Lymphome B à grandes cellules

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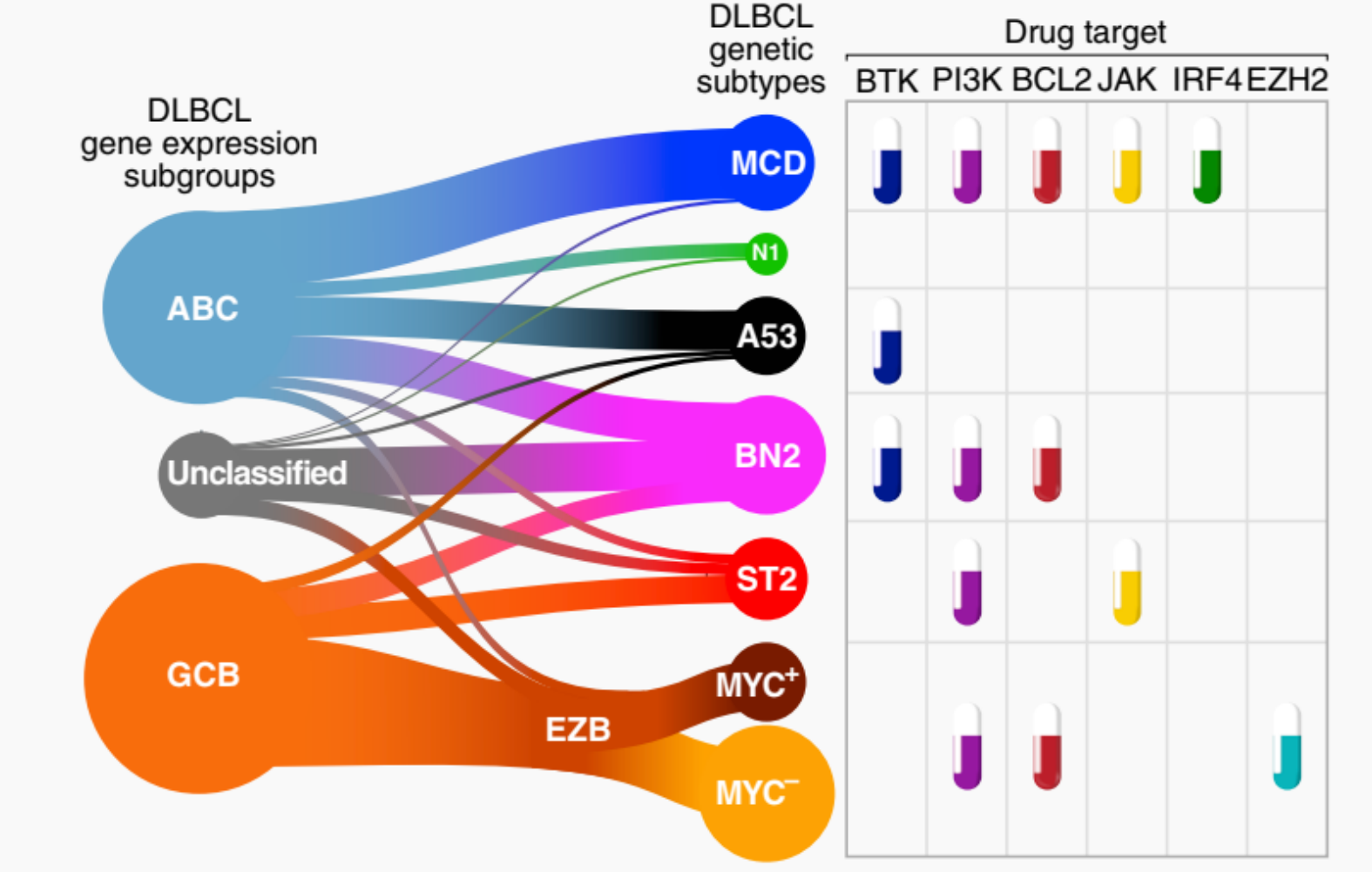
Liens d’intérêt

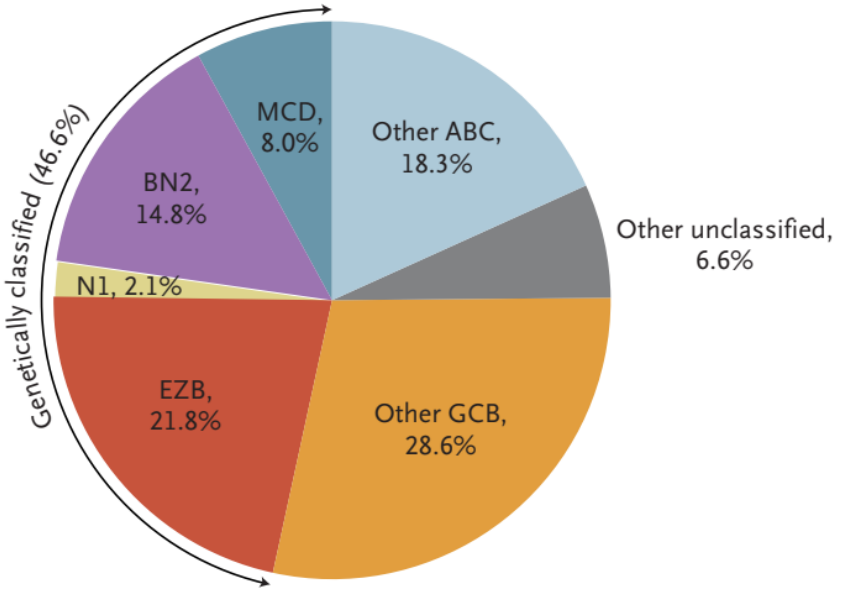
- Consultancy and Advisory board: Roche, Takeda, BMS, MSD, Gilead/Kite, Janssen, ADC therapeutics, Beigene

- Research funding: Roche, Gilead

WHO 2022

	WHO Classification, 5th edition	WHO Classification, revised 4th edition
	Large B-cell lymphomas	
DLBCL	Diffuse large B-cell lymphoma, NOS	(Same)
DLBCL	T-cell/histiocyte-rich large B-cell lymphoma	(Same)
DLBCL	Diffuse large B-cell lymphoma/ high grade B-cell lymphoma with *MYC* and *BCL2* rearrangements	High-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements
DLBCL	ALK-positive large B-cell lymphoma	(Same)
DLBCL	Large B-cell lymphoma with *IRF4* rearrangement	(Same)
DLBCL	High-grade B-cell lymphoma with 11q aberrations	Burkitt-like lymphoma with 11q aberration
	Lymphomatoid granulomatosis	(Same)
DLBCL	EBV-positive diffuse large B-cell lymphoma	EBV-positive diffuse large B-cell lymphoma, NOS
DLBCL	Diffuse large B-cell lymphoma associated with chronic inflammation	(Same)
DLBCL	Fibrin-associated large B-cell lymphoma	*Not previously included* (Previously considered a subtype of diffuse large B-cell lymphoma associated with chronic inflammation)
	Fluid overload-associated large B-cell lymphoma	*Not previously included*
	Plasmablastic lymphoma	(Same)
	Primary large B-cell lymphoma of immune-privileged sites	*Not previously included*, encompassing primary diffuse large B-cell lymphoma of the CNS in revised 4th edition (*plus primary large B-cell lymphoma of the vitreoretina and primary large B-cell lymphoma of the testis)*
	Primary cutaneous diffuse large B-cell lymphoma, leg type	(Same)
	Intravascular large B-cell lymphoma	(Same)
PMBL	Primary mediastinal large B-cell lymphoma	(Same)
	Mediastinal grey zone lymphoma	B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classic Hodgkin lymphoma
DLBCL	High-grade B-cell lymphoma, NOS	(Same)



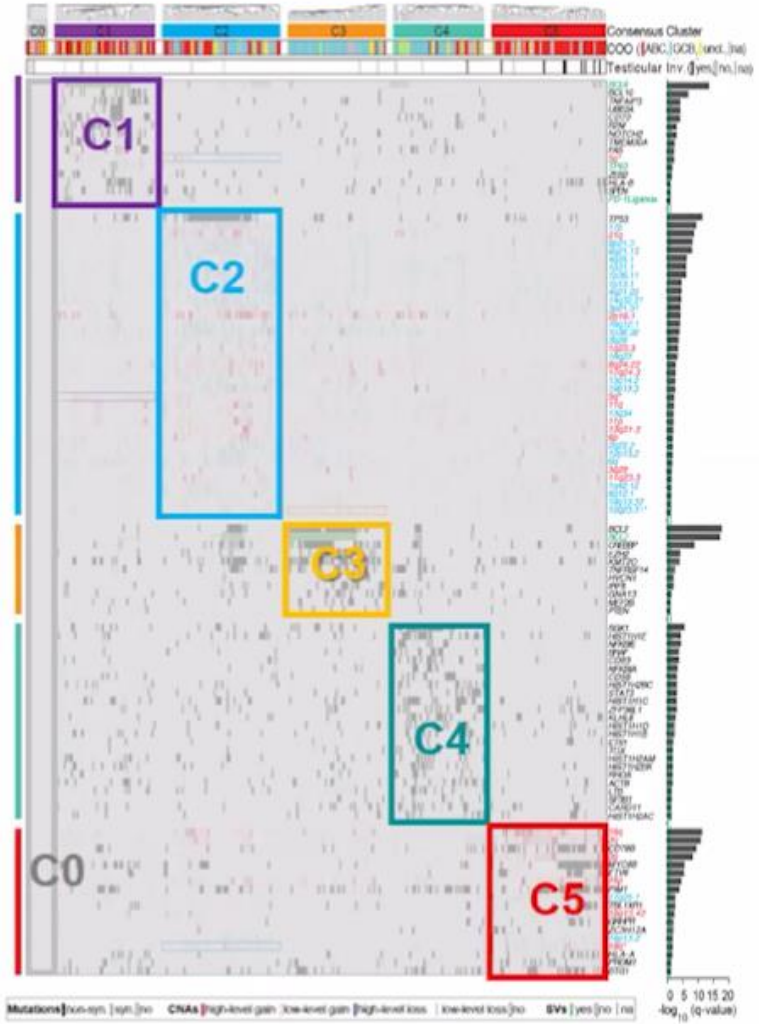


Whole Exome + Transcriptome Sequencing

Wright GW al , Cancer Cell 2020
Schmitz R al, NEJM 2018

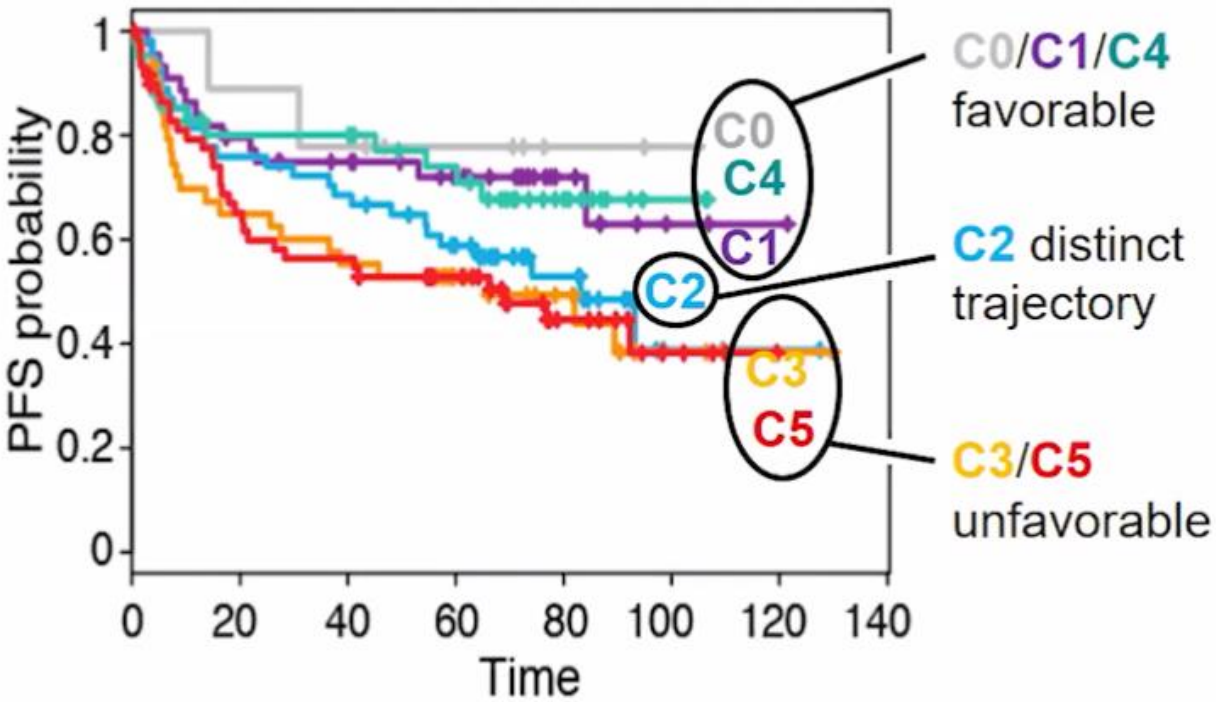
Genetically-distinct DLBCL Subsets are Predictive for Outcome

Genetically-distinct DLBCLs



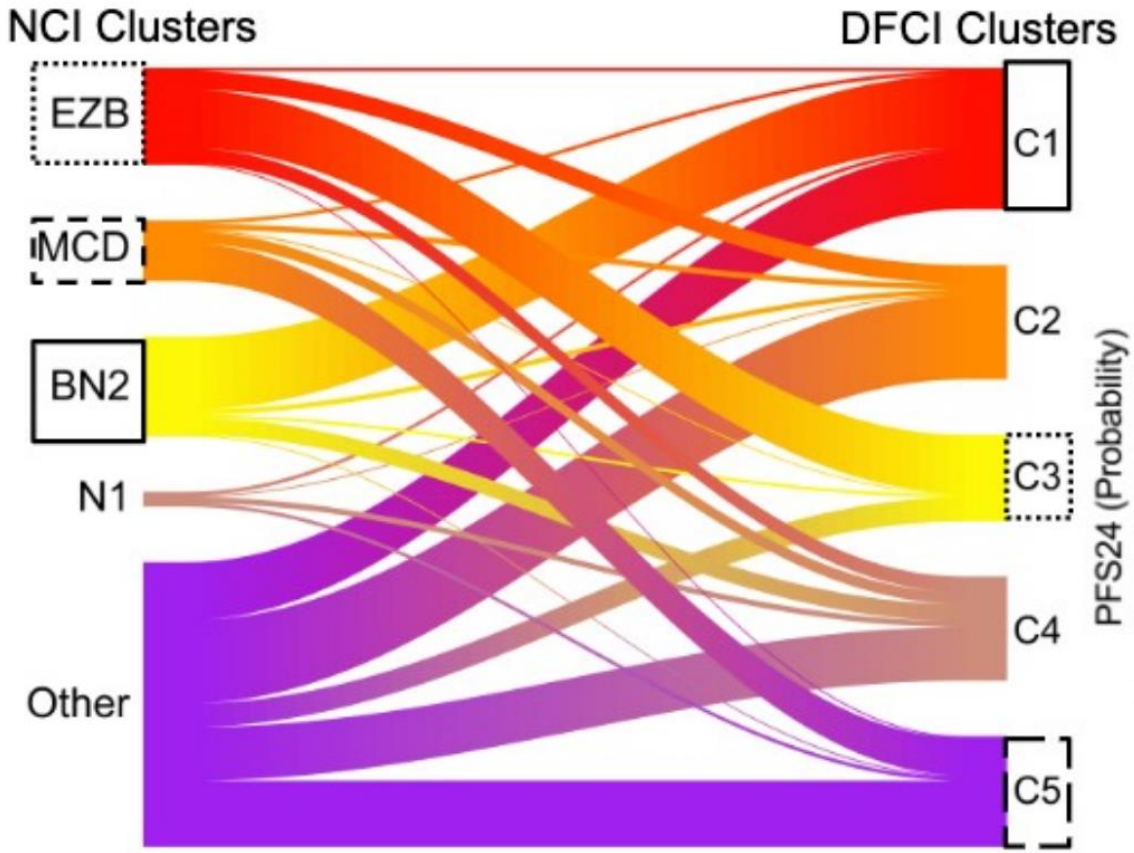
Whole Exome Sequencing

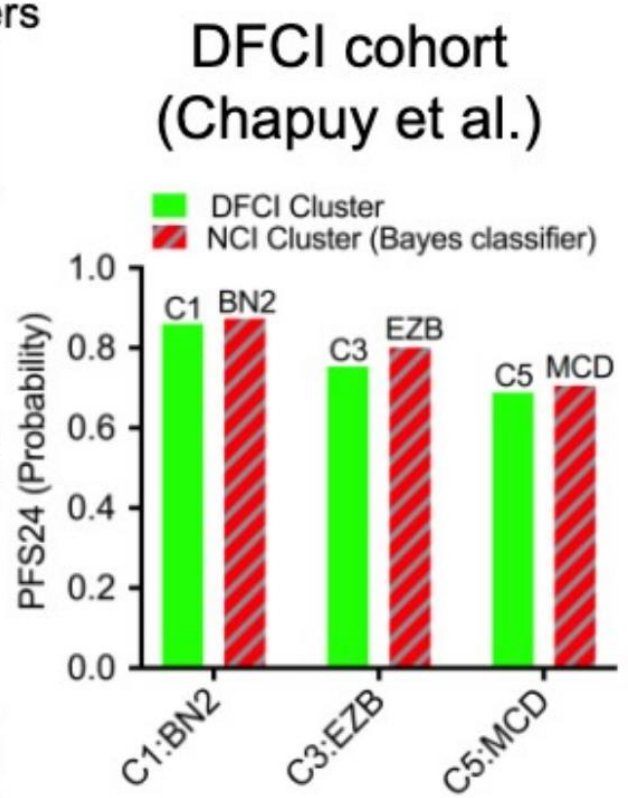
Predictive for Outcome

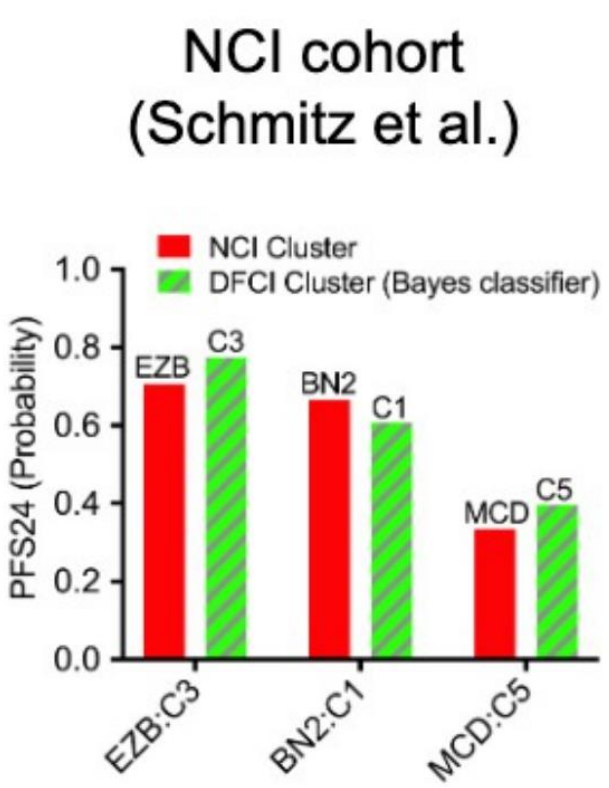


Chapuy, Stewart, Dunford et al. *Nat Med;* 2018; 24(5):679-690

Clusters Largely Overlap

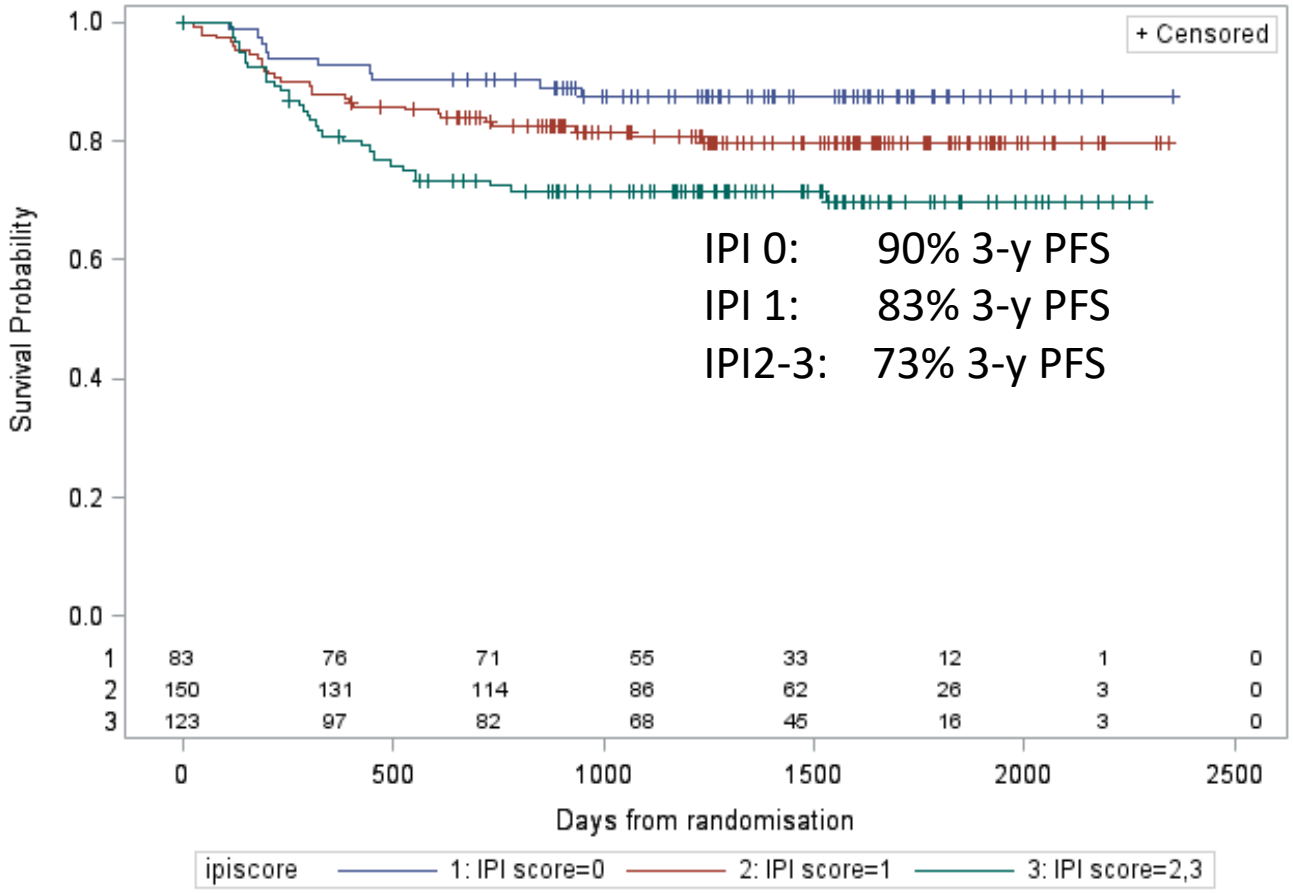






Esfahani MS et al, ASH 2019

PFS by aaIPI group for DLBCL<60years



Courtesy of David Cunnigham

< 60 ans aaIPI 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

Regular Article

blood

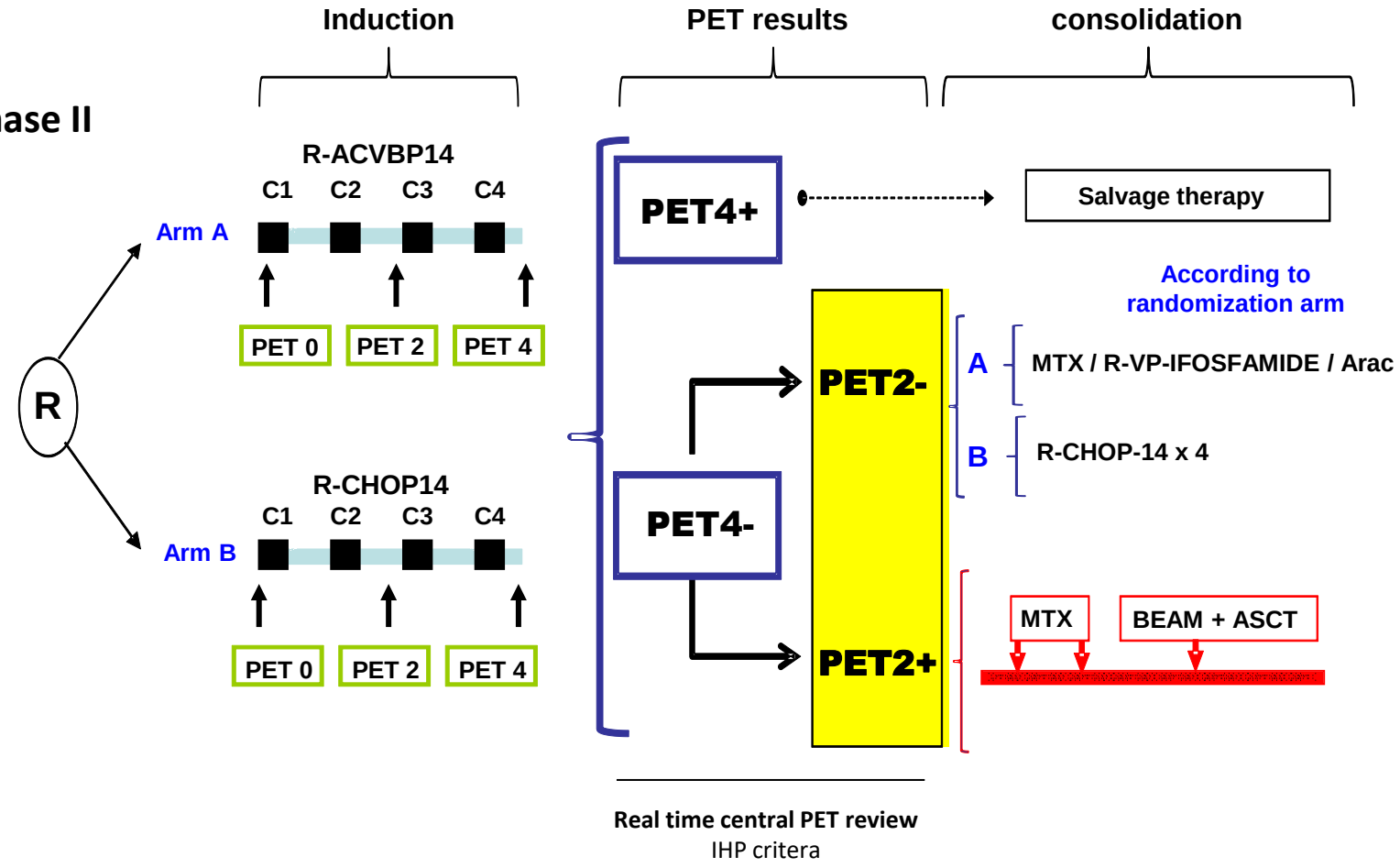
CLINICAL TRIALS AND OBSERVATIONS

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. Morschhauser[21]

BLOOD, 14 SEPTEMBER 2017 • VOLUME 130, NUMBER 11

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



ASCT avoided in 26% of pts

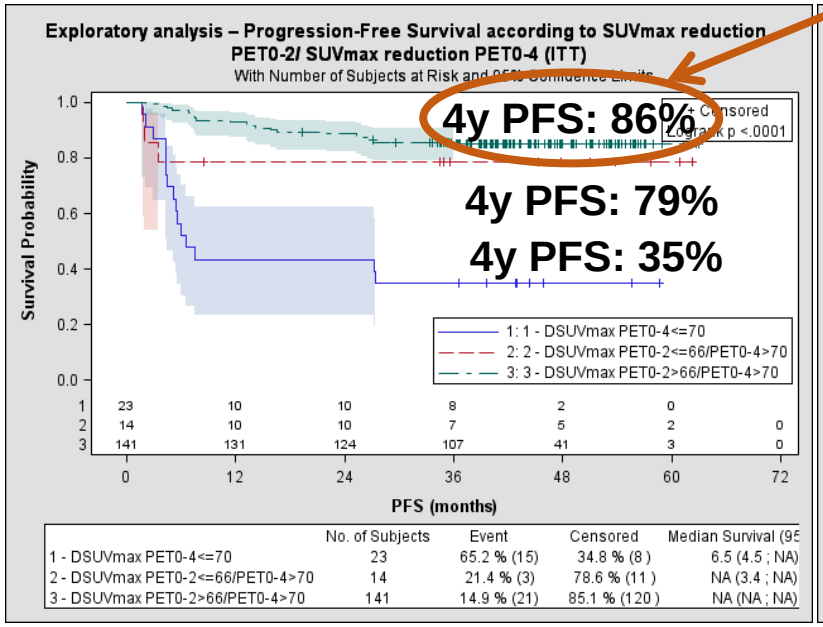
PET2/4 neg: 85% 4y PFS

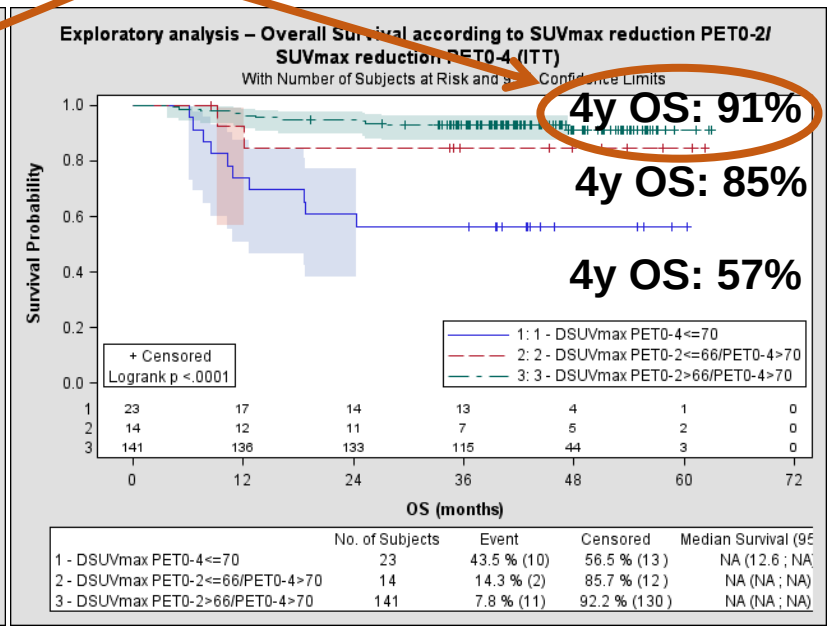
SUVmax reduction improves early prognosis value of interim positron emission tomography scans in diffuse large B-cell lymphoma

