**A Genome-Wide Association Study of Event-Free Survival in Diffuse Large B-cell Lymphoma treated with immunochemotherapy**

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## Supplementary Methods

### Study Patients

***LYSA-03B cohort*.** The LYSA-03B program consisted of six prospective, multicenter studies that included 1704 DLBCL patients aged 18 years and older. Patients were stratified on age and age-adjusted International Prognosis Index (aaIPI) for treatment allocation in four randomized phase III and two phase II studies.[1-5] Detailed treatment data are provided in Table S1. The follow-up of the patients were as follows: during the first 2 years after treatment, assessment consisted of physical examination and laboratory tests every 3 months, and computed tomography (CT) of the chest, abdomen, and pelvis every 6 months; thereafter, physical examination and laboratory tests were done every 6 months and CT every year for five years.

***SPORE-I and SPORE-II cohorts*.** The US cohorts consisted of newly diagnosed DLBCL patients aged 18 years and older prospectively enrolled in the Molecular Epidemiology Resource (MER), a prospective observational study from the University of Iowa/Mayo Clinic Lymphoma Specialized Program of Research Excellence (SPORE).[6] This is an observational study and treatment was selected by each treating physician as part as routine clinical care. The details of the treatments for the SPORE cohorts are presented in Table S1. In the SPORE cohorts, all patients were systematically contacted every 6 months for the first 3 years and then annually thereafter, and all self-reported events were validated against medical records.

***GOELAMS-075 cohort*.** GOELAMS-075 is a prospective, multicenter randomized phase III trial of 340 DLBCL patients.[7] Inclusion criteria were patients aged 18 to 60 years old with Ann Arbor stage I-II and bulky disease ≥7 cm or Ann Arbor stage III-IV. For this study, the subjects consisted of 294 patients with a verified DLBCL diagnosis and available germline DNA. The details of the treatment arms are presented in Table S1. In this trial, the first year of follow-up after treatment consisted of a physical examination and laboratory tests every 3 months, and a

computed tomography (CT) of the chest, abdomen, and pelvis every 6 months. Thereafter, physical examination, laboratory tests and CT-scan were done every 6 months for three years, then annually thereafter.

**Stage 1 (Discovery) Genotyping**

***LYSA-03B GWAS.*** A total of 557,124 SNPs were genotyped with Illumina HapMap 550K Genotyping BeadChips (Illumina, San Diego, USA). SNPs that failed genotyping, monomorphic SNPs, SNPs with more than 2 alleles, and SNPs with call rates <95% were removed, leaving 552,942 SNPs for analysis. The initial LYSA-03B cohort contained 550 patients with GWAS data; 5 patients were excluded after population stratification analysis (PC1>0.08), 1 patient was excluded due to relatedness, and 4 patients were excluded due sex inconsistencies, resulting in 540 patients included in the analysis.

***SPORE-I GWAS.*** A total of 561,278 SNPs were genotyped with Illumina HapMap 660W Genotyping BeadChips (Illumina, San Diego, USA). SNPs that failed genotyping, monomorphic SNPs, SNPs with more than 2 alleles, and SNPs with call rates <95% were removed, leaving 557,093 SNPs for analysis. The initial SPORE-I cohort included 318 patients treated with immunochemotherapy; 2 cases were excluded after population stratification analysis (PC1>0.08) and 4 additional cases were excluded due to missing SNP data from one chromosome, leaving a total of 312 patients for the analysis.

**Genotyping in Stage 2**

***SNP selection.*** Based on the discovery meta-analysis, we ranked the 200 top genotyped or imputed SNPs by *P*-value (Table S2), and then selected 76 SNPs for replication based on *P*-value, MAF>0.05, LD pattern of the SNPs (selecting an additional SNP from the same LD block in case of technical failure), and an Illumina design score ≥0.6. In the same genotyping assay, we included 12 SNPs with potential function that were in LD based on our bioinformatics

analysis (methods below) with the top SNPs (Table S3). Two of the SNPs were selected as potential cis-eQTL SNPs with additional evidence from ENCODE regulatory regions; one SNP was located in a conserved CpG island; one SNP was conserved and was reported in 10 or more ENCODE regulatory regions; two SNPs were conserved and in transcription factor binding sites; and six SNPs were highly conserved and inside EZH2-histone binding sites.

***Genotyping Assays.*** The genotyping of the selected 76 SNPs, plus the 12 functional SNPs and 8 additional SNPs unrelated to this project (total N=96 SNPs), was conducted using the VeraCode Illumina technology 96-well microplates at the Medical Genotyping Facility at Mayo Clinic for both the SPORE-I and SPORE-II samples and at INSERM U918, Centre Henri Becquerel, Rouen, France for the GOELAMS-75 samples. At Mayo, 2 SNPs failed genotyping and one was monomorphic; 3 samples were dropped; the concordance rate of duplicate samples was 100%. At Rouen, 1 SNP failed genotyping; no samples were dropped; the concordance rate of duplicate samples was 100%.

***Technical validation.*** For technical validation, we re-genotyped all SPORE-1 samples for the 96 SNPs, and observed 99.9% concordance between genotypes on the Illumina 660W and the Illumina VeraCode. We used the VeraCode genotypes for the final meta-analysis.

**Bioinformatics**

We used bioinformatics approaches to better understand the potential functional impacts of candidate SNPs, based on the assumption that the SNPs in strong LD with tag SNPs might be the actual functional SNPs. We tested whether the tag SNPs as well all the SNPs in strong LD with the tag SNPs: 1) intersect with genomic regions of evolutionary conservation; 2) intersect with regulatory elements and histone markers sites, as well as transcription factor binding sites (TFBS), silencers and enhancers; 3) whose genotypic alleles correlate with gene expression by mining existing eQTL data sets; and 4) are located within the microRNA-mRNA binding sites.

We downloaded the functional tracks contributed to the UCSC Golden Path (hg19) database from various research projects. The conservation elements calculated by either phastCons or phyloP methods (http://compgen.bscb.cornell.edu/phast/) were used to intersect the SNP locations and identify SNPs located in the conserved regions. The transcription factor binding sites (TFBS) from the BIOBASE's TRANSFAC Suite, and the VISTA Enhancer track (http://enhancer.lbl.gov/) were downloaded from the Golden Path to identify SNPs inside the putative distant-acting transcriptional enhancers. Additional regulatory domain tracks from the ENCODE project (http://genome.ucsc.edu/ENCODE/) were used to find SNPs located in the histone marker sites. We also used the HapMap human lymphoblastoid cell line eQTL data in seeQTL database[8] to categorize both *cis*- and *trans*-effects of the SNPs on gene expression. In addition, the polymorphic sites inside the microRNA-mRNA binding domains were downloaded (http://202.38.126.151/hmdd/mirsnp/download/) and overlapped with the SNPs.

In the first step, we used bioinformatics tools to identify potentially SNPs in linkage disequilibrium (LD) with top SNPs from the discovery meta-analysis (Table S2); Twelve SNPs were identified (Table S8) as potential functional SNPs and included in the replication genotyping. Next, for the top replication SNPs (N=2, Table 2), we updated SNPs in LD with the sentinel SNPs using 1000 Genomes. We identified 20 SNPs on chr6 that were in strong LD ($r^2 \geq 0.7$) with rs7765004, and one SNP on chr5 that was in strong LD with rs7712513 (Table S6). The functional potential of these 23 SNPs are described in the main text.

## Supplementary Tables

**Table S1. Treatments of patients included in the LYSA trials and SPORE cohorts.**

| Study | Age | aaIPI | N | Induction therapy | Consolidation therapy | Clinicaltrials.gov |
|---|---|---|---|---|---|---|
| **Stage 1 (discovery) cohorts** | | | | | | |
| ***LYSA 2003B*** | | | | | | |
| LNH05-1B | 60-65 | all | 3 | R-CHOP-21 X4 | R-CHOP-21 X4 | NCT00135499 |
| LNH03-1B[1] | 18-65 | 0 | 47 | R-ACVBP X3 | SCR | NTC00135499 |
| LNH03-2B[2] | 18-59 | 1 | 127 | R-CHOP-21 X4: 70<br>R-ACVBP X4: 57 | R-CHOP-21 X4<br>SCR | NCT00140595 |
| LNH03-3B[3] | 18-60 | 2-3 | 95 | R-ACVBP X4 | HD-MTX X2, BEAM+ASCT | NCT00144807 |
| LNH03-6B[4] | 60-80 | ≥1 | 209 | R-CHOP-21 X4: 106<br>R-CHOP-14 X4: 103 | R-CHOP-21 X4<br>R-CHOP-14 X4 | NCT00144755 |
| LNH03-7B[5] | ≥80 | all | 59 | R-low-dose-CHOP X6 | | NCT01087424 |
| ***SPORE-I*** | 20-92 | | | | | |
| | | | 274 | R-CHOP-21 | | |
| | | | 19 | ER-CHOP-21 | | |
| | | | 7 | R-CHOP-21 + 90Yttrium-ibritumomab tiuxetan | | |
| | | | 5 | R-EPOCH | | |
| | | | 4 | R-CHOP-21/R-ICE | | |
| | | | 3 | R2-CHOP | | |
| **Stage 2 cohorts** | | | | | | |
| ***GOELAMS-075***[7] | 18-60 | All* | 294 | R-CHOP-14 X4: 154<br>R-CEEP X2, HD-MTX-AraC X2: 140 | R-CHOP-14 X4<br>BEAM+ASCT | NCT 00561379 |
| ***SPORE-II*** | 18-88 | | | | | |
| | | | 327 | R-CHOP-21 | | |
| | | | 32 | R-EPOCH | | |
| | | | 18 | R2-CHOP-21 | | |
| | | | 7 | R-hyperCVAD | | |
| | | | 5 | R-MACOB-B | | |
| | | | 1 | R-CHOP-21/R-ICE | | |
| | | | 1 | R-CHOP-21 + 90Yttrium-ibritumomab tiuxetan | | |

