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

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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) 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.

INTRODUCTION

Immunotherapy 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.
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

Coprimary 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).

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

| Characteristic                        | R² (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. (%)                     |              |                  |                  |
| 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. (%)                    |              |                  |                  |
| 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. (%)                 |              |                  |                  |
| 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.

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

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

A 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.
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 ($R^2 = 107$ 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).
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% vs 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 (vs 12 patients in 2017) reported ≥ 1 grade 5 treatment emergent adverse event: nine (vs 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...
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, chemofree alternative to R-chemo on the basis of immunomodulation in patients with advanced untreated FL in need of treatment.

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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 LYSYA Scientific Committee. If the project is validated by LYSYA 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.

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**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  
**Armondo 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, Gilead Sciences, Adtra-Zenea  
**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, Allegan  
**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, Mabiq, 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, Loox/Lilly, Molecular Partners, Nordic Nanovector, RAPT Therapeutics, Takeda, Incyte  
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