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)

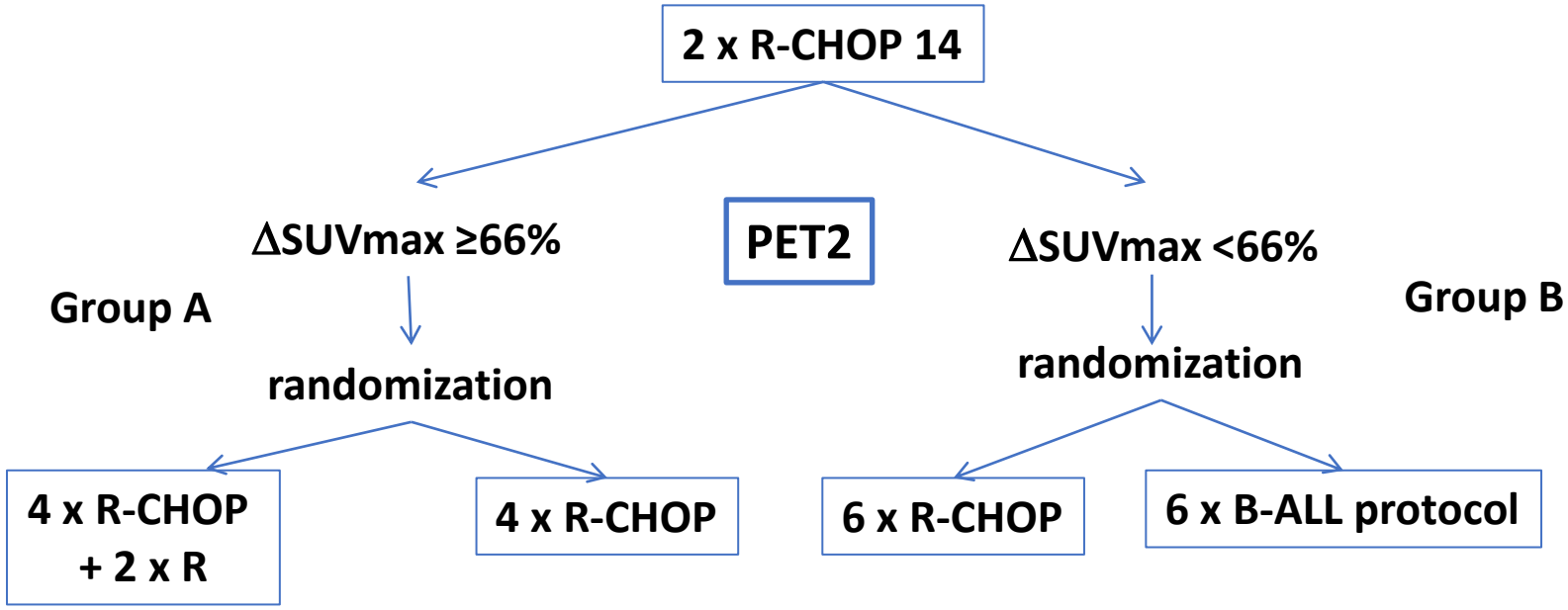
BLOOD, 7 JULY 2011 • VOLUME 118, NUMBER 1

80% of the whole population





PET Guided Therapy of **A**ggressive **L**ymphomas **– (PETAL Trial)**



1072 pts 18-80 y with agressive lymphoma

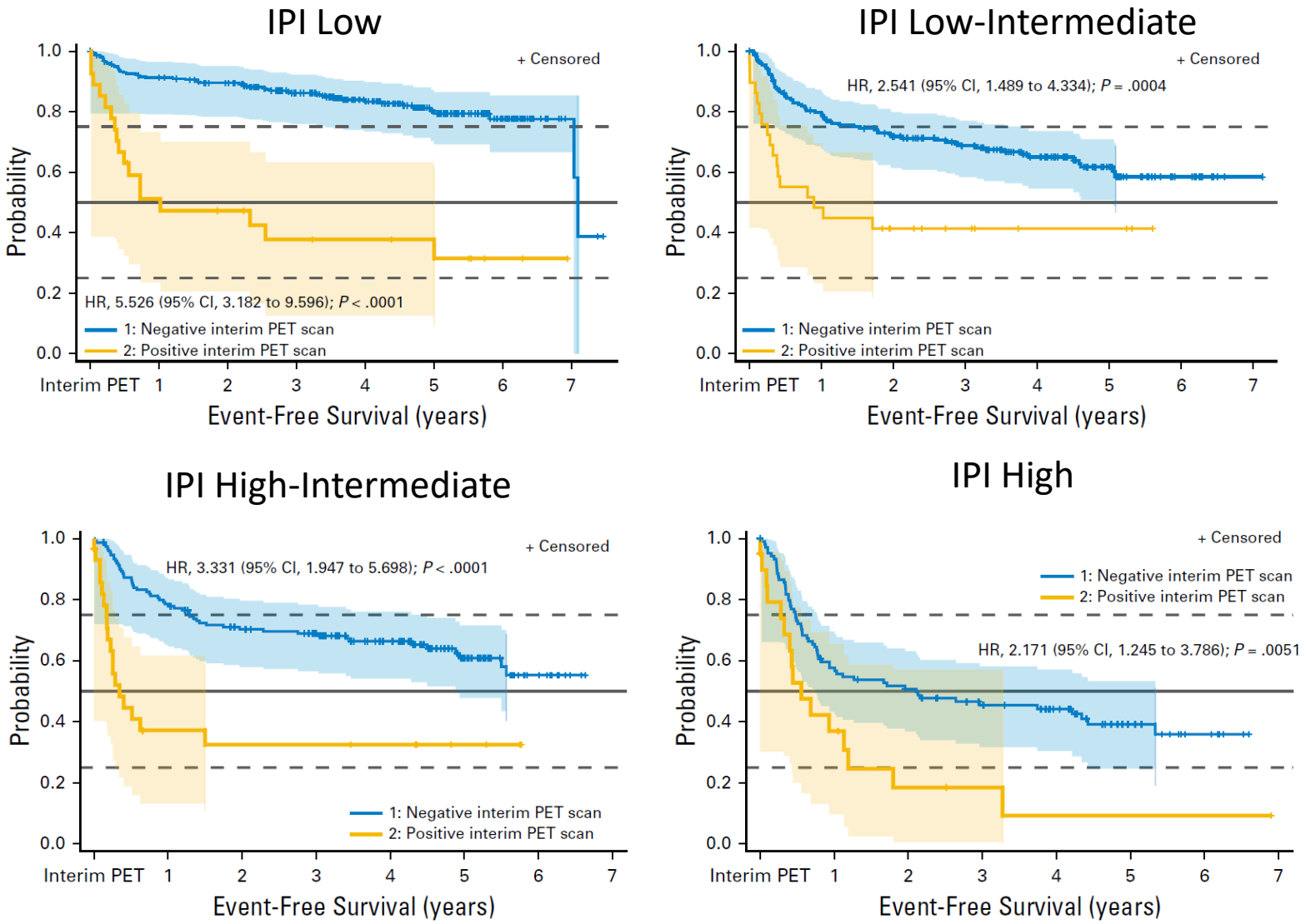
853 pts evaluables (83 (10%) T-NHL)
83% of B lymphoma = DLBCL
Follow Up 33 months

Main objective: increase 2y-TTF

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

Durhsen U et al, JCO 2018

PETAL: EFS by IPI according to PET2 result



ΔSUVmax cutoff 66%
12.5% positive PET2

Median FU = 44 months

Durhsen U et al, JCO 2018

Perspective

blood

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

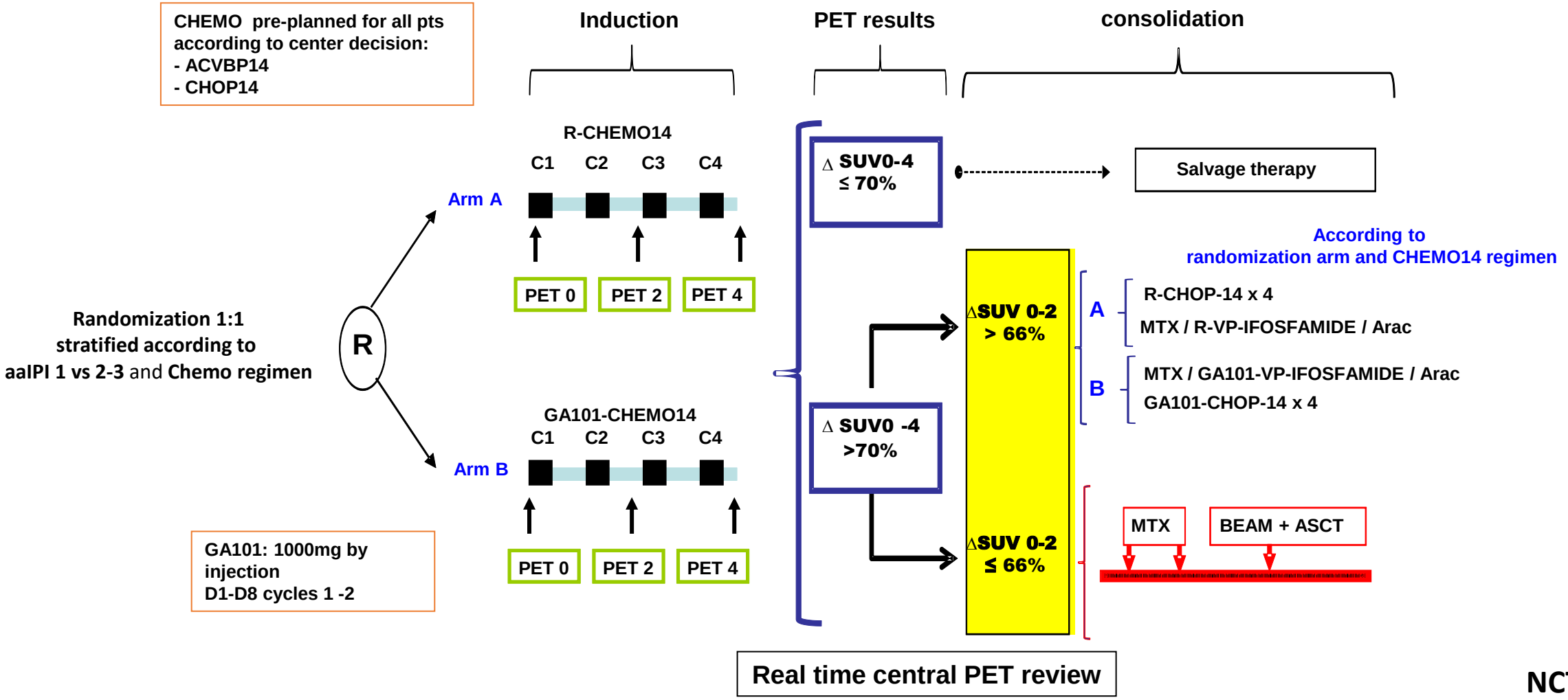
Steven Le Gouill[1-3] and René-Olivier Casasnovas[4,5]

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

GAINED: Study design

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

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



NCT01659099

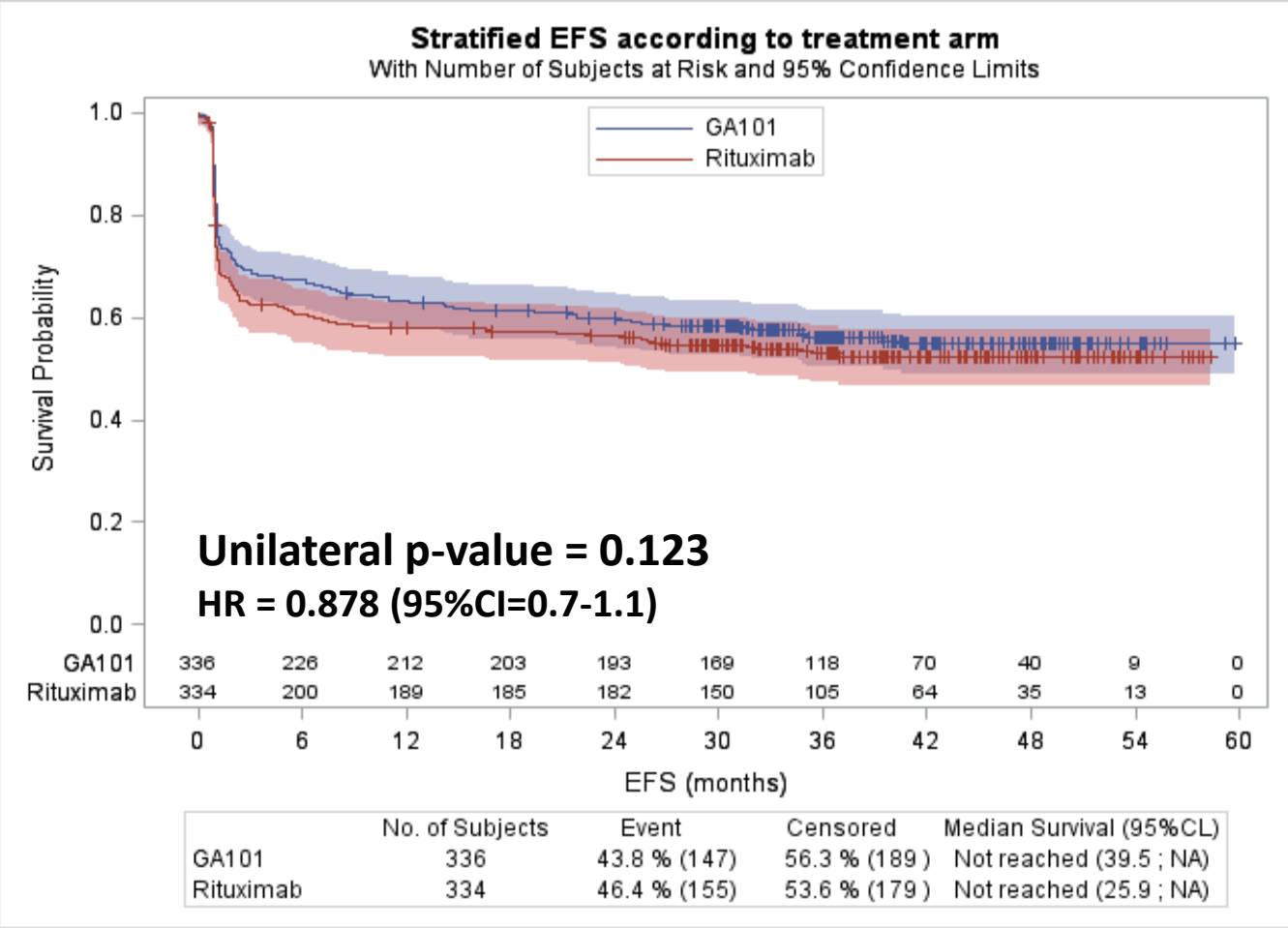
Casasnovas et al, ASH 2017; LeGouill et al Blood 2021

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	

Casasnovas et al, ASH 2017; LeGouill et al Blood 2021

GAINED: EFS (Primary endpoint)



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

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

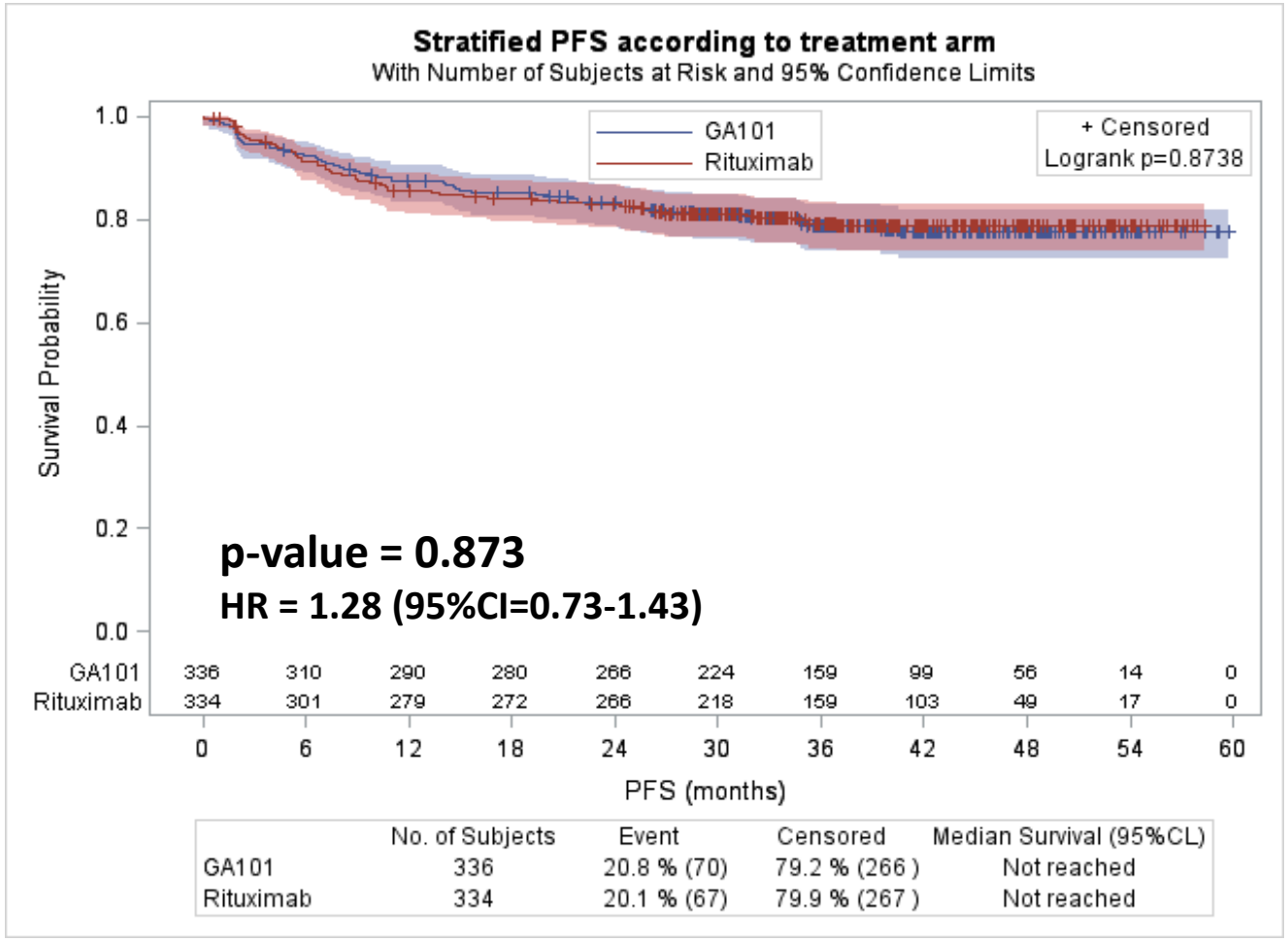
Median follow up = 36.7 months

Stopping date december 31 2017

*Testing the superiority of the experimental arm

Casasnovas et al, ASH 2017; LeGouill et al Blood 2021

GAINED: PFS according to the randomization arm

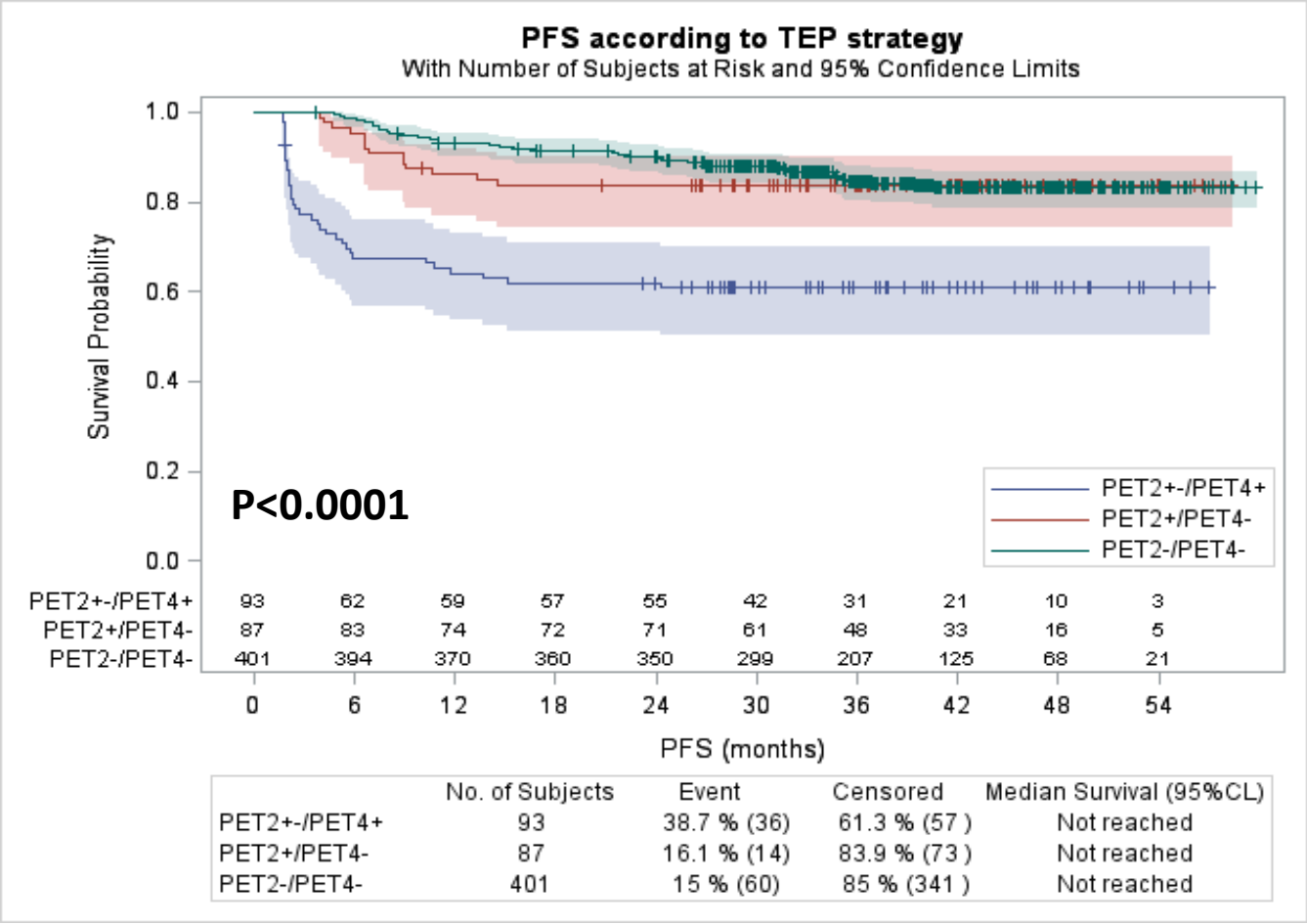


R-chemo: 2y-PFS = 83%; 4y-PFS = 78.8%

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

Casasnovas et al, ASH 2017; LeGouill et al Blood 2021

PFS according to the PET driven strategy



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

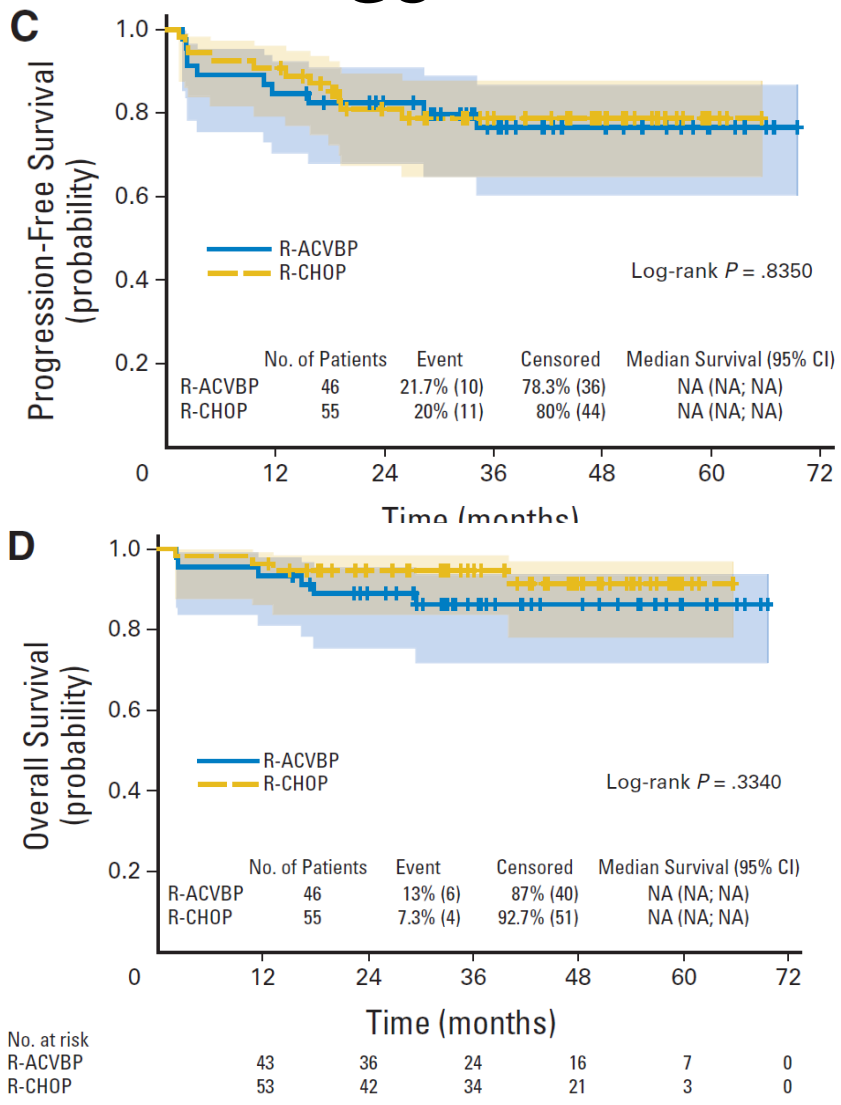
- PET2+/PET4- pts: 3y-PFS = 83.9%; HR = 1.11; p <0.71

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

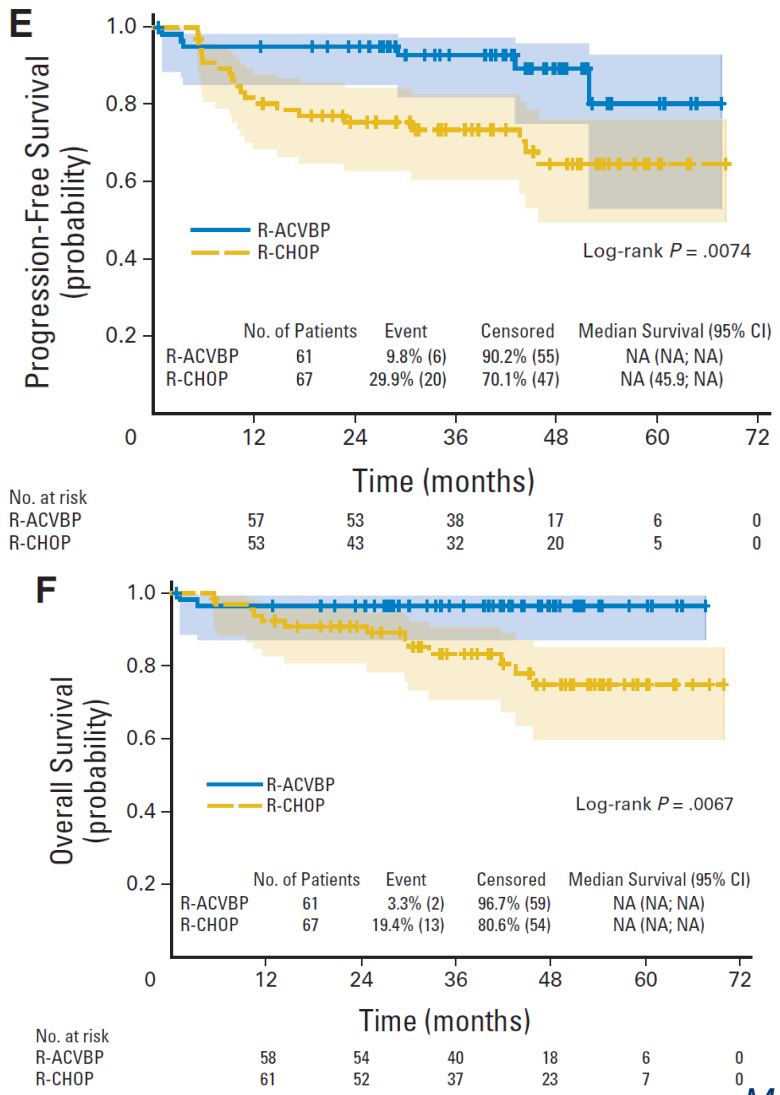
Casasnovas et al, ASH 2017; LeGouill et al Blood 2021

