LYMPHOMA CANADA | LYMPHOME CANADA

CLL & SLL: Current Management & Treatment

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Chronic Lymphocytic Leukemia

Prolonged clinical course
"**C**hronic"

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

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

Small Lymphocytic Lymphoma

Prolonged clinical course
"**S**mall"

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

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

Same disease. Different location.

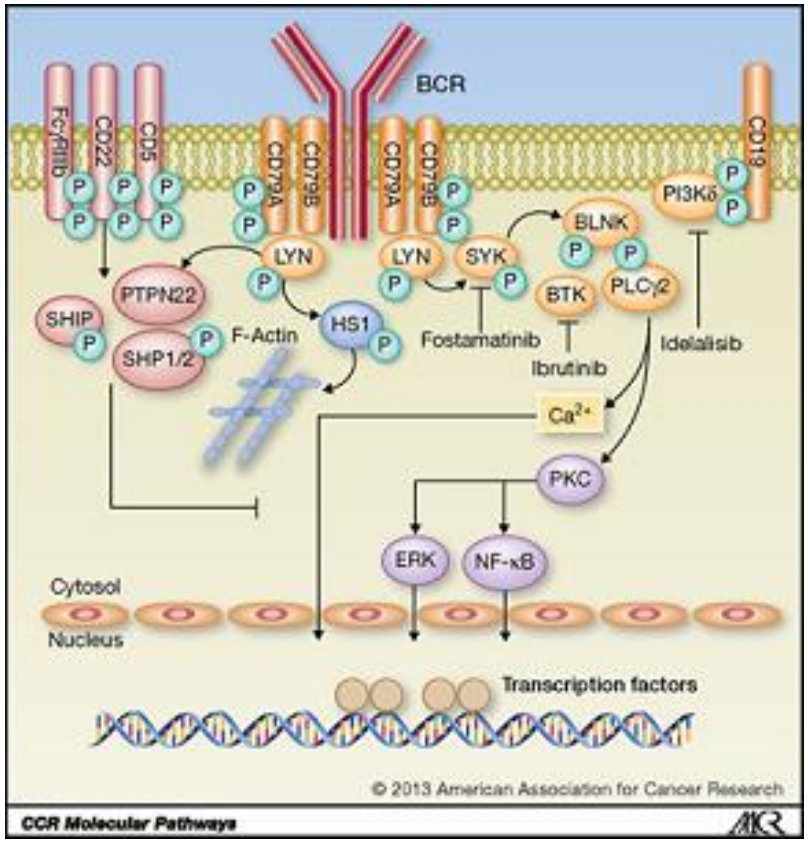
CLL & SLL look the same under a microscope.

If more cancer cells are in the lymphatic system: SLL

If more cancer cells are in the blood: CLL

We refer to both as CLL in this presentation unless there is something specific where we have to distinguish between the two.

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

Causes

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

Symptoms

Symptoms from low white blood cells

- Recurrent infections

Symptoms from low red blood cells (anemia)

- Shortness of breath and fatigue

Symptoms from low platelets

- Bleeding or bruising

Other

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

Complete blood count (CBC)

Hematology Reports

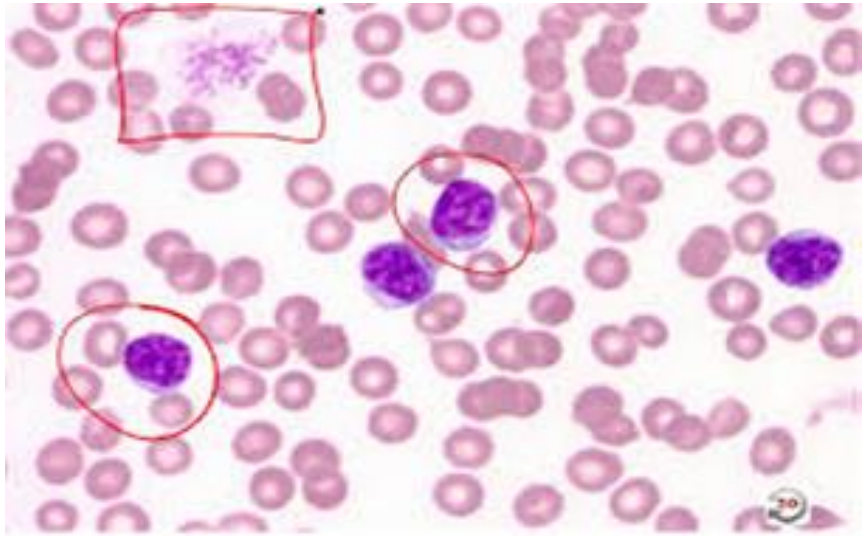
SPECIMEN: **3 cc EDTA BLOOD (Lavender Top)**

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

lymphocytosis →

No symptoms in 30-40% of people

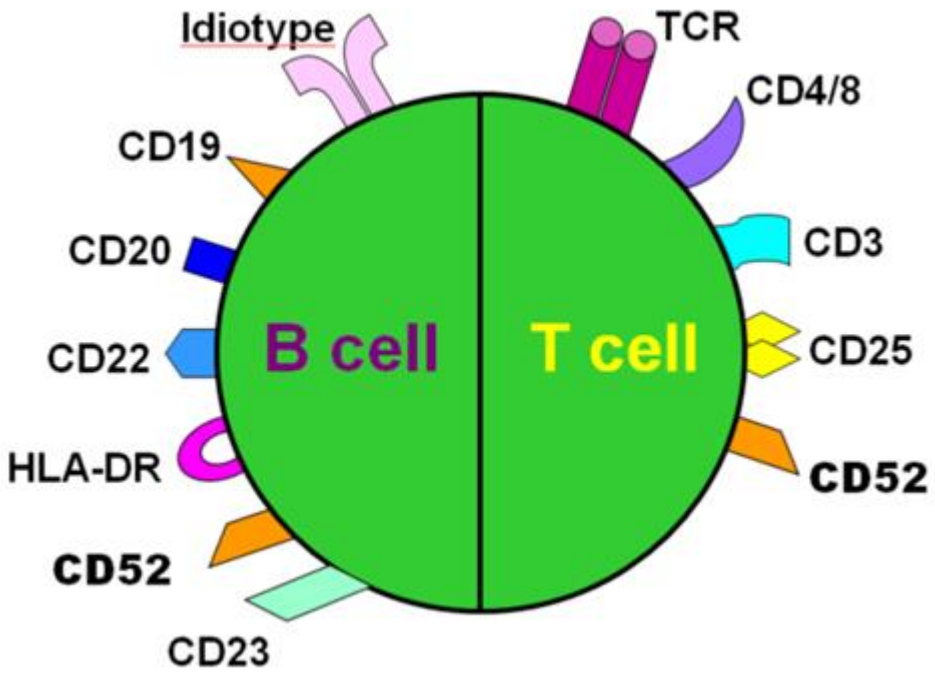
Peripheral blood smear



- Lymphocytosis
- “Smudge” cells

Flow cytometry (a blood test)

