LEUKEMIA & LYMPHOMA SOCIETY® fighting blood cancers someday is today®

Welcome & Introductions

Dr. Brander's slides are available for download at www.LLS.org/programs

LEUKEMIA & LYMPHOMA SOCIETY® fighting blood cancers someday is today®

Living with Chronic Lymphocytic Leukemia (CLL)

Danielle M. Brander, MD
***Assistant Professor,* Division of Hematologic Malignancies & Cellular Therapy**
CLL & Indolent Lymphomas Team Leader
Duke Cancer Institute
Durham, NC

LEUKEMIA & LYMPHOMA SOCIETY® fighting blood cancers
someday is today®

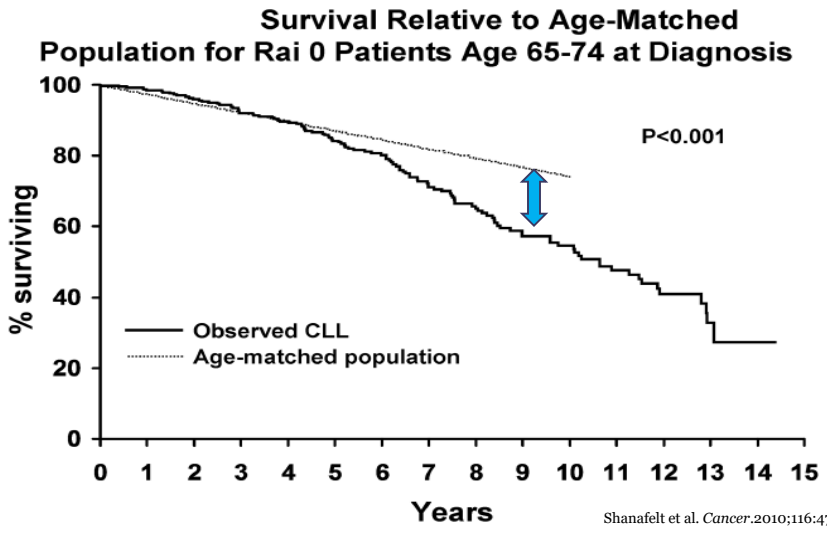
Disclosures

Danielle M. Brander, MD, has affiliations with AbbVie, Genentech, Gilead, Pharmacyclics, and Teva Pharmaceuticals (*Consultant*).

Disclosures (2)

- Content is presented and referenced to the best of our knowledge
- In order to teach to a broad audience, generalizations on CLL are made. However, CLL can vary greatly person to person, and the details of a patient's CLL are critically important in specific recommendations – I encourage discussion with your doctor if questions arise.
- Please do not copy or reproduce slides without written permission from the author(s).

Historical Treatments and Survival



Shanafelt et al. *Cancer*.2010;116:4777

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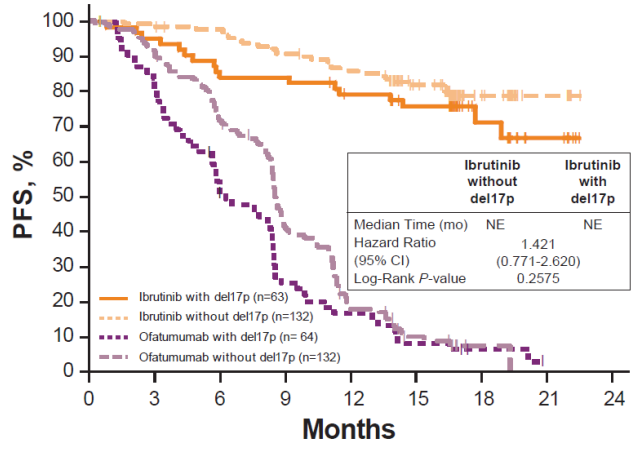
In the Era of Novel Treatments:



- Even with high risk del17p, patients treated with ibrutinib did well
- Other studies also support that traditional markers in CLL not as predictive in the modern era of treatment options with ibrutinib

Brown et al. Leukemia accepted article preview 8 June 2017; doi:10.1038/leu.2017.175
Kipps et al. Hematological Oncology. Volume 35, June 2017 Issue Supplement S2.

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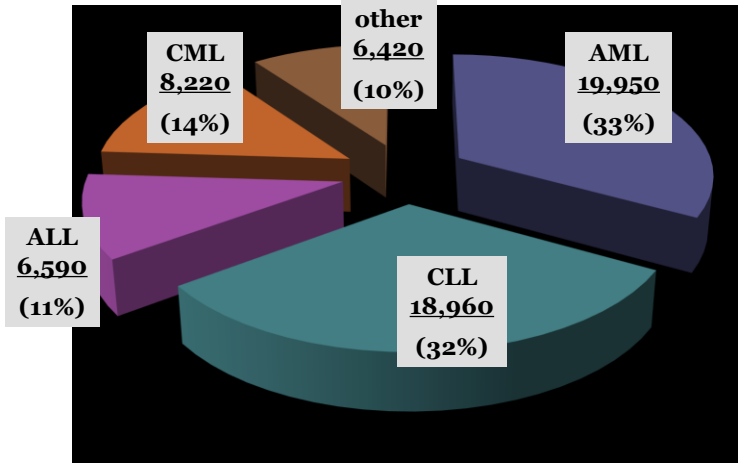
Leukemia in the US: 2016 Diagnoses

60,140 new cases



SEER Database, 2015 Cancer Statistics, posted April 2016. http://seer.cancer.gov/csr/1975_2013/,

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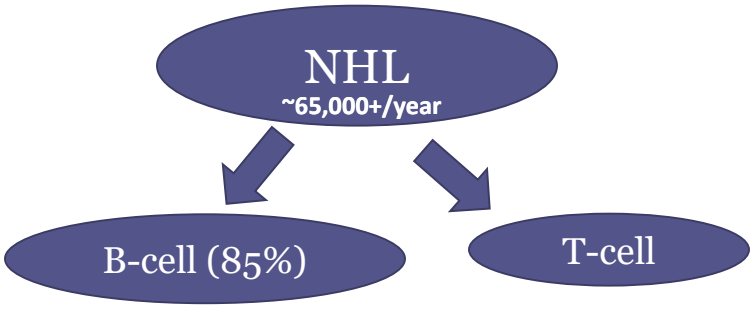
NHL in the US: Subtypes



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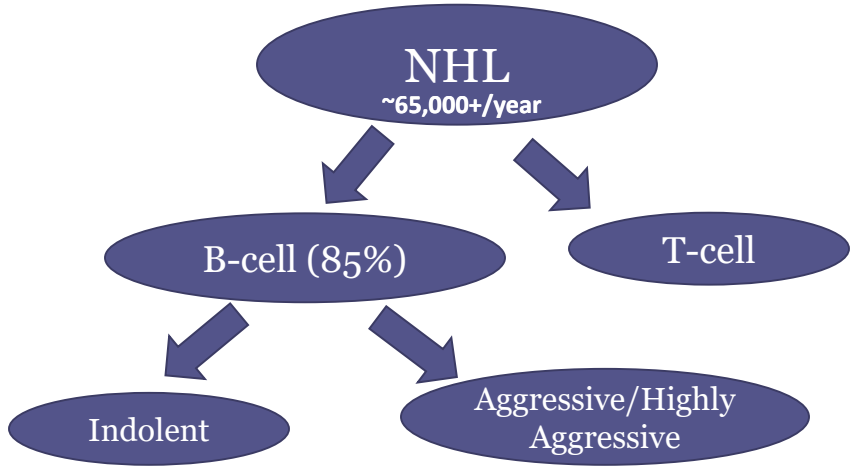
NHL in the US: Subtypes



(30-40%)

- **SLL/CLL**
- Follicular (FL)
- Marginal zone (MZL)
- Lymphoplasmacytic (LPL)

(60-70%)

- DLBCL
- Mantle Cell (MCL)
- Burkitt

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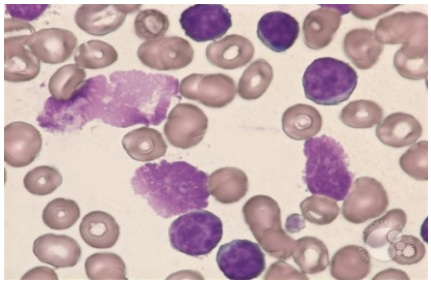
Chronic Lymphocytic Leukemia

- US Epidemiology:
  - Incidence: ~19,000/year
  - US Prevalence: ~130,000 cases
- Median age at diagnosis: 71 years
- Male to female ratio: 2 to 1
- Immunophenotype (CD5+ CD10- CD23+)
  - Differential (FISH)



Siegel et al. *CA Cancer J Clin.* 2015;65:5.
Maslak. ASH Imagebank. 2013. Image 19393.

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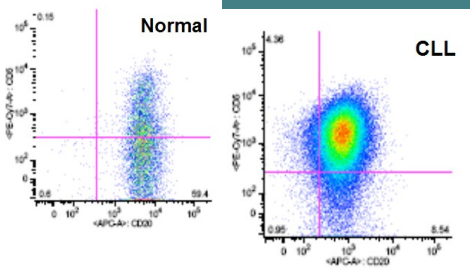
CLL diagnosis: phenotype*

Blood
Lymph node Biopsy
Bone marrow bx (rarely)

- Immunophenotype



* Generalization for "typical CLL"

CLL diagnosis: phenotype*

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Lymph node Biopsy
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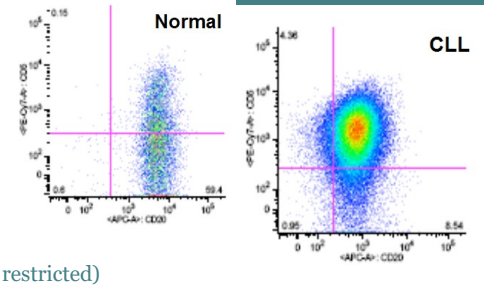

- Immunophenotype
  - monoclonal B-cell (light chain restricted)
  - CD5+
  - CD19+
  - CD20 (dim), CD22 (dim), sIg(dim)
  - CD23+(bright)

T-cell marker*

B-cell markers*

* Generalization for "typical CLL"

CLL diagnosis: phenotype*

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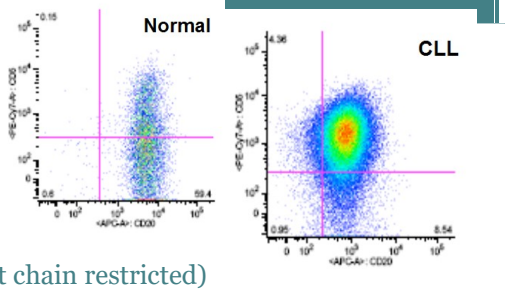
Lymph node Biopsy
Bone marrow bx (rarely)



