American Society of Hematology
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Lenalidomide plus rituximab for previously untreated advanced follicular lymphoma: the 10-year RELEVANCE trial analysis

Tracking no: BLD-2026-033126R1

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Abstract:
In the multinational, phase 3 RELEVANCE trial, 1,030 patients with previously untreated follicular lymphoma were randomized to receive rituximab plus lenalidomide (R2; n=513) or rituximab-based immunochemotherapy (R-Chemo; n=517). In the final analysis, at 120 months of follow-up, median PFS was comparable between the treatment groups: 110.6 months with R2 versus 102.8 months with R-Chemo, according to Independent Review Committee assessment. The 10-year PFS rates were 46.4% and 46.6%, respectively. Median overall survival (OS) and time-to-next lymphoma treatment (TTNLT) were not reached in either arm; 10-year OS rates were 82.4% and 81.1%, respectively, and 10-year TTNLT rates were 62.2% and 66.3%, respectively. Overall, patients with POD24 had a poorer prognosis compared to those without POD24 (HR, 6.215; P<0.0001); however, no difference was observed between the study groups. The incidence of second primary malignancies (SPMs) was 2.11 cases per 100 patient-years (95% CI, 1.80-2.46). Only 9 transformations occurred after 24 months (3 with R2 versus 6 with R-chemo). In each study group, 87 patients died, mainly due to lymphoma progression and SPMs. This long-term follow-up of RELEVANCE confirmed that R2 provides a chemo-free alternative to immunochemotherapy in this patient population. Trial registration: NCT01476787 and NCT01650701; EudraCT: 2011-002792-42.

Conflict of interest: COI declared - see note

COI notes: P.F. reports honoraria from Roche/Genentech, Janssen, Gilead Sciences, Amgen, AbbVie, and AstraZeneca; consulting or advisory role for Roche/Genentech, Janssen, AbbVie, Gilead Sciences, Amgen, and AstraZeneca; speakers' bureau membership for Roche/Genentech, AbbVie, Amgen, Janssen, and Gilead Sciences; research funding for Roche/Genentech, Gilead Sciences, Janssen, AbbVie, and Amgen; and travel, accommodations, and expenses from Amgen, Gilead Sciences, Janssen, Roche/Genentech, and AbbVie. J.W. reports consultancy for AbbVie/GenMab, AstraZeneca, Nurix,

