PET based response evaluation of Follicular Lymphoma according to Lugano classification:

where we are in daily practice?

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PET in daily practice for FL
Questions

- Are the Deauville criteria used?
- What about level 3 – reproducibility?
- Negative – is it used to discriminate between 1 and 2?
- Positive – is it used to discriminate between 4 and 5?
- If interim PET is performed and is negative – is PET performed again at the end of therapy?
- What impact has a positive PET at the end of treatment in FL?

Follicular Lymphoma: response assessment

- Indolent yet ~15% patients will die within 5 years, incl 50% of early progressors.

  Casulo, JCO 2015

- High risk FLIPI / FLIPI-2 scores fail to clearly identify these patients.

  Solal-Celigny, Blood 2004, Federico, JCO 2009

- Predictive value of PET assessment after first-line rituximab-chemotherapy for high tumor burden FL reported in three prospective trials …

  Trotman JCO 2011, Dupuis JCO 2012, Luminari Ann Oncol 2013

- and confirmed in a pooled analysis of centrally reviewed scans in these trials.

  Trotman Lancet Haematology 2014

- Recommendation to use PET-CT for FL in the 2014 Lugano criteria.

  Cheson, Barrington , JCO 2007

- Minimal data, and low therapeutic rationale for interim PET.

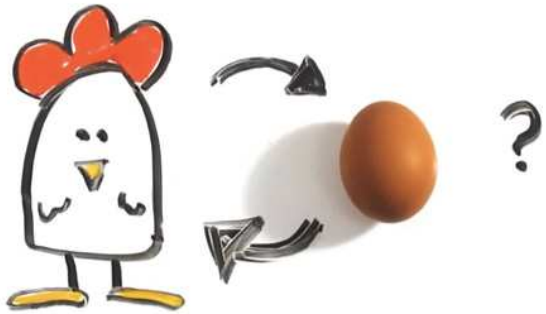
  Dupuis JCO 2012

- No results of response adapted therapeutic studies.

PET for Follicular Lymphoma

Australia

- PET reimbursed for early stage disease under consideration for RT
- A 2014 application for MBS reimbursement of PET for baseline & response assessment to 1st & 2nd line chemotherapy undergoing scientific & economic review - Nov 2016.
  Application hampered by:
  - limited sensitivity/specificity data for PET vs. CT in FL and
  - lack of a demonstrated impact of postinduction PET on outcome,
  hence cost-benefit analysis is weak.
- We can't study a PET-adapted therapeutic approach because we can't get the scans – neither through federal funding nor PET company support!



PET in daily practice for FL

Australia

Leakage / “Work-arounds” to access scans using existing indications

- Baseline PET requested for patients with ES disease on clinical examination.
- With heterogeneity and 30% risk of histologic transformation the presence of parameters suggestive of such (e.g. rapidly growing bulky disease, B symptoms and a rising LDH) often prompt physicians to order PET scanning for “*features suggestive of transformation to aggressive lymphoma”*.

PET Reports:

- Statements such as “*an area with SUVmax of 15 suggestive of more aggressive disease*” are typical in reports.
- When postinduction PET is performed Deauville criteria are rarely used
  - Although repeatedly asking for DS in patients on clinical trials might prompt practice change!

PET in daily practice for FL

Internationally

Recent UK NICE guidelines:
“for people diagnosed with other subtypes or stages of non-Hodgkin's lymphoma not listed in recommendation 1.2.1, consider PET to confirm staging if the results will alter management”.

"For people with other subtypes of non-Hodgkin's lymphoma not listed in recommendation 1.2.4, do not routinely offer PET to assess response at completion of planned treatment unless the results will alter management.“

I propose postinduction-PET will result in closer clinical follow-up of the poorer prognosis group who remain PET-positive. Management is not just treatment.

- PET not reimbursed for FL at all in Germany but “we recommend PET especially in localized cases and suspected transformation”.
- Readily available in USA, France, Italy and Korea.
- Only for those who can afford it in China, more commonly in baseline than EOT.

PET in daily Practice for FL

Are the Deauville criteria used?

Not reported by my nuclear medicine service provider.

But they should be …

Postinduction PET review concordance

(3 independent reviewers)

