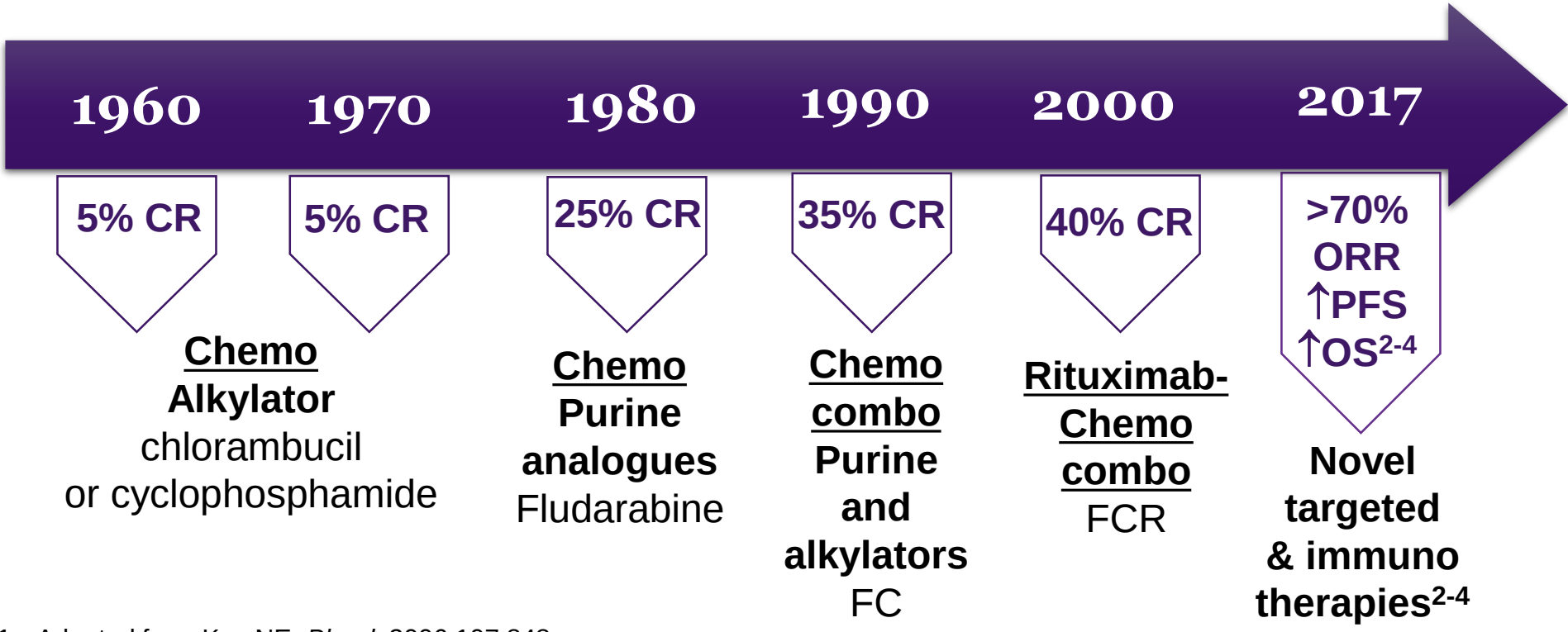
LYMPHOMA CANADA

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

CLL: Future Therapies

Dr. Anca Prica

Treatment Options: 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
OS, overall survival
PFS, progression-free survival
ORR, overall response rate

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

Clinical trials are carefully planned research studies where the most-promising discoveries and results from laboratory studies are tested with patients.

Trials may look at:

- new treatments, tests or procedures
- lifestyle choices
- the impact of cancer on you and your family

New & Improved Treatments

A clinical trial can test many aspects of treatment:

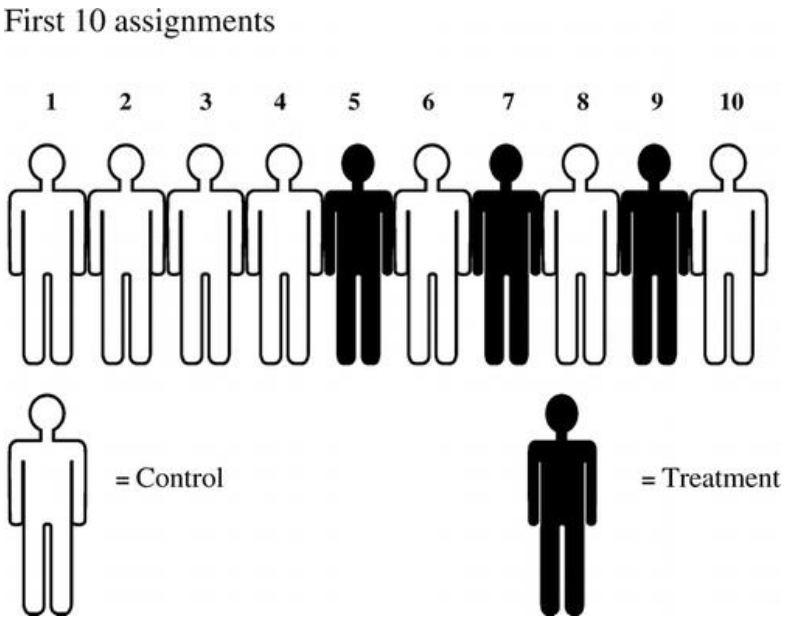
- The safety and effectiveness of new medications;
- The addition of new medications to standard treatments;
- Potential new methods of administering standard treatments (e.g. oral versus IV, inpatient versus outpatient).

Clinical Trial Safety

- Clinical trials are carefully examined and approved by ethics committees and must meet rigorous Health Canada and medical standards.
- A large amount of detailed research is conducted on any new treatment or procedure before it reaches the stage where it is tested on patients.
- Healthcare professionals work very hard to minimize the risks of participating in a clinical trial.

Clinical Trial Phases

Why are phase 3 large trials important?



Pros:

- High quality cancer care: VIP and access to care at leading health care facilities during trial
- Access to novel therapies not available to the public
- The new treatment may have less side-effects than the standard therapy
- Help others by furthering science
  tissue samples
- Free to you – often parking covered or subsidized
- Active role in a decision that affects your life

Cons:

- Worse or unexpected side effects
- The new treatment may not work
- More visits and tests
- If randomized, you may not get the experimental agent/intervention
- The new treatment may not be available to you immediately once trial ends.

Dr. David Porter

“Immunotherapy is revolutionizing cancer care. We are now using completely new approaches in the treatment of the disease. It took a long time to get here, although it seems so logical to try stimulating and manipulating the immune system to attack cancer cells. The potential in oncology right now is enormous and seemingly limitless. Some of the issues we are grappling with are how to control the immune system and how to target it to go after specific types of tumors.”

Jodi Fisher Horowitz Professor in Leukemia Care Excellence and Director of Blood and Marrow Transplantation at the Abramson Cancer Center of the University of Pennsylvania

