Ibrutinib + Rituximab Versus Placebo + Rituximab in Patients With Previously Untreated Follicular Lymphoma: Primary Analysis of the Phase 3 PERSPECTIVE Study

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Ibrutinib + Rituximab Might Provide a Chemotherapy-Free Treatment Option for Patients With Previously Untreated FL Who Are Older or Have Comorbidities

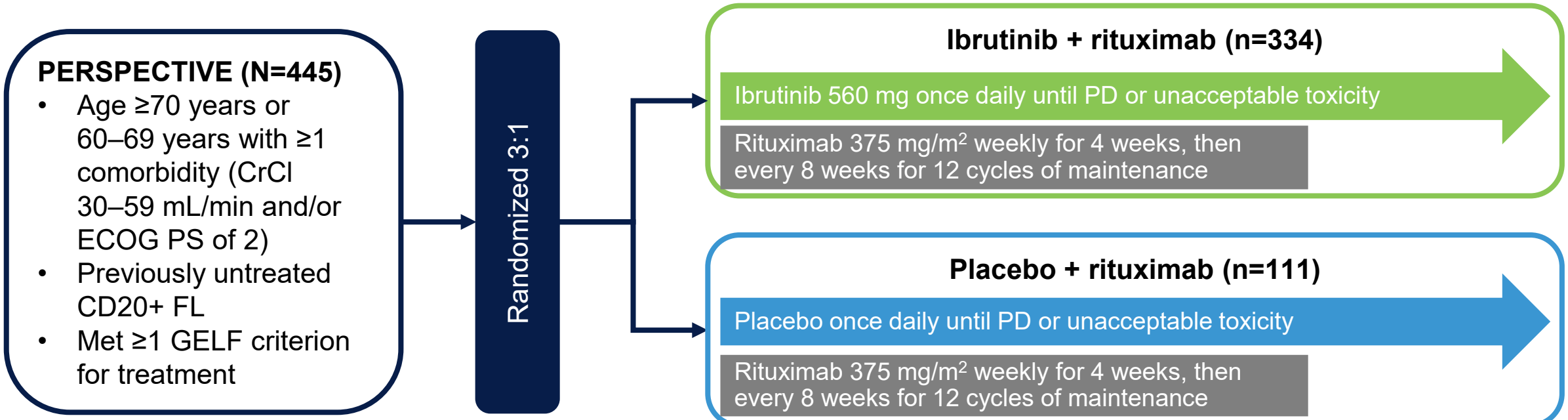
- In younger and fit patients, standard first-line treatment for advanced-stage follicular lymphoma (FL) involves an anti-CD20 antibody (rituximab or obinutuzumab) in combination with chemotherapy[1-3]
- First-line treatment with single-agent rituximab is recommended in older patients and in those with comorbid conditions who are not eligible for CIT[1-3]
  - For such patients, a chemotherapy-free regimen with increased efficacy over single-agent rituximab and with an acceptable safety profile could be an attractive treatment option
  - The combination of ibrutinib, a once-daily Bruton tyrosine kinase inhibitor, with rituximab has shown promising activity with durable responses in patients with previously untreated FL in phase 2 studies[4,5]

Here, we report primary analysis results from the multinational, randomized, double-blind, placebo-controlled phase 3 PERSPECTIVE study (PCYC-1141; NCT02947347) evaluating the efficacy and safety of ibrutinib + rituximab versus placebo + rituximab in patients with previously untreated FL not eligible for CIT due to age and/or comorbidities

CIT, chemoimmunotherapy; FL, follicular lymphoma.

[1]Carbone A et al. *Nat Rev Dis Primers.* 2019;5:83. [2]Jacobsen E. *Am J Hematol.* 2022;97:1638–1651. [3]Dreyling M et al. *Ann Oncol.* 2021;32:298–308. [4]Fowler NH et al. *Br J Haematol.* 2020;189:650–660. [5]Østenstad B et al. *Blood.* 2023;41(suppl 2):117–119.

PERSPECTIVE: A Phase 3 Study of Ibrutinib + Rituximab Versus Placebo + Rituximab in Patients With Previously Untreated FL Not Eligible for CIT



Stratification: Age, FLIPI-1 score, and ECOG PS

- **Primary end point:**
  - PFS by investigator assessment per Cheson 2014 criteria using FDA censoring rules
    - Sensitivity analyses of PFS were performed based on IRC assessment and using global censoring rules

- **Secondary end points (tested hierarchically in the following order):**
  - ORR by investigator assessment per Cheson 2014 criteria
  - OS
  - IRR rates

CrCl, creatinine clearance; ECOG PS, Eastern Cooperative Oncology Group performance status; FDA, US Food and Drug Administration; FLIPI, Follicular Lymphoma International Prognostic Index; GELF, Groupe d'Etude des Lymphomes Folliculaires; IRC, independent review committee; IRR, infusion-related reaction; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival.

Baseline Characteristics Were Well Balanced Between Study Treatment Arms

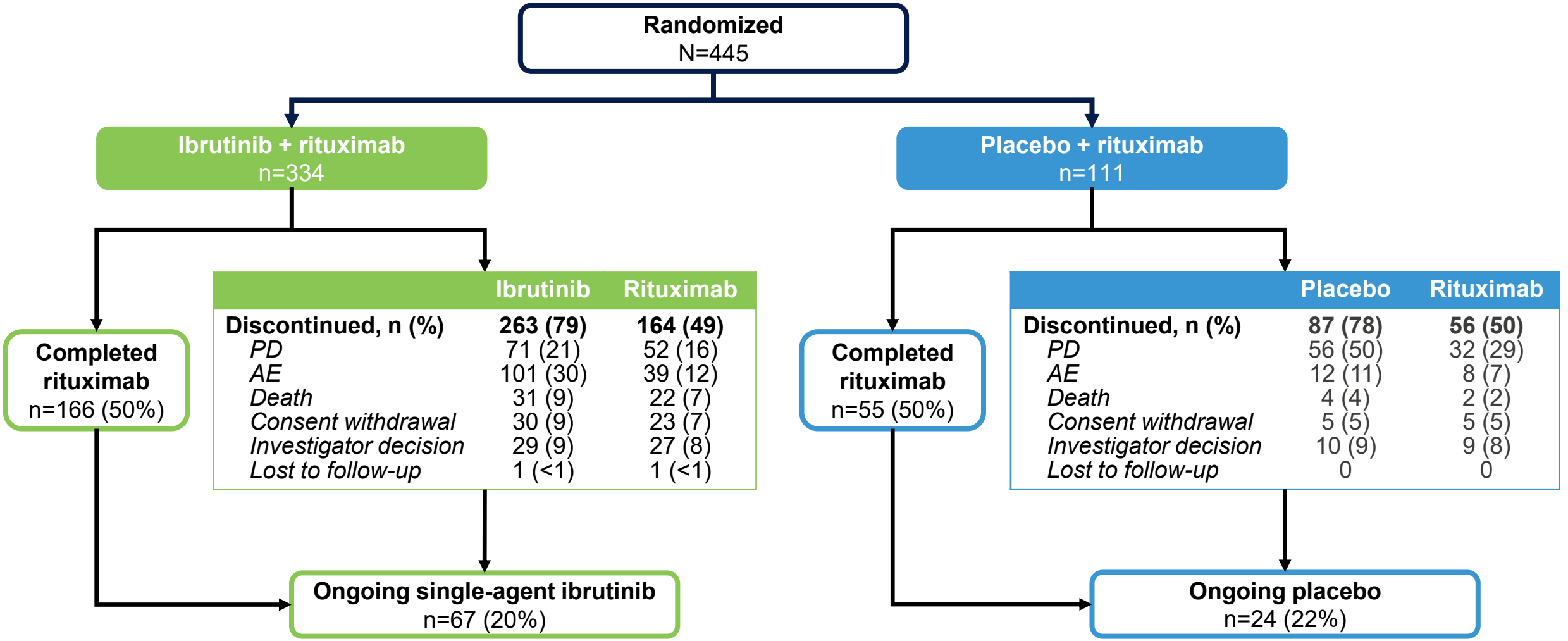
Characteristic	Ibrutinib + rituximab n=334	Placebo + rituximab n=111
Age		
Median (range), years	74 (60–87)	75 (61–88)
60–69 years, n (%)	69 (21)	22 (20)
≥70 years, n (%)	265 (79)	89 (80)
Sex, n (%)		
Male	151 (45)	58 (52)
Female	183 (55)	53 (48)
ECOG PS, n (%)		
0	120 (36)	37 (33)
1	130 (39)	47 (42)
2	84 (25)	27 (24)
CrCl, n (%)		
<30 mL/min	7 (2)	1 (1)
30 to <60 mL/min	108 (32)	36 (32)
≥60 mL/min	219 (66)	74 (67)
Median time since initial diagnosis (range), months	2.3 (0.4–176.0)	2.5 (0.1–114.0)

