Supplemental materials

Methods

Study design and treatments

Eligible patients: 1) had a histologically confirmed diagnosis of CD20-positive indolent non-Hodgkin lymphoma (iNHL) with histologic subtype limited to follicular lymphoma (FL) grade 1, 2, or 3a, small lymphocytic lymphoma with absolute lymphocyte count $<5\times10^9$/L at study entry, lymphoplasmacytic lymphoma/Waldenström macroglobulinemia, and marginal zone lymphoma (splenic, nodal, or extra-nodal); 2) had relapsed or progressed after ≥1 but ≤3 lines of therapy, including rituximab, and/or rituximab biosimilars, and/or anti-CD20 monoclonal antibody-based immunochemotherapy and alkylating agents; 3) without Waldenström macroglobulinemia had to have ≥1 bi-dimensionally measurable lesion (not previously irradiated) according to the Lugano classification; 4) affected by Waldenström macroglobulinemia who did not have ≥1 bi-dimensionally measurable lesion in the baseline radiologic assessment had to have measurable disease, defined as the presence of immunoglobulin M paraprotein with a minimum immunoglobulin M level ≥2× the upper limit of normal and positive immunofixation test. Patients were excluded if they had: medical conditions including histologically confirmed diagnosis of FL grade 3b or transformed disease, or chronic lymphocytic leukemia; resistance to rituximab, rituximab biosimilars, or anti-CD20 monoclonal antibody (eg, obinutuzumab) at any line of therapy; history or concurrent condition of interstitial lung disease of any severity and/or severely impaired lung function; lymphomatous involvement of the central nervous system; glycated hemoglobin >8.5% at screening; or uncontrolled hypertension despite optimal medical management.

Study endpoints and assessments

Duration of response (DoR) was defined as the time (days) from first observed tumor response (complete response, very good partial response, partial response, or minor response) until progressive disease (PD) or death from any cause, whichever occurred first. Complete response rate (CRR) was defined as the proportion of patients who had a best overall response of complete response during the study. Death related to PD was any death except death due to an adverse event (AE) unrelated to progression and death with a specification of "other" as reason (which excludes PD). Overall survival (OS) was defined as the time (days) from randomization until death from any cause. Time to improvement in DRS-P of ≥3 points, as measured by the Functional Assessment of Cancer Therapy – Lymphoma Symptom Index-18 questionnaire, was defined as time from randomization to first increase in DRS-P of ≥3 points from baseline before progression. This endpoint was evaluated only for patients with a baseline DRS-P of ≤30 points. Time to deterioration in DRS-P of ≥3 points was defined as the time (days) from randomization to the occurrence of first reduction in DRS-P score from a baseline of ≥3 points, radiologic or biochemical progression for patients with Waldenström macroglobulinemia without lesions evaluable by imaging, or death from any cause, whichever occurred first.

Sample size determination

The sample size calculation was based on progression-free survival (PFS) and was conducted on the full analysis set, which included all randomized patients. It was calculated that approximately 280 PFS events would be required to detect a 50% increase in PFS assuming a 1-sided alpha of 0.025, power of 92%, and a randomization ratio of 1:1 between the treatment arms. Due to health authority interest in a powered result for PFS in the FL population following completion of all patient study treatment, primary completion was extended to

when ~280 PFS events were reached in the iNHL population. At this point, it was expected that there would be sufficient PFS events in the FL population (~192 PFS events) to achieve an adequately powered comparison between the experimental and control arms.

Pharmacokinetic analyses

Plasma samples were collected and analyzed for copanlisib pharmacokinetics on day 1 (before infusion and 55 minutes after the start of infusion) and day 8 (before infusion and 5-15 minutes, 55 minutes, and 1.5-5 hours after the start of infusion) of cycle 1 and on day 8 (before infusion and 55 minutes after the start of infusion) of cycles 3 and 6. Pharmacokinetic samples were analyzed using a validated liquid chromatography/mass spectrometry assay with a lower limit of quantification of 2 ng/mL. Copanlisib concentrations were analyzed using a previously established population pharmacokinetic model.[1] Copanlisib population pharmacokinetic model-predicted exposure metrics were derived to investigate exposure–response relationships, including static average concentration during investigated time periods and the time-varying exposure metric using population pharmacokinetic model-predicted moving average concentration over 4 weeks. Exposure–response time-to-event analyses investigated relationships between copanlisib exposure and PFS and time to first serious treatment-emergent adverse event and grade ≥3 treatment-emergent adverse event using previously conducted methodology.[1]

Biomarker analyses

Cytokine levels were measured in plasma samples at baseline to investigate whether a relationship exists between cytokine concentrations and copanlisib efficacy in patients with iNHL. Cytokine evaluations were conducted using the U-PLEX Biomarker Group 1 (human) 71-Plex (Meso Scale Diagnostics, Rockville, MD, USA). Cytokine analytes were captured through sandwich immunoassay, binding to biotinylated antibodies connected to U-PLEX

plates, as well as antibodies linked to electro-chemiluminescent labels (MSD GOLD™ SULFO-TAG; Meso Scale Diagnostics). The levels of cytokines were determined by measuring the emitted light from the bound antibody label. A median cut-off limit of 0.356 pg/mL (with a limit of detection of 0.711 pg/mL) was used to differentiate between low or undetectable and high levels of interleukin-2.

Reference

1. Morcos PN, Moss J, Austin R, et al. Copanlisib population pharmacokinetics from phase I–III studies and exposure–response relationships in combination with rituximab. *CPT Pharmacometrics Syst Pharmacol*. 2023;12(11):1666-1686.

Supplemental Table 1. Efficacy results in the SLL, LPL/WM, and other iNHL subtypes (full analysis set)

	SLL		
	Copanlisib + R-B (n=19)		**Placebo + R-B (n=20)**
PFS per independent radiologic review			
Median PFS [95% CI], mo	27.7 [10.9-50.2]		23.5 [11.7-38.9]
HR [95% CI]		0.94 [0.43-2.03]	
P value		0.43	
OS per independent radiologic review			
Median OS [95% CI], mo	NE [10.9-NE]		NE [49.7-NE]
HR [95% CI]		1.36 [0.39-4.70]	
P value		0.69	
Objective tumor responses per independent radiologic review			
ORR, n (%) [95% CI]	16 (84.2) [60.4-96.6]		16 (80.0) [56.3-94.3]

	LPL/WM		
	Copanlisib + R-B (n=25)		**Placebo + R-B (n=14)**
PFS per independent radiologic review			
Median PFS [95% CI], mo	44.0 [27.4-NE]		42.8 [12.3-46.7]
HR [95% CI]		0.59 [0.25-1.40]	
P value		0.11	
OS per independent radiologic review			
Median OS [95% CI], mo	65.6 [56.9-NE]		NE [17.2-NE]
HR [95% CI]		0.56 [0.17-1.83]	
P value		0.16	
Objective tumor responses per independent radiologic review			
ORR, n (%) [95% CI]	22 (88.0) [68.8-97.5]		13 (92.9) [66.1-99.8]

	Other iNHL (non-FL)		
	Copanlisib + R-B (n=87)		**Placebo + R-B (n=84)**
PFS per independent radiologic review			
Median PFS [95% CI], mo	44.0 [30.7-63.5]		33.3 [22.1-44.9]
HR [95% CI]		0.81 [0.53-1.24]	
P value		0.16	
Objective tumor responses per independent radiologic review			
ORR, n (%) [95% CI]	79 (90.8) [82.7-95.9]		70 (83.3) [73.6-90.6]

CI, confidence interval; DoR, duration of response; HR, hazard ratio; LPL/WM, lymphoplasmacytic lymphoma/Waldenström macroglobulinemia; MZL, marginal zone lymphoma; NE, not evaluable; ORR, objective response rate; OS, overall survival; R-B, rituximab and bendamustine; SLL, small lymphocytic lymphoma.

*Includes patients with responses in the full analysis set.

Supplemental Table 2. Summary of best overall response across subtypes

	Overall iNHL	
	Copanlisib + R-B (n=262)	**Placebo + R-B (n=262)**
Best overall response (Lugano classification or Owen criteria), n (%) [95% CI]		
CR	101 (38.5) [32.6-44.7]	108 (41.2) [35.2-47.4]
VGPR*	5 (1.9) [0.6-4.4]	2 (0.8) [0.1-2.7]
PR	116 (44.3) [38.2-50.5]	115 (43.9) [37.8-50.1]
MR	2 (0.8) [0.1-2.7]	2 (0.8) [0.1-2.7]
SD	8 (3.1) [1.3-5.9]	15 (5.7) [3.2-9.3]
PD	5 (1.9) [0.6-4.4]	3 (1.1) [0.2-3.3]
Unconfirmed SD	1 (0.4) [0.0-2.1]	2 (0.8) [0.1-2.7]
Not evaluable	1 (0.4) [0.0-2.1]	3 (1.1) [0.2-3.3]
Not available	23 (8.8) [5.6-12.9]	12 (4.6) [2.4-7.9]
Response rate (Lugano classification or Owen criteria), n (%) [95% CI]		
ORR <CR, VGPR, PR, MR>	224 (85.5) [80.6-89.5]	227 (86.6) [81.9-90.5]

Disease control rate <CR, VGPR, PR, SD>	232 (88.5) [84.1-92.1]	242 (92.4) [88.5-95.3]
	FL	
	Copanlisib + R-B (n=175)	**Placebo + R-B (n=178)**
Best overall response (Lugano classification), n (%) [95% CI]		
CR	74 (42.3) [34.9-50.0]	81 (45.5) [38.0-53.1]
PR	73 (41.7) [34.3-49.4]	74 (41.6) [34.2-49.2]
SD	4 (2.3) [0.6-5.7]	9 (5.1) [2.3-9.4]
PD	5 (2.9) [0.9-6.5]	2 (1.1) [0.1-4.0]
Unconfirmed SD	1 (0.6) [0.0-3.1]	2 (1.1) [0.1-4.0]
Not evaluable	1 (0.6) [0.0-3.1]	2 (1.1) [0.1-4.0]
Not available	17 (9.7) [5.8-15.1]	8 (4.5) [2.0-8.7]
Response rate (Lugano classification), n (%) [95% CI]		
ORR (CR, PR)	147 (84.0) [77.7-89.1]	155 (87.1) [81.2-91.6]
Disease control rate (CR, PR, SD)	151 (86.3) [80.3-91.0]	164 (92.1) [87.2-95.6]
CR rate	74 (42.3) [34.9-50.0]	81 (45.5) [38.0-53.1]

