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ORIGINAL REPORT

Lenalidomide Maintenance Compared With Placebo in Responding Elderly Patients With Diffuse Large B-Cell Lymphoma Treated With First-Line Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone

Catherine Thieblemont, Hervé Tilly, Maria Gomes da Silva, Rene-Olivier Casasnovas, Christophe Fruchart, Franck Morschhauser, Corinne Haioun, Julien Lazarovici, Anida Grosicka, Aurore Perrot, Judith Trotman, Catherine Sebban, Dolores Caballero, Richard Greil, Koen van Eygen, Amos M. Cohen, Hugo Gonzalez, Reda Bouabdallah, Lucie Oberic, Bernadette Corront, Bachra Choufi, Armando Lopez-Guillermo, John Catalano, Achiel Van Hoof, Josette Briere, Jose Cabeçadas, Gilles Salles, Philippe Gaulard, Andre Bosly, and Bertrand Coiffier

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

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Corresponding author: Catherine Thieblemont, MD, PhD, Hôpital Saint-Louis, Hemato-oncology 1 Ave Claude Vellefaux, 75010 Paris, France; e-mail: catherine.thieblemont@aphp.fr.

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ABSTRACT

Purpose
The standard treatment of patients with diffuse large B-cell lymphoma (DLBCL) is rituximab in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). Lenalidomide, an immunomodulatory agent, has shown activity in DLBCL. This randomized phase III trial compared lenalidomide as maintenance therapy with placebo in elderly patients with DLBCL who achieved a complete response (CR) or partial response (PR) to R-CHOP induction.

Methods
Patients with previously untreated DLBCL or other aggressive B-cell lymphoma were 60 to 80 years old, had CR or PR after six or eight cycles of R-CHOP, and were randomly assigned to lenalidomide maintenance 25 mg/d or placebo for 21 days of every 28-day cycle for 24 months. The primary end point was progression-free survival (PFS).

Results
A total of 650 patients were randomly assigned. At the time of the primary analysis (December 2015), with a median follow-up of 39 months from random assignment, median PFS was not reached for lenalidomide maintenance versus 58.9 months for placebo (hazard ratio, 0.708; 95% CI, 0.537 to 0.933; $P = .01$). The result was consistent among analyzed subgroups (eg, male *v* female, age-adjusted International Prognostic Index 0 or 1 *v* 2 or 3, age younger than 70 *v* ≥ 70 years), response (PR *v* CR) after R-CHOP, and positron emission tomography status at assignment (negative *v* positive). With longer median follow-up of 52 months (October 2016), overall survival was similar between arms (hazard ratio, 1.218; 95% CI, 0.861 to 1.721; $P = .26$). Most common grade 3 or 4 adverse events associated with lenalidomide versus placebo maintenance were neutropenia (56% *v* 22%) and cutaneous reactions (5% *v* 1%), respectively.

Conclusion
Lenalidomide maintenance for 24 months after obtaining a CR or PR to R-CHOP significantly prolonged PFS in elderly patients with DLBCL.

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ASSOCIATED CONTENT

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Data Supplement
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INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is the most common non-Hodgkin lymphoma, accounting for 30% to 40% of all cases in high-income countries.[1] Advances in molecular profiling by gene expression profiling allowed for the identification of two major DLBCL molecular subtypes: germinal center B-cell–like (GCB) and activated B-cell–like (ABC),[2] arising from different genetic mechanisms.[3,4] Immunohistochemistry-based classification defines only GCB and non-GCB subtypes.[5]

The R-CHOP regimen (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone),

administered with curative intent, is currently considered the standard of care therapy for patients of all ages with newly diagnosed DLBCL, regardless of molecular subtype.[6-10] However, 3-year progression-free survival (PFS) and overall survival (OS) rates remain at 60% and 70%, respectively.[11] Patients with ABC DLBCL have a significantly worse outcome than patients with GCB DLBCL.[12] Attempts to improve the efficacy of R-CHOP by either adding cytotoxic drugs[13] or administering dose-intensified R-CHOP[11,14-19] have not improved outcomes, except in specific subsets of young patients.[20] Some 30% to 40% of patients continue to experience disease progression or relapse, mostly during the first 2 years,[21] and the majority will succumb to lymphoma.

The introduction of new drugs to R-CHOP may be an option to improve patient outcomes; treatments are currently under evaluation either in combination with R-CHOP (RX-CHOP, X for new drug) or after R-CHOP as maintenance therapy (R-CHOP→X). Maintenance therapy corresponds to a treatment continuously administered for a prolonged time period, typically with a single agent. The goal is to better control the disease after initial therapy by improving the quality of response, delaying disease progression, and increasing long-term survival. This approach is difficult to apply with classic cytotoxic agents because of amplified toxicities. In the context of targeted therapies, such as monoclonal antibodies, kinase inhibitors, and demethylating agents, maintenance strategies have been used in clinical trials in a broad range of neoplasia[22-25] and recently in lymphoma.[26,27]

Lenalidomide, an oral immunomodulator with direct antineoplastic activity and immunologic effects, has shown significant activity in relapsed DLBCL alone or with rituximab.[28-30] Its mechanisms of action are distinct from both traditional chemotherapy and rituximab, and lenalidomide has shown proven efficacy and tolerability when used in combination with R-CHOP in phase II trials.[31-35] This provides a strong rationale for the addition of lenalidomide to first-line induction therapy in DLBCL or in the form of maintenance therapy after R-CHOP. The Lymphoma Study Association (LYSA), in close collaboration with other academic research groups in some participating countries (Arbeitsgemeinschaft Medikamentöse Tumortherapie, Australasian Leukaemia and Lymphoma Group, and Grupo Español de Linfomas y Trasplantes de Médula Ósea [GELTAMO]), undertook a study to compare lenalidomide maintenance with placebo in elderly patients with DLBCL who responded to first-line R-CHOP.

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METHODS

Study Design and Procedures

The REMARC study is an international, multicenter, double-blind, randomized, placebo-controlled phase III trial that was sponsored in 2009 by the Lymphoma Academic Research Organization (LYSARC). The study was conducted in accordance with the International Conference on Harmonization for Good Clinical Practice guidelines and the Declaration of Helsinki and was approved by local- and country-specific ethics review committees. Each patient provided written informed consent in compliance with national requirements before study enrollment and/or evaluation of patient eligibility for the study. The trial is registered at www.clinicaltrials.gov as NCT01122472.

Patients

Patients were eligible if they were 60 to 80 years old, Eastern Cooperative Oncology Group performance status 0 to 2, Ann Arbor stage II to IV at diagnosis, age-adjusted international prognostic index ≥ 1 at diagnosis,[36] and had untreated, histologically proven CD20$^+$ DLBCL according to 2008 WHO criteria.[37] Eligible DLBCL histologies included de novo transformed DLBCL from low-grade lymphoma (follicular or others), DLBCL associated with small-cell infiltration in bone marrow, CD20$^+$ B-cell lymphoma with intermediate features between DLBCL and Burkitt's lymphoma or with intermediate features between DLBCL and Hodgkin lymphoma, follicular lymphoma grade 3B, and CD20$^+$ aggressive B-cell lymphoma unclassifiable. All patients were required to have achieved a partial response (PR) or complete response (CR) after first-line treatment. Responding patients were randomly assigned (1:1) to 24 months of maintenance with either lenalidomide or placebo. Stratification was realized according to country and the response to R-CHOP (PR and CR).

Treatment

R-CHOP induction. All patients received six or eight cycles of R-CHOP–14 or –21 at standard doses (Fig 1). Two cycles of rituximab could be administered after six cycles at the investigator's discretion. CNS prophylaxis was applied at the investigator's discretion. Patients were included in the trial either before induction (registration 1) or after induction (registration 2).

