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RESEARCH ARTICLE

A comparison of the prognostic performance of the Lugano 2014 and RECIL 2017 response criteria in patients with NHL from the phase III GOYA and GALLIUM trials

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Abstract

The Lugano 2014 criteria are the standard for response assessment in lymphoma. We compared the prognostic performance of Lugano 2014 and the more recently developed response evaluation criteria in lymphoma (RECIL 2017), which relies primarily on computed tomography and uses unidimensional measurements, in patients with previously untreated diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL) from the phase III GOYA and GALLIUM trials, respectively. Concordance between responses according to the Lugano 2014 and RECIL 2017 criteria was analyzed. Landmark analyses of progression-free survival (PFS) and overall survival (OS) by end of treatment (EOT) and end of induction (EOI) response status according to RECIL 2017 and Lugano 2014 criteria, and prognostic value of response at EOT/EOI were also compared. Overall, 1333 patients were included from GOYA and 502 from GALLIUM. Complete response (CR) status according to RECIL 2017 criteria showed high concordance with complete metabolic response (CMR) status by Lugano 2014 criteria in both GOYA (92.5%) and GALLIUM (92.4%). EOT and EOI CR/CMR status by both criteria was highly prognostic for PFS in GOYA (RECIL 2017 [CR]: hazard ratio [HR], 0.35 [95% confidence interval [CI] 0.26–0.46]; Lugano 2014 [CMR]: HR, 0.35 [95% CI 0.26–0.48]; both $p < .0001$) and GALLIUM (RECIL 2017 [CR]: HR, 0.35 [95% CI 0.23–0.53]; Lugano 2014 [CMR]: HR, 0.21 [95% CI 0.14–0.31]; both $p < .0001$). In conclusion, response categorization by RECIL 2017 is similar to that by Lugano 2014 criteria, with high concordance observed. Both were prognostic for PFS and OS.

KEYWORDS
GALLIUM, GOYA, Lugano 2014, NHL, RECIL 2017, response criteria

1 | INTRODUCTION

B-cell lymphoma is the most prevalent non-Hodgkin lymphoma (NHL) [1]. Diffuse large B-cell lymphoma (DLBCL), an aggressive form of NHL, is the most common B-cell lymphoma histological subtype and comprises approximately 30% of cases [1]. Rituximab, an anti-CD20 monoclonal antibody (mAb), in combination with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP), is a standard front-line therapy for patients with DLBCL [2, 3]. Standard therapy with rituximab plus CHOP is curative in approximately 60% of patients with DLBCL; however, the remainder of patients are refractory to or relapse after treatment and poor outcomes are observed in this patient population [4]. In the phase III GOYA study, obinutuzumab in combination with CHOP did not improve progression-free survival (PFS) compared with rituximab plus CHOP in patients with previously untreated DLBCL [5].

Follicular lymphoma (FL), an indolent NHL, is the second most common histological subtype of NHL, accounting for approximately 20% of cases [1]. The standard of care for FL in the first-line setting is either rituximab or the more recently developed anti-CD20 mAb obinutuzumab in combination with chemotherapy [6]. In the phase III GALLIUM study, obinutuzumab in combination with chemotherapy demonstrated a significant improvement in PFS compared with rituximab plus chemotherapy in patients with previously untreated FL [7]. Despite the efficacy observed with available therapies and prolonged median overall survival (OS), FL is still considered incurable and most patients will eventually relapse [8].

Evaluation of treatment response remains essential for patient management in both DLBCL and FL to enable timely treatment interventions and comparison of novel therapies. The National Cancer Institute-sponsored international consensus response criteria for NHL guidelines were first published and generally recognized in 1999 (Cheson 1999 criteria) [9]. The criteria were subsequently revised to incorporate fluorodeoxyglucose-positron emission tomography (FDG-PET) as a metabolic index, eliminating the unconfirmed complete response (CRu) category (Cheson 2007 criteria) [10]. A further revision to the Cheson 2007 criteria was published in 2014 as the Lugano 2014 criteria, which are the current standard response assessment criteria for use in lymphoma [11]. The most important changes in the Lugano 2014 imaging criteria included incorporation of the Deauville 5-point scoring (DS) system for visual assessment of treatment response using PET/computed tomography (CT) into the standard management of FDG-avid lymphomas [11]. Notably, the DS is a qualitative assessment that provides a categorical classification of response. In non-FDG-avid lymphomas or where PET is not available, assessment of treatment response using the Lugano 2014 response criteria requires bi-dimensional measurements of up to six CT target lesions [11]. Progressive disease (PD) can also be determined via CT assessment, and can be based on an increase in the size of a single lesion [11].

More recently, the response evaluation criteria in lymphoma (RECIL) 2017, a variation of the Response Evaluation Criteria in Solid Tumours (RECIST), [12] were developed as an alternative to the Lugano 2014 criteria [13]. Pilot studies of lymphoma-adapted RECIST supported the hypothesis that they would yield similar response rates to the Cheson 2007 criteria [14, 15]. These data led to the development of RECIL, which was introduced and endorsed at the International Workshop on Non-Hodgkin Lymphoma in 2016. The objective of the RECIL classification was to simplify the Lugano 2014 criteria and the assessment of morphological changes, mainly through the use of a maximum of three CT target lesions and a uni-dimensional measurement system (Table S1). While the DS remains an integral component of the RECIL 2017 criteria, more emphasis is placed on morphological response on CT than with the Lugano 2014 criteria. This is because of the deemed inability of PET-based response alone to accurately define response categories, particularly in the setting of novel drugs that may alter metabolism in both tumor and normal tissue [13]. One more consideration would be to add more certainty to those cases with equivocal metabolic changes in the setting of partial response and PD. Furthermore, CT assessment is generally more commonly available than PET, largely due to its relatively low cost.