	MZL	
	Copanlisib + R-B (n=43)	**Placebo + R-B (n=49)**
Best overall response (Lugano classification), n (%) [95% CI]		
CR	19 (44.2) [29.1-60.1]	18 (36.7) [23.4-51.7]
PR	20 (46.5) [31.2-62.3]	25 (51.0) [36.3-65.6]
SD	3 (7.0) [1.5-19.1]	4 (8.2) [2.3-19.6]
PD	0	0
Unconfirmed SD	0	0
Not evaluable	0	1 (2.0) [0.1-10.9]
Not available	1 (2.3) [0.1-12.3]	1 (2.0) [0.1-10.9]
Response rate (Lugano classification), n (%) [95% CI]		
ORR (CR, PR)	39 (90.7) [77.9-97.4]	43 (87.8) [75.2-95.4]
Disease control rate (CR, PR, SD)	42 (97.7) [87.7-99.9]	47 (95.9) [86.0-99.5]
CR rate	19 (44.2) [29.1-60.1]	18 (36.7) [23.4-51.7]

	SLL	
	Copanlisib + R-B (n=19)	**Placebo + R-B (n=20)**
Best overall response (Lugano classification), n (%) [95% CI]		
CR	7 (36.8) [16.3-61.6]	7 (35.0) [15.4-59.2]
PR	9 (47.4) [24.4-71.1]	9 (45.0) [23.1-68.5]
SD	1 (5.3) [0.1-26.0]	2 (10.0) [1.2-31.7]
PD	0	1 (5.0) [0.1-24.9]
Unconfirmed SD	0	0
Not evaluable	0	0
Not available	2 (10.5) [1.3-33.1]	1 (5.0) [0.1-24.9]
Response rate (Lugano classification), n (%) [95% CI]		
ORR (CR, PR)	16 (84.2) [60.4-96.6]	16 (80.0) [56.3-94.3]
Disease control rate (CR, PR, SD)	17 (89.5) [66.9-98.7]	18 (90.0) [68.3-98.8]
CR rate	7 (36.8) [16.3-61.6]	7 (35.0) [15.4-59.2]

	LPL/WM	
	Copanlisib + R-B (n=25)	**Placebo + R-B (n=14)**
Lugano classification, n (%) [95% CI]		
CR	1 (4.0) [0.1-20.4]	1 (7.1) [0.2-33.9]
PR	3 (12.0) [2.5-31.2]	3 (21.4) [4.7-50.8]
SD	0	0
PD	0	0
Unconfirmed SD	0	0
Not evaluable	0	0
Owen criteria, n (%) [95% CI]		
CR	0	1 (7.1) [0.2-33.9]
VGPR	5 (20.0) [6.8-40.7]	2 (14.3) [1.8-42.8]
PR	11 (44.0) [24.4-65.1]	4 (28.6) [8.4-58.1]
MR	2 (8.0) [1.0-26.0]	2 (14.3) [1.8-42.8]
SD	0	0
PD	0	0

Unconfirmed SD	0	0
Not evaluable	0	0
Best overall response (Lugano classification or Owen criteria), n (%) [95% CI]		
CR	1 (4.0) [0.1-20.4]	2 (14.3) [1.8-42.8]
VGPR	5 (20.0) [6.8-40.7]	2 (14.3) [1.8-42.8]
PR	14 (56.0) [34.9-75.6]	7 (50.0) [23.0-77.0]
MR	2 (8.0) [1.0-26.0]	2 (14.3) [1.8-42.8]
SD	0	0
PD	0	0
Unconfirmed SD	0	0
Not evaluable	0	0
Not available	3 (12.0) [2.5-31.2]	1 (7.1) [0.2-33.9]
Response rate (Lugano classification or Owen criteria), n (%) [95% CI]		
ORR (CR, VGPR, PR, MR)	22 (88.0) [68.8-97.5]	13 (92.9) [66.1-99.8]
Disease control rate (CR, VGPR, PR, MR, SD)	22 (88.0) [68.8-97.5]	13 (92.9) [66.1-99.8]
CR rate	1 (4.0) [0.1-20.4]	2 (14.3) [1.8-42.8]

	Other iNHL (non-FL)	
	Copanlisib + R-B (n=87)	**Placebo + R-B (n=84)**
Best overall response (Lugano classification or Owen criteria), n (%) [95% CI]		
CR	27 (31.0) [21.5-41.9]	27 (32.1) [22.4-43.2]
VGPR	5 (5.7) [1.9-12.9]	2 (2.4) [0.3-8.3]
PR	43 (49.4) [38.5-60.4]	41 (48.8) [37.7-60.0]
MR	2 (2.3) [0.3-8.1]	2 (2.4) [0.3-8.3]
SD	4 (4.6) [1.3-11.4]	6 (7.1) [2.7-14.9]
PD	0	1 (1.2) [0.0-6.5]
Unconfirmed SD	0	0
Not evaluable	0	1 (1.2) [0.0-6.5]
Not available	6 (6.9) [2.6-14.4]	4 (4.8) [1.3-11.7]
Response rate (Lugano classification or Owen criteria), n (%) [95% CI]		
ORR (CR, PR)	77 (88.5) [79.9-94.3]	72 (85.7) [76.4-92.4]
Disease control rate (CR, PR, SD)	81 (93.1) [85.6-97.4]	8 (92.9) [85.1-97.3]

CR rate	27 (31.0) [21.5-41.9]	27 (32.1) [22.4-43.2]

CI, confidence interval; CR, complete response; LPL/WM, lymphoplasmacytic lymphoma/Waldenström macroglobulinemia; MR, minor response; MZL, marginal zone lymphoma; PD, progressive disease; PR, partial response; R-B, rituximab and bendamustine; SD, stable disease; SLL, small lymphocytic lymphoma; VGPR, very good partial response.

*VGPR is included per Owen criteria for patients with Waldenström macroglobulinemia and is defined through detection via immunofixation of immunoglobulin M protein with ≥90% reduction in serum immunoglobulin M level from baseline, complete resolution of extramedullary disease, and no new signs or symptoms of active disease.

Supplemental Table 3. Summary of copanlisib/placebo-related TEAEs (safety analysis set)

	Copanlisib + R-B (n=263)			**Placebo + R-B (n=257)**		
	All grade	Grade 3	Grade 4	All grade	Grade 3	Grade 4
Any copanlisib/placebo-related TEAE, n (%)	250 (95.1)	97 (36.9)	138 (52.5)	214 (83.3)	69 (26.8)	87 (33.9)
Most common copanlisib/placebo-related TEAEs occurring in ≥20% of patients in either treatment arm, n (%)						
Hyperglycemia	143 (54.4)	93 (35.4)	12 (4.6)	43 (16.7)	11 (4.3)	0
Hypertension	107 (40.7)	84 (31.9)	0	35 (13.6)	17 (6.6)	0
Decreased neutrophil	99 (37.6)	36 (13.7)	53 (20.2)	73 (28.4)	27 (10.5)	28 (10.9)
Nausea	80 (30.4)	2 (0.8)	0	50 (19.5)	1 (0.4)	0
Decreased white blood cell count	77 (29.3)	41 (15.6)	15 (5.7)	56 (21.8)	31 (12.1)	9 (3.5)
Neutropenia	68 (25.9)	28 (10.6)	35 (13.3)	61 (23.7)	24 (9.3)	30 (11.7)
Anemia	67 (25.5)	13 (4.9)	0	44 (17.1)	8 (3.1)	1 (0.4)
Decreased platelet count	63 (24.0)	11 (4.2)	4 (1.5)	41 (16.0)	4 (1.6)	1 (0.4)

Decreased lymphocyte count	61 (23.2)	10 (3.8)	50 (19.0)	38 (14.8)	9 (3.5)	29 (11.3)
Pyrexia	54 (20.5)	5 (1.9)	0	14 (5.4)	0	0
Copanlisib/placebo-related TEAEs leading to discontinuation of copanlisib/placebo*, n (%)	41 (15.6)	26 (9.9)	7 (2.7)	10 (3.9)	7 (2.7)	3 (1.2)

Medical Dictionary for Regulatory Activities version 26.0. Common Terminology Criteria for Adverse Events version 4.03.

R-B, rituximab and bendamustine; TEAE, treatment-emergent adverse event.

*Includes 1 grade 5 event in the copanlisib arm.

