

Biological characterization of adult *MYC*-translocation-positive mature B-cell lymphomas other than molecular Burkitt lymphoma

Sietse M. Aukema,^{1,2,3} Markus Kreuz,⁴ Christian W Kohler,⁵ Maciej Rosolowski,⁴ Dirk Hasenclever,⁴ Michael Hummel,⁶ Ralf Küppers,⁷ Dido Lenze,⁶ German Ott,⁸ Christiane Pott,⁹ Julia Richter,¹ Andreas Rosenwald,¹⁰ Monika Szczepanowski,¹¹ Carsten Schwaenen,¹² Harald Stein,⁶ Heiko Trautmann,⁹ Swen Wessendorf,¹² Lorenz Trümper,¹³ Markus Loeffler,⁴ Rainer Spang,⁵ Philip M. Kluin,² Wolfram Klapper,⁸ and Reiner Siebert¹ for the Molecular Mechanisms in Malignant Lymphomas (MMML) Network Project

¹Institute of Human Genetics, University Hospital Schleswig-Holstein Campus Kiel/Christian-Albrechts University Kiel, Germany; ²Department of Pathology & Medical Biology, University of Groningen, University Medical Center Groningen, the Netherlands; ³Department of Hematology, University of Groningen, University Medical Center Groningen, the Netherlands; ⁴Institute for Medical Informatics, Statistics and Epidemiology, University of Leipzig, Germany; ⁵Statistical Bioinformatics, Institute of Functional Genomics, University of Regensburg, Germany; ⁶Institute of Pathology, Campus Benjamin Franklin, Charité-Universitätsmedizin Berlin, Germany; ⁷Institute of Cell Biology (Cancer Research), University of Duisburg-Essen, Medical School, Essen, Germany; ⁸Department of Clinical Pathology, Robert-Bosch-Krankenhaus, and Dr. Margarete Fischer-Bosch Institute of Clinical Pathology, Stuttgart, Germany; ⁹Second Medical Department, University Hospital Schleswig-Holstein Campus Kiel/Christian-Albrechts University Kiel, Germany; ¹⁰Institute of Pathology, University of Würzburg, Germany; ¹¹Institute of Hematopathology, University Hospital Schleswig-Holstein Campus Kiel/ Christian-Albrechts University Kiel, Germany; ¹²Department of Internal Medicine III, University Hospital of Ulm, Germany; ¹³Department of Hematology and Oncology, Georg-August University of Göttingen, Germany

A full list of MMML-members is provided in the Online Supplementary Appendix.

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Correspondence: rsiebert@medgen.uni-kiel.de

Supplementary appendix to “Biologic characterization of adult *MYC*-translocation positive mature B-cell lymphomas other than molecular Burkitt lymphoma”

Sietse M. Aukema^{1,2,3}, Markus Kreuz⁴, Christian W Kohler⁵, Maciej Rosolowski⁴, Dirk Hasenclever⁴, Michael Hummel⁶, Ralf Küppers⁷, Dido Lenze⁶, German Ott⁸, Christiane Pott⁹, Julia Richter¹, Andreas Rosenwald¹⁰, Monika Szczepanowski¹¹, Carsten Schwaenen¹², Harald Stein⁶, Heiko Trautmann⁹, Swen Wessendorf¹², Lorenz Trümper¹³, Markus Loeffler⁴, Rainer Spang⁵, Philip M. Kluin², Wolfram Klapper⁸ and Reiner Siebert¹ for the Molecular Mechanisms in Malignant Lymphomas (MMML) Network Project

Statement of equal authors' contribution: SMA, MK and CWK contributed equally to the work

¹Institute of Human Genetics, University Hospital Schleswig-Holstein Campus Kiel/Christian-Albrechts University Kiel, Germany

²Department of Pathology & Medical Biology, University Medical Center Groningen, Groningen, the Netherlands

³Department of Hematology, University Medical Center Groningen, Groningen, the Netherlands

⁴Institute for Medical Informatics, Statistics and Epidemiology, University of Leipzig, Germany

⁵Statistical Bioinformatics, Institute of Functional Genomics, University of Regensburg, Germany

⁶Institute of Pathology, Campus Benjamin Franklin, Charité–Universitätsmedizin Berlin, Germany

⁷Institute of Cell Biology (Cancer Research), University of Duisburg-Essen, Medical School, Essen, Germany

⁸Department of Hematology, Asklepios Klinik St. Georg, Hamburg, Germany

⁹Second Medical Department, University Hospital Schleswig-Holstein Campus Kiel/Christian-Albrechts University Kiel, Germany

¹⁰Institute of Pathology, University of Würzburg, Germany

¹¹Institute of Hematopathology, University Hospital Schleswig-Holstein Campus Kiel/ Christian-Albrechts University Kiel,

¹²Department of Internal Medicine III, University Hospital of Ulm, Ulm, Germany

¹³Department of Hematology and Oncology, Georg-August University of Göttingen, Germany

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I Members of the Network Project of the Deutsche Krebshilfe “Molecular Mechanisms in Malignant Lymphomas” (Alphabetical order)

