SUVmax reduction improves early prognosis value of interim positron emission tomography scans in diffuse large B-cell lymphoma

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Short Title: Interim PET SUVmax reduction in DLBCL

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Abstract

The prognostic value of interim PET interpreted according to visual criteria is a matter of debate in diffuse large B cell lymphoma (DLBCL). Maximal standardized uptake value reduction (ΔSUVmax) may better predict outcome. To compare the prognostic value of both methods, we analysed PET done at baseline (PET0), after 2 (PET2) and 4 cycles (PET4) in 85 patients with aaIPI 2-3 factors DLBCL enrolled on a prospective multicenter trial. All images were centrally reviewed and interpreted both visually according to the International Harmonization Project (IHP) criteria, and by computing ΔSUVmax between PET0 and PET2 (ΔSUVmaxPET0-2), or PET4 (ΔSUVmaxPET0-4). Optimal cut-off to predict progression or death was 66% for ΔSUVmaxPET0-2 and 70% for ΔSUVmaxPET0-4. Outcomes did not differ significantly whether PET2 and PET4 were visually positive or negative. Inversely, ΔSUVmaxPET0-2 analysis (>66% v ≤66%) identified patients with significantly different 2-year PFS (77% v 57%; p=0.0282) and OS (93% v 60%; p<0.0001). ΔSUVmax PET0-4 analysis (>70% v ≤70%) seemed even more predictive for 2-year PFS (83 v 40%, p<0.0001) and OS (94% v 50%, p<0.0001). ΔSUVmax analysis of sequential interim PET is feasible for high risk DLBCL in a multicenter setting and better predicts outcome than visual analysis based on IHP criteria. The study was registered at http://clinicaltrials.gov as NCT00498043.
Introduction

$^{18}$F-FDG PET was shown to improve both primary staging$^1$ and response assessment at completion of first line therapy of diffuse large B-cell lymphoma (DLBCL)$^2,^3,$ and was recently implemented in the standardized response criteria for lymphoma$^4.$ However, there is an increasing interest in using interim PET performed after 1 to 4 cycles of chemotherapy$^5,$ in order to predict response to induction treatment and drive consolidation therapy.

The prognostic value of interim PET based on visual analysis remains controversial in diffuse large B cell lymphoma (DLBCL). In a prospective study of 90 patients with DLBCL, a positive PET after 2 cycles (PET2) identified poor responders regardless of their treatment or age adjusted international prognostic index (aIPI) score$^6.$ Similarly, PET after 4 cycles of induction treatment (PET4) was also shown to predict outcome$^7.$ Conversely, in a recent report on 97 DLBCL patients with aIPI 1-3, PFS was similar for patients with either a positive or a negative PET4. Moreover, only 5 out of the 38 patients with a positive PET4 had biopsy proven active disease$^8.$ These discrepancies on the predicting value of interim PET may either be due to the heterogeneity of the visual criteria used so far$^5$ or reflect the lack of interobserver reproducibility in interpreting PET images on the basis of entirely visual criteria$^9.$ Semiquantification of standardized uptake values (SUVs) may reduce false-positive interim PET interpretations but whether SUV analysis better predicts outcome than visual analysis has not been clearly established yet$^{10,11}.$ Therefore, a comparison of interim PET results based on SUV analysis to those based on visual criteria could be helpful to establish their respective prognostic value.

In 2007, the GELA started a prospective multicenter trial in previously untreated young patients with high risk DLBCL. The intensity of consolidation was driven by a centralized assessment of both PET 2 and 4 using the most recently published International Harmonization Project (IHP) visual criteria at that time. An exploratory analysis of SUVmax reduction ($\Delta$SUVmax) between baseline PET and either PET2 or PET4 was performed simultaneously during the central review process. Here, we report the comparison between
the results of the visual and ΔSUVmax analysis and demonstrate that the latter semiquantitative approach better predicts outcome than visual analysis.
Patients and methods

