SUPPLEMENTARY MATERIALS

Matching-adjusted Indirect Comparison of Brexucabtagene Autoleucel (ZUMA-2) and Pirtobrutinib (BRUIN) in Patients with Relapsed/Refractory Mantle Cell Lymphoma Previously Treated with a Covalent Bruton Tyrosine Kinase Inhibitor

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Table S1: Comparison of key trial eligibility criteria in ZUMA-2 and BRUIN

Characteristic	ZUMA-2 (brexu-cel; NCT02601313)	BRUIN (pirtobrutinib; NCT03740529)
Study design	Phase 2, open-label, multi-center, single-arm	Phase 1/2, open-label, multi-center, single-arm
Study start date	November 9, 2015	November 16, 2018
Estimated study completion date	June 2025	October 2023
Study location	20 sites (France, Germany, Netherlands, US)	27 sites (Australia, France, Italy, Poland, UK, US)
Age	≥18 years	≥18 years
Disease or condition of interest	MCL	MCL
Prior therapy	**Up to 5 prior regimens**, including: • Anthracycline or bendamustine-containing chemotherapy, and • Anti-CD20 monoclonal antibody, and • Ibrutinib or acalabrutinib	**≥2 prior lines** of therapy
Prior auto-SCT	Yes, but not within 6 weeks of informed consent	Yes, but not within 60 days of study start
Prior allo-SCT	**No**	**Yes, but not within 60 days of study start**
Prior CAR T-cell therapy	**No**	**Yes, but not within 60 days of study start**
Prior cBTKi treatment	Required	**Not required**
Relapsed or refractory disease definition	• Disease progression after last regimen, or • Refractory disease is defined failure to achieve a CR or PR to the last regimen	• Relapsed: evidence of **disease progression in a patient who previously achieved a CR or PR for ≥6 months** • Refractory: treatment failure defined as less than CR or PR or progression **within 6 months from last dose of therapy**
ECOG PS	0-**1**	0-**2**[a]
Creatine clearance	**≥60 cc/min**	**≥30 mL/min**
Possible need for urgent therapy for ongoing or impending oncologic emergency	No	**Not reported**
Cardiac atrial or cardiac ventricular lymphoma involvement	No	**Not reported**
History of clinically significant cardiac disease	**Yes, but not within 12 months of enrollment**	**Yes, but not within 6 months of enrollment**
CNS lymphoma involvement	No	No

Bolded text indicates observed between-study differences.
allo-SCT, allogeneic stem cell transplant; auto-SCT, autologous stem cell transplant; cBTKi, covalent Bruton tyrosine kinase inhibitor; CAR, chimeric antigen receptor; CNS, central nervous system; CR, complete response; ECOG, Eastern Cooperative Oncology Group; MCL, mantle cell lymphoma; PR, partial response; PS, performance status; UK, United Kingdom; US, United States.
[a] Only 1 enrolled patient had ECOG PS of 2

Table S2: Comparison of efficacy outcomes definitions in ZUMA-2 and BRUIN

Outcome	ZUMA-2 (NCT02601313)	BRUIN (NCT03740529)
Tumor response	ORR is defined as the incidence of a CR or a PR per the Lugano Classification (Cheson et al, 2014), as determined by an independent radiology review committee.	The estimate of the ORR is calculated based on the maximum likelihood estimator (i.e., crude proportion of patients with best objective response of PR or better based on Lugano 2014 criteria as determined by IRC or by the treating investigator).
Duration of response	DOR is defined as the time from their first objective response to disease progression or death.	DOR is calculated for patients who achieve a response of PR or better. For such patients, DOR is defined as the number of months from the start date of the first documented response to the earlier of the documentation of definitive disease progression or death from any cause.
Progression-free survival	ITT population: PFS is defined as the time from the enrolment date to the date of disease progression or death from any cause. mITT population: PFS is defined as the time from the anti-CD19 CAR T-cell infusion date to the date of disease progression or death from any cause.	PFS is derived for each patient as the number of months from the date of the first dose of study drug to the earlier of documented progressive disease or death due to any cause.
Overall survival	ITT population: OS is defined as the time from the enrolment date to the date of death from any cause. mITT population: OS is defined as the time from anti-CD19 CAR T cell infusion to the date of death from any cause.	OS is derived for each patient as the number of months from the date of the first dose of study drug to the date of death, irrespective of cause.

