LYMPHOME CANADA

CONFÉRENCIERS SPÉCIALISÉS
CONFÉRENCE TRAITEMENT
AIDE NATIONALE SUR APPUI
LE LYMPHOME ÉDUCATION
RÉSEAUTAGE LEADERSHIP
LES 15 ET 16 SEPTEMBRE 2017
BÉNÉVOLES MONTRÉAL (QC)
SOUTIEN AUX SURVIVANTS

CLL: disease specific biology and current treatment

Dr. Nathalie Johnson

Disclosures

- Consultant and Advisory boards
  - Roche, Abbvie, Gilead, Jansson, Lundbeck,Merck

- Research funding
  - Roche, Abbvie, Lundbeck

Outline

- CLL 101
  - Biology (unmutated vs mutated and TP53)
- Symptoms
- Diagnosis
- Treatment options
  - First line: chemotherapy vs ibrutinib
  - Relapse (see “future therapy session”)

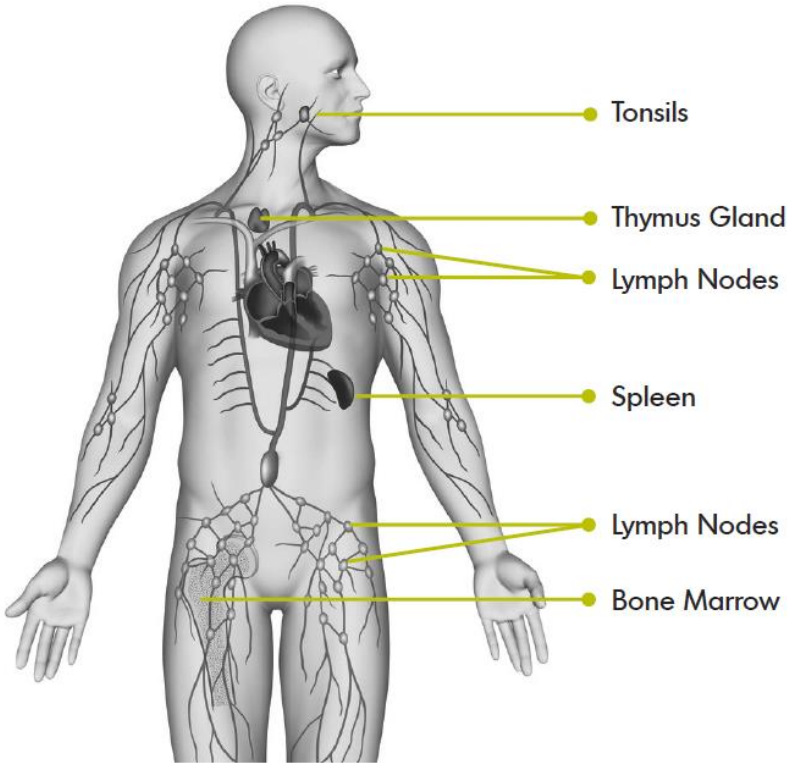
Chronic Lymphocytic Leukemia

Prolonged clinical course
"**C**hronic"

A particular type of blood cell – B lymphocyte
"**L**ymphocytic"

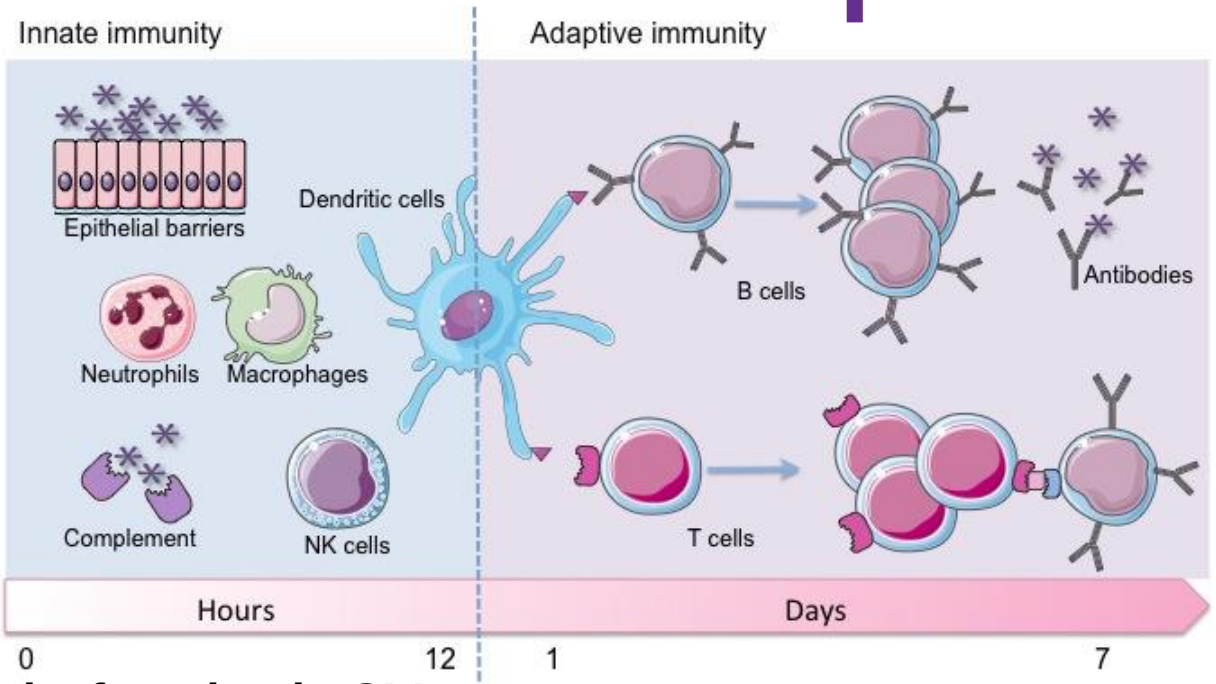
Cancer of white blood cells
"**L**eukemia" – white blood

Lymphatic system



LYMPHATIC SYSTEM

Cellular components of immune response



Immune dysfunction in CLL:

1) Decrease normal immune cell numbers

2) Abnormal immune function (auto-immunity)

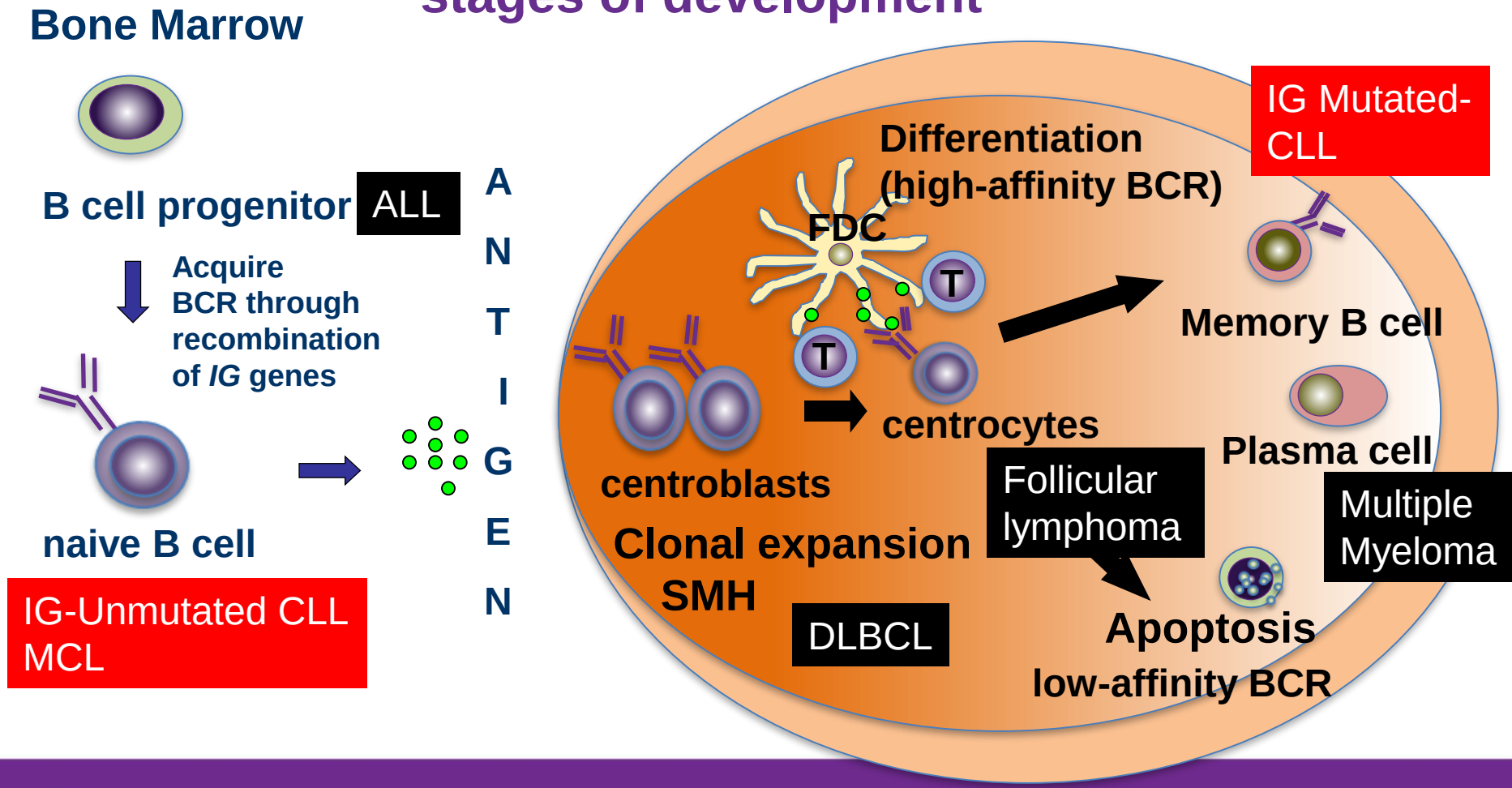
3) Immune side-effects from chemo and novel therapies