In this analysis, our objective was to compare the prognostic performance of the Lugano 2014 and RECIL 2017 criteria at the end of treatment (EOT) and end of induction (EOI) in patients with DLBCL and FL enrolled in the large, phase III GOYA (NCT01287741) [5] and GALLIUM (NCT01332968) [7] trials, respectively.

2 | METHODS

2.1 | Study design and patient population

GOYA was a multicenter, open-label, randomized, phase III trial of obinutuzumab plus CHOP compared with rituximab plus CHOP in patients with previously untreated DLBCL [5]. GALLIUM was a multicenter, open-label, randomized, phase III trial of obinutuzumab plus chemotherapy compared with rituximab plus chemotherapy (followed by 2 years of obinutuzumab or rituximab maintenance in respective arms) in patients with previously untreated FL [7]. The full study designs for both the GOYA and GALLIUM trials have been previously reported [5, 7]. Both studies were conducted in accordance with the principles of the Declaration of Helsinki, International Council for Harmonization Good Clinical Practice guidelines, and other applicable regulations and laws. The study protocols were approved by Independent Ethics Committees and Institutional Review Boards. All patients provided signed informed consent prior to study entry.

2.2 | Clinical assessments

In GOYA, EOT response was prospectively assessed by the investigator and an independent review committee (IRC) according to Cheson 2007 criteria [10]. With the evolution of a standardized international consensus and the subsequent publication of the Lugano 2014 criteria, an exploratory assessment of response was performed retrospectively

TABLE 1 Concordance between RECIL 2017 and Lugano 2014 response status at EOT in GOYA and at EOI in GALLIUM.

GOYA								
		Lugano 2014 criteria assessment						
		CMR	PMR	SD	PMD	NE	NA	Total
RECIL 2017 criteria assessment	CR	894 (67.0%)	8 (0.6%)	0	0	3 (0.2%)	0	*905*
	PR	39 (2.9%)	79 (5.9%)	7 (0.5%)	36 (2.7%)	0	0	*161*
	MR	15 (1.1%)	4 (0.3%)	2 (0.1%)	4 (0.3%)	1 (<0.1%)	0	*26*
	SD	7 (0.5%)	1 (<0.1%)	2 (0.1%)	1 (<0.1%)	0	0	*11*
	PD	3 (0.2%)	5 (0.4%)	7 (0.5%)	19 (1.4%)	0	0	*34*
	NE	5 (0.4%)	0	0	2 (0.1%)	0	0	*7*
	NA	3 (0.2%)	0	1 (<0.1%)	1 (<0.1%)	0	185 (13.9%)	*190 (14.2%)*
	Total	*966 (72.4%)*	*97 (7.3%)*	*19 (1.4%)*	*63 (4.7%)*	*4 (0.3%)*	*185 (13.9%)*	*1334 (100.0%)*
GALLIUM								
		Lugano 2014 criteria assessment						
		CMR	PMR	SD	PMD	NE	NA	Total
RECIL 2017 criteria assessment	CR	416 (69.9%)	6 (1.0%)	0	0	0	0	*422 (70.9%)*
	PR	17 (2.9%)	28 (4.7%)	7 (1.2%)	17 (2.9%)	0	0	*69 (11.6%)*
	MR	5 (0.8%)	0	2 (0.3%)	1 (0.2%)	0	5 (0.8%)	*13 (2.2%)*
	SD	3 (0.5%)	0	1 (0.2%)	1 (0.2%)	0	2 (0.3%)	*7 (1.2%)*
	PD	1 (0.2%)	1 (0.2%)	2 (0.3%)	0	0	0	*4 (0.7%)*
	NE	8 (1.3%)	1 (0.2%)	0	2 (0.3%)	0	54 (9.1%)	*65 (10.9%)*
	NA	0	0	0	0	0	15 (2.5%)	*15 (2.5%)*
	Total	*450 (75.6%)*	*36 (6.1%)*	*12 (2.0%)*	*21 (3.5%)*	*0*	*76 (12.8%)*	*595 (100.0%)*

Abbreviations: CMR, complete metabolic response; CR, complete response; EOI, end of induction; EOT, end of treatment; MR, minor response; NA, not available; NE, not evaluable; PMD, progressive metabolic disease; PMR, partial metabolic response; PD, progressive disease; PR, partial response; RECIL, response evaluation criteria in lymphoma; SD, stable disease.

at EOT by an IRC according to these criteria [11]. FDG-PET scans were mandatory in sites with a PET scanner [16]. Similarly, in GALLIUM, tumor response was prospectively assessed at EOI by both the local investigator and an IRC according to Cheson 2007 criteria, [10] and then retrospectively by an IRC according to Lugano 2014 criteria [11]. FDG-PET scans were mandatory in the first 170 patients recruited at sites with a PET scanner and optional thereafter. Details on the clinical results of both trials have been previously published [5, 7, 16, 17].

In both GOYA and GALLIUM, response assessments were calculated retrospectively according to RECIL 2017 criteria via a statistical software program based on investigator assessments of lesion dimensions and the presence of bone marrow involvement, as well as IRC-determined DS data [13].

