INTERIM PET IN DLBCL - 2011

CON ….

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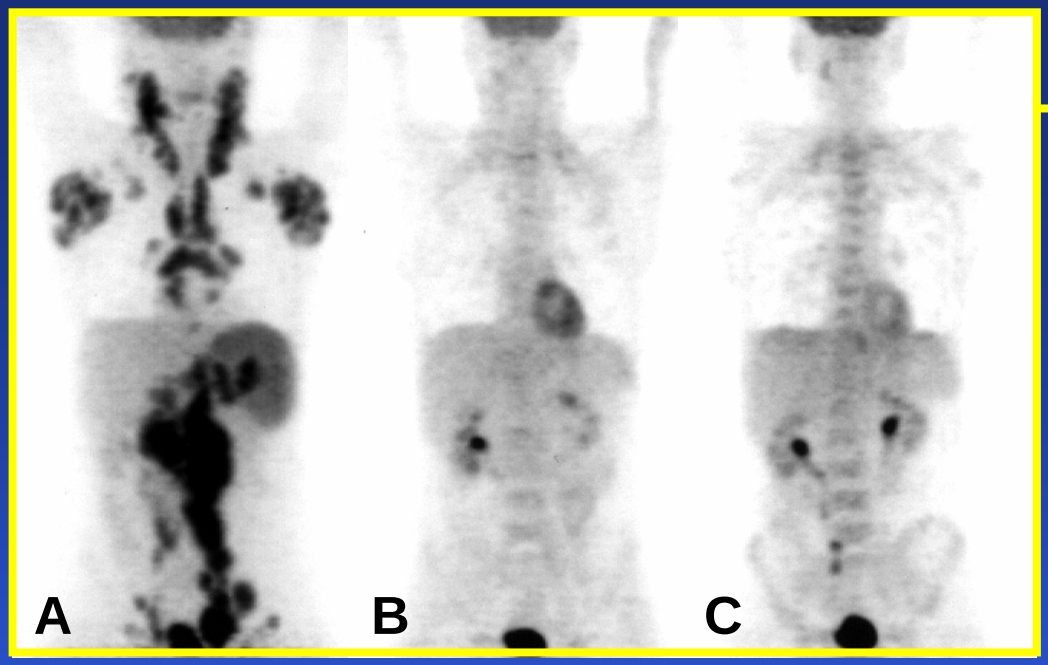
“In the absence of effective therapies, criteria to measure response are irrelevant”

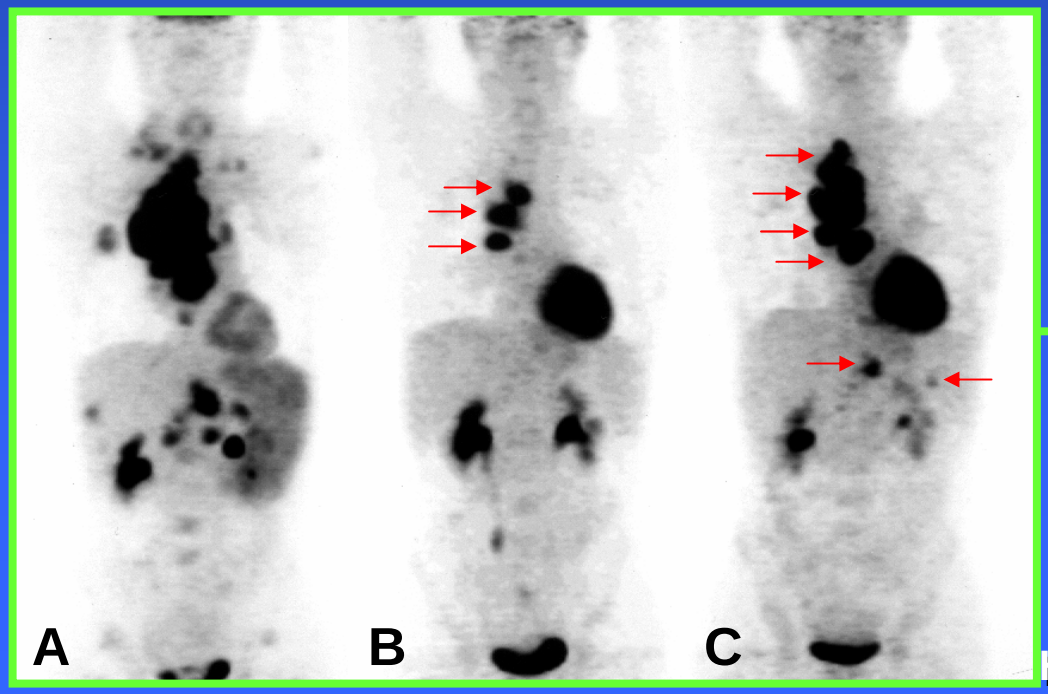
Cheson, 2008

Or: The indication/application of a (new) imaging modality is justified by its impact on patient management

