Supplementary Material

Supplemental Table 1: Identified Confounders and their Relevance for r/r DLBCL[a]

Identified confounders	Relevance for r/r DLBCL, rated by medical experts	Data availability in JULIET and CORAL follow-up (% of non-missing values for variables available in both studies)[b]
Age at initial diagnosis (>40 to ≤60 vs. >60 to <75 vs. ≥75 years)	very important	Available in both studies (JULIET: FAS 100%; ITT 100% CORAL: FAS 100%; ITT 100%)
Performance status (ECOG 0 or 1 vs. 2 to 4)	very important	Available in both studies (JULIET: FAS 100%; ITT 100% CORAL: FAS 16.9%; ITT 13.9%)
Serum LDH level (normal vs. >1 to ≤3 vs. >3 ULN)	very important	Available in both studies (JULIET: FAS 100%; ITT 100% CORAL: FAS 79.2%; ITT 67.7%)
Ann Arbor disease stage (I, II vs. III, IV)	very important	Available in both studies (JULIET: FAS 100%; ITT 100% CORAL: FAS 81.2%; ITT 70.3%)
Extranodal site involvement (0 or 1 vs. ≥2 extranodal organs)	very important	Available in both studies (JULIET: FAS 100%; ITT 100% CORAL: FAS 82.1%; ITT 71.4%)
Status of disease (refractory to all prior lines, refractory to last line, relapse after last line)	very important	Available in both studies (JULIET: FAS 100%; ITT 100% CORAL: FAS 100%; ITT 100%)
Time to first relapse after diagnosis (<12 vs. ≥12 vs. >24 months)	very important	Available in both studies (JULIET: FAS 97.4%; ITT 98.2% CORAL: FAS 100%; ITT 100%)
Number of relapses	very important	Available in both studies (JULIET: FAS 100%; ITT 100% CORAL: FAS 100%; ITT 100%)
Double/triple gene hits (*MYC*/*BCL2*/*BCL6*), *MYC-IG* rearrangement	very important	Not available in CORAL follow-up

Identified confounders	Relevance for r/r DLBCL, rated by medical experts	Data availability in JULIET and CORAL follow-up (% of non-missing values for variables available in both studies)[b]
Previous HCT (yes, no)	very important	Available in both studies (JULIET: FAS 100%; ITT 100% CORAL: FAS 100%; ITT 100%)
Bulky disease (yes, no)	very important	Not available in CORAL follow-up
Molecular subtype (GCB, ABC)	less important	Not available in CORAL follow-up
Hepatitis B infection	not important	Not available in CORAL follow-up

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Abbreviations: ABC: activated B-cell; DLBCL: diffuse large B cell lymphoma; ECOG: Eastern Cooperative Oncology Group; GCB: germinal center B-cell; HCT: hematopoietic cell transplantation; LDH: lactate dehydrogenase; r/r: relapsed or refractory; ULN: upper limit of normal

Note

[a] Relevant confounders were defined as "very important" or "less important" by clinical experts

[b] If data were not available in both groups for a variable, it was not included in the analyses and missingness was not assessed.

Supplemental Table 2. Treatment Line Distribution for the JULIET and CORAL Follow-up populations (FAS and ITT)

FAS

Line distribution after selection	Unadjusted Analyses		Adjusted Analyses	
	JULIET FAS (N=114)	CORAL Follow-up FAS (N=170)	JULIET FAS (N=111)	CORAL Follow-up FAS (N=145)
2L	5 (4.4%)	0 (0.0%)	5 (4.5%)	0 (0.0%)
3L	50 (43.9%)	137 (80.6%)	50 (45.0%)	118 (81.4%)
4L	36 (31.6%)	22 (12.9%)	34 (30.6%)	19 (13.1%)
5L	14 (12.3%)	7 (4.1%)	14 (12.6%)	5 (3.4%)
6L	8 (7.0%)	3 (1.8%)	7 (6.3%)	1 (0.7%)
7L	1 (0.9%)	1 (0.6%)	1 (0.9%)	2 (1.4%)
ITT				
	JULIET ITT (N=166)	CORAL Follow-up ITT (N=205)	JULIET ITT (N=163)	CORAL Follow-up ITT (N=205)[a]
2L	6 (3.6%)	0 (0.0%)	6 (3.7%)	0 (0.0%)
3L	72 (43.4%)	157 (76.6%)	72 (44.2%)	159 (77.6%)
4L	52 (31.3%)	32 (15.6%)	50 (30.7%)	33 (16.1%)
5L	20 (12.0%)	11 (5.4%)	20 (12.3%)	9 (4.4%)
6L	11 (6.6%)	4 (2.0%)	10 (6.1%)	1 (0.5%)
7L-9L	5 (3.0%)	1 (0.5%)	5 (3.0%)	3 (1.5%)