Pathology group: Thomas F.E. Barth¹, Heinz-Wolfram Bernd², Sergio B. Cogliatti³, Alfred C. Feller², Martin L. Hansmann⁴, Michael Hummel⁵, Wolfram Klapper⁶, Dido Lenze⁵, Peter Möller¹, Hans-Konrad Müller-Hermelink⁷, Ilske Oschlies⁶, German Ott²⁰, Andreas Rosenwald⁷, Harald Stein⁵, Monika Szczepanowski⁶, **Genetics group:** Thomas F.E. Barth¹, Petra Behrmann⁸, Peter Daniel⁹, Judith Dierlamm⁸, Stefan Gesk¹⁰, Eugenia Haralambieva⁷, Lana Harder¹⁰, Paul-Martin Holterhus¹¹, Ralf Küppers¹², Dieter Kube¹³, Peter Lichter¹⁴, Jose I. Martín-Subero¹⁰, Peter Möller¹, Eva M. Murga-Peñas⁸, German Ott²⁰, Shoji Pellissery¹⁰, Claudia Philipp¹², Christiane Pott¹⁵, Armin Pscherer¹⁴, Julia Richter¹⁰, Andreas Rosenwald⁷, Itziar Salaverria¹⁰, Carsten Schwaenen¹⁶, Reiner Siebert¹⁰, Heiko Trautmann¹⁵, Martina Vockerodt¹⁷, Swen Wessendorf¹⁶, **Bioinformatics group:** Stefan Bentink¹⁸, Hilmar Berger¹⁹, Christian W Kohler¹⁸, Dirk Hasenclever¹⁹, Markus Kreuz¹⁹, Markus Loeffler¹⁹, Maciej Rosolowski¹⁹, Rainer Spang¹⁸. **Clinical group for pediatric lymphoma:** Birgit Burkhardt²¹, Alfred Reiter²¹, Wilhelm Woessmann²¹ **Project coordination:** Benjamin Stürzenhofecker¹³, Lorenz Trümper¹³, Maren Wehner¹³. **Steering committee:** Markus Loeffler¹⁹, Reiner Siebert¹⁰, Harald Stein⁵, Lorenz Trümper¹³.

¹Institute of Pathology, University Hospital of Ulm, Germany, ²Institute of Pathology, University Hospital Schleswig-Holstein Campus Lübeck, Germany, ³Institute of Pathology, Kantonsspital St. Gallen, Switzerland, ⁴Institute of Pathology, University Hospital of Frankfurt, Germany, ⁵Institute of Pathology, Campus Benjamin Franklin, Charité–Universitätsmedizin Berlin, Germany, ⁶Department of Pathology, Hematopathology Section, University Hospital Schleswig-Holstein Campus Kiel/ Christian-Albrechts University Kiel, Germany, ⁷Institute of Pathology, University of Würzburg, Germany, ⁸University Medical Center Hamburg-Eppendorf, Hamburg, Germany, ⁹Department of Hematology, Oncology and Tumor Immunology, University Medical Center Charité, Germany, ¹⁰Institute of Human Genetics, University Hospital Schleswig-Holstein Campus Kiel/Christian-Albrechts University Kiel, Germany, ¹¹Division of Pediatric Endocrinology and Diabetes, Department of Pediatrics, University Hospital Schleswig-Holstein Campus Kiel / Christian-Albrechts University Kiel, Germany, ¹²Institute for Cell Biology (Tumor Research), University of Duisburg-Essen, Germany, ¹³Department of Hematology and Oncology, Georg-August University of Göttingen, Germany, ¹⁴German Cancer Research Center (DKFZ), Heidelberg, Germany,

¹⁵Second Medical Department, University Hospital Schleswig-Holstein Campus Kiel/ Christian-Albrechts University Kiel, Germany, ¹⁶Cytogenetic and Molecular Diagnostics, Internal Medicine III, University Hospital of Ulm, Germany, ¹⁷Department of Pediatrics I, Georg-August University of Göttingen, Germany, ¹⁸Institute of Functional Genomics, University of Regensburg, Germany, ¹⁹Institute for Medical Informatics, Statistics and Epidemiology, University of Leipzig, Germany ²⁰Institute of Clinical Pathology, Robert-Bosch-Krankenhaus, Stuttgart, Germany, ²¹ NHL-BFM Study Center Department of Pediatric Hematology and Oncology, Justus-Liebig-University. Giessen, Germany

II Supplementary Materials and Methods

Sample selection, pathology review and description of the cohort

All lymphomas were investigated as part of the Molecular Mechanisms in Malignant Lymphomas (MMML) network project. In this project germinal center mature B-cell lymphomas and follicular lymphomas were separately collected from the other lymphomas. In all cases selection criteria were the availability of fresh frozen tissue and a tumor cell content of $\geq 50\%$.⁽¹⁻³⁾ Some cases in the present study have been included in previously published studies (GEO accession numbers GSE4475 and GSE22470).^(1, 2, 4) In addition, for 32 lymphomas a new GEO was created (GEO accession number GSE44164). All pediatric *MYC*+ lymphomas (age ≤ 18) and all lymphomas with a molecular Burkitt lymphoma (mBL) gene expression signature (including three cases of DHL with mBL GEP) were excluded and were not part of the study cohort of the present study (Supplementary Figure S1). In addition were those lymphomas without a *MYC* break not subject of investigation and not included in the study. Although these (pediatric) *MYC*+ lymphomas with a mBL GEP and all lymphomas without a *MYC* break were not subject of investigation and not included in the study cohort, they were, solely for purposes of comparison with SHL and DHL, included in certain analyses. The three cases of DHL with mBL GEP were not included in any of aforementioned analyses.

All lymphomas were evaluated by expert hematopathologists independently and a final consensus panel diagnosis was made based on histopathological features in one, two or three rounds of evaluation. For the cases with diagnosis “unclassifiable DLBCL/BL”, atypical Burkitt or Burkitt-like lymphomas was the term used at time of panel review. No pairs (e.g. multiple biopsies from the same patient) were included in the study. In case multiple biopsies were available, the primary biopsy was selected. The cases in the current study are not derived from a population based registry and, due to the retrospective nature of the current study clinical data was not available in all cases. Moreover, patients have been treated with a variety of regimens, which included immunotherapy (Rituximab) only in a small minority of cases. In 7 cases the material analyzed was known to be from relapsing disease and in these cases survival analysis started at diagnosis.

