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LE LYMPHOME ÉDUCATION
RÉSEAUTAGE LEADERSHIP
LES 15 ET 16 SEPTEMBRE 2017
BÉNÉVOLES MONTRÉAL (QC)
SOUTIEN AUX SURVIVANTS

CLL: future therapies

Dr. Nathalie Johnson

Disclosures

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

- Research funding
  - Roche, Abbvie, Lundbeck

Outline

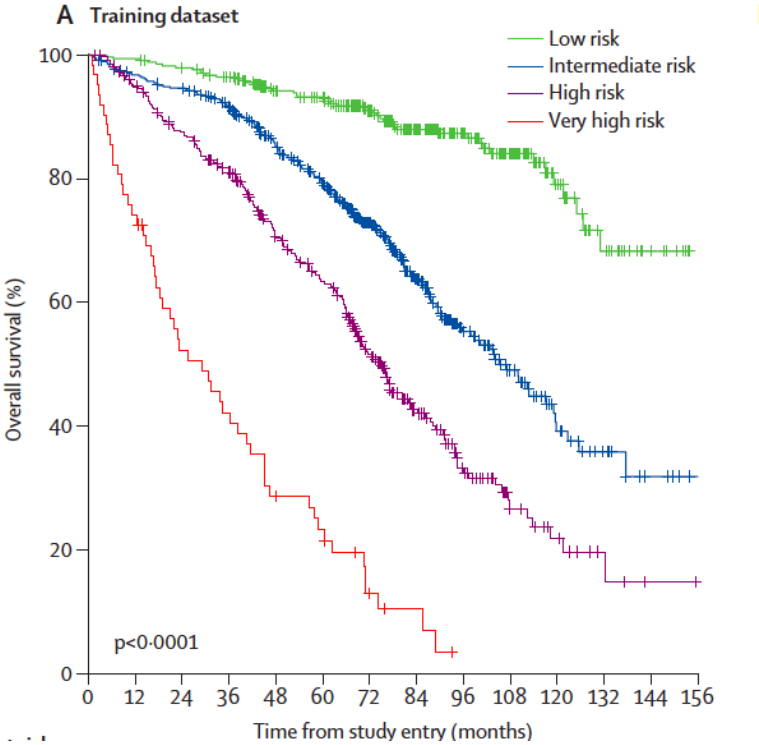
- Treatment of relapsed CLL:
  - Clinical trials versus standard of care
- Health Canada approved “new therapies”
  - BTK inhibitor: ibrutinib
  - PI3K inhibitor: idelalisib
  - BCL2 inhibitor: venetoclax
- Potential future therapies
  - Combinations of chemotherapy and novel agents
  - Immunotherapy
  - Therapy based on minimal residual disease testing

Disease biology predicts duration of response in CLL and provides a rationale to use “chemo-free” alternatives

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

Treatment Decision: 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

Clinical Trials

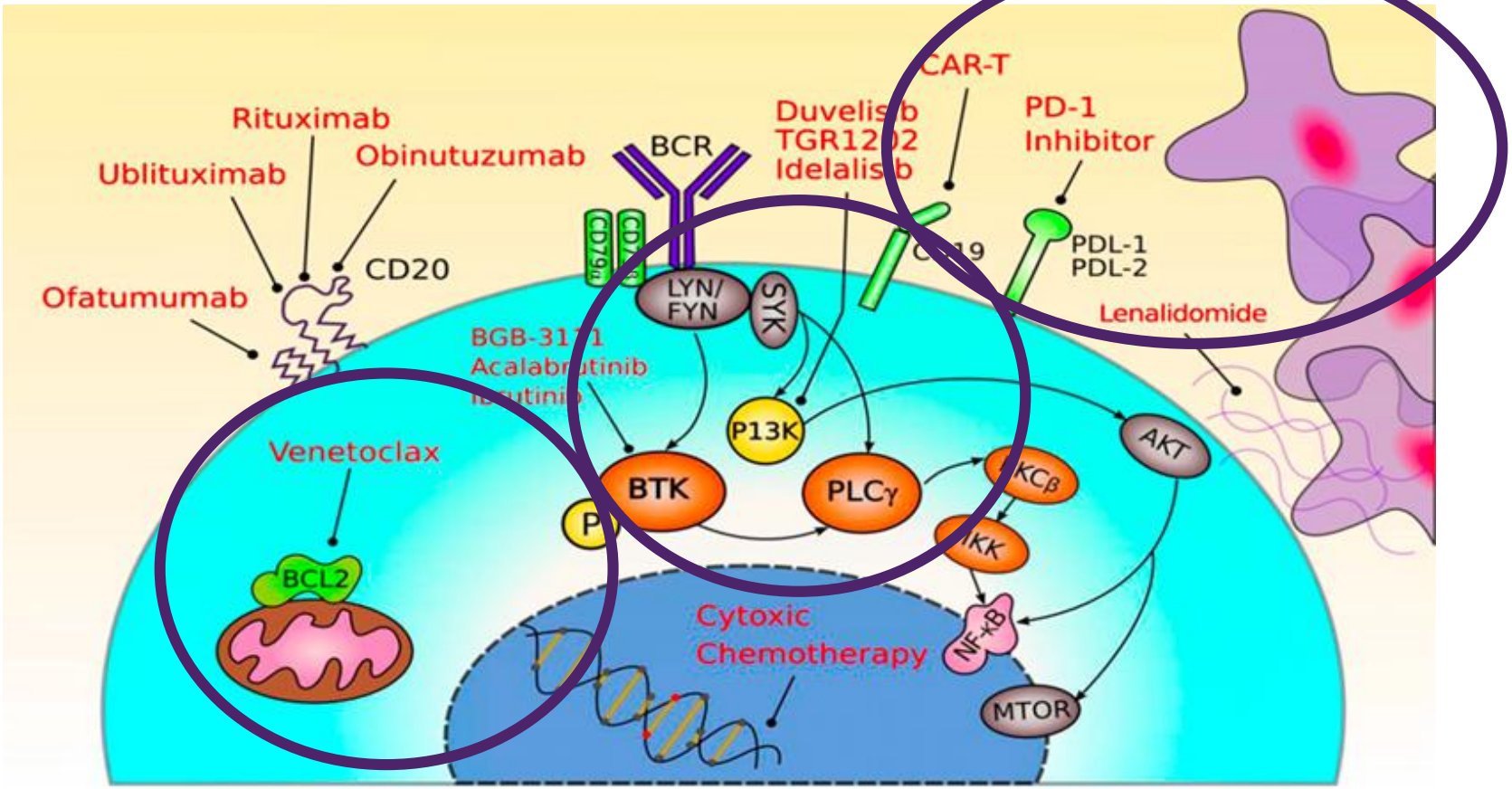
Phase 1:
Is this safe?

Phase 2:
Is this effective?

Phase 3:
Is this better than standard of care?

