La TEP dans le lymphome
Impacts cliniques en 2017

Olivier Casasnovas

Hématologie Clinique – CHU Dijon

Incidence and Anatomic Regions Detected by FDG PET Relation to Histologic Types According to World Health Organization Classification

Histology	No. of patients/Total					
	Total no. (%)	Head and neck	Chest	Abdomen	Pelvis	Others
ALCL	25/25 (100)	9/9	3/3	3/3	2/2	8/8
AITL	34/34 (100)	12/12	8/8	10/10	2/2	2/2
NK/T-nasal	30/30 (100)	9/9	6/6	5/5	1/1	9/9
PTCL	54/55 (98)	20/20	10/11	9/9	6/6	9/9
Burkitt	21/21 (100)	2/2	6/6	5/5	3/3	5/5
DLBCL	268/276 (97)	79/81	41/43	60/61	28/28	60/63*
FL	175/193 (91)	55/58	38/43	34/39	40/42	8/11†
MALT‡	89/109 (82)	28/30	16/19	10/11	5/7	30/42§
SMZL	10/19 (53)	2/3	1/2	4/9	3/5	0/0
MCL	51/51 (100)	23/23	9/9	6/6	9/9	4/4
SLL	9/18 (50)	3/6	4/5	2/4	0/3	0/0
HL	73/75 (97)	31/31	23/24	11/12	2/2	6/6
Subcutaneous panniculitis-like T	5/7 (71)	0/0	0/2	0/0	2/2	3/3
Total no. (%)	844/913 (92.4)	273/284 (96.1)	165/181 (91.2)	159/174 (91.4)	103/112 (92.8)	144/162 (88.9)

35%

10%

Maximum Standardized Uptake Value in Four Types of Lymphoma

Histology	Median SUV max
NK/T-cell lymphoma	9.4
DLBCL	9.9
Indolent B-cell lymphoma	3.3*
HL	6.6†

Tsukamoto et al Cancer 2007; 110: 652

Why using PET in curable lymphoma?

- We need
  - a precise determination of initial disease extent
  - knowledge about prognostic and predictive factors
  - accurate and early assessment of responsiveness to therapy

- In order to
  - Improve the cure rates in patients with risk factors
  - Reduce toxicity of treatment
  - Optimize the balance between the risk of overtreatment and undertreatment

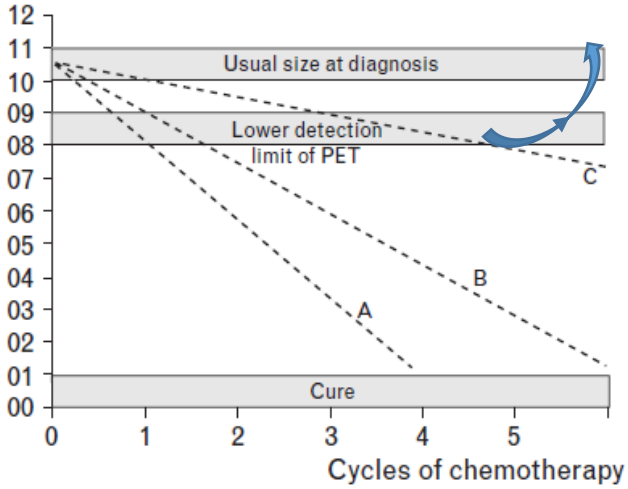
PET can satisfy some of these needs
Staging / Response assessment / Prognosis

Impact de la réponse intérimaire

Interim PET

- Much more than CT which measures the tumor size, functionnal imaging which evaluates the activity of the tumor cells appears to be more relevant for early response assessment

- PET allows analyzing during treatment a continuous metabolic process
  - PET after 1 or 2 cycles:
    - Analyses the response of cells with the highest level of proliferation
    - Identifies early responding patients (chemosensitivity)
    - A negative PET is not required
  - PET after 3 to 4 cycles:
    - Allows identifying tumor re-growth
    - Identifies late responding patients



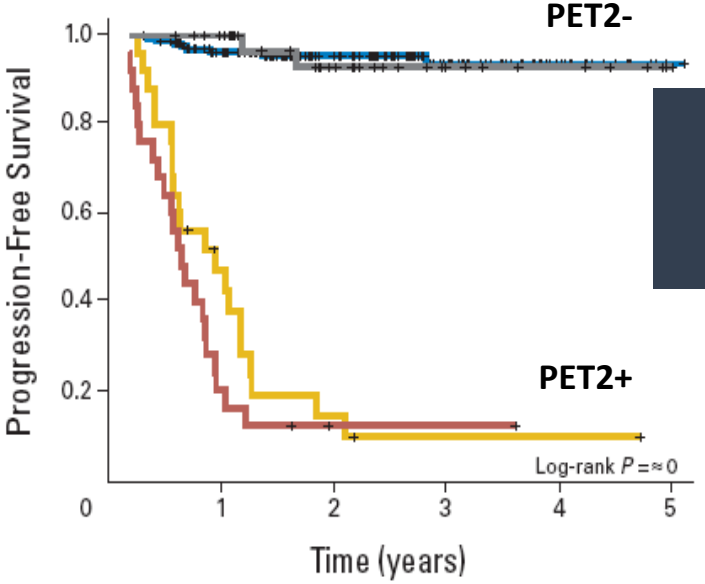
Y Kasamon et al, Curr Opin Oncol 2008; 20: 206

Adapter le traitement selon la réponse intérimaire

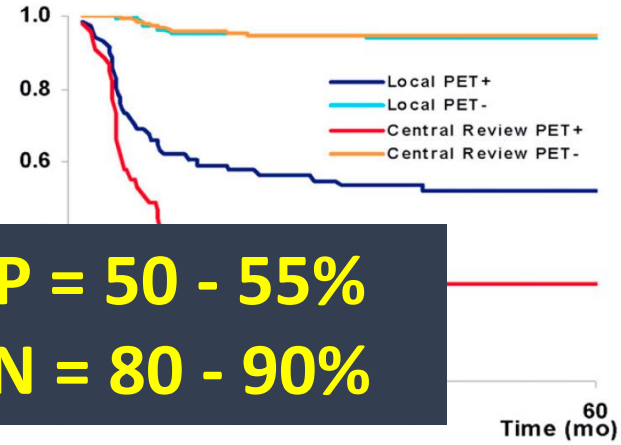
- Désescalader le traitement des patients chimiosensibles (iPET-): limiter la toxicité à long terme avec un contrôle tumoral identique

- Escalader le traitement des patients répondeurs lents (iPET+): réverser le pronostic péjoratif des iPET+

Prognosis value of early PET interpreted according to 5PS in HL

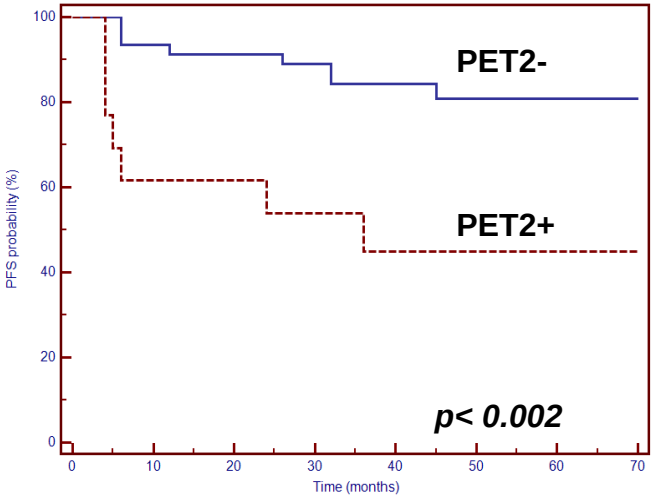


Gallamini A, JCO 2007; 25: 3746



VPP = 50 - 55%
VPN = 80 - 90%

Biggi, JNM 2013



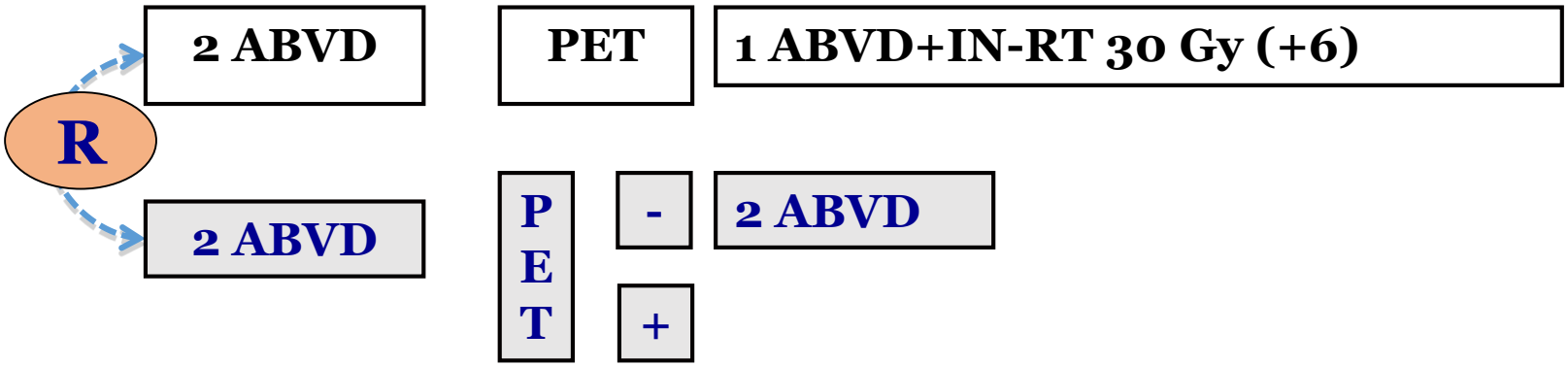
Rossi, JNM 2014

Peut-on se passer de la radiothérapie?

EORTC/LYSA
Médiastin/Thorax > 0.35 ≥ 4 aires ganglionnaires B et VS ≥ 30 ou A et VS ≥ 50 Age ≥ 50

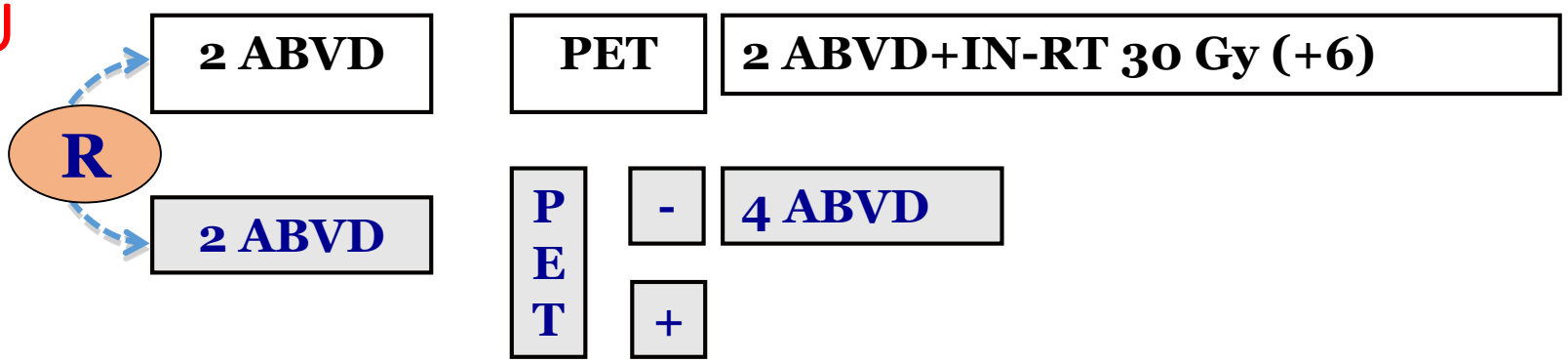
PET2- = 83% (465/562)

