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Cytogenetic and molecular abnormalities in Waldenström's macroglobulinemia patients: correlations and prognostic impact

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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. TP53abn and del6g 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), TP53abn (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 cells¹. 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 patients⁴. 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 diagnosis⁷, along with prognosis in some studies^{7,8} but not confirmed in others⁹, and have been considered as predictive for response to ibrutinib10. Other mutations have been described at a lower frequency (5-20%) in ARID1A, CD79B, SPI1 or TP53 genes¹¹⁻¹⁴, 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 del6q¹⁵.

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 refined²⁰ 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 status¹¹. 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 ICT³⁴. 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 classification¹ 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 described⁴, 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 \geq 3 clonal aberrations were present in CBA, respectively. Highly CK (high-CK) and non-high-CK were respectively defined if \geq 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 Novaseg6000 flow cell and the onboard cluster method

(Illumina, San Diego, CA). Targeted sequencing was analyzed according to previously described algorithms with minor modifications²². 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 criteria². 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 $(P \le 0.05)$ 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 malignancies²²⁻²⁷. *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 \geq 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 TP53abn (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 TP53abn (6/12 [50%] vs. 2/15 [13%], P=0.03) while no difference was observed in terms of specific gene mutation frequencies.

Of note, TP53abn 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 TP53abn (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 TP53abn 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 TP53abn (44% vs. 21%, P=0.02) and SP11 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), P=0.03 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), P=0.030 (**Figure 2** and **Supplemental Figure S1**). In multivariate analyses, only P=0.03 for PFS and IPSSWM (P=0.03) and 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 TP53abn for PFS and IPSSWM and TP53abn 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 CLL²⁰. 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 tri18⁴. 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 study³⁷. Although del6q and CXCR4 mutations have been suggested to be mutually exclusive³⁸, 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 del6q³⁷. 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 suggested¹⁵. We also brought more information about del17p (7%)/TP53abn 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 CLL²⁰, 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 described⁷. 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 suggested¹³. 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 TP53abn

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.

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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

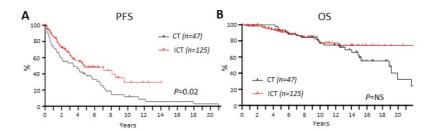


Figure 2. Respective progression free-survival (PFS) and overall survival (OS) for the following recurrent molecular/cytogenetic abnormalities in the entire cohort: *MYD88/CXCR4* status (A, B), del6q (C, D), *TP53*abn (E, F), non-high-CK and high-CK (I, J). Abbreviations: abn, abnormalities; CA, cytogenetic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

