Chronic Lymphocytic Leukemia: ***Basics***

Diagnosis
Staging and how the disease progresses
Prognostic markers
Active surveillance (W+W)
Indications for Treatment
Immune conditions
Seeing a CLL Specialist

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A. Ferrajoli, Disclosures

Eli-Lilly	Research support to MDACC
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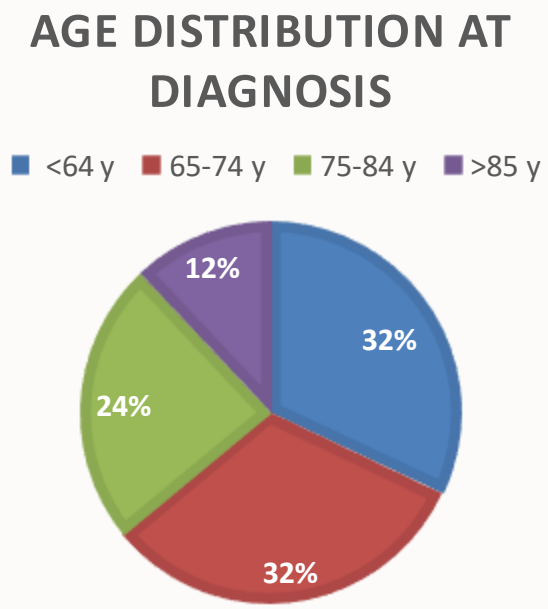
Beigene	Advisory Board
Janssen	Advisory Board
Astra-Zeneca	Advisory Board

Chronic Lymphocytic Leukemia (CLL): SEER Data

US 2024(ext): 20,700 new cases of CLL

4.9/100,000 person per year

US prevalence is 215,107



New case per 100,000 Persons		
Male		Female
7.7	White	4.1
4.6	Black	2.2
1.6	Asian/PI	0.8
4.4	American Indian/AN	NS
2.7	Hispanic	1.6
6.3	**ALL RACES**	**3.3**

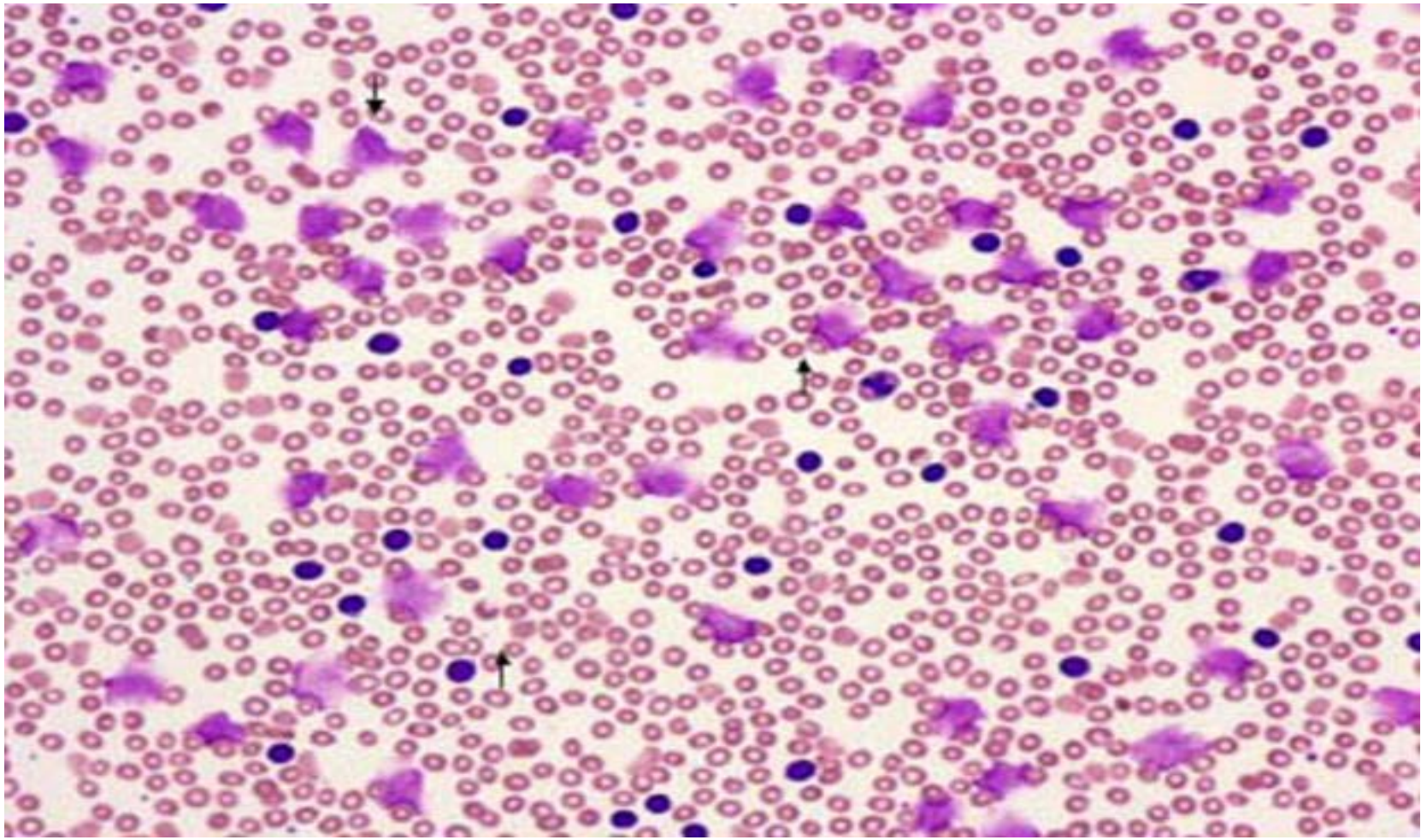
SEER . Available at: http://seer.cancer.gov/statfacts/html/clyl.html. Accessed 3/16/2025

Diagnosis of CLL: NCI-WG 1996/2008/2018

- Small, mature lymphocytes ≥ 5000/μL for at least 3 months
- Lymphocytes ≥ 30% in bone marrow
- ≤ 55% atypical/immature lymphoid cells in peripheral blood
- Clonal expansion of abnormal B lymphocytes
  - **Low density of surface Ig (IgM or IgD) with κ or λ light chains restriction**
  - **B-cell surface antigens (CD19, CD20, CD23); CD20 dim**
  - **CD5 surface antigen**
  - **The hallmark is the presence of cells with CD5/CD19 co-expression**

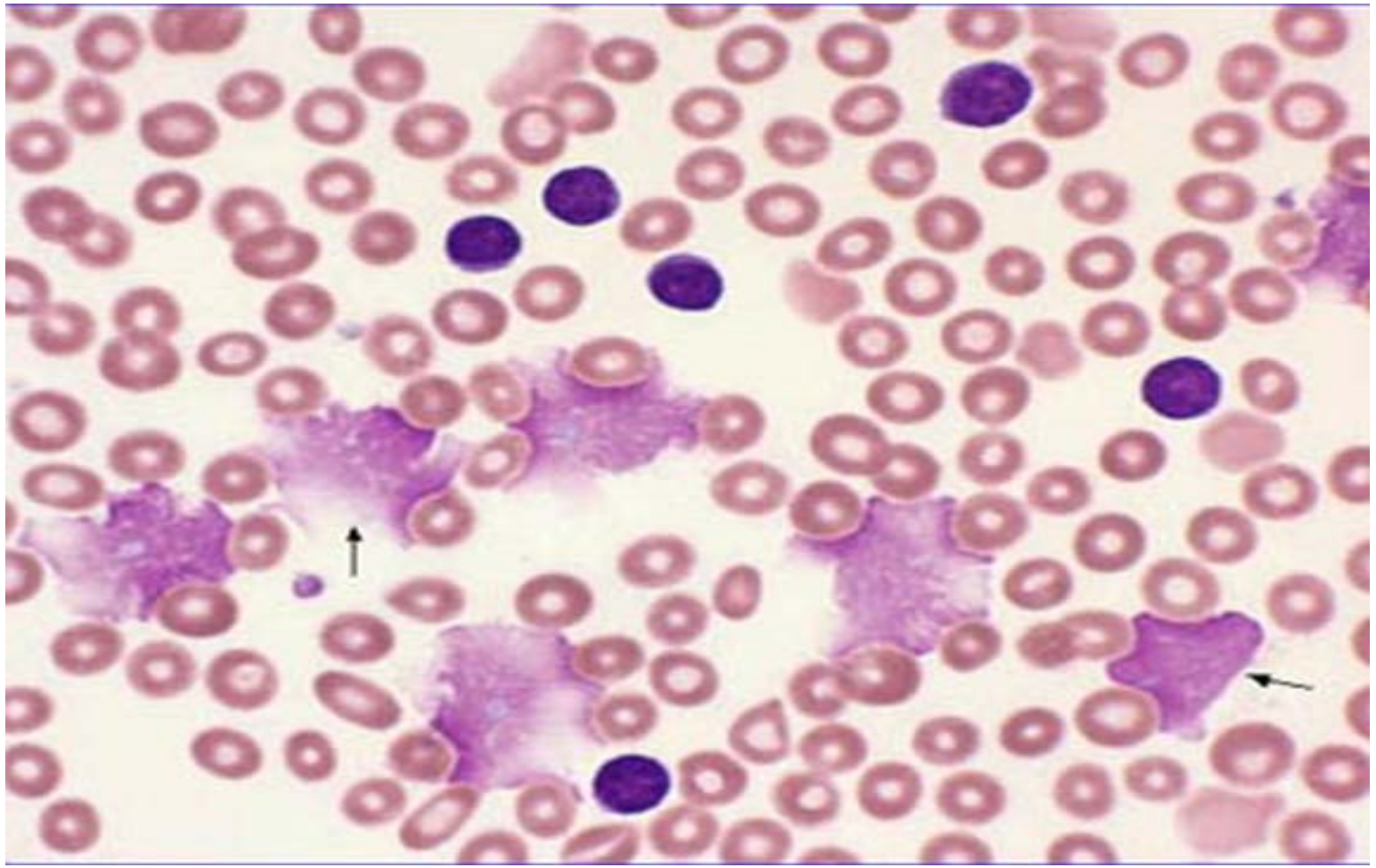
Cheson BD et al. Blood1996;87:4990-4997; Hallek et al. Blood 2008 and Blood 2018 ;131:2745-2760

CLL: Low-power View of Peripheral Smear



Showing Small Lymphocytes and Numerous “Smudge“ Cells

CLL: Higher Power View of the Same Peripheral Smear



Showing Small Lymphocytes and “Smudge" or “Basket" Cells or “Gumprecht Shadows”

