Original Study

Baseline Total Metabolic Tumor Volume is Prognostic for Refractoriness to Immunochemotherapy in DLBCL: Results From GOYA

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Abstract

Prognostic indicators are required to identify patients with diffuse large B-cell lymphoma (DLBCL) who are at risk of early treatment failure. A secondary analysis of data from the GOYA study identified risk factors for primary chemorefractory disease and disease progression within 12 months (POD12). Total metabolic tumor volume has prognostic value in identifying patients at risk of early treatment failure.

Introduction: A good response to initial therapy is key to maximizing survival in patients with diffuse large B-cell lymphoma (DLBCL), but patients with chemorefractory disease and early progression have poor outcomes. **Patients and Methods:** Data from the GOYA study in patients with DLBCL who received first-line rituximab or obinutuzumab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) were analyzed. Positron emission tomography/computed tomography (PET/CT)-derived characteristics associated with total metabolic tumor volume (TMTV) and clinical risk factors for primary chemorefractory disease and disease progression within 12 months (POD12) were explored. **Results:** Of those patients fulfilling the criteria for analysis, 108/1126 (10%) were primary chemorefractory and 147/1106 (13%) had POD12. Primary chemorefractory and POD12 status were strongly associated with reduced overall survival. After multivariable analysis of clinical and imaging-based risk factors by backward elimination, only very high TMTV (quartile [Q] 1 vs. Q4 odds ratio [OR]: 0.45; $P = .006$) and serum albumin levels (low vs. normal OR of 1.86; $P = .004$) were associated with primary chemorefractoriness. After additionally accounting for *BCL2*/*MYC* translocation in a subset of patients, TMTV and *BCL2*/*MYC* double-hit status remained as significant predictors of primary chemorefractoriness (Q1 vs. Q4 OR: 0.32, $P = .01$ and double-hit vs. no-hit OR of 4.47, $P = .02$, respectively). Risk factors including very high TMTV, high sum of the product of the longest diameters (SPD), geographic region (Asia), short time since diagnosis, extranodal involvement and low serum albumin were retained for POD12. **Conclusion:** PET-derived TMTV has prognostic value in identifying patients at risk of early treatment failure.

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Introduction

Diffuse large B-cell lymphoma (DLBCL) is a clinically and biologically heterogeneous disease with a variable prognosis.[1,2] Standard treatment for patients aged under 80 years with DLBCL is rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP).[3,4] Many patients in this category, including those with advanced disease,[5] achieve durable survival with this type of immunochemotherapy.[6,7] However, approximately 10% to 15% of patients are reported to have disease that is refractory to

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R-CHOP, and an additional 20% to 25% relapse after an initial response.[1]

Response to initial therapy is one of the most important factors influencing survival in patients with DLBCL. A retrospective analysis of data from the British Columbia Cancer Agency Lymphoid Cancer Database showed that patients younger than 70 years of age with primary chemorefractory disease, defined as nonresponding disease (stable disease or progressive disease [PD]) while on R-CHOP, or with progression within 3 months after conclusion of treatment with R-CHOP, had particularly poor outcomes, with a median overall survival of just 10 months.[8] The international, retrospective SCHOLAR-1 study also showed that patients with DLBCL who were refractory to first-line treatment had poor survival outcomes, with a median overall survival of 6.3 months from the start of salvage therapy.[9] Optimization of first-line therapy is therefore critically important.[1]

Risk stratification tools incorporating multiple clinical characteristics and independent factors are recognized as prognostic for DLBCL outcomes.[1,2] The best-known of these is the International Prognostic Index (IPI),[10] which is based on 5 clinical features present at diagnosis. Although the IPI was developed before the introduction of targeted therapy, it has subsequently been shown to retain its prognostic utility in patients treated with rituximab.[11] However, to our knowledge, a prognostic model dedicated to predicting risk of non-response, or early relapse after initial therapy, is not currently available.

Because of the clinical and molecular heterogeneity of DLBCL, it is challenging to identify patients at initial diagnosis who may be more likely to be chemorefractory or progress early.[12] Clinical characteristics additional to those included in the IPI, *BCL2/MYC* rearrangements and positron emission tomography/computed tomography (PET/CT)-derived measures of disease burden could help determine prognosis and inform the selection of appropriate treatment.[12]

Obinutuzumab plus CHOP (G-CHOP) showed activity and acceptable toxicity in the first-line treatment of 100 patients with advanced DLBCL in the phase II GATHER study.[13] GOYA (NCT01287741), a phase III study comparing G-CHOP with R-CHOP, showed that baseline total metabolic tumor volume (TMTV) and total lesion glycolysis (TLG) measurements were independent predictors of progression-free survival (PFS) in patients with DLBCL after first-line immunochemotherapy.[14] These results are consistent with the findings of a meta-analysis of 27 studies (17 including patients with DLBCL) investigating the prognostic value of TMTV and TLG in 2729 patients with lymphoma.[15] The results of the meta-analysis, which included 21 studies that evaluated the association between TMTV and PFS/overall survival, showed that patients with high baseline TMTV had a worse prognosis for PFS (hazard ratio [HR] of 3.05; 95% confidence interval [CI], 2.55-3.64, $P \leq .00001$) and overall survival (HR of 3.07; 95% CI, 2.47-3.82, $P \leq .00001$) than those with a low TMTV.[15] Here we report a secondary analysis of GOYA to characterize and identify quantitative PET imaging and clinical risk factors for primary chemorefractory disease and early relapse (progression of disease within 12 months; POD12) in patients with DLBCL.

