Treatment of patients with *MYC* rearrangement positive large B-cell lymphoma with R-CHOP plus lenalidomide: results of a multicenter phase II HOVON trial

Martine E.D. Chamuleau,[1] Coreline N. Burggraaff,[1] Marcel Nijland,[2] Katerina Bakunina,[3] Rogier Mous,[4] Pieternella J. Lugtenburg,[5] Daan Dierickx,[6] Gustaaf W. van Imhoff,[2] Joost S.P. Vermaat,[7] Eric A.F.Marijt,[7] Otto Visser,[8] Caroline Mandigers,[9] Yavuz M. Bilgin,[10] Aart Beeker,[11] Mark F. Durian,[12] Bas P. van Rees,[13] Lara H. Bohmer,[14] Lidwine W. Tick,[15] Rinske S. Boersma,[16] Tjeerd J.F. Snijders,[17] Harry C. Schouten,[18] Harry R. Koene,[19] Eva de Jongh,[20] Nathalie Hijmering,[21] Arjan Diepstra,[22] Anke van de Berg,[22] Anne I.J. Arens,[23] Julia Huijbregts,[24] Otto Hoekstra,[25] Josee M. Zijlstra,[1] Daphne de Jong[21] and Marie José Kersten[26]

[1]Department of Hematology, Amsterdam UMC, VU University Amsterdam, Cancer Center Amsterdam, Amsterdam, the Netherlands; [2]Department of Hematology, UMC Groningen, University of Groningen, Groningen, the Netherlands; [3]Department of Hematology, HOVON Data Centre, Erasmus MC Cancer Institute, Rotterdam, the Netherlands; [4]Department of Hematology, UMC Utrecht Cancer Centre, University Medical Centre Utrecht, Utrecht, the Netherlands; [5]Department of Hematology Erasmus MC Cancer Institute, Rotterdam, the Netherlands; [6]Department of Hematology, University Hospitals Leuven, Leuven, Belgium; [7]Department of Hematology, Leiden University Medical Centre, Leiden, the Netherlands; [8]Department of Hematology, Oncology Centre Isala, Zwolle, the Netherlands; [9]Department of Hematology, Canisius-Wilhelmina Hospital, Nijmegen, the Netherlands; [10]Department of Internal Medicine, Admiraal de Ruijter Hospital Goes, the Netherlands; [11]Department of Internal Medicine, Spaarne Gasthuis, Hoofddorp, the Netherlands; [12]Department of Internal Medicine, Tweesteden Hospital, Tilburg, the Netherlands; [13]Department of Internal Medicine, Tjongerschans Hospital, Heerenveen, the Netherlands; [14]Department of Internal Medicine, Haga Hospital, Den Haag, the Netherlands; [15]Department of Internal Medicine, Máxima Medisch Centrum, Veldhoven, the Netherlands; [16]Department of Internal Medicine, Amphia Hospital, Breda, the Netherlands; [17]Department of Hematology, Medisch Spectrum Twente, Enschede, the Netherlands; [18]Department of Hematology, Maastricht UMC, Maastricht, the Netherlands; [19]Department of Internal Medicine, St Antonius Hospital, Nieuwegein, the Netherlands; [20]Department of Internal Medicine, Albert Schweitzer Hospital, Dordrecht, the Netherlands; [21]Department of Pathology, Amsterdam UMC, location VU University Amsterdam, Amsterdam, the Netherlands; [22]Department of Pathology and Medical Biology, UMC Groningen, University of Groningen, Groningen, the Netherlands; [23]Department of Radiology and Nuclear Medicine, Radboud University Medical Centre, Nijmegen, the Netherlands; [24]Department of Radiology and Nuclear Medicine, Gelre Hospital, Apeldoorn, the Netherlands; [25]Department of Radiology and Nuclear Medicine, Amsterdam UMC, VU University Amsterdam, Amsterdam, the Netherlands and [26]Department of Hematology, Amsterdam UMC, University of Amsterdam, Cancer Center Amsterdam, Amsterdam, the Netherlands