Difference: Traditional Chemotherapy & Novel Agents

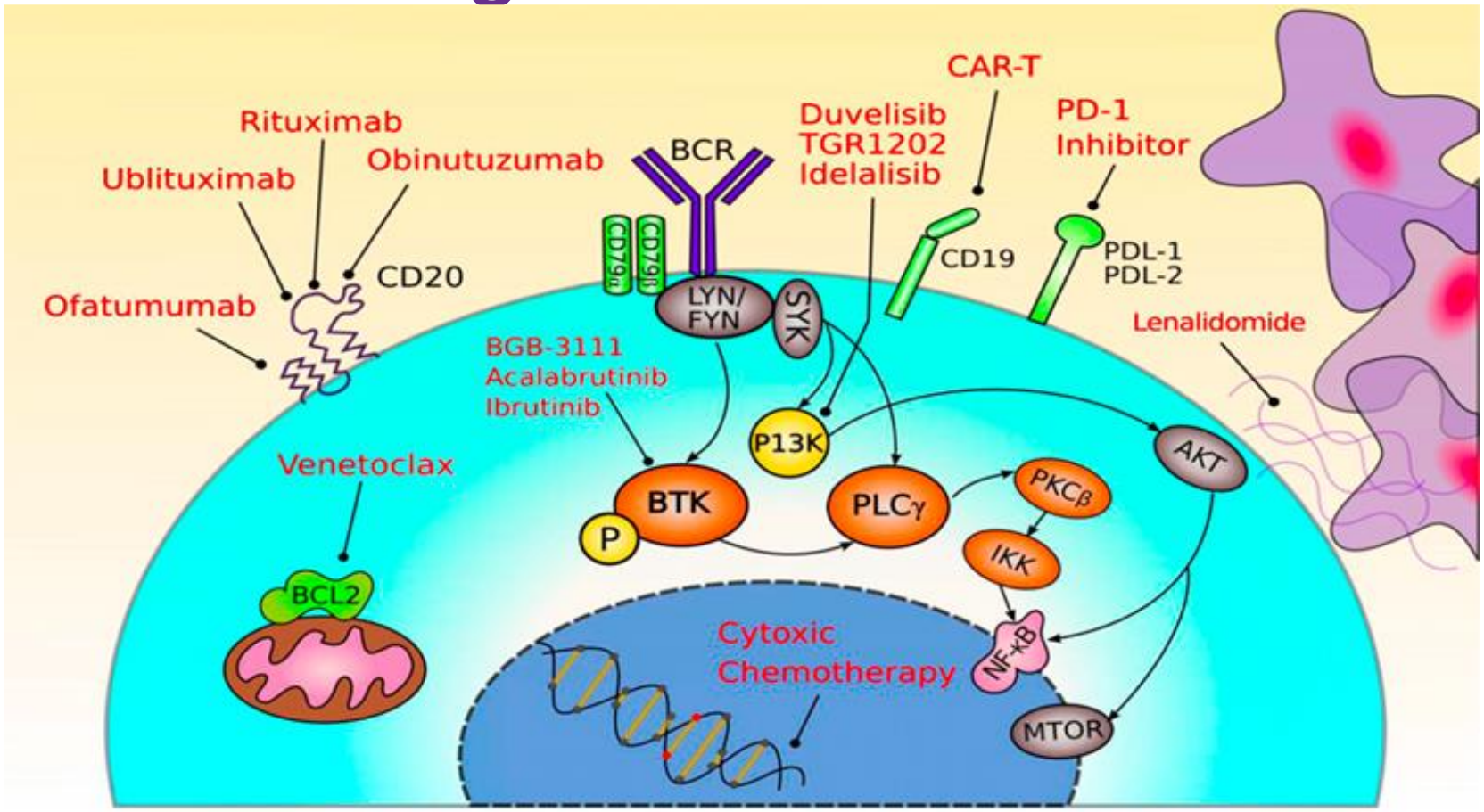
Chemotherapy

- 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 Targets

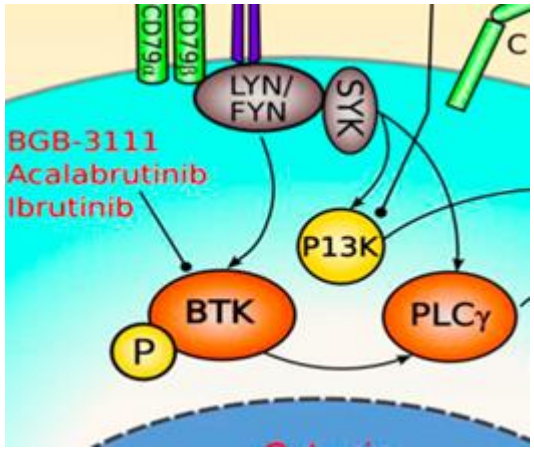


Ongoing/Planned Studies – over 1000!!

- Lenalidomide based
  - Maintenance study
  - Rituximab
  - Chlorambucil
- BTK Inhibitor based
  - Ibrutinib/Nivolumab
  - GS 4059/Entospletinib
- PI-3K Inhibitor based
  - Idelalisib/Ofatumumab
  - Dulelisib/Ofatumumab
- Venetoclax based
  - Obinutuzumab
  - Rituximab
  - Ibrutinib
  - Bendamustine/Rituximab
- Obinutuzumab based
  - Bendamustine
- Vaccines
- Autologous T cells
  - CART

BTK Inhibitors

- BTK, a protein essential for the survival and proliferation of the tumour cells.
  - Ibrutinib
- More selective and potent BTK inhibitors are being investigated.
  - ACP-196 (acalabrutinib)
  - ONO/GS-4059
  - BGB-3111, CC-292



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%).

