

The role of interim PET in Hodgkin and non-Hodgkin lymphomas

Singapore, December 20th, 2015

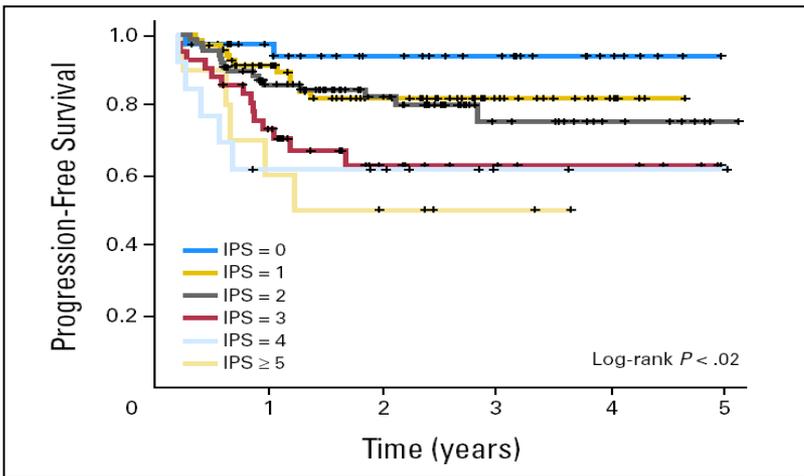
Pr. Andrea Gallamini
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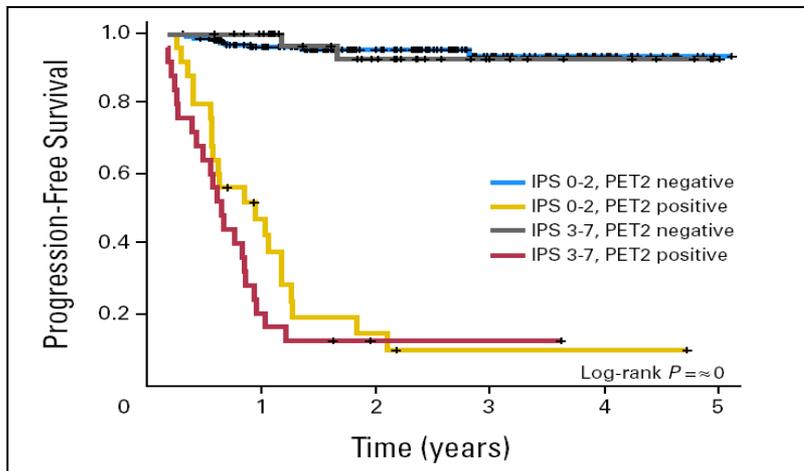
Disclosure slide

Takeda, MSD consultancy.

	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



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)

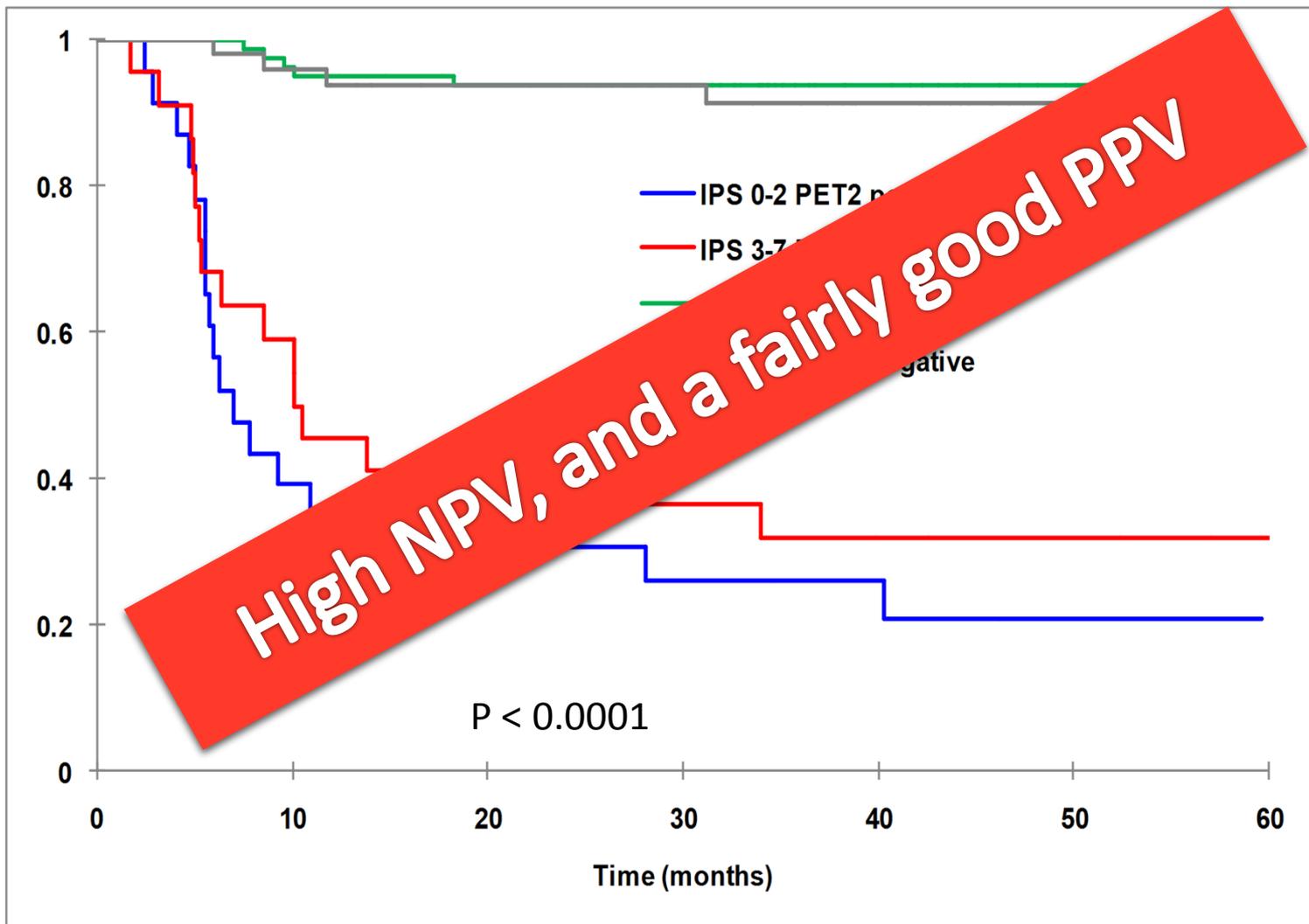


- ❑ Score 1 no uptake
- ❑ Score 2 uptake \leq mediastinum
- ❑ Score 3 uptake $>$ mediastinum but \leq liver

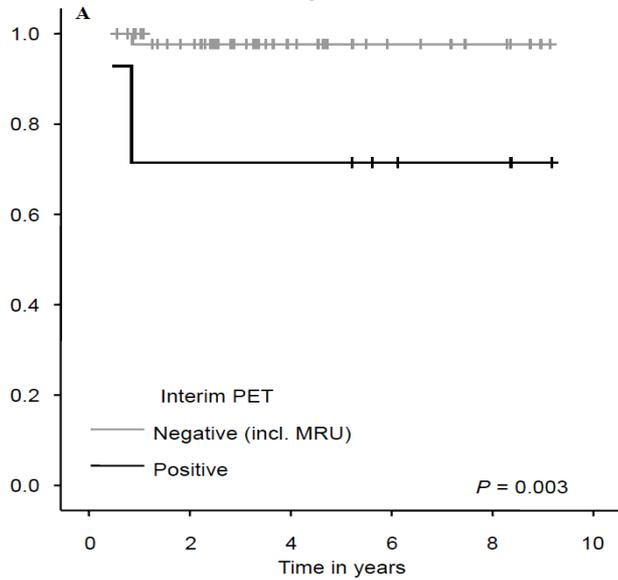
- ❑ Score 4: moderately \uparrow uptake $>$ liver
- ❑ Score 5 markedly \uparrow uptake $>$ liver and/or new sites of disease

Positivity threshold

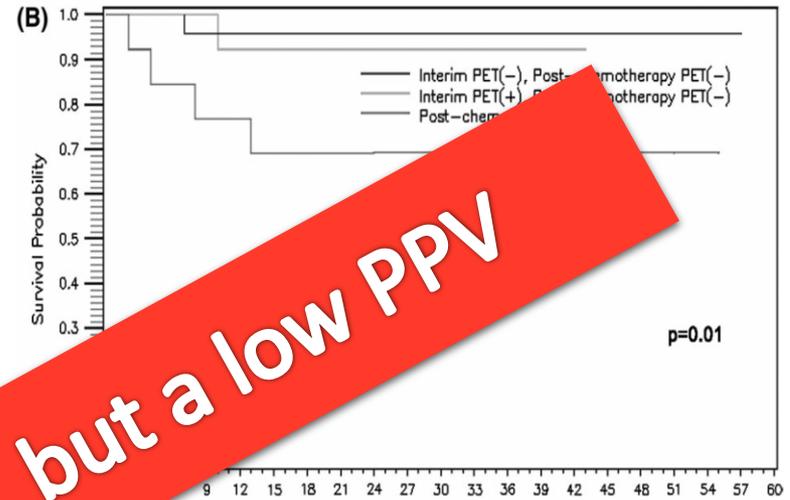
Advanced stage HL (N= 260).



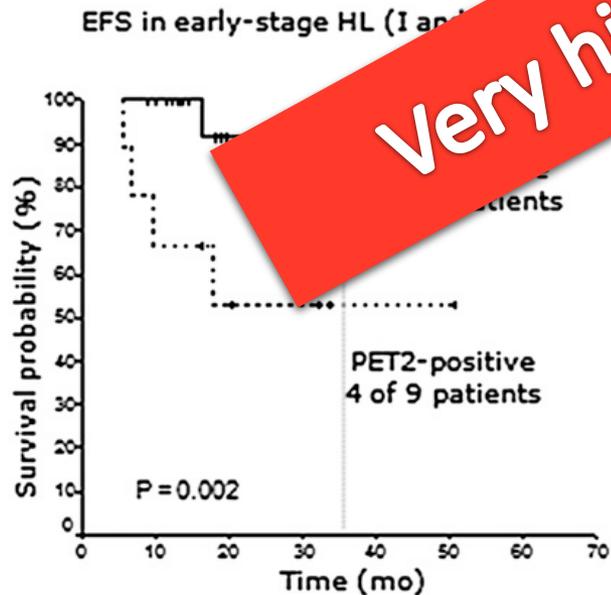
Early stage HL.