CAR, chimeric antigen receptor; CR, complete response; DOR, duration of response; ITT, intention-to-treat; mITT, modified intention-to-treat; IRC, independent review committee; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response.

Table S3: Baseline characteristics of ZUMA-2 (ITT population) before and after matching to BRUIN

Characteristic		Observed ZUMA-2 ITT N=74	BRUIN N=90	MAIC-adjusted ZUMA-2 ITT	
				Base case model[a] ESS=43.1	Sensitivity analysis[b] ESS=16.6
ESS reduction (% of original sample size)		--	--	41.8	77.6
Morphology	**Blastoid**	26	9	**9**	**9**
sMIPI	**High risk**	18	22	**22**	**22**
	Intermediate risk	42	56	**56**	**56**
Prior lines of therapy	**>3**	35	34	**34**	**34**
Disease stage	**IV**	86	78	**78**	**78**
Prior auto-SCT	**Yes**	42	19	**19**	**19**
TP53 mutation[c]	**Yes**	17[c]	47[c]	17	**47**
Ki-67 index[d]	**≥30%**	83	74[d]	83	**74**
Bulky disease	**≥10 cm**	14	3	17	21
Bone marrow involvement	**Yes**	58	51	60	70
Extranodal disease	**Yes**	58	39	60	66
Prior ibrutinib	**Yes**	84	66	88	90
Sex	**Male**	84	80	83	88

All values reported in percentages. Variables shaded in grey were not included in the indicated model.
[a] Includes five prognostic variables (bolded values).
[b] Includes seven prognostic variables (bolded values).
[c] Data missing for a high proportion of patients in both trials (51% of patients in ZUMA-2 and 60% of patients in BRUIN).
[d] Data missing for a high proportion of patients in BRUIN (62% of patients).
auto-SCT, autologous stem cell transplant; ESS, effective sample size; ITC, indirect treatment comparison; ITT, intention-to-treat; MAIC, matching-adjusted indirect comparison; sMIPI, simplified Mantle Cell Lymphoma International Prognostic Index..

Table S4: Naïve and MAIC-weighted relative treatment effect estimates of brexu-cel (ZUMA-2 mITT population) versus pirtobrutinib for ORR and CR

Outcome	Before matching					After matching				
	Brexu-cel		Pirtobrutinib		Brexu-cel vs. pirtobrutinib	Brexu-cel		Pirtobrutinib		Brexu-cel vs. pirtobrutinib
	N	Event (%)	N	Event (%)	OR (95% CI) p-value	ESS	Event (%)	N	Event (%)	OR (95% CI) p-value
ZUMA-2 mITT vs. BRUIN: Base-case model (5 variables)										
ORR	68	62 (91)	90	51 (57)	**7.90 (3.10-20.15)** p < 0.01	39.1	36.4 (93)	90	51 (57)	**10.39 (2.81-38.46)** p < 0.01
CR	68	46 (68)	90	17 (19)	**8.98 (4.32-18.68)** p < 0.01	39.1	27.4 (70)	90	17 (19)	**10.11 (4.26-24.00)** p < 0.01
ZUMA-2 mITT vs. BRUIN: Sensitivity model (7 variables)										
ORR	68	62 (91)	90	51 (57)	**7.90 (3.10-20.15)** p < 0.01	16.5	15.9 (96)	90	51 (57)	**18.95 (1.50-238.71)** p = 0.02
CR	68	46 (68)	90	17 (19)	**8.98 (4.32-18.68)** p < 0.01	16.5	12.8 (78)	90	17 (19)	**15.01 (4.20-53.70)** p < 0.01

Bolded OR values are statistically significant at a 0.05 level.