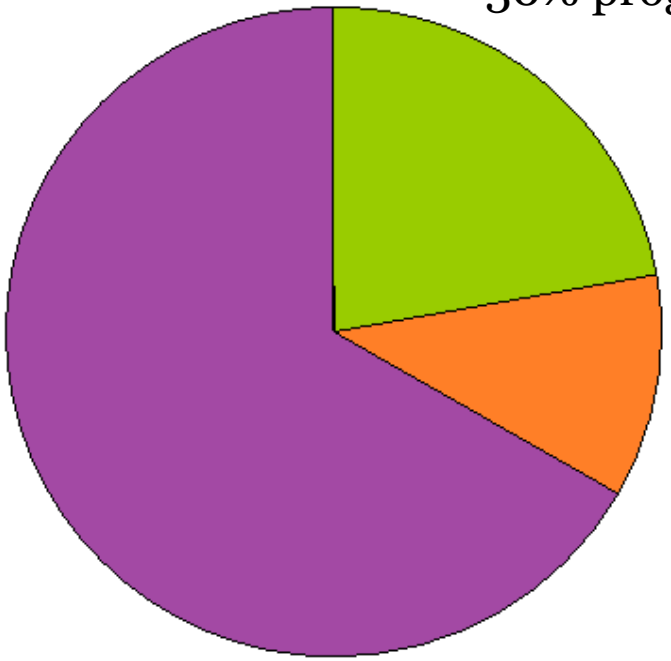
- Reads the cell's surface like a barcode
- Detects extremely low levels of CLL in blood (or marrow)
- CLL: CD19+, CD20+, CD200+, CD23+, CD5+



How CLL may progress over time

30% progression-free for years and years

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



15 % → Aggressive disease from onset

Rai Staging System

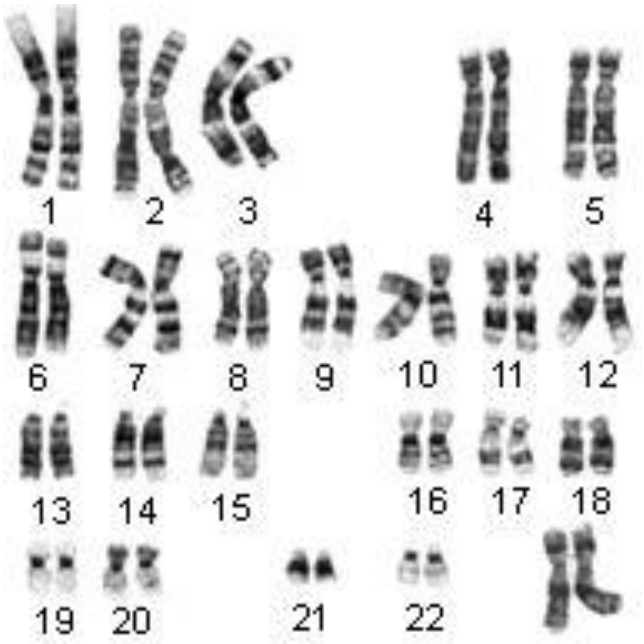
Rai Classification System			
Stage	**Description**		**Risk Status (Modified Rai)**
0	Lymphocytosis, lymphocytes in blood >5.0 x 109/L		Low
I	Stage 0 with enlarged node(s)		Intermediate
II	Stage 0–I with enlarged spleen, enlarged liver, or both		Intermediate
III	Stage 0–II with anemia (hemoglobin <110 g/L)		High
IV	Stage 0–III with low platelets (<100,000)		High

Adapted from Hallek M, et al. *Blood*. 2008;111(12):5446–5556.

Immunoglobulin gene mutation status (a research blood test)

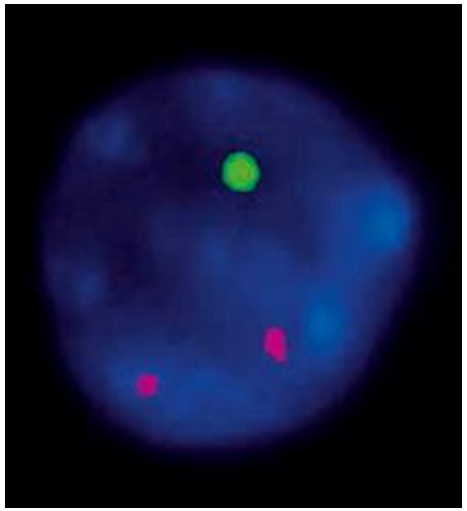
-Also called V-gene mutational status
-A given patient's CLL can have a mutated or unmutated V gene test result
-It stays the same way throughout the years
-The CLL may behave more aggressively if it is unmutated
-Currently remains a research test used mainly in clinical trials only

FISH status:
chromosome abnormalities can be predictors of response to some treatments



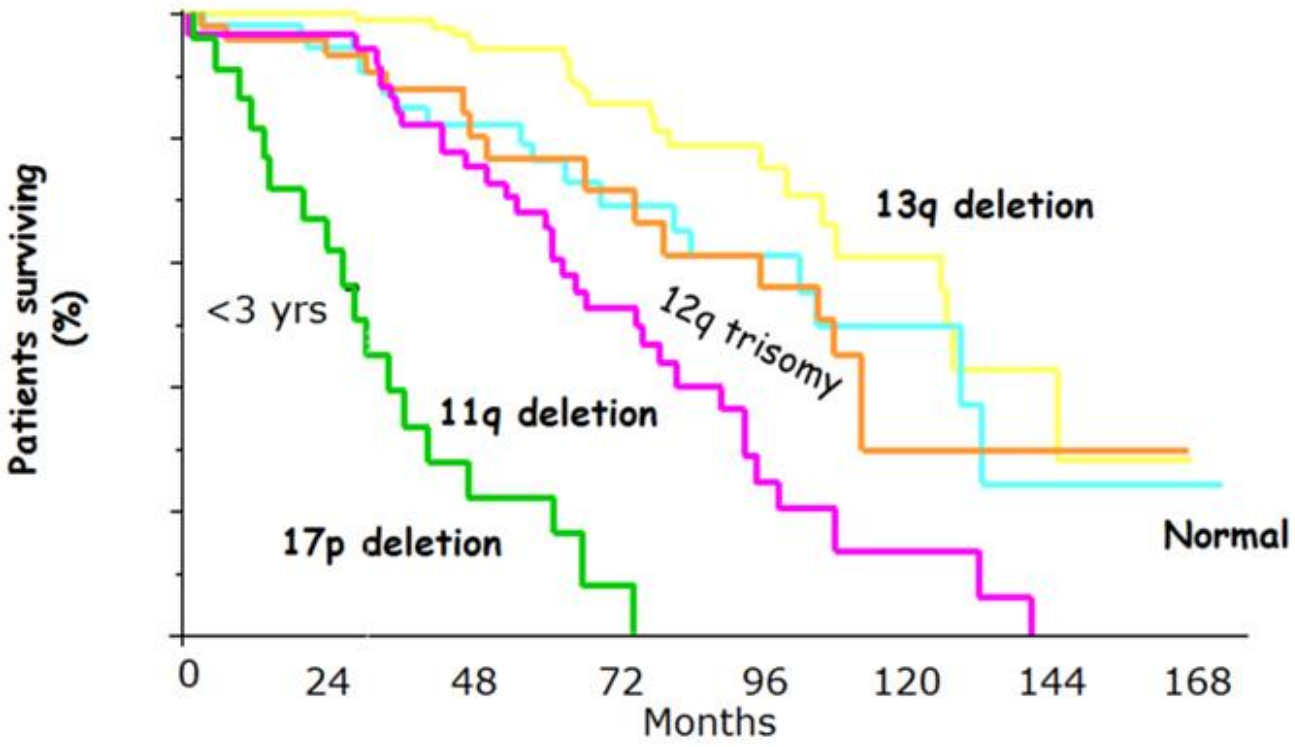
Normal karyotype: 46 chromosomes

Missing one green signal:
"deletion" of a chromosome arm



Fluorescence in situ hybridization

Deletion in chromosome 17p (TP53 gene) is the most important predictor of response – but we now have effective therapies for this



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

Richter's Transformation: more aggressive than CLL

- 1928 Maurice Richter
- Rapid clinical change with the rise of a biologically aggressive subclone of large B cells
- Results in Diffuse Large B Cell Lymphoma
- Incidence varies in literature (2-15%)
- Risks that can lead to this are poorly understood

