LYMPHOMA CANADA

EXPERT SPEAKERS HOPE
NATIONAL NETWORKING
AID CONFERENCE FORUM
ON LYMPHOMA SUPPORT
CAREGIVERS EDUCATION
SEPTEMBER 29 - 30, 2017
SURVIVORS TORONTO, ON
THERAPIES SIDE EFFECTS

CLL & SLL:
Current Management & Treatment

Dr. Peter Anglin

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

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.

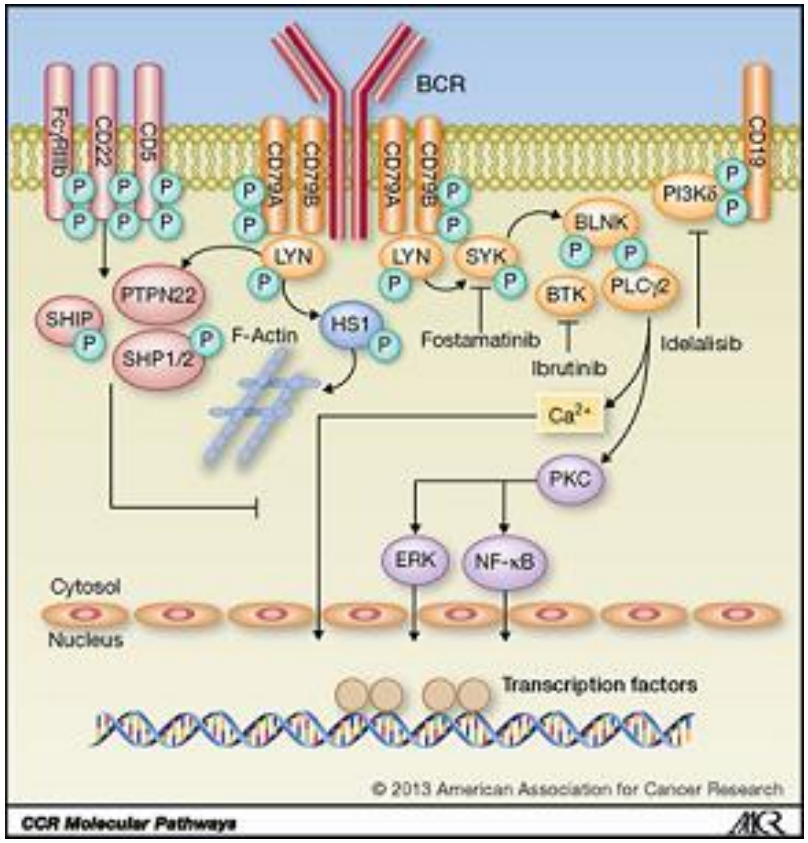
CLL & SLL look the same under a microscope.

More cancer cells in the lymphatic system: SLL

More cancer cells in the peripheral 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

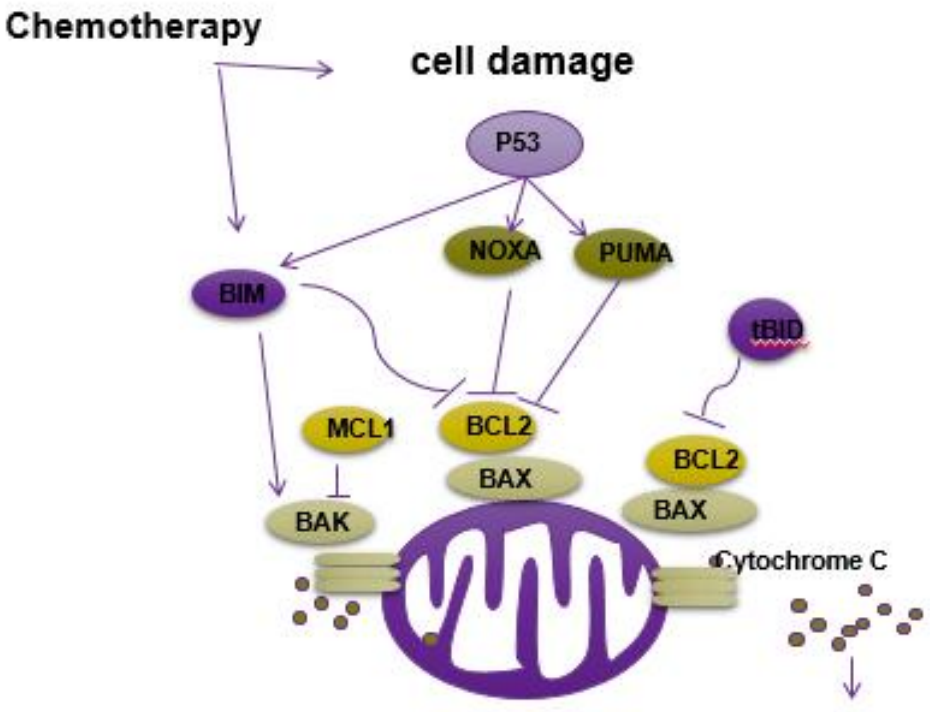


Binding to the BCR provides a survival signal "feed me"

Important mediators that transmit BCR signals are:

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

CLL cells depend on BCL2 to survive



Mitochondria "cellular motor"
2 critical roles:

- Provide energy
- Decide cell fate (to live or die)

In CLL, genetic damage triggers P53, the "guardian of the genome", which in turns stimulates cell death if there is too much damage. BCL2 protects the cell from dying. Cells can also disable P53 to help them survive.

Mitochondrial collapse is an irreversible step to cell death

Deng et al. Cancer Cell. 2007 Aug;12(2):171-85

Causes

- 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.

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

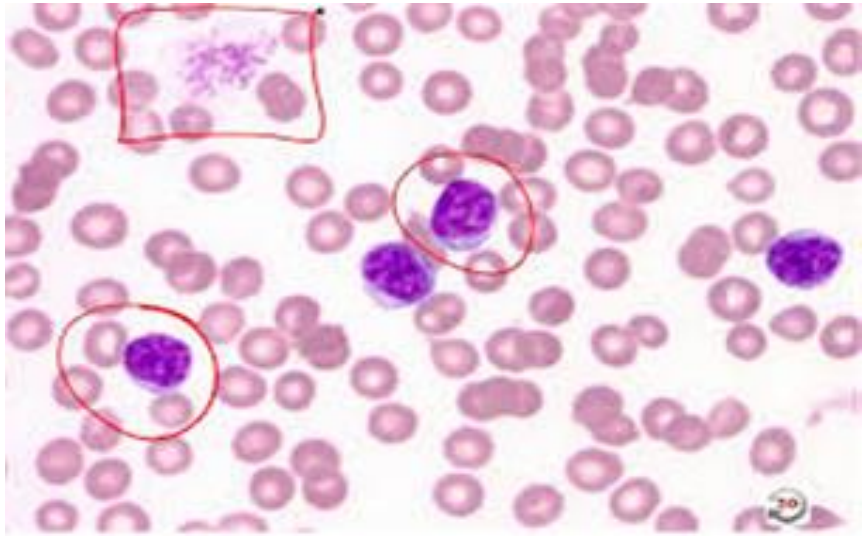
SPECIMEN: **3 cc EDTA BLOOD (Lavender Top)**