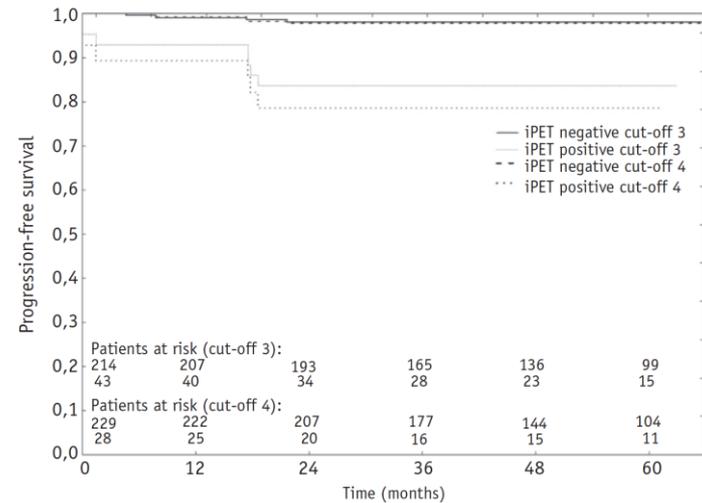
Hutchings M.: Annals of Oncology 2005; 16: 1160



Sher DJ: Annals of Oncology 2009; 20: 1848-53



Cerci J.: J Nucl Med 2010; 51:1337-43



Simontacchi G. Int J Radiation Oncol Biol Phys, 2015; 92: 1077-83.

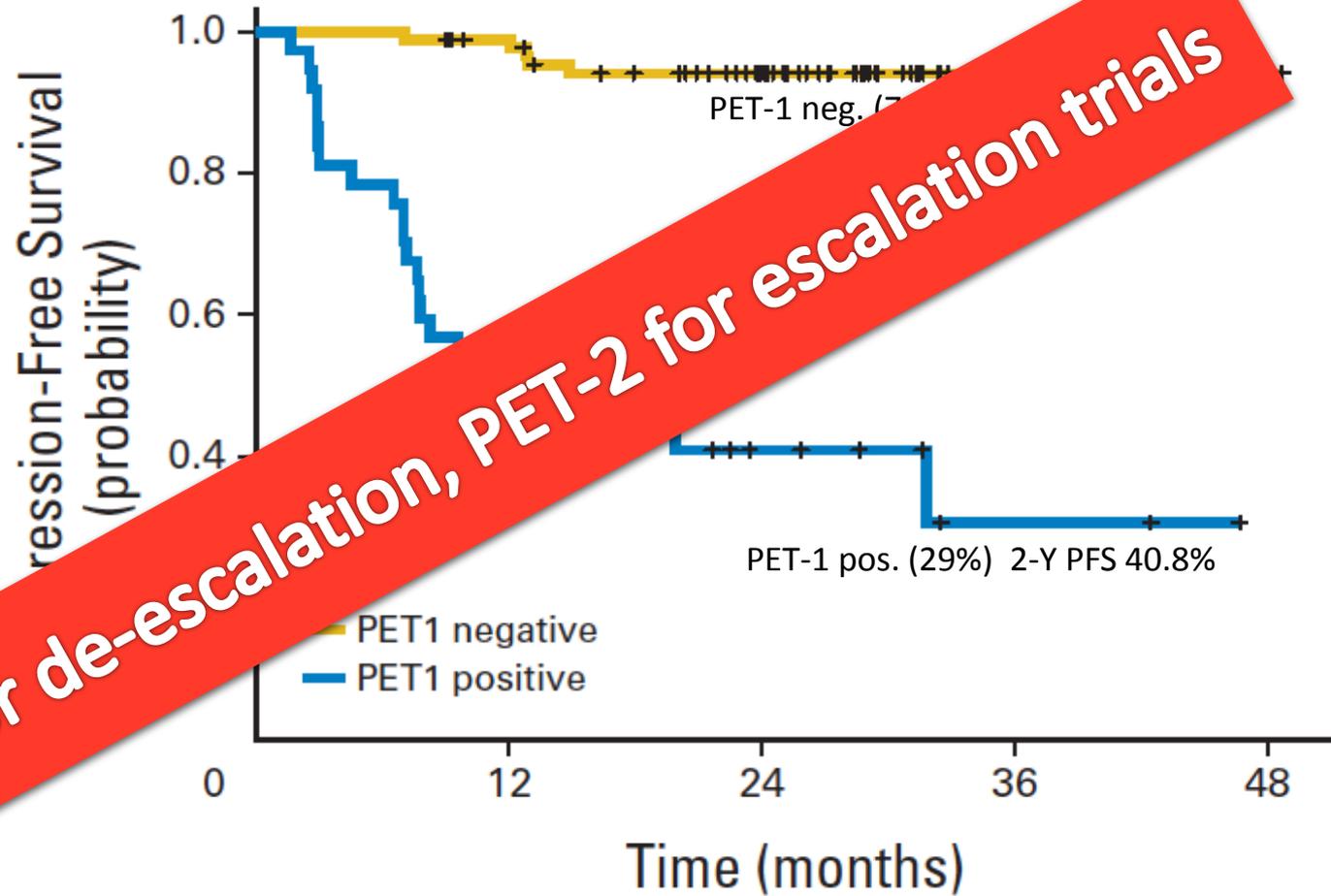
Very high NPV, but a low PPV

What is the best
“interim” time point ?

Anticipating interim PET after the 1st ABVD cycle

Stage I	10
Stage IIA	34
Stage IIB	24
Stage III	24
Stage IV	34
<hr/>	
Total	126

54%

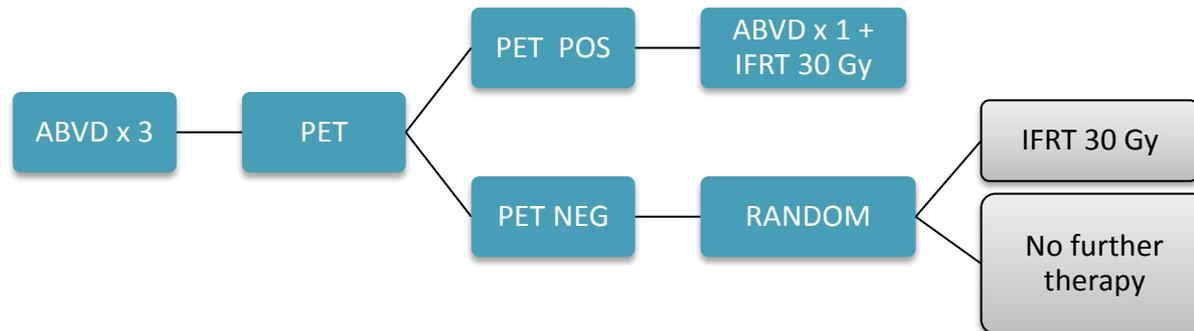


- Interpretation key: 5-PS
- 14 PET1-positive patients converted to a negative PET2
- All PET1-negative patients(N=88) were also PET2-negative.

PET response- adapted
trials in HL

Results of a Trial of PET-Directed Therapy for Early-Stage Hodgkin's Lymphoma

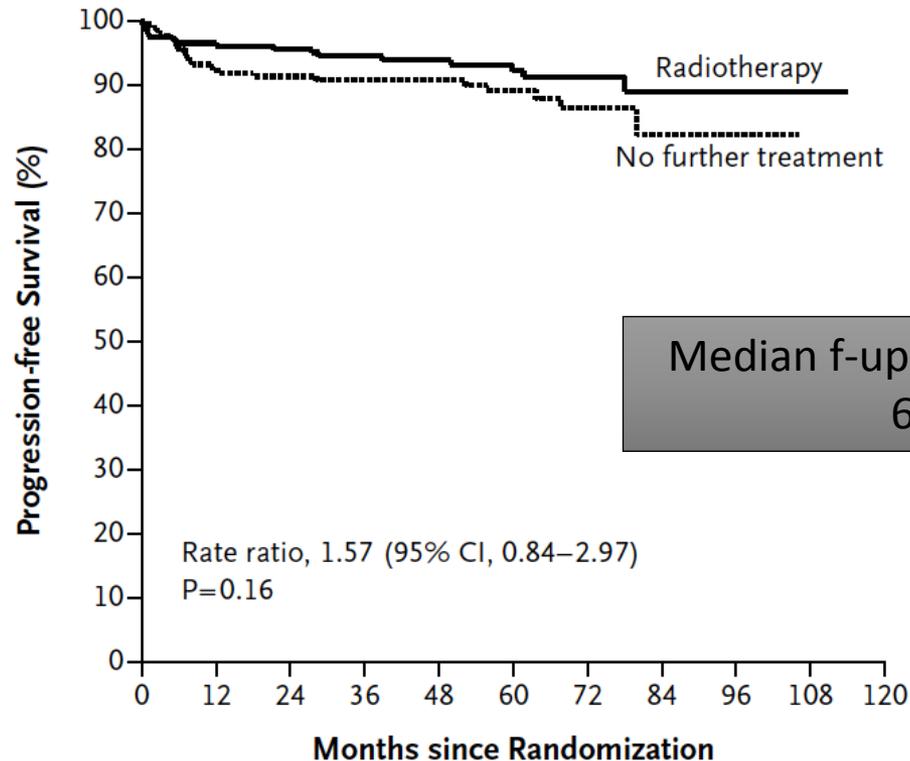
John Radford, M.D., Tim Illidge, M.D., Ph.D., Nicholas Counsell, M.Sc., Barry Hancock, M.D., Ruth Pettengell, M.D., Peter Johnson, M.D., Jennie Wimperis, D.M., Dominic Culligan, M.D., Bilyana Popova, M.Sc., Paul Smith, M.Sc., Andrew McMillan, M.B., Alison Brownell, M.B., Anton Kruger, M.B., Andrew Lister, M.D., Peter Hoskin, M.D., Michael O'Doherty, M.D., and Sally Barrington, M.D.



- Non inferiority phase III trial
- End Point: **<6% in 3-y PFS** in non-irradiated Vs. irradiated arm.
- 2003-2010: 602 pts. 400 randomized: IFRT Vs. NFT.
- Stage I A or II A, by CT scan,
- No mediastinal bulky
- Median Follow-up: 48.6 months

RAPID: Intention to treat analysis

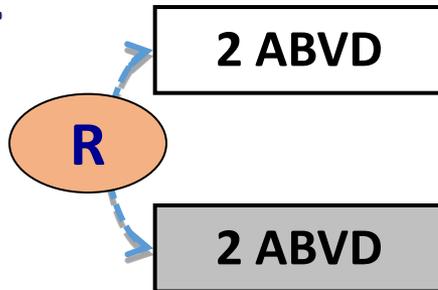
A Intention-to-Treat Analysis



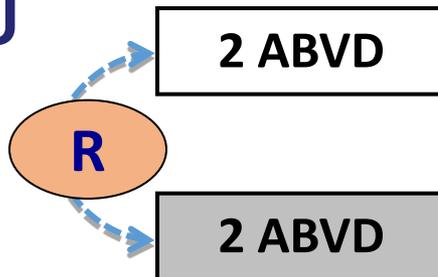
3 year PFS: 94.6% (PET –ve, IFRT), 90.8% (PET –ve, NFT)