Maintenance. Maintenance treatment started within 12 weeks after the first day of the last R-CHOP cycle or last rituximab alone (Fig 1). Lenalidomide or placebo was administered at the starting dose of 25 mg/d, days 1 to 21 of every 28-day cycle for 24 months (maximum, 26 cycles) until completion of maintenance treatment, disease progression or relapse, unacceptable toxicity, or patient refusal. A dose-reduction schedule was applied according to toxicity (Appendix Table A1, online only). For

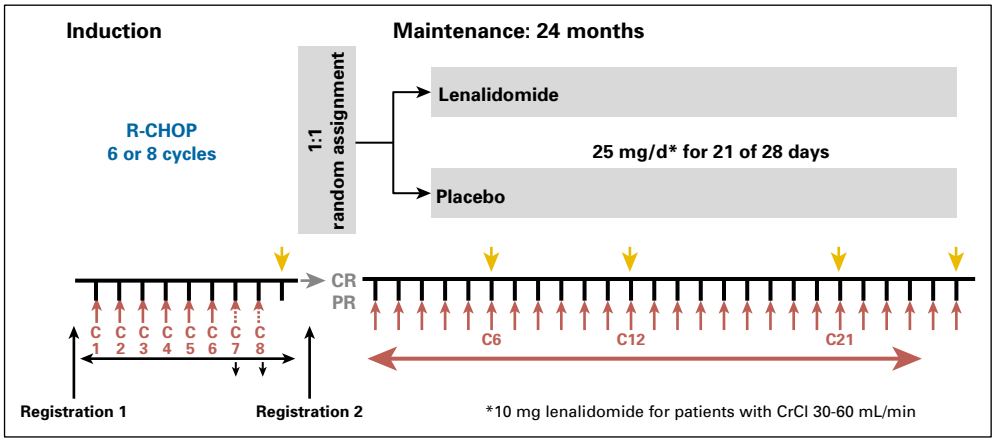

Fig 1. REMARC study design (ClinicalTrials.gov identifier NCT01122472). Patients received six or eight cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) induction; those responding to induction with a complete response (CR) or partial response (PR) were randomly assigned 1:1 to 24 months of maintenance with lenalidomide or placebo treatment. Lenalidomide was administered at a dose of 25 mg/d on days 1 to 21 of each 28-day cycle; the starting dose was reduced to 10 mg/d for patients with creatinine clearance (CrCl) of 30 to 60 mL/min. Patients could be registered in the study at two different stages: before R-CHOP induction or after. Red arrow signifies treatment with study drug; gold arrow signifies response assessments. C, cycle.

patients with moderate renal insufficiency (creatinine clearance, 30 to 60 mL/min), the starting dose of lenalidomide was 10 mg/d.

Evaluation of Response

After R-CHOP induction, response assessment was analyzed between 3 and 8 weeks after day 1 of the last induction cycle with a positron emission tomography–computerized tomography (PET) scan before randomization. Bone marrow examination was repeated at the end of induction if positive at diagnosis.

During maintenance, tumor response assessment was performed clinically every three cycles and with contrast-enhanced computed tomography scans at cycles six (6 months), 12 (12 months), and 21 (18 months), at the end of maintenance or time of discontinuation from treatment, then annually. Repeat PET scan evaluation was requested in responding patients who were PET positive at randomization.

Evaluation of Toxicity

All adverse events (AEs) reported by the patient or observed by the investigator were collected from the case report form in predefined categories. An AE was defined as any adverse change from the patient's baseline condition, whether it was considered related to treatment or not. Each AE was graded according to the National Cancer Institute Common Terminology Criteria grading system version 4. The following AEs were recorded in additional detail: grade 3 to 5 toxicities, grade 2 to 5 infections and neurologic toxicities, and any toxicity (regardless of grade) resulting in dose modification.

Pathology and Cell of Origin Characterization

Histologic diagnoses were centrally reviewed by expert pathologists (J.B., J.C., and P.G.). Expression of CD10, *BCL6*, and *MUM1* was examined by immunohistochemistry to classify all cases as GCB or non-GCB using the Hans algorithm.[5] Cell of origin was also determined in a subset of patients by molecular testing from formalin-fixed paraffin-embedded tissue using NanoString gene expression profiling technology.[38]

Statistical Analysis

The primary end point of the study was PFS defined using European Medicines Agency censoring rules[39] as first documented disease progression or relapse assessed by a blinded independent response committee or death from any cause, whichever occurred first from random assignment. The sample size was calculated based on an overall 2-year PFS of 80% and hazard ratio (HR) of 1.55 (placebo *v* lenalidomide), with 80% power and an overall two-sided α level of 5%. A total of 160 events were required for the primary PFS analysis. The cutoff date for PFS was December 31, 2015.

Secondary end points were safety, the percentage of patients who converted from PR to CR, event-free survival, event-free survival at 24 months, and OS. An additional data cutoff was performed only for the OS analysis on October 31, 2016.

The primary and secondary end points were analyzed following the intent-to-treat principle using the maintenance Full Analysis Set population, which included all patients randomly assigned to the maintenance phase of the trial. Relapse and progression were determined per Cheson 2007 criteria.[40] Survival analyses were performed by the Kaplan-Meier method,[41] and groups were compared using an unstratified log-rank test. Only variables that differed at the 0.10 level from univariate Cox regression analysis were included in the multivariate model. A forward selection stepwise procedure was used to identify the variables in the final model. To assess treatment after adjusting relevant covariates, treatment effect was included in the model regardless of univariate result. Patient characteristics were compared between study arms with χ^2 test or Fisher's exact test for discrete variables and with Wilcoxon Mann-Whitney test for continuous variables. Statistical analyses were carried out using SAS version 9.3 (SAS Institute, Cary, NC).

RESULTS

Characteristics of Patients

From May 2009 to May 2014, 796 patients were enrolled, including 784 patients in the analysis set either at diagnosis (n = 437, registration 1) or at the end of R-CHOP induction (n = 347, registration 2; Fig 2). At randomization (ie, end of R-CHOP), 650 patients had achieved a CR (n = 495; 78% lenalidomide and 75% placebo) or PR (n = 152; 21% lenalidomide and 25% placebo), with the exception of two patients with progressive disease and one with stable disease; Table 1). A positive PET scan was present in 84 patients (55% of the patients with PR), including 41 (59%) randomly assigned to lenalidomide and 43 (52%) to placebo. Baseline characteristics at randomization are listed in Table 1.

Maintenance Completion

Among patients randomly assigned to lenalidomide, 196 (61%) prematurely discontinued treatment, 111 (34%) completed maintenance, and 16 (5%) remained on maintenance at the time of primary analysis (Fig 2). Among those in the placebo arm, 134 (41%) prematurely discontinued treatment, 169 (52%) completed maintenance, and 24 (7%) remained on maintenance.

PFS

With a median follow-up of 39 months (range, 0.0 to 74.1 months), median PFS was not reached in the lenalidomide arm but was estimated at 58.9 months in the placebo arm (HR favoring lenalidomide, 0.708; 95% CI, 0.537 to 0.933; $P = .0135$; Fig 3A). The 2-year PFS was improved from 75% (95% CI, 70% to 80%) to 80% (95% CI, 75% to 84%) in the lenalidomide group. The PFS benefit of lenalidomide maintenance over placebo was seen in all analyzed subgroups predefined in the protocol (Appendix Fig A1, online only; Data Supplement).

Overall Survival

At a longer median follow-up of 52 months, median OS was not reached in either group. The 2-year OS was estimated at 87% (95% CI, 82% to 90%) for lenalidomide versus 89% (95% CI, 85% to 92%) for placebo (log-rank test $P = .2640$; HR, 1.218; 95% CI, 0.861 to 1.721; Fig 3B). Lymphoma was the main cause of death, including 41 (59%) of 69 patients in the lenalidomide arm compared with 37 (62%) of 60 patients in the placebo arm (Appendix Table A2, online only). Other causes of death included other cancers (six for lenalidomide and seven for placebo) and concurrent illness (seven for lenalidomide arm and two for placebo).

