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Abstract

While Waldenström macroglobulinemia (WM) is characterized by an almost unifying mutation in *MYD88*, clinical presentation at diagnosis and response to therapy can be widely different among WM patients. Current prognostic tools only partially address this clinical heterogeneity. Limited data compiling both molecular and cytogenetic information have been used in risk prognostication in WM. To investigate the clinical impact of genetic alterations in WM, we evaluated cytogenetic and molecular abnormalities by chromosome banding analyses (CBA), FISH and targeted NGS in a retrospective cohort of 239 WM patients, including 187 patients treated by first-line chemotherapy or immunochemotherapy. Most frequent mutations were identified in *MYD88* (93%), *CXCR4* (29%), *MLL2* (11%), *ARID1A* (8%), *TP53* (8%), *CD79A/B* (6%), *TBL1XR1* (4%) and *SPI1* (4%). The median number of cytogenetic abnormalities was two (range, 0-22). Main cytogenetic abnormalities were 6q deletion (del6q) (27%), trisomy 4 (tri4) (12%), tri18 (11%), del13q (11%), tri12 (7.5%) and del17p (7%). Complex karyotype (CK) was observed in 15% (n=31) of cases, including 5% (n=12) of highly CK (high-CK). *TP53* abnormalities (*TP53*abn) were present in 15% of evaluable patients. *TP53*abn and del6q were associated with CK/high-CK (P<0.05). Fifty-three percent of patients with hyperviscosity harbored *CXCR4* mutations. Cytogenetic and molecular abnormalities did not significantly impact time to first treatment and response to therapy. Prognostic factors associated with shorter PFS were del6q (P=0.01), *TP53*abn (P=0.002) and high-CK (P=0.01). These same factors as well as IPSSWM, tri4, *CXCR4* frameshift and *SPI1* mutations were significantly associated with lower OS (P<0.05). These results argue for integration of both cytogenetic and molecular screening in evaluation of first-line WM patients.

Introduction

Waldenström's macroglobulinemia (WM) is a rare mature B-cell lymphoproliferative disorder characterized by the presence of serum monoclonal IgM associated with bone marrow infiltration by lymphoplasmacytic cells[1]. WM is a mostly indolent but still incurable disease for which there is a wide clinical heterogeneity. Some patients never require treatment while others have symptomatic disease upon diagnosis harboring hyperviscosity syndrome, bulky adenopathy and/or profound cytopenias and rapidly relapse after first-line (1L) immunochemotherapy. Different biomarkers have been developed to predict this heterogeneity. The International Prognostic Scoring System for WM (IPSSWM) and its revised version used simple clinical and biological parameters to stratify patients into, respectively, three and five distinct risk prognostic groups that are highly correlated with overall survival (OS)[2,3]. As observed in several other B-cell malignancies, it has been suggested that acquired cytogenetic and molecular abnormalities could also provide prognostic value in WM but it is still a matter of debate. Cytogenetic abnormalities identified in WM include deletion of the long arm of chromosome 6 (del6q) (20-40%), del13q (10-15%), trisomy 18 (tri18) (10%), tri4 (8%) and deletion of the short arm of chromosome 17 (del17p) (8%)[4-6]. Only few data exist regarding the impact of cytogenetic abnormalities in WM but shorter progression-free survival (PFS) has been reported for del17p patients[4]. Next-generation sequencing (NGS) studies revealed that the most common somatic mutations were activating mutations in *MYD88* and *CXCR4* genes, present in respectively more than 90% and 30% of WM patients. Both these mutations have been associated with specific clinical and biological presentation at diagnosis[7], along with prognosis in some studies[7,8] but not confirmed in others[9], and have been considered as predictive for response to ibrutinib[10]. Other mutations have been described at a lower frequency (5-20%) in *ARID1A*, *CD79B*, *SPI1* or *TP53* genes[11-14], the last two mutations being associated with poor survival but in single and limited series. Recently, we have also reported two groups of WM according to DNA methylation patterns, related to normal memory B-cells and plasma cells profiles, and respectively significantly associated to *CXCR4* mutations and del6q[15].

Cytogenetic analyses combining chromosomal banding analysis (CBA) and fluorescent *in situ* hybridization (FISH) have been widely used in hematologic malignancies to evaluate and predict patient's prognosis. Both technics have limitations but are complementary. In B-cell lymphoproliferative disorders, such as chronic lymphocytic leukemia (CLL) and WM, one limitation of CBA was the relative difficulty in obtaining sufficient metaphases but this has been overcome by the introduction of modern cell stimulation protocols, allowing for robust CBA[16,17]. Importance of CBA has been emphasized by the association of karyotypic complexity with shorter treatment-free and OS in many hematologic malignancies and in particular CLL[18,19]. Recently, karyotypic complexity in CLL has been refined[20] demonstrating that complex karyotype (CK) comprises different subgroups with distinct prognosis, depending on the type of associated abnormalities, and that not all CK are of poor prognosis. Data regarding chromosomal abnormalities and karyotypic complexity are in contrast scarce in WM.

Immunochemotherapy (ICT), consisting in the association of an anti-CD20 monoclonal antibody and an alkylating agent, is part of the standard of care for WM patients. However, ICT use is still unsatisfactory, leading to non-complete responses and inevitable recurrence. Alternative treatments have been developed to obtain longer responses, consisting mainly in BTK inhibitors (BTKi) (ibrutinib, acalabrutinib, zanubrutinib) in monotherapy or in association with an anti-CD20 monoclonal antibody[21,29,32]. Although these latter regimens are efficient, data are lacking to choose one treatment or another according to a specific molecular or cytogenetic abnormality.

Recent advances in deciphering precise genomic landscape in WM have led to the proposition of a precision-guided treatment approach using *MYD88* and *CXCR4* mutational status[11]. While various studies have confirmed the relevance of this approach in WM patients receiving ibrutinib[10,29-31], other studies have

shown more controversial results[32,33], either regarding the impact of *CXCR4* mutations and/or in the specific context of ICT[34]. Finally, very limited data compiling both molecular and cytogenetic information are actually available and used in risk prognostication in WM.

The aim of this study was to evaluate clinical and biological characteristics of WM patients along with cytogenetic and molecular abnormalities, the potential association of CK with recurrent mutations identified in WM and their impact on outcome.

Patients and methods

Patients

This retrospective study included 239 WM patients diagnosed from 1988 to 2020 and followed up in Pitié-Salpêtrière hospital (Paris, France). Diagnosis, treatment initiation and response criteria followed the WHO classification[1] and recommendations from the tenth International Workshop Waldenström's Macroglobulinemia (IWWM)[21]. All cases were selected based on the availability of chromosome banding analyses (CBA)/FISH and/or DNA material sufficient for evaluation of *MYD88* and *CXCR4* mutations. Written consent for bone marrow (BM) and biological analyses were obtained in accordance with the declaration of Helsinki and with ethical approval from national (CNIL 2212382) and local (CPP Ile-De-France 05/21/2014) ethics committees.

Cytogenetic analyses

CBA were successfully performed in 219 patients according to the usual techniques as previously described[4], with 12-O-tetradecanoyl-phorbol-13-acetate (28 patients) until 2006 and CpG-oligonucleotides plus interleukin 2 stimulation (191 patients). All karyotypes (K) were described according to the International System for Human Cytogenetic Nomenclature (ISCN 2020). FISH was performed on interphase nuclei and metaphases, following standard procedures and using specific probes: *ATM* (11q22), *TP53* (17p13.1) (Metasystems), *BCL2* (18q21) (Zytovision), D12Z1 (12p11-q11), D13S319 (13q14), *LAMP1* (13q34) Metasystems, D6Z1 (6p11-q11)/SEC63 (6q21)/*MYB* (6q23) Metasystems, *FIP1L1/CHIC2/PDGFRA* (4q12) Deletion/Fusion Cytocell [4].

To consider a karyotype normal, a minimum of 15 metaphases had to be examined. Single-cell abnormalities were taken into consideration only if verified by FISH analysis. A karyotype was defined as complex (CK) if ≥ 3 clonal aberrations were present in CBA, respectively. Highly CK (high-CK) and non-high-CK were respectively defined if ≥ 5 and 3 or 4 clonal aberrations were identified. CBA was performed at WM diagnosis or before the administration of any treatment in respectively 85/219 (39%) and in 99/219 (45%), with a median of 39 [1-92] months between diagnosis and karyotype in this latter situation.

Mutation analyses

Genomic DNA was extracted using the QiAmp DNA micro kit (Qiagen) from non-sorted bone marrow (BM) samples. Routine sequencing of *MYD88* L265P and *CXCR4* S338X mutations was performed by restriction fragment length polymorphism (RFLP) and allele-specific polymerase chain reaction (AS-PCR) for respectively 199 and 189 patients. Among them, 168 BM samples were analyzed by targeted sequencing, including three tumor controls pairs analyzed by whole-exome sequencing. Twenty-one recurrently mutated genes in WM or other lymphoproliferative B-cell disorders from our experience or in the literature were selected for targeted sequencing (see **Supplementary Tables S1** for genomic coordinates of targeted regions and for the list of genes) using TWIST custom capture kit (Bioscience, San Francisco, CA). Libraries were generated with addition of paired-end adaptors (NEXTflex, Bioo Scientific, Austin, TX) before paired-end sequencing (2 x 100 bp reads) using an Illumina Novaseq6000 flow cell and the onboard cluster method

(Illumina, San Diego, CA). Targeted sequencing was analyzed according to previously described algorithms with minor modifications[22]. Briefly, sequence reads were mapped to the reference genome GRCh38 using the Burrows–Wheeler Aligner (BWA) alignment tool. PCR duplicates were removed using Picard tools - Mark Duplicates (version 1.119). Local realignment around indels and base quality score recalibration were performed using GATK 3.2 (Genome Analysis Tool Kit). The number of reads containing single-nucleotide variations (SNV) and indels was enumerated using Varscan (v2.3.7). Functionally annotated variants were filtered according to the following criteria: synonymous variants and variants located outside coding regions were filtered; polymorphisms described in Kaviar, gnomAD and the 1000 Genomes Project were removed; variants with coverage < 30X and less than ten supporting reads and variants with an allelic fraction lower than 1% were filtered; the remaining variants, evaluated as candidate somatic mutations, were manually reviewed and tagged as oncogenic using different criteria based on information retrieved from the literature, sequence conservation and *in silico* prediction of effect. The mean read depth within the targeted regions was 2000X.

In total, both *MYD88* L265P and *CXCR4* S338X status were available for 189 samples, targeted NGS for 168 and both cytogenetic and targeted NGS analyses for 165.

Abnormalities of *TP53* were defined by the presence of del(17p) and/or *TP53* mutations.

Statistical analyses

Main clinical and biological characteristics were collected at diagnosis and treatment initiation: age, hyperviscosity syndrome, lymphadenopathy, splenomegaly, hemoglobin level, platelet count, serum IgM monoclonal level, ß2-microglobulin (B2M), albumin, LDH. The International Prognostic Scoring System for WM (IPSSWM) was calculated according to previous published criteria[2]. Cytogenetic (FISH [del6q, trisomy 4, trisomy 12, del13q, del11q, del17p], chromosomal aberrations) and molecular abnormalities were analyzed as described above. Quantitative variables are presented as mean and standard deviation or median and range according to their distribution. Categorical variables are presented as numbers and related percentage. Primary and secondary endpoints were time to first treatment (TFT) for asymptomatic WM, and response to therapy, relapse rate, progression-free survival (PFS) and overall survival (OS) for the whole population. OS and PFS were calculated from the date of diagnosis/evaluation until the date of death from any cause or date of last follow up and date of progression, respectively. Variables included in univariate analyses included: age, B2M, IPSSWM, cytogenetic abnormalities (del6q, tri12, tri4, tri18, del13q, del11q, del17p), CK and high-CK, mutations (*MYD88, CXCR4, CD79B, ARID1A, MLL2, TP53, SPI1*). We excluded variables interesting less than 5 patients. Univariable Cox regression was applied to assess the prognostic significance of cytogenetic and molecular abnormalities, CK/high-CK and other prognostic factors on survival outcome. *P*-values were adjusted for age and multiplicity (Benjamini-Hochberg method). Multivariable Cox regression models were implemented to test the simultaneous effect of factors on outcomes, taking into account the relative effect of the remaining parameters. For the multivariable analysis, we considered only cases with available data for all the factors included in the model and variables that were significant ($P \leq 0.05$) in univariate analyses. Biostatistic analyses were performed with the help of GenoSplice (Paris, France). Kaplan-Meier analysis was performed to construct survival curves and the log rank test used to determine differences between groups. The X2 or Fisher's exact test were used to compare data distribution in different subgroups. The significance level of $p < 0.05$ was applied and statistical analyses were performed using the software SAS 9.3 (SAS Inc, Cary, NC) and R 3.0.2 (http://www.R-project.org).

Results

Clinical characteristics

Main clinical characteristics of the whole WM cohort are detailed in **Table 1**. The study population comprised 239 patients, including 63% of male. Median age at WM diagnosis was 65 years old (range, 28-88). WM was symptomatic at evaluation in 59% of patients. During the follow-up, 187/239 (78%) WM patients required first-line (1L) therapy. The indications for 1L therapies are listed in **Supplemental Table S2**. Those therapies consisted of chemotherapy (CT), immuno-CT (ICT), anti-CD20 monoclonal antibody alone, or other type in, respectively, 47/187 (25%), 125/187 (67%), 14/187 (7.5%) and 1/187 (0.5%) cases. ICT included dexamethasone-cyclophosphamide-rituximab (DRC), bendamustine-rituximab (BR) and fludarabine-rituximab based regimens in respectively 63/187 (34%), 36/187 (19%) and 23/187 (12%) (details regarding all the different types of treatment are provided in **Supplemental Table S3**). The median follow-up for the whole WM cohort was 6 years. Median PFS of patients receiving 1L therapy was 51 months and 5-year-OS was 91%. Forty-nine of 239 patients (20%) have died, due to WM progression or transformation, therapy-related toxicity, other causes and of unknown origin in respectively 28 (57%), 12 (24%), 6 (12%) and 3 (7%) cases (**Supplemental Table S4**).

Cytogenetic and mutational abnormalities

The distribution and frequency of gene alterations is represented in **Figure 1**. The most frequent mutations were identified in *MYD88* (93%), *CXCR4* (29%), *MLL2/KMT2D* (11%), *ARID1A* (8%), *TP53* (8%), *CD79A/B* (6%), *TBL1XR1* (4%), and *SPI1* (4%) (see **Supplemental Table S5** for details and list of mutations identified by targeted NGS). *MYD88* mutations other than the classical L265P (V217F, M232T and S243N) were found in 5 (2%) cases. Among the 7% *MYD88* wild-type (WT) cases, we observed mutations in other recurrently mutated genes such as *ARID1A, MLL2, CD79B* or *TNFAIP3*. *CXCR4* mutations were frameshift (FS) and nonsense (NS) in respectively 35 and 56% and more than half of them (55%) affected S338 amino-acid. *CXCR4* mutations affecting S338 amino-acid were mainly NS (23/27 (85%) cases) while NS mutations represented 5/21 (24%) cases of those affecting other amino-acids. Mutations identified in *CD79A/B*, *TBL1XR1*, *CARD11* (1%), *EZH2* (4%), *TNFAIP3* (3%), *NFKBIE* (2%) corresponded mainly to those previously described in other B-cell malignancies[22-27]. *SPI1* and *IKZF3* (3%) mutations were respectively hotspot Q226E and L162R[13,28].