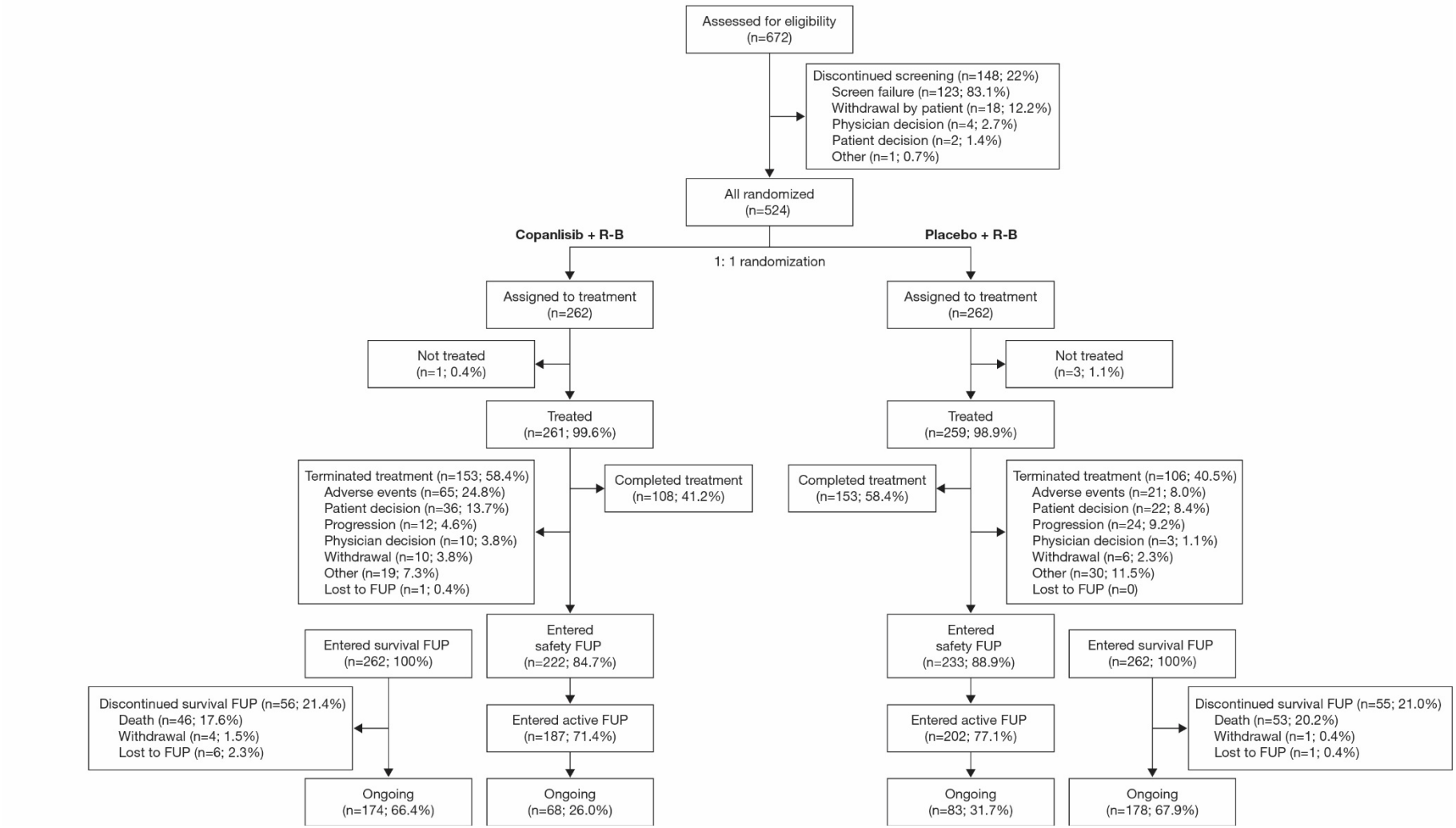
Supplemental Table 4. Summary of concomitant anti-infective medications ending after the start of study drug (full analysis set)

	Copanlisib + R-B (n=262)	**Placebo +R-B (n=262)**
Anti-infectives for systemic use, n (%)	246 (93.9)	198 (75.6)
Antibacterials	226 (86.3)	177 (67.6)
Antivirals	190 (72.5)	146 (55.7)
Antimycotics	75 (28.6)	34 (13.0)
Antimycobacterials	5 (1.9)	4 (1.5)

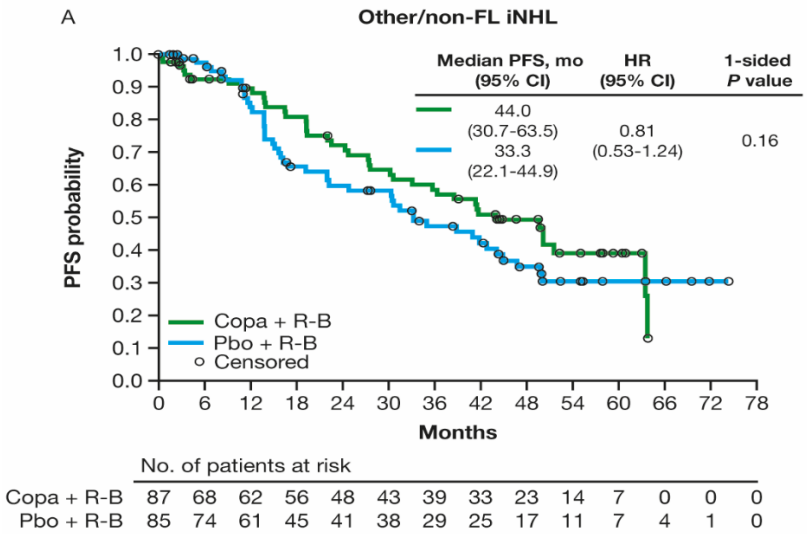
Medications taken within the treatment period are included in this table. This includes all medications that ended after the start of study drug (regardless of when they began).

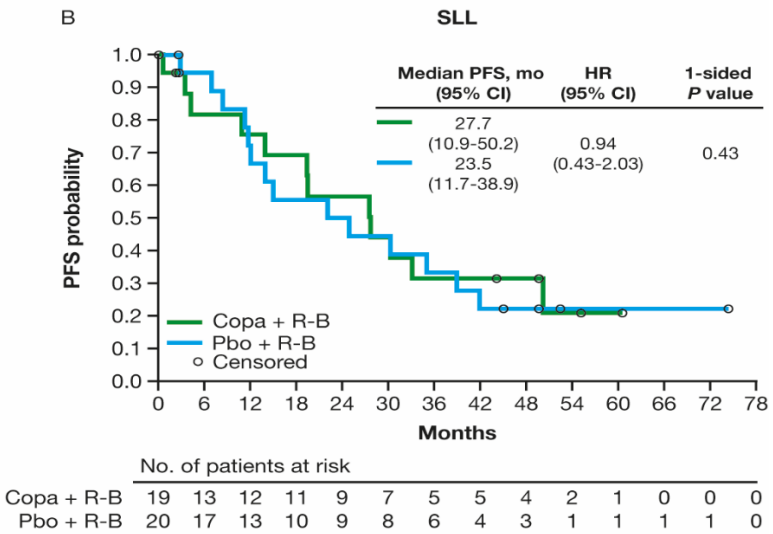
R-B, rituximab and bendamustine.

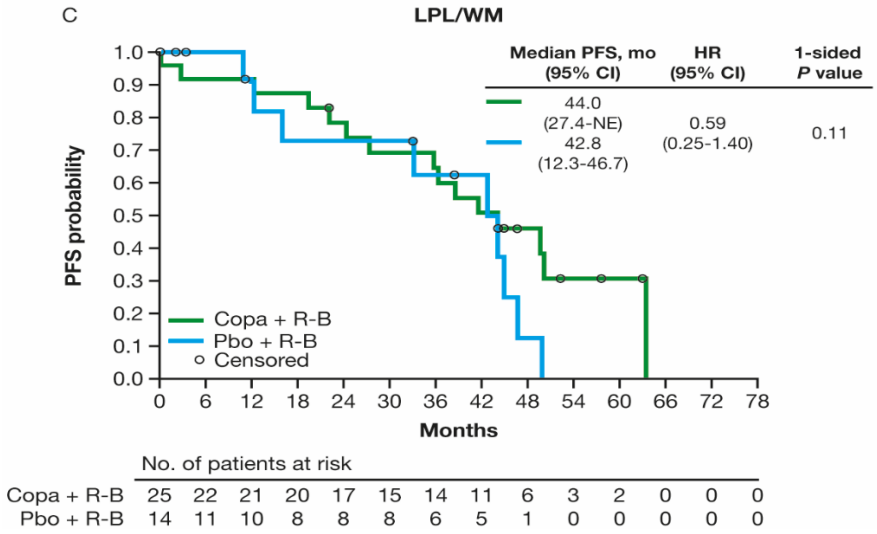
Supplemental Figure 1. CONSORT diagram. FUP, follow-up; R-B, rituximab and bendamustine.



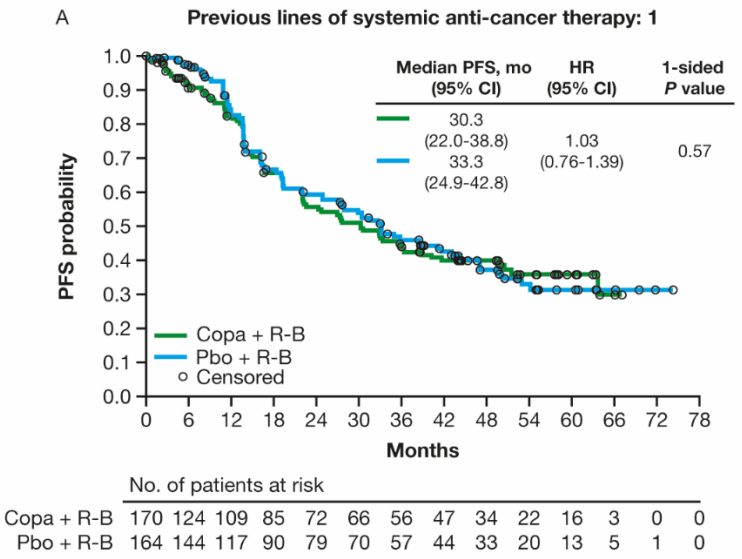
Supplemental Figure 2. Kaplan–Meier curves of PFS for other/non-FL iNHL (A), SLL (B), and LPL/WM (C) (full analysis set). CI, confidence interval; Copa, copanlisib; HR, hazard ratio; LPL/WM, lymphoplasmacytic lymphoma/Waldenström macroglobulinemia; NE, not evaluable; Pbo, placebo; R-B, rituximab and bendamustine; SLL, small lymphocytic lymphoma