Cell of Origin

Analysis of outcomes on the basis of cell of origin (COO) per Hans criteria in patients with DLBCL only showed a statistically significant difference in median PFS in favor of lenalidomide (60.9 months; 95% CI, 59.8 months to not reached) over placebo (52.7 months; 95% CI, 40.5 months to not reached) in patients with a GCB profile (HR, 0.491; 95% CI, 0.245 to 0.985; $P = .04$). No significant difference was seen in patients with a non-GCB profile (HR, 1.081; 95% CI, 0.670 to 1.746; $P = .75$). For OS, there was no

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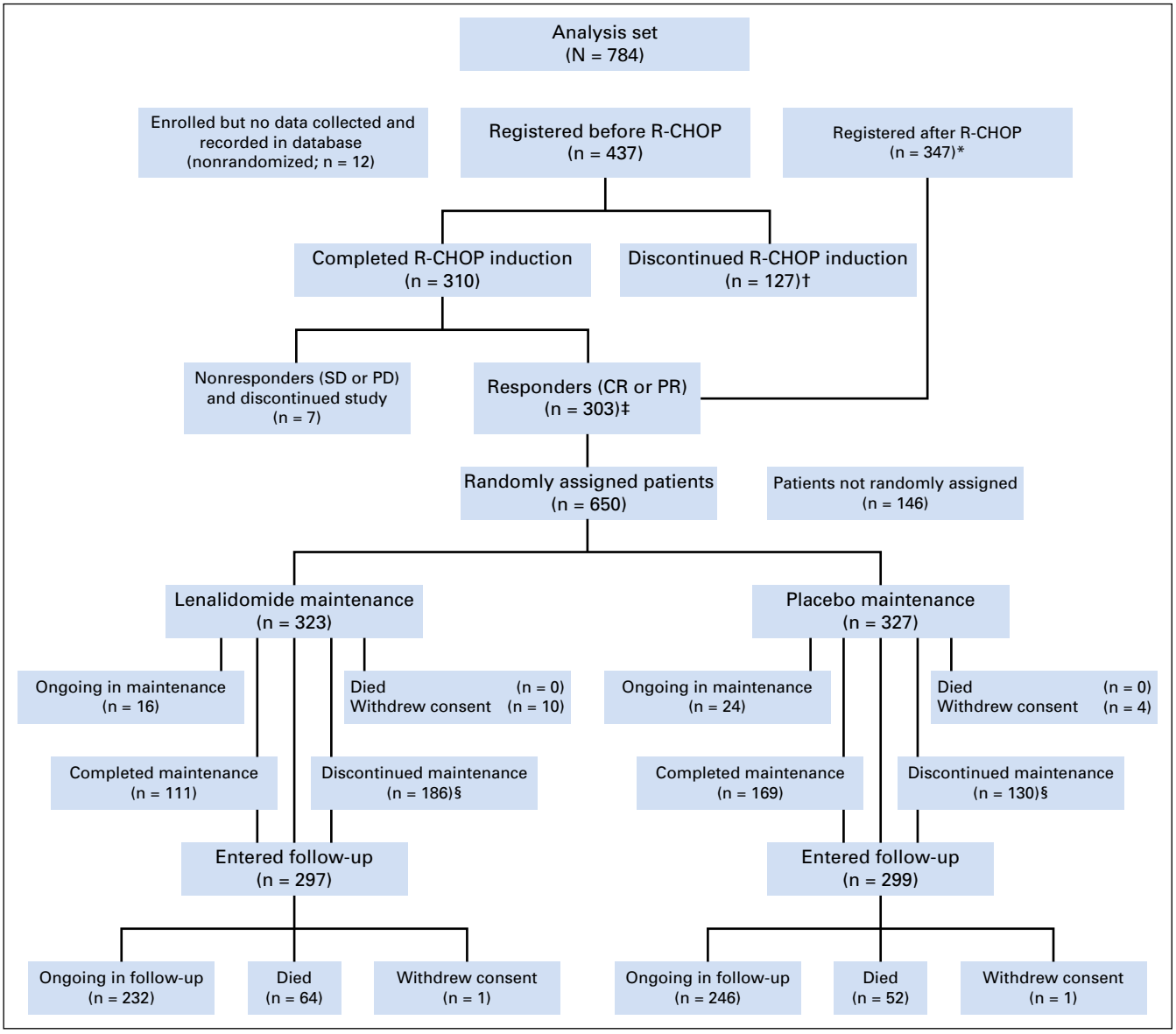

Fig 2. REMARC study CONSORT diagram. (*)Includes two patients with progressive disease (PD; determined by central review retrospectively after randomization) to rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) induction. (†)Includes treatment failure (n = 39; 31%), toxicity (n = 3; 3%), death (n = 9; 7%) including n = 1 lymphoma progression, patient voluntary withdrawal (n = 14; 11%), major protocol violation (n = 7; 6%), other reasons (n = 55; 43%). (‡)Includes one patient with a response of stable disease (SD; determined by central review retrospectively after randomization) to R-CHOP induction. (§)Reasons for discontinuing lenalidomide maintenance were: toxicity in 116 (62%), treatment failure in 36 (19%), and other causes in 34 (18%), which included patient decision (n = 27), concurrent illness (n = 1), investigator decision (n = 3), and other reasons (n = 3). Reasons for discontinuing placebo maintenance were: treatment failure in 54 patients (42%); toxicity in 53 patients (41%); one major protocol violation; and other causes in 22 (17%), which included patient decision (n = 10), noncompliance (n = 4), investigator decision (n = 2), and other reasons (n = 6). CR, complete response; PR, partial response.

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difference in either the GCB ($P = .92$) or the non-GCB ($P = .07$) groups. Per NanoString, there was no difference in PFS for patients with GCB-like, ABC-like, or unclassified DLBCL (log-rank $P = .15$, $P = .82$, and $P = .31$, respectively; Figs 3C to 3E) and no difference in OS (log-rank $P = .73$, $P = .29$, and $P = .42$, respectively).

Conversion From PR to CR and Response Rate at the End of Maintenance

In the lenalidomide arm, 23 (33%) patients converted from PR to CR during maintenance compared with 24 (29%) patients in the placebo group ($P = .56$; Table 2). On the basis of central review, 18 (21%) patients converted from PET-positive to PET-negative in the lenalidomide arm versus 13 (14%) patients in placebo arm ($P = .20$). The median time of conversion was approximately 6 months and was similar in both groups.

Safety

The safety population included a total of 645 patients who received at least one dose of maintenance treatment. The median average daily dose was 19.8 mg/d (range, 5.2 to 25.0 mg/d) in

Table 1. Demographic Patient Characteristics by Study Arm at Diagnosis

Characteristic	Lenalidomide (n = 323)	Placebo (n = 327)	*P*
Age, years			
Median (range)	69 (58-80)	68 (59-80)	.25
≥ 70	146 (45)	137 (42)	.41
Sex			
Male	183 (57)	180 (55)	.68
Female	140 (43)	147 (45)	
Histology			
DLBCL NOS	225 (70)	233 (71)	.04
FL 3B	2 (1)	3 (1)	
De novo transformed	31 (10)	16 (5)	
Other*	32 (10)	38 (12)	
Central review missing	33 (10)	37 (11)	
ECOG performance status			
2	252 (78)	237 (72)	.16
≥ 2	65 (20)	80 (24)	
Ann Arbor clinical stage			
I-II	33 (10)	42 (13)	—
III-IV	290 (90)	285 (87)	
aaIPI			
0-1	125 (39)	124 (38)	.86
2-3	185 (57)	189 (58)	
Missing	13 (4)	14 (4)	
No. of extranodal sites			
≤ 1	160 (50)	167 (51)	.70
1	163 (51)	160 (49)	
Elevated LDH (> ULN)			
No	118 (37)	116 (35)	.77
Yes	193 (60)	199 (61)	
Missing	12 (4)	12 (4)	
B symptoms			
No	200 (62)	205 (63)	.76
Yes	122 (38)	119 (36)	
Missing	1 (0.3)	3 (1)	
Bulky mass (> 10 cm)			
No	255 (79)	251 (77)	—
Yes	68 (21)	74 (23)	
Missing	0	2 (1)	
β2 microglobulin			
3 mg/L	107 (33)	126 (39)	
≥ 3 mg/L	110 (34)	102 (31)	.21
Missing	106 (33)	99 (30)	
Albumin			
≤ 35 g/L	91 (28)	91 (28)	.73
35 g/L	172 (53)	183 (56)	
Missing	60 (19)	53 (16)	
CIRS score			
0-6	223 (69)	251 (77)	—
≥ 7	100 (31)	76 (33)	
R-CHOP induction†			
6 cycles R-CHOP	119 (37)	118 (36)	—
8 cycles R-CHOP	204 (63)	208 (64)	
Response to R-CHOP			
CR	251 (78)	244 (75)	.25
PR	69 (21)	83 (25)	
ORR	320 (99)	327 (100)	
If PR	(n = 69)	(n = 83)	
Positive PET (local)	41 (59)	43 (52)	—
Bone marrow involvement	28 (41)	39 (47)	
GCB/non-GCB profile (by Hans algorithm)	(n = 192)	(n = 201)	
GCB	86 (45)	94 (47)	.69
Non-GCB	106 (55)	107 (53)	
GCB/ABC profile (by NanoString technology)‡	(n = 151)	(n = 167)	
ABC	63 (42)	58 (35)	.06
GCB	59 (39)	79 (47)	
Unclassified	24 (16)	25 (15)	
N/A	5 (3)	5 (3)	

NOTE. Data are presented as No. (%) unless otherwise noted.