The median number of cytogenetic abnormalities per sample was two (0-22). No cytogenetic abnormality was detected by CBA in 87/191 (40%), and by both CBA and FISH in 55/166 (33%) evaluable cases. Cytogenetic abnormalities identified by CBA and/or FISH were as follows, in decreasing order of frequency: del6q (27%), tri4 (12%), tri18 (11%), del13q (11%), tri12 (8%), del17p (7%), tri3 (6%) and del11q (5%). *TP53* abnormalities (*TP53*abn) (either del17p and/or *TP53* mutation) were present in 15% of 165 evaluable patients.

CK was observed in 15% (n=31/219) of cases, comprising three, four and ≥ five chromosomal aberrations (high-CK) in respectively 7% (n=13), 3% (n=6) and 5% (n=12) of cases. Details of the 31 CK (either non-high-CK or high-CK) are provided in **Supplemental Table S6**. Among the 31 CK, 15 (48%) included at least one trisomy (one trisomy, n=6; two, n=6; three, n=2; four, n=1), while, among the 12 high-CK, 7 (58%) included at least one trisomy (one trisomy, n=4; two, n=2; three, n=1).

Correlation between cytogenetic and mutational alterations

Significant associations between different genetic alterations are synthetized in **Supplemental Tables S7**. We did not observe specific mutations or cytogenetic abnormalities associated with *MYD88* WT status. *CXCR4* S338 mutations were significantly associated with CK (*P*=0.05) and *TP53*abn (*P*=0.03), while the

presence of *TP53*abn was associated with CK, either non-high-CK (*P*=0.02) or high-CK (*P*=0.0005). Del6q was associated with many other cytogenetic abnormalities (del13q, del11q, del17p, tri4) and non-high-CK/high-CK (*P*<0.0001). Del6q and *CXCR4* mutations were not exclusive in our series, as 18/51 del6q cases detected by CBA and/or FISH and explored by targeted NGS also harbored *CXCR4* mutations (S338, n=10; other amino-acid, n=8). Tri4 and tri18 were significantly associated with each other (*P*=0.02) as del17p and *TP53* mutations (*P*=0.03).

Specific comparisons between non-high-CK and high-CK (**Supplemental Tables S8**) showed that this latter harbored significantly more frequent del6q (by CBA and/or FISH, 11/12 [92%] vs. 9/19 [47%], *P*=0.02), del17p (5/12 [42%] vs. 1/19 [5%], *P*=0.02) and *TP53*abn (6/12 [50%] vs. 2/15 [13%], *P*=0.03) while no difference was observed in terms of specific gene mutation frequencies.

Of note, *TP53*abn were not equally distributed among CK subgroups as they were more frequently observed in CK without trisomies and more particularly in high-CK without trisomies. Only two *TP53*abn (n=2/14, 1 del17p, 1 *TP53* mutation) were identified in CK with trisomies (vs. 6/13 [45%] in CK without trisomies, *P*=0.07). More precisely, the two *TP53*abn were identified in high-CK with trisomies (n=2/7 vs. 4/5 in high-CK without trisomies, P=0.07) while none was observed in non-high-CK with trisomies (n=0/7 vs. 2/8 in non-high-CK without trisomies, *P*=0.15).

Correlation between genetic alterations and disease phenotype

Significant associations between genetic alterations and disease phenotype are synthetized in **Supplementary Table S9**. When comparing the population carrying an abnormality to that without the same abnormality, lymphoplasmacytic BM infiltration was significantly increased in patients with *CXCR4* mutations (56% vs. 41%, *P*=0.02), del6q (53% vs. 36%, *P* = 0.001), tri4 (58% vs. 35%, *P*=0.003) and/or non-high-CK (55% vs. 35%, *P*=0.02)/high-CK (68% vs. 43%, *P*=0.003); the presence of lymphadenopathy in those with *TP53*abn (44% vs. 21%, *P*=0.02) and *SPI1* mutations (67% vs. 23%, *P*=0.03). No significant correlation was observed between genetic alterations and IPSSWM.

In more detail, *CXCR4* mutations were also significantly associated with increased serum IgM levels (28 vs. 18 g/L, *P*=0.05), symptomatic hyperviscosity at presentation (17% vs. 6%, *P*=0.04; 53% of patients with symptomatic hyperviscosity at presentation harbored *CXCR4* mutations), and *CXCR4* mutated patients had more frequently platelet count < 100 x 10^9/L (11/48 [23%] vs. 5/120 [4%], *P*=0.0002). *TBL1XR1* mutations were associated with the lowest serum IgM levels (9.5 vs. 20 g/L, *P*=0.0007). Del6q patients had lower hemoglobin level (101 vs. 120 g/L, *P*<0.001) and tri4 lower hemoglobin (91 vs. 116 g/L, *P*=0.003) and more frequently platelet count < 100 x 10^9/L (9/27 [33%] vs. 19/183 [10%], *P*=0.001) that may reflect in both cases the increased BM infiltration described above.

Outcomes

Among the 239 WM patients of our cohort, 179 (75%) were asymptomatic at diagnosis. The median time to first therapy (TFT) for asymptomatic WM at diagnosis was 43 months (range, 7-236). Only elevated B2M was associated with shorter TFT (*P*=0.02). Cytogenetic and molecular abnormalities were not significantly associated with TFT; only a trend for shorter TFT was observed in tri12 and del6q patients (**Supplemental Table S10**).

Among the 187 (87%) symptomatic WM who received 1L therapy, response rates were distributed as followed: 6% (n=11) complete response (CR), 11% (n=21) very good partial response (VGPR), 49% (n=91) PR, 24% (n=45) stable disease (SD) and 10% (n=19) progressive disease (PD). No significant correlation was

observed between cytogenetic/mutational abnormalities and response. One hundred and two (54%) patients further experienced relapse with a median time of 55 months (range, 3-255). Univariate analyses of clinical and biological variables associated with relapse, PFS and OS are represented in **Table 2** and **Supplemental Table S10**. Prognostic factors associated with shorter PFS included del6q (*P*=0.01), *TP53*abn (*P*=0.002) and high-CK (*P*=0.01) (**Figure 2**). OS was pejoratively impacted by IPSSWM (*P*=0.002), del6q (*P*=0.027), tri4 (*P*=0.026), *CXCR4* frameshift (*P*=0.047), *SPI1* mutations (*P*=0.037), *TP53*abn (*P*=0.002) and high-CK (*P*=0.008) (**Figure 2** and **Supplemental Figure S1**). In multivariate analyses, only *TP53*abn (*P*=0.03) for PFS and IPSSWM (*P*=0.03) and *TP53*abn (*P*=0.04) for OS retained significant.

As the entire cohort of WM patients received two main different types of 1L therapies (CT and ICT), we compared PFS and OS of these two subgroups (respectively, 5-year PFS, 40 vs. 50% [*P*=0.02]; 10-year OS, 76 vs. 78% [*P*=0.3]; **Supplemental Figure S1**). The repartition of main cytogenetic and molecular abnormalities was similar in these two subgroups (**Supplemental Table S11**). We then specifically analyzed prognostic factors for PFS and OS in 1L ICT patients (**Figure 3** and **Supplemental Table S12**). Del6q, high-CK, *TP53* abnormalities negatively impacted PFS (**Figure 3**) while only IPSSWM and *TP53* abnormalities were significantly associated with shorter OS in univariate analysis in this specific population. In multivariate analyses, only *TP53*abn for PFS and IPSSWM and *TP53*abn for OS retained significant (**Supplemental Table S12**).

Regarding more specifically the outcomes of CK, the pejorative impact on PFS and OS was stronger for high-CK compared to non-high-CK. High-CK was one of the most impactful prognostic factors, being associated with one of the shortest median PFS of 20 months and a 5-year OS of 75%. CK with trisomies were associated with a trend to better PFS compared to CK without trisomies (**Supplemental Figure S2**).

Nine patients experienced transformed WM in the course of the disease. For the seven patients for whom cytogenetic and molecular screening were available, all harbored either high-CK (n=4/7, 57%, all these four including del6q) and/or *TP53* abnormalities (n=6/7, 87%) (see **Supplemental Table S13** for details regarding cytogenetic and molecular abnormalities of these samples).

Discussion

Our comprehensive approach integrating CBA, FISH and targeted NGS analyses in a large cohort of WM patients offered the opportunity to study the prognostic impact of both molecular and cytogenetic abnormalities and, to our knowledge, for the first time the one of high-CK that has been recently emphasized in CLL[20]. In this series, we confirmed many of the already published WM biological features but also extended our knowledge of particular associations between different genomic characteristics and finally highlighted prognostic factors associated with those, which could be of importance in future 1L therapeutic strategies in WM patients.

Our cohort harbored main characteristics of WM real-life patients: median age of 65 years, 80% of kappa isotype, mean IgM level around 20 g/L, > 90% *MYD88* L265P, 30% *CXCR4* mutations, and respective 5-year and 10-year OS of 91% and 75%. IPSSWM strongly impacted OS (**Table 1** and **Supplemental Figure S1**) supporting the validity and reliability of our cohort. However, our study harbored notable limitations due in part to its retrospective design encompassing a long period of time, including patients with missing data and receiving diverse therapies. Since many patients have a smoldering disease not requiring therapy, the analysis of OS performed from the date of diagnosis date can be in part misleading. More, the absence of patients treated in 1L by BTKi that have actually no marketing authorization in France for 1L WM limited the possibility to infer which therapies between ICT and BTKi will more benefit for certain

cytogenetic/molecular abnormalities. Further prospective studies are thus clearly warranted to address this important question.

Chromosomal abnormalities have been little studied so far in WM and information about frequencies and characteristics of the most recurrent abnormalities is therefore of interest. In this respect, we confirmed our previous results regarding the occurrence of del6q (27%) and tri4 (12%) and their respective association with CK and tri18[4]. Frequency of del6q was slightly lower in our cohort than that historically reported in the literature (40-50%)[35,36] but was concordant with the one (28/93 [30%]) identified in symptomatic WM of a recent Spanish study[37]. Although del6q and *CXCR4* mutations have been suggested to be mutually exclusive[38], we did not observe this exclusivity in our series. This difference could be due in part by the technics used for del6q identification (CBA and/or FISH vs. RQ-PCR). Del6q and tri4 cases had more aggressive presentation with increased BM involvement, lower hemoglobin and platelet counts, and shorter PFS and OS, confirming recent published data for del6q[37]. Del6q-associated poor prognosis may be in part due to its association with CK and more particularly with high-CK as nearly all these latter (11/12, 92%) harbored del6q and plead for its potential implication in chromosomal instability. Further studies will be necessary to confirm that del6q could represent a particular group of patients with potential specific methylation profile, association with *VH3* usage, CD38 expression and enrichment in plasmacytoid lymphocytes as previously suggested[15]. We also brought more information about del17p (7%)/*TP53*abn and CK frequencies, that are confirmed to be recurrent events in WM as previously described[4,12,39]. Other trisomies than tri4 such as tri18 and tri3 were recurrent representing respectively 11 and 6% of cases.

We provided more precise characterization of CK in WM, especially high-CK, which was positively associated in our cohort with the presence of del6q and *TP53*abn. As described in CLL[20], not all CK were equivalent, as in particular (i) the pejorative impact on PFS and OS was stronger for high-CK compared to non-high-CK and (ii) CK with trisomies were associated with a lower frequency of *TP53*abn and a trend to better PFS compared to CK without trisomies. This latter point will need to be confirmed in largest cohorts of patients.

Regarding main somatic gene mutations, frequencies were relatively similar to those previously described for *CXCR4*, *ARID1A*, *CD79A/B*, *TP53* and *SPI1*[7,11-14]. No significantly relevant association with cytogenetics was observed for most gene mutations (**Supplemental Tables S5**), except for the ones described above for *TP53* and *CXCR4*. The number of mutated cases was too small for *EZH2, IKZF3, PRDM1, TNFAIP3, CARD11, ETV6* and *HIST1H1E* to draw reliable conclusions. *CXCR4* mutated patients represented around one third of the cohort and presented with increased BM infiltration, serum IgM levels and symptomatic hyperviscosity as previously described[7]. Somatic mutations in *ARID1A* were identified in 8% of patients, including NS and FS variants, but were not associated with specific clinical presentation.

Interestingly, various gene mutations were associated with outcome. We did observe a trend for shorter PFS for non-*MYD88* L265P cases but this was not confirmed if we integrated others (non-L265P) *MYD88* mutated cases in the analysis. Definitive conclusions are difficult to draw in this particular population regarding the small number of patients. The poor prognosis of *SPI1* mutations was confirmed as previously suggested[13]. *CXCXR4* S338 and/or NS mutations did not affect outcomes in our cohort while *CXCR4* FS have a slight significant pejorative impact on OS (**Supplemental Figure S1**). These results are different from what has been described in WM patients treated with BTKi ibrutinib for whom the presence of *CXCR4* NS mutations impacted survival outcomes [40,41]. Further studies will be necessary to interrogate the hypothesis that BTKi and ICT may be beneficial specifically for *CXCR4* FS and NS respective populations. Interesting information is also provided in this WM cohort receiving 1L (I)CT regarding the pejorative role of *TP53*abn

for PFS and OS in uni- and multivariate analyses, emphasizing its potential predictive value for considering 1L targeted therapies in this specific population as described in CLL. This pejorative impact on PFS and OS was confirmed in the group of patients who specifically received 1L ICT (n=125) in uni- and multivariate analyses (**Figure 3** and **Supplemental Table S12**). The negative impact of del6q and high-CK on PFS was also confirmed in this specific group of patients in univariate but not multivariate analysis (**Supplemental Table S12**).

Finally, as WM is frequently an asymptomatic disease at diagnosis, prognostic factors predicting evolution to symptomatic disease are of importance. Only B2M was significantly associated with shorter TFT in our cohort and we failed to demonstrate any significant association between cytogenetic/molecular abnormalities and TFT. Larger studies in asymptomatic WM may be necessary to fully explore these potential associations.

In conclusion, our work is one of the first to describe a cohort of WM patients treated by (I)CT with comprehensive analysis of both cytogenetic and molecular abnormalities, providing important information for prognosis prediction and therapy selection. In particular, a negative impact of del6q, *TP53*abn and high-CK has been demonstrated on both PFS and OS. Prospective studies are warranted to confirm these prognostic factors, the potential role of 1L targeted therapies in high-risk WM and the use of both cytogenetic and molecular screening for guiding therapeutic strategy between BTKi and ICT in 1L WM patients.

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Contribution statement: DK, FNK and DRW designed the research, analyzed data and wrote the manuscript. DK, CB, LS, JC, EC and DRW performed experiments. DK, NG, CBG, MB, CB, FD, EC, SS, VL, FNK and DRW recruited patients. All authors reviewed and approved the manuscript.

Conflict-of-interest disclosure: No relevant COI

Data availability statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

1. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood.* 2016;127(20):2375-2390.
2. Morel P, Duhamel A, Gobbi P, et al. International prognostic scoring system for Waldenstrom macroglobulinemia. *Blood.* 2009;113(18):4163-4170.
3. Kastritis E, Morel P, Duhamel A, et al. A revised international prognostic score system for Waldenstrom's macroglobulinemia. *Leukemia.* 2019;33(11):2654-2661.
4. Nguyen-Khac F, Lambert J, Chapiro E, et al. Chromosomal aberrations and their prognostic value in a series of 174 untreated patients with Waldenstrom's macroglobulinemia. *Haematologica.* 2013;98(4):649-654.