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Correspondence: *MARTINE E.D. CHAMULEAU* - m.chamuleau@amsterdamumc.nl/m.chamuleau@vumc.nl

SUPPLEMENTAL DATA

Study protocol

Complete protocol is available as supplemental file and on line at the HOVON website: http://www.hovon.nl/studies/studies-per-ziektebeeld/nhl.html?action=showstudie&studie_id=107&categorie_id=1

National screening program to support implementation of FISH screening in pathology practice

To support timely diagnosis of *MYC+* LBCL and optimal enrolment in the present clinical trial, a nationwide diagnostic support program for *MYC* rearrangement assessment by fluorescence *in situ* hybridization (FISH) was implemented.[1]

In brief, at registration of *de novo* aggressive B-cell lymphoma in the program, limited financial support was provided for FISH diagnostics. With this support, pathology labs, who did not have these assays available in-house were invited to submit cases to dedicated regional reference laboratories to guarantee access to standard FISH testing for *MYC*, *BCL2* and *BCL6*. An initiating quality control validation was performed prior to acceptance as reference or "in-house" lab (August 2013, coordinators D. de Jong, P.M. Kluin). Both technical quality and scoring reproducibility were monitored. Validation was repeated as more labs implemented FISH diagnostics over time during trial accrual. At initial quality control validation, labs performed FISH according to routine procedures with standard commercial probes: *MYC* Break-apart provided by Vysis/Abbott (n=7) DAKO (n=7) and Kreatech (n=1); BCL2 Break-apart provided by Vysis/Abbott (n=6), DAKO (n=9); BCL6 break-apart provided by Vysis/Abbott (n=4), DAKO (n=6) and Kreatech (n=1). Initially, 10/15 labs were accepted as reference or "in-house" lab based on optimal performance and 5 labs were rejected based on insufficient quality (high false negative and/or false positive rate). During trial accrual, 7 additional labs passed quality assessment criteria and were accepted. It should be noted, that over time *MYC* Break-apart from DAKO was replaced for Vysis/Abbot by most labs based on the results of the validation round.

Central pathology review

Central pathology review included classification according to the criteria of the WHO classification 2008 and 2017, including appropriate immunohistochemistry (IHC) for at least CD20, CD10, BCL6 and BCL2 and confirmation of *MYC* rearrangement status based on complete pathology/molecular reports. In case of equivocal documentation, FISH assays

were repeated at the HOVON Pathology Facility. *BCL2* and *BCL6* FISH results were completed when sufficient material was available. In cases with sufficient material COO classification was determined by IHC (Hans algorithm) and by using gene expression profiling (Nanostring Lymph2CX assay: raw counts obtained by Nanostring gene expression analysis were uploaded at the Lymphoma/Leukemia Molecular Profiling Project website.[2]

Imaging assessments and central PET-CT review

Contrast-enhanced CT scans and ^{18}F-FDG PET scans combined with low-dose CT scans (PET-CT) were performed at baseline, after 3 cycles of treatment (interim PET (iPET-CT)), and at EOT. The EOT PET-CT scan was scheduled 6-8 weeks after the last lenalidomide administration. Treatment response at iPET-CT and EOT PET-CT was assessed according to the Lugano criteria using the visual Deauville 5-point scoring system.[3,4] Deauville scores of 1-3 were interpreted as CMR, while scores 4 and 5 indicated stable or progressive disease. PET-CT scans were anonymized and uploaded to a Keosys (Imagys) web-based viewing and reporting system and centrally reviewed by two independent experienced nuclear medicine physicians of the HOVON Imaging Working Group who were blinded for survival outcome. In case of discordance, a third reviewer performed adjudication. PET-CT scans were performed and reviewed in compliance with EANM guidelines.[5] Patients with CMR at iPET-CT but with a positive EOT PET-CT scan were classified as progressive metabolic disease (PMD) at EOT, even when the EOT scan was in partial metabolic response (PMR) compared to the pre-treatment PET-CT scan.

