Total metabolic tumor volume as a survival predictor for patients with diffuse large B-cell lymphoma in the GOYA study

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SUPPLEMENTARY MATERIAL

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Study design and PET assessments

In brief, eligible patients were aged ≥18 years, with previously untreated, CD20-positive diffuse large B-cell lymphoma (DLBCL). Patients were randomly assigned in a 1:1 ratio to receive eight 21-day cycles of obinutuzumab 1000 mg by intravenous infusion (Days 1, 8, and 15 of Cycle 1, and Day 1 of Cycles 2–8) or rituximab 375 mg/m^2 by intravenous infusion (Day 1 of Cycles 1–8), plus six or eight cycles of standard-dose cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy. The primary endpoint was investigator-assessed progression-free survival. Secondary endpoints included overall survival.

^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT) FDG-PET/CT scans followed a standardized protocol; baseline and FDG-PET/CT scans were mandatory at sites with access to a PET scanner. Each patient's blood glucose level was measured to ensure that it was between 72–180 mg/dL before intravenous injection of the radiotracer (FDG 370–740 MBq [10–20 mCi]). All centers followed a quality-control/assessment program for PET scans and acquired phantom PET scans were submitted to the contract research organization (ICON Medical Imaging, North Wales, PA, USA) for approval prior to image acquisition. PET images were segmented using a semi-automated workflow program (MIM Software Inc, OH, USA), with a tumor threshold of 1.5 times the mean SUV (SUV_{mean}) of the liver +2 standard deviations. A minimum lesion volume of 1 mL was required for segmentation.

The prognostic value of the quantitative PET parameters was analyzed for the overall population and according to International Prognostic Index (IPI) risk categories and DLBCL cell-of-origin subtype. PET metrics were analyzed, adjusting for IPI score and cell-of-origin subtype.

Patient population

Of 1,414 patients included in the GOYA study intent-to-treat (ITT) population, 1,305 (92.3%) were included in the PET ITT population. One hundred thirteen patients (8.0%) were not included in the PET ITT population, due to: not having evaluable lesions following surgical excision of a lesion prior to baseline PET imaging; having lesions that were too small, as we limited our evaluation to those lesions measuring >1 mL; having CT scans only without PET imaging; and lacking measurable disease by Lugano criteria.

Supplementary Table 1. Demographics and baseline characteristics of the PET ITT and GOYA ITT populations

	PET ITT (N = 1,305)	GOYA ITT (N = 1,414)
Median age, years (range)	62.0 (18–86)	62.0 (18–86)
Male, n (%)	691 (53.0)	750 (53.0)
Geographic region, n (%)		
Eastern Europe	160 (12.3)	196 (13.9)
Western Europe	399 (30.6)	426 (30.1)
North America	208 (15.9)	216 (15.3)
Asia	484 (37.1)	514 (36.4)
Other	54 (4.1)	62 (4.4)
Median time from diagnosis to randomization, months (range)	[N = 1,300] 0.79 (0.0–36.3)	[N = 1,408] 0.79 (0.0–36.3)
ECOG PS, n (%)	[N = 1,304]	[N = 1,413]
0–1	1143 (87.7)	1228 (86.9)
2	161 (12.3)	185 (13.1)
Ann Arbor stage, n (%)	[N = 1,305]	[N = 1,413]
I or II	314 (24.1)	340 (24.1)
III or IV	991 (75.9)	1073 (75.9)
IPI risk score, n (%)		
0–2	734 (56.2)	782 (55.3)
3–5	571 (43.8)	632 (44.7)
Serum LDH elevated, n (%)	[N = 1,301] 748 (57.5)	[N = 1,409] 591 (41.9)
Extranodal involvement, n (%)	877 (67.2)	950 (67.2)
Median SPD, mm (range)	[N = 1,302] 4,395 (0–510,000)	[N = 1,410] 4,447 (0–510,000)
Cell-of-origin, n (%)	[N = 861]	[N = 933]
GCB	494 (57.4)	540 (57.9)
ABC	227 (26.4)	243 (26.0)
Unclassified	140 (16.3)	150 (16.1)

ABC, activated B-cell-like; ECOG PS, Eastern Cooperative Oncology Group performance status; GCB, germinal center B-cell-like; IPI, International Prognostic Index; ITT, intent-to-treat; LDH, lactate dehydrogenase; PET, positron emission tomography; SPD, sum of products of diameters of up to six target lesions.