H10F

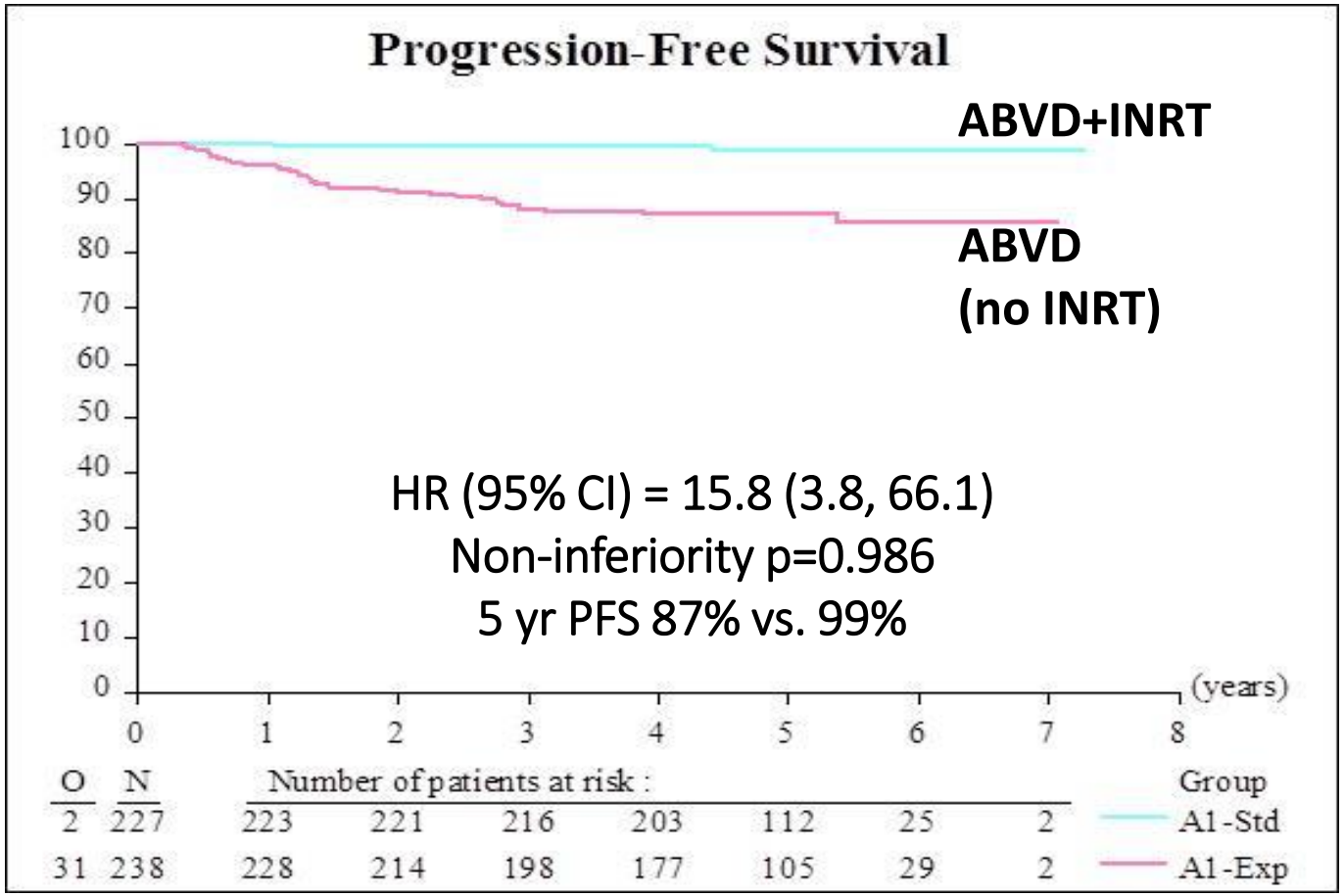


PET2- = 70% (594/858)

H10U



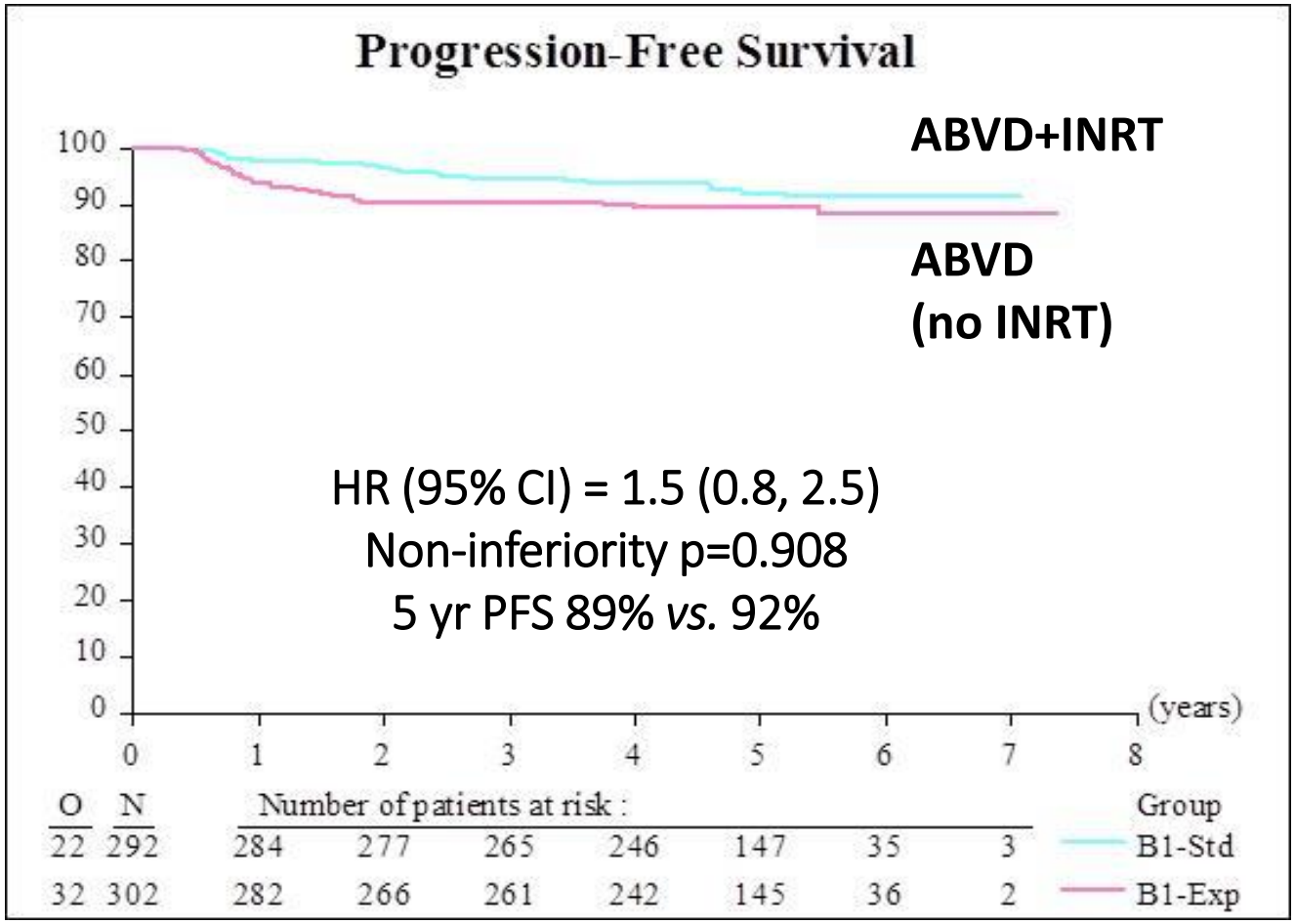
PET negative group: no INRT *vs.* ABVD+INRT
FAVORABLE: PFS



HR: Hazard Ratio ABVD no INRT *vs.* ABVD+INRT

M. André, JCO 2017

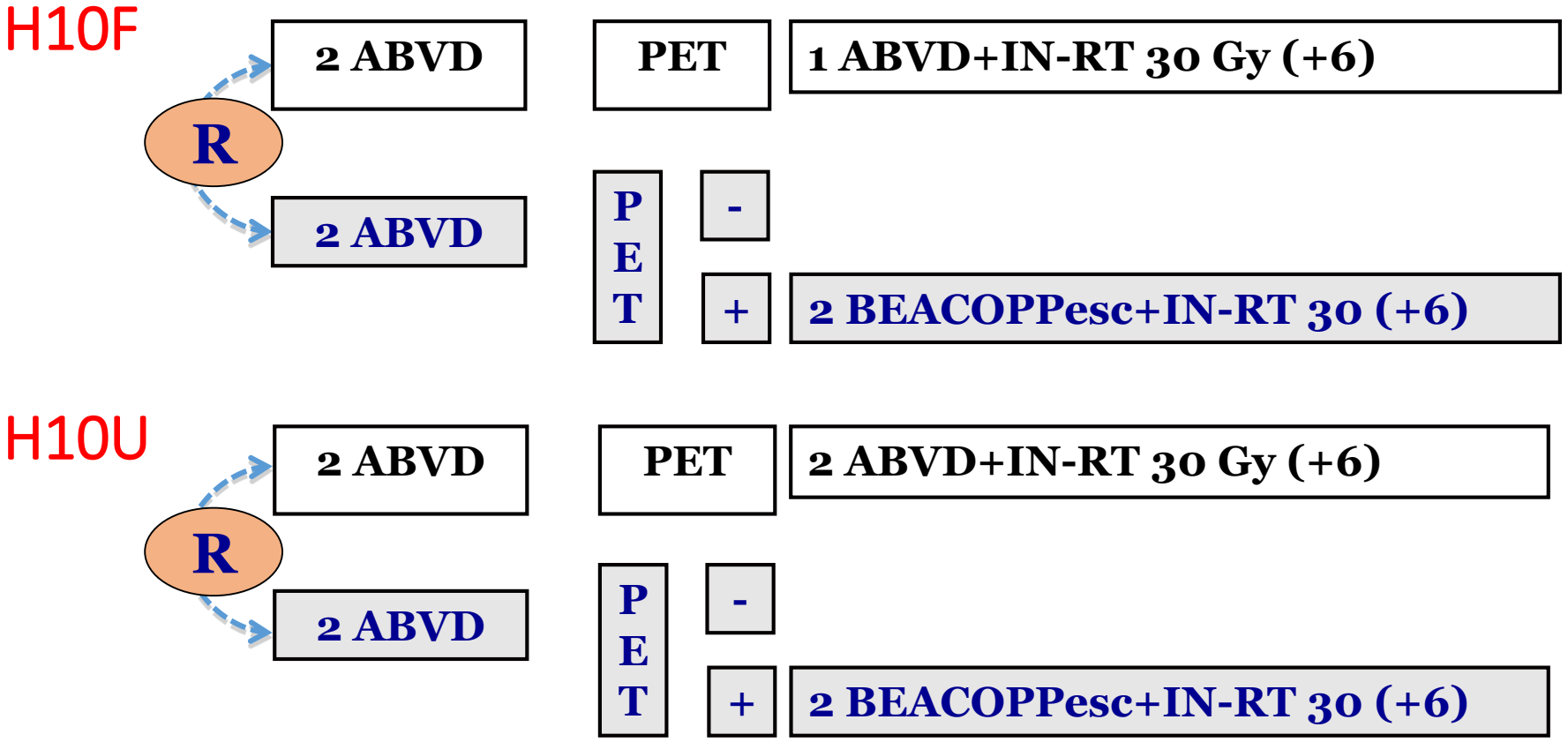
PET negative group: no INRT *vs.* ABVD+INRT
UNFAVORABLE: PFS



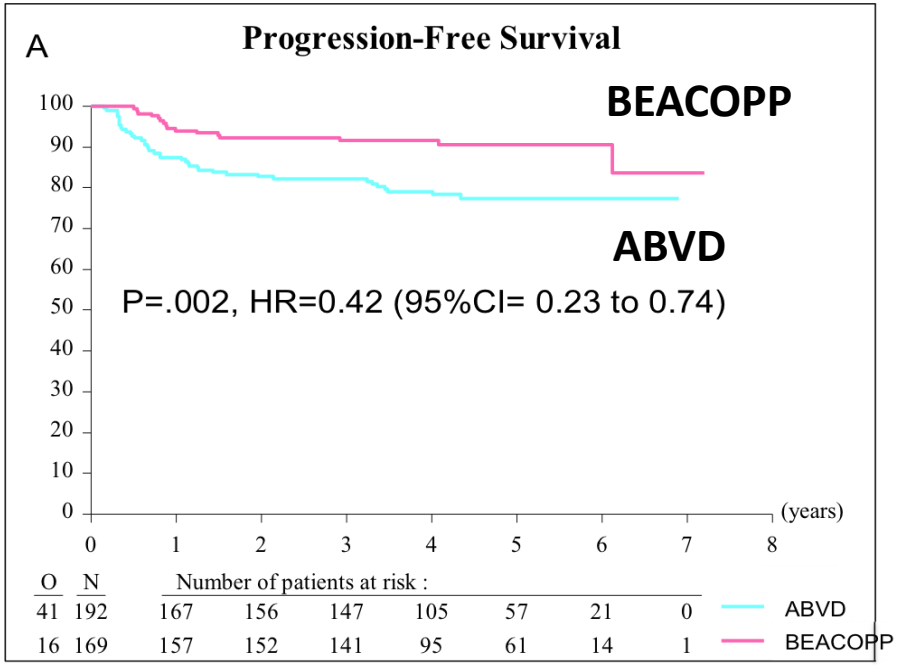
HR: Hazard Ratio ABVD no INRT *vs.* ABVD+INRT

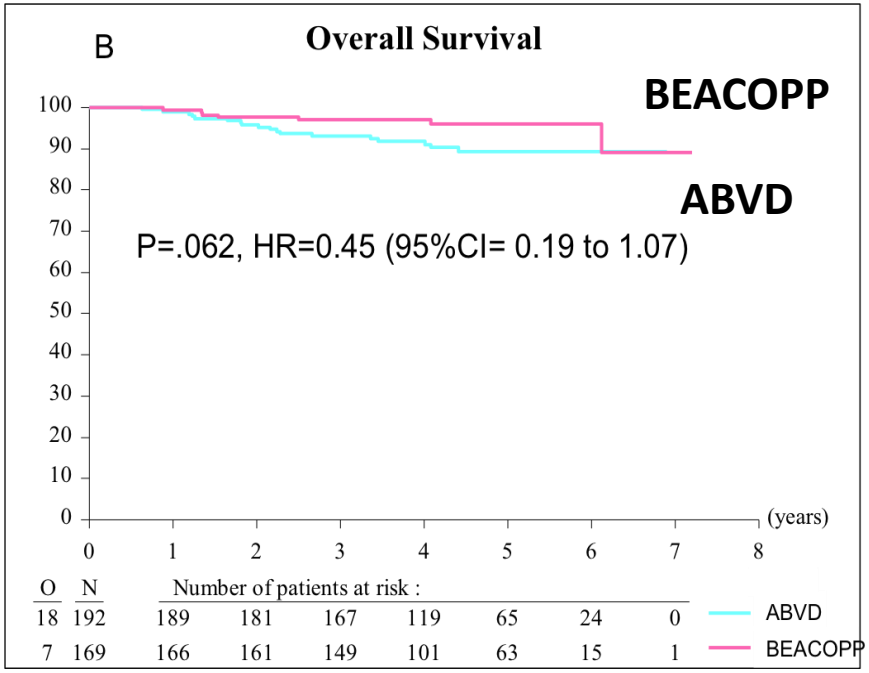
M. André, JCO 2017

Doit on escalader les TEP2+?