Statistical analyses

In order to take the two-stage sampling nature intrinsic to the study design into account, the primary study endpoint was estimated using the method proposed by Jung[6], which uses the design parameters and the interim analysis results. The design poses a one-sided hypothesis that the response rate is larger or equal to 60%, which we evaluated at a 5% significance level. For the construction of the corresponding two-sided 90% CI the method of Koyama was followed.[7] Both methods are implemented in the R software package "OneArmPhaseTwoStudy".[8]

The secondary survival endpoints were evaluated using the Kaplan-Meier method. Univariate logistic and Cox proportional hazards regression models were used to assess the effect on EOT response rate and the survival endpoints of the following baseline characteristics: BM involvement, WHO PS

categorized as 0, 1, 2 or 3, disease stage I-II versus III-IV, presence of B symptoms, presence of concomitant diseases, IPI, number of extranodal localizations categorized as 0, 1, 2 or more, and age as continuous variable. The predictive value of CMR at interim response evaluation for CMR at EOT was assessed through positive predictive value (PPV) and negative predictive value (NPV), where response was simplified to "CMR" versus "no-CMR". PPV was defined as the proportion of patients without EOT PET-CT CMR among the patients without CMR on iPET, and NPV was defined as the proportion of patients with EOT PET-CT CMR among the patients with CMR on iPET. The effect of CMR at EOT on OS was independently evaluated using achievement of CMR as a time-dependent covariate in a Cox proportional hazards regression model, and visualized using the Kaplan-Meier method with a landmark at 7 months.

Exploratory analyses consisted of descriptive subgroup analyses based on rearrangement group (SH versus DH and TH) as determined by central pathology review. Analyses were performed by tabulation of response rate and Kaplan-Meier curves for OS by rearrangement group. All analyses, except analysis of the primary endpoint for which R software was used, were performed using Stata software, version 15. Data cut-off was June 28, 2019.

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Supplementary Table S1: Treatment schedule

Agent	Dose/day	Route of administration	Days
Day 1	Cyclophosphamide	750 mg/m^2	i.v.
	Vincristine	1.4 mg/m^2 (max 2 mg)	i.v.
	Doxorubicin	50 mg/m^2	i.v.
	Rituximab	375 mg/m^2	i.v.
Day 1–5	Prednisone	100 mg	p.o
Day 1-14	Lenalidomide	15 mg	p.o
Day 2	Pegfilgrastim	6 mg	s.c

Table S1. Treatment schedule of R2CHOP. The R2CHOP scheme consist of R-CHOP21 with lenalidomide 15 mg on 1-14. Additionally, patients received at least 4 intrathecal administrations of methotrexate or cytarabine.