Characteristic	Ibrutinib + rituximab n=334	Placebo + rituximab n=111
FL WHO grade, n (%)		
1	100 (30)	37 (33)
2	157 (47)	53 (48)
3a	77 (23)	20 (18)
Missing	0	1 (1)
Ann Arbor stage, n (%)		
II	53 (16)	17 (15)
III	110 (33)	36 (32)
IV	171 (51)	58 (52)
FLIPI-1 score, n (%)		
Low (0–1)	30 (9)	7 (6)
Intermediate (2)	83 (25)	30 (27)
High (≥3)	221 (66)	74 (67)
Number of nodal areas involved, n (%)		
≤4	163 (49)	56 (50)
≥5	171 (51)	55 (50)
Bulky disease >7 cm, n (%)[a]	137 (41)	49 (44)

- An older patient population, per study design
- Meaningful proportion of patients with an ECOG PS score of 2
- Predominantly high FLIPI-1 score, Ann Arbor stage IV

WHO, World Health Organization.
[a]Any nodal or extranodal tumor mass with a diameter of >7 cm.

PERSPECTIVE: Patient Disposition at Data Cutoff (21 Feb 2024)



	Ibrutinib	Rituximab
Discontinued, n (%)	**263 (79)**	**164 (49)**
PD	71 (21)	52 (16)
AE	101 (30)	39 (12)
Death	31 (9)	22 (7)
Consent withdrawal	30 (9)	23 (7)
Investigator decision	29 (9)	27 (8)
Lost to follow-up	1 (<1)	1 (<1)

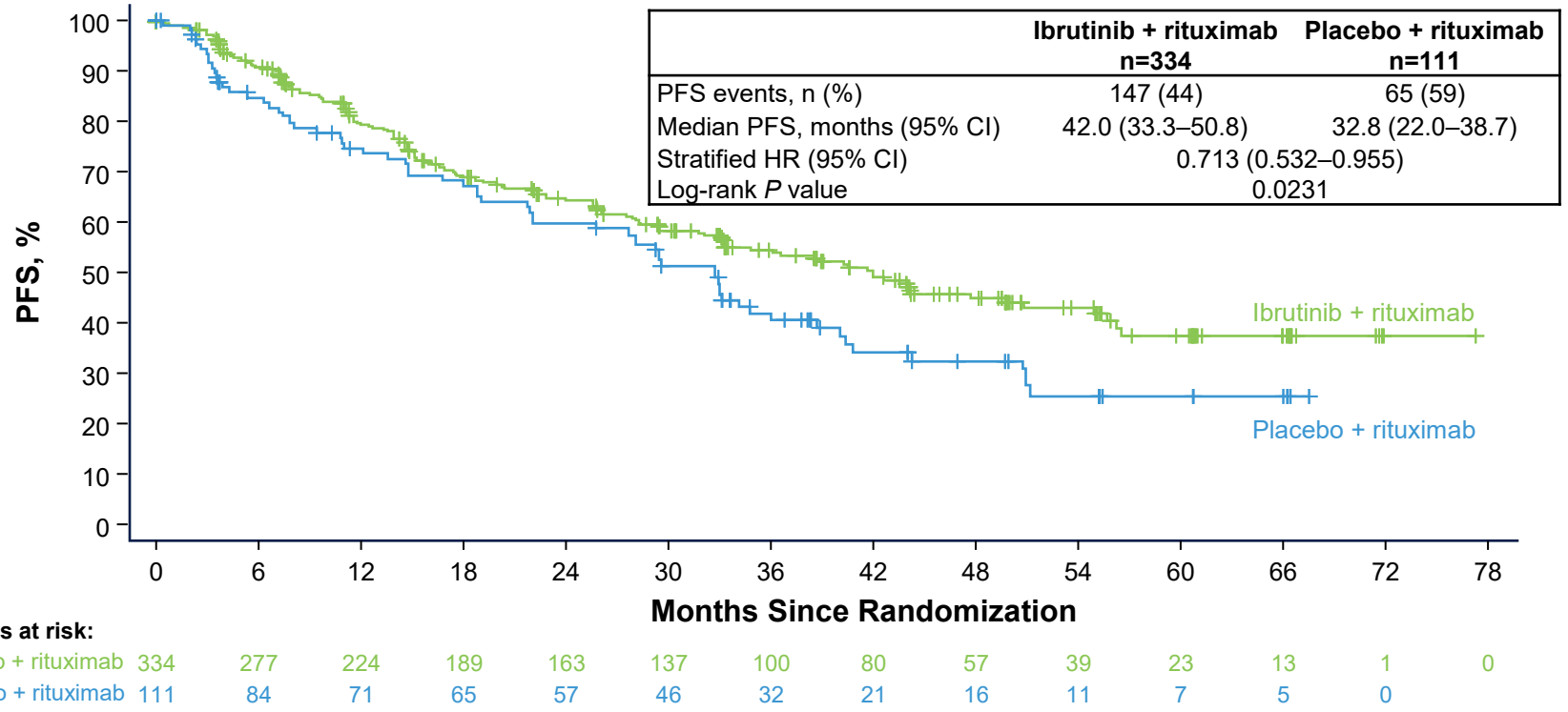
	Placebo	Rituximab
Discontinued, n (%)	**87 (78)**	**56 (50)**
PD	56 (50)	32 (29)
AE	12 (11)	8 (7)
Death	4 (4)	2 (2)
Consent withdrawal	5 (5)	5 (5)
Investigator decision	10 (9)	9 (8)
Lost to follow-up	0	0

AE, adverse event.