Curtesy of Lara a. Aqrawi, inspired by Abbas

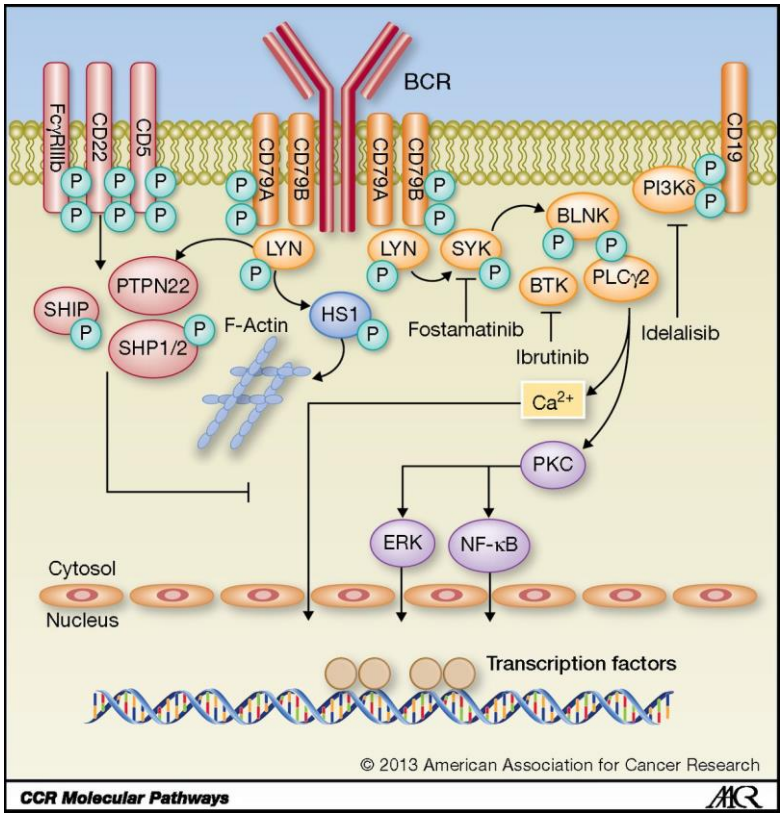
Causes of CLL

- We do not know what causes most cases of CLL.
- There is no way to prevent CLL.
- You can not catch CLL from someone else.
- In some families, more than one blood relative has CLL.

Difference between CLL and other B cell lymphomas: it highjack normal B cells at different stages of development



CLL cells depend on extra-cellular signals that are transmitted by the B cell receptor



Binding to the BCR provides a survival signal "feed me"

Important mediators that transmit BCR signals are:

BTK, the target of ibrutinib
PI3k, the target of Idelalisib

Symptoms

Symptoms from Low White Blood Cells

- Recurrent infections

Symptoms from Low Red Blood Cells

- Shortness of breath and fatigue

Symptoms from Low Platelets

- Bleeding

Other

- Symptoms from consequences of enlarged lymph nodes: may affect internal organs (kidneys- back pain, lungs- cough)
- “B symptoms”: fevers, night sweats and weight loss
- Profound fatigue

Complete blood count (CBC)

Hematology Reports

SPECIMEN: **3 cc EDTA BLOOD (Lavender Top)**

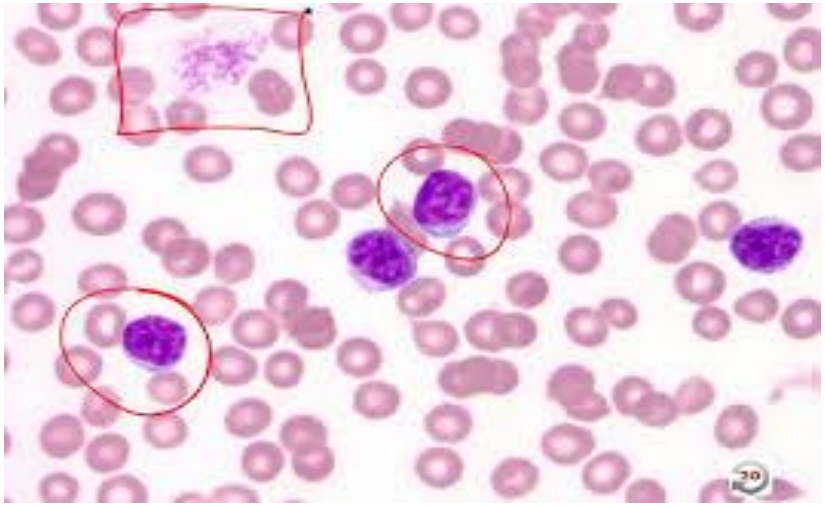
ANALYTE	RESULT			UNIT	REFERENCE RANGE
	LOW	NORMAL	HIGH		
Hemoglobin (Hb)	12.4			g/dl	13.7 - 16.3
Total RBC		6.4		x10^12/l	4.5 - 6.5
Hct	41			%	41.9 - 48.7
MCV	63			fl	75.0 - 95.0
MCH	19			pg	26.0 - 32.0
MCHC	30			g/dl	32.0 - 36.0
Platelet Count		240		x10^9/l	150.0 - 400.0
WBC Count (TLC)		7.7		x10^9/l	4.0 - 11.0
Neutrophils		59		%	40.0 - 75.0
Lymphocytes		34		%	20.0 - 45.0
Monocytes		03		%	2.0 - 10.0
Eosinophils		04		%	1.0 - 6.0

Impaired production of red blood cells, platelets and neutrophils

Lymphocytosis

No symptoms in 30-40% of people

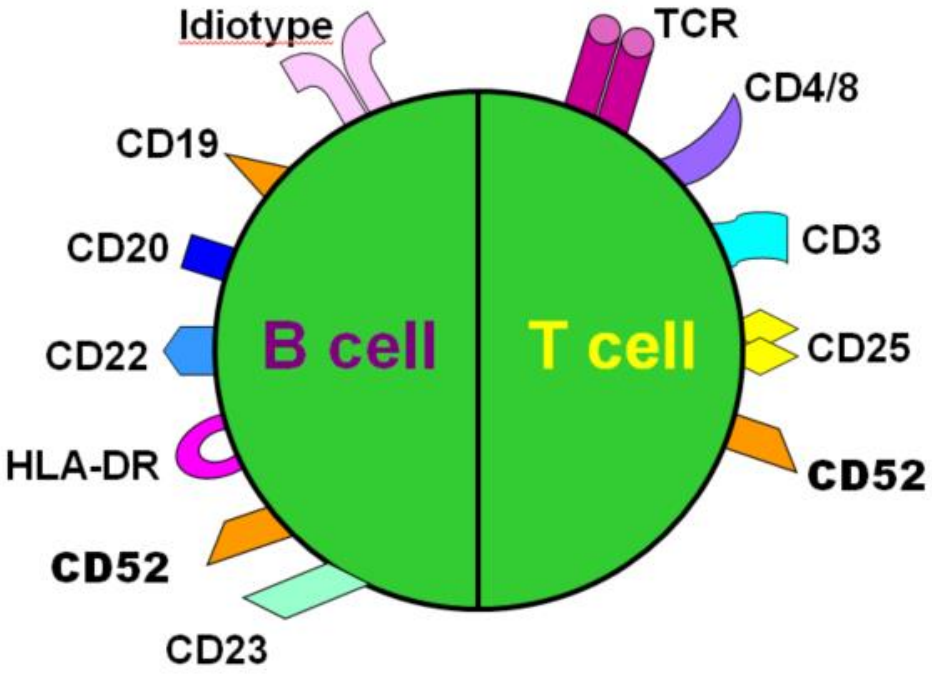
Peripheral blood smear



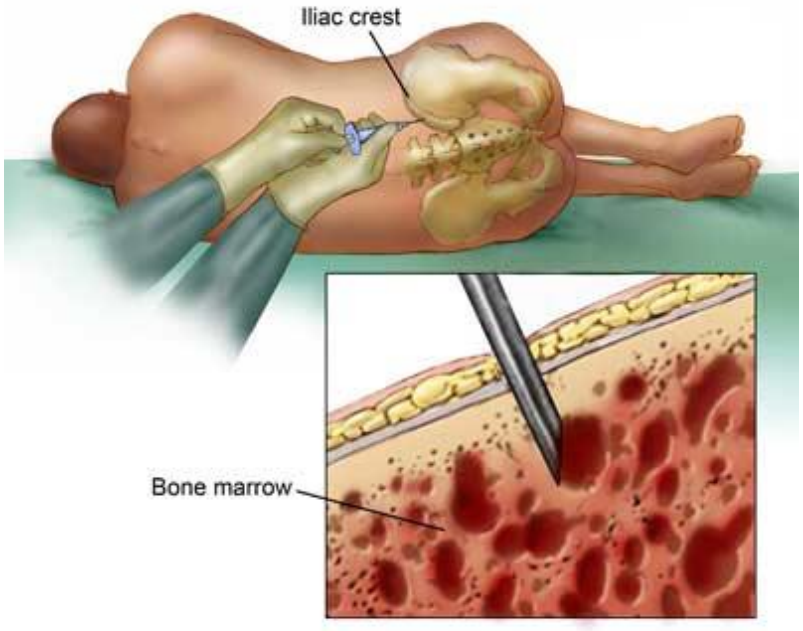
- Lymphocytosis
- Low platelets
- Size and shape of red blood cells
- Quantity of other immune cells (neutrophils)

