^{18}F-FDG PET for Measurement of Response and Prediction of Outcome to Relapsed or Refractory Mantle Cell Lymphoma Therapy with Bendamustine–Rituximab

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In a single-arm, phase 2 clinical trial, bendamustine–rituximab (BR) demonstrated an overall response rate of 82% among 45 patients with relapsed or refractory mantle cell lymphoma (MCL), with manageable tolerability. A prespecified ^{18}F-FDG PET analysis was conducted to assess the predictive value of the metabolic response to BR compared with the response by International Working Group (IWG) criteria. **Methods:** Adult patients with relapsed or refractory MCL underwent ^{18}F-FDG PET at screening and after 6 cycles of BR therapy. Scans were reviewed by a central facility and scored using the 5-point Deauville scale, comparing uptake to the liver and mediastinum in up to 6 lesions, to determine metabolic response rates, indicated by negative posttreatment scans. Metabolic responses were compared with study outcomes assessed by IWG criteria. **Results:** Complete ^{18}F-FDG PET data were available for 32 of 45 patients. All patients had positive baseline scans, with baseline scores ranging from 4 to 5. Complete metabolic responses (CMR) were observed in 24 (75%) patients after 6 cycles of BR. Patients attaining a CMR had a 96% overall response rate by IWG criteria, with 62.5% achieving a complete response. Of the 8 patients not attaining a CMR, 6 responded to BR but none achieved a complete response. CMR was associated with a greater 1-y progression-free survival of 91.5%, compared with 12.5% without CMR; a longer median duration of response of 20.6 mo, compared with 7.8 mo; and improved overall survival at 1 y. ^{18}F-FDG PET data from patients with refractory or advanced disease demonstrated CMR in more than half. **Conclusion:** Compared with positive end-of-treatment ^{18}F-FDG PET, negative scans, indicating a CMR, were predictive of improved 1-y survival, duration of response, and overall survival for patients with relapsed or refractory MCL receiving BR.

Key Words: ^{18}F-fluorodeoxyglucose positron emission tomography; bendamustine; rituximab; mantle cell lymphoma

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Mantle cell lymphoma (MCL) remains a challenging subtype of non-Hodgkin lymphoma (NHL), with unmet needs, due to its tendency to be aggressive and to present as an advanced-stage disease (*1–4*). Although overall survival (OS) has improved in recent decades, OS after first-line therapy lingers between 4 and 5 y, with reports of progression-free survival (PFS) between 3 and 4 y (*2–5*). Relapse is high, and management of relapsed or refractory MCL is difficult because of frequent chemoresistance and the numerous comorbidities seen in this typically elderly patient population. Poor prognosis is reported for relapsed or refractory disease, with OS in the range of 1–2 y and complete response (CR) rates observed in less than 30% of patients (*1,2,4*).

Revised International Working Group (IWG) criteria for malignant lymphoma from 2007 included ^{18}F-FDG PET, because the modality had become standard for Hodgkin lymphoma (HL) and it was subsequently recommended for assessing posttreatment response in HL and diffuse large B-cell lymphoma (DLBCL) (*6,7*). A consensus statement from the Imaging Subcommittee further clarified the use of ^{18}F-FDG PET to assess posttreatment responses in lymphoma, establishing the value of PET for the detection of residual disease for curable lymphomas, HL, and DLBCL (*7*). The imaging group recommended timing for follow-up scans and advocated visual scoring as adequate to determine a positive or negative result based on ^{18}F-FDG uptake in mediastinal blood pool, liver, and spleen. With limited data to determine the role of PET in MCL and other aggressive NHL subtypes, recommendations were restricted to use in clinical trials with objective overall response as an endpoint to validate the use of ^{18}F-FDG PET in this context (*7*). In 2009, an international workshop in Deauville, France, discussed the utility of visual assessment criteria compared with quantitative approaches using SUV to gauge the presence or absence of disease. A 5-point Deauville score (DS) assessment using ^{18}F-FDG uptake in the mediastinum and liver was formally adopted as the preferred scoring method as opposed to semiquantitative methods (*8–10*).

