LYSA
PET adapted programs

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3 phase III trials

- **DLBCL**
  - **LNH 09-1B**: aaIPI = 0, 18 – 80y : ongoing
  - **GAINED**: aaIPI = 1-3, 18 – 60y : accrual completed

- **Hodgkin Lymphoma**
  - **AHL2011**: advanced HL, 16 – 60y: accrual completed

PET Logistic/review

- PET0, 2 and 4 are successively downloaded on **IMAGYS web platform**

- Review by **2 nuclear medicine experts**

- **Therapeutic strategy depends on review result** (2 same results needed to send conclusion (either local+expert, either 2 experts)

- Results of review send by email to the investigator, CRA monitor, project manager, PET Coordinator and Local Nuclear physician.

LNH2009-1B

Randomized Phase III study evaluating the non inferiority of a treatment adapted to the early response evaluated with 18F-FDG PET compared to a standard treatment, for patients aged from 18 to 80 years with low risk (aa IPI = 0) diffuse large B-cells non hodgkin's lymphoma CD 20+
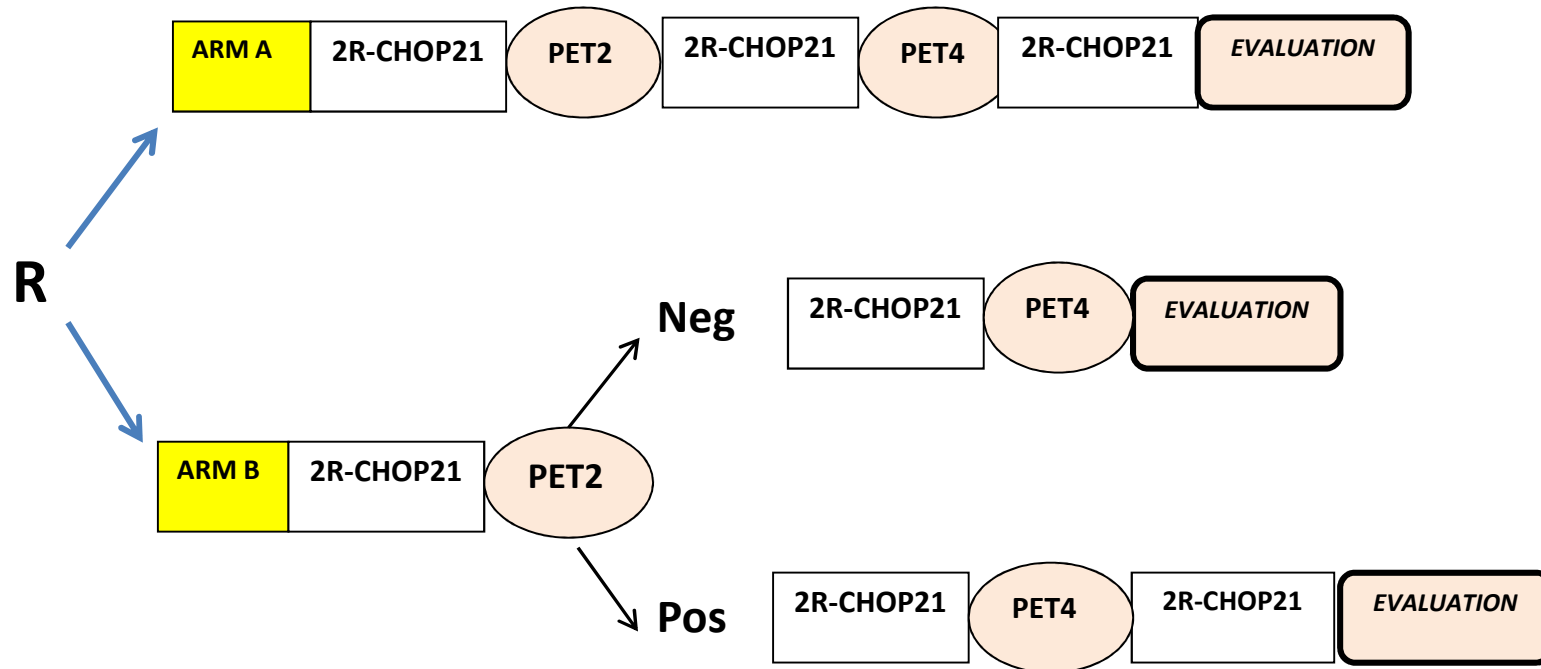
Sponsor: LYSARC
Chairmen: S. Bologna & JN Bastie
Statistical coordinator: M Fournier
Project manager: F. Morand

