Treatment of Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma

Chronic Lymphocytic Leukemia – (CLL)

- Common hematologic malignancy, particularly in western countries
- Accounts for 1/3 of leukemias worldwide.
- Predominantly affects older adults; median age at diagnosis ~70 years.
- Usually asymptomatic at diagnosis; found on routine CBC.
- Elevated WBC and ALC.
- Immunophenotype: $CD5^+$, $CD19^+$, $CD20^+$ (usually dim), $CD23^+$
- In the US, CLL is staged using the Rai System.
- Outside the US, the Binet System is often used.

Diagnosis – CLL/SLL

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2018
Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

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Discussion

DIAGNOSIS[a]

ESSENTIAL:

- **Hematopathology review of all slides with at least one paraffin block representative of the tumor, if the diagnosis was made on a lymph node or bone marrow biopsy.**
- **Flow cytometry of blood adequate for diagnosis of CLL/SLL (biopsy generally not required)**
  - **CLL diagnosis requires presence of monoclonal B lymphocytes ≥5 x 10^9/L in peripheral blood**
  - **Clonality of B cells should be confirmed by flow cytometry**
  - **Adequate immunophenotyping to establish diagnosis by flow cytometry using cell surface markers:[b,c] kappa/lambda, CD19, CD20, CD5, CD23, CD10; if flow is used to establish diagnosis, also include cytospin for cyclin D1 or FISH for t(11;14); t(11q;v). CD200 may be useful to distinguish from MCL.**
  - **SLL diagnosis requires presence of lymphadenopathy and/or splenomegaly with B lymphocytes ≤5 x 10^9/L in peripheral blood**
  - **SLL diagnosis should be confirmed by histopathology evaluation of lymph node biopsy**
- **If diagnosis is not established by flow cytometry, then proceed with lymph node biopsy. Bone marrow aspirate with biopsy if consult material is nondiagnostic. An FNA or core needle biopsy alone is not generally suitable for the initial diagnosis of lymphoma. In certain circumstances, when a lymph node is not easily accessible for excisional or incisional biopsy, a combination of core biopsy and FNA biopsies in conjunction with appropriate ancillary techniques for the differential diagnosis (immunohistochemistry, flow cytometry) may be sufficient for diagnosis.**
  - **Adequate immunophenotyping to establish diagnosis by IHC panel:[b] CD3, CD5, CD10, CD20, CD23, cyclin D1. LEF1 may be useful to distinguish from MCL.**
- **Absolute monoclonal B lymphocyte count[c]**

INFORMATIVE FOR PROGNOSTIC AND/OR THERAPY DETERMINATION:[d]

- **FISH to detect: +12; del(11q); del(13q); del(17p)**
- **TP53 sequencing**
- **CpG-stimulated metaphase karyotype for complex karyotype**
- **Molecular analysis to detect: IGHV mutation status[e]**

CLL/SLL → **See Workup for CLL/SLL (CSLL-2)**

Monoclonal B-cell lymphocytosis (MBL)
- **Absolute monoclonal B lymphocyte count <5 x 10^9/L**
- **All lymph nodes <1.5 cm**
- **No anemia**
- **No thrombocytopenia**

→ **Observe**

[a]CLL = chronic lymphocytic leukemia; SLL = small lymphocytic lymphoma. Cases diagnosed as B-cell prolymphocytic leukemia (B-PLL) are excluded from this guideline.

[b]Typical immunophenotype: CD5+, CD23+, CD43+/-, CD10-, CD19+, CD20 dim, sIg dim+, and cyclin D1-. Note: Some cases may be sIg bright+, CD23- or dim, and some MCL may be CD23+; cyclin D1 immunohistochemistry or FISH for t(11;14) should be considered in all cases and should be done in cases with an atypical immunophenotype (CD23 dim or negative, CD20 bright, sIg bright).

[c]Absolute monoclonal B lymphocyte count <5000/mm^3 in the absence of adenopathy or other clinical features of lymphoproliferative disorder is MBL. Cells of same phenotype may be seen in reactive lymph nodes; therefore, diagnosis of SLL should only be made when effacement of lymph no

[d]See Proc

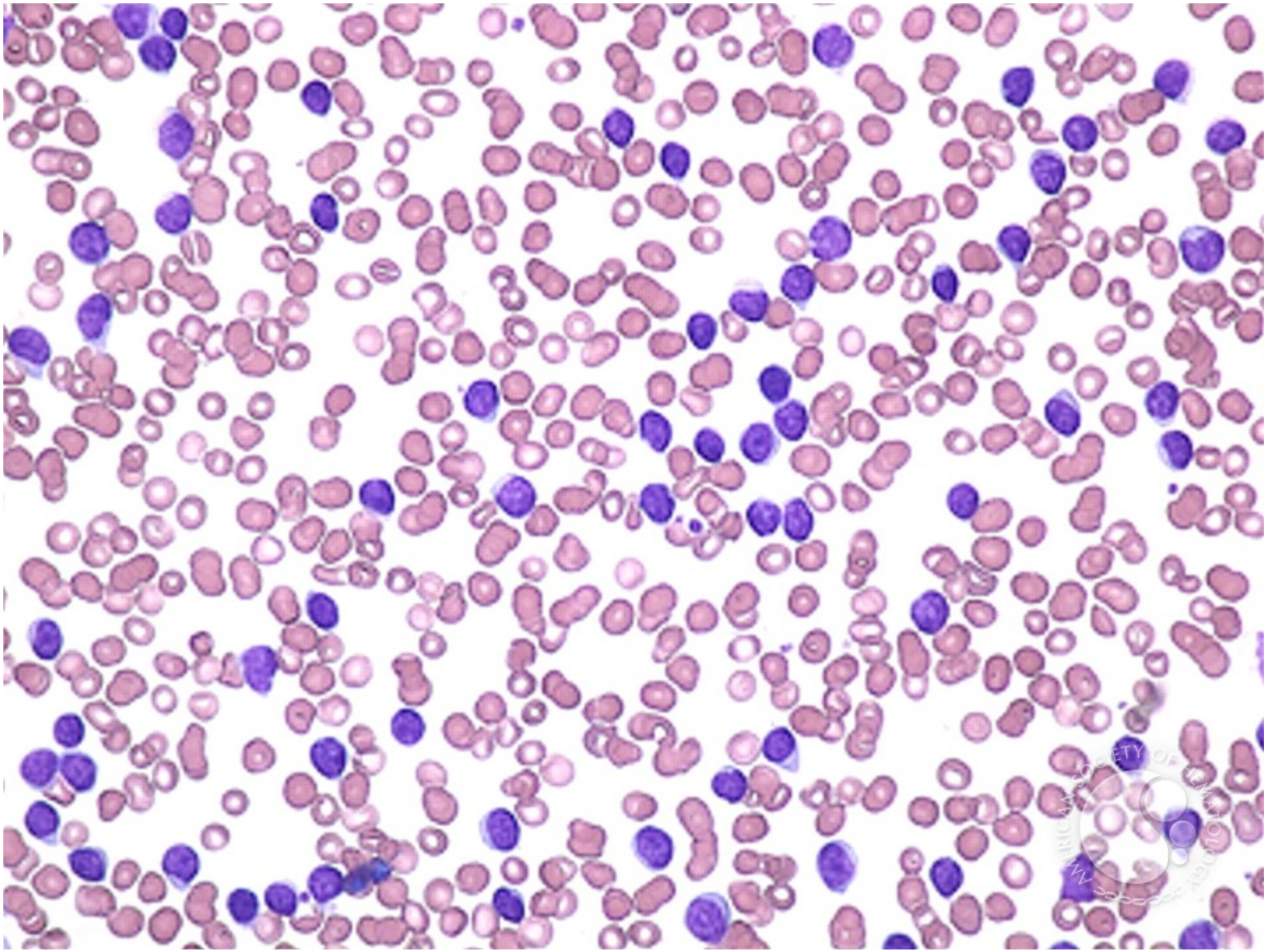
[e]If not ava methylat mutation outside t

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clini

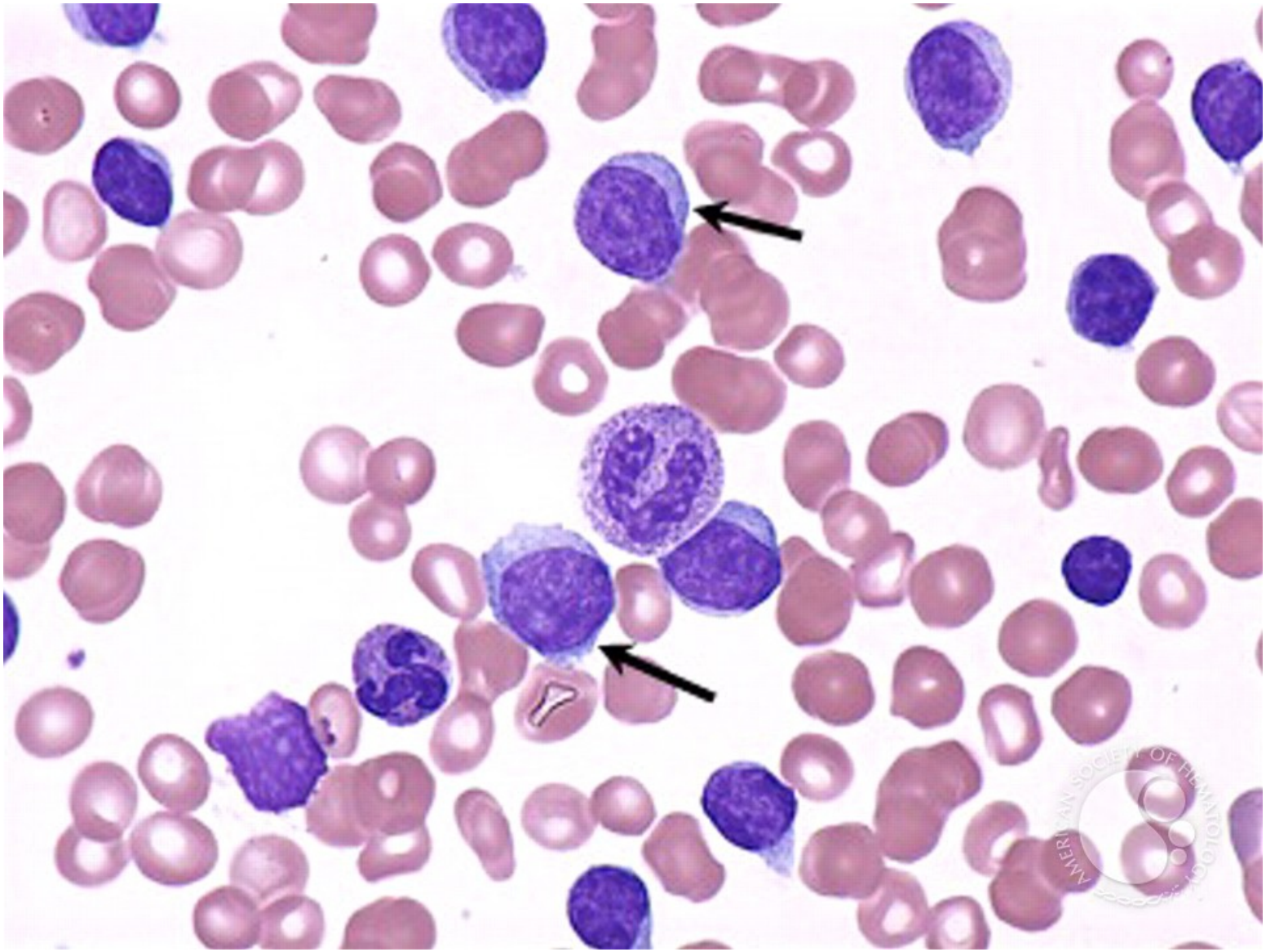
Table 1. Diagnosis of CLL

Clonal expansion of abnormal B lymphocytes in PB
At least 5 × 10^9 B lymphocytes/L (5000/μL)
Lymphoid cells ≤ 55% atypical/immature
Low density of surface Ig (IgM or IgD) with κ or λ light chains
B-cell surface antigens (CD19, $CD20^{dim}$, CD23)
CD5 surface antigen