Principles of CLL treatment

- Establish treatment goals
- Establish prognostic factors (FISH test)
- Decide on
  - standard therapy: based on consensus guidelines from published Phase 3 randomized clinical trials and availability of drugs
  - clinical trials: novel therapies or novel combination therapies not otherwise available as standard of care

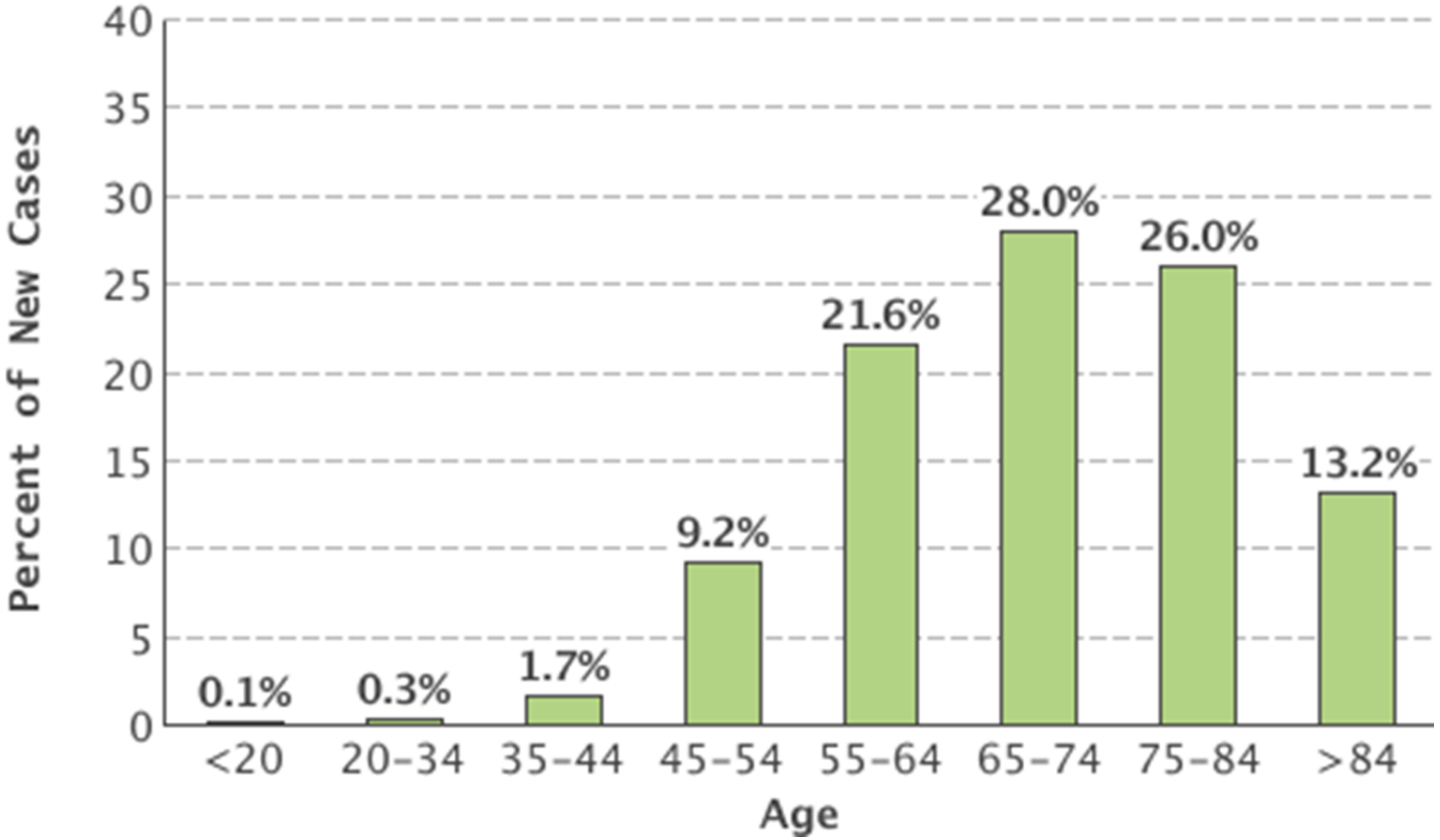
Watch and wait

- Synonyms: observation, active surveillance 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 for when needed.

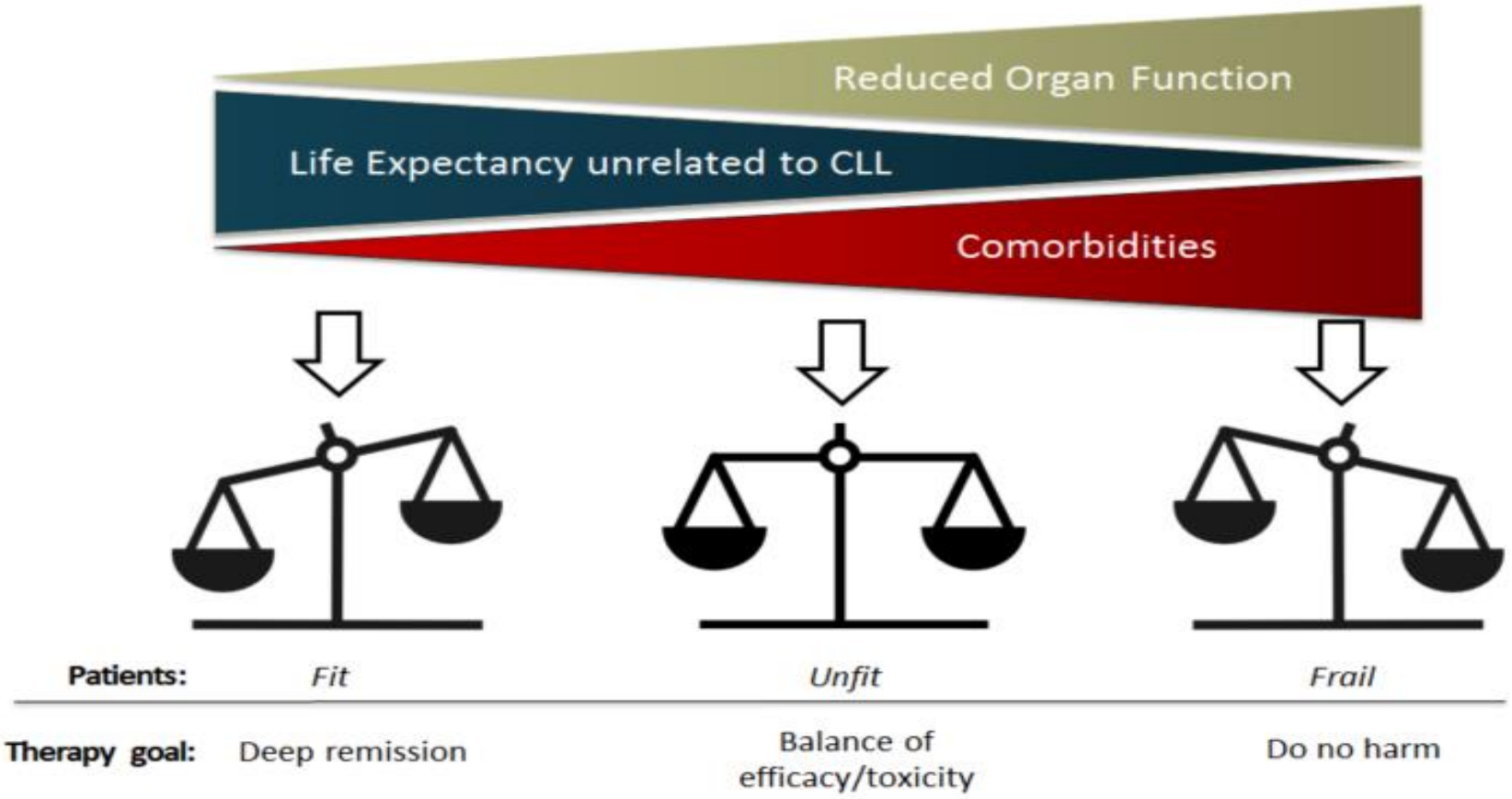
Indications for treatment

- **Symptoms**
  - Severe fatigue, fevers, night sweats, pain from enlarged nodes
- **Organ dysfunction**
  - Bone marrow dysfunction (low blood counts), nodes compressing organs
- **(Rapid lymphocyte doubling time < 6 months)**
- **Complications of CLL not responding to therapy**
  - Auto-immune hemolytic anemia or ITP (very low platelets)

