Supplementary Material

Supplement to: P.W.M. Johnson, et al., Clinical impact of ibrutinib plus R-CHOP in untreated DLBCL co-expressing BCL2 and MYC in the phase 3 PHOENIX trial. Blood Adv (2023).

Supplemental Table 1. Baseline demographic and clinical characteristics of patients included in this analysis.

Characteristics	High *BCL2* and *MYC* co-expression			No high *BCL2* and *MYC* co-expression			Overall population		
	Ibrutinib + R-CHOP n = 123	Placebo + R-CHOP n = 111	Total N = 234	Ibrutinib + R-CHOP n = 263	Placebo + R-CHOP n = 269	Total N = 532	Ibrutinib + R-CHOP n = 386	Placebo + R-CHOP n = 380	Total N = 766
Age, median (range) years	63.0 (21-88)	61. 0 (19-86)	62.0 (19-88)	63.0 (19-84)	61.0 (19-87)	62.0 (19-87)	63.0 (19-88)	61.0 (19-87)	62.0 (19-88)
<60 years, n (%)	47 (38.2)	50 (45.0)	97 (41.5)	102 (38.8)	118 (43.9)	220 (41.4)	149 (38.6)	168 (44.2)	317 (41.4)
≥60 years, n (%)	76 (61.8)	61 (55.0)	137 (58.5)	161 (61.2)	151 (56.1)	312 (58.6)	237 (61.4)	212 (55.8)	449 (58.6)
Male, n (%)	62 (50.4)	61 (55.0)	123 (52.6)	140 (53.2)	148 (55.0)	288 (54.1)	202 (52.3)	209 (55.0)	411 (53.7)
Time from diagnosis to randomization, median (range), days	26 (6-302)	26 (9-223)	26 (6-302)	27 (4-266)	27 (6-349)	27 (4-349)	27 (4-302)	26 (6-349)	26 (4-349)
Ann Arbor stage, n (%)									
I-II	29 (23.6)	28 (25.2)	57 (24.4)	64 (24.3)	61 (22.7)	125 (23.5)	93 (24.1)	89 (23.4)	182 (23.8)
III-IV	94 (76.4)	83 (74.8)	177 (75.6)	199 (75.7)	208 (77.3)	407 (76.5)	293 (75.9)	291 (76.6)	584 (76.2)
Bulky tumor (long axis ≥10 cm), n (%)									
Yes	14 (11.4)	16 (14.4)	30 (12.8)	40 (15.2)	37 (13.8)	77 (14.5)	54 (14.0)	53 (13.9)	107 (14.0)
No	109 (88.6)	95 (85.6)	204 (87.2)	223 (84.8)	232 (86.2)	455 (85.5)	332 (86.0)	327 (86.1)	659 (86.0)
Extra nodal sites ≥1, n (%)									
Yes	82 (66.7)	73 (65.8)	155 (66.2)	179 (68.1)	194 (72.1)	373 (70.1)	261 (67.6)	267 (70.3)	528 (68.9)
No	41 (33.3)	38 (34.2)	79 (33.8)	84 (31.9)	75 (27.9)	159 (29.9)	125 (32.4)	113 (29.7)	238 (31.1)
ECOG PS, n (%)									
0-1	115 (93.5)	91 (82.0)	206 (88.0)	236 (89.7)	232 (86.2)	468 (88.0)	351 (90.9)	323 (85.0)	674 (88.0)
≥2	8 (6.5)	20 (18.0)	28 (12.0)	27 (10.3)	37 (13.8)	64 (12.0)	35 (9.1)	57 (15.0)	92 (12.0)
R-IPI risk group,* n (%)									
Low (1-2)	72 (58.5)	65 (58.6)	137 (58.5)	146 (55.5)	147 (54.6)	293 (55.1)	218 (56.5)	212 (55.8)	430 (56.1)
High (3-5)	51 (41.5)	46 (41.4)	97 (41.5)	117 (44.5)	122 (45.4)	239 (44.9)	168 (43.5)	168 (44.2)	336 (43.9)
Elevated LDH, n (%)									
Yes	72 (58.5)	62 (55.9)	134 (57.3)	141 (53.6)	143 (53.2)	284 (53.4)	213 (55.2)	205 (53.9)	418 (54.6)
No	51 (41.5)	46 (41.4)	100 (42.7)	122 (46.4)	126 (46.8)	248 (46.6)	173 (44.8)	175 (46.1)	348 (45.4)

*R-IPI risk group based on clinical database.

ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-IPI, Revised International Prognostic Index.

Supplemental Table 2. Summary of response by DE status.

