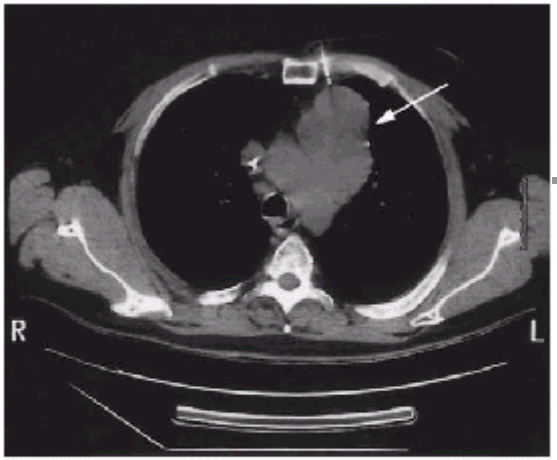
Place de l'autogreffe en première ligne pour les LNH BDGC

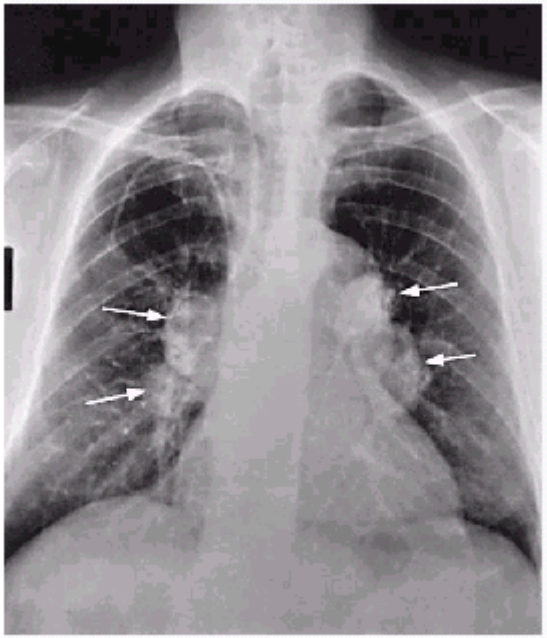
Pr Nicolas Mounier
Onco-Hématologie
CHU de Nice

Cas Clinique

- Un homme de 48 ans est admis à l'hôpital pour altération de l'état général et toux. Il est tabagique à 50 paquets.année et consomme de l'alcool régulièrement. Il est hypertendu depuis 17 ans et diabétique non-insulino-dépendant. Il présente une masse thoracique et l'auscultation est sans particularité en dehors de crépitants des deux bases. Le performance status est à 2. Pouls : 100. Température : 37,9°C. Fréquence respiratoire : 17. Tension : 175/80. LDH = 3N
- Le scanner et la radio de thorax sont documentés sur la figure 1.

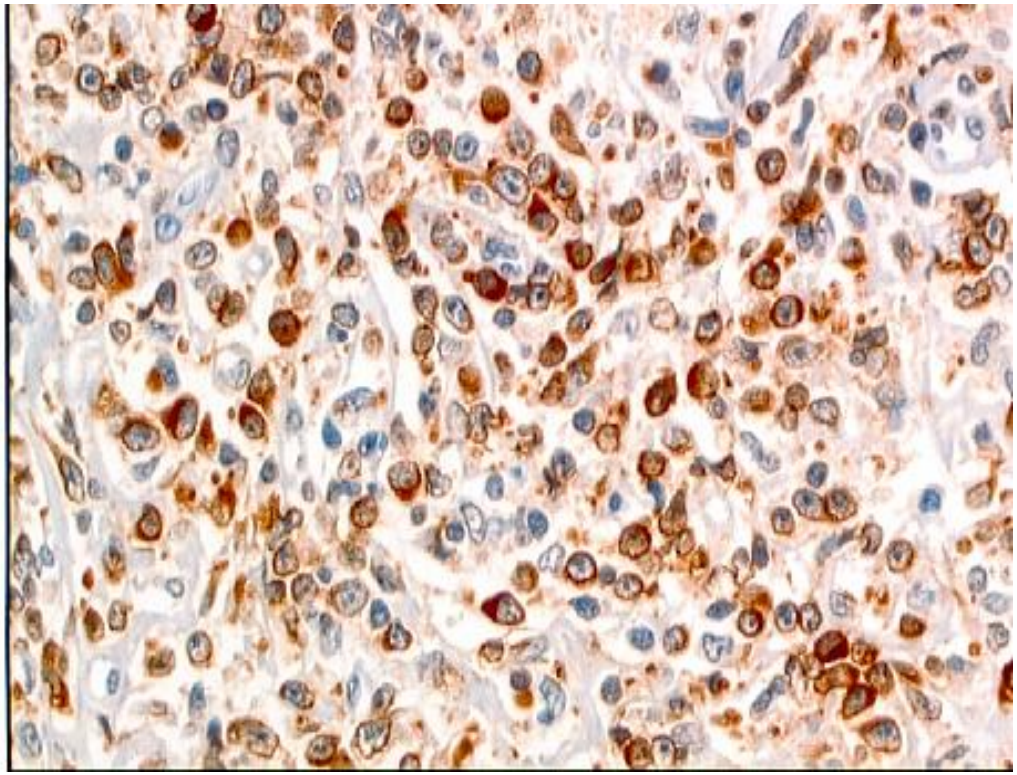


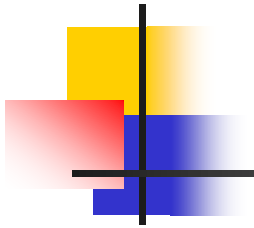
A



C

La biopsie sous scanner montre un lymphome B diffus à grandes cellules B, Bcl2+ en immunohistochimie





1- Quel complément de bilan ?

VOLUME 25 · NUMBER 5 · FEBRUARY 10 2007

JOURNAL OF CLINICAL ONCOLOGY

SPECIAL ARTICLE

Revised Response Criteria for Malignant Lymphoma

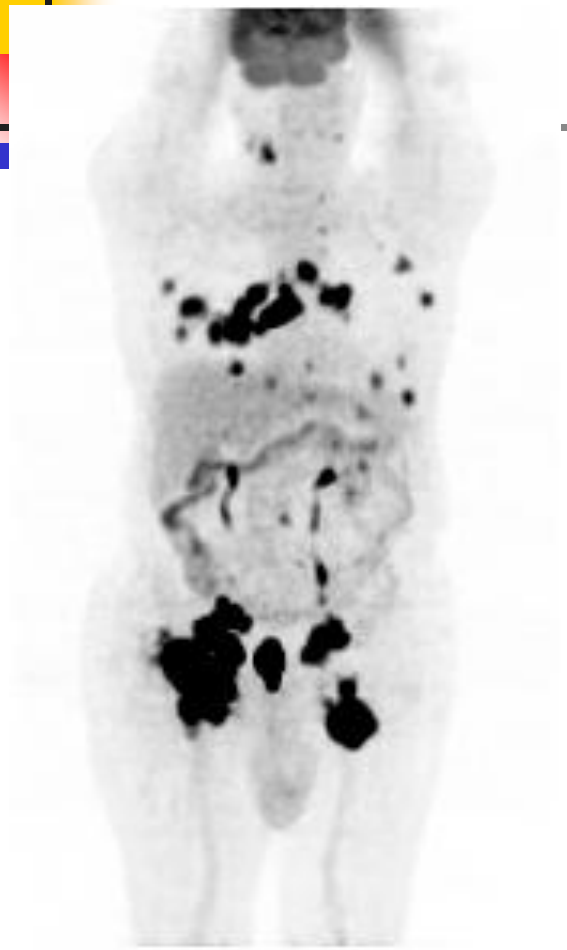
Bruce D. Cheson, Beate Pfistner, Malik E. Juweid, Randy D. Gascoyne, Lena Specht, Sandra J. Horning, Bertrand Coiffier, Richard I. Fisher, Anton Hagenbeek, Emanuele Zucca, Steven T. Rosen, Sigrid Stroobants, T. Andrew Lister, Richard T. Hoppe, Martin Dreyling, Kensei Tobinai, Julie M. Vose, Joseph M. Connors, Massimo Federico, and Volker Diehl

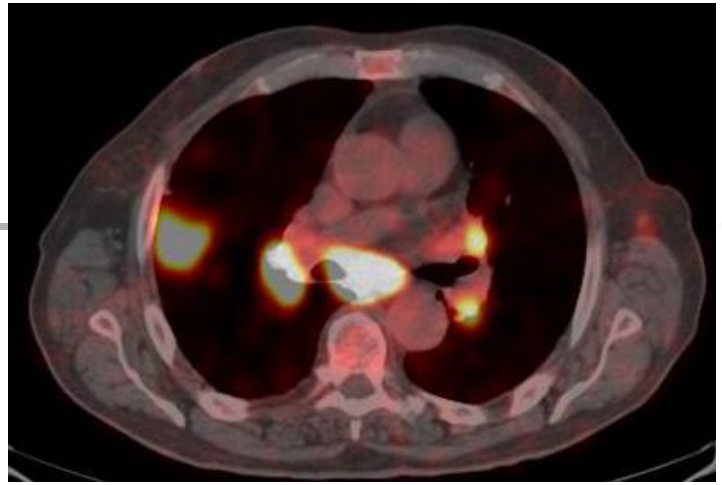
Table 1. Recommended Timing of PET (PET/CT) Scans in Lymphoma Clinical Trials

Histology	Pretreatment	Mid-Treatment	Response Assessment	Post-Treatment Surveillance
Routinely FDG avid				
DLBCL	Yes*	Clinical trial	Yes	No
HL	Yes*	Clinical trial	Yes	No
Follicular NHL	Not	Clinical trial	Not	No
MCL	Not	Clinical trial	Not	No
Variably FDG avid				
Other aggressive NHLs	Not	Clinical trial	Not‡	No
Other indolent NHLs	Not	Clinical trial	Not‡	No

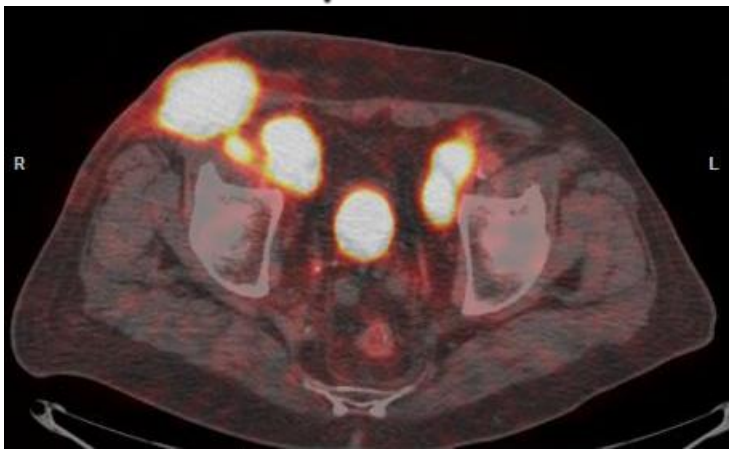
Abbreviations: PET, positron emission tomography; CT, computed tomography; FDG, [^{18}F]fluorodeoxyglucose; DLBCL, diffuse large B-cell lymphoma; HL, Hodgkin's lymphoma; NHL, non-Hodgkin's lymphoma; MCL, mantle-cell lymphoma; ORR, overall response rate; CR, complete remission.
*Recommended but not required pretreatment.
†Recommended only if ORR/CR is a primary study end point.
‡Recommended only if PET is positive pretreatment.