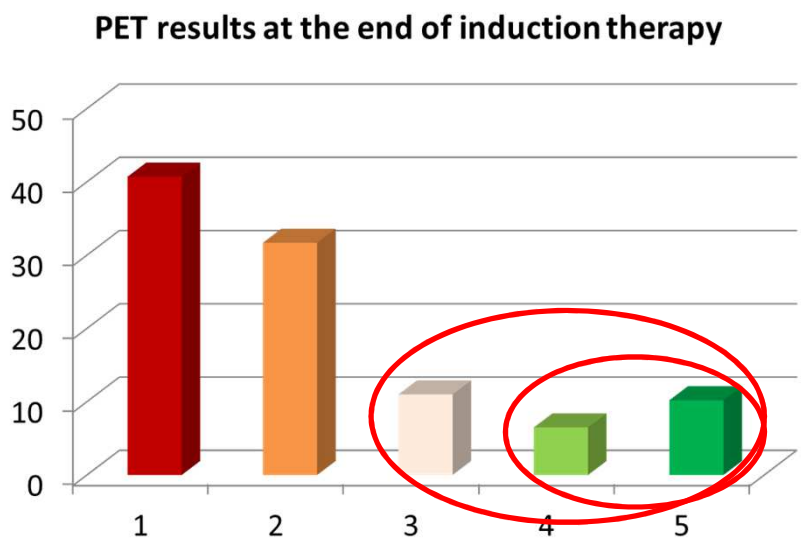
	Concordance (κ) Cut-off ≥3	Concordance (κ) Cut-off ≥4
PRIMA	0.55	0.70
FOLL05	0.30	0.60
PET Folliculaire	0.57	0.71
	Moderate agreement	**Substantial agreement**

Postinduction PET status

(n = 246)

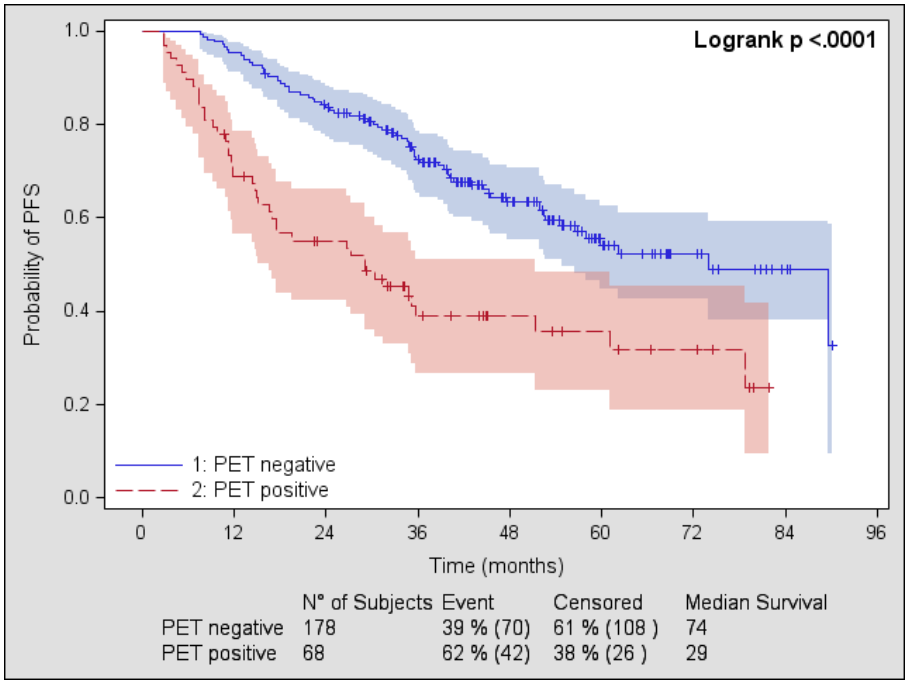
68 (28%) PET+ with cut-off ≥3
(uptake > mediastinum)

41 (17%) PET+ with cut-off ≥4
(uptake moderately > liver)