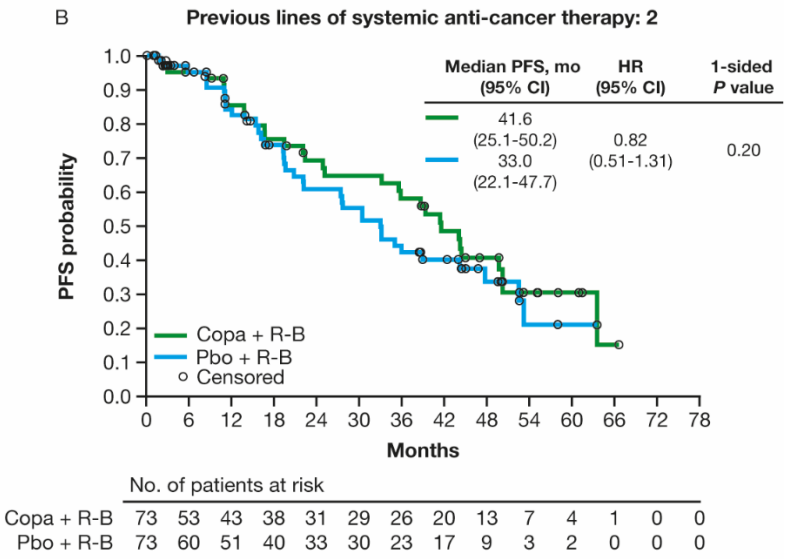

A
Other/non-FL iNHL
Median PFS, mo (95% CI)
HR (95% CI)
1-sided P value
44.0 (30.7-63.5)
33.3 (22.1-44.9)
0.81 (0.53-1.24)
0.16
PFS probability
Copa + R-B
Pbo + R-B
Censored
Months
No. of patients at risk
Copa + R-B 87 68 62 56 48 43 39 33 23 14 7 0 0 0
Pbo + R-B 85 74 61 45 41 38 29 25 17 11 7 4 1 0

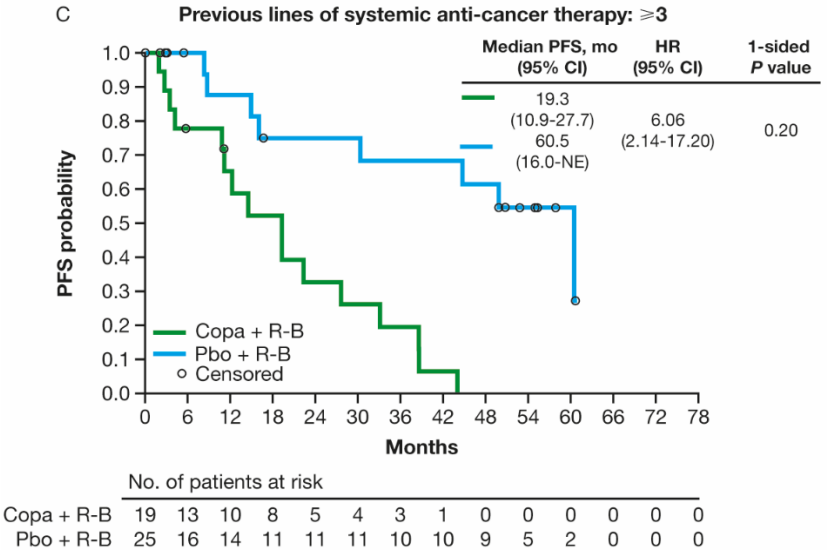

B
SLL
Median PFS, mo (95% CI)
HR (95% CI)
1-sided P value
27.7 (10.9-50.2)
23.5 (11.7-38.9)
0.94 (0.43-2.03)
0.43
PFS probability
Copa + R-B
Pbo + R-B
Censored
Months
No. of patients at risk
Copa + R-B 19 13 12 11 9 7 5 5 4 2 1 0 0 0
Pbo + R-B 20 17 13 10 9 8 6 4 3 1 1 1 1 0


C
LPL/WM
Median PFS, mo (95% CI)
HR (95% CI)
1-sided P value
44.0 (27.4-NE)
42.8 (12.3-46.7)
0.59 (0.25-1.40)
0.11
PFS probability
Copa + R-B
Pbo + R-B
Censored
Months
No. of patients at risk
Copa + R-B 25 22 21 20 17 15 14 11 6 3 2 0 0 0
Pbo + R-B 14 11 10 8 8 8 6 5 1 0 0 0 0 0

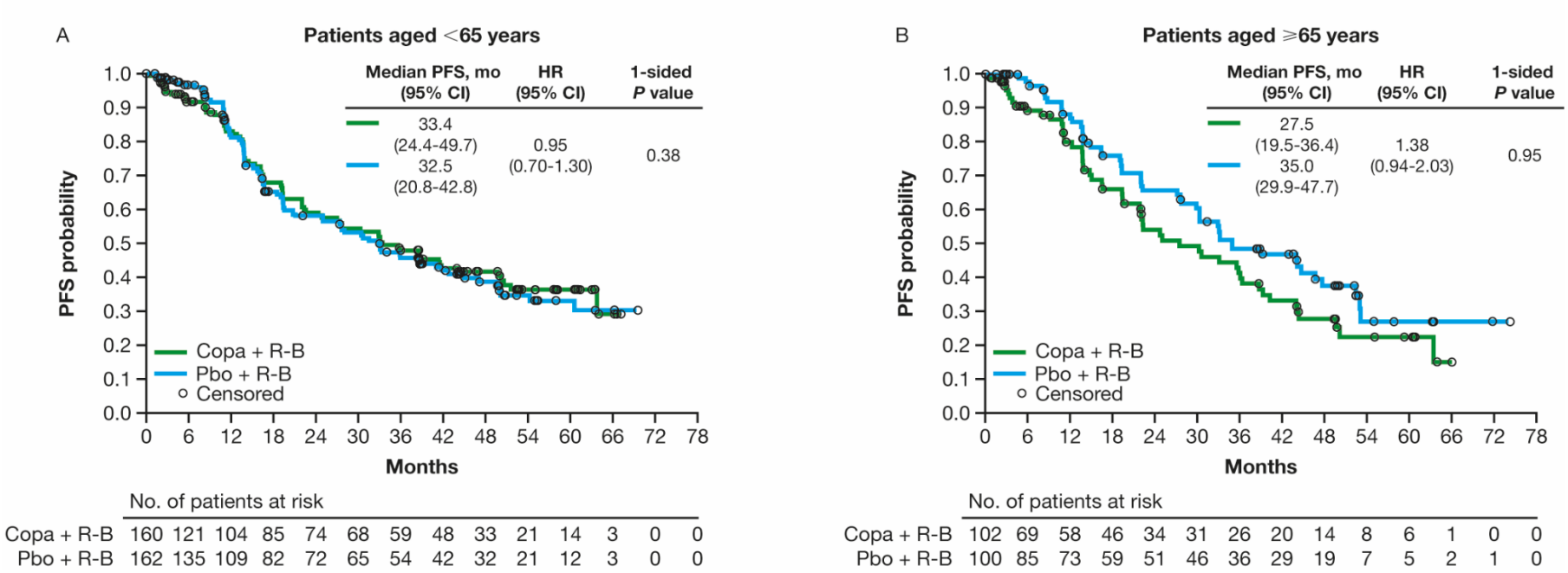
Supplemental Figure 3. Kaplan–Meier curves of PFS data by previous lines of systemic anti-cancer therapy. CI, confidence interval; Copa, copanlisib; HR, hazard ratio; NE, not evaluable; Pbo, placebo; R-B, rituximab and bendamustine.


A
Previous lines of systemic anti-cancer therapy: 1
Median PFS, mo (95% CI)
HR (95% CI)
1-sided P value
30.3 (22.0-38.8)
33.3 (24.9-42.8)
1.03 (0.76-1.39)
0.57
PFS probability
Copa + R-B
Pbo + R-B
Censored
Months
No. of patients at risk
Copa + R-B 170 124 109 85 72 66 56 47 34 22 16 3 0 0
Pbo + R-B 164 144 117 90 79 70 57 44 33 20 13 5 1 0

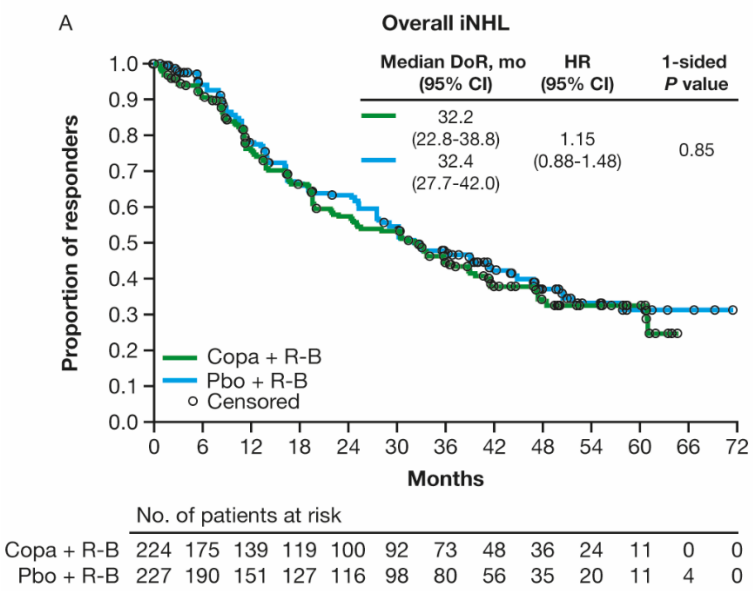

B
Previous lines of systemic anti-cancer therapy: 2
Median PFS, mo (95% CI)
HR (95% CI)
1-sided P value
41.6 (25.1-50.2)
33.0 (22.1-47.7)
0.82 (0.51-1.31)
0.20
PFS probability
Copa + R-B
Pbo + R-B
Censored
Months
No. of patients at risk
Copa + R-B 73 53 43 38 31 29 26 20 13 7 4 1 0 0
Pbo + R-B 73 60 51 40 33 30 23 17 9 3 2 0 0 0

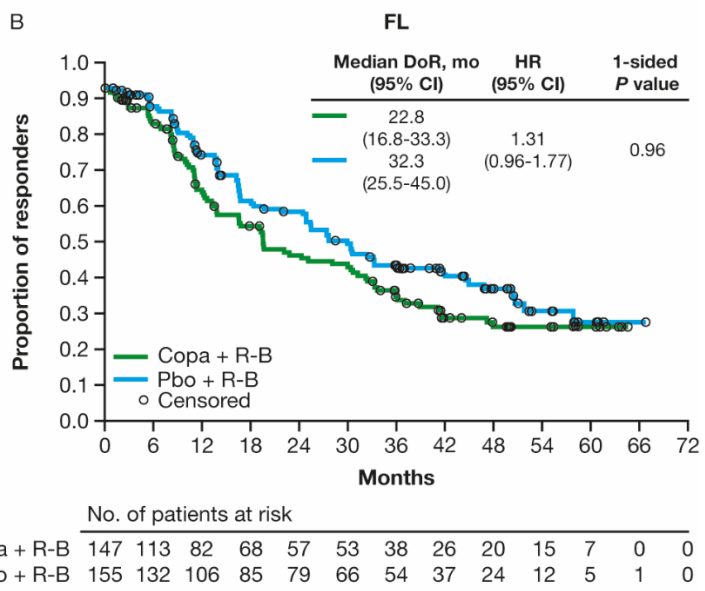

C
Previous lines of systemic anti-cancer therapy: ⩾3
Median PFS, mo (95% CI)
HR (95% CI)
1-sided P value
19.3 (10.9-27.7)
60.5 (16.0-NE)
6.06 (2.14-17.20)
0.20
PFS probability
Copa + R-B
Pbo + R-B
Censored
Months
No. of patients at risk
Copa + R-B 19 13 10 8 5 4 3 1 0 0 0 0 0 0
Pbo + R-B 25 16 14 11 11 11 10 10 9 5 2 0 0 0

