Evolving View of the In-Vivo Kinetics of Chronic Lymphocytic Leukemia B Cells
Nicholas Chiorazzi and Manlio Ferrarini

B-cell chronic lymphocytic leukemia (B-CLL) has long been considered a disease of “accumulation,” due to a presumed defect in programmed cell death. Recent data, however, suggest that B-CLL cells are born at a normal to an accelerated rate, with the rate of proliferation varying among patients. In addition, differences in birth rates, activation state, and inducibility appear to exist among subpopulations of cells within individual leukemic clones. The extent to which such dissimilarities influence clinical course and outcome is still unclear. This review examines the evidence supporting the existence of a proliferative compartment in B-CLL and the role that proliferating cells might play in the progression and evolution of this disease.

I. Introduction
B-cell chronic lymphocytic leukemia (B-CLL) is a liquid tumor consisting of a clonal CD19+/CD5+ B lymphocyte population. The disease is diagnosed primarily in individuals in the fifth and sixth decades of life with some patients having an indolent clinical course. For four decades, B-CLL has been considered a disease of “accumulation,” due to a presumed defect in programmed cell death, with “immunologically incompetent” B-CLL cells building up over time to produce disease.1

However, the new perspective emerging from recent investigations suggests first that B-CLL cells derive from competent B lymphocytes selected for clonal expansion and eventual transformation by multiple encounters and responses to (auto)antigen(s). The transformed B cells, particularly from patients with the worst prognostic markers, appear to retain their ability to respond to signals delivered through several cell surface receptors, indicating they have at least partial immune competence. Second, and perhaps more surprisingly, rather than being sluggish, B-CLL cells are born at a normal or even accelerated rate, with the rate of proliferation varying among patients and even among subpopulations of cells within the leukemic clones of individual patients. The extent to which such dissimilarities for editorial suggestions. These studies were supported in part by RO1 grants CA81554 and CA87956 from the National Cancer Institute and a M01 General Clinical Research Center Grant (RR018535) from the National Center for Research Resources, the Associazione Italiana Ricerca sul Cancro (AIRC), and MIUR of Italy. The Karches Family Foundation, The Peter Jay Sharp Foundation, The Marks Family Foundation, the Jean Walton Fund for Lymphoma & Myeloma Research, and the Joseph Eletto Leukemia Research Fund also provided support for these studies.

NC: The Feinstein Institute for Medical Research, North Shore – LIJ Health System, Manhasset, NY, 11030; and Departments of Medicine and of Cell Biology, North Shore University Hospital and Albert Einstein College of Medicine, Manhasset and Bronx, NY 11030 and 10461
MF: Division of Medical Oncology C, Istituto Nazionale per la Ricerca sul Cancro, Genova 16132, Italy; and Dipartimento di Oncologia Clinica e Sperimentale, Università di Genova 16132

Acknowledgments: We thank the current and past members of our laboratories, in particular Dr. Bradley T. Messmer, for the information presented in this review, Dr. Marc Hellerstein for invaluable advice and help with mass spectrometry analyses, and Drs. Charles C. Chu, Rajendra Damle, and Sophia Yancopoulos for editorial suggestions. These studies were supported in part by RO1 grants CA81554 and CA87956 from the National Cancer Institute and a M01 General Clinical Research Center Grant (RR018535) from the National Center for Research Resources, the Associazione Italiana Ricerca sul Cancro (AIRC), and MIUR of Italy. The Karches Family Foundation, The Peter Jay Sharp Foundation, The Marks Family Foundation, the Jean Walton Fund for Lymphoma & Myeloma Research, and the Joseph Eletto Leukemia Research Fund also provided support for these studies.

Correspondence: Nicholas Chiorazzi, MD, The Feinstein Institute for Medical Research, 350 Community Dr., Manhasset NY 11030; Phone 516-562-1085; Fax 516-562-1011; Email nchizzi@nshs.edu
influence clinical course and outcome is still unclear. In this review we examine primarily the contribution of proliferation to the progression and evolution of B-CLL; the matter of immune competence has been addressed recently.2

