haematologica
Journal of the Ferrata Storti Foundation

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Received: June 13, 2026.
Accepted: September 15, 2026.

Citation: Julia Wang, Dongni Yi, Yajuan Gao, Fang Yang, Robin R. Klebig, Jonas Paludo, Javier L. Munoz, Muhamad Alhaj Moustafa, Madiha Iqbal, Julio C. Chavez, Yucai Wang and Jithma P. Abeykoon. Rituximab maintenance following frontline bendamustine-rituximab in mantle cell lymphoma: a systematic review and meta-analysis. Haematologica. 2026 Sept 24. doi: 10.3324/haematol.2026.301413 [Epub ahead of print]

Rituximab maintenance following frontline bendamustine-rituximab in mantle cell lymphoma: a systematic review and meta-analysis

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Running head: Rituximab maintenance after BR in MCL

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Author contributions: J.W., Y.W., and J.P.A. conceived and designed the study. J.W. and Y.W. collected the data. J.W., Y.W., and J.P.A. performed the data analysis. J.W. drafted the first version of the manuscript. Y.W. and J.P.A. critically revised the manuscript. D.Y., Y.G., R.R.K., J.P., J.L.M., M.A.M., M.I., and J.C.C. contributed to data interpretation and critically revised the manuscript for important intellectual content. All authors reviewed and approved the final manuscript.

Data-sharing statement: Our data were derived from published studies, which are publicly available in the original sources. No new patient-level data were generated or collected for this meta-analysis. Details regarding data extraction and analytic code are available from the corresponding author upon reasonable request.

Trial registration: Not applicable.

Acknowledgment: The authors thank all investigators whose published studies were included in this systematic review and meta-analysis. Their contributions made this work possible.

Funding: None

Conflict of interest disclosure

JP reports research funding from Karyopharm, Biofourmis, and AstraZeneca, and honoraria from AbbVie, all paid to his institution.

JLM reports consulting for Pharmacyclics/AbbVie, Bayer, Gilead/Kite, BeiGene, Pfizer, Janssen, Celgene/BMS, Kyowa, Alexion, Fosun Kite, Seattle Genetics, Karyopharm, Aurobindo, Verastem, Genmab, Genzyme, Genentech/Roche, ADC Therapeutics, Epizyme, BeiGene, Novartis, MorphoSys/Incyte, MEI, TG Therapeutics, AstraZeneca, Eli Lilly; research funding from Bayer, Gilead/Kite, Celgene, Merck, Portola, Incyte, Genentech, Pharmacyclics, Seattle Genetics, Janssen, Millennium, Novartis, BeiGene; and honoraria from Targeted Oncology, OncView, Curio, and Physicians' Education Resource.

MAM reports consultancy for Genetech, AbbVie, and Acrotech.

JCC reports consulting for Genetech, Genmab, BMS, Kite/Gilead; and research support from Genmab.

YW reports research funding (to institution) from Incyte, InnoCare, Loxo Oncology, Eli Lilly, MorphoSys, Novartis, Genentech, Genmab, AbbVie, BeiGene, BeOne, Merck, AstraZeneca, and Bristol Myers Squibb; participation in advisory boards (compensation to institution) for Eli Lilly, Loxo Oncology, TG Therapeutics, Incyte, InnoCare, Kite, Janssen, BeiGene, BeOne, AstraZeneca, Genmab, and AbbVie; consultancy (compensation to institution) for InnoCare and AbbVie; and honoraria (to institution) from Kite.

JPA reports research funding from Qurion, CRISPR Therapeutics, Eli Lilly and BioMed Valley Discoveries for clinical trials, all paid to his institution.

To the Editor,

Frontline immunochemotherapy in mantle cell lymphoma (MCL) continues to evolve, yet bendamustine–rituximab (BR) remains a widely used standard-of-care regimen, particularly in older, unfit, or transplant-ineligible patients. While rituximab maintenance has demonstrated a clear survival benefit following R-CHOP induction in transplant-ineligible patients,[1] as well as after autologous stem cell transplantation (ASCT),[2] its role after BR remains uncertain. The randomized phase II MAINTAIN trial, conducted within the StiL NHL7-2008 study, did not demonstrate a statistically significant improvement in progression-free survival (PFS) or overall survival (OS) with rituximab maintenance compared with observation.[3] However, several observational studies have reported improved outcomes with rituximab maintenance in this setting,[4,5] resulting in discrepant findings between prospective and observational evidence.

Clarifying the benefit of rituximab maintenance following BR is clinically important. BR is frequently used in routine practice, and although maintenance strategies represent a relatively low-toxicity intervention with the potential to prolong remission, adoption of rituximab maintenance has been variable in clinical practice. In addition, its use following frontline BR in MCL has been inconsistently incorporated across clinical trials, which may complicate the interpretation of trial results for application to clinical practice. Given these considerations, a systematic synthesis of the available evidence is needed to better define the role of rituximab maintenance after frontline BR in MCL.

We therefore performed a systematic review and meta-analysis of randomized clinical trials and observational studies evaluating rituximab maintenance versus observation after frontline BR following PRISMA guidelines. PubMed/MEDLINE, Embase, and major hematology and oncology conference proceedings (including ASH, ASCO, and EHA) were searched from inception through April 2026. Ethical approval (Institution Review Board review) and patient consent were not required because only published, anonymized data were used. Eligible studies included

randomized trials and observational cohort or registry studies reporting hazard ratios (HRs) with 95% confidence intervals (CIs) for PFS and/or OS, or sufficient data for HR estimation (Supplemental Figure 1A). For non–clinical trial studies, event-free survival (EFS) or time to next treatment or death (TTNT) were treated as proxies for PFS in this analysis. Study selection and data extraction were performed independently by two investigators (J.W. and Y.W.), with discrepancies resolved by consensus. Heterogeneity across studies was assessed using the I^2 statistic. Publication bias was assessed through visual inspection of funnel plots. HRs and corresponding 95% CIs were pooled using an inverse-variance method. A random effects model (DerSimonian–Laird) was used for the primary analysis to account for potential between-study variability, and common effect models were applied in sensitivity analyses to evaluate the robustness of the findings.