Supplementary Table S2: Pathology review results

		Immunohistochemistry							FISH			GEP	Classification	
Patient number	Eligible	CD20 0= negative (<95%), 1=positive (>95%)	BCL2 0=negative (<50%) 1=positive (50%), 9=not available	MYC-IHC 0=negative (<40%), 1=positive (>40%), 9=not available	CD10 0=negative, 1=positive, 9=not available	BCL6 0=negative (<40%) 1=positive (>40%), 9=not available	MUM1 0=negative (<40%), 1=positive (>40%), 9= not available	GCB/non GCB, 9=not available	MYC-BA 0=neg 1=pos	BCL2-BA 0=neg 1=pos	BCL6-BA 0=neg 1=pos	ABC/GCB/ undeterminate 9=not available	WHO 2008	WHO 2017
1	yes	1	0	1	1	1	9	GCB	1	0	1	GCB	DLBCL	HGBCL, DH/TH
2	yes	1	1	9	0	1	9	9	1	1	1	ABC	DLBCL	HGBCL, DH/TH
3	yes	1	1	9	1	1	9	GCB	1	1	1	GCB	DLBCL	HGBCL, DH/TH
4	yes	1	1	0	1	1	9	GCB	1	1	1	poor quality	BCL-U	HGBCL, DH/TH
5	yes	1	1	9	1	1	0	GCB	1	0	1	9	DLBCL	HGBCL, DH/TH
6	yes	1	1	1	1	1	9	GCB	1	1	0	9	BCL-U	HGBCL, DH/TH
7	yes	1	0	9	1	1	9	GCB	1	9	1	9	DLBCL	HGBCL, DH/TH
8	no								0					
9	no								0					
10	yes	1	1	1	1	1	9	GCB	1	1	0	9	BCL-U	HGBCL, DH/TH
11	yes	1	0	1	1	9	9	GCB	1	0	0	GCB	dd DLBCL or BCL-U	HGBCL, NOS
12	yes	1	0	1	1	1	9	GCB	1	0	0	9	DLBCL	DLBCL
13	yes	1	1	1	1	1	9	GCB	1	1	0	9	dd DLBCL or BCL-U	HGBCL, DH/TH
14	yes	1	1	9	1	1	9	GCB	1	1	0	9	DLBCL	HGBCL, DH/TH
15	yes	1	1	1	9	9	9	9	1	1	0	GCB	DLBCL	HGBCL, DH/TH
16	yes	1	0	0	1	1	0	GCB	1	0	0	9	DLBCL	DLBCL
17	yes	1	1	1	1	1	9	GCB	1	1	9	GCB	DLBCL	HGBCL, DH/TH
18	yes	1	1	1	1	1	9	GCB	1	1	1	GCB	DLBCL	HGBCL, DH/TH
19	yes	1	1	1	1	1	9	GCB	1	1	9	9	DLBCL	HGBCL, DH/TH
20	yes	1	0	1	1	1	9	GCB	1	0	0	GCB	DLBCL	DLBCL
21	yes	1	1	1	1		9	GCB	1	1	0	poor quality	DLBCL	HGBCL, DH/TH
22	yes	1	1	0	1	1	0	GCB	1	1	0	GCB	BCL-U	HGBCL, DH/TH
23	yes	1	1	9	1	1	9	GCB	1	1	1	9	DLBCL	HGBCL, DH/TH
24	yes	1	1	1	0	1	1	non-GCB	1	0	1	9	DLBCL	HGBCL, DH/TH
25	yes	1	1	1	0	1	9	9	1	0	9	9	DLBCL	dd DLBCL or HGBCL, DH/TH
26	yes	1	1	9	0	1	0	GCB	1	9	9	9	DLBCL	dd DLBCL or HGBCL, DH/TH
27	yes	1	1	9	1	1	9	GCB	1	1	0	9	DLBCL	HGBCL, DH/TH
28	yes	1	0	1	1	1	1	GCB	1	1	9	9	dd DLBCL or BCL-U	HGBCL, DH/TH
29	yes	1	0	1	0	1	1	non-GCB	0	0	1	9	DLBCL	HGBCL, DH/TH
30	yes	1	1	0	1	1	9	GCB	1	1	1	9	DLBCL	HGBCL, DH/TH
31	yes	1	1	0	0	1	1	non-GCB	1	0	1	9	DLBCL	HGBCL, DH/TH
32	yes	1	1	1	1	1	9	GCB	1	1	0	GCB	DLBCL	HGBCL, DH/TH
33	yes	1	1	1	1	0	9	GCB	1	1	0	GCB	DLBCL	HGBCL, DH/TH
34	yes	1	0	1	1	1	9	GCB	1	0	0	9	DLBCL	DLBCL
35	yes	1	1	9	1	1	0	GCB	1	9	9	9	BCL-U	dd HGBCL, NOS or HGBCL, DH/TH
36	yes	1	0	1	1	1	9	GCB	1	1	0	GCB	DLBCL	HGBCL, DH/TH
37	yes	1	0	9	1	1	9	GCB	1	9	9	9	DLBCL	dd DLBCL or HGBCL, DH/TH