Age can affect treatment choice



Establish goals of therapy



Differences between chemotherapy and novel agents

Chemotherapy

- Damages/binds DNA, triggers cell death

Novel Agents

- Trigger cell death via a different mechanism
  - Anti-CD20 antibodies
  - BTK inhibitors
  - PI3Kdelta inhibitors
  - BCL2 inhibitors

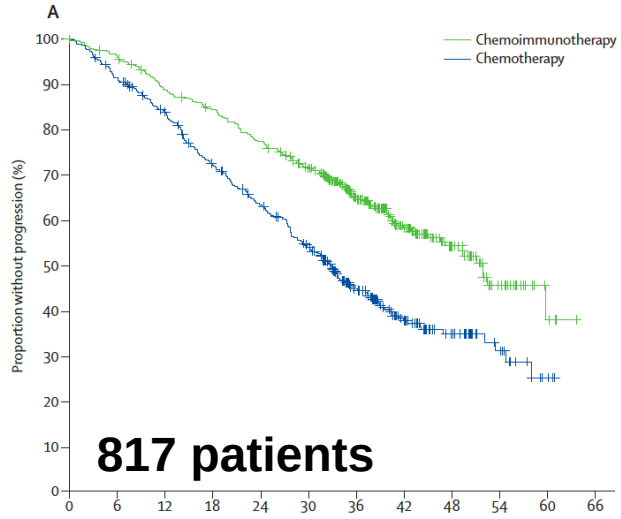
Novel therapies approved by Health Canada

Therapy	Class of Agent	Indication(s)
Bendamustine (TREANDA)	Antineoplastic alkylating agent	Previously untreated CLL
Obinutuzumab (GAZYVA)	Monoclonal type II anti-CD20 antibody	Previously untreated CLL (in combination with chlorambucil)
Ibrutinib (IMBRUVICA)	Bruton's Tyrosine Kinase (BTK) inhibitor	Relapsed CLL; previously untreated CLL with 17p deletion or for whom FCR is inappropriate
Idelalisib (ZYDELIG)	Phosphoinositide 3 kinase-delta (PI3K-δ) inhibitor	Relapsed CLL
Venetoclax (VENCLEXTA)	BH3 mimetic (BCL2 antagonist)	Relapsed CLL with 17p deletion or for whom there are no other available treatment options

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

CLL8 trial

FCR significantly better than FR 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

Toxicity of FCR:

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

Short term: neutropenia, infections (25%)

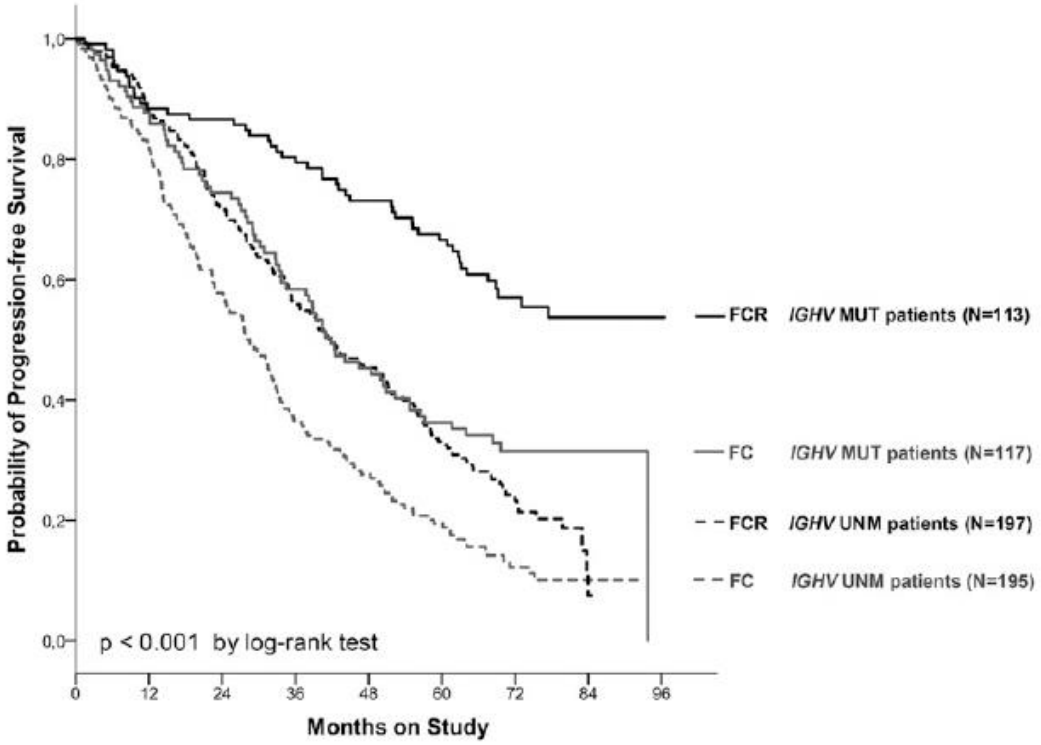
Treatment related mortality (2-5%)

20% don't finish all 6 courses

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

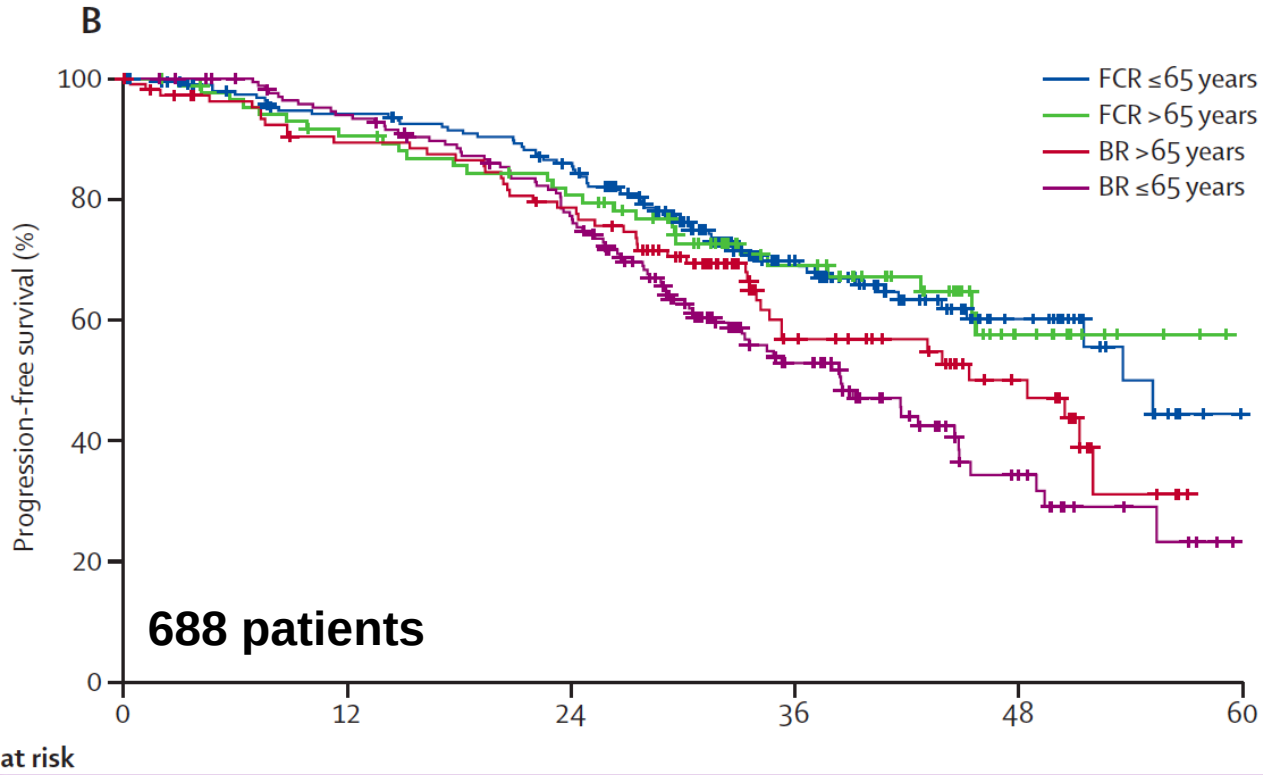
Hallek M, et al. *Lancet*. 2010;376(9747):1164-1174.

