

Case Report

Prognosis of a Chinese patient with chronic lymphocytic leukemia who acquired a TP53 mutation following treatment with a BTK inhibitor

Yan-Ling Ding^{1,2}, Jie Li¹, Jun Yuan¹, Qiang Wei³, Yan Li¹

¹Department of Haematology, Hebei General Hospital, Shijiazhuang 050051, Hebei, The People's Republic of China; ²Department of Graduate School, Hebei North University, Zhangjiakou 075000, Hebei, The People's Republic of China; ³Department of Nuclear Medicine, Hebei General Hospital, Shijiazhuang 050051, Hebei, The People's Republic of China

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Abstract: Chronic lymphocytic leukemia (CLL) is a common type of adult leukemia that occurs in Western countries, and its incidence has gradually increased in China in recent years. The characteristics of CLL are highly heterogeneous. Despite promising response rates achieved with targeted therapy, new targets still need to be expanded due to the heterogeneous of disease. Bruton's tyrosine kinase inhibitor (BTKi) has been used in the treatment of *TP53* mutation. In this report, we present a case with myeloid differentiation primary response 88 (*MYD88*) mutation who developed a *TP53* mutation after application of BTKi. Here, the patient was CLL unmutated (U-CLL) with *MYD88* (L265P) mutation before initial treatment. After traditional treatment, the effect was not good, and BTKi was used for treatment, then *TP53* mutation appeared. It is well known that immunoglobulin heavy chain unmutated (IGHV-U) and *TP53* mutation in CLL indicate poor prognosis. The case suggests that whenever *TP53* mutation occurs, BTKi is the best choice. This result is considered to be related to signal pathways. We aim to add to the collective knowledge by highlighting this rare cases of CLL with *MYD88* (L265P) mutation in an Asian patient.

Keywords: Pathogenesis of chronic lymphocytic leukemia, signal pathways, *MYD88* (L265P) mutation, *TP53* mutation, diagnosis, prognosis

Introduction

Chronic lymphocytic leukemia, which is a clonal proliferative tumour of mature B lymphocytes that occurs mainly in middle-aged and elderly people, is characterised by the aggregation of lymphocytes in the peripheral blood, bone marrow, spleen, and lymph nodes [1]. Because high frequencies of the hotspot *MYD88* (L265P) mutation is observed in B-cell tumors such as extranodal diffuse large B-cell lymphoma and Waldenström macroglobulinaemia (WM), this mutation can potentially serve as a marker of these diseases [2]. In the last decade, substantial advances have been made in the field of CLL research, including the identification of recurrent mutations [3]. Although the *MYD88* mutation is helpful for identifying WM [4], it is not specific to this disease and in fact plays an important role in the pathogenesis of CLL.

MYD88 is a typical junction protein that connects the downstream inflammatory signalling pathway to members of the toll-like receptor (TLR) and interleukin-1 (IL-1) receptor families [5, 6]. It activates nuclear factor-kappa B (NF-κB) and its related signalling pathway, promoting the proliferation and survival of B cells [2]. The NF-κB pathway is one of the main pathways in the pathogenesis of CLL. Sequencing studies have identified mutations in the *MYD88* as being important oncogenic drivers in B-cell lymphomas [2]. Mutations in different signalling pathways have been identified in CLL, some of which are associated with the disease prognosis [7]. For example, mutations in tumour protein 53 (*TP53*), ataxia telangiectasia mutated (*ATM*), neurogenic locus notch homolog protein 1 (*NOTCH1*), splicing factor 3B subunit 1 (*SF3B1*), and baculoviral IAP repeat containing 3 (*BIRC3*) are associated with a poor outcome

The pathogenesis of chronic lymphocytic leukemia

[7, 8]. *MYD88* mutations in CLL have not been commonly described, and their prognostic impact is not clearly defined [7, 8].

Genetic lesions in CLL can be categorised according to several biological pathways, such as those related to inflammation and B-cell receptor (BCR), NOTCH1 signalling, and NF- κ B signalling [3]. The coordination of these deregulated biological pathways drive CLL leukaemogenesis in humans [9]. *MYD88* not only acts as a signal transducer in the typical NF- κ B pathway but also affects the signal transduction of the BCR pathway [2]. The TP53 pathway is a complex cellular stress response network. Some researchers have elucidated many other pathways that TP53 participates in, including DNA damage, cell metabolism, autophagy, ferroptosis, and pathways that involve the generation of reactive oxygen species, with the first two receiving more attention [10]. BTKi, which inhibits BCR-initiated signalling pathways, which promotes cell apoptosis, helps overcome patients with TP53 mutation [11].