2.3 | Statistical analyses

All patients with available PET data were included in the analyses. Treatment arms were pooled for the assessment of concordance between RECIL 2017 and Lugano 2014 criteria. The impact of covariates on PFS and OS was assessed by multivariate Cox analysis adjusting for International Prognostic Index (GOYA) or Follicular Lymphoma International Prognostic Index (GALLIUM) score, number of planned CHOP cycles (GOYA) or chemotherapy regimen (GALLIUM), and geographic location. Landmark analyses of PFS and OS by complete response/complete metabolic response (CR/CMR) status according to RECIL 2017 and Lugano 2014 criteria at EOT in GOYA and EOI in GALLIUM were performed (study arms were merged for GOYA as the outcomes were similar between obinutuzumab plus CHOP and rituximab plus CHOP). The prognostic value of response at EOT in GOYA and EOI in GALLIUM was compared using Kaplan–Meier methodology and stratified log-rank tests. The prognostic value of response at EOI by treatment arm in GALLIUM was also assessed.

3 | RESULTS

3.1 | Patient population

As previously reported, 1418 patients with previously untreated DLBCL were enrolled in the GOYA trial (obinutuzumab plus CHOP, $n = 706$; rituximab plus CHOP, $n = 712$) [5]. Of these, 1334 patients had available PET data (obinutuzumab plus CHOP, $n = 669$; rituximab plus CHOP, $n = 665$), and 1137 had evaluable data for both RECIL and

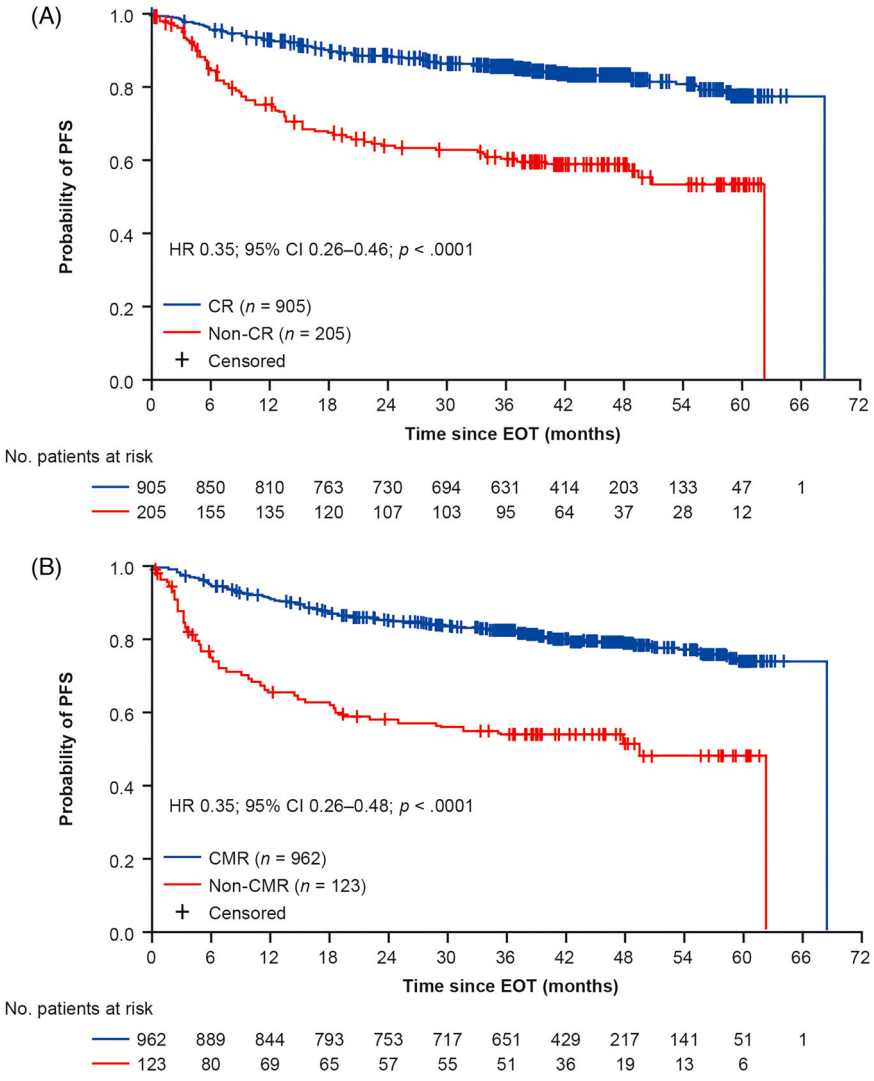

FIGURE 1 Landmark Kaplan–Meier curves for PFS by EOT response status according to (A) RECIL 2017 and (B) Lugano 2014 criteria in the GOYA study, and by treatment and EOI response status by (C) RECIL 2017 and (D) Lugano 2014 criteria in the GALLIUM study. Chemo, chemotherapy; CMR, complete metabolic response; CR, complete response; EOI, end of induction; EOT, end of treatment; G, obinutuzumab; No., number; PFS, progression-free survival; R, rituximab; RECIL, response evaluation criteria in lymphoma.

Lugano assessment at EOT (obinutuzumab plus CHOP, $n = 563$; rituximab plus CHOP, $n = 574$; Figure S1). In GALLIUM, 1202 patients with previously untreated FL (obinutuzumab plus chemotherapy, $n = 601$; rituximab plus chemotherapy, $n = 601$) were enrolled [7]. Of these, 595 patients had PET-evaluable data at baseline (obinutuzumab plus chemotherapy, $n = 297$; rituximab plus chemotherapy, $n = 298$), and 515 patients had data evaluable for both RECIL and Lugano assessment at EOI (obinutuzumab plus chemotherapy, $n = 262$; rituximab plus chemotherapy, $n = 253$).

