original reports

ROBUST: A Phase III Study of Lenalidomide Plus R-CHOP Versus Placebo Plus R-CHOP in Previously Untreated Patients With ABC-Type Diffuse Large B-Cell Lymphoma

Grzegorz S. Nowakowski, MD[1]; Annalisa Chiappella, MD[2]; Randy D. Gascoyne, MD[3]; David W. Scott, MBChB, PhD[3]; Qingyuan Zhang, MD[4]; Wojciech Jurczak, MD, PhD[5]; Muhit Özcan, MD, PhD[6]; Xiaonan Hong, MD[7]; Jun Zhu, MD[8]; Jie Jin, MD[9]; David Belada, MD[10]; Juan Miguel Bergua, MD[11]; Francesco Piazza, MD[12]; Heidi Mócikova, MD[13]; Anna Lia Molinari, MD[14]; Dok Hyun Yoon, MD[15]; Federica Cavallo, MD[16]; Monica Tani, MD[17]; Kazuhito Yamamoto, MD, PhD[18]; Koji Izutsu, MD[19]; Koji Kato, MD[20]; Myron Czuczman, MD[21]; Sarah Hersey, MS, MBA, RAC[22]; Adrian Kilcoyne, MD[21]; Jacqueline Russo, BS[21]; Krista Hudak, PharmD[21]; Jingshan Zhang, PhD[21]; Steve Wade, BS[23]; Thomas E. Witzig, MD[1]; and Umberto Vitolo, MD[2]; on behalf of the ROBUST Trial Investigators

abstract

PURPOSE Patients with the activated B-cell-like (ABC) subtype of diffuse large B-cell lymphoma (DLBCL) historically showed inferior survival with standard rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). Phase II studies demonstrated that adding the immunomodulatory agent lenalidomide to R-CHOP improved outcomes in ABC-type DLBCL. The goal of the global, phase III ROBUST study was to compare lenalidomide plus R-CHOP (R2-CHOP) with placebo/R-CHOP in previously untreated, ABC-type DLBCL.

METHODS Histology and cell-of-origin type were prospectively analyzed by central pathology prior to random assignment and study treatment. Patients with ABC-DLBCL received lenalidomide oral 15 mg/d, days 1-14/21 plus standard R-CHOP21 versus placebo/R-CHOP21 for six cycles. The primary end point was progression-free survival (PFS) per independent central radiology review.

RESULTS A total of 570 patients with ABC-DLBCL (n = 285 per arm) were stratified by International Prognostic Index score, age, and bulky disease, and randomly assigned to R2-CHOP or placebo/R-CHOP. Baseline demographics were similar between arms. Most patients completed six cycles of treatment: 74% R2-CHOP and 84% placebo/R-CHOP. The most common grade 3/4 adverse events for R2-CHOP versus placebo/R-CHOP were neutropenia (60% *v* 48%), anemia (22% *v* 14%), thrombocytopenia (17% *v* 11%), and leukopenia (14% *v* 15%). The primary end point of PFS was not met, with a hazard ratio of 0.85 (95% CI, 0.63 to 1.14) and $P = .29$; median PFS has not been reached for either arm. PFS trends favoring R2-CHOP over placebo/R-CHOP were seen in patients with higher-risk disease.

CONCLUSION ROBUST is the first DLBCL phase III study to integrate biomarker-driven identification of eligible ABC patients. Although the ROBUST trial did not meet the primary end point of PFS in all patients, the safety profile of R2-CHOP was consistent with individual treatments with no new safety signals.

J Clin Oncol 39:1317-1328. © 2021 by American Society of Clinical Oncology

ASSOCIATED CONTENT

See accompanying editorial on page 1314

Appendix

Protocol

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

Accepted on December 15, 2020 and published at ascopubs.org/journal/jco on February 23, 2021: DOI https://doi.org/10.1200/JCO.20.01366

INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) comprises one-third of patients with mature B-cell non-Hodgkin lymphoma as the most common type of aggressive lymphoma.[1,2] Standard first-line therapy for advanced-stage DLBCL currently relies on the anti-CD20 antibody rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP).[3-5] Although > 50% of patients experience long-term disease control with R-CHOP, approximately 30% in remission ultimately relapse at increasing rates, upon which outcomes are poor.[3-6] Numerous trials attempted to improve outcomes by investigating alternate regimens, adding combination agents,[7-9] and exchanging rituximab for type II anti-CD20 antibody obinutuzumab[10]; to date, none have demonstrated a clinically significant improvement.

DLBCL is a heterogeneous disease with two major biologically distinct pathophysiologic entities based on cell-of-origin (COO) and classified as germinal center B-cell-like (GCB) and activated B-cell-like (ABC) subtypes by gene expression profiling (GEP).[11,12] These were discovered by GEP,[11,13] then later translated into an immunohistochemistry (IHC) algorithm

CONTEXT

Key Objective

What is the potential improvement in outcomes with the combination of lenalidomide plus rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) over standard R-CHOP in previously untreated patients with diffuse large B-cell lymphoma who had activated B-cell-like disease (typically associated with worse prognosis)?

Knowledge Generated

The global, phase III ROBUST study did not meet the primary end point for significantly improved progression-free survival with the lenalidomide/R-CHOP combination over control R-CHOP, although response rates were very high (91% overall response rate) in both study arms and median overall survival was not reached. The safety profile of lenalidomide plus R-CHOP was generally well tolerated, with no new safety signals with the addition of lenalidomide.

Relevance

Despite the lack of statistically significant efficacy benefit of lenalidomide with R-CHOP, these study results provide support for ongoing and future analyses to further evaluate the potential effect of pharmacokinetics or dosing, molecular classification, and mutational status in patients with diffuse large B-cell lymphoma.

categorizing them as GCB and non-GCB.[14] GEP-based models recognize a third "unclassified" category that cannot be assigned to either main subtype with sufficient confidence.[15] Patients with ABC-DLBCL treated with R-CHOP historically demonstrated inferior survival (5-year overall survival [OS]: approximately 50% ABC *v* approximately 80% GCB; $P < .001$).[16]

Preclinical studies established lenalidomide's antiproliferative activity in ABC-DLBCL cells through increasing interferon-stimulated gene transcription and activation of immunomodulatory mechanisms.[17-19] Phase II studies showed activity of lenalidomide monotherapy with tolerable safety in relapsed or refractory DLBCL.[20,21] Coupled with analyses demonstrating a significant clinical response in non-GCB versus GCB-type DLBCL,[22] these studies provided the basis for further evaluation of first-line lenalidomide with R-CHOP (R2-CHOP). Results from two independent, single-arm, phase II studies (REAL07 and MC078E) of R2-CHOP suggested that improved survival may be achieved in non-GCB DLBCL, and with manageable safety.[23,24] MC078E compared R2-CHOP-treated patients with contemporaneous R-CHOP-only controls, demonstrating that adding lenalidomide may improve survival in non-GCB DLBCL.[24] Longer follow-up of REAL07/MC078E combined non-GCB data showed durable efficacy with 5-year progression-free survival (PFS) of 65% and 5-year OS of 74%.[25] These initial results[23,24] provided proof-of-concept for ROBUST (ClinicalTrials.gov identifier: NCT02285062; EudraCT number 2013-004054-21), which prospectively compared efficacy and safety of first-line R2-CHOP with placebo/R-CHOP in ABC-type DLBCL.

METHODS

Patients

Eligible patients with CD20+, ABC-type DLBCL were of age 18-80 years, Eastern Cooperative Oncology Group performance status ≤ 2, Ann Arbor stage II-IV disease, and International Prognostic Index (IPI) score of ≥ 2. ABC subtype was determined using the NanoString Lymphoma Subtyping Test performed on NanoString's nCounter Dx analysis system (NanoString Technologies, Inc, Seattle, WA).[13] Additional eligibility criteria are provided in the Appendix (online only).

Trial Design or Treatments

ROBUST was a multicenter, international, randomized, double-blind, phase III trial (Appendix Fig A1, online only). During screening, the central pathology laboratory confirmed disease diagnosis and CD20 status, and identified COO subtype as ABC or non-ABC (GCB and unclassified). Following eligibility confirmation, patients were stratified by IPI score (2 *v* ≥ 3), age (< 65 *v* ≥ 65 years), and bulky disease (< 7 cm [nonbulky] *v* ≥ 7 cm [bulky]), and randomly assigned 1:1 to R2-CHOP or placebo/R-CHOP.

Lenalidomide dose was selected based on risk-benefit considerations from proof-of-concept studies (REAL07 and MC078E).[23,24] Treatment included lenalidomide (or placebo) 15 mg oral on days 1-14 of every 21-day cycle plus R-CHOP21 (rituximab 375 mg/m^2 intravenous [IV] day −1 or 1, cyclophosphamide 750 mg/m^2 IV day 1, doxorubicin 50 mg/m^2 IV day 1, vincristine 1.4 mg/m^2 [maximum 2.0 mg total] IV day 1, and prednisone [or prednisolone] 100 mg oral days 1-5 [IV day 1 of prednisone or prednisolone, or equivalent methylprednisolone or dexamethasone dose]). Treatment was continued for six cycles, or until intolerability, inadequate response, disease progression, consent withdrawal, or death, whichever occurred first. Two additional rituximab doses (1 dose/21-day cycle) were permitted at cycles 7 and 8 if prespecified and considered standard of care per local practice. Investigators could prospectively give prespecified local radiotherapy consolidation after chemotherapy to treat a particular bulky disease site (≥ 7 cm) or large mass.

Neutropenia prophylaxis with either granulocyte-colony stimulating factor or granulocyte macrophage-colony stimulating factor was required every cycle per local practices. Additional prophylaxis recommendations are in the Appendix. Growth factor prophylaxis was recommended, and blood product transfusions were allowed per protocol in accordance with ASCO/European Society for Medical Oncology guidelines.[26,27]

All patients received the same lenalidomide starting dose regardless of baseline creatinine clearance levels. Lenalidomide dose adjustments were planned to manage toxicity (Appendix). Rituximab and chemotherapy dose modifications were allowed per clinical practice of the investigator's institution per approved prescribing information.

The trial adhered to Good Clinical Practice per the International Conference on Harmonisation Guideline E6 under ethical principles of the Declaration of Helsinki. Study conduct followed guidance from each site's institutional review board, independent ethics committee, and regulatory authorities. All patients provided written informed consent before trial enrollment.

Efficacy and Safety Assessments

For the primary efficacy analysis, the intent-to-treat population included all randomly assigned patients regardless of receiving study treatment. The primary end point was PFS per 2014 International Working Group criteria[28] (amended from the original protocol following 2007 International Working Group criteria[29]), as assessed by Independent Radiology Adjudication Committee with Food and Drug Administration censoring rules applied.[30] Investigator-assessed results provided additional sensitivity analyses.

PFS was defined as the time from random assignment to objective disease progression or death from any cause, whichever occurred first. Secondary end points were event-free survival (EFS; key secondary), OS, response rates, duration of response, time to next lymphoma treatment, and safety. EFS was defined as the time from random assignment to initiation of disease progression, relapse from complete response, initiation of subsequent anti-lymphoma therapy, or death because of any cause. Response assessments included computed tomography and positron emission tomography scans and evaluation of laboratory or clinical data.

The safety population included all patients receiving ≥ 1 dose of any study treatment. Treatment-emergent adverse events (TEAEs) were coded per the Medical Dictionary for Drug Regulatory Activities v21.0 and classified by National Cancer Institute Common Terminology Criteria for Adverse Events v4.03 (tumor flare reaction and skin rash per v3.0).

Statistical Analyses

Superiority in PFS was defined as achieving hazard ratio (HR) = 0.625 for R2-CHOP over placebo/R-CHOP (ie, 37.5% risk reduction in disease progression) for an estimated median PFS improvement of 24 months with placebo/R-CHOP to 38 months with R2-CHOP (two-sided $P < .05$). The study was powered to measure 192/560 PFS events for 90% power and included interim futility analysis at 50% (96 events). If the event rate fell < 2 events/mo before reaching 192 events, final analysis was performed when ≥ 170 events occurred (86% power).

Demographics or characteristics and safety were summarized using descriptive statistics, and categorical variables using frequency tabulations. Time-to-event end points using an HR with two-sided 95% CI were estimated by Kaplan-Meier procedure, stratified log-rank test for treatment efficacy, and Cox proportional hazards model. Binary end points (eg, response rate) were summarized in frequency and percent by arm; stratified Cochran-Mantel-Haenszel test evaluated treatment efficacy. All statistical analyses used SAS software version ≥ 9.2 (SAS Institute, Cary, NC).

RESULTS

Patients

From February 17, 2015 to August 3, 2017, the central pathology laboratory screened samples from 2,109 patients; 570 patients with ABC-DLBCL met eligibility criteria for enrollment at 257 active study centers in 21 countries (Fig 1). Of 2,109 screened patients, exclusions were predominantly because 49% were non-ABC subtype and 24% failed other eligibility criteria (main reasons: 8% inadequate lymph node or biopsy specimen available, 5% non-Ann Arbor stage II-IV, 4% non-IPI ≥ 2, and 3% unable to adhere to protocol requirements, 1% because of a small or insufficient core or tissue biopsy).

In the intent-to-treat analysis, 285 patients in each arm were randomly assigned 1:1 to experimental R2-CHOP and control placebo/R-CHOP groups. Baseline demographics were similar between arms. Overall, patients had a median age of 65 years (52% ≥ 65 and 2% ≥ 80 years of age); 42% IPI 2/58% IPI ≥ 3 score; 88% stage III/IV disease; and 34% bulky disease (Table 1). Median time from initial diagnosis or biopsy date to treatment was 31 days for both arms (R2-CHOP: range, 6-114 days; placebo/R-CHOP: range, 8-98 days). Median follow-up time for all surviving patients was 27.1 months (range, 0-47 months).

Two patients on R2-CHOP and one on placebo/R-CHOP were randomly assigned but never received treatment, and therefore are excluded from the safety population. Adverse events (AEs) were the most frequent reason for discontinuation of lenalidomide or placebo (17% R2-CHOP *v* 11% placebo/R-CHOP; Appendix Table A2, online only).

Efficacy

Primary end point. The primary end point of PFS was not met (HR, 0.85; 95% CI, 0.63 to 1.14; $P = .29$; Table 2; Fig 2A). Median PFS was not reached in either arm; 2-year PFS was 67% for R2-CHOP and 64% for placebo/R-CHOP.

