

# Impact of [<sup>18</sup>F]Fluorodeoxyglucose Positron Emission Tomography Response Evaluation in Patients With High-Tumor Burden Follicular Lymphoma Treated With Immunochemotherapy: A Prospective Study From the Groupe d'Etudes des Lymphomes de l'Adulte and GOELAMS

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See accompanying editorial on page 4285

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## A B S T R A C T

### Purpose

[<sup>18</sup>F]Fluorodeoxyglucose positron emission tomography (PET) is widely used for the staging and restaging of patients with aggressive lymphoma, but less is known about the utility of PET in patients with follicular lymphoma (FL). In a prospective study, we evaluated the prognostic value of PET performed during treatment and at the end of treatment in 121 patients with FL treated with first-line immunochemotherapy.

### Patients and Methods

Patients with previously untreated high-tumor burden FL were treated with six cycles of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) plus two cycles of rituximab, without rituximab maintenance. PET was performed before treatment, after four cycles of R-CHOP (interim PET), and at the end of treatment (final PET). PET scans were centrally reviewed.

### Results

The total number of patients included was 121. Median age was 57 years. After central review, interim PET (n = 111) was negative in 76% of patients, and final PET (n = 106) was negative in 78%. With a median follow-up of 23 months, 2-year progression-free survival rates were 86% for interim PET-negative versus 61% for interim PET-positive patients (P = .0046) and 87% for final PET-negative versus 51% for final PET-positive patients (P < .001), respectively. Two-year overall survival also significantly differed according to final PET results: 100% versus 88% (P = .0128).

### Conclusion

PET performed either after four cycles of R-CHOP or at the end of therapy was strongly predictive of outcome in this prospective study. Therapeutic intervention based on PET results during or after inductive treatment should be evaluated.

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## INTRODUCTION

Follicular lymphoma is the second most common non-Hodgkin lymphoma subtype. Although a slowly evolving form of cancer associated with long survival times, it remains incurable. No consensus exists regarding optimal initial therapy, but rituximab combined with chemotherapy is a widely recognized standard of care in high-tumor burden patients.<sup>1-4</sup> Although initially associated with high response rates, this approach is followed by a continuous relapse pattern, with a median

time to progression of approximately 4 years in patients receiving R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone).<sup>5</sup> Response duration is related to quality of response.<sup>6</sup> Some patients either do not respond or relapse early after therapy and have a particularly dismal outcome. Early identification of this subgroup of patients could lead to early therapeutic changes and potentially to a better prognosis.

[<sup>18</sup>F]Fluorodeoxyglucose (FDG) positron emission tomography (PET) is a widely employed

method of metabolic imaging. In both Hodgkin and diffuse large B-cell lymphoma (DLBCL), residual abnormalities on PET after treatment are associated with an unfavorable outcome, and PET-response adapted therapy is being explored as a means of improving outcomes.<sup>7</sup> The International Harmonization Project (IHP) recommendations provide guidelines for PET imaging and response criteria for end-of-treatment evaluation in Hodgkin and DLBCL, but they do not recommend use of PET in follicular lymphoma outside of clinical trials.<sup>8,9</sup> The so-called Deauville criteria were specifically developed for the interpretation of PET performed early during the course of therapy.<sup>10</sup>

Follicular lymphoma is almost always FDG avid, irrespective of tumor grade.<sup>11-14</sup> Several studies have shown an adverse prognostic impact of positive post-therapeutic PET in patients with follicular lymphoma.<sup>15-18</sup> However, these were small retrospective studies performed in heterogeneously treated patients, without homogeneous PET interpretation criteria. More recently, a study performed in 122 patients from the PRIMA (Primary Rituximab and Maintenance) trial indicated that at the end of initial treatment, positive PET (according to review of local investigators' conclusions) was associated with a two-fold decrease in progression-free survival (PFS; 32.9% v 70.7% at 42 months).<sup>19</sup> However, this study was retrospective, and PET scans were not centrally reviewed.

The study presented herein is the first prospective study to our knowledge aiming to evaluate the prognostic value of PET in patients with high-tumor burden follicular lymphoma treated with first-line R-CHOP midtreatment (after four cycles) and at the end of therapy, with a centralized review of all PET scans.

