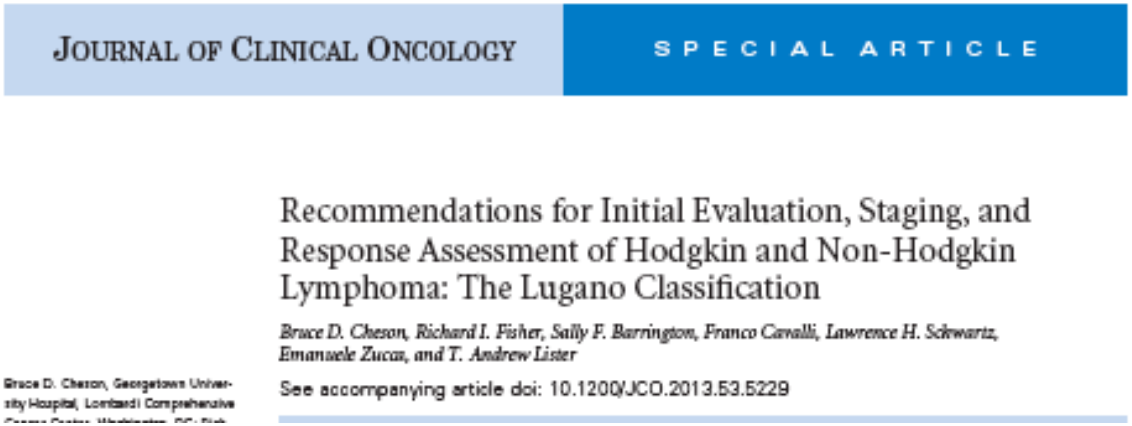
RETE ONCOEMATOLOGICA
DEL PIEMONTE E VALLE D'AOSTA
24 Novembre 2017
Centro Congressi Torino Incontra
Via Nino Costa, 8 - Torino

Ruolo della PET alla diagnosi ed al termine del trattamento:

Stefano Luminari (Reggio Emilia)

Con il Patrocinio di SIE – Società Italiana di Ematologia e di FIL Fondazione Italiana Linfomi e rete oncologica Piemontese
Torino, 24 novembre 2017
Incontro di aggiornamento sui disordini linfoproliferativi
e sui protocolli della Fondazione Italiana Linfomi



- FDG-PET CT : is the preferred method for staging and restaging in FDG-Avid Lymphomas (All but CLL, MZL, IC,…)
- The use of Deauville Criteria criteria is recommended for restaging
- With FDG-PET BMB is not necessary in
  - HL
  - DLBCL if BMB results do not affect treatment decisions (Stage I-II)

Cheson, B.D., Fisher, R.I., Barrington SF et al. (2014), Journal of Clinical Oncology
Cheson, B. D., Horning, S. J. et al (1999). Journal of clinical oncology
Cheson, B. D., Pfistner, B. et al. (2007). Journal of Clinical Oncology
Kostakoglu, L., & Cheson, B. D. (2013). Frontiers in oncology

FDG PET in the staging of LG-NHL

Can FDG-PET add clinically useful details to initial staging/workup?

- Qualitative analysis
  - Initial stage is modified in 18-31%
    Fulham 2006, Karam 2006, Wirth 2008, Janikova 2008
  - FDG-PET detects more EN sites (Bone, Spleen, GI, skin, …)
    Tychyj-Pinel EJNM 2013, Luminari Ann Oncol 2013
  - Migration to advanced stages in 60% of stage I-II
    Luminari Ann Oncol 2013
  - Prognostic assessment is modified Luminari Ann Oncol 2013
    - FLIPI risk migration in 25% (18% low to hi; 7% hi to low)
    - FLIPI2 not affected

Outcome of curative radiotherapy for localised follicular lymphoma in the era of ^{18}F-FDG PET-CT staging:

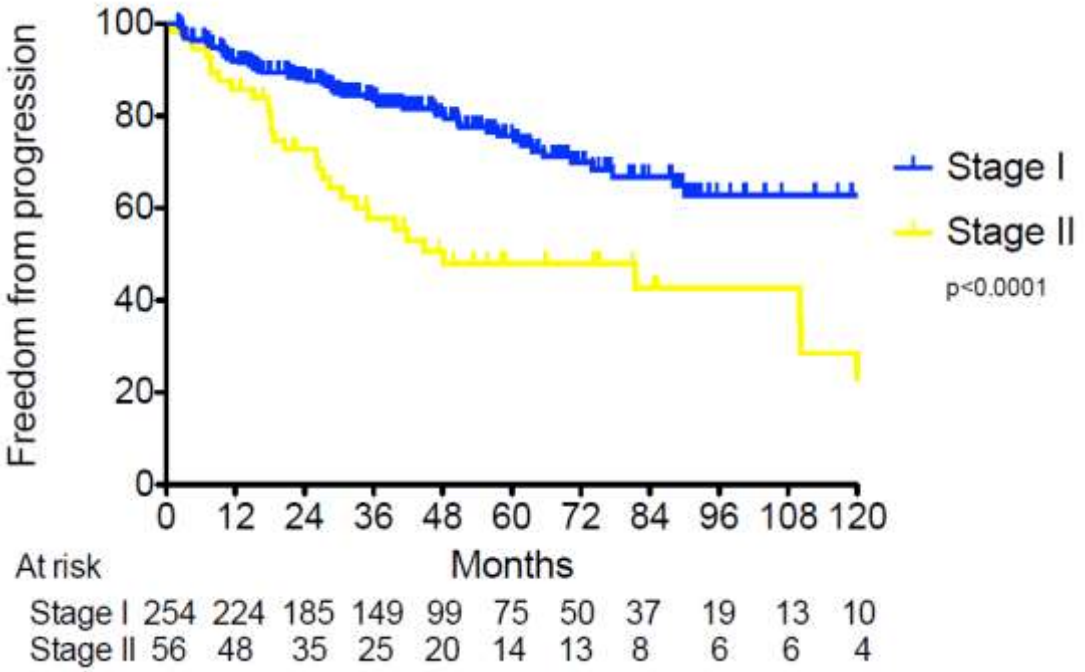
an international collaborative study on behalf of ILROG

310 pts treated from 2000-2016

- Stage I = 74.3%
- Stage II = 48.1%

(p<0.0001)

Figure 2. FFP by stage



ILROG

Brady et al. XIV ICML: 2017

Can FDG-PET add clinically useful details to initial staging/workup?

- Quantitative assessment (FL 15%)
  - In 81% of indolent lymphomas SUV is < 10
  - With SUV >13 most cases are aggressive
  - The Likelihood for aggressive disease increases in parallel with increased SUV
  - PET can be used to guide the site of optimal biopsy

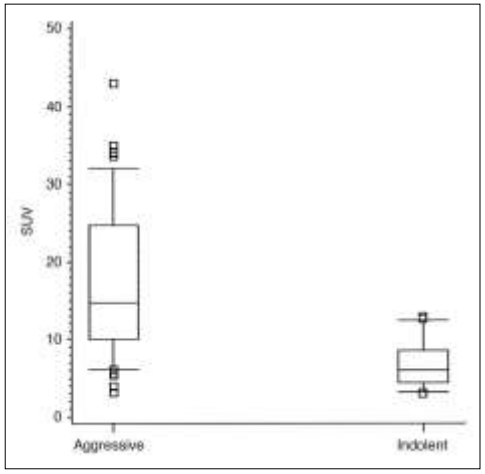


Fig 3. Box plots showing distribution of standard uptake value (SUV) among patients with aggressive and indolent lymphoma. The box represents the lower and upper quartiles and the median is marked with a horizontal line inside the box. The whiskers are the 10th and 90th percentiles with outlying observations individually plotted by squares outside the whiskers.

