Supplementary Material

Supplementary Tables

Supplementary Table 1. Available and analyzed biomarker data

Cohort	Time to event data	Biomarker data	BCL2 by IHC
Arthur[30]	PFS, OS	RNA-Seq, IHC, NanoString	Yes
Reddy[32]	OS	RNA-Seq	Yes
Schmitz[31]	PFS, OS	RNA-Seq	No
GOYA[21]	PFS, OS	RNA-Seq, IHC, PCR	Yes

IHC, immunohistochemistry; OS, overall survival; PCR, polymerase chain reaction; PFS, progression-free survival; RNA-Seq, RNA sequencing.

Supplementary Table 2. Association between PFS and increased *FCGR2B* expression (RNA-Seq) in the Arthur and Schmitz DLBCL cohorts and according to COO. Cox regression results based on *FCGR2B* expression represented as continuous variable.

	Cohort	Total n	Hazard ratio	95% CI	*P*-value
Univariate analysis					
All cases	Arthur	372	1.09	1.01-1.19	.0360
All cases	Schmitz	229	1.13	1.02-1.26	.0243
Multivariate analysis[a]					
All cases	Arthur	322	1.12	1.02-1.23	.0209
All cases	Schmitz	188	1.15	1.01-1.31	.0335
Univariate analysis					
COO					
GCB	Arthur	204	1.14	1.03-1.26	.0150
GCB	Schmitz	108	1.04	0.87-1.23	.68
ABC	Arthur	120	1.09	0.91-1.31	.36
ABC	Schmitz	79	1.14	0.91-1.43	.25

[a]Includes adjustment for International Prognostic Index, COO and BCL2 protein expression.

ABC, activated B cell; CI, confidence interval; COO, cell of origin; DLBCL, diffuse large B-cell lymphoma; GCB, germinal center B cell; RNA-Seq, RNA sequencing.

Supplementary Table 3. Association between OS and increased *FCGR2B* expression levels (RNA-Seq) in the Arthur, Schmitz and Reddy DLBCL cohorts and according to COO. Cox regression results based on *FCGR2B* expression represented as continuous variable.

	Cohort	Total n	Hazard ratio	95% CI	*P*-value
Univariate analysis					
All cases	Arthur	372	1.07	0.98-1.17	.13
All cases	Schmitz	234	1.07	0.96-1.20	.22
All cases	Reddy	454	1.21	1.04-1.42	.0167
Multivariate analysis[a]					
All cases	Arthur	346	1.08	0.98-1.18	.11
All cases	Schmitz	189	1.06	0.93-1.22	.38
All cases	Reddy	387	1.10	0.92-1.32	.29
Univariate analysis					
COO					
GCB	Arthur	204	1.10	0.98-1.22	.11
GCB	Schmitz	110	1.00	0.84-1.20	.96
GCB	Reddy	196	1.19	0.96-1.47	.11
ABC	Arthur	120	1.09	0.90-1.33	.38
ABC	Schmitz	82	1.02	0.80-1.30	.87
ABC	Reddy	187	1.06	0.80-1.41	.68

[a]Includes adjustment for International Prognostic Index, COO and BCL2 protein expression.

ABC, activated B cell; CI, confidence interval; COO, cell of origin; DLBCL, diffuse large B-cell lymphoma; GCB, germinal center B cell; OS, overall survival; RNA-Seq, RNA sequencing.

Supplementary Table 4. Association between PFS/OS and increased *FCGR2B* expression (NanoString) in the Arthur DLBCL cohort. Cox regression results based on *FCGR2B* expression represented as continuous variable.

	Total n	Hazard ratio	95% CI	*P*-value
PFS Univariate analysis				
All cases	325	1.13	1.04-1.23	.0048
PFS Multivariate analysis[a]				
All cases	288	1.13	1.02-1.24	.0140
OS Univariate analysis				
All cases	325	1.09	1.00-1.20	.0621
OS Multivariate analysis[a]				
All cases	288	1.09	0.99-1.21	.0745

[a]Includes adjustment for International Prognostic Index, cell of origin and BCL2 protein expression.

CI, confidence interval; DLBCL, diffuse large B-cell lymphoma; OS, overall survival; PFS, progression-free survival.

Supplementary Table 5. Association between PFS and FcγRIIB protein expression by IHC on DLBCL tumors in the Arthur cohort

	FcγRIIB by IHC	Total n	Hazard ratio	95% CI	*P*-value
All cases	Low (vs negative)	331	0.97	0.69-1.36	.86
All cases	High (vs negative)	331	1.53	0.97-2.39	.0644
All cases	High (vs negative + low)	331	1.56	1.05-2.31	.0270
By COO					
GCB	High (vs negative + low)	172	1.95	1.17-3.27	.0110
ABC	High (vs negative + low)	98	1.32	0.65-2.66	.44

ABC, activated B cell; CI, confidence interval; COO, cell of origin; DLBCL, diffuse large B-cell lymphoma; FcγRIIB, Fc gamma receptor IIB; GCB, germinal center B cell; IHC, immunohistochemistry; PFS, progression-free survival.

Supplementary Table 6. Association between OS and FcγRIIB protein expression by IHC on DLBCL tumors in the Arthur cohort

	FcγRIIB by IHC	Total n	Hazard ratio	95% CI	*P*-value
All cases	Low (vs negative)	331	0.99	0.69-1.41	.93
All cases	High (vs negative)	331	1.40	0.87-2.24	.16
All cases	High (vs negative + low)	331	1.41	0.93-2.14	.10
By COO					
GCB	High (vs negative + low)	172	1.73	1.00-2.99	.0482
ABC	High (vs negative + low)	98	1.40	0.69-2.86	.35

ABC, activated B cell; CI, confidence interval; COO, cell of origin; DLBCL, diffuse large B-cell lymphoma; FcγRIIB, Fc gamma receptor IIB; GCB, germinal center B cell; IHC, immunohistochemistry; OS, overall survival.

