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

• **Decisional PET interpretation: 5PS criteria** \((1,2,3, \text{ vs } 4,5)\)

• **Additionnal prospective analysis:**
  – \(\Delta \text{SUV}_{\text{max}}\)
  – Hypermetabolic Tumor volume / CT Tumor volume
  – Total lesion glycolysis
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 feasible (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 $\Delta$SUVmax PET0-2 and PET0-4

2y PFS: 88%
2y PFS: 77%
2y PFS: 44%

Median FU = 26 months

Casasnovas et al, Blood 2011
LNH 2007-3B: OS according to ΔSUVmax PET0-2 and PET0-4

Median FU = 26 months

Casasnovas et al, Blood 2011
GAINED

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

CHEMO14 according to center decision:
- ACVBP14
- CHOP14

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

Induction

PET results

consolidation

R-CHEMO14

Arm A

C1 C2 C3 C4

Δ SUV0-4

≤ 70%

4+

Δ SUV 0-2

> 66%

2+/4-

PET 0

PET 2

PET 4

Δ SUV0-4

> 70%

4-

According to randomization arm and CHEMO14 regimen

R-CHOP-14 x 4
MTX / R-VP-IFOSFAMIDE / Arac

MTX / GA101-VP-IFOSFAMIDE / Arac
GA101-CHOP-14 x 4

Salvage therapy

Arm B

Δ SUV 0-2

≤ 66%

2+/4-

MTX

BEAM + ASCT

R

Arm A

R-CHEMO14

Arm B

GA101-CHEMO14

Δ SUV 0-4

> 70%

4-

C1 C2 C3 C4

R

C1 C2 C3 C4
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
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: $\Delta \text{SUV}_{\text{max}}$ PET0-2 < or > 66%
  – PET4: $\Delta \text{SUV}_{\text{max}}$ PET0-4 < or > 70%
  – But:
    • If SUVmax of PET0 < 10 and $\Delta \text{SUV}_{\text{max}}$ < cutoff value: 5PS
    • If $\Delta \text{SUV}_{\text{max}}$ > 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

Log-rank tests:
A v B v C  p<0.0001
A v B  p=0.040
B v C  p<0.0001
A v C  p<0.0001

BEA esc  82%
C/ABVD  64%

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

Viviani S, NEJM 2011; 365: 203
HD15

5y FFTF: 6 Besc = 90.8%
8 Besc = 84.9%
5y OS: 6 Besc = 96.2%
8 Besc = 91.8%
P<0.01

Engert A et al, Lancet 2012
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
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