Primary End Point: PFS Was Significantly and Robustly Improved With Ibrutinib + Rituximab Versus Placebo + Rituximab

- **Median follow-up:**
  - 53.7 months (range, 0.03–82.8)

Primary End Point: Investigator-Assessed PFS (FDA Censoring Rules[a])



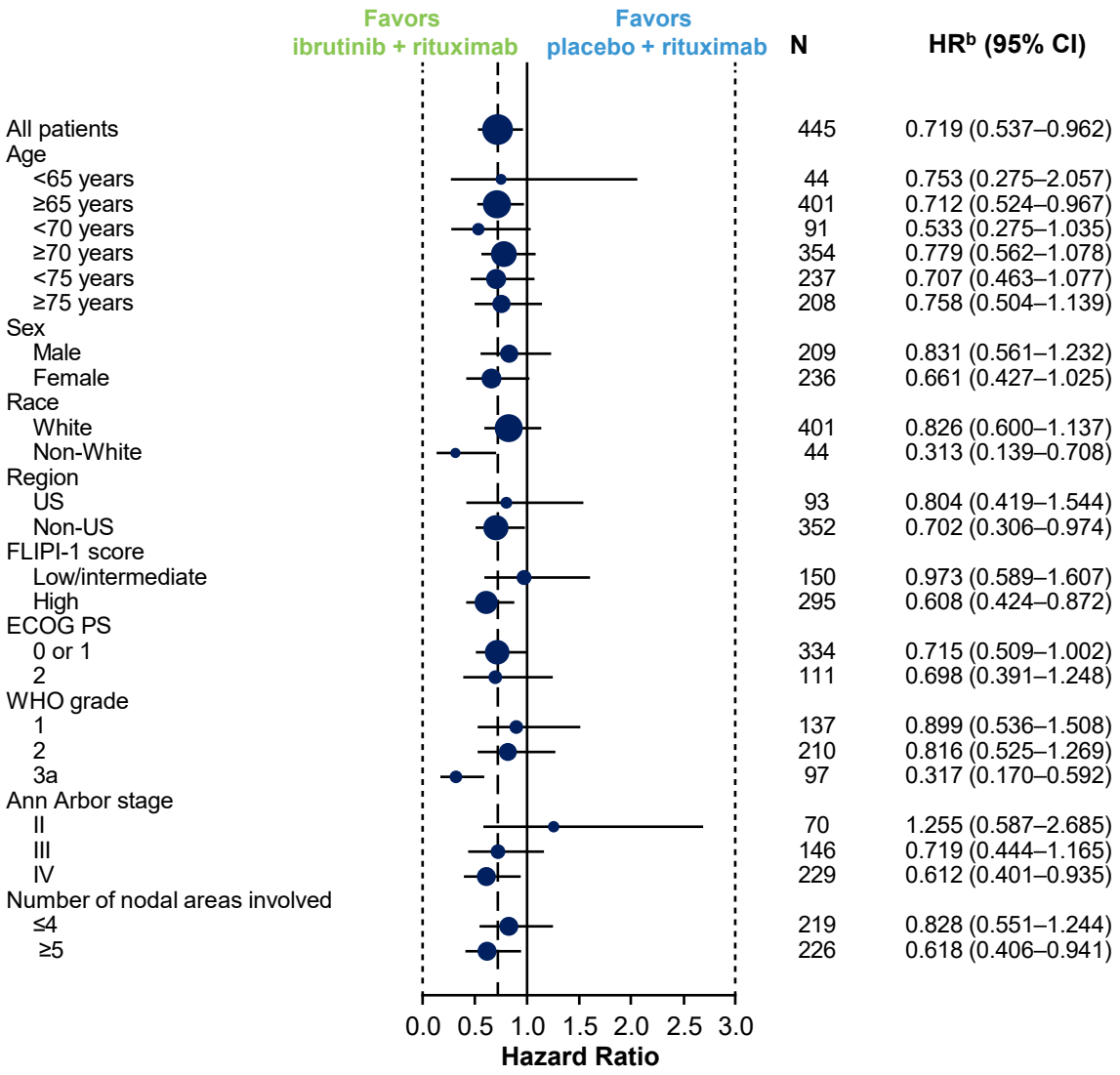
	Ibrutinib + rituximab n=334	Placebo + rituximab n=111
PFS events, n (%)	147 (44)	65 (59)
Median PFS, months (95% CI)	42.0 (33.3–50.8)	32.8 (22.0–38.7)
Stratified HR (95% CI)	0.713 (0.532–0.955)	
Log-rank *P* value	0.0231	

Median PFS, months	FDA censoring rules[a]				Global censoring rules[b]			
	Ibrutinib + rituximab n=334	Placebo + rituximab n=111	HR (95% CI)	Log-rank *P* value	Ibrutinib + rituximab n=334	Placebo + rituximab n=111	HR (95% CI)	Log-rank *P* value
Investigator assessment	42.0	32.8	0.713 (0.532–0.955)	0.0231	40.6	32.7	0.725 (0.545–0.965)	0.0274
IRC assessment	44.0	32.8	0.729 (0.537–0.990)	0.0419	44.0	32.8	0.735 (0.544–0.993)	0.0440

[a]Patients who did not experience PD or death, had subsequent anticancer therapy prior to PD, or were missing ≥2 consecutive assessments were censored at the last adequate disease assessment.
[b]Patients who did not experience PD or death or had subsequent anticancer therapy prior to PD were censored at the last adequate disease assessment.

The PFS[a] Benefit With Ibrutinib + Rituximab Versus Placebo + Rituximab Was Generally Consistent Across Subgroups

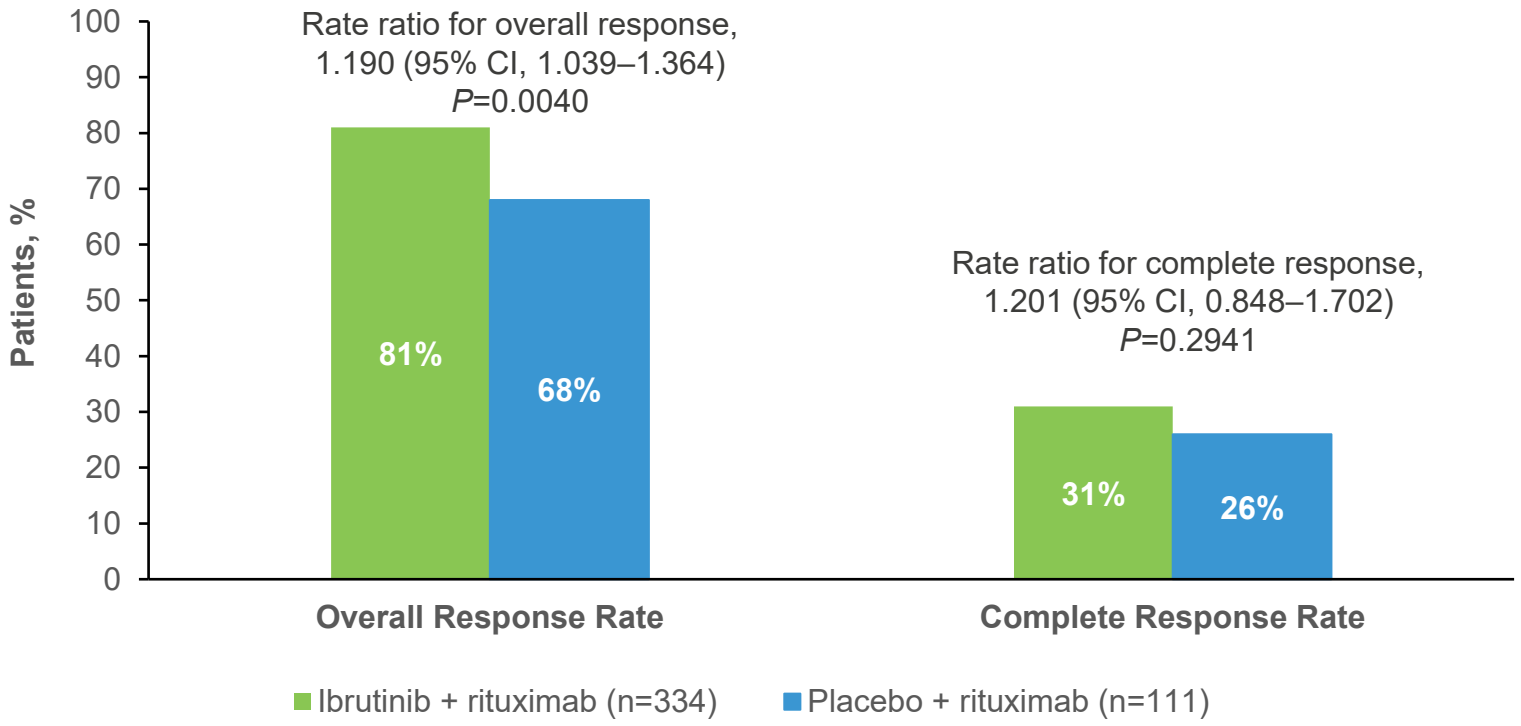
- PFS benefit with ibrutinib + rituximab was greater in patients with a high disease burden (Ann Arbor III–IV and 5 or more nodal areas) and in those with worse prognosis (high FLIPI-1 score)
- PFS benefit was observed with ibrutinib + rituximab irrespective of age, sex, race, region, and ECOG PS score