LNH2007-3B study design

The LNH2007-3B trial was a prospective multicenter, randomized phase II trial of 2 induction regimen, R-CHOP14 versus R-ACVBP, followed by a PET-driven consolidation treatment in previously untreated young patients with high risk DLBCL. The primary endpoint was the complete response (CR) rate according to the revised IWG criteria after 4 cycles of induction. In order to detect a CR rate higher than 50% after 4 cycles of R-ACVBP or R-CHOP14, we calculated that a sample size of 101 assessable patients in each randomization arm would provide 85% power at an overall 2.5% (1-sided) significance level. The overall sample size was brought up to 222 patients including 111 patients in each arm, to allow for a 10% drop-out rate. An interim analysis was planned after the inclusion of 52 assessable patients in each induction arm. The secondary endpoints included toxicity, overall survival and progression-free survival (PFS). This study was approved by the ethics committee of Lyon and the national regulatory agency according to French regulatory laws. All patients provided written informed consent in accordance with the Declaration of Helsinki. The study was registered as NCT 00498043 at clinical-trials.gov.

Eligibility criteria

Patients eligible for the present study were 18 to 59 years old with a previously untreated histologically proven CD20+ DLBCL and an aaIPI score of 2 or 3. A baseline PET scan (PET0) was mandatory with at least one evaluable hypermetabolic lesion. All patients had to be eligible for high dose therapy followed by autologous stem cell transplantation (ASCT). Patients with known positive human immunodeficiency viral status, active viral hepatitis B and C or central nervous system involvement by lymphoma were excluded.

Treatment

Patients were randomly assigned to receive as induction treatment 4 cycles of either R-ACVBP14 (rituximab (375mg/m²), cyclophosphamide (1200mg/m²), doxorubicin (75mg/m²),
given intravenously (IV) on day 1; vindesine (2mg/m²) and bleomycin (10mg) given IV on days 1 and 5; prednisone (60mg/m²) given orally on days 1 through 5, and intrathecal methotrexate (15mg) on day 2, recycling at day 14) or R-CHOP14 (in mg/m²: rituximab (375), cyclophosphamide (750), doxorubicin (50), vincristine (2) given IV on day 1, prednisone (60) given orally on days 1 through 5, and intrathecal methotrexate (15mg) on day 2; recycling at day 14). The consolidation treatment was driven by centrally reviewed PET assessment after 2 and 4 cycles of induction immuno-chemotherapy interpreted according to visual criteria (Figure 1). Patients who were classified as PET2 and PET4 negative received consolidation with sequential conventional dose immuno-chemotherapy consisting of: -in the R-ACVBP arm, 2 cycles of high dose Methotrexate (3g/m²), then 4 cycles of Rituximab (375mg/m²), ifosfamide (1.5g/m²), etoposide (300mg/m²) given IV on day 1 and 2 cycles of cytarabine (100mg/m² subcutaneous on days 1 through 4); -in the R-CHOP14 arm, 4 additional cycles of R-CHOP14. Patients classified as PET2 positive and PET4 negative received 2 cycles of high dose Methotrexate (3g/m²) and then a consolidative high dose therapy (BEAM or Z-BEAM) followed by ASCT. For these PET2 positive patients, peripheral stem cell harvest was performed using G-CSF after the third cycle of induction treatment. Patients classified as PET4 positive were removed from the study no matter what the results of PET2 were, and treated at the discretion of the investigator. A biopsy of the residual hypermetabolic mass was recommended whenever possible.

PET restaging

Two PET examinations at mid (PET2) and end of induction (PET4) were required for full assessment and scheduled 2 weeks after the second and the 4th cycle of immuno-chemotherapy respectively. G-CSF was stopped 48 hours before PET. Each patient was scanned on the same camera for baseline, and subsequent PET scans. A whole body acquisition was started 60 ± 10 minutes after a 5MBq/Kg ¹⁸F-FDG injection, working from groin up to the head. The administered activity of FDG, the time of injection and the time of the scan beginning were recorded.
Visual analysis of PET

A blinded central review in real time of the PET images was organized using the positoscope network\(^\text{12}\). For each patient, the data and images of the PET0, PET2, and PET4 were sent within 24 hours of the examination to at least 2 of 3 PET experts (MM, ABR, or SB) composing the central panel. PET2 and PET4 were binary interpreted as positive or negative. Interpretation criteria used the rules proposed by the International Harmonization Project (IHP) in Lymphoma\(^\text{3}\) with the following precisions: the “clearly increased activity relative to the reference background” which defines positive residual uptake in the IHP criteria should be at least 25% higher than this background. A first central review was performed within 72 hours of receiving PET2 images and the final result sent back to the investigator to allow planning of stem cell harvest after cycle 3 in case PET2 was positive. A second central review was done within 72 hours of receiving PET4 images and the final result was sent back to the investigator together with the per-protocol recommended consolidation treatment allocation. In addition, a central exploratory analysis of PET2 and PET4 using the Deauville criteria\(^\text{7}\) was done post hoc on all study patients to see if whether they would better predict outcome than IHP criteria.