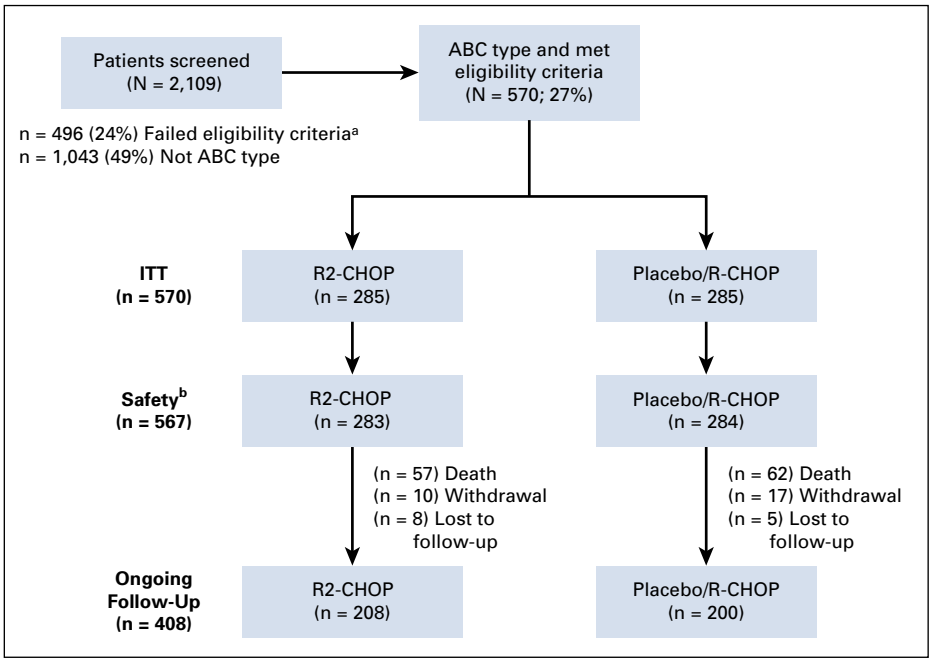

FIG 1. R2-CHOP and placebo/R-CHOP CONSORT diagram (flow of patients from screening to analysis). [a]Main reasons for failing eligibility criteria: 8% inadequate lymph node or biopsy specimen available, 5% not Ann Arbor stage II-IV, 4% not International Prognostic Index ≥ 2, and 3% unable to adhere to protocol requirements. [b]Two R2-CHOP and one placebo/R-CHOP patients were randomly assigned, but never received lenalidomide/placebo or R-CHOP. ABC, activated B-cell-like; ITT, intention to treat; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; R2-CHOP, lenalidomide plus R-CHOP.

Secondary and exploratory efficacy end points. The key secondary efficacy end point EFS was also not met (HR, 1.04 [95% CI, 0.80 to 1.34]; $P = .73$); medians were not reached (Table 2; Fig 2B). EFS included n = 10 R2-CHOP and n = 8 placebo/R-CHOP with stable disease or positron emission tomography-positive partial responses who initiated new therapy. OS data were immature; estimated 2-year OS rates were 79% R2-CHOP and 80% placebo/R-CHOP; medians were not reached (Table 2; Fig 2C). Of patients who died, 93/119 deaths (78%) were because of progressive disease (< 2% each from AEs or other causes). Overall response rates were 91% for both arms, with 69% versus 65% complete responses for R2-CHOP versus placebo/R-CHOP, respectively (Table 2). Median time to next antilymphoma treatment was not reached in either arm.

Exploratory subgroup analyses of PFS suggested a positive trend in 2-year PFS favoring R2-CHOP (*v* placebo/R-CHOP) in patients with IPI ≥ 3 (59% *v* 50%, $P = .09$; Fig 3), nonbulky disease (73% *v* 66%, $P = .05$), and lower baseline creatinine clearance 30 to < 60 mL/min (69% *v* 45%, $P = .03$; Fig 4).

Safety

The safety population included 283 R2-CHOP and 284 placebo/R-CHOP patients. Treatment in both arms was given for a median of 18.1 weeks (range, 0.3-29.0 weeks). Overall, 89% of R2-CHOP and 91% of placebo/R-CHOP patients completed six cycles of R-CHOP backbone, and 75% R2-CHOP and 84% placebo/R-CHOP completed six cycles of both lenalidomide or placebo and R-CHOP. The median relative dose intensity of lenalidomide or placebo was 15.0 mg/d for both arms; individual R-CHOP components showed similar dose intensities between arms. More than 80% of patients in both arms received a relative dose intensity of > 90% lenalidomide or placebo.

Nearly all patients experienced ≥ 1 any-grade TEAE (99% R2-CHOP and 98% placebo/R-CHOP patients), and 78% R2-CHOP and 71% placebo/R-CHOP patients had ≥ 1 grade ≥ 3 TEAE. Serious TEAEs were observed in 37% R2-CHOP versus 31% placebo/R-CHOP patients. In the respective R2-CHOP versus placebo/R-CHOP arms, dose reductions of lenalidomide or placebo were reported in 26% versus 16% of patients (mainly because of AEs) at a median time to first dose reduction of 72 and 53 days. Dose interruptions of lenalidomide or placebo were reported in 79% versus 73% of patients (mainly because of AEs), and median time to first dose interruption was 22 days for both arms. Discontinuation rates for R2-CHOP versus placebo/R-CHOP, respectively, because of AEs were 17% versus 11%, predominantly because of neutropenia (8% *v* 5%; Appendix Table A2). Dose reductions or delays because of individual R-CHOP components were similar in both arms.

Most common grade 3/4 TEAEs (≥ 10%) for R2-CHOP versus placebo/R-CHOP, respectively, were neutropenia

TABLE 1. Baseline Demographic and Disease Characteristics (Intent-to-Treat Population)

Characteristic	R2-CHOP (n = 285)	Placebo/R-CHOP (n = 285)	Total (N = 570)
Median age, years (range)	65 (21-82)	65 (28-83)	65 (21-83)
Age ≥ 65[a]	147 (52)	148 (52)	295 (52)
Age ≥ 70	94 (33)	91 (32)	185 (32)
Age ≥ 80	8 (3)	6 (2)	14 (2)
Male sex	164 (58)	143 (50)	307 (54)
ECOG PS[b]			
0	129 (45)	111 (39)	240 (42)
1	104 (36)	118 (41)	222 (39)
2	52 (18)	56 (20)	108 (19)
Ann Arbor stage			
II	37 (13)	33 (12)[c]	69 (12)
III	80 (28)	98 (34)	178 (31)
IV	168 (59)	154 (54)	322 (56)
IPI risk score[a]			
Intermediate (2)	121 (42)	120 (42)	241 (42)
High (3-5)	164 (58)	165 (58)	329 (58)
Bulky disease (≥ 7 cm)[a]	97 (34)	99 (35)	196 (34)
CrCl, mL/min			
≥ 30 to < 60	41 (14)	39 (14)	80 (14)
≥ 60	244 (86)	245 (86)	489 (86)
Missing	0 (0)	1 (0.4)	1 (0.2)
Elevated LDH[d]	177 (62)	176 (62)	353 (62)
Received two extra prespecified doses of rituximab	154 (54)	155 (54)	309 (54)
Received prespecified consolidation radiotherapy	17 (6)	8 (3)	25 (4)
Geographic distribution			
Europe	124 (44)	150 (53)	274 (48)
Asia-Pacific	111 (39)	92 (33)	203 (36)
North America	24 (8)	23 (8)	47 (8)
Other	26 (9)	20 (7)	46 (8)

NOTE. All data are no. (%) unless otherwise stated. There were no significant between-group differences in the characteristics evaluated at baseline. Percentages may not sum to 100 because of rounding.

Abbreviations: CrCl, creatinine clearance; ECOG PS, Eastern Cooperative Oncology Group performance status; IPI, International Prognostic Index; LDH, lactate dehydrogenase; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; R2-CHOP, lenalidomide plus R-CHOP.

[a]Patient stratification factors.

[b]An ECOG PS score of 0 indicates no symptoms and 1 indicates mild symptoms; higher scores indicate greater disability.

[c]Included one patient with ineligible stage I disease and one missing patient in the placebo plus R-CHOP arm.

[d]Elevated LDH levels were > 234 U/L.

(60% *v* 48%), anemia (22% *v* 14%), thrombocytopenia (17% *v* 11%), leukopenia (14% *v* 15%), febrile neutropenia (14% *v* 9%), and lymphopenia (11% *v* 8%; Table 3). More than 89% of patients in each arm received concomitant growth factors throughout the six cycles of study treatment (95% during cycle 1).

During the entire study` duration, 57 patients (20%) receiving R2-CHOP and 62 (22%)` receiving placebo/R-CHOP died; the primary cause was because of malignant disease or complications thereof (49 [17%] and 44 [16%], respectively; Appendix Table A3, online only). All other causes occurred in < 3% of patients per arm (because of AEs, unknown reasons, second primary malignancies [SPMs], or other). Death was because of SPMs for 2 patients/arm (R2-CHOP: acute myeloid leukemia and squamous cell carcinoma of the tongue; placebo/R-CHOP: lung and gastric adenocarcinomas).

TABLE 2. Efficacy Outcomes (Intent-to-Treat Population)

Variable	R2-CHOP (n = 285)	Placebo/R-CHOP (n = 285)	HR (95% CI)	*P*
Median PFS as assessed by IRAC, months (95% CI)	NR (NR to NR)	NR (35.5 to NR)	0.85 (0.63 to 1.14)	.29
PFS probability at 2 years, % (SE)	67 (3)	64 (3)	—	—
Median EFS as assessed by IRAC, months (95% CI)	NR (NR to NR)	NR (31.3 to NR)	1.04 (0.80 to 1.34)	.73
EFS probability at 2 years, % (SE)	59 (3)	61 (3)	—	—
Median OS, months (95% CI)	NR (NR to NR)	NR (NR to NR)	0.93 (0.65 to 1.32)	.64
OS probability at 2 years, % (SE)	79 (2.5)	80 (2.5)	—	—
Best response as assessed by IRAC				
ORR, no. (% [95% CI])	259 (91 [87 to 94])	259 (91 [87 to 94])	—	1.00
CR, no. (% [95% CI])	197 (69 [63 to 74])	185 (65 [59 to 70])	—	.29
PR, no. (%)	62 (22)	74 (26)	—	—
SD, no. (%)	6 (2)	2 (1)	—	—
PD, no. (%)	5 (2)	4 (1)	—	—
Unevaluable, no. (%)[a]	15 (5)	20 (7)	—	—
Median DOR as assessed by IRAC, months (95% CI)	NR (NR to NR)	NR (33.7 to NR)	0.85 (0.62 to 1.16)	.31
Median TTNLT as assessed by IRAC, months (95% CI)	NR (NR to NR)	NR (NR to NR)	1.17 (0.86 to 1.59)	.32

NOTE. Data cutoff: March 15, 2019.

Abbreviations: CR, complete response; DOR, duration of response; EFS, event-free survival; HR, hazard ratio; IRAC, Independent Radiology Adjudication Committee; NR, not reached; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; R2-CHOP, lenalidomide plus R-CHOP; SD, stable disease; SE, standard error; TTNLT, time to next antilymphoma treatment.

[a]Patients were unevaluable because of missing post-baseline response assessments; patients still contributed to time-to-event analyses.

DISCUSSION

In patients with ABC-DLBCL from ROBUST, adding lenalidomide to R-CHOP did not improve efficacy over placebo/R-CHOP. Response rates were very high (91% overall response rate) overall, median OS was not reached, and survival or SPMs continue to be followed. The R2-CHOP safety profile was generally well tolerated (no new safety signals), consistent with known profiles for individual agents.

At a median 27.1-month follow-up for survivors, placebo/R-CHOP results were interesting in that control patients had better outcomes than originally projected. Median PFS/OS were not reached; 2-year PFS and OS were 64% and 80%, respectively. Longer PFS for control patients were recently confirmed by the GOYA study, evaluating cyclophosphamide, doxorubicin, vincristine, and prednisone plus rituximab or obinutuzumab; median PFS was not reached for patients with ABC-DLBCL (median 29-month follow-up), and 3-year PFS was 58% R-CHOP and 61% obinutuzumab plus cyclophosphamide, doxorubicin, vincristine, and prednisone.[10] Multiple studies showed that R-CHOP-treated patients with ABC or non–GCB-type DLBCL expect to have 2-year PFS of ≤ 40% and 2-year OS of approximately 50%,[16,24] whereas more recent studies experienced a similar phenomenon to ROBUST. Bortezomib plus R-CHOP failed to show improved PFS over R-CHOP in non-GCB patients (per IHC) from the PYRAMID phase II study (2-year PFS: 78% R-CHOP *v* 82% bortezomib/R-CHOP)[8] or in the REMoDL-B phase III study of patients with ABC-DLBCL (per GEP), with 30-month PFS of 65% R-CHOP versus 73% bortezomib/R-CHOP.[7] The randomized phase III PHOENIX study of ibrutinib/R-CHOP versus placebo/R-CHOP was similarly disappointing with no significant difference between arms for the EFS primary end point (or other survival end points) in either non-GCB patients prospectively selected by IHC or ABC patients retrospectively evaluated by GEP.[9] Exploratory analyses from PHOENIX identified a treatment interaction for EFS, PFS, and OS favoring the ibrutinib-containing arm in patients < 60 years of age. Additional exploratory evaluations of PFS and OS in ROBUST based on age cutoffs of < 60 and ≥ 60 years of age showed no significant treatment interaction (Fig 4, Appendix Fig A2, online only). Although these independent phase II-III studies used various techniques for identifying non-GCB or ABC types, interestingly, R-CHOP control arms performed similarly to the active treatment arm, and with OS rates ≥ 80% after 2-3 years of follow-up.[7-9]

In ROBUST, there was a positive trend for PFS favoring R2-CHOP in 58% of patients with IPI score ≥ 3. This trend was not observed in the E1412 study, although IPI cutoffs evaluated in E1412 varied by including IPI groups of 2-3 versus 4-5.[31] Despite the difference, we continue to believe that IPI prognostic factors remain valid in the post-rituximab era for patients receiving R-chemotherapy-based treatment