Long-term survival with FCR: If IGVH is mutated, ~60% still in remission after 8 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

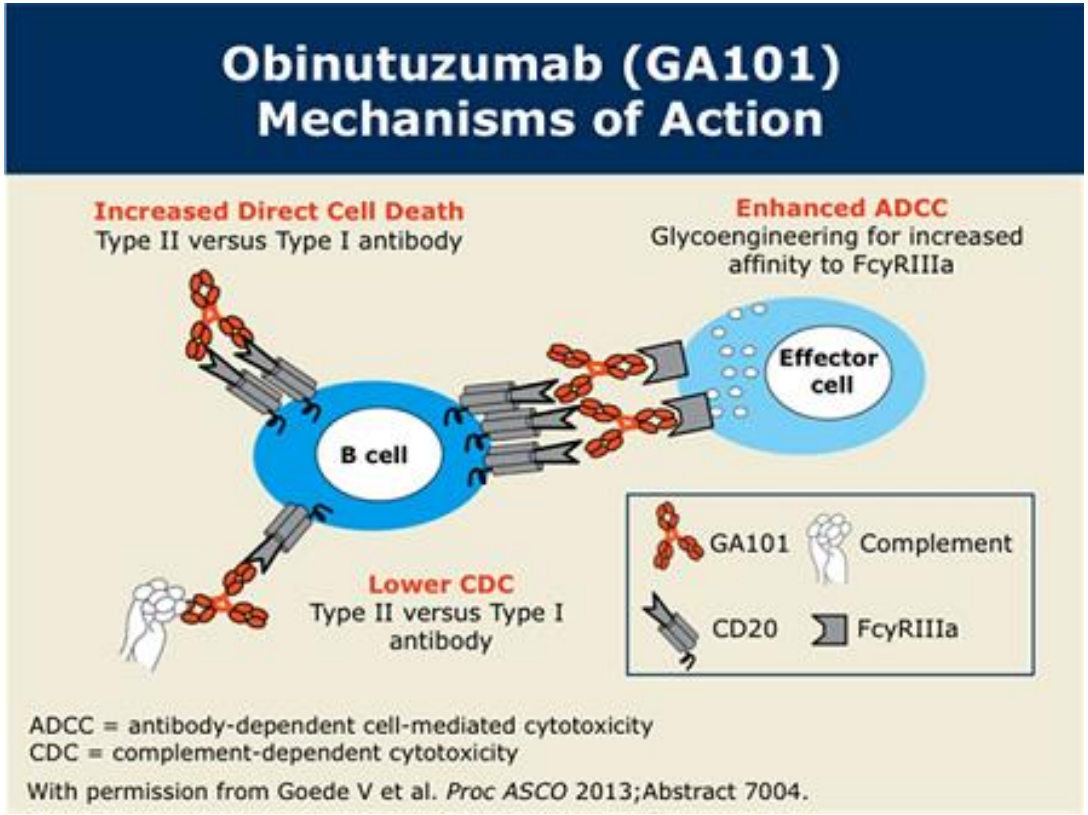
CLL10 trial

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.

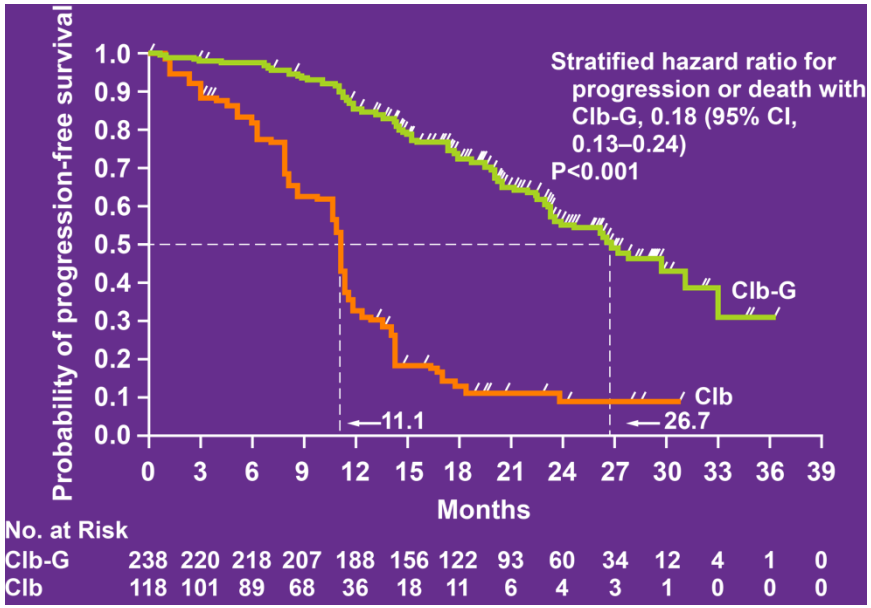
PFS= progression free survival

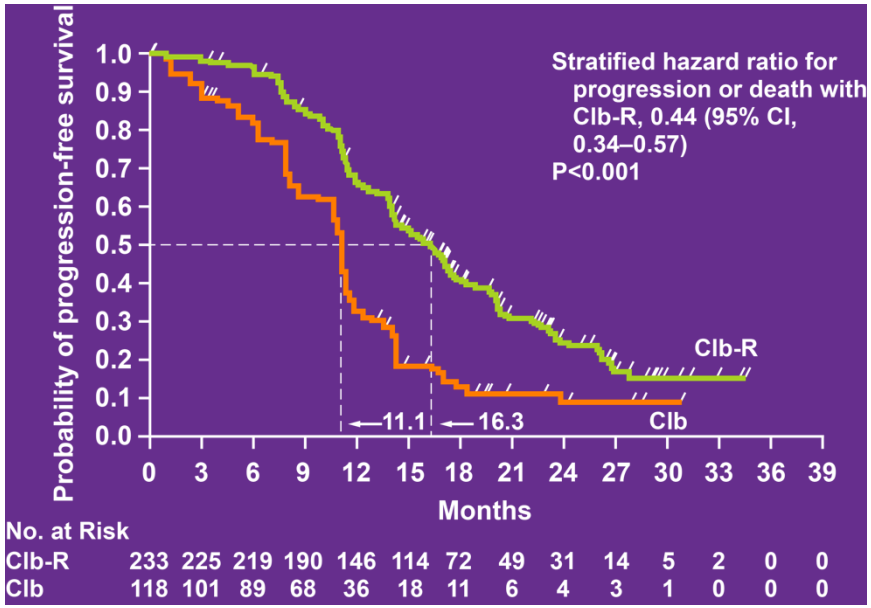
Obinutuzumab: novel anti-CD20 with increased direct cell death