EORTC H10 (#20051) in early-stage HL : study design

H10F

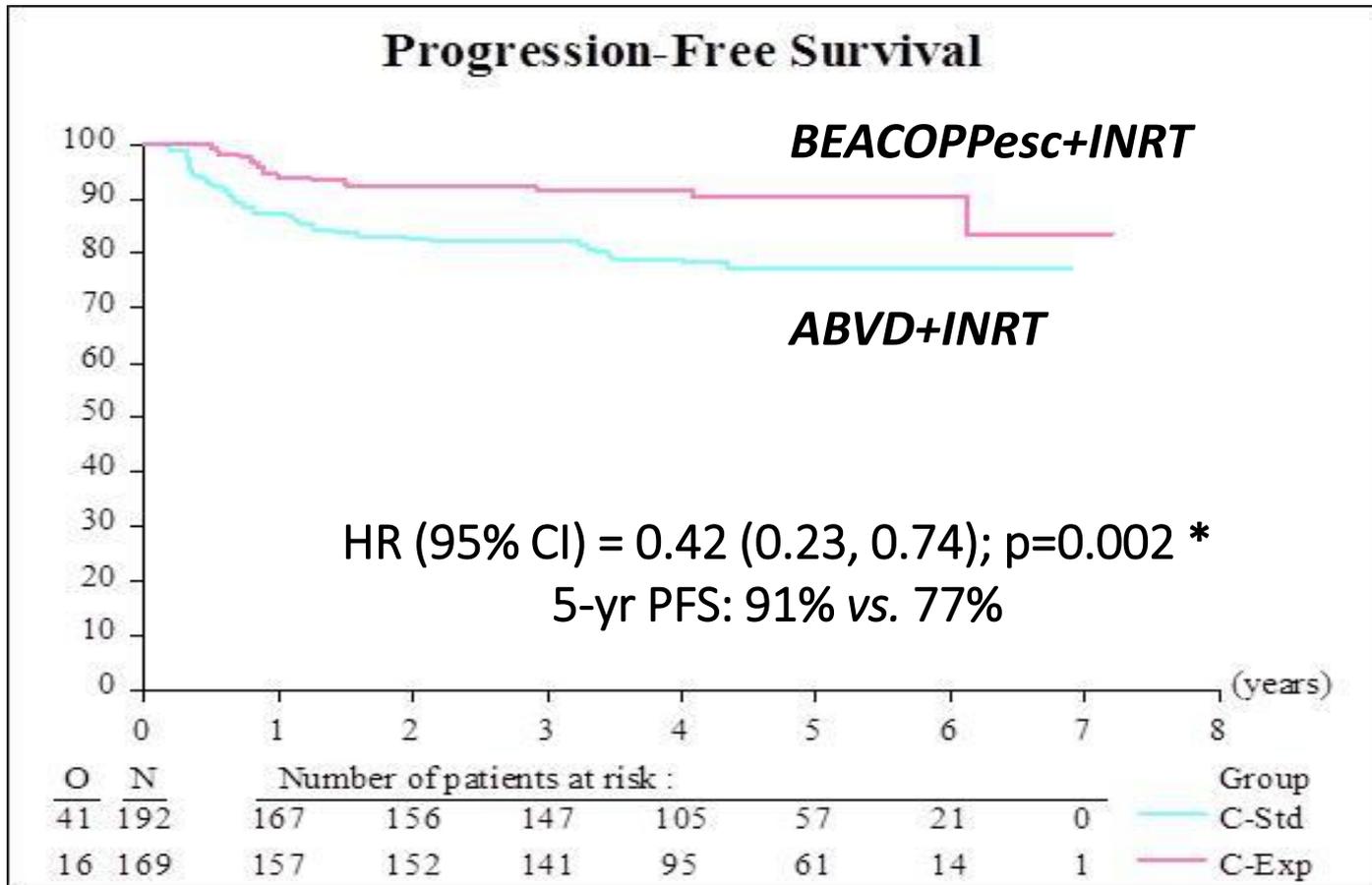


H10U

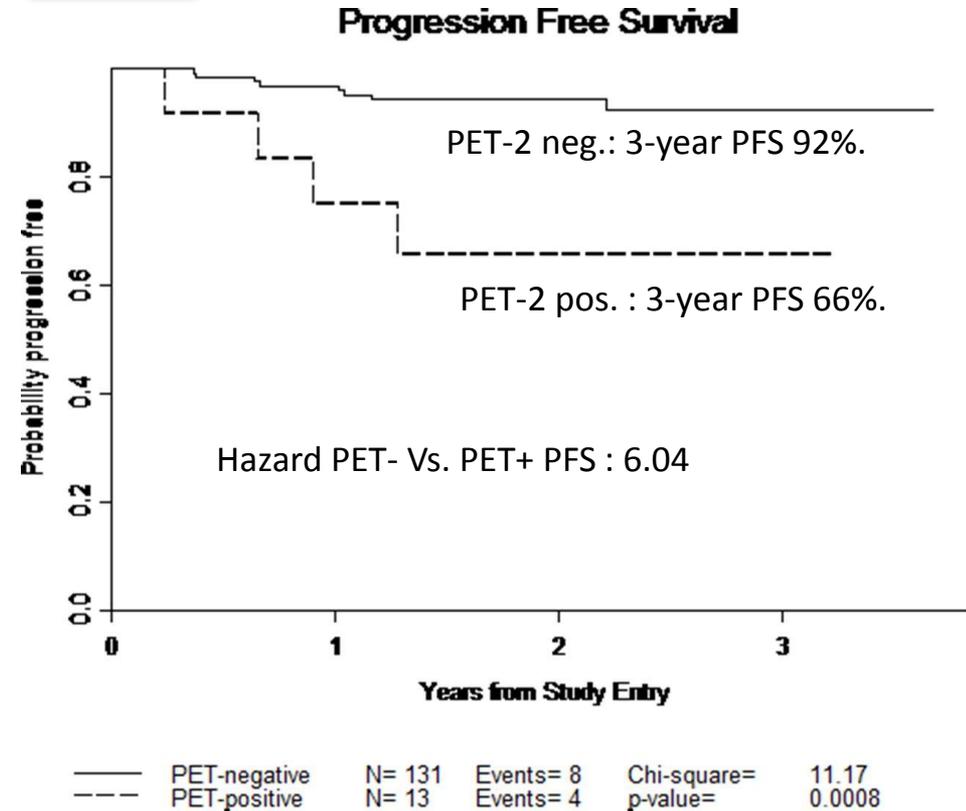
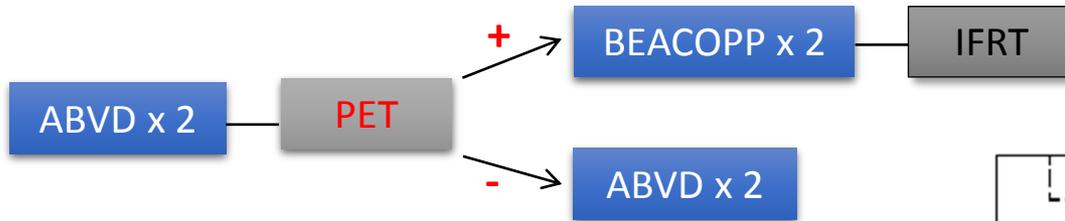


HL - CS I/II - untreated - 15-70 yrs - no NLPHL

PET+ group: BEACOPPesc vs. ABVD (PFS)



PET-response adapted Tx in early-stage HL (CALGB/Alliance 50604 trial)

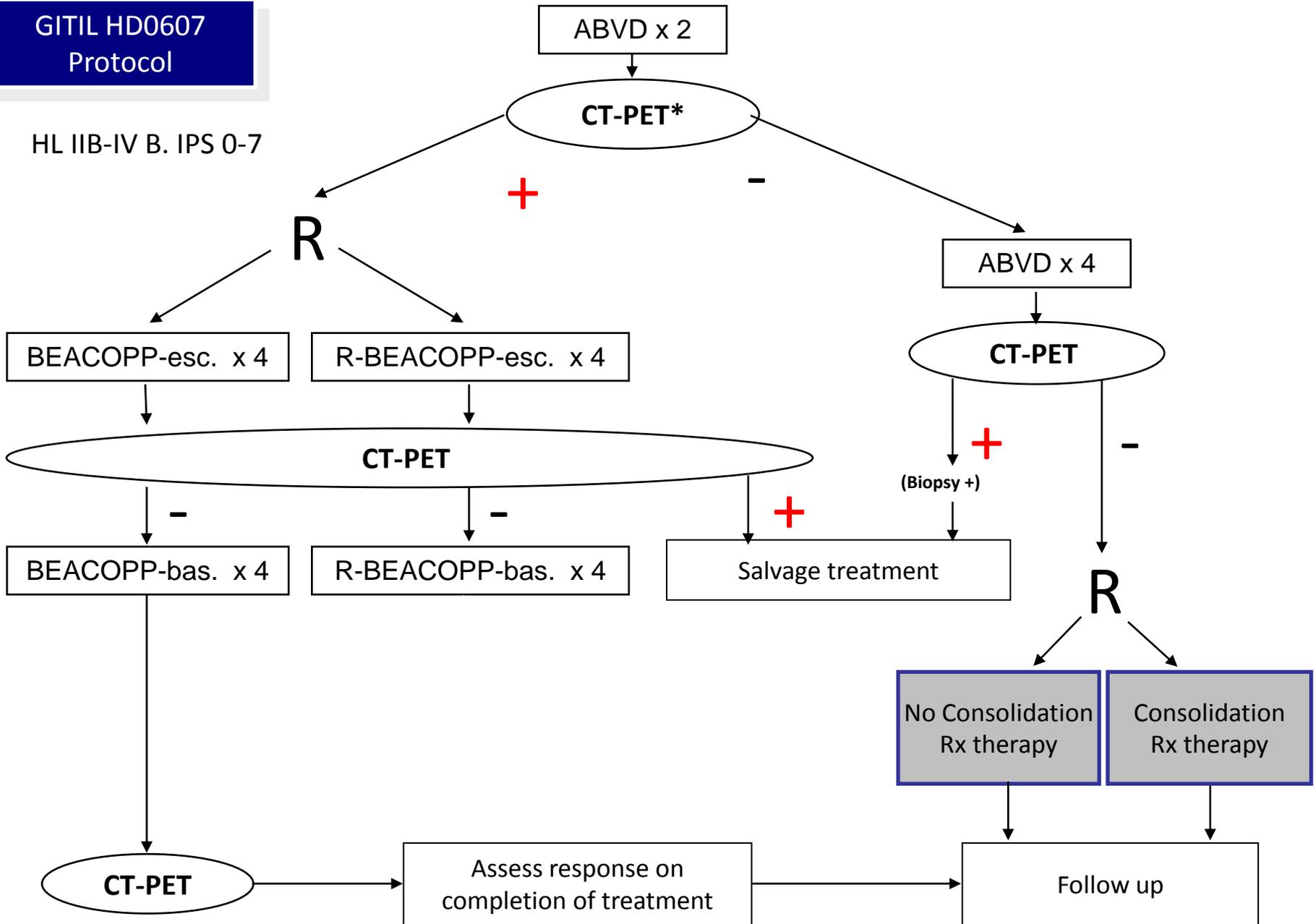


- 164 untreated HL pts with non-bulky stages I/II
- Primary objective of 3-year PFS $\geq 85\%$ for PET-negative p.
- Secondary endpoint: HR between PET-2+ and PET- ≤ 3.84

