LYSA ongoing programs with decisional interim PET

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3 phase III trials

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

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

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

LNH2009-1B: rationale

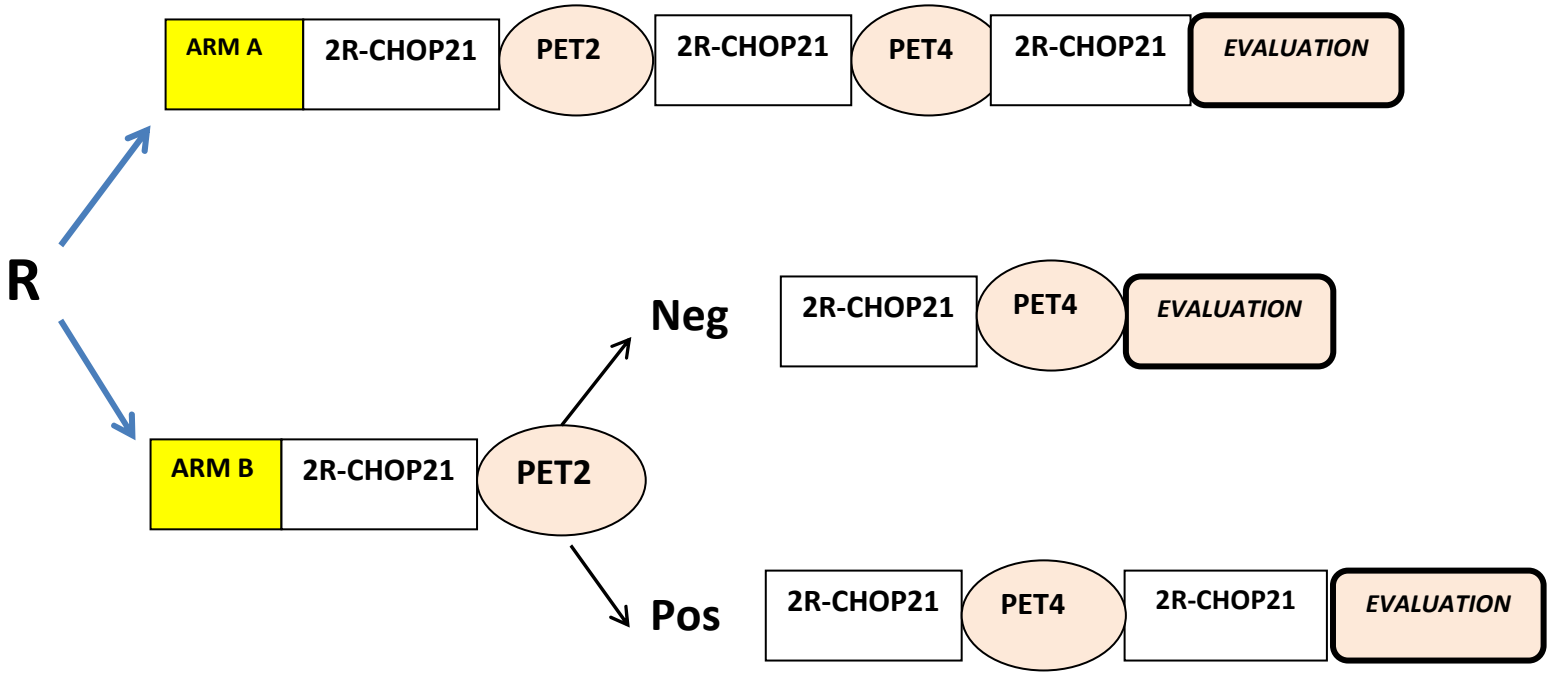
- **Previous results**:
  - **Before the rituximab era**
    - ACVBP was superior to CHOP + RT in 18-60y pts *(Reyes F, NEJM 2005)*
    - 4 x CHOP21 + RT is not superior to CHOP21 in pts > 60y *(Bonnet C, JCO 2007)*
  - **Since the Rituximab availability**:
    - MinT: 6 x R-CHOP21 > 6 x CHOP21 in 18-60y pts *(*Pfreundschuh M, Lancet Oncol 2008*)*
    - Ricover 60: 6-8 R-CHOP14 > 6-8 CHOP14 in pts > 60y (30% aaIPI=0) *(*Pfreundschuh M, Lancet Oncol 2008*)*

- 6 x R-CHOP21 is considered by GELA/LYSA as the standard treatment of patients with aaIPI = 0 aged from 18 to 80 years

Gela

LNH 2009-1B

DLBCL: 18-80 y, aaIPI=0



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: Assumptions

- **Phase III trial stratified by age (≤60 vs >60 yrs) and presence or not of high tumor burden (>10 cm)**
- Primary end point: **PFS**
- **Assumptions : Non inferiority in term of PFS of the strategy driven by PET**, compared to the treatment no monitored by early PET
  - **Standard arm : 3-year PFS = 80%**
  - **3y-PFS >70% in the experimental arm (HR = 1.6)**
- **Sample size: N = 420 patients recruited over 3 years** with a minimum follow-up of 3 years (**114 events)**