- Immunophenotype
  - monoclonal B-cell (light chain restricted)
  - CD5+
  - CD19+
  - CD20 (dim), CD22 (dim), sIg(dim)
  - CD23+(bright)

T-cell marker*

B-cell markers*

- Distinguish from mantle cell lymphoma (MCL)
  - immunophenotype
  - FISH: t11;14
  - Cyclin D1

* Generalization for "typical CLL"

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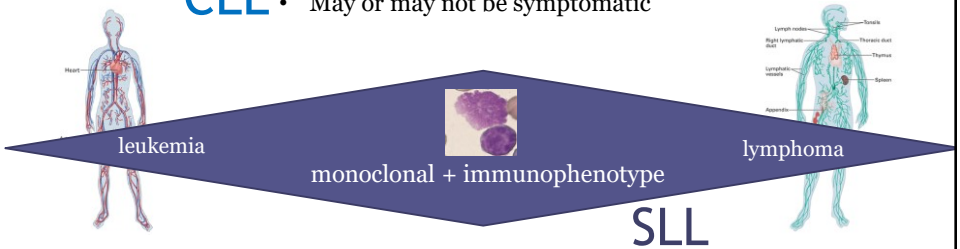
CLL vs. SLL vs. MBL

CLL
- At least 5 x 10^9 monoclonal Bcells/L*
- May or may not be symptomatic



SLL
- Small lymphocytic lymphoma
- < 5 x 10^9 mBcells/L*
- + symptoms, cytopenias, LAD, or splenomegaly

Hallek et al. *Blood.* 2008;111:5446.
Marti et al. *Br J Haematol.* 2005 ;130:325.
Shim et al. *Blood.* 2014;123:1319.
Biology:exploring life online. http://bodell.mtchs.org

* some variation in definition of malignant vs Bcells

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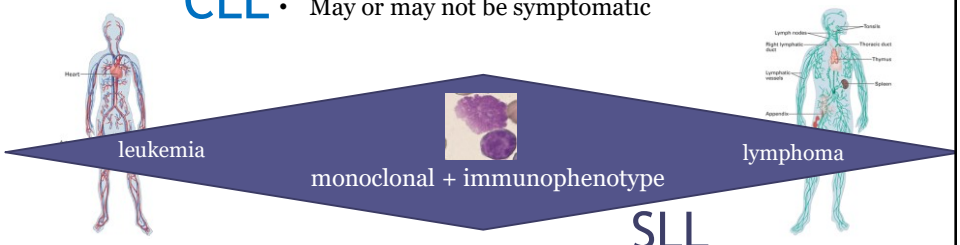
CLL vs. SLL vs. MBL

CLL
- At least 5 x 10^9 monoclonal Bcells/L*
- May or may not be symptomatic



MBL
- Monoclonal B-cell lymphocytosis
- < 5 x 10^9 mBcells/L*
- No symptoms, cytopenias, LAD or splenomegaly
- 1-2%/yr progress to CLL
- 2.5-5% or more of the population

SLL
- Small lymphocytic lymphoma
- < 5 x 10^9 mBcells/L*
- + symptoms, cytopenias, LAD, or splenomegaly

Hallek et al. *Blood.* 2008;111:5446.
Marti et al. *Br J Haematol.* 2005 ;130:325.
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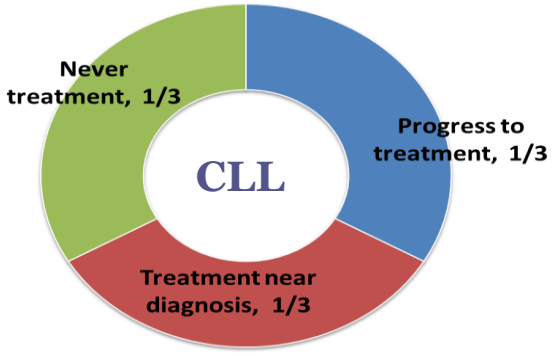
CLL: Dynamic Monitoring vs Treatment



- Rationale against treatment on diagnosis for asymptomatic patients

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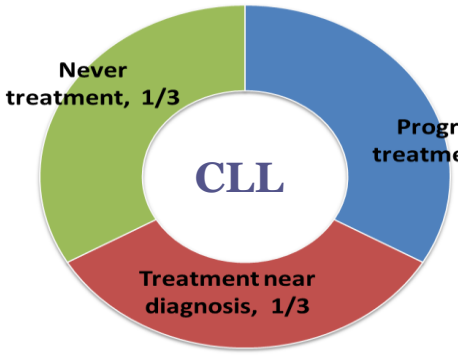
CLL: Dynamic Monitoring vs Treatment



70-80% of all CLL patients will require therapy

- Rationale against treatment on diagnosis for asymptomatic patients

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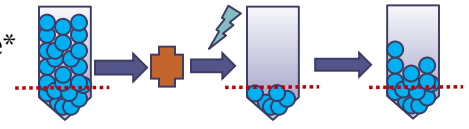
Rationale on asymptomatic early therapy

1. CLL is treatable, but not curable*



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Rationale on asymptomatic early therapy

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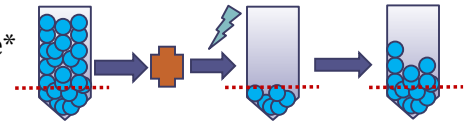
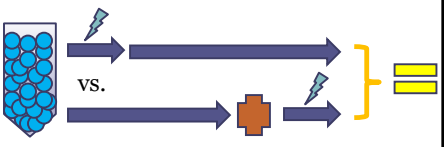


2. Studies of treatment at diagnosis vs. treatment on indications: no difference in survival



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Rationale on asymptomatic early therapy

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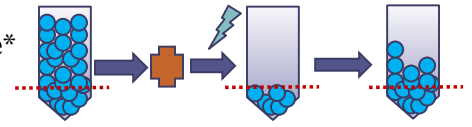

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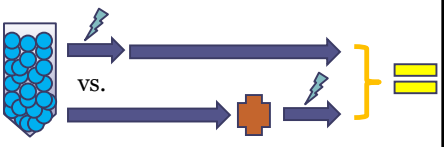

3. Not all patients will require treatment and all treatments have some side effects

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Rationale on asymptomatic early therapy

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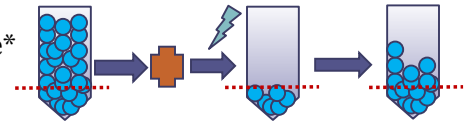

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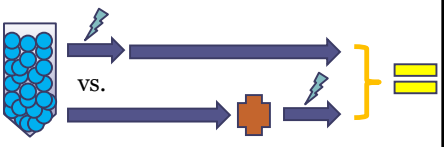
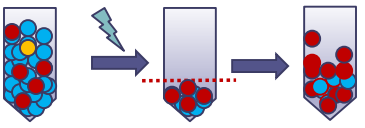


3. Not all patients will require treatment and all treatments have some side effects

4. After treatment, the CLL can come back with more aggressive cells ("clonal evolution")



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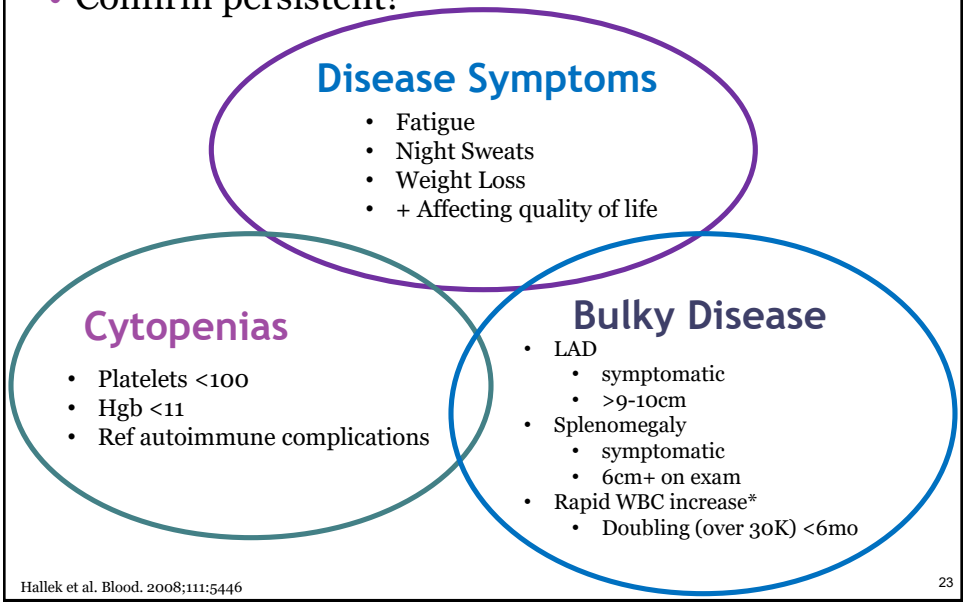
Treatment indications: Risks vs. Benefits

Amazon.com.uk 22

CLL/SLL: Indications for treatment

- Confirm persistent!



Hallek et al. Blood. 2008;111:5446

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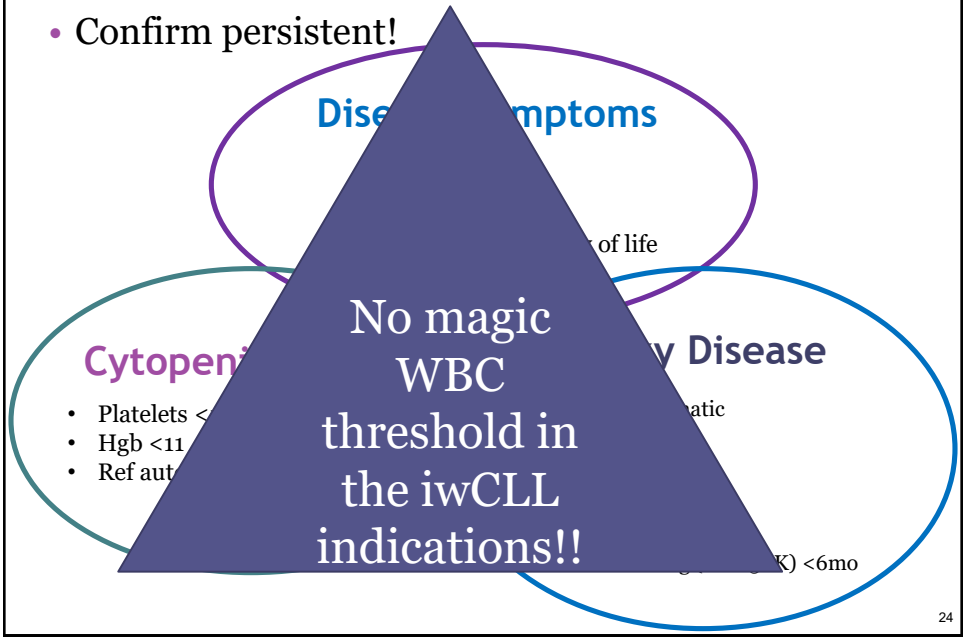
CLL/SLL: Indications for treatment

- Confirm persistent!