Supplementary Table 7. Demographic and baseline characteristics of patients with DLBCL in the GOYA cohort according to treatment group (BEP)

Characteristic[a] n (%)	BEP RNA-Seq R-CHOP (n = 271)	BEP RNA-Seq G-CHOP (n = 281)
Age		
Median, years (range)	63 (18-83)	63 (18-85)
Female, n (%)	124 (45.8)	140 (49.8)
Number of chemotherapy cycles		
6	208 (76.8)	194 (69.0)
8	63 (23.2)	87 (31.0)
Geographic region		
Asia	45 (16.6)	44 (15.7)
Eastern Europe	52 (19.2)	70 (24.9)
Western Europe	108 (39.9)	108 (38.4)
North America	50 (18.5)	43 (15.3)
Other	16 (5.9)	16 (5.7)
IPI		
Low	53 (19.6)	54 (19.2)
Low-intermediate	96 (35.4)	98 (34.9)
High-intermediate	82 (30.3)	79 (28.1)
High	40 (14.8)	50 (17.8)
Ann Arbor stage at diagnosis		
I/II	64 (23.6)	70 (24.9)
III/IV	207 (76.4)	211 (75.1)
COO, n	265	273
GCB	154 (58.1)	144 (52.7)
ABC	71 (26.8)	80 (29.3)
Unclassified	40 (15.1)	49 (18.0)
DHITsig, n	154	144
Positive	21 (13.6)	11 (7.6)
Negative	133 (83.4)	133 (92.4)
BCL2 by IHC, n	210	223
Positive	103 (49.0)	103 (46.2)
Negative	107 (51.0)	120 (53.8)

[a]All data are n (%) unless otherwise stated.

ABC, activated B cell; BEP, biomarker-evaluable population; COO, cell of origin; DLBCL, diffuse large B-cell lymphoma; GCB, germinal center B cell; G-CHOP, obinutuzumab plus cyclophosphamide, doxorubicin, vincristine and prednisone; IHC, immunohistochemistry; IPI, International Prognostic Index; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone.

Supplementary Table 8. Association between PFS and increased *FCGR2B* expression (RNA-Seq) in the GOYA DLBCL cohort by treatment. Cox regression results based on *FCGR2B* expression represented as continuous variable.

	Treatment	Total n	Hazard ratio	95% CI	*P*-value
Univariate analysis					
All cases	R-CHOP	271	1.26	1.00-1.58	.0455
All cases	G-CHOP	281	0.91	0.69-1.20	.50
Multivariate analysis[a]					
All cases	R-CHOP	206	1.32	0.98-1.79	.0695
All cases	G-CHOP	220	0.92	0.68-1.24	.58
Univariate analysis					
COO					
GCB	R-CHOP	154	1.22	0.92-1.63	.16
GCB	G-CHOP	144	0.89	0.61-1.32	.57
ABC	R-CHOP	71	1.35	0.74-2.46	.33
ABC	G-CHOP	80	1.12	0.60-2.09	.72

[a]Includes adjustment for International Prognostic Index, COO and BCL2 protein expression.

ABC, activated B cell; CI, confidence interval; COO, cell of origin; DLBCL, diffuse large B-cell lymphoma; GCB, germinal center B cell; G-CHOP, obinutuzumab plus cyclophosphamide, doxorubicin, vincristine and prednisone; PFS, progression-free survival; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone; RNA-Seq, RNA sequencing.

Supplementary Table 9. Treatment effect (G-CHOP vs R-CHOP) on PFS within the low and high *FCGR2B* expression (RNA-Seq) in the GOYA DLBCL cohort

	Treatment	Total n	Subgroup n	Hazard ratio	95% CI	*P*-value
Univariate analysis						
FCGR2B expression						
≤median (low)	G-CHOP vs R-CHOP	276	147 vs 129	1.58	1.00-2.50	.0503
>median (high)	G-CHOP vs R-CHOP	276	134 vs 142	0.67	0.44-1.02	.0622
Treatment:biomarker interaction						.0064
Multivariate analysis[a]						
FCGR2B expression						
≤median (low)	G-CHOP vs R-CHOP	213	117 vs 96	1.87	1.10-3.18	.0216
>median (high)	G-CHOP vs R-CHOP	213	103 vs 110	0.80	0.49-1.32	.39
Treatment:biomarker interaction						.0249

[a]Includes adjustment for International Prognostic Index, cell of origin and BCL2 protein expression.

CI, confidence interval; DLBCL, diffuse large B-cell lymphoma; G-CHOP, obinutuzumab plus cyclophosphamide, doxorubicin, vincristine and prednisone; IHC, immunohistochemistry; PFS, progression-free survival; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone; RNA-Seq, RNA sequencing.

Supplementary Table 10. Association between OS and increased *FCGR2B* expression (RNA-Seq) in the GOYA DLBCL cohort by treatment. Cox regression results based on *FCGR2B* expression represented as continuous variable.

	Treatment	Total n	Hazard ratio	95% CI	*P*-value
Univariate analysis					
All cases	R-CHOP	271	1.25	0.93-1.67	.14
All cases	G-CHOP	281	0.86	0.61-1.21	.39
Multivariate analysis[a]					
All cases	R-CHOP	206	1.32	0.88-1.95	.18
All cases	G-CHOP	220	0.78	0.53-1.15	.21
Univariate analysis					
COO					
GCB	R-CHOP	154	1.22	0.84-1.76	.30
GCB	G-CHOP	144	0.81	0.48-1.35	.42
ABC	R-CHOP	71	1.32	0.62-2.79	.47
ABC	G-CHOP	80	0.96	0.50-1.84	.91

[a]Includes adjustment for International Prognostic Index, COO and BCL2 protein expression.

ABC, activated B cell; CI, confidence interval; COO, cell of origin; DLBCL, diffuse large B-cell lymphoma; G-CHOP, obinutuzumab plus cyclophosphamide, doxorubicin, vincristine and prednisone; IHC, immunohistochemistry; GCB, germinal center B cell; OS, overall survival; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone; RNA-Seq, RNA sequencing.