Typical Morphology of CLL Cells

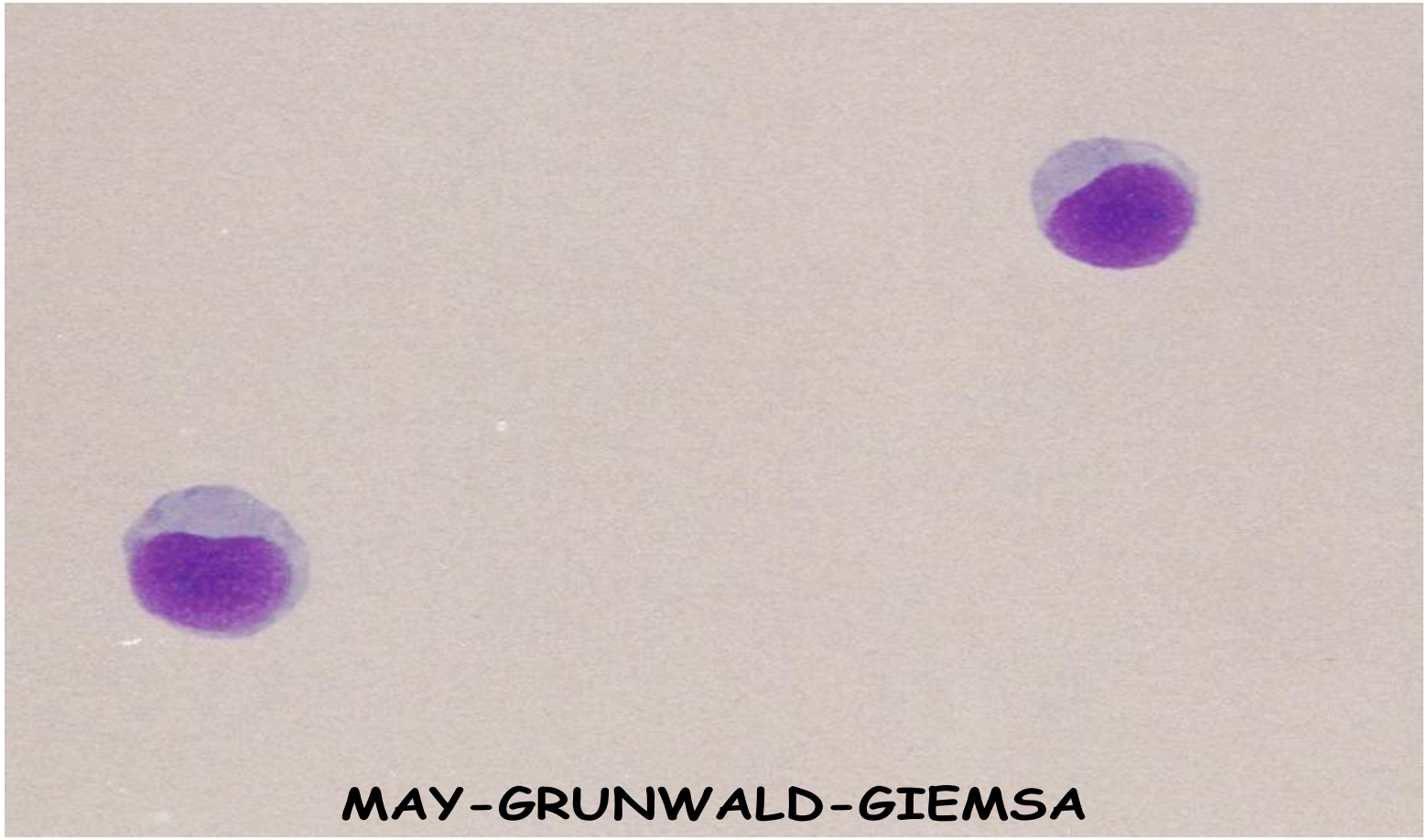
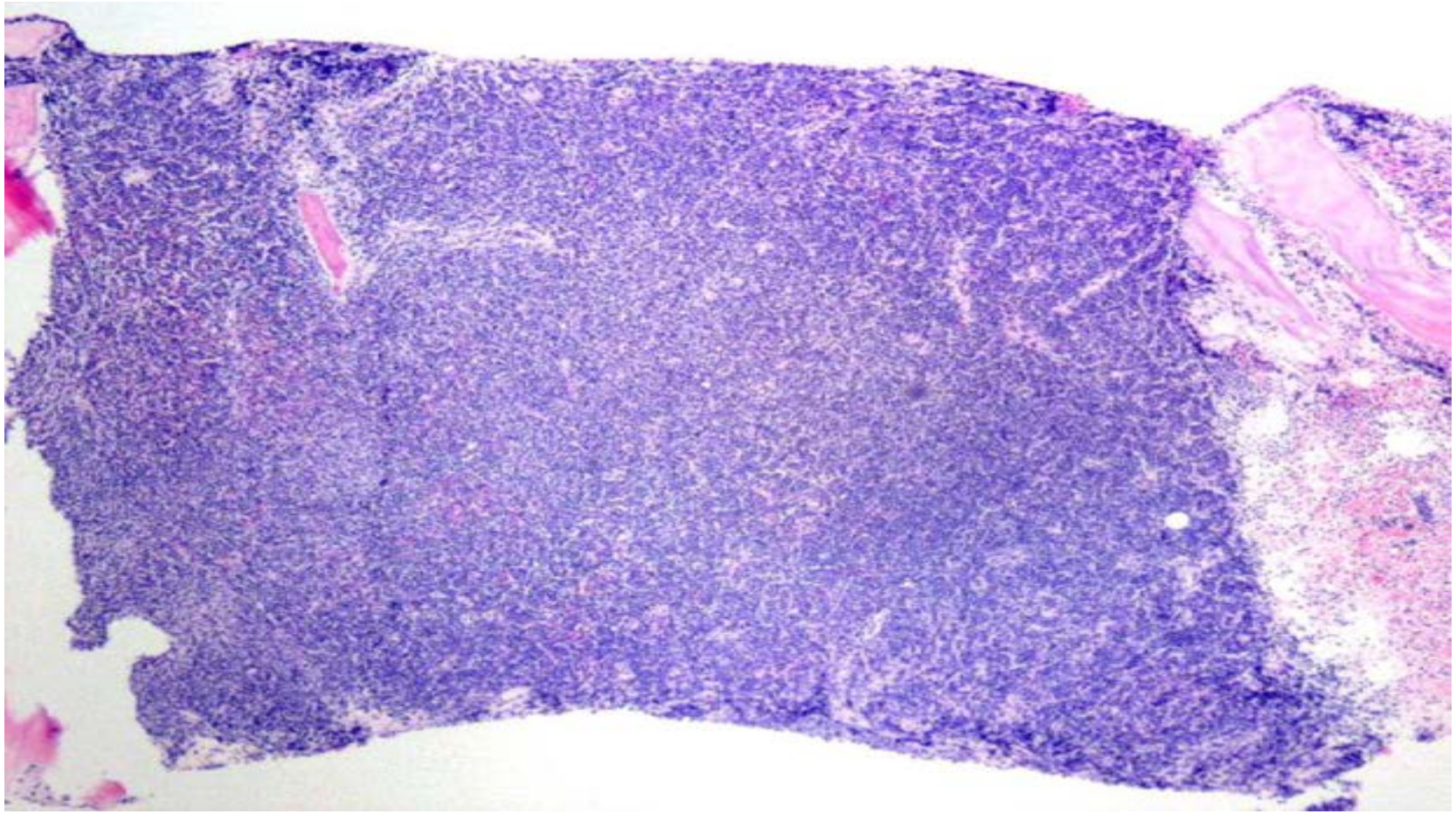
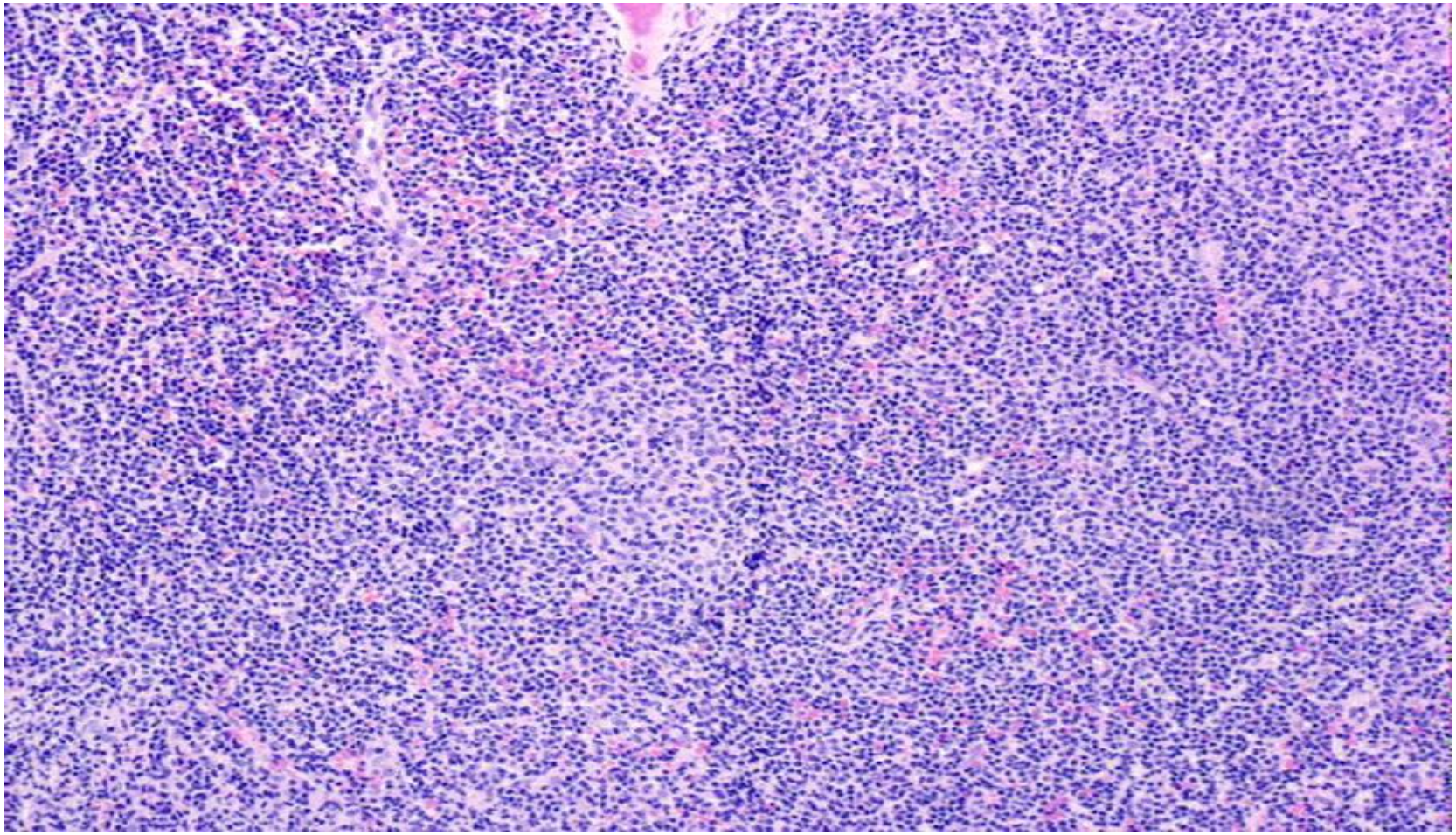


Image courtesy of Dr. Ferrajoli

CLL: Bone Marrow Biopsy Showing Diffuse Replacement of the Marrow

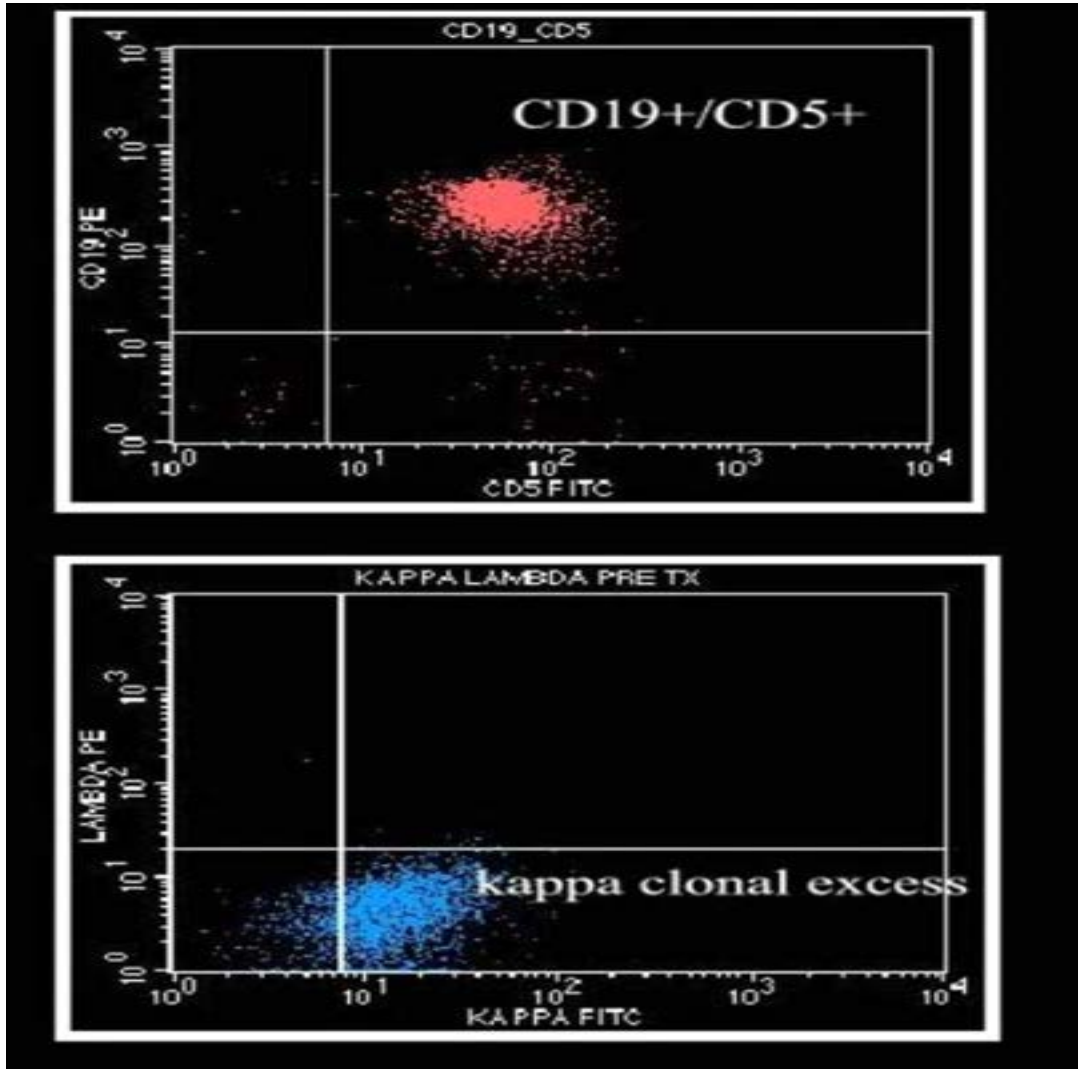


CLL: Marrow Biopsy Showing Diffuse Marrow Replacement by Small Lymphocytes



(Higher Magnification)