Methods

Study Design and Participants

GOYA was an open-label, multicenter, randomized, phase III study, the design of which has been described previously.[16] Briefly, eligible patients were aged ≥18 years with previously untreated DLBCL; Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 to 2; adequate hematologic, liver, and kidney function; left ventricular ejection fraction of ≥50%; and an IPI score of ≥2, or IPI 1 and aged ≤60 years (with or without bulky disease), or IPI 0 with bulky disease (at least 1 lesion ≥7.5 cm).

A total of 1418 patients were recruited and randomly assigned (1:1) to receive eight 21-day cycles of obinutuzumab (n = 706) or rituximab (n = 712), plus 6 or 8 cycles of CHOP. The primary endpoint was investigator (INV)-assessed PFS, with overall survival as a secondary endpoint.

GOYA was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization guidelines for Good Clinical Practice. The protocol was approved by the ethics committees of participating centers. All patients provided written informed consent.

Data Sharing Statement

Qualified researchers may request access to individual patient level data through the clinical study data request platform (https://vivli.org/). Further details on Roche's criteria for eligible studies are available here (https://vivli.org/members/ourmembers/). For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here (https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm).

Clinical Assessments and Outcomes

Baseline clinical characteristics and overall survival outcomes were evaluated for 2 subpopulations of patients in the GOYA study. These were (1) primary chemorefractory patients, defined as those with lack of metabolic response or progressive metabolic disease at end of treatment (EOT) by independent review committee assessment according to Lugano 2014 criteria,[17] or INV-assessed PD (INV-PD) before EOT as shown clinically and/or by CT; (2) POD12 patients, defined as those with INV-PD by CT (including death due to PD) within 12 months from randomization.

Imaging Analyses

PET and CT examinations were conducted, at sites where a PET scanner was available, at the baseline disease assessment (within 5 weeks prior to randomization) and at the EOT response assessment (cycle 8; 6-8 weeks after the last dose of study drug). Additional disease measurements by CT were conducted every 3 months up to follow-up month 24, then every 6 months up to follow-up month 48 and again at month 60.

Whole body TMTV analyses were performed by an independent central panel and images were segmented using an adaptive method with a threshold equal to 1.5 times the average standardized uptake value of the liver using PET Encore workstation (MIM software Inc. Cleveland, OH). TMTVs were calculated as the sum of all the metabolic tumor volumes of the individual lesions.

Biomarker Analysis

BCL2 and *MYC* translocations were assayed by Vysis LSI Dual Color Break Apart fluorescence in situ hybridization (FISH) probes (Abbott Laboratories, Chicago, IL) in pretreatment tumor samples from biomarker-evaluable patients, with FISH-positive defined as ≥50% of tumor cells harboring break apart signal. Concurrent translocation of both the *MYC* and *BCL2* genes was termed "double-hit" lymphoma.

Statistical Analysis

Kaplan–Meier analysis was used to estimate the overall survival distribution. To assess the potential impact of immortal time bias, a 12-month landmark analysis was performed for patients with POD12. The prognostic impact of baseline clinical characteristics on primary chemorefractoriness or POD12 was assessed by univariable logistic regression analysis. Variables were deemed to be associated if $P \leq .15$ by the Wald test (ie, probability that the estimate exceeds χ^2). Covariates associated with primary chemorefractoriness or POD12 at the $P \leq .15$ level were then entered into a multivariable logistic regression analysis using backward elimination as the primary analysis method (significance cut-off $P < .05$). Since *BCL2* and/or *MYC* translocation (FISH) status was only available in a subset of patients (n = 444 in the primary chemorefractory analysis population and n = 428 in the POD12 analysis population), the effects of these markers and clinical variables were assessed in a secondary multivariable logistic regression analysis. The *P*-values have not been adjusted for multiple testing and are exploratory in nature.

Patient TMTV measurements were divided into quartiles (Q1-Q4) based on the observed distribution, and the proportions of primary chemorefractory or POD12 patients in each quartile were calculated.

The prognostic value of TMTV findings at baseline for primary chemorefractoriness and POD12 were assessed for their positive predictive value and negative predictive value. For the primary chemorefractory group, positive predictive value = 0.137 and negative predictive value = 0.945. This means that for a patient with a high TMTV the risk of having chemorefractory disease is 14%; a patient with low TMTV has a very low risk (approximately 5%).

Results

Patient Populations and Baseline Demographics

Of the 1418 patients randomized in the GOYA study between July 2011 and June 2014, a total of 1334 (94%) had a PET/CT scan with detectable lesions at baseline, and TMTV measurements were available for 1313/1334 (98%) (Supplemental Figure 1). A total of 1126 fulfilled the criteria for primary chemorefractory analysis (complete baseline variables associated with chemorefractoriness for univariable and multivariable analysis) and 1106 for POD12 status analysis. Of those analyzed, 108/1126 (10%) patients were considered primary chemorefractory and 147/1106 (13%) had progression of disease within 12 months. Baseline demographics and disease characteristics are shown for these analysis populations in Table 1.

The primary chemorefractory population displayed more advanced disease than the population of patients with no chemorefractory event (Ann Arbor stage III/IV in 83% vs. 75% of patients, respectively; Table 1); 21% of the primary chemorefractory, 28% of the POD12 and 14% of both non-chemorefractory and no-POD12 event patients were in the IPI high (≥4) risk group. Baseline TMTV was higher in the chemorefractory and POD12 populations, compared with the non-chemorefractory and no-POD12 populations, respectively (Figure 1; Table 1). There were greater proportions of patients classified as primary chemorefractory or POD12 in TMTV Q4 than in the other quartiles (Figure 2). The percentage of patients with high TMTV (Q4) at baseline was 45% in the primary chemorefractory population, 49% in the POD12 population, and 21% to 22% in the non-chemorefractory/no-POD12 event populations.