LNH A GRANDES CELLULES





ADP médiastinales et hilaires
Lésion pulmonaire



ADP iliaques externes et inguinales

STADE IV

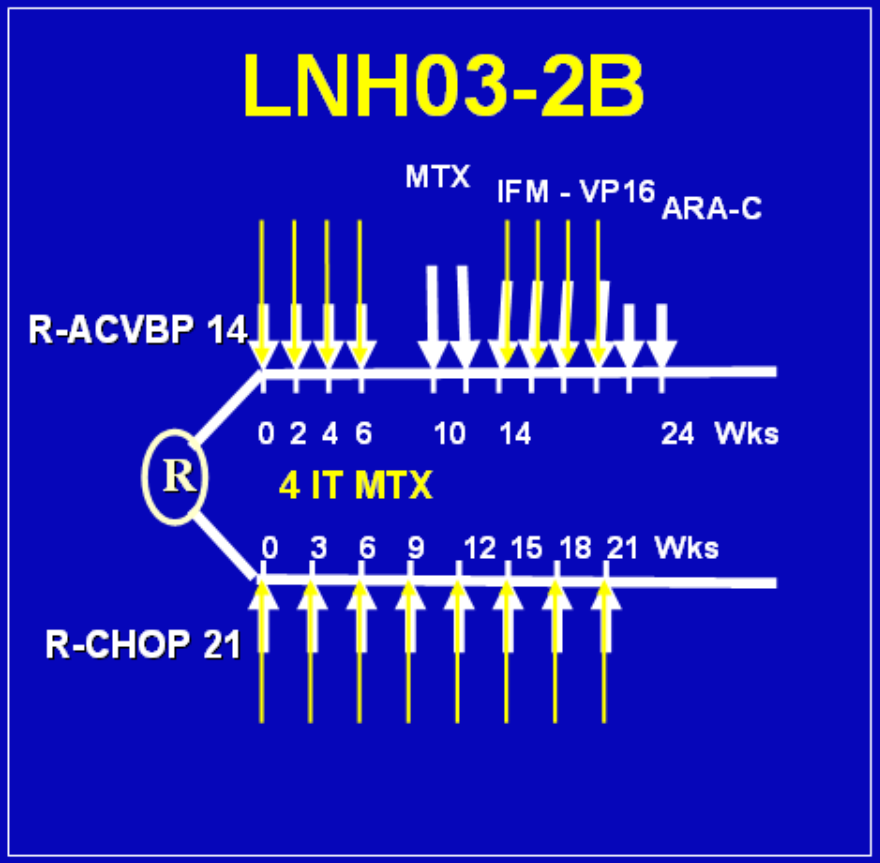
SUV de 4 à 30

2- Quel traitement d'induction ?

- R-CHOP ?
- PL ?

Role of chemotherapy dose intensity in the context of immunochemotherapy ?

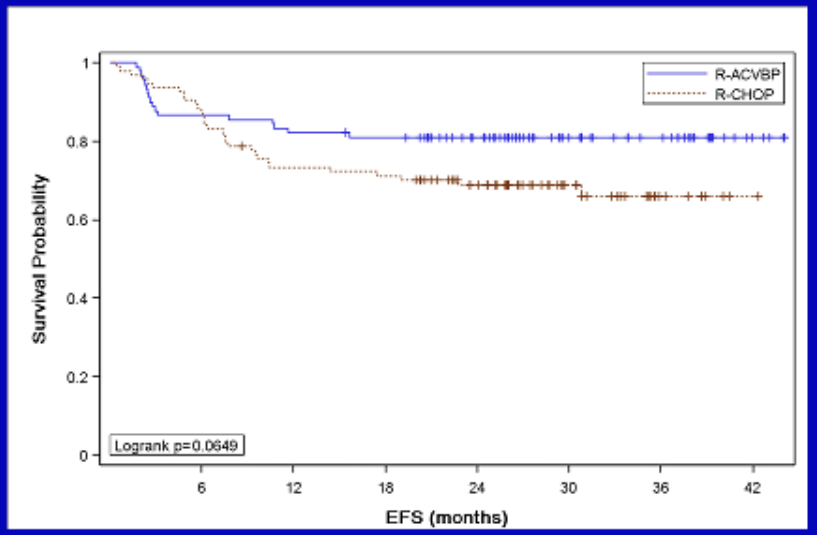
LNH03-2B



PI: Recher C., Tilly H. & Muller D

Patients < 60 yr, aa-IPI=1

R-ACVBP14 > R-CHOP 21
2y- PFS: 85% vs 75%



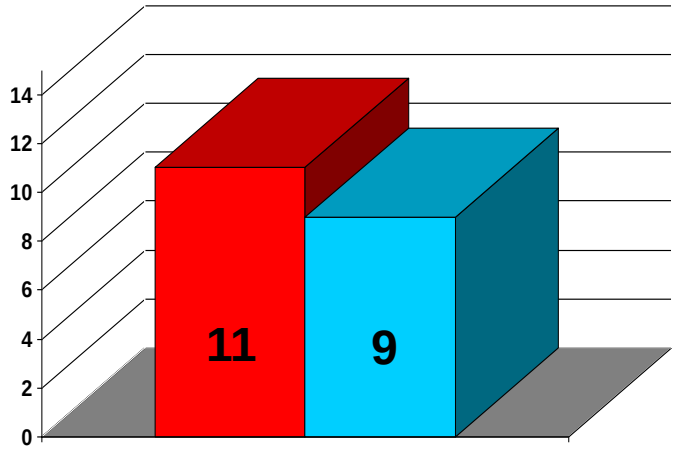
Gela

CNS relapse, role of rituximab:controversial

NO

GELA 98.5

- R-CHOP n = 202
- CHOP n = 197



No efficacy of systemic Rituximab

Feugier P. Ann Oncol 2004; 15: 129-133

395 elderly pts 60–80 yrs

- CNS relapse risk: 5.3%
- No CNS prophylaxis
- CSF concentrations of systemic rituximab (375

Table 1. CSF levels in patients with CNS lymphoma who were treated intravenously with rituximab plus high-dose methotrexate or Ara-C

Patient no.	Week	Serum rituximab	CSF rituximab
1	4	345.7 μg/mL	0.44 μg/mL
2	8	—	0.6 μg/mL
3	1	355.4 μg/mL	0.48 μg/mL
4*	1	273.8 μg/mL	LTR†

Patients received rituximab at 375 mg/m² intravenously weekly for 8 treatments. Rituximab levels were determined in serum and atraumatic CSF specimens collected simultaneously at the completion of the rituximab infusion.

— indicates not available.

*Patient no. 4 had malignant CSF cytology but no contrast-enhancing lesions on MRI.

†The assay result was less than the reportable limit.