Supplementary Table 11. Association between PFS and FcγRIIB protein expression by IHC on tumors and macrophages in the GOYA DLBCL cohort by treatment

	Treatment	Total n	Subgroup n	Hazard ratio	95% CI	*P*-value
Univariate analysis						
FcγRIIB expression on tumor (status)						
Positive vs negative	R-CHOP	127	26 vs 101	2.17	1.04-4.50	.0378
Positive vs negative	G-CHOP	324	24 vs 110	1.37	0.66-2.87	.40
FcγRIIB expression on macrophages (grouped)						
High vs negative + low	R-CHOP	121	107 vs 14	1.39	0.42-4.57	.59
High vs negative + low	G-CHOP	128	109 vs 19	0.44	0.22-0.91	.0258
Multivariate analysis						
FcγRIIB expression on tumor (status)						
Positive vs negative	R-CHOP	116	25 vs 91	3.05	1.14-8.16	.0264
Positive vs negative	G-CHOP	123	21 vs 102	1.51	0.67-3.41	.32
FcγRIIB expression on macrophages (grouped)						
High vs negative + low	R-CHOP	110	100 vs 10	2.56	0.32-20.39	.37
High vs negative + low	G-CHOP	117	102 vs 15	0.39	0.18-0.88	.0227

[a]Includes adjustment for International Prognostic Index, cell of origin and BCL2 protein expression.

CI, confidence interval; DLBCL, diffuse large B-cell lymphoma; FcγRIIB, Fc gamma receptor IIB; G-CHOP, obinutuzumab plus cyclophosphamide, doxorubicin, vincristine and prednisone; IHC, immunohistochemistry; PFS, progression-free survival; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone.

Supplementary Table 12. Treatment effect (G-CHOP vs R-CHOP) on PFS within the low and high FcγRIIB protein expression by IHC on tumors and macrophages in the GOYA DLBCL cohort

	Treatment	Total n	Subgroup n	Hazard ratio	95% CI	*P*-value
Univariate analysis						
FcγRIIB expression on tumor (status)						
Negative	G-CHOP vs R-CHOP	211	110 vs 101	1.42	0.82-2.46	.21
Positive	G-CHOP vs R-CHOP	50	24 vs 26	0.88	0.37-2.13	.78
FcγRIIB expression on macrophages (grouped)						
Negative + low	G-CHOP vs R-CHOP	33	19 vs 14	3.16	0.86-11.53	.08
High	G-CHOP vs R-CHOP	216	109 vs 107	0.96	0.57-1.59	.86
Multivariate analysis[a]						
FcγRIIB expression on tumor (status)						
Negative	G-CHOP vs R-CHOP	193	102 vs 91	1.66	0.90-3.08	.11
Positive	G-CHOP vs R-CHOP	46	21 vs 25	0.80	0.26-2.44	.70
FcγRIIB expression on macrophages (grouped)						
Negative + low	G-CHOP vs R-CHOP	25	15 vs 10	10.01	0.89-112.16	.06
High	G-CHOP vs R-CHOP	202	102 vs 100	0.95	0.55-1.64	.87

[a]Includes adjustment for International Prognostic Index, cell of origin and BCL2 protein expression.

CI, confidence interval; DLBCL, diffuse large B-cell lymphoma; FcγRIIB, Fc gamma receptor IIB; G-CHOP, obinutuzumab plus cyclophosphamide, doxorubicin, vincristine and prednisone; IHC, immunohistochemistry; PFS, progression-free survival; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone.

Supplementary Table 13. Association between OS and FcγRIIB protein expression by IHC on tumors and macrophages in the GOYA DLBCL cohort by treatment

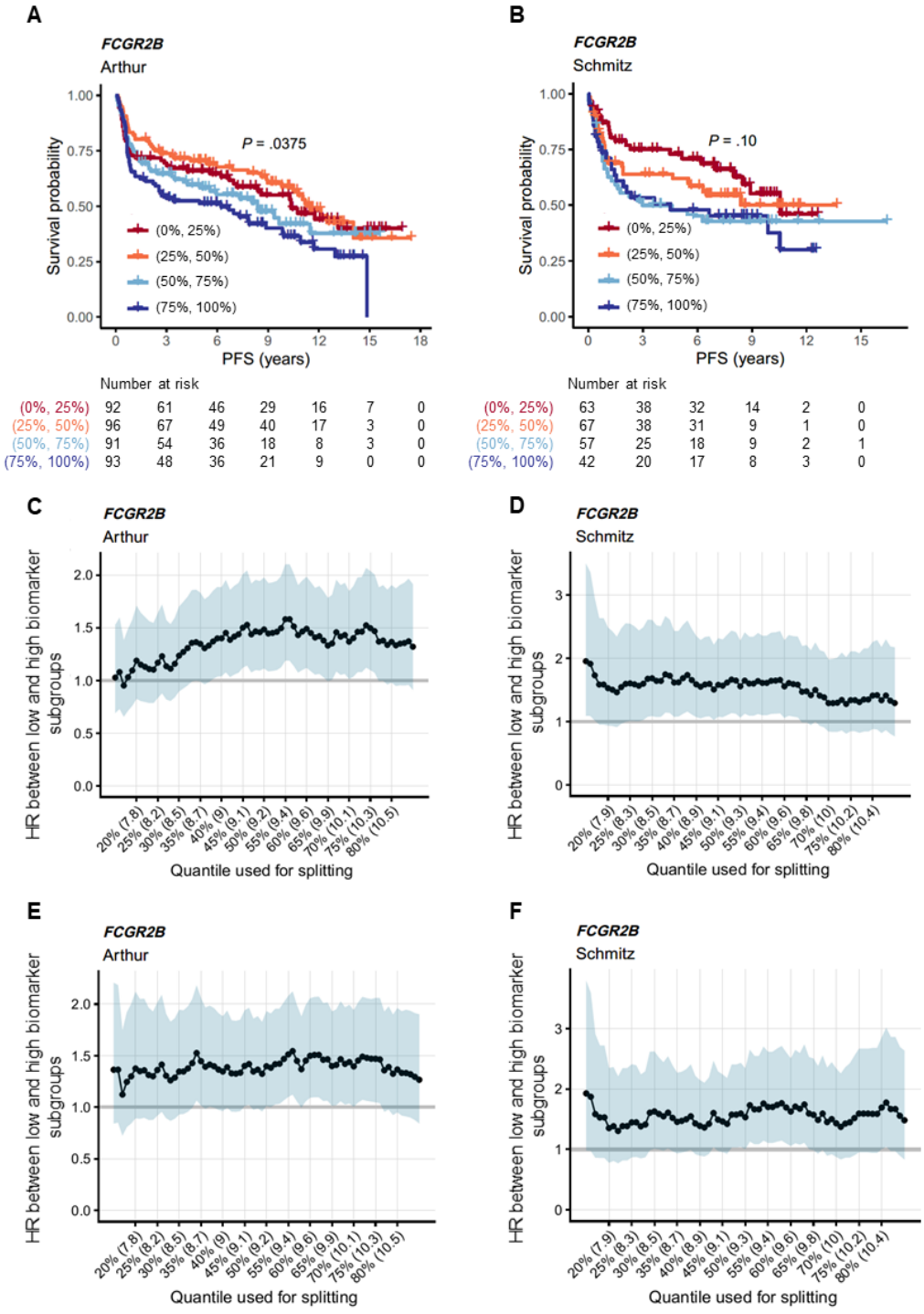
	Treatment	Total n	Subgroup n	Hazard ratio	95% CI	*P*-value
Univariate analysis						
FcγRIIB expression on tumor (status)						
Positive vs negative	R-CHOP	127	26 vs 101	1.61	0.66-3.93	.29
Positive vs negative	G-CHOP	324	24 vs 110	1.86	0.82-4.21	.13
FcγRIIB expression on macrophages (grouped)						
High vs negative + low	R-CHOP	121	107 vs 14	1.39	0.33-5.95	.65
High vs negative + low	G-CHOP	128	109 vs 19	0.42	0.18-1.00	.0506
Multiivariate analysis						
FcγRIIB expression on tumor (status)						
Positive vs negative	R-CHOP	116	25 vs 91	1.89	0.57-6.31	.30
Positive vs negative	G-CHOP	123	21 vs 102	2.05	0.84-5.01	.12
FcγRIIB expression on macrophages (grouped)						
High vs negative + low	R-CHOP	110	100 vs 10	>100	NA	1.00
High vs negative + low	G-CHOP	117	102 vs 15	0.31	0.12-0.80	.0159