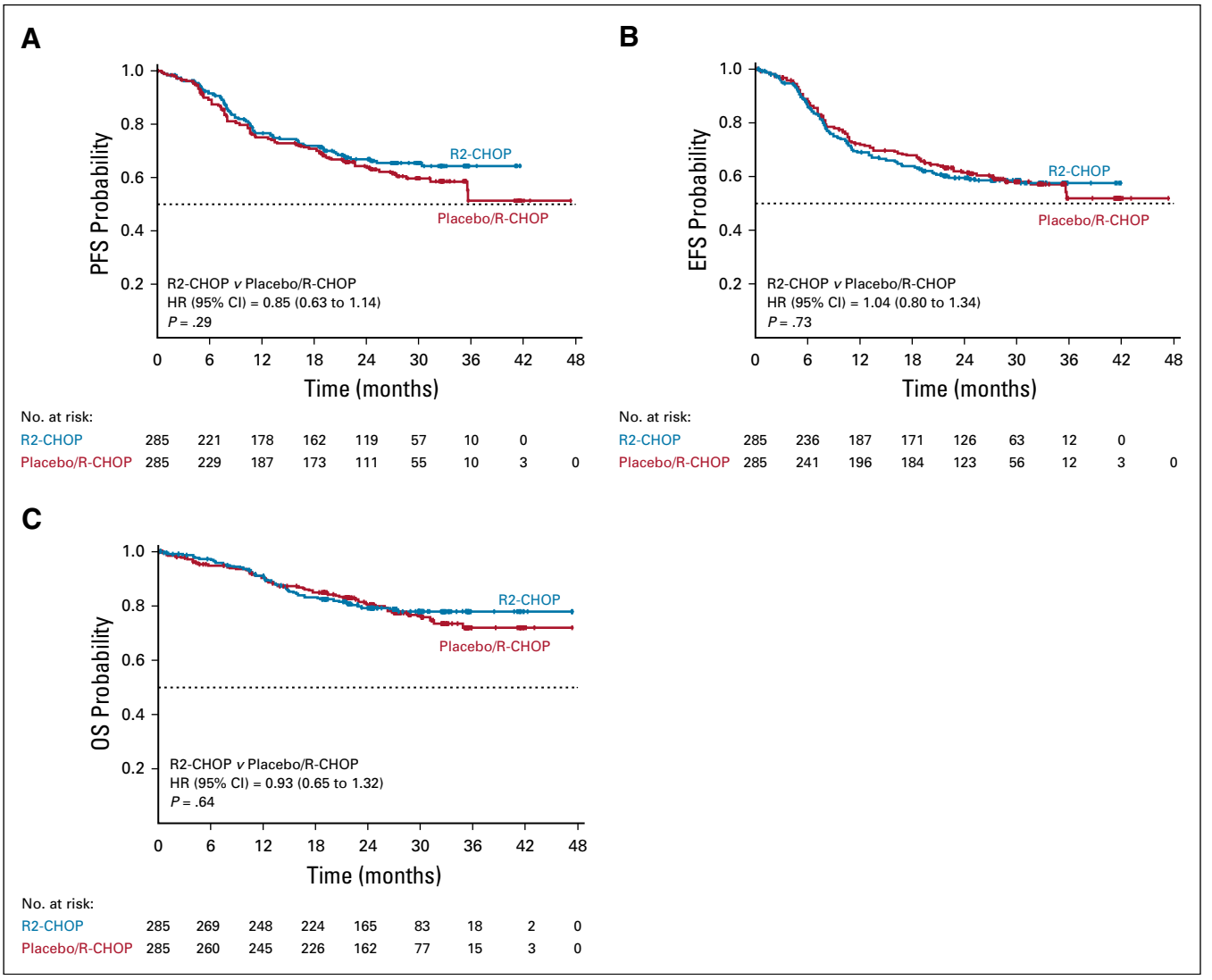

FIG 2. PFS, EFS, and OS in the intent-to-treat population: (A) progression-free survival by Independent Radiology Adjudication Committee (IRAC) assessment; (B) event-free survival by IRAC assessment; (C) OS. EFS, event-free survival; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; R2-CHOP, lenalidomide plus R-CHOP.

(except ≥ 1 extranodal disease site),[32] historically showing 3-year PFS of 59% for IPI 3 and 56% for IPI 4-5.[33]

Prior studies of lenalidomide in DLBCL supported prioritizing treatment in ABC-type patients based on disease biology and clinical benefit.[22-24] However, there appears to be additional complexity within COO subtypes,[34] leading to possible variable outcomes independent of IPI. Regional variability in ABC-type patient proportions worldwide may also contribute some differences,[35] although this remains to be determined with further study. Based on molecular classifier analyses within ABC type, further subgroups may show differential outcomes. Ongoing analyses of biomarker and mutational profiles for ROBUST's ABC patients will help identify whether variable genetic profiles affected outcomes. Moreover, further classification of types may help provide a biologic basis for novel/novel drug combinations in DLBCL.

A potential limitation here was median time from initial diagnosis (or first biopsy) to treatment initiation. Although COO sample identification was streamlined to 2.4 calendar days for time from central pathology sample receipt to COO results being provided to the study site,[35] median time from diagnosis to treatment initiation was longer at 31 days. In this global study, many patients were referred from smaller community practices to treatment centers. It is a common practice for referral centers to re-review pathology considering diagnostic difficulties in non-Hodgkin lymphoma. This can cause an additional delay, apart from the need to access and submit tissue for central review and COO assay. Similarly, many referral centers require fluorescent in situ hybridization for double-hit or triple-hit lymphoma, typically not done at community practices for additional delays. It is possible that this longer time may have led to selection bias

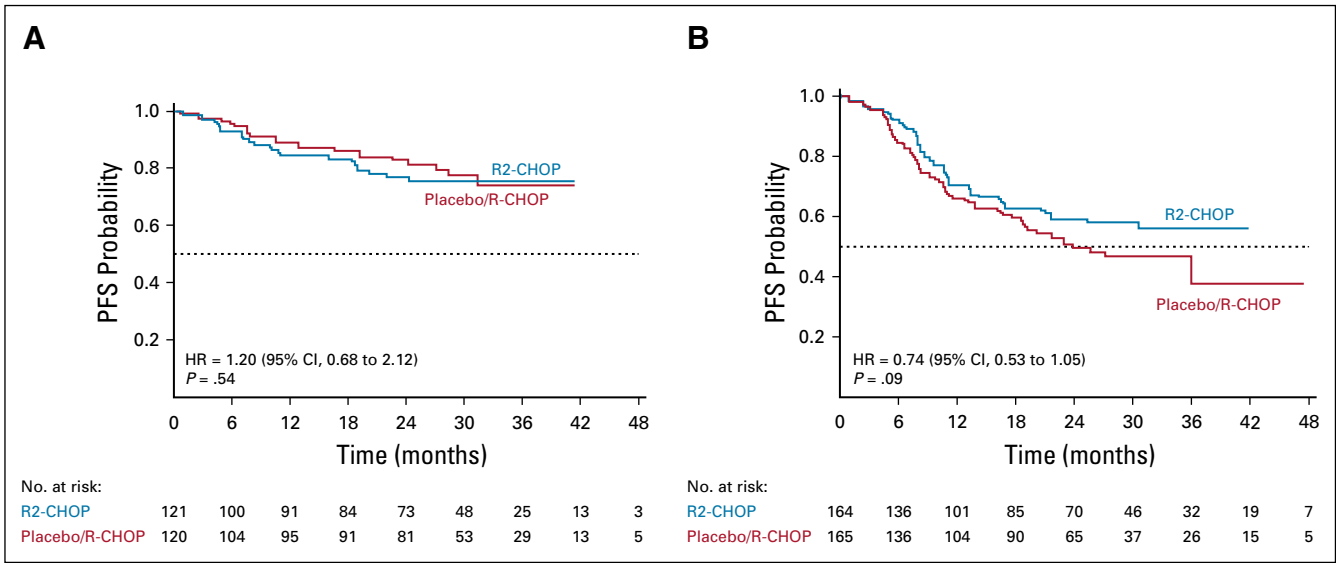

FIG 3. PFS based on IPI status (A) IPI = 2 and (B) IPI ≥ 3 (intent-to-treat population). HR, hazard ratio; IPI, International Prognostic Index; PFS, progression-free survival; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; R2-CHOP, lenalidomide plus R-CHOP.

for patients with less high-risk disease. Recently, the E1412 study of first-line R2-CHOP versus R-CHOP alone reported a median time from diagnosis to treatment of 21 days; patients were enrolled without prospective COO selection, and efficacy outcomes showed a significant PFS difference between arms, irrespective of COO subtype.[31] Recently reported evidence from large patient cohorts from the University of Iowa and Mayo Clinic (n = 986) and LYSA LNH-2003 (n = 1,444) showed that diagnosis-to-treatment interval (DTI) was an important clinical factor in newly diagnosed DLBCL.[36] Patients who received anthracycline-based immunochemotherapy demonstrated a significant

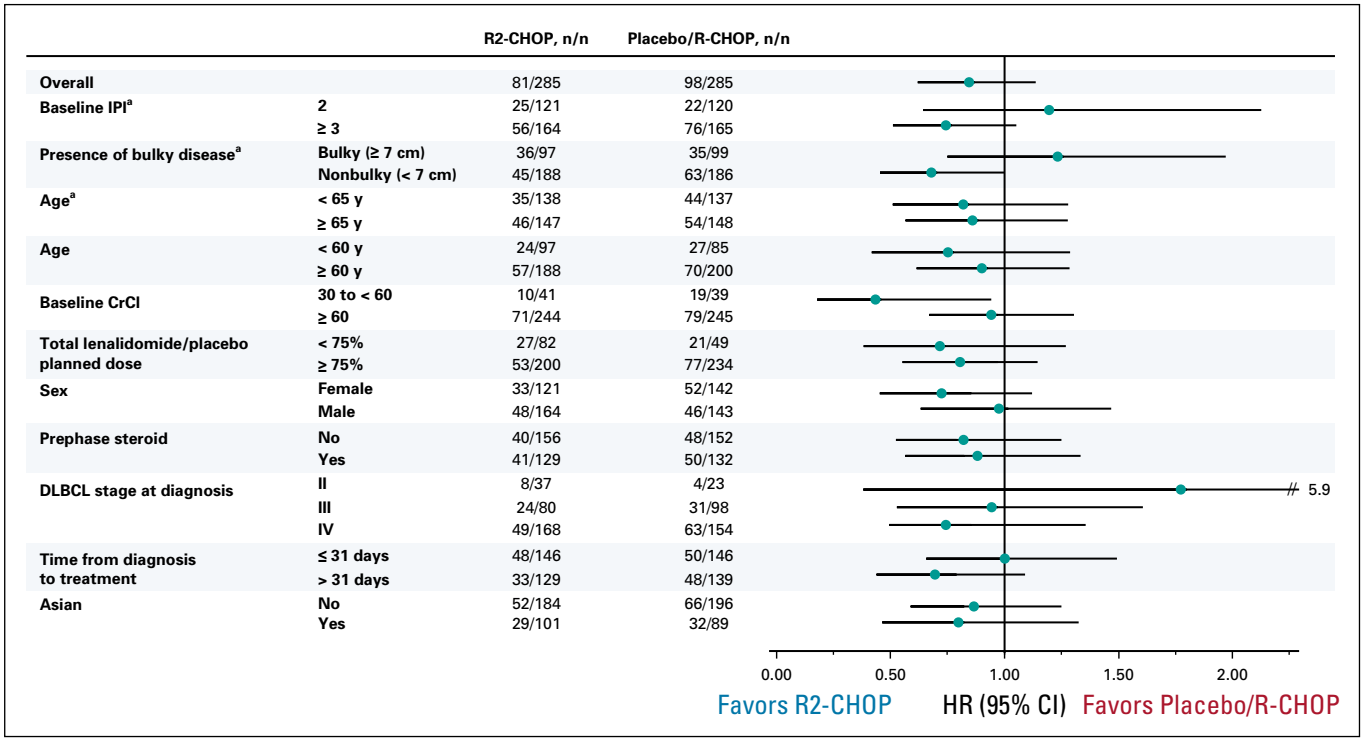

FIG 4. Subgroup analyses of progression-free survival by Independent Radiology Adjudication Committee in the intent-to-treat population treated with R2-CHOP versus placebo/R-CHOP. [a]Prespecified stratification factor. CrCl, creatinine clearance; DLBCL, diffuse large B-cell lymphoma; HR, hazard ratio; IPI, International Prognostic Index; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; R2-CHOP, lenalidomide plus R-CHOP.

TABLE 3. TEAEs During the Treatment Period in the Safety Population (≥ 15% Any Grade and Adverse Events of Interest)

	R2-CHOP (n = 283)		Placebo/R-CHOP (n = 284)	
TEAEs	**Any Grade**	**Grade ≥ 3**	**Any Grade**	**Grade ≥ 3**
Neutropenia	189 (67)	169 (60)	153 (54)	137 (48)
Febrile neutropenia[a]	39 (14)	39 (14)	25 (9)	25 (9)
Anemia	128 (45)	63 (22)	101 (36)	39 (14)
Constipation	92 (33)	1 (< 1)	81 (29)	0 (0)
Thrombocytopenia	72 (25)	47 (17)	55 (19)	32 (11)
Nausea	65 (23)	3 (1)	67 (24)	4 (1)
Pyrexia	58 (20)	0 (0)	46 (16)	10 (4)
Diarrhea	52 (18)	6 (2)	42 (15)	3 (1)
Peripheral sensory neuropathy	51 (18)	1 (< 1)	51 (18)	5 (2)
Leukopenia	50 (18)	40 (14)	50 (18)	42 (15)
Alopecia	48 (17)	0 (0)	43 (15)	0 (0)
Fatigue	40 (14)	5 (2)	50 (18)	3 (1)
Infusion-related reaction[a]	28 (10)	2 (< 1)	33 (12)	8 (3)
Deep vein thrombosis[a,b]	4 (1)	2 (< 1)	4 (1)	2 (< 1)
Tumor lysis syndrome[a]	2 (< 1)	1 (< 1)	1 (< 1)	1 (< 1)

NOTE. Data are given as no. (%).

Abbreviations: R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; R2-CHOP, lenalidomide plus R-CHOP; TEAE, treatment-emergent adverse event.

[a]Denotes an adverse event of interest.