Flow cytometry

- Read the cell's surface like a barcode
- Detect extremely low levels of CLL in blood or marrow
- CLL: CD19+, CD5+, CD200+, CD23+

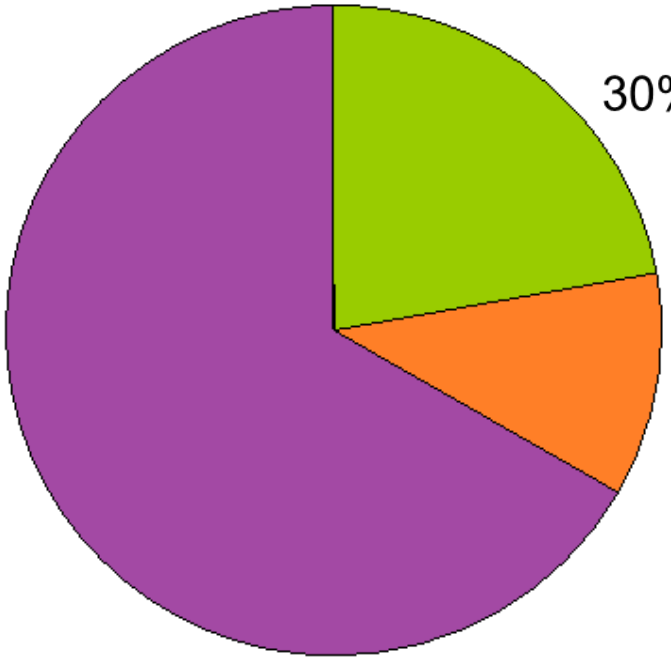


Assessment of bone marrow function in some patients



Disease progression

Majority → Median of 5 years without symptoms followed by progression and complications



30% → Disease free for years and years

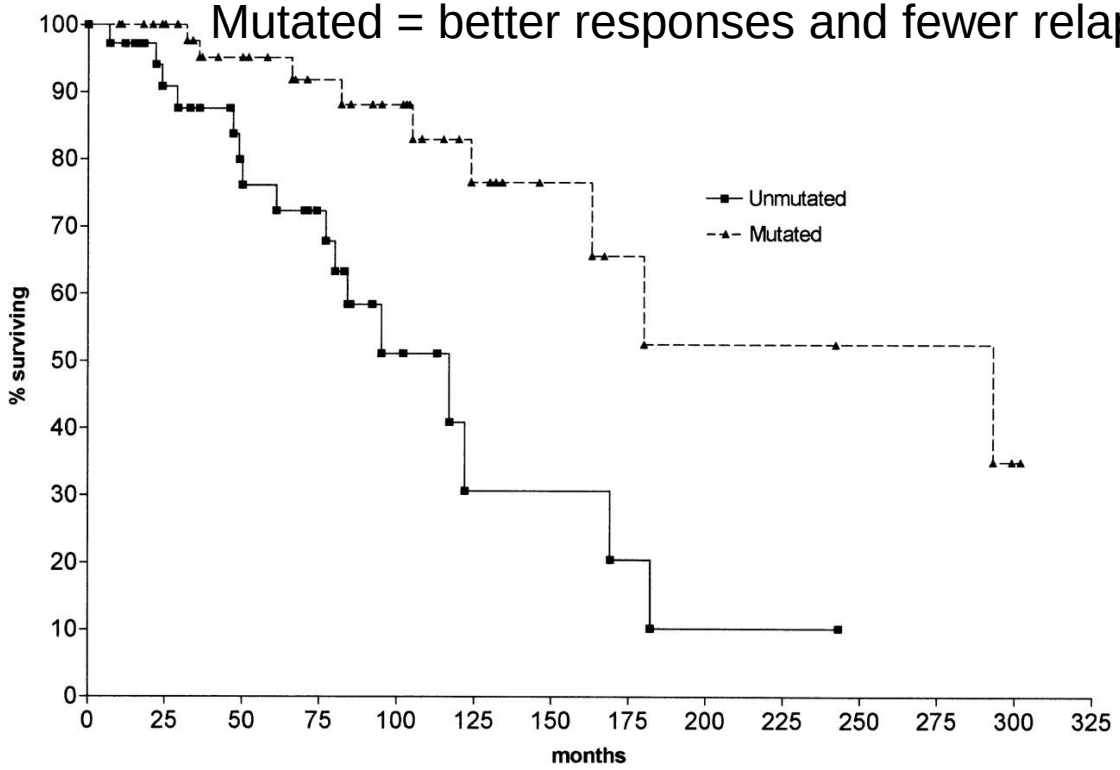
15 % → Aggressive disease from onset

Rai staging system

Rai Classification System			
Stage	**Description**	**Median Survival (Months)**	**Risk Status (Modified Rai)**
0	Lymphocytosis, lymphocytes in blood >15,000/mcL and >40% lymphocytes in the bone marrow	140	Low
I	Stage 0 with enlarged node(s)	100	Intermediate
II	Stage 0–1 with splenomegaly, hepatomegaly, or both	70	Intermediate
III	Stage 0–II with hemoglobin <11.0 g/dL or hematocrit <33%	20	High
IV	Stage 0–III with platelets <100,000/mcL	20	High

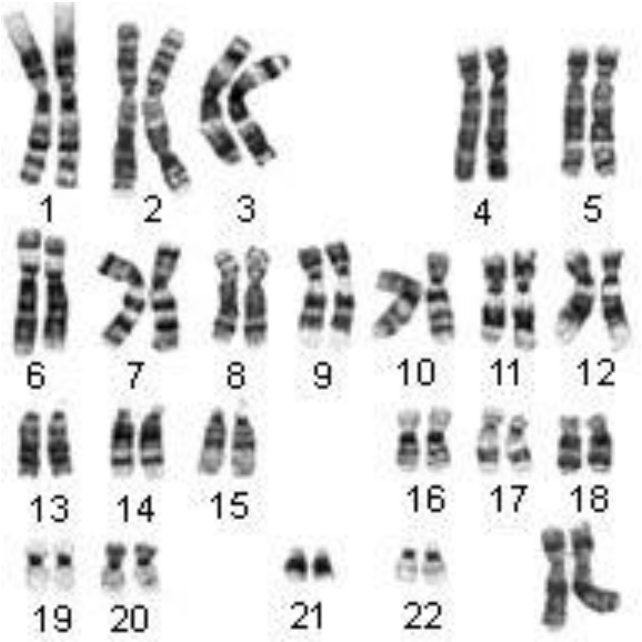
Immunoglobulin gene (IGVH) mutation status: Mutated is better than unmutated

Mutated = better responses and fewer relapses (top curve)



Hamblin et al. Blood, 1999

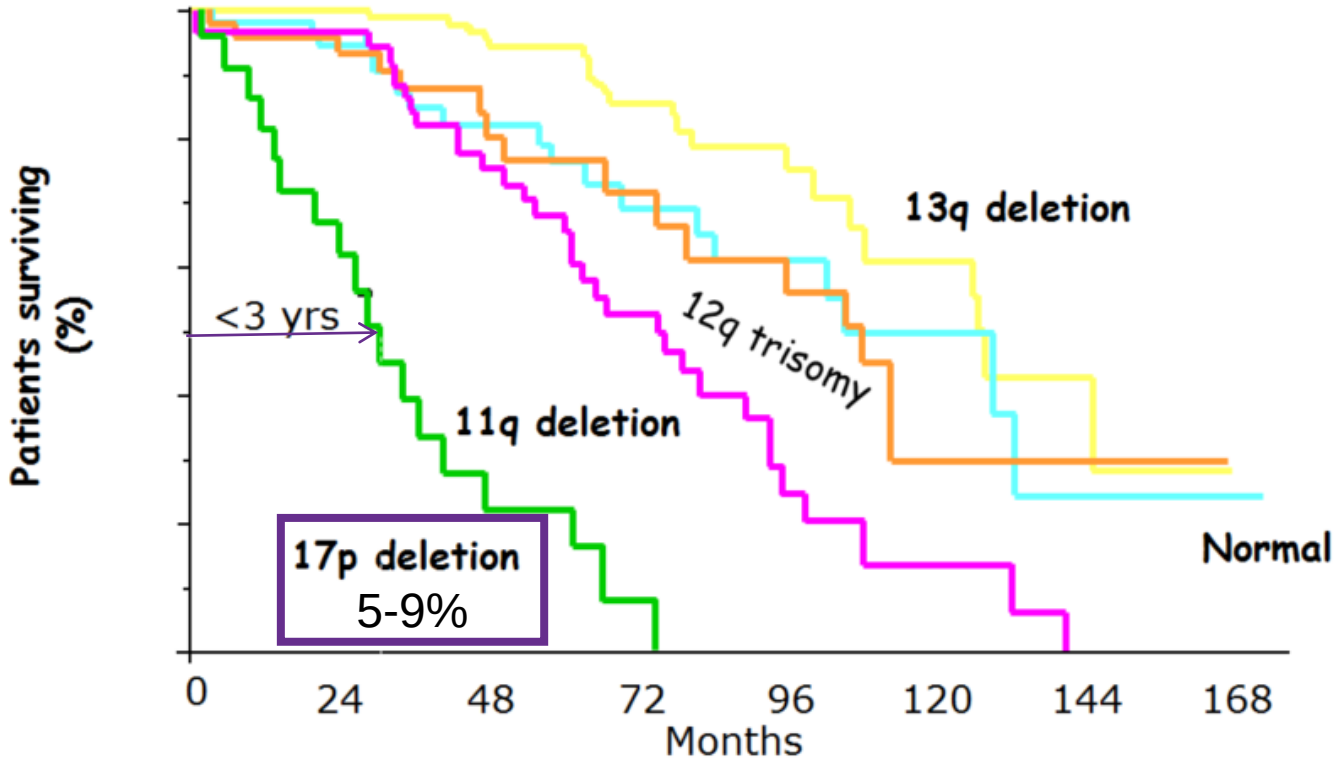
Cytogenetic status:
chromosome abnormalities are important predictors of response to chemotherapy