aaIPI denotes age-adjusted IPI; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; CHOP-14 was administered every 14 days and CHOP-21 was administered every 21 days; R-ACVBP, rituximab, cyclophosphamide, doxorubicin, vindesine, bleomycin, prednisone, every 14 days; SCR, sequential consolidative regimen (two cycles of high-dose methotrexate, four cycles of rituximab combined with etoposide and ifosfamide, two cycles of cytarabine; each consolidation being given at 2-week intervals); R-low-dose CHOP, rituximab, cyclophosphamide 400 mg/m$^2$ on day 1, doxorubicin 25 mg/m$^2$ on day 1, vincristine 1 mg on day 1, and prednisone 60 mg/m$^2$ on days 1-5; HD-MTX, high-dose methotrexate; BEAM, BCNU, etoposide, cytarabine, melphalan; ASCT, autologous stem-cell transplantation; R-EPOCH, rituximab, continuous infusion of etoposide, doxorubicin and vincristine, prednisone, cyclophosphamide; R-MACOB-B, rituximab, methotrexate, cyclophosphamide, vincristine, bleomycin and prednisone; ER-CHOP-21, Epratuzumab (360 mg/m$^2$) on day 1 with R-CHOP-21; R-ICE, rituximab, ifosfamide, carboplatine, etoposide; R-HyperCVAD, rituximab, cyclophosphamide, vincristine, doxorubicin, dexamethasone

*Ann Arbor stage I-II with the presence of a bulky disease >7cm or Ann Arbor stage III-IV.

**Supplemental Table 2. Association results for selected SNPs with event-free survival from stage 1 cohorts and meta-analysis, stage 2 cohorts, and final meta-analysis of all cohorts ***

