



LYMPHOMA
CANADA

SAVE THE DATE RESEARCH
EXPERT SPEAKERS HOPE
NATIONAL NETWORKING
AID CONFERENCE FORUM
ON LYMPHOMA SUPPORT
CAREGIVERS EDUCATION
SEPTEMBER 15 - 16, 2017
SURVIVORS MONTRÉAL, QC
THERAPIES SIDE EFFECTS

INDOLENT LYMPHOMAS - FUTURE

Dr Kelly Davison
MUHC

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



What are 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

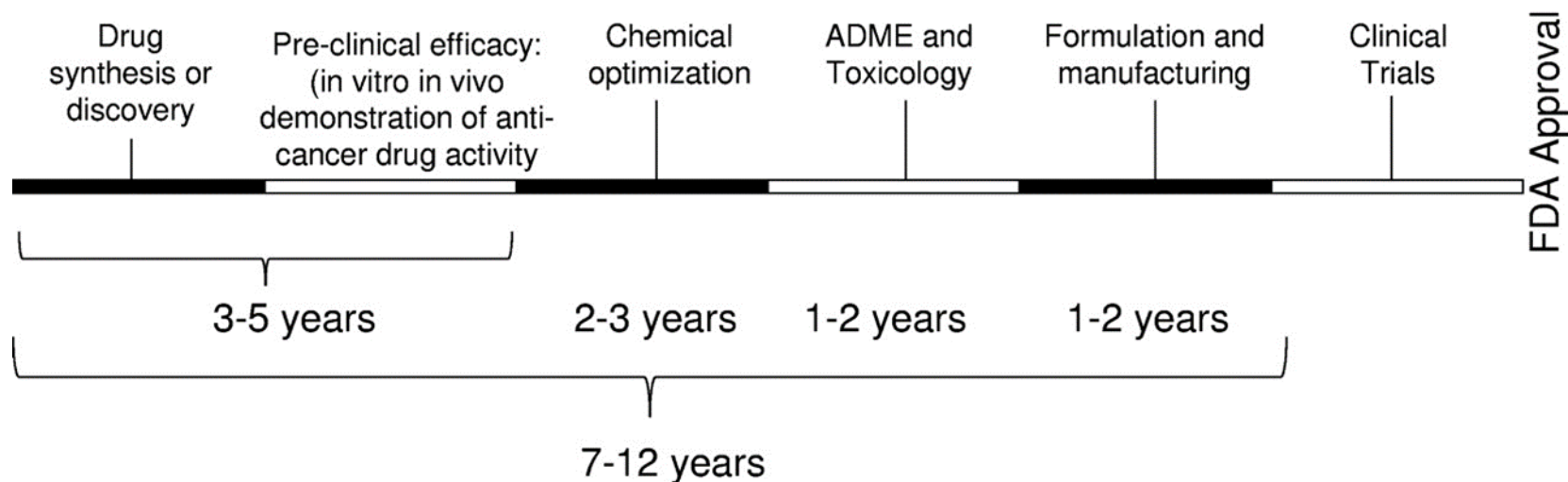
- Clinical trials are carefully examined and approved by ethics committees and must meet rigorous Health Canada and medical standards.
- A large amount of detailed research is conducted on any new treatment or procedure before it reaches the stage where it is tested on patients.
- Healthcare professionals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



