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End-of-treatment PET/CT predicts PFS and OS in DLBCL after first-line treatment: results from GOYA

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Key Points

- End-of-treatment PET CR is highly prognostic for PFS and OS in DLBCL after first-line immunochemotherapy.
- Meta-analyses are necessary to support the substitution of PET CR for PFS as an effective and practical surrogate end point.

GOYA was a randomized phase 3 study comparing obinutuzumab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) vs standard-of-care rituximab plus CHOP in patients with previously untreated diffuse large B-cell lymphoma (DLBCL). This retrospective analysis of GOYA aimed to assess the association between progression-free survival (PFS) and overall survival (OS) with positron emission tomography (PET)–based complete response (CR) status. Overall, 1418 patients were randomly assigned to receive 8 21-day cycles of obinutuzumab (n = 706) or rituximab (n = 712) plus 6 or 8 cycles of CHOP. Patients received a mandatory fluoro-2-deoxy-D-glucose–PET/computed tomography scan at baseline and end of treatment. After a median follow-up of 29 months, the numbers of independent review committee–assessed PFS and OS events in the entire cohort were 416 (29.3%) and 252 (17.8%), respectively. End-of-treatment PET CR was highly prognostic for PFS and OS according to Lugano 2014 criteria (PFS: hazard ratio [HR], 0.26; 95% confidence interval [CI], 0.19-0.38; $P < .0001$; OS: HR, 0.12; 95% CI, 0.08-0.17; $P < .0001$), irrespective of international prognostic index score and cell of origin. In conclusion, the results from this prospectively acquired large cohort corroborated previously published data from smaller sample sizes showing that end-of-treatment PET CR is an independent predictor of PFS and OS and a promising prognostic marker in DLBCL. Long-term survival analysis confirmed the robustness of these data over time. Additional meta-analyses including other prospective studies are necessary to support the substitution of PET CR for PFS as an effective and practical surrogate end point. This trial was registered at www.clinicaltrials.gov as #NCT01287741.

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Qualified researchers may request access to individual patient–level data through the clinical study data request platform (https://vivli.org/). Additional details on Roche's criteria for eligible studies are available at https://vivli.org/members/ourmembers/. For details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, visit https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm.

The full-text version of this article contains a data supplement.

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Introduction

Although diffuse large B-cell lymphoma (DLBCL) is potentially curable with standard-of-care treatment combining the anti-CD20 antibody rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), patients experiencing disease relapse after first-line therapy have poor outcomes.[1] Therefore, development of new treatments to improve clinical outcomes is an essential aspect of improving patient outcomes. However, inherent to lymphoma registry trials, the commonly used clinical end points require extended study duration to determine efficacy of novel drugs. In clinical studies, median progression-free survival (PFS) or event-free survival is generally not reached by the time of primary analysis; follow-up of at least 2 years is required to determine treatment efficacy. This protracted observation period may be superseded with a faster prognostic surrogate end point for PFS that could be used for accelerated approval of new treatment options, which would provide fast access to efficacious antilymphoma drugs and early termination of the development phase of potentially ineffective drugs.

Positron emission tomography (PET) imaging with fluoro-2-deoxy-D-glucose (FDG), particularly when integrated with PET/computed tomography (CT), has proven a valuable tool for assessment of treatment response, because it can distinguish active lymphoma from residual fibrotic masses.[2] Consequently, FDG PET/CT has played a key role in staging and assessment of response to treatment since the development of revised response criteria for malignant lymphoma (Cheson 2007 criteria),[3] further supported by updated response guidelines[4] incorporating the Deauville 5-point scale as a treatment assessment tool (standard Lugano 2014 criteria).

In small DLBCL cohorts, end-of-treatment PET was found to correlate with patient outcomes, as measured by PFS, event-free survival, and overall survival (OS).[5-9] However, there is a paucity of published data from large-scale phase 2 or 3 clinical trials that could help guide oncology practice on use of end-of-induction PET/CT as a substitute for PFS and potential surrogate marker for outcomes.