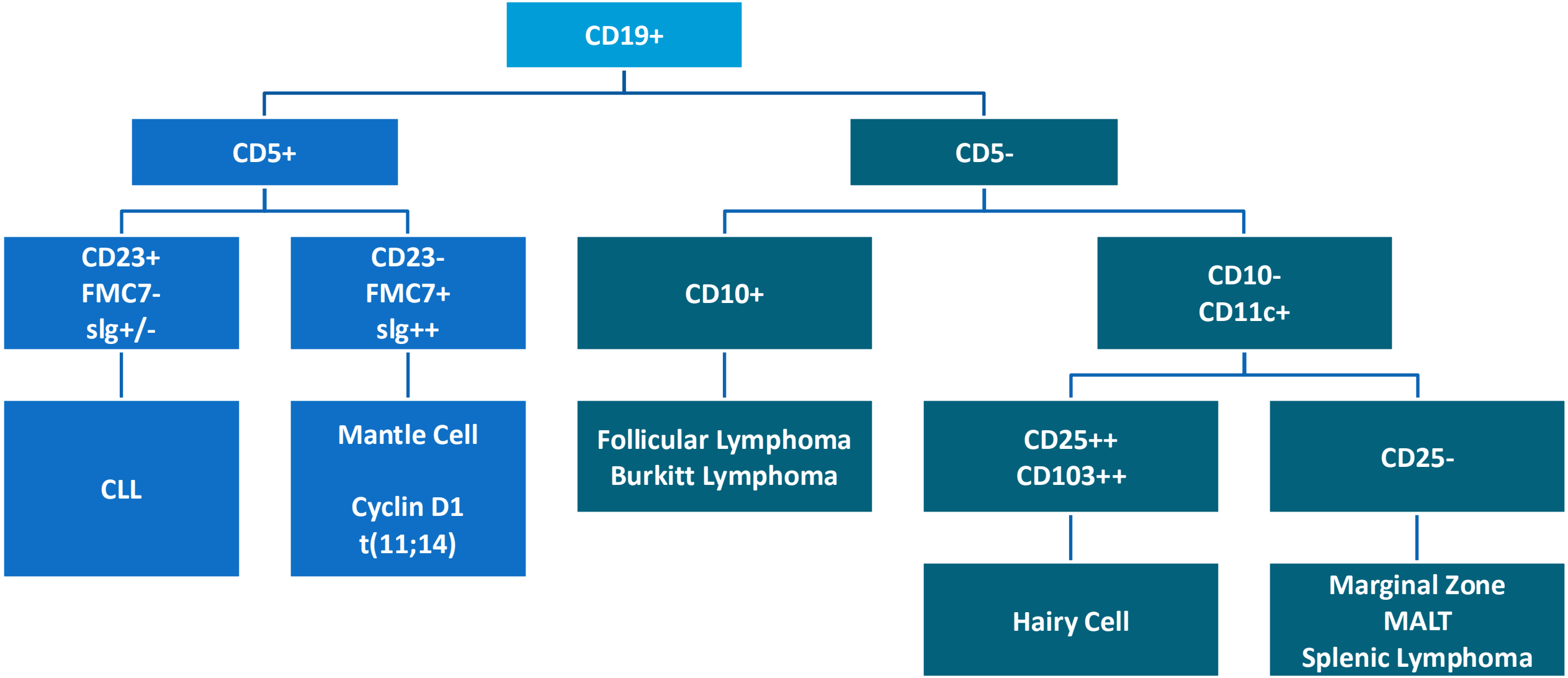
CLL: CD19 and CD5 Co-expression/Surface Kappa/Lambda



- Blood lymphocyte phenotyping is required and sufficient for diagnosis of typical CLL
- A panel of CD19, CD5, CD20, CD23, κ, and λ is usually sufficient
- In borderline cases, markers such as CD43, CD79b, CD81, CD200, CD10, or ROR1 may help to refine the diagnosis
- The most important point is to differentiate from mantle cell lymphoma (MCL): Cyclin D1 expression is a hallmark of MCL

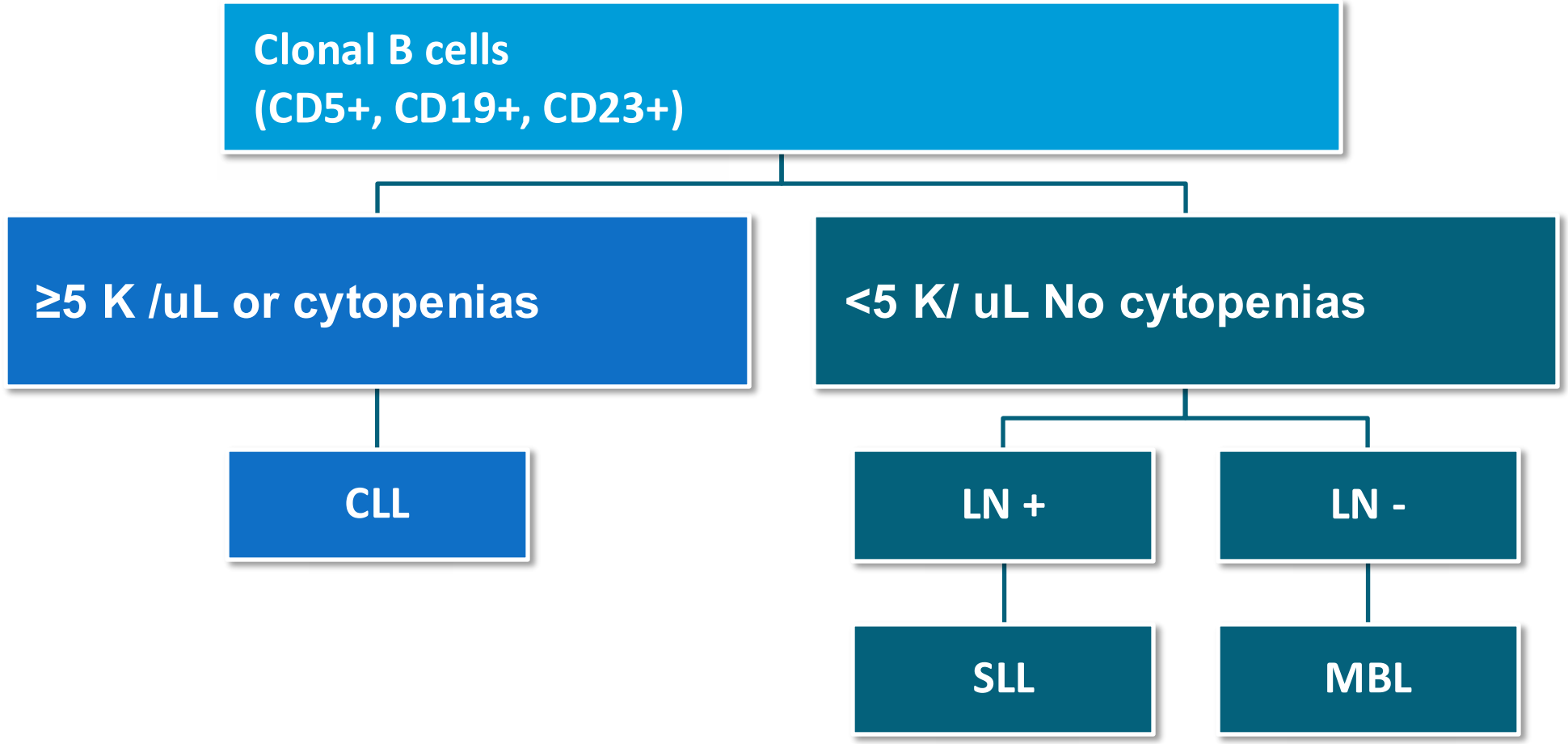
Image courtesy of Dr. Ferrajoli
Hallek et al. Blood 2018 ;131:2745-2760

CD19+ Lymphoproliferative Diseases



LPD = lymphoproliferative disease

Chronic Lymphocytic Leukemia vs. Small Lymphocytic Lymphoma vs. Monoclonal B Lymphocytosis [CLL-SLL-MBL]



Presentation of CLL

- Lymphocytosis (elevated lymphocyte count) on routine blood count
- Lymphadenopathies
- Hepatomegaly and/or splenomegaly (enlarged liver or spleen)
- Recurrent infections
- Fever, weight loss
- Anemia and/or thrombocytopenia

Sporadic CLL

- Chernobyl exposure (ionizing radiation)
- Presumed related to Agent Orange by Veteran Administration
- Immunological disorders and immunosuppressive therapies
- Pesticides/chemical fertilizers
- Smoking
- Petrochemical industrial complexes
  - Benzene
  - Ionizing radiation
  - Particulate matters

Familial CLL

- Prevalence: 6-10% patients
- Dominant inheritance pattern
- Paternal to youngest son (Maternal no preference)
- Increased sibling concordance
- Anticipation (~20 years)
- Up to 18% of first-degree relatives will have a detectable MBL clone
- *POT1* is found to be mutated in approximately 4% of patients with CLL. Recent studies reported germline variants in *POT1* in patients with familial CLL and in familial melanoma, cardiac angiosarcoma, glioma and colorectal cancer

Reviewed in WierniK PH. Curr. Treat.Options in Oncol, 2015; Speedy HE et al. Blood 19:2319-2326, 2016

Clinical Course of CLL

- Asymptomatic at diagnosis
- Diagnosis often incidental
- Initial symptoms: lymph node ↑
- Progression: bone marrow impairment

- Hypogammaglobulinemia
- Unique complications:
  - Autoimmune phenomena
  - Richter's transformation
  - Exaggerated response to arthropod attacks
  - Suboptimal response to vaccinations

Clinical Staging of CLL

Rai Stage	3-Stage System	Clinical Features
0	Low risk	Lymphocytosis in blood and marrow
I		Lymphadenopathy
II	Intermediate risk	Splenomegaly +/- hepatomegaly
III	High risk	Anemia
IV		Thrombocytopenia

Binet Stage	Clinical Features
A	Hemoglobin ≥10 g/dL Platelets ≥100,000/ mm3 < 3 enlarged nodal areas
B	Hemoglobin ≥10 g/dL Platelets ≥100,000/ mm3 > 3 enlarged nodal areas
C	Hemoglobin ≤10 g/dL Platelets ≤100,000/ mm3 And any number of enlarged nodal areas

Rai K et al. Blood. 1975;46:219
Binet JL et al. Cancer 1981; 48:198

Indications to Initiate Treatment

- ❑ B-symptoms (systemic symptoms) :
  - ✓ Weight loss (10%)
  - ✓ Fatigue (PS 2)
  - ✓ Fevers (100.5 °F)
  - ✓ Night sweats (1 month)
- ❑ Progressive leukocytosis with lymphocytosis:
  - ✓ Lymphocyte doubling time of less than 6 months
- ❑ Development or worsening of:
  - ✓ Anemia
  - ✓ Thrombocytopenia