| | | | | | | Stage 1 Cohorts | | | | | | | | Stage 2 Cohorts | | | | | | Final Meta-analysis | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | LYSA 03B | | | SPORE-I | | | Stage 1 Meta | | SPORE-II | | | GOELAMS 075 | | | | | | |
| SNP | Chr | Position | Nearest gene (s) | Effect Allele | Other Allele | MAF | Hazard Ratio | P Value | MAF | Hazard Ratio | P Value | Hazard Ratio | P Value | MAF | Hazard Ratio | P Value | MAF | Hazard Ratio | P Value | Hazard Ratio | (95% | CI) | P Value |
| rs7547204 | 1 | 227560909 | *LOC100130466* | A | G | 0.14 | 1.51 | 0.0017 | 0.11 | 1.53 | 0.021 | 1.52 | 9.87E-05 | 0.12 | 0.71 | 0.077 | 0.12 | 0.44 | 0.018 | 1.18 | 0.99 | 1.42 | 0.062 |
| rs6670816 | 1 | 227610592 | *LOC100130466* | C | A | 0.13 | 1.50 | 0.0028 | 0.10 | 1.73 | 0.0026 | 1.58 | 2.74E-05 | 0.10 | 0.69 | 0.081 | 0.11 | 0.45 | 0.031 | 1.24 | 1.03 | 1.48 | 0.024 |
| rs6682883† | 1 | 227635598 | *BTF3P9* | A | G | 0.12 | 1.48 | 0.0072 | 0.09 | 1.83 | 0.00084 | 1.61 | 2.79E-05 | 0.09 | 0.61 | 0.033 | 0.10 | 0.52 | 0.070 | 1.24 | 1.03 | 1.51 | 0.026 |
| rs951711 | 1 | 240083438 | *CHRM3* | G | A | 0.09 | 1.65 | 0.00040 | 0.11 | 1.29 | 0.13 | 1.50 | 2.26E-04 | 0.10 | 1.27 | 0.22 | 0.10 | 1.23 | 0.46 | 1.42 | 1.19 | 1.69 | 0.00012 |
| rs6547989 | 2 | 30250567 | *ALK* | A | C | 0.45 | 0.78 | 0.024 | 0.46 | 0.71 | 0.0082 | 0.75 | 5.85E-04 | 0.43 | 0.98 | 0.89 | 0.44 | 0.91 | 0.57 | 0.84 | 0.74 | 0.94 | 0.0042 |
| rs17049327 | 2 | 130058565 | *LOC151121* | G | A | 0.34 | 0.68 | 0.0020 | 0.34 | 0.74 | 0.023 | 0.71 | 1.39E-04 | 0.50 | 0.98 | 0.91 | 0.42 | 0.99 | 0.97 | 0.81 | 0.70 | 0.93 | 0.0023 |
| rs13386960 | 2 | 130062954 | *LOC151121* | G | A | 0.34 | 0.68 | 0.0020 | 0.34 | 0.74 | 0.023 | 0.71 | 1.39E-04 | 0.41 | 1.01 | 0.95 | 0.34 | 1.02 | 0.90 | 0.84 | 0.74 | 0.95 | 0.0070 |
| rs4954799 | 2 | 138885880 | *HNMT* | C | A | 0.14 | 1.50 | 0.0043 | 0.13 | 1.72 | 0.0012 | 1.58 | 1.89E-05 | 0.13 | 1.03 | 0.85 | 0.14 | 0.76 | 0.32 | 1.32 | 1.12 | 1.56 | 0.0013 |
| rs7597777 | 2 | 138888963 | *HNMT* | A | C | 0.14 | 1.47 | 0.0068 | 0.13 | 1.77 | 0.0011 | 1.58 | 3.22E-05 | 0.12 | 1.01 | 0.95 | 0.14 | 0.76 | 0.32 | 1.31 | 1.10 | 1.55 | 0.0024 |
| rs1533904 | 2 | 138914802 | *RPL15P5* | T | A | 0.21 | 1.41 | 0.0069 | 0.19 | 1.68 | 0.00038 | 1.52 | 1.22E-05 | 0.20 | 1.00 | 0.99 | 0.21 | 0.84 | 0.46 | 1.27 | 1.09 | 1.47 | 0.0016 |
| rs1522908 | 2 | 138921018 | *RPL15P5* | G | A | 0.21 | 1.41 | 0.0069 | 0.19 | 1.64 | 0.00057 | 1.51 | 1.66E-05 | 0.20 | 1.02 | 0.89 | 0.21 | 0.84 | 0.46 | 1.27 | 1.10 | 1.47 | 0.0014 |
| rs2375751 | 2 | 138924970 | *RPL15P5* | G | A | 0.21 | 1.43 | 0.0049 | 0.19 | 1.68 | 0.00038 | 1.53 | 8.30E-06 | 0.20 | 0.99 | 0.94 | 0.21 | 0.84 | 0.46 | 1.27 | 1.10 | 1.47 | 0.0014 |
| rs1851530 | 2 | 138939202 | *RPL15P5* | A | G | 0.21 | 1.36 | 0.016 | 0.19 | 1.54 | 0.0022 | 1.44 | 1.20E-04 | 0.20 | 1.01 | 0.97 | 0.21 | 0.83 | 0.42 | 1.23 | 1.06 | 1.42 | 0.0057 |
| rs16867434 | 2 | 182359592 | *ITGA4* | G | A | 0.09 | 1.39 | 0.028 | 0.10 | 1.47 | 0.038 | 1.42 | 2.64E-03 | 0.09 | 1.12 | 0.57 | 0.10 | 1.09 | 0.76 | 1.30 | 1.08 | 1.57 | 0.0050 |
| rs6743973 | 2 | 217270093 | *SMARCAL1* | C | G | 0.36 | 0.62 | 0.00020 | 0.34 | 0.77 | 0.046 | 0.69 | 4.57E-05 | 0.34 | 0.98 | 0.90 | 0.38 | 0.96 | 0.82 | 0.80 | 0.70 | 0.92 | 0.0015 |
| rs3755141 | 2 | 217277249 | *SMARCAL1* | A | G | 0.30 | 0.62 | 0.00030 | 0.29 | 0.78 | 0.067 | 0.69 | 1.03E-04 | 0.29 | 0.92 | 0.54 | 0.32 | 1.07 | 0.69 | 0.80 | 0.70 | 0.92 | 0.0022 |
| rs12694650† | 2 | 225897517 | *DOCK10* | A | C | 0.21 | 1.72 | 7.27E-06 | 0.24 | 1.18 | 0.28 | 1.49 | 2.59E-05 | 0.21 | 1.03 | 0.81 | 0.22 | 0.91 | 0.67 | 1.27 | 1.10 | 1.47 | 0.0012 |
| rs9631008 | 2 | 225923560 | *DOCK10* | C | G | 0.18 | 1.78 | 4.79E-06 | 0.23 | 1.16 | 0.34 | 1.50 | 3.17E-05 | 0.19 | 0.95 | 0.75 | 0.18 | 0.86 | 0.51 | 1.25 | 1.07 | 1.45 | 0.0040 |
| rs13423031 | 2 | 225926871 | *DOCK10* | T | A | 0.18 | 1.78 | 4.79E-06 | 0.23 | 1.16 | 0.34 | 1.50 | 3.17E-05 | 0.19 | 0.95 | 0.75 | 0.18 | 0.86 | 0.51 | 1.25 | 1.07 | 1.45 | 0.0040 |
| rs6786870 | 3 | 70268777 | *UQCRHP4* | A | G | 0.05 | 2.26 | 0.00012 | 0.05 | 1.74 | 0.022 | 2.02 | 1.04E-05 | 0.04 | 0.96 | 0.88 | 0.05 | 1.39 | 0.38 | 1.63 | 1.27 | 2.10 | 0.00014 |
| rs7628347 | 3 | 70288359 | *UQCRHP4* | G | A | 0.05 | 2.26 | 0.00012 | 0.05 | 1.96 | 0.0073 | 2.13 | 2.95E-06 | 0.04 | 0.99 | 0.96 | 0.05 | 1.44 | 0.34 | 1.74 | 1.34 | 2.26 | 3.18E-05 |
| **rs9852987** | **3** | **70293612** | ***UQCRHP4*** | **A** | **G** | **0.05** | **2.46** | **2.22E-05** | **0.05** | **2.10** | **0.0030** | **2.30** | **2.54E-07** | 0.04 | 1.00 | 1.00 | 0.05 | 1.35 | 0.43 | 1.78 | 1.38 | 2.30 | 9.87E-06 |
| rs1553090 | 3 | 111180433 | *CD96* | A | G | 0.21 | 1.52 | 0.00014 | 0.20 | 1.26 | 0.089 | 1.41 | 5.70E-05 | 0.24 | 1.13 | 0.40 | 0.22 | 0.89 | 0.57 | 1.27 | 1.11 | 1.45 | 0.00057 |
| rs1391367 | 3 | 111180557 | *CD96* | G | A | 0.21 | 1.51 | 0.00019 | 0.21 | 1.28 | 0.067 | 1.41 | 5.20E-05 | 0.24 | 1.13 | 0.40 | 0.22 | 0.89 | 0.57 | 1.27 | 1.11 | 1.45 | 0.00052 |
| rs1574478 | 3 | 112829996 | *C3orf17* | A | C | 0.42 | 0.74 | 0.0050 | 0.44 | 0.65 | 0.0015 | 0.70 | 2.88E-05 | 0.39 | 1.08 | 0.50 | 0.36 | 1.44 | 0.040 | 0.88 | 0.77 | 0.99 | 0.037 |
| rs7623035 | 3 | 112835265 | *BOC* | A | G | 0.42 | 0.74 | 0.0044 | 0.43 | 0.67 | 0.0021 | 0.71 | 3.36E-05 | 0.39 | 1.07 | 0.56 | 0.35 | 1.42 | 0.048 | 0.87 | 0.77 | 0.99 | 0.032 |
| rs4383482 | 3 | 112844292 | *BOC* | G | C | 0.45 | 0.74 | 0.0049 | 0.46 | 0.71 | 0.0094 | 0.73 | 1.35E-04 | 0.42 | 1.02 | 0.85 | 0.39 | 1.55 | 0.013 | 0.89 | 0.78 | 1.00 | 0.058 |
| rs2602738 | 4 | 24901114 | *CCDC149* | G | A | 0.14 | 1.69 | 8.01E-05 | 0.12 | 1.31 | 0.14 | 1.55 | 4.95E-05 | 0.15 | 0.91 | 0.59 | 0.15 | 0.59 | 0.063 | 1.24 | 1.04 | 1.47 | 0.015 |
| rs4697076 | 4 | 24908601 | *CCDC149* | G | A | 0.14 | 1.69 | 8.01E-05 | 0.12 | 1.31 | 0.14 | 1.55 | 4.95E-05 | 0.15 | 0.91 | 0.59 | 0.15 | 0.59 | 0.063 | 1.24 | 1.04 | 1.47 | 0.015 |
| rs16899823 | 5 | 81957222 | *RPL5P16* | A | G | 0.09 | 1.34 | 0.099 | 0.10 | 2.05 | 0.00023 | 1.62 | 2.28E-04 | 0.09 | 1.20 | 0.35 | 0.10 | 1.36 | 0.19 | 1.45 | 1.20 | 1.76 | 0.00014 |
| **rs7712513** | **5** | **121918208** | ***ARGFXP1*** | **C** | **A** | **0.35** | **1.40** | **0.0016** | **0.34** | **1.46** | **0.0028** | **1.43** | **1.48E-05** | **0.31** | **1.33** | **0.020** | **0.35** | **1.33** | **0.079** | **1.39** | **1.23** | **1.57** | **2.08E-07** |
| rs9384878 | 6 | 113975118 | *LOC100652953* | A | G | 0.37 | 0.69 | 0.0014 | 0.35 | 0.65 | 0.0019 | 0.67 | 9.19E-06 | 0.37 | 0.91 | 0.49 | 0.35 | 0.83 | 0.29 | 0.75 | 0.66 | 0.86 | 3.25E-05 |
| rs62416033† | 6 | 114063850 | *LOC100652953* | A | G | 0.19 | 1.27 | 0.075 | 0.15 | 1.54 | 0.0026 | 1.39 | 7.91E-04 | 0.14 | 1.20 | 0.29 | 0.18 | 1.03 | 0.91 | 1.30 | 1.11 | 1.52 | 0.0011 |
| **rs7765004** | **6** | **114071720** | ***LOC100652953*** | **C** | **A** | **0.33** | **1.34** | **0.0085** | **0.30** | **1.52** | **0.0013** | **1.42** | **4.35E-05** | **0.30** | **1.44** | **0.0030** | **0.32** | **1.14** | **0.48** | **1.38** | **1.22** | **1.57** | **7.09E-07** |
| rs6918103† | 6 | 114077090 | *LOC100652953* | A | G | 0.29 | 1.26 | 0.045 | 0.25 | 1.52 | 0.0022 | 1.37 | 4.46E-04 | 0.25 | 1.47 | 0.0035 | 0.28 | 1.12 | 0.55 | 1.36 | 1.19 | 1.55 | 8.98E-06 |
| rs6923574† | 6 | 114078016 | *LOC100652953* | G | A | 0.29 | 1.26 | 0.045 | 0.25 | 1.52 | 0.0022 | 1.37 | 4.46E-04 | 0.25 | 1.47 | 0.0042 | 0.28 | 1.12 | 0.55 | 1.35 | 1.18 | 1.55 | 1.03E-05 |
| rs11969684 | 6 | 114081600 | *LOC100652953* | A | G | 0.19 | 1.34 | 0.027 | 0.14 | 1.82 | 0.00013 | 1.52 | 3.21E-05 | 0.12 | 1.20 | 0.30 | 0.17 | 1.06 | 0.79 | 1.38 | 1.18 | 1.62 | 8.30E-05 |
| rs6939322 | 6 | 114121484 | *LOC100652953* | A | C | 0.19 | 1.28 | 0.072 | 0.14 | 1.81 | 0.00015 | 1.48 | 1.26E-04 | 0.13 | 1.05 | 0.79 | 0.18 | 1.04 | 0.87 | 1.31 | 1.12 | 1.54 | 0.0010 |
| rs618368 | 6 | 158078716 | *ZDHHC14* | A | G | 0.38 | 0.66 | 0.00034 | 0.43 | 0.76 | 0.036 | 0.71 | 4.76E-05 | 0.39 | 0.99 | 0.95 | 0.41 | 1.01 | 0.97 | 0.82 | 0.72 | 0.93 | 0.0018 |
| rs6944016 | 7 | 138380477 | *RPL17P27* | A | G | 0.06 | 1.75 | 0.0037 | 0.06 | 1.85 | 0.0063 | 1.79 | 6.84E-05 | 0.07 | 0.95 | 0.85 | 0.05 | 0.98 | 0.96 | 1.46 | 1.15 | 1.84 | 0.0017 |
| rs336439 | 8 | 634607 | *ERICH1* | G | A | 0.38 | 0.72 | 0.0038 | 0.34 | 0.65 | 0.0019 | 0.69 | 2.68E-05 | 0.37 | 0.84 | 0.16 | 0.39 | 1.02 | 0.92 | 0.77 | 0.68 | 0.88 | 9.20E-05 |
| rs899144 | 8 | 4508703 | *CSMD1* | A | G | 0.38 | 0.71 | 0.0018 | 0.42 | 0.64 | 0.00063 | 0.68 | 4.69E-06 | 0.39 | 1.04 | 0.74 | 0.36 | 1.01 | 0.95 | 0.81 | 0.71 | 0.92 | 0.0010 |
| rs17202769 | 8 | 59386354 | *CYP7A1* | G | A | 0.18 | 1.51 | 0.0012 | 0.14 | 1.49 | 0.023 | 1.50 | 7.80E-05 | 0.16 | 0.88 | 0.44 | 0.19 | 1.31 | 0.18 | 1.31 | 1.11 | 1.53 | 0.0010 |
| rs17202790 | 8 | 59386544 | *CYP7A1* | A | T | 0.18 | 1.51 | 0.0012 | 0.14 | 1.49 | 0.023 | 1.50 | 7.80E-05 | 0.16 | 0.88 | 0.44 | 0.19 | 1.30 | 0.19 | 1.30 | 1.11 | 1.53 | 0.0011 |
| **rs2035376** | **8** | **72761190** | ***LOC100132891*** | **A** | **G** | **0.32** | **1.57** | **6.90E-05** | **0.27** | **1.58** | **0.0012** | **1.57** | **2.85E-07** | 0.26 | 1.18 | 0.21 | 0.31 | 0.90 | 0.56 | 1.34 | 1.18 | 1.53 | 1.29E-05 |
| **rs6472637** | **8** | **72768125** | ***LOC100132891*** | **G** | **A** | **0.32** | **1.57** | **6.90E-05** | **0.27** | **1.58** | **0.0012** | **1.57** | **2.85E-07** | 0.26 | 1.17 | 0.23 | 0.30 | 0.89 | 0.52 | 1.34 | 1.17 | 1.53 | 1.63E-05 |
| **rs1600797** | **8** | **72784886** | ***LOC100132891*** | **G** | **A** | **0.30** | **1.53** | **0.00019** | **0.28** | **1.71** | **0.00010** | **1.60** | **8.88E-08** | 0.28 | 1.11 | 0.43 | 0.33 | 0.90 | 0.55 | 1.33 | 1.17 | 1.52 | 2.03E-05 |
| **rs9298183** | **8** | **72786073** | ***LOC100132891*** | **G** | **A** | **0.30** | **1.54** | **0.00011** | **0.29** | **1.83** | **1.08E-05** | **1.65** | **7.64E-09** | 0.29 | 1.06 | 0.66 | 0.34 | 0.87 | 0.43 | 1.34 | 1.17 | 1.53 | 1.28E-05 |
| rs10840480 | 11 | 10754380 | *CTR9* | C | A | 0.16 | 0.60 | 0.0028 | 0.16 | 0.53 | 0.0012 | 0.57 | 1.16E-05 | 0.17 | 0.74 | 0.070 | 0.16 | 1.06 | 0.79 | 0.69 | 0.58 | 0.83 | 5.77E-05 |
| rs3794369 | 13 | 23757442 | *SGCG* | A | G | 0.19 | 1.37 | 0.016 | 0.19 | 1.46 | 0.015 | 1.41 | 6.65E-04 | 0.18 | 1.40 | 0.022 | 0.20 | 1.08 | 0.72 | 1.35 | 1.16 | 1.57 | 8.35E-05 |
| rs473598 | 13 | 113801189 | *F10* | A | G | 0.12 | 1.51 | 0.0036 | 0.15 | 1.37 | 0.044 | 1.45 | 4.40E-04 | 0.14 | 1.42 | 0.021 | 0.14 | 0.78 | 0.34 | 1.35 | 1.15 | 1.59 | 0.00023 |
| rs5960 | 13 | 113801737 | *F10* | G | A | 0.12 | 1.57 | 0.0013 | 0.15 | 1.41 | 0.029 | 1.50 | 1.14E-04 | 0.14 | 1.40 | 0.028 | 0.14 | 0.81 | 0.40 | 1.38 | 1.17 | 1.62 | 8.72E-05 |
| rs1263811 | 14 | 21993498 | *SALL2* | G | A | 0.17 | 1.53 | 0.0019 | 0.12 | 1.74 | 0.0010 | 1.61 | 7.59E-06 | 0.14 | 1.02 | 0.90 | 0.17 | 0.82 | 0.43 | 1.33 | 1.13 | 1.57 | 0.00073 |
| rs7140317 | 14 | 33575703 | *NPAS3* | A | C | 0.04 | 1.86 | 0.0031 | 0.03 | 2.24 | 0.0060 | 1.98 | 6.32E-05 | 0.05 | 0.69 | 0.24 | 0.05 | 1.39 | 0.26 | 1.52 | 1.17 | 1.97 | 0.0018 |
| rs17100147† | 14 | 33578139 | *NPAS3* | A | G | 0.05 | 1.79 | 0.0094 | 0.04 | 1.90 | 0.0090 | 1.84 | 2.34E-04 | 0.06 | 0.55 | 0.07 | 0.05 | 1.19 | 0.60 | 1.39 | 1.07 | 1.82 | 0.014 |
| rs7147346† | 14 | 35500702 | *SRP54* | A | G | 0.45 | 0.85 | 0.13 | 0.46 | 0.76 | 0.029 | 0.81 | 9.92E-03 | 0.47 | 0.92 | 0.49 | 0.45 | 1.01 | 0.95 | 0.86 | 0.76 | 0.98 | 0.020 |
| rs2415263 | 14 | 35630319 | *KIAA0391* | C | A | 0.47 | 1.44 | 0.00094 | 0.46 | 1.25 | 0.079 | 1.35 | 2.62E-04 | 0.44 | 1.24 | 0.077 | 0.47 | 1.01 | 0.95 | 1.26 | 1.12 | 1.43 | 0.00020 |
| rs2415267 | 14 | 35630544 | *KIAA0391* | G | A | 0.47 | 1.44 | 0.00094 | 0.46 | 1.25 | 0.079 | 1.35 | 2.62E-04 | 0.44 | 1.25 | 0.065 | 0.46 | 0.97 | 0.88 | 1.26 | 1.11 | 1.42 | 0.00024 |

| | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| rs12436216† | 14 | 35809414 | *PSMA6* | A | G | 0.41 | 0.71 | 0.0022 | 0.44 | 0.94 | 0.64 | 0.80 | 8.71E-03 | 0.43 | 0.85 | 0.19 | 0.40 | 1.05 | 0.76 | 0.85 | 0.75 | 0.96 |
| rs17826697 | 14 | 95137473 | *LOC100288028* | C | A | 0.49 | 1.58 | 1.63E-05 | 0.43 | 1.14 | 0.30 | 1.37 | 8.28E-05 | 0.45 | 0.91 | 0.44 | 0.38 | 1.15 | 0.31 | 1.20 | 1.06 | 1.35 |
| rs12441380 | 15 | 94864581 | *MCTP2* | A | G | 0.22 | 1.40 | 0.0078 | 0.20 | 1.71 | 0.00045 | 1.51 | 1.86E-05 | 0.19 | 1.00 | 0.98 | 0.22 | 0.91 | 0.66 | 1.29 | 1.11 | 1.50 |
| rs11852581 | 15 | 94866804 | *MCTP2* | A | C | 0.23 | 1.40 | 0.0072 | 0.21 | 1.60 | 0.0020 | 1.48 | 5.38E-05 | 0.21 | 1.09 | 0.57 | 0.22 | 0.95 | 0.79 | 1.29 | 1.11 | 1.49 |
| rs11075189† | 16 | 13432963 | *SHISA9* | A | G | 0.52 | 1.56 | 5.98E-05 | 0.47 | 1.32 | 0.022 | 1.45 | 6.25E-06 | 0.45 | 0.86 | 0.20 | 0.51 | 1.01 | 0.97 | 1.19 | 1.05 | 1.34 |
| rs12598965 | 16 | 13438488 | *SHISA9* | A | G | 0.52 | 1.55 | 7.21E-05 | 0.47 | 1.28 | 0.043 | 1.42 | 1.71E-05 | 0.45 | 0.88 | 0.30 | 0.51 | 1.01 | 0.96 | 1.18 | 1.05 | 1.34 |
| rs11643620† | 16 | 20729699 | *THUMPD1* | A | G | 0.12 | 1.46 | 0.018 | 0.13 | 1.61 | 0.0043 | 1.53 | 2.31E-04 | 0.13 | 0.86 | 0.40 | 0.13 | 1.14 | 0.58 | 1.28 | 1.07 | 1.52 |
| rs16970587 | 16 | 20740517 | *THUMPD1* | A | G | 0.12 | 1.46 | 0.018 | 0.13 | 1.61 | 0.0043 | 1.53 | 2.31E-04 | 0.13 | 0.86 | 0.40 | 0.13 | 1.14 | 0.58 | 1.28 | 1.07 | 1.52 |
| rs3815019† | 16 | 20916286 | *DCUN1D3* | A | G | 0.06 | 1.14 | 0.58 | 0.08 | 1.41 | 0.086 | 1.29 | 9.55E-02 | 0.08 | 0.69 | 0.14 | 0.09 | 1.29 | 0.35 | 1.12 | 0.89 | 1.41 |
| rs41137 | 16 | 55430314 | *RPL31P56* | A | G | 0.07 | 2.04 | 8.30E-05 | 0.06 | 1.45 | 0.14 | 1.82 | 5.01E-05 | 0.05 | 0.94 | 0.83 | 0.07 | 0.60 | 0.22 | 1.45 | 1.13 | 1.85 |
| rs243858 | 16 | 55457621 | *MMP2* | A | G | 0.08 | 1.82 | 0.00053 | 0.07 | 1.53 | 0.076 | 1.71 | 1.18E-04 | 0.06 | 1.02 | 0.94 | 0.07 | 0.69 | 0.32 | 1.40 | 1.12 | 1.76 |
| rs243857 | 16 | 55458156 | *MMP2* | C | G | 0.04 | 2.08 | 0.0011 | 0.03 | 1.40 | 0.29 | 1.83 | 1.02E-03 | 0.02 | 0.84 | 0.72 | 0.03 | 0.17 | 0.082 | 1.56 | 1.12 | 2.18 |
| rs2253971 | 16 | 55910804 | *CES5A* | G | A | 0.29 | 1.42 | 0.0025 | 0.33 | 1.57 | 0.00078 | 1.49 | 7.25E-06 | 0.28 | 1.03 | 0.83 | 0.35 | 1.12 | 0.52 | 1.28 | 1.13 | 1.46 |
| rs2253986 | 16 | 55911022 | *CES5A* | A | C | 0.29 | 1.44 | 0.0015 | 0.32 | 1.53 | 0.0017 | 1.48 | 8.59E-06 | 0.27 | 1.01 | 0.94 | 0.33 | 1.19 | 0.35 | 1.29 | 1.13 | 1.47 |
| rs6499810† | 16 | 55979981 | *CES5A* | A | G | 0.32 | 1.32 | 0.018 | 0.35 | 1.55 | 0.00091 | 1.41 | 7.09E-05 | 0.31 | 1.02 | 0.89 | 0.37 | 1.07 | 0.70 | 1.24 | 1.09 | 1.41 |
| rs8082455 | 17 | 14299892 | *HS3ST3B1* | A | G | 0.30 | 1.44 | 0.00054 | 0.29 | 1.20 | 0.16 | 1.34 | 3.46E-04 | 0.26 | 1.06 | 0.66 | 0.28 | 0.85 | 0.41 | 1.20 | 1.06 | 1.37 |
| rs9954200 | 18 | 24424005 | *AQP4* | C | G | 0.30 | 0.81 | 0.078 | 0.32 | 0.53 | 8.36E-06 | 0.69 | 3.07E-05 | 0.30 | 0.96 | 0.75 | 0.33 | 0.69 | 0.046 | 0.76 | 0.66 | 0.87 |
| rs3763043 | 18 | 24435818 | *AQP4* | A | G | 0.30 | 0.82 | 0.086 | 0.32 | 0.54 | 0.000014 | 0.69 | 4.88E-05 | 0.30 | 0.99 | 0.91 | 0.34 | 0.71 | 0.068 | 0.77 | 0.67 | 0.88 |
| rs17056997 | 18 | 73120936 | *C18orf62* | G | C | 0.08 | 1.85 | 0.00026 | 0.11 | 1.26 | 0.20 | 1.55 | 3.91E-04 | 0.09 | 0.63 | 0.06 | 0.10 | 0.81 | 0.49 | 1.22 | 1.00 | 1.49 |
| rs17057005 | 18 | 73123275 | *C18orf62* | A | G | 0.09 | 1.79 | 0.00054 | 0.11 | 1.25 | 0.21 | 1.51 | 7.26E-04 | 0.09 | 0.68 | 0.10 | 0.10 | 0.77 | 0.41 | 1.20 | 0.99 | 1.47 |
| rs12327156 | 18 | 73207329 | *C18orf62* | C | G | 0.07 | 2.28 | 1.69E-06 | 0.09 | 1.26 | 0.23 | 1.74 | 1.33E-05 | 0.07 | 0.73 | 0.23 | 0.09 | 0.91 | 0.75 | 1.39 | 1.12 | 1.71 |
| rs4243295 | 18 | 73210566 | *C18orf62* | G | A | 0.07 | 2.28 | 1.69E-06 | 0.09 | 1.24 | 0.25 | 1.73 | 1.60E-05 | 0.07 | 0.73 | 0.23 | 0.09 | 0.91 | 0.75 | 1.38 | 1.12 | 1.71 |
| rs4305166 | 18 | 73241222 | *C18orf62* | A | G | 0.08 | 1.73 | 0.00029 | 0.11 | 1.26 | 0.19 | 1.51 | 3.23E-04 | 0.08 | 0.83 | 0.43 | 0.09 | 0.81 | 0.51 | 1.28 | 1.06 | 1.55 |
| rs3923116 | 18 | 73284997 | *LOC100505853* | A | G | 0.06 | 1.96 | 2.51E-05 | 0.08 | 1.28 | 0.26 | 1.70 | 4.50E-05 | 0.06 | 0.87 | 0.59 | 0.12 | 0.99 | 0.97 | 1.33 | 1.10 | 1.62 |
| rs952057 | 18 | 73285585 | *LOC100505853* | A | G | 0.06 | 1.96 | 2.51E-05 | 0.08 | 1.28 | 0.26 | 1.70 | 4.50E-05 | 0.07 | 0.89 | 0.55 | 0.07 | 1.08 | 0.79 | 1.36 | 1.11 | 1.66 |
| rs6046975 | 20 | 20619306 | *RALGAPA2* | G | A | 0.10 | 1.84 | 8.27E-05 | 0.09 | 1.40 | 0.080 | 1.65 | 3.13E-05 | 0.13 | 0.99 | 0.96 | 0.11 | 0.81 | 0.47 | 1.33 | 1.10 | 1.60 |
| rs5957334 | 23 | 119343783 | *EEF1A1P30* | G | A | 0.07 | 1.31 | 0.048 | 0.05 | 2.49 | 7.10E-07 | 1.64 | 5.78E-06 | 0.08 | 1.07 | 0.71 | 0.06 | 0.67 | 0.27 | 1.39 | 1.16 | 1.65 |

