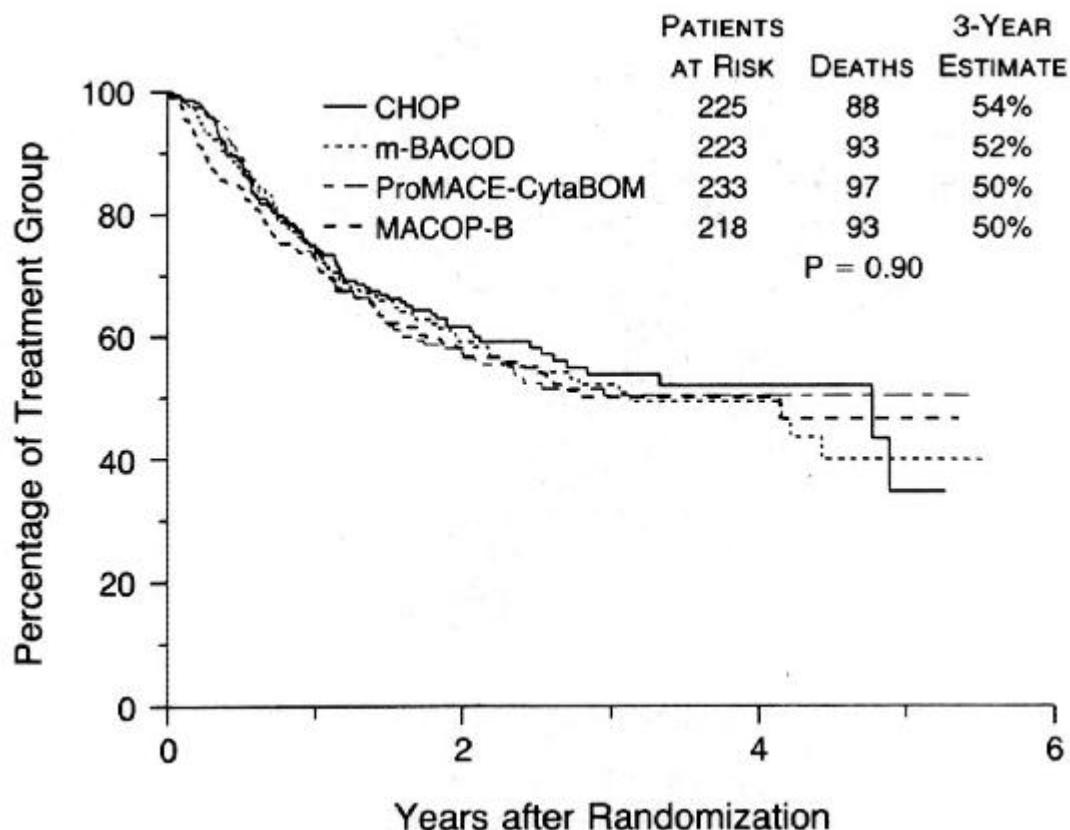


Comment améliorer le R-CHOP ?

Hervé Tilly
herve.tilly@chb.unicancer.fr



CHOP and the others



Improvements at the pre-rituximab era

Table 1. Significant results obtained with dose-dense, dose-intense or HDT regimens with CHOP or CHOP-like before the rituximab area.

Reference	Patients	Control Arm	Experimental Arm	Endpoint	EFS (%)	OS (%)
Pfreundschuh ³⁷	<60 years, low risk (IPI 0 or 1)	CHOP-14/21	CHOEP-14/21	5 years	58 vs. 69	80 vs. 84 [†]
Reyes ⁸	<60 years, IPI=0	CHOP	ACVBP + consolidation	5 years	74 vs. 82	81 vs. 90
Carde ⁹	<70 years, stage III-IV	CHOP	CHVmP-VB	5 years	26 vs. 43*	28 vs. 48
Tilly ¹⁰	60-69 years, aa IPI > 0	CHOP	ACVBP + consolidation	5 years	29 vs. 39	38 vs. 46
Pfreundschuh ⁷	>60 years, all risk	CHOP	CHOP-14	5 years	33 vs. 44	41 vs. 53
Haioun ⁴¹	<60 years, aaIPI 2 or 3	ACVBP	ACVBP + HDT	8 years	39 vs. 55 [†]	49 vs. 64
Gianni ¹²	<60 years, all risk	MACOP-B	Sequential HDT	5 years	49 vs. 76	55 vs. 81 [‡]
Milpied ¹³	<60 years, aa IPI 1 or 2	CHOP	CEEP + HDT	4 years	37 vs. 55	56 vs. 71 [‡]

*Freedom from progression; [†]disease free survival; [‡]p value not significant for overall survival.

Dose dense (CHOP-14, CHOEP, ...)

Dose intense (ACVBP, megaCHOP, ...)

Consolidation with High Dose Therapy supported by ASCT

R-CHOP in first line

GELA study: 10 year follow-up

Figure 4. Progression-free survival.

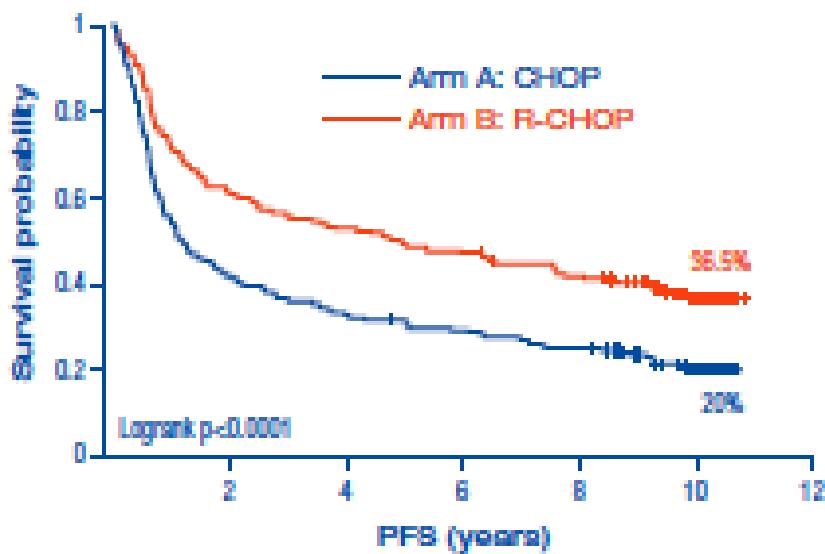
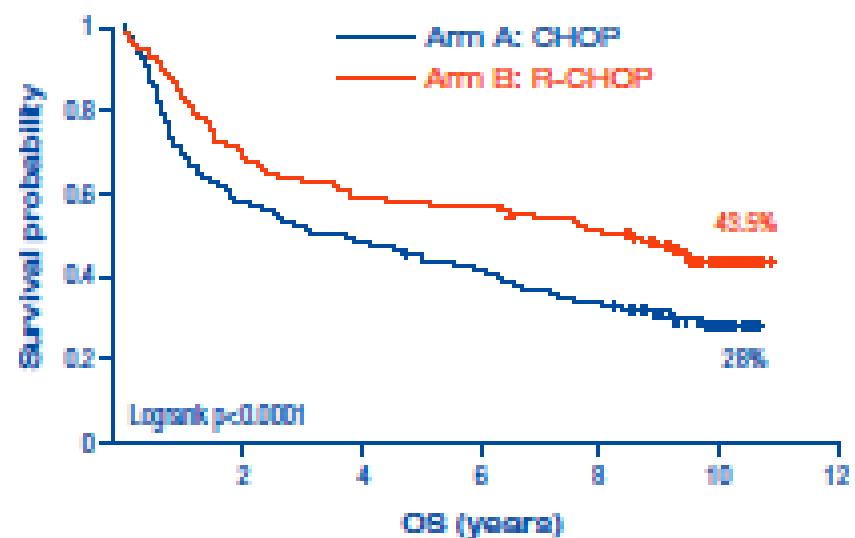


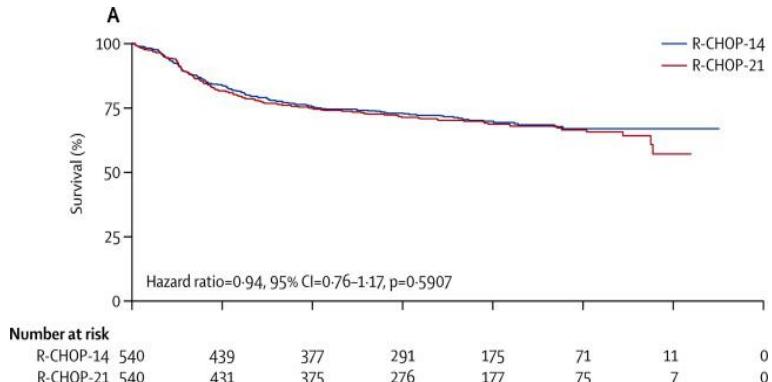
Figure 6. Overall survival.



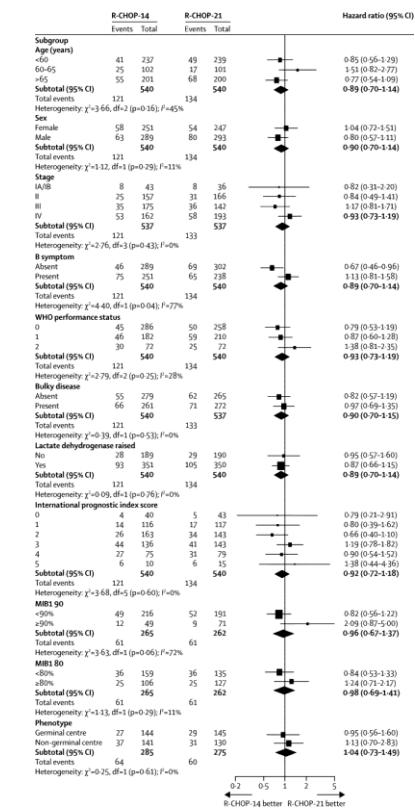
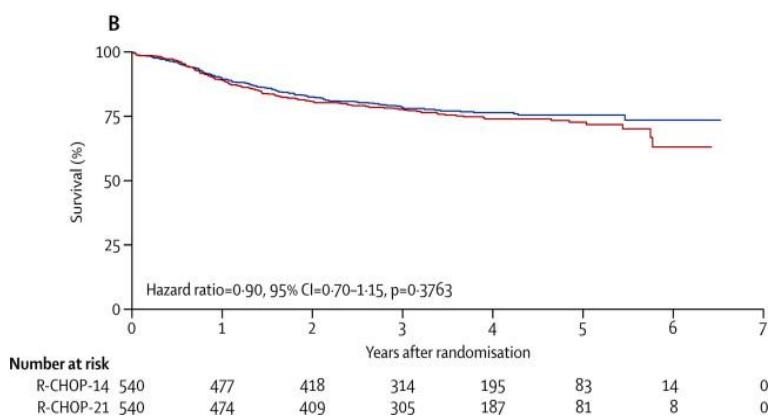
Dose-dense

R-CHOP 21 vs R-CHOP 14

PFS



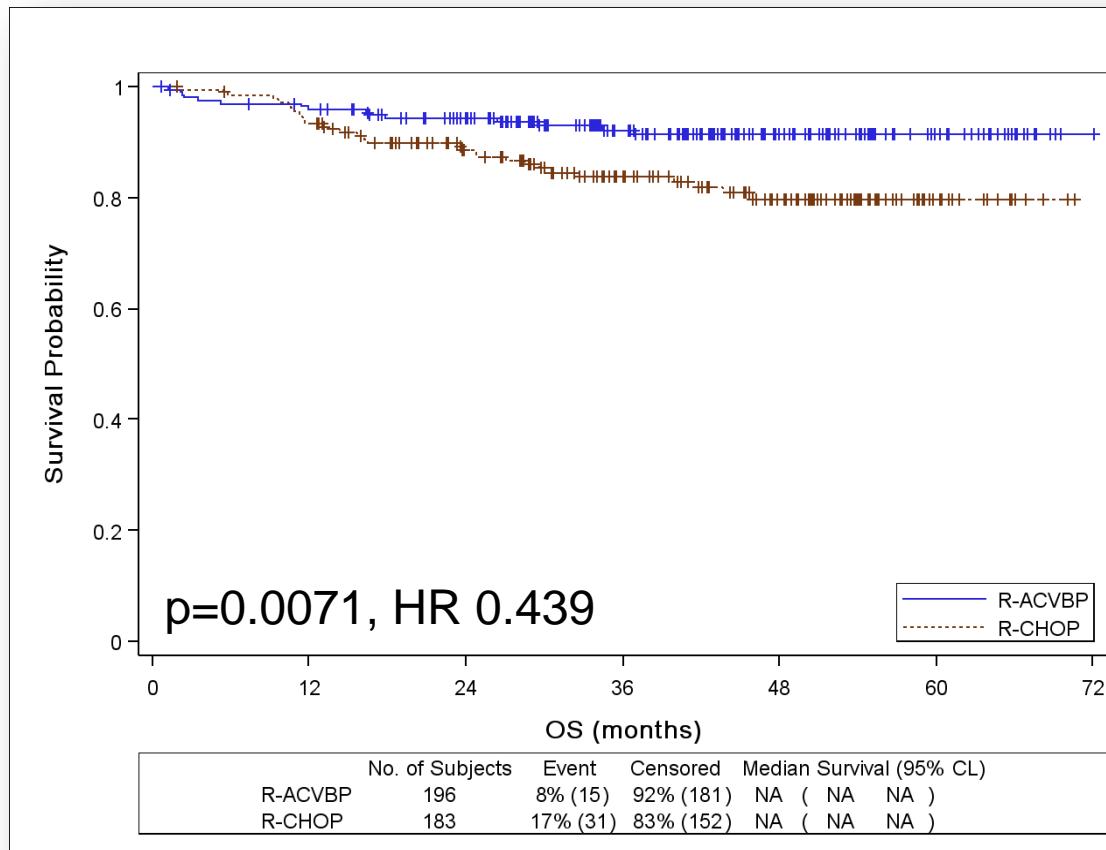
OS



Cunningham D et al. Lancet 2013;381:1817-26.
Delarue R et al. Lancet Oncol. 2013;14:525-33

