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Management of high risk Chronic Lymphocytic Leukaemia (CLL) patients in Australia

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ABSTRACT

Background: Chronic lymphocytic leukaemia (CLL) frequently responds to chemoimmunotherapy combining cytotoxic chemotherapy and monoclonal antibodies. However, CLL is associated with significant genetic heterogeneity, and some high-risk forms are known to be chemo-resistant and associated with early relapse. *Aims*: The aim of this paper is to review the current treatment paradigm of patients with high risk disease, in particular those with del(17p) and *TP53* variants. *Results*: A 'watch and wait' approach is recommended for all patients who are asymptomatic. When symptomatic, FISH testing should be performed and gene sequencing considered subsequently to identify del(17p) and *TP53* variants respectively. In the front-line setting, treatment within a clinical trial is the preferred option. In the relapsed or refractory setting, patients with del(17p) or *TP53* aberrations should be offered treatment with a novel agent such as ibrutinib, idelalisib-rituximab or venetoclax. However, of note, at the date of this publication venetoclax is not PBS reimbursed, and ibrutinib will not be reimbursed until 1 December 2017. *Conclusions*: Testing for del(17p) and TP53 variants identifies high-risk CLL that requires specialist management.

KEYWORDS: Leukaemia, Chronic Lymphocytic; Therapeutics; Australia

INTRODUCTION

Chronic lymphocytic leukaemia (CLL) is a B-cell originated cancer of the immune system. It is the most common leukaemia occurring in adults in the Western world.[1] While the disease is clinically and genetically heterogeneous, it has a distinctive immunophenotypic repertoire that allows it to be differentiated from other B cell lymphomas.[1] Additionally, more than 80% of patients with newly diagnosed CLL carry a genetic aberration.[2, 3]

The majority of patients are asymptomatic at diagnosis,[1] and typically in early stage disease patients undergo a 'watch and wait' period prior to starting active therapy. Treatment is initiated in patients who have significant constitutional symptoms (weight loss, fatigue, fever and night sweats in the absence of infection), bulky disease, progressive lymphocytosis, autoimmune anaemia or thrombocytopenia, recurrent infections or Richter's transformation.[4, 5] Recently a number of prognostic markers and clinic-biological features have been identified in CLL that allow early stratification of the disease.[6] The most important of these are deletion and/or mutation of the *TP53* gene.

p53 is an important tumour suppressor that is activated in response to cellular stresses.[7] Once activated, p53 triggers either cell-cycle arrest and DNA repair, or cell death.[7] Functional impairment in p53 leads to reduced cell death, chemo-refractoriness and uncontrolled cell growth. Loss of p53 function in CLL can occur due to del(17p) or *TP53* variants.[7] While *TP53* variants often coincide with del(17p)

(80-90%), sole *TP53* variants can also occur in the absence of del(17p).[8, 9] Aberrations in *TP53* are detected by gene sequencing. Testing by fluorescence in situ hybridisation (FISH) may miss more than 30% of all *TP53* abberations.[7, 9]

The only validated predictive markers in CLL are del(17p) and *TP53* variants.[10-12] The incidence of *TP53* aberrations at diagnosis is small (< 5%), but increases with disease progression and additional lines of treatment (40-50%).[13, 14] Untreated, and patients in first-line therapy present with *TP53* aberrations in 9 to 15% of cases.[13, 15-17] However, just under half of refractory patients, and half of patients with Richter's transformation, will have aberrations in *TP53*.[13, 14] *TP53* variants can also be present at a subclonal level, and these patients have equally poor survival outcomes.[18] Overall response rate (ORR), overall survival (OS) and progression free survival (PFS) in patients with del(17p) or *TP53* variants receiving chemoimmunotherapy (fludarabine, cyclophosphamide, rituximab (FCR)) or chemotherapy (fludarabine, cyclophosphamide (FC), fludarabine monotherapy or chlorambucil monotherapy) are significantly less than that observed in other patients.[15-17] In the CLL8 study, those with aberrations in *TP53* had ORR, PFS and OS of 75.0%, 15.4 months and 42.2 months respectively compared to 98.2%, 59.0 months and not reached (median follow-up 70 months) in patients with wild-type *TP53*.[17]

To date, there has been little reimbursement in Australia for genetic testing in CLL. However, the weight of evidence for the prognostic importance of TP53 aberration

requires us to re-evaluate our clinical strategies and routinely include this important assessment when making treatment decisions for patients with CLL. Other genetic features associated with differences in clinical response include del(11q), del(13q), *BIRC3, ATM, NOTCH1,* trisomy 21, *SF3B1,* and unmutated *IGVH*.[10] None of these influence treatment decision making at present.

