Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Morschhauser F, Fowler NH, Feugier P, et al. Rituximab plus lenalidomide in advanced untreated follicular lymphoma. N Engl J Med 2018;379:934-47. DOI: 10.1056/NEJMoa1805104

Supplementary Appendix

Supplement to: Morschhauser F, Fowler NH et al. Rituximab plus either lenalidomide or chemotherapy in follicular lymphoma

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Supplementary Methods

Patients

Patients were required to have histologically confirmed CD20+ follicular lymphoma (FL) grade 1-3a, with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 2, stage II-IV disease, bidimensionally measurable disease with at least one lesion > 2 cm not previously irradiated, requiring treatment, and having no prior systemic treatment for lymphoma. Patients were required to be in need of treatment according to Groupe d'Etude des Lymphomes Folliculaires (GELF) criteria as evidenced by at least one of the following: bulky disease defined as: a nodal or extranodal (except spleen) mass > 7 cm in its greater diameter or involvement of at least 3 nodal or extranodal sites (each with a diameter greater than > 3 cm); presence of at least one of the following B symptoms: fever (> 38 degrees Celsius) of unclear etiology, night sweats, weight loss greater than 10% within the prior 6 months; symptomatic splenomegaly; compression syndrome (ureteral, orbital, gastrointestinal); any one of the following cytopenias due to lymphoma: hemoglobin < 10 g/dL (6.25 mmol/L), platelets < 100 x 10^9/L , or absolute neutrophil count < 1.5 x 10^9/L; pleural or peritoneal serous effusion (irrespective of cell content); and/or lactate dehydrogenase or β2 microglobulin greater than the upper limit or normal.

Exclusion criteria included evidence of grade 3b FL or transformed lymphoma; corticosteroid use ≤4 weeks prior to enrollment, unless at a dose equivalent to <10 mg/day of prednisone; seropositivity for or active viral infection of hepatitis B or C virus, or human immunodeficiency virus; life expectancy < 6 months; prior history of malignancies, other than FL, unless disease free for ≥10 years; prior use of lenalidomide; neuropathy grade >1; presence or history of central nervous system involvement of lymphoma; high risk for a thromboembolic

event and unwilling to take venous thromboembolic prophylaxis; serum aspartate transaminase or alanine transaminase >3 times upper limit of normal, except in patients with documented liver involvement of lymphoma; total bilirubin >2.0 mg/dL except in cases of Gilbert's syndrome and documented liver or pancreatic involvement of lymphoma; creatinine clearance <30 mL/min; and pregnant or lactating females.

Study Design

Patients were stratified by FLIPI score (0-1 vs 2 vs 3-5), age (>60 vs ≤60 years), and lesion size (>6 vs ≤ 6 cm) and randomized 1:1 to rituximab plus lenalidomide or rituximab plus chemotherapy. A Follicular Lymphoma International Prognostic Index (FLIPI) score indicates low (0-1), intermediate (2), and high (3-5) risk groups based on a scoring system giving 1 point for each of the following risk factors: hemoglobin < 12 g/L, > 4 nodal areas (with the exception of spleen), > 60 years of age, > normal lactate dehydrogenase levels, and Ann Arbor stage III/IV disease.[1] When these prognostic factors were originally defined from 1795 patients with follicular lymphoma, the low-, intermediate-, and high-risk groups were comprised of 36%, 37%, and 27% of patients, respectively, with respective 10-year overall survival rates of 71%, 51%, and 36%.[1]

Patients randomized to the R-chemo group received investigator's choice of one of three possible combination regimens: R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone), R-B (rituximab and bendamustine), or R-CVP (rituximab, cyclophosphamide, vincristine, and prednisone). R-CHOP (rituximab 375 mg/m^2 intravenous [IV] day 1, cyclophosphamide 750 mg/m^2 IV day 1, doxorubicin 50 mg/m^2 IV day 1, vincristine 1.4 mg/m^2 IV day 1, and prednisone 100 mg/day oral [PO] days 1-5) included six 21-day cycles

followed by two 21-day cycles of rituximab 375 mg/m^2, and 7 weeks later, responding patients continued with rituximab 375 mg/m^2 every 8 weeks for 12 cycles. R-B (rituximab 375 mg/m^2 IV day 1, bendamustine 90 mg/m^2 IV day 1-2) was given for six 28-day cycles; and 8 weeks later, responding patients continued with rituximab 375 mg/m^2 every 8 weeks for 12 cycles. R-CVP (rituximab 375 mg/m^2 IV day 1, cyclophosphamide 750 mg/m^2 IV day 1, vincristine 1.4 mg/m^2 IV day 1, prednisone 40 mg/day PO days 1–5) was given for eight 21-day cycles; and 7 weeks later, responding patients continued with rituximab 375 mg/m^2 every 8 weeks for 12 cycles. The total treatment duration was 120 weeks for both study arms.

For patients receiving lenalidomide and who were at high risk for a thromboembolic event, prophylaxis with aspirin (70–325 mg/day), low molecular weight heparin, or warfarin was recommended. Patients in the lenalidomide arm received prophylaxis for tumor lysis syndrome, including allopurinol, rasburicase, or equivalent (per institutional guidelines) and were to be well-hydrated during the first week of treatment. In both arms, growth factor use was not administered prophylactically (except in high-risk patients) and should be used in accordance with ASCO/ESMO guidelines.[22,23]

For the co-primary endpoint of CR/CRu rate at 120 weeks, two interim analyses for futility were pre-planned. In the first interim futility analysis, the futility boundary to establish superiority was crossed, no safety issues clearly seen, and the DMC initially recommended stopping the study as per their charter. At this time, all patients had been enrolled in the study, and the majority had completed induction. Due to the lack of a significant safety signal between arms, a discussion occurred between the Joint Data Review Board (JDRB) and the DMC, and it was blinded to the investigators and study teams, and the DMC agreed to continue the study.

The DMC reinforced the monitoring of events until the second interim futility analysis, when they recommended continuation of the study. The co-primary endpoint PFS was analyzed as an interim superiority analysis in the current analysis presented in the manuscript.

Response was assessed by 1999 IWG criteria (which included computed tomography [CT] scans) with the following schedule: 12 weeks after the first dose (-1 week/+2 weeks), 24 weeks after the first dose (-1 week/+4 weeks), 36 weeks after the first dose (-1 week/+2 weeks), 52 weeks after the first dose (-1 week/+2 weeks), 76 weeks after the first dose (-1 week/+3 weeks), 100 weeks after the first dose (-1 week/+3 weeks), 120 weeks after the first dose (-1 week/+4 weeks), and then every 6 months (± 4 weeks) for 5 years and then every year (± 4 weeks) until disease progression or relapse. CT scans were required at the above timepoints; FDG-PET scans could be submitted as an addition, but not in lieu of, CT scans at 24, 76, and 120 weeks. To confirm CR/CRu, patients with positive bone marrow at screening were required to have a post-screening bone marrow biopsy to confirm CR/CRu within 28 days of first achieving radiological, clinical, and biochemical CR/CRu. Patients with negative bone marrow biopsy at screening or those not in CR/CRu did not require further bone marrow biopsy.

Hematology laboratory evaluations (red blood cell count, hemoglobin, hematocrit, white blood cell count and differential, absolute neutrophil count, and platelet count) within 48 hours of day 1 of every treatment cycle. Hematology laboratory evaluations for cycle 1, day 8 and 15 and cycle 2-4, day 15 hematology labs were required only for patients in the R^2 arm and suggested for patients in the R-chemo arm to monitor for cytopenias; evaluations for cycles 5-6, day 15 were required for all patients.

