The role of PET-CT in Follicular Lymphoma

"Prognostic and Predictive"

Judith Trotman – University Sydney

Massimo Federico – University Modena

Menton 2012

How we used to look at FL

1. Indolent B-cell lymphoma of mostly elderly
2. Watch and wait an accepted approach
3. Good response to treatment
4. Constant relapses
5. Shorter duration of subsequent remissions
6. Risk of transformation into aggressive NHL
7. Incurable disease

The changing face of FL in recent years

1. Common B-cell lymphoma - >60yrs is not so old!
2. Better pre-treatment prognostic indices – assist in triaging who to W+W
3. Excellent reponse to immuno-chemotherapy
4. Duration of remissions prolonged by maintenance Rituximab or salvage therapies
5. Risk of transformation into aggressive NHL
6. Death from lymphoma becoming a later event
7. Potentially curable disease

Follicular lymphoma: Prognosis: Pre-treatment

Histology

- Grade 1-3a correlates poorly with outcome
- Poor reproducibility 3a vs. 3b
- Transformation to Gd3b poor risk - requiring anthracyclines

Recognised heterogeneity in patient outcomes

- FLIPI (>4 Nodal areas / LDH / Age>60 / Stage III-IV / Hb<12) *Solal-Celigny 2004*
  - 5yr OS 91 vs. 53%, Low vs. High risk
  - 10yr OS 71 vs. 36%
- FLIPI2 (B_2M>ULN / LoDLIN>6cm / BMI / Hb<12 / Age>60)
  - 3yr PFS 89 vs. 57%
  - 3yr OS 99 vs. 82%

Federico 2009

Treatment of symptomatic Stage II-IV Follicular Lymphoma

Practice advances improving PFS: (& probably OS with longer f/u)

•Chemotherapy backbone

- CHOP supplanting CVP (& Fludarabine) with better PFS (PRIMA and FOLL05)
- Bendamustine supplanting CHOP with better PFS (STiL)

•Addition of Rituximab

- to induction chemotherapy
- as maintenance therapy (EORTC and PRIMA)

Difficult to predict median OS of newly diagnosed patient in 2012

•>10-15 years? i.e. an effective cure for many

PET at Diagnosis in FL

- Almost universally but not uniformly FDG avid

  Elstrom 2003, Blum 2003, Wohrer 2006, Weiler-Sagie 2010, Tychy-Pinel 2011
- PET at diagnosis does not always equal pre-treatment PET
- SUVmax ≥10 correlates with treatment within 6/12 (n=78)

  Svoboda ASH 2011
- Potential relevance for Watch and Wait approach / timing of clinical + imaging follow-up

PET Staging of FL

- To identify localised disease (~10%) amenable to RT
- PET upstaging:
  - 18-31% overall Fulham 2006, Karam 2006, Wirth 2008, Janikova 2008
  - early stage up to 60% Luminari ASH 2011
- More extranodal disease : ~50% bone, spleen, GIT, skin

  Tychyj-Pinel ICML 2011, Luminari ASH 2011
- Limited sensitivity/specificity for BM involvement
  - In patients with BMI only 34% were PET+
  - In PET-ve 43% of patients had BMI Luminari ASH 2011

Pre-treatment SUV in FL

- Earlier small studies, patient and scan heterogeneity
- Poor correlation of SUV_{max} with histologic grade

Wohrer 2006, Karam 2006

- No clear cut-off defines transformation

SUV_{max} <11.7 = indolent disease, SUV>17 always = transformation

Bodet-Milin 2008

- Biopsy the most FDG avid lesion to detect transformation?

Often logistically difficult in abdomen. Relevant if using R-CHOP?

- Proposed that intra-patient range in SUV_{max} i.e. highest – lowest more discriminatory for transformation than SUV_{max}?

Wondergem ASH 2011

3 multicentre first-line studies in AS FL

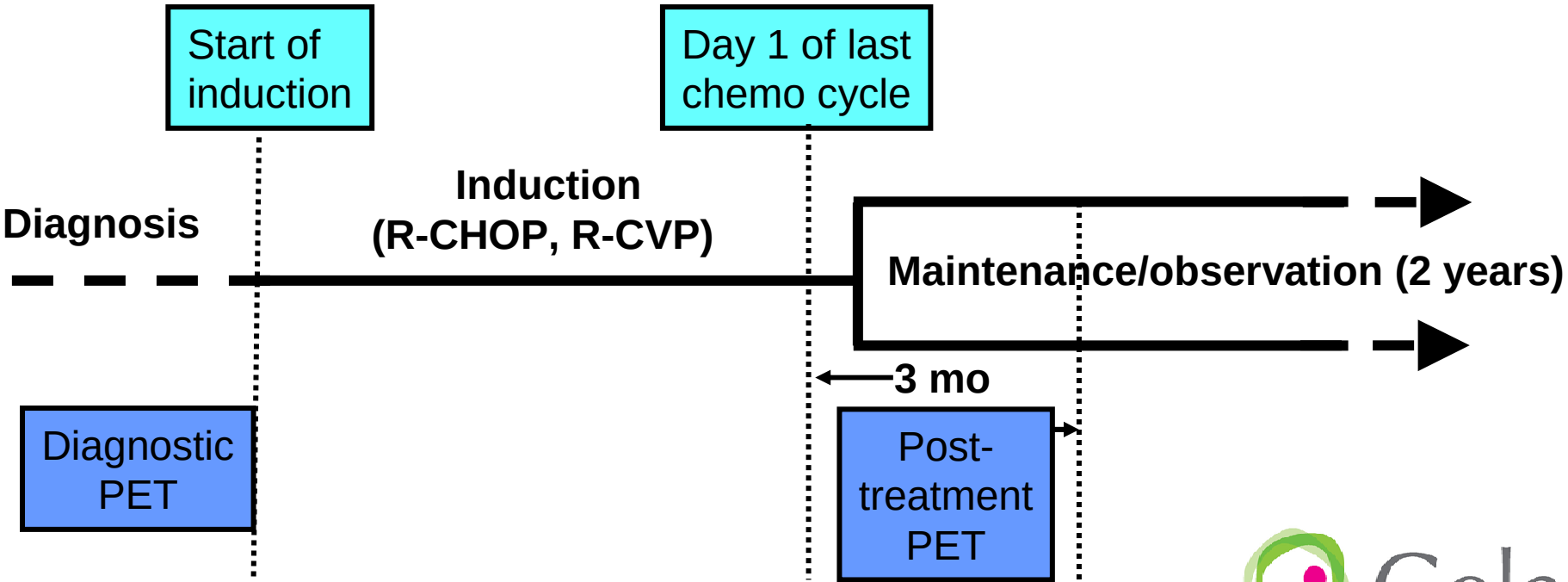
- PET in PRIMA *Trotman / Salles*
- FOLL05 *Luminari / Federico*
- PET Folliculaire *Dupuis / Meignan*