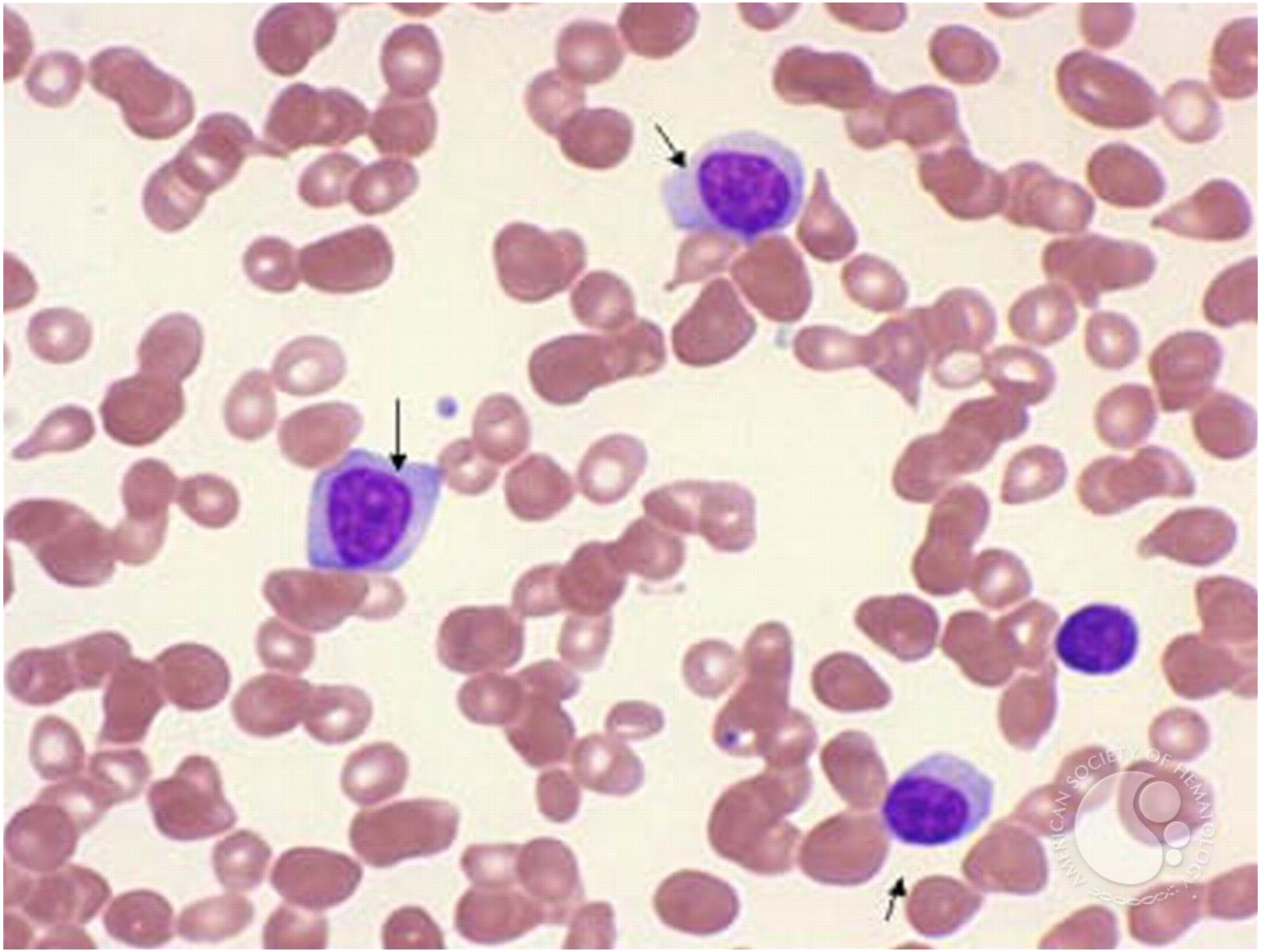
Chronic Lymphocytic Leukemia - 1



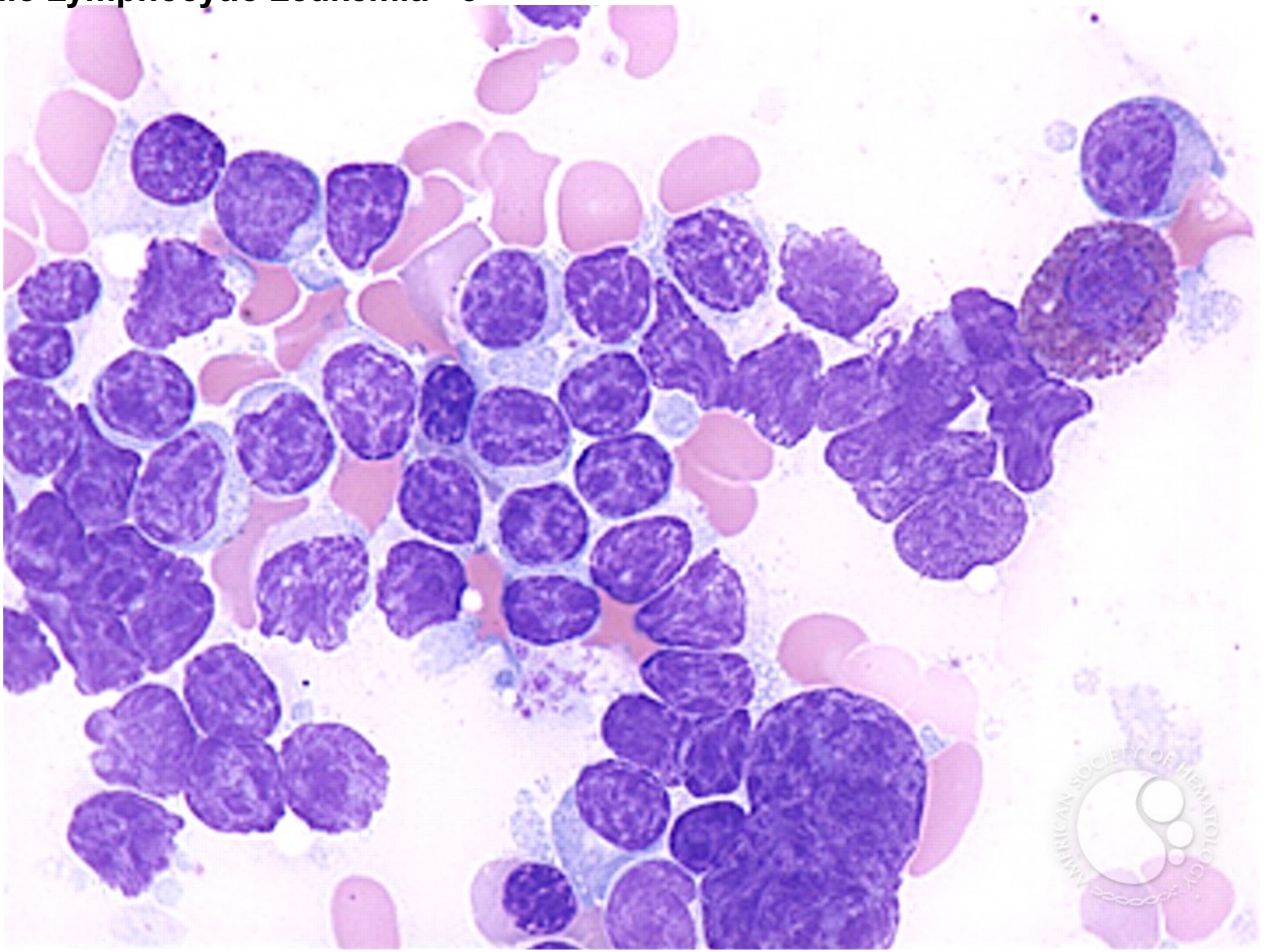
Chronic Lymphocytic Leukemia - 2

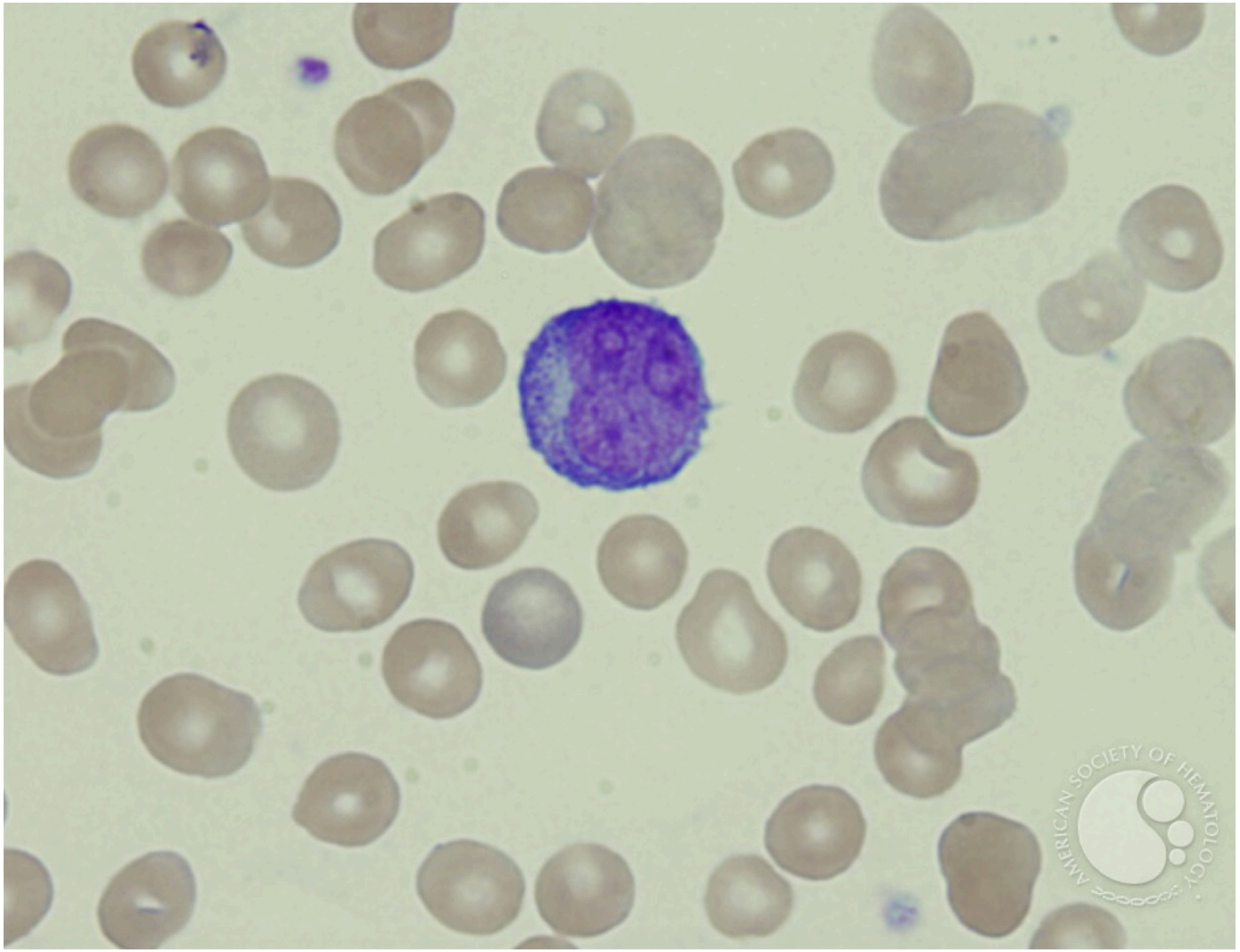


Chronic Lymphocytic Leukemia: Thrombocytopenia - 3.



Chronic Lymphocytic Leukemia - 5





"Prolymphocyte with two prominent nucleoli (clear spaces) in the peripheral blood of a patient with the prolymphocytic variant of chronic lymphocytic leukemia (CLL)." - ASH Image Bank

Rai Staging

- Stage 0: Lymphocytosis: ALC > 5,000/µL
- Stage 1: Enlargement of lymph nodes
- Stage 2: Enlargement of spleen or liver
- Stage 3: Anemia
- Stage 4: Thrombocytopenia

Binet Staging

- Stage A:
  - **Fewer than** three areas of enlarged lymphoid tissue.
  - No anemia
  - No thrombocytopenia
  - Lymphadenopathy in the neck, axillary, inguinal regions, or splenic involvement
- Stage B:
  - **Three or more** areas of enlarged lymphoid tissue
  - No anemia
  - No thrombocytopenia
- Stage C:
  - Anemia and/or thrombocytopenia, regardless of lymphadenopathy or splenomegaly

Prognosis

Several factors aid in predicting prognosis:

- Clinical stage
- Tumor burden
- Lymphocyte doubling time
- Morphologic features
  - Presence of prolymphocytes
- Chromosomal abnormalities
  - del(13q): favorable prognosis
  - del(17p): poor prognosis (*TP53* deletion)
- Immunophenotypic markers
  - Elevated CD38 and ZAP-70 have been associated with shorter survival

Prognostic Significance of Chromosomal Abnormalities

