The background of the slide is a microscopic image of a blood smear. It features numerous small, round cells with dark purple nuclei and light blue cytoplasm, characteristic of lymphocytes. These cells are densely packed in some areas and more sparse in others. The overall color palette is dominated by the purple and blue of the stained cells against a lighter, off-white background.

Treatment of Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma



Chronic Lymphocytic Leukemia

- Relatively common hematologic malignancy.
- Accounts for 1/3 of all leukemias world wide.
- Predominantly affects older adults-median age 70-72 years.
- Usually asymptomatic at diagnosis; found on routine CBC.
- Elevated WBC and ALC.
- Phenotype on flow cytometry: CD5+, CD23+, CD19+, CD20+.
- In the United States, CLL is staged using the Rai System.
- Outside United States, the Binet System is often used.

Rai Staging

- Stage 0: Lymphocytosis
- Stage 1: Enlargement of lymph nodes
- Stage 2: Enlargement of spleen or liver
- Stage 3: Anemia
- Stage 4: Thrombocytopenia



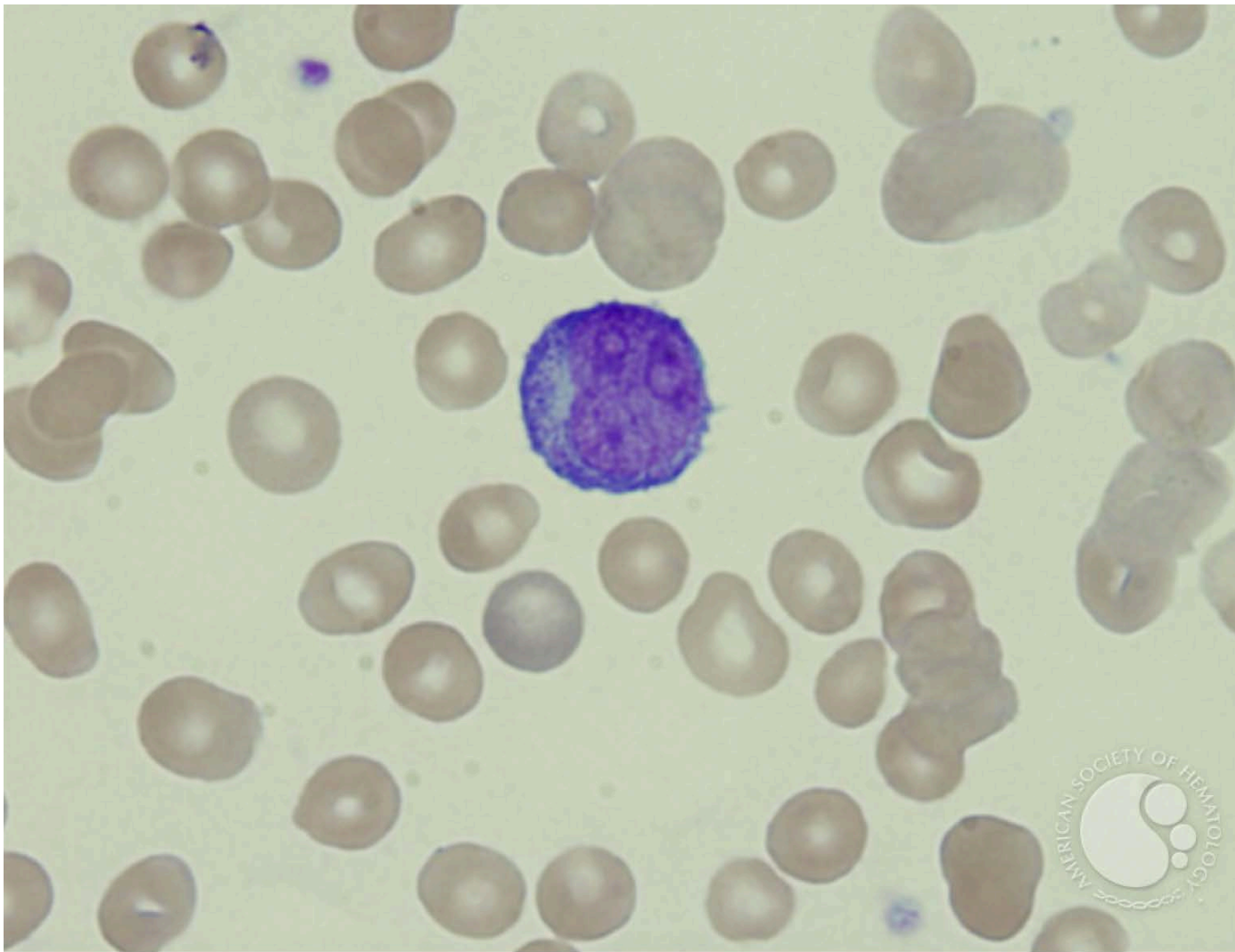
Binet Staging

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

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*)
- Immunophenotypic markers
 - Elevated CD38 and ZAP-70 have been associated with shorter survival



“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

Prognostic Significance of Chromosomal Abnormalities

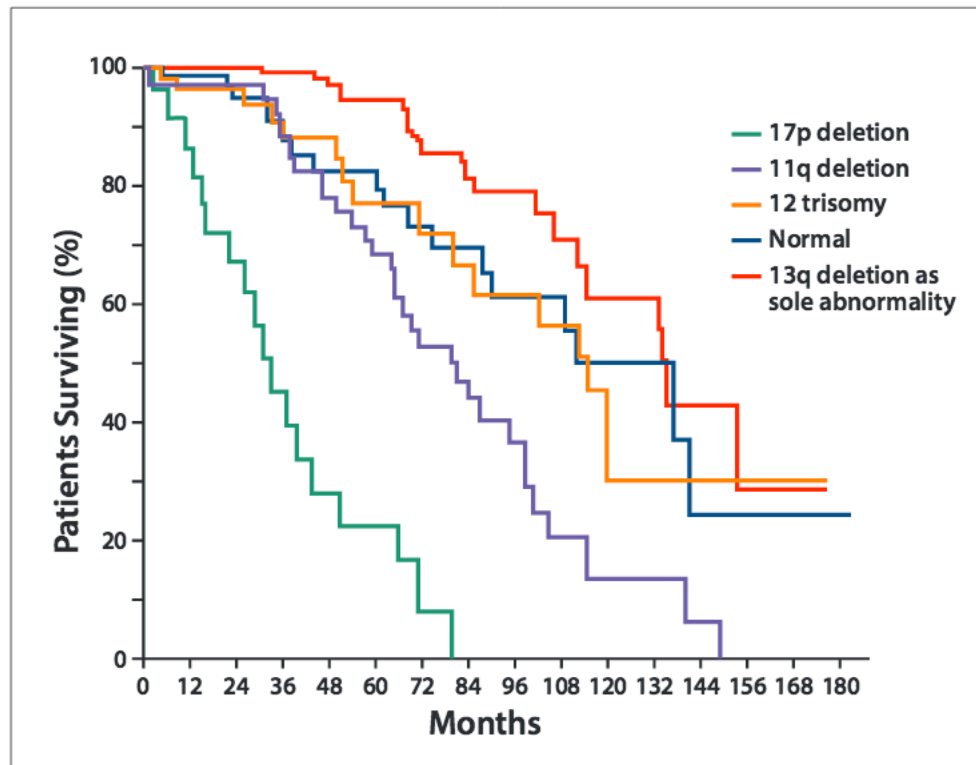


Figure 1. Chromosomal abnormalities are critically important to prognosis in patients with chronic lymphocytic leukemia. Adapted from Döhner H et al. *N Engl J Med.* 2000;343(26):1910-1916.⁵