SUV-Based assessment of \(^{18}\)F-FDG uptake

An analysis of the \(\Delta\text{SUV}_{\text{max}}\) between baseline PET and PET2 (\(\Delta\text{SUV}_{\text{max, PET0-2}}\)) or PET4 (\(\Delta\text{SUV}_{\text{max, PET0-4}}\)) was performed during the central review process, with no influence on the consolidation treatment allocation. For each PET, the tumor with the most intense \(^{18}\)F-FDG uptake was identified among all foci using a graded color-scaled. The hottest volumetric region was determined and the SUVmax was calculated as previously described\(^\text{10}\). To assess the \(\Delta\text{SUV}_{\text{max}}\), the hottest tumor in any region or organ on PET2 or PET4 was used for comparison, even if its location differed from the initial hottest tumor in PET0.
Statistics

The level of agreement on PET visual interpretation between the on-site and the review panel was analyzed using non-weighted kappa statistics\textsuperscript{14}.

Receiver-operating-characteristics (ROC) analysis\textsuperscript{15} was used to determine an optimal cut-off for $\Delta$SUVmaxPET$_{0-2}$ and $\Delta$SUVmaxPET$_{0-4}$ in predicting disease progression or death. For $\Delta$SUVmaxPET$_{0-2}$, ROC analysis identified that the two cut-offs of 62\% and 66\% respectively had the best sensitivity and specificity to predict an event occurrence. Since a 66\% cut-off had been previously identified on prior independent series\textsuperscript{10,16}, this threshold was chosen to analyse our series. For $\Delta$SUVmaxPET$_{0-4}$ the cut-off identified by ROC curve was 70\%.

PFS was defined as the time from randomization to first progression, relapse and either death, whatever the cause, or last follow-up. OS was defined as the time from randomization to death from any cause, or last follow-up. Estimates of survival were calculated according to the Kaplan-Meier method and compared with the log-rank test.

Differences between the results of comparative tests were considered significant if the two-sided P value was less than 0.05. All statistical analyses were performed using the Statistical Application System software (SAS, version 9.1.3, SAS institute, Cary, NC).
Results

Patients of the planned interim analysis evaluable for PET analysis

One hundred and thirteen patients were enrolled in 45 centres and randomized between October 2007 and April 2009. Their characteristics are detailed in the table 1. Two patients were removed from the study before treatment due to the investigator’s decision (n=1) and the patient’s consent withdrawal, 2 were prematurely withdrawn due to treatment toxicity before any PET restaging and 7 completed induction treatment without performing PET2 (n=2), PET4 (n=1) or both (n=4), leaving 102 patients (90%) evaluable for PET analysis. With a median follow-up of 19 months (range: 3-28), 20 patients progressed of whom 11 died from disease progression and 2 additional patients died without progression.

PET2 analysis

Among the 102 patients who underwent PET2 examination, PET2 was negative in 40 (39%) and positive in 62 (61%) patients according to the on-site interpretation while central review concluded to 35 (34%) negative and 67 (67%) positive cases. So central review was in agreement with the on-site interpretation in 89% of cases (Table2) leading to a Kappa coefficient of 0.769 (0.64-0.898, 95%CI). PET was assessed by both visual and ΔSUVmax analysis for 85 of these 102 patients (Table1). For the 17 remaining patients, ΔSUVmax calculation was impossible due to the lack of images with attenuation correction in 2 cases or some PET technical data in 15 cases, including errors in the recorded 18F-FDG injected activity. After cycle 2, the median SUVmax was 3.1 (range: 1.3-16.2) corresponding to a median ΔSUVmaxPET0-2 of 81.4% (range: 21.3-96.5). Seventy (82%) patients of whom 25 were PET2 negative displayed a ΔSUVmaxPET0-2>66% (Table3). Forty-five (78%) of the 58 PET2 positive patients achieved a ΔSUVmaxPET0-2>66%. Inversely, only 2 of the 15 patients (18%) with ΔSUVmaxPET0-2≤66% had negative PET2 according to visual criteria. These 2 patients had low baseline SUVmax of respectively 3.8 and 4.9.
PET4 analysis