Safety is primary concern! Reviewed by ethics committee
Rigorous documentation of response and side effects

Novel Targets: different mechanism of action



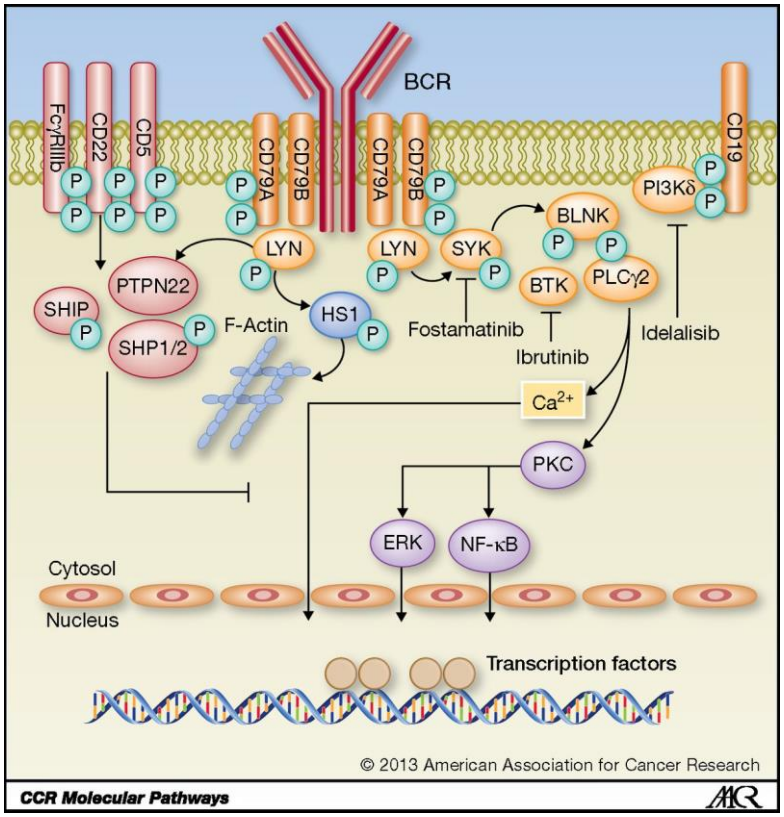
Brown, Hallek and Pagel; ASCO education book 2016

Novel therapies approved by Health Canada for CLL

Therapy	Class of Agent	Indication(s)
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

CD, cluster of differentiation.

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

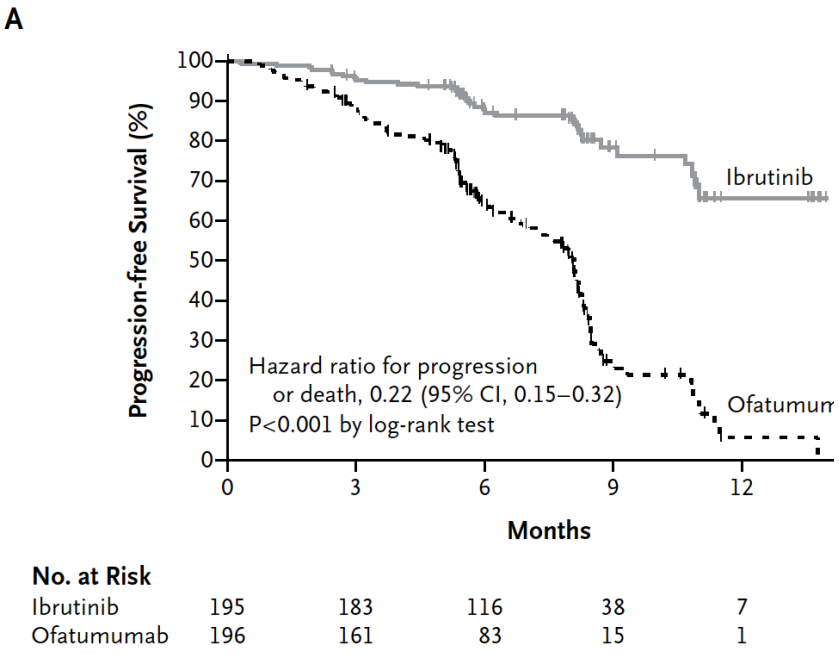


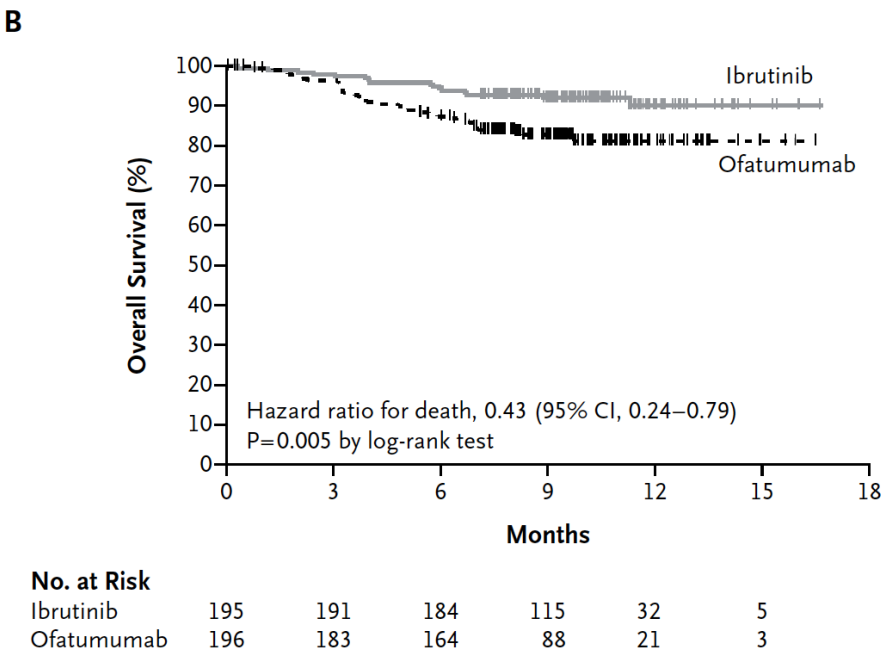
Binding to the BCR provides a survival signal "feed me"

Important mediators that transmit BCR signals are:

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

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



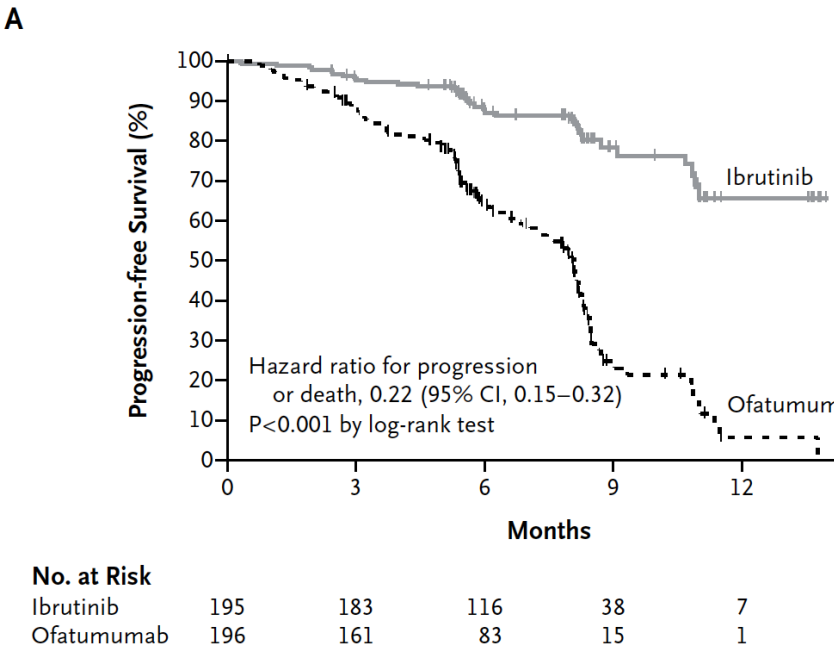


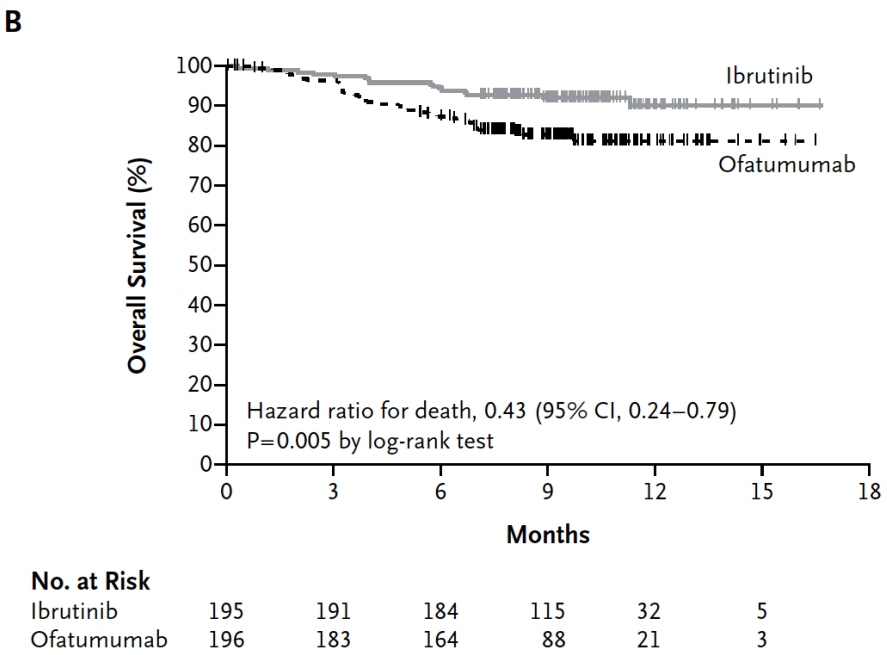
Byrd et al. NEJM 2014

Overall response: 40% Ibru vs 4% Ofa

No difference in response based on 17p del status

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





Byrd et al. NEJM 2014

Overall response: 40% Ibru vs 4% Ofa

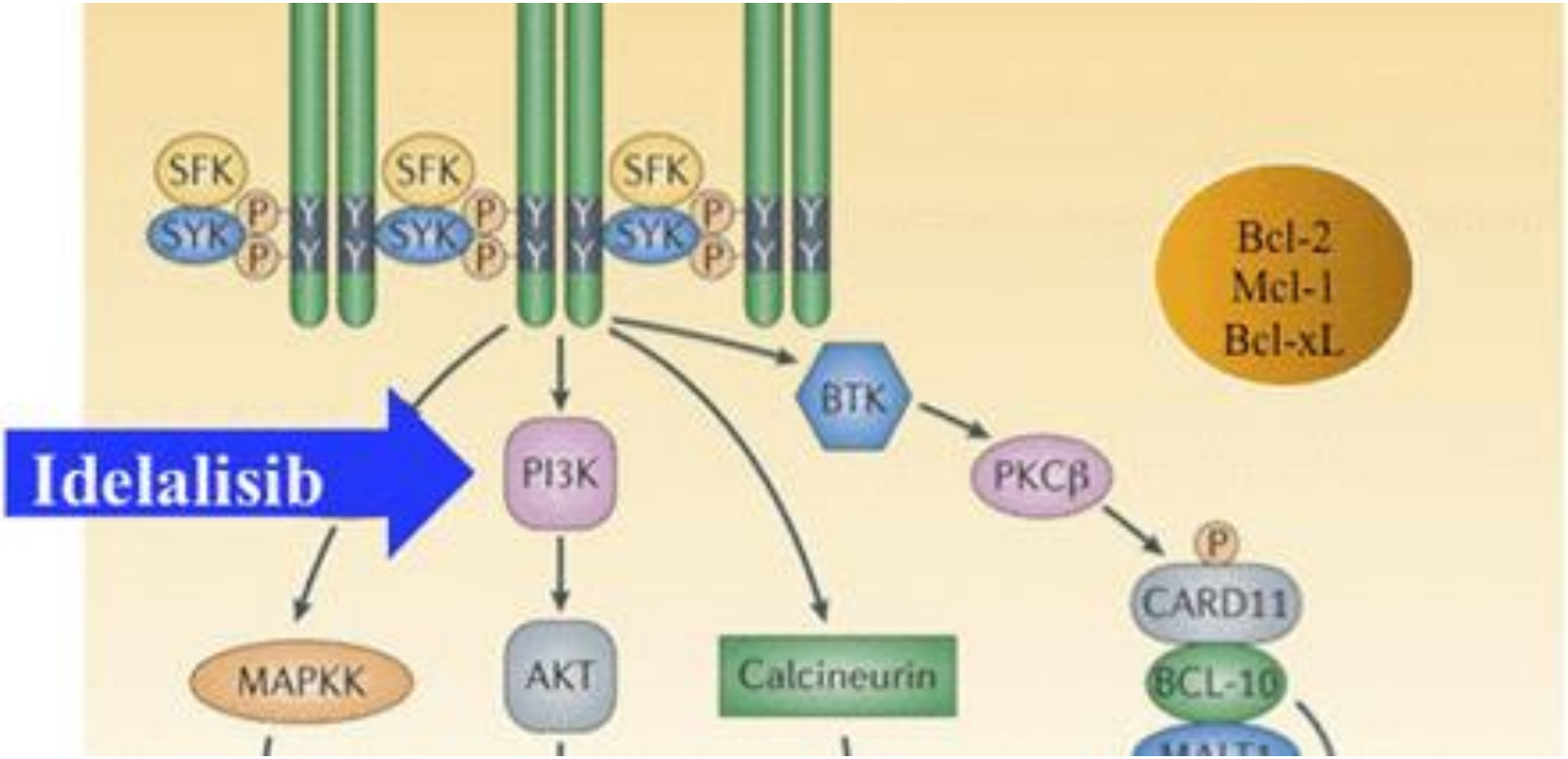
No difference in response based on 17p del status

Acalabrutinib

- Phase I/II 60-patient study, median 3 prior therapies, **ORR 95%.**
- **del17p population**, the ORR was **100%**.
- The median PFS was 14.3 months, with 1 fatal progression and 1 disease progression.
- Able to inhibit 94% of BTK target occupancy after 7 days of dosing
- There were no episodes of atrial fibrillation or major bleeding events.
- Two percent of patients had grade 4 febrile neutropenia, and serious AEs consisted of pneumonia (10%), autoimmune hemolytic anemia (3%), and pyrexia (3%).

Byrd JC, Harrington B, O'Brien S, et al. Acalabrutinib (ACP-196) in relapsed chronic lymphocytic leukemia [published online December 7, 2015]. *N Engl J Med*. doi:10.1056/NEJMoa1509981.