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Traditional Prognostics: Staging Systems

Rai	Findings	Survival (mo)
0	Lymphocytosis only	> 120
I	Lymphocytosis + lymphadenopathy	95
II	Lymphocytosis + > spleen and/or liver	72
III	Lymphocytosis + anemia (Hgb < 11.0 g/dL)	30
IV	Lymphocytosis + platelets < 100	30

Binet	Findings	Survival (mo)
A	Hgb ≥ 10, Plts ≥ 100, < 3 involved areas*	> 120
B	Hgb ≥ 10, Plts ≥ 100, ≥ 3 involved areas*	84
C	Hgb < 10, or Plts < 100	24

*Involved areas include cervical, axillary, or inguinal nodes, spleen, or liver.

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

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Traditional Prognostics: Staging Systems

Rai	Findings	Survival (mo)
0	Lymphocytosis only	**Low risk (Rai 0): > 10 years**
I	Lymphocytosis + lymphadenopathy	95
II	Lymphocytosis + > spleen and/or liver	72
III	Lymphocytosis + anemia (Hgb < 11.0 g/dL)	30
IV	Lymphocytosis + platelets < 100	30

Intermediate risk (Rai 1/2): 5-7 years

High risk (Rai 3/4): 1-3 years

Binet	Findings	Survival (mo)
A	Hgb ≥ 10, Plts ≥ 100, < 3 involved areas*	> 120
B	Hgb ≥ 10, Plts ≥ 100, ≥ 3 involved areas*	84
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Traditional Prognostics: Staging Systems

Rai	Findings	Survival (mo)
0	Lymphocytosis only	w risk (Rai 0): > 10 years
I	Lymphocytosis +	95
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III	Ly	30
IV	Lymphocy	

Interm -7 years

Hi

Binet	Find	Survival (mo)
A	H	> 120
B		84
C		24

*Involv

Treatments and supportive care available very different today

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

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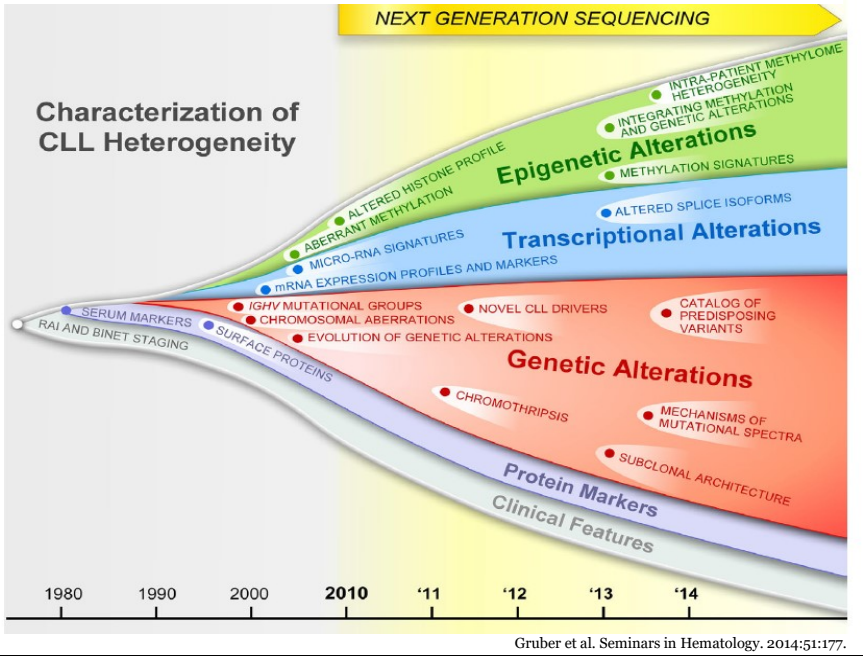
Understanding CLL Heterogeneity



Gruber et al. Seminars in Hematology. 2014:51:177.

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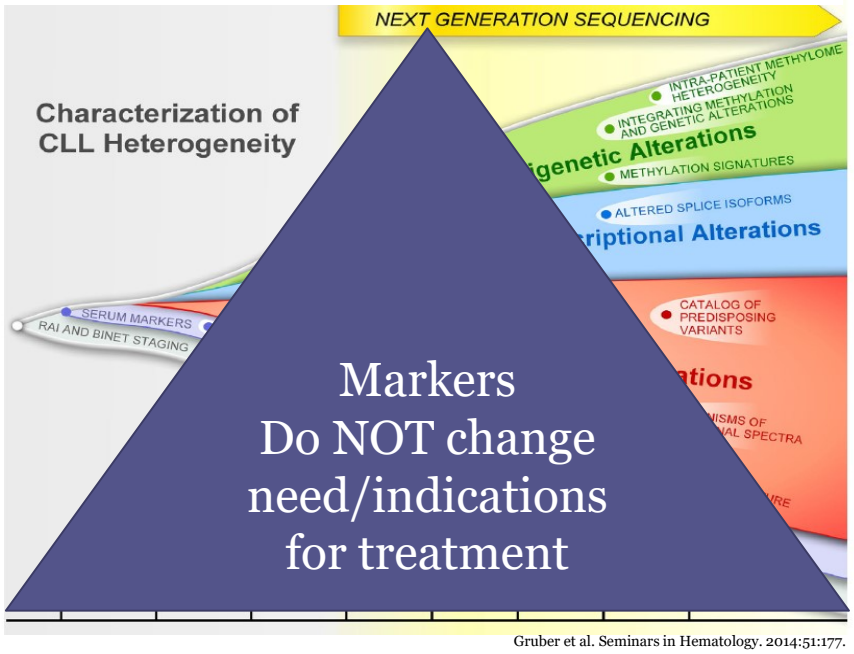
Understanding CLL Heterogeneity



Gruber et al. Seminars in Hematology. 2014:51:177.

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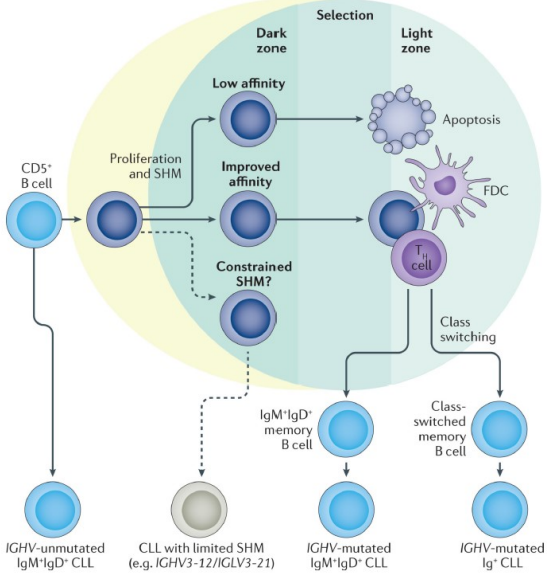
IGHV mutational status



Kipps et al. Nat Rev Dis Primers. doi:10.1038/nrdp.2016.96

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FISH

- **Late 1980-1990s:** FISH (interphase)

	Chromosome banding		Interphase cytogenetics	
	n	%	*n*	%
Trisomy 12	112/604	19	36/245	15
Structural 13q aberrations	62/604	10	129/245	53
Structural 11q aberrations	49/604	8	48/250	19
Structural 6q aberrations	36/604	6	18/208	9
Structural 17p aberrations	22/604	4	20/243	8

N Engl J Med. 2000;343:1910.
J Mol Med. 1999;77:266.

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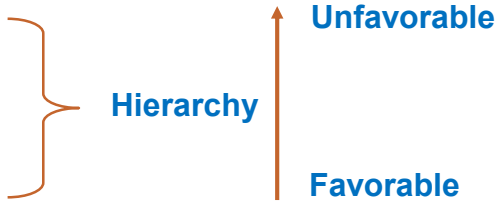
(Brief) Summary of Genomic/Molecular Prognostic Factors

- **FISH defects**
  - 17p deletion
  - 11q deletion
  - 12q trisomy
  - Normal
  - 13q deletions



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Hierarchy: Unfavorable → Favorable

- **Immunoglobulin heavy chain variable region *(IGHV)***
  - ≤ 2% mutation = unmutated
  - Unmutated: higher risk

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Hierarchy: Unfavorable → Favorable

- **Immunoglobulin heavy chain variable region *(IGHV)***
  - ≤ 2% mutation = unmutated
  - Unmutated: higher risk

- **CD38 status (≥ 30% = higher risk)**
- **ZAP-70 status (≥ 20% = higher risk)**

Often included with flow but IGHV more important and less variable

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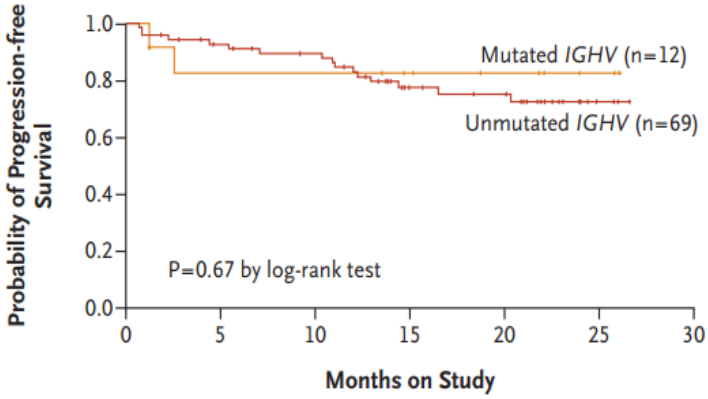
Responses *IGHV UM* and novel agents - ibrutinib



* Included all previously treated patients (median 4 prior)

N Engl J Med 2013;369:32

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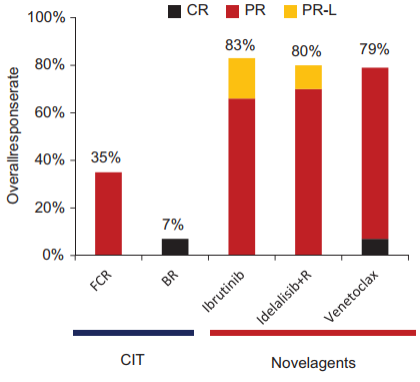
Responses and Progression rates for patients with CLL & TP53 dysregulation