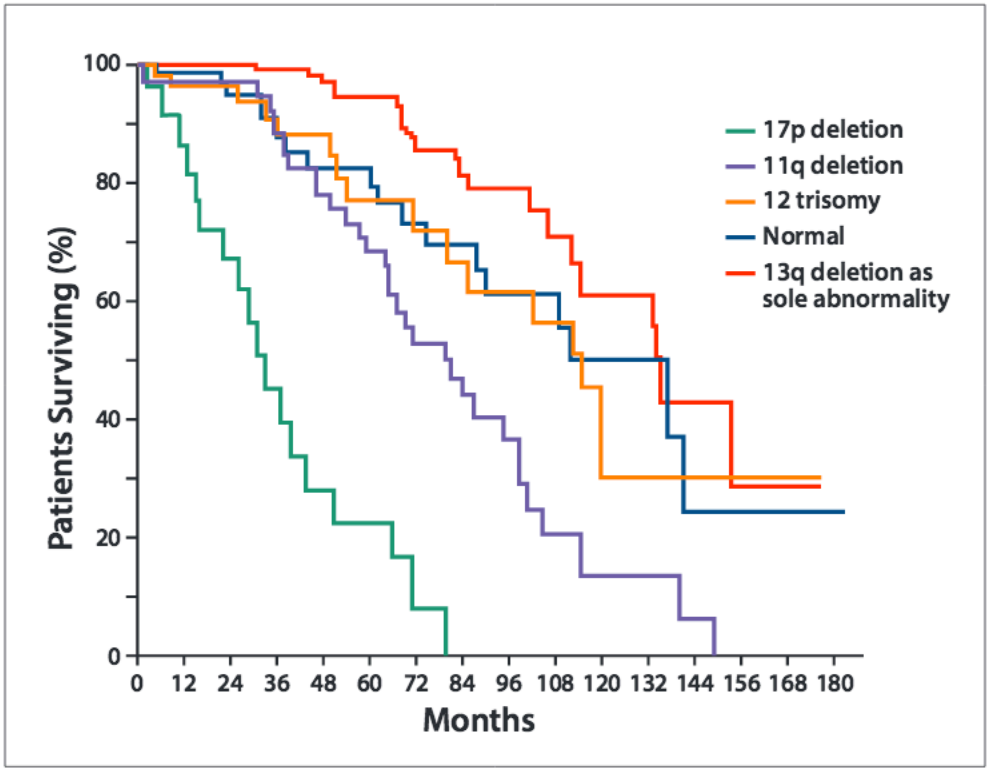


Figure 1. Chromosomal abnormalities are critically important to prognosis in patients with chronic lymphocytic leukemia. Adapted from Döhner H et al. *N Engl J Med.* 2000;343(26):1910-1916.[5]

Immunophenotypic Differentiation of CLL from Other B-lineage Lymphomas

Table 2. Immunophenotypic and genetic features of other B-cell lymphomas that may be confused with CLL

Neoplasm	SIg	cIg	CD5	CD10	CD23	CD43	Cyclin D1	Bcl-6 protein*	Genetic abnormality (%)	IgVH genes
CLL	+	−/+	+	−	+	+	−	−	del13q (50); del 11q (20); trisomy 12 (20); del 17p (10)	50% unmutated
LPL	+	+	−	−	−	−/+	−	−	t(9;14)-*PAX5R*	Mutated
MCL	+	−	+	−	−	+	+	−	t(11;14)-*BCL1R*	Unmutated (rarely mutated)
FL	+	−	−	+	−/+	−	−	+	t(14;18)-*BCL2R*	Mutated, ongoing
Extranodal and nodal MZL	+	−/+	−	−	−/+	−/+	−	−	trisomy 3; t(11;18)-*API2/MLT*; t(1;14)-*BCL10R*	Mutated, ongoing
Splenic MZL	+	−/+	−	−	−	−	−	−	del 7q21-32 (40)	50% mutated

LPL indicates lymphoplasmacytic lymphoma; MCL, mantle cell lymphoma; FL, follicle center lymphoma; MZL, marginal zone lymphoma; +, more than 90% positive; −/+, less than 50% positive; and −, less than 10% positive.

*Residual GC may be + in MZL, MCL.

Prognostic Significance of CD38 Expression and Ig V Gene Mutation Status

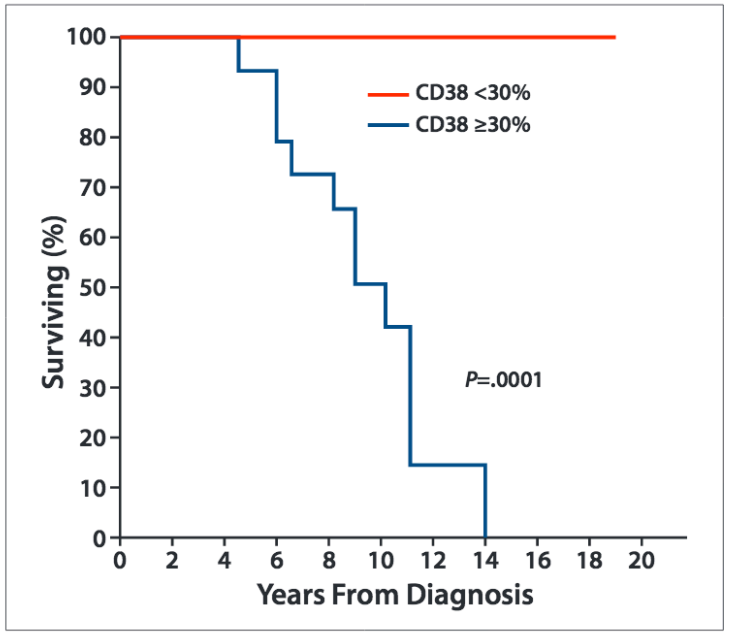


Figure 2. Elevated expression levels of CD38 and ZAP-70 have been associated with shorter survival in patients with chronic lymphocytic leukemia. Adapted from Damle RN et al. *Blood*. 1999;94(6):1840-1847.[7]