Clinical Trial Phases



Timeline for new drug discovery



Sukhai M A et al. Blood 2011;117:6747-6755

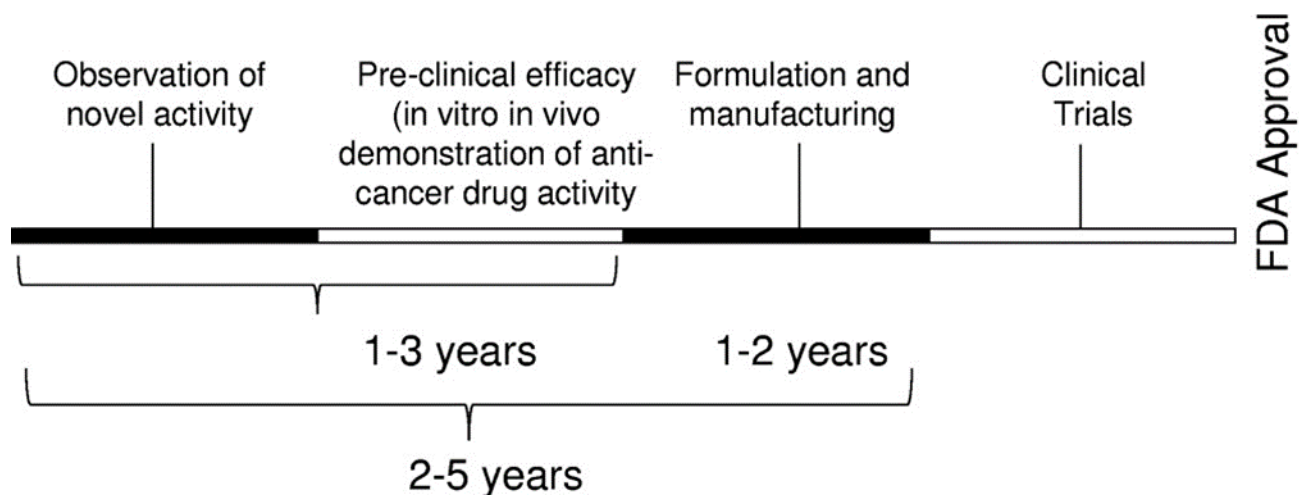


LYMPHOMA
CANADA | LYMPHOME
CANADA



lymphoma.ca · lymphome.ca

Timeline for drug repurposing



Sukhai M A et al. Blood 2011;117:6747-6755

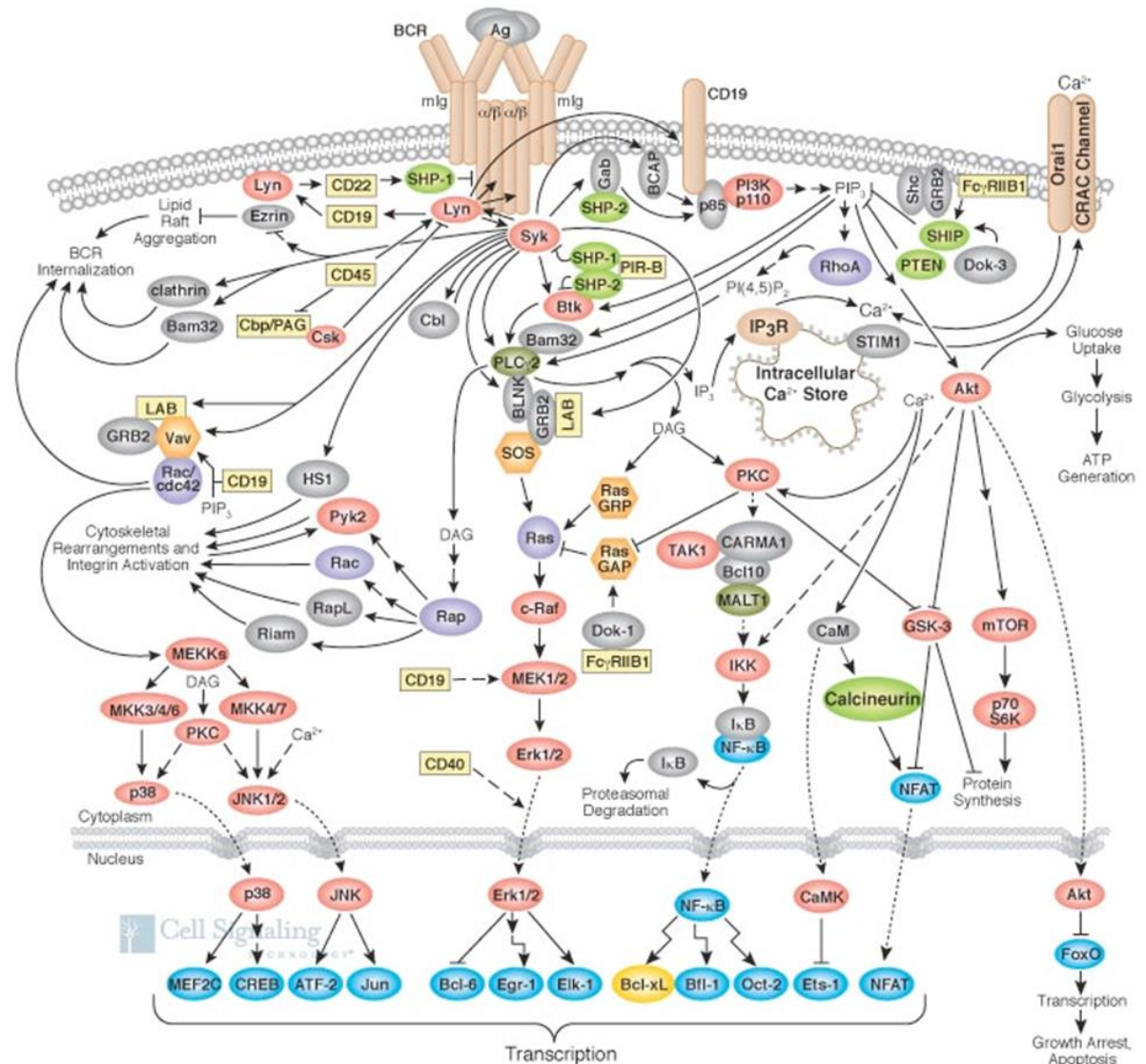


LYMPHOMA
CANADA | LYMPHOME
CANADA



lymphoma.ca · lymphome.ca

Many targets...

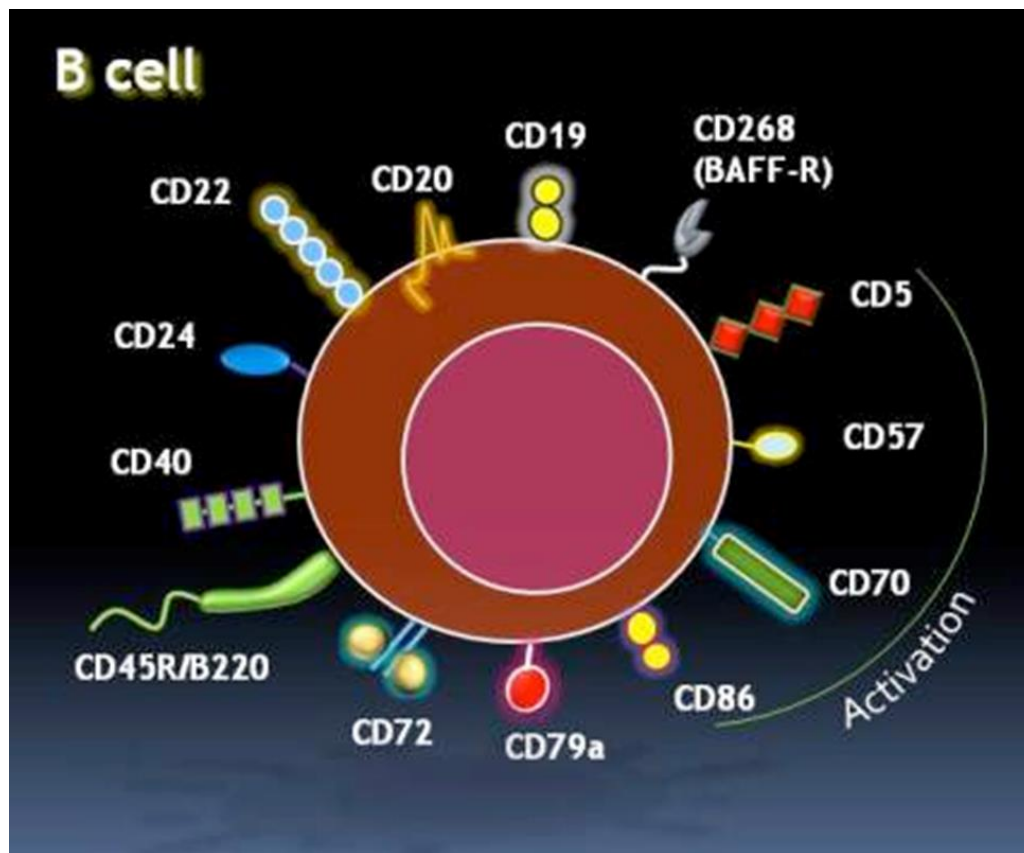


LYMPHOMA
CANADA | LYMPHOME
CANADA



lymphoma.ca · lymphome.ca

Cell surface targets



- CD20 is a good target
- Expressed on >90% B cell lymphomas

www.myelomacinderella.net



LYMPHOMA
CANADA | LYMPHOME
CANADA



lymphoma.ca · lymphome.ca

Immuno-oncology

"Immuno" in Immuno-Oncology (I-O) refers to your immune system.

I-O uses drugs known as immunotherapies that target your body's immune system to help fight cancer.



LYMPHOMA
CANADA | LYMPHOME
CANADA



lymphoma.ca · lymphome.ca

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.”