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

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

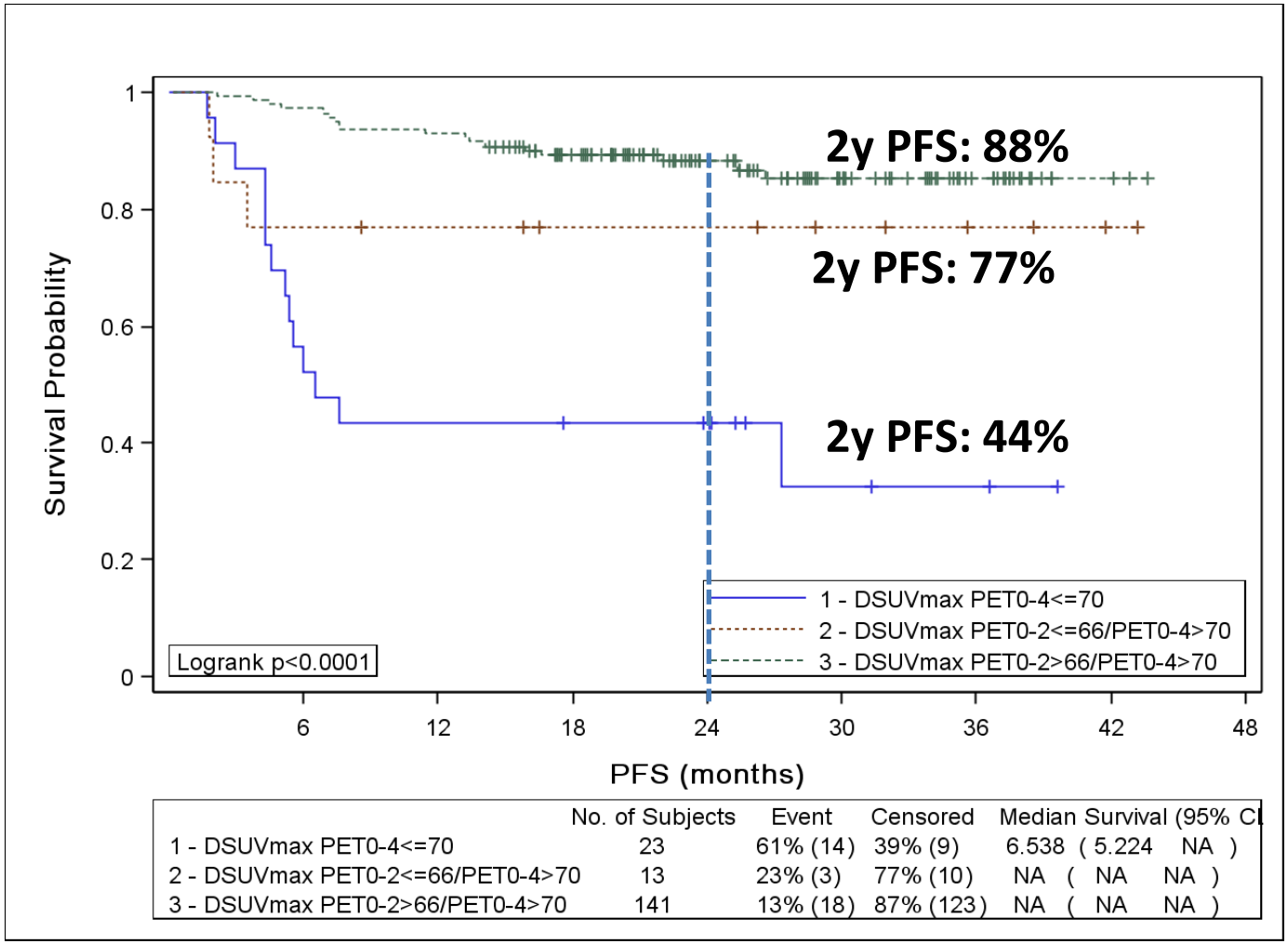
Statistical coordinator: J.P. Jais

Project manager: Alexia Schwartzmann

GAINED: rationale

- **Previous results**:
  - **aaIPI 2-3**:
    - **LNH07-3B**: R-ACVBP14 or R-CHOP14 ± ASCT in a PET guided strategy: 75% 2y-PFS *(Casasnovas O, Blood 2011)*
    - **GOELAMS 075**: R-CHOP14 ± ASCT in a PET guided strategy : 75% 2y-PFS *(Milpied N, ASH 2010)*
  - **aaIPI 1**:
    - **LNH03-2B**: R-ACVBP14: 2y-PFS 89% *(Recher C, Lancet 2011)*
- **GA101** (Obinutuzumab) is a good candidate to improve disease control:
  - Phase II Rituximab relapsed/refractory DLBCL: 30% ORR, 15% RC/RCu *(Morschhauser F, ASH 2011*)
  - Combination with CHOP21 is feasable *(Radford J, ASH 2011)*
- **Patients stratification**:
  - Interim PET on the basis of visual analysis allows safely to avoid ASCT in 30% of patients *(Casasnovas Blood 2011)*
  - PET guided strategy using ΔSUVmax criteria may avoid ASCT in 80% of patients