II. The Controversy
To what extent do accumulation and proliferation contribute to the pathobiology of B-CLL?

A. Original view:
B-CLL is a disease primarily resulting from the accumulation of clonal B lymphocytes that do not die
A number of clinical and laboratory observations have led to this view. First, some patients with the disease live for many years after the diagnosis is first made, never requiring therapy and dying with leukemia rather than because of it.3 Second, by light microscopy circulating leukemic cells resemble small, resting lymphocytes with a high nuclear to cytoplasmic ratio. The nuclear chromatin of these cells is usually condensed, suggesting minimal metabolic activity.4 Finally, even using sensitive flow cytometric techniques, B-CLL cells progressing through the cell cycle are rarely detected in the blood.5

B. Evolving view:
B-CLL is a disease of clonal B lymphocytes that replicate at a normal to higher than normal rate and do not appear to have an inherent apoptotic defect
Even though most B-CLL cells have a small resting appearance when evaluated by light microscopy, somewhat larger cells with more cytoplasm and less condensed chromatin are seen in some patients.6 The numbers of these prolymphocytes and atypical lymphocytes often are initially small, but in some patients they increase with time and presage a less favorable clinical outcome. Richter’s transformation, the conversion to a more aggressive, rapidly proliferating lymphoma, is seen more frequently in patients with increasing numbers of prolymphocytes.7 Both findings establish a link between cell proliferation and clinical outcome.

Regarding clinical course, two subgroups of B-CLL exist which differ in IgVH gene mutation status8 (mutated B-CLL [M-CLL] and unmutated B-CLL [U-CLL]), CD389 and ZAP-7010 levels, and gene expression profiles,10,11 and these subgroups have different clinical outcomes.9,12 The cases with leukemic clones containing minimal or no mutations and elevated numbers of CD38+ and ZAP-70+ cells are at a much higher risk for clinical decompensation than those cases with clones with significant mutations and few CD38+ or ZAP-70+ cells. Irrespective of the subgroup to which a patient belongs, the leukemic cells always display surface activation markers, albeit with some differences. U-CLL cases resemble B cells that have been recently induced (e.g., increased proportion of CD69+ cells and levels of HLA-DR), whereas M-CLL cells exhibit markers that emerge later after an activation stimulus.13 In addition, cells from U-CLL more frequently express the unfavorable prognostic markers CD389 and ZAP-70.14,15 Gene expression profiles suggest that cells from both B-CLL subgroups most closely resemble antigen-experienced, memory B cells.10,11

In addition, since telomere length can be an index of the number of times a cell has replicated, the finding that B-CLL cells have shorter telomeres than normal age-matched B cells16 not only suggests that the leukemic cells divide, but that they have done so more frequently than the stem cells giving rise to normal B-cell counterparts. The leukemic cells from poor outcome U-CLL patients have even shorter telomeres than those of patients in the good outcome M-CLL subgroup, implying that the rate of cycling of the leukemic cells from U-CLL patients or their progenitors is more rapid than that of M-CLL patients.

Finally, although there is a virtual absence of cycling cells in the blood of B-CLL patients, ill-defined areas of apparent proliferation are seen in the bone marrow and affected lymph nodes. These “proliferation centers” contain larger cells with less condensed nuclear chromatin that display the cell cycle marker Ki-67.17 These may be the primary sites of clonal growth.4

C. Evidence that B-CLL cells require exogenous signals to survive
Several observations suggest that B-CLL cells are not immortal, but require signals delivered through cell surface receptors to maintain viability. The most obvious is the inability of B-CLL cells to remain viable in vitro.18 Unless B-CLL cells are cultured in the presence of other cell types19 or soluble cytokines and chemokines20 or other molecules that engage important cell surface receptors such as the BCR,21 in particular the IgD form of the receptor,22 CD38,23 and CD40,24 they undergo apoptosis more rapidly than normal B lymphocytes. This is in keeping with the lack of a defined apoptotic defect inherent to the clone. The extent to which these survival mechanisms affect the entire clonal population is unclear as only a subset of clonal members will have the opportunity to receive and respond to trophic, survival signals due to anatomic locations of survival signals, trafficking differences among B-CLL cells, etc. Therefore, it would not be surprising if many members of the B-CLL clone could not survive for long periods to remain a part of the “accumulating” pool.