5. Schop RF, Kuehl WM, Van Wier SA, et al. Waldenstrom macroglobulinemia neoplastic cells lack immunoglobulin heavy chain locus translocations but have frequent 6q deletions. *Blood.* 2002;100(8):2996-3001.
6. Terre C, Nguyen-Khac F, Barin C, et al. Trisomy 4, a new chromosomal abnormality in Waldenstrom's macroglobulinemia: a study of 39 cases. *Leukemia.* 2006;20(9):1634-1636.
7. Treon SP, Cao Y, Xu L, Yang G, Liu X, Hunter ZR. Somatic mutations in MYD88 and CXCR4 are determinants of clinical presentation and overall survival in Waldenstrom macroglobulinemia. *Blood.* 2014;123(18):2791-2796.
8. Poulain S, Roumier C, Decambron A, et al. MYD88 L265P mutation in Waldenstrom macroglobulinemia. *Blood.* 2013;121(22):4504-4511.
9. Abeykoon JP, Paludo J, King RL, et al. MYD88 mutation status does not impact overall survival in Waldenstrom macroglobulinemia. *Am J Hematol.* 2018;93(2):187-194.
10. Treon SP, Xu L, Hunter Z. MYD88 Mutations and Response to Ibrutinib in Waldenstrom's Macroglobulinemia. *N Engl J Med.* 2015;373(6):584-586.
11. Treon SP, Xu L, Guerrera ML, et al. Genomic Landscape of Waldenstrom Macroglobulinemia and Its Impact on Treatment Strategies. *J Clin Oncol.* 2020;38(11):1198-1208.
12. Poulain S, Roumier C, Bertrand E, et al. TP53 Mutation and Its Prognostic Significance in Waldenstrom's Macroglobulinemia. *Clin Cancer Res.* 2017;23(20):6325-6335.
13. Roos-Weil D, Decaudin C, Armand M, et al. A Recurrent Activating Missense Mutation in Waldenstrom Macroglobulinemia Affects the DNA Binding of the ETS Transcription Factor SPI1 and Enhances Proliferation. *Cancer Discov.* 2019;9(6):796-811.
14. Gustine JN, Tsakmaklis N, Demos MG, et al. TP53 mutations are associated with mutated MYD88 and CXCR4, and confer an adverse outcome in Waldenstrom macroglobulinaemia. *Br J Haematol.* 2019;184(2):242-245.
15. Roos-Weil D, Giacopelli B, Armand M, et al. Identification of 2 DNA methylation subtypes of Waldenstrom macroglobulinemia with plasma and memory B-cell features. *Blood.* 2020;136(5):585-595.
16. Haferlach C, Bacher U. Cytogenetic methods in chronic lymphocytic leukemia. *Methods Mol Biol.* 2011;730:119-130.
17. Nguyen-Khac F, Borie C, Callet-Bauchu E, Eclache V, Struski S. Cytogenetics in the management of chronic lymphocytic leukemia: an update by the Groupe francophone de cytogenetique hematologique (GFCH). *Ann Biol Clin (Paris).* 2016;74(5):561-567.
18. Thompson PA, O'Brien SM, Wierda WG, et al. Complex karyotype is a stronger predictor than del(17p) for an inferior outcome in relapsed or refractory chronic lymphocytic leukemia patients treated with ibrutinib-based regimens. *Cancer.* 2015;121(20):3612-3621.
19. Baliakas P, Iskas M, Gardiner A, et al. Chromosomal translocations and karyotype complexity in chronic lymphocytic leukemia: a systematic reappraisal of classic cytogenetic data. *Am J Hematol.* 2014;89(3):249-255.
20. Baliakas P, Jeromin S, Iskas M, et al. Cytogenetic complexity in chronic lymphocytic leukemia: definitions, associations, and clinical impact. *Blood.* 2019;133(11):1205-1216.
21. Castillo JJ, Advani RH, Branagan AR, et al. Consensus treatment recommendations from the tenth International Workshop for Waldenstrom Macroglobulinaemia. *Lancet Haematol.* 2020;7(11):e827-e837.
22. Damm F, Mylonas E, Cosson A, et al. Acquired initiating mutations in early hematopoietic cells of CLL patients. *Cancer Discov.* 2014;4(9):1088-1101.

23. Lenz G, Davis RE, Ngo VN, et al. Oncogenic CARD11 mutations in human diffuse large B cell lymphoma. *Science.* 2008;319(5870):1676-1679.
24. Mansouri L, Sutton LA, Ljungstrom V, et al. Functional loss of IkappaBepsilon leads to NF-kappaB deregulation in aggressive chronic lymphocytic leukemia. *J Exp Med.* 2015;212(6):833-843.
25. Morin RD, Johnson NA, Severson TM, et al. Somatic mutations altering EZH2 (Tyr641) in follicular and diffuse large B-cell lymphomas of germinal-center origin. *Nat Genet.* 2010;42(2):181-185.
26. Davis RE, Ngo VN, Lenz G, et al. Chronic active B-cell-receptor signalling in diffuse large B-cell lymphoma. *Nature.* 2010;463(7277):88-92.
27. Gonzalez-Aguilar A, Idbaih A, Boisselier B, et al. Recurrent mutations of MYD88 and TBL1XR1 in primary central nervous system lymphomas. *Clin Cancer Res.* 2012;18(19):5203-5211.
28. Landau DA, Tausch E, Taylor-Weiner AN, et al. Mutations driving CLL and their evolution in progression and relapse. *Nature.* 2015;526(7574):525-530.
29. Treon SP, Tripsas CK, Meid K, et al. Ibrutinib in previously treated Waldenstrom's macroglobulinemia. *N Engl J Med.* 2015;372(15):1430-1440.
30. Treon SP, Meid K, Gustine J, et al. Long-Term Follow-Up of Ibrutinib Monotherapy in Symptomatic, Previously Treated Patients With Waldenstrom Macroglobulinemia. *J Clin Oncol.* 2021;39(6):565-575.
31. Dimopoulos MA, Trotman J, Tedeschi A, et al. Ibrutinib for patients with rituximab-refractory Waldenstrom's macroglobulinaemia (iNNOVATE): an open-label substudy of an international, multicentre, phase 3 trial. *Lancet Oncol.* 2017;18(2):241-250.
32. Dimopoulos MA, Tedeschi A, Trotman J, et al. Phase 3 Trial of Ibrutinib plus Rituximab in Waldenstrom's Macroglobulinemia. *N Engl J Med.* 2018;378(25):2399-2410.
33. Tomowiak C, Poulain S, Herbaux C, et al. Obinutuzumab and idelalisib in symptomatic patients with relapsed/refractory Waldenstrom macroglobulinemia. *Blood Adv.* 2021;5(9):2438-2446.
34. Laribi K, Poulain S, Willems L, et al. Bendamustine plus rituximab in newly-diagnosed Waldenstrom macroglobulinaemia patients. A study on behalf of the French Innovative Leukaemia Organization (FILO). *Br J Haematol.* 2019;186(1):146-149.
35. Ocio EM, Schop RF, Gonzalez B, et al. 6q deletion in Waldenstrom macroglobulinemia is associated with features of adverse prognosis. *Br J Haematol.* 2007;136(1):80-86.
36. Chang H, Qi C, Trieu Y, et al. Prognostic relevance of 6q deletion in Waldenstrom's macroglobulinemia: a multicenter study. *Clin Lymphoma Myeloma.* 2009;9(1):36-38.
37. Garcia-Sanz R, Dogliotti I, Zaccaria GM, et al. 6q deletion in Waldenstrom macroglobulinaemia negatively affects time to transformation and survival. *Br J Haematol.* 2021;192(5):843-852.
38. Guerrera ML, Tsakmaklis N, Xu L, et al. MYD88 mutated and wild-type Waldenstrom's Macroglobulinemia: characterization of chromosome 6q gene losses and their mutual exclusivity with mutations in CXCR4. *Haematologica.* 2018;103(9):e408-e411.
39. Wang Y, Gali VL, Xu-Monette ZY, et al. Molecular and genetic biomarkers implemented from next-generation sequencing provide treatment insights in clinical practice for Waldenstrom macroglobulinemia. *Neoplasia.* 2021;23(4):361-374.
40. Gustine JN, Xu L, Tsakmaklis N, et al. CXCR4 (S338X) clonality is an important determinant of ibrutinib outcomes in patients with Waldenstrom macroglobulinemia. *Blood Adv.* 2019;3(19):2800-2803.

41. Castillo JJ, Xu L, Gustine JN, et al. CXCR4 mutation subtypes impact response and survival outcomes in patients with Waldenstrom macroglobulinaemia treated with ibrutinib. *Br J Haematol.* 2019;187(3):356-363.

Figures legends

Figure 1. Mutational and cytogenetic analyses of Waldenström macroglobulinemia (WM) samples by chromosome banding analysis (CBA), FISH and/or targeted sequencing. Each column represents a patient sample and each row a mutated gene (italic) or cytogenetic abnormality. The percentage of each mutated gene or cytogenetic abnormality in the whole cohort are indicated on the right of the grid. Complex karyotypes (CK) are represented at the top for highly CK (high-CK) and non-high-CK in respective dark blue and light blue. Colored box: presence; white box: absence; light grey box: not available.

Supplemental Figure S1

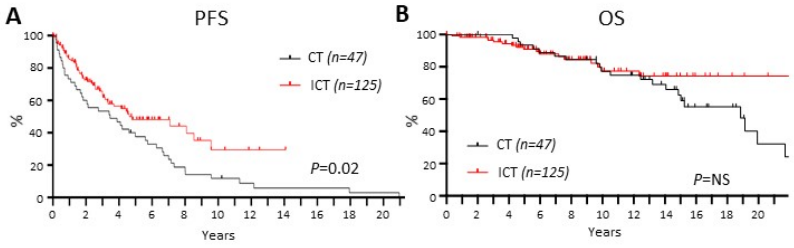


Figure 2. Respective progression free-survival (PFS) and overall survival (OS) for the following recurrent molecular/cytogenetic abnormalities in the entire cohort: *MYD88*/*CXCR4* status (A, B), del6q (C, D), *TP53*abn (E, F), non-high-CK and high-CK (I, J). Abbreviations: abn, abnormalities; CA, cytogenetic abnormalities; high-CK, highly complex karyotype; mut, mutated; WT, wild-type.

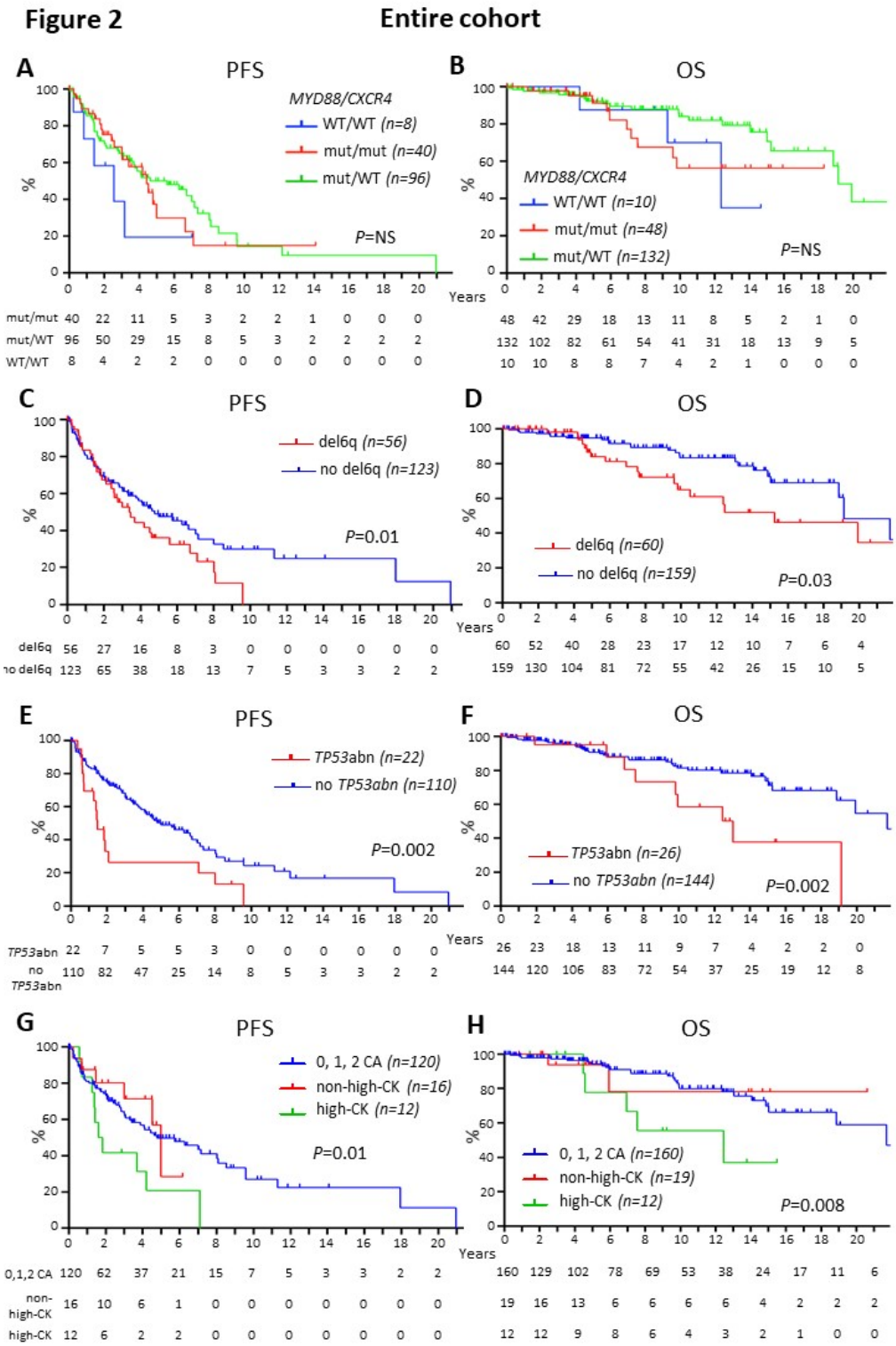
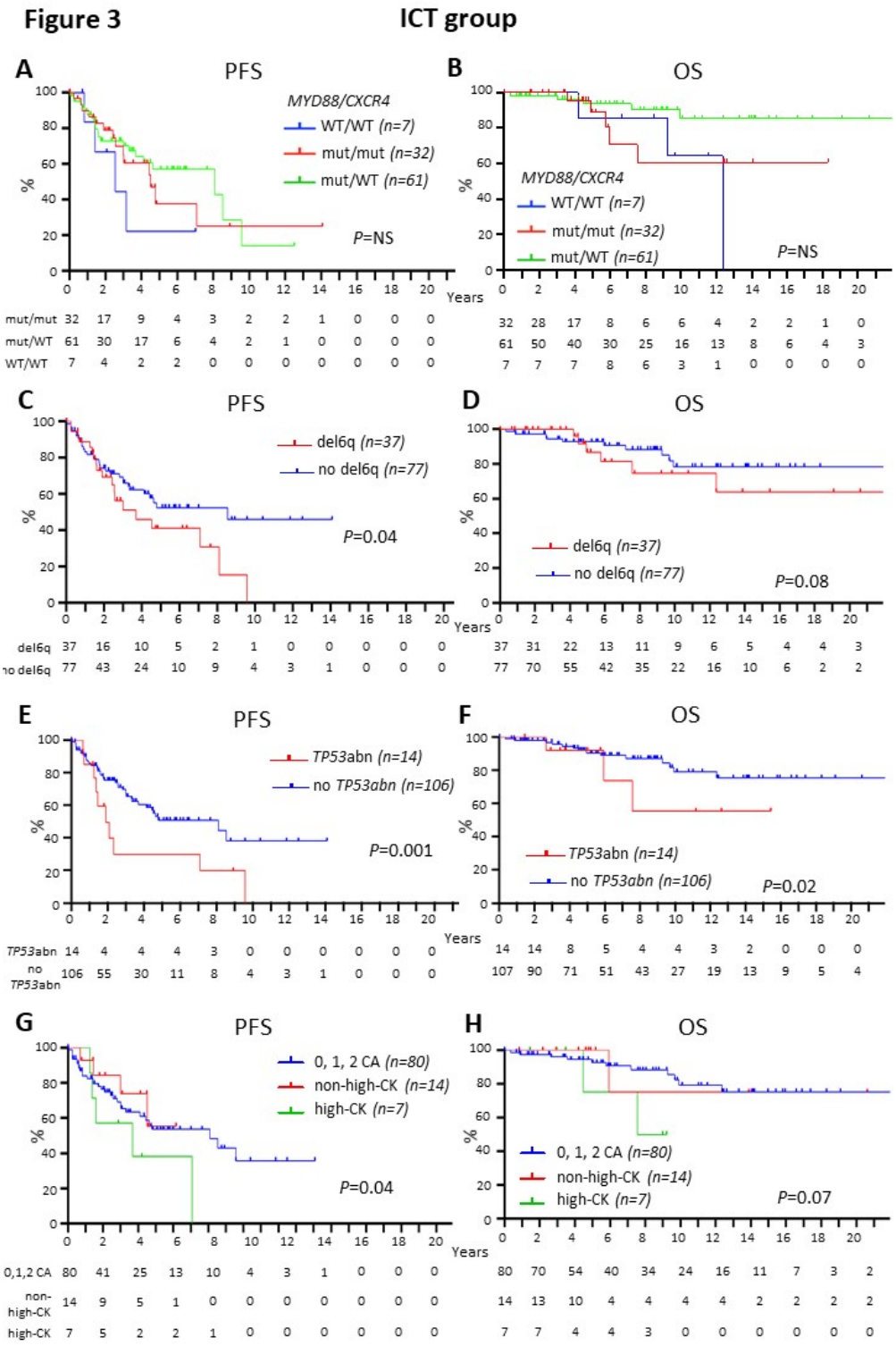


Figure 3. Respective progression free-survival (PFS) and overall survival (OS) for the following recurrent molecular/cytogenetic abnormalities in patients who received first-line immunochemotherapy (ICT): *MYD88*/*CXCR4* status (A, B), del6q (C, D), *TP53*abn (E, F), non-high-CK and high-CK (I, J). Abbreviations: abn, abnormalities; CA, cytogenetic abnormalities; high-CK, highly complex karyotype; mut, mutated; WT, wild-type.