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



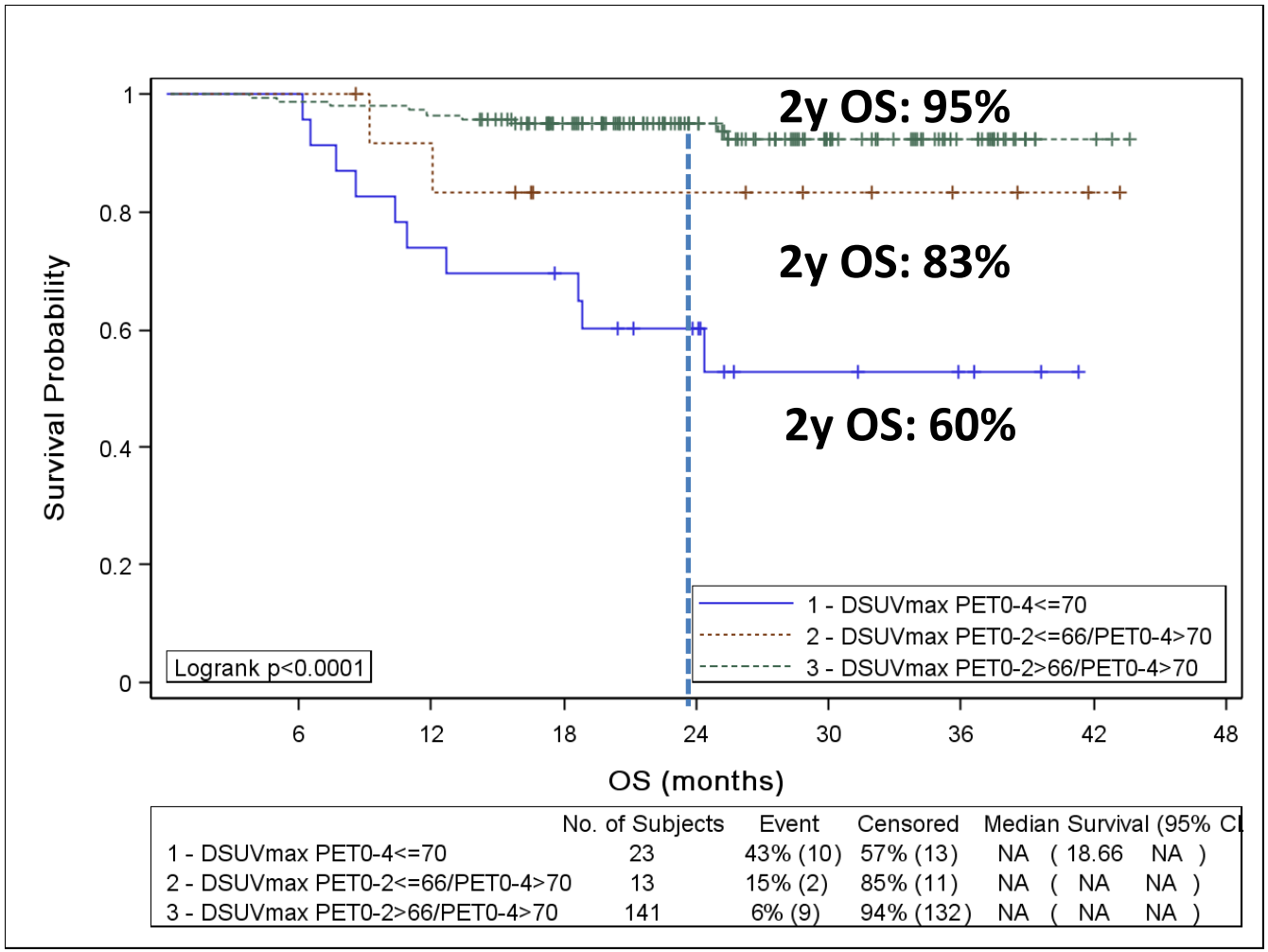
	No. of Subjects	Event	Censored	Median Survival (95% CI
1 - DSUVmax PET0-4<=70	23	61% (14)	39% (9)	6.538 (5.224 NA)
2 - DSUVmax PET0-2<=66/PET0-4>70	13	23% (3)	77% (10)	NA (NA NA)
3 - DSUVmax PET0-2>66/PET0-4>70	141	13% (18)	87% (123)	NA (NA NA)

Gela Gelarc

Median FU = 26 months

Casasnovas et al, Blood 2011

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



	No. of Subjects	Event	Censored	Median Survival (95% CI
1 - DSUVmax PET0-4<=70	23	43% (10)	57% (13)	NA (18.66 NA)
2 - DSUVmax PET0-2<=66/PET0-4>70	13	15% (2)	85% (11)	NA (NA NA)
3 - DSUVmax PET0-2>66/PET0-4>70	141	6% (9)	94% (132)	NA (NA NA)