Supplementary Table 2. Demographics and baseline characteristics according to high (≥ median) or low (< median) baseline TLG in the PET ITT population (n = 1,305)

	High TLG (N = 653)	Low TLG (N = 652)	P-value*
Median age, years (range)	61.0 (18–86)	63.0 (18–85)	0.002
Male, n (%)	366 (56.0)	325 (49.8)	0.027
Median time from diagnosis to randomization, months (range)	[N = 650] 0.69 (0.0–36.3)	[N = 650] 0.95 (0.0–8.7)	0
Ann Arbor stage, n (%)			0
I or II	116 (17.8)	198 (30.4)	
III or IV	537 (82.2)	454 (69.6)	
IPI score, n (%)			0
0–2	265 (40.6)	470 (72.1)	
3	235 (36.0)	139 (21.3)	
4–5	153 (23.4)	43 (6.6)	
ECOG PS, n (%)	[N = 652]	–	0
0–1	535 (82.1)	609 (93.4)	
2–3	117 (18.0)	43 (6.6)	
Any extranodal involvement, n (%)	467 (71.5)	409 (62.7)	0.0008
Serum LDH elevated, n (%)	[N = 650] 518 (79.7)	[N = 651] 227 (34.9)	0
Median SPD, mm (range)	7,880 (160–510,000)	[N = 649] 2,557 (0–194,400)	0
Cell-of-origin subtype, n (%)	[N = 428]	[N = 433]	0.877
GCB	249 (58.2)	245 (56.6)	
ABC	110 (25.7)	117 (27.0)	
Unclassified	69 (16.1)	71 (16.4)	

*Kruskal-Wallis rank sum test (numeric variables) or Fisher's exact test (categorical variables)
ABC, activated B-cell-like; ECOG PS, Eastern Cooperative Oncology Group performance status; GCB, germinal center B-cell-like; IPI, International Prognostic Index; ITT, intent to treat; LDH, lactate dehydrogenase; PET, positron emission tomography; SPD, sum of products of diameter of up to six target lesions; TLG, total lesion glycolysis

Supplementary Table 3. Demographics and baseline characteristics according to baseline TMTV and TLG quartiles in the PET ITT population (n = 1,305)