PREDICTIVE VALUE OF INTERIM PET EARLY TREATMENT EVALUATION

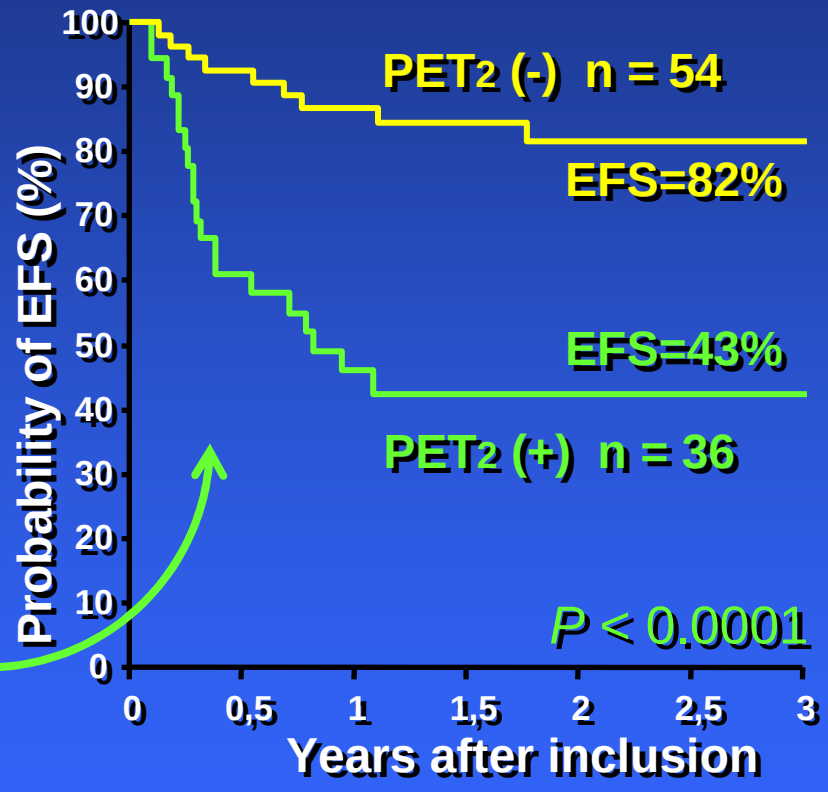
Study DLBCL	n	PET after . . .	2 years PET-	2 years PET+
Jerusalem , 2000	28	3 cycles	62% (PFS)	0% (PFS)
Spaepen, 2002	43	3-4 cycles	85% (PFS)	4% (PFS)
Kostakoglu, 2002	24	1 cycle	85% (PFS)	<15%
Haioun, Itti, 2005	83	2 cycles	82% (EFS)	43% (EFS)
			5 years	
Mikhaeel, 2005	57	2-3 cycles	87% (PFS)	34% (PFS)
Dupuis, Itti, 2009	103	4 cycles	80% (EFS)	36% (EFS)





Early response

NHL 90 pts (2000-2004)
PET0, PET2, PET4
Visual assessment



NB: 2 years median follow-up

Haioun & Itti et al. *Blood* 2005;105:1376-81

HOWEVER ….

“ Although PET is now widely used in the management of patients with DLBCL, the data available assessing its usefullness were initially derived from patients who were NOT treated with Rituximab”

Han et al., Annals of Oncology 20, 309-318 (2009)

THREE MAJOR STUDIES ON INTERIM PET IN DLBCL

	Spaepen (n=70)	Haioun (n=90)	Mikhaeel (n=121)
% DLBCL cases	67%	94%	79%
Rituximab (combined with CHOP)	0%	41%	0%

Spaepen et al., Ann. Oncol. 13, 1356-1363 (2002)
Haioun et al., Blood 106, 1376-1381 (2005)
Mikhaeel et al., Ann. Oncol. 16, 1514-1523 (2005)

EARLY/MID-THERAPY PET (AFTER 2-4 COURSES) IN DLBCL: CHOP VS R-CHOP

CHOP	n	Rituximab	PPV%	NPV%	Sens %	PFS PET pos	PFS PET neg
Spaepen	70	no	100	84	85	4%	85%
Haioun	90	41%	44	90	76	43%	82%
Mikhaeel	121	no	71	90	88	30%	93%
R-CHOP							
Han	40	100%	33	68	33	77%	83%

NB: PFS in all 4 studies at 2 years

Han et al., Annals of Oncology 20, 309-318 (2009)

INTERIM PET/CT FAILED TO PREDICT DIFFERENT OUTCOME IN DLBCL PATIENTS TREATED WITH RITUXIMAB-CHOP (6-8 COURSES)

n=82	at median FU of 18 months
PET2 neg. (n=55; 67%)	46/55 (84%) in CCR
PET2 pos. (n=27)	20/27 (74%) in CCR

Conclusion: Interim PET failed to predict outcome

NB: PET neg. vs PET pos. after 6-8x R-CHOP: 84% CCR vs 61% CCR (p=0.015)

Pregno et al., ASH 2009 (abstract # 99) and EHA 2010 (abstract # 680)

EPRATUZUMAB AND RITUXIMAB IN COMBINATION WITH CHOP (ER-CHOP) IN PREVIOUSLY UNTREATED DLBCL: INTERIM PET AFTER 2 COURSES

n=69	EFS 24 mnths	OS 24 mnths
PET2 neg. (n-54; 78%)	73%	83%
PET2 pos. (n=15; 22%)	60%	73%
	p=0.25	p=0.17

Conclusion: Early PET scan during therapy does not significantly predict outcome.

NB: PET neg. vs PET pos. after 6x ER-CHOP: OS 92% vs 57% (p=0.01)

Micallef et al., ASH 2009 (Abstract # 137)