GOYA was a phase 3 study comparing obinutuzumab, a glycoengineered type 2 anti-CD20 antibody, plus CHOP (G-CHOP) vs rituximab plus CHOP (R-CHOP) in patients with previously untreated DLBCL. The study did not meet the primary end point, and no difference in PFS was found between G-CHOP and R-CHOP after a median observation of 29 months (28.5% vs 30.2%; hazard ratio [HR], 0.92; 95% confidence interval [CI], 0.76-1.11; $P = .39$).[10] In this prespecified secondary analysis, the objective was to investigate correlation of end-of-treatment FDG PET responses with PFS to provide further evidence for PET complete response (CR) assessed according to Cheson 2007 criteria and PET CR assessed according to standard Lugano 2014 criteria as alternative end points to PFS in DLBCL.

Methods

Study design and participants

GOYA was an open-label, multicenter, randomized phase 3 study. The GOYA study design and patient population have been previously described.[11] In brief, eligible patients were age ≥18 years with previously untreated, histologically documented, $CD20^+$ DLBCL. Patients were randomly assigned 1:1 to receive 8 21-day cycles of obinutuzumab at 1000 mg on days 1, 8, and 15 of cycle 1 and day 1 of cycles 2 to 8 or rituximab at 375 mg/m^2 on day 1 of cycles 1 to 8, plus 6 or 8 cycles of standard-dose CHOP chemotherapy (supplemental Figure 1).

GOYA was conducted in accordance with the International Conference on Harmonisation guidelines for Good Clinical Practice. The protocol was approved by the ethics committees of participating centers. All patients provided written informed consent.

Clinical assessments

FDG PET/CT scanning was mandatory at sites where a PET/CT scanner was available. Patients had an FDG PET/CT scan at baseline (1-35 days before first dose of study treatment) and end of treatment (6-8 weeks after last dose of antibody) or in the event of early discontinuation (4-8 weeks after last dose of antibody). All PET/CT scans followed a standardized protocol with prespecified time windows (data supplement). Blood glucose values were required to be <200 mg/dL in all patients, and all scans were to be obtained within the specified time window. Bone marrow biopsy was also performed at baseline.

Treatment response (CT plus PET scan) at end of treatment was prospectively assessed by independent review committee according to Cheson 2007 criteria, which uses mediastinal blood pool as the cutoff to define a positive result[3] (defined as PET CR or at least partial response [PR]; supplemental Table 1). Response was also assessed retrospectively according to Lugano 2014 criteria, which uses liver background uptake as the cutoff to define a positive result[4,11] (defined by PET as CR or at least PR; supplemental Table 1). Deauville scores of 1 to 3 were considered to indicate complete metabolic response and 4 to 5 to indicate noncomplete metabolic response. In addition, a modification to Lugano 2014 criteria was applied (PR confirmed by CT; in patients with bone marrow involvement at baseline, CR had to be confirmed with negative bone marrow at end of treatment).

The independent review committee comprised 2 expert radiologists who were blinded to clinical outcome and a third radiologist to adjudicate on differences in attributed responses. The final independent review committee response was assessed by an independent clinician who combined radiological data with bone marrow and other biopsy information. The independent review committee was used only for the primary analysis, and subsequent tumor response and progression continued to be assessed by the investigator using conventional clinical, laboratory, and CT examinations.

Cell-of-origin analysis

Cell-of-origin classification (germinal center B cell–like [GCB], activated B cell–like [ABC], or unclassified) was determined using the NanoString Lymphoma Subtyping Research-Use-Only assay (NanoString Technologies, Inc., Seattle, WA).[12,13]

Outcomes

The primary objective was to determine the prognostic value of end-of-treatment PET-based response using Lugano 2014 criteria with respect to independent review committee–assessed PFS and OS in patients with previously untreated DLBCL.

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Secondary objectives were to investigate any difference in PFS prediction between Cheson 2007 or standard Lugano 2014 criteria and modified Lugano 2014 criteria and evaluate the long-term prognostic value of end-of-treatment PET-based response using standard Lugano 2014 criteria with respect to investigator-assessed PFS and OS.

Exploratory analyses included correlation of PET-based response by standard and modified Lugano 2014 criteria, with stratification of patients according to international prognostic index (IPI) scores and cell of origin, where data were available.

Statistical analysis

Analyses were conducted in the PET intent-to-treat (ITT) population, which consisted of all randomly assigned patients who had a baseline PET scan with detectable lesions. Treatment arms were pooled for this secondary imaging analysis.

