AZIENDA ULSS N. 6 - VICENZA
DIVISIONE DI EMATOLOGIA

VII edizione

FONDAZIONE PROGETTO EMATOLOGIA

GIORNATE EMATOLOGICHE VICENTINE

VII edizione

10-11-12 Ottobre 2016
Palazzo Bonin Longare
Vicenza

L'uso della PET nel Linfoma di Hodgkin in stadio avanzato.

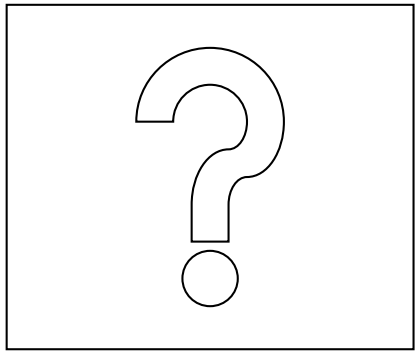
Martedì 11 Ottobre 2016

Pr. Andrea Gallamini
Département de recherche et innovation médicale
Hôpital A. Lacassagne. Nice (France).

CAL Nice
Centre Antoine-Lacassagne
Centre Régional de Lutte contre le Cancer

Baseline PET scan in advanced-stage HL

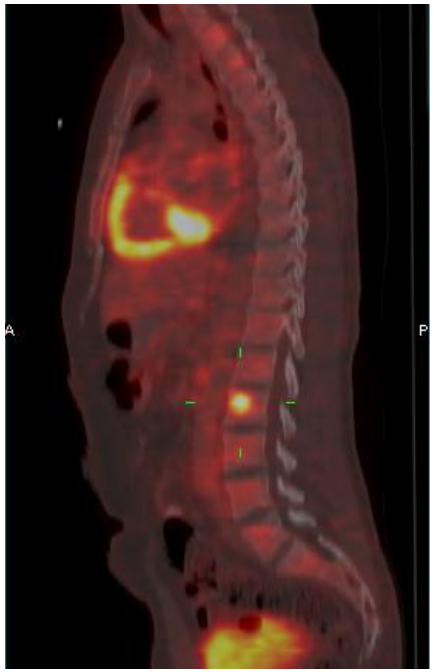
Are there prognostic messages



Baseline PET/CT in RATHL study: staging

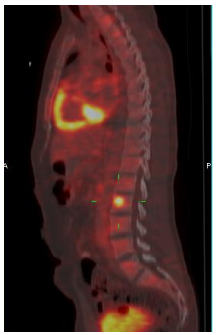
- 1171 staging PET/CT available for review
- Agreement between clinical and PET/CT staging in 938 (80%) patients
- 159 (14%) were upstaged
- 74 were (6%) downstaged

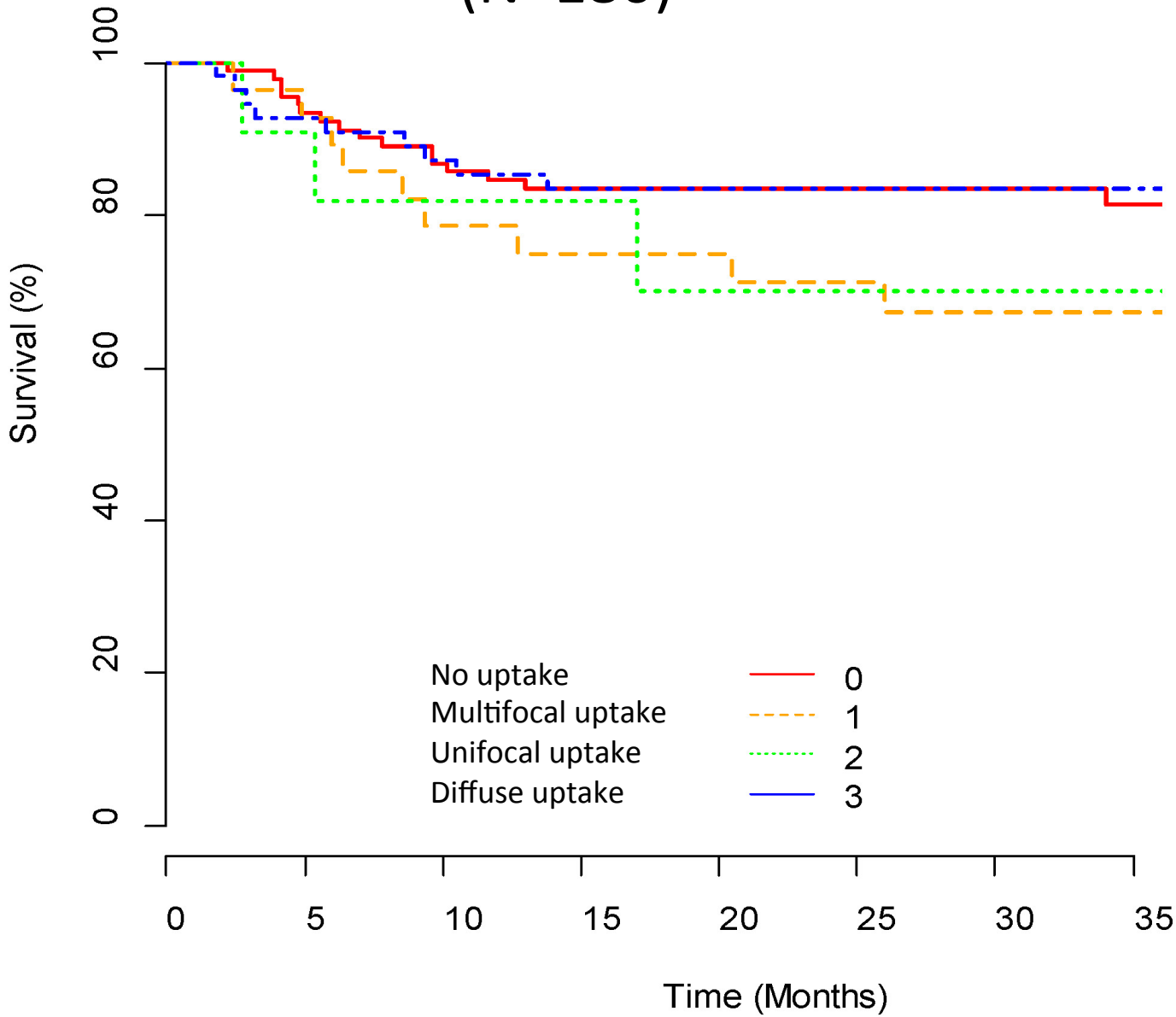
Upstaging by PET-CT due to	N (% of upstaged patients)
Extranodal disease on PET-CT in the following sites	118 (74.2)
Bone marrow	92
Lung	11
Liver	2
Pleura	1
Multiple organs	12
Nodal disease	35 (22.0)
Normal sized nodes that were FDG avid below the diaphragm	20
Normal sized nodes that were FDG avid above the diaphragm	7
Splenic FDG avid foci	7
Both of the above	1



Barrington SF: Blood 2016; 127(12): 1531-38

Pattern of FDG uptake in BM and HL outcome (N=180)

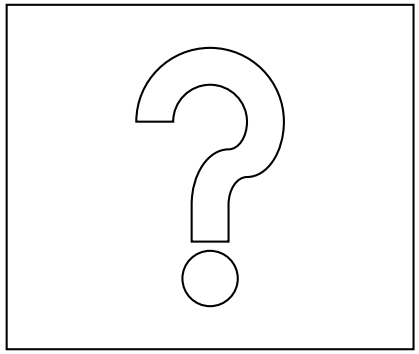




Zwarthoed C, Gallamini A: J Nucl Med 2016: submitted

Interim PET scan in HL

Are the interpretation rules validated



Deauville 5-point scale for interim PET interpretation

- Validation cohort: 260 advanced-stage, ABVD treated HL p. from 8 international centers.
- Blinded Independent Central review by 6 experts by visual assessment only.
- The Cohen k for agreement between pairs of reviewers was 0.69- 0.84 (good, very good)
- Overall agreement was .76 (excellent)

- Score 1 no uptake
- Score 2 uptake ≤ mediastinum
- Score 3 uptake > mediastinum but ≤ liver

Positivity threshold

- Score 4: moderately ↑uptake > liver
- Score 5 markedly ↑uptake > liver and/or new sites of disease

Barrington S: Eur J. Nucl Med Mol Imaging. 2010;;37:1824-33
Meignan M. Leukemia & Lymphoma 2009; 50(8): 1257–1260
Biggi A.: J Nucl Med 2013; 54:683–690
Gallamini A: Haematologica. 2014 Jun;99(6):1107-13