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

lymphocytosis →

No symptoms in 30-40% of people

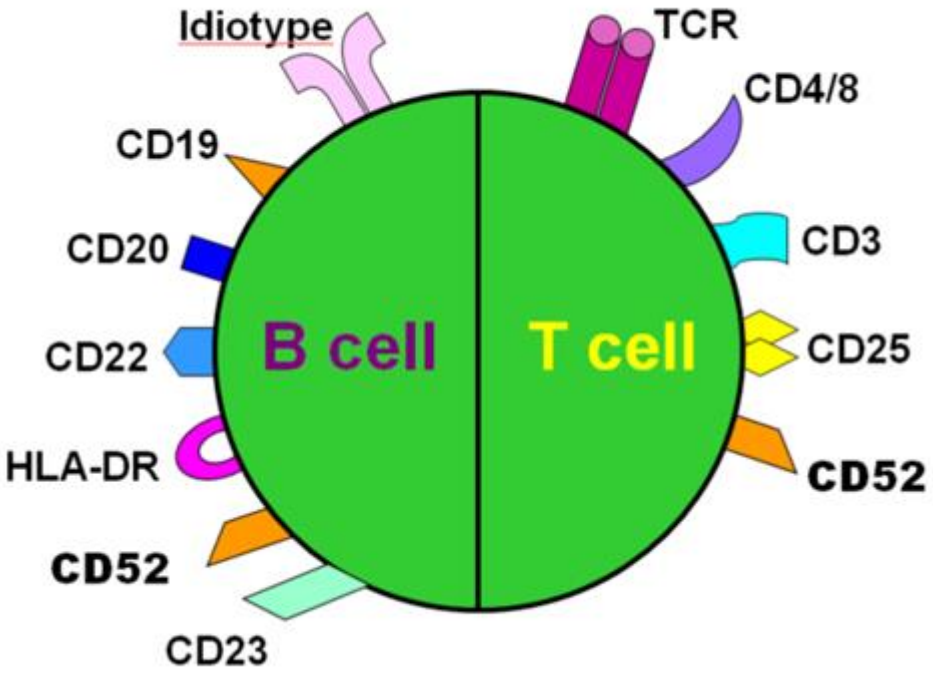
Peripheral blood smear



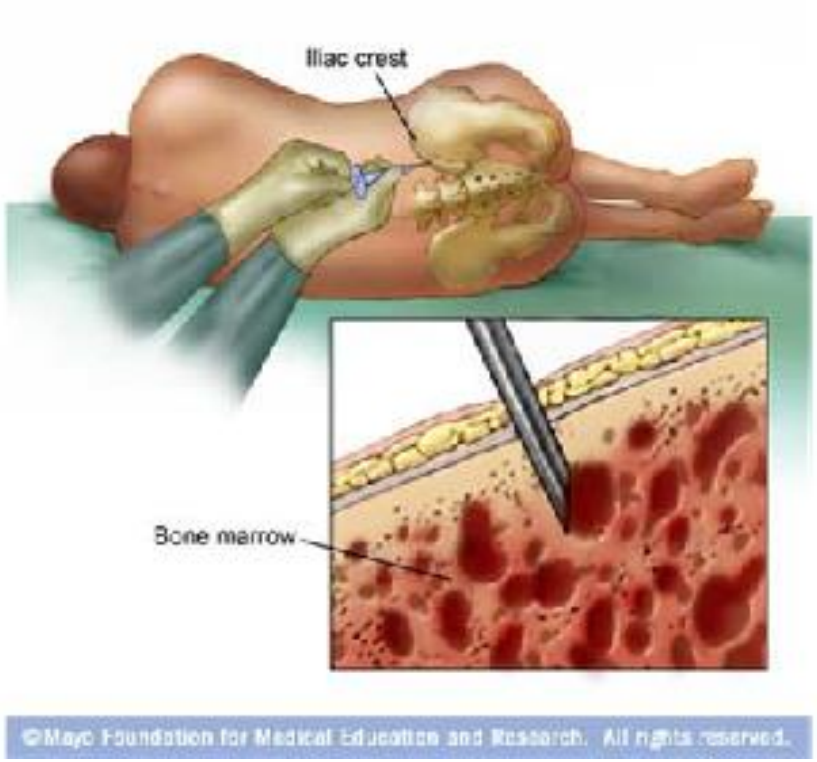
- Lymphocytosis
- Low platelets
- Size and shape of red blood cells
- Quantity of other immune cells (neutrophils)