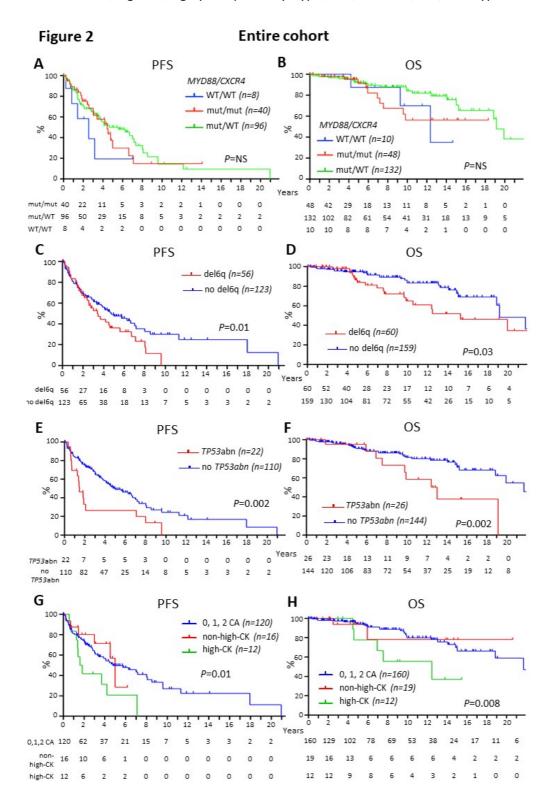
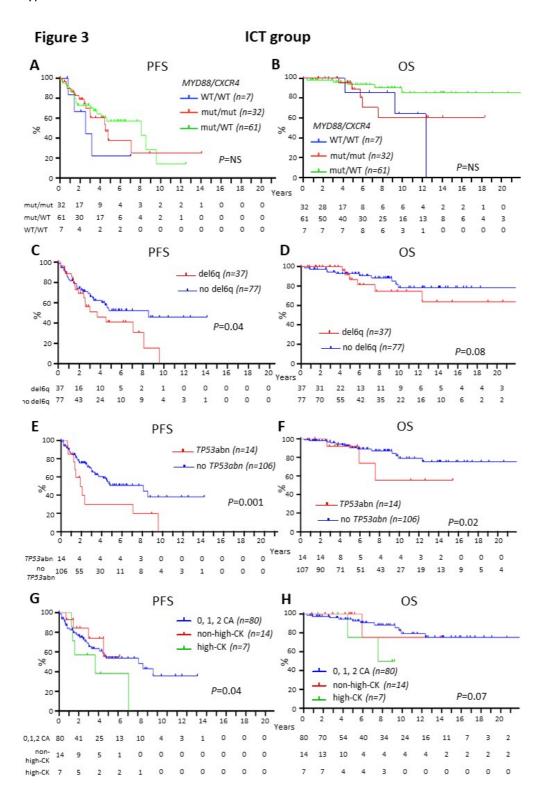


Figure 3. Respective progression free-survival (PFS) and overall survival (OS) for the following recurrent molecular/cytogenetic abnormalities in patients who received first-line immunochemotherapy (ICT): *MYD88/CXCR4* status (A, B), del6q (C, D), *TP53* abn (E, F), non-high-CK and high-CK (I, J). Abbreviations: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

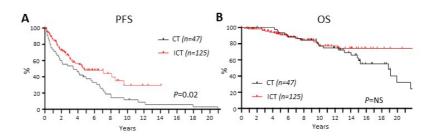
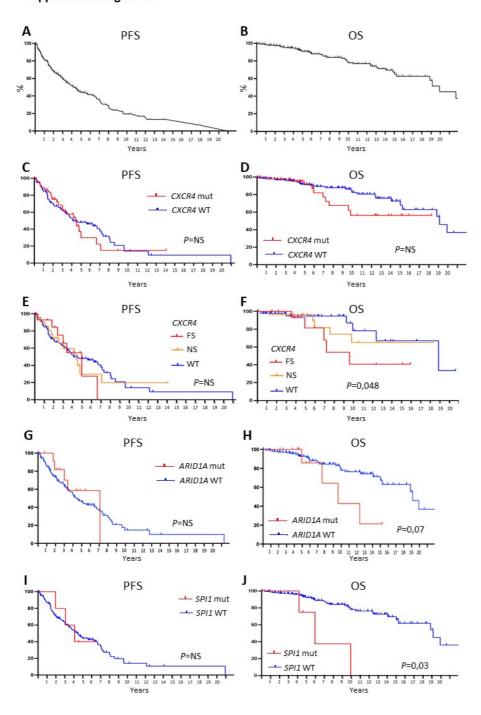
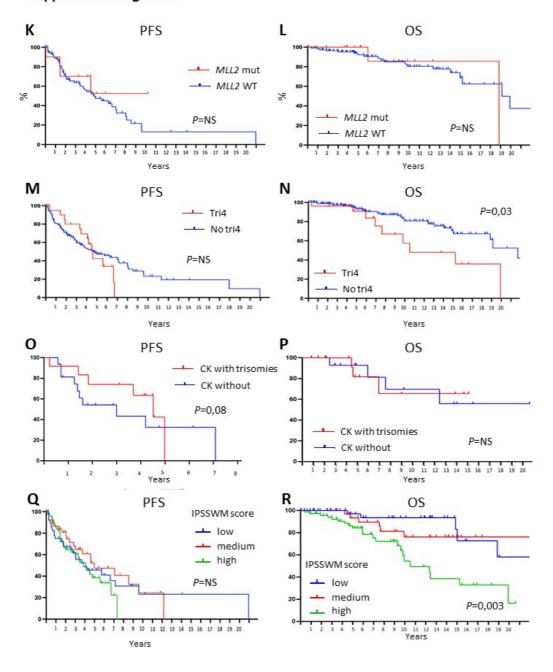