HR, hazard ratio.

[a]As assessed by investigators using FDA censoring rules (patients who did not experience PD or death, had subsequent anticancer therapy prior to PD, or were missing ≥2 consecutive assessments were censored at the last adequate disease assessment). [b]Hazard ratios were estimated by unstratified Cox regression.

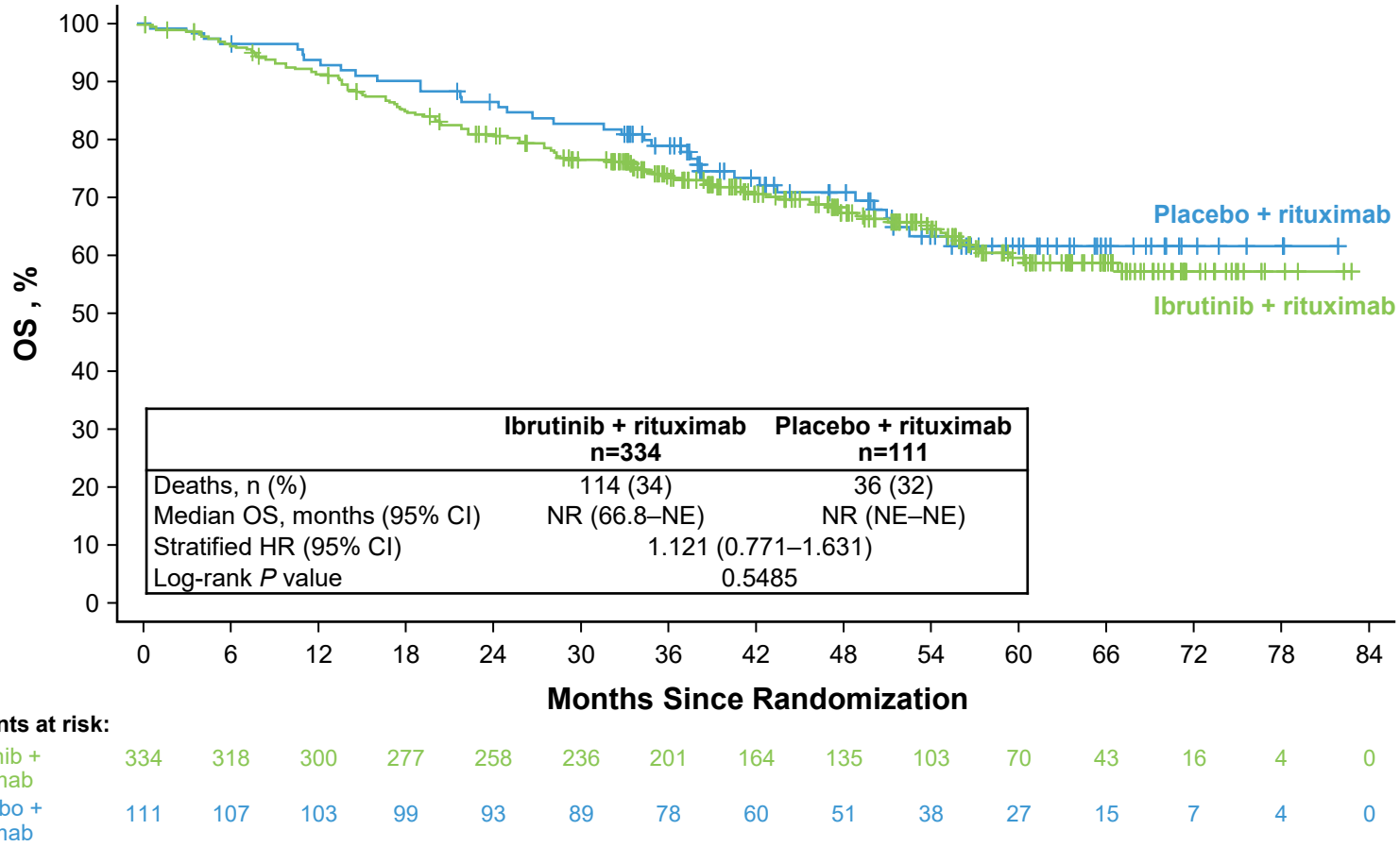
ORR Was Significantly Improved With Ibrutinib + Rituximab Versus Placebo + Rituximab



- Median DOR[a] was longer in the ibrutinib + rituximab arm than in the placebo + rituximab arm: 44.3 months (95% CI, 36.6–NE) versus 34.6 months (95% CI, 29.2–47.3)[b] (as assessed by investigators among responders)

DOR, duration of response.
[a]Using FDA censoring rules. [b]DOR was not included in the prespecified hierarchical testing procedure; results are descriptive only.

No Significant Difference in OS Was Observed With Ibrutinib + Rituximab Versus Placebo + Rituximab



	Ibrutinib + rituximab n=334	Placebo + rituximab n=111
Deaths, n (%)	114 (34)	36 (32)
Median OS, months (95% CI)	NR (66.8–NE)	NR (NE–NE)
Stratified HR (95% CI)	1.121 (0.771–1.631)	
Log-rank *P* value	0.5485	

Causes of Death (ITT Population)

Deaths, n (%)	Ibrutinib + rituximab n=334	Placebo + rituximab n=111
All deaths	114 (34)	36 (32)
AE	47 (14)	8 (7)
Underlying disease	23 (7)	10 (9)
Unknown	14 (4)	7 (6)
Other[a]	30 (9)	11 (10)

- Subsequent anticancer therapy was received by 34% of patients in the ibrutinib + rituximab arm versus 61% of patients in the placebo + rituximab arm

ITT, intent-to-treat; NE, not estimable; NR, not reached.
[a]Deaths that were reported after the treatment-emergent safety period and were not related to FL were captured as “other.”