In the patient reported herein, the monoclonal B lymphocytosis in the peripheral blood was less than $5 \times 10^9/L$, the lymph nodes were enlarged in many places, and there was no hepatosplenomegaly [1]. Gene hotspot detection revealed a *MYD88* (L265P) mutation which was unique to this patient. This case report mainly focuses on the pathogenesis of CLL with *MYD88* mutations and the prognosis of this patient who acquired a *TP53* mutation after BTK inhibitor treatment. There are not many reports on the prognosis of patients who acquire a *TP53* mutation after BTK inhibitor treatment.

Case presentation

A 65-year-old woman who was diagnosed with a bilateral shoulder mass more than seven months prior was admitted to our hospital on 16 July 2020. The following detailed medical history was obtained: body temperature, 36.5°C; pulse, 70 bpm; respiration, 18 bpm; blood pressure, 104/68 mmHg; conscious; and no yellow staining of the skin and mucosa. Multiple enlarged lymph nodes could be palpated in the bilateral neck, the right supraclavicular region, the submandibular area, both armpits, and the groin. The largest node, which

measured approximately 5 cm in size, was located in the right armpit region. The liver and spleen were not palpable.

The laboratory findings at the time of admission are presented in **Table 1**. Her serum levels of vascular endothelial growth factor (VEGF) and IgM were elevated. The lymph node pathology, bone marrow cytology, and biopsy results are shown in **Figure 1** and the positron emission tomography (PET)/computed tomography (CT) scans in **Figure 2**. Flow cytometric analysis showed positivity for the cell markers CD19, CD20, CD22, and FMC7. Peripheral blood tested negative for IGHV mutation. Fluorescence in situ hybridization (FISH) analysis performed on the left cervical lymph node revealed cell positivity for CEP12 and negativity for D13S319, AT-rich interaction domain 2 (*ATM*; gene symbol *ARID2*), and *TP53* (**Figure 3**). Her karyotype was normal. We also found an *MYD88* (L265P) mutation frequency of 35% and B-cell lymphoma 6 protein (*BCL-6*), forkhead box protein 1 (*FOXO1*), and F-box and WD repeat domain containing 7 (*FBXW7*) mutations. On the basis of these findings, the patient was diagnosed with CLL (Binet B, Rai I).

The patient received four cycles of bendamustine (100 mg, days 1-2), followed by four cycles of a BR regimen (bendamustine 100 mg, days 1-2; rituximab 500 mg, day 0). After these eight cycles of treatment, the follow-up CT scan indicated that the lymph nodes had not decreased obviously (**Figure 2**). Therefore, the patient was treated with the BTKi zanubrutinib for over 6 months (**Figures 2-4**). Subsequent analysis revealed obviously decreased bone marrow cells to the *MYD88* (L265P) mutation, but mutations in the *TP53* and *ARID2* genes had been acquired. After 5 months of zanubrutinib treatment, *TP53* gene and *MYD88* (L265P) mutation showed a downward trend. Abnormally mature monoclonal B cells are still visible on the detection of tiny residual cells in the bone marrow. The patient was followed up recently, the results showed β 2-MG and VEGF were negative. Complete blood count and biochemistry were normal. Echocardiography showed no obvious abnormality. Ultrasound indicated that there was little change in lymph node size from the last review. At the time of this report, the patient was stable.