At the end of induction treatment, 98 (96%) patients underwent PET4 examination. PET4 was negative according to on-site and review board interpretation for respectively 56 (57%) and 50 (51%) patients (Table2). Review was in agreement with on-site conclusions in 92% of cases, leading to a Kappa coefficient of 0.836 (0.728-0.945, 95%CI).

After cycle 4, the median SUVmax was 2.5 (range: 1–19) for the 84 assessable patients corresponding to a median ΔSUVmaxPET0-4 of 85.7% (range: 20–97.1). Seventy-four patients (88%) including 41 (55%) who had a negative PET4, achieved a ΔSUVmaxPET0-4>70% (Table3). Thirty-three (80%) of the 41 PET4 positive patients showed a ΔSUVmaxPET0-4>70%. Again, among the 10 patients (12%) with a ΔSUVmaxPET0-4≤70%, PET4 was considered negative in the 2 cases with low baseline SUVmax (3.8 and 4.9).

Ten patients who had a positive PET4 underwent a biopsy of the residual hypermetabolic mass. In two cases the biopsy showed an active lymphoma disease and was associated to a ΔSUVmaxPET0-4≤70%. The remaining 8, all with a ΔSUVmaxPET0-4>70% had no evidence of lymphoma.

PFS and OS according to PET2 results

PET2 results assessed by visual analysis according to IHP criteria had no influence on PFS (Figure 2A) and OS (p=0.5861 and p=0.336 respectively): the 2-year estimate for PFS and OS were 73% and 93% respectively for patients with a negative PET2 compared to 77% and 84% for patients achieving a positive PET2. Similar results were observed with Deauville criteria: the 2-year PFS estimate for patients with a PET2 residual mass showing a FDG uptake higher than the liver was 79% compared to 88% (p=0.825) for patients with a lower uptake. Conversely, ΔSUVmaxPET0-2 identified 2 groups of patients with significantly different PFS (p=0.0282; Figure 2B) and OS (p<0.0001): the 2-year estimate for PFS and OS were 57% and 60% respectively for patients with a ΔSUVmaxPET0-2≤66%, compared to 77% and 93% for patients achieving a ΔSUVmaxPET0-2>66%. Patients who remained PET2
positive and had a $\Delta{\text{SUVmaxPET0-2}} \leq 66\%$ had a significantly poorer PFS ($p=0.014$) (Figure 2C) and OS ($p<0.0001$; data not shown), than patients having a negative PET2 or achieving a $\Delta{\text{SUVmaxPET0-2}} > 66\%$.

**PFS and OS according to PET4 results**

Patients with visual positive PET4 according to IHP criteria had a trend to poorer outcome than patients achieving a negative PET4 both in term of PFS ($p=0.0615$) (Figure 3A) or in OS ($p=0.054$): the 2-year estimate for PFS and OS were 73% and 83% for PET4 positive patients and 81% and 94% for PET4 negative patients. Using the Deauville criteria, the trend was similar with a 69% 2-year PFS estimate for patients with a PET4 residual mass showing a FDG uptake higher than the liver compared to 82% ($p=0.065$) for patients with a lower uptake. $\Delta{\text{SUVmaxPET0-4}}$ ($>70\%$ $v \leq 70\%$) was more accurate to identify patients with significantly different 2-year PFS (83 $v$ 40%) or OS (94% $v$ 50%) ($p<0.0001$ for both): the median PFS and OS were 5 and 13 months respectively for patients with $\Delta{\text{SUVmaxPET0-4}} \leq 70\%$, and were not reached for patients achieving a $\Delta{\text{SUVmaxPET0-4}} > 70\%$ (Figures 3B).

Six of the 8 patients who remained PET4 positive with a $\Delta{\text{SUVmaxPET0-4}} \leq 70\%$ relapsed within 8 months of diagnosis of whom 5 died of progression, while patients with a $\Delta{\text{SUVmaxPET0-4}} > 70\%$ or a negative PET had a 2-year PFS of more than 90% (Figures 3C).

