



HAL
open science

Six-Year Results From RELEVANCE: Lenalidomide Plus Rituximab (R 2) Versus Rituximab-Chemotherapy Followed by Rituximab Maintenance in Untreated Advanced Follicular Lymphoma

Franck Morschhauser, Loretta Nastoupil, Pierre Feugier, Jean-Marc Schiano de Colella, Hervé Tilly, Maria Lia Palomba, Emmanuel Bachy, Christophe Fruchart, Edward N Libby, Rene-Olivier Casasnovas, et al.

► To cite this version:

Franck Morschhauser, Loretta Nastoupil, Pierre Feugier, Jean-Marc Schiano de Colella, Hervé Tilly, et al.. Six-Year Results From RELEVANCE: Lenalidomide Plus Rituximab (R 2) Versus Rituximab-Chemotherapy Followed by Rituximab Maintenance in Untreated Advanced Follicular Lymphoma. Journal of Clinical Oncology, 2022, 40 (28), pp.3239-3245. 10.1200/JCO.22 . inserm-04783079

HAL Id: inserm-04783079

<https://inserm.hal.science/inserm-04783079v1>

Submitted on 14 Nov 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial - NoDerivatives 4.0 International License

Six-Year Results From RELEVANCE: Lenalidomide Plus Rituximab (R²) Versus Rituximab-Chemotherapy Followed by Rituximab Maintenance in Untreated Advanced Follicular Lymphoma

Franck Morschhauser, MD, PhD¹; Loretta Nastoupil, MD²; Pierre Feugier, MD, PhD³; Jean-Marc Schiano de Colella, MD⁴; Hervé Tilly, MD⁵; Maria Lia Palomba, MD⁶; Emmanuel Bachy, MD, PhD⁷; Christophe Fruchart, MD⁸; Edward N. Libby, MD⁹; Rene-Olivier Casasnovas, MD¹⁰; Ian W. Flinn, MD, PhD¹¹; Corinne Haioun, MD¹²; Hervé Maisonneuve, MD¹³; Loïc Ysebaert, MD, PhD¹⁴; Nancy L. Bartlett, MD¹⁵; Kamal Bouabdallah, MD¹⁶; Pauline Brice, MD¹⁷; Vincent Ribrag, MD¹⁸; Steven Le Gouill, MD, PhD¹⁹; Nicolas Daguindau, MD²⁰; Stéphanie Guidez, MD²¹; Gian Matteo Pica, MD²²; Alejandro Martín García-Sancho, MD, PhD²³; Armondo López-Guillermo, MD²⁴; Jean-François Larouche, MD²⁵; Kiyoshi Ando, MD²⁶; Maria Gomes da Silva, MD, PhD²⁷; Marc André, MD²⁸; Wu Kalung, MD²⁹; Laurie H. Sehn, MD, MPH³⁰; Koji Izutsu, MD, PhD³¹; Guillaume Cartron, MD, PhD³²; Argýrios Gkasiámis, MD³³; Russell Crowe, MA³³; Luc Xerri, MD, PhD⁴; Nathan H. Fowler, MD²; and Gilles Salles, MD⁶

Clinical trials frequently include multiple end points that mature at different times. The initial report, typically based on the primary end point, may be published when key planned co-primary or secondary analyses are not yet available. Clinical Trial Updates provide an opportunity to disseminate additional results from studies, published in JCO or elsewhere, for which the primary end point has already been reported.

The RELEVANCE trial (ClinicalTrials.gov identifier: [NCT01650701](https://clinicaltrials.gov/ct2/show/study/NCT01650701)) showed that lenalidomide plus rituximab (R²) provided similar efficacy to rituximab plus chemotherapy (R-chemo) in patients with advanced-stage, previously untreated follicular lymphoma (FL). We report the second interim analysis of the RELEVANCE trial after 6 years of follow-up. Patients with previously untreated grade 1-3a FL were assigned 1:1 to R² or R-chemo, followed by rituximab maintenance. Coprimary end points were complete response (confirmed/unconfirmed) at week 120 and progression-free survival (PFS). At median follow-up of 72 months, 6-year PFS was 60% and 59% for R² and R-chemo, respectively (hazard ratio = 1.03 [95% CI, 0.84 to 1.27]). Six-year overall survival was estimated to be 89% in both groups. Median PFS and overall survival were not reached in either group. Overall response after progression was 61% and 59%, and 5-year estimated survival rate after progression was 69% and 74% in the R² and R-chemo groups, respectively. The transformation rate per year in the R² and R-chemo groups was 0.68% and 0.45%, and secondary primary malignancies occurred in 11% and 13% ($P = .34$), respectively. No new safety signals were observed. R² continues to demonstrate comparable, durable efficacy and safety versus R-chemo in previously untreated patients with FL and provides an acceptable chemo-free alternative.

J Clin Oncol 40:3239-3245. © 2022 by American Society of Clinical Oncology

Creative Commons Attribution Non-Commercial No Derivatives 4.0 License 

ASSOCIATED CONTENT

[Data Supplement](#)

[Protocol](#)

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

Accepted on July 1, 2022 and published at ascopubs.org/journal/jco on August 10, 2022; DOI <https://doi.org/10.1200/JCO.22.00843>

INTRODUCTION

Immunochemotherapy has remained the frontline gold standard for patients with follicular lymphoma (FL) needing systemic therapy¹⁻³; however, FL has been shown to be immune-responsive to nonchemotherapy regimens.⁴⁻⁶ Lenalidomide is an immunomodulatory agent with multiple properties, including altering the production of cytokines, and increasing T-cell costimulation and natural killer cell cytotoxicity.⁷⁻⁹ The combination of lenalidomide and rituximab (ie, R²) has shown promising activity with high response rates in

patients with previously untreated FL in phase II trials¹⁰⁻¹² and in the phase III RELEVANCE trial comparing R² versus rituximab plus chemotherapy (R-chemo).¹³ Previous results from RELEVANCE showed similar efficacy of R² to R-chemo in both coprimary end points of complete response confirmed/unconfirmed (CR/CRu) at 120 weeks and progression-free survival (PFS).¹³ Long-term follow-up data regarding the toxicity and efficacy of R² on large numbers of patients, qualifying for Groupe d'Etude des Lymphomes Folliculaires criteria, are highly needed.