Table 3. Sensitivity and Specificity of SUV to Distinguish Between Indolent and Aggressive Lymphoma, Based on Biopsies From Site of Highest SUV in the PET Study (n = 69)

SUV	6.4	7.4	8.6	10	12	13.1
Sensitivity	92	85	75	71	63	58
Specificity	50	56	69	81	94	100

NOTE. Numbers in table correspond to solid line in ROC curve in Figure 4. Entries are restricted to SUV numbers for which measurements were available in this patient set.
Abbreviations: SUV, standardized uptake value; PET, position emission tomography.

VOLUME 23 · NUMBER 21 · JULY 20 2005

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

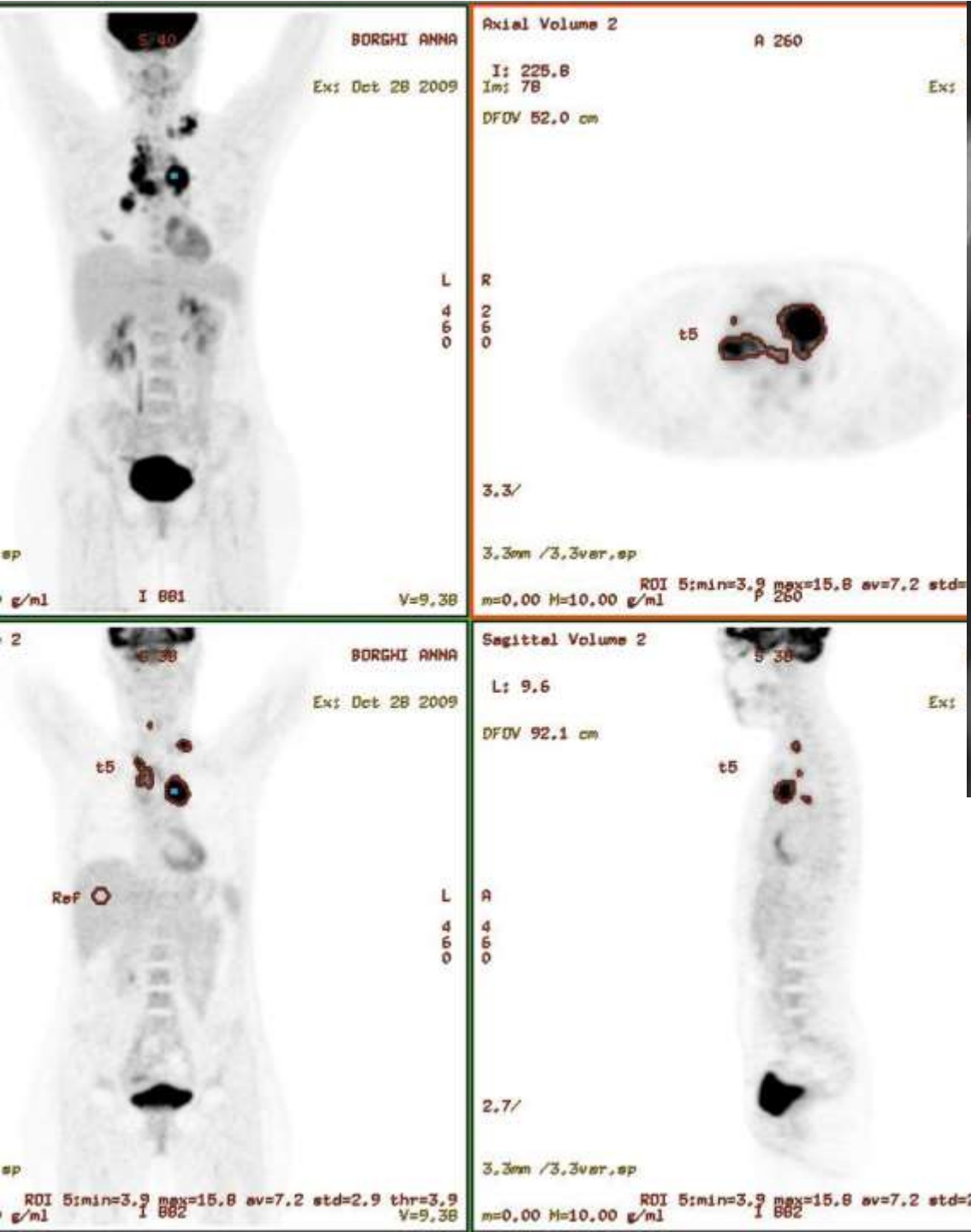
Intensity of ^{18}Fluorodeoxyglucose Uptake in Positron Emission Tomography Distinguishes Between Indolent and Aggressive Non-Hodgkin's Lymphoma

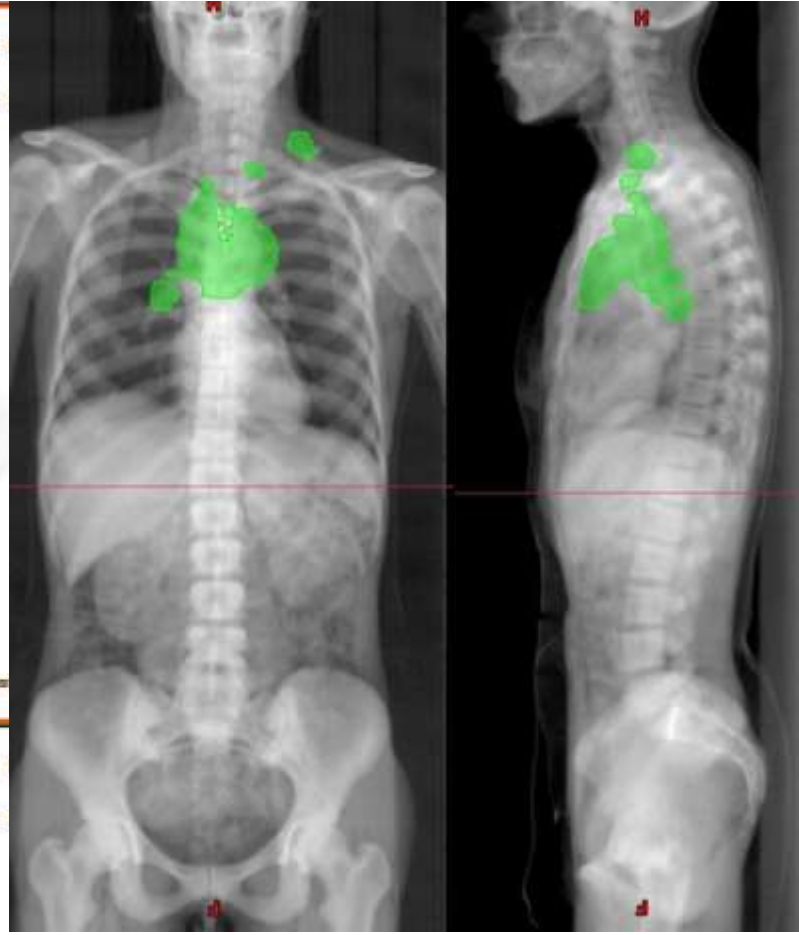
Heiko Schöder, Ariela Noy, Mithat Gönen, Lijun Weng, David Green, Yusuf E. Erdi, Steven M. Larson, and Henry W.D. Yeung

Can FDG-PET add clinically useful details to initial staging/workup?