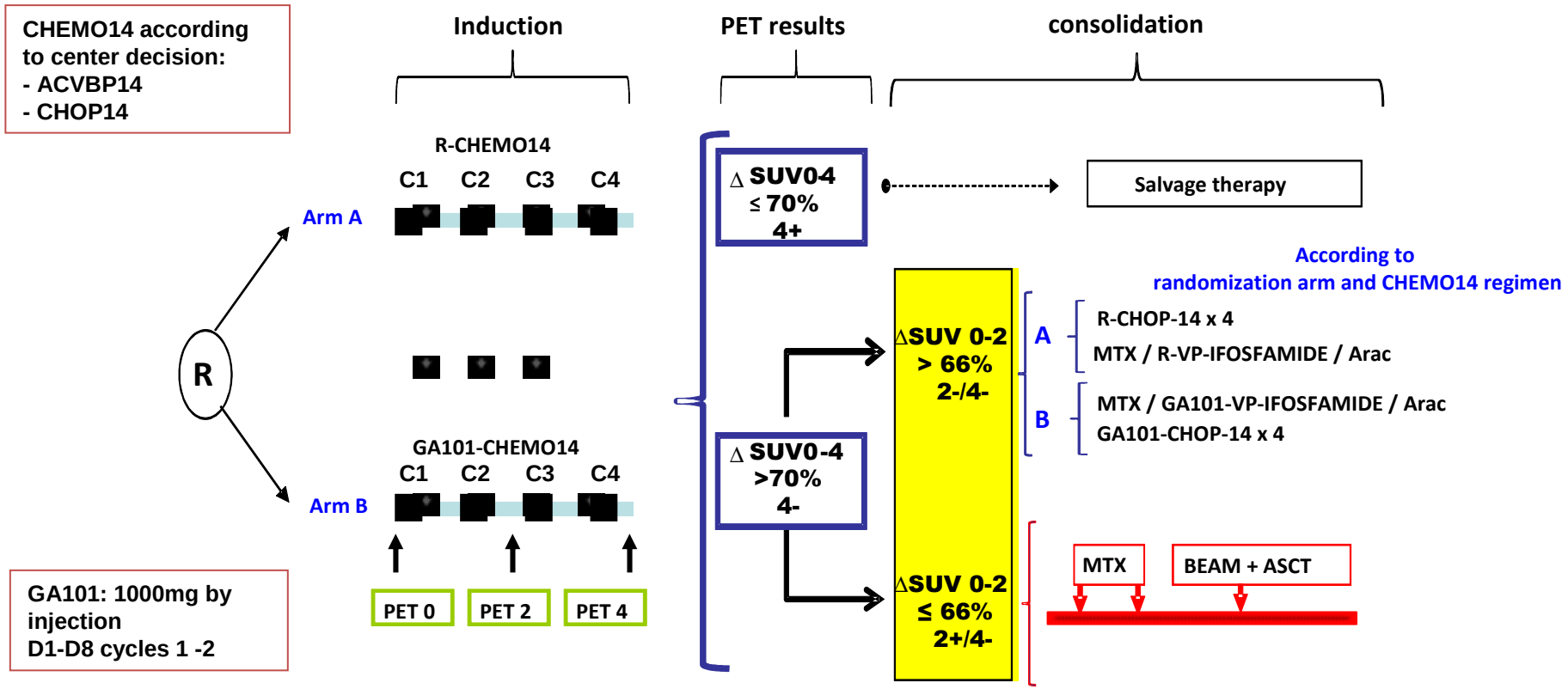
Gela Gelarc

Median FU = 26 months

Casasnovas et al, Blood 2011

GAINED

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



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**: PET positivity according to ΔSUVmax criteria after 2 or 4 induction cycles, 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

Lysa THE LYMPHOMA STUDY ASSOCIATION

Lysarc THE LYMPHOMA ACADEMIC RESEARCH ORGANISATION

GAINED: PET / CT Imaging

- **PET review**
  - **Créteil: E Itti, M Meignan**
  - **Dijon: A Berriolo-Riedinger, O Humbert**
  - **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**