III. Direct Measurements of the Proliferative Capacities of B-CLL Cells in Vivo
Since the observations mentioned above fail to unequivocally resolve the relative contributions of cellular accumulation and proliferation, in vivo measurements of the proliferative potential of B-CLL cells are essential. Although this need has been acknowledged for decades, in vivo kinetic studies have been hampered for many years by the inability to safely, accurately, and conveniently mark and quantify proliferating cells in healthy and ill subjects.
A. Direct measurement of DNA synthesis and cell proliferation of B-CLL cells in vivo

A1. Approach: In the last decade, Hellerstein and colleagues introduced isotopic labeling techniques that use deuterium (²H) to label DNA of dividing cells as a measure of cell birth.²³ By one embodiment of this approach, ²H, taken orally as heavy water (²H₂O), is metabolically incorporated into the covalent C-H bonds of the deoxyribose moiety of replicating DNA but not into stable, non-replicating DNA. Once inserted, the presence of ²H in DNA of cells is quantified by mass spectrometry.²⁶ This approach is safe for humans because deuterium is not radioactive and has no known toxicities at the levels achieved in these studies. Furthermore, the number of cells needed for these assays (10⁷-10⁹) and the accuracy of the measurements obtained using mass spectrometry make the ²H-labeling approach very easy to exploit in practice, provided that the leukemic cells are purified in order to exclude labeled DNA from other proliferating cells. In B-CLL, purification is readily achieved because the leukemic cells express surface membrane CD5 and CD19, markers found on only a minor fraction of adult human B cells.

Messmer et al used ³H-labeling of replicating DNA to directly measure the birth rates of B-CLL cells in vivo.²⁷ In this pulse/chase approach, patients drank ~60 mL of ²H₂O daily for 12 weeks to achieve a level of ~1-2% of ²H₂O in total body water. At regular intervals (~1-2 weeks), CD5⁺/CD19⁺ B-CLL cells were purified from circulating mononuclear cells, and genomic DNA was isolated from these cells to measure ³H enrichment.

Serum samples were also collected at the same time intervals to quantify the enrichment of ³H₂O in blood. Equilibrium levels were usually reached by 14 days, maintained throughout the 12-week labeling period, and decreased after ceasing ³H₂O intake. These values were used to calculate cellular birth rates as well as to assure that sufficient levels of ³H₂O were achieved for adequate cellular labeling and that patients were compliant with the protocol.

A2. Kinetics of B-CLL cell birth rates: Using three mathematical methods to analyze the data (see reference ²⁷ for details), normal to above normal proliferation of B-CLL cells was identified in every patient. Depending on the case, from 0.11% to 1.76% of the entire clone divided each day (Table 1). Figure 1 (see Color Figures, page 512) illustrates kinetic patterns of patients with faster and slower birth rates. If one assumes the leukemic cell burden in a typical patient to range between 1 × 10⁸ to 1 × 10⁹, then at a minimum between 1 × 10⁷ to 1 × 10⁸ B-CLL cells were produced daily. Thus, cellular proliferation occurred in each B-CLL patient, at levels that equal or exceed those of B cells from four normal subjects studied.

A3. Estimation of clonal growth and death rates. Clonal growth rates were calculated by fitting an exponential curve to the WBC counts obtained at each blood drawing, from the beginning to the end of the study period. The growth rates for the cohort of patients ranged from –1.052 to +0.712% per day (Table 1). In patients whose WBC levels increased or remained virtually unchanged, positive or essentially zero growth rates were computed; for several patients, WBC counts declined during the 6-month study period, yielding a negative growth rate.

Of note, birth rates and growth rates did not correlate in all patients. For example, in one subject, CLL 408, with an especially high birth rate (1.09% of the clone per day), WBC number fell during the course of the study; for others, birth rates exceeded growth rates. Both of these discrepancies strongly suggested that concomitant leukemic cell death occurred.

Therefore, B-CLL cell death rates were estimated by subtracting growth rates from birth rates (Table 1). Accordingly, from –0.33% to +2.14% of the clonal cells were eliminated from the blood daily.²⁷ For these calculations it was assumed that, in the absence of identifiable changes in the size of measurable peripheral lymphoid tissues, elimination from the blood represented cell death, a reasonable assumption given the impaired recirculation of the majority of leukemic cells in B-CLL.²⁸ Furthermore, labeling over a period of months likely resulted in equilibrium between tissue and blood compartments in most subjects.²⁷

Cumulatively, these data indicate that the observed blood lymphocyte counts in all B-CLL patients represent a
dynamic interplay between ongoing birth and death within the clones, not simply a linear, monotonous accumulation of inert leukemic cells.