SUV in FL

- Poor correlation of SUV with histologic grading (FL)
  Wohrer 2006, Karam 2006
- Possible correlation with proliferation index
  Colleter EANM 2013 P729
- In patients with Indolent lymphoma and clinical suspect of Transformation Bodet-Millin 2008
  - SUV_{max} > 17 always = transformation
  - SUV_{max} < 11.7 = indolent disease,
- Prognostic role of SUV_{max}? Thychy Pinel EJNM 2013

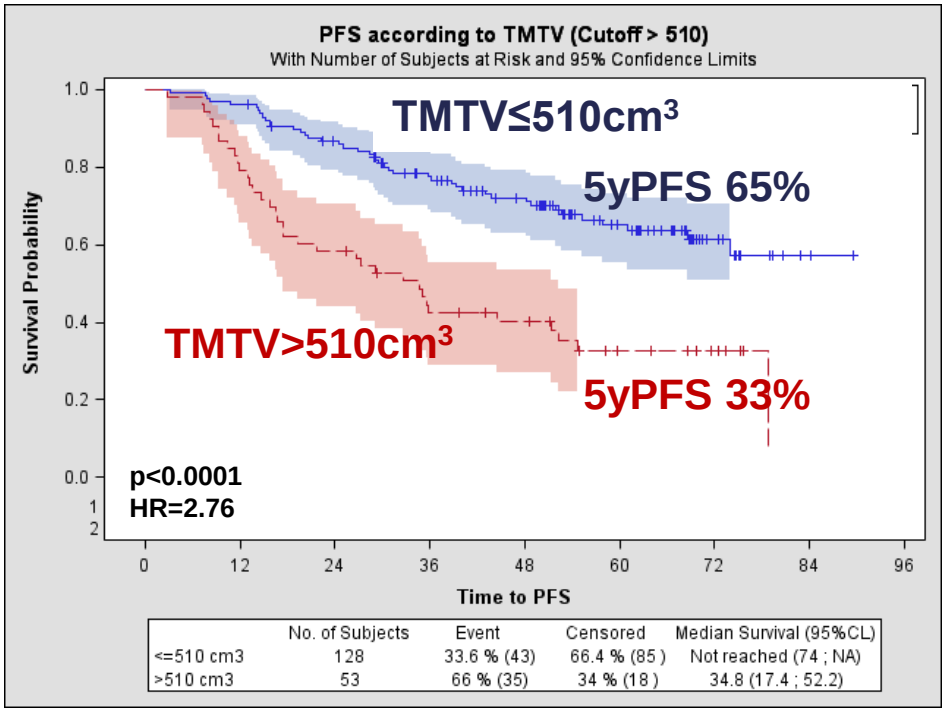


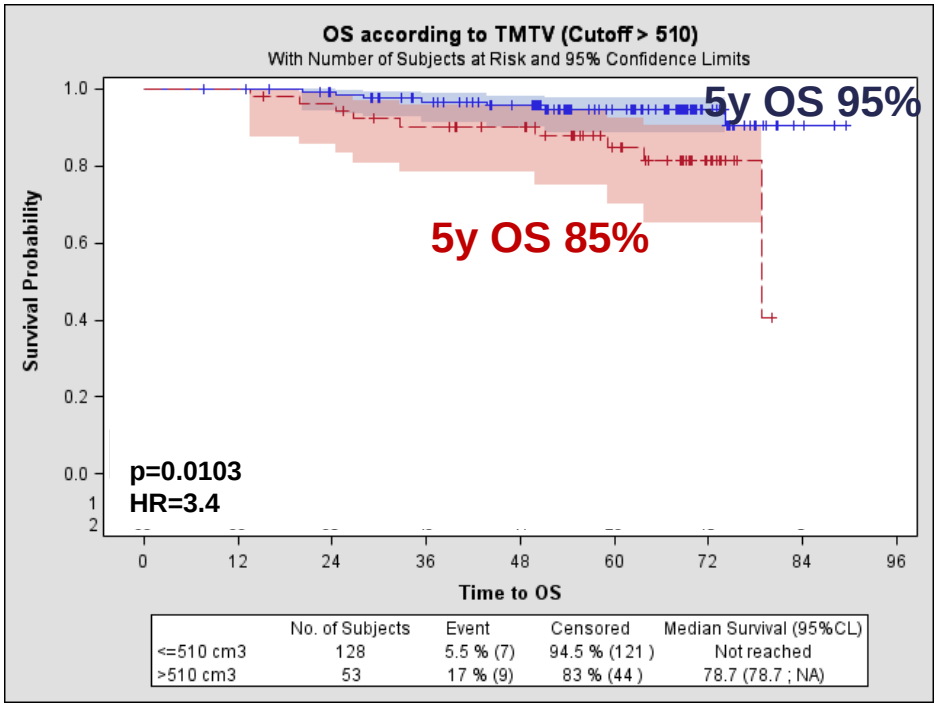


All the individual lesion volumes are added together to give the **total metabolic tumour volume at baseline (TMTV0).**

41% SUV method used

TOTAL METABOLIC TUMOR VOLUME IN FL: A STRONG PREDICTOR OF PFS AND OS





- Median PFS for patients with low TMTV : > 6years
- Median PFS for patients with high TMTV : < 3 years

M Meignan, 2016, J Clin Oncol

High TMTV (>510cm^3)

- 53 patients (29%) had a high TMTV

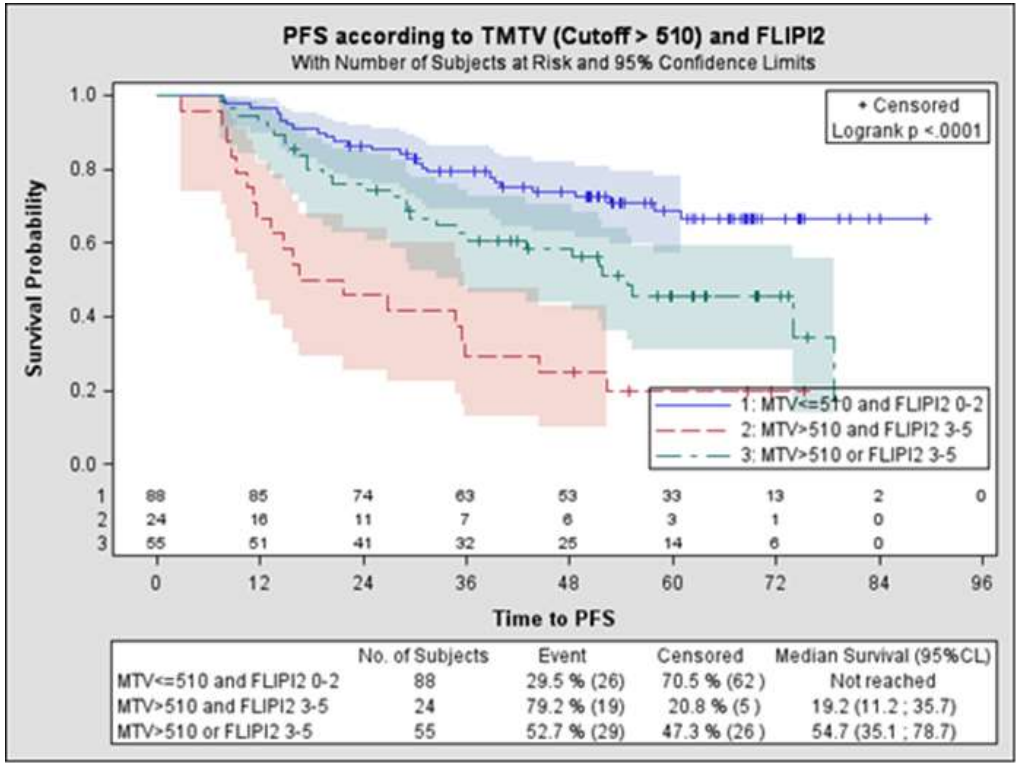
- Significantly associated with:
  - Stage III-V
  - Greater extra nodal and bone marrow involvement
  - Higher FLIPI and FLIPI2
  - Elevated LDH and β2 microglobulin

TMTV and FLIPI2: HTB Follicular Lymphoma

MVA, only TMTV (HR 2.3, p =0.002)
& FLIPI2 (HR 2.2, p =0.002) independent predictors of PFS.