Lenalidomide Dose Modifications

Lenalidomide dose modifications were allowed at 5-mg increments. If a dose-limiting toxicity (DLT) occurred on or after day 15 of a cycle, treatment was held until the end of the cycle and the dose was reduced in the subsequent cycle. If a DLT occurred before day 15 of a cycle, treatment was held until recovery and restarted without dose reduction for the remainder of the cycle and reduced in subsequent cycles. If lenalidomide dosing was interrupted for toxicity or cycle delayed, it could be restarted only if the absolute neutrophil count (ANC) was ≥ 1,000 cells/mm^3, the platelet count was ≥ 50,000 cells/mm^3, lenalidomide related allergic reaction or hypersensitivity not requiring discontinuation resolved to ≤ grade 1, or any other lenalidomide-related adverse event (AE) not requiring discontinuation had resolved to grade ≤2 (except where noted below). In the instance of grade ≥3 neutropenia (grade 3 lasting ≥7 days or associated with fever, any grade 4), lenalidomide was held, complete blood counts (CBCs) were monitored every 7 days, and growth factor use was permitted. Lenalidomide was also held in the instance of grade ≥3 thrombocytopenia (complete blood counts were monitored); grade 2 allergic reaction or hypersensitivity; grade ≥3 constipation; grade ≥3 venous thrombosis/embolism (anticoagulation was started, dose restarted at original level at investigators discretion); newly developed grade ≥3 peripheral neuropathy (restarted if resolved to grade ≤1); grade ≥3 tumor flare reaction (non-steroidal anti-inflammatory drugs, corticosteroids, and/or narcotics were initiated; restarted if resolved to grade ≤1); grade ≥2 tumor lysis syndrome (restarted if resolved to grade 0); and grade 3 non-desquamating rash (restarted if resolved to grade ≤1). If patients had symptoms of hyperthyroid and thyroid-simulating hormones were less than the lower limit of normal, lenalidomide was held and

restarted at the same dose if endocrine evaluation ruled out hyperthyroidism or restarted at the next lower dose if hyperthyroidism was confirmed and alternative etiologies were eliminated. For liver function tests, lenalidomide was interrupted if alanine transaminase was grade ≥3 and resumed at original doses if levels returned to baseline within 14 days or at a decreased dose if recovery was beyond 14 days. Lenalidomide was permanently discontinued in the instance of grade ≥3 allergic reaction, grade 4 rash, or any grade desquamating rash.

Dose modifications of chemotherapy were allowed in accordance with the clinical practice of the investigator's institution and in line with the approved prescribing information of each agent. There were no dose adjustments for rituximab. In case of delay due to lenalidomide-induced toxicity, rituximab was also postponed until the dose-limiting toxicity had resolved and lenalidomide was restarted.

Statistical Analysis

There are three planned analyses for PFS. To control the overall type I error for PFS, an alpha spending function of gamma family with parameter –2.5 was applied. It was estimated that approximately 228 PFS events (i.e., 0.50 information) would occur at the first interim PFS analysis, and 342 PFS events (i.e., 0.75 information) were required at the second interim PFS analysis. The final PFS analysis will be performed based on a total of 456 PFS events. A statistically significant treatment effect on PFS will be reached if the two-sided P value is ≤0.011 at the first interim PFS analysis, ≤0.019 at the second interim PFS analysis, or ≤0.039 at the final PFS analysis.

All statistical analyses were performed using SAS software version 9.2 or higher (SAS Institute, Cary, NC) and AdClin software version 3.2.2 or higher (AdClin S.A., Paris, France). The

power calculation for the response rates was performed using EAST v5.4 software based on the large sample z-test with unspooled variance estimate. It was hypothesized that the median PFS would be 83 months in the R-chemo group, with a 30% increase in the R^2 group (corresponding hazard ratio of 0.7692). For 80% power to detect this difference with two-sided $\alpha = 0.05$, a total of 456 progression/relapse/death events was required.

Supplementary Results

Dosing

In the R^2 arm, 53 patients started lenalidomide at 10 mg due to creatinine clearance rate of < 60 mL/min, whereas 454 patients started at the 20 mg dose.

Transformations

Among the 17 patients with transformation, a majority had transformations to DLBCL (9/10 in R^2 arm and 7/7 in R-chemo arm), and 1 patient had granulocytic sarcoma (R^2 arm) rather compatible with transdifferentiation (as described by Xerri et al[2]).

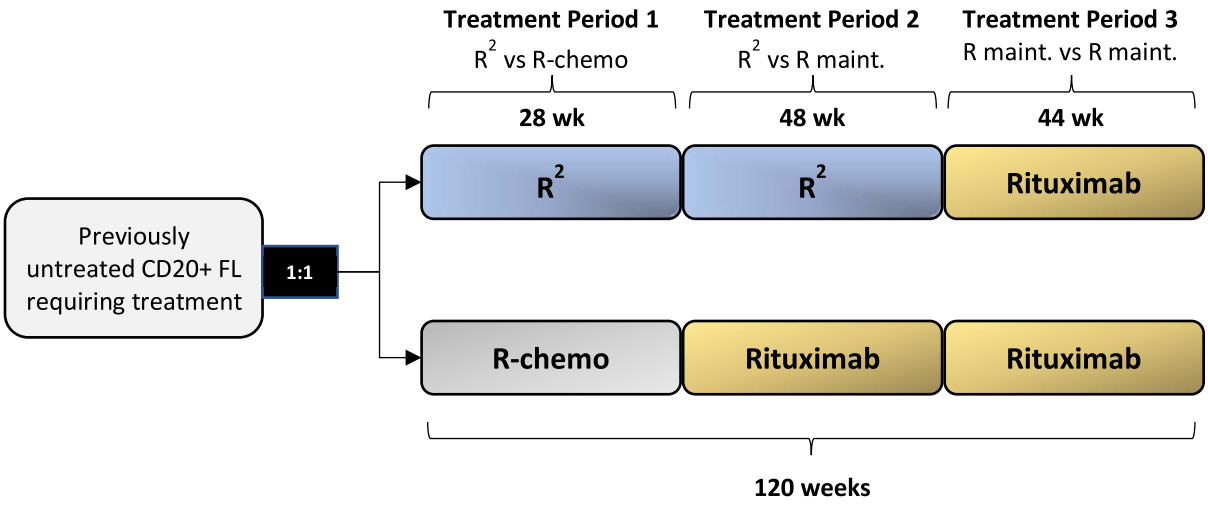
Thromboembolic Events

Venous thromboembolic events occurred in 3% of patients for both arms; arterial thromboembolic events occurred in 2% R^2 versus <1% R-chemo of patients; and mixed thromboembolism occurred in 2% of patients for both arms. 78% of R^2 patients and 28% R-chemo received either anti-coagulant or anti-platelet concomitant medications.

Deaths Related to Study Treatment

One 68-year-old male patient with high-risk FLIPI (FLIPI score=4) and bulky disease (>7 cm) in the R^2 arm died 9 days after randomization of related pulmonary embolism during cycle 1. One 88-year-old male patient with intermediate FLIPI in the R-chemo arm died 70 days after randomization of related septic shock after receiving 2 cycles of R-B induction treatment.

Supplementary Figure S1. RELEVANCE Study Design.



R^2 treatment: six cycles of lenalidomide 20 mg/day on days 2-22 every 28 days (10 mg if creatinine clearance ≥30-<60 ml/min). Patients responding after six cycles with CR/CRu then received 12 cycles of lenalidomide 10 mg/day. Patients exhibiting a partial response (PR) after six cycles received three or six additional cycles of lenalidomide at 20 mg until achieving a CR/CRu. All patients received lenalidomide at 10 mg in remaining cycles for a total of 18 cycles. Rituximab 375 mg/m^2 was given on days 1, 8, 15, and 22 of cycle 1 and day 1 of cycles 2-6; responders continued rituximab every 8 weeks for 12 cycles.

R-chemo treatment regimens were selected based on investigator's choice of one of three possible combination regimens: R-CHOP, R-B, or R-CVP.

R-CHOP: rituximab 375 mg/m^2 IV day 1, cyclophosphamide 750 mg/m^2 IV day 1, doxorubicin 50 mg/m^2 IV day 1, vincristine 1.4 mg/m^2 IV day 1, and prednisone 100 mg/day [PO days 1-5) for six 21-day cycles followed by two 21-day cycles of rituximab 375 mg/m^2, and 7 weeks later, responding patients continued with rituximab 375 mg/m^2 every 8 weeks for 12 cycles