Normal karyotype: 46 chromosomes

Fluorescence in situ hybridization

Deletion in chromosome 17p (TP53 gene) is the most important predictor of response



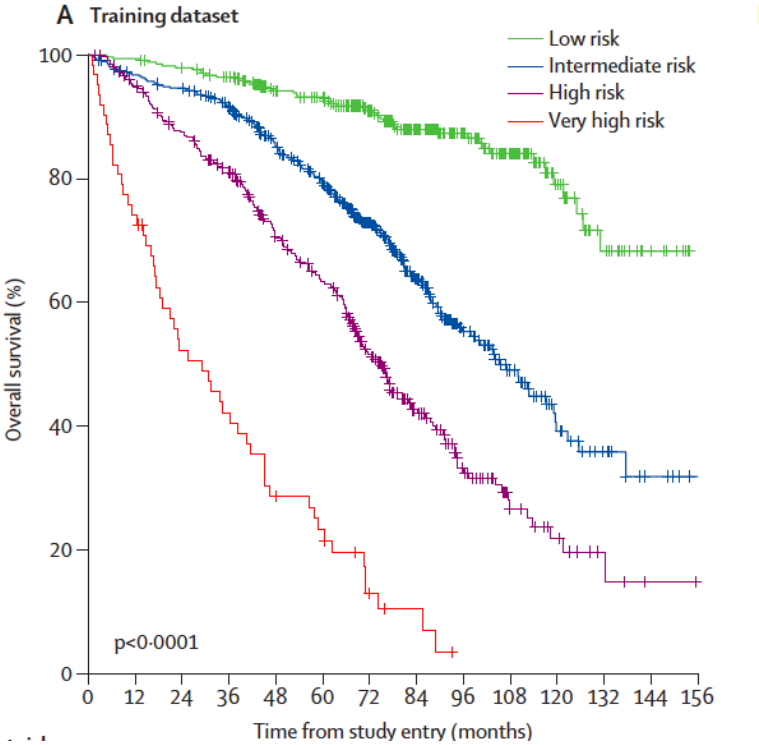
Döhner H, et al. *N Engl J Med*. 2000;343:1910-1916.

International prognostic index for CLL

3472 treatment-naive CLL patients treated on 13 clinical trials 1950-2010

Risk factors:

17p del(TP53 mut)	4 pts
IGVH unmutated	2 pts
B2M > 3.5	2 pts
Rai > 1 to 4	1 pt
Age > 65 yo	1 pt



10 year overall survival

Low risk (0-1) = 79%

Intermed (2-3) = 39%

High (4-6) = 22%
Very high (7-10)= 4%

International CLL-IPI working group; Lancet Oncology 2016

Richter Transformation: poor outcome

- 1928 Maurice Richter
- Rapid clinical change with the rise of a biologically aggressive sub clone of large lymphoid blasts
  - Diffuse Large B Cell Lymphoma
  - Hodgkin Lymphoma
  - T Cell Lymphomas
- Incidence varies in literature (2-15%)
- 2-4 years from diagnosis
- Risk poorly understood

Principles of CLL Treatment

- Establish treatment goals
- Establish prognostic factors (genetics)
- Decide on
  - When to initiate therapy (observation initially)
  - Standard therapy: based on consensus guidelines from prior phase 3 randomized clinical trials and availability of drugs
  - Clinical trials: novel therapies or novel combination therapies not otherwise available as standard of care

“Watch and Wait”

- Synonyms: “Watch and Worry”. “Observation” or “deferred therapy”
- Suitable for patients with no symptoms or organ dysfunction
- Rationale:
  - No improvement in overall survival to start therapy before needed
  - Chemotherapy can induce symptoms (side effects) in an asymptomatic patient
  - The best responses to a regimen occur with the first exposure to the drugs (i.e. less effective the second time), therefore usually reserve best treatments when needed.

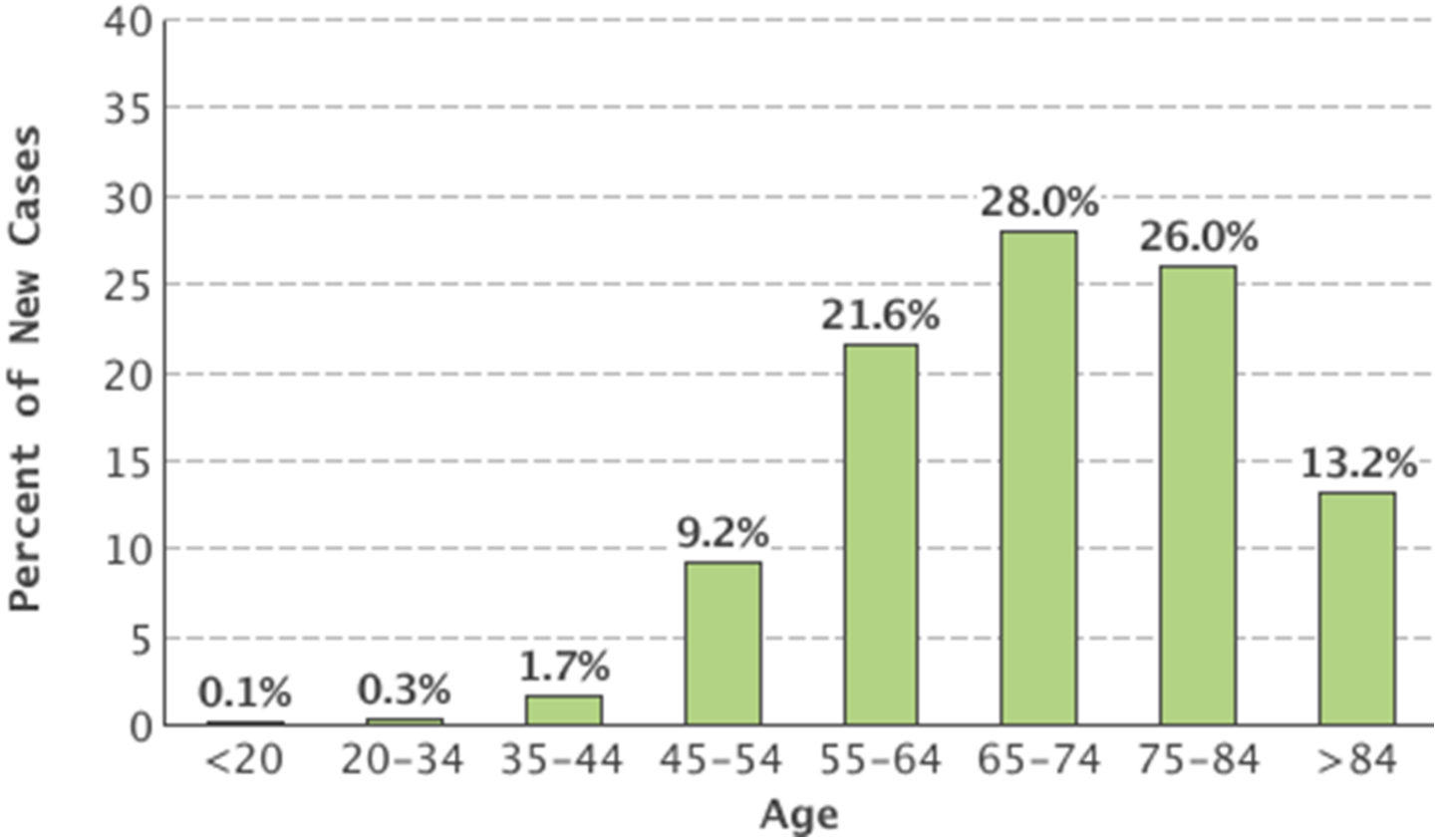
Supportive Care

- Promote wellbeing
- Vaccination
  - Annual flu shot
  - Vaccine record
- Majority of patients with CLL will experience serious infection. Keep track of your infections & how long they last.
- Stop smoking, avoid tanning beds, wear sunscreen, check your skin.