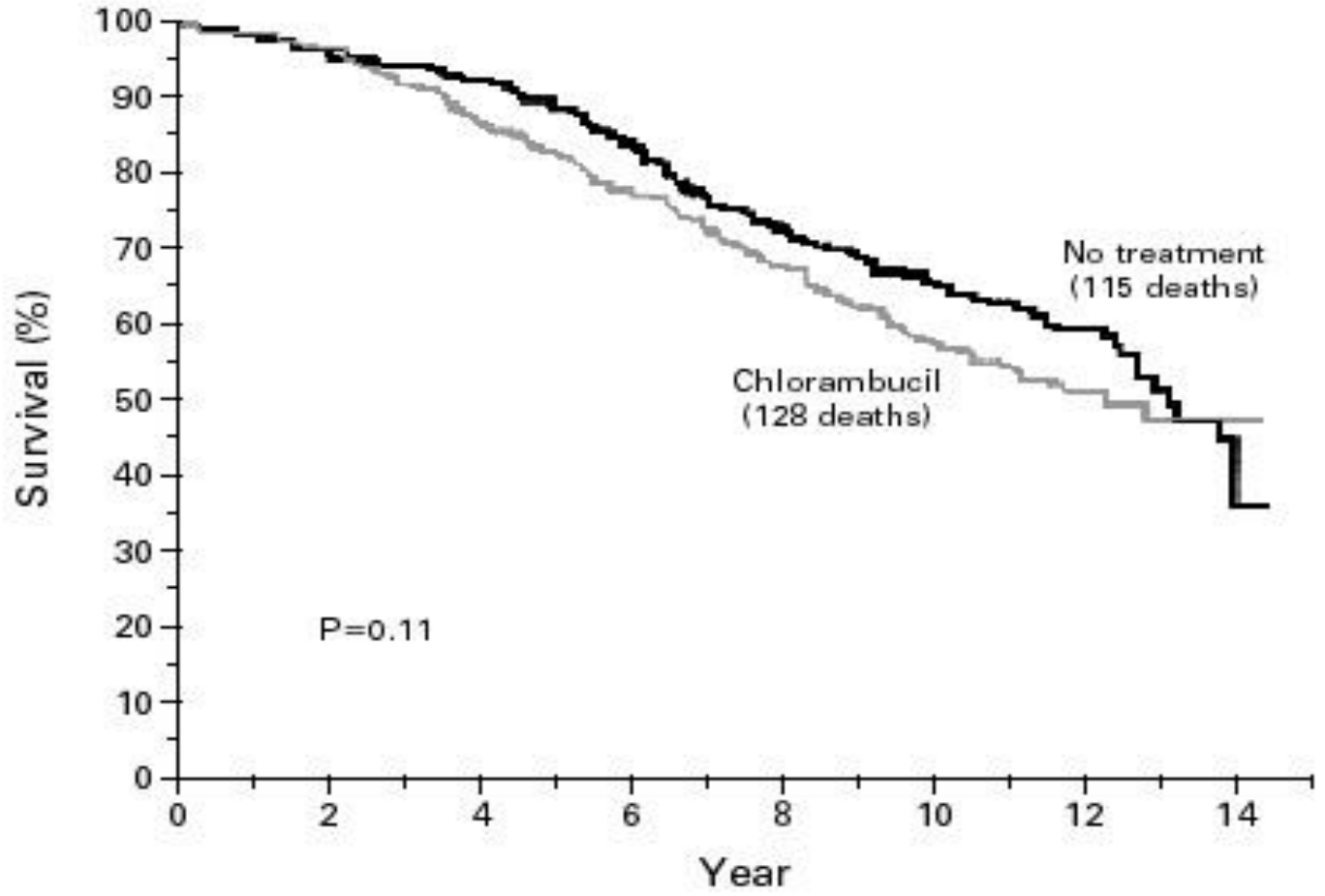
  (progressive marrow involvement)
- ❑ Splenomegaly (massive/progressive/symptomatic)
- ❑ Lymphadenopathy (progressive/symptomatic, bulky)
- ❑ Autoimmune complications poorly responsive to corticosteroids
- ❑ Extra nodal involvement like skin, gastro-intestinal tract

“Watch and Wait”

- Early intervention with treatment of asymptomatic, early-stage patients has not demonstrated a survival benefit.
- 1980-1990: Two randomized French studies of early vs deferred treatment with chlorambucil or chlorambucil + prednisone. No overall survival benefit.[1]
- What about novel therapies?

[1]Dighiero, *N Engl J Med* 1998

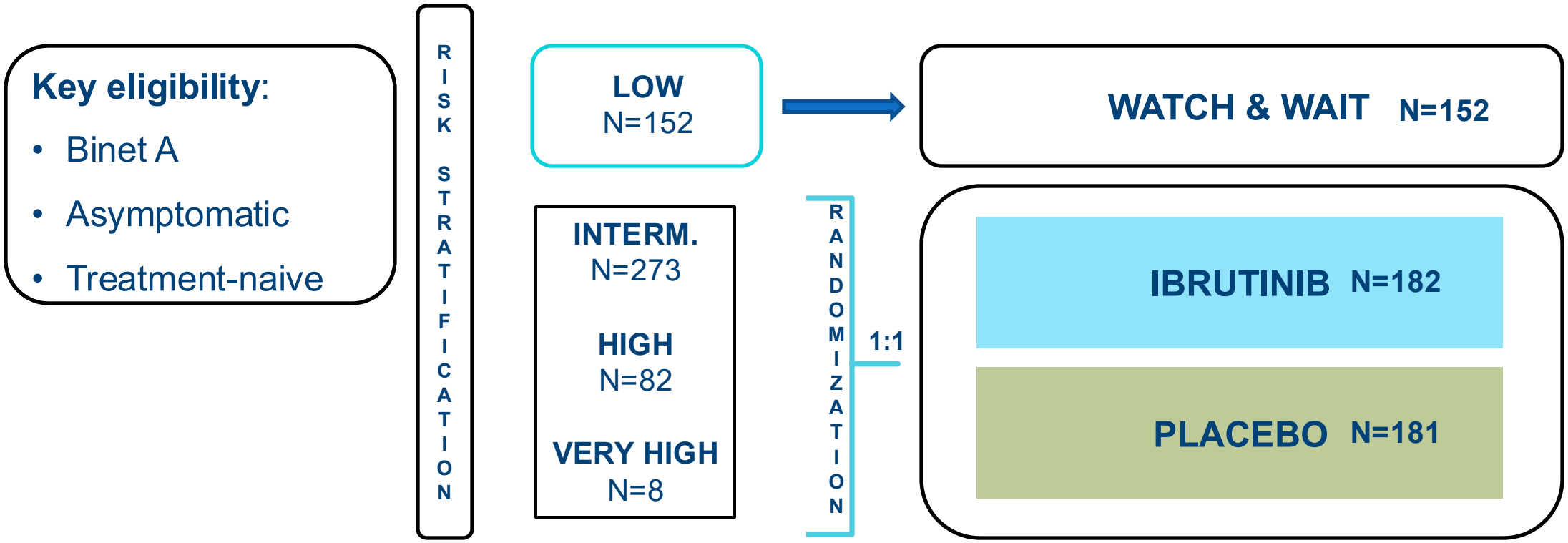
Kaplan–Meier Estimates of Mortality Due to CLL-Related Causes, Second Cancers, and Unknown Causes in the First Trial: No Survival Benefit for Early Intervention with Chlorambucil



No. at Risk															
Chlorambucil	301	296	284	277	264	246	230	205	191	179	132	86	54	26	2
No treatment	308	291	283	266	247	230	213	196	179	159	114	70	39	17	7

Dighiero G et al. N Engl J Med 1998;338:1506-1514.

CLL 12 Study Design
First-line IBR VS. Placebo in high-risk CLL:



Phase III, placebo-controlled, double-blind, multicenter trial

Primary endpoint EFS: time from randomization until **symptomatic** PD, new treatment, death

Secondary endpoints: survival, PFS, TFS, TTNT, ORR, safety

π_2 : median EFS from 24 to 48 months with ibrutinib (superiority test)

Langerbeins, et al. J Clin Oncol 2025

CLL-12: first-line IBR *vs* Placebo in high-risk CLL: Overall Survival, EFS, PFS and TTNT

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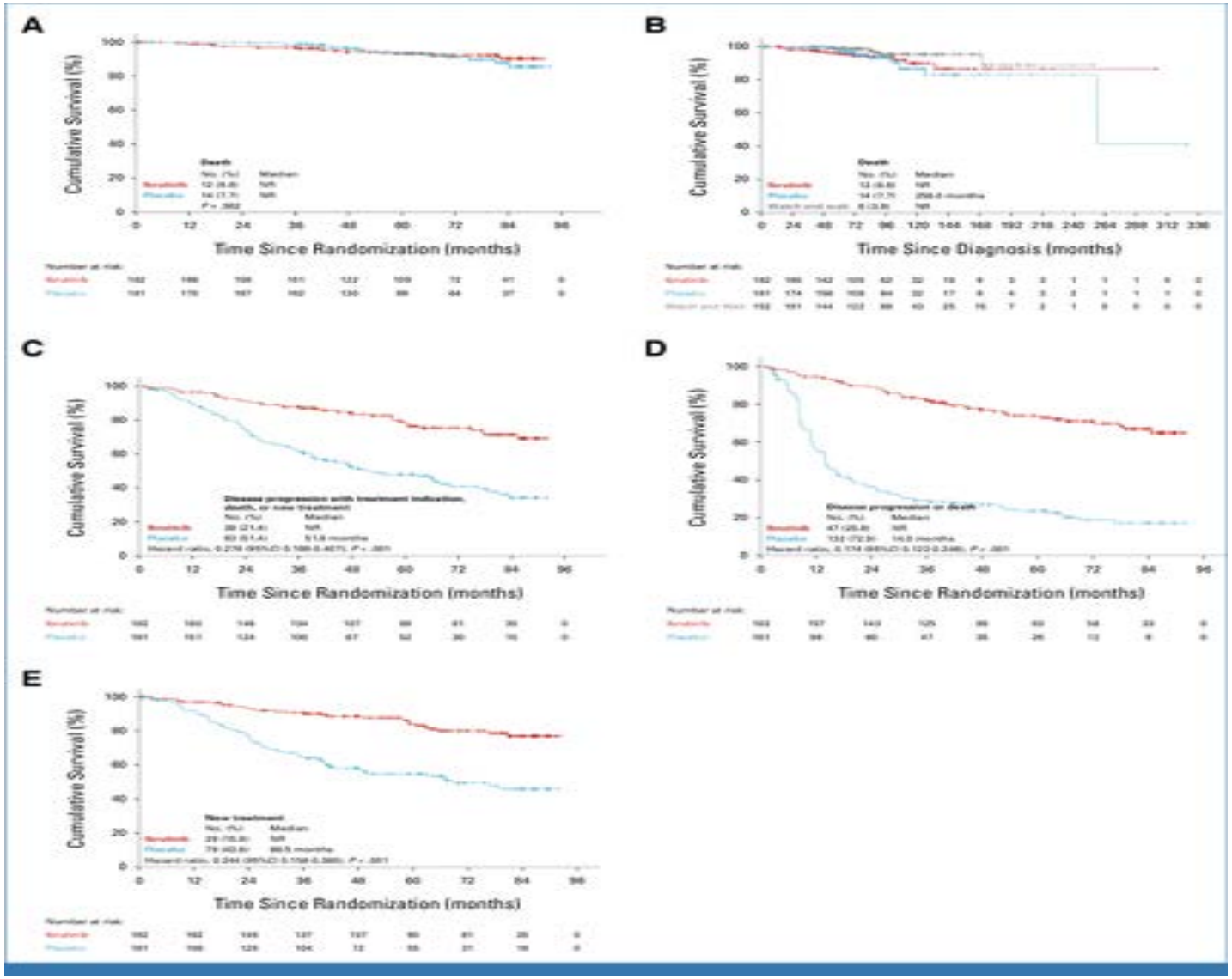