WHEN TO PERFORM TP53 VARIANT TESTING

TP53 variant testing should only be integrated into the diagnostic work up of patients when they transition from 'watch and wait' to active treatment.[19] Pragmatically, either FISH testing or whole genome SNP array is recommended as the first step then subsequent consideration to TP53 sequence analysis can be given. Copy neutral loss of heterozygosity can be detected by SNP array implying biallelic loss of TP53 function. Patients should then be re-tested when further treatment is required as many *TP53* mutated minor clones expand to the dominant clone following chemotherapy.[20] FISH testing in conjunction with gene sequencing is recommended for comprehensive assessment of del(17p) and *TP53* variants particularly for younger patients where therapeutic options including the prospect of allogeneic transplant are being considered long term.[11, 19]

Testing recommendations

1. Test only when active treatment is required.
2. Re-test when a subsequent line of treatment is required.

3. Test using both FISH and gene sequencing.

OPTIMAL CLL TREATMENT IN PATIENTS WITH DEL(17P) AND TP53 VARIANT

Early, stable disease

As with all CLL diagnoses, the standard treatment of early stable disease is 'watch and wait'. Clinical evaluations (history and examination) should continue every three to 12 months, until the patient has symptomatic or active disease.[21] Once the patient requires treatment, they should have their del(17p) and *TP53* variant status assessed (see above).

Some patients may be recognised at an early (asymptomatic) stage of their disease, to carry del(17p) and/or *TP53* variants. However these patients can experience an indolent disease course and treatment decisions must not be made on the basis of potential TP53 dysfunction alone.[22, 23] Therefore, it is recommended to observe these patients closely, and seek out novel agent access opportunities when the time for treatment nears. These patients should not be treated in the absence of active disease as discussed below.

Advanced, active disease (front-line therapy)

Currently, chemoimmunotherapy is the only available reimbursed option for first line therapy for patients in Australia. This includes FCR for the fit patients or alternatively Chlorambucil combined with ofatumumab or obinutuzumab in the unfit patient cohort.

However, Ibrutinib monotherapy is efficacious in first-line treatment of patients, including those with del(17p).[24] The European Society for Medical Oncology (ESMO) guidelines recommend treatment with ibrutinib front-line for patients with *TP53* aberrations.[25] Ibrutinib is registered in Australia as a front-line treatment for patients with del(17p), although it is not currently reimbursed in this setting.

Idelalisib-rituximab has been assessed in the front-line setting in patients with del(17p) (NCT02044822). However the study was prematurely terminated due to safety concerns. Other studies of idelalisib monotherapy in front-line CLL reported severe hepatotoxicity.[26] The ESMO guidelines state that idelalisib is only recommended front-line in patients who are not suitable for Btk inhibitors (e.g. ibrutinib) due to severe infectious complications,[25] however it is not registered, or reimbursed in this setting in Australia. Venetoclax is active in TP53 mutant CLL in the relapsed setting, but has not been adequately studied for treatment in the front-line setting (NCT02242942). It is not registered or reimbursed in this setting in Australia. Further information on the mechanism of action of ibrutinib, idelalisib and venetoclax and their safety profiles can be found in Table 1.

The optimal sequencing of ibrutinib, idelalisib and venetoclax is still under discussion.[27] Clinical trials are actively engaged in addressing these issues, including the investigation of combination front line therapy with ibrutinib and venetoclax. In the absence of clinical outcome data, decisions must be made taking into account patient age, comorbidities and ability to participate in a clinical trial.