LNH 2009-1B

DLBCL: 18-80 y, aaIPI=0

Planned accrual = 650 pts: 566 patients enrolled

Non inferiority of the experimental arm
Standard arm : 80% 3y-PFS ; Experimental arm: 3y-PFS >70% (HR=1.6)

LNH 2009-1B: inclusion criteria

- Patient with histologically proven CD20+
  - **Diffuse large B-cell lymphoma (DLBCL) (WHO classification 2008)**
  - **Follicular lymphoma grade 3B**
- Age from **18 to 80 years**
- Patient not previously treated
- Ann Arbor Stage : I or II
- Normal level of LDH.
- ECOG performance status (PS) < 2.
- **Age-adjusted international prognostic index (aaIPI) = 0**
- **Baseline PET (PET0) performed before any treatment, even in absence of known lesion** (for stage I for which the lesion has been removed for diagnostic reason)
- Having previously signed a written informed consent

LNH 2009-1B: PET / CT Imaging

- **PET review**
  - Nancy: P. Olivier
  - Toulouse: A. Julian
  - UC Louvain: T. Vander Borght

- **Decisional PET interpretation: 5PS criteria** (1,2,3, vs 4,5)

- Additionnal prospective analysis:
  - ΔSUVmax
  - Hypermetabolic Tumor volume / CT Tumor volume
  - Total lesion glycolysis

LNH09-1B - Global Recruitment

Current recruitment
Initial estimated recruitment
New estimated recruitment since April 2013
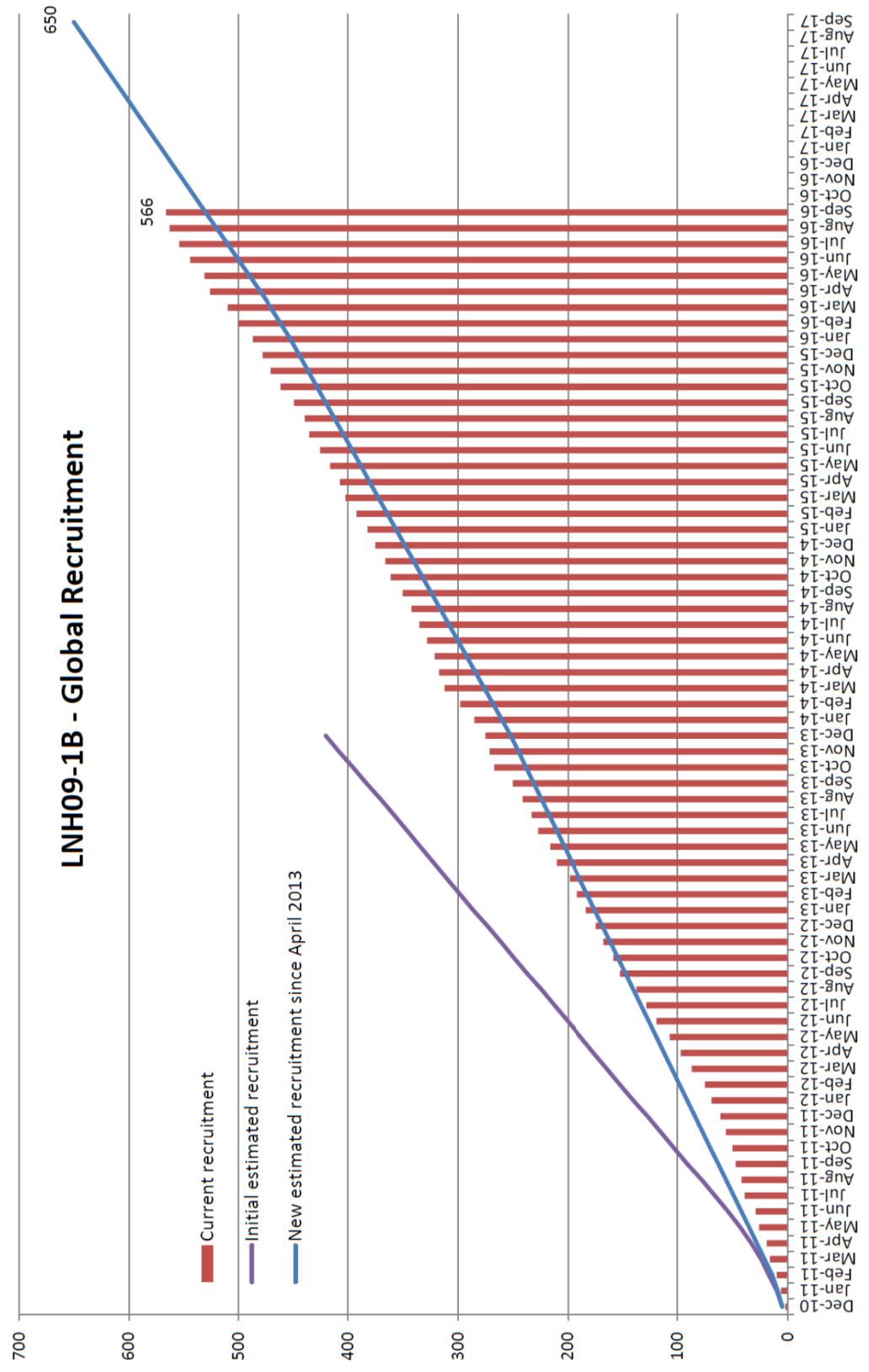
GA In NEwly Diagnosed DLBCL
GAINED