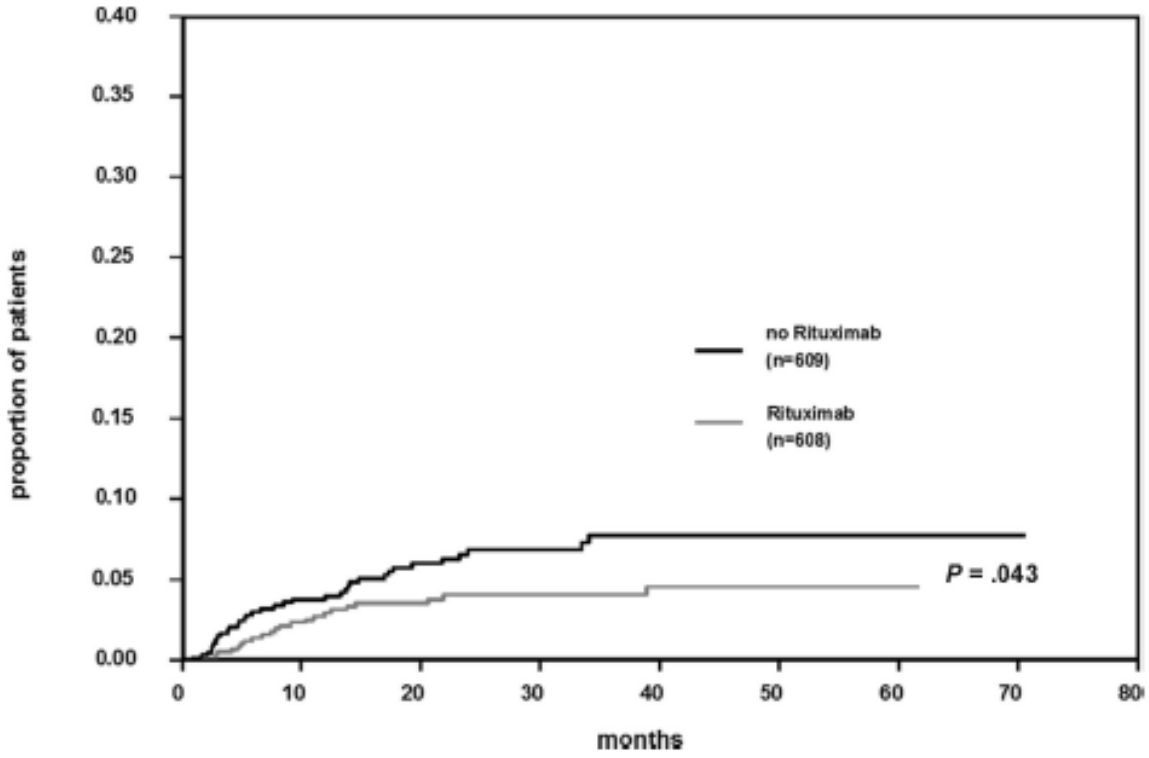
Rubenstein JL Blood 2003

Role of rituximab : controversial

RICOVER - 60

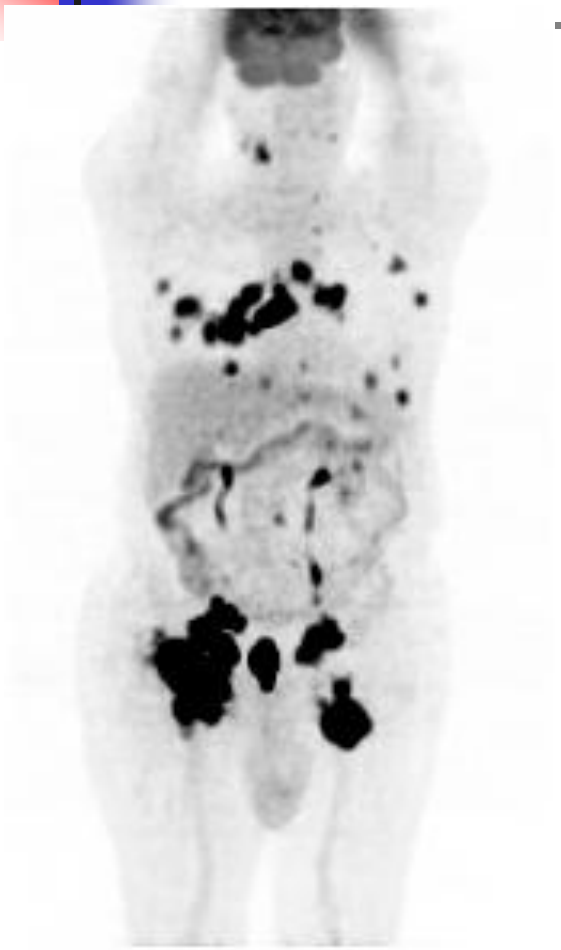
YES

Cumulative risk of CNS disease in patients treated with and without rituximab together with chemotherapy



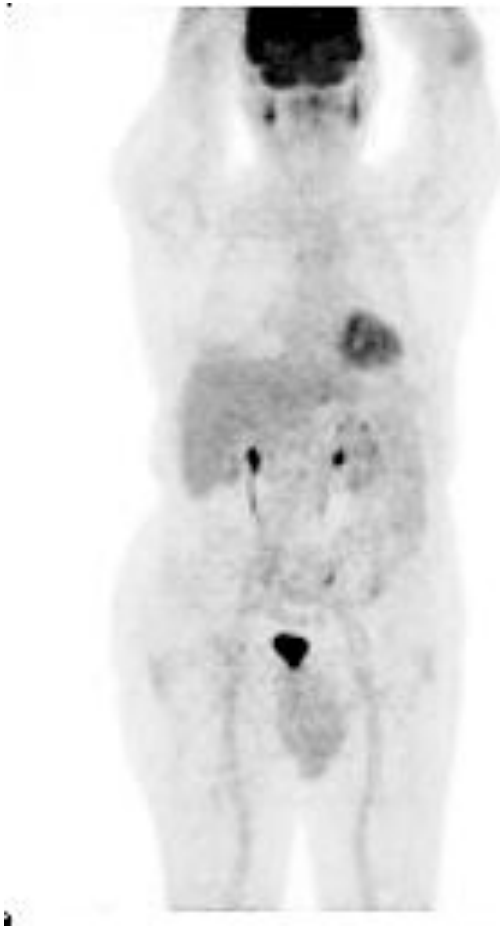
Boehme V., Blood 2009

LNH A GRANDES CELLULES B



Après 2 cycles

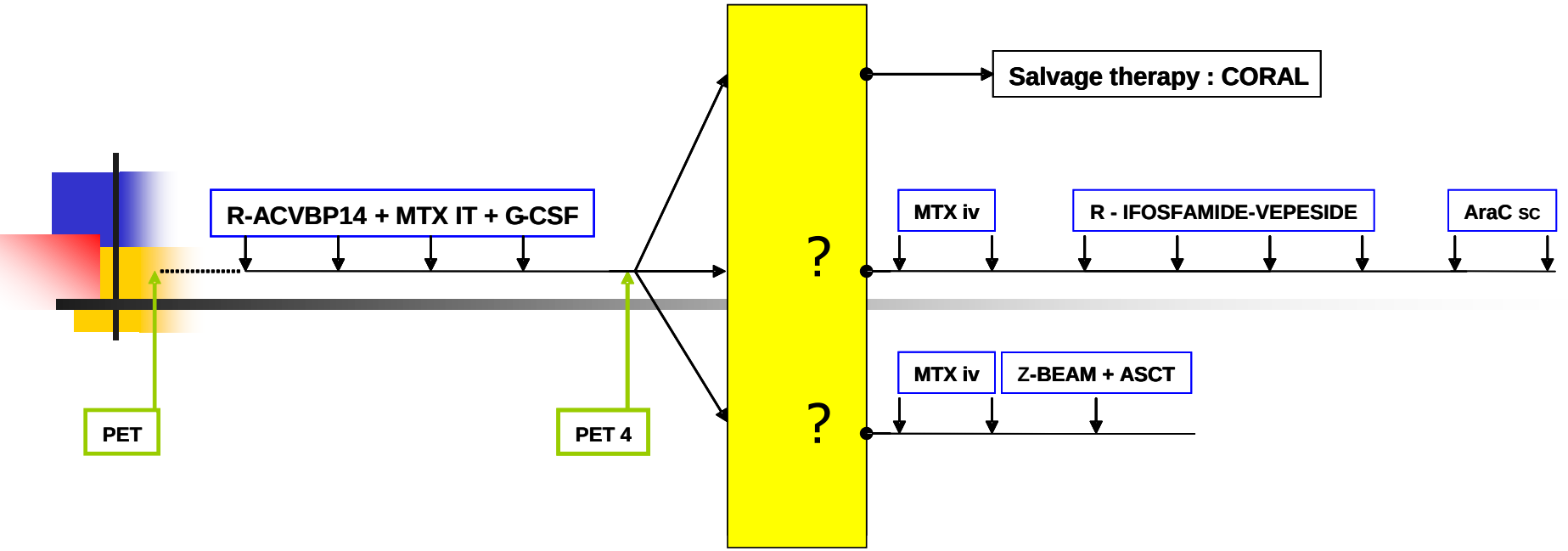
R-ACVBP



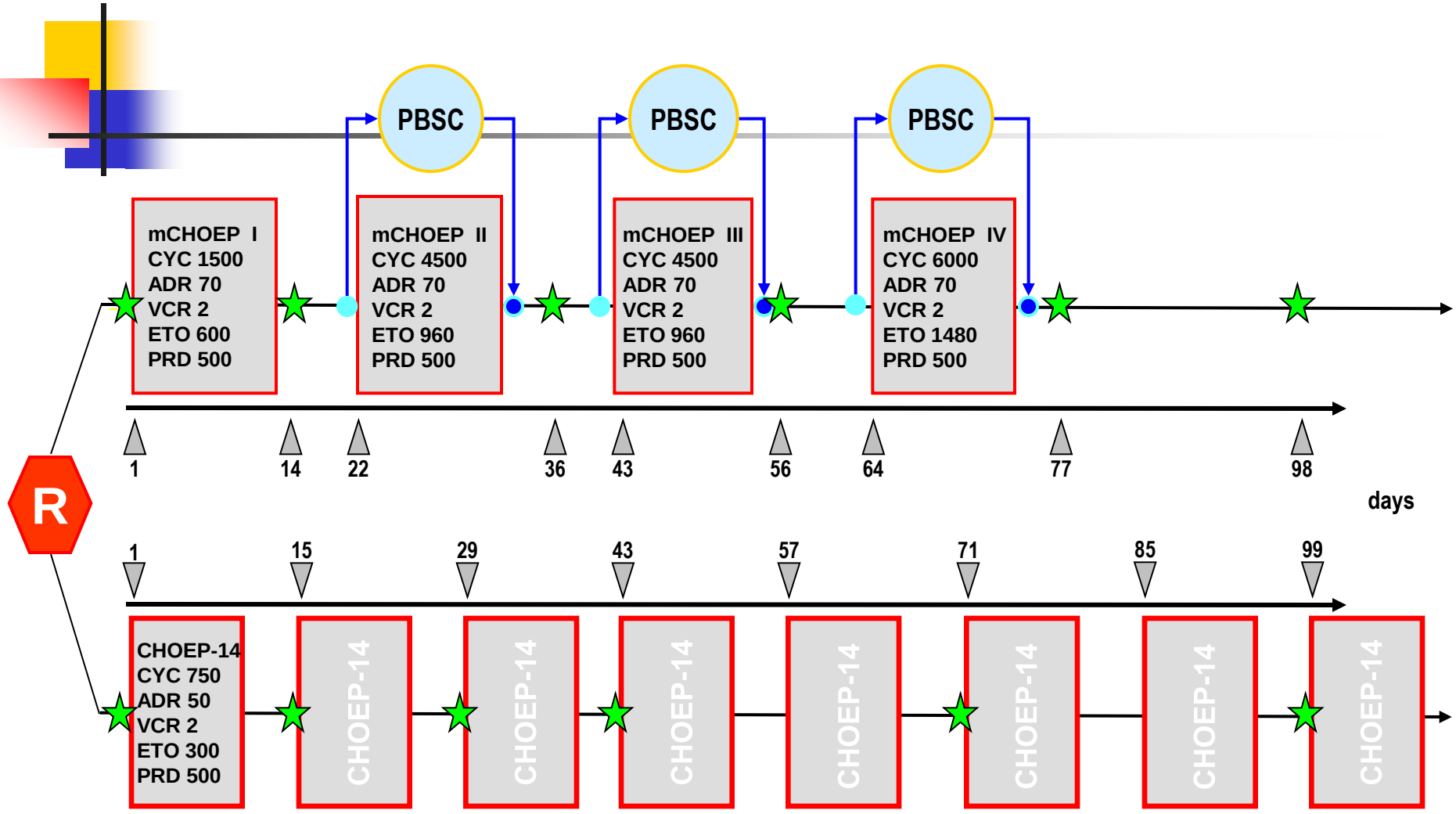
Idem après 4

1 PL seulement

3 - Quelle consolidation ?