A total of 242 publications were identified, of which 7 studies met inclusion criteria, comprising 2,698 patients (Supplemental Figure 1B). These included one randomized clinical trial (MAINTAIN)[3] and six observational studies reflecting real-world practice (3 observational studies [predominantly academic centers][5-7], 1 Flatiron-based study,[4] 1 SEER-Medicare-based study,[8] and 1 Danish registry-based study[9]) (Table 1). The British Columbia study (n=190) allowed ASCT after BR (n=71);[7] all other studies excluded patients who underwent ASCT. Among all patients considered “eligible for” rituximab maintenance (Table 1), 1,370 patients (50.8%) received it. Median follow-up ranged from 3.1–6.1 years, and reported maintenance schedules varied, most commonly every 2–3 months for up to 2–3 years (Table 1).

All included studies reported OS outcomes, while five studies (including the MAINTAIN trial) reported PFS (or EFS or TTNT). The degree of heterogeneity among studies was low for PFS (I^2=0%, p=0.65) and low to moderate for OS (I^2=27%, p=0.22) (Figure 1). Publication bias assessment was limited by the total number of studies. Nevertheless, funnel plot inspection did not suggest significant publication bias for PFS or OS (Supplemental Figure 2).

Rituximab maintenance was associated with a statistically significant improvement in PFS (pooled HR 0.56, 95% CI 0.49–0.63, p<0.001) (Figure 1A). Similarly, rituximab maintenance was also associated with a statistically significant OS benefit (pooled HR 0.64, 95% CI 0.52–0.77, p<0.001) (Figure 1B). Analyses using a common effect model yielded similar estimates for both PFS and OS (Figure 1). In a sensitivity analysis excluding the British Columbia study that allowed ASCT after BR,[7] the results remained consistent, with similar PFS (pooled HR 0.56, 95% CI 0.49–0.63, p<0.001) and OS (pooled HR 0.63, 95% CI 0.51–0.78, p<0.001) estimates. Leave-one-out sensitivity analyses also demonstrated consistent findings, with no individual study materially altering the pooled PFS or OS estimates (Supplemental Figure 3A). Subgroup analyses stratified by endpoint (PFS vs EFS vs TTNT) or outcome measurement starting time (from BR start vs from an end-of-BR landmark) were also supportive of the overall results (Supplemental Figures 3B-D). Collectively, these findings demonstrate a consistent and clinically meaningful association between rituximab maintenance and improved PFS and OS outcomes following frontline BR in MCL.

Several factors may explain the differences between the MAINTAIN trial and observational studies. First, the MAINTAIN trial was relatively small (n=122) and may have been underpowered to detect modest differences in PFS (median 72.3 vs 54.7 months, HR 0.71, 95% CI 0.41–1.23).[3] Second, patient selection in clinical trials often differs from that in real-world populations, with trial participants generally fitter and having fewer comorbidities. In contrast, observational studies may better reflect the broader population treated in routine practice, including older patients and those ineligible for more intensive therapies, among whom maintenance strategies may provide greater relative benefit. Third, differences in treatment era, geographic region, access to subsequent therapies, and supportive care may also have contributed. The MAINTAIN trial was conducted in Germany and Austria and enrolled patients treated earlier than those included in several large

North American observational studies; differences in post-relapse treatment options may therefore have influenced OS outcomes.

There is plausible biological rationale supporting rituximab maintenance in MCL, as prolonged CD20-directed therapy may help suppress minimal residual disease and delay clonal regrowth after induction treatment. In transplant-ineligible patients, the European MCL Elderly trial demonstrated significant improvements in remission duration and OS following R-CHOP induction, while the randomized LyMa trial showed improved PFS and OS after ASCT.[1,2] Our meta-analysis now extends this body of evidence to patients treated with first-line BR (without ASCT), suggesting that the benefit of rituximab maintenance in MCL may reflect sustained immunologic control of residual disease irrespective of the induction backbone.

Our findings suggest that contemporary clinical trials using BR as the control arm should ideally incorporate rituximab maintenance to reflect current evidence-based practice. This approach was adopted in trials such as ENRICH[10] and ECHO,[11] whereas the MANGROVE[12] trial did not include rituximab maintenance following BR; therefore, differences in maintenance strategy should be considered when interpreting efficacy across these studies. In contrast, other bendamustine-based regimens, such as R-BAC500[13] and V-RBAC,[14] incorporate additional active agents (e.g., cytarabine and/or venetoclax) and represent distinct induction strategies rather than conventional BR. Accordingly, the findings in our meta-analysis should not be directly extrapolated to these intensified regimens.

The strengths of this analysis include a comprehensive and systematic literature search, inclusion of both randomized controlled trials and real-world observational studies, and the robustness of findings across multiple sensitivity analyses. The consistency of PFS and OS effect estimates across study designs and sensitivity analyses strengthens the overall signal supporting rituximab maintenance after BR in MCL. Nevertheless, several limitations should be acknowledged. First, the majority of included evidence is derived from observational studies, which are inherently

subject to selection bias, confounding by indication, and heterogeneity in treatment practices, and formal risk-of-bias assessment was not comprehensively performed. Although the consistency of results and the generally low-to-moderate statistical heterogeneity support the robustness of the findings, residual confounding cannot be excluded. Second, variability in maintenance schedules, duration of therapy, subsequent therapies, follow-up across studies, rituximab maintenance eligible population definition, and endpoints definition and calculation may have influenced reported outcomes. Third, patient-level data were not available, limiting the ability to adjust for key prognostic variables or perform subgroup analyses. In particular, the lack of data on biologically relevant factors such as Ki-67 proliferation index, *TP53* alterations, and blastoid or pleomorphic morphology precluded assessment of whether benefit differs across high-risk subgroups. Lastly, our study focused on efficacy and did not address adverse events of rituximab maintenance.