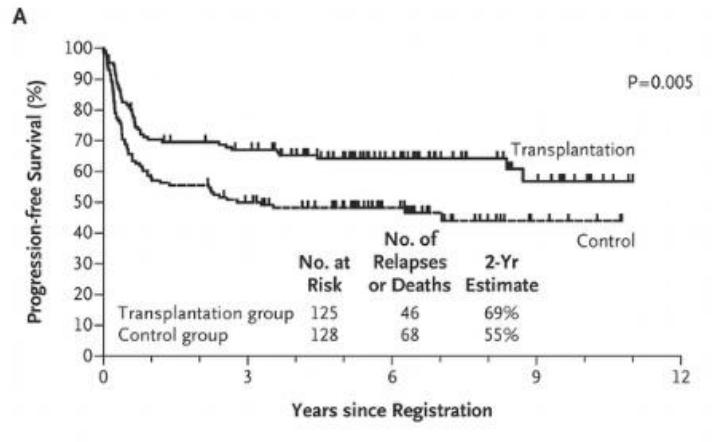
Dose intense

R-ACVBP vs R-CHOP, patients <60, aalPI=1

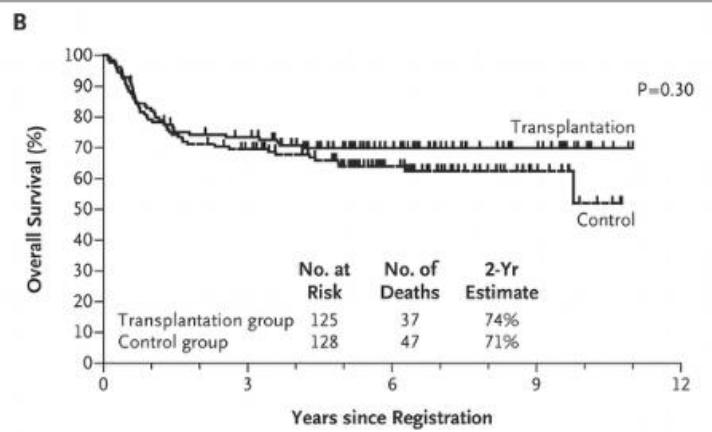
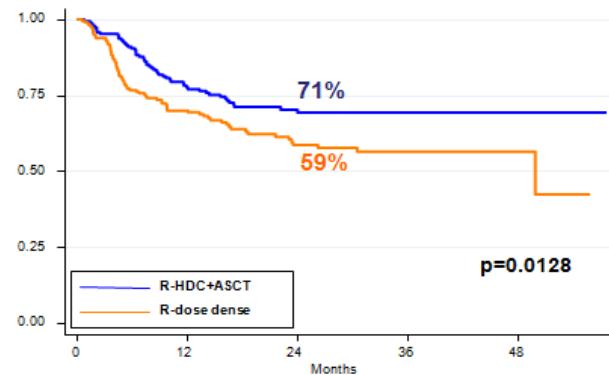


R-ACVBP
R-CHOP

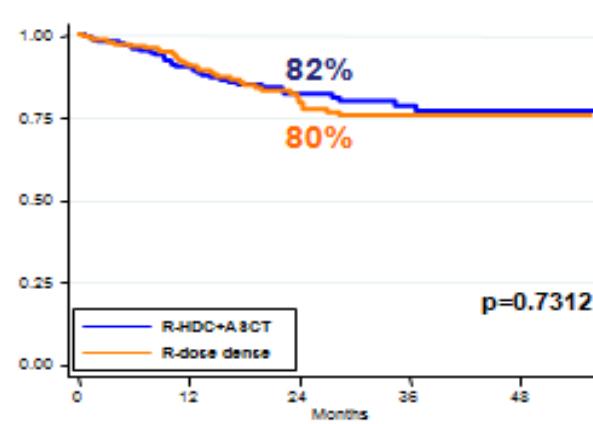
Consolidation by HDT and ASCT



EFS



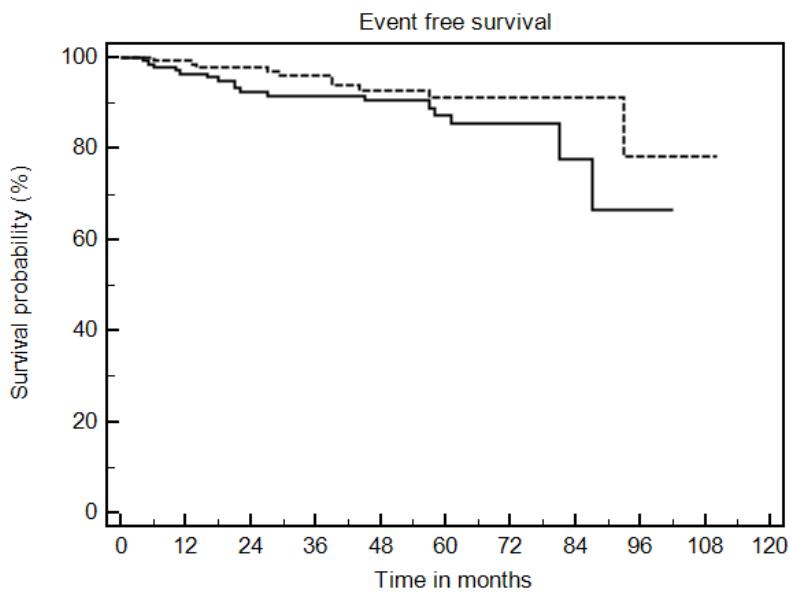
OS



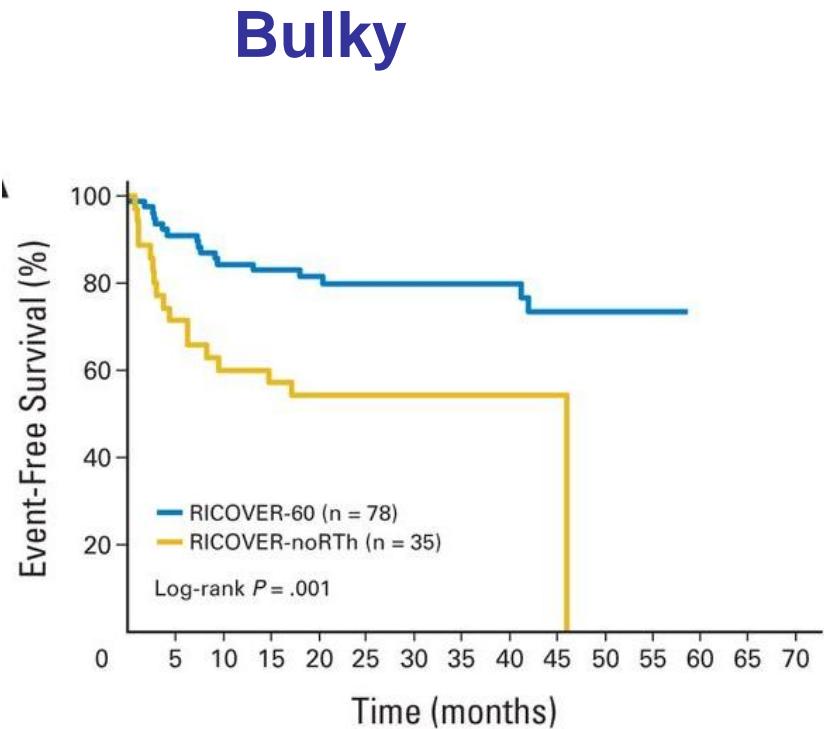
Stiff PJ et al. N Engl J Med 2013;369:1681-1690.
Vitolo U et al. ICML 2011.

Still a place for radiotherapy ?

Non-bulky



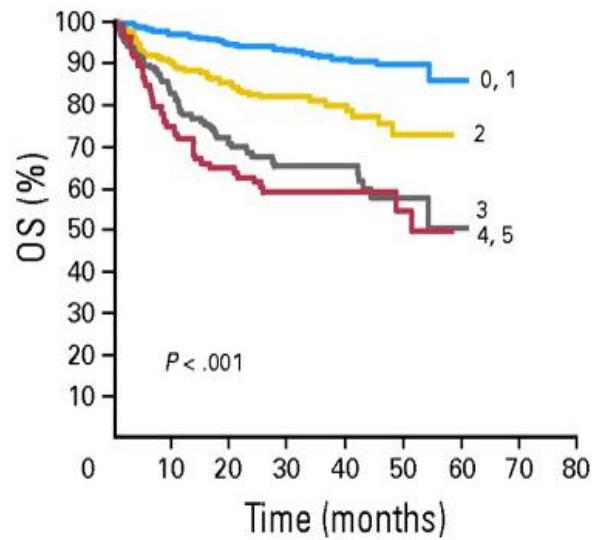
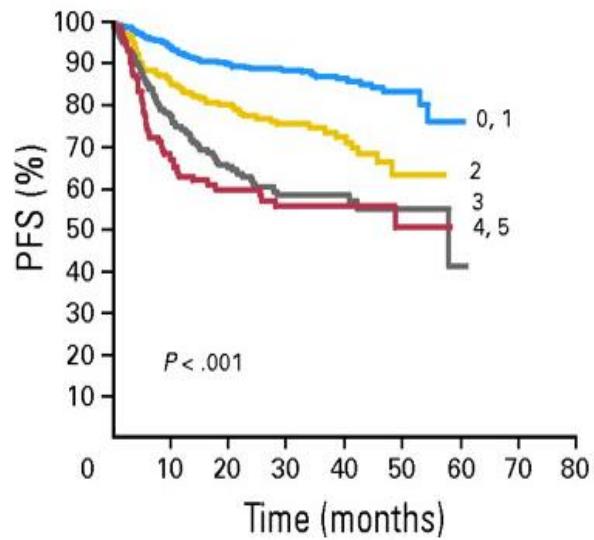
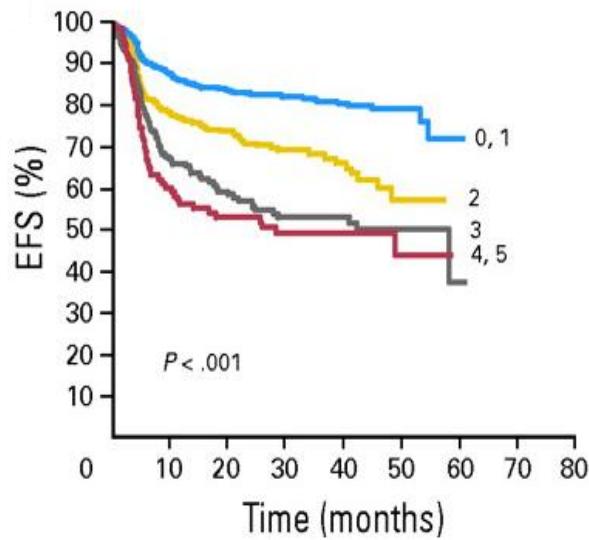
Bulky



Held G et al. J Clin Oncol 2014;32:1112-8
Lamy T et al. ASH 2014

IPI still valid in the rituximab era

All trials (18 to 80 years of age, all IPI groups; n = 1,062)



Standard: ESMO guidelines 2015

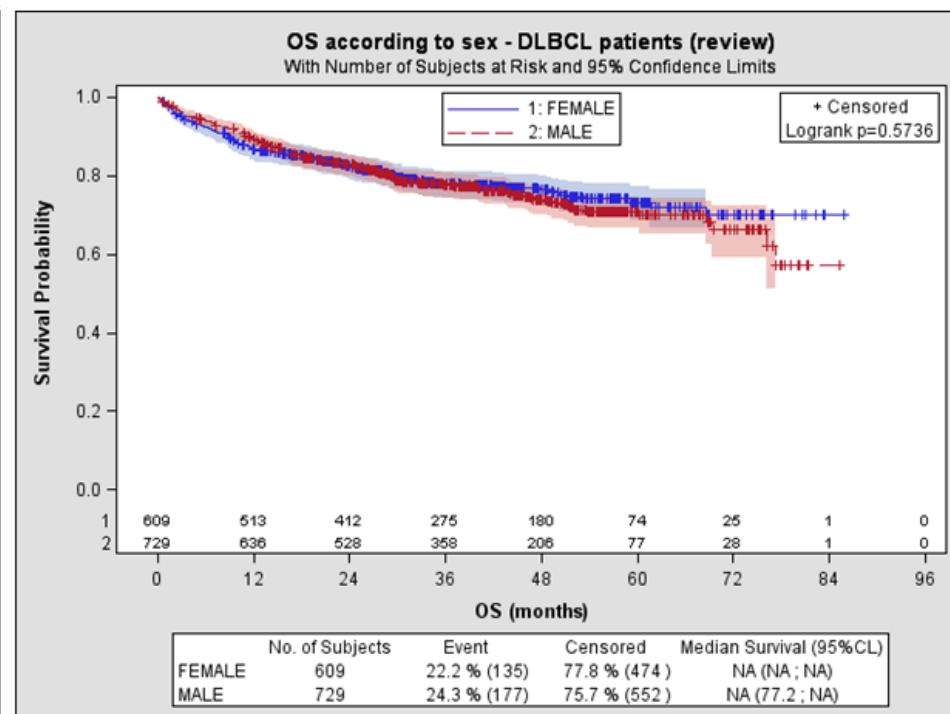
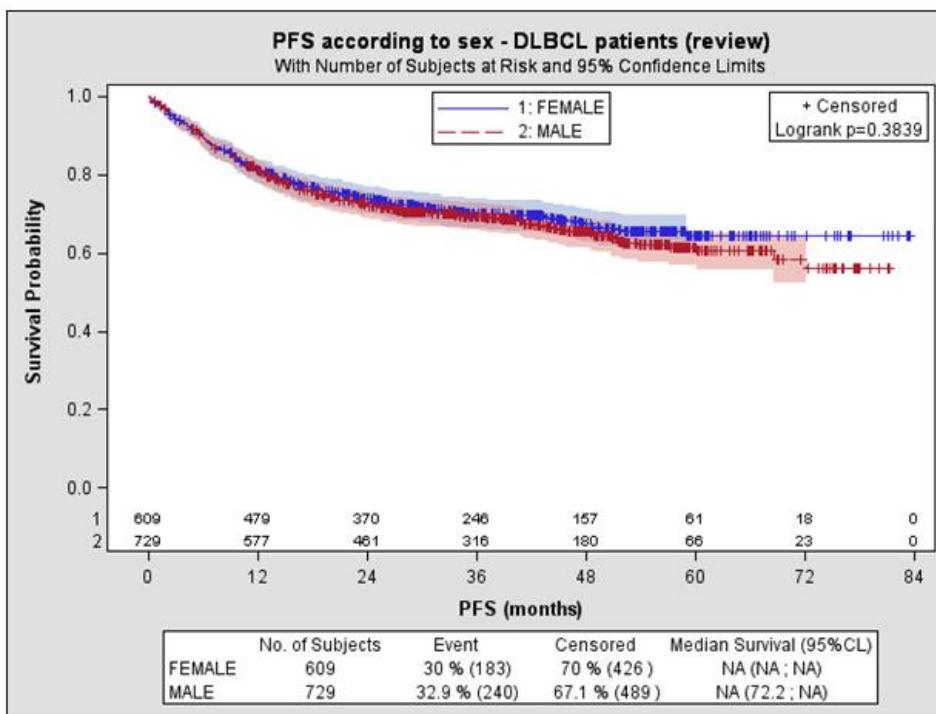
Age	aalPI Status	Treatment
≤ 80	0, No bulk	6 R-CHOP 21
≤ 60	0, Bulk 1	R-ACVBP + consolidation 6 R-CHOP 14/21 + radiotherapy on bulk
≤ 60	2-3	8 R-CHOP 21 6 R-CHOP 14 +2R <i>Options:</i> 6 R-CHOEP 14 R-CHOP/R-ACVBP + ASCT
60-80	1-3, Fit	8 R-CHOP 21 6 R-CHOP 14 +2R
> 80	0-3	6 R mini-CHOP
> 60	Unfit	6 R-C(X)OP

CNS prophylaxis in patients at risk for CNS relapse

Tilly H et al. Ann Oncol 2015;26(5):116-25.