Figure S2. Progression free-survival (PFS) (A) and overall survival (OS) (B) of the whole WM cohort and respective PFS/OS for the following recurrent molecular/cytogenetic abnormalities: *CXCR4* mutated vs. WT (C, D), *CXCR4* WT vs. nonsense (NS) vs. frameshift (FS) mutations (E,F), *ARID1A* (G,H), *SPI1* (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	20, 200 (0.0)	
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)	
11 33 abnormances (del1/p) 17 33 mutation)	20/ 1/0 (13)	
Abbreviations: CBA, chromosome banding analysis;		
IPSS, international prognostic scoring system; WM,		
Waldenström macroglobulinemia		

Table 2. Uni- and multivariate analyses of variables associated with PFS	variate analy	rses of variable	es associated		and OS in the entire cohort.	tire cohort.						
			PFS	S					SO	S		
	n	Univariate (n=187)	37)	Mul	Multivariate* (n=121)	121)	n	Univariate (n=239)	(68	Mul	Multivariate* (n=136)	(98)
	HR	IC 95%	Ь	HR	IC 95%	Ь	HR	IC 95%	Ь	HR	1C 95%	Ь
BZM		1	NS					-	NS			
IPSSWM		1	NS				3.70	1.47-9.10	0.002	3.06	1.26-5.96	0.03
De l 6q	2.24	1.17-4.29	0.01		1	NS	2.02	1.07-3.83	0.027		1	NS
Tri4		ı	NS				2.38	1.08-5.22	0.026		ı	NS
CK		ı	NS					1	NS			
High-CK	3.29	1.23-8.79	0.01		1	NS	3.44	1.30-9.10	0.01		ı	NS
<i>TP53</i> 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		ı	NS				2.56	1.00-6.66	0.047		ı	NS
SP/1 mutations		1	NS				4.10	1.01-12.4	0.037	-	ı	NS
*For multivariable analyses, we considered only variables that were si	yses, we cor	usidered only v	variables tha	t were signif	icant (P ≤ 0.05)) in univariate	e analyses ar	gnificant (P \leq 0.05) in univariate analyses and cases with available data for all the factors included in the model	available data	រ for all the fa	actors included	d 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