Landmark independent review committee–assessed PFS and OS from end of treatment (henceforth PFS and OS) were estimated using the Kaplan-Meier method and compared according to PET CR status by log-rank test. For each landmark analysis, patients were included if they were at risk (according to the end point considered) 1 day after their end-of-treatment visit, with a particular emphasis on the 2.5 years after end-of-treatment visit (~3 years after random assignment). Positive predictive values (PPVs) and negative predictive values (NPVs) were read from Kaplan-Meier estimates of the landmark PFS rate 2.5 years after end of treatment, where PPV was 1 minus the landmark PFS rate among patients without PET CR and NPV was the landmark PFS rate among patients with PET CR.[14] Covariate effects were estimated using multivariable Cox models. Association between PFS and PET status at end of treatment, as well as study stratification factors (IPI score, number of planned CHOP cycles [6 or 8], and geographic region), was assessed using a multivariable Cox model. A P value $<.05$ was considered significant, and statistical analyses were conducted using SAS software (version 9.4; SAS Institute, Inc., Cary, NC).

Results

Patient population and baseline demographics

Patient disposition for the GOYA study has been previously described.[10] Of the 1418 patients randomly assigned in the GOYA study between July 2011 and June 2014, 1346 (95%) had evaluable baseline and end-of-treatment PET/CT scans. Of these, 1334 (99%) had a PET/CT scan with detectable lesions at baseline (PET ITT; supplemental Figure 1). Baseline demographics and disease characteristics were similar between PET ITT and overall GOYA ITT populations (supplemental Table 2).

Concordance between response criteria for malignant lymphoma

Independent review committee–assessed FDG PET/CT response rates at end of treatment according to Cheson 2007 and Lugano 2014 criteria demonstrated high concordance, with 79% (917 of 1160 patients with valid response) agreement in the classification of response (supplemental Table 2). Concordance between the classification of patients as PET CR according to standard and modified Lugano 2014 criteria was excellent (95%; supplemental Table 3).

Prognostic value of end-of-treatment FDG PET/CT response for PFS and OS

At the time of final analysis, with additional follow-up (median, 47.7 months), the numbers of investigator-assessed PFS and OS events in the entire cohort were 457 (32.2%) and 290 (20.5%), respectively. End-of-treatment PET CR was confirmed to be highly prognostic of PFS and OS when using standard Lugano 2014 response criteria (Figure 1), with a 2.5-year landmark PFS rate of 83.5% vs 51.2% for patients with no PET CR and a 2.5-year OS rate of 92.9% vs 56.8% for patients with no PET CR. As such, at the 2.5-year landmark, the PPV for PFS was 48.8% in patients without PET CR, and the NPV in patients with PET CR was 83.5%; the PPV for OS was 43.2% in patients without PET CR, and the NPV was 92.9% for patients with PET CR.

At the time of primary analysis, after a median follow-up of 29 months, the numbers of independent review committee–assessed PFS and OS events in the entire cohort were 416 (29.3%) and 252 (17.8%), respectively. End-of-treatment PET CR was highly prognostic for PFS and OS using Cheson 2007 and standard and modified Lugano 2014 criteria (supplemental Figures 2 and 3). Of the 1096 patients still at risk at end of treatment, only 122 (12.7%) of 963 with end-of-treatment PET CR and 43 (32.3%) of 133 without end-of-treatment PET CR had relapsed disease by the time of this analysis (standard Lugano 2014 criteria; supplemental Figure 2C). Landmark PFS rates (2.5 years after end of treatment [ie, 3 years after random assignment]) were higher in patients with end-of-treatment PET achieving PET CR vs those with no PET CR, according to Cheson 2007 (2.5-year landmark PFS, 85.6% vs 64.7%; HR, 0.35; 95% CI, 0.26-0.47; $P < .0001$) and standard Lugano 2014 criteria (2.5-year landmark PFS, 85.7% vs 53.5%; HR, 0.26; 95% CI, 0.19-0.38; $P < .0001$; supplemental Figure 2).

Furthermore, landmark OS rates 2.5 years after end of treatment were improved in patients with end-of-treatment PET achieving PET CR vs those with no PET CR, according to Cheson 2007 (93.4% vs 67.0%; HR, 0.18; 95% CI, 0.13-0.25; $P < .0001$) and standard Lugano 2014 criteria (93.5% vs 55.6%; HR, 0.12; 95% CI, 0.08-0.17; $P < .0001$; supplemental Figure 3).