PFS and OS in a large population

1338 DLBCL pts, 18-60 years, included in five trials LNH 03 program

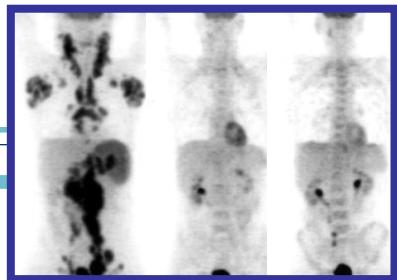


Comment améliorer le R-CHOP ?

- Modulation en fonction de la réponse
 - TEP intermédiaire
 - Maladie résiduelle
- Prendre en compte la biologie
 - GC ou ABC
 - Mutations à cibler
 - MYC et double hit
 - Antigènes de surface : anticorps
 - Immunologie
 - Autres voies, épigénétique,...

Comment améliorer le R-CHOP ?

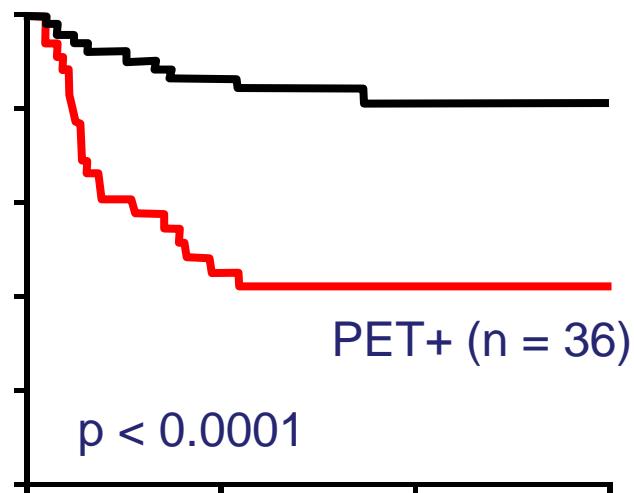
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 - MYC et double hit
 - Antigènes de surface : anticorps
 - Immunologie
 - Autres voies, épigénétique,...



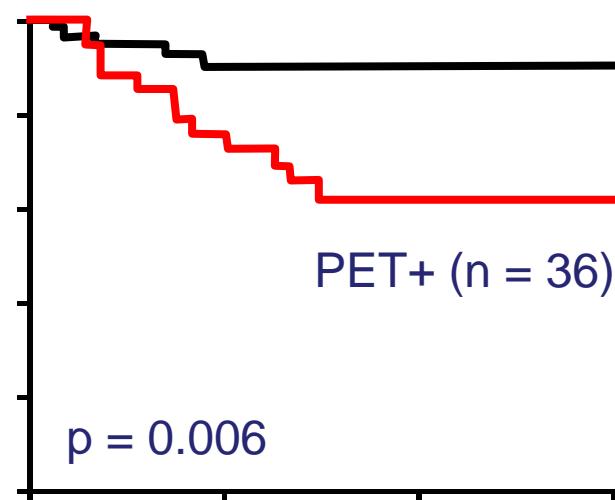
Interim PET

Interim PET after 2 cycles may help stratify patients ?

Event-free survival

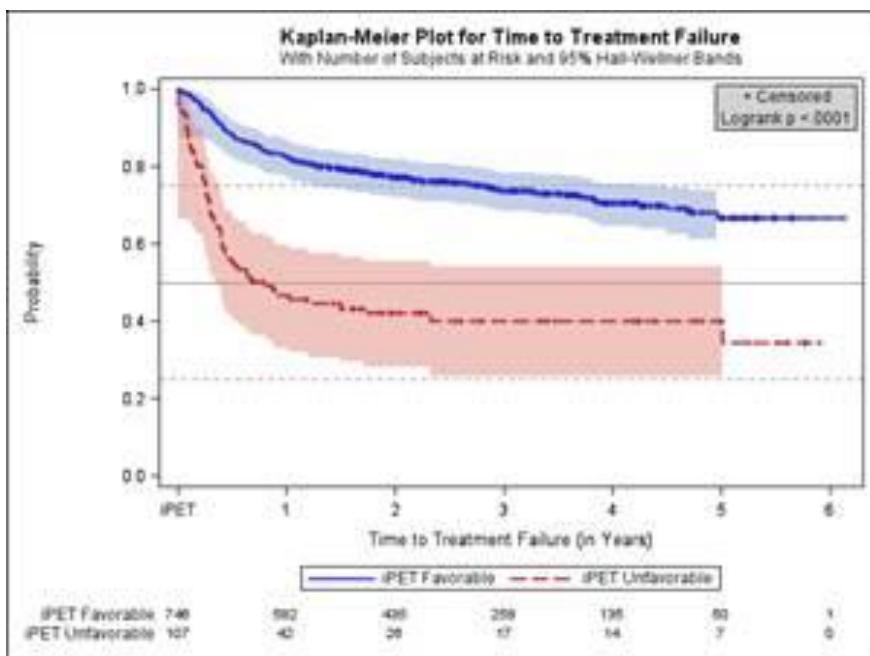


Overall survival

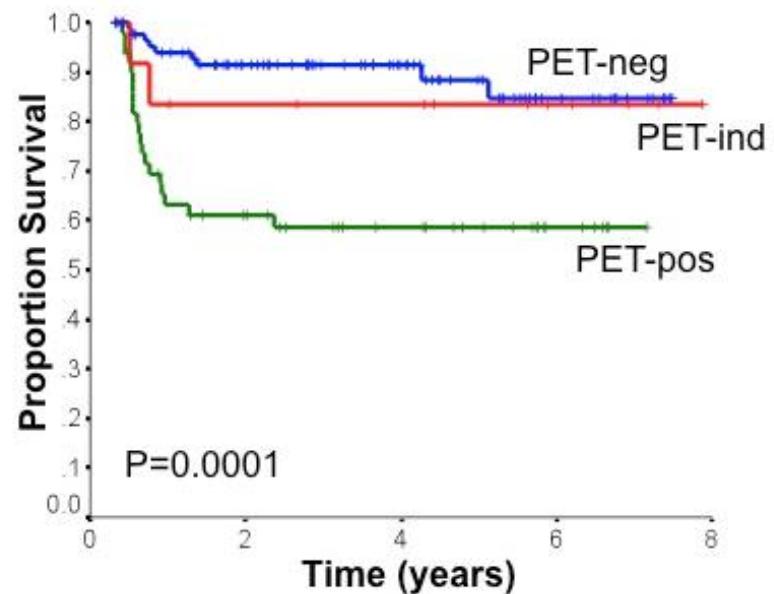


To intensify treatment in **positive** interim PET?

PETAL trial



BC trial



Duerhsen U et al. ASH 2014.
Sehn L et al. ASH 2014.

Interim PET

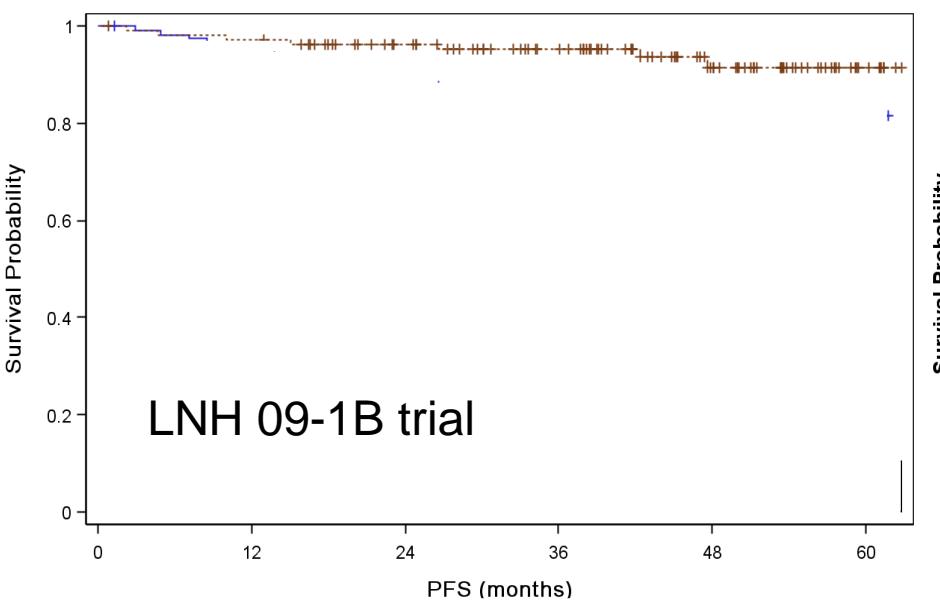
Study	N	Interim PET after...	Median follow-up (months)	PET neg	PET pos	Rituximab
<i>Jerusalem Haematologica</i> 2000	28 (16 DLBCL)	median of 3 cycles	17.5	PFS 2y=62%	PFS 2y=0%	X
<i>Spaepen Ann Oncol</i> 2002	70 (47 DLBCL)	3-4 cycles	36.3	PFS 2y=85%	PFS 2y=4%	X
<i>Kostakoglu J Nucl Med</i> 2002	30 (13 DLBCL)	1 cycle	19	PFS 2y=85%	PFS 2y<15%	X
<i>Mikhaeel Ann Oncol</i> 2005	120 (75 DLBCL)	2-3 cycles	24.4	PFS 5y=87%	PFS 5y=34%	?
<i>Haioun Blood</i> 2005	90 (85 DLBCL)	2 cycles	24	EFS 2y=82%	EFS 2y=43%	41%
<i>Dupuis, Itti Ann Oncol</i> 2009	103 (all DLBCL)	4 cycles	53	EFS 5y=80%	EFS 5y=36%	49%
<i>Casasnovas, Blood</i> 2011	102 (all DLBCL)	2 & 4 cycles	19	PFS 2y=81%	PFS 2y=73%	100%

To decrease treatment in **negative** interim PET?

IPI=0

Treatment by 6 R-CHOP

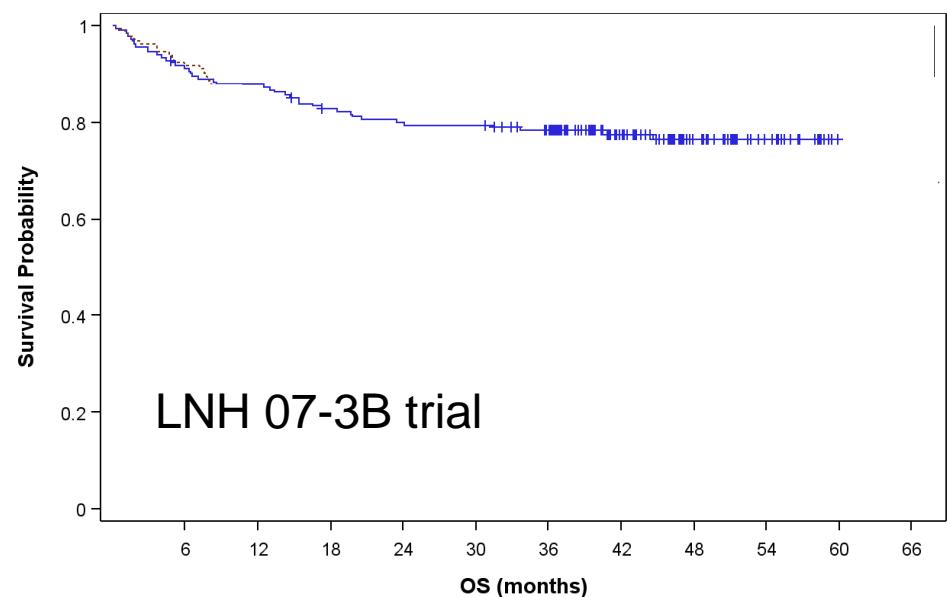
→ only 4 R-CHOP ?



<60, IPI=2-3

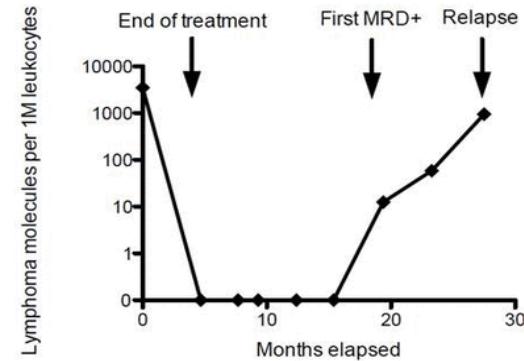
Treatment by ACVBP+ASCT

→ omit ASCT ?