With the advent of hybrid imaging systems, practice guidelines now include the use of ^{18}F-FDG PET in conjunction with CT for the staging of ^{18}F-FDG–avid lymphomas, including MCL, and for assessing treatment response in HL, follicular lymphoma, and DLBCL (*4,8,9*). End-of-treatment scans have a high negative predictive value for aggressive NHL ranging from 80% to 100%, but a less well-defined positive predictive value of 50%–100% (*9*), and there is a lack of outcome data in MCL to establish the

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role of ^{18}F-FDG PET as a reliable response measure. A retrospective analysis of patients with MCL treated with R-Hyper-CVAD (cyclophosphamide-fractionated, doxorubicin, vincristine, dexamethasone, and rituximab alternating with cytarabine, methotrexate, and rituximab) found that a positive posttreatment ^{18}F-FDG PET scan was associated with lower PFS (*11*). ^{18}F-FDG PET results were also predictive for PFS in a study of patients with DLBCL treated with bendamustine and rituximab (BR) (*12*).

Current treatment guidelines for relapsed or refractory MCL recommend rituximab-containing chemotherapy regimens (*4*). Combination BR has demonstrated efficacy with manageable tolerability as a first-line therapy for mixed patient populations with indolent NHL or MCL (*3,13*) and for relapsed or refractory disease (*2,14,15*).

A phase 2, single-arm study of BR in 45 patients with refractory or relapsed MCL recently reported an overall response rate (ORR) of 82% (primary endpoint) (*16*). This study also included prospective functional imaging with ^{18}F-FDG PET to assess for complete metabolic response (CMR) compared with time-to-event outcomes and responses by IWG criteria (*6*). The present analysis investigates whether patients with refractory or relapsed MCL who convert from PET-positive to PET-negative after BR (e.g., those demonstrating CMR) fare better based on standard outcome measures, and whether ^{18}F-FDG PET/CT has potential value in assessing treatment efficacy endpoints.

MATERIALS AND METHODS

This is a secondary analysis from the previously described multicenter, open-label, single-arm, phase 2 study of patients with CD20-positive B-cell relapsed or refractory nonblastoid MCL treated with bendamustine (90 mg/m^2) and rituximab (375 mg/m^2) for 6 planned 28-d cycles (*16*). Principal methods for the parent study were previously described (*16*).

Patients

Patients had histopathologically confirmed nonblastoid-type, CD20-positive relapsed or refractory B-cell MCL; an Eastern Cooperative Oncology Group performance status of 2 or less; and an estimated life expectancy of 3 mo or more. Relapsed disease was defined as having achieved CR with a previous therapy, but demonstrating recurrent disease greater than 6 mo after the last dose. Refractory disease was defined as either a lack of CR while undergoing previous therapy or the loss of CR less than 6 mo after the last dose (*16*). Key exclusion criteria included blastoid-type MCL, prior high-dose chemotherapy with allogeneic stem cell transplantation, or other active malignancy within 3 y.

The protocol was approved by the appropriate institutional review board (or equivalent) at each study site. All patients signed an informed consent form, and the study was conducted in accordance with the Good Clinical Practice consolidated guidance approved by the International Conference on Harmonisation. The clinical trial registration number is NCT00891839.

Treatment

Bendamustine was administered as an intravenous infusion of 90 mg/m^2 on days 1 and 2 of a 28-d cycle, and rituximab was administered as an intravenous infusion of 375 mg/m^2 on day 1 of each cycle. The treatment period consisted of 6 cycles; however, patients could receive up to 8 cycles if they had not achieved CR and did not have disease progression (*16*).