[a]Includes adjustment for International Prognostic Index, cell of origin and BCL2 protein expression.

CI, confidence interval; DLBCL, diffuse large B-cell lymphoma; FcγRIIB, Fc gamma receptor IIB; G-CHOP, obinutuzumab plus cyclophosphamide, doxorubicin, vincristine and prednisone; IHC, immunohistochemistry; NA, not available; OS, overall survival; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone.

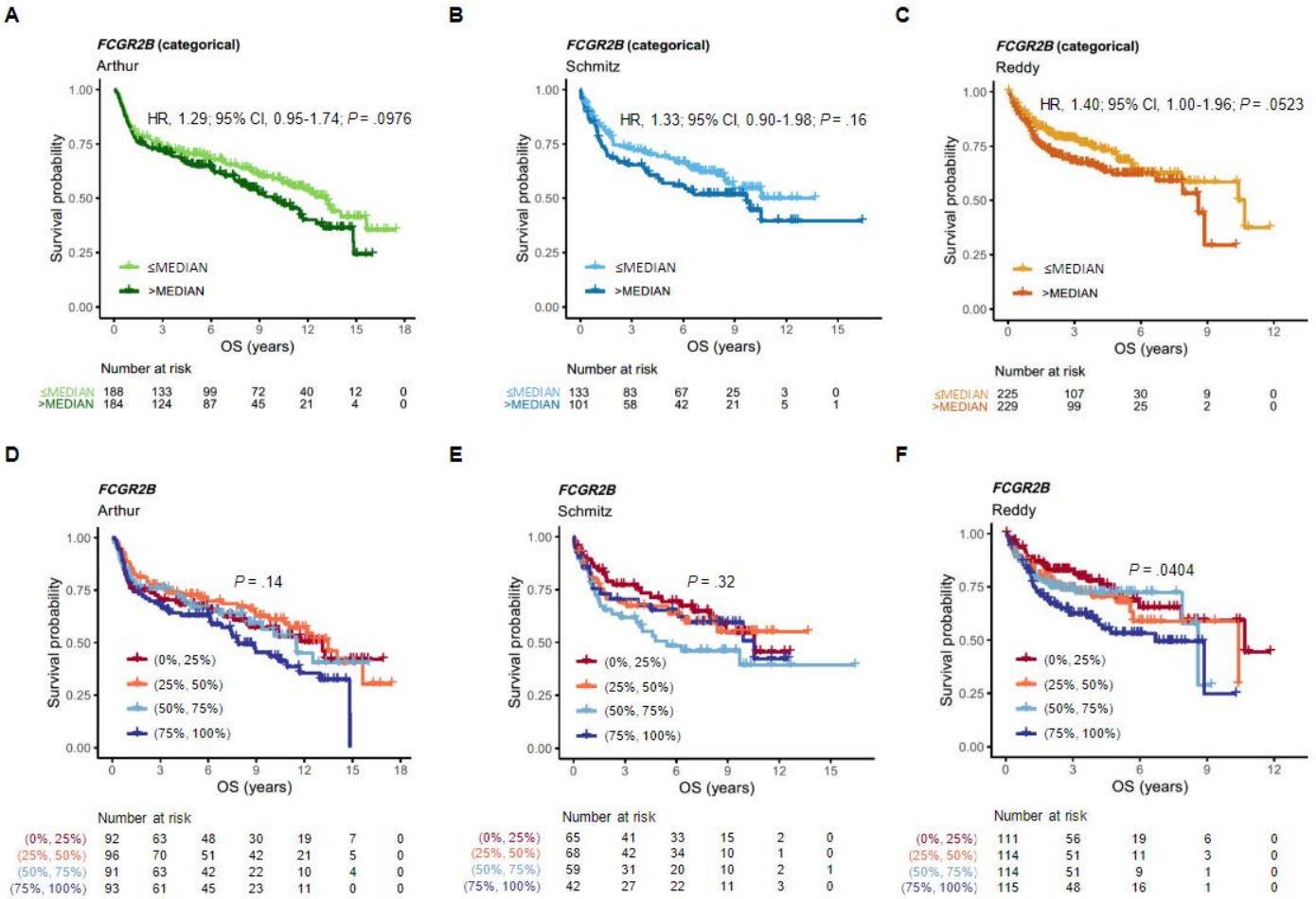
Supplementary Figures

Supplementary Figure 1. Detailed evaluation of the association between PFS and *FCGR2B* expression by RNA-Seq in patients treated with R-CHOP in the Arthur and the Schmitz cohort. Kaplan–Meier curves for PFS based on *FCGR2B* expression according to stratification by quartiles and the corresponding p-values from the log-rank test (A, B). Evaluation of the robustness of the stratification threshold used to dichotomize samples into low and high *FCGR2B* expression subgroups. Various thresholds were used, the corresponding HR between low and high *FCGR2B* expression subgroups and the corresponding 95% CIs from the univariate (C, D), and multivariate (E, F) Cox regression are plotted