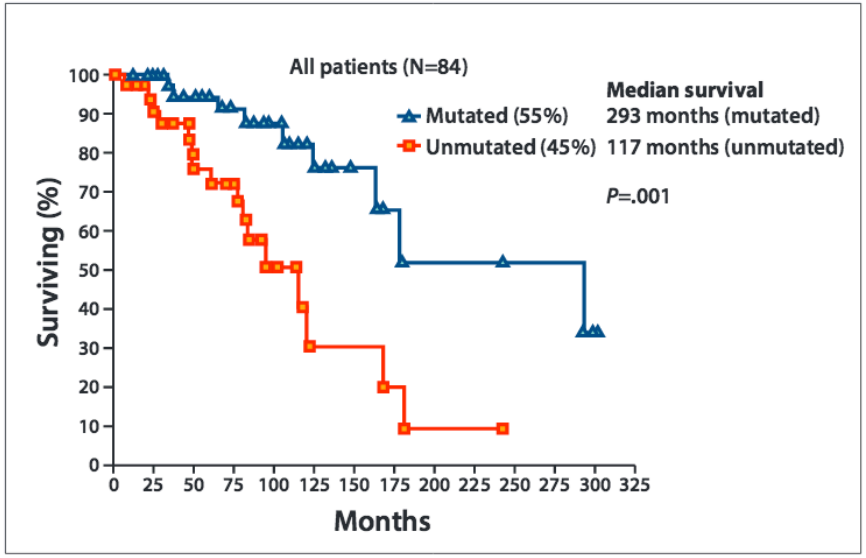
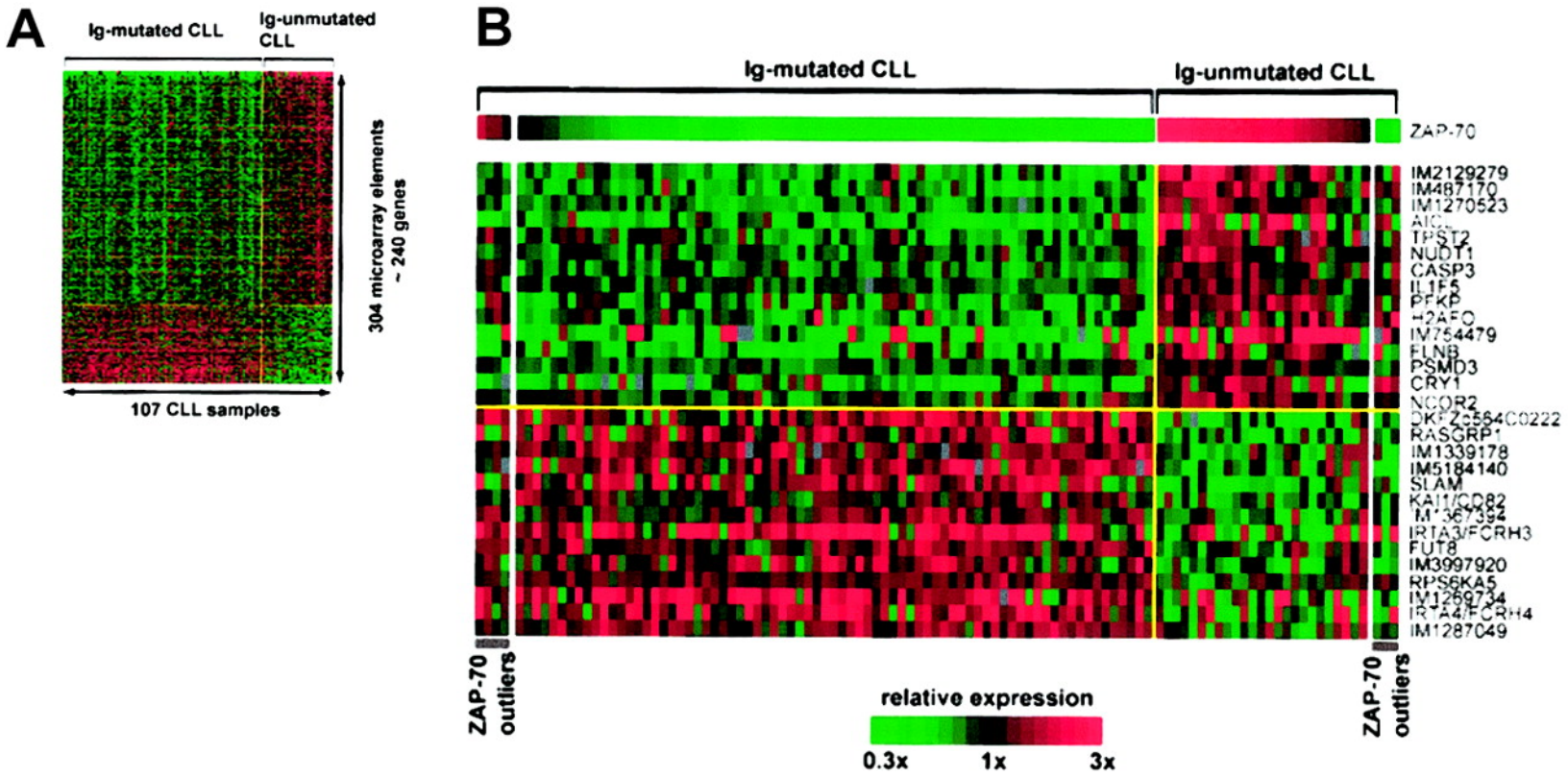


Figure 3. The mutational status of the *IGHV* gene has prognostic significance in chronic lymphocytic leukemia. *IGHV*, immunoglobulin heavy-chain variable. Adapted from Hamblin TJ et al. *Blood*. 1999;94(6):1848-1854.[8]

Gene expression profiling of Ig-mutated and -unmutated CLL



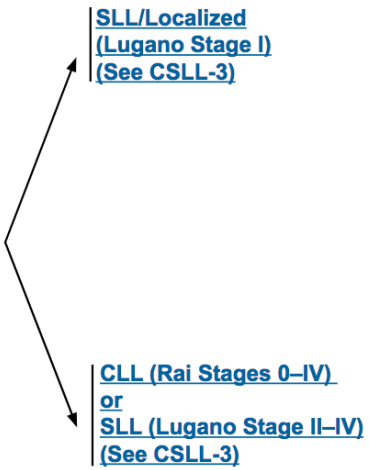
Adrian Wiestner *et al.*, Blood 2003;101:4944-4951

Diagnostic Workup

WORKUP

ESSENTIAL:
- **History and physical exam including measurement of size of liver and spleen**
- **Performance status**
- **B symptoms**
- **CBC with differential**
- **Comprehensive metabolic panel**

USEFUL UNDER CERTAIN CIRCUMSTANCES:
- **Quantitative immunoglobulins**
- **Reticulocyte count, haptoglobin, and direct Coombs' test**
- **Chest/abdominal/pelvic CT with contrast of diagnostic quality, if clinically indicated[f]**
- **Beta-2-microglobulin**
- **LDH**
- **Uric acid**
- **Unilateral bone marrow aspirate + biopsy at initiation of therapy**
- **Hepatitis B testing[g] if treatment contemplated**
- **MUGA scan/echocardiogram if anthracycline- or anthracenedione-based regimen is indicated**
- **Pregnancy testing in women of child-bearing age if systemic therapy or RT planned**
- **Discussion of fertility issues and sperm banking**
- **PET/CT scan to direct nodal biopsy, if histologic transformation is suspected. See HT-1.**



[f]Outside clinical trials, CT scans are not necessary for diagnosis, surveillance, routine monitoring of treatment response, or progression. May be warranted for symptoms or to evaluate bulky disease.
[g]Hepatitis B testing is indicated because of the risk of reactivation during treatment (eg, immunotherapy, chemoimmunotherapy, chemotherapy, targeted therapy). Tests include hepatitis B surface antigen and core antibody for a patient with no risk factors. For patients with risk factors or previous history of hepatitis B, add e-antigen. If positive, check viral load and consult with gastroenterologist.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Treatment (1)

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Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

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PRESENTATION[h]

Consider prophylaxis for tumor lysis syndrome (See CSLL-C)

See monoclonal antibody and viral reactivation (CSLL-C)

SLL/Localized (Lugano[i] Stage I) → **Locoregional RT (24–30 Gy)[j] (if indicated)** → **Observe**

CLL (Rai Stages[i] 0-IV) or SLL (Lugano[i] Stages II-IV)

- **SLL** →
- **CLL Rai Low (0) and Intermediate (I-II) risk[i]** →
- **CLL Rai High (III-IV) risk[i]** → **Progressive cytopenia[n]**

Evaluate for indications for treatment:[k]
- **Eligible for clinical trial[l]**
- **Significant disease-related symptoms:**
  - **Fatigue (severe)**
  - **Night sweats**
  - **Weight loss**
  - **Fever without infection**
- **Threatened end-organ function**
- **Progressive bulky disease (spleen >6 cm below costal margin, lymph nodes >10 cm)**
- **Progressive anemia**
- **Progressive thrombocytopenia[m]**

No indication → **Observe**

Indication present →
- **Re-evaluate[o]**
  - **FISH**
  - **TP53 mutation status**
  - **Karyotype**
- **Imaging as appropriate**

→ **CLL/SLL Without Deletion of 17p/TP53 Mutation (See CSLL-4)**

→ **CLL/SLL With Deletion of 17p/TP53 Mutation (See CSLL-6)**

Histologic transformation or Histologic progression of CLL → **See HT-1**

[h] See Supportive Care for Patients with CLL/SLL (CSLL-C).
[i] See Rai and Binet Classification Systems (CSLL-B 1 of 2) and Lugano Modification of Ann Arbor Staging System (CSLL-B 2 of 2).
[j] The dose is delivered in 1.5–2.0 Gy/fraction. See NCCN Guidelines for B-Cell Lymphomas, Principles of Radiation Therapy for additional details.
[k] Absolute lymphocyte count alone is not an indication for treatment unless above 200–300 x 10^9/L or symptoms related to leukostasis.
[l] Given incurability with conventional therapy, consider including clinical trial as first-line therapy.
[m] Platelet counts >100,000 cells/mm^3 are typically not associated with clinical risk.
[n] Select patients with mild, stable cytopenia (ANC <1000/μL, Hgb <11 g/dL, or platelet <100,000/μL) may continue to be followed with observation.
[o] Re-evaluation of FISH [t(11;14); t(11q;v); +12; del(11q); del(13q); del(17p)] and TP53 mutation status is necessary prior to initiation of treatment.

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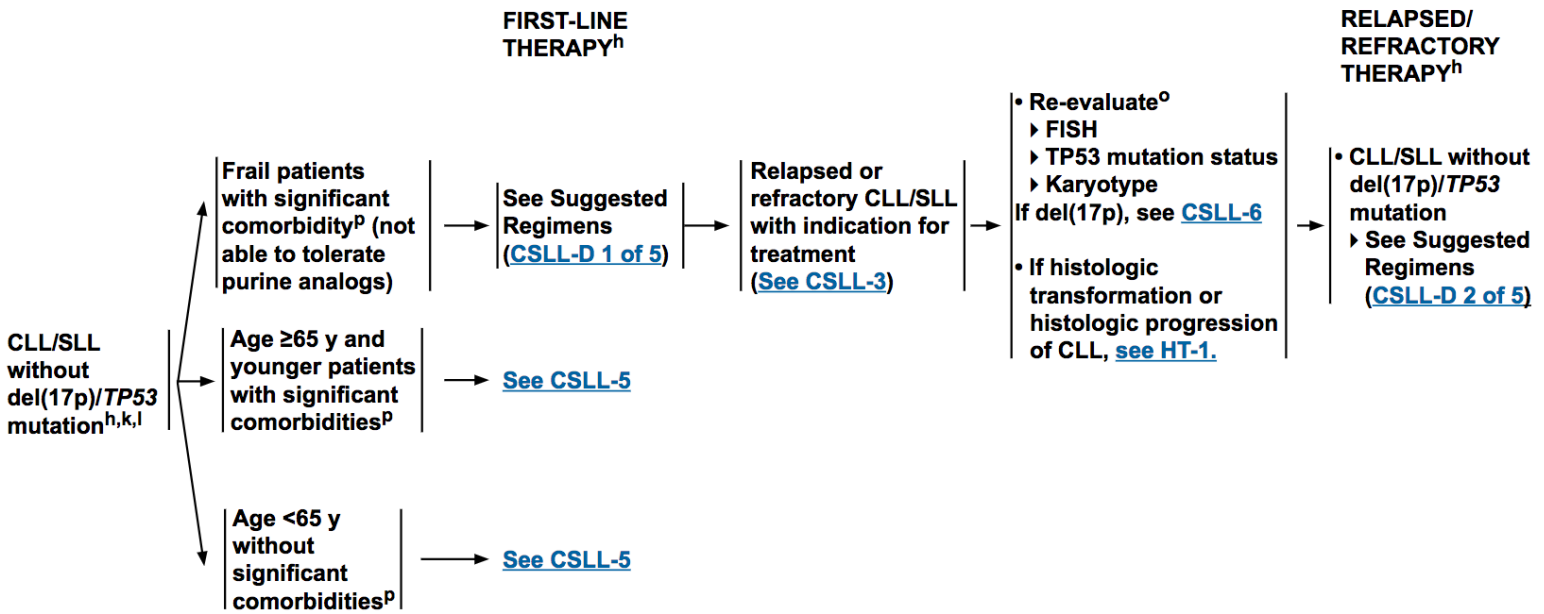
Treatment (2)

CLL/SLL WITHOUT DELETION OF 17p/*TP53* MUTATION[h,k,l]



Consider prophylaxis for tumor lysis syndrome (See CSLL-C)

See monoclonal antibody and viral reactivation (CSLL-C)

[h]See Supportive Care for Patients with CLL/SLL (CSLL-C).
[k]Absolute lymphocyte count alone is not an indication for treatment unless above 200–300 x 10^9/L or symptoms related to leukostasis.
[l]Given incurability with conventional therapy, consider including clinical trial as first-line therapy.
[o]Re-evaluation of FISH [t(11;14); t(11q;v); +12; del(11q); del(13q); del(17p)] and TP53 mutation status is necessary prior to initiation of treatment.
[p]Salvi F, Miller MD, Grilli A, et al. A manual of guidelines to score the modified cumulative illness rating scale and its validation in acute hospitalized elderly patients. J Am Geriatr Soc 2008;56:1926-1931.