A RANDOMIZED PHASE III STUDY USING A PET-DRIVEN STRATEGY AND COMPARING GA101 VERSUS RITUXIMAB IN COMBINATION WITH A CHEMOTHERAPY DELIVERED EVERY 14 DAYS (ACVBP OR CHOP) IN DLBCL CD20+ LYMPHOMA UNTREATED PATIENTS FROM 18 TO 60 YEARS PRESENTING WITH 1 OR MORE ADVERSE PROGNOSTIC FACTORS OF THE AGE-ADJUSTED IPI
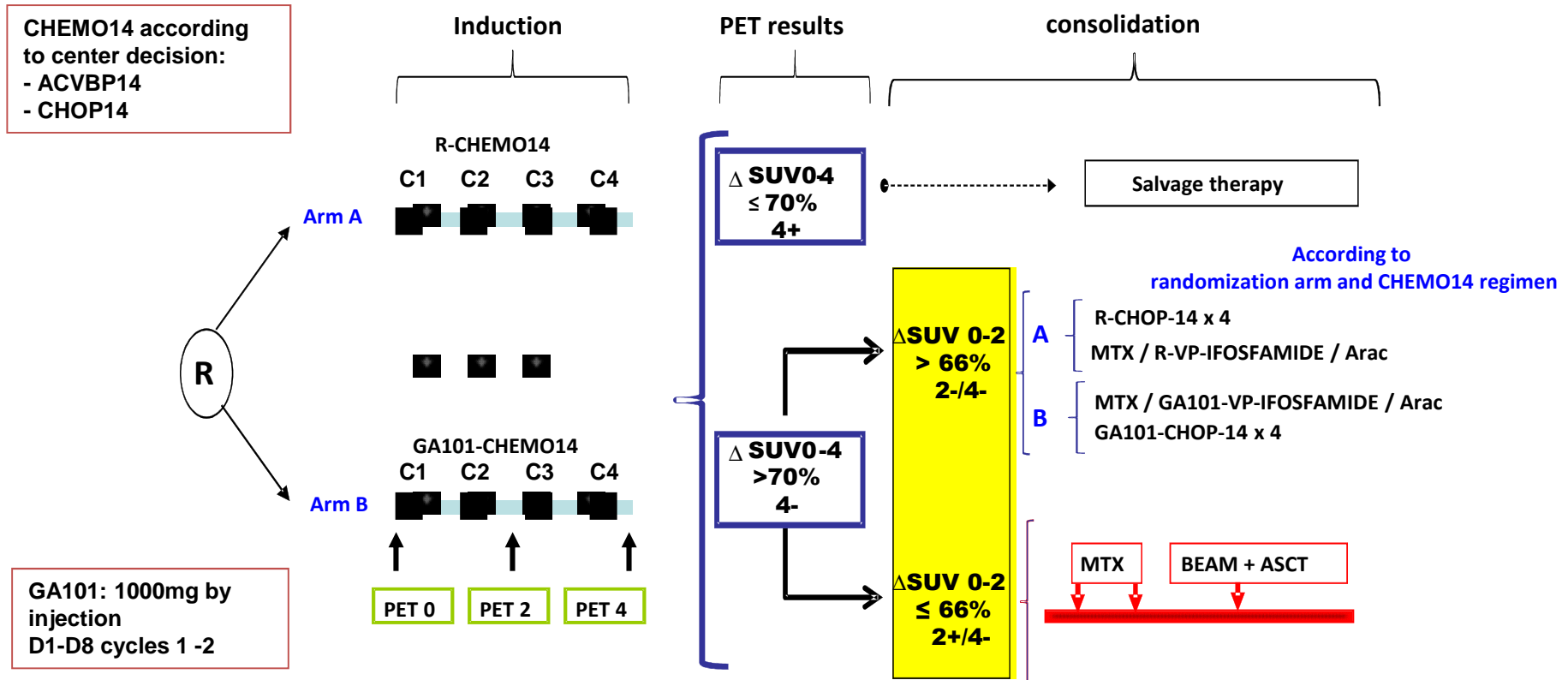
Sponsor: LYSARC