CI, confidence interval; HR, hazard ratio; PFS, progression-free survival; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone; RNA-Seq, RNA sequencing.

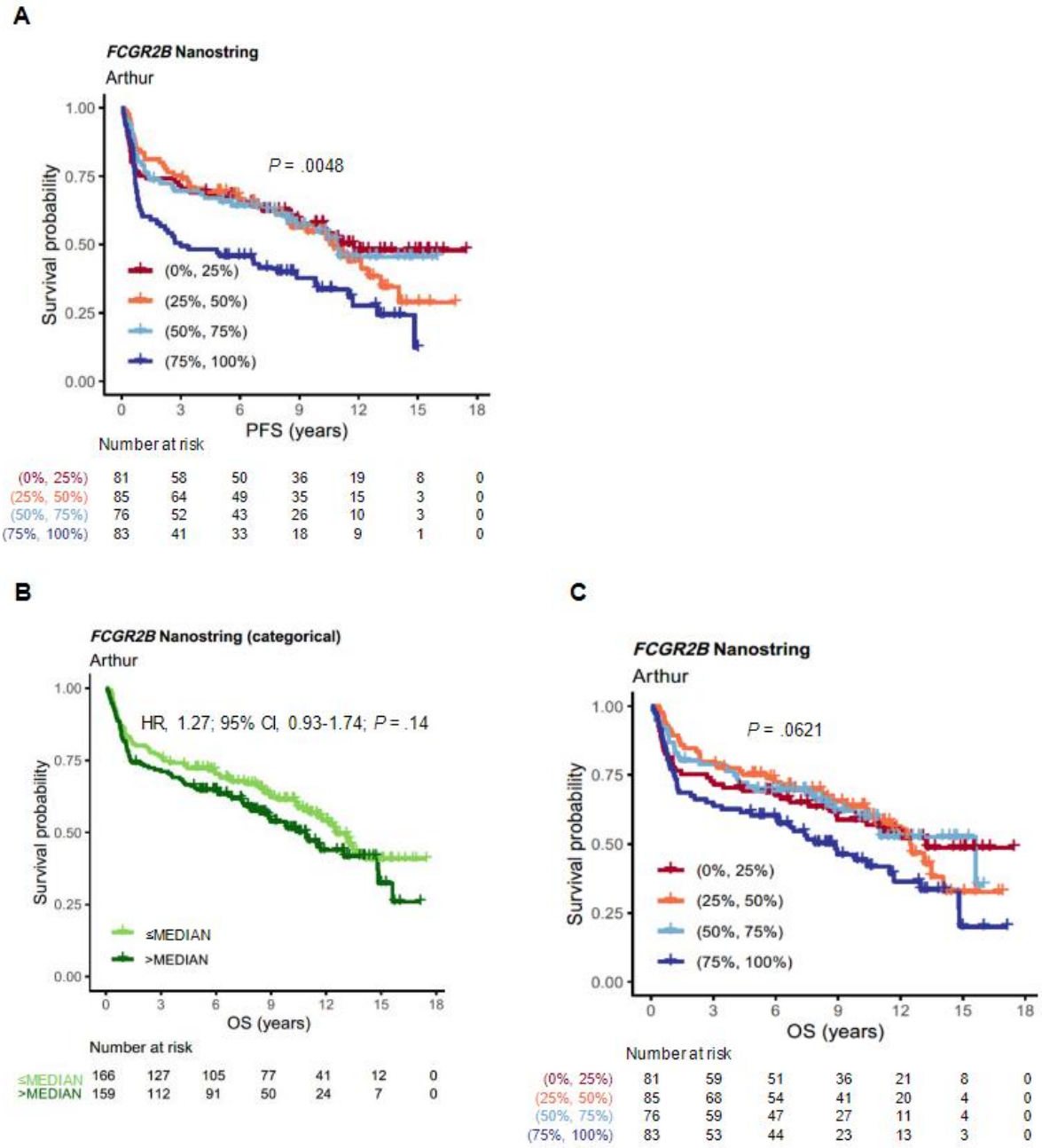
Supplementary Figure 2. Association of *FCGR2B* expression measured by RNA-Seq with OS in patients with DLBCL treated with R-CHOP in the Arthur, Schmitz and Reddy cohorts. Kaplan–Meier curves for OS based on *FCGR2B* expression according to stratification by median (A, B, C) and quartiles[a] (D, E, F), respectively



[a]P-values from the log-rank test.

DLBCL, diffuse large B-cell lymphoma; OS, overall survival; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone; RNA-Seq, RNA sequencing.