3.2 | Concordance between RECIL and Lugano response status

In GOYA, CR status at EOT according to RECIL 2017 criteria showed high concordance with CMR status by Lugano 2014 criteria, with 92.5% (894/966) of patients achieving a CMR by Lugano 2014 having a CR by RECIL 2017 (Table 1). Of those with partial metabolic response (PMR) by Lugano 2014, 81.4% (79/97) had a partial response (PR) by RECIL 2017. Poorer concordance was observed for patients with disease progression, with 63.5% (40/63) of patients with progressive metabolic disease (PMD) by Lugano 2014 criteria having a PR or minor response (MR) by RECIL 2017. Overall, 68.3% (43/63) of patients had PMD by Lugano 2014 and non-PD by RECIL 2017 at EOT (PR, $n = 36$; MR, $n = 4$; stable disease, $n = 1$; not evaluable, $n = 2$). None of these patients received subsequent lymphoma treatment within 30 days of EOT response assessment, and 34.9% (15/43) of these patients had no PFS event at any time point as assessed by CT by Cheson 2007 and may therefore be considered false positives.

In GALLIUM, high concordance was observed for CMR/CR status, with 92.4% (416/450) of patients with a CMR by Lugano 2014 classified as CR by RECIL 2017 (Table 1). In total, 3.8% (17/450) of patients had a CMR by Lugano 2014 but were classified as PR by RECIL 2017 and 1.4% (6/422) of patients had a CR by RECIL 2017 but were classified as PMR by Lugano 2014. Of the 36 patients with a PMR by Lugano 2014, 16.7% (6/36) had a CR by RECIL 2017 and 24.6% (17/69) of patients with a PR by RECIL 2017 had a CMR by Lugano 2014. Twenty-one patients had a PMD by Lugano 2014, 18 of these (85.7%) were classified as PR/MR by RECIL 2017.

