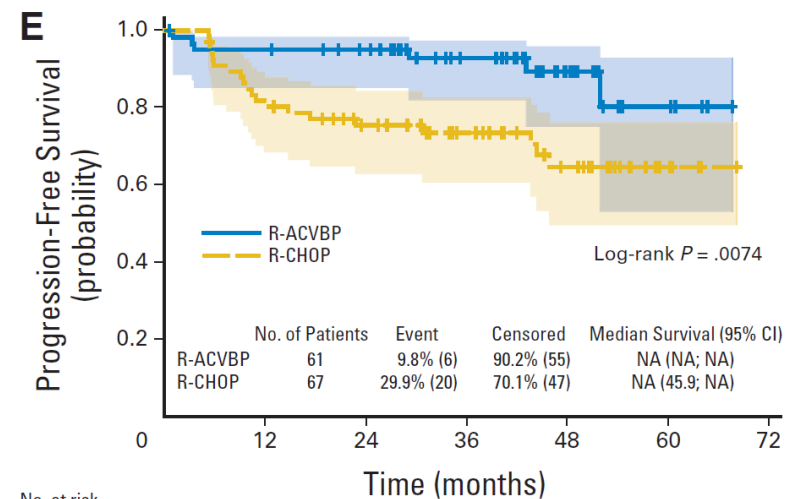
GC



No. at risk

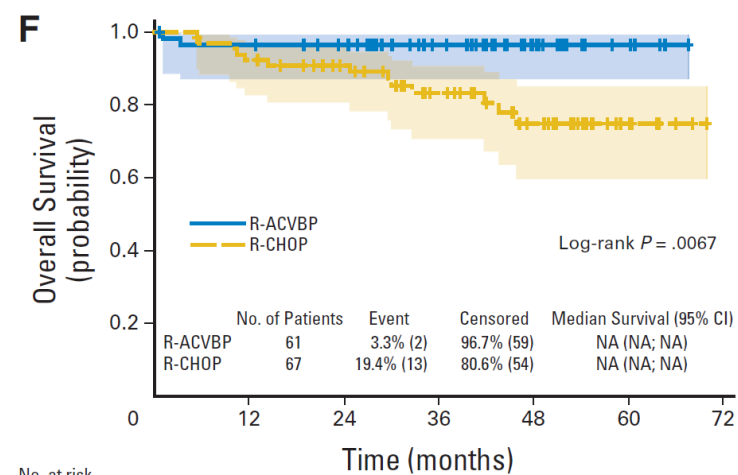
	0	12	24	36	48	60	72
R-ACVBP	43	36	24	16	7	0	0
R-CHOP	53	42	34	21	3	0	0

Non GC



No. at risk

	0	12	24	36	48	60	72
R-ACVBP	57	53	38	17	6	0	0
R-CHOP	53	43	32	20	5	0	0



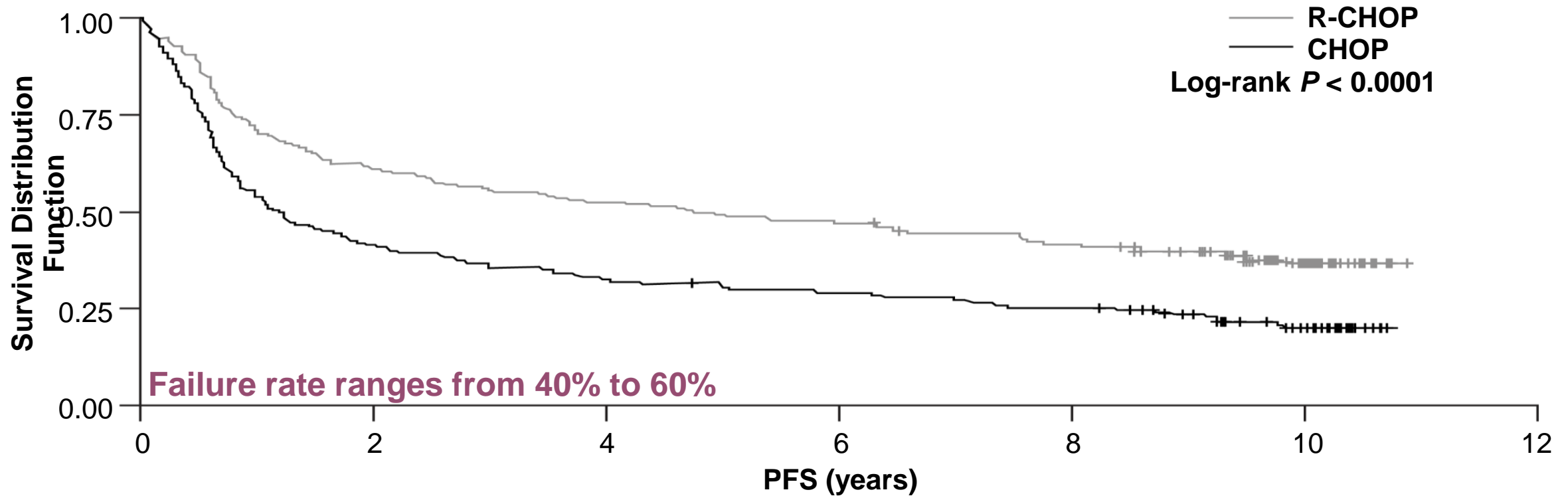
No. at risk

	0	12	24	36	48	60	72
R-ACVBP	58	54	40	18	6	0	0
R-CHOP	61	52	37	23	7	0	0

60 - 80 ans aalPI 1-3

LNH-98.5 Study

median follow-up of 10 years
Progression-Free Survival



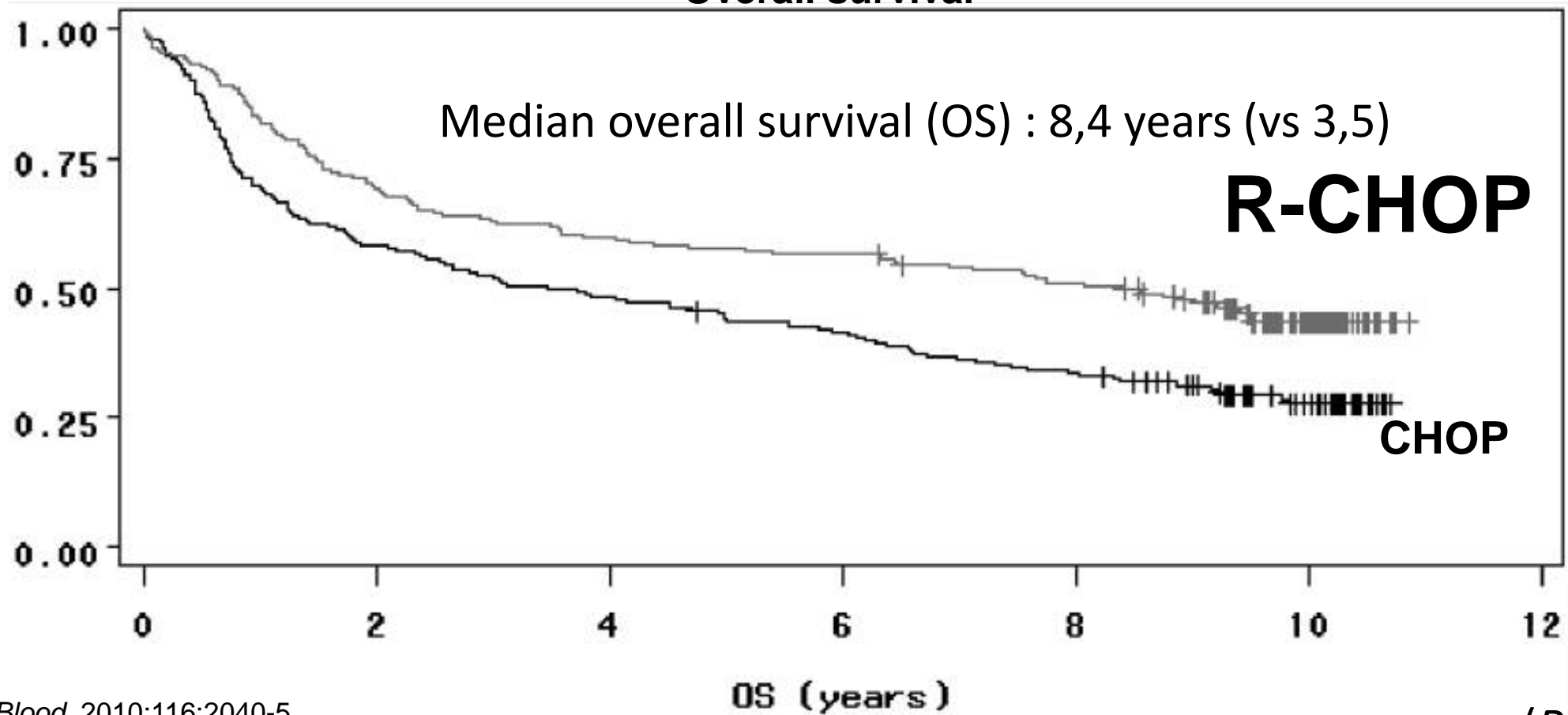
Coiffier et al. *Blood*. 2010;116:2040-5.

CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; R-CHOP, CHOP and rituximab.

LNH-98.5 Study

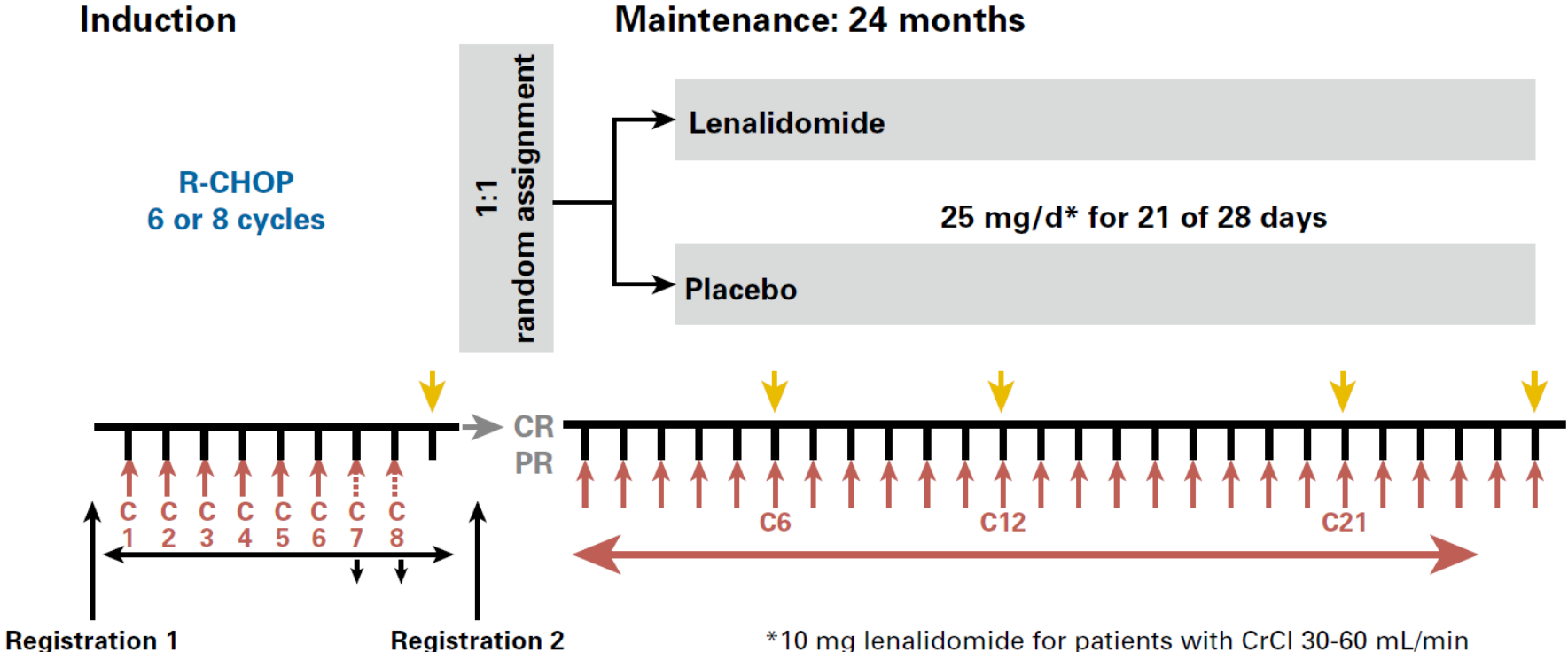
Median follow-up of 10 years

Overall survival

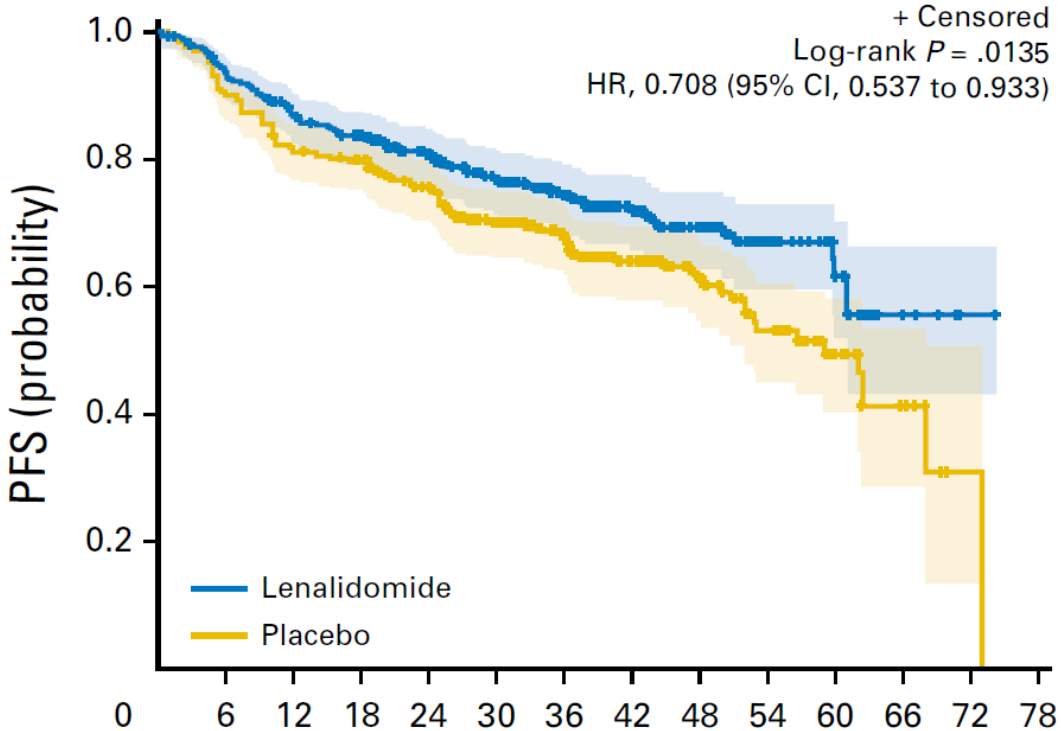


($P < .0001$)