Prognostic Significance of Immunophenotypic Markers

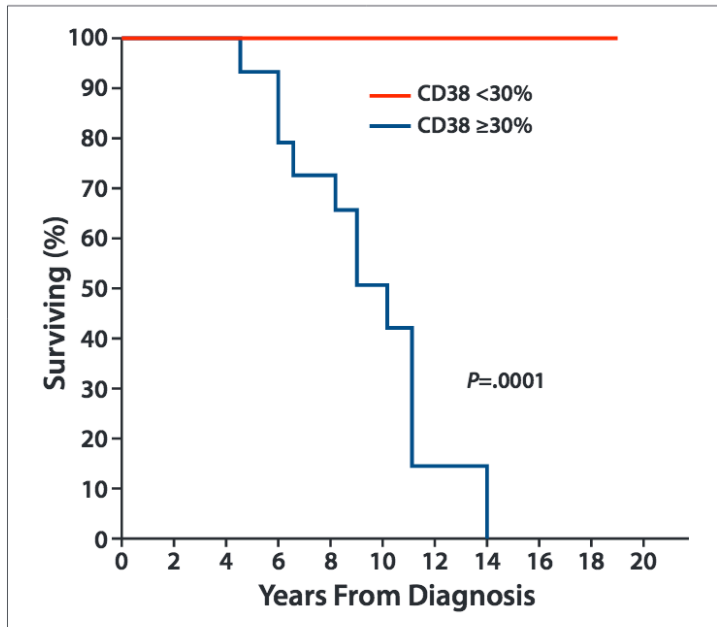


Figure 2. Elevated expression levels of CD38 and ZAP-70 have been associated with shorter survival in patients with chronic lymphocytic leukemia. Adapted from Damle RN et al. *Blood*. 1999;94(6):1840-1847.⁷

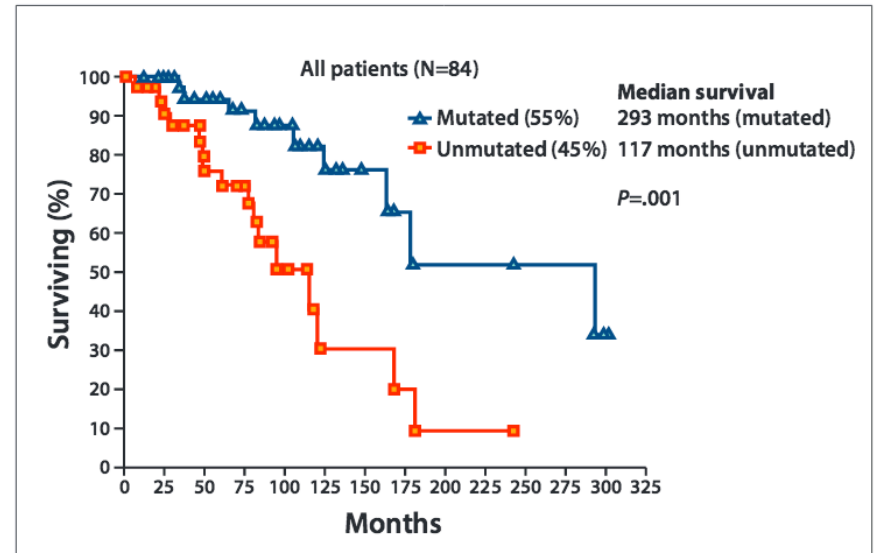


Figure 3. The mutational status of the *IGHV* gene has prognostic significance in chronic lymphocytic leukemia. *IGHV*, immunoglobulin heavy-chain variable. Adapted from Hamblin TJ et al. *Blood*. 1999;94(6):1848-1854.⁸

Treatment

- 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 the standard of care.

Ibrutinib

- Approved by the FDA in 2016 for the frontline setting.
- Useful for elderly and high-risk patients and can be used alone or with chlorambucil.
- Act 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 in the peripheral blood, where they are cleared and then lead to remission.