Abbreviations: FAS: full analysis set; L: line; ITT: intent-to-treat
Notes:
[a] For the CORAL follow-up ITT population, among those without a documented 3L+ treatment, the relapse date from last-line treatment was used as the index date. Those patients were counted based on the treatment, if they should receive one, after the relapse date from last line (i.e., a record for patient without 3L treatment but with relapse date for 2L, was considered as 3L).

Supplemental Table 3. Patient Characteristics for the JULIET FAS and CORAL Follow-up FAS, Adjusted Analyses

	JULIET (N=111)	CORAL Follow-up (N=145)		Standardized mean difference[a] (JULIET vs. CORAL Follow-up)	
		FSW	SMRW	FSW	SMRW
Confounders Included for Adjusted Analyses					
Age at initial diagnosis (years)					
≤ 60	73.0%	71.1%	71.4%	0.041	0.035
> 60	27.0%	28.9%	28.6%	-0.041	-0.035
Mean	50.9	51.4	51.4	-0.043	-0.042
Ann Arbor disease stage					
I or II	23.4%	23.9%	24.1%	-0.011	-0.015
III or IV	76.6%	76.1%	75.9%	0.011	0.015
Extranodal site involvement					
0 - 1	56.8%	55.9%	56.5%	0.018	0.004
≥ 2 extranodal organs	43.2%	44.1%	43.5%	-0.018	-0.004
Status of disease					
Relapsed after last line	45.0%	49.5%	47.4%	-0.089	-0.048
Refractory to all lines	18.0%	17.6%	17.6%	0.012	0.010
Refractory to last line but not to all lines	36.9%	33.0%	34.9%	0.083	0.042
Time to 2L start after diagnosis (months)					
< 12	55.9%	53.3%	54.6%	0.051	0.026
≥ 12 and ≤ 24	24.3%	24.2%	23.2%	0.004	0.027
> 24	19.8%	22.5%	22.2%	-0.066	-0.059
Prior HCT[b]					
Yes	50.5%	52.4%	51.0%	-0.038	-0.010
No	49.5%	47.6%	49.0%	0.038	0.010
Number of relapses excluding refractory[c]					
Mean	1.5	1.5	1.5	-0.017	-0.019
Confounders Excluded Due to Missing in the Adjusted Analyses					
Serum LDH level					
Normal (LDH ≤ ULN)	58.6%	71.7%	72.3%	-0.279	-0.293
Elevated (LDH > ULN)	41.4%	28.3%	27.7%	0.279	0.293
ECOG					

0 - 1	100.0%	100.0%	100.0%	--	--

Other Baseline Variables

Age (years)					
< 40	15.3%	12.6%	12.5%	0.080	0.080
≥ 40 and < 65	64.0%	78.5%	79.8%	-0.326	-0.357
≥ 65	20.7%	8.9%	7.7%	0.336	0.381
Mean	53.5	54.1	54.1	-0.045	-0.044
Sex					
Female	39.6%	34.5%	34.3%	0.108	0.110
Male	60.4%	65.5%	65.7%	-0.108	-0.110
Ann Arbor disease stage at diagnosis					
I or II	30.8%	35.3%	35.3%	-0.095	-0.096
III or IV	69.2%	64.7%	64.7%	0.095	0.096
IPI[d]					
< 2 risk factors	27.0%	7.0%	7.0%	0.551	0.555
≥ 2 risk factors	73.0%	93.0%	93.0%	-0.551	-0.555
Number of prior lines of therapies, mean	2.7	2.4	2.4	0.367	0.353

