original reports

Relevance of Bone Marrow Biopsies for Response Assessment in US National Cancer Institute National Clinical Trials Network Follicular Lymphoma Clinical Trials

Sarah C. Rutherford, MD[1]; Jun Yin, PhD[2]; Levi Pederson, MS[2]; Gabriela Perez Burbano, MS[2]; Betsy LaPlant, MS[2]; Mazyar Shadman, MD[3]; Hongli Li, MS[3]; Michael L. LeBlanc, PhD[3]; Vaishalee P. Kenkre, MD[4]; Fangxin Hong, PhD[5]; Kristie A. Blum, MD[6]; Travis Dockter, MS[2]; Peter Martin, MD[1]; Sin-Ho Jung, PhD[7]; Barbara Grant, MD[8]; Cara Rosenbaum, MD[1]; Chaitra Ujjani, MD[3]; Paul M. Barr, MD[9]; Joseph M. Unger, PhD[3]; Bruce D. Cheson, MD[10]; Nancy L. Bartlett, MD[11]; Brad Kahl, MD[11]; Jonathan W. Friedberg, MD[9]; Sumithra J. Mandrekar, PhD[2]; and John P. Leonard, PhD[1]

abstract

PURPOSE Bone marrow biopsies (BMB) are performed before/after therapy to confirm complete response (CR) in patients with lymphoma on clinical trials. We sought to establish whether BMB add value in assessing response or predict progression-free survival (PFS) or overall survival (OS) outcomes in follicular lymphoma (FL) subjects in a large, multicenter, multitrial cohort.

METHODS Data were pooled from seven trials of 580 subjects with previously untreated FL through Alliance for Clinical Trials in Oncology (Alliance) and SWOG Cancer Research Network (SWOG) completing enrollment from 2008 to 2016.

RESULTS Only 5/580 (0.9%) had positive baseline BMB, CR on imaging, and subsequent positive BMB ($P < .0001$). Therefore, BMB were irrelevant to response in 99% of subjects. A sensitivity analysis of 385 FL subjects treated on an Eastern Cooperative Oncology Group study was included. In the Eastern Cooperative Oncology Group cohort, 5/385 (1.3%) had BMB that affected response assessment. Since some subjects do not undergo confirmatory BMB, we performed a landmark survival analysis from first radiologic CR with data from 580 subjects from Alliance and SWOG. Of subjects with CR on imaging (n = 187), PFS and OS were not significantly different among those with negative BMB to confirm CR (n = 47) versus those without repeat BMB (n = 140; PFS: adjusted hazard ratio, 1.10, 95% CI, 0.62 to 1.94, log-rank $P = .686$; OS: hazard ratio, 0.59, 95% CI, 0.23 to 1.53, log-rank $P = .276$).

CONCLUSION We conclude that BMB add little value to response assessment in subjects with FL treated on clinical trials and we recommend eliminating BMB from clinical trial requirements. BMB should also be removed from diagnostic guidelines for FL except in scenarios in which it may change management including confirmation of limited stage and assessment of cytopenias. This would reduce cost, patient discomfort, resource utilization, and potentially remove a barrier to trial enrollment.

J Clin Oncol 41:336-342. © 2022 by American Society of Clinical Oncology

ASSOCIATED CONTENT

Appendix

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on May 16, 2022 and published at ascopubs.org/journal/jco on July 5, 2022: DOI https://doi.org/10.1200/JCO.21.02301

INTRODUCTION

Clinical trial requirements can be burdensome and deter patients from participation. Initiatives through ASCO focus on simplifying such protocols in a patient-centered approach to encourage enrollment.[1-3] In clinical practice of follicular lymphoma (FL), utility of bone marrow biopsies (BMB) is controversial. The National Comprehensive Cancer Network (NCCN) guidelines for FL recommend BMB and aspiration in certain circumstances including to confirm stage I-II disease in patients being considered for radiotherapy or in those who require investigation of cytopenias. They note that BMB can be omitted for patients being observed without treatment.[4] The European Society for Medical Oncology Clinical Practice Guidelines advise that BMB and aspiration should be done in all patients with newly diagnosed FL, particularly those with suspected early-stage disease.[5] Response criteria for clinical trials in lymphoma require that BMB be performed at baseline and then repeated to confirm complete response (CR) in those with positive baseline BMB.[6-8]

We hypothesized that only rarely do subjects have a positive baseline BMB, CR on imaging, and then a positive subsequent BMB—the only scenario in which BM assessment could change response determination. We then investigated 99 subjects with FL treated

CONTEXT

Key Objective

Are bone marrow biopsies (BMB) relevant for response assessment in follicular lymphoma (FL) clinical trials?

Knowledge Generated

In 99% of subjects with FL enrolled on National Clinical Trials Network clinical trials, response is unchanged on the basis of BMB results. Among subjects with complete response on imaging, there is no progression-free survival or overall survival difference in those with negative confirmatory BMB versus those who do not undergo the procedure.

Relevance *(S. Lentzsch)*

BMB should be removed from diagnostic guidelines for FL except in scenarios in which it may change management including confirmation of limited stage and assessment of cytopenias.*

*Relevance section written by *JCO* Associate Editor Suzanne Lentzsch, MD, PhD.

on clinical trials at a single institution and found that 1.0% had a BMB that could have affected response assessment.[9] We performed a similar analysis of the randomized GALLIUM clinical trial, which enrolled untreated subjects with FL to obinutuzumab plus chemotherapy versus rituximab plus chemotherapy followed by obinutuzumab or rituximab maintenance.[10] We found that only 5/1,202 subjects (0.4%) had BMB that affected response assessment when computed tomography (CT)–based International Working Group (IWG) 2007 response criteria were used.[11] The GALLIUM trial required fluorodeoxyglucose-positron emission tomography (PET) imaging in the first 170 enrolled subjects, and PET was optional in subsequent subjects. PET was performed in 282 patients with positive/indeterminate baseline BMB. Two hundred thirteen of these patients underwent confirmatory BMB. Of 213 subjects with positive or indeterminate baseline BMB who underwent PET and repeat BMB after treatment, BMB were relevant for response assessment in a maximum of 10 (4.7%, five positive BMB and five indeterminate). We sought to confirm these results in subjects with untreated FL enrolled on National Cancer Institute National Clinical Trials Network (NCTN) trials. Our goals were to validate findings of preliminary studies to foster efforts to simplify future clinical trial requirements for subjects who may be discouraged from participation in clinical trials, and to change practice guidelines requiring BMB in the majority of patients with FL. In addition to encouraging patient participation in clinical trials and minimizing patient discomfort, this effort would also decrease cost and utilization of resources.

METHODS

We identified all clinical trials completing enrollment in the modern therapeutic era from 2008 to 2016 by the Alliance for Clinical Trials (Alliance and legacy Cancer and Leukemia Group B [CALGB]) and SWOG Cancer Research Network (SWOG) of subjects with untreated FL for which BMB results at baseline and during response assessment, and best response by imaging, were available. All studies were approved by the institutional review board at each participating site, and informed consent forms were signed by all subjects enrolled on the trials. For each study, and for all studies combined, we calculated the proportion of subjects with positive baseline BMB, CR on imaging after treatment, and positive repeat BMB using the total number of subjects enrolled as the denominator. These are the only subjects in whom BMB would affect response assessment. The majority of studies used IWG 2007 guidelines with five of eight protocols stating that BMB morphology and immunohistochemistry were required to be negative (with goal $>$ 20 mm core) but that bone marrow aspirate was not required to be negative to confirm CR. Those five protocols indicated that a small population of clonal lymphocytes by flow cytometry in the bone marrow aspirate was considered a CR until data became available demonstrating a clear difference in patient outcome. Similarly, IWG 2007 guidelines indicate that histologically normal bone marrows with a small ($<$ 2%) B-cell population detected by flow cytometry should be considered normal.[7] The SWOG and Eastern Cooperative Oncology Group (ECOG) studies did require both biopsies and aspirates to be negative to confirm CR.