Janssen, Morphosys/Incyte, ADC Therapeutics, Bristol Myers Squibb, Genentech, Inc., Kite/Gilead, Allogene, Novartis, Regeneron, and Pfizer; and research funding from AstraZeneca, Nurix, Janssen, Morphosys/Incyte, ADC Therapeutics, Bristol Myers Squibb, Genentech, Inc., Kite/Gilead, Allogene, Novartis, and Regeneron. J.M.S De C. reports honoraria from Janssen, Pfizer, Sanofi, BMS, GSK, and Amgen; advisory board membership for Pfizer; and travel, accommodations, and expenses from Pfizer, Sanofi, Janssen, and Amgen. H.T. reports honoraria from Roche; consulting or advisory role for Roche, and Celgene/Bristol Myers Squibb; and research funding from Roche/Genentech (Inst). M.L.P. reports stock and other ownership interests for Seres Therapeutics; honoraria from Seres Therapeutics, Thymofox, and Garuda Therapeutics; consulting or advisory role for BeOne, Galapagos, Novartis, and Bristol Meyer Squibb; research funding from Seres Therapeutics; and intellectual property rights for Juno intellectual property rights (Inst). E.J. reports travel, accommodations, and expenses from Janssen-Cilag. G-L.D. reports research funding from Takeda, and Ideogen; educational grant from Amgen; and travel, accommodations, and expenses from Takeda, and Kite. A.D. reports honoraria from AbbVie, BeOne, and Janssen-Cilag; consulting or advisory role for AbbVie, BeOne, and Janssen-Cilag; and travel, accommodations, expenses from AbbVie, BeOne, and Janssen-Cilag. I.F. reports consulting or advisory role for Abbvie, BeiGene, Genentech, Genmab, KITE, and Vincerx; and research funding from AbbVie(Inst), AstraZeneca(Inst), BeiGene(Inst), Bristol Myers Squibb(Inst), City of Hope National Medical Center(Inst), Genentech(Inst), Gilead Sciences(Inst), InnoCare Pharma, Incyte, Janssen(Inst), Kite Pharma(Inst), Lilly(Inst), Merck(Inst), MorphoSys(Inst), Novartis(Inst), Nurix(Inst), Pfizer(Inst), Roche(Inst), 2seventy bio(Inst). F.L. reports honoraria from Takeda, AstraZeneca, Bristol Myers Squibb, and Janssen; advisory board membership for Miltenyi, Kyowa kirin, and Bristol Myers Squibb; travel expenses from Roche, Gilead, Abbvie, and Beigene; and research funding from Bristol Myers Squibb and Roche. L.Y. reports advisory board membership and research grants from Abbvie, AstraZeneca, BeOne, Bristol Myers Squibb, Gilead/Kite, Johnson & Johnson, and Roche. C.T. reports honoraria from Takeda, Incyte, Bayer, Kite, Gilead, Novartis, Bristol Myers Squibb, Abbvie, F. Hoffmann-La Roche Ltd, Amgen, Cellectis, and Janssen; research funding from Hospira and BMS/Celgene; consulting or advisory role for Kite, Amgen, AbbVie, Novartis, Roche, Gilead, Takeda, BMS/Celgene, Incyte, and Cellectis; consultancy for Kite, Amgen, AbbVie, Novartis, Gilead, Cellectis, Roche, and BMS/Celgene; and travel, accommodations, and expenses from Kite Pharma/Gilead, Amgen, AbbVie, Novartis, Gilead, Cellectis, Roche, BMS/Celgene, and Janssen. V.R. is an employee of Pegascy and reports research funding from Astex Pharmaceuticals and GSK; consultancy for Abbvie and Lilly; honoraria from Ipsen, Beigene, Incyte and AstraZeneca; and travel, accommodations, and expenses from Pfizer and AstraZeneca. T.G. reports consulting or advisory role for Gilead Sciences, Takeda, Bristol Myers Squibb, MSD, and Roche; and travel, accommodations, and expenses from Roche, Bristol Myers Squibb, Kyte/Gilead, and Takeda. A.D. reports honoraria from Sanofi, Roche, Janssen-Cilag, BMS, and Pfizer; and travel, accommodations, and expenses from Sanofi. S.G. reports consulting or advisory role for Kite/Gilead, Incyte, AstraZeneca, Abbvie, Roche, Takeda, BMS, Novartis, and Johnson & Johnson; and travel, accommodations, and expenses from Kite/Gilead and AstraZeneca. R.H. reports honoraria from Kite/Gilead, Novartis, Bristol-Myers Squibb/Celgene, Incyte, Janssen, MSD, Takeda, Amgen, Abbvie, and Roche; Board of Directors or advisory committees' membership for Kite/Gilead, Novartis, Bristol-Myers Squibb/Celgene, Tessa Therapeutics, Abbvie and Roche. M.G Da S. reports consulting or advisory role for Janssen-Cilag, Roche, Lilly, and Clinical Care Options; Speakers' Bureau membership for Janssen-Cilag, Abbvie, Gilead Sciences, and Beigene; research funding from AstraZeneca; and travel, accommodations, and expenses from Roche, Abbvie, Janssen-Cilag, Gilead Sciences, Beigene, and Lilly. F.B. reports research funding from Gilead Sciences (Inst); and travel, accommodations, and expenses Roche, BeOne, Takeda, Abbvie, Kite/Gilead, and Janssen. G.C. reports honoraria, and advisory/consultancy fees from Roche, Bristol-Myers Squibb, Beigen, Novartis, Kite/Gilead, Takeda, AstraZeneca, Abbvie, Janssen, Ownards Therapeutic, and MabQi. A.M.G-S. reports honoraria from Abbvie, AstraZeneca, BeOne, BMS, Gilead/Kite, Ideogen, Incyte, Janssen, Kyowa Kirin, Lilly, Roche, Sobi, and Takeda; consulting or advisory role for Abbvie, AstraZeneca, BeOne, BMS, Genmab, Gilead/Kite, GSK, Ideogen, Incyte, Janssen, Kyowa Kirin, Lilly, Miltenyi, Regeneron, Roche, Sobi, and Takeda; and research support from Gilead/Kite. H.E reports research funding, honoraria, or consulting fees from AbbVie, Genentech, Inc., Kite, Gilead Sciences, Takeda, Acerta, AstraZeneca, BeiGene and Juno. M.C reports research funding from Innate Pharma, Johnson & Johnson, Bristol Myers Squibb, Griffols, and LFB; consulting or advisory role for CSL Behring, Johnson & Johnson, AstraZeneca, Lilly, Amgen, and AbbVie; and travel, accommodations, and expenses from Pfizer, Griffols, CSL Behring, AstraZeneca, Lilly, Gilead Sciences, and BeOne. A.L.G. reports honoraria from Roche; consulting or advisory role for Roche, Kite/Gilead, Celgene/Bristol Myers Squibb, Incyte, Takeda, Kern Pharma, Pfizer, and Janssen; research funding from Janssen, Roche, and Celgene/Bristol Myers Squibb; and travel, accommodations, and expenses from Roche and Kite/Gilead. P.A. reports honoraria from AbbVie, Gilead, AstraZeneca, Beigene, Lilly, and Johnson & Johnson; consulting or advisory role for Johnson & Johnson, Regeneron, AbbVie, Gilead, Bristol Myers Squibb, Roche, Incyte; and travel, accommodations, and expenses from Roche, AbbVie, Johnson & Johnson, and Lilly. J.A. reports consulting or advisory role for Kite/Gilead, Incyte, AbbVie, Takeda, and Bristol Myers Squibb; and travel, accommodations, and expenses from AbbVie, Roche, and Janssen. C.S. reports honoraria from Roche, Incyte, BeOne, and Janssen; consulting or advisory role for Janssen, Roche, Bristol Myers Squibb, AstraZeneca, and Incyte; and travel, accommodations, and expenses from Roche and Kite/Gilead. K.I. reports consultancy for Bristol Myers Squibb, Eisai, AbbVie, Kyowa Kirin, Genmab, Zenyaku, Symbio, Nihon Shinyaku, BeOne Medicines, Tanabe Mitsubishi, and Daiichi Sankyo; research funding from AstraZeneca, AbbVie, Incyte, Bristol Myers Squibb, Novartis, Daiichi Sankyo, Chugai, Beigene, Genmab, LOXO Oncology, and Regeneron; and honoraria from

AbbVie, Eisai, Bristol Myers Squibb, AstraZeneca, Takeda, Johnson & Johnson Innovative Medicines, Kyowa Kirin, Chugai, MSD, Genmab, Eli Lilly, Symbio, Gilead, Ono Pharmaceuticals, Novartis, Meiji Seika Pharma, Nihon Shinyaku, and Nihon Kayaku. G.C. reports honoraria from AbbVie, Bristol Myers Squibb, Kite/Gilead, Roche, and Incyte; and consulting or advisory role for Roche, Kite/Gilead, Bristol Myers Squibb, and Johnson & Johnson. L.H.S. reports honoraria from Amgen, AbbVie, BMS, Kite/Gilead Sciences, JanssenOrtho, Merck, Roche/Genentech, AstraZeneca, Incyte, and Genmab; consulting or advisory role for Amgen, AbbVie, BMS, Kite/Gilead Sciences, JanssenOrtho, Merck, Roche/Genentech, AstraZeneca, Incyte, and Genmab; and research funding from Roche/Genentech (Inst). A.G. and M.L.Y are employees of Bristol Myers Squibb. L.C. is an employee of LYSARC. N.F. is an employee of BostonGene and reports consulting or advisory role for Roche/Genentech, TG Therapeutics, Bayer, Novartis, and Bristol Myers Squibb/Pfizer; and research funding from Roche, Celgene, Gilead Sciences, TG Therapeutics, Novartis, AbbVie, and BeiGene. G.S. reports consulting or advisory role for AbbVie, BeOne, Bristol Myers Squibb, Canopy, Daiichi Sankyo, Ellipses Genentech/Roche, Genmab, Incyte, Janssen, Ipsen, Kite/Gilead, Lilly, Merck, and Novartis; and research funding from AbbVie, Genentech, Genmab Janssen, and Ipsen, managed by his institution. F.M. reports honoraria from Roche/Genentech, Chugai/Roche, and Eisai; consulting or advisory role for Roche/Genentech, Gilead Sciences, Celgene, Bristol Myers Squibb, AbbVie, Epizyme, Servier, AstraZeneca, Novartis, and Genmab; and expert testimony for Roche/Genentech. N.G., N.M., N.B., L.F., J.B., and L.X. report no conflict of interest for this study.