5-year PFS

- Low TMTV & low FLIPI2
  69%
- High TMTV or int-high FLIPI2
  46% (HR 2.1, p=0.007)
- High TMTV & int-high FLIPI2
  20% (HR 5.0, p <0.0001)



FDG PET in Restaging of FL

How is response assessed in FL -1

CT:

- Difficult assessment (sum of the product of transverse diameters of 6 largest nodes) Cheson 2007
- Limited capacity to assess extranodal disease
- Only one study demonstrated an OS impact of CR/CRu over PR Bachy 2009
- CT based CR vs PR not so important in the postinduction setting (PR to CR conversion) Salles Lancet Oncology 2010

Can FDG-PET improve restaging assessment?

Post induction PET is prognostic for PFS

Study	PET + rate	f-up months	PFS (+ vs -)	HR (Range)	Multiv. correction
PET in PRIMA (Trotman JCO 2011)	26%	**42**	**33% vs 71%**	**3,3**	IWC resp. FLIPI Therapy, Bulk
PET FOLL05 (Luminari ASH 2011)	24%	**36**	**35% vs 66%**	**2,6 1,5 – 4,3**	IWC resp FLIPI Therapy
PET FL (Dupuis JCO 2012)	24%	**24**	**51% vs 87%**	**6.6 2,6 – 16,5**	-

Deauville criteria

Score 1 no uptake

Score 2 uptake ≤ mediastinum

Score 3 uptake > mediastinum but ≤ liver

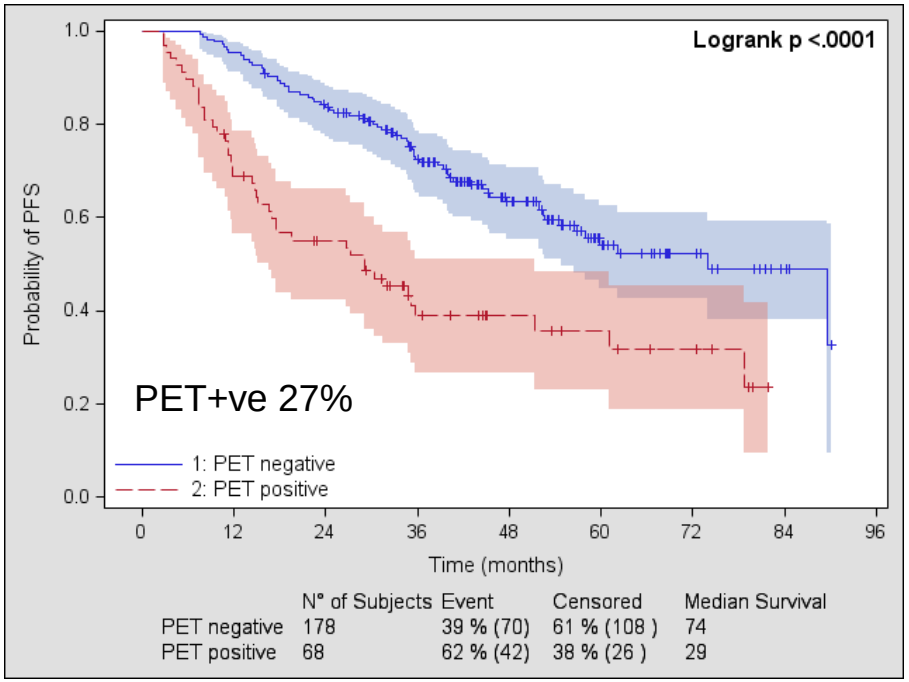
Score 4: moderately ↑uptake > liver

Score 5 markedly ↑uptake > liver

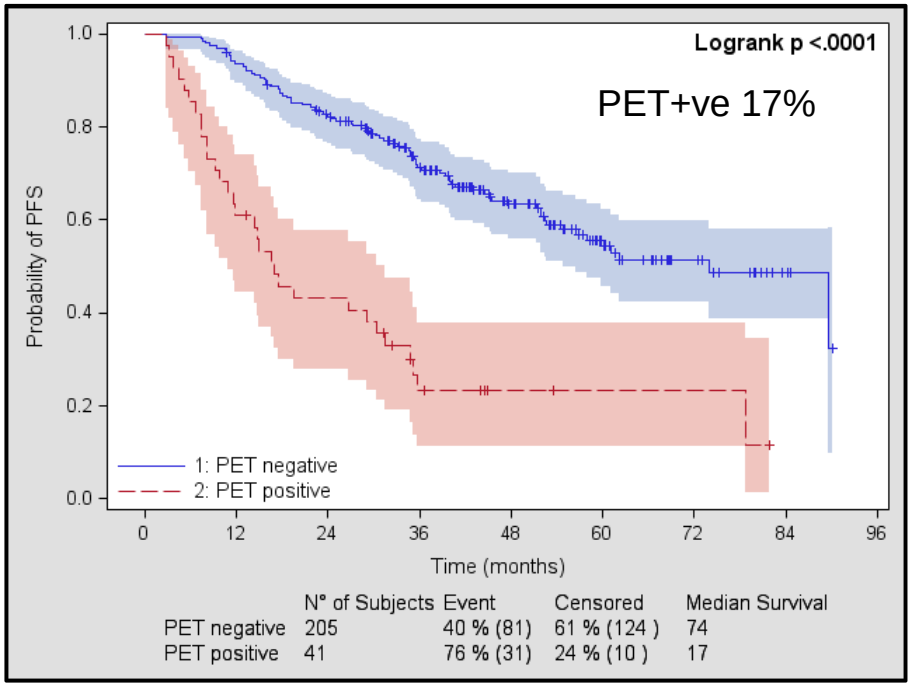
FDG-PET is prognostic after induction therapy

Both PET cutoffs predictive of PFS

Score ≥3 (Mediastinum)



Score ≥4 (Liver)