The Safety Profile of Ibrutinib + Rituximab Was Consistent With Known Safety Profiles of the Individual Agents

- **Median duration of treatment:**
  - Ibrutinib + rituximab: 22.1 months (range, 0.03–82.3)
  - Placebo + rituximab: 22.1 months (range, 0.4–71.2)

AE, n (%)	Ibrutinib + rituximab n=330	Placebo + rituximab n=111
Any AE	324 (98)	106 (95)
Grade ≥3 AEs	259 (78)	63 (57)
Serious AEs	204 (62)	45 (41)
AEs leading to death[a]	48 (15)	6 (5)
AEs leading to discontinuation	144 (44)	16 (14)
Ibrutinib/placebo only	84 (25)	6 (5)
Rituximab only	2 (1)	0
Both	58 (18)	10 (9)
AEs leading to dose reduction[b]		
Ibrutinib/placebo only	80 (24)	3 (3)

AE, n (%)	Ibrutinib + rituximab n=330	Placebo + rituximab n=111
Most frequent any-grade AEs[c]		
Diarrhea	120 (36)	16 (14)
COVID-19	83 (25)	23 (21)
Fatigue	73 (22)	14 (13)
Nausea	70 (21)	12 (11)
Neutropenia	68 (21)	11 (10)
Urinary tract infection	67 (20)	12 (11)
Most frequent grade ≥3 AEs[d]		
Neutropenia	52 (16)	8 (7)
Pneumonia	30 (9)	5 (5)
Hypertension	27 (8)	6 (5)
COVID-19	21 (6)	2 (2)
COVID-19 pneumonia	21 (6)	3 (3)
Diarrhea	21 (6)	2 (2)
Grade ≥3 atrial fibrillation	15 (5)	2 (2)

- In the ITT population, IRRs occurred in 21% of patients in the ibrutinib + rituximab arm versus 27% in the placebo + rituximab arm (rate ratio 0.787 [95% CI, 0.544–1.137])

[a]AEs leading to death in ≥3 patients in the ibrutinib + rituximab arm were COVID-19 pneumonia (n=10), COVID-19 (n=6), septic shock (n=4), cardiac arrest (n=3), and pneumonia (n=3). [b]Dose reduction of rituximab was not permitted per protocol. [c]Occurring in ≥20% of patients in either arm. [d]Occurring in ≥5% of patients in either arm.

COVID-19 in the PERSPECTIVE Study

- Overall, 327 of these older and/or unfit patients (73%) received study treatment during the pandemic (Jan 27, 2020, onwards): ibrutinib + rituximab, 73%; placebo + rituximab, 74%
  - 39% of patients in the ibrutinib + rituximab arm and 42% in the placebo + rituximab arm received ≥1 COVID-19 vaccine dose

- COVID-19–related AEs of any grade occurred in 28% of patients who received ibrutinib + rituximab and 23% of those who received placebo + rituximab
  - Among patients diagnosed with COVID-19 infection, 33% and 30%, respectively, received antiviral and/or monoclonal antibody treatments for COVID-19

- Consistent with other studies conducted during the global pandemic that included a BTK inhibitor and an anti-CD20 antibody,[1-2] grade ≥3 COVID-19 AEs were more frequent in patients who received ibrutinib + rituximab (12% of patients) than in those who received placebo + rituximab (4%)

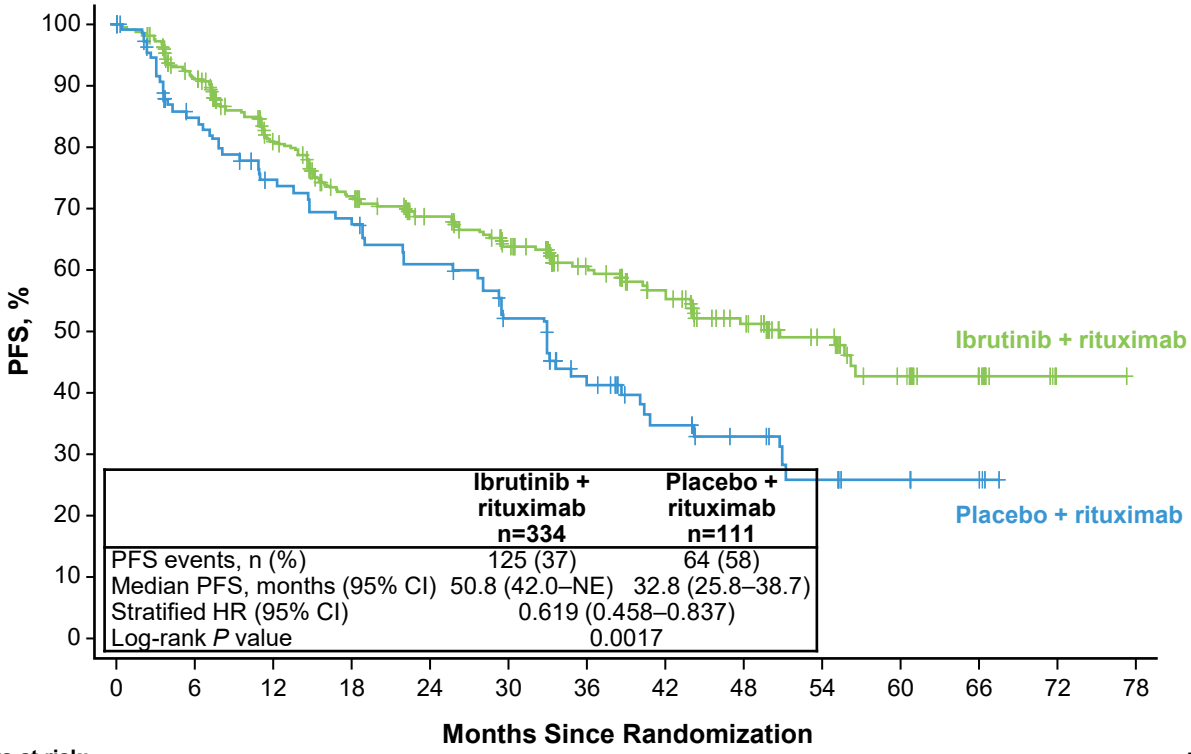
- In the ITT population, COVID-19–related death occurred in 9% and 7% of patients in the 2 arms, respectively

BTK, Bruton tyrosine kinase.

[1]Wang M et al. *J Clin Oncol.* 2025;JCO-25-00690 [online ahead of print]. [2]Zinzani PL et al. *J Clin Oncol*. 2023;41(33):5107-5117.