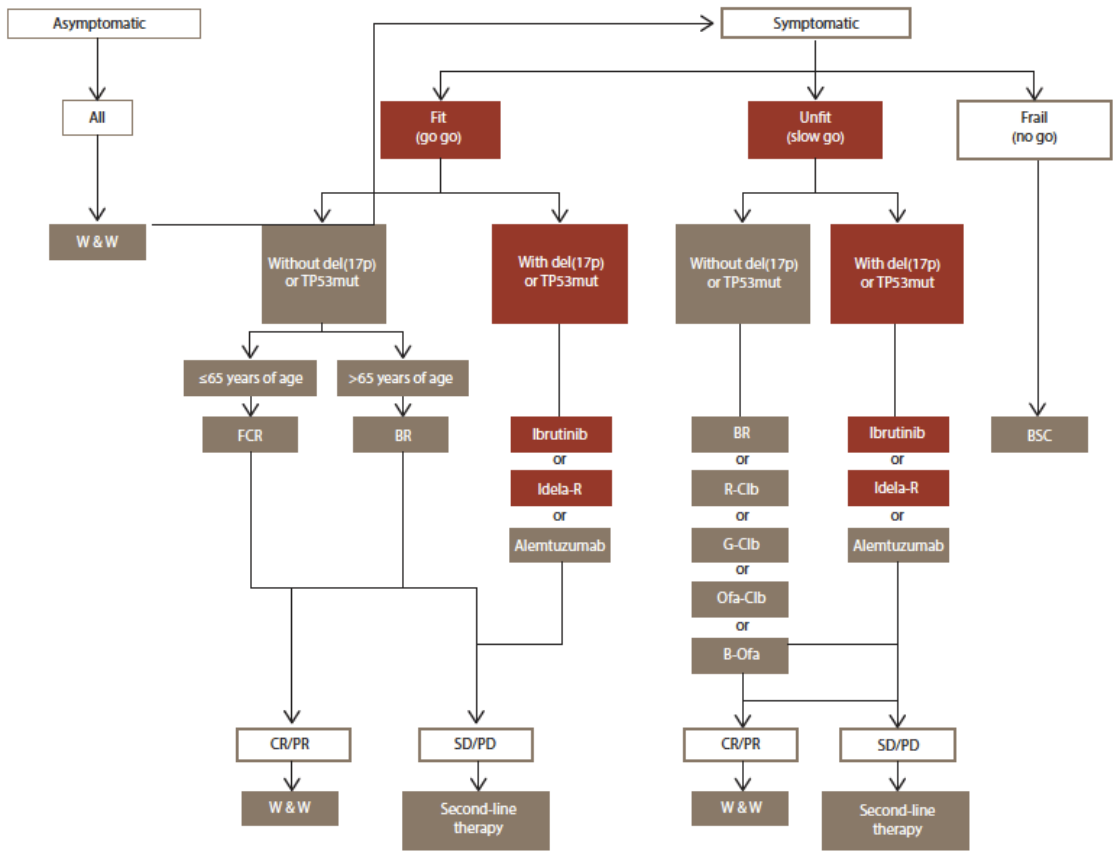
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Treatment: Frontline

- First-line regimens depend on patient age, general health, disease-related factors, and patient's individual treatment goals.
- Older patients with comorbidities:
  - Chlorambucil monotherapy, rituximab monotherapy, or combination of chlorambucil and rituximab (a regimen used primarily outside the US).
- Younger patients without comorbidities:
  - Combination chemoimmunotherapy regimens, such as bendamustine and rituximab, or fludarabine, cyclophosphamide, and rituximab (FCR) have become standard of care.

Frontline Treatment: German CLL Study Group

Figure 1. German CLL first-line treatment guidelines



B-Ofa = bendamustine, ofatumumab; BR = bendamustine, rituximab; BSC = best supportive care; CLL = chronic lymphocytic leukemia; CR = complete response; del(17p) = deletion 17p; FCR = fludarabine, cyclophosphamide, rituximab; G-Clb = obinutuzumab, chlorambucil; Idela-R = idelalisib, rituximab; Ofa-Clb = ofatumumab, chlorambucil; PD = progressive disease; PR = partial response; R-Clb = rituximab, chlorambucil; TP53mut = TP53 mutation; W & W = watch and wait

Ibrutinib

- Approved by the FDA in 2016 for the frontline setting.
- Useful for elderly and high-risk patients (e.g., *TP53* deletion)
- Acts by interfering with key signaling events that are activated in CLL cells within the microenvironment of secondary lymphoid tissues.
- Administered orally.
- Works by a redistribution of the CLL cells out of the lymphoid tissues into the peripheral blood, where they are cleared and then lead to remission.

Persistent Lymphocytosis with Ibrutinib

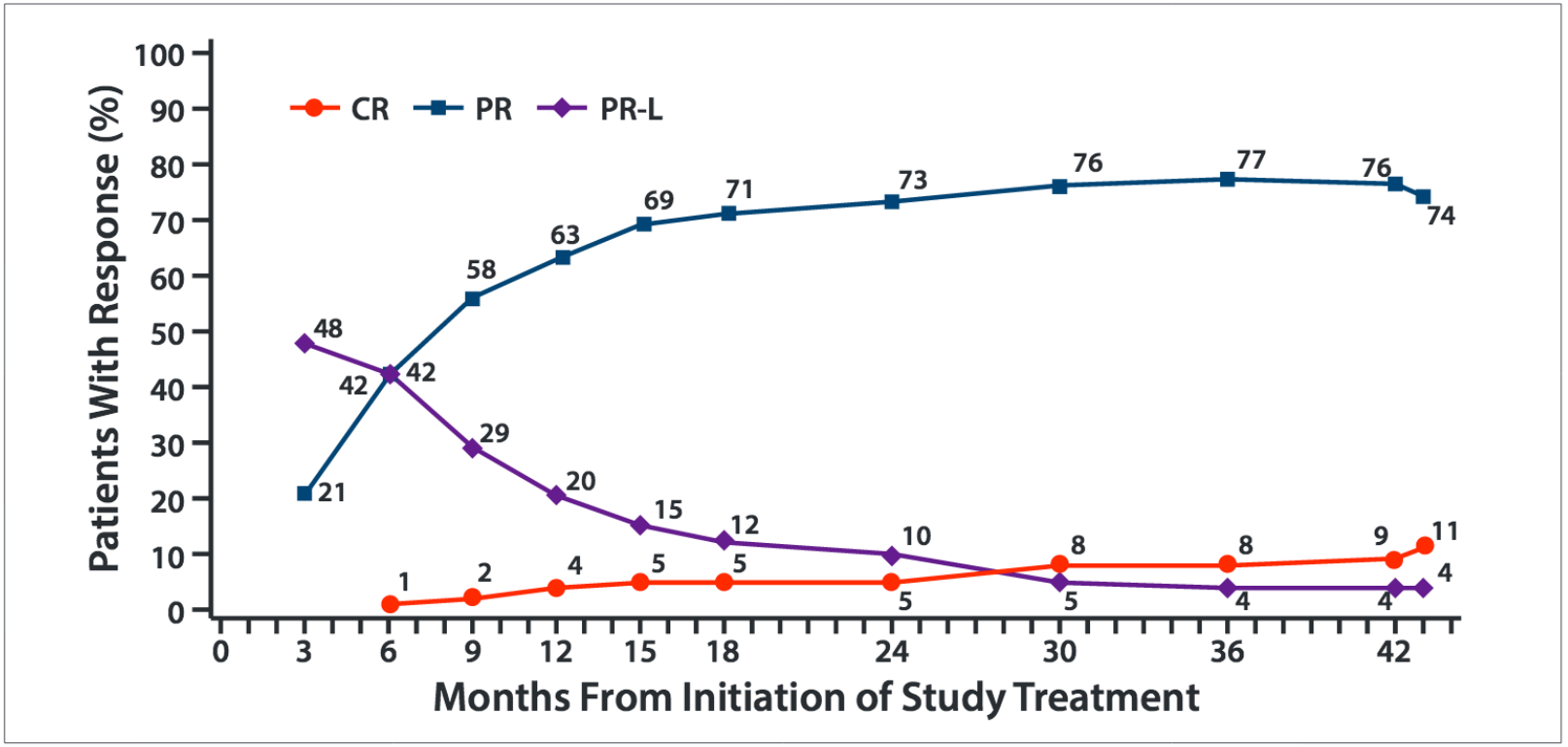


Figure 7. Cumulative best responses seen with single-agent ibrutinib after 3 years of follow-up among patients with chronic lymphocytic leukemia (symptomatic treatment-naive or relapsed/refractory) or small lymphocytic lymphoma. CR, complete response; PR, partial response; PR-L, partial response with lymphocytosis. Adapted from Byrd JC et al. *Blood.* 2015;125(16):2497-2506.[9]