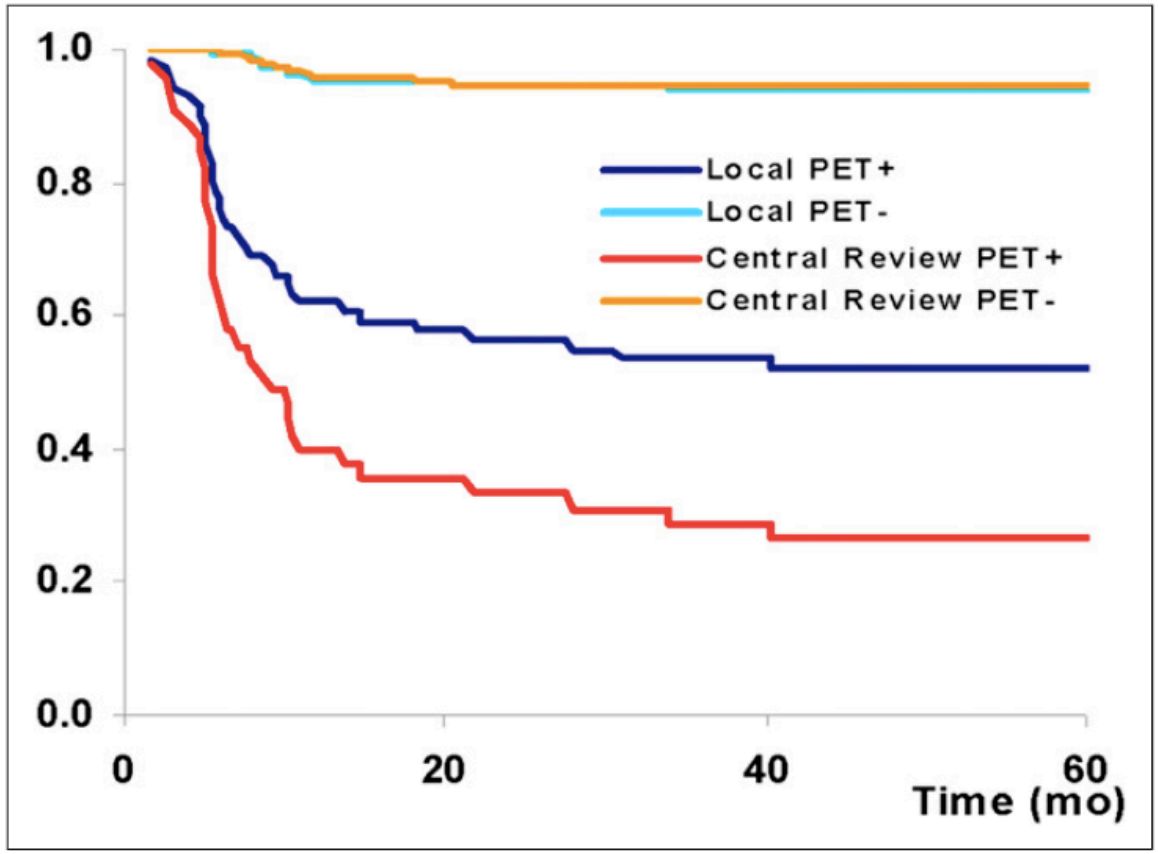


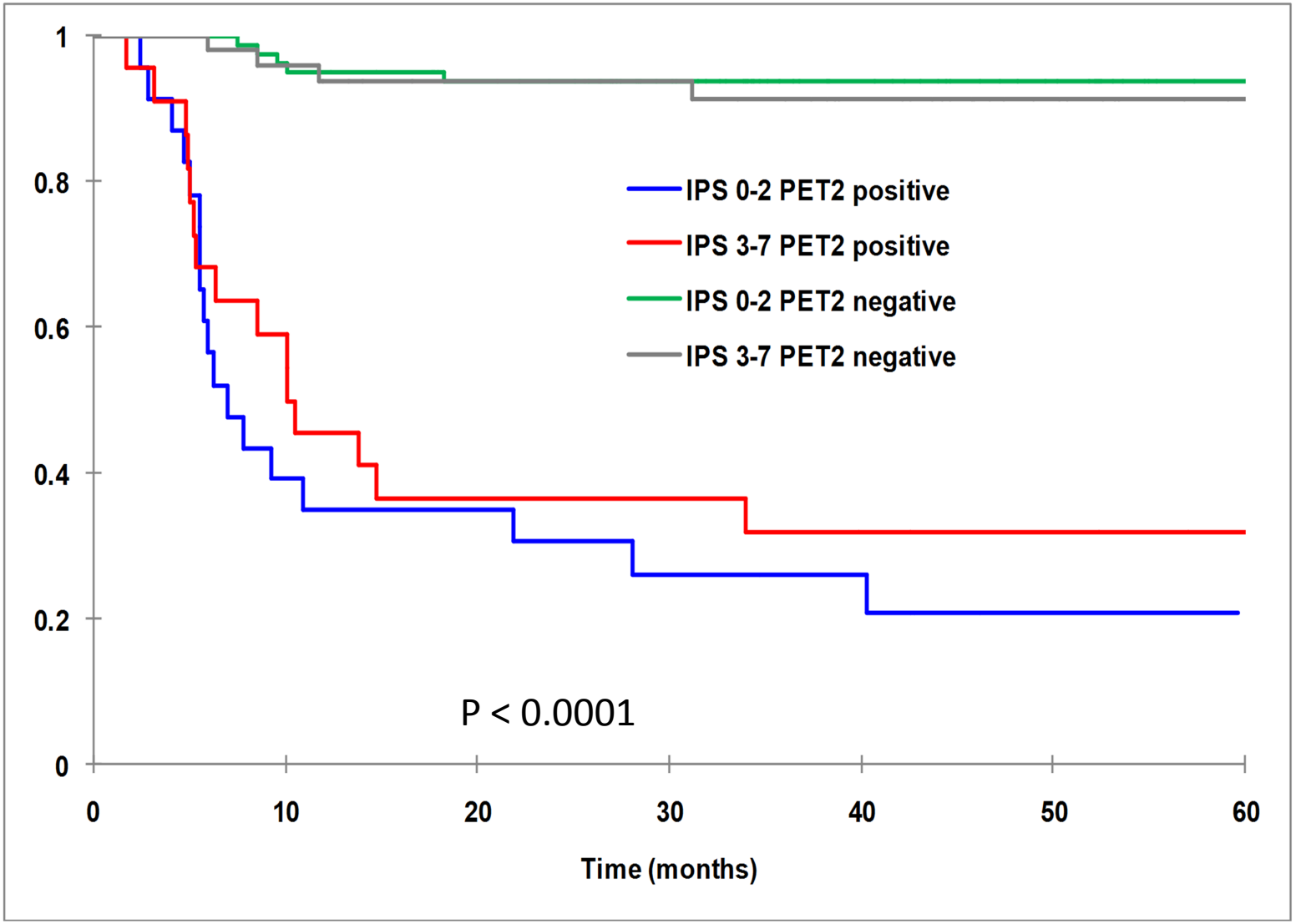
TABLE 2

Agreement Between Pairs of Reviewers with Respect to Negative vs. Positive PET Scans Using Cohen κ

	Reviewer 1	Reviewer 2	Reviewer 3	Reviewer 4	Reviewer 5	Reviewer 6
Reviewer 1	1	0.73	0.77	0.77	0.75	0.73
Reviewer 2	0.73	1	0.71	0.75	0.69	0.70
Reviewer 3	0.77	0.71	1	0.83	0.77	0.77
Reviewer 4	0.77	0.75	0.83	1	0.83	0.84
Reviewer 5	0.75	0.69	0.77	0.83	1	0.78
Reviewer 6	0.73	0.70	0.77	0.84	0.78	1

Biggi A.: J Nucl. Med 2013; 54, 683-90

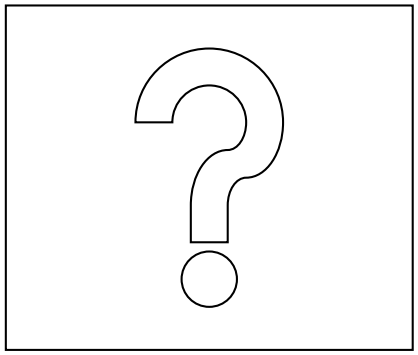
Advanced stage HL (N= 260).



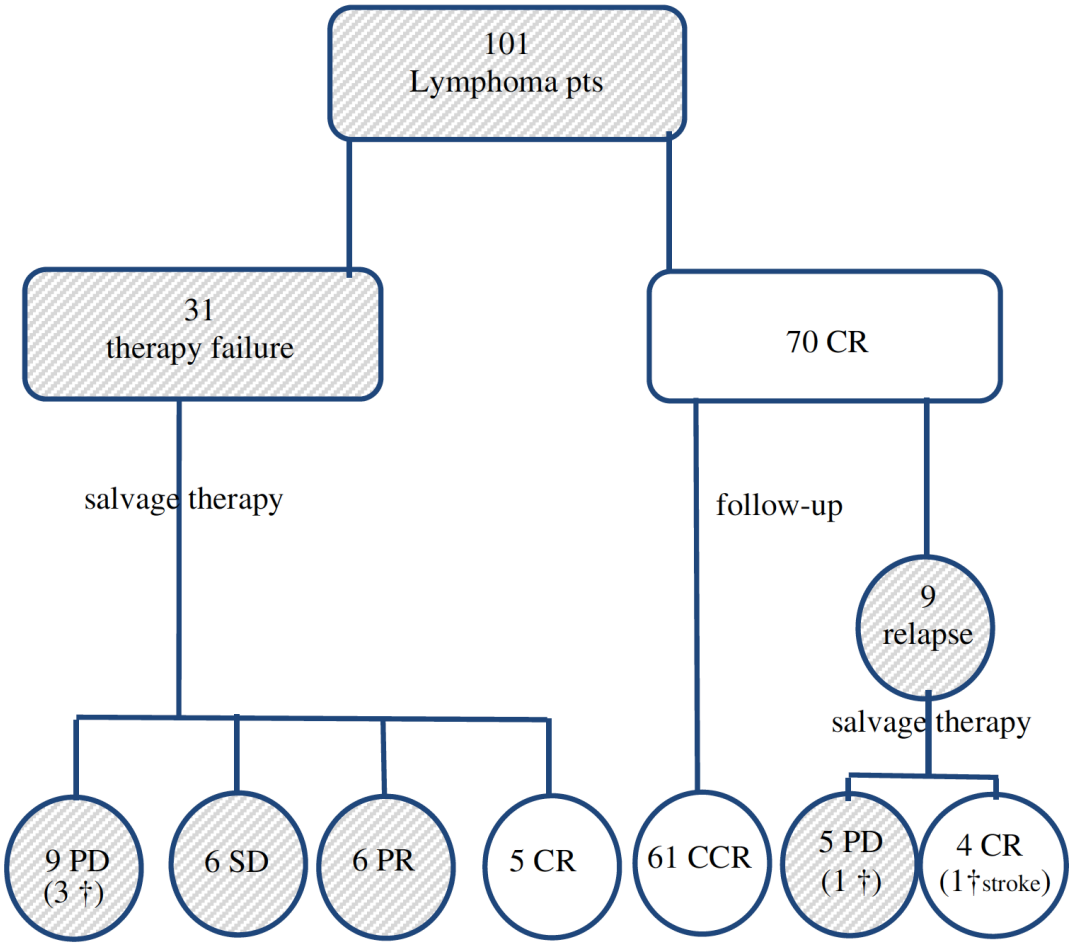
Gallamini A: Haematologica. 2014 Jun;99(6):1107-13

End-of treatment PET scan

Are the interpretation rules validated



Diagnostic accuracy of FDG PET/CT for clinical evaluation at the end of treatment of HL and NHL: a comparison of the Deauville Criteria (DC) and the International Harmonization Project Criteria (IHPC)

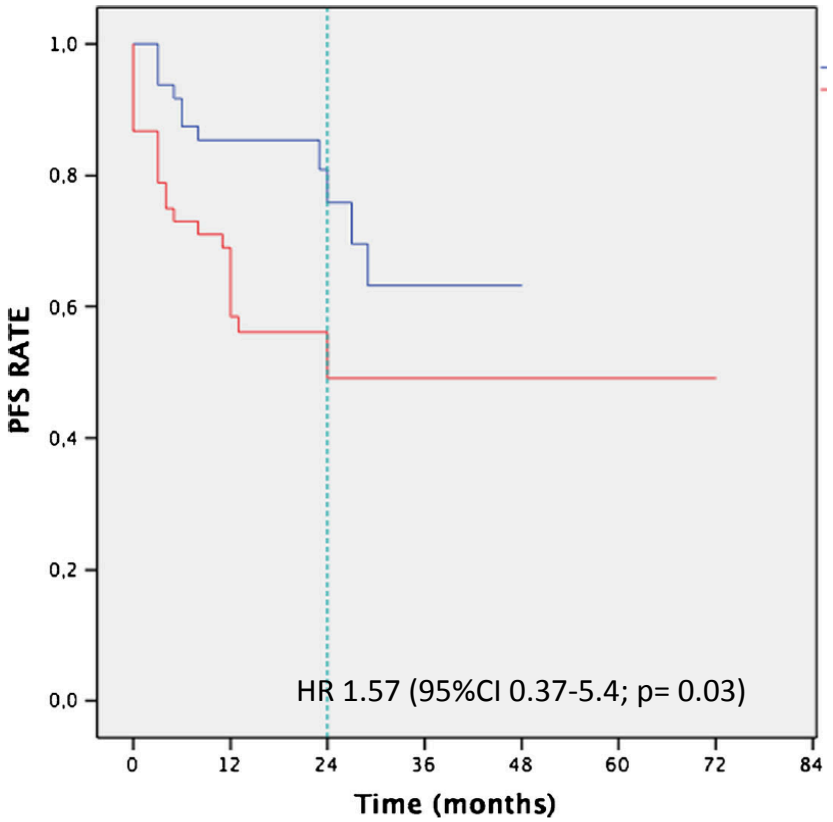


N=101

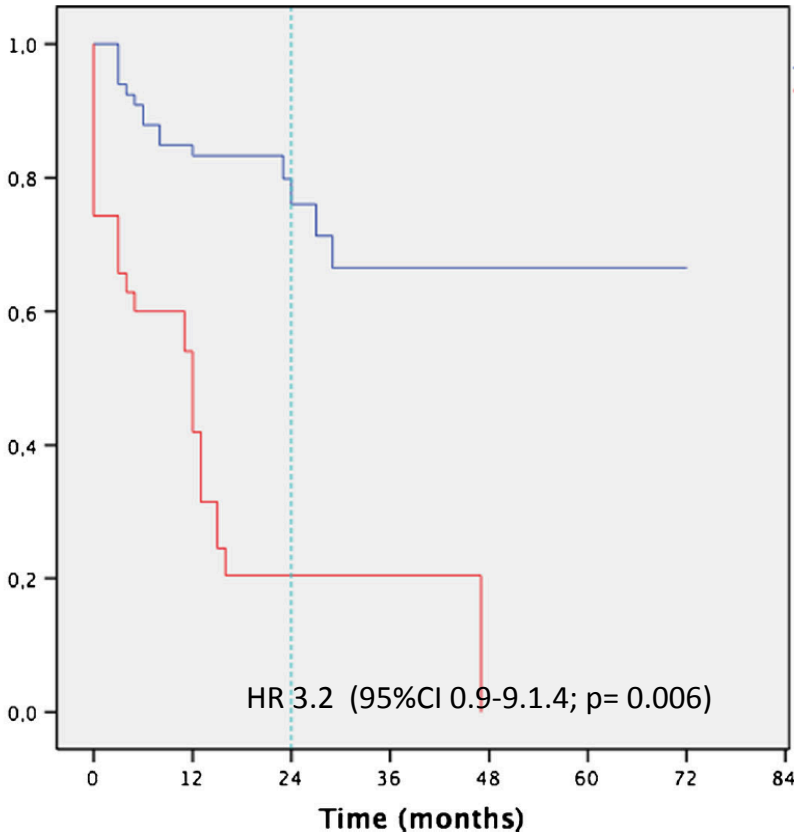
HL	35
DLBCL	37
FL	16
MZL + MALT	4
ALCL	2
LPL	2
MCL	2
Other	3