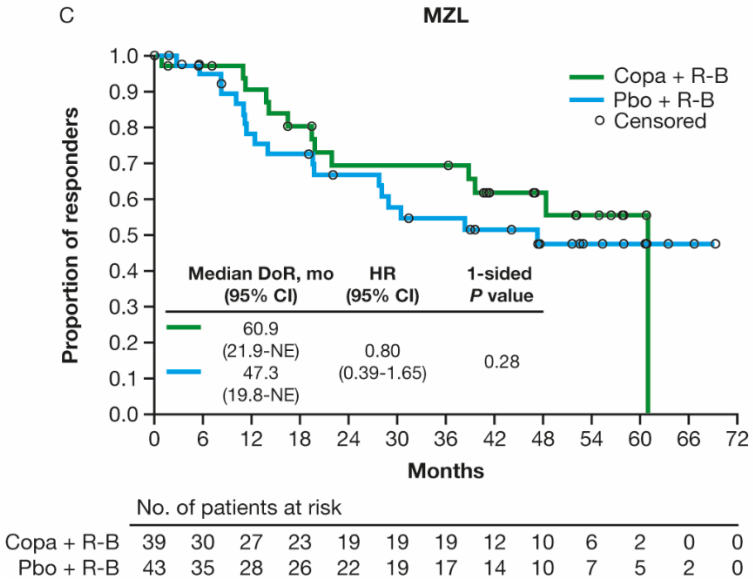
Supplemental Figure 4. Kaplan–Meier curves of PFS data in patients aged <65 years (A) and ≥65 years (B). CI, confidence interval; Copa, copanlisib; HR, hazard ratio; Pbo, placebo; R-B, rituximab and bendamustine.



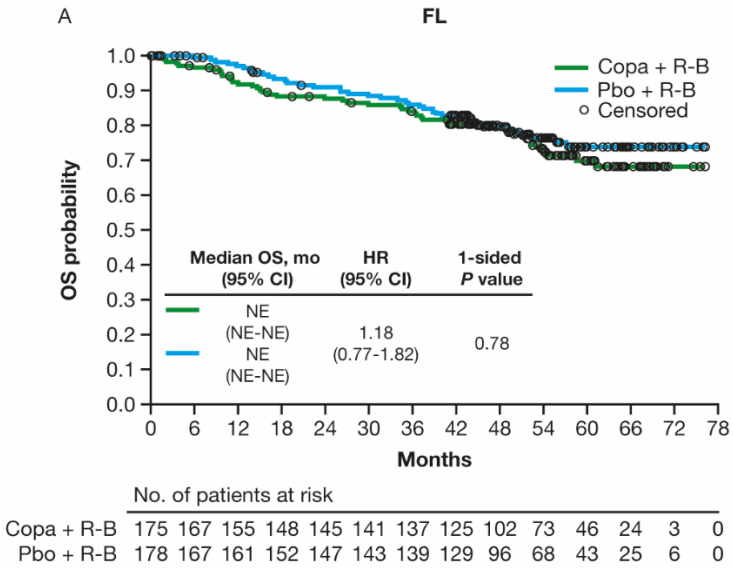
Supplemental Figure 5. Kaplan–Meier curves of DoR in patients with iNHL (A), FL (B), and MZL (C) subtypes. CI, confidence interval; Copa, copanlisib; DoR, duration of response; HR, hazard ratio; MZL, marginal zone lymphoma; Pbo, placebo; R-B, rituximab and bendamustine.

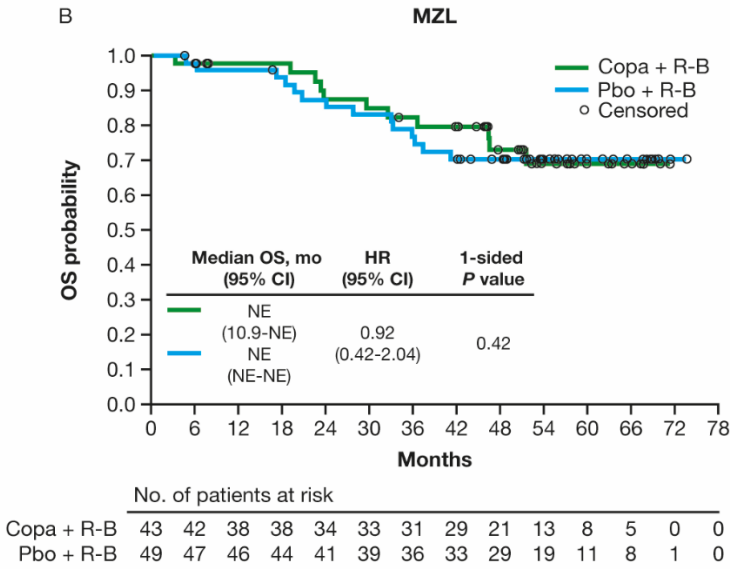

A
Overall iNHL
Median DoR, mo (95% CI)
HR (95% CI)
1-sided P value
32.2 (22.8-38.8)
32.4 (27.7-42.0)
1.15 (0.88-1.48)
0.85
Proportion of responders
Copa + R-B
Pbo + R-B
Censored
Months
No. of patients at risk
Copa + R-B 224 175 139 119 100 92 73 48 36 24 11 0 0
Pbo + R-B 227 190 151 127 116 98 80 56 35 20 11 4 0

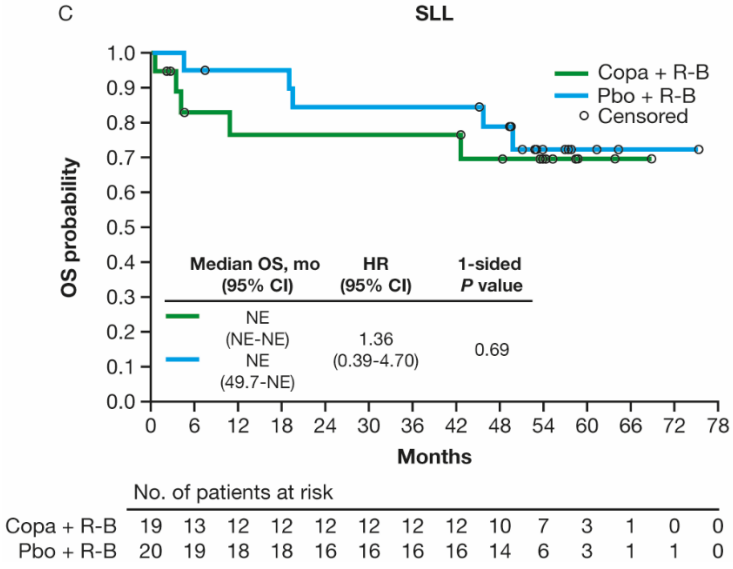

B
FL
Median DoR, mo (95% CI)
HR (95% CI)
1-sided P value
22.8 (16.8-33.3)
32.3 (25.5-45.0)
1.31 (0.96-1.77)
0.96
Proportion of responders
Copa + R-B
Pbo + R-B
Censored
Months
No. of patients at risk
Copa + R-B 147 113 82 68 57 53 38 26 20 15 7 0 0
Pbo + R-B 155 132 106 85 79 66 54 37 24 12 5 1 0

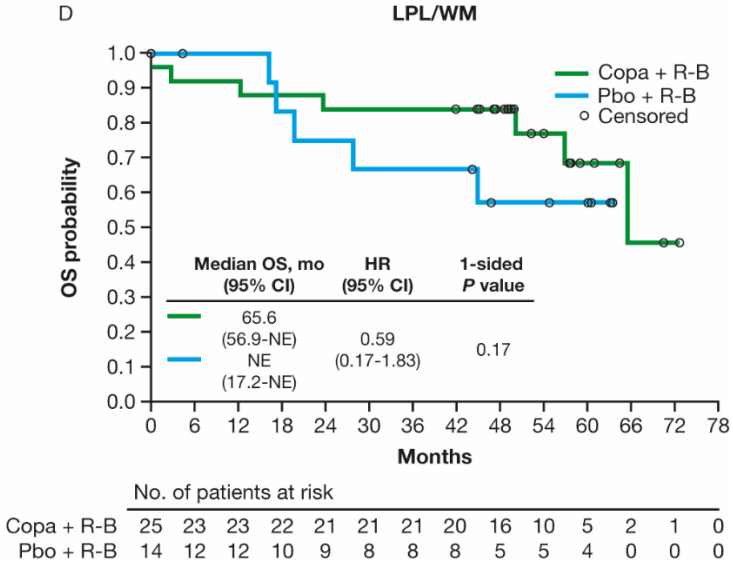

C
MZL
Copa + R-B
Pbo + R-B
Censored
Median DoR, mo (95% CI)
HR (95% CI)
1-sided P value
60.9 (21.9-NE)
47.3 (19.8-NE)
0.80 (0.39-1.65)
0.28
Proportion of responders
Months
No. of patients at risk
Copa + R-B 39 30 27 23 19 19 19 12 10 6 2 0 0
Pbo + R-B 43 35 28 26 22 19 17 14 10 7 5 2 0

Supplemental Figure 6. Kaplan–Meier curves of OS across FL (A), MZL (B), SLL (C), and LPL/WM (D) subtypes. CI, confidence interval; Copa, copanlisib; HR, hazard ratio; LPL/WM, lymphoplasmacytic lymphoma/Waldenström macroglobulinemia; MZL, marginal zone lymphoma; NE, not evaluable; OS, overall survival; Pbo, placebo; R-B, rituximab and bendamustine; SLL, small lymphocytic lymphoma.