Statistical analysis was conducted by the Alliance Statistics and Data Center. We tested against the null hypothesis that this proportion was $\geq$ 10%, versus the alternative hypothesis that this proportion was $<$ 10% (the threshold below which BMB would be considered inconsequential for response assessment), using a one-sided exact binomial test. With 500 subjects, we would have 99% power to reject that this proportion is $>$ 10% when the true proportion is 5% using a binary test of a single proportion with one-sided alpha = .025. The power calculation was not a design feature of the study. This is a secondary analysis using existing data from completed NCTN clinical trials. Response criteria were CT-based. Imaging was not used to assess for BM involvement. BMB were unilateral in six clinical trials and bilateral in two.

TABLE 1. Summary of Studies

Trial	Years of Enrollment	Treatment	No. of Subjects	Response Criteria
CALGB50701	2008-2009	Phase II: epratuzumab/rituximab in FL	59	IWG 2007
CALGBA50803	2010-2011	Phase II: lenalidomide/rituximab in FL	64	IWG 2007
CALGBA50901	2012-2014	Phase II: ofatumumab (500 or 1,000 mg) in FL	46	IWG 2007
CALGBA50904	2011-2016	Phase II: ofatumumab/bendamustine *v* ofatumumab/bendamustine/bortezomib in FL	130	IWG 2007
A51103	2013-2014	Phase I: rituximab/lenalidomide/ibrutinib in FL	22	IWG 2007
S0016	2002-2008	Phase III: R-CHOP *v* I-131 tositumomab-CHOP in FL	175	Study defined
S0801	2009-2010	Phase II: I-131 tositumomab-CHOP in FL	84	IWG 2007
Total for Alliance and SWOG trials			580	
E4402	2003-2008	Phase III: rituximab extended schedule or retreatment trial for low-tumor-burden FL	385	IWG 1999
Total for ECOG trial			385	
Total for all trials			965	

Abbreviations: CALGB, part of the Alliance for Clinical Trials in Oncology; ECOG, Eastern Cooperative Oncology Group; FL, follicular lymphoma; IWG, International Working Group; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone.

Because confirmatory BMB were not completed in all indicated subjects, landmark survival analyses compared progression-free survival (PFS) and overall survival (OS) of subjects with CR on imaging and negative BMB versus subjects with CR on imaging without repeat BMB. This analysis was performed in subjects with a positive baseline BMB. Subjects with CR on imaging were categorized as having negative repeat BMB or no repeat BMB within 60 days of the first CR on imaging. PFS was defined from time of CR to progression or death. OS was defined as time of first CR to death. The time-to-event end points were calculated using a landmark analysis approach from first radiologic CR and estimated using Kaplan-Meier, and compared using log-rank tests, as well as univariate and multivariate Cox models adjusted for age, sex, stage, and Follicular Lymphoma International Prognostic Index (FLIPI) score, and stratified by treatment arm within study. An ECOG trial was analyzed separately as a sensitivity analysis, as it included only one time point for follow-up bone marrow assessment (13 weeks), in contrast to the Alliance and SWOG studies with repeated evaluations of response by imaging and BMB.

To investigate whether cytopenias were associated with positive findings of FL on initial BMB, we identified subjects enrolled on the five Alliance clinical trials whose baseline blood counts were available and met any of the following criteria: absolute neutrophil count $< 1.0 \times 10^9$/L, hemoglobin < 12 g/dL, or platelet count $< 100 \times 10^9$/L. We compared baseline BMB results of subjects with and without one or more cytopenias by these criteria.

RESULTS

We identified seven studies meeting inclusion criteria that completed enrollment of a total of 580 subjects with FL, the majority of whom had advanced stage disease, from 2008 to 2016 through Alliance and SWOG (Table 1). One patient with no baseline BMB result was excluded. Five studies were phase II and one each were phase I and phase III. Six of the studies used IWG 2007 criteria for response assessment and one used study-defined criteria. Subject characteristics are listed in Table 2. Median age was 55 years (51% male, 96% stage III-IV, and 88% grade I-II). FLIPI scores were low in 20%, intermediate in 46%, and high risk in 35%. Chemotherapy-based regimens were administered to 67% of subjects. Baseline BMB were positive in 55%. Of subjects enrolled on Alliance clinical trials with available information (n = 191), there was no association between subjects with one or more cytopenia at baseline and positive initial BMB results ($P = .8465$; Appendix Table A1 [online only]).

Only 5/580 (0.8%) FL subjects in Alliance and SWOG trials had positive baseline BMB, CR on imaging, and subsequent positive BMB ($P < .0001$; Appendix Table A2, online only). Of 344 subjects with a CR on imaging after treatment, 1.5% (5/344) had BMB that altered response assessment. See Appendix Figures A1A and A1B (online only) for CONSORT diagrams for Alliance and SWOG, and ECOG trials.

The landmark survival analysis from time of first radiologic CR was performed in subjects with previously untreated FL enrolled on Alliance and SWOG trials. Of subjects with CR on imaging (n = 187), PFS and OS were not different among subjects with negative BMB within 60 days of CR on imaging (n = 47) versus subjects without repeat BMB within 60 days of imaging (n = 140; PFS: $HR_{adj} = 1.10$, 95% CI, 0.62 to 1.94, log-rank $P = .686$; OS: HR = 0.59, 95% CI, 0.23 to 1.53, log-rank $P = .276$; Fig 1 and Appendix Table A2).

TABLE 2. Subject Characteristics

Characteristic	Alliance and SWOG (N = 580)
Age at diagnosis, years	
No.	532
Mean (SD)	54.9 (11.49)
Median	55.0
Range	25.0-90.0
Missing	48
Age at registration, years	
No.	579
Mean (SD)	55.8 (11.44)
Median	55.4
Range	25.0-90.0
Missing	1
Sex, No. (%)	
Male	297 (51.2)
Female	283 (48.8)
Ann Arbor stage, No. (%)	
II	23 (4.0)
III	211 (36.4)
IV	346 (59.7)
FL grade, No. (%)	
I	128 (27.2)
I/II	150 (31.8)
II	136 (28.9)
III	11 (2.3)
IIIa	46 (9.8)
Missing	109
FLIPI risk group, No. (%)	
Low risk	113 (19.6)
Intermediate risk	265 (45.9)
High risk	199 (34.5)
Missing	3
Treatment type, No. (%)	
Chemotherapy plus targeted therapy	388 (67.0)
Targeted therapy	191 (33.0)
Missing	1
Baseline BM result, No. (%)	
Negative	259 (44.7)
Positive	321 (55.3)

Abbreviations: BM, bone marrow; FL, follicular lymphoma; FLIPI, Follicular Lymphoma International Prognostic Index; SD, standard deviation.