LNH03-2B: R-CHOP / R-ACVBP

GC

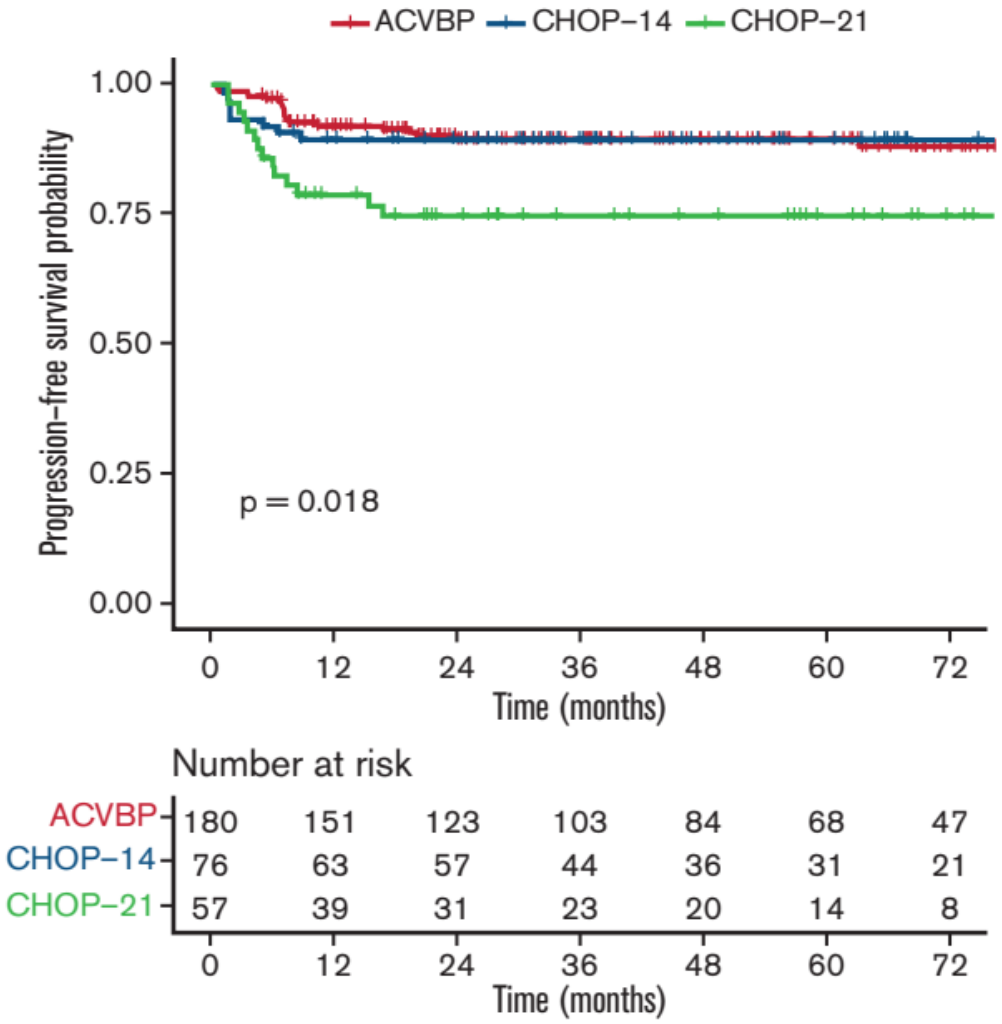


Non GC



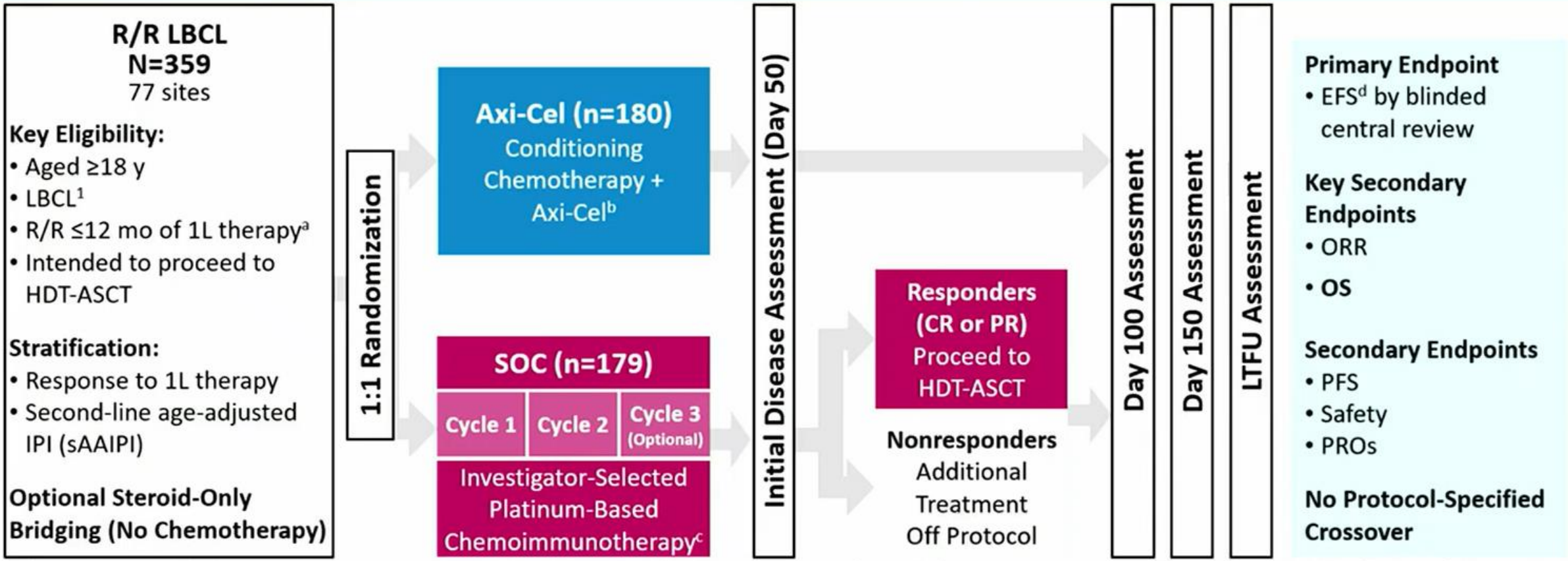
Molina T et al, JCO 2014

PMBL: Chemotherapy



Camus V et al, Blood Adv 2021

ZUMA-7 Study Schema and Endpoints

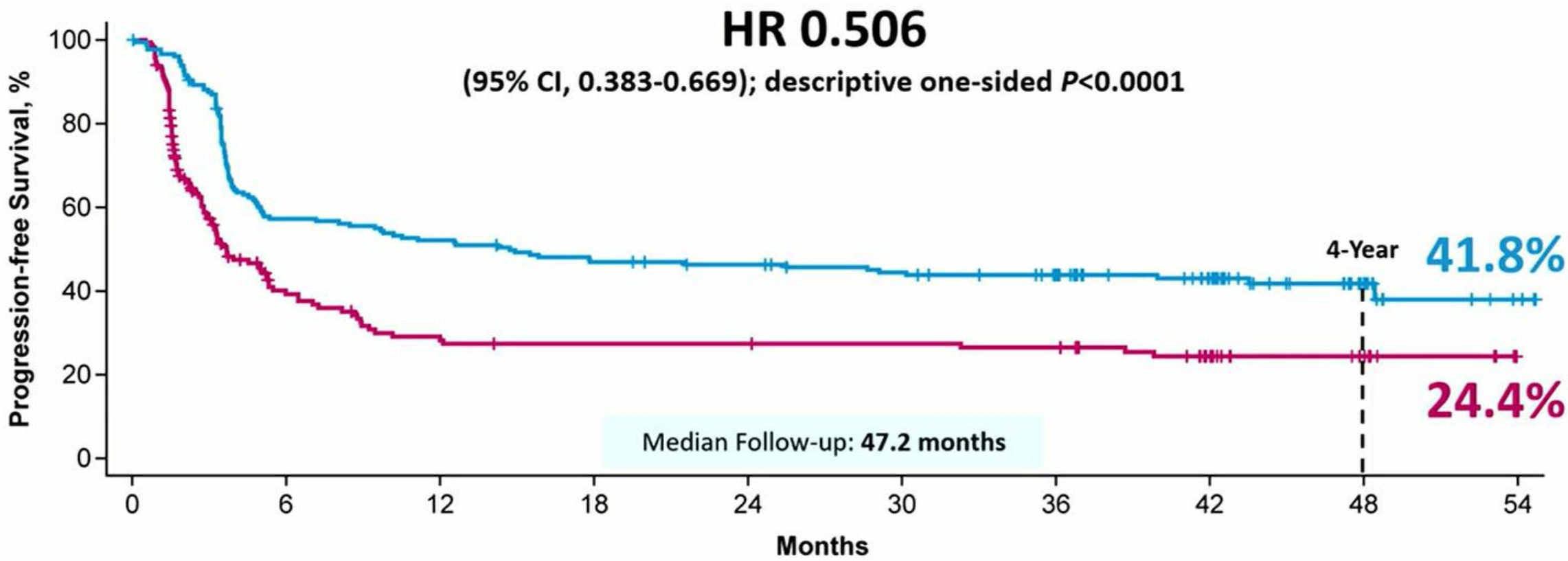


[a] Refractory disease was defined as no complete response to 1L therapy; relapsed disease was defined as complete response followed by biopsy-proven disease relapse ≤12 months from completion of 1L therapy. [b] Axi-cel patients underwent leukapheresis followed by conditioning chemotherapy with cyclophosphamide (500 mg/m²/day) and fludarabine (30 mg/m²/day) 5, 4, and 3 days before receiving a single axi-cel infusion (target intravenous dose, 2×10^6 CAR T cells/kg). [c] Protocol-defined SOC regimens included R-GDP, R-DHAP, R-ICE, or R-ESHAP. [d] EFS was defined as time from randomization to the earliest date of disease progression per Lugano Classification,[2] commencement of new lymphoma therapy, or death from any cause.

1. Swerdlow SH, et al. *Blood*. 2016;127:2375-2390. 2. Cheson BD, et al. *J Clin Oncol*. 2014;32:3059-3068.

1L, first line; axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; CR, complete response; EFS, event-free survival; HDT-ASCT, high-dose therapy with autologous stem cell transplantation; IPI, International Prognostic Index; LBCL, large B-cell lymphoma; LTFU, long-term follow-up; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; PRO, patient-reported outcome; R/R, relapsed/refractory; SOC, standard of care.

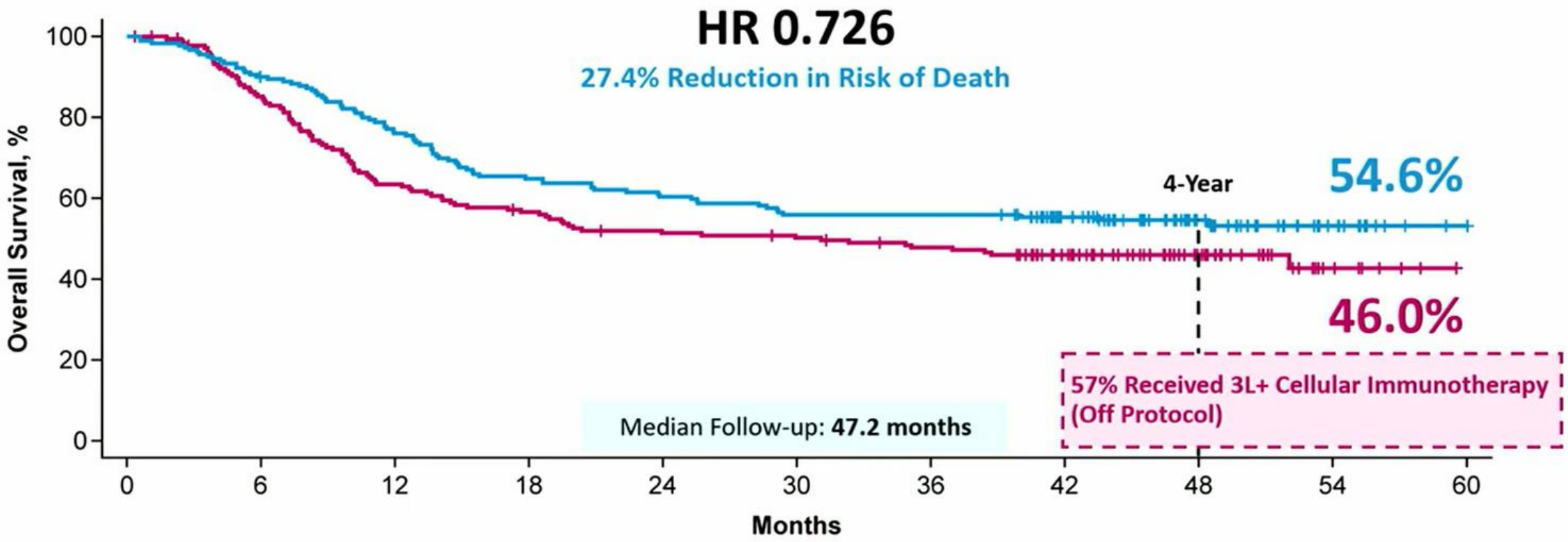
PFS By Investigator Confirmed Benefit of Axi-Cel Over SOC



No. at Risk										
Axi-Cel	180	100	91	81	77	71	63	45	22	3
SOC	179	47	33	31	31	30	29	18	8	0

Axi-cel, axicabtagene ciloleucel; HR, hazard ratio; PFS, progression-free survival; SOC, standard of care.

Axi-Cel Improved Overall Survival Versus Standard of Care



- 57% (n=102/179) of SOC patients received subsequent cellular immunotherapy (off protocol)
- Despite the increased survival in the SOC arm versus historical studies, axi-cel increased survival over SOC[a,b]

[a] Approximately 30% for early R/R LBCL in ORCHARRD (van Imhoff GW, et al. *J Clin Oncol*. 2017;35:544-551). [b] <40% for those with prior rituximab and early R/R LBCL in CORAL (Gisselbrecht C, et al. *J Clin Oncol*. 2010;28:4184-4190).
3L, third line; axi-cel, axicabtagene ciloleucel; HR, hazard ratio; LBCL, large B-cell lymphoma; R/R, relapsed/refractory; SOC, standard of care.

Key Safety Data At Primary Overall Survival Analysis

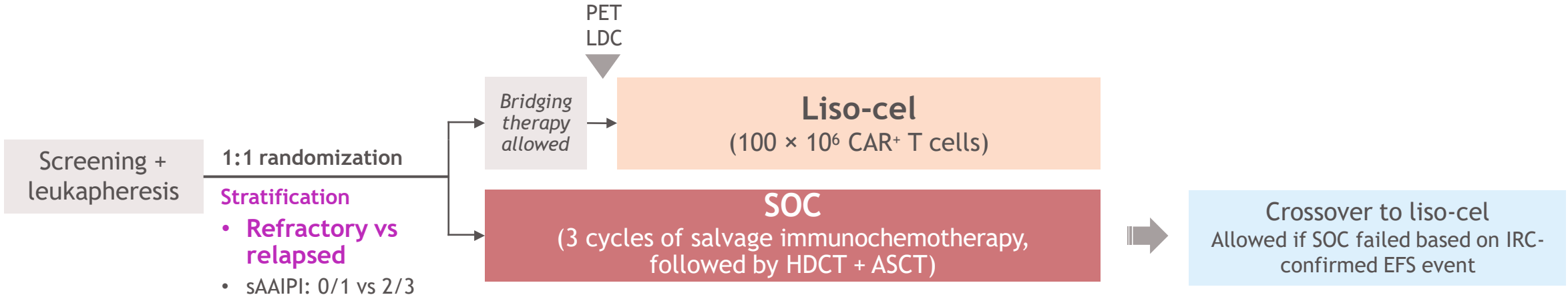
AEs of Interest, %	Axi-Cel n=170		SOC n=168	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
CRS	92%	6%	–	–
Neurologic event	61%	21%	20%	1%
Hypogammaglobulinemia	11%	0%	1%	0%
Cytopenia	80%	75%	80%	75%
Infections	45%	16%	32%	12%

- No changes in cumulative treatment-related serious or fatal AEs occurred since the primary EFS analysis

Reason for Death	Axi-Cel n=170	SOC n=168
Progressive disease, n (%)	51 (30)	71 (42)
Grade 5 AE during protocol-specific reporting period, n (%)	8 (5)[a]	2 (1)[b]
New or secondary malignancy, n (%)	2 (1)[c]	0
Other reason for death,[d] n (%)	13 (8)	18 (11)
Definitive therapy-related mortality,[e] n/N (%)	1/170 (1)[f]	2/64 (3)[g]

Data here are presented for the safety analysis set. Fewer SOC patients remained in the AE reporting period post-progression or start of new lymphoma therapy; thus, cross-arm comparisons of AE rates warrant cautious interpretation. [a] COVID-19 (n=2), sepsis (n=2), hepatitis B reactivation, myocardial infarction, pneumonia, and progressive multifocal leukoencephalopathy (n=1 each). [b] Acute respiratory distress syndrome and cardiac arrest (n=1 each). [c] One patient died of acute myeloid leukemia and one died of lung adenocarcinoma, both deemed unrelated to study treatment per investigator assessment. [d] Includes fatal AEs that occurred outside of the protocol-specified AE reporting window. COVID-19 (n=4), other infection/inflammation (n=3), neurologic organ failure (n=2), respiratory organ failure, cardiac organ failure, progressive disease, and unknown (n=1 each) in the axi-cel arm. Other infection/inflammation (n=7), unknown (n=5), COVID-19 (n=4), respiratory organ failure, and cardiopulmonary/neurologic organ failure (n=1 each) in the SOC arm. [e] Related to axi-cel or high-dose therapy with autologous stem cell transplantation. [f] Hepatitis B reactivation. [g] Cardiac arrest and acute respiratory distress syndrome (n=1 each).
AE, adverse event; axi-cel, axicabtagene ciloleucel; CRS, cytokine release syndrome; EFS, event-free survival; SOC, standard of care.

TRANSFORM: study design



Key patient eligibility criteria

- Age 18—75 years
- Aggressive NHL
  - DLBCL NOS, DLBCL transformed from indolent NHL, HGBCL with *MYC* and *BCL2* and/or *BCL6* rearrangements with DLBCL histology (double/triple hit), FL3B, PMBCL, and THRBCL
- Refractory or relapsed[a] ≤ 12 months after 1L treatment containing an anthracycline and a CD20-targeted agent
- ECOG performance status ≤ 1
- Eligible for ASCT
- Secondary CNS lymphoma allowed
- LVEF > 40% for inclusion
- No minimum absolute lymphocyte count

Primary endpoint

- EFS (per IRC)

Key secondary endpoints

- CR rate (per IRC), PFS (per IRC), OS

Other secondary endpoints

- Duration of response (per IRC), ORR (per IRC), PFS on next line of treatment
- Safety, patient-reported outcomes

Exploratory endpoints

- Cellular kinetics
- B-cell aplasia

[a]Time of relapse was calculated from the date of first disease assessment confirming CR with 1L therapy to the date of first assessment demonstrating relapse.

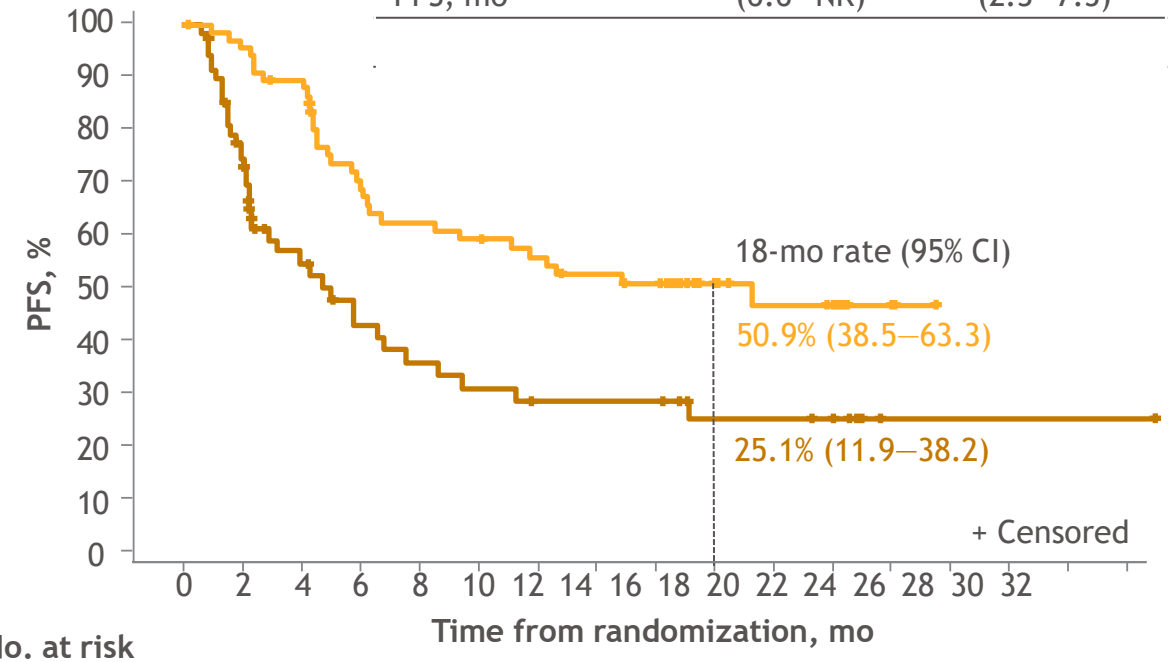
ASCT, autologous stem cell transplantation; EFS, event-free survival; FL3B, follicular lymphoma grade 3B; HDCT, high-dose chemotherapy; HGBCL, high-grade B-cell lymphoma; IRC, independent review committee; LDC, lymphodepleting chemotherapy; NOS, not otherwise specified; PMBCL, primary mediastinal B-cell lymphoma; R-DHAP, rituximab plus dexamethasone, cytarabine, and cisplatin; R-GDP, rituximab plus gemcitabine, dexamethasone, and cisplatin; R-ICE, rituximab plus ifosfamide, carboplatin, and etoposide; sAAIPI, secondary age-adjusted International Prognostic Index; THRBCL, T-cell/histiocyte-rich large B-cell lymphoma.

Nastoupil LJ, et al. ICML 2023 [Abstract #138]

PFS per IRC by prior response status (ITT set)

Refractory

	Liso-cel arm (n = 67)	SOC arm (n = 70)
Median (95% CI)[a] PFS, mo	19.2 (6.6—NR)	4.9 (2.3—7.5)

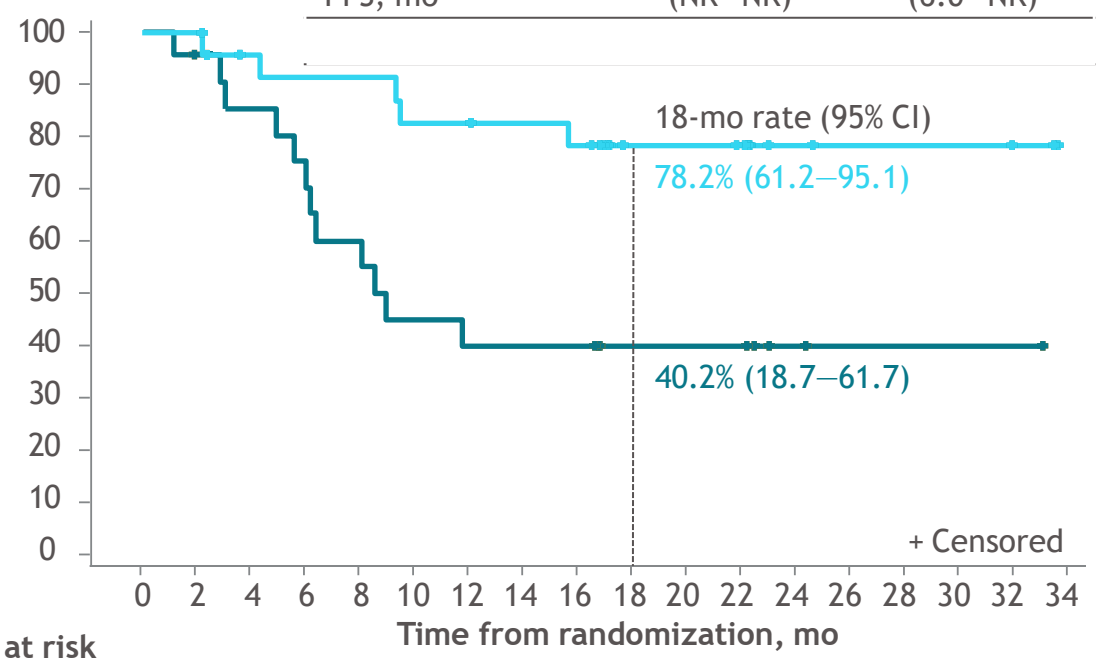


No. at risk

Liso-cel	67	63	57	42	39	37	34	31	29	15	11	9	2	0			
SOC	70	46	25	18	15	13	11	11	11	7	7	5	1	1	1	1	1

Relapsed

	Liso-cel arm (n = 25)	SOC arm (n = 22)
Median (95% CI)[a] PFS, mo	NR (NR—NR)	9.0 (6.0—NR)



No. at risk

Liso-cel	25	25	22	21	21	19	19	18	17	10	10	9	4	3	3	3	3	0
SOC	22	20	17	15	12	9	8	8	8	5	5	5	2	1	1	1	1	0

- PFS in the overall study population: NR (95% CI, 12.6—NR) versus 6.2 months (95% CI, 4.3—8.6); HR, 0.400; 95% CI, 0.261—0.615; $P < 0.0001$[1]

[a]Median estimates of time to event are Kaplan-Meier product-limit estimates; [b]Based on a stratified Cox proportional hazards model.

1. Abramson JS, et al. *Blood* 2023;141:1675—1684.

Nastoupil LJ, et al. ICML 2023 [Abstract #138]

OS by prior response status (ITT set)

	Refractory		Relapsed	
	Liso-cel arm (n = 67)	SOC arm (n = 70)	Liso-cel arm (n = 25)	SOC arm (n = 22)
Median OS (95% CI), months[b]	29.5 (22.2—NR)	20.9 (15.1—NR)	NR (NR—NR)	NR (17.9—NR)
12-month OS rate, % (95% CI)[a]	80.4 (70.8—89.9)	67.3 (56.0—78.5)	91.7 (80.6—100.0)	86.4 (72.0—100.0)
18-month OS rate, % (95% CI)[a]	68.0 (56.7—79.3)	55.8 (43.6—67.9)	87.3 (73.9—100.0)	75.2 (56.1—94.3)

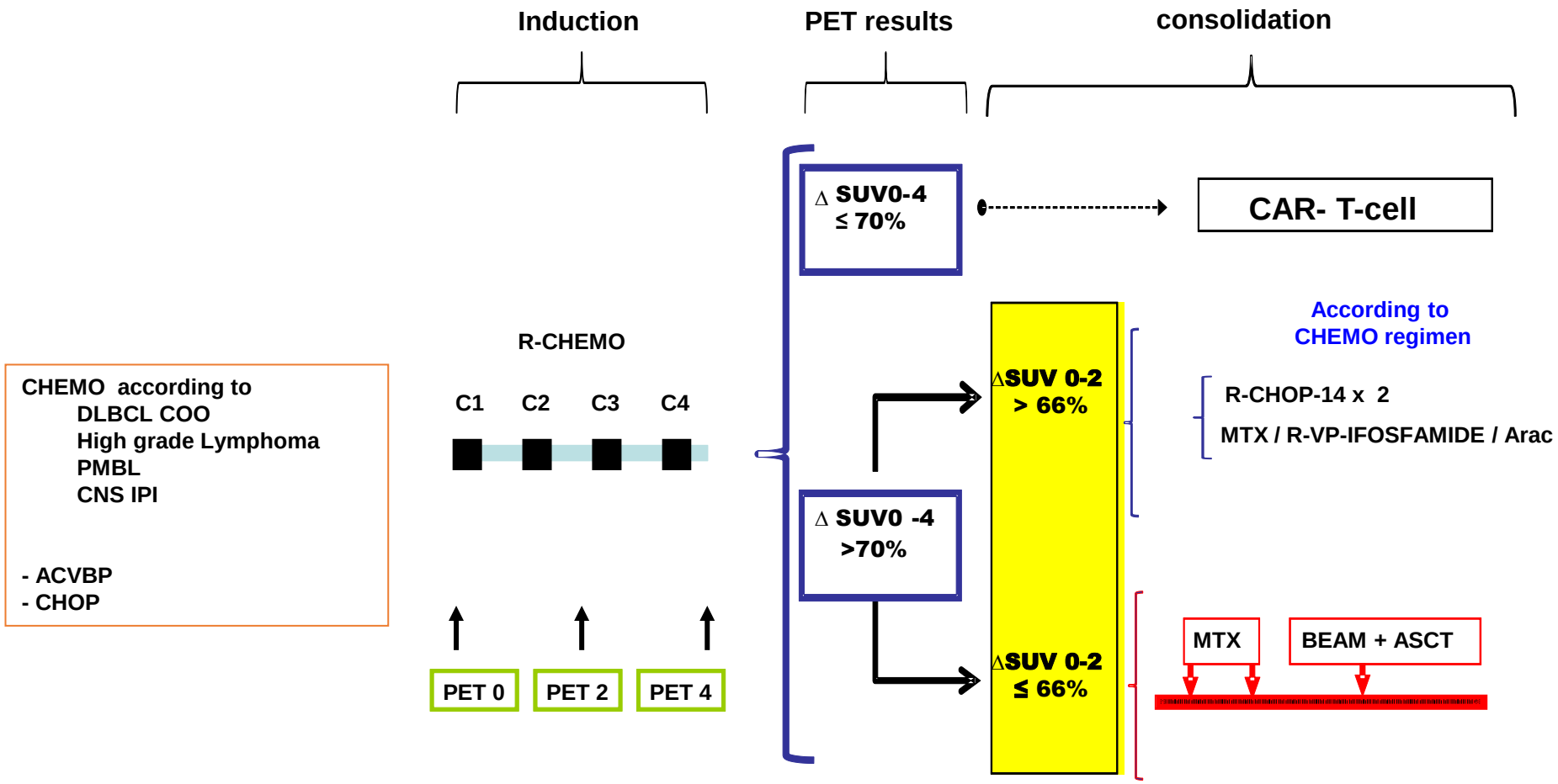
- Similar to EFS and PFS, OS subgroup analyses were consistent with results from the overall study population (NR [95% CI, 29.5—NR]) for liso-cel versus 29.9 months (95% CI, 17.9—NR) for SOC (HR, 0.724; 95% CI, 0.443—1.183; *P* = 0.0987)[1]

[a]Greenwood's formula; [b]Median estimates of time to event are Kaplan-Meier product-limit estimates.