## PATIENTS AND METHODS

This nonrandomized study was undertaken between September 2007 and November 2009 in one Italian and 13 French centers. Patients received four cycles of R-CHOP plus two cycles of R-CHOP and two cycles of rituximab in case of response based on conventional criteria (partial response [PR] or complete response [CR]/unconfirmed complete response [CRu]). They were evaluated before therapy, after four R-CHOP cycles, and at the end of therapy by conventional methods (clinical examination, computed tomography [CT] scan, and bone marrow biopsy) and PET. Physicians were required not to modify therapy according to PET results. However, they were not blinded to the results of local PET interpretation.

### Study Objectives

The primary objective was to compare PFS according to PET review board conclusion at cycle four and at the end of treatment. PFS was defined as the delay between inclusion and date of first documented evidence of progressive disease, relapse, or death resulting from any cause. The primary end point was used to determine sample size; in the FL (Follicular Lymphoma) 2000 trial, the estimated 2-year PFS was 80%.<sup>3</sup> Assuming that 33% patients would have a positive PET, 2-year PFS can be estimated at 65% for PET-positive patients and 90% for PET-negative patients; assuming that the distributions would be exponential, if we wished to detect a change in 2-year PFS from 65% to 90% between groups, 24 events would have to be observed to provide 90% power at the overall 5% (two sided) significance level. Recruiting 120 patients over 2 years, the last included patient should undergo follow-up for 18 months to observe the desired number of events.

### Patients

Patients were eligible if they were between 18 and 80 years of age and had untreated follicular lymphoma (grade 1, 2, or 3A) diagnosed by lymph node biopsy (performed within 4 months of study registration). Eligibility required at least one criterion of high tumor burden, namely: bulky disease

(one lesion > 7 cm), three separate nodes  $\geq$  3 cm, symptomatic splenomegaly, organ compression by tumor, pleural or peritoneal effusion, raised serum lactate dehydrogenase or  $\beta_2$ -microglobulin, or B symptoms.<sup>20</sup> Patients had to have Eastern Cooperative Oncology Group performance status of  $\leq$  2<sup>21</sup> and adequate hematologic function (unless poor function resulted from lymphoma).

Key noneligibility criteria were: diagnosis of follicular lymphoma grade 3B or transformation into DLBCL, CNS involvement, life expectancy < 6 months, history of cancer (apart from adequately treated nonmelanoma skin cancer or in situ cervical cancer), and poor renal or hepatic function (except as a result of lymphoma). Patients with known HIV infection or active hepatitis B or C virus infection were also excluded.

The study was approved by the ethics committee (Comité de Protection des Personnes) of Paris IX-Créteil and was undertaken in accordance with the Declaration of Helsinki. Patients were required to provide informed consent before registration.

### Treatment

Patients were to receive R-CHOP (rituximab 375 mg/m<sup>2</sup> intravenously on day 1, cyclophosphamide 750 mg/m<sup>2</sup> intravenously on day 1, vincristine 1  $\times$  4 mg/m<sup>2</sup> [capped at 2 mg] intravenously on day 1, doxorubicin 50 mg/m<sup>2</sup> intravenously on day 1, and prednisone 40 mg/m<sup>2</sup> orally on days 1 to 5, every 3 weeks) for six cycles, plus two additional cycles of rituximab 375 mg/m<sup>2</sup> every 3 weeks. Four patients received an antiangiogenic agent in addition to R-CHOP in the setting of a separate phase Ib/II trial.<sup>22</sup> No form of maintenance treatment was planned.

### Response Evaluation and PET Scan Modalities

Responses according to conventional diagnostic methods were qualified by each investigator in accordance with the 1999 International Workshop Criteria (IWC).<sup>23</sup> No central reviews of bone marrow biopsies or CT scans could be planned in this study because of cost constraints; thus, conventional responses were based on investigator conclusion. After the end of treatment, patients were observed on a regular basis (clinical examination every 3 months and CT scan every 6 months during the first 2 years), and investigators were requested to deliver information on patient outcome on a 6-month basis.