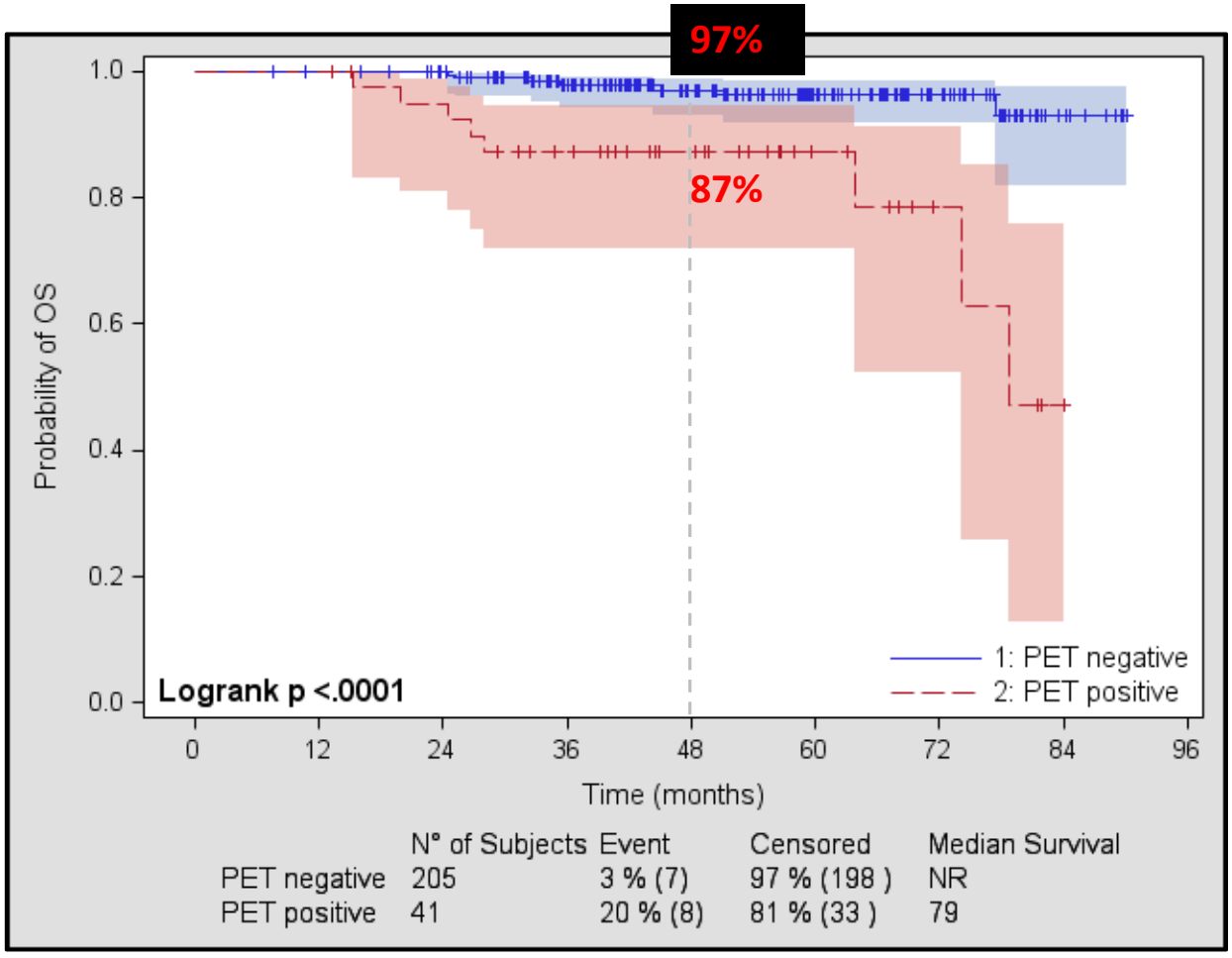
HR 3.9 (95% CI 2.5–5.9, *P* <.0001)

Median PFS:

16.9 (10.8–31.4) vs 74.0 mo (54.7–NR)

Trotman J, et al. Lancet Hematol. 2014; 1(1)

Postinduction PET status (cutoff ≥4) and Overall Survival



HR 6.7, 95% CI 2.4–18.5, *P* = 0.0002

Median OS: 79 months vs NR

Trotman J, et al. ASCO 2014: Abstract 8502.

Summary: Post-induction PET status

- Restaging with FDG-PET is highly prognostic for PFS and OS after induction immunochemotherapy
- 5PS cut-off ≥4 (liver) is the best cutoff

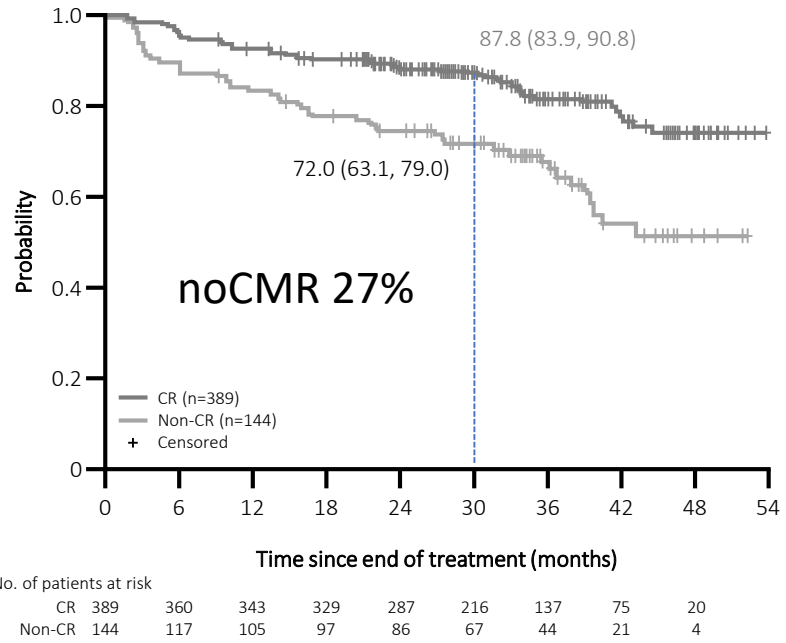
Open issues:

- Quantitative methods?
- To be fully validated PET restaging should be studied under the conditions of currently available and next therapies
  - R-maintenance
  - R-Bendamustine, R-Lenalidomide
  - G- chemio
- Possible integrations with other prognostic factors
- Therapeutic intervention based on PET results after induction treatment should be evaluated in the future

Landmark (from EOI) PFS analysis: by PET criteria

PFS for non-CR/CMR vs CR/CMR status according to IRC*

IHP 2007 criteria (N=533)[1]

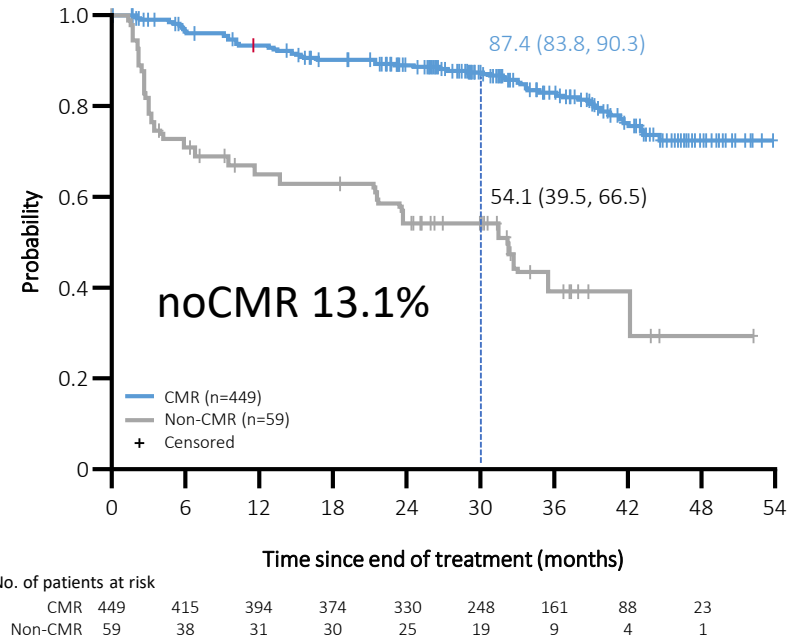


No. of patients at risk

CR	389	360	343	329	287	216	137	75	20
Non-CR	144	117	105	97	86	67	44	21	4

HR 0.37 (95% CI 0.25, 0.56); p<0.0001

Lugano 2014 criteria (N=508)[2,3]