REMARC

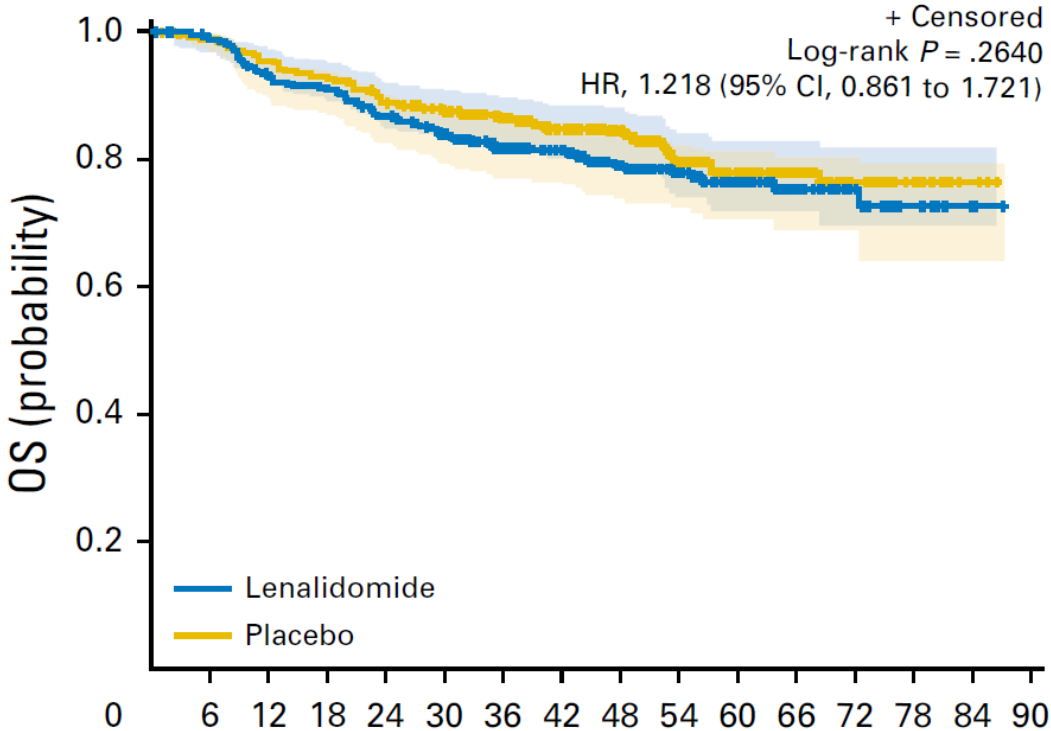


REMARC



No. at risk:

	0	6	12	18	24	30	36	42	48	54	60	66	72	78
Lenalidomide	323	291	265	250	214	172	137	97	70	42	23	6	1	0
Placebo	327	290	259	250	213	173	137	94	62	42	19	8	1	0



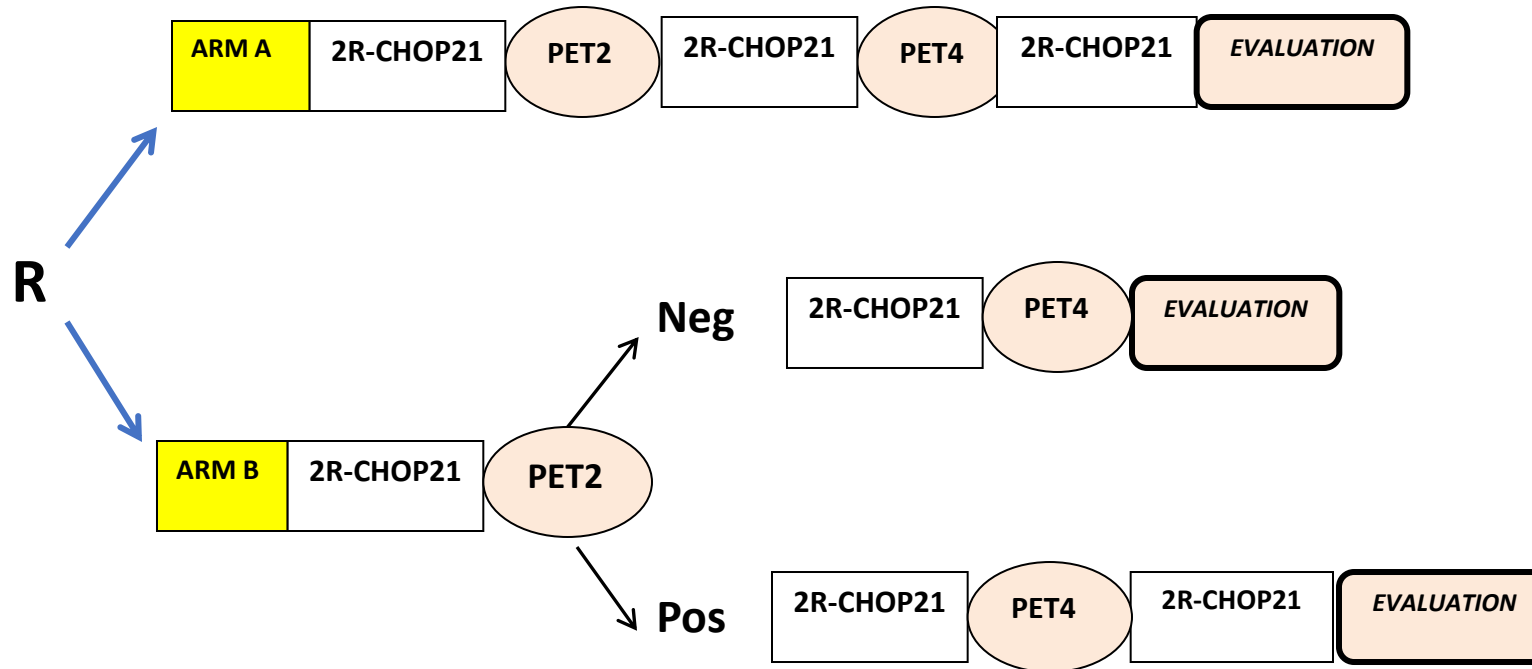
No. at risk:

	0	6	12	18	24	30	36	42	48	54	60	66	72	78	84	90
Lenalidomide	323	312	292	285	271	250	217	188	152	112	79	50	27	12	1	0
Placebo	327	319	308	299	285	272	240	209	164	117	83	58	34	12	3	0

18 - 80 ans aalPI 0

LNH 2009-1B

DLBCL: 18-80 y, aaPI=0



Central decisional PET interpretation: 5PS criteria (1,2,3, vs 4,5)

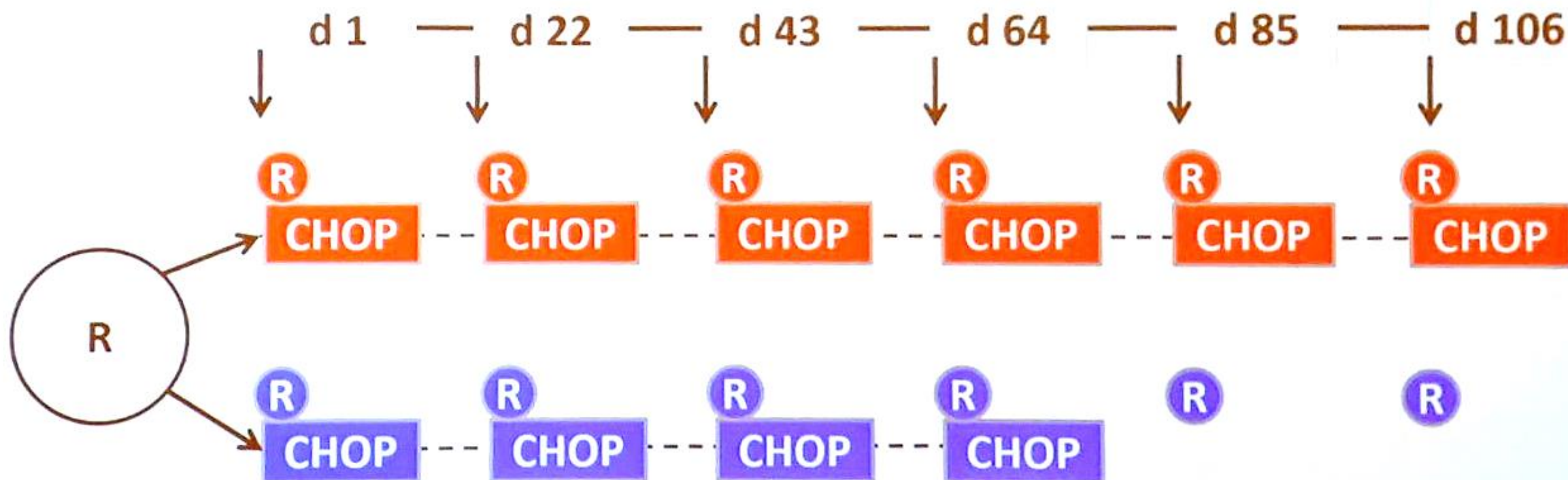
Non inferiority of the experimental arm

Standard arm : 80% 3y-PFS ; Experimental arm: 3y-PFS >70% (HR=1.6)

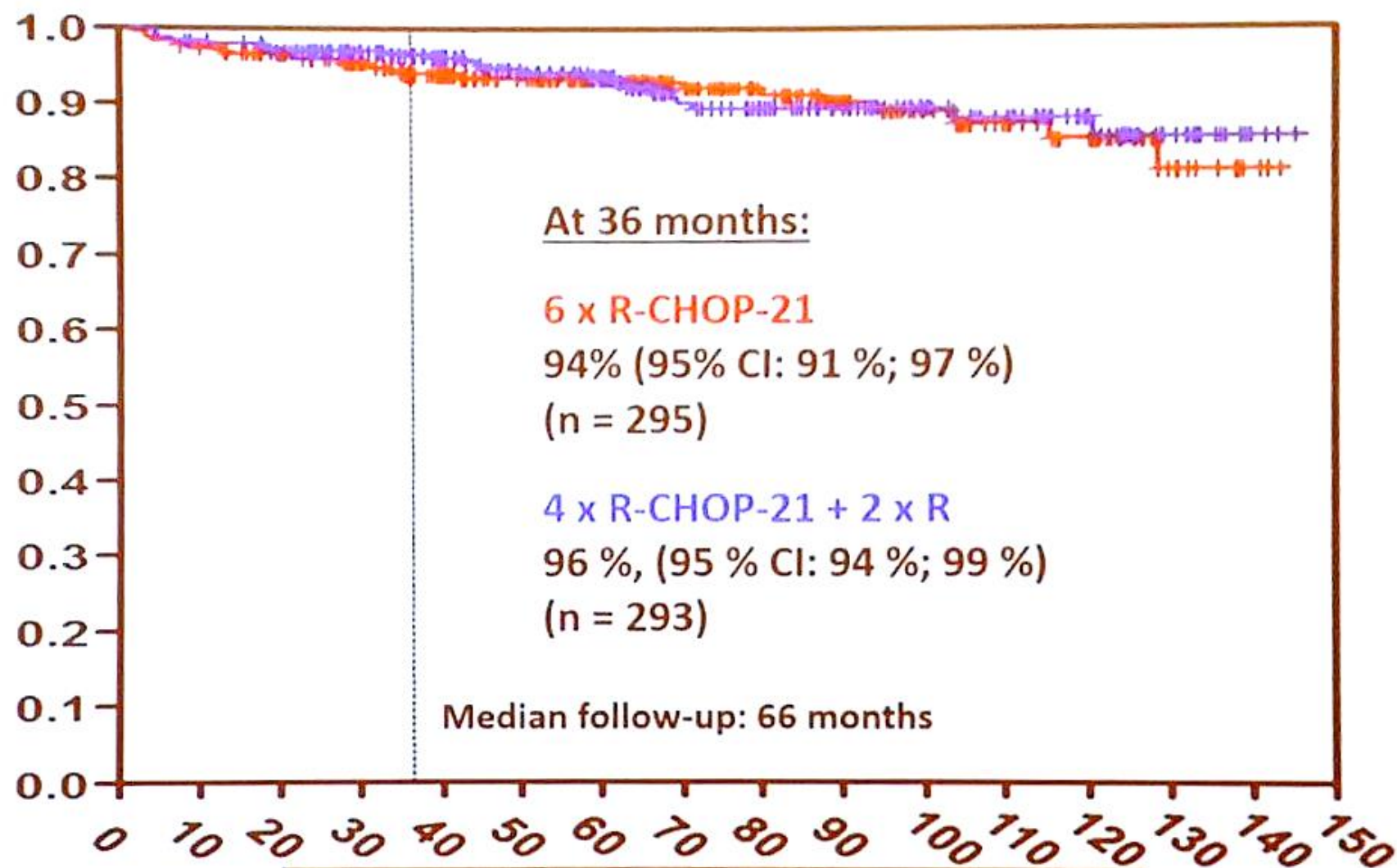


FLYER: Study Design

- Front-line treatment of aggressive B-cell lymphoma
- 18-60 years, stage I/II, aaIPI = 0, no bulk (max. diameter < 7.5 cm)



Primary Endpoint: PFS

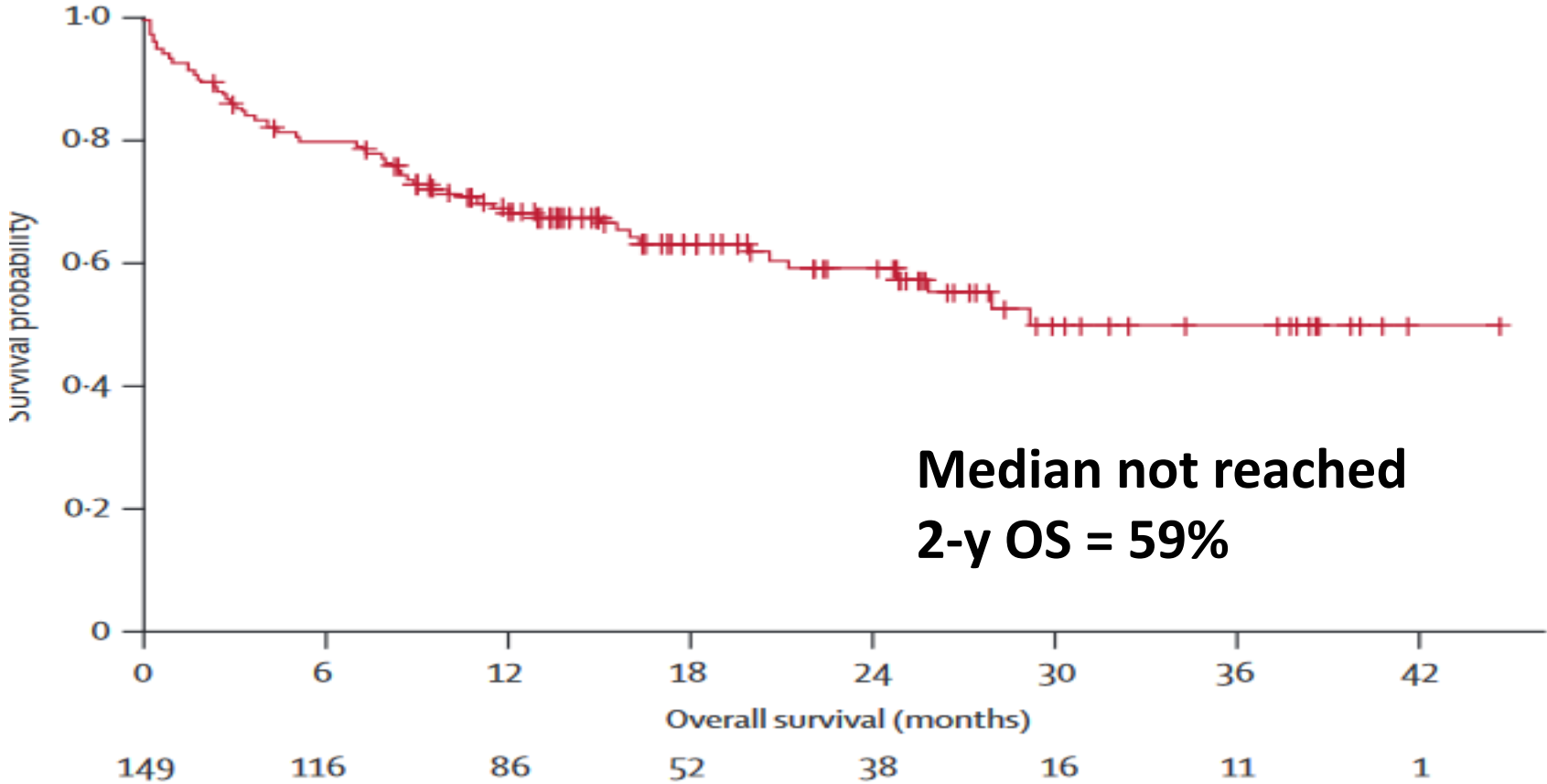


80 ans et plus

LNH 03-7B

Patients **over 80 years** – 2006 -2009, median age 83y (80-95)