*SNPs in bold were either P<5x10$^{-7}$ in either the stage 1 meta-analysis or the final meta-analysis

†Selected based on bioinformatics annotation for potential function

**Table S3. Sensitivity analyses for top SNPs**

| SNP | Endpoint | Model | HR | 95% CI | LR chisq | *P* |
|---|---|---|---|---|---|---|
| rs7712513 | EFS | Meta-analysis (current) | 1.39 | 1.23-1.57 | | 2.08E-07 |
| | EFS | Pooled analysis, adjusted for age, sex, aaIPI, study and treatment | 1.39 | 1.23-1.57 | 26.87 | 2.18E-07 |
| | EFS | Pooled analysis, R-CHOP treated only, adjusted for age, sex, aaIPI | 1.41 | 1.24-1.61 | 25.29 | 4.93E-07 |
| | OS | Meta-analysis (current) | 1.49 | 1.29-1.72 | | 3.53E-08 |
| | OS | Pooled analysis, adjusted for age, sex, aaIPI, study and treatment | 1.50 | 1.30-1.73 | 30.8 | 2.86E-08 |
| | OS | Pooled analysis, R-CHOP treated only, adjusted for age, sex, aaIPI | 1.53 | 1.31-1.79 | 28.6 | 8.90E-08 |
| rs7765004 | EFS | Meta-analysis (current) | 1.38 | 1.22-1.57 | | 7.09E-07 |
| | EFS | Pooled analysis, adjusted for age, sex, aaIPI, study and treatment | 1.39 | 1.22-1.58 | 24.12 | 9.05E-07 |
| | EFS | Pooled analysis, R-CHOP treated only, adjusted for age, sex, aaIPI | 1.39 | 1.20-1.60 | 19.15 | 1.21E-05 |
| | OS | Meta-analysis (current) | 1.47 | 1.27-1.71 | | 5.36E-07 |
| | OS | Pooled analysis, adjusted for age, sex, aaIPI, study and treatment | 1.47 | 1.26-1.70 | 24 | 9.63E-07 |
| | OS | Pooled analysis, R-CHOP treated only, adjusted for age, sex, aaIPI | 1.43 | 1.21-1.69 | 16.8 | 4.15E-05 |

**Table S4. Association of the two-risk model SNPs at 5q23.2 (rs7712513) and 6q21(rs7765004) with EFS for pooled cohorts**

| | All (N=1,537) | | | aaIPI 0-1 (N=801) | | | aaIPI 2-3 (N=736) | | |
|---|---|---|---|---|---|---|---|---|---|
| Risk Alleles | N | Events | HR (95% CI)* | N | Events | HR (95% CI)** | N | Events | HR (95% CI)** |
| 0 | 318 | 84 | 1.00 (Ref.) | 174 | 37 | 1.00 (Ref) | 144 | 47 | 1.00 (Ref) |
| 1 | 606 | 188 | 1.23 (0.95 - 1.59) | 309 | 72 | 1.03 (0.69 - 1.54) | 297 | 116 | 1.29 (0.92 - 1.81) |
| 2 | 450 | 171 | 1.72 (1.32 - 2.23) | 238 | 65 | 1.36 (0.91 - 2.05) | 212 | 106 | 1.88 (1.33 - 2.64) |
| 3+ | 163 | 86 | 2.76 (2.03 - 3.73) | 80 | 28 | 1.63 (1.00 - 2.67) | 83 | 58 | 3.60 (2.44 - 5.31) |
| P trend test | | | $1.78 \times 10^{-12}$ | | | 0.02 | | | $1.09 \times 10^{-11}$ |
| Per Risk Allele | | | 1.40 (1.28 - 1.54)* | | | 1.20 (1.03 - 1.39)** | | | 1.53 (1.35 - 1.73)** |

* Proportional Hazards model controlled for age, sex, aaIPI, study and treatment.

** Proportional Hazards model controlled for age and sex, study and treatment.

**Table S5. Correlation between the two SNP genotypes at 5q23.2 and 6q21 and tumor gene expression for 73 LYSA-03B patients with corresponding GWAS and GEP**