PET response-adapted trials in advanced-stage HL

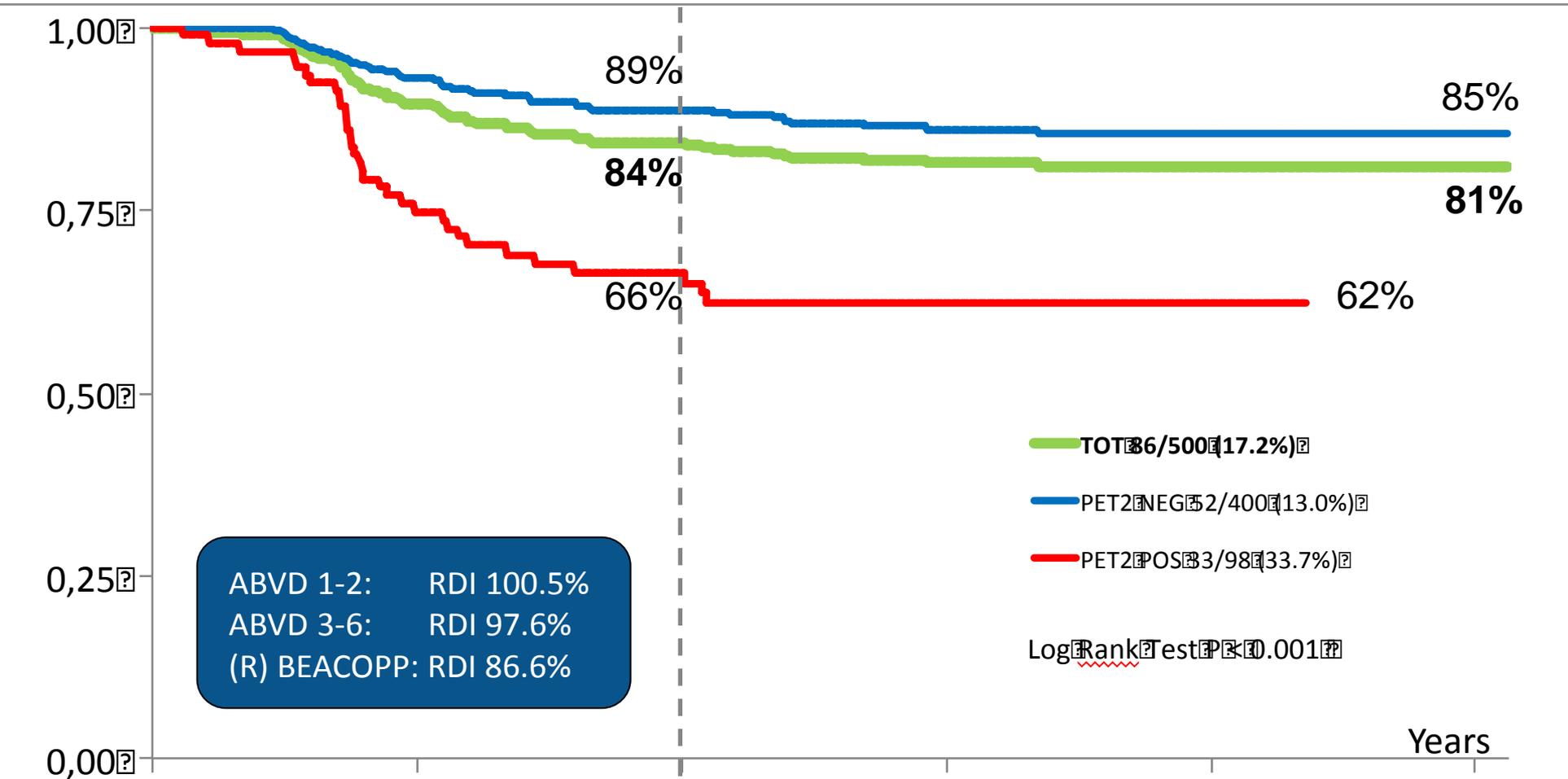
Trial Name	Sample	Stage	End-point	Before PET-2	PET-2 neg. arm	PET-2 pos. arm	PET Key Interpret.
Israeli H2	300	I-IV	3-y PFS	ABVDx2	ABVDx4	EBx4 HD+ASCT	Dynamic score
AHL (LYSA)	798	IIB-IVB	5-y PFS	EBx2	EB x 6 ABVDx2	EBx6	5-PS
HD 18 (GHSG)	1500	IIB-IVB	5-Y PFS	EBx2	EB x 6 ABVDx4	EBx6 ±R	5-PS ^m
HD 0607 (FIL/GITIL)	750	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 Aculte Leukemia Group



* Blinded Independent Central Review

Failure Free Survival according to PET2 result



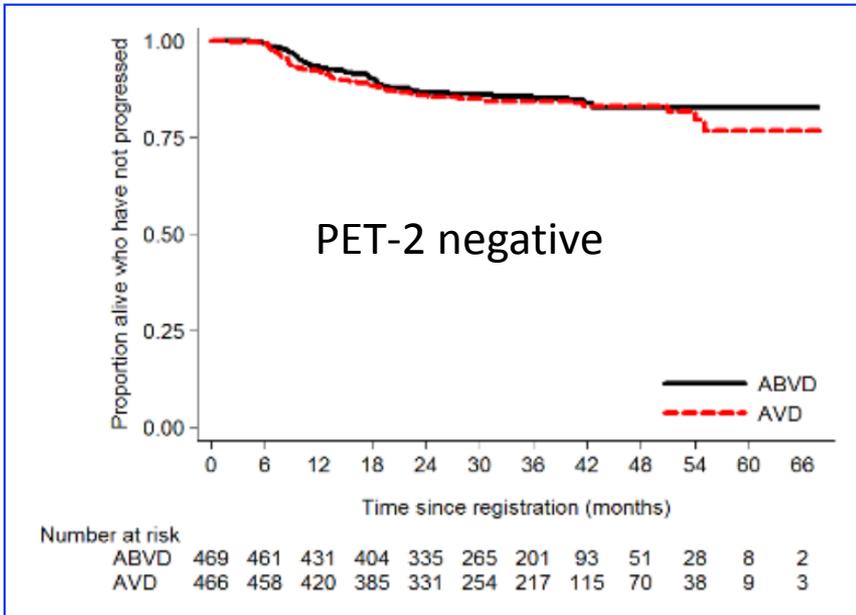
ABVD 1-2: RDI 100.5%
 ABVD 3-6: RDI 97.6%
 (R) BEACOPP: RDI 86.6%

	0	1	2	3	4	5						
TOT	500*	(51)	417	(23)	338	(10)	212	(1)	37	(0)	1	(1)
PET2 NEG	400	(27)	351	(16)	290	(7)	186	(1)	30	(0)	1	(1)
PET2 POS	98	(23)	66	(7)	48	(3)	26	(0)	7	(0)	0	(-)

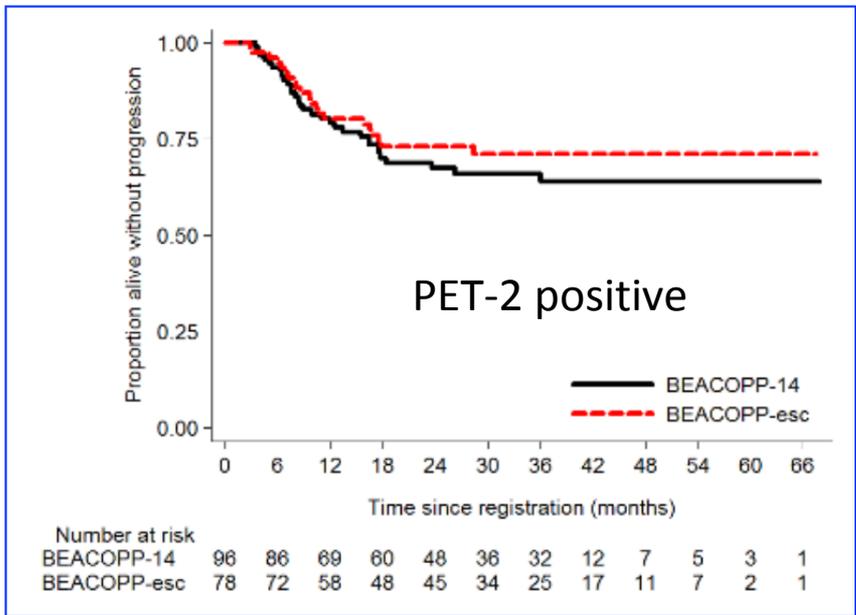
* 1 pt died before PET2 evaluation and 1 patient is missing for PET2