Impact of COVID-19 Deaths on PFS and OS: Improved Ibrutinib + Rituximab Arm Outcomes After Censoring

Investigator-Assessed PFS (COVID-19 Censoring[a])

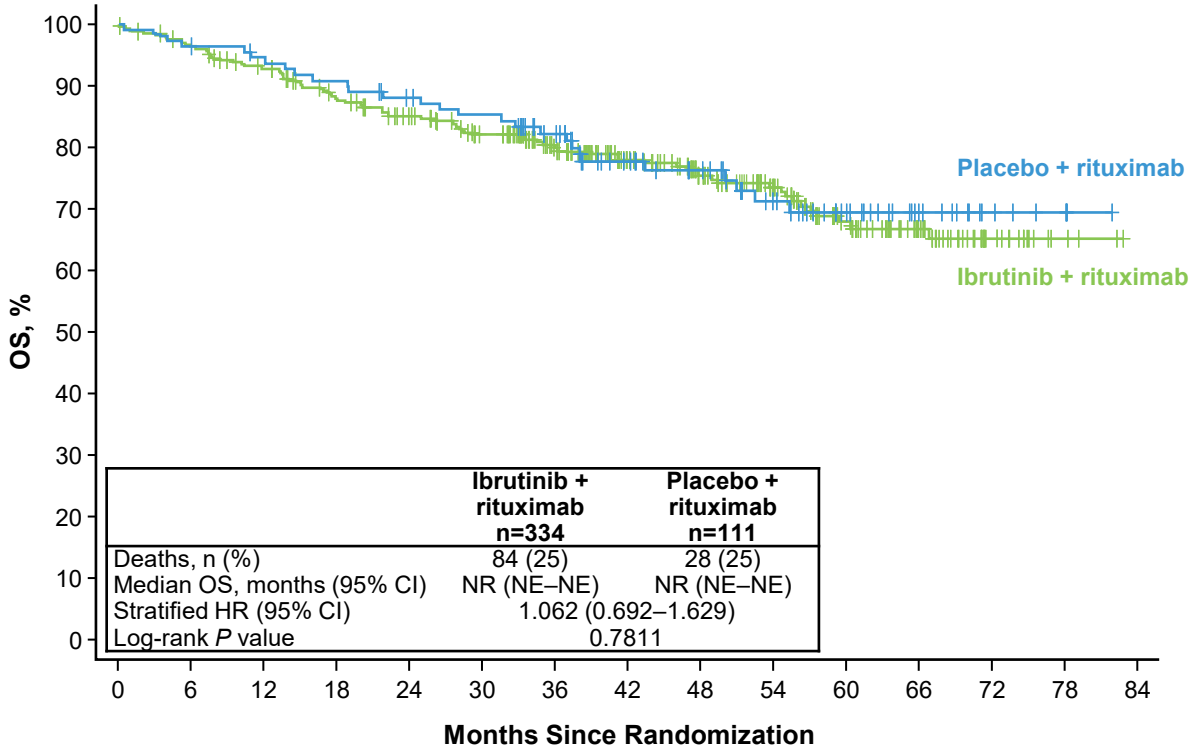


	Ibrutinib + rituximab n=334	Placebo + rituximab n=111
PFS events, n (%)	125 (37)	64 (58)
Median PFS, months (95% CI)	50.8 (42.0–NE)	32.8 (25.8–38.7)
Stratified HR (95% CI)	0.619 (0.458–0.837)	
Log-rank *P* value	0.0017	

Patients at risk:

Ibrutinib + rituximab	334	277	221	187	161	135	100	79	57	39	23	13	1	0
Placebo + rituximab	111	84	71	65	57	46	32	21	16	11	7	5	0	

OS (COVID-19 Censoring[b])



	Ibrutinib + rituximab n=334	Placebo + rituximab n=111
Deaths, n (%)	84 (25)	28 (25)
Median OS, months (95% CI)	NR (NE–NE)	NR (NE–NE)
Stratified HR (95% CI)	1.062 (0.692–1.629)	
Log-rank *P* value	0.7811	

Patients at risk:

Ibrutinib + rituximab	334	318	300	277	258	236	201	164	135	103	70	43	16	4	0
Placebo + rituximab	111	107	103	99	93	89	78	60	51	38	27	15	7	4	0

- Censoring for COVID-19 deaths resulted in a more pronounced treatment effect for ibrutinib + rituximab versus placebo + rituximab, with a longer estimated median PFS in the ibrutinib + rituximab arm

[a]Patients who had subsequent anticancer therapy prior to PD, were missing ≥2 consecutive assessments, or died due to COVID-19 without PD were censored at the last adequate overall disease assessment. [b]Patients who died due to COVID-19 were censored 1 day prior to death.

Conclusions

Ibrutinib + rituximab significantly improved PFS versus placebo + rituximab in patients with previously untreated FL not eligible for CIT

Ibrutinib + rituximab also significantly improved ORR, but there was no significant difference in OS between the treatment arms

COVID-19 events had a meaningful impact on PFS and OS, similar to findings from other studies of BTK inhibitors in lymphoid malignancies[1-3]

The safety profile of ibrutinib + rituximab was consistent with the known safety profiles of the individual agents

This study supports the effectiveness of ibrutinib + rituximab for the treatment of FL, specifically in older/unfit patients who are not eligible for aggressive CIT regimens

[1]Wang M et al. *J Clin Oncol.* 2025;JCO-25-00690 [online ahead of print]. [2]Brown JR et al. *N Engl J Med*. 2025;392:748–762. [3]Tam CS et al. *Lancet Oncol*. 2022;23:1031–1043.

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Disclosures

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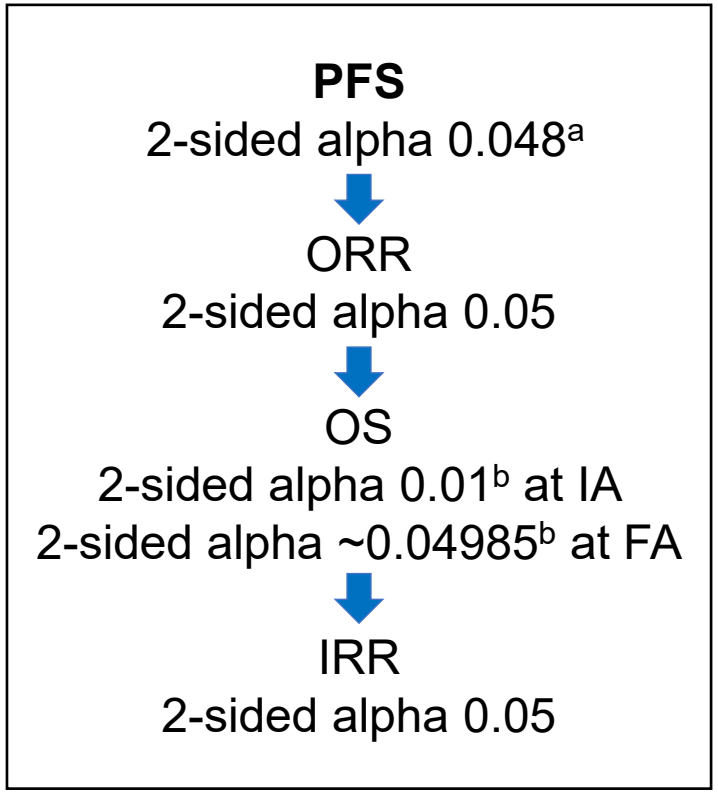
Supplementary Information

Hierarchical Order of Closed Testing Procedure and PFS Censoring Rules

Hierarchical Testing



US FDA PFS censoring rules:

- At the last non-PD assessment
- **Subsequent anticancer therapy**
- **Missing ≥2 consecutive assessments regardless of PFS event status**