Flow cytometry

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

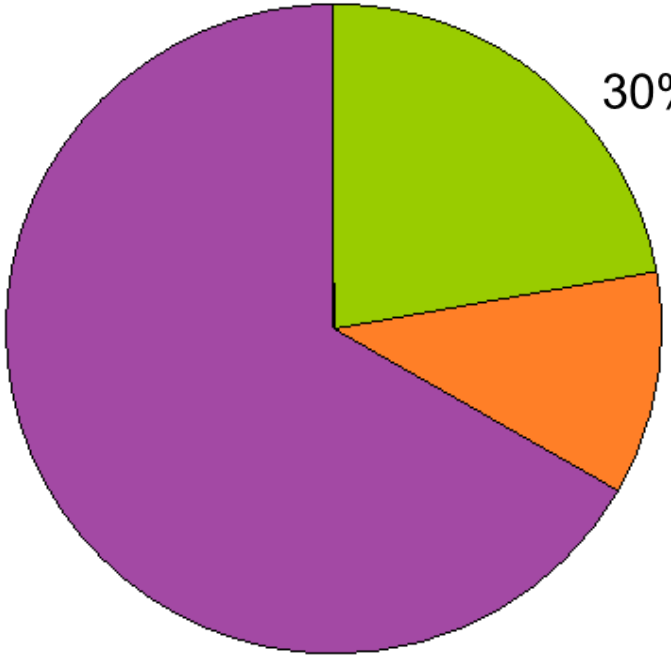


Assessment of bone marrow function in some patients



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

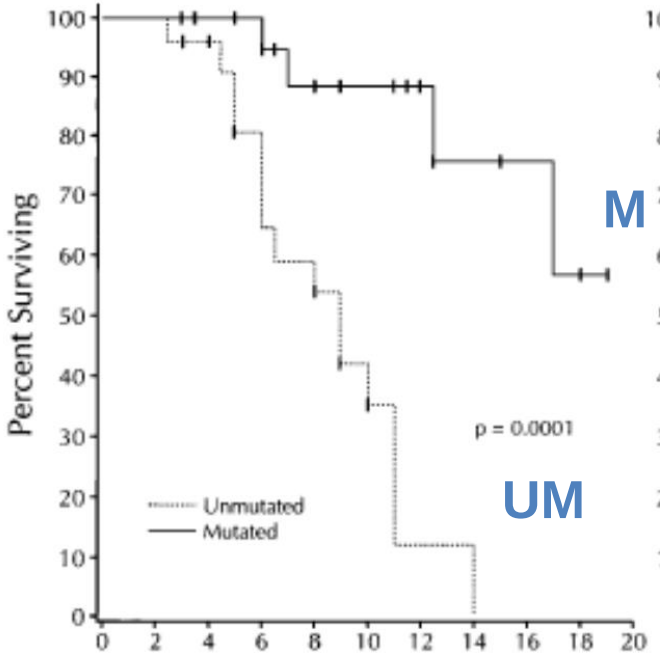
Rai staging system

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

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

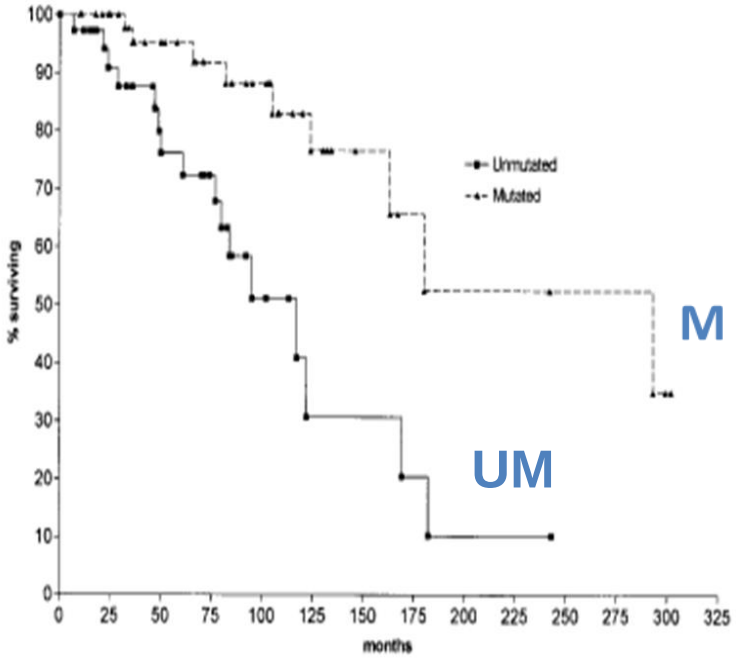
Immunoglobulin gene mutation status

Unmutated is more aggressive than mutated



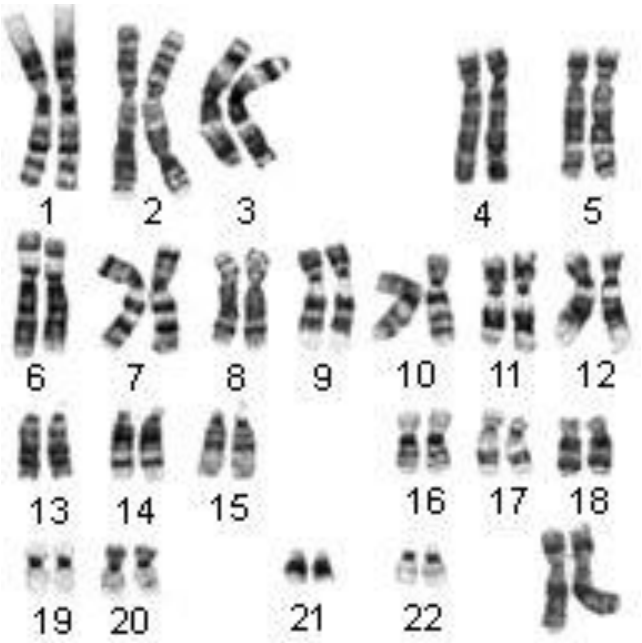
Damle et al

Blood, 1999



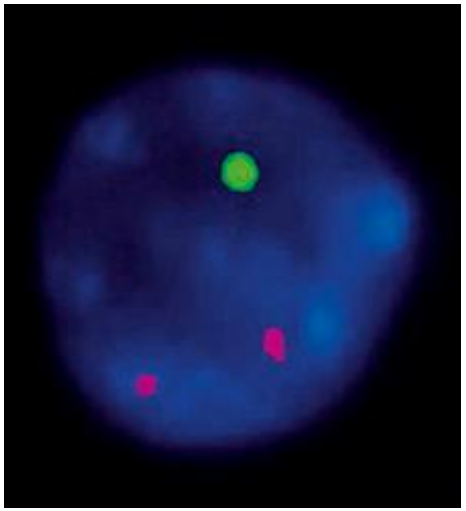
Hamblin et al

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



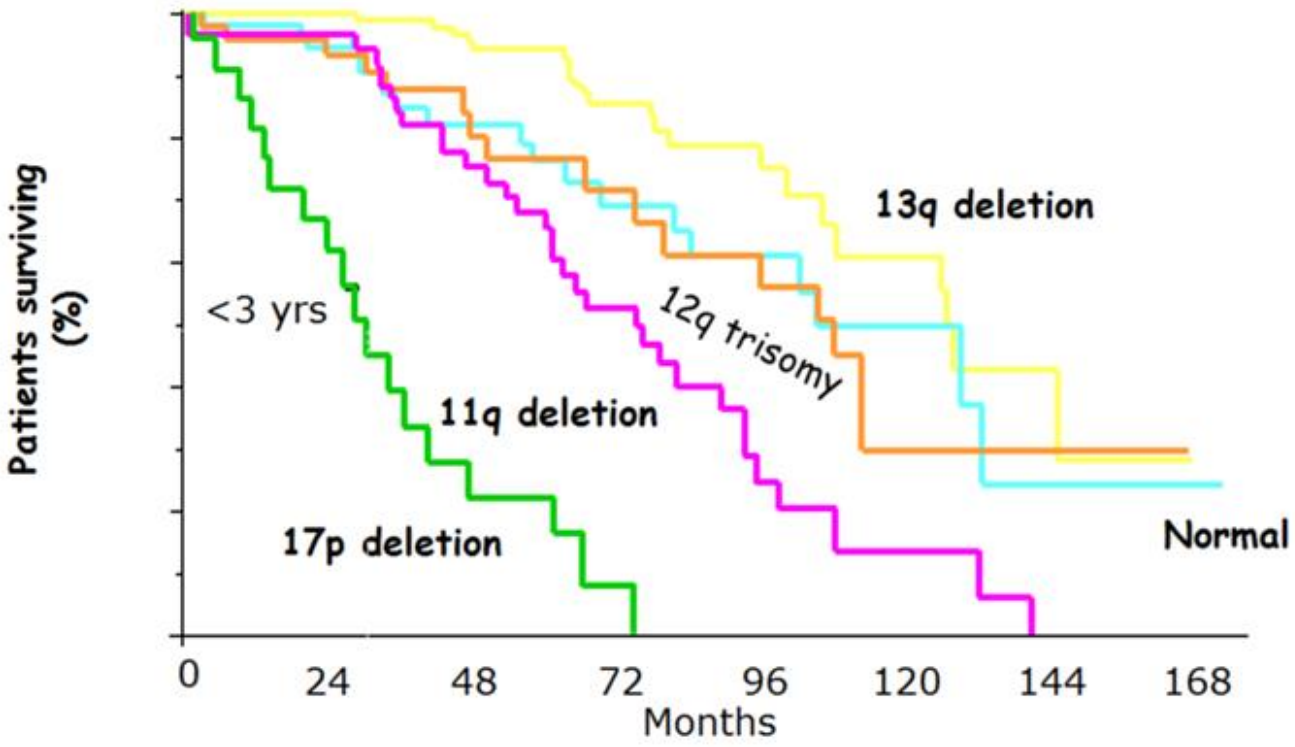
Normal karyotype: 46 chromosomes

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



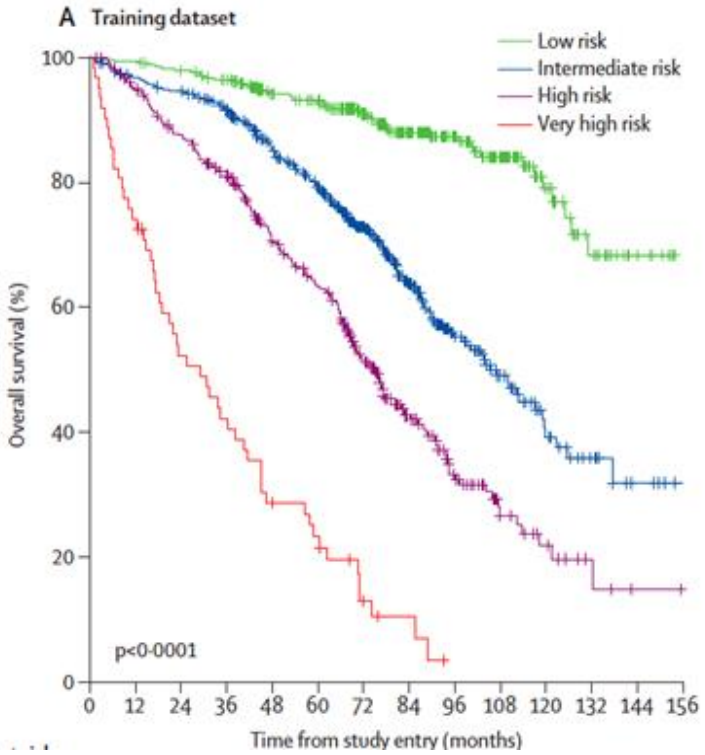
Döhner H, et al. *N Engl J Med*. 2000;343:1910-1916.

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 mutation	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%

Intermediate (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
  - 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

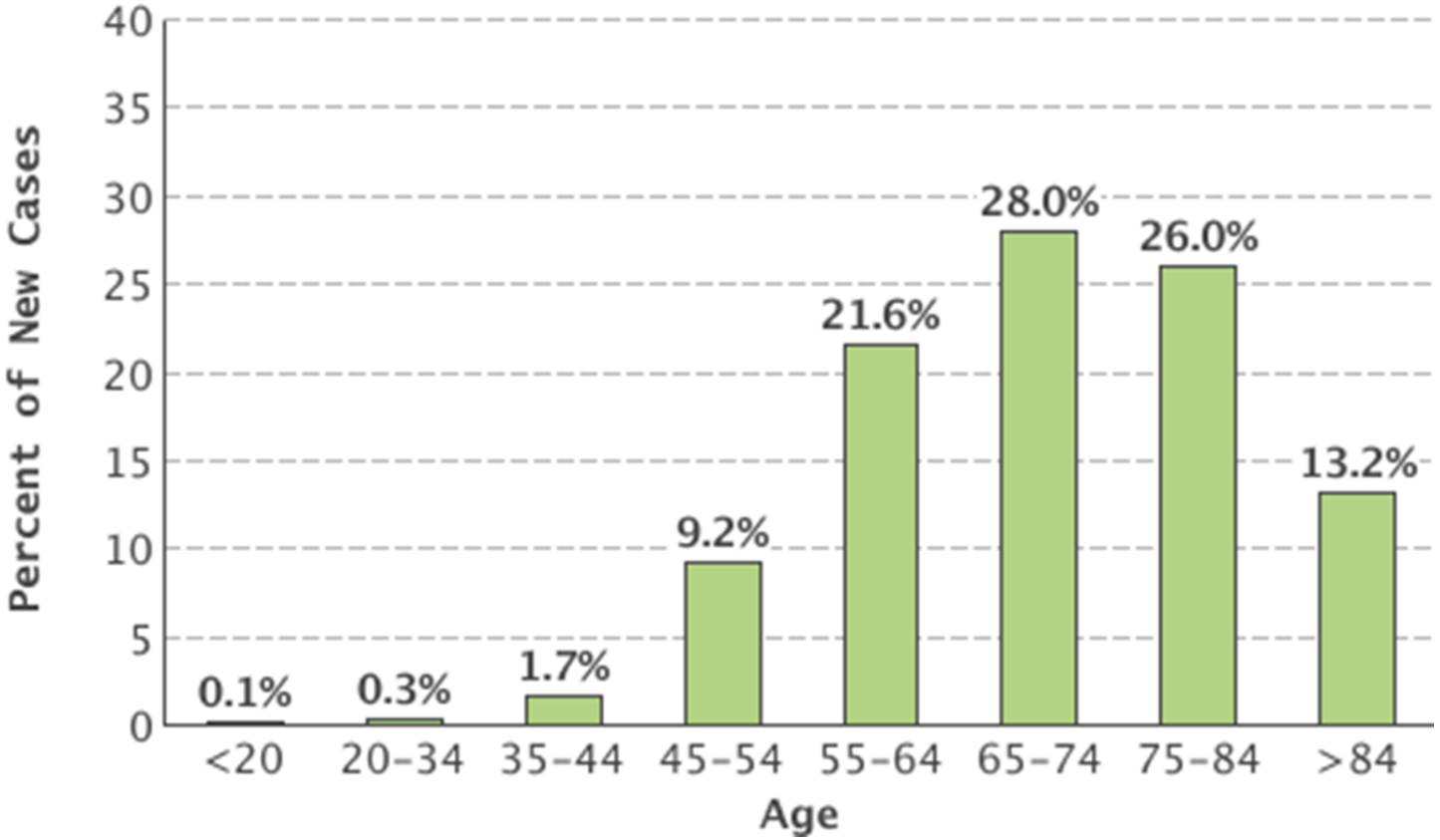
Watch and wait

- Synonyms: Watch and Worry; observation, 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 when needed.