H10 trial: outcome of PET2 positive patients according to treatment arm





M André et al JCO 2017

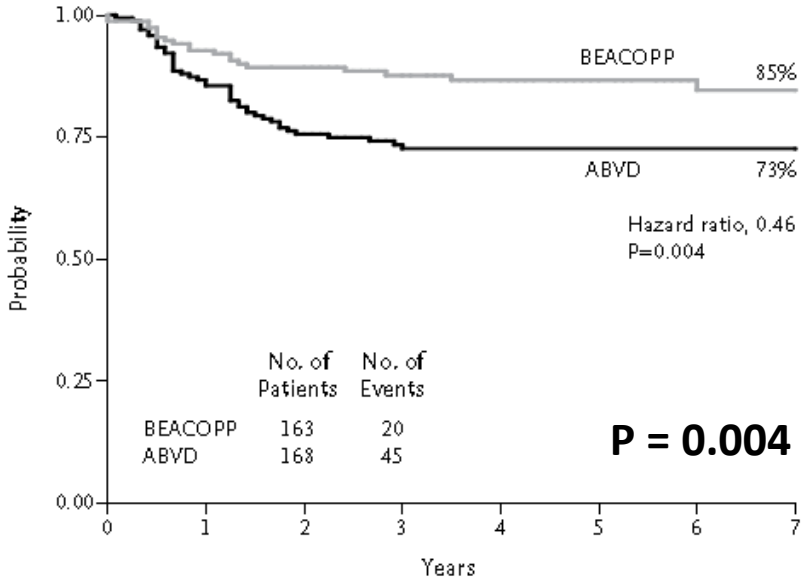
BEACOPP vs ABVD in advanced HL

Stage IIB- IV

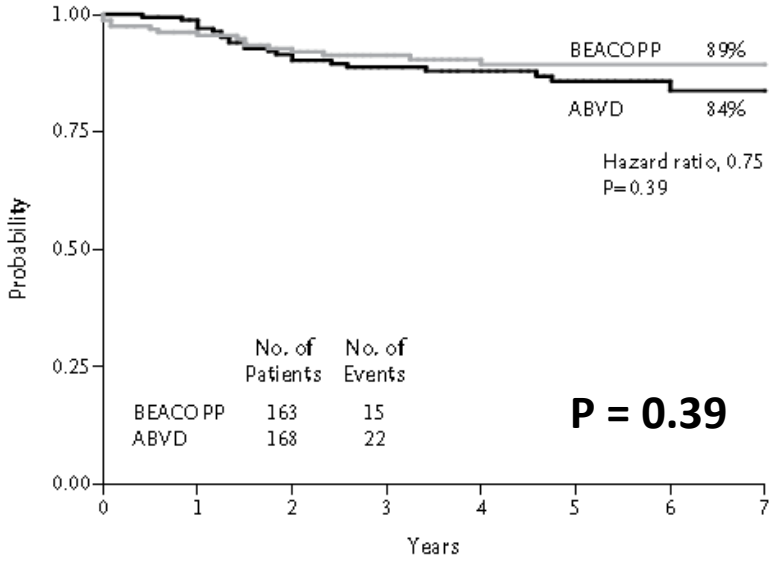
BEACOPP [esc x 4 + Baseline x 4] vs ABVD x 6/8

Median FU = 61 months

PFS



OS

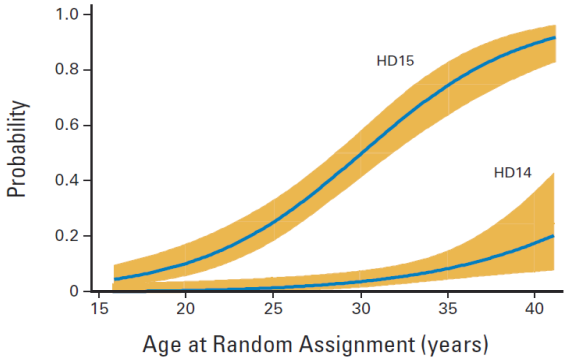


Viviani S, NEJM 2011; 365: 203

BEACOPPesc: toxicité long terme

- Infertilité **Behringer K, JCO, 2013**

Aménorrhée 4 ans après fin Chimio

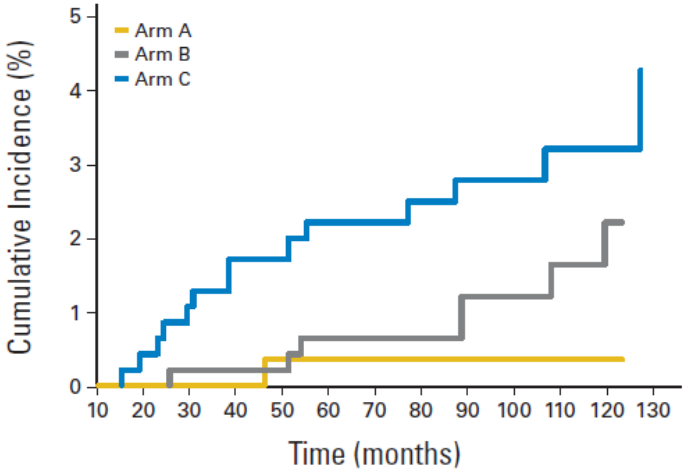


6-8 BEACOPPesc

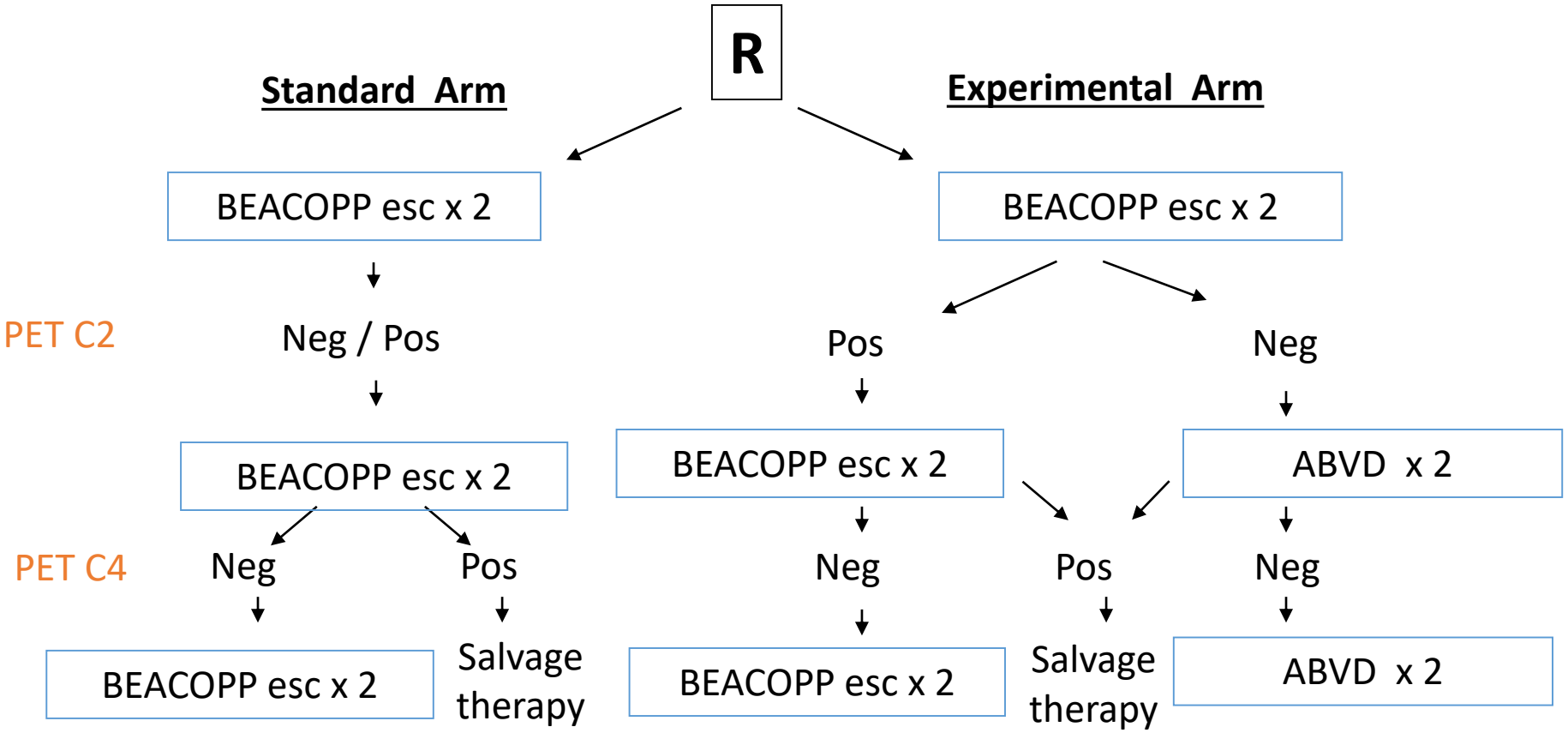
2 BEACOPPesc + 2 ABVD
ou 4 ABVD

- LAM / MDS secondaires

Engert A, JCO 2009



AHL 2011



Non inferiority of the experimental arm
Standard arm : 85% 5y-PFS ; Experimental arm: 5y-PFS > 75% (HR=1.77)

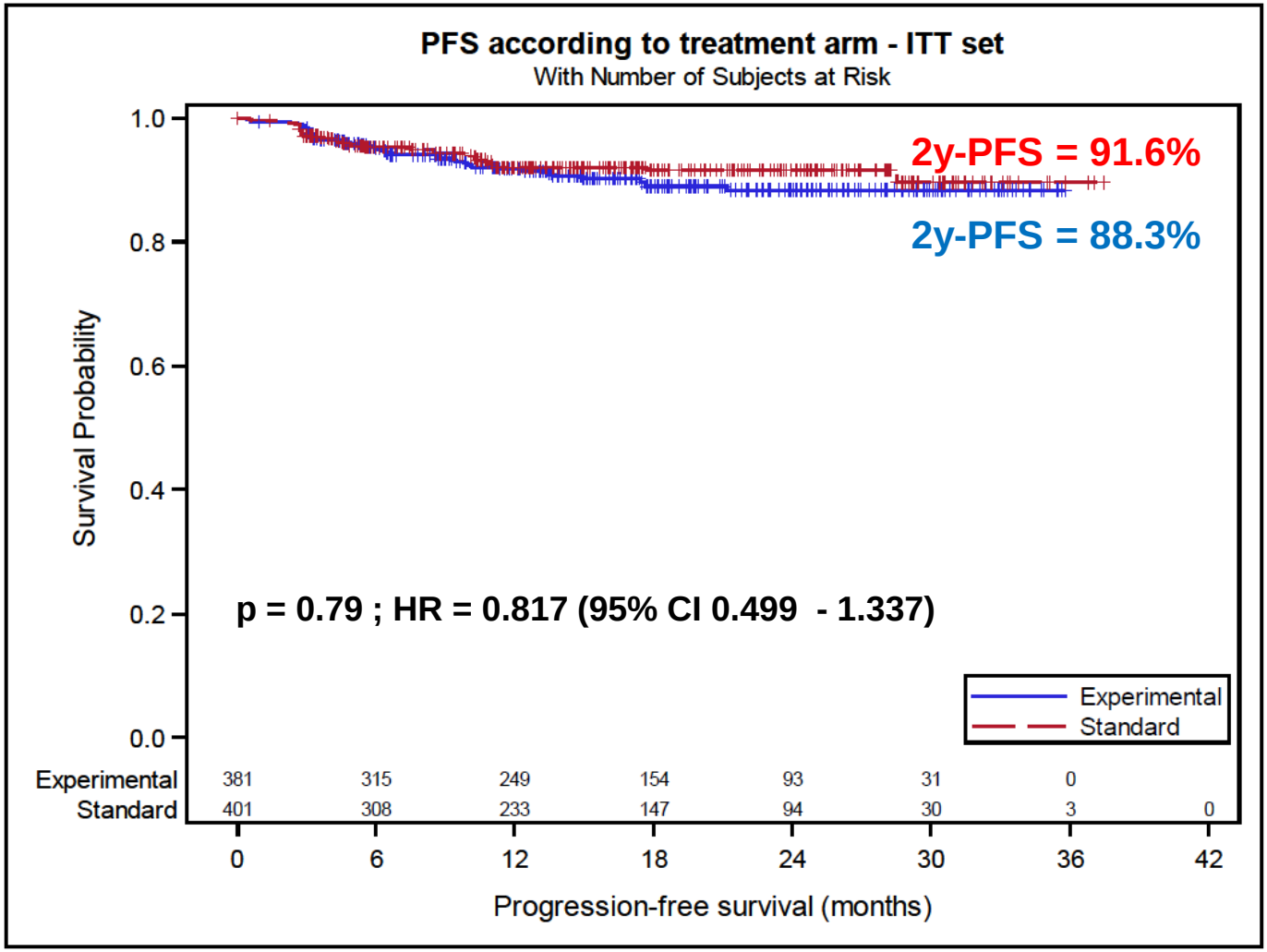
AHL2011: PET2 results (central review)