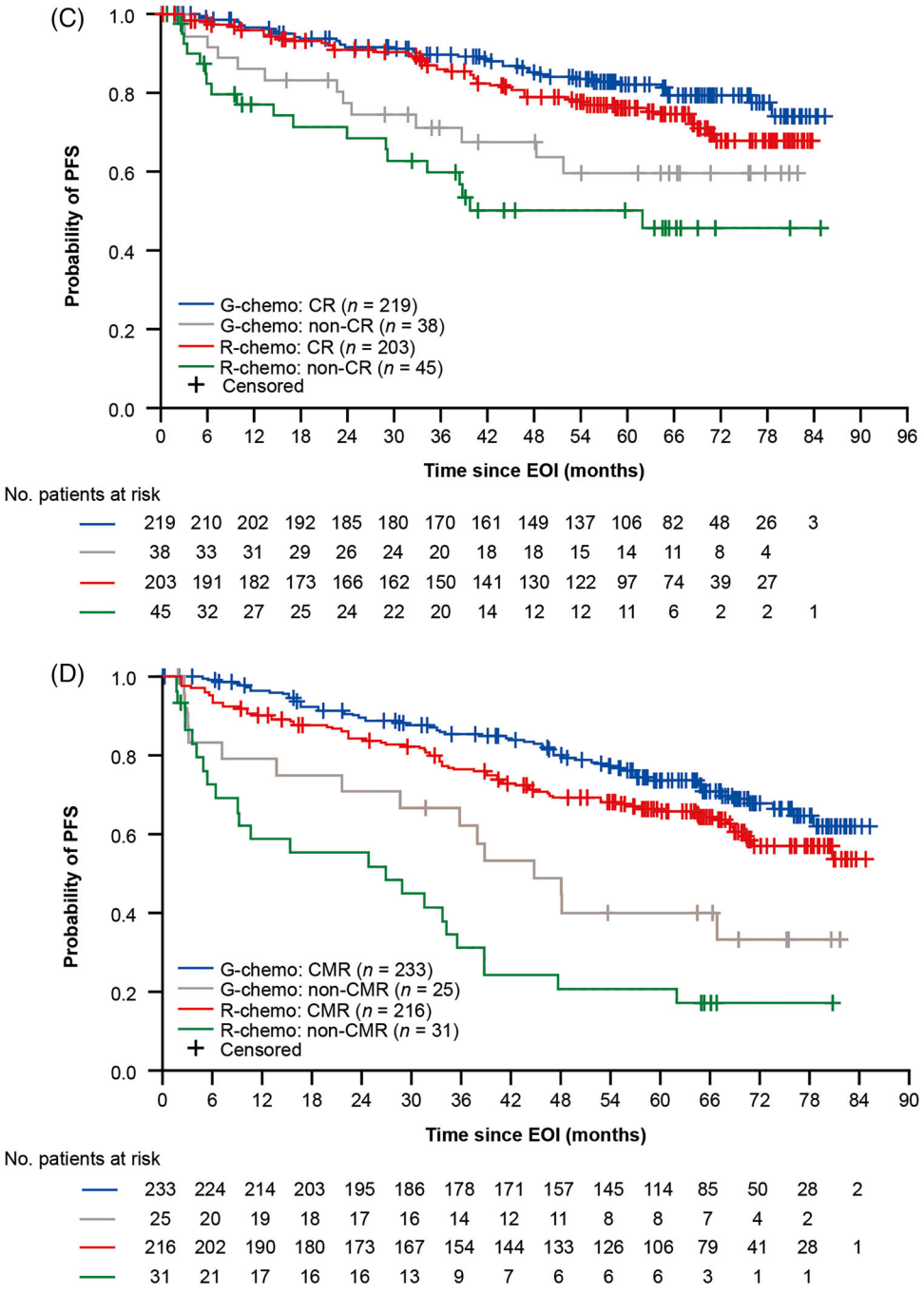

FIGURE 1 Continued

3.3 | Landmark PFS

In the GOYA study, EOT CR/CMR status as assessed by both RECIL 2017 and Lugano 2014 criteria was prognostic for PFS (Figure 1A,B). Based on RECIL 2017 criteria, CR was significantly associated with improved PFS versus non-CR, with a hazard ratio (HR) of 0.35 (95% confidence interval [CI] 0.26–0.46, $p < .0001$). Similarly, CMR as assessed by Lugano 2014 criteria was significantly associated with improved PFS versus non-CMR, with an HR of 0.35 (95% CI 0.26–0.48, $p < .0001$). These findings were confirmed by a multivariate Cox regression analysis (RECIL 2017: HR, 0.33 [95% CI 0.25–0.44]; Lugano: HR, 0.33 [95% CI 0.24–0.45]; $p < .0001$). Three-year PFS rates according to RECIL 2017 criteria were 75.0% and 74.8% in patients treated with obinutuzumab plus chemotherapy and rituximab plus chemotherapy, respectively, and 71.4% and 69.8% according to Cheson 2007 criteria.

Similarly, in GALLIUM, EOI CR/CMR status was prognostic for PFS according to both RECIL 2017 and Lugano 2014 criteria (Figure 1C,D). In a multivariate Cox regression analysis, CR as assessed by RECIL 2017 criteria was significantly associated with improved PFS versus non-CR, with an HR of 0.35 (95% CI 0.23–0.53; $p < .0001$).

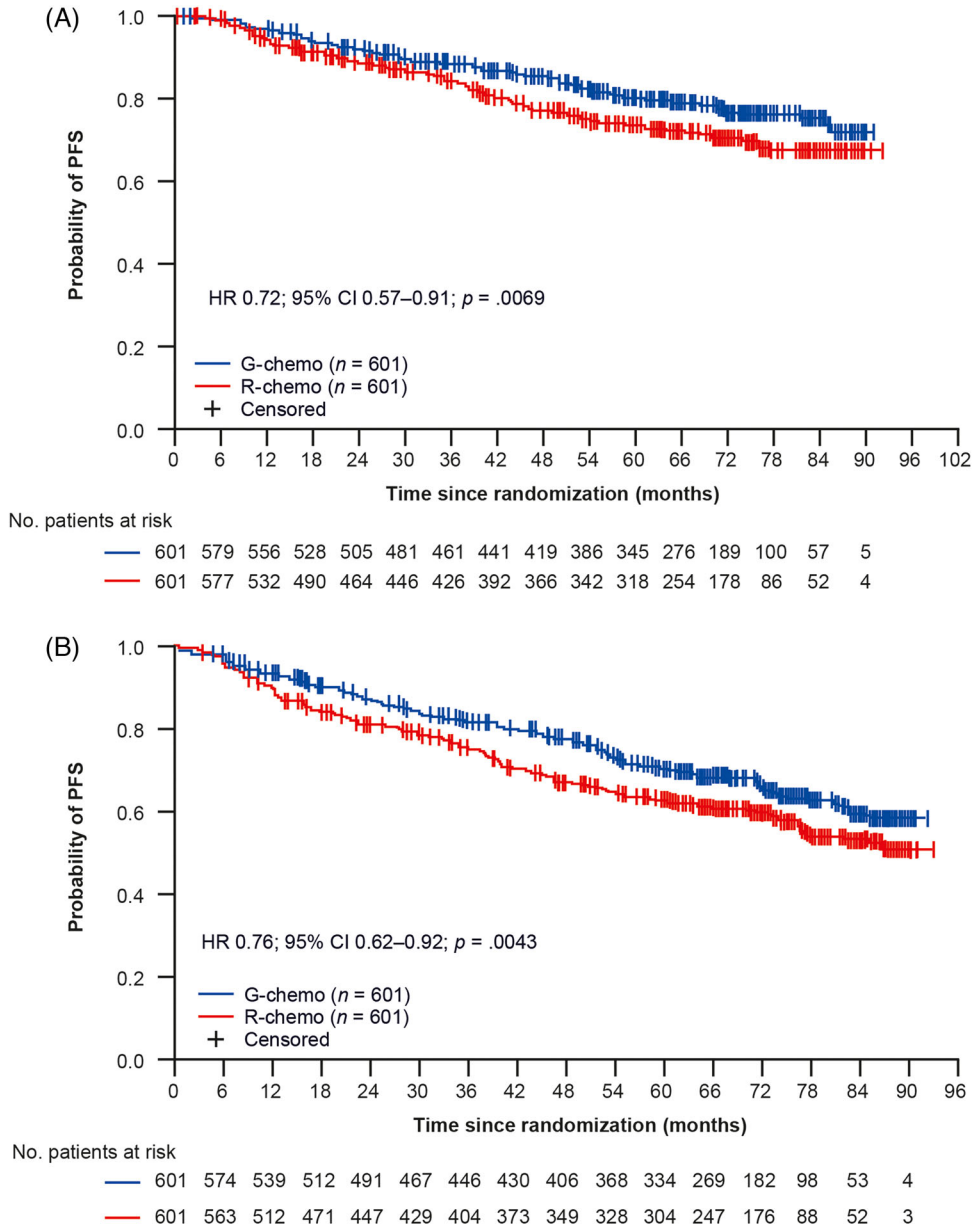

FIGURE 2 Kaplan–Meier curves for PFS from randomization by treatment arm according to (A) RECIL 2017 and (B) Cheson 2007 criteria in the GALLIUM study. Chemo, chemotherapy; CI, confidence interval; G, obinutuzumab; HR, hazard ratio; No., number; PFS, progression-free survival; R, rituximab; RECIL, response evaluation criteria in lymphoma.