	TMTV quartiles				TLG quartiles			
	Q1 (1 to 103 cm^3) (N = 326)	Q2 (104 to 351 cm^3) (N = 326)	Q3 (351 to 879 cm^3) (N = 326)	Q4 (879 to 17,115 cm^3) (N = 327)	Q1 (1 to 876 cm^3) (N = 326)	Q2 (880 to 2,951 cm^3) (N = 326)	Q3 (2,954 to 7,810 cm^3) (N = 326)	Q4 (7,811 to 54,600 cm^3) (N = 327)
Median age, years (range)	63.5 (19–85)	61.0 (18–84)	61.0 (18–86)	61.0 (18–82)	63.0 (19–85)	62.0 (18–84)	61.0 (18–86)	60.0 (18–82)
Male, n (%)	162 (49.7)	163 (50.0)	180 (55.2)	186 (56.9)	154 (47.2)	171 (52.5)	179 (54.9)	187 (57.2)
Median time from diagnosis to randomization, months (range)	1.05 (0.0–8.7)	0.89 (0.1–5.3)	0.72 (0.0–13.2)	0.69 (0.1–36.3)	1.08 (0.0–8.7)	0.89 (0.1–5.3)	0.72 (0.0–36.3)	0.69 (0.1–7.5)
Ann Arbor stage, n (%)								
I or II	108 (33.1)	110 (33.7)	68 (20.9)	28 (8.6)	105 (32.2)	93 (28.5)	79 (24.2)	37 (11.3)
III or IV	218 (66.9)	216 (66.3)	258 (79.1)	299 (91.4)	221 (67.8)	233 (71.5)	247 (75.8)	290 (88.7)
IPI score, n (%)								
0–2	258 (79.1)	220 (67.5)	163 (50.0)	93 (28.4)	258 (79.1)	211 (64.7)	170 (52.1)	95 (29.1)
3	55 (16.9)	80 (24.5)	107 (32.8)	132 (40.4)	56 (17.2)	84 (25.8)	98 (30.1)	136 (41.6)
4–5	13 (4.0)	26 (8.0)	56 (17.2)	102 (31.2)	12 (3.7)	31 (9.5)	58 (17.8)	96 (29.4)
ECOG PS 2, n (%)	27 (8.3)	17 (5.2)	37 (11.3)	80 (24.5)	23 (7.1)	20 (6.1)	41 (12.6)	77 (23.5)
Any extranodal involvement, n (%)	209 (64.1)	198 (60.7)	224 (68.7)	246 (75.2)	202 (62.0)	207 (63.5)	223 (68.4)	245 (74.9)
Serum LDH elevated, n (%)	76 (23.4)	162 (49.7)	230 (71.2)	280 (85.6)	83 (25.5)	149 (45.7)	232 (71.8)	284 (86.9)
Median SPD, mm (range)	1,536 (108–13,501)	4,113 (0–194,400)	6,288 (160–510,000)	10,563 (595–56,572)	1,553 (108–13,501)	3,846 (0–194,400)	6,175 (160–510,000)	10,674 (300–56,572)
Cell-of-origin subtype, n (%)	[N = 226]	[N = 213]	[N = 201]	[N = 221]	[N = 224]	[N = 209]	[N = 200]	[N = 228]
GCB	117 (51.8)	131 (61.5)	112 (55.7)	134 (60.6)	120 (53.6)	125 (59.8)	121 (60.5)	128 (56.1)
ABC	64 (28.3)	58 (27.2)	50 (24.9)	55 (24.9)	61 (27.2)	56 (26.8)	45 (22.5)	65 (28.5)
Unclassified	45 (19.9)	24 (11.3)	39 (19.4)	32 (14.5)	43 (19.2)	28 (13.4)	34 (17.0)	35(15.4)

ABC, activated B-cell-like; ECOG PS, Eastern Cooperative Oncology Group performance status; GCB, germinal center B-cell-like; IPI, International Prognostic Index; ITT, intent to treat; LDH, lactate dehydrogenase; PET, positron emission tomography; Q, quartile; SPD, sum of products of diameter of up to six target lesions; TLG, total lesion glycolysis; TMTV, total metabolic tumor volume.

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Supplementary Table 4. Cox multivariate regression model evaluating effect of TMTV and TLG in addition to IPI categories on investigator-assessed progression-free survival

Covariate	Hazard ratio (95% CI)	P-value*
TMTV (366 cm^3 cut-off)		
TMTV (high v low)		0.002
IPI 0–2	1.59 (1.18, 2.14)	
IPI 3–5	1.93 (1.41, 2.65)	
IPI (3–5 v 0–2)		0.114
Low TMTV	1.31 (0.94, 1.83)	
High TMTV	1.59 (1.21, 2.08)	
TLG (3,004 g)		
TLG (high v low)		0.016
IPI 0–2	1.44 (1.07, 1.94)	
IPI 3–5	1.64 (1.21, 2.23)	
IPI (3–5 v 0–2)		0.031
Low TLG	1.43 (1.03, 1.97)	
High TLG	1.64 (1.24, 2.13)	

*Wald test

Hazard ratios adjusted for treatment group (obinutuzumab v rituximab), geographic region, gender and SPD.

CI, confidence interval; IPI, International Prognostic Index; TLG, total lesion glycolysis; TMTV, total metabolic tumor volume

Supplementary Table 5. Cox multivariate regression model for the cell-of-origin subpopulation evaluating effect of TMTV in addition to IPI categories on investigator-assessed progression-free survival