Ibrutinib with Bendamustine/Rituximab

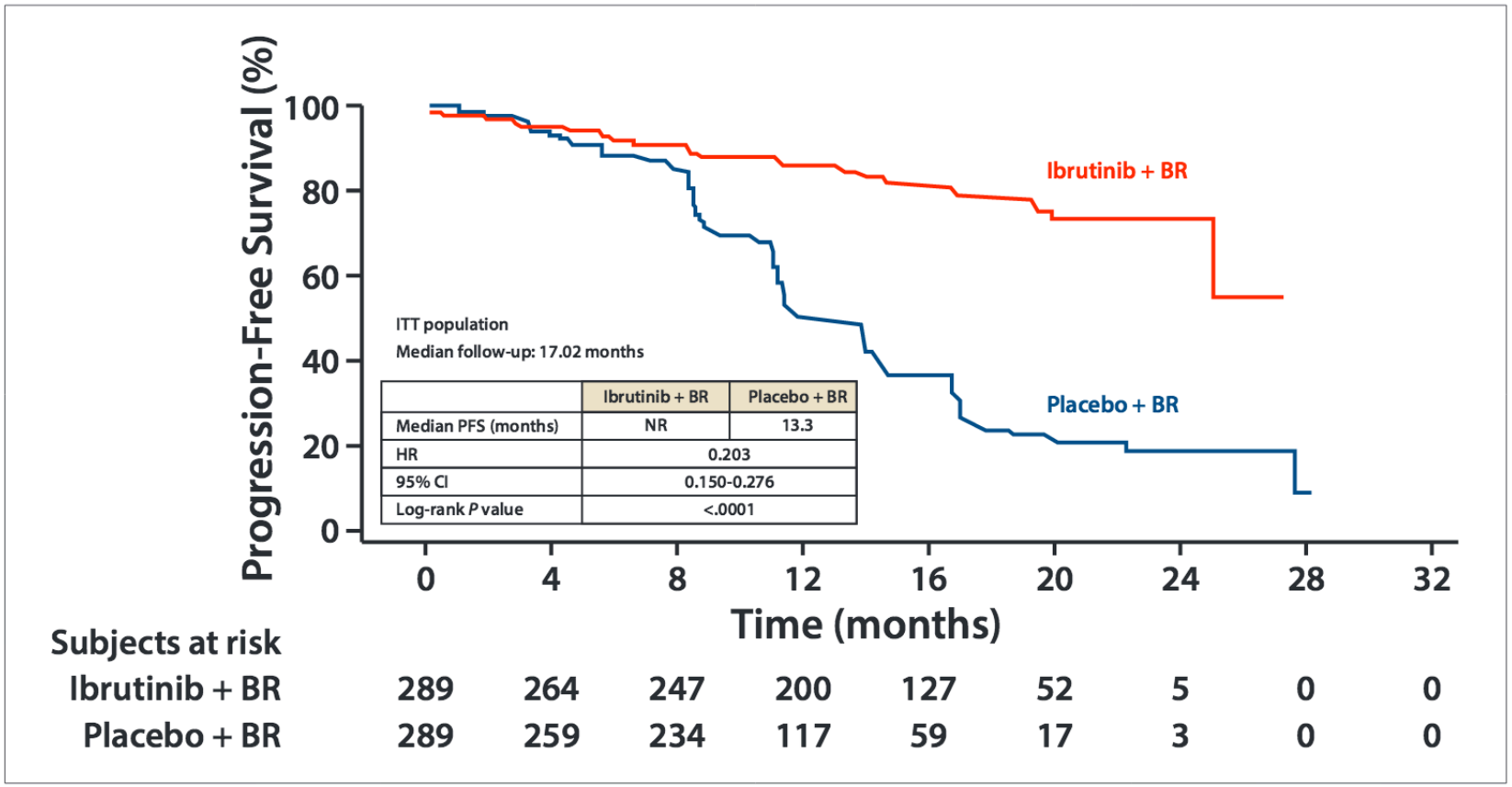


Figure 8. PFS in the phase 3 HELIOS trial, which evaluated ibrutinib plus BR vs placebo plus BR in patients with relapsed/refractory chronic lymphocytic leukemia or small lymphocytic lymphoma. BR, bendamustine and rituximab; HELIOS, Ibrutinib Combined With Bendamustine and Rituximab Compared With Placebo, Bendamustine, and Rituximab for Previously Treated Chronic Lymphocytic Leukaemia or Small Lymphocytic Lymphoma; ITT, intent-to-treat; PFS, progression-free survival. Adapted from Chanan-Khan A et al. *Lancet Oncol.* 2016;17(2):200-211.[12]

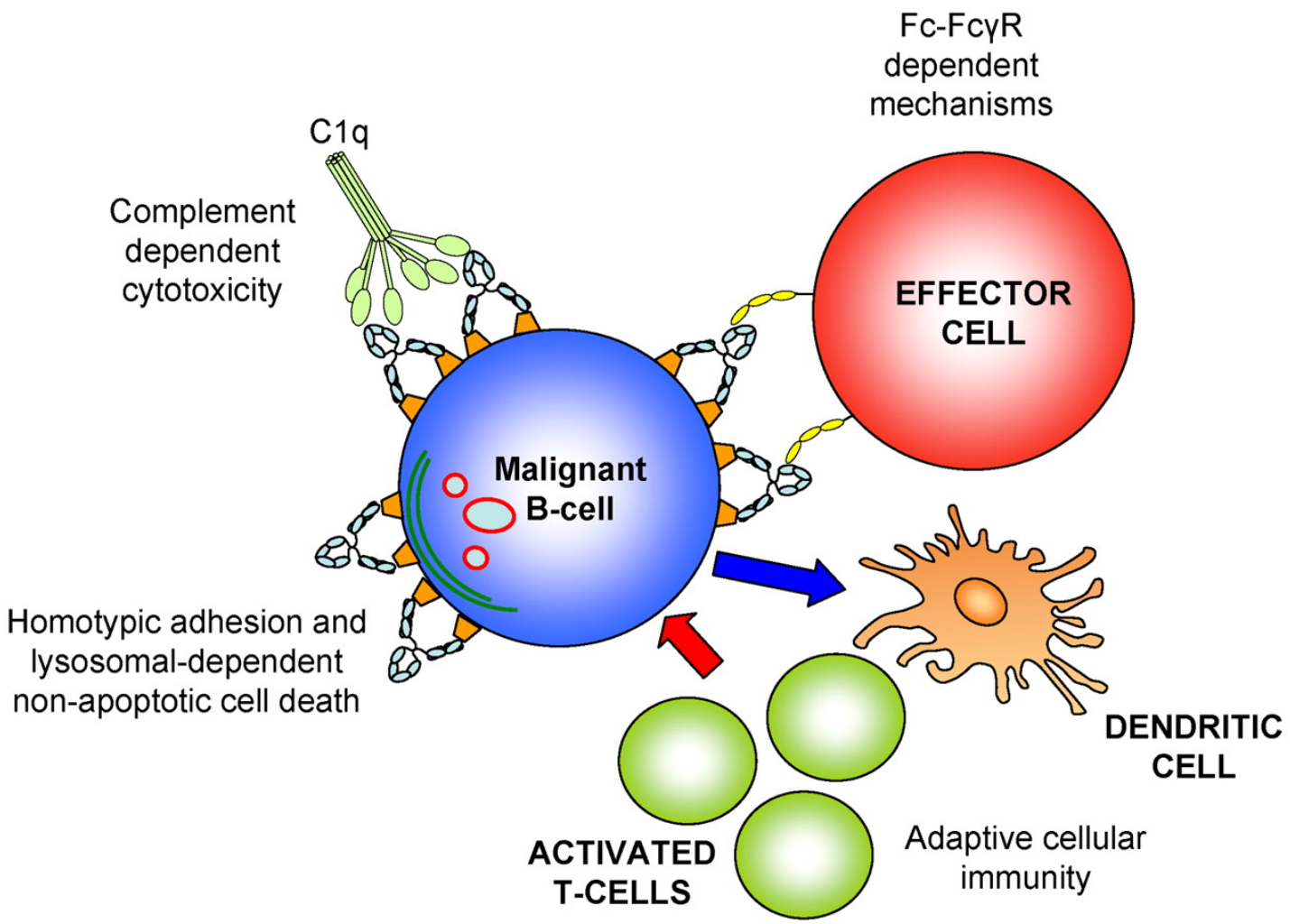
Idelalisib

- Selective inhibitor of PI3 kinase delta that is FDA-approved for relapsed CLL in combination with rituximab.
- Dosed orally, twice daily.
- Safety profile is different than of idelalisib in that adverse advents are much higher and more sever.
- At this time should only be used in the salvage setting.

Venetoclax

- Orally administered inhibitor of BCL-2.
- BCL-2 is an antiapoptotic protein crucial to the survival of CLL cells.
- Indicated for patients with 17p deletion after 1 or more previous therapies.
- Approved by the FDA in April 2016.
- Adverse events include tumor lysis syndrome that can be life-threatening. Patients must be hospitalized when drug is administered.
- ORR was 79% in recent trial with 20% CR.

Potential anti-CD20 mAb Effector Mechanisms



Waleed Alduaij, and Tim M. Illidge Blood 2011;117:2993-3001

Commercially Available anti-CD20 mAbs

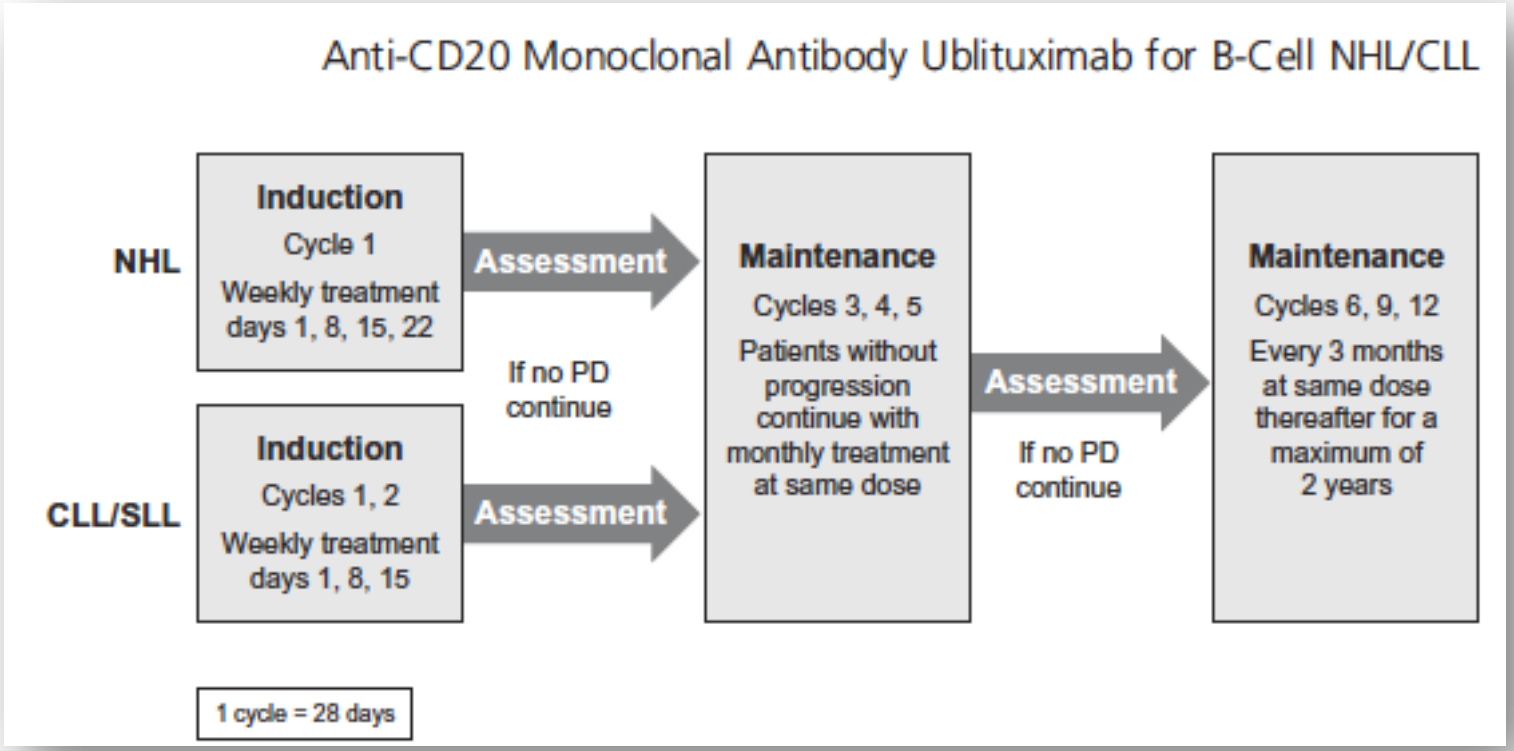
Table 2 Comparison of commercially available anti-CD20 antibodies