When assessed by Lugano 2014 criteria, CMR was associated with improved PFS versus non-CMR, with an HR of 0.21 (95% CI 0.14–0.31; $p < .0001$). Three-year landmark PFS rates for patients with a CR/CMR at EOI were higher by RECIL 2017 criteria in comparison with Lugano 2014 in both treatment arms (89.7% and 86.0% for obinutuzumab plus chemotherapy and rituximab plus chemotherapy, respectively, by RECIL 2017; 85.0% and 76.4% for obinutuzumab plus chemotherapy and rituximab plus chemotherapy, respectively, by Lugano 2014).

In order to assess if the PFS benefit achieved with obinutuzumab plus chemotherapy versus rituximab plus chemotherapy in the GALLIUM study was similar when assessed by RECIL 2017 and Cheson 2007 criteria, PFS from randomization by treatment arm was assessed according to these criteria. The Kaplan–Meier-assessed PFS benefit observed with the obinutuzumab treatment arm was similar by RECIL 2017 and Cheson 2007 criteria (Figure 2).

3.4 | Landmark OS

In GOYA, EOT CR status by RECIL 2017 criteria was highly prognostic for OS versus non-CR, with an HR of 0.24 (95% CI 0.18–0.33, $p < .0001$); the prognostic performance with Lugano 2014 criteria was similar (CMR vs. non-CMR: HR 0.33, 95% CI 0.22–0.49, $p < .0001$).