NCRI RATHL trial: PFS according to PET-2 status

1214 patients
Median f-up 34.7 months



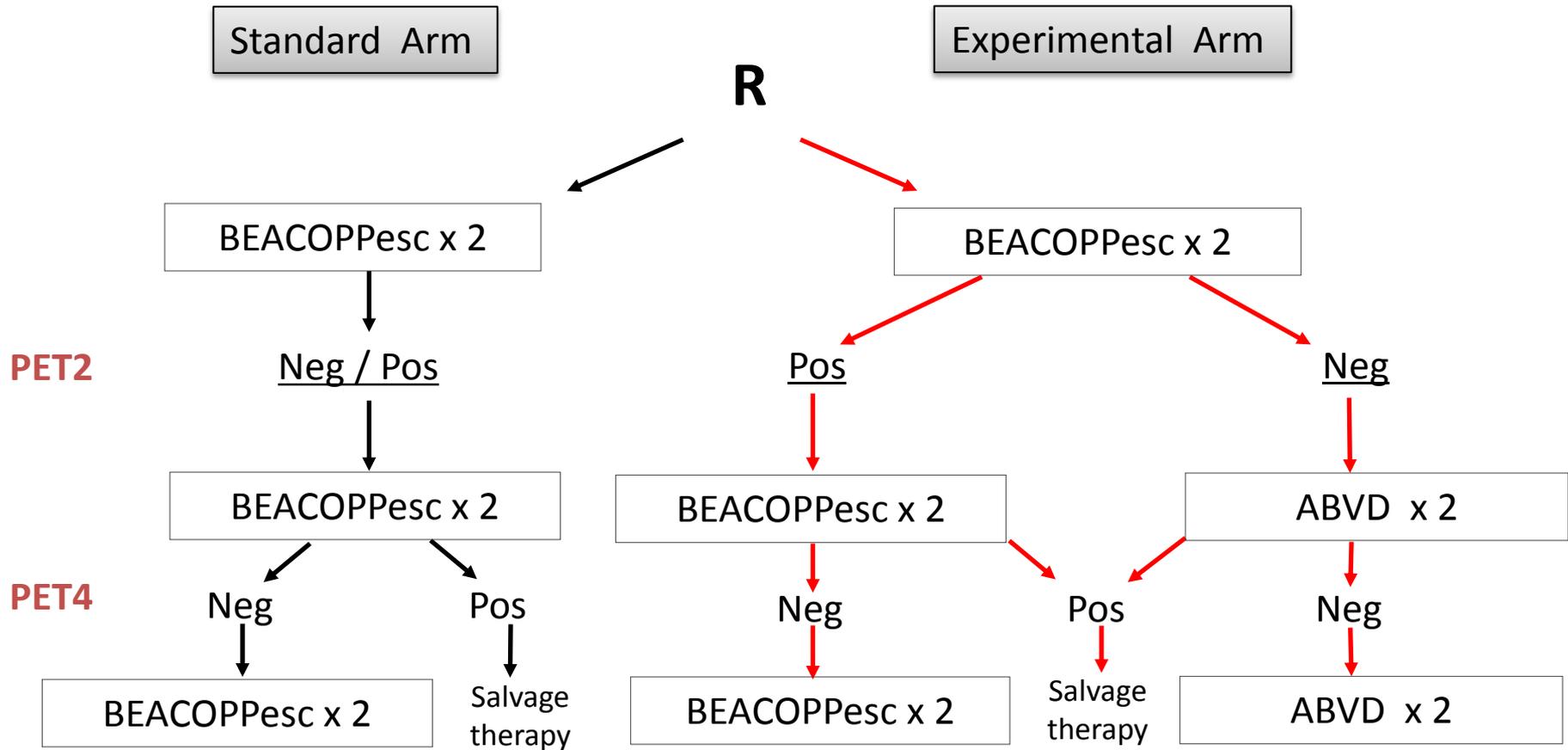
3-y PFS, ABVD 85.4%
3-Y PFS AVD: 84.4%



3-Y PFS BEACOPP-14: 66.0%
3-Y PFS eBEACOPP: 71.1%

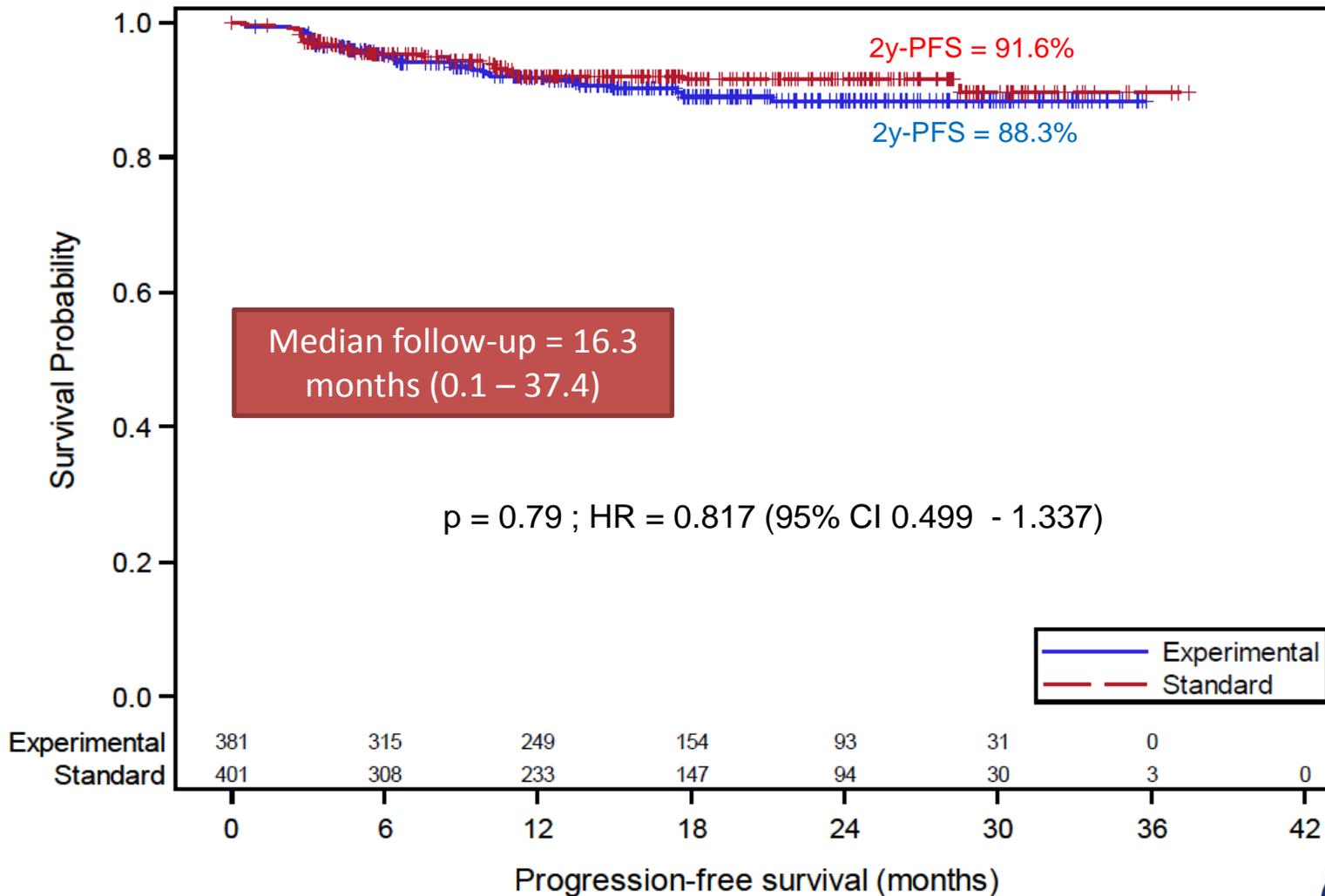
AHL 2011: Study design

NCT01358747



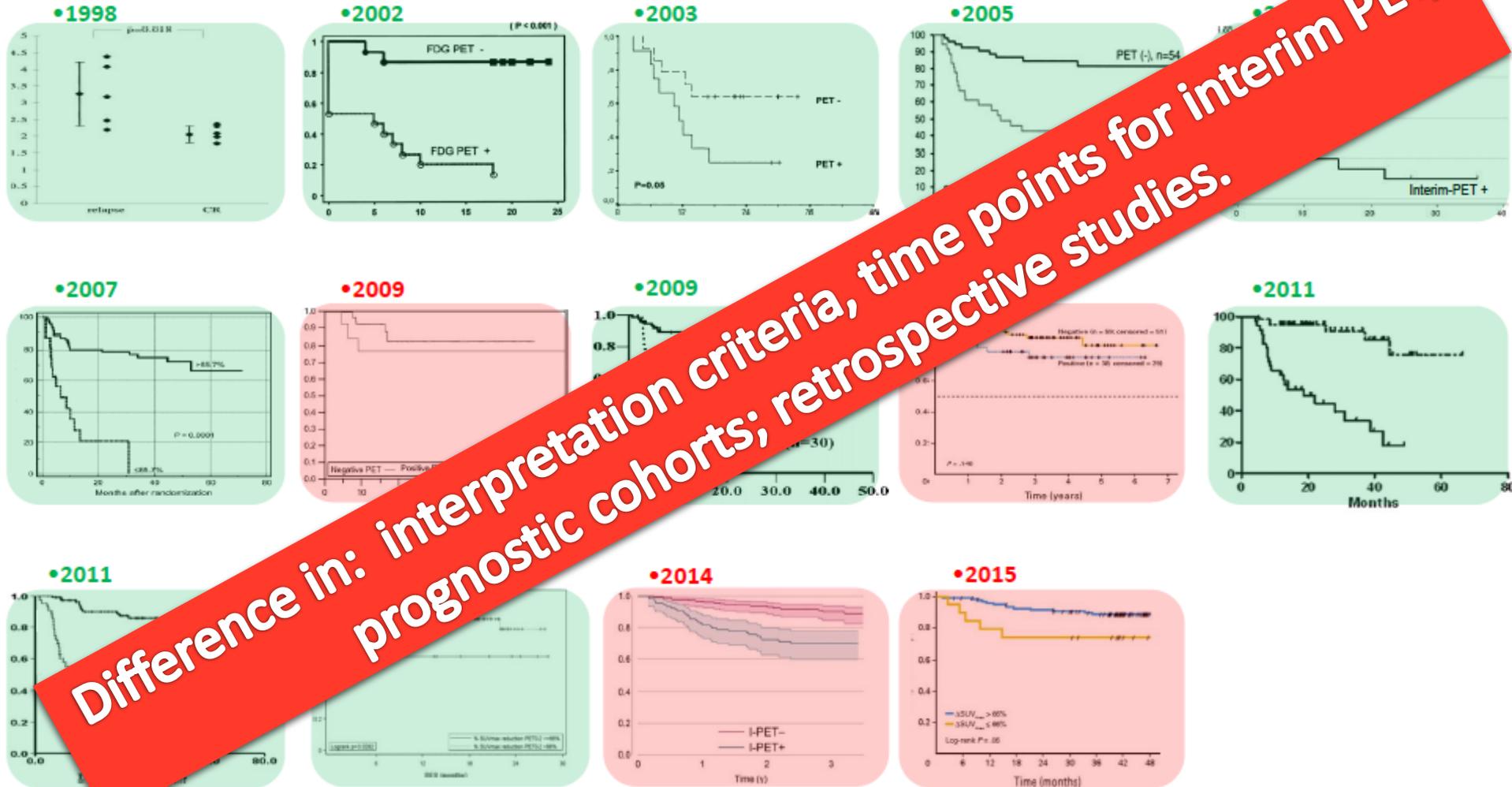
AHL 2011: PFS according to treatment arm

PFS according to treatment arm - ITT set
With Number of Subjects at Risk



**Interim PET in DLBCL:
Yes, not or not yet ?**

Interim PET in DLBCL



Significantly associated with PFS

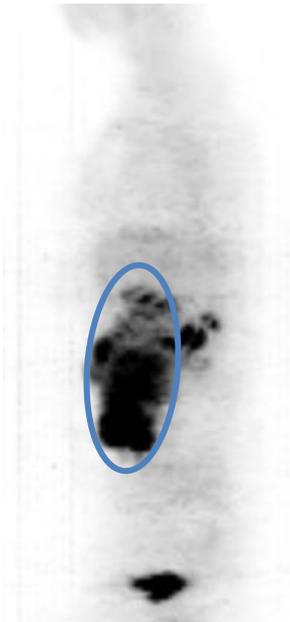


Not associated with PFS

Interim-PET in aggressive Lymphoma

Variable: Interval Chemotherapy – PET/CT

A
Pre-
treatment



SUV_{max}: 16,5

SUV_{max} reduction: ---

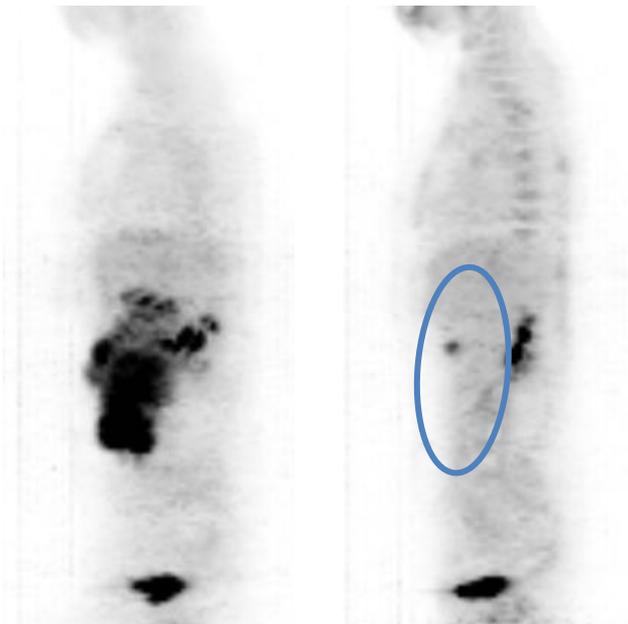
Visual score: positive

Interim-PET in aggressive Lymphoma

Variable: Interval Chemotherapy – PET/CT

A
Pre-treatment

B
Interim day 13



SUV _{max} :	16,5	7,3
SUV _{max} reduction:	---	56%
Visual score:	positive	positive