Survival Outcomes by Population

The primary chemorefractory and POD12 populations showed worse overall survival outcomes than patient populations without these characteristics (Figure 3). Median overall survival was 14.4 months in the primary chemorefractory population but was not reached in those with no primary chemorefractory event (2-year overall survival 28.6% vs. 94.1%, respectively). In the POD12 population, the median overall survival was 14.9 months; overall survival was not reached in those with no POD12 event (2-year overall survival 28.7% vs. 92.5%, respectively). The results of the 12-month landmark analysis also showed that patients with POD12 had worse overall survival outcomes than those without (Supplemental Figure 2).

Univariable Analysis

The baseline variables associated with chemorefractoriness in patients with primary chemorefractory disease or POD12 are shown in Table 2 ($P \leq .15$ by Wald test for exceeding the χ^2 value). The results indicate that a number of clinical characteristics were strongly associated with primary chemorefractoriness: Ann Arbor stage, IPI risk group, sum of the product of the longest tumor diameters (SPD) quartiles, bulky disease, extranodal involvement, elevated lactate dehydrogenase (LDH), low hemoglobin, low albumin, very high TMTV (Q4), time since diagnosis, *BCL2* translocation, *MYC* translocation, and *BCL2/MYC* double-hit translocations. These baseline clinical variables were also significantly associated with POD12, except for *BCL2* or *MYC* translocation and *BCL2/MYC* double-hit translocations. However, age, geographic region, and bone marrow involvement were also significantly associated with events in the POD12 population, but not in the primary chemorefractory population.

Multivariable Analysis

Baseline variables associated with primary chemorefractory disease and POD12 by univariable analysis were entered into

Figure 1 Baseline TMTV Distribution of Patients with (A) Primary Chemorefractoriness vs. Non-Primary Chemorefractory and (B) POD12 vs. without POD12.
POD12 = investigator-assessed disease progression within 12 mo; TMTV = total metabolic tumor volume.