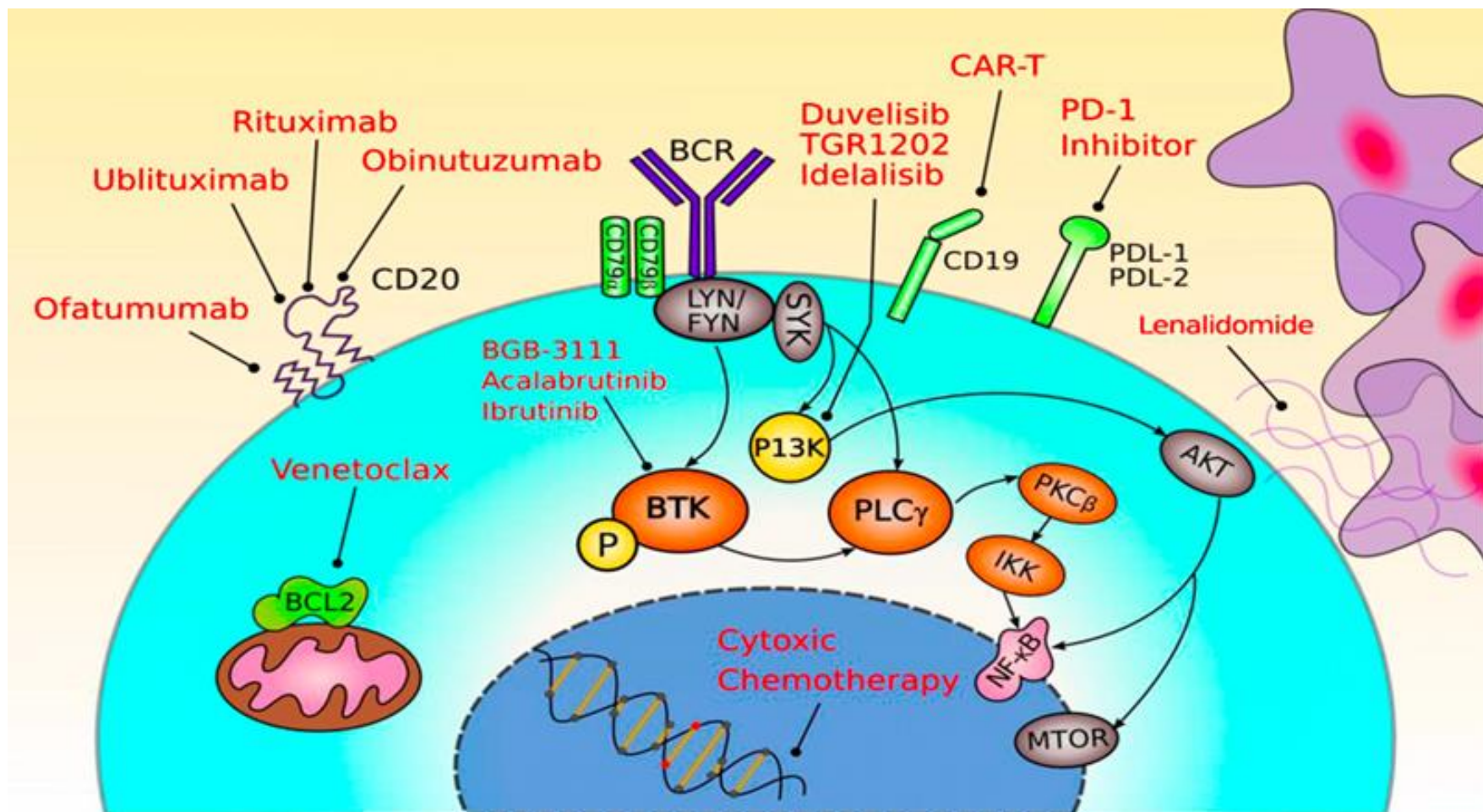
Jodi Fisher Horowitz Professor in Leukemia Care Excellence and Director of Blood and Marrow Transplantation at the Abramson Cancer Center of the University of Pennsylvania



LYMPHOMA
CANADA | LYMPHOME
CANADA

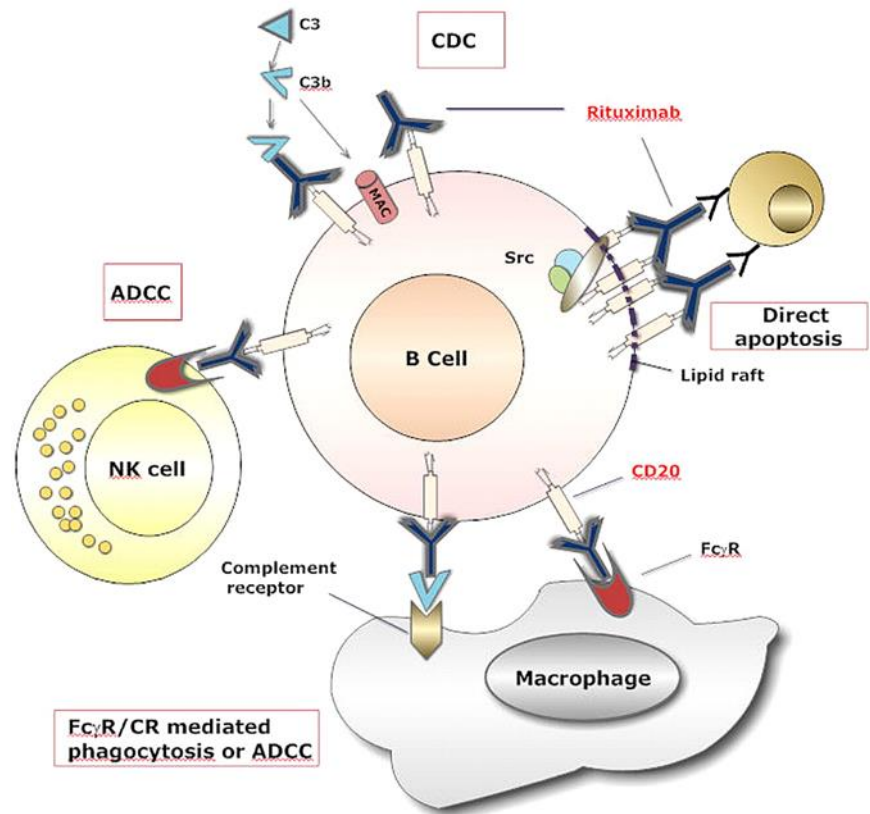


lymphoma.ca · lymphome.ca



Monoclonal antibodies

- Mimicking the immune system
- Rituxan
- Development of novel anti-CD20 MAbs with activity in rituximab-resistant disease



LYMPHOMA CANADA | LYMPHOME CANADA



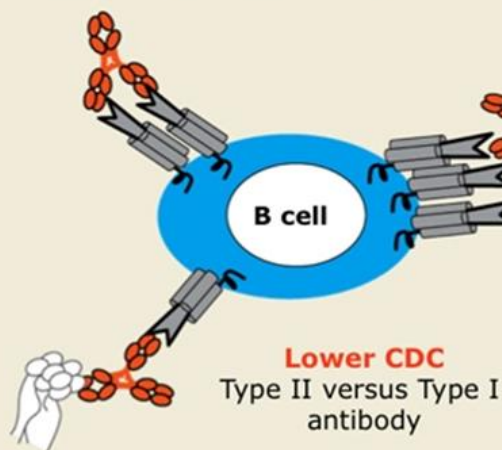
lymphoma.ca · lymphome.ca

Obinutuzumab

Obinutuzumab (GA101) Mechanisms of Action

Increased Direct Cell Death

Type II versus Type I antibody

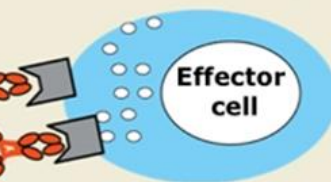


Lower CDC

Type II versus Type I antibody

Enhanced ADCC

Glycoengineering for increased affinity to FcγRIIIa



ADCC = antibody-dependent cell-mediated cytotoxicity

CDC = complement-dependent cytotoxicity

With permission from Goede V et al. *Proc ASCO* 2013;Abstract 7004.

Phase III GALLIUM trial: 40 months+ follow-up, obinutuzumab (Gazyva) plus chemotherapy in the first-line setting reduced the risk of disease progression or death by 32% versus rituximab (Rituxan) plus chemotherapy in patients with follicular lymphoma.