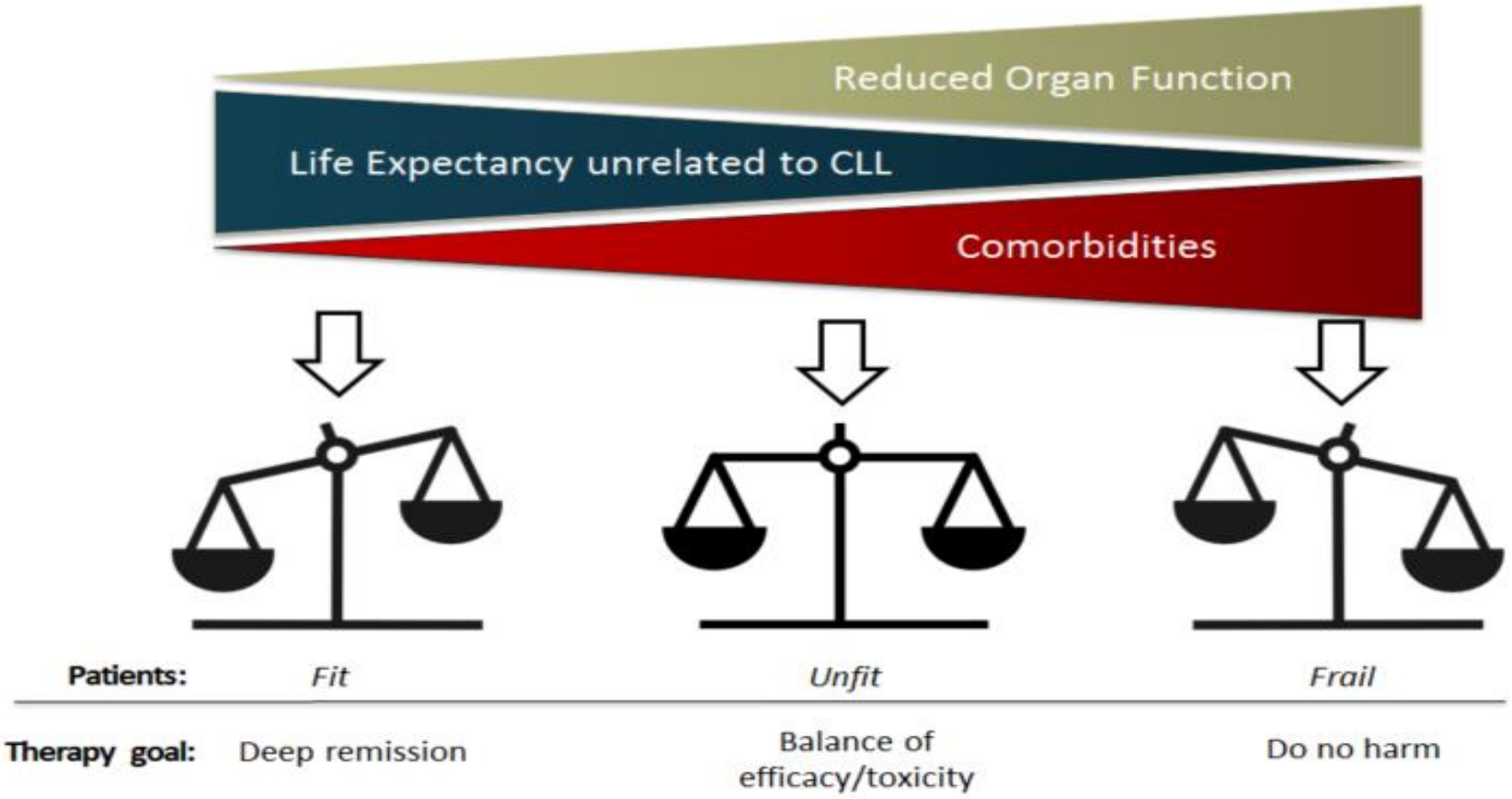
Indications for treatment

- **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

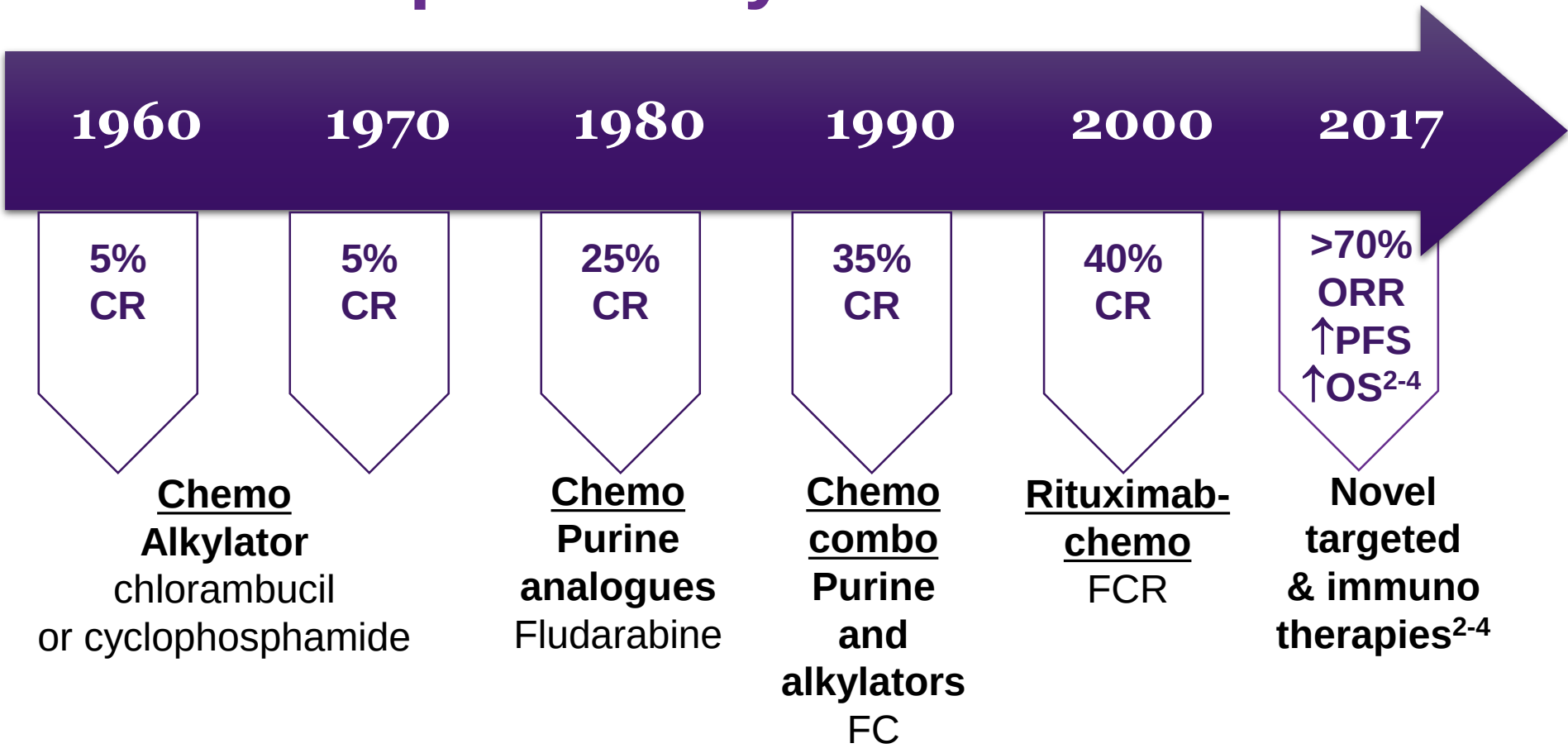
Age of diagnosis affects treatment choice



Establish goals of therapy



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.

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Decision regarding treatment: standard of care versus clinical trial

Standard of care

- Treatment decision usually based on a prior large trial comparing the old standard to new standard
- Offered in most hospitals
- Less testing/scans

Clinical trial**

- Access to new options or new drugs
- Can be high risk/high gain
- More rigorous testing

Differences between chemotherapy and novel agents

Chemotherapy

- Damages/binds DNA, triggering a P53 response, triggers cell death if the damage too extensive

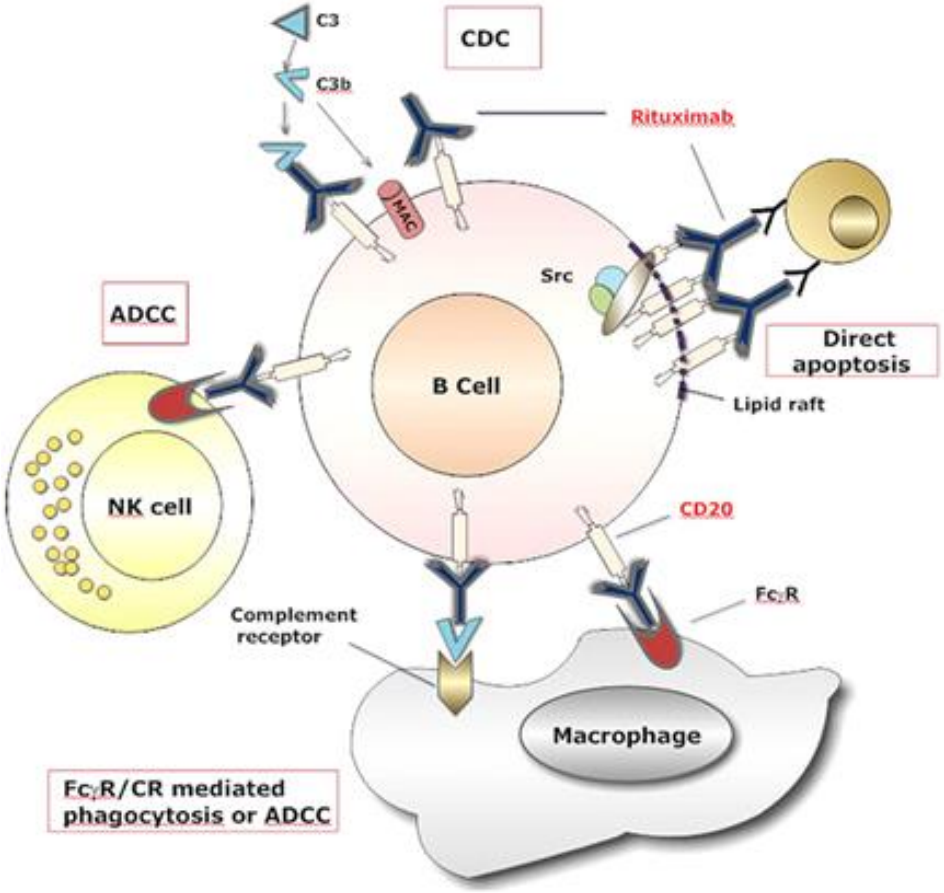
Novel Agents

- 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

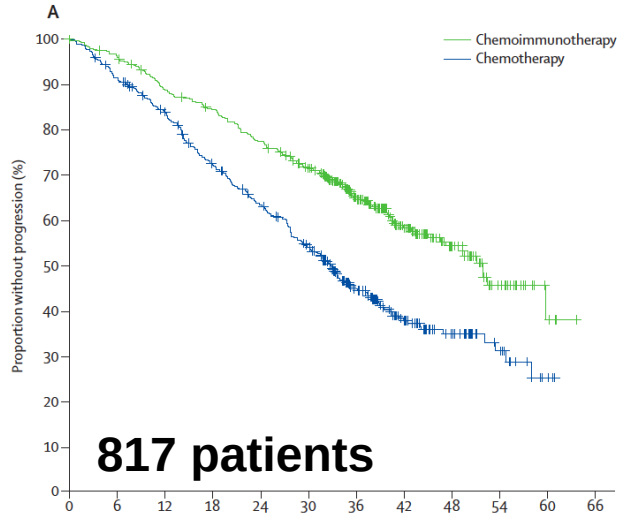
Rituximab


C3
C3b
CDC
Rituximab
MAC
Src
ADCC
Direct apoptosis
B Cell
Lipid raft
NK cell
CD20
FcγR
Complement receptor
Macrophage
FcγR/CR mediated phagocytosis or ADCC