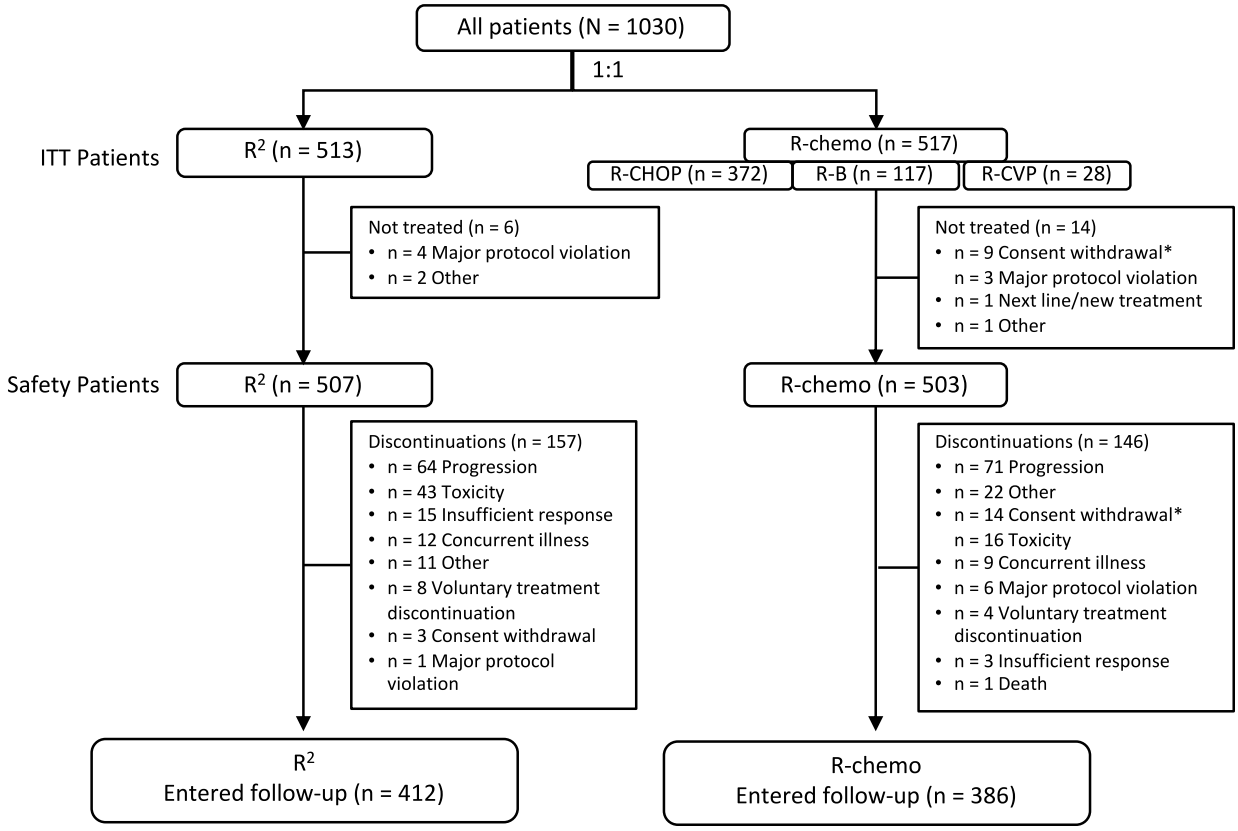
R-B: rituximab 375 mg/m^2 IV day 1 and bendamustine 90 mg/m^2 IV day 1-2 were given for six 28-day cycles; and 8 weeks later, responding patients continued with rituximab 375 mg/m^2 every 8 weeks for 12 cycles

R-CVP: rituximab 375 mg/m^2 IV day 1, cyclophosphamide 750 mg/m^2 IV day 1, vincristine 1.4 mg/m^2 IV day 1, and prednisone 40 mg/day PO days 1–5 were given for eight 21-day cycles; and 7 weeks later, responding patients continued with rituximab 375 mg/m^2 every 8 weeks for 12 cycles

The total treatment duration was 120 weeks for both study arms.

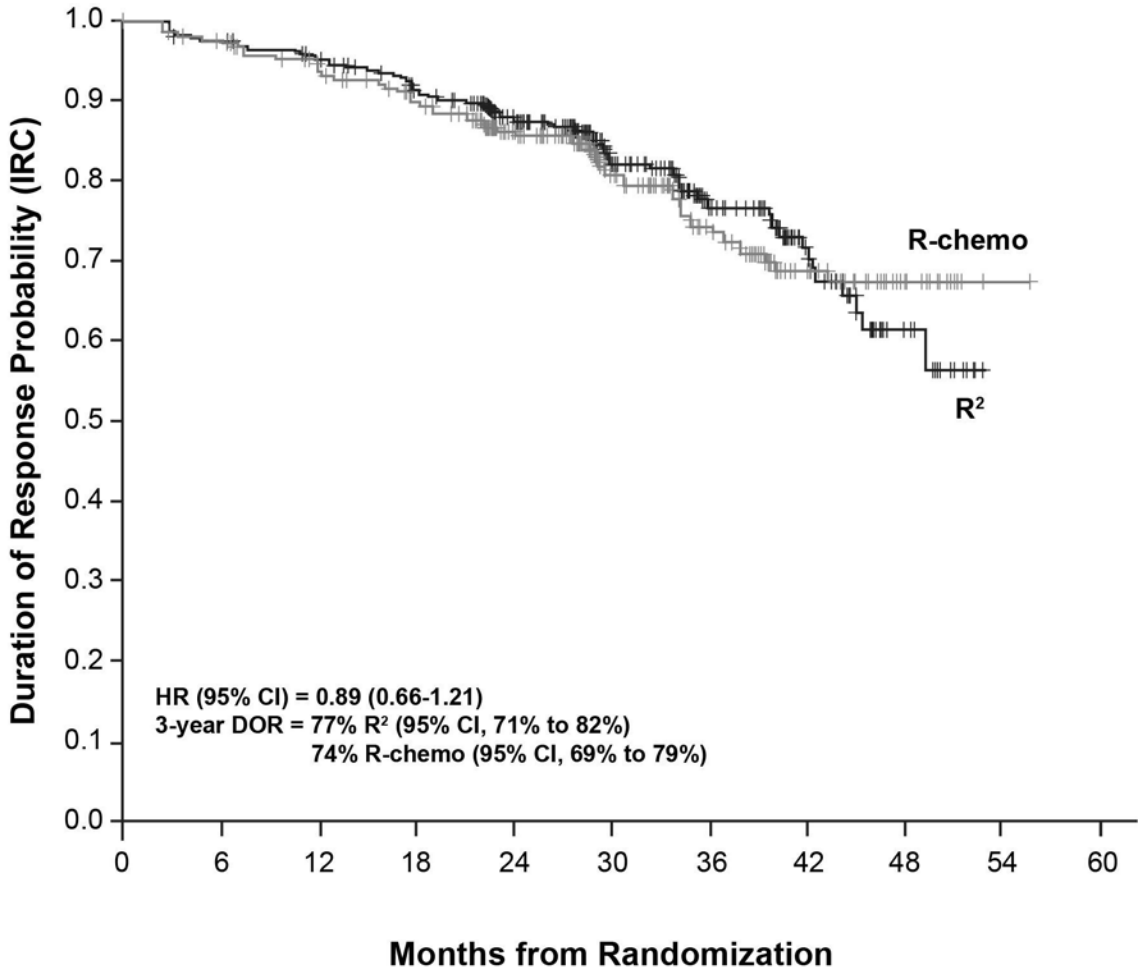
Supplementary Figure S2. CONSORT Diagram.

*Withdrawal of consent during the entire study was unexpectedly over-represented among R-B patients, with 24 of 117 patients (vs. 12 of 400 among R-CHOP/R-CVP patients) who withdrew consent at randomization (n = 5), treatment period 1 (n = 5), treatment periods 2-3 (n = 11), and follow-up (n = 3).



Supplementary Figure S3. Kaplan-Meier Curves of Duration of Response by A. IRC Assessment and B. Investigator Assessment (Intention-to-Treat Population).