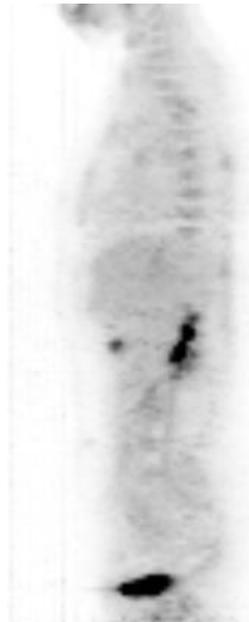
Interim-PET in aggressive Lymphoma

Variable: Interval Chemotherapy – PET/CT

A
Pre-treatment



B
Interim day 13



C
Interim day 20



SUV_{max}: 16,5

7,3

2,8

SUV_{max} reduction: ---

56%

83%

Visual score: positive

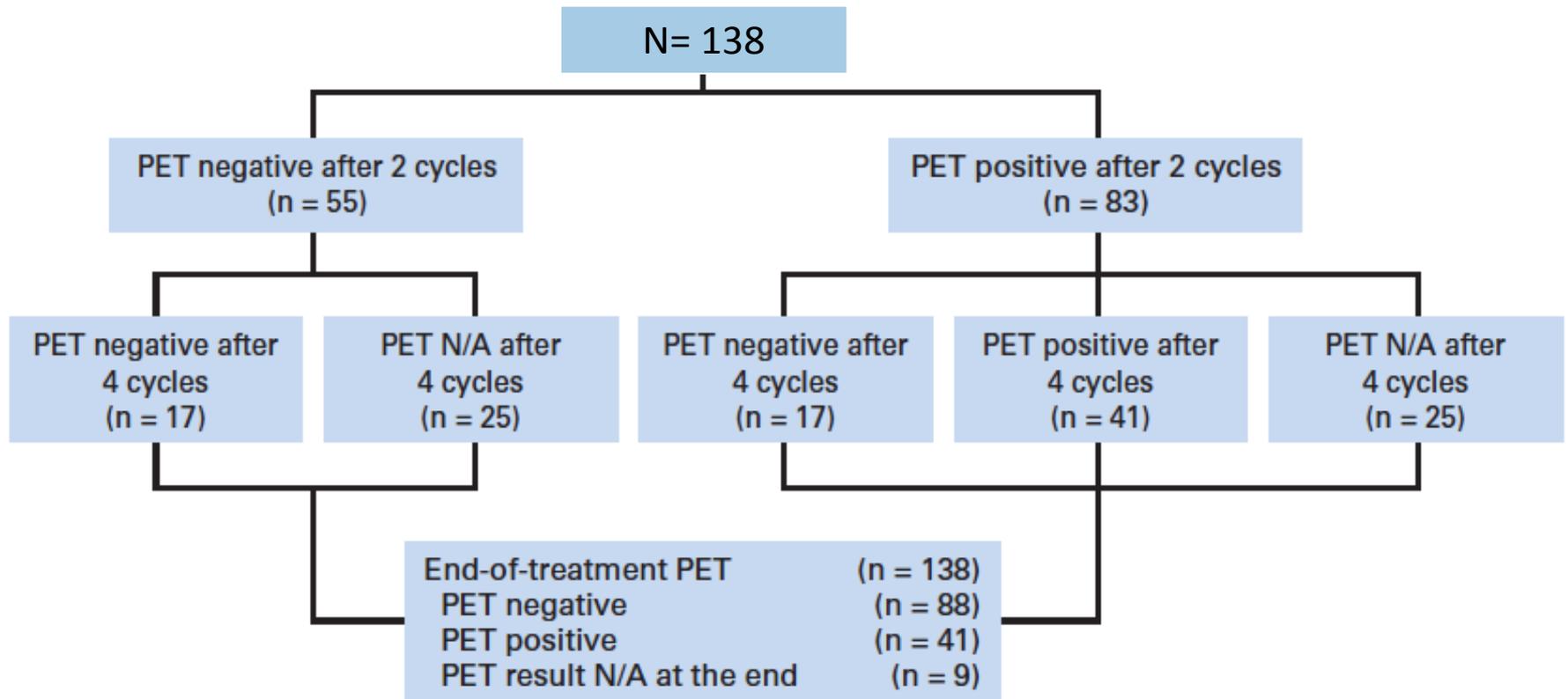
positive

negative

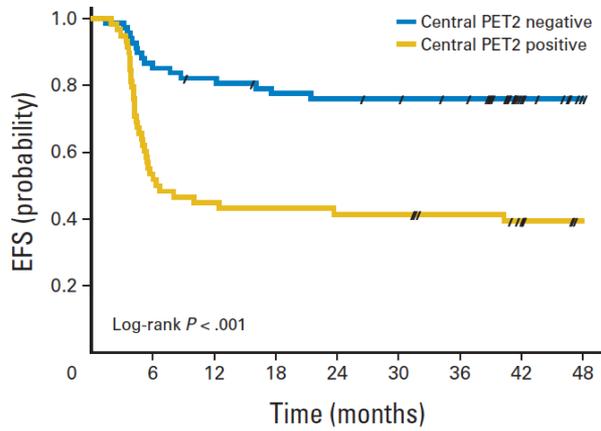
The predictive role on PFS and OS of i-PET in DLBCL

- Treatment: R-CHOP-14 x 6 + 2R
- I-PET after 2 R-CHOP, 4 CHOP, and E-PET after 2R.
- No Tx change based on PET2 or PET4 results
- Interpretation key: 5-PS
- IPS 0-2 in 98 p. (71%)

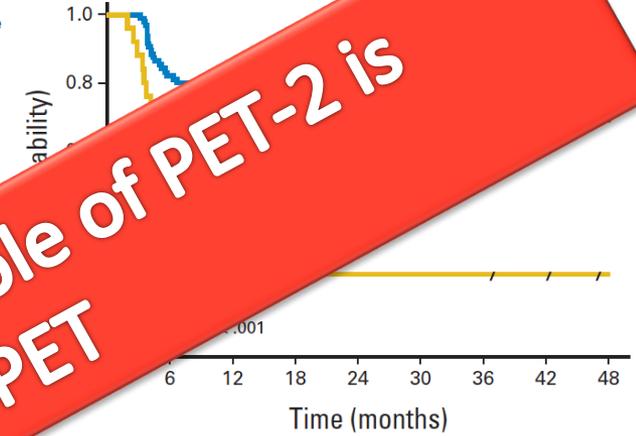
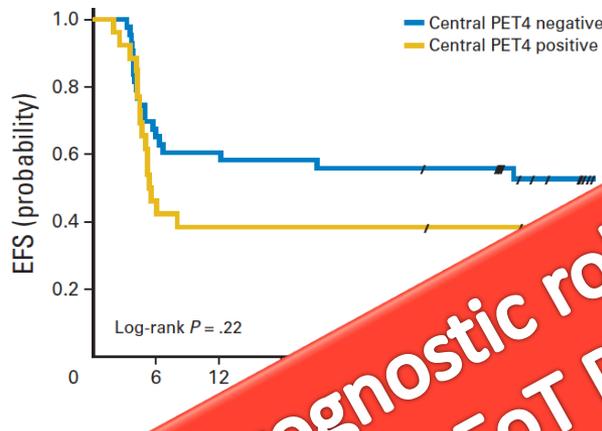
SAKK 38/07 trial



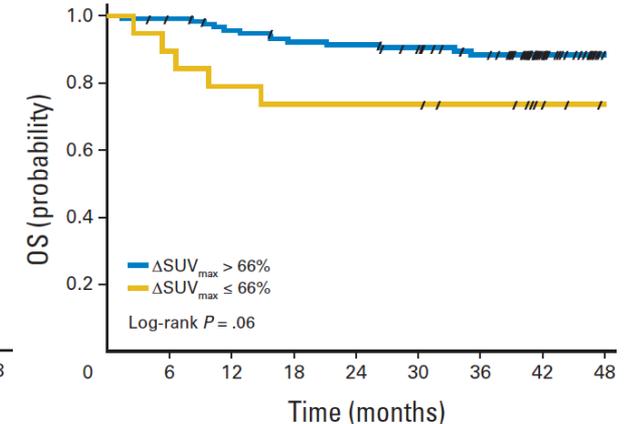
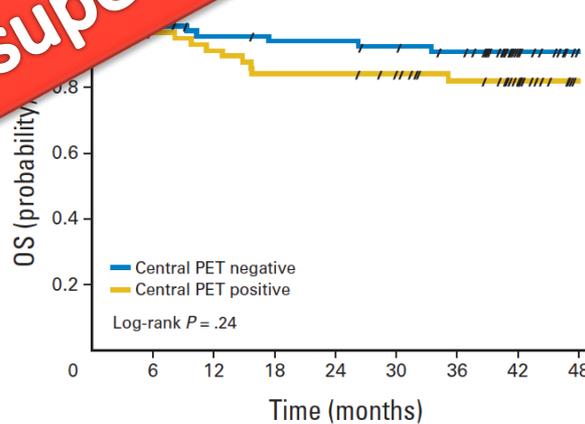
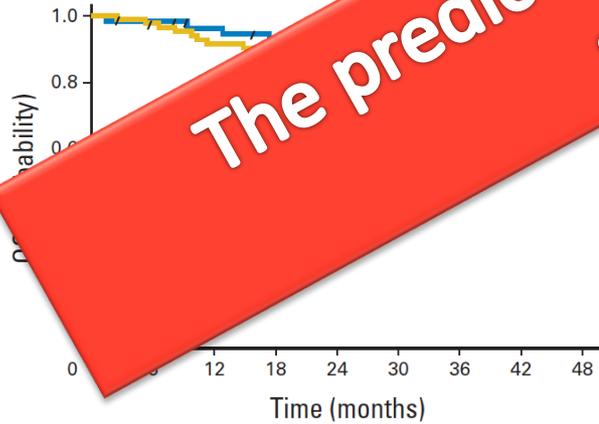
Interim (PET-2, PET-4) Vs. final PET (PET-6): EFS, OS