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

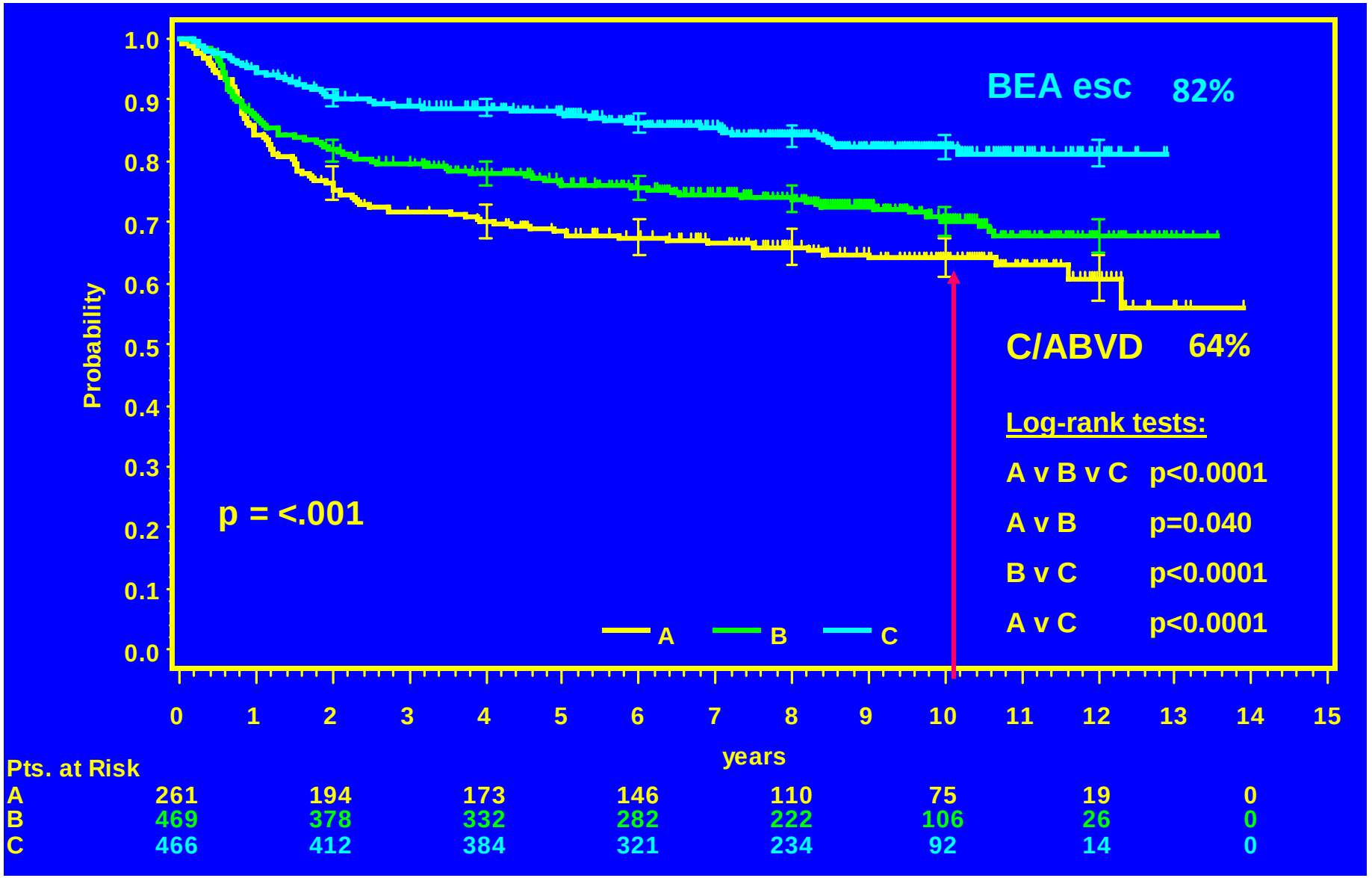
Sponsor: LYSARC

Chairman: R.O.Casasnovas

Statistical coordinator: J.P. Jais

Project manager: Stephanie Picard

HD9 – 10-years FFTF by treatment arm



Engert A, JCO 2009; 27: 2548

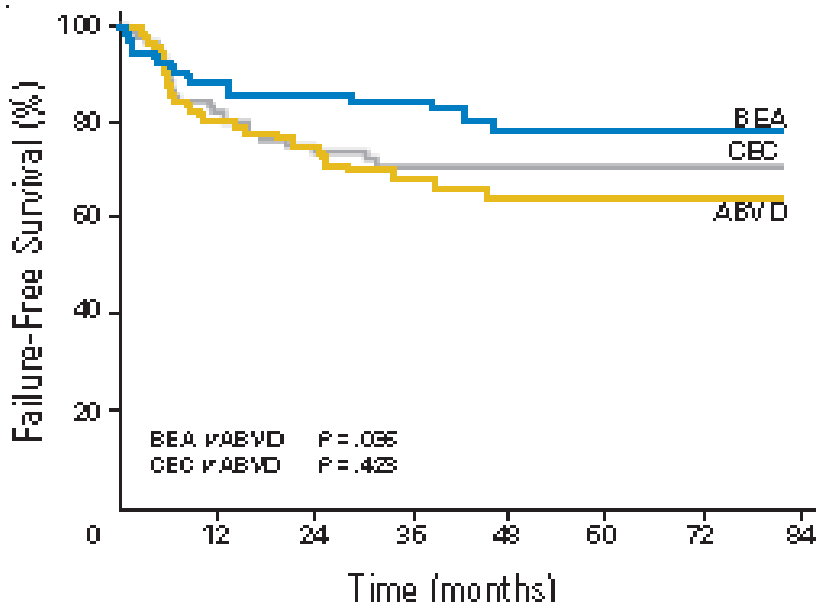
BEACOPP vs ABVD

Stage IIB- IV

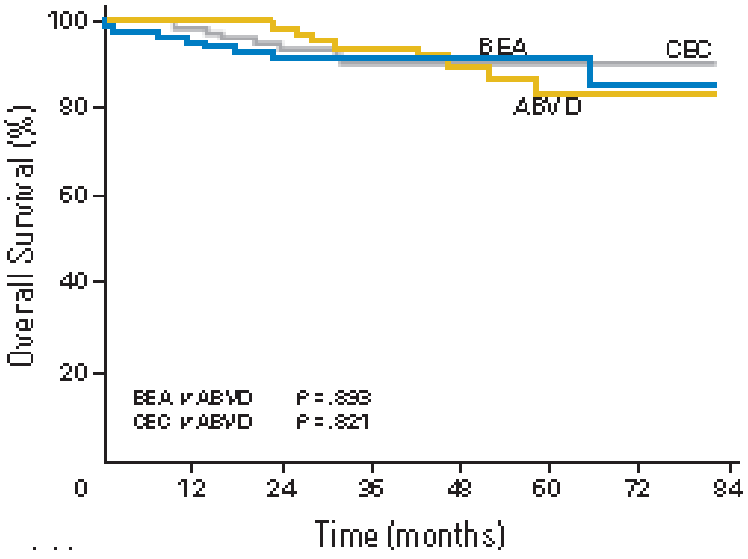
BEACOPP [esc x 4 + Baseline x 2] vs ABVD x 6