Chairmen: R.O.Casasnovas & S. Le Gouill

Statistical coordinator: J.P. Jais
Project manager: Alexia Schwartzmann

GAINED
DLBCL, 18-60y, aaIPI = 1-3: Phase III – 2 arms

GAINED: PET / CT Imaging

- **PET review**
  - Créteil: E Itti, M Meignan
  - Dijon: A Berriolo-Riedinger, S Kanoun
  - Nantes: F Bodéré, C Milin

- **Decisional PET interpretation**
  - PET2: ΔSUVmax PET0-2 < or >66%
  - PET4: ΔSUVmax PET0-4 < or >70%
  - But:
    - If SUVmax of PET0 < 10 and ΔSUVmax < cutoff value: 5PS
    - If ΔSUVmax > cutoff value and SUVmax interim PET >5: 5PS

- **Additionnal prospective analysis:**
  - Hypermetabolic Tumor volume / CT Tumor volume
  - Total lesion glycolysis

GAINED: Assumptions

- **Phase III trial stratified on aaIPI (1 vs 2-3) and Chemotherapy**

- **Primary end point: EFS**

- **Assumptions**
  - **Improvement of the 2y-EFS of 8% in the GA101-Chemo14 arm (HR = 0.73)**
  - **Standard arm : 2y-EFS of 65%**
  - **Event**: <u>PET positivity according to ∆SUVmax criteria after 2 or 4 induction cycles</u>, progression or relapse, modification of planned treatment out of progression or death of any cause

- **Sample size: 670 patients** (drop out = 10%) recruited over **3 years,** with a minimum follow-up of 3 years