Fallanca F. Eur. J Nucl Med. Mol Imaging 2016;

IHP criteria



Score 1-3 Vs. 4-5

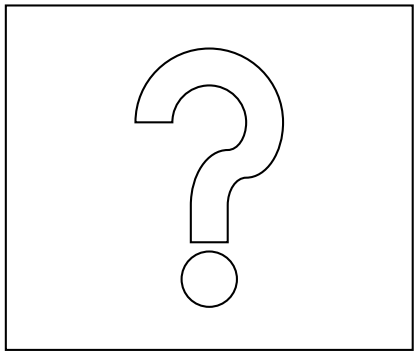


	Sensitivity	Specificity	PPV	NPV	Accuracy
IHP	97%	67%	57%	98%	76%
5-PS	92%	**87%**	**74%**	92%	86%

Fallanca F. Eur. J Nucl Med. Mol Imaging 2016;

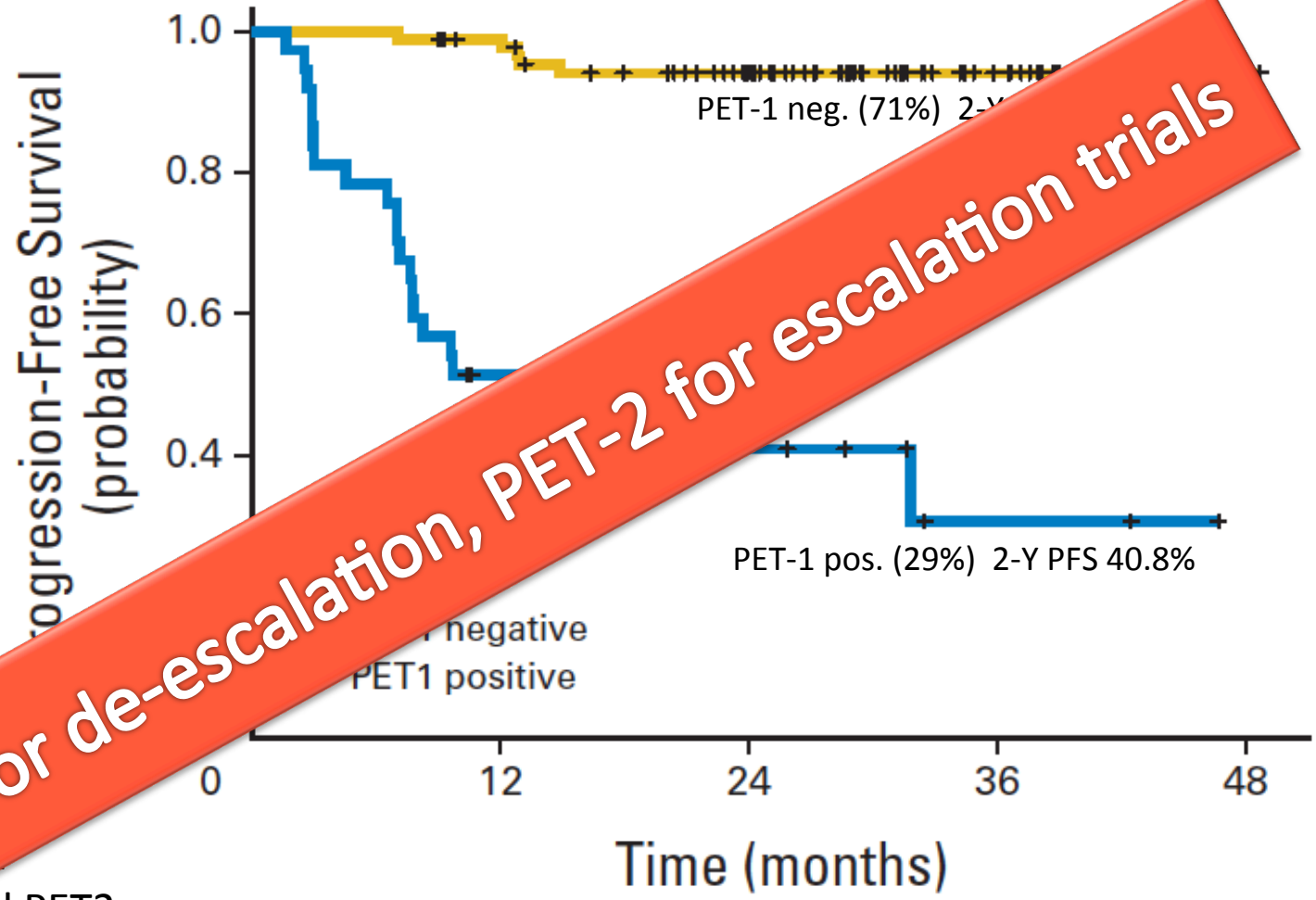
Interim PET timing

What is the best time point for interim response assessment



Anticipating interim PET after the 1st ABVD cycle

Stage I Stage IIA Stage IIB	54%	
Stage III	24	
Stage IV	34	
Total		126



PET-1 best for de-escalation, PET-2 for escalation trials

- 12
- 1 and PET2
- ion key: 5-PS
- 1 (38%) PET1-positive patients converted to a negative PET2
- All PET1-negative patients (N=88) were also PET2-negative.

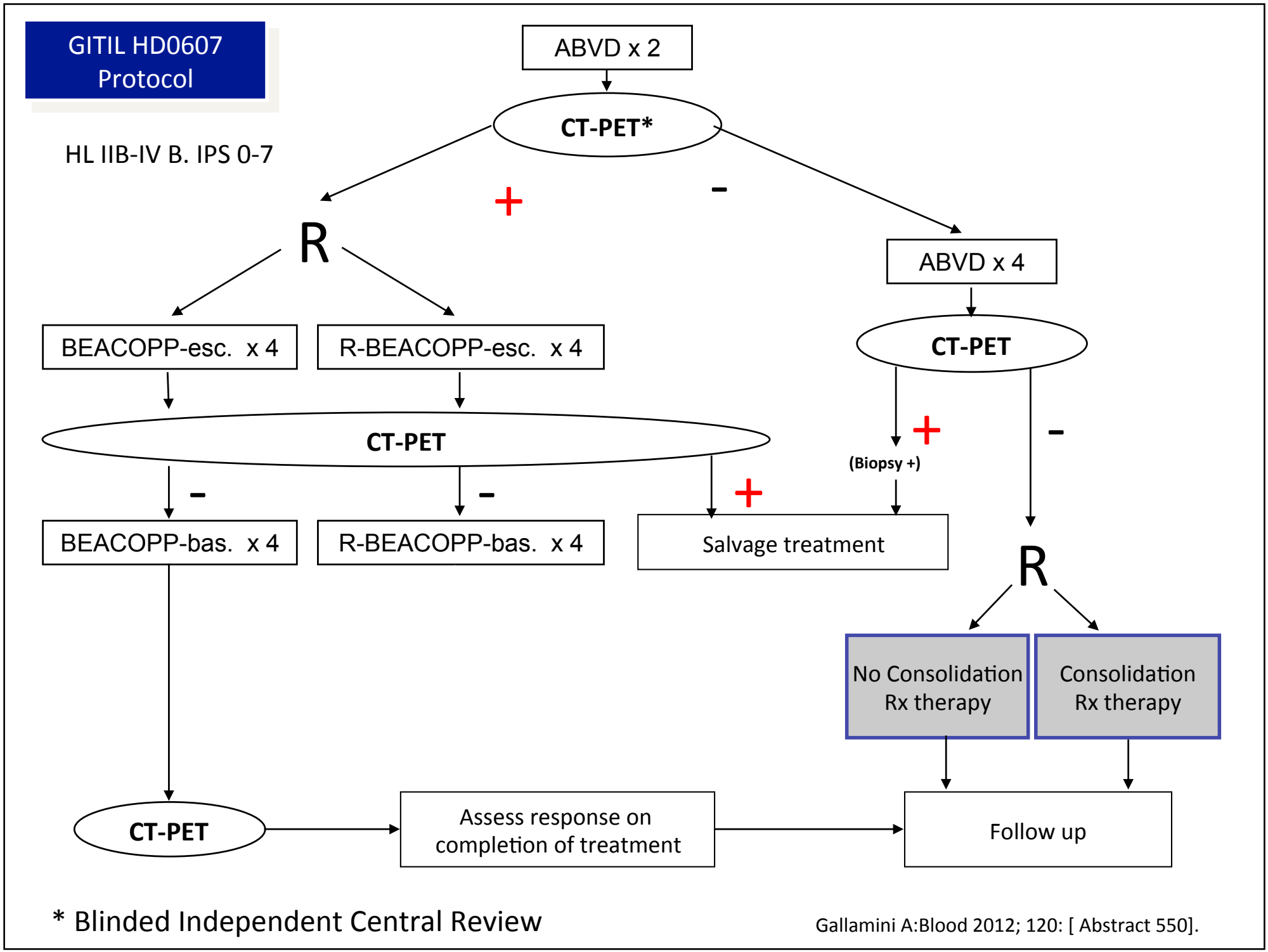
Hutchings M: J Clin Oncol. 2014; 32(25):2705-11

PET response-adapted trials in advanced-stage HL

Trial Name	Sample	Stage	End-point	Before PET-2	PET-2 neg. arm	PET-2 pos. arm	PET Key Interpret.
Israeli H2	300	I-IV	3-y PFS	ABVDx2	ABVDx4	EBx4 HD+ASCT	Dynamic score
AHL (LYSA)	798	IIB-IVB	5-y PFS	EBx2	EB x 6 ABVDx2	EBx6	5-PS
HD 18 (GHSG)	1500	IIB-IVB	5-Y PFS	EBx2	EB x 6 ABVDx4	EBx6 ±R	5-PS^{m}
HD 0607 (FIL/GITIL)	770	IIB-IVB	3-y PFS	ABVDx2	ABVDx4 +/- RT	EBx2 + BB x 4	5-PS
RATHL (NCRI)	1200	II-IVB	3-y PFS	ABVDx2	ABVDx4 AVD x 4	EBx4 B-14 x 6	5-PS
S0813 (SWOG-CALGB)	230	III-IVB	2-y PFS	ABVDx2	ABVDx4	EBx6 Bx6 (HIV+)	5-PS
HD 0801 (FIL)	300	IIB-IVB	2-y PFS	ABVDx2	ABVDx4 +/- RT	IGEVx4+ ASCT	IHP