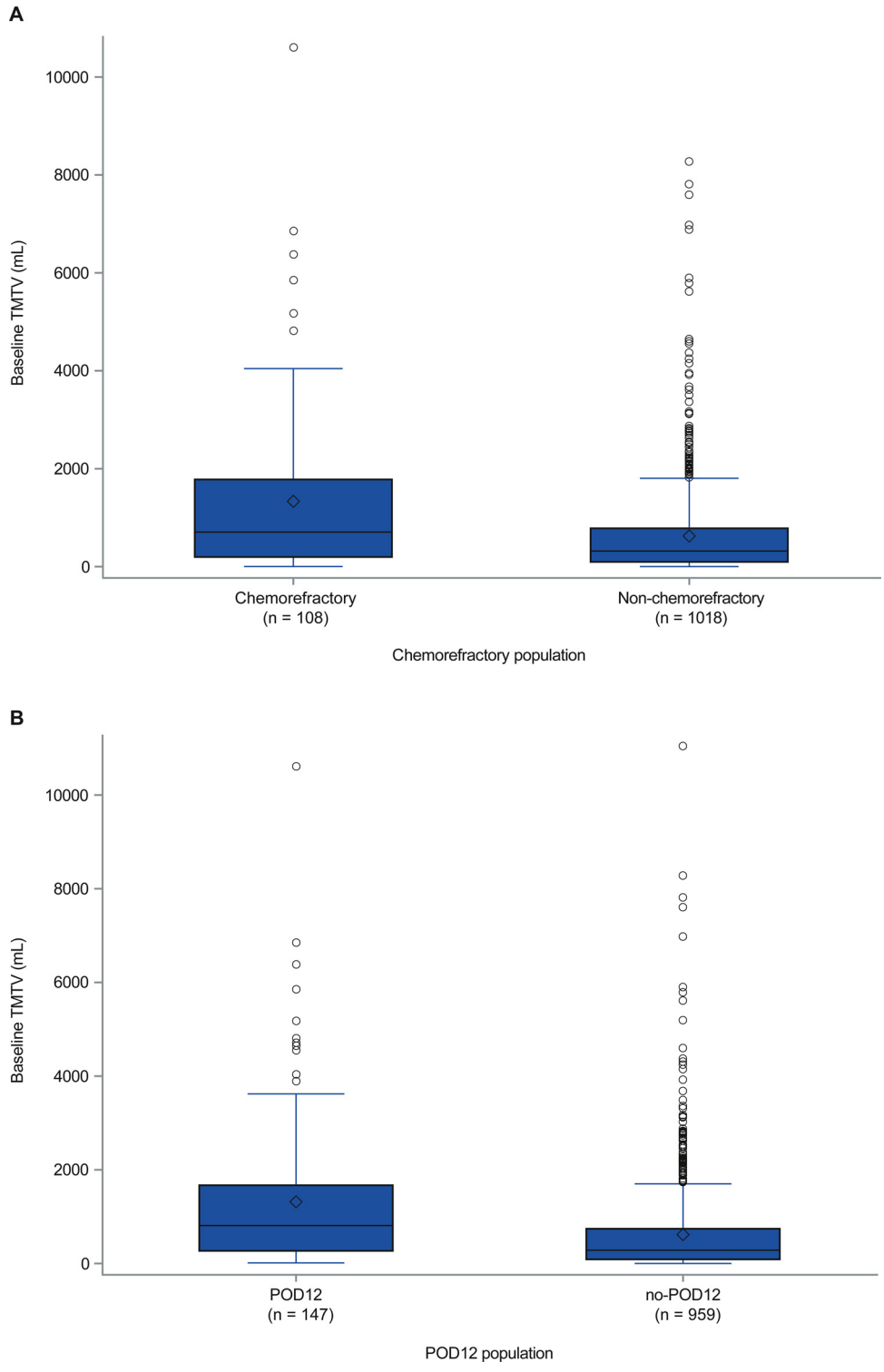


Figure 2 Proportion of Patients with (A) Primary Chemorefractoriness and (B) POD12 by Baseline TMTV Quartile. Two-sided *P*-values from Fischer's Exact Test. *P*-values are exploratory and were not adjusted for multiple testing. POD12 = investigator-assessed disease progression within 12 mo; Q = quartile; TMTV = total metabolic tumor volume.