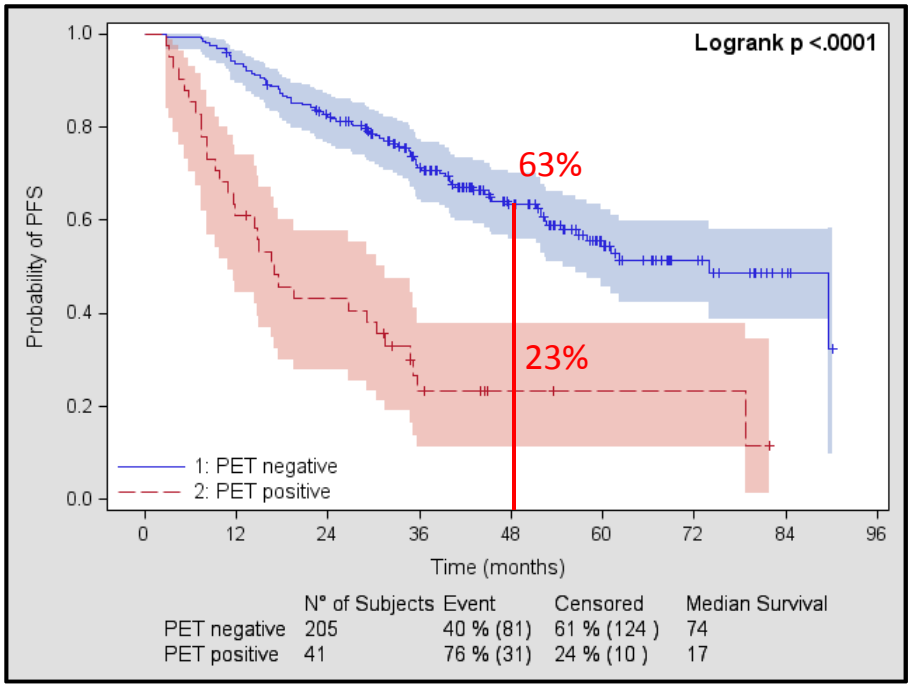


Both PET cut-offs predictive of PFS

Score ≥3



Score ≥4

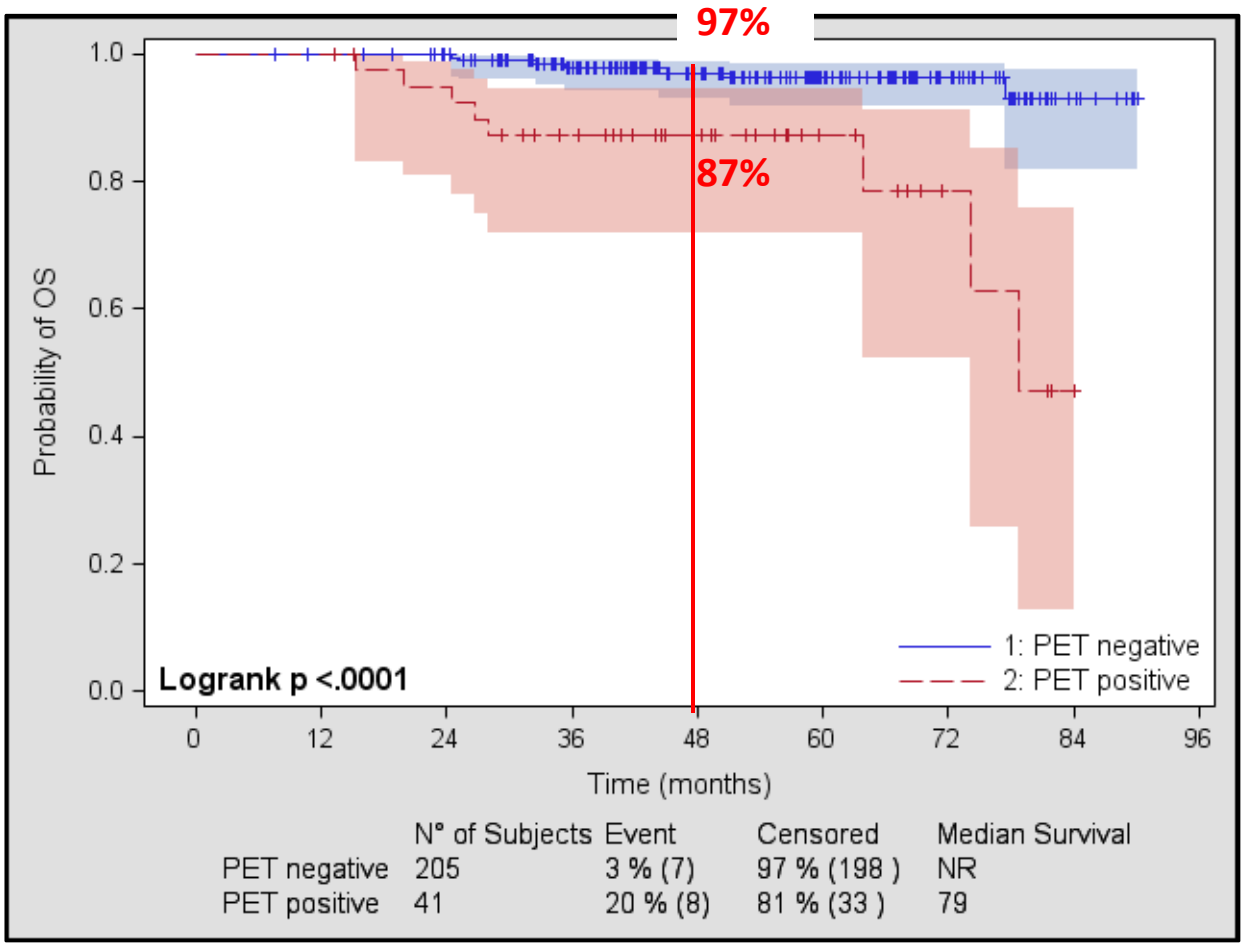


HR 3.9 (95% CI 2.5-5.9, p<.0001)

Median PFS:

17 (10.8-31.4) vs. 74 mo (54.7-NR)