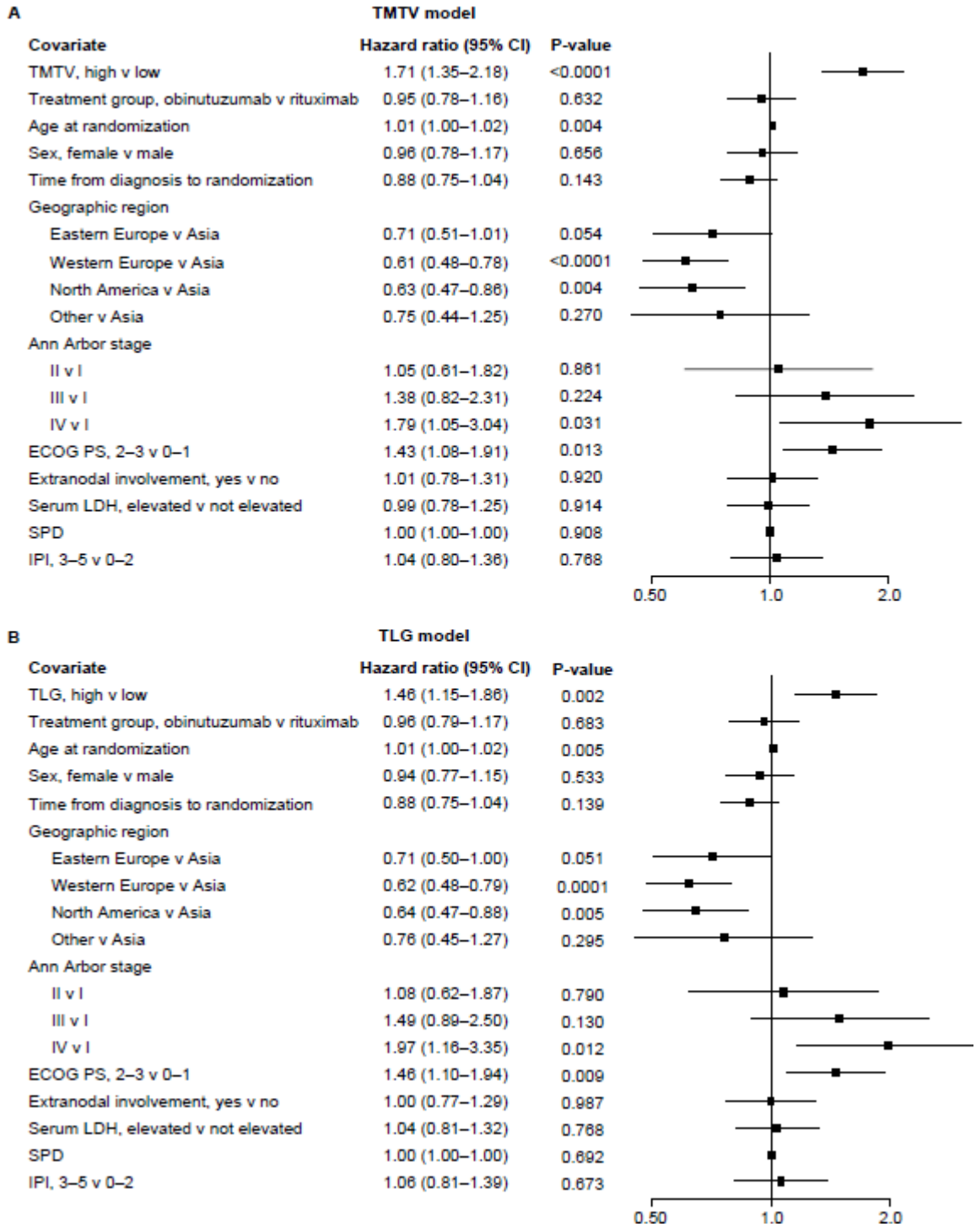
Covariate	Hazard ratio (95% CI)	P-value*
TMTV (366 cm^3 cut-off)		
TMTV (high v low)		0.006
IPI 0–2	1.71 (1.16, 2.50)	
IPI 3–5	1.59 (1.11, 2.29)	
IPI (3–5 v 0–2)		0.017
Low TMTV	1.61 (1.09, 2.38)	
High TMTV	1.50 (1.06, 2.12)	

*Wald test

Hazard ratios adjusted for treatment group (obinutuzumab v rituximab), cell-of-origin category (GCB v ABC/unclassified), geographic region, sex and SPD.