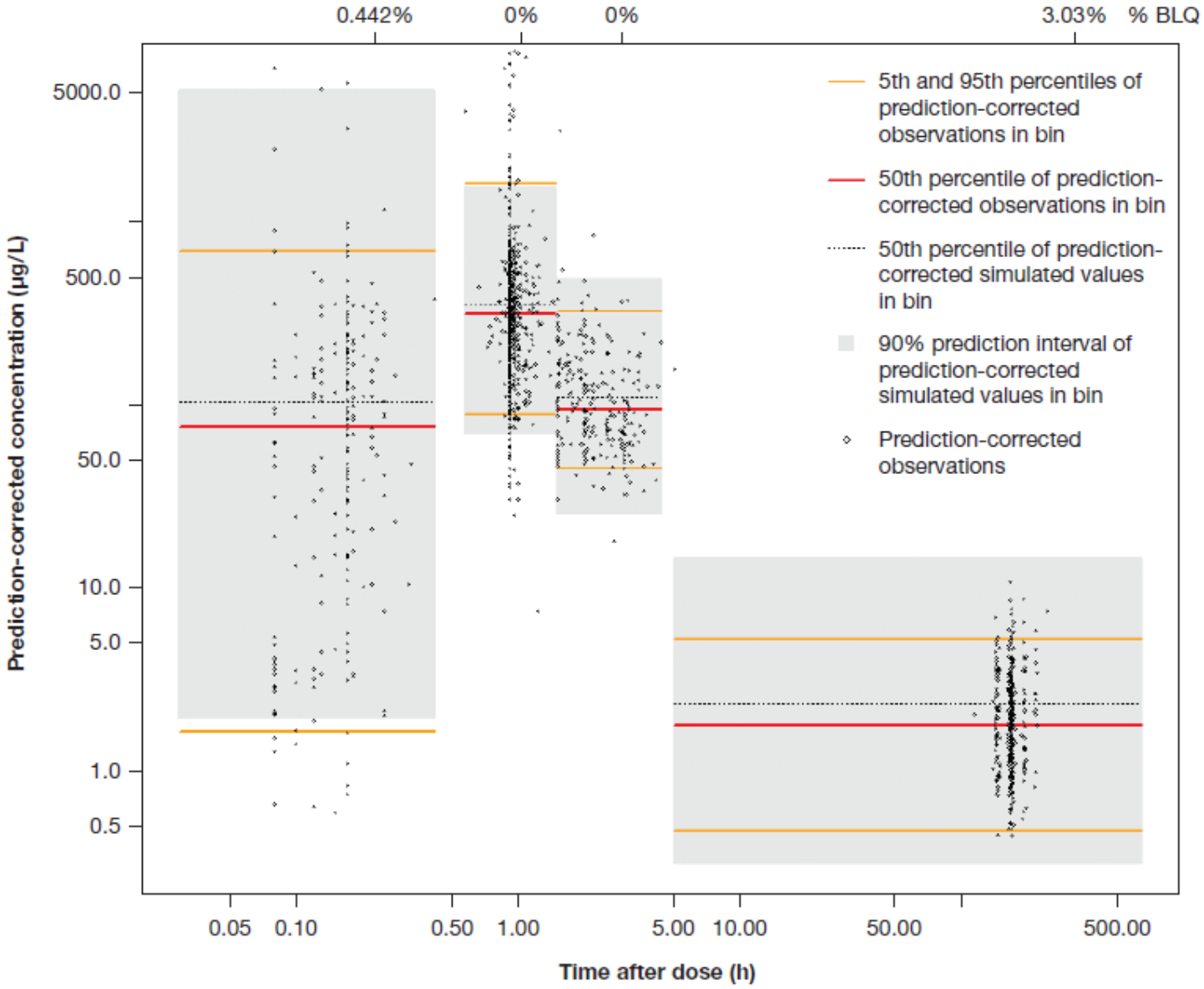

A
FL
OS probability
Copa + R-B
Pbo + R-B
Censored
Median OS, mo (95% CI)
HR (95% CI)
1-sided P value
NE (NE-NE)
NE (NE-NE)
1.18 (0.77-1.82)
0.78
Months
No. of patients at risk
Copa + R-B 175 167 155 148 145 141 137 125 102 73 46 24 3 0
Pbo + R-B 178 167 161 152 147 143 139 129 96 68 43 25 6 0


B
MZL
OS probability
Copa + R-B
Pbo + R-B
Censored
Median OS, mo (95% CI)
HR (95% CI)
1-sided P value
NE (10.9-NE)
NE (NE-NE)
0.92 (0.42-2.04)
0.42
Months
No. of patients at risk
Copa + R-B 43 42 38 38 34 33 31 29 21 13 8 5 0 0
Pbo + R-B 49 47 46 44 41 39 36 33 29 19 11 8 1 0

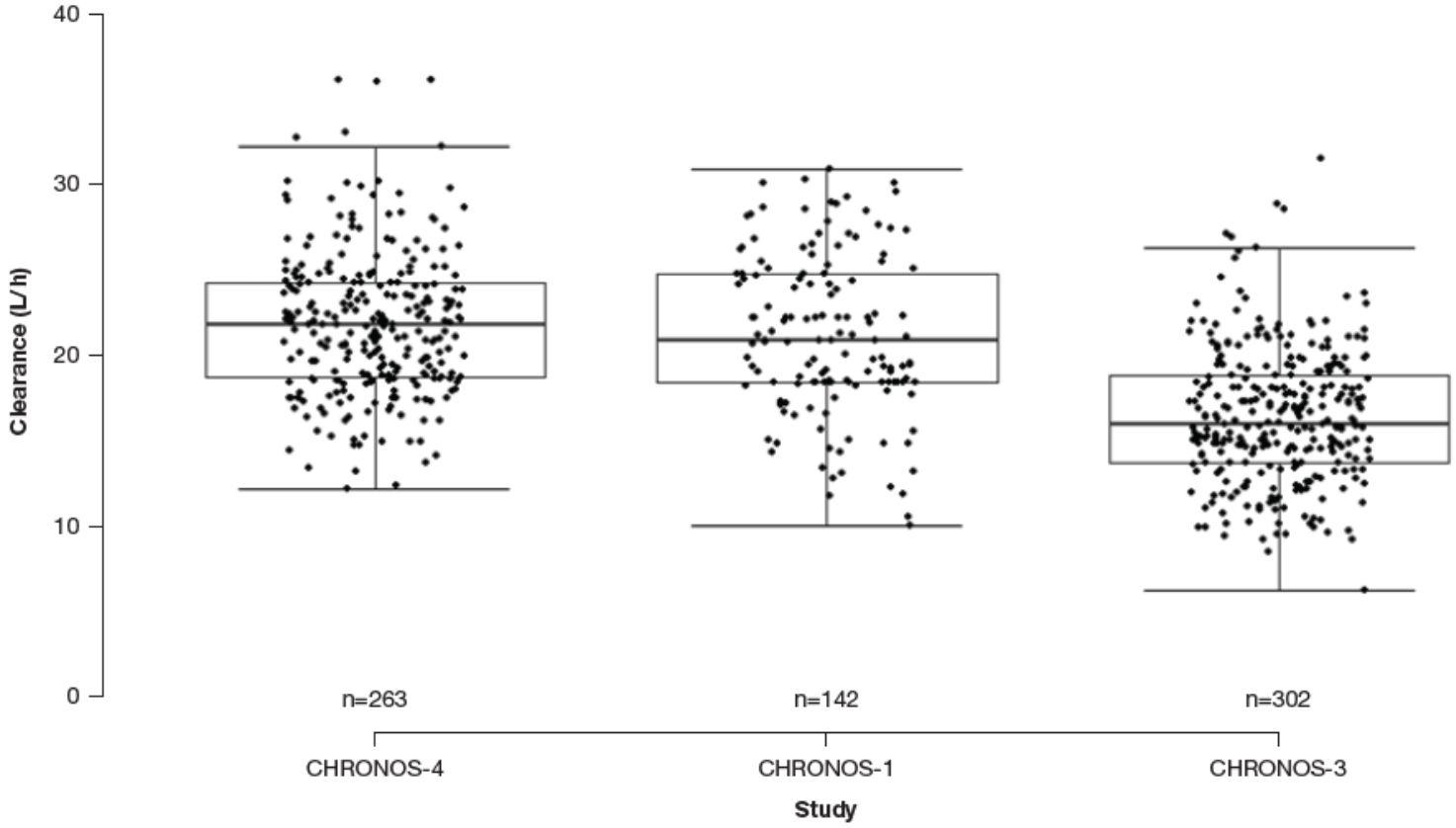

C
SLL
OS probability
Copa + R-B
Pbo + R-B
Censored
Median OS, mo (95% CI)
HR (95% CI)
1-sided P value
NE (NE-NE)
NE (49.7-NE)
1.36 (0.39-4.70)
0.69
Months
No. of patients at risk
Copa + R-B 19 13 12 12 12 12 12 12 10 7 3 1 0 0
Pbo + R-B 20 19 18 18 16 16 16 16 14 6 3 1 1 0


D
LPL/WM
OS probability
Copa + R-B
Pbo + R-B
Censored
Median OS, mo (95% CI)
HR (95% CI)
1-sided P value
65.6 (56.9-NE)
NE (17.2-NE)
0.59 (0.17-1.83)
0.17
Months
No. of patients at risk
Copa + R-B 25 23 23 22 21 21 21 20 16 10 5 2 1 0
Pbo + R-B 14 12 12 10 9 8 8 8 5 5 4 0 0 0