After exclusion of all pediatric cases (age ≤ 18 years) and all adult lymphomas with a mBL gene

expression profile 80 *MYC*⁺ lymphomas were left for further analysis. Although in one case there was an *IGH-MYC* fusion in the absence of detectable splitting of the *MYC* BAP probe used (due to either distal breakpoints or insertions), for reasons of readability we refer to all those cases as having *MYC* breaks. This cohort consisted of 48 lymphomas with a “molecular intermediate” (48/80,60%) and 32 lymphomas with a “non-molecular BL” (32/80,40%) gene expression profile. There were 41 females (51%) and 39 males (49%). DLBCL (inclusive DLBCL/FL3B) was the most frequent morphological diagnosis (n=58 ; 73%). By GEP, 55 (69%) lymphomas were classified as GCB-like, 14 (18%) as ABC-like and 11 (14%) as unclassifiable. In 47/80 (59%) cases *MYC* was juxtaposed to one of the immunoglobulin loci (called “*IG-MYC*”) whereas 33/80 (41%) lymphomas did not show this juxtaposition (called “non-*IG-MYC*”).

Molecular cytogenetics (FISH)

Interphase fluorescence in situ hybridization (FISH) was performed as previously described.(1, 4, 5) Generally, all cases were screened with a panel of *MYC*, *IGH-MYC*, *BCL6*, and *IGH-BCL2* probes. Cases were defined as “*MYC* positive” if the tumor cells either showed splitting with *MYC* BAP and/or fusion signals with the *MYC-IGH* probe. By definition, all cases positive for *IGH-BCL2* and/or *IGH-MYC* fusion were called *IGH* break positive. In all other cases an *IGH* BAP probe was applied. For identification of *MYC* partners the following probe assays were used in a cytogenetic algorithm (Supplemental Figure S1). FISH probes in bold indicate home-brew probes.(1, 6) All others Abbott-Vysis, Downers-Grove, IL. *IGH-MYC-CEP8* = tri-color dual fusion with centromere 8 probe; *MYC* = dual color break-apart (BAP); *BCL6* = BAP ; ***MYC-BCL6*** = dual color dual fusion (DCDF); ***IGL*** BAP, ***IGK*** BAP, ***MYC-IGK*** DCDF; ***MYC-IGL*** DCDF ; **9p13** BAP (centromeric of *PAX5*); **9p13-MYC** DCDF. “X-*MYC*” indicates a not identified non-*IG-MYC* partner. *IGH-MYC* negative cases that were negative for *BCL6* break (or positive for *BCL6* break but negative for *MYC-BCL6* fusion) were either pre-screened with *IGK/L* BAP probes for potential *IGK/L* involvement or were directly evaluated with *MYC-IGK/L* DCDF probes. It cannot be excluded that incidental cases with a *BCL6* break outside the MBR (e.g. ABR) might have remained undetected with the *BCL6* BAP used.(7) *MYC-IGK/L* negative cases (or *IGK/L* positive but *MYC-IGK/L* negative cases) were either pre-screened with 9p13 BAP probes for potential 9p13 involvement or directly evaluated with 9p13-*MYC* DCDF probes. It should be emphasized that only in the case of positive *MYC-IGK/L* fusion or 9p13-*MYC* fusion they were assigned to the *IG-MYC* or 9p13-*MYC* group, as positive splitting for *IGK/L* or 9p13

alone does not reliably identify them as a *MYC* partner (e.g. break in the *MYC* and the *IGL* locus could be a t(8;22)/*IGL-MYC* fusion or a t(22;oncogene) and t(partner;*MYC*) translocation.(8, 9) The same situation is applicable for positive splitting of 9p13 (e.g. could be a t(8;9)(q24;p13) or t(partner;*MYC*) translocation and t(9;partner)(p13;partner).(9, 10)

Bioinformatical and statistical analysis

Copy number analysis: To compare the incidence of copy number aberrations between lymphoma subgroups we performed a clone-wise comparison of CN gains and losses using Fisher`s exact test. For visualization the P-values were transformed to the negative log10 scale in which 2 corresponds to a nominal P-value of 0.01 and 1.3 to a P-value of 0.05 (see Suppl. Fig. 4C). The overall genetic complexity (i.e. the number of aberrant regions per sample) was compared by the Mann–Whitney U test between subgroups.

Gene expression analysis:

Differential gene expression analysis was performed using “linear models for microarrays“ generated with the Bioconductor package *limma*⁽¹¹⁾ in version 3.12.0. Resulting *p values* were adjusted according to Benjamini and Hochberg⁽¹²⁾ and a significance level for differentially expressed genes was set to 0.05. Permutation scores for SAM-Plots were computed by the Bioconductor package *twilight*⁽¹³⁾ in version 1.32.

Comparison of gene expression profiles between *BCL2*⁺/*MYC*⁺ and *BCL6*⁺/*MYC*⁺ DHL: For the differentially expressed gene tags from the comparison of gene expression profiles of *BCL2*⁺/*MYC*⁺ and *BCL6*⁺/*MYC*⁺ DHL an expression value from the differentially expressed gene tags was used to calculate a single representative value (index) for each sample by fitting a standard additive model with independent gene and sample effects using Tukey’s median polish procedure.(14) Samples were sorted according to their individual index, starting with the lowest index at the very left end of the colorbar. Hereafter the indices of the *BCL2*⁺/*BCL6*⁺/*MYC*⁺ “triple-hit” lymphomas (which were not included in the previous comparison) were added.