Preprint server: No;

Author contributions and disclosures: F.M. and G.S. participated in the conception and design, performed clinical data assembly and analysis L.C. performed the statistical analysis. F.M. contributed to the development of the first draft and subsequent drafts. All authors provided study material or patients and approved the final draft of the manuscript.

Non-author contributions and disclosures: Yes; Julie Nassif, Pharm D, and Thomas Rohban, MD, of Partner 4 Health (Paris, France) provided medical writing support in accordance with current Good Publication Practice guidelines, funded by LYSARC.

Agreement to Share Publication-Related Data and 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 LYSA Scientific Committee. If the project is validated by LYSA 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-recherchelymphome.org/lysarc/or contact contact@lysarc.org. This manuscript presents the final analysis of a long-term trial, with two interim analyses previously published: 1- Morschhauser F, et al. N Engl J Med. 2018;379(10):934-947. 2- Morschhauser F, et al. J Clin Oncol. 2022;40(28):3239-3245.

Clinical trial registration information (if any): This trial was registered at www.clinicaltrials.gov as # NCT01476787 and # NCT01650701 (EudraCT number: 2011-002792-42).

Brief Report

TITLE PAGE

Journal: Blood

Title: Lenalidomide plus rituximab for previously untreated advanced follicular lymphoma: the 10-year RELEVANCE trial analysis

Short title for the running head: The 10-year RELEVANCE trial analysis

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Word count: Text: 1,499 (limit: 1,500); Abstract: 195 (limit: 200)

Number of figures and tables: 3 (limit: 3)

Number of references: 16 (limit: 25)

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 LYSA Scientific Committee. If the project is validated by LYSA 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-recherchelymphome.org/lysarc/or contact contact@lysarc.org.

KEY POINTS

- Rituximab plus lenalidomide resulted in 10-year PFS, TTNLT, and OS rates comparable to immunochemotherapy rates in previously untreated FL
- The incidence of second primary malignancies was 2.11 cases per 100 patient-years, with comparable rates in both treatment groups

ABSTRACT

In the multinational, phase 3 RELEVANCE trial, 1,030 patients with previously untreated follicular lymphoma were randomized to receive rituximab plus lenalidomide (R2; n=513) or rituximab-based immunochemotherapy (R-Chemo; n=517). In the final analysis, at 120 months of follow-up, median PFS was comparable between the treatment groups: 110.6 months with R2 *versus* 102.8 months with R-Chemo, according to Independent Review Committee assessment. The 10-year PFS rates were 46.4% and 46.6%, respectively. Median overall survival (OS) and time-to-next lymphoma treatment (TTNLT) were not reached in either arm; 10-year OS rates were 82.4% and 81.1%, respectively, and 10-year TTNLT rates were 62.2% and 66.3%, respectively. Overall, patients with POD24 had a poorer prognosis compared to those without POD24 (HR, 6.215; P<0.0001); however, no difference was observed between the study groups. The incidence of second primary malignancies (SPMs) was 2.11 cases per 100 patient-years (95% CI, 1.80-2.46). Only 9 transformations occurred after 24 months (3 with R2 *versus* 6 with R-chemo). In each study group, 87 patients died, mainly due to lymphoma progression and SPMs. This long-term follow-up of RELEVANCE confirmed that R2 provides a chemo-free alternative to immunochemotherapy in this patient population. Trial registration: NCT01476787 and NCT01650701; EudraCT: 2011-002792-42.

Introduction

Immunochemotherapy regimens incorporating anti-CD20 monoclonal antibodies have significantly improved outcome of patients with previously untreated advanced follicular lymphoma (FL) with median overall survival (OS) close to 20 years, highlighting the importance of long-term follow-up care for survivors.[1,2] Lenalidomide combined with rituximab (R2) is approved in the United States and Europe for the treatment of adult patients with previously treated FL.[3,4] This combination has also been investigated in patients with previously untreated FL, with varying tumor burden, in several Phase 2 studies,[5-8] and in RELEVANCE, a large, prospective, phase 3 trial.[9,10] At a median follow-up of 37.9 months (first interim analysis), RELEVANCE trial showed similar efficacy of R2 to rituximab plus chemotherapy (R-Chemo) in both coprimary end points – complete response confirmed/ unconfirmed (CR/CRu) at 120 weeks and progression-free survival (PFS).[9] The 3-year PFS rates were 77% and 78%, respectively, and the OS rate was 94% for both groups.[9] In the second interim analysis (median follow-up, 72 months), the 6-year PFS rates were 60% and 59%, respectively, and the OS rate was 89% for both groups.[10] Here, we report the 10-year preplanned final analysis of RELEVANCE allowing mature assessment of PFS.

Study design

Details of the study design and conduct, inclusion and exclusion criteria, and dosing regimens and schedules (supplemental Figure S1) of RELEVANCE trial have been previously published.[9] RELEVANCE was a multicenter, multinational, randomized (1:1), open-label, phase 3 trial in which patients with previously untreated grade 1 to 3a FL were randomly assigned to receive either R2 or one of three R-Chemo regimens (supplemental Figure S1), followed by rituximab

maintenance in both groups. Randomization was stratified according to Follicular Lymphoma International Prognostic Index (FLIPI) score (low risk, 0 or 1; intermediate risk, 2; high risk, 3 to 5), age (≤60 versus >60 years), and lesion size (≤6 versus >6 cm).

The final analysis for PFS, assessed by the Independent Review Committee using the International Working Group criteria[11] was to be performed upon the occurrence of 456 PFS events among all randomized patients, or once a median follow-up of 9.5 years was reached, whichever came first. Time-to-next lymphoma treatment (TTNLT) and OS were analyzed at the time of the final PFS analysis. Prespecified subgroup analyses for PFS were performed according to several prognostic factors, including FLIPI score and POD24 (defined as progression of disease or death due to lymphoma within 24 months of initial immunochemotherapy). Safety analyses focused mainly on the incidence of second primary malignancies (SPMs). Details on endpoints and statistical analyses are provided in the supplemental Methods.