TABLE 1. Baseline Demographic and Disease Characteristics (ITT population)

Characteristic	R ² (n = 513)	R-Chemo (n = 517)	Total (N = 1,030)
Age, median, years (range)	59 (30-89)	59 (23-83)	59 (23-89)
> 70, No. (%)	80 (16)	78 (15)	158 (15)
Male sex, No. (%)	251 (49)	251 (49)	502 (49)
ECOG PS, No. (%) ^a			
0	341 (67)	345 (67)	686 (67)
1	157 (31)	157 (30)	314 (30)
2	13 (3)	14 (3)	27 (3)
NE	2 (< 1)	1 (< 1)	3 (< 1)
Ann Arbor stage, No. (%)			
I-II	30 (6)	40 (8)	70 (7)
III-IV	483 (94)	477 (92)	960 (93)
Bulky disease (> 7 cm), No. (%)	218 (43)	199 (39)	417 (40)
FL grade, No. (%) ^b			
1-2	437 (85)	443 (86)	880 (85)
3a	65 (13)	63 (12)	128 (12)
Lactate dehydrogenase > ULN, No. (%)	156 (30)	137 (26)	293 (28)
Beta-2 microglobulin > ULN, No. (%)	261 (51)	262 (51)	523 (51)
B-symptoms, No. (%)	141 (28)	134 (26)	275 (27)
FLIPI score, No. (%) ^c			
Low risk (0-1)	77 (15)	76 (15)	153 (15)
Intermediate risk (2)	183 (36)	191 (37)	374 (36)
High risk (3-5)	253 (49)	250 (48)	503 (49)

NOTE. From the study by Morschhauser et al.¹³ Reprinted with permission from Massachusetts Medical Society.

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; FL, follicular lymphoma; FLIPI, Follicular Lymphoma International Prognostic Index; ITT, intent-to-treat; NE, not evaluable/missing; R², lenalidomide plus rituximab; R-chemo, rituximab plus chemotherapy; ULN, upper limit of normal.

^aAn ECOG PS score of 0 indicates no symptoms and 1 indicates mild symptoms; higher scores indicate greater disability.

^bFL grade was unspecified or not FL, grade 1-3a in 11 patients in each group.

^cA FLIPI score indicates low (0-1), intermediate (2), and high (3-5) risk groups on the basis of a scoring system giving 1 point for each of the following risk factors: hemoglobin < 12 g/L, > 4 nodal areas (except for spleen), age > 60 years, > normal lactate dehydrogenase levels, and Ann Arbor stage III/IV disease.

Reported here are updated efficacy and safety results of the RELEVANCE trial at 6 years.

METHODS

Details of the RELEVANCE study design have been published previously.¹³

Patients were randomly assigned 1:1 to receive R² or R-chemo (investigator's choice of rituximab + cyclophosphamide, doxorubicin, vincristine, and prednisone, rituximab + bendamustine, or rituximab + cyclophosphamide, vincristine, and prednisone), followed by maintenance rituximab. Lenalidomide and rituximab dose were as previously described.¹³

Copriary end points were CR/CRu at 120 weeks and PFS by Independent Review Committee (IRC) on the basis of 1999 International Working Group criteria¹⁴ and were performed in

the intention-to-treat population. Post hoc exploratory analyses on survival from a risk-defining event (Landmark approach) according to progression of disease within 2 years of first-line therapy (POD24) were performed. Survival from a risk-defining event was from time of POD24 or from 2 years after random assignment for the non-POD24 reference group.

RESULTS

Patient Characteristics and Treatment

From December 2011 through November 2014, 1,030 patients were randomly assigned: 513 to R² and 517 to R-chemo (rituximab + cyclophosphamide, vincristine, and prednisone = 28, rituximab + bendamustine = 117, rituximab + cyclophosphamide, doxorubicin, vincristine, and prednisone = 372). Baseline characteristics were similar in the two groups (Table 1).