	Treatment arm					
	Standard		**Experimental**		**All**	
	n = 401		**n = 381**		**n = 782**	
PET2						
Evaluable	386	96%	368	97%	754	96%
Negative	**338**	**88%**	**319**	**87%**	657	87%
Positive	48	12%	49	13%	97	**13%**

In an intent to treat basis, 84% of patients received 2 x BEACOPPesc + 4 x ABVD in the experimental arm

Casasnovas RO, ASH 2015; Abs 577

AHL 2011: PFS according to treatment arm



Median follow-up = 16.3 months (0.1 – 37.4)

Lysa THE LYMPHOMA STUDY ASSOCIATION

Lysarc THE LYMPHOMA ACADEMIC RESEARCH ORGANISATION

Casasnovas RO, ASH 2015; Abs 577

AHL2011: interim PET results (central review)

		Treatment arm: Standard n = 401		Treatment arm: Experimental n = 381		All n = 782	
PET2							
	Evaluable	386	96%	368	97%	754	96%
	Negative	**338**	**88%**	**319**	**87%**	657	87%
	Positive	48	12%	49	13%	97	**13%**
PET4							
	Evaluable	373	93%	348	92%	721	92%
	Negative	**347**	**93%**	**332**	**95%**	679	94%
	Positive	26	7%	16	5%	42	**6%**

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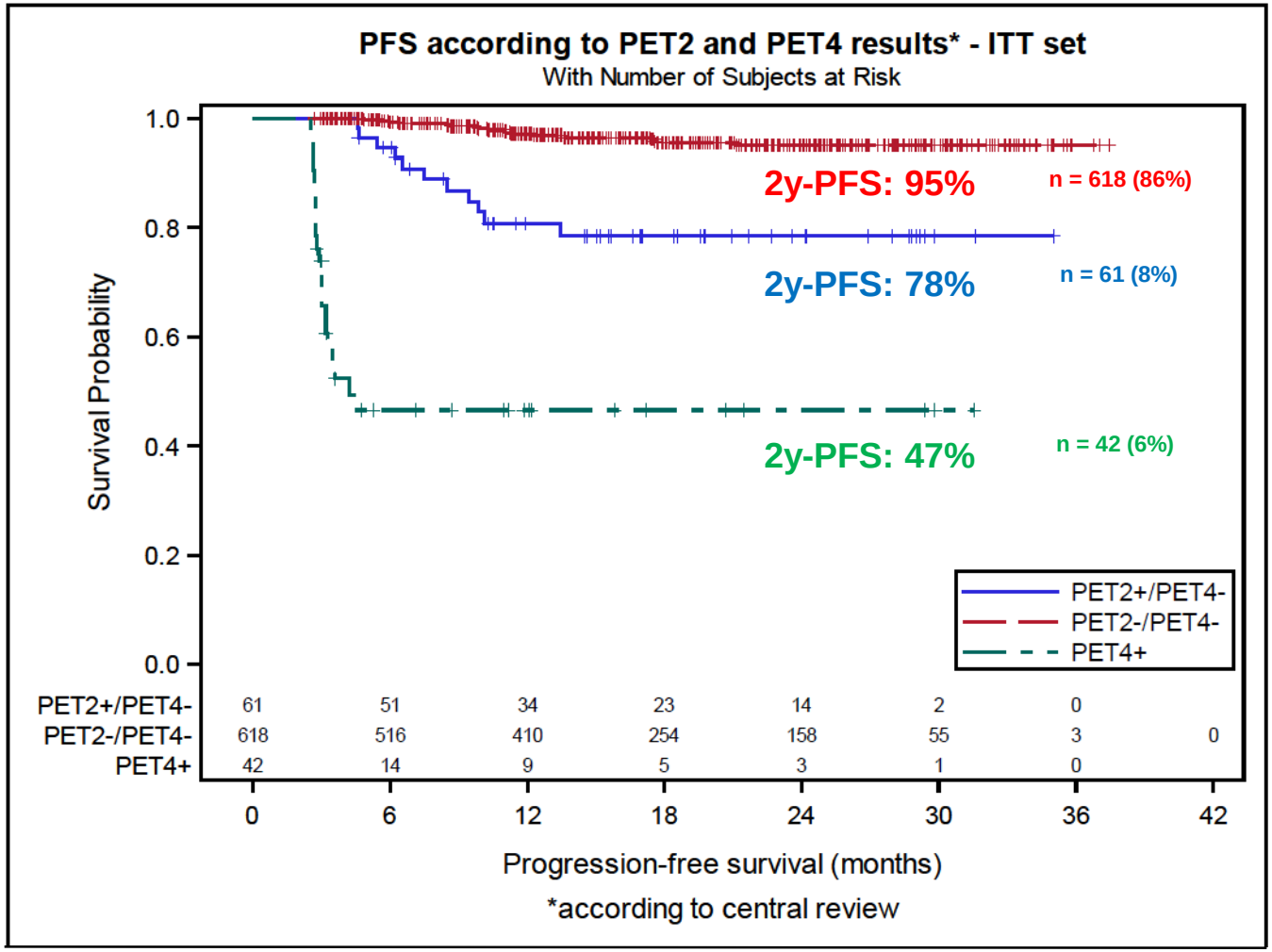
Casasnovas RO, ASH 2015; Abs 577

AHL 2011: PFS according to the PET driven strategy



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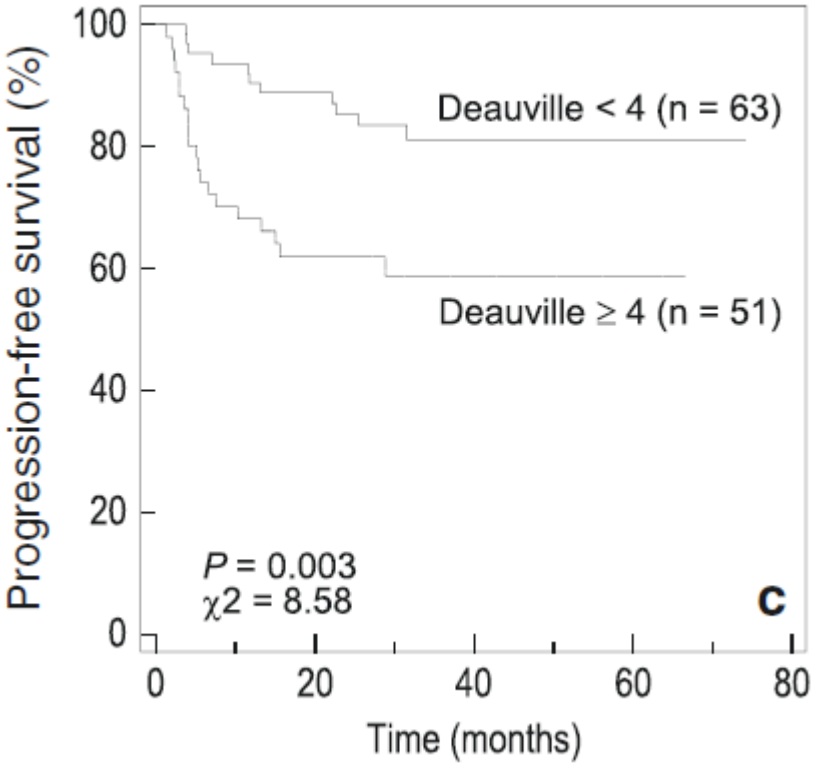
Casasnovas RO, ASH 2015; Abs 577

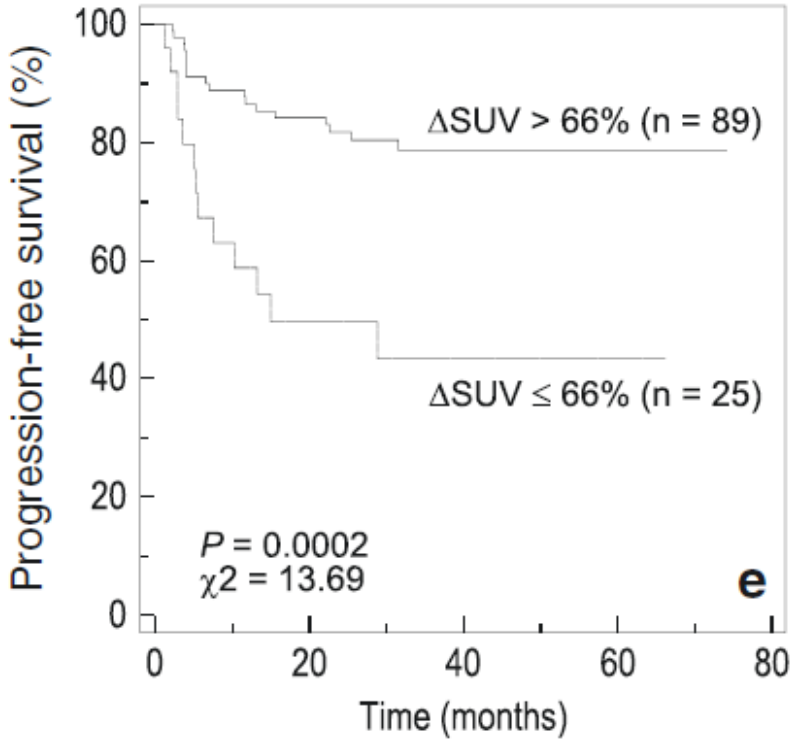
DLBCL International Validation Study (IVS) PET2 interpretation

114 DLBCL treated with R-Chemo – aaIPI = 2-3: 65%, aaIPI = 1: 29%
FU = 39 months



3y PFS : 81% v 59%

K = 0.66 (3 observers)



3y PFS : 80% v 40%

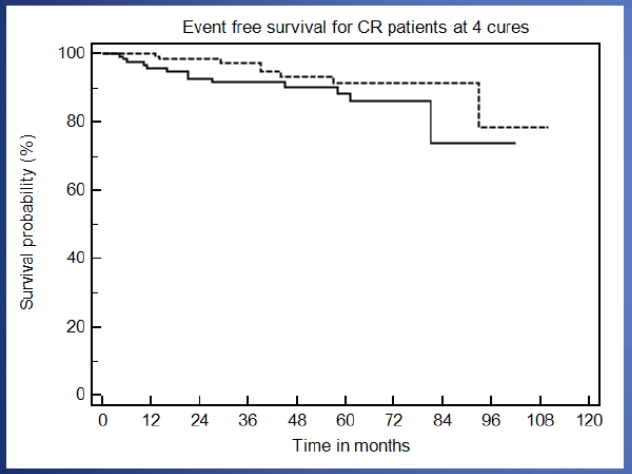
K = 0.83 (3 observers)

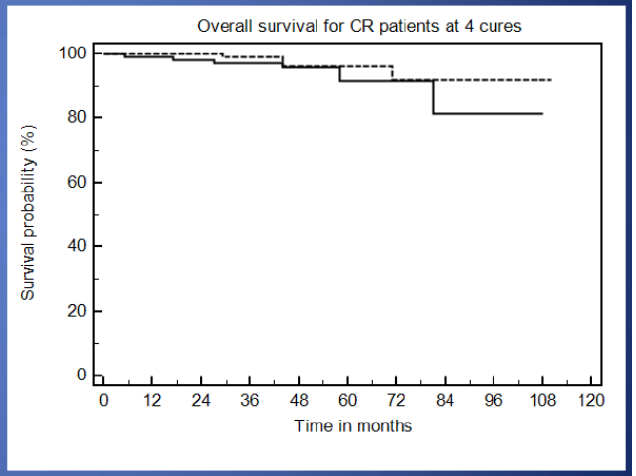
E. Itti et al, EJNM 2013

R-CHOP with or without Radiotherapy in Non-Bulky Limited-Stage DLBCL: Results of the Prospective Randomized Phase III 02-03 Trial from the Lysa/Goelams Group