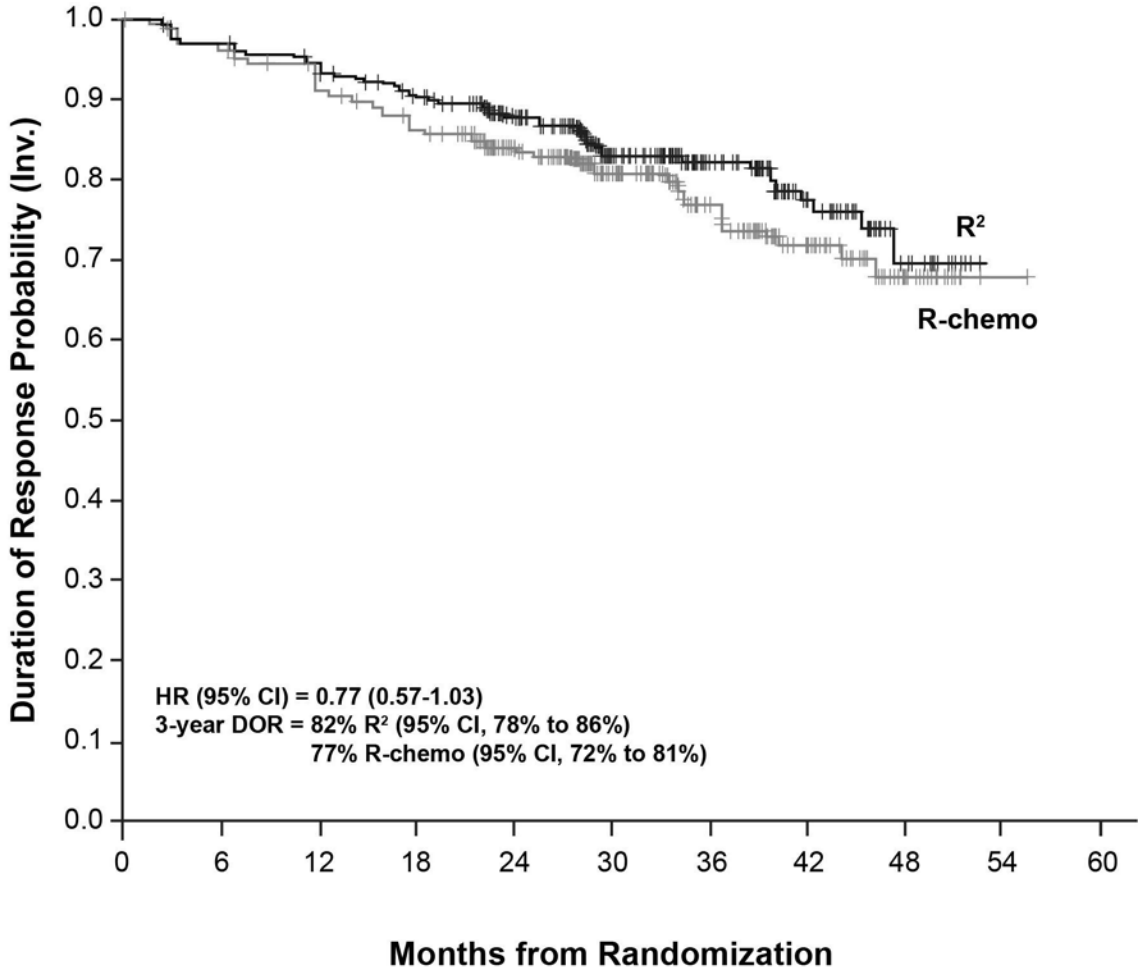
A. By IRC Assessment



Number of Patients at Risk

R²	431	405	389	361	286	177	108	51	14	0	
R-chemo	459	433	407	379	280	169	105	53	15	1	0

B. By Investigator Assessment

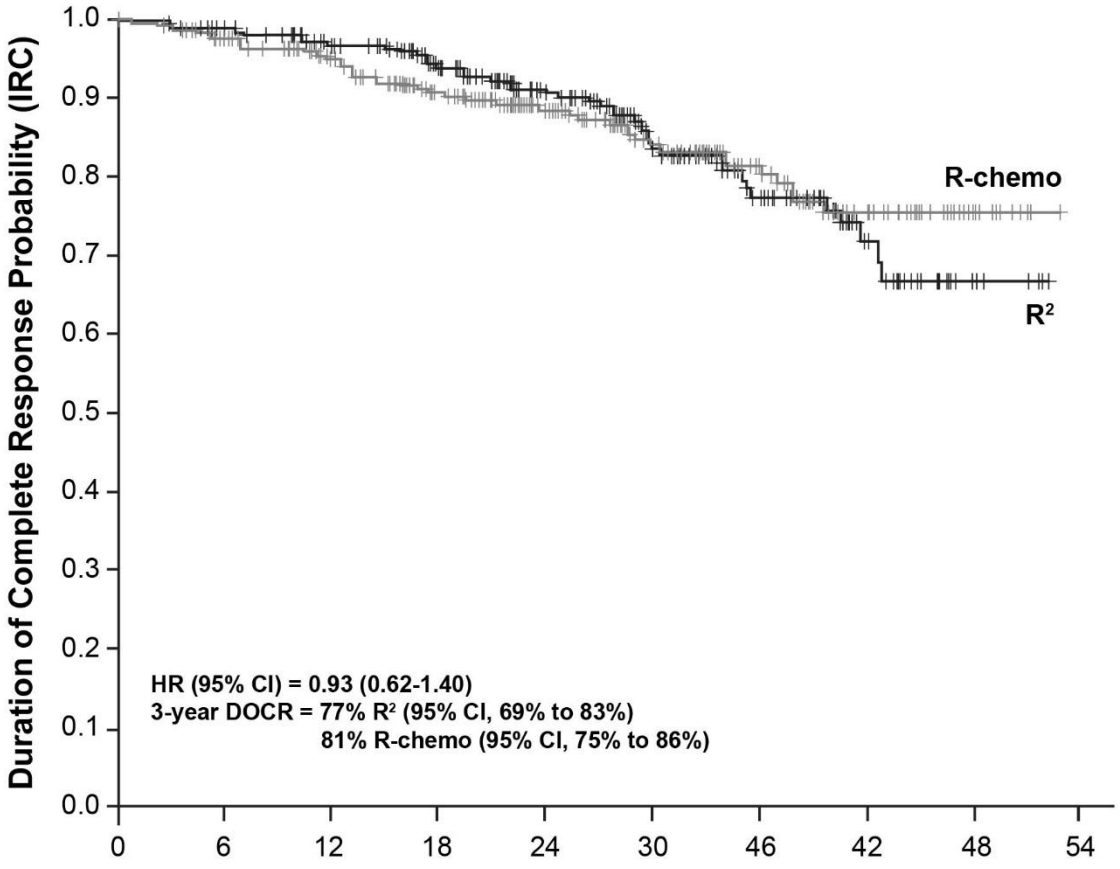


Number of Patients at Risk

R²	443	420	403	382	310	188	114	58	14	0	
R-chemo	475	443	415	389	294	186	119	62	19	1	0

Supplementary Figure S4. Kaplan-Meier Curves of Duration of Complete Response by A. IRC Assessment and B. Investigator Assessment (Intention-to-Treat Population).