PET was performed in each center on a dedicated PET scanner according to standardized modalities, taking into account the technical characteristics of each camera. Patients fasted for at least 6 hours before each scan and had to have a blood glucose concentration < 10 mmol/L. They were administered intravenous injections of 3.5 to 8 MBq/kg (minimal activity, 185 MBq) FDG and were asked to lie in supine position for 1 hour to avoid muscular uptake. Imaging was performed to cover a volume starting from the upper thigh to the skull base. Images were reconstructed iteratively with and without attenuation correction. PET quality control (regular testing of image quality performed by a qualified physicist as recommended by the SFPMP [French Society of Medical Physics]) was required from each center.

Central review was performed by three experienced nuclear medicine physicians (A.B.-R., A.J., M.M.) on a Positroscope workstation (Kéosys, Saint-Herblain, France).<sup>24</sup> Differences between observers were resolved by majority view. PET results were reported using the Deauville 5-point scale.<sup>10</sup> Two different thresholds were compared to define positivity and negativity: residual activity greater than the liver activity (scores 4 and 5 on 5-point scale), and residual activity greater than the mediastinal blood pool (scores 3, 4, and 5 on 5-point scale).

### Statistical Analysis

Quantitative variables were summarized in tables displaying sample size, mean, standard deviation, median, and range. Qualitative variables were described in terms of percentages of the number of patients examined.

Censored data were presented as Kaplan-Meier plots of time to first event and summary tables of Kaplan-Meier estimates for criterion rates at fixed time points, with 95% CIs.<sup>25</sup> For the primary criterion, survival end points were analyzed using the log-rank test. Estimates of prognostic factors were expressed as hazard ratios based on the Cox proportional hazards model with 95% CIs.<sup>26</sup> All statistical tests were two sided and performed using a 5% level of

**Table 1.** Main Baseline Demographics and Clinical Characteristics\*

Characteristic	No.	%
Age, years		
Median	57	
Range	28-76	
≥ 60	54	45
Male sex	63	53
Ann Arbor stage III/IV	110 of 118	93
ECOG performance status ≥ 1	47 of 117	40
B symptoms	21	18
Bone marrow lymphoma involvement	64 of 109	58
Lactate dehydrogenase > ULN	31 of 117	26
Hemoglobin < 120 g/L	23	19
> Four nodal areas	68	57
β <sub>2</sub> -microglobulin ≥ 3 mg/L	26 of 84	31
FLIPI score		
Low (none to one risk factors)	17 of 116	15
Intermediate (two risk factors)	50 of 116	43
High (three to five risk factors)	49 of 116	42
Initial local diagnosis of FL (other than grade 3B)	119	100
Central pathologic review performed	109	91
Confirmed FL (other than grade 3B)	97	88
Diagnosis of other lymphoma subtype†	4	4
Unclassifiable or not assessable for technical reasons	8	8

Abbreviations: ECOG, Eastern Cooperative Oncology Group; FL, follicular lymphoma; FLIPI, Follicular Lymphoma International Prognostic Index; ULN, upper limit of normal.  
 \*N = 119 unless otherwise indicated.  
 †Transformed (n = 3); aggressive B cell, unclassifiable (n = 1).

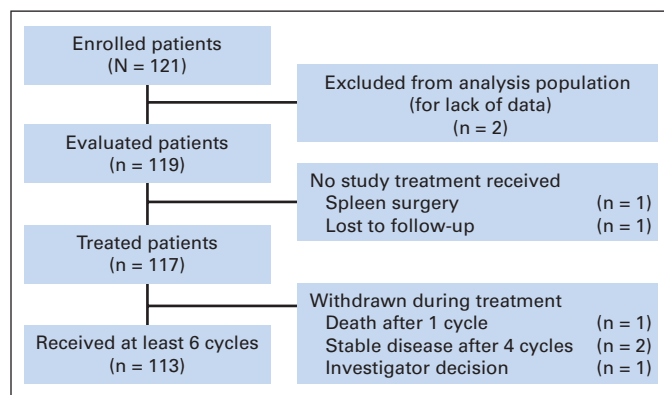


Fig 1. Trial profile.

and only 106 received the second one, mainly because of investigator decision.

**PET Scan Conclusions**

The initial PET scan was available for 117 treated patients. Only one initial PET was considered negative (no significant uptake above background). At cycle four, one patient had no PET review because of early death, and five had no review because of absence of adequate data transfer to reviewers. Of 111 centrally reviewed patients, 84 (76%) had a negative PET at the intermediate assessment. Eleven patients had no end-of-treatment PET review: four because PET was not performed on investigator decision, and seven because of inadequate data transfer to reviewers. Of 106 centrally reviewed end-of-treatment PETs, 83 (78%) were considered negative.