Postinduction PET status (cut-off ≥4) and Overall Survival



HR 6.7, 95% CI 2.4-18.5, p=0.0002

Median OS: 79 months vs. NR

KM curves for local PET reporting correlate closely with score ≥3 / mediastinal cut-off

n = 224

n = 439

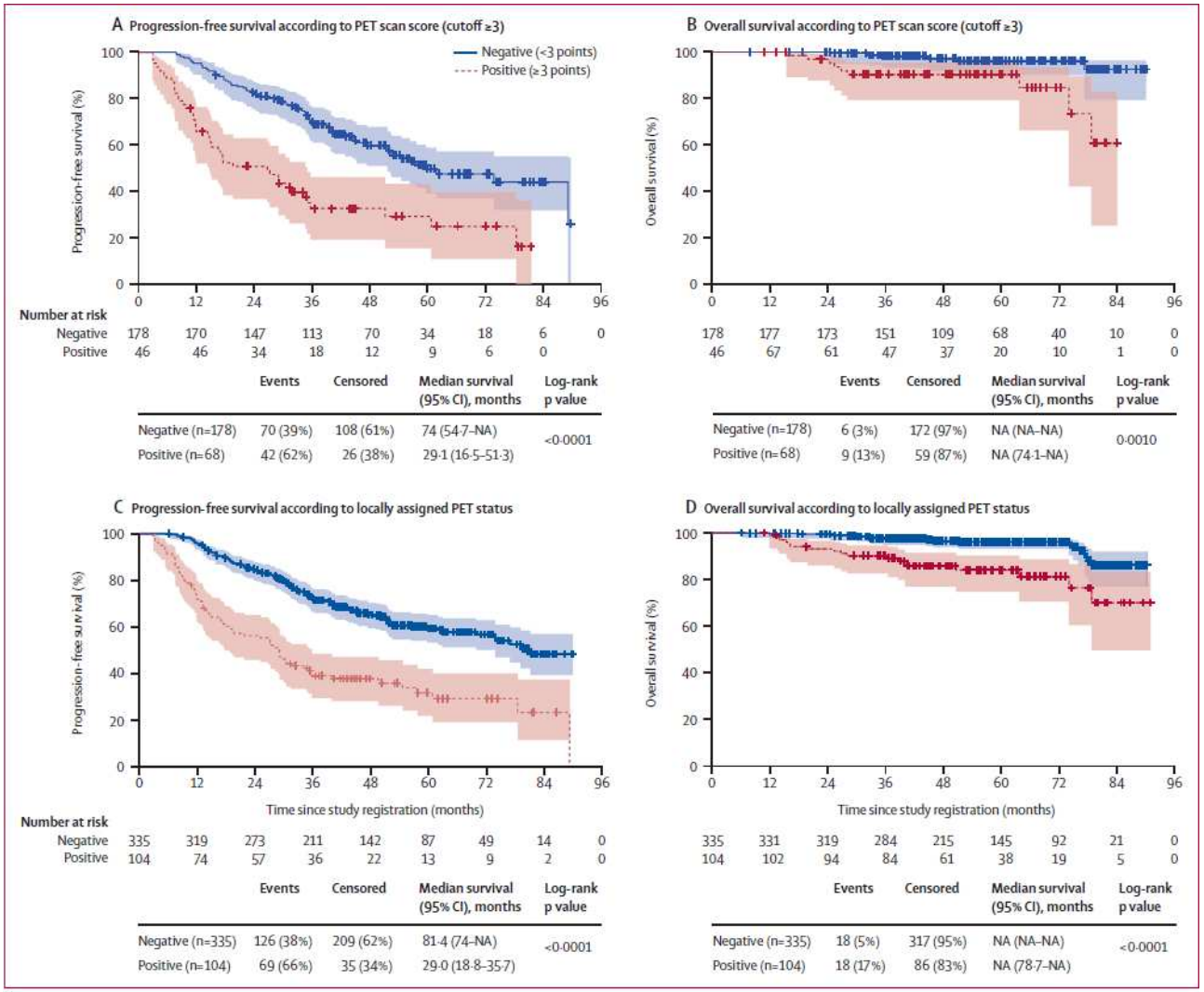


***Figure 4*: Progression-free and overall survival according to post-induction PET scan status (cutoff ≥3), and according to local PET scan result in all patients with local PET assessment**
Prognostic effect of post-induction PET-CT status according to a cutoff score of 3 or higher on the five-point Deauville scale (negative score is <3 and positive score is ≥3), on progression-free survival (A) and overall survival (B) in all patients with centrally reviewed post-induction PET scans, and prognostic effect of post-induction PET-CT status according to local PET assessment on progression-free

Should the Deauville criteria be used?

Yes.

Because of better concordance and clearer separation of the PFS curves a score ≥4 should be applied.

Is interim PET used?

In my practice no:

we usually have a clear idea of responders clinically, and postinduction PET is more predictive than interim PET in this indolent NHL.