EFS and OS for CR patients at C4

R-CHOP ------ R-CHOP + RT





HR 0.54 (95% CI 0.23 to 1.27), p=0.16

5y EFS 90 ± 2.3 % vs 88 ± 3.5 %

HR 0.54 (95% CI 0.16 to 1.75), p=0.31

5y OS 94 ± 2 % vs 91.7 ± 3.5 %

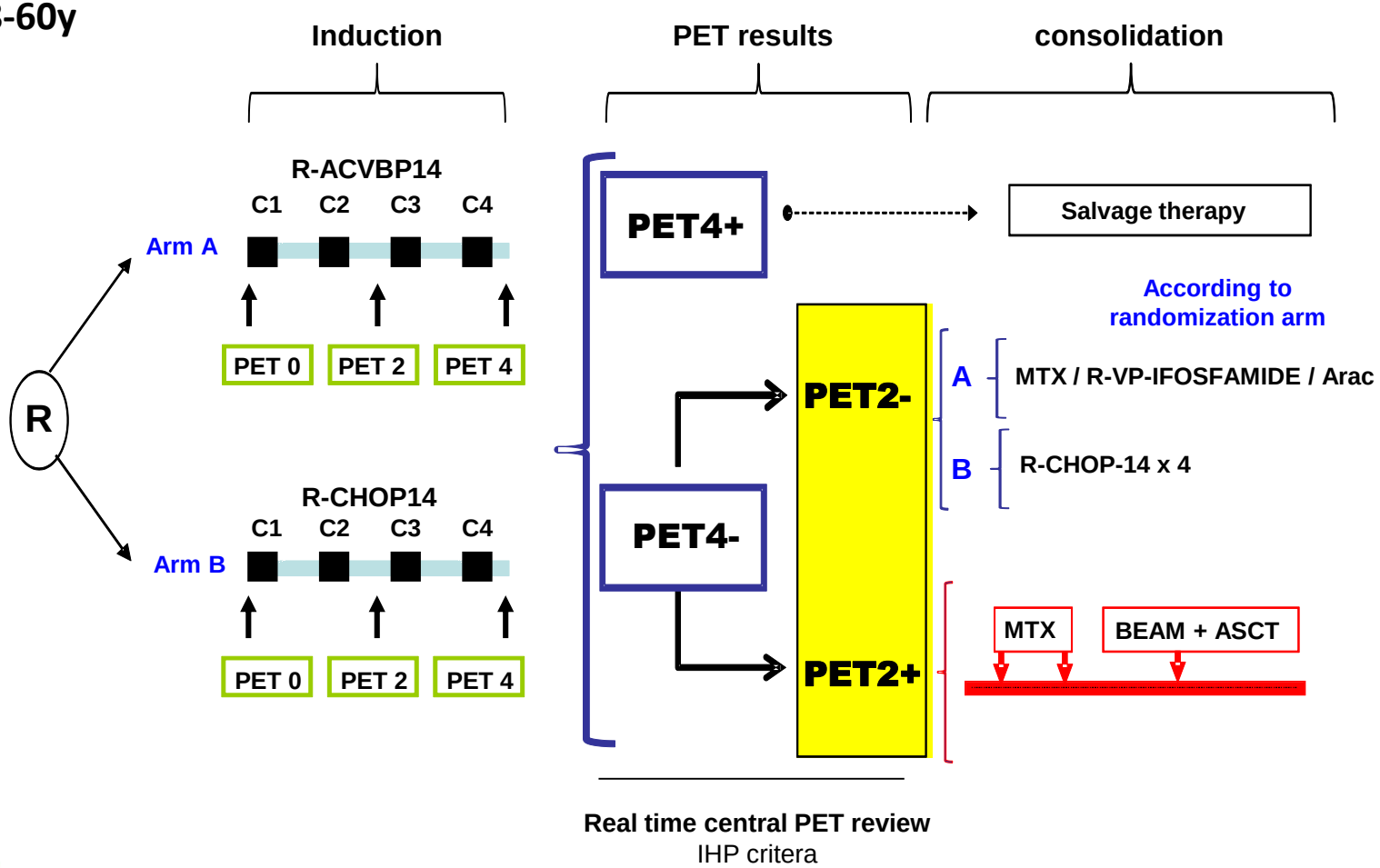
Radiotherapy can be avoided in PET4 negative patients without impairing outcome

T Lamy et al., ASH 2014, abstr 393

LNH 2007-3B

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

NCT00498043



Casasnovas et al, Blood 2011

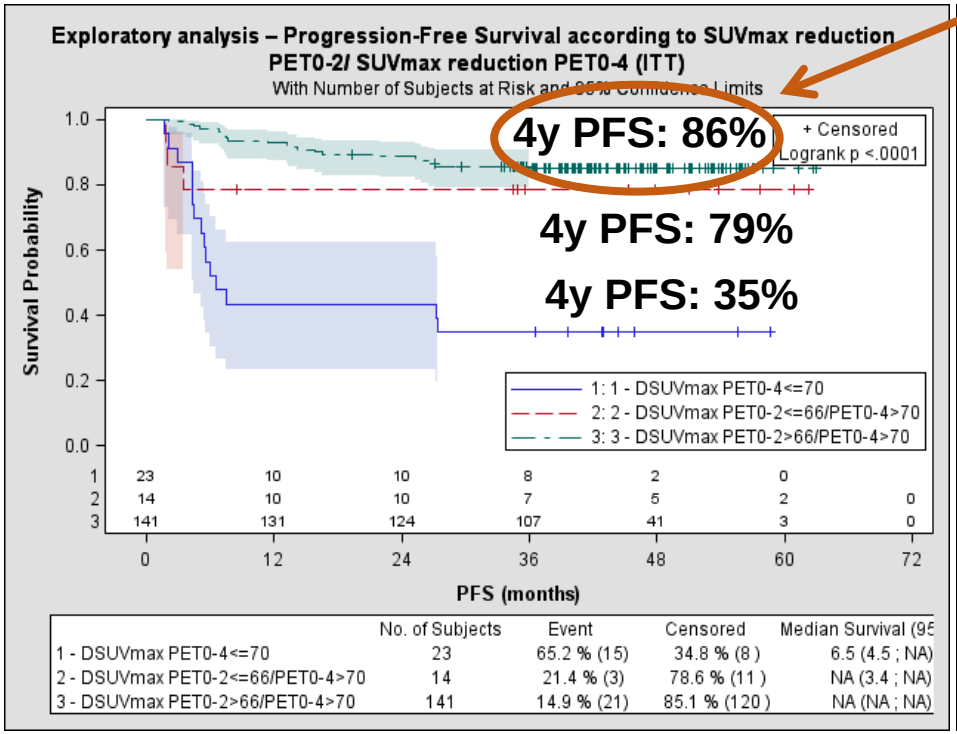
LNH 2007-3B: Actual Consolidation treatment

	ASCT	Chemo	Salvage
% of patients	24%	**26%**	50%
2y-PFS	87%	**83%**	75%

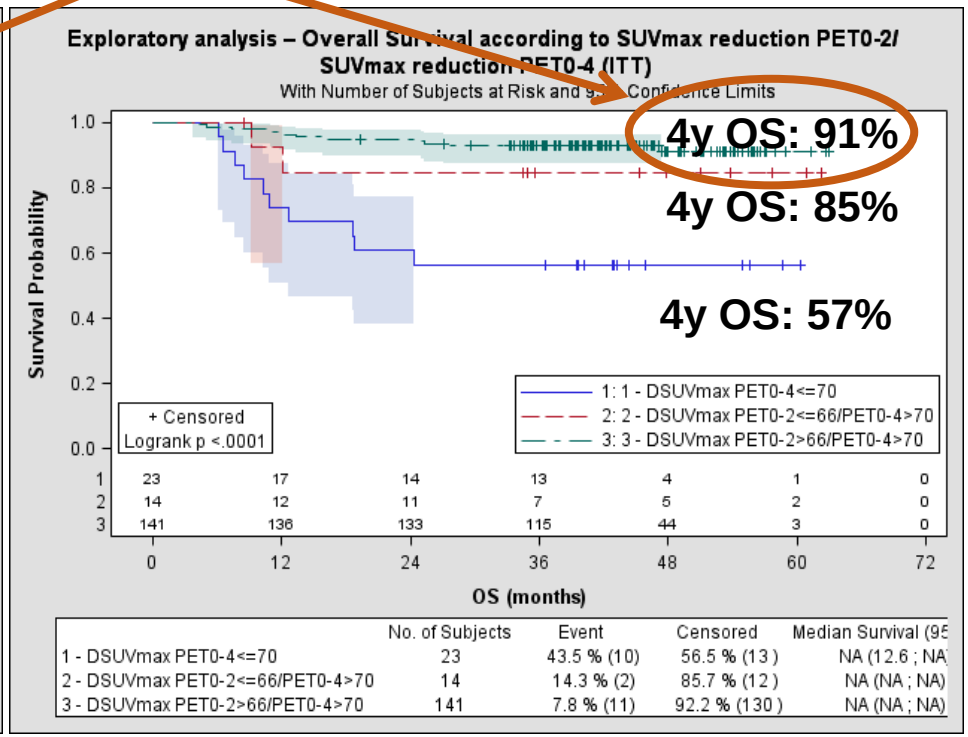
RO. Casasnovas et al, ASCO 2014; Abstr 8503

LNH 2007-3B
Outcome according to ΔSUVmax PET0-2 and PET0-4

80% of the whole population



	No. of Subjects	Event	Censored	Median Survival (95
1 - DSUVmax PET0-4<=70	23	65.2 % (15)	34.8 % (8)	6.5 (4.5 ; NA)
2 - DSUVmax PET0-2<=66/PET0-4>70	14	21.4 % (3)	78.6 % (11)	NA (3.4 ; NA)
3 - DSUVmax PET0-2>66/PET0-4>70	141	14.9 % (21)	85.1 % (120)	NA (NA ; NA)

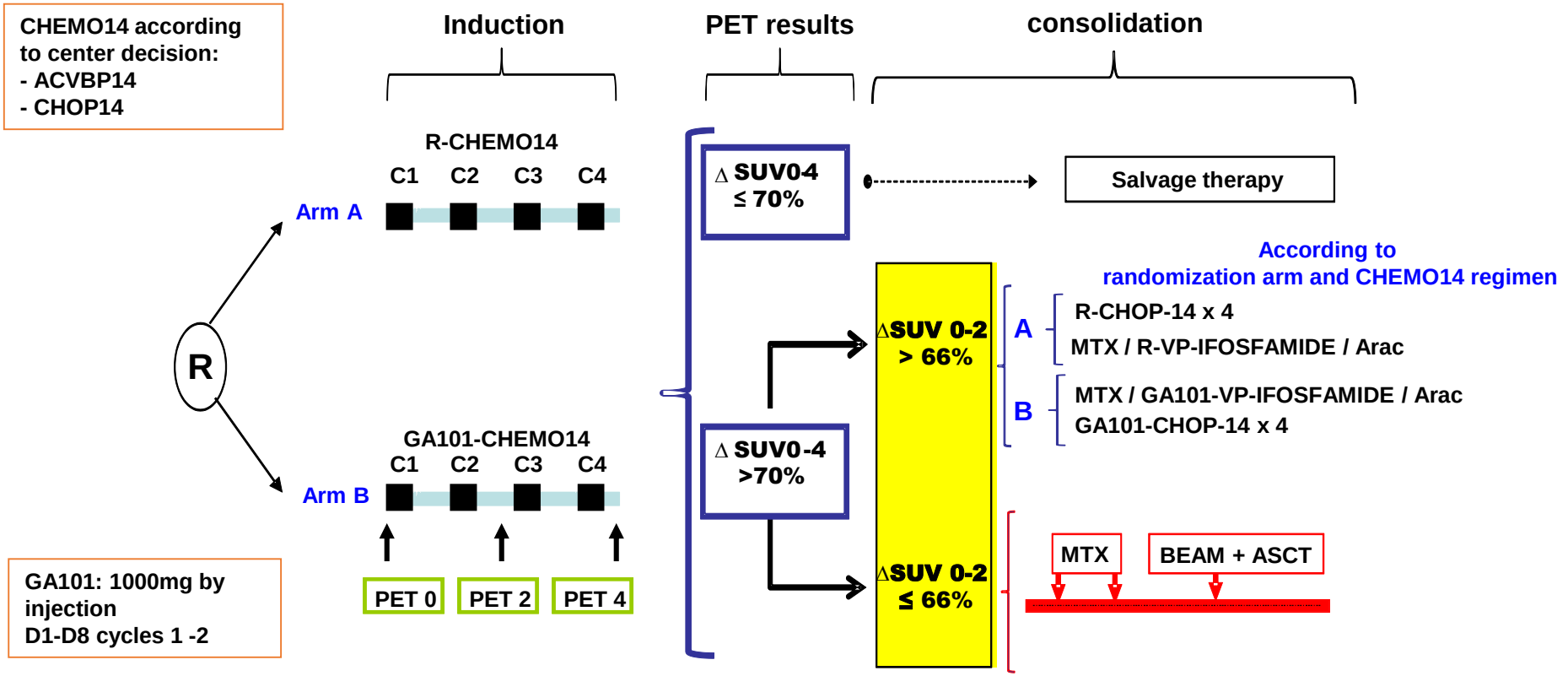


	No. of Subjects	Event	Censored	Median Survival (95
1 - DSUVmax PET0-4<=70	23	43.5 % (10)	56.5 % (13)	NA (12.6 ; NA
2 - DSUVmax PET0-2<=66/PET0-4>70	14	14.3 % (2)	85.7 % (12)	NA (NA ; NA)
3 - DSUVmax PET0-2>66/PET0-4>70	141	7.8 % (11)	92.2 % (130)	NA (NA ; NA)