^{18}F-FDG PET Procedures and Efficacy Assessment

Prespecified ^{18}F-FDG PET/CT was performed twice: at screening and after the completion of cycle 6 (day 28 ± 7 d) or, for patients discontinuing before the cycle 6 assessment, 30 d after completion of therapy. Combined ^{18}F-FDG PET/CT provided nearly simultaneous acquisition of both metabolic and anatomic data. Patients with a target fasting glucose less than 150 mg/dL fasted 4–6 h before imaging, and the test was postponed in patients with a serum glucose of more than 200 mg/dL. Patients received a 370- to 740-MBq (10–20 mCi) dose of ^{18}F-FDG, depending on body weight, followed by a 50- to 70-min uptake period. Hydration during the uptake period was encouraged, with voiding immediately before imaging. The same instrument was

TABLE 1
Baseline Demographic and Clinical Characteristics

Variable	Baseline data
Mean age (y)	68 (range, 52–78)
Sex (*n*)	
Male	22 (69%)
Female	10 (31%)
Lymphoma status (*n*)	
Relapsed	17 (53%)
Refractory	15 (47%)
MIPI (*n*)	
≤3 (low risk)	17 (53%)
4–5 (intermediate risk)	9 (28%)
≥6 (high risk)	6 (19%)
Mean MIPI ± SD	3.78 ± 1.60
Presence of B symptoms (*n*)	7 (22%)
Previous cancer surgery (*n*)	8 (25%)
Previous radiation therapy (*n*)	6 (19%)
Previous chemotherapy (*n*)	
Prior rituximab	32 (100%)
Prior alkylator	31 (97%)
Response to the most recent rituximab-based chemotherapy (*n*)	
Complete	16 (50%)
Partial	6 (19%)
Stable disease	4 (13%)
Progressive disease	5 (16%)
Not available	1 (3%)
Cyclin D1 status (*n*)	
Positive	17 (53%)
Negative	8 (25%)
Not available	7 (22%)
LDH level (*n*)	
<250 IU/L	20 (63%)
250–450 IU/L (reference range)	4 (13%)
>450 IU/L	7 (22%)
Not available	1 (3%)
β2-microglobulin level (*n*)	
1.1–2.8 mg/L (reference range)	31 (97%)
>2.8 mg/L	1 (3%)

LDH = lactate dehydrogenase.

TABLE 2
DS by ^{18}F-FDG PET Conversion

Variable	^{18}F-FDG PET results		
	CMR (n = 24)	Non-CMR (n = 8)	Total (n = 32)
DS at baseline (n)			
4	8 (33)	1 (13)	9 (28)
5	16 (67)	7 (88)	23 (72)
DS at cycle 6 (n)			
1	8 (33)	0	8 (25)
2	13 (54)	0	13 (41)
3	3 (13)	0	3 (9)
4	0	4 (50)	4 (13)
5	0	4 (50)	4 (13)
Response by baseline variables (n)			
Relapsed disease*	15 (88)	2 (12)	17 (53)
Refractory disease*	9 (60)	6 (40)	15 (47)
MIPI category (n)			
≤3*	15 (88)	2 (12)	17 (53)
4–5*	5 (56)	4 (44)	9 (28)
>5*	4 (67)	2 (33)	6 (19)

*Percentage based on category total.
Data in parentheses are percentages.

used for pretherapy and posttherapy imaging from the skull vertex through the pelvis, with consistent arm positioning. All scans were reviewed at a central academic facility for consistent metabolic response grading by 2 of the authors, nuclear medicine specialists. Uptake of ^{18}F-FDG was assessed for up to 6 index lesions and scored using the 5-point DS (1, no uptake; 2, uptake less than or equal to the mediastinum; 3, uptake greater than the mediastinum, but less than or equal to the liver; 4, uptake moderately increased above liver at any site; and 5, marked increase in uptake [more than double liver maximum] at any site) (*8*). Lesion uptake greater than that of the liver was considered as representing disease; therefore, scores of 4 and 5 represent persistent disease.