**A4. Relationship between in vivo B-CLL cell kinetics and disease activity and progression.** Although the cohort studied was not large (n = 19), Messmer et al found a correlation between higher birth rates (≥ 0.35% of the clone being born each day) and disease progression and/or requirement for therapy, preceding, during, or following the study period (Table 2). Since birth and growth rates did not necessarily move coordinately, the proliferative rate of the clone appeared more important in determining clinical course than changes in WBC or absolute lymphocyte counts.

This concept was supported by analysis of de-labeling curves for 4 patients whose birth rates were measured again 1-2 years after 2H2O intake ended. In these patients, the kinetic estimates were on target over the prolonged interval, implying stable disease and an unchanged clinical course, which in fact was the case for these patients. One could envision that if the level of cellular proliferation determined at a follow-up blood drawing changed significantly, either higher or lower than predicted by extrapolating from the value measured at the initial study, this might raise concern about changes in birth or death within the clone and presage a change in clinical course. A national trial is currently being conducted to analyze the kinetics of a large cohort of new-onset B-CLL cases and to correlate these with various prognostic parameters and disease course, to determine the clinical utility of the 3H-labeling technique in B-CLL. In this regard, there was a trend in the initial study for higher birth rates being associated with U-CLL; this did not reach statistical significance.

### IV. Questions Arising from the Finding that Proliferation Can Be Considerable in B-CLL

Although the preceding data indicate that the proliferative compartment at a point in time in B-CLL is relatively small, it is crucial to understand the extent to which all cells of the clone can amplify, the relative rates of division that fractions of the clone can undergo (if not all cells do so at once), and the extent to which this proliferation is spontaneous or induced.

#### A. Are all or only a fraction of cells in a B-CLL clone dividing and can those cells that have divided be identified phenotypically?

These are important pathophysiologic as well as therapeutic considerations that we are trying to answer by sub-fractionating B-CLL cells from patients who have ingested 3H2O, using combinations of cell surface markers and isolation by fluorescence-activated cell sorting. Because CD38 is known to be relevant to disease course and possibly pathogenesis, in preliminary studies we have isolated CD19+/CD5+/CD38+ and CD19+/CD5+/CD38- cells from 9 patients at week 8, well into the pulse/maintenance phase of the study (C Calissano et al, 2006 submitted).

When DNA from these fractions was analyzed, mean 3H enrichment in the CD38+ population was approximately twofold higher than that in the CD38- fraction. Enhanced 3H uptake into the CD38+ population was detected in every patient, with CD38+/CD38- labeling ratios ranging from slight (1.15) to high (5.58). In 4 patients, this ratio was well above 2.0. These *in-vivo* findings indicate that within an individual B-CLL patient, the leukemic subpopulation marked by surface membrane CD38 contains more cells that have recently undergone cell division than the CD38- fraction.

These kinetic analyses are complemented by the finding that more CD38+ cells co-express markers of cellular activation and proliferation than the CD38- cells from an individual patient (CD69, CD62L, ZAP-70, and Ki-67; R

### Table 2. In vivo birth rates of B-CLL cells correlate with disease progression.

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Birth Rate (%/day)</th>
<th>Active/ Progressive Disease</th>
<th>Treatment</th>
<th>Mutation Status (%) difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>400</td>
<td>1.76</td>
<td>Yes</td>
<td>Pre and Post</td>
<td>0.0</td>
</tr>
<tr>
<td>408</td>
<td>1.09</td>
<td>No</td>
<td>No</td>
<td>0.3</td>
</tr>
<tr>
<td>189</td>
<td>0.81</td>
<td>Yes</td>
<td>Pre and Post</td>
<td>0.3, 6.8</td>
</tr>
<tr>
<td>472</td>
<td>0.54</td>
<td>Yes</td>
<td>No</td>
<td>0.0</td>
</tr>
<tr>
<td>169</td>
<td>0.49</td>
<td>Yes</td>
<td>Post</td>
<td>5.1</td>
</tr>
<tr>
<td>360</td>
<td>0.48</td>
<td>No</td>
<td>No</td>
<td>0.3</td>
</tr>
<tr>
<td>355</td>
<td>0.45</td>
<td>Yes</td>
<td>Post</td>
<td>0.0</td>
</tr>
<tr>
<td>336</td>
<td>0.41</td>
<td>Yes</td>
<td>Post</td>
<td>2.0</td>
</tr>
<tr>
<td>403</td>
<td>0.39</td>
<td>Yes</td>
<td>Post</td>
<td>0.0</td>
</tr>
<tr>
<td>282</td>
<td>0.39</td>
<td>Yes</td>
<td>Pre and Post</td>
<td>2.4</td>
</tr>
<tr>
<td>321</td>
<td>0.29</td>
<td>No</td>
<td>No</td>
<td>0.3</td>
</tr>
<tr>
<td>418</td>
<td>0.28</td>
<td>No</td>
<td>No</td>
<td>4.0</td>
</tr>
<tr>
<td>331</td>
<td>0.24</td>
<td>No</td>
<td>No</td>
<td>3.7</td>
</tr>
<tr>
<td>332</td>
<td>0.24</td>
<td>Yes</td>
<td>Post</td>
<td>1.0</td>
</tr>
<tr>
<td>107</td>
<td>0.23</td>
<td>No</td>
<td>No</td>
<td>6.9</td>
</tr>
<tr>
<td>280</td>
<td>0.22</td>
<td>No</td>
<td>No</td>
<td>—</td>
</tr>
<tr>
<td>394</td>
<td>0.18</td>
<td>No</td>
<td>No</td>
<td>0.0</td>
</tr>
<tr>
<td>109</td>
<td>0.11</td>
<td>No</td>
<td>No</td>
<td>7.1</td>
</tr>
</tbody>
</table>