RO. Casasnovas et al, ASCO 2014; Abstr 8503

GA In NEwly Diagnosed DLBCL - GAINED

DLBCL, 18-60y, aaIPI= 1-3: Phase III – 2 arms



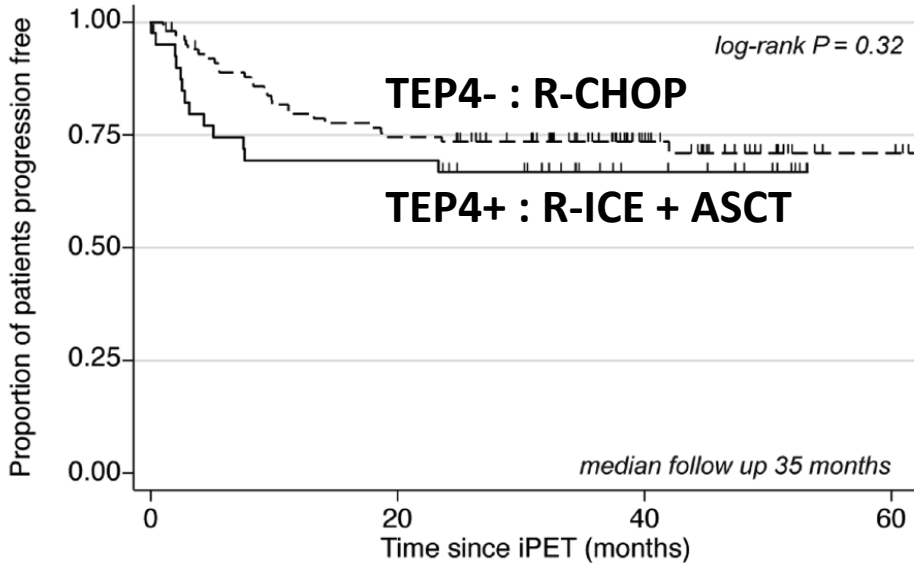
Early treatment intensification with R-ICE and 90Y-ibritumomab tiuxetan (Zevalin)-BEAM stem cell transplantation in patients with high-risk diffuse large B-cell lymphoma patients and positive interim PET after 4 cycles of R-CHOP-14

Mark Hertzberg,[1] Maher K. Gandhi,[2,3] Judith Trotman,[4] Belinda Butcher,[5] John Taper,[6] Amanda Johnston,[7] Devinder Gill,[3] Shir-Jing Ho,[8] Gavin Cull,[9] Keith Fay,[10] Geoff Chong,[11] Andrew Grigg,[12] Ian D. Lewis,[13] Sam Milliken,[14] William Renwick,[15] Uwe Hahn,[16] Robin Filshie,[17] George Kannourakis,[18] Anne-Marie Watson,[19] Pauline Warburton,[20] Andrew Wirth,[21] John F. Seymour,[22] Michael S. Hofman[23] and Rodney J. Hicks;[23] on behalf of the Australasian Leukaemia Lymphoma Group (ALLG)

Haematologica 2017
Volume 102(2):356-363

PFS

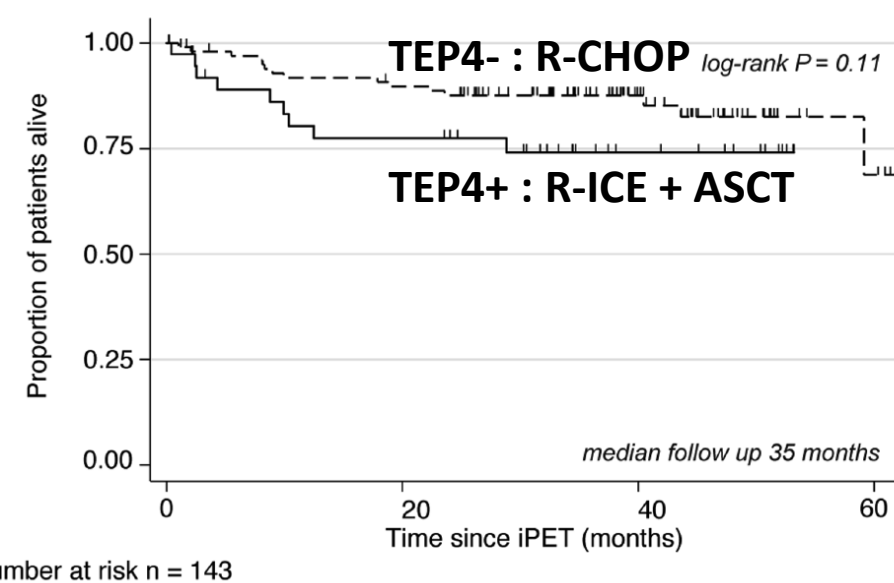
A



Number at risk n = 143						
iPET-positive	42	27	27	22	11	7
iPET-negative	101	80	73	62	32	13

OS

B



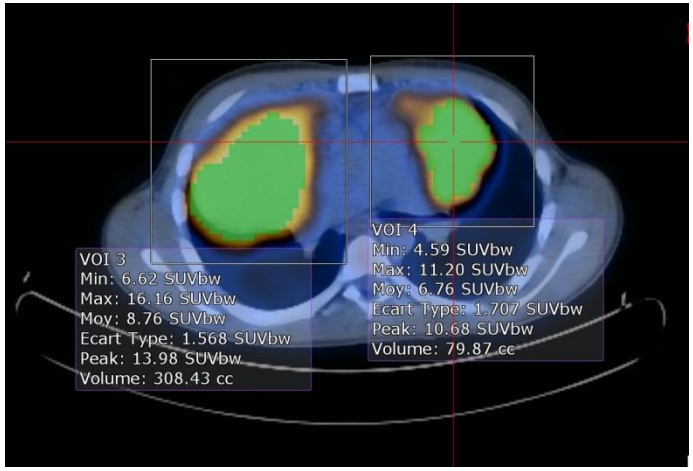
Number at risk n = 143						
iPET-positive	42	29	27	22	11	7
iPET-negative	101	89	86	71	38	15

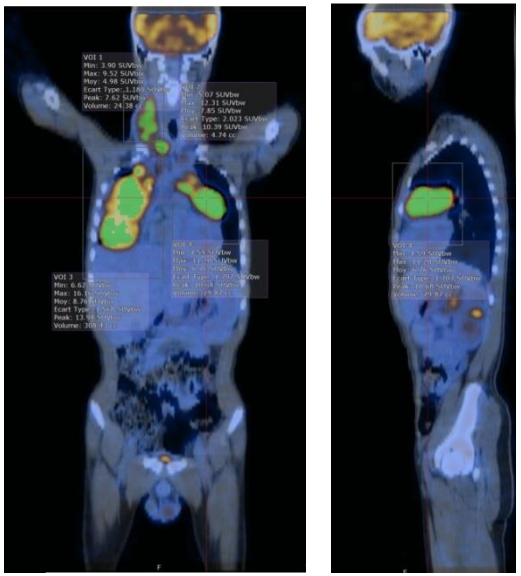
29% TEP4+ (IWG 2007)

Impact du volume métabolique

TMTV Assessment

- Using the Beth Israel Plug-in *(Kanoun S, PLoS One 2015)*
- A region of interest (ROI) was drawn around each foci FDG uptake.
- In each ROI, voxels presenting a threshold of 41% SUVmax were incorporated to define tumor volumes *(Meignan M, EJNM 2014)*
- Extranodal involvement :
  - the liver, lung and bone marrow were considered involved only if there was focal uptake,
  - Spleen involvement was considered if there was focal uptake or diffuse uptake >150 % of the liver background.
- All the individual tumors volume were added to compute the TMTV