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

CLL 11 trial: Obinutuzumab + Chlorambucil or Rituximab + Chlorambucil vs Chlorambucil Alone

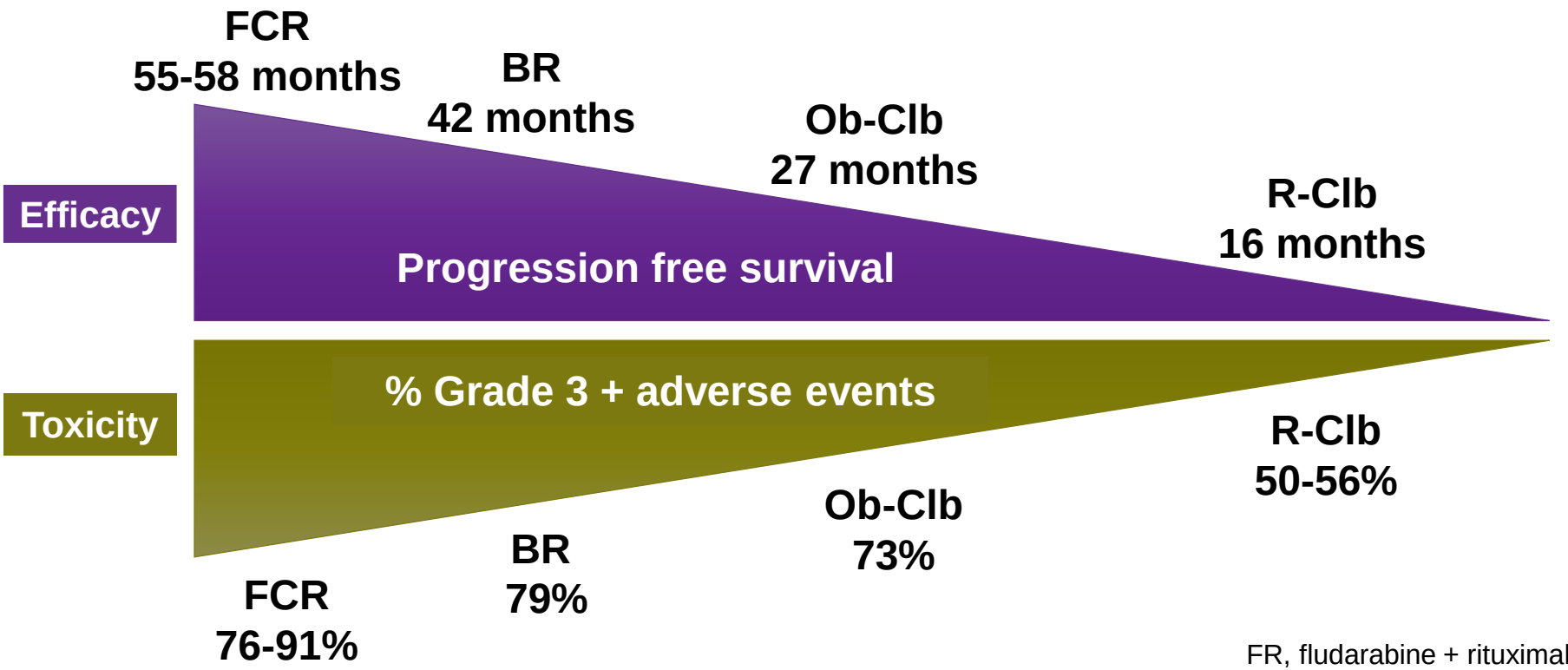




Goede V, et al. *N Engl J Med*. 2014;370(12):1101-1110.

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

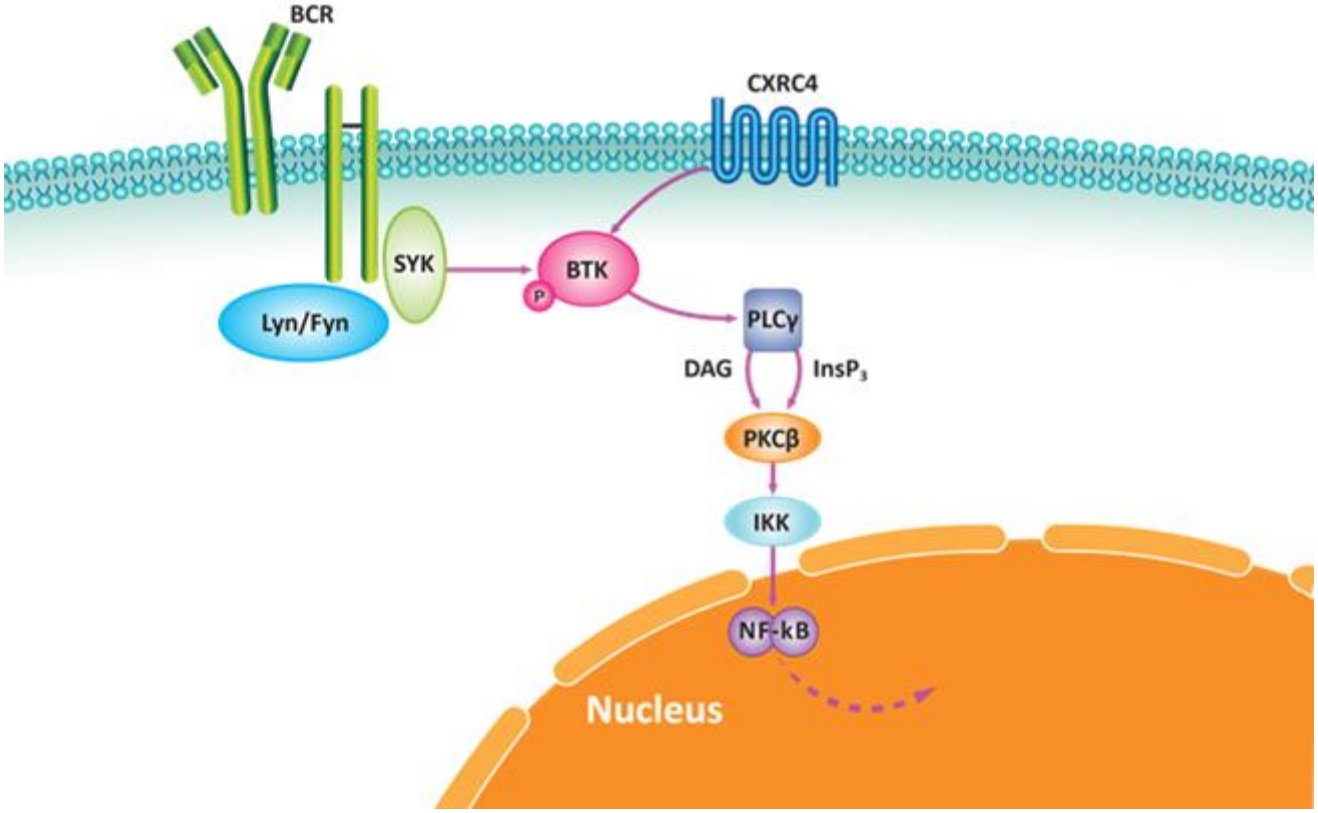
The Balance Between Efficacy and Safety in Front Line CLL



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 (Bruton's tyrosine kinase)