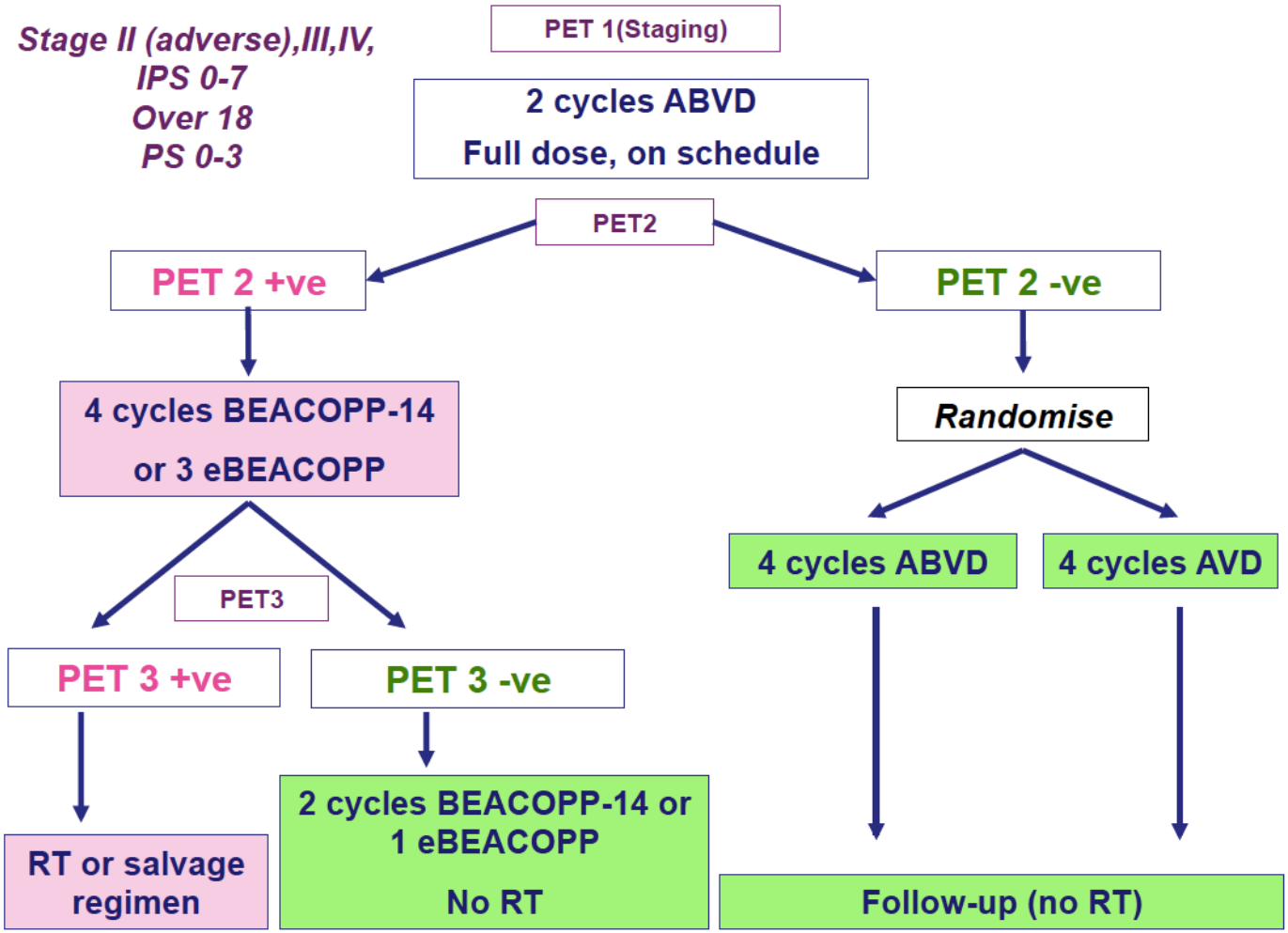
EB= Escalated BEACOPP; R= Rituximab; **RT**= Consolidation Radiotherapy; **LYSA**= Lymphoma Study group de l'Adulte; **GHSG**= German Hodgkin Lymphoma Study Group; **FIL**= Italian Foundation on Lymphoma; **GITIL**= Italian : Group For Innovative Therapy of Lymphoma**; NCRI**=National Cancer Research Institute; **SWOG**: South Western Oncology Group; **CALGB**= Cancer and Acute Leukemia Group

Gallamini A: Clin Transl Imaging (2015) 3:283–294


GITIL HD0607 Protocol
HL IIB-IV B. IPS 0-7
ABVD x 2
CT-PET*
+
-
R
ABVD x 4
BEACOPP-esc. x 4
R-BEACOPP-esc. x 4
CT-PET
CT-PET
+
(Biopsy +)
-
-
-
+
BEACOPP-bas. x 4
R-BEACOPP-bas. x 4
Salvage treatment
R
No Consolidation Rx therapy
Consolidation Rx therapy
CT-PET
Assess response on completion of treatment
Follow up
* Blinded Independent Central Review
Gallamini A:Blood 2012; 120: [Abstract 550].

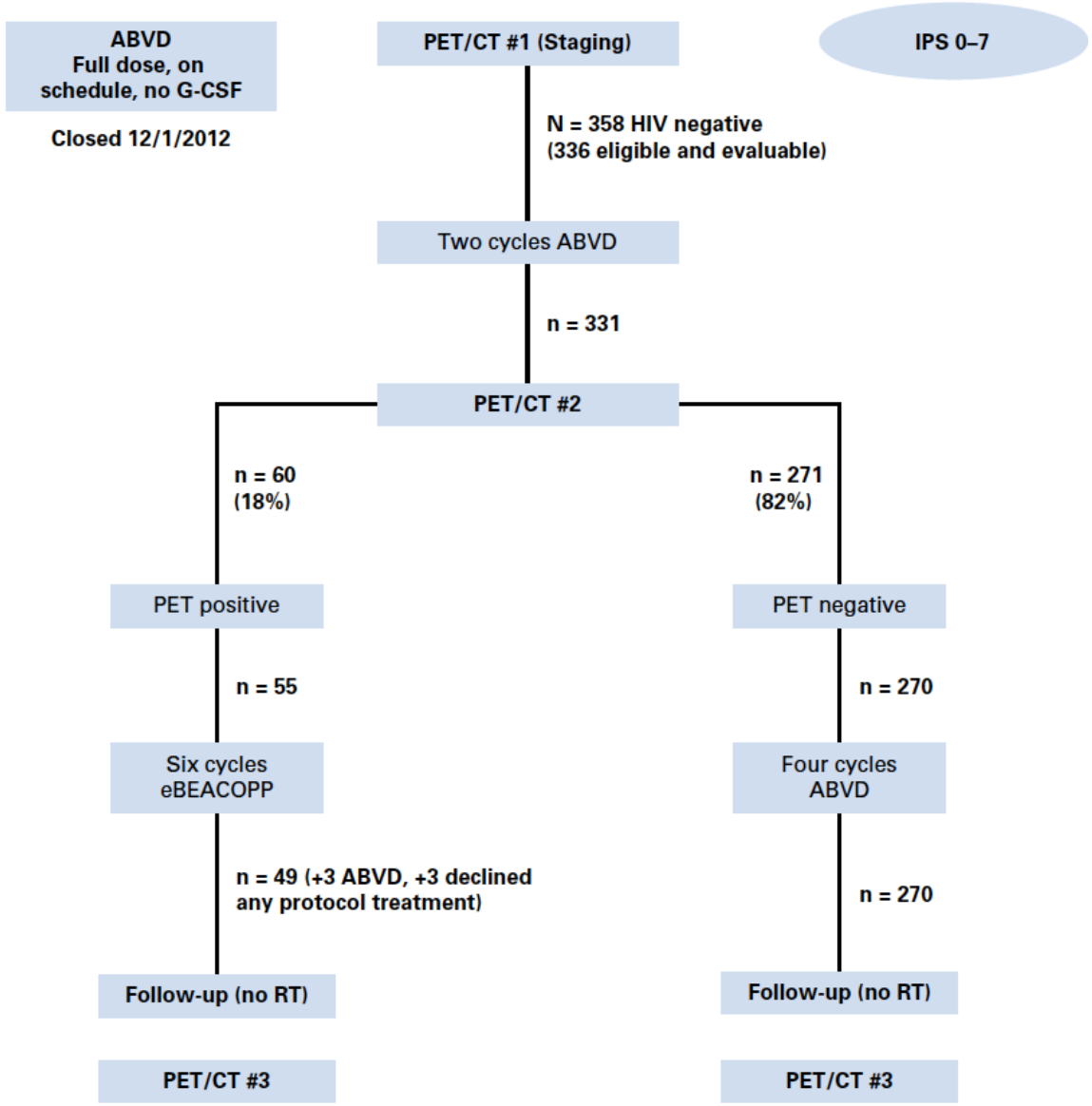
The NEW ENGLAND JOURNAL of MEDICINE

Adapted Treatment Guided by Interim PET-CT Scan in Advanced Hodgkin's Lymphoma



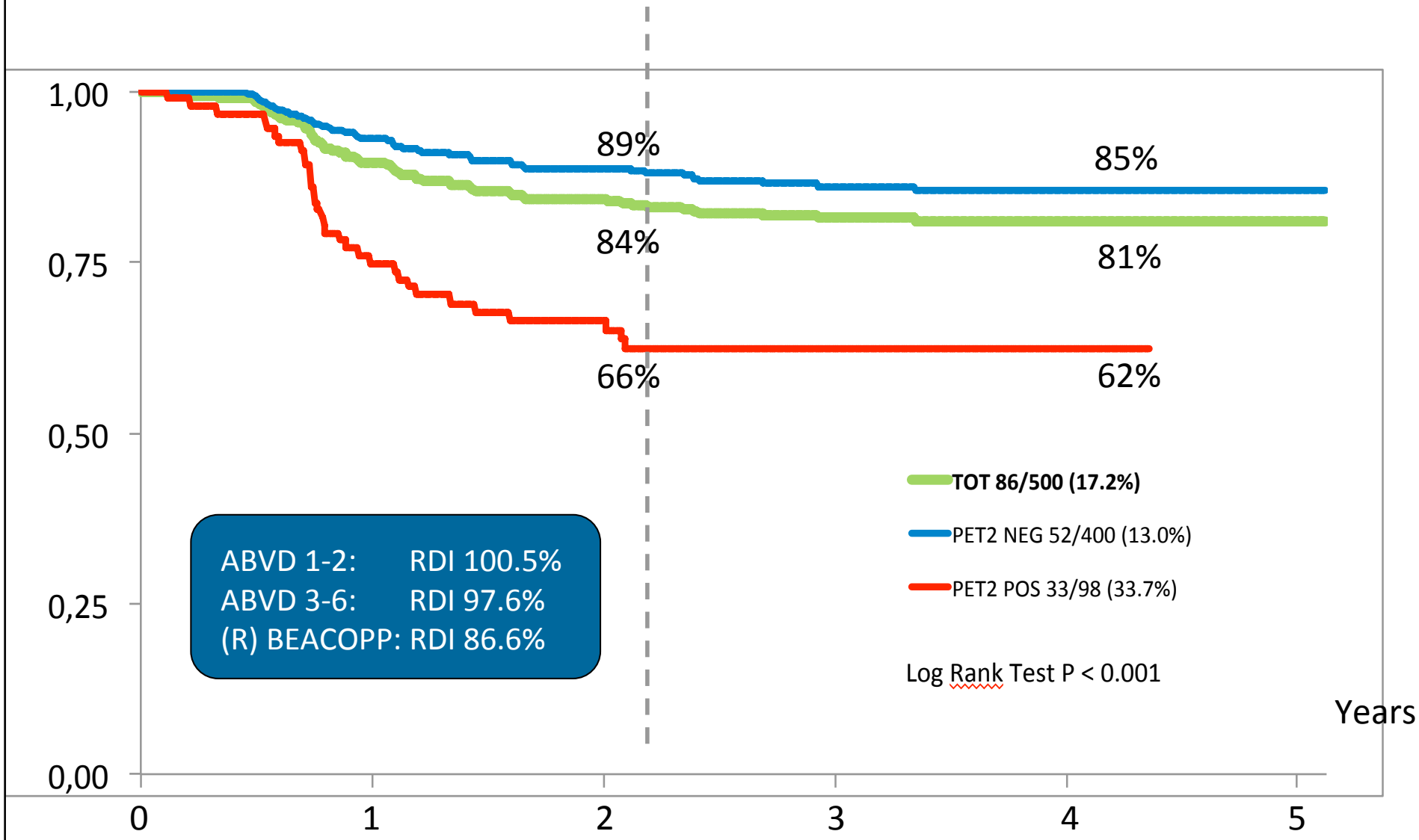
P. Johnson NEJM 2016; 374(25); 2419-29

SWOG S0816 trial: on study patients



Press O. J Clin Oncol 2016; 34: 2020-7.