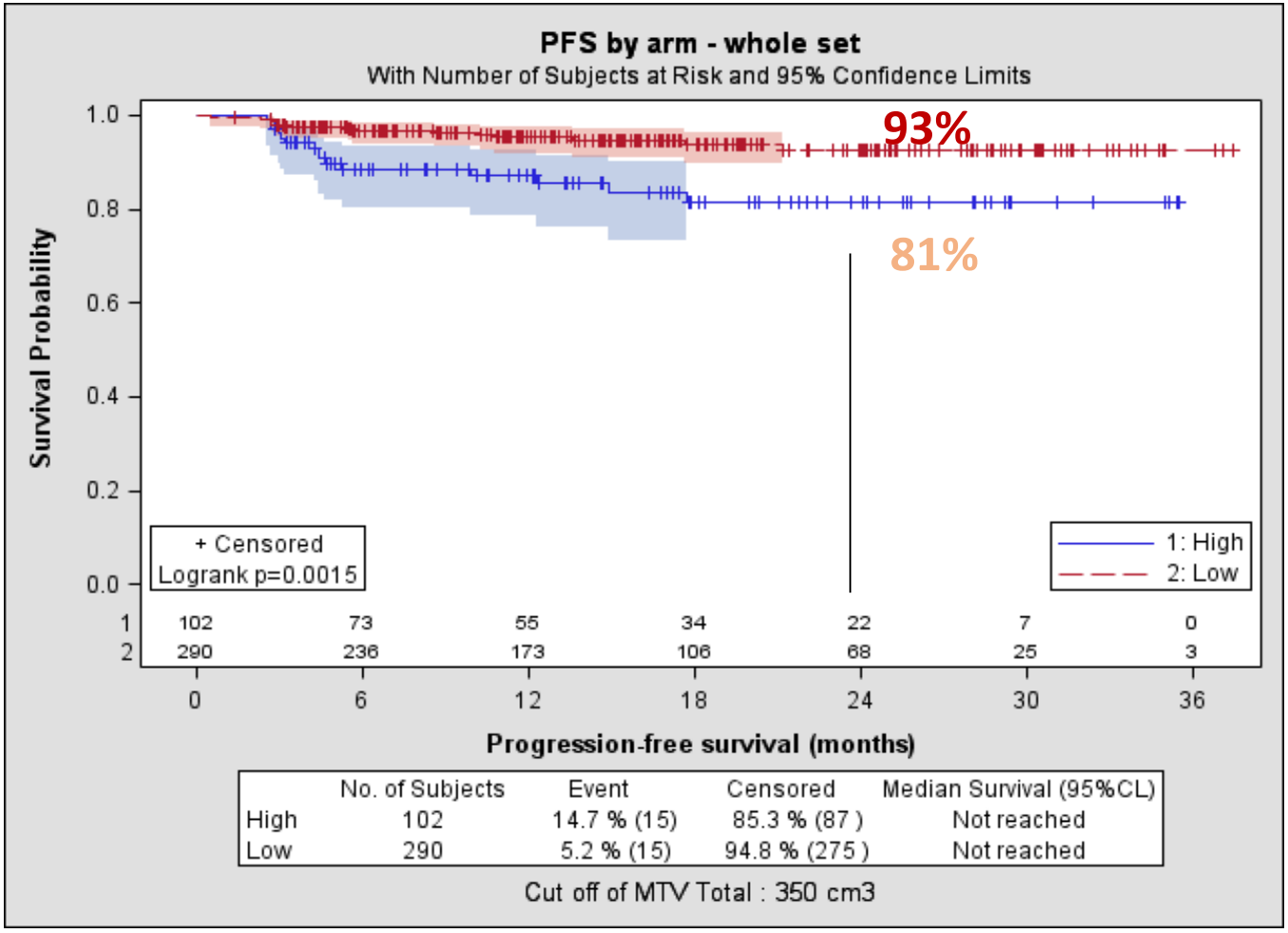




Casasnovas RO, ASCO 2016; Abs 7509

AHL2011

PFS according to the TMTV

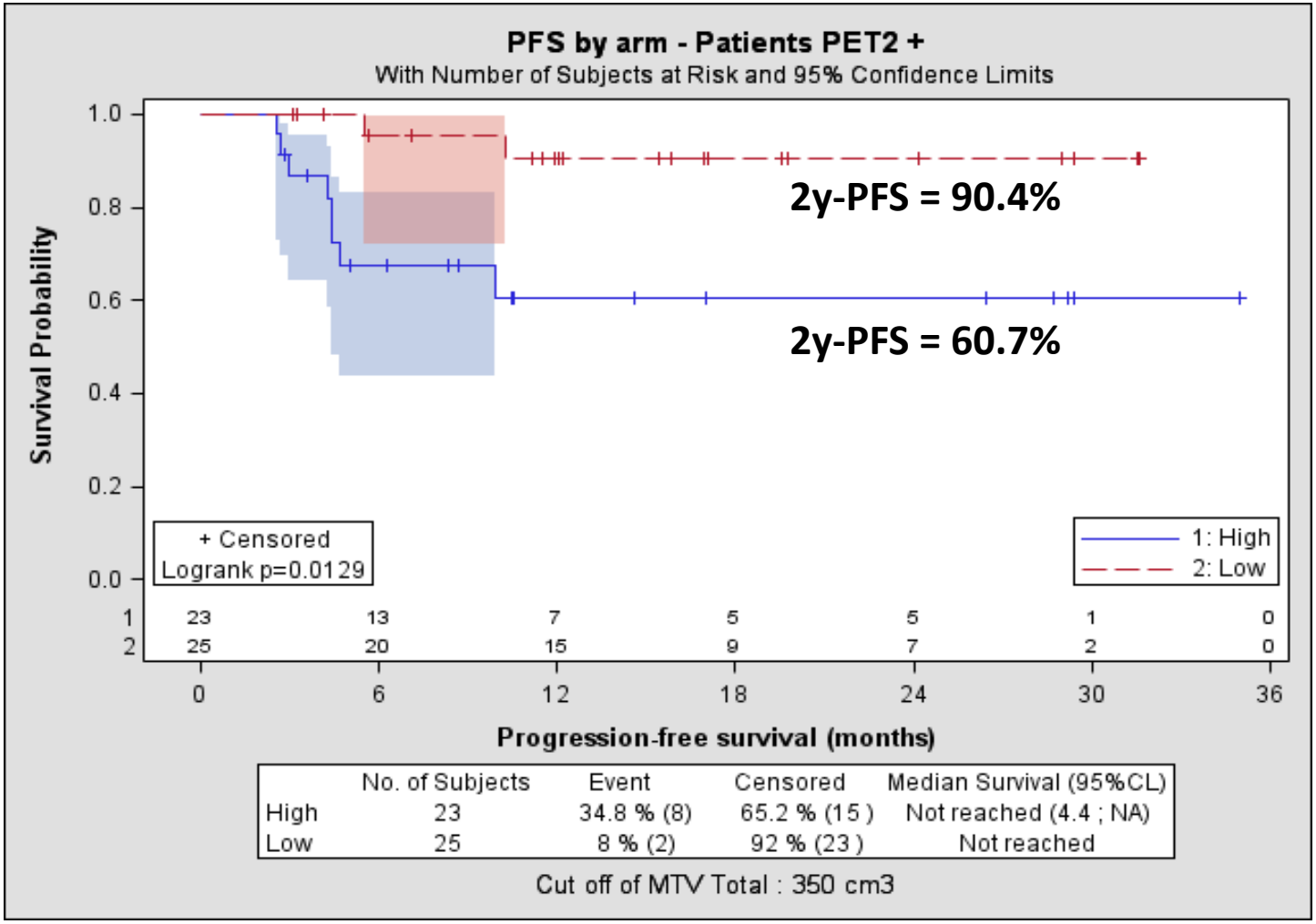


26% High TMTV

Casasnovas RO, ASCO 2016; Abs 7509

AHL 2011

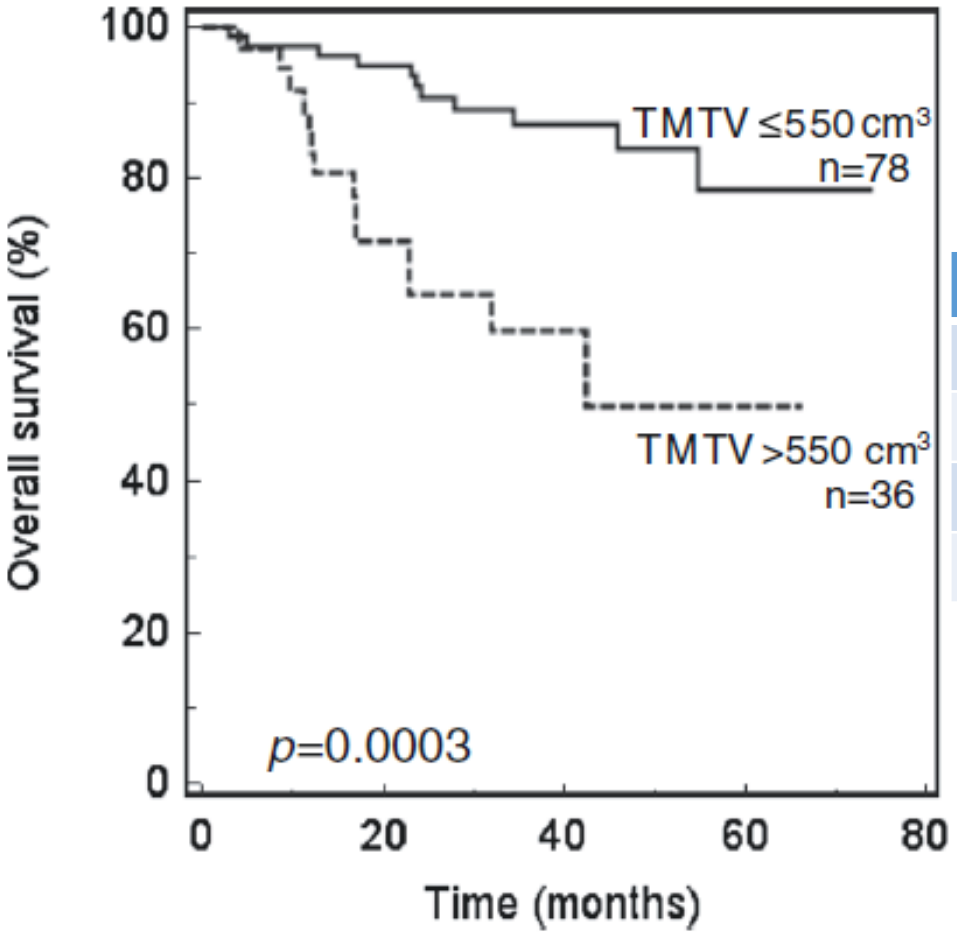
PFS according to TMTV in PET2+ patients



48% of High TMTV (cut-off = 350 ml)

TMTV impacts the outcome of DLBCL pts

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



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**

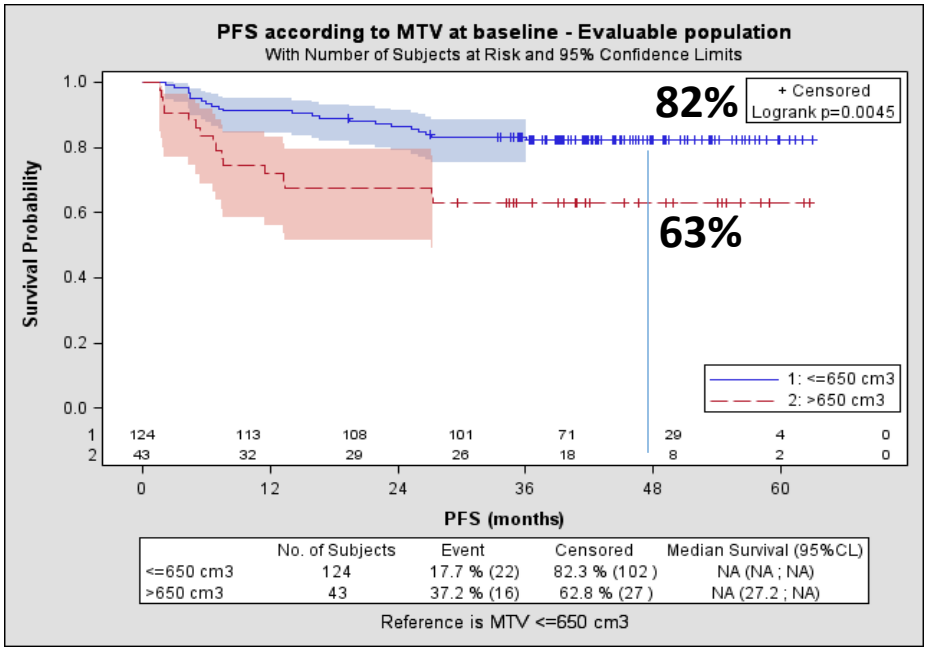
Sassanelli et al, EJNM 2014; 41: 2017

LNH 2007-3B: Impact of TMTV on outcome

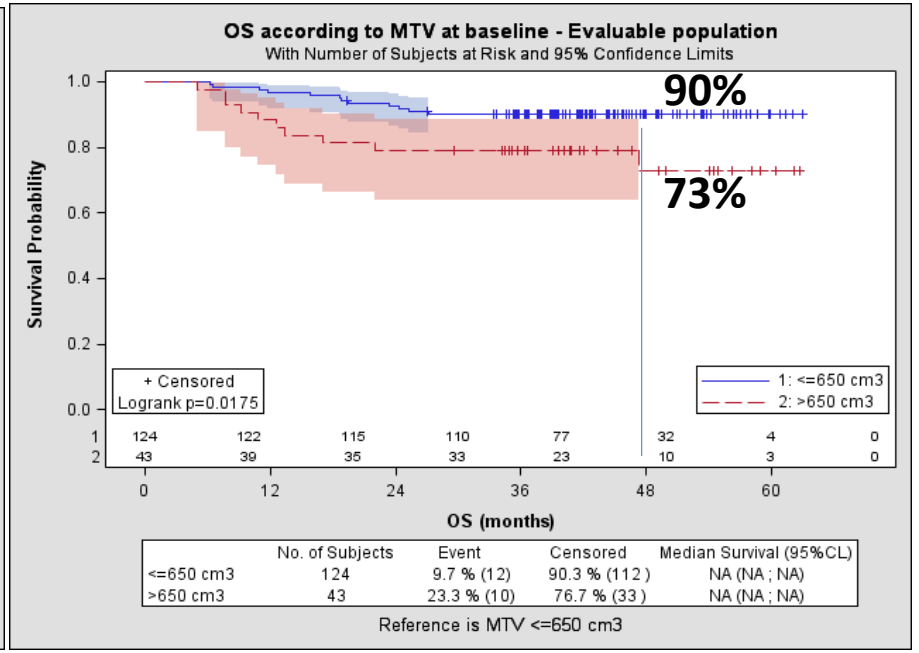
167 DLBCL
18-59y, aaIPI= 2-3

TMTV cut-off = 650 ml

PFS



OS

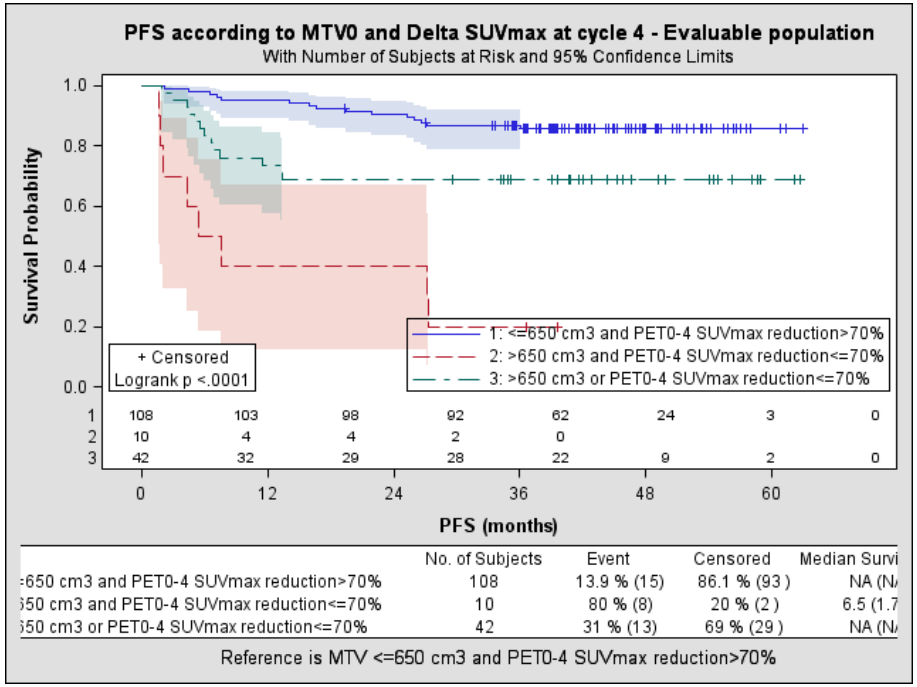


Median Follow up = 44.4 month

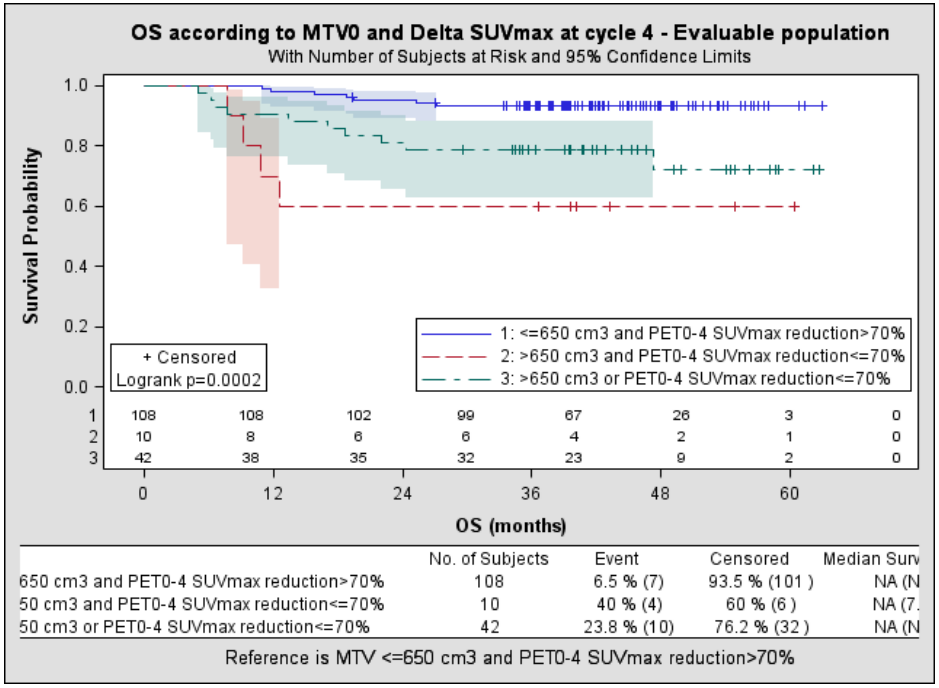
Casasnovas RO et al , ICML 2015, Abst 83