In exploratory subgroup analysis, 2.5-year investigator-assessed landmark PFS rates were higher in patients with PET CR vs those without, irrespective of IPI score, according to standard Lugano 2014 criteria (Figure 2). Among patients with PET CR, those with IPI scores of 0 to 2 had lower PFS than those with scores of 3 to 5 (2.5-year PFS rate, 77.4% vs 87.9%; Figure 2). PFS was higher in patients with PET CR vs those without, irrespective of cell of origin. Among patients with PET CR, landmark investigator-assessed PFS was significantly lower for the ABC/unclassified group vs the GCB group (HR, 1.56; 95% CI, 1.15-2.12; $P = .0445$; Figure 3). Similarly, in patients without PET CR, PFS was lower in the ABC/unclassified group vs the GCB group (Figure 3).

Multivariate analyses confirmed that end-of-treatment PET CR vs no PET CR was highly prognostic for PFS and OS, independent of IPI, number of planned CHOP cycles, and geographic region (Table 1; supplemental Table 4).

Discussion

This secondary analysis of the phase 3 GOYA trial demonstrates that end-of- treatment FDG PET, as assessed by standard[4,11]

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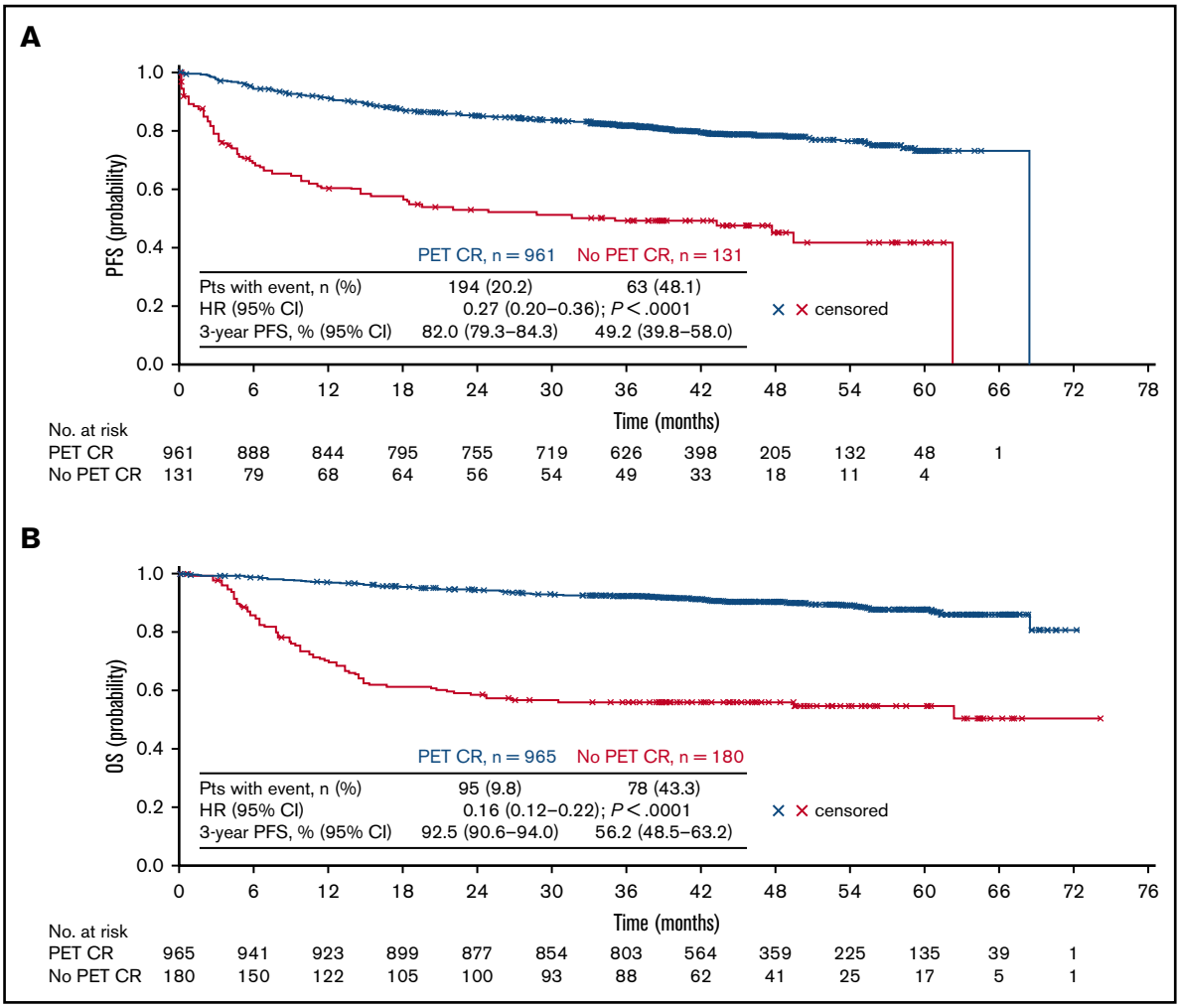