Two clinical trials conducted by ECOG that met inclusion criteria were identified (E4402 and E2408). E2408 was excluded because the data were not available at the time of our data collection. A sensitivity analysis was conducted on the 385 subjects with untreated FL on RESORT (E4402), a phase III trial of rituximab extended schedule versus retreatment at progression. Because imaging results were mandated only at an interim point (and therefore the results are not necessarily reflective of best response), we were unable to combine the analysis with that from the Alliance and SWOG trials. Characteristics of subjects on the ECOG trial were similar to those enrolled on Alliance and SWOG trials (Appendix Tables A3 and A4, online only). Of 385 subjects enrolled on the ECOG trial, only five (1.3%) had BMB that affected response assessment (Appendix Fig A1B).

DISCUSSION

In conclusion, we establish that BMB do not affect response assessment in NCTN clinical trials enrolling subjects with untreated FL. We analyzed two different data sets with close to 1,000 total subjects, and the results of BMB changed response assessment in only 10 subjects (about 1%). On average, in the primary data set, one subject's response assessment was altered for every 116 subjects required to undergo BMB. A significant percentage of subjects with CR on imaging did not undergo confirmatory BMB (99/198, 50% in Alliance/SWOG trials; and 22/47, 47% in the ECOG trial). Although reasons for the omissions were not recorded, we presume that both patient and physician preference may have been the primary contributing factors (Appendix Tables A5 and A6, online only).

The landmark survival analysis was performed to compare outcomes in subjects who did not undergo BMB with those who did have confirmatory BMB, and we found no difference in PFS and OS. Therefore, BMB do not enable identification of distinct PFS/OS outcomes in FL patients with positive findings at baseline.

In another subtype of lymphoma, classical Hodgkin lymphoma, BMB were formerly required as part of diagnostic workup beginning with the guidelines established by the Committee on Hodgkin's Disease Staging Classification in 1971.[12] With incorporation of CT imaging into practice guidelines, recommendations were changed in 1989 to include BMB as a requirement in only those HL patients with stage III-IV disease or stage II disease with high-risk features in whom bone marrow involvement would change management.[13] When PET-CT became routinely used in staging of HL, this modality was established to accurately assess for bone marrow involvement in that disease.[14] A retrospective study of 454 patients with HL concluded that BMB do not alter risk assessment or treatment decisions in these patients, and the procedures were subsequently eliminated from staging requirements.[8,15-17] In diffuse large B-cell lymphoma (DLBCL), multiple studies have determined that PET-CT accurately reveals bone marrow involvement.[18-20] Therefore, NCCN guidelines state that BMB are not necessary in DLBCL if PET-CT detects bone disease.[4] Our findings from a retrospective review of the GOYA study indicate that BMB have minimal impact on response assessment in patients with DLBCL as well.[11]

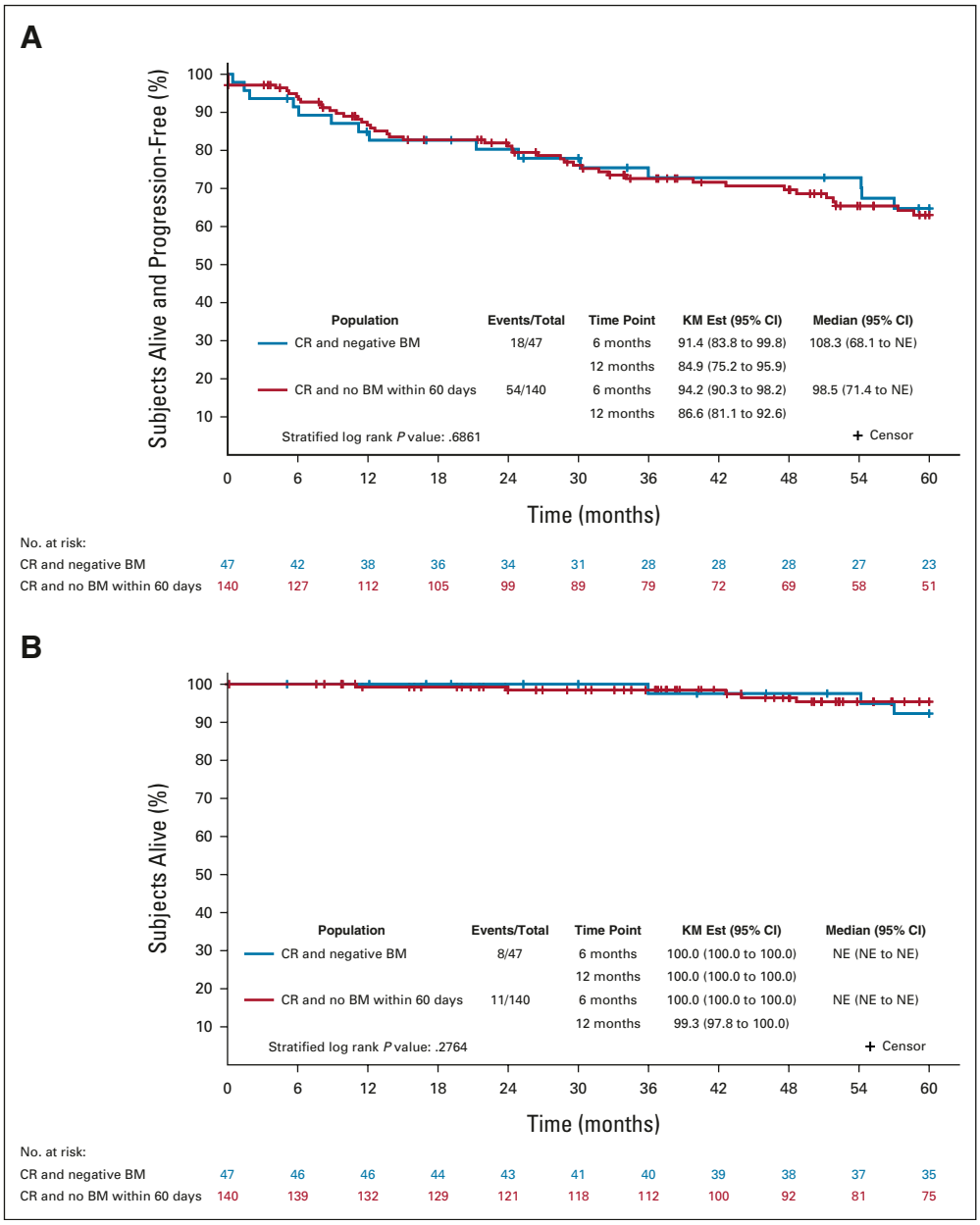

FIG 1. Landmark survival analysis. For subjects with positive BMB at baseline and subsequent CR on imaging, (A) progression-free survival and (B) overall survival were not different between those patients who had negative BMB within 60 days of the first CR on imaging (n = 47) and those who did not undergo repeat BMB within 60 days (n = 140). BM, bone marrow; BMB, bone marrow biopsy; CR, complete response; KM, Kaplan-Meier; NE, not evaluable.

Guidelines for FL still require routine staging BMB, although the procedures are inconsistently done in clinical practice.[4,5] NCCN guidelines do specifically note that the procedures can be eliminated in those who are being followed without treatment.[4] Our study indicates that BMB are unnecessary for response assessment and do not affect PFS or OS.