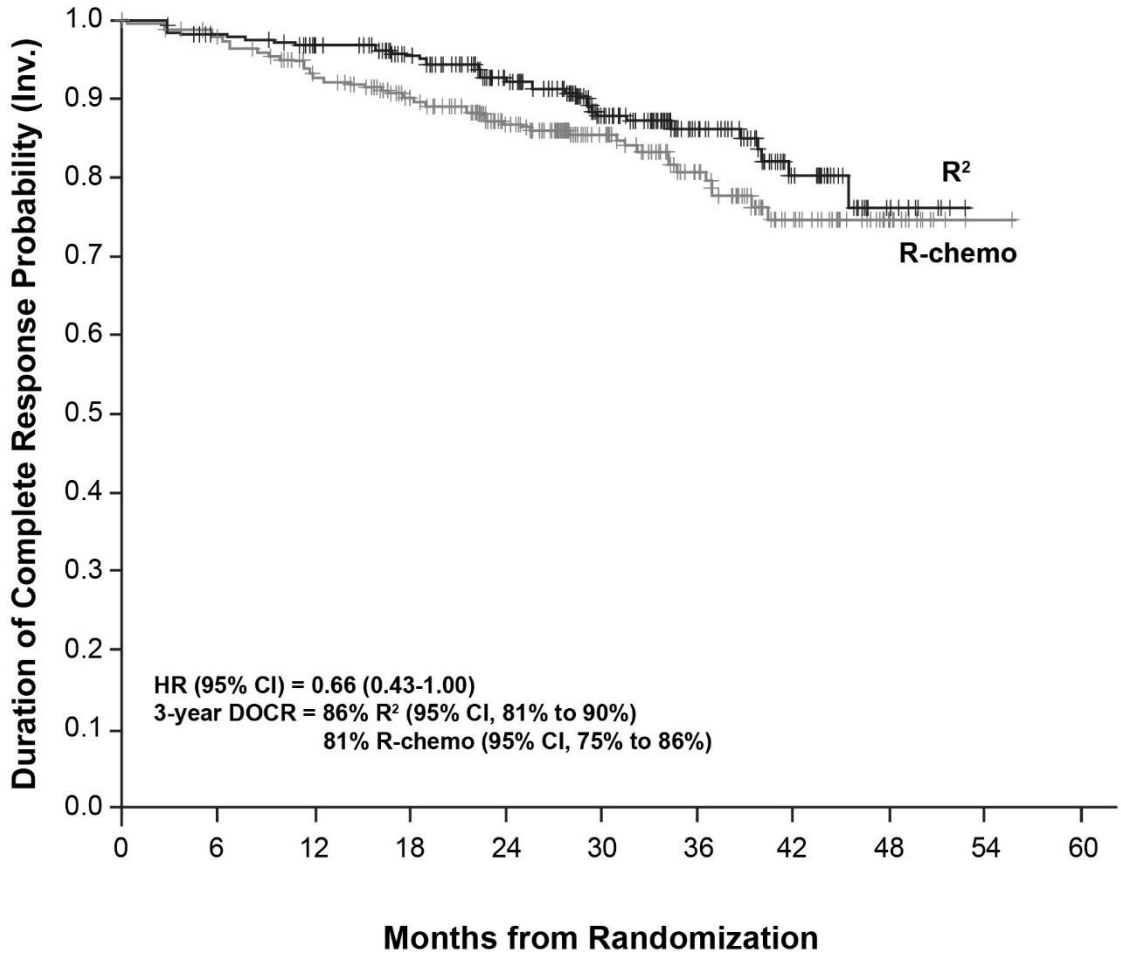
A. By IRC Assessment



Number of Patients at Risk

R²	304	279	252	220	166	105	66	28	6	0
R-chemo	345	315	276	231	171	113	75	38	11	0

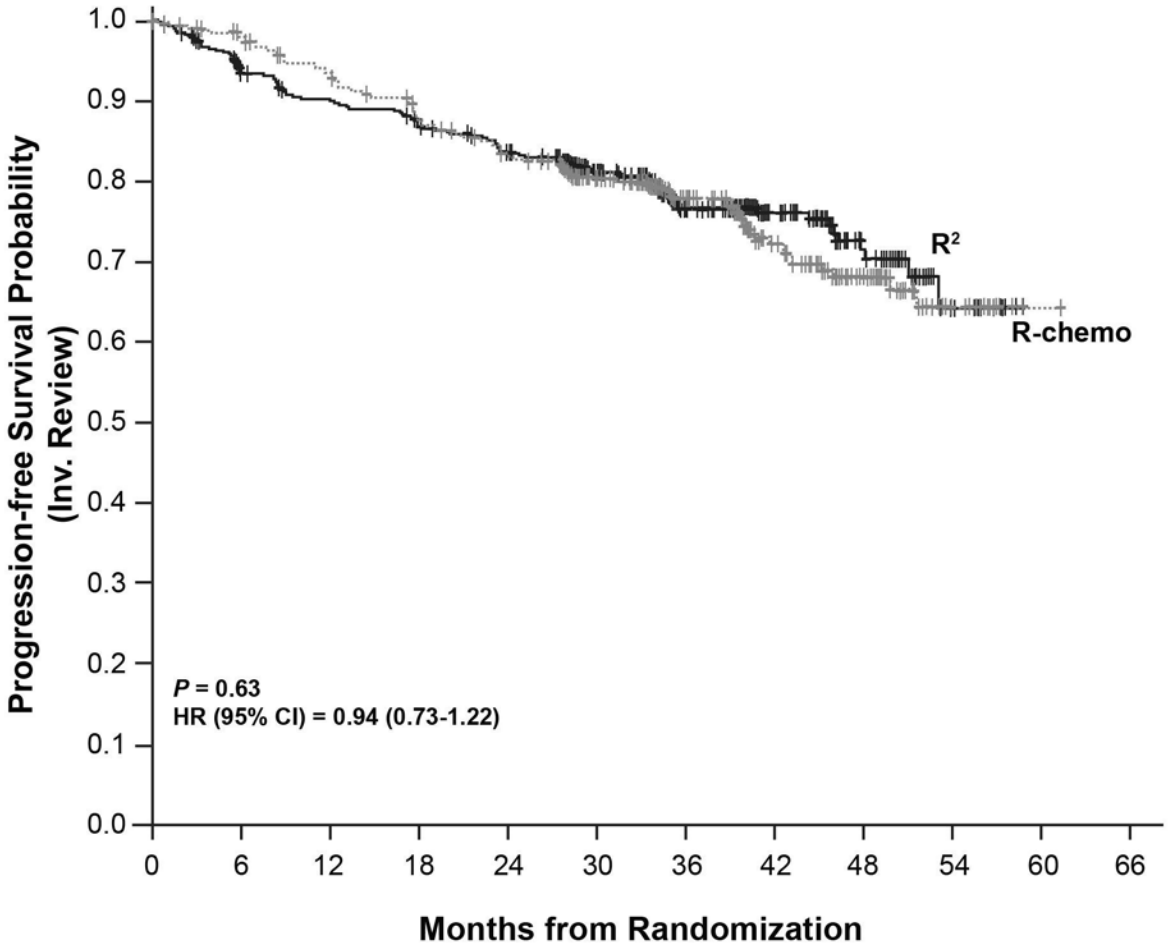
B. By Investigator Assessment



Number of Patients at Risk

R²	331	305	287	261	205	132	82	39	9	0	
R-chemo	363	339	308	279	208	132	80	41	16	1	0

Supplementary Figure S5. Kaplan-Meier Curve of Progression-Free Survival by Investigator Assessment (Intention-to-Treat Population).