Treatment	DE status	Response, n (%)					
		CR	PR	SD	PD	NE	NA
Ibrutinib + R-CHOP	**DE, n = 123**	83 (67.5)	28 (22.8)	1 (0.8)	1 (0.8)	1 (0.8)	9 (7.3)
	Non-DE, n = 263	174 (66.2)	58 (22.1)	0 (0.0)	8 (3.0)	0 (0.0)	23 (8.7)
	Total, n = 386	257 (66.6)	86 (22.3)	1 (0.3)	9 (2.3)	1 (0.3)	32 (8.3)
Placebo + R-CHOP	**DE, n = 111**	72 (64.9)	31 (27.9)	1 (0.9)	4 (3.6)	1 (0.9)	2 (1.8)
	Non-DE, n = 269	184 (68.4)	66 (24.5)	2 (0.7)	4 (1.5)	0 (0.0)	13 (4.8)
	Total, n = 380	256 (67.4)	97 (25.5)	3 (0.8)	8 (2.1)	1 (0.3)	15 (3.9)

CR, complete response; DE, *BCL2/MYC* double-expressor lymphoma by RNA sequencing; GEP, gene expression profiling; NA, not assessed; NE, non-evaluable; PD, progressive disease; PR, partial response; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; SD, stable disease.

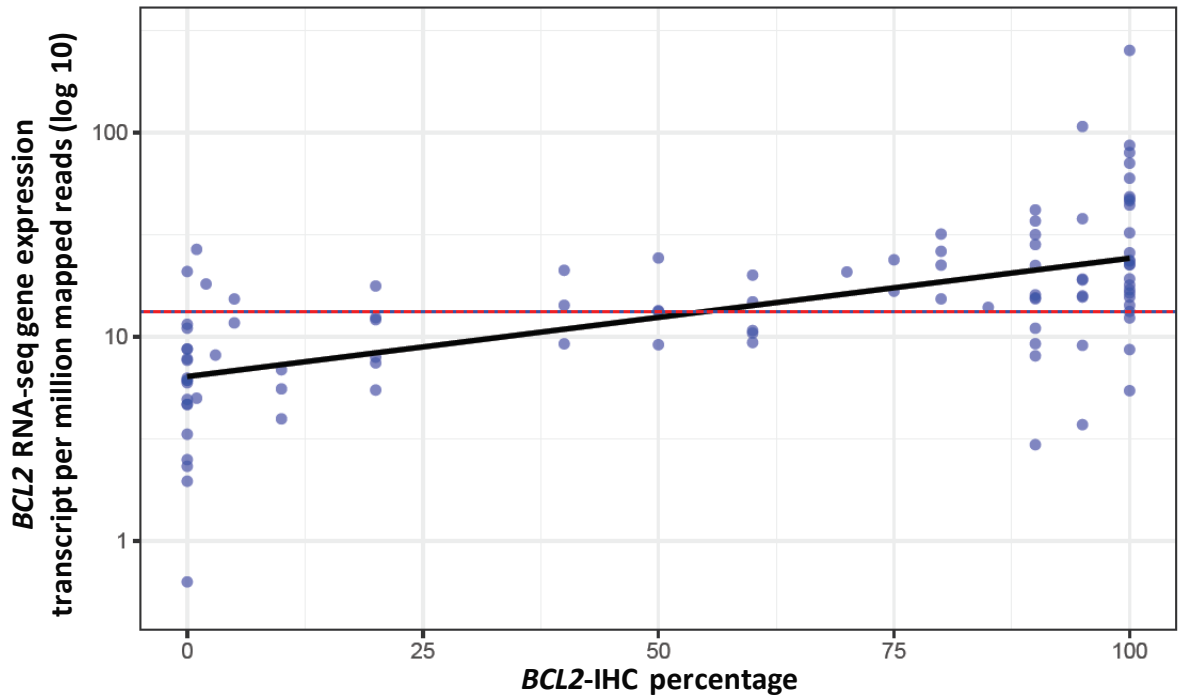
Supplemental Table 3. Proportion of patients with DE lymphoma in the DLBCL subtypes*,†

		DE calls (RNA-seq)	
		DE, n (%)	**Non-DE, n (%)**
ABC calls (HTG EdgeSeq)	**ABC, n = 540**	193 (35.7)	347 (64.3)
	GCB/Unclassified, n = 165	24 (14.5)	141 (85.5)
MCD/N1/BN2 calls (LymphGen)	**MCD, n = 109**	48 (44.0)	61 (56.0)
	Non-MCD, n = 656	186 (28.4)	470 (71.6)
	N1, n = 28	11 (39.2)	17 (60.8)
	Non-N1, n = 737	223 (30.3)	514 (69.7)
	BN2, n = 46	10 (21.7)	36 (78.3)
	Non-BN2, n = 719	224 (31.2)	495 (68.8)