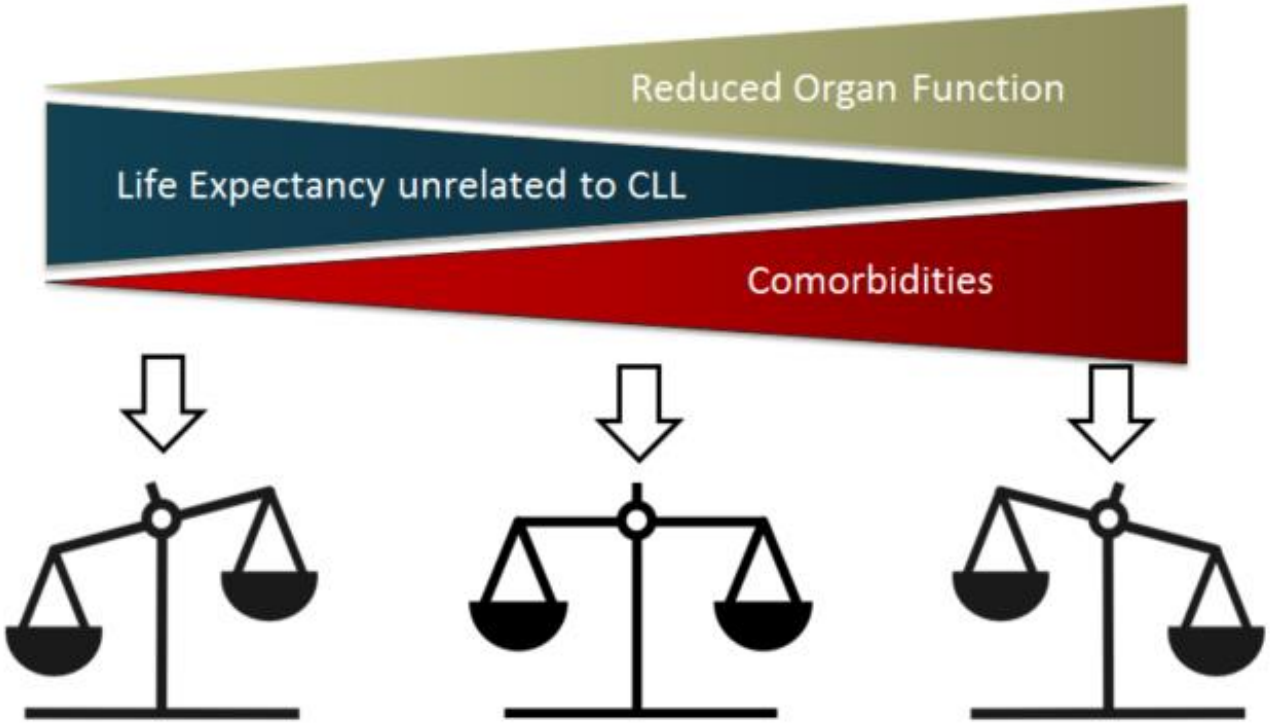
Indications for Treatment

- **Symptoms**
  - **Severe fatigue, fevers, night sweats, pain**
- **Organ dysfunction**
  - **Marrow dysfunction, nodes compressing organs**
- **Rapid lymphocyte doubling time < 6 months**
- **Complications of CLL not responding to therapy**
  - **Auto-immune hemolytic anemia**

Age of diagnosis affects treatment choice

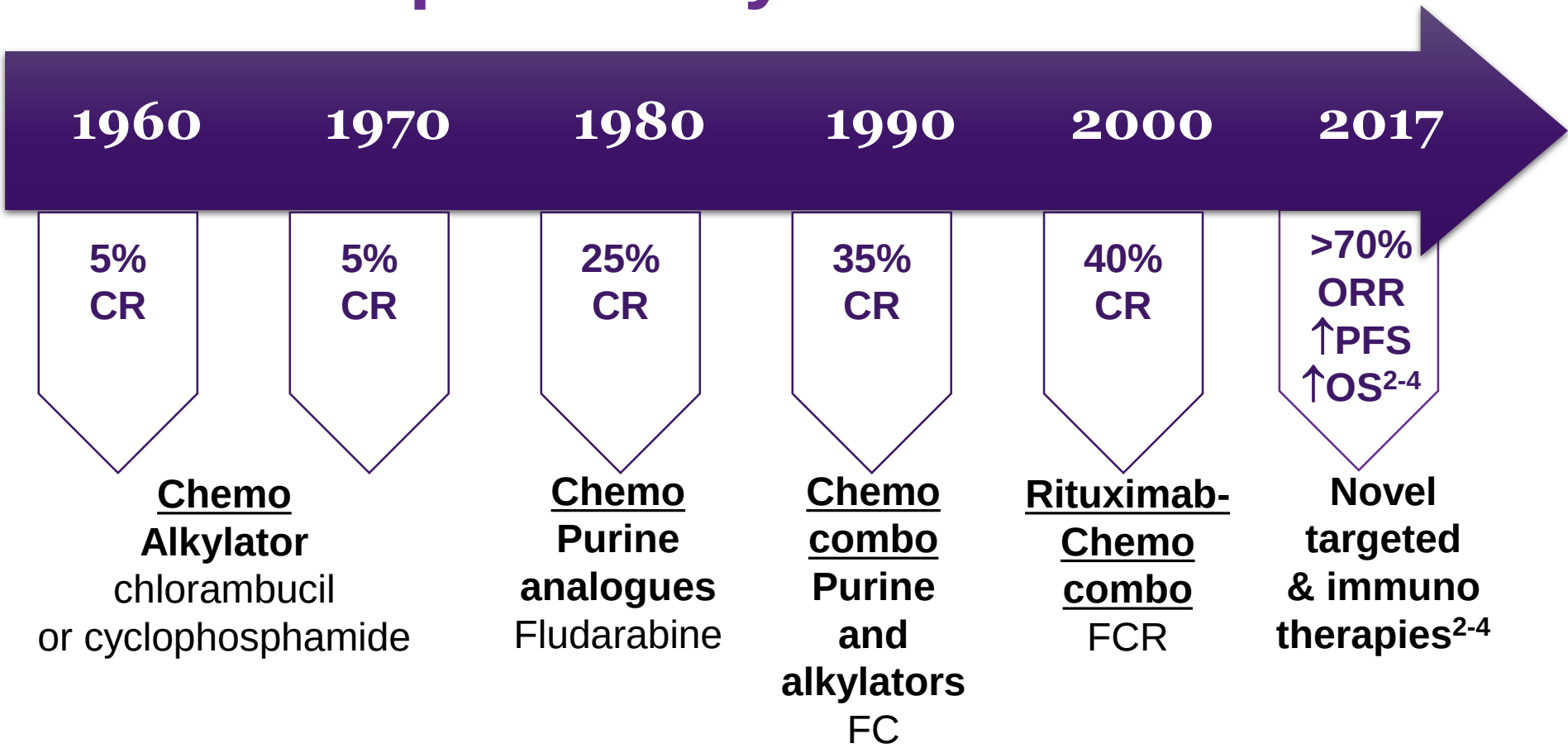


Establish goals of therapy



PATIENTS:	**FIT**	**UNFIT**	**FRAIL**
GOAL	**DEEP REMISSION**	**BALANCE EFFICACY/TOXICITY**	**DO NO HARM**

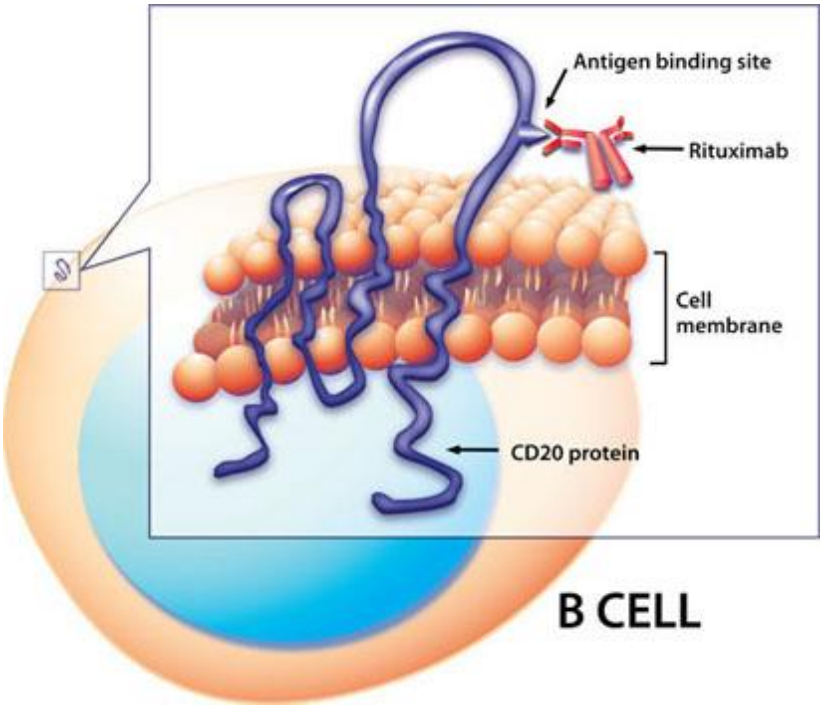
CLL: Treatment Options have improved by Decade

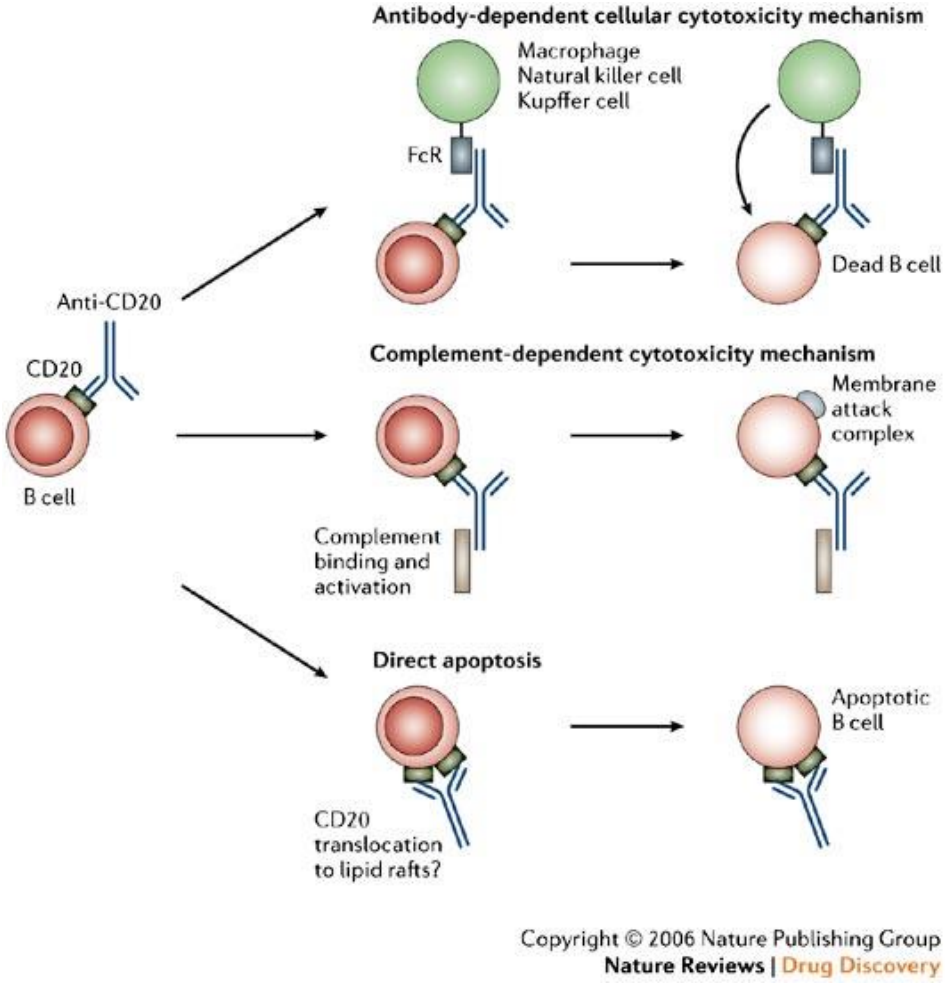


1. Adapted from Kay NE. *Blood*. 2006;107:848.
2. Goede V, et al. *N Engl J Med*. 2014;370(12):1101-1110.
3. Byrd JC, et al. *N Engl J Med*. 2013 Jul 4;369(1):32-42.
4. Furman RR, et al. *N Engl J Med*. 2014;370(11):997-1007.