In conclusion, this systematic review and meta-analysis demonstrates that rituximab maintenance following frontline BR induction in MCL is associated with significant improvements in both PFS and OS, providing a strong rationale for its incorporation into contemporary management strategies and future clinical trial design. From a clinical perspective, these findings support its use in patients who respond to frontline BR and are suitable for ongoing therapy. While toxicity data were not systematically assessed in this analysis, rituximab is generally considered to have a manageable safety profile in clinical practice, which may further support its feasibility as a maintenance approach. Importantly, treatment decisions should remain individualized, taking into account patient characteristics, comorbidities, infection risk, and patient preferences.

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Table 1. Summary of Included Studies

Study	Study setting	N (total)	n (RM)	n (no RM)	RM schedule	Median follow-up (years)	Endpoint calculation	Median PFS/EFS/TTNT, RM vs no RM	PFS/EFS/TTNT: HR (95% CI)	PFS/EFS/TTNT: P value	Median OS, RM vs no RM	OS: HR (95% CI)	OS: P value
Rummel et al, 2016	StiL randomized clinical trial	122	60	62	Every 2 months for 2 years	4.9	PFS and OS from trial registration (BR start) in patients responding to BR	72.3 vs 54.7 months	0.71 (0.41–1.23), UVA	0.2267	NR vs NR	1.51 (0.70–3.25), UVA	0.2974
Hill et al, 2019	US multicenter retrospective study	135	78	57	–	3.1	OS from first systemic treatment in patients responding to BR	–	–	–	NR vs 6 years	0.28 (0.10–0.79), MVA including MIPI	0.016
Villa et al, 2020	British Columbia observational study	190	144	46	Weekly x8 (22%), or every 3 months for 2 years (78%)	3.1	PFS and OS from BR initiation (landmark analysis[1])	–	1.03 (0.24–4.40), UVA	0.969	–	1.13 (0.15–8.67), UVA	0.905
Martin et al, 2022	US Flatiron database	1106	427	679	–	3.8	TTNT and OS from BR start in RM-eglible[2] cohort	65.3 vs 37.7 months	0.51 (0.42–0.62), UVA	0.001	89.5 vs 78.1 months	0.66 (0.52–0.84), UVA	0.001
Di et al, 2023	US SEER-Medicare database	198	98	100	–	5.7	OS from BR start in RM-eligible[3] patients	–	–	–	–	0.58 (0.35–0.97), UVA[4]	–
Wang et al, 2026	North America multicenter observational study	703	394	309	Most commonly every 2-3 months for 2-3 years	5.8	EFS and OS from the 3-month landmark after BR completion in RM-eligible[5] patients	49.9 vs 29.7 months	0.58 (0.48–0.71), MVA including sex and simplified MIPI	0.001	109.5 vs 74.2 month	0.59 (0.46–0.75), MVA including sex and simplified MIPI	0.001
Brieghel et al, 2026	Danish National Lymphoma Registry	244	169	75	–	6.1	TTNT and OS from the 3-month landmark after BR completion in RM-eligible[5] patients	6.1 vs 4.2 years	0.59 (0.40–0.86), MVA[6]	–	7.0 vs 5.1 years	0.62 (0.41–0.93), MVA[6]	–

[1]Univariate landmark analyses were performed by excluding patients with progressive disease, death, or loss to follow-up within 18 months of BR initiation.

[2]RM-eligible cohort included patients who were alive and did not initiate second-line treatment within 8 months of starting BR.

[3]In order to minimize the potential immortal bias, for the non-RM group, the authors included patients who had a treatment gap (recipients of second-line therapy) or survival (no second-line therapy given) of ≥200 days after the completion of the first-line therapy, to ensure a sufficient amount of time to have been considered for RM.

[4]The analysis was performed in a matched study sample using propensity score matching (ratio=1:1, greedy nearest neighbor with caliper=0.10) based on age, sex, race, marital status, Medicaid dual coverage, residence, poverty, frailty, comorbidities (modified Elixhauser index), year of diagnosis, extranodal disease, stage, first-line regimen (R-CHOP vs. BR), and duration of first-line therapy.

[5]Patients who achieved a response to BR and had no evidence of progressive disease or second-line therapy by the landmark (3-month after BR completion) were deemed eligible for rituximab maintenance.

[6]An overlap-weighted propensity score matched Cox model including age, sex, polypharmacy, Charlson comorbidity index, and MIPI.

Abbreviations: BR, bendamustine and rituximab; CI, confidence interval; EFS, event-free survival; HR, hazard ratio; MIPI, mantle cell lymphoma international prognostic index; MVA, multivariable analysis; NR: not reached; OS, overall survival; PFS, progression-free survival; RM, rituximab maintenance; TTNT, time to next treatment or death; UVA, univariable analysis.

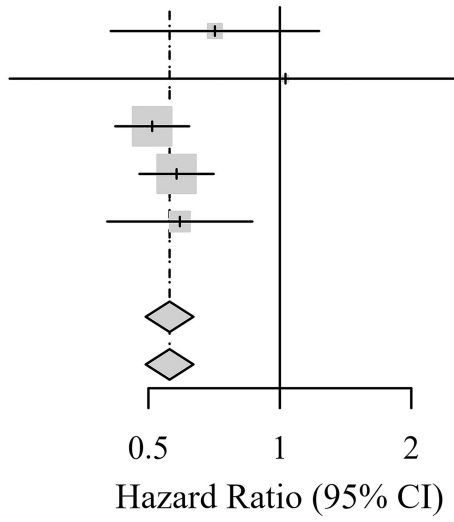
Figure legends

Figure 1. **Association of rituximab maintenance with progression-free and overall survival following frontline bendamustine–rituximab in mantle cell lymphoma.** Forest plot of (A) progression-free survival and (B) overall survival associated with rituximab maintenance following frontline bendamustine–rituximab in mantle cell lymphoma. Squares represent study-specific estimates, horizontal lines indicate 95% CIs, and diamonds represent pooled estimates.