- Each with limitations
- Each with the same messages
- >350 patients in total

PRIMA PET Analysis

Trotman J, JCO 2011

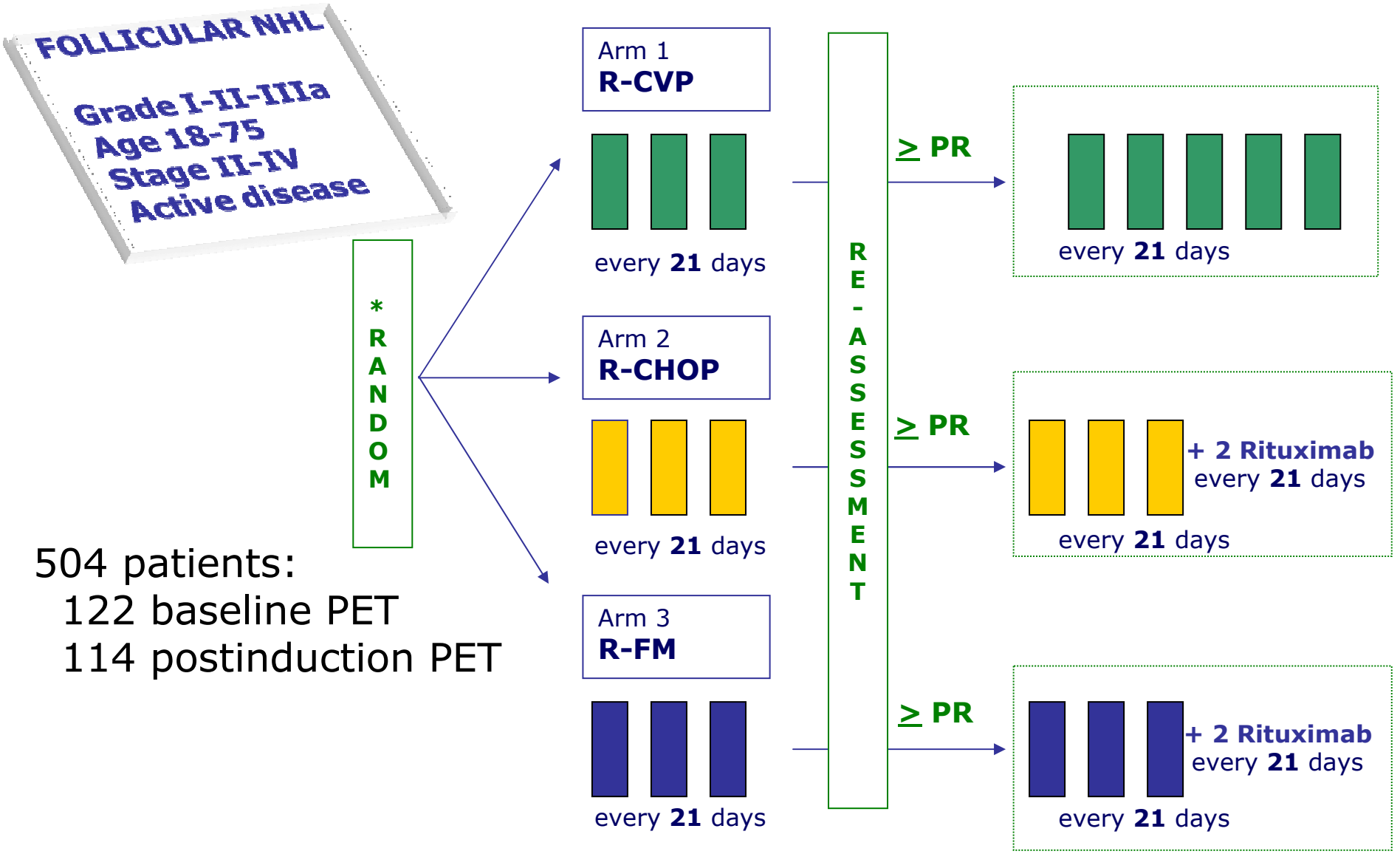
- 120 scans at diagnosis, 122 post-induction
- Positive or negative scan defined by local investigator
- Post-induction scan within 3 months of last chemo



Gela

FOLL05 Study

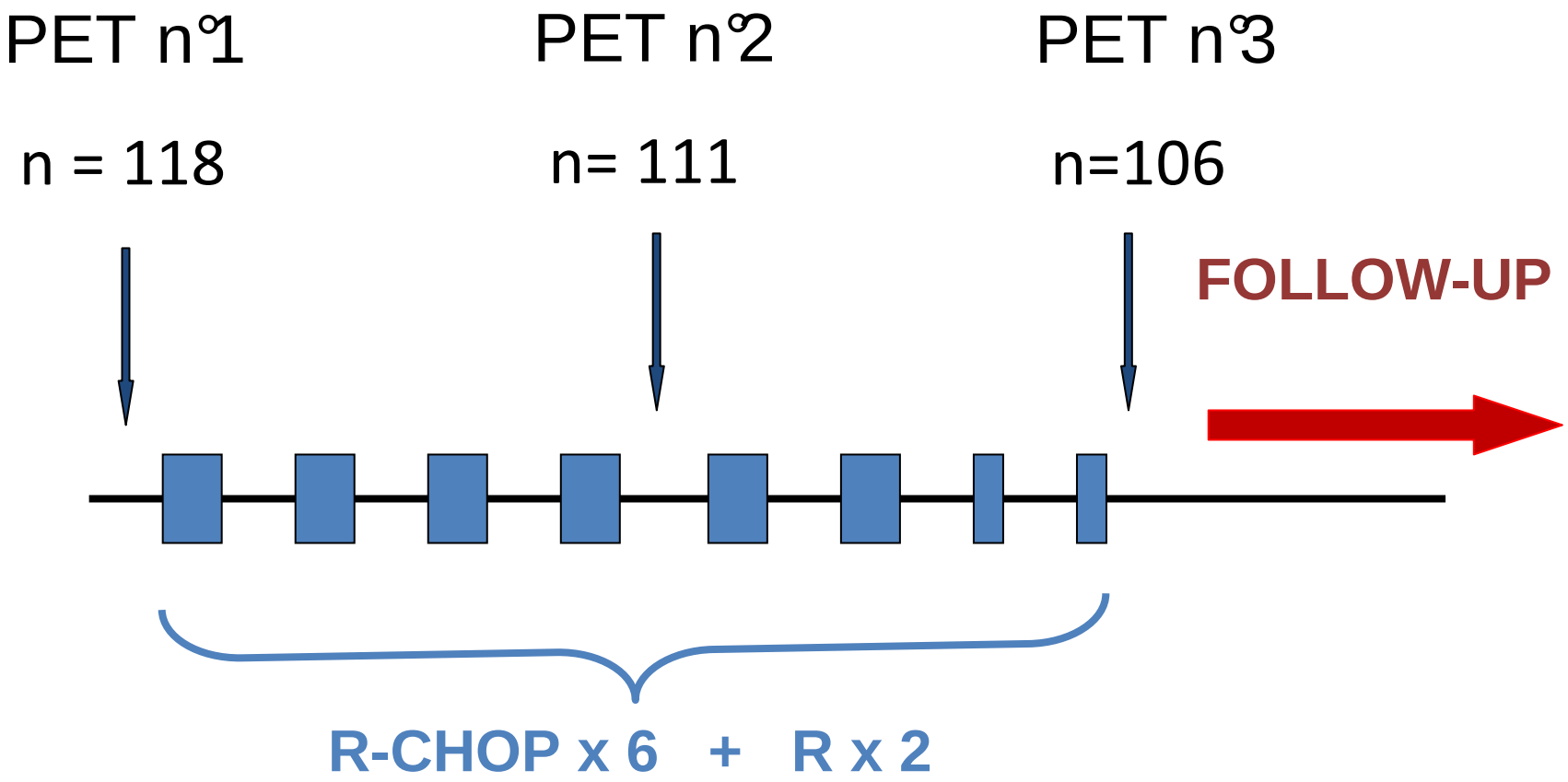
Federico M, ASH 2011



504 patients:
122 baseline PET
114 postinduction PET

PET Folliculaire

Dupuis J 2012



PET-CT Pre-Treatment

	PRIMA Trotman, JCO 2011	PRIMA Central review. Tychyj-Pinel, ICML 2011	FOLL05 Luminari, ASH 2011	PET Folliculaire Dupuis, Menton in press JCO 2012
Patients	120 Retrospective	59	122 Retrospective	118 Prospective
Treatment	R-CHOP (75%), R-CVP +/- R maintenance		R-CHOP vs. R-CVP vs. R-FM	R-CHOP
% PET+ at diagnosis	99	98	98 18% upstaged	99
SUV_{max} range	na	4.6-35.0	na	3.3-35.6
SUV_{max} median	na	10.7 Higher in mediastinum & abdomen than peripheral nodes	na	9.5
Extranodal	na	52% Bone/spleen/GIT/ skin	46% Bone/spleen/GIT	na