DSHNHL 2002-1 -- R-MegaCHOEP study design after amendment 1 for CD20-pos. B-NHL – Schmitz ASH 2009



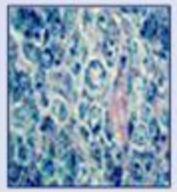
PRD and VCR doses are absolute, all others are per m²

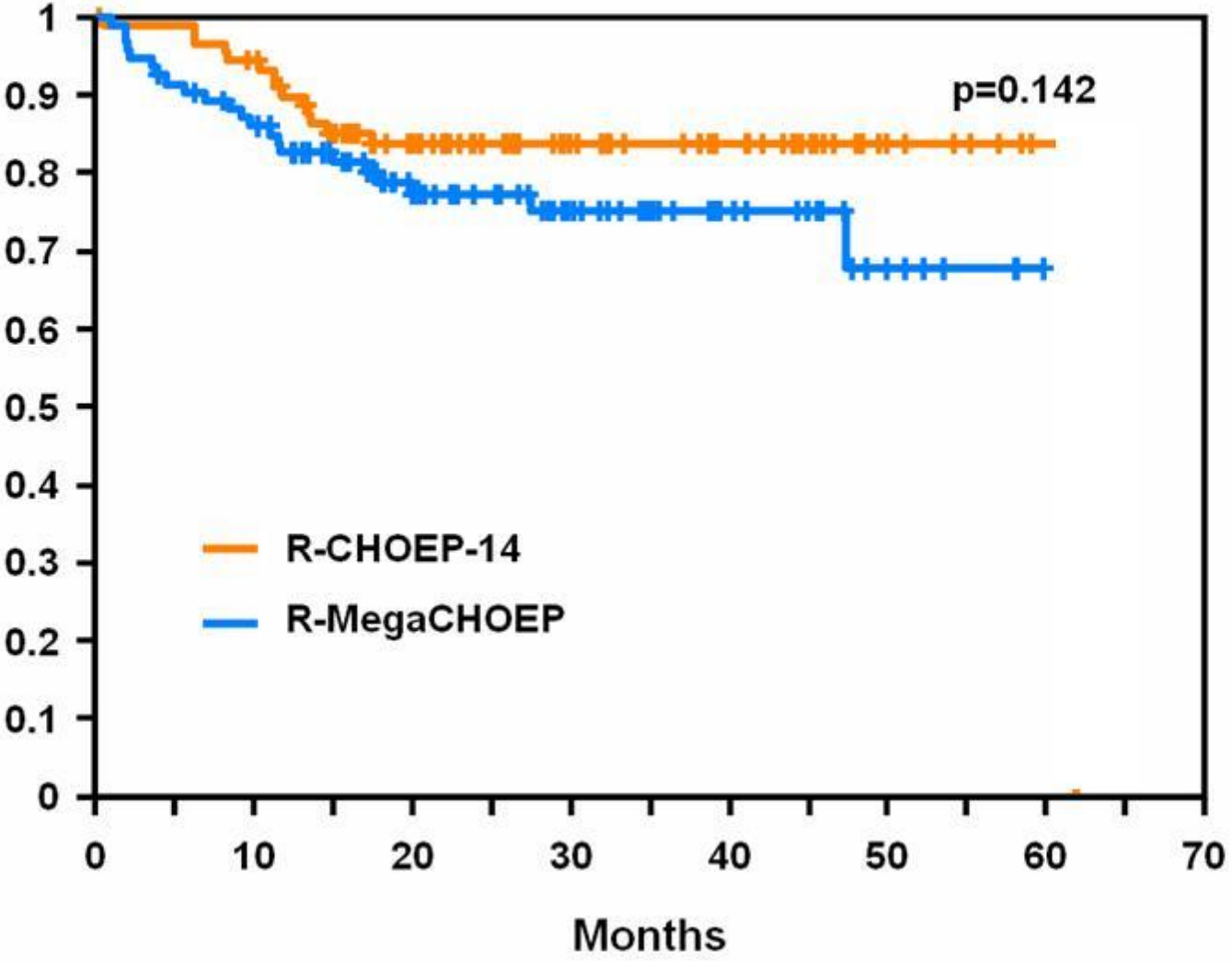
★ Rituximab (375mg/m²)

DSHNHL 2002-1 -- R-MegaCHOEP
Course of therapy

	R-CHOEP-14 (n=91)	R-MegaCHOEP (n=94)
as per protocol	86.8 %	60.6 %
early termination of chemotherapy	2.2 %	11.7 %
early termination of rituximab	0 %	14.9 %
early termination of both	9.9 %	11.7 %
Unknown	1.1 %	1.1 %

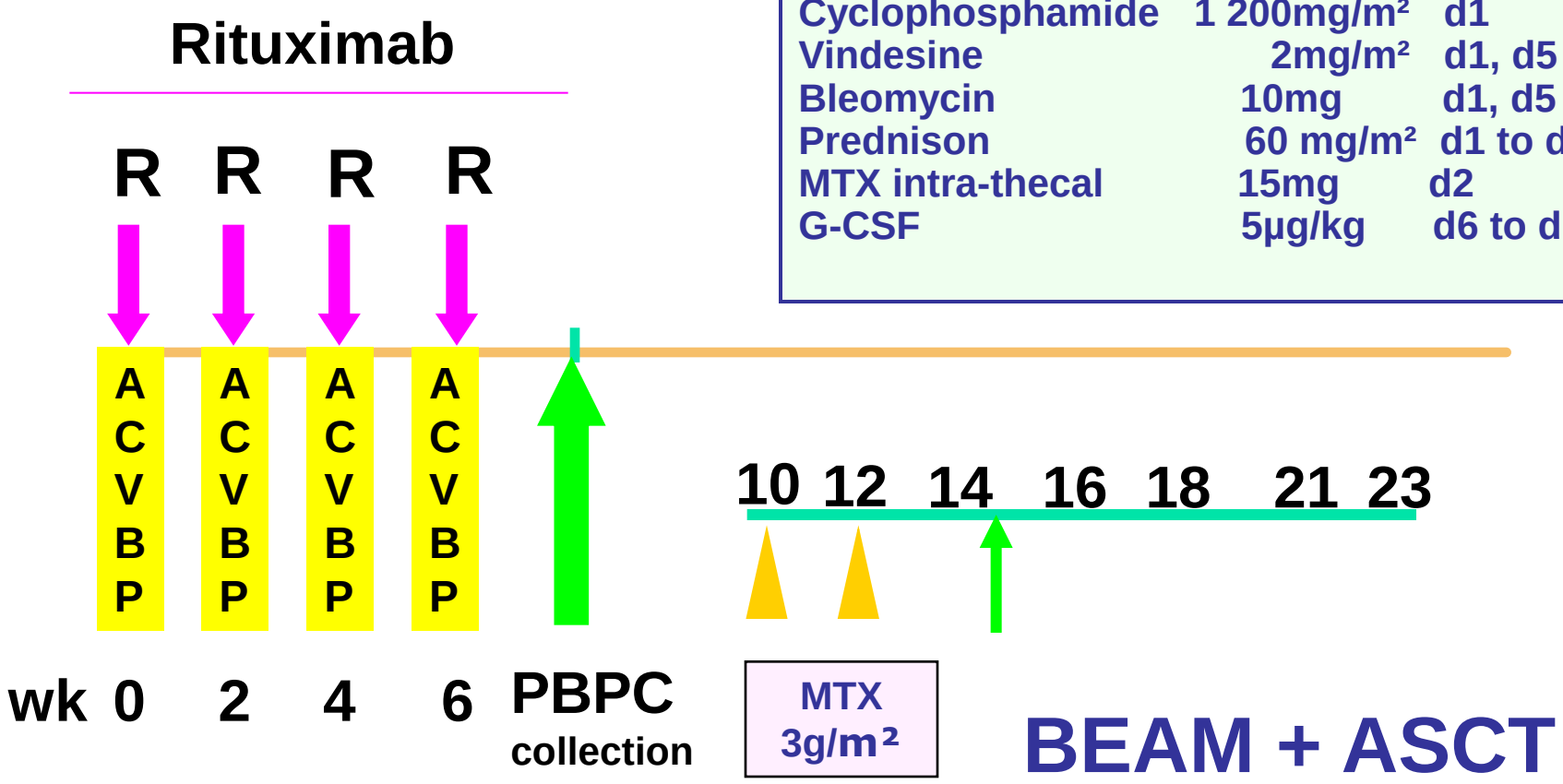
DSHNHL 2002-1 -- MegaCHOEP
Overall survival





Mounier ASCO 2009 : to improve upfront ASCT with pre-transplant Rituximab combined with ACVBP

Doxorubicin	75mg/m²	d1
Cyclophosphamide	1 200mg/m²	d1
Vindesine	2mg/m²	d1, d5
Bleomycin	10mg	d1, d5
Prednison	60 mg/m²	d1 to d5
MTX intra-thecal	15mg	d2
G-CSF	5µg/kg	d6 to d13