Patients with *TP53* variants have a poor prognosis, even after FCR therapy,[28] with the likelihood of increasing drug resistant and genetically unstable disease. As ibrutinib, idelalisib and venetoclax are not reimbursed in Australia in the front-line setting, where possible patients should be treated in the context of a clinical trial.

Relapsed or refractory disease

Choice of treatment in the relapsed or refractory setting depends on the duration of response following front-line treatment, and whether the patient has developed del(17p) or *TP53* variants or a complex karyotype (3 or more cytogenetic abnormalities which frequently includes TP53 abnormalities). There are differences of opinion between USA and European sources regarding the importance of two versus three year remissions particularly following FCR. Therefore broadly speaking, if the initial response was longer than two or three years, and the patient does not have del(17p) or *TP53* variants, then re-treatment with chemoimmunotherapy (FCR or BR) may be considered a reasonable approach, or switching from FCR to BR or vice-versa could be considered.[21] However, myeloid toxicity and the risk of myelodysplasia is a significant concern, particularly in the older population and a bone marrow biopsy is suggested prior to considering repeat chemo-immunotherapy as second line therapy. If the patient has a response lasting less than three years and particularly if less than two, or has del(17p) or *TP53* aberrations on re-testing, then patients should be offered treatment with idelalisib-rituximab, ibrutinib, or venetoclax or clinical trial with other novel agents.

The incidence of *TP53* aberrations and del(17p) increases with the use of DNA damaging agents at relapse,[13, 14] and therefore careful consideration needs to be made of the patient's overall status prior to making any treatment recommendation. In particular, comorbidities, renal function, cardiovascular status, requirement for anticoagulants, evidence of myelodysplasia, pneumonitis and inflammatory bowel risks need to be taken into consideration.

Combining idelalisib with rituximab in patients with relapsed or refractory CLL significantly improves PFS and OS, even in patients with del(17p) or *TP53* mutations (PFS in these high risk groups HR 0.13, 95% CI 0.07 to 0.27; compared to placebo-rituximab).[29] In the overall patient population (low- and high-risk), the median progression free survival was 19.4 months in the idelalisib-rituximab arm, but was 6.5 months in the placebo-rituximab arm.[29] For high-risk groups (del(17p) or *TP53* mutation), the median progression free survival was not reached for the idelalisib-rituximab arm, but was 4.0 months in the placebo-rituximab arm.[29] Addition of rituximab to idelalisib blunted and shortened the duration of lymphocytosis that has been observed when idelalisib is used as monotherapy.[30] The most common adverse events associated with idelalisib-rituximab therapy include pyrexia, fatigue, nausea, chills and diarrhoea.[30] Grade 3 diarrhoea and grade 3 rash was reported in patients administered idelalisib-rituximab, but not those treated with placebo-rituximab. [30] The combination of idelalisib with rituximab is registered and reimbursed for patients with relapsed or refractory disease who are not suitable for chemoimmunotherapy (including those patients with del(17p)).

The overall response rate and PFS is significantly better in patients treated with ibrutinib compared to ofatumumab (PFS at 12-months 79% vs 17%, respectively for those with del(17p); 88% vs 16%, respectively for those with *TP53* variants). The most common adverse events for ibrutinib are diarrhoea, musculoskeletal pain, haemorrhage and bruising, rash, nausea, pyrexia and neutropenia.[31] Ibrutinib should be used with caution in patients with underlying cardiovascular comorbidities, or in those that require anticoagulation. Ibrutinib is registered and will be reimbursed in the relapsed or refractory CLL setting from 1st December 2017.[31]

Venetoclax induces rapid onset apoptosis of CLL cells in patients via a *TP53* independent mechanism.[32] Initial reports have shown patients treated with venetoclax achieve an ORR of 79%, even in a heavily pre-treated cohort with poor cytogenetic risk.[33] The ORR in those with del(17p) was 71%.[33] PFS and OS outcomes have not yet been reported. In Australia, venetoclax is indicated for the treatment of patients with relapsed or refractory CLL with del(17p) or in patients where there are no other treatment options.[34] It is not currently reimbursed for either indication.