CI, confidence interval; CR, complete response; ESS, effective sample size; mITT, modified intention-to-treat; OR, odds ratio; ORR, overall response rate.

Table S5: Naïve and MAIC-weighted relative treatment effect estimates of brexu-cel (ZUMA-2 mITT population) versus pirtobrutinib for OS, PFS, and DOR

Outcome	Before matching					After matching				
	Brexu-cel		Pirtobrutinib		Brexu-cel vs. pirtobrutinib	Brexu-cel		Pirtobrutinib		Brexu-cel vs. pirtobrutinib
	N	Median (months)	N	Median (months)	HR (95% CI) p-value	ESS	Median (months)	N	Median (months)	HR (95% CI) p-value
ZUMA-2 mITT vs. BRUIN: Base-case model (5 variables)										
DOR	62	28.2	51	17.6	0.67 (0.38-1.17) p=0.16	35.7	36.5	51	17.6	0.60 (0.31-1.17) p=0.13
PFS	68	25.8	90	6.9	**0.48 (0.31-0.75)** p<0.01	39.1	29.3	90	6.9	**0.44 (0.25-0.75)** p<0.01
OS	68	46.4	90	23.5	0.68 (0.41-1.12) p=0.13	39.1	47.6	90	23.5	0.61 (0.34-1.10) p=0.10
ZUMA-2 mITT vs. BRUIN: Sensitivity model (7 variables)										
DOR	62	28.2	51	17.6	0.67 (0.38-1.17) p=0.16	15.3	28.2	51	17.6	0.59 (0.25-1.39) p=0.23
PFS	68	25.8	90	6.9	**0.48 (0.31-0.75)** p<0.01	16.5	29.3	90	6.9	**0.41 (0.20-0.85) p=0.02**
OS	68	46.4	90	23.5	0.68 (0.41-1.12) p=0.13	16.5	58.5	90	23.5	0.50 (0.23-1.11) p=0.09

Bolded HR values are statistically significant at a 0.05 level.
CI, confidence interval; DOR, duration of response; ESS, effective sample size; HR, hazard ratio; mITT, modified intention-to-treat; OS, overall survival; PFS, progression-free survival.

Table S6: Naïve and MAIC-weighted relative treatment effect estimates of brexu-cel (ZUMA-2 ITT population) versus pirtobrutinib for ORR and CR

Outcome	Before matching					After matching				
	Brexu-cel		Pirtobrutinib		Brexu-cel vs. pirtobrutinib	Brexu-cel		Pirtobrutinib		Brexu-cel vs. pirtobrutinib
	N	Event (%)	N	Event (%)	OR (95% CI) p-value	ESS	Event (%)	N	Event (%)	OR (95% CI) p-value
ZUMA-2 ITT vs. BRUIN: Base-case model (5 variables)										
ORR	74	62 (84)	90	51 (57)	**3.95 (1.87-8.33)** p<0.01	43.1	36.8 (85)	90	51 (57)	**4.48 (1.75-11.52)** p<0.01
CR	**74**	46 (62)	90	17 (19)	**7.05 (3.48-14.30)** p<0.01	43.1	27.9 (65)	90	17 (19)	**7.87 (3.48-17.84)** p<0.01

ZUMA-2 ITT vs. BRUIN: Sensitivity model (7 variables)										
ORR	**74**	62 (84)	90	51 (57)	**3.95 (1.87-8.33)** p<0.01	16.6	15.5 (93)	90	51 (57)	**10.67 (1.49-76.55)** p=0.02
CR	**74**	46 (62)	90	17 (19)	**7.05 (3.48-14.30)** p<0.01	16.6	12.6 (76)	90	17 (19)	**13.53 (3.90-46.86)** p<0.01

Bolded OR values are statistically meaningful at a 0.05 level of significance.
CI, confidence interval; CR, complete response; ESS, effective sample size; ITT, intention-to-treat; OR, odds ratio; ORR, overall response rate.