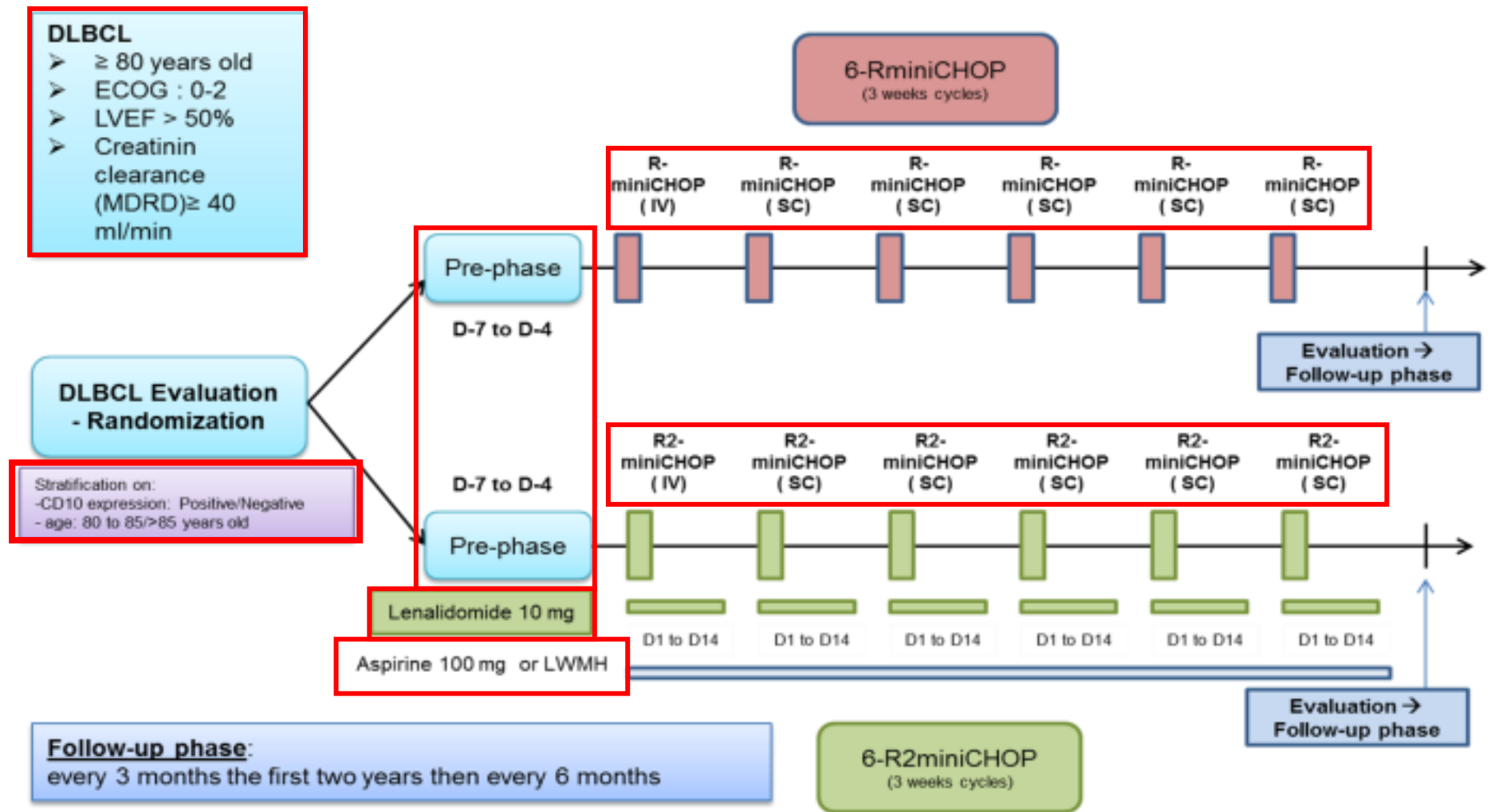
Multicentre, single arm, phase II trial : R-miniCHOP - LYSA



Neutropenia : 39%

Febrile neutropenia : 7%

SENIOR : Study Design



SENIOR: Patients characteristics

	R-miniCHOP	R2-miniCHOP
	n = 127	n = 122
Median Age [range]	83 [80-94]	83 [80-96]
> 85 y	32 (25.2%)	29 (23.8%)
M/F	56/71	57/65
CD10+	48 (37.8%)	43 (35.2%)
GC/non GC(%)	41/62(64%)	54/55(50%)
IPI		
0-2	32 (25.4%)	33 (27.7%)
3-5	94 (74.6%)	86 (72.3%)
PS ≥ 2	36 (28.3%)	27 (22.1%)
PS < 2	91 (71.7%)	95 (77.9%)
Bulky >10 cm	26 (20.5%)	19 (15.6%)
LDH > UNL	88 (69.8%)	71 (59.7%)
stage		
I-II	22 (17.3%)	16 (13.1%)
III-IV	105 (82.7%)	106 (86.9%)

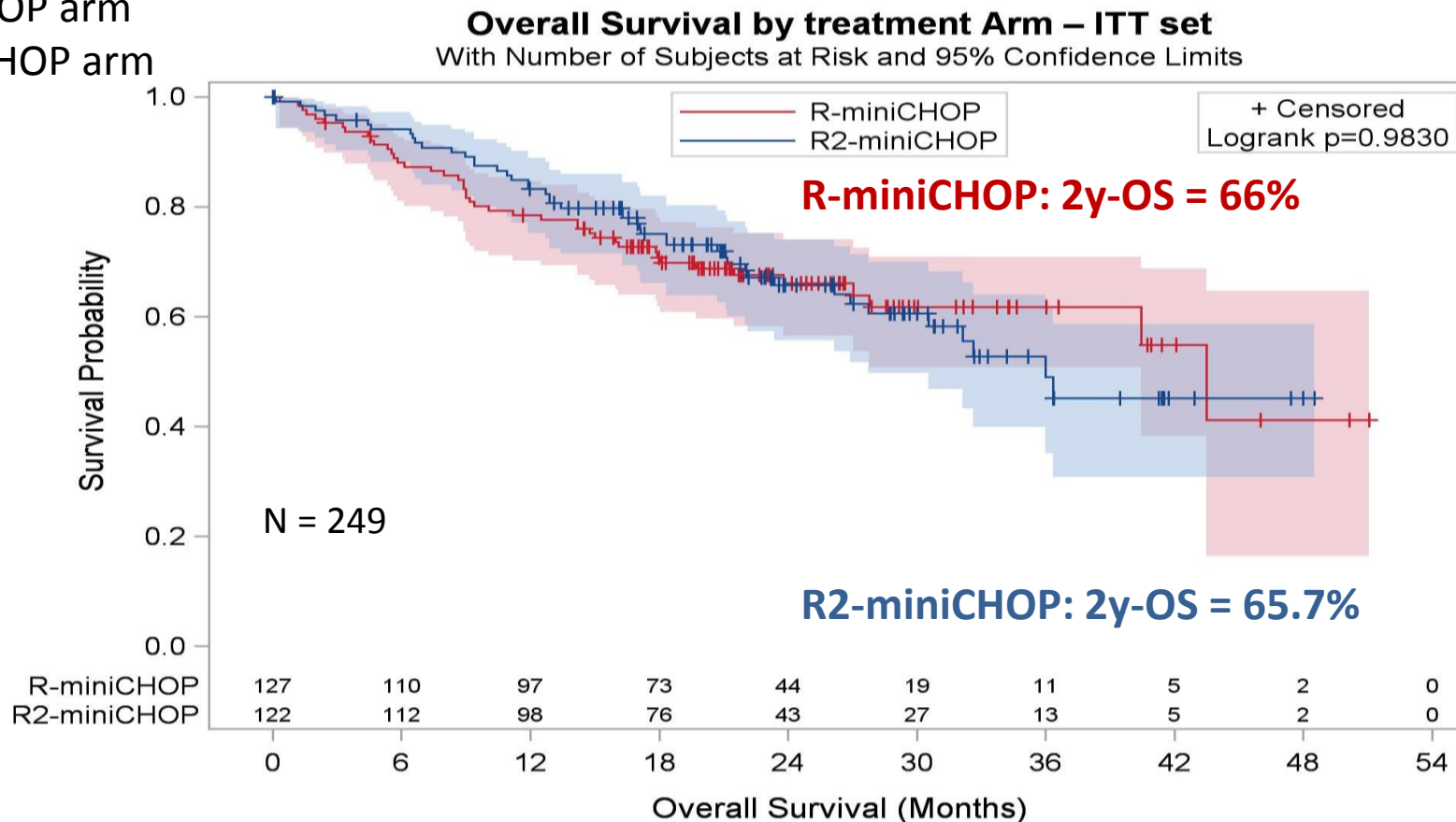
* determined by Hans in 212 available samples



SENIOR: Overall Survival (primary endpoint)

81 % of pts completed treatment

- 79% in R-miniCHOP arm
- 83% in R2-miniCHOP arm



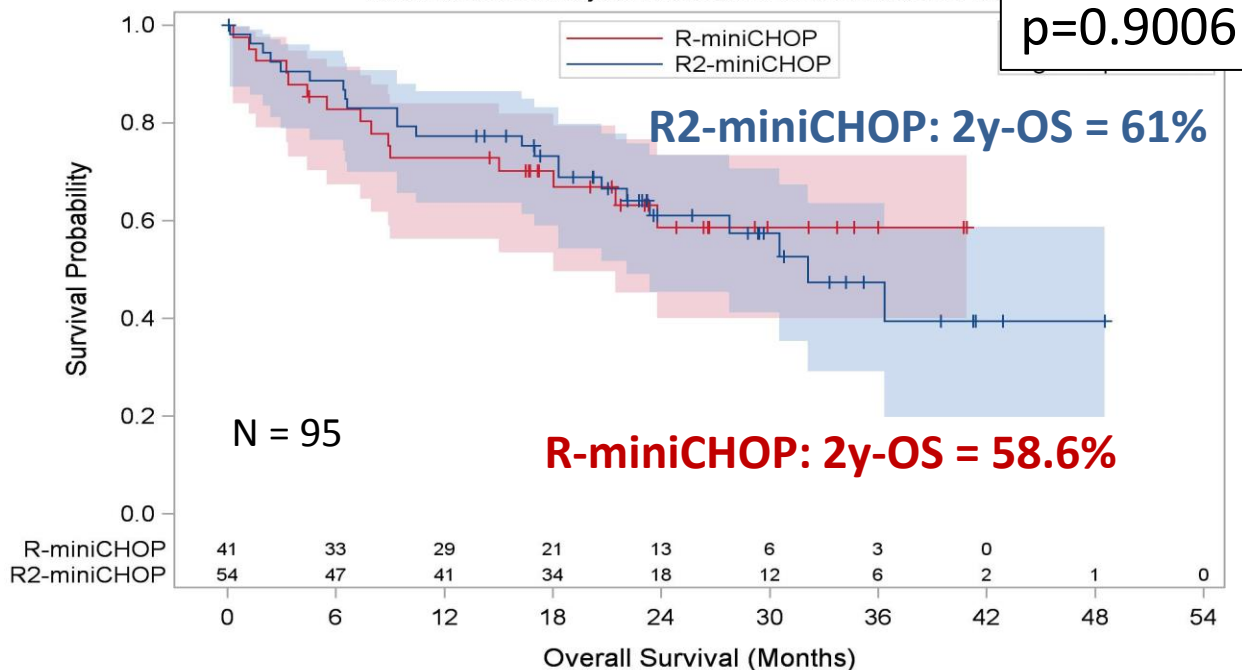
**Median follow up
25.1 months**

	No. of Subjects	Event	Censored	Median Survival (95%CL)
R-miniCHOP	127	34.6 % (44)	65.4 % (83)	43.5 (40.4 ; NA)
R2-miniCHOP	122	36.9 % (45)	63.1 % (77)	36 (27.8 ; NA)

SENIOR: OS according to Hans classification

GCB

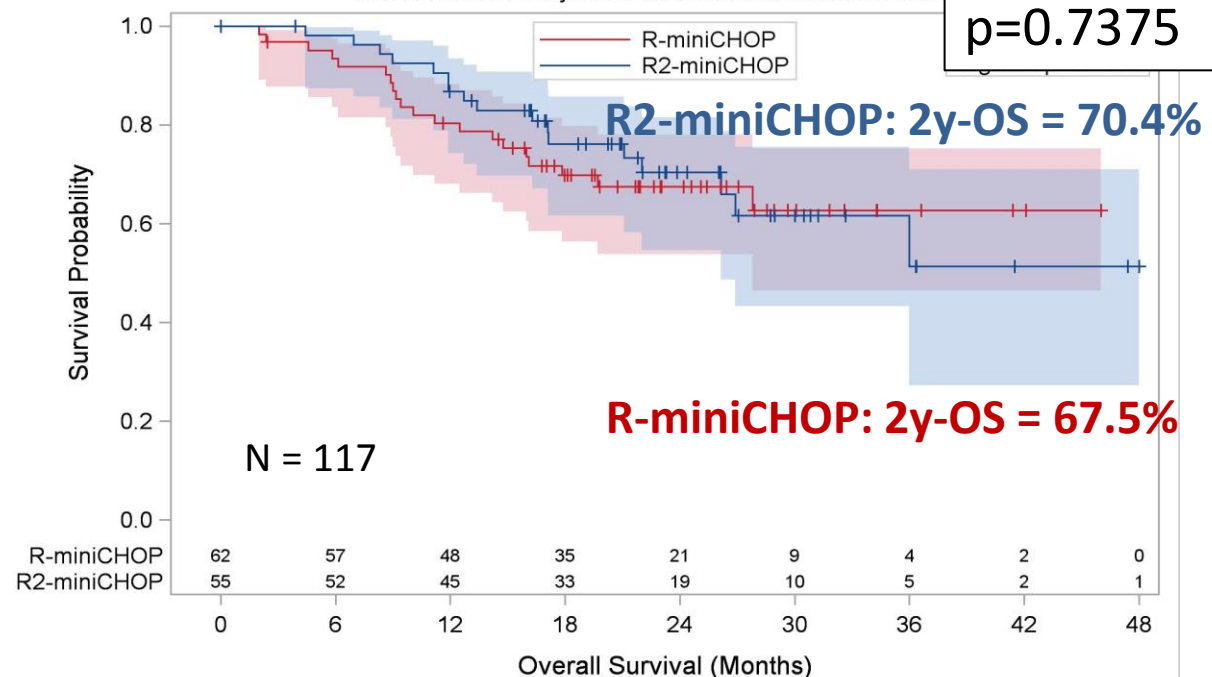
Overall Survival by Arm - GC (Hans)
With Number of Subjects at Risk and 95% Confidence Limits



	No. of Subjects	Event	Censored	Median Survival (95%CL)
R-miniCHOP	41	36.6 % (15)	63.4 % (26)	Not reached (18 ; NA)
R2-miniCHOP	54	42.6 % (23)	57.4 % (31)	32.1 (22.1 ; NA)