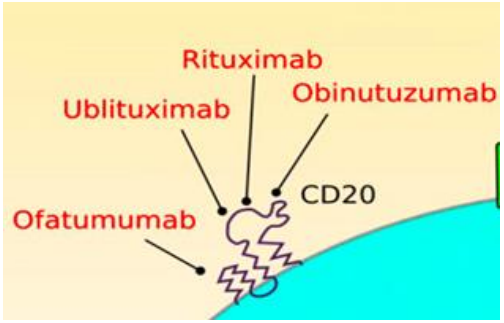
Byrd JC, Harrington B, O'Brien S, et al. Acalabrutinib (ACP-196) in relapsed chronic lymphocytic leukemia [published online December 7, 2015]. *N Engl J Med*. doi:10.1056/NEJMoa1509981.

Acalabrutinib

- 33 CLL & SLL patients intolerant to ibrutinib
- ORR was 79% (1 CR, 15 PR, 7 PRL, 6 SD)
- 24 patients (73%) still on acalabrutinib
- 27% patients stopped treatment (3- disease progression; 3- adverse events; 1- other non-related illness; 2- other)
- 36% patients experienced recurrent adverse events, most either decreased in severity or remained unchanged in severity on acalabrutinib compared with on ibrutinib

Awan FT, Schuh A, MD PhD, Brown JR, et al. Acalabrutinib monotherapy in patients with ibrutinib intolerance: Results from the phase 1/2 ACE-CL-001 clinical study.

TG-1101 (Ublituximab)



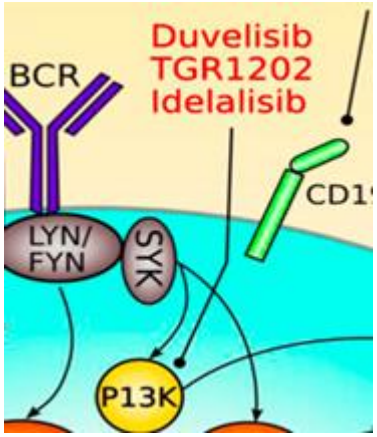
- Monoclonal antibody that targets CD20 antigen, with enhanced clinical activity and potency.
- Phase 3 GENUINE Study - TG-1101 (ublituximab) plus ibrutinib increasing Overall Response Rate (ORR) over ibrutinib alone in high risk pts (17p or 11q del, p53 mut)

	TG-1101 plus Ibrutinib	Ibrutinib	P-value
Treated Population (n)	n=59	n=58	
Overall Response Rate	80 %	47 %	P<0.001

Sharman JP, Farber CM, Mahadevan D, et al. Ublituximab (TG-1101), a novel glycoengineered anti-CD20 antibody, in combination with ibrutinib is safe and highly active in patients with relapsed and/or refractory chronic lymphocytic leukaemia: results of a phase 2 trial. *Br J Haematol*. 2017;176(3):412-420.

PI3K Inhibitors

- The PI3K pathway is important in regulating the cell cycle
- It is directly related to cellular inactivity, proliferation, cancer, and longevity.
- When it goes awry, it is a key component of survival in a variety of cancers, including CLL



Duvelisib IPI-145

- Oral inhibitor of both delta & gamma isoforms PI3K
- Phase I/II study of monotherapy: 54 heavily pretreated patients. Best ORR was 55% in 49 evaluable patients, including 1 CR and 26 PRs.
- Adverse events included transient cytopenias (31% neutropenia, 11% thrombocytopenia, 15% febrile neutropenia, and 11% pneumonia). Treatment discontinued in 31% of patients due to adverse events, and in another 24% of patients because of disease progression.
- DUO study (randomized phase III) results anticipated soon
- Many combination trials

Susan O'Brien, Manish Patel, Brad S. Kahl, et al. Duvelisib (IPI-145), a PI3K-δ,γ Inhibitor, Is Clinically Active in Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia. *Blood 2014 124:3334*.

TGR-1202 (Umbralisib)

- Monotherapy, oral, significant structural differences to other PI3K inhibitors
- In a dose escalation study of 16 patients with CLL
  - ORR was 88%, 2 CR and 14 PR
  - 2 SD; no PD
- Markedly differentiated safety profile from other PI3Kδ inhibitors to date
- Most frequent reported AE's: nausea, diarrhea, fatigue, vomiting and neutropenia; limited G 3/4 events.