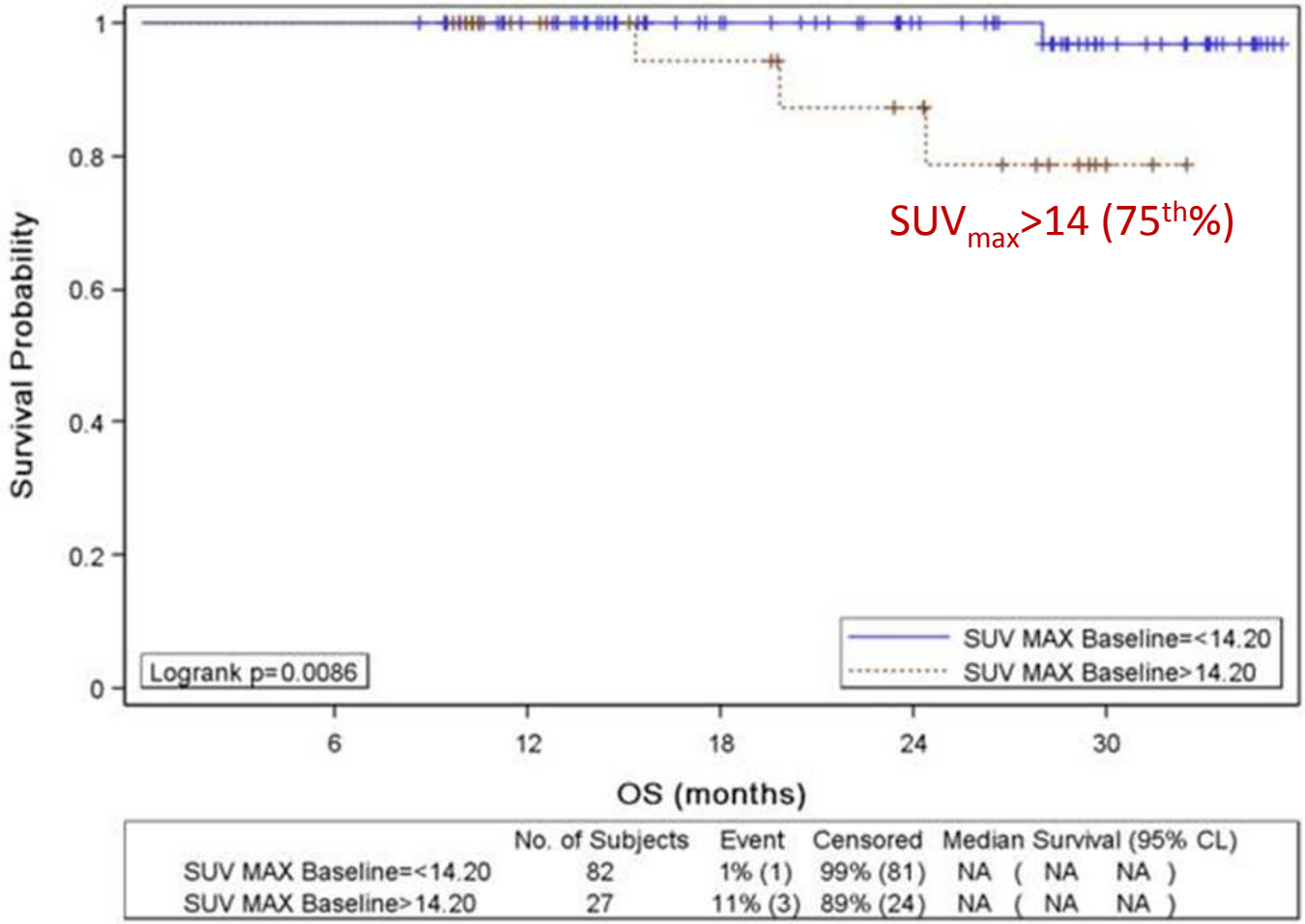
LS2

Diapositive 13

LS2 In this dense slide i suggest to report list of sites, like PRIMA column; then Bone, Spleen, GIT
FOR BONE, PET and Histo agreement was 60%. This was mostly represented by agrrement on negative cases 44%. Cases with boths histo and PET positive were 24/142 (17%)
Luminari Stefano; 31/08/2012