The pathogenesis of chronic lymphocytic leukemia

Table 1. The laboratory findings

CRP	CRP	9.23 mg/L↑
CBC	WBC	3.36 × 10 ⁹ /L↓
	LY	1.42 × 10 ⁹ /L
	RBC	3.43 × 10 ¹² /L↓
	HB	109.00 g/L↓
	PLT	224.00 × 10 ⁹ /L
ESR	ESR	44 mm/h↑
Coagulation	Fbg	2.46 g/L
	DD	0.39 mg/L FEU
Coombs test	Direct Coombs test	Negative
	Indirect Coombs test	Negative
β2 Microglobulin	β2-MG	2.41 μg/mL
Biochemistry	TP	72 g/L
	Alb	37.4 g/L↓
	Glob	29.9 g/L
	ALP	57.3 U/L
	LDH	134.7 U/L
	Mb	24 ng/mL
	FBG	5.6 mmol/L
	K	4.4 mmol/L
	Mg	0.9 mmol/L
	TG	0.92 mmol/L
	HDL	1.03 mmol/L↓
	Apo A1	1.00 g/L↓
	VEGF	VEGF
Lymphocyte immune analysis	CD3+	72.59%
	CD3+CD4+	29.33%↓
	CD3+CD8+	40.77%↑
	CD4/CD8	0.72↓
	NK cells	12.49%↓
Immunoglobulin	B cells	14.01%↑
	IgM	11.2 g/L↑
Serum protein electrophoresis	GAMMA	16.3%

Notes: ↑Denotes above the upper limit of the reference range; ↓denotes below the lower limit of the reference range. Abbreviations: CBC, complete blood count; CRP, C-reactive protein; WBC, white blood cell; LY, lymphocyte; RBC, red blood cell; Hb, haemoglobin; PLT, platelet; ESR, erythrocyte sedimentation rate; Fbg, fibrinogen; DD, D-dimer; TP, total protein; Alb, albumin; Glob, globulin; ALP, alkaline phosphatase; LDH, lactate dehydrogenase; Mb, myoglobin; FBG, fasting blood glucose; TG, triglyceride; HDL, high-density lipoprotein; Apo A1, Apolipoprotein A1; VEGF, vascular endothelial growth factor; NK, natural killer cell.

Discussion

CLL represents a heterogeneous disease with a highly variable clinical course [7]. *MYD88* mutations in CLL are not well characterized. Earlier reports yielded conflicting results in terms of clinicopathologic presentation and prognostic impact of *MYD88* mutations in CLL patients [8].

MYD88 is a key molecule in innate immunity [5], which is located on chromosome 3p22.2 [7], where it not only acts as a signalling adaptor in the canonical NF-κB pathway but also plays an important role in BCR signalling [2]. In normal physiology, stimulation of the BCR activates NF-κB as well as the phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR) and nuclear factor of activated T cells (NFAT) pathways [2, 9]. Subsequently, BTK is activated through its phosphorylation, whereupon it activates phospholipase C γ 2 (PLC γ 2), thereby initiating activation of the NF-κB pathway [2]. As the *MYD88* (L265P) mutant constitutively activates the NF-κB pathway, it is regarded as an important oncogenic driver in B-cell non-Hodgkin lymphoma [9]. Previous studies on the prognostic impact of *MYD88* mutations in CLL also have been discordant [7, 8].

Michele et al. [12] found that Bcl-6 expression was limited mainly to follicle center lymphomas (FCL), whereas the great majority of CLL lacked immunoreactivity for Bcl-6. In CLL, a fragment of the first intron of *BCL6* is a target of the somatic hypermutation process [13]. In early-stage patients with CLL, Jantus Lewintre et al. [13] found no correlation between expression and the mutations or polymorphism in *BCL6*, but high levels of *BCL6* can discriminate patients with a worse prognosis. *FOXO1* is highly expressed in normal B cells of the germinal centre as well as in non-Hodgkin lymphomas [14].

The main regulator of germinal center (GC) formation *BCL6* is also a *FOXO* target [15]. The mutation of *FOXO1* is caused by the *FOXO1*-Grb2-associated binder 1 (*GAB1*)-protein activator of interferon-induced protein kinase (*PACT*) axis induced by CLL cells [16]. Additionally, *FOXO1* was reported to be a regulator of B-cell death, and its inactivation via