Figure 1. Investigator-assessed survival from end of treatment according to PET CR status assessed by standard Lugano 2014 response criteria (PET ITT population). (A) PFS (n = 1092). (B) OS (n = 1145). Final data cutoff, 31 January 2018. According to standard Lugano 2014 response criteria, no PET CR includes PR, nonresponse, and progressive disease patients with no progressive disease event by primary end point definition (investigator-assessed PFS). *P* values by log-rank test.

Lugano 2014 response criteria, is prognostic for PFS in patients with previously untreated DLBCL. Notably, at the time of primary analysis, of the patients with PET CR at end of treatment determined by standard Lugano criteria, only 12.7% had disease progression, compared with 32.3% of those without PET CR. Furthermore, the PET CR group had significantly longer OS after end of treatment in comparison with the group with no PET CR. These results from a phase 3 trial, 1 of the largest to date determining the prognostic value of FDG PET, are consistent with previously reported smaller studies indicating the potential for using end-of-treatment PET CR as an independent prognostic factor for relapse or progressive disease in patients with DLBCL undergoing first-line therapy.[5,7,9,15-18]

In a prospective study of 138 patients with DLBCL that used the Deauville 5-point scale for assessment, Mamot et al[4] demonstrated that end-of-treatment PET positivity by central review was associated with a significantly higher 2-year event-free survival rate in patients with vs without PET CR after R-CHOP treatment (71.5% vs 24.0%; $P < .001$).[9] In a population-based cohort of 223 patients with DLBCL treated with R-CHOP or R-CHOP–like immunochemotherapy, Bishton et al[15] showed higher 5-year OS rates in patients with vs without PET CR using Cheson 2007 criteria (75.4% vs 35.6%; $P = .0001$). In that study, however, patients classified as high risk (>6) according to the National Comprehensive Cancer Network (NCCN) IPI score, which risk stratifies patients based on 5 clinical variables (age, Eastern Cooperative Oncology Group performance status, lactate dehydrogenase, extranodal sites, and Ann Arbor stage) providing scores ranging from 0 to 8,[19] had poor outcomes (5-year PFS and OS rates both 38.5% in patients with PET CR), whereas patients with NCCN IPI scores of 0 to 5 had excellent outcomes (5-year PFS and OS rates of 75.9% to 94.1%).[15]

More recently, in a retrospective study of 185 patients with de novo DLBCL where the Deauville 5-point scale was used to assess treatment outcomes, Kanemasa et al[16] reported that only 13.2% of patients with end-of-treatment PET CR experienced disease relapse after treatment with R-CHOP or R-CHOP–like treatment. Furthermore, patients with end-of-treatment PET CR