Efficacy Assessment of BR by ^{18}F-FDG PET

A key secondary endpoint in the overall study protocol, and the key endpoint for this substudy, was the rate of CMR assessed by lesion conversion from ^{18}F-FDG PET–positive to ^{18}F-FDG PET–negative based on Deauville imaging criteria assessed in the 6 index lesions as identified in the baseline scan. The protocol predates adoption of the Lugano guidelines (*6,8–10*). CMR was defined as no new lesions and complete disappearance of uptake sufficient to represent disease in all 6 index lesions and any additional lesions believed to represent lymphoma; partial reduction or no reduction or increase in uptake were recorded as non-CMR. ^{18}F-FDG PET results were then compared with the primary efficacy assessment of ORR based on the 2007 IWG revised criteria as previously described (*6,16*).

Statistical Analysis

ORR and CR were calculated based on 2007 IWG guidelines for enrolled patients treated with 1 dose or more of BR and on complete ^{18}F-FDG PET data (*6,16*). Two-sided 95% confidence intervals (1-sided α of 5%) of ORR and CR rate were based on exact binomial distributions and assessed at baseline and cycles 3 and 6. At least 3 y of follow-up were conducted. PFS, duration of response (DOR), and OS were estimated by the Kaplan–Meier method. Univariate logistic regression was used to identify potential predictors for survival. Patient risk was assessed using the MCL International Prognostic Index (MIPI).

RESULTS

The study began enrollment in June 2009, with the last patient enrolled 2 y later and the last follow-up visit completed in March 2014 (*16*). Complete ^{18}F-FDG PET data were available for 32 of 45 enrolled patients (Table 1). All scans were positive at baseline (DS 4 or 5) (Table 2). On final analysis, the rate of conversion from ^{18}F-FDG PET–positive to –negative (i.e., CMR) after BR was 75% (24/32). Figure 1 illustrates pretherapy and posttherapy ^{18}F-FDG PET scans from a patient showing CMR (Fig. 1A) and from a patient without CMR, that is, partial response (Fig. 1B). Overall findings showed that CMR was mostly associated with greater than 1-point improvement in DS from baseline compared with non-CMR (Fig. 2).

Among the 32 patients with full ^{18}F-FDG PET data, the ORR was 91% (29/32) by the end of cycles 3 and 6 (Table 3), by IWG criteria, with 47% (15/32) of patients attaining a CR. Stratified by ^{18}F-FDG PET, results have shown that, through 3-y follow-up, patients with a CMR had greater ORR and CR (96% [23/24] and 75% [18/24], respectively) than patients not exhibiting a CMR (75% [6/8] ORR and 0% CR) (Tables 3 and 4). Response by IWG criteria improved over time in metabolic responders, but no changes in IWG-measured responses were observed after cycle 3 in patients who did not achieve a CMR (Table 3). Among patients with complete ^{18}F-FDG PET data, the Kaplan–Meier-estimated PFS at 1 y was 71%, median DOR was 17 mo, and Kaplan–Meier-estimated 1-y OS was 87% (Supplemental Tables 1–3 [supplemental materials are available at http://jnm.snmjournals.org]). Although patients with refractory disease and higher MIPI risk category tended to have a greater incidence