Supplemental Figures legends

Figure S1. Progression free-survival (PFS) (A) and overall survival (OS) (B) of WM patients who received either 1L chemotherapy (CT, n=47) or immunochemotherapy (ICT, n=125).

Supplemental Figure S1

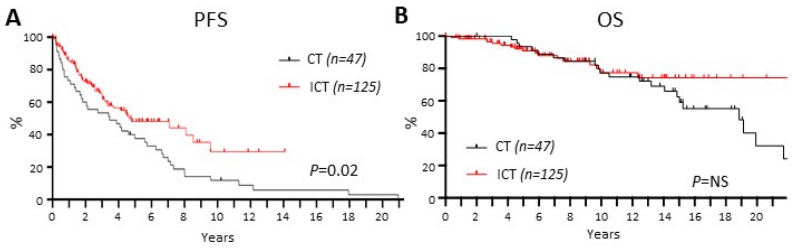
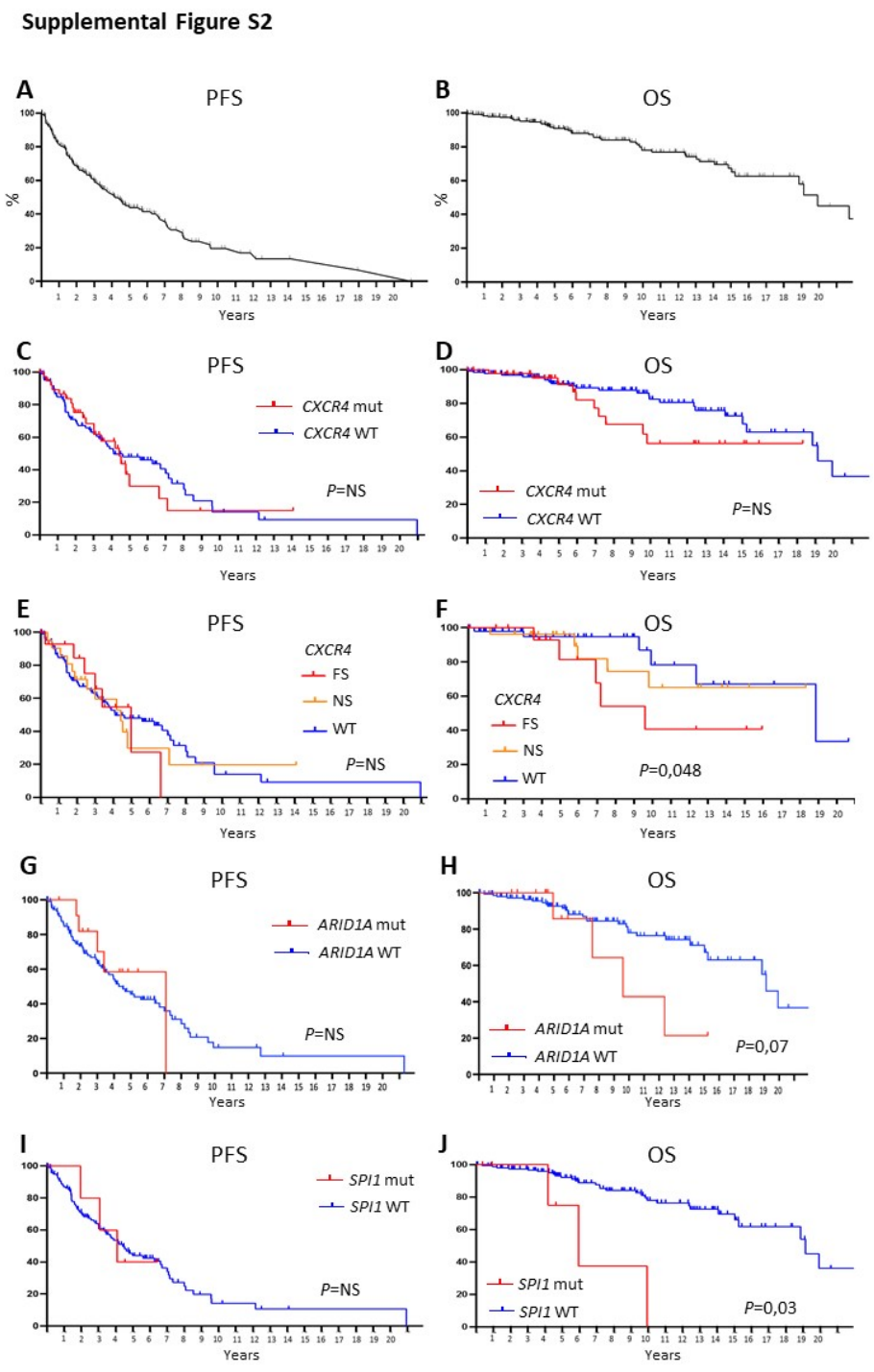
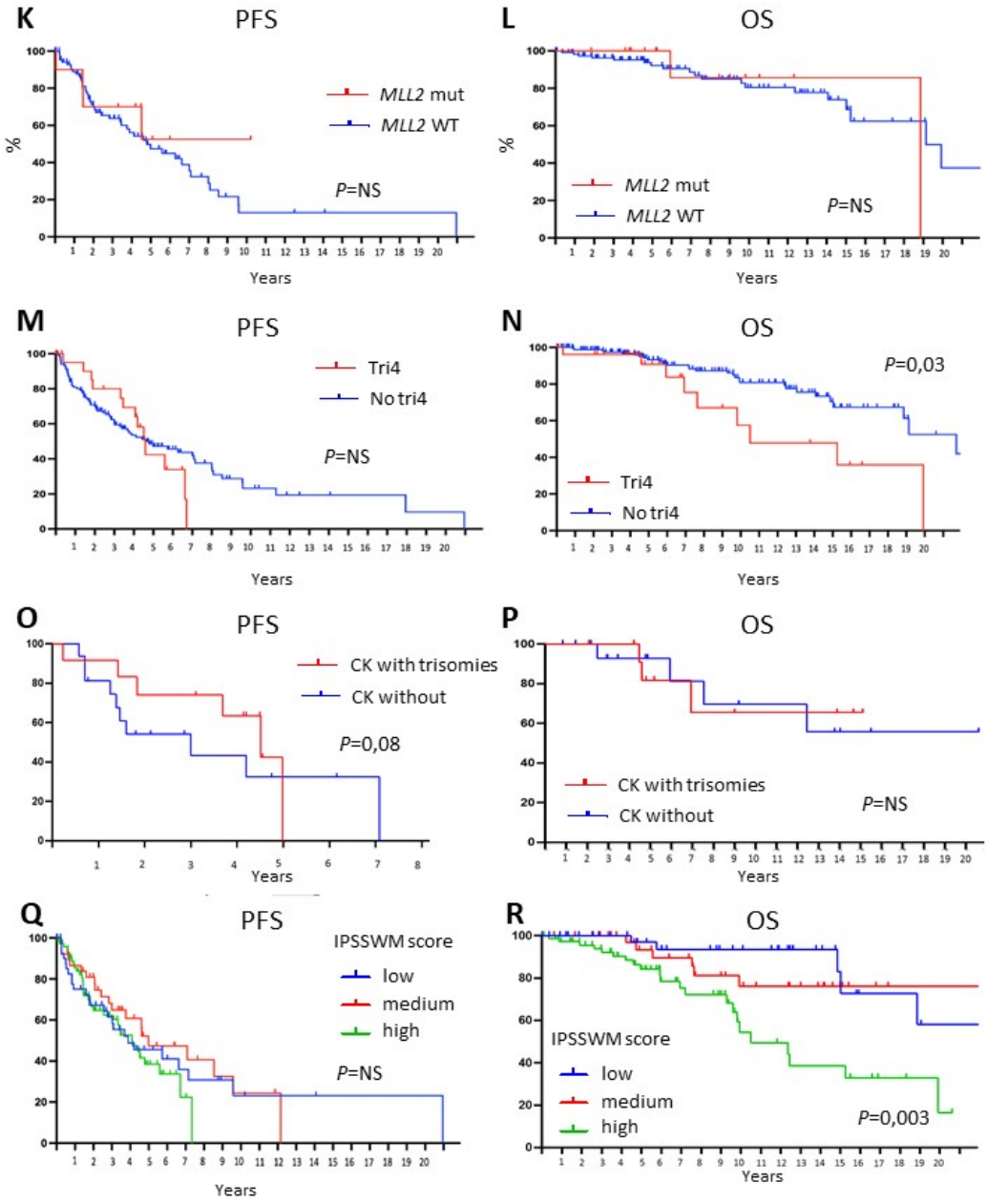


Figure S2. Progression free-survival (PFS) (A) and overall survival (OS) (B) of the whole WM cohort and respective PFS/OS for the following recurrent molecular/cytogenetic abnormalities: *CXCR4* mutated vs. WT (C, D), *CXCR4* WT vs. nonsense (NS) vs. frameshift (FS) mutations (E,F), *ARID1A* (G,H), *SPI1* (I,J), *MLL2* (K,L), tri4 (M,N), CK with/without trisomies (O,P) and IPSSWM (Q,R).



Supplemental Figure S2



Tables

Table 1. Main characteristics of the whole WM cohort		
	n (%)	
Total	239 (100)	
Median age at WM diagnosis, years (range)		65 (28-88)
Sex, male	155/239 (63)	
Clinical and biological parameters at evaluation		
Adenopathy ≥ 1,5 cm	57/230 (25)	
Splenomegaly	32/230 (14)	
Hemoglobin, mean in g/dL (range)		11.5 (4.2-16.3)
Hemoglobin < 11,5 g/dL	114/233 (49)	
Platelets, mean (G/L)		242 (26-630)
Platelets < 100 G/L, yes (%)	78/229 (34)	
IgM, mean in g/L (range)		18 (2-78)
Isotype, kappa	184/232 (80)	
Bone marrow infiltration, mean in % (range)		44 (10-100)
Requiring first-line therapy	187/239 (78)	
IPSSWM		
Low	43/156 (27)	
Intermediate	39/156 (25)	
High	74/156 (48)	
Type of first-line therapies		
Alkylating agents	47/187 (25)	
Immunochemotherapy (ICT)	125/187 (68)	
Anti-CD20 monotherapy	14/187 (7)	
Other	1/187 (1)	
Cytogenetic abnormalities by CBA and/or FISH		
del6q	60/219 (27)	
tri4	27/219 (12)	
del13q	25/219 (11)	
tri18	25/219 (11)	
tri12	17/219 (8)	
del17p	16/219 (7)	
del11q	11/219 (5)	
complex karyotype (CK)	31/219 (14)	
highly CK (high-CK)	12/219 (5)	
missing data	20/239 (8.5)	
Mutations		
MYD88	186/199 (93)	
L265P mutation	181/186 (97)	
Other *MYD88* mutations	5/186 (3)	
CXCR4	48/168 (29)	
S338	27 (55)	
Other	21 (45)	
***TP53* abnormalities** (del17p/*TP53* mutation)	26/170 (15)	
Abbreviations: CBA, chromosome banding analysis; IPSS, international prognostic scoring system; WM, Waldenström macroglobulinemia		

Table 2. Uni- and multivariate analyses of variables associated with PFS and OS in the entire cohort.

	PFS						OS					
	Univariate (n=187)			Multivariate* (n=121)			Univariate (n=239)			Multivariate* (n=136)		
	HR	*IC 95%*	*P*	HR	*IC 95%*	*P*	HR	*IC 95%*	*P*	HR	*IC 95%*	*P*
B2M	-	-	NS				-	-	NS			
IPSSWM	-	-	NS				3.70	1.47-9.10	0.002	3.06	1.26-5.96	0.03
Del6q	2.24	1.17-4.29	0.01	-	-	NS	2.02	1.07-3.83	0.027	-	-	NS
Tri4	-	-	NS				2.38	1.08-5.22	0.026	-	-	NS
CK	-	-	NS				-	-	NS			
High-CK	3.29	1.23-8.79	0.01	-	-	NS	3.44	1.30-9.10	0.01	-	-	NS
***TP53* abn**	3.19	1.48-6.85	0.002	2.9	1.08-5.33	0.03	2.95	1.43-6.07	0.002	2.41	1.19-4.83	0.04
***CXCR4* FS mutations**	-	-	NS				2.56	1.00-6.66	0.047	-	-	NS
***SPI1* mutations**	-	-	NS				4.10	1.01-12.4	0.037	-	-	NS

*For multivariable analyses, we considered only variables that were significant ($P \leq 0.05$) in univariate analyses and cases with available data for all the factors included in the model.

Abbreviations : B2M, beta2microglobulin; CI, confidence interval; CK, complex karytotype; high-CK, highly CK; HR, hazard ratio; IPSSWM, international prognostic scoring system for Waldenström macroglobulinemia; NS, non significant; PFS, progression-free survival; OS, overall survival.