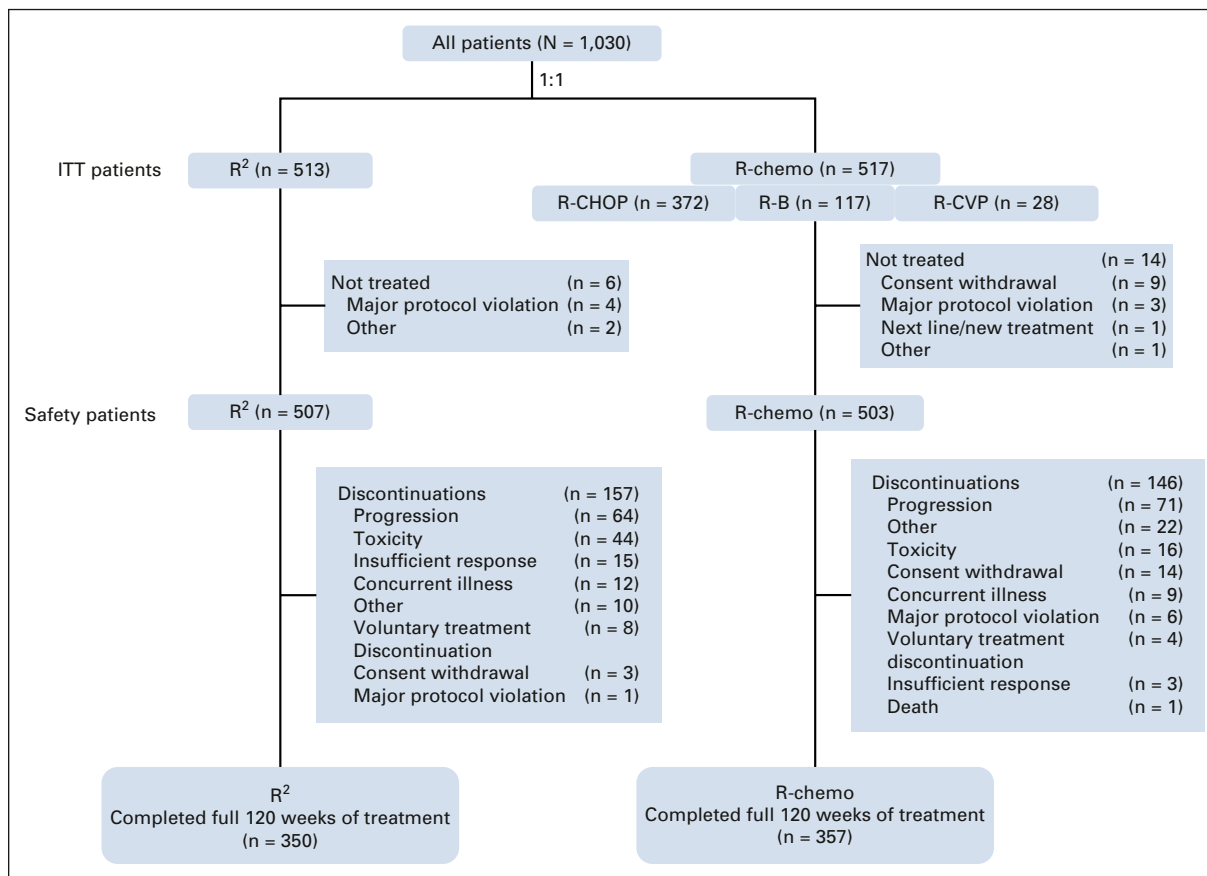


FIG 1. CONSORT diagram. ITT, intent-to-treat; R², lenalidomide plus rituximab; R-B, rituximab + bendamustine; R-chemo, rituximab plus chemotherapy; R-CHOP, rituximab + cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CVP, rituximab + cyclophosphamide, vincristine, and prednisone.

Five hundred seven (99%) R² and 503 (97%) R-chemo patients received ≥ 1 dose of study drug, and 350 (69%) and 357 (71%) patients have completed the full 120 weeks of treatment, respectively (Fig 1). Premature treatment discontinuations occurred in 157 R² (31%) and 146 (29%) R-chemo patients, most commonly for progressive disease (R² = 64 and R-chemo = 71) and toxicity (R² = 44 and R-chemo = 16). Premature discontinuations from study occurred in 111 R² (22%) and 119 (23%) R-chemo patients, most commonly because of death (R² = 54% and R-chemo = 49%) and consent withdrawal (R² = 27% and R-chemo = 40%). Relapse or progression within 24 months of initiation (POD24) occurred in 124 (12%) patients in total, including 67 and 57 patients in the R² and R-chemo groups, respectively. In the R² and R-chemo groups, 419 and 400 patients have entered clinical follow-up, respectively.

Efficacy

The results for the coprimary end points (CR/CRu and PFS on the basis of IRC) were similar to those of the first analysis. Overall response rate (ORR) in the R² and R-chemo groups was 61% and 65% with CR/CRu rates of 48% and 53% ($P = .10$), respectively (Table 2). PFS did not differ significantly between groups (hazard ratio = 1.03 [95% CI, 0.84 to 1.27],

$P = .78$). After a median follow-up of 72.0 months and total number of 354 PFS events, median PFS was not reached in either group (Fig 2A). Six-year PFS rates in the R² and R-chemo groups were 60% (95% CI, 55 to 64) and 59% (95% CI, 54 to 64, Table 2), respectively. Efficacy results from investigator assessment were similar to those by IRC (Table 2 and Data Supplement [online only]).

Median overall survival (OS) was not reached in either group. Six-year OS was estimated to be 89% in both groups (Table 2 and Fig 2B). Similarly, event-free survival and time to next antilymphoma treatment did not differ significantly between the groups (Data Supplement). Exploratory analysis on the three different R-chemo groups showed no statistical difference in PFS, by IRC and investigator, nor OS (Data Supplement).

Additional treatment was provided to 206 patients after relapse (R² = 107 and R-chemo = 99; Data Supplement). ORR in those patients was 61% and 59% in the R² and R-chemo groups, respectively, with respective CR/CRu rates of 37% and 45% (Data Supplement). Survival after progression did not differ significantly between groups (Data Supplement).

TABLE 2. Efficacy Results in the ITT Population

Variable	R ² (n = 513)	R-Chemo (n = 517)	P
Response and PFS Independent Review Committee Review			
Overall response, No. (%)	313 (61)	338 (65)	
Complete response + complete response unconfirmed, No. (%; 95% CI)	247 (48; 44 to 53)	276 (53; 49 to 58)	.10
Complete response, No. (%)	142 (28)	169 (33)	
Complete response unconfirmed, No. (%)	105 (21)	107 (21)	
Partial response, No. (%)	66 (13)	62 (12)	
Stable disease, No. (%)	2 (0.4)	0	
PD/death, No. (%)	89 (17)	78 (15)	
Not evaluated/not done/missing, No. (%)	109 (21)	101 (20)	
PFS at 6 years, % (95% CI)	60 (55 to 64)	59 (54 to 64)	
HR (95% CI)	1.03 (0.84 to 1.27)		.78
Response and PFS Investigator Review			
Overall response, No. (%)	335 (65)	352 (68)	
Complete response + complete response unconfirmed, No. (%; 95% CI)	283 (55; 51 to 60)	299 (58; 53 to 62)	.38
Complete response, No. (%)	201 (39)	242 (47)	
Complete response unconfirmed, No. (%)	82 (16)	57 (11)	
Partial response, No. (%)	52 (10)	53 (10)	
Stable disease, No. (%)	0	0	
PD/death, No. (%)	90 (18)	95 (18)	
Not evaluated/not done/missing, No. (%)	88 (17)	70 (14)	
PFS at 6 years, % (95% CI)	64 (60 to 69)	63 (58 to 67)	
HR (95% CI)	0.92 (0.74 to 1.14)		.42
OS Rate			
OS at 6 years, %	89	89	
HR	1.00		

Abbreviations: HR, hazard ratio; ITT, intent-to-treat; OS, overall survival; PD, progressive disease; PFS, progression-free survival; R², lenalidomide plus rituximab; R-chemo, rituximab plus chemotherapy.