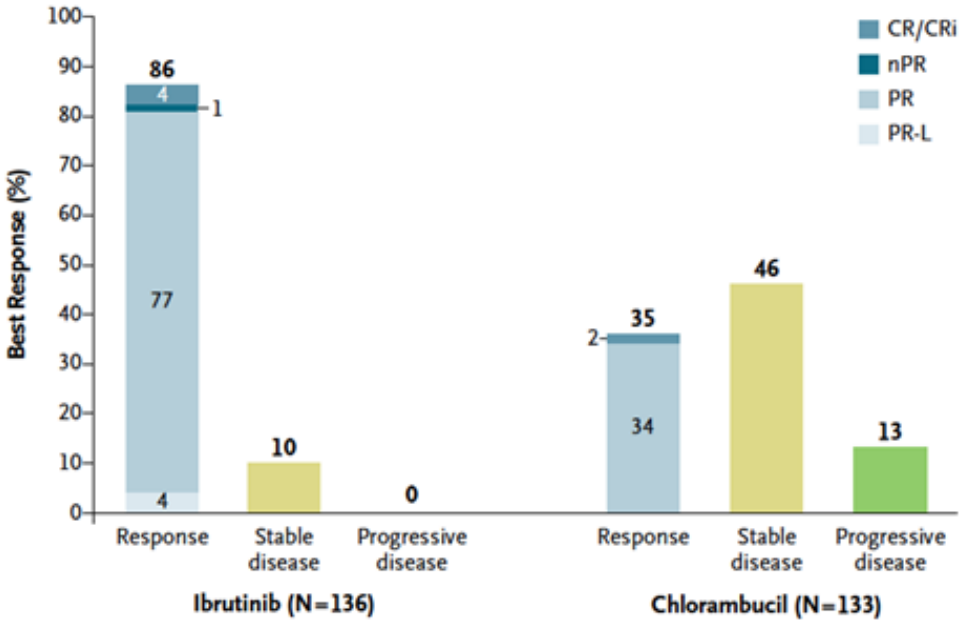
Ibrutinib

Overall response of 71% but only ~5% achieve a complete response

Potential side effects:

- Cardiac arrythmias/atrial fibrillation
- Bleeding

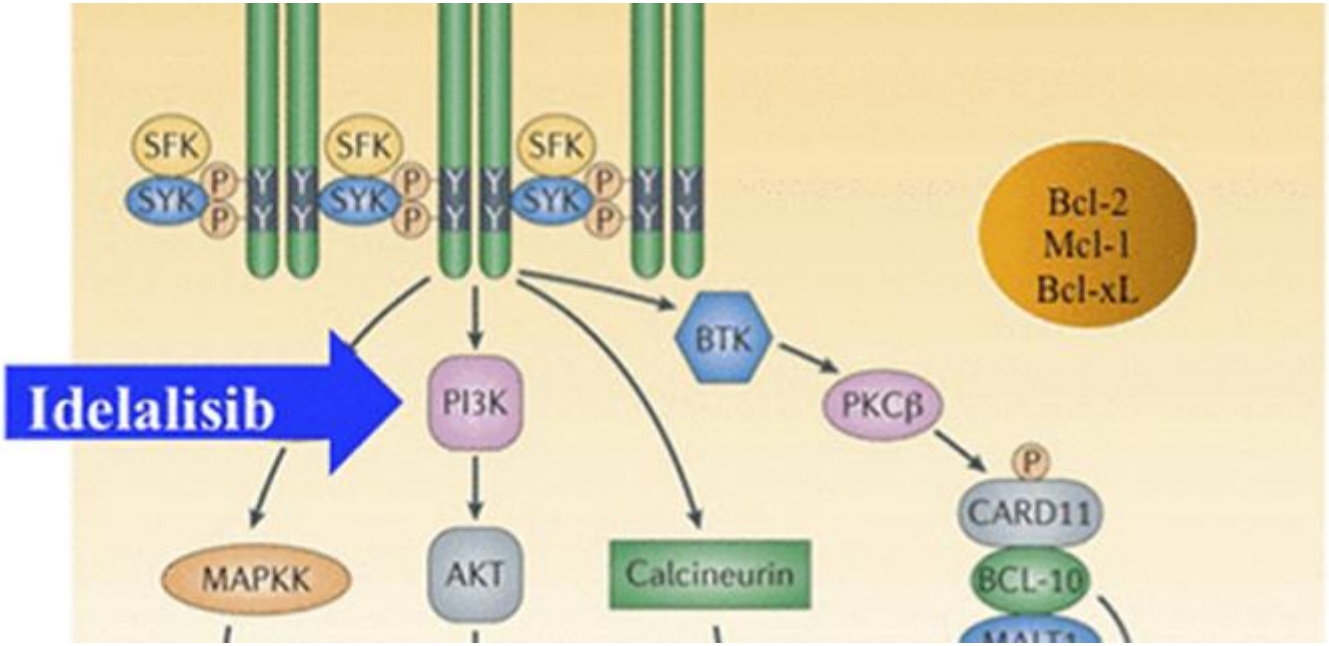
Overall Response Rate	Ibrutinib	Chlorambucil	Rate Ratio (95% CI)	P Value
	% of patients			
With PR-L	86	35	2.42 (1.91–3.07)	<0.001
Without PR-L	82	35	2.32 (1.82–2.95)	<0.001



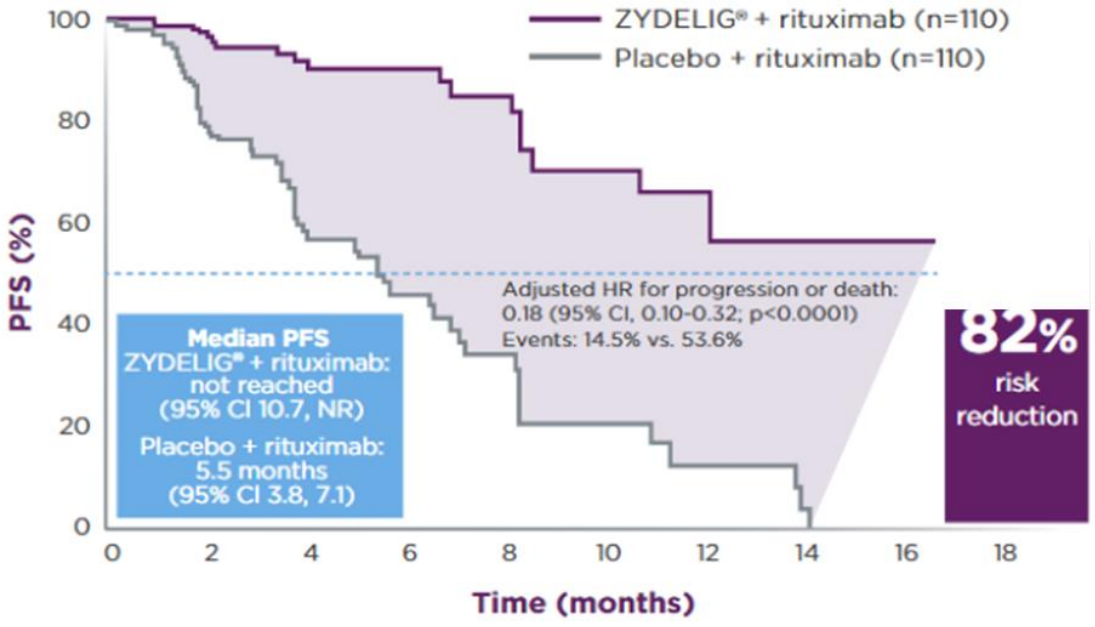
Treatment options for relapsed CLL

- If relapse occurs > 3 years after FCR or FR, could repeat immuno-chemotherapy
- More often, we would use the newer therapie (taken orally, continuous daily therapy, expensive)
  - BCR inhibitors (ibrutinib and idelalisib)
  - BCL2 Inhibitor (venetoclax)
  - Clinical trial with other novel agents
- Cellular therapies: CAR-T (trial), allogeneic transplant

Idelalisib targets PI3Kδ in CLL (and normal B & T cells)