No. of patients at risk

CMR	449	415	394	374	330	248	161	88	23
Non-CMR	59	38	31	30	25	19	9	4	1

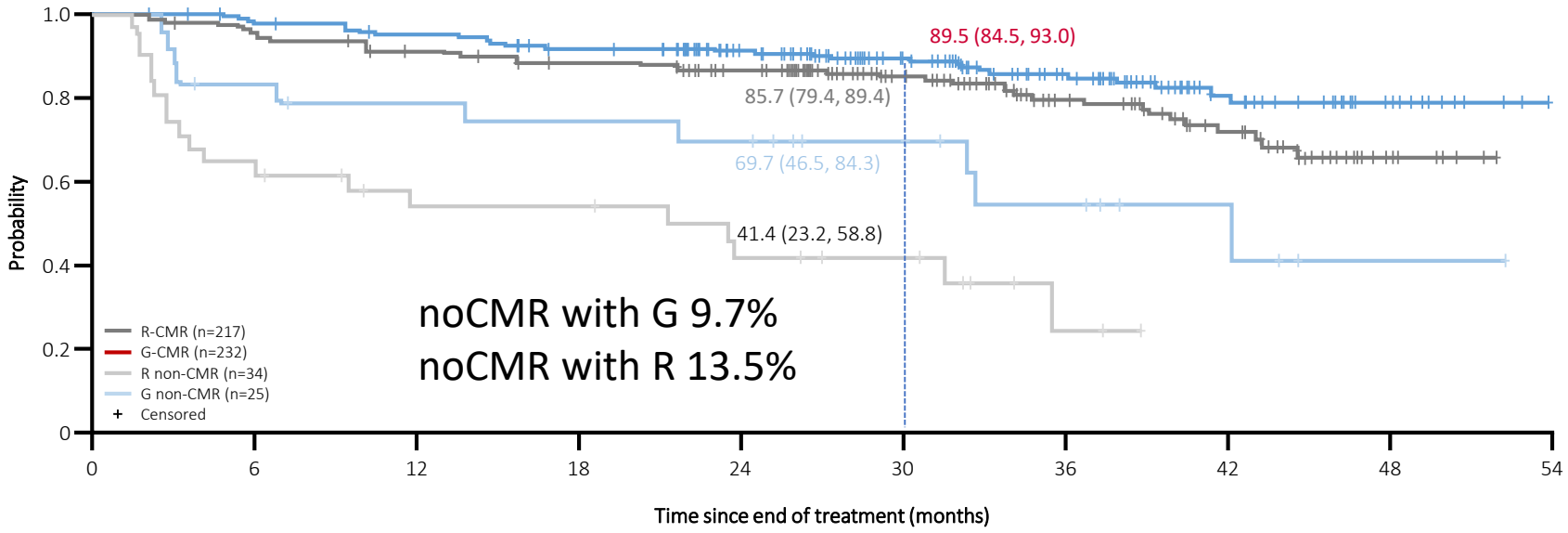
HR 0.21 (95% CI 0.13, 0.34); p<0.0001

*Patients who died or progressed (CT-based PD assessment or started next anti-lymphoma treatment) before or at EOI were excluded

1. Cheson BD, et al. JCO 2007;25:579–86
2. Barrington SF, et al. JCO 2014;32:3048–58
3. Cheson BD, et al. JCO 2014;32:3059–68

Landmark (from EOI) PFS analysis: by antibody arm

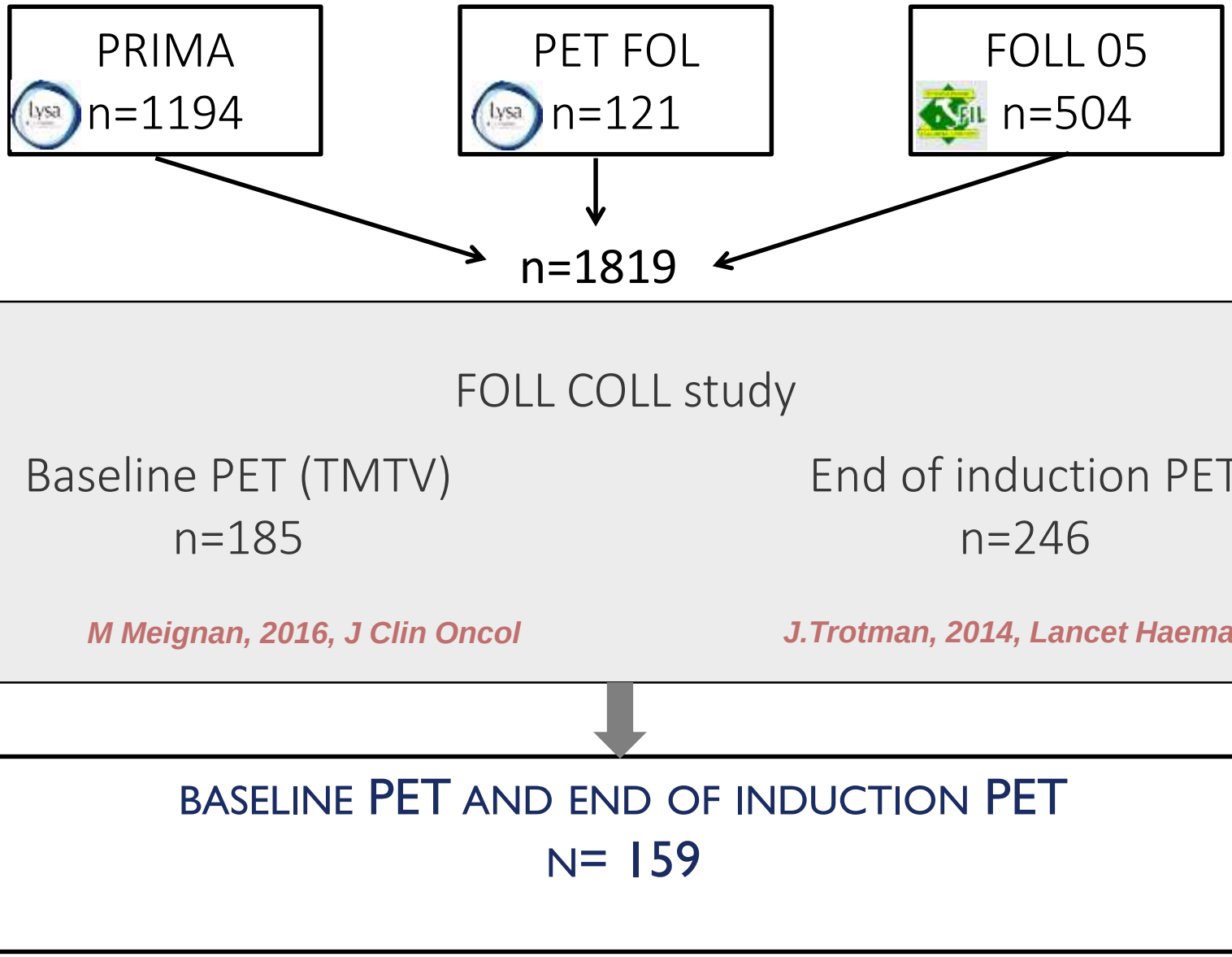
PFS for non-CMR vs CMR status using Lugano 2014 criteria (N=508)



	R-CMR, n=217	*G-CMR, n=232*	*R non-CMR, n=34*	*G non-CMR, n=25*
2.5-year PFS from EOI, % (95% CI)	85.7 (79.4, 89.4)	89.5 (84.5, 93.0)	41.4 (23.2, 58.8)	69.7 (46.5, 84.3)
HR (95% CI)		0.7 (0.4, 1.0); p=0.06		0.5 (0.2, 1.2); p=0.10

Integration of baseline and post-induction prognostic factors

High tumor burden follicular lymphoma



FOLL COLL study

Baseline PET (TMTV)

n=185

297 cm^3 median TMTV

29% high TMTV (>510cm^3)

M Meignan, 2016, J Clin Oncol

End of induction PET

n=246

16.6% positive PET (DS≥4)

J.Trotman, 2014, Lancet Haematol

baseline PET and end of induction PET

n= 159

260 cm^3 median TMTV

28% high TMTV (>510 cm^3)

16% positive PET (DS≥4)

TMTV and end of induction PET

- Associated factors

The frequency of PET positivity was significantly higher in patients with high TMTV (29% vs 11%, p=0.01).