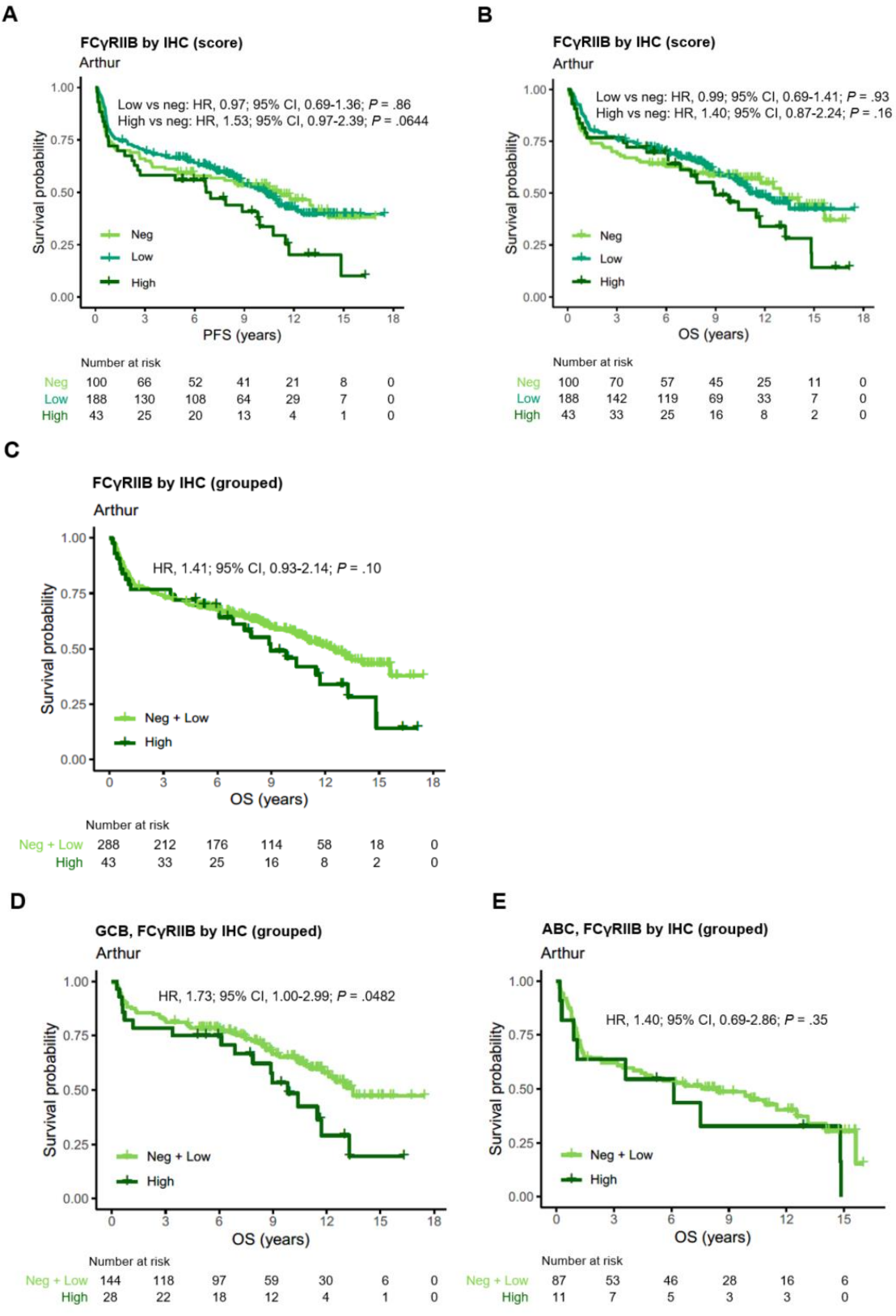
Supplementary Figure 3. Association of *FCGR2B* expression measured by NanoString with clinical outcome in patients with DLBCL treated with R-CHOP in the Arthur cohort. Kaplan-Meier curves presenting survival as defined by PFS based on *FCGR2B* expression according to stratification by quartiles[a] (A). Kaplan–Meier curves presenting survival as defined by OS based on *FCGR2B* expression according to stratification by median (B) and quartiles[a] (C)



[a]P-values from the log-rank test.

DLBCL, diffuse large B-cell lymphoma; OS, overall survival; PFS, progression-free survival; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone.

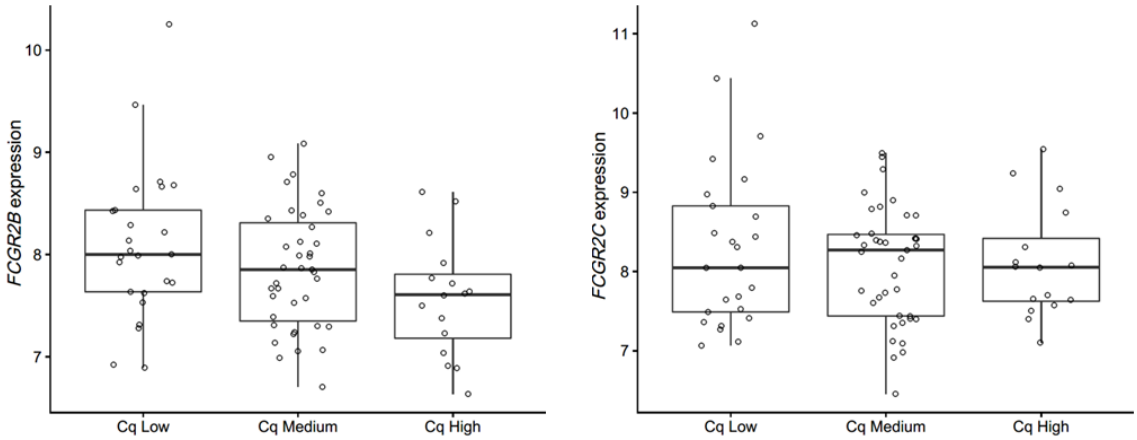
Supplementary Figure 4. Prognostic effect of FcγRIIB protein expression on DLBCL tumors as measured by IHC[a]. Kaplan–Meier curves for OS according to high, low and negative FcγRIIB tumor expression in the Arthur cohort (A) and according to stratification by COO (B, C)



[a]Tumor membrane staining for FcγRIIB was defined as high (at least medium intensity staining with >50% positive cells); low (membrane positive, low intensity staining or <50% positive cells); or negative (cytoplasmic staining or negative membrane staining).

ABC, activated B cell; COO, cell of origin; DLBCL, diffuse large B-cell lymphoma; FcγRIIB, Fc gamma receptor IIB; GCB, germinal center B cell; IHC, immunohistochemistry; OS, overall survival.