The pathogenesis of chronic lymphocytic leukemia

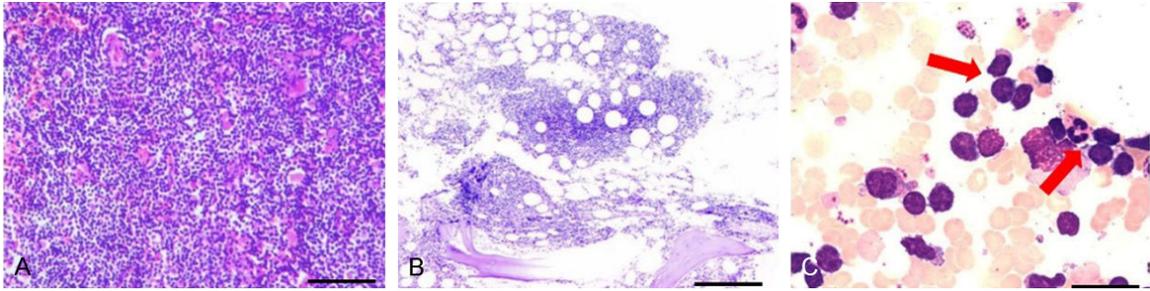


Figure 1. Immunostaining of specimen and bone marrow (BM) morphology. A: $\times 100$. The immunostaining of left cervical lymph node. Heteromorphic lymphoid cells are diffused and infiltrated, with medium to small cells, sparse cytoplasm, slightly irregular round and oval nuclei, granular chromatin, inconspicuous nucleoli and hard to find mitosis. Bar = 100 μm . B: $\times 40$. The immunostaining of BM biopsy specimen. Patchy atypical small lymphocyte infiltration is common in bone marrow stroma. Bar = 160 μm . C: $\times 1000$. Morphology of BM. This kind of cells are small in size, mostly quasi-round or irregular, less cytoplasm, and pseudopod-like protuberance can be seen at the edge. Bar = 10 μm .

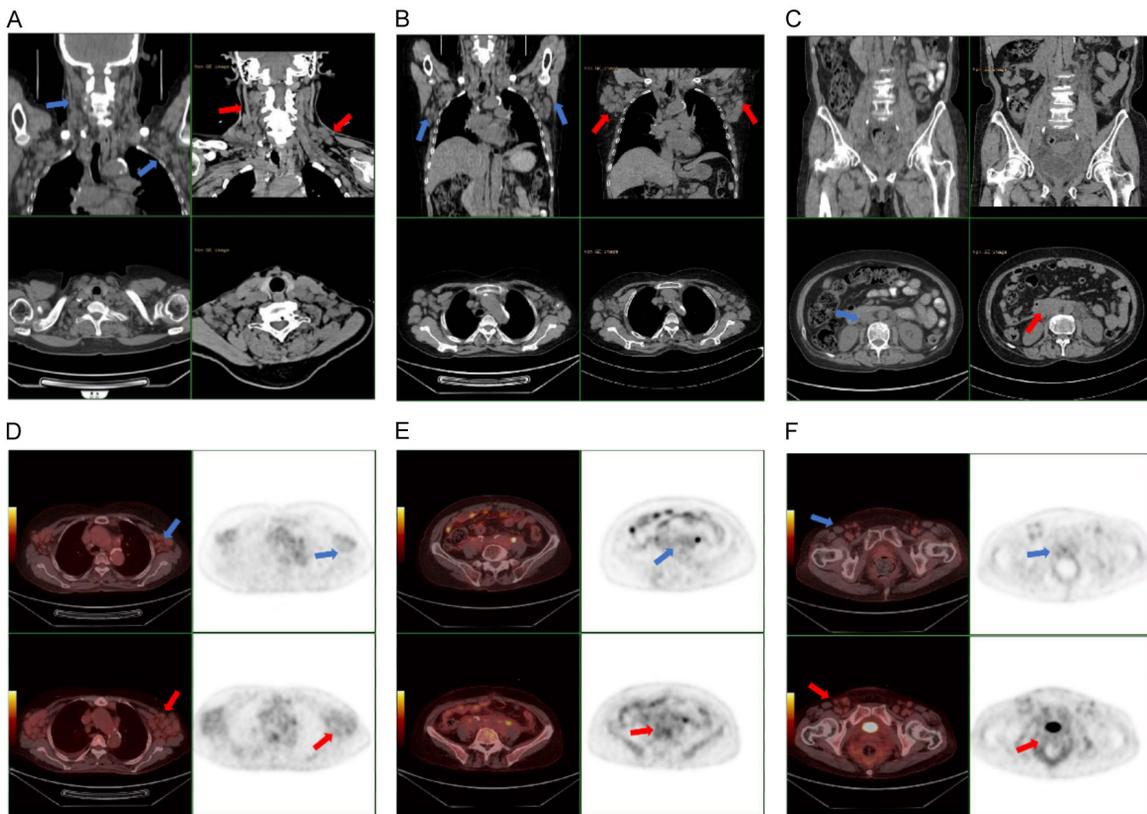


Figure 2. Images of computed tomography and PET/CT (Blue arrow: After treatment of zanubrutinib. Red arrow: Before treatment of zanubrutinib). A-C: Images of computed tomography. It can be seen that the lymph nodes are obviously reduced, and some tend to be normal. D-F: Images of PET/CT. Extensive lymph node enlargement significantly reduced and metabolism of lymph node decreased after chemotherapy.