LNH 2007-3B
Outcome according to ΔSUVmax PET0-2 and PET0-4

Casasnovas et al, ASCO 2014, Abst 8503
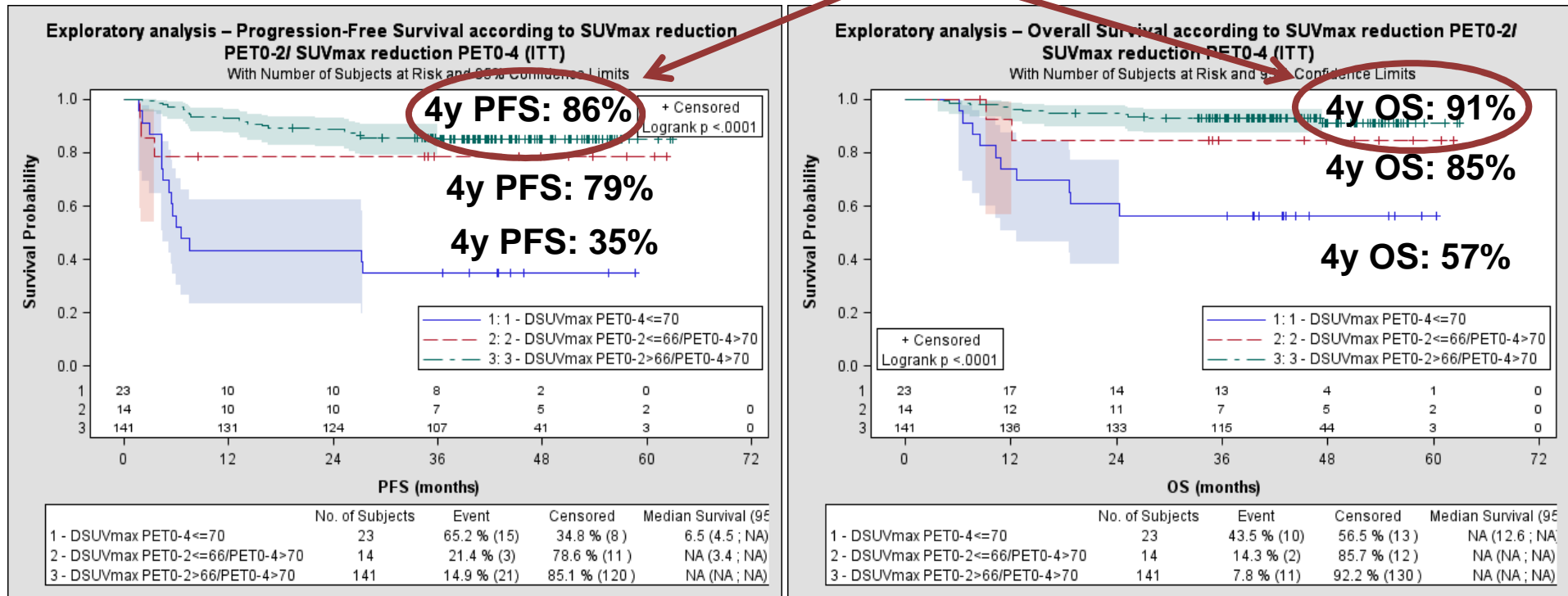
AHL 2011

Randomized phase III study of a treatment driven by early PET response compared to a treatment not monitored by early PET in patients with Ann Arbor Stage III-IV or high risk IIB Hodgkin lymphoma

Sponsor: LYSARC
Chairman: R.O.Casasnovas
Statistical coordinator: J.P. Jais
Project manager: Stephanie Picard