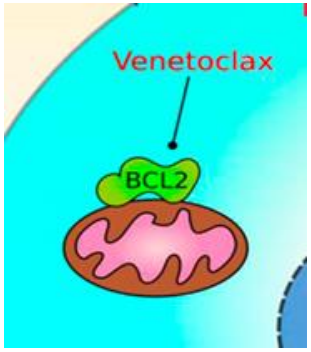
Howard A. Burris, Ian Flinn, Matthew Alexander Lunning, et al. Long-term follow-up of the PI3Kδ inhibitor TGR-1202 to demonstrate a differentiated safety profile and high response rates in CLL and NHL: Integrated-analysis of TGR-1202 monotherapy and combined with ublituximab. *ASCO 2016 Abstract 7512*

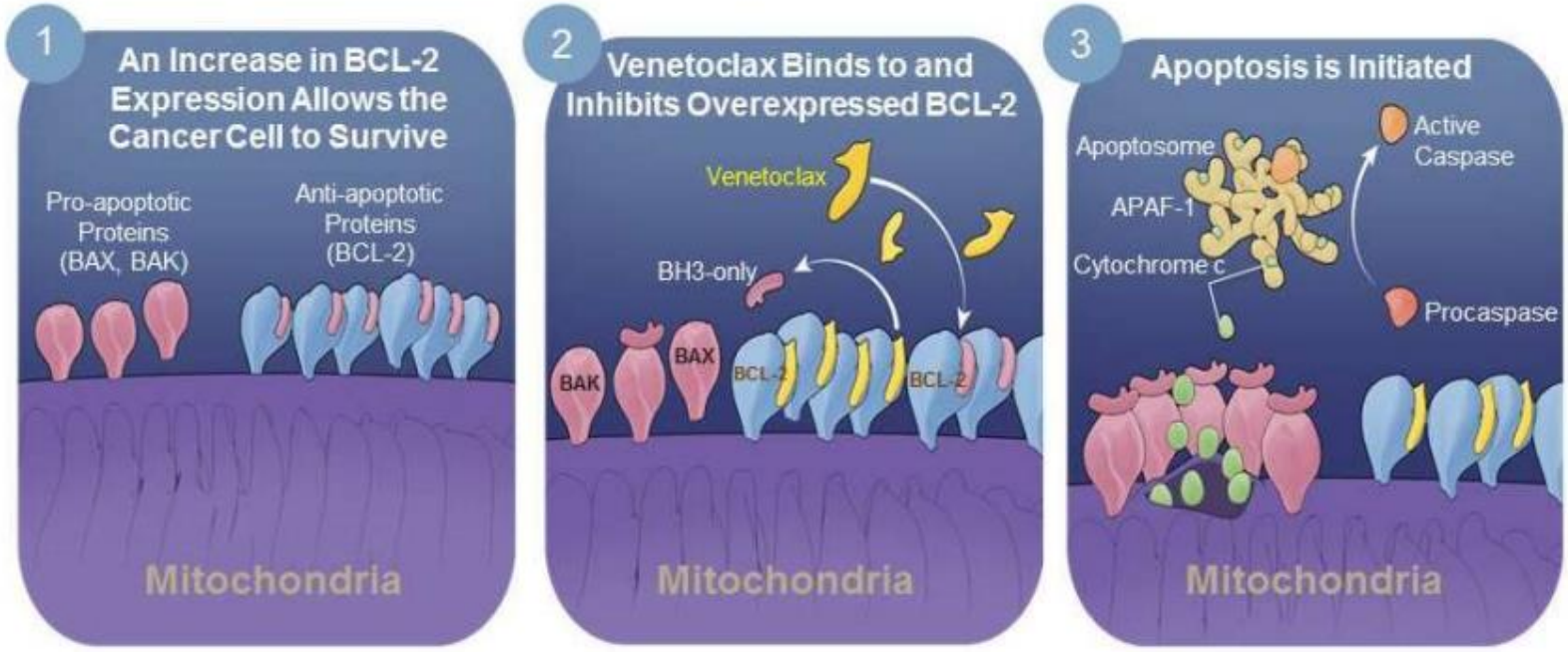
Safety Profile Comparison PI3K Inhibitors

	Idela + Ofa (ASCO 16)[2] n=173	Idelalisib (CLL & NHL)[1] n=256	Duvelisib (ASCO 15)[3] n=18	TGR-1202 (ASCO 16)[4] n=165
	Grade 3/4	Grade 3/4	Grade 3/4	Grade 3/4
Diarrhea/colitis	23%	10%	22%	4%
Pneumonia	20%	16%	N/A	5%
ALT/AST Elevations	13%	7-11%	17%	3%
Discontinued due to AE	39%	12%	33%	<8%