Table S7: Naïve and MAIC-weighted relative treatment effect estimates of brexu-cel (ZUMA-2 ITT population) versus pirtobrutinib for OS, PFS, and DOR

Outcome	Before matching					After matching				
	Brexu-cel		Pirtobrutinib		Brexu-cel vs. pirtobrutinib	Brexu-cel		Pirtobrutinib		Brexu-cel vs. pirtobrutinib
	N	Median (months)	N	Median (months)	HR (95% CI) p-value	ESS	Median (months)	N	Median (months)	HR (95% CI) p-value
ZUMA-2 ITT vs. BRUIN: Base-case model (5 variables)										
DOR	**62**	28.2	51	17.6	0.67 (0.38-1.17) p=0.16	35.9	45.6	51	17.6	0.57 (0.29-1.12) p=0.10
PFS	**74**	24	90	6.9	**0.52 (0.34-0.80)** p<0.01	43.1	30.5	90	6.9	**0.45 (0.27-0.77)** p<0.01
OS	**74**	44.2	90	23.5	0.78 (0.49-1.26) p=0.31	43.1	48.2	90	23.5	0.68 (0.39-1.20) p=0.18
ZUMA-2 ITT vs. BRUIN: Sensitivity model (7 variables)										
DOR	**62**	28.2	51	17.6	0.67 (0.38-1.17) p=0.16	15.0	28.2	51	17.6	0.57 (0.24-1.38) p=0.21
PFS	**74**	24	90	6.9	**0.52 (0.34-0.80)** p<0.01	16.6	30.5	90	6.9	**0.41 (0.20-0.84)** p=0.01
OS	**74**	44.2	90	23.5	0.78 (0.49-1.26) p=0.31	16.6	59.2	90	23.5	0.53 (0.24-1.15) p=0.11

Bolded HR values are statistically meaningful at a 0.05 level of significance.
CI, confidence interval; DOR, duration of response; ESS, effective sample size; HR, hazard ratio; ITT, intention-to-treat; OS, overall survival; PFS, progression-free survival.