Pre-treatment SUV in FL

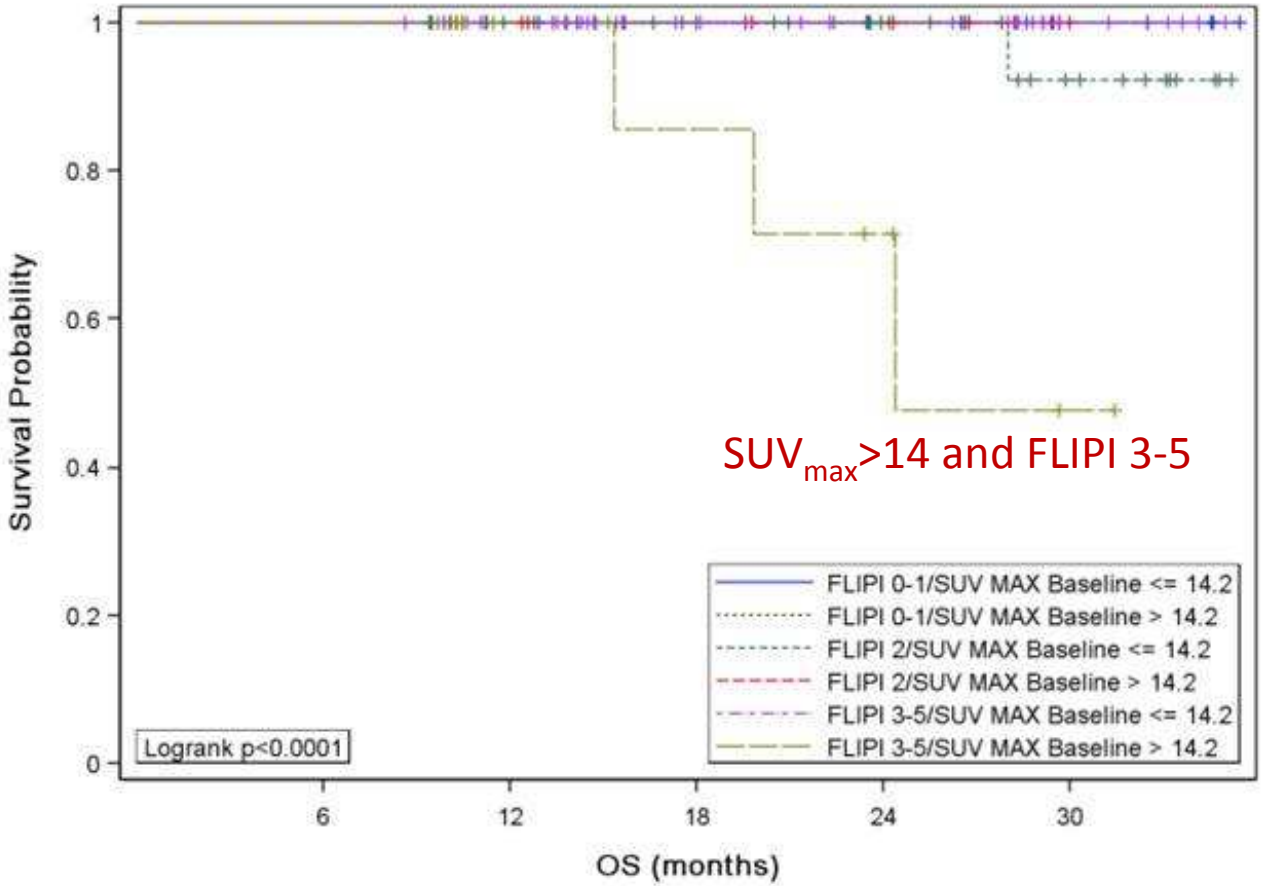
PET Folliculaire Dupuis, Menton 2012



	No. of Subjects	Event	Censored	Median Survival (95% CL)
SUV MAX Baseline=<14.20	82	1% (1)	99% (81)	NA (NA NA)
SUV MAX Baseline>14.20	27	11% (3)	89% (24)	NA (NA NA)

Pre-treatment FLIPI and SUV

PET Folliculaire Dupuis, Menton 2012



Post-induction therapy:
Limitations of conventional response assessment:

CT:

- Limited capacity to assess extranodal disease
- No prognostic impact of CR/CRu/PR in all 3 studies at 24-42m f/u
- Took 10 years to demonstrate an OS impact of CR/CRu over PR

Bachy 2009

Molecular remission

- Restricted primer sets and sensitivity issues
- No universal marker (unavailable in~50%)
- Bcl2 discordance in marrow, blood and nodal compartments
- Timing of MRD is uncertain
- BMBx not appealing to patients!

IHP Revised response criteria:

"PET not routinely recommended pre-treatment or for response assessment in FL"

Cheson 2007

- Has the heterogeneity of uptake and indolent/incurable nature of FL fostered scepticism of the role of PET and a paucity of studies?

- Yet widespread clinical PET use internationally

  Bishu 2007, Zinzani 2007, Janikova 2008, Jacobs 2008, Lopci 2010, Le Dortz 2010

- Not reimbursed for FL in Germany, Australia. Elsewhere?

Post-induction PET-CT

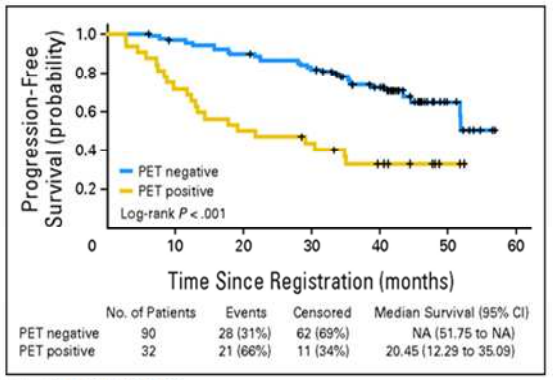
	PRIMA	PRIMA Central review	FOLL05	PET Folliculaire
PET+ after induction	32/122, 26%	IHP 2007, 22% 5PS ≥3, 22% 5PS ≥4, 13%	26/104*, 25%	23/106, 22% 5PS ≥4
PET assessment	Local clinician interpretation of PET report	Central review x2 + adjudicator κ 0.83/0.84/0.91	Local interpretation Few centrally reviewed	Central review x3 κ 0.7
PFS PET+ vs. PET-	33 vs. 71% at 42mo	25 vs. 61% at 42mo	48 vs. 84% UVA at 36 mo	51 vs. 87% at 24 mo
	HR 3.3, P=0.001	HR 3.0, p=0.01	HR 2.3, p=0.036	HR 6.6, p<0.0001
Median PFS	21mo vs. NR>52mo			27mo vs. NR
OS PET+ vs. PET-	42mo 79 vs. 97%		NS, p= 0.26	2yr 88 vs. 100%

PFS

OS

PRIMA
(med 42mo f/u)

Prognostic impact of postinduction positron emission tomography–computed tomography (PET-CT) on progression-free survival (PFS) in 122 patients.

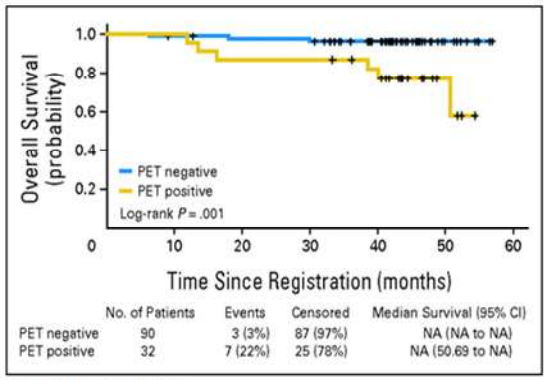


	No. of Patients	Events	Censored	Median Survival (95% CI)
PET negative	90	28 (31%)	62 (69%)	NA (51.75 to NA)
PET positive	32	21 (66%)	11 (34%)	20.45 (12.29 to 35.09)

Trotman J et al. JCO 2011;29:3134-3200

JOURNAL OF CLINICAL ONCOLOGY

Prognostic impact of postinduction positron emission tomography–computed tomography (PET-CT) on overall survival (OS) in 122 patients.

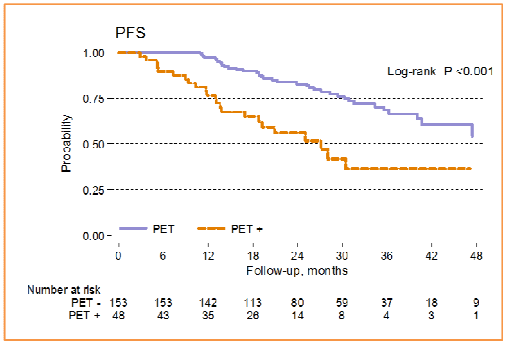


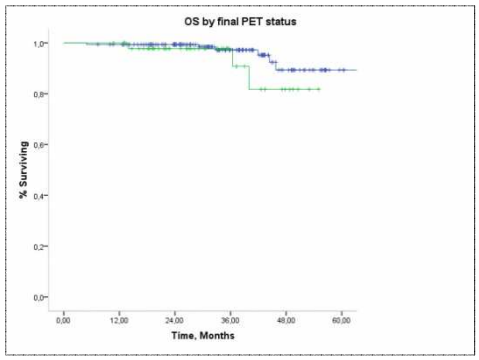
	No. of Patients	Events	Censored	Median Survival (95% CI)
PET negative	90	3 (3%)	87 (97%)	NA (NA to NA)
PET positive	32	7 (22%)	25 (78%)	NA (50.69 to NA)