Responses



Rossi et al. Leukemia & Lymphoma, DOI: 10.1080/10428194.2016.1250264

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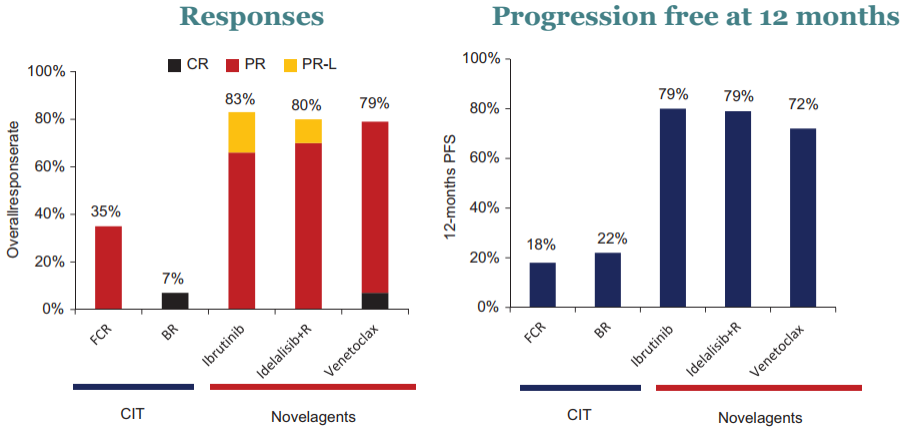
Responses and Progression rates for patients with CLL & TP53 dysregulation



Rossi et al. Leukemia & Lymphoma, DOI: 10.1080/10428194.2016.1250264 37

Low frequency of FISH/IGHV testing

- Connect CLL US Database (2010 – 2014)
  - First line (n=889)
  - Second line (n=260)

Test	% tested (first line)	% tested (2nd line)
Metaphase cytogenetics	39%	31.2%
FISH	58%	40.4%
IGHV	7.9%	5%

Mato et al. *BJH*. 2016;175:892 38

Summary: diagnosis & initial work up

- Flow cytometry
- Laboratory testing
  - CBC, CMP
  - LDH
  - B2M
  - FISH
  - IGHV mutation analysis
  - Others by case (if need treatment: TP53 mutation and full chromosome analysis)

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Summary: diagnosis & initial work up

- Flow cytometry
- Laboratory testing
  - CBC, CMP
  - LDH
  - B2M
  - FISH
  - IGHV mutation analysis
  - Others by case (if need treatment: TP53 mutation and full chromosome analysis)
- Imaging
  - Not needed for most patients
    - High risk
    - symptoms
- Bone marrow
  - Not needed unless for low counts or would change treatment recommendations

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Highlights of CLL Treatment Options

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Clinical Trials!

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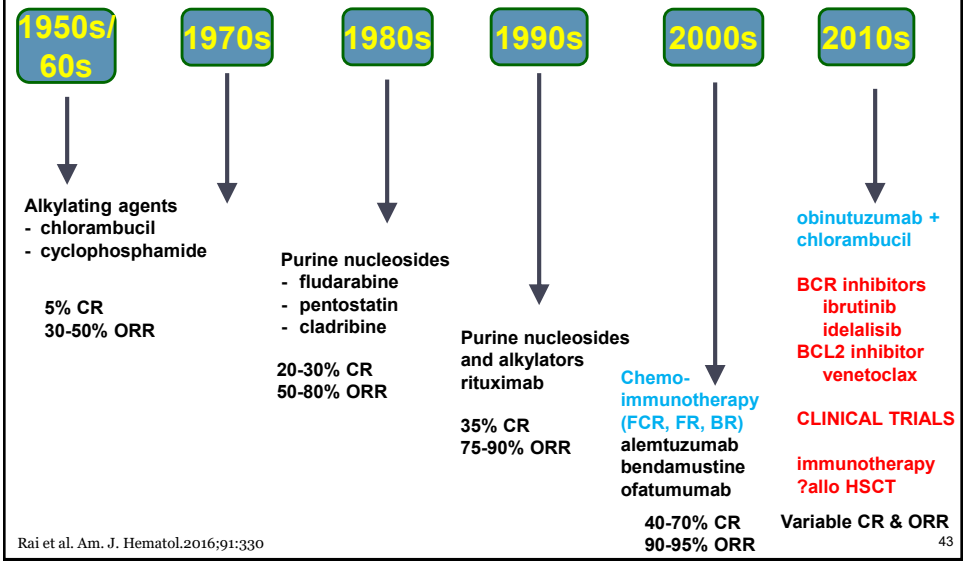
Brief History - CLL
Approved Treatment Options



Rai et al. Am. J. Hematol.2016;91:330

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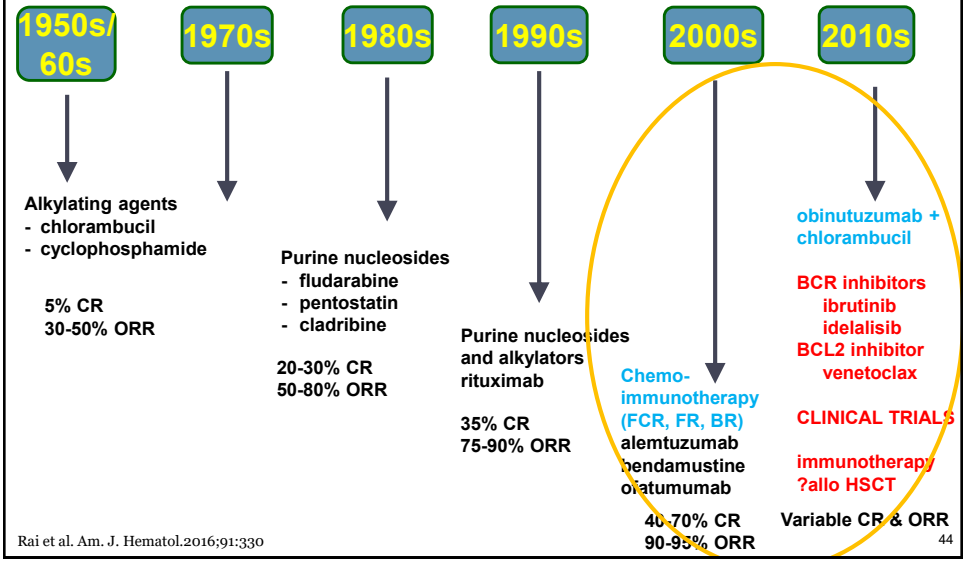
Brief History - CLL
Approved Treatment Options



Rai et al. Am. J. Hematol.2016;91:330

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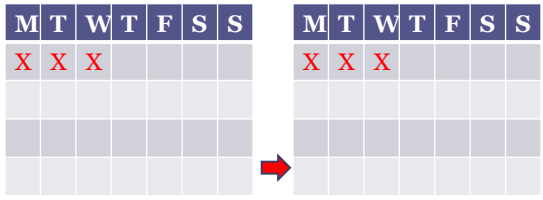
Treatment Basics: Chemotherapy vs Targeted Agents

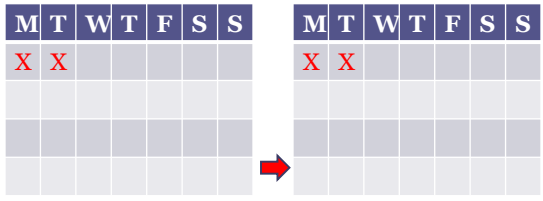
IV – intravenous

- FCR = Fludarabine + Cyclophosphamide + Rituximab



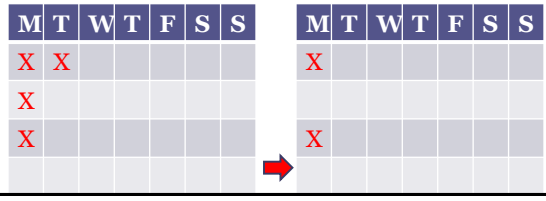
for 4-6 total cycles

- BR = Bendamustine + Rituximab



for 4-6 total cycles

- G-Clb = chlorambucil + obinutuzumab (G)



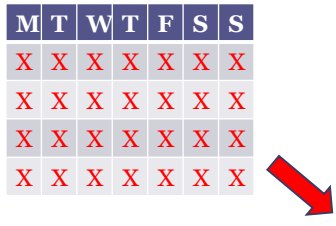
for 4-6 total cycles

45

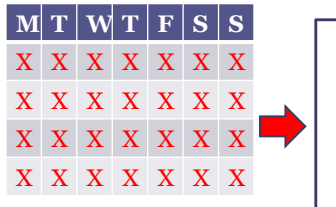
Treatment Basics: Chemotherapy vs Targeted Agents

PO – by mouth

- ibrutinib
  - targets BTK

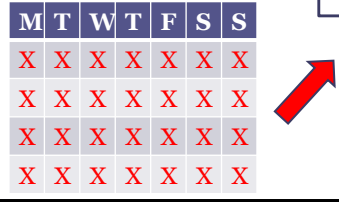


- idelalisib + rituximab
  - targets PI3Kdelta
  - specific rituximab schedule (limited)



Targeted drug given continuously unless not tolerated or resistance develops

- venetoclax
  - targets BCL2
  - dose ramp up (5 weeks)
  - sometimes given with anti-CD20 antibody



46

Treatment Basics: Other Terminology

iwCLL Responses

- Complete Response (CR)
- Partial Response (PR)
- Partial Response + lymphocytosis (PR-L)*
- Stable Disease (SD)
- Progressive Disease (PD)

Duration of Response & Survival

- Progression Free Survival (PFS)
- Overall Survival (OS)

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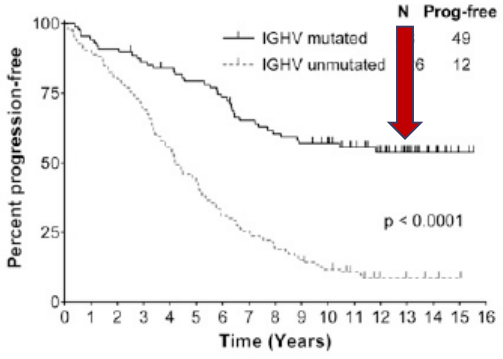
Rationale for frontline chemoimmunotherapy (CIT): durable remissions for some patients

FCR

- **MDACC:** 300pts received treatment with FCR
  - Plateau in PFS: no relapses beyond 10.4 years in 42 patients with favorable risk (mutated IGHV, no del17p or del11q)



Blood. 2008;112: 975-980.
Blood. 2015;126(16):1921.
Blood. 2016;127(3):303.
Blood. 2016;127(2):208.
Blood. 2015;126(16):1921.