A

Study	logHR	SE	Weight (common)	Weight (random)	HR	95% CI
Rummel 2016	−0.3425	0.28	5.3%	5.3%	0.71	[0.41; 1.23]
Villa 2020	0.0296	0.74	0.7%	0.7%	1.03	[0.24; 4.41]
Martin 2022	−0.6733	0.10	41.8%	41.8%	0.51	[0.42; 0.62]
Wang 2026	−0.5447	0.10	41.4%	41.4%	0.58	[0.48; 0.71]
Brieghel 2026	−0.5276	0.20	10.8%	10.8%	0.59	[0.40; 0.87]
Common effect model			**100.0%**	.	**0.56**	**[0.49; 0.63]**
Random effects model			.	**100.0%**	**0.56**	**[0.49; 0.63]**

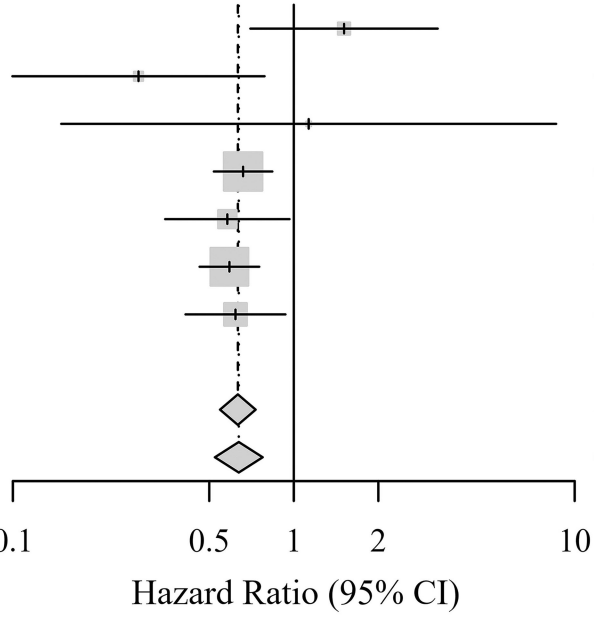
Heterogeneity: $I^2 = 0.0\%$, $\tau^2 = 0$, $p = 0.6497$



B

Study	logHR	SE	Weight (common)	Weight (random)	HR	95% CI
Rummel 2016	0.4121	0.39	3.6%	5.9%	1.51	[0.70; 3.25]
Hill 2019	−1.2730	0.53	2.0%	3.4%	0.28	[0.10; 0.79]
Villa 2020	0.1222	1.03	0.5%	0.9%	1.13	[0.15; 8.59]
Martin 2022	−0.4155	0.12	37.1%	31.1%	0.66	[0.52; 0.84]
Di 2023	−0.5447	0.26	8.2%	11.8%	0.58	[0.35; 0.97]
Wang 2026	−0.5276	0.12	35.8%	30.5%	0.59	[0.46; 0.75]
Brieghel 2026	−0.4780	0.21	12.7%	16.4%	0.62	[0.41; 0.93]
Common effect model			**100.0%**	.	**0.63**	**[0.55; 0.73]**
Random effects model			.	**100.0%**	**0.64**	**[0.52; 0.77]**