Trotman J et al. JCO 2011;29:3134-3200

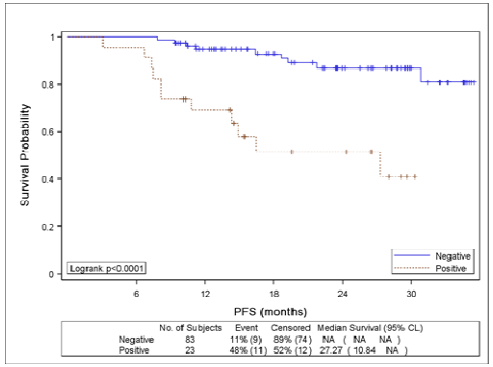
JOURNAL OF CLINICAL ONCOLOGY

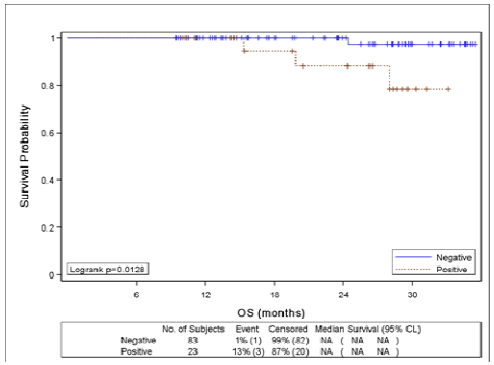
FOLL05
(med 28mo f/u)





PET Folliculaire
(med 24mo f/u)





Technical issues

Reporter concordance

- PET Folliculaire: 3 reviewers κ 0.7
- PRIMA central review: 2 reviewers κ 0.8-0.9
- Better with standardised acquisition and modern scanners?

Metabolic tumour volume? Total Lesion Glycolysis?

Role of contrast enhanced PET/CT?

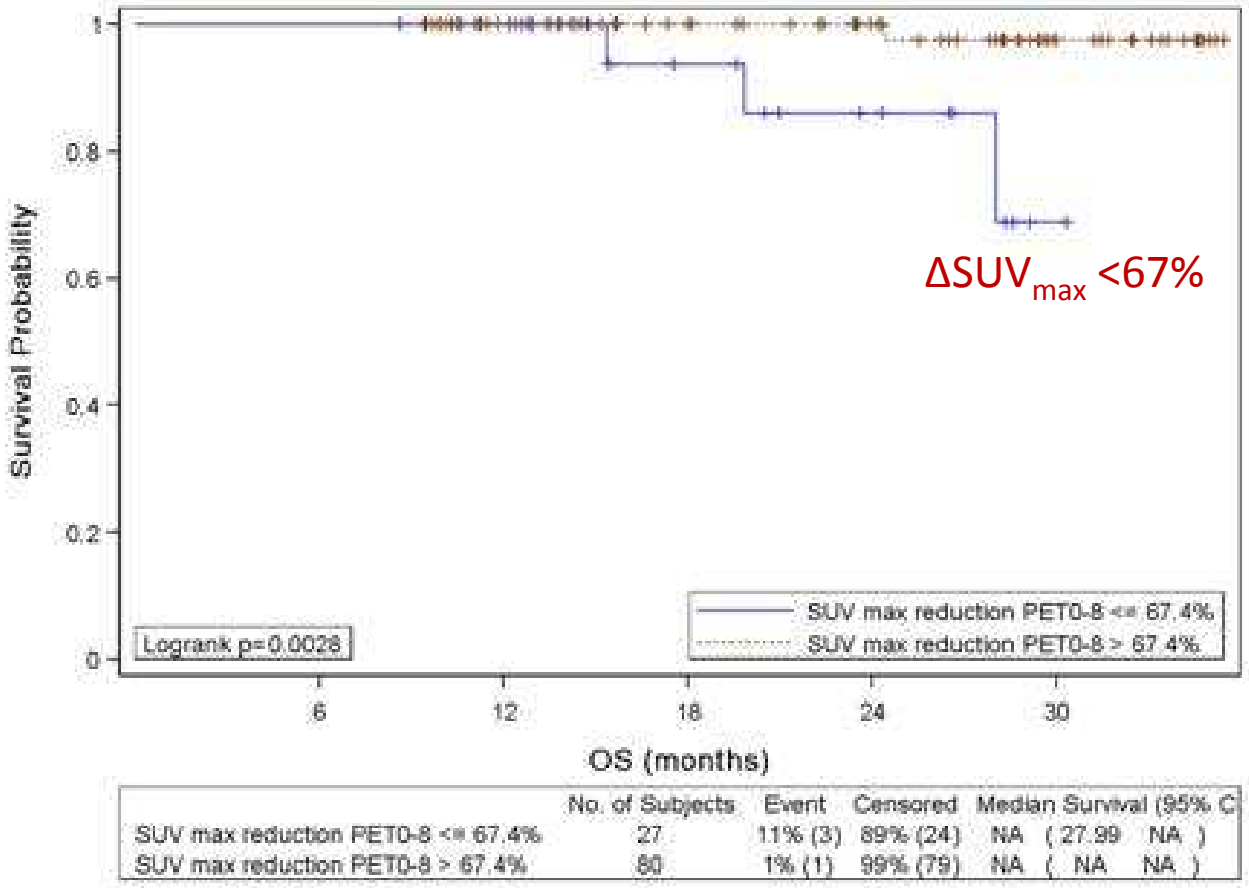
What criteria for post-induction PET+?

- 5PS (cut off ≥4)? Lower cut-off in relapsed setting?
- What about residual uptake in large mesenteric masses?

  Role for comparison of pre- and post treatment PET / ΔSUVmax?

ΔSUV in FL

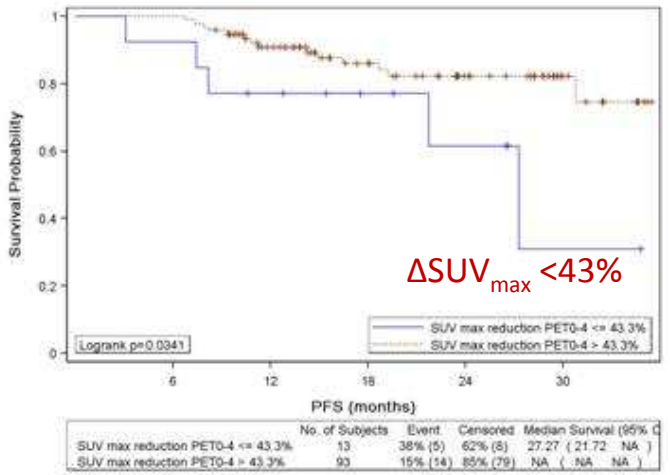
PET Folliculaire Dupuis, Menton 2012



Interim PET

- PET Folliculaire study – iPET+ after 4 R-CHOP
- 2yr PFS 61% vs. 86% in PET+ (p=0.0046)
- Lower PPV than postinduction
- ΔSUV after 4 cycles predictive for PFS

Du

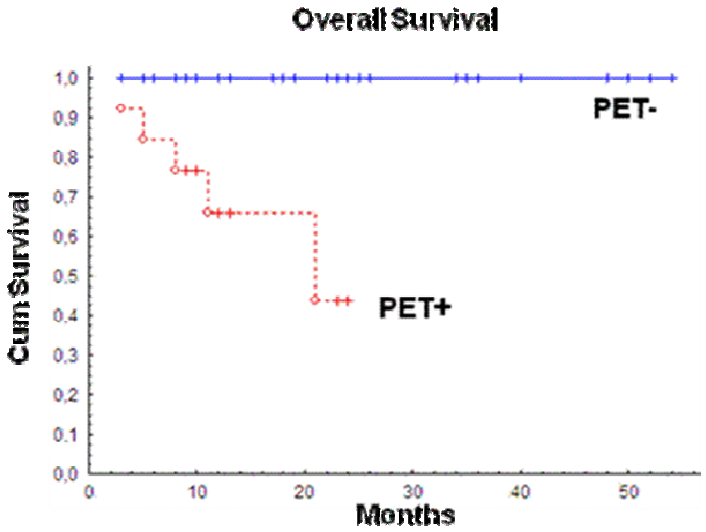


- Very good NPV in both PRIMA and PET Folliculaire studies
- Not the same clinical urgency to detect the poor risk population as in HL and DLBCL