Median FU = 41 months

FFP



OS



Federico M, JCO ,2009

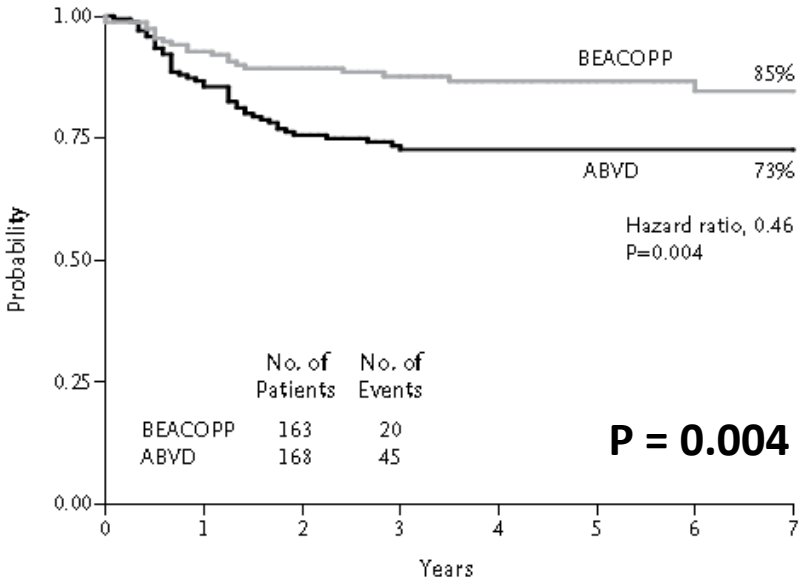
BEACOPP vs ABVD

Stage IIB- IV

BEACOPP [esc x 4 + Baseline x 4] vs ABVD x 6/8

Median FU = 61 months

FFP



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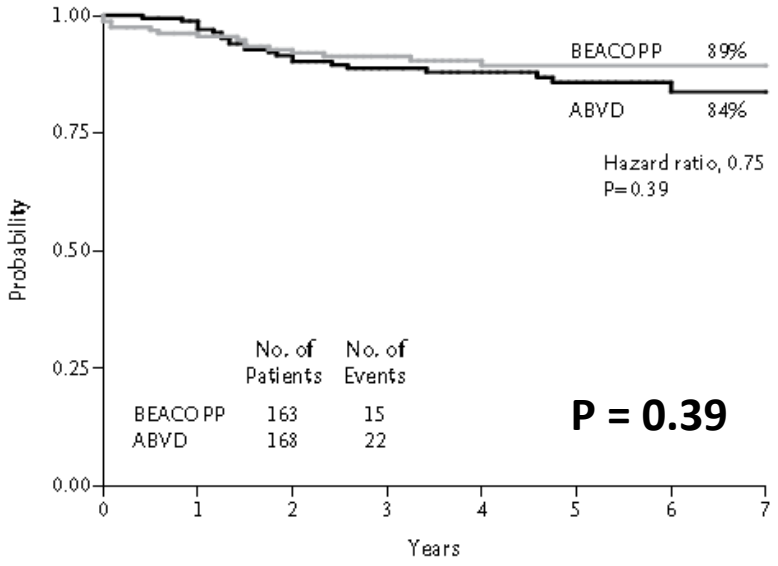
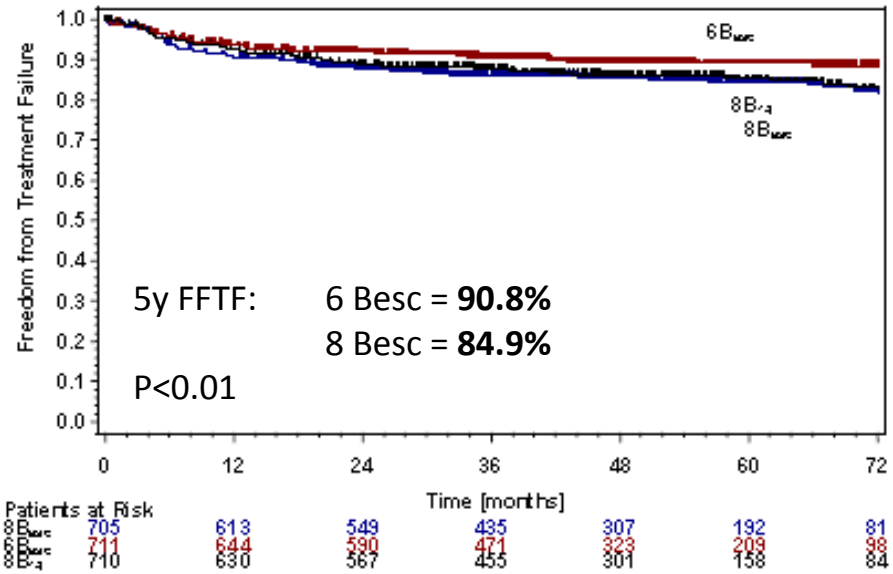
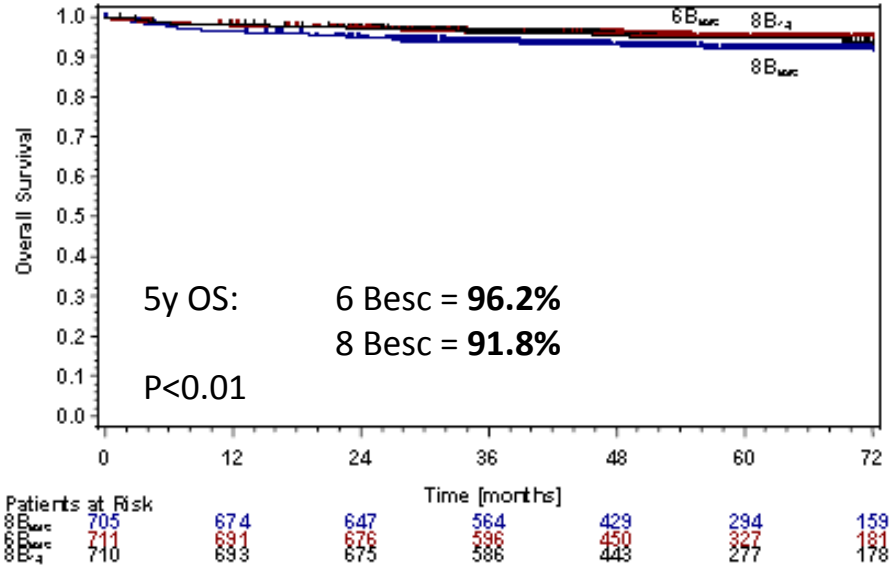