Among those reviewed, 104 patients had complete data available at cycles four and eight. With a cutoff value of ≥ 4 to define PET positivity, among 78 patients with a negative PET at cycle four, 72 (92%) remained negative at end-of-treatment evaluation, but six (8%) reverted to positive at the end of treatment. On the other hand, nine of 26 positive patients at cycle four became negative; however, 17 (65%) of 26 remained positive.

**Concordance Among Conclusions of Review Board Members**

The mean κ coefficient between the three observers was calculated for each PET interpretation according to the chosen level of positivity: The mean κ coefficient was 0.707, corresponding to a good level of agreement (values > 0.7 are usually considered satisfactory) when using liver activity as a threshold level. When using mediastinal blood pool activity as a threshold to define positivity, the mean κ coefficient was compatible with a moderate level of agreement, with a value of 0.57.

**Concordance in Response Designations Between 1999 IWC and PET at the End of Treatment**

At end of treatment, 104 patients had both a centrally reviewed PET and a formal response designation according to IWC. On the basis of IWC, 54 had achieved CR; 20, CRu; 26, PR; and three, stable disease, whereas one had experienced disease progression. As expected, only one (2%) of 54 patients achieving CR had a positive PET. However, 50% of patients (10 of 20) achieving CRu and 34% of patients (nine of 26) achieving PR still had a positive

significance. Agreement between PET conclusions was assessed by simple κ coefficient calculation.<sup>27</sup>

**RESULTS**

A total of 121 patients were enrolled onto this study from September 18, 2007, to November 18, 2009. On review, seven patients did not fulfill the criteria for high tumor mass, although they had been deemed as requiring treatment by the investigator.

**Demographic and Other Baseline Characteristics**

The median age of the study population was 57 years, and 63% of patients were men. The main baseline characteristics are summarized in Table 1.

The study is summarized in Figure 1: Two patients were excluded from the full analysis set because of lack of data. Two patients did not receive any study treatment and were thus excluded from the intent-to-treat analysis: One patient had to undergo urgent splenectomy because of splenic rupture resulting from lymphoma, and the other was lost to follow-up before receiving any study treatment. Thus, 117 analyzable patients received at least one treatment cycle. One patient died as a result of infectious complications after the first cycle. The other 116 patients completed the first four treatment cycles. Three patients did not continue with planned treatment after four cycles because of insufficient response (stable disease; n = 2) or investigator decision (n = 1). Six cycles of R-CHOP were administered to 113 patients, but only 107 received the first additional rituximab injection,

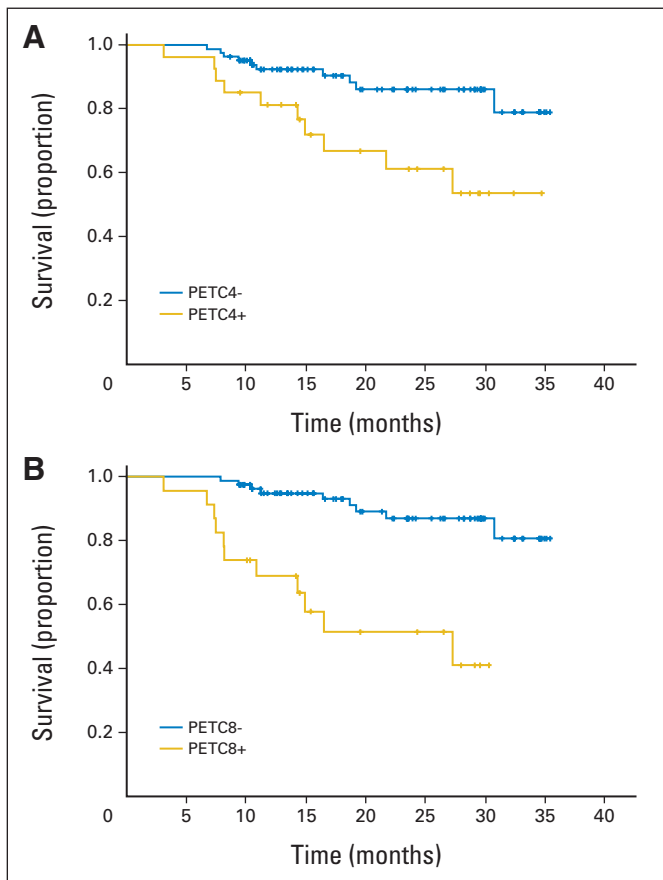
PET at the end of treatment. Overall, 21 (20%) of 104 patients had discordant response designations, and 83 (80%) of 104 had concordant designations.