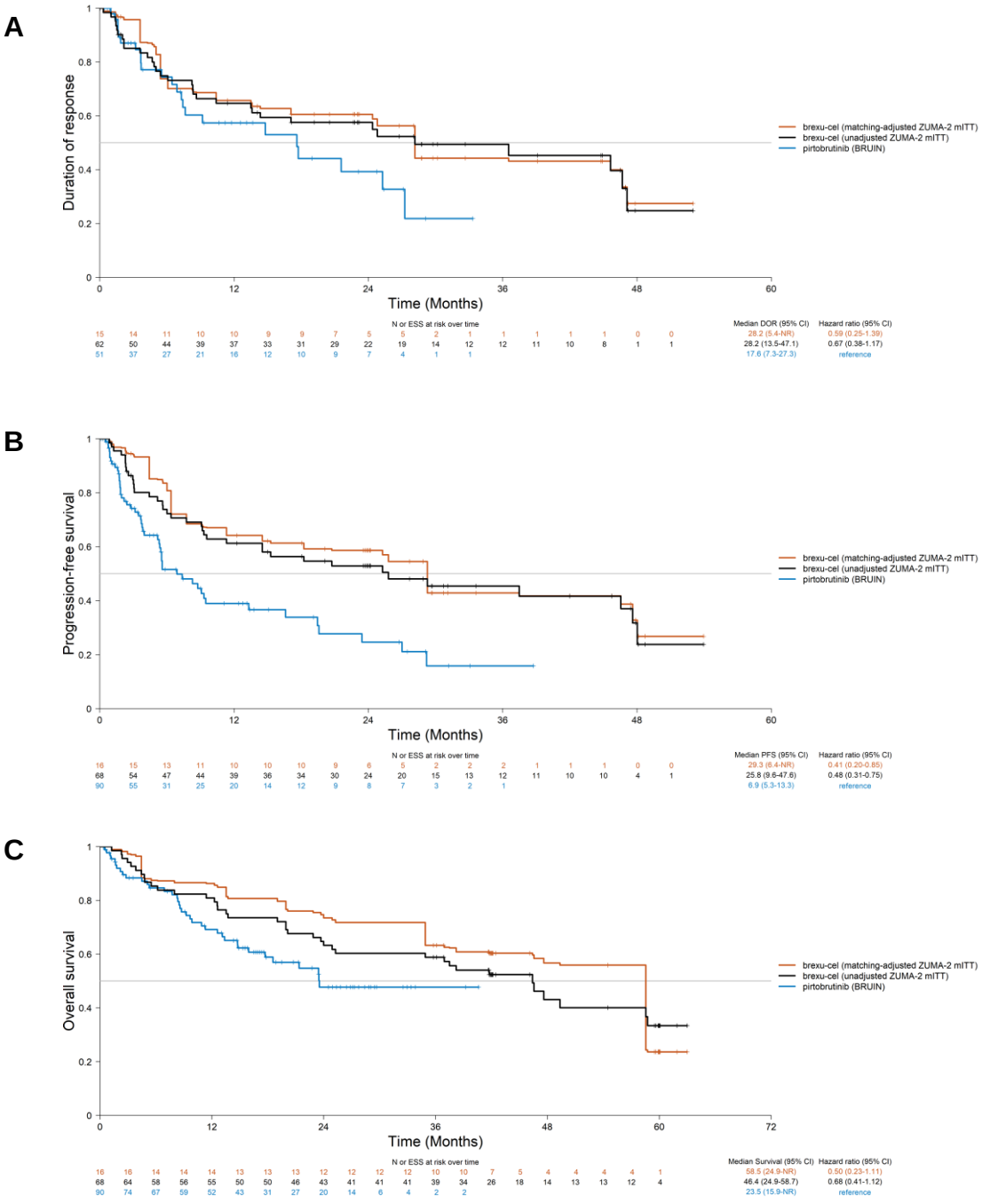

Figure S1: Sensitivity analysis MAIC of brexu-cel (ZUMA-2 mITT population) versus pirtobrutinib (BRUIN) for (A) DOR, (B) PFS, and (C) OS.

For ZUMA-2, the Kaplan-Meier curves were based on individual patient data whereas for BRUIN, published Kaplan-Meier curves were digitized and individual patient data were reconstructed using the Guyot et al. 2012 algorithm. CI, confidence interval; DOR, duration of response; ESS, effective sample size; MAIC, matching-adjusted indirect comparison; mITT, modified intention-to-treat; OS, overall survival; PFS, progression-free survival.