LYMPHOMA
CANADA | LYMPHOME
CANADA

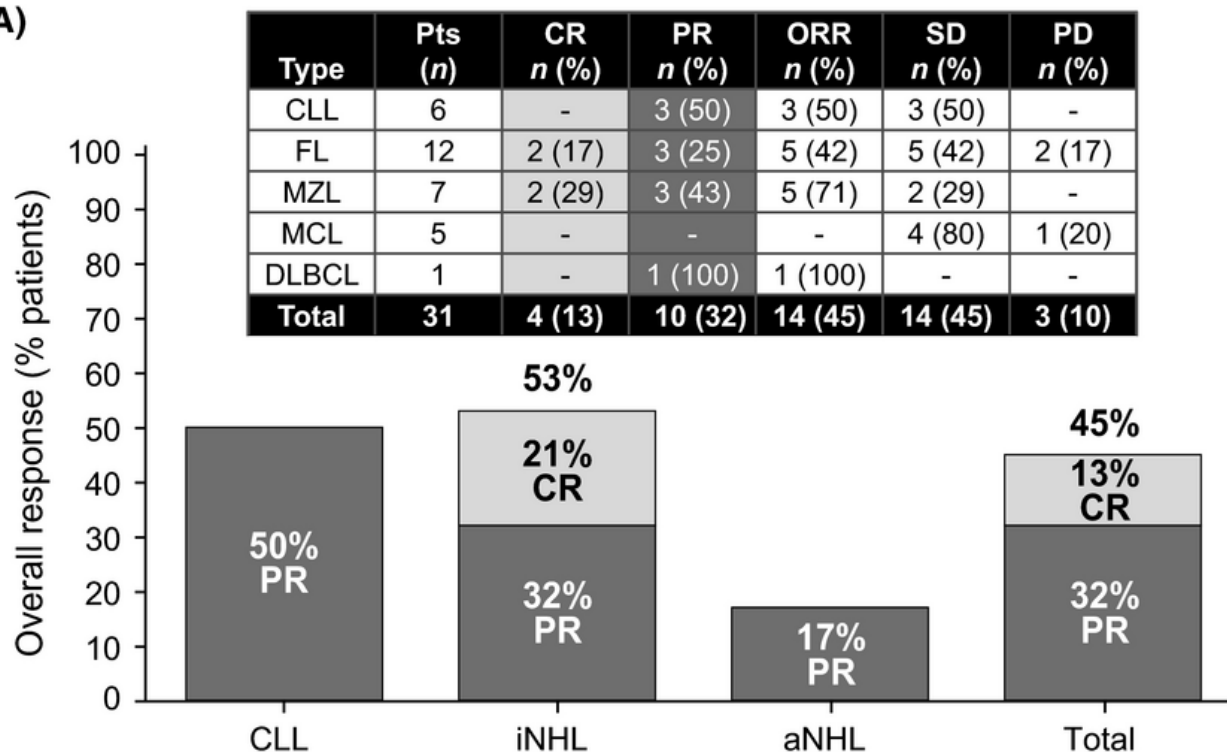


lymphoma.ca · lymphome.ca

Ublituximab (TG-1101)

Type I, chimeric, glycoengineered anti-CD20 recombinant IgG1 MAb that targets CD20 antigen, with enhanced clinical activity and potency.

(A)



A phase 1/2 trial of ublituximab, Ahmed Sawas, et al. Feb 2017



LYMPHOMA
CANADA | LYMPHOME
CANADA



lymphoma.ca · lymphome.ca

Targeted Therapies

Targeted therapies are drugs or other substances that block the growth and spread of cancer by interfering with specific molecules ("molecular targets") that are involved in the growth, progression, and spread of cancer.

- B cell focus in lymphoma
- T cells largely unaffected by targeted therapies so patients stay healthier during treatment



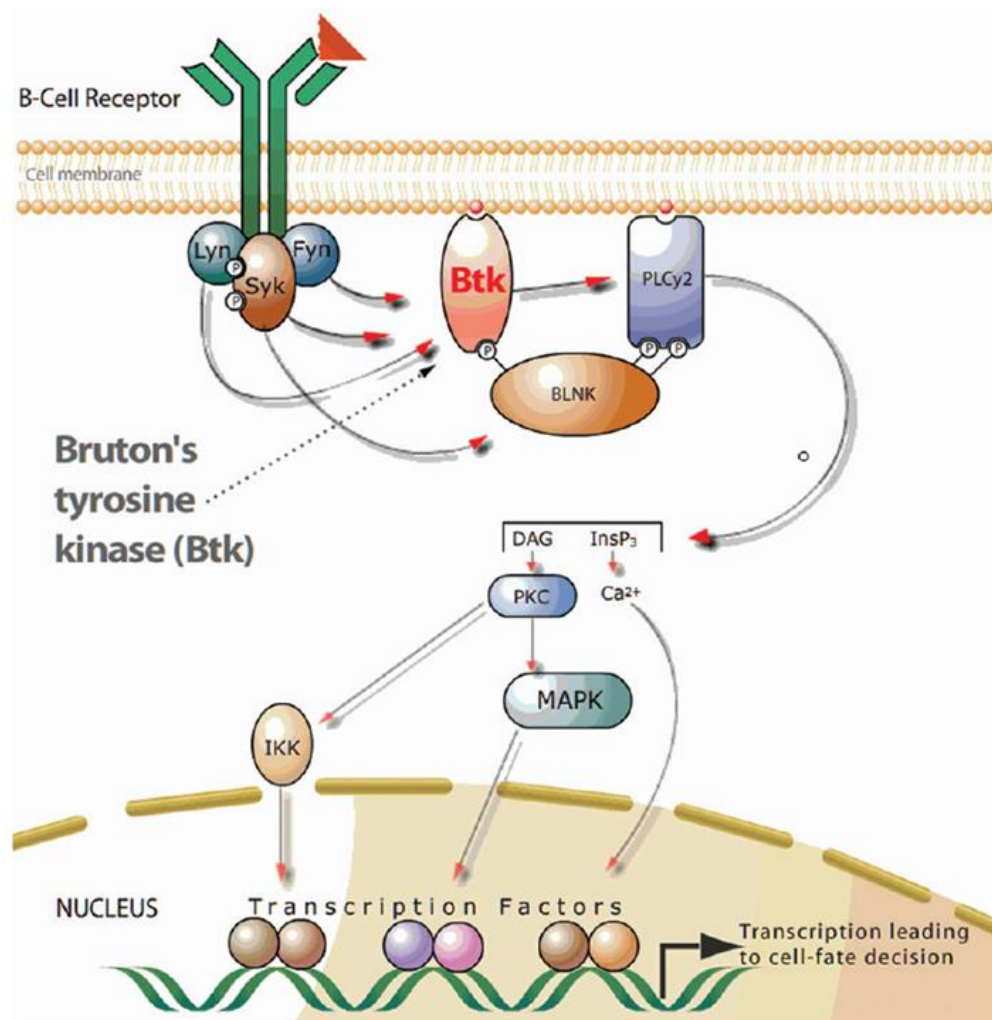
Bruton's Tyrosine Kinase (BTK) Inhibitors