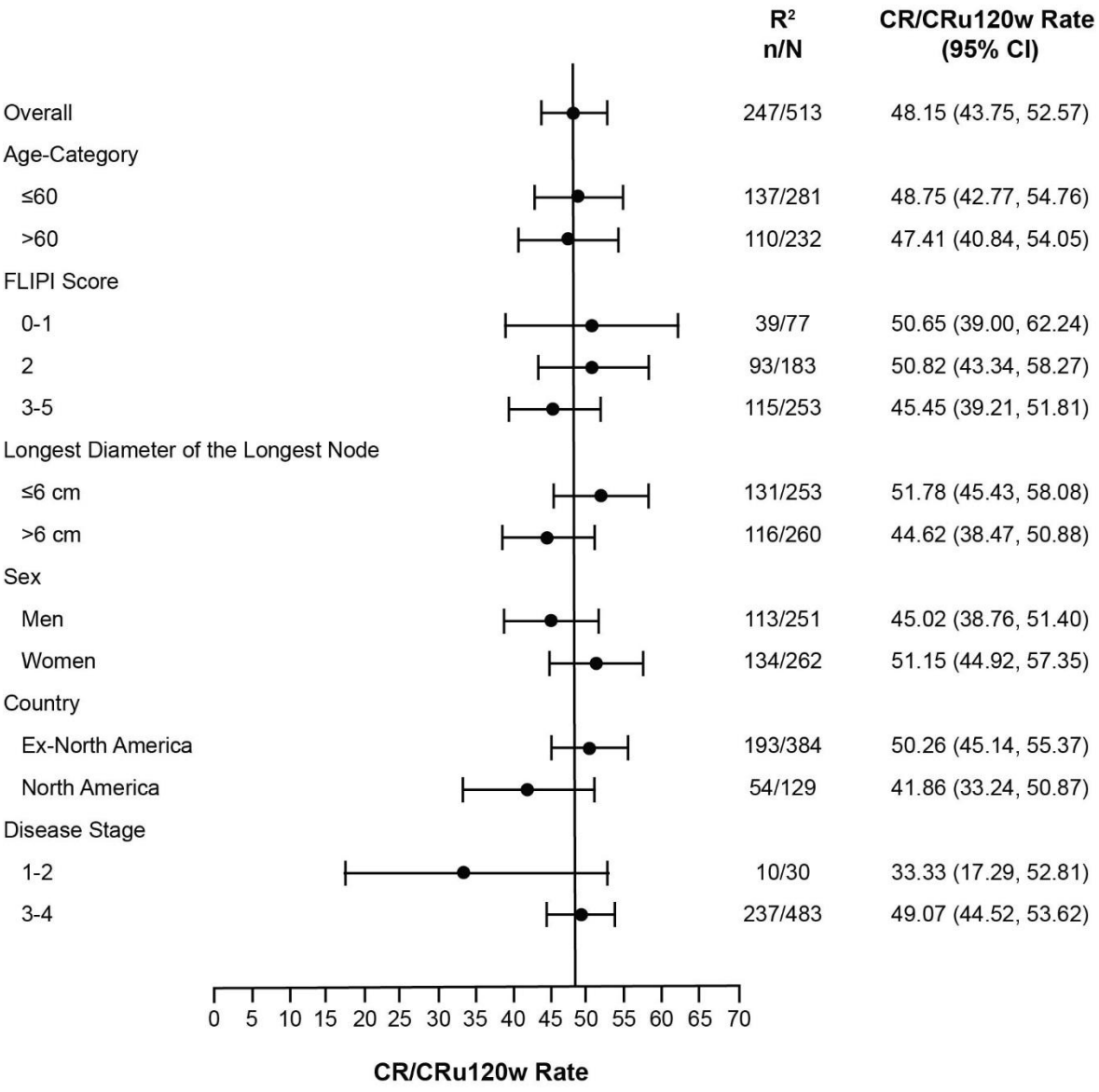


Number of Patients at Risk

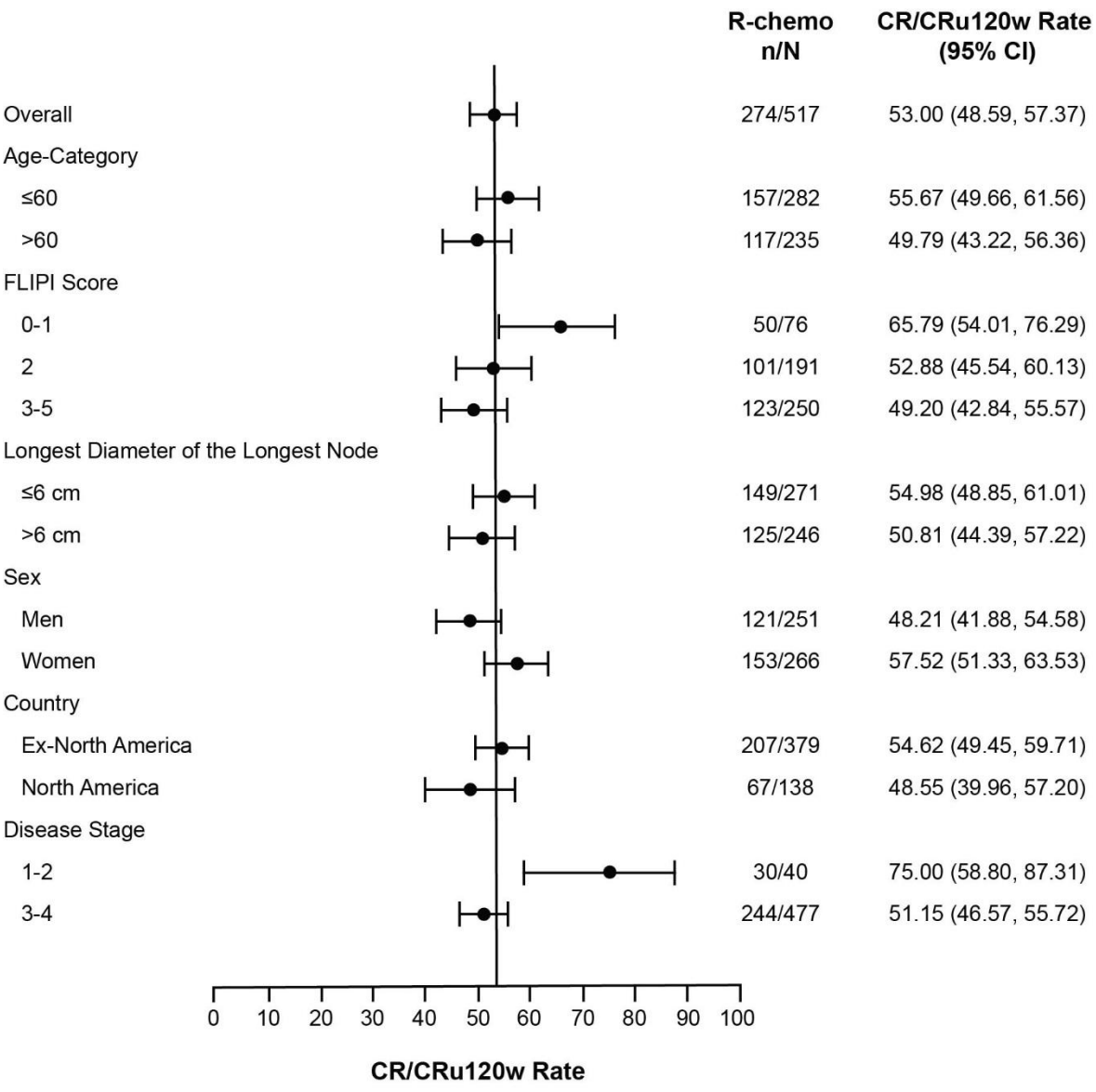
R²	513	443	423	404	385	306	184	114	56	13	0	
R-chemo	517	480	451	418	392	297	188	119	57	15	1	0

Supplementary Figure S6. Forest Plot of CR/CRu120w Within Each Treatment Group at 120 weeks (Intention-to-Treat Population).

A. For the R^2 arm

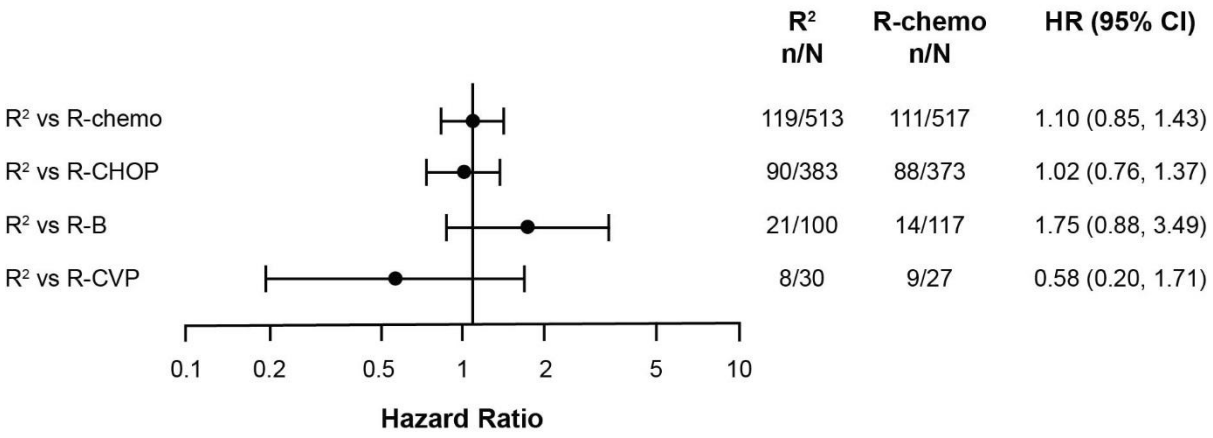


B. For the R-chemo arm

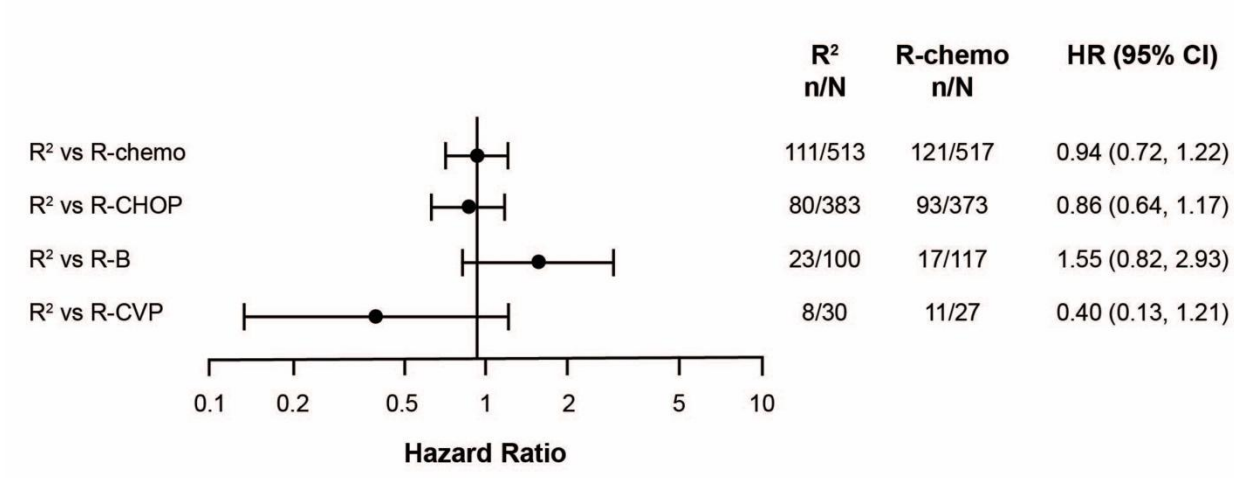


Supplementary Figure S7. Forest Plot of PFS Comparing R^2 With Each R-chemo Regimen by A. IRC Assessment and B. Investigator Assessment (Intention-to-Treat Population). Hazard ratio was calculated from a Cox model as R-Len (R^2) arm vs R-chemo regimen. Subgroup analysis was performed based on the choice of R-chemo regimens prior to randomization. Note: Per protocol, the study was not designed nor powered to compare R^2 with individual R-chemo regimens. The 2 study arms (R^2 vs composite R-chemo) were randomized, but individual chemotherapy regimens were not randomized, and the choice of specific R-chemo regimens was according to the discretion of the investigator's/patient's choice. Per protocol, standard of care chemotherapy regimen must be available by prescription, generally reimbursed by the health system and used routinely to treat previously untreated patients with FL at the study centers. Therefore, comparison with R^2 by chemo regimens is susceptible to bias.