ABC, activated B-cell-like; CI, confidence interval; GCB, germinal center B-cell-like; IPI, International Prognostic Index; SPD, sum of products of diameters of up to six target lesions; TMTV, total metabolic tumor volume

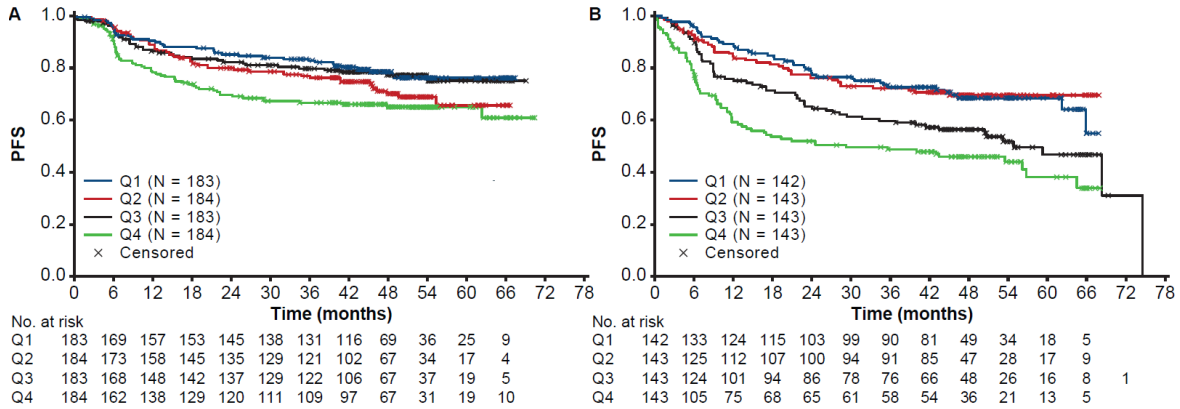
Supplementary Figure 1. Multivariable Cox regression model evaluating factors associated with investigator-assessed PFS and (A) high TMTV (≥366 cm^3) or (B) high TLG (≥ median; PET ITT population; n = 1,305)



CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; IPI, International Prognostic Index; ITT, intent to treat; LDH, lactate dehydrogenase; PET, positron

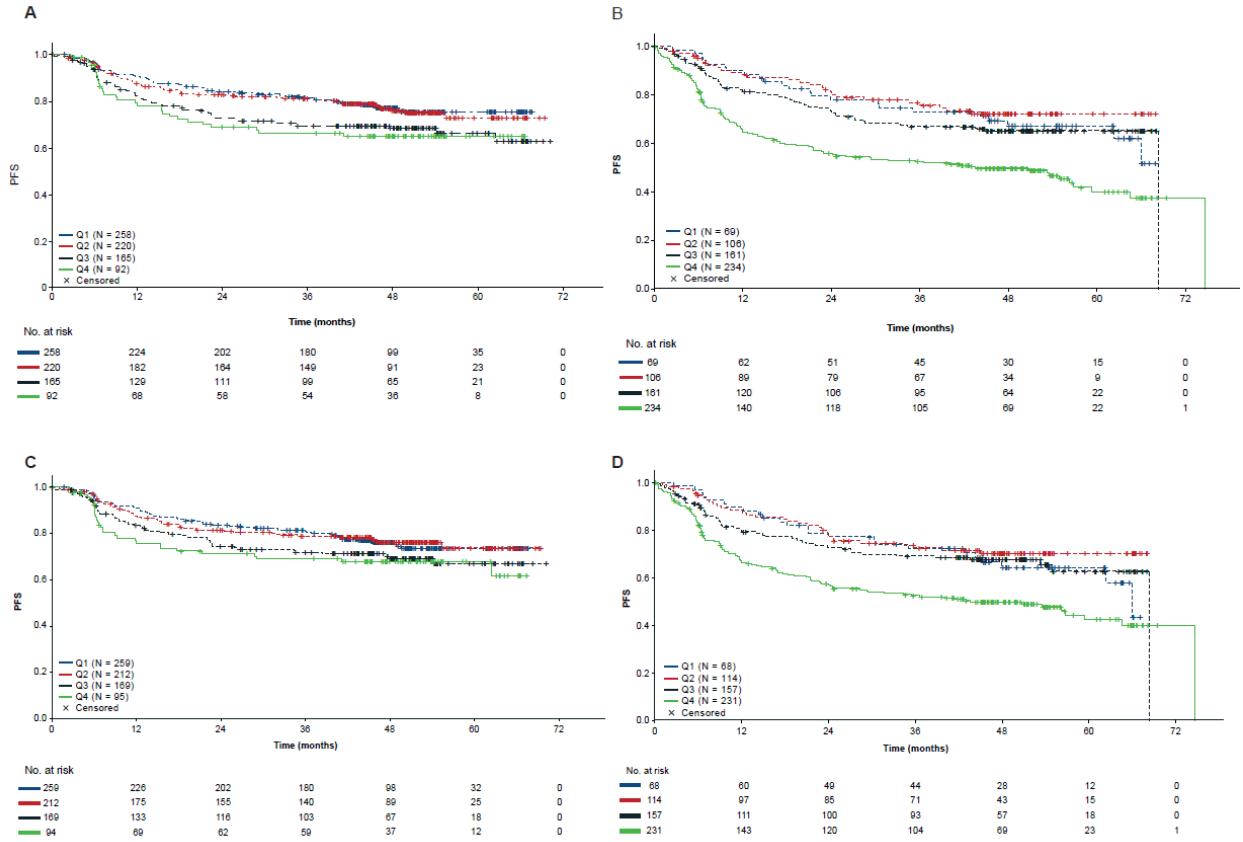
emission tomography; PFS, progression-free survival; SPD, sum of products of diameters of up to six target lesions; TMTV, total metabolic tumor volume; TLG, total lesion glycolysis.