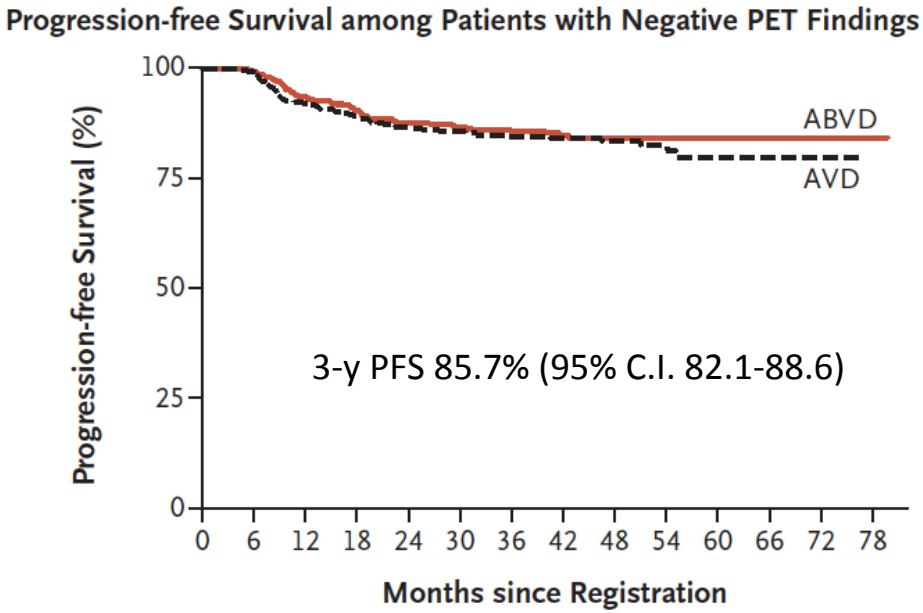
Failure Free Survival according to PET2 result

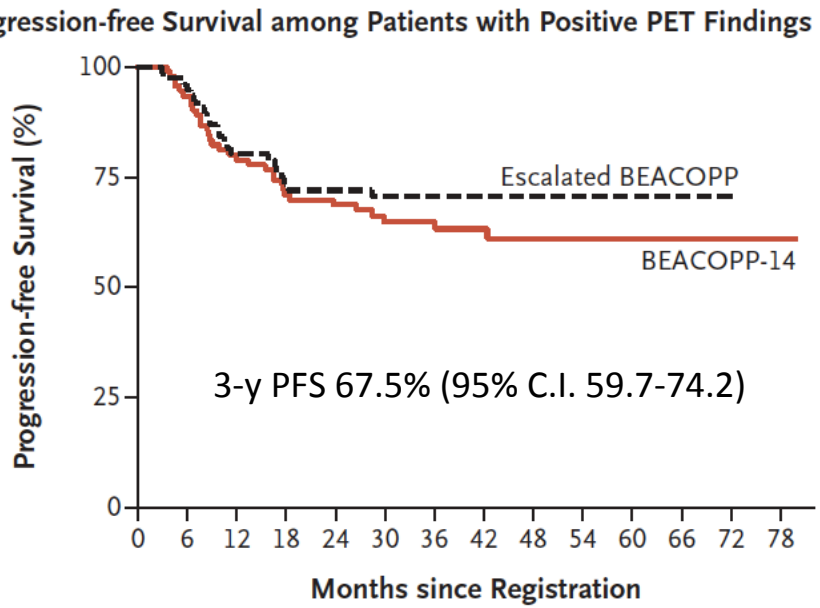


Gallamini A: Hematol Oncol 2015; 33 (Suppl. 1 June 2015): 163, Abstract 118.

RATHL study: 3-Y PFS according to PET-2

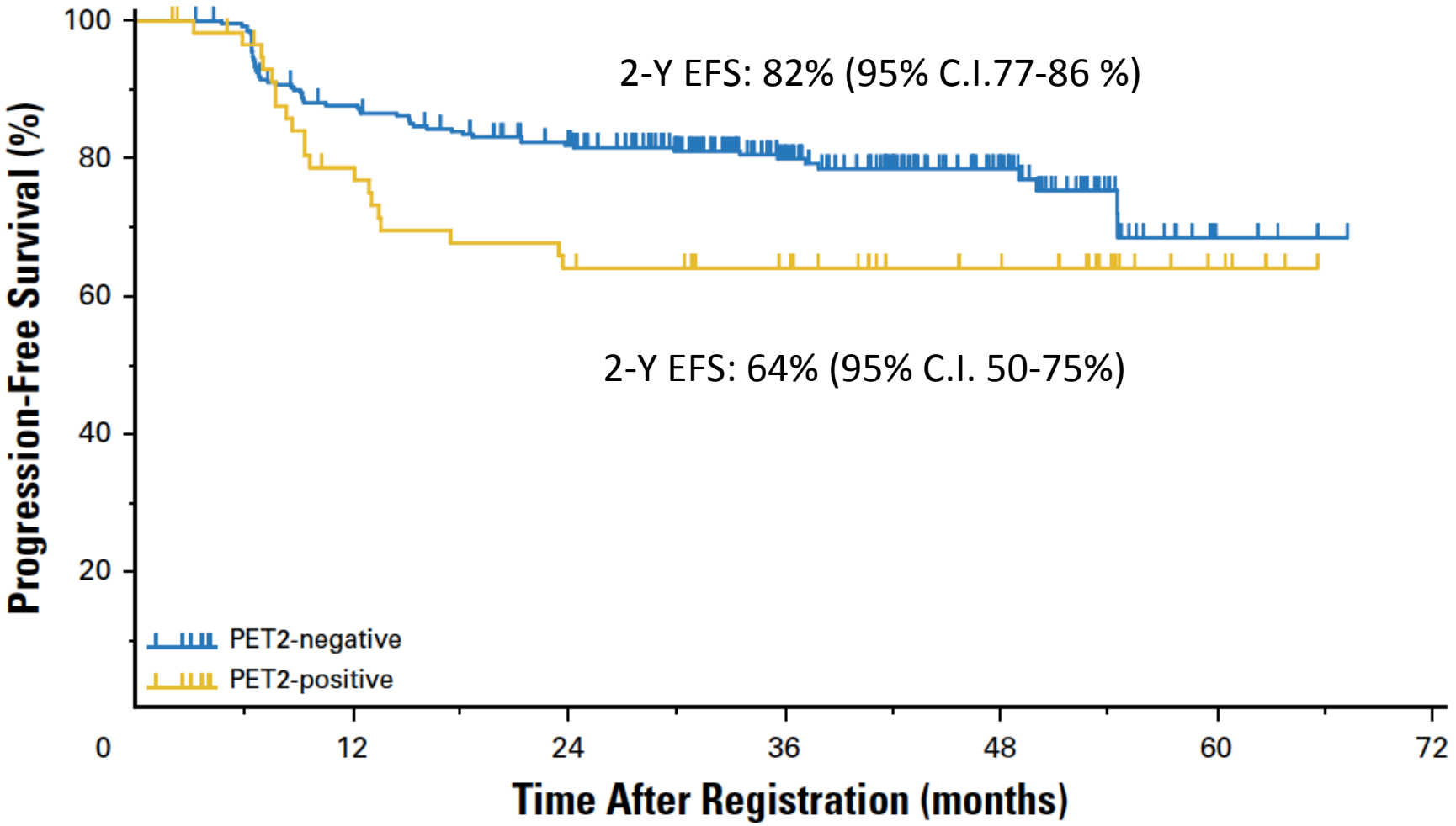
1119 patients
Median f-up 34.7 months





P. Johnson NEJM 2016; 374(25); 2419-29

SWOG S0816 trial: 2-Y EFS



Press O. J Clin Oncol 2016; 34: 2020-7.

Comparative results in PET-adapted clinical trials starting with ABVD in advanced-stage HL.

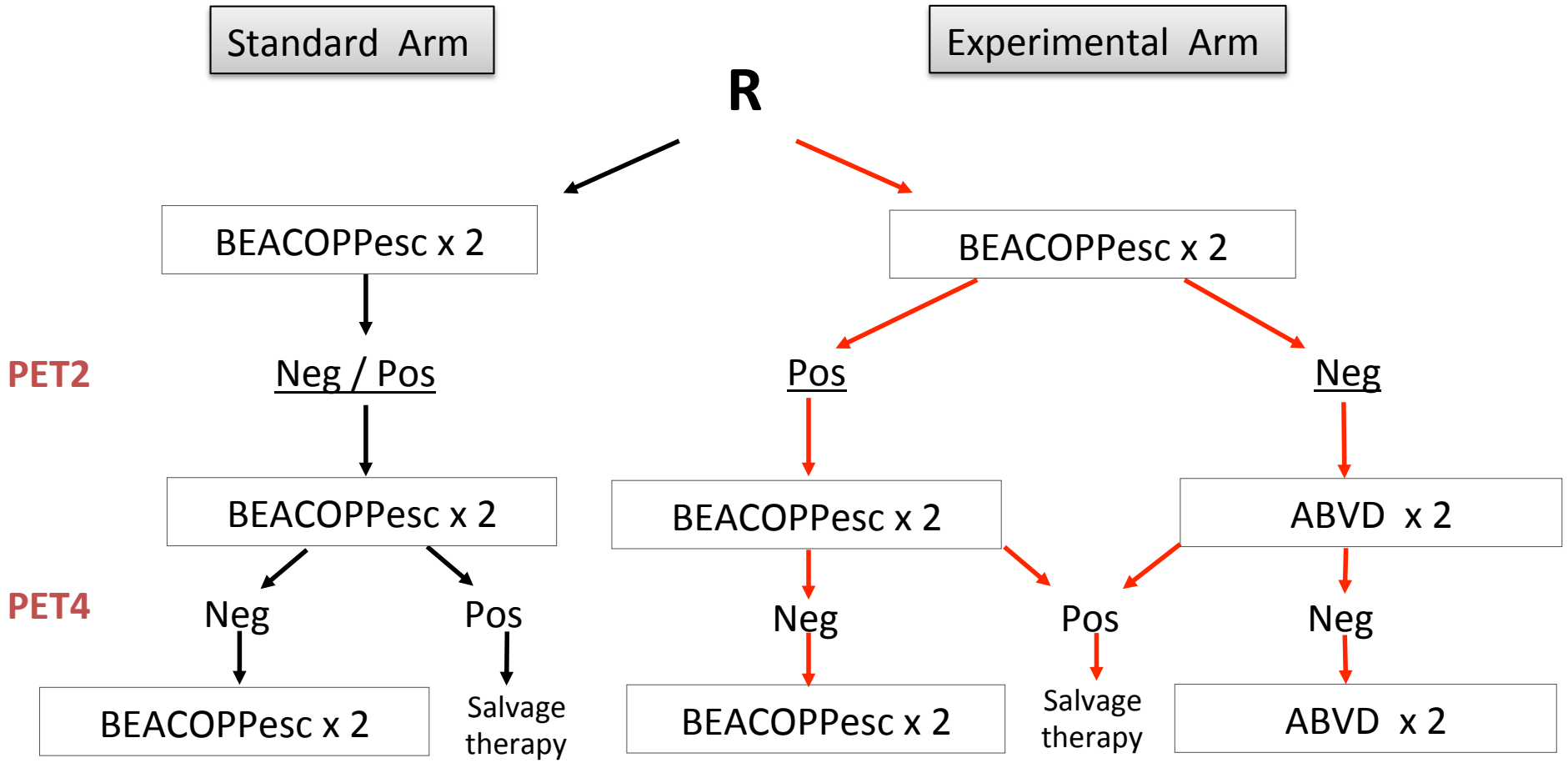
Trial	Stage	N°	PET-2 key	PET-2+ (%)	PET-2- (%)	PET-2 -ve PFS	PET-2 +ve PFS
GITIL HD 0607[1]	IIB-IVB	773	DS	19	81	89%	66%
NCRI RATHL	IIB-IVB*	1119	DS	16	84	85%	67%
SWOG S0816	III-IV	336	DS	18	82	82%	64%
Total/Mean	--	**2228**	**DS**	**18**	**82**	**85%**	**66%**