[1]Aggregated from Idelalisib prescribing information; [2] Jones et al. ASCO 2015; [3]Patel et al. ASCO 2015; [4]Aggregated from Burris et al. ASCO 2016

BCL-2 Inhibitor





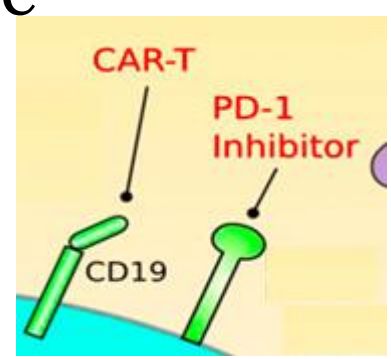
Venetoclax + Rituximab

- Phase 1b trials with 49 relapsed/refractory CLL or SLL patients
- ORR 86%
- CR 47%
- MRD-negative status in bone marrow of 24 (49%) patients
- 12 patients have durable remission after elective treatment cessation

Andrew W. Roberts , Shuo Ma , Danielle Brander, et al. Venetoclax (ABT-199 / GDC-0199) Combined with Rituximab Induces Deep Responses In Patients With Relapsed/Refractory Chronic Lymphocytic Leukemia. *EHA 2015 Abstract S431*

PD-1/PD-L1 inhibitors

- Programmed Cell Death protein
- PD-1 and PD-L1 turn off T-cell activation, preventing T cells from attacking the cancer.
- PD-1/PD-L1 inhibitors ability to achieve anticancer effects in the form of durable responses, improvements in survival, less toxicity for patients.



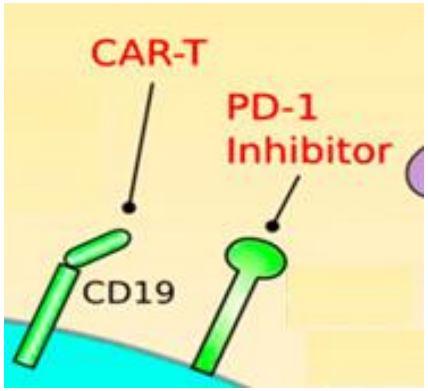
Pembrolizumab

- 25 CLL patients – 16 relapsed and 9 Richter's Transformation (RT)
- ORR relapsed CLL 0%
- ORR RT 44%
- Thought is these drugs will have to be used in combination with another agent that is effective against the underlying CLL

Ding W. et al. Pembrolizumab in patients with CLL and Richter transformation or with relapsed CLL. Blood. 2017 Jun 29; 129 (26): 3419–3427. DOI: 1182/blood-2017-02-765685. Epub 2017 Apr 18.

CAR-T Therapy

- Manipulate T cells so that they can recognize tumor cells and kill them
- Isolate a patient's own T cells and genetically modifying them to express chimeric antigen receptors or novel T cell receptors that recognize tumor cells.
- Modified cells are designed to attack the CD19 protein expressed on the surface of B cell malignancies.
- The reengineered cells are expanded and then injected back into the patient.



CAR-T Therapy

- 24 patients with high risk disease
- ORR 4 weeks post infusion 74%
  - CR 21%, PR 53%
  - 15/17 evaluable patients no longer had detectable marrow disease by flow cytometry
- 6 patients received a second dose of CAR T-cells following persistent or relapsed disease; two achieved CR
- CAR T-cells were detectable in all evaluable patients over 6-months after receiving the CAR-T infusion

Turtle C.J. et al. Durable Molecular Remissions in Chronic Lymphocytic Leukemia Treated With CD19-Specific Chimeric Antigen Receptor–Modified T Cells After Failure of Ibrutinib. Journal of Clinical Oncology. 2017 Jul 17.

CAR-T Therapy

- CRS = 83% pts, 20/24 pts (Grade 4 = 1 pt., Grade 5 = 1 pt.)
- Neurotoxicity = 33% pts, 8/24 pts (Grade 3 = 5 pts, Grade 5 = 1 pt.)
  - One patient died from neurotoxicity, but this was reversible in all other patients
- Median hospitalization duration was 9-days (0–49 days)
- A higher percentage of leukemic B-cells in the marrow before CAR-T infusion was associated with development of CRS and neurotoxicity after infusion

Turtle C.J. et al. Durable Molecular Remissions in Chronic Lymphocytic Leukemia Treated With CD19-Specific Chimeric Antigen Receptor–Modified T Cells After Failure of Ibrutinib. Journal of Clinical Oncology. 2017 Jul 17.