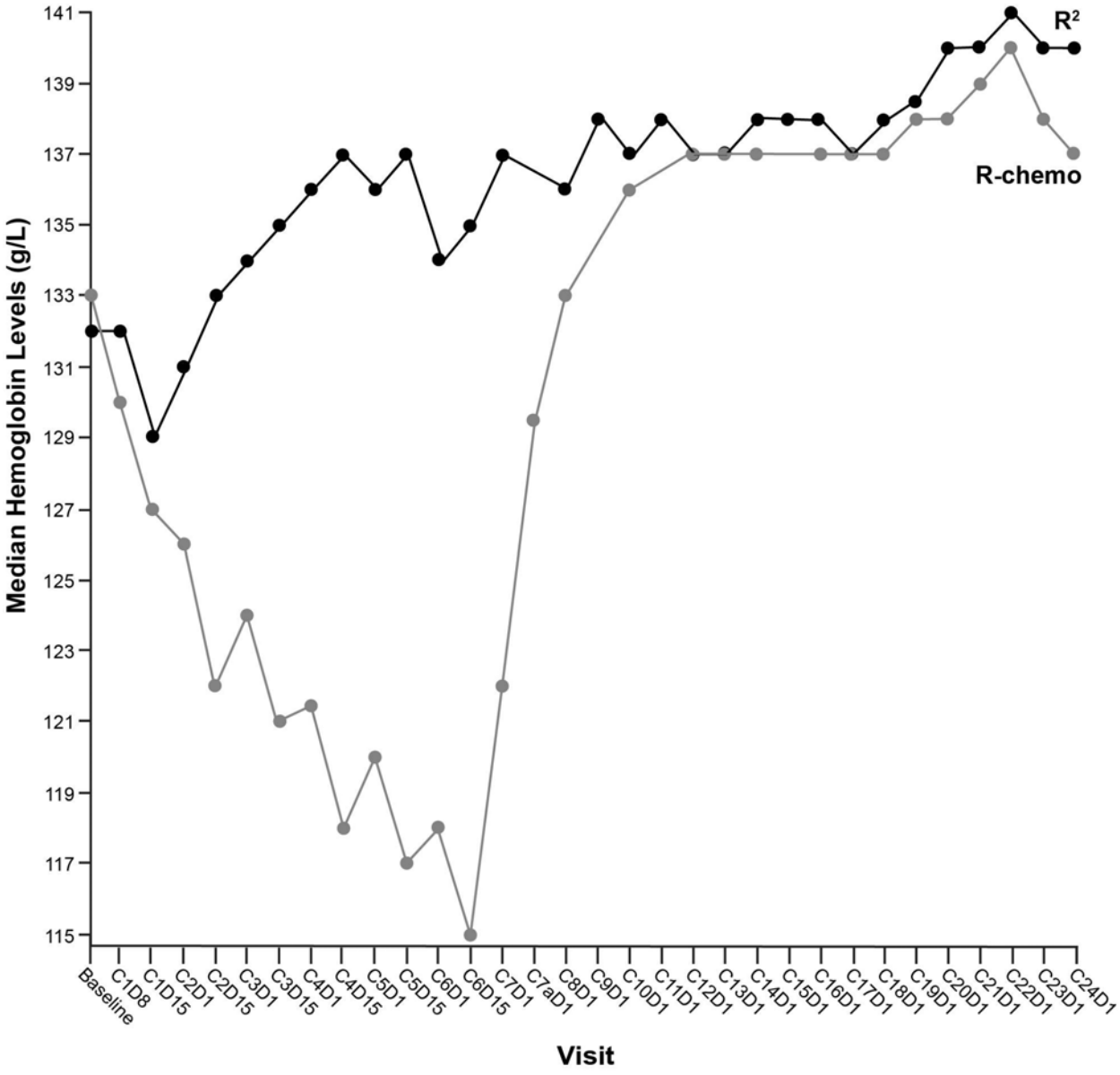
A. By IRC Assessment



B. By Investigator Assessment



Supplementary Figure S8. Median Hemoglobin Levels by Visit and Treatment Arm (Safety Population).



Supplementary Table S2. Baseline Characteristics (ITT Population) Including Each R-chemo Arm.

Characteristic	R[2] (N = 513)	All R-chemo (N = 517)	R-CHOP (N = 372)	R-B (N = 117)	R-CVP (N = 28)	Total (N = 1030)
Age — yr						
Median	59	59	59	57	71	59
Range	30-89	23-83	23-83	30-83	27-83	23-89
> 70 yr of age, no. (%)	80 (16)	78 (15)	50 (13)	14 (12)	14 (50)	158 (15)
Male — no. (%)	251 (49)	251 (49)	170 (46)	67 (57)	14 (50)	502 (49)
ECOG PS — no. (%)*						
0	341 (66)	345 (67)	250 (67)	80 (68)	15 (54)	686 (67)
1	157 (31)	157 (30)	111 (30)	35 (30)	11 (39)	314 (30)
2	13 (3)	14 (3)	11 (3)	1 (1)	2 (7)	27 (3)
NE	2 (<1)	1 (<1)	0	1 (1)	0	3 (<1)
Ann Arbor stage— no. (%)						
I - II	30 (6)	40 (8)	34 (9)	4 (3)	2 (7)	70 (7)
III - IV	483 (94)	477 (92)	338 (91)	113 (97)	26 (93)	960 (93)
Bulky disease (> 7 cm) — no. (%)	218 (42)	199 (38)	157 (42)	33 (28)	9 (32)	417 (40)
Follicular lymphoma grade — no. (%)†						
1-2	437 (85)	443 (86)	314 (84)	104 (89)	25 (89)	880 (85)
3a	65 (13)	63 (12)	50 (13)	11 (9)	2 (7)	128 (12)
Lactate dehydrogenase > ULN – no. (%)	156 (30)	137 (26)	96 (26)	27 (23)	14 (50)	293 (28)
Beta-2 microglobulin > ULN – no. (%)	261 (51)	262 (51)	184 (50)	61 (52)	17 (61)	523 (51)
B-symptoms – no. (%)	141 (28)	134 (26)	89 (24)	35 (30)	10 (36)	275 (27)
FLIPI score — no. (%)‡						
Low risk (0-1)	77 (15)	76 (15)	59 (16)	17 (15)	0	153 (15)
Intermediate risk (2)	183 (36)	191 (37)	134 (36)	47 (40)	10 (36)	374 (36)
High risk (3-5)	253 (49)	250 (48)	179 (48)	53 (45)	18 (64)	503 (49)

ULN, upper limit of normal; FLIPI, Follicular Lymphoma International Prognostic Index.

*An Eastern Cooperative Oncology Group (ECOG) performance-status score of 0 indicates no symptoms and 1 indicates mild symptoms; higher scores indicate greater disability.

†Follicular lymphoma grade was unspecified or not FL grade 1-3a in 11 patients in each arm.

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

Supplementary Table S3. Treatment-Emergent Adverse Events by Treatment Arm and Specific R-chemotherapy Arm (Safety Population).

			R-chemo Arms		
Patients, %	**R^2 (N = 507)**	**R-chemo (N = 503)**	**R-CHOP (N = 365)**	**R-B (N = 112)**	**R-CVP (N =26)**
At least one TEAE	100	99	99	98	100
At least one grade 3/4 TEAE	65	68	73	53	73
At least one grade 5 TEAE	1	1	1	1	0
At least one SAE	35	29	30	29	27
At least one TEAE leading to early discontinuation of study treatment	11	3	3	5	0
At least one TEAE leading to dose reduction	36	14	14	10	31
At least one TEAE leading to dose interruption	59	35	33	41	31

Abbreviations: SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Supplementary Table S4. Treatment-Emergent Adverse Events by Chemotherapy Regimen and Grade in the Safety Population (≥ 10% in Either R^2 or R-chemo and Selected Relevant TEAEs).