*Stage IIA enrolled if bulky or ≥ 3 nodal sites

Gallamini A, Kostakoglu L: Ann Oncol. 2015 Jun;26(6):1045-7

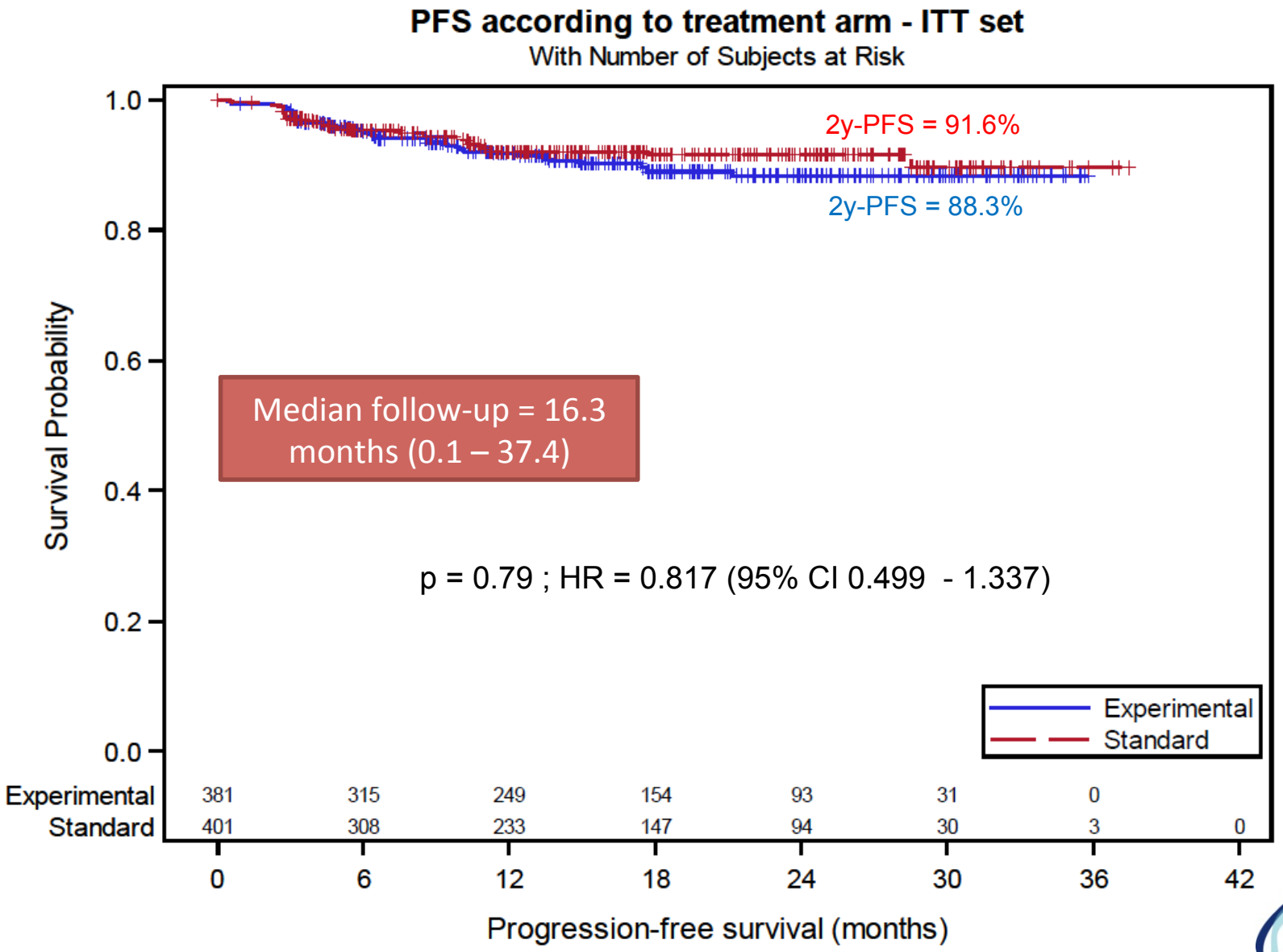
AHL 2011: Study design

NCT01358747



Casasnovas O. : Blood 2015; 126(23), Abstr. 577

AHL 2011: PFS according to treatment arm

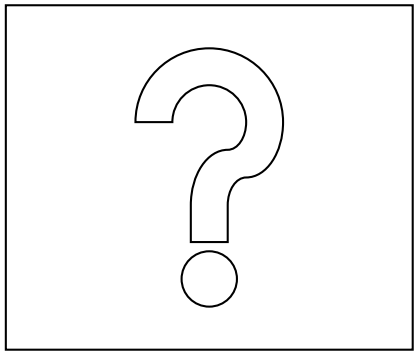


Casasnovas O. : Blood 2015; 126(23), Abstr. 577

Interim PET in advanced HL: problems.

- PET-2 strong predictor of outcome
- NPV suboptimal: ~12% still relapse.

Could we increase its NPV

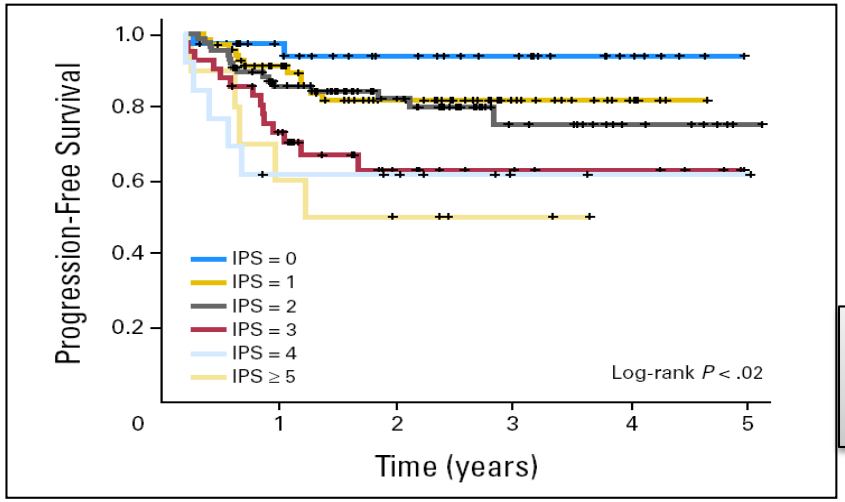


Association between baseline factors and PFS following negative PET-2

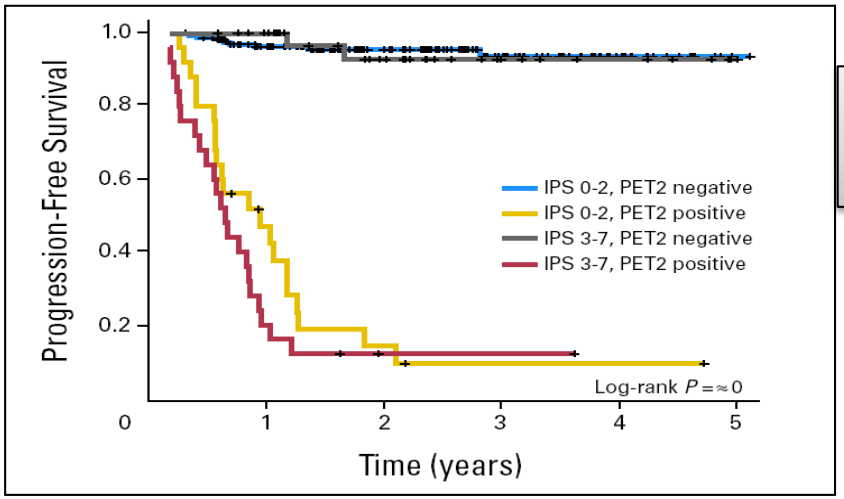
		Hazard ratio (95% CI)	p	3 year PFS %
Stage	II III IV	1.00 1.64 (1.09-2.47) 1.85 (1.23-2.81)	0.008	88.8 84.0 80.0
IPS	0-2 ≥3	1.00 1.41 (1.01-1.97)	0.043	86.7 81.6
Bulk	- +	1.00 0.80 (0.55-1.18)	0.263	87.8 83.8
PET-2 score	1 2 3	1.00 1.09 (0.62-1.90) 1.28 (0.72-2.27)	0.555	87.9 85.4 83.4

Johnson P: Hematol Oncol 2015; 33 (Suppl. 1 June 2015): 102, Abstract 008.

	Prognostic factors	Predictive factors
PROS	Available at baseline for all patients	Include both known and unknown factors
	Allow comparison between groups	Accurate
CONS	Retrospectively arisen	Available only during treatment
	Unspecific	Treatment-restricted



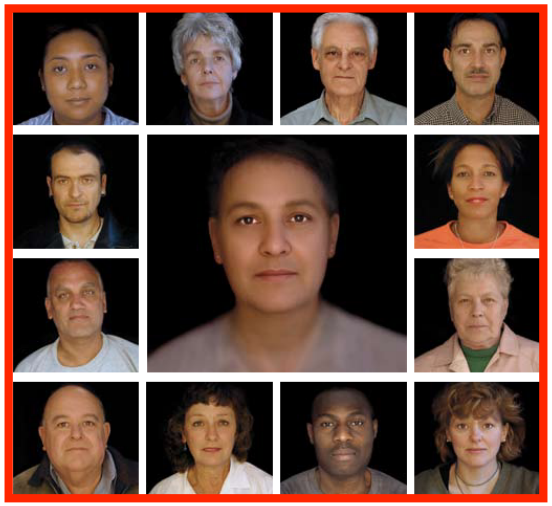
Prognostic factor



Predictive factor

When Averages Hide Individual Differences in Clinical Trials

Analyzing the results of clinical trials to expose individual patients' risks might help doctors make better treatment decisions



American Scientist 95:60, 2007

Gallamini.A: J Clin Oncol 25:3746-3752.

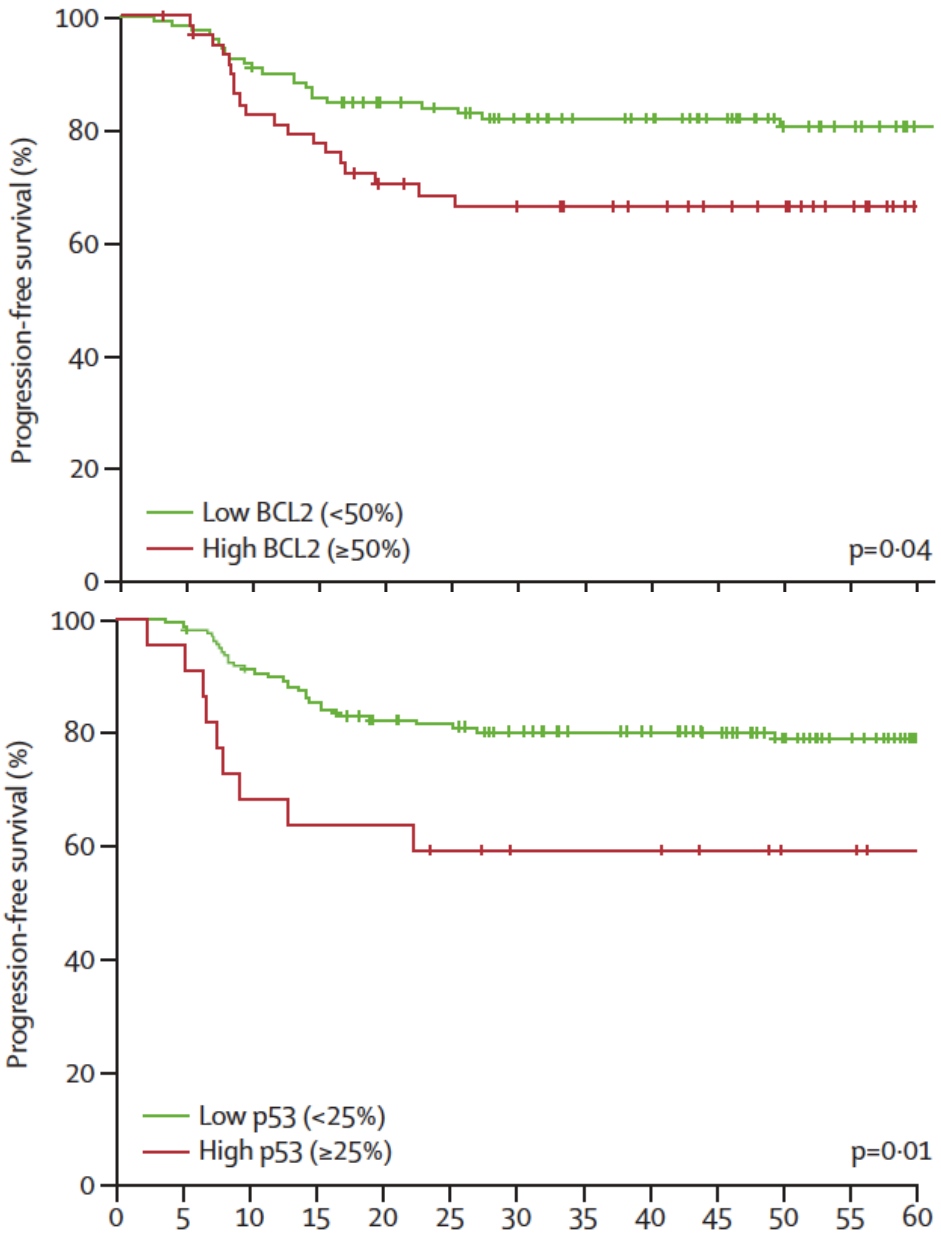
The combined role of biomarkers and interim PET scan in prediction of treatment outcome in classical Hodgkin's lymphoma: a retrospective, European, multicentre cohort study