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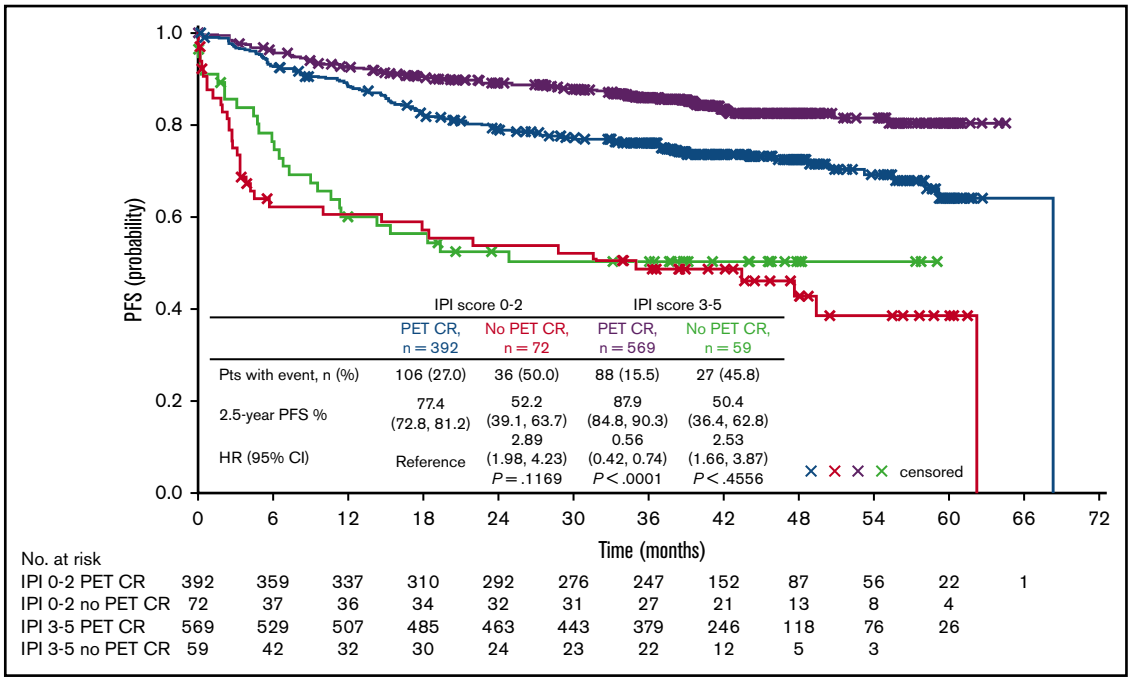

Figure 2. Kaplan-Meier analysis of investigator-assessed PFS according to PET CR status for patients with IPI scores of 0 to 2 and 3 to 5 by standard Lugano 2014 criteria (PET ITT population, n = 1092). According to standard Lugano 2014 response criteria, no PET CR includes PR, nonresponse, and progressive disease patients with no progressive disease event by the primary end point definition (investigator-assessed PFS). *P* values by log-rank test.

had significantly longer OS and PFS than those with CT CR (5-year OS rate, 87.5% vs 62.4%; $P = .003$; 5-year PFS rate, 81.4% vs 60.2%; $P = .009$).

Consistent with the findings of Bishton et al,[15,20] Kanemasa et al,[16] using data collected for the NCCN non-Hodgkin lymphoma database, showed that when patients with PET CR were further