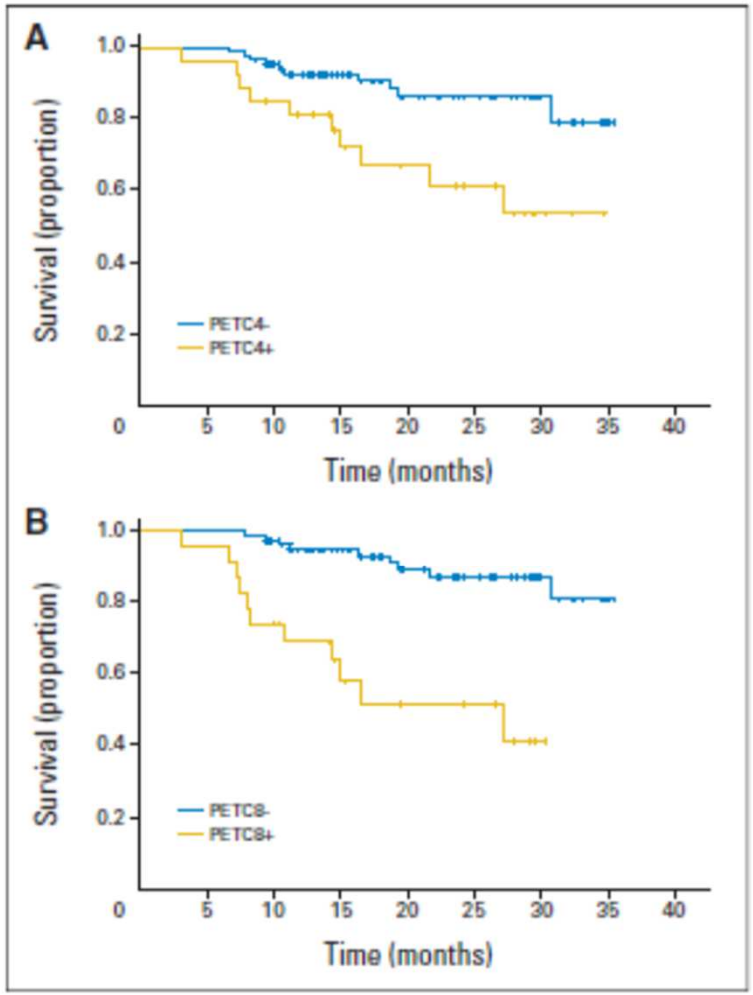


Fig 2. Progression-free survival according to positron emission tomography (PET) review at (A) four cycles and (B) eight cycles (threshold ≥ 4). PETC4−, negative PET scan at four cycles; PETC4+, positive PET scan at four cycles; PETC8−, negative PET scan at eight cycles; PETC8+, positive PET scan at eight cycles.

Dupuis J, JCO 2012

What impact has the positive PET at the end in different lymphoma subtypes?

No data yet to support a postinduction PET-adapted approach.

- I consider local radiotherapy if isolated PET+ lesion
- Closer clinical follow-up for PET+ patients, less frequent for PET-

Current trials:

- FOLL12 - recruiting well 600 patients.
- UK PETReA study – under design
- RePLy – ALLG study R^2 in patients who remain PET+ after 2nd line R-chemo – recruiting slowly.