Heterogeneity: $I^2 = 26.8\%$, $\tau^2 = 0.0172$, $p = 0.2244$

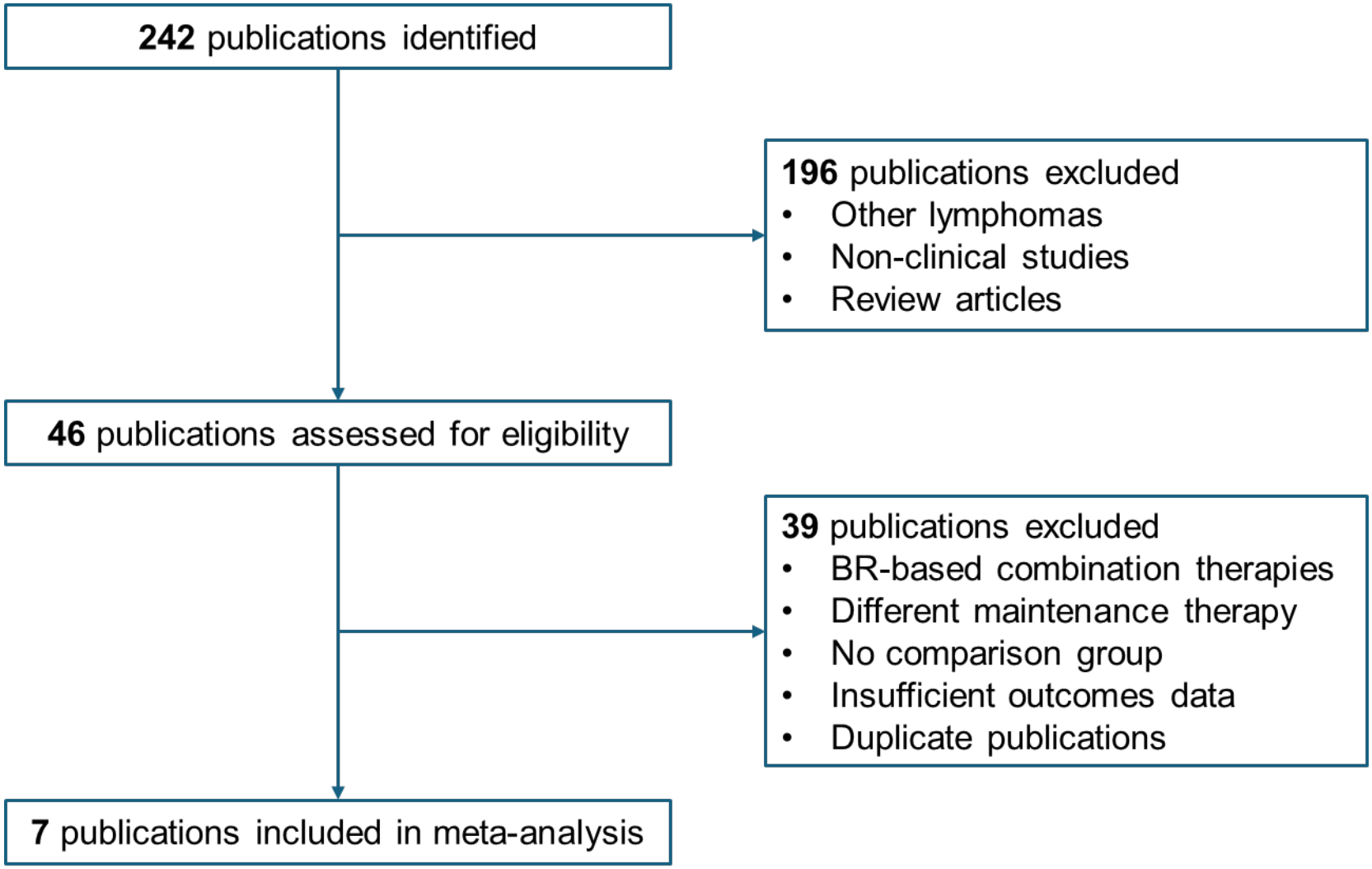


Supplemental Figure 1. Study Selection Process. (A) Inclusion and Exclusion Criteria for Study Selection. (B) Flow Diagram of Study Identification and Selection