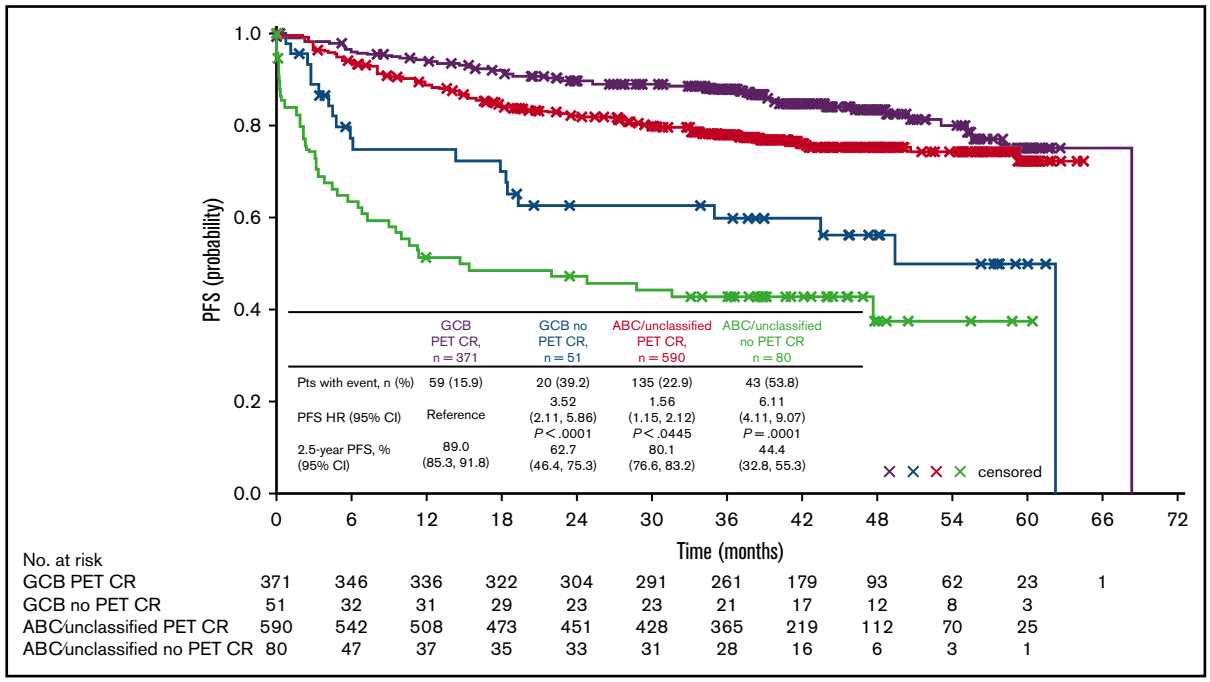

Figure 3. Kaplan-Meier analysis of investigator-assessed PFS according to cell of origin for patients with and without PET CR by standard Lugano 2014 criteria (PET ITT population, n = 1092). According to standard Lugano 2014 response criteria, no PET CR includes PR, nonresponse, and progressive disease patients with no progressive disease event by the primary end point definition (investigator-assessed PFS). *P* values by log-rank test.

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Table 1. Cox multivariate regression model for independent review committee–assessed PFS and OS

PET criteria	HR (95% CI) PFS	HR (95% CI) OS
PET CR vs no PET CR*	0.28 (0.21-0.38)	0.17 (0.12-0.23)
	$P < .0001$†	$P < .0001$†

*Standard Lugano 2014. Model included PET status at end of treatment and stratification factors: IPI risk group (low-intermediate, high-intermediate, or high), n of planned CHOP cycles (6 or 8), and geographic region (Asia, eastern European Union, western European Union, North America, or other).

†Log-rank test.

stratified according to NCCN IPI score, those with high-risk scores (>6) had a particularly poor prognosis, despite achieving PET CR, with 5-year PFS and OS rates of 53.8% and 61.8%, respectively. In contrast, the multivariate analysis in our study showed that PET CR was highly prognostic for PFS and OS using standard Lugano 2014 criteria, independent of IPI, number of planned CHOP cycles, and geographic region.

A number of characteristics of the aforementioned retrospective studies could have contributed to the differences in subgroup results compared with the present analysis. These include study design, potential selection bias, limited patient numbers in each stratification group, use of suboptimal and varying response interpretation criteria, and old-generation PET scanners. It is also important to note that IPI continues to be used as a risk scoring system in PET-staged DLBCL patients.[21] Although treatment protocols for the abovementioned studies differed from ours, the clear congruence was that risk of disease relapse or progression was significantly reduced for patients with end-of-treatment PET CR compared with those without.

Assignment of DLBCL into cell-of-origin subtypes may be important for better directing targeted therapies with selective biological activity for either the GCB or ABC subgroup. Consistent with previous reports by Scott et al[22] and Painter et al[23], the primary analysis of the GOYA study suggested that GCB subtype was associated with better outcomes in comparison with ABC and unclassified subtypes, irrespective of treatment arm.[10] In this subsequent analysis, we demonstrated that the 2.5-year PFS rate was higher in patients with PET CR vs those without, irrespective of cell of origin. Kanemasa et al[16] found that among patients with PET CR, the GCB subgroup had a better 5-year PFS rate than those with non-GCB DLBCL (94.8% vs 64.2%; $P = .017$). However, that study was performed in a retrospective cohort of only 146 patients. In our study, the PET CR/no PET CR survival curves diverged to a greater extent for the ABC/unclassified subgroup than for the GCB subgroup, which may provide further credence to the heterogeneity of DLBCL. Additional genetic complexity within each subtype was recently discovered, which has expanded the landscape of recurrent genetic drivers.[24,25]