Supplementary Figure 2. Kaplan–Meier analysis of investigator-assessed progression-free survival according to baseline TMTV quartiles in patients with IPI scores of (A) 0–2 and (B) 3–5



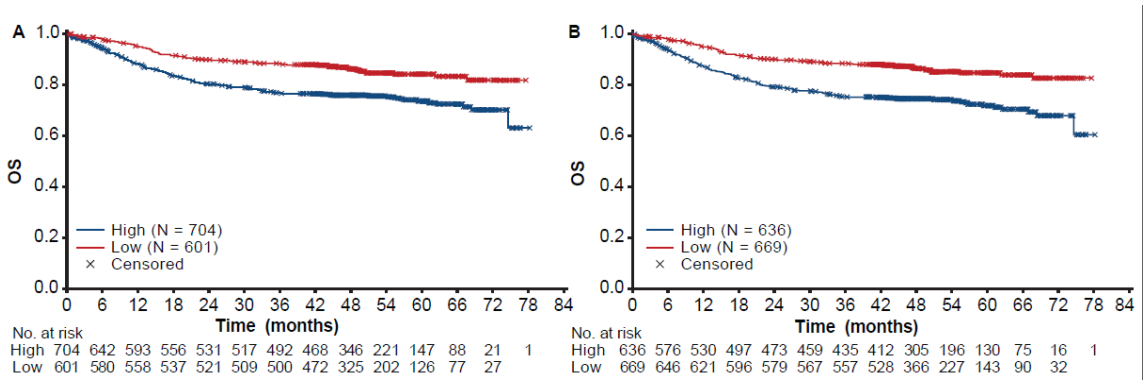
IPI, International Prognostic Index; Q, quartile; TMTV, total metabolic tumor volume.

Supplementary Figure 3. Kaplan–Meier analysis of investigator-assessed progression-free survival according to baseline TMTV quartiles for patients in the (A) low IPI group and (B) high IPI group, and according to baseline TLG quartiles in patients in the (C) low IPI group and (D) high IPI group