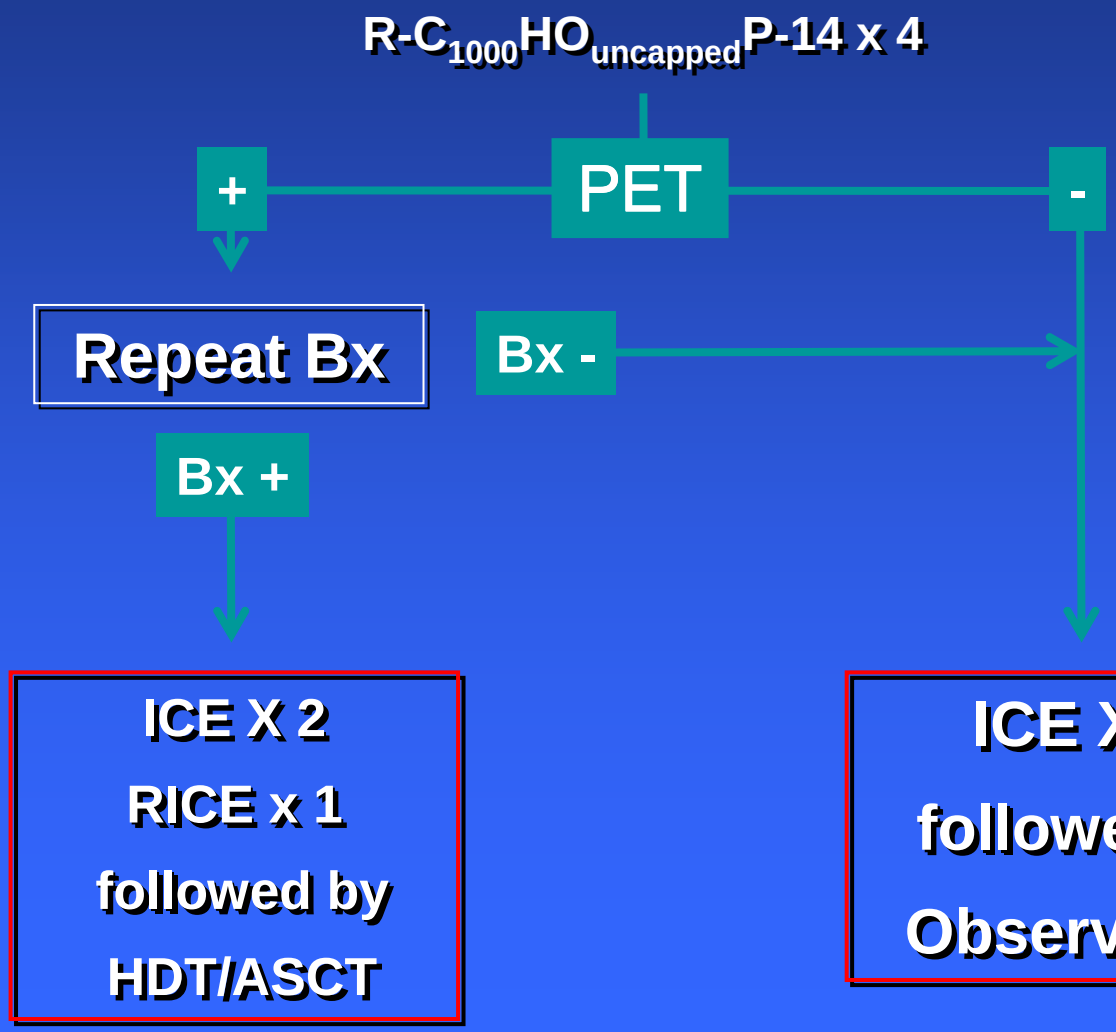
FALSE POSITIVE PET RESULTS ….

Risk-adapted dose-dense immunochemotherapy determined by interim FDG-PET in advanced stage diffuse large B-cell lymphoma

Moskowitz et al., JCO 28, 1896-1903 (2010)

MSKCC 01-142: DLBCL: RISK ADAPTED FOR THERAPY

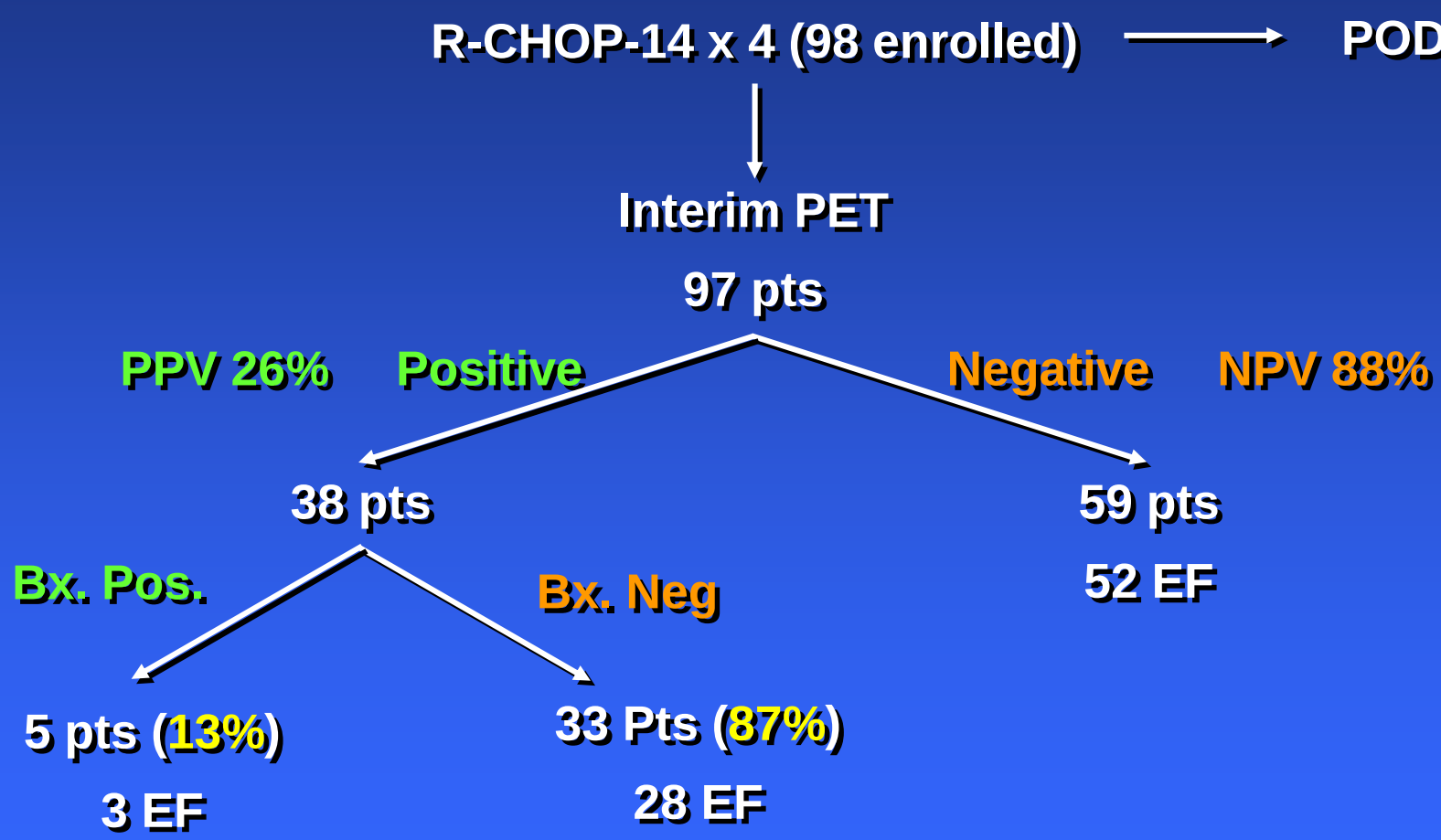
CS IIX, III OR IV DISEASE, AGE-ADJUSTED IPI 1, 2, OR 3 RISK FACTORS, TRANSPLANT ELIGIBLE