1. Based on National Cancer Institute criteria (BD Cheson et al. Blood 1996;87:4990-4997)
2. Timed in relation to the heavy water protocol
3. Percent difference in nucleotide sequence between the expressed IgVH gene of the B-CLL patient and the most similar germline counterpart.
4. This leukemic clone expressed two VHDJH rearrangements.
B. Do B-CLL cells also proliferate in an antigen-independent manner? However, not all cellular proliferation may occur because members of the leukemic clone engage antigen via the BCR or other ligands via additional receptors, especially if the relevant antigens are localized to discrete anatomic compartments and if many of the cells of the clone are impaired in their recirculation capacity, thereby inhibiting antigen encounter.

Homeostatic proliferation is designed to maintain an adequately sized and diverse cellular pool. There are currently no direct data documenting the level of homeostatic proliferation in B-CLL. However, since this process is normally limited and inhibited by mature, follicular B lymphocytes, the immune-deficient state that most B-CLL patients develop could promote the emergence of an antigen-independent proliferating clonal pool. Since in the normal setting these cells emerge from stem cells, a similar process could occur in B-CLL via leukemic stem cells. Because these stem cells would have the IgH and L chain variable region rearrangements encoding the BCR of the leukemic cell, the stem cell progeny would be susceptible to antigen stimulation and the physiologic effects mentioned above. Indeed, both M-CLL and U-CLL could be replenished by an antigen-independent mechanism, but only the U-CLL cases might receive an antigen-dependent drive because of their enhanced polyautoreactivity and retained ability to be stimulated through the BCR; in contrast, M-CLL might not, either because of a lack of antigen reactivity and/or an inability to respond to such signals (Figure 2; see Color Figures, page 512).

V. Potential Clinical Implications

Whether cell turnover in vivo is facilitated by external signals or not, the existence of a sizable proliferating pool of leukemic cells in B-CLL has clinical relevance. This rate of cell division may promote mutation, resulting in the creation of cells with new genetic lesions that bestow a growth advantage for the leukemic clone and impart deleterious consequences for the patient. Such clonal evolution with the appearance and outgrowth of variants with ominous chromosomal abnormalities (e.g., deletions at 11q and 17p) is well known in B-CLL. Since the CD38+ cells represent the major component of the proliferative compartment, these cells in particular might be more susceptible to developing such lesions, and indeed cases with high numbers of CD38+ cells are enriched in chromosomal aberrations and p53 dysfunction. The concept that these dividing cells represent a feeder population for clonal maintenance, growth, and diversification is consistent with the findings that active progressive disease correlates with higher birth rates. Thus, this reservoir of dividing leukemic cells could be a prime therapeutic target to limit clonal burden and prevent dangerous clonal evolution.

Hematology 2006
References

1. Damesske W. Chronic lymphocytic leukemia - an accumula-
tive disease of immunologically incompetent lymphocytes.

2. Chiorazzi N, Rai KR, Ferrarini M. Chronic lymphocytic

3. Rai KR, Patel DV. Chronic Lymphocytic Leukemia. In:


5. Andreff M. Flow cytometry in leukemia. In: Melamed MR,
Mendelsohn ML, eds. Flow cytometry and cell sorting. New
York: Alan R. Liss; 1990:697.