Abbreviations: aaIPI, age-adjusted International Prognostic Index; ABC, activated B-cell like; CIRS, cumulative illness rating scale; CR, complete response; DLBCL, diffuse large B-cell lymphoma; DLBCL NOS, DLBCL not otherwise specified; ECOG, Eastern Cooperative Oncology Group; FL, follicular lymphoma; GCB, germinal center B-cell like; IT, intrathecal; LDH, lactate dehydrogenase; N/A, not applicable; ORR, overall response rate; PET, positron emission tomography; PR, partial response; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; ULN, upper limit of normal.

*Other included B-cell lymphoma with intermediate features between DLBCL and Burkitt's lymphoma; B-cell lymphoma with intermediate features between DLBCL and Hodgkin disease; composite: FL 3B and DLBCL; composite: DLBCL and Hodgkin disease.

†Patients received R-CHOP every 21 days (n = 594) or every 14 days (n = 55). CNS prophylaxis was provided in 332 patients (51%; lenalidomide arm, n = 52.5%; placebo arm, n = 50.5%), 323 with IT methotrexate (from one to six IT, mostly four IT, n = 216 [33%]) and nine (1%) with two cycles of intravenous methotrexate.

‡In patients with DLBCL-NOS only.

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lenalidomide arm and 25.0 mg/d for placebo (range, 5.1 to 25.0 mg/d; Appendix Fig A2, online only). The median number of maintenance cycles received in lenalidomide arm was 15 (range, 1 to 26) versus 25 (range, 1 to 26) in the placebo arm. In the lenalidomide arm, 72% of patients had at least one dose reduction compared with 42% in the placebo arm, and 36% stopped because of the toxicities due to treatment versus 16%, respectively.

From this safety set, 564 patients (87%) reported at least one treatment-emergent adverse event (TEAE), 296 patients (92%) in the lenalidomide arm and 268 patients (83%) in the placebo arm. At least one serious TEAE was reported in 99 patients (31%) in the lenalidomide arm and 91 patients (28%) in the placebo arm. Details of the most common observed grade 3 or 4 AEs are listed in Table 3. TEAEs leading to dose reductions were reported in 66% and 32% of patients, respectively. Occurrence of second primary malignancies observed during or after maintenance was similar in both arms: 32 (10%) versus 41 (13%).

DISCUSSION

To our knowledge, the REMARC study is the first phase III trial evaluating a maintenance strategy in DLBCL to show a benefit in PFS. None of the previously reported trials adding a novel drug to R-CHOP, either in combination during induction (such as with bevacizumab[42]) or after R-CHOP as maintenance (as with rituximab,[7,43,44] enzastaurin,[26] or everolimus[27]) have achieved such a benefit.

The PFS benefit of lenalidomide maintenance was equally important in patients who achieved a CR as in those achieving a PR. Interestingly, patients with PR, particularly those with a positive PET scan, converted to CR within 6 months in both arms,

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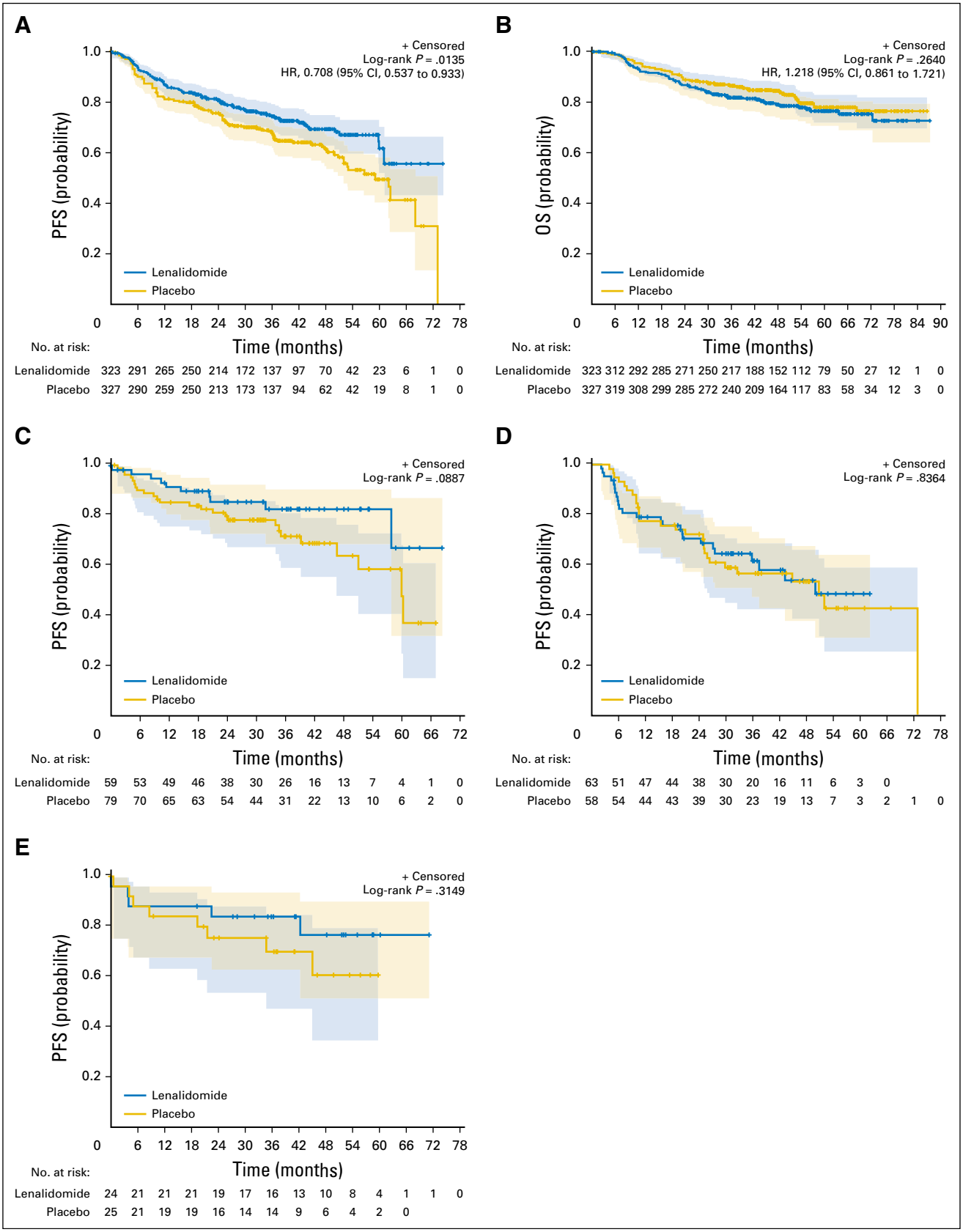

Fig 3. Progression-free survival (PFS) and overall survival (OS) according to maintenance treatment and PFS by cell of origin. (A) PFS in all patients; (B) OS in all patients; (C) PFS in germinal center B-cell–like type diffuse large B-cell lymphoma (DLBCL; NanoString); (D) PFS in activated B-cell–like type DLBCL (NanoString); and (E) PFS in unclassified-type DLBCL (NanoString). Data cutoff for PFS was December 31, 2015 and for OS was October 31, 2016.

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Table 2. Response Rate and Conversion from PR to CR with Maintenance Treatment

Response or Conversion	Lenalidomide (n = 323)	Placebo (n = 327)	*P*
Response after maintenance	(n = 323)	(n = 327)	
CR	192 (59)	183 (56)	.37
PR	21 (7)	29 (9)	
ORR	213 (66)	212 (65)	.77
Conversion from PR* to CR	(n = 69)	(n = 83)	
PR* to CR	23 (33)	24 (29)	.56
PET positive to PET negative	18 (21)	13 (14)	.20
Median time to conversion, months (range)	5.9 (3.9-26.5)	5.6 (3.2-24.8)	.52

NOTE. Data are presented as No. (%) unless otherwise noted.
Abbreviations: CR, complete response; ORR, overall response rate; PET, positron emission tomography; PR, partial response; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone.
*Included patients with a PR after R-CHOP induction therapy; see Table 1 for baseline PET positivity and bone marrow involvement values.