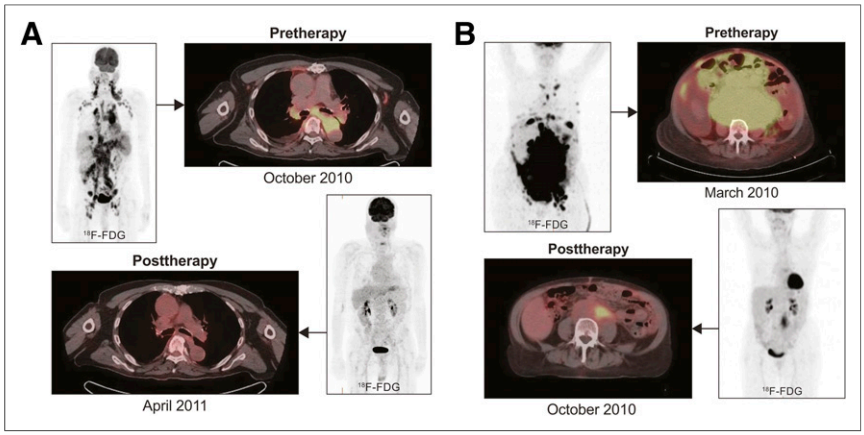

FIGURE 1. (A) Pretherapy and posttherapy ^{18}F-FDG PET/CT scans for patients showing a CMR to BR. (B) Pretherapy and posttherapy scans for patients without CMR (partial response) after BR.

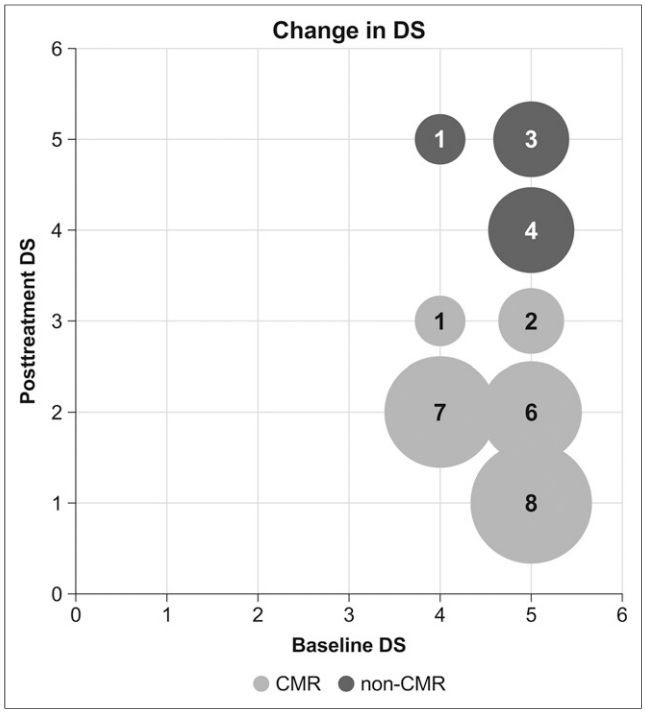

FIGURE 2. Changes in DS from baseline (*x*-axis) to posttreatment (*y*-axis) with no. of patients in each category. Responders improved so that posttreatment scans showed at most uptake ≤ uptake by the liver with no new areas representing new disease (DS 3).

of non-CMR than those with relapsed disease or lower risk disease, patients with refractory disease and higher risk attained a CMR more often than not (Table 2).

Outcomes stratified by metabolic response show that CMR predicted substantial improvements in PFS, DOR, and OS throughout the protocol-defined 3-y follow-up (Figs. 3–5; Supplemental Tables 1–3). A negative end-of-treatment ^{18}F-FDG PET scan, indicating a CMR, was associated with 7-fold-greater Kaplan–Meier-estimated PFS at 1 y than those with non-CMR (91.5% vs. 12.5%, respectively) (Fig. 3; Supplemental Table 1). The median DOR was less than 1 y for patients who did not achieve CMR (7.8 mo) but was more than twice as long for patients with CMR (20.6 mo) (Fig. 4; Supplemental Table 2).

At last follow-up, 7 patients from both the CMR and the non-CMR groups had died, and both groups lost 1 patient to follow-up, leaving 16 survivors in the CMR group and none in the non-CMR group (Fig. 5; Supplemental Table 3). Adverse events and toxicity were previously reported and were within expectations of bendamustine-associated myelotoxicity and lymphopenia (*16*). No new safety signals were identified.