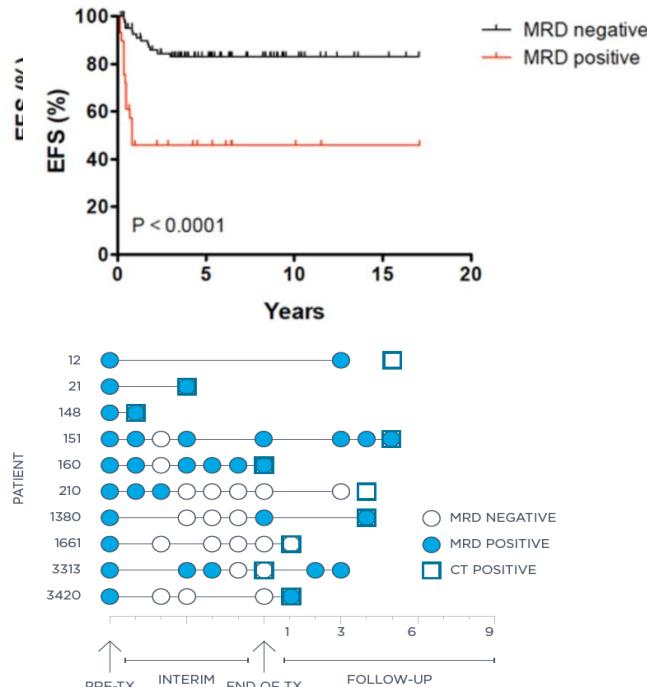


Residual disease evaluation

Detectable clonal DNA in all pts at baseline in PBL (naked DNA)



Interim MRD status predicts outcome



Detection of early relapse

Armand P et al. Br J Haematol 2013;163:123-6.

Rochewski M et al. Lancet Oncol 2015;16:541-9.

Camus V et al. Leuk Lymph 2016; DOI:10.3109/10428194

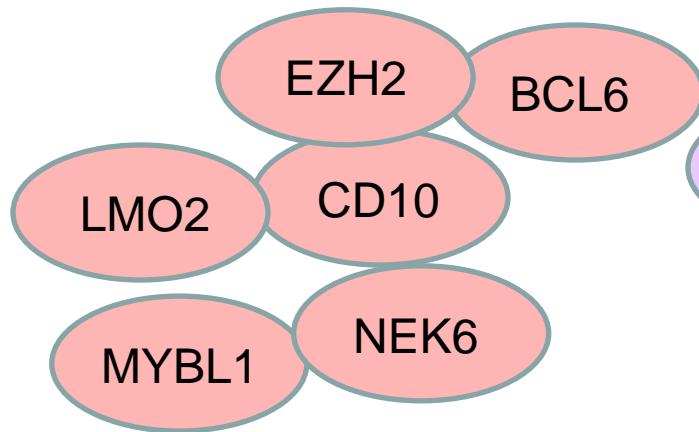
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 - Autres voies, épigénétique,...

Two distinct diseases

GC B-cell like

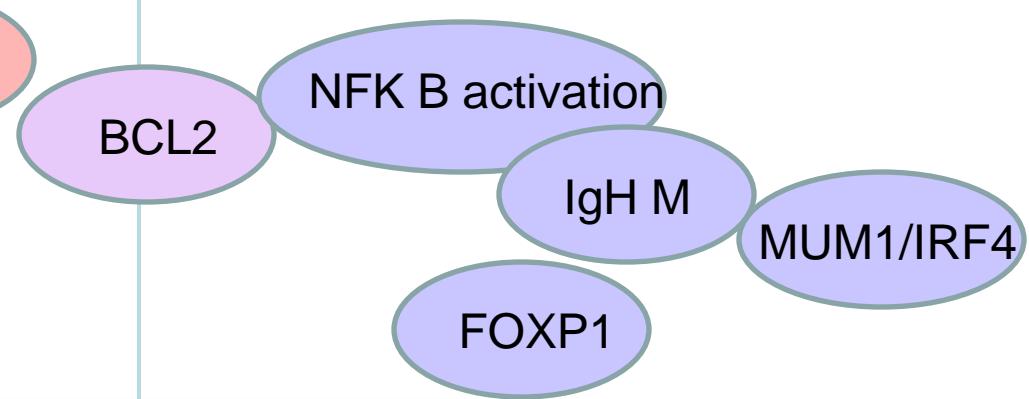
BCL2 translocations, t(14;18)
C-rel amplification



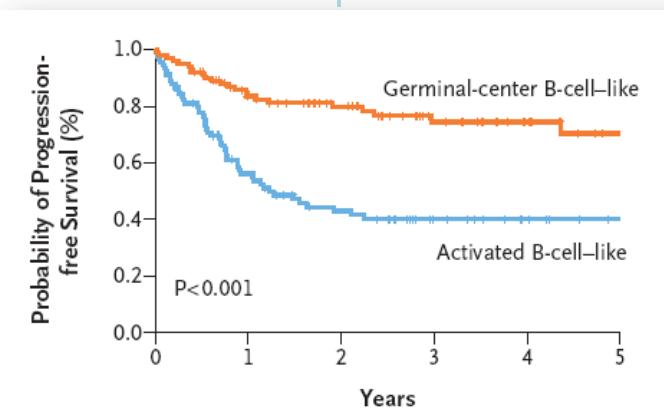
Mir-125b
Mir-17-92

Activated B-cell (ABC) like

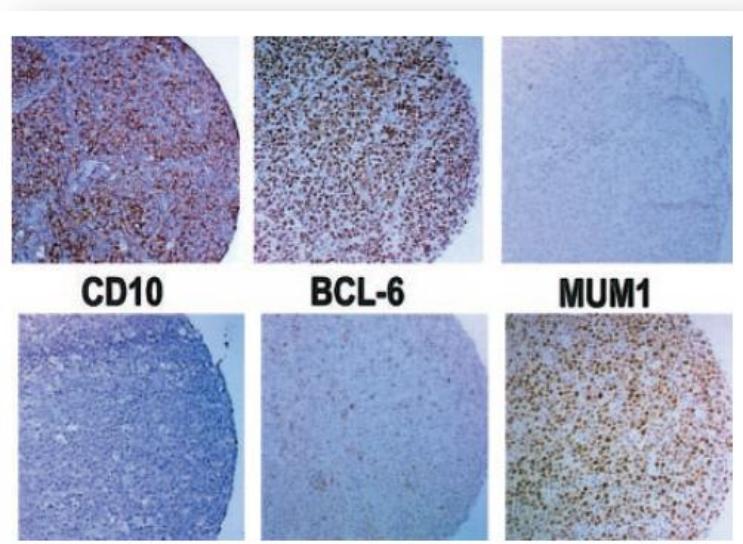
+3
18q21 amplification
BCL6 translocations



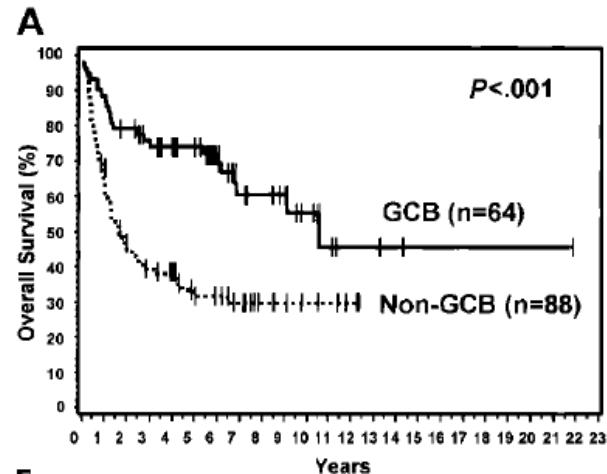
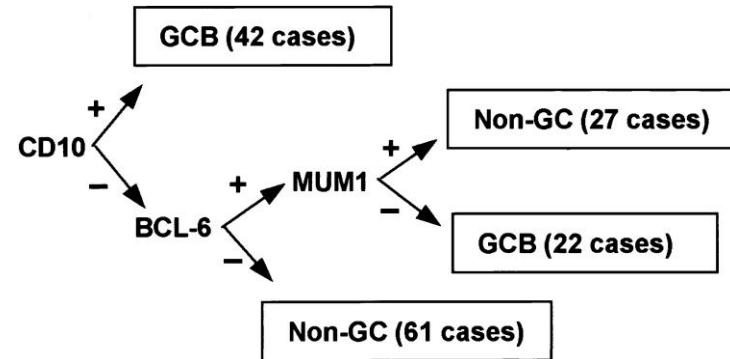
Mir-155
Mir-21
Mir-223



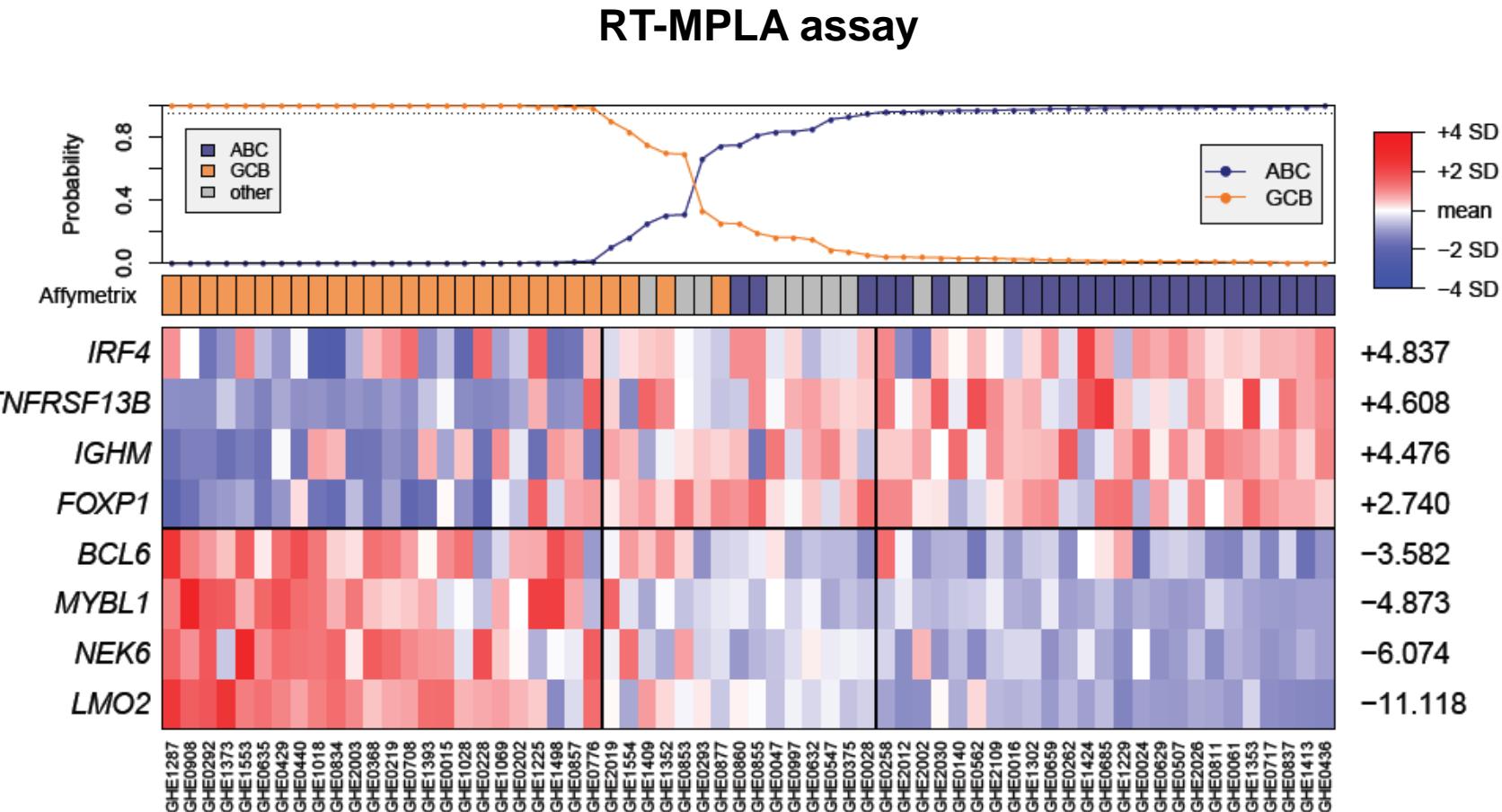
Immunohistochemistry as a surrogate



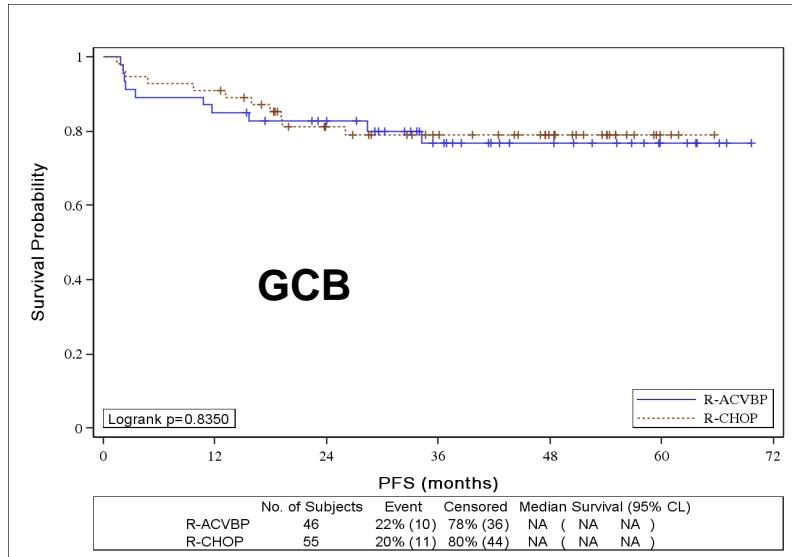
Discordances with cDNA: 20%



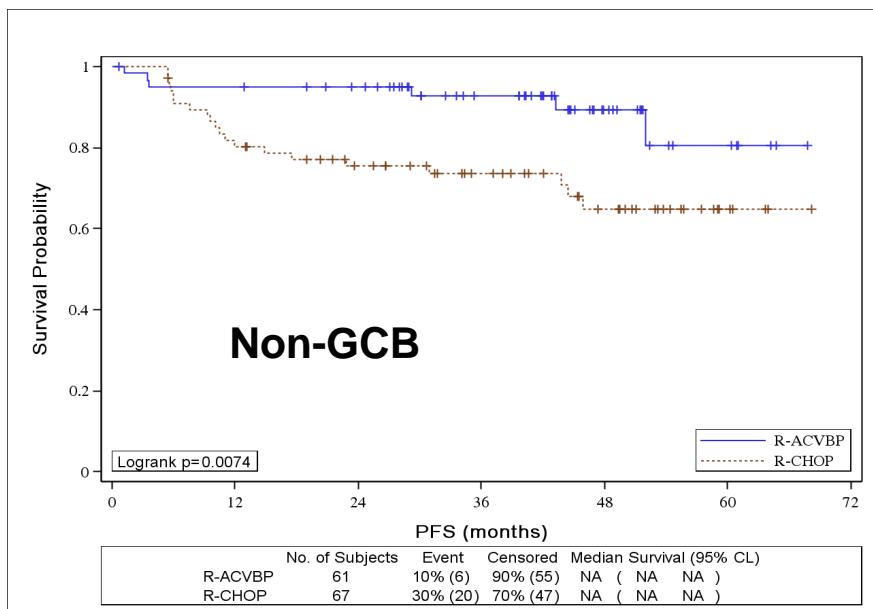
New methods



Different efficacy of chemotherapy regimens ?