[b]For the four patients in each arm with any-grade deep vein thrombosis, prophylaxis was low-molecular-weight heparin for two patients, nonsteroidal anti-inflammatory drug for one patient, and one patient received no prophylaxis.

association between shorter DTI, worse clinical factors (elevated lactate dehydrogenase, poor Eastern Cooperative Oncology Group performance status, B symptoms, and higher IPI) and lower EFS rate at 24 months. The converse was also true; patients with longer DTI demonstrated improved 24-month EFS, meaning that longer times to initiate treatment represented a higher willingness to wait for treatment (ie, lower-risk disease, better overall health, and fitness), increasing the likelihood of better outcomes. A similar association was reported in GOYA study patients; shorter PFS was observed for patients with < 15 days from diagnosis to random assignment and < 8 days from diagnosis to screening, potentially because of higher-risk disease.[37]

Although REAL07 and MC078E phase II studies of lenalidomide + R2-CHOP suggested similar outcomes despite different dosing schema,[23,24] a potential limitation in ROBUST may be from the lower total lenalidomide dose. Indeed, studies in relapsed or refractory DLBCL demonstrating activity of single-agent lenalidomide mainly used the dose of 25 mg daily. However, other studies have used the 20 mg daily dose with rituximab[38]; the proper lenalidomide dose in combination with other agents remains an open issue.

Overall, the safety profile for both ROBUST arms was as expected, with no new safety findings. Most patients completed six cycles in both arms (74% R2-CHOP and 84% placebo/R-CHOP), with 80% of patients receiving > 90% relative dose intensity of lenalidomide or placebo. The most common grade 3/4 TEAEs were neutropenia, anemia, and thrombocytopenia for both arms, although > 89% of patients received concomitant growth factors throughout treatment.

Despite the lack of benefit of lenalidomide with R-CHOP observed here, ongoing and future analyses will further evaluate the potential effect of pharmacokinetics or dosing, molecular classification, and mutational status. The meaning of IPI findings and why worse prognosis patients had better PFS when receiving lenalidomide remain to be further elucidated. It is also important to address the role of timing from diagnosis to initial treatment and further evaluate genetic classifiers that may inherently affect outcomes. These data will broaden our understanding to support future assessments of next-generation immunomodulatory agents (CELMoDs), which have displayed promising preclinical activity in B-cell lymphoma.[18]

AFFILIATIONS

[1]Division of Hematology, Mayo Clinic, Rochester, MN

[2]Division of Hematology, A.O.U. Città della Salute e della Scienza Hospital and University, Torino, Italy

[3]Centre for Lymphoid Cancer, British Columbia Cancer, Vancouver, British Columbia, Canada
[4]Harbin Medical University Cancer Hospital, Harbin, Heilongjiang, China
[5]Maria Sklodowska-Curie Institute—Oncology Centre, Cracow, Poland
[6]Department of Hematology, Ankara University, Ankara, Turkey
[7]Cancer Hospital, Fudan University, Shanghai, China
[8]Beijing Cancer Hospital, Beijing, China
[9]The First Affiliated Hospital of Medical School of Zhejiang University, First Hospital of Zhejiang Province, Hangzhou, Zhejiang, China
[10]Fourth Department of Internal Medicine-Hematology, Charles University Hospital and Faculty of Medicine, Hradec Králové, Czech Republic
[11]Servicio de Hematologia, Hospital Universitario San Pedro de Alcántara, Cáceres, Spain
[12]Division of Hematology, Department of Medicine, University of Padova and Azienda Ospedaliera di Padova, Padova, Italy
[13]Department of Internal Medicine and Haematology, Faculty Hospital Kralovske Vinohrady, Prague, Czech Republic
[14]UO Ematologia, Ospedale Degli Infermi, Rimini, Italy
[15]Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea
[16]AOU Città della Salute e della Scienza di Torino, Turin, Italy
[17]U.O. Ematologia, Dipartimento Oncologia e Ematologia, Ospedale Santa Maria delle Croci, Ravenna, Italy
[18]Department of Hematology and Cell Therapy, Aichi Cancer Center Hospital, Nagoya, Japan
[19]National Cancer Center Hospital, Tokyo, Japan
[20]Department of Medicine and Biosystemic Science, Kyushu University Faculty of Medicine, Fukuoka City, Japan
[21]Clinical Research and Development, Celgene Corporation, Summit, NJ
[22]Translational Development, Precision Medicine and Companion Diagnostics, Celgene Corporation, Summit, NJ
[23]Department of Statistical Programming, Celgene Corporation, Overland Park, KS

CORRESPONDING AUTHOR

Grzegorz S. Nowakowski, MD, Division of Hematology, Mayo Clinic, 201 First Street SW, Rochester, MN 55902; e-mail: Nowakowski.Grzegorz@mayo.edu.

STUDY GROUPS

A comprehensive list of ROBUST study investigators and institutions is shown in Appendix Table A1 (online only).

PRIOR PRESENTATION

Presented in part as an oral presentation (abstract #005) at the 2019 International Conference for Malignant Lymphoma, Lugano, Switzerland, June 18-22, 2019.

SUPPORT

Supported by Celgene Corporation, a Bristol-Myers Squibb Company, Princeton, NJ. This study was conducted with the scientific support of the Fondazione Italiana Linfomi and the Mayo Clinc.

CLINICAL TRIAL INFORMATION

ClinicalTrials.gov identifier: NCT02285062; EudraCT 2013-004054-21.

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.20.01366.

DATA SHARING STATEMENT

Data requests may be submitted to Celgene, A Bristol Myers Squibb Company at https://vivli.org/ourmember/celgene/ and must include a description of the research proposal.

AUTHOR CONTRIBUTIONS

Conception and design: Grzegorz S. Nowakowski, Annalisa Chiappella, David W. Scott, Wojciech Jurczak, Jun Zhu, Myron Czuczman, Thomas E. Witzig, Umberto Vitolo
Administrative support: Juan Miguel Bergua, Adrian Kilcoyne
Provision of study materials or patients: Wojciech Jurczak, Jie Jin, Juan Miguel Bergua, Francesco Piazza, Anna Lia Molinari, Kazuhito Yamamoto
Collection and assembly of data: Grzegorz S. Nowakowski, Annalisa Chiappella, Randy D. Gascoyne, David W. Scott, Qingyuan Zhang, Muhit Özcan, Xiaonan Hong, Jun Zhu, Jie Jin, David Belada, Juan Miguel Bergua, Francesco Piazza, Heidi Mócikova, Anna Lia Molinari, Federica Cavallo, Monica Tani, Kazuhito Yamamoto, Koji Izutsu, Koji Kato, Myron Czuczman, Sarah Hersey, Adrian Kilcoyne, Jacqueline Russo, Krista Hudak, Thomas E. Witzig, Umberto Vitolo
Data analysis and interpretation: Grzegorz S. Nowakowski, Annalisa Chiappella, David W. Scott, Jie Jin, Dok Hyun Yoon, Federica Cavallo, Monica Tani, Kazuhito Yamamoto, Koji Izutsu, Myron Czuczman, Sarah Hersey, Adrian Kilcoyne, Jacqueline Russo, Krista Hudak, Jingshan Zhang, Steve Wade, Thomas E. Witzig, Umberto Vitolo
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

ACKNOWLEDGMENT

We would like to dedicate this work to the memory of Bertrand Coiffier after his untimely passing. Prof Coiffier was a foremost expert in the field and has our utmost respect for his significant contributions to the ROBUST study and to the field overall. Thank you to patients, families, caregivers, and investigators who participated in the ROBUST clinical study. Thank you to the Fondazione Italiana Linfomi (FIL) and Mayo Clinic for providing significant contributions and support for the study. Thank you to the international board of expert pathologists for providing histopathology review, and independent expert hematologist for clinical assessment and imaging review. Thank you to the data monitoring committee (DMC) that served as an independent expert advisory group to evaluate safety and efficacy throughout the study, including Bertrand Coiffier, MD (chair); Martin Dreyling MD; David Maloney MD, PhD; John Leonard MD; and Weichung Shih, PhD. The authors received editorial support in the preparation of this manuscript from Julie Kern, PhD, CMPP of Bio Connections LLC, funded by Celgene Corporation. The authors directed development of the manuscript and are fully responsible for all content and editorial decisions for this manuscript.

REFERENCES

1. Armitage JO, Weisenburger DD: New approach to classifying non-Hodgkin's lymphomas: Clinical features of the major histologic subtypes. Non-Hodgkin's lymphoma classification project. J Clin Oncol 16:2780-2795, 1998
2. Swerdlow SH, Campo E, Harris NL, et al: WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Lyon, France, International Agency for Research on Cancer, 2008

3. Coiffier B, Lepage E, Briere J, et al: CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. N Engl J Med 346:235-242, 2002
4. Habermann TM, Weller EA, Morrison VA, et al: Rituximab-CHOP versus CHOP alone or with maintenance rituximab in older patients with diffuse large B-cell lymphoma. J Clin Oncol 24:3121-3127, 2006
5. Tilly H, Gomes da Silva M, Vitolo U, et al: Diffuse large B-cell lymphoma (DLBCL): ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 26:v116-v125, 2015 (suppl 5)
6. Wang Y, Farooq U, Link BK, et al: Late relapses in patients with diffuse large B-cell lymphoma treated with immunochemotherapy. J Clin Oncol 37:1819-1827, 2019
7. Davies A, Cummin TE, Barrans S, et al: Gene-expression profiling of bortezomib added to standard chemoimmunotherapy for diffuse large B-cell lymphoma (REMoDL-B): An open-label, randomised, phase 3 trial. Lancet Oncol 20:649-662, 2019
8. Leonard JP, Kolibaba KS, Reeves JA, et al: Randomized phase II study of R-CHOP with or without bortezomib in previously untreated patients with non-germinal center B-cell-like diffuse large B-cell lymphoma. J Clin Oncol 35:3538-3546, 2017
9. Younes A, Sehn LH, Johnson P, et al: Randomized phase III trial of ibrutinib and rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone in non-germinal center B-cell diffuse large B-cell lymphoma. J Clin Oncol 37:1285-1295, 2019
10. Vitolo U, Trneny M, Belada D, et al: Obinutuzumab or rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone in previously untreated diffuse large B-cell lymphoma. J Clin Oncol 35:3529-3537, 2017
11. Alizadeh AA, Eisen MB, Davis RE, et al: Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. Nature 403:503-511, 2000
12. Rosenwald A, Wright G, Chan WC, et al: The use of molecular profiling to predict survival after chemotherapy for diffuse large-B-cell lymphoma. N Engl J Med 346:1937-1947, 2002
13. Scott DW, Wright GW, Williams PM, et al: Determining cell-of-origin subtypes of diffuse large B-cell lymphoma using gene expression in formalin-fixed paraffin-embedded tissue. Blood 123:1214-1217, 2014
14. Hans CP, Weisenburger DD, Greiner TC, et al: Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray. Blood 103:275-282, 2004
15. Wright G, Tan B, Rosenwald A, et al: A gene expression-based method to diagnose clinically distinct subgroups of diffuse large B cell lymphoma. Proc Natl Acad Sci U S A 100:9991-9996, 2003
16. Lenz G, Wright G, Dave SS, et al: Stromal gene signatures in large-B-cell lymphomas. N Engl J Med 359:2313-2323, 2008
17. Chamberlain PP, Lopez-Girona A, Miller K, et al: Structure of the human Cereblon-DDB1-lenalidomide complex reveals basis for responsiveness to thalidomide analogs. Nat Struct Mol Biol 21:803-809, 2014
18. Hagner PR, Man HW, Fontanillo C, et al: CC-122, a pleiotropic pathway modifier, mimics an interferon response and has antitumor activity in DLBCL. Blood 126:779-789, 2015
19. Zhang LH, Kosek J, Wang M, et al: Lenalidomide efficacy in activated B-cell-like subtype diffuse large B-cell lymphoma is dependent upon IRF4 and cereblon expression. Br J Haematol 160:487-502, 2013
20. Wiernik PH, Lossos IS, Tuscano JM, et al: Lenalidomide monotherapy in relapsed or refractory aggressive non-Hodgkin's lymphoma. J Clin Oncol 26: 4952-4957, 2008
21. Witzig TE, Vose JM, Zinzani PL, et al: An international phase II trial of single-agent lenalidomide for relapsed or refractory aggressive B-cell non-Hodgkin's lymphoma. Ann Oncol 22:1622-1627, 2011
22. Hernandez-Ilizaliturri FJ, Deeb G, Zinzani PL, et al: Higher response to lenalidomide in relapsed/refractory diffuse large B-cell lymphoma in nongerminal center B-cell-like than in germinal center B-cell-like phenotype. Cancer 117:5058-5066, 2011
23. Vitolo U, Chiappella A, Franceschetti S, et al: Lenalidomide plus R-CHOP21 in elderly patients with untreated diffuse large B-cell lymphoma: Results of the REAL07 open-label, multicentre, phase 2 trial. Lancet Oncol 15:730-737, 2014
24. Nowakowski GS, LaPlant B, Macon WR, et al: Lenalidomide combined with R-CHOP overcomes negative prognostic impact of non-germinal center B-cell phenotype in newly diagnosed diffuse large B-cell lymphoma: A phase II study. J Clin Oncol 33:251-257, 2015
25. Castellino A, Chiappella A, LaPlant BR, et al: Lenalidomide plus R-CHOP21 in newly diagnosed diffuse large B-cell lymphoma (DLBCL): Long-term follow-up results from a combined analysis from two phase 2 trials. Blood Cancer J 8:108, 2018
26. Crawford J, Caserta C, Roila F, et al: Hematopoietic growth factors: ESMO clinical practice guidelines for the applications. Ann Oncol 21:v248-v251, 2010 (suppl 5)
27. Smith TJ, Bohlke K, Lyman GH, et al: Recommendations for the use of WBC growth factors: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol 33:3199-3212, 2015
28. 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
29. Cheson BD, Pfistner B, Juweid ME, et al: Revised response criteria for malignant lymphoma. J Clin Oncol 25:579-586, 2007
30. Food and Drug Administration (FDA), Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research (US): Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. Rockville, MD, US Food and Drug Administration, 2007
31. Nowakowski GS, Hong F, Scott DW, et al: Addition of lenalidomide to R-CHOP (R2CHOP) improves outcomes in newly diagnosed diffuse large B-cell lymphoma (DLBCL): First report of ECOG-ACRIN1412 a randomized phase 2 US intergroup study of R2CHOP vs R-CHOP. Hematol Oncol (ICML Abstract) 37:37-38, 2019 (suppl; abstr 006)
32. Shipp MA, Harrington DP, Anderson JR, et al: A predictive model for aggressive non-Hodgkin's lymphoma: International Non-Hodgkin's Lymphoma Prognostic Factors Project. N Engl J Med 329:987-994, 1993
33. Ziepert M, Hasenclever D, Kuhnt E, et al: Standard International Prognostic Index remains a valid predictor of outcome for patients with aggressive CD20+ B-cell lymphoma in the rituximab era. J Clin Oncol 28:2373-2380, 2010
34. Chapuy B, Stewart C, Dunford AJ, et al: Molecular subtypes of diffuse large B cell lymphoma are associated with distinct pathogenic mechanisms and outcomes. Nat Med 24:679-690, 2018
35. Nowakowski GS, Chiappella A, Witzig TE, et al: Variable global distribution of cell-of-origin from the ROBUST phase 3 study in diffuse large B-cell lymphoma. Haematologica 105:e72-e75, 2019
36. Maurer MJ, Ghesquieres H, Link BK, et al: Diagnosis-to-treatment interval is an important clinical factor in newly diagnosed diffuse large B-cell lymphoma and has implication for bias in clinical trials. J Clin Oncol 36:1603-1610, 2018
37. Szafer-Glusman E, Liu J, Peale FV Jr, et al: A simulation analysis to evaluate the effect of prospective biomarker testing on progression-free survival (PFS) in DLBCL. Blood 130:abstract 419, 2017

38. Zinzani PL, Pellegrini C, Gandolfi L, et al: Combination of lenalidomide and rituximab in elderly patients with relapsed or refractory diffuse large B-cell lymphoma: A phase 2 trial. Clin Lymphoma Myeloma Leuk 11:462-466, 2011

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

ROBUST: A Phase III Study of Lenalidomide Plus R-CHOP Versus Placebo Plus R-CHOP in Previously Untreated Patients With ABC-Type Diffuse Large B-Cell Lymphoma

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).