	High TMTV	Low TMTV	*total*
Positive eiPET	13	13	*26*
Negative eiPET	31	102	*133*
total	*44*	*115*	*159*

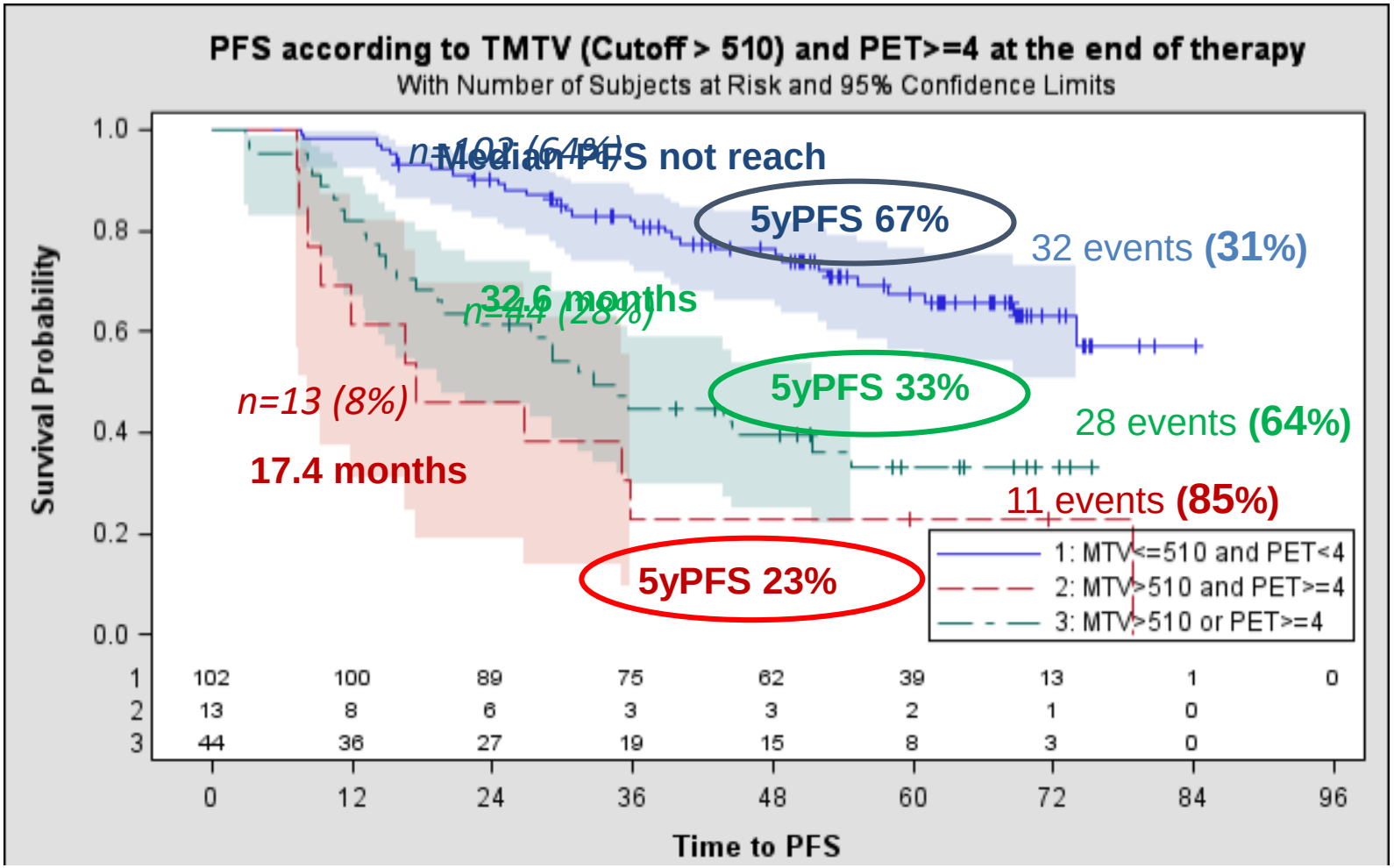
TMTV and end of induction PET

- Independent factors (multivariate analysis)

	PFS			OS		
	HR	*95% CI*	*p-value*	*HR*	*95% CI*	*p-value*
TMTV>510 cm^3	2.34	1.4-3.9	**0.0010**	2.8	0.9-9.0	0.08
Positive eiPET	2.34	1.3-4.1	**0.0035**	3.3	1.1-9.7	0.036

Multivariate analyses of PFS /OS including TMTV (Cutoff > 510) and response as time-dependent covariate and stratified by study - FOLLCOLL Population

TMTV and end of induction PET Impact on PFS

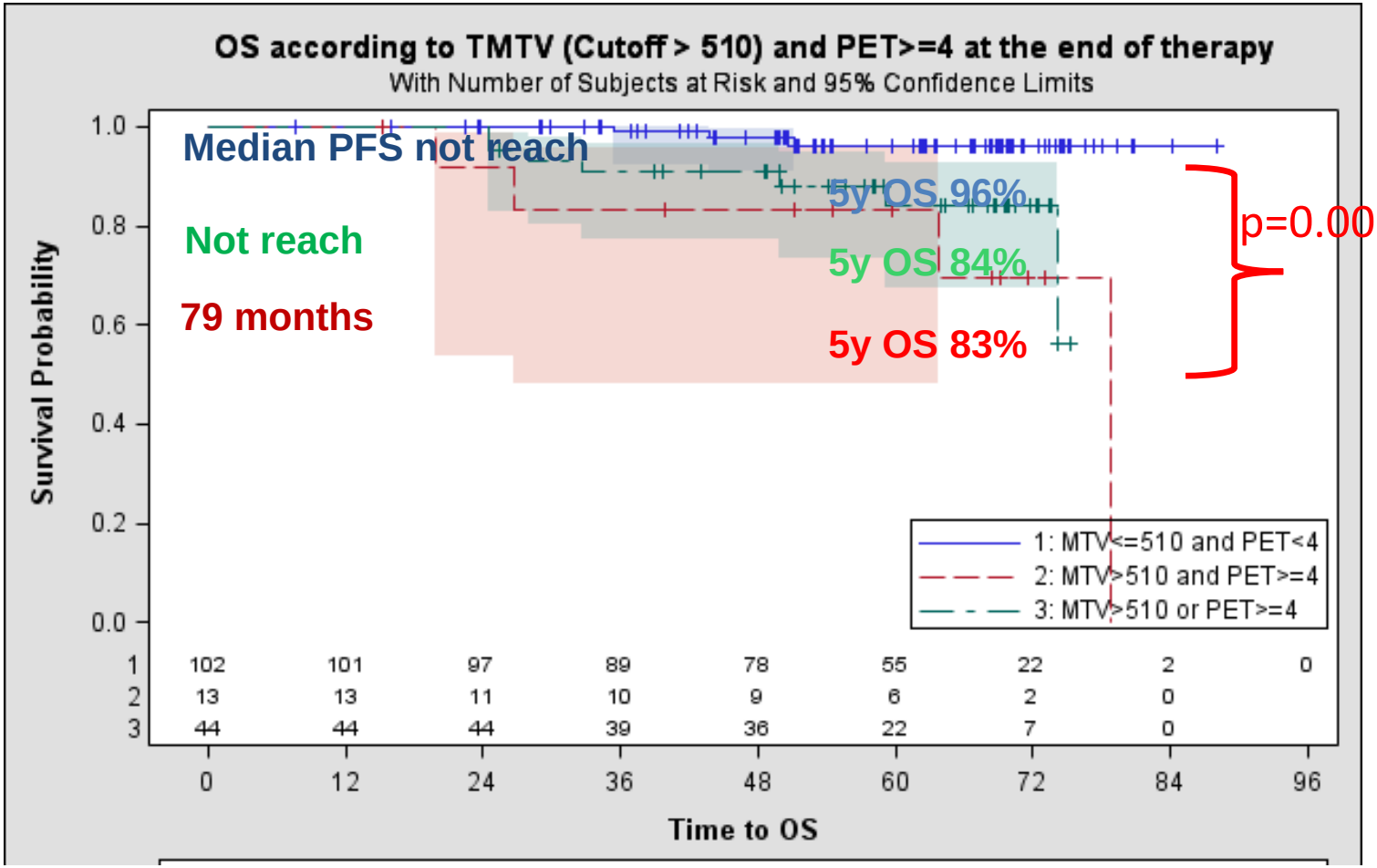


TMTV and induction PET

	events	PPV	2y PFS	5y PFS
High TMTV (n=44)	30	68	59	31.3
Positive Induction PET (n=26)	20	77	50	26.9
High TMTV AND pos PET (n=13)	11	**85**	46.2	23.1

	events	NPV	2y PFS	5y PFS
Low TMTV (n=115)	41	68	86.1	63.2
negative Induction PET (n=133)	51	77	84	59.6
low TMTV AND neg PET (n=102)	32	**69**	90.2	67.5