Supplemental Table S1. List of targeted genes and genomic coordinates

Gene	RefSeq sequences (coding transcripts)	Chromosomic region	Targeted exons
CARD11	NM_032415	7p22.2	exon 4-9
CD79A	NM_001783	19q13.2	exon 4-5
CD79B	NM_000626	17q23.3	exon 5-6
MYD88	NM_002468	3p22	all
TP53	NM_001126112	17p12	exon 2-11
CXCR4	NM_003467	2q21	all
SPI1	NM_003120	11p11.2	all
TNFAIP3	NM_001270508	6q23.3	all
PRDM1	NM_001198	6q21	all
EZH2	NM_004456	7q36.1	all
MLL2	NM_003482	12q13.12	all
ARID1A	NM_006015	1p36.11	all
IKZF3	NM_012481	17q12	exon 5
NOTCH2	NM_024408	1p12	exon 34
KLF2	NM_016270	19p13.11	all
NFKBIE	NM_004556	6p21.1	all
HIST1H1E	NM_005321	6p22.2	all
CREBBP	NM_004380	16p13.3	exon 23-27
TBL1XR1	NM_001321193	3q26.32	all
ETV6	NM_001987	12p13.2	all
IRF4	NM_002460	6p25.3	exon 2-3

Supplemental Table S2. Different indications of therapy

Type of indications	Number (%)
Symptoms related to BM involvement	119 (64)
Anemia	101 (54)
Thrombopenia	18 (10)
Bulky extramedullary disease	33 (18)
Symptomatic hyperviscosity	14 (7)
Bing-Neel syndrome	4 (2)
Other IgM related complications (cryoglobulinemia, amyloidosis, acquired vWF disease, neuropathy)	17 (9)
Total	187 (100)

Supplemental Table S3. Details regarding different types of first-line therapies

	Number of patients
Chemotherapy	**47**
Chlorambucil	34
Fludarabine	10
Cyclophosphamide	1
CHOP	1
Fludarabine-Cyclophosphamide	1
Immunochemotherapy	**125**
Dexamethasone-Rituximab-Cyclophosphamide (DRC)	61
Dexamethasone-Rituximab-Cyclophosphamide (DRC) + Bortezomib	2
Fludarabine-Rituximab (FR)	13
Fludarabine-Cyclophosphamide-Rituximab (FCR)	10
Bendamustine-Rituximab (BR)	36
Rituximab-Chlorambucil	1
Rituximab-miniCHOP	1
Bortezomib-Dexamethasone-Rituximab (BDR)	1
Rituximab monotherapy	**14**
Other (bortezomib/dexamethasone)	**1**

Supplemental Table S4. Causes of death (n=49)

Type of cause	Number (%)
WM progression	24 (49)
Transformed WM	4 (8)
Therapy-related toxicity	12 (24)
Other	6 (12)
Unknown	3 (7)
Total	49 (100)