1. Abramson JS, et al. *Blood* 2023;141:1675—1684.

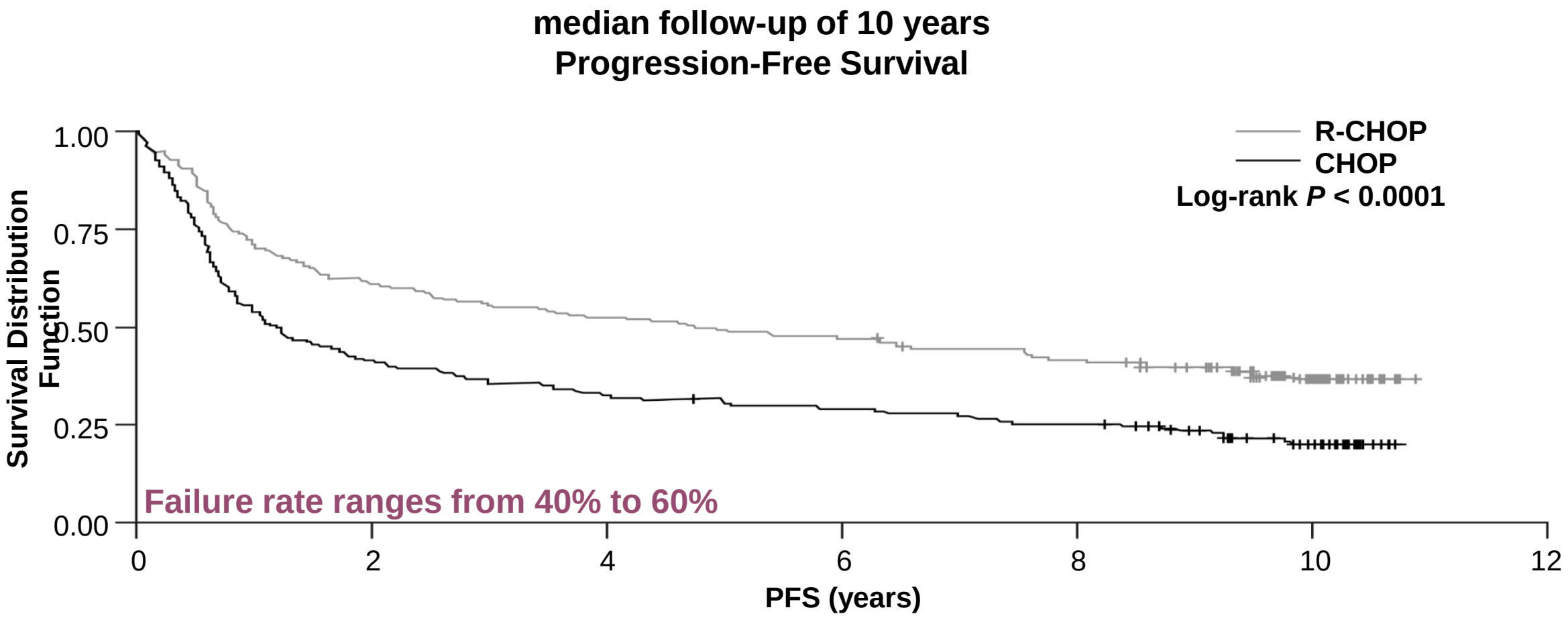
Nastoupil LJ, et al. ICML 2023 [Abstract #138]

Modified « GAINED » strategy in aaIPI 1-3 DLBCL



60 - 80 ans aaIPI 1-3

LNH-98.5 Study

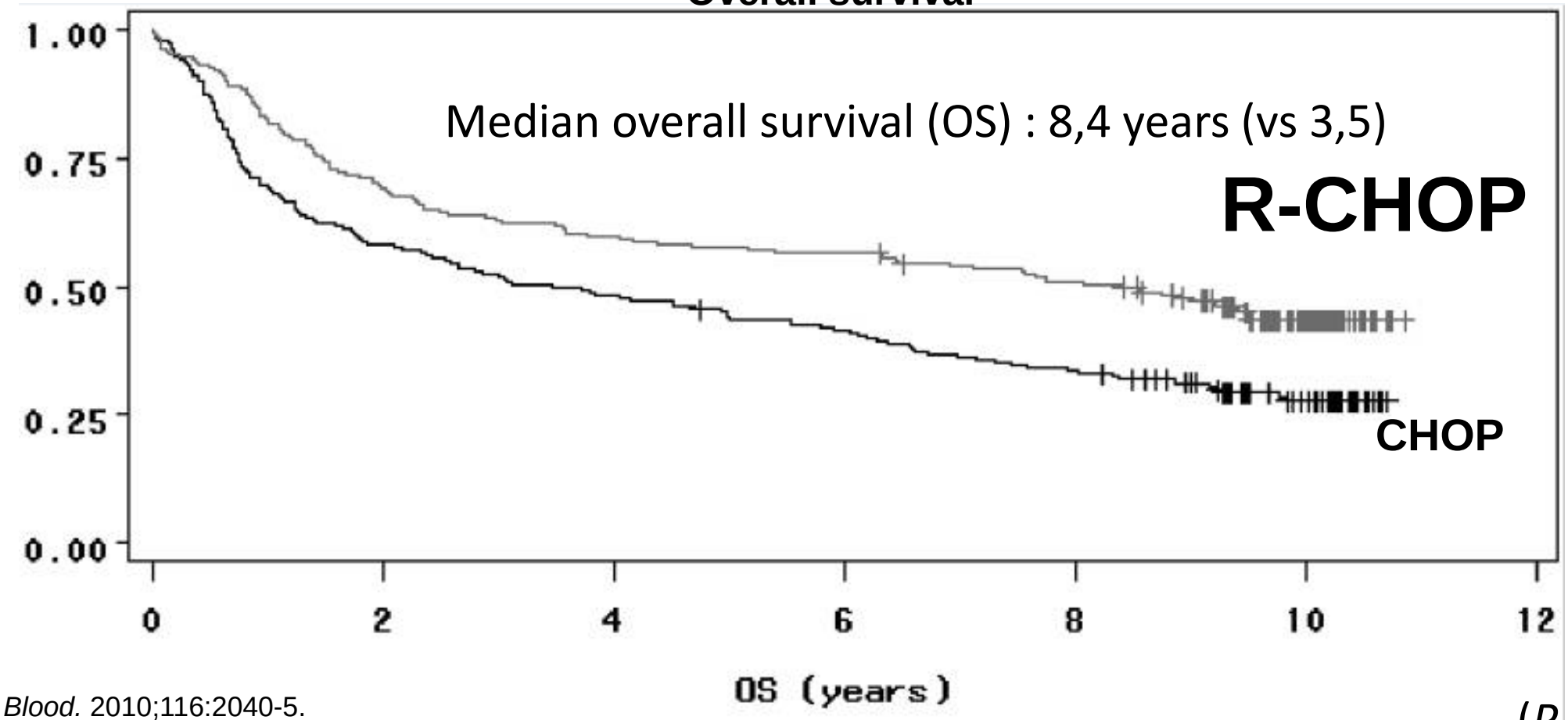


Coiffier et al. *Blood.* 2010;116:2040-5.
CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; R-CHOP, CHOP and rituximab.

LNH-98.5 Study

Median follow-up of 10 years

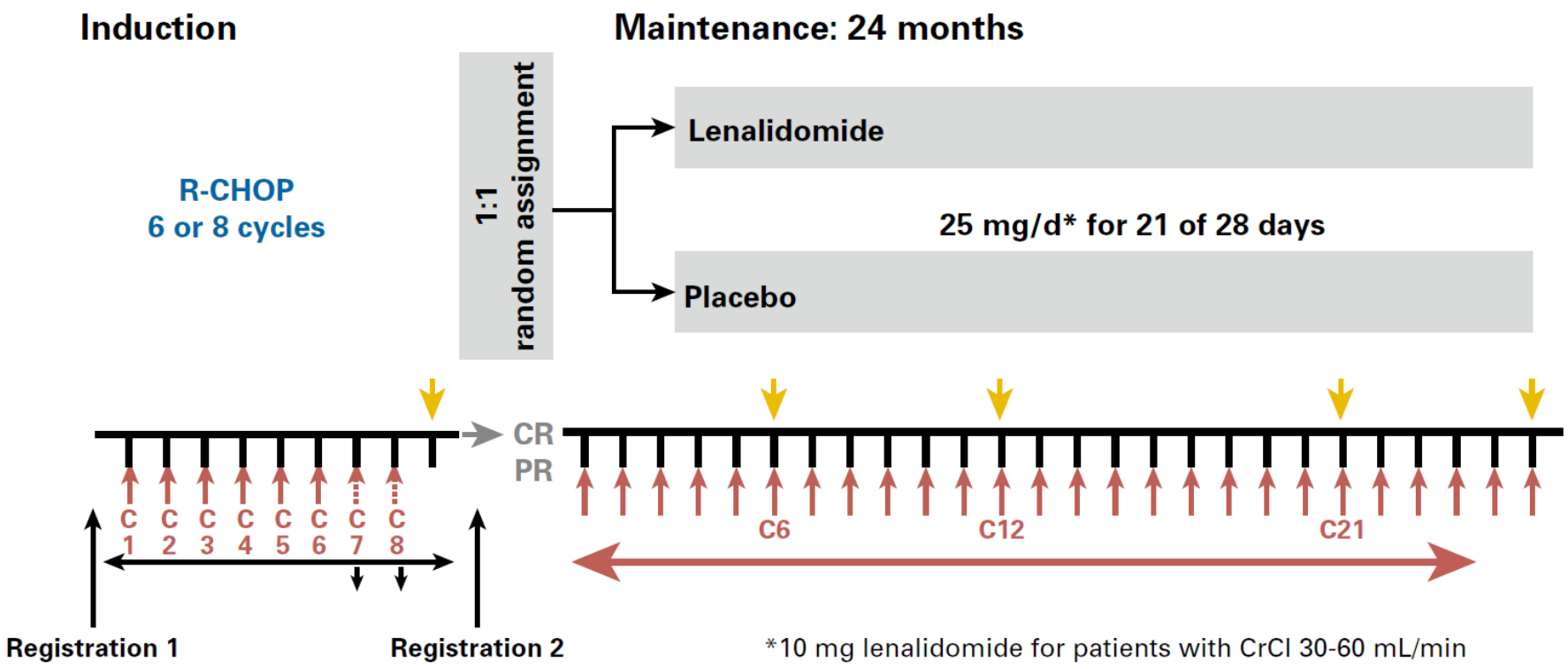
Overall survival



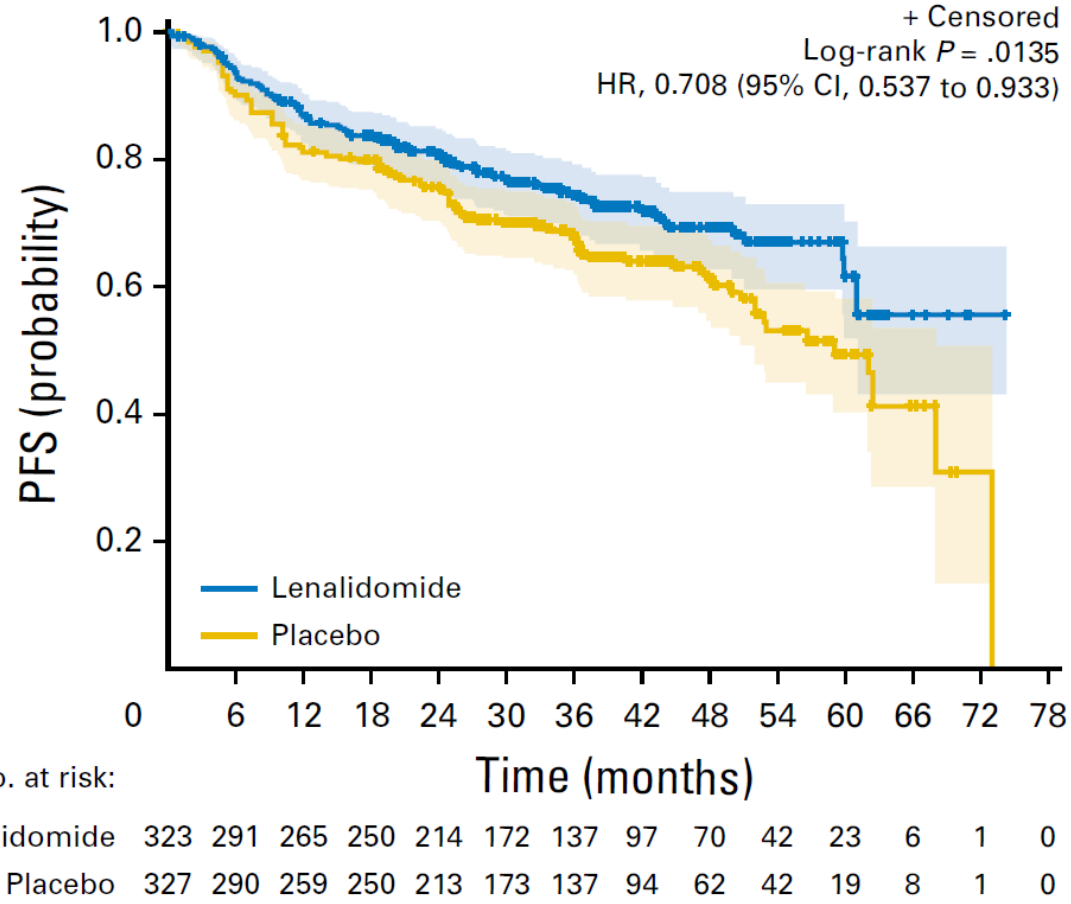
Coiffier et al. *Blood.* 2010;116:2040-5.
CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; R-CHOP, CHOP and rituximab.

(*P* < .0001

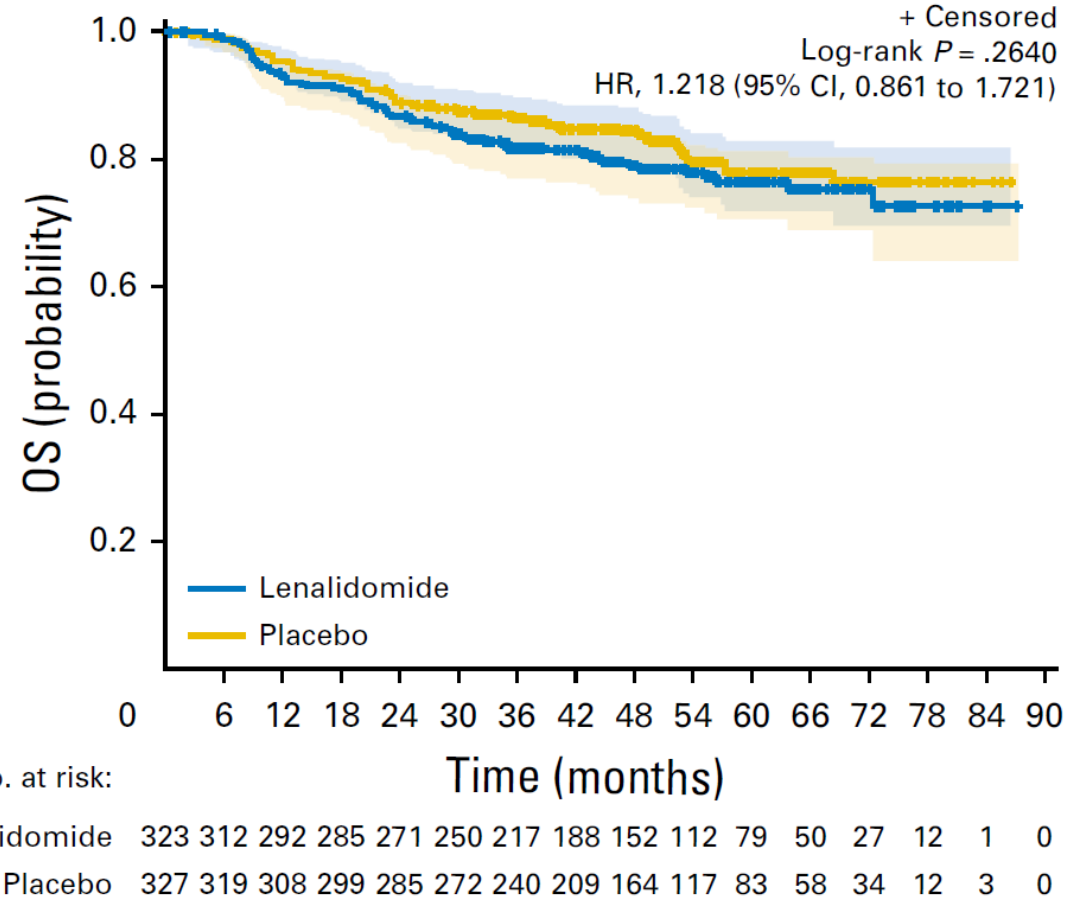
REMARC


Induction
Maintenance: 24 months
R-CHOP
6 or 8 cycles
1:1
random assignment
Lenalidomide
25 mg/d* for 21 of 28 days
Placebo
CR
PR
C 1
C 2
C 3
C 4
C 5
C 6
C 7
C 8
C6
C12
C21
Registration 1
Registration 2
*10 mg lenalidomide for patients with CrCl 30-60 mL/min

REMARC



No. at risk:														
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

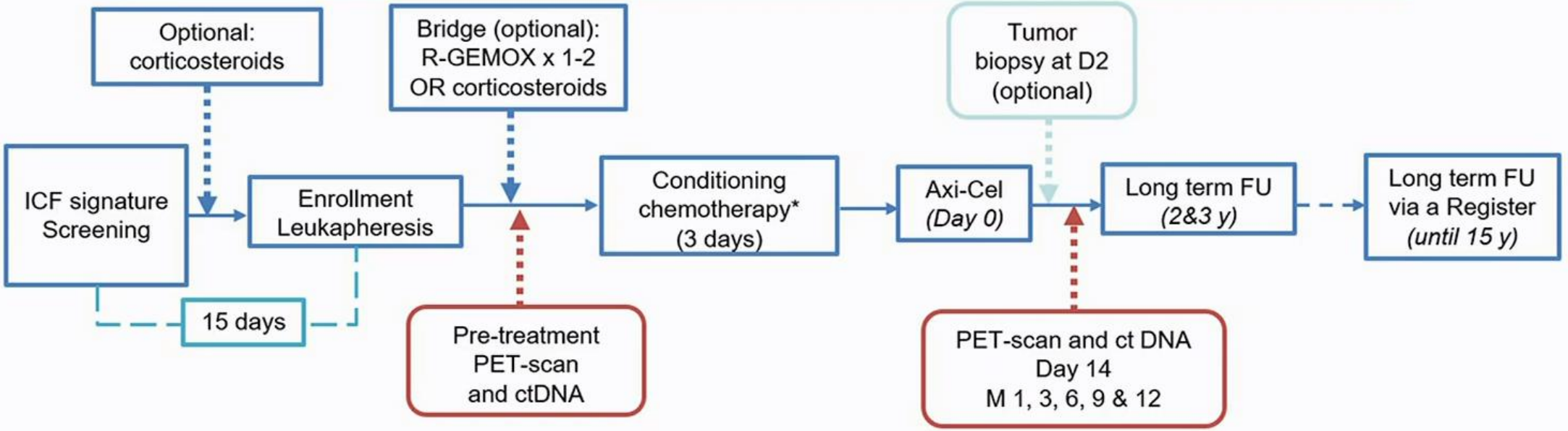


No. at risk:																
Lenalidomide	323	312	292	285	271	250	217	188	152	112	79	50	27	12	1	0
Placebo	327	319	308	299	285	272	240	209	164	117	83	58	34	12	3	0

ALYCANTE

Study design

- Phase II, single arm, open label, prospective, multicenter study
- 20 centers in France
- N = 62 patients infused between April 26th, 2021, and June 15th, 2022
- Data cutoff = January 19th, 2023



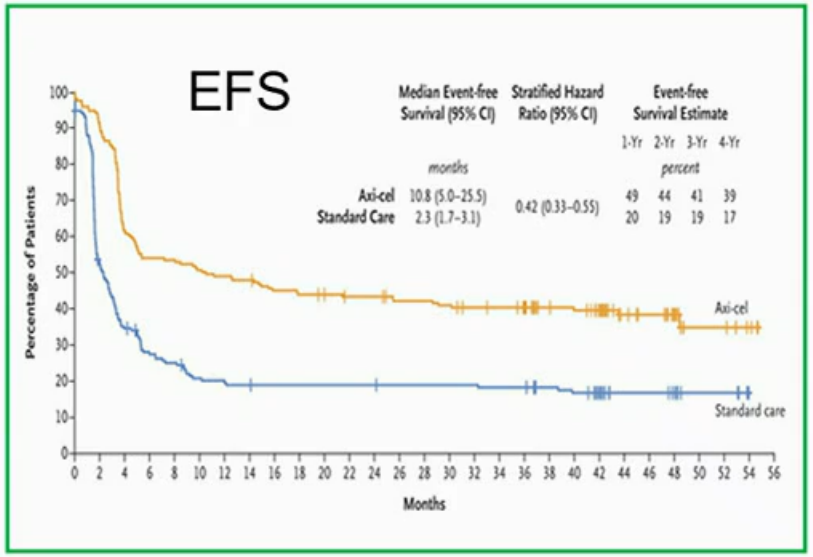
*Fludarabine 30 mg/m²/day + cyclophosphamide 500 mg/m²/day
For patients with creatinin clearance between 40 and 60 mL/min: fludarabine will be reduced to 25 mg/m²/day (cyclophosphamide will remain unchanged at 500 mg/m²/day)

Rationale

Outcome of R/R LBCL patients in 2nd line therapy

ASCT-eligible

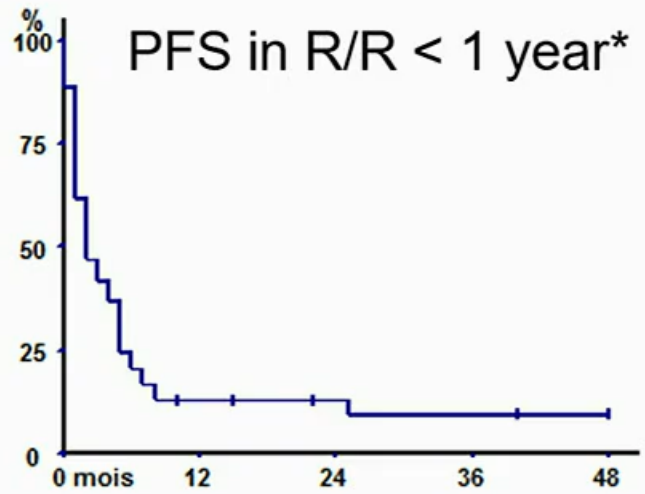
Axi-cel vs SOC (ZUMA-7)



N = 359
Median FU = 47 months

ASCT-ineligible

R-GEMOX (SOC)



N = 60
Median FU = 22 months

Axi-cel (ALYCANTE)

Hypothesis:

↑ CR at 3 months
from 12% with SOC*
to 34% with Axi-Cel

Power : 96%
α (one-sided) : 5%

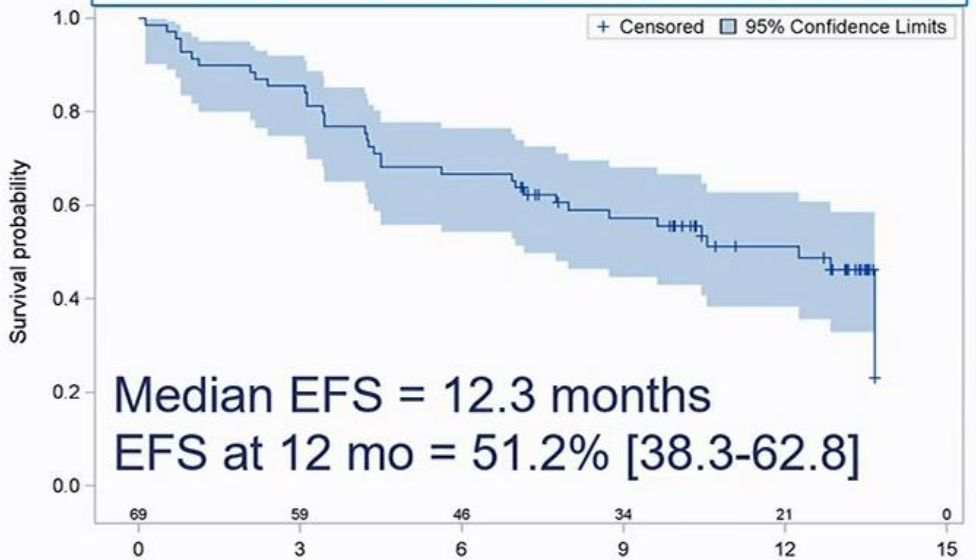
N = 40+22= 62
Median FU = 12 months

Westin et al, NEJM 2023

*Adapted from Cazelles et al, Leukemia & Lymphoma 2021

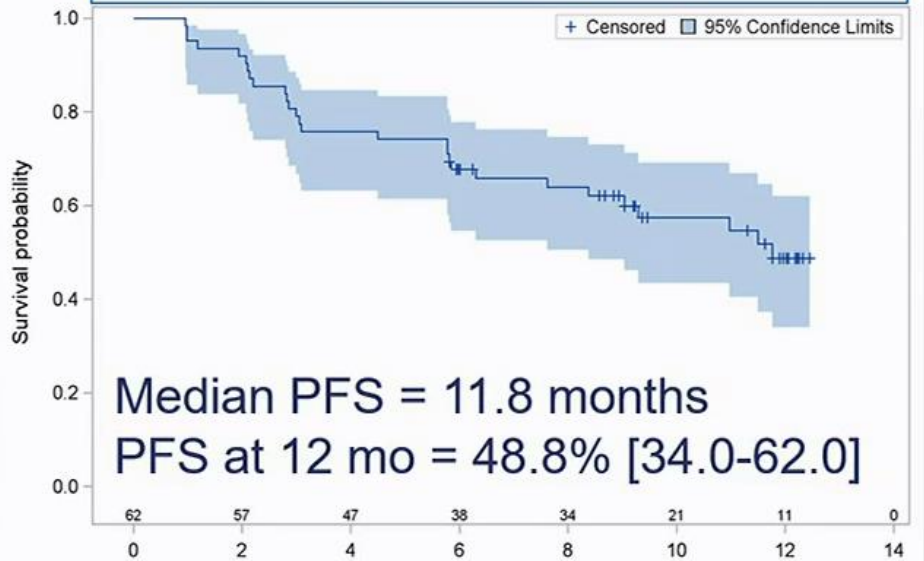
Survival : EFS and PFS

EFS* from leukapheresis



No. of subjects	Event	Censored	Median survival (95% CI)
69	50.7 % (35)	49.3 % (34)	12.3 (7.2 ; NA)

PFS from infusion



No. of subjects	Event	Censored	Median survival (95% CI)
62	45.2 % (28)	54.8 % (34)	11.8 (8.4 ; NA)

Median (range) on-study follow-up at time of analysis** : 12 months [2.1-17.9]

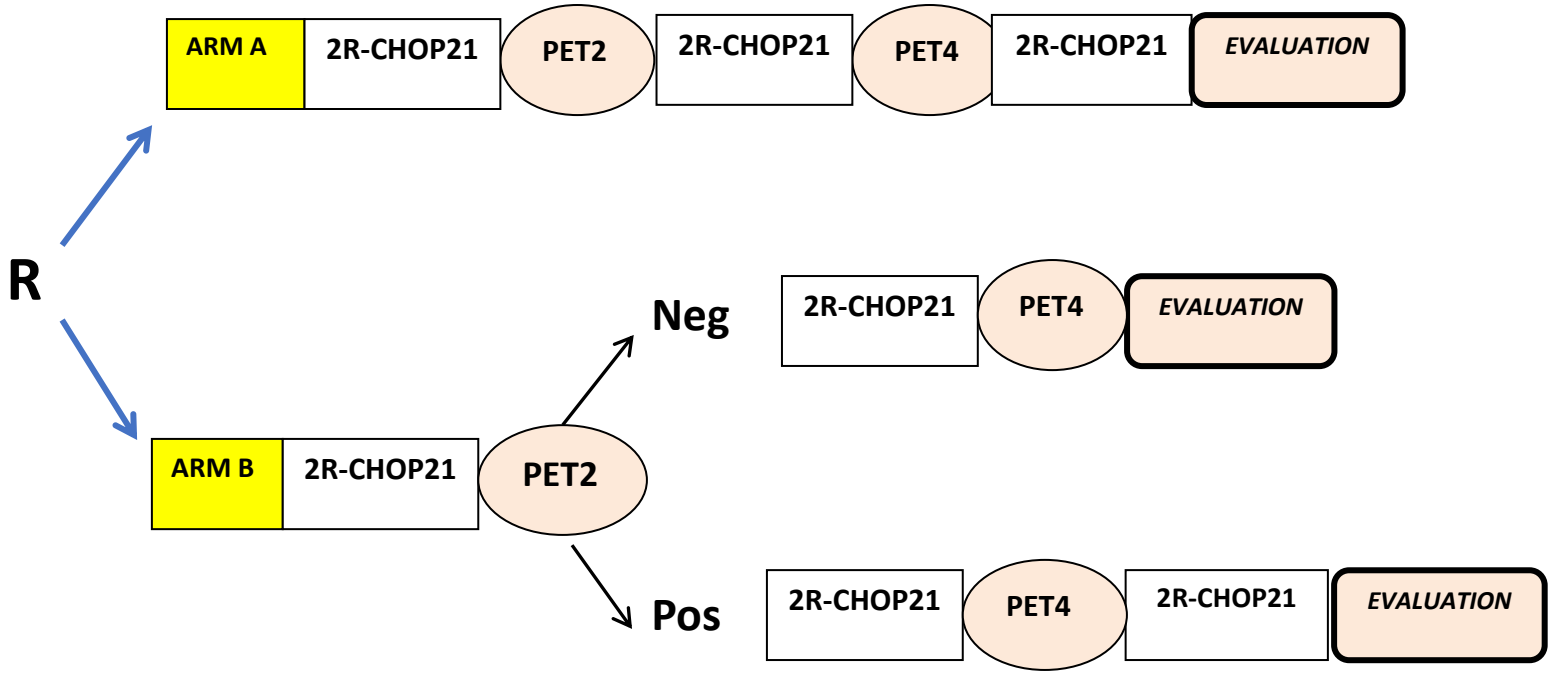
*EFS = time between leukapheresis and any event preventing Axi-cel infusion if Axi-cel is never infused; or death, disease progression, or instauration of a new lymphoma therapy for lymphoma progression after Axi-cel infusion
Patients without documented event at the time of analysis have been censored at the time of last visit with adequate assessment.
**from Axi-cel infusion