Histologic transformation was documented in 13/513 and 11/517 patients in the R² and R-chemo groups, respectively, over the 72-month follow-up period. The cumulative incidence of transformation at 6 years in the R² and R-chemo groups was 4.4% and 3.3%, and transformation rates per year were 0.68% and 0.45%.

Subgroup analyses of PFS were consistent with the first interim analysis. The efficacy of R² continued to be independent of conventional prognostic factors including disease stage, Follicular Lymphoma International Prognostic Index score, bulky disease, and age (Data Supplement). Early POD (ie, POD24) was associated with worsened 5-year survival of 59.5% (95% CI, 49.9 to 67.8) versus 95.2% (95% CI, 93.3 to 96.6) for the reference group ($P < .0001$, Data Supplement). In patients with

POD24, 5-year survival was similar in both groups (59% v 60%, $P = .9693$, Data Supplement).

Safety

The overall safety profile in both groups was consistent with the first interim analysis, and no new safety signals were detected.

Fifteen patients (v 12 patients in 2017) reported ≥ 1 grade 5 treatment emergent adverse event: nine (v six reported in 2017) in the R² group and six patients (no change) in the R-chemo group. New grade 5 treatment emergent adverse events included chronic obstructive pulmonary disease ($n = 1$) and adenocarcinoma of the colon ($n = 2$).

Patients with second primary malignancies increased from 38 (7%) in 2017 to 57 (11%) in 2020 in the R² group and

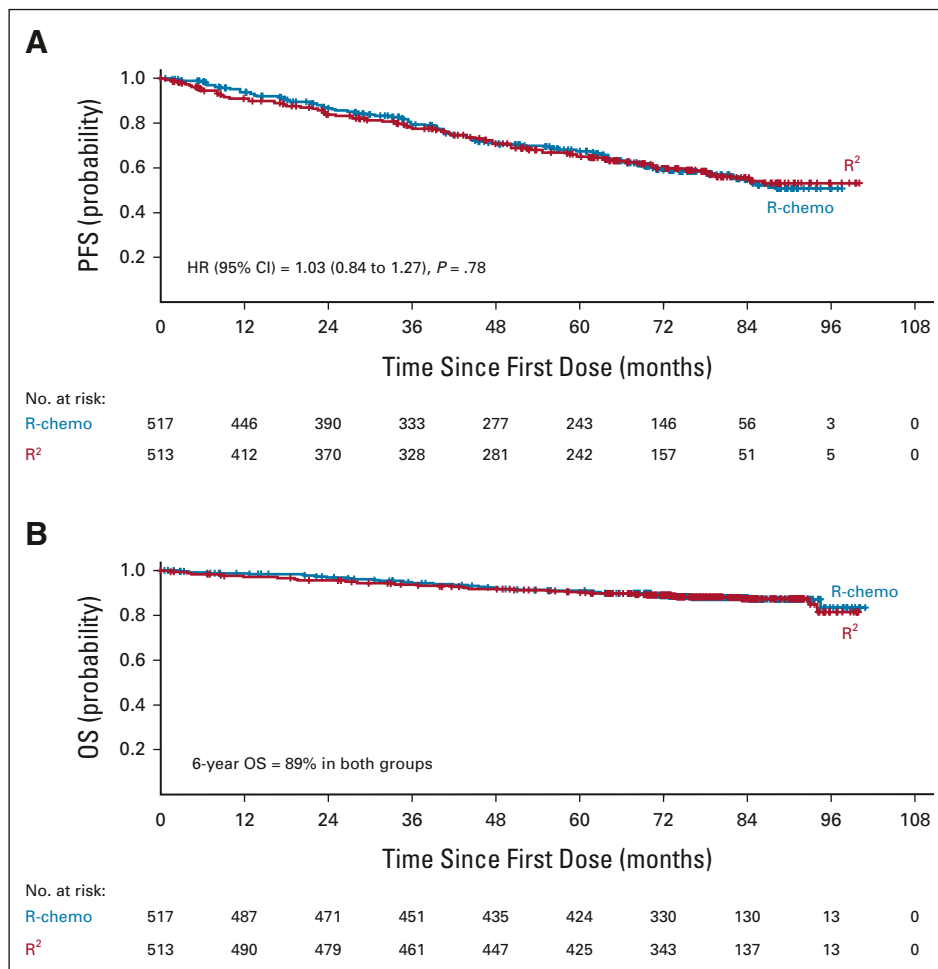


FIG 2. PFS by IRC (A) and OS (B) in the ITT Population. HR, hazard ratio; IRC, independent review committee; ITT, intention-to-treat; OS, overall survival; PFS, progression-free survival; R², lenalidomide plus rituximab; R-chemo, rituximab plus chemotherapy.

48 (10%) to 67 (13%) in the R-chemo group (*P* = .34, Data Supplement).

Deaths increased from 66 reported in 2017 to 114 reported here: 59 (12%) versus 55 (11%) in the R² versus R-chemo groups (Data Supplement). Eight deaths occurred on treatment (R² = 3 and R-chemo = 5). Death from lymphoma was higher in the R² group (*n* = 29) versus R-chemo group (*n* = 17), but death from other causes was higher in the R-chemo group (R², *n* = 6; R-chemo, *n* = 13), particularly death from cardiac disorder (R², *n* = 0; R-chemo, *n* = 4).

DISCUSSION

The primary analysis from RELEVANCE demonstrated similar PFS with R² and R-chemo. With long-term follow-up reported here (median 72 months), the coprimary end point of PFS on the basis of IRC remains unchanged as PFS did not differ significantly between groups. Overall, both groups maintained very favorable outcomes with similar 6-year PFS

rates (60% R² v 59% R-chemo) and excellent 6-year OS rates of 89%. Together, these data show that R² and R-chemo yield similar durable responses in untreated patients with FL in need of therapy.

ORR to subsequent treatment, OS in patients with POD24, and survival after progression were similar in both groups. Together, these data show that disease aggressiveness was similar after progression of both R² and R-chemo, and response to subsequent therapy is not compromised by either treatment.