Supplemental Table S5. Somatic mutations identified by targeted NGS analyses

Gene	HGVSp	HGVSc	Consequence	SAMPLE	variant_id
ARID1A	NP_006006.3:p.Asn935ValfsTer5	NM_006015.6:c.2799_2802del	frameshift_variant	LEBRE	Somatic:chr1:26766286:GGATT>G>-:deletion:HIGH:frameshift_variant:ARID1A
ARID1A	NP_006006.3:p.Gln1127Ter	NM_006015.6:c.3379C>T	stop_gained	FRAMA2	Somatic:chr1:26771299:C>T>T:SNV:HIGH:stop_gained:ARID1A
ARID1A	NP_006006.3:p.Gln1614Ter	NM_006015.6:c.4840C>T	stop_gained	AREMA	Somatic:chr1:26775067:C>T>T:SNV:HIGH:stop_gained:ARID1A
ARID1A	NP_006006.3:p.Gln200Ter	NM_006015.6:c.598C>T	stop_gained	LEGPH	Somatic:chr1:26697001:C>T>T:SNV:HIGH:stop_gained:ARID1A
ARID1A	NP_006006.3:p.Gln2100Ter	NM_006015.6:c.6298C>T	stop_gained	PERJO	Somatic:chr1:26780196:C>T>T:SNV:HIGH:stop_gained:ARID1A
ARID1A	NP_006006.3:p.Gln2128Ter	NM_006015.6:c.6382C>T	stop_gained	MESAN	Somatic:chr1:26780280:C>T>T:SNV:HIGH:stop_gained:ARID1A
ARID1A	NP_006006.3:p.Gln372Ter	NM_006015.6:c.1114C>T	stop_gained	JOLJE	Somatic:chr1:26697517:C>T>T:SNV:HIGH:stop_gained:ARID1A
ARID1A	NP_006006.3:p.Gly105AlafsTer2	NM_006015.6:c.314_335del	frameshift_variant	LABPI	Somatic:chr1:26696716:GGGAACGCGGGCCCTAGGCCCGC>G>-:deletion:HIGH:frameshift_variant:ARID1A
ARID1A	NP_006006.3:p.Gly827ArgfsTer45	NM_006015.6:c.2477dup	frameshift_variant	TISFR	Somatic:chr1:26763029:G>GC>C:insertion:HIGH:frameshift_variant:ARID1A
ARID1A	NP_006006.3:p.Pro1560His	NM_006015.6:c.4679C>A	missense_variant	LANGI	Somatic:chr1:26774906:C>A>A:SNV:MODERATE:missense_variant:ARID1A
ARID1A	NP_006006.3:p.Pro459Ala	NM_006015.6:c.1375C>G	missense_variant	POUEV	Somatic:chr1:26731176:C>G>G:SNV:MODERATE:missense_variant:ARID1A
ARID1A	NP_006006.3:p.Ser744Ter	NM_006015.6:c.2231C>G	stop_gained	PETAN	Somatic:chr1:26761453:C>G>G:SNV:HIGH:stop_gained:ARID1A
ARID1A	NP_006006.3:p.Tyr215ThrfsTer17	NM_006015.6:c.642del	frameshift_variant	DESFR	Somatic:chr1:26697043:TC>T>-:deletion:HIGH:frameshift_variant:ARID1A
CARD11	NP_001311210.1:p.Arg337Gln	NM_001324281.2:c.1010G>A	missense_variant	DESMA	Somatic:chr7:2938686:C>T>T:SNV:MODERATE:missense_variant:CARD11
CARD11	NP_001311210.1:p.Asn191Ser	NM_001324281.2:c.572A>G	missense_variant	CANPA	Somatic:chr7:2944324:T>C>C:SNV:MODERATE:missense_variant:CARD11
CD79A	NP_001774.1:p.Ile202Thr	NM_001783.4:c.605T>C	missense_variant	DEVFR	Somatic:chr19:41880904:T>C>C:SNV:MODERATE:missense_variant:CD79A
CD79B	.	NM_000626.4:c.550-1G>A	splice_acceptor_varia	ILIMA	Somatic:chr17:63929476:C>T>T:SNV:HIGH:splice_acceptor_variant:CD79B
CD79B	NP_000617.1:p.Glu197Gly	NM_000626.4:c.590A>G	missense_variant&spl	BONCO	Somatic:chr17:63929435:T>C>C:SNV:MODERATE:missense_variant&splice_region_variant:CD79B
CD79B	NP_000617.1:p.Gly189ThrfsTer17	NM_000626.4:c.565_580del	frameshift_variant	GILAL	Somatic:chr17:63929444:TGATCTTCCTCCATGCC>T>-:deletion:HIGH:frameshift_variant:CD79B
CD79B	NP_000617.1:p.Leu199Gln	NM_000626.4:c.596T>A	missense_variant	HALJO	Somatic:chr17:63929320:A>T>T:SNV:MODERATE:missense_variant:CD79B
CD79B	NP_000617.1:p.Tyr196Asn	NM_000626.4:c.586T>A	missense_variant	BENBE	Somatic:chr17:63929439:A>T>T:SNV:MODERATE:missense_variant:CD79B
CD79B	NP_000617.1:p.Tyr196Cys	NM_000626.4:c.587A>G	missense_variant	BENBE	Somatic:chr17:63929438:T>C>C:SNV:MODERATE:missense_variant:CD79B
CD79B	NP_000617.1:p.Tyr196Cys	NM_000626.4:c.587A>G	missense_variant	LABPI	Somatic:chr17:63929438:T>C>C:SNV:MODERATE:missense_variant:CD79B
CXCR4	NP_001008540.1:p.Arg338Ter	NM_001008540.2:c.1012C>T	stop_gained	BEAJE	Somatic:chr2:136114928:G>A>A:SNV:HIGH:stop_gained:CXCR4
CXCR4	NP_001008540.1:p.Arg338Ter	NM_001008540.2:c.1012C>T	stop_gained	CANPA	Somatic:chr2:136114928:G>A>A:SNV:HIGH:stop_gained:CXCR4
CXCR4	NP_001008540.1:p.Glu347Ter	NM_001008540.2:c.1039_1043del	frameshift_variant	DARRO	Somatic:chr2:136114896:AGACTC>A>-:deletion:HIGH:frameshift_variant:CXCR4
CXCR4	NP_001008540.1:p.Glu347Ter	NM_001008540.2:c.1037_1038insA	frameshift_variant	FRAMA2	Somatic:chr2:136114902:A>AT>T:insertion:HIGH:frameshift_variant:CXCR4
CXCR4	NP_001008540.1:p.Gly340ArgfsTer9	NM_001008540.2:c.1014_1017dup	frameshift_variant	MESAN	Somatic:chr2:136114922:C>CACCT>ACCT:insertion:HIGH:frameshift_variant:CXCR4
CXCR4	NP_001008540.1:p.Gly340ArgfsTer9	NM_001008540.2:c.1014_1017dup	frameshift_variant	PAIER	Somatic:chr2:136114922:C>CACC>ACC:insertion:HIGH:frameshift_variant:CXCR4
CXCR4	NP_001008540.1:p.Gly340Ter	NM_001008540.2:c.1018G>T	stop_gained	TISFR	Somatic:chr2:136114922:C>A>A:SNV:HIGH:stop_gained:CXCR4
CXCR4	NP_001008540.1:p.Leu330ProfsTer18	NM_001008540.2:c.988dup	frameshift_variant	DAVJA	Somatic:chr2:136114951:A>AG>G:insertion:HIGH:frameshift_variant:CXCR4
CXCR4	NP_001008540.1:p.Leu333ProfsTer15	NM_001008540.2:c.997dup	frameshift_variant	JUGNA	Somatic:chr2:136114942:A>AG>G:insertion:HIGH:frameshift_variant:CXCR4
CXCR4	NP_001008540.1:p.Ser328ValfsTer20	NM_001008540.2:c.981dup	frameshift_variant	JOLJE	Somatic:chr2:136114958:A>AC>C:insertion:HIGH:frameshift_variant:CXCR4
CXCR4	NP_001008540.1:p.Ser342IlefsTer6	NM_001008540.2:c.1023_1024insA	frameshift_variant	CHAMI	Somatic:chr2:136114916:A>AT>T:insertion:HIGH:frameshift_variant:CXCR4
CXCR4	NP_001008540.1:p.Ser342IlefsTer6	NM_001008540.2:c.1023_1024insA	frameshift_variant	GYNJI	Somatic:chr2:136114916:A>AT>T:insertion:HIGH:frameshift_variant:CXCR4
CXCR4	NP_001008540.1:p.Ser342PhefsTer6	NM_001008540.2:c.1024dup	frameshift_variant	DESMA	Somatic:chr2:136114915:G>GA>A:insertion:HIGH:frameshift_variant:CXCR4
CXCR4	NP_001008540.1:p.Ser342Ter	NM_001008540.2:c.1025C>G	stop_gained	AREMA	Somatic:chr2:136114915:G>C>C:SNV:HIGH:stop_gained:CXCR4
CXCR4	NP_001008540.1:p.Ser342Ter	NM_001008540.2:c.1025C>G	stop_gained	CHAIT	Somatic:chr2:136114915:G>C>C:SNV:HIGH:stop_gained:CXCR4
CXCR4	NP_001008540.1:p.Ser342Ter	NM_001008540.2:c.1025C>A	stop_gained	DEBLA	Somatic:chr2:136114915:G>T>T:SNV:HIGH:stop_gained:CXCR4
CXCR4	NP_001008540.1:p.Ser342Ter	NM_001008540.2:c.1025C>G	stop_gained	DIGPI	Somatic:chr2:136114915:G>C>C:SNV:HIGH:stop_gained:CXCR4
CXCR4	NP_001008540.1:p.Ser342Ter	NM_001008540.2:c.1025C>G	stop_gained	DJEYO	Somatic:chr2:136114915:G>C>C:SNV:HIGH:stop_gained:CXCR4
CXCR4	NP_001008540.1:p.Ser342Ter	NM_001008540.2:c.1025C>G	stop_gained	FERJE	Somatic:chr2:136114915:G>C>C:SNV:HIGH:stop_gained:CXCR4
CXCR4	NP_001008540.1:p.Ser342Ter	NM_001008540.2:c.1025C>G	stop_gained	GILAL	Somatic:chr2:136114915:G>C>C:SNV:HIGH:stop_gained:CXCR4
CXCR4	NP_001008540.1:p.Ser342Ter	NM_001008540.2:c.1025C>G	stop_gained	LABPI	Somatic:chr2:136114915:G>C>C:SNV:HIGH:stop_gained:CXCR4
CXCR4	NP_001008540.1:p.Ser342Ter	NM_001008540.2:c.1025C>G	stop_gained	LANCH	Somatic:chr2:136114915:G>C>C:SNV:HIGH:stop_gained:CXCR4
CXCR4	NP_001008540.1:p.Ser342Ter	NM_001008540.2:c.1025C>G	stop_gained	LECER	Somatic:chr2:136114915:G>C>C:SNV:HIGH:stop_gained:CXCR4
CXCR4	NP_001008540.1:p.Ser342Ter	NM_001008540.2:c.1025C>G	stop_gained	LEGPH	Somatic:chr2:136114915:G>C>C:SNV:HIGH:stop_gained:CXCR4
CXCR4	NP_001008540.1:p.Ser342Ter	NM_001008540.2:c.1025C>G	stop_gained	MESMO	Somatic:chr2:136114915:G>C>C:SNV:HIGH:stop_gained:CXCR4
CXCR4	NP_001008540.1:p.Ser342Ter	NM_001008540.2:c.1025C>A	stop_gained	MORNA	Somatic:chr2:136114915:G>T>T:SNV:HIGH:stop_gained:CXCR4
CXCR4	NP_001008540.1:p.Ser342Ter	NM_001008540.2:c.1025C>A	stop_gained	ROUMA	Somatic:chr2:136114915:G>T>T:SNV:HIGH:stop_gained:CXCR4
CXCR4	NP_001008540.1:p.Ser342Ter	NM_001008540.2:c.1025C>A	stop_gained	RUDBE	Somatic:chr2:136114915:G>T>T:SNV:HIGH:stop_gained:CXCR4
CXCR4	NP_001008540.1:p.Ser342Ter	NM_001008540.2:c.1025C>G	stop_gained	SASPA	Somatic:chr2:136114915:G>C>C:SNV:HIGH:stop_gained:CXCR4
CXCR4	NP_001008540.1:p.Ser342Ter	NM_001008540.2:c.1025C>G	stop_gained	TAHI	Somatic:chr2:136114915:G>C>C:SNV:HIGH:stop_gained:CXCR4
CXCR4	NP_001008540.1:p.Ser342Ter	NM_001008540.2:c.1025C>G	stop_gained	LIJKO	Somatic:chr2:136114915:G>C>C:SNV:HIGH:stop_gained:CXCR4
CXCR4	NP_001008540.1:p.Ser342Ter	NM_001008540.2:c.1025C>G	stop_gained	POICA	Somatic:chr2:136114915:G>C>C:SNV:HIGH:stop_gained:CXCR4
CXCR4	NP_001008540.1:p.Ser342Ter	NM_001008540.2:c.1025C>G	stop_gained	LECBR	Somatic:chr2:136114915:G>C>C:SNV:HIGH:stop_gained:CXCR4
CXCR4	NP_001008540.1:p.Ser342Ter	NM_001008540.2:c.1025C>G	stop_gained	GHPLE	Somatic:chr2:136114915:G>C>C:SNV:HIGH:stop_gained:CXCR4
CXCR4	NP_001008540.1:p.Ser342Ter	NM_001008540.2:c.1025C>G	stop_gained	FRAMA2	Somatic:chr2:136114915:G>C>C:SNV:HIGH:stop_gained:CXCR4
CXCR4	NP_001008540.1:p.Ser342Ter	NM_001008540.2:c.1025C>A	stop_gained	MUMFR	Somatic:chr2:136114915:G>T>T:SNV:HIGH:stop_gained:CXCR4
CXCR4	NP_001008540.1:p.Ser342Ter	NM_001008540.2:c.1025C>A	stop_gained	GIBCL	Somatic:chr2:136114915:G>T>T:SNV:HIGH:stop_gained:CXCR4
CXCR4	NP_001008540.1:p.Ser345HisfsTer2	NM_001008540.2:c.1033_1034del	frameshift_variant	BERBE	Somatic:chr2:136114905:GGA>G>-:deletion:HIGH:frameshift_variant:CXCR4
CXCR4	NP_001008540.1:p.Ser345HisfsTer2	NM_001008540.2:c.1033_1034del	frameshift_variant	PETAN	Somatic:chr2:136114905:GGA>G>-:deletion:HIGH:frameshift_variant:CXCR4
CXCR4	NP_001008540.1:p.Ser345HisfsTer2	NM_001008540.2:c.1033_1034del	frameshift_variant	ZAIRO	Somatic:chr2:136114905:GGA>G>-:deletion:HIGH:frameshift_variant:CXCR4
CXCR4	NP_001008540.1:p.Ser345LeufsTer24	NM_001008540.2:c.1032_1035del	frameshift_variant	KOSVA	Somatic:chr2:136114904:TGGAA>T>-:deletion:HIGH:frameshift_variant:CXCR4
CXCR4	NP_001008540.1:p.Ser345PhefsTer3	NM_001008540.2:c.1033dup	frameshift_variant	DOUGE	Somatic:chr2:136114906:G>GA>A:insertion:HIGH:frameshift_variant:CXCR4
CXCR4	NP_001008540.1:p.Ser348ValfsTer2	NM_001008540.2:c.1040dup	frameshift_variant	PLUFR	Somatic:chr2:136114899:C>CT>T:insertion:HIGH:frameshift_variant:CXCR4
CXCR4	NP_001008540.1:p.Thr322AsnfsTer26	NM_001008540.2:c.964dup	frameshift_variant	SELMO	Somatic:chr2:136114975:G>GT>T:insertion:HIGH:frameshift_variant:CXCR4
CXCR4	NP_001008540.1:p.Thr346Asn	NM_001008540.2:c.1037C>A	missense_variant	FRAMA2	Somatic:chr2:136114903:G>T>T:SNV:MODERATE:missense_variant:CXCR4
CXCR4	NP_001008540.1:p.Val344CysfsTer4	NM_001008540.2:c.1029dup	frameshift_variant	OMETH	Somatic:chr2:136114910:C>CA>A:insertion:HIGH:frameshift_variant:CXCR4
CXCR4	NP_001008540.1:p.Val344CysfsTer4	NM_001008540.2:c.1029dup	frameshift_variant	LEGRE	Somatic:chr2:136114910:C>CA>A:insertion:HIGH:frameshift_variant:CXCR4
ETV6	NP_001978.1:p.Val166Met	NM_001987.5:c.496G>A	missense_variant	PREFR	Somatic:chr12:11869456:G>A>A:SNV:MODERATE:missense_variant:ETV6
EZH2	NP_001190176.1:p.Ile55Met	NM_001203247.2:c.165C>G	missense_variant	DEWYV	Somatic:chr7:148846551:G>C>C:SNV:MODERATE:missense_variant:EZH2
EZH2	NP_001190176.1:p.Ile55Met	NM_001203247.2:c.165C>G	missense_variant	PIEVE	Somatic:chr7:148846551:G>C>C:SNV:MODERATE:missense_variant:EZH2
EZH2	NP_001190176.1:p.Lys510Arg	NM_001203247.2:c.1529A>G	missense_variant&spl	DUPLI	Somatic:chr7:148815508:T>C>C:SNV:MODERATE:missense_variant&splice_region_variant:EZH2
EZH2	NP_001190176.1:p.Lys510Arg	NM_001203247.2:c.1529A>G	missense_variant&spl	HELRO	Somatic:chr7:148815508:T>C>C:SNV:MODERATE:missense_variant&splice_region_variant:EZH2
EZH2	NP_001190176.1:p.Lys510Arg	NM_001203247.2:c.1529A>G	missense_variant&spl	LABPI	Somatic:chr7:148815508:T>C>C:SNV:MODERATE:missense_variant&splice_region_variant:EZH2
EZH2	NP_001190176.1:p.Lys510Arg	NM_001203247.2:c.1529A>G	missense_variant&spl	PETGE	Somatic:chr7:148815508:T>C>C:SNV:MODERATE:missense_variant&splice_region_variant:EZH2
EZH2	NP_001190176.1:p.Lys510Arg	NM_001203247.2:c.1529A>G	missense_variant&spl	SURPA	Somatic:chr7:148815508:T>C>C:SNV:MODERATE:missense_variant&splice_region_variant:EZH2
EZH2	NP_001190176.1:p.Lys510Arg	NM_001203247.2:c.1529A>G	missense_variant&spl	TARAN	Somatic:chr7:148815508:T>C>C:SNV:MODERATE:missense_variant&splice_region_variant:EZH2
HIST1H1E	NP_005312.1:p.Ala123Pro	NM_005321.2:c.367G>C	missense_variant	BEAJE	Somatic:chr6:26156757:G>C>C:SNV:MODERATE:missense_variant:HIST1H1E
HIST1H1E	NP_005312.1:p.Ala164Val	NM_005321.2:c.491C>T	missense_variant	SONAL	Somatic:chr6:26156881:C>T>T:SNV:MODERATE:missense_variant:HIST1H1E
HIST1H1E	NP_005312.1:p.Ala47Gly	NM_005321.2:c.140C>G	missense_variant	DUPLI	Somatic:chr6:26156530:C>G>G:SNV:MODERATE:missense_variant:HIST1H1E
HIST1H1E	NP_005312.1:p.Asn108Tyr	NM_005321.2:c.322A>T	missense_variant	SEBMO	Somatic:chr6:26156712:A>T>T:SNV:MODERATE:missense_variant:HIST1H1E
HIST1H1E	NP_005312.1:p.Gly103Asp	NM_005321.2:c.308G>A	missense_variant	LEBRE	Somatic:chr6:26156698:G>A>A:SNV:MODERATE:missense_variant:HIST1H1E
HIST1H1E	NP_005312.1:p.Gly70Ala	NM_005321.2:c.209G>C	missense_variant	DEBLA	Somatic:chr6:26156599:G>C>C:SNV:MODERATE:missense_variant:HIST1H1E
HIST1H1E	NP_005312.1:p.Leu84Arg	NM_005321.2:c.251T>G	missense_variant	COGSI	Somatic:chr6:26156641:T>G>G:SNV:MODERATE:missense_variant:HIST1H1E
HIST1H1E	NP_005312.1:p.Lys207Glu	NM_005321.2:c.619A>G	missense_variant	LAVPH	Somatic:chr6:26157009:A>G>G:SNV:MODERATE:missense_variant:HIST1H1E
HIST1H1E	NP_005312.1:p.Ser102Pro	NM_005321.2:c.304T>C	missense_variant	DAVJA_Plaque	Somatic:chr6:26156694:T>C>C:SNV:MODERATE:missense_variant:HIST1H1E
HIST1H1E	NP_005312.1:p.Ser89Asn	NM_005321.2:c.266G>A	missense_variant	GILAL	Somatic:chr6:26156656:G>A>A:SNV:MODERATE:missense_variant:HIST1H1E
HIST1H1E	NP_005312.1:p.Thr45IlefsTer44	NM_005321.2:c.134del	frameshift_variant	DEVFR	Somatic:chr6:26156523:AC>A>-:deletion:HIGH:frameshift_variant:HIST1H1E
IKZF3	NP_001244337.1:p.Leu128Arg	NM_001257408.2:c.383T>G	missense_variant	BIRMU	Somatic:chr17:39791523:A>C>C:SNV:MODERATE:missense_variant:IKZF3
IKZF3	NP_001244337.1:p.Leu128Arg	NM_001257408.2:c.383T>G	missense_variant	DEVFR	Somatic:chr17:39791523:A>C>C:SNV:MODERATE:missense_variant:IKZF3
IKZF3	NP_001244337.1:p.Leu128Arg	NM_001257408.2:c.383T>G	missense_variant	MORFR	Somatic:chr17:39791523:A>C>C:SNV:MODERATE:missense_variant:IKZF3
IKZF3	NP_001244337.1:p.Leu128Arg	NM_001257408.2:c.383T>G	missense_variant	NGUFR	Somatic:chr17:39791523:A>C>C:SNV:MODERATE:missense_variant:IKZF3
KMT2D	NP_003473.3:p.Arg5392Cys	NM_003482.3:c.16174C>T	missense_variant	NEWCH	Somatic:chr12:49022754:G>A>A:SNV:MODERATE:missense_variant:KMT2D
KMT2D	NP_003473.3:p.Cys778SerfsTer152	NM_003482.3:c.2333del	frameshift_variant	DIGPI	Somatic:chr12:49051349:GC>G>-:deletion:HIGH:frameshift_variant:KMT2D
KMT2D	NP_003473.3:p.Gly1235ValfsTer95	NM_003482.3:c.3704del	frameshift_variant	GIRCH	Somatic:chr12:49049883:AC>A>-:deletion:HIGH:frameshift_variant:KMT2D
KMT2D	NP_003473.3:p.Gly2954ValfsTer50	NM_003482.3:c.8861del	frameshift_variant	MARIS1	Somatic:chr12:49038494:AC>A>-:deletion:HIGH:frameshift_variant:KMT2D
KMT2D	NP_003473.3:p.Gly2954ValfsTer50	NM_003482.3:c.8861del	frameshift_variant	MARMA1	Somatic:chr12:49038494:AC>A>-:deletion:HIGH:frameshift_variant:KMT2D
KMT2D	NP_003473.3:p.Gly5189Arg	NM_003482.3:c.15565G>A	missense_variant	MESMO	Somatic:chr12:49026401:C>T>T:SNV:MODERATE:missense_variant:KMT2D
KMT2D	NP_003473.3:p.Leu2594ArgfsTer97	NM_003482.3:c.7781del	frameshift_variant	DIGPI	Somatic:chr12:49039988:CA>C>-:deletion:HIGH:frameshift_variant:KMT2D
KMT2D	NP_003473.3:p.Leu806ProfsTer6	NM_003482.3:c.2416dup	frameshift_variant	NGUPH	Somatic:chr12:49051266:A>AG>G:insertion:HIGH:frameshift_variant:KMT2D
KMT2D	NP_003473.3:p.Lys1149Ter	NM_003482.3:c.3445A>T	stop_gained	DUPLI	Somatic:chr12:49050143:T>A>A:SNV:HIGH:stop_gained:KMT2D
KMT2D	NP_003473.3:p.Met1166TyrfsTer18	NM_003482.3:c.3494dup	frameshift_variant	ILIMA	Somatic:chr12:49050093:A>AG>G:insertion:HIGH:frameshift_variant:KMT2D
KMT2D	NP_003473.3:p.Met1941Val	NM_003482.3:c.5821A>G	missense_variant	DEWYV	Somatic:chr12:49042607:T>C>C:SNV:MODERATE:missense_variant:KMT2D
KMT2D	NP_003473.3:p.Phe2494SerfsTer49	NM_003482.3:c.7479del	frameshift_variant	AYMMO	Somatic:chr12:49040290:AC>A>-:deletion:HIGH:frameshift_variant:KMT2D
KMT2D	NP_003473.3:p.Pro305HisfsTer29	NM_003482.3:c.914del	frameshift_variant	LEBRE	Somatic:chr12:49053246:TG>T>-:deletion:HIGH:frameshift_variant:KMT2D
KMT2D	NP_003473.3:p.Pro984Leu	NM_003482.3:c.2951C>T	missense_variant	COGJE	Somatic:chr12:49050637:G>A>A:SNV:MODERATE:missense_variant:KMT2D
KMT2D	NP_003473.3:p.Thr4368TyrfsTer4	NM_003482.3:c.13101dup	frameshift_variant	MOUDA	Somatic:chr12:49031603:T>TA>A:insertion:HIGH:frameshift_variant:KMT2D
KMT2D	NP_003473.3:p.Trp5217Ter	NM_003482.3:c.15650G>A	stop_gained	COGSI	Somatic:chr12:49026316:C>T>T:SNV:HIGH:stop_gained:KMT2D
KMT2D	NP_003473.3:p.Tyr2199IlefsTer65	NM_003482.3:c.6595del	frameshift_variant	FERJE	Somatic:chr12:49041174:TA>T>-:deletion:HIGH:frameshift_variant:KMT2D
MYD88	NP_001166037.2:p.Ala125Thr	NM_001172566.2:c.373G>A	missense_variant	CAGJA	Somatic:chr3:38140801:G>A>A:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166037.2:p.Trp114Arg	NM_001172566.2:c.340T>C	missense_variant	HORCE	Somatic:chr3:38140768:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	AREMA	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	AYMMO	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	BAOTE	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	BARHA	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	BEAJE	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	BENBE	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	BENSL	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	BERBE	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	BIRMU	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	BLAMA	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	BONCO	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	BUGMA	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	CANPA	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	CESFE	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	CHAFR	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	CHAIT	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	CHAJE	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	CHAMI	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	CHAMO	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	CHECL	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	COGJE	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	COGSI	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	DARRO	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	DAVGE	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	DAVJA	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	DAVJA_Plaque	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	DAVMA	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	DEBLA	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	DELHE	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	DELTA	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	DESFR	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	DESMA	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	DETMA	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	DEVFR	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	DEWYV	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	DIGPI	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	DJEYO	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	DOUGE	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	DRAJE	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	DUBEM2	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	DUPLI	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	DURPA	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	FABMI	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	FALSE	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	FERJE	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	FOUJE	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	FRAMA1	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	FRAMA2	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	GACJE	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	GAYLA	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	GHATA	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	GILAL	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	GIRCH	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	GIRPA	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	GONJE	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	GOUMI	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	GRARO	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	HALJO	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	HELRO	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	HOUMI	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	ILIMA	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	JACGI	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	JOLJE	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	JOUNO	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	JUGNA	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	KOSVA	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	LABPI	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	LACEL	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	LAMEM	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	LAMMO	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	LANCH	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	LAVPH	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	LEBRE	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	LECER	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	LECGR	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	LECJE	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	LEGPH	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	LEGRE	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	LEGWI	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	LEJJP	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	LERJE	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	MARIS2	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	MARMA2	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	MARYV	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	MAYLA	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	MESAN	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	MESMO	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	MORCH	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	MORFR	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	MORLA	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	MORNA	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	MOUDA	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	NDENI	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	NEWCH	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	NGUFR	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	NGUPH	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	NICPH	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	NOUAU	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	PASBE	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	PASJA	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	PEATH	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	PERJO	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	PETAN	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	PETGE	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	PIEVE	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	PINDA	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	PLUFR	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	POTYV	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	POUER	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	POUEV	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	PREGU	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	QUINI	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	RAUEV	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	RENJO	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	ROUMA	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	ROUMI	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	RUDBE	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	SALJE	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	SANRE	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	SASPA	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	SEBMO	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	SELMO	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	SONAL	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	SOUEV	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	TAHI	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	TARAN	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	THOCH	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	TISFR	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	TONLU	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Leu260Pro	NM_001172567.2:c.779T>C	missense_variant	YAHDJ	Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Val204Phe	NM_001172567.2:c.610G>T	missense_variant	BOUMO	Somatic:chr3:38140534:G>T>T:SNV:MODERATE:missense_variant:MYD88
MYD88	NP_001166038.2:p.Val204Phe	NM_001172567.2:c.610G>T	missense_variant	NAPMI	Somatic:chr3:38140534:G>T>T:SNV:MODERATE:missense_variant:MYD88
NFKBIE	NP_004547.3:p.Arg198SerfsTer79	NM_004556.3:c.592_637del	frameshift_variant	CHAIT	Somatic:chr6:44261679:TCTGGCCGCCCTTCCAGCAGGCAGCGGGCACAGGCCAAGTGCTGGCG>T>-:deletion:HIGH:frameshift_variant:NFKBIE
NFKBIE	NP_004547.3:p.Tyr115SerfsTer13	NM_004556.3:c.342_345del	frameshift_variant	DETMA	Somatic:chr6:44265001:TGTAA>T>-:deletion:HIGH:frameshift_variant:NFKBIE
NFKBIE	NP_004547.3:p.Tyr115SerfsTer13	NM_004556.3:c.342_345del	frameshift_variant	KOSVA	Somatic:chr6:44265001:TGTAA>T>-:deletion:HIGH:frameshift_variant:NFKBIE
PRDM1	NP_001189.2:p.His621Pro	NM_001198.4:c.1862A>C	missense_variant	LEGRE	Somatic:chr6:106106459:A>C>C:SNV:MODERATE:missense_variant:PRDM1
PRDM1	NP_001189.2:p.Leu450Phe	NM_001198.4:c.1348C>T	missense_variant	BARHA	Somatic:chr6:106105508:C>T>T:SNV:MODERATE:missense_variant:PRDM1
PRDM1	NP_001189.2:p.Trp136Leu	NM_001198.4:c.407G>T	missense_variant	MORNA	Somatic:chr6:106095730:G>T>T:SNV:MODERATE:missense_variant:PRDM1
SPI1	NP_001074016.1:p.Gln227Glu	NM_001080547.2:c.679C>G	missense_variant	BIRMU	Somatic:chr11:47355364:G>C>C:SNV:MODERATE:missense_variant:SPI1
SPI1	NP_001074016.1:p.Gln227Glu	NM_001080547.2:c.679C>G	missense_variant	CHAIT	Somatic:chr11:47355364:G>C>C:SNV:MODERATE:missense_variant:SPI1
SPI1	NP_001074016.1:p.Gln227Glu	NM_001080547.2:c.679C>G	missense_variant	JOUNO	Somatic:chr11:47355364:G>C>C:SNV:MODERATE:missense_variant:SPI1
SPI1	NP_001074016.1:p.Gln227Glu	NM_001080547.2:c.679C>G	missense_variant	BARHA	Somatic:chr11:47355364:G>C>C:SNV:MODERATE:missense_variant:SPI1
SPI1	NP_001074016.1:p.Gln227Glu	NM_001080547.2:c.679C>G	missense_variant	MORFR	Somatic:chr11:47355364:G>C>C:SNV:MODERATE:missense_variant:SPI1
SPI1	NP_001074016.1:p.Gln227Glu	NM_001080547.2:c.679C>G	missense_variant	YAHDJ	Somatic:chr11:47355364:G>C>C:SNV:MODERATE:missense_variant:SPI1
TBL1XR1	.	NM_001321193.2:c.926-1G>C	splice_acceptor_varia	DURPA	Somatic:chr3:177038435:C>G>G:SNV:HIGH:splice_acceptor_variant:TBL1XR1
TBL1XR1	NP_001308122.1:p.Asp370Gly	NM_001321193.2:c.1109A>G	missense_variant	BENBE	Somatic:chr3:177038111:T>C>C:SNV:MODERATE:missense_variant:TBL1XR1
TBL1XR1	NP_001308122.1:p.Asp463Val	NM_001321193.2:c.1388A>T	missense_variant	DAVGE	Somatic:chr3:177032999:T>A>A:SNV:MODERATE:missense_variant:TBL1XR1
TBL1XR1	NP_001308122.1:p.Gly285Glu	NM_001321193.2:c.854G>A	missense_variant	DRAJE	Somatic:chr3:177047310:C>T>T:SNV:MODERATE:missense_variant:TBL1XR1
TBL1XR1	NP_001308122.1:p.His307Pro	NM_001321193.2:c.920A>C	missense_variant	MESAN	Somatic:chr3:177046134:T>G>G:SNV:MODERATE:missense_variant:TBL1XR1
TBL1XR1	NP_001308122.1:p.Ser459Asn	NM_001321193.2:c.1376G>A	missense_variant	MARIS1	Somatic:chr3:177033011:C>T>T:SNV:MODERATE:missense_variant:TBL1XR1
TBL1XR1	NP_001308122.1:p.Tyr395Asp	NM_001321193.2:c.1183T>G	missense_variant	SELMO	Somatic:chr3:177034265:A>C>C:SNV:MODERATE:missense_variant:TBL1XR1
TNFAIP3	NP_001257436.1:p.Arg271Gln	NM_001270507.2:c.812G>A	missense_variant	NGUFR	Somatic:chr6:137877082:G>A>A:SNV:MODERATE:missense_variant:TNFAIP3
TNFAIP3	NP_001257436.1:p.Arg271Ter	NM_001270507.2:c.811C>T	stop_gained	MARIS1	Somatic:chr6:137877081:C>T>T:SNV:HIGH:stop_gained:TNFAIP3
TNFAIP3	NP_001257436.1:p.Arg271Ter	NM_001270507.2:c.811C>T	stop_gained	MARMA1	Somatic:chr6:137877081:C>T>T:SNV:HIGH:stop_gained:TNFAIP3
TNFAIP3	NP_001257436.1:p.Asn170Ser	NM_001270507.2:c.509A>G	missense_variant	GACJE	Somatic:chr6:137875710:A>G>G:SNV:MODERATE:missense_variant:TNFAIP3
TNFAIP3	NP_001257436.1:p.Gln362ArgfsTer24	NM_001270507.2:c.1084del	frameshift_variant	MORFR	Somatic:chr6:137878528:GC>G>-:deletion:HIGH:frameshift_variant:TNFAIP3
TNFAIP3	NP_001257436.1:p.Ser459Ter	NM_001270507.2:c.1376C>A	stop_gained	LYKE	Somatic:chr6:137878821:C>A>A:SNV:HIGH:stop_gained:TNFAIP3
TP53	NP_000537.3:p.Arg273His	NM_000546.5:c.818G>A	missense_variant	ROUMI	Somatic:chr17:7673802:C>T>T:SNV:MODERATE:missense_variant:TP53
TP53	NP_000537.3:p.Arg282Trp	NM_000546.5:c.844C>T	missense_variant	CHAMI	Somatic:chr17:7673776:G>A>A:SNV:MODERATE:missense_variant:TP53
TP53	NP_000537.3:p.Arg337Ser	NM_000546.5:c.1009C>A	missense_variant	MESMO	Somatic:chr17:7670700:G>T>T:SNV:MODERATE:missense_variant:TP53
TP53	NP_000537.3:p.Asp281Val	NM_000546.5:c.842A>T	missense_variant	ROUMA	Somatic:chr17:7673778:T>A>A:SNV:MODERATE:missense_variant:TP53
TP53	NP_000537.3:p.Glu343SerfsTer2	NM_000546.5:c.1027del	frameshift_variant	TISFR	Somatic:chr17:7670681:TC>T>-:deletion:HIGH:frameshift_variant:TP53
TP53	NP_000537.3:p.Leu257Val	NM_000546.5:c.769C>G	missense_variant	LABPI	Somatic:chr17:7674194:G>C>C:SNV:MODERATE:missense_variant:TP53
TP53	NP_000537.3:p.Leu265Arg	NM_000546.5:c.794T>G	missense_variant	DEBLA	Somatic:chr17:7673826:A>C>C:SNV:MODERATE:missense_variant:TP53
TP53	NP_000537.3:p.Met246Lys	NM_000546.5:c.737T>A	missense_variant	PINDA	Somatic:chr17:7674226:A>T>T:SNV:MODERATE:missense_variant:TP53
TP53	NP_000537.3:p.Phe270Leu	NM_000546.5:c.808T>C	missense_variant	MESMO	Somatic:chr17:7673812:A>G>G:SNV:MODERATE:missense_variant:TP53
TP53	NP_000537.3:p.Thr230ProfsTer16	NM_000546.5:c.688_691del	frameshift_variant	HOUMI	Somatic:chr17:7674271:GTGGT>G>-:deletion:HIGH:frameshift_variant:TP53
TP53	NP_000537.3:p.Tyr220Cys	NM_000546.5:c.659A>G	missense_variant	GACJE	Somatic:chr17:7674872:T>C>C:SNV:MODERATE:missense_variant:TP53
TP53	NP_000537.3:p.Val157Asp	NM_000546.5:c.470T>A	missense_variant	DJEYO	Somatic:chr17:7675142:A>T>T:SNV:MODERATE:missense_variant:TP53
TP53	NP_000537.3:p.Val197Ala	NM_000546.5:c.590T>C	missense_variant	BOUMO	Somatic:chr17:7674941:A>G>G:SNV:MODERATE:missense_variant:TP53