Single-Agent Ibrutinib

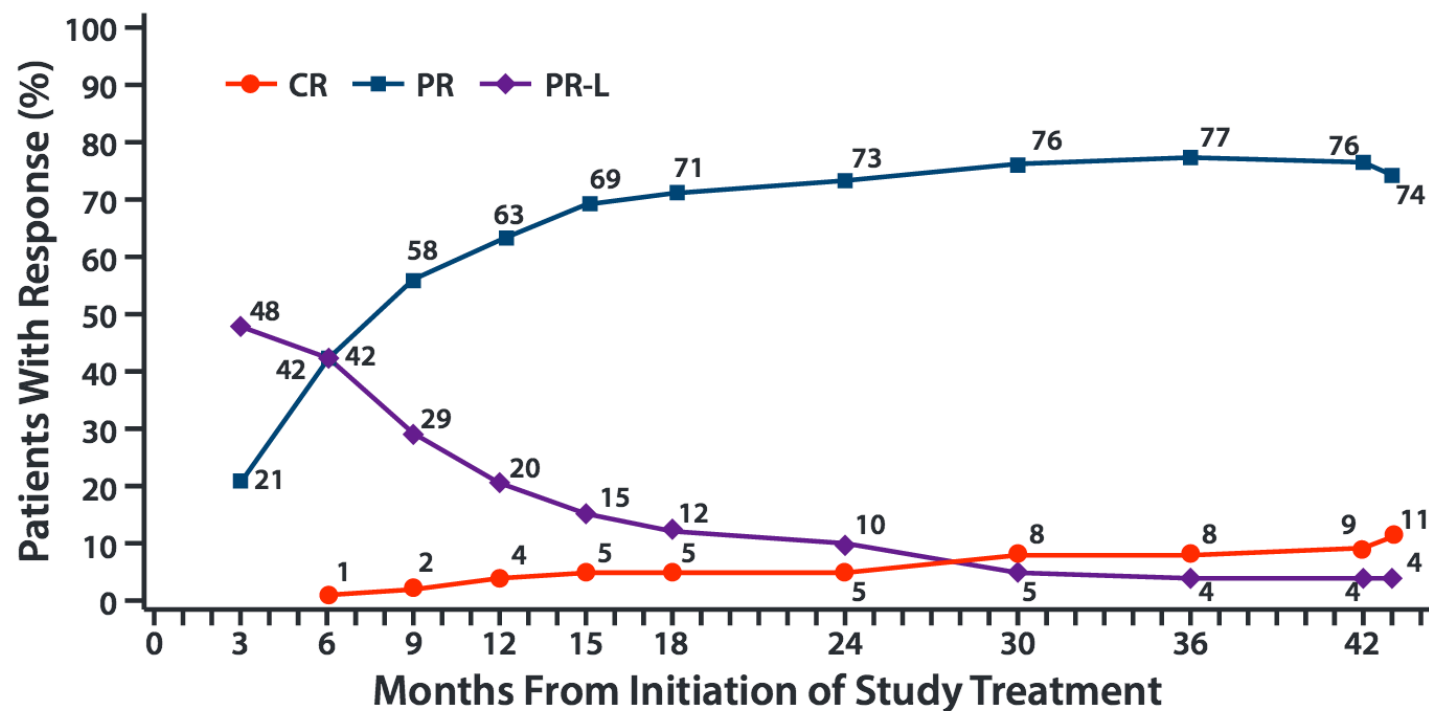


Figure 7. Cumulative best responses seen with single-agent ibrutinib after 3 years of follow-up among patients with chronic lymphocytic leukemia (symptomatic treatment-naïve or relapsed/refractory) or small lymphocytic lymphoma. CR, complete response; PR, partial response; PR-L, partial response with lymphocytosis. Adapted from Byrd JC et al. *Blood*. 2015;125(16):2497-2506.⁹

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 events are much higher and more severe.
- At this time should only be used in the salvage setting.