Allogeneic haematopoietic stem cell transplantation (HSCT).

Long-term, minimal residual disease negative control can be obtained following allo-HSCT in patients with high-risk CLL.[35] Outcomes following allo-HSCT are no different in those with *TP53* variants compared to *TP53* wild-type (overall survival HR 1.21, 95% CI 0.54 to 2.74, p=0.64; and progression free survival HR 0.82, 95% CI

0.43 to 1.58, p=0.56).[35] Allogeneic stem cell transplantation is the only curative therapy and is indicated in very high risk (del(17p) or *TP53* variants) disease.[21] For most patients, participation in a clinical trial of a novel agent is preferred over frontline allogeneic transplantation. In the age of novel agents, the optimal timing of allogeneic transplantation is a topic of much debate. Increasingly, allogeneic stem cell transplants are being deferred in patients responding well to novel agents, until such time as resistance to one or more targeted drugs, or until complications such as Richter's transformation, occur. Whether such deferrals lead to compromised transplant outcomes is currently unknown.

Treatment recommendations for high-risk patients

1. A **watch and** wait approach to asymptomatic patients is recommended.
2. Patients with high risk, active or symptomatic CLL should be screened for participation in a clinical trial **front-line therapy.**
3. In the **relapsed or refractory setting,** consider treatment with ibrutinib, idelalisib-rituximab or venetoclax, with the choice dependent on the patient's overall status and comorbidities.

FUTURE DIRECTIONS

While the only validated predictive markers in CLL are del(17p) and *TP53* variants,[10-12] other cytogenetic aberrations predict aggressive CLL, with short time to first treatment. These include *ATM*, del(11q), *NOTCH1*, and *SF3B1*. Variants in *ATM*

result in impaired p53-mediated DNA damage response, and shorter treatment-free intervals.[36, 37] Further, in patients with del(11q), inactivation of the second *ATM* allele is associated with reduced survival, although in the era of novel agents, the outcome for those with and without del(11q) appear the same.[36] Patients with clonal *NOTCH1* variants have shorter times to first treatment, shorter overall survival, and increased risk of Richter's transformation compared to those with wild-type *NOTCH1*.[38, 39] Those with NOTCH1 mutations do not seem to respond to the addition of rituximab, however this data has not yet swayed clinical practice.[17, 40] The predictive value of *SF3B1* remains unclear.

Treatment of patients with complex karyotypes, that is those with three or more chromosomal abnormalities, is an area of emerging research. The attainment of minimal residual disease status post treatment is a significant predictive indicator of progression free and overall survival in the era of FCR chemo-immunotherapy. However in the era of novel agents, a post treatment predictive marker and the ability to assess tumour load prospectively remain the subject of further research.

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REFERENCES

1 Zenz T, Mertens D, Kuppers R, Dohner H, Stilgenbauer S. From pathogenesis to treatment of chronic lymphocytic leukaemia. *Nat Rev Cancer*. 2010; **10**: 37-50.

2 Sutton LA, Hadzidimitriou A, Baliakas P, Agathangelidis A, Langerak AW, Stilgenbauer S*, et al.* Immunoglobulin genes in chronic lymphocytic leukemia: key to understanding the disease and improving risk stratification. *Haematologica*. 2017; **102**: 968-71.

3 Dohner H, Stilgenbauer S, Benner A, Leupolt E, Krober A, Bullinger L*, et al.* Genomic aberrations and survival in chronic lymphocytic leukemia. *N Engl J Med*. 2000; **343**: 1910-6.

4 Hallek M, Cheson BD, Catovsky D, Caligaris-Cappio F, Dighiero G, Dohner H*, et al.* Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. *Blood*. 2008; **111**: 5446-56.

5 Cramer P, Hallek M. Prognostic factors in chronic lymphocytic leukemia-what do we need to know? *Nature reviews Clinical oncology*. 2011; **8**: 38-47.

6 Baliakas P, Mattsson M, Stamatopoulos K, Rosenquist R. Prognostic indices in chronic lymphocytic leukaemia: where do we stand how do we proceed? *J Intern Med*. 2016; **279**: 347-57.