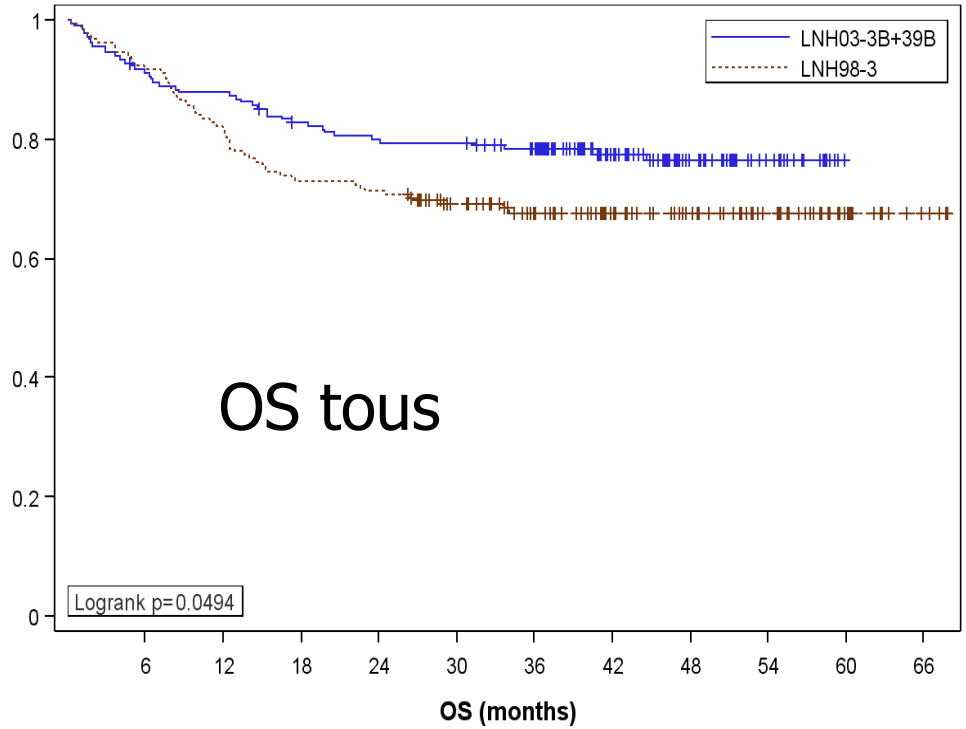
GCSF support, Cotrimoxazol and acyclovir prophylaxis

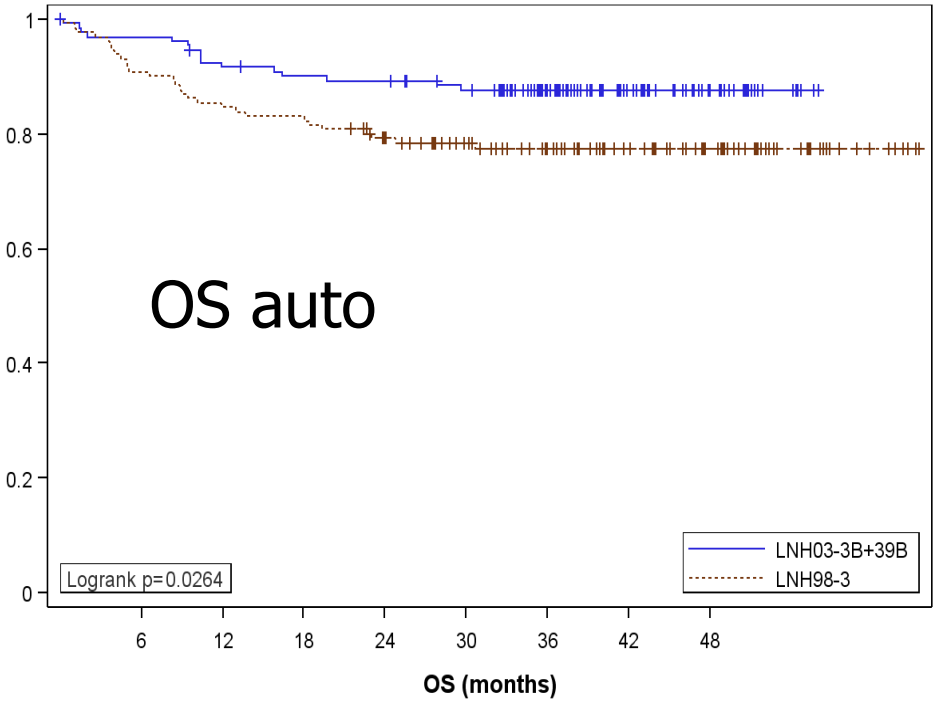
Matched control study :

Overall Survival

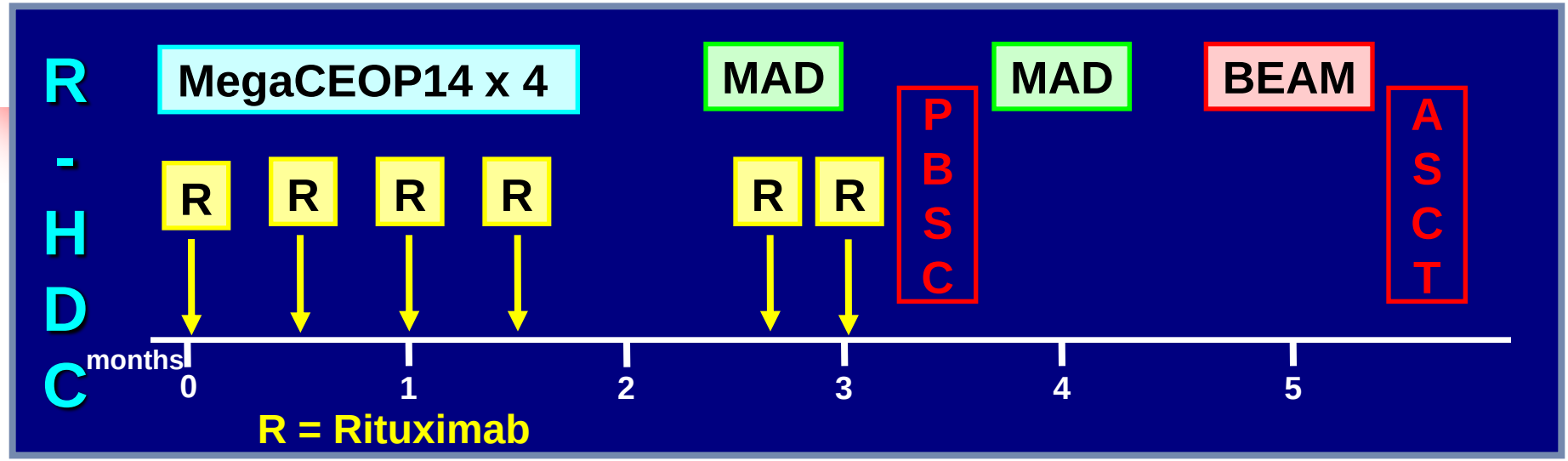
R-IPI

Good 42%
Poor 58%





R-Dose Dense + HDC supplemented with Rituximab + ASCT in first line DLBCL aaIPI2-3



Induction chemotherapy	Intensified chemotherapy MAD (HD-ARAC + Mitoxantrone x 3 days)	High dose chemotherapy BEAM + ASCT
Months 1 and 2	Months 3 and 4	Month 5

R-MEGACEOP14
R 375 mg/m^2 d 1
Epi 110 mg/m^2 d 3
Ctx 1200 mg/m^2 d 3
Vcr 1.4 mg/m^2 d 3
Pdn 40 mg/m^2 dd 1→ 5
G-CSF 5 mcg/kg dd 5→ 12

R-MAD
Mito 8 mg/m^2 dd 1→ 3
ARA-C 2 g/m^2/12h dd 1→ 3
Dex 4 mg/m^2/12h dd 1→ 3
R 375 mg/m^2 d 4 and d -1PBSC
G-CSF 5 µg/Kg d 4→