B-cell receptor signalling to AKT was found to be critical to the survival of mature B cells [14]. There is an interdependent balance between AKT activity and the FOXO1-GAB1 axis [16]. BTK inhibitors affect this balance and inhibit cata-

tonic AKT phosphorylation, thereby inhibiting cell proliferation [16].

In the case of this patient, genetic screening of the bone marrow lymphoma cells after zanu-

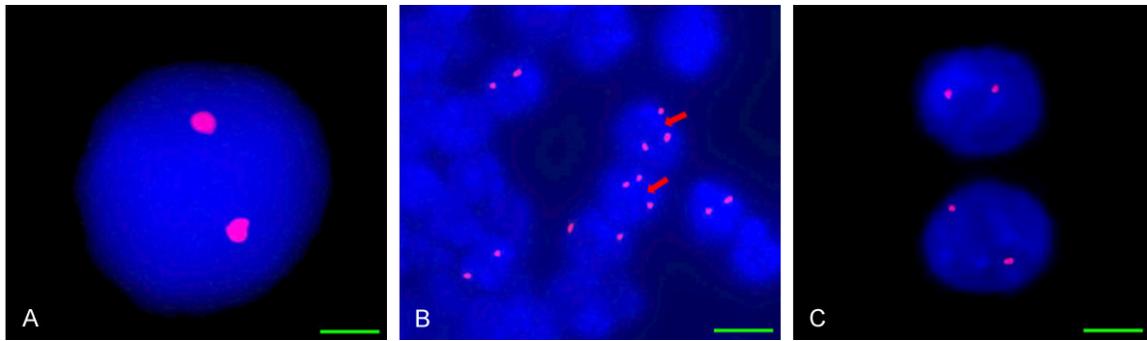


Figure 3. FISH specimen. A: Normal. B: Initial diagnosis of lymph node FISH (before treatment): CEP12 (+). C: After eight cycles chemotherapy and zanubrutinib for over 6 months of treatment, bone marrow FISH: CEP12 (-). Bar = 10 μ m.

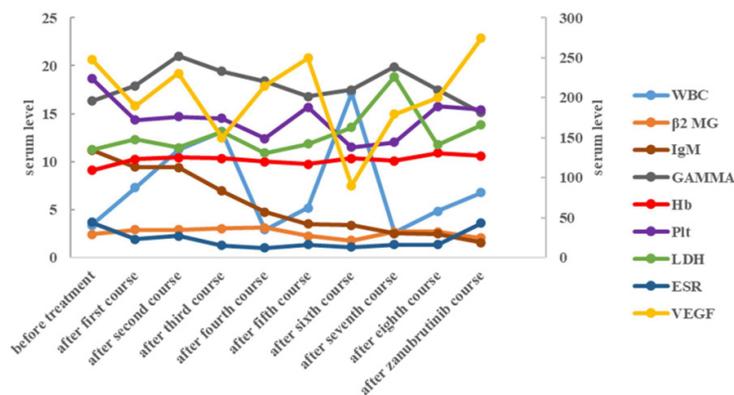


Figure 4. The changes of WBC, β 2-MG, IgM, GAMMA, Hb, PLT, LDH, ESR, VEGF. The series of WBC, β 2-MG, IgM, GAMMA are drawn on the primary axis (on left axis), and the series of Hb, PLT, LDH, ESR, VEGF are drawn on the secondary axis (on right axis).

brutinib treatment revealed that the expression of *MYD88* (L265P) mutation decreased but was positive for *TP53* and *ARID2* mutations. It is known that zanubrutinib can inhibit BTK and NF- κ B signal transduction and is an effective molecular targeted therapy for chronic lymphoblastic leukaemia [1]. BTKi potently inhibits BCR signalling, downregulate NF- κ B signalling, and rapidly reduce tumour burdens through a combination of tumour proliferation inhibition and increased apoptosis [17-19]. However, they also increase the expression of miRNA targets, including tumour suppressors, and cause decreased cell proliferation [19]. Among the miRNAs that have been tested, miR-22, miR-34a, miR-146b, and miR-181b were found to be significantly downregulated in patient CLL cells following ibrutinib treatment [19]. This leads to increased expression of multiple tumour suppressors, including *ARID1B*,