Supplemental Table S6. Details of non-highly complex karyotypes (non-high CK) and high-CK.

	Patient	Karyotype according to ISCN 2020
Non-high CK	1	46,XY,t(6;6)(q12;q2?6),del(11)(q14)[2]/46,XY,del(6)(q12),del(11)(q14)[2]/46,XY[16]
	2	46,X,-X,+4[2]/47,sl,+18[2]/46,XX[16]
	3	48,XY,+12,+18[2]/48,sl,+3,-12[1]/46,XY[17]
	4	46,XY,del(6)(q12)[1]/46,sl,-Y,+9[19]
	5	47,X,-X,+4,+18[11]/46,XX[9]
	6	49,XY,+4,+15,+18[11]/46,XY[9]
	7	48,XX,+3,+12[1]/48,XX,+12,+18[1]/46,XX[10]
	8	46,XY[19]/50, XY, del(6q),+4,+8,+10,+12 [1]
	9	45,X,-Y,del(6)(q12),del(7)(q22q3?5)[3]/46,XY[17]
	10	45,X,-Y,-6,add(15)(q?26),+mar[cp2]/46,XY[18]
	11	47,XY,del(9)(p12),t(18;21)(q23;q21),+19[cp15]/46,XY[5]
	12	94,XXYY,der(6)t(3;6)(q11;q11)x2,+18,+18[3]/92,XXYY[1]/46,XY[16]
	13	46,XX,del(6)(q1?4q24),?der(16)[1]/46,XX,add(11)(q11)[1]/46,XX[18]
	14	48,XX,+4,del(9)(q2?1q?31),+12[3]/48,sl,dup(17)(q12q2?5)[10]/46,XX[7]
	15	45,X,-X[2]/45,sl,der(11)t(8;11)(q?22;q?22)[13]/46,sl,+12[4]/47,sdl1,+18[1]
	16	46,XY,del(6)(q?21q?24)[2]/46,idem,der(22)t(1;22)(q1?1;p1?3)[2]/46,XY,del(20)(q11)[6]/46,XY [10]
	17	46,XY,del(6)(q11)[13]/45,sl,-4,der(17)t(4;17)(p11;q11),der(22)t(4;22)(q12;q13)[3]/46,XY[4]
	18	47,XX,+3[2]/48,sl,+12[2]/46,XX,der(8)t(3;8)(q?12;p?12),t(14;19)(q1?1;?p12)[13]/46,XX[3]
	19	46,XY,t(3;11)(3pter->3p10::11p1?4->11pter;11p1?4->11q2?5::3q21->3qter),del(6)(q?16q2?4)[13]/47,XY,+4[1]/46,XY[6]
High-CK	20	46,XX,der(1)t(1;11)(q?21;p1?2),der(11)t(1;11)(q?21;p1?2)t(11;18)(q22;q2?2),der(18)t(11;18)(q22;q2?2)[cp11]/46,XX[2]
	21	46,XY,?der(4)t(4;6;7),der(6)t(4;6)(?q;q22),del(6)(q24),der(7)t(4;7;?10),der(10)[13]/46,XX[7]
	22	46,XY,+4,del(6)(q21q2?4),i(8)(q10),-13,der(20)t(13;20)(q3?1;q13)[17]/46,XY[3]
	23	47,XY,t(1;9)(p34;p24),t(3;15)(p26;q21),+4,del(6)(q1?5q2?2),del(13)(q14q31)[cp2]/46,XY[18]
	24	44,X,-Y,add(2)(p2?4),ins(4;8)(q?;?q),del(6)(q16;q24),-8,der(12)del(12)(p11)del(12)(q11), der(13)t(12;13)(q12;q1?3),add(17)(p12),-20,+mar1[cp3]/44,idem,-11,add(12)(p13),+mar2[cp5]/ 43,idem,-11,add(18)(q2?1)[cp4]
	25	45,XY,del(6)(q1?3),add(12)(q2?4),-14,add(17)(p1?2),?der(18)[cp8]/ 45,XY,del(3)(p?21),add(5)(p1?4),del(6)(q1?3),-14,add(17)(p1?2)[cp3]/46,XY[9]
	26	46,XY,del(17)(p11)[10]/45,sl,del(6)(q2?1q2?3),-16[3]/46,sl,+mar[4]/46,XY,del(13)(q1?3q2?1)[2]/46,XY[1]
	27	46,XY,add(8)(q24),del(12)(p1?2)[4]/49,sl,+4,+7,+9,add(22)(q?12)[10]/46,XY[6]
	28	45,X,-X,der(3)t(3;6)(p11;p11)x2,-6,der(11)t(3;11)(?;q22)[2]/45,idem,t(1;15)(q4?3;q1?2)[4] /46,XX[14]
	29	45,Y,add(X)(q28),add(2)(p1?2),der(?2),der(6)t(2;6)(q11;q11),-10,der(11)t(11;10)(q22;q21)[4]/46,sl,-add(X), add(17)(q2?5),-21,+mar[1]/46,XY[15
	30	46,XX,del(2)(p?16),del(6)(q2?2),-8,der(12),add(17)(p12),add(17)(p1?2),+mar[cp4]/46,XX[16]
	31	81-84,XXYY,-1,-1,der(3)t(3;3)(p26;q2?2)x2,der(6)t(6;7)(q11;q11)x2,-7,-7,-8,-9,-10,-11, der(12)t(1;12)(q1?2;q?11),-13,-14,-14,-15,-17,+3~4mar,+?r[cp3]/45,X,-Y[3]/46,XY[14]

Supplemental Table S7. Correlations between mutations and cytogenetic abnormalities. Cells in yellow, orange, red correspond to respective P ≤ 0.05, P ≤ 0.01, P ≤ 0.001. Correlations were non significant or non applicable/relevant in respective dark grey and black cells.