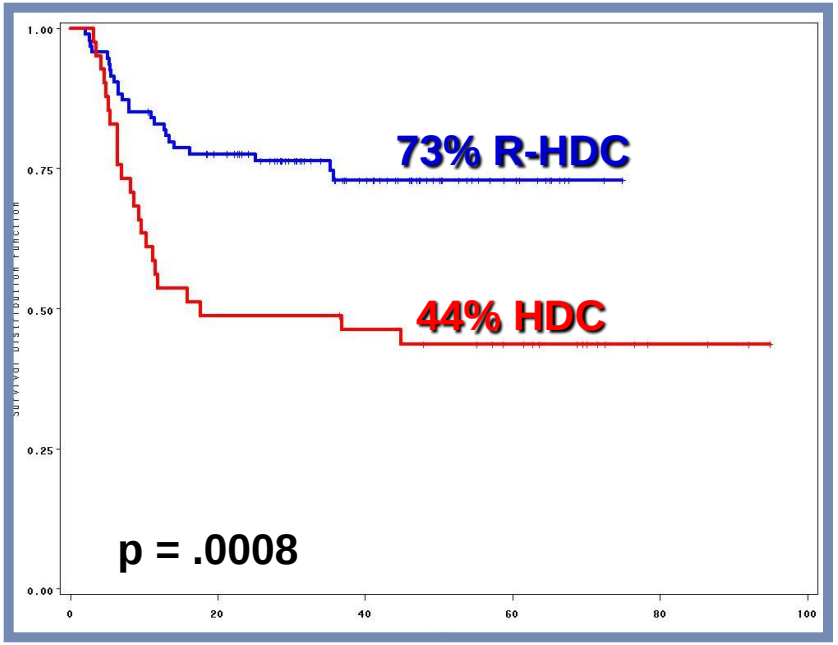
Tarella, Haematologica 2009

Retrospective Comparison: Rituximab-HDC+ASCT vs HDC+ASCT

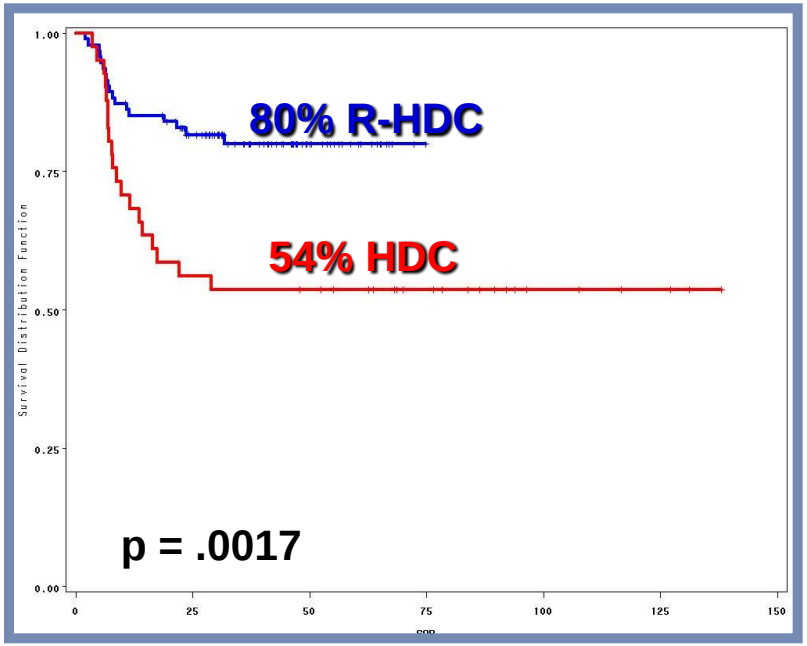
R-HDC 94 patients CR 82%

HDC 41 patients CR 68%

4-yrs Failure-Free Survival



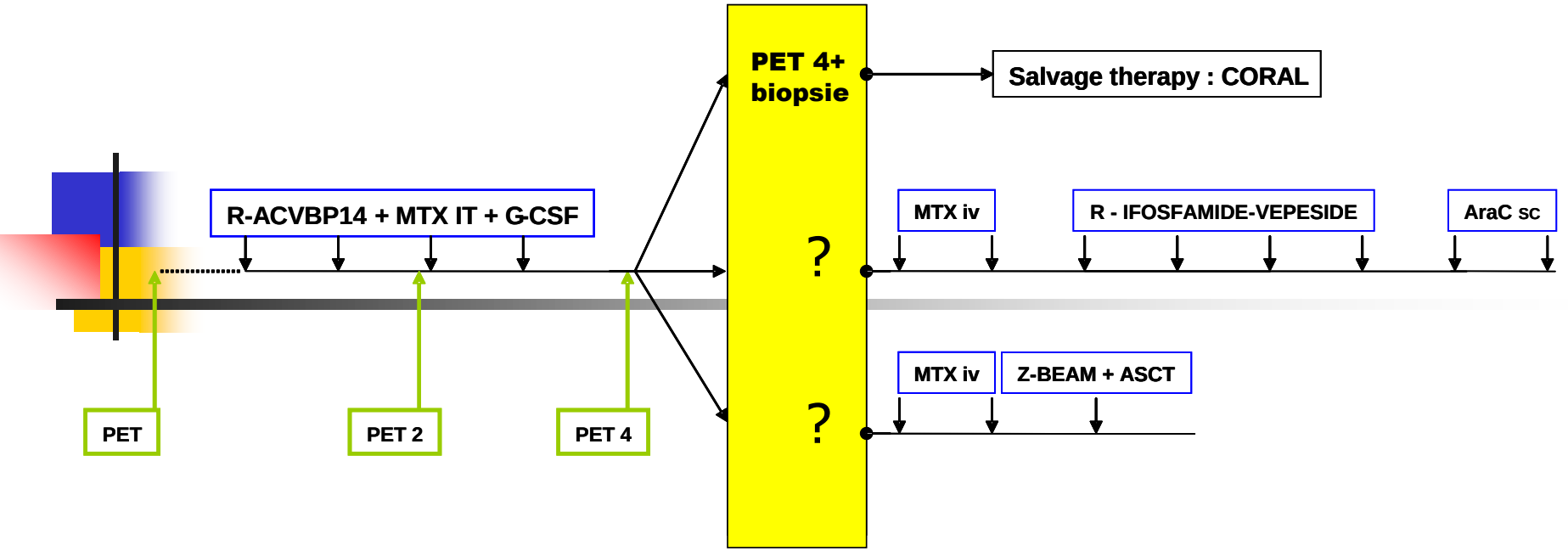
4-yrs Overall Survival



Cox's model: adjusted Hazard Ratio

FFS R-HDC vs HDC	= 0.44 (95% CI=0.24-0.81, p=.01)
OS R-HDC vs HDC	= 0.45 (95% CI=0.22-0.90, p=.03)

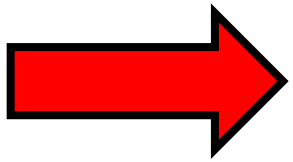
4 - Quelle place pour le PET précoce ?



…evolving concepts in prognostic factors.

…moving from a prognosis based on the attribution of the patients to different risk classes toward an individual risk definition for the single patient…

From a “risk-adapted” therapy…..



…..to a “response-adapted” therapy.

Notable examples:

MRD detection by molecular biology

Early interim-PET during treatment

CRITERES DE REPONSE

VOLUME 25 · NUMBER 5 · FEBRUARY 10 2007

JOURNAL OF CLINICAL ONCOLOGY

SPECIAL ARTICLE

Revised Response Criteria for Malignant Lymphoma

Bruce D. Cheson, Beate Pfistner, Malik E. Juweid, Randy D. Gascoyne, Lena Specht, Sandra J. Horning, Bertrand Coiffier, Richard I. Fisher, Anton Hagenbeek, Emanuele Zucca, Steven T. Rosen, Sigrid Stroobants, T. Andrew Lister, Richard T. Hoppe, Martin Dreyling, Kensei Tobinai, Julie M. Vose, Joseph M. Connors, Massimo Federico, and Volker Diehl

Table 2. Response Definitions for Clinical Trials

Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
CR	Disappearance of all evidence of disease	(a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative (b) Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative
PR	Regression of measuable disease and no new sites	≥ 50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT	≥ 50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR or PD	(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET (b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT		
Relapsed disease or PD	Any new lesion or increase by ≥ 50% of previously involved sites from nadir	Appearance of a new lesion(s) > 1.5 cm in any axis, ≥ 50% increase in SPD of more than one node, or ≥ 50% increase in longest diameter of a previously identifed node > 1 cm in short axis Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy	> 50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

Abbreviations: CR, complete remission; FDG, [^{18}F]fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography; PR, partial remission; SPD, sum of the product of the diameters; SD, stable disease; PD, progressive disease.

CRITERES DE REALISATION

Use of Positron Emission Tomography for Response Assessment of Lymphoma: Consensus of the Imaging Subcommittee of International Harmonization Project in Lymphoma

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- TEP pré thérapeutique:
  - Non obligatoire mais facilite l'interprétation du post thérapeutique
- TEP post thérapeutique:
  - Minimum 3 sem ap. chimiothérapie
  - 8 à 12 sem ap. la radiothérapie
- TEP en cours de traitement par chimio:
  - Respecter un délai max avec la chimiothérapie:
    - Si J1 = J14; TEP entre J10 et J13
    - Si J1 = J21; TEP entre J17 et J20

Malik E. Juweid, Sigrid Stroobants, Otto S. Hoekstra, Felix M. Mottaghy, Markus Dietlein, Ali Guermazi, Gregory A. Wiseman, Lale Kostakoglu, Klemens Scheidhauer, Andreas Buck, Ralph Naumann, Karoline Spaepen, Rodney J. Hicks, Wolfgang A. Weber, Sven N. Reske, Markus Schwaiger, Lawrence H. Schwartz, Josee M. Zijlstra, Barry A. Siegel, and Bruce D. Cheson

CRITERES D'INTERPRETATION

Use of Positron Emission Tomography for Response Assessment of Lymphoma: Consensus of the Imaging Subcommittee of International Harmonization Project in Lymphoma

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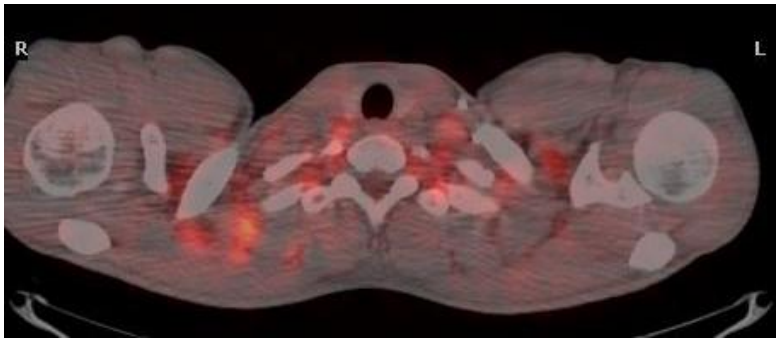
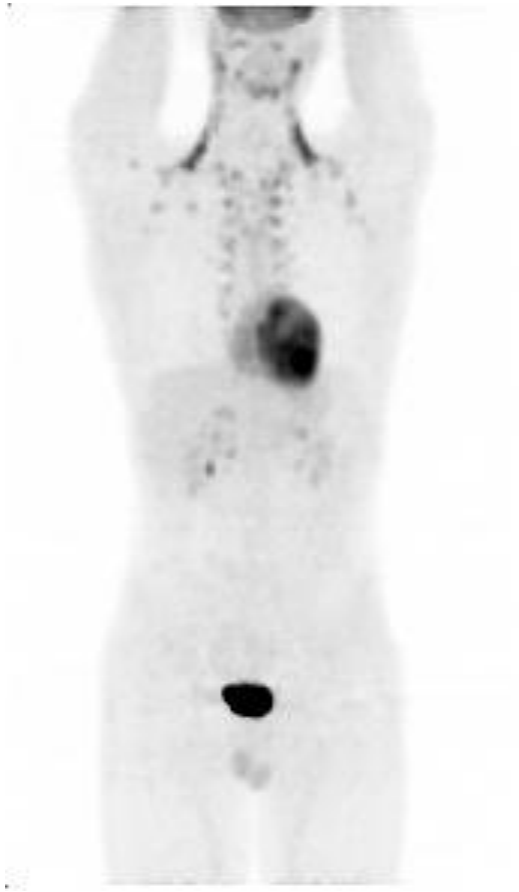
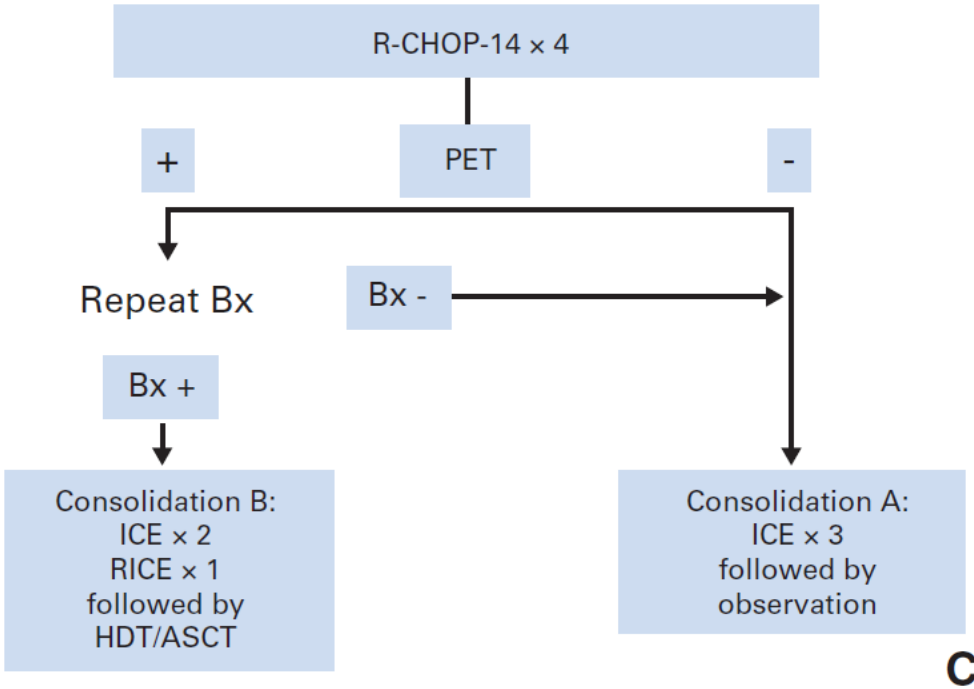
JOURNAL OF CLINICAL ONCOLOGY