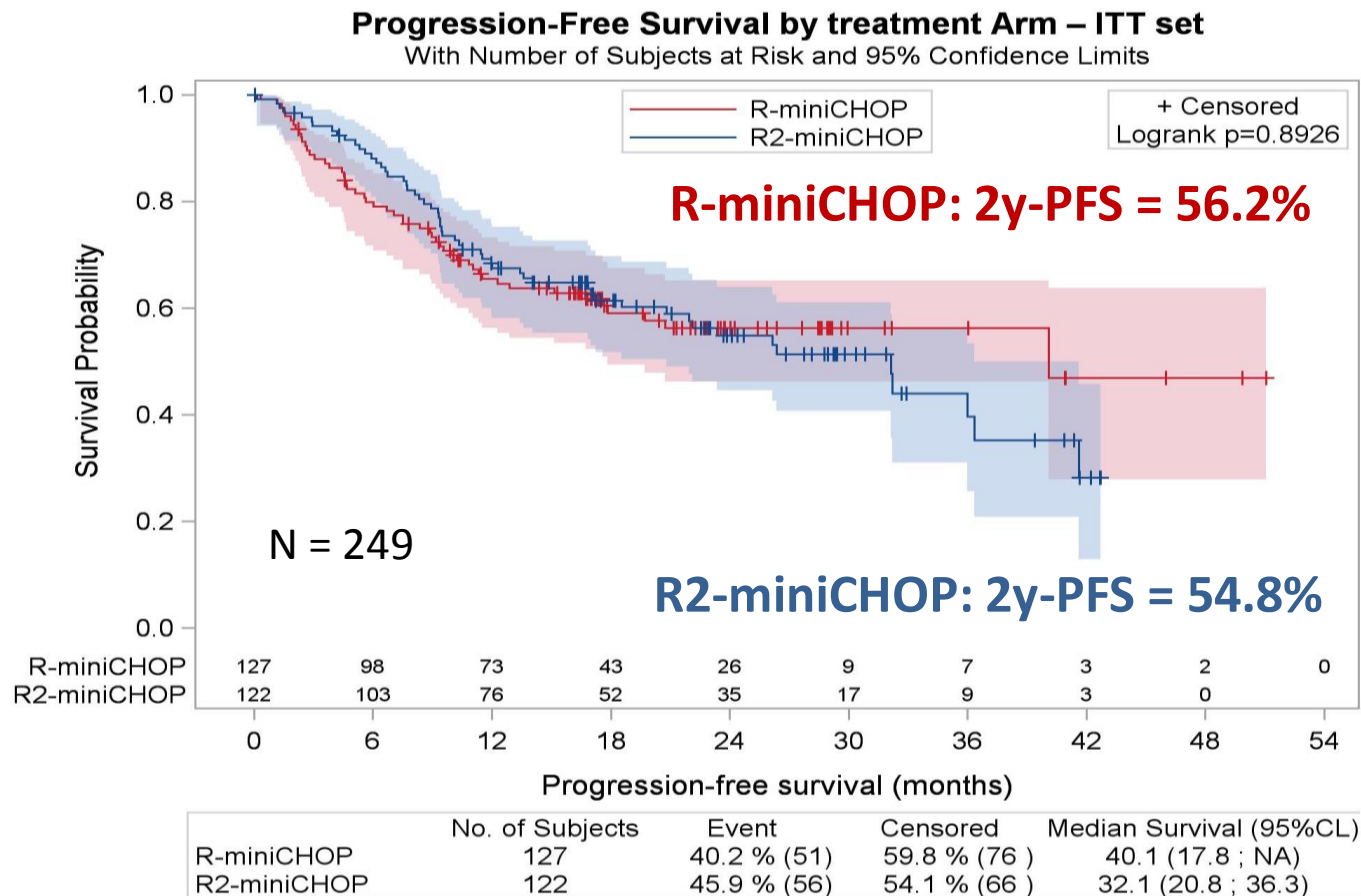
Non-GCB

Overall Survival by Arm - Non GC (Hans)
With Number of Subjects at Risk and 95% Confidence Limits



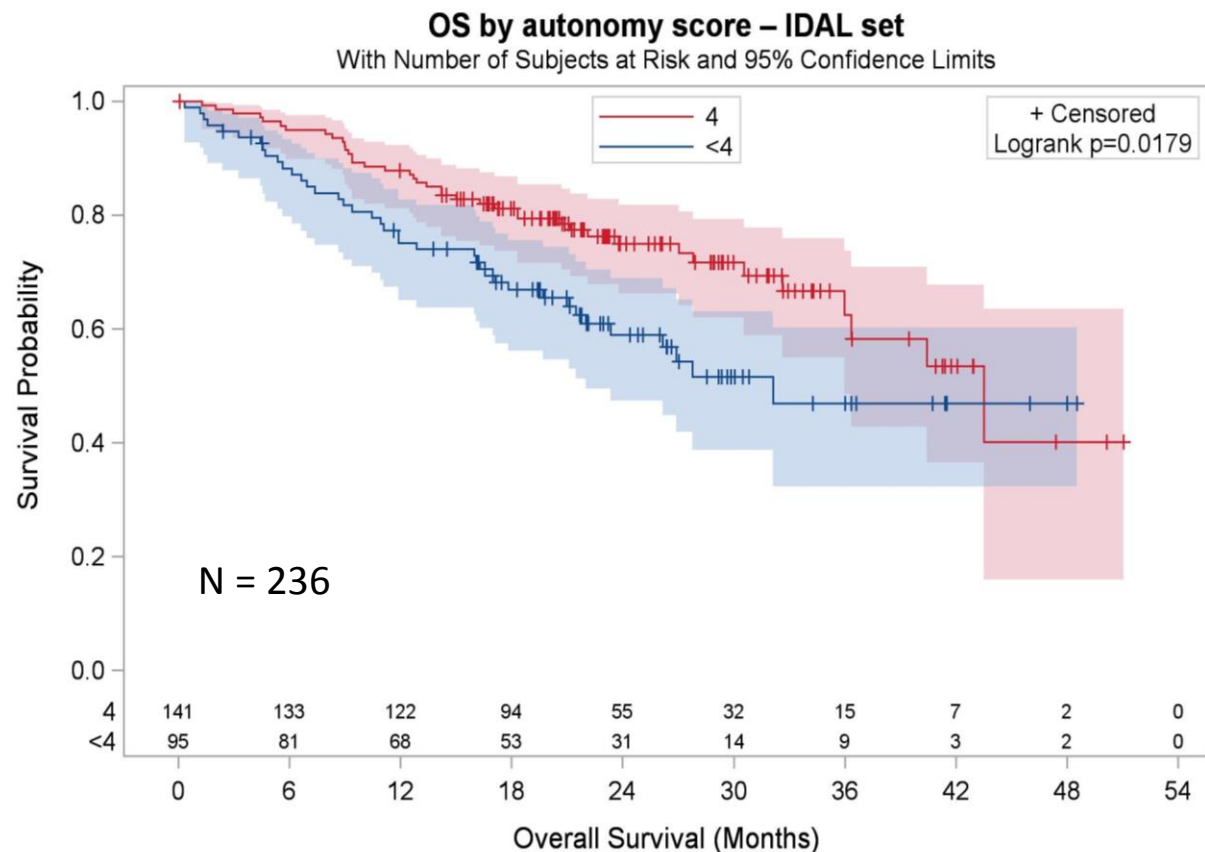
	No. of Subjects	Event	Censored	Median Survival (95%CL)
R-miniCHOP	62	32.3 % (20)	67.7 % (42)	Not reached (27.8 ; NA)
R2-miniCHOP	55	30.9 % (17)	69.1 % (38)	Not reached (26.2 ; NA)

SENIOR: PFS according to treatment arm

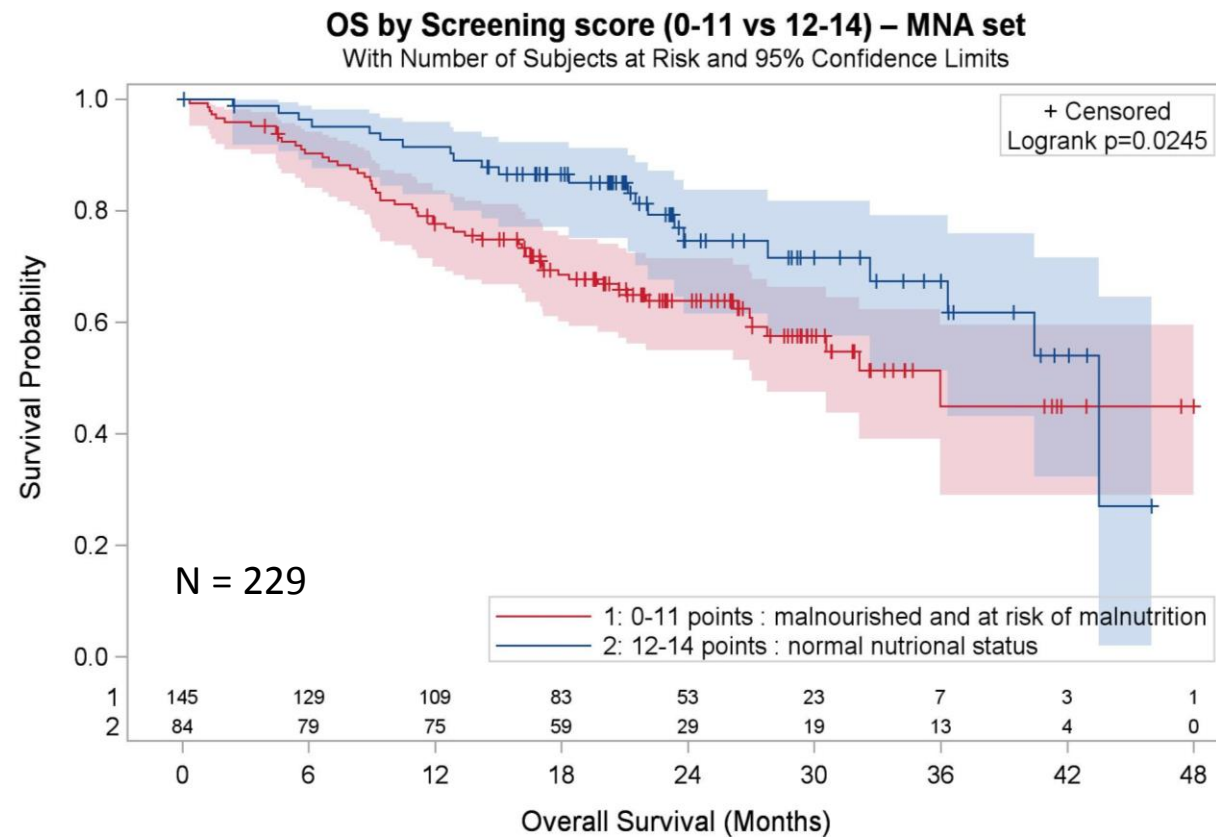




Geriatric scales: IADL (Instrumental Activities of Daily Living) and MNA (Mini Nutritional Assessment)



	No. of Subjects	Event	Censored	Median Survival (95%CL)
4	141	28.4 % (40)	71.6 % (101)	43.5 (36 ; NA)
<4	95	41.1 % (39)	58.9 % (56)	32.1 (22 ; NA)



	No. of Subjects	Event	Censored	Median Su
1 points : malnourished and at risk of malnutrition	145	38.6 % (56)	61.4 % (89)	36 (
2 points : normal nutritional status	84	26.2 % (22)	73.8 % (62)	43.5 (

R-CHOP + X

R-CHOP + X: Phase II studies

Target	Study	n	Population	Study	R-CHOP +/-	Result
CD79b	GO29562	70	All comers	Phase 2	Polatuzumab (CHP)	76% CR; 2y PFS = 83%
BCL2	CAVALLI	211	All comers	Phase 2	Venetoclax	69% CR; 2y PFS = 79%
EZH2	EPI-RCHOP	115	All comers (60-80y)	Phase 2	Tazemetostat	?
Syk	ENTO-RCHOP	121	All comers (60-80y)	Phase 2	Entospletinib	?

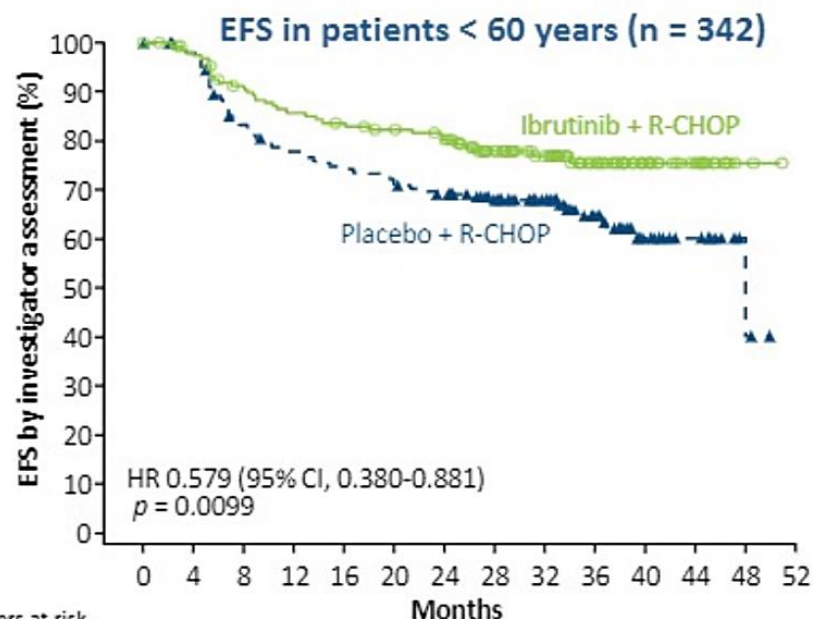
R-CHOP + X: Randomized studies

Target	Study label	n	Population	Study	R-CHOP +/-	Result
NK-KB	PYRAMID	206	non GCB (Hans)	Rand phase 2	Bortezomib	No EFS improvement
NK-KB	REMoDL-B	918	ABC/GC/Unclassified (GEP)	Rand phase 3	Bortezomib	No PFS improvement
BTK	PHOENIX	838	non GCB (Hans)	Rand phase 3	Ibrutinib	No PFS improvement
Cereblon	ROBUST	570	ABC (GEP - nanostring)	Rand phase 3	Lenalidomide	No PFS improvement
Cereblon	ECOG-ACRIN 1412	349	All comers	Rand phase 2	Lenalidomide	Improved PFS (HR 0.66)
Cereblon	SENIOR	249	All comers (>80y)	Rand phase 3	Lenalidomide	No OS or PFS improvement
CD79b	POLARIX	875	All comers	Rand phase 3	Polatuzumab (CHP)	?