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which suggested that induction treatment may be more responsible for this conversion than the maintenance treatment. The PFS benefit was also observed based on subgroup analysis of clinical characteristics at diagnosis (age, sex, International Prognostic Index).

Lenalidomide is an IMiD immunomodulatory agent with activity in lymphoid malignancies occurring primarily through immune modulation (eg, T-cell immune synapse enhancement and natural killer cell/T-cell effector augmentation) and antiproliferative effects.[45-47] The strategy in REMARC was to take advantage of this potential to repair T-cell immune synapse dysfunction by lenalidomide, as reported in follicular lymphoma and chronic lymphocytic leukemia,[48,49] to eradicate resting lymphoma cells after R-CHOP induction, avoiding both early and late relapse.

Table 3. Treatment-Emergent Grade 3 or 4 Adverse Events (safety population: n = 645)

Adverse Events	Lenalidomide (n = 322)	Placebo (n = 323)
Neutropenia	181 (56)	72 (22)
Infection	25 (8)	18 (6)
Cardiac disorders	18 (6)	11 (3)
Cutaneous reaction	16 (5)	4 (1)
Thrombocytopenia	8 (3)	2 (1)
Venous thromboembolic event	6 (1)	1 (0.3)
Diarrhea and constipation	5 (2)	2 (1)
Hepatic disorder	4 (1)	6 (2)
Peripheral neuropathy	2 (1)	6 (2)
SPMs observed during and after maintenance		
Patients with ≥ 1 SPM	32 (10)	41 (13)
≥ 1 hematologic SPM	7 (2)	5 (2)
≥ 1 solid tumor	12 (4)	18 (6)
≥ 1 solid tumor, including nonmelanoma skin cancer	27 (8)	37 (11)
Deaths associated with SPMs*	9 (3)	9 (3)

NOTE. Data are presented as No. (%) unless otherwise noted.
Abbreviation: SPM, second primary malignancy.
*Deaths due to invasive SPMs in the lenalidomide arm included three cases of myelodysplastic syndrome and one each of the following: acute myeloid leukemia, acute lymphocytic leukemia, malignant lung neoplasm, metastatic neoplasm, esophageal adenocarcinoma, and oropharyngeal squamous cell carcinoma. Deaths due to invasive SPMs in the placebo arm included two cases of acute myeloid leukemia and one each of the following: myelodysplastic syndrome, refractory anemia with an excess of blasts, bladder cancer, lung adenocarcinoma, malignant melanoma, neuroendocrine tumor, and rectal adenocarcinoma.

It has been shown that lenalidomide reduces T regulatory cells, activates $CD8^+$ T cells, and skews T-helper (TH) subsets with TH1.TH2 response.[50] It is unlikely that, in a maintenance setting like REMARC, the clinical benefit observed in the lenalidomide arm could be due to a direct tumoricidal effect-with upregulation of interferon-stimulated genes that require cereblon expression, but rather an immunomodulatory mechanism. This speculation has been made in at least one other lenalidomide maintenance trial in chronic lymphocytic leukemia[51] and is supported by the observation that PR-to-CR conversion is similar between the lenalidomide maintenance and placebo in this trial (Table 2) and in the second lenalidomide maintenance trial.[51] This effect is COO independent. This may explain COO results in REMARC that are contrary to previous reports of preferential activity of lenalidomide in ABC-DLBCL. Interestingly, a recent report of lenalidomide maintenance in relapsed DLBCL showed similarly identical PFS in GC (n = 20) and non-GC (n = 19) cases ($P = .67$) and in the small subgroups of GCB-DLBCL (n = 11) and ABC-DLBCL (n = 10; data not shown).[52] It will be important in REMARC to identify any reliably predictive biomarkers to understand the effect of lenalidomide and better use this drug in routine treatment of aggressive B-cell lymphoma, including DLBCL, FL3B, and transformed indolent lymphoma.

At the time of this analysis, we do not yet fully understand the basis for lack of OS benefit despite the positive PFS data, other than that this is not due to excessive toxicity in the experimental arm. We speculate the reason may be differences in the outcomes after progression or some other unrecognized reason.

Finally, although lenalidomide toxicities were as expected, with more grade 3 and 4 neutropenia and cutaneous reactions resulting in more premature discontinuations, even for patients with minimal exposure to the drug, the benefit of lenalidomide on PFS was still present (data not shown). Of note, the rate of second primary malignancies was similar in both arms.

In conclusion, REMARC achieved its primary end point of a statistically significant and clinically meaningful improvement in PFS for patients receiving lenalidomide maintenance, with an anticipated and manageable safety profile. To our knowledge, this is the first randomized study showing that an immunomodulatory agent as maintenance therapy prolongs PFS for patients with DLBCL after responding to R-CHOP.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

AUTHOR CONTRIBUTIONS

Conception and design: Catherine Thieblemont, Bertrand Coiffier
Provision of study materials or patients: Dolores Caballero, Amos M. Cohen, Reda Bouabdallah, John Catalano, Jose Cabeçadas
Collection and assembly of data: Catherine Thieblemont, Hervé Tilly, Maria Gomes da Silva, Rene-Olivier Casasnovas, Christophe Fruchart, Franck Morschhauser, Corinne Haioun, Julien Lazarovici, Anida Grosicka, Aurore Perrot, Judith Trotman, Catherine Sebban, Dolores Caballero, Richard Greil, Koen van Eygen, Amos M. Cohen, Hugo Gonzalez, Reda Bouabdallah, Lucie Oberic, Bernadette Corront, Bachra Choufi, Armando Lopez-Guillermo, Achiel Van Hoof, Josette Briere, Jose Cabeçadas, Gilles Salles, Philippe Gaulard, Bertrand Coiffier
Data analysis and interpretation: Catherine Thieblemont, Anida Grosicka, John Catalano, Andre Bosly, Bertrand Coiffier
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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Affiliations

Catherine Thieblemont, Assistance Publique-Hôpitaux de Paris, Hôpital Saint-Louis; Diderot University, Sorbonne Paris-Cité; **Catherine Thieblemont** and **Josette Briere**, Descartes University; **Josette Briere**, Hôpital Necker, Paris; **Hervé Tilly**, University of Rouen, Institut National de la Santé et de la Recherche Médicale U1245, Rouen; **Rene-Olivier Casasnovas**, Centre Hospitalier Universitaire Dijon; Institut National de la Santé et de la Recherche Médicale UMR1231, Dijon; **Christophe Fruchart**, Institut d'Hématologie de Basse Normandie, Centre Hospitalier Universitaire, Caen; **Franck Morschhauser**, Centre Hospitalier Universitaire Régional de Lille, Lille; **Corinne Haioun** and **Philippe Gaulard**, Assistance Publique-Hôpitaux de Paris, Groupe Hospitalier Mondor; **Philippe Gaulard**, Institut National de la Santé et de la Recherche Médicale U955; Université Paris-Est, Créteil; **Julien Lazarovici**, Gustave Roussy Cancer Center, Villejuif; **Aurore Perrot**, University Hospital, Vandoeuvre les Nancy; **Catherine Sebban**, Centre Leon Berard, University Claude Bernard Lyon 1; **Gilles Salles**, Hospices Civils de Lyon, Université Claude Bernard U1052, Lyon; **Hugo Gonzalez**, Centre Hospitalier René Dubos, Pontoise; **Reda Bouabdallah**, Institut Paoli Calmettes, Marseille; **Lucie Oberic**, Institut Universitaire du Cancer-Oncopole de Toulouse, Toulouse; **Bernadette Corront**, Centre Hospitalier Régional Annecy, Annecy; **Bachra Choufi**, Centre Hospitalier Dr Duchenne, Boulogne-sur-mer; **Gilles Salles** and **Bertrand Coiffier**, Institut National de la Santé et de la Recherche Médicale U1052, Hospices Civils de Lyon, Pierre-Benite, France; **Maria Gomes da Silva** and **Jose Cabeçadas**, Instituto Português de Oncologia de Lisboa Francisco Gentil, Lisboa, Portugal; **Anida Grosicka**, Medical University of Silesia, Katowice, Poland; **Judith Trotman**, Concord Repatriation General Hospital, University of Sydney, Concord; **John Catalano**, Frankston Hospital and Monash University, Frankston, Australia; **Dolores Caballero**, Hospital Universitario de Salamanca, Salamanca; **Armando Lopez-Guillermo**, Hospital Clinic Barcelona, Barcelona, Spain; **Richard Greil**, Paracelsus Medical University Salzburg, Salzburg Cancer Research Institute; Arbeitsgemeinschaft Medikamentöse Tumortherapie, Salzburg, Austria; **Koen van Eygen**, Algemeen Ziekenhuis Groeninge Hospital, President Kennedylaan 4, Kortrijk; **Achiel Van Hoof**, Algemeen Ziekenhuis Sint Jan AV, Brugge; **Andre Bosly**, UCL Mont Godinne, Yvoir, Belgium; and **Amos M. Cohen**, Rabin Medical Center, Beilinson Hospital, Davidoff Cancer Center, Tel-Aviv University, Ramat-Aviv, Israel.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Lenalidomide Maintenance Compared With Placebo in Responding Elderly Patients With Diffuse Large B-Cell Lymphoma Treated With First-Line Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. 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/site/ifc.