-- not calculated

Abbreviations: 2L; second line; alloHCT: allogeneic hematopoietic cell transplantation; autoHCT: autologous hematopoietic cell transplantation; CR: complete response; ECOG: Eastern Cooperative Oncology Group; FAS: full analysis set; FSW: fine stratification weight; HCT: hematopoietic cell transplantation; IPI: International Prognostic Index; LDH: lactate dehydrogenase; PR: partial response; SMRW: standardized mortality ratio weight; SD: standard deviation; ULN: upper limit of normal

Notes:
[a] Used a threshold of 0.1 in standardized mean difference to indicate meaningful imbalance per Austin (2009)[30] and Austin (2014).[31]
[b] Prior HCT only included prior autoHCT because records with an alloHCT prior to index date were excluded.
[c] The number of relapses was defined as the total number of lines prior to the index treatment where patient had a CR or PR as the response and relapsed later.
[d] The IPI includes the following risk factors: age > 60 years, elevated lactate dehydrogenase level, stage III or IV disease, ECOG performance status ≥ 2, and two or more extranodal sites.

Supplemental Table 4. Comparison of OS for the JULIET FAS vs. CORAL Follow-up FAS, Sensitivity Analyses I-III

Method	N		Median OS (Months), Estimate (95% CI)		HR (JULIET vs. CORAL Follow-up)	
	JULIET	CORAL Follow-up	JULIET	CORAL Follow-up	Estimate (95% CI)	P-value
Sensitivity I						
Unadjusted analyses	114	170	11.07 (6.64, 23.85)	6.21 (5.16, 7.59)	0.61 (0.45, 0.81)	<.001*
Adjusted analyses[a]						
FSW	111	136	12.48 (6.64, 28.68)	4.04 (2.76, 5.88)	0.41 (0.29, 0.57)	<.001*
SMRW	111	136	12.48 (6.64, 28.68)	4.04 (3.38, 5.75)	0.43 (0.31, 0.59)	<.001*
Sensitivity II						
Unadjusted analyses	114	170	11.07 (6.64, 23.85)	5.36 (4.34, 6.37)	0.54 (0.41, 0.73)	<.001*
Adjusted analyses[b]						
FSW	111	140	12.48 (6.64, 28.68)	4.86 (3.58, 6.14)	0.48 (0.34, 0.66)	<.001*
SMRW	111	140	12.48 (6.64, 28.68)	4.86 (3.58, 6.14)	0.49 (0.35, 0.66)	<.001*
Sensitivity III						
Unadjusted analyses	114	122	11.07 (6.64, 23.85)	4.34 (3.52, 5.39)	0.51 (0.37, 0.69)	<.001*
Adjusted analyses[c]						
FSW	111	122	12.48 (6.64, 28.68)	4.86 (3.58, 6.37)	0.52 (0.36, 0.73)	<.001*
SMRW	111	122	12.48 (6.64, 28.68)	4.86 (3.55, 6.21)	0.52 (0.37, 0.71)	<.001*

*p <0.05.

Abbreviations: 2L: second line; CI: confidence interval; FAS: full analysis set; FSW: fine stratification weight; HR: hazard ratio; HCT: hematopoietic cell transplantation; LDH: lactate dehydrogenase; OS: overall survival; PS: propensity score; SMRW: standardized mortality ratio weight

Notes:

[a] Age at initial diagnosis, Ann Arbor disease stage, extranodal site involvement, status of disease, time to 2L start after diagnosis, prior HCT, and number of relapses were adjusted in the PS model.

[b] Age at initial diagnosis, LDH, Ann Arbor disease stage, extranodal site involvement, status of disease, time to 2L start after diagnosis, prior HCT, and number of relapses were adjusted in the PS model.

[c] Age at initial diagnosis, status of disease, time to 2L start after diagnosis, prior HCT, and number of relapses were adjusted in the PS model.