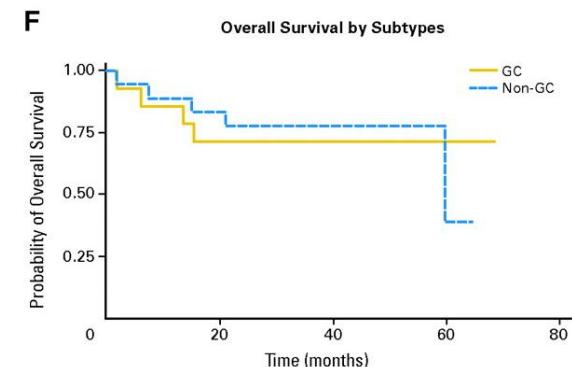
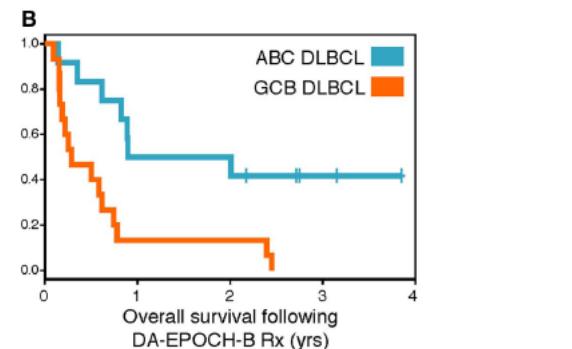
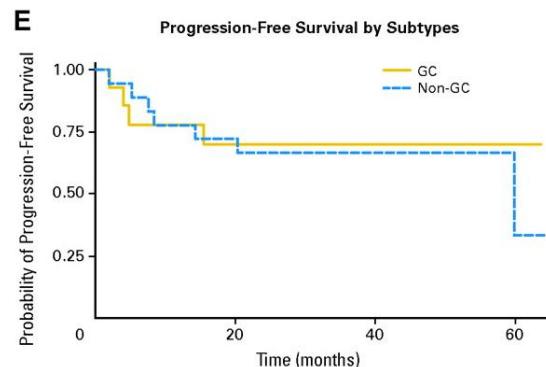
R-ACVBP vs R-CHOP



Bortezomib in ABC DLBCL

Differential efficacy of bortezomib ?

BR-CHOP enhances outcome of non-GC DLBCL ?

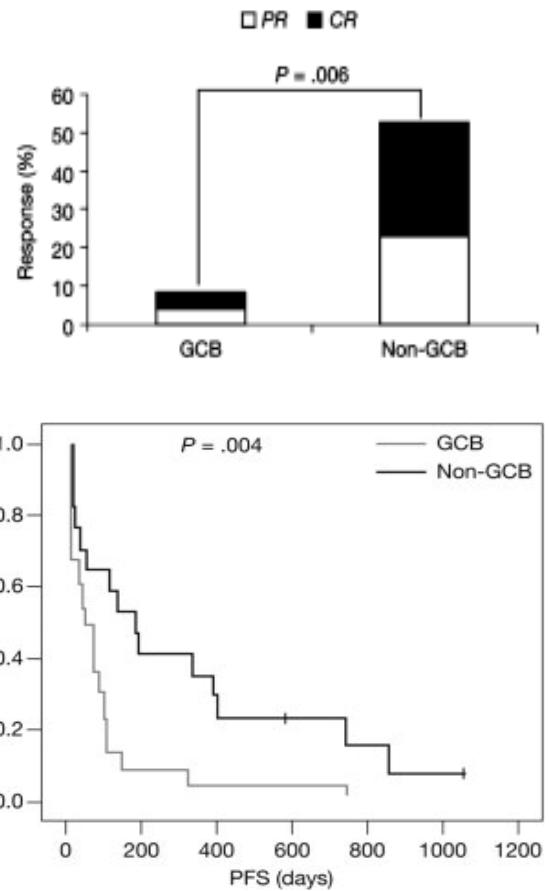
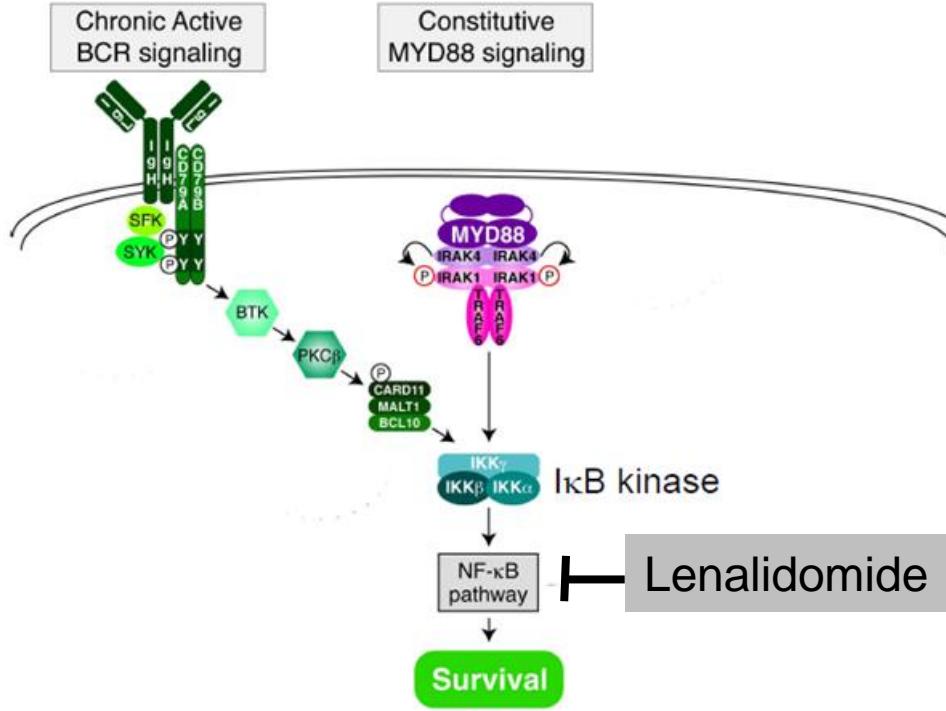


Prospective studies of Bortezomib in ABC DLBCL

Study	Country	N	Phase	Tech.	Design
PYRAMID	US	206	2	IHC	R-CHOP / BR-CHOP
LYM2034	Multi	164	2	IHC	R-CHOP / BR-CAP
	Spain	127	2	IHC	R-CHOP / BR-CAP
REMoDL-B	UK	1132	3	Mol	R-CHOP all DLBCL At cycle 2 R-CHOP / BR-CHOP

Offner F et al. Blood 2015;126:1893-901.
Davies AJ et al. ASH 2015
Leonard JP et al. ASH 2015

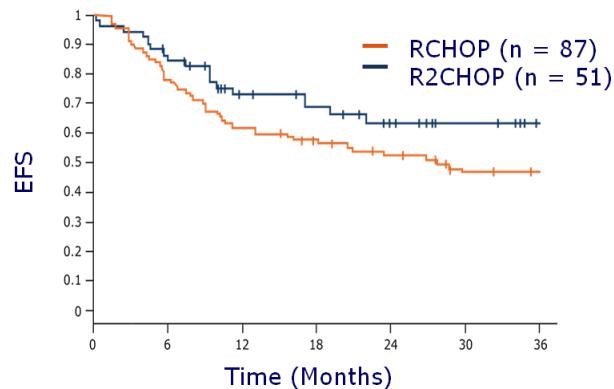
Lenalidomide in ABC DLBCL



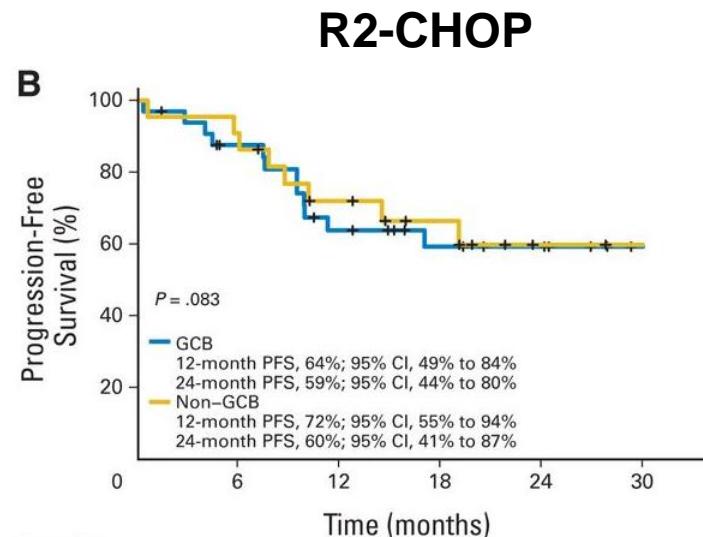
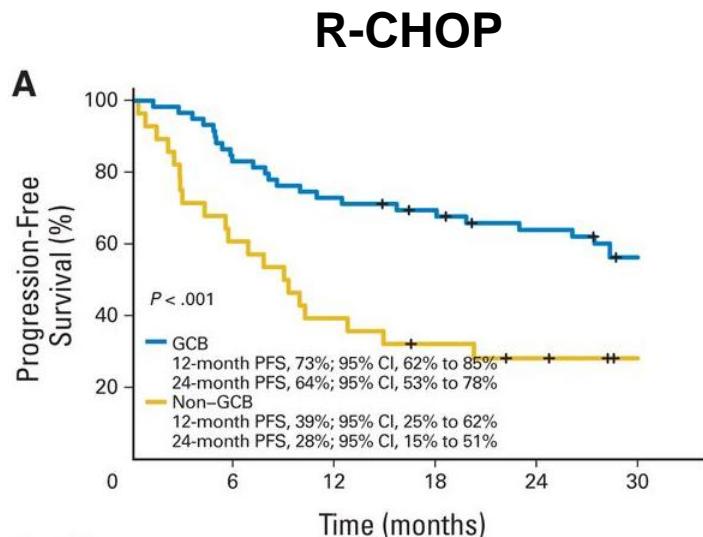
Hernandez-Ilizaliturri FJ et al. Cancer 2011;117:5058-66
Yang Y et al. Cancer Cell 2012;21:723–37.

R2-CHOP in DLBCL

Historical comparison



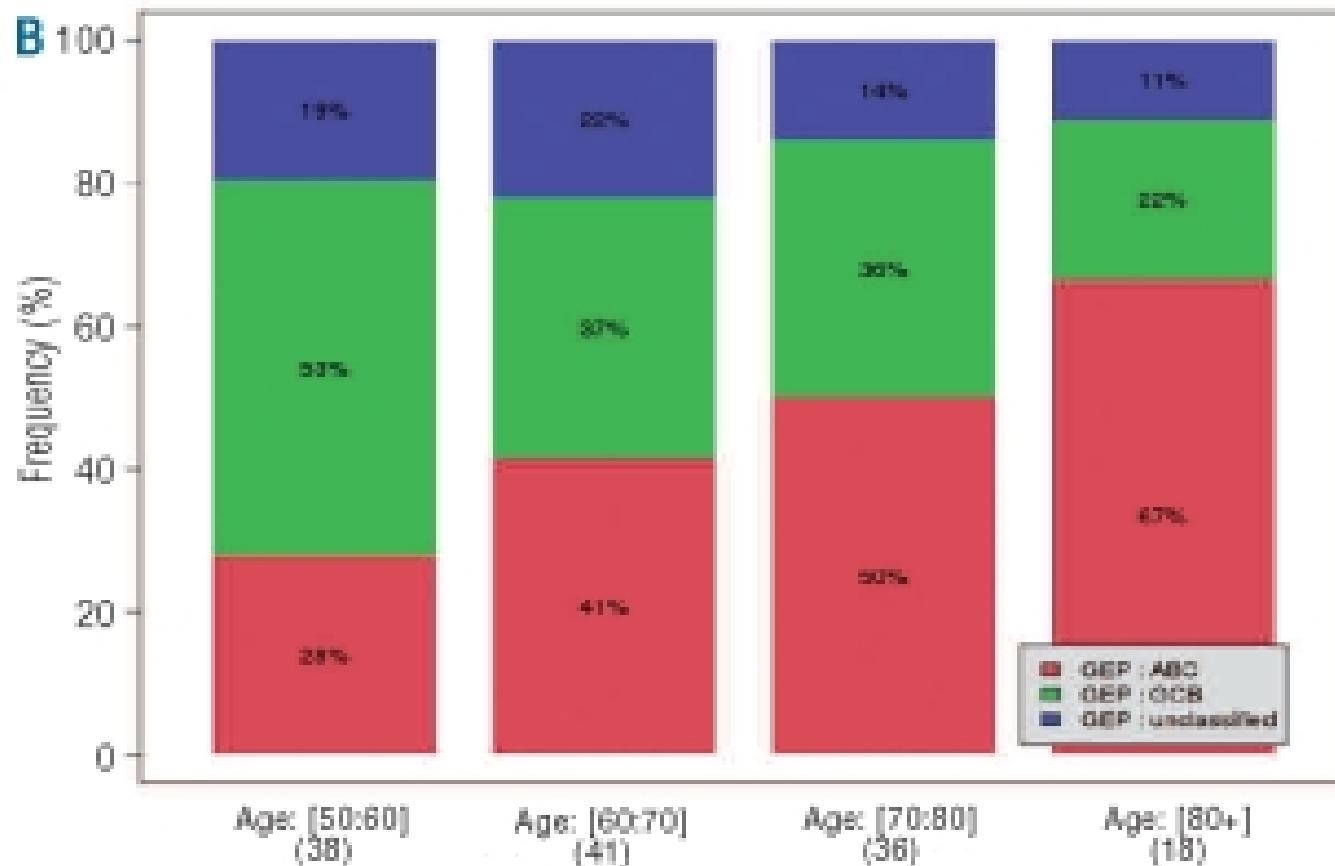
CR rate 80%



Lenalidomide and R-CHOP in DLBCL

Study	Country	N	Phase	Tech.	Design
NCI	US	300	2	IHC	R-CHOP / R2-CHOP
ROBUST	Multi	560	3	Mol	R-CHOP / R2-CHOP
SENIOR	LYSA	252 >80 yr	3	IHC	R-miniCHOP / R2-miniCHOP
REMARC	LYSA	640	3	IHC	R-CHOP -> CR, PR Lenalidomide/surveillance