CR, complete response;
PFS, progression-free survival;
ORR, overall response rate;
OS, overall survival.

Rituximab

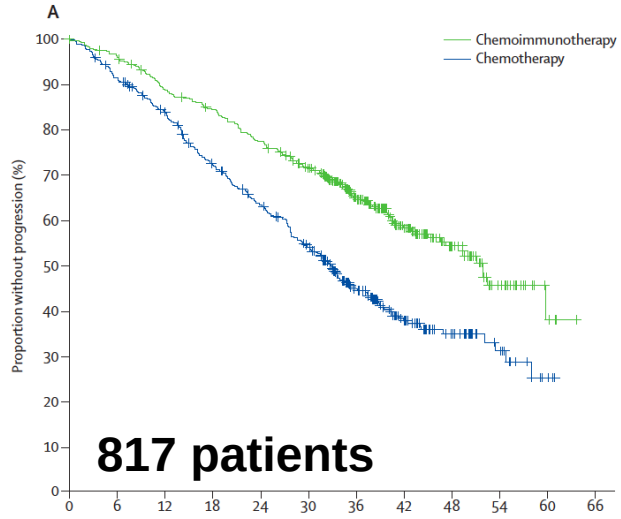




FIT and < 65 years old : FCR fludarabine, cyclophosphamide and rituximab

CLL8 trial

FCR significantly better than FC for progression-free and overall survival



Definition of FIT= Physically active, no health problems and normal renal function but only ~25% of CLL patients meet these criteria

Efficacy of FCR:

Complete remission: 45%

Remission duration: 4-5 years (average-all)

Toxicity of FCR:

60-80% get at least one grade 3-4 toxicity

Short term: neutropenia, infections (25%)

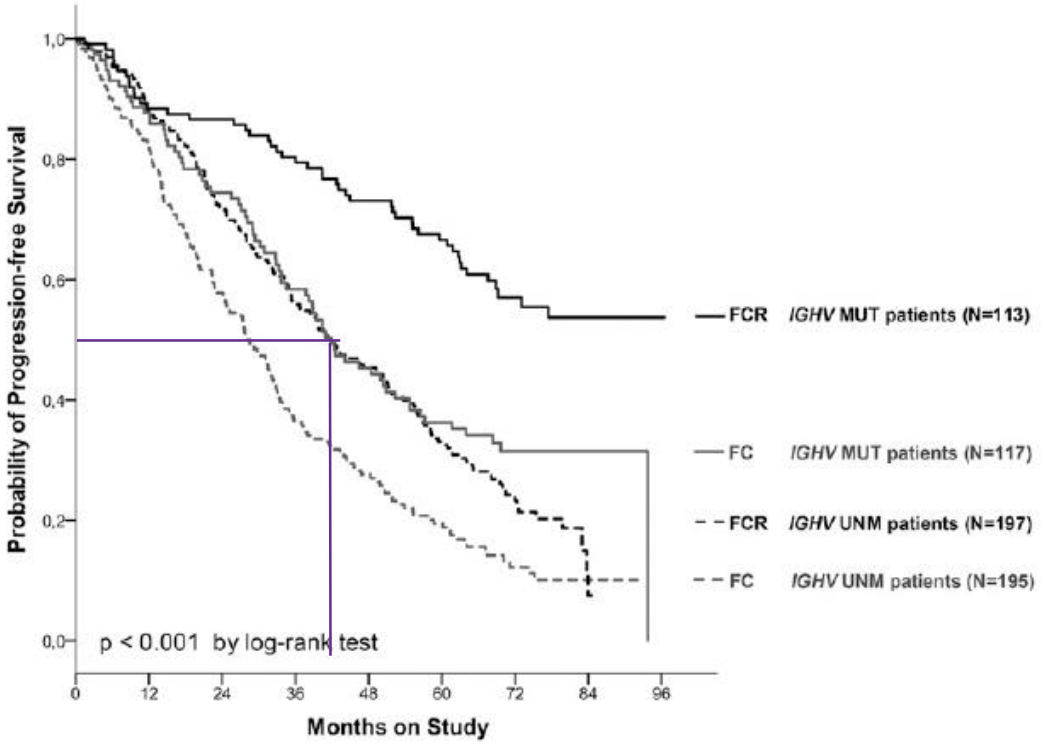
Treatment related mortality (2-5%)

20% don't finish all 6 courses

Long term toxicity: 15% (5% MDS/AML)

Hallek M, et al. *Lancet*. 2010;376(9747):1164-1174.

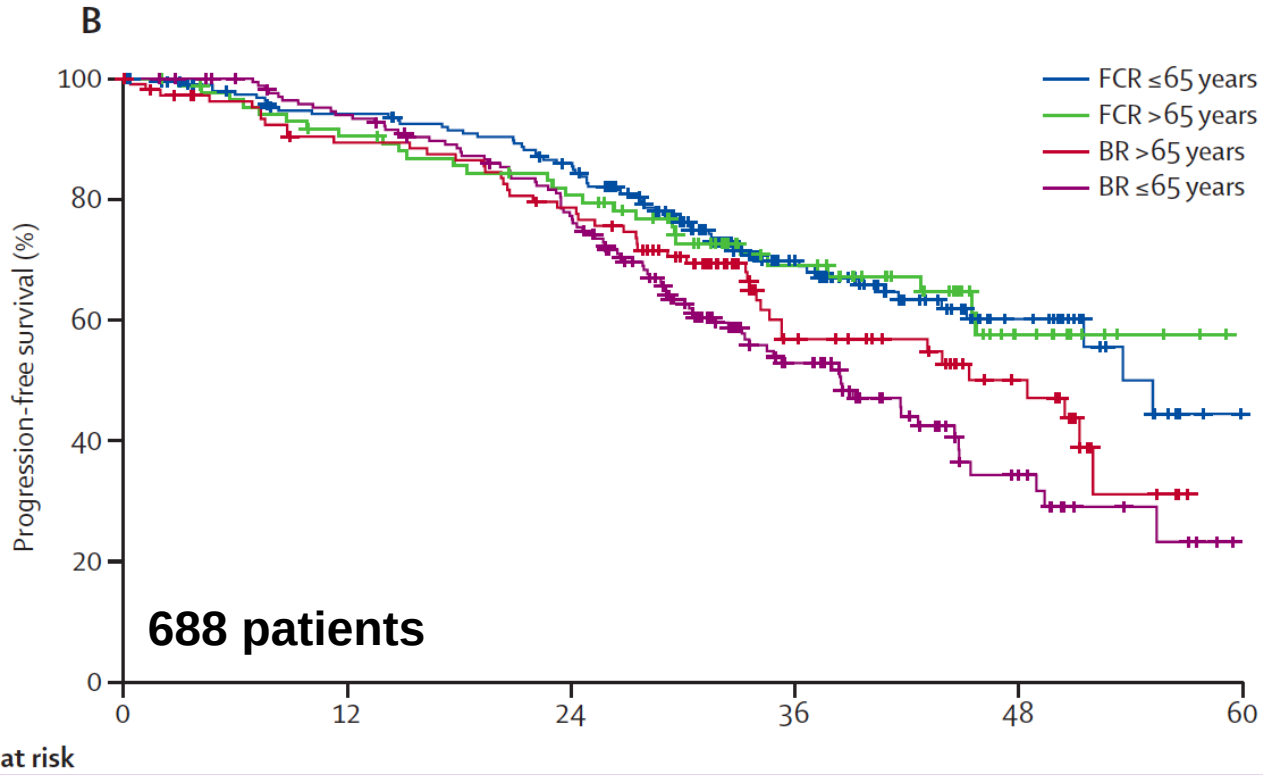
Long term survival with FCR for IGVH mutated patients: ~60% are still in remission after 8 years



Median remission duration for unmutated < 4 years

Fisher et al. Updated results from the CLL8 trial. Blood 2016

FIT and > 65 years old or UNFIT: bendamustine and rituximab (BR)