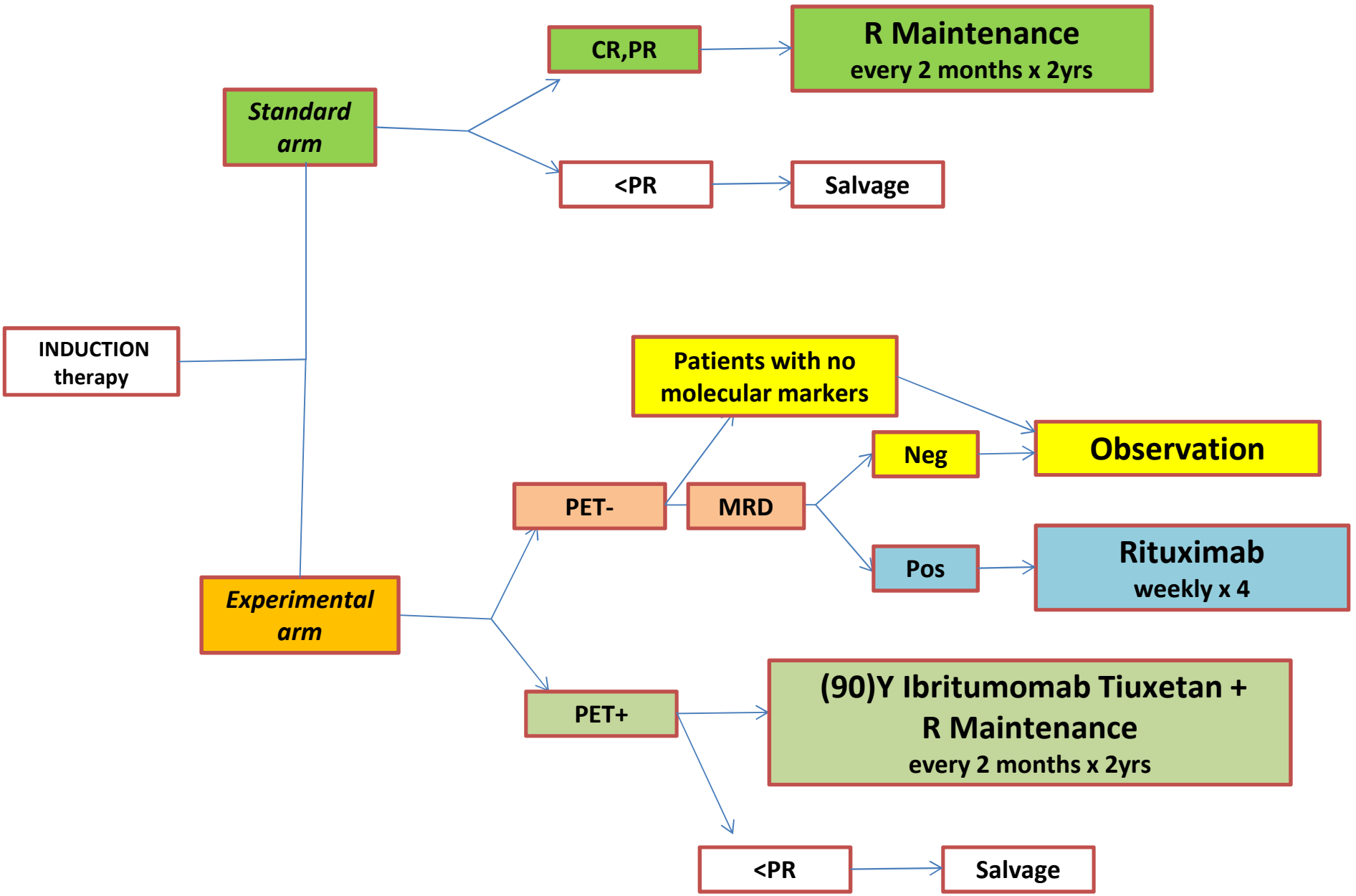
Fondazione Italiana Linfomi (FIL)

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

TRIAL DESIGN

Maintenance



Conclusion

- PET scanning is not uniformly performed for FL internationally.
- Being a more sensitive and predictive imaging modality is not sufficient for some national funders.
- We may need data from successful PET-adapted approaches before such funding will flow.
- We need standardisation of PET staging and response assessment with the 5PS cut-off of ≥4.
- We should agree on developing a common, reproducible methodology for baseline TMTV for data collection / prognostication and ultimately PET-adapted induction approaches.

- Thank-you

PFS in PRIMA/FOLL05/PET FOLLICULAIRE for the 95% of patients achieving CT/BMAT based CR/CRu/PR

SD/PD vs.

- PR, HR 4.2
- CRu, HR 5.6
- CR, HR 7.8 , p<.0001

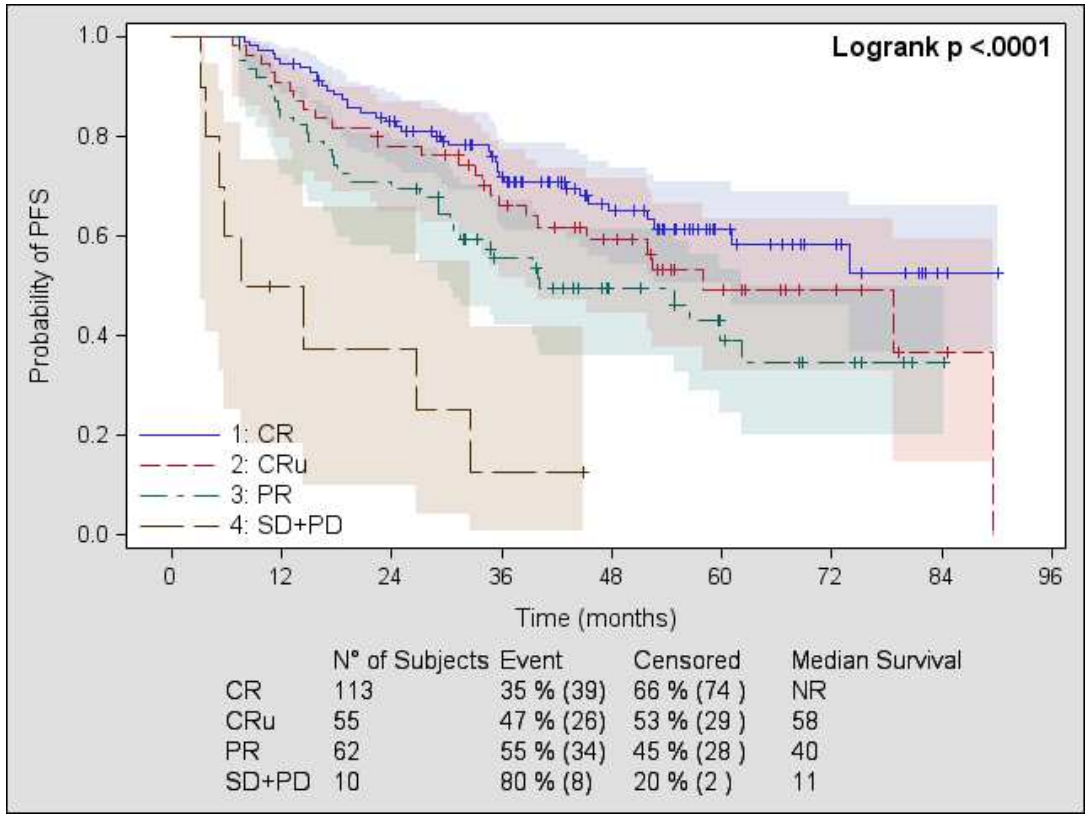
PR vs.