Lugano 2014 criteria became available after the initiation and during the conduct of this study. Interestingly, in our study, modification of Lugano 2014 criteria by integrating bone marrow biopsy results into the final PET CR definition did not significantly improve the prognostic value of end-of-treatment PET imaging, suggesting that standard Lugano 2014 criteria may be sufficient in future studies. Only 5% of patients showed no PET CR according to modified Lugano 2014 criteria in cases where standard Lugano 2014 criteria indicated PET CR. Similarly, Kanemasa et al[16] observed bone marrow relapse in only 2.6% of patients who achieved PET CR. Given the conventional use of Lugano 2014 criteria in response assessment, it has been proposed that investigations should continue to evaluate the potential value of bone marrow biopsy in DLBCL when applying these criteria.[26]

Lugano 2014 criteria are superior to International Harmonisation Project criteria, yielding fewer false-positive results and improving categorization of response classification. Our data showed high concordance with 79% agreement in the classification of response with overlapping 2.5-year landmark PFS at 86% using these 2 criteria sets. There was a trend toward better HR for PET CR when determined by Lugano 2014 criteria vs Cheson 2007 criteria, reflecting improvement in false-positive rates.

The clinical impact of using PET CR as a surrogate efficacy end point could be significant. Removing the need for long follow-up periods required to establish PFS may allow early efficacy interim analyses to expedite and shorten the duration of phase 3 trials and clinical development of new treatments. Notably, the predictive value of negative end-of-treatment PET is higher than that of a positive result, and this finding is in line with previous reports. This may in turn lead to underrating of an otherwise effective treatment in some patients. A positive PET result may not be highly predictive of an unfavorable outcome, and this should be weighed against the potential benefit of early efficacy analysis. It must be acknowledged that the results of this study warrant further confirmation by other large data from phase 3 trials before adopting PET CR as a surrogate end point alternative to PFS. Considering the phenotypical and genotypical heterogeneity of DLBCL, it is conceivable that parameters additional to PET CR could be harnessed to increase accuracy of prediction. Analysis of data from the GOYA trial using PET-derived measures found that baseline total metabolic tumor volume and tumor lesion glycolysis measurements were predictors of PFS and OS in DLBCL after first-line immunochemotherapy.[27] Ultimately, evidence from additional front-line trials, together with meta-analysis of large, prospective, controlled data sets, is needed to gain the required knowledge to begin reducing our reliance on assessment of PFS or OS.

Several other limitations of the current analysis should be acknowledged. Although GOYA was a prospective study, response assessment by Lugano 2014 was performed retrospectively. However, this limitation is mitigated by the systematic acquisition of PET data across almost all centers, inclusion of central imaging review, use of strict quality controls for data acquisition and analysis, and large sample size. Although the 2 study arms were combined for this analysis, this is unlikely to have had a negative impact, because there was no significant treatment effect in the GOYA study. Ideally, a larger group of patients with cell-of-origin data available would have strengthened the findings, with RNA extraction and cell-of- origin classification only possible in 933 patients.

In summary, this study demonstrated that end-of-treatment PET CR is highly prognostic for PFS and OS in DLBCL after first-line immunochemotherapy, using Cheson 2007 and standard Lugano 2014 response criteria. Furthermore, the prognostic value of end-of-treatment PET CR in relation to PFS and OS is sustained over time. Importantly, this is the largest prospectively acquired patient

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population to date in which the prognostic value of FDG PET has been confirmed in patients with DLBCL. In addition, cell of origin remained associated with prognosis in patients with PET CR, whereas IPI did not. These results support the potential for using end-of-treatment PET CR as a surrogate marker of overall outcome in DLBCL patients with GCB and ABC/unclassified subtypes.

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Authorship

Contribution: L.K. wrote the first draft of the manuscript; all authors critically reviewed the manuscript for scientific content and approved the final version for submission; M.M., T.N., A.-M.C., and L.K. designed the study; M.M. and E.G.-B. conducted the study; M.M., E.G.-B., N.C., and A.P. were responsible for recruitment and follow-up of patients; E.G.-B., N.C., L.H.S., U.V., D.B., G.S., M.M., M.Z.O., N.C., X.H., Y.S., Y.T., and M.T. performed data collection; F.M., T.N., N.C., U.V., G.S., M.M., and M.Z.O. analyzed the data; and D.S., F.M., T.N., N.C., U.V., G.S., A.-M.C., and M.M. performed data interpretation.

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