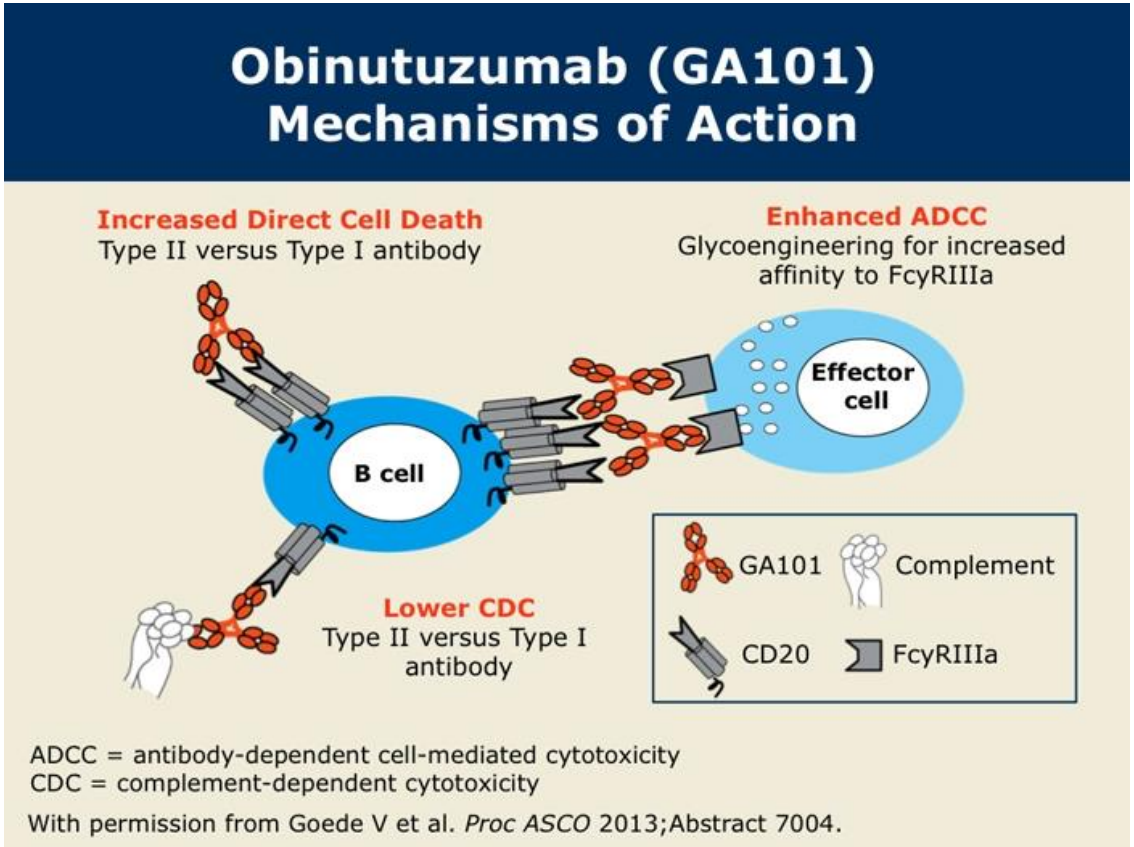
Definition of UNFIT:
Age > 70 or younger patients with co-morbidities

CLL10 trial

FCR is better than BR except in > 65 year old where BR is as effective but less toxic than FCR

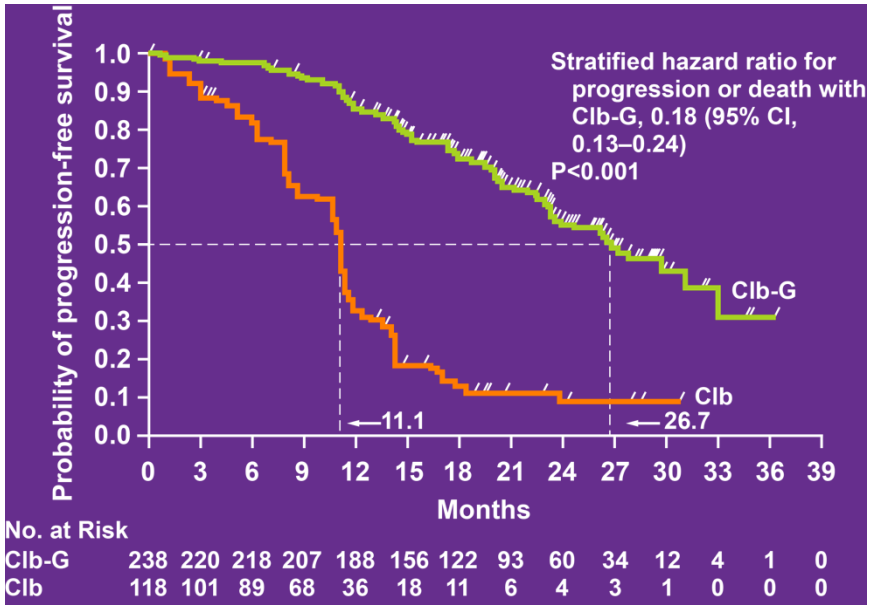
Hallek M, et al. *Lancet*. 2010;376(9747):1164-1174.

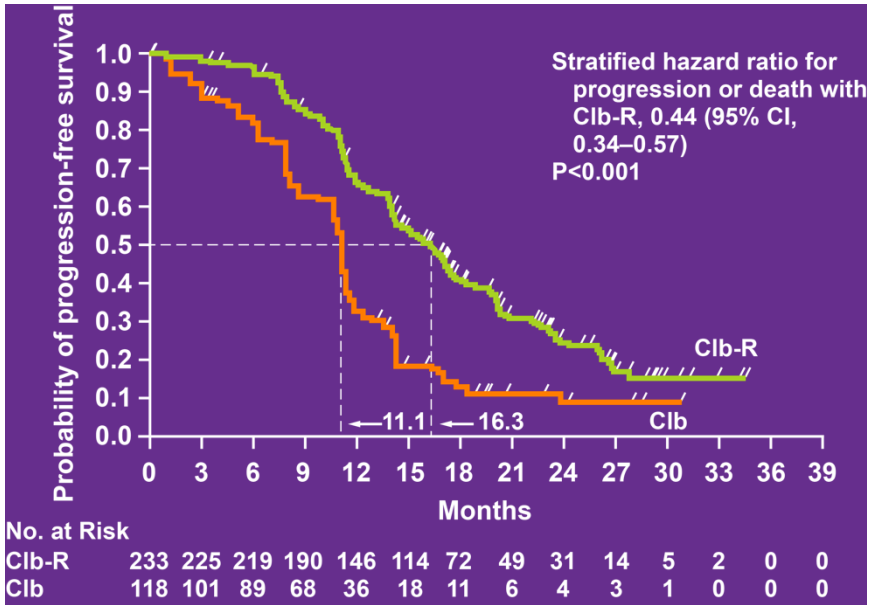
Obinutuzumab: novel anti-CD20 with increased direct cell death



FIT and > 65 years old or UNFIT: chlorambucil and obinutuzumab

CLL 11 trial: obinutuzumab + chlorambucil or rituximab + chlorambucil vs chlorambucil alone

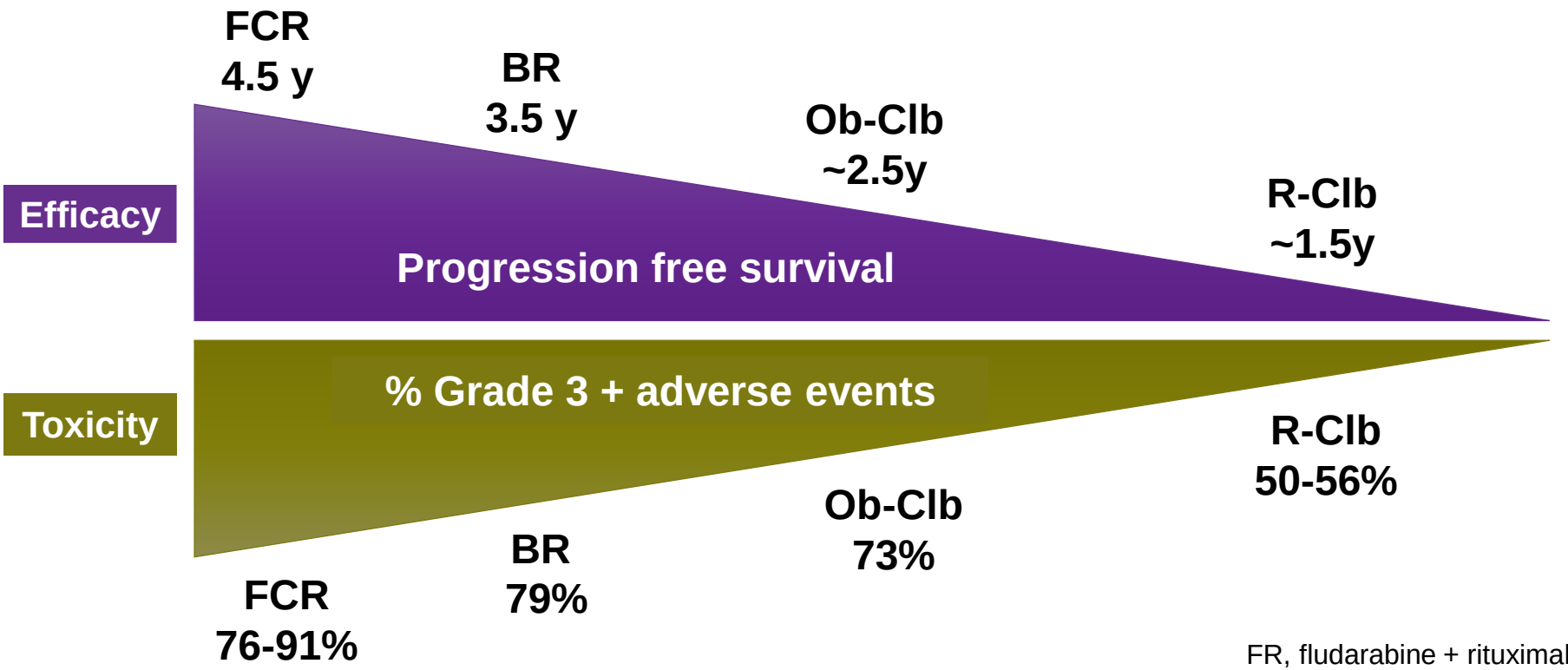




Goede V, et al. *N Engl J Med*. 2014;370(12):1101-1110.