ARID2, *ATM*, *CYLD* lysine 63 deubiquitinase (*CYLD*), *FOXP1*, histone deacetylase 1 (*HDAC1*), inhibitor of Bruton's tyrosine kinase (*IBTK*), phosphatase and tensin homologue (*PTEN*), and suppressor of mothers against decapentaplegic 4 (*SMAD4*) [19]. *TP53* mutated is the most important biomarker of CLL. miR-34a, of which *TP53* is a direct target, has been reported to be altered in CLL and is associated with the disease progression and outcomes [20, 21]. *TP53* modulates gene products through the induction of miRNAs that are controlled by p53 at the

transcriptional level. The activation process of *TP53* is regulated by modifications such as phosphorylation and acetylation, which mediate a variety of cellular functions of p53, including apoptosis, ferroptosis, cell cycle arrest, metabolism, autophagy, stem cell differentiation, DNA repair, and senescence. All these cellular pathways are thought to contribute to the tumor suppressor function of p53 [22]. Recent studies have reduced the *TP53* mutation cutoff to at least 5% VAF, but this must be evaluated in prospective clinical trial cohorts [23]. Clonal expansion of low-burden *TP53* mutations in CLL is associated with intense chemoimmunotherapy but not with targeted therapy [24]. With regard to the *TP53* gene mutation, regardless of whether it is a mutation or deletion, it is the most important marker of poor prognosis for CLL [24]. It is also a reliable marker for chemotherapy-resistant diseases [24]. At present, the

patient was still positive for serum immunostasis electrophoresis. Bone marrow minimal residual disease (MRD) was positive, but the *MYD88* (L265P) mutation rate was still decreasing. After relevant examination evaluation, BTKi non-target events, such as hypertension and atrial fibrillation, did not occur. Although the *TP53* mutation appeared after the application of BTK inhibitors, its mutation rate also descended. The patient was diagnosed with U-CLL. U-CLL patients show a significantly poorer outcome [25]. Whether there is a link between the patient's current status and the absence of IGHV genes mutation. There is still no relevant report. We found that the emergence of the new mutations post BTK inhibitor therapy had no adverse effect on our patient. Further confirmation of the specific targets of the CLL pathogenesis pathway corresponding to each mutated gene would help toward the development of future therapeutic strategies for this malignant disease.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Yan Li, Department of Haematology, Hebei General Hospital, No. 348, Heping West Road, Shijiazhuang 050051, Hebei, The People's Republic of China. Tel: +86-189-31866300; E-mail: liyan98_win@163.com