V Legends to Supplementary Figures:

- Figure S1 Simplified, schematic representation of *MYC* - FISH - panel and algorithm for detection of *MYC* breaks and identification of *MYC* partner.
- Figure S2 Flow-chart of MMML cohort and case selection. All analyses were, unless stated explicitly otherwise, performed on DSII. *DSIII contains all DLBCL without any FL component (n=55).
- Figure S3 *MYC*⁺ lymphomas had significantly higher *MYC* expression compared to *MYC*(-) lymphomas (p< 0.001) but lower compared to *IG-MYC* mBL (p<0.001).
- Figure S4 Array-CGH of SHL in panel A and DHL in panel B. Gains are depicted in green and losses in red. Clone-wise comparison in panel C, green and red peaks indicate imbalances in the frequency of gains and losses respectively between the two groups.
- Figure S5 Comparison of overall survival between *BCL6*⁺/*MYC*⁺ and *BCL2*⁺/*MYC*⁺ DHL. *BCL6*⁺/*MYC*⁺ show a significant trend towards inferior survival (p=0.040) compared to *BCL2*⁺/*MYC*⁺. Survival of "triple-hit" lymphomas is (due to small number) not included in statistical analysis and only displayed.
- Figure S6 Lymphomas with *IG-MYC* translocation showed significantly higher *MYC* expression than those with non-*IG-MYC* translocation (p=0.040). *IG-MYC* versus *MYC* negative and non-*IG-MYC* versus *MYC* negative lymphomas (p<0.001 for each comparison). *IG-MYC* mBL showed higher *MYC* expression compared to *IG-MYC* non-mBL/intermediate (p= 0.003).
- Figure S7 Overall survival of *MYC*⁺ lymphomas (with non-mBL or Intermediate GEP) with either *IG* or non-*IG* gene partner. Dark grey line represents lymphomas with one of the *IG* loci as *MYC* partner (*IG-MYC*), light grey those with a non-*IG* *MYC* partner.
- Figure S8 Composite survival curve of *IG-MYC* SHL (DSII) versus non-*IG-MYC* SHL (DSII) versus all DHL (DSII) vs *IG-MYC* mBL (DSI) with very favorable outcome of *IG-MYC* mBL compared to all other lymphomas with *MYC* break (p<0.01 for comparison

of all groups, $p < 0.001$ for *IG-MYC* mBL versus all other *MYC+* lymphomas). Among the *IG-MYC* mBL are 41 pediatric patients.