5 years survival rate **Extimated 10 year survival rate:**

Ibrutinib **93.3% (95% CI,89.3-97.3)** **89.8% (95% CI,83.3-96.3)**

Placebo **93.6% (95%CI, 89.5-97.7)** **86.5% (95% CI,78.7-94.3)**

W&W **97.9% (95%CI, 95.6-100)** **95.3% (95% CI,99.1-99.4)**

EFS: Ibrutinib NR vs Placebo 51.6 months HR, 0,276, *P*<.001

PFS: Ibrutinib NR vs Placebo 14.0 months HR 0.174, *P*<.001

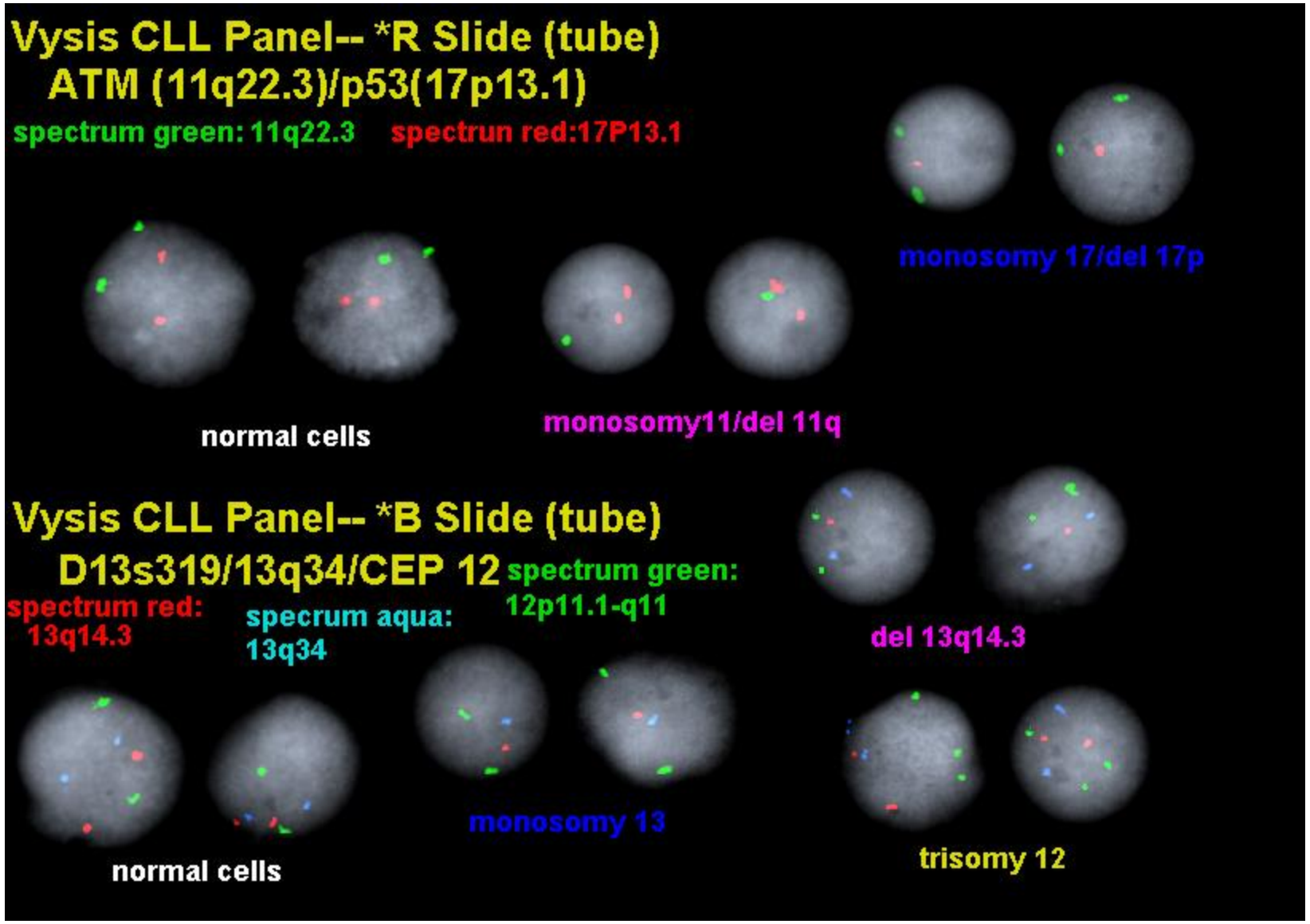
TTNT: **Ibrutinib** NR vs Placebo 68.5 months HR 0.244, *P*<.001

Langerbeins, et al. J Clin Oncol 2025

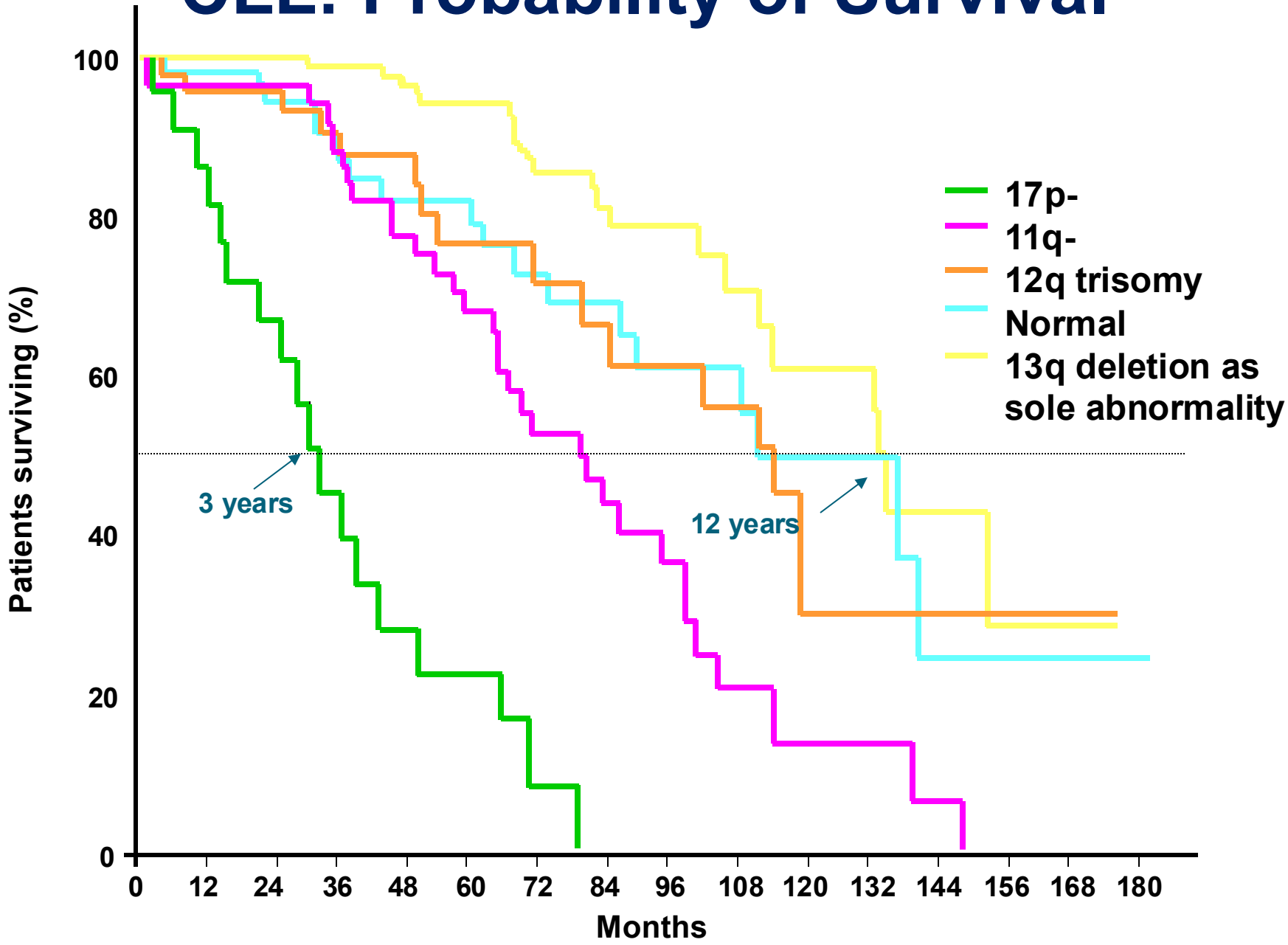
Prognostic Factors Associated With Shorter Survival in CLL

- TP53 mutation by NGS
- FISH cytogenetic abnormalities
  - 17p deletion
  - 11q deletion
- Unmutated (<2% homology with germline) immunoglobulin heavy chain variable gene (*IGHV*)
- Complex and high-complex (≥ 3 abn and ≥ 5 abn) karyotype
- Expression of ZAP-70 (≥ 20% positive)
- Expression of CD38 (≥ 30% positive)

Fluorescent In Situ Hybridization



CLL: Probability of Survival



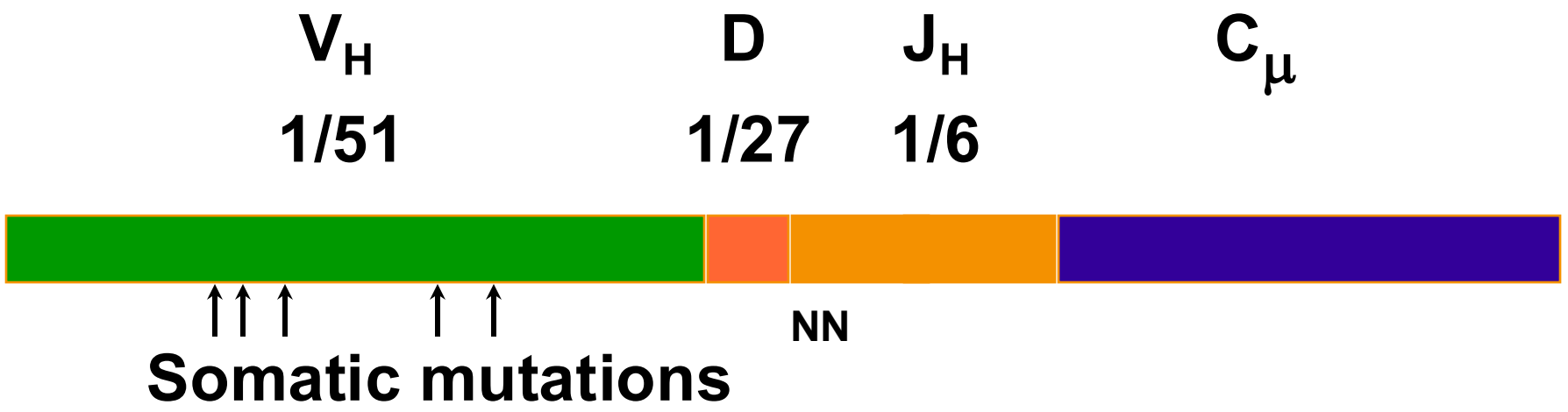
N Engl J Med., Döhner H et al. Genomic Aberrations and Survival in Chronic Lymphocytic Leukemia, 2000;343:1910-1916.

Genomic Aberrations in CLL Interphase FISH Results—82% Abnormal

Abnormality	No. Patients	(%)
13q deletion	178	(55)
11q deletion	58	(18)
trisomy 12	53	(16)
17p deletion	23	(7)
6q deletion	21	(6)

N Engl J Med., Döhner H et al. Genomic Aberrations and Survival in Chronic Lymphocytic Leukemia, 2000;343:1910-1916.