BMB in FL are still useful in select circumstances including for confirmation of stage I disease in which radiotherapy can be administered with curative intent. The stage I FL patient population was studied prospectively in the National LymphoCare Study, and those who underwent rigorous staging including imaging and BMB had longer PFS compared with those who did not.[21] In addition, in FL patients with significant cytopenias, BMB can help determine the etiology. Interestingly, in our study, there was no association found between baseline cytopenias and positive findings on BMB.

Limitations of our study include its retrospective nature and response criteria variation in NCTN FL clinical trials. The

CT-based IWG 2007 criteria were the response criteria in place at the time when the trials included in our study were performed. Current clinical trials primarily use the PET-based Lugano criteria. The two do not differ with respect to BMB recommendations; therefore, we expect our findings and conclusions to also apply when Lugano criteria are used to determine response. Our prior investigation of the GALLIUM data set found that a minimal number of subjects with FL who underwent PET imaging had alteration in response assessment on the basis of BMB. Because of differences in timing of BMB requirements, we were unable to include FL subjects from the ECOG trial in the primary analysis; however, findings with this cohort were similar to those in the primary group. We cannot rule out the influence of tumor bulk in the patient population studied in our analysis, but we think it is unlikely that this would affect our findings. The broad inclusion criteria are an advantage of our study, which make our conclusions applicable to the wide variety of patients with FL receiving frontline therapy. We note that bone marrow assessments may have been limited by technical issues including size of core, as well as lack of central review. In addition, a significant number of subjects did not undergo confirmatory BMB. This may indicate the hesitancy of both patients and physicians regarding invasive procedures, especially when the results would not change management. The landmark survival analysis confirms there is no difference in PFS or OS in subjects with CR on imaging regardless of BMB results.

Less invasive diagnostic tests including liquid biopsies are currently being investigated in lymphomas. Circulating tumor DNA levels of *BCL2/IgH* rearrangement and V(D)J immunoglobulin sequences correlate with PFS in FL.[22-25] In mantle cell lymphoma, higher levels of circulating tumor DNA are associated with bone marrow involvement.[26] These types of assays may eventually provide a surrogate for bone marrow involvement in lymphomas and become part of standard staging and monitoring of lymphomas including FL.

BMB requirements may discourage participation in clinical trials and add pain, expense, and time without providing necessary information in enrolled FL subjects. Furthermore, for 99% of patients with FL (including 96% with advanced stage disease), we show no benefit to marrow assessment on either prognosis or response assessment, validating previously published smaller experiences. Based upon these results, BMB should be eliminated from diagnostic guidelines in FL, and no longer incorporated as response assessments in clinical trials for patients with FL. This strategy is consistent with initiatives including the American Board of Internal Medicine Foundation's Choosing Wisely Campaign, as well as joint efforts by ASCO and Friends of Cancer Research to maximize value of medical interventions and modernize eligibility criteria and therefore make clinical care and trial enrollment more patient-focused.[1-3,27]

AFFILIATIONS

[1]Weill Department of Medicine, Division of Hematology and Medical Oncology, Meyer Cancer Center, Weill Cornell Medicine and NewYork-Presbyterian Hospital, New York, NY
[2]Mayo Clinic, Rochester, MN
[3]Fred Hutchinson Cancer Research Center, Seattle, WA
[4]University of Wisconsin, Madison, WI
[5]Dana-Farber Cancer Institute, Boston, MA
[6]Emory University, Winship Cancer Institute, Atlanta, GA
[7]Duke University, Raleigh, NC
[8]University of Vermont, Burlington, VT
[9]University of Rochester, Wilmot Cancer Institute, Rochester, NY
[10]Scientific Advisor, Lymphoma Research Foundation, New York, NY
[11]Washington University School of Medicine, Siteman Cancer Center, St Louis, MO

CORRESPONDING AUTHOR

Sarah C. Rutherford, MD, Weill Cornell Medicine and NewYork-Presbyterian Hospital, 1305 York Ave, Y-764, New York, NY 10021; Twitter: @drsarahruth; e-mail: sar2014@med.cornell.edu.

DISCLAIMER

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

PRIOR PRESENTATION

Presented in abstract form at the American Society of Clinical Oncology Annual Meeting, virtual, May 29-31, 2020.

SUPPORT

Supported by the National Cancer Institute of the National Institutes of Health under Award Numbers U10CA180821 and U10CA180882 (to the Alliance for Clinical Trials in Oncology), UG1CA233339, UG1CA233247, UG1CA233253, UG1CA233277, UG1CA233328, U10CA180888, and U10CA180819. https://acknowledgments.alliancefound.org. Also supported in part by Celgene (50803) and GSK (50901, 50904).

CLINICAL TRIAL INFORMATION

NCT00553501, NCT01145495, NCT01190449, NCT01286272, NCT01829568, NCT00006721, NCT00770224, NCT00075946

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/jco.21.02301.

DATA SHARING STATEMENT

Data sharing requests should be made to sar2014@med.cornell.edu for deidentified data. Such requests will be considered by the study team after publication following review and approval of proposals, and with appropriate data-sharing agreements in place.

AUTHOR CONTRIBUTIONS

Conception and design: Sarah C. Rutherford, Jun Yin, Levi Pederson, Sumithra J. Mandrekar, John P. Leonard

Provision of study materials or patients: Mazyar Shadman, Hongli Li, Michael L. LeBlanc, Vaishalee Kenkre, Fangxin Hong, Kristie A. Blum, Travis Dockter, Peter Martin, Sin-Ho Jung, Barbara Grant, Cara Rosenbaum, Chaitra Ujjani, Paul M. Barr, Joseph M. Unger, Bruce D. Cheson, Nancy L. Bartlett, Brad Kahl, Jonathan W. Friedberg, Sumithra J. Mandrekar, John P. Leonard

Collection and assembly of data: Sarah C. Rutherford, Jun Yin, Levi Pederson, Gabriela Perez Burbano, Mazyar Shadman, Hongli Li, Michael L. LeBlanc, Vaishalee P. Kenkre, Fangxin Hong, Kristie A. Blum, Travis Dockter, Barbara Grant, Chaitra Ujjani, Joseph M. Unger, Bruce D. Cheson, Nancy L. Bartlett, Brad Kahl

Data analysis and interpretation: Sarah C. Rutherford, Jun Yin, Levi Pederson, Gabriela Perez Burbano, Betsy LaPlant, Mazyar Shadman, Vaishalee P. Kenkre, Kristie A. Blum, Peter Martin, Sin-Ho Jung, Cara Rosenbaum, Paul M. Barr, Joseph M. Unger, Nancy L. Bartlett, Brad Kahl, Jonathan W. Friedberg, Sumithra J. Mandrekar, John P. Leonard