Ibrutinib – R CHOP



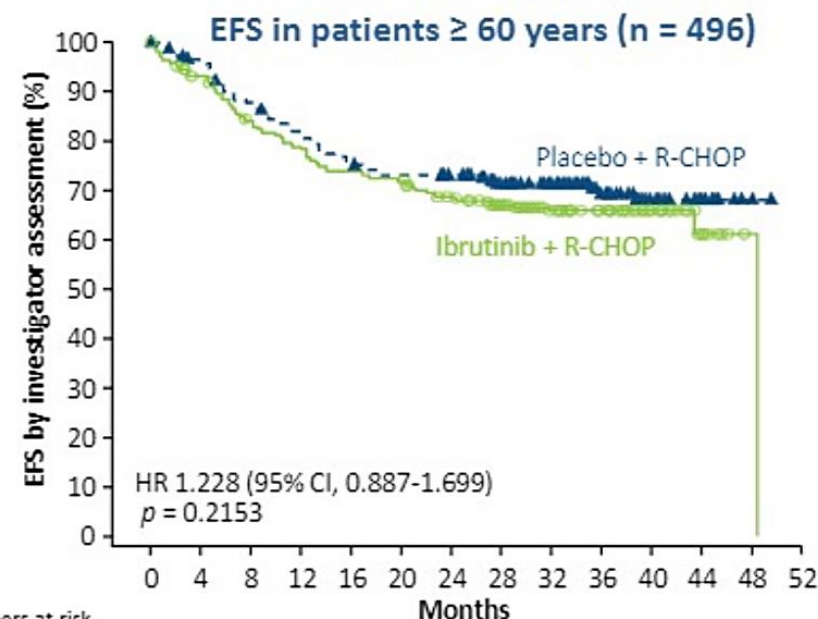
- In a prespecified exploratory analysis, ibrutinib + R-CHOP improved EFS and OS in patients < 60 years¹



Numbers at risk	0	4	8	12	16	20	24	28	32	36	40	44	48	52
Ibrutinib + R-CHOP	156	146	133	125	121	117	113	93	72	44	27	13	2	0
Placebo + R-CHOP	186	177	148	137	132	127	120	104	78	52	24	16	3	0

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- Ibrutinib + R-CHOP did not improve EFS and OS in patients ≥ 60 years¹
- Higher frequency of AEs leading to discontinuation in elderly patients¹



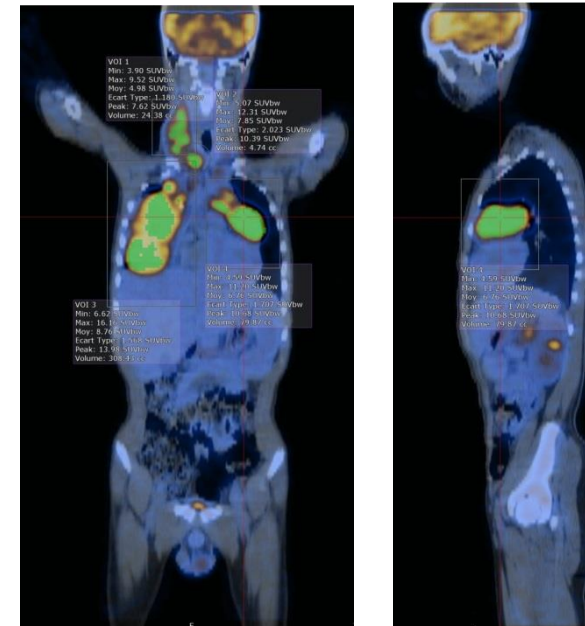
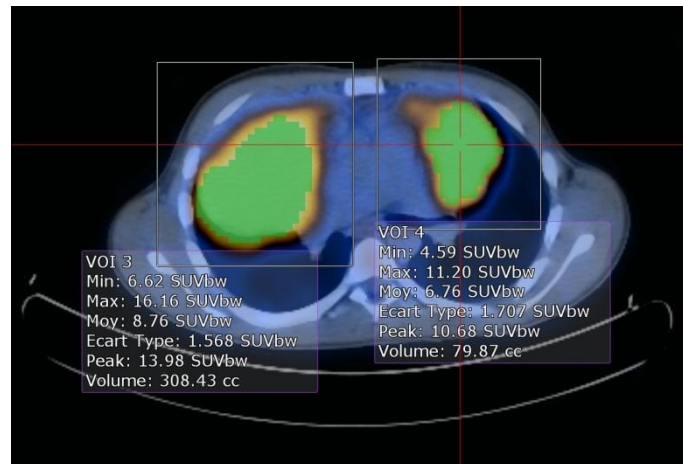
Numbers at risk	0	4	8	12	16	20	24	28	32	36	40	44	48	52
Ibrutinib + R-CHOP	263	228	203	191	179	174	163	140	107	76	36	12	1	0
Placebo + R-CHOP	233	213	193	179	165	159	157	140	106	66	36	17	2	0

1. Younes A, et al. *J Clin Oncol.* 2019;37:1285-1295.

Nouvelles modalités d'évaluation

Baseline total metabolic volume (TMTV)

- A region of interest (ROI) is drawn around each foci FDG uptake
- In each ROI, hypermetabolic voxels are selected. Several methods have been published:
 - **Fixed SUV cut-off** : voxels with a **SUV ≥ 2.5** are incorporated in the volume
 - Based on the SUVmax of each ROI: voxels presenting a **SUV $> 41\%$ SUVmax of the ROI** are incorporated in the volume*
- All individual tumors volume are added to compute the TMTV

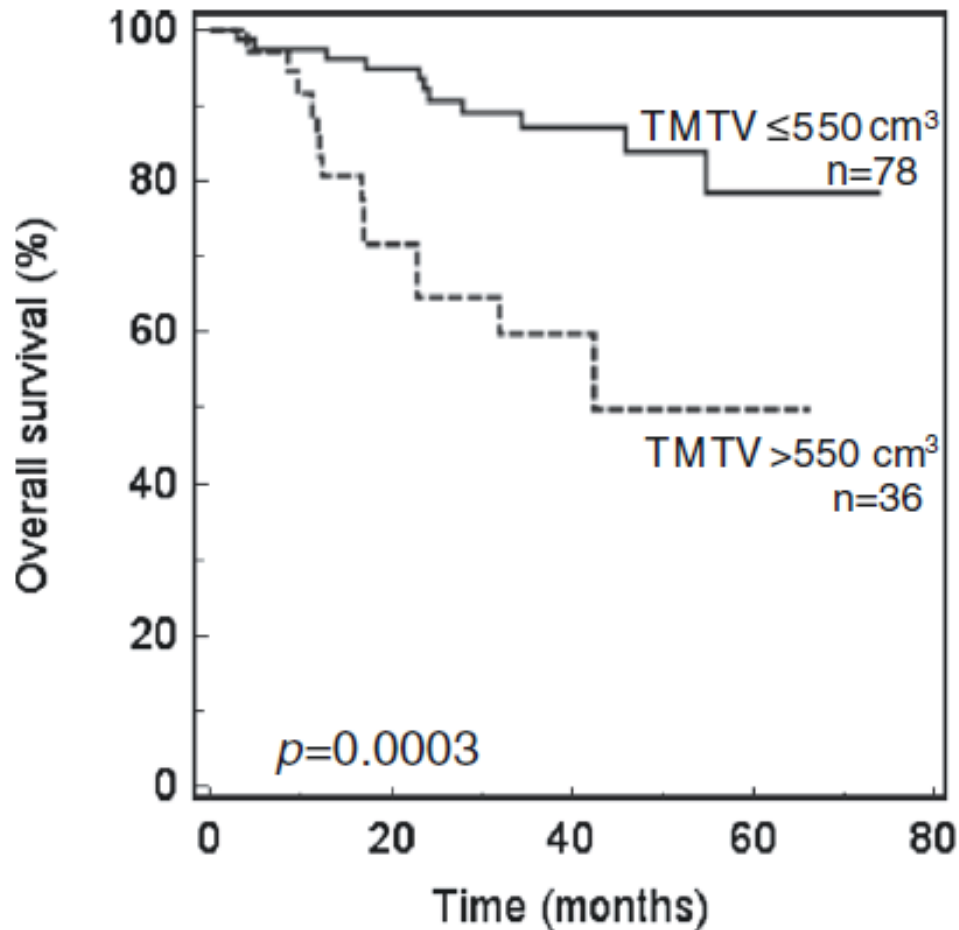


*Boellaard R et al. *EJNM*. 2010; 37: 181

Meignan M et al. *EJNM* 2014; 41: 1113

TMTV impacts the outcome of DLBCL pts

114 DLBCL pts, 31% >60y, aaIPI>1 = 65%, median FU = 39 months



Method: 41% SUVmax thresholding
 Median TMTV = 315 ml
 Cut-off = 550 ml

Multivariate analysis

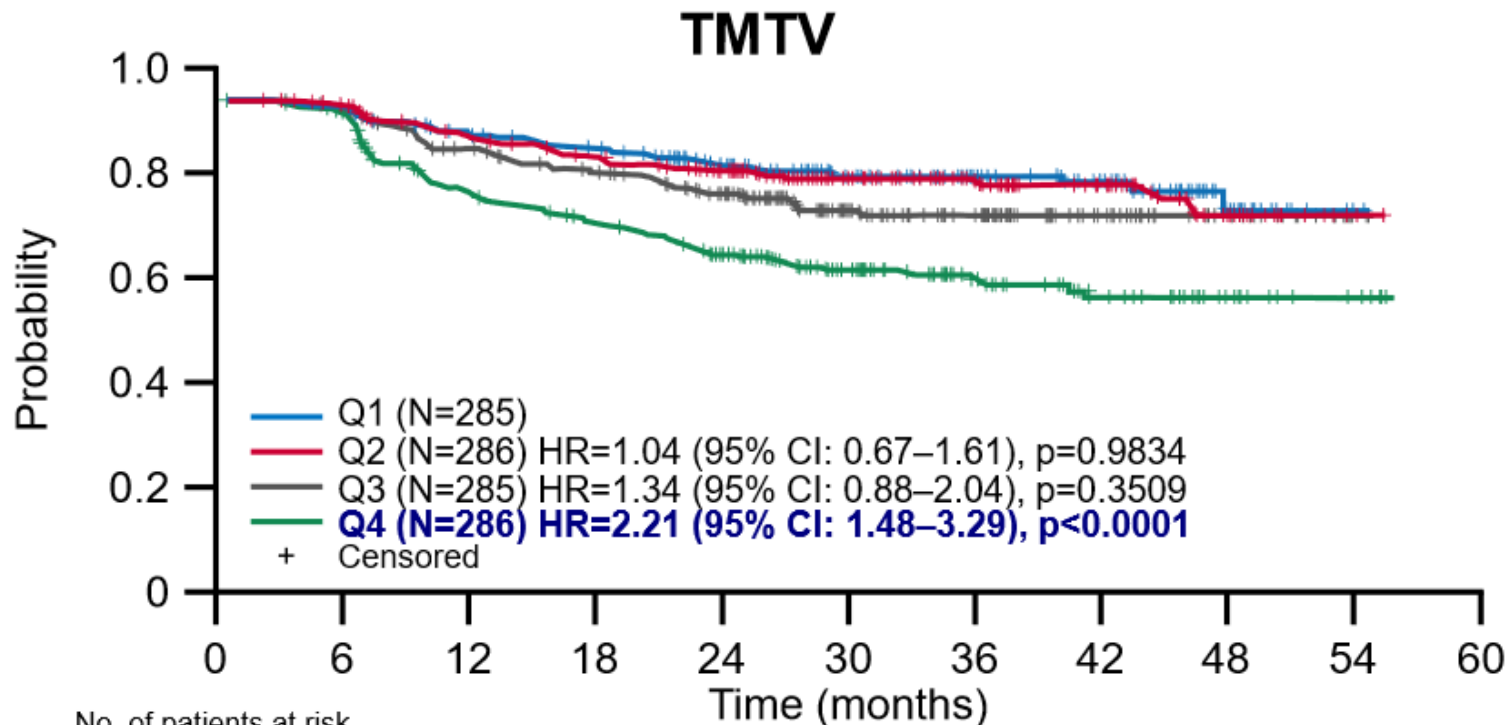
	PFS		OS	
	RR	P	RR	P
aaIPI 0-1/2-3	0.86	0.72	1.77	0.28
Bulk ≥ 10cm	0.68	0.35	0.61	0.28
TMTV > 550ml	2.65	0.03	4.11	0.002

Prognostic value of baseline TMTV for PFS

(TMTV split in quartiles , GOYA study)

1418 DLBCL ≥18 y, IPI≥2, IPI=0 if Bulk≥7.5, IPI 1 (not age)

Method: 1.5 x liver SUVmean
Median TMTV = 336 cm³



No. of patients at risk												
		0	6	12	18	24	30	36	42	48	54	60
Q1	285	270	250	238	199	112	71	56	20	1		
Q2	286	268	238	222	193	110	69	41	12	1		
Q3	285	270	228	212	172	104	77	42	20	1		
Q4	286	266	209	193	165	100	65	42	17	4		

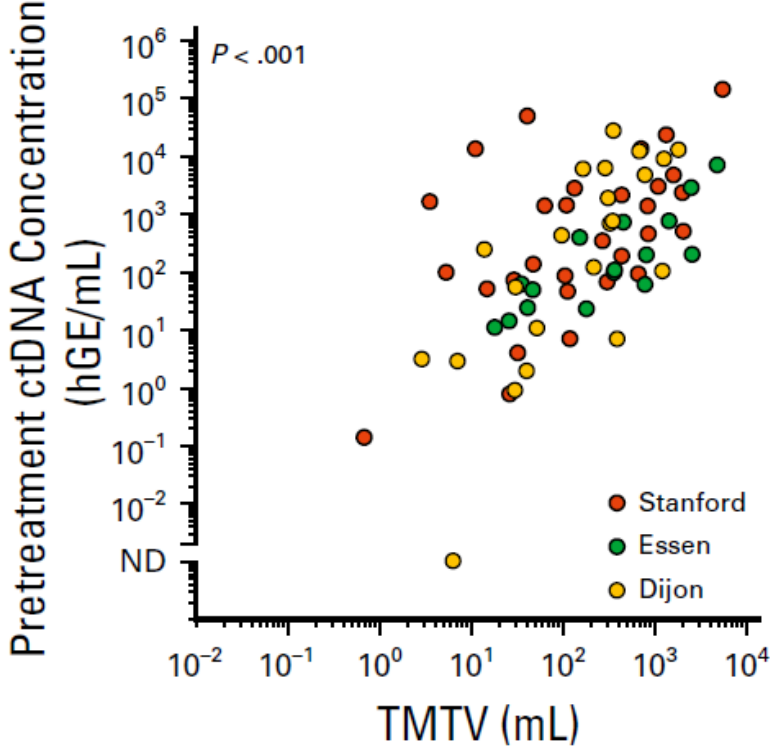
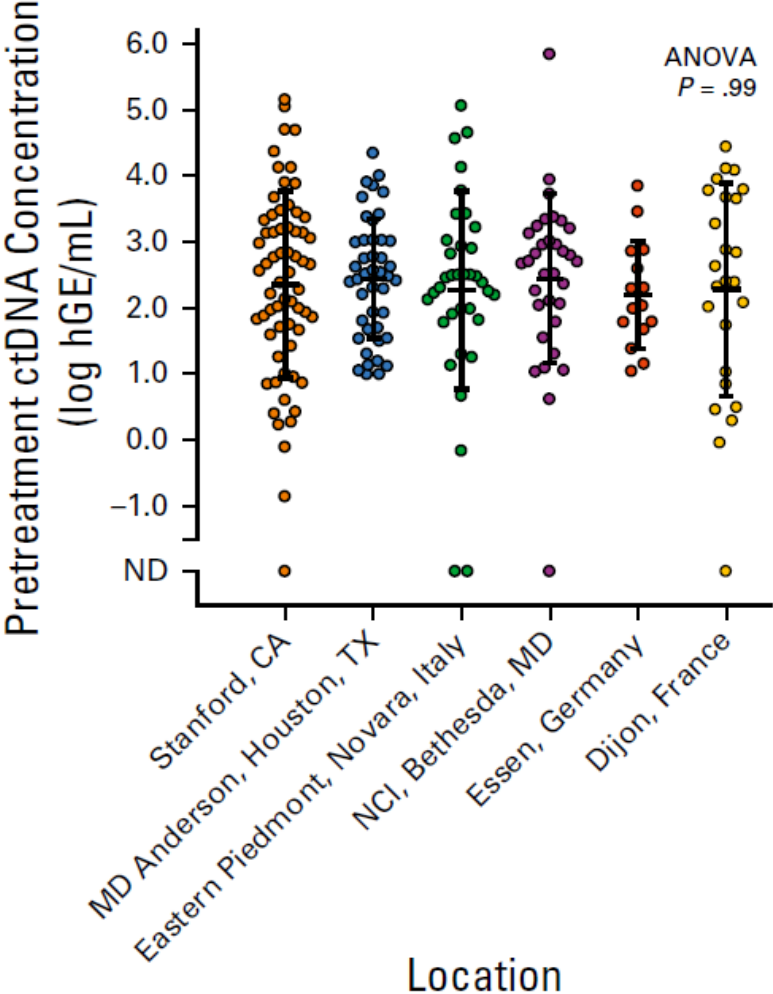
Factor*	HR	Wald 95% CI	P-value
TMTV Q4 vs Q1	1.91	1.10–3.30	0.0211
COO ABC vs GCB	2.09	1.44–3.03	0.0001
IPI High vs low-intermediate	1.86	1.17–2.96	0.0088
Geographic region Western Europe vs Asia	0.61	0.41–0.92	0.0192
Time from initial diagnosis to randomization	0.66	0.46–0.95	0.0232