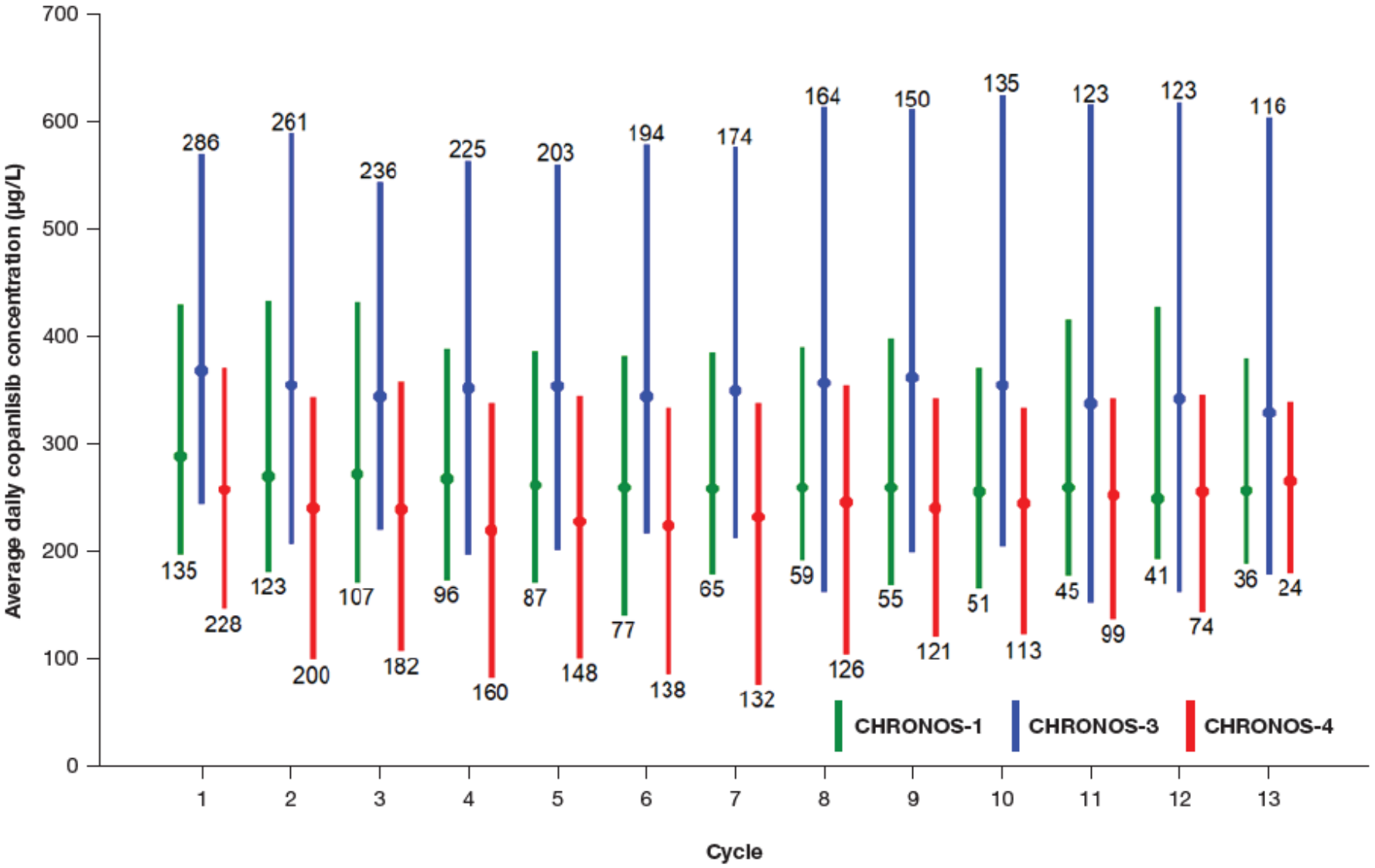
Supplemental Figure 7. Prediction-corrected visual predictive checks of the final copanlisib population pharmacokinetics model in describing copanlisib pharmacokinetics in CHRONOS-4. All yellow lines and shaded regions correspond to model simulations and all gray lines correspond to observed data. Black dots represent the prediction-corrected observations that are greater than the lower limit of quantification; red horizontal lines represent the 50th percentiles of prediction-corrected observations in the bin; yellow horizontal lines represent the 5th and 95th percentiles of prediction-corrected observations in the bin; black dotted horizontal lines represent the 50th percentile of prediction-corrected simulated values in the bin; gray shaded areas represent the range between the 10th and 90th percentiles of prediction-corrected simulated values in the bin; the numbers along the top of the plot represent the percentage of observations in the bin that are less than the lower limit of quantification. BLQ, below the limit of quantification.


0.442%
0%
0%
3.03%
% BLQ
5000.0
500.0
50.0
10.0
5.0
1.0
0.5
Prediction-corrected concentration (µg/L)
0.05
0.10
0.50
1.00
5.00
10.00
50.00
500.00
Time after dose (h)
5th and 95th percentiles of prediction-corrected observations in bin
50th percentile of prediction-corrected observations in bin
50th percentile of prediction-corrected simulated values in bin
90% prediction interval of prediction-corrected simulated values in bin
Prediction-corrected observations

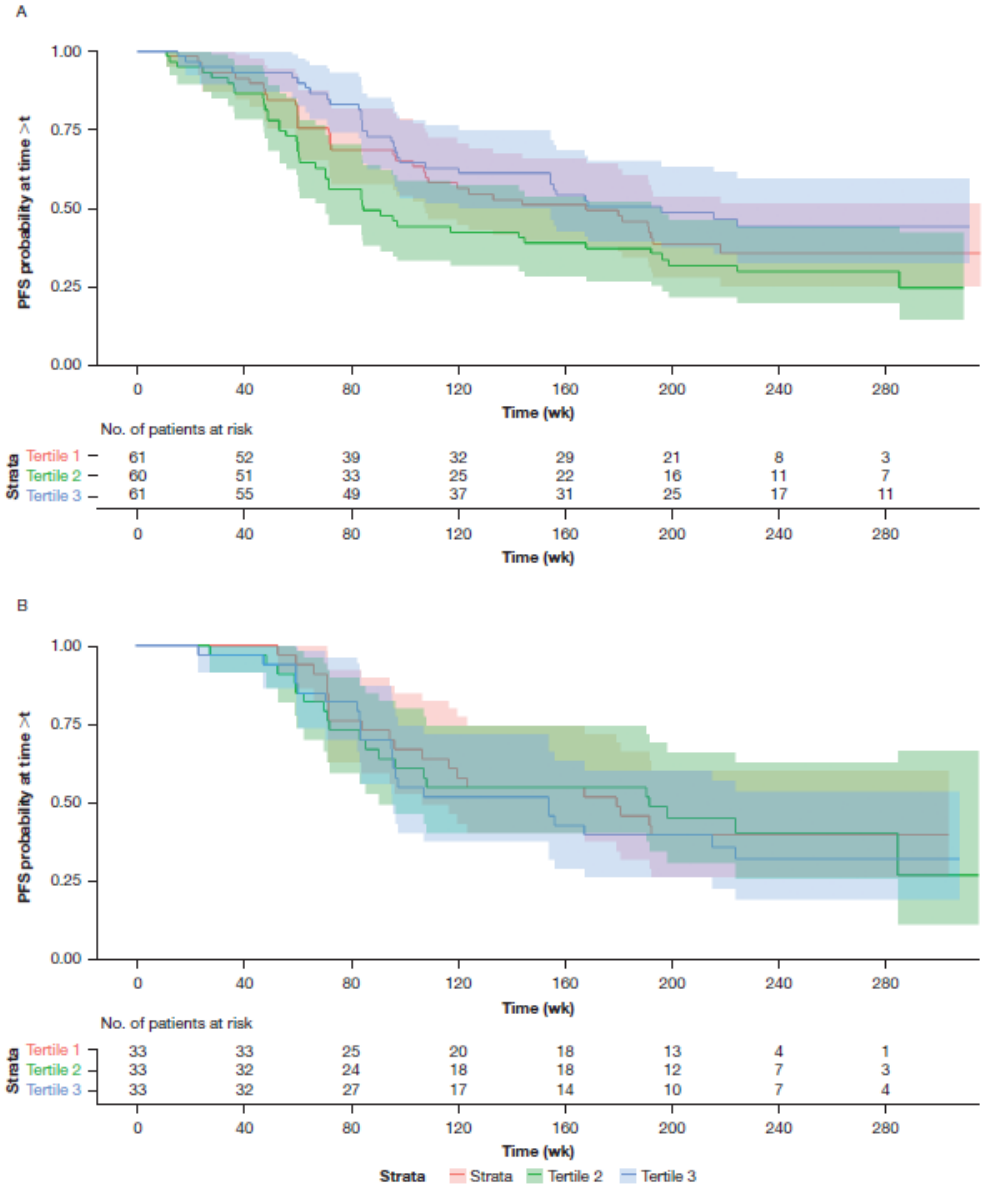
Supplemental Figure 8. Distribution of copanlisib clearance across CHRONOS-4, CHRONOS-3, and CHRONOS-1. Boxes give the interquartile ranges of all clearance within each study. The central black line in the middle of each box gives the median clearance of that study. The whiskers extend by out from the edge of the boxes at a factor 1.5*interquartile range in each direction. The black circles provide the individual clearance for each patient.



Supplemental Figure 9. Distribution of average daily copanlisib concentration across CHRONOS-1, CHRONOS-3, and CHRONOS-4. Average daily copanlisib concentrations within each dosing cycle are shown for CHRONOS-1 (Study 16349; green), CHRONOS-3 (Study 17067; blue), and CHRONOS-4 (Study 17833; red). Vertical bars give the 5th-95th range of average daily copanlisib concentration seen in patients treated with copanlisib for that dosing cycle, with the dots representing the median. The numbers at the bottom of the green and red bars and at the top of the blue bars represent the number of patients treated with copanlisib who completed that cycle from the study related to that color. Patients treated with copanlisib must have either taken all 3 doses within a dosing cycle or have started the next dosing cycle to be included.