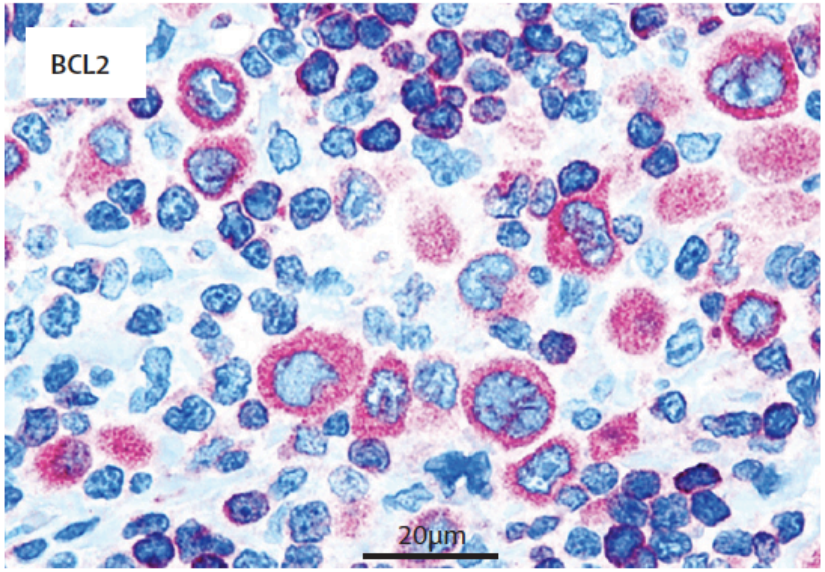
Claudio Agostinelli, Andrea Gallamini*, Luisa Stracqualursi*, Patrizia Agati*, Claudio Tripodo, Fabio Fuligni, Maria Teresa Sista, Stefano Fanti, Alberto Biggi, Umberto Vitolo, Luigi Rigacci, Francesco Merli, Caterina Patti, Alessandra Romano, Alessandro Levis, Livio Trentin, Caterina Stelitano, Anna Borra, Pier Paolo Piccaluga, Stephen Hamilton-Dutoit, Peter Kamper, Jan Maciej Zaucha, Bogdan Małkowski, Waldemar Kulikowski, Joanna Tajer, Edyta Subocz, Justyna Rybka, Christian Steidl, Alessandro Broccoli, Lisa Argnani, Randy D Gascoyne, Francesco d'Amore, Pier Luigi Zinzani†, Stefano A Pileri†*

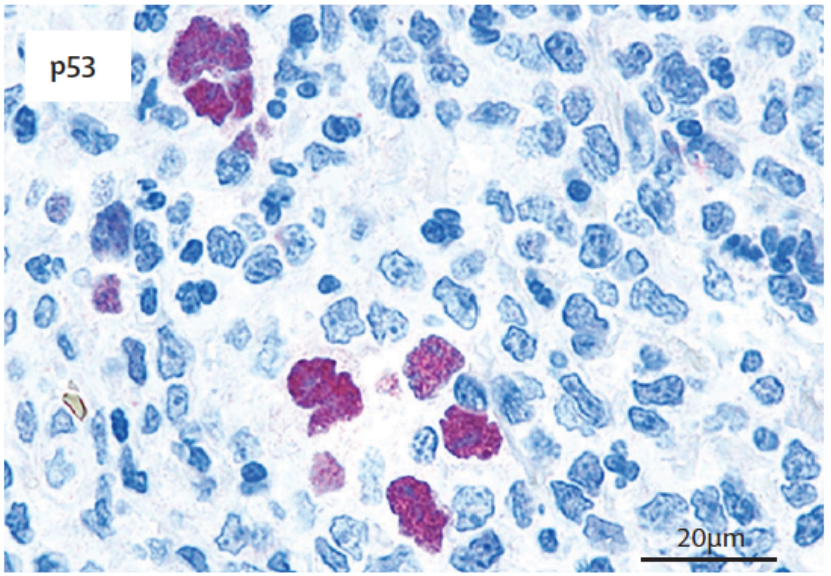
- International retrospective study form Italian, Danish and Polish in ABVD-treated cHL patients
- Retrospective test in 208 pts (training set), validated in 102 pts.
- Assessed biomarkers on HRS cells.
- Evaluated biomarkers in microenvironmental cells from TMAs.
- Cox multivariate and Classification and Regression Tree (CART) analysis