DISCUSSION

For the 32 patients with available data, negative posttreatment ^{18}F-FDG PET, indicating a CMR, was predictive of greater PFS, DOR, and OS for patients with MCL treated with BR. CMRs were observed across the range of MIPI categories and among patients with relapsed or refractory MCL. Although the size of the study population was modest, these results are among relatively few reports from drug-treatment studies that included prespecified ^{18}F-FDG PET central analysis.

Reports assessing the predictive value of ^{18}F-FDG PET after chemotherapy (most retrospective, with some prospective analyses in time-to-event studies) include the following hematologic malignancies: MCL (*11,17,18*), follicular lymphoma (*19,20*), chronic lymphoid leukemia/DLBCL (*12,21–23*), and peripheral T-cell lymphomas (*24*).

Most studies in MCL have been conducted in the first-line setting and, as in our second-line study, have included a rituximab component in keeping with current guidelines (*4*). One retrospective analysis found a predictive value of ^{18}F-FDG PET for PFS (but not OS) for patients treated with first-line R-Hyper-CVAD, which contains rituximab, like our study (*11*). Likewise, another retrospective study found ^{18}F-FDG PET useful to predict PFS at 1 y in patients with MCL receiving rituximab and cytarabine- or anthracycline-based therapies (*18*). A third retrospective review of

TABLE 3
Comparison of ^{18}F-FDG PET– and IWG-Assessed Responses

Variable	^{18}F-FDG PET results		
	CMR (n = 24)	Non-CMR (n = 8)	Total (n = 32)
IWG best overall response on treatment (n)			
Complete response	14 (58)	0	14 (44)
Partial response	8 (33)	6 (75)	14 (44)
Stable disease	1 (4)	2 (25)	3 (9)
Progressive or relapsed disease	1 (4)	0	1 (3)
IWG best response by the end of cycle 3 (n)			
Complete response	3 (13)	0	3 (9)
Partial response	17 (71)	6 (75)	23 (72)
Stable disease	3 (13)	2 (25)	5 (16)
Not evaluated	1 (4)	0	1 (3)
IWG best response by the end of cycles 3 and 6 (n)			
Complete response	15 (63)	0	15 (47)
Partial response	8 (33)	6 (75)	14 (44)
Stable disease	0	2 (25)	2 (6)
Not evaluated	1 (4)	0	1 (3)
IWG best overall response through 3-y follow-up* (n)			
Complete response	18 (75)	0	18 (57)
Partial response	5 (21)	6 (75)	11 (34)
Stable disease	0	2 (25)	2 (6)
Progressive or relapsed disease	1 (4)	0	1 (3)

*New lymphoma treatments permitted during follow-up.
Data in parentheses are percentages.

TABLE 4
Metabolic and IWG Response for PFS, DOR, and OS

Variable	Metabolic response		IWG best overall response		
	CMR (n = 24)	Non-CMR (n = 8)	CR + PR (n = 29)	CR (n = 18)	Stable disease, progressive disease, or relapsed disease (n = 3)
PFS					
Median (95% CI) (mo)	23.8 (17.2–41.5)	10.7 (5.4–11.8)	22.1 (16.2–38.4)	38.4 (16.4–42.9)	5.4 (2.4–11.8)
Kaplan–Meier estimate at 12 mo (no. at risk)	91.48 (21)	12.50 (1)	78.57 (22)	100.00 (17)	0.00 (0)
DOR					
Median (95% CI) (mo)	20.6 (14.6–38.8)	7.8 (4.9–14.3)	17.0 (13.3–35.5)	35.5 (13.8–40.3)	NA
Kaplan–Meier estimate at 12 mo (no. at risk)	86.36 (18)	16.67 (1)	71.43 (19)	88.24 (15)	NA
OS					
Median (95% CI) (mo)	NR (32.1–NR)	14.2 (8.6–18.8)	NR (28.9–NR)	NR (32.1–NR)	16.1 (8.6–NR)
Kaplan–Meier estimate at 12 mo (no. at risk)	100.00 (23)	50.00 (4)	89.29 (25)	100.00 (17)	66.67 (2)

CI = confidence interval; NA = not applicable; NR = not reached.