Catherine Thieblemont
Honoraria: Celgene, Bayer HealthCare Pharmaceuticals, AbbVie, Janssen
Consulting or Advisory Role: Celgene, Bayer HealthCare Pharmaceuticals, AbbVie, Janssen
Research Funding: Roche
Travel, Accommodations, Expenses: Celgene

Hervé Tilly
Consulting or Advisory Role: Roche, Karyopharm Therapeutics, Celgene
Research Funding: Celgene (Inst)
Travel, Accommodations, Expenses: Roche

Maria Gomes da Silva
Consulting or Advisory Role: Janssen-Cilag, Celgene, Bristol-Myers Squibb, Takeda Pharmaceuticals, Gilead Sciences
Speakers' Bureau: Bristol-Myers Squibb, Janssen-Cilag, Celgene, Takeda Pharmaceuticals, Ferrer
Research Funding: Gilead Sciences
Travel, Accommodations, Expenses: Roche, Celgene, Janssen-Cilag, Gilead Sciences

Rene-Olivier Casasnovas
Honoraria: Roche, Takeda Pharmaceuticals, Gilead, Bristol-Myers Squibb, Sanofi
Consulting or Advisory Role: Roche, Takeda Pharmaceuticals, Gilead, Bristol-Myers Squibb, Merck Sharp & Dohme
Research Funding: Roche (Inst), Gilead Sciences (Inst), Takeda Pharmaceuticals (Inst)
Travel, Accommodations, Expenses: Roche, Takeda Pharmaceuticals

Christophe Fruchart
Travel, Accommodations, Expenses: Roche

Franck Morschhauser
Honoraria: Celgene, Roche, Gilead Sciences, Servier, Janssen-Cilag
Consulting or Advisory Role: Roche, Celgene, Gilead Sciences, Servier

Corinne Haioun
Honoraria: Roche, Celgene, Janssen-Cilag, Gilead Sciences, Takeda Pharmaceuticals, Sandoz
Consulting or Advisory Role: Celgene, Roche

Julien Lazarovici
Travel, Accommodations, Expenses: Roche, Takeda Pharmaceuticals

Anida Grosicka
No relationship to disclose

Aurore Perrot
Honoraria: Janssen, Bristol-Myers Squibb, Sanofi

Judith Trotman
No relationship to disclose

Catherine Sebban
No relationship to disclose

Dolores Caballero
No relationship to disclose

Richard Greil
Honoraria: Celgene, Roche, Bristol-Myers Squibb, Amgen, Takeda Pharmaceuticals, Boehringer Ingelheim, Novartis
Research Funding: Amgen, Celgene, Roche, Bristol-Myers Squibb, Merck, Novartis
Travel, Accommodations, Expenses: Roche, Amgen, Bristol-Myers Squibb, Takeda Pharmaceuticals, Janssen

Koen van Eygen
Consulting or Advisory Role: Janssen-Cilag
Research Funding: Celgene (Inst), Janssen-Cilag (Inst)

Amos M. Cohen
No relationship to disclose

Hugo Gonzalez
No relationship to disclose

Reda Bouabdallah
No relationship to disclose

Lucie Oberic
No relationship to disclose

Bernadette Corront
No relationship to disclose

Bachra Choufi
No relationship to disclose

Armando Lopez-Guillermo
Consulting or Advisory Role: Celgene, Roche, Janssen-Cilag, Gilead Sciences, Novartis/Pfizer
Research Funding: Roche

John Catalano
Consulting or Advisory Role: Celgene, Roche, Gilead Sciences
Travel, Accommodations, Expenses: Amgen, Bristol-Myers Squibb, Celgene

Achiel Van Hoof
Honoraria: Roche, Janssen Pharmaceuticals, AbbVie
Consulting or Advisory Role: Roche, AbbVie, Janssen Pharmaceuticals, Gilead

Josette Briere
No relationship to disclose

Jose Cabeçadas
Consulting or Advisory Role: Celgene
Patents, Royalties, Other Intellectual Property: PRC primers for clonality IVS
Travel, Accommodations, Expenses: Roche, AstraZeneca, Takeda Pharmaceuticals, Janssen Pharmaceuticals

Gilles Salles
Honoraria: Genentech, Amgen, Mundipharma, Janssen-Cilag, Bristol-Myers Squibb, Celgene, Servier, Gilead Sciences, Merck
Consulting or Advisory Role: Genentech, Gilead Sciences, Janssen-Cilag, Celgene, Novartis, Merck
Research Funding: Genentech (Inst)
Travel, Accommodations, Expenses: Genentech

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Philippe Gaulard
Honoraria: Takeda Pharmaceuticals
Research Funding: Takeda Pharmaceuticals, Celgene

Andre Bosly
Consulting or Advisory Role: Roche
Speakers' Bureau: Roche
Travel, Accommodations, Expenses: Gilead Sciences

Bertrand Coiffier
Honoraria: Celgene, Mundipharma, Gilead Sciences, AstraZeneca, Pfizer, Celltrion, Novartis
Consulting or Advisory Role: Celgene, Mundipharma, Gilead Sciences, AstraZeneca, Pfizer, Celltrion, Novartis

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Lymphoma Study Association:

François Boue, Hôpital Antoine Béclère, Clamart, France
Olivier Lambotte, Centre Hospitalier Universitaire Bicêtre, Le Kremlin-Bicêtre, France
Hassan Farhat, Hôpital Andre Mignot, Le Chesnay, France
Sabine Brechignac, Hôpital Avicenne, Bobigny, France
Bruno Anglaret, Hôpital de Valence, Valence, France
Hubert Orfeuvre, CH de Bourg en Bresse, Bourg en Bresse, France
Amine Belhabri, Hôpital des Chanaux, Mâcon, France
Margaret Macro, Centre Hospitalier Universitaire Clémenceau, Côte de Nacre, Caen, France
Laurence Sanhes, Centre Hospitalier Marechal Joffre, Hôpital Saint-Jean, Perpignan, France
Michel Fabbro, Centre Val d'Aurelle, Paul Lamarque, Montpellier, France
Sakher Aladen, Clinique Mathilde, Rouen, France
Malek Aoudjhane, Hôpital Saint Antoine, Paris, France
Abderrazak El Yamani, Centre Hospitalier de Blois, Blois, France
Nadia Ali Ammar, Centre Hospitalier de Blois de Troyes, Troyes, France
Antoine Thyss, Centre Antoine Lacassagne, Nice, France
Hervé Naman, Centre Azuréen de Cancérologie, Mougins, France
Claudine Sohn, Hôpital Front Pre, Toulon, France
Alain Delmer, Centre Hospitalier Universitaire Robert Debré, Reims Cedex, France
Dominique Bordessoule, Hôpital Universitaire Dupuytren, Limoges, France
Sophie Lefort, Centre Hospitalier de Blois de Brive, Brive la Gaillarde, France
Dominique Devesa-Mansour, Centre Hospitalier de Blois Guéret, Guéret, France
Jean-Claude Eisenmann, Centre Hospitalier Universitaire de Mulhouse, Hôpital Emile Muller, Mulhouse, France
Jean-Marc Limacher, Hôpital Pasteur, Hôpitaux Civils de Colmar, Colmar, France
Gian Matteo Pica, Centre Hospitalier de Blois de Chambery, Chambery Cedex, France
Philippe Carassou, Centre Hospitalier Régional de Metz - Hôpital Bon Secours, Metz, France
Jean Gabarre, Hôpital de la Pitie Salpêtrière, Paris 13, France
Marc Simon, Centre Hospitalier de Blois Valenciennes, Valenciennes, France
Jean-Michel Pignon, Centre Hospitalier de Blois Dunkerque, Dunkerque, France
Pauline Lionne-Huygue, Centre Hospitalier de Blois d'Arras, Arras, France
Pierre Feugier, Centre Hospitalier Universitaire Brabois, Vandoeuvre les Nancy, France
Régis Costello, Hôpital de la Conception, Marseille Cedex 05, France
Hacène Zerazhi, Centre Hospitalier de Blois d'avignon, Hôpital Henri Duffaut, Avignon, France
Frederic Bauduer, Hôpital De Bayonne, Bayonne, France
Alain Devidas, Centre Hospitalier Sud Francilien, Corbeil Essonnes, France
Zora Marjanovic, Hôpital Saint Antoine, Paris, France
Richard Delarue, Hôpital Necker, Paris, France
Olivier Fitoussi, Polyclinique Bordeaux Nord Aquitaine, Bordeaux, France
Katell Le Du, Clinique Victor Hugo, Le Mans, France
Isabelle Moullet, Clinique De La Sauvegarde, Lyon Cedex 9, France
Carole Soussain, Centre René Huguenin, Saint-Cloud, France
Jean-Michel Miclea, Hôpital Louis Pasteur, Le Coudray, France
Marie-Pierre Moles-Moreau, Centre Hospitalier Universitaire Angers, Angers, France
Rémy Gressin, Centre Hospitalier Universitaire de Grenoble, Grenoble, France
Pascal Godmer, Centre Hospitalier de Blois de Bretagne Atlantique, Hôpital Chubert, Vannes, France
Hervé Maisonneuve, Centre Hospitalier de Blois Départemental, La Roche-sur-Yon, France
Steven Le Gouill, Centre Hospitalier Universitaire Hôtel-Dieu, Nantes, France
Guillaume Cartron, Centre Hospitalier Universitaire de Montpellier, Montpellier, France
Jan Lemmens, Algemeen Ziekenhuis Sint-Augustinus, Wilrijk, Belgium

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Christophe Bonnet, Centre Hospitalier Universitaire Sart Tilman, Liege, Belgium
Gaëtan Vanstraelen, Centre Hospitalier de Blois de la Tourelle-Peltzer, Verviers, Belgium
Dries Deeren, Heilig Hart Ziekenhuis, Roeselare, Belgium
Marie Maerevoet, Université Libre de Bruxelles, Hôpital Erasme, Bruxelles, Belgium
Dominique Bron, Institut Jules Bordet, Bruxelles, Belgium
Fabienne Trullemans, Algemeen Ziekenhuis Vub, Jette, Belgium
Eric Van Den Neste, Université Catholique Louvain St Luc, Bruxelles, Belgium
Thierry Connerotte, Clinique St Pierre, Ottignies, Belgium
Andre Efira, Centre Hospitalier Universitaire Brugmann, Bruxelles, Belgium
Nicole Straetmans, Hôpital Jolimont, Haine St Paul, Belgium
Valérie Robin, Centre Hospitalier Universitaire Ambroise Paré, Mons, Belgium
Delphine Pranger, Grand Hôpital Charleroi, Charleroi, Belgium
Pierre Zachee, Ziekenhuis Netwerk Antwerpen Stuivenberg, Antwerpen, Belgium
Marc Andre, Université Catholique Mont Godinne, Yvoir, Belgium
Oussama Hamdan, Centre de Sante des Fagnes, Chimay, Belgium
Pascal Pierre, Hôpital Saint Joseph, Arlon, Belgium

Australia: Australasian Leukaemia and Lymphoma Group

Robert Blum, Bendigo Hospital, Bendigo, Australia
Sundra Ramanathan, St George, Sydney New South Wales, Australia
David J.L. Joske, Sir Charles Gairdner, Nedlands, Australia
Ali Bazargan, St Vincent's Hospital Melbourne, Fitzroy, Australia
Anna Johnston, Royal Hobart Hospital, Hobart, Tasmania
James D'rozario, Canberra Hospital, Garran, Australia
Christopher Steer, Border Medical Oncology, Wodonga, Australia
Jillian Demalmanche, Mater Newcastle Hospital, Waratah, Australia
Geoff Chong, Austin Hospital, Heidelberg, Australia
Tara Cochrane, Gold Coast Hospital, Southport Queensland, Australia

Arbeitsgemeinschaft Medikamentöse Tumortherapie:

Ulrich Jäger, Universitätsklinik F. Innere Medizin I, Akh Wien, Vienna, Austria
Michael Fridrik, Akh Linz, Linz, Austria
Wolfgang Willenbacher, Medizinische Universität Innsbruck, Innsbruck, Austria
Michael Girschikofsky, Krankenhaus der Elisabethinen Linz GmbH, Linz, Austria
Josef Thaler, Klinikum Wels-Grieskirchen GmbH, Wels, Austria

Grupo Español de Linfomas y Trasplantes de Médula Ósea:

Lourdes Escoda, Hospital Joan XXIII, Tarragona, Spain
Ana Muntañola, Hospital Mutua Terrassa, Terrassa, Spain
Javier Briones, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain
Elena Pérez Ceballo, Hospital Universitario Morales Meseguer, Murcia, Spain
Concepción Nicolás Garcia, Hospital Central de Asturias, Oviedo, Spain
Silvia Fernández Ferrero, Hospital de León, Leon, Spain
Carlos Grande Garcia, Hospital Universitario 12 de Octubre, Madrid, Spain
Lucía Villalón, Hospital Fundación Alcorcón, Alcorcón, Spain
Jorge Gayoso Cruz, Hospital General Universitario Gregorio Marañon, Madrid, Spain
Jose Ma Moraleda Jimenez, Hospital Universitario Virgen de la Arrixaca, Murcia, Spain
Ma José Ramírez Sanchez, Hospital de Jerez, Jerez de la Frontera, Cádiz, Spain
Miguel Angel Canales, Hospital Universitario La Paz, Madrid, Spain
Fatima De La Cruz Vicente, Hospital Virgen del Rocío, Sevilla, Spain

Israel:

Uri Abadi, Meir Medical Center, Kfar Saba, Israel
Itai Levi, Soroka Hospital, Beer-Sheva, Israel
Dina Attias, Bnai Zion Medical Center, Haifa, Israel
Michael Bennett, Ha'emek Medical Center, Afula, Israel
Lev Shvidel, Kaplan Medical Center, Rehovot, Israel
Gil Lugassy, Barzilai Medical Center, Ashkelon, Israel

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Poland:
Krzysztof Warzocha, Instytut Hematologii i Transplantologii, Warsaw, Poland
Jan Walewski, Centrum Onkologii, Instytut, Klinika Nowotworów Układu Chłonnego, Warszawa, Poland
Ewa Kalinka-Warzocha, Regionalny Osrodek Onkologiczny, Lodz, Poland
Portugal:
José Mario Mariz, Instituto Português de Oncologia de Porto Francisco Gentil, Porto, Portugal
Switzerland:
Anne Cairoli, Centre Pluridisciplinaire d'Oncologie, Lausanne, Switzerland