This similar incidence of histologic transformation reported in the first interim analysis was maintained after longer follow-up reported here, and the rate of transformation over 72 months was < 1% per year in both groups, which is well within the historical rate of 2%-3%, demonstrating that R² does not increase risk for histologic transformation compared with R-chemo.¹⁵

The overall safety profile in both groups is consistent with the first interim analysis, and no new safety signals were

detected. The safety profile of R² is distinct from that of R-chemo but manageable. Both treatments were generally well tolerated with the additional follow-up, and treatment/study discontinuation rates were similar.

In summary, R² provides an acceptable, long-term, chemo-free alternative to R-chemo on the basis of immunomodulation in patients with advanced untreated FL in need of treatment.

AFFILIATIONS

- ¹University of Lille, CHU Lille, Lille, France
²The University of Texas MD Anderson Cancer Center, Houston, TX
³Nancy University Hospital, Vandoeuvre-lès-Nancy, France
⁴Institut Paoli Calmettes, CRCM, AMU, Marseille, France
⁵Centre Henri Becquerel, Rouen, France
⁶Memorial Sloan Kettering Cancer Center, New York, NY
⁷Hospices Civils de Lyon and Claude Bernard Lyon 1 Université, Lyon, France
⁸CH de Dunkerque, Dunkerque, France
⁹University of Washington, Seattle, WA
¹⁰CHU Dijon-Bourgogne, Dijon, France
¹¹Sarah Cannon Research Institute and Tennessee Oncology, Nashville, TN
¹²Henri Mondor Université Hôpital, UPEC, Créteil, France
¹³Centre Hospitalier Départemental Vendée, La Roche-sur-Yon, France
¹⁴Institut Universitaire du Cancer Toulouse-Oncopole, Toulouse, France
¹⁵Washington University School of Medicine, St Louis, MO
¹⁶Bordeaux University Hospital, Bordeaux, France
¹⁷Hôpital Saint-Louis, Paris, France
¹⁸Institut Gustave Roussy, Villejuif, France
¹⁹Institut Curie, Paris, France
²⁰Anecy Hôpital, Anecy, France
²¹CHU de Poitiers, Poitiers, France
²²Centre Hospitalier Métropole Savoie Chambéry, Chambéry, France
²³Hospital Universitario de Salamanca, IBSAL, CIBERONC, Salamanca, Spain
²⁴Hospital Clínic de Barcelona, Barcelona, Spain
²⁵CHU de Québec, Québec, Canada
²⁶Tokai University School of Medicine, Kanagawa, Japan
²⁷Instituto Português de Oncologia de Lisboa, Lisboa, Portugal
²⁸CHU UCL Namur, Yvoir, Belgium
²⁹ZNA Stuivenberg, Antwerp, Belgium
³⁰BC Cancer Centre for Lymphoid Cancer, Vancouver, Canada
³¹National Cancer Center Hospital, Tokyo, Japan
³²CHU Montpellier, Montpellier, France
³³Bristol Myers Squibb, Princeton, NJ

CORRESPONDING AUTHOR

Franck Morschhauser, MD, Centre Hospitalier Universitaire Régional de Lille, 2 Av. Oscar Lambret, 59000 Lille, France; e-mail: franck.morschhauser@chru-lille.fr.

PRIOR PRESENTATION

Presented at the 63rd American Society of Hematology (ASH) Annual Meeting & Exposition, December 11–14, 2021, Atlanta, GA.

SUPPORT

Supported by Celgene, a Bristol Myers Squibb Company, and the Lymphoma Academic Research Organisation (LYSARC).

CLINICAL TRIAL INFORMATION

NCT01650701

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by authors are available with this article at DOI <https://doi.org/10.1200/JCO.22.00843>.

DATA SHARING STATEMENT

Proposals should be submitted to the study PI and Coordinating Investigator, Franck Morschhauser. If he agrees with the collaboration/sharing, the project should be presented to LYSARC Scientific Committee. If the project is validated by LYSARC Scientific Committee, a Data Transfer Agreement compliant with GDPR and French Data Protection laws should be signed. DTA includes data protection rules and responsibilities of each party, data security, and storing information.

For more information, please visit <https://experts-recherche-lymphome.org/lysarc/> or contact contact@lysarc.org.

AUTHOR CONTRIBUTIONS

Conception and design: Franck Morschhauser, Nathan H. Fowler, Gilles Salles

Provision of study materials or patients: Loretta Nastoupil, Pierre Feugier, Emmanuel Bachy, Christophe Fruchart, Corinne Haioun, Hervé Maisonneuve, Kamal Bouabdallah, Pauline Brice, Vincent Ribrag, Steven Le Gouill, Alejandro Martín García-Sancho, Jean-François Larouche, Guillaume Cartron, Gilles Salles

Collection and assembly of data: Franck Morschhauser, Loretta Nastoupil, Pierre Feugier, Jean-Marc Schiano de Colella, Hervé Tilly, Maria Lia Palomba, Emmanuel Bachy, Christophe Fruchart, Edward N. Libby, Rene-Olivier Casanovas, Ian W. Flinn, Hervé Maisonneuve, Loïc Ysebaert, Nancy L. Bartlett, Kamal Bouabdallah, Pauline Brice, Steven Le Gouill, Nicolas Daguindau, Stéphanie Guidez, Gian Matteo Pica, Alejandro Martín García-Sancho, Armondo López-Guillermo, Kiyoshi Ando, Maria Gomes da Silva, Marc André, Wu Kalung, Laurie H. Sehn, Koji Izutsu, Guillaume Cartron, Russell Crowe, Luc Xerri, Nathan H. Fowler, Gilles Salles

Data analysis and interpretation: Franck Morschhauser, Loretta Nastoupil, Hervé Tilly, Maria Lia Palomba, Emmanuel Bachy, Edward N. Libby, Corinne Haioun, Loïc Ysebaert, Nancy L. Bartlett, Vincent Ribrag, Steven Le Gouill, Alejandro Martín García-Sancho, Jean-François Larouche, Marc André, Wu Kalung, Laurie H. Sehn, Guillaume Cartron, Argyrios Gkasiamis, Nathan H. Fowler, Gilles Salles

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

ACKNOWLEDGMENT

The authors would like to thank patients, families, caregivers, and investigators who participated in the RELEVANCE clinical study, the Lymphoma Academic Research Organisation (LYSARC), and to the numerous research and study groups including the Australasian Leukaemia and Lymphoma Group (ALLG), the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG), the German Low Grade Lymphoma Study Group (GLSG), the Lymphoma Study Association (LYSA), and the Grupo Español de Linfomas y Trasplantes de Médula Ósea (GELTAMO) cooperative groups for participating in the study. Medical writing and editorial assistance were provided by Benjamin Levine, PhD, of Bio Connections LLC, funded by Bristol Myers Squibb. The authors directed development of the manuscript and were fully responsible for all content and editorial decisions for this manuscript.