Results and discussion

Between December 2011 and November 2014, a total of 1,030 patients (ITT population) were randomly assigned to receive either R2 or R-Chemo; 1,010 received at least one dose of study treatment and 819 entered clinical follow-up (419 and 400, respectively). Patient disposition and demographics are presented in supplemental Figure S2 and Table S1. Of the 1,030 patients, 71 (6.9%) were lost to follow-up: 7.2% in the R2 group and 6.6% in the R-Chemo group (supplemental Figures S2 and S3). Among these 71 patients, 15 (21.1%) were lost during treatment period and had experienced progression or relapse, with similar proportions in both study groups (supplemental Figure S3). During the follow-up period, 98 patients (23.4%) with

R2 and 92 (23.0%) with R-Chemo discontinued the study, most commonly because of death (45.9% and 58.7%, respectively).

At the cut-off date of 30 April 2024, median follow-up was 118.2 months (9.85 years), comparable between study groups. Both co-primary endpoints, CR/CRu rate at 120 weeks[9] and PFS, did not significantly differ between study groups. Median PFS was 110.6 months (95% CI, 84.4-not reached) with R2 compared to 102.8 months (95% CI, 82.8-not reached) with R-Chemo; estimated PFS rates were 46.4% and 46.6%, respectively (Figure 1A; supplemental Table S2). Median PFS did not differ between groups when stratified by age, FLIPI score, and longest diameter of the largest node (110.6 and 102.8 months, respectively). Median OS and TTNLT were not reached in either group (Figure 1B and 1C). The estimated 10-year OS rates were 82.4% with R2 and 81.1% with R-Chemo, and the TTNLT rates were 62.2% and 66.3%, respectively (supplemental Table S2). TTNLT did not significantly differ between treatment groups (estimated HR, 1.186 [95% CI, 0.954-1.475]; stratified P=0.123). A total of 227 patients received treatment for progression or relapse, 118 with R2 and 109 with R-Chemo; most administered treatments consisted of immunochemotherapy combinations (supplemental Table S3). Supplemental Figure S4 presents the post-hoc analysis of PFS and OS by chemotherapy regimen and Supplemental Figure S5 the cumulative incidence of histologic transformation.

The efficacy results observed with R-Chemo in RELEVANCE align with findings from long-term follow-up of patients who received R-Chemo induction followed by rituximab maintenance in the randomized phase 3 studies, PRIMA[12] and GALLIUM[13] (supplemental Table S2). In PRIMA,[12] the projected 10-year PFS, OS and TTNLT rates were 51.1%, 80.1% and 53.4%,

respectively.[12] In GALLIUM,[13] the 7-year investigator-assessed PFS, TTNLT, and OS rates were similar to those reported with R-Chemo in RELEVANCE (7-year PFS rate, 55.7% versus 54.5%; TTNLT rate, 65.4% versus 69.9%; OS rate, 87.2% versus 87.0%). Similarly, the efficacy results observed with R2 in RELEVANCE were similar to those observed in the phase 2 Swiss Group for Clinical Cancer Research (SAKK) study, SAKK 35/10,[6] where patients received a short R2 induction of 18 weeks without any maintenance (median follow-up, 9.5 years; median PFS, 9.3 years; median TTNLT and OS, not reached).[6] Although cross-trials comparisons should be interpreted cautiously due to differences in design, sample size, treatment duration and maintenance, these results question the optimal duration of each drug, and the benefit of keeping R2 beyond 6 months for optimal disease control when both drugs are combined.[6]

Subgroup analyses of PFS showed that the efficacy of R2 remained independent of several conventional prognostic factors (Figure 2) such as bulk and high-risk FLIPI (Figures 3A and 3B). A non-statistically significant trend was observed for the benefit of R-Chemo in patients with FL at Ann Arbor stage I or II disease and in those enrolled in North America. Patients with POD24 had a poorer prognosis compared to those without POD24, with a statistically significant difference (estimated HR, 6.215 [95% CI, 4.487-8.608]; P<0.0001) (Figure 3C). The 8-year survival rates were 50.9% (95% CI, 41.9-59.3) and 88.1% (95% CI, 85.5-90.3), respectively. Among patients with POD24, no statistically significant survival difference was observed between the two treatment groups (Figure 3D) confirming its validity for predicting worse outcome after R2 treatment in the first-line setting. Contrary to conventional clinical factors, a biomarker such as the memory-like FL subtype, which can be identified in routine practice with

an immunohistochemistry algorithm — as shown in the context of RELEVANCE[14] — may help better select patients that could benefit from R2 over R-chemo.

Among the 1,010 patients in the Safety set, almost all patients (99.3%) reported at least one treatment-emergent adverse event (TEAE) over the course of the study (100% with R2 and 98.6% with R-Chemo). There were no new or unexpected safety findings in the long-term follow-up, notably regarding infections. Overall, 15 patients (1.5%) had a Grade 5 TEAE.[10]

In RELEVANCE, 207 SPMs were reported in 164 patients – 79 patients (15.6%) in the R2 group and in 85 patients (16.9%) in the R-Chemo group – majority of which were solid tumors. Non-melanoma skin cancers were reported in 22 (4.3%) and 32 patients (6.4%), respectively (supplemental Table S4). Slightly higher rates of SPMs were reported in RELEVANCE compared to those in SAKK 35/10 (13%)[6] and GALLIUM (16.1%).[13] This difference may be attributed to the planned rigorous SPM reporting procedures prespecified in RELEVANCE. Still, the cumulative incidence of SPMs was low at 2.11 cases per 100 patient-years. Since there is no statistically significant difference between the treatment groups, concerns brought up earlier are somehow alleviated, confining the higher rates of SPMs to lenalidomide in the myeloma setting only.[15,16]

A total of 174 deaths occurred over the full study duration, 87 patients in each group. The most common primary cause of death was lymphoma, followed by SPMs – 3.2% with R2 and 2.8% with R-Chemo (supplemental Table S5). Slightly lower rates were reported in SAKK 35/10[6] (1.8% with R-Chemo) and PRIMA[12] (1.3% with R2). While disease control remains the primary

objective in FL, SPMs remain a main concern in the long-term follow-up of patients treated with either an immunochemotherapy or an immunomodulatory regimen.

This large study has several strengths notably its head-to-head design comparing R2 with R-Chemo regimens, the planned extended duration of follow-up, and high patient retention rate. However, randomization was limited to treatment arms (R2 and R-Chemo, 1:1), without stratification of specific chemotherapy regimens, precluding direct comparisons across these regimens.