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

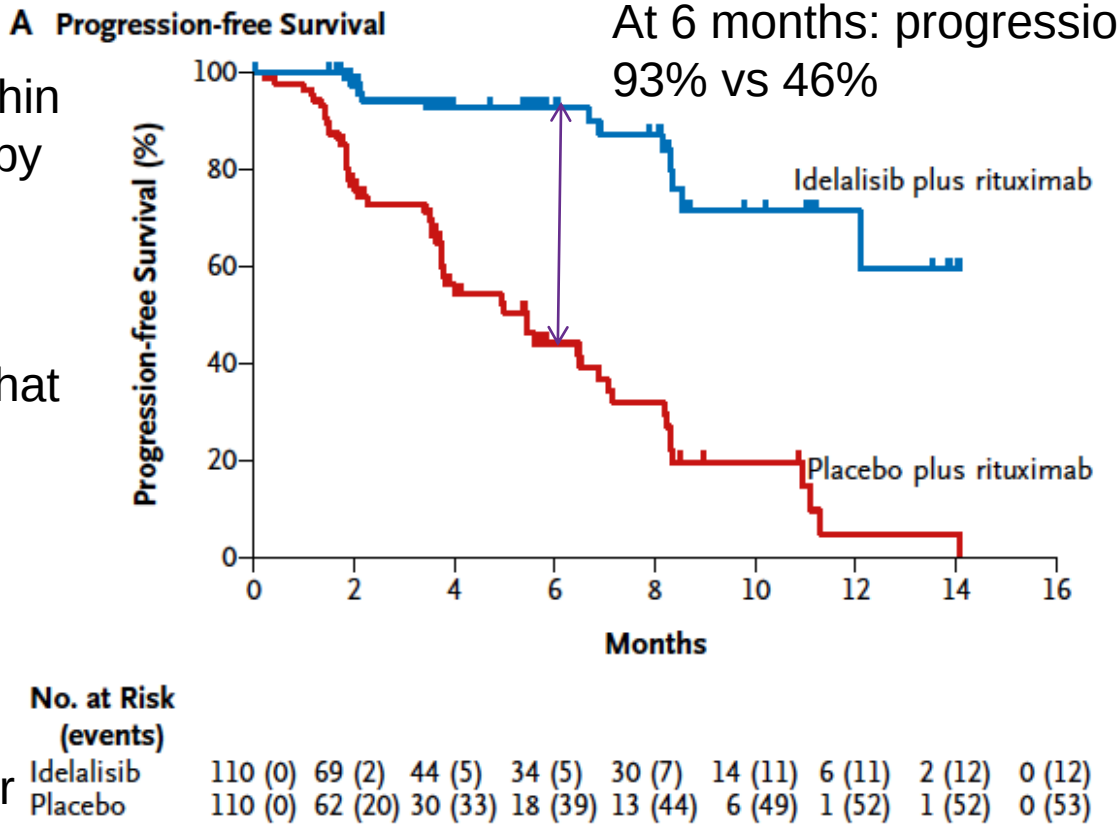


Idelalisib & rituximab is superior to rituximab

220 relapsed CLL within 2 years of prior therapy
40% 17p deleted
Heavily pre-treated
And “frail”
> 3 prior treatments that included rituximab in~90% of patients

ORR: 81% vs 13%

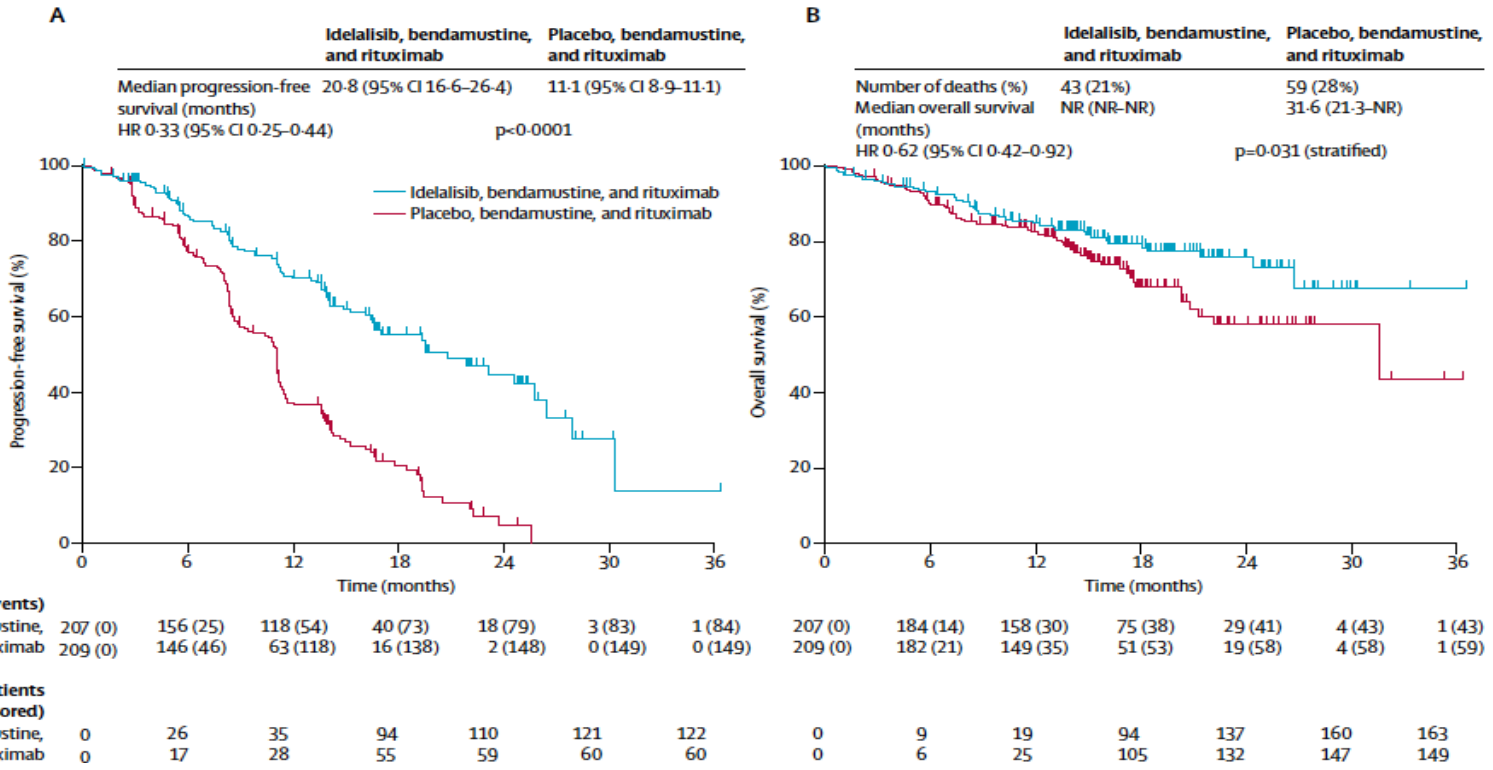
Overall survival: 92% vs 82% at 1 year



At 6 months: progression free survival 93% vs 46%

Furman et al. NEJM; 2014 Mar 13;370(11):997-1007 ;

Idelalisib +BR is superior to BR in relapsed CLL (PFS and OS)