38	yes	1	0	1	1	0	9	GCB	1	0	0	GCB	DLBCL	DLBCL
39	yes	1	0	0	0	1	9	9	1	0	1	9	DLBCL	HGBCL, DH/TH
40	yes	1	1	1	1	1	9	GCB	1	1	0	GCB	DLBCL	HGBCL, DH/TH
41	yes	1	1	0	0	1	1	non-GCB	1	1	0	GCB	DLBCL	HGBCL, DH/TH
42	yes	1	1	1	1	1	1	GCB	1	1	0	GCB	DLBCL	HGBCL, DH/TH
43	yes	1	0	9	0	1	1	non-GCB	1	0	1	9	DLBCL	HGBCL, DH/TH
44	yes	1	9	1	9	9	1	9	1	1	0	GCB	DLBCL	HGBCL, DH/TH
45	yes	1	0	1	1	1	9	GCB	1	9	9	9	BCL-U	dd HGBCL, NOS or HGBCL, DH/TH
46	yes	1	1	0	1	1	9	GCB	1	1	0	GCB	BCL-U	HGBCL, DH/TH
47	yes	1	1	9	1	1	0	GCB	1	1	0	9	DLBCL	HGBCL, DH/TH
48	yes	1	1	1	9	9	9	9	1	0	0	ABC	dd DLBCL or BCL-U	dd DLBCL or HGBCL, NOS
49	yes	1	1	9	1	1	1	GCB	1	0	0	9	BCL-U	HGBCL, NOS
50	yes	1	1	1	1	1	0	GCB	1	0	0	poor quality	DLBCL	DLBCL
51	yes	1	1	1	9	1	0	GCB	1	1	0	poor quality	DLBCL	HGBCL, DH/TH
52	yes	1	1	1	0	1	0	GCB	1	0	0	ABC	DLBCL	DLBCL
53	yes	1	0	1	1	1	0	GCB	1	1	1	GCB	DLBCL	HGBCL, DH/TH
54	yes	1	1	1	1	1	0	GCB	1	0	1	poor quality	DLBCL	HGBCL, DH/TH
55	yes	1	1	1	1	1	0	GCB	1	1	1	9	DLBCL	HGBCL, DH/TH
56	yes	1	1	1	1	1	0	GCB	1	1	9	9	BCL-U	HGBCL, DH/TH
57	yes	1	1	1	1	1	0	GCB	1	1	0	GCB	DLBCL	HGBCL, DH/TH
58	yes	1	0	1	1	1	0	GCB	1	0	0	GCB	DLBCL	DLBCL
59	yes	1	0	1	9	9	9	9	1	0	0	9	BCL-U	HGBCL, NOS
60	yes	1	1	1	1	1	9	GCB	1	1	0	GCB	DLBCL	HGBCL, DH/TH
61	yes	1	1	1	1	0	9	GCB	1	0	1	GCB	DLBCL	HGBCL, DH/TH
62	yes	1	1	9	1	1	0	GCB	1	1	0	9	BCL-U	HGBCL, DH/TH
63	yes	1	1	1	1	0	0	GCB	1	0	0	GCB	DLBCL	DLBCL
64	no								1				synchronous follicular lymphoma	
65	yes	1	1	9	9	9	9	9	1	0	0	9	DLBCL	DLBCL
66	yes	1	9	1	1	1	9	GCB	1	0	0	GCB	DLBCL	DLBCL
67	yes	1	1	9	1	1	0	GCB	1	1	0	GCB	DLBCL	HGBCL, DH/TH
68	yes	1	9	9	1	9	9	GCB	1	9	9	9	DLBCL	dd DLBCL or HGBCL, DH/TH
69	yes	1	1	9	9	0	0	9	1	9	9	9	DLBCL	DLBCL
70	yes	1	1	1	1	9	9	GCB	1	1	0		DLBCL	HGBCL, DH/TH
71	yes	1	1	1	1	1	0	GCB	1	1	0	9	DLBCL	HGBCL, DH/TH
72	yes	1	1	0	0	1	1	non-GCB	1	0	1	ABC	DLBCL	HGBCL, DH/TH
73	yes	1	0	9	1	1	0	GCB	1	0	0	9	DLBCL	DLBCL
74	yes	1	1	1	1	1	9	GCB	1	1	0	GCB	DLBCL	HGBCL, DH/TH
75	yes	1	1	1	9	9	9	9	1	0	0	unclassified	DLBCL	DLBCL
76	yes	1	0	1	1	1	1	GCB	1	0	1	GCB	DLBCL	HGBCL, DH/TH
77	yes	1	0	1	9	9	9	9	1	0	0	ABC	DLBCL	DLBCL
78	yes	1	1	1	0	1	1	non-GCB	1	0	0	ABC	dd DLBCL or BCL-U	dd DLBCL or HGBCL, NOS
79	yes	1	1	1	1	1	0	GCB	1	9	9	9	DLBCL	dd DLBCL or HGBCL, DH/TH
80	yes	1	1	1	0	1	1	non-GCB	1	0	1	ABC	DLBCL	HGBCL, DH/TH
81	yes	1	0	1	1	1	1	GCB	1	0	0	GCB	DLBCL	DLBCL
82	yes	1	1	1	1	1	nd	GCB	1	1	0	poor quality	BCL-U	HGBCL, DH/TH
83	yes	1	1	1	0	1	0	GCB	1	0	1	unclassified	DLBCL	HGBCL, DH/TH
84	yes	1	0	0	1	1	0	GCB	1	0	0	GCB	DLBCL	DLBCL
85	yes	1	1	1	1	1	9	GCB	1	1	1	9	DLBCL	HGBCL, DH/TH