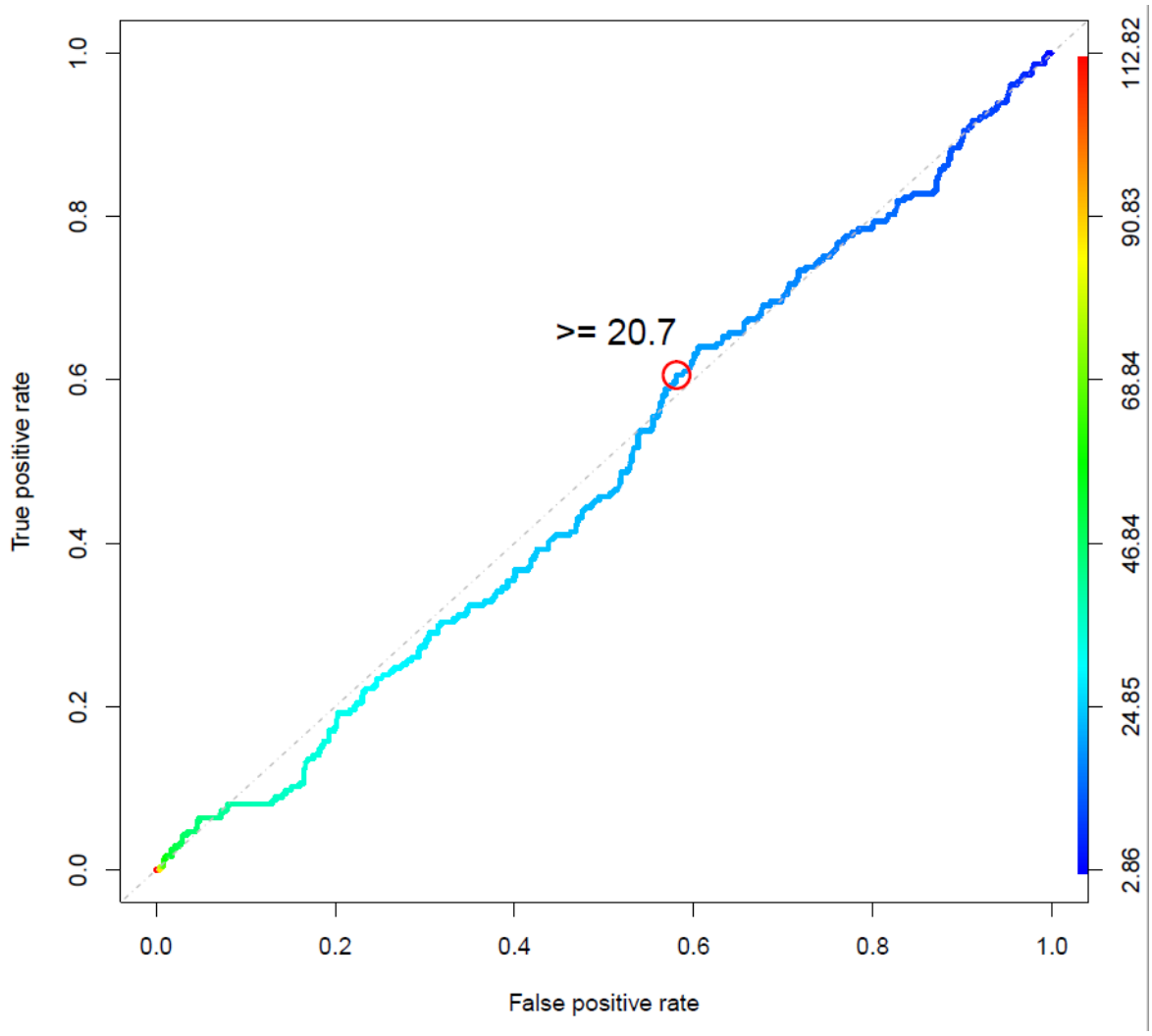
IPI, International Prognostic Index; TLG, total lesion glycolysis; TMTV, total metabolic tumor volume.