Chromosomal alterations

Gene mutations and chromosome localizati	Chr		del6q	del13q	del17p	del11q	tri12	tri18	tri4	CK	high-CK	*TP53abn*
	1p	***ARID1A***	3,78E-01	2,32E-01	2,36E-01	5,28E-02	3,48E-01	6,72E-01	7,05E-01	7,27E-01	1,00E+00	3,82E-01
	2q	***CXCR4*** S338	2,42E-01	5,04E-02	6,79E-01	6,35E-01	1,00E+00	7,42E-01	5,52E-02	4,70E-02	3,74E-01	2,36E-02
		CXCR4 other	4,51E-01	7,40E-01	1,00E+00	1,00E+00	6,83E-01	3,10E-01	3,30E-01	7,64E-01	3,63E-01	1,00E+00
		CXCR4 all	1,86E-01	3,30E-01	1,00E+00	1,00E+00	1,00E+00	1,00E+00	2,90E-02	2,48E-01	1,00E+00	1,29E-01
	3p	***MYD88*** L265P	1,54E-01	1,00E+00	6,05E-01	6,02E-01	1,38E-01	2,31E-01	4,74E-01	4,69E-01	6,16E-01	6,99E-01
		MYD88 other	1,75E-01	1,67E-01	1,00E+00	1,00E+00	1,00E+00	1,00E+00	1,00E+00	5,83E-01	1,00E+00	4,96E-01
		MYD88 all	NA	NA	NA	NA	NA	NA	NA	NA	NA	1,00E+00
	3q	***TBL1XR1***	1,00E+00	1,00E+00	1,00E+00	1,00E+00	4,07E-01	4,87E-01	1,00E+00	1,00E+00	1,00E+00	1,00E+00
	6p	***HIST1H1E***	3,30E-01	6,77E-01	5,45E-01	5,45E-01	2,44E-01	1,49E-01	2,12E-01	1,00E+00	1,00E+00	6,25E-01
	7q	***EZH2***	2,68E-01	3,54E-01	4,32E-01	9,05E-02	1,00E+00	5,97E-01	1,00E+00	6,30E-01	1,04E-01	1,00E+00
	11p	***SPI1***	1,77E-01	5,70E-01	1,00E+00	1,00E+00	3,69E-01	4,99E-01	1,94E-01	1,00E+00	1,00E+00	1,00E+00
	12q	***MLL2***	7,73E-01	6,92E-01	1,00E+00	3,51E-01	1,00E+00	1,00E+00	1,00E+00	4,83E-01	1,00E+00	1,00E+00
	17p	***TP53***	1,00E-01	2,10E-02	3,40E-02	5,77E-01	1,00E+00	1,00E+00	4,23E-01	1,18E-01	3,70E-02	
	17q	***CD79B***	2,73E-01	6,28E-01	1,12E-01	4,72E-01	3,12E-02	6,04E-01	3,57E-01	6,86E-01	5,52E-01	2,99E-01
	17q	***IKZF3***	1,77E-01	1,00E+00	2,95E-01	1,00E+00	1,00E+00	4,99E-01	5,90E-01	5,83E-01	1,00E+00	4,80E-01

CK, complex karyotype; high-CK, highly CK; NA, not applicable (too few cases)

Gene mutations

	MYD88 L265P	***MYD88*** other	***MYD88*** all	***CXCR4*** S338	***CXCR4*** other	***CXCR4*** all	***ARID1A***	***TP53***	***MLL2***	***TBL1XR1***	***SPI1***	***CD79B***	***EZH2***	***HIST1H1E***	***IKZF3***
MYD88 L265P				1,06E-01	2,48E-01	3,09E-02	7,97E-01	8,20E-01	8,63E-01	7,91E-01	6,83E-01	9,05E-01	5,61E-01	4,92E-01	7,29E-01
MYD88 other				1,00E+00	1,00E+00	1,00E+00	1,00E+00	3,40E-01	NA	NA	1,00E+00	1,00E+00	1,00E+00	1,00E+00	1,00E+00
MYD88 all			0,857	3,85E-01	5,04E-01	1,81E-01	9,42E-01	6,60E-01	NA	NA	8,29E-01	9,76E-01	7,53E-01	7,05E-01	8,56E-01
CXCR4 S338							3,32E-01	4,39E-03	3,99E-01	1,00E+00	6,17E-01	1,26E-01	7,66E-01	4,96E-01	1,00E+00
CXCR4 other							3,22E-03	8,42E-01	8,70E-01	1,10E-01	1,00E+00	1,00E+00	7,16E-01	7,87E-01	1,00E+00
CXCR4 all							2,75E-03	3,24E-02	0,622	0,411	0,857	0,464	0,759	0,619	1
ARID1A								0,304	0,805	0,407	1	0,559	0,171	0,635	1
TP53									0,778	1	1	0,531	0,531	0,606	1
MLL2										1	NA	0,519	0,223	0,11	NA
TBL1XR1											NA	0,209	1	1	NA
SPI1												1	1	1	0,171
CD79B													0,404	0,471	0,247
EZH2														0,471	1
HIST1H1E															0,295
IKZF3															

Chromosomal alterations

	del6q	del13q	del17p	del11q	tri12	tri18	tri4	CK	high-CK	*TP53abn*
del6q		5,10E-03	1,10E-02	4,20E-03	9,00E-01	9,50E-01	3,20E-02	6,23E-02	1,56E-04	5,15E-03
del13q			4,70E-03	1,50E-01	6,10E-01	8,00E-01	5,70E-02	6,00E-02	4,00E-01	9,00E-02
del17p				6,10E-01	1,00E+00	8,70E-01	1,00E+00	1,32E-02	5,90E-04	
del11q					6,30E-01	7,70E-01	7,90E-01	6,35E-02	8,10E-02	7,78E+01
tri12						2,90E-01	3,30E-01	7,90E-02	6,65E-01	8,00E-01
tri18							2,10E-02	2,00E-01	7,77E-01	8,18E+01
tri4								7,50E-04	2,10E-02	6,25E-01
CK										2,30E-02
high-CK										2,50E-04
TP53abn										

Supplemental Tables S8. Cytogenetic and mutational characteristics of non-highly-complex karyotype (non-high-CK) and highly CK (high-CK). ns, non significant

CBA +/- FISH	Non-high-CK	High-CK	*P* value
6q deletion			
Yes	9/19 (47%)	11/12 (92%)	**0,0201 (*)**
No	10/19 (53%)	1/12 (8%)	
11q deletion			
Yes	3/19 (16%)	3/12 (25%)	0,65 (ns)
No	16/19 (84%)	9/12 (75%)	
13q deletion			
Yes	2/19 (10%)	6/12 (50%)	**0,0316 (*)**
No	17/19 (90%)	6/12 (50%)	
17p deletion			
Yes	1/19 (5%)	5/12 (42%)	**0,0217 (*)**
No	18/19 (95%)	7/12 (58%)	
Trisomy 12			
Yes	5/19 (26%)	1/12 (8%)	0,363 (ns)
No	14/19 (74%)	11/12 (92%)	
Trisomy 4			
Yes	5/19 (26%)	4/12 (33%)	0,7039 (ns)
No	14/19 (74%)	8/12 (67%)	
Trisomy 18			
Yes	6/19 (32%)	1/12 (8%)	0,2015 (ns)
No	13/19 (68%)	11/12 (92%)	
Trisomy 3			
Yes	3/19 (16%)	3/12 (25%)	0,6526 (ns)
No	16/19 (84%)	9/12 (75%)	

Mutations	Non-high-CK	High-CK	*P* value
MYD88			
Yes	17/18 (94%)	11/11 (100%)	> 0,9999 (ns)
No	1/18 (6%)	0/11 (0%)	
CXCR4			
Yes	8/18 (44%)	3/11 (27%)	0,4486 (ns)
No	10/18 (56%)	8/11 (73%)	
ARID1A			
Yes	2/16 (13%)	1/11 (9%)	> 0,9999 (ns)
No	14/16 (87%)	10/11 (91%)	
TP53			
Yes	1/16 (6%)	3/11 (27%)	0,2729 (ns)
No	15/16 (94%)	8/11 (73%)	
MLL2			
Yes	3/13 (23%)	1/8 (13%)	> 0,9999 (ns)
No	10/13 (77%)	7/8 (87%)	
TBL1RX1			
Yes	1/13 (8%)	0/8 (0%)	> 0,9999 (ns)
No	12/13 (92%)	8/8 (100%)	
SPI1			
Yes	1/16 (6%)	0/11 (0%)	> 0,9999 (ns)
No	15/16 (94%)	11/11 (100%)	
CD79B			
Yes	0/16 (0%)	1/11 (9%)	0,4074 (ns)
No	16/16 (100%)	10/11 (91%)	

Supplemental Table S8. Correlations between disease phenotype and mutational/cytogenetic abnormalities**.** Cells in yellow, orange, red correspond to respective P ≤ 0.05, P ≤ 0.01, P ≤ 0.001. Correlations were non significant or non applicable/relevant in respective dark grey and black cells. NS, non significant.

Disease phenotype	Mutational/cytogenetic alterations												
	MYD88	***CXCR4***	***ARID1A***	***MLL2***	***CD79A/B***	***TBL1XR1***	***SPI1***	**del6q**	**tri18**	**tri4**	**CK**	**high-CK**	***TP53abn***
Lymphadenopathy	NS	NS	NS	NS	NS	NS	3,32E-02	NS	NS	NS	NS	NS	2,24E-02
Splenomegaly	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Serum IgM level	NS	4,90E-02	NS	NS	NS	7,50E-04	NS	NS	NS	NS	NS	NS	NS
BM infiltration	NS	1,60E-02	NS	NS	NS	NS	NS	1,00E-03	NS	8,03E-03	2,70E-03	3,04E-03	NS
Hemoglobin < 10,5 g/dL	NS	NS	NS	NS	NS	NS	NS	5,00E-05	NS	3,40E-03	7,30E-03	3,70E-02	NS
Platelet count < 100 G/L	NS	2,00E-04	NS	NS	NS	NS	NS	NS	NS	5,20E-03	NS	NS	NS
Hyperviscosity syndrome	NS	4,02E-02	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
IPSSWM score	NS	NS	NS	NS	NS	NA	NA	NS	NS	NS	NS	NS	NS

BM, bone marrow; CK, complex karyotype; high-CK, highly CK; NA, not applicable (too few cases)

Supplemental Table S10. Univariate analyses of variables associated with time to first treatment (TFT) (n=239) and relapse (n=101).

	Time to first treatment		
	HR	***IC 95%***	***P***
B2M	2.27	1.11-4.6	0.02
IPSSWM	-	-	NS
Del6q	2.01	0.90-2.57	0.08
Trisomy 12	1.98	0.91-2.42	0.07
CK	-	-	NS
High-CK	-	-	NS
TP53 abn	-	-	NS
CXCR4 mutations	-	-	NS

As only one variable was significant in univariate analysis, multivariate analysis was not performed.
Abbreviations : B2M, beta2microglobulin; CI, confidence interval; CK, complex karytotype; high-CK, highly CK; HR, hazard ratio; IPSSWM, international prognostic scoring system for Waldenström macroglobulinemia; NS, non significant

	Relapse		
	HR	***IC 95%***	***P***
B2M	-	-	NS
IPSSWM	-		NS
Del6q	2.02	1.09-3.73	0.02
Tri4	-	-	NS
CK	-	-	NS
High-CK	3.09	1.57-8.02	0.01
TP53 abn	3.52	1.49-7.87	0.002
CXCR4 FS mutations	-	-	NS
SPI1 mutations	-	-	NS

Abbreviations : B2M, beta2microglobulin; CI, confidence interval; CK, complex karytotype; high-CK, highly CK;

Supplemental Table S11. Repartition of cytogenetic and molecular abnormalities according to chemotherapy (CT, n=47) and immunochemotherapy (ICT, n=125) groups of treatment

Mutations	CT	ICT	*P* value
MYD88			
Yes	33/33 (100)	97/105 (92)	0,1
No	0/33 (0)	8/105 (8)	
CXCR4			
Yes	7/33 (21)	32/100 (32)	0,238
No	26/33 (79)	68/100 (68)	
ARID1A			
Yes	2/33 (6)	10/86 (12)	0,37
No	31/33 (94)	76/86 (88)	
TP53			
Yes	4/33 (12)	6/86 (7)	0,365
No	29/33 (88)	80/86 (93)	
MLL2			
Yes	1/23 (4)	8/69 (12)	0,31
No	22/23 (96)	61/69 (88)	
TBL1RX1			
Yes	1/23 (4)	2/69 (3)	0,74
No	22/23 (96)	67/69 (97)	
SPI1			
Yes	2/33 (6)	3/86 (3)	0,9
No	31/33 (93)	83/86 (97)	
CD79B			
Yes	2/33 (6)	5/86 (6)	0,96
No	31/33 (88)	81/86 (94)	
TP53 abnormalities			
Yes	6/46 (13)	14/122 (11)	0,78
No	40/46 (87)	108/122 (89)	

CBA +/- FISH	CT	ICT	*P* value
6q deletion			
Yes	17/44 (39)	37/114 (32)	0,1
No	27/44 (61)	77/114 (68)	
13q deletion			
Yes	9/44 (20)	14/113 (12)	0,2
No	35/44 (80)	99/113 (88)	
17p deletion			
Yes	4/43 (9)	9/114 (8)	0,78
No	39/43(91)	105/114 (92)	
Trisomy 4			
Yes	8/41 (19)	14/107 (13)	0,1
No	33/41 (81)	93/107 (87)	
Trisomy 18			
Yes	5/41 (12)	10/114 (9)	0,53
No	36/41 (88)	104/114 (91)	
Complex karyotype			
Yes	7/34 (20)	20/111 (18)	0,3
No	27/34 (80)	81/111 (82)	

Supplemental Table S12. Uni- and multivariate analyses of variables associated with PFS and OS in ICT group (n=125).

	PFS						OS					
	Univariate (n=125)			Multivariate* (n=91)			Univariate (n=125)			Multivariate* (n=88)		
	HR	*IC 95%*	*P*	HR	*IC 95%*	*P*	HR	*IC 95%*	*P*	HR	*IC 95%*	*P*
B2M	-	-	NS				-	-	NS			
IPSSWM	-	-	NS				3.11	1.15-5.10	0.002	2.74	1.09-4.44	0.02
Del6q	1.98	1.02-2.89	0.04	-	-	NS	-	-	NS			
Tri4	-	-	NS				-	-	NS			
CK	-	-	NS				-	-	NS			
High-CK	2.21	1.08-3.87	0.04	-	-	NS	-	-	NS			
***TP53* abn**	3.35	1.39-6.02	0.001	3.19	1.48-6.85	0.01	2.09	1.30-3.18	0.002	1.96	1.22-2.46	0.05
***CXCR4* FS mutations**	-	-	NS				-	-	NS			
***SPI1* mutations**	-	-	NS				-	-	NS			

*For multivariable analyses, we considered only variables that were significant (P ≤ 0.05) in univariate analyses and cases with available data for all the factors included in the model.

Abbreviations : B2M, beta2microglobulin; CI, confidence interval; CK, complex karytotype; high-CK, highly CK; HR, hazard ratio; IPSSWM, international prognostic scoring system for Waldenström macroglobulinemia; NS, non significant; PFS, progression-free survival; OS, overall survival.

Supplemental Table S13. Cytogenetic and molecular data of WM samples from nine patients who experienced transformed WM.

Mutated genes	Number of karyotypic abnormalities	Karyotype
MYD88, CXCR4, ARID1A, TP53, CD79B, EZH2	15	44,X,-Y,add(2)(p2?4),ins(4;8)(q?;?q),del(6)(q16;q24),-8,der(12)del(12)(p11)del(12)(q11), der(13)t(12;13)(q12;q1?3),add(17)(p12),-20,+mar1[cp3]/44,idem,-11,add(12)(p13),+mar2[cp5]/ 43,idem,-11,add(18)(q2?1)[cp4]
MYD88	5	94,XXYY,der(6)t(3;6)(q11;q11)x2,+18,+18[3]/92,XXYY[1]/46,XY[16]
MYD88, CXCR4, TP53	2	49,XY,del(6)(q),+4,+8,+10,+12 [5]/46,XY[15]
MYD88, CD79B, IKZF3	2	45,X,-X,del(17)(p12)[19]
MYD88, CXCR4, TP53, MLL2	3	47,XY,del(9)(p12),t(18;21)(q23;q21),+19[15]/46,XY[5]
MYD88, HIST1H1E	22	81-84,XXYY,-1,-1,der(3)t(3;3)(p26;q2?2)x2,der(6)t(6;7)(q11;q11)x2,-7,-7,-8,-9,-10,-11, der(12)t(1;12)(q1?2;q?11),-13,-14,-14,-15,-17,+3~4mar,+?r[cp3]/45,X,-Y[3]/46,XY[14]
Not available	2	48,XY,+3,+18[2]/46,XY[18]
Not available	7	46,XX,del(2)(p?16),del(6)(q2?2),-8,der(12),add(17)(p12),add(17)(p1?2),+mar[cp4]/46,XX[16]
MYD88	5	46,XY,del(5)(q3?2),add(9)(p2?3)[3]/46,XY[17]