**Impact of post-induction therapy on PFS according to PET results**

Using IHP criteria, 2-year PFS was similar in the groups of patients who received ASCT or sequential consolidation but significantly worse for PET4 positive patients given salvage therapy ($p=0.0065$; Figure 4A). Using $\Delta{\text{SUVmax}}$, patients with $\Delta{\text{SUVmaxPET0-2}} \leq 66\%$ given consolidative ASCT and patients with $\Delta{\text{SUVmaxPET0-4}} \leq 70\%$ given salvage therapy had a significantly worse PFS than patients with $\Delta{\text{SUVmaxPET0-2}} > 66\%$ (53% $v$ 100%; $p=0.0164$) and patients with $\Delta{\text{SUVmaxPET0-4}} > 70\%$ (0% $v$ 83%; $p<0.0001$) given the same post induction therapy, respectively (Figure 4B).
Discussion

The present analysis on 85 patients enrolled in a prospective multicenter trial with central PET assessment shows that semiquantitative analysis using ΔSUVmax after 2 and 4 courses of induction treatment better predicts PFS and OS than visual analysis based on IHP criteria. Visual analysis produced an excess of positive results for PET2 and PET4 leading to a poor predictive value for PFS and OS. With ΔSUVmax analysis, 78% PET2 positive and 80% PET4 positive patients had a ΔSUVmax over the cut-off value and a favourable 2-y PFS estimate of 77% and 83%, respectively. Thus, these patients classified as poor responders to immuno-chemotherapy according to visual analysis were indeed good responders and identified as such by ΔSUVmax analysis. Interestingly, the 80% PET4 positive patients reclassified as good responders using ΔSUVmaxPET0-4 in our series is consistent with the 87% patients with false positive PET4 based on visual analysis in the study by Moskowitz et al.8.

The ΔSUVmax cut-off values estimated by ROC analysis and used to distinguish good and bad responders were similar in our series to those previously reported in independent cohorts either after 2 or 4 cycles of induction treatment10,11,16. Thus these thresholds appear to be robust and reproducible regardless of age and IPI in DLBCL patients treated with either CHOP or CHOP-like regimen combined or without Rituximab.

The disappointing positive predictive value of early PET using modified IHP criteria was not related to discrepancies between readers since the reproducibility between on-site and centralized PET interpretation was quite satisfactory, with respectively a good and a very good agreement for PET2 and PET4, according to k statistic. The agreement between readers appears to be much better in our study than the one observed by Horning10. Moreover, in our series the few discrepancies between on-site and experts readers were overcome by using a real-time PET review process. Another hypothesis would be that post-induction may have impacted outcome, especially high dose therapy which may have improved outcome of PET2 positive patients, thereby erasing the predictive value of visual
PET. However, patients who received ASCT or sequential consolidation had similar PFS. Moreover, PET2 positive patients who received high dose consolidative therapy, and PET4 positive patients who received salvage therapy still could be split into good and poor prognostic subsets using △SUVmax (Figure 4B).

False positive results based on visual PET assessment could proceed from numerous other reasons. First, FDG uptake is not specific for lymphoma cells and can also be observed as well in inflammatory as infectious processes or after bone marrow stimulation. However, with the same tracer, semiquantitative analysis reduces dramatically the risk of attributing a positive result to residual lymphoma. In our series, the 8 PET4 positive patients who achieved a △SUVmaxPET0-4>70% and underwent a biopsy of the residual hypermetabolic mass, had no evidence of lymphoma. Also, the mediastinal blood pool area or the nearby background might not be the optimal reference background to visually compare the residual uptake in early PET. The liver could be a better reference background and was shown to generate less false positive PET2 results. However the Deauville criteria applied to our series did not significantly improve the accuracy of PET to identify subgroups of patients with different outcome. In fact, visual assessment may lead to inaccurate interpretations regardless of the background tissue used, specifically when the unique minimal residual FDG uptake on restaging PET is close to that of the reference tissue and also in case of residual tumor with a size around two centimetres. In all these different situations, △SUVmax calculation is less subjective and helps distinguish which positive results may be related to significant residual lymphoma and impacts outcome.

