LYSA
PET adapted programs

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3 phase III trials

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

• **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.
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
DLBCL: 18-80 y, aalPl=0

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:**
  - $\Delta$SUVmax
  - 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:**
  - aalPI 2-3:
    - LNH07-3B: R-ACVBP14 or R-CHOP14 ± ASCT in a PET guided strategy: 75% 4y-PFS *(Casasnovas O, Blood 2011 and ASCO 2014)*
  - aalPI 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 feasible *(Radford J, ASH 2011)*
- **Patients stratification:**
  - Interim PET on the basis of visual analysis allows safely to avoid ASCT in 25% of patients *(Casasnovas Blood 2011 and ASCO 2014)*
  - PET guided strategy using ΔSUVmax criteria may avoid ASCT in 80% of patients
LNH 2007-3B
Outcome according to $\Delta$SUVmax PET0-2 and PET0-4

4y PFS: 79%
4y PFS: 86%
4y PFS: 35%

4y OS: 91%
4y OS: 85%
4y OS: 57%

80% of the whole population

Median FU = 45 months

Casasnovas et al, ASCO 2014, Abst 8503
GAINED
DLBCL, 18-60y, aaIPI = 1-3: Phase III – 2 arms

CHEMO14 according to center decision:
- ACVBP14
- CHOP14

Induction

PET results

Consolidation

According to randomization arm and CHEMO14 regimen

Arm A

R-CHEMO14

Δ SUV0-4

≤ 70%

4+

R-CHOP-14 x 4

MTX / R-VP-IFOSFAMIDE / Arac

PET 0

PET 2

PET 4

Δ SUV 0-2

> 66%

2+/4-

MTX / R-VP-IFOSFAMIDE / Arac

Δ SUV0-4

> 70%

4-

B

GA101-CHEMO14

PET results

Δ SUV 0-2

≤ 66%

2+/4-

MTX / GA101-VP-IFOSFAMIDE / Arac

GA101-CHOP-14 x 4

Salvage therapy

R-CHOP-14 x 4

MTX / R-VP-IFOSFAMIDE / Arac

MTX / GA101-VP-IFOSFAMIDE / Arac

GA101-CHOP-14 x 4

Consolidation

Salvage therapy

Induction

PET 2

PET 4

Δ SUV 0-2

≤ 66%

2+/4-

MTX / BEAM + ASCT

PET 0

Δ SUV0-4

≤ 70%

4+

C1 C2 C3 C4

R

C1 C2 C3 C4

According to randomization arm and CHEMO14 regimen

Arm B

GA101: 1000mg by injection D1-D8 cycles 1 -2
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
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
GAINED Accrual

Interim analysis planned Q2 2015
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
## BEACOPP vs ABVD

<table>
<thead>
<tr>
<th>Chemotherapy</th>
<th>Disease control</th>
<th>OS</th>
<th>p</th>
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<tbody>
<tr>
<td></td>
<td>n</td>
<td>p</td>
<td>p</td>
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<tr>
<td><strong>Federico M</strong></td>
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<tr>
<td>2009 HD2000</td>
<td>4 BEACOPPesc + 2 BEACOPPs</td>
<td>98</td>
<td>5y-PFS</td>
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<tr>
<td></td>
<td>6 ABVD</td>
<td>99</td>
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<td><strong>Viviani S 2011</strong></td>
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<tr>
<td>6/8 ABVD</td>
<td>4 BEACOPPesc + 4 BEACOPPs</td>
<td>168</td>
<td>7y-PFS</td>
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<td></td>
<td>163</td>
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<td>85%</td>
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<td><strong>Carde P 2012</strong></td>
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<tr>
<td>H3-4 IPS 3+</td>
<td>8 ABVD</td>
<td>275</td>
<td>4y-PFS</td>
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<td></td>
<td>274</td>
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<td>83%</td>
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<td><strong>Mounier N 2013</strong></td>
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<tr>
<td>H3-4 IPS 0-2</td>
<td>8 ABVD</td>
<td>80</td>
<td>5-PFS</td>
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<tr>
<td></td>
<td>70</td>
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<td>93%</td>
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</table>
HD15

Engert A et al., Lancet 2012

5y FFTF: 
6 Besc = 90.8%  
8 Besc = 84.9%  
P<0.01

5y OS: 
6 Besc = 96.2%  
8 Besc = 91.8%  
P<0.01

Causes of death – no. (%)

<table>
<thead>
<tr>
<th>Cause</th>
<th>8x BEACOPP standard (N=705)</th>
<th>8x BEACOPP modified (N=711)</th>
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<tbody>
<tr>
<td>Total</td>
<td>53 (7.5)</td>
<td>33 (4.6)</td>
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<tr>
<td>Hodgkin lymphoma</td>
<td>13 (1.9)</td>
<td>11 (1.5)</td>
</tr>
<tr>
<td>Toxicity of study chemotherapy</td>
<td>16 (2.3)</td>
<td>6 (0.9)</td>
</tr>
<tr>
<td>Secondary neoplasia</td>
<td>13 (1.9)</td>
<td>5 (0.7)</td>
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<tr>
<td>Toxicity of salvage treatment</td>
<td>2 (0.3)</td>
<td>2 (0.3)</td>
</tr>
<tr>
<td>Other</td>
<td>6 (0.9)</td>
<td>6 (0.9)</td>
</tr>
<tr>
<td>Unspecified</td>
<td>4 (0.6)</td>
<td>3 (0.4)</td>
</tr>
</tbody>
</table>
Non inferiority of the experimental arm
Standard arm : 85% 5y-PFS ; Experimental arm: 5y-PFS > 75% (HR=1.77)
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.
AHL2011

- May 2011 - May 2014:
  823 pts included (810 planned)

- 49th event on June 2014

- 800 pts will be included in the interim analysis planned in May 2015
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