CI, confidence interval; Clb, chlorambucil alone; Clb-G, chlorambucil + obinutuzumab; Clb-R, chlorambucil + rituximab.

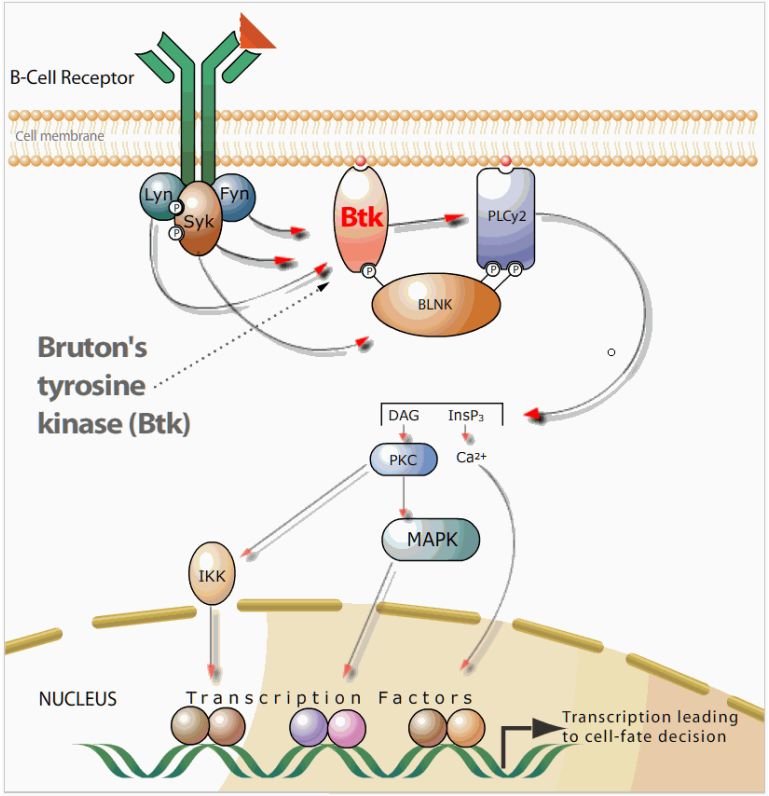
The Balance Between Efficacy and Safety in Front Line CLL



FR, fludarabine + rituximab;
FC, fludarabine + cyclophosphamide;
Ob-Clb, obinutuzumab + chlorambucil;
R-Clb, rituximab + chlorambucil.

Owen C, et al. *Clin Lymphoma Myeloma Leuk*. 2015;15(6):303-313.

Ibrutinib inhibits BTK downstream of the B cell receptor

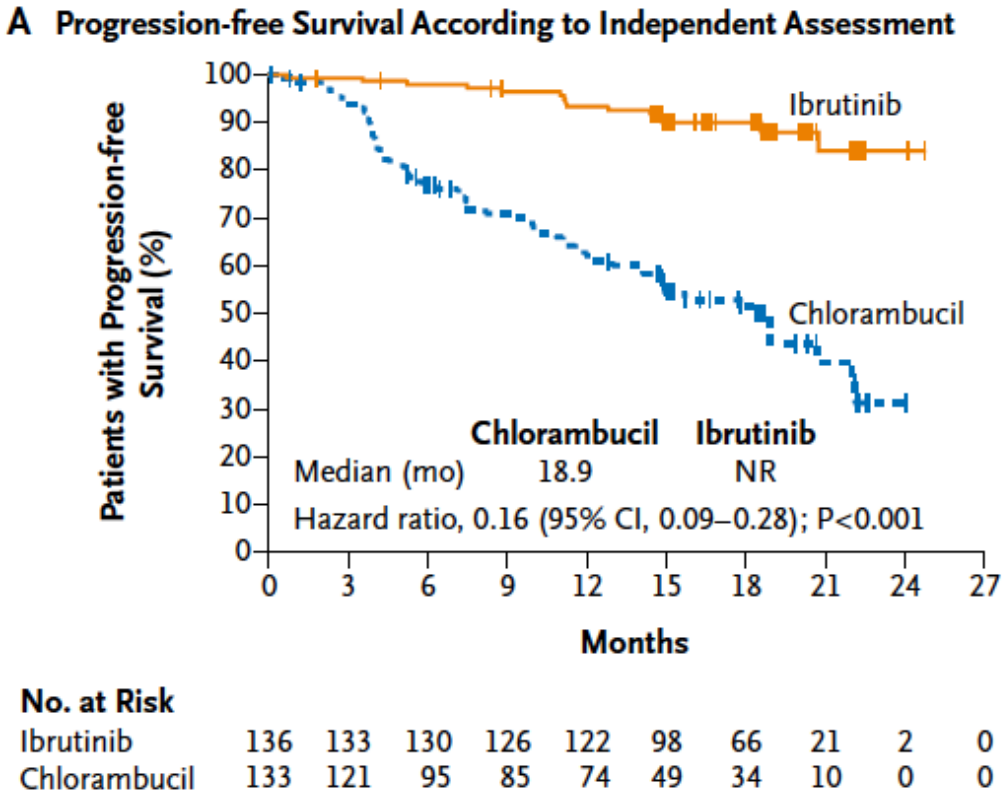


Resonate 17 trial: Ibrutinib is active in 17p-deleted CLL

- Rationale: median progression free survival for 17p-del is 11 months with FCR chemotherapy
- Resonate 17 enrolled 144 patients with 17p-del. relapsed CLL who received ibrutinib 420 mg daily
- Overall response 83% (64% PR)
- 2 year progression free survival: 63%
- Reasons for stopping ibrutinib:
  - Disease progression: 24%
  - Toxicity:17%
- Severe infections: 30%
- Major bleeding: 8%

O'Brien et al. Lancet Oncol 2016;10:1409-1418

Resonate 2 trial: Ibrutinib improves progression free and overall survival compared to chlorambucil in elderly patients



Excluded 17p del CLL

Burget et al. NEJM 2015

Ibrutinib needs to be taken daily
Overall response of 71% but only ~5% achieve a complete response

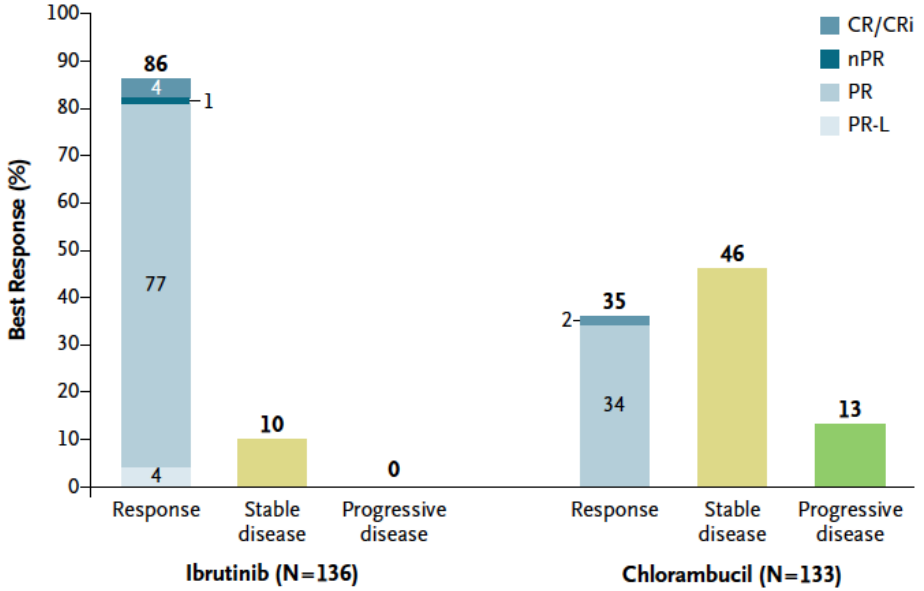
Ibrutinib inhibits 19 other kinases and can have serious side effects:

< 10 % patients in trials
-Cardiac arrythmias (10%)
-Major bleeding (7%)
--Hypertension (14%)

Opportunistic infections
Arthralgias
Rash
Edema

B Best Response

Overall Response Rate	Ibrutinib	Chlorambucil	Rate Ratio (95% CI)	P Value
	% of patients			
With PR-L	86	35	2.42 (1.91–3.07)	<0.001
Without PR-L	82	35	2.32 (1.82–2.95)	<0.001



Burget et al. NEJM 2015 and Brown et al. JCO 2017

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COMMENTS AND CONTROVERSIES

Chemoimmunotherapy Is Not Dead Yet in Chronic Lymphocytic Leukemia

Jennifer R. Brown, *Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA*
Neil E. Kay, *Mayo Clinic, Rochester, MN*

"Thus, although the Food and Drug Administration has approved ibrutinib for any line of therapy in any age CLL patient, we urge significant caution in its widespread adoption for frontline therapy, particularly in young, fit patients with a long life expectancy in whom we have no data on frontline ibrutinib and who recently have been suggested to have a higher-risk of relapse."

Summary of treatment options for patients with untreated CLL in Canada (2017)

- FCR is considered the standard of care for patients who are young, physically fit (25% of patients)

- If ineligible for FCR:
  - BR for all patients ≥ 65 years and fit
  - Chlorambucil-obinutuzumab for unfit patients or fit ≥ 65 years
  - Ibrutinib for patients with del 17p or unable to tolerate chemo-immunotherapy
  - Clinical trial