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%)

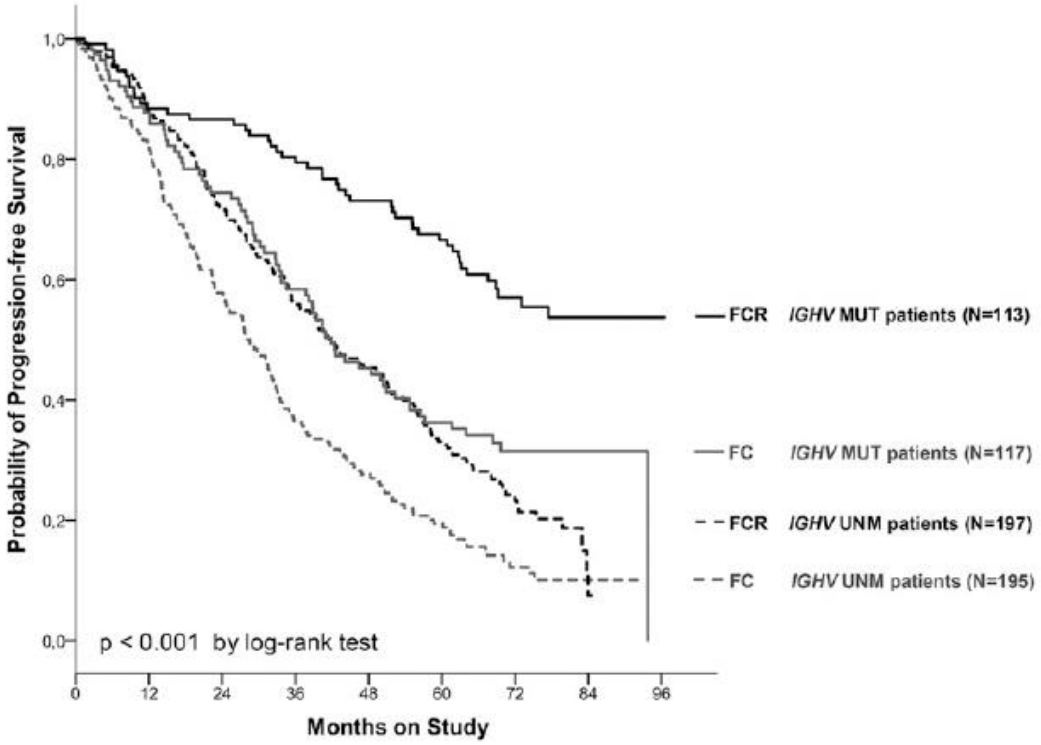
Treatment related mortality (2-5%)

20% don't finish all 6 courses

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

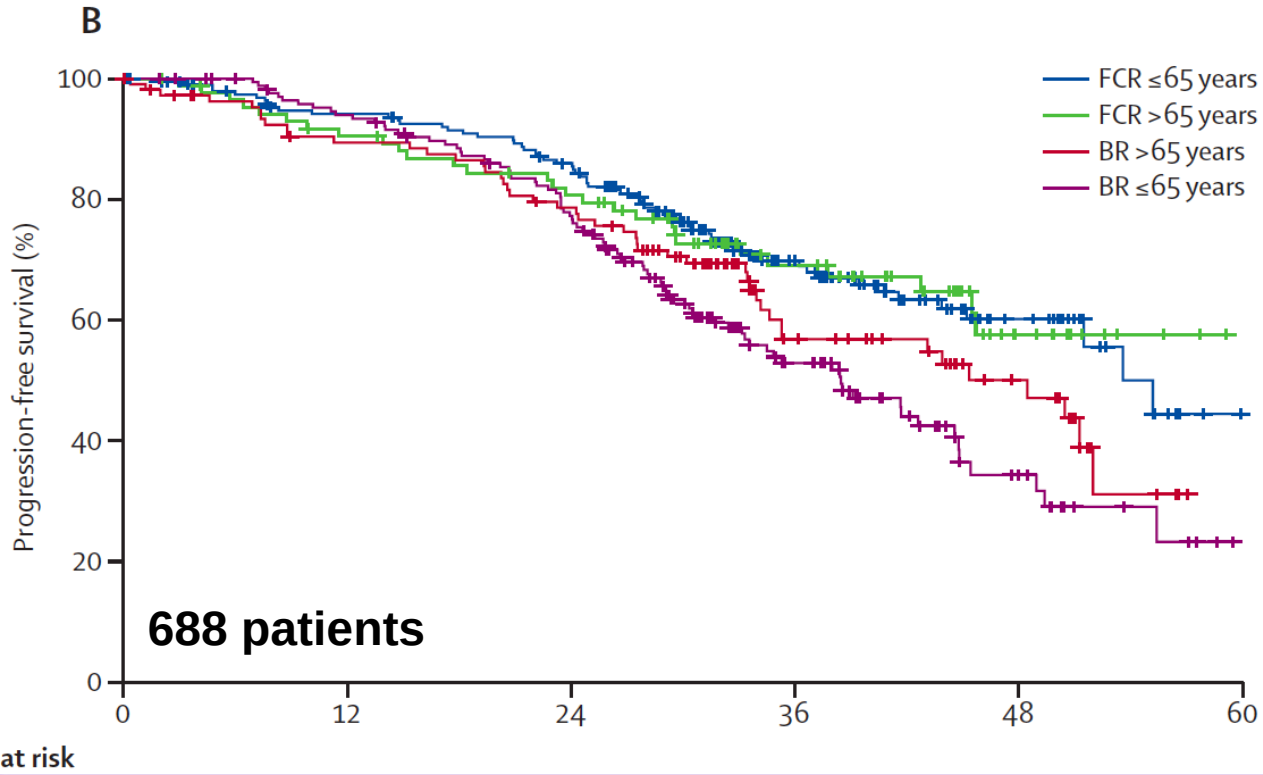
Hallek M, et al. *Lancet*. 2010;376(9747):1164-1174.

Long term survival with FCR: IGVH mutated status benefits the most with ~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

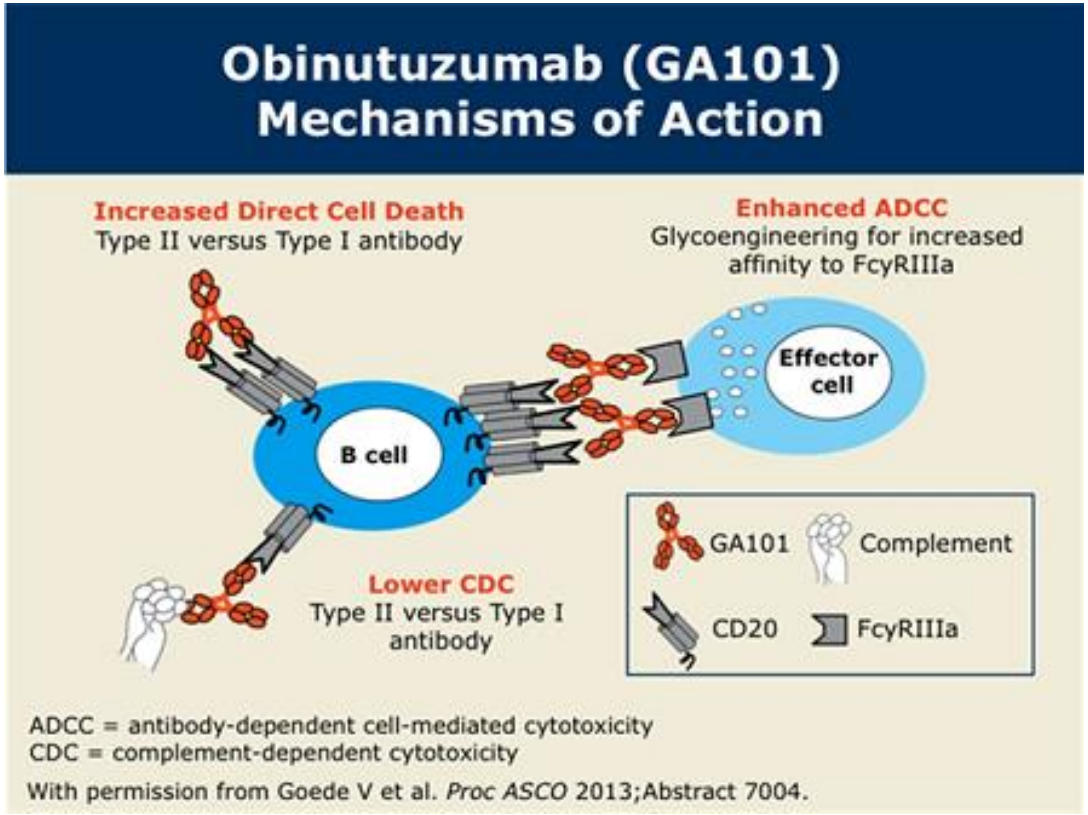
CLL10 trial

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.