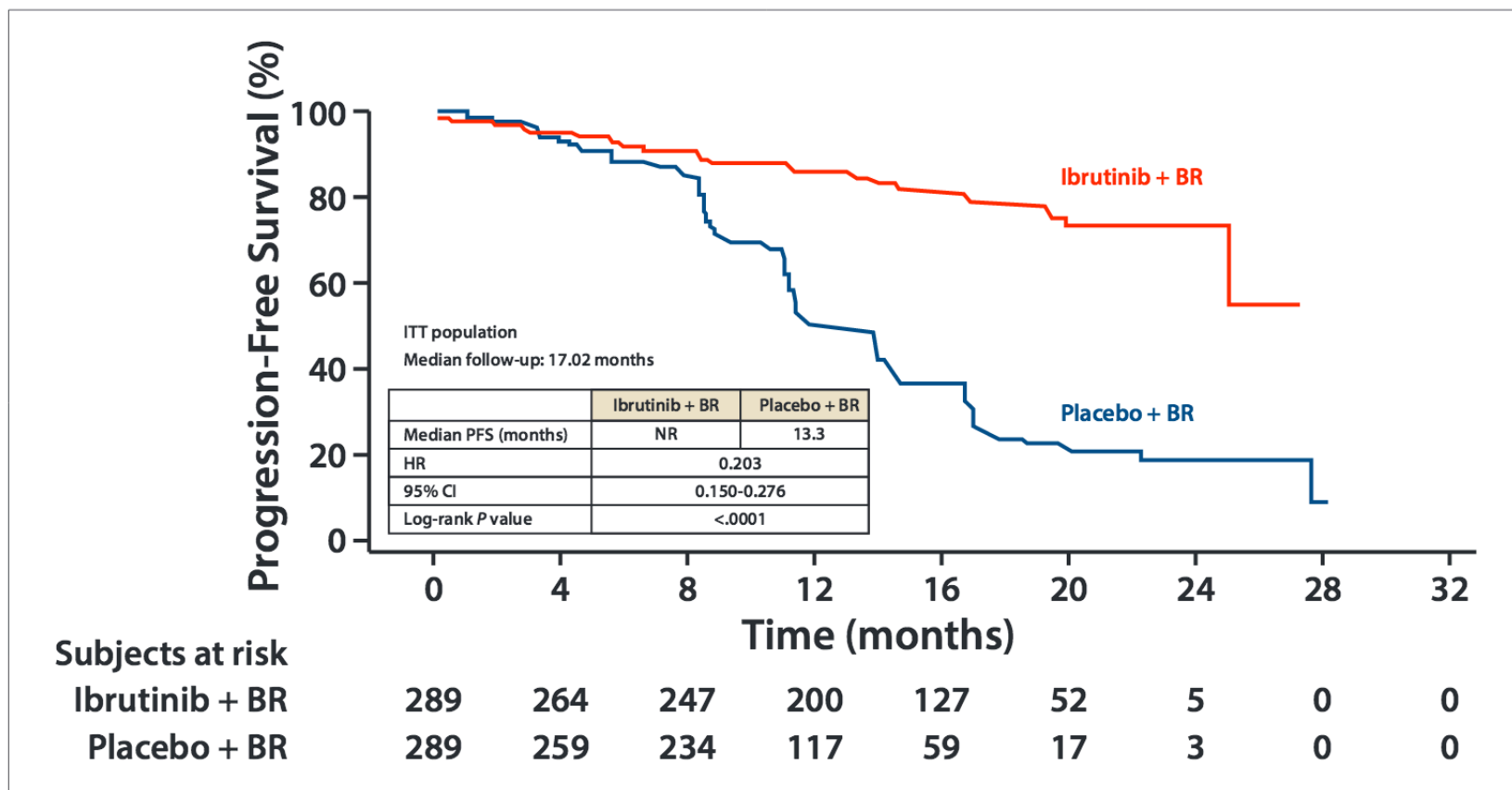


Figure 8. PFS in the phase 3 HELIOS trial, which evaluated ibrutinib plus BR vs placebo plus BR in patients with relapsed/refractory chronic lymphocytic leukemia or small lymphocytic lymphoma. BR, bendamustine and rituximab; HELIOS, Ibrutinib Combined With Bendamustine and Rituximab Compared With Placebo, 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

Venetoclax

- Orally administered inhibitor of BCL-2.
- BCL-2 is an antiapoptotic protein crucial to the survival of CLL cells.
- Used for patients with the 17p deletion and have been on 1 previous treatment.
- Approved by the FDA in April 2016.
- Adverse events include tumor lysis syndrome. Patients must be hospitalized when drug is administered.
- ORR was 79% in recent trial and 20% CR.

Summary

- Many patients do not require treatment until they become symptomatic.
- Variety of effective regimens are available for treatment:
 - FCR: fludarabine (Fludara), cyclophosphamide (Cytosan), and rituximab
 - Bendamustine (sometimes with rituximab)
 - FR: fludarabine and rituximab
 - CVP: cyclophosphamide, vincristine, and prednisone (sometimes with rituximab, R-CVP)
 - CHOP: cyclophosphamide, doxorubicin, vincristine (Oncovin), and prednisone
 - Chlorambucil combined with prednisone, rituximab, obinutuzumab, or ofatumumab
 - PCR: pentostatin (Nipent), cyclophosphamide, and rituximab
 - Alemtuzumab (Campath)
 - Fludarabine (alone)
 - Ibrutinib (alone)

References

- Clinical Advances in Hematology & Oncology, Volume 14, Issue 5, Supplement 8, May 2016
- <http://www.cancer.org/cancer/leukemia-chroniclymphocyticcll/detailedguide/leukemia-chronic-lymphocytic-treating-treatment-by-risk-group>
- NCCN Guidelines:
https://www.nccn.org/professionals/physician_gls/f_guidelines.asp#site