- Prospective, biopsy controlled determination of "positive PET"
- Therapy interval 2 weeks +/- G-CSF
- PET 10-14 days post cycle 4
- Treatment is adapted by biopsy, not PET
- No radiation therapy permitted except for testicular disease
- IT methotrexate for aaHR, paranasal sinus, testis, BM

DLBCL: RISK ADAPTED THERAPY

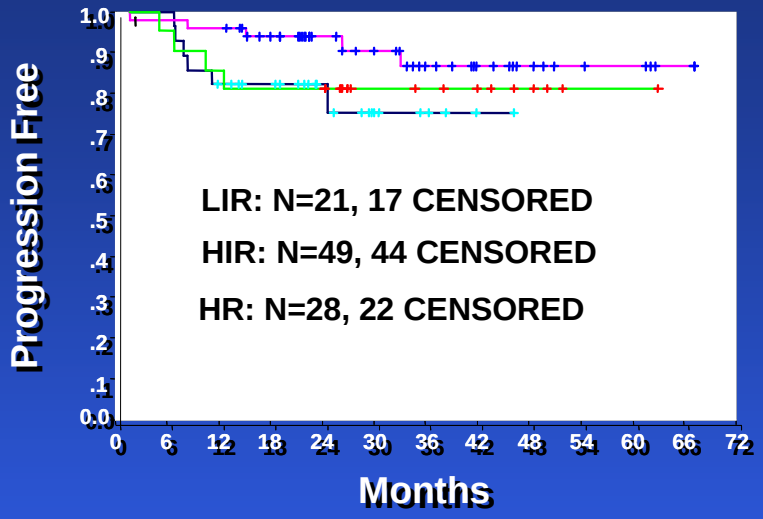
MSKCC 01-142



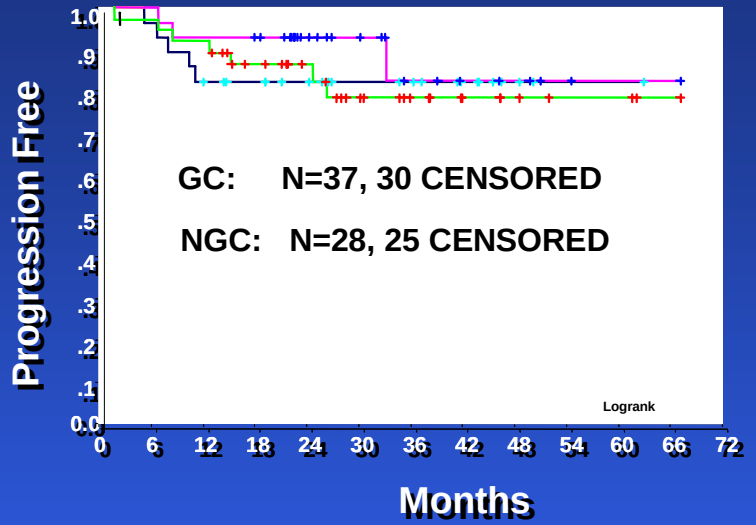
Total of 10 patients dead of disease

MSKCC 01-142: OUTCOME BY PREVIOUSLY IDENTIFIED PROGNOSTIC FACTORS

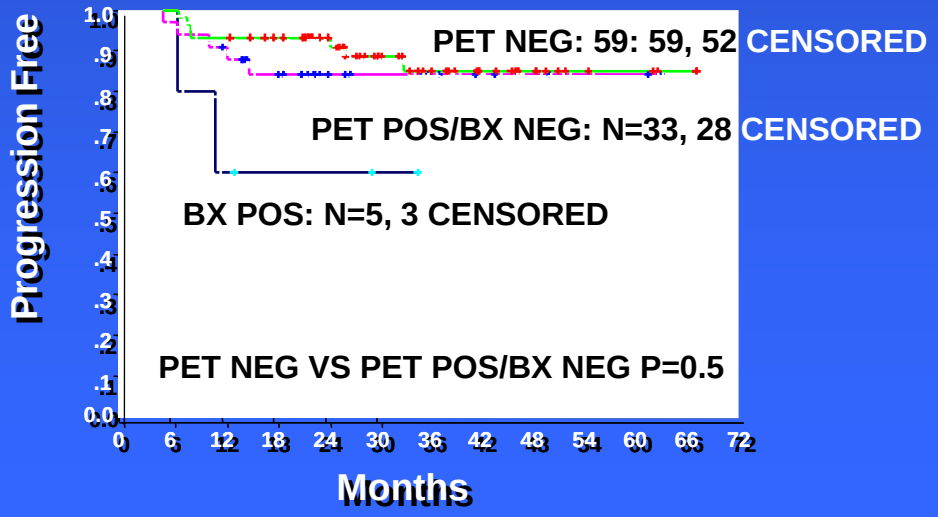
PFS: AGE ADJUSTED IPI



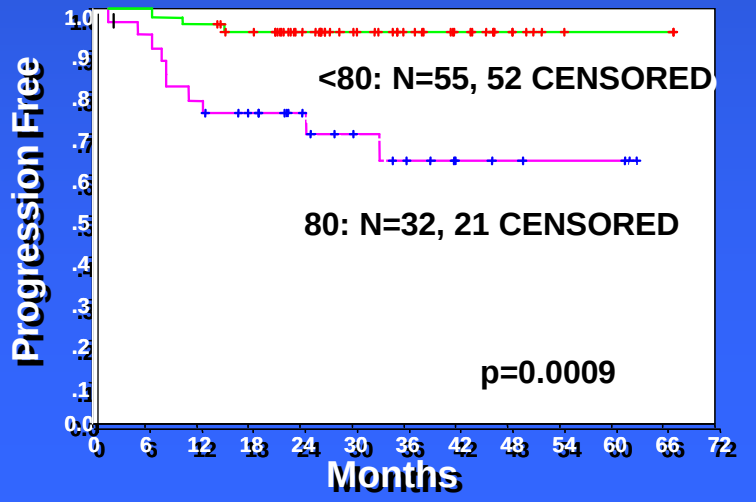
PFS: CELL OF ORIGIN