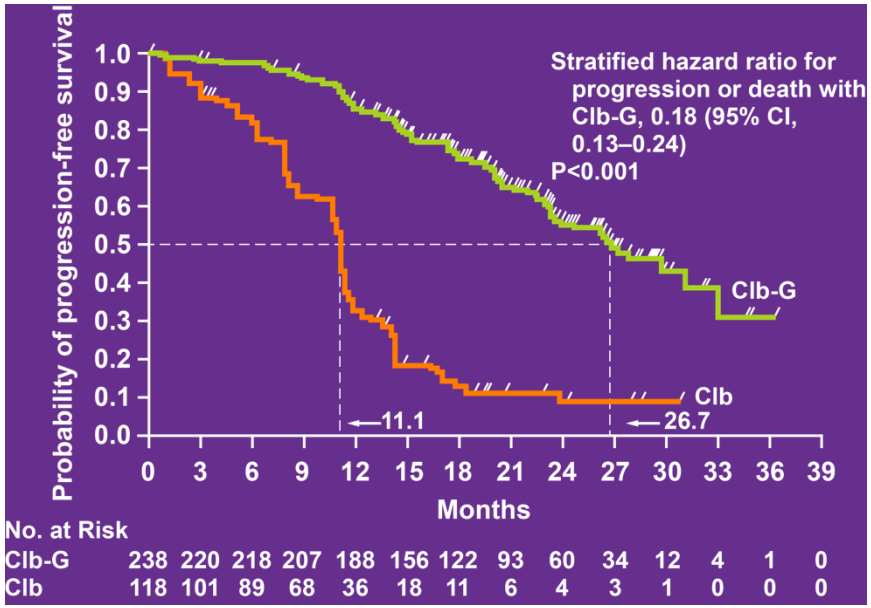
PFS= progression free survival

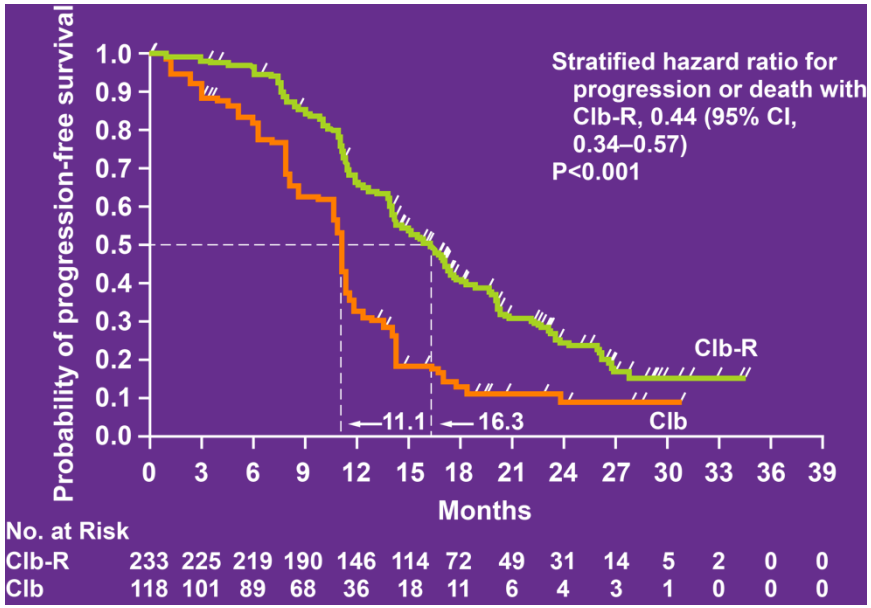
Obinutuzumab: novel anti-CD20 with increased direct cell death



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

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

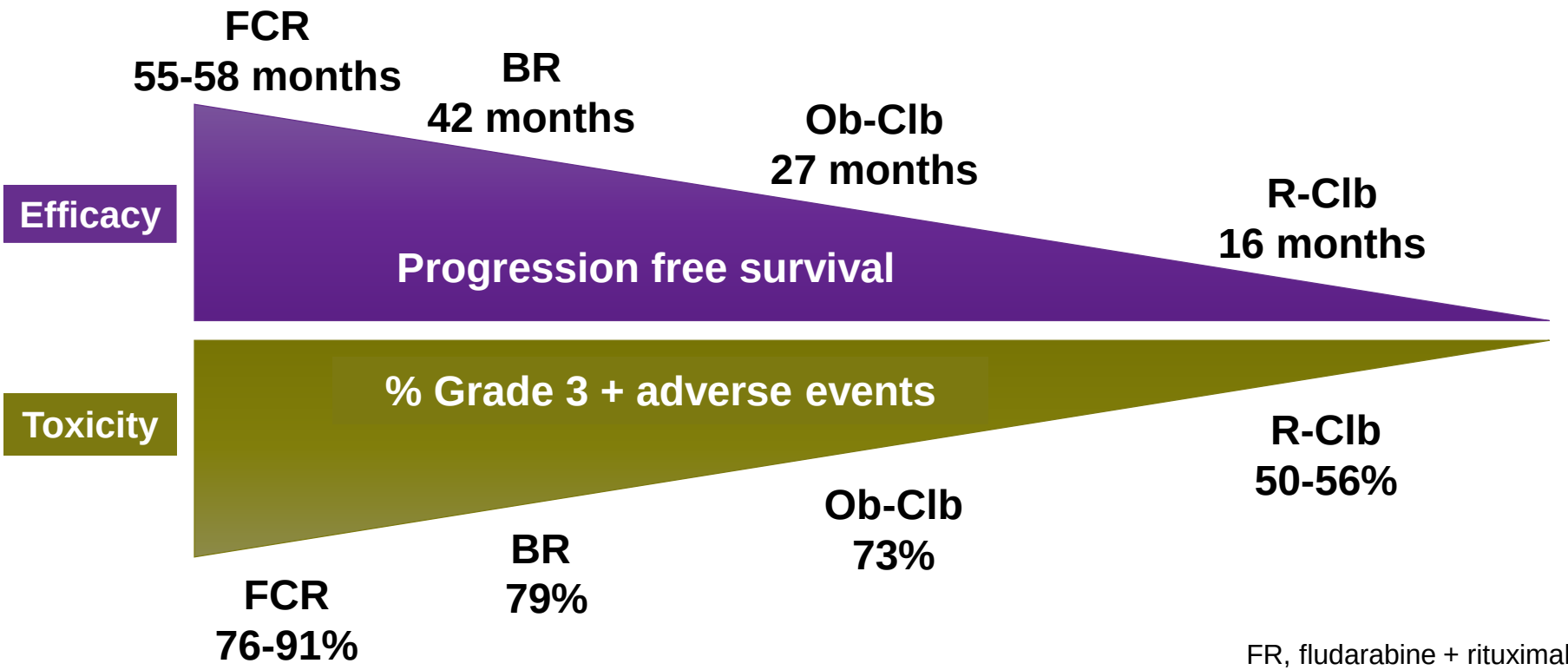




Goede V, et al. *N Engl J Med*. 2014;370(12):1101-1110.

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

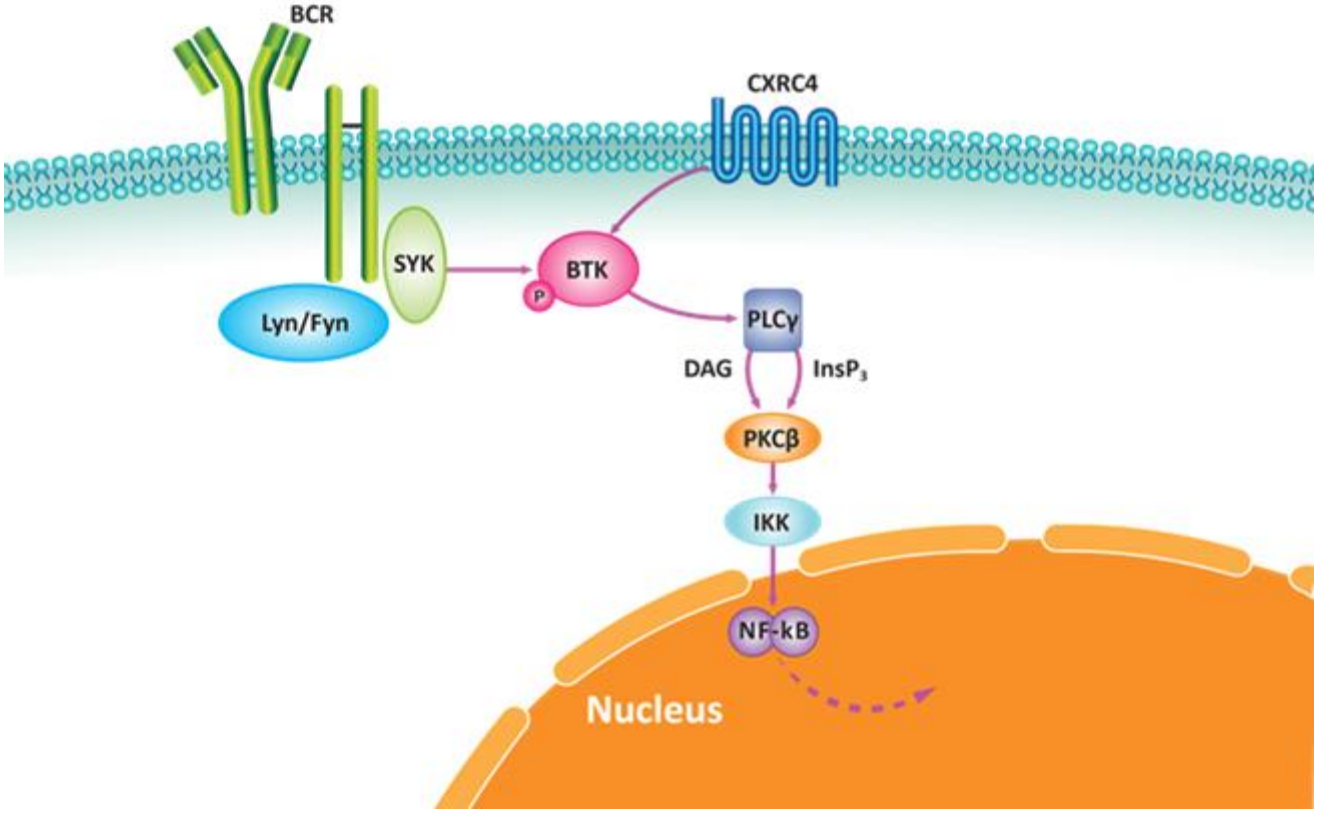
The Balance Between Efficacy and Safety in Front Line CLL