Figure S1

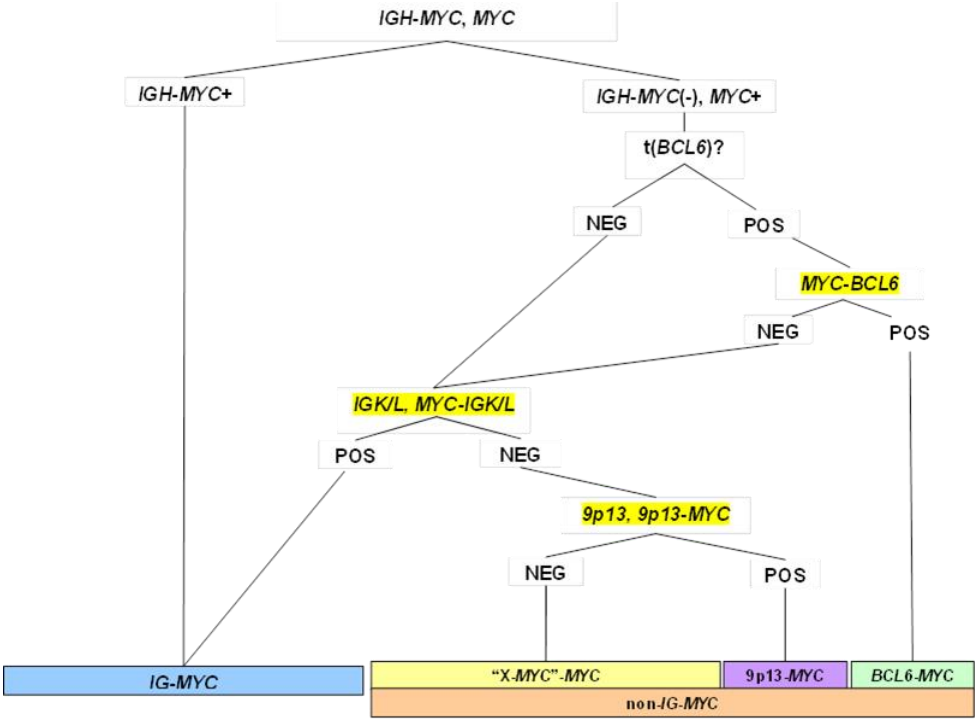


Figure S2

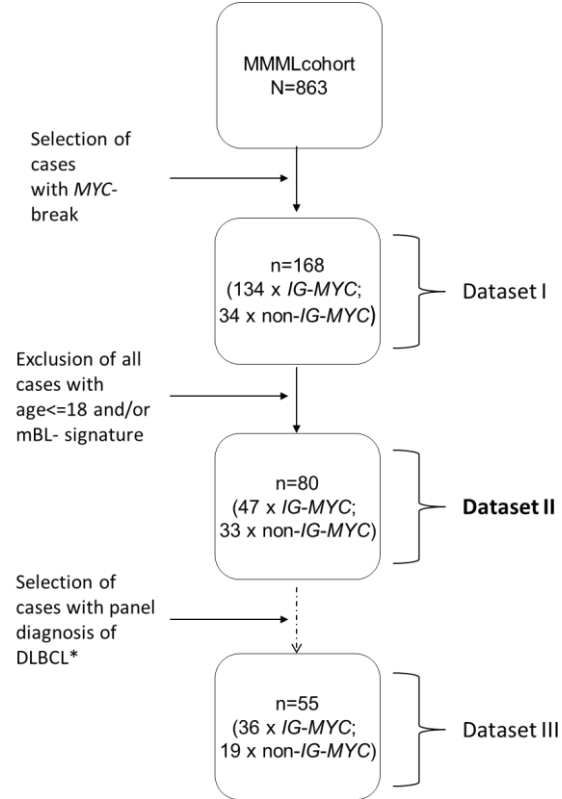


Figure S3

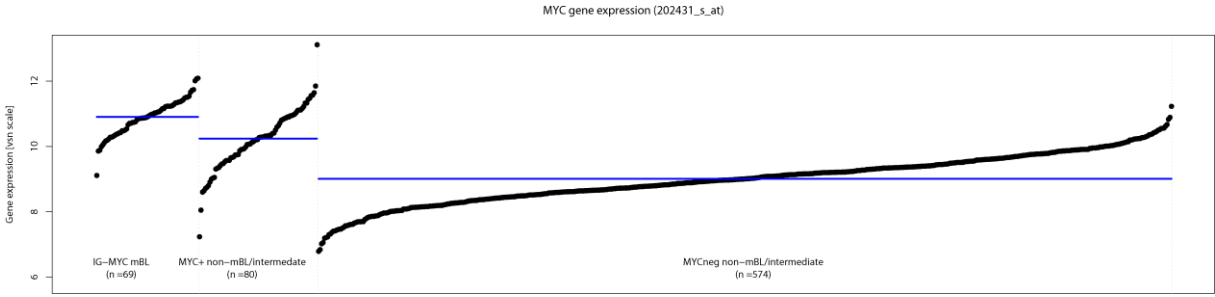


Figure S4

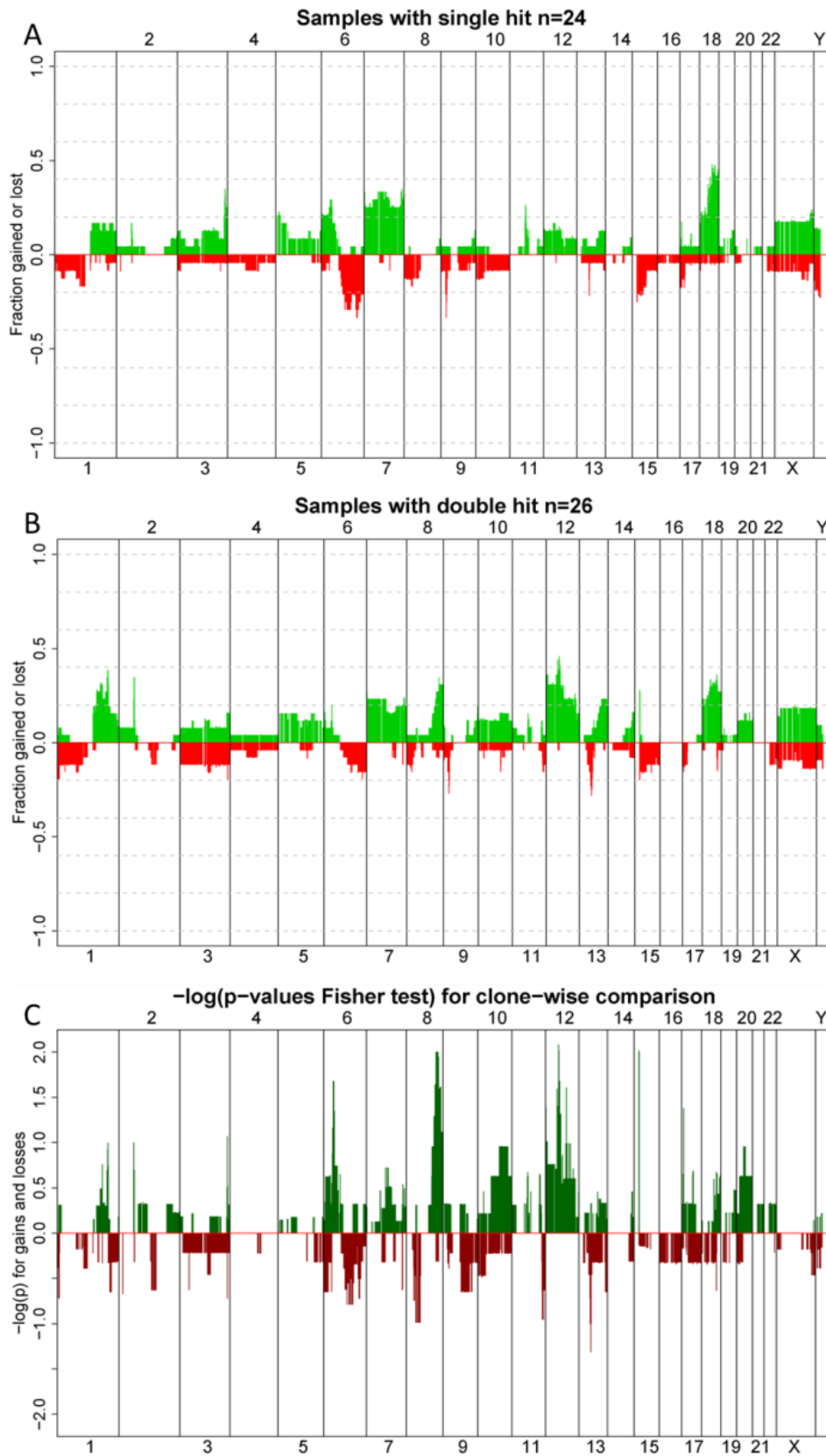


Figure S5

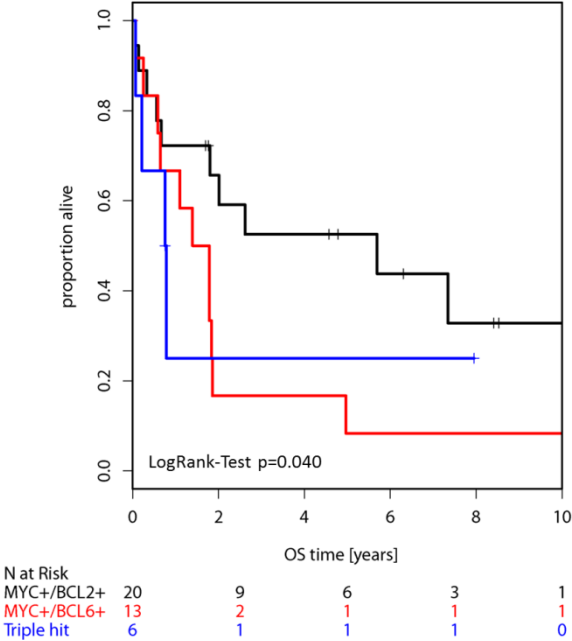


Figure S6

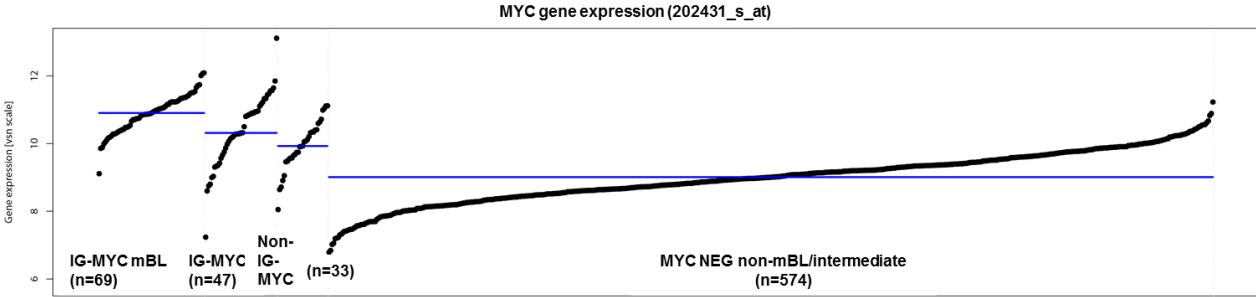


Figure S7

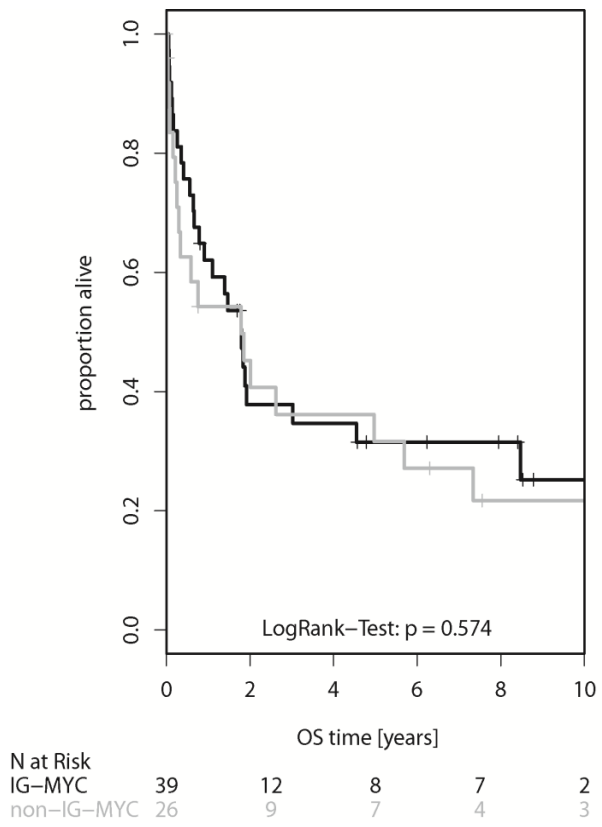
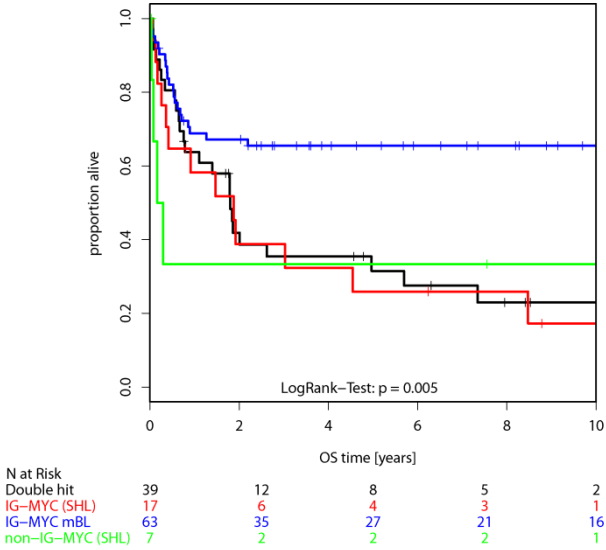


Figure S8



VII Supplementary Tables

Supplementary Table I: treatment characteristics		
THERAPY	Single Hit (SHL)	Double hit (DHL)
CHOP-like (+/- RT)	8 (26)	13 (28)
R-CHOP-like (+/- RT)	3 (10)	4 (9)
Other*	5 (16)	11 (23)
No primary CT or only RT	2 (6)	3 (6)
No data	13 (42)	16 (34)
Total	31 (100)	47 (100)

Percentages are provided between parentheses () and may not be equal to 100 as result of rounding.; RT, radiotherapy; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; *includes for SHL COPBLAM, cyclophosphamide, vincristine, prednisone, bleomycin, doxorubicin, procarbazine (+/- RT) n=2; CHOP + high-dose therapy (n=1); cyclophosphamide + mitoxantron (n=1) and COP (n=1);for DHL (R)-DEXABEAM/BEAM; dexamethasone, carmustine, etoposide, cytarabine, melphalan (n=2); B-ALL treatment regimen (n=1); SAKK 35/98 protocol (n=2); R-VACOP-B (n=1; rituximab + etoposide, doxorubicin, cyclophosphamide, vincristine, prednisolone, bleomycin); M-BACOD (n=1, methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine, dexamethasone); IMVP (n=1, iphosphamide, methotrexate, etoposide);vincristine + prednisolone (n=1); COP (n=1); CEOP (n=1)