	RefSeq sequences	Chromosomic	Targeted
Gene	(coding transcripts)	region	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
СНОР	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 HGVSp variant_id NP 006006.3:p.Asn935ValfsTer NM_006015.6:c.2799_2802del Somatic:chr1:26766286:GGATT>G>-:deletion:HIGH:frameshift_variant:ARID1A frameshift_variant LEBRE 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 AREMA Somatic:chr1:26775067:C>T>T:SNV:HIGH:stop_gained:ARID1A stop_gained 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 NP 006006.3:p.Gln2100Ter ARID1A 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 Somatic:chr1:26780280:C>T>T:SNV:HIGH:stop_gained:ARID1A stop_gained JOLJE ARID1A NP_006006.3:p.Gln372Ter NM_006015.6:c.1114C>T stop_gained 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 missense_variant LANGI Somatic:chr1:26774906:C>A>A:SNV:MODERATE:missense variant:ARID1A ARID1A NP_006006.3:p.Pro1560His NM_006015.6:c.4679C>A NP_006006.3:p.Pro459Ala Somatic:chr1:26731176:C>G>G:SNV:MODERATE:missense_variant:ARID1A ARID1A NM_006015.6:c.1375C>G missense_variant POUEV ARID1A PETAN NP_006006.3:p.Ser744Ter NM_006015.6:c.2231C>G stop_gained 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 missense_variant CANPA Somatic:chr7:2944324:T>C>C:SNV:MODERATE:missense variant:CARD11 NM 001324281.2:c.572A>G CD79A NP_001774.1:p.lle202Thr NM_001783.4:c.605T>C Somatic:chr19:41880904:T>C>C:SNV:MODERATE:missense_variant:CD79A missense_variant DEVFR CD79B splice acceptor variarILIMA NM_000626.4:c.550-1G>A Somatic:chr17:63929476:C>T>T:SNV:HIGH:splice_acceptor_variant:CD79B NP 000617.1:p.Glu197Gly CD79B NM 000626.4:c.590A>G Somatic:chr17:63929435:T>C>C:SNV:MODERATE:missense variant&splice region variant:CD79B missense variant&spl BONCO NP_000617.1:p.Gly189ThrfsTer17 CD79B 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 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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 NP_001008540.1:p.Leu330ProfsTer18 frameshift_variant DAVJA Somatic:chr2:136114951:A>AG>G:insertion:HIGH:frameshift_variant:CXCR4 NM_001008540.2:c.988dup 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 Somatic:chr2:136114916:A>AT>T:insertion:HIGH:frameshift variant:CXCR4 NP 001008540.1:p.Ser342IlefsTer6 NM_001008540.2:c.1023_1024insA frameshift_variant GYNJI NP_001008540.1:p.Ser342PhefsTer6 Somatic:chr2:136114915:G>GA>A:insertion:HIGH:frameshift_variant:CXCR4 CXCR4 NM_001008540.2:c.1024dup frameshift_variant DESMA 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 Somatic:chr2:136114915:G>C>C:SNV:HIGH:stop_gained:CXCR4 stop_gained CXCR4 NP 001008540.1:p.Ser342Ter NM 001008540.2:c.1025C>G CHAIT 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 NP 001008540.1:p.Ser342Ter CXCR4 NM_001008540.2:c.1025C>G stop_gained DIGPI Somatic:chr2:136114915:G>C>C:SNV:HIGH:stop_gained:CXCR4 NP_001008540.1:p.Ser342Ter Somatic:chr2:136114915:G>C>C:SNV:HIGH:stop_gained:CXCR4 NM_001008540.2:c.1025C>G stop_gained CXCR4 FERJE NP_001008540.1:p.Ser342Ter NM_001008540.2:c.1025C>G stop_gained Somatic:chr2:136114915:G>C>C:SNV:HIGH:stop_gained:CXCR4 CXCR4 NP 001008540.1:p.Ser342Ter NM 001008540.2:c.1025C>G GILAL Somatic:chr2:136114915:G>C>C:SNV:HIGH:stop_gained:CXCR4 stop_gained CXCR4 NP_001008540.1:p.Ser342Ter NM_001008540.2:c.1025C>G LABPI Somatic:chr2:136114915:G>C>C:SNV:HIGH:stop_gained:CXCR4 stop_gained CXCR4 NP_001008540.1:p.Ser342Ter NM_001008540.2:c.1025C>G LANCH Somatic:chr2:136114915:G>C>C:SNV:HIGH:stop_gained:CXCR4 stop_gained 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 NP 001008540.1:p.Ser342Ter CXCR4 NM 001008540.2:c.1025C>G MESMO Somatic:chr2:136114915:G>C>C:SNV:HIGH:stop_gained:CXCR4 stop_gained CXCR4 NP_001008540.1:p.Ser342Ter NM_001008540.2:c.1025C>A MORNA Somatic:chr2:136114915:G>T>T:SNV:HIGH:stop_gained:CXCR4 