Proportion of ABC subtype increases with age

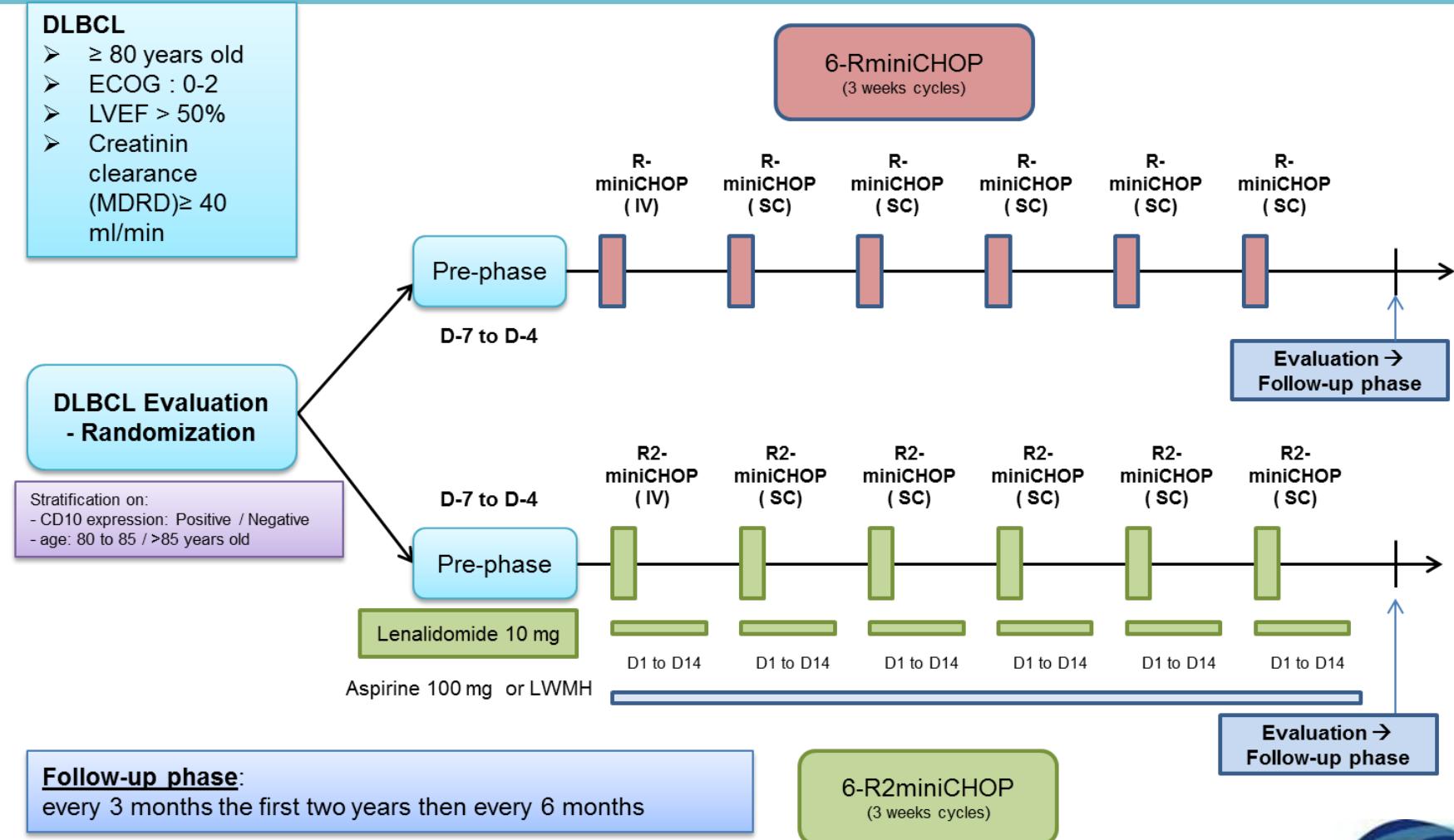


SENIOR Study Design

age ≥ 80

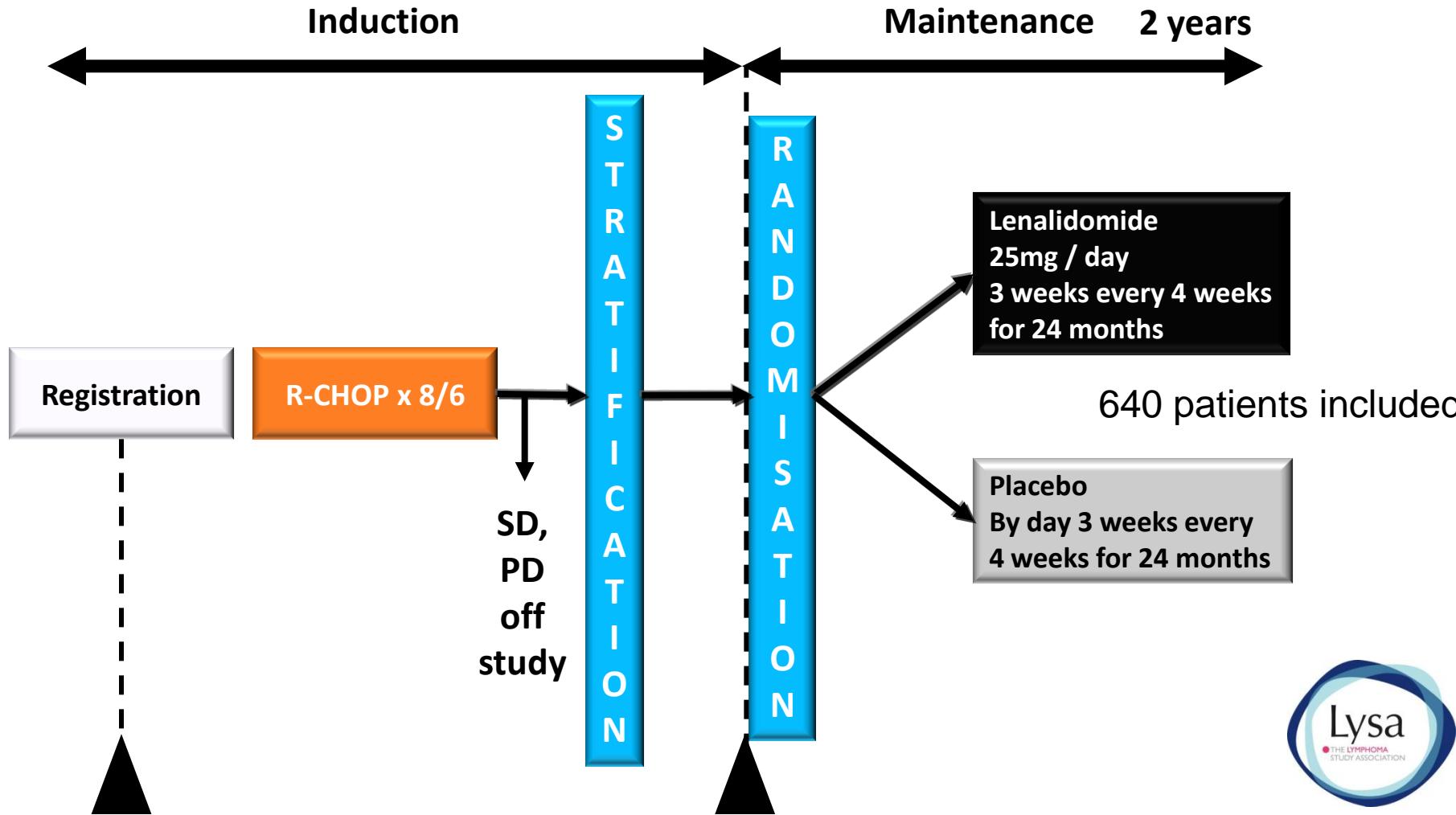
DLBCL

- ≥ 80 years old
- ECOG : 0-2
- LVEF > 50%
- Creatinin clearance (MDRD) ≥ 40 ml/min

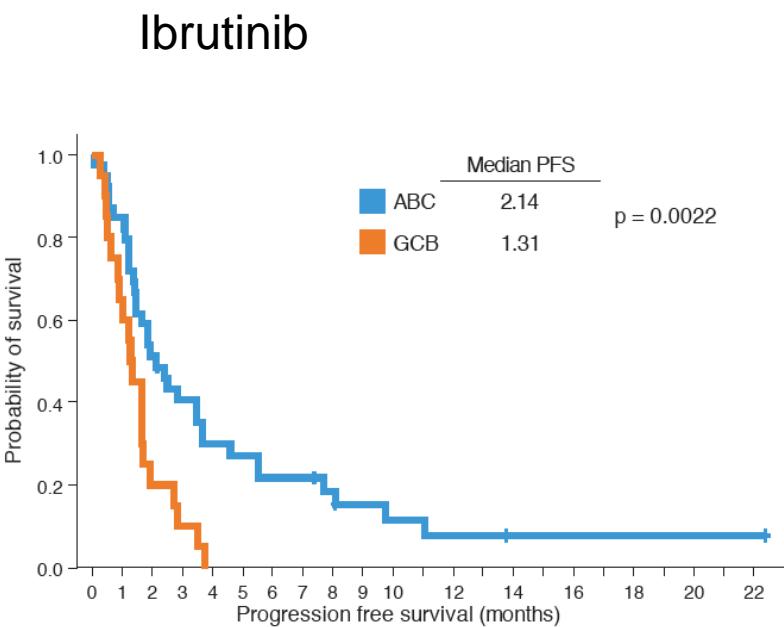
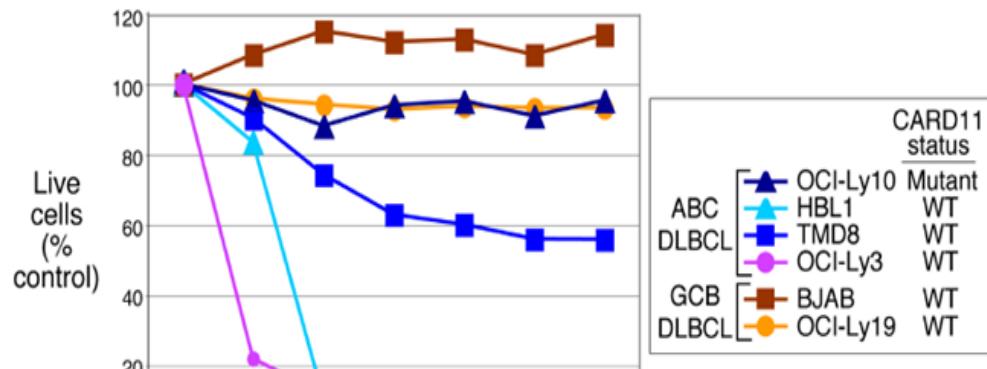
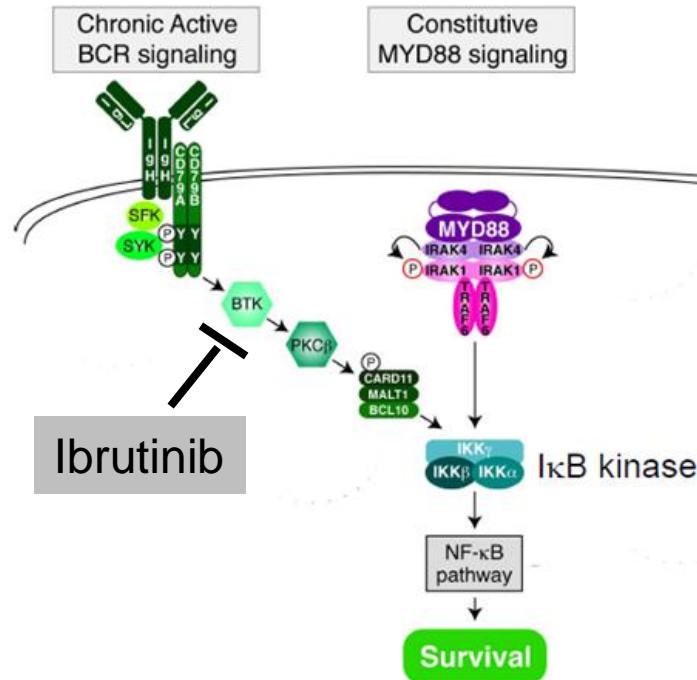


ReMaRC study: Design

age 61-80



Blockade of BCR signaling by ibrutinib in ABC



Yang Y et al. Cancer Cell 2012;21:723–37.

Wilson WH et al. Nat Med 2015;21:922–9.

RI-CHOP

**Phase Ib of R-CHOP and Ibrutinib.
Recommended dose: 560 mg/d**

Response N = 22	
ORR	100%
CR	91%
PR	9%

Younes A et al. Lancet Oncol. 2014;15:1019-26.