Supplementary Figure 4. Kaplan–Meier analysis of overall survival according to baseline TMTV cut-offs of (A) 366 cm^3 and (B) 300 cm^3



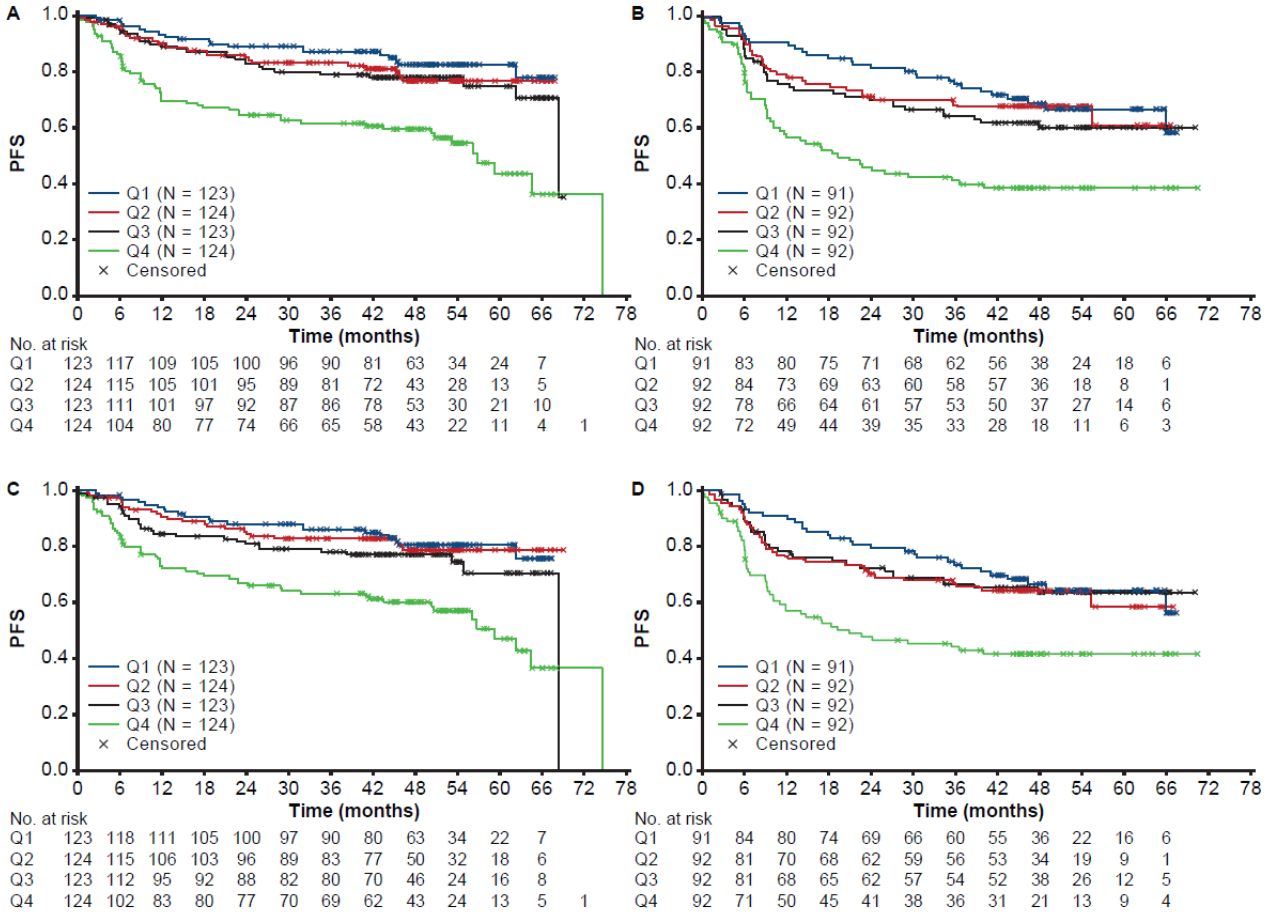
TMTV, total metabolic tumor volume.

Supplementary Figure 5. SUV_{max} receiver operating characteristic curve for 2-year progression-free survival



SUV_{max}, maximum standardized uptake value.

Supplementary Figure 6. Kaplan–Meier analysis of investigator-assessed progression-free survival according to baseline TMTV quartiles in patients with (A) GCB subtype and (B) ABC/unclassified subtype, and according to baseline TLG quartiles in patients with (C) GCB subtype and (D) ABC/unclassified subtype



ABC, activated B-cell-like; GCB, germinal center B-cell-like; Q, quartile; TLG, total lesion glycolysis; TMTV, total metabolic tumor volume.