Agostinelli C, Gallamini A. et al, Lancet Haem 2016 e-pub online

Biomarkers on HRS Cells and outcome in cHL

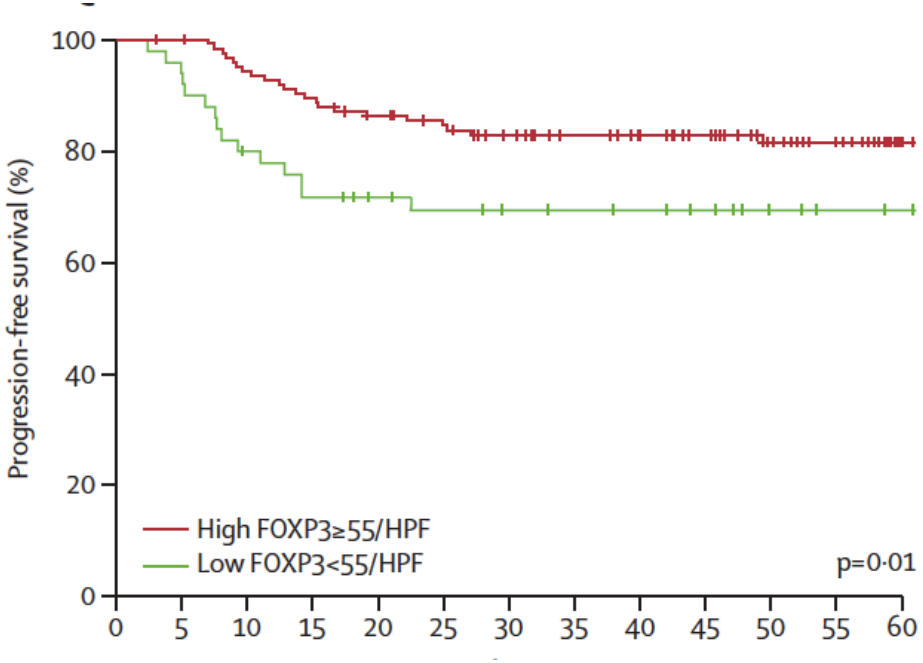


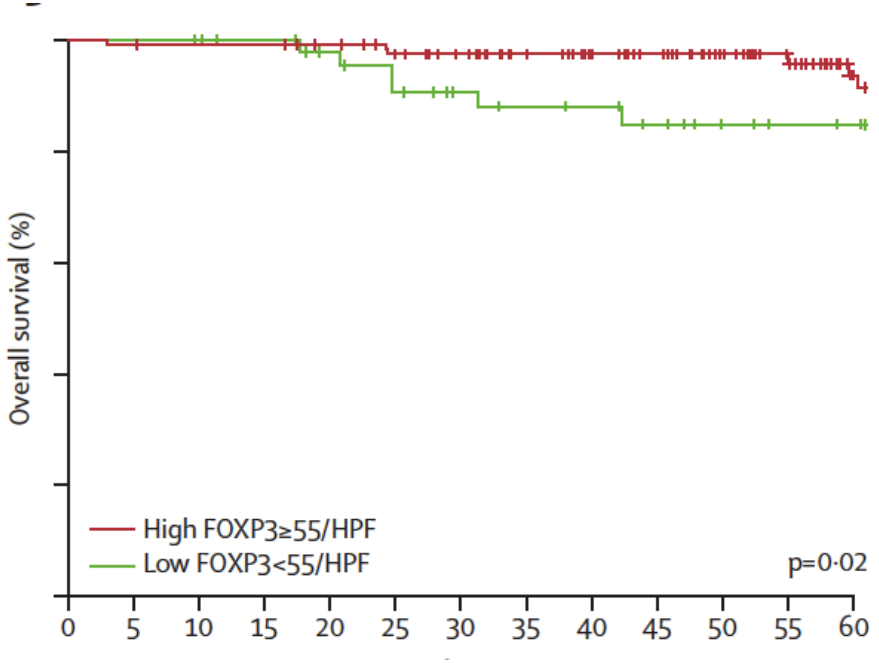




Agostinelli C, Gallamini A et al, Lancet Haematol 2016 e-pub on line

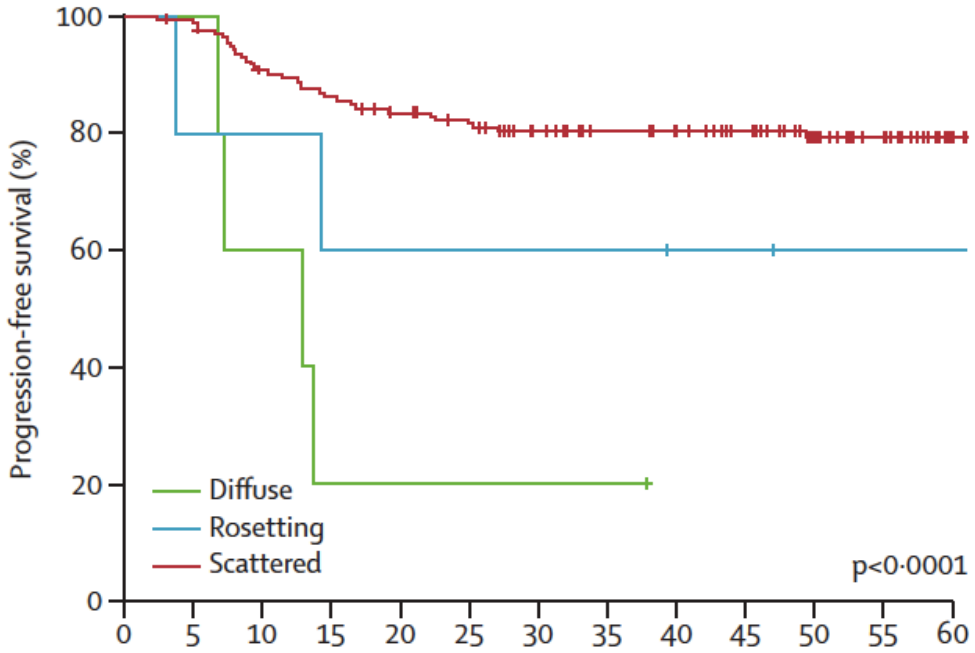
FOXP3 in ME cells and Outcome in cHL

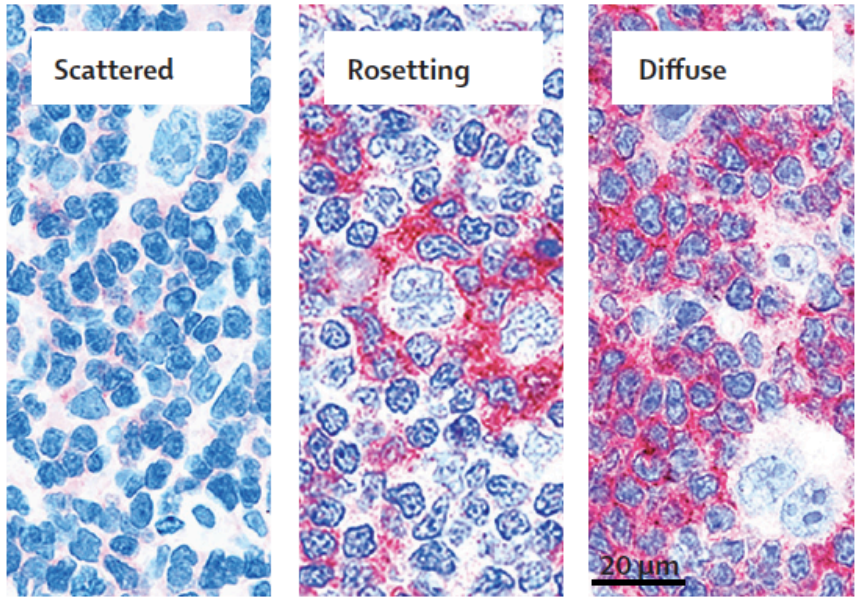




Agostinelli C, Gallamini A et al, Lancet Haematol 2016 e-pub on line

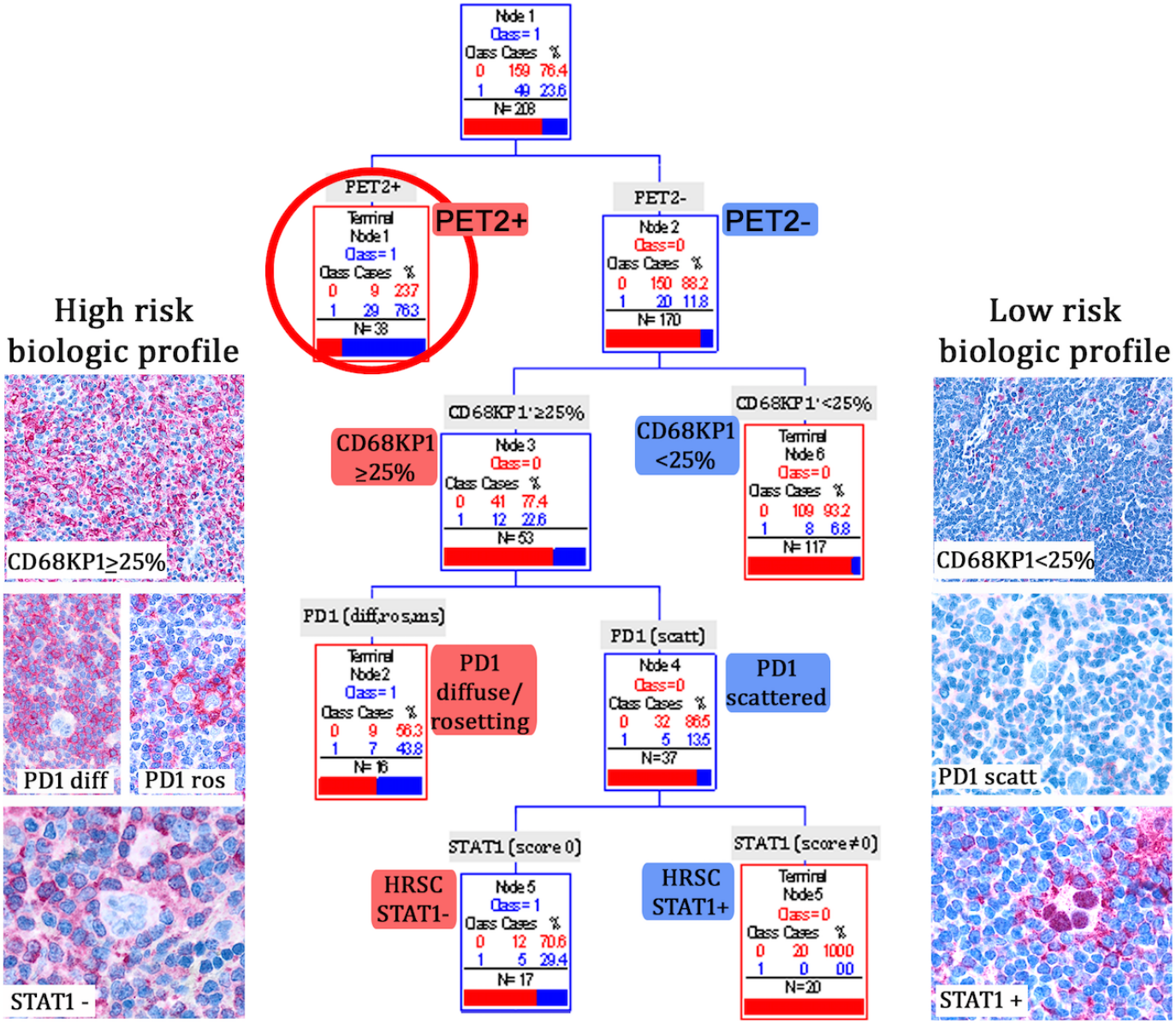
PD1 in ME cells and Outcome in cHL



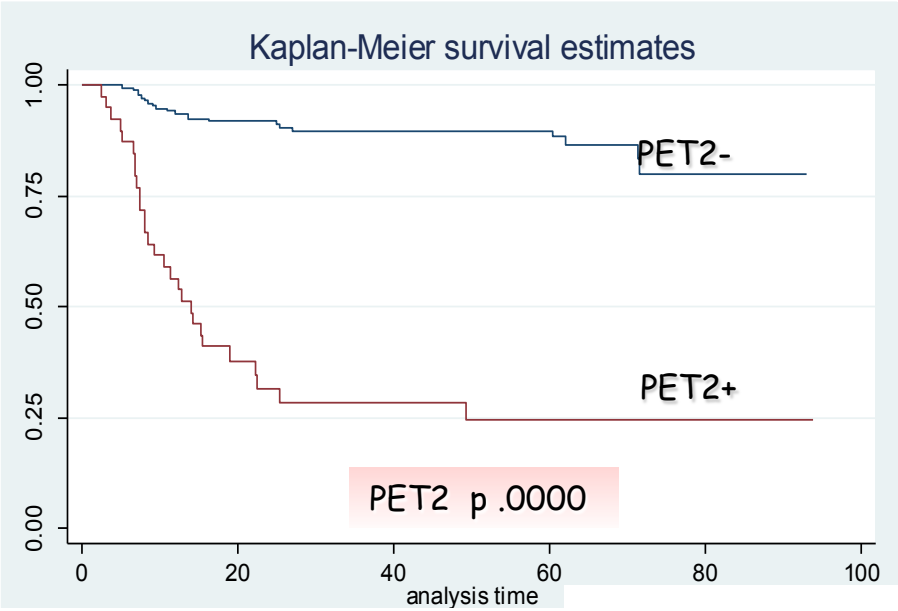


Agostinelli C, Gallamini A et al, Lancet Haematol 2016 e-pub on line

Classification and regression tree (CART) analysis

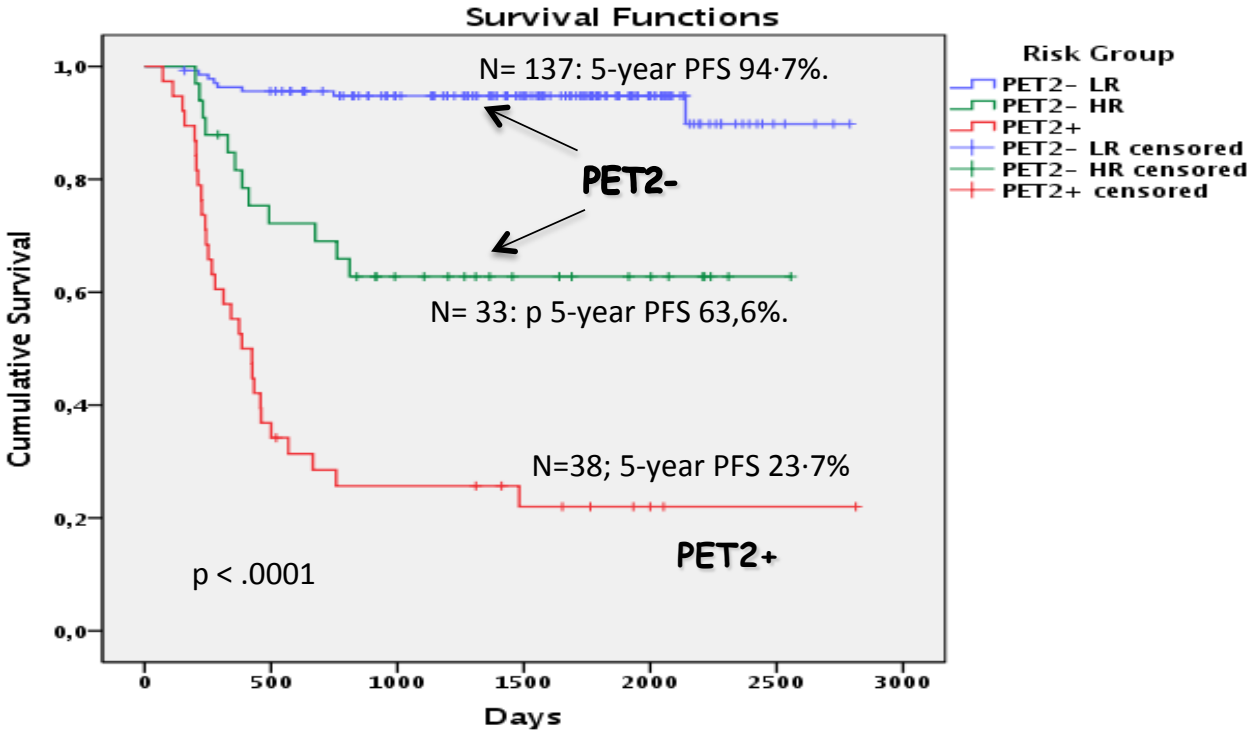


Agostinelli C, Gallamini A et al, Lancet Haematol 2016 e-pub on line



From PET-2…

…to PET-2 and TMAs.



Agostinelli C, Gallamini A et al, Lancet Haematol 2016 e-pub on line

PET-2 negative patients and treatment outcome

PET-2 negative low-risk class:
a) Low value of CD68KP1 (< 25%) ;
b) CD68KP1 ≥ 25%, but scattered PD1 pattern and positive STAT1 in RCS;

PET-2 negative high-risk class:
a) CD68KP1 ≥ 25% and diffuse or rosetting PD1 pattern;
b) CD68KP1 ≥ 25%, scattered PD1 pattern and negative STAT1 in RCS.

Agostinelli C, Gallamini A et al, Lancet Haematol 2016 e-pub on line

Conclusions

- Deauville 5-PS for interim and and-of treatment PET/CT interpretation has been validated and proved simple and reproducible.
- PET response-adapted strategy proved feasible in clinical trials and now it is adopted as standard care in several centers
- The optimal time point for interim response is advanced-stage disease is after 2 ABVD courses
- ABVD treatment intensification in PET-2 positive patients improved 3-Y PFS by 5-10% compared to historical ABVD data
- The NPV of PET-2 could be improved by the combined use of biomarkers

Acknowledgements

On behalf of FIL/GITIL

A. Nagler, A. Avigdor Hematology Dept Tel Hashomer Hospital, Tel Aviv.
C. Tarella, D. Gottardi Hematology Dept. Ospedale Mauriziano, Torino.
S. Viviani, P Corradini Medical Oncology, Istituto Tumori, Milano.
R. Sorasio, D. Rapezzi Hematology Dept., S. Croce Hospital , Cuneo.
G. Pizzolo R. Zanotti Hematology Chair University of Verona.
L. Trentin, R. Zambello; Experimental medicine Dept., Padoa University,
M. Cantonetti. Hematology Chair University Tor Vergata, Roma.
P. Leoni, M Gini. Hematology Chair ASO Ospedali Riuniti, Ancona.
F. Pane, M Picardi: Hematology Chair Policlinico Federico II Napolli.
C. Patti Hematology Dept, Opsedale V. Cervello, Palermo.
G. La Nasa G, Haematology Dept. Ospedale R. Binaghi, Cagliar.i
G. Saglio, G. Parvis Internal medicine Dept. University of Turin, Torino.
P. Gavarotti, Hematology Chair, University of Turin, Torino.
F. Ciceri, A Ferreri, Medical Oncology, IRCCS Ospedale S. Raffaele, Milano.
M. Gobbi, I Plerri Hematology Chair University of Genoa.
A. Rambaldi, A. Rossi Hematology Dept., Ospedali Riuniti di Bergamo.
C. Schiavotto Hematology Dept. Ospedale S. Bortolo, Vicenz.a
S. Cortelazzo A Billio Hematology Dpt. Ospedale di Bolzano.
I Maiolino V. Zoli. Hematology Dpt. Ospedale S. Camillo Forlanini. Roma.
B. Falini, U Flenghi Hematology Chair University of Perugia.
A. Olivieri ,M. Ciminiello Haematology Dept, Ospedale S. Carlo, Potenza.
G. Di Raimondo, A. Romano Hematology Dept. University of Catania.

For Imaging exchange:

A. Stancu, C. Chauvie, Dixit S.r.L,National Nuclear Physics Institute, Turin, Italy

For central PET scan review

A Biggi Nuclear Medicine S. Croce Hospital Cuneo
F. Fallanca Nuclear Medicine IRCCS S. Raffaele Hospital Milan
U Ficola Nuclear Medicine La Maddalena Hospital Palermo
A Chiaravalloti Nuclear Medicine Tor Vergata University Rome
M Gregianin Nuclear Medicine IOV Oncology Institute, Padua

For data collecting, analysis and statistics :

G. Prosperini, M Scarano Epidemiology and Clinical Pharmacology Institute Mario Megri, Italy

Thank you for the attention

Pr. Andrea Gallamini

Research, Innovation and Statistics.

A. Lacassagne Cancer Center, Nice - France

andreagallamini@gmail.com