PFS: BY INTERIM PET/BIOPSY

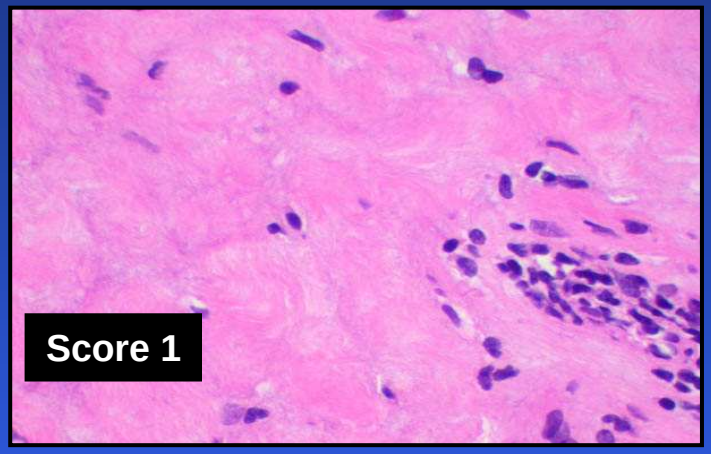


PFS: PROLIFERATION BY KI-67

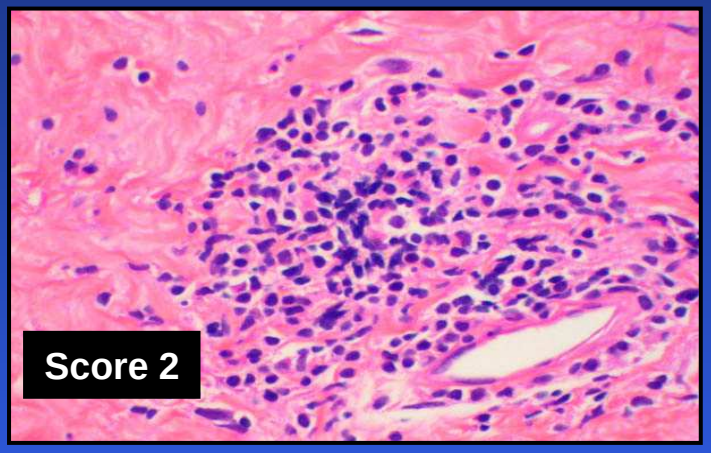


INFLAMMATION SCORE FOR INTERIM BIOPSIES

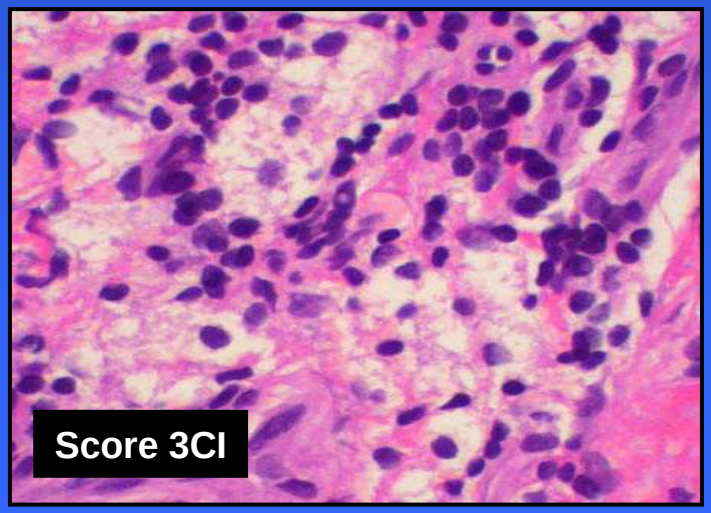
mild, focal, minute, acute or chronic inflammation, fibrosis



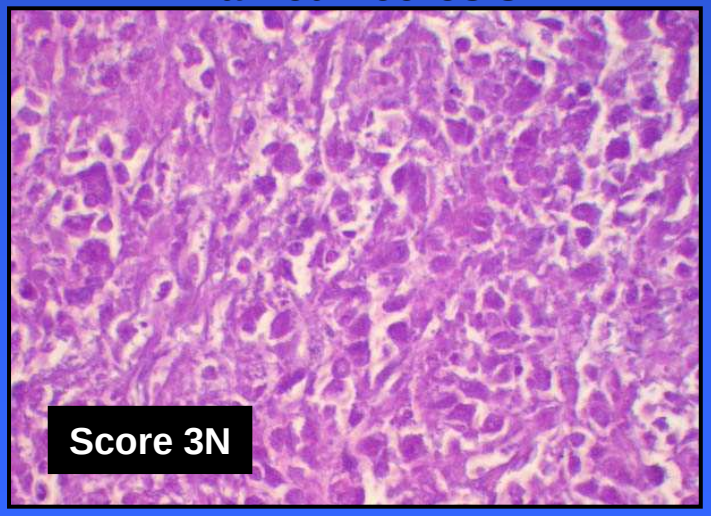
moderate inflammation with macrophages



marked inflammation



marked necrosis



A POSITIVE STUDY …. R-CHOP14 (N=24), R-CHOP21 (N=57) OR R-ACVBP (N=31) IN DLBCL: INTERIM PET AFTER 2 COURSES

n=112	Est. 5 yrs PFS*	Est. 5 yrs. OS**
PET2 neg. (n=70; 63%)	81%	88%
PET2 pos. (n=42; 37%)	47%	62%
	p<0.0001	p<0.0034