- CR/CRu, HR 1.7 (1.1-2.5)
  p=0.02

CRu/PR vs.

- CR, HR 1.6 (1.1-2.4), p=0.02

No impact on OS.



	N° of Subjects	Event	Censored	Median Survival
CR	113	35 % (39)	66 % (74)	NR
CRu	55	47 % (26)	53 % (29)	58
PR	62	55 % (34)	45 % (28)	40
SD+PD	10	80 % (8)	20 % (2)	11

Trotman, Lancet Haematology 2014

OBJECTIVES

Primary objective

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

Secondary objectives

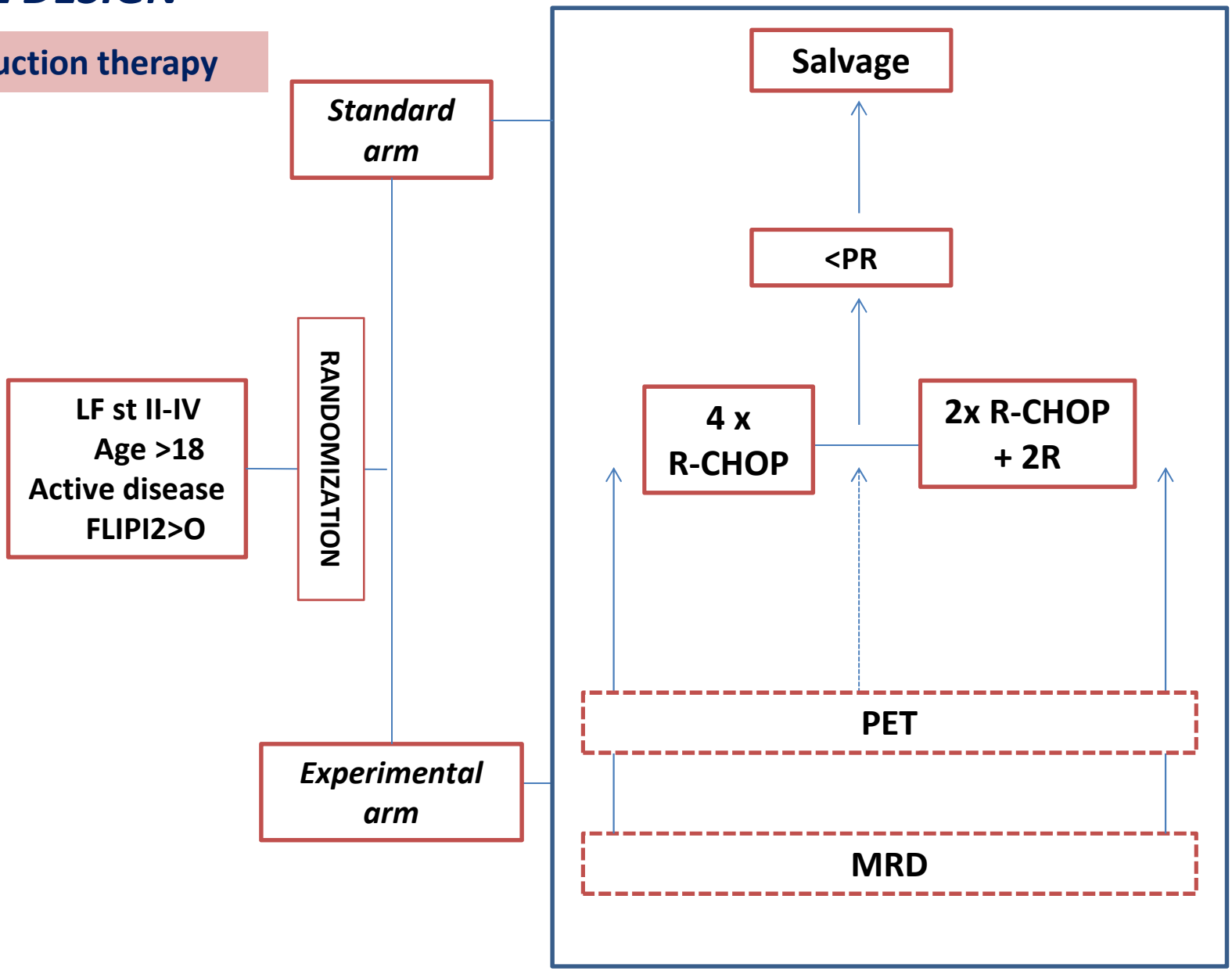
- To evaluate the efficacy of maintenance with observation or pre-emptive Rituximab therapy administered on the basis of MRD status in patients at low risk of progression after induction chemoimmunotherapy.