Grzegorz S. Nowakowski
Consulting or Advisory Role: Celgene, MorphoSys, Genentech, Selvita, Debiopharm Group, Kite/Gilead
Research Funding: Celgene, NanoString Technologies, MorphoSys

Annalisa Chiappella
Honoraria: Celgene, Gilead-Kite, Janssen Oncology, Roche, Servier
Consulting or Advisory Role: Celgene, Gilead-Kite, Janssen-Cilag, Takeda, iQone

David W. Scott
Consulting or Advisory Role: Celgene, Janssen, Abbvie, AstraZeneca
Research Funding: Janssen, Roche/Genentech, NanoString Technologies
Patents, Royalties, Other Intellectual Property: Named inventor on a pending patent describing gene expression profiling in prognostication in classical Hodgkin lymphoma. As a member of the LLMPP I am potentially a named inventor on a pending patent on the use of gene expression profiling to assign cell-of-origin in diffuse large B-cell lymphoma. I am a named inventor on a pending patent on the use of gene expression profiling to determine the proliferation signature in mantle cell lymphoma. Named inventor on a pending patent describing using gene expression profiling to identify molecular subtypes of GCB-DLBCL.

Wojciech Jurczak
Research Funding: Janssen-Cilag, Acerta Pharma/AstraZeneca, Merck, Loxo, TG Therapeutics, BeiGene

Muhit Özcan
Honoraria: Takeda
Research Funding: Janssen, Celgene, Takeda, Bayer, Merck, Archigen Biotech, Roche, Pharmacyclics, Abbvie
Travel, Accommodations, Expenses: Takeda, Sanofi, Roche, Bristol-Myers Squibb, Abdi Ibrahim, Amgen, Janssen

David Belada
Consulting or Advisory Role: Roche, Gilead Sciences, Janssen-Cilag, Takeda, MorphoSys, Debiopharm Group
Research Funding: Roche, Gilead Sciences, Janssen-Cilag, Takeda, MorphoSys, Pharmacyclics, Archigen Biotech
Travel, Accommodations, Expenses: Gilead Sciences, Takeda, Roche

Juan Miguel Bergua
Consulting or Advisory Role: Daiichi Sankyo
Travel, Accommodations, Expenses: Roche/Genentech

Dok Hyun Yoon
Honoraria: Celltrion, Roche, Janssen, Amgen, Celgene, Samyang, Kirin Pharmaceuticals
Consulting or Advisory Role: Roche, Janssen, Amgen¸Celgene, Green Cross
Research Funding: Samyang, Abclone, Roche/Genentech, Janssen Oncology, Amgen, Genmab, Boryung

Federica Cavallo
Honoraria: Takeda, Janssen-Cilag, Gilead Sciences
Consulting or Advisory Role: Janssen-Cilag, Gilead Sciences
Travel, Accommodations, Expenses: Celgene

Kazuhito Yamamoto
Honoraria: Kyowa Hakko Kirin, Takeda, Janssen, Bristol-Myers Squibb, Celgene, Sumitomo Dainippon, Ono Pharmacuetical, Chugai Pharma, Novartis, Otsuka, Mundipharma, Eisai, MSD, Meiji Seika Kaisha, Sanofi, Nippon Shinyaku, Abbvie, GlaxoSmithKline
Consulting or Advisory Role: Ono Pharmaceutical, Meiji Seika Kaisha, Chugai Pharma, Bristol-Myers Squibb, Kyowa Hakko Kirin, Takeda, Celgene, HUYA Bioscience International, Stemline Therapeutics, Eisai, Janssen, AstraZeneca, Daiichi Sankyo, Abbvie
Research Funding: Chugai Pharma, Novartis, ARIAD, Takeda, Gilead Sciences, Abbvie, Ono Pharmaceutical, Celgene, Solasia Pharma, MSD, Eisai, Zenyaku Kogyo, Bayer, SymBio Pharmaceuticals, AstraZeneca, Incyte, Mundipharma, Yakult Pharmaceutical

Koji Izutsu
Honoraria: Takeda, Chugai Pharma, Eisai, Janssen, Abbvie, Novartis, MSD, Dainippon Sumitomo Pharma, Ono Pharmaceutical, Mundipharma, HUYA Bioscience International, AstraZeneca, Bayer, Bristol-Myers Squibb, Kyowa Hakko Kirin, Fujifilm, Celgene
Consulting or Advisory Role: Bayer, Celgene, AstraZeneca
Research Funding: Eisai, Chugai Pharma

Koji Kato
Honoraria: Takeda, MSD, Kyowa-Kirin, Janssen, Celgene, Ono, Mundi, Dainippon-Sumitomo, Bristol-Myers Squibb
Consulting or Advisory Role: AbbVie, AstraZeneca, Celgene, Chugai, Eisai, Janssen, Novartis, Daiichi Sankyo
Research Funding: Chugai, Takeda, Kyowa Kirin, AbbVie, Novartis, Eisai, Janssen, Celgene, Ono, Novartis, Daiichi Sankyo

Myron Czuczman
Employment: Celgene
Stock and Other Ownership Interests: Celgene

Sarah Hersey
Stock and Other Ownership Interests: Novartis, Johnson & Johnson, Bristol-Myers Squibb
Other Relationship: Bristol-Myers Squibb

Adrian Kilcoyne
Employment: Celgene
Stock and Other Ownership Interests: Celgene

Jacqueline Russo
Employment: Celgene/Bristol-Myers Squibb, Kite Pharma
Stock and Other Ownership Interests: Celgene/Bristol-Myers Squibb, Kite Pharma

Krista Hudak
Employment: Bristol-Myers Squibb, Novartis
Stock and Other Ownership Interests: Bristol-Myers Squibb, Novartis

Jingshan Zhang
Employment: Celgene, Bristol-Myers Squibb
Stock and Other Ownership Interests: Bristol-Myers Squibb
Travel, Accommodations, Expenses: Celgene

Steve Wade
Employment: Bristol-Myers Squibb
Stock and Other Ownership Interests: Bristol-Myers Squibb

Thomas E. Witzig
Consulting or Advisory Role: Karyopharm Therapeutics, Abbvie/Genentech, Seattle Genetics, Celgene, Incyte, Epizyme, Cellectar, Tessa Therapeutics, Portola Pharmaceuticals, MorphoSys, ADC Therapeutics
Research Funding: Celgene, Acerta Pharma, Kura Oncology, Acrotech Biopharma, Karyopharm Therapeutics
Patents, Royalties, Other Intellectual Property: I am co-inventor on a patent application filed by Mayo Clinic and pending on the combination of CRM1 inhibitors with salicylates. Please note—simply filed—not even close to being granted.

Umberto Vitolo
Consulting or Advisory Role: Gilead Sciences, Janssen, Celgene, Regeneron
Speakers' Bureau: Gilead Sciences, Celgene, Abbvie, Roche, Janssen Oncology
Travel, Accommodations, Expenses: Celgene, Gilead Sciences, Roche

No other potential conflicts of interest were reported.

APPENDIX
SUPPLEMENTAL METHODS

Patients

Patients with unclassified or germinal center B-cell-like (GCB)-type diffuse large B-cell lymphoma (DLBCL) were excluded. Patient tissue biopsies were prospectively evaluated by central pathology to confirm CD20+, ABC-type DLBCL status. Cell-of-origin (COO) type and histology were analyzed from formalin-fixed, paraffin-embedded excisional or surgical or core needle biopsy samples. Histology was classified by the following World Health Organization 2008 subclassifications[2]: not otherwise specified (NOS), associated with chronic inflammation, or with positive Epstein-Barr virus in the elderly. Patient age was 18-80 years; patients older than 80 years could be included if their Eastern Cooperative Oncology Group (ECOG) performance status (PS) was ≤ 1, each individual organ system score was ≤ 2 per the modified Cumulative Illness Rating Scale for comorbidities, and patients were otherwise eligible for full-dose rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) per local practices. Additional patient inclusion criteria included: ECOG PS ≤ 2; Ann Arbor stage II-IV disease; International Prognostic Index (IPI) score of ≥ 2; bi-dimensionally measurable disease by computed tomography (CT) or magnetic resonance imaging (MRI) with at least one lesion ≥ 1.5 cm in the longest diameter and measurable in two perpendicular directions; and candidacy for six cycles of R-CHOP21. Laboratory requirements were the following: absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L; platelets $\geq 75 \times 10^9$/L; hemoglobin ≥ 7.5 g/dL (4.7 mmol/L); serum aspartate or alanine transaminase ≤ 3.0 upper limit of normal (ULN); serum total bilirubin ≤ 2.0 mg/dL (34 μmol/L); and calculated creatinine clearance (Cockcroft-Gault formula) of ≥ 30 mL/min.

Two negative pregnancy tests were required for females of childbearing potential, and all patients were required to prevent pregnancy via abstinence or use of contraception.

Exclusion criteria were unclassified or GCB-type DLBCL; active central nervous system or meningeal lymphoma; post-transplant lymphoproliferative disorder cases; transformed NHL or composite DLBCL or follicular lymphoma; active infection with hepatitis B or C or human immunodeficiency virus; left ventricular ejection fraction $< 45\%$; grade ≥ 2 peripheral neuropathy; history of other malignancies (unless disease-free for ≥ 5 years); life expectancy < 6 months; unwillingness to take venous thromboembolic prophylaxis; and prior use of lenalidomide.

Trial Design and Treatments

The lenalidomide dose was selected based on risk-benefit considerations from two proof-of-concept studies, which administered lenalidomide 15 mg/day, days 1-14 in the REAL07 study and 25 mg/day, days 1-10 in the MC078E study.[23,24] Because the efficacy outcomes were similar, the lower dose from the REAL07 study was selected for ROBUST based on the best data on feasibility and lower incidence of severe adverse events (AEs), suggesting a better benefit:risk profile.

Lenalidomide dose reductions to the following levels were allowed: 10, 5, and 2.5 mg. If lenalidomide dosing was interrupted for toxicity or the cycle delayed, lenalidomide could be restarted only if the laboratory parameters recovered as follows: ANC $\geq 1.0 \times 10^9$/L; platelet count $\geq 75 \times 10^9$/L; and any other nonhematologic AE resolved to grade ≤ 2 (except where noted below). A mandatory lenalidomide hold was required in the instance of grade 4 neutropenia lasting ≥ 7 days or grade 3/4 febrile neutropenia, grade 4 thrombocytopenia, grade 2 or 3 nondesquamating rash, grade 2 allergic reaction or hypersensitivity, grade ≥ 3 constipation, grade ≥ 3 venous thrombosis or embolism, grade ≥ 2 tumor lysis syndrome, elevated aspartate or alanine transferase ($> 3 \times$ ULN) or bilirubin ($\geq 3 \times$ ULN), or another grade ≥ 3 nonhematologic AE. Lenalidomide was permanently discontinued in the instance of grade ≥ 3 desquamating or grade 4 nondesquamating rash, and grade ≥ 3 allergic reaction or hypersensitivity. For other, lenalidomide-related nonhematologic AEs grade ≥ 3, lenalidomide was withheld until the AE resolved to grade ≤ 2, and then restarted at the same or next lower dose level per the investigator's discretion.

For patients at risk for CNS involvement, CNS lymphoma prophylaxis with four to eight doses of concomitant intrathecal methotrexate and/or cytarabine during study treatment was recommended. Patients were recommended to receive prophylaxis for tumor lysis syndrome (allopurinol, rasburicase, or equivalent per institutional guidelines) and be well hydrated during the first week of treatment. For patients at high risk for a venous thromboembolic event, prophylactic anticoagulation therapy with low-molecular-weight heparin, heparin, or warfarin was recommended. Premedication with an antiemetic for nausea prophylaxis, acetaminophen or diphenhydramine for rituximab infusion reaction prophylaxis, and prophylaxis for *Pneumocystis* were permitted per local practice. Growth factor and blood product transfusions were allowed during treatment and follow-up periods, and were used in accordance with the American Society of Clinical Oncology/European Society for Medical Oncology guidelines.[26,27]

Efficacy and Safety Assessments

The key secondary end point was event-free survival, which was defined as the time from random assignment to initiation of disease progression, relapse from complete response (CR), initiation of subsequent antilymphoma therapy, or death because of any cause. CR was defined as the percentage of patients who ever achieved a CR after initiating study treatment and prior to initiation of subsequent antilymphoma treatment.

Response assessments included CT and positron emission tomography scans and evaluation of laboratory or clinical data after cycle 3; once 3-4 weeks after completing cycle 6; every 12 weeks from week 34 to 154 (± 1 week); and weeks 180, 206, 258, and 310 (± 2 weeks) until first progression.

Supplemental Results

Futility analysis. An interim futility analysis of PFS at the 50% information level (96 events) was performed with a data cutoff of June 30, 2017. The data monitoring committee (composed of independent, external oncologists and a biostatistician) met on November 6, 2017, to review the interim analysis data and agreed to allow the study to continue as planned.