| rs | Chr | Position | Assembly | Candidate genes | Distance | Probeset* | P value† | P value‡ |
|---|---|---|---|---|---|---|---|---|
| rs7712513 | 5 | 121,918,208 | GRCh37.p10 | *MGC32805* | 103,426 | 1554781_at | **0.013** | **0.0032** |
| rs7712513 | 5 | 121,918,208 | GRCh37.p10 | *PPIC* | 440,870 | 204518_s_at | **0.014** | **0.029** |
| rs7712513 | 5 | 121,918,208 | GRCh37.p10 | *LOC100505841* | 399,850 | 231434_at | **0.034** | **0.010** |
| rs7712513 | 5 | 121,918,208 | GRCh37.p10 | *ZNF474* | 428,942 | 1556907_at | 0.065 | |
| rs7712513 | 5 | 121,918,208 | GRCh37.p10 | *PPIC* | 440,870 | 204517_at | 0.070 | |
| rs7712513 | 5 | 121,918,208 | GRCh37.p10 | *SNX2* | 192,483 | 202113_s_at | 0.26 | |
| rs7712513 | 5 | 121,918,208 | GRCh37.p10 | *SNX2* | 192,483 | 202114_at | 0.28 | |
| rs7712513 | 5 | 121,918,208 | GRCh37.p10 | *SNX24* | 262,941 | 239693_at | 0.28 | |
| rs7712513 | 5 | 121,918,208 | GRCh37.p10 | *SNX2* | 192,483 | 232049_at | 0.65 | |
| rs7712513 | 5 | 121,918,208 | GRCh37.p10 | *SNCAIP* | 118,414 | 219511_s_at | 0.70 | |
| rs7712513 | 5 | 121,918,208 | GRCh37.p10 | *LOC101927379* | 46,439 | 1562801_at | 0.73 | |
| rs7712513 | 5 | 121,918,208 | GRCh37.p10 | *SNCAIP* | 118,414 | 237833_s_at | 0.97 | |
| rs7712513 | 5 | 121,918,208 | GRCh37.p10 | *SNX24* | 262,941 | 218705_s_at | 0.99 | |
| rs7712513 | 5 | 121,918,208 | GRCh37.p10 | *SNX24* | 262,941 | 222716_s_at | 0.99 | |
| rs7712513 | 5 | 121,918,208 | GRCh37.p10 | *LOC101927357* | 1,014 | No probeset | | |
| rs7712513 | 5 | 121,918,208 | GRCh37.p10 | *ARGFXP1* | 93,187 | No probeset | | |
| rs7712513 | 5 | 121,918,208 | GRCh37.p10 | *LOC101927328* | 259,155 | No probeset | | |
| rs7765004 | 6 | 114,071,720 | GRCh37.p10 | *LOC101927794* | 365,565 | 1559620_at | **0.037** | 0.11 |
| rs7765004 | 6 | 114,071,720 | GRCh37.p10 | *HDAC2* | 185,600 | 201833_at | **0.045** | **0.020** |
| rs7765004 | 6 | 114,071,720 | GRCh37.p10 | *HS3ST5* | 305,030 | 240479_at | 0.072 | |
| rs7765004 | 6 | 114,071,720 | GRCh37.p10 | *MARCKS* | 106,807 | 201668_x_at | 0.41 | |
| rs7765004 | 6 | 114,071,720 | GRCh37.p10 | *MARCKS* | 106,807 | 225897_at | 0.44 | |
| rs7765004 | 6 | 114,071,720 | GRCh37.p10 | *MARCKS* | 106,807 | 201669_s_at | 0.58 | |
| rs7765004 | 6 | 114,071,720 | GRCh37.p10 | *LOC285758* | 117,458 | 1557359_at | 0.68 | |
| rs7765004 | 6 | 114,071,720 | GRCh37.p10 | *MARCKS* | 106,807 | 201670_s_at | 0.71 | |
| rs7765004 | 6 | 114,071,720 | GRCh37.p10 | *HDAC2* | 185,600 | 242141_at | 0.93 | |
| rs7765004 | 6 | 114,071,720 | GRCh37.p10 | *FLJ34503* | 153,831 | 1553448_at | 0.94 | |
| rs7765004 | 6 | 114,071,720 | GRCh37.p10 | *RPL30P8* | 79,305 | No probeset | | |
| rs7765004 | 6 | 114,071,720 | GRCh37.p10 | *LOC101927686* | 95,997 | No probeset | | |
| rs7765004 | 6 | 114,071,720 | GRCh37.p10 | *RPS27AP11* | 168,519 | No probeset | | |
| rs7765004 | 6 | 114,071,720 | GRCh37.p10 | *LOC101927768* | 241,337 | No probeset | | |
| rs7765004 | 6 | 114,071,720 | GRCh37.p10 | *NUDT19P3* | 269,493 | No probeset | | |
| rs7765004 | 6 | 114,071,720 | GRCh37.p10 | *RPSAP43* | 333,643 | No probeset | | |
| rs7765004 | 6 | 114,071,720 | GRCh37.p10 | *RNA5SP213* | 470,125 | No probeset | | |

*All probesets annotated to a gene located at less than 500 kb from the SNP location according to the NCBI Gene database were considered.

†The difference of expression between the three genotypes was evaluated by Kruskal-Wallis test.

‡Wilcoxon test evaluated the differential expression between the two genotypes for significant results with a P value<0.05 with Kruskal-Wallis test.

**Table S6. Bioinformatics Summary of Selected SNPs**

| SNPs in LD with rs7765004 | chr | Genome Position | DPRIME | DELTASQ | Evolutionary Conserved | Conserved Transcription Factor Binding Sites | Potental Histone Marker Sites in ENCODE | eQTL target Genes in seeQTL | microRNA Binding Sites |
|---|---|---|---|---|---|---|---|---|---|
| SNPs in LD with rs7765004 | | | | | | | | | |
| rs55705700 | chr6 | 114068514 | 1.00 | 0.876 | - | - | YES | - | - |
| **rs7765004** | chr6 | 114071720 | - | - | - | - | YES | *MARCKS* | - |
| rs9387174 | chr6 | 114073471 | 1.00 | 0.942 | - | - | YES | - | - |
| rs9374426 | chr6 | 114074366 | 1.00 | 1.000 | - | - | YES | - | - |
| rs9387176 | chr6 | 114074493 | 1.00 | 1.000 | - | - | YES | - | - |
| rs9372374 | chr6 | 114074659 | 1.00 | 1.000 | - | - | YES | - | - |
| 114074913 | chr6 | 114074913 | 1.00 | 0.823 | - | - | YES | - | - |
| rs9372375 | chr6 | 114074915 | 1.00 | 0.898 | - | - | YES | - | - |
| rs9374427 | chr6 | 114074916 | 1.00 | 0.898 | - | - | YES | - | - |
| rs9372376 | chr6 | 114074965 | 1.00 | 0.988 | - | - | YES | - | - |
| 114075203 | chr6 | 114075203 | 0.98 | 0.942 | - | - | YES | - | - |
| rs9400667 | chr6 | 114075819 | 1.00 | 1.000 | - | - | YES | - | - |
| rs6940434 | chr6 | 114076884 | 1.00 | 0.887 | - | - | YES | - | - |
| rs6918103 | chr6 | 114077090 | 1.00 | 0.887 | Yes | - | YES | - | - |
| rs9384882 | chr6 | 114077332 | 1.00 | 0.887 | - | - | YES | - | - |
| rs6923574 | chr6 | 114078016 | 1.00 | 0.887 | - | Yes | YES | *MARCKS* | - |
| rs7760821 | chr6 | 114078403 | 1.00 | 0.887 | - | - | YES | - | - |
| rs4496829 | chr6 | 114079720 | 1.00 | 0.887 | - | - | YES | - | - |
| rs4574672 | chr6 | 114079778 | 1.00 | 0.887 | - | - | YES | - | - |
| rs6568807 | chr6 | 114082542 | 1.00 | 0.887 | - | - | YES | - | - |
| rs954621 | chr6 | 114082720 | 1.00 | 0.887 | - | - | YES | - | - |
| SNPs in LD with rs7712513 | | | | | | | | | |
| **rs7712513** | chr5 | 121918208 | - | - | - | - | - | - | - |
| rs10477635 | chr5 | 121914456 | 0.95 | 0.904 | - | - | - | - | - |

**Table S7. Association of previously published SNPs for DLBCL outcome in the first stage meta-analysis GWAS**

| | | | | Allele | | LYSA-03B | | | SPORE-I | | | Combined |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| SNP | Chr | Position | Nearest Gene | Effect | Other | HR | 95%CI | P value | HR | 95%CI | P value | P value |
| rs5361 | 1 | 169701060 | *SELE* | T | G | 1.19 | (0.83-1.55) | 0.34 | 1.45 | (0.97-1.93) | 0.13 | 0.09 |
| rs1800896 | 1 | 206946897 | *IL10* | T | C | 1.12 | (0.91-1.32) | 0.29 | 1.14 | (0.89-1.39) | 0.30 | 0.14 |
| rs1800587 | 2 | 113542960 | *IL1A* | A | G | 1.20 | (0.95-1.46) | 0.15 | 1.09 | (0.82-1.37) | 0.53 | 0.13 |
| rs1126580 | 2 | 219000966 | *CXCR2* | A | G | 0.98 | (0.77-1.19) | 0.84 | 0.72 | (0.48-0.97) | 0.01 | 0.08 |
| rs1799977 | 3 | 37053568 | *MLH1:RPL29P11* | A | G | 1.16 | (0.93-1.38) | 0.20 | 0.79 | (0.53-1.04) | 0.07 | 0.92 |
| rs1870377 | 4 | 55972974 | *VEGFR2:KDR* | A | T | 1.20 | (0.92-1.47) | 0.20 | 1.13 | (0.82-1.44) | 0.43 | 0.14 |
| rs324058 | 5 | 40961894 | *C7* | A | C | 0.99 | (0.74-1.24) | 0.94 | 0.91 | (0.64-1.19) | 0.51 | 0.65 |
| rs585800 | 5 | 78427208 | *BHMT* | A | T | 1.13 | (0.87-1.38) | 0.36 | 1.07 | (0.79-1.35) | 0.64 | 0.31 |
| rs1056503 | 5 | 82648977 | *XRCC4* | T | G | 0.94 | (0.63-1.25) | 0.70 | 1.11 | (0.73-1.49) | 0.59 | 0.99 |
| rs909253 | 6 | 31540313 | *LTA:LOC100287329:LTB:TNF* | A | G | | | | 0.99 | (0.73-1.25) | 0.92 | 0.92 |
| rs1800629 | 6 | 31543031 | *LTB:TNF:LTA:LOC100287329* | A | G | | | | 0.83 | (0.52-1.14) | 0.25 | 0.25 |
| rs1800796 | 7 | 22766246 | *LOC541472:IL6* | C | G | 1.21 | (0.73-1.69) | 0.43 | 1.37 | (0.81-1.93) | 0.27 | 0.19 |
| rs3087554 | 8 | 27455442 | *CLU:GULOP* | T | C | 1.01 | (0.63-1.38) | 0.97 | 1.16 | (0.74-1.57) | 0.49 | 0.65 |
| rs10508293 | 10 | 5141137 | *AKR1C3* | A | G | 1.15 | (0.84-1.45) | 0.38 | 1.01 | (0.68-1.35) | 0.94 | 0.46 |
| rs526934 | 11 | 59633493 | *TCN1* | A | G | 1.03 | (0.74-1.33) | 0.83 | 1.17 | (0.83-1.52) | 0.37 | 0.47 |
| rs1979276 | 17 | 18231998 | *SHMT1:SMCR8* | A | G | 0.89 | (0.67-1.11) | 0.28 | 1.04 | (0.78-1.29) | 0.78 | 0.50 |
| rs16942 | 17 | 41244000 | *BRCA1* | T | C | 1.16 | (0.95-1.37) | 0.16 | 0.98 | 0.72-1.24) | 0.89 | 0.31 |
| rs2243828 | 17 | 56358884 | *MPO* | A | G | 0.76 | (0.52-1.00) | 0.03 | 1.03 | (0.71-1.35) | 0.86 | 0.11 |
| rs13181 | 19 | 45854919 | *ERCC2:KLC3* | T | G | 1.20 | (0.97-1.42) | 0.12 | 0.98 | (0.74-1.21) | 0.84 | 0.26 |
| rs1883112 | 22 | 37256846 | *NCF4* | A | G | 0.98 | (0.76-1.19) | 0.83 | 1.25 | (1.00-1.50) | 0.08 | 0.38 |