Zelenetz et al. Lancet Oncol. 2017 Mar;18(3):297-311

Idelalisib increases the risk of serious infections including CMV, PCP

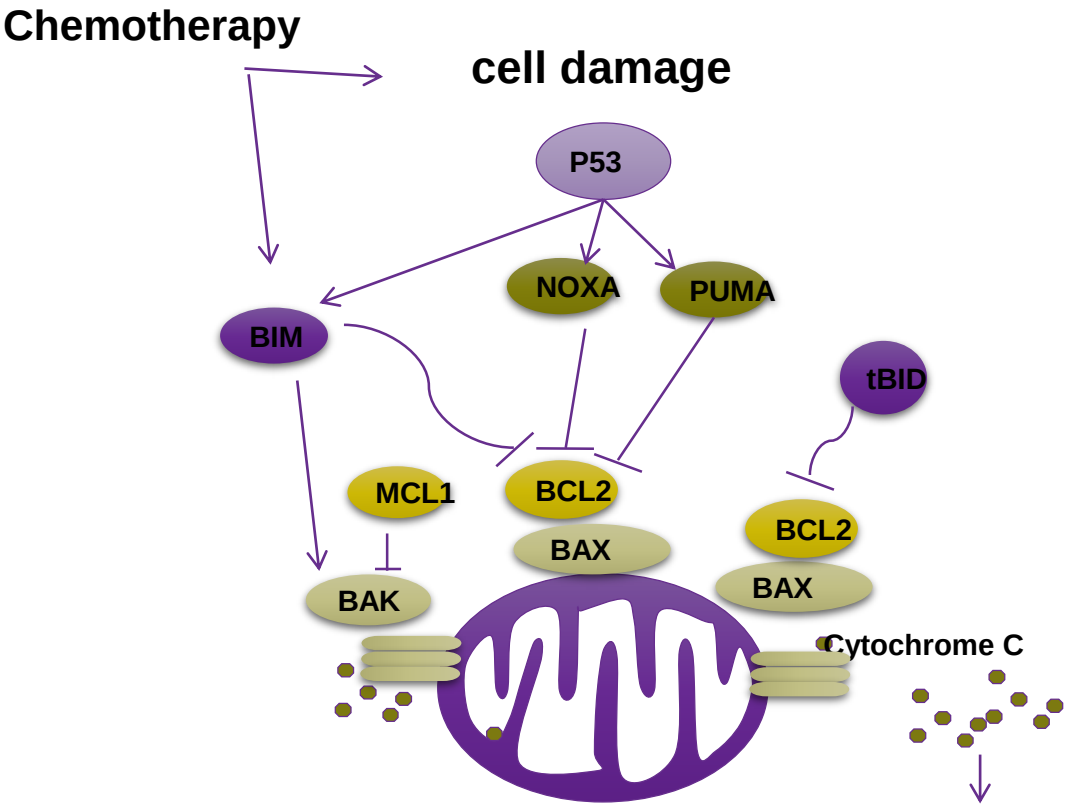
	Idelalisib, bendamustine, and rituximab (n=207)	Placebo, bendamustine, and rituximab (n=209)
Any serious adverse event	140 (68%)	92 (44%)
Febrile neutropenia	41 (20%)	10 (5%)
Pneumonia	29 (14%)	15 (7%)
Pyrexia	24 (12%)	11 (5%)
Sepsis	10 (5%)	3 (1%)
Diarrhoea	10 (5%)	1 (<1%)
Treatment related death	**11%**	**7%**

Zelenetz et al. Lancet Oncol. 2017 Mar;18(3):297-311

“Real world” adverse events with idelalisib (single agent)

- 94% of patients eventually discontinue idelalisib due to toxicity
  - Pneumonitis
  - Colitis
  - Transaminitis
  - Infection

CLL cells depend on BCL2 to survive

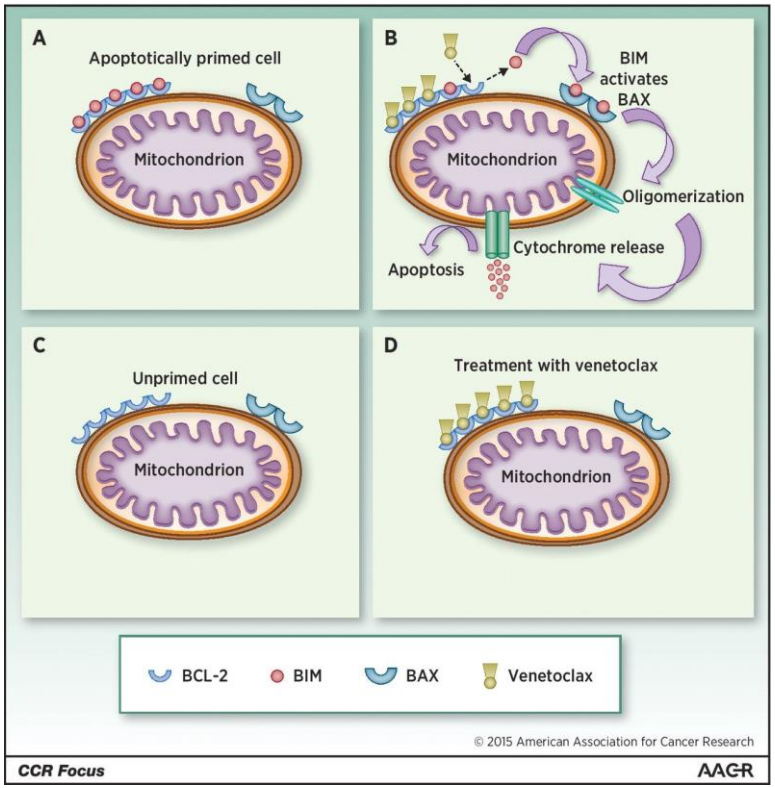


Mitochondria: cellular motor
2 critical roles:
provide energy
Decide cell fate (to live or die) in the face of adversity