28 available end-of-treatment scans (all in patients receiving rituximab-containing treatment) did not observe a statistically significant association between CMR and 3-y survival; however, no deaths were reported among patients with negative end-of-treatment scans, making a trend for better OS but not 3-y event-free survival (*25*). Similarly, a retrospective analysis of posttreatment ^{18}F-FDG PET scans for patients with MCL initially treated with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone found no differences in OS or PFS at 3 y between patients with positive and negative scans (*26*). The authors of the latter 2 studies suggest that diverse treatment regimens, small sample size, and varying length of follow-up may explain the differences between their findings and those that saw predictive value of ^{18}F-FDG PET (*25,26*).

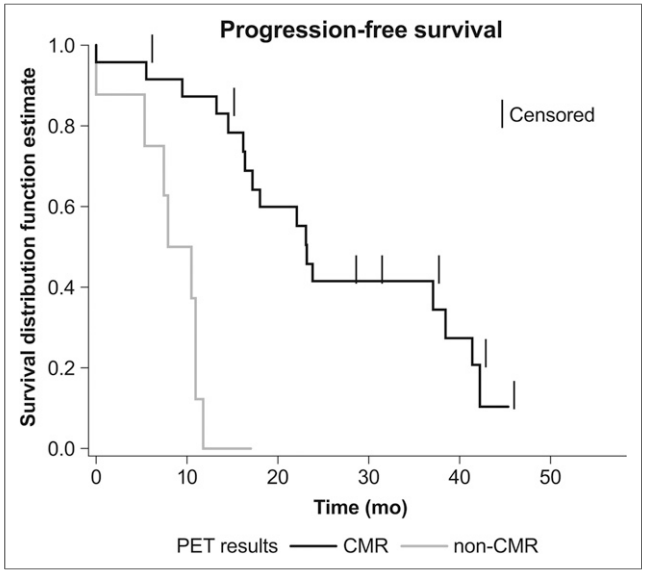

FIGURE 3. Kaplan–Meier analysis of PFS for patients treated with BR by metabolic response.

A retrospective review of 51 patients newly diagnosed with aggressive lymphomas (including 13 patients with MCL) treated with rituximab-containing regimens (*27*), assessed by ^{18}F-FDG PET, found that all patients with MCL achieved a CR by IWG criteria, with only 1 relapse occurring during follow-up. Three patients failed to show a CMR on the posttreatment scan. The discussion focuses on potential reduction in the positive predictive value of posttreatment scans resulting from residual inflammation caused by rituximab. The authors point to greater positive predictive values of ^{18}F-FDG PET observed in studies treating NHL without rituximab (*27*), an observation, in the primary setting, that might predict only a modest predictive value in our second-line BR study.

Although there are few data on the prognostic use of ^{18}F-FDG PET in patients with relapsed or refractory MCL, limited evidence is not consistent with the hypothesis that rituximab negatively affects the predictive value of ^{18}F-FDG PET. In a mixed first-line and relapsed or refractory setting, 1 study reported a significant link between a positive posttreatment ^{18}F-FDG PET and lower PFS for patients treated with BR and cytarabine in a study including prospective ^{18}F-FDG PET with time-to-event endpoints (*17*). A bendamustine study (120 mg/m^2 given in 6 cycles of 21 d) without rituximab was conducted in relapsed or refractory patients with follicular lymphoma or MCL (*28*). Results showed a metabolic reduction in target lesions among patients achieving CR, although the authors note that the role of ^{18}F-FDG PET in assessing response was not clear.