Safety. The incidence of treatment-emergent adverse events (TEAEs) was analyzed for patients by age < 65 years ($n = 274$) and ≥ 65 years ($n = 293$) and summarized by treatment arm for the safety population. In general, the incidences of the TEAEs were similar between the two age subgroups. For the more commonly occurring AEs in the two treatment arms, notable (≥ 10 percentage points) differences observed between the two age subgroups (< 65 and ≥ 65 years, respectively), with the higher incidence in the older ≥ 65 years subgroup, were as follows: anemia (37.2% and 52.7% in the R2-CHOP arm; 29.9% and 40.8% in placebo/R-CHOP arm), febrile neutropenia (8.8% and 18.5% in R2-CHOP), constipation (27.0% and 37.7% in R2-CHOP), diarrhea (13.1% and 23.3% in R2-CHOP; 9.5% and 19.7% in placebo/R-CHOP), and peripheral edema (5.1% and 18.5% in R2-CHOP).

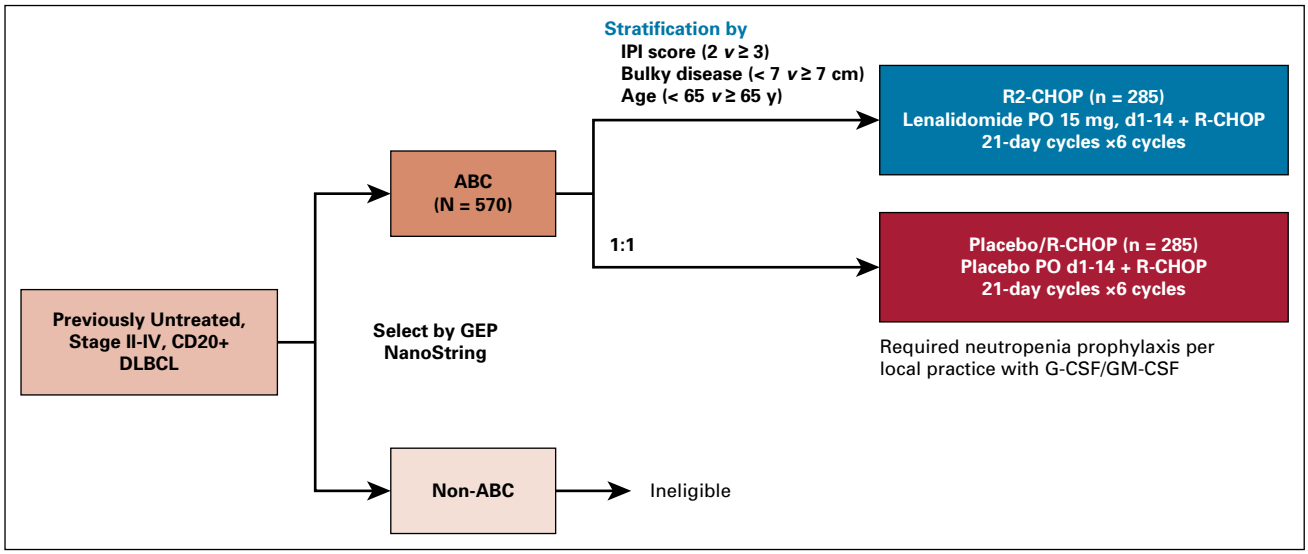

FIG A1. ROBUST study design (ClinicalTrials.gov identifier: NCT02285062; EudraCT 2013-004054-21). Following confirmation of CD20 positivity and identification of ABC-type by gene expression profiling, patients were stratified by IPI score, bulky disease, and age, and randomly assigned 1:1 to R2-CHOP or placebo/R-CHOP. Patients with non–ABC-type DLBCL were ineligible for the study. Treatment included the following: lenalidomide (or placebo) 15 mg oral (PO) on days 1-14 of every 21-day dosing cycle plus R-CHOP21 (rituximab 375 mg/m^2 intravenous [IV] day −1 or 1, cyclophosphamide 750 mg/m^2 IV day 1, doxorubicin 50 mg/m^2 IV day 1, vincristine 1.4 mg/m^2 [maximum 2.0 mg total] IV day 1, and prednisone [or prednisolone] 100 mg PO days 1-5 [IV day 1 was acceptable]). Treatment was continued until six cycles were complete, or until intolerability, inadequate response, disease progression, or withdrawal of consent, whichever occurred first. Two additional doses of single-agent rituximab (one dose per 21-day cycle) were permitted if prespecified and considered standard of care per local practice. ABC, activated B-cell-like; DLBCL, diffuse large B-cell lymphoma; IPI, International Prognostic Index; IV, intravenous; PO, oral; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R2-CHOP, lenalidomide plus R-CHOP.

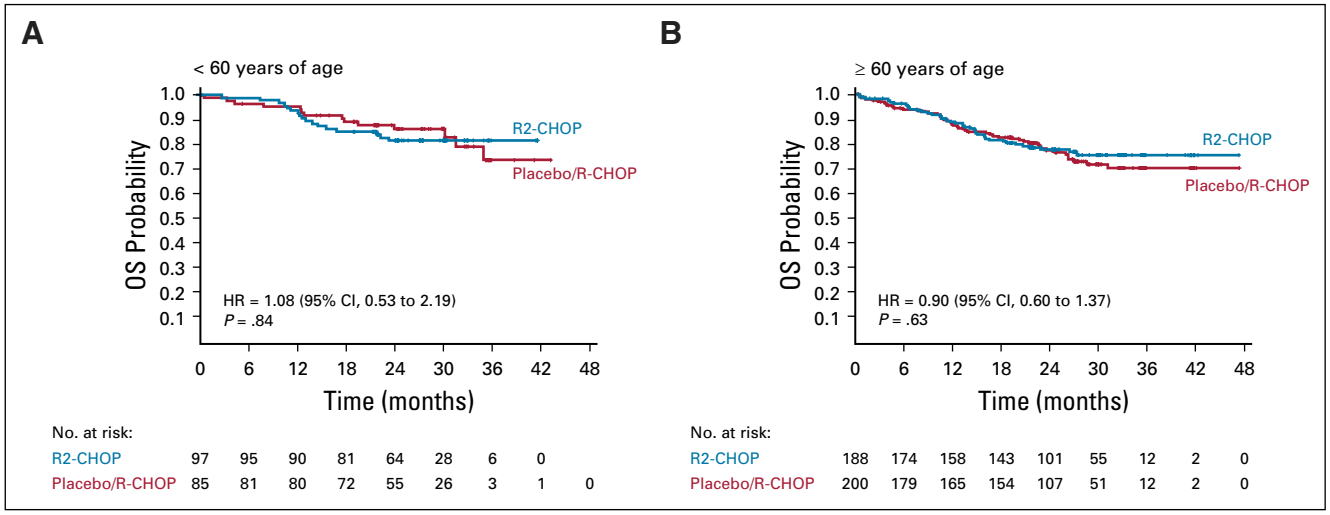

FIG A2. Overall survival based on treatment group and age < 60 years (A) and ≥ 60 years (B) (ITT population). R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R2-CHOP, lenalidomide plus R-CHOP.

TABLE A1. List of ROBUST Study Investigators

Principal Investigator	Site Location
Uri Abadi	Meir Medical Center, Kfar Saba, Israel
Yasunobu Abe	National Hospital Organization Kyushu Cancer Center, Fukuoka-city, Fukuoka, Japan
David Aboulafia	Virginia Mason Medical Center, Seattle, WA
Pau Abrisqueta	Hospital Universitari Vall d'Hebron, Barcelona, Spain
Abdulwahab Al Tourah	British Columbia Cancer Agency—Fraser Valley Centre, Surrey, British Columbia, Canada
Sergey Alekseev	FSBI "Research Oncology Institution n.a. N.N. Petrov" of the RF MoH, Saint Petersburg, Russia
Alvaro Alencar	Memorial Cancer Institute at Memorial Regional Hospital, Hollywood, FL
Achille Ambrosetti	AOU Integrata di Verona-Unversita di Verona-Policlinico G.B. Rossi, Verona, Italy
Daniel Anderson	HealthPartners Riverside Clinic, Minneapolis, MN
Kiyoshi Ando	Tokai University Hospital, Isehara, Kanagawa, Japan
Marc André	Cliniques Universitaires UCL de Mont-Godinne, Yvoir, Belgium
Francesco Angrilli	Ospedale Civile Santo Spirito di Pescara, Pescara, Italy
Luca Arcaini	Fondazione IRCCS Policlinico San Matteo, Pavia, Italy
Reyes Arranz	Hospital Universitario de La Princesa, Madrid, Spain
Irit Avivi	Tel Aviv Sourasky Medical Center, Tel Aviv, Israel
Giuseppe Avvisati	Policlinico Universitario Campus Bio-Medico, Rome, Italy
Orhan Ayyildiz	Dicle University Faculty Of Medicine Hospital, Internal Disease Hematology Department, Diyarbakir, Turkey
Johanna Baars	NKI-AVL, Amsterdam, the Netherlands
Veronika Bachanova	University of Minnesota Medical Center, Minneapolis, MN
Christopher L. Bacon	St James's Hospital, Dublin Ireland
Monica Balzarotti	Istituto Clinico Humanitas, Rozzano, Italy
Anne Banos	Ce H de La Côte Basque, Bayonne, France
J. Bargay Lleonart	Hospital Son Llàtzer, Palma de Mallorca, Islas Baleares, Spain
Roberta Battistini	Azienda Ospedaliera San Camillo Forlanini, Roma, Italy
Anne Beaven	Duke Cancer Institute, Durham, NC
Joseph T. Beck	Highlands Oncology Group, Rogers, AR
Aart Beeker	Spaarne-Gasthuis, Hoofddorp, the Netherlands
David Belada	Fourth Department of Internal Medicine-Hematology, Charles University Hospital and Faculty of Medicine, Hradec Králové, Czech Republic
Jose L. Bello Lopez	Complejo Hospitalario Universitario de Santiago, Santiago de Compostela, A Coruña, Spain
Neil Belman	St Luke's University Health Network, Bethlehem, PA
Dina Ben-Yehuda	Hadassah Medical Organization, Ein Kerem, Jerusalem, Israel
Isabelle Bence-Bruckler	Pharmacy Department, Ottawa Hospital, Ottawa, Ontario, Canada
Juan Miguel Bergua Burgués	Servicio de Hematologia, Hospital Universitario San Pedro de Alcántara, Cáceres, Spain
Alberto Bessudo	California Cancer Associates for Research and Excellence Inc, Encinitas, CA
Fontanet Bijou	Institut Bergonié, Bordeaux, France
Ian Bilmon	Westmead Hospital, Westmead, New South Wales, Australia
Robert Blum	Bendigo Health, The Bendigo Hospital Campus, Medical Oncology Unit, Bendigo, Victoria, Australia
Sabela Bobillo	Hospital Universitari Vall d'Hebron, Barcelona, Spain
Ralph Boccia	Center for Cancer and Blood Disorders, Bethesda, MD
Rinske Boersma	Amphia Ziekenhuis, Breda, the Netherlands
Lara H. Böhmer	Haga Ziekenhuis, Den Haag, the Netherlands

(continued on following page)

TABLE A1. List of ROBUST Study Investigators (continued)

Principal Investigator	Site Location
Serge Bologna	CHU de Nancy-Hôpitaux de Brabois, Vandoeuvre-lès-Nancy, France
Christophe Bonnet	CHU de Liège—Sart Tilman, Domaine Universitaires du Sart Tilman B35, Liège, Belgium
Alberto Bosi	Azienda Ospedaliera Universitaria Careggi, Firenze, Italy
Kamal-Krimo Bouabdallah	University Hospital Haut-Léveque, Pessac, France
Javier M. Briones	Hospital de la Santa Creu i Sant Pau, Barcelona, Spain
Fernando Cabanillas	Hospital Española Auxilio Mutuo de Puerto Rico, Inc, Farmacia Clinica Auxilio Mutuo, Hato Rey, Puerto Rico
Catello Califano	P.O. "Andrea Tortora" di Pagani, Pagani, Salerno, Italy
Philip Campbell	Geelong Hospital, Geelong, Victoria, Australia
Miguel A. Canales Albendea	Hospital Universitario La Paz, Madrid, Spain
Angelo M. Carella	IRCCS Az. Osp. Universitaria San Martino—IST, Genova, Italy
Guillaume Cartron	Hôpital Saint-Eloi, Montpellier, France
Kimberly Cartwright	Wollongong Hospital, Wollongong, New South Wales, Australia
Susana M. C. Carvalho	Instituto Português de Oncologia de Lisboa Francisco Gentil, Lisboa, Portugal
Michael Castine III	Hematology/Oncology Clinic LLP, Baton Rouge, LA
Januario Castro	UC San Diego Moores Cancer Center, La Jolla, CA
John Catalano	Peninsula Health, Frankston Hospital, Frankston, Victoria, Australia
Federica Cavallo	AOU Città della Salute e della Scienza di Torino, Turin, Italy
Martine E. D Chamuleau	VU Medisch Centrum, Amsterdam, the Netherlands
Arvind Chaudhry	Medical Oncology Associates, PS, Spokane, WA
Chih-Cheng Chen	Chang Gung Medical Foundation Chiayi Chang Gung Memorial Hospital, Pu-zi City, Chiayi County, Taiwan
Annalisa Chiappella	AOU Città della Salute e della Scienza di Torino, Turin, Piemonte, Italy
Seok-Goo Cho	The Catholic University of Korea, Seoul St Mary's Hospital, Seoul, Republic of Korea
Yuvraj Choudhary	Virginia Cancer Institute, Richmond, VA
Angela G. Congiu	Azienda Ospedaliera Universitaria San Martino, Genova, Italy
Paolo Corradini	Fondazione IRCSS INT, Milano, Italy
John Crown	St Vincent's University Hospital, Dublin, Ireland
Michael Crump	Princess Margaret Cancer Centre, Toronto, Ontario, Canada
Juan Cuevas	St Louis Cancer Care LLP, Bridgeton, MO
Ricardo J. S. M. da Costa	Hospital Garcia de Orta, E.P.E, Almada, Portugal
Nicolas Daguindau	C H Annecy Genevois, Pringy Cedex, France
Iwona Danielewicz	Szpitale Wojewódzkie w Gdyni Sp. z o. o., Gdyńskie Centrum Onkologii Oddział Chemioterapii, Gdynia, Poland
Dries Deeren	AZ Delta, Roeselare, West-Vlaanderen, Belgium
Luis de la Cruz Merino	Hospital Universitario Virgen Macarena, Sevilla, Spain
Richard Delarue	Hôpital Necker, Paris, France
Muzaffer Demir	Trakya Universitesi Tip Fakultesi Hastanesi, Balkan Yerleşkesi,Hematoloji Bilim Dali, Edirne, Turkey
Hilde Demuynck	Regionaal Ziekenhuis Jan Yperman VZW, Leper, Belgium
Pierre Desjardins	Centre de Santé et de Services Sociaux Champlain Charles LeMoyne, Greenfield Park, Quebec, Canada
Francesco Di Raimondo	Presidio "Ferrarotto Alessi", Azienda Ospedaliero-Universitaria Policlinico Vittorio Emanuele, Catania, Italy
Andrei M. Dobrescu	Regional Cancer Care Associates LLC - Somerville, Somerville, NJ