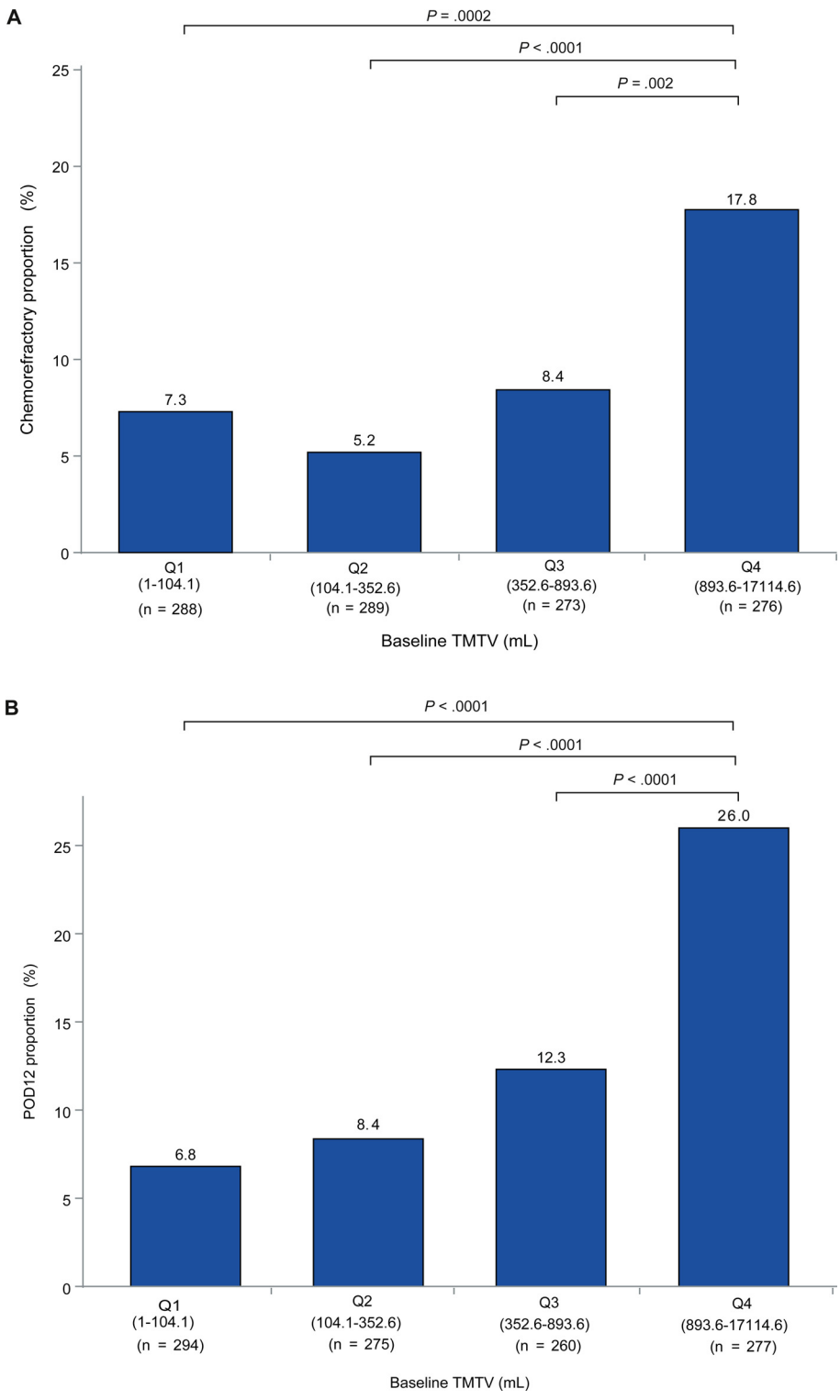


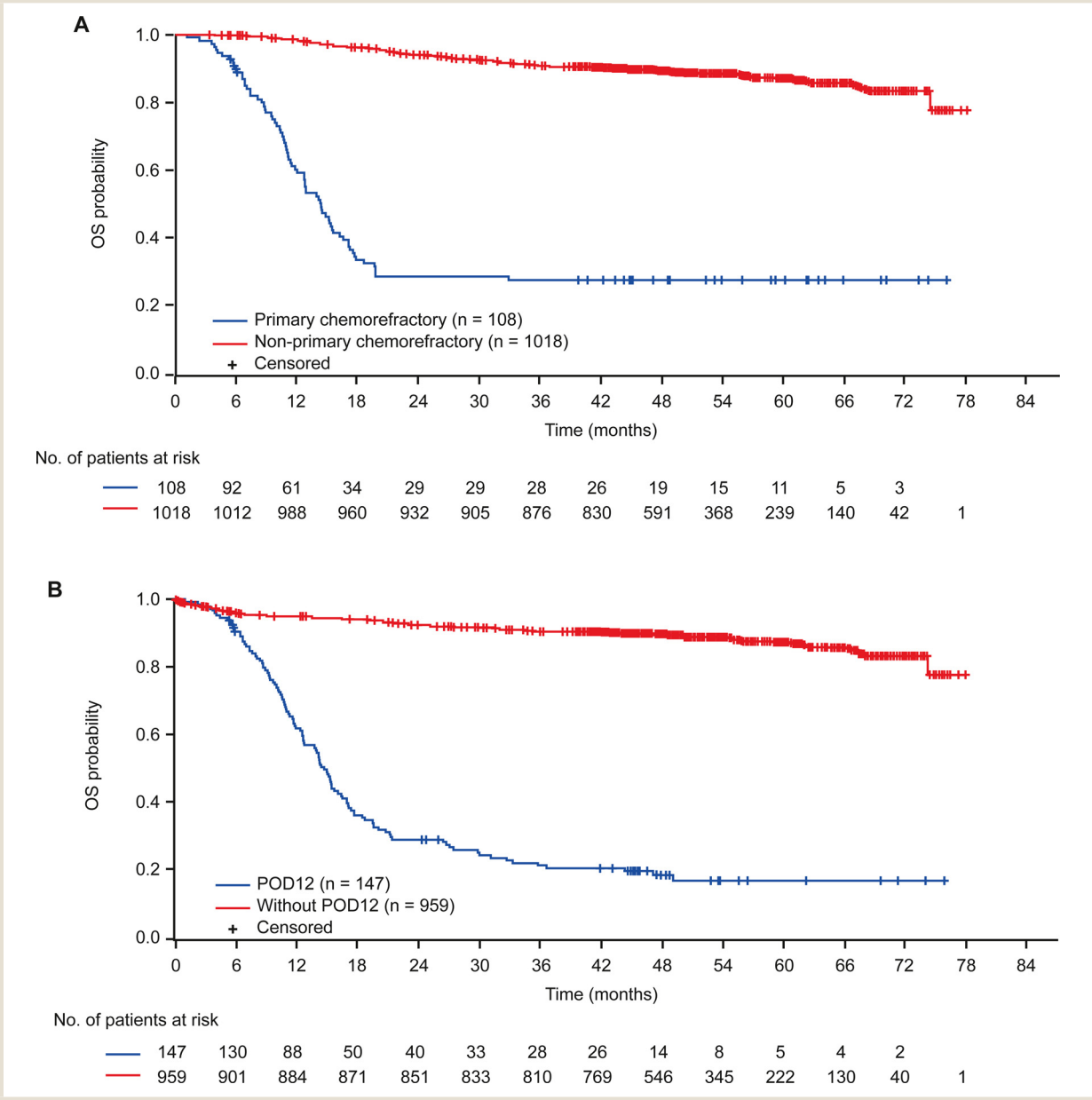
Table 1 Baseline Demographics and Clinical Characteristics

Characteristic, n (%) Unless Stated	Primary Chemorefractory Patients (n = 108)	Non-Primary Chemorefractory Patients (n = 1018)	Patients With POD12 (n = 147)	Patients Without POD12 (n = 959)
Age >60 y	58 (54)	537 (53)	71 (48)	543 (57)
Geographic region				
Asia	48 (44)	376 (37)	74 (50)	356 (37)
W Europe	29 (27)	309 (30)	39 (27)	272 (28)
E Europe	10 (9)	128 (13)	15 (10)	125 (13)
N America	16 (15)	161 (16)	14 (10)	163 (17)
Other	5 (5)	44 (4)	5 (3)	43 (5)
ECOG PS				
0-1	94 (87)	902 (89)	116 (79)	850 (89)
2-3	14 (13)	116 (11)	31 (21)	109 (11)
Ann Arbor stage III/IV at diagnosis	90 (83)	762 (75)	126 (86)	720 (75)
IPI high-risk group (score ≥4)	23 (21)	141 (14)	41 (28)	130 (14)
Elevated serum LDH >1 × ULN	77 (71)	568 (56)	108 (74)	522 (54)
SPD, mm^2				
Q1 (0-2000)	13 (12)	274 (27)	19 (13)	273 (29)
Q2 (2000-4380)	26 (24)	256 (25)	26 (18)	250 (26)
Q3 (4380-8596)	30 (28)	253 (25)	45 (31)	227 (24)
Q4 (8596-510000)	39 (36)	235 (23)	57 (39)	209 (22)
BM involvement	14 (13)	102 (10)	26 (18)	98 (10)
Median time from initial diagnosis to randomization, months (range)	0.69 (0.1-2.7)	0.82 (0.0-13.2)	0.66 (0.0-3.2)	0.85 (0.0-36.3)
Bulky disease (≥7.5 cm)	49 (45)	348 (34)	69 (47)	310 (32)
Extranodal involvement	76 (70)	680 (67)	115 (78)	633 (66)
Low hemoglobin <LLN	66 (61)	513 (50)	96 (65)	487 (51)
Albumin <LLN	50 (46)	281 (28)	70 (48)	269 (28)
BCL2 by FISH	n = 46	n = 463	n = 63	n = 436
Positive	15 (33)	92 (20)	16 (25)	92 (21)
Negative	22 (48)	258 (56)	32 (51)	242 (56)
Undetermined	9 (20)	113 (24)	15 (24)	102 (23)
MYC by FISH	n = 37	n = 410	n = 48	n = 383
Positive	7 (19)	36 (9)	7 (15)	41 (11)
Negative	25 (68)	322 (79)	34 (71)	292 (76)
Undetermined	5 (14)	52 (13)	7 (15)	50 (13)
Double hit[a]	n = 37	n = 407	n = 48	n = 380
	4 (11)	10 (3)	3 (6)	13 (3)
TMTV, cm^3				
Q1 (1-104.1)	21 (19)	267 (26)	20 (14)	274 (29)
Q2 (104.1-352.6)	15 (14)	274 (27)	23 (16)	252 (26)
Q3 (352.6-893.6)	23 (21)	250 (25)	32 (22)	228 (24)
Q4 (893.6-17114.6)	49 (45)	227 (22)	72 (49)	205 (21)