AHL 2011

R

Standard Arm **Experimental Arm**

Standard Arm:
BEACOPP esc x 2

Experimental Arm:
BEACOPP esc x 2 → Pos / Neg

PET C2

Neg / Pos

Pos → BEACOPP esc x 2

Neg → ABVD x 2

BEACOPP esc x 2

PET C4

Neg → BEACOPP esc x 2

Pos → Salvage therapy

Neg → BEACOPP esc x 2

Pos → Salvage therapy

Neg → ABVD x 2
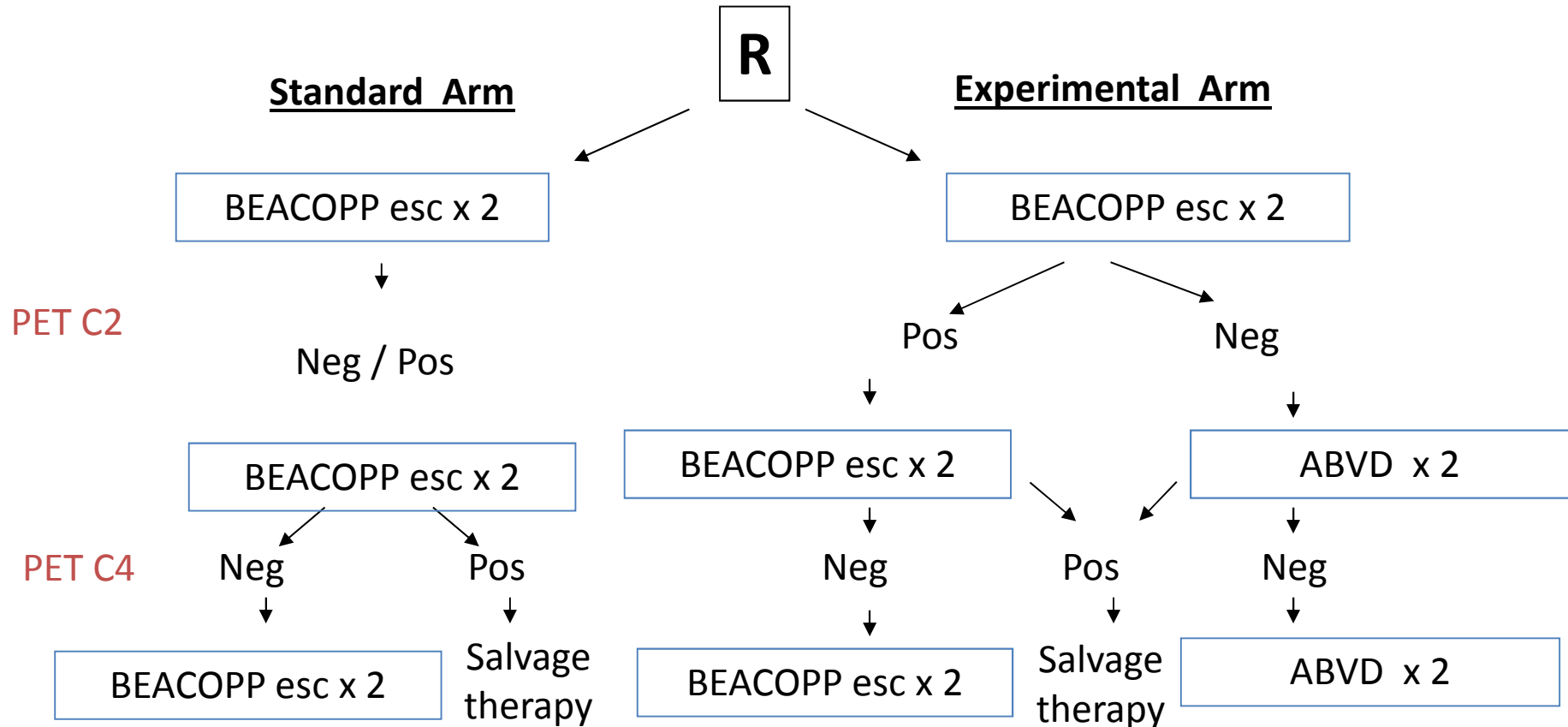
Non inferiority of the experimental arm
Standard arm : 85% 5y-PFS ; Experimental arm: 5y-PFS > 75% (HR=1.77)

Lysa — THE LYMPHOMA STUDY ASSOCIATION

Lysarc — THE LYMPHOMA ACADEMIC RESEARCH ORGANISATION

AHL 2011: PET / CT IMAGING

- **PET review**
  - Creteil: M.Meignan
  - Dijon: A. Berriolo Riedinger
  - St Cloud: V. Edeline

- **Decisional PET interpretation: modified 5PS criteria (1,2,3, vs 4,5)**

- **Additionnal prospective analysis:**
  - ΔSUVmax
  - Hypermetabolic Tumor volume / CT Tumor volume
  - Total lesion glycolysis

AHL2011: PET Review criteria

Local and review interpretations <u>had to follow the 5PS criteria modified as following</u>:

The 5-point scale:

- 1. No uptake.
- 2. Uptake $\leq$ mediastinum.
- 3. Uptake > mediastinum but $\leq$ liver.
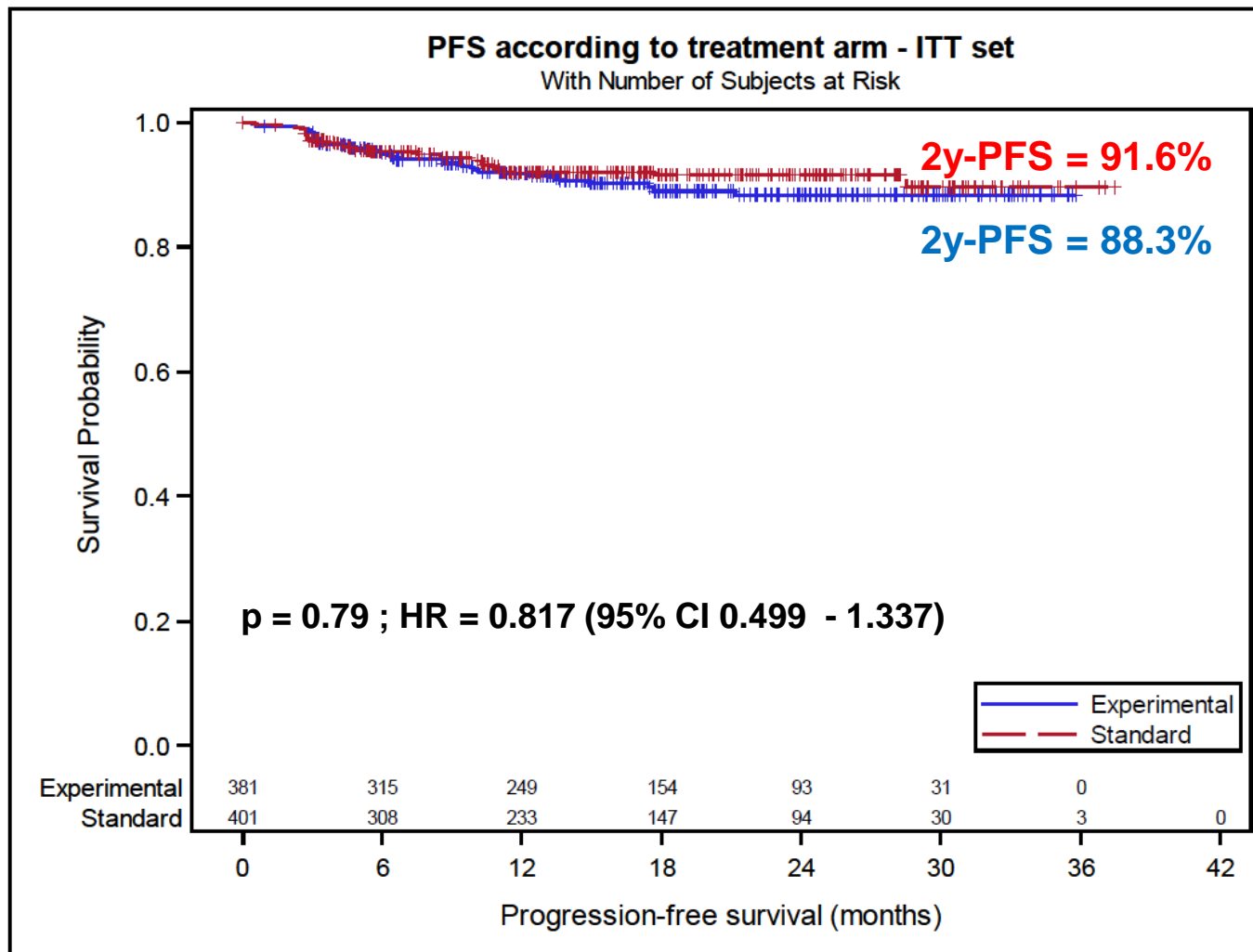- 4. Uptake moderately more than liver uptake, at any site.

  A moderately uptake more than liver uptake is define as an uptake more or equal than 140% of SUV max liver (assessed on 3 slides on the liver middle region)

- 5. Markedly increased uptake at any site or new sites of disease.