In conclusion, the final analysis of RELEVANCE confirmed the absence of differences in efficacy outcomes between R2 and R-Chemo and the lack of new safety concerns, positioning R2 as a valid chemo-free alternative for patients with previously untreated, advanced FL. We believe these 10-year follow-up results may constitute a benchmark for long-term expectations and comparisons with new promising chemo-free combinations currently tested in the front-line setting of FL.

Acknowledgements:

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

Medula Osea (GELTAMO) cooperative groups for participating in the study, as well as Christian Gisselbrecht and André Bosly for independent central clinical review. The authors would also like to thank Julie Nassif, Pharm D, and Thomas Rohban, MD, of Partner 4 Health (Paris, France) for providing medical writing support in accordance with current Good Publication Practice guidelines, funded by LYSARC.

Authorship Contributions:

F.M. and G.S. participated in the conception and design, performed clinical data assembly and analysis L.C. performed the statistical analysis. F.M. contributed to the development of the first draft and subsequent drafts. All authors provided study material or patients and approved the final draft of the manuscript.

Conflicts of Interest Disclosure:

P.F. reports honoraria from Roche/Genentech, Janssen, Gilead Sciences, Amgen, AbbVie, and AstraZeneca; consulting or advisory role for Roche/Genentech, Janssen, AbbVie, Gilead Sciences, Amgen, and AstraZeneca; speakers' bureau membership for Roche/Genentech, AbbVie, Amgen, Janssen, and Gilead Sciences; research funding for Roche/Genentech, Gilead Sciences, Janssen, AbbVie, and Amgen; and travel, accommodations, and expenses from Amgen, Gilead Sciences, Janssen, Roche/Genentech, and AbbVie. J.W. reports consultancy for AbbVie/GenMab, AstraZeneca, Nurix, Janssen, Morphosys/Incyte, ADC Therapeutics, Bristol Myers Squibb, Genentech, Inc., Kite/Gilead, Allogene, Novartis, Regeneron, and Pfizer; and research funding from AstraZeneca, Nurix, Janssen, Morphosys/Incyte, ADC Therapeutics, Bristol Myers Squibb, Genentech, Inc., Kite/Gilead, Allogene, Novartis, and Regeneron. J.M.S

De C. reports honoraria from Janssen, Pfizer, Sanofi, BMS, GSK, and Amgen; advisory board membership for Pfizer; and travel, accommodations, and expenses from Pfizer, Sanofi, Janssen, and Amgen. H.T. reports honoraria from Roche; consulting or advisory role for Roche, and Celgene/Bristol Myers Squibb; and research funding from Roche/Genentech (Inst). M.L.P. reports stock and other ownership interests for Seres Therapeutics; honoraria from Seres Therapeutics, Thymofox, and Garuda Therapeutics; consulting or advisory role for BeOne, Galapagos, Novartis, and Bristol Meyer Squibb; research funding from Seres Therapeutics; and intellectual property rights for Juno intellectual property rights (Inst). E.J. reports travel, accommodations, and expenses from Janssen-Cilag. G-L.D. reports research funding from Takeda, and Ideogen; educational grant from Amgen; and travel, accommodations, and expenses from Takeda, and Kite. A.D. reports honoraria from AbbVie, BeOne, and Janssen-Cilag; consulting or advisory role for AbbVie, BeOne, and Janssen-Cilag; and travel, accommodations, expenses from AbbVie, BeOne, and Janssen-Cilag. I.F. reports consulting or advisory role for Abbvie, BeiGene, Genentech, Genmab, KITE, and Vincerx; and research funding from AbbVie(Inst), AstraZeneca(Inst), BeiGene(Inst), Bristol Myers Squibb(Inst), City of Hope National Medical Center(Inst), Genentech(Inst), Gilead Sciences(Inst), InnoCare Pharma, Incyte, Janssen(Inst), Kite Pharma(Inst), Lilly(Inst), Merck(Inst), MorphoSys(Inst), Novartis(Inst), Nurix(Inst), Pfizer(Inst), Roche(Inst), 2seventy bio(Inst). F.L. reports honoraria from Takeda, AstraZeneca, Bristol Myers Squibb, and Janssen; advisory board membership for Miltenyi, Kyowa kirin, and Bristol Myers Squibb; travel expenses from Roche, Gilead, Abbvie, and Beigene; and research funding from Bristol Myers Squibb and Roche. L.Y. reports advisory board membership and research grants from Abbvie, AstraZeneca, BeOne, Bristol Myers Squibb, Gilead/Kite, Johnson & Johnson, and Roche. C.T. reports honoraria from Takeda,

Incyte, Bayer, Kite, Gilead, Novartis, Bristol Myers Squibb, Abbvie, F. Hoffmann-La Roche Ltd, Amgen, Cellectis, and Janssen; research funding from Hospira and BMS/Celgene; consulting or advisory role for Kite, Amgen, AbbVie, Novartis, Roche, Gilead, Takeda, BMS/Celgene, Incyte, and Cellectis; consultancy for Kite, Amgen, AbbVie, Novartis, Gilead, Cellectis, Roche, and BMS/Celgene; and travel, accommodations, and expenses from Kite Pharma/Gilead, Amgen, AbbVie, Novartis, Gilead, Cellectis, Roche, BMS/Celgene, and Janssen. V.R. is an employee of Pegascy and reports research funding from Astex Pharmaceuticals and GSK; consultancy for Abbvie and Lilly; honoraria from Ipsen, Beigene, Incyte and AstraZeneca; and travel, accommodations, and expenses from Pfizer and AstraZeneca. T.G. reports consulting or advisory role for Gilead Sciences, Takeda, Bristol Myers Squibb, MSD, and Roche; and travel, accommodations, and expenses from Roche, Bristol Myers Squibb, Kyte/Gilead, and Takeda. A.D. reports honoraria from Sanofi, Roche, Janssen-Cilag, BMS, and Pfizer; and travel, accommodations, and expenses from Sanofi. S.G. reports consulting or advisory role for Kite/Gilead, Incyte, AstraZeneca, Abbvie, Roche, Takeda, BMS, Novartis, and Johnson & Johnson; and travel, accommodations, and expenses from Kite/Gilead and AstraZeneca. R.H. reports honoraria from Kite/Gilead, Novartis, Bristol-Myers Squibb/Celgene, Incyte, Janssen, MSD, Takeda, Amgen, Abbvie, and Roche; Board of Directors or advisory committees' membership for Kite/Gilead, Novartis, Bristol-Myers Squibb/Celgene, Tessa Therapeutics, Abbvie and Roche. M.G Da S. reports consulting or advisory role for Janssen-Cilag, Roche, Lilly, and Clinical Care Options; Speakers' Bureau membership for Janssen-Cilag, Abbvie, Gilead Sciences, and Beigene; research funding from AstraZeneca; and travel, accommodations, and expenses from Roche, Abbvie, Janssen-Cilag, Gilead Sciences, Beigene, and Lilly. F.B. reports research funding from Gilead Sciences (Inst); and travel, accommodations, and expenses