* PFS > in PET2 neg. – in all regimens

** OS > in PET2 neg. R-CHOP 21 (p=0.0225), but not in PET2 neg. dose-dense regimens (p=0.133)

Safar et al., ASH 2009 (Abstract # 98); see also Yang, EHA 2010 (abstract # 669; n=153)

FALSE POSITIVE INTERIM PET IN DLBCL DUE TO:

Rituximab
G-CSF
Dose-dense regimens
Timing of PET - < 2 weeks post chemotherapy
- < 2 months post radiotherapy

Infection/inflammation
Tumor necrosis
Thymus hyperplasia
Other (secondary) malignancies
Sarcoidosis/other granulomatosis diseases
Brown fat, muscles
Etc.

DIFFERENCES BETWEEN STUDIES?

- Different NHL subtypes included
- Different treatment regimens +/- G-CSF
- Timing of PET
- PET methodology
- Criteria to assess response (PET pos. vs PET neg.)

INTERPRETATION OF PET

- Visual assessment
- Change in SUVmax

INTEROBSERVER VARIATION IN JUDGEMENT ….

PET IN DLBCL: AN INDEPENDENT EXPERT NUCLEAR MEDICINE EVALUATION OF THE ECOG 3404 STUDY

- 3 experts scored 38 interim scans after 3x R-CHOP
- Agreement was 68% for ECOG criteria* (κ statistic 0.455)
  71% for London criteria* (κ statistic 0.502)
- Source of disagreement: para-aortic, spleen, bone

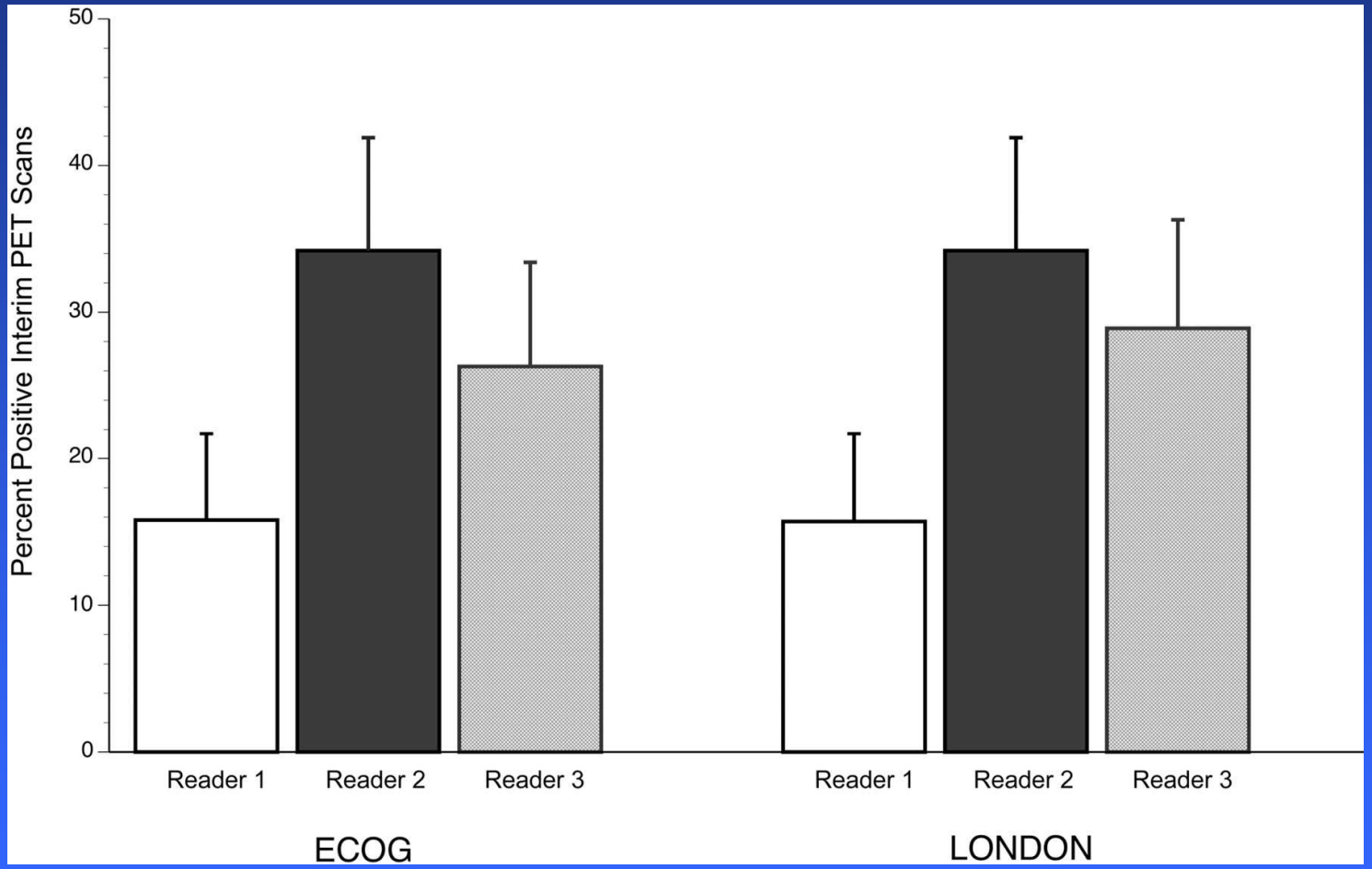
Conclusion: Moderate reproducibility among experts
Need to standardize PET interpretation

* Modifications of the International Harmonizaton Project

Horning et al., Blood 115, 775-777 (2010)