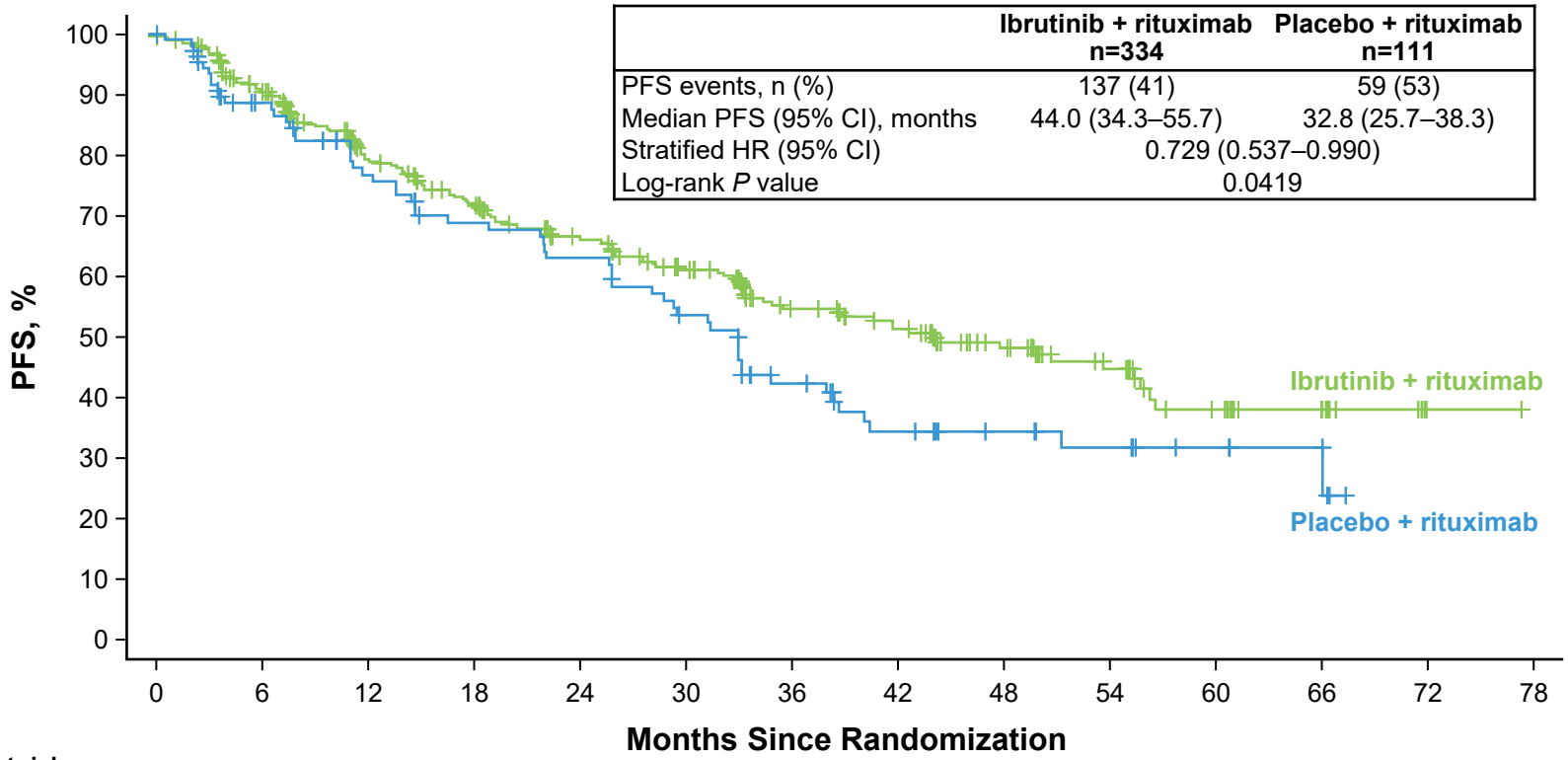
Global PFS censoring rules:

- At the last non-PD assessment
- **Subsequent anticancer therapy**

FA, final analysis; IA, interim analysis; IRR, infusion-related reaction; PD, progressive disease; PFS, progression-free survival.
[a]α=0.002 was spent at Interim Analysis (July 2022). [b]Based on Haybittle-Peto boundary.

Sensitivity Analyses: PFS Was Significantly and Robustly Improved With Ibrutinib + Rituximab Versus Placebo + Rituximab

Sensitivity Analysis: Independent Review Committee-Assessed PFS (FDA Censoring Rules[a])



	Ibrutinib + rituximab n=334	Placebo + rituximab n=111
PFS events, n (%)	137 (41)	59 (53)
Median PFS (95% CI), months	44.0 (34.3–55.7)	32.8 (25.7–38.3)
Stratified HR (95% CI)	0.729 (0.537–0.990)	
Log-rank *P* value	0.0419	

Patients at risk:

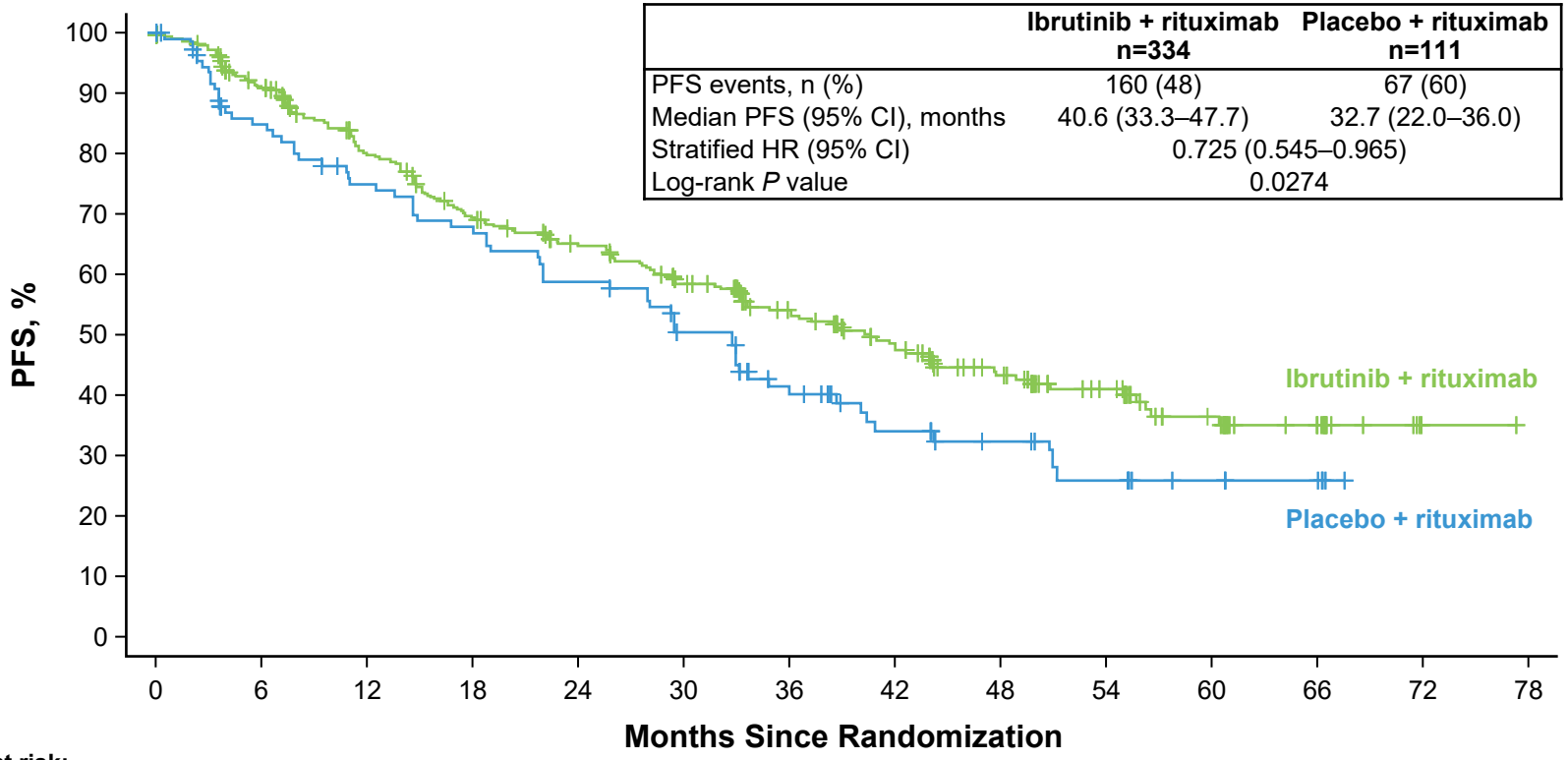
Ibrutinib + rituximab	334	279	220	192	160	131	91	75	53	36	20	12	1	0
Placebo + rituximab	111	85	69	59	54	44	30	21	15	12	7	5	0	