Table S2. Central pathology review data on 85 *MYC+* LBCL patients treated with R2CHOP.

BA= break apart, NOS= not otherwise specified

Supplementary Table S3: Predictive value of PET results

Table S3A: predictive value of EOT PET for progression (or death) within 1 year

	progression within 1 year	
CMR at EOT	no	yes
no	5	22
yes	51	4

PPV	81
NPV	93

Table S3B: predictive value of interim PET for EOT PET-CT result

	CMR EOT *	
CMR at interim	no	yes
no	15	10
yes	12	45

	%
PPV	60
NPV	79

Table S3. Positive and negative predictive value of PET results. Table S3A: Positive and negative predictive values of EOT PET-CT scan for progression within 1 year. Table S3B: Positive and negative predictive values of interim PET-CT scan for EOT result. Response was simplified to "CMR" versus "no CMR"**.**

*2 patients missing interim PET (due to progression) and 1 patient missing EOT PET-CT (off protocol due to toxicity) were counted as failures

Supplementary Figure S1: Survival according to rearrangement status

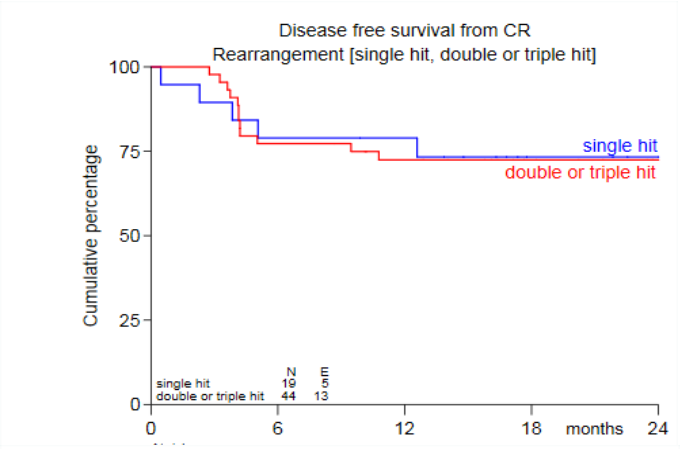

Figure S1A

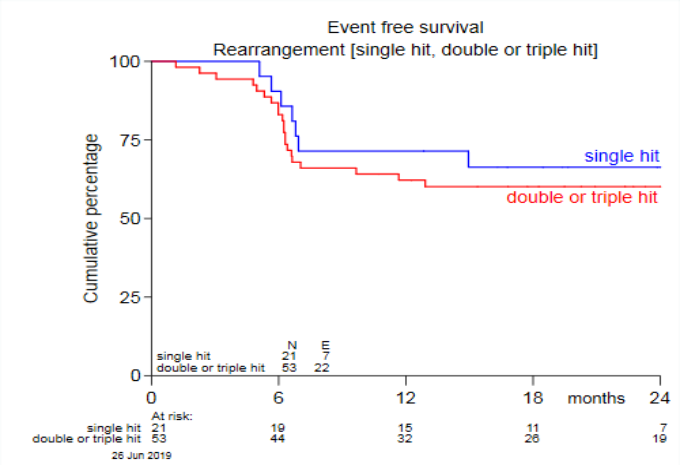

Figure S1B

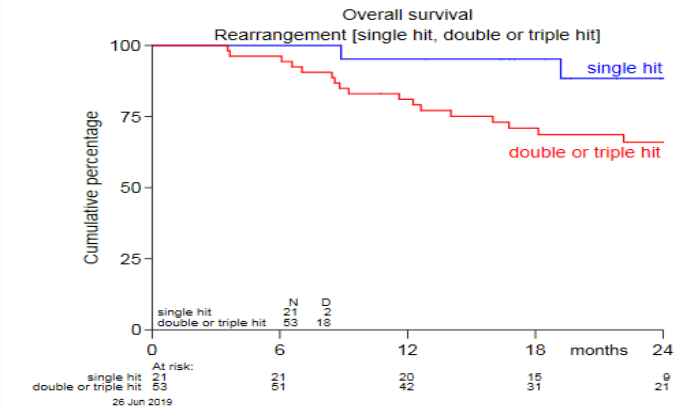

Figure S1C