REFERENCES

1. Luminari S, Manni M, Galimberti S, et al: Response-adapted postinduction strategy in patients with advanced-stage follicular lymphoma: The FOLL12 study. *J Clin Oncol* 40:729-739, 2022
2. Flinn IW, van der Jagt R, Kahl B, et al: First-line treatment of patients with indolent non-Hodgkin lymphoma or Mantle-cell lymphoma with bendamustine plus rituximab versus R-CHOP or R-CVP: Results of the BRIGHT 5-year follow-up study. *J Clin Oncol* 37:984-991, 2019
3. Rummel MJ, Maschmeyer G, Ganser A, et al: Bendamustine plus rituximab (B-R) versus CHOP plus rituximab (CHOP-R) as first-line treatment in patients with indolent lymphomas: Nine-year updated results from the StiL NHL1 study. *J Clin Oncol* 35:7501-7501, 2017
4. Ghielmini M, Schmitz SF, Cogliatti SB, et al: Prolonged treatment with rituximab in patients with follicular lymphoma significantly increases event-free survival and response duration compared with the standard weekly x 4 schedule. *Blood* 103:4416-4423, 2004
5. Hainsworth JD, Litchy S, Shaffer DW, et al: Maximizing therapeutic benefit of rituximab: Maintenance therapy versus re-treatment at progression in patients with indolent non-Hodgkin's lymphoma — A randomized phase II trial of the Minnie pearl cancer research network. *J Clin Oncol* 23:1088-1095, 2005
6. Rohatiner AZ, Gregory WM, Peterson B, et al: Meta-analysis to evaluate the role of interferon in follicular lymphoma. *J Clin Oncol* 23:2215-2223, 2005
7. Bjorklund CC, Lu L, Kang J, et al: Rate of CRL4(CRBN) substrate Ikaros and Aiolos degradation underlies differential activity of lenalidomide and pomalidomide in multiple myeloma cells by regulation of c-Myc and IRF4. *Blood Cancer J* 5:e354, 2015
8. Gandhi AK, Kang J, Havens CG, et al: Immunomodulatory agents lenalidomide and pomalidomide co-stimulate T cells by inducing degradation of T cell repressors Ikaros and Aiolos via modulation of the E3 ubiquitin ligase complex CRL4(CRBN.). *Br J Haematol* 164:811-821, 2014
9. Lopez-Girona A, Mendy D, Ito T, et al: Cereblon is a direct protein target for immunomodulatory and antiproliferative activities of lenalidomide and pomalidomide. *Leukemia* 26:2326-2335, 2012
10. Fowler NH, Davis RE, Rawal S, et al: Safety and activity of lenalidomide and rituximab in untreated indolent lymphoma: An open-label, phase 2 trial. *Lancet Oncol* 15:1311-1318, 2014
11. Martin P, Jung SH, Pitcher B, et al: A phase II trial of lenalidomide plus rituximab in previously untreated follicular non-Hodgkin's lymphoma (NHL): CALGB 50803 (alliance). *Ann Oncol* 28:2806-2812, 2017
12. Zucca E, Rondeau S, Vanazzi A, et al: Short regimen of rituximab plus lenalidomide in follicular lymphoma patients in need of first-line therapy. *Blood* 134:353-362, 2019
13. Morschhauser F, Fowler NH, Feugier P, et al: Rituximab plus lenalidomide in advanced untreated follicular lymphoma. *N Engl J Med* 379:934-947, 2018
14. Cheson BD, Horning SJ, Coiffier B, et al: Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. NCI Sponsored International Working Group. *J Clin Oncol* 17:1244, 1999
15. Fischer T, Zing NPC, Chiattonne CS, et al: Transformed follicular lymphoma. *Ann Hematol* 97:17-29, 2018



AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**Six-Year Results From RELEVANCE: Lenalidomide Plus Rituximab (R²) Versus Rituximab-Chemotherapy Followed by Rituximab Maintenance in Untreated Advanced Follicular 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](#)).

Franck Morschhauser

Honoraria: Roche/Genentech, Chugai/Roche, Eisai
Consulting or Advisory Role: Roche/Genentech, Gilead Sciences, Celgene, Bristol Myers Squibb, AbbVie, Epizyme, Servier, AstraZeneca, Novartis, Genmab
Expert Testimony: Roche/Genentech

Loretta Nastoupil

Honoraria: Gilead Sciences, Novartis, Bayer, Janssen Oncology, TG Therapeutics, Bristol Myers Squibb, ADC Therapeutics, Morphosys, Epizyme, Genmab, Takeda, Genentech/Roche
Research Funding: Janssen Biotech, Celgene, Genentech/Roche, Epizyme, Novartis, IgM Biosciences, Caribou Biosciences, Gilead Sciences, Allogene Therapeutics, Takeda

Pierre Feugie

Honoraria: Roche/Genentech, Janssen, Gilead Sciences, Amgen, AbbVie, AstraZeneca

Consulting or Advisory Role: Roche/Genentech, Janssen, AbbVie, Gilead Sciences, Amgen, AstraZeneca

Speakers' Bureau: Roche/Genentech, AbbVie, Amgen, Janssen, Gilead Sciences

Research Funding: Roche/Genentech, Gilead Sciences, Janssen, AbbVie, Amgen

Travel, Accommodations, Expenses: Amgen, Gilead Sciences, Janssen, Roche/Genentech, AbbVie