Viviani S, NEJM 2011; 365: 203

HD15

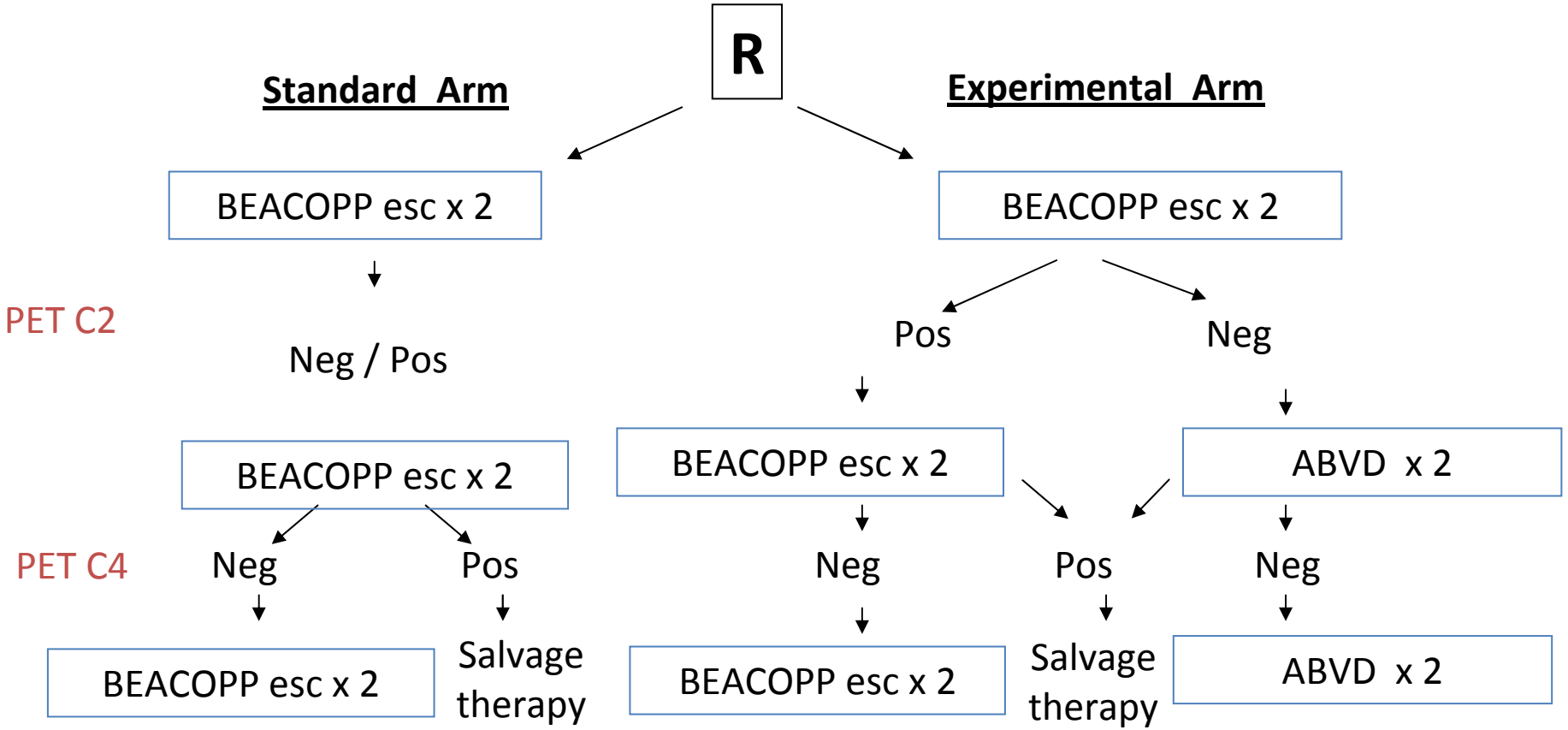




Causes of death – no. (%)	8x BEACOPP$_{escalated}$ (N=705)	6x BEACOPP$_{escalated}$ (N=711)
Total	53 (7·5)	33 (4·6)
Hodgkin lymphoma	13 (1·8)	11 (1·5)
Toxicity of study chemotherapy	15 (2·1)	6 (0·8)
Secondary neoplasia	13 (1·8)	5 (0·7)
Toxicity of salvage treatment	2 (0·3)	2 (0·3)
Other†	6 (0·9)	6 (0·8)
Unclear	4 (0·6)	3 (0·4)

Engert A et al , Lancet 2012

AHL 2011



Non inferiority of the experimental arm

AHL 2011: Assumptions

- **Phase III trial stratified on Stage (IIB vs III/IV) and IPS**
- **Primary end point: PFS**
- **Assumptions: Non inferiority in term of PFS of the strategy driven by PET**, compared to the treatment no monitored by early PET
  - **Standard arm : 85% 5y-PFS**
  - **The 5y-PFS should be superior to 75% in the experimental arm (HR=1.77)**
- **Sample size: 810 patients recruited over 6 years, with a minimum follow-up of 1 year (97 events)**

AHL 2011: INCLUSION CRITERIA

- Patient with a first diagnosis of classical Hodgkin lymphoma according to WHO criteria excluding nodular lymphocyte predominant subtype
- Age of 16 to 60 years
- No previous treatment for Hodgkin lymphoma
- Ann Arbor stages:
  - **IIB with mediastinum/thorax > 0.33 or extra nodal localization**
  - **III**
  - **IV**
- **Baseline 18-FDG PET scan (PET0) performed before any treatment with at least one hypermetabolic lesion**
- WHO performance status <3
- With a minimum life expectancy of 3 months
- Having previously signed a written informed consent
- The patient must be covered by a social security system

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 had to follow the 5PS criteria modified as following:

The 5-point scale:

•1. No uptake.