(continued on following page)

TABLE A1. List of ROBUST Study Investigators (continued)

Principal Investigator	Site Location
Toshihiko Doi	National Cancer Center Hospital East, Kashiwa, Chiba, Japan
Sean Dolan	Saint John Regional Hospital, Saint John, New Brunswick, Canada
Eva Ma Donato Martin	Hospital Universitario Doctor Peset, Valencia, Spain
Xin Du	Guangdong General Hospital, Guangzhou, Guangdong, China
Nazik Durdu-Rayman	Vlietland Ziekenhuis, Schiedam, the Netherlands
Marc Durian	Elisabeth-TweeSteden Ziekenhuis, Tilburg, the Netherlands
Richard Eek	Border Medical Oncology, Wodonga, Victoria, Australia
Hyeon Seok Eom	National Cancer Center, Gyeonggi-do, Republic of Korea
Bulent Eser	Erciyes University Faculty of Medicine Mehmet Kemal Dedeman, Hematology Oncology Hospital, Kayseri Melikgazi, Turkey
Alberto Fabbri	Azienda Ospedaliera Universitaria Senese, Siena, Italy
Charles Farber	Regional Cancer Care Associates LLC—Morristown, Carol G. Simon Cancer Center, Morristown, NJ
Pier P. Fattori	IRCSS I.R.S.T, Meldola, Italy
Ji-Feng Feng	Jiangsu Cancer Hospital, Nanjing, Jiangsu, China
Ru Feng	Nanfang Hospital of Southern Medicine University, Guangzhou, Guangdong, China
Burhan Ferhanoğlu	American Hospital Hematology Department, Istanbul, Turkey
Eugenio Fernandez	Centre d 'Oncologie, Hôpitaux Universitaire de Genève-Rue, Genève, Suisse, Switzerland
Andrés J. M. Ferreri	IRCSS Ospedale S. Raffaele, Milano, Italy
Pierre Feugier	CHU de Nancy-Hôpitaux de Brabois, Vandoeuvre-lès-Nancy, France
Natalie Fischer	Kantonsspital Winterthur- Medizinische Onkologie, Winterthur, Switzerland
Robin Filshie	St Vincent's Hospital, Melbourne, Victoria, Australia
Scott Fleischauer	Texas Oncology Arlington North, Arlington, TX
Patricia Font Lopez	Hospital General Universitario Gregorio Marañón, Madrid, Spain
Anne Fortune	Mater Misericordiae University Hospital, Dublin, Ireland and Mater Private Hospital, Dublin, Ireland
Roberto Freilone	Ospedale di Ivrea, Ivrea, Torino, Italy
Carl Freter	Saint Louis University Cancer Center, St Louis, MO
Hiroshi Fujiwara	Ehime University Hospital, Shitsukawa, Toon, Ehime, Japan
Yousuf Gaffar	University of Maryland St Joseph Medical Center Cancer Institute, Townson, MD
Gianluca Gaidano	Azienda Ospedaliera Universitaria "Maggiore della Carità", Novara, Italy
Peter Ganly	Canterbury Health Laboratories, Christchurch, Canterbury, New Zealand
Gregory Gareth	Monash Health, Monash Medical Centre, Clayton, Victoria, Australia
Randy D. Gascoyne	Centre for Lymphoid Cancer, British Columbia Cancer, Vancouver, BC, Canada
Anupkumar George	Capital and Coast District Health Board, Wellington Hospital, Newtown, Wellington, North Island, New Zealand
Guido Gini	AOU Ospedali Riuniti di Ancona, Toretto di Ancona, Ancona, Italy
Marilia Gomes	Centro Hospitalar e Universitário de Coimbra EPE, Coimbra, Portugal
Maria Gomes da Silva	Instituto Português de Oncologia de Lisboa Francisco Gentil, Lisboa, Portugal
José Gomez Codina	Hospital Universitari i Politecnic La Fe de Valencia, Valencia, Spain
Cristina M. A. P. Gonçalves	Centro Hospitalar do Porto EPE - Hospital de Santo António, Porto, Portugal
Andre Goy	John Theurer Cancer Center at Hackensack University Medical Center, Hackensack, NJ
Carlos Grande García	Hospital Universitario 12 de Octubre, Madrid, Spain
Cliona Grant	St James's Hospital, Dublin Ireland
Mariella Grasso	Azienda Sanitaria Ospedaliera "S. Croce e Carle," Cuneo, Italy
Richard H. Greenberg	Regional Cancer Care Associates LLC-Cherry Hill, Cherry Hill, NJ

(continued on following page)

TABLE A1. List of ROBUST Study Investigators (continued)

Principal Investigator	Site Location
Andrew Grigg	Austin Health-Hospital, Heidelberg, Victoria, Australia
Fátima Guedes	Hospital Distrital da Figueira da Foz EPE, Figueira da Foz, Portugal
Ronit Gurion	Rabin Medical Center, Beilinson Campus, Petach Tikva, Israel
Birol Guvenc	Cukurova University Faculty of Medicine, Internal Diseases Hematology Department, Adana, Balcali, Turkey
Sibel K. Hacioglu	Pamukkale University Faculty of Medicine Hospital, Department of Hematology, Denizli, Kinikli, Turkey
Corinne Haioun	Hôpital Henri Mondor, Créteil, France
Janusz Halka	Samodzielny Publiczny Zaklad Opieki Zdrowotnej Ministerstwa Spraw Wewnetrznych z Warminsko-Mazurskim Centrum Onkologii, Oddzial Hematologii, Olsztyn, Poland
Kiyohiko Hatake	The Cancer Institute Hospital of Japanese Foundation For Cancer Research, Koto-ku, Tokyo, Japan
Timothy Hawkins	Auckland DHB, Auckland City Hospital, Auckland, Auckland Region, New Zealand
Amjad Hayat	University Hospital Galway, Galway, Ireland
José Á. Hernández Rivas	Hospital Universitario Infanta Leonor, Madrid, Spain
Eduardo R. Herranz	Hospital Universitario de Valme, Sevilla, Spain
Xiaonan Hong	Fudan University Shanghai Cancer Center, Shanghai, China
Netanel Avraham Horowitz	Rambam Health Care Campus, Haifa, Israel
Robert Hoyer	Memorial Hospital, Colorado Springs, CO
Jianda Hu	Fujian Medical University Union Hospital, Fuzhou, Fujian, China
Huiqiang Huang	Sun Yatsen University Cancer Center, Guangzhou Guangdong, China
Takayuki Ikezoe	Kochi Medical School Hospital, Oko-cho, Nankoku-shi, Kochi, Japan
Kenichi Ishizawa	Yamagata University Hospital, Iida-Nishi, Yamagata, Yamagata, Japan
Iris Isufi	Smilow Cancer Hospital at Yale-New Haven, New Haven, CT
Koji Izutsu	National Cancer Center Hospital, Tokyo, Japan
Deepa Jeyakumar	UC Irvine Medical Center, Chao Family Comprehensive Cancer Center, Orange, CA
Jie JIn	The First Affiliated Hospital of Medical School of Zhejiang University, First Hospital of Zhejiang Province, Hangzhou, Zhejiang, China
Zhengming Jin	The First Affiliated Hospital of Soochow University, Suzhou, Jiangsu, China
Wojciech Jurczak	Jagiellonian University, Kraków, Poland
Yoshihiro Kameoka	Akita University Hospital, Hiroomote, Akita-shi, Akita, Japan
Zevad Kanaan	UT/Memorial Hermann Cancer Center, Houston, TX
Barry Kaplan	Queens Medical Associates PC, Fresh Meadows, NY
Kasra Karmalou	John Muir Medical Centre, Concord, CA
Koji Kato	Kyushu University Faculty of Medicine, Fukuoka-City, Japan
Xiaoyan Ke	Peking University Third Hospital, Haidian District, Beijing, China
Stephan D. Kendall	Utah Cancer Specialists, Salt Lake City, UT
Robert M. Kessler	Cancer Center at West Jefferson Medical Center New Orleans Physicians Services, Inc, Marrero, LA
Nadia Khan	Fox Chase Cancer Center, Philadelphia, PA
Toru Kiguchi	Japan Mutual Aid Association of Public School Teachers Chugoku Central Hospital, Kamiiwanari, Miyuki-cho, Fukuyama, Hirosima, Japan
Allanah Kilfoyle	MidCentral DHB, Palmerston North Hospital, Palmerston North, Manawatu- Wanganui, New Zealand
Saadettin Kilickap	Hacettepe Universitesi Tip Fakultesi Onkoloji Hastanesi, Preventif Onkoloji Anabilim Dali, Sihhiye, Ankara, Turkey
Jin-Seok Kim	Severance Hospital Yonsei University Health System, Seoul, Republic of Korea
Won Seog Kim	Samsung Medical Center, Seoul, Republic of Korea

(continued on following page)

TABLE A1. List of ROBUST Study Investigators (continued)

Principal Investigator	Site Location
Wanda Knopinska-Posluszny	Samodzielny Publiczny Zaklad Opieki Zdrowotnej Ministerstwa Spraw Wewnetrznych z Warminsko-Mazurskim Centrum Onkologii, Oddzial Hematologii, Olsztyn, Poland
Tsutomu Kobayashi	University Hospital, Kyoto Prefectural University of Medicine, Kyoto-city, Kyoto, Japan
Maya Koren-Michowitz	Assaf Harofeh Medical Center, Beer Yaakov, Zerifin, Israel
Mauro Krampera	AOU Integrata di Verona- Unversita di Verona-Policlinico G.B. Rossi, Verona, Italy
Kazimierz Kuliczkowski	Samodzielny Publicczny Szpital Kliniczny Nr 1 we Wroclawiu, Klinika Hematologii Nowotworow Krwi I Transplantacji Szpiku, Wroclaw, Poland
Charles S. Kuzma	FirstHealth Outpatient Cancer Center, Pinehurst, NC
Alexey Kuzmin	SAHI (Republican Clinical Oncology Dispensary Ministry of Healthcare of the Tatarstan Republic), Kazan, Russia
Thierry Lamy De La Chapelle	CHRU Rennes-Hôpital Pontchaillou, Rennes Cedex 9, France
Vincent Launay	CH Yves le Foll, Saint Brieuc, France
Aleksandr Lazaryan	University of Minnesota Medical Center, Minneapolis, MN
Steven Le Gouill	CHU Hôtel Dieu, Nantes Cedex, France
Maria B. L. Leijs	Maasstad Ziekenhuis, Rotterdam, the Netherlands
Jan Lemmens	GZA St Augustinus, Wilrijk, Belgium
Itai Levi	Soroka University Medical Centre, Beer-Sheva, Israel
Lawrence Lewkow	Virginia Cancer Institute, Richmond, VA
Wei Li	First Hospital of Jilin University, Changchun, Jilin, China
Anna M. Liberati	AOS Maria Di Terni, Terni, Italy
Jiazhuo Liu	West China Hospital of Sichuan University, Chengdu, Sichuan, China
Armando G. López	Hospital Clinic, Barcelona, Spain
Javier Lopez	Hospital Universitario Ramón y Cajal, Madrid, Spain
Paulo Lúcio	Fundação Champalimaud, Lisboa, Portugal
Stefano Luminari	Azienda Ospedaliero—Universitaria Policlinico di Modena, Modena, Italy
Hongbin Ma	West China Hospital of Sichuan University, Chengdu, Sichuan, China
Viguria A. Ma Cruz	Complejo Hospitalario de Navarra, Pamplona, Navarra, Spain
Hervé Maisonneuve	CHD Vendée, Hôpital de la Roche-sur-Yon, La Roche-sur-Yon Cedex 9, France
Ignazio Majolino	Azienda Ospedaliera San Camillo Forlanini, Roma, Italy
Salman Malad	Cancer Center of Acadiana—Lafayette General Medical Center, Lafayette, LA
Christoph Mamot	Kantonsspital Aarau AG- Zentrum für Onkologie, Hämatologie und Tranfusionsmedizin, Tellstrasse, Aarau, Switzerland
Maurizio Martelli	Azienda Policlinico Umberto I, Roma, Italy
Alejandro Martin Garcia-Sancho	Hospital Universitario de Salamanca, Salamanca, Spain
Jiří Mayer	Fakultní Nemocnice Brno, Interní Hematologická a Onkologická Klinika, Brno, Czech Republic
Matthew McKinney	Duke Cancer Institute, Durham, NC
Francesco Merli	AO Acrispedale di Reggio Emilia Santa Maria Nuova/IRCSS, Reggio Emilia, Italy
Martha Mims	Baylor College of Medicine, Houston, TX
Yosuke Minami	National Cancer Center Hospital East, Kashiwa, Chiba, Japan
Monique C. Minnema	UMC Utrecht, Utrecht, the Netherlands
Heidi Mócikova	Faculty Hospital Kralovske Vinohrady, Prague, Czech Republic
Anna L. Molinari	Ospedale Degli Infermi, Rimini, Italy
Luigina Mollica	Hôpital Maisonneuve-Rosement, Montreal, Quebec, Canada
Michael R. Moore	Willis-Knighton Cancer Center, Shreveport, LA
Masakazu Mori	Kochi Medical School Hospital, Oko-cho, Nankoku-shi, Kochi, Japan

(continued on following page)

TABLE A1. List of ROBUST Study Investigators (continued)