Jean Marc Schiano de Colella

Honoraria: Amgen, Takeda

Hervé Tilly

Honoraria: Bristol Myers Squibb, Roche

Consulting or Advisory Role: Roche, Incyte, Celgene/Bristol Myers Squibb

Research Funding: Roche/Genentech (Inst)

Travel, Accommodations, Expenses: Roche, Janssen

Maria Lia Palomba

Stock and Other Ownership Interests: Seres Therapeutics (I), Notch Therapeutics (I), Pluto Immunotherapeutics (I)

Honoraria: Seres Therapeutics (I), Vor Biopharma (I), Rheos Medicines (I), Frazier Healthcare Partners (I), Nektar (I), Notch Therapeutics (I), Ceramedix (I), Lygenesis (I), Pluto Immunotherapeutics (I), GlaxoSmithKline (I), Thymofox (I), Garuda Therapeutics (I)

Consulting or Advisory Role: Seres Therapeutics (I), Novartis, BeiGene, Synthekine, MustangBio

Research Funding: Seres Therapeutics (I)

Patents, Royalties, Other Intellectual Property: Intellectual Property Rights (I), Juno intellectual property rights (Inst)

Emmanuel Bachy

Honoraria: Gilead Sciences, Roche, Amgen, Janssen-Cilag, Novartis, Takeda

Consulting or Advisory Role: Roche, Gilead Sciences, Incyte, Takeda

Research Funding: Amgen Foundation (Inst)

Travel, Accommodations, Expenses: Janssen-Cilag, Roche, Gilead Sciences, Incyte

Edward N. Libby

Honoraria: Curio Science

Consulting or Advisory Role: Pharmacylics/Janssen

Research Funding: GlaxoSmithKline (Inst), Janssen (Inst), Genentech (Inst), BeiGene (Inst)

Rene-Olivier Casasnovas

Honoraria: Roche/Genentech, Takeda, Gilead Sciences, Bristol Myers Squibb, Merck, AbbVie, Celgene, Janssen, Amgen

Consulting or Advisory Role: Roche/Genentech, Takeda, Gilead Sciences, Bristol Myers Squibb, Merck, AbbVie, Celgene, Janssen, Incyte, ADC Therapeutics

Research Funding: Roche/Genentech (Inst), Gilead Sciences (Inst), Takeda (Inst)

Travel, Accommodations, Expenses: Roche/Genentech, Takeda, Gilead Sciences, Janssen, AbbVie

Ian W. Flinn

Consulting or Advisory Role: AbbVie (Inst), Seattle Genetics (Inst), TG Therapeutics (Inst), Verastem (Inst), Roche (Inst), Gilead Sciences (Inst), Kite, a Gilead company (Inst), Janssen (Inst), BeiGene (Inst), Takeda (Inst), AstraZeneca (Inst), Juno Therapeutics (Inst), Unum Therapeutics (Inst), MorphoSys (Inst), Nurix (Inst), Shanghai Yingli Pharmaceuticals (Inst), Genentech (Inst), Great Point Partners (Inst), Iksuda Therapeutics (Inst), Novartis (Inst), Pharmacylics (Inst), Century Therapeutics (Inst), Hutchison MediPharma (Inst), Servier (Inst), Vincerox Pharma (Inst), Genmab (Inst), Innocare (Inst)

Research Funding: Acerta Pharma (Inst), Agios (Inst), Celgene (Inst), Constellation Pharmaceuticals (Inst), Genentech (Inst), Gilead Sciences (Inst), Incyte (Inst), Infinity Pharmaceuticals (Inst), Janssen (Inst), Kite, a Gilead company (Inst), Novartis (Inst), Pharmacylics (Inst), Portola Pharmaceuticals (Inst), Roche (Inst), TG Therapeutics (Inst), Trillium Therapeutics (Inst), AbbVie (Inst), ArQule (Inst), BeiGene (Inst), Curis (Inst), FORMA Therapeutics (Inst), Forty Seven (Inst), Merck (Inst), Pfizer (Inst), Verastem (Inst), AstraZeneca (Inst), Unum Therapeutics (Inst), MorphoSys (Inst), Seattle Genetics (Inst), IGM Biosciences (Inst), Loxo (Inst), Rhizen Pharmaceuticals (Inst), Triact Therapeutics (Inst), Bristol Myers Squibb (Inst), CALGB (Inst), CTI (Inst), Fate Therapeutics (Inst), Millennium (Inst), TCR2 Therapeutics (Inst), Tessa Therapeutics (Inst), City of Hope (Inst), CALIBR (Inst), Bio-Path Holdings, Inc (Inst), Nurix (Inst), Innocare (Inst), Myeloid Therapeutics (Inst)

Corinne Haioun

Honoraria: Novartis, Amgen, Servier/Pfizer, Gilead Sciences

Consulting or Advisory Role: Roche, Celgene, Janssen-Cilag, Gilead Sciences, Takeda, Miltenyi Biotec, AbbVie, ADC Therapeutics

Travel, Accommodations, Expenses: Roche, Celgene, Amgen

Loic Ysebaert

Consulting or Advisory Role: AbbVie, Janssen-Cilag, Roche, Gilead Sciences, BeiGene, Celgene/Bristol Myers Squibb

Speakers' Bureau: AstraZeneca

Research Funding: Roche (Inst), Janssen-Cilag (Inst), Gilead Sciences (Inst)

Nancy L. Bartlett

Consulting or Advisory Role: Seattle Genetics, Roche/Genentech, ADC Therapeutics, BTG, Acerta Pharma

Research Funding: Seattle Genetics (Inst), Kite, a Gilead company (Inst), Merck (Inst), Bristol Myers Squibb (Inst), Celgene (Inst), Immune Design (Inst), Forty Seven (Inst), Janssen (Inst), Pharmacylics (Inst), Millennium (Inst), ADC Therapeutics (Inst), Autolus (Inst), Roche/Genentech (Inst), Pfizer (Inst), Affimed Therapeutics (Inst)