PET after 2nd line therapy

Ysebaert, ASH 2011

- 41 patients treated with either R-FC/R-DHAP + ASCT
- CR/CRu in 68/72%
- PET negative 24/36%
- Achieving PET negative status after re-induction the only factor associated with superior OS post-autograft (p=0.0003)



Summary:
PET in FL at Diagnosis/Pre-Treatment

- Universally, but not uniformly, FDG avid lymphoma
- Upstaging in ~20%, higher in Early Stage
- ~50% patients have extranodal involvement
- Poor sensitivity for BM involvement
- Role of SUVmax in predicting time to treatment during W & W?
- Role of SUVmax in predicting treatment outcome?
- Role of SUVmax in directing biopsy to identify transformation?

Summary: Post-induction PET status

- Highly prognostic for both PFS and OS after first line R-CHOP

  Identifies ~25% patients for whom FL is not an indolent disease
- Time to incorporate PET in international response criteria
- Response adapted therapies require study
- 5PS cut-off ≥4 a promising platform. ΔSUV_{max}?

Caveats:

- Insufficient data in context of Rituximab maintenance
- No data on patients receiving Rituximab - Bendamustine

  (GALLIUM study: PET pre-treatment and post-induction in >170 FL patients with ~70% receiving Bendamustine chemotherapy in Ga101 vs. Rituximab RCT)
- No data for Rituximab - Lenalidomide (RELEVANCE study)

What does the clinician /patient want in a post-treatment prognostic factor?

- Good PPV

  Important for study of a response directed intensification of therapy
- Good NPV

  Reassurance

- Better sensitivity?

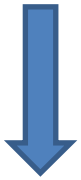
  Probably not – we know FL remains ‘incurable’.

  We want to detect active disease most likely to progress early.
- Better specificity?

  No. The experienced PET physician can distinguish FL from other pathologies, but … specificity surely better with comparison of pre & post therapy scans cf. isolated interpretation according to 5PS?

PET in Follicular Lymphoma:
Lessons learnt from other lymphomas

What should the next FL studies be?
What we need?



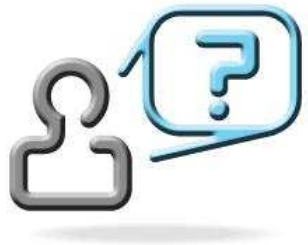
Larger cohorts

to better characterise pre-treatment PET

- *correlation with histologic grade?*
- *impact of SUVmax on both Time, and Response, to First Treatment?*
- *impact on the role of W and W and Rituximab monotherapy?*

What should the next FL studies be?

Questions



- Can we now derive a **Post-induction FLIPI**?

- Can a post-treatment PET adapted therapeutic approach improve outcomes in patients remaining PET+?

  What therapy to study: ASCT? RIT? Lenalidomide? other?

- Given the current crowded first-line FL study arena and the principle of therapy intensification is a response adapted approach best studied first in relapse?

  Australian study 2013 – Lenalidomide consolidation in relapsed FL remaining PET+ after R-chemo. 1° endpoint: conversion of PET+ to PET-

Impact of final PET result on PFS, in absence of maintenance

Follow-up : 28 months

Final PET +: 24%

3yr PFS:

37% PET+

69% PET-

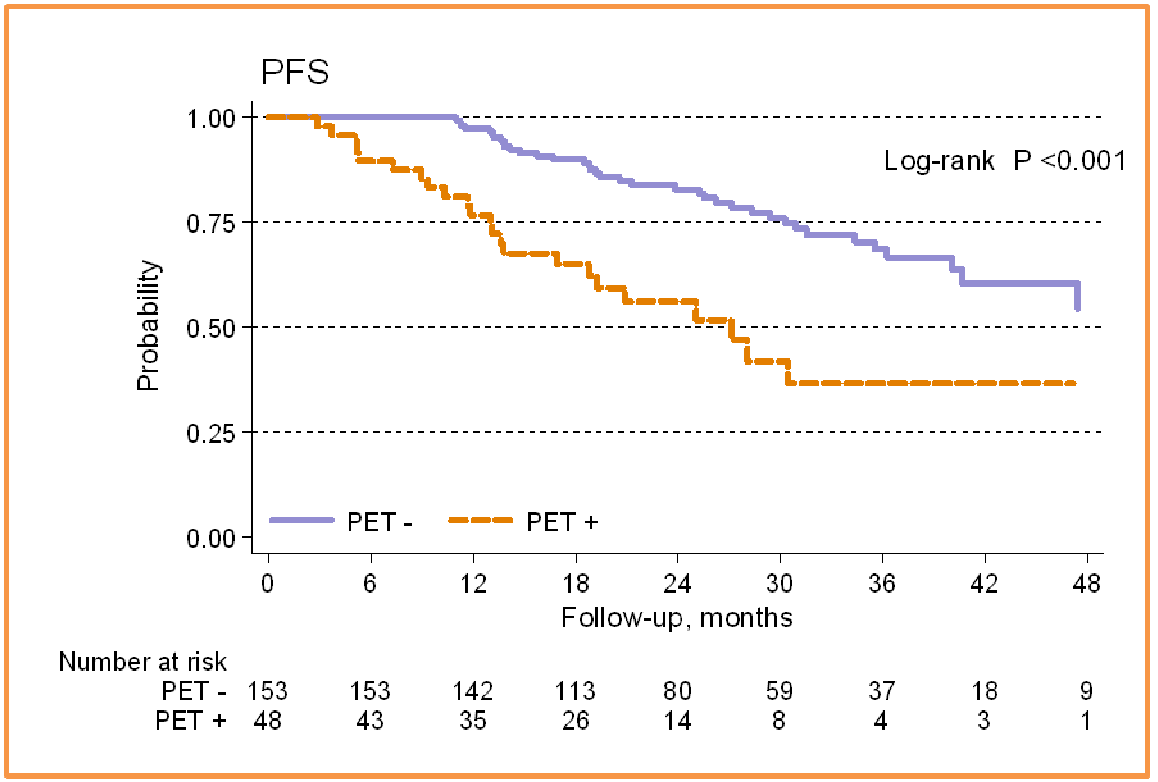
<u>Cox regression for PFS:</u>

PET + (HR 3.8: IC 2,1 - 6.7)

FLI2 3-5 (HR 2.5: IC 1.5 - 4.2)

F gender (HR 0.4: IC 0.3 - 0.8)

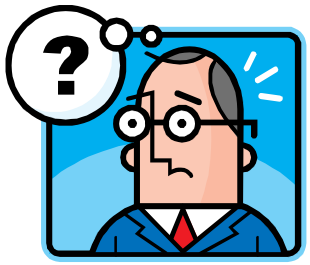
<CR (HR 1.4: IC 0.8 – 2,3)



S Luminari et al, Abs # 2636

Conclusion from these studies

In FL patients treated in first line, FDG-PET performed either after 4 cycles of R-CHOP or at the end of immunochemotherapy **is strongly predictive of outcome**



FDG-PET in Follicular Lymphoma ?