In this current study of BR in relapsed or refractory MCL, all of the patients had received rituximab in previous therapy, and 6 of the 8 patients without a metabolic response did respond to BR by IWG criteria, but none achieved a CR. Although IWG responses

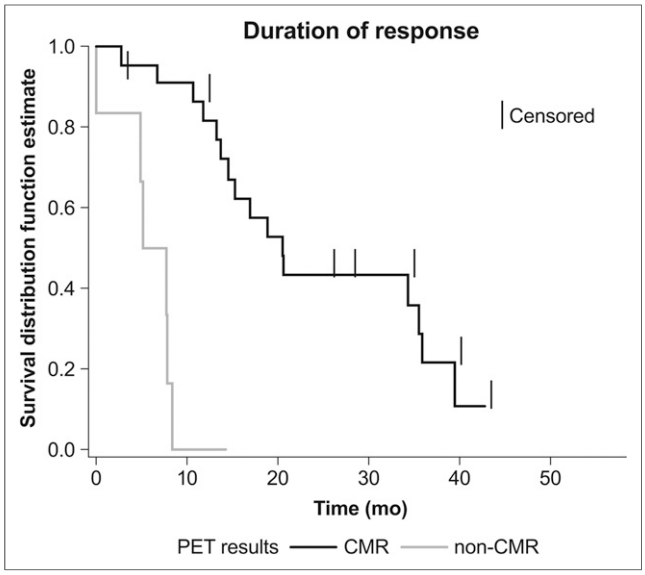

FIGURE 4. Kaplan–Meier analysis of DOR for patients treated with BR by metabolic response.

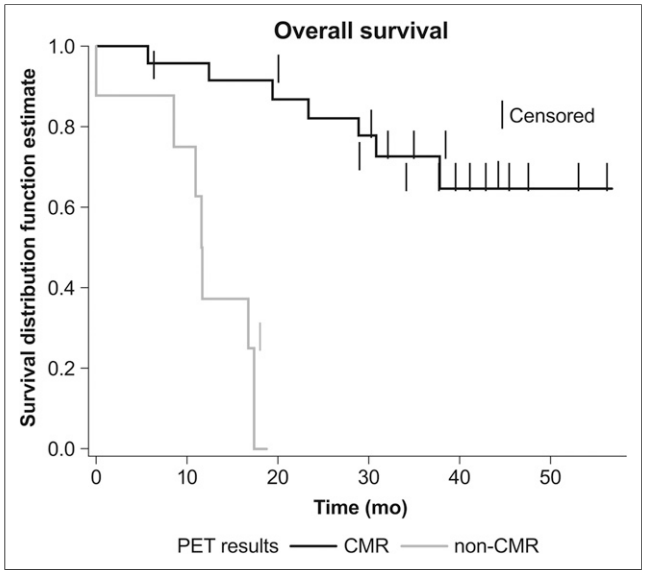

FIGURE 5. Kaplan–Meier analysis of overall response for patients treated with BR by metabolic response.

were assessed after cycle 3, most CRs were not observed until after cycle 6. Patients without a CMR did not show improvements in IWG response beyond cycle 3.

CONCLUSION

Data from this report of heavily pretreated older patients with advanced, relapsed or refractory MCL treated with BR add to the growing body of evidence to support the use of ^{18}F-FDG PET to predict substantial improvement in time-to-event treatment outcomes. Posttreatment ^{18}F-FDG PET showing CMR was a sensitive indicator of response to therapy in both relapsed or refractory MCL and across the range of MIPI categories, which may provide useful clinical practice insight and warrants further investigation.

DISCLOSURE

Daniel A. Graf is currently at the University of Texas Medical Branch at Galveston. Mihaela C. Munteanu is a former employee and shareholder of Teva, has owned stock/held an ownership interest in Janssen, and is currently an employee of ImmunoGen, Inc. Myron S. Czuczman has served as consultant to Teva and Mundipharma, has received an honorarium for serving as an educational meeting chairman for Mundipharma, and is currently an employee of Celgene. This research was sponsored by and conducted by Teva Branded Pharmaceutical Products R&D, Inc., Frazer, PA. Medical writing assistance was funded by Teva. No other potential conflict of interest relevant to this article was reported.

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