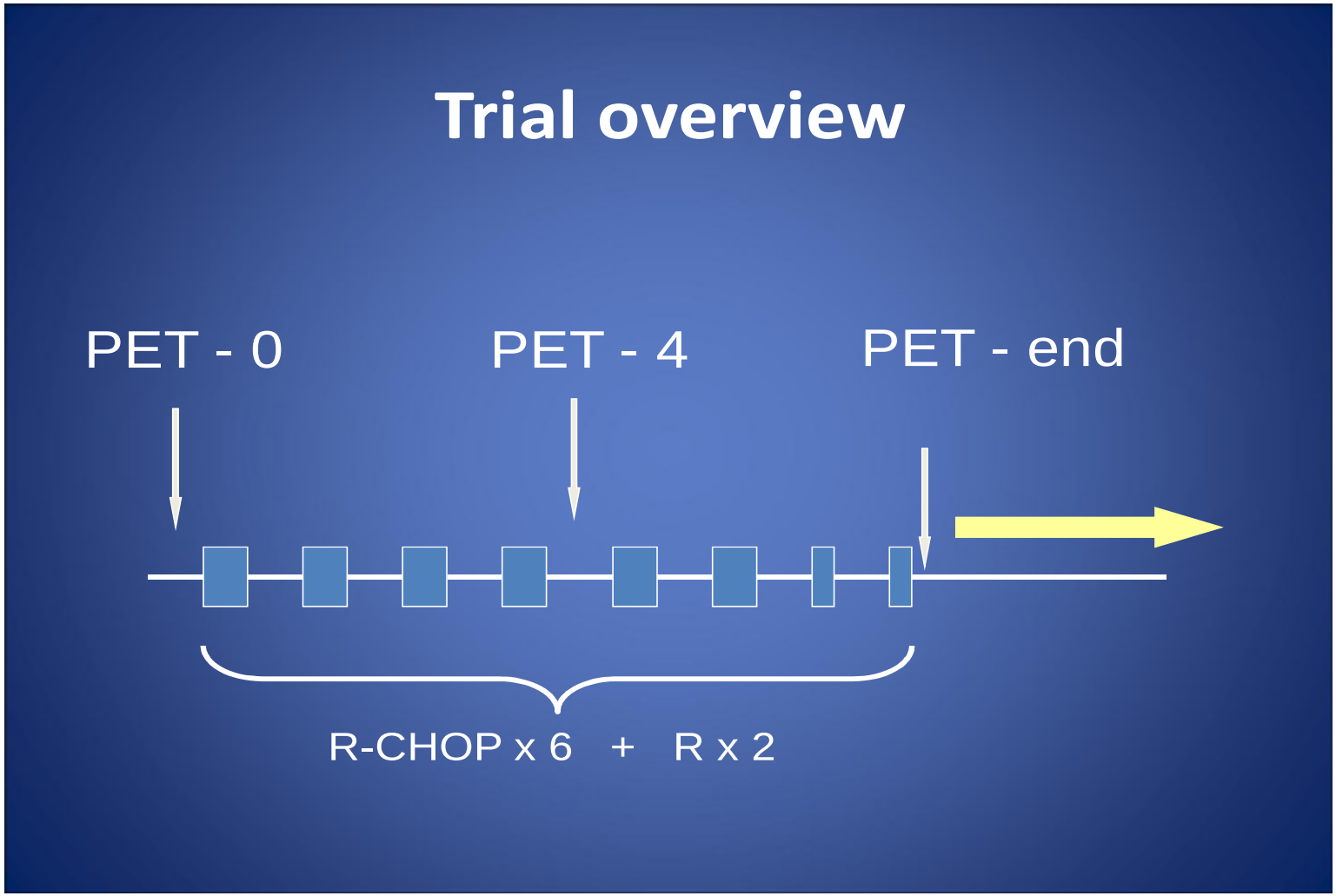
- To evaluate the efficacy of intensified maintenance with (90)Y Ibritumomab Tiuxetan followed by Rituximab maintenance therapy in patients at high risk of progression after induction chemoimmunotherapy.

- 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.