References

- [1] Hallek M and Al-Sawaf O. Chronic lymphocytic leukemia: 2022 update on diagnostic and therapeutic procedures. *Am J Hematol* 2021; 96: 1679-1705.
- [2] de Groen RAL, Schrader AMR, Kersten MJ, Pals ST and Vermaat JSP. *MYD88* in the driver's seat of B-cell lymphomagenesis: from molecular mechanisms to clinical implications. *Haematologica* 2019; 104: 2337-2348.
- [3] Kikushige Y. Pathogenesis of chronic lymphocytic leukemia and the development of novel therapeutic strategies. *J Clin Exp Hematol* 2020; 60: 146-158.
- [4] Shekhar R, Naseem S, Binota J, Varma N and Malhotra P. Frequency of *MYD88* L256P mutation and its correlation with clinico-hematological profile in mature B-cell neoplasm. *Hematol Oncol Stem Cell Ther* 2021; 14: 231-239.
- [5] Deguine J and Barton GM. *MyD88*: a central player in innate immune signaling. *F1000Prime Rep* 2014; 6: 97.
- [6] Improgo MR, Tesar B, Klitgaard JL, Magori-Cohen R, Yu L, Kasar S, Chaudhary D, Miao W, Fernandes SM, Hoang K, Westlin WF, Kim HT and Brown JR. *MYD88* L265P mutations identify a prognostic gene expression signature and a pathway for targeted inhibition in CLL. *Br J Haematol* 2019; 184: 925-936.
- [7] Shuai W, Lin P, Strati P, Patel KP, Routbort MJ, Hu S, Wei P, Khoury JD, You MJ, Loghavi S, Tang Z, Fang H, Thakral B, Medeiros LJ and Wang W. Clinicopathological characterization of chronic lymphocytic leukemia with *MYD88* mutations: L265P and non-L265P mutations are associated with different features. *Blood Cancer J* 2020; 10: 86.
- [8] Putowski M and Giannopoulos K. Perspectives on precision medicine in chronic lymphocytic leukemia: targeting recurrent mutations-*NOTCH1*, *SF3B1*, *MYD88*, *BIRC3*. *J Clin Med* 2021; 10: 3735.
- [9] Ngo VN, Young RM, Schmitz R, Jhavar S, Xiao W, Lim KH, Kohlhammer H, Xu W, Yang Y, Zhao H, Shaffer AL, Romesser P, Wright G, Powell J, Rosenwald A, Muller-Hermelink HK, Ott G, Gascoyne RD, Connors JM, Rimsza LM, Campo E, Jaffe ES, Delabie J, Smeland EB, Fisher RI, Braziel RM, Tubbs RR, Cook JR, Weisenburger DD, Chan WC and Staudt LM. Oncogenically active *MYD88* mutations in human lymphoma. *Nature* 2011; 470: 115-119.
- [10] Hernández Borrero LJ and El-Deiry WS. Tumor suppressor p53: biology, signaling pathways, and therapeutic targeting. *Biochim Biophys Acta Rev Cancer* 2021; 1876: 188556.
- [11] Morabito F, Gentile M, Monti P, Recchia AG, Menichini P, Skafi M, Atrash M, De Luca G, Bossio S, Al-Janazreh H, Galimberti S, Salah Z, Morabito L, Mujahed A, Hindiyeh M, Dono M, Fais F, Cutrona G, Neri A, Tripepi G, Fronza G and Ferrarini M. *TP53* dysfunction in chronic lymphocytic leukemia: clinical relevance in the era of B-cell receptors and *BCL-2* inhibitors. *Expert Opin Investig Drugs* 2020; 29: 869-880.
- [12] Raible MD, Hsi ED and Alkan S. *Bcl-6* protein expression by follicle center lymphomas. A marker for differentiating follicle center lymphomas from other low-grade lymphoproliferative disorders. *Am J Clin Pathol* 1999; 112: 101-107.
- [13] Jantus Lewintre E, Reinoso Martin C, Garcia Ballesteros C, Pendas J, Benet Campos C, Mayans Ferrer JR and Garcia-Conde J. *BCL6*: somatic mutations and expression in early-stage chronic lymphocytic leukemia. *Leuk Lymphoma* 2009; 50: 773-780.
- [14] Xie L, Ushmorov A, Leithauser F, Guan H, Steidl C, Farbinger J, Pelzer C, Vogel MJ, Maier HJ, Gascoyne RD, Moller P and Wirth T. *FOXO1* is a tumor suppressor in classical Hodgkin lymphoma. *Blood* 2012; 119: 3503-3511.