3 months CMR = 71%

18 - 80 ans aaIPl 0

LNH 2009-1B

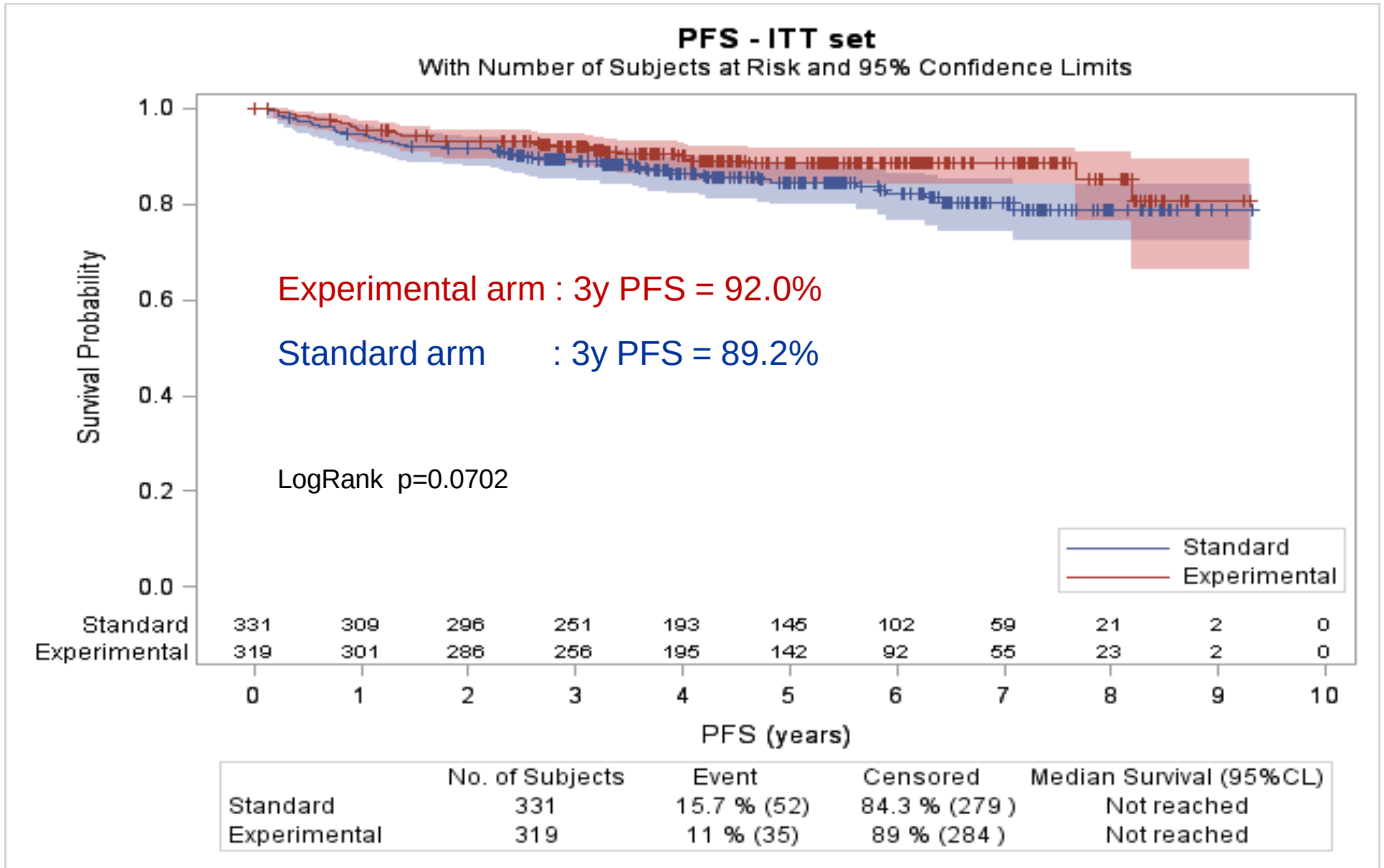
DLBCL: 18-80 y, aaIPI=0



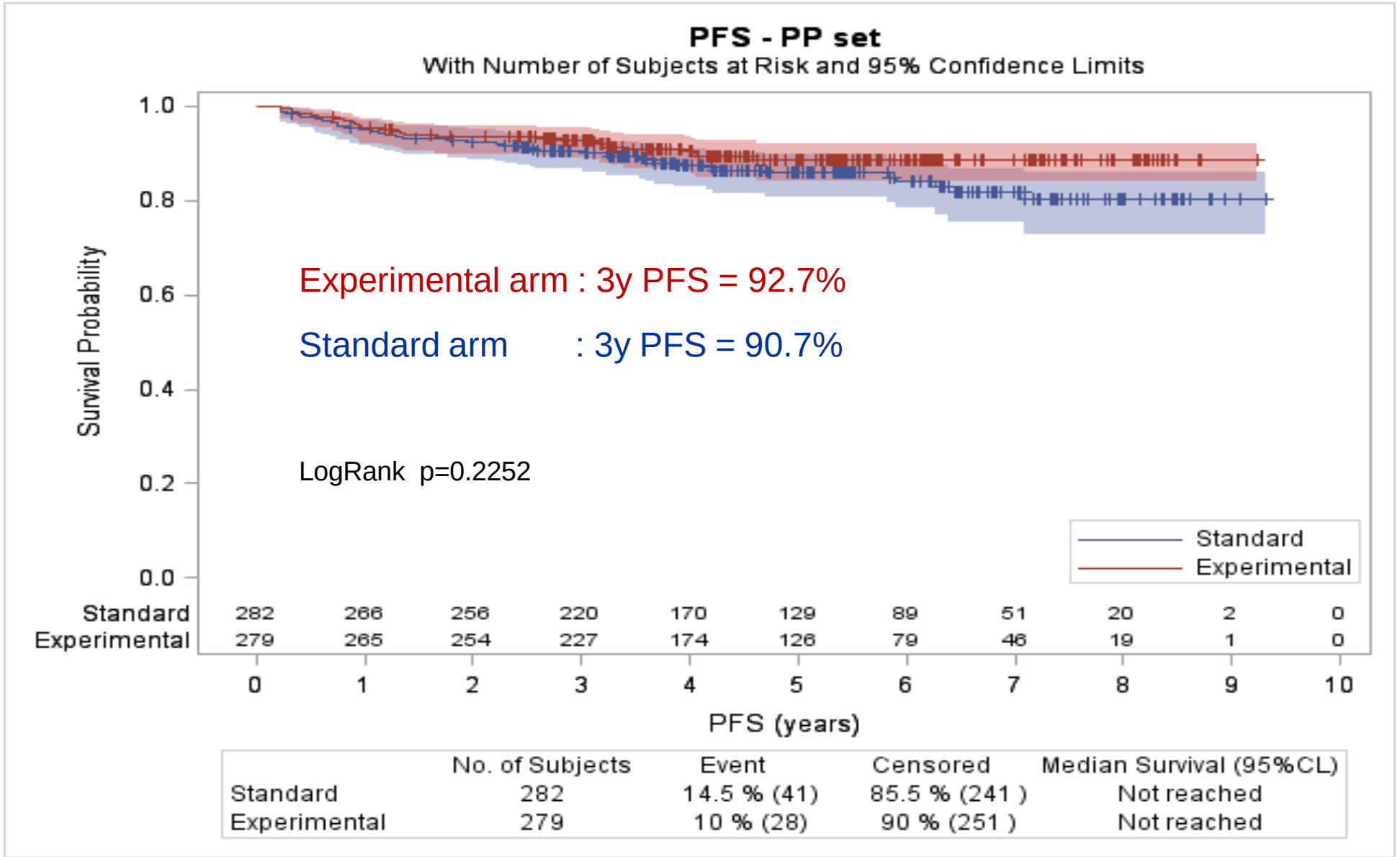
Central decisional PET interpretation: 5PS criteria (1,2,3, vs 4,5)

Non inferiority of the experimental arm
Standard arm : 80% 3y-PFS ; Experimental arm: 3y-PFS >70% (HR=1.6)

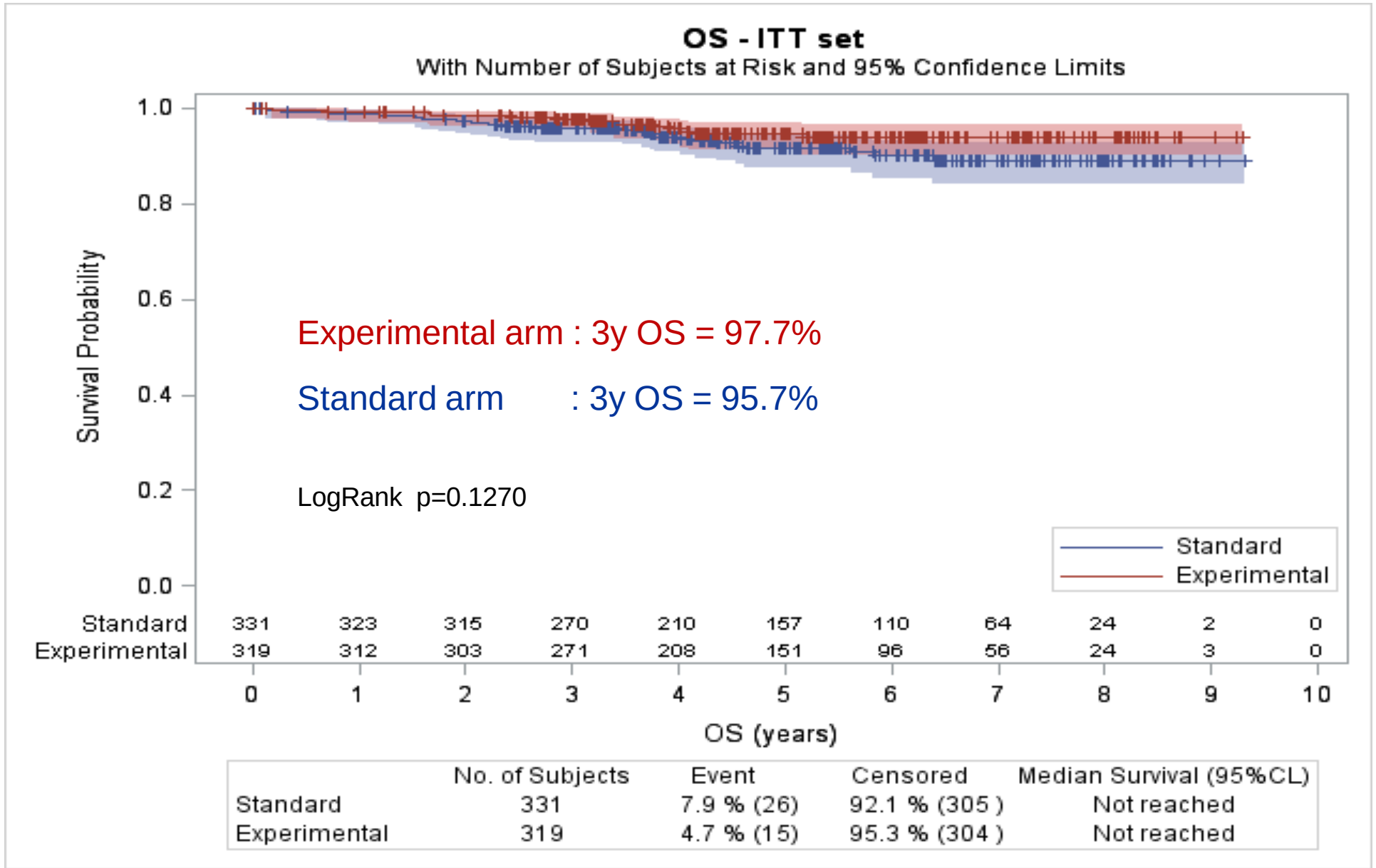
PFS – ITT set


PFS - ITT set
With Number of Subjects at Risk and 95% Confidence Limits
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
Experimental arm : 3y PFS = 92.0%
Standard arm : 3y PFS = 89.2%
LogRank p=0.0702
Standard
Experimental
Standard 331 309 296 251 193 145 102 59 21 2 0
Experimental 319 301 286 256 195 142 92 55 23 2 0
0 1 2 3 4 5 6 7 8 9 10
PFS (years)
No. of Subjects Event Censored Median Survival (95%CL)
Standard 331 15.7 % (52) 84.3 % (279) Not reached
Experimental 319 11 % (35) 89 % (284) Not reached

PFS – PP set

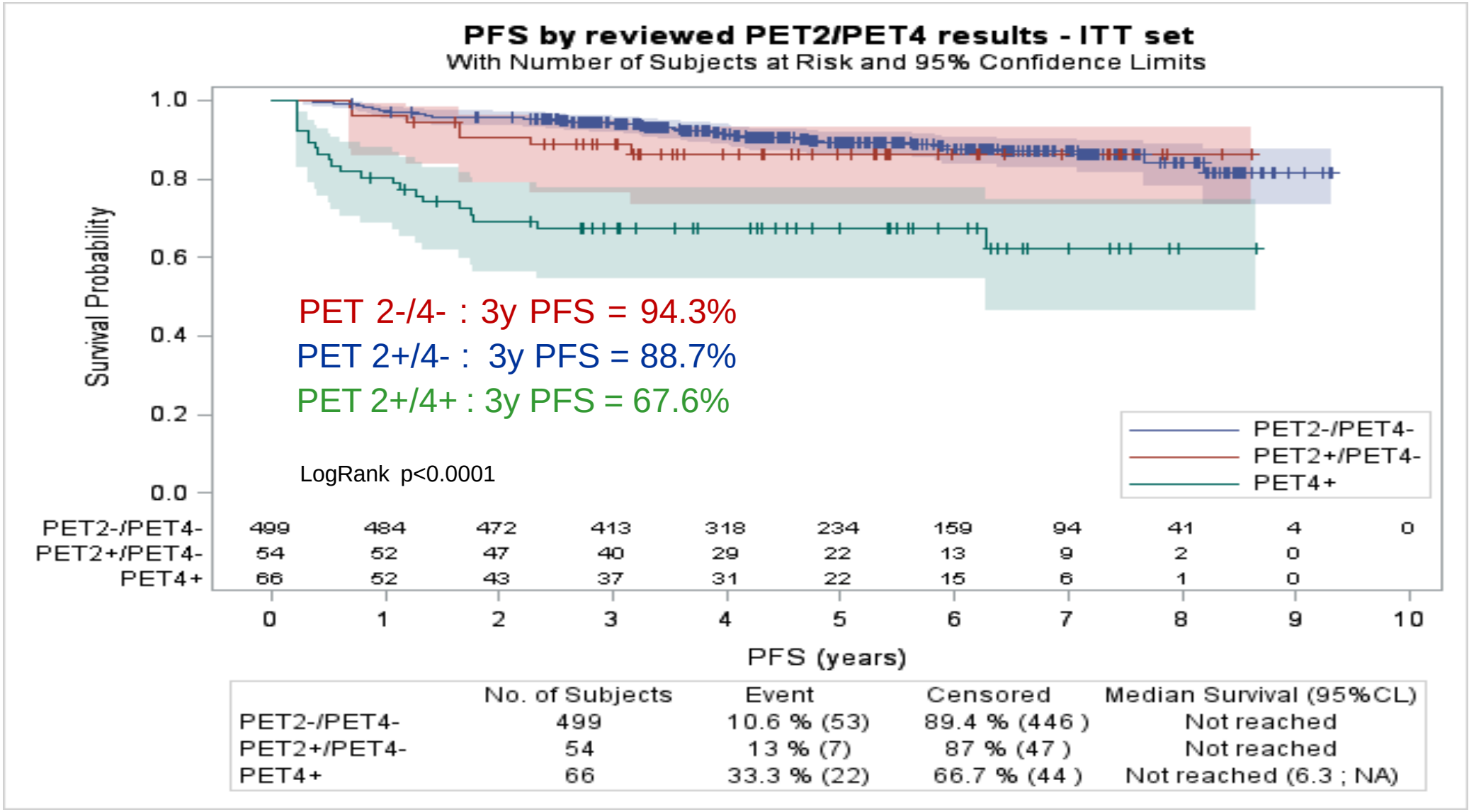

PFS - PP set
With Number of Subjects at Risk and 95% Confidence Limits
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
Experimental arm : 3y PFS = 92.7%
Standard arm : 3y PFS = 90.7%
LogRank p=0.2252
Standard
Experimental
Standard 282 266 256 220 170 129 89 51 20 2 0
Experimental 279 265 254 227 174 126 79 46 19 1 0
0 1 2 3 4 5 6 7 8 9 10
PFS (years)
No. of Subjects Event Censored Median Survival (95%CL)
Standard 282 14.5 % (41) 85.5 % (241) Not reached
Experimental 279 10 % (28) 90 % (251) Not reached

OS – ITT set



	No. of Subjects	Event	Censored	Median Survival (95%CL)
Standard	331	7.9 % (26)	92.1 % (305)	Not reached
Experimental	319	4.7 % (15)	95.3 % (304)	Not reached

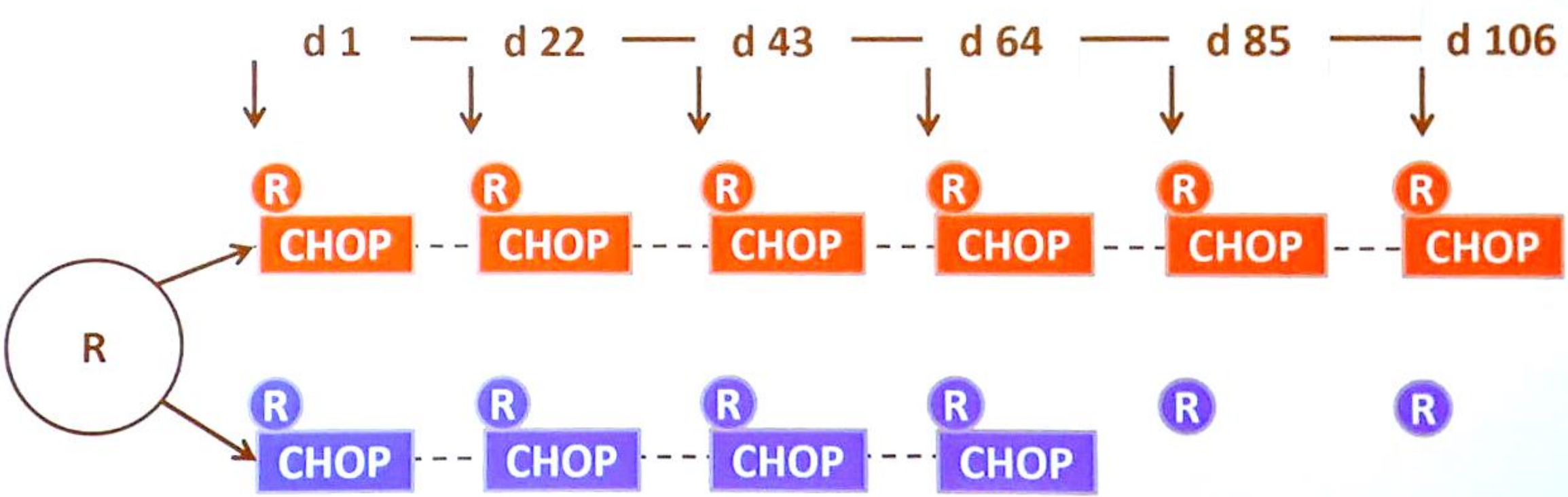
PFS by PET results in whole population



	No. of Subjects	Event	Censored	Median Survival (95%CL)
PET2-/PET4-	499	10.6 % (53)	89.4 % (446)	Not reached
PET2+/PET4-	54	13 % (7)	87 % (47)	Not reached
PET4+	66	33.3 % (22)	66.7 % (44)	Not reached (6.3 ; NA)