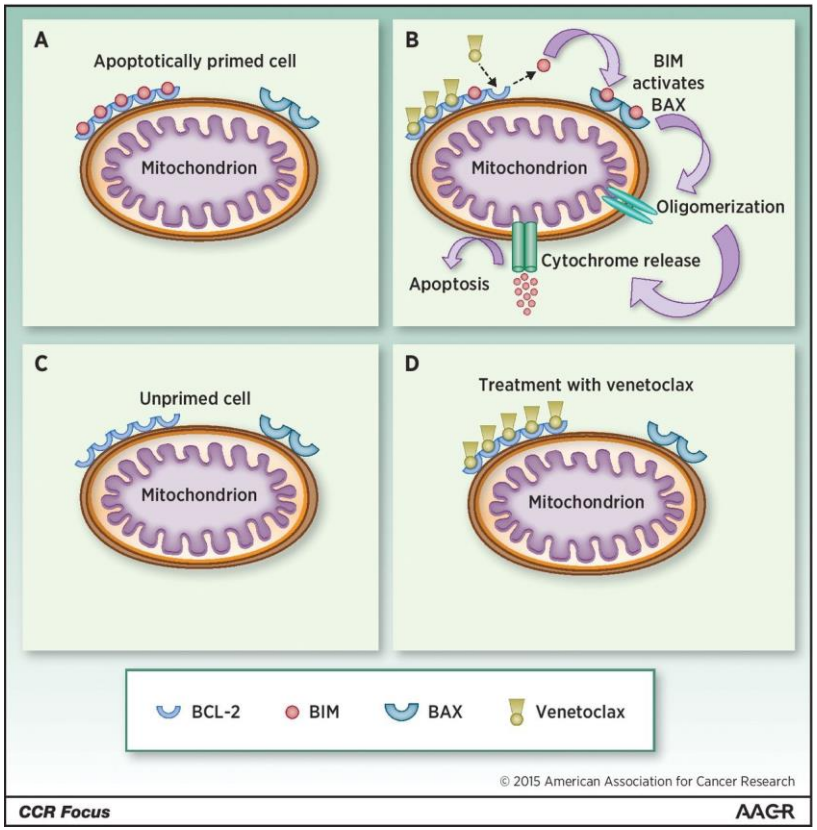
Idelalisib & Rituximab



	Month	0	2	4	6	8	10	12	14	16	18
N at risk (events)	ZYDELIG® + rituximab	110 (0)	87 (3)	54 (7)	35 (8)	30 (10)	17 (14)	7 (15)	2 (16)	1 (15)	0 (16)
	Placebo + rituximab	110 (0)	69 (21)	37 (37)	19 (44)	14 (49)	6 (54)	3 (56)	1 (58)	0 (59)	0 (59)

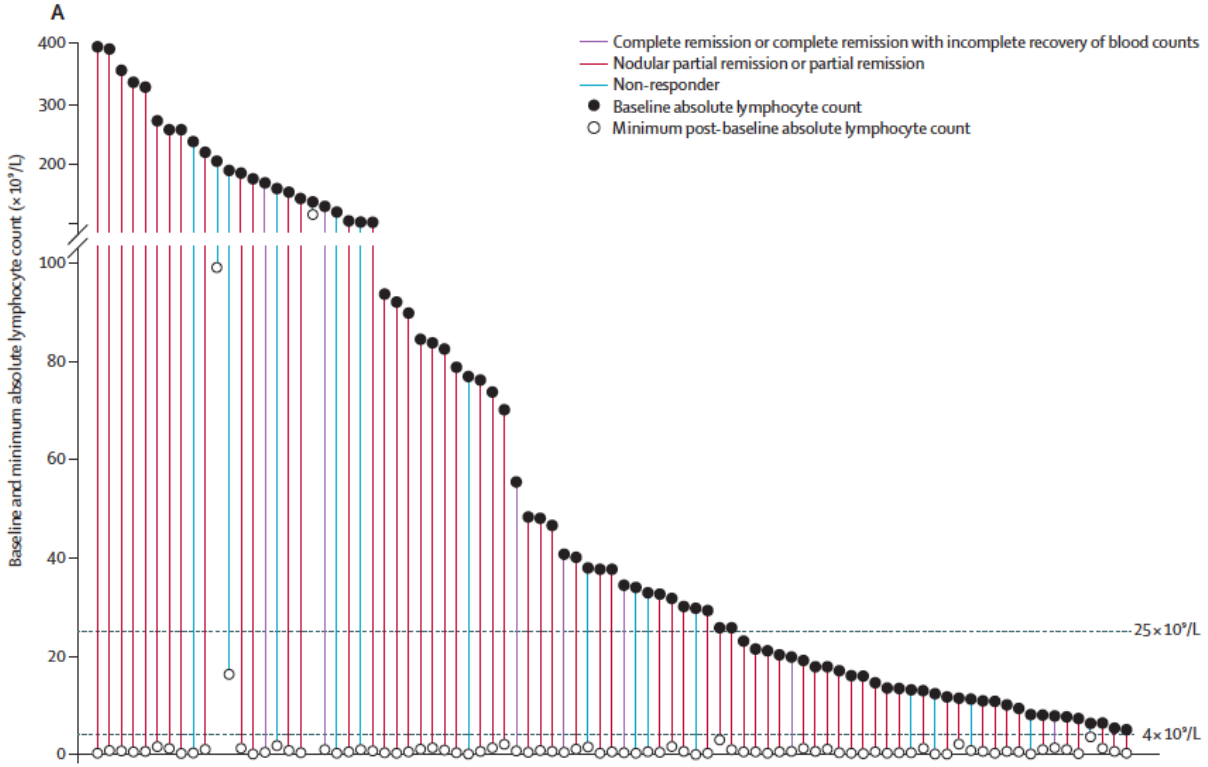
At 24 weeks, disease progression occurred in 12 patients (10.9%) with Zydelig + rituximab vs 53 patients (48.2%) with placebo[1]

Venetoclax kills CLL cells that are “primed” to die



Concept by Antony Letai

Venetoclax induces rapid clearance of peripheral blood lymphocytes



Stilgenbauer et al. *Lancet Oncol. 2016 Jun;17(6):768-78*

Allogeneic Transplantation CLL

Table 1. Summary of Transplant Characteristics and Survival in the Largest Reported Prospective Studies of RIC HSCT in CLL

	Fred Hutchinson Cancer Center[8]	German CLL Study Group[10,48]	MD Anderson Cancer Center[9]	Dana-Farber Cancer Institute[11]
Number of patients	82	90	86	76
Conditioning regimen	Flu/low-dose TBI	Flu/Cy ± ATG	Flu/Cy ± R	Flu/Bu
Donors, % sibling/% MUR	63/37	41/59	50/50	37/63
Median follow-up, months	60	72	37	61
Median PFS, %	39 (at 5 y)	38 (at 6 y)	36 (at 6 y)	43 (at 6 y)
Median OS, %	50 (at 5 y)	58 (at 6 y)	51 (at 6 y)	63 (at 6 y)

ATG, antithymocyte globulin; Bu, busulfan; CLL, chronic lymphocytic leukemia; Cy, cyclophosphamide; Flu, fludarabine; HSCT, hematopoietic stem cell transplantation; MUR, matched unrelated donor; OS, overall survival; PFS, progression-free survival; R, rituximab; RIC, reduced-intensity conditioning; TBI, total body irradiation; y, years.

Fabienne McClanahan, Clinical Advances in Hematology & Oncology Volume 13, Issue 9 September 2015

Supportive Care

- Promote well-being
- Vaccination
  - Annual flu shot, pneumonia vaccine
  - Vaccine record
- Majority of patients with CLL will experience serious infections. Keep track of your infections & how long they last.
- Some patients benefit from antibody injections (immunoglobulin IV or under the skin=Hyzentra)

Questions?