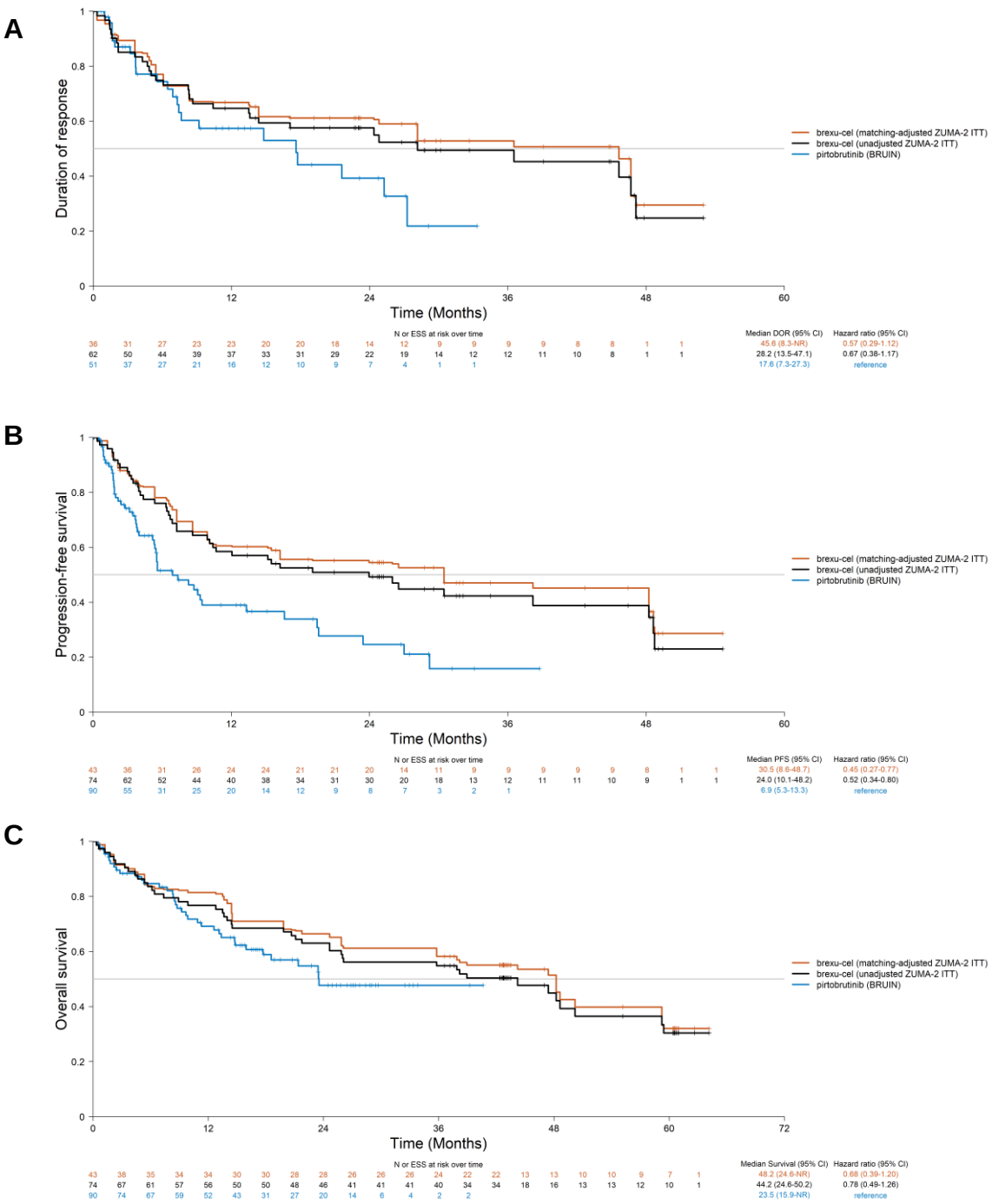

Figure S2: Base-case MAIC of brexu-cel (ZUMA-2 ITT population) versus pirtobrutinib (BRUIN) for (A) OS, (B) PFS, and (C) DOR.

For ZUMA-2, the Kaplan-Meier curves were based on individual patient data whereas for BRUIN, published Kaplan-Meier curves were digitized and individual patient data were reconstructed using the Guyot et al. 2012 algorithm. CI, confidence interval; DOR, duration of response; ESS, effective sample size; ITT, intention-to-treat; MAIC,

matching-adjusted indirect comparison; OS, overall survival; PFS, progression-free survival.