Supplementary Table II: Full list of differentially expressed gene tags between *BCL2*⁺/*MYC*⁺ & *BCL6*⁺/*MYC*⁺ DHL

	GENE	Description	PROBE	BCL2 vs BCL6 (↑) / (↓)
1			206302_s_at	(↓)
2			209079_x_at	(↑)
3			211066_x_at	(↑)
4			211725_s_at	(↓)
5			212181_s_at	(↓)
6			213454_at	(↓)
7			214290_s_at	(↓)
8			215836_s_at	(↑)
9			216146_at	(↑)
10			218233_s_at	(↓)
11			218280_x_at	(↓)
12	ACOT13	acyl-CoA thioesterase 13	204565_at	(↓)
13	ADCK2	aarF domain containing kinase 2	221893_s_at	(↑)
14	ADM	adrenomedullin	202912_at	(↓)
15	AEN	apoptosis enhancing nuclease	219361_s_at	(↓)
16	APOL2	apolipoprotein L, 2	221653_x_at	(↓)
17	APOO	apolipoprotein O	221620_s_at	(↓)
18	ASB13	ankyrin repeat and SOCS box containing 13	218862_at	(↑)
19	ATP1B1	ATPase, Na ⁺ /K ⁺ transporting, beta 1 polypeptide	201242_s_at	(↓)
20	ATP1B1	ATPase, Na ⁺ /K ⁺ transporting, beta 1 polypeptide	201243_s_at	(↓)
21	AVEN	apoptosis, caspase activation inhibitor	219366_at	(↓)
22	BACH2	BTB and CNC homology 1, basic leucine zipper transcription factor 2	221234_s_at	(↑)
23	BATF	basic leucine zipper transcription factor, ATF-like	205965_at	(↓)
24	BCCIP	BRCA2 and CDKN1A interacting protein	218264_at	(↓)
25	BCL2A1	BCL2-related protein A1	205681_at	(↓)
26	BHLHE41	basic helix-loop-helix family, member e41	221530_s_at	(↓)
27	BID	BH3 interacting domain death agonist	204493_at	(↓)
28	BLNK	B-cell linker	207655_s_at	(↓)
29	BPGM	2,3-bisphosphoglycerate mutase	203502_at	(↓)
30	BSPRY	B-box and SPRY domain containing	218792_s_at	(↓)
31	BTBD2	BTB (POZ) domain containing 2	207722_s_at	(↑)
32	BYSL	bystin-like	203612_at	(↓)
33	C3orf37	chromosome 3 open reading frame 37	201678_s_at	(↑)
34	CASP7	caspase 7, apoptosis-related cysteine peptidase	207181_s_at	(↓)
35	CCR10	chemokine (C-C motif) receptor 10	220565_at	(↓)
36	CD44	CD44 molecule (Indian blood group)	204489_s_at	(↓)
37	CDYL	chromodomain protein, Y-like	203098_at	(↓)
38	CHST2	carbohydrate (N-acetylglucosamine-6-O) sulfotransferase 2	203921_at	(↓)
39	CKAP4	cytoskeleton-associated protein 4	200999_s_at	(↓)

40	CMC2	COX assembly mitochondrial protein 2 homolog (S. cerevisiae)	218447_at	(↓)
41	COL9A3	collagen, type IX, alpha 3	204724_s_at	(↓)
42	COX7B	cytochrome c oxidase subunit VIIb	202110_at	(↓)
43	CPOX	coproporphyrinogen oxidase	204172_at	(↓)
44	CSNK2B	casein kinase 2, beta polypeptide	201390_s_at	(↓)
45	CYB5R2	cytochrome b5 reductase 2	220230_s_at	(↓)
46	DIP2C	DIP2 disco-interacting protein 2 homolog C (Drosophila)	212504_at	(↑)
47	ECI1	enoyl-CoA delta isomerase 1	209759_s_at	(↓)
48	EEF1E1	eukaryotic translation elongation factor 1 epsilon 1	204905_s_at	(↓)
49	EHD1	EH-domain containing 1	209037_s_at	(↓)
50	ENTPD1	ectonucleoside triphosphate diphosphohydrolase 1	207691_x_at	(↓)
51	ENTPD1	ectonucleoside triphosphate diphosphohydrolase 1	209473_at	(↓)
52	ENTPD1	ectonucleoside triphosphate diphosphohydrolase 1	209474_s_at	(↓)
53	EXOSC8	exosome component 8	215136_s_at	(↓)
54	FARS2	phenylalanyl-tRNA synthetase 2, mitochondrial	204282_s_at	(↓)
55	FARS2	phenylalanyl-tRNA synthetase 2, mitochondrial	204283_at	(↓)
56	FBXL18	F-box and leucine-rich repeat protein 18	215068_s_at	(↑)
57	FDX1	ferredoxin 1	203647_s_at	(↓)
58	FEZ1	fasciculation and elongation protein zeta 1 (zygin I)	203562_at	(↓)
59	FRG1	FSHD region gene 1	204145_at	(↓)
60	FTSJ1	FtsJ RNA methyltransferase homolog 1 (E. coli)	205324_s_at	(↓)
61	FUT8	fucosyltransferase 8 (alpha (1,6) fucosyltransferase)	203988_s_at	(↓)
62	GNG7	guanine nucleotide binding protein (G protein), gamma 7	206896_s_at	(↑)
63	HCK	hemopoietic cell kinase	208018_s_at	(↓)
64	HSPE1	heat shock 10kDa protein 1 (chaperonin 10)	205133_s_at	(↓)
65	IER5	immediate early response 5	218611_at	(↓)
66	IFNAR2	interferon (alpha, beta and omega) receptor 2	204785_x_at	(↓)
67	IL12A	interleukin 12A (natural killer cell stimulatory factor 1, cytotoxic lymphocyte maturation factor 1, p35)	207160_at	(↓)
68	IQGAP2	IQ motif containing GTPase activating protein 2	203474_at	(↓)
69	IRF4	interferon regulatory factor 4	204562_at	(↓)
70	IVNS1ABP	influenza virus NS1A binding protein	201362_at	(↓)
71	IVNS1ABP	influenza virus NS1A binding protein	201363_s_at	(↓)
72	IVNS1ABP	influenza virus NS1A binding protein	206245_s_at	(↓)
73	KIAA0355	KIAA0355	203288_at	(↑)
74	KLF11	Kruppel-like factor 11	218486_at	(↓)
75	KREMEN2	kringle containing transmembrane protein 2	219692_at	(↓)
76	LPP	LIM domain containing preferred translocation partner in lipoma	202822_at	(↑)
77	LSM2	LSM2 homolog, U6 small nuclear RNA associated (S. cerevisiae)	209449_at	(↓)
78	LSM6	LSM6 homolog, U6 small nuclear RNA associated (S. cerevisiae)	205036_at	(↓)
79	MAP3K5	mitogen-activated protein kinase kinase kinase 5	203837_at	(↓)
80	MAPK10	mitogen-activated protein kinase 10	204813_at	(↑)
81	MIPEP	mitochondrial intermediate peptidase	204305_at	(↓)
82	MME	membrane metallo-endopeptidase	203434_s_at	(↑)