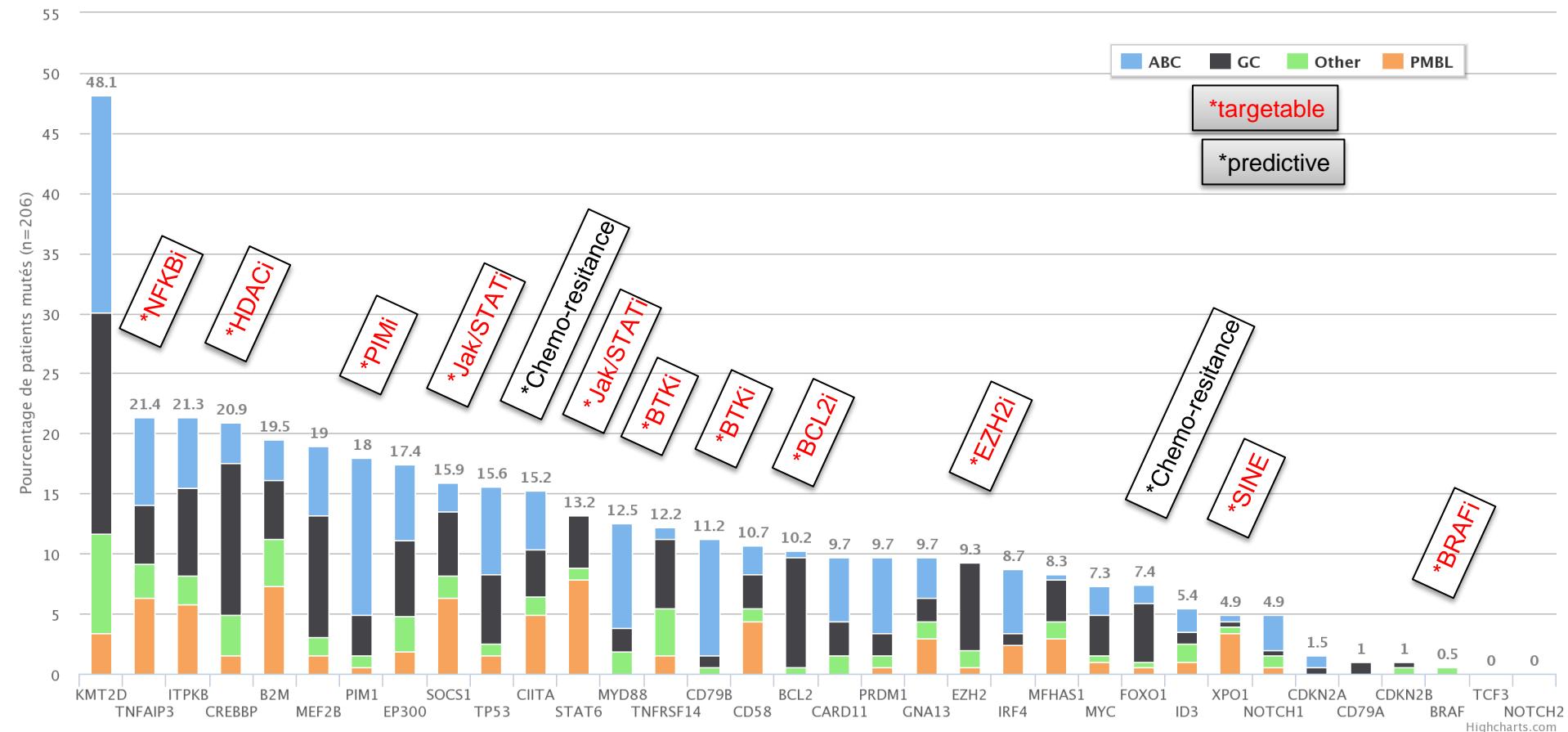
Completed trial

PHOENIX: Phase 3: R-CHOP+/- ibrutinib in non-GC DLBCL

Comment améliorer le R-CHOP ?

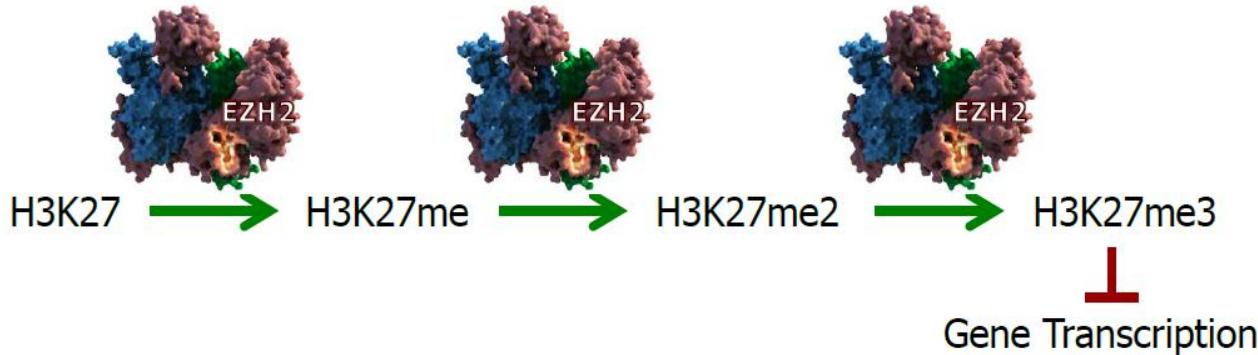
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Targetable mutations according to COO



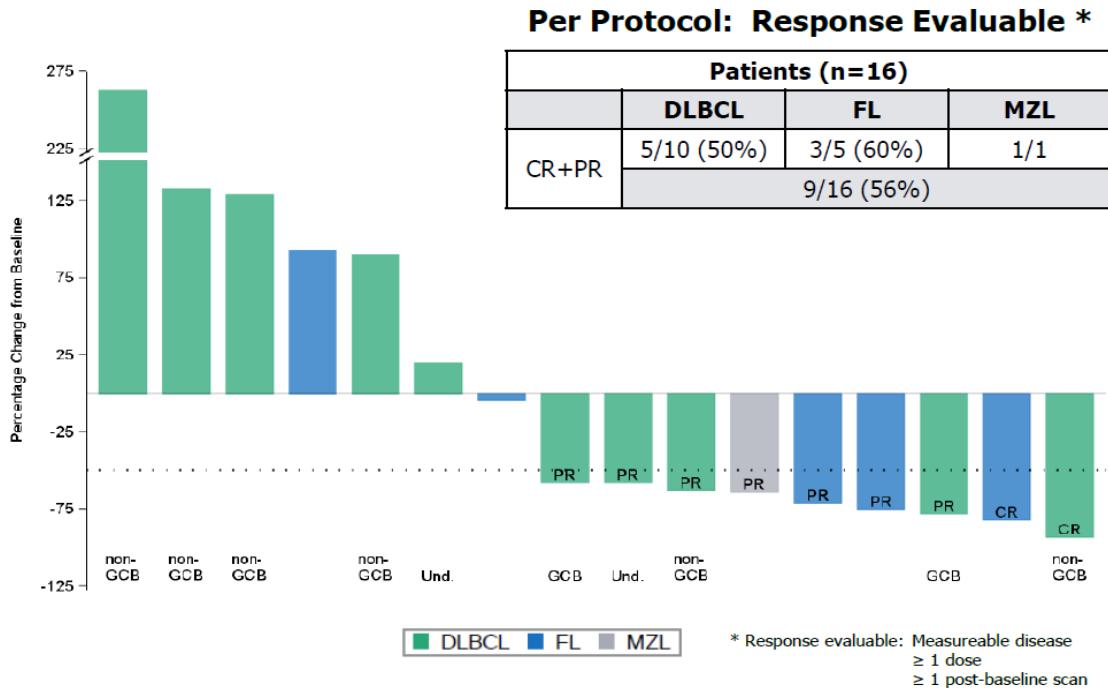
EZH2 inhibitors

- EZH2 = catalytic subunit of the complex PRC2 which methylate H3K27
- Aberrant trimethylation of H3K27 is oncogenic

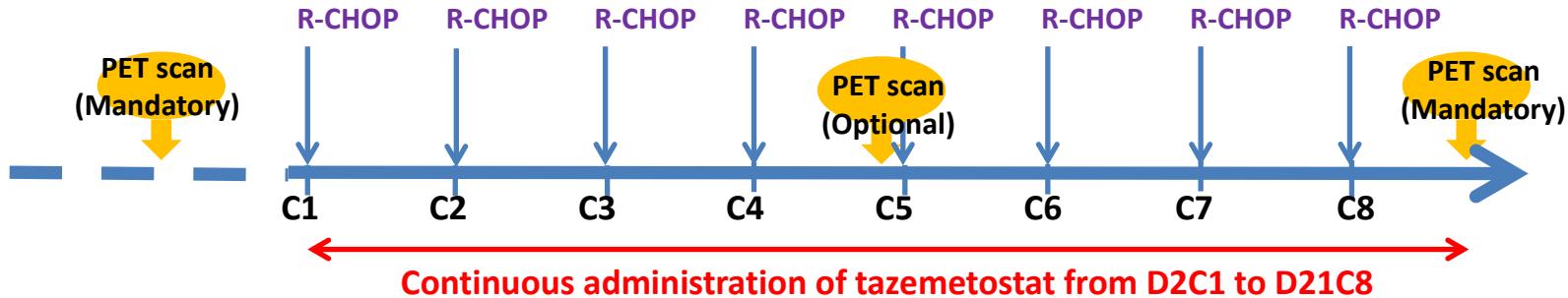


- EZH2 mutation within the catalytic domain: 10% NHL (GC DLBCL, FL)
- Mutant act in concert with WT EZH2
 - high level of H3K27me3
 - lymphomagenesis
- In vitro: lymphoma cells + EZH2 inhibitors
 - Inhibits intracellular H3K27 trimethylation
 - Inhibition of proliferation