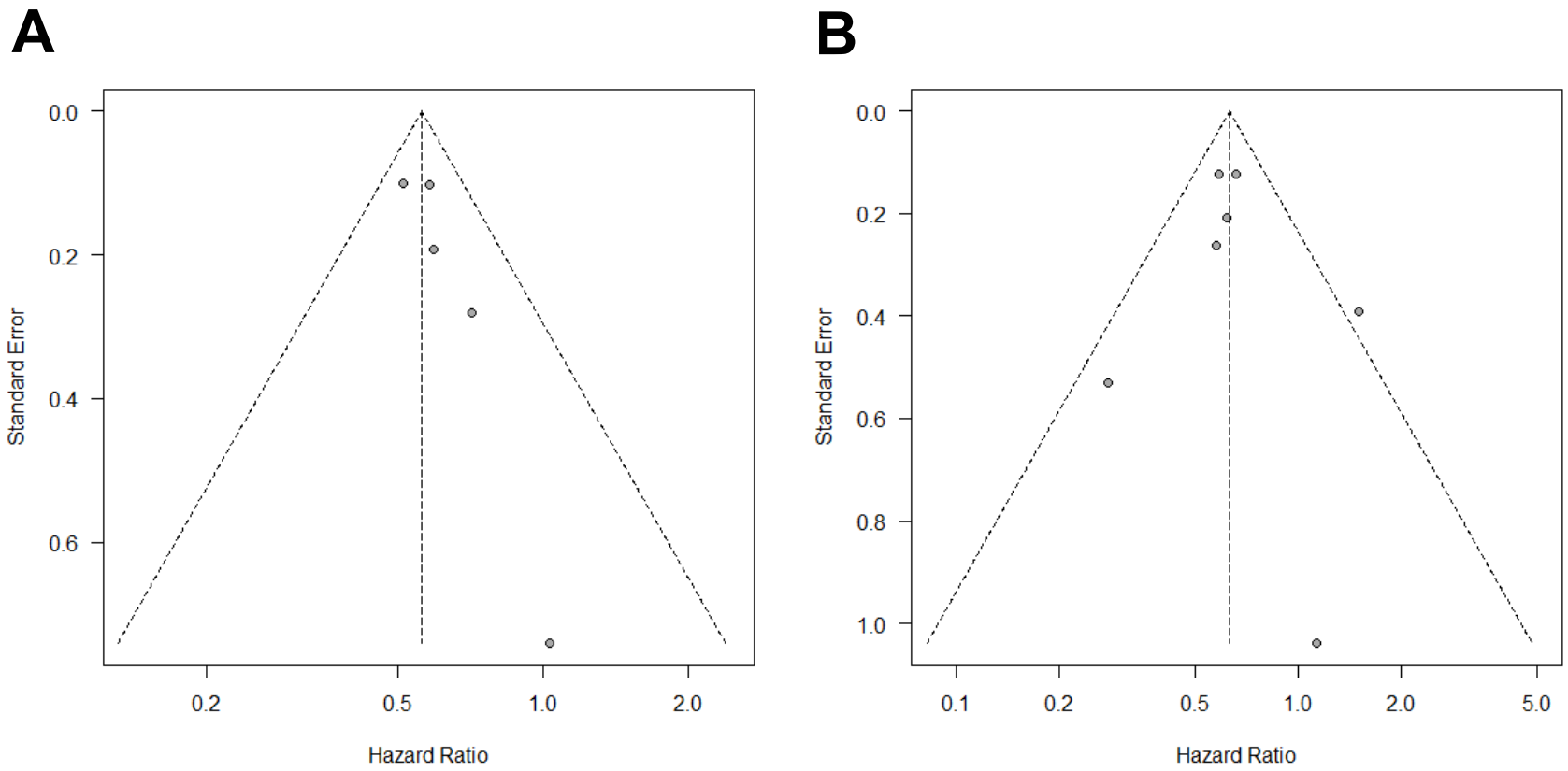
A

Domain	Inclusion criteria	Exclusion criteria
Study design	Randomized controlled trials, prospective or retrospective observational cohort studies, and registry-based studies evaluating rituximab maintenance after frontline bendamustine–rituximab (BR).	Case reports, case series, reviews, editorials, commentaries, letters without original data, protocols, preclinical studies, and duplicate publications.
Population	Adult patients (≥18 years) with newly diagnosed mantle cell lymphoma who received frontline BR induction and were subsequently managed with rituximab maintenance or observation/no maintenance.	Pediatric populations; studies including mixed lymphoma subtypes without separate mantle cell lymphoma results; studies evaluating relapsed/refractory disease only; studies in which patients did not receive frontline BR.
Intervention	Rituximab maintenance administered following completion of frontline BR induction.	Maintenance strategies not including rituximab or studies in which the effect of rituximab maintenance could not be isolated.
Comparator	Observation, no maintenance, or equivalent surveillance strategy following frontline BR.	Studies without an appropriate comparison group.
Outcomes	Studies reporting progression-free survival (PFS), overall survival (OS), event-free survival (EFS), or time to next treatment or death (TTNT), with hazard ratios (HRs) and 95% confidence intervals (CIs) or sufficient data for HR estimation. For observational studies, EFS or TTNT were considered proxies for PFS.	Studies without survival outcomes or insufficient data to estimate HRs.
Publication characteristics	Full-text articles and eligible conference abstracts presented at major hematology or oncology meetings (ASH, ASCO, and EHA).	Duplicate reports of the same study population (the most complete or most recent dataset was included), non-original publications, and studies with insufficient information for data extraction.
Language	English-language publications.	Non-English publications.

B


242 publications identified
196 publications excluded
• Other lymphomas
• Non-clinical studies
• Review articles
46 publications assessed for eligibility
39 publications excluded
• BR-based combination therapies
• Different maintenance therapy
• No comparison group
• Insufficient outcomes data
• Duplicate publications
7 publications included in meta-analysis

Supplemental Figure 2. Funnel Plot for Assessment of Publication Bias. (A) Publications on progression-free survival; (B) Publications on overall survival.



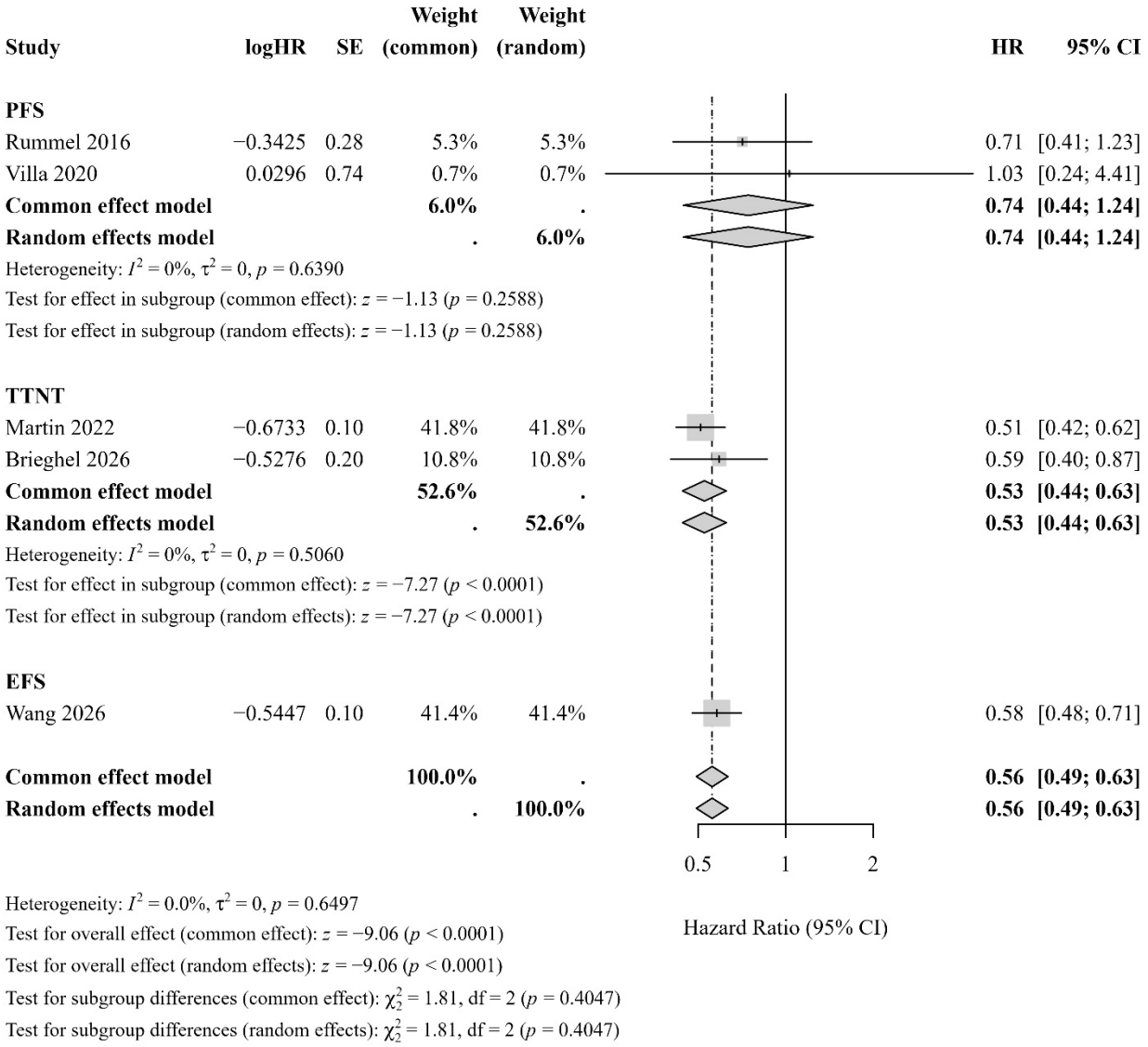
Supplemental Fig 3. Results of Sensitivity Analyses