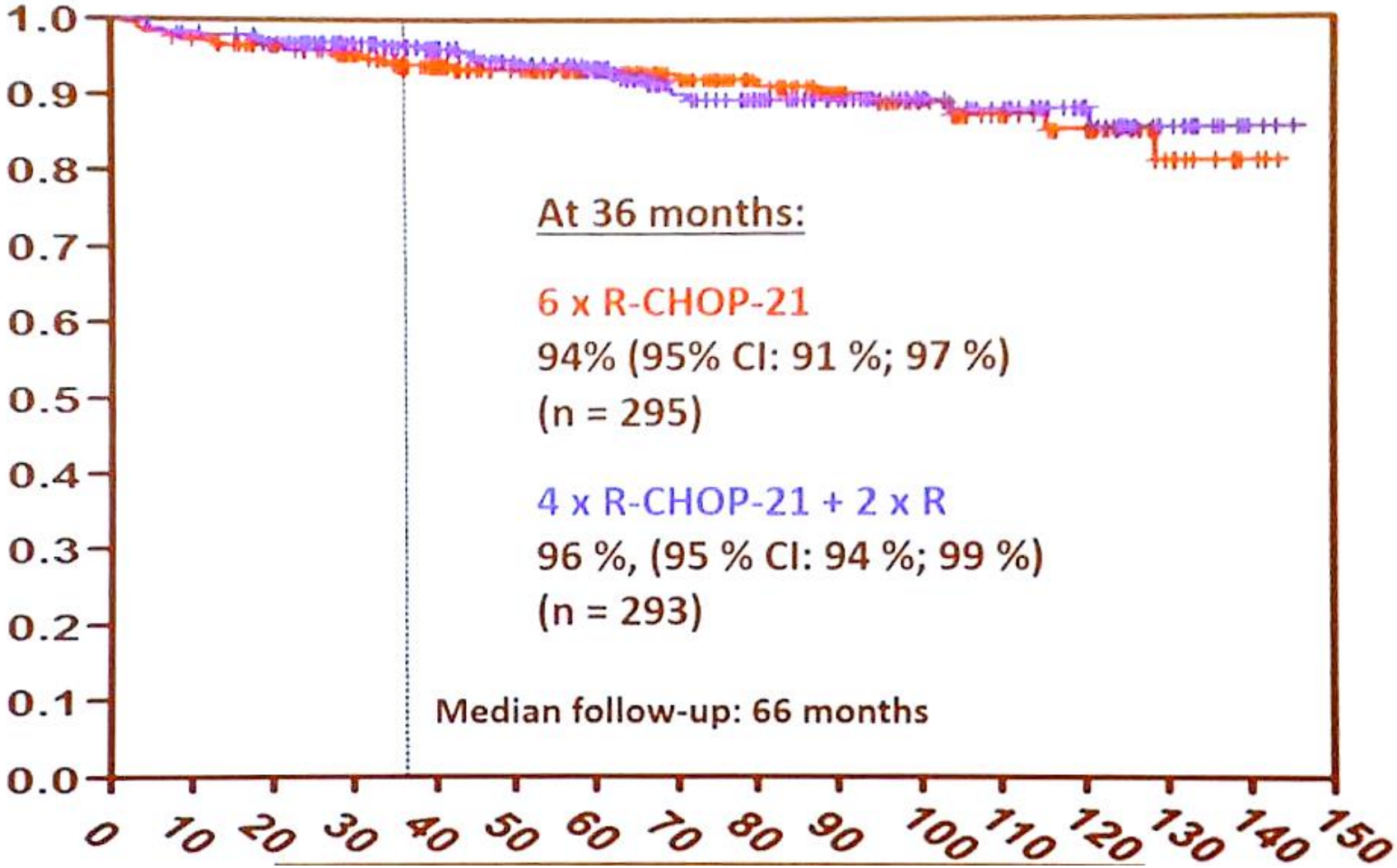
FLYER: Study Design

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



V Poeschel, ASH 2018, Abs 781

Primary Endpoint: PFS



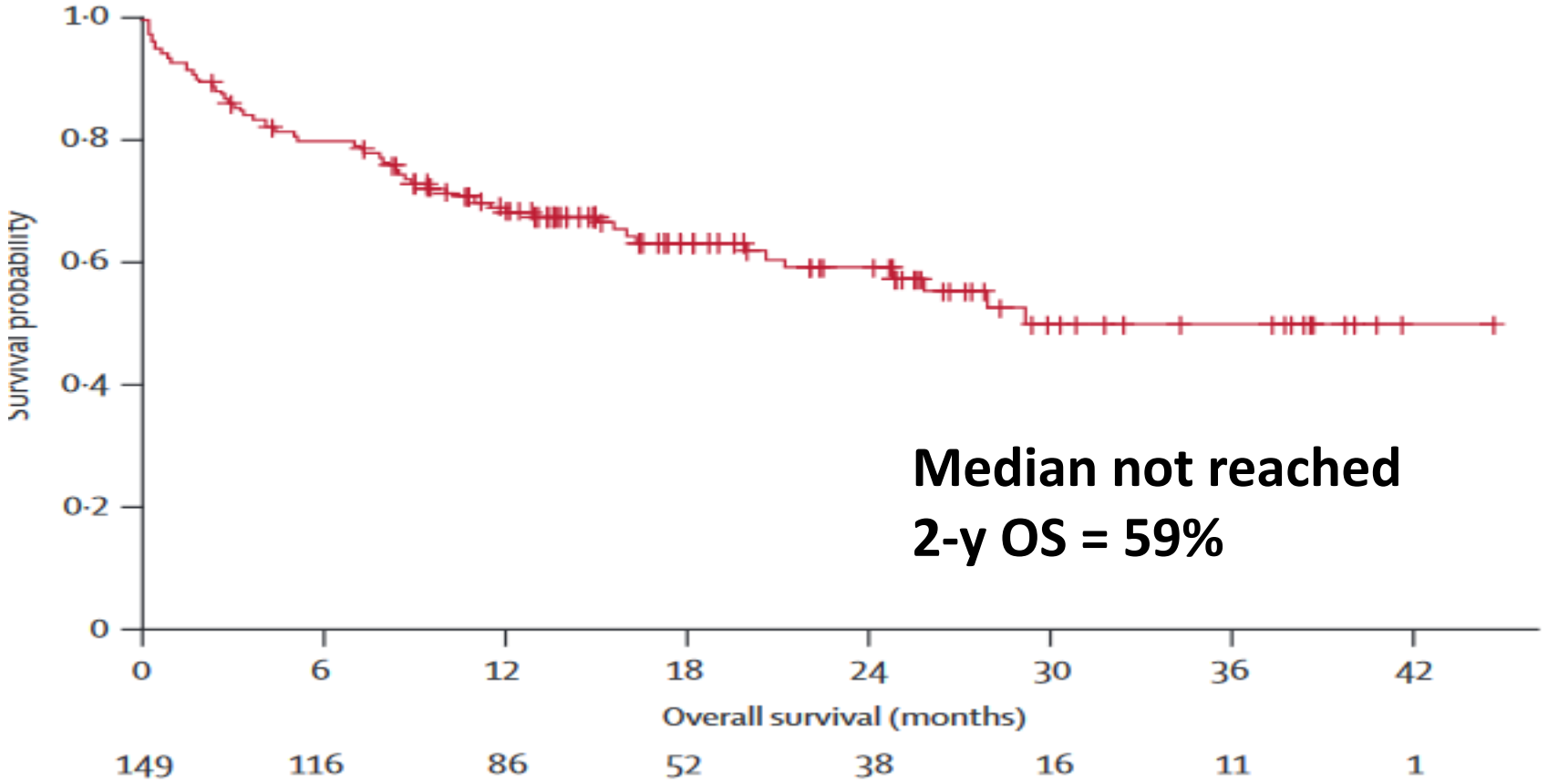
V Poeschel, ASH 2018, Abs 781

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



Median not reached

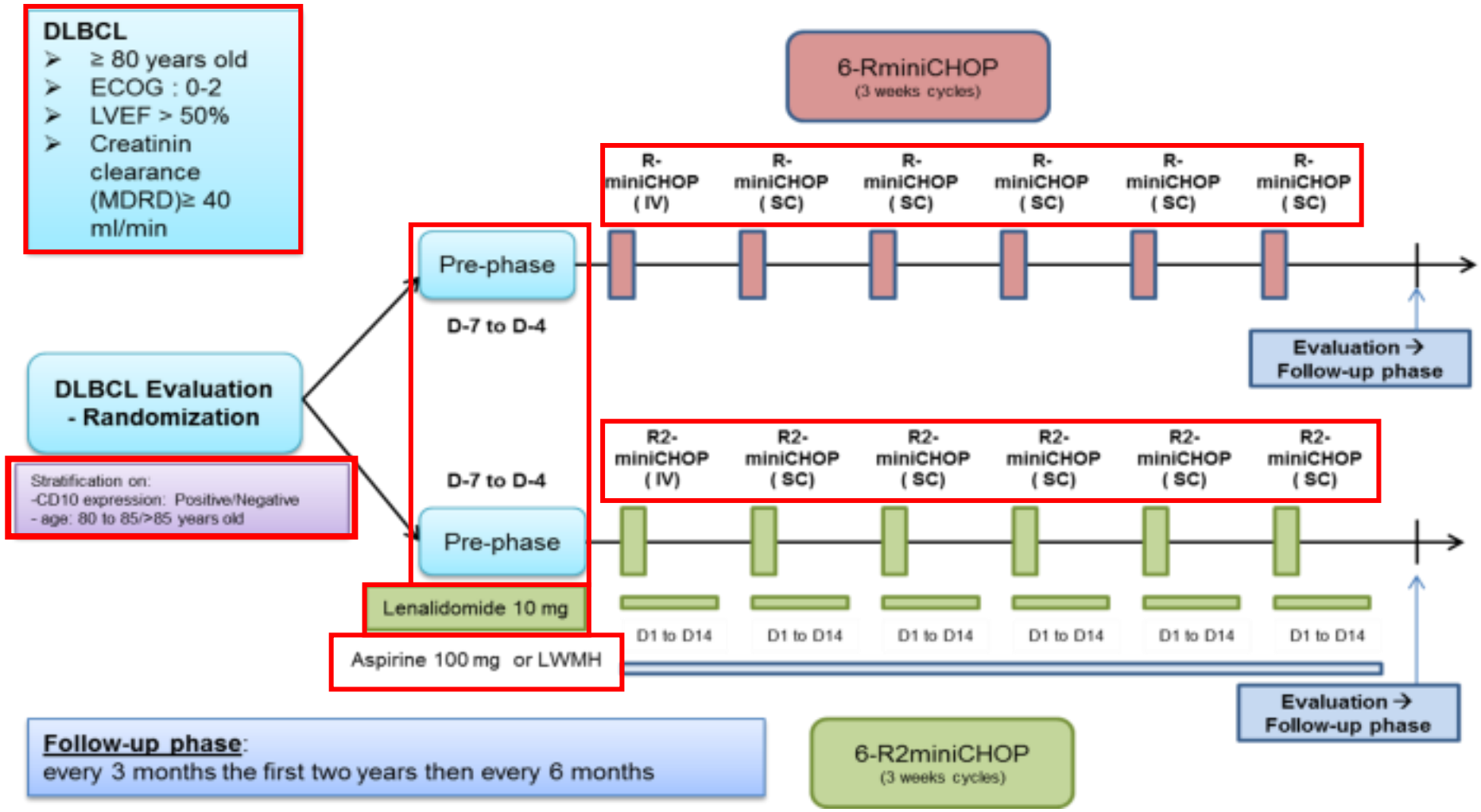
2-y OS = 59%

Neutropenia : 39%

Febrile neutropenia : 7%

Peyrade et al. Lancet oncol 2011

SENIOR : Study Design

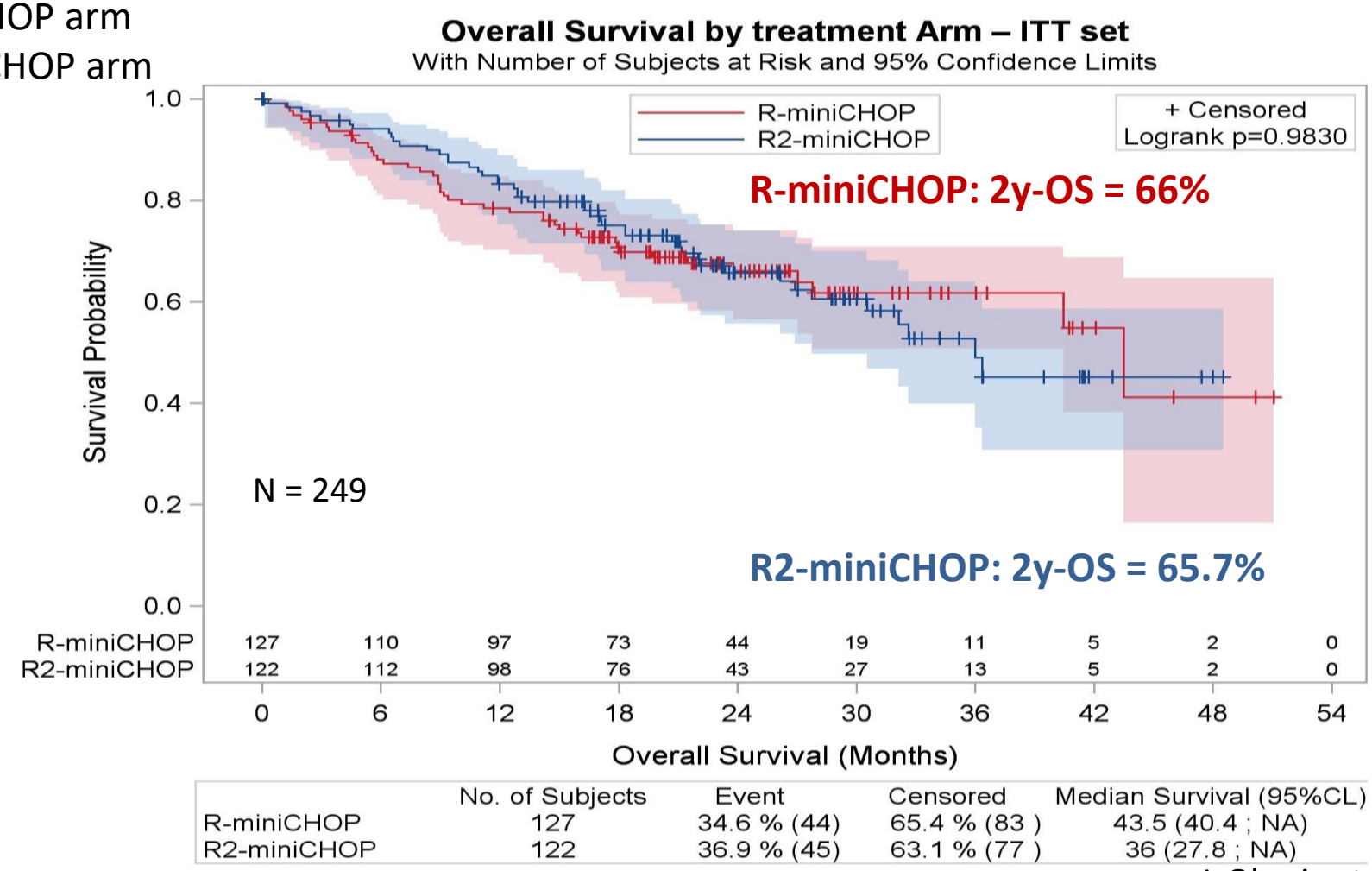


L Oberic et al , ASH 2019

SENIOR: Overall Survival (primary endpoint)

81 % of pts completed treatment

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

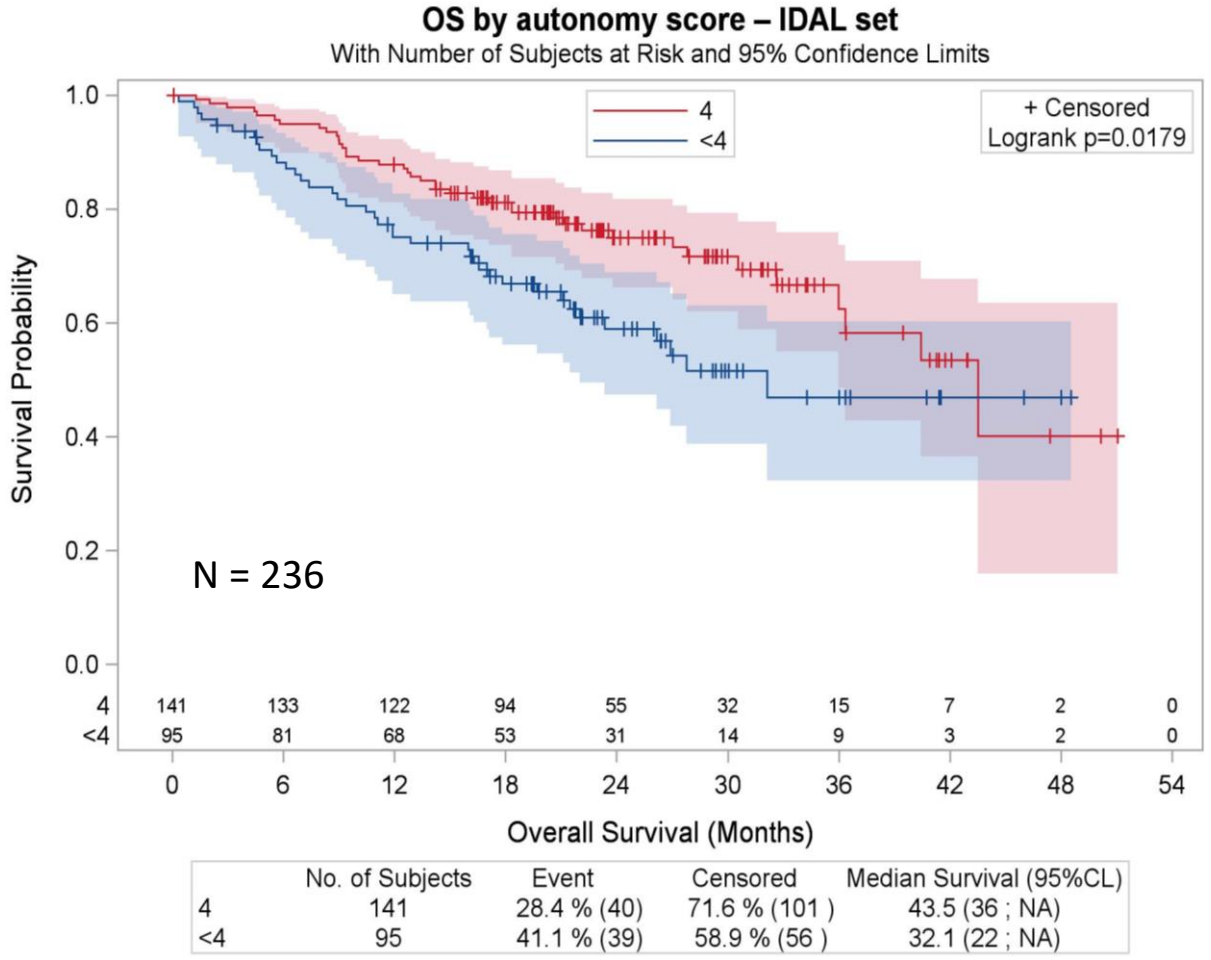


	No. of Subjects	Event	Censored	Median Survival (95%CL)
R-miniCHOP	127	34.6 % (44)	65.4 % (83)	43.5 (40.4 ; NA)
R2-miniCHOP	122	36.9 % (45)	63.1 % (77)	36 (27.8 ; NA)

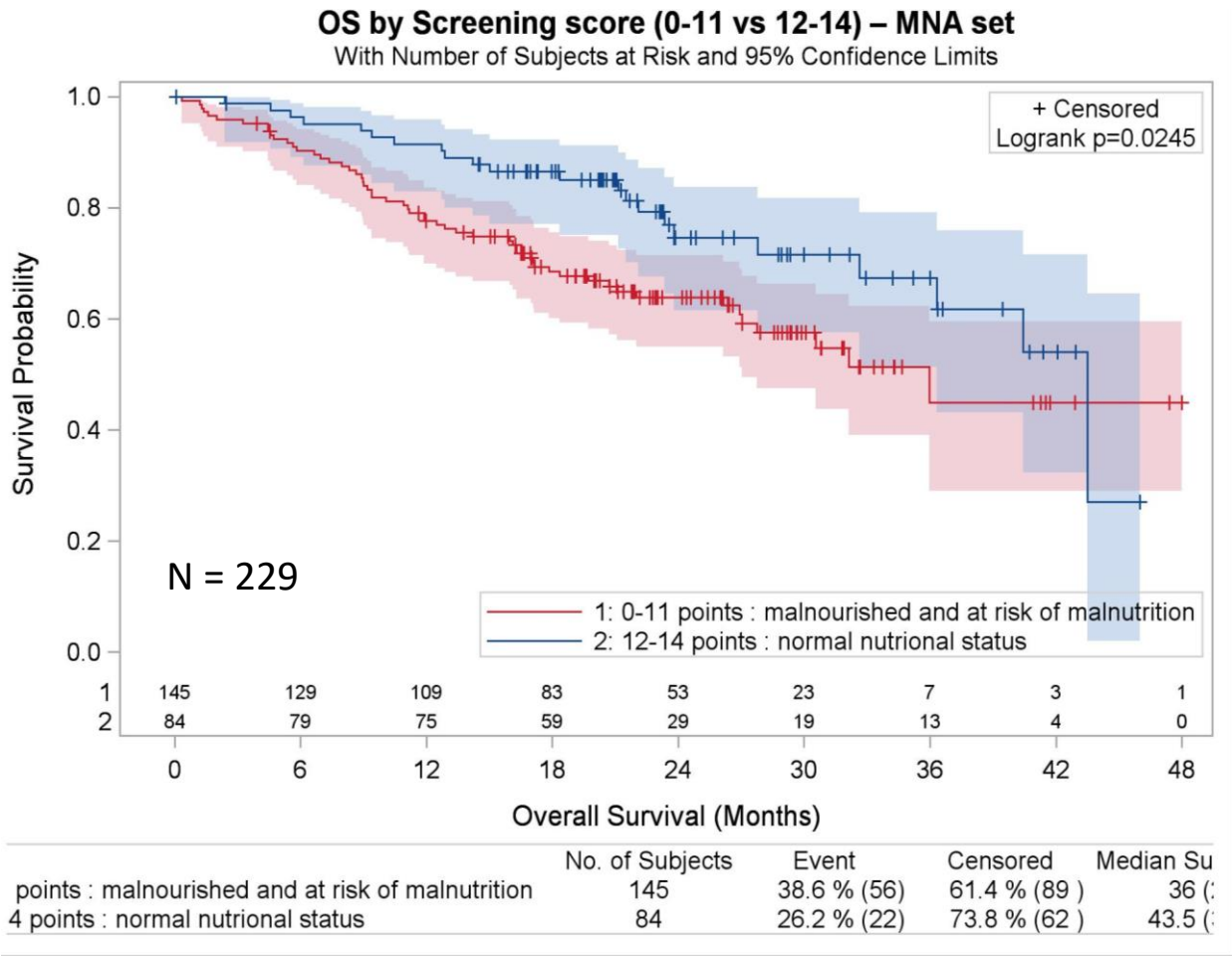
Median follow up 25.1 months

L Oberic et al , ASH 2019

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

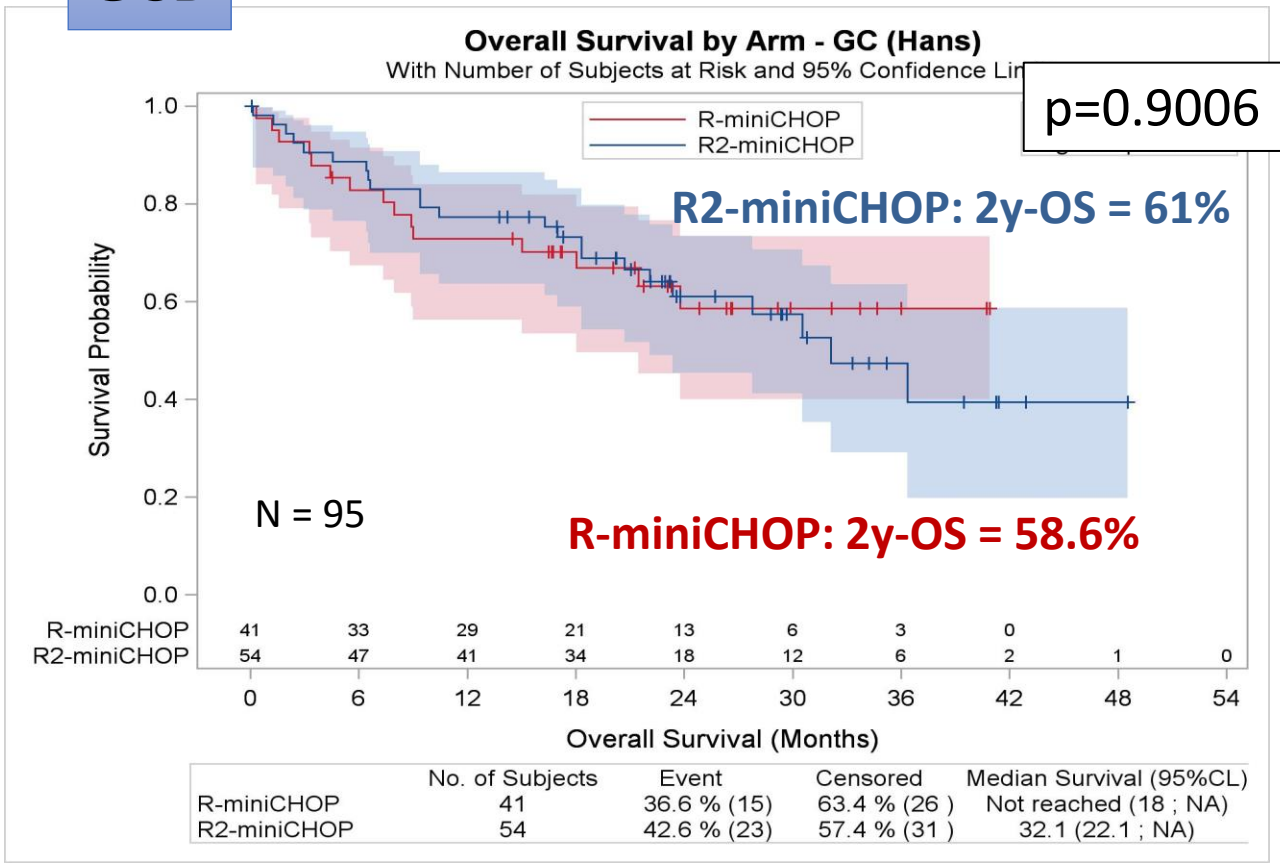


	No. of Subjects	Event	Censored	Median Su
points : malnourished and at risk of malnutrition	145	38.6 % (56)	61.4 % (89)	36 (:
4 points : normal nutrional status	84	26.2 % (22)	73.8 % (62)	43.5 (:

L Oberic et al , ASH 2019

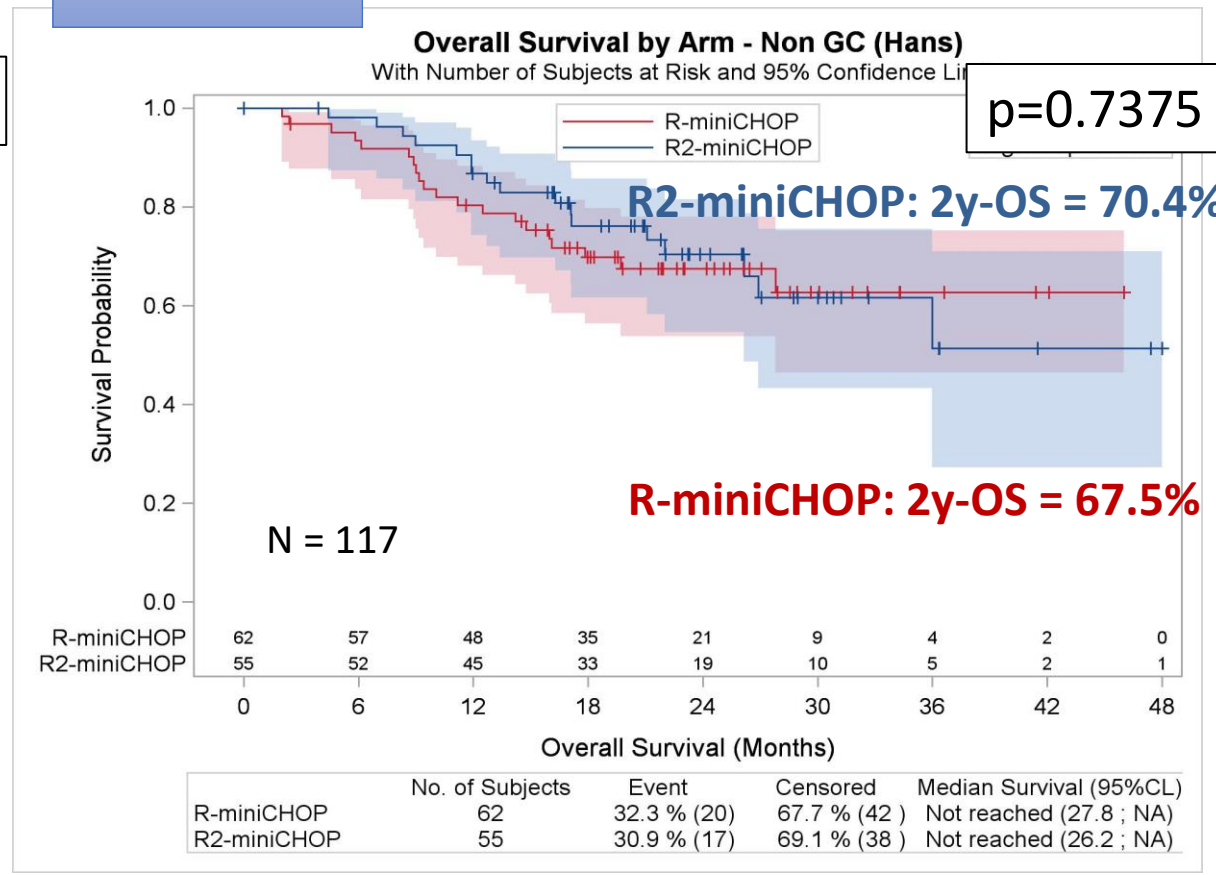
SENIOR: OS according to Hans classification

GCB



	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)

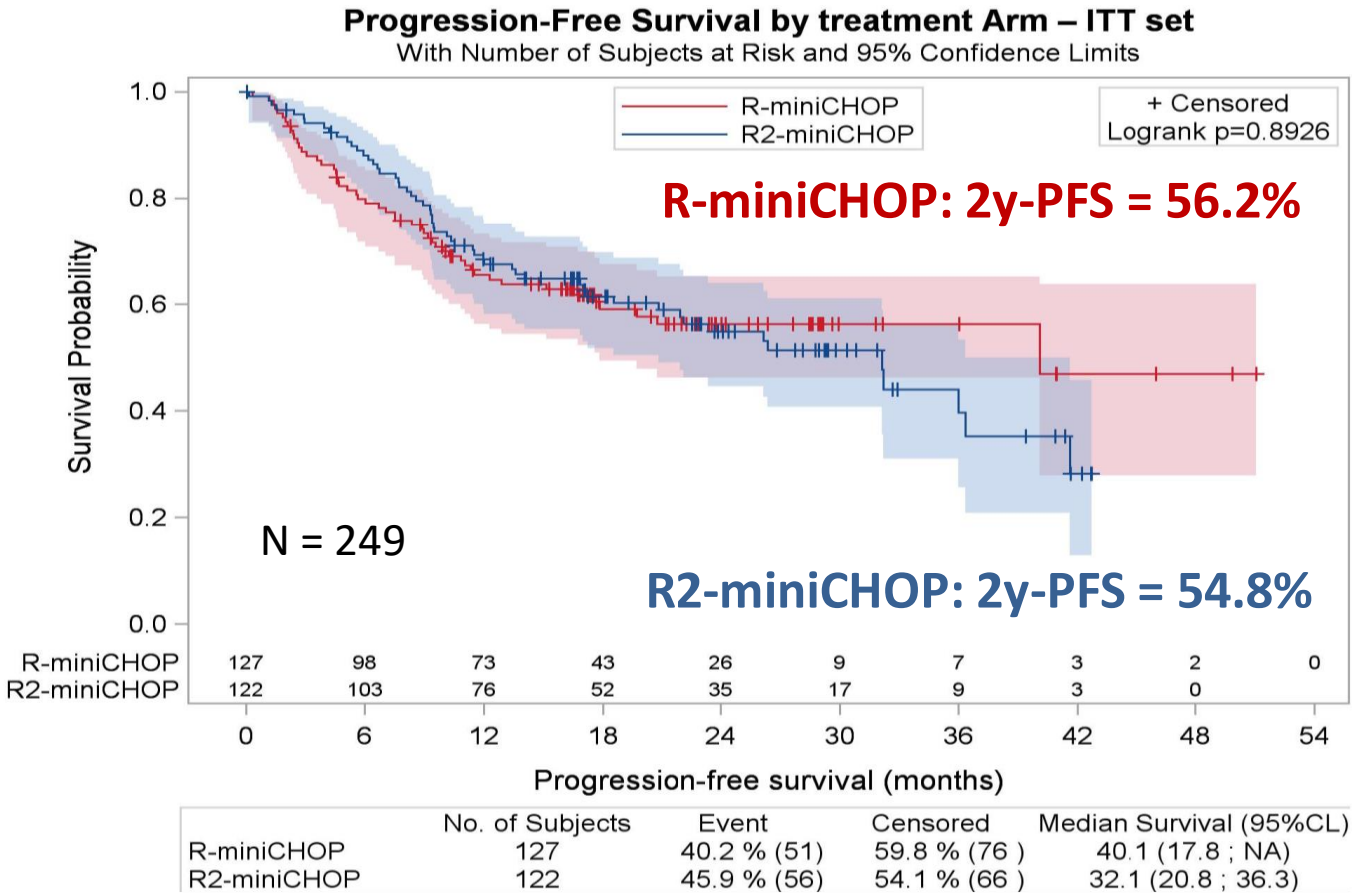
Non-GCB



	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)

L Oberic et al , ASH 2019

SENIOR: PFS according to treatment arm



	No. of Subjects	Event	Censored	Median Survival (95%CL)
R-miniCHOP	127	40.2 % (51)	59.8 % (76)	40.1 (17.8 ; NA)
R2-miniCHOP	122	45.9 % (56)	54.1 % (66)	32.1 (20.8 ; 36.3)

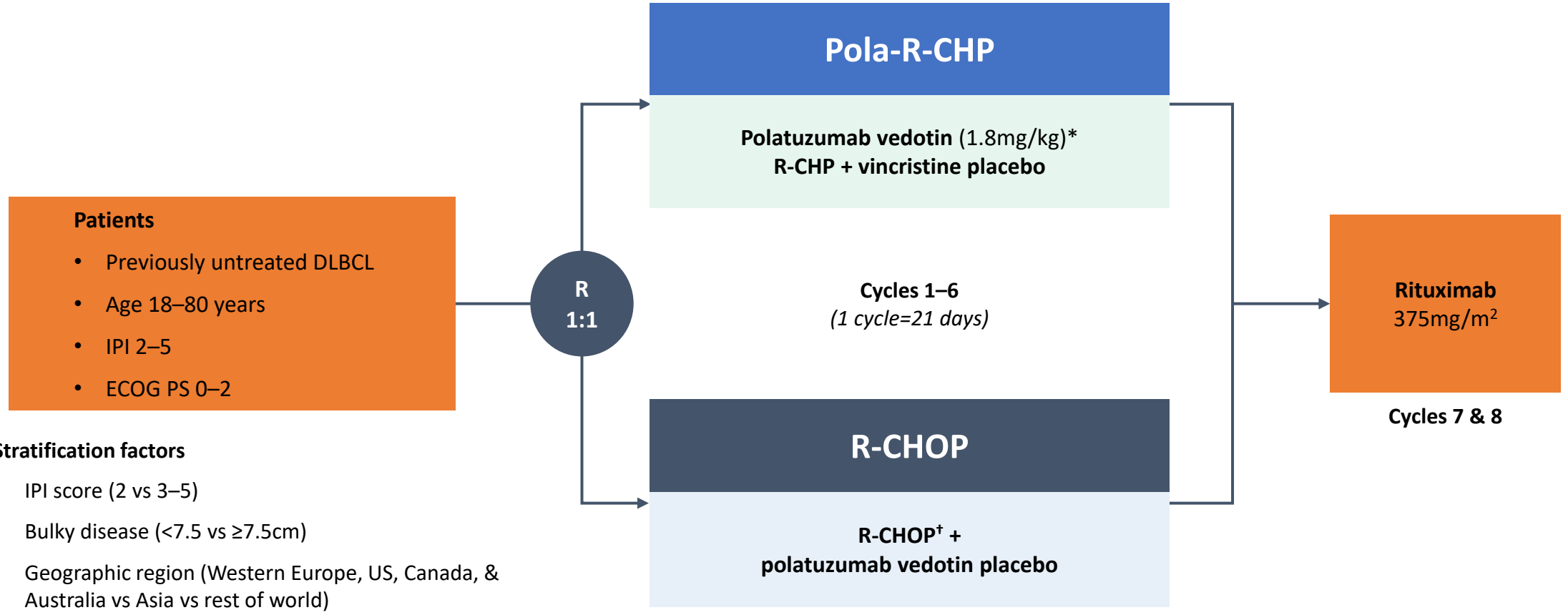
L Oberic et al , ASH 2019

R-CHOP + X

R-CHOP + X: randomized studies

X	Study		n	Primary endpoint		Sub pop of interest
Ibrutinib	PHOENIX	Non GCB	838	PFS	Not reached	Age < 60y
Bortezomib	REMoDL-B	Stage I-IV	1076	PFS	Not reached	ABC & High Grade (GEP)
	PYRAMID	Non GCB	206	PFS	Not reached	
Bevacizumab	MAIN	>18y	787	PFS	Not reached / Toxicity	No
Obinutuzumab	GOYA	IPI>=1	1414	PFS	Not reached	No
	GAINED	aaIPI1-3	670	EFS	Not reached	No
Lenalidomide	ROBUST	ABC	570	PFS	Not reached	No
	SENIOR	>80y	249	OS	Not reached (OS, PFS)	
Polatuzumab	POLARIX	IPI 2-5	879	PFS	Improved 2y-PFS (76.7% v 70.2%) not OS	ABC?