To a lesser extent △SUVmax analysis can also generate false positive results. This occurred in 2 patients, when baseline SUVmax was low, leading to a △SUVmax lower than the defined cut-off value. Both cases were easily identified since PET2 and PET4 were negative according to visual analysis. The main drawback of the △SUVmax analysis is related to the absolute requirement of a baseline PET to allow a △SUVmax calculation. This could be a concern in high-risk DLBCL patients who need a pressing treatment, specifically in a
multicenter trial setting. In this prospective trial, cooperation between the hematologists and
the nuclear medicine physicians was good and PET0 requirement did not bias recruitment
since even patients with clinical features requiring urgent treatment such as bulk (18%) or
poor PS (24%) were enrolled (Table 1). In a multicenter trial setting, a last restriction to
perform a quantitative PET assessment remained the quality of technical data transmitted to
allow the SUVmax calculation and specifically, the weight of the patient at time of PET
examination and the injected activity of \(^{18}\text{F-FDG}\) are critical. In this study some of these data
were lost during either the data anonymization process or the data loading from on-site to
review panel computers due to software bugs.

With a median follow-up of 19 months, \(\Delta\text{SUV}_{\text{maxPET0-4}}\) analysis allowed to pick out the
worst group of patients who experienced induction failure or early relapse. Most progressive
diseases were identified before the 6th month after randomization, suggesting a weak impact
of consolidative high dose therapy and conventional salvage strategies in these poor-risk
patients, as reported in the CORAL study\textsuperscript{18}. Thus, \(\Delta\text{SUV}_{\text{maxPET0-4}}\) seems to be a good
way to identify patients who could be candidate to alternative experimental strategy after
induction treatment. Conversely, longer follow-up is needed to conclude on the value of
\(\Delta\text{SUV}_{\text{maxPET0-2}}\) in the context of the risk adapted consolidative therapy. Also, the value of
analysing sequential interim PET and the impact on outcome of the kinetic of response
remains to be examined and will be presented at the final analysis of the LNH2007-3B trial,
in the whole population and in each induction treatment arm.

In conclusion, these encouraging results, suggest the use of \(\Delta\text{SUV}_{\text{max}}\) in addition to visual
analysis to interpret interim PET for DLBCL patients, specifically when a therapeutic decision
is to be guided by interim PET results. Longer follow-up and analysis of the whole trial
population is warranted to confirm the role of sequential interim PET in the context of the risk
adapted consolidation treatment.
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Contribution

ROC and FM were responsible for the conduct of the study and drafted the report which all co-authors critically revised for significant scientific content.


ROC, MM, ABR, JPJ, CH, FM contributed to data analysis and interpretation.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

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References


Tables and figures

Table 1: Patients characteristics

Table 2: Agreement between on-site and review board conclusions for PET2 and PET4 visual assessment

Table 3: PET results according to visual and SUVmax reduction assessment

Figure 1: Scheme of the treatment according to the LNH2007-3B trial

Figure 2: Progression free survival of 85 patients according to:
- PET2 visual assessment (positive versus negative), Panel A
- SUVmax reduction between PET0 and PET2 (>66% versus ≤ 66%), Panel B
- PET2 analysis combining visual and quantitative assessment, Panel C

Figure 3: Progression free survival of 84 patients according to:
- PET4 visual assessment (positive versus negative), Panel A
- SUVmax reduction between PET0 and PET4 (>70% versus ≤70%), Panel B
- PET4 analysis combining visual and quantitative assessment, Panel C

Figure 4: Impact of post-induction treatment on patients’ progression free survival according to:
- PET driven post-induction treatment, Panel A
- PET driven post-induction treatment and SUVmax reduction analysis, Panel B
### Table 1

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Figure 1:
Figure 2

A

B

C
Figure 3

A

B

C
Figure 4

A

B

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SUVmax reduction improves early prognosis value of interim positron emission tomography scans in diffuse large B-cell lymphoma

René-Olivier Casasnovas, Michel Meignan, Alina Berriolo-Riedinger, Stéphane Bardet, Anne Julian, Catherine Thieblemont, Pierre Vera, Serge Bologna, Josette Brière, Jean-Philippe Jais, Corinne Haioun, Bertrand Coiffier and Franck Morschhauser