Supplemental Table 5. Patient Characteristics for the JULIET ITT and CORAL Follow-up ITT Populations, Adjusted Analyses

	JULIET (N=163)	CORAL Follow-up (N=205)		Standardized mean difference[a] (JULIET vs. CORAL Follow-up)	
		FSW	SMRW	FSW	SMRW
Confounders Included For Adjusted Analyses					
Demographics					
Age at initial diagnosis (years)					
≤ 60	65.0%	70.4%	63.1%	-0.116	0.041
> 60	35.0%	29.6%	36.9%	0.116	-0.041
Mean	53.2	51.5	52.4	0.146	0.069
Status of disease					
Relapsed after last line	41.1%	47.2%	42.6%	-0.124	-0.031
Refractory to all lines	17.2%	15.2%	16.1%	0.053	0.030
Refractory to last line but not to all lines	41.7%	37.5%	41.3%	0.085	0.008
Time to 2L start after diagnosis (months)					
< 12	57.7%	57.5%	59.5%	0.004	-0.037
≥ 12 and ≤ 24	25.2%	24.3%	23.6%	0.021	0.036
> 24	17.2%	18.3%	16.9%	-0.028	0.008
Prior HCT[b]					
Yes	45.4%	47.4%	43.8%	-0.040	0.031
No	54.6%	52.6%	56.2%	0.040	-0.031
Number of relapses excluding refractory[c]					
Mean	1.4	1.5	1.4	-0.103	-0.002
Confounders Excluded Due to Missing in Adjusted Analyses					
Serum LDH level					
Normal (LDH ≤ ULN)	63.8%	67.5%	63.9%	-0.077	-0.002
Elevated (LDH > ULN)	36.2%	32.5%	36.1%	0.077	0.002
Ann Arbor disease stage					
I or II	21.5%	34.0%	36.4%	-0.283	-0.334
III or IV	78.5%	66.0%	63.6%	0.283	0.334
Extranodal site involvement					
0 - 1	57.1%	75.9%	75.2%	-0.407	-0.390

≥ 2 extranodal organs	42.9%	24.1%	24.8%	0.407	0.390
ECOG					
0 - 1	100.0%	100.0%	100.0%	--	--
Other Baseline Variables					
Age (years)					
< 40	12.9%	12.9%	12.6%	0.000	0.010
≥ 40 and < 65	60.1%	78.8%	77.8%	-0.413	-0.390
≥ 65	27.0%	8.4%	9.6%	0.503	0.461
Mean	55.7	53.9	54.7	0.146	0.079
Sex					
Female	38.0%	34.9%	36.7%	0.065	0.027
Male	62.0%	65.1%	63.3%	-0.065	-0.027
Ann Arbor disease stage at diagnosis					
I or II	26.8%	38.1%	36.1%	-0.245	-0.203
III or IV	73.2%	61.9%	63.9%	0.245	0.203
IPI[d]					
< 2 risk factors	20.2%	11.3%	10.3%	0.246	0.278
≥ 2 risk factors	79.8%	88.7%	89.7%	-0.246	-0.278
Number of prior lines of therapies, mean	2.8	2.4	2.4	0.410	0.473

-- standardized mean difference not calculated

Abbreviations: 2L; second line; alloHCT: allogenic hematopoietic cell transplantation; autoHCT: autologous hematopoietic cell transplantation; CR: complete response; ECOG: Eastern Cooperative Oncology Group; FSW: fine stratification weight; HCT: hematopoietic cell transplantation; IPI: International Prognostic Index; ITT: intent-to-treat; LDH: lactate dehydrogenase; PR: partial response; SMRW: standardized mortality ratio weight; SD: standard deviation; ULN: upper limit of normal

Notes:

[a] Use a threshold of 0.1 in standardized mean difference to indicate meaningful imbalance per Austin (2009)[30] and Austin (2014).[31]

[b] Prior HCT only included prior autoHCT because records with an alloHCT prior to index date were excluded.

[c] The number of relapses was defined as the total number of lines prior to the index treatment where patient had a CR or PR as the response and relapsed later.

[d] The IPI includes the following risk factors: age >60 years, elevated lactate dehydrogenase level, stage III or IV disease, ECOG performance status ≥ 2, and two or more extranodal sites.