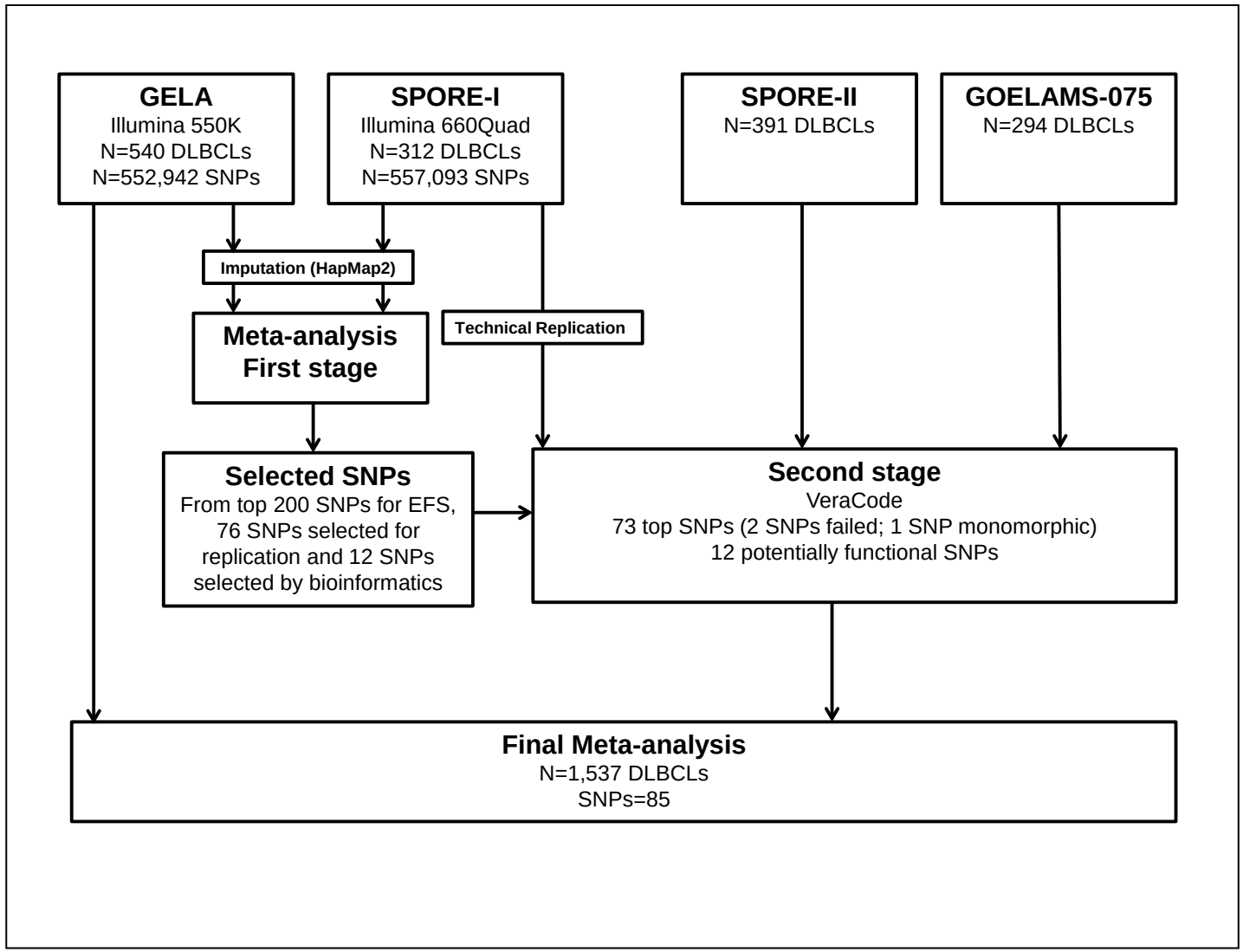
**Table S8. Potentially functional SNPs* included in the second stage**

| Sentinel SNP | Potentially Functional SNP | Chr | Position | $r^2$ | Nearest gene (s) | Bioinformatics selection |
|---|---|---|---|---|---|---|
| rs6670816 | rs6682883 | 1 | 227635598 | 0.82 | *BTF3P9* | Conserved CpG Island |
| rs9631008 | rs12694650 | 2 | 225897517 | 0.81 | *DOCK10* | EZH2 Histone Binding Sites |
| rs6939322 | rs62416033 | 6 | 114063850 | 0.83 | *LOC100652953* | EZH2 Histone Binding Sites |
| rs11969684 | rs6918103 | 6 | 114077090 | 0.55 | *LOC100652953* | EZH2 Histone Binding Sites |
| rs7765004 | rs6923574 | 6 | 114078016 | 0.87 | *LOC100652953* | cis-eQTL and ENCODE Regulatory |
| rs7140317 | rs17100147 | 14 | 33578139 | 0.87 | *NPAS3* | Conserved, TFBS Sites |
| rs2415263 | rs7147346 | 14 | 35500702 | 0.57 | *SRP54* | cis-eQTL and ENCODE Regulatory |
| rs2415267 | rs12436216 | 14 | 35809414 | 0.55 | *PSMA6* | Conserved, >=10 ENCODE |
| rs12598965 | rs11075189 | 16 | 13432963 | 0.95 | *SHISA9* | EZH2 Histone Binding Sites |
| rs16970587 | rs11643620 | 16 | 20729699 | 0.99 | *THUMPD1* | Conserved, TFBS Sites |
| rs16970587 | rs3815019 | 16 | 20916286 | 0.53 | *DCUN1D3* | EZH2 Histone Binding Sites |
| rs2253971 | rs6499810 | 16 | 55979981 | 0.83 | *CES5A* | EZH2 Histone Binding Sites |

*Sentinel SNP is a top SNP in the first stage which was selected for the second stage.