Figure S1. Survival according to rearrangement status. Figure S1A: Disease Free Survival of SH vs DH/TH *MYC+* LBCL patients revealed no significant differences. Figure S1B: Event Free Survival of SH vs DH/TH *MYC+* LBCL patients revealed no significant differences. Figure S1C: Overall survival analysis indicated that DH/TH patients had a tendency for higher risk of death compared to SH patients (HR 4.18, p=0.055; 95% CI 0.97-18.02). Eight patients with unknown *BCL2* and *BCL6* rearrangement were not included in this analysis.

Supplementary Figure S2: Survival according to rearrangement status

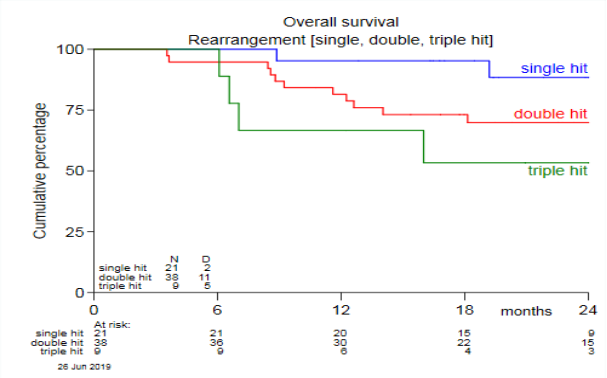

Figure S2A

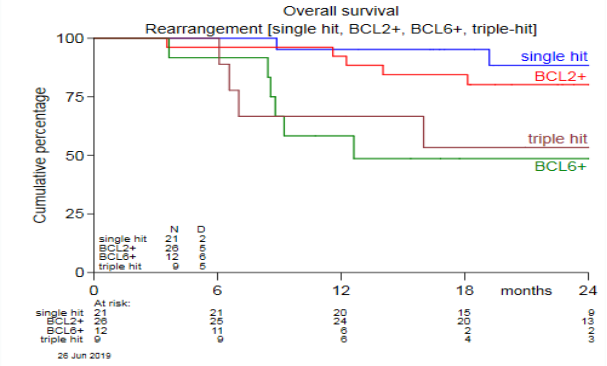

Figure S2B

Figure S2. Overall survival according to rearrangement status (SH vs DH vs TH). Figure S2A: Overall survival of *MYC+* LBCL patients according rearrangement status SH vs DH vs TH revealed no significant differences. Figure S2B: Overall survival of *MYC+* LBCL patients according rearrangement status SH vs DH MYC/BCL2 vs DH MYC/BCL6 vs TH revealed no significant differences.

Eight patients with unknown *BCL2* and *BCL6* rearrangement were not included in this analysis.