Roche, BeOne, Takeda, Abbvie, Kite/Gilead, and Janssen. G.C. reports honoraria, and advisory/consultancy fees from Roche, Bristol-Myers Squibb, Beigen, Novartis, Kite/Gilead, Takeda, AstraZeneca, Abbvie, Janssen, Ownards Therapeutic, and MabQi. A.M.G-S. reports honoraria from Abbvie, AstraZeneca, BeOne, BMS, Gilead/Kite, Ideogen, Incyte, Janssen, Kyowa Kirin, Lilly, Roche, Sobi, and Takeda; consulting or advisory role for Abbvie, AstraZeneca, BeOne, BMS, Genmab, Gilead/Kite, GSK, Ideogen, Incyte, Janssen, Kyowa Kirin, Lilly, Miltenyi, Regeneron, Roche, Sobi, and Takeda; and research support from Gilead/Kite. H.E reports research funding, honoraria, or consulting fees from AbbVie, Genentech, Inc., Kite, Gilead Sciences, Takeda, Acerta, AstraZeneca, BeiGene and Juno. M.C reports research funding from Innate Pharma, Johnson & Johnson, Bristol Myers Squibb, Griffols, and LFB; consulting or advisory role for CSL Behring, Johnson & Johnson, AstraZeneca, Lilly, Amgen, and AbbVie; and travel, accommodations, and expenses from Pfizer, Griffols, CSL Behring, AstraZeneca, Lilly, Gilead Sciences, and BeOne. A.L.G. reports honoraria from Roche; consulting or advisory role for Roche, Kite/Gilead, Celgene/Bristol Myers Squibb, Incyte, Takeda, Kern Pharma, Pfizer, and Janssen; research funding from Janssen, Roche, and Celgene/Bristol Myers Squibb; and travel, accommodations, and expenses from Roche and Kite/Gilead. P.A. reports honoraria from AbbVie, Gilead, AstraZeneca, Beigene, Lilly, and Johnson & Johnson; consulting or advisory role for Johnson & Johnson, Regeneron, AbbVie, Gilead, Bristol Myers Squibb, Roche, Incyte; and travel, accommodations, and expenses from Roche, AbbVie, Johnson & Johnson, and Lilly. J.A. reports consulting or advisory role for Kite/Gilead, Incyte, AbbVie, Takeda, and Bristol Myers Squibb; and travel, accommodations, and expenses from AbbVie, Roche, and Janssen. C.S. reports honoraria from Roche, Incyte, BeOne, and Janssen; consulting or advisory role for Janssen, Roche, Bristol Myers Squibb, AstraZeneca, and Incyte; and travel, accommodations,

and expenses from Roche and Kite/Gilead. K.I. reports consultancy for Bristol Myers Squibb, Eisai, AbbVie, Kyowa Kirin, Genmab, Zenyaku, Symbio, Nihon Shinyaku, BeOne Medicines, Tanabe Mitsubishi, and Daiichi Sankyo; research funding from AstraZeneca, AbbVie, Incyte, Bristol Myers Squibb, Novartis, Daiichi Sankyo, Chugai, Beigene, Genmab, LOXO Oncology, and Regeneron; and honoraria from AbbVie, Eisai, Bristol Myers Squibb, AstraZeneca, Takeda, Johnson & Johnson Innovative Medicines, Kyowa Kirin, Chugai, MSD, Genmab, Eli Lilly, Symbio, Gilead, Ono Pharmaceuticals, Novartis, Meiji Seika Pharma, Nihon Shinyaku, and Nihon Kayaku. G.C. reports honoraria from AbbVie, Bristol Myers Squibb, Kite/Gilead, Roche, and Incyte; and consulting or advisory role for Roche, Kite/Gilead, Bristol Myers Squibb, and Johnson & Johnson. L.H.S. reports honoraria from Amgen, AbbVie, BMS, Kite/Gilead Sciences, JanssenOrtho, Merck, Roche/Genentech, AstraZeneca, Incyte, and Genmab; consulting or advisory role for Amgen, AbbVie, BMS, Kite/Gilead Sciences, JanssenOrtho, Merck, Roche/Genentech, AstraZeneca, Incyte, and Genmab; and research funding from Roche/Genentech (Inst). A.G. and M.L.Y are employees of Bristol Myers Squibb. L.C. is an employee of LYSARC. N.F. is an employee of BostonGene and reports consulting or advisory role for Roche/Genentech, TG Therapeutics, Bayer, Novartis, and Bristol Myers Squibb/Pfizer; and research funding from Roche, Celgene, Gilead Sciences, TG Therapeutics, Novartis, AbbVie, and BeiGene. G.S. reports consulting or advisory role for AbbVie, BeOne, Bristol Myers Squibb, Canopy, Daiichi Sankyo, Ellipses Genentech/Roche, Genmab, Incyte, Janssen, Ipsen, Kite/Gilead, Lilly, Merck, and Novartis; and research funding from AbbVie, Genentech, Genmab Janssen, and Ipsen, managed by his institution. F.M. reports honoraria from Roche/Genentech, Chugai/Roche, and Eisai; consulting or advisory role for Roche/Genentech, Gilead Sciences, Celgene, Bristol Myers Squibb, AbbVie, Epizyme, Servier, AstraZeneca,

Novartis, and Genmab; and expert testimony for Roche/Genentech. N.G., N.M., N.B., L.F., J.B., and L.X. report no conflict of interest for this study.

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FIGURES

Figure 1. Progression-free survival as assessed by Independent Review Committee (A), overall survival (B) and time-to-next lymphoma treatment (C)

CL, confidence limit; EMA, European Medicines Agency; P, P-value.