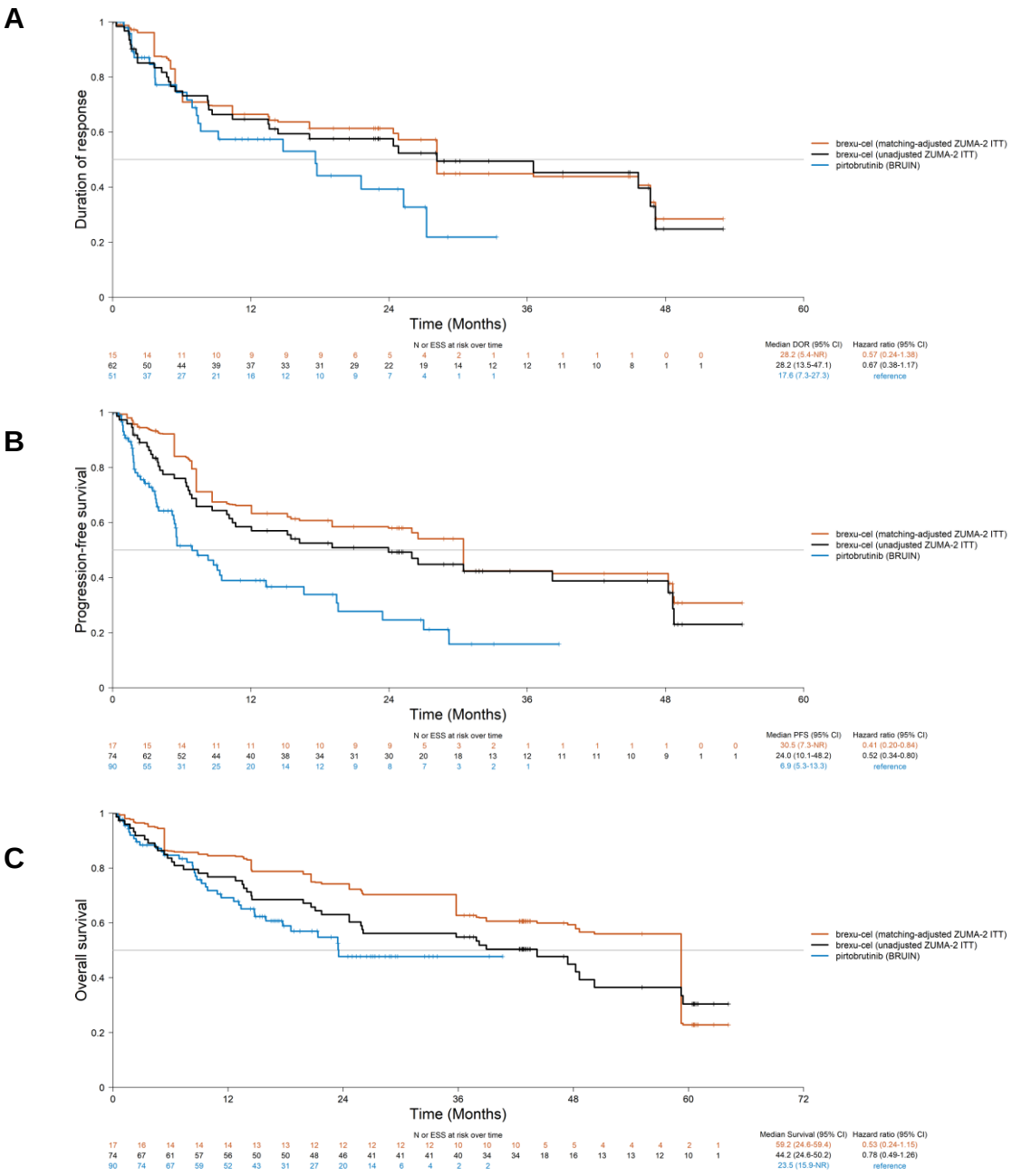

Figure S3: Sensitivity analysis MAIC of brexu-cel (ZUMA-2 ITT population) and pirtobrutinib (BRUIN) for (A) DOR, (B) PFS, and (C) OS.

For ZUMA-2, the Kaplan-Meier curves were based on individual patient data whereas for BRUIN, published Kaplan-Meier curves for BRUIN were digitized and individual patient data were reconstructed using the Guyot et al. 2012 algorithm. Tick marks (+) indicate data censoring. CI, confidence interval; DOR, duration of response; ESS, effective sample size; ITT, intention-to-treat; MAIC, matching-adjusted indirect comparison; OS, overall survival; PFS, progression-free survival.