Antibody	Obinutuzumab	Rituximab	Ofatumumab
Trade name (EU)	Gazyvaro	MabThera	Arzerra
Manufacturer	Roche	Roche	GlaxoSmithKline
Antibody type	II	I	I
IgG subclass	IgG1	IgG1	IgG1
Structure	Humanized	Chimeric	Fully human
Binding to CD20 epitope	Large loop	Large loop	Large and small loop
Binding to lipid rafts	–	++	++++
ADCC	++++	++	++
CDC	+	++	++++
Direct cell death induction	++++	+	+

Abbreviations: ADCC, antibody-dependent cellular cytotoxicity; CDC, complement-dependent cytotoxicity; I Ig, immunoglobulin.

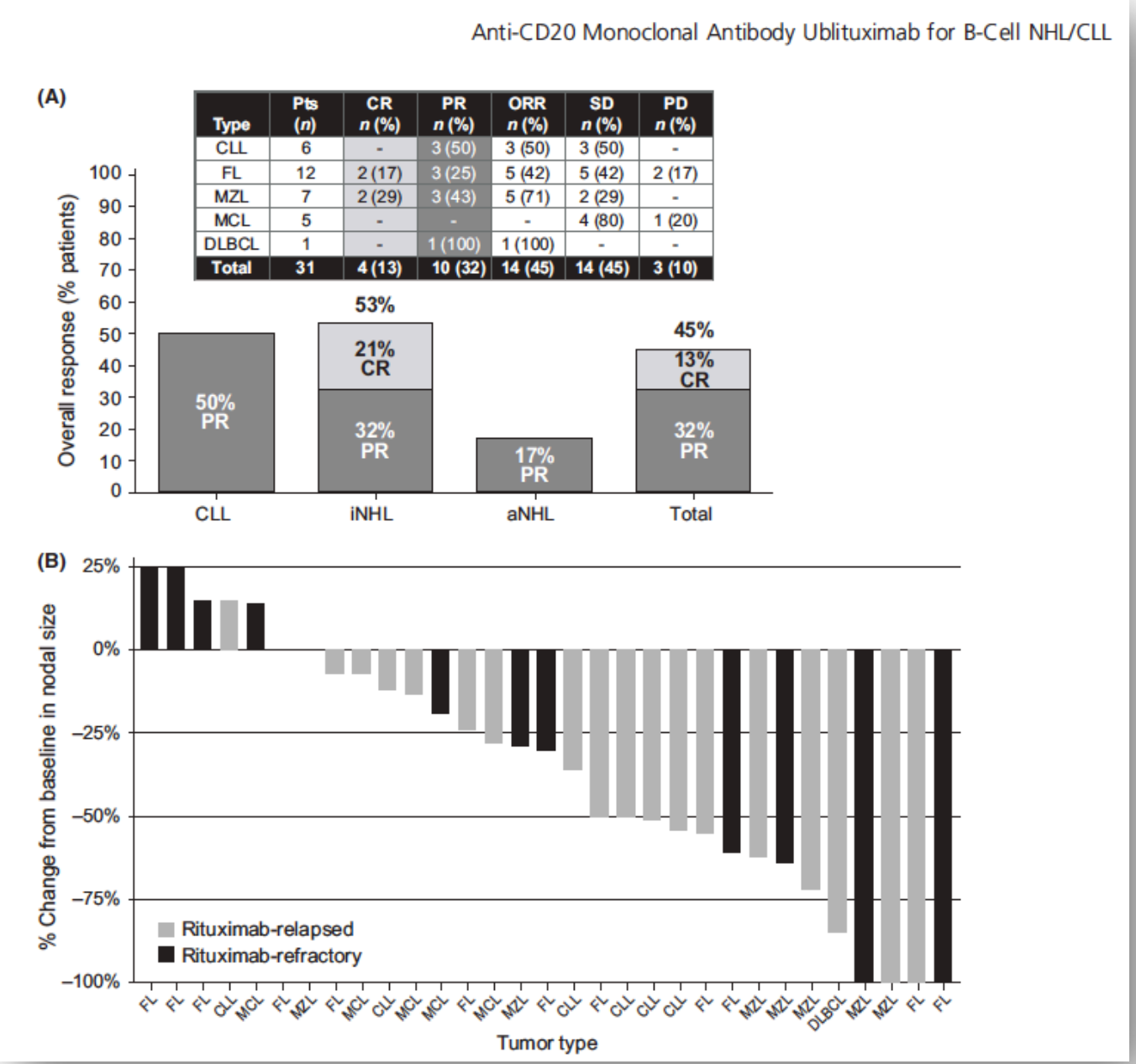
http://doi.org/10.2147/PGPM.S55501

Ublituximab: anti-CD20 mAb



http://doi.org/10.1111/bjh.14534

Ublituximab: anti-CD20 mAb



http://doi.org/10.1111/bjh.14534

Ublituximab: anti-CD20 mAb

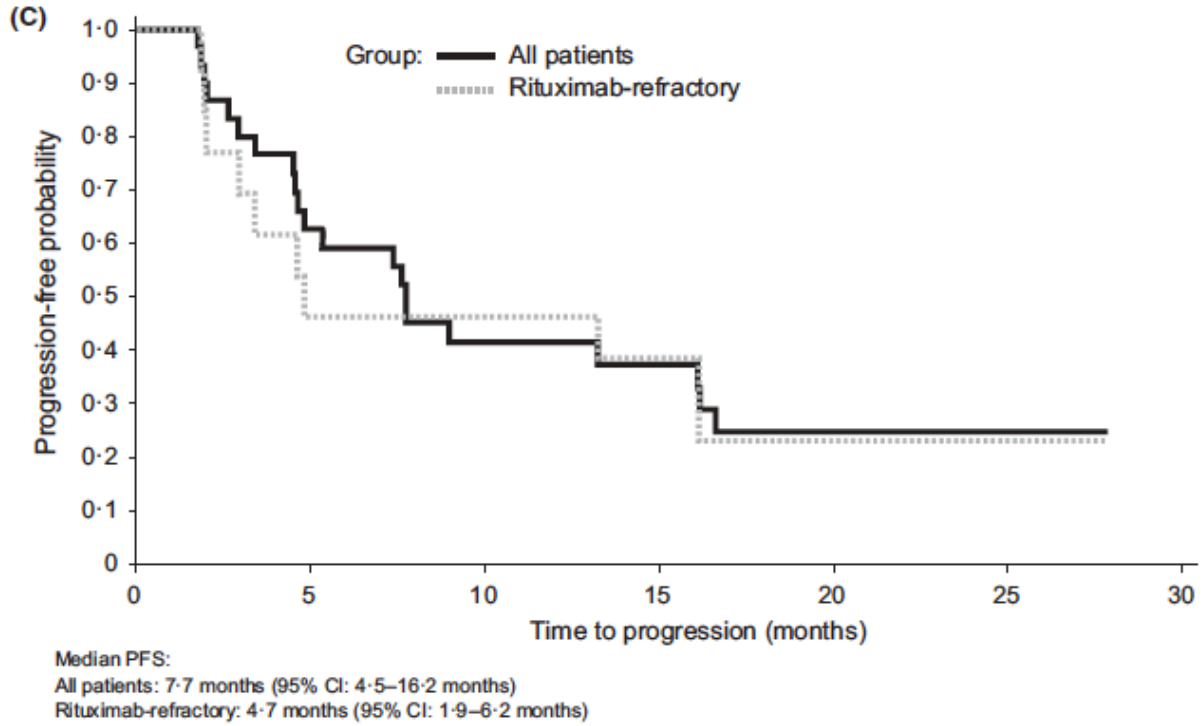


Fig 2. Treatment Response. (A) Overall response by lymphoma subtype. (B) Individual patient best percentage change from baseline in nodal size. (C) Progression-free survival. aNHL, aggressive non-Hodgkin lymphoma; CI, confidence interval; CLL, chronic lymphocytic leukaemia; CR, complete response; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; iNHL, indolent non-Hodgkin lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; ORR, overall response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