7 Surget S, Khoury MP, Bourdon JC. Uncovering the role of p53 splice variants in human malignancy: a clinical perspective. *Onco Targets Ther*. 2013; **7**: 57-68.

8 Pospisilova S, Sutton LA, Malcikova J, Tausch E, Rossi D, Montserrat E*, et al.* Innovation in the prognostication of chronic lymphocytic leukemia: how far beyond TP53 gene analysis can we go? *Haematologica*. 2016; **101**: 263-5.

9 Malcikova J, Pavlova S, Kozubik KS, Pospisilova S. TP53 mutation analysis in clinical practice: lessons from chronic lymphocytic leukemia. *Hum Mutat*. 2014; **35**: 663-71.

10 Sutton LA, Rosenquist R. Deciphering the molecular landscape in chronic lymphocytic leukemia: time frame of disease evolution. *Haematologica*. 2015; **100**: 7-16.

11 Puiggros A, Blanco G, Espinet B. Genetic abnormalities in chronic lymphocytic leukemia: where we are and where we go. *Biomed Res Int*. 2014; **2014**: 435983.

12 Mertens D, Stilgenbauer S. Prognostic and predictive factors in patients with chronic lymphocytic leukemia: relevant in the era of novel treatment approaches? *J Clin Oncol*. 2014; **32**: 869-72.

13 Rossi D, Spina V, Deambrogi C, Rasi S, Laurenti L, Stamatopoulos K*, et al.* The genetics of Richter syndrome reveals disease heterogeneity and predicts survival after transformation. *Blood*. 2011; **117**: 3391-401.

14 Trbusek M, Malcikova J. TP53 aberrations in chronic lymphocytic leukemia. *Adv Exp Med Biol*. 2013; **792**: 109-31.

15 Zenz T, Eichhorst B, Busch R, Denzel T, Habe S, Winkler D*, et al.* TP53 mutation and survival in chronic lymphocytic leukemia. *J Clin Oncol*. 2010; **28**: 4473-9.

16 Gonzalez D, Martinez P, Wade R, Hockley S, Oscier D, Matutes E*, et al.* Mutational status of the TP53 gene as a predictor of response and survival in patients with chronic lymphocytic leukemia: results from the LRF CLL4 trial. *J Clin Oncol*. 2011; **29**: 2223-9.

17 Stilgenbauer S, Schnaiter A, Paschka P, Zenz T, Rossi M, Dohner K*, et al.* Gene mutations and treatment outcome in chronic lymphocytic leukemia: results from the CLL8 trial. *Blood*. 2014; **123**: 3247-54.

18 Rossi D, Khiabanian H, Spina V, Ciardullo C, Bruscaggin A, Fama R*, et al.* Clinical impact of small TP53 mutated subclones in chronic lymphocytic leukemia. *Blood*. 2014; **123**: 2139-47.

19 Pospisilova S, Gonzalez D, Malcikova J, Trbusek M, Rossi D, Kater AP*, et al.* ERIC recommendations on TP53 mutation analysis in chronic lymphocytic leukemia. *Leukemia*. 2012; **26**: 1458-61.

20 Malcikova J, Stano-Kozubik K, Tichy B, Kantorova B, Pavlova S, Tom N*, et al.* Detailed analysis of therapy-driven clonal evolution of TP53 mutations in chronic lymphocytic leukemia. *Leukemia*. 2015; **29**: 877-85.

21 Eichhorst B, Robak T, Montserrat E, Ghia P, Hillmen P, Hallek M*, et al.* Chronic lymphocytic leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2015; **26 Suppl 5**: v78-84.

22 Tam CS, Shanafelt TD, Wierda WG, Abruzzo LV, Van Dyke DL, O'Brien S*, et al.* De novo deletion 17p13.1 chronic lymphocytic leukemia shows significant clinical heterogeneity: the M. D. Anderson and Mayo Clinic experience. *Blood*. 2009; **114**: 957-64.

23 Best OG, Gardiner AC, Davis ZA, Tracy I, Ibbotson RE, Majid A*, et al.* A subset of Binet stage A CLL patients with TP53 abnormalities and mutated IGHV genes have stable disease. *Leukemia*. 2009; **23**: 212-4.