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 downstream of B cell receptor



Ibrutinib

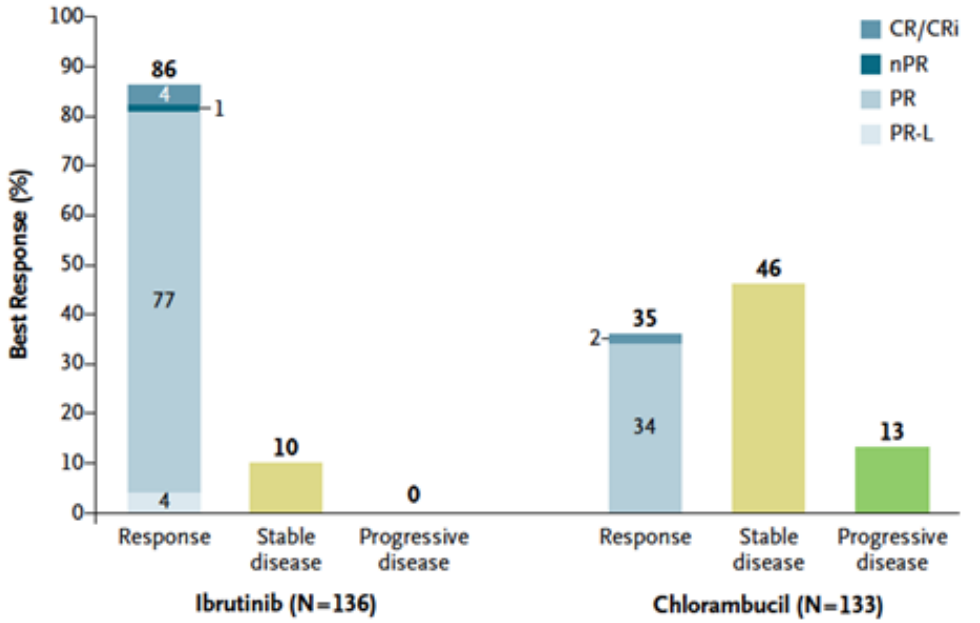
Overall response of 71% but only ~5% achieve a complete response

Ibrutinib inhibits 19 other kinases

Serious side effects:

- Neutropenia
- Cardiac arrythmias
- 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

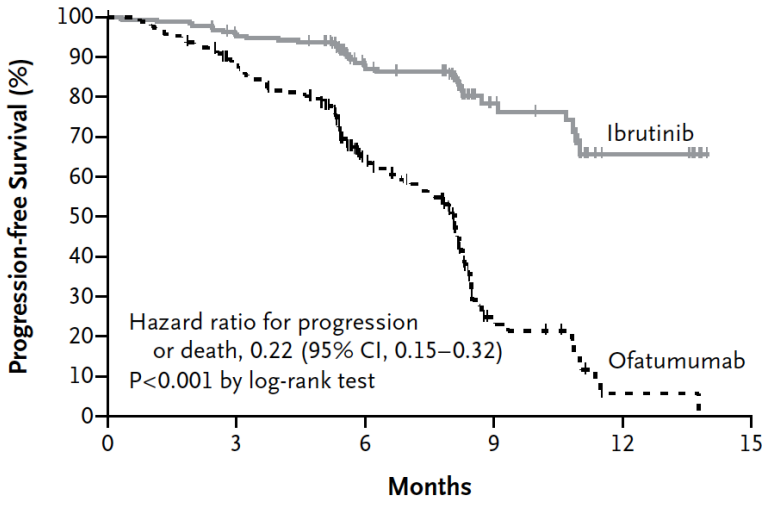


Resonate trial

Ibrutinib is superior to Ofatumumab in terms of progression free survival and overall survival in patients with relapsed CLL

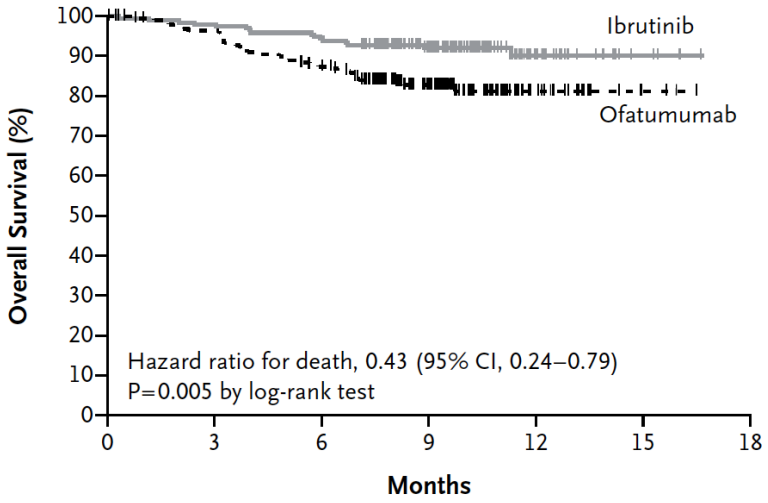
Overall response: 40% Ibru vs 4% Ofatumumab. No difference in response based on 17p del status

A



No. at Risk						
Ibrutinib	195	183	116	38	7	
Ofatumumab	196	161	83	15	1	0

B

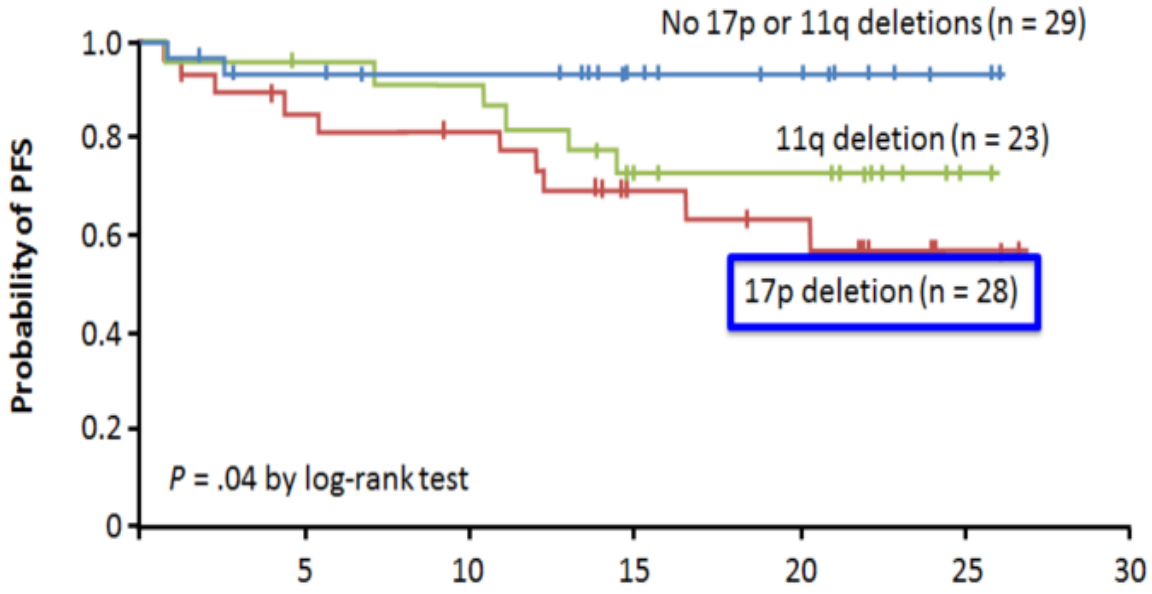


No. at Risk						
Ibrutinib	195	191	184	115	32	5
Ofatumumab	196	183	164	88	21	3

Byrd et al. NEJM 2014

Ibrutinib

17p del still has a worse outcome compared to other genetic abnormalities

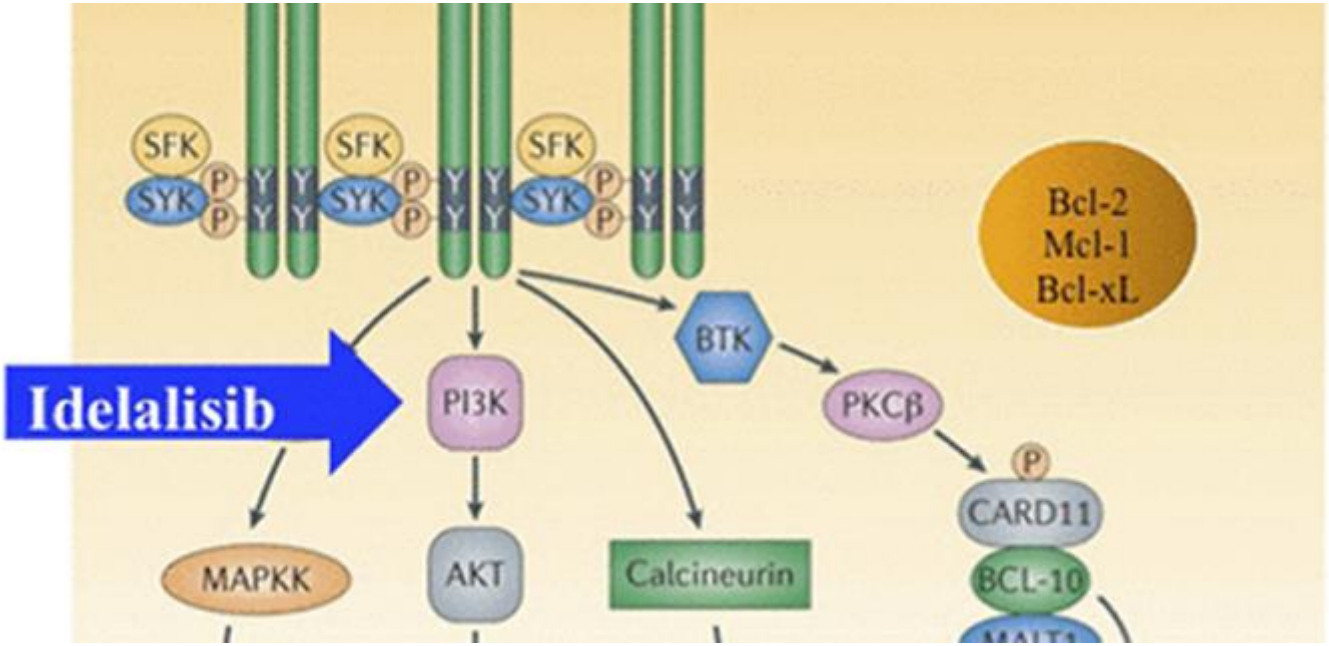


Byrd JC, et al. N Engl J Med. 2013;369:32-42.