DLBCL: Baseline TMTV and ctDNA concentration

CAPP-seq genotyping

Feature	
Total size	314 kb
# genes	334
Fusions	<i>BCL2</i> <i>BCL6</i> <i>MYC</i>
SNVs / pt	134
Depth	~2000x

ctDNA detectable in 98% of patients at baseline



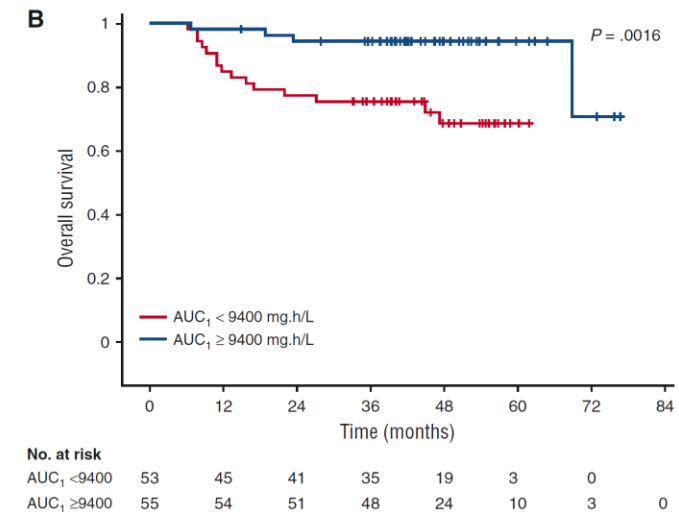
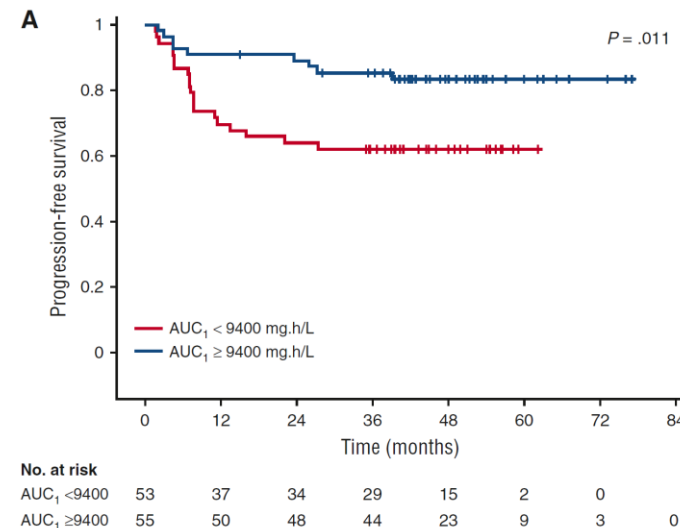
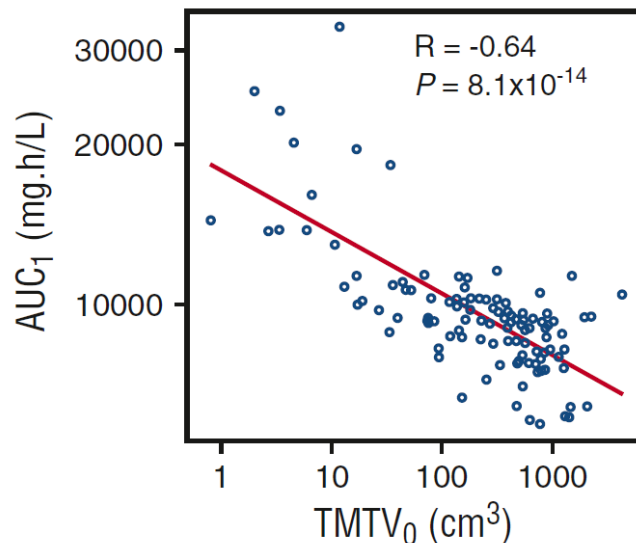
CLINICAL TRIALS AND OBSERVATIONS

Rituximab exposure is influenced by baseline metabolic tumor volume and predicts outcome of DLBCL patients: a Lymphoma Study Association report

Mira Tout,¹ Olivier Casasnovas,² Michel Meignan,³ Thierry Lamy,⁴ Franck Morschhauser,⁵ Gilles Salles,⁶ Emmanuel Gyan,⁷ Corinne Haioun,⁸ Mélanie Mercier,⁹ Pierre Feugier,¹⁰ Sami Boussetta,¹¹ Gilles Paintaud,^{1,12} David Ternant,^{1,12} and Guillaume Cartron^{13,14}

2616

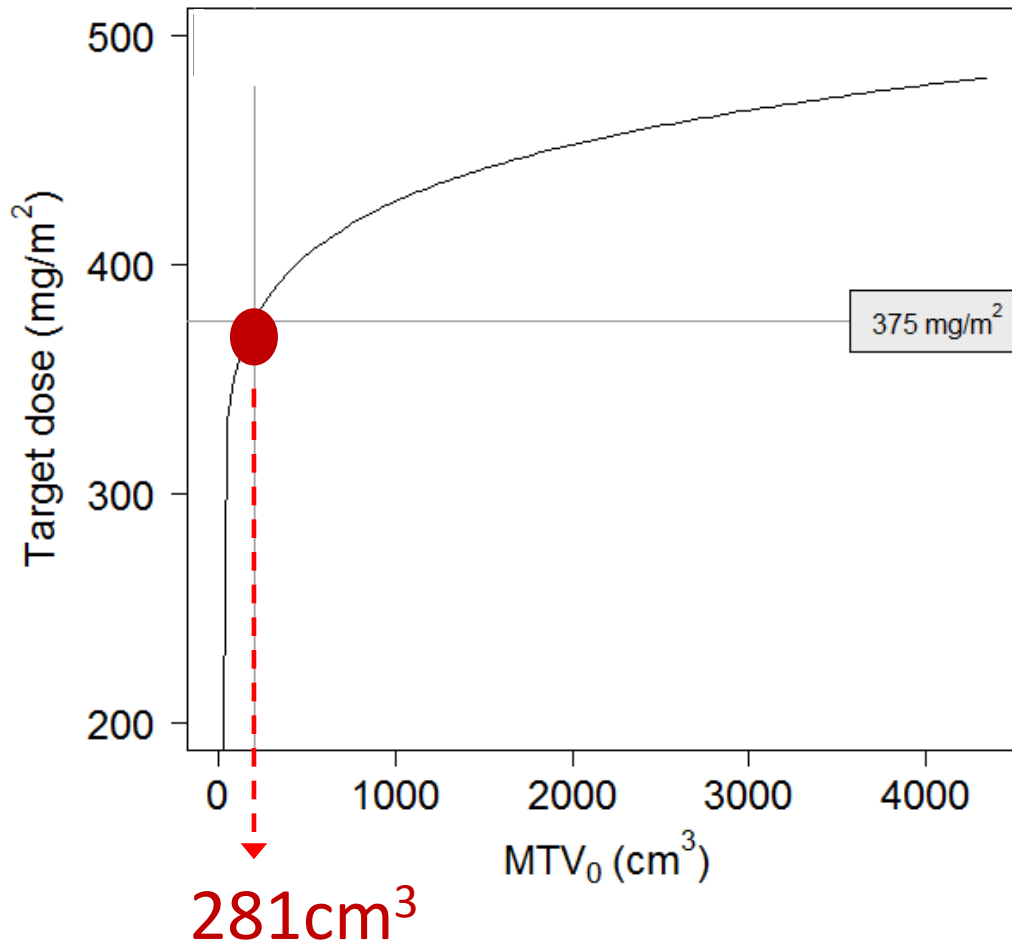
BLOOD, 11 MAY 2017 • VOLUME 129, NUMBER 19



Target dose of Rituximab according to TMTV

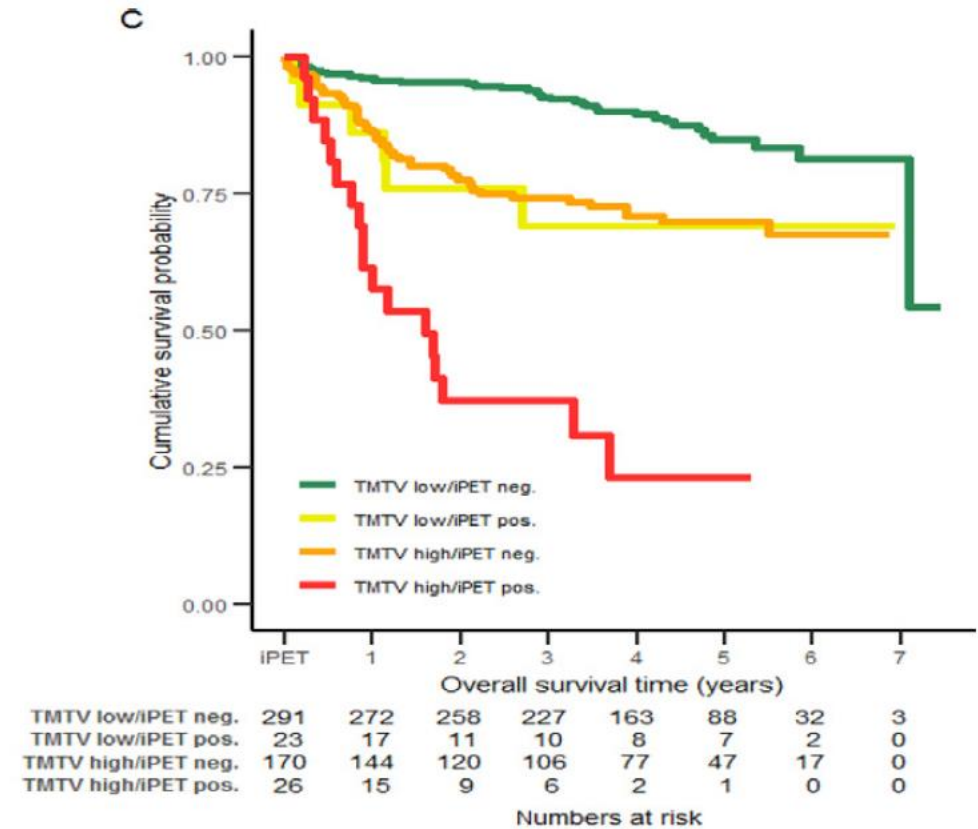
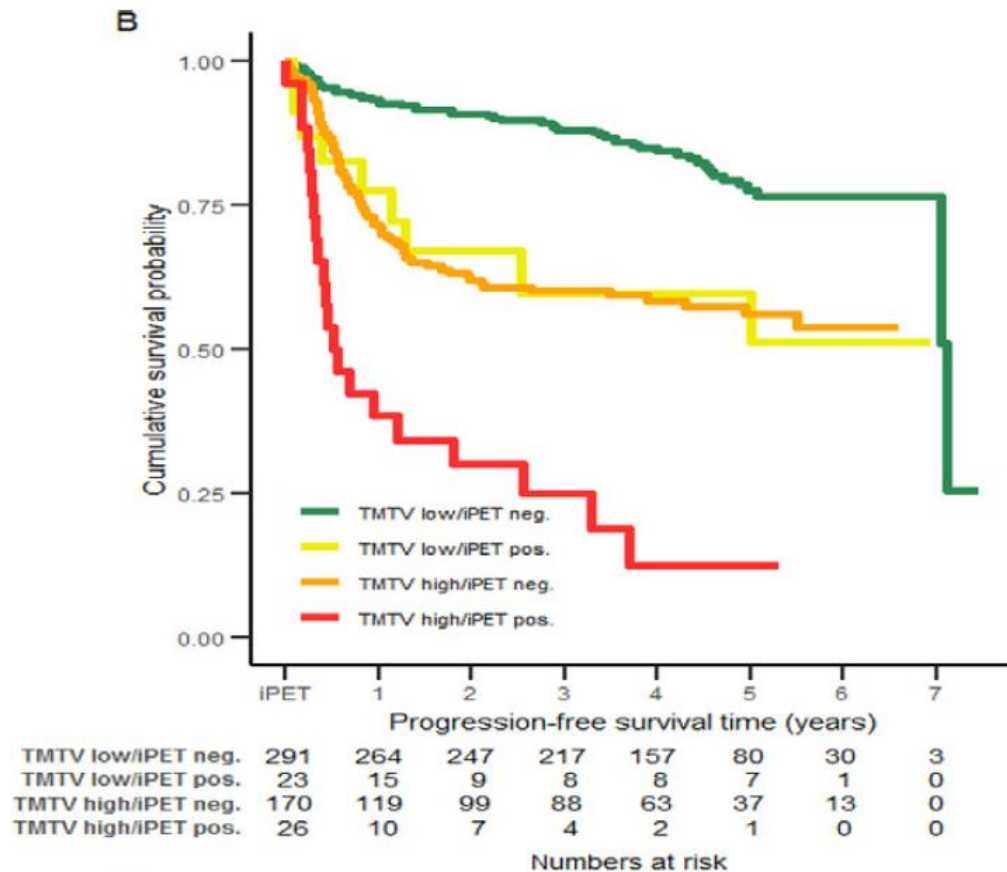


$$\text{Target dose (mg/m}^2\text{)} = 237.59 \times (\text{TMTV})^{0.081}$$



Standard dose of 375 mg/m² is suitable if TMTV < 281 cm³

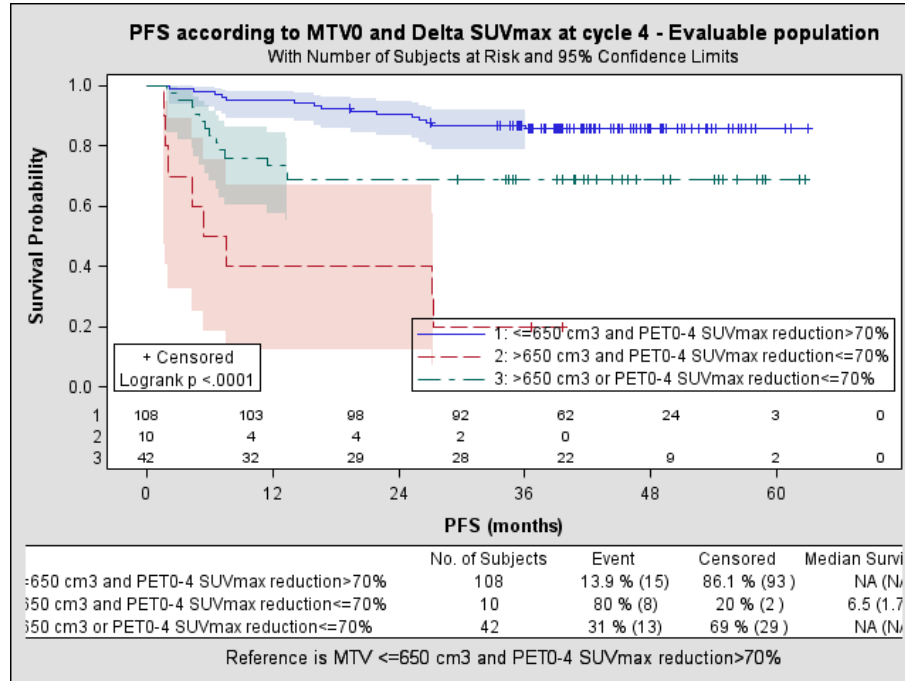
PETAL: TMTV & PET2



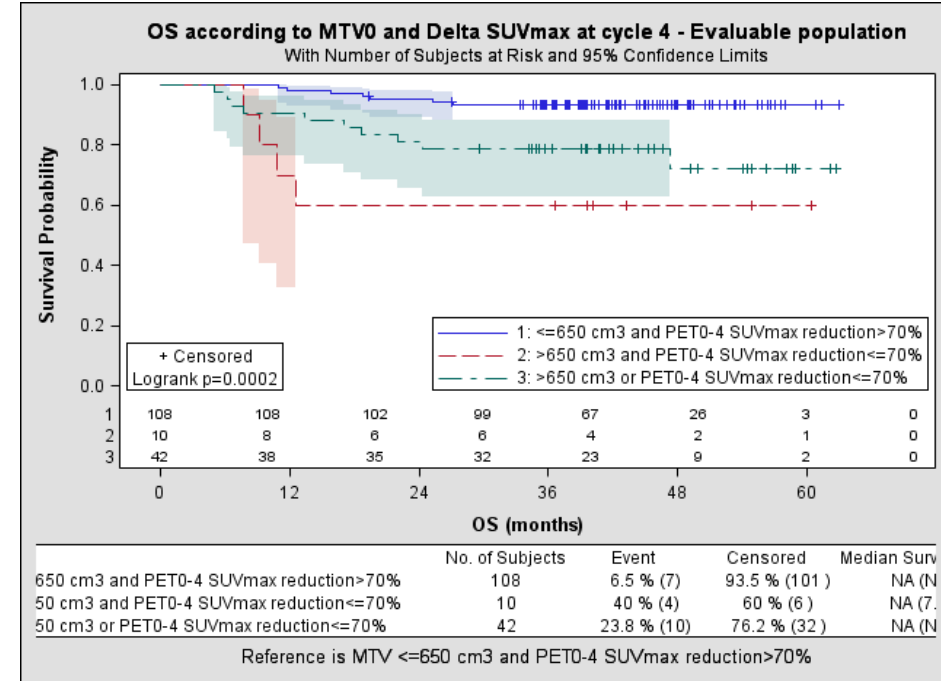
LNH 2007-3B: outcome according to TMTV and Δ SUVmax 0-4