24 O'Brien SM, Furman RR, Coutre SE, Flinn IW, Burger J, Blum K*, et al.* 233 Five-Year Experience with Single-Agent Ibrutinib in Patients with Previously Untreated and Relapsed/Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Leukemia. *American Society for Hematology*. San Diego 2016.

25 ESMO Guidelines Committee. eUpdate – Chronic Lymphocytic Leukaemia Treatment Recommendations. Available from

http://www.esmo.org/Guidelines/Haematological-Malignancies/Chronic-Lymphocytic-Leukaemia/eUpdate-Treatment-Recommendations. Vol. 2017. 2017.

26 Lampson BL, Kasar SN, Matos TR, Morgan EA, Rassenti L, Davids MS*, et al.* Idelalisib given front-line for treatment of chronic lymphocytic leukemia causes frequent immune-mediated hepatotoxicity. *Blood*. 2016; **128**: 195-203.

27 Mato AR, Hill BT, Lamanna N, Barr PM, Ujjani CS, Brander DM*, et al.* Optimal sequencing of ibrutinib, idelalisib, and venetoclax in chronic lymphocytic leukemia: results from a multicenter study of 683 patients. *Ann Oncol*. 2017; **28**: 1050-56.

28 Hallek M, Fischer K, Fingerle-Rowson G, Fink AM, Busch R, Mayer J*, et al.* Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: a randomised, open-label, phase 3 trial. *Lancet*. 2010; **376**: 1164-74.

29 Gilead Sciences Pty Ltd. ZYDELIG approved product information. Available from https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2015-PI-01225-1. 2017.

30 Furman RR, Sharman JP, Coutre SE, Cheson BD, Pagel JM, Hillmen P*, et al.* Idelalisib and rituximab in relapsed chronic lymphocytic leukemia. *N Engl J Med*. 2014; **370**: 997-1007.

31 Janssen-Cilag Pty Ltd. Imbruvica approved product information. Available at https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2015-PI-01676-1. 2016.

32 Anderson MA, Deng J, Seymour JF, Tam C, Kim SY, Fein J, *et al.* The BCL2 selective inhibitor venetoclax induces rapid onset apoptosis of CLL cells in patients via a TP53-independent mechanism. *Blood*. 2016; **127**: 3215-24.

33 Roberts AW, Davids MS, Pagel JM, Kahl BS, Puvvada SD, Gerecitano JF, *et al.* Targeting BCL2 with Venetoclax in Relapsed Chronic Lymphocytic Leukemia. *N Engl J Med*. 2016; **374**: 311-22.

34 AbbVie Pty Ltd. Venetoclax approved product information. Available from https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2017-PI-01048-1&d=20171006161146224 83. 2017.

35 Dreger P, Schnaiter A, Zenz T, Bottcher S, Rossi M, Paschka P, *et al.* TP53, SF3B1, and NOTCH1 mutations and outcome of allotransplantation for chronic lymphocytic leukemia: six-year follow-up of the GCLLSG CLL3X trial. *Blood*. 2013; **121**: 3284-8.

36 Rossi D, Gaidano G. The clinical implications of gene mutations in chronic lymphocytic leukaemia. *Br J Cancer*. 2016; **114**: 849-54.

37 Guarini A, Marinelli M, Tavolaro S, Bellacchio E, Magliozzi M, Chiaretti S, *et al.* ATM gene alterations in chronic lymphocytic leukemia patients induce a distinct

gene expression profile and predict disease progression. *Haematologica*. 2012; **97**: 47-55.

38 Rossi D, Rasi S, Fabbri G, Spina V, Fangazio M, Forconi F*, et al.* Mutations of NOTCH1 are an independent predictor of survival in chronic lymphocytic leukemia. *Blood*. 2012; **119**: 521-9.

39 Nadeu F, Delgado J, Royo C, Baumann T, Stankovic T, Pinyol M*, et al.* Clinical impact of clonal and subclonal TP53, SF3B1, BIRC3, NOTCH1, and ATM mutations in chronic lymphocytic leukemia. *Blood*. 2016; **127**: 2122-30.