- BTK is a protein that plays a critical role in the growth and survival of B-cells
- New therapies stops BTK from working, killing the malignant B-cells
 - Ibrutinib
- More selective and potent BTK inhibitors are being investigated.
 - ACP-196
 - ONO/GS-4059
 - BGB-3111, CC-292

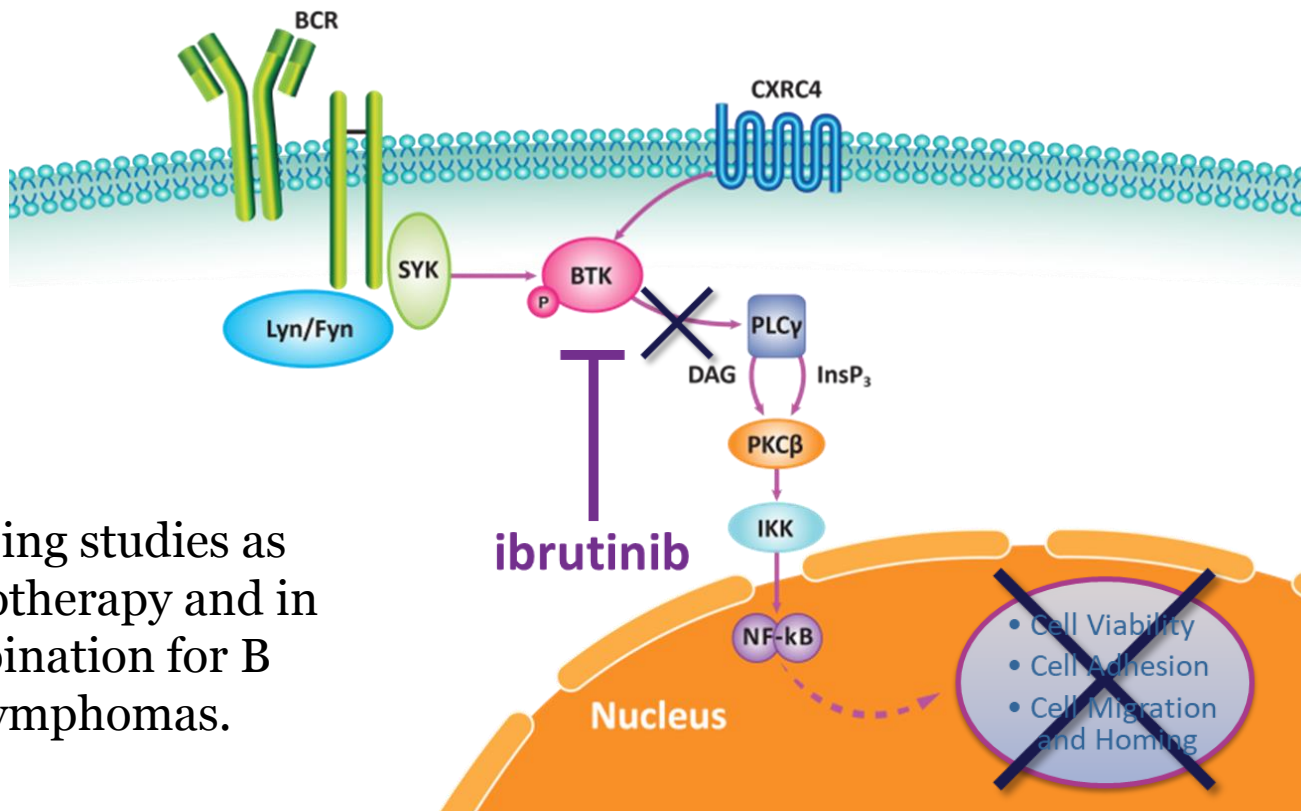


Ibrutinib

- First in class, potent, irreversible BTK inhibitor
- Many trials in combination with other drugs



Ibrutinib



Ongoing studies as monotherapy and in combination for B cell lymphomas.



LYMPHOMA
CANADA | LYMPHOME
CANADA



lymphoma.ca · lymphome.ca

Acalabrutinib

- Second generation BTK inhibitor
- More potent, fewer side effects
- 61 patients with CLL demonstrated safety and efficacy. At a median follow-up of 14.3 months, patients exhibited an overall response rate of 95%.
- FDA breakthrough designation for MCL – trial results expected soon
- Designated as an orphan medicinal product by the EMA for CLL/SLL, MCL, and lymphoplasmacytic lymphoma (Waldenström's macroglobulinaemia)
- Multiple trials underway as single agent and in combination



Tirabrutinib ONO/GS4059

- Highly potent & selective oral therapy
- Phase I: 90 patients enrolled with CLL & NHL
- MCL patients ORR 92%, 11/12 patients
- 75% AE grade 1 or 2; grade 3 & 4 mainly hematological & spontaneously recovered during treatment
- Less bleed risk; no clinically significant diarrhea, cardiac dysrhythmias or arthralgia were observed



BGB-3111

- Highly specific BTK inhibitor
- Active in patients with Waldenström macroglobulinemia (WM)
- 42 patients in the efficacy population demonstrated a best objective response rate (ORR) of 90%.
 - 18 (43%) patients showed very good partial response
 - 14 (33%) patients achieved partial response
 - 6 (14%) patients showed minor response
 - Stable disease was demonstrated by the remaining 4 (10%) patients

Trotman J, Opat S, Marlton P, et al. Bruton's tyrosine kinase (BTK) inhibitor BGB-3111 demonstrates high very good partial response (VGPR) rate in patients with Waldenström macroglobulinemia (WM). Hematol Oncol. [published online June 7, 2017]