### Survival Analysis

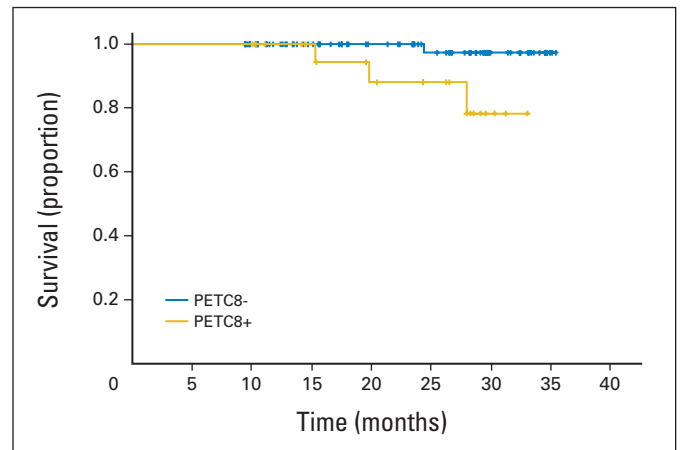
With date of last contact censored at stopping date (most recent date with 10% of patients presenting with an earlier date of last contact), the median duration of follow-up for the intent-to-treat population was 23 months. The estimated 2-year PFS for the whole population is 79.6%, and the estimated 2-year overall survival (OS) is 96.4%.

Using liver activity as a threshold to define positivity (scores 4 and 5 of 5-point scale) allowed the best separation in terms of prognosis (data not shown). Results are thus given using the following criteria. PFS differed significantly according to the results of both PET performed after four cycles and at the end of treatment. The estimated PFS at 2 years was 86% in patients with a negative PET at cycle four versus 61% in those with a positive PET ( $P = .0046$ ) and 87% in patients with a negative PET at the end of treatment versus 51% in those with a positive PET ( $P < .001$ ; Fig 2).

Two-year OS also significantly differed according to final PET results: 100% versus 88% ( $P = .0128$ ), whereas the results of the PET performed at cycle four did not have a significant impact on OS (Fig 3).



**Fig 2.** Progression-free survival according to positron emission tomography (PET) review at (A) four cycles and (B) eight cycles (threshold  $\geq 4$ ). PETC4-, negative PET scan at four cycles; PETC4+, positive PET scan at four cycles; PETC8-, negative PET scan at eight cycles; PETC8+, positive PET scan at eight cycles.



**Fig 3.** Overall survival according to final positron emission tomography (PET) review at eight cycles (threshold  $\geq 4$ ). PETC8-, negative PET scan at eight cycles; PETC8+, positive PET scan at eight cycles.

Standard response evaluation using 1999 IWC criteria was less proficient in predicting PFS than response evaluation with PET. Two-year PFS was 67.7% for patients achieving PR according to 1999 IWC criteria, compared with 83.2% for patients achieving CR or CRu ( $P = .1063$ ).

Patients who had a positive PET at four cycles and eventually converted to a negative PET ( $n = 9$ ) did not have a significantly different PFS than those for whom both examinations were negative ( $n = 72$ ; 2-year PFS, 72.9%  $\nu$  88.9%). Those patients who converted from a negative PET at four cycles to a positive end-of-treatment PET ( $n = 6$ ) had, on the other hand, a PFS that did not significantly differ from that of patients for whom both examinations were positive ( $n = 16$ ; 2-year PFS, 33.3%  $\nu$  51.9%). Three of these patients had histologic or cytologic disease transformation at relapse.