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

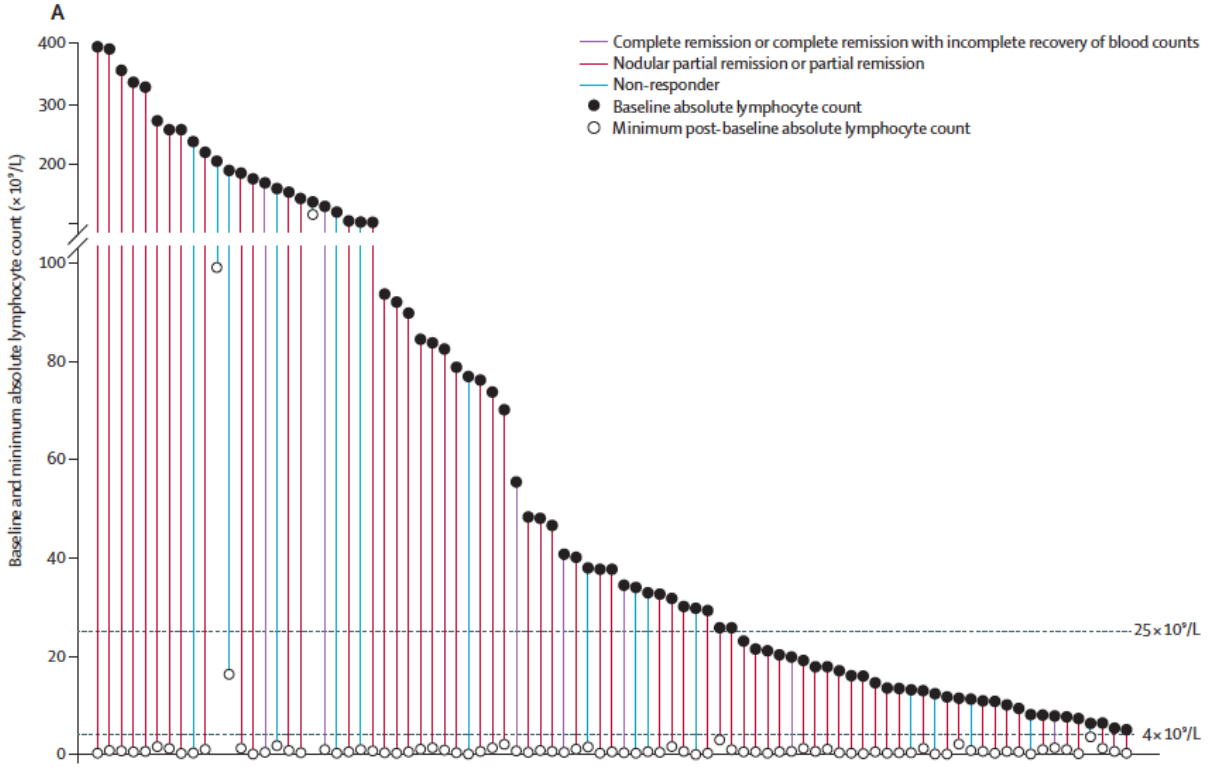
Mitochondrial collapse is an irreversible step to cell death

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 is 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)

Median progression free survival: 25 months

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

Venetoclax plus rituximab in relapsed or refractory chronic lymphocytic leukaemia: a phase 1b study

John F Seymour*, Shuo Ma*, Danielle M Brander, Michael Y Choi, Jacqueline Barrientos, Matthew S Davids, Mary Ann Anderson, Anne W Beaven, Steven T Rosen, Constantine S Tam, Betty Prine, Suresh K Agarwal, Wijith Munasinghe, Ming Zhu, L Leanne Lash, Monali Desai, Elisa Cerri, Maria Verdugo, Su Young Kim, Rod A Humerickhouse, Gary B Gordon, Thomas J Kipps, Andrew W Roberts