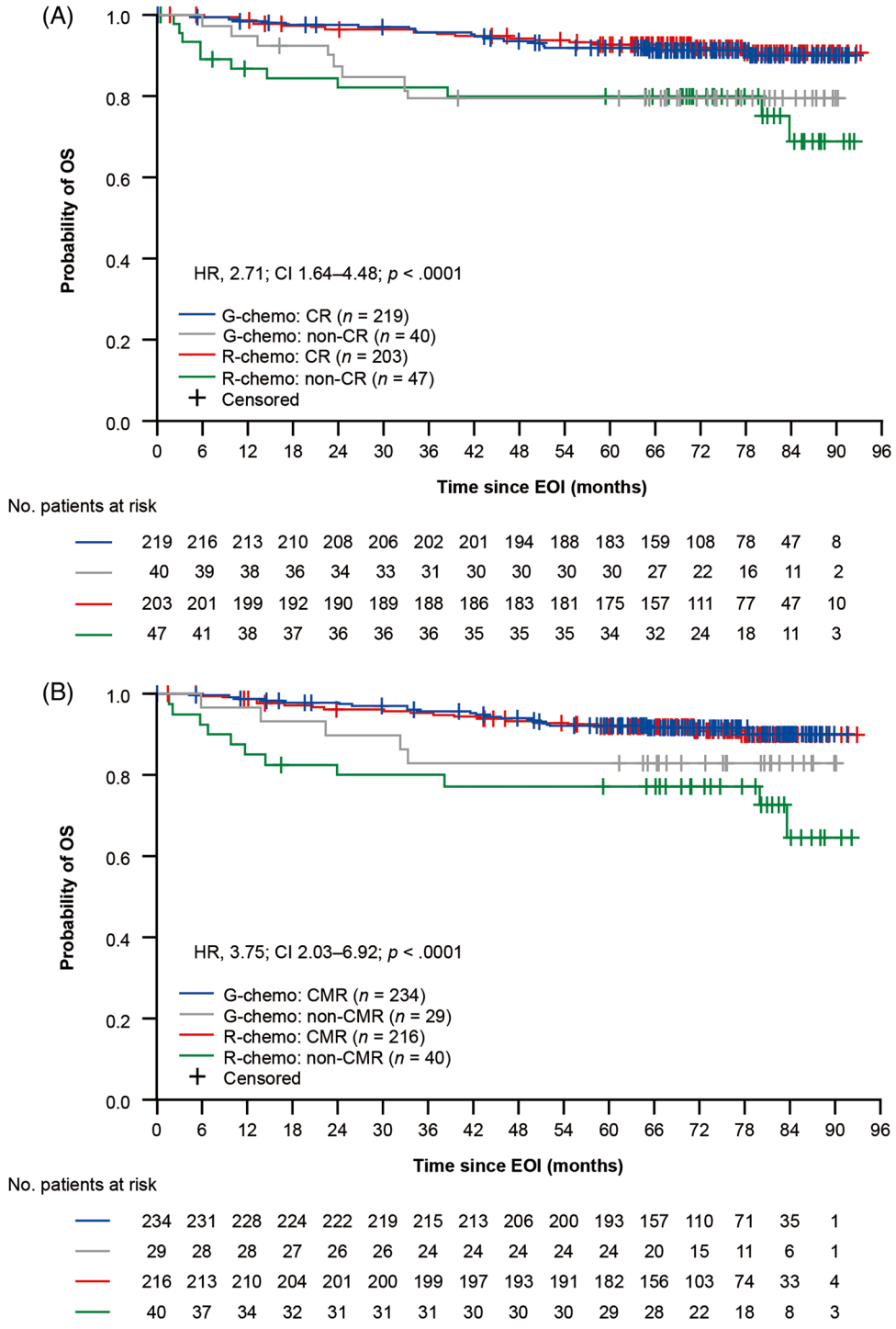

FIGURE 3 Kaplan–Meier curves for OS by EOI response status according to (A) RECIL 2017 and (B) Lugano 2014 criteria in the GALLIUM study. Chemo, chemotherapy; CMR, complete metabolic response; CR, complete response; EOI, end of induction; G, obinutuzumab; No., number; OS, overall survival; R, rituximab.

In GALLIUM, CR/CMR status at EOI was also prognostic for OS according to Lugano 2014 and RECIL 2017 criteria in both treatment arms (Figure 3). Based on RECIL 2017 criteria, CR was significantly associated with improved OS versus non-CR, with an HR of 2.71 (95% CI 1.64–4.48; $p = .0001$). CMR by Lugano 2014 criteria was also found to be associated with improved OS compared with non-CMR, with an HR of 3.75 (95% CI 2.03–6.92; $p < .0001$). Three-year landmark OS rates according to RECIL 2017 criteria were 95.8% and 86.7% in patients treated with obinutuzumab plus chemotherapy who had a CR and non-CR,

respectively, and 96.0% and 83.0% in patients treated with rituximab plus chemotherapy.

4 | DISCUSSION

In the current study we demonstrate that CR by RECIL 2017 criteria showed high concordance with CMR by Lugano 2014 criteria in patients with previously untreated DLBCL and FL treated with immunochemotherapy in the phase III GOYA and GALLIUM trials. The concordance between the RECIL 2017 and Lugano 2014 response assessment criteria observed here is in agreement with previous studies. High correlation between uni- and bi-dimensional measurements, as utilized in the RECIL 2017 and Lugano 2014 criteria, respectively, was observed in a study of 2983 patients with lymphoma [13]. In addition, concordance between response assessment by RECIL 2017 and Lugano 2014 at EOT was demonstrated in a study of a small number of patients with DLBCL ($n = 41$) and FL ($n = 13$) [18]. The concordance between the two response criteria is not surprising due to the similarity in the definitions for CR/CMR. While the RECIL 2017 criteria require a >30% decrease in the sum of the longest diameters of the lesions, most lesions with normalization of FDG-PET have a decrease in size of this magnitude.

CR/CMR status at EOT in GOYA and EOI in GALLIUM by both RECIL 2017 and Lugano 2014 criteria was observed to be highly prognostic for PFS in patients with previously untreated DLBCL and FL, respectively. It is noteworthy that in previous analyses of GOYA and GALLIUM, EOT/EOI response by Lugano 2014 criteria has demonstrated a strong association with PFS [16, 17]. A strong association has also been observed between EOT response and 2-year complete remission status according to both RECIL 2017 and Lugano 2014 criteria in a previous study of 41 patients with DLBCL [18]. CR/CMR status at EOT/EOI was also found to be prognostic for OS according to both Lugano 2014 and RECIL 2017 criteria in both the GOYA and GALLIUM studies.

Response assessment using the RECIL 2017 criteria may provide time savings over CT assessment using Lugano 2014 criteria due to the number of target lesion measurements required (≤3 vs. ≤6) and the use of uni- versus bi-directional measurements, respectively. This is particularly relevant during follow-up in clinical trials where serial CT scans are performed to monitor for PD. The RECIL 2017 criteria are now being utilized in ongoing clinical trials in patients with aggressive B-cell NHL, Hodgkin lymphoma, and peripheral T-cell lymphomas [19, 20]. In addition, the focus on CT assessment facilitates distinction between true and false-positive EOT PET scans and offers a quantitative measure (i.e., tumor shrinkage) to determine PR that is absent from the PET-based Lugano 2014 response criteria (Table S1) [11, 21].

It should be noted that some novel immunomodulatory agents can also be associated with false positives during response assessment, whereby clinical and imaging findings can be suggestive of PD but are actually a result of immune phenomena, namely tumor flare or pseudoprogression. As a result, the lymphoma response to immunomodulatory therapy criteria have been developed (based on the Lugano 2014 response criteria) [22]. These response criteria include the category 'indeterminate response', designed to classify such ambiguous findings until they can be confirmed as either pseudo- or true progression by additional imaging or biopsy.

The main strength of the current study was its use of large datasets and prospectively collected images from two phase III studies in different indications (DLBCL and FL). Limitations included the retrospective evaluation and extrapolation of RECIL measurement, and the lack of data available to assess the association between PMR/PR and PFS separately to non-CR.

In conclusion, high concordance was observed for CR assessment by Lugano 2014 and RECIL 2017 criteria in patients with DLBCL and FL. RECIL 2017 criteria were prognostic for survival outcomes in patients with DLBCL and FL as previously demonstrated for Lugano 2014 criteria. RECIL 2017 criteria may provide a simpler alternative to Lugano 2014 criteria to assess response over time and survival outcomes in some patients with previously untreated DLBCL or FL, due to the use of uni-dimensional measurements and smaller number of target lesions to follow. However, a prospective study to validate the use of RECIL 2017 compared with the Lugano 2014 criteria in routine clinical practice is required.