POLARIX: A randomized double-blinded study

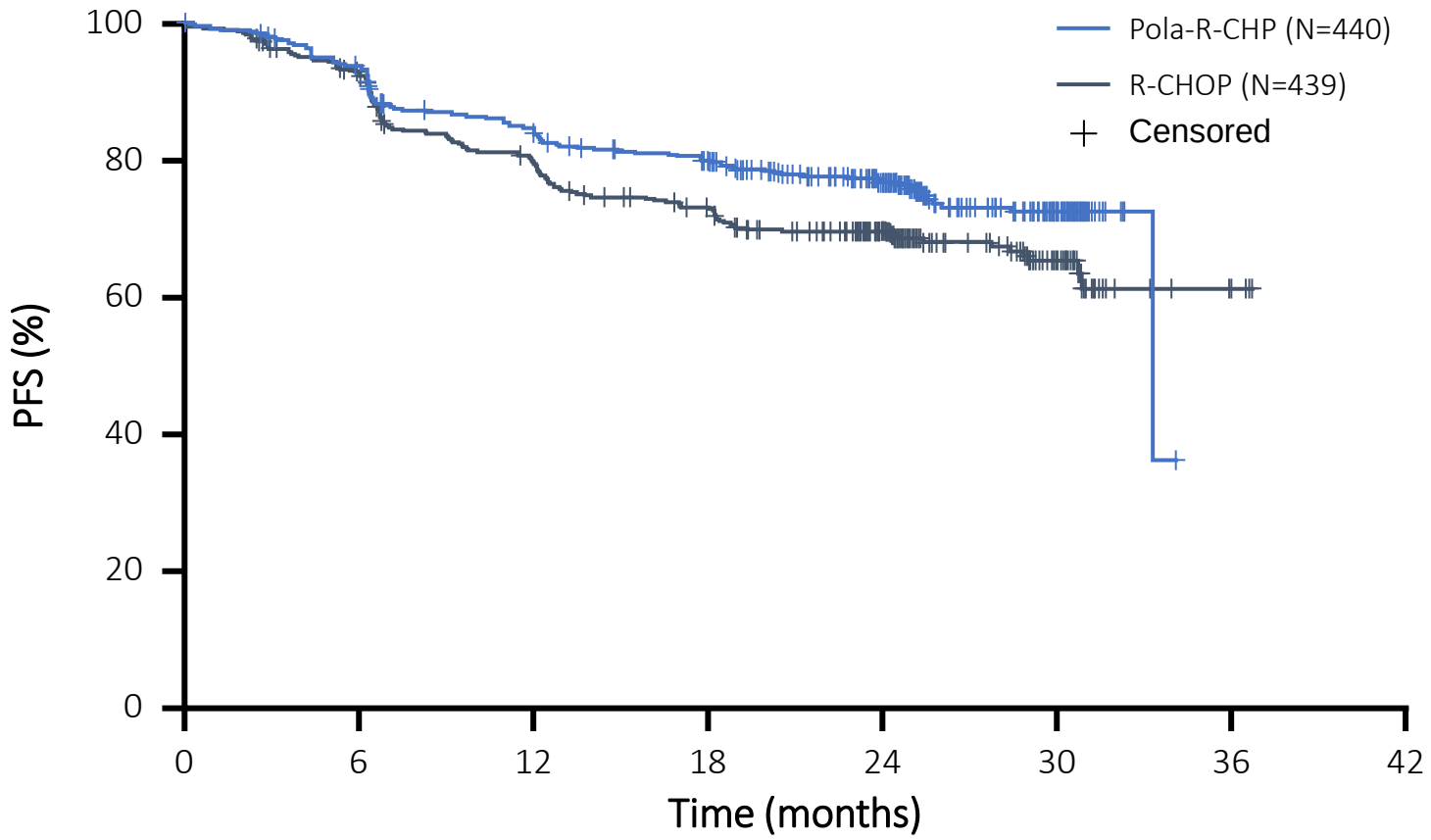


*IV on Day 1; †R-CHOP: IV rituximab 375mg/m², cyclophosphamide 750mg/m², doxorubicin 50mg/m², and vincristine 1.4mg/m² (max. 2mg) on Day 1, plus oral prednisone 100mg once daily on Days 1–5.
IPI, International prognostic index; ECOG PS, Eastern Cooperative Oncology Group performance status; R, randomized.

Tilly H et al , NEJM 2022

Primary endpoint: Progression-free survival

Pola-R-CHP significantly improved PFS versus R-CHOP



No. of patients at risk

Pola-R-CHP	440	404	353	327	246	78	NE	NE
R-CHOP	439	389	330	296	220	78	3	NE

HR 0.73 **(P<0.02)**

95% CI: 0.57, 0.95

- Pola-R-CHP demonstrated a **27% reduction in the relative risk of disease progression, relapse, or death** versus R-CHOP
- **24-month PFS:** 76.7% with Pola-R-CHP versus 70.2% with R-CHOP (**Δ=6.5%**)

ITT population. Data cut-off: June 28, 2021; median 28.2 months' follow-up.
NE, not evaluable.

Safety summary

Safety profiles were similar with Pola-R-CHP and R-CHOP

n (%)	Pola-R-CHP (N=435)	R-CHOP (N=438)
Any-grade adverse events	426 (97.9)	431 (98.4)
Grade 3–4	251 (57.7)	252 (57.5)
Grade 5	13 (3.0)	10 (2.3)
Serious adverse events	148 (34.0)	134 (30.6)
Adverse events leading to:		
Discontinuation of any study drug	27 (6.2)	29 (6.6)
Polatuzumab vedotin / vincristine	19 (4.4)	22 (5.0)
Dose reduction of any study drug	40 (9.2)	57 (13.0)

Data cut-off: June 28, 2021.

R-CHOP + CD20xCD3

- R-CHOP – Glofitamab:
  - Phase I B : N = 56; ORR 93.5%; CR 76%
- R-CHOP – Epcoritamab
- R-CHOP - Odronextamab

Study Design: EPCORE™ NHL-2 Arm 1

A phase 1b/2, open-label trial evaluating the safety and antitumor activity of epcoritamab + R-CHOP in adults with previously untreated DLBCL[a]

Key inclusion criteria

- Newly diagnosed CD20+ DLBCL[b]
  - DLBCL, NOS
  - T-cell/histiocyte-rich DLBCL
  - Double-hit or triple-hit DLBCL[c]
  - FL grade 3B
- IPI score ≥3
- ECOG PS 0–2
- Measurable disease by CT or MRI
- Adequate organ function

Data cutoff: January 31, 2023
Median follow-up: 14.2 mo
ClinicalTrials.gov: NCT04663347

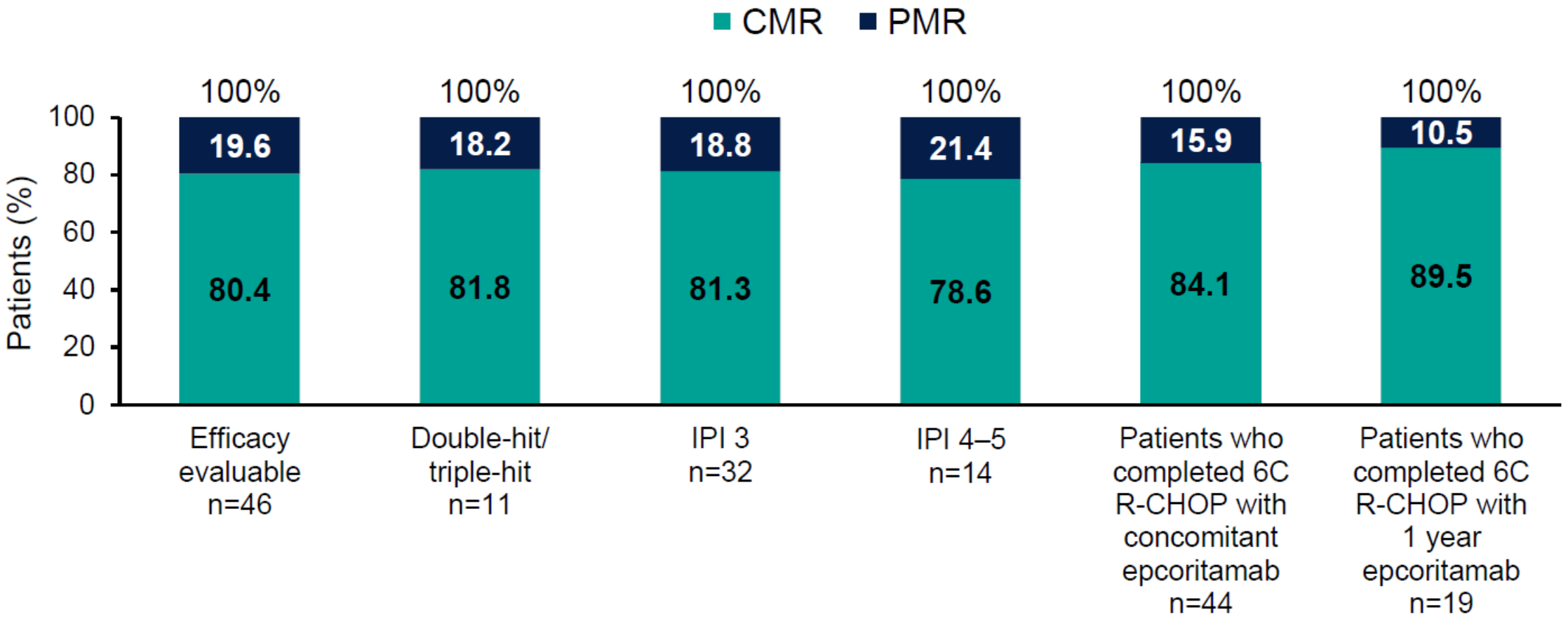
Treatment regimen: Concomitant epcoritamab SC 48 mg + R-CHOP

	Agent	C1–C4	C5–C6	C7+
	Epcoritamab SC 48 mg	QW	Q3W	Q4W Up to 1 year
R-CHOP	Rituximab IV 375 mg/m^2	Q3W		
R-CHOP	Cyclophosphamide IV 750 mg/m^2	Q3W		
R-CHOP	Doxorubicin IV 50 mg/m^2	Q3W		
R-CHOP	Vincristine[d] IV 1.4 mg/m^2	Q3W		
R-CHOP	Prednisone IV or oral 100 mg/d	D1–5 of each cycle		

Primary objective: Antitumor activity[e]

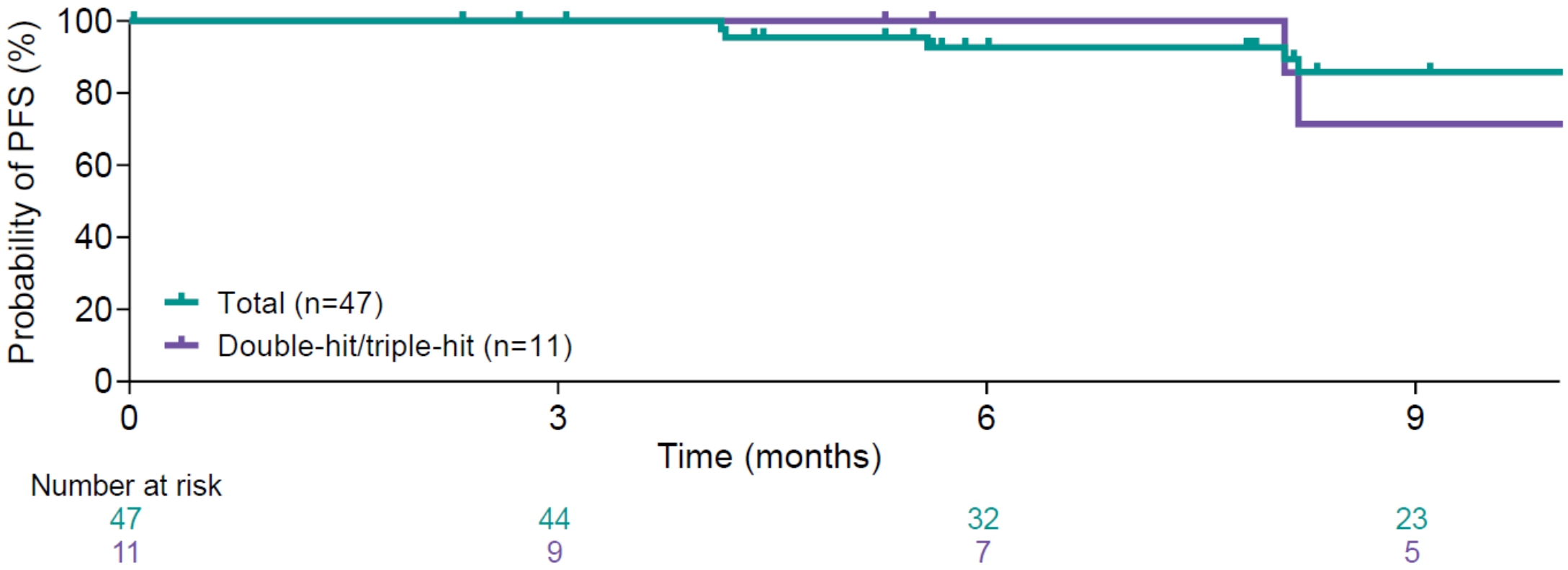
[a]Patients received SC epcoritamab with 2 step-up doses (SUD) before the first full dose and corticosteroid prophylaxis to mitigate CRS. R-CHOP was given in 21-d cycles. Subsequent cycles of epcoritamab were 28 d. [b]De novo or histologically transformed from FL or nodal marginal zone lymphoma. [c]Classified as HGBCL, with *MYC* and *BCL2* and/or *BCL6* translocations. [d]Recommended maximum 2 mg. [e]Tumor response was evaluated by PET-CT obtained at 6, 12, 18, 24, 36, and 48 wk, and every 24 wk thereafter, until disease progression.

High Rates of Complete Response Across Subgroups



Data cutoff: January 31, 2023. Best response was based on modified response-evaluable population, defined as patients with ≥1 target lesion at baseline and ≥1 postbaseline response evaluation and patients who died within 60 d of first trial treatment prior to first assessment. One patient was not considered response evaluable because this patient withdrew consent from the trial without receiving a response evaluation.

Progression-Free Survival



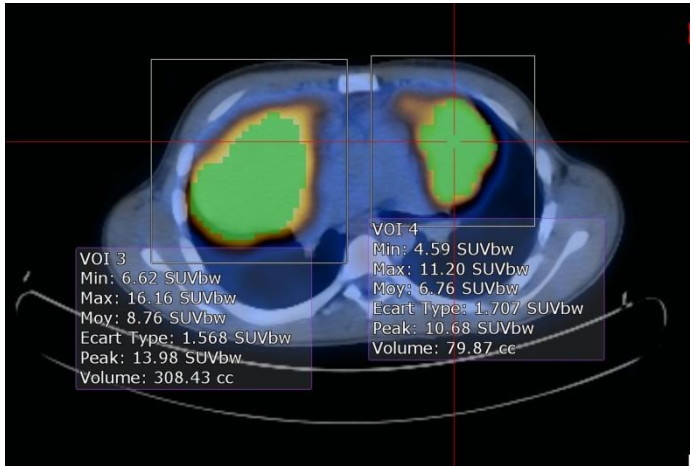
Median PFS was not reached in the overall population

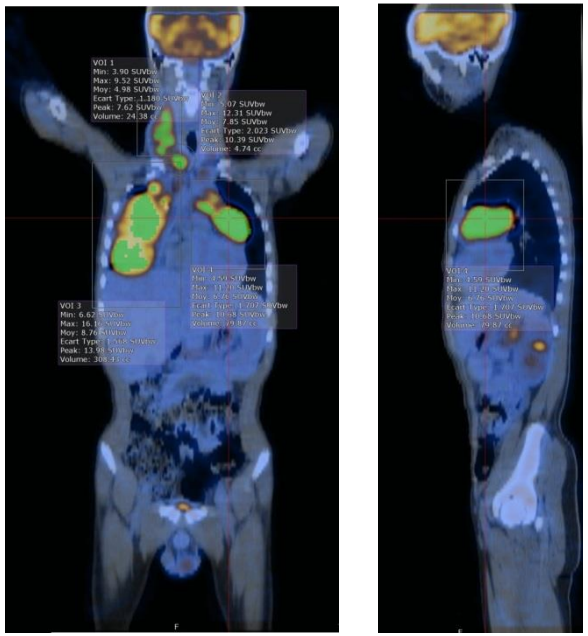
Kaplan–Meier estimated probability of progression-free survival.

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

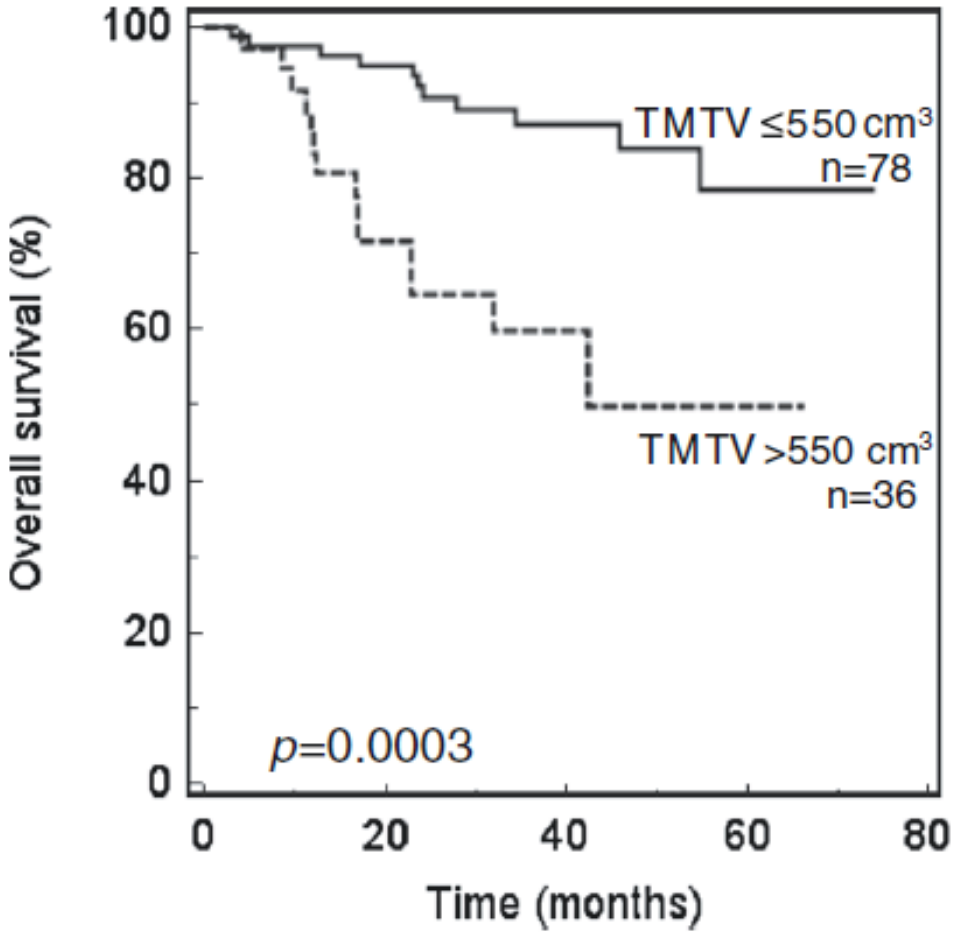




*Boellaard R et al. EJNM. 2010; 37: 181
Meignan M et al. EJNM 2014; 41: 1113

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**

Sassanelli et al, EJNM 2014; 41: 2017

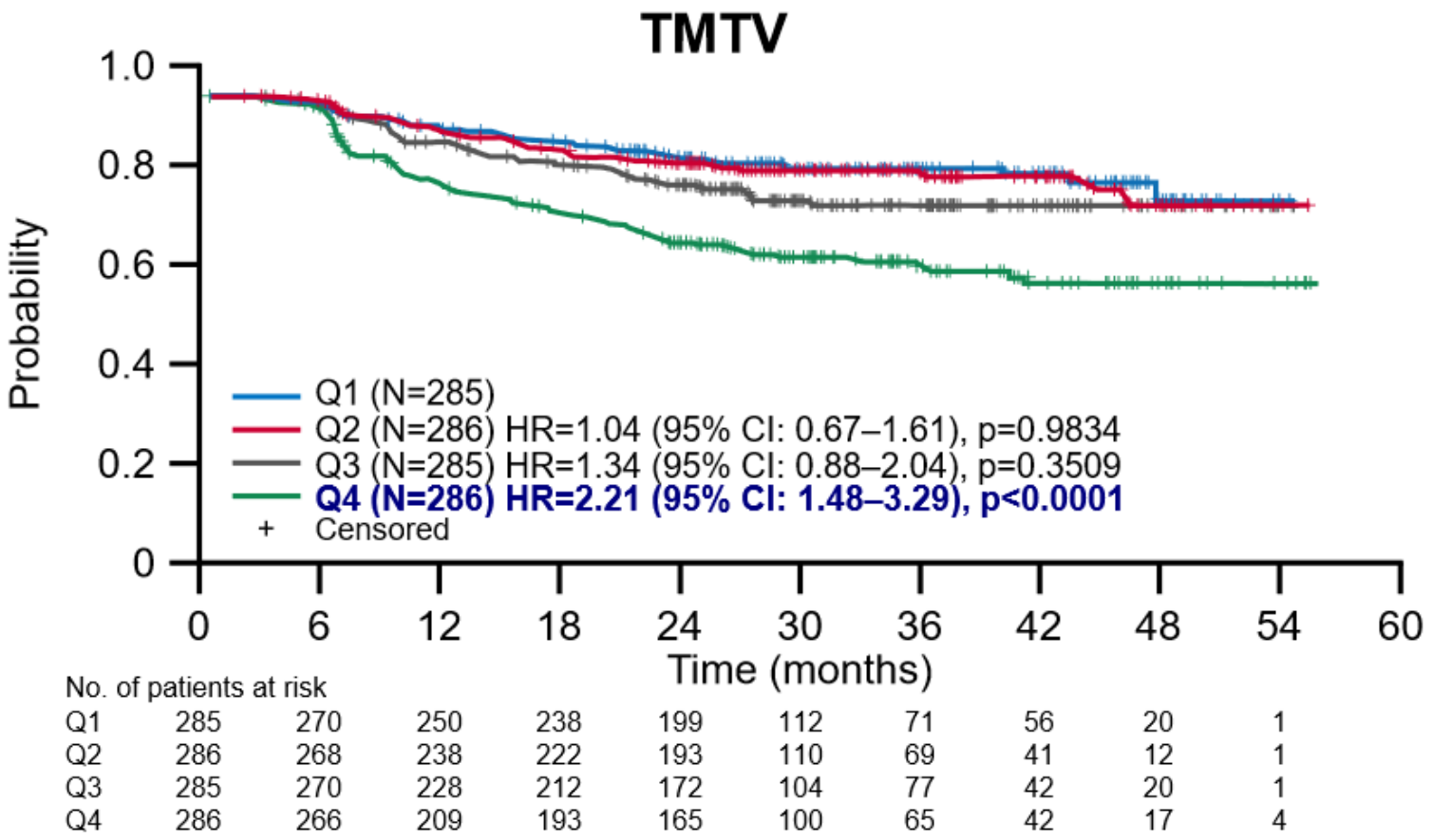
Prognostic value of baseline TMTV for PFS

(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



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

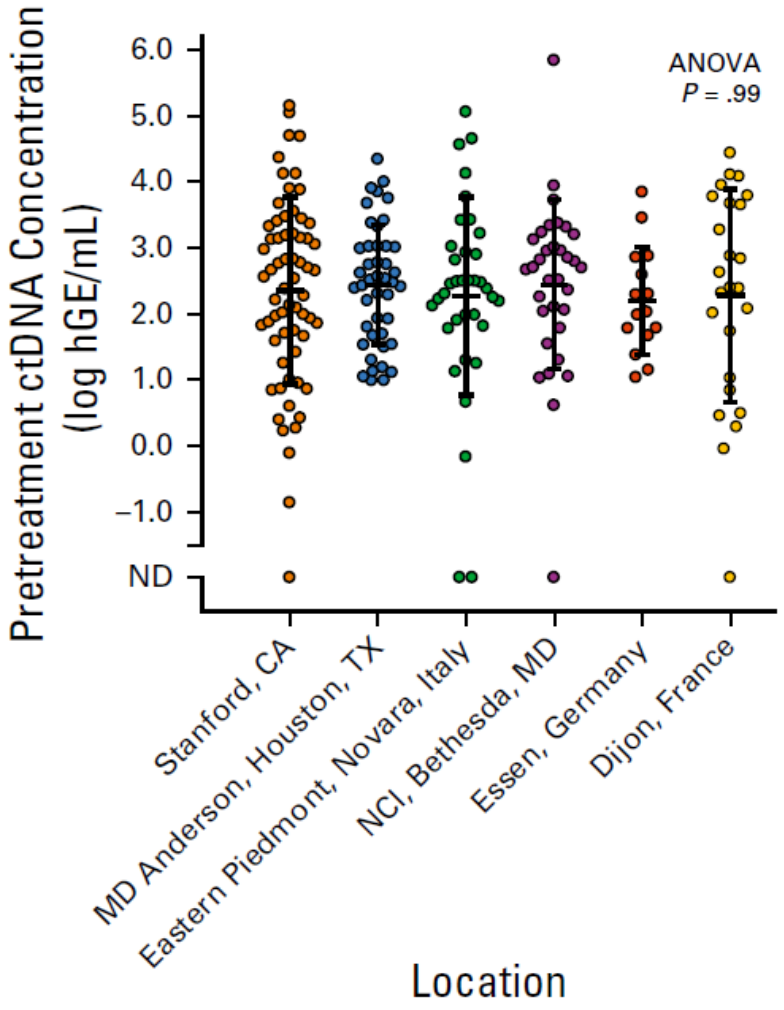
Kostakoglu, ASH 2017

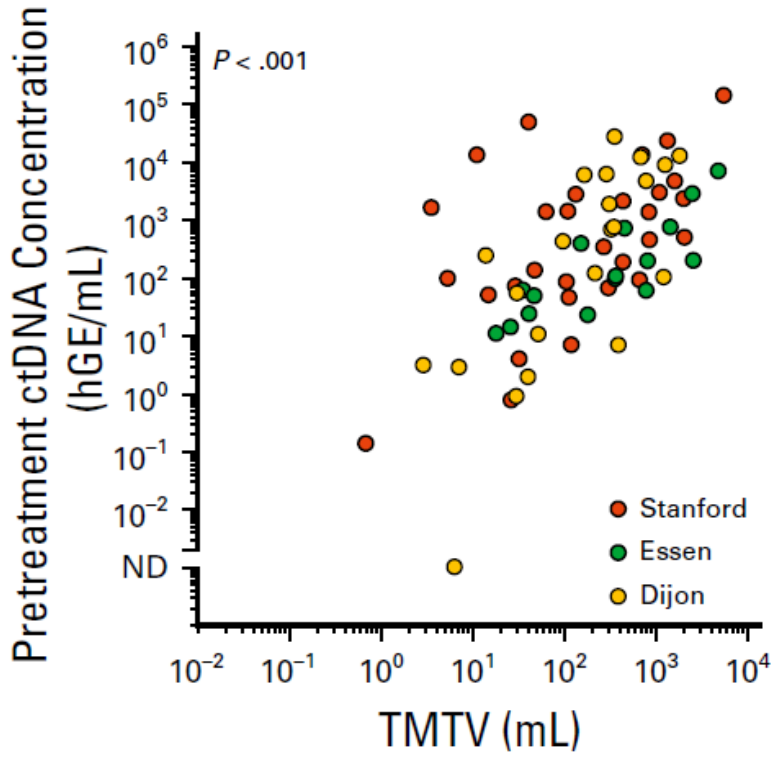
DLBCL: Baseline TMTV and ctDNA concentration

CAPP-seq genotyping

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

ctDNA detectable in 98% of patients at baseline





D. Kurtz et al , JCO 2018

Regular Article

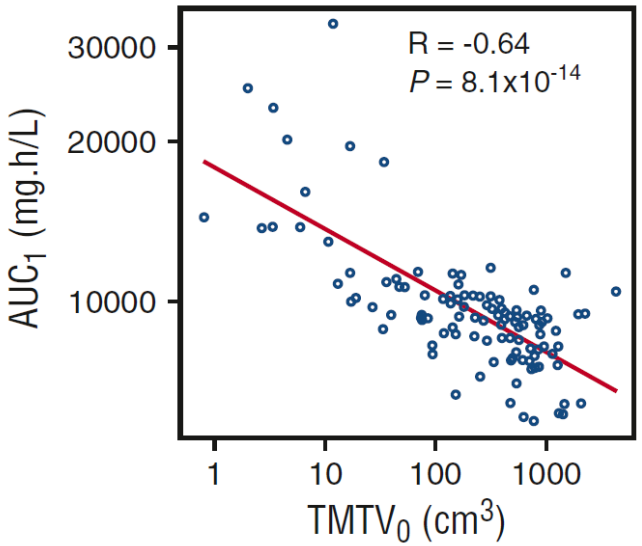
blood

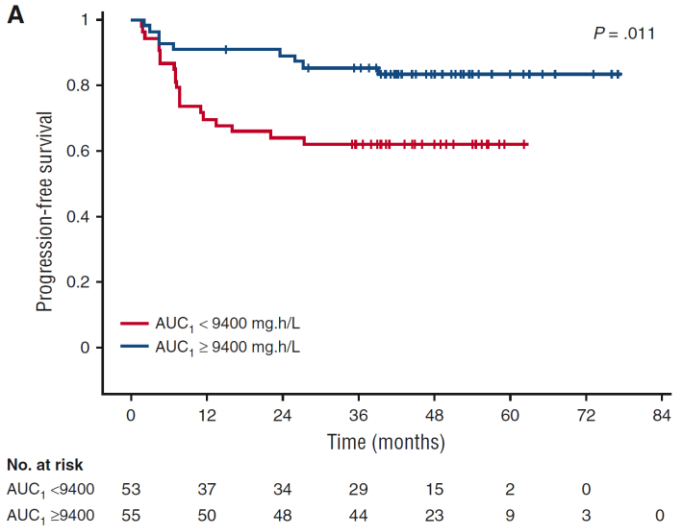
Lysa THE LYMPHOMA STUDY ASSOCIATION

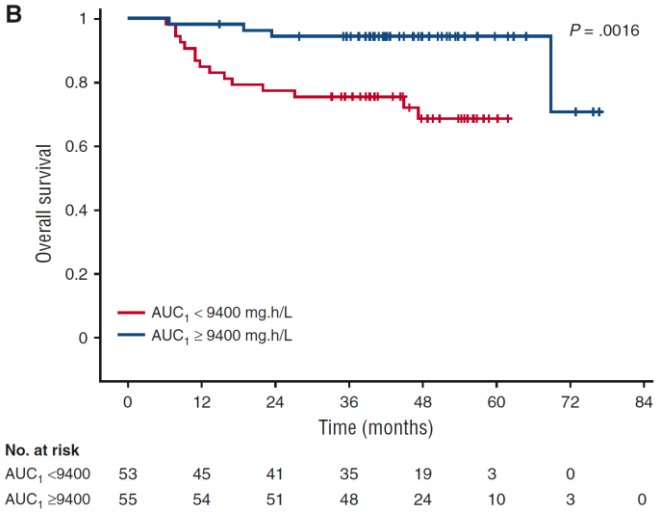
CLINICAL TRIALS AND OBSERVATIONS

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]