PFS



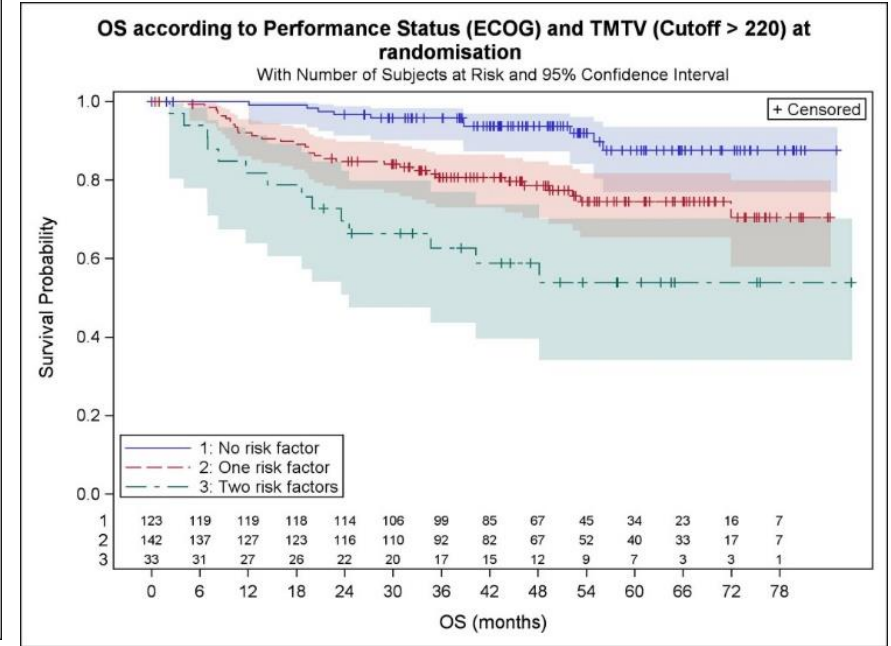
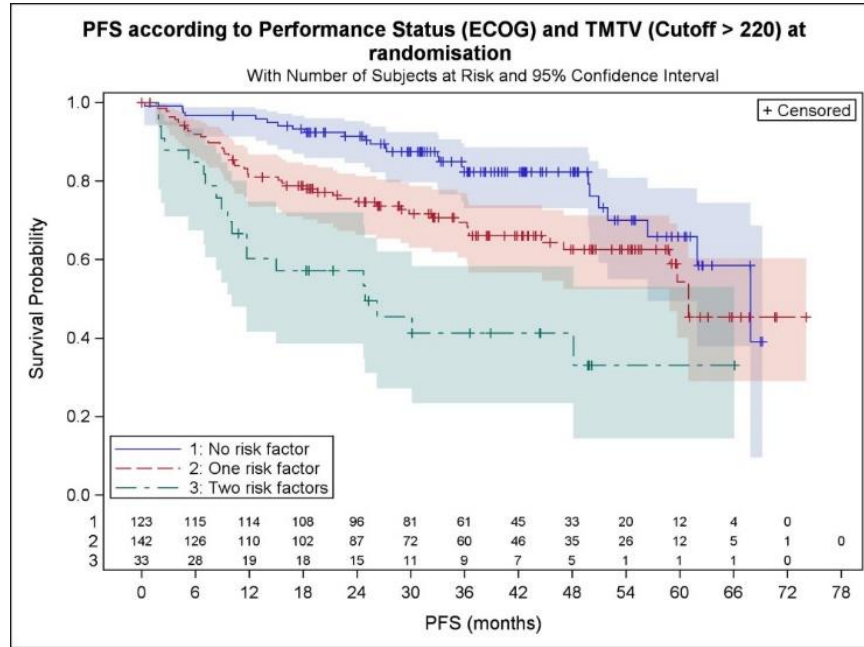
OS



	4y-PFS	4y-OS
TMTV0 \leq 650 ml and Δ SUVmax0-4 >70% (n = 108; 68%)	86%	93%
TMTV0 > 650 ml or Δ SUVmax0-4 \leq 70% (n = 42; 26%)	69%	72%
TMTV0 > 650 ml and Δ SUVmax0-4 \leq 70% (n = 10; 6%)	20%	60%



REMARC: Baseline TMTV and PS combination

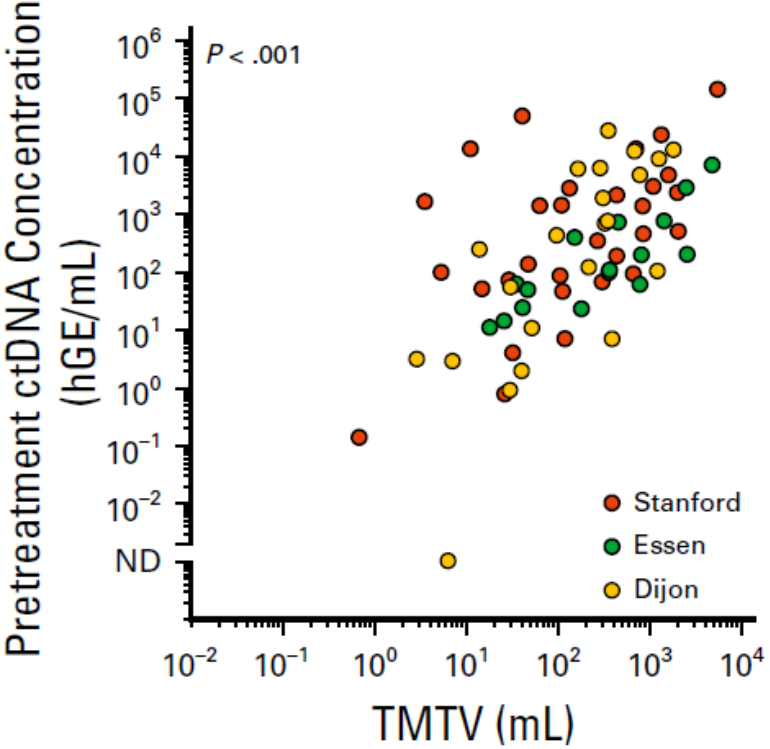
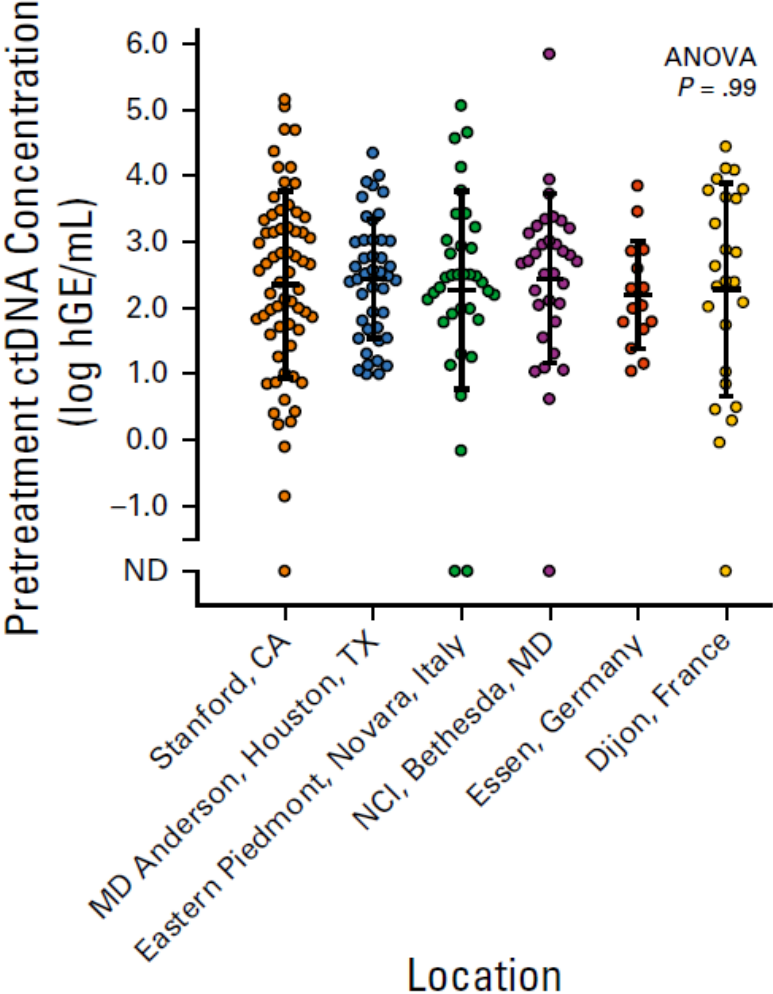


	4 y PFS	4 y OS
No risk factor	82%	94%
1 risk factor	63% (HR:1.9 CI:1.2-3.0)	79% (HR=3.0 CI:1.5-6.2)
2 risk factors	41% (HR=4.4 CI:2.4-8.1)	59% (HR=6.6 CI:2.9-14.9)

DLBCL: Baseline TMTV and ctDNA concentration

CAPP-seq genotyping

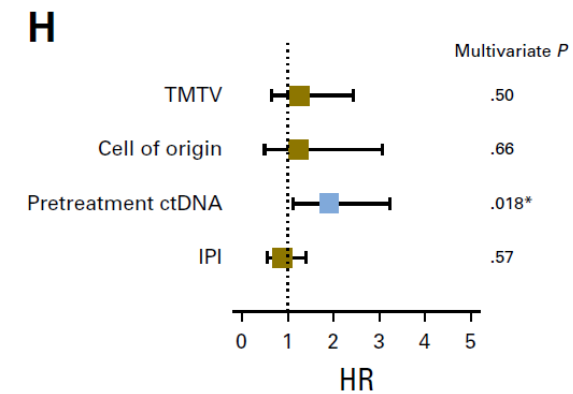
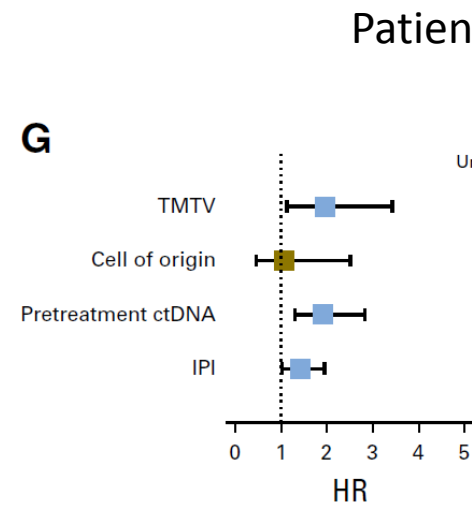
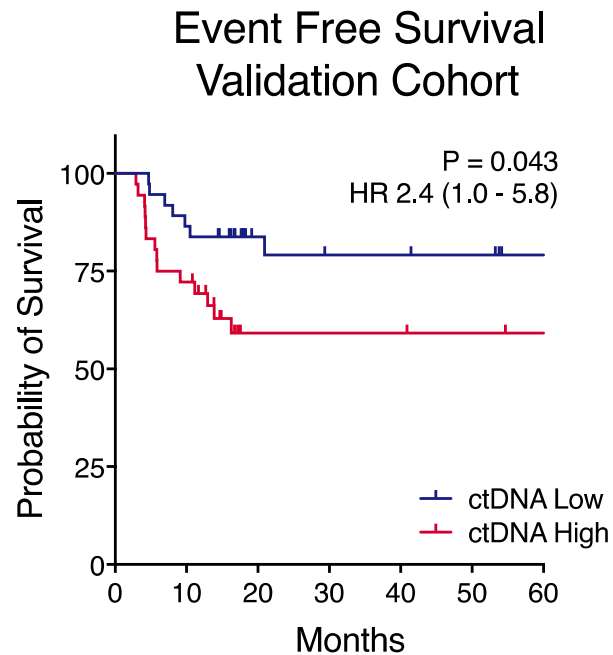
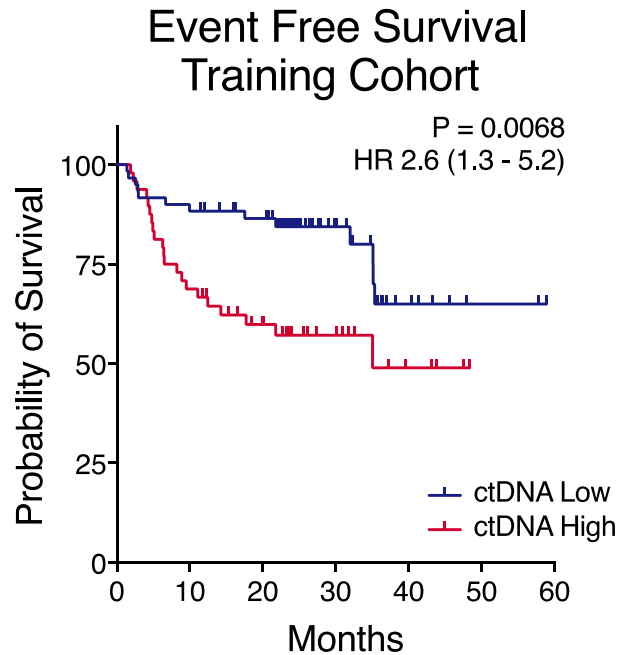
Feature	
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# genes	334
Fusions	<i>BCL2</i> <i>BCL6</i> <i>MYC</i>
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Depth	~2000x



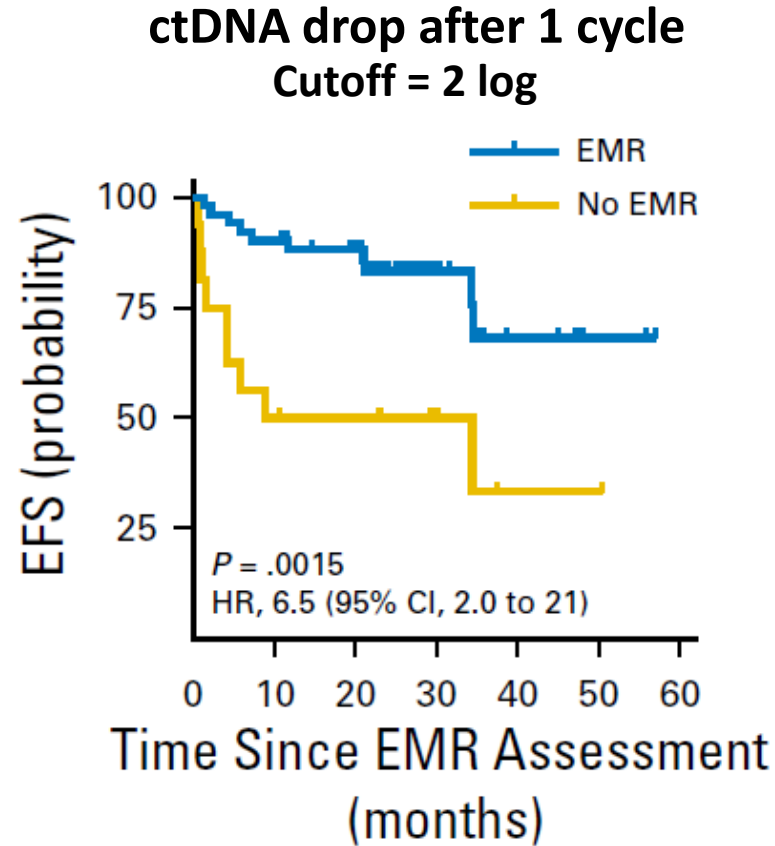
ctDNA detectable in 98% of patients at baseline