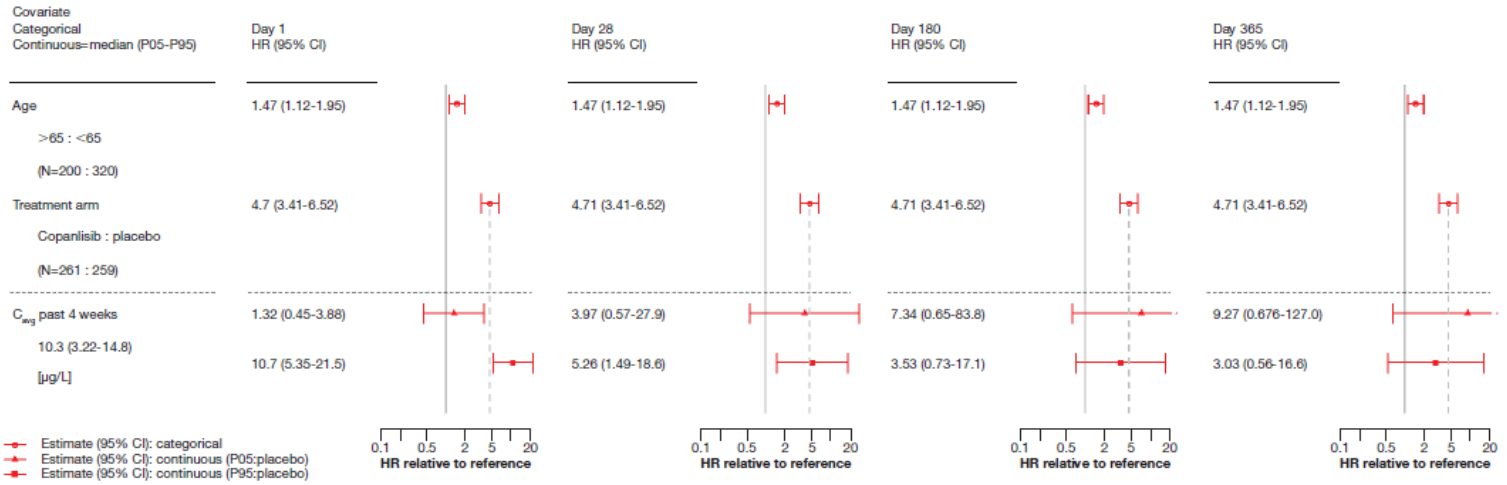

Average daily copanlisib concentration (µg/L)
700
600
500
400
300
200
100
0
1
2
3
4
5
6
7
8
9
10
11
12
13
Cycle
135
286
228
123
261
200
107
236
182
96
225
160
87
203
148
77
194
138
65
174
132
59
164
126
55
150
121
51
135
113
45
123
99
41
123
74
36
116
24
CHRONOS-1
CHRONOS-3
CHRONOS-4

Supplemental Figure 10. Exposure–efficacy analyses. Kaplan–Meier survival curves with 95% confidence intervals and risk table for PFS in copanlisib-treated patients who completed at least 3 dosing cycles stratified by tertiles of average daily copanlisib concentration from their first 3 dosing cycles (A) and copanlisib-treated patients who completed at least 11 dosing cycles stratified by tertiles of average daily copanlisib concentration from their first 11 dosing cycles (B).

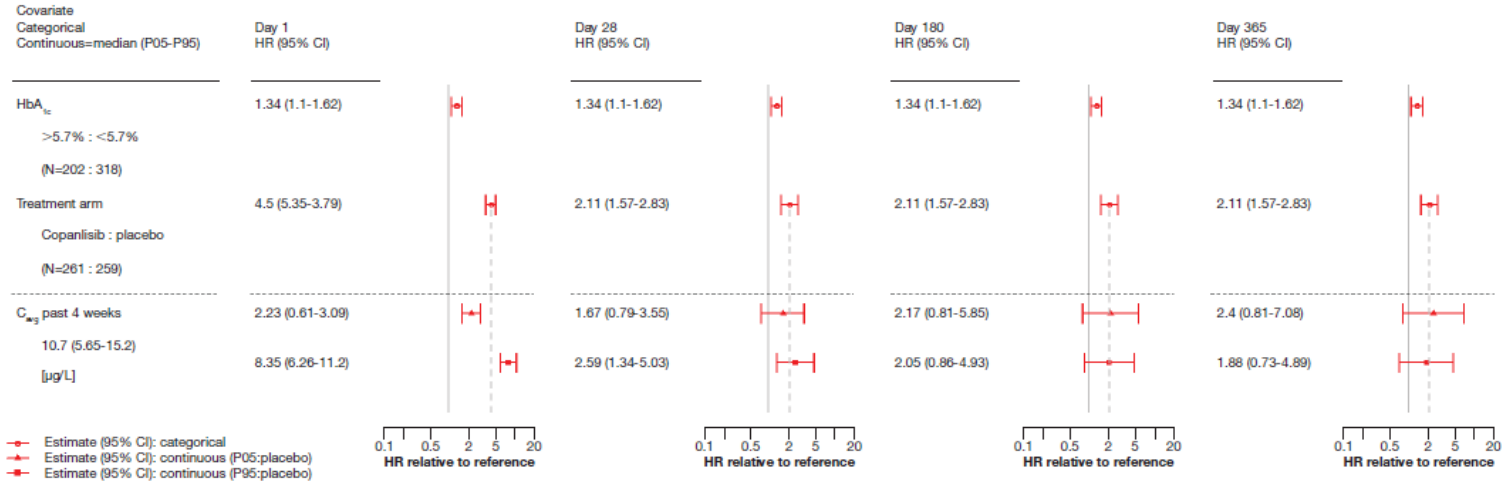

A
1.00
0.75
0.50
0.25
0.00
PFS probability at time >t
0
40
80
120
160
200
240
280
Time (wk)
No. of patients at risk
Strata
Tertile 1 61 52 39 32 29 21 8 3
Tertile 2 60 51 33 25 22 16 11 7
Tertile 3 61 55 49 37 31 25 17 11
Time (wk)
B
1.00
0.75
0.50
0.25
0.00
PFS probability at time >t
0
40
80
120
160
200
240
280
Time (wk)
No. of patients at risk
Strata
Tertile 1 33 33 25 20 18 13 4 1
Tertile 2 33 32 24 18 18 12 7 3
Tertile 3 33 32 27 17 14 10 7 4
Time (wk)
Strata
Strata
Tertile 2
Tertile 3

Supplemental Figure 11. Exposure–safety analyses. Forest plot of ER analyses for time to first serious TEAE (A) or time to first grade ≥3 TEAE (B). The forest plots are split into 2 sections with the x-axis displaying the HR relative to the reference category. The top section (above the horizontal dotted line) shows the result of an initial covariate search for (A) serious TEAEs in all patients or (B) grade ≥3 TEAEs in all patients. Categorical covariates are shown on the far left, with categories and corresponding prevalence (in parentheses) given below each category. HRs and their 95% CIs are shown numerically and visually (red open circles and lines) at 4 different time points since first copanlisib or placebo dose (1 day, 28 days, 180 days, and 365 days). The latter category shown for each covariate is the reference. The vertical dotted line is placed at the point estimate of the HR for copanlisib versus placebo. The bottom section (below the horizontal dotted line) shows the result of testing copanlisib exposure variables for (A) serious TEAEs or (B) grade ≥3 TEAEs in copanlisib-treated patients only. Exposure variables are shown on the far left, with the median given immediately below and the 5th and 95th percentiles shown in parentheses. HRs and their 95% CIs are shown numerically and visually (red triangles for the 5th percentile, red squares for the 95th percentile, and lines). HRs are adjusted to be relative to placebo for all copanlisib exposure variables shown. As in the top section, the HRs have been plotted at 4 different time points since randomization (1 day, 28 days, 180 days, and 365 days). C_{avg}, average concentration; CI, confidence interval; ER, exposure–response; HbA_{1c}, glycated hemoglobin; HR, hazard ratio; TEAE, treatment-emergent adverse event.

A


Covariate
Categorical
Continuous=median (P05-P95)
Day 1
HR (95% CI)
Day 28
HR (95% CI)
Day 180
HR (95% CI)
Day 365
HR (95% CI)
Age
>65 : <65
(N=200 : 320)
1.47 (1.12-1.95)
1.47 (1.12-1.95)
1.47 (1.12-1.95)
1.47 (1.12-1.95)
Treatment arm
Copanlisib : placebo
(N=261 : 259)
4.7 (3.41-6.52)
4.71 (3.41-6.52)
4.71 (3.41-6.52)
4.71 (3.41-6.52)
C_{avg} past 4 weeks
10.3 (3.22-14.8)
[µg/L]
1.32 (0.45-3.88)
10.7 (5.35-21.5)
3.97 (0.57-27.9)
5.26 (1.49-18.6)
7.34 (0.65-83.8)
3.53 (0.73-17.1)
9.27 (0.676-127.0)
3.03 (0.56-16.6)
0.1 0.5 2 5 20
HR relative to reference
Estimate (95% CI): categorical
Estimate (95% CI): continuous (P05:placebo)
Estimate (95% CI): continuous (P95:placebo)

B


Covariate
Categorical
Continuous=median (P05-P95)
Day 1
HR (95% CI)
Day 28
HR (95% CI)
Day 180
HR (95% CI)
Day 365
HR (95% CI)
HbA_{1c}
>5.7% : <5.7%
(N=202 : 318)
1.34 (1.1-1.62)
1.34 (1.1-1.62)
1.34 (1.1-1.62)
1.34 (1.1-1.62)
Treatment arm
Copanlisib : placebo
(N=261 : 259)
4.5 (5.35-3.79)
2.11 (1.57-2.83)
2.11 (1.57-2.83)
2.11 (1.57-2.83)
C_{avg} past 4 weeks
10.7 (5.65-15.2)
[µg/L]
2.23 (0.61-3.09)
8.35 (6.26-11.2)
1.67 (0.79-3.55)
2.59 (1.34-5.03)
2.17 (0.81-5.85)
2.05 (0.86-4.93)
2.4 (0.81-7.08)
1.88 (0.73-4.89)
0.1 0.5 2 5 20
HR relative to reference
Estimate (95% CI): categorical
Estimate (95% CI): continuous (P05:placebo)
Estimate (95% CI): continuous (P95:placebo)

Supplemental Figure 12. Kaplan–Meier curves of PFS (A) and OS (B) by IL-2 baseline levels in patients with FL. CI, confidence interval; Copa, copanlisib; HR, hazard ratio; IL-2, interleukin-2; NE, not evaluable; OS, overall survival; Pbo, placebo; R-B, rituximab and bendamustine.