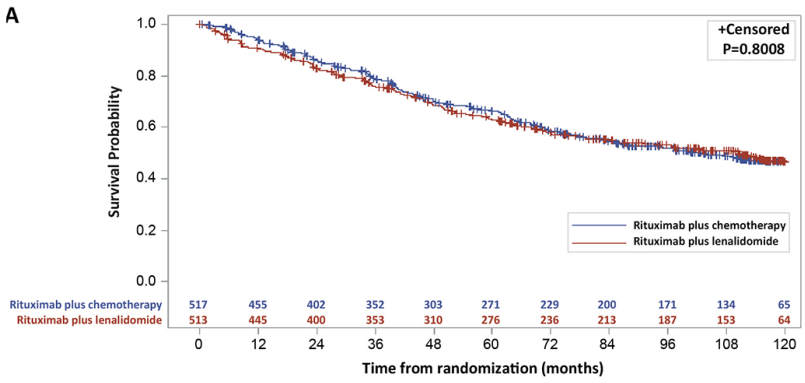
Figure 2. Progression free survival according to baseline characteristics - Prognostic factors assessment

CI, confidence interval; FLIPI, Follicular Lymphoma International Prognostic Index; HR, hazard ratio; LoDLIN, diameter of the largest lymph node.

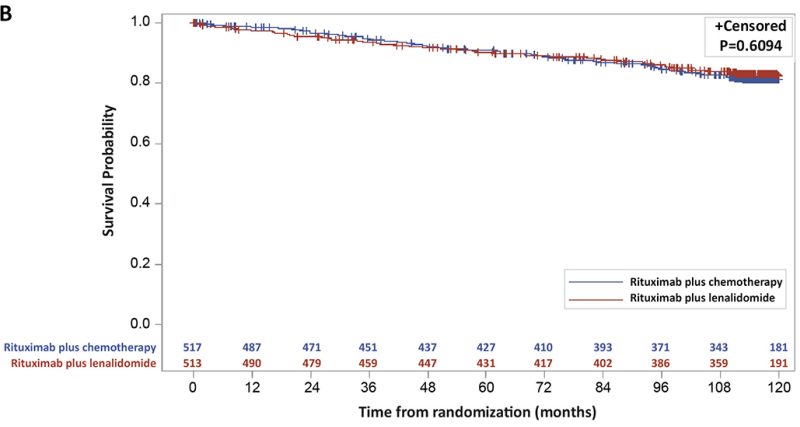
Figure 3. Subgroup analysis of progression free survival according to FLIPI 3 to 5 assessed by IRC (A) and investigator (B) and overall survival (Landmark approach) according to POD24 presence versus absence (C) and according to treatment group in POD24 patients (D)

CL, confidence limit; FLIPI, Follicular Lymphoma International Prognostic Index; P, P-value

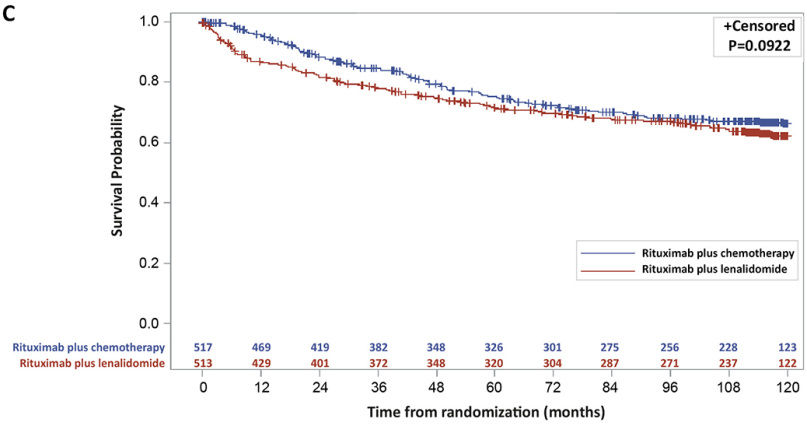
Figure 1



	No. of Patients	Event	Censored	Median Survival (95% CL)
Rituximab plus chemotherapy	517	43.5% (225)	56.5% (292)	102.8 (82.8 ; not reached)
Rituximab plus lenalidomide	513	45.6% (234)	54.4% (279)	110.6 (84.4 ; not reached)

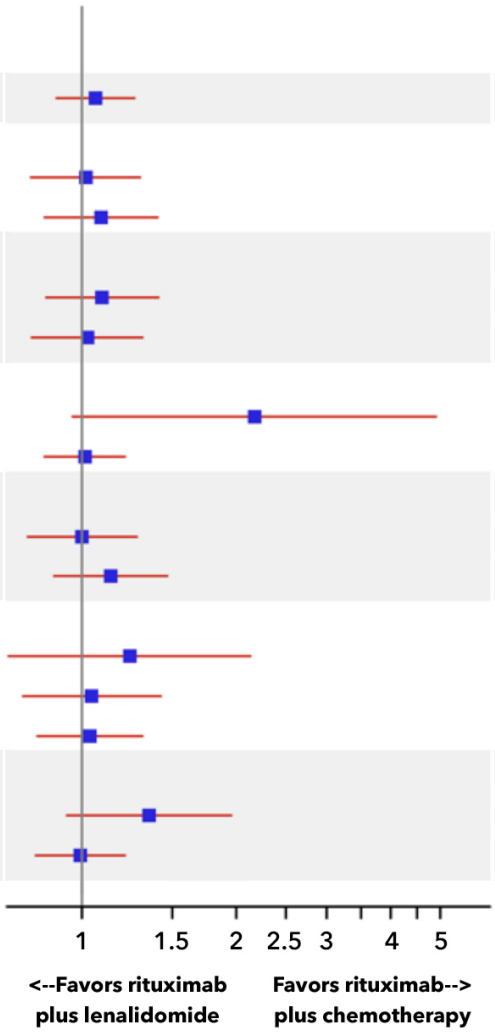


	No. of Patients	Event	Censored	Median Survival (95% CL)
Rituximab plus chemotherapy	517	16.8% (87)	83.2% (430)	Not reached
Rituximab plus lenalidomide	513	16% (82)	84% (431)	Not reached



	No. of Patients	Event	Censored	Median Survival (95% CL)
Rituximab plus chemotherapy	517	29% (150)	71% (367)	Not reached
Rituximab plus lenalidomide	513	34.3% (176)	65.7% (337)	Not reached