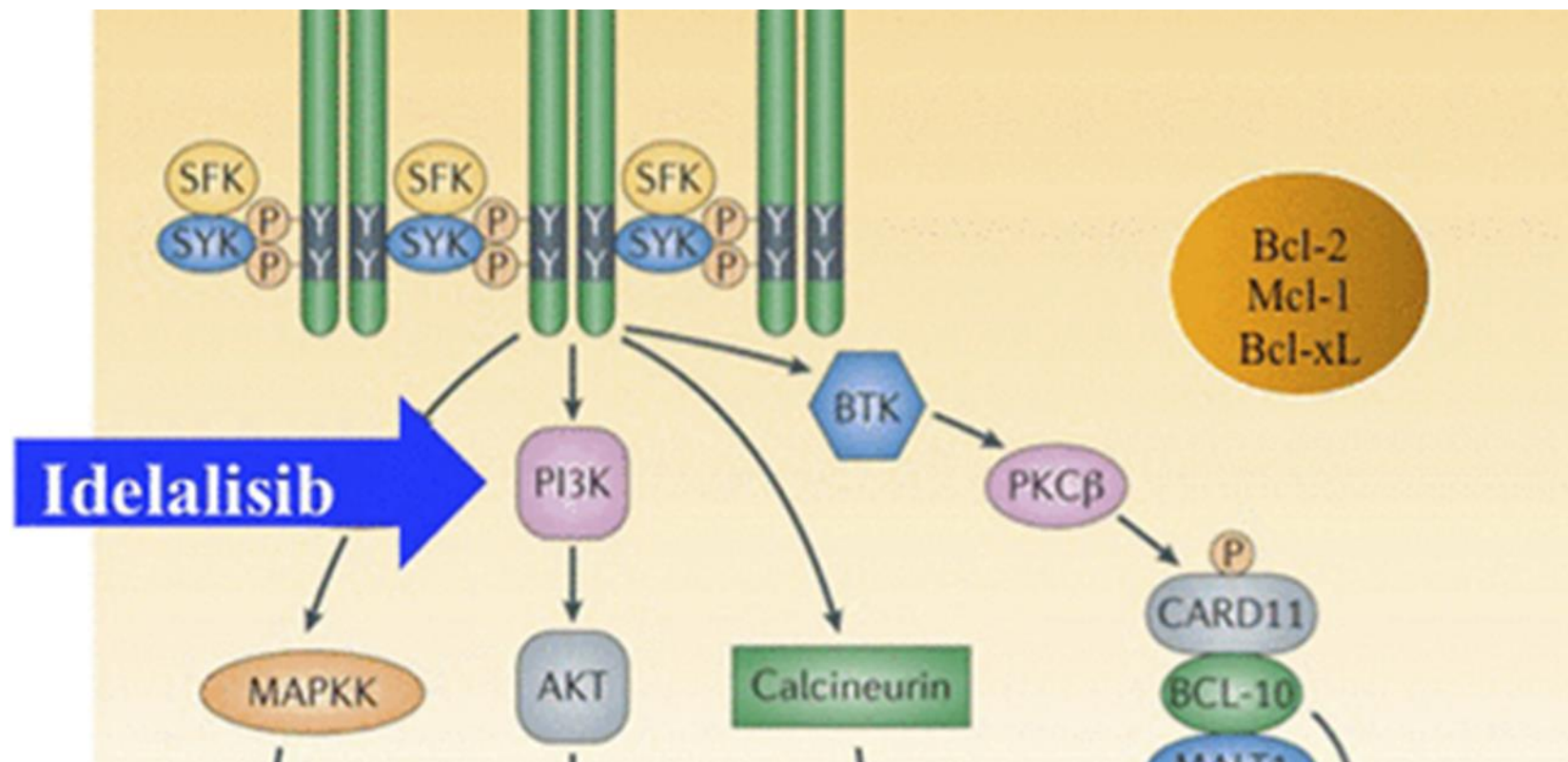


PI3K inhibitor

- The PI3K pathway is important in regulating the cell cycle
- It is directly related to cellular inactivity, proliferation, cancer, and longevity.



Idelalisib



Umbralisib (TGR-1202)

- Unique structure and improved tolerability
- Monotherapy, oral
- Combined ublituximab (TG-1101), ibrutinib, and umbralisib (TGR-1202) showed that the combination was well tolerated and had activity across heavily pretreated patients with high-risk B-cell malignancies
 - 4 patients with MCL ORR of 100%
 - ORR of 100% was also demonstrated in 2 patients with MZL
 - 80% in 5 patients with follicular lymphoma

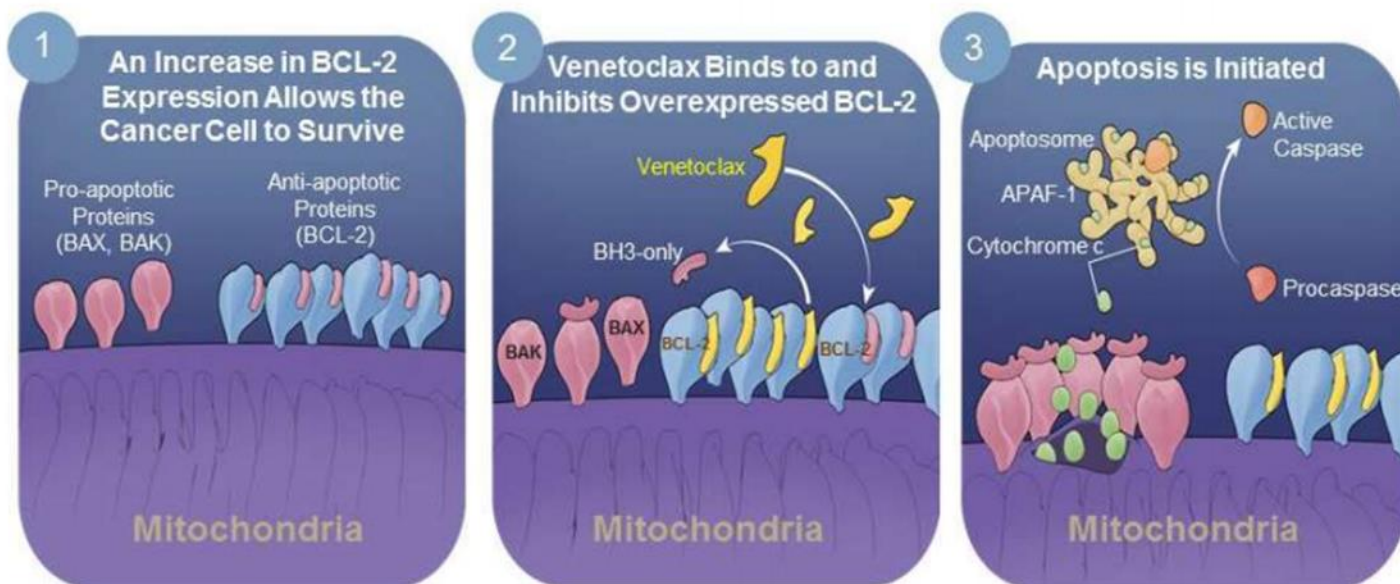


Copanlisib

- CHRONOS-1 study Copanlisib showed an objective response rate (ORR) of 59.2% without inducing major colitis events or elevation of hepatic transaminases in patients with relapsed or refractory indolent B-cell lymphoma
 - 17 patients (12%) with complete response
 - 67 patients (47.2%) showing partial response
 - Stable disease attained by 42 patients (29.6
 - 3 patients (2.1%) experienced progressive disease

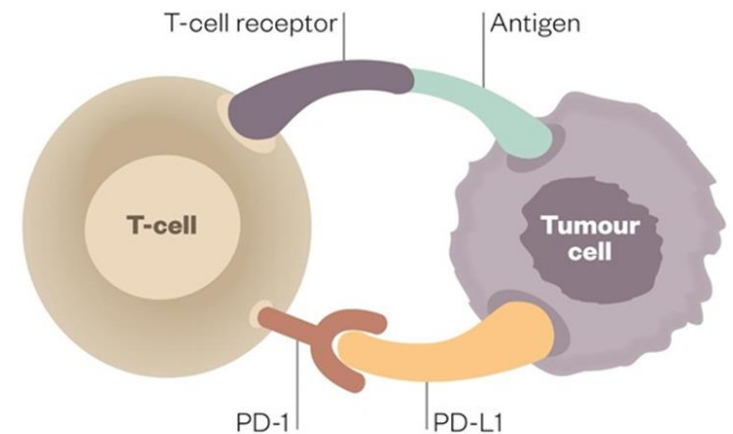


Bcl-2 Inhibitor: Venetoclax



Immune checkpoint inhibitors

- PD = 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 achieve anticancer effects in the form of durable responses, improvements in survival, and less toxicity for patients.
- Binding of T-cells to PD-L1/2 inhibits T-cell function and blunts the normal immune response