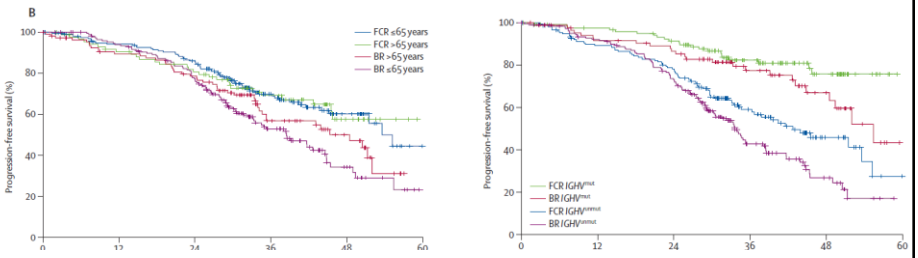
- Similar plateau in CLL8 and Rossi et al FCR studies

48

Rationale for frontline chemoimmunotherapy (CIT): durable remissions for some patients

Bendamustine and Rituximab

- CLL10 (FCR vs BR frontline): 561 randomized
  - Severe infections all pts: 39.8% vs. 25.4% (NS)
  - Infections older pts: 48.4% vs. 26.8% (p=.001)
  - PFS: NS difference in age > 65yo
  - M-IGHV improved PFS, no interaction with treatment type
  - No difference in OS to date

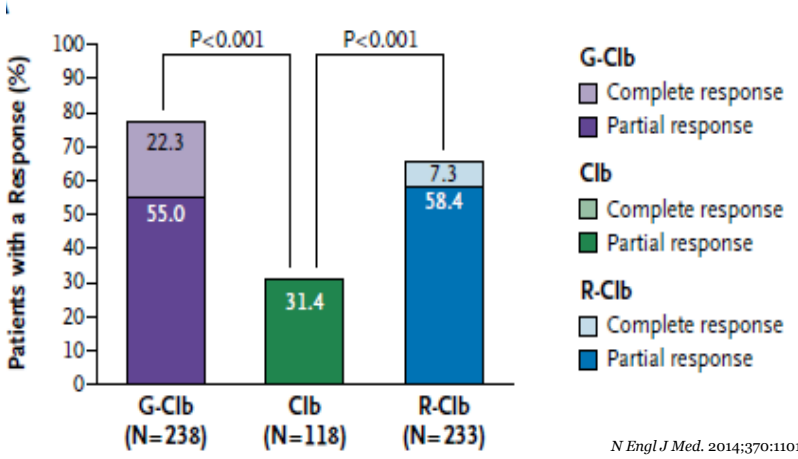


Lancet Oncol 2016; 17: 928.

49

Anti-CD20 antibodies: obinutuzumab (G)

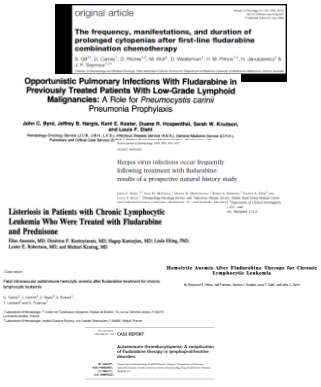
- 781 CLL, treatment naive
- Randomized 1:1:1
- Median PFS advantage (R-Clb vs G-Clb 15.2 vs 26.7 mo)



N Engl J Med. 2014;370:1101

50

Chemoimmunotherapy (CIT): Considering the Toxicities


original article

The frequency, manifestations, and duration of prolonged cytopenias after first-line fludarabine combination chemotherapy

Opportunistic Pulmonary Infections With Fludarabine in Previously Treated Patients With Low-Grade Lymphoid Malignancies: A Role for *Pneumocystis carinii* Pneumonia Prophylaxis

John C. Byrd, Jeffrey B. Hargis, Kent E. Kester, Duane R. Hospenthal, Sarah W. Knutson, and Laura F. Dietz

Herpes virus infections occur frequently following treatment with fludarabine: results of a prospective natural history study

Listeriosis in Patients with Chronic Lymphocytic Leukemia Who Were Treated with Fludarabine and Prednisone

Hemolytic Anemia After Fludarabine Therapy for Chronic Lymphocytic Leukemia

CASE REPORT

Autoimmune thrombocytopenia: A complication of fludarabine therapy in lymphoproliferative disorders.

Addressing risks

- Support cytopenias: can recover without complications
  - In long term follow of CLL8, prolonged cytopenias did not translate to increased MDS/AML
- Assessing DAT positivity
  - AIHA in 8% DAT-neg patients; 28% DAT-positive patients
- Prophylaxis for infections

Annals of Internal Medicine.1992;117:466-469.
British Journal of Hematology. 1999;105:445-447.
JCO. 1998;16:1885-1889.
Hematol Cell Therapy. 1996;38:359-360.
Clin Lab Haem. 2006;22:175-178.
Blood. 2008;111:1820-1826.
Annals of Oncology. 2010; 21: 331-334.
Clin Oncol. 1995; 13:2431-2448.
Blood. 2008; 112: 975-980.
American Journal of Hematology. 1995; 49: 135-142.
J Clin Oncol.1995;13:2431-2448.

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Novel Targeted Inhibitors

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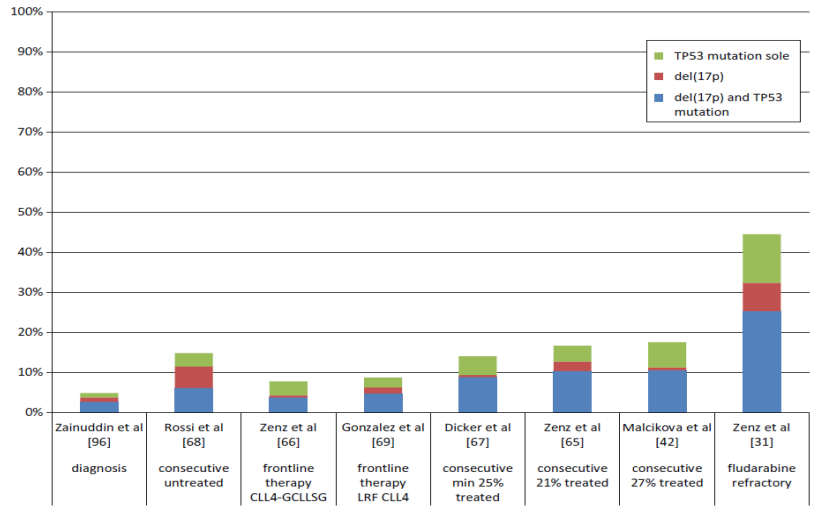
TP53 mutation and del17p

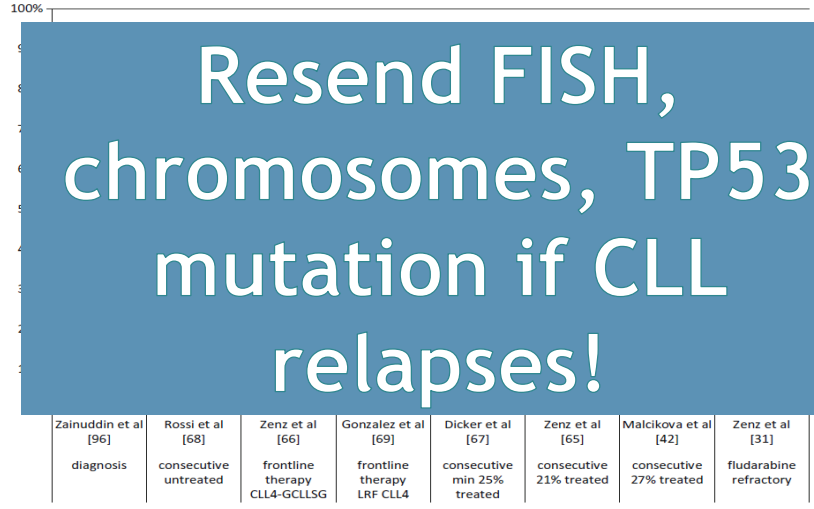


- Percentage of patients with TP53 mutation and not del17p

S. Malek (ed.), Advances in Chronic Lymphocytic Leukemia, Advances in Experimental Medicine and Biology 792, DOI 10.1007/978-1-4614-8051-8_5,

53

TP53 mutation and del17p

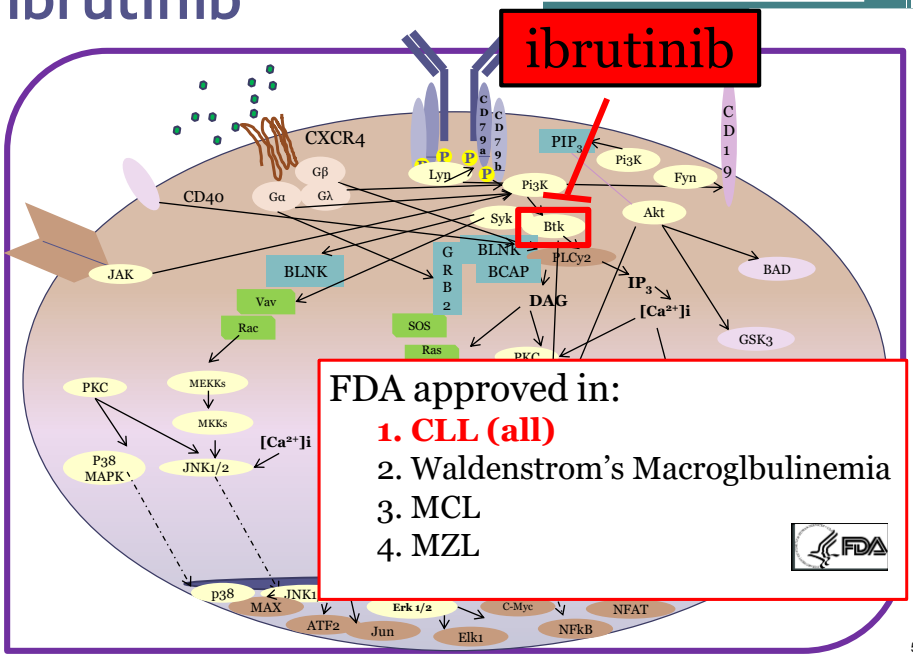


- Percentage of patients with TP53 mutation and not del17p

S. Malek (ed.), Advances in Chronic Lymphocytic Leukemia, Advances in Experimental Medicine and Biology 792, DOI 10.1007/978-1-4614-8051-8_5,

54

ibrutinib

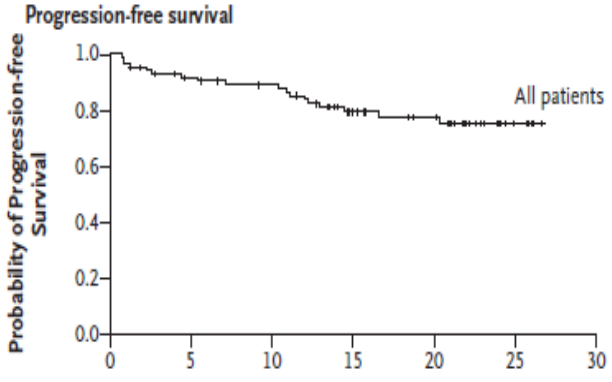


FDA approved in:

1. **CLL (all)**
2. Waldenstrom's Macroglbulinemia
3. MCL
4. MZL

55

ibrutinib in CLL



- Phase Ib/II expansion in CLL/SLL (85 pts; high risk!)
  - Daily dosing of ibrutinib (420mg , 840mg in 34 patients)
  - ORR 71%, plus 15-21% achieved PR-L
  - At 26 months, OS was 83%
- Phase III ibrutinib vs ofatumumab led to approval

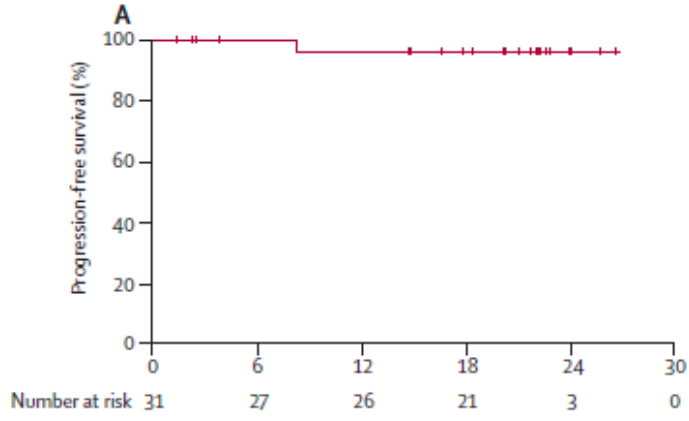
Byrd et al. *N Engl J Med. 2013;369:32.*

56

ibrutinib in frontline CLL

Frontline Ibrutinib Monotherapy

- 31 patients
- Age> 65 years
- Responses: 71% ORR, *and* 13% PR with lymphocytosis



O'Brien et al. *Lancet Oncol . 2014;* 15: 48.

57

ibrutinib in CLL: extended follow up

- Responses continuous, although…
  - Time to best response, median: 7.4 mo (1.7-42.5 mo)
  - Time to CR, median: 21.2 mo (4.6-42.5)
- ORRs very high, but…
  - TN: 84% (23% CR)
  - R/R: 90% (7% CR)

Blood. 2015;125:2497.

58

ibrutinib in CLL: extended follow up

- Responses continuous, although…
  - Time
  - Time
- ORRs very high, but…
  - TN: 8
  - R/R:

Best responses take time

CR rates low

Blood. 2015;125:2497. 59

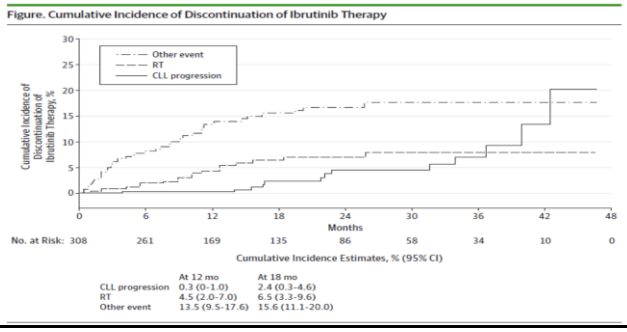
ibrutinib in CLL: extended follow up

- Responses continuous, although…
  - Time
  - Time
- ORRs very high, but…
  - TN: 8
  - R/R:

Best responses take time

CR rates low

- Many do well, but…
  - discontinuations



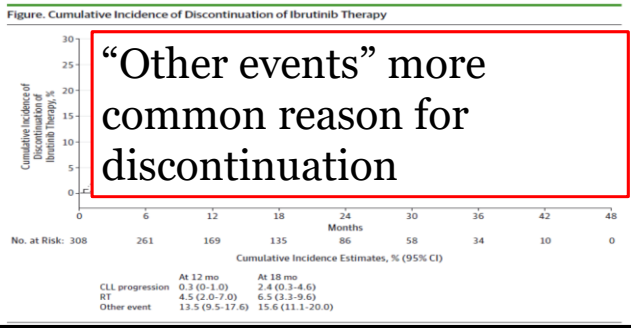
Blood. 2015;125:2497. 60

ibrutinib in CLL: extended follow up

- Responses continuous, although…
  - Time
  - Time
- ORRs very high, but…
  - TN: 8
  - R/R:
- Many do well, but…
  - discontinuations

Best responses take time

CR rates low



"Other events" more common reason for discontinuation

Blood. 2015;125:2497.

61

Putting it together for Frontline CLL treatment in US: Young (≤65 yo) & fit

(90% of all CLL)

Suitable for systemic therapy → YES → **Clinical trial available & eligible ?** → YES → Clinical trial encouraged

No → **TP53 (?other high risk features)**

YES → **BCR inhibitor (ibrutinib based) HDMP + rituximab**

Questions: Role of allo HSCT Anti-CD20s

No → **FCR (especially if M-IGHV, non del17p/11q) ibrutinib**

Questions: IGHV mutation status to make treatment decisions (favor yes)

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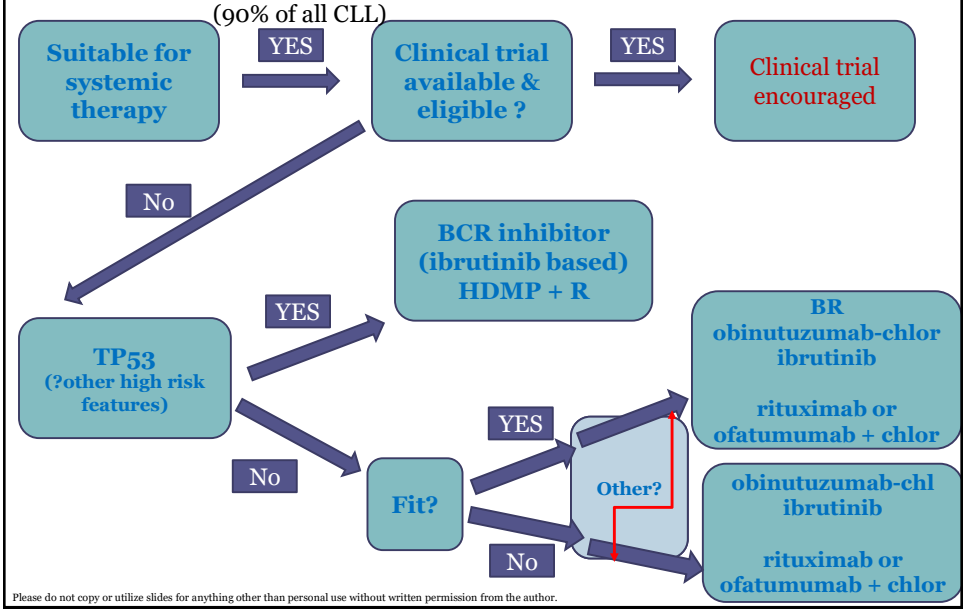
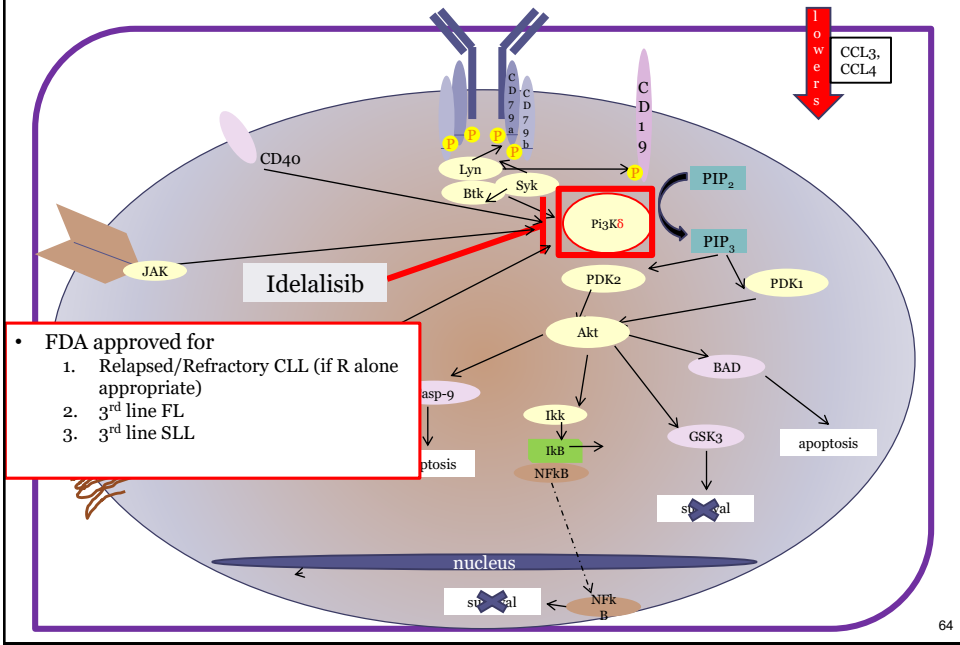
Frontline CLL in US: >65/70 yo OR any age with renal impairment +/- co-morbidity

(90% of all CLL)



Targeting BCR Signaling: PI3K pathway



- FDA approved for
  1. Relapsed/Refractory CLL (if R alone appropriate)
  2. 3rd line FL
  3. 3rd line SLL

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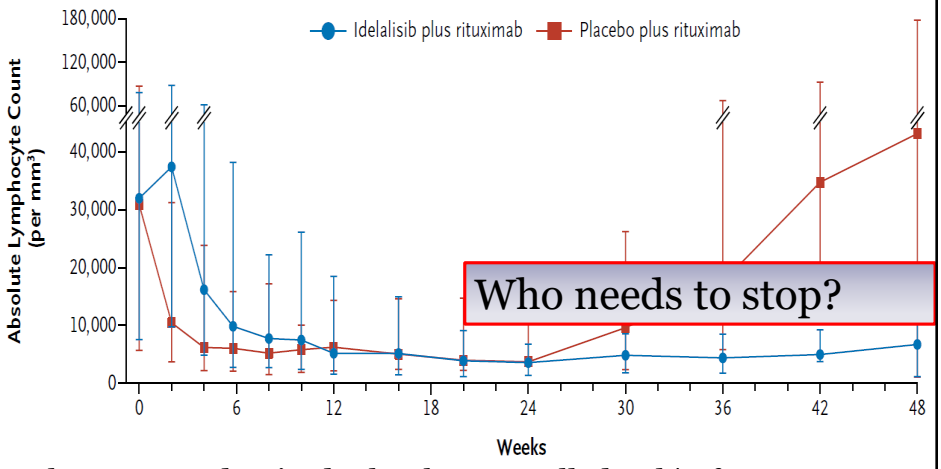
Idelalisib