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

REFERENCES

1. Rubin EH, Scroggins MJ, Goldberg KB, et al: Strategies to maximize patient participation in clinical trials. Am Soc Clin Oncol Ed Book 37:216-221, 2017
2. Lichtman SM, Harvey RD, Damiette Smit MA, et al: Modernizing clinical trial eligibility criteria: Recommendations of the American Society of Clinical Oncology-Friends of Cancer Research Organ Dysfunction, Prior or Concurrent Malignancy, and Comorbidities Working Group. J Clin Oncol 35:3753-3759, 2017
3. Nipp RD, Hong K, Paskett ED: Overcoming barriers to clinical trial enrollment. Am Soc Clin Oncol Ed Book 39:105-114, 2019
4. Zelenetz AD, Gordon LI, Abramson JS, et al: NCCN guidelines insights: B-cell lymphomas, version 3.2019. J Natl Compr Canc Netw 17:650-661, 2019
5. Dreyling M, Ghielmini M, Rule S, et al: Newly diagnosed and relapsed follicular lymphoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 32:298-308, 2021
6. 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
7. Cheson BD, Pfistner B, Juweid ME, et al: Revised response criteria for malignant lymphoma. J Clin Oncol 25:579-586, 2007
8. Cheson BD, Fisher RI, Barrington SF, et al: Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: The Lugano classification. J Clin Oncol 32:3059-3068, 2014
9. Rutherford SC, Li V, Ghione P, et al: Bone marrow biopsies do not impact response assessment for follicular lymphoma patients treated on clinical trials. Br J Haematol 179:242-245, 2017
10. Marcus R, Davies A, Ando K, et al: Obinutuzumab for the first-line treatment of follicular lymphoma. N Engl J Med 377:1331-1344, 2017
11. Rutherford SC, Herold M, Hiddemann W, et al: Impact of bone marrow biopsy on response assessment in immunochemotherapy-treated lymphoma patients in GALLIUM and GOYA. Blood Adv 4:1589-1593, 2020
12. Carbone PP, Kaplan HS, Musshoff K, et al: Report of the Committee on Hodgkin's Disease Staging Classification. Cancer Res 31:1860-1861, 1971
13. Lister TA, Crowther D, Sutcliffe SB, et al: Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds meeting. J Clin Oncol 7:1630-1636, 1989
14. Hutchings M, Loft A, Hansen M, et al: Position emission tomography with or without computed tomography in the primary staging of Hodgkin's lymphoma. Haematologica 91:482-489, 2006
15. El-Galaly TC, d'Amore F, Mylam KJ, et al: Routine bone marrow biopsy has little or no therapeutic consequence for positron emission tomography/computed tomography-staged treatment-naive patients with Hodgkin lymphoma. J Clin Oncol 30:4508-4514, 2012
16. Barrington SF, Mikhaeel NG, Kostakoglu L, et al: Role of imaging in the staging and response assessment of lymphoma: Consensus of the International Conference on Malignant Lymphomas Imaging Working Group. J Clin Oncol 32:3048-3058, 2014
17. Eichenauer DA, Aleman BMP, André M, et al: Hodgkin lymphoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 29: iv19-iv29, 2018 (suppl 4)
18. Khan AB, Barrington SF, Mikhaeel NG, et al: PET-CT staging of DLBCL accurately identifies and provides new insight into the clinical significance of bone marrow involvement. Blood 122:61-67, 2013
19. Berthet L, Cochet A, Kanoun S, et al: In newly diagnosed diffuse large B-cell lymphoma, determination of bone marrow involvement with 18F-FDG PET/CT provides better diagnostic performance and prognostic stratification than does biopsy. J Nucl Med 54:1244-1250, 2013
20. Adams HJA, Kwee TC, de Keizer B, et al: FDG PET/CT for the detection of bone marrow involvement in diffuse large B-cell lymphoma: Systematic review and meta-analysis. Eur J Nucl Med Mol Imaging 41:565-574, 2014
21. Friedberg JW, Byrtek M, Link BK, et al: Effectiveness of first-line management strategies for stage I follicular lymphoma: Analysis of the National LymphoCare study. J Clin Oncol 30:3368-3375, 2012
22. Galimberti S, Luminari S, Ciabatti E, et al: Minimal residual disease after conventional treatment significantly impacts on progression-free survival of patients with follicular lymphoma: The FIL FOLL05 trial. Clin Cancer Res 20:6398-6405, 2014
23. Zohren F, Bruns I, Pechtel S, et al: Prognostic value of circulating Bcl-2/IgH levels in patients with follicular lymphoma receiving first-line immunochemotherapy. Blood 126:1407-1414, 2015
24. Sarkozy C, Huet S, Carlton VEH, et al: The prognostic value of clonal heterogeneity and quantitative assessment of plasma circulating clonal IG-VDJ sequences at diagnosis in patients with follicular lymphoma. Oncotarget 8:8765-8774, 2017
25. Delfau-Larue MH, van der Gucht A, Dupuis J, et al: Total metabolic tumor volume, circulating tumor cells, cell-free DNA: Distinct prognostic value in follicular lymphoma. Blood Adv 2:807-816, 2018
26. Agarwal R, Chan YC, Tam CS, et al: Dynamic molecular monitoring reveals that SWI-SNF mutations mediate resistance to ibrutinib plus venetoclax in mantle cell lymphoma. Nat Med 25:119-129, 2019
27. ABIM Foundation; ACP-ASIM Foundation; European Federation of Internal Medicine: Medical professionalism in the new millennium: A physician charter. Ann Intern Med 136:243-246, 2002

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Relevance of Bone Marrow Biopsies for Response Assessment in US National Cancer Institute National Clinical Trials Network Follicular Lymphoma Clinical Trials

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/authors/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

Sarah C. Rutherford
Consulting or Advisory Role: Kite, a Gilead company, Dova Pharmaceuticals, ADC Therapeutics, Juno/Celgene, Karyopharm Therapeutics
Research Funding: Genentech (Inst), Karyopharm Therapeutics (Inst)

Jun Yin
Employment: Mayo Clinic

Mazyar Shadman
Consulting or Advisory Role: AbbVie, Genentech, AstraZeneca, Sound Biologics, Cellectar, Pharmacyclics, BeiGene, Bristol Myers Squibb/Celgene, MorphoSys, Innate Pharma, Kite, a Gilead company, Adaptive Biotechnologies, Epizyme, Fate therapeutics, Lilly, Regeneron, Adaptimmune, MustangBio, TG Therapeutics, MEI Pharma
Research Funding: Pharmacyclics (Inst), Acerta Pharma (Inst), Merck (Inst), TG Therapeutics (Inst), BeiGene (Inst), Celgene (Inst), Genentech (Inst), MustangBio (Inst), AbbVie (Inst), Sunesis Pharmaceuticals (Inst), Bristol Myers Squibb/Celgene

Michael L. LeBlanc
Consulting or Advisory Role: Agios

Vaishalee P. Kenkre
Research Funding: Novartis (Inst), MEI Pharma (Inst), Celgene/Bristol Myers Squibb (Inst), Seattle Genetics (Inst), Abbott Laboratories (Inst), Gilead Sciences (Inst)

Fangxin Hong
Employment: Pfizer
Consulting or Advisory Role: Merck Sharp & Dohme

Kristie A. Blum
Honoraria: American Society of Hemotology, Leidos Biomedical Research/NCI
Research Funding: Genentech/Roche (Inst), Seattle Genetics (Inst), BMSi (Inst)
Travel, Accommodations, Expenses: American Society of Hemotology

Peter Martin
Consulting or Advisory Role: Janssen, BeiGene, Karyopharm Therapeutics, Kite/Gilead, Verastem, ADC Therapeutics, Bristol Myers Squibb/Celgene, Epizyme, Merck, MorphoSys, Takeda
Research Funding: Karyopharm Therapeutics (Inst)

Sin-Ho Jung
Consulting or Advisory Role: Samsung

Cara Rosenbaum
Stock and Other Ownership Interests: Merck/Organon
Consulting or Advisory Role: Takeda, Janssen Biotech, Akcea Therapeutics, GlaxoSmithKline, Oncopeptides
Research Funding: Amgen, GlaxoSmithKline, Janssen Oncology, Karyopharm Therapeutics