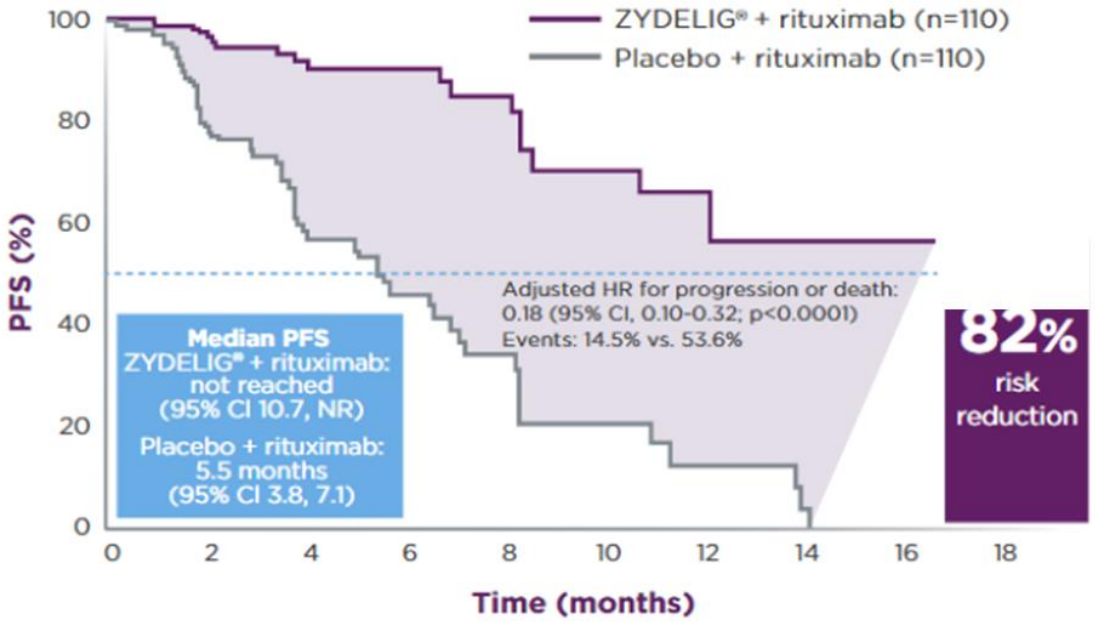
Treatment options for relapsed CLL

- If relapse occurs > 2-3 years, can repeat immuno-chemotherapy
- Targeted therapy (small molecules- taken orally, expensive)
  - BCR inhibitors (ibrutinib and idelalisib)
  - BCL2 Inhibitor (venetoclax) – on trial/compassionate patient access program
- Clinical trial with other novel agents
- Cellular therapies: CAR-T (trial), allogeneic transplant

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



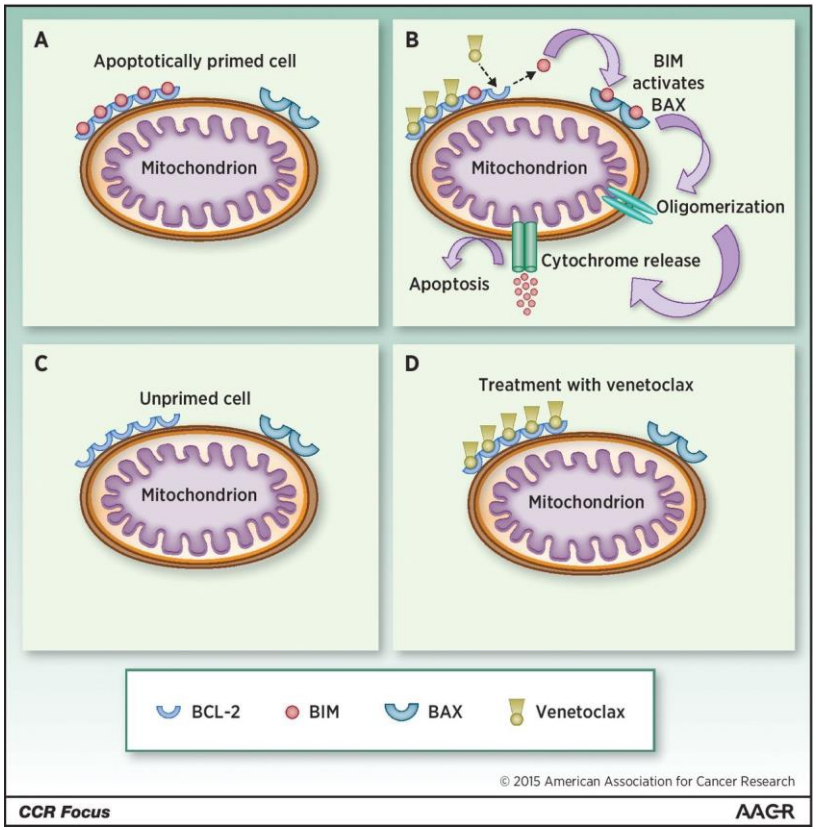
Idelalisib & Rituximab



	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)

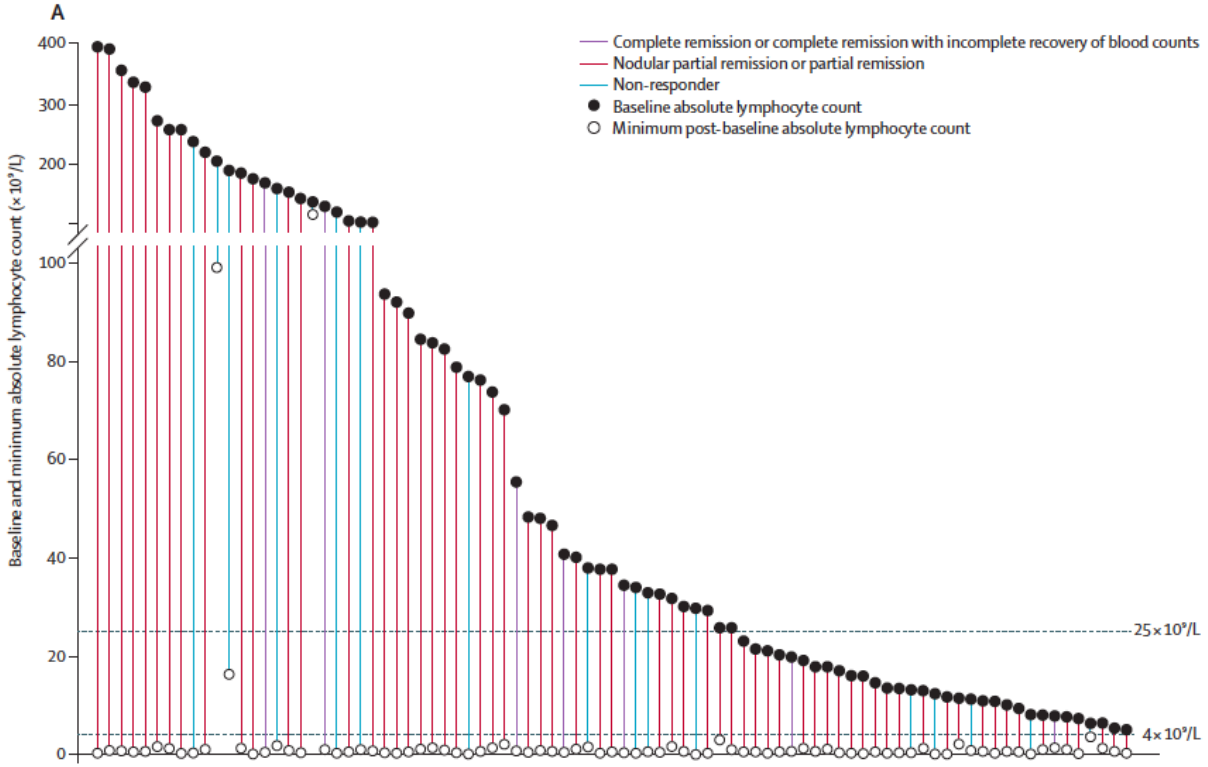
At 24 weeks, disease progression occurred in 12 patients (10.9%) with Zydelig + rituximab vs 53 patients (48.2%) with placebo[1]

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*

Venetoclax active in 17p del CLL

Response	All (n=78)	del(17p) (n=19)	Fludarabine Refractory (n=41)	IGHV Unmutated n=24)
ORR, n (%)	60 (77)	15 (79)	31 (76)	18 (75)
CR, n (%)	18 (23)	5 (26)	9 (22)	7 (29)
PR,[a] n (%)	42 (54)	10 (53)	22 (54)	11 (46)
SD, n (%)	10 (13)	2 (11)	7 (17)	2 (8)
PD, n (%)	2 (3)	1 (5)	1 (3)	2 (8)
D/C before first (week 6) assessment, n (%)	6 (8)	1 (5)	2 (5)	2 (8)

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 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.

Questions?