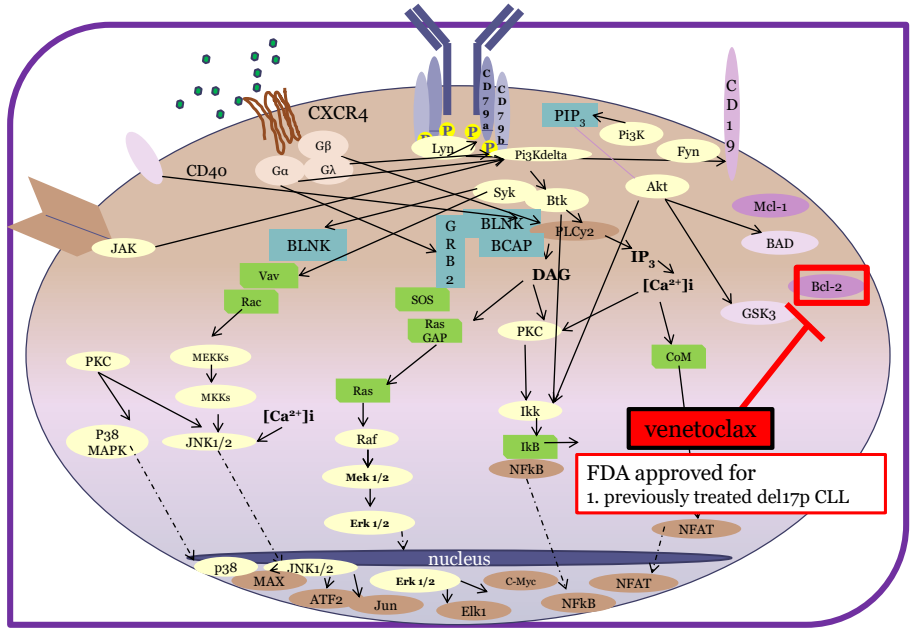


- Phase III randomized, placebo controlled, rel/ref CLL
  - 220 pts, R +/- idelalisib
  - PFS: 93% vs 46% at 24 wks
  - OS: 92% vs 80% at 52 weeks

N Engl J Med. 2014;370:997.
N Engl J Med. 2014;370:1008.

65

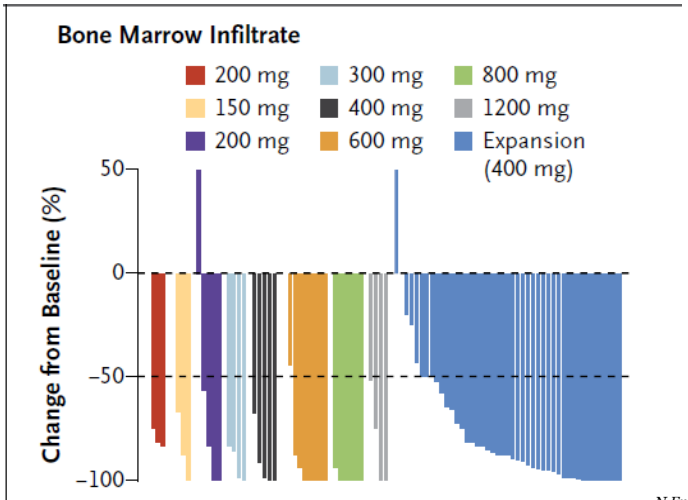
Targeting anti-apoptosis with Bcl-2 inhibition



66

venetoclax

- High single agent responses in high risk patients
  - Includes bone marrow CRs



N Engl J Med. 2016;374:311.

67

CLL frontline or relapsed/refractory treatments: considering toxicities

chemoimmunotherapy

Toxicity varies by regimen

- Cytopenias
- Infections
- Autoimmune complications
- Clonal evolution
- Second Malignancies including MDS/AML

ibrutinib

bleeding risks
- phase I/II Studies: ICH: 2%
- followup (3yr): 7% gr 3

cardiovascular risks
- a fib: range up to 16%
- HTN

other
- GI/diarrhea
- rash
- arthralgia/arthritis
- infections

idelalisib

- cytopenias
- LFT abnormalities
- colitis (diarrhea)
- pneumonitis
- drug-drug (CYP3A)
- infections

venetoclax

tumor lysis
- Can be rapid
- dose ramp up & hospitalization needs

cytopenias (gr ¾)
- neutropenia (41%)
- anemia (12%)
- thrombocytopenia (12%)

other (all grades)
- diarrhea (52%)
- nausea (47%)
- fatigue (40%)

NEJM. 2014;371:213.
Blood. 2014;124:3829.
Blood. 2015;125:2497
Leukemia & Lymphoma. 2015;56:277.
NEJM. 2016;374:311.

68

CLL frontline or relapsed/refractory treatments: considering toxicities

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cardiovascular risks

- a fib: range up to 16%
- HTN

other

- GI/diarrhea
- rash
- arthralgia/arthritis
- infections

What is comprehensive physical, emotional, and financial toxicity of each of these regimens?

idelalisib

- cytopenias
- LFT abnormalities
- colitis (diarrhea)
- pneumonitis
- drug-drug (CYP3A)
- infections

venetoclax

tumor lysis

- Can be rapid
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NEJM. 2014;371:213.
Blood. 2014;124:3829.
Blood. 2015;125:2497
Leukemia & Lymphoma. 2015;56:277.
NEJM. 2016;374:311.

69

ibrutinib and idelalisib: understanding toxicity

Table 3. Most common reasons for kinase inhibitor (KI) discontinuation in patients who have discontinued ibrutinib or idelalisib.

	Ibrutinib	Idelalisib
Toxicity	51% (n=73)	52% (n=18)
CLL Progression	28% (n=40)	31% (n=11)
Richter's transformation	8% (n=11)	6% (n=2)
Cellular therapies (CAR T cells or allogeneic SCT)	2% (n=3)	0% (n=0)
Unrelated death / Other	11% (n=16)	11% (n=4)

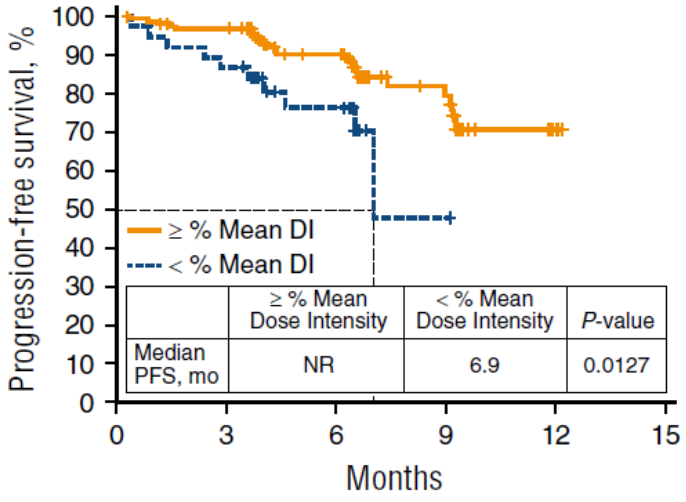
***note this are reasons for discontinuation, not discontinuation rates**
***KI=kinase inhibitor (ibrutinib and idelalisib)**

Mato et al. *Blood*. 2016;128:2199

70

Ibrutinib Outcomes with Adherence

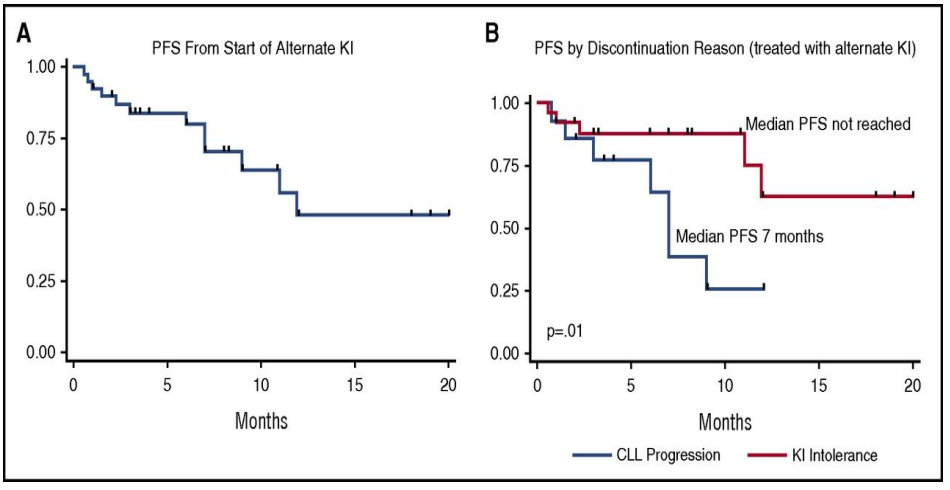
Dose Intensity (DI)



	≥ % Mean Dose Intensity	< % Mean Dose Intensity	*P*-value
Median PFS, mo	NR	6.9	0.0127

Barr et al. 2017;129:2612

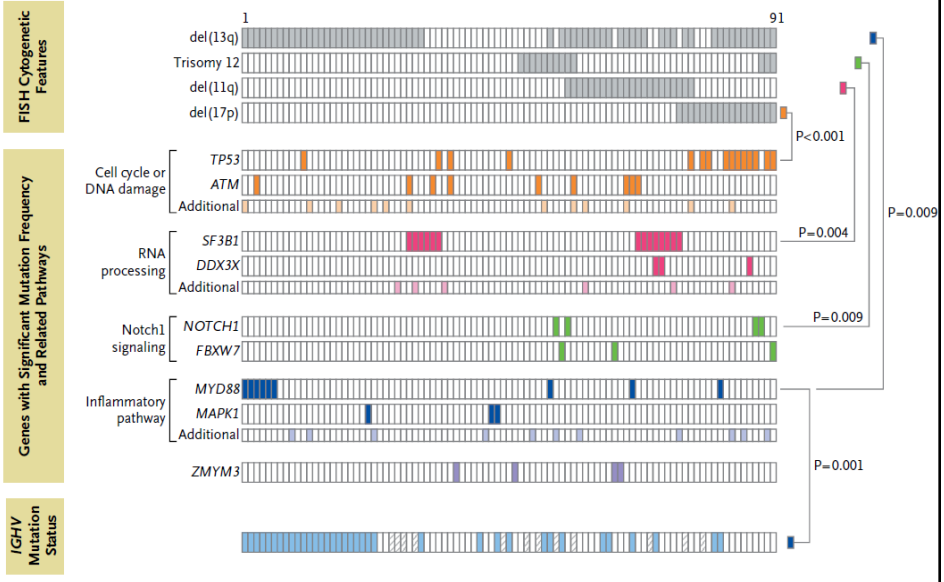
Treatment with alternate KIs



Mato et al. *Blood.* 2016;128:2199

Moving Forward: Novel genomic/molecular risks and Minimal Residual Disease (MRD) in CLL

Recurrent Somatic Mutations in CLL



- Some recurrent mutations are associated with known prognostic features

Wang et al. N Engl J Med. 2011;365:2497.