Chaitra Ujjani
Honoraria: AstraZeneca, Pharmacyclics, Kite/Gilead, AbbVie, Genentech, MorphoSys, TG Therapeutics, Janssen, Incyte, BeiGene, Lilly
Consulting or Advisory Role: AstraZeneca, Epizyme, Atara Biotherapeutics
Research Funding: Pharmacyclics (Inst), AbbVie (Inst), Lilly, AstraZeneca/MedImmune, Adaptive Biotechnologies, Kite, a Gilead company

Paul M. Barr
This author is a member of the *Journal of Clinical Oncology* Editorial Board. Journal policy recused the author from having any role in the peer review of this manuscript.
Consulting or Advisory Role: Pharmacyclics, AbbVie, Seattle Genetics, Genentech, Novartis, Infinity Pharmaceuticals, Janssen, Merck, TG Therapeutics, MorphoSys, AstraZeneca, BeiGene, MEI Pharma, Bristol Myers Squibb/Celgene, Bayer
Research Funding: Pharmacyclics (Inst), AstraZeneca (Inst)

Bruce D. Cheson
Leadership: SymBio Pharmaceuticals
Consulting or Advisory Role: TG Therapeutics, AbbVie, Pharmacyclics/Janssen, Morphosys, Celgene, Karyopharm Therapeutics, Epizyme, Gilead Sciences, SymBio Pharmaceuticals, Parexel, Lilly, Imaging Endpoints
Speakers' Bureau: MorphoSys/Incyte, BeiGene, Lilly, TG Therapeutics
Research Funding: TG Therapeutics (Inst), Seattle Genetics (Inst), Bristol Myers Squibb (Inst), Gilead Sciences (Inst)
Travel, Accommodations, Expenses: SymBio Pharmaceuticals

Nancy L. Bartlett
Consulting or Advisory Role: Seattle Genetics, Roche/Genentech, ADC Therapeutics, BTG, Acerta Pharma
Research Funding: Seattle Genetics (Inst), Kite, a Gilead company (Inst), Merck (Inst), Bristol Myers Squibb (Inst), Celgene (Inst), Immune Design (Inst), Forty Seven (Inst), Janssen (Inst), Pharmacyclics (Inst), Millennium (Inst), ADC Therapeutics (Inst), Autolus (Inst), Roche/Genentech (Inst), Pfizer (Inst), Affimed Therapeutics (Inst)

Brad Kahl
This author is a member of the *Journal of Clinical Oncology* Editorial Board. Journal policy recused the author from having any role in the peer review of this manuscript.
Consulting or Advisory Role: Celgene, AbbVie, Pharmacyclics, Acerta Pharma, ADC Therapeutics, Genentech, Roche, AstraZeneca, BeiGene, Bayer, MEI Pharma, Kite/Gilead, MorphoSys, Janssen, Bristol Myers Squibb, Incyte, Genmab
Research Funding: Genentech (Inst), Acerta Pharma (Inst), ADC Therapeutics (Inst), Celgene (Inst)

Jonathan W. Friedberg
This author is the Editor-in-Chief of *Journal of Clinical Oncology*. Journal policy recused the author from having any role in the peer review of this manuscript.
Research Funding: Enterome (Inst)
Patents, Royalties, Other Intellectual Property: Patient on bone marrow microenvironment signals

Sumithra J. Mandrekar
Honoraria: BeiGene
Consulting or Advisory Role: Flatiron Health, Harbinger Oncology, Inc
Other Relationship: Beigene

John P. Leonard
Consulting or Advisory Role: Celgene, Bristol Myers Squibb, Gilead Sciences, Epizyme, Bayer, Genentech/Roche, ADC Therapeutics, MEI Pharma, AstraZeneca, Merck, Morphosys, Karyopharm Therapeutics, Sutro Biopharma, Miltenyi Biotec, Regeneron, Akcea Therapeutics, Sandoz, Nordic Nanovector, Genmab, AbbVie, Incyte, Janssen Oncology, Eisai, MustangBio, Second Genome
Research Funding: Celgene (Inst), Alliance for Clinical Trials in Oncology (Inst), Takeda (Inst), Pfizer (Inst), National Cancer Institute (Inst), Janssen Oncology (Inst), Epizyme (Inst), Genentech (Inst)
Travel, Accommodations, Expenses: BeiGene

No other potential conflicts of interest were reported.

APPENDIX

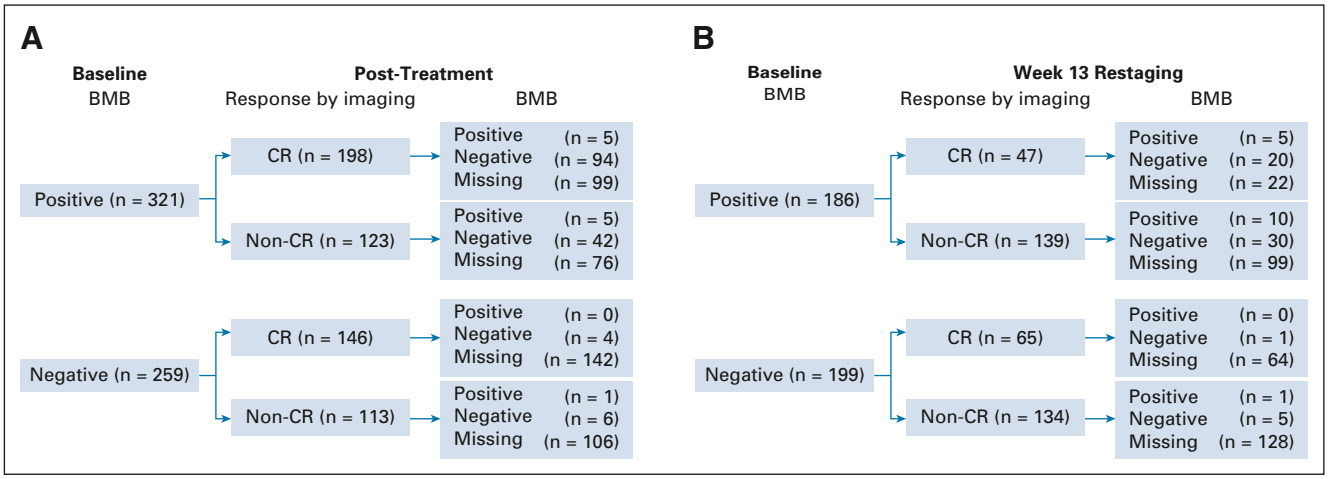

FIG A1. (A) Flow diagram for Alliance and SWOG trials. (B) Flow diagram for the ECOG trial. BMB, bone marrow biopsy; CR, complete response; ECOG, Eastern Cooperative Oncology Group.

TABLE A1. Baseline BMB Results in Patients With Normal Versus Decreased Blood Counts in Alliance Studies With Data Available (N = 191)

	Baseline BMB Result				
Blood Count	**Positive (n = 99)**	**Negative (n = 91)**	**Missing (n = 1)**	**Total (N = 191)**	***P***
Baseline blood counts, No. (%)					.8465[a]
Normal	76 (76.8)	69 (75.8)	1 (100.0)	146 (76.4)	
Decreased[b]	23 (23.2)	22 (24.2)	0 (0.0)	45 (23.6)	

Abbreviation: BMB, bone marrow biopsy.