Pembrolizumab

- PD-1 inhibitor, used for many types of cancer
- Relapsed follicular lymphoma Phase II trial in combination with rituximab, overall response rate (ORR) was 65%, including a complete response rate of 50%
- 20 patients evaluated to date; the best response was stable disease in 3 patients and 4 patients had progressive disease

Nastoupil LJ, Westin J, Fowler N, et al. High response rates with pembrolizumab in combination with rituximab in patients with relapsed follicular lymphoma: interim results of an open-label, phase II study. *Hematological Oncology*, 35(S2): 120-121. doi:10.1002/hon.2437_108



LYMPHOMA
CANADA | LYMPHOME
CANADA



lymphoma.ca · lymphome.ca

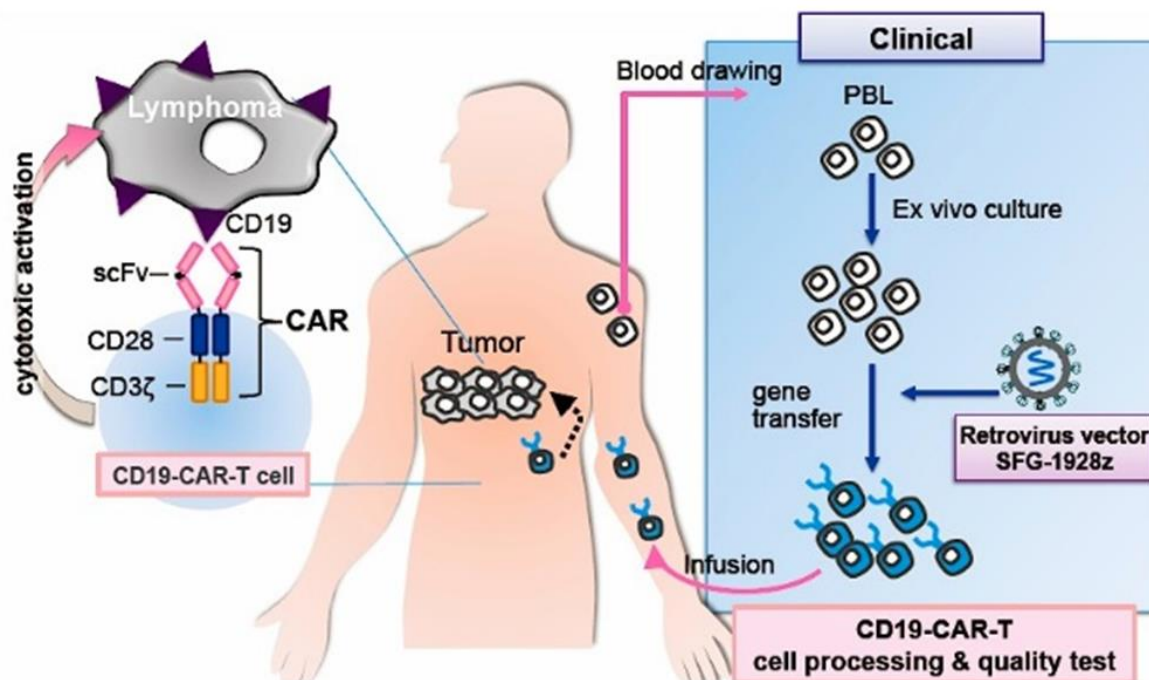
Nivolumab

- PD-1 inhibitor
- Phase 1 study (CA209-039), nivolumab well tolerated and exhibited antitumor activity in extensively pretreated patients with relapsed or refractory B- and T-cell lymphomas.
 - Patients with FL, ORR 40%
 - 2 patients with cutaneous T-cell lymphoma (CTCL) responded
 - 1 of 2 patients with peripheral T-cell lymphoma (PTCL) continued to have an ongoing response at 79 weeks.



Chimeric antigen receptor gene therapy (CAR-T)

Adoptive Immuno-Gene Therapy using CAR-T-cells for Refractory B Cell Non-Hodgkin Lymphoma



Differences between small molecules and biologics

- Small Molecules:

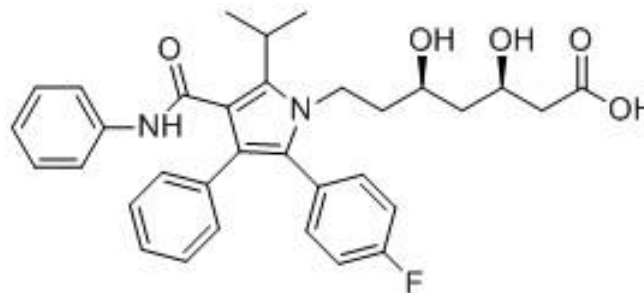
- made via chemical synthesis *in vitro*

- potentially made via different synthetic routes

Synthetic route A →

Synthetic route B →

Synthetic route C →



Atorvastatin: lipid lowering agent

Reference compound = Lipitor

- Irrespective of the synthetic route, all compounds have the same chemistry/molecular weight **$C_{33}H_{35}O_5N_2F$: 558.62g/mol**
 - all generic small molecules have identical chemical formulas and structures

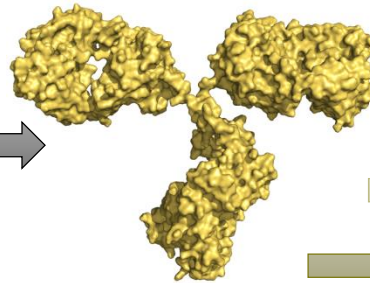
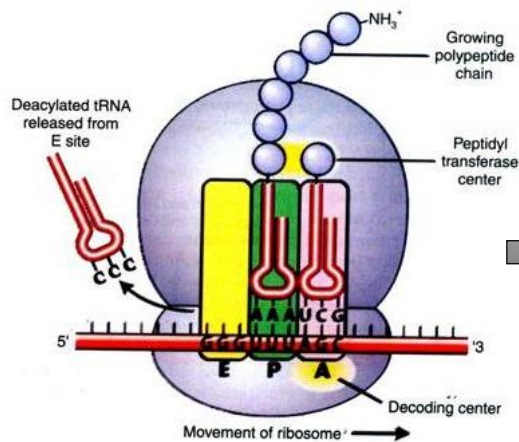


Differences between small molecules and biologics

- Proteins

-made *in vivo* using a host organisms' cellular machinery

-template encoded by DNA-RNA and all molecules are synthesized identically by the ribosome



The final protein product may be subject to numerous post-translational modifications that can alter the chemistry of the molecule