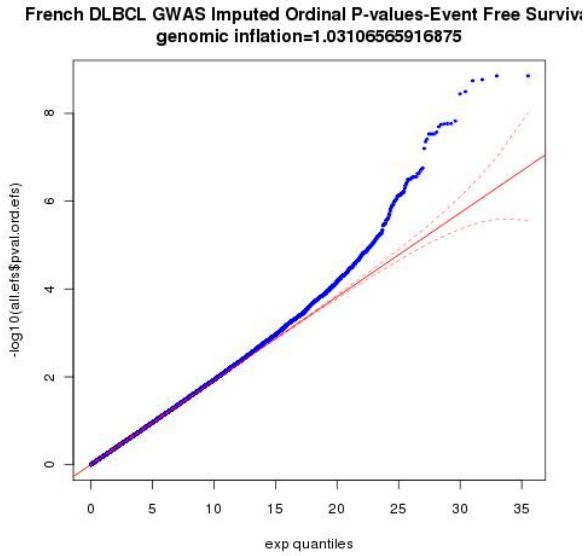
## SUPPLEMENTARY FIGURES

**Figure S1.** Flowchart of Study Design



**Supplementary Figure 2.** Q-Q plots for the GWAS analyses for event-free survival

## 2A. LYSA-03B GWAS




## 2B. SPORE-I GWAS

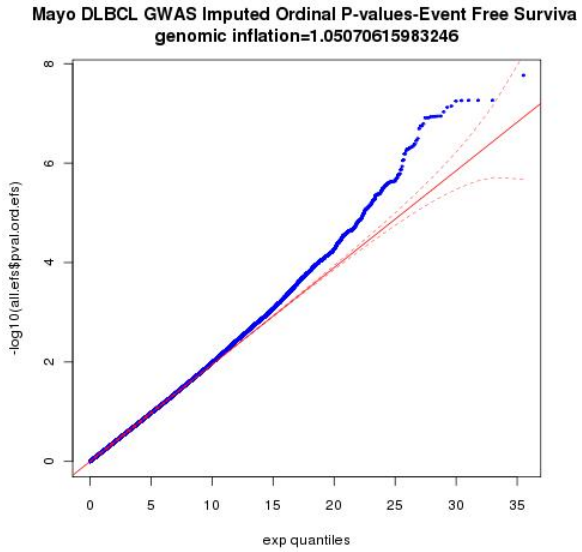
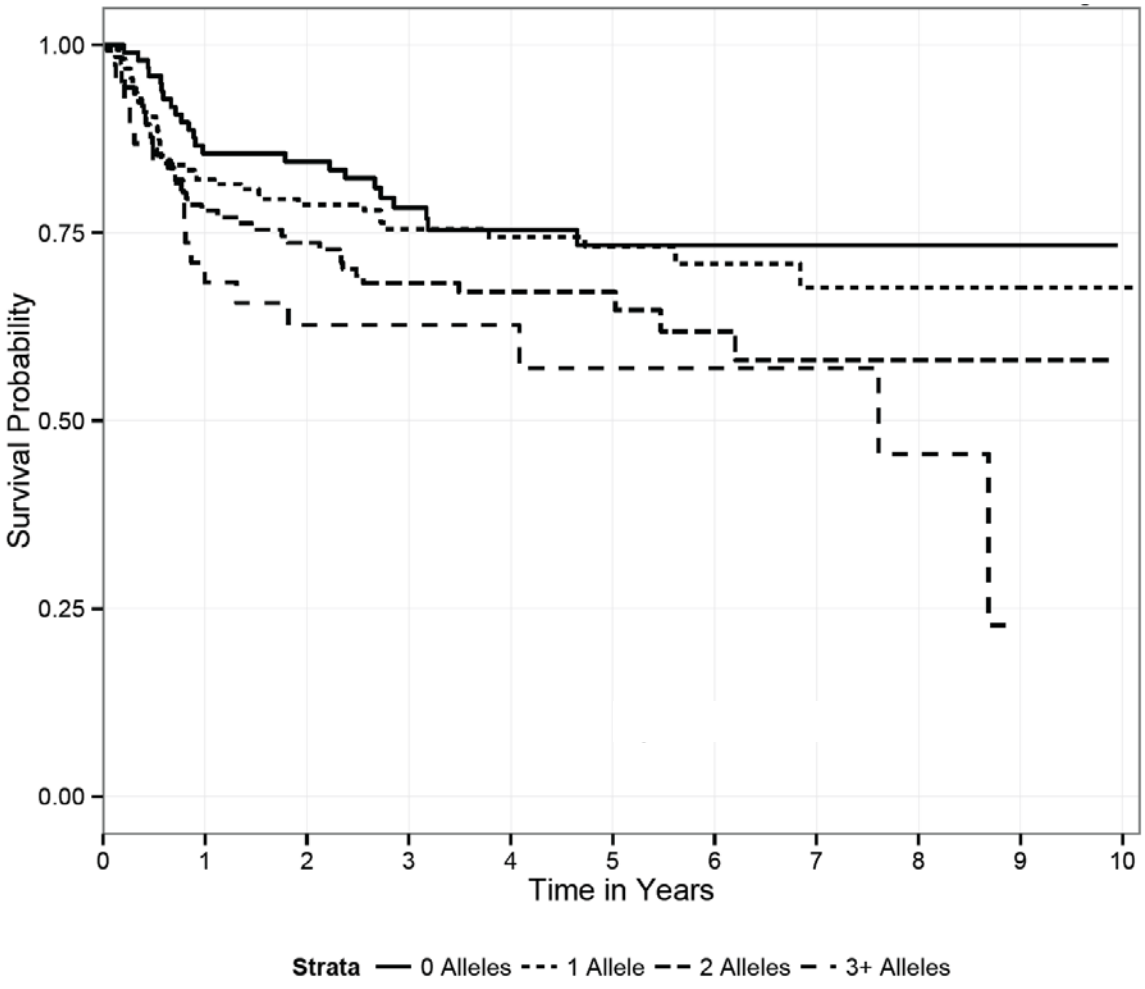


**Figure S3.** Multi-SNP risk score for event-free survival, pooled analysis of all 4 cohorts.

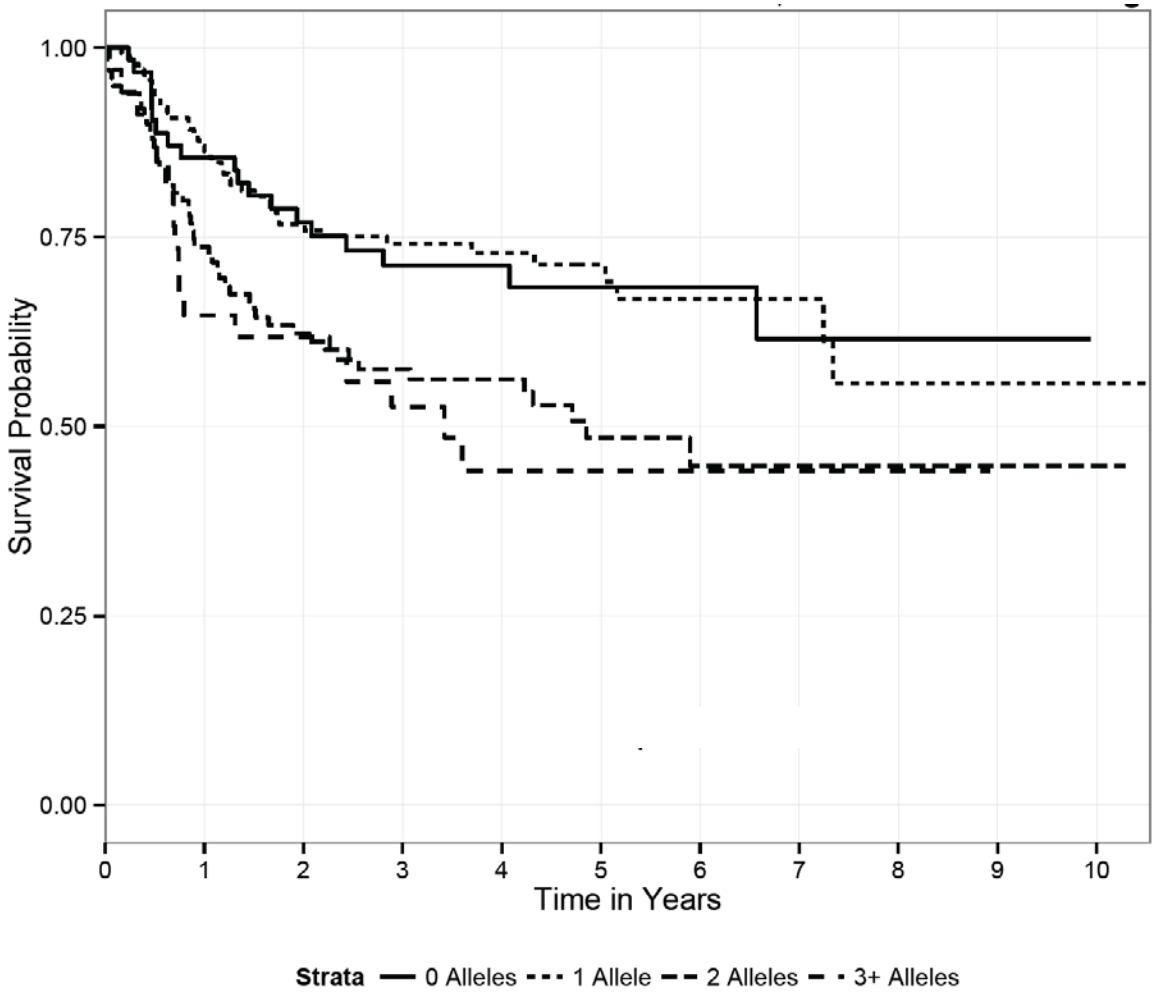
**S3A.** Patients with DLBCL of GCB origin. *P*=0.036 from the log-rank test; *P*=0.001 from the Cox model (adjusted for age, sex and aaIPI).




| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **3+ Alleles** | 38 | 26 | 20 | 16 | 11 | 7 | 7 | 5 | 2 | 0 | 0 |
| **2 Alleles** | 123 | 95 | 85 | 65 | 49 | 28 | 17 | 8 | 4 | 3 | 0 |
| **1 Allele** | 157 | 128 | 112 | 83 | 63 | 45 | 27 | 17 | 8 | 2 | 1 |
| **0 Alleles** | 97 | 82 | 77 | 55 | 43 | 29 | 19 | 10 | 5 | 1 | 0 |

Numbers at risk

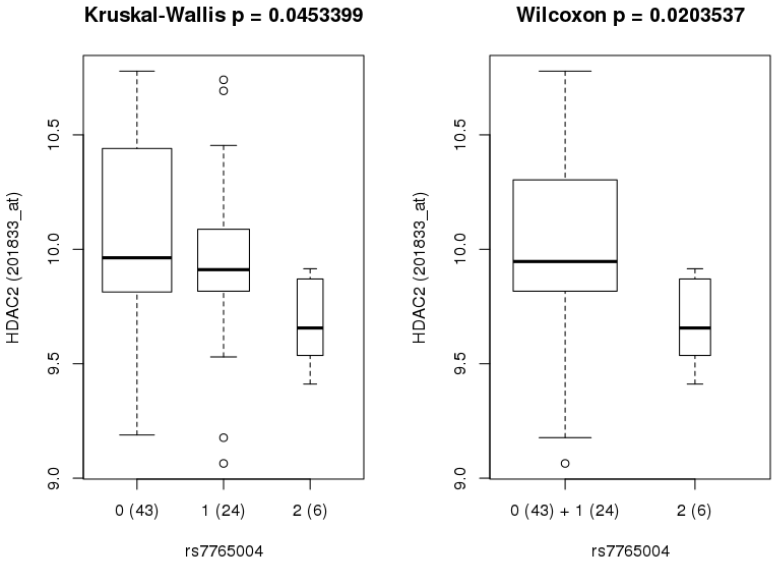
**S3B.** Patients with DLBCL of non-GCB origin. *P*=0.0034 from the log-rank test; *P*=0.020 from the Cox model (adjusted for age and sex).




| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **3+ Alleles** | 34 | 22 | 21 | 16 | 8 | 5 | 2 | 2 | 1 | 0 | 0 |
| **2 Alleles** | 99 | 72 | 59 | 43 | 38 | 19 | 10 | 7 | 5 | 3 | 1 |
| **1 Allele** | 141 | 119 | 98 | 74 | 53 | 34 | 22 | 13 | 8 | 6 | 4 |
| **0 Alleles** | 62 | 52 | 43 | 35 | 27 | 15 | 11 | 6 | 2 | 1 | 0 |

Numbers at risk

**Figure S4.** Correlation between rs7765004 and *HDAC2* expression




**Legend: 0 denotes AA genotype; 1, AC genotype and 2, CC genotype**

## References for Appendix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**7.** Milpied NJ, Legouill S, Lamy T, et al: No benefit of first-line rituximab (R) - high-dose therapy (R-HDT) over R-CHOP14 for young adults with diffuse large B-cell lymphoma. Preliminary results of the GOELAMS 075 prospective multicentre randomized trial. Blood 116:685, 2010

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