CLL: B-Cell Diversity
V_H Rearrangement and Mutation

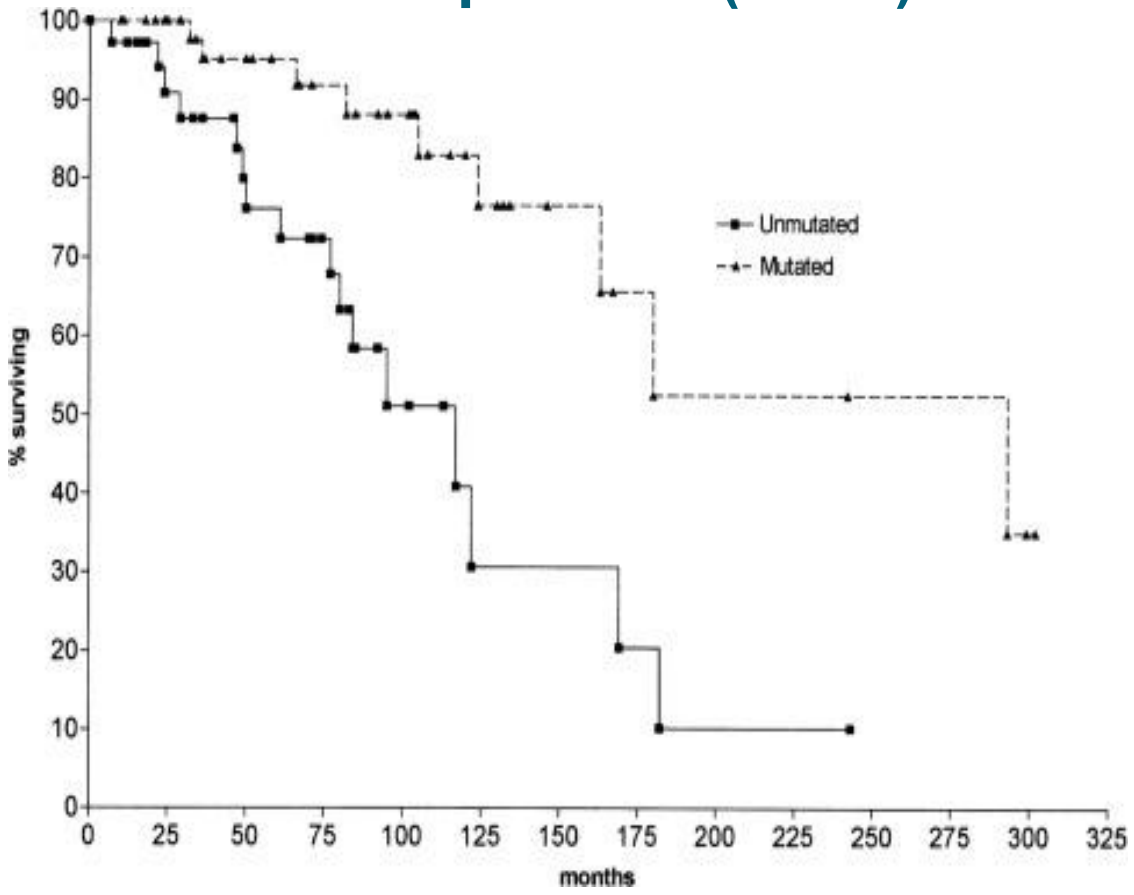


V_H in B-cell chronic lymphocytic leukemia

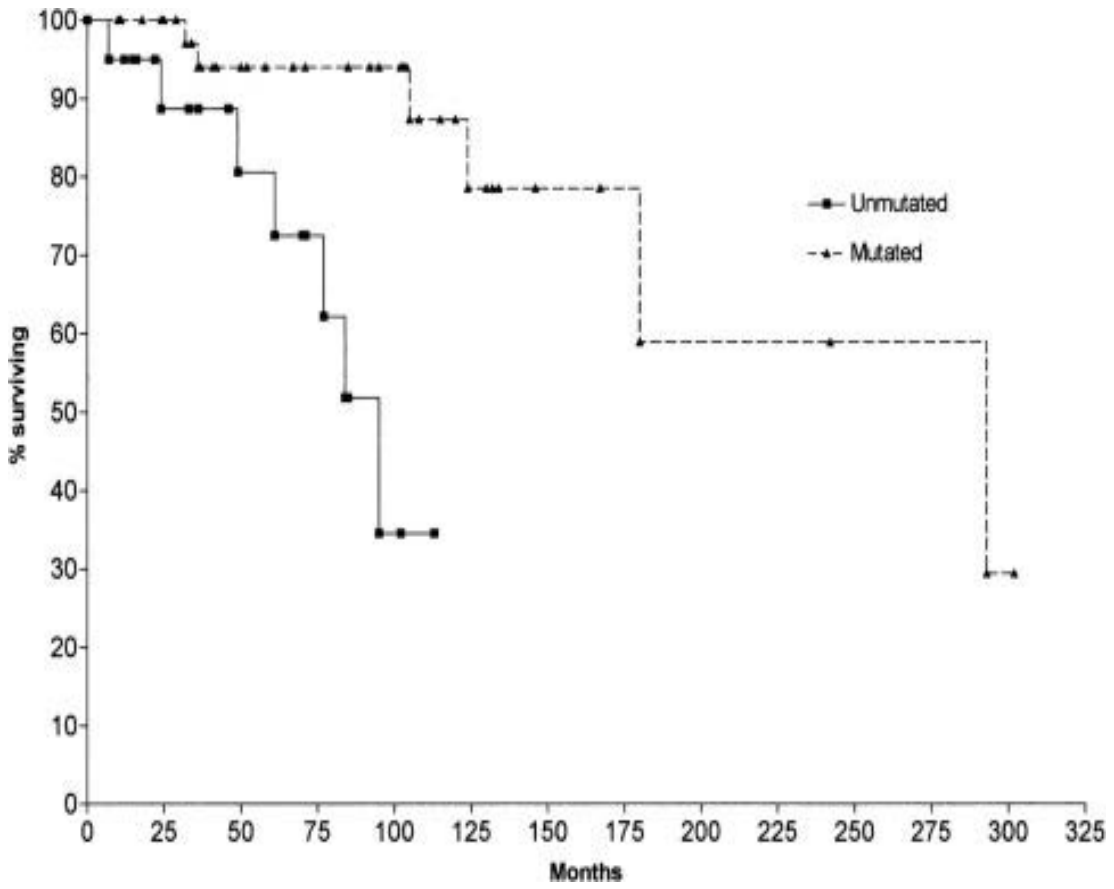
- Somatic mutations (< 98% homology)

Survival of Patients with CLL: Mutated vs. Unmutated IgV_H

All patients (N=84)



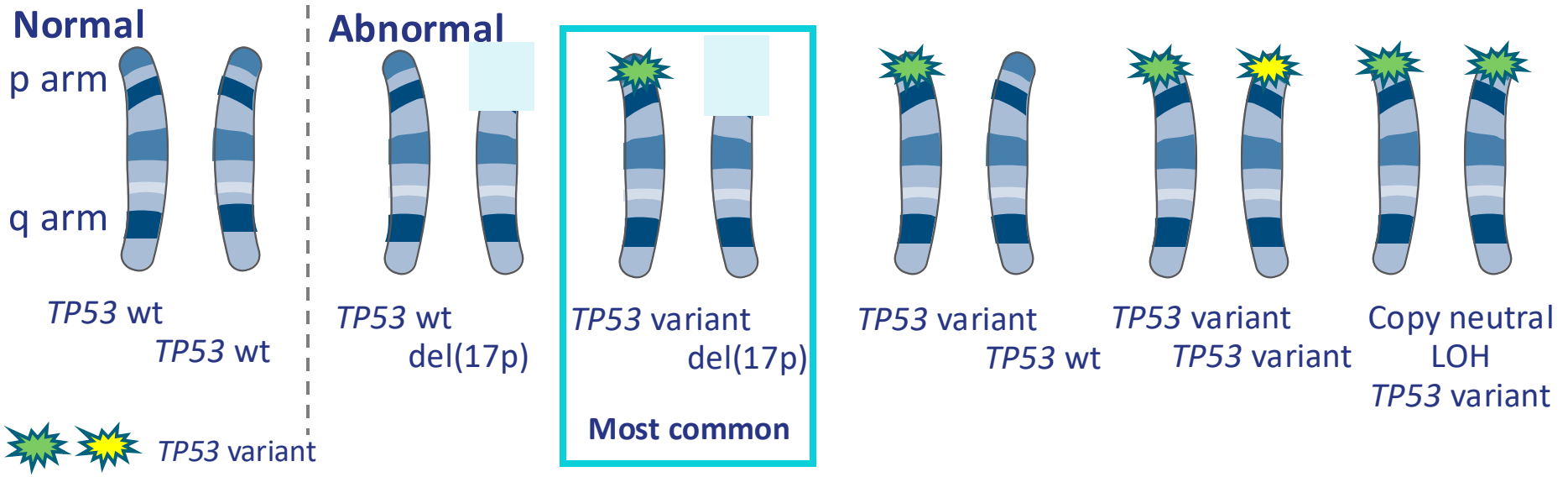
Stage-A CLL patients (n=62)



Hamblin TJ et al. Blood. 1999;94:1848-1854.

TP53 alterations should be determined in all patients at the time of treatment decision

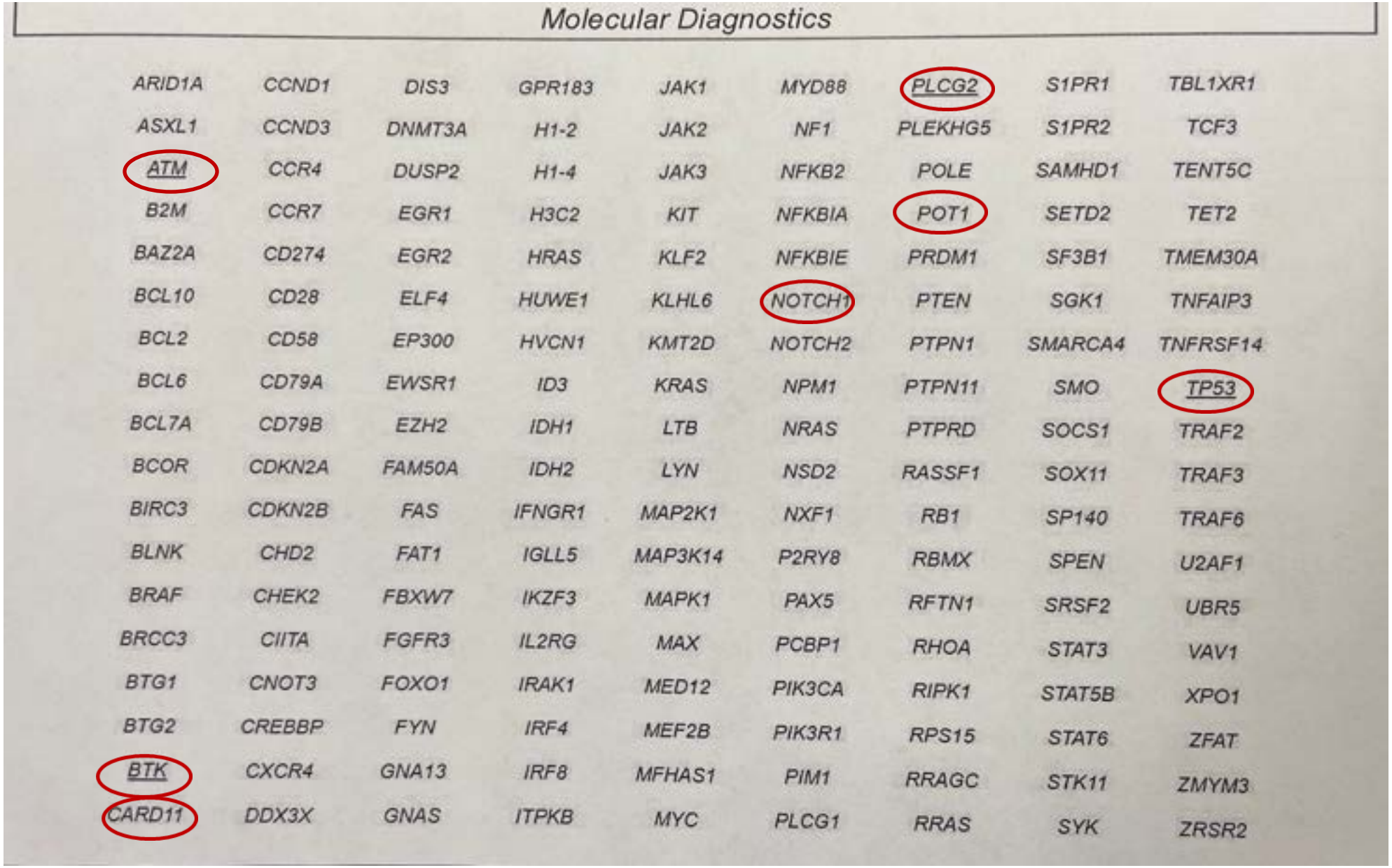
- Loss of p53 function in CLL can occur due to del(17p) and/or *TP53* variants