  A markedly uptake more than liver uptake is define as an uptake more or equal than 200% of SUV max liver (assessed on 3 slides on the liver middle region)
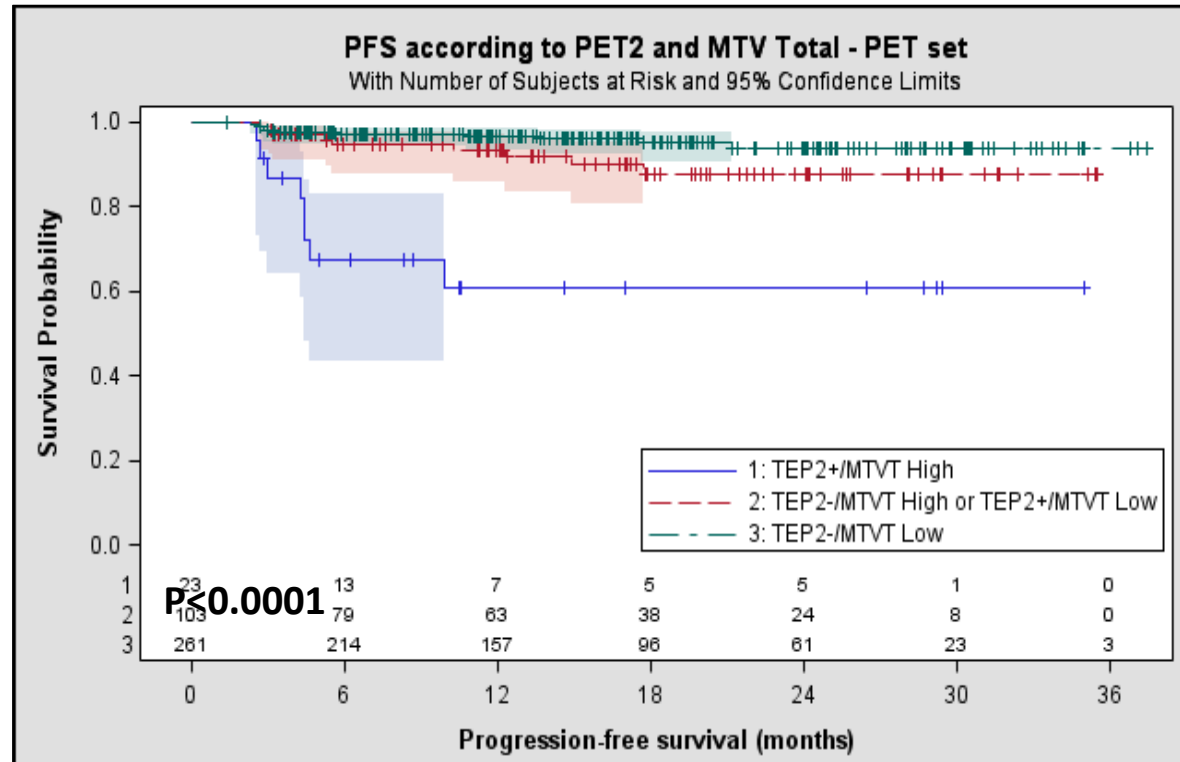
➢ **PET positive** is defined by scale level 4 and 5 (as described above)

➢ **PET negative** is defined by scale level 1, 2 and 3.

AHL 2011: PFS according to treatment arm

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

2y-PFS = 91.6%

2y-PFS = 88.3%

Median follow-up
16.3 months (0.1 – 37.4)

p = 0.79 ; HR = 0.817 (95% CI 0.499 - 1.337)

Experimental
Standard

	0	6	12	18	24	30	36	42
Experimental	381	315	249	154	93	31	0	
Standard	401	308	233	147	94	30	3	0

Survival Probability

Progression-free survival (months)

Casasnovas O, ASH 2015, abs 577

AHL2011: PFS according to TMTV and PET2 results

PFS according to PET2 and MTV Total - PET set
With Number of Subjects at Risk and 95% Confidence Limits

Legend:
- 1: TEP2+/MTVT High
- 2: TEP2-/MTVT High or TEP2+/MTVT Low
- 3: TEP2-/MTVT Low

P<0.0001

	2y-PFS	HR
TMTV ≤ 350 ml and negative PET2 (n = 261; 67%)	93.8%	1
TMTV > 350 ml or positive PET2 (n = 103; 26%)	87.9%	2.08 (95%CI: 0.86 – 5.03)
TMTV > 350 ml and positive PET2 (n = 23; 6%)	60.7%	10.9 (95%CI: 4.38 – 27.32)

Casasnovas RO, ASCO 2016; Abs 7509

Conclusions

- The strategies tested are based on the good PET NPV in order to deescalate therapy without impairing the disease control

- The criteria used to interpret interim PET varies according to the studies
  - DS score for aaIPI=0 DLBCL
  - ΔSUVmax for aaIPI>0 DLBCL

- More mature results are needed to validate these PET-guided strategies:
  - Final analysis of AHL 2011 planned next year
  - 3rd interim analysis of GAINED planned in summer 2017