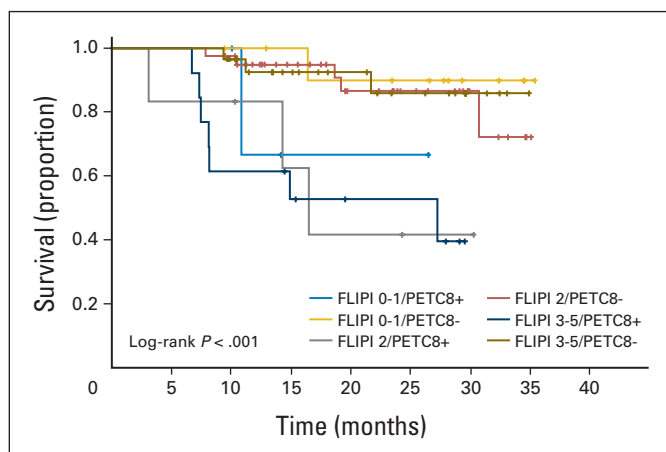
PFS and OS did not differ significantly according to FLIPI (Follicular Lymphoma International Prognostic Index), either when considering three categories or when considering only two groups (0 to 2  $\nu$  3 to 5; data not shown). The influence of PET results on PFS was observed within each subgroup according to FLIPI (Fig 4).

## DISCUSSION

This study confirms the prognostic value of PET in patients with follicular lymphoma, which has already been suggested by several retrospective studies.<sup>15-19</sup> This prognostic value is maintained whatever the FLIPI category. Although there is no firm consensus on the optimal first-line regimen in high-tumor burden follicular lymphoma, the R-CHOP regimen used in this study is a widely used option chosen by 73% of investigators in the PRIMA trial<sup>5</sup> and by 55% of physicians choosing rituximab plus chemotherapy as a treatment option in the US National LymphoCare Study.<sup>28</sup> Our conclusions should be extended to patients treated with other approaches with caution, but the prognostic role of a positive PET has also been suggested for patients treated with radioimmunotherapy.<sup>29</sup>

None of our patients received maintenance treatment with rituximab, which has been shown to provide a PFS benefit in patients treated in the first line.<sup>5</sup> In the retrospective analysis of PET scans





**Fig 4.** Progression-free survival according to Follicular Lymphoma International Prognostic Index (FLIPI) score and final positron emission tomography (PET) review. PETC8+, positive PET scan at eight cycles; PETC8-, negative PET scan at eight cycles.

performed at the end of treatment in the PRIMA trial, a nonsignificant inferior PFS was observed in nine PET-positive patients among 47 receiving maintenance (55.6% v 77.4%;  $P = .18$ ).<sup>19</sup> It was not expected that the PFS values observed in our study would be similar to those observed in the PRIMA study, given the fact that half of these patients received maintenance rituximab. This might in part be related to shorter follow-up. The prognostic value of PET in patients with follicular lymphoma should be studied prospectively in the future in patients receiving maintenance rituximab.

In our study, response evaluation with PET had a superior predictive power than investigator-assessed IWC response. However, almost every patient achieving CR according to IWC also achieved metabolic CR by PET (53 of 54 patients; Table 2); thus, PET could be reserved for patients who have not reached CR.

On the whole, these results strongly support moving away from response criteria that are based solely on CT, as recommended in the 2007 IHP for patients with Hodgkin lymphoma or DLBCL.<sup>9</sup> In our opinion, end-of-treatment response evaluation by PET/CT should be included in future first-line follicular lymphoma trials. Using the Deauville 5-point scale for PET interpretation, defining positivity with a threshold of  $\geq 4$ , provided the best separation in terms of PFS at the

end of treatment. Interestingly, a significant separation in terms of PFS was also found using a lower cutoff ( $\geq 3$ ;  $P < .001$ ), which is roughly equivalent to using standard end-of-treatment IHP criteria (same reference background to define PET positivity). However, because using a threshold of  $\geq 4$  provided the best levels of concordance among observers, it seems logical to propose this cutoff value for future studies.

PET is able to provide a meaningful surrogate for PFS in this patient population, allowing for future exploration of response-adapted treatment strategies in follicular lymphoma, as they are now under investigation in patients with other lymphoma subtypes.<sup>30,31</sup>

Evaluation by PET before four cycles, as has been evaluated in other lymphoma subtypes, has to the best of our knowledge never been evaluated in patients with follicular lymphoma. PET scans performed both after four cycles of therapy and at the end of treatment were able to predict PFS, but approximately 15% of patients (15 of 104) had discordant results between interim and final PET results, and interim PET was not predictive of OS in this study. Thus, on the basis of our data, we would suggest waiting until the end of induction treatment before performing PET and deciding on eventual treatment modifications.