LOH: loss of heterozygosity; wt: wild type

1. Surget S, *et al. Onco Targets Ther* 2014; 7:57–68. 2. Malcikova J, *et al. Hum Mutat* 2014; 35:663–671.

NGS Panel for CLL



Molecular Diagnostics

ARID1A	CCND1	DIS3	GPR183	JAK1	MYD88	PLCG2	S1PR1	TBL1XR1
ASXL1	CCND3	DNMT3A	H1-2	JAK2	NF1	PLEKHG5	S1PR2	TCF3
ATM	CCR4	DUSP2	H1-4	JAK3	NFKB2	POLE	SAMHD1	TENT5C
B2M	CCR7	EGR1	H3C2	KIT	NFKBIA	POT1	SETD2	TET2
BAZ2A	CD274	EGR2	HRAS	KLF2	NFKBIE	PRDM1	SF3B1	TMEM30A
BCL10	CD28	ELF4	HUWE1	KLHL6	NOTCH1	PTEN	SGK1	TNFAIP3
BCL2	CD58	EP300	HVCN1	KMT2D	NOTCH2	PTPN1	SMARCA4	TNFRSF14
BCL6	CD79A	EWSR1	ID3	KRAS	NPM1	PTPN11	SMO	TP53
BCL7A	CD79B	EZH2	IDH1	LTB	NRAS	PTPRD	SOCS1	TRAF2
BCOR	CDKN2A	FAM50A	IDH2	LYN	NSD2	RASSF1	SOX11	TRAF3
BIRC3	CDKN2B	FAS	IFNGR1	MAP2K1	NXF1	RB1	SP140	TRAF6
BLNK	CHD2	FAT1	IGLL5	MAP3K14	P2RY8	RBMX	SPEN	U2AF1
BRAF	CHEK2	FBXW7	IKZF3	MAPK1	PAX5	RFTN1	SRSF2	UBR5
BRCC3	CIITA	FGFR3	IL2RG	MAX	PCBP1	RHOA	STAT3	VAV1
BTG1	CNOT3	FOXO1	IRAK1	MED12	PIK3CA	RIPK1	STAT5B	XPO1
BTG2	CREBBP	FYN	IRF4	MEF2B	PIK3R1	RPS15	STAT6	ZFAT
BTK	CXCR4	GNA13	IRF8	MFHAS1	PIM1	RRAGC	STK11	ZMYM3
CARD11	DDX3X	GNAS	ITPKB	MYC	PLCG1	RRAS	SYK	ZRSR2

CLL-International Prognostic Index (CLL-IPI)

Variable	Adverse Factor	Grading
TP53/17p	Mutated/deleted	4
IGHV status	Unmutated	2
β2M	> 3.5 mg/L	2
Clinical stage	Binet B/C or Rai II-IV	1
Age	> 65 years	1
Prognostic score		0-10

Risk Group	Score	5 years	10 years
Low	0-1	91%	87% NR
Intermediate	2-3	80%	40% 104 months
High	4-6	53%	16% 63 months
Very High	7-10	19%	0% 31 months

IPI-WG Lancet Oncol. 2016 Jun;17(6):779-790

CLL-ipi in the era of targeted drugs

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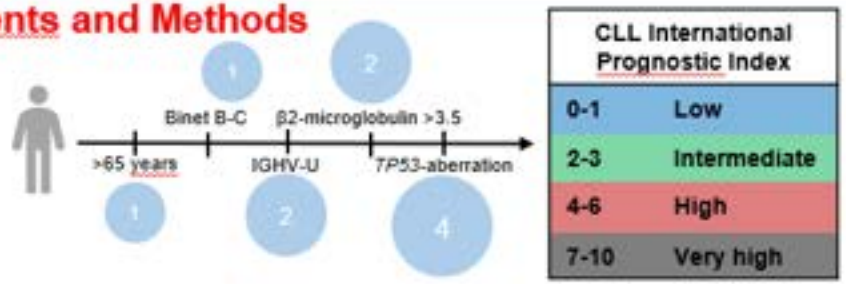
Patients and Methods



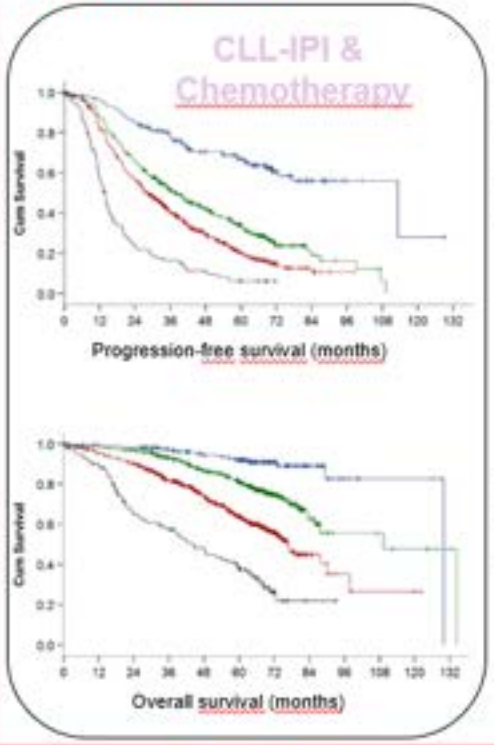
CLL International Prognostic Index	
0-1	Low
2-3	Intermediate
4-6	High
7-10	Very high

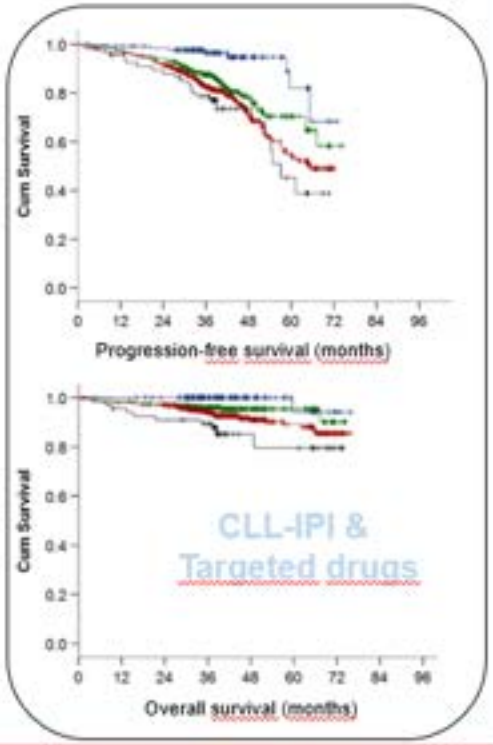
Patients with treatment-naive CLL (n=2,247)

Patients treated with chemo-immunotherapy (n=1,256)

Patients treated with targeted drugs (n=991)

Main Outcomes





Conclusion: The CLL-IPI retains prognostic value for progression-free survival, but its impact appears diminished in predicting overall survival in CLL-patients treated with targeted drugs.

Improved survival with targeted therapies versus chemoimmunotherapy underscores the need to reevaluate prognostic tools amid treatment shifts.

Langerbeins P. Reassessing the chronic lymphocytic leukemia International Prognostic Index in the era of targeted therapies. Blood. 2024 Jun 20;143(25):2588-2598.

Chronic Lymphocytic Leukemia (CLL): SEER Data

68% in 1975

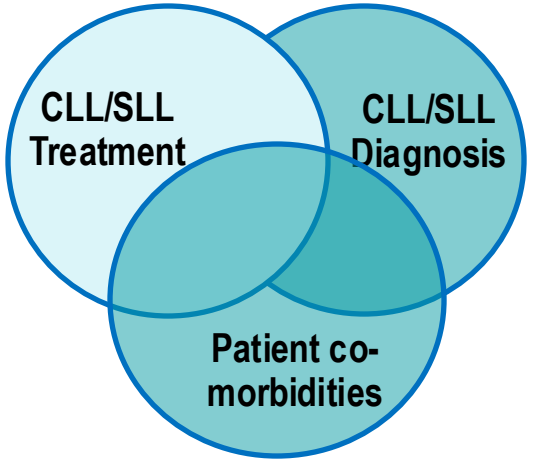
5-year relative survival: 88.5% (2014-2020)

5-year estimated survival for 2022: 94%

SEER . Available at: http://seer.cancer.gov/statfacts/html/clyl.html.

Immunodysfunction/Unique Complications of CLL

- Hypogammaglobulinemia
- Autoimmune phenomena
- Exaggerated response to arthropod attacks
- Suboptimal response to vaccinations
- Excess of other primary malignancies



Gordon M. et al Am J Hematol, 2022

Autoimmune Complications of CLL

Due to immunodysfunction, 10% of patients will have autoimmune complications

Autoimmune cytopenias (AIC)

- Autoimmune hemolytic anemia (5-10%)
  - Coombs' positive (IgG warm antibodies most common)
  - Clinical hemolysis
  - Cold Agglutinin Disease with IgM antibodies
- Immune-mediated thrombocytopenia (1-5%)
- Evan Syndrome (ITP+AIHA)
- Pure red cell aplasia (<1%)
- Autoimmune Granulocytopenia (<1%)

Uncommon autoimmune diseases (avWD, Myasthenia Gravis, Angioedema, Glomerulonephritis, Vasculitis etc.)

acDW, Acquired von Willebrand disease; CLL, Chronic lymphocytic leukemia.

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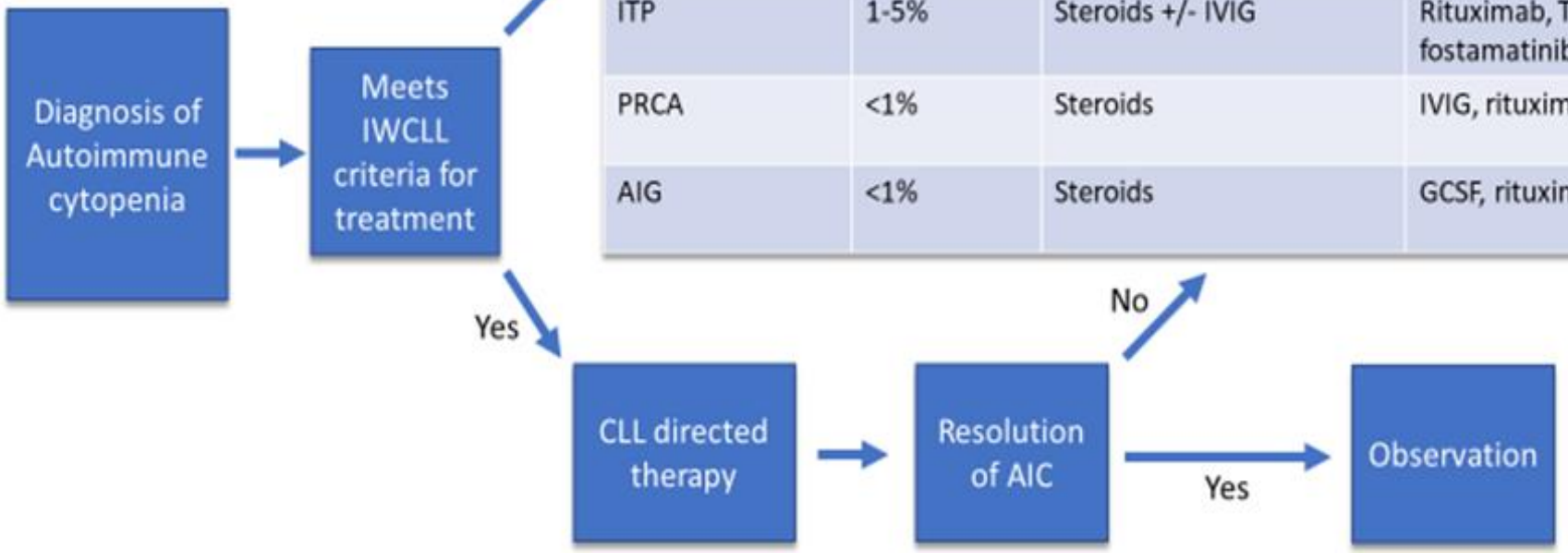
Treatment of Autoimmune Cytopenia in CLL



Condition	Incidence	First line	Additional lines
wAIHA	5-10%	Steroids +/- rituximab	IVIG, CIT, ibrutinib, venetoclax
CAD	1-2%	Rituximab +/- bendamustine	Sutimlimab, bortezomib
ITP	1-5%	Steroids +/- IVIG	Rituximab, TPO agonists, fostamatinib
PRCA	<1%	Steroids	IVIG, rituximab
AIG	<1%	Steroids	GCSF, rituximab, IVIG

AIG, autoimmune granulocytopenia; CAD, Cold agglutinin disease; CIT, Chemoimmunotherapy; CLL, Chronic lymphocytic leukemia; GCSF, granulocyte-colony stimulating factor; ITP, Immune thrombocytopenia; IVIG, Intravenous immune globulin; PRCA, Pure red cell aplasia; wAIHA, Warm antibody hemolytic anemia.