Appendix

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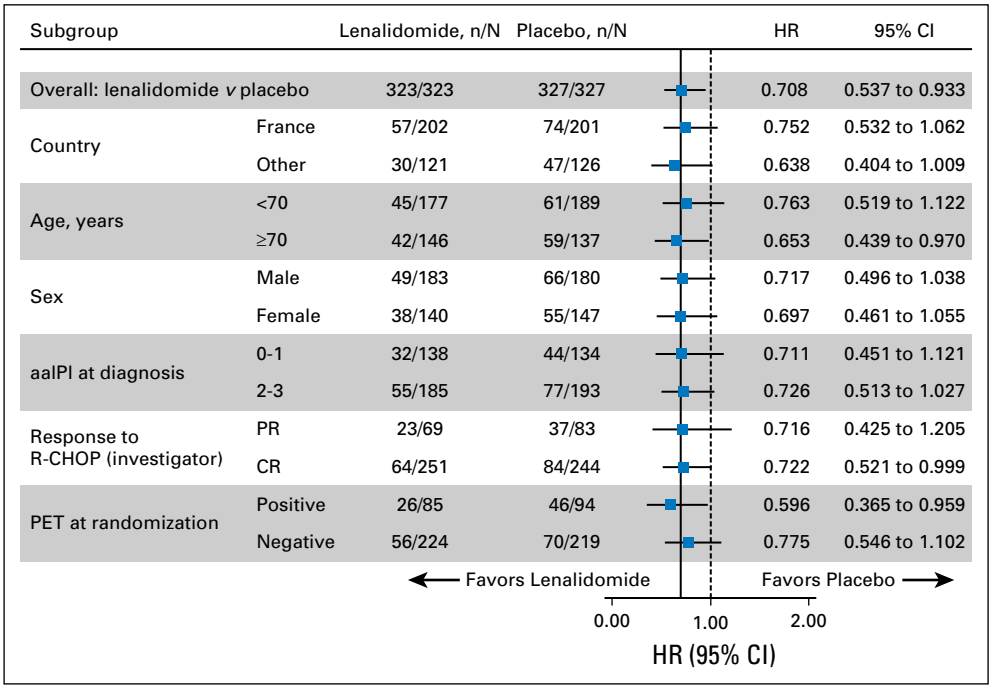

Fig A1. REMARC subgroup analysis of progression-free survival (PFS) by European Medicines Agency Censoring Rules (Central Review). aaIPI, age-adjusted International Prognostic Index; CR, complete response; HR, hazard ratio; PET, positron emission tomography; PR, partial response; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone.

	Lenalidomide (n = 322)	Placebo (n = 323)
Median average daily dose, mg (range)	19.8 (5.2-25.0)	25.0 (5.1-25.0)
Median number of maintenance cycles	15.0	25.0
At least one dose reduction due to toxicity	72%	42%
Discontinuations due to toxicity	36%	16%

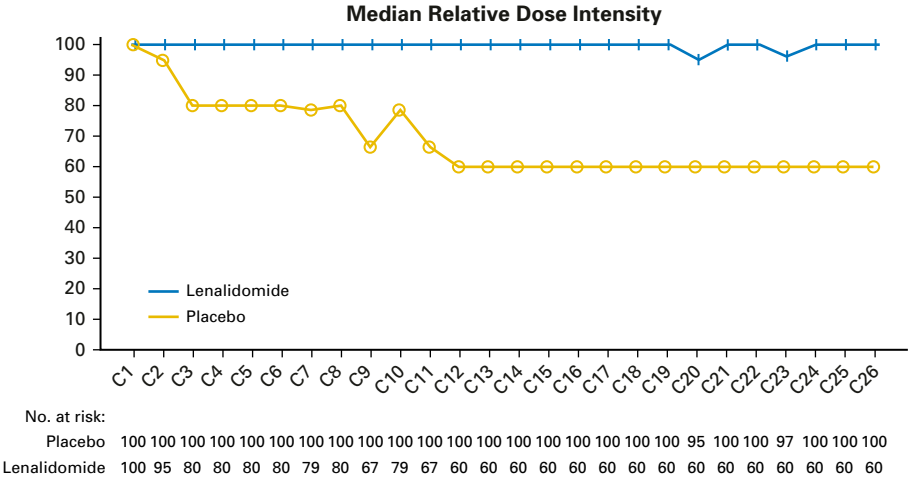

Fig A2. Treatment exposure of lenalidomide and placebo maintenance and median relative dose intensity per cycle (C) and over time.

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Table A1. REMARC Maintenance Dose Adjustments

Treatment Cycle	Management of Toxicity and Lenalidomide/Placebo Treatment	Dose Adjustment
Starting dose CrCl ≥ 60 mL/min	25 mg/d, days 1-21 administered every 28 days for 24 months (maximum, 26 cycles)	Cycle 1, day 1: patient must have ANC ≥ $1,000 \times 10^6$/L, platelets ≥ $60,000 \times 10^6$/L, and any other toxicity resolved to grade ≤ 1 before first intake
Starting dose CrCl 30-60 mL/min	Lower starting dose to 10 mg/d	Dose can be escalated to 15 mg after two cycles if tolerated (ie, absence of grade 3 or 4 toxicity) and CrCl > 30 mL/min
Cycles 1-3	If grade 1 to 4 AE occurs regardless of relationship to study treatment	Reduce dose by 5-mg increment in next cycle
	If any grade 1 or 2 AE or grade 1 infection or neurologic toxicity	Continue study drug in current cycle and reduce dose in next cycle
	If grade 3 or 4 AE or grade 2 infection or neurologic toxicity	Stop study drug in current cycle* and reduce dose in next cycle
Cycle 4+	If drug-related toxicities Hematologic toxicities: if ANC < $1,000 \times 10^6$/L or platelets < $60,000 \times 10^6$/L Neurologic and infection toxicity grade ≥ 2 Elevated liver enzymes Any other toxicity grade ≥ 3 except for lymphopenia, DVT, or alopecia	Stop study drug in current cycle* and reduce dose in next cycle
	If CrCl reduced to 30-60 mL/min	Stop study drug in current cycle* and reduce dose to 10 mg in next cycle
	If drug-related toxicities Desquamating (blistering) rash grade ≥ 3 or nondesquamating rash grade 4 Grade 3 or 4 allergic reaction or hypersensitivity CrCl < 30 mL/min	Permanently discontinue study treatment
Throughout study	If DVT	Temporarily cease study drug and start antithrombotic treatment (heparin/warfarin [INR, 2-3]) Maintain anticoagulation therapy while on study drug On symptom resolution and per investigator, study drug may be resumed without dose reduction (except during the first three cycles for patients starting with 25 mg)
Throughout study	If febrile neutropenia or anemia	G-CSF is allowed to treat febrile neutropenia ESA is allowed to treat anemia in symptomatic patients with nonmyeloid tumors receiving chemotherapy per EMA guidance (June 2008); these patients should receive low molecular weight heparin or warfarin for DVT prophylaxis

Abbreviations: AE, adverse event; ANC, absolute neutrophil count; CrCl, creatinine clearance; DVT, deep vein thrombosis; EMA, European Medicines Agency; ESA, erythropoietic stimulating factor; G-CSF, granulocyte colony-stimulating factor; INR, international normalized ratio; ULN, upper limit of normal.

*After study drug cessation for toxicity, the next cycle may not commence until at least day 29 of the preceding cycle. Toxicities must have resolved to ≤ grade 1, with the exception of the following hematology parameters: ANC ≥ $1,000 \times 10^6$/L and platelets ≥ $60,000 \times 10^6$/L. If toxicity is not resolved within 6 weeks after the last intake of study drug, it must be stopped permanently.

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Table A2. REMARC Causes of Death After Randomization to Maintenance

Cause of Death	Lenalidomide, No. (%)	Placebo, No. (%)	All Patients, No.
Death	(n = 322)	(n = 323)	(N = 645)
No	253 (79)	263 (81)	516
Yes	69 (21)	60 (19)	129
Causes of death	(n = 69)	(n = 60)	(n = 129)
Lymphoma	41 (59)	37 (65)	78
Other cancer	6 (9)	7 (10)	13
Concurrent illness	7 (10)	3 (4)	10
Toxicity of additional treatment	2 (3)	1 (2)	3
Toxicity of study treatment	0	2 (4)	2
Unknown	1 (1)	3 (4)	4
Other reasons	12 (17)	7 (12)	19
Septic shock	2 (17)	1 (14)	3
Pneumonia	1 (8)	1 (14)	2
Septicemia	1 (8)	1 (14)	2
Cerebral hemorrhage due to a fall down the stairs	1 (8)	0	1
Circulatory insufficiency	1 (8)	0	1
Heart attack	1 (8)	0	1
Hemorrhage after laryngeal biopsy	1 (8)	0	1
Multiorgan failure	1 (8)	0	1
Neurologic disease without specific diagnosis	1 (8)	0	1
Respiratory infection	1 (8)	0	1
Sepsis	1 (8)	0	1
Cardiac arrest during beam cardiogenic shock	0	1 (14)	1
Cerebrovascular accident	0	1 (14)	1
Respiratory distress	0	1 (14)	1

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