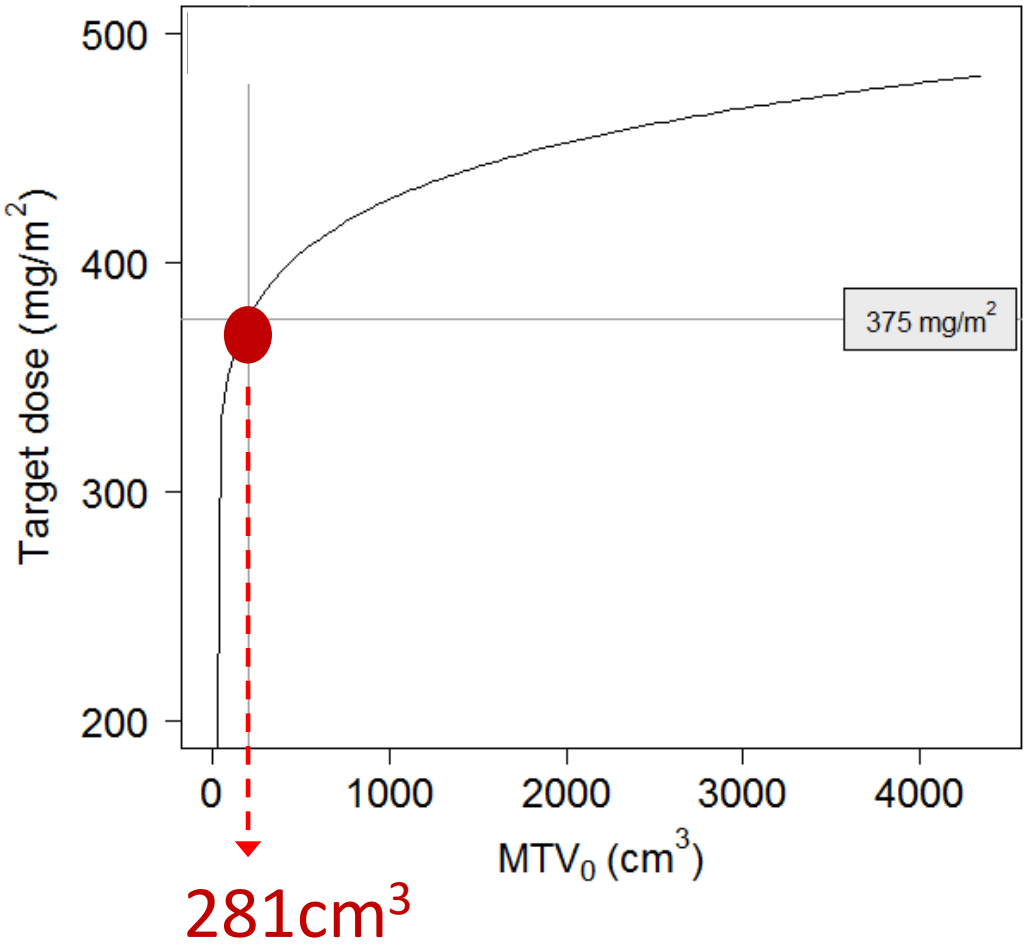






Target dose of Rituximab according to TMTV

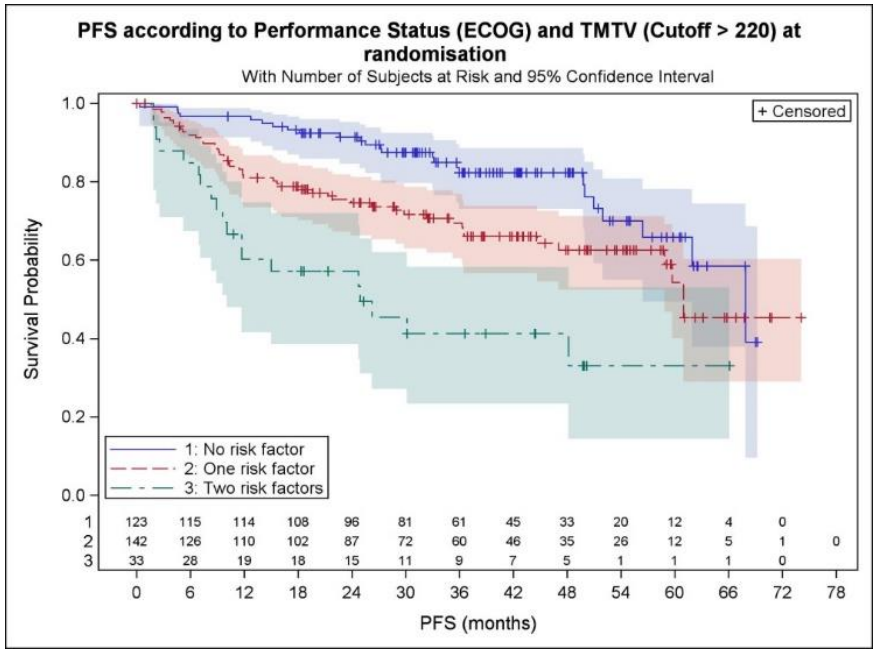
$$\text{Target dose}\left(\mathbf{mg/m^2}\right) = \mathbf{237.59} \times (\mathbf{TMTV})^{\mathbf{0.081}}$$

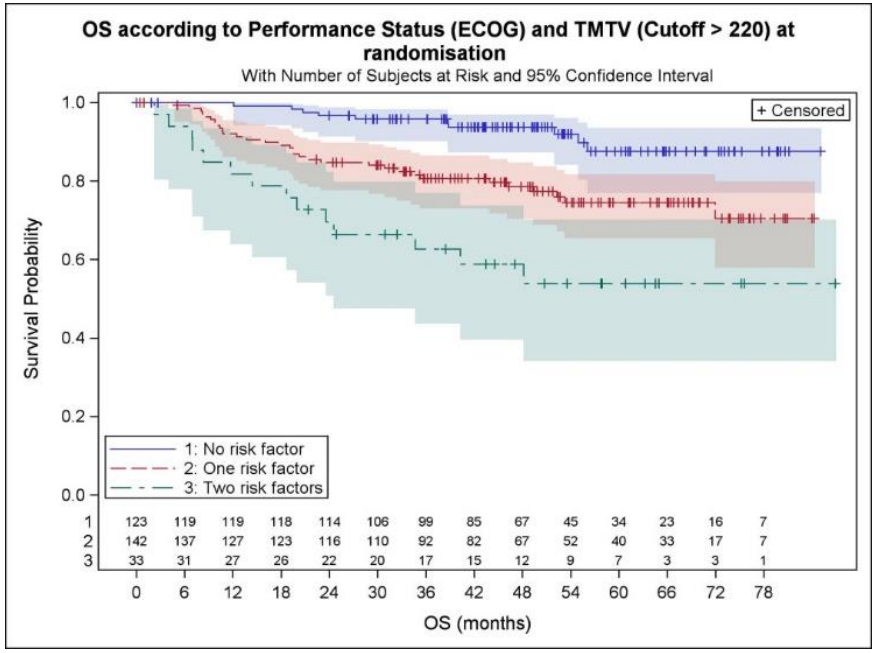


Standard dose of 375 mg/m2 is suitable if TMTV <281 cm³

Tout, Casasnovas et al Blood, 2017

REMARC: Baseline TMTV and PS combination

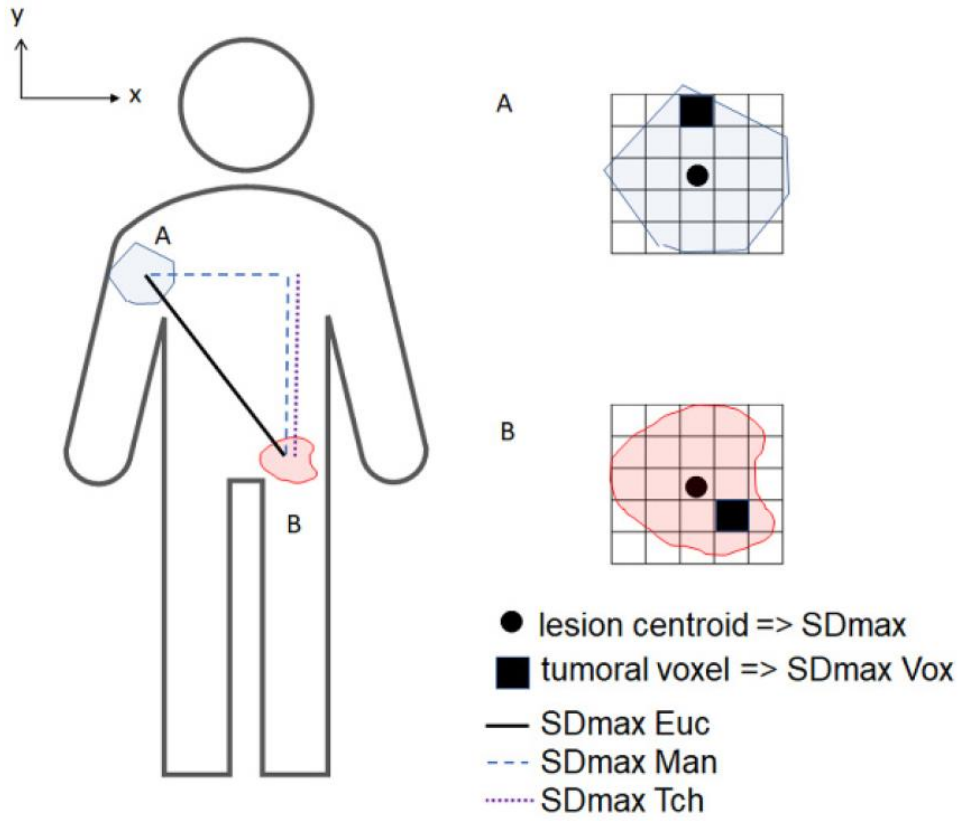


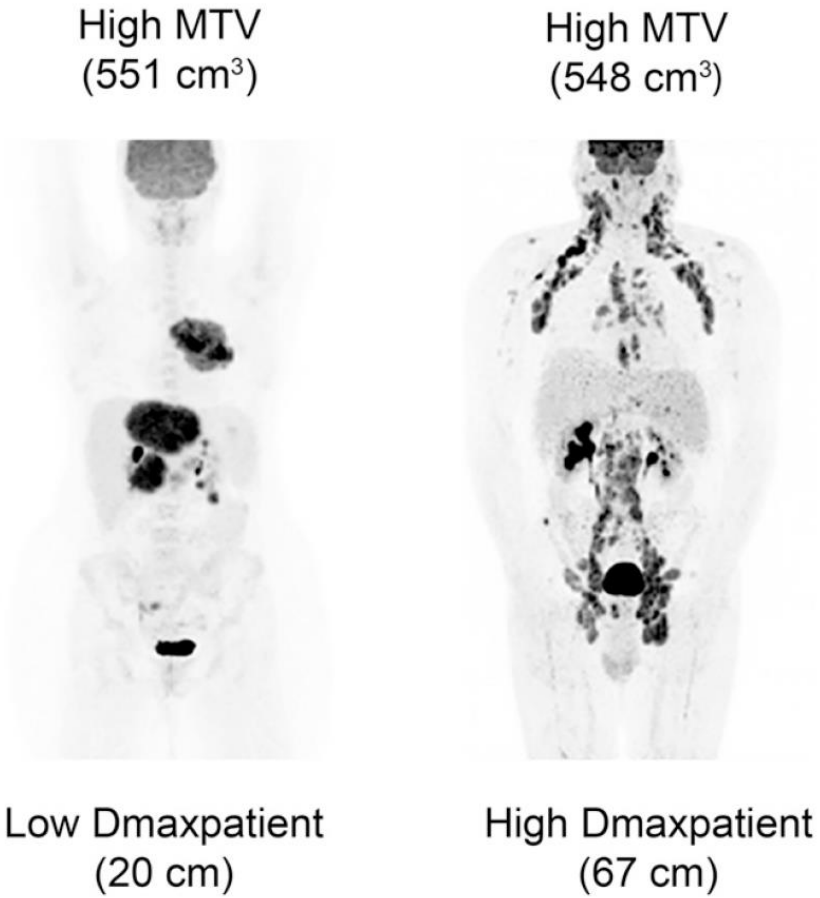


	4 y PFS	4 y OS
No risk factor	82%	94%
1 risk factor	63% (HR:1.9 CI:1.2-3.0)	79% (HR=3.0 CI:1.5-6.2)
2 risk factors	41% (HR=4.4 CI:2.4-8.1)	59% (HR=6.6 CI:2.9-14.9)

L. Vercellino et al, Blood 2020

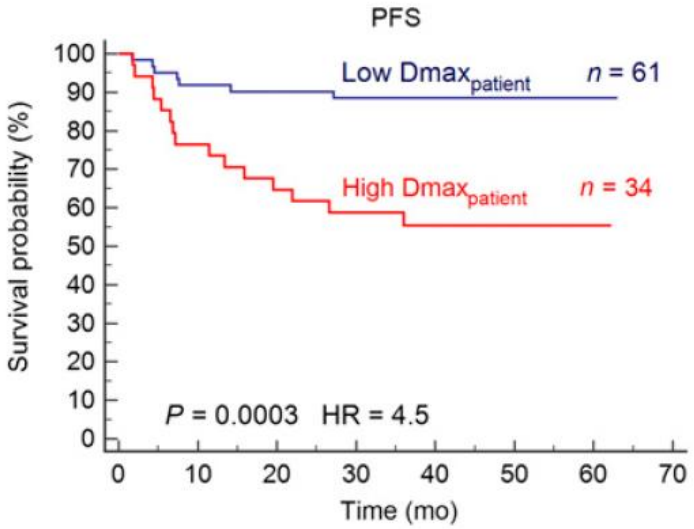
Dissemination features in DLBCL

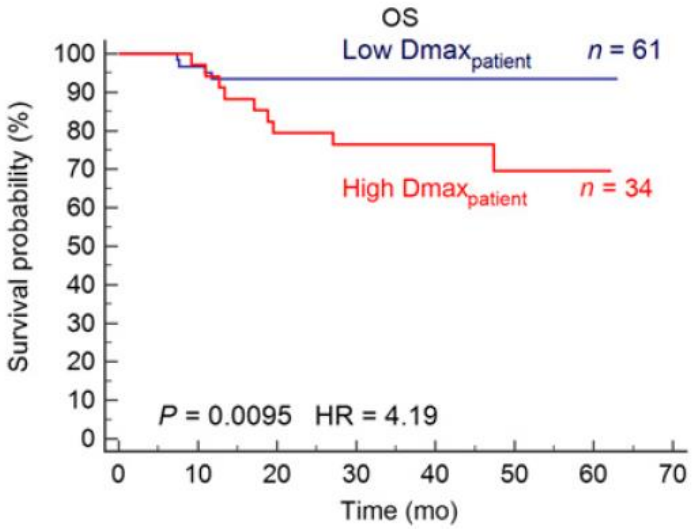


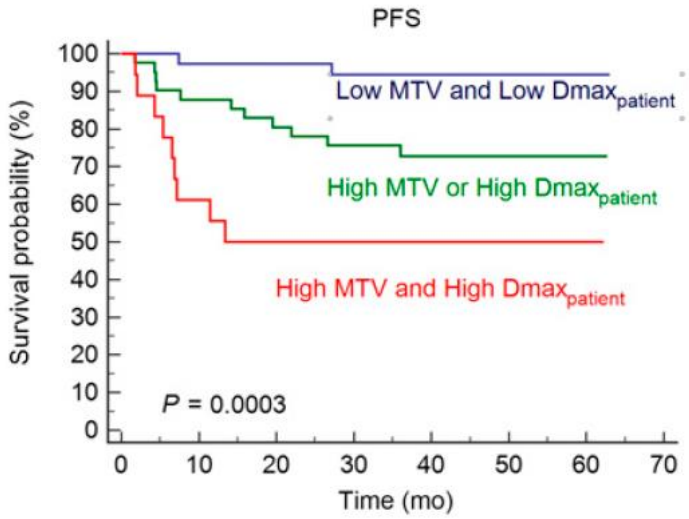


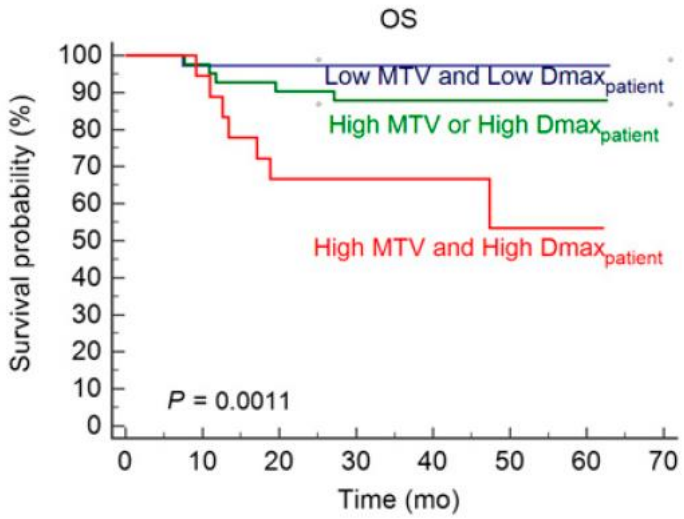
AS. Cottereau et al , JNM 2020, Cancers 2021, Ann Oncol 2021

Dissemination features in DLBCL





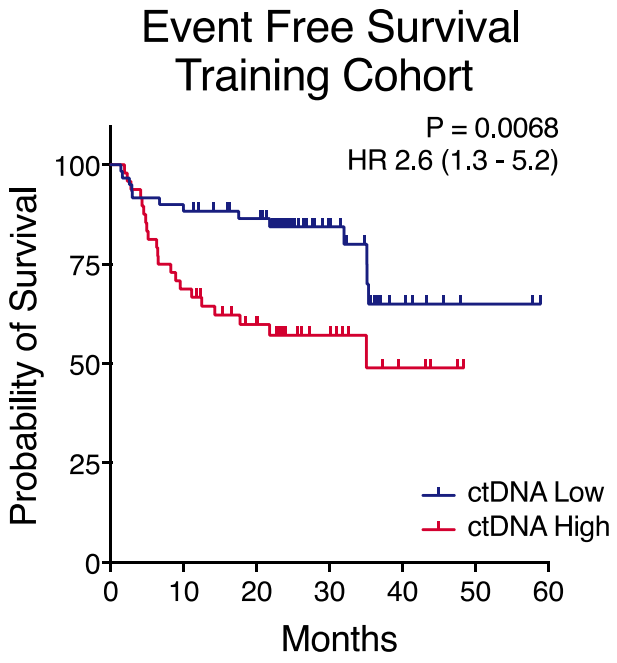


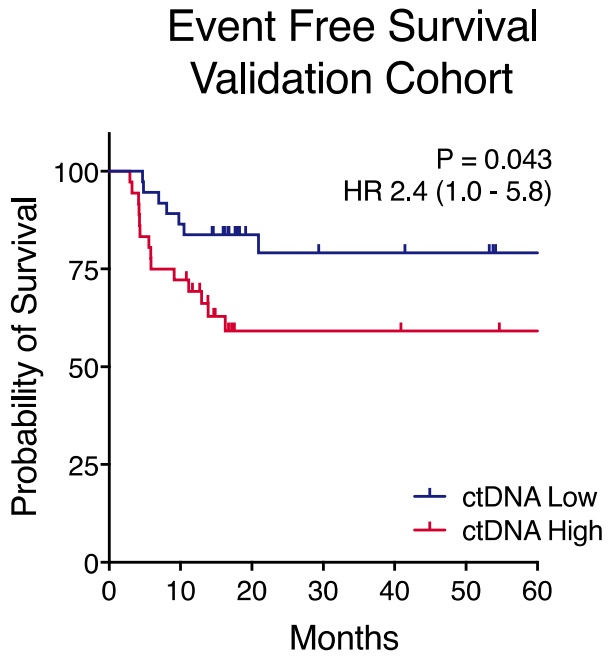


AS. Cottereau et al , JNM 2020, Cancers 2021, Ann Oncol 2021

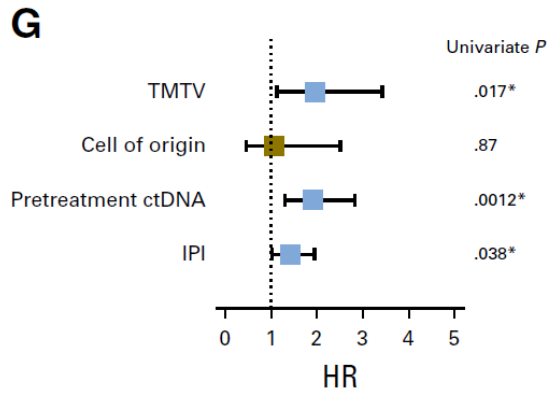
Prognosis value of pretreatment ctDNA concentration

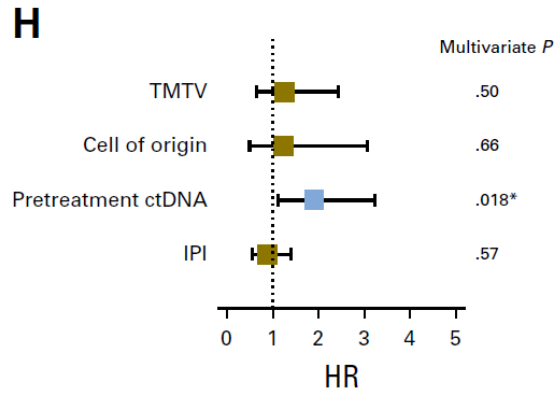
181 patients with large B cell lymphomas receiving frontline therapy
ctDNA quantified prior to first 3 cycles of therapy by targeted sequencing (CAPP-Seq)





Patients with TMTV available

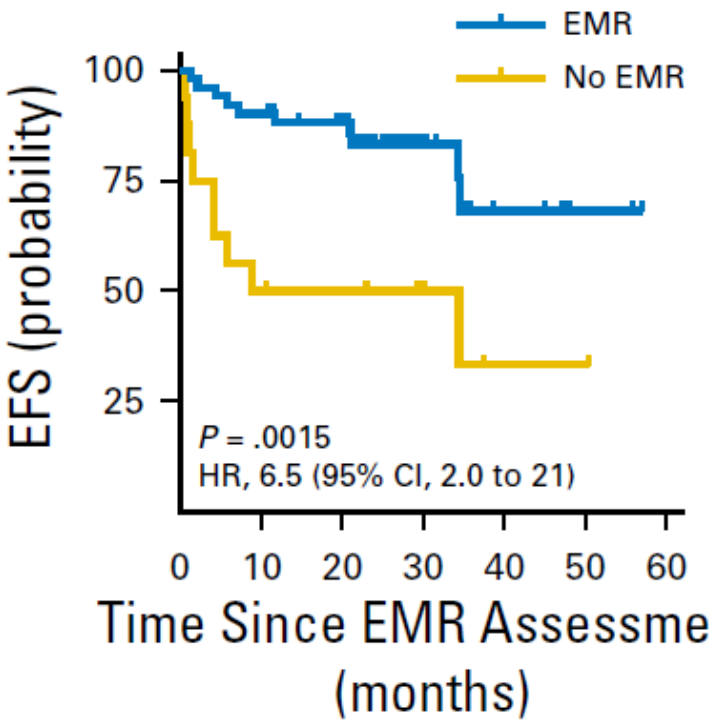




D. Kurtz et al , JCO 2018

ctDNA concentration reduction and outcome

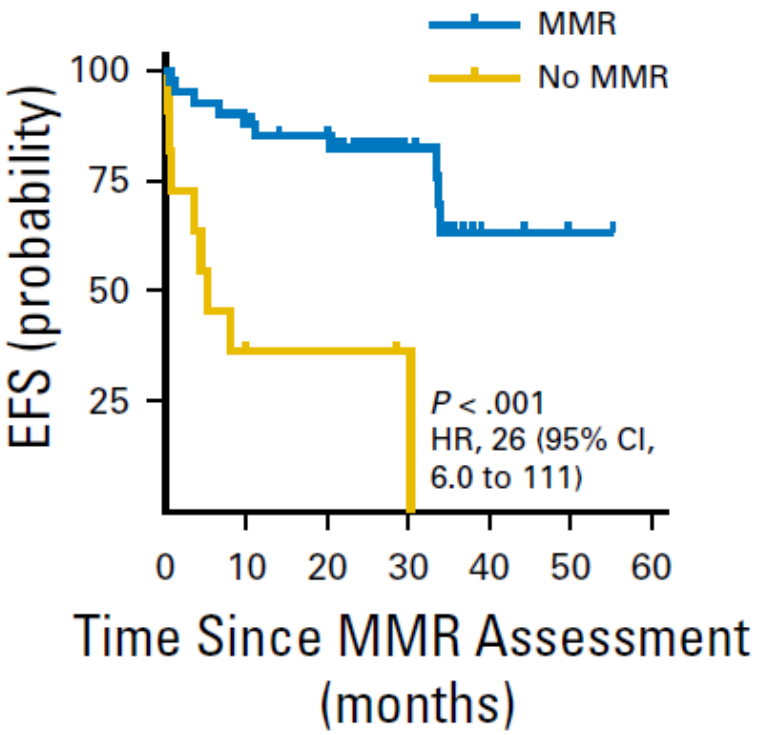
ctDNA drop after 1 cycle
Cutoff = 2 log



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

ctDNA drop after 2 cycles
Cutoff = 2.5 log

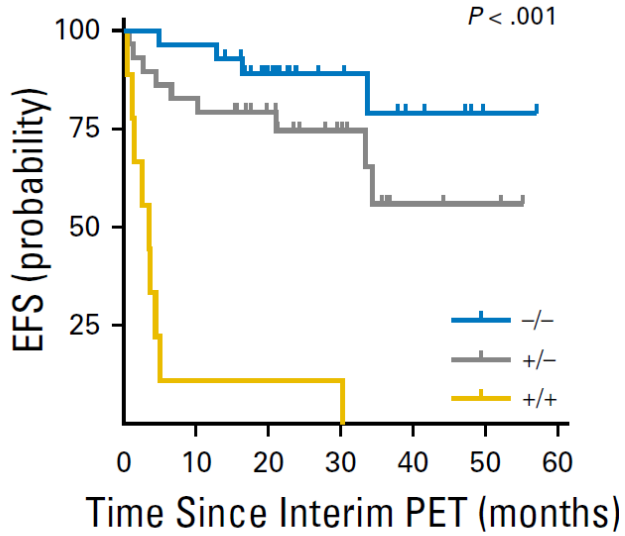


No. at risk:							
MMR	41	36	31	14	3	1	0
No MMR	11	4	3	1	0	0	0

21% of pts did not achieved MMR

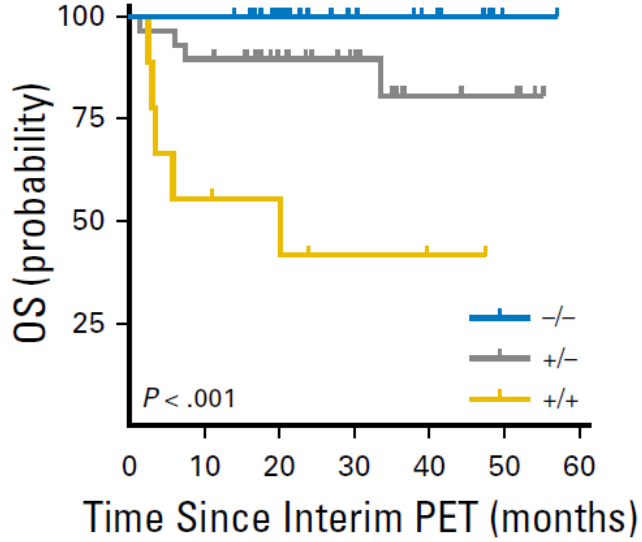
D. Kurtz et al , JCO 2018

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 HR (95% CI)	Univariable P	Multivariable HR (95% CI)	Multivariable 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)	.900
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*

D. Kurtz et al , JCO 2018

Conclusions

- aaIPI=0 < 80 ans
  - <60 ans no bulk : 4 x R-CHOP
  - Résultats LNH09-1B: 4 x R-CHOP pour les TEP2-

- aaIPI=1-3 <60 ans
  - Stratégie GAINED « modifiée »
  - Interim PET = ΔSUVmax
  - Choix de la chimio: ACVBP pour non GC, CNS IPI élevé, PMBL bulky

- aaIPI=1-3 60 – 80 ans
  - 6 x R-CHOP (TEP4-)
  - 4 x R-CHOP + CAR T (TEP4+)

- > 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