PET-2



PET-6



The predictive and prognostic role of PET-2 is superseded by EoT PET

PET response- adapted trials in DLBCL

PETAL-Studie

Design

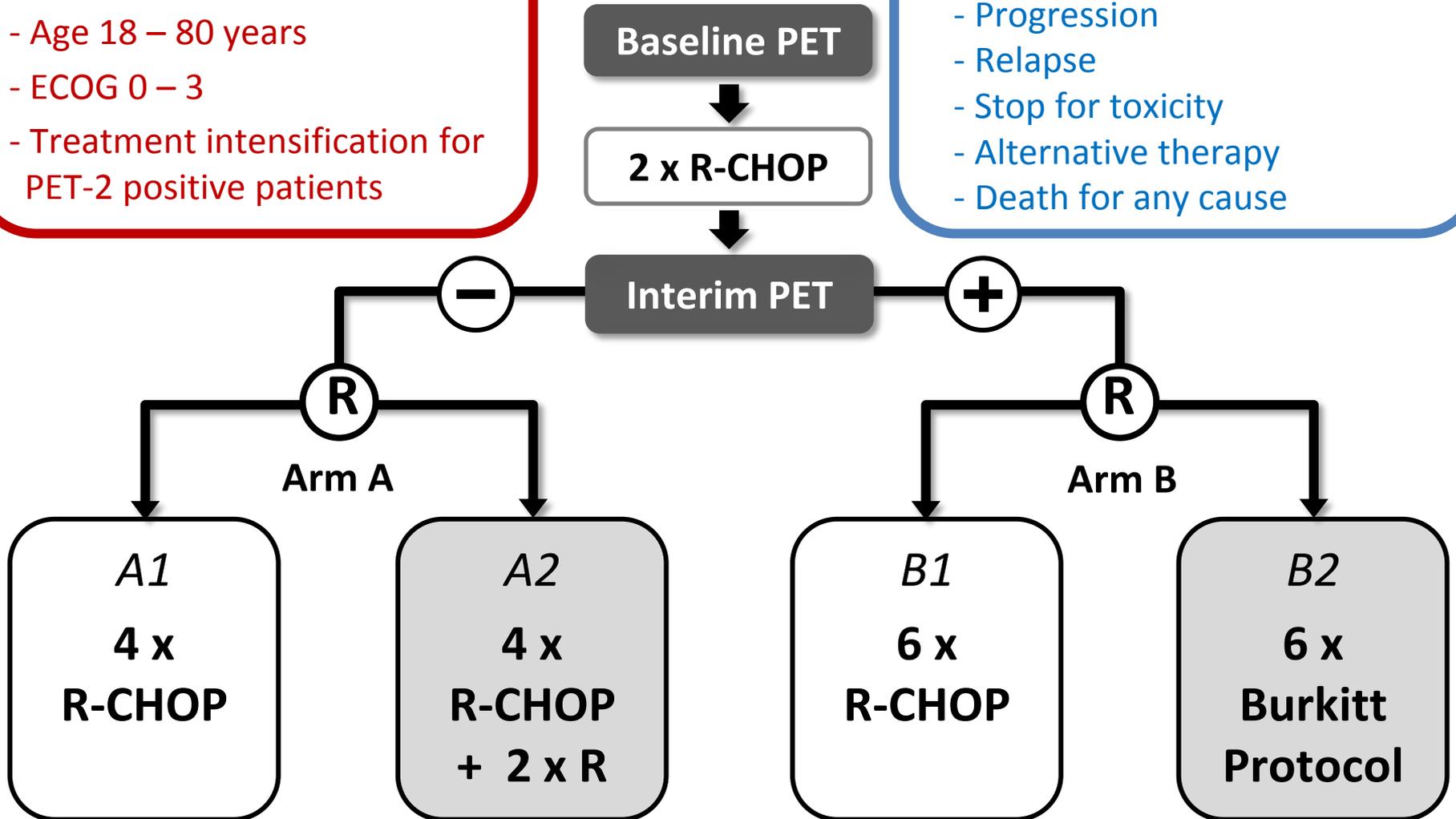
Inclusion Criteria

- Aggressive B- or T-NHL
- Age 18 – 80 years
- ECOG 0 – 3
- Treatment intensification for PET-2 positive patients

Primary Endpoint

Time to treatment failure

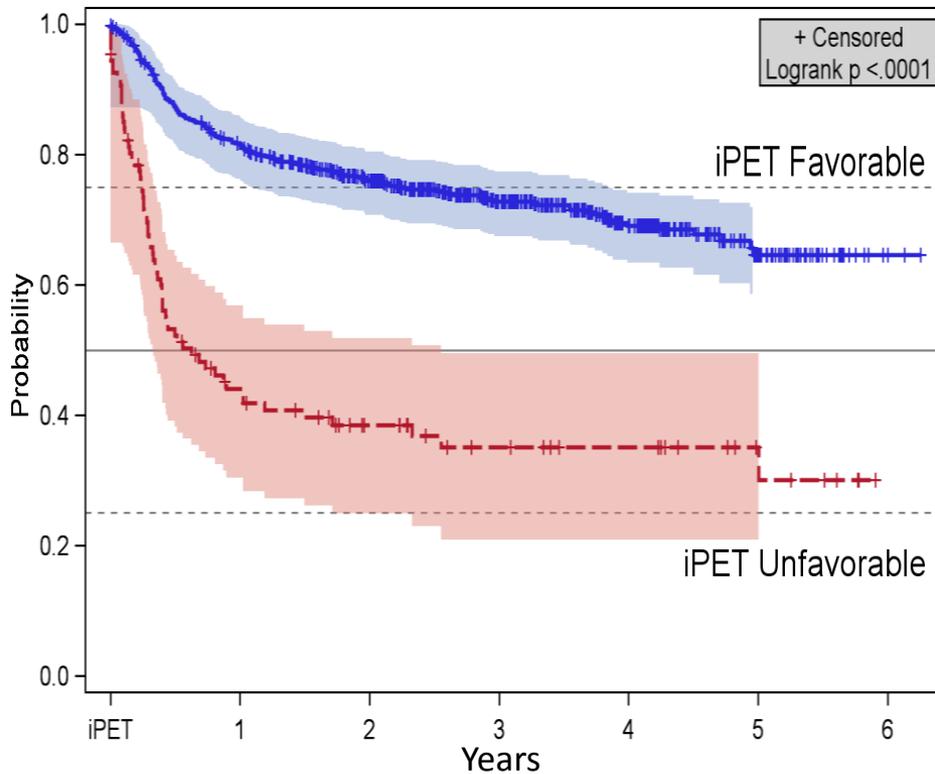
- Progression
- Relapse
- Stop for toxicity
- Alternative therapy
- Death for any cause



PETAL-Study

Treatment outcome according to PET-2 (N= 861)

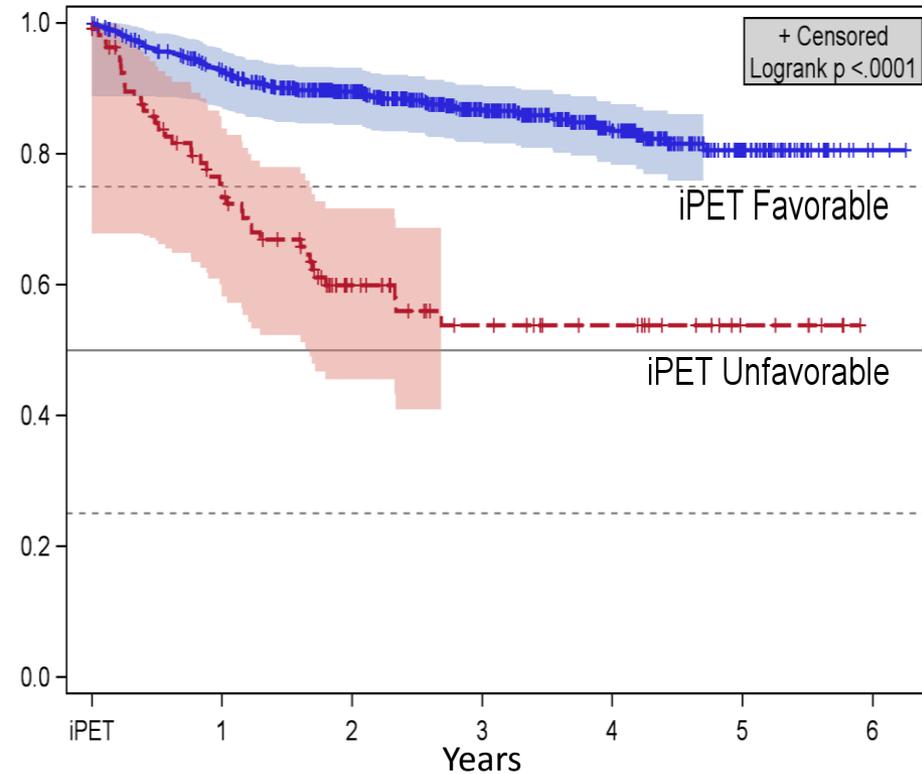
Time to treatment failure



753	586	452	280	150	52	3
108	41	27	18	14	7	0

Duersen U: Blood 2014; 124 (21) [abstr.]

Overall Survival

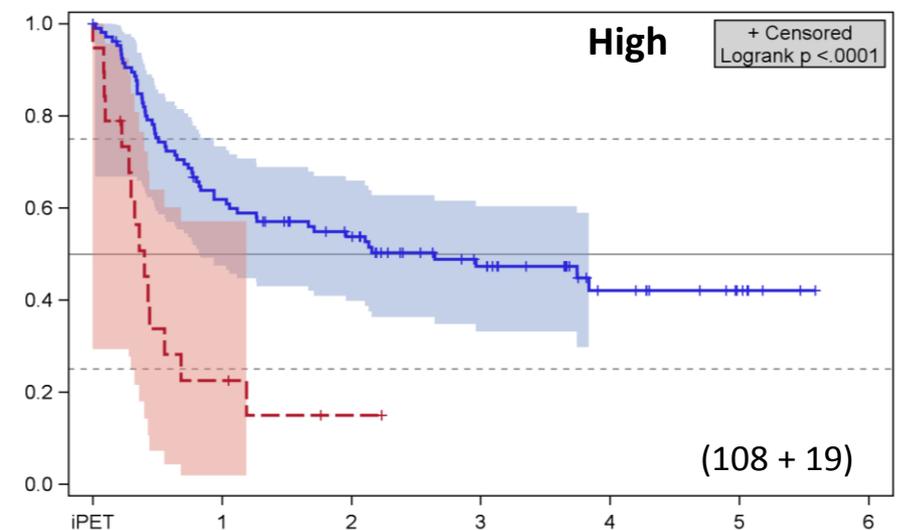
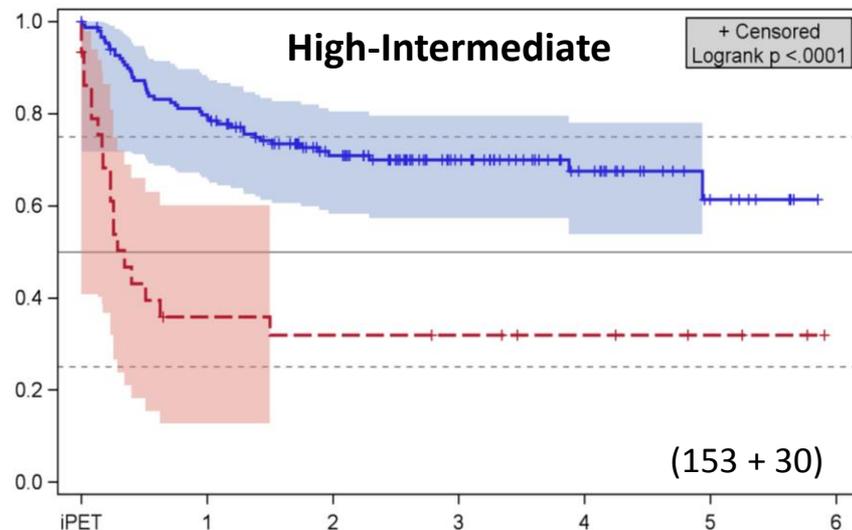
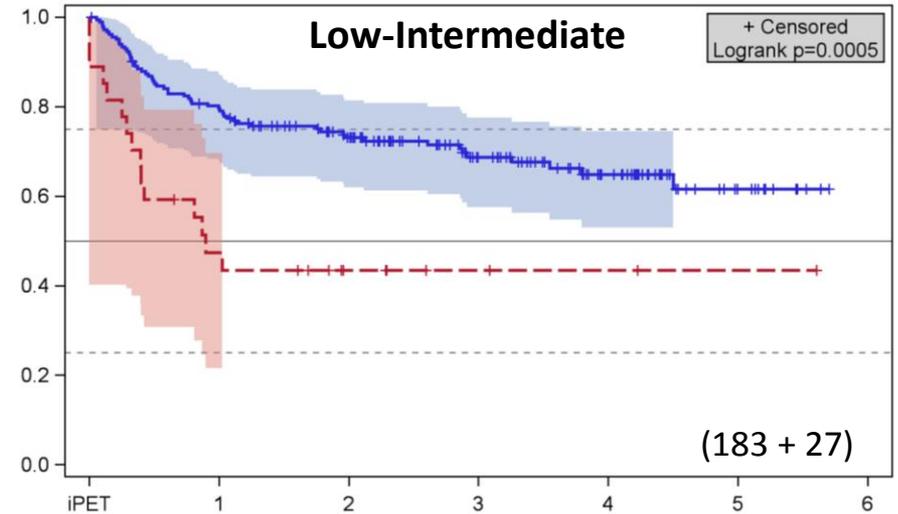
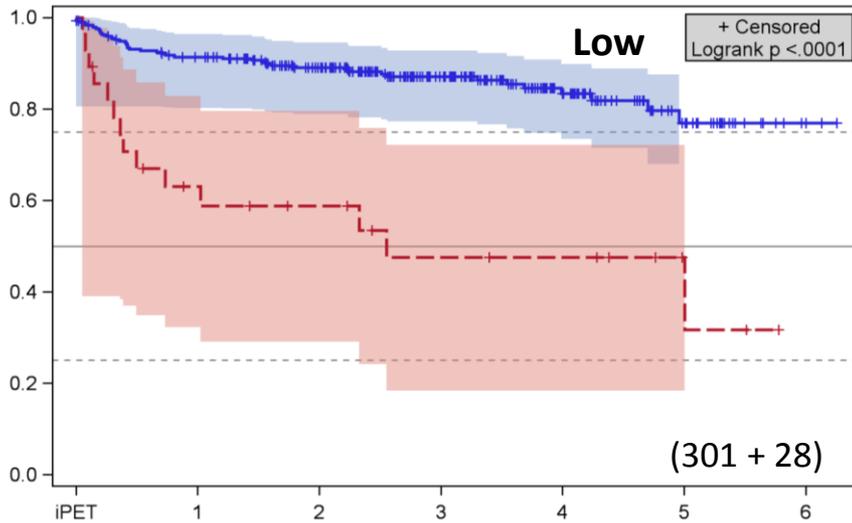