These modifications can have a number of important implications

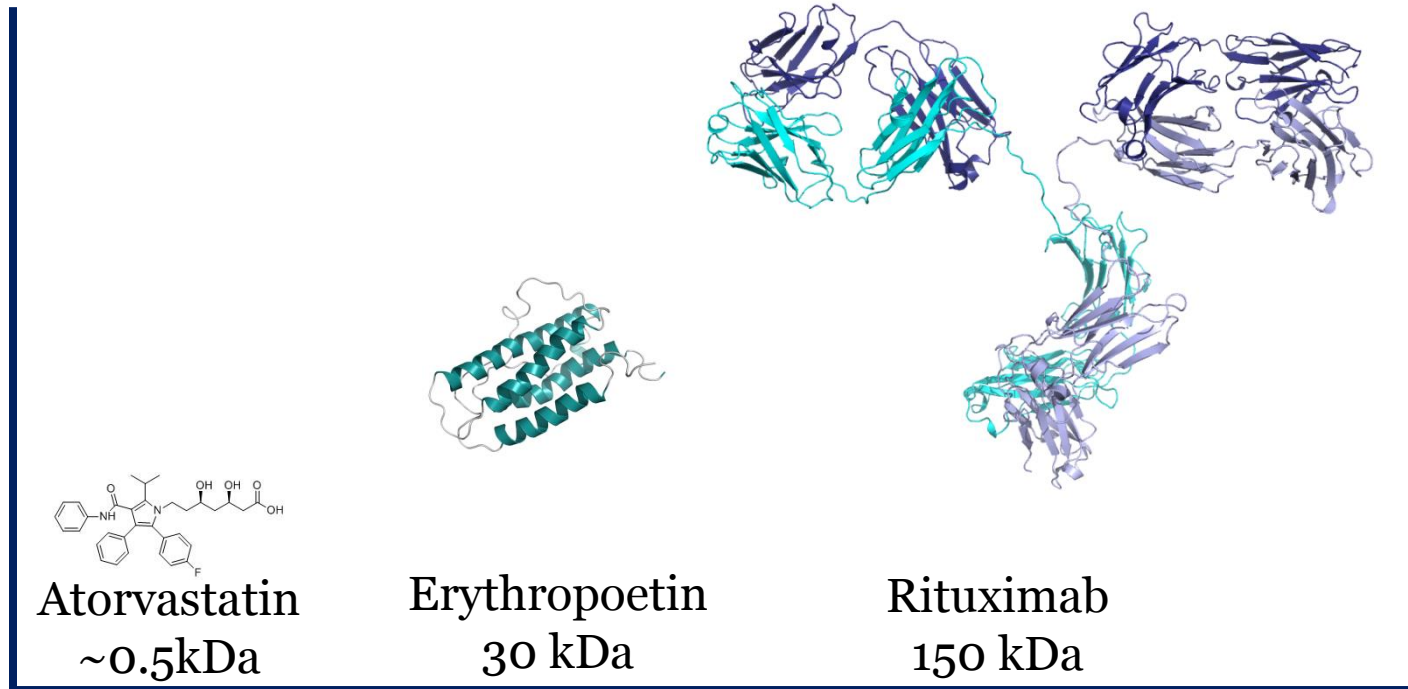


LYMPHOMA
CANADA | LYMPHOME
CANADA



lymphoma.ca · lymphome.ca

Biologics and their inherent complexity



-a crucial difference between small molecules and biologics is that an increase in complexity and heterogeneity make it more difficult to accurately characterize the active pharmaceutical mixture.



The manufacturing processes influence biologics



- Details of the manufacturing process will affect the final product
- Manufacturing details and quality control are often proprietary and closely guarded company secrets



LYMPHOMA
CANADA | LYMPHOME
CANADA



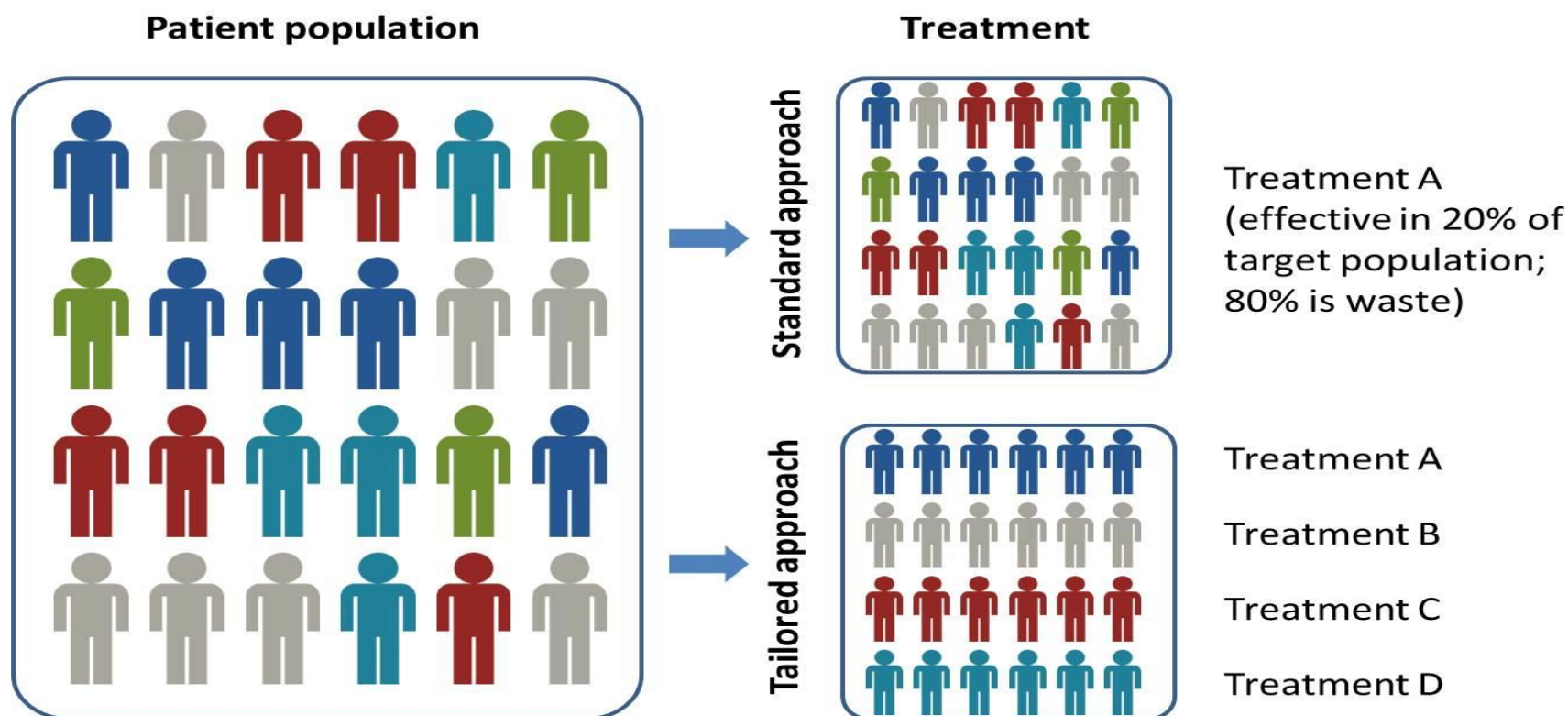
lymphoma.ca · lymphome.ca

Biosimilars in lymphoma

- SEBs currently used in supportive care (G-CSF, EPOs)
- Currently no approved SEB for lymphoma treatment in Canada
- ~13 SEBs in development for rituximab
- Market authorization for rituximab SEBs expected in Europe in 2017; expected to enter Canadian market in 2020
- Very limited awareness of SEBs in Canadian lymphoma patient community



Precision Medicine



Personalized medicine

- Personalized treatments
 - Not all people Are The Same
 - Match treatment to the patient's genetic profile
- Not all tumors are the same
 - Match treatment to the tumour's genetic profile
- Re-educate the patient's own immune system to attack the tumour