Allogeneic Transplantation CLL

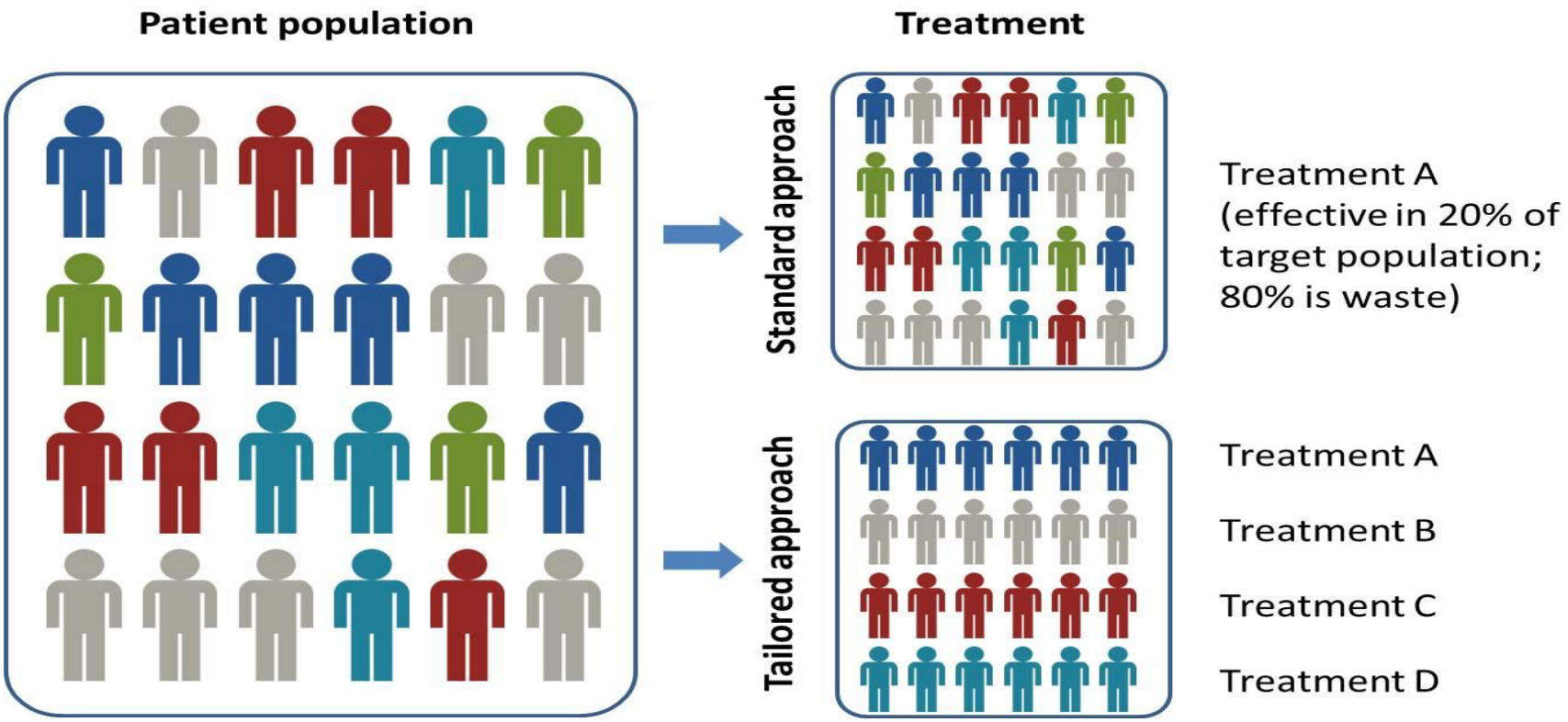
Table 1. Summary of Transplant Characteristics and Survival in the Largest Reported Prospective Studies of RIC HSCT in CLL

	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

Precision Medicine



Future Focus

- Sequencing – which treatment when?
- Combinations of drugs is going to be critically important.
- Still need new treatments for older patients.
- Still need better options for Richter's transformation.