					R-chemo Arms					
	R^2 (N = 507)		R-chemo (N = 503)		R-CHOP (N = 365)		R-B (N = 112)		R-CVP (N = 26)	
Adverse Event — no. (%)	**All Grade**	**Grade 3-4**	**All Grade**	**Grade 3-4**	**All Grade**	**Grade 3-4**	**All Grade**	**Grade 3-4**	**All Grade**	**Grade 3-4**
Any event	506 (100)	330 (65)	498 (99)	344 (68)	362 (99)	266 (73)	110 (98)	59 (53)	26 (100)	19 (73)
Neutropenia*	381 (75)	160 (32)	386 (77)	252 (50)	288 (79)	208 (57)	75 (67)	30 (27)	23 (88)	14 (54)
Anemia*	333 (66)	0	446 (89)	0	341 (93)	0	82 (73)	0	23 (88)	0
Thrombocytopenia*	268 (53)	11 (2)	266 (53)	8 (2)	192 (53)	7 (2)	69 (62)	1 (1)	5 (19)	0
Cutaneous reactions†	220 (43)	36 (7)	120 (24)	5 (1)	83 (23)	4 (1)	34 (30)	1 (1)	3 (12)	0
Diarrhea	187 (37)	10 (2)	95 (19)	6 (1)	52 (14)	4 (1)	37 (33)	1 (1)	6 (23)	1 (4)
Constipation	178 (35)	1 (<1)	167 (33)	5 (1)	111 (30)	5 (1)	43 (38)	0	13 (50)	0
Rash	146 (29)	20 (4)	39 (8)	1 (<1)	21 (6)	0	17 (15)	1 (1)	1 (4)	0
Asthenia	145 (29)	4 (<1)	140 (28)	4 (<1)	129 (35)	4 (1)	5 (4)	0	6 (23)	0
Fatigue	115 (23)	1 (<1)	147 (29)	4 (<1)	67 (18)	2 (<1)	74 (66)	2 (2)	6 (23)	0
Cough	103 (20)	0	69 (14)	1 (<1)	44 (12)	1 (<1)	21 (19)	0	4 (15)	0
Nausea	100 (20)	0	209 (42)	8 (2)	130 (36)	5 (1)	72 (64)	2 (2)	7 (27)	1 (4)
Pyrexia	97 (19)	2 (<1)	73 (15)	0	45 (12)	0	24 (21)	0	4 (15)	0
Bronchitis	83 (16)	4 (<1)	91 (18)	1 (<1)	80 (22)	1 (<1)	6 (5)	0	5 (19)	0
Pruritus	82 (16)	2 (<1)	33 (7)	0	22 (6)	0	8 (7)	0	3 (12)	0
Abdominal pain	78 (15)	4 (<1)	46 (9)	4 (<1)	32 (9)	3 (1)	12 (11)	1 (1)	2 (8)	0
Back pain	78 (15)	2 (<1)	65 (13)	1 (<1)	49 (13)	0	11 (10)	0	5 (19)	1 (4)
Myalgia	73 (14)	0	29 (6)	1 (<1)	16 (4)	1 (<1)	11 (10)	0	2 (8)	0
Arthralgia	71 (14)	3 (<1)	70 (14)	1 (<1)	42 (12)	1 (<1)	23 (21)	0	5 (19)	0
Peripheral edema	69 (14)	0	47 (9)	1 (<1)	31 (8)	0	12 (11)	0	4 (15)	1 (4)
Muscle spasms	68 (13)	0	21 (4)	0	16 (4)		3 (3)		2 (8)	
Headache	67 (13)	1 (<1)	60 (12)	1 (<1)	32 (9)	1 (<1)	25 (22)	0	3 (12)	0
Infusion-related reaction	66 (13)	7 (1)	56 (11)	1 (<1)	25 (7)	1 (<1)	30 (27)	0	1 (4)	0

Adverse Event — no. (%)	R² (N = 507)		R-chemo (N = 503)		R-chemo Arms					
					R-CHOP (N = 365)		R-B (N = 112)		R-CVP (N = 26)	
	All Grade	Grade 3-4	All Grade	Grade 3-4	All Grade	Grade 3-4	All Grade	Grade 3-4	All Grade	Grade 3-4
Rhinitis	56 (11)	0	34 (7)	0	34 (9)		0	0	0	0
Dyspnea	55 (11)	1 (<1)	52 (10)	2 (<1)	33 (9)	1 (<1)	14 (13)	0	5 (19)	1 (4)
Viral upper respiratory tract infection	48 (10)	0	32 (6)	0	22 (6)	0	8 (7)	0	2 (8)	0
Upper respiratory tract infection	47 (9)	0	55 (11)	0	22 (6)	0	28 (25)	0	5 (19)	0
Paresthesia	37 (7)	0	57 (11)	0	46 (13)	0	8 (7)	0	3 (12)	0
Upper abdominal pain	37 (7)	0	53 (11)	0	46 (13)	0	6 (5)	0	1 (4)	0
Vomiting	34 (7)	2 (<1)	94 (19)	7 (1)	61 (17)	5 (1)	31 (28)	2 (2)	2 (8)	0
Peripheral neuropathy	35 (7)	1 (<1)	79 (16)	3 (<1)	71 (19)	3 (1)	6 (5)	0	2 (8)	0
Insomnia	31 (6)	2 (<1)	58 (12)	2 (<1)	34 (9)	2 (<1)	21 (19)	0	3 (12)	0
Tumor flare reaction	30 (6)	7 (1)	1 (< 1)	0	1 (<1)	0	0	0	0	0
Leukopenia	21 (4)	8 (2)	48 (10)	30 (6)	39 (11)	26 (7)	7 (6)	3 (3)	2 (8)	1 (4)
Febrile neutropenia	11 (2)	11 (2)	34 (7)	33 (7)	27 (7)	26 (7)	6 (5)	6 (5)	1 (4)	1 (4)
Tumor lysis syndrome	7 (1)	6 (1)	5 (1)	3 (<1)	3 (1)	1 (<1)	2 (2)	2 (2)	0	0
Alopecia	5 (1)	0	45 (9)	3 (<1)	39 (11)	3 (1)	4 (4)	0	2 (8)	0

*Based on laboratory tests. All anemia events were grade 1.

†Cutaneous reactions included preferred terms from skin and subcutaneous tissue disorders, gastrointestinal disorders, general disorders and administration site conditions, infections and infestations, and reproductive system and breast disorders system organ classes.

Supplementary Table S5. Infections Associated with Grade 3/4 Neutropenia (Safety Population) and Use of Concomitant Antimicrobial Medications (Intention-to-Treat Population).

	R^2 (N = 507)	**R-chemo (N = 503)**
Patients with grade 3/4 neutropenia – no. (%)	160 (32)	252 (50)
Patients with concurrent any-grade infection – no. (%)	27 (5)	62 (12)
Patients with concurrent grade 3/4 infection – no. (%)	10 (2)	20 (4)
Patients with grade 4 neutropenia – no. (%)	41 (8)	154 (31)
Patients with concurrent any-grade infection – no. (%)	6 (1)	33 (7)
Patients with concurrent grade 3/4 infection – no. (%)	5 (1)	11 (2)
Use of concomitant antimicrobial agents – no. (%)	**R^2 (N = 513)**	**R-chemo (N = 517)**
Antibacterial medication	382 (74)	404 (78)
Antiviral medication	200 (39)	247 (48)
Antifungal medication	51 (10)	83 (16)

Supplementary Table S6. Incidence of Second Primary Malignancies Across Treatment Arms (Safety Population).

			R-chemo Arms		
	R^2 (N = 507)	**R-chemo (N = 503)**	**R-CHOP (N = 365)**	**R-B (N = 112)**	**R-CVP (N =26)**
Second primary malignancies, all cases – no. (%)	38 (7)	48 (10)	29 (8)	16 (14)	3 (12)
Invasive second primary malignancies – no. (%)	25 (5)	27 (5)	20 (5)	7 (6)	0
Hematologic – no. (%)	4 (<1)	2 (<1)	1 (<1)	1 (<1)	0
Solid tumor – no. (%)	21 (4)	26 (5)	19 (5)	7 (6)	0
Non-invasive second primary malignancies – no. (%)	13 (3)	21 (4)	9 (2)	9 (8)	3 (12)

Supplementary References

1. Solal-Celigny P, Roy P, Colombat P, et al. Follicular Lymphoma International Prognostic Index. Blood. 2004;104:1258-65.

2. Xerri L, Dirnhofer S, Quintanilla-Martinez L, et al. The heterogeneity of follicular lymphomas: from early development to transformation. Virchow Arch. 2016;468:127-39.