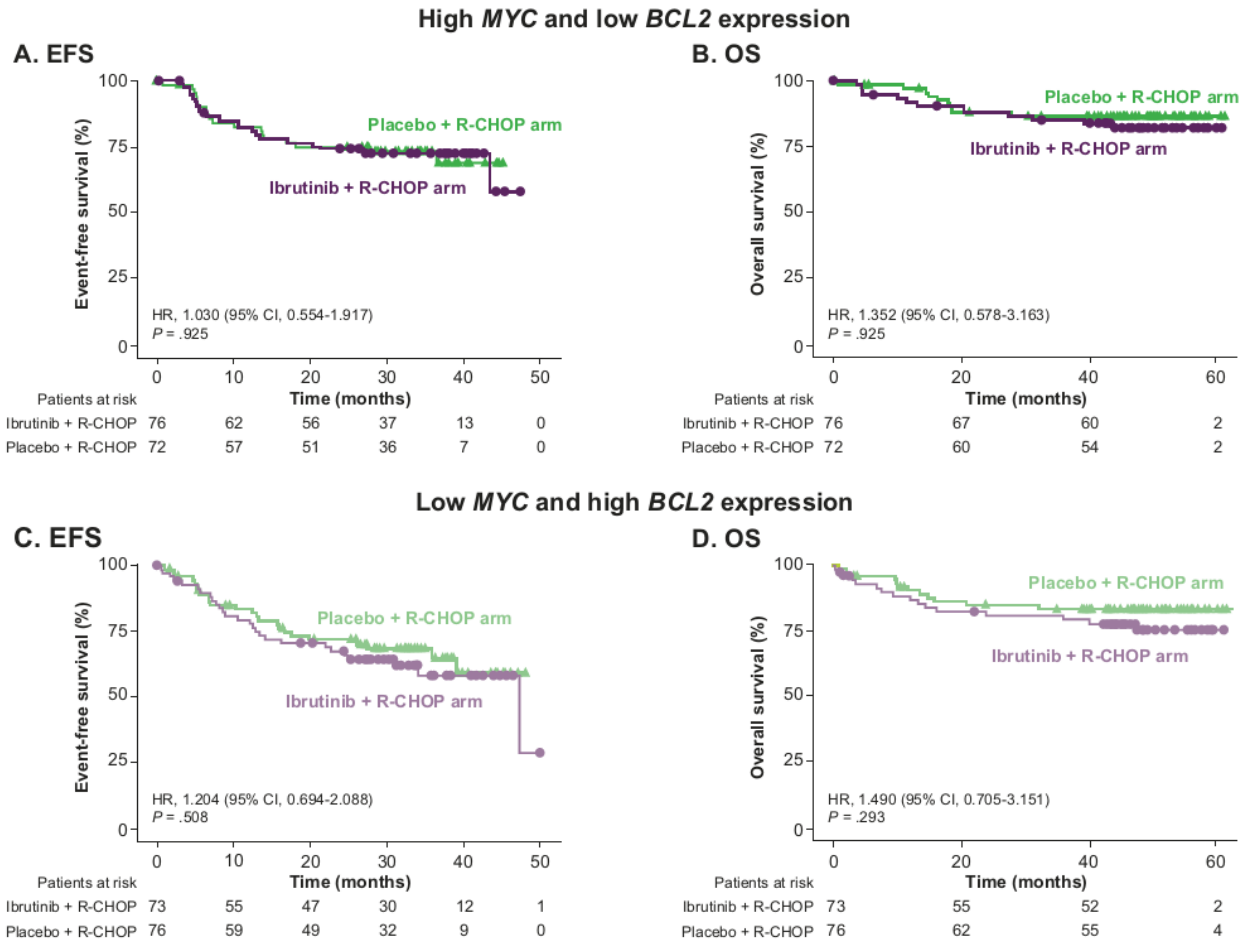
*A53 subtype could not be inferred as assessing aneuploidy was not allowed by methods employed in the analysis.

†Patient counts by assay – total: 838 patients; LymphGen (MCD/N1/BN2 calls): 773 patients; RNA-seq (DE calls): 766 patients; HTG EdgeSeq (ABC calls): 747 patients; RNA-seq/LymphGen overlap: 765 patients; HTG EdgeSeq/LymphGen overlap: 709 patients; RNA-seq/HTG EdgeSeq overlap: 705 patients; overlap of all three assays: 704 patients.

A53, aneuploid with *TP53* inactivation; ABC, activated B-cell–like; BN2, *BCL6* fusion and *NOTCH2* mutation; DE, *BCL2/MYC* double-expressor lymphoma by RNA sequencing; GCB, germinal center B-cell–like; MCD, *MYD88*^{L265P}*/CD79B*-mutated; N1, *NOTCH1*-mutated; RNA-seq, RNA sequencing.



Supplementary Figure 1. *BCL2* expression cutoff. Colored lines represent the optimal *BCL2* RNA-seq-based cutoff for approximating calls from IHC *BCL2* 50% (dotted blue line) and the median *BCL2* RNA-seq expression value for the full study (solid red line). IHC, immunohistochemistry; RNA-seq, RNA sequencing.



Supplementary Figure 2. EFS and OS in patients with high *MYC* and low *BCL2* expression (A, B), and low *MYC* and high *BCL2* expression (C, D) by RNA-seq in the ibrutinib plus R-CHOP vs placebo plus R-CHOP. CI, confidence interval; EFS, event-free survival; HR, hazard ratio; ITT, intent-to-treat; OS, overall survival; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; RNA-seq; RNA sequencing.