AUTHOR CONTRIBUTIONS

Study design: CW and DS. *Study conduct*: MM, LK, and JT. *Recruitment and follow-up of patients*: MM, AJD, and JT. *Data analysis*: AK, FM, TN, CW, DS, GS, and LK. *Data interpretation*: MM, AK, FM, TN, CW, AJD, DS, GS, LK, and JT. All authors critically reviewed and edited the manuscript, provided their final approval of the manuscript and are accountable for all aspects of the work.

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CONFLICT OF INTEREST STATEMENT

Lale Kostakoglu is a consultant at F. Hoffmann-La Roche Ltd, Genentech, Inc. and reports consulting and honoraria fees from F. Hoffmann-La Roche Ltd. Maurizio Martelli has served on a consulting and advisory board and speaker's bureau for F. Hoffmann-La Roche Ltd, Janssen, Novartis, Gilead Sciences and Sandoz; and reports travel, accommodations and other expenses from F. Hoffmann-La Roche Ltd. Laurie H. Sehn reports research funding from F. Hoffmann-La Roche Ltd and Genentech, Inc. and consulting and honoraria fees from F. Hoffmann-La Roche Ltd, Genentech, Inc., AbbVie, Amgen, Apobiologix, Acerta, AstraZeneca, Celgene, Gilead Sciences, Janssen, Kite Pharma, Karyopharm, Lundbeck, Merck, MorphoSys, Seattle Genetics, Takeda, Teva, TG Therapeutics and Verastem. Andrew Davies reports research funding from F. Hoffmann-La Roche Ltd and Genentech, Inc, AstraZeneca/Acerta Pharma, MSD and consulting and honoraria fees from F. Hoffmann-La Roche Ltd, Genentech, Inc., AbbVie,

Acerta/AstraZeneca, Celgene, Genmab, Gilead Sciences, Kite Pharma and Incyte. Marek Trněný reports honoraria and consulting fees from Janssen, Gilead Sciences, Bristol-Meyers Squibb, Amgen, AbbVie, Takeda, F. Hoffmann-La Roche Ltd, MorphoSys and Incyte; consulting for Celgene; and travel, accommodation and other expenses from AbbVie, Gilead Sciences, Bristol-Meyers Squibb, Takeda, F. Hoffmann-La Roche Ltd and Janssen. Michael Herold reports a consultancy/advisory role with Celgene, Gilead and F. Hoffmann-La Roche Ltd and research funding from F. Hoffmann-La Roche Ltd. Umberto Vitolo reports a consulting or advisory role for Janssen, Celgene, Juno Therapeutics, Kite Pharma, Genmab and Incyte; speaker's bureau fees from F. Hoffmann-La Roche Ltd, Janssen, Celgene, Gilead Sciences, Servier and AbbVie; research funding from Celgene; and travel, accommodations or other expenses from Celgene, F. Hoffmann-La Roche Ltd and AbbVie. Wolfgang Hiddemann reports honoraria from F. Hoffmann-La Roche Ltd, Janssen, Gilead Sciences and Celgene; a consulting/advisory role for F. Hoffman-La Roche Ltd, Janssen and Gilead Sciences; speakers' bureau for F. Hoffmann-La Roche Ltd, Janssen and Gilead Sciences; research funding from F. Hoffmann-La Roche Ltd, Janssen and Bayer; and travel expenses/accommodation from F. Hoffmann-La Roche Ltd, Janssen and Gilead Sciences. Judith Trotman reports research funding from F. Hoffmann-La Roche Ltd, BMS, BeiGene, Pharmacyclics, Janssen and Cellectar. Andrea Knapp is employed by and has equity ownership interests in F. Hoffmann-La Roche Ltd. Federico Mattiello is an employee of F. Hoffmann-La Roche Ltd. Tina G. Nielsen is an employee and stockholder of F. Hoffmann-La Roche Ltd. Deniz Sahin is an employee and stockholder of F. Hoffmann-La Roche Ltd. Gila Sellam is an employee and stockholder of F. Hoffmann-La Roche Ltd. Carol Ward is an employee and stockholder of F. Hoffmann-La Roche Ltd. Anas Younes is employed by and has stock and other ownership interests in AstraZeneca; has received honoraria from Merck, F. Hoffmann-La Roche Ltd, Takeda, Janssen, AbbVie, Curis and Epizyme; reports a consulting or advisory role with Bio-Path Holdings Inc, Xynomic Pharma, Epizyme, F. Hoffmann-La Roche Ltd, Celgene and HCM; has received research funding from Janssen, Curis, F. Hoffmann-La Roche Ltd, Genentech, Inc., Merck, Bristol-Myers Squibb, Syndax; and other relationship with AstraZeneca.

DATA AVAILABILITY STATEMENT

For eligible studies qualified researchers may request access to individual patient level clinical data through a data request platform. At the time of writing this request platform is Vivli: https://vivli.org/ourmember/roche/. For up-to-date details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here: https://go.roche.com/data_sharing. Anonymized records for individual patients across more than one data source external to Roche cannot, and should not, be linked due to a potential increase in risk of patient re-identification.

ETHICS STATEMENT

The study protocols were approved by Independent Ethics Committees and Institutional Review Boards before study start; protocol amendments were also approved by these bodies before implementing any changes.

PATIENT CONSENT STATEMENT

All patients provided signed informed consent prior to study entry.

CLINICAL TRIAL REGISTRATION

GALLIUM (NCT01332968); GOYA (NCT01287741)

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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