A. Leave-One-Out Sensitivity Analyses

	PFS, common effect model					PFS, random effects model				
Removed Study	**HR**	**95% CI**	**P value**	**Tau²**	**I²**	**HR**	**95% CI**	**P value**	**Tau²**	**I²**
None	0.56	0.49—0.63	<0.0001	0	0%	0.56	0.49—0.63	<0.0001	0	0%
Rummel 2016	0.55	0.48—0.63	<0.0001	0	0%	0.55	0.48—0.63	<0.0001	0	0%
Villa 2020	0.56	0.49—0.63	<0.0001	0	0%	0.56	0.49—0.63	<0.0001	0	0%
Martin 2022	0.6	0.51—0.70	<0.0001	0	0%	0.6	0.51—0.70	<0.0001	0	0%
Wang 2026	0.54	0.46—0.64	<0.0001	0	0%	0.54	0.46—0.64	<0.0001	0	0%
Brieghel 2026	0.56	0.49—0.63	<0.0001	0	0%	0.56	0.49—0.63	<0.0001	0	0%
	OS, common effect model					**OS, random effects model**				
Removed Study	**HR**	**95% CI**	**P value**	**Tau²**	**I²**	**HR**	**95% CI**	**P value**	**Tau²**	**I²**
None	0.63	0.55—0.73	<0.0001	0.0172	26.80%	0.64	0.52—0.77	<0.0001	0.0172	26.80%
Rummel 2016	0.61	0.53—0.71	<0.0001	0	0%	0.61	0.53—0.71	<0.0001	0	0%
Hill 2019	0.64	0.55—0.75	<0.0001	0.0062	13.10%	0.65	0.55—0.77	<0.0001	0.0062	13.10%
Villa 2020	0.63	0.54—0.73	<0.0001	0.0227	36.50%	0.63	0.51—0.78	<0.0001	0.0227	36.50%
Martin 2022	0.62	0.51—0.74	<0.0001	0.0432	37.50%	0.64	0.48—0.85	0.0019	0.0432	37.50%
Di 2023	0.64	0.55—0.74	<0.0001	0.0281	38.10%	0.65	0.51—0.82	0.0003	0.0281	38.10%
Wang 2026	0.66	0.55—0.79	<0.0001	0.0388	35.20%	0.66	0.50—0.87	0.0037	0.0388	35.20%
Brieghel 2026	0.63	0.54—0.74	<0.0001	0.0317	38.90%	0.64	0.50—0.83	0.0005	0.0317	38.90%

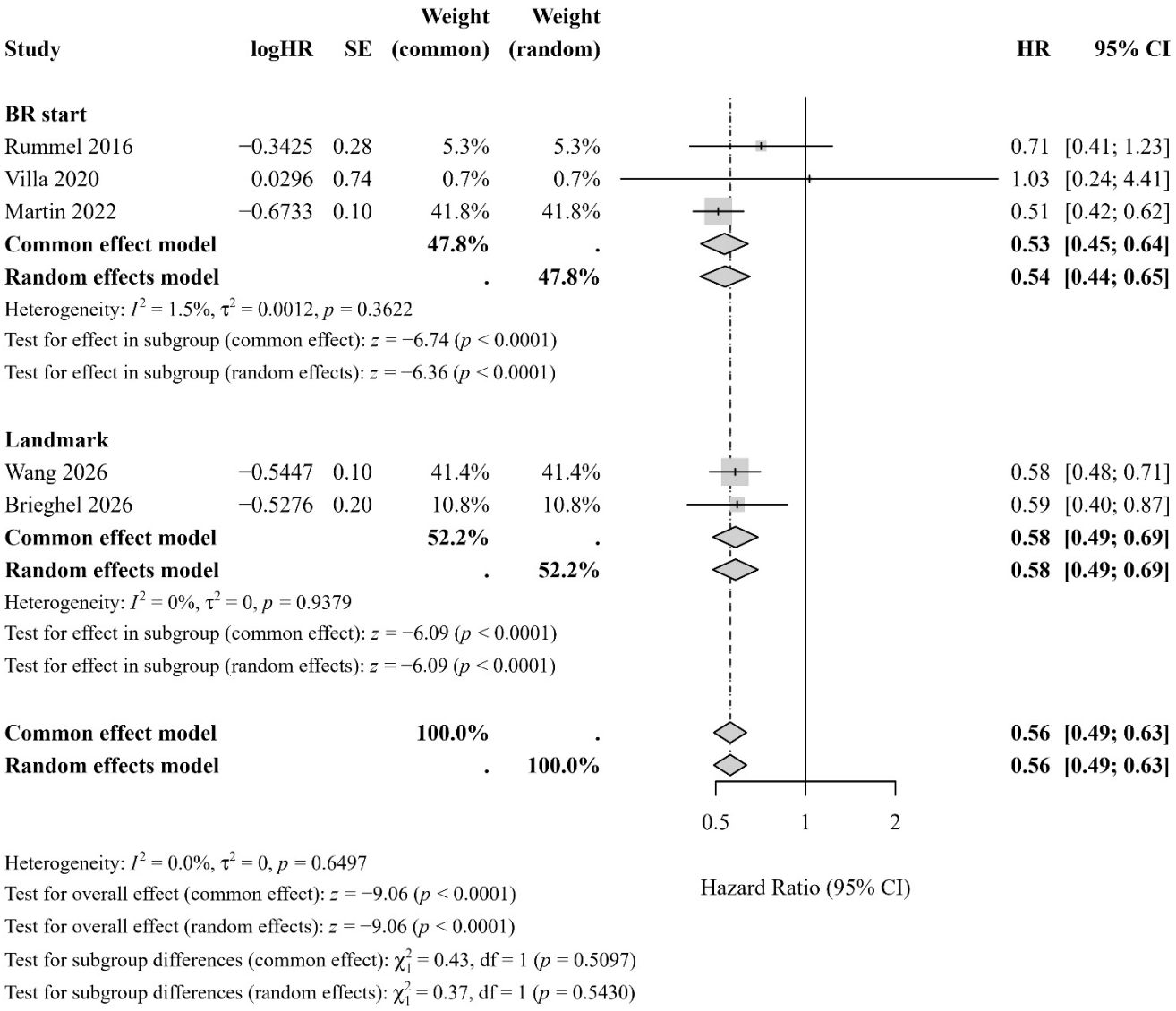
Abbreviations: CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