[a]Patients who did not experience PD or death, had subsequent anticancer therapy prior to PD, or were missing ≥2 consecutive assessments were censored at the last adequate disease assessment.

Sensitivity Analyses: PFS Was Significantly and Robustly Improved With Ibrutinib + Rituximab Versus Placebo + Rituximab

Sensitivity Analysis: Investigator-Assessed PFS (Global Censoring Rules[a])

	Ibrutinib + rituximab n=334	Placebo + rituximab n=111
PFS events, n (%)	160 (48)	67 (60)
Median PFS (95% CI), months	40.6 (33.3–47.7)	32.7 (22.0–36.0)
Stratified HR (95% CI)	0.725 (0.545–0.965)	
Log-rank *P* value	0.0274	



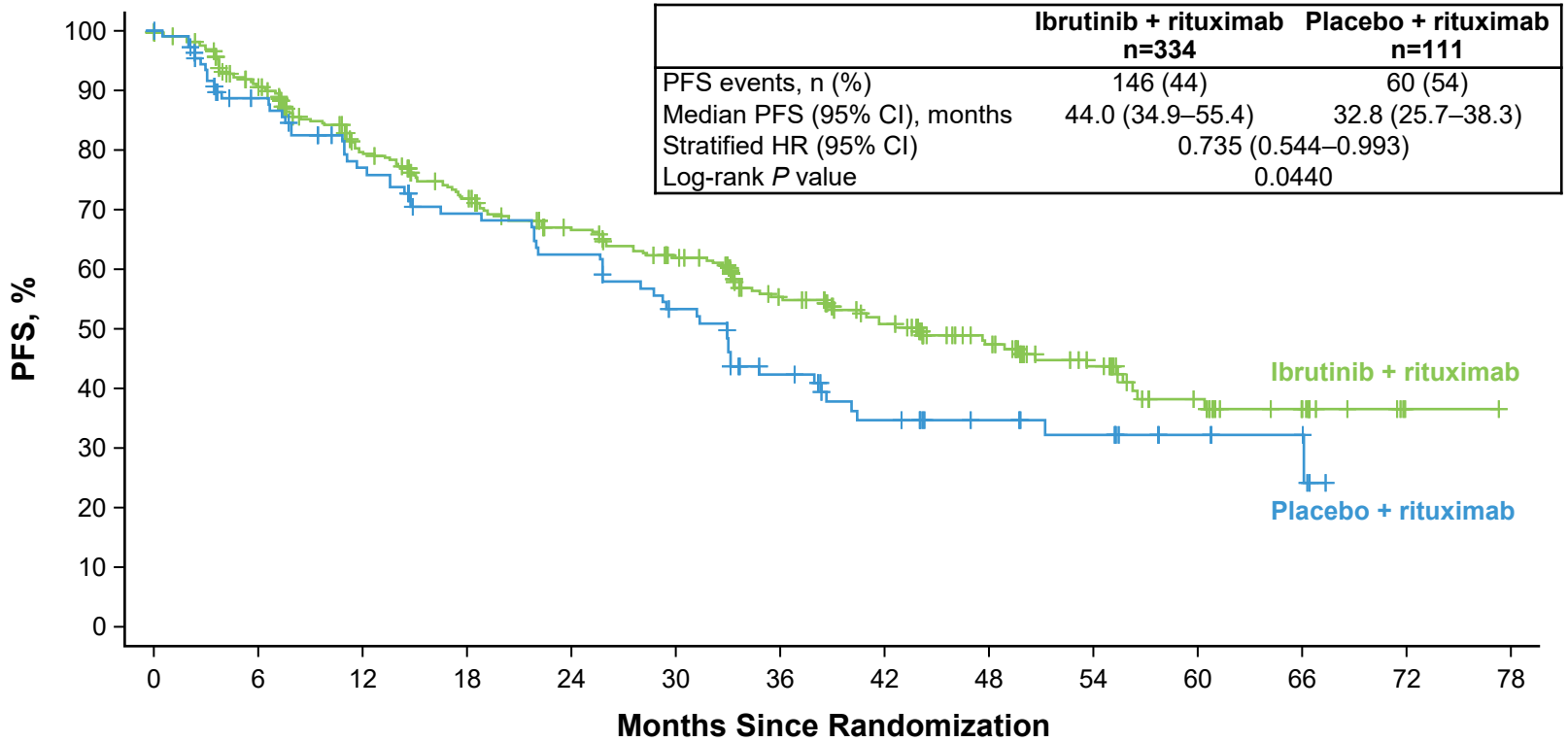
Patients at risk:

Ibrutinib + rituximab	334	282	233	199	177	151	114	90	65	45	26	14	1	0
Placebo + rituximab	111	86	74	67	58	47	33	22	17	12	7	5	0	

[a]Patients who did not experience PD or death or had subsequent anticancer therapy prior to PD were censored at the last adequate disease assessment.

Sensitivity Analyses: PFS Was Significantly and Robustly Improved With Ibrutinib + Rituximab Versus Placebo + Rituximab

Sensitivity Analysis: Independent Review Committee-Assessed PFS (Global Censoring Rules[a])



	Ibrutinib + rituximab n=334	Placebo + rituximab n=111
PFS events, n (%)	146 (44)	60 (54)
Median PFS (95% CI), months	44.0 (34.9–55.4)	32.8 (25.7–38.3)
Stratified HR (95% CI)	0.735 (0.544–0.993)	
Log-rank *P* value	0.0440	

Patients at risk:

Ibrutinib + rituximab	334	282	227	199	173	149	108	86	62	42	23	13	1	0
Placebo + rituximab	111	86	71	61	55	45	31	22	16	13	7	5	0	

[a]Patients who did not experience PD or death or had subsequent anticancer therapy prior to PD were censored at the last adequate disease assessment.