Abbreviations: BM = bone marrow; ECOG PS = Eastern Cooperative Oncology Group performance status; E = Eastern = FISH = fluorescence in situ hybridization; IPI = International Prognostic Index; LDH = lactate dehydrogenase; LLN = lower limit of normal; N = North; POD12 = investigator-assessed disease progression within 12 months; Q = quartile; SPD = sum of the product of the longest diameters; TMTV = total metabolic tumor volume; ULN = upper limit of normal; W = Western.
[a] Dual gene translocations of *BCL2* and *MYC*.

the multivariable analysis (backward elimination). Very high (Q4) TMTV (Q1 vs. Q4 OR of 0.45; $P = .006$) and low serum albumin levels (low vs. normal OR of 1.86; $P = .004$) remained independently associated with primary chemorefractoriness (Table 3). Extranodal involvement, short time since diagnosis, high SPD quartiles and geographic region were retained in the POD12 group only (in addition to very high TMTV and low albumin) although eliminated from the analysis of the primary chemorefractory population. This indicated that, when other variables are accounted for, these factors were not significantly associated with primary chemorefractoriness.

Figure 3 Kaplan–Meier Estimation of Overall survival (OS) from Start of Treatment (A) in the Primary and Non-primary Chemorefractory Populations and (B) in Patients with and without POD12.
POD12 = investigator-assessed disease progression within 12 mo.



A secondary multivariable analysis, which included the effects of *BCL2* and/or *MYC* translocation (FISH), in addition to clinical and imaging variables, was carried out in a subset of patients. The results of this secondary multivariable analysis are shown in Table 3. In the presence of these prognostic variables, only very high TMTV (Q1 vs. Q4 OR of 0.32, $P = .01$) and *BCL2/MYC* double-hit status (double-hit vs. no-hit OR of 4.47, $P = .02$) remained significant predictors of primary chemorefractoriness (after backward elimination, n = 444). For the POD12 population, *BCL2/MYC* double-hit status was not significant in the univariable analysis and therefore was not entered into the multivariable model (no secondary multivariable analysis).

Discussion

This secondary analysis of the phase III GOYA trial confirmed prior reports[8, 9] of poor survival outcomes in patients with primary chemorefractory disease and in those experiencing early disease progression after initial therapy for DLBCL. Given this dismal outcome it is important to identify factors predicting early treatment failure after currently available therapies so that patients at

Table 2 Univariable Analysis of Baseline Variables Associated with Chemorefractoriness and POD12 in Primary Chemorefractory and POD12 Analysis Populations, Respectively

Variable at Baseline	Primary Chemorefractory Analysis Population (n = 1126)			POD12 Analysis Population (n = 1106)		
	Odds Ratio	95% CI	*P* Value (Wald)	Odds Ratio	95% CI	*P* Value (Wald)
Age >60 (Y vs. N)	1.04	0.70-1.55	.851	0.72	0.51-1.01	**.059**
Ann Arbor stage						
III/IV vs. I/II	1.68	0.99-2.84	**.053**	1.99	1.23-3.23	**.005**
IPI risk group (3-5 vs. 0-2)	1.75	1.18-2.62	**.006**	1.99	1.40-2.83	**<.001**
Time from initial diagnosis to randomization	0.62	0.42-0.92	**.018**	0.48	0.33-0.70	**<.001**
SPD quartiles			**.002**			**<.0001**
Q2 vs. Q1	2.14	1.08-4.26	**.030**	1.49	0.81-2.77	.201
Q3 vs. Q1	2.50	1.28-4.90	**.008**	2.85	1.62-5.01	**<.001**
Q4 vs. Q1	3.50	1.82-6.71	**<.001**	3.92	2.26-6.79	**<.0001**
Geographic region			.593			**.025**
Asia vs. Western Europe	1.36	0.84-2.21	.214	1.45	0.95-2.20	**.082**
Eastern Europe vs. Western Europe	0.83	0.39-1.76	.632	0.84	0.45-1.58	.581
North America vs. Western Europe	1.06	0.56-2.01	.861	0.60	0.32-1.14	**.117**
Other vs. Western Europe	1.21	0.45-3.29	.708	0.81	0.30-2.17	.677
Bulky disease (Y vs. N)	1.60	1.07-2.39	**.022**	1.85	1.30-2.63	**<.001**
Extranodal involvement (Y vs. N)	1.71	1.15-2.55	**.009**	2.42	1.70-3.44	**<.0001**
Bone marrow involvement (Y vs. N)	1.34	0.74-2.43	.340	1.89	1.18-3.03	**.008**
LDH elevated vs. normal	1.97	1.27-3.04	**.002**	2.32	1.57-3.42	**<.0001**
Hemoglobin (<LLN) (Y vs. N)	1.55	1.03-2.32	**.035**	1.82	1.27-2.62	**.001**
Albumin (<LLN) (Y vs. N)	2.26	1.51-3.38	**<.0001**	2.33	1.64-3.32	**<.0001**
TMTV quartiles			**<.0001**			**<.0001**
Q1 vs. Q4	0.36	0.21-0.63	**.0003**	0.21	0.12-0.35	**<.0001**
Q2 vs. Q4	0.25	0.14-0.46	**<.0001**	0.26	0.16-0.43	**<.0001**
Q3 vs. Q4	0.43	0.25-0.72	**.0015**	0.40	0.25-0.63	**<.0001**
BCL2 (FISH)			**.136**			.707
Positive vs. negative	1.91	0.95-3.84	**.069**	1.32	0.69-2.51	.406
Undetermined vs. negative	0.93	0.42-2.09	.868	1.11	0.58-2.14	.751
MYC (FISH)			**.139**			.667
Positive vs. negative	2.51	1.01-6.20	**.047**	1.47	0.61-3.52	.392
Undetermined vs. negative	1.24	0.45-3.38	.676	1.20	0.51-2.86	.677
BCL2/MYC (FISH) DH vs. no DH	4.81	1.43-16.19	**.011**	1.88	0.52-6.86	.338