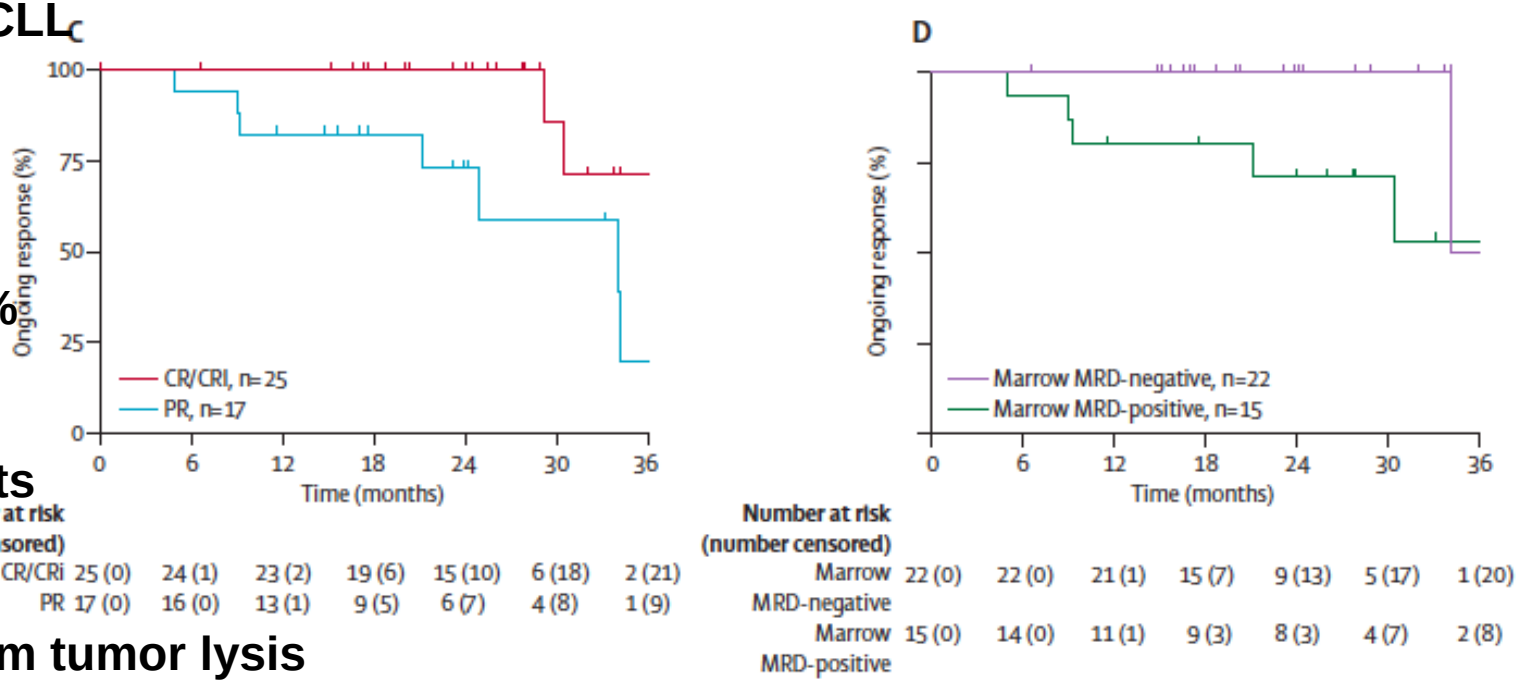
49 Relapsed CLL

ORR: 86%
CR: 50%

MRD-neg: 57%
2-y PFS: 82%

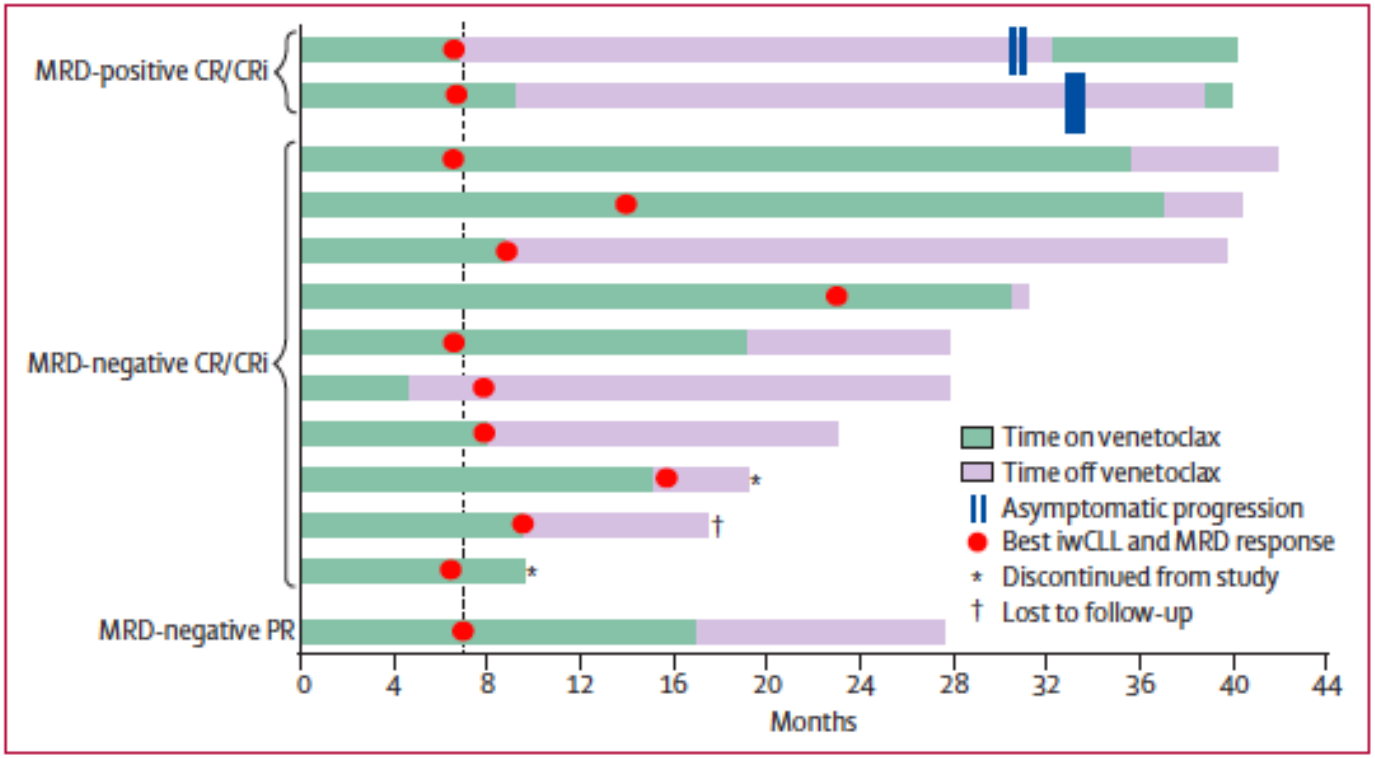
Adverse events 76%

One death from tumor lysis



Seymour et al. Lancet Oncol 2017; 18: 230–40

Can venetoclax be stopped??



Seymour et al. Lancet Oncol 2017; 18: 230–40

Gradual ramp up in dose to prevent tumour lysis syndrome

Tablets not actual size.

Patients with bulky adenopathy require admission to hospital for their first dose

Management of tumor lysis: hydration, rasburicase, management of hyperkalemia

Summary of novel agents

Agent	Unique Features	Select Key Trials	Progression-Free Survival
BTK Inhibitors			
Ibrutinib	First-in-class BTK inhibitor	RESONATE, R/R CLL, ibrutinib vs. ofatumumab, FDA approved[37]	R/R CLL single-agent: 26 mos = 75%[39]
		RESONATE-17, R/R CLL and front-line 17p deletion under FDA review[38]	del17p R/R CLL single-agent: 12 mos = 79%[38]
		RESONATE-2, first-line, ibrutinib vs. chlorambucil FDA approved[49]	First-line single-agent: 18 mos = 94%[49]
Pi3K Inhibitors			
Idelalisib	First-in-class PI3K inhibitor targeting δ isoform	Study 116, R/R CLL, idelalisib/rituximab vs. rituximab, FDA approved.[57]	R/R CLL with rituximab (45% with del(17p)): median 19.4 mos[57]
		Study 115, R/R CLL BR/idelalisib vs. BR under FDA review[59]	R/R CLL with BR: median 23.1 mos[59]
		Phase II first line, idelalisib and rituximab in 64 patients older than age 65 with ORR of 97%[64]	First line with rituximab: 36 mos = 83%[64]
Bcl-2 Inhibitor			
Venetoclax	Lacks targeting of Bcl-xL	Phase I/expansion R/R CLL, venetoclax single agent, under FDA review[72]	R/R CLL single agent: median 25 mos[72]
		Phase Ib R/R CLL, venetoclax and rituximab in 49 patients with ORR of 86%[73]	R/R CLL with rituximab (33% with del(17p)): 24 mos = 83%.[73]

Brown, Hallek and Pagel; ASCO education book 2016

Optimal sequencing of ibrutinib, idelalisib, and venetoclax in chronic lymphocytic leukemia: results from a multicenter study of 683 patients

Surprisingly, almost half of our patients discontinued KI therapy due to toxicity. This observation is critical as it appears to be in conflict with the clinical trial findings that led to approving ibrutinib and idelalisib, which showed progression of disease as a major reason for drug discontinuation [1, 4, 22, 23]. Furthermore, the nature of these toxicities is somewhat different to what has been previously reported. In fact, while atrial fibrillation as a toxicity reason for discontinuation was noted in 13.5% of patients in our analysis, it was not cited amongst the top adverse events in the original ibrutinib study [2]. Additionally three recent reports suggest a higher rate of atrial fibrillation than what was initially reported in the initial ibrutinib studies in CLL [24–26].Similarly, pneumonitis, which is classically associated with idelalisib, was observed in 9% of patients as a toxicity reason for discontinuation in our ibrutinib cohort as well [27].

Mato et al. Annals of Oncology 28: 1050–1056, 2017

Side effects of novel therapies

- **Ibrutinib**
  - Cardiac arrythmias
  - Bleeding
  - Hypertension
  - Opportunistic infections
- **Idelalisib**
  - Opportunistic infections
  - Colitis/diarrhea
- **Venetoclax**
  - Neutropenia
  - Nausea
  - Tumor lysis

Advantage: oral medications

<u>Disadvantages:</u>
Some have low complete responses
Use indefinitely until progression
Cost (~$8,000 to 12,000/month)

<u>Unanswered questions:</u>
Best sequence of drugs
Best combination of drugs

Allogeneic Transplantation is an option in young patients with relapsed CLL

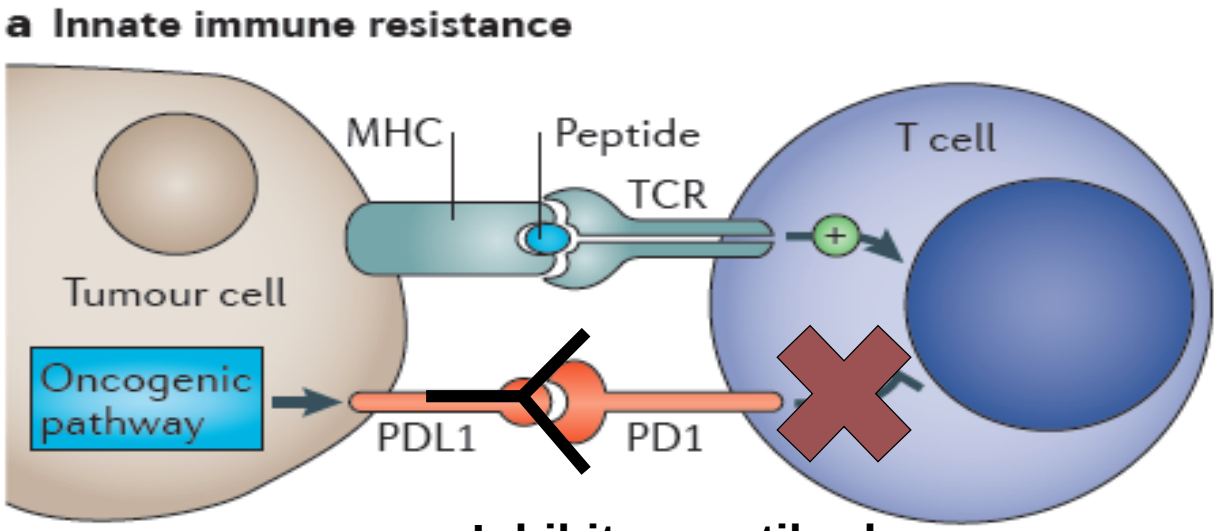
Table 1. Summary of Transplant Characteristics and Survival in the Largest Reported Prospective Studies of RIC HSCT in CLL