Kamal Bouabdallah

Honoraria: Roche, Takeda Science Foundation, AbbVie, Kite/Gilead

Consulting or Advisory Role: Roche, Takeda, Kite/Gilead

Travel, Accommodations, Expenses: Roche, Takeda

Pauline Brice

Research Funding: Takeda, BMS

Travel, Accommodations, Expenses: Roche, Amgen, AbbVie/Genentech

Vincent Ribrag

Honoraria: AZD, Infinity Pharmaceuticals, Gilead Sciences, NanoString Technologies, Roche, Novartis, AbbVie

Consulting or Advisory Role: Infinity Pharmaceuticals, PharmaMar, Gilead Sciences, NanoString Technologies, Bristol Myers Squibb, MSD, Roche/Genentech, Immune Design, Roche, Incyte

Research Funding: arGEN-X BVBA, Epizyme (Inst), argenx (Inst), Astex Pharmaceuticals (Inst), GlaxoSmithKline/Adaptimmune (Inst)

Expert Testimony: Servier

Travel, Accommodations, Expenses: Roche, Bristol Myers Squibb, AZD

Steven Le Gouill

Honoraria: Roche/Genentech

Consulting or Advisory Role: Roche/Genentech

Research Funding: Roche/Genentech

Travel, Accommodations, Expenses: Roche/Genentech

Stéphanie Guidez**Consulting or Advisory Role:** Kite/Gilead, Incyte, AstraZeneca**Travel, Accommodations, Expenses:** Janssen, Sanofi**Alejandro Martín García-Sancho****Honoraria:** Roche, Janssen-Cilag, Celgene, Servier, Gilead Sciences, Takeda, Eusa Pharma, Novartis**Consulting or Advisory Role:** Roche, MorphoSys, Kyowa Hakko Kirin, iQONE, EUSA Pharma, Gilead Sciences, Novartis, Servier, Incyte, BMS, ADC Therapeutics, Lilly, Miltenyi Biomedicine**Research Funding:** Janssen (Inst), Teva (Inst)**Expert Testimony:** Gilead Sciences**Travel, Accommodations, Expenses:** Roche, Celgene, Servier, Gilead Sciences, Kern Pharma, Janssen Oncology**Armando López-Guillermo****Honoraria:** Roche**Consulting or Advisory Role:** Roche, Kite/Gilead, Celgene/Bristol Myers Squibb, Incyte, Takeda, Kern Pharma, Pfizer, Janssen**Research Funding:** Janssen, Roche, Celgene/Bristol Myers Squibb**Travel, Accommodations, Expenses:** Roche, Kite/Gilead**Jean-François Larouche****Consulting or Advisory Role:** Gilead Sciences, AstraZeneca Canada**Research Funding:** Roche Canada (Inst), AstraZeneca Canada (Inst), Incyte (Inst), Genmab (Inst)**Maria Gomes da Silva****Consulting or Advisory Role:** Janssen-Cilag, Bristol Myers Squibb, Takeda, Gilead Sciences, AbbVie, Roche, ADC Therapeutics, Merck Sharp and Dome**Speakers' Bureau:** Janssen-Cilag, Takeda, Gilead Sciences**Research Funding:** Gilead Sciences (Inst), AstraZeneca**Travel, Accommodations, Expenses:** Roche, Celgene, Janssen-Cilag, Gilead Sciences**Marc André****Consulting or Advisory Role:** Takeda, BMSi**Research Funding:** Takeda (Inst), Roche (Inst)**Travel, Accommodations, Expenses:** Roche, Celgene, Gilead Sciences, AdtraZeneca**Laurie H. Sehn****Honoraria:** Amgen, Apobiologix, AbbVie, Celgene, Gilead Sciences, Janssen-Ortho, Karyopharm Therapeutics, Kite, a Gilead company, Lundbeck, Merck, Roche/Genentech, Seattle Genetics, Takeda, Teva, TG Therapeutics,

AstraZeneca, Acerta Pharma, Morphosys, Incyte, Debiopharm Group, Sandoz-Novartis, Verastem, Genmab

Consulting or Advisory Role: Celgene, AbbVie, Seattle Genetics, TG Therapeutics, Janssen, Amgen, Roche/Genentech, Gilead Sciences, Lundbeck, Amgen, apobiologix, Karyopharm Therapeutics, Kite, a Gilead company, Merck, Takeda, Teva, TG therapeutics, AstraZeneca, Acerta Pharma, MorphoSys, Incyte, Debiopharm Group, Sandoz-Novartis, Genmab, Verastem**Research Funding:** Roche/Genentech (Inst), Teva (Inst)**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 Kirin, Fujifilm, Celgene, Janssen, Daiichi Sankyo, Allergan**Consulting or Advisory Role:** Bayer, Celgene, AstraZeneca, Ono Pharmaceutical, Kyowa Kirin, AstraZeneca, AbbVie**Research Funding:** Eisai, Chugai Pharma**Guillaume Cartron****Honoraria:** Gilead Sciences, Janssen, Celgene, Roche, AbbVie, Novartis**Consulting or Advisory Role:** Roche, Celgene, Mabq, MedxCell**Travel, Accommodations, Expenses:** Roche**Argyrios Gkasiamis****Employment:** BMS**Russell Crowe****Stock and Other Ownership Interests:** Bristol Myers Squibb**Luc Xerri****Consulting or Advisory Role:** EUSA Pharma, EUSA Pharma, EUSA Pharma**Nathan H. Fowler****Employment:** BostonGene**Consulting or Advisory Role:** Roche/Genentech, TG Therapeutics, Bayer, Novartis, Bristol Myers Squibb/Pfizer**Research Funding:** Roche, Celgene, Gilead Sciences, TG Therapeutics, Novartis, AbbVie, BeiGene**Gilles Salles****Stock and Other Ownership Interests:** Owkin**Honoraria:** AbbVie, Bayer, Regeneron**Consulting or Advisory Role:** Roche/Genentech, Janssen, Novartis, morphosys, Epizyme, Genmab, Debiopharm Group, Velosbio, BMS, BeiGene, Incyte, Miltenyi Biotec, Ipsen, AbbVie, Kite/Gilead, Loxo/Lilly, Molecular Partners, Nordic Nanovector, RAPT Therapeutics, Takeda, incyte

No other potential conflicts of interest were reported.