83	MME	membrane metallo-endopeptidase	203435_s_at	(↑)
84	MRPS18B	mitochondrial ribosomal protein S18B	208907_s_at	(↓)
85	MRPS18B	mitochondrial ribosomal protein S18B	217408_at	(↓)
86	MSRB1	methionine sulfoxide reductase B1	217977_at	(↓)
87	MYBL1	v-myb myeloblastosis viral oncogene homolog (avian)-like 1	213906_at	(↑)
88	NAMPT	nicotinamide phosphoribosyltransferase	217739_s_at	(↓)
89	NMI	N-myc (and STAT) interactor	203964_at	(↓)
90	NOL7	nucleolar protein 7, 27kDa	202882_x_at	(↓)
91	NOL7	nucleolar protein 7, 27kDa	210097_s_at	(↓)
92	NOP56	NOP56 ribonucleoprotein homolog (yeast)	200874_s_at	(↓)
93	NQO1	NAD(P)H dehydrogenase, quinone 1	210519_s_at	(↓)
94	NTAN1	N-terminal asparagine amidase	213061_s_at	(↓)
95	NTAN1	N-terminal asparagine amidase	213062_at	(↓)
96	NUDCD3	NudC domain containing 3	201270_x_at	(↑)
97	NXT2	nuclear transport factor 2-like export factor 2	209628_at	(↓)
98	PAIP1	poly(A) binding protein interacting protein 1	209063_x_at	(↓)
99	PAK1	p21 protein (Cdc42/Rac)-activated kinase 1	209615_s_at	(↓)
100	PFN2	profilin 2	204992_s_at	(↑)
101	PHF16	PHD finger protein 16	204866_at	(↓)
102	PIM1	pim-1 oncogene	209193_at	(↓)
103	PIM2	pim-2 oncogene	204269_at	(↓)
104	PLBD1	phospholipase B domain containing 1	218454_at	(↓)
105	POLR1C	polymerase (RNA) I polypeptide C, 30kDa	207515_s_at	(↓)
106	POLR1C	polymerase (RNA) I polypeptide C, 30kDa	209317_at	(↓)
107	POLR3K	polymerase (RNA) III (DNA directed) polypeptide K, 12.3 kDa	218866_s_at	(↓)
108	PPAN	peter pan homolog (Drosophila)	221649_s_at	(↓)
109	PTPN2	protein tyrosine phosphatase, non-receptor type 2	213136_at	(↓)
110	RABAC1	Rab acceptor 1 (prenylated)	203136_at	(↑)
111	RASGRF1	Ras protein-specific guanine nucleotide-releasing factor 1	210550_s_at	(↓)
112	RBM47	RNA binding motif protein 47	218035_s_at	(↓)
113	RDX	radixin	212398_at	(↓)
114	RPP40	ribonuclease P/MRP 40kDa subunit	213427_at	(↓)
115	SEC61B	Sec61 beta subunit	203133_at	(↓)
116	SH3BP5	SH3-domain binding protein 5 (BTK-associated)	201811_x_at	(↓)
117	SLC19A2	solute carrier family 19 (thiamine transporter), member 2	209681_at	(↓)
118	SNRPC	small nuclear ribonucleoprotein polypeptide C	201342_at	(↓)
119	SPRED2	sprouty-related, EVH1 domain containing 2	212458_at	(↑)
120	ST7	suppression of tumorigenicity 7	207871_s_at	(↓)
121	STAP1	signal transducing adaptor family member 1	220059_at	(↑)
122	SUCLG2	succinate-CoA ligase, GDP-forming, beta subunit	214835_s_at	(↓)
123	SYNRG	synergyn, gamma	221937_at	(↑)
124	TGIF1	TGFB-induced factor homeobox 1	203313_s_at	(↓)
125	TIMM17A	translocase of inner mitochondrial membrane 17 homolog A (yeast)	215171_s_at	(↓)

126	TNFRSF13B	tumor necrosis factor receptor superfamily, member 13B	207641_at	(↓)
127	TPM2	tropomyosin 2 (beta)	204083_s_at	(↓)
128	TRAM2	translocation associated membrane protein 2	202369_s_at	(↓)
129	TTC9	tetratricopeptide repeat domain 9	213172_at	(↑)
130	UBB	ubiquitin B	217144_at	(↓)

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