•2. Uptake ≤ mediastinum.

•3. Uptake > mediastinum but ≤ liver.

•4. Uptake moderately more than liver uptake, at any site.

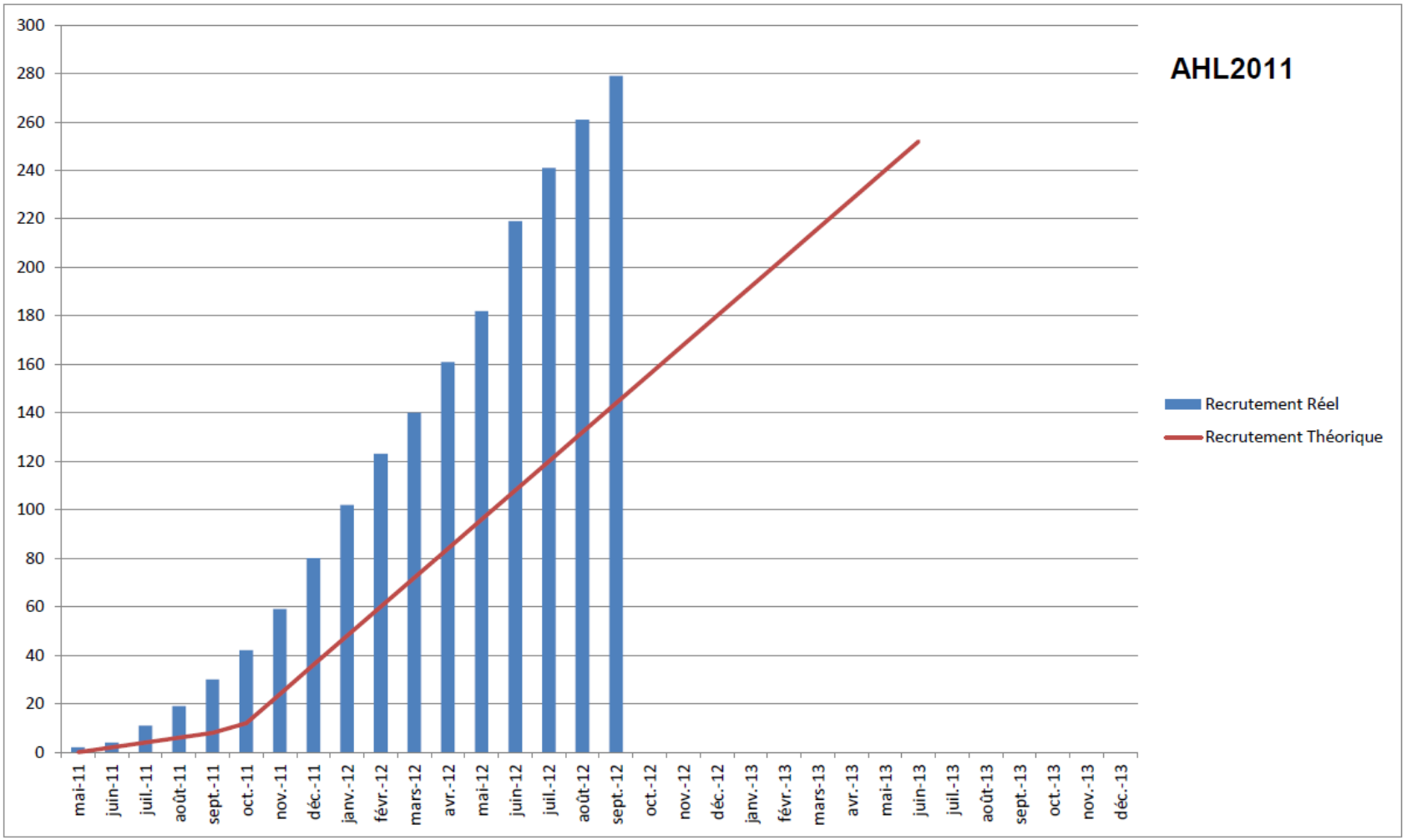
A moderately uptake more than liver uptake is define as an uptake more or equal than 140% of SUV max liver (assessed on 3 slides on the liver middle region)

•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


AHL2011
Recrutement Réel
Recrutement Théorique
300
280
260
240
220
200
180
160
140
120
100
80
60
40
20
0
mai-11
juin-11
juil.-11
août-11
sept.-11
oct.-11
nov.-11
déc.-11
janv.-12
févr.-12
mars-12
avr.-12
mai-12
juin-12
juil.-12
août-12
sept.-12
oct.-12
nov.-12
déc.-12
janv.-13
févr.-13
mars-13
avr.-13
mai-13
juin-13
juil.-13
août-13
sept.-13
oct.-13
nov.-13
déc.-13

AHL 2011: PET review

October 3, 2012:

- **28/260 (11%) PET2+**
- **6/190 (3%) PET4+**

Conclusions

- In curable diseases (HL, DLBCL), in which long term therapeutic related events matter and have to be reduced, the good PET NPV may help to drive therapeutic strategy

- Early PET may identify good risk patients who could benefit of a reduced exposure:
  - To intensified chemotherapy regimen (BEACOPPesc)
  - To an extensive number of cycles of chemotherapy
  - To intensified high dose therapy consolidation (BEAM + ASCT)

  Without impairing disease control