753	652	511	319	173	57	3
108	71	37	23	17	7	0

Courtesy A Huettmann, Oct 2015

PETAL-Study

Interim-PET vs. IPI (Time to treatment failure)



Years

Courtesy A Huettmann, Oct 2015

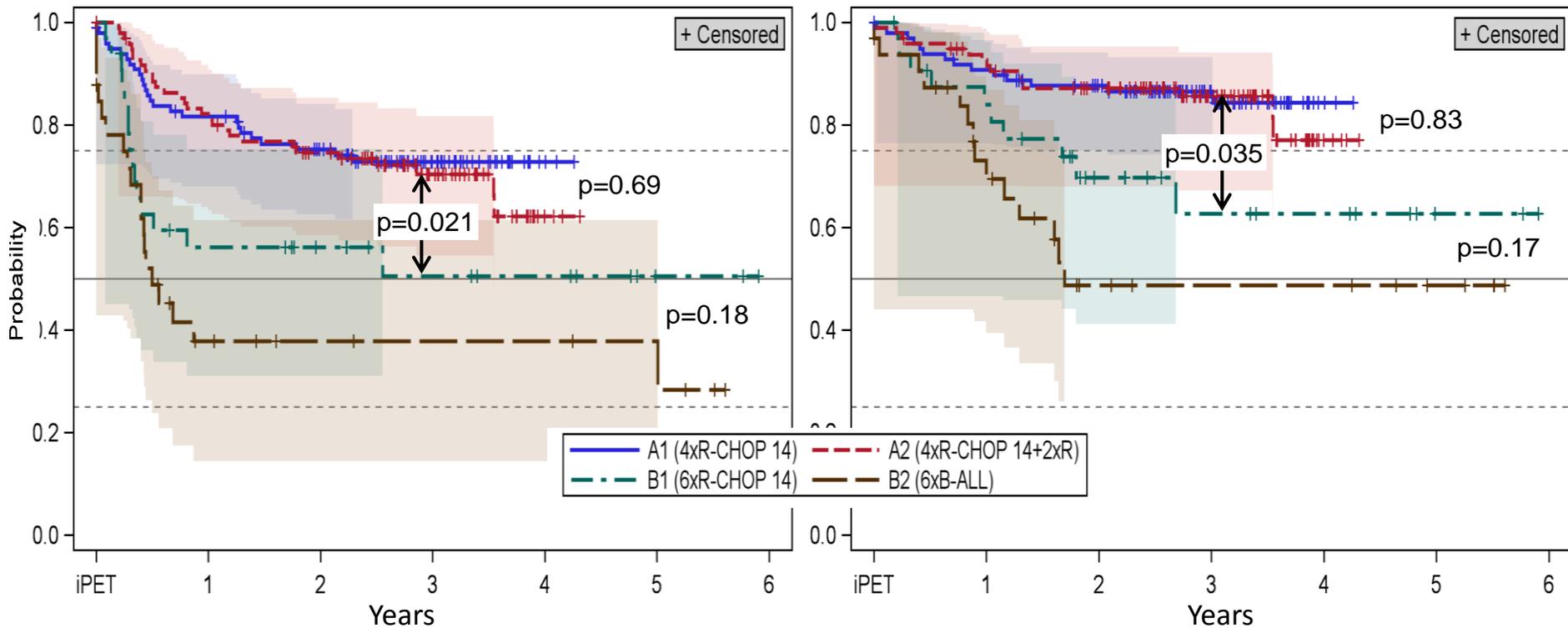
Years

PETAL-Study

DLBCL only: Randomisation A1 vs A2 und B1 vs B2 (N=263).

Time to treatment failure

Overall Survival



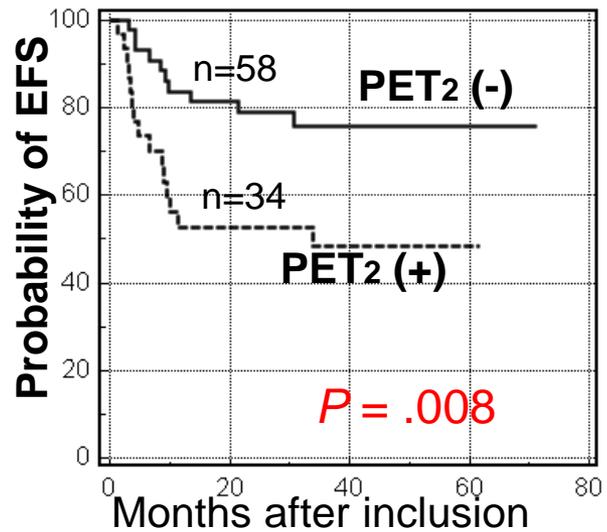
100	79	67	34	3	0	A1 (4xR-CHOP 14)	100	88	77	40	3	0
97	77	66	34	3	0	A2 (4xR-CHOP 14+2xR)	97	86	76	41	4	0
33	17	13	9	7	2	B1 (6xR-CHOP 14)	33	25	14	9	7	2
33	9	6	5	5	4	B2 (6xB-ALL)	33	19	9	7	7	4

Deauville 5-PS performance in DLBCL

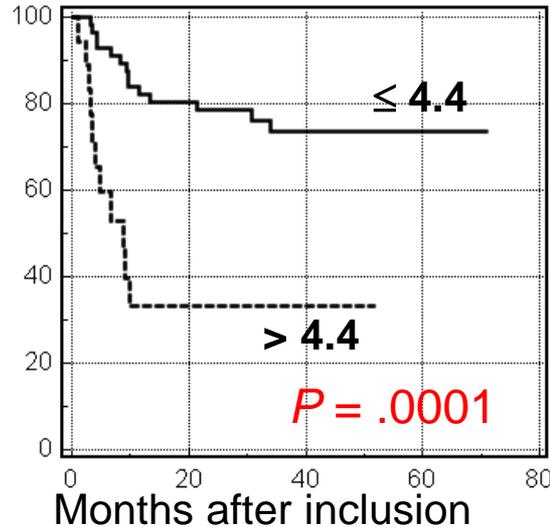
Visual and SUV analysis for PET scan interpretation

Early response assessment (2 cycles), =92 pts

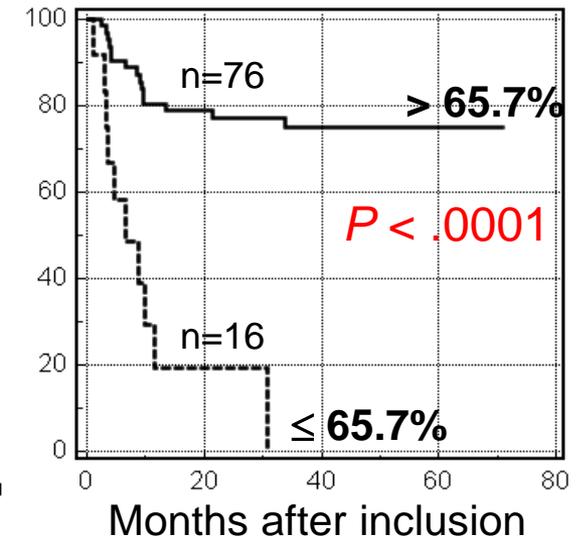
Visual Analysis
(positive or negative)



SUV Analysis
(SUV_{max})



SUV Analysis
(Δ SUV_{max} PET₀/PET₂)



- Decreases the number of false positive studies
- 14/17 patients reclassified with Δ SUV_{max}
- 2/3 reduction threshold

EANM recommendations for Q-PET in multicenter studies

Factor	Absolute SUV			Standard needed for:	Relative SUV (Δ)
	Use of SUV (baseline or residual)*			Use of percentage changes in SUVs (longitudinal studies)	
	Target lesion eligibility	Prognostic factor	Predictive factor	Hottest lesion(s)/scan (PERCIST criteria)	Same lesion(s) for all scans in subject's longitudinal study (EORTC criteria)
Biologic					
Uptake period	H	H	H	H	M-INTRA (>60 min)
Patient motion or breathing (instructions)	H	H	H	H	H
Patient comfort [†]	M	M	M	M	M
Inflammation [‡]	M	M	M	M	M
Physical					
Scan acquisition parameters	H	H	H	H	M-INTRA
Image reconstruction methods, image quality, and quantification	H	H	H	H	M-INTRA
ROI and VOI	H	H	H	H	H
SUV normalization	H	H	H	H	H
Blood glucose level correction	H	H	H	H	H
Contrast agents used during CT-AC	H	H	H	M	M

H = **Harmonizing** performance standard

M = Minimal performance standard

M-INTRA: M with intra-patient reproducibility

6th International Workshop on PET in Lymphoma

Menton (France), September 20-21, 2016



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