Prognosis value of pretreatment ctDNA concentration

181 patients with large B cell lymphomas receiving frontline therapy
 ctDNA quantified prior to first 3 cycles of therapy by targeted sequencing (CAPP-Seq)



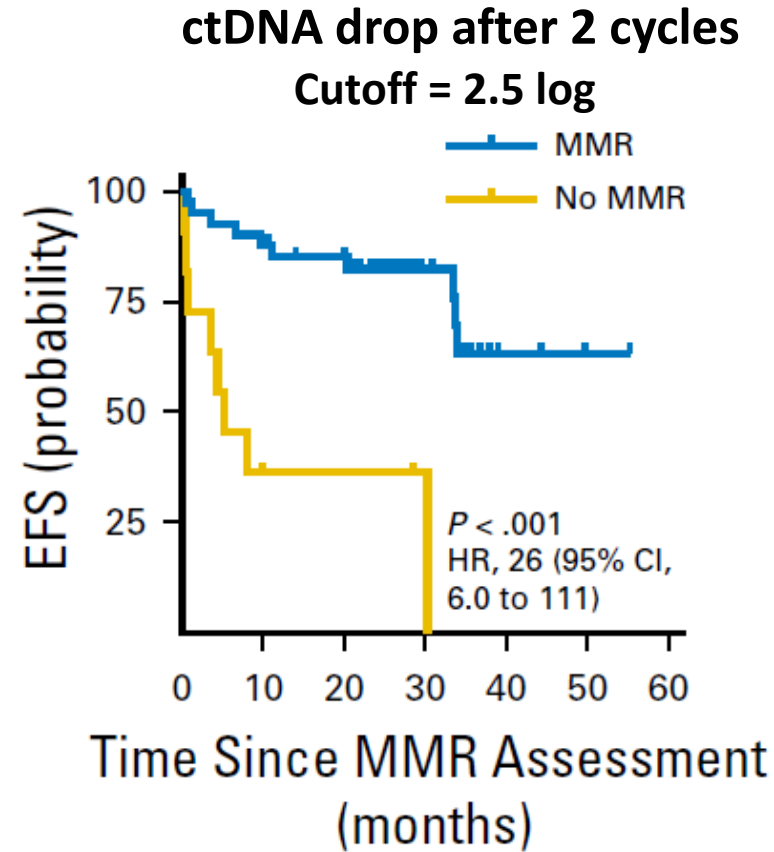
ctDNA concentration reduction and outcome



No. at risk:

EMR	51	46	38	15	5	2	0
No EMR	16	8	7	4	1	1	0

24% of pts did not achieved EMR

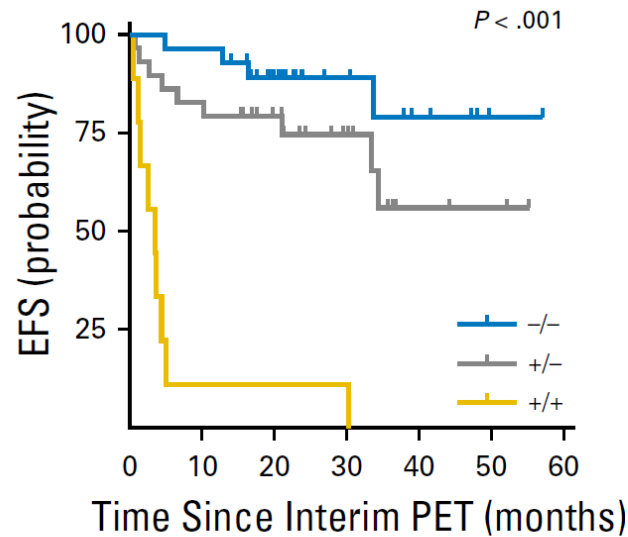


No. at risk:

MMR	41	36	31	14	3	1	0
No MMR	11	4	3	1	0	0	0

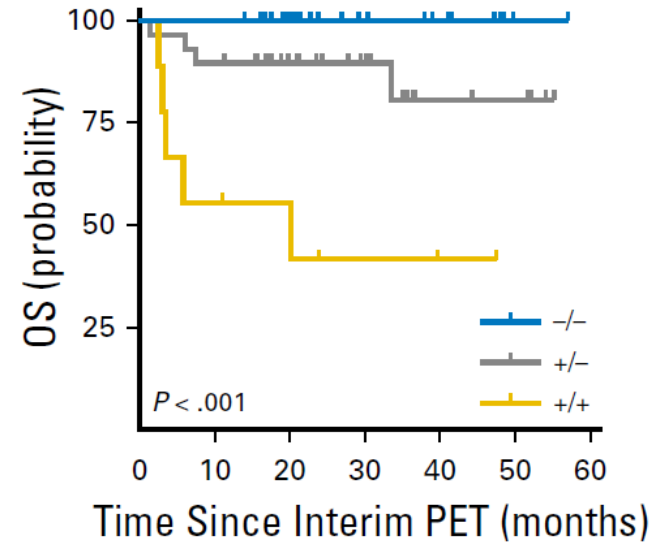
21% of pts did not achieved MMR

Combining interim PET and molecular response better predicts patients outcome



No. at risk:

-/-	28	27	18	10	6	1	0
+/-	29	24	18	10	3	2	0
+/+	9	1	1	1	0	0	0

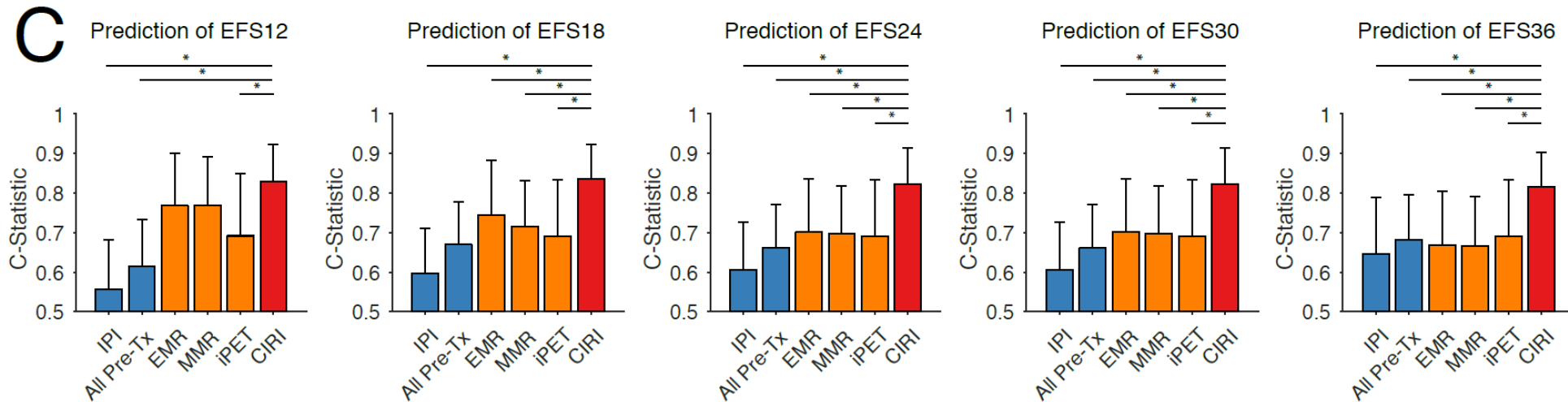
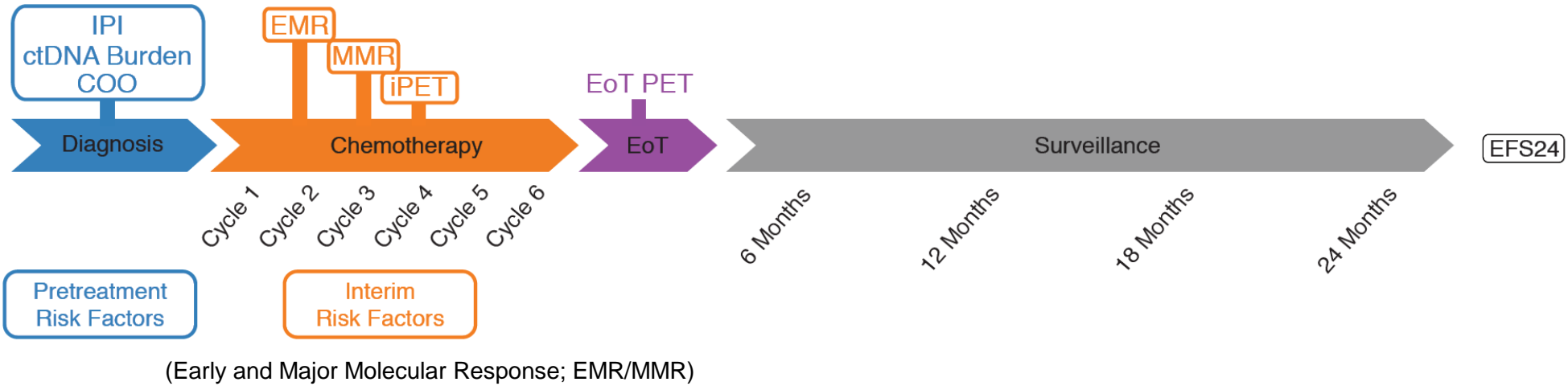


No. at risk:

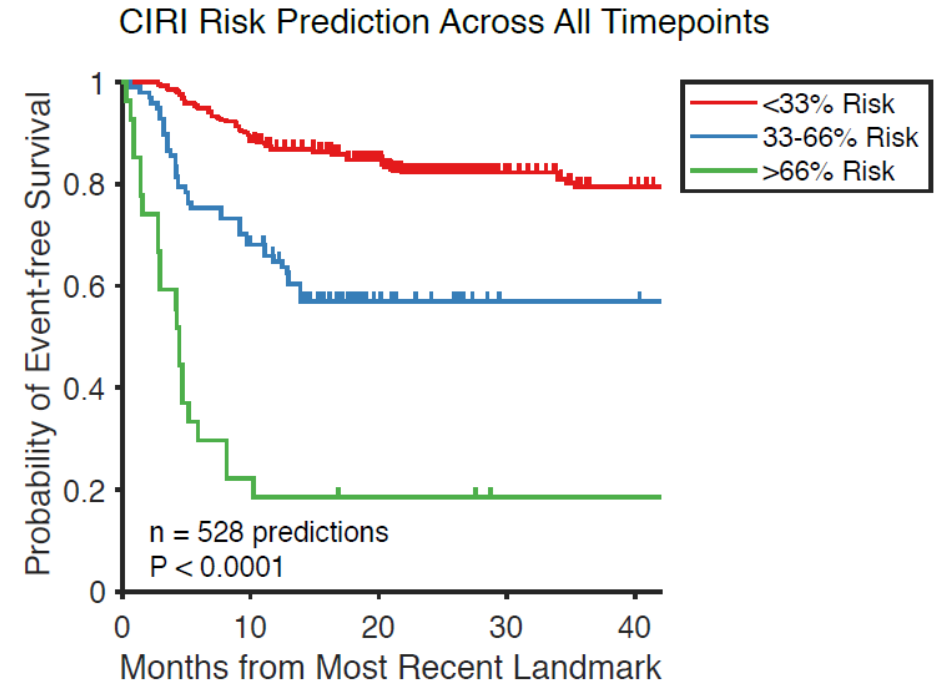
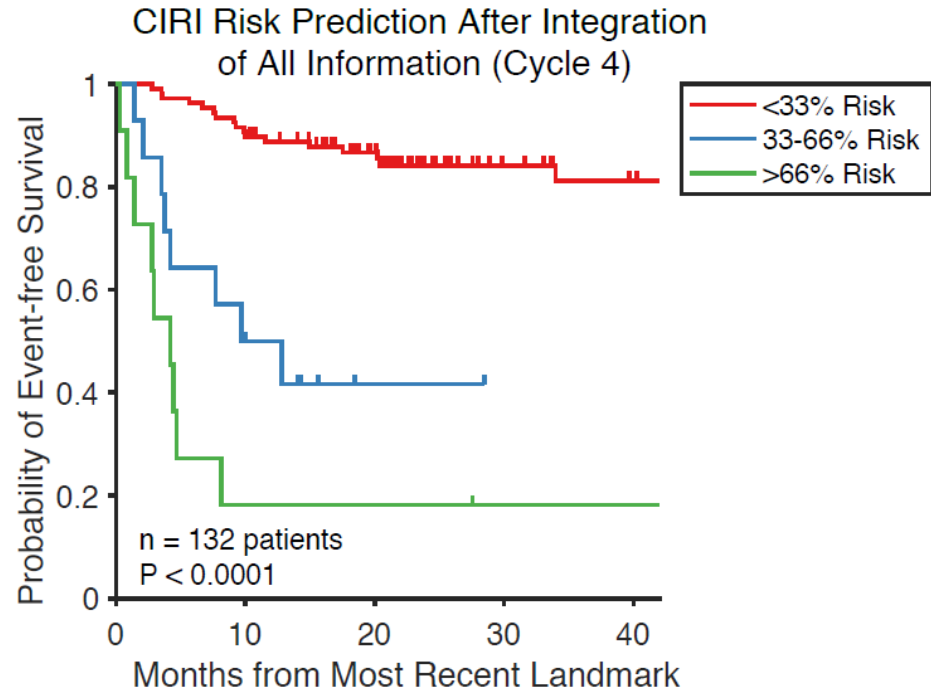
-/-	28	28	21	12	9	1	0
+/-	29	26	19	12	5	4	0
+/+	9	5	4	2	1	0	0

Parameter	Univariable		Multivariable	
	HR (95% CI)	P	HR (95% CI)	P
EFS				
IPI (0 to 5)	1.21 (0.87 to 1.69)	.25	0.93 (0.63 to 1.37)	.71
Pretreatment ctDNA (low v high)	2.77 (1.08 to 7.13)	.034*	2.97 (0.92 to 9.62)	.070
Molecular response†	5.93 (2.52 to 13.95)	< .001*	8.58 (3.3 to 22.32)	< .001*
Interim PET (positive v negative)	3.74 (1.46 to 9.57)	.006*	3.45 (1.27 to 9.34)	.015*
OS				
IPI (0 to 5)	1.36 (0.82 to 2.23)	.23	1.14 (0.63 to 2.25)	.670
Pretreatment ctDNA (low v high)	3.12 (0.65 to 15.05)	.16	1.13 (0.16 to 8.21)	.888
Molecular response†	5.27 (1.41 to 19.78)	.014*	4.15 (1.17 to 15.57)	.029*
Interim PET (positive v negative)	22.35 (2.83 to 2868)	< .001*	16.87 (1.96 to 2214)	.005*

Continuous Individualized Risk Index (CIRI) (Bayesian proportionnal Hazard approach)



CIRI risk prediction: updated risk over time



Conclusions

- aalPI=0 < 80 ans
 - <60 ans no bulk : 4 x R-CHOP
 - Résultats LNH09-1B: 4 x R-CHOP pour les TEP2-
- aalPI=1-3 <60 ans
 - Stratégie GAINED
 - Interim PET = Δ SUVmax
 - Choix de la chimio: ACVBP pour non GC, CNS IPI élevé, PMBL bulky
- aalPI=1-3 >60 ans
 - 6 x R-CHOP
- > 80 ans
 - 6 x R-miniCHOP
- Importance des nouvelles modalités d'évaluation à la baseline et de monitoring de la maladie sous et après traitement