stop_gained Somatic:chr2:136114915:G>T>T:SNV:HIGH:stop_gained:CXCR4 stop_gained CXCR4 NP_001008540.1:p.Ser342Ter NM_001008540.2:c.1025C>A ROUMA NM 001008540.2:c.1025C>A stop_gained NP_001008540.1:p.Ser342Ter Somatic:chr2:136114915:G>T>T:SNV:HIGH:stop_gained:CXCR4 CXCR4 SASPA NP_001008540.1:p.Ser342Ter NM_001008540.2:c.1025C>G stop_gained Somatic:chr2:136114915:G>C>C:SNV:HIGH:stop_gained:CXCR4 CXCR4 NP 001008540.1:p.Ser342Ter NM 001008540.2:c.1025C>G TAHI Somatic:chr2:136114915:G>C>C:SNV:HIGH:stop_gained:CXCR4 stop gained CXCR4 NP_001008540.1:p.Ser342Ter NM 001008540.2:c.1025C>G LIJKO Somatic:chr2:136114915:G>C>C:SNV:HIGH:stop_gained:CXCR4 stop_gained NM 001008540.2:c.1025C>G CXCR4 NP 001008540.1:p.Ser342Ter stop_gained POICA Somatic:chr2:136114915:G>C>C:SNV:HIGH:stop gained:CXCR4 NP_001008540.1:p.Ser342Ter NM_001008540.2:c.1025C>G Somatic:chr2:136114915:G>C>C:SNV:HIGH:stop_gained:CXCR4 stop_gained 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 Somatic:chr2:136114915:G>C>C:SNV:HIGH:stop_gained:CXCR4 CXCR4 NM_001008540.2:c.1025C>G stop_gained NP_001008540.1:p.Ser342Ter FRAMA2 NM 001008540.2:c.1025C>A Somatic:chr2:136114915:G>T>T:SNV:HIGH:stop gained:CXCR4 CXCR4 NP_001008540.1:p.Ser342Ter MUMFR stop_gained 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 NM 001008540.2:c.1033 1034del frameshift variant BERBE NP_001008540.1:p.Ser345HisfsTer2 Somatic:chr2:136114905:GGA>G>-:deletion:HIGH:frameshift_variant:CXCR4 CXCR4 Somatic:chr2:136114905:GGA>G>-:deletion:HIGH:frameshift variant:CXCR4 NP_001008540.1:p.Ser345HisfsTer2 NM_001008540.2:c.1033_1034del frameshift_variant PETAN CXCR4 NP_001008540.1:p.Ser345HisfsTer2 NM 001008540.2:c.1033 1034del frameshift variant 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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 NP 001190176.1:p.Lys510Arg EZH2 NM 001203247.2:c.1529A>G Somatic:chr7:148815508:T>C>C:SNV:MODERATE:missense_variant&splice_region_variant:EZH2 missense variant&spl SURPA NP_001190176.1:p.Lys510Arg NM_001203247.2:c.1529A>G Somatic:chr7:148815508:T>C>C:SNV:MODERATE:missense_variant&splice_region_variant:EZH2 missense_variant&spl TARAN Somatic:chr6:26156757:G>C>C:SNV:MODERATE:missense_variant:HIST1H1E HIST1H1E NP_005312.1:p.Ala123Pro NM_005321.2:c.367G>C missense variant BEAJE 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 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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 DUPLI Somatic:chr12:49050143:T>A>A:SNV:HIGH:stop_gained:KMT2D stop gained 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 Somatic:chr12:49042607:T>C>C:SNV:MODERATE:missense_variant:KMT2D missense variant DEWYV NP_003473.3:p.Phe2494SerfsTer49 KMT2D 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 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missense_variant NICPH Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88 NM_001172567.2:c.779T>C MYD88 NP_001166038.2:p.Leu260Pro 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 missense_variant PEATH MYD88 NP_001166038.2:p.Leu260Pro NM_001172567.2:c.779T>C 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 missense_variant PINDA MYD88 NP_001166038.2:p.Leu260Pro NM_001172567.2:c.779T>C Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88 NP_001166038.2:p.Leu260Pro MYD88 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 NM 001172567.2:c.779T>C missense variant POUEV Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense variant:MYD88 NP 001166038.2:p.Leu260Pro 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 Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense variant:MYD88 missense variant RAUEV 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 NP 001166038.2:p.Leu260Pro MYD88 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 Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88 