High-dose therapy with stem-cell transplantation has been abandoned in the first line because its benefits in terms of PFS were counterbalanced by excessive late toxicity. However, it remains a frequently used option in relapsed patients, for whom it seems to offer better outcomes.<sup>32</sup> Such an approach obviously represents an appealing strategy in post-therapy PET-positive patients. Other approaches, such as using new drugs (eg, lenalidomide and so on) as maintenance therapy in PET-positive patients, also seem particularly attractive.

#### AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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**Manuscript writing:** All authors

**Final approval of manuscript:** All authors

**Table 2.** Concordance in Response Designations Between International Workshop Criteria and PET at the End of Treatment

Response	PET Review Board Conclusion (No. of patients)		Total
	Negative	Positive	
Complete response	53	1	54
Unconfirmed complete response	10	10	20
Partial response	17	9	26
Stable disease	1	2	3
Progressive disease	0	1	1
Not evaluated	2	0	2
<b>Total</b>	<b>83</b>	<b>23</b>	<b>106</b>

Abbreviation: PET, positron emission tomography.

## REFERENCES

1. Marcus R, Imrie K, Solal-Celigny P, et al: Phase III study of R-CVP compared with cyclophosphamide, vincristine, and prednisone alone in patients with previously untreated advanced follicular lymphoma. *J Clin Oncol* 26:4579-4586, 2008
2. Herold M, Haas A, Srock S, et al: Rituximab added to first-line mitoxantrone, chlorambucil, and prednisolone chemotherapy followed by interferon maintenance prolongs survival in patients with advanced follicular lymphoma: An East German Study Group Hematology and Oncology Study. *J Clin Oncol* 25:1986-1992, 2007
3. Salles G, Mounier N, de Guibert S, et al: Rituximab combined with chemotherapy and interferon in follicular lymphoma patients: Results of the GELA-GOELAMS FL2000 study. *Blood* 112:4824-4831, 2008
4. Hiddemann W, Kneba M, Dreyling M, et al: Frontline therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) significantly improves the outcome for patients with advanced-stage follicular lymphoma compared with therapy with CHOP alone: Results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. *Blood* 106:3725-3732, 2005
5. Salles G, Seymour JF, Offner F, et al: Rituximab maintenance for 2 years in patients with high tumour burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA): A phase 3, randomised controlled trial. *Lancet* 377:42-51, 2011
6. Bachy E, Brice P, Delarue R, et al: Long-term follow-up of patients with newly diagnosed follicular lymphoma in the prirituximab era: Effect of response quality on survival—A study from the groupe d'étude des lymphomes de l'adulte. *J Clin Oncol* 28:822-829, 2010
7. Meignan M, Gallamini A, Haioun C, et al: Report on the Second International Workshop on interim positron emission tomography in lymphoma held in Menton, France, 8-9 April 2010. *Leuk Lymphoma* 51:2171-2180, 2010
8. Juweid ME, Stroobants S, Hoekstra OS, et al: Use of positron emission tomography for response assessment of lymphoma: Consensus of the Imaging Subcommittee of International Harmonization Project in Lymphoma. *J Clin Oncol* 25:571-578, 2007
9. Cheson BD, Pfistner B, Juweid ME, et al: Revised response criteria for malignant lymphoma. *J Clin Oncol* 25:579-586, 2007
10. Meignan M, Gallamini A, Meignan M, et al: Report on the First International Workshop on interim-PET scan in lymphoma. *Leuk Lymphoma* 50:1257-1260, 2009
11. Jerusalem G, Beguin Y, Najjar F, et al: Positron emission tomography (PET) with 18F-fluorodeoxyglucose (18F-FDG) for the staging of low-grade non-Hodgkin's lymphoma (NHL). *Ann Oncol* 12:825-830, 2001
12. Karam M, Novak L, Cyriac J, et al: Role of fluorine-18 fluoro-deoxyglucose positron emission tomography scan in the evaluation and follow-up of patients with low-grade lymphomas. *Cancer* 107:175-183, 2006