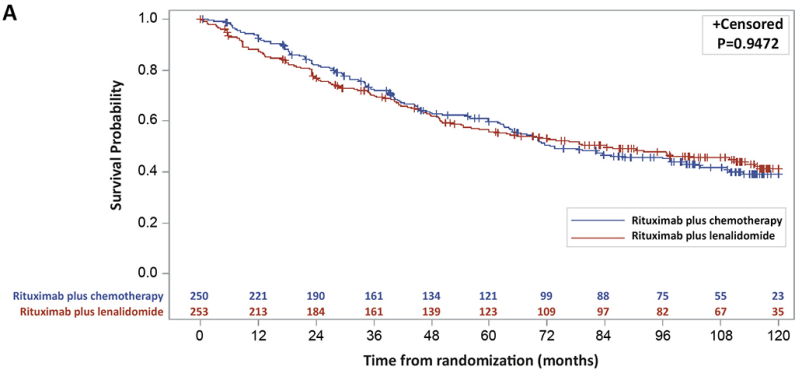
Figure 2



Subgroup	Overall			Rituximab plus lenalidomide			Rituximab plus chemotherapy		
	N	HR	95% CI	N	Events	10y-PFS	N	Events	10y-PFS
Overall	1,030	1.06	[0.89;1.27]	513	246	46.4	517	230	46.6
Sex									
Male	502	1.01	[0.79;1.3]	251	130	42.2	251	116	43.7
Female	528	1.09	[0.84;1.41]	262	116	50.6	266	114	49.3
Age									
≤60	563	1.09	[0.85;1.41]	281	123	47.9	282	111	53.3
>60	467	1.02	[0.79;1.32]	232	123	44.6	235	119	38.8
Disease stage									
1-2	70	2.17	[0.95;4.92]	30	14	46.8	40	10	72.7
3-4	960	1.01	[0.84;1.22]	483	232	46.4	477	220	44.3
LoDLIN									
≤6cm	525	1.00	[0.78;1.29]	253	120	47.9	272	125	44.2
>6cm	505	1.14	[0.88;1.47]	260	126	44.7	245	105	49.2
FLIPI									
0-1	153	1.24	[0.71;2.14]	77	29	55.9	76	24	64.0
2	374	1.04	[0.76;1.43]	183	79	48.9	191	77	49.8
3-5	501	1.03	[0.81;1.31]	251	137	41.6	250	129	39.1
Country									
North America	267	1.35	[0.93;1.97]	129	60	35.6	138	51	46.6
Other than North America	763	0.99	[0.81;1.22]	384	186	48.9	379	179	46.3

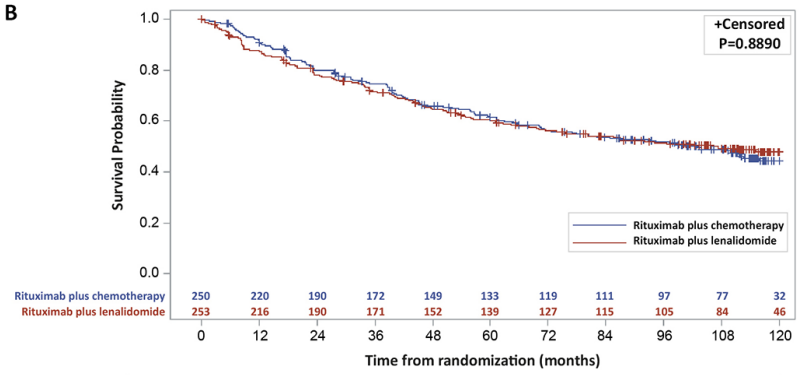
Figure 3

A



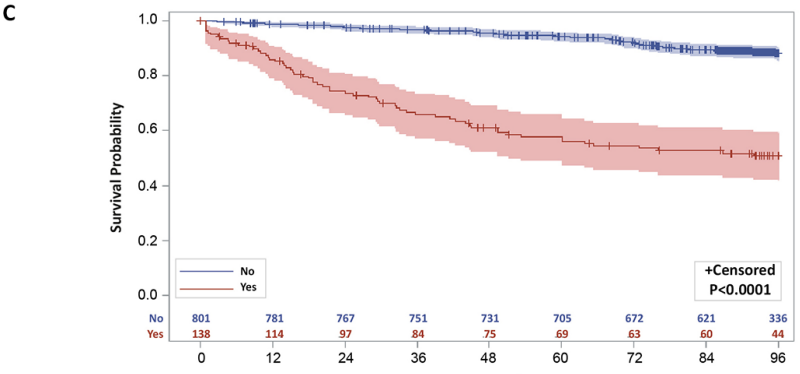
	No. of Patients	Event	Censored	Median Survival (95% CL)
Rituximab plus chemotherapy	250	51.2% (128)	48.8% (122)	72.6 (64.2 ; 100.7)
Rituximab plus lenalidomide	253	51% (129)	49% (124)	84.4 (59.9 ; 113.1)

B



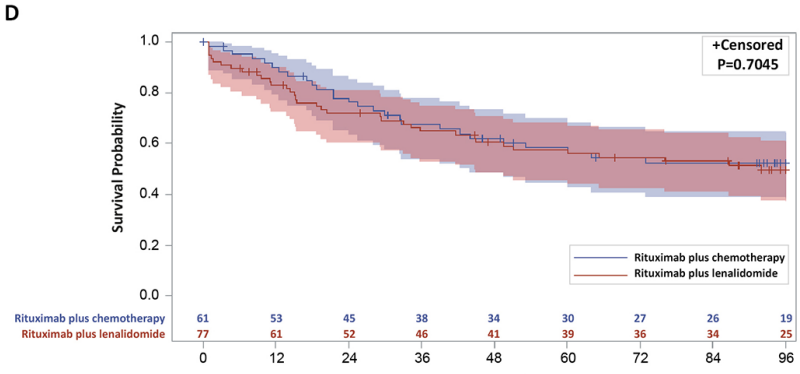
	No. of Patients	Event	Censored	Median Survival (95% CL)
Rituximab plus chemotherapy	250	48.8% (122)	51.2% (128)	102.7 (71.3 ; not reached)
Rituximab plus lenalidomide	253	48.2% (122)	51.8% (131)	105.7 (71.5 ; not reached)

C



	No. of Patients	Event	Censored	Median Survival (95% CL)
No	801	10.9% (87)	89.1% (714)	Not reached
Yes	138	45.7% (63)	54.3% (75)	Not reached (51.2 ; not reached)

D



	No. of Patients	Event	Censored	Median Survival (95% CL)
Rituximab plus chemotherapy	61	44.3% (27)	55.7% (34)	Not reached (44 ; not reached)
Rituximab plus lenalidomide	77	46.8% (36)	53.2% (41)	91.9 (44.7 ; not reached)