	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

Immunotherapy: PD1 blockade re-establishes T cell activation



Constitutive oncogenic signalling induces PDL1 expression on tumour cells

Pardol D; The blockade of immune checkpoints in cancer immunotherapy; Nature Reviews Cancer; 2012; p252-264

Pembrolizumab is active in a subset of patients with "Richter's transformation (RT)"

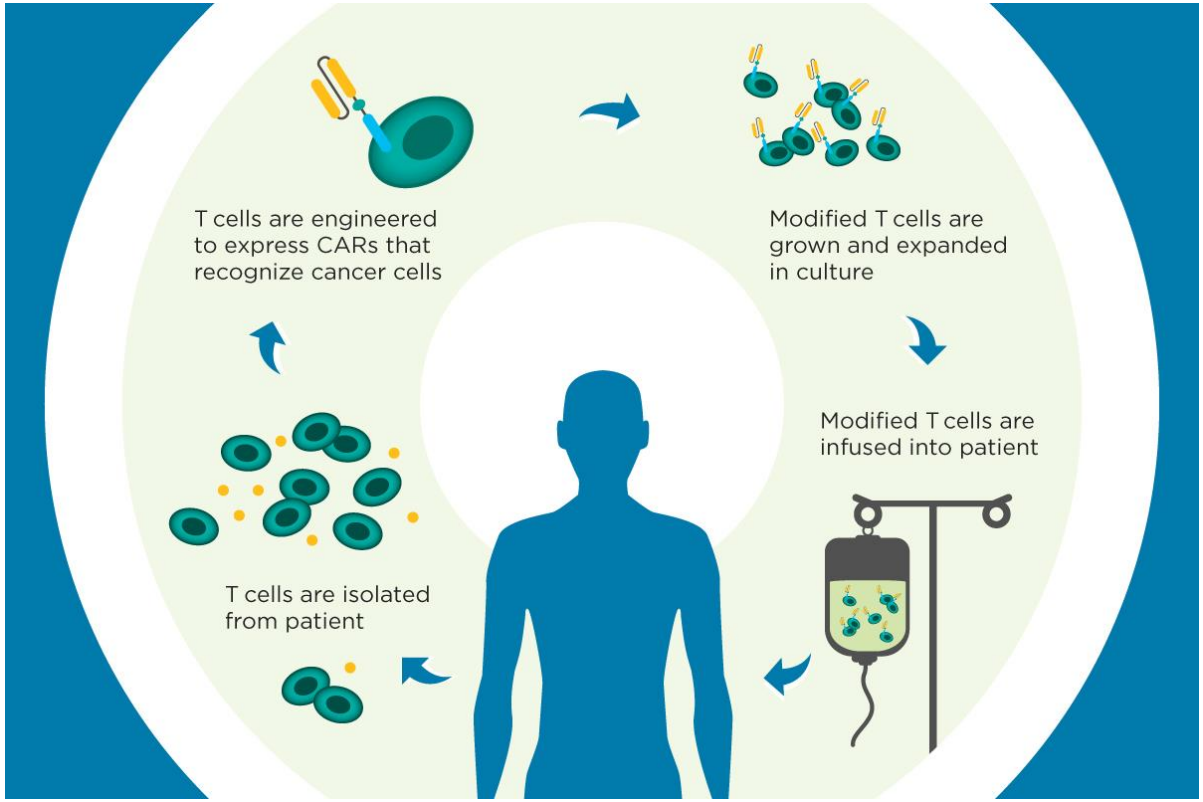
Table 3. Clinical activity of pembrolizumab in trial patients

Response	RT (n = 9)	CLL (n = 16)	Total (n = 25)
CR, no. (%)	1 (11)	0	1 (4)
PR, no. (%)	2 (22)	0	2 (8)
PMR, no. (%)	1 (11)	0	1 (4)
SD, no. (%)	4 (44)	5 (31)	9 (36)
PD,* no. (%)	1 (11)	8 (50)	9 (36)
Could not be evaluated,† no. (%)	0	3 (19)	3 (12)
ORR, % (95% CI)	44 (14-79)	0 (—)	16 (5-36)
Median PFS, mo, (95% CI)	5.4 (2.8-12.2)	2.4 (1.2-3.3)	3.0 (2.1-5.4)
Median OS, mo, (95% CI)	10.7 (4.4-NR)	11.2 (2.8-NR)	10.7 (4.4-NR)

Heavily pre-treated patients, most had failed ibrutinib

Ding et al. Blood 2017; 129(26): 3419-3427

CAR-T cell therapy



Chimeric antigen receptor (CAR) helps T cells identify tumor cells

T cells recognizes tumor cells as foreign and attacks them

Mskcc.org

CAR-T can induce durable remissions in relapsed/refractory CLL

- 24 ibrutinib-resistant CLL (many exhausted all lines)
- Responses:
  - 21% complete response
  - 53% partial response
- Toxicities
  - 83% cytokine release syndrome
  - 33% developed neurotoxicity

Turtle et al. JCO 2017; 35 (26):3010-3020

Challenges:

- Delay in treatment given the need to custom prepare cells
- Costs: very expensive (not yet FDA approved)
- Toxicities: cytokine release syndrome (need hospitalization)

Cost of new therapies is an issue

Regarding CAR-T cell therapy:

"While both external and Novartis' quantitative assessments of these values indicate that a cost-effective price could be $600,000 to $750,000, we recognize the importance of this paradigm-shifting therapy and are setting the price at $475,000 for this one-time treatment," Dana Cooper, a spokesman for Novartis, said in an interview with OncLive.

Tony Hagen @oncobiz
Published Online: *Wednesday, Aug 30, 2017*

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, acalabrutinib)
- Idelalisib
- BCL2 Inhibitor (venetoclax) – on trial/compassionate patient access program

Clinical trial with other novel agents

Cellular therapies: CAR-T (trial) versus allogeneic transplant

Future Focus

- Sequencing – which treatment when?
- What are best combinations of drugs? Optimize efficacy and minimize toxicity
- Can we stop therapy when disease is no longer detectable- i.e. no minimal residual disease (MRD)?
- Is CLL curable with new treatment options?
- Need better options for Richter's transformation
- Need to consider cost/benefit ratio