missense_variant ROUMI 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 missense_variant SASPA NP_001166038.2:p.Leu260Pro NM_001172567.2:c.779T>C Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88 missense_variant SEBMO MYD88 NP_001166038.2:p.Leu260Pro NM_001172567.2:c.779T>C 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 Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense variant:MYD88 missense variant SONAL 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 NP 001166038.2:p.Leu260Pro Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88 MYD88 NM 001172567.2:c.779T>C missense_variant TAHI missense_variant TARAN MYD88 NP_001166038.2:p.Leu260Pro NM_001172567.2:c.779T>C Somatic:chr3:38141150:T>C>C:SNV:MODERATE:missense_variant:MYD88 NP_001166038.2:p.Leu260Pro MYD88 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 missense_variant BOUMO MYD88 NP_001166038.2:p.Val204Phe NM_001172567.2:c.610G>T 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 NP_004547.3:p.Tyr115SerfsTer13 NM 004556.3:c.342_345del NFKBIE 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 Somatic:chr6:106106459:A>C>C:SNV:MODERATE:missense_variant:PRDM1 missense_variant LEGRE Somatic:chr6:106105508:C>T>T:SNV:MODERATE:missense_variant:PRDM1 PRDM1 NP_001189.2:p.Leu450Phe NM_001198.4:c.1348C>T missense_variant BARHA 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 NP_001074016.1:p.Gln227Glt NM_001080547.2:c.679C>G missense_variant BIRMU Somatic:chr11:47355364:G>C>C:SNV:MODERATE:missense_variant:SPI1 NP 001074016.1:p.Gln227Glu missense variant CHAIT SPI1 NM 001080547.2:c.679C>G 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 NP_001074016.1:p.Gln227Glu SPI1 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 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 splice_acceptor_variar DURPA NM 001321193.2:c.926-1G>C Somatic:chr3:177038435:C>G>G:SNV:HIGH:splice_acceptor_variant:TBL1XR1 TBL1XR1 NP_001308122.1:p.Asp370Gly NM_001321193.2:c.1109A>G Somatic:chr3:177038111:T>C>C:SNV:MODERATE:missense_variant:TBL1XR1 missense_variant BENBE TBL1XR1 NP_001308122.1:p.Asp463Val Somatic:chr3:177032999:T>A>A:SNV:MODERATE:missense_variant:TBL1XR1 NM_001321193.2:c.1388A>T missense_variant DAVGE 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 Somatic:chr3:177046134:T>G>G:SNV:MODERATE:missense variant:TBL1XR1 TBL1XR1 NP_001308122.1:p.His307Pro NM_001321193.2:c.920A>C missense_variant MESAN TBL1XR1 NP 001308122.1:p.Ser459Asn Somatic:chr3:177033011:C>T>T:SNV:MODERATE:missense_variant:TBL1XR1 NM 001321193.2:c.1376G>A missense variant MARIS1 missense_variant SELMO Somatic:chr3:177034265:A>C>C:SNV:MODERATE:missense variant:TBL1XR1 TBL1XR1 NP_001308122.1:p.Tyr395Asp NM_001321193.2:c.1183T>G NM_001270507.2:c.812G>A TNFAIP3 NP_001257436.1:p.Arg271Gln 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 MARIS1 Somatic:chr6:137877081:C>T>T:SNV:HIGH:stop gained:TNFAIP3 stop_gained 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 frameshift_variant MORFR TNFAIP3 NP_001257436.1:p.Gln362ArgfsTer24 NM_001270507.2:c.1084del Somatic:chr6:137878528:GC>G>-:deletion:HIGH:frameshift_variant:TNFAIP3 TNFAIP3 NP_001257436.1:p.Ser459Ter Somatic:chr6:137878821:C>A>A:SNV:HIGH:stop_gained:TNFAIP3 NM_001270507.2:c.1376C>A stop_gained LYKE 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 missense_variant ROUMA Somatic:chr17:7673778:T>A>A:SNV:MODERATE:missense variant:TP53 TP53 NP_000537.3:p.Asp281Val NM_000546.5:c.842A>T NP_000537.3:p.Glu343SerfsTer2 TP53 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 NM 000546.5:c.737T>A missense_variant PINDA Somatic:chr17:7674226:A>T>T:SNV:MODERATE:missense_variant:TP53 NP_000537.3:p.Met246Lys 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 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