B. PFS/EFS/TTNT subgroup analysis stratified by endpoint



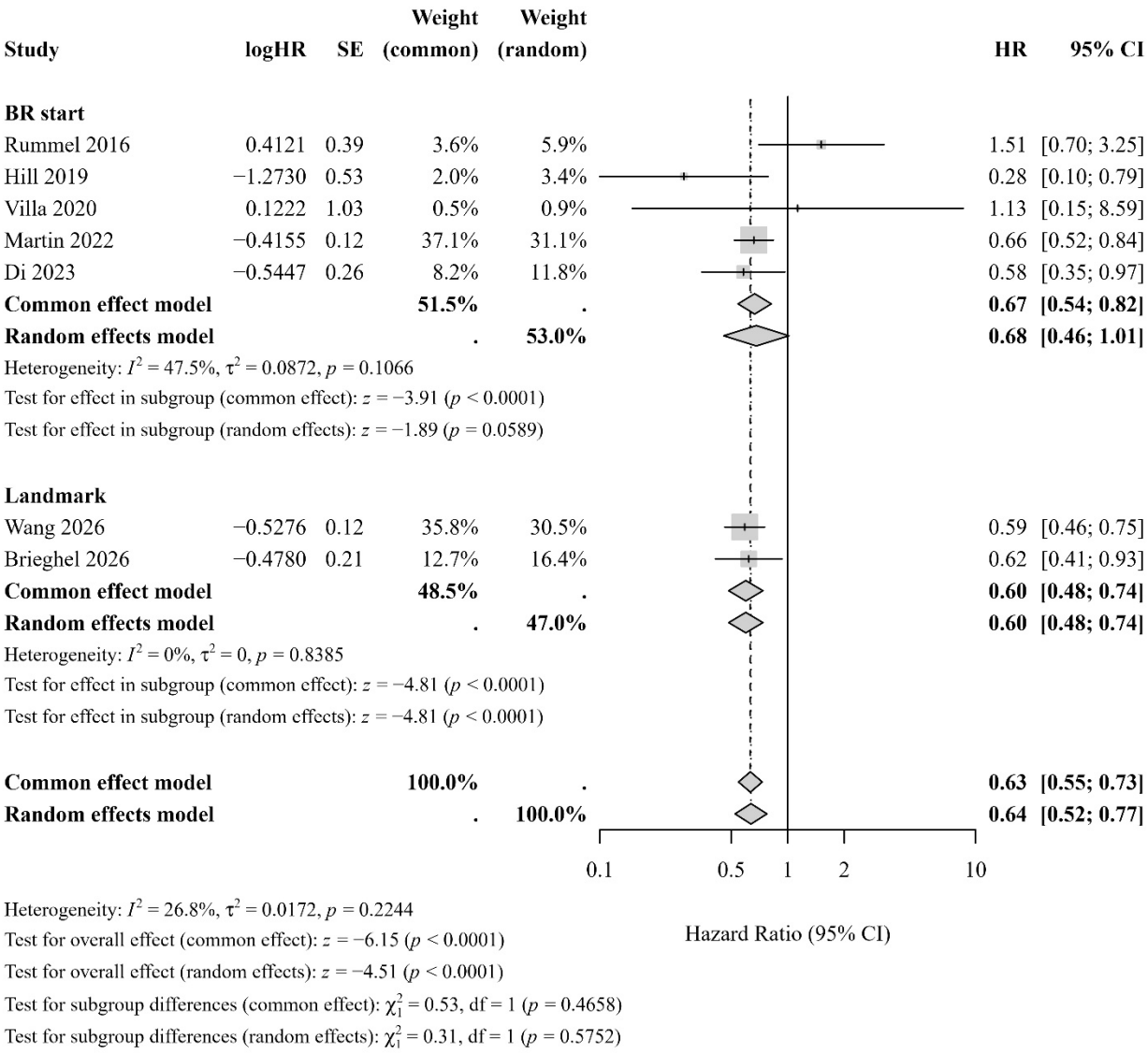
Abbreviations: EFS. Event-free survival; PFS, progression-free survival; TTNT, time to next treatment.

C. PFS/EFS/TTNT subgroup analysis stratified by outcome measurement starting time



Abbreviations: EFS. Event-free survival; PFS, progression-free survival; TTNT, time to next treatment.

D. Overall surivval subgroup analysis stratified by outcome measurement starting time



Heterogeneity: I^2 = 26.8%, τ^2 = 0.0172, p = 0.2244

Test for overall effect (common effect): z = −6.15 (p < 0.0001)

Test for overall effect (random effects): z = −4.51 (p < 0.0001)

Test for subgroup differences (common effect): χ^2_1 = 0.53, df = 1 (p = 0.4658)

Test for subgroup differences (random effects): χ^2_1 = 0.31, df = 1 (p = 0.5752)