http://doi.org/10.1111/bjh.14534

Autoimmune Complications in Patients with CLL

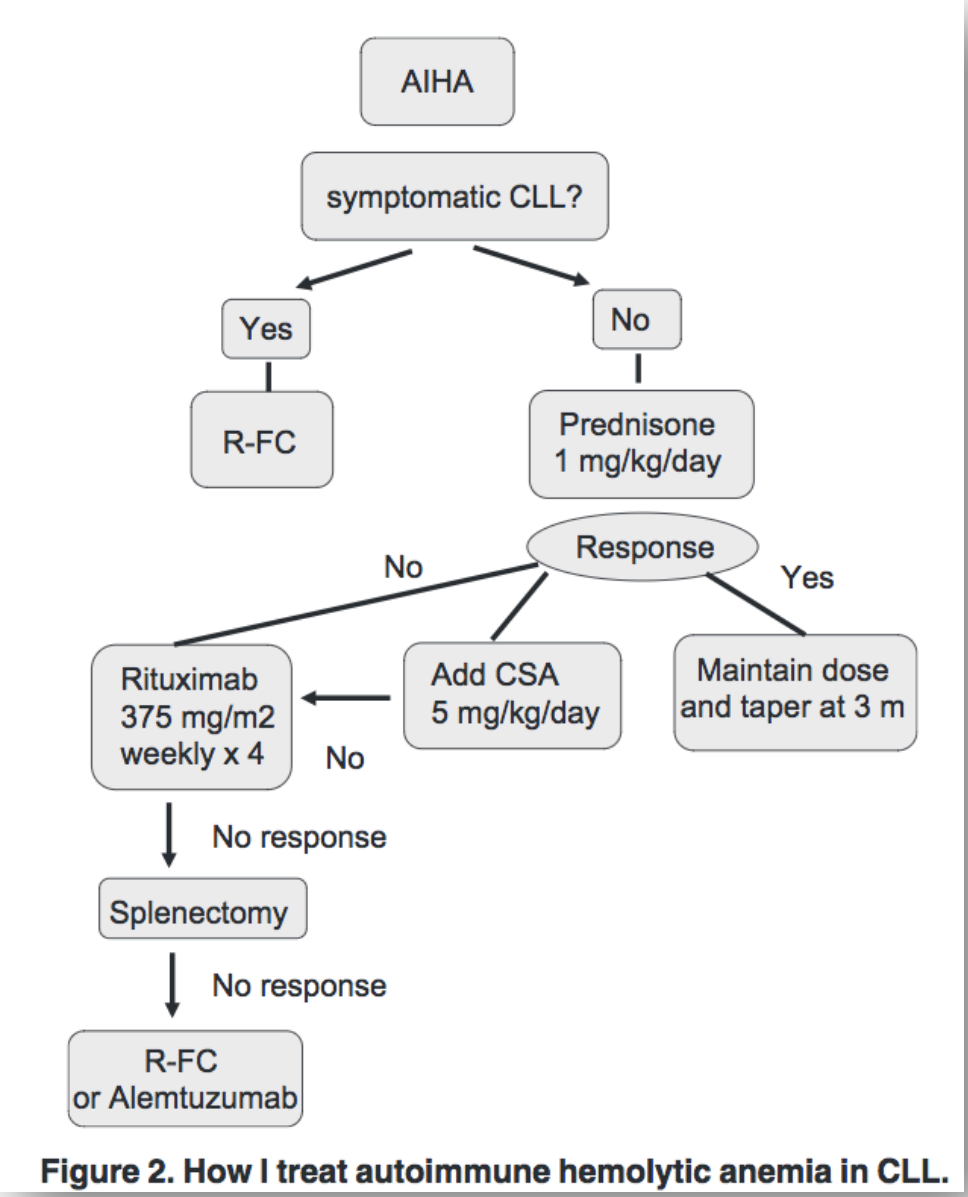
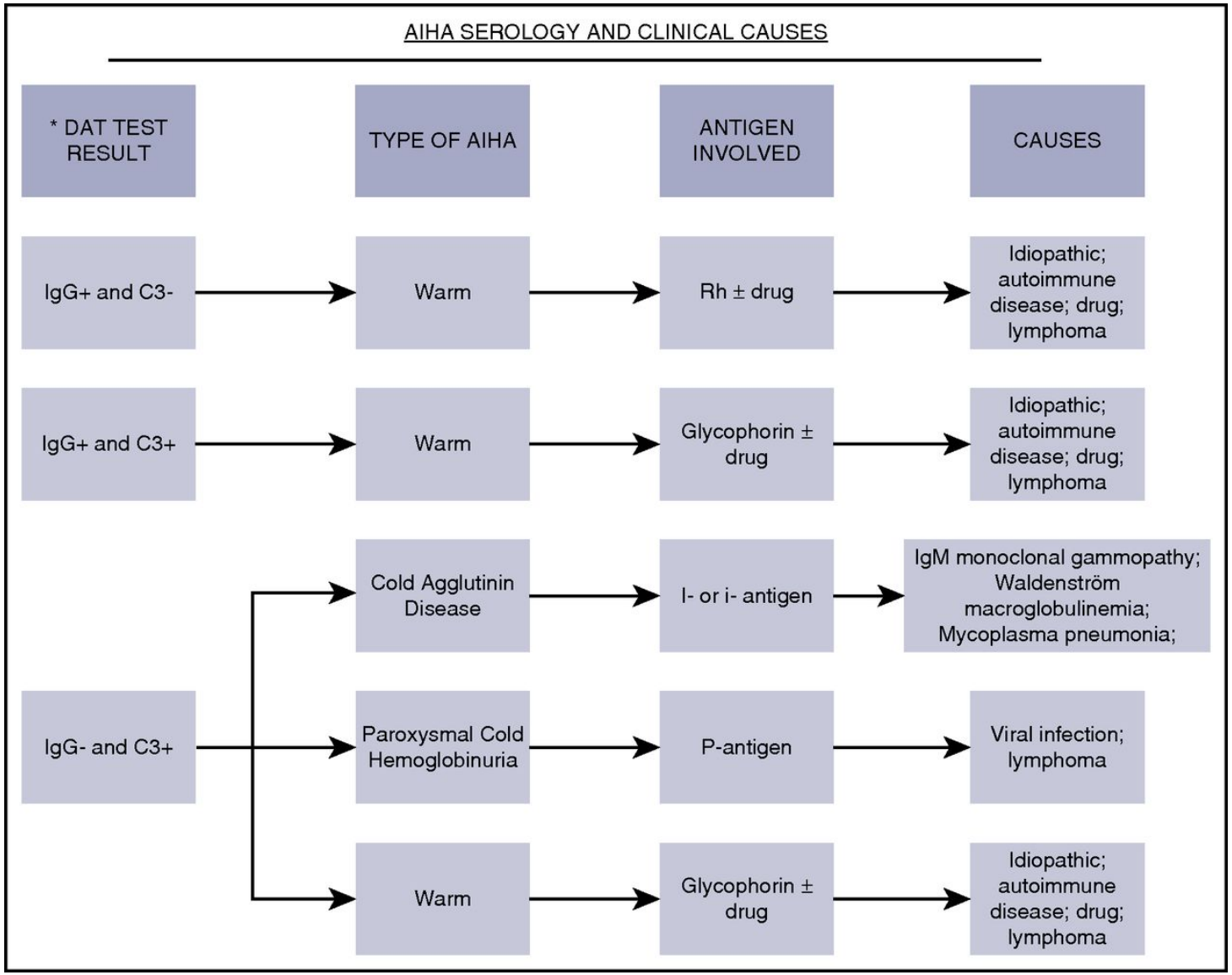


Figure 2. How I treat autoimmune hemolytic anemia in CLL.

Direct antiglobulin test in diagnosis of hemolytic anemia



Ronald S. Go et al. Blood 2017;129:2971-2979

Supportive Care for Patients with CLL

SUPPORTIVE CARE FOR PATIENTS WITH CLL/SLL

Autoimmune Cytopenias
- Autoimmune hemolytic anemia (AIHA): Diagnosis with reticulocyte count, haptoglobin, DAT
  - AIHA that develops in setting of treatment with fludarabine: stop, treat, and avoid subsequent fludarabine
- Immune thrombocytopenic purpura (ITP): Evaluate bone marrow for cause of low platelets
- Pure red cell aplasia (PRCA): Evaluate for parvo B19 and bone marrow evaluation
- Treatment: Corticosteroids, rituximab, IVIG, cyclosporin A, splenectomy, eltrombopag, or romiplostim (ITP)

Blood Product Support
- Transfuse according to institutional or published standards
- Irradiate all blood products to avoid transfusion-associated GVHD

Cancer Screening
- Standard screening guidelines should be closely followed for breast, cervical, colon, and prostate cancers

Non-Melanomatous Skin Cancer
- Patients with CLL/SLL have a higher risk of developing non-melanomatous skin cancers
- Risk factors include caucasians and a history of intensive sun exposure at a young age
- For patients at-risk, annual dermatalogic skin screening is recommended

Rare Complications of Monoclonal Antibody Therapy
- Rare complications such as mucocutaneous reactions including paraneoplastic pemphigus, Steven-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis can occur. Consultation with a dermatologist is recommended for management of these complications. Re-challenge with the same monoclonal antibody in such settings is not recommended. It is unclear that re-challenge with alternative CD20 antibodies poses the same risk of recurrence.

Recurrent Sinopulmonary Infections (requiring IV antibiotics or hospitalization)
- Antimicrobials as appropriate
- Evaluate serum IgG, if <500 mg/dL
  - begin monthly IVIG 0.3–0.5 g/kg,
  - adjust dose/interval to maintain nadir level of approximately 500 mg/dL

Rituximab Rapid Infusion
- If no infusion reactions were experienced with prior cycle of rituximab, a rapid infusion over 90 minutes can be used.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Continued on next page

Summary

- Many patients with CLL/SLL do not require treatment until they become symptomatic.
- Autoimmune complications can arise which include:
  - Autoimmune hemolytic (AIHA): Diagnosis with reticulocyte count, haptoglobin, DAT
    AIHA that develops in setting of treatment with fludarabine: stop, treat, and avoid subsequent fludarabine
  - Immune thrombocytopenic purpura (ITP): Evaluate bone marrow for cause of low platelets
  - Pure red cell aplasia (PRCA): Evaluate for parvo B19 and bone marrow evaluation
  - Treatment: Corticosteroids, rituximab, IVIG, cyclosporin A, splenectomy, eltrombopag, or romiplostim (ITP)
- Variety of effective regimens are available:
  - FCR: fludarabine, cyclophosphamide, and rituximab
  - Bendamustine (usually with rituximab)
  - FR: fludarabine and rituximab
  - CVP: cyclophosphamide, vincristine, and prednisone (sometimes with rituximab, R-CVP)
  - CHOP: cyclophosphamide, doxorubicin, vincristine, and prednisone
  - Chlorambucil combined with prednisone, rituximab, obinutuzumab, or ofatumumab
  - PCR: pentostatin, cyclophosphamide, and rituximab
  - Alemtuzumab
  - Fludarabine
  - Ibrutinib

https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf

References

- Clinical Advances in Hematology & Oncology, Volume 14, Issue 5, Supplement 8, May 2016
- Go, R. S., Winters, J. L., & Kay, N. E. (2017). How I treat autoimmune hemolytic anemia. Blood, 129(22), 2971-2979. Accessed November 22, 2017. https://doi.org/10.1182/blood-2016-11-693689.
- Board Review 2017 - CLL and Hairy Cell Leukemia, Susan O'Brien, MD, UC Irvine Health
- Gribben, J. G. (2010). How I treat CLL up front. Blood, 115(2), 187-197. Accessed November 23, 2017. https://doi.org/10.1182/blood-2009-08-207126.
- http://www.cancer.org/cancer/leukemia-chroniclymphocyticcll/detailedguide/leukemia-chronic-lymphocytic-treating-treatment-by-risk-group
- Alduaij, W., & Illidge, T. M. (2011). The future of anti-CD20 monoclonal antibodies: are we making progress?. Blood, 117(11), 2993-3001. Accessed November 23, 2017. https://doi.org/10.1182/blood-2010-07-298356.
- Smolej, L. (2015). Targeted treatment for chronic lymphocytic leukemia: clinical potential of obinutuzumab. *Pharmacogenomics and Personalized Medicine*, *8*, 1–7. http://doi.org/10.2147/PGPM.S55501
- Sawas, A., Farber, C. M., Schreeder, M. T., Khalil, M. Y., Mahadevan, D., Deng, C., … O'Connor, O. A. (2017). A phase 1/2 trial of ublituximab, a novel anti-CD20 monoclonal antibody, in patients with B-cell non-Hodgkin lymphoma or chronic lymphocytic leukaemia previously exposed to rituximab. *British Journal of Haematology*, *177*(2), 243–253. http://doi.org/10.1111/bjh.14534
- https://imagebank.hematology.org/
- NCCN Guidelines:

https://www.nccn.org/professionals/physician_gls/f_guidelines.asp#site