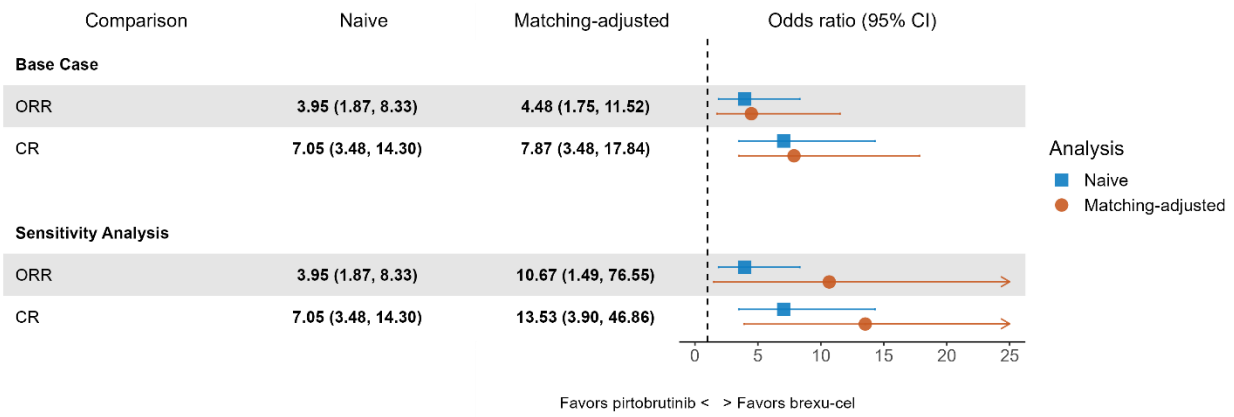

Figure S4: Odds ratios for ORR and CR for brexu-cel (ZUMA-2 ITT population) versus pirtobrutinib (BRUIN).

Dashed vertical line indicates an odds ratio of 1. CI, confidence interval; CR, complete response; ITT, intention-to-treat; MAIC, matching-adjusted indirect comparison; ORR, overall response rate.

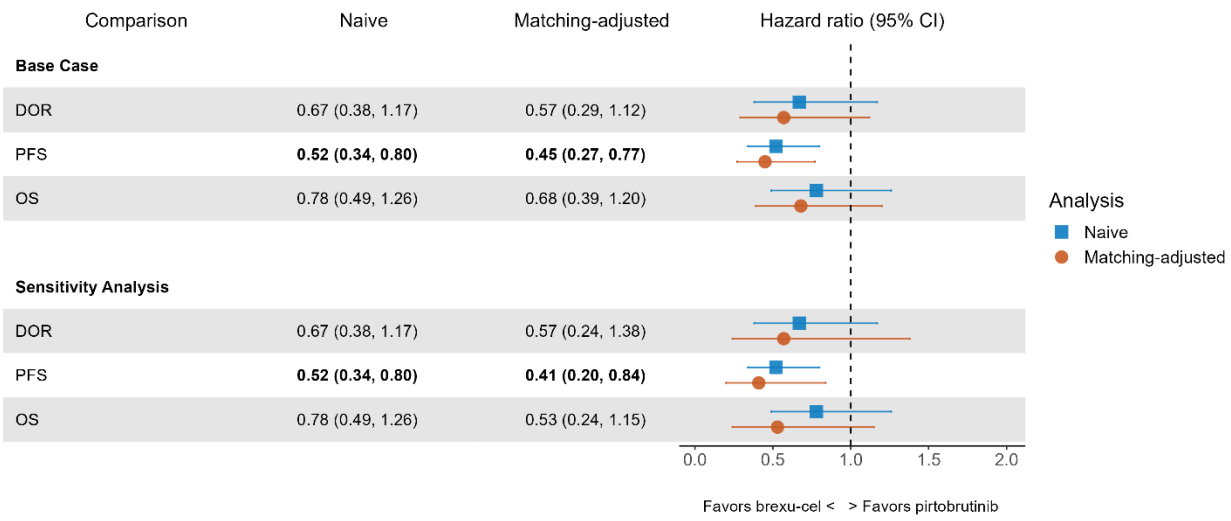

Figure S5: Hazard ratios for OS, PFS, and DOR for brexu-cel (ZUMA-2 ITT population) versus pirtobrutinib (BRUIN).

CI, confidence interval; DOR, duration of response; ITT, intention-to-treat; MAIC, matching-adjusted indirect comparison; OS, overall survival; PFS, progression-free survival.