PROPORTION OF INTERIM-PET CASES INTERPRETED AS POSITIVE BY READER, ACCORDING TO THE ECOG AND LONDON CRITERIA

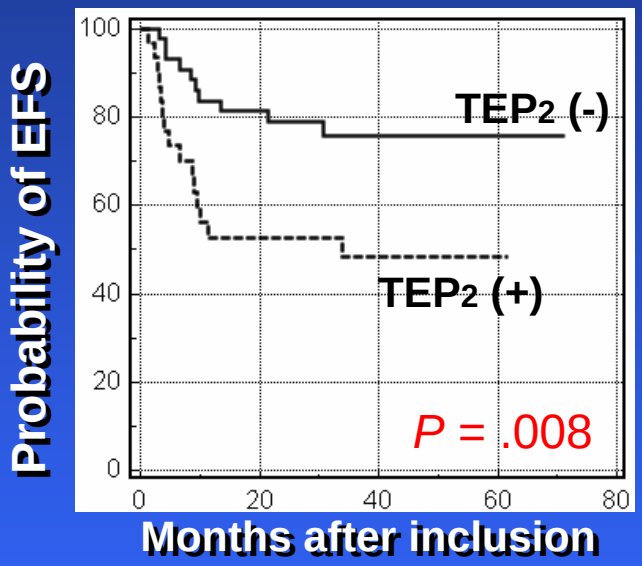
blood
JOURNAL OF THE AMERICAN SOCIETY OF HEMATOLOGY



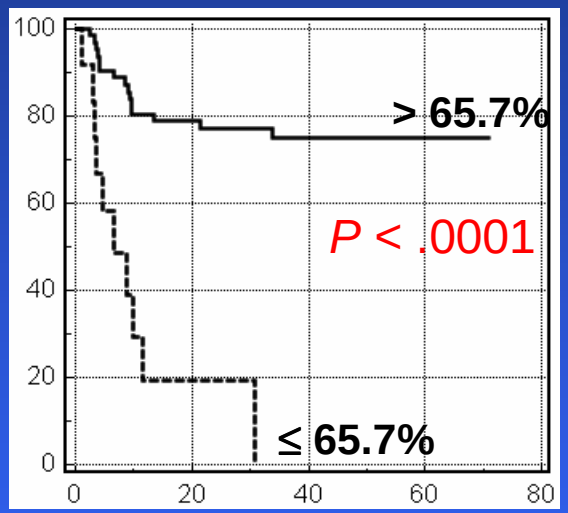
Horning, S. J. et al. Blood 2010;115:775-777

VISUAL AND SUV ANALYSIS
EARLY RESPONSE ASSESMENT (2 CYCLES), N=92 PTS

Visual Analysis
(positive or negative)



SUV Analysis
(ΔSUVmax PET0/PET2)



→ Decreases the number of false positive studies
→ 14/17 FP patients reclassified with ΔSUVmax

→ 2 cycles: ΔSUV performs better than visual!

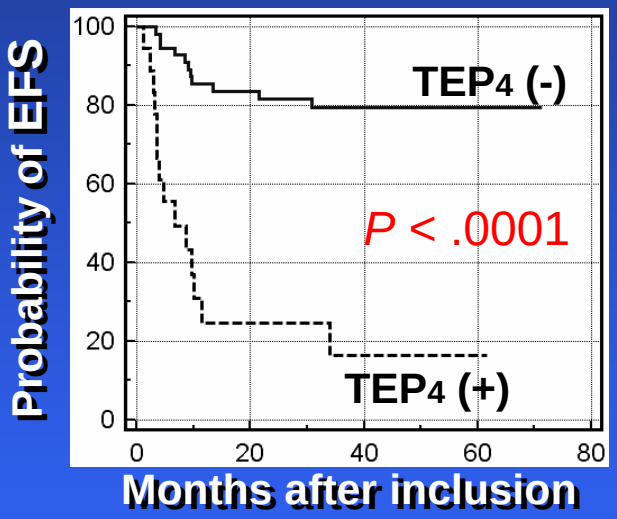
Lin, Itti et al. *J Nucl Med* 2007;48:1626-32

VISUAL AND SUV ANALYSIS

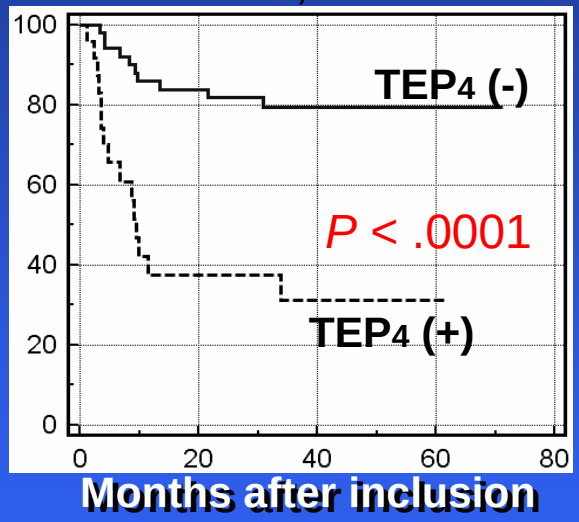
END INDUCTION (4 CYCLES), N=80 PTS

Visual analysis

(Créteil criteria)
PPV:78,NPV:82

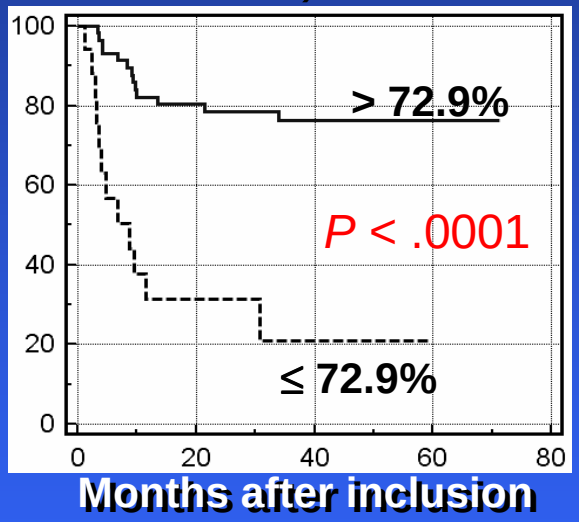


(Juweid criteria)
PPV:62,NPV:82



SUV analysis

(ΔSUVmax PET0/PET4)
PPV:70,NPV:79



→ Créteil criteria > Juweid criteria (end of therapy)