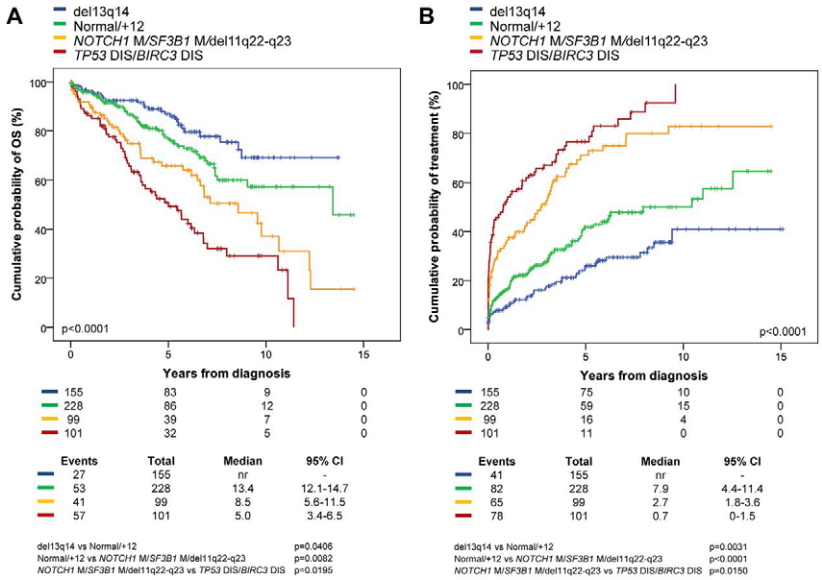
40 Pozzo F, Bittolo T, Arruga F, Bulian P, Macor P, Tissino E*, et al.* NOTCH1 mutations associate with low CD20 level in chronic lymphocytic leukemia: evidence for a NOTCH1 mutation-driven epigenetic dysregulation. *Leukemia*. 2016; **30**: 182-9.

41 Rossi D, Rasi S, Spina V, Bruscaggin A, Monti S, Ciardullo C*, et al.* Integrated mutational and cytogenetic analysis identifies new prognostic subgroups in chronic lymphocytic leukemia. *Blood*. 2013; **121**: 1403-12.

42 Food and Drug Administration. Venetoclax Prescribing Information (US). Available from https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/208573s000lbl.pdf. Accessed 16 October 2017. 2016.

FIGURE LEGENDS

Figure 1: Kaplan-Meier estimates of OS and treatment-free survival according to the integrated mutational and cytogenetic model in the training series. (A) OS. (B) Probability of progressive disease requiring treatment according to IWCLL-NCI guidelines as indicated by treatment-free interval.[41]



TABLES

Table 1: Selected agents used in treatment of high-risk CLL

Agent	Mechanism of action	Safety Profile
Ibrutinib	Inhibits Bruton's tyrosine kinase (BTK), leading to sustained inhibition of BTK enzymatic activity, leading to reduced signalling through the B cell surface receptor. Inhibits B cell proliferation and survival *in vivo* and cell migration and substrate adhesion *in vitro.*[31]	Cardiac signals: atrial fibrillation and other arrhythmias, hypertension[3] Bleeding and platelet dysfunction, infection, interstitial lung disease, hepatotoxicity[3]
Idelalisib	Inhibits phosphatidylinositol 3-kinase p110δ (PI3Kδ), which is hyperactive in B-cell malignancies and is central to multiple signalling pathways that drive proliferation, survival, homing and retention of malignant cells in lymphoid tissues and bone marrow. Idelalisib induces apoptosis and inhibits proliferation in cell lines derived from malignant B-cells and in primary tumour cells.[29]	Hepatotoxicity, pneumonitis, colitis, rash, CMV[29]
Venetoclax	Inhibits BCL-2, an anti-apoptotic protein. BCL-2 s overexpressed in CLL, where it mediates tumour cell survival and has been associated with resistance to chemotherapeutics. Venetoclax helps restore the process of apoptosis.[42]	Tumour lysis syndrome[42]

APPENDICES

Nil