[a]Chi-square *P* value.

[b]Absolute neutrophil count $< 1.0 \times 10^9$/L, hemoglobin < 12 g/dL, or platelet count $< 100 \times 10^9$/L.

TABLE A2. Proportion of Subjects With Positive BMB at Baseline, CR on Post-Therapy Imaging, and Positive Repeat BMB

Subject Population	**Events (No. of subjects)**	**Binomial Proportion (95% CI)**	**One-Sided *P***
All studies (Alliance and SWOG)	5 (580)	0.0086 (0.0028 to 0.0200)	< .0001
Phase I studies	0 (22)	Not evaluable	1.0000
Phase II studies	2 (383)	0.0052 (0.0006 to 0.0187)	< .0001
Phase III studies	3 (175)	0.0171 (0.0035 to 0.0493)	< .0001
CALGB 50904	0 (130)	Not evaluable	1.0000
CALGB 50901	1 (46)	0.0217 (0.0006 to 0.1153)	.0480
A51103	0 (22)	Not evaluable	1.0000
CALGB 50701	0 (59)	Not evaluable	1.0000
CALBG 50803	1 (64)	0.0156 (0.0004 to 0.0840)	.0096
S0016	3 (175)	0.0171 (0.0035 to 0.0493)	< .0001
S0801	0 (84)	Not evaluable	1.0000

Abbreviations: BMB, Bone marrow biopsy; CALGB, Alliance and legacy Cancer and Leukemia Group B; CR, complete response.

TABLE A3. Subject Characteristics (Alliance and SWOG *v* ECOG studies)

	Alliance and SWOG	ECOG
Characteristic	**Total (N = 580)**	**Total (N = 385)**
Age at diagnosis, years		
No.	532	384
Mean (SD)	54.9 (11.49)	59.0 (11.67)
Median	55.0	58.2
Range	25.0-90.0	25.1-86.2
Missing	48	1
Age at registration, years		
No.	579	384
Mean (SD)	55.8 (11.44)	59.4 (11.66)
Median	55.4	58.8
Range	25.0-90.0	25.2-86.4
Missing	1	1
Sex, No. (%)		
Male	297 (51.2)	185 (48.1)
Female	283 (48.8)	200 (51.9)
Ann Arbor stage, No. (%)		
I	0 (0.0)	2 (0.5)
II	23 (4.0)	1 (0.3)
III	211 (36.4)	184 (47.9)
IV	346 (59.7)	197 (51.3)
Missing	0	1
FL grade, No. (%)		
I	128 (27.2)	0 (0.0)
I/II	150 (31.8)	0 (0.0)
II	136 (28.9)	0 (0.0)
III	11 (2.3)	0 (0.0)
IIIa	46 (9.8)	0 (0.0)
Missing	109	385
FLIPI risk group, No. (%)		
Low risk	113 (19.6)	67 (17.4)
Intermediate risk	265 (45.9)	179 (46.5)
High risk	199 (34.5)	139 (36.1)
Missing	3	0
Treatment type, No. (%)		
Chemotherapy plus targeted therapy	388 (67.0)	0 (0.0)
Targeted therapy	191 (33.0)	385 (100.0)
Missing	1	0
Baseline BM result, No. (%)		
Negative	259 (44.7)	199 (51.7)
Positive	321 (55.3)	186 (48.3)

Abbreviations: BM, bone marrow; ECOG, Eastern Cooperative Oncology Group; FL, follicular lymphoma; FLIPI, Follicular Lymphoma International Prognostic Index; SD, standard deviation.

TABLE A4. Subject Characteristics by Study

Characteristic	Study							
	50904 (N = 130)	50901 (N = 46)	A051103 (N = 22)	50701 (N = 59)	50803 (N = 64)	S0016 (N = 175)	S0801 (N = 84)	E4402 (N = 385)
Age at diagnosis, years								
No.	130	NA	21	59	64	174	84	384
Mean (SD)	59.7 (11.78)	NA	54.9 (12.17)	54.3 (12.28)	52.5 (10.06)	53.4 (10.73)	53.0 (11.02)	59.0 (11.67)
Median	61.0	NA	54.0	53.0	53.0	53.9	51.8	58.2
Range	25.0-87.0	NA	36.0-80.0	32.0-90.0	30.0-79.0	28.8-77.8	28.6-79.8	25.1-86.2
Age at registration, years								
No.	130	45	22	59	64	175	84	384
Mean (SD)	60.2 (11.84)	60.2 (10.46)	55.0 (12.14)	54.9 (12.37)	53.3 (9.99)	53.9 (10.60)	53.3 (10.97)	59.4 (11.66)
Median	62.0	59.0	53.5	54.0	53.0	54.0	52.3	58.8
Range	25.0-88.0	40.0-85.0	36.0-81.0	32.0-90.0	32.0-79.0	28.9-77.9	28.9-79.9	25.2-86.4
Sex, No. (%)								
Male	70 (53.8)	25 (54.3)	15 (68.2)	24 (40.7)	31 (48.4)	92 (52.6)	40 (47.6)	185 (48.1)
Female	60 (46.2)	21 (45.7)	7 (31.8)	35 (59.3)	33 (51.6)	83 (47.4)	44 (52.4)	200 (51.9)
Ann Arbor stage, No. (%)								
I	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)
II	2 (1.5)	1 (2.2)	1 (4.5)	2 (3.4)	5 (7.8)	9 (5.1)	3 (3.6)	1 (0.3)
III	42 (32.3)	26 (56.5)	4 (18.2)	19 (32.2)	26 (40.6)	61 (34.9)	33 (39.3)	184 (47.9)
IV	86 (66.2)	19 (41.3)	17 (77.3)	38 (64.4)	33 (51.6)	105 (60.0)	48 (57.1)	197 (51.3)
Missing	0	0	0	0	0	0	0	1
FL grade, No. (%)								
I	33 (26.8)	22 (47.8)	2 (9.1)	32 (56.1)	39 (62.9)	0 (0.0)	NA	NA
I/II	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	150 (93.2)	NA	NA
II	63 (51.2)	18 (39.1)	14 (63.6)	22 (38.6)	19 (30.6)	0 (0.0)	NA	NA
III	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	11 (6.8)	NA	NA
IIIa	27 (22.0)	6 (13.0)	6 (27.3)	3 (5.3)	4 (6.5)	0 (0.0)	NA	NA
Missing	7	0	0	2	2	14	84	385
FLIPI risk group, No. (%)								
Low risk	0 (0.0)	10 (22.2)	3 (13.6)	12 (20.7)	21 (32.8)	52 (29.7)	15 (17.9)	67 (17.4)
Intermediate risk	38 (29.5)	35 (77.8)	11 (50.0)	28 (48.3)	41 (64.1)	77 (44.0)	35 (41.7)	179 (46.5)
High risk	91 (70.5)	0 (0.0)	8 (36.4)	18 (31.0)	2 (3.1)	46 (26.3)	34 (40.5)	139 (36.1)
Missing	1	1	0	1	0	0	0	0

(continued on following page)

TABLE A4. Subject Characteristics by Study (continued)

Characteristic	Study							
	50904 (N = 130)	50901 (N = 46)	A051103 (N = 22)	50701 (N = 59)	50803 (N = 64)	S0016 (N = 175)	S0801 (N = 84)	E4402 (N = 385)
Treatment type, No. (%)								
Chemotherapy plus targeted therapy	129 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	175 (100.0)	84 (100.0)	0 (0.0)
Targeted therapy	0 (0.0)	46 (100.0)	22 (100.0)	59 (100.0)	64 (100.0)	0 (0.0)	0 (0.0)	385 (100.0)
Missing	1	0	0	0	0	0	0	0
Baseline BM result, No. (%)								
Negative	54 (41.5)	29 (63.0)	5 (22.7)	26 (44.1)	32 (50.0)	76 (43.4)	37 (44.0)	199 (51.7)
Positive	76 (58.5)	17 (37.0)	17 (77.3)	33 (55.9)	32 (50.0)	99 (56.6)	47 (56.0)	186 (48.3)

Abbreviations: BM, bone marrow; FL, follicular lymphoma; FLIPI, Follicular Lymphoma International Prognostic Index; NA, not available; SD, standard deviation.