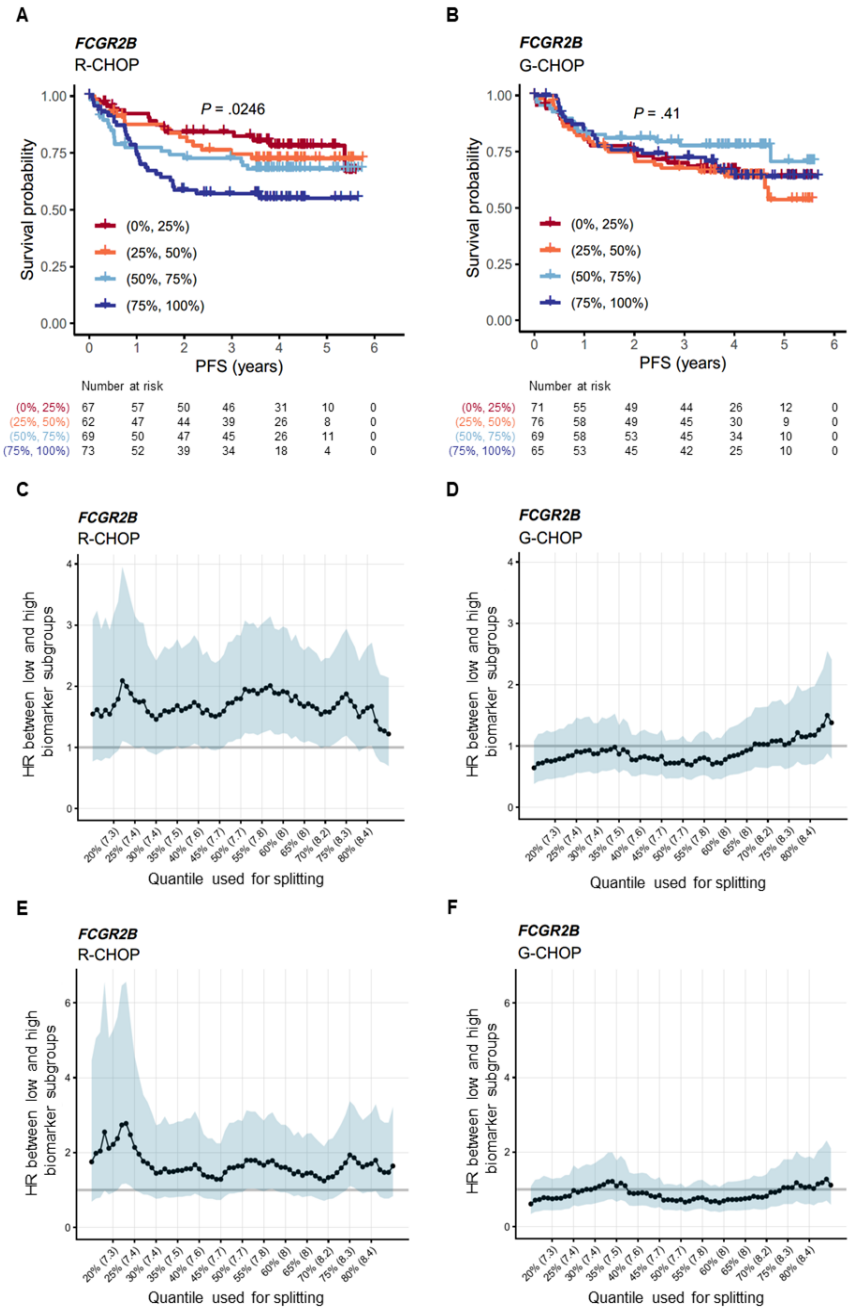
Supplementary Figure 5. Validation of *FCGR2B* RNA-Seq measurement by qPCR in GOYA[a]



[a]Primers specific to *FCGR2B* and its paralog *FCGR2C* were used to quantify the expression of each gene and stratify tumors into Cq Low, Medium, or High expression. The correlation between RNA-Seq and qPCR expression was determined by a Kruskal-Wallis H test.

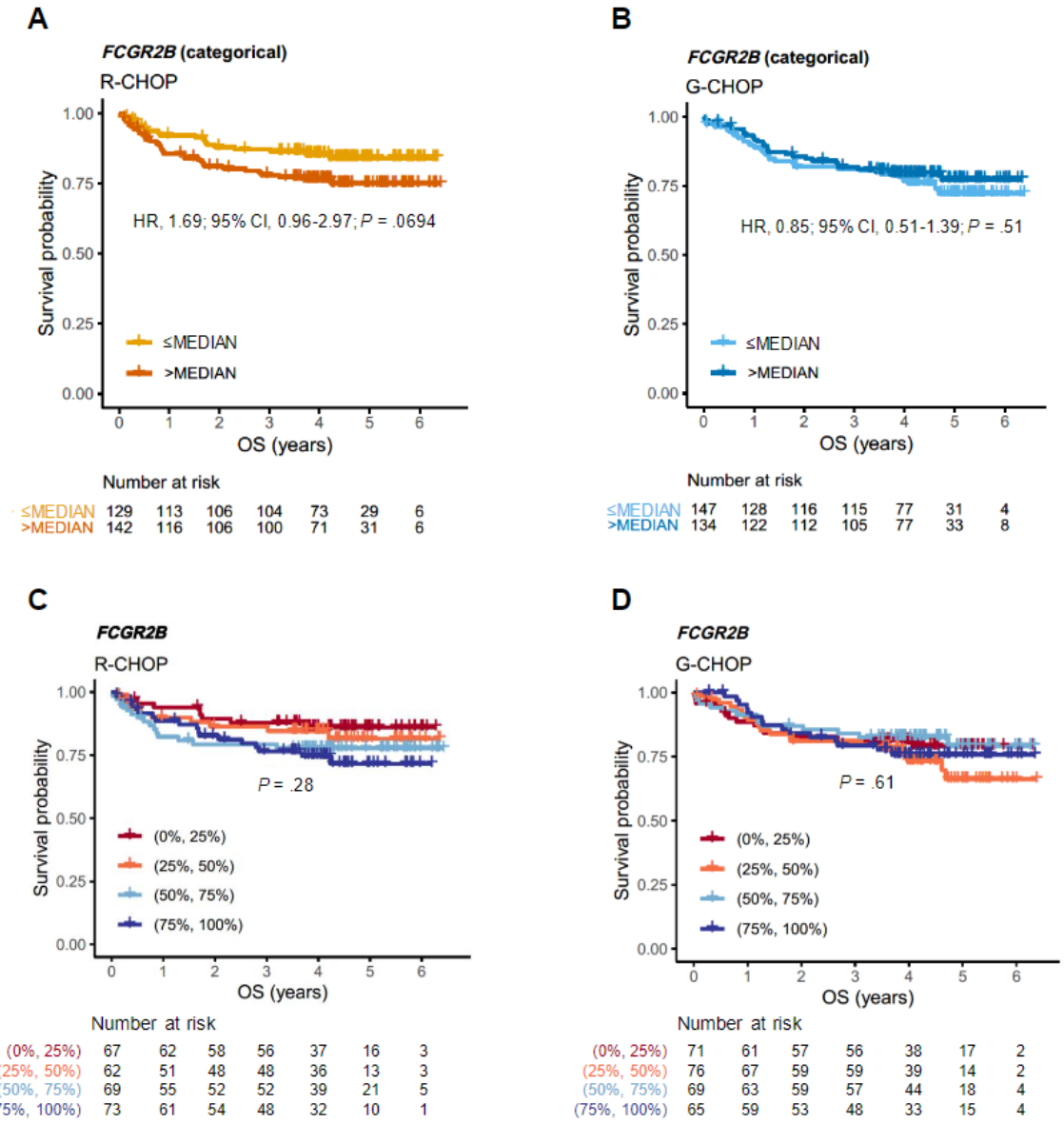
Cq, quantification value; qPCR, quantitative polymerase chain reaction; RNA-Seq, RNA sequencing.