- Interprétation visuelle:
  - Image anormale: fixation focale ou diffuse supérieure au bruit de fond dans une localisation incompatible avec l'anatomie ou la physiologie normale.
  - SUV non nécessaire
    - Exception: TEP en cours de traitement
    - Etudes prospectives en cours

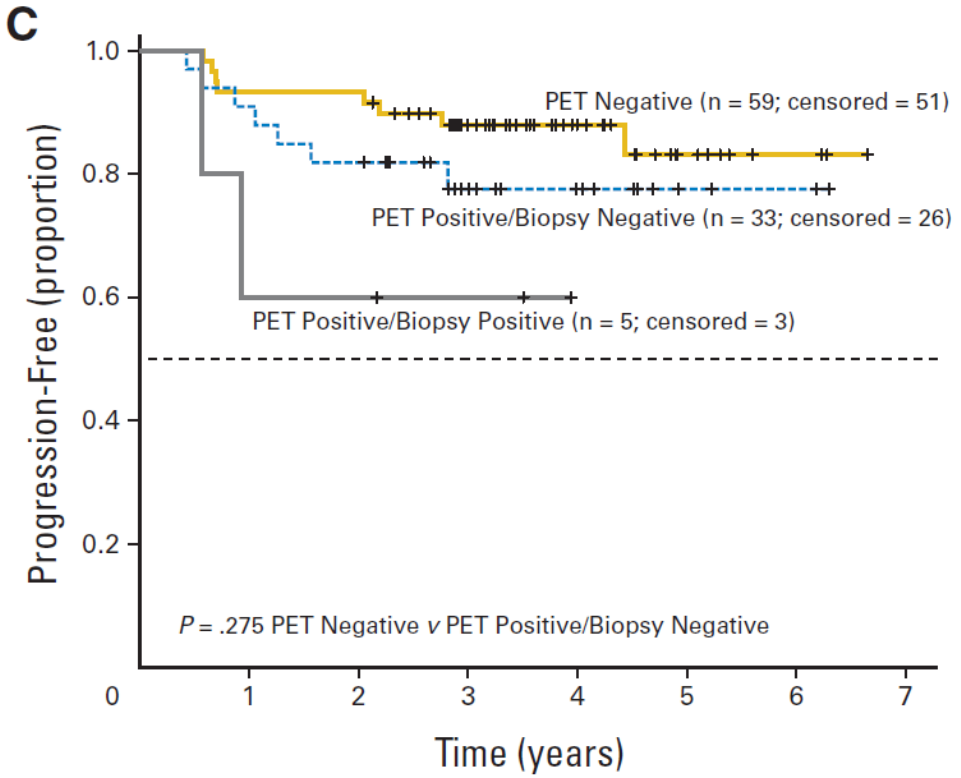
- FP:
  - Rebond thymique (hyperplasie)
  - Infection
  - Inflammation
  - Sarcoïdose
  - Graisse brune



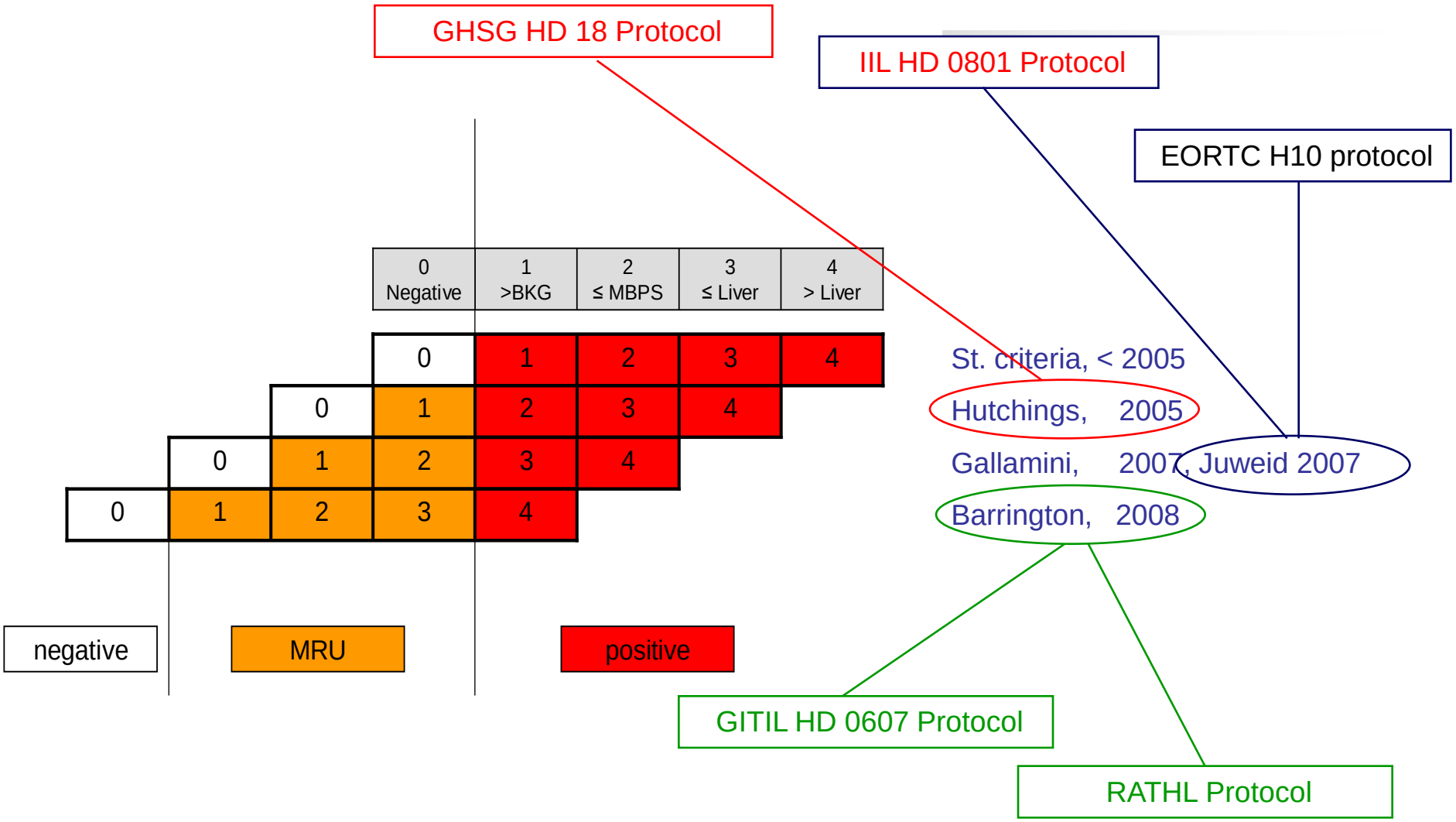




Craig H. Moskowitz JCO 2010



The MRU definition, as the time goes by.