TMTV AND END OF INDUCTION PET IMPACT ON OS

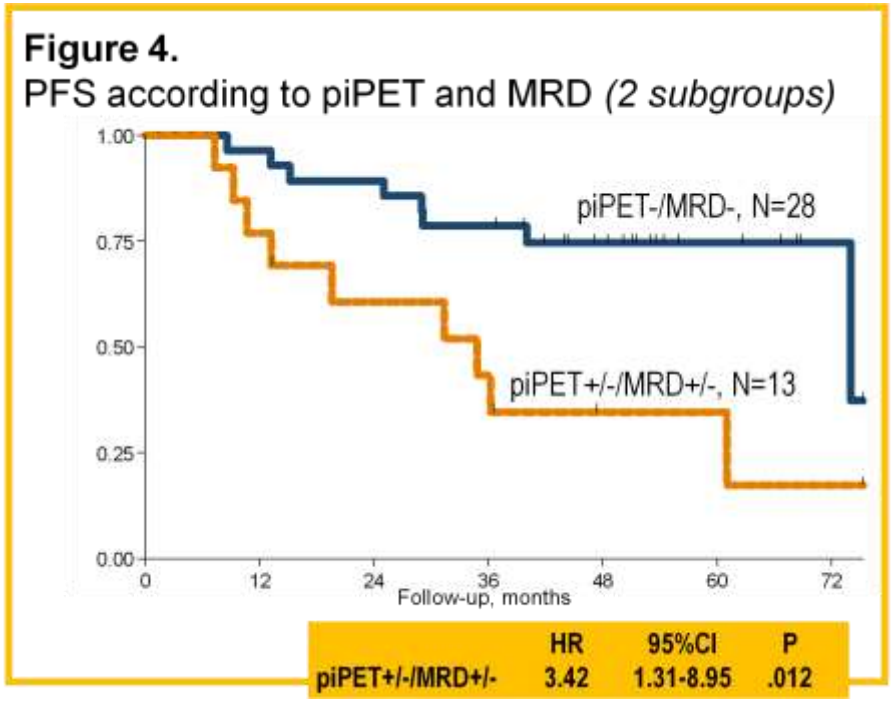


PET response and Minimal Residual Disease impact on Progression-Free Survival in Patients with Follicular Lymphoma (N=41)

Distribution of cases according to piPET and MRD

	MRD -	MRD+
piPET-	28 (68%)	8 (20%)
piPET+	2 (5%)	3 (7%)

P = 0.110 K=.249(FAIR)



30% at high risk

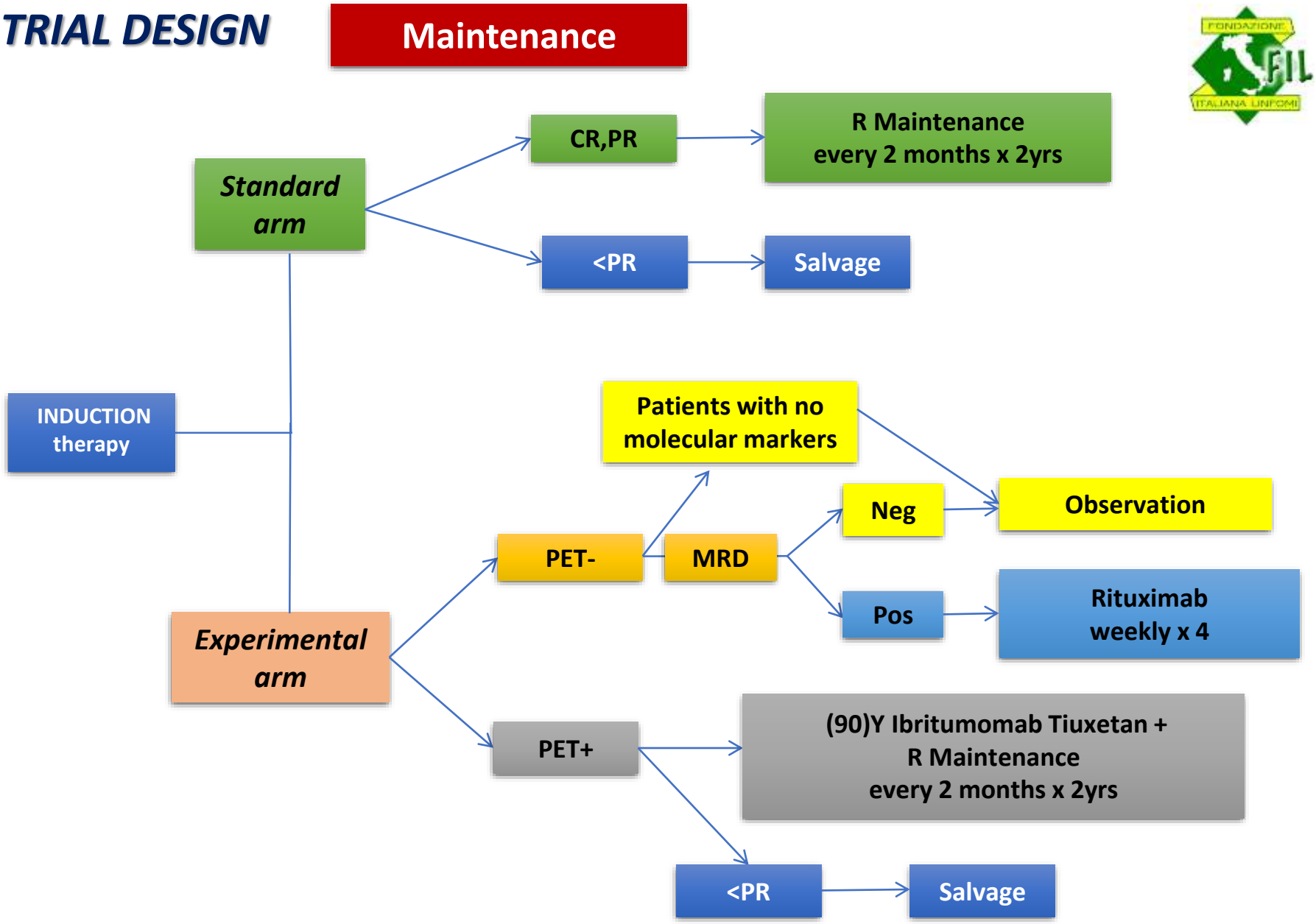
Luminari et al. Haematologica 2015

Primary objective

Evaluate whether

a **PET** and **MRD response-based maintenance** therapy is **not less effective** in terms of PFS than a standard maintenance therapy with R in patients with untreated, advanced FL

TRIAL DESIGN



PET REVIEW (FOLL12)

554 end treatment PET

479 PET- (86%)

75 PET+ (14%)

DS 4-5

7th international workshop on PET in lymphoma and myeloma

Palais de l'Europe, Menton, France, October 4th-6th, 2018

http://www.lymphomapet.com

PILM
International Workshop on PET in Lymphoma & Myeloma