Supplemental Table 6. Comparison of OS for the JULIET ITT vs. CORAL Follow-up ITT Populations, Sensitivity Analyses I-III

Method	N		Median OS (Months), Estimate (95% CI)		HR (JULIET vs. CORAL Follow-up)	
	JULIET	CORAL Follow-up	JULIET	CORAL Follow-up	Estimate (95% CI)	P-value
Sensitivity I						
Unadjusted analyses	166	205	8.25 (5.82, 11.70)	6.11 (5.16, 7.52)	0.74 (0.57, 0.94)	0.016*
Adjusted analyses[a]						
FSW	163	205	8.25 (5.82, 12.42)	4.34 (3.29, 5.52)	0.58 (0.46, 0.82)	<.001*
SMRW	163	205	8.25 (5.82, 12.42)	5.13 (3.52, 6.08)	0.61 (0.48, 0.80)	<.001*
Sensitivity II						
Unadjusted analyses	166	205	8.25 (5.82, 11.70)	5.13 (3.88, 6.21)	0.65 (0.51, 0.83)	<.001*
Adjusted analyses[b]						
FSW	163	151	8.25 (5.82, 12.42)	4.34 (3.38, 5.78)	0.53 (0.40, 0.70)	<.001*
SMRW	163	151	8.25 (5.82, 12.42)	3.81 (3.29, 5.26)	0.52 (0.39, 0.67)	<.001*
Sensitivity III						
Unadjusted analyses	166	148	8.25 (5.82, 11.70)	3.84 (3.25, 5.16)	0.59 (0.45, 0.77)	<.001*
Adjusted analyses[c]						
FSW	163	148	8.25 (5.82, 12.42)	4.34 (3.48, 6.08)	0.61 (0.46, 0.80)	<.001*
SMRW	163	148	8.25 (5.82, 12.42)	3.98 (3.19, 5.88)	0.59 (0.45, 0.77)	<.001*

*p <0.05.

Abbreviations: CI: confidence interval; FSW: fine stratification weight; HR: hazard ratio; ITT: intent-to-treat; OS: overall survival; PS: propensity score; SMRW: standardized mortality ratio weight

Notes:

[a] Age at initial diagnosis, status of disease, time to 2L start after diagnosis, prior HCT, and number of relapses were included to adjust in the PS model.

[b] Age at initial diagnosis, LDH, Ann Arbor disease stage, extranodal site involvement, status of disease, time to 2L start after diagnosis, prior HCT, and number of relapses were included to adjust in the PS model.

[c] Age at initial diagnosis, status of disease, time to 2L start after diagnosis, prior HCT, and number of relapses were included to adjust in the PS model.

Supplemental Table 7. Comparison of OS and ORR for the JULIET FAS (n=68 FAS subset) vs. CORAL Follow-up FAS

OS

Method	N		Median OS, months (95% CI)		HR (JULIET vs. CORAL Follow-up)	
	JULIET	CORAL Follow-up	JULIET	CORAL Follow-up	Estimate (95% CI)	P-value
Unadjusted analyses	68	170	11.66 (5.62, 28.68)	5.36 (4.34, 6.37)	0.58 (0.41, 0.82)	0.002*
Adjusted analyses[a]						
FSW	67	145	11.66 (5.62, 28.68)	4.44 (3.38, 5.45)	0.44 (0.31, 0.65)	<.001*
SMRW	67	145	11.66 (5.62, 28.68)	3.88 (3.38, 5.13)	0.45 (0.30, 0.66)	<.001*

ORR

Method	N		ORR (%)		Response rate difference (JULIET Main Cohort vs. CORAL Follow-up)	
	JULIET Main Cohort	CORAL Follow-up	JULIET Main Cohort	CORAL Follow-up	Estimate (95% CI)	P-value
Unadjusted analyses	68	170	51%	31%	0.21 (0.07, 0.35)	0.004*
Adjusted analyses[a]						
FSW	67	145	52%	17%	0.35 (0.19, 0.48)	<.001*
SMRW	67	145	52%	19%	0.33 (0.19, 0.48)	<.001*

*p<0.05

Abbreviations: 2L: second line; CI: confidence interval; FAS: full analysis set; FSW: fine stratification weight; HR: hazard ratio; HCT: hematopoietic cell transplantation; ORR: overall response rate; OS: overall survival; SMRW: standardized mortality ratio weight

Notes:
[a] Age at initial diagnosis, Ann Arbor disease stage, extranodal site involvement, status of disease, time to 2L start after diagnosis, prior HCT, and number of relapses were included in the adjusted analyses.