Supplementary Figure 6. Detailed evaluation of the association between PFS and *FCGR2B* expression measured by RNA-Seq in patients with DLBCL treated with R-CHOP or G-CHOP in GOYA. Kaplan–Meier curves for PFS based on *FCGR2B* expression according to stratification by quartiles and the corresponding p-values from the log-rank test (A, B). Evaluation of the robustness of the stratification threshold used to dichotomize samples into low and high *FCGR2B* expression subgroups. Various thresholds were used, the corresponding HR between low and high *FCGR2B* expression subgroups and the corresponding 95% CIs from the univariate (C, D), and multivariate (E, F) Cox regression are plotted.



CI, confidence interval; DLBCL, diffuse large B-cell lymphoma; G-CHOP, obinutuzumab plus cyclophosphamide, doxorubicin, vincristine and prednisone; HR, hazard ratio; PFS, progression-free survival; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone; RNA-Seq, RNA sequencing.

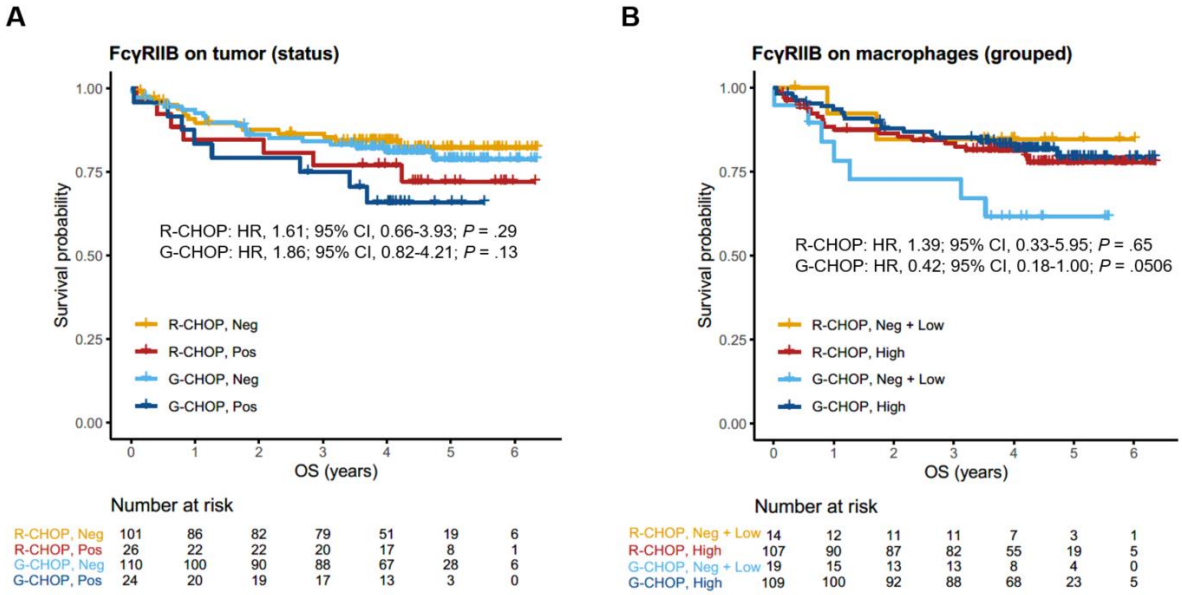
Supplementary Figure 7. Association of *FCGR2B* expression by RNA-Seq with OS in patients with DLBCL treated with R-CHOP or G-CHOP in GOYA. Kaplan–Meier curves for OS based on *FCGR2B* expression according to stratification by median (A, B) and quartiles[a] (C, D)



[a]P-values from the log-rank test.

DLBCL, diffuse large B-cell lymphoma; G-CHOP, obinutuzumab plus cyclophosphamide, doxorubicin, vincristine and prednisone; OS, overall survival; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone; RNA-Seq, RNA sequencing.

Supplementary Figure 8. Prognostic effect of FcγRIIB protein expression on DLBCL tumors and macrophages in GOYA as measured by IHC[a]. Kaplan–Meier curves for OS according to positive and negative FcγRIIB protein expression on DLBCL tumors (A), and according to high, or low/negative expression on macrophages (B)



[a]Tumors were assessed as negative or positive for FcγRIIB membrane staining. FcγRIIB on macrophages was defined as high (at least medium intensity staining with >50% positive cells); low (membrane positive, low intensity staining or <50% positive cells); or negative (cytoplasmic staining or membrane negative).

DLBCL, diffuse large B-cell lymphoma; FcγRIIB, Fc gamma receptor IIB; IHC, immunohistochemistry; OS, overall survival.