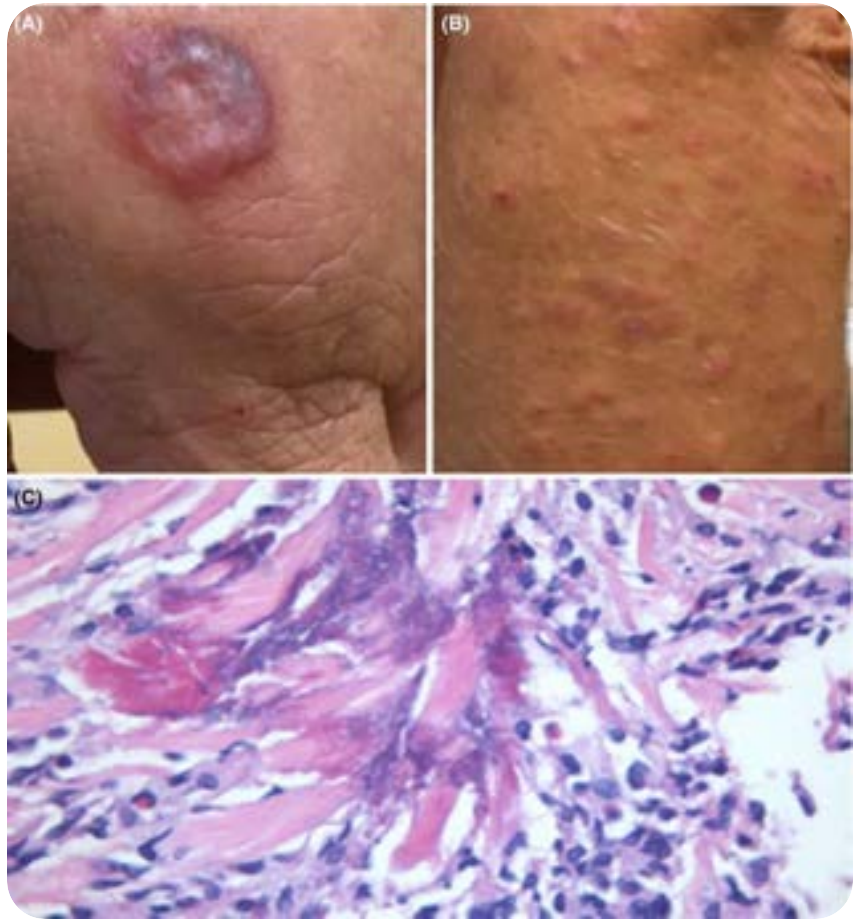
Gordon M. et al Am J Hematol, 2022

Exaggerated Response to Arthropod Attacks in CLL

- Type IV delayed hypersensitivity reaction
- Dermis is rich in T cells and eosinophils

- Clear arthropod bite may be present or not
- Eosinophilic dermatoses
- Well's syndrome: eosinophilic cellulitis

- Eosinophilic infiltrate rich of lymphohistocytic cells with "flame figures" due to eosinophilic degranulation
- No evidence of leukemic infiltrate



Lachowietz C et al. Clin Cas Rep 2018:9:1893-1895, First reported in ….Weed RI Blood 1965

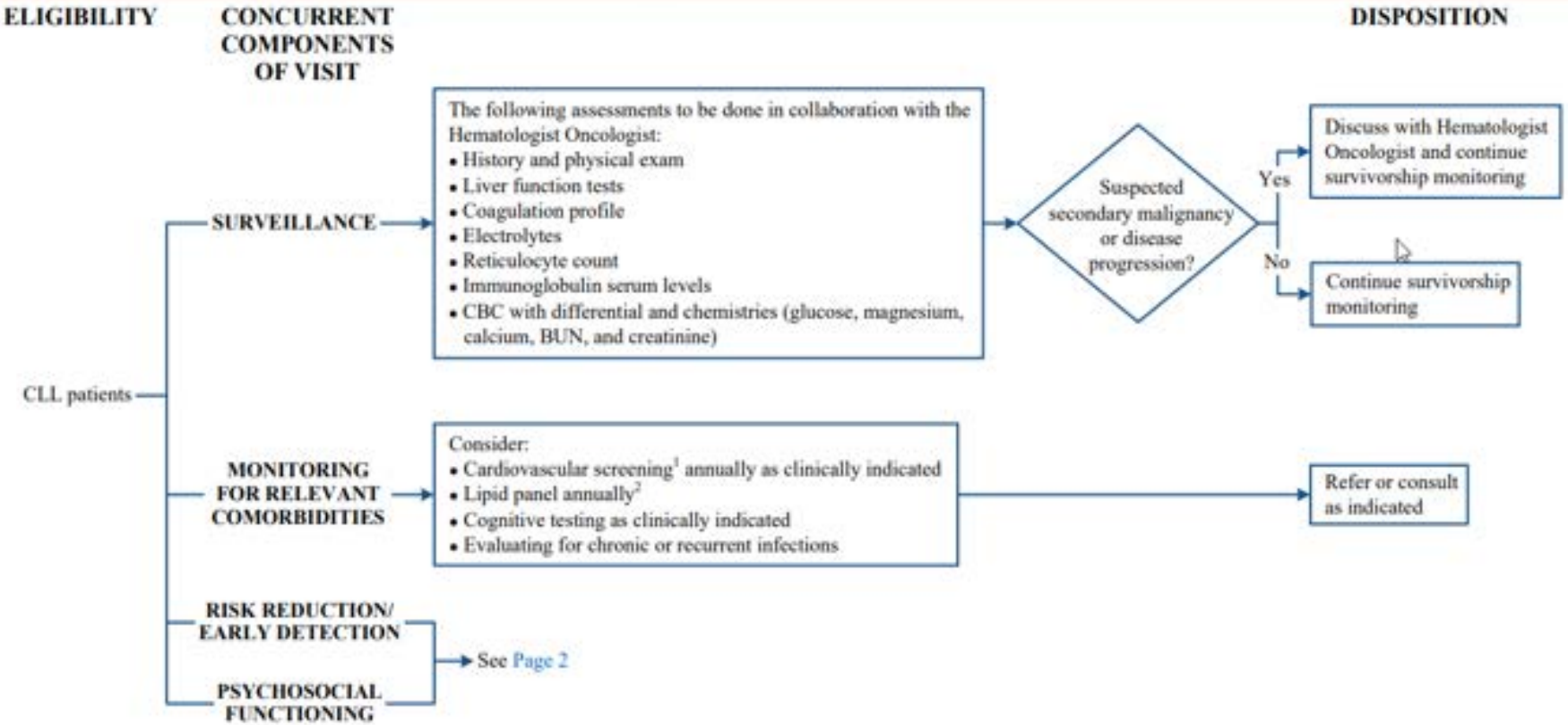
Why to see a specialist in CLL?

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Survivorship Clinic – Chronic Lymphocytic Leukemia (CLL)

*The National Cancer Institute defines a person with cancer as a survivor **from the time of diagnosis until the end of life***

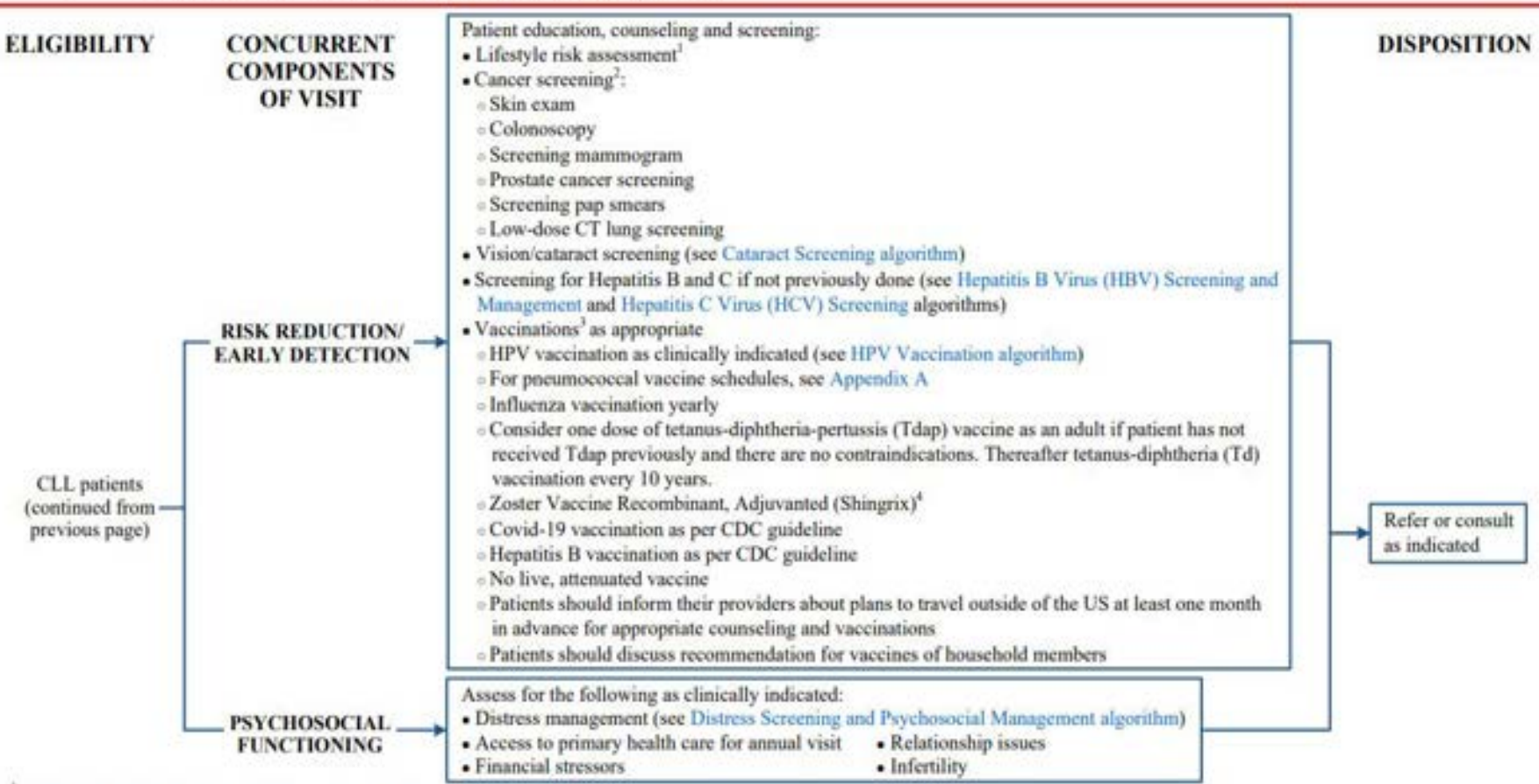
Survivorship – Chronic Lymphocytic Leukemia (CLL)



[1] Consider use of Vanderbilt's ABCDE's approach to cardiovascular health
[2] Labs may be monitored by primary care provider (PCP)

Department of Clinical Effectiveness V1
Approved by The Executive Committee of the Medical Staff on 11/15/2023

Survivorship – Chronic Lymphocytic Leukemia (CLL)



[1] See Physical Activity, Nutrition, and Tobacco Cessation Treatment algorithms; ongoing reassessment of lifestyle risks should be a part of routine clinical practice
[2] Includes breast, cervical (if appropriate), colorectal, lung, pancreatic, prostate, and skin cancer screening
[3] Based on Centers for Disease Control and Prevention (CDC) guidelines
[4] Can be administered > 6 months after anti-CD20 monoclonal antibody treatment

Department of Clinical Effectiveness V1
Approved by The Executive Committee of the Medical Staff on 11/15/2023

Healthy Diet & Exercise Research Study for Individuals with CLL

HEALTH4CLL

Individuals with CLL are capable to increasing activity, despite age and fatigue

Coaching, self-monitoring, and reminders resulted in a high study retention

Overall, interventions are effective in increasing activity, reasonable to deliver interventions via distance-based approaches

Potential benefit on the immunosystem

Benefit extended beyond the study time and HEALTH4CLL2 is ongoing

Lee CY et al .J Cancer Surviv, 2024 online ahead of print

Thank you for the invitation

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