6. Matutes E, Polliaic A. Morphological and immunophenotypic
features of chronic lymphocytic leukemia. Rev Clin Exp

of large cells in bone marrow in patients with chronic

leukemia B cells express restricted sets of mutated and
unmutated antigen receptors. J Clin Invest. 1998;102:1515-
1525.

and CD38 expression as novel prognostic indicators in

genotype to immunoglobulin mutation geno-
2001;194:1639-1647.

of B cell chronic lymphocytic leukemia reveals a homoge-
2001;194:1625-1638.

12. Hamblin TJ, Davis Z, Gardiner A, Oscier DG, Stevenson
FK. Unmutated Ig VH genes are associated with a more
1999;94:1848-1854.

cytic leukemia cells express a surface membrane pheno-
type of activated, antigen-experienced B lymphocytes.

a surrogate for immunoglobulin-variable-region mutations in
2003;348:1764-1775.

15. Rassenti LZ, Hunykh L, Toy TL, et al. ZAP-70 compared with
immunoglobulin heavy-chain gene mutation status as a
predictor of disease progression in chronic lymphocytic

to telomerase activity delineate distinctive replicative
features of the B-CLL subgroups defined by immunoglobulin

on CD40 stimulation and interleukins proliferation and
2001;97:2777-2783.

distinguishes two groups of B-cell chronic lymphocytic
leukemias with different responses to anti-IgM antibodies

Kipps TJ. Blood-derived nurse-like cells protect chronic
lymphocytic leukemia B cells from spontaneous apoptosis
through stromal cell-derived factor-1. Blood. 2000;96:2655-
2663.

20. Chiorazzi N, Ferrarini M. B Cell Chronic Lymphocytic
Leukemia: Lessons learned from studies of the B cell

cells promoted by engagement of the antigen receptor.

differentiation of CD38-positive B-chronic lymphocytic
leukemia cells induced by cross-linking of surface IgM or

23. Deaglio S, Vaisitti T, Bergui L, et al. CD38 and CD100 lead a
network of surface receptors relaying positive signals for B-

24. Ranheim EA, Kipps TJ. Activated T cells induce expression
of B7/BB1 on normal or leukemic B cells through a CD40-

25. Hellerstein MK. Measurement of T-cell kinetics: recent

isotope-mass spectrometric measurement of DNA synthe-

ments document the dynamic cellular kinetics of chronic

28. Stryckmans PA, Debususscher L, Collard E. Cell kinetics in
1977;8:159-167.

29. Deaglio S, Vaisitti T, Aydin S, Ferrero E, Malavasi F. In-
tandem insight from basic science combined with clinical
research: CD38 as both marker and key component of the
pathogenetic network underlying chronic lymphocytic

30. Woodland RT, Schmidt MR. Homeostatic proliferation of B

31. Lam KP, Kuhn R, Rajewsky K. In vivo ablation of surface
immunoglobulin on mature B cells by inducible gene

32. Stevenson FK, Caligaris-Cappio F. Chronic lymphocytic
leukemia: revelations from the B-cell receptor. Blood.
2004;103:4389-4395.

33. Zufo S, Cutrona G, Mangiola M, Ferrarini M. Role of surface
IgM and IgD on survival of the cells from B-cell chronic

34. Lanham S, Hamblin T, Oscier D, Ibbotson R, Stevenson F,
Puckham G. Differential signaling via surface IgM is
associated with VH gene mutation status and CD38
2003;101:1087-1093.

35. Herve M, Xu K, Ng YS, et al. Unmutated and mutated
chronic lymphocytic leukemia derive from common self-
reactive B cell precursors despite expressing different

CD38 expression level, genomic aberrations, and survival in

37. Ottaggi L, Viaggi S, Zunino A, et al. Chromosome aberra-
tions evaluated by comparative genomic hybridization in B-
cell chronic lymphocytic leukemia: correlation with CD38

38. Lin K, Sherrington PD, Dennis M, Matrai Z, Cawley JC, Pettitt
AR. Relationship between p53 dysfunction, CD38 expres-
sion, and IgV(H) mutation in chronic lymphocytic leukemia.
BLOOD. 2002;100:1404-1409.