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

PFS



OS

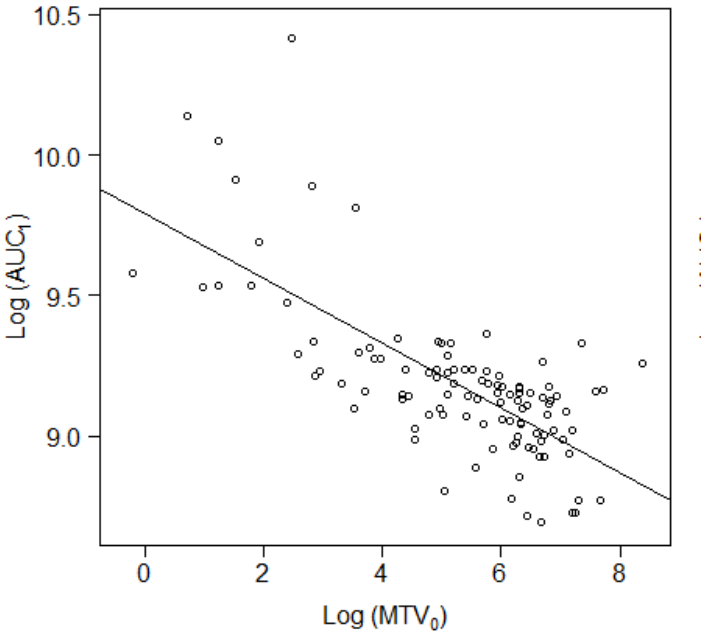


	4y-PFS	4y-OS
TMTV0 ≤ 650 ml and ΔSUVmax0-4>70% (n = 108; 68%)	86%	93%
TMTV0 > 650 ml or ΔSUVmax0-4≤70% (n = 42; 26%)	69%	72%
TMTV0 > 650 ml and ΔSUVmax0-4≤70% (n = 10; 6%)	20%	60%

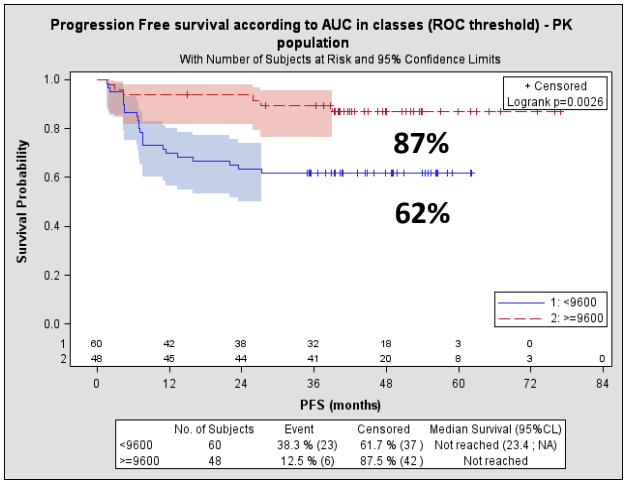
Casasnovas RO et al , ICML 2015, Abst 83

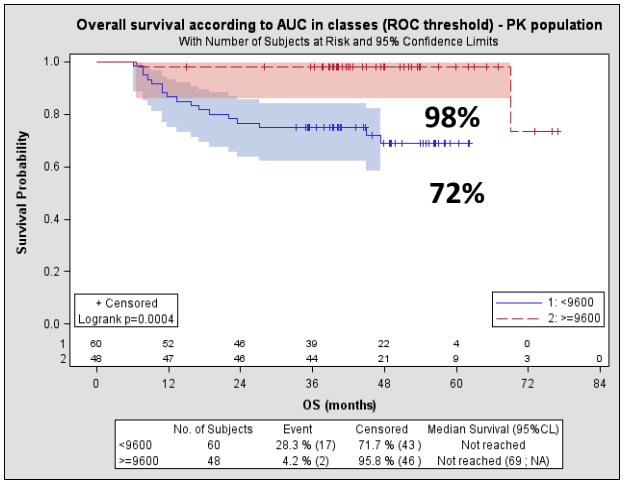
TMTV impacts DLBCL pts prognosis through its influence on Rituximab PK

High TMTV are related to lower rituximab AUC1 ($R^2 = 0.51$, $p < 0.0001$)



AUC1 < 9600 mg.h/l are associated to lower reponse rate, shorter PFS and OS

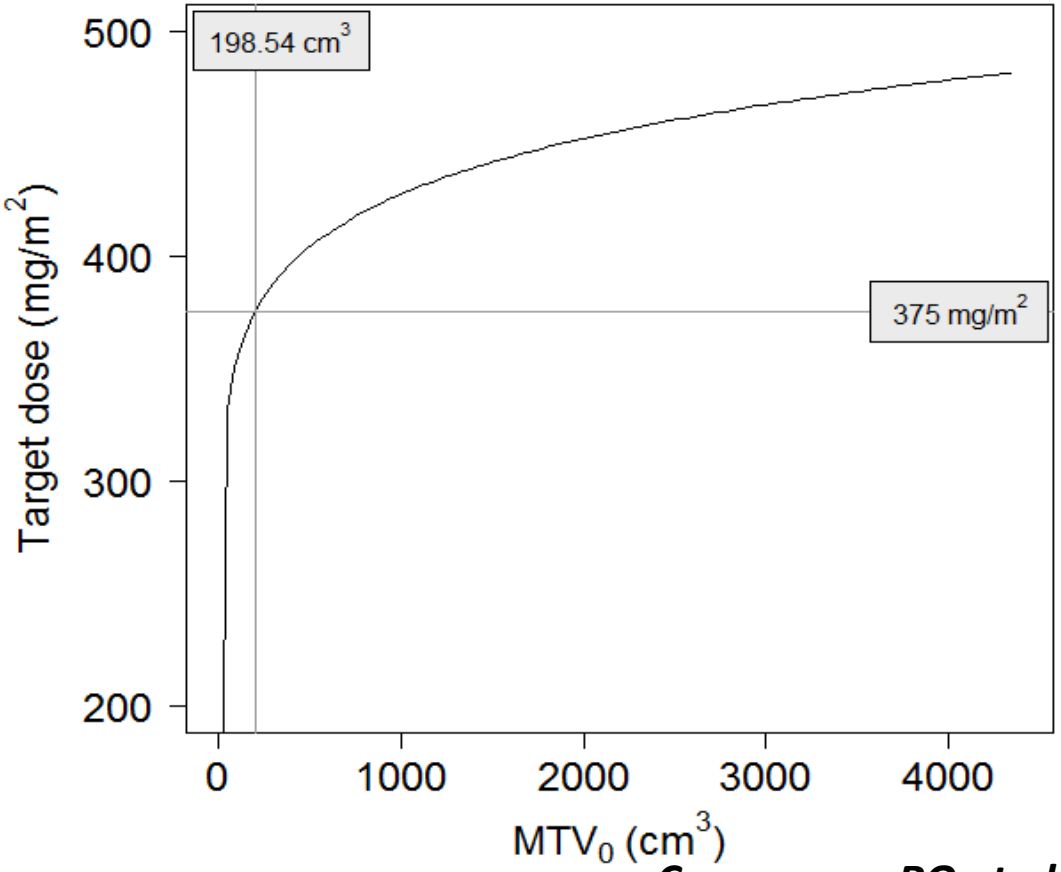




Casasnovas RO et al , ICML 2015, Abst 252
Tout M, RO Casasnovas et al submitted

Dose optimale de Rituximab selon le volume métabolique

$$\textbf{\textit{Dose cible}}\ (mg/m^2) = 257.59 \times (MTV_0)^{0.081}$$



Casasnovas RO et al , ICML 2015, Abst 252

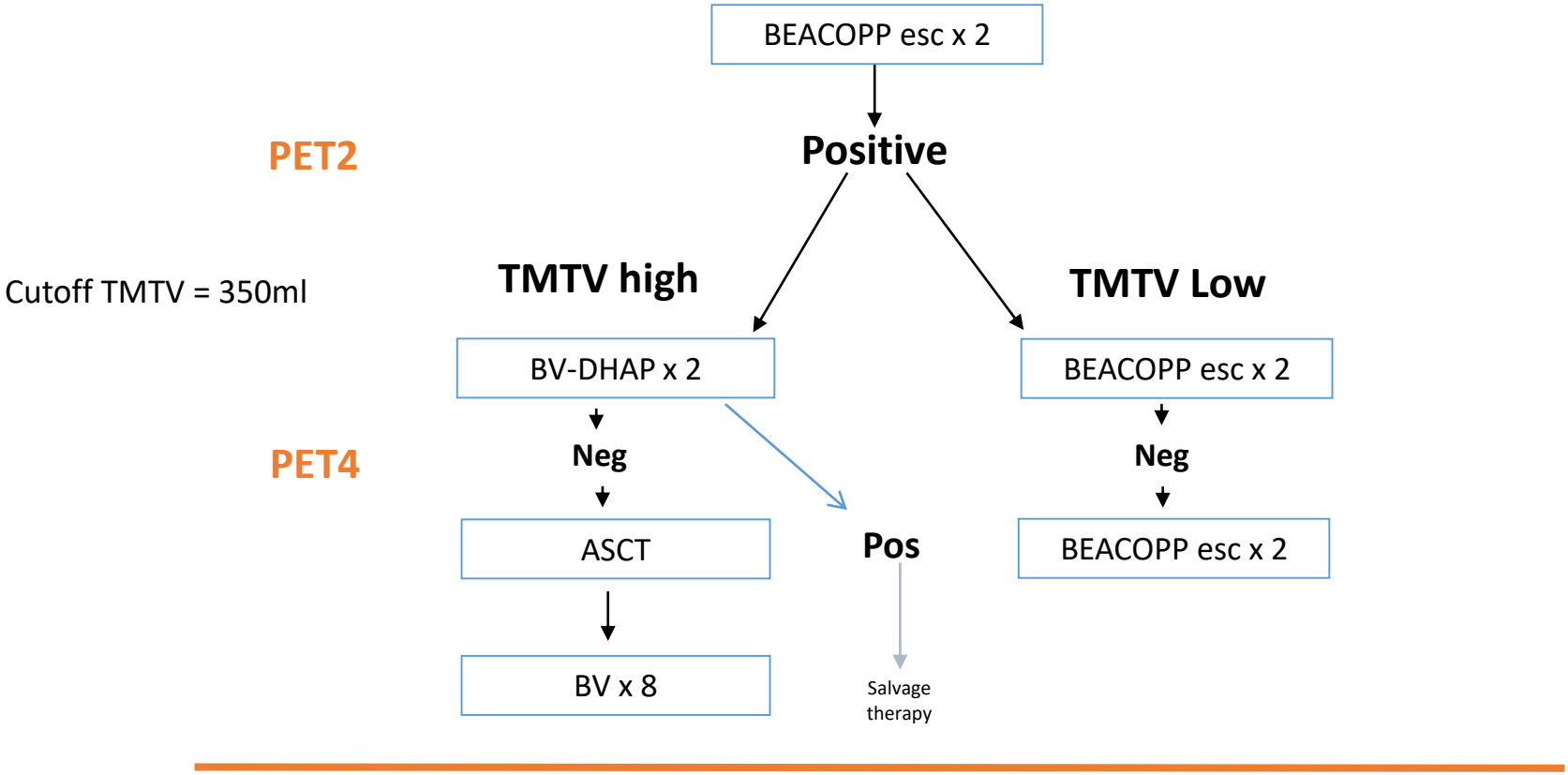
Conclusions

- La **TEP intérimaire (TEP2 / TEP4)** doit faire partie de la prise en charge des patients atteints de DLBCL et LH
  - S Legouill and O. Casasnovas, Blood 2017 (DLBCL)
  - C. Rossi and O. Casasnovas, Bull Cancer 2017 (HL)

- Les stratégies TEP guidées :
  - Nécessitent l'utilisation de **critères de positivité adaptés**
  - Nécessitent une **juste interprétation des TEP** et une bonne coopération Nucléariste/Hématologue
  - Permettent **d'optimiser le rapport efficacité / tolérance du traitement**

- **Le volume métabolique** reste encore du domaine de l'expérimentation:
  - Permet associé à la réponse précoce une meilleure stratification pronostique des patients
  - Doit démontrer son utilité pour guider le traitement ou adapter les doses d'anticorps thérapeutique (DLBCL)

Phase II study of Brentuximab Vedotin-DHAP followed by ASCT and BV maintenance in patients with baseline high total metabolic tumor volume (TMTV) Hodgkin Lymphoma (HL) and PET positive after 2 cycles of escalated BEACOPP (BEACOPPesc)



Improving PFS of PET2+ patients

Phase II study for PET2+ patients: increase 2y-PFS 70% -> 85%

Expected PET2+ patients accrual = 36 pts/y

Aknowledgements

- LYSA
  - LYSA-IMage
    - **A. Berriolo-Riedinger (Dijon)**
    - **S. Kanoun (Dijon)**
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    - F. Morschhauser (Lille)
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  - Co-PI GAINED
    - S. Le Gouill (Nantes)
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    - T. Lamy (Rennes)
    - G. Cartron (Montpellier)
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- LYSARC
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