The pathogenesis of chronic lymphocytic leukemia

- [15] Shore AM, White PC, Hui RC, Essafi A, Lam EW, Rowe M and Brennan P. Epstein-Barr virus represses the FoxO1 transcription factor through latent membrane protein 1 and latent membrane protein 2A. *J Virol* 2006; 80: 11191-11199.
- [16] Seda V, Vojackova E, Ondrisova L, Kostalova L, Sharma S, Loja T, Mladonicka Pavlasova G, Zicha D, Kudlickova Peskova M, Krivanek J, Liskova K, Kren L, Benes V, Musilova Litzmanova K, Borsky M, Oppelt J, Verner J, Pospisilova S, Brychtova Y, Panovska A, Tan Z, Zhang S, Doubek M, Amruz Cerna K, Mayer J and Mraz M. FoxO1-GAB1 axis regulates homing capacity and tonic AKT activity in chronic lymphocytic leukemia. *Blood* 2021; 138: 758-772.
- [17] Herman SE, Mustafa RZ, Gyamfi JA, Pittaluga S, Chang S, Chang B, Farooqui M and Wiestner A. Ibrutinib inhibits BCR and NF- κ B signaling and reduces tumor proliferation in tissue-resident cells of patients with CLL. *Blood* 2014; 123: 3286-3295.
- [18] Herman SE, Niemann CU, Farooqui M, Jones J, Mustafa RZ, Lipsky A, Saba N, Martyr S, Soto S, Valdez J, Gyamfi JA, Maric I, Calvo KR, Pedersen LB, Geisler CH, Liu D, Marti GE, Aue G and Wiestner A. Ibrutinib-induced lymphocytosis in patients with chronic lymphocytic leukemia: correlative analyses from a phase II study. *Leukemia* 2014; 28: 2188-2196.
- [19] Saleh LM, Wang W, Herman SE, Saba NS, Anastas V, Barber E, Corrigan-Cummins M, Farooqui M, Sun C, Sarasua SM, Zhao Z, Abousamra NK, Elbaz O, Abdelghaffar HA, Wiestner A and Calvo KR. Ibrutinib downregulates a subset of miRNA leading to upregulation of tumor suppressors and inhibition of cell proliferation in chronic lymphocytic leukemia. *Leukemia* 2017; 31: 340-349.
- [20] Dufour A, Palermo G, Zellmeier E, Mellert G, Duchateau-Nguyen G, Schneider S, Benthous T, Kakadia PM, Spiekermann K, Hiddemann W, Braess J, Truong S, Patten N, Wu L, Lohmann S, Dorman D, GuhaThakurta D, Yeh RF, Salogub G, Solal-Celigny P, Dmoszynska A, Robak T, Montillo M, Catalano J, Geisler CH, Weisser M and Bohlander SK. Inactivation of TP53 correlates with disease progression and low miR-34a expression in previously treated chronic lymphocytic leukemia patients. *Blood* 2013; 121: 3650-3657.
- [21] Fabbri M, Bottoni A, Shimizu M, Spizzo R, Nicoloso MS, Rossi S, Barbarotto E, Cimmino A, Adair B, Wojcik SE, Valeri N, Calore F, Sampath D, Fanini F, Vannini I, Musuraca G, Dell'Aquila M, Alder H, Davuluri RV, Rassenti LZ, Negrini M, Nakamura T, Amadori D, Kay NE, Rai KR, Keating MJ, Kipps TJ, Calin GA and Croce CM. Association of a microRNA/TP53 feedback circuitry with pathogenesis and outcome of B-cell chronic lymphocytic leukemia. *JAMA* 2011; 305: 59-67.
- [22] Huang J. Current developments of targeting the p53 signaling pathway for cancer treatment. *Pharmacol Ther* 2021; 220: 107720.
- [23] Bomben R, Rossi FM, Vit F, Bittolo T, Zucchetto A, Papotti R, Tissino E, Pozzo F, Degan M, Polesel J, Bulian P, Marasca R, Reda G, Laurenti L, Olivieri J, Chiarenza A, Laureana R, Postorino M, Del Principe MI, Cuneo A, Gentile M, Morabito F, Fronza G, Tafuri A, Zaja F, Foà R, Di Raimondo F, Del Poeta G and Gattei V. Clinical impact of TP53 disruption in chronic lymphocytic leukemia patients treated with ibrutinib: a campus CLL study. *Leukemia* 2023; 37: 914-918.
- [24] Malcikova J, Pavlova S, Kunt Vonkova B, Radova L, Plevova K, Kotaskova J, Pal K, Dvorackova B, Zenatova M, Hynst J, Ondrouskova E, Panovska A, Brychtova Y, Zavacka K, Tichy B, Tom N, Mayer J, Doubek M and Pospisilova S. Low-burden TP53 mutations in CLL: clinical impact and clonal evolution within the context of different treatment options. *Blood* 2021; 138: 2670-2685.
- [25] Rodríguez-Caballero A, Fuentes Herrero B, Oliva Ariza G, Criado I, Alcoceba M, Prieto C, Pérez Caro M, García-Montero AC, González Díaz M, Forconi F, Sarmiento-Ribeiro AB, Almeida J and Orfao A. The hydropathy index of the HCDR3 region of the B-cell receptor identifies two subgroups of IGHV-mutated chronic lymphocytic leukemia patients with distinct outcome. *Front Oncol* 2021; 11: 723722.