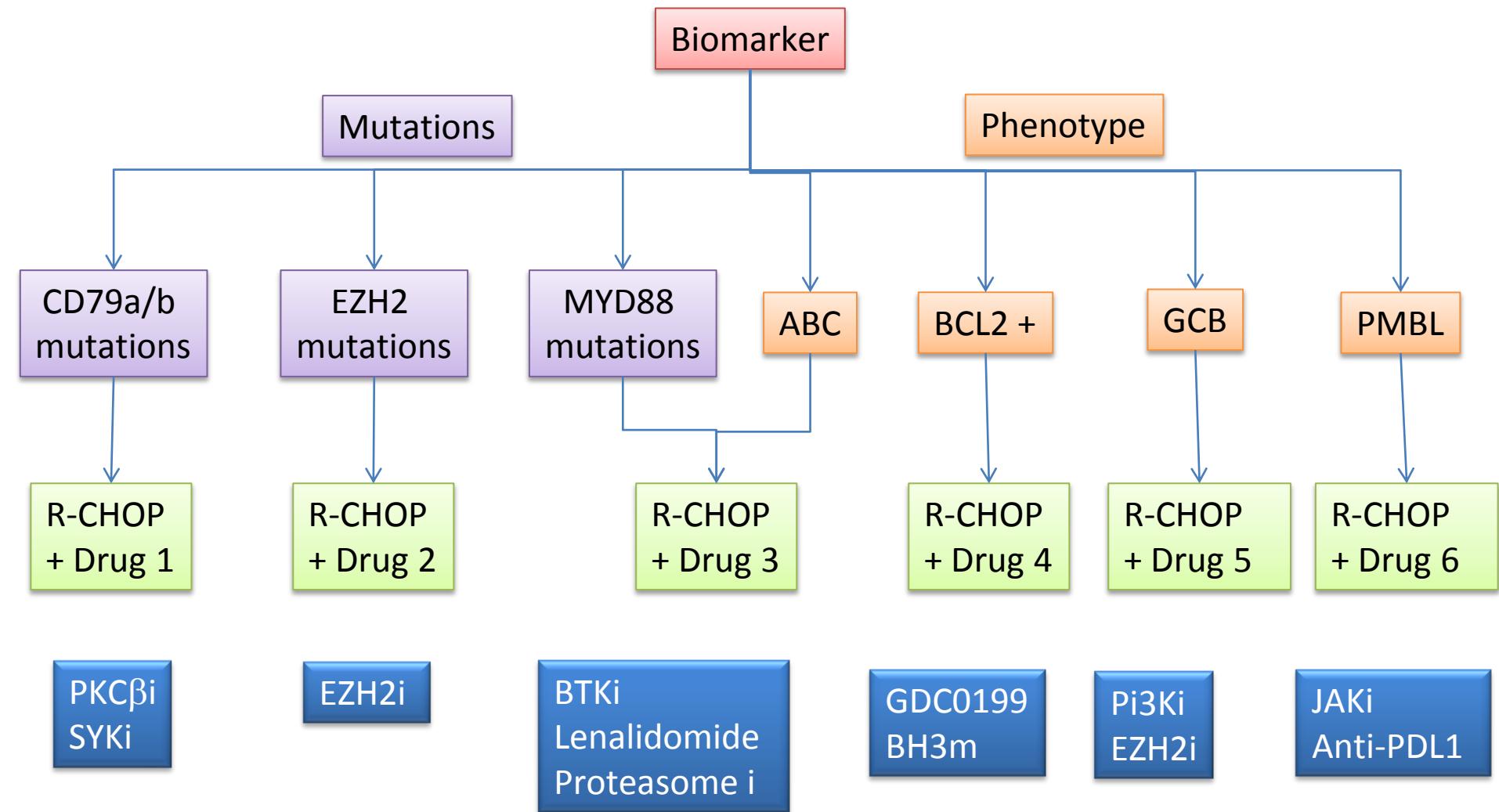
EZH2 inhibitors and R-CHOP



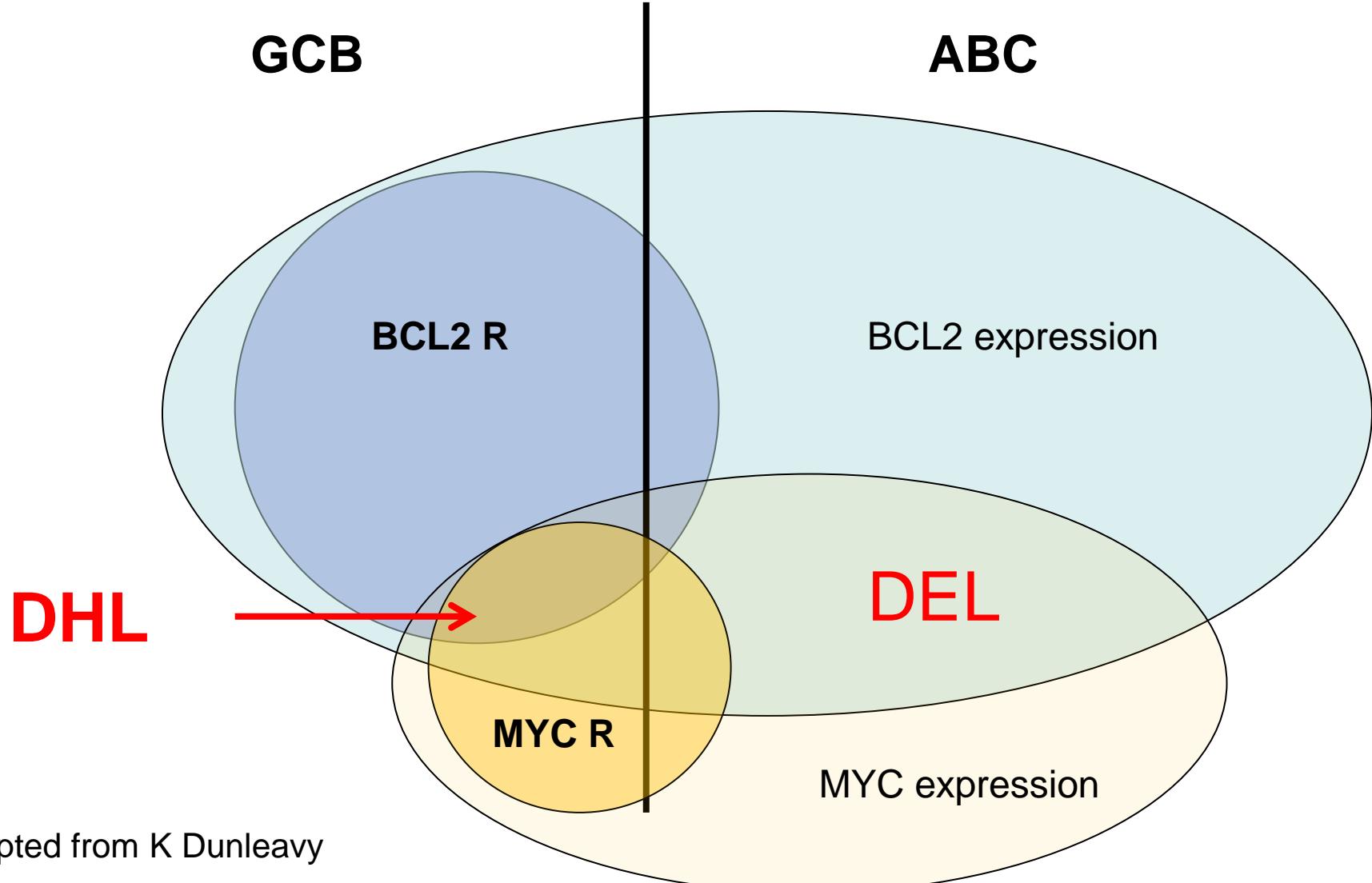
Ribrag V et al. ICML 2014.



Targeted frontline combinations



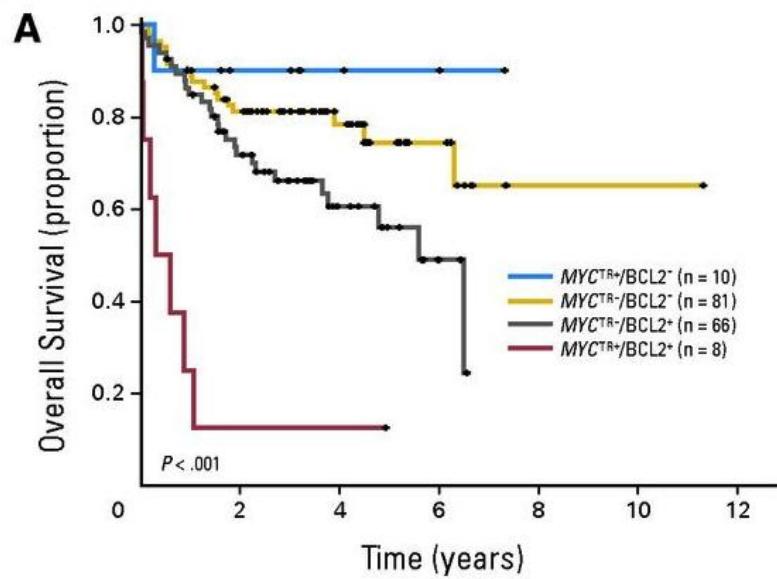
MYC and BCL2



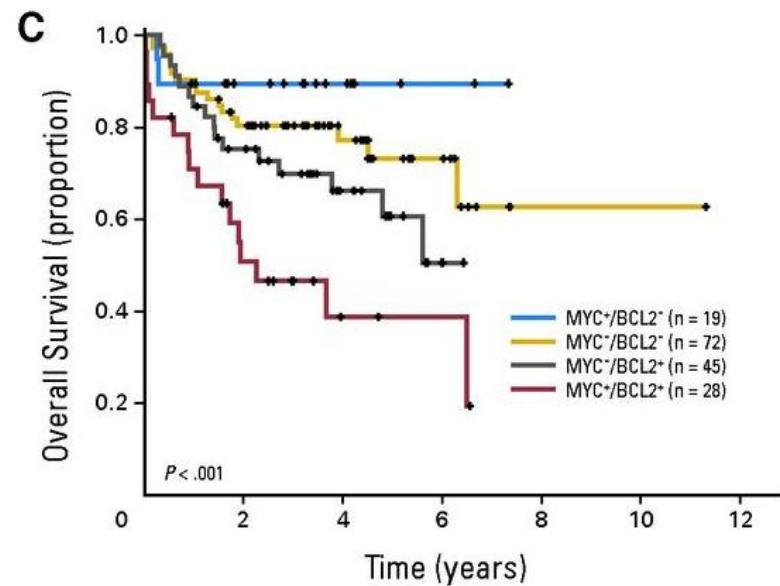
Adapted from K Dunleavy

MYC and BCL2

Translocation



Expression



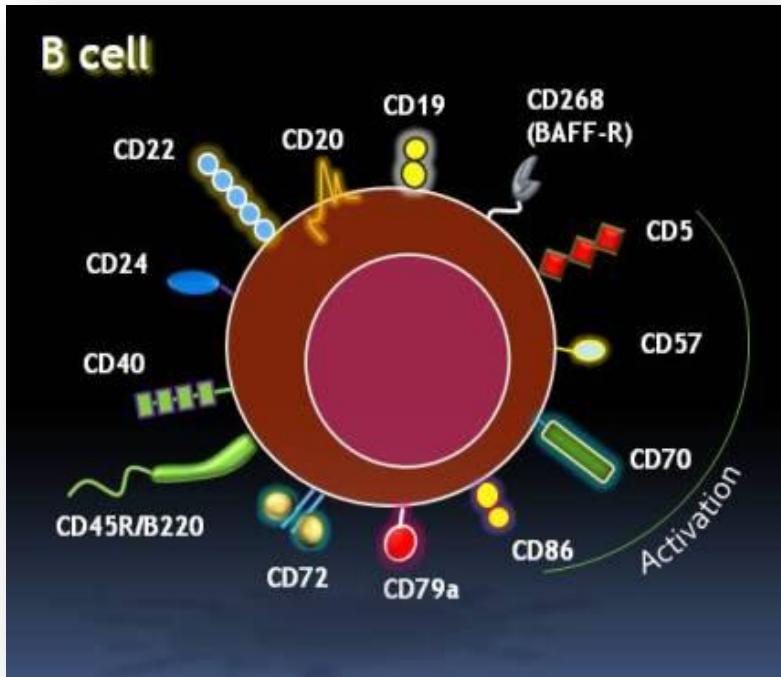
Rearrangement	MYC	BCL2	BCL6
%	10-15%	20%	30%

Double or triple hit < 5%

Comment améliorer le R-CHOP ?

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 - Maladie résiduelle
- Prendre en compte la biologie
 - GC ou ABC
 - Mutations à cibler
 - MYC et double hit
 - Antigènes de surface : anticorps
 - Immunologie
 - Autres voies, épigénétique,...

Targeted therapies in DLBCL: antibodies



- Better use of rituximab
- New anti CD20 antibodies
- New targets: anti CD19, CD22, CD79a, CD38 ...
- New conjugates: toxins, radiotherapy...
- New mechanisms: Anti-PD1, Anti-PDL1

Obinutuzumab phase III trials in DLBCL

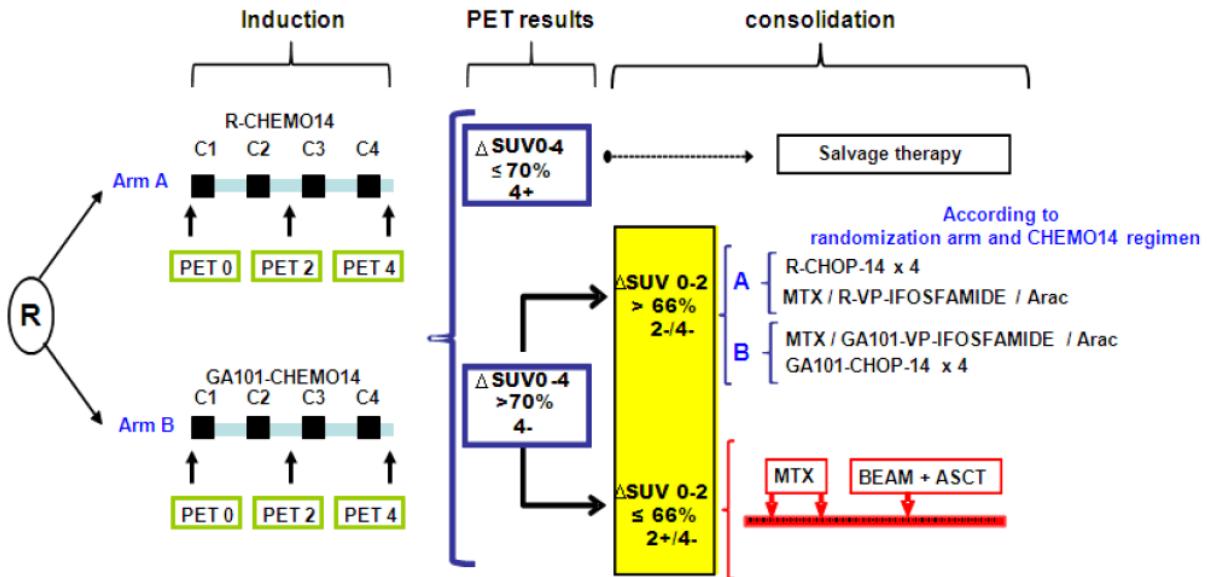
GOYA

Previously untreated CD20+ DLBCL (n=1400)

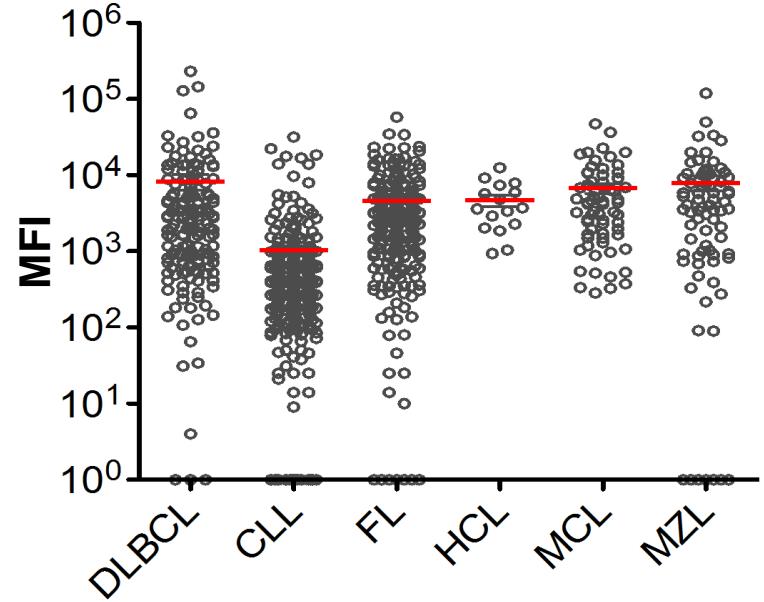
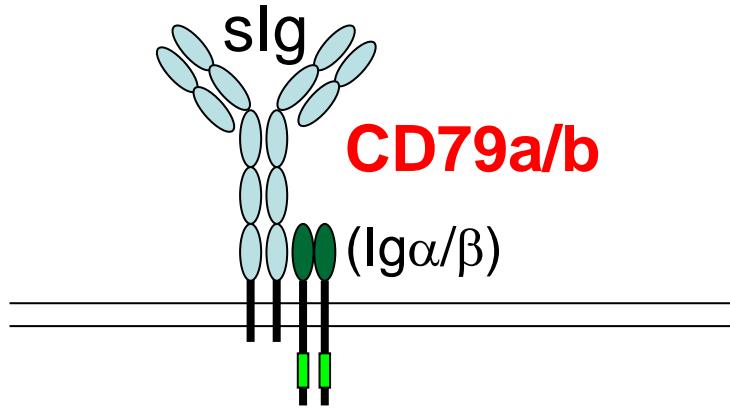
Obinutuzumab 1000 mg + CHOP x 6 or 8 (n=700)

Rituximab 375 mg/m² + CHOP x 6 or 8 (n=700)

**GAINED
(PET-driven)**



Polatuzumab + R-CHP



Phase 1b/2

Newly diagnosed DLBCL
Age 60-80
Age-adjusted IPI : 2-3

Comment améliorer le R-CHOP ?

- Modulation en fonction de la réponse
 - TEP intermédiaire
 - Maladie résiduelle
- Prendre en compte la biologie
 - GC ou ABC
 - Mutations à cibler
 - MYC et double hit
 - Antigènes de surface : anticorps
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Conclusion

- Le traitement de première ligne reste essentiel dans les lymphomes B à grandes cellules
- Le R-CHOP reste aujourd’hui un standard pour la plupart des patients
- C’est une association qui permet de recevoir de nouvelles molécules

Merci