Logistic regression, with association indicated in bold for by $P \leq .15$ (Wald test); P values in bold were deemed to be associated.
Abbreviations: CI = confidence interval; DH = double hit; FISH = fluorescence in situ hybridization; IPI = International Prognostic Index; LDH = lactate dehydrogenase; LLN = lower limit of normal; N = no; POD12 = investigator-assessed disease progression within 12 months; Q = quartile; SPD = sum of the product of the longest diameters; TMTV = total metabolic tumor volume; Y = yes.

high risk can be considered for alternative therapeutic strategies, eg, enrollment in clinical trials of novel agents. In this exploratory, hypothesis-generating study, multivariable analyses demonstrated that very high TMTV (Q4) and low serum albumin levels at baseline were the only independent clinical prognostic factors for primary chemorefractoriness. In a previous analysis of the GOYA study, baseline TMTV and TLG measurements were identified as independent predictors of PFS after first-line immunochemotherapy.[14] Here, our results suggest that when moving from PFS to early efficacy endpoints, such as chemorefractoriness and POD12, the prognostic value of TMTV is mainly observed for very high volumes. Additionally, albumin has previously been identified as a predictor for R-CHOP tolerability, highlighting the importance of this variable in DLBCL.[18] Other patient and disease characteristics, including the 5 components of IPI (age, ECOG PS, Ann Arbor stage, elevated LDH and extranodal involvement), appeared less important as predictors of response to initial treatment. A broader range of factors, including extranodal involvement and SPD, retained significance in the multivariable analysis of risk factors for POD12.

Interestingly, a secondary analysis, taking into consideration *MYC* and *BCL2* translocation status in the biomarker-evaluable subset, identified double-hit status and very high TMTV as being independently associated with primary chemorefractoriness. While

Table 3 Multivariable Analysis of Baseline Variables Associated with Chemorefractoriness and POD12 in Primary Chemorefractory and POD12 Analysis Populations, Respectively

Prognostic Variable	Primary Chemorefractory Analysis Population (n = 1126)			POD12 Analysis Population (n = 1106)		
	Odds Ratio	95% CI	*P* Value (Wald)	Odds Ratio	95% CI	*P* Value (Wald)
Backward elimination without *BCL2/MYC*						
Geographic region						**.040**
Asia vs. Western Europe	-	-	-	1.56	1.00-2.44	.052
Eastern Europe vs. Western Europe	-	-	-	1.09	0.55-2.13	.808
North America vs. Western Europe	-	-	-	0.62	0.32-1.20	.156
Other vs. Western Europe	-	-	-	0.95	0.34-2.64	0.916
Extranodal involvement (Y vs. N)	-	-	-	1.93	1.32-2.81	**<.001**
TMTV quartiles			**.0002**			**.004**
Q1 vs. Q4	0.45	0.26-0.79	**.006**	0.52	0.26-1.04	.065
Q2 vs. Q4	0.30	0.16-0.55	**.0001**	0.40	0.22-0.71	**.002**
Q3 vs. Q4	0.44	0.26-0.75	**.003**	0.47	0.29-0.77	**.003**
Time from initial diagnosis to randomization	-	-	-	0.68	0.47-0.99	**.042**
SPD quartiles						**.037**
Q2 vs. Q1	-	-	-	1.53	0.79-2.97	.205
Q3 vs. Q1	-	-	-	2.49	1.28-4.84	**.007**
Q4 vs. Q1	-	-	-	2.40	1.20-4.80	**.013**
Albumin (<LLN) (Y vs. N)	1.86	1.22-2.85	**.004**	1.57	1.06-2.32	**.024**
Backward elimination[a] with *BCL2/MYC* (*n* = 444)						
TMTV quartiles			**.003**			
Q1 vs. Q4	0.32	0.13-0.78	.012	-	-	-
Q2 vs. Q4	0.13	0.04-0.44	**.001**	-	-	-
Q3 vs. Q4	0.41	0.17-1.01	.053	-	-	-
BCL2/MYC FISH (DH vs. non-DH)	4.47	1.23-16.22	**.023**	-	-	-

Covariates from the univariable analysis associated with primary chemorefractoriness or POD12 at the $P \leq .15$ level were entered into this multivariable logistic regression analysis using backward elimination as the primary analysis method (significance cut-off $P < .05$; Wald test); P values in bold were deemed to be associated.
Abbreviations: CI = confidence interval; DH = double hit; LLN = lower limit of normal; N = no; POD12 = investigator-assessed disease progression within 12 months; Q = quartile; SPD = sum of the product of the longest diameters; TMTV = total metabolic tumor volume; Y = yes.
[a] For the POD12 population *BCL2/MYC* (FISH) DH was not significant in the univariable analysis and therefore was not entered into the multivariable model.

double-hit status did not retain significance in the multivariable analysis for POD12, the number of biomarker-evaluable patients in this subgroup was limited.