13. Wöhrer S, Jaeger U, Kletter K, et al: 18F-fluoro-deoxy-glucose positron emission tomography (18F-FDG-PET) visualizes follicular lymphoma irrespective of grading. *Ann Oncol* 17:780-784, 2006
14. Weiler-Sagie M, Bushelov O, Epelbaum R, et al: (18F)FDG avidity in lymphoma readdressed: A study of 766 patients. *J Nucl Med* 51:25-30, 2010
15. Zinzani PL, Musuraca G, Alinari L, et al: Predictive role of positron emission tomography in the outcome of patients with follicular lymphoma. *Clin Lymphoma Myeloma* 7:291-295, 2007
16. Bishu S, Quigley JM, Bishu SR, et al: Predictive value and diagnostic accuracy of F-18-fluoro-deoxy-glucose positron emission tomography treated grade 1 and 2 follicular lymphoma. *Leuk Lymphoma* 48:1548-1555, 2007
17. Janikova A, Bolcak K, Pavlik T, et al: Value of [18F]fluorodeoxyglucose positron emission tomography in the management of follicular lymphoma: The end of a dilemma? *Clin Lymphoma Myeloma* 8:287-293, 2008
18. Le Dortz L, De Guibert S, Bayat S, et al: Diagnostic and prognostic impact of 18F-FDG PET/CT in follicular lymphoma. *Eur J Nucl Med Mol Imaging* 37:2307-2314, 2010
19. Trotman J, Fournier M, Lamy T, et al: Positron emission tomography-computed tomography (PET-CT) after induction therapy is highly predictive of patient outcome in follicular lymphoma: Analysis of PET-CT in a subset of PRIMA trial participants. *J Clin Oncol* 29:3194-3200, 2011
20. Solal-Celigny P, Lepage E, Brousse N, et al: Recombinant interferon alfa-2b combined with a regimen containing doxorubicin in patients with advanced follicular lymphoma: Groupe d'Etude des Lymphomes de l'Adulte. *N Engl J Med* 329:1608-1614, 1993
21. A predictive model for aggressive non-Hodgkin's lymphoma: The International Non-Hodgkin's Lymphoma Prognostic Factors Project. *N Engl J Med* 329:987-994, 1993
22. Kuhnowski F, Thieblemont C, Jardin F, et al: A phase I study of IV aflibercept (Afl) in combination with R-CHOP in untreated patients (pts) with B-cell lymphoma. *J Clin Oncol* 28:575s, 2010 (suppl 15; abstr 8010)
23. Cheson BD, Horning SJ, Coiffier B, et al: Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas: NCI Sponsored International Working Group. *J Clin Oncol* 17:1244, 1999
24. Meignan M, Itti E, Bardet S, et al: Development and application of a real-time on-line blinded independent central review of interim PET scans to determine treatment allocation in lymphoma trials. *J Clin Oncol* 27:2739-2741, 2009
25. Kaplan E, Meier P: Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 53:457-481, 1958
26. Cox D: Regression model and lifetables. *J R Stat Soc Ser B* 34:187-220, 1972
27. Kramer MS, Feinstein AR: Clinical biostatistics: LIV. The biostatistics of concordance. *Clin Pharmacol Ther* 29:111-123, 1981
28. Friedberg JW, Taylor MD, Cerhan JR, et al: Follicular lymphoma in the United States: First report of the national LymphoCare study. *J Clin Oncol* 27:1202-1208, 2009
29. Lopci E, Santi I, Derenzini E, et al: FDG-PET in the assessment of patients with follicular lymphoma treated by ibrutinomab tiuxetan Y 90: Multicentric study. *Ann Oncol* 21:1877-1883, 2010
30. Casasnovas RO, Meignan M, Berriolo-Riedinger A, et al: SUVmax reduction improves early prognosis value of interim positron emission tomography scans in diffuse large B-cell lymphoma. *Blood* 118:37-43, 2011
31. Gallamini A, Patti C, Viviani S, et al: Early chemotherapy intensification with BEACOPP in advanced-stage Hodgkin lymphoma patients with a interim-PET positive after two ABVD courses. *Br J Haematol* 152:551-560, 2011
32. Le Gouill S, De Guibert S, Planche L, et al: Impact of the use of autologous stem cell transplantation at first relapse both in naive and previously rituximab exposed follicular lymphoma patients treated in the GELA/GOELAMS FL2000 study. *Haematologica* 96:1128-1135, 2011