Principal Investigator	Site Location
Gerardo Musuraca	IRCSS I.R.S.T, Meldola, Italy
Pellegrino Musto	IRCSS Centro Di Riferimento Oncologico della Basilicata, Rionero in Vulture, Potenza, Italy
Arnon Nagler	Chaim Sheba MC, Tel-Hashomer, Ramat-Gan, Israel
Neil Nagovski	Memorial Cancer Institute at Memorial Regional Hospital, Hollywood, FL
Mohit Narang	Maryland Oncology Hematology, P.A., Columbia, MD
Robert Nickelson	Willis-Knighton Cancer Center, Shreveport, LA
Concepción G. Nicolás	Hospital Universitario Central de Asturias, Oviedo, Asturias, Spain
Grzegorz Nowakowski	Mayo Clinic, Rochester, MN
Lucie Oberic	Institut Universitaire du Cancer, Toulouse, France
Isabel Oliveira	Instituto Português de Oncologia do Porto Francisco Gentil EPE, Porto, Portugal
Annibali Ombretta	Policlinico Universitario Campus Bio-Medico, Rome, Italy
Stephen Opat	Monash Health, Monash Medical Centre, Clayton, Victoria, Australia
Derville O'Shea	Health Service Executive, Cork University Hospital, Cork, Ireland
Dzhelil Osmanov	FSBI "Russian Oncology Research Center n.a. Blokhin" of Ministry of Healthcare of RF, Moscow, Russia
Lindsay Overton	Wenatchee Valley Hospital and Clinics, Wenatchee, WA
Caryolyn Owen	Tom Baker Cancer Centre, Calgary, Alberta, Canada
Muhit Özcan	Ankara University, Ankara, Turkey
Guner H. Ozsan	Dokuz Eylul University Faculty of Medicine Hematology Department, Izmir, Balcova, Turkey
John Pagel	Swedish Cancer Institute, Seattle, WA
Tomáš Papaji	Fakultní Nemocnice Olomouc, Hemato-Onkologická Klinika, Olomouc, Czech Republic
Fabrizio Pane	AOU Federico II, Via Sergio Pansini, Napoli, Italy
Carlos Panizo Santos	Clinica Universidad de Navarra, Pamplona, Navarra, Spain
Guido Parvis	AOU San Luigi Gonzaga, Orbassano, Torino, Italy
Vincenzo Pavone	Azienda Ospedaliera Cardinale G Panico Pia Fondazione di Culto e Religione, Tricase(LE), Italy
David Peace	University of Illinois Cancer Center, Chicago, IL
Jaime Pérez de Oteyza	Centro Integral Oncologico Clara Campal (CIOCC), Madrid, Spain
Ma Angeles Pérez Saenz	Hospital Universitario Fundación Jimenez Diaz, Madrid, Spain
Francesco Piazza	University of Padova and Azienda Ospedaliera di Padova, Padova, Italy
Antonio Pinto	IRCCS Istituto Naz Studio e Cura Tumori—"Fond G. Pascale", Napoli, Italy
Andrew W. Pippas	John B. Amos Cancer Center, Columbus, GA
Samantha Pozzi	Azienda Ospedaliero—Universitaria Policlinico di Modena, Modena, Italy
Vishnu Prakash	Virginia Mason Medical Center, Seattle, WA
Elena Prieto	Hospital Universitario Fundación Jimenez Diaz, Madrid, Spain
Vít Procházka	Fakultní Nemocnice Olomouc, Hemato-Onkologická Klinika, Olomouc, Czech Republic
Debra Prow	McFarland Clinic P.C., Ames, IA
Hans Pruijt	Jeroen Bosch Ziekenhuis, Hertogenbosch, the Netherlands
Radhakrishnan Ramchandren	Karmanos Cancer Institute, Detroit, MI
Brian Randolph	Southeastern Regional Medical Center, Newnan, GA
Christopher M. Reynolds	St Joseph Mercy Hospital, Cancer Care Center, Ann Arbor, MI
Vincent Ribrag	Institut Gustave Roussy, Villejuif, France
Adan Rios	UT/Memorial Hermann Cancer Center, Houston, TX
Syed Rizvi	UT Southwestern Medical Center, Dallas, TX
Guillermo Rodriguez Garcia	Hospital Universitario Virgen del Rocio, Sevilla, Spain

(continued on following page)

TABLE A1. List of ROBUST Study Investigators (continued)

Principal Investigator	Site Location
María J. Rodríguez-Salazar	Hospital Universitario de Canarias, Canarias, Spain
Giuseppe Rossi	Azienda Ospedaliera Spedali Civili di Brescia, Brescia, Italy
Rosa Ruchlemer	Shaare Zedek Medical Center, Jerusalem, Israel
Antonio Rueda Dominguez	Hospital Costa del Sol, Marbella, Málaga, Spain
Marco Ruiz	Memorial Cancer Institute at Memorial Regional Hospital, Hollywood, FL
Chiara Rusconi	Azienda Ospedaliera Ospedale Niguarda Ca'Granda, Milan, Italy
Piotr Rzepecki	Wojskowy Instytut Medyczny, Klinice Chorob Wewnetrznych i Hematologii, Warszawa, Poland
Rustem Safin	SAHI (Republican Clinical Oncology Dispensary Ministry of Healthcare of the Tatarstan Republic), Kazan, Russia
Muhammad Salim	Allan Blair Cancer Centre, Regina, Saskatchewan, Canada
Antonio Salar Silvestre	Hospital del Mar, Barcelona, Spain
Juan M. Sancho	Hospital Universitario Germans Trias i Pujol., Barcelona, Spain
Flavia Salvi	Azienda Ospedaliera Nazionale SS Antonio e Biagio e Cesare Arrigo Alessandria, Alessandria, Italy
Hakan I. Sari	Pamukkale University Faculty of Medicine Hospital, Department of Hematology, Denizli, Kinikli, Turkey
Ahmed Sawas	Columbia University Medical Center Herbert Irving Pavilion, New York, NY
María J. Sayas Lloris	Hospital Universitario Doctor Peset, Valencia, Spain
David W. Scott	Centre for Lymphoid Cancer, British Columbia Cancer, Vancouver, BC, Canada
Ofer Shpilberg	Assuta Medical Center, Hematology Division & Clinical Trials Division, Tel Aviv, Israel
Robert Siegel	Saint Francis Hospital Cancer Centre, Greenville, SC
Giorgina Specchia	Azienda Ospedale Unicersitaria Consorziale Policlinico di Bari, Bari, Italy
Michele Spina	Centro Di Riferimento Oncologico IRCSS, Aviano (PN), Italy
Anastasios Stathis	Ospedale San Giovanni, Via Ospedale, Bellinzona, Switzerland, Switzerland
Piero M. Stefani	Azienda ULSS n.9 Ospedale Ca'Foncello, Treviso, Italy
Caterina Stelitano	Grande Ospedale "Bianchi-Melacrino-Morelli", Reggio Calabria, Italy
Lesley Street	Tom Baker Cancer Centre, Calgary, Alberta, Canada
Youko Suehiro	National Hospital Organization Kyushu Cancer Center, Fukuoka-city, Fukuoka, Japan
Cheolwon Suh	Asan Medical Center, Seoul, Republic of Korea
Jeffrey Szer	Royal Melbourne Hospital, Parkville, Victoria, Australia
Agostino Tafuri	Azienda Ospedaliera Universitari, Roma, Italy
Monica Tani	U.O. Ematologia, Dipartimento Oncologia e Ematologia, Ospedale Santa Maria delle Croci, Ravenna, Italy
Masafumi Taniwaki	University Hospital, Kyoto Prefectural University of Medicine, Kyoto-city, Kyoto, Japan
Adrian Tempescul	CHU Brest - Hôpital Morvan, Brest Cedex, France
Maria J. Terol Castera	Hospital Clínico Universitario de Valencia, Valencia, Spain
Yasuhito Terui	The Cancer Institute Hospital of Japanese Foundation For Cancer Research, Koto-ku, Tokyo, Japan
Catherine Thiéblemont	Hôpital Saint Louis, Paris, France
Maria C. Tisi	Azienda ULSS 8 "Berica"—Ospedale S. Bortolo, Vicenza, Italy
Marek Trněný	Všeobecná Fakultní Nemocnice v Praze, I. Interní Klinika—Klinika Hematologie, Prague, Czech Republic
Kunihiro Tsukasaki	National Cancer Center Hospital East, Kashiwa, Chiba, Japan
Anil Tulpule	USC/Norris Comprehensive Cancer Center, Los Angeles, CA
Gayane Tumyan	FSBI "Russian Oncology Research Center n.a. Blokhin" of Ministry of Healthcare of RF, Moscow, Russia
Joseph Tuscano	University of California Davis Comprehensive Cancer Center, Sacramento, CA

(continued on following page)

TABLE A1. List of ROBUST Study Investigators (continued)

Principal Investigator	Site Location
Levent Undar	Akdeniz University Tip Fakultesi Hastanesi Ic Hastaliklari anabilim Dali, Hematoloji Bilim Dali, Dumlupinar Bulvari, Arapsuyu, Konyaalti, Antalya, Turkey
Isabelle Vande Broek	AZ Nikolaas, Sint-Niklaas, Oost-Vlaanderen, Belgium
Eric Van Den Neste	Cliniques Universitaires Saint-Luc, Brussels, Belgium
Rozemarijn Stephanie van Rijn	Medisch Centrum Leeuwarden, Leeuwarden, the Netherlands
Fernanda Vargas	Hospital Garcia de Orta, E.P.E, Almada, Portugal
Carlo Visco	Azienda ULSS 8 "Berica"—Ospedale S. Bortolo, Vicenza, Italy
Umberto Vitolo	AOU Città della Salute e della Scienza di Torino, Turin, Piemonte, Italy
Stefano Volpetti	Azienda Ospedaliero Universitaria S.Maria Della Misericordia di Udine, Udine, Italy
Madhuri Vusirikala	UT/Memorial Hermann Cancer Center, Houston, TX
Patricia Walker	Peninsula Health, Frankston Hospital, Frankston, Victoria, Australia
John Wallmark	Maryland Oncology Hematology PA, Rockville, MD
Ming-Chung Wang	Chang Gung Medical Foundation Kaohsiung Chang Gung Memorial Hospital, Niao-sung District, Kaoshiung, Taiwan
Po-Nan Wang	Chang Gung Medical Foundation, Linkou Branch, Taoyuan, Taiwan
Donald Wender	Siouxland Regional Cancer Center dba June E. Nylen Cancer Center, Sioux City, IA
Thomas E. Witzig	Mayo Clinic, Rochester, MN
Tomasz Wozny	SPZOZ MSW w Poznanium im. Prof. Ludwika Bierkowskiego, Oddzial Hematologii, Poznan, Wielkopolskie, Poland
Tomasz Wrobel	Samodzielny Publicczny Szpital Kliniczny Nr 1 we Wroclawiu, Klinika Hematologii Nowotworow Krwi I Transplantacji Szpiku, Wroclaw, Poland
Wei Xu	Jiangsu Province Hospital, Nanjing, Jiangsu, China
Abdulraheem Yacoub	The University of Kansas Cancer Center and Medical Pavilion, Westwood, KS
Go Yamamoto	Toranomon Hospital, Minato-ku, Tokyo, Japan
Kazuhito Yamamoto	Aichi Cancer Center Hospital, Nagoya, Japan
Shenmiao Yang	Peking University People's Hospital, Xicheng District, Beijing, China
Ming Yao	National Taiwan University Hospital, Taipei City, Taiwan
Victor Yazbeck	Virginia Commonwealth University Massey Cancer Center, Dalton Oncology Clinic, Richmond, VA
Su-Peng Yeh	China Medical University Hospital, Taichung City, Taiwan
Charles Yen	Millennium Oncology, Houston, TX
Mustafa N. Yenerel	Istanbul Universitesi Istanbul Tip Fakultesi, Ic Hastaliklari Anabilim Dali, Hematoloji Bilim Dali, Fatih, Capa, Istanbul, Turkey
Hisayuki Yokoyama	National Hospital Organization Sendai Medical Center, Sendai-City, Miyagi, Japan
Dok Hyun Yoon	Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea
Francesco Zaja	Azienda Ospedaliero Universitaria S.Maria Della Misericordia di Udine, Udine, Italy
Francesco Zallio	Azienda Ospedaliera Nazionale SS Antonio e Biagio e Cesare Arrigo Alessandria, Alessandria, Italy
Jan Zaucha	Szpitale Wojewódzkie w Gdyni Sp. z o. o., Gdyńskie Centrum Onkologii Oddział Chemioterapii, Gdynia, Poland
Huilai Zhang	Tianjin Medical University Cancer Institute & Hospital, Hexi District, Tianjin, China
Li Zhang	West China Hospital of Sichuan University, Chengdu, Sichuan, China
Qingyuan Zhang	Harbin Medical University Cancer Hospital, Nangang District, Harbin, Heilongjiang, China
Wei Zhang	Peking Union Medical College Hospital, Wangfujing, Dongcheng District, Beijing, China
Xi Zhang	The Second Affiliated Hospital of Army Medical University, PLA, Chongqing, China
Jianfeng Zhou	Tongji Hospital, Tongji Medical College Huazhong University of Science and Technology, Wuhan, Hubei, China
Jun Zhu	Beijing Cancer Hospital, Haidian District, Beijing, China
Pier Luigi Zinzani	A.O.U Policlinico S. Orsola Malpighi, Bologna, Italy

TABLE A2. TEAEs (≥ 1%) Leading to Lenalidomide or Placebo Discontinuation

TEAEs, No. (%)	R2-CHOP (n = 283)	Placebo/R-CHOP (n = 284)
Patients with at least 1 TEAE leading to lenalidomide or placebo discontinuation	49 (17)	32 (11)
Neutropenia	23 (8)	15 (5)
Thrombocytopenia	8 (3)	3 (1)
Febrile neutropenia	7 (2)	2 (1)
Leukopenia	6 (2)	2 (1)
Pulmonary embolism	4 (1)	1 (< 1)

Abbreviations: R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R2-CHOP, lenalidomide plus R-CHOP; TEAE, treatment-emergent adverse event.

TABLE A3. Causes of Death in the R2-CHOP and Placebo/R-CHOP Treatment Arms

Causes of Death, No. (%)	R2-CHOP (n = 283)	Placebo/R-CHOP (n = 284)
Overall deaths	57 (20)	62 (22)
Malignant disease or complications thereof	49 (17)	44 (15)
Adverse event (not otherwise specified)	3 (1)	7 (2)
Unknown cause (not assessable or insufficient data)	3 (1)	6 (2)
Second primary malignancy[a]	2 (1)	2 (1)
Death from other cause	0	3 (1)

Abbreviations: R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R2-CHOP, lenalidomide plus R-CHOP.

[a]Second primary malignancies included 1 acute myeloid leukemia and 1 squamous cell carcinoma of the tongue the R2-CHOP arm, and 1 each lung and gastric adenocarcinomas in the placebo/R-CHOP arm.