Therapeutic intervention based on PET results after induction treatment should be evaluated in the future

Fondazione Italiana Linfomi (FIL)

FOLL12

A multicenter, phase III, randomized study to evaluate the efficacy of a response-adapted strategy to define maintenance after standard chemoimmunotherapy in patients with advanced-stage Follicular Lymphoma

OBJECTIVES

Primary objective

To evaluate whether a PET and MRD response-based maintenance therapy is more effective in terms of Progression-Free Survival (PFS) than a standard maintenance therapy with Rituximab in patients with untreated, advanced, follicular lymphoma.

Secondary objectives

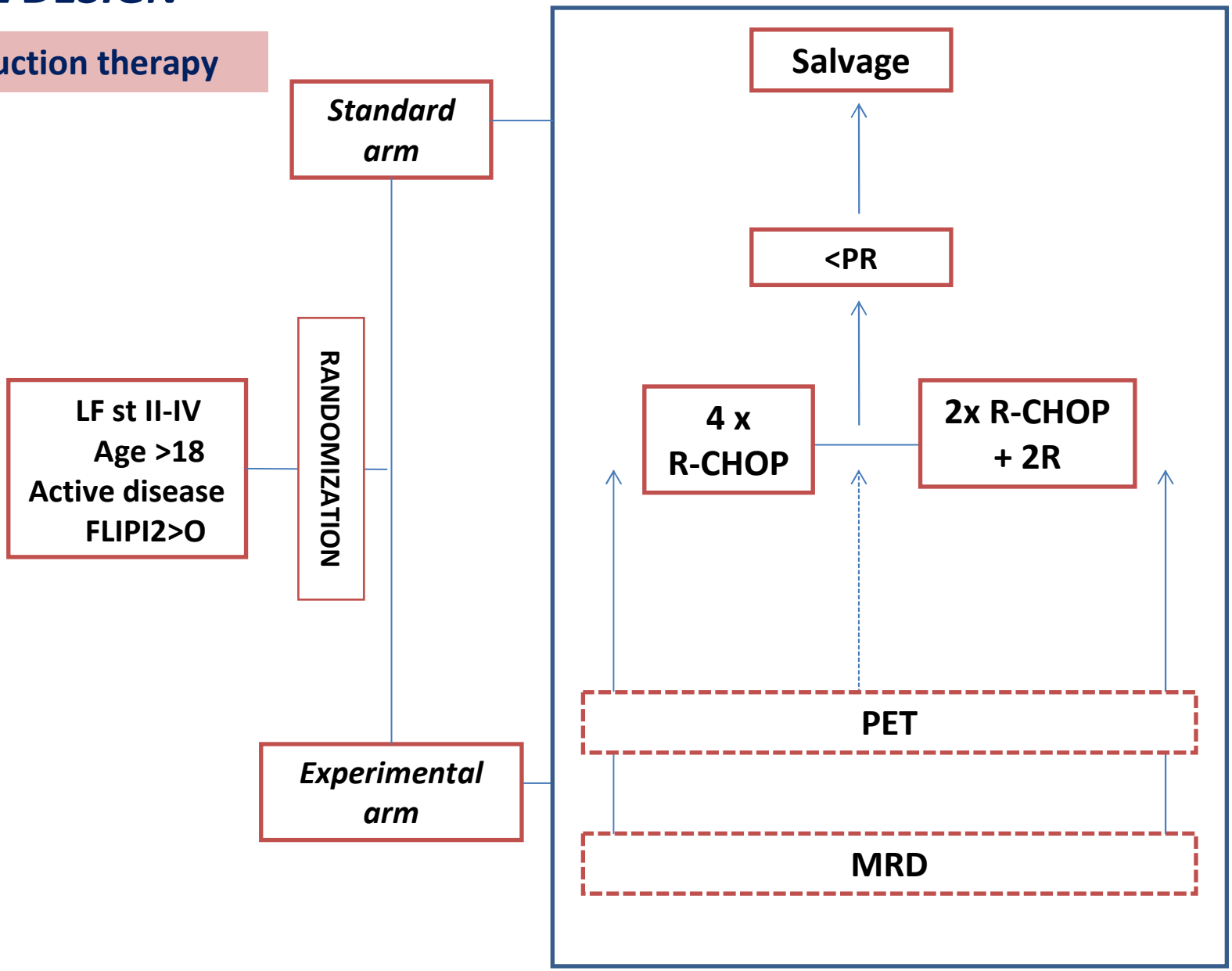
- To evaluate the efficacy of maintenance with observation or pre-emptive Rituximab therapy administered on the basis of MRD status in patients at low risk of progression after induction chemoimmunotherapy.

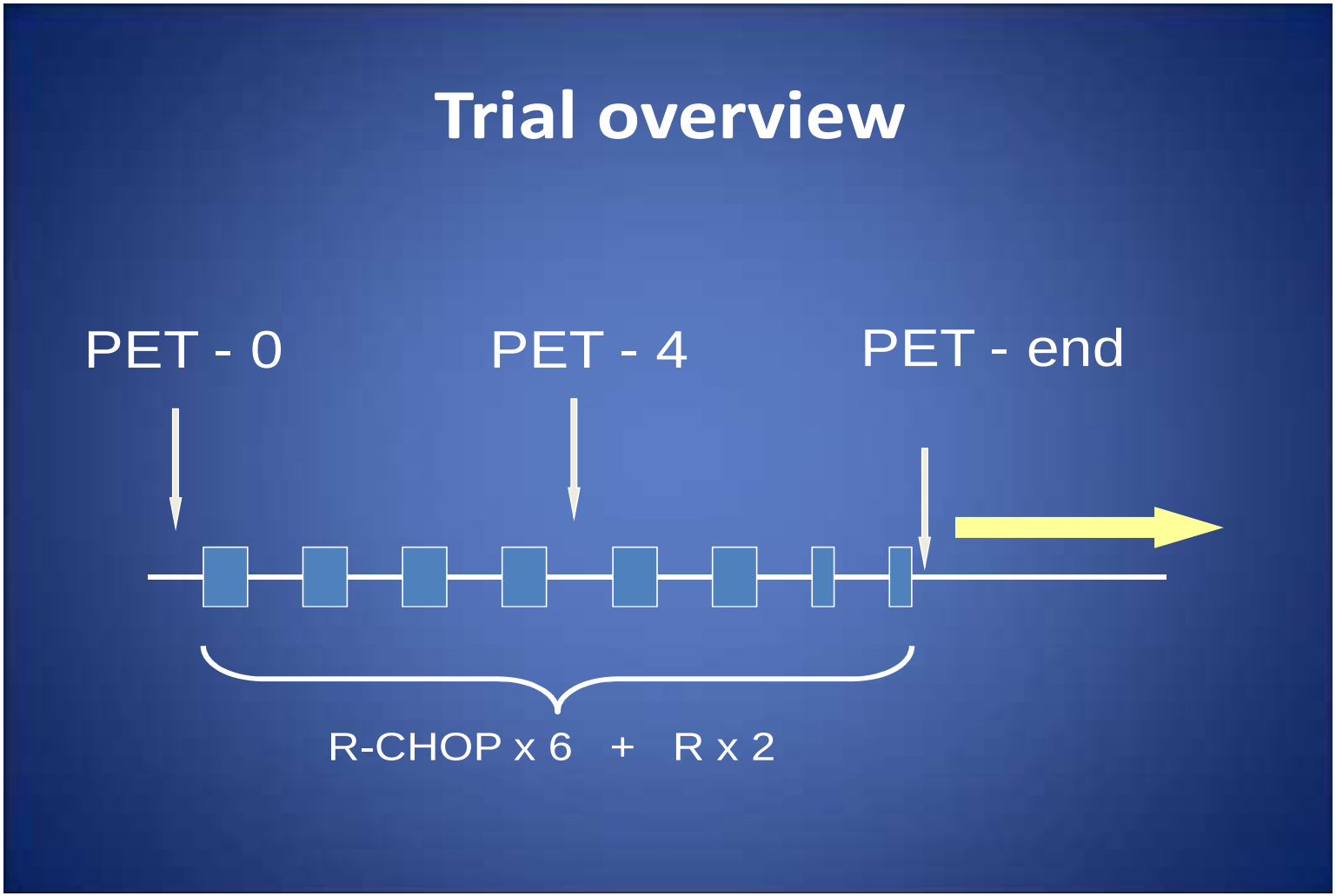
- To evaluate the efficacy of intensified maintenance with (90)Y Ibritumomab Tiuxetan followed by Rituximab maintenance therapy in patients at high risk of progression after induction chemoimmunotherapy.