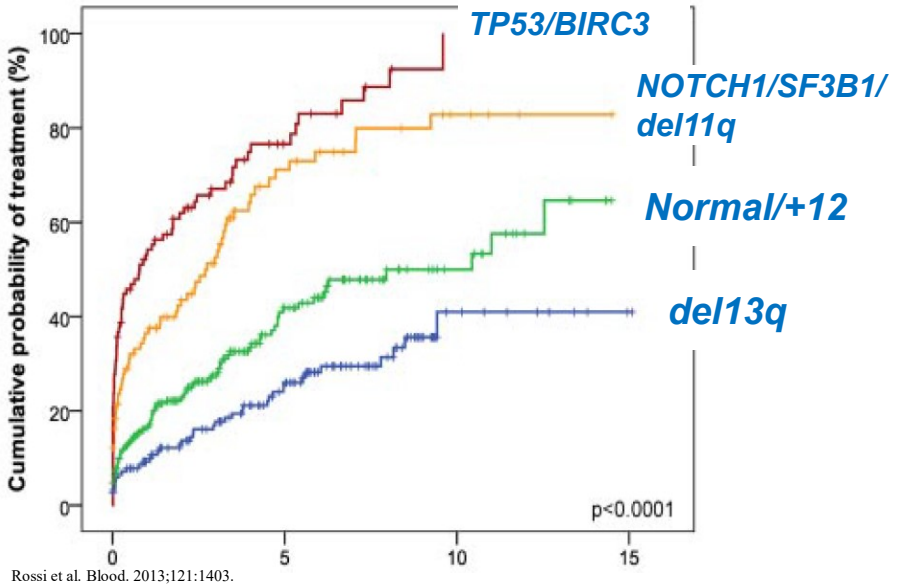
Recurrent Somatic Mutations in CLL

- Some recurrent mutations are associated with known prognostic features

Wang et al. N Engl J Med. 2011;365:2497.

75

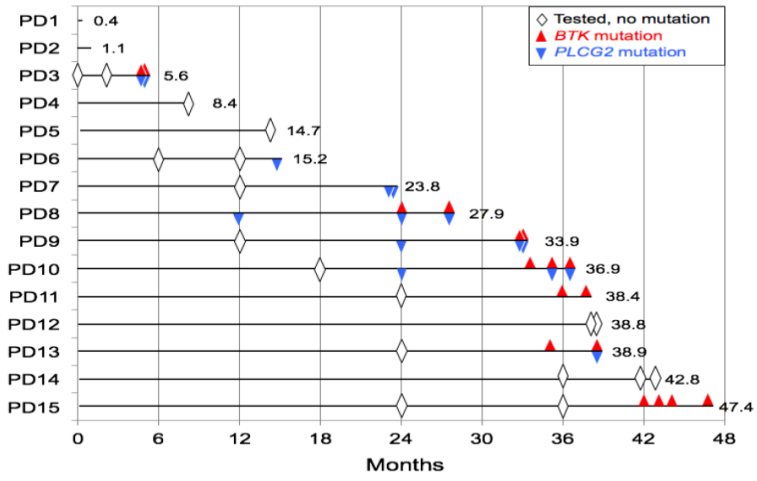
Integrating mutations: Time to first treatment



Rossi et al. Blood. 2013;121:1403.

76

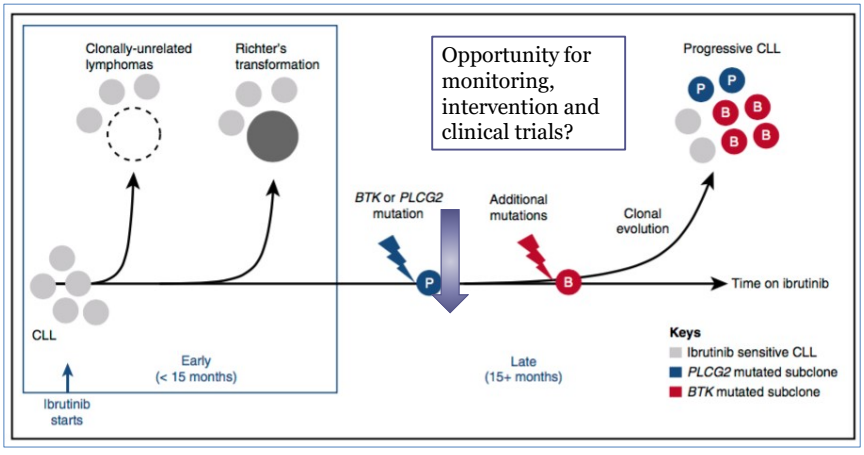
Risks for ibrutinib acquired resistance



- Mutations detected up to 15 mos b/f progression

Ahn et al. Blood. doi:10.1182/blood-2016-06-719294 77

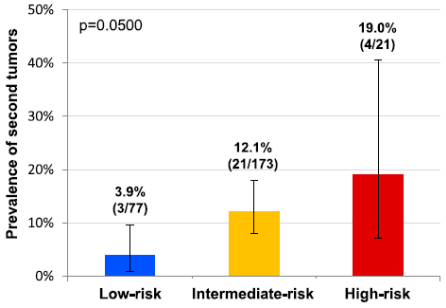
Science ⇔ Clinical Trials ⇔ Practice



Ahn et al. Blood. doi:10.1182/blood-2016-06-719294 78

Recognizing power of disease biology (biomarkers) vs therapy in adverse events

- In very favorable risk FCR-treated CLL, life expectancy matched normal general population
- Richter's syndrome still diagnosed in ibrutinib treated patients (including frontline)



Blood. 2015;126(16):1921

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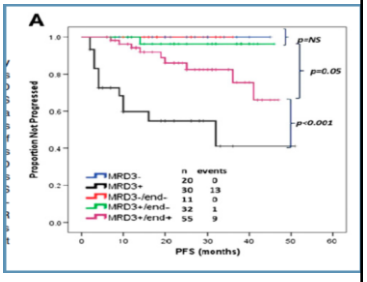
MRD neg & durable responses

- **MDACC FCR:** MRD marrow
  - Treated for 3-6 cycles, MRD bone marrow assessed at each
  - PFS similar by ending MRD status
    - 3 vs 6 cycles (didn't matter how much to get there)



JCO. 2012;30:980-988.
Blood. 2014;123:3727-3732.
Blood. 2015;126(16):1921-1924
Blood. 2016;127(3):303

80

MRD neg & durable responses

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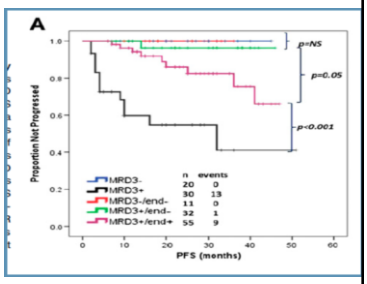
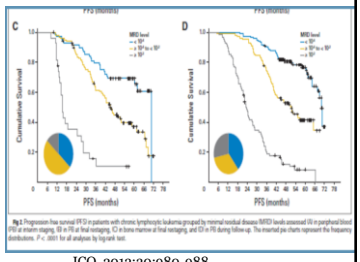


- **CLL8:** MRD on blood & marrow
  - Post treatment "low" MRD associated with longer PFS and OS
    - FCR vs. FC (didn't matter what to get there)
    - *But* more "low" MRD pts in FCR



JCO. 2012;30:980-988.
Blood. 2014;123:3727-3732.
Blood. 2015;126(16):1921-1924
Blood. 2016;127(3):303

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BCR/BCL2 Inhibitors: CRRs and MRD

- **Ibrutinib:**
  - Rel/Ref CRs: 0, 2%, 7%, 12%
  - Frontline CRs: 14%
    (23%-longer follow up)
  - MRD: ? As monotherapy
- **Idelalisib + rituximab:**
  - Rel/Ref CR: 0%
  - Frontline CRs: 19%
  - MRD: ? As monotherapy

Brander et al, iwCLL 2017
Lancet Oncol 2017; 18: 230

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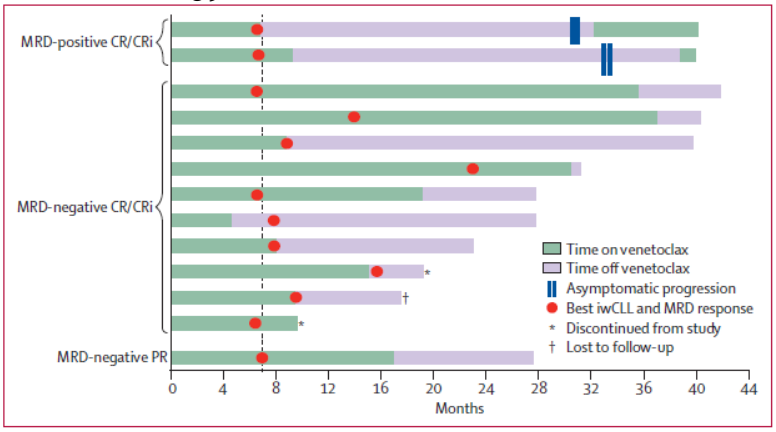
BCR/BCL2 Inhibitors: CRRs and MRD

- **Venetoclax + rituximab (n=49):**
  - Ability to stop therapy in CR or MRD-negative status and maintain
  - MRD- rate: 59%



Brander et al, iwCLL 2017
Lancet Oncol 2017; 18: 230

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Thank you for your attention, and thank you to our patients and care team members

www.pbs.com; national library of medicine

Danielle M. Brander, MD
Assistant Professor
Duke University
Division of Hematologic Malignancies & Cellular Therapy

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Living with Chronic Lymphocytic Leukemia (CLL)

LEUKEMIA & LYMPHOMA SOCIETY® fighting blood cancers — someday is today®

Q&A Session

Ask a question by phone:

- Press star (*) then the number 1 on your keypad.

Ask a question by web:

- Click “Ask a question”
- Type your question
- Click “Submit”

Due to time constraints, we can take only one (1) question per person. Once you’ve asked your question, the operator will transfer you back into the audience line.

Living with Chronic Lymphocytic Leukemia (CLL)

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SUPPORT RESOURCES

- **Online chats:** Online moderated chat forums: **www.LLS.org/chat**
- **What to ask:** Questions to ask your treatment team: **www.LLS.org/whattoask**
- **Free education materials: www.LLS.org/booklets**
- **Past CLL education programs: www.LLS.org/programs**
- **For information on leukemia: www.LLS.org/leukemia**
- **Information Resource Center:** Speak one-on-one with an Information Specialist who can assist you through cancer treatment, financial, and social challenges.
  - **E-MAIL: infocenter@LLS.org**
  - **TOLL-FREE PHONE: (800) 955- 4572**