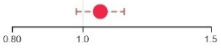
Supplementary Fig. S12: Clinical impact of immune checkpoint expressing macrophages in non-double hit DLBCL patients

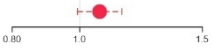
A

All patients	OS HR (95% CI)	P
CD68+ (n=168)	1.09 (1.02−1.17)	0.018
CD163+ (n=167)	1.01 (0.99−1.04)	0.269
T cell high group		
CD68+ (n=97)	1.12 (1.01−1.32)	0.028
CD163+ (n=96)	1.02 (0.99−1.05)	0.246
T cell low group		
CD68+ (n=67)	1.14 (1.00−1.30)	0.050
CD163+ (n=67)	1.06 (0.98−1.14)	0.157



B

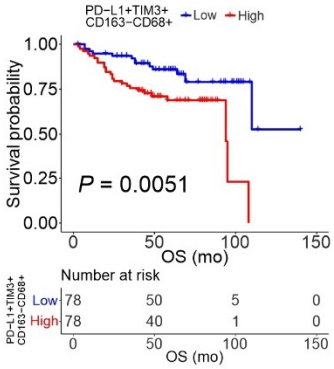
All patients	PFS HR (95% CI)	P
CD68+ (n=168)	1.08 (1.01−1.16)	0.018
CD163+ (n=167)	1.01 (0.98−1.04)	0.490
T cell high group		
CD68+ (n=97)	1.10 (1.01−1.21)	0.032
CD163+ (n=96)	1.01 (0.98−1.04)	0.682
T cell low group		
CD68+ (n=67)	1.12 (0.98−1.27)	0.089
CD163+ (n=67)	1.07 (0.99−1.15)	0.078



C All patients

Macrophage subtype	OS HR (95% CI)	P
PD−L1+CD68+ (n=167)	1.16 (0.94−1.43)	0.155
PD−L1+CD163+CD68+ (n=166)	1.06 (0.78−1.43)	0.728
PD−L1+CD163−CD68+ (n=167)	1.84 (1.19−2.86)	0.006*
TIM3+CD68+ (n=157)	1.13 (1.02−1.26)	0.026
TIM3+CD163+CD68+ (n=156)	1.11 (0.94−1.31)	0.221
TIM3+CD163−CD68+ (n=157)	1.25 (1.05−1.50)	0.014
PD−L1+TIM3+CD68+ (n=157)	1.28 (0.95−1.72)	0.107
PD−L1+TIM3+CD163+CD68+ (n=156)	0.97 (0.56−1.69)	0.923
PD−L1+TIM3+CD163−CD68+ (n=157)	2.85 (1.62−5.00)	<0.001*
PD−1+CD68+ (n=163)	1.26 (1.03−1.55)	0.028
PD−1+CD163+CD68+ (n=160)	1.40 (1.02−1.92)	0.037
PD−1+CD163−CD68+ (n=163)	1.38 (0.91−2.10)	0.128

D



E Model 1

Variable	OS HR (95% CI)	P
PD−L1+TIM3+CD163−CD68+	2.18 (1.18−4.02)	0.013
IPI 3−5 (n=71/154)	3.54 (1.95−10.6)	<0.001

F Model 2

Variable	OS HR (95% CI)	P
PD−L1+TIM3+CD163−CD68+	2.81 (1.27−6.26)	0.011
IPI 3−5 (n=71/154)	1.96 (0.76−5.05)	0.162
ABC (n=52/120)	4.42 (1.54−12.6)	0.007

G Model 3

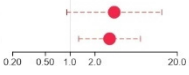
Variable	OS HR (95% CI)	P
PD−L1+TIM3+CD163−CD68+	2.56 (1.11−5.92)	0.028
IPI 3−5 (n=71/154)	2.08 (0.80−5.46)	0.135
ABC (n=52/120)	3.68 (1.21−11.2)	0.022
DPE (n=43/130)	1.40 (0.57−3.44)	0.462

H T cell high group

Macrophage subtype	OS HR (95% CI)	P
PD−L1+CD68+ (n=97)	1.22 (0.95−1.57)	0.116
PD−L1+CD163+CD68+ (n=96)	1.08 (0.77−1.51)	0.665
PD−L1+CD163−CD68+ (n=97)	2.14 (1.28−3.60)	0.004*
TIM3+CD68+ (n=91)	1.17 (1.02−1.33)	0.023
TIM3+CD163+CD68+ (n=90)	1.11 (0.91−1.35)	0.287
TIM3+CD163−CD68+ (n=91)	1.33 (1.07−1.64)	0.009*
PD−L1+TIM3+CD68+ (n=91)	1.33 (0.95−1.88)	0.100
PD−L1+TIM3+CD163+CD68+ (n=90)	1.00 (0.55−1.82)	0.994
PD−L1+TIM3+CD163−CD68+ (n=91)	3.40 (1.73−6.69)	<0.001*
PD−1+CD68+ (n=97)	1.29 (1.01−1.64)	0.039
PD−1+CD163+CD68+ (n=95)	1.50 (1.06−2.12)	0.024
PD−1+CD163−CD68+ (n=97)	1.30 (0.77−2.20)	0.331

I T cell low group

Macrophage subtype	OS HR (95% CI)	P
PD−L1+CD68+ (n=67)	1.23 (0.75−2.01)	0.422
PD−L1+CD163+CD68+ (n=67)	1.20 (0.48−2.96)	0.696
PD−L1+CD163−CD68+ (n=67)	1.93 (0.67−5.55)	0.224
TIM3+CD68+ (n=65)	1.29 (0.97−1.72)	0.083
TIM3+CD163+CD68+ (n=65)	1.61 (0.97−2.66)	0.065
TIM3+CD163−CD68+ (n=65)	1.28 (0.84−1.94)	0.246
PD−L1+TIM3+CD68+ (n=65)	2.55 (0.90−7.27)	0.079
PD−L1+TIM3+CD163+CD68+ (n=65)	2.14 (0.23−20.2)	0.507
PD−L1+TIM3+CD163−CD68+ (n=65)	6.52 (1.31−32.6)	0.022
PD−1+CD68+ (n=64)	2.33 (1.23−4.43)	0.010
PD−1+CD163+CD68+ (n=63)	3.43 (0.91−13.0)	0.069
PD−1+CD163−CD68+ (n=64)	3.01 (1.27−7.16)	0.013



Supplementary Fig. S12: Clinical impact of immune checkpoint expressing macrophages in non-double hit DLBCL patients. A-B) Forest plot visualizing the impact of macrophages and CD163+ macrophages on OS (A) and PFS (B) in the entire mIHC cohort and in the T cell high and T cell low groups, as evaluated by Cox regression univariate analyses with continuous variables. C) Forest plot visualizing the impact of immune checkpoint expressing macrophages on OS in the mIHC cohort, as evaluated by Cox regression univariate analyses with continuous variables. D) Kaplan-Meier (log-rank test) survival plot depicts OS in the patients with high and low proportion of PD-L1+TIM3+CD163-macrophages using median cut-off in the mIHC cohort. E-G) Forest plots visualizing the impact of PD-L1+TIM3+CD163-macrophages on OS in Cox multivariate analyses with IPI (E), IPI and molecular subtype (F), and IPI, molecular subtype, and double protein expression (DPE) (G) in the mIHC cohort. H-I) Forest plots visualizing the impact of immune checkpoint expressing macrophages on OS in the T cell high (H) and low (I) groups, as evaluated by Cox regression univariate analyses with continuous variables in the mIHC cohort. Double-hit lymphomas were excluded from all analyses. Bad cores were also removed from all analyses. *P≤0.05 after FDR correction.