The Deauville criteria for interim PET

PET reporting

NEGATIVE SCAN
Score 1 no uptake
Score 2 uptake ≤ mediastinum
Score 3 uptake > mediastinum but ≤ liver

POSITIVE SCAN
Score 4: moderately ↑uptake > liver
Score 5 markedly ↑uptake > liver

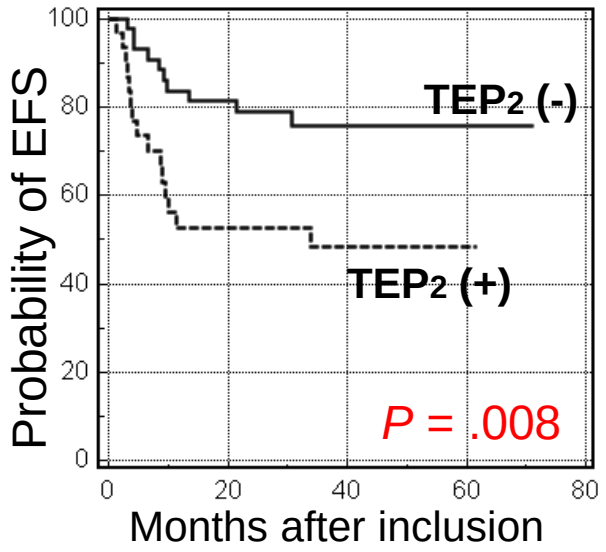
***Score X**:*
new areas of uptake unlikely to be related to lymphoma

A baseline PET/CT should be performed prior to initiation of therapy.
An interim PET is performed early during induction chemotherapy.
Preservation of the continuous nature of the data instead of reporting a binary decision, i.e. either an ordinal visual score or SUV data is recommended.
A visual analysis using a five points scale is first applied.
The preferable reference would be the mediastinum a the liver

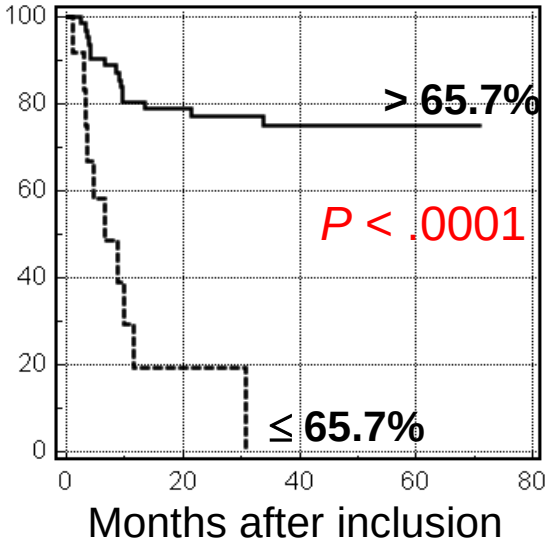
Meignan, Leukemia & lymphoma 2009

Visual and SUV analysis
Early response assessment (2 cycles), n=92 pts

Visual Analysis
(positive or negative)



SUV Analysis
(ΔSUVmax PET0/PET2)

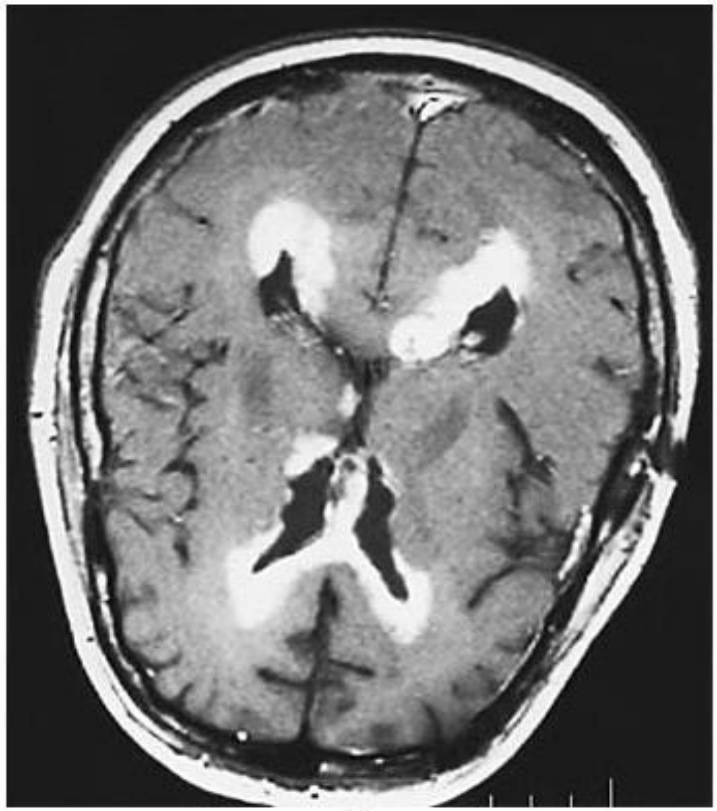


→ Decrease the number of false positive studies
→ 14/17 FP patients reclassified with ΔSUVmax
→ 2 cycles: ΔSUV performs better than visual
→ Robust and objective index for multicenter trials

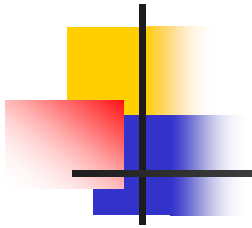
Lin, Itti et al. ***J Nucl Med*** 2007;48:1626-32

Cas Clinique, la suite après la conso standard

Malheureusement, le patient est réhospitalisé 3 mois plus tard, avec des signes neurologiques.



B



5- Quel pronostic ?
Peut on rattraper les échecs ?

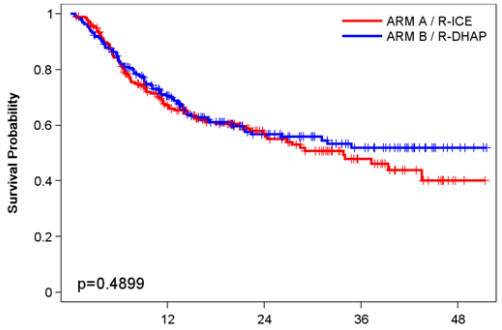
CORAL CONCLUSION

- R-ICE and R-DHAP have similar activity and mobilization ability with less adverse events for R ICE.
- Prognostic factors affecting response and survival:
  relapse < 12 months, secondary IPI>1, prior rituximab

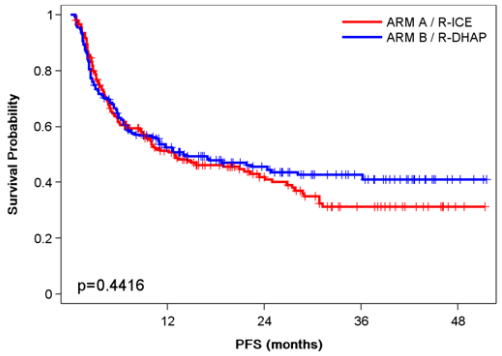
WORST RESULTS : RESPONSE RATE 50%
PFS 30%
BEST RESULTS : RESPONSE RATE 80%
PFS 60%

- A new profile of relapses and refractory patients after rituximab will come out from this trial, and will help the design of future study with new drugs.
- A bio CORAL program is on going to better understand this population of poor prognosis patients

Il faut faire bien dès le début.



OVERALL SURVIVAL ACCORDING TO TREATMENT ARM (INDUCTION ITT)



PROGRESSION-FREE SURVIVAL ACCORDING TO TREATMENT ARM (INDUCTION ITT)

Orlando ASCO May 2009 / Coral study C. Gisselbrecht

Rechute SNC

Carole Soussain, JCO 2008

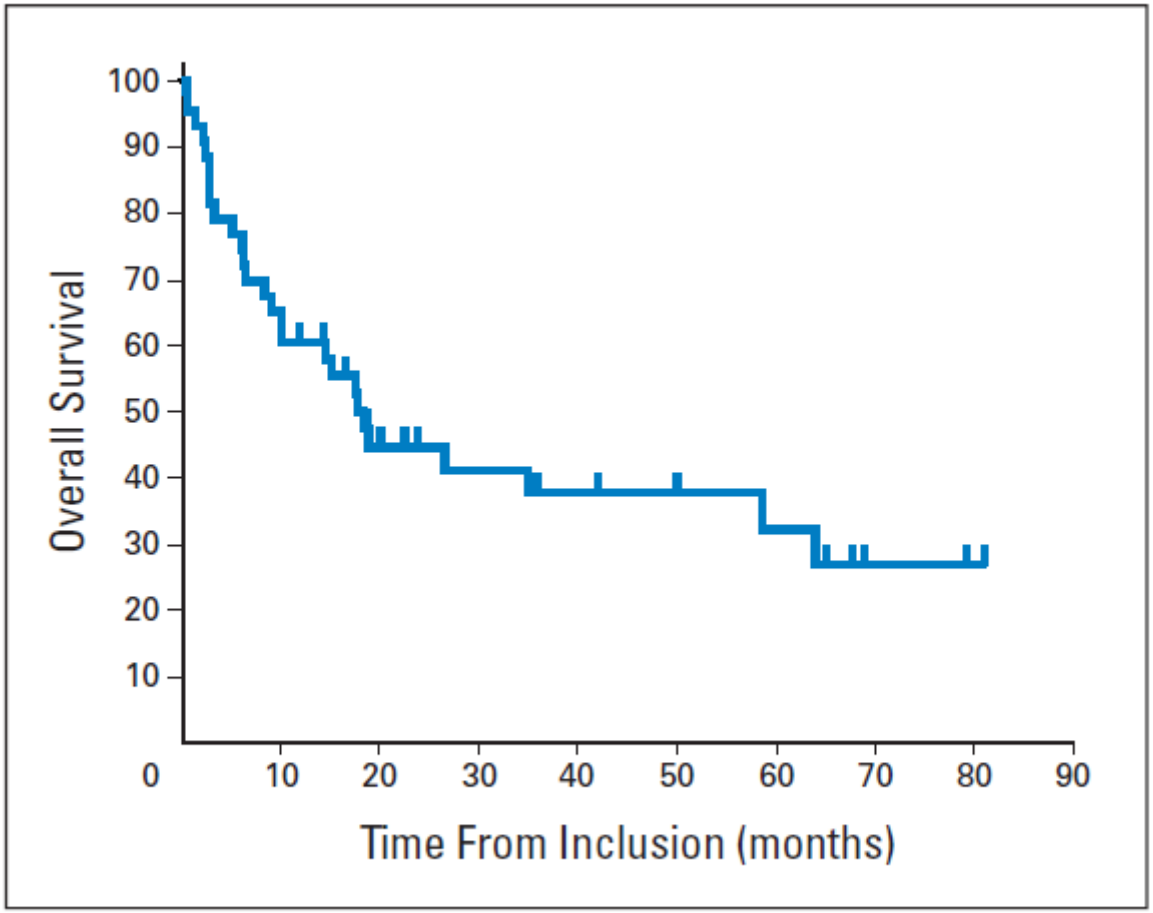


Fig 1. Overall survival of the whole study population.

LNH07-3B Trial : coming soon ?