TABLE A5. Univariable and Multivariable Cox Proportional Hazards Models

PFS (from first CR by imaging) Cox PH Model Results

Category	No. of Events/No. of Subjects	Hazard Ratio (95% CI)	*P*
Univariable (unstratified) population	72/187		.7155
CR and negative BMB	18/47	Reference	
CR and no BMB within 60 days	54/140	1.10 (0.65 to 1.88)	.7155
Univariable (stratified)[a] population	72/187		.7447
CR and negative BMB	18/47	Reference	
CR and no BMB within 60 days	54/140	1.10 (0.62 to 1.94)	.7447
Multivariable (unstratified) population	72/187		.8980
CR and negative BMB	18/47	Reference	
CR and no BMB within 60 days	54/140	1.04 (0.60 to 1.79)	.8980
Age at registration, years (step size: 10)		1.20 (0.93 to 1.56)	.1677
Sex			.4654
Male	32/83	Reference	
Female	40/104	0.83 (0.51 to 1.36)	.4654
FLIPI risk group			.8608
Low risk	15/37	0.84 (0.41 to 1.74)	.6459
Intermediate risk	30/77	0.85 (0.46 to 1.57)	.6137
High risk	27/73	Reference	
Treatment type			.1336
Chemotherapy plus targeted therapy	50/134	0.65 (0.37 to 1.14)	.1336
Targeted therapy	22/53	Reference	
Multivariable (stratified)[a] population	72/187		.8167
CR and negative BMB	18/47	Reference	
CR and no BMB within 60 days	54/140	1.07 (0.60 to 1.91)	.8167
Age at registration, years (step size: 10)		1.13 (0.88 to 1.46)	.3347
Sex			.8685
Male	32/83	Reference	
Female	40/104	0.96 (0.56 to 1.62)	.8685
FLIPI risk group			.4418
Low risk	15/37	0.62 (0.29 to 1.31)	.2091
Intermediate risk	30/77	0.76 (0.41 to 1.40)	.3720
High risk	27/73	Reference	

OS (from first CR by imaging) Cox PH Model Results

Category	No. of Events/No. of Subjects	Hazard Ratio (95% CI)	*P*
Univariable (unstratified) population	19/187		.2831
CR and negative BMB	8/47	Reference	
CR and no BMB within 60 days	11/140	0.61 (0.24 to 1.51)	.2831
Univariable (stratified)[a] population	19/187		.2759
CR and negative BMB	8/47	Reference	
CR and no BMB within 60 days	11/140	0.59 (0.23 to 1.53)	.2759
Multivariable (unstratified) population	19/187		.2832
CR and negative BMB	8/47	Reference	
CR and no BMB within 60 days	11/140	0.60 (0.24 to 1.52)	.2832

(continued on following page)

TABLE A5. Univariable and Multivariable Cox Proportional Hazards Models (continued)

OS (from first CR by imaging) Cox PH Model Results

Category	No. of Events/No. of Subjects	Hazard Ratio (95% CI)	*P*
Age at registration, years (step size: 10)		1.04 (0.62 to 1.74)	.8736
Sex			.8264
Male	9/83	Reference	
Female	10/104	0.90 (0.35 to 2.29)	.8264
FLIPI risk group			.6130
Low risk	5/37	1.06 (0.31 to 3.55)	.9276
Intermediate risk	6/77	0.62 (0.20 to 1.94)	.4115
High risk	8/73	Reference	
Treatment type			.7770
Chemotherapy plus targeted therapy	17/134	1.26 (0.26 to 6.18)	.7770
Targeted therapy	2/53	Reference	
Multivariable (stratified)[a] population	19/187		.2155
CR and negative BMB	8/47	Reference	
CR and no BMB within 60 days	11/140	0.53 (0.20 to 1.44)	.2155
Age at registration, years (step size: 10)		1.03 (0.59 to 1.78)	.9221
Sex			.7110
Male	9/83	Reference	
Female	10/104	0.83 (0.31 to 2.22)	.7110
FLIPI risk group			.4579
Low risk	5/37	1.27 (0.37 to 4.36)	.7074
Intermediate risk	6/77	0.59 (0.19 to 1.88)	.3736
High risk	8/73	Reference	

Abbreviations: BMB, bone marrow biopsy; CR, complete response; FLIPI, Follicular Lymphoma International Prognostic Index; OS, overall survival; PFS, progression-free survival; PH, proportional hazard.

[a]Stratified by treatment arm within study.

TABLE A6. Characteristics of Patients With Positive Baseline BMB and Complete Response on Imaging

Characteristic	BMB Completion Status: Assessed (n = 99)	BMB Completion Status: Not Assessed (n = 99)	Total (N = 198)
Age at diagnosis, years			
No.	91	99	190
Mean (SD)	52.5 (9.94)	52.2 (10.84)	52.4 (10.39)
Median	53.7	50.3	51.7
Range	33.0-77.5	30.1-82.0	30.1-82.0
Age at registration, years			
No.	99	99	198
Mean (SD)	53.0 (9.72)	52.6 (10.80)	52.8 (10.25)
Median	53.8	52.0	53.0
Range	34.0-77.5	31.2-82.0	31.2-82.0
Sex, No. (%)			
Male	42 (42.4)	45 (45.5)	87 (43.9)
Female	57 (57.6)	54 (54.5)	111 (56.1)
Ann Arbor stage, No. (%)			
III	2 (2.0)	5 (5.1)	7 (3.5)
IV	97 (98.0)	94 (94.9)	191 (96.5)
FL grade, No. (%)			
I	24 (29.3)	16 (23.9)	40 (26.8)
I/II	31 (37.8)	26 (38.8)	57 (38.3)
II	25 (30.5)	17 (25.4)	42 (28.2)
III	2 (2.4)	1 (1.5)	3 (2.0)
IIIa	0 (0.0)	7 (10.4)	7 (4.7)
Missing	17	32	49
FLIPI risk group, No. (%)			
Low risk	19 (19.2)	19 (19.2)	38 (19.2)
Intermediate risk	46 (46.5)	37 (37.4)	83 (41.9)
High risk	34 (34.3)	43 (43.4)	77 (38.9)
Treatment type, No. (%)			
Chemotherapy plus targeted therapy	71 (71.7)	73 (73.7)	144 (72.7)
Targeted therapy	28 (28.3)	26 (26.3)	54 (27.3)

Abbreviations: BMB, bone marrow biopsy; FL, follicular lymphoma; FLIPI, Follicular Lymphoma International Prognostic Index.