NP_000537.3:p.Val157Asp

NP_000537.3:p.Val197Ala

TP53

NM_000546.5:c.470T>A

NM_000546.5:c.590T>C

missense_variant DJEYO

Somatic:chr17:7675142:A>T>T:SNV:MODERATE:missense_variant:TP53

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
	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]
K	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]
Non-high	10	45,X,-Y,-6,add(15)(q?26),+mar[cp2]/46,XY[18]
on-	11	47,XY,del(9)(p12),t(18;21)(q23;q21),+19[cp15]/46,XY[5]
Z	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]
	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]
\checkmark	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]
h-C	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]
High-CK	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]

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

								Gene mutations	5						
	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			0,857	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				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			_			_									

				Chron	nosomal alter	ations				
	del6q	del13q	del17p	del11q	tri12	tri18	tri4	CK	high-CK	TP53al
del6q		5,10E-03	1,10E-02	4,20E-03	9,00E-01	9,50E-01	3,20E-02	8,23E-07	1,56E-06	5,15E-
del13q			4,70E-03	1,50E-01	6,10E-01	8,00E-01	5,70E-02	6,00E-02	4,00E-01	9,00E-
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+
tri12						2,90E-01	3,30E-01	7,90E-02	6,65E-01	8,00E-
tri18							2,10E-02	2,00E-01	7,77E-01	8,18E+
tri4								7,50E-04	2,10E-02	6,25E-
CK										2,30E-
high-CK										5,50E-
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 $P \le 0.05$, $P \le 0.01$, $P \le 0.001$. Correlations were non significant or non applicable/relevant in respective dark grey and black cells. NS, non significant.

Disease phenotype

						Mutationa	/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			
<i>TP53</i> 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	СТ	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	СТ	ICT	P value		
6q deletion					
Yes	17/44 (39)	37/114 (32)	0,1		
No	27/44 (61)	77/114 (68)	0,1		
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).

			P	FS					(os		
	ı	Jnivariate (n=12	5)	M	lultivariate* (n=9	1)	ι	Jnivariate (n=12	5)	IV	lultivariate* (n=8	88)
	HR	IC 95%	Р	HR	IC 95%	Р	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			
СК	-	-	NS				-	-	NS			
High-CK	2.21	1.08-3.87	0.04	-	-	NS	-	-	NS			
<i>TP53</i> 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.

	Number of	
	karyotypic	
Mutated genes	abnormalities	Karyotype
		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),
MYD88, CXCR4, ARID1A, TP53,		der(13)t(12;13)(q12;q1?3),add(17)(p12),-20,+mar1[cp3]/44,idem,-11,add(12)(p13),+mar2[cp5]/ 43,idem,-
CD79B, EZH2	15	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]
		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,
MYD88, HIST1H1E	22	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]