The importance of serum albumin for early outcomes supports findings from a previous study in which the prognostic nutritional index (which includes serum albumin concentration) was an effective prognostic indicator in patients with DLBCL.[19]

Our data indicate that assessment of baseline TMTV could inform risk stratification to identify patients who are unlikely to respond to or relapse early after R-CHOP. TMTV at staging has previously been shown to be a potentially important prognostic factor for long-term outcomes in DLBCL. Data from 147 patients with DLBCL showed that combining TMTV with results of early PET response assessment improves the predictive power of interim PET.[20] Similar findings were reported in 510 patients with DLBCL in a post hoc analysis of the PET-guided therapy of aggressive non-Hodgkin lymphomas (PETAL) trial.[21] TMTV also appears to be a valid prognostic indicator in elderly individuals with DLBCL undergoing treatment with R-CHOP.[22] Vercellino *et al.* reported an association between high pretreatment TMTV and inferior PFS and overall survival in patients aged 60 to 80 years, and found that TMTV combined with ECOG PS may identify a high-risk DLBCL population.[22] This combination of TMTV and ECOG PS was also found to identify a high-risk DLBCL population in an analysis of data from multiple cohorts of large clinical trials (PETAL and GOYA) and real world European data.[23] A French group has additionally reported that risk stratification in DLBCL can be improved by combining baseline TMTV with features characterizing lesion dissemination using PET.[24]

Considering the complexity of DLBCL disease biology, other potential underlying molecular variables associated with high TMTV should be explored as potential predictors of early treatment failure. Evidence suggests that combining baseline TMTV with gene profiling has predictive value and may improve overall risk stratification in DLBCL. In an analysis of 114 patients with DLBCL treated with R-CHOP or R-CHOP-like regimens, 5-year PFS and overall survival were 37% and 39%, respectively, in patients with high TMTV (optimal cut-off 261 cm^3), significantly lower than the 72% and 83%, respectively, observed in patients with low TMTV.[25] A multivariable analysis carried out as part of this investigation showed

TMTV, activated B-cell/germinal center B-cell cell-of-origin phenotype and IPI to be independent predictors of both PFS and overall survival. The authors suggested that an integrated risk model based on baseline PET/CT in addition to gene expression profiling could have robust predictive value.[25]

A recent retrospective analysis of GOYA investigated the added value of image texture features (ITF, ie, "radiomics" evaluating tumor heterogeneity) using PET/CT data sets, and found that a model including ITF and significant clinical features could predict survival probability for patients with untreated DLBCL with good precision.[26] TMTV was combined with ITF, cell-of-origin, and prognostic clinical factors to identify 3 prognostic subgroups of treatment failure risk: low (55% of patients), intermediate (34%), and high (11%), which were associated with the probability of survival at 2 and 4 years. PET/CT findings (evaluated during treatment or at EOT), encompassing markers such as TMTV and TLG, are useful for predicting PFS or overall survival in patients with DLBCL receiving first-line R-CHOP chemotherapy.[27-29]

Established prognostic biomarkers in DLBCL include *MYC* and *BCL2* gene alterations;[1,30] our multivariable analysis indicated an association between primary chemorefractoriness and *BCL2/MYC* double-hit status.

Integration of imaging markers, such as TMTV, into risk stratification for DLBCL, together with improved understanding of the tumor microenvironment and other biomarkers under investigation, has the potential to refine the prediction of outcomes and guide management in patients with DLBCL, which may lead to improved outcomes. In addition, further studies are needed to validate the present findings.

Clinical Practice Points

- Response to initial therapy is one of the most important factors influencing survival in patients with diffuse large B-cell lymphoma, but patients with chemorefractory disease and early progression have poor outcomes. Risk stratification tools incorporating multiple clinical characteristics and independent factors are recognized as prognostic for clinical outcomes. The International Prognostic Index (IPI) is based on 5 clinical features present at diagnosis and has prognostic utility in patients treated with rituximab. However, to our knowledge, a prognostic model dedicated to predicting risk of non-response, or early relapse after initial therapy, is not currently available for patients with diffuse large B-cell lymphoma.
- Data from this secondary analysis of the GOYA study suggest that very high baseline total metabolic tumor volume and low baseline albumin levels are prognostic markers for refractoriness to immunochemotherapy in patients with diffuse large B-cell lymphoma.
- Assessment of baseline total metabolic tumor volume could inform risk stratification to identify patients who are unlikely to respond to or relapse early after R-CHOP treatment so that they be considered for alternative therapeutic strategies such as enrollment in clinical trials of novel agents.

Author Contributions

All authors critically reviewed the manuscript for scientific content and approved the final version for submission. ICR, GS: Study design. MM, LS, UV, GS: Study conduct. MM, LS, UV: Recruitment and follow-up of patients. ICR, LS, GS: Data collection. ICR, LS, TN, GS, DK, LK: Data analysis. ICR, LS, TN, GS, AB, DK, LK: Data interpretation.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clml.2022.04.010.

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