- To compare a response-based maintenance therapy with a standard maintenance therapy in terms of toxicity.

TRIAL DESIGN

Induction therapy



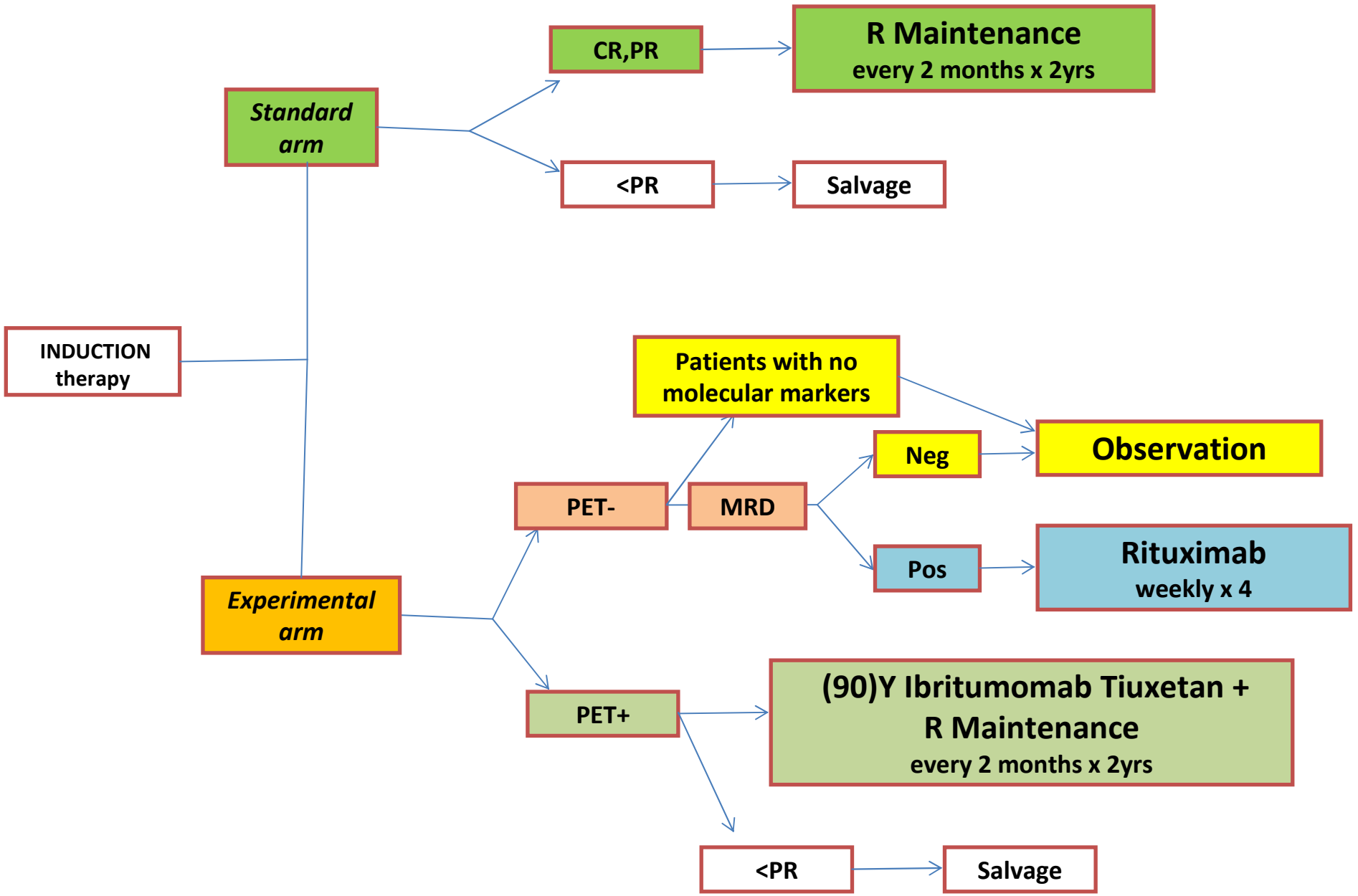


Central review:

Five expert nuclear medicine reviewers will score the scans according to the Deauville score.

TRIAL DESIGN

Maintenance



Inclusion criteria(1)

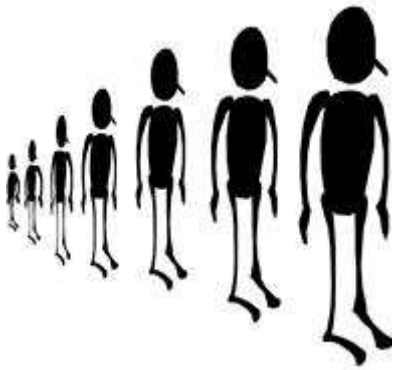
- Histological diagnosis of B-Cell Follicular Lymphoma (FL), grade I, II, IIIa according to WHO classification
- ECOG performance status 0-2
- Age ≥18 years
- Ann Arbor stage II-IV
- FLIPI2 score > 0
- Presence of evaluable/measurable disease after diagnostic biopsy

Inclusion criteria(2)

- At least one of the following criteria for defining **active disease**:

  - systemic symptoms
  - cytopenia due to bone marrow involvement
  - LDH> upper normal value
  - any nodal or extranodal tumor mass with a diameter >7cm
  - involvement of >= 3 nodal sites, each with a diameter of >= 3cm
  - extranodal disease
  - rapidly progressive disease

FOLL12 sample size and activation status



Accrual 4 years

Follow-up 3 years from the last accrued

Sample Size **546** + 10% dropout* = **602 (301 by arm)**

70-75 participating sites

First active site : **Messina Papardo**

(EC approval 25/07/2012)

What should the next FL studies be?
What we need?

Larger cohorts

What should the next FL studies be?

Can we now derive

a **Post-induction FLIPI**?

We will check!!

What should the next FL studies be?

Can **a post-treatment PET adapted therapeutic approach** improve outcomes in patients remaining PET+?

FOLL12 has been designed with this ambitious goal!

What should the next FL studies be?

Given the first-line FL study arena and the principle of therapy intensification, should a **response adapted approach** be investigated in patients with relapsed FL?

YES, a response adapted approach should be **also** investigated in patients with relapsed FL


RESPONSE ADAPTED THERAPY
NEW DRUGS
... ¿will allow us ...?
Picasso - Muerte del toro

Remission monitoring

- No data
- No reason to think it would be worthwhile given poor specificity in other lymphoma histologies
- No rationale given re-treatment is usually reserved until symptomatic progression/relapse