→ **4 cycles: Good performance of visual analysis**

ΔSUV is more objective

Itti et al. *J Nucl Med* 2009;50:527-33

Conclusions

- SUV semiquantification reduces false positive interim PET interpretation after 2 courses
- Its performance is equivalent to visual analysis after 4 courses

Explanations

- An index expressing metabolic reduction is expected to be more discriminating for assessment of response after 2 courses than after 4 courses (most of the therapeutic effect occurs early)
- Local inflammation probably less often present after 4 courses

SUV MAX REDUCTION IN DLBCL
(LNH 2007 – 3B TRIAL GELA: R-CHOP VS R-ACVBP)

	PFS	OS
	at 2 years	
Δ SUV max – PET 0-2		
> 66%	77%	93%
≤ 66%	57%	60%
Δ SUV max – PET 0-4		
> 70%	83%	94%
≤ 70%	40%	50%

NB: Outcomes did not differ significantly whether PET2 and PET4 were visually positive or negative (IHP or Beauville criteria)
Casasnovas et al., Blood 118, 37-43, 2011

VISUAL ANALYSIS PET2 AND PET4: POOR PREDICTIVE VALUE FOR PFS AND OS

- 78% of PET2 positive and 80%* of PET4 positive patients had a Δ SUV max above the cut off value (PFS at 2 years: 77% and 83%, respectively)

- Thus, patients classified as poor responders to R-chemo according to visual analysis were good responders as identified by Δ SUV max analysis

* 85% false positive PET4 – visual analysis! (Moskowitz et al., 2010)

CAN THE SUV VALUE OF INTERIM PET BE USED TO DETERMINE THE NEED FOR RESIDUAL MASS BIOPSY IN DLBCL?

(Juweid, Smith, Itti and Meignan, JCO 28, e719-720, 2010: comments to Moskowitz data)

"A cut off SUV at interim PET of ≤ 3.5 was associated with a very low likelyhood of a positive biopsy"

		positive biopsy (NHL+)	
Interim SUV at biopsy site (n=36)	≤ 3.5	1/20	(5%; 0.1-24.9%)
	> 3.5	4/16	(25%; 7.3-52.4%)

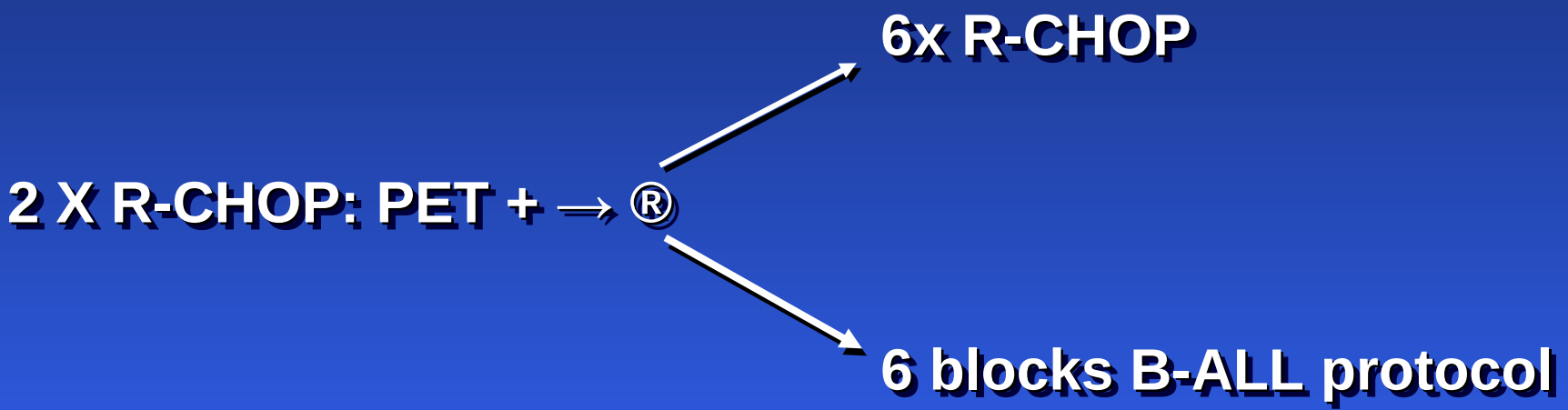
"The cut off SUV value of 3.5 would have spared more than half of the patients (20/36) with positive interim PET a biopsy with a low yield of finding NHL (1/20 = 5%)"

CONCLUSIONS

1. The PET/CT scan at the end of treatment is – so far – the most powerful predictor of outcome

2. Interim scanning has not been shown to improve survival and thus should be restricted to clinical trials!

THE PETAL TRIAL IN DLBCL



NB: - 3 week interval chemo → PET
- no hematopoietic growth factors
- SUV based interim PET assessment

ANSWERS TO QUESTIONS FROM OUR CHAIRMAN …

Q1: Is there any evidence that early PET has a prognostic role in DLBCL?

A1: Yes, there is “any evidence” - needs confirmation in large trials

Q2: Should we report early interim PET in DLBCL qualitatively or quantitatively?

A2: Most probably quantitatively – Δ SUV max ... Need more data

NB: majority of interim PET(+) pts are primarily refractory (IVS)

Q3: Is histological confirmation the "gold" standard reference for patients with mid-treatment positive PET? (e.g. after 4 cycles)

A3: According to Itti et al. (2009) and Casasnovas (2011) – based on SUV analysis – probably not ....

or: not below a certain SUV value .... (Moskowitz, 2010)

Q4: Is interim PET feasible in multicenter clinical trials?

A4: Yes!

Q5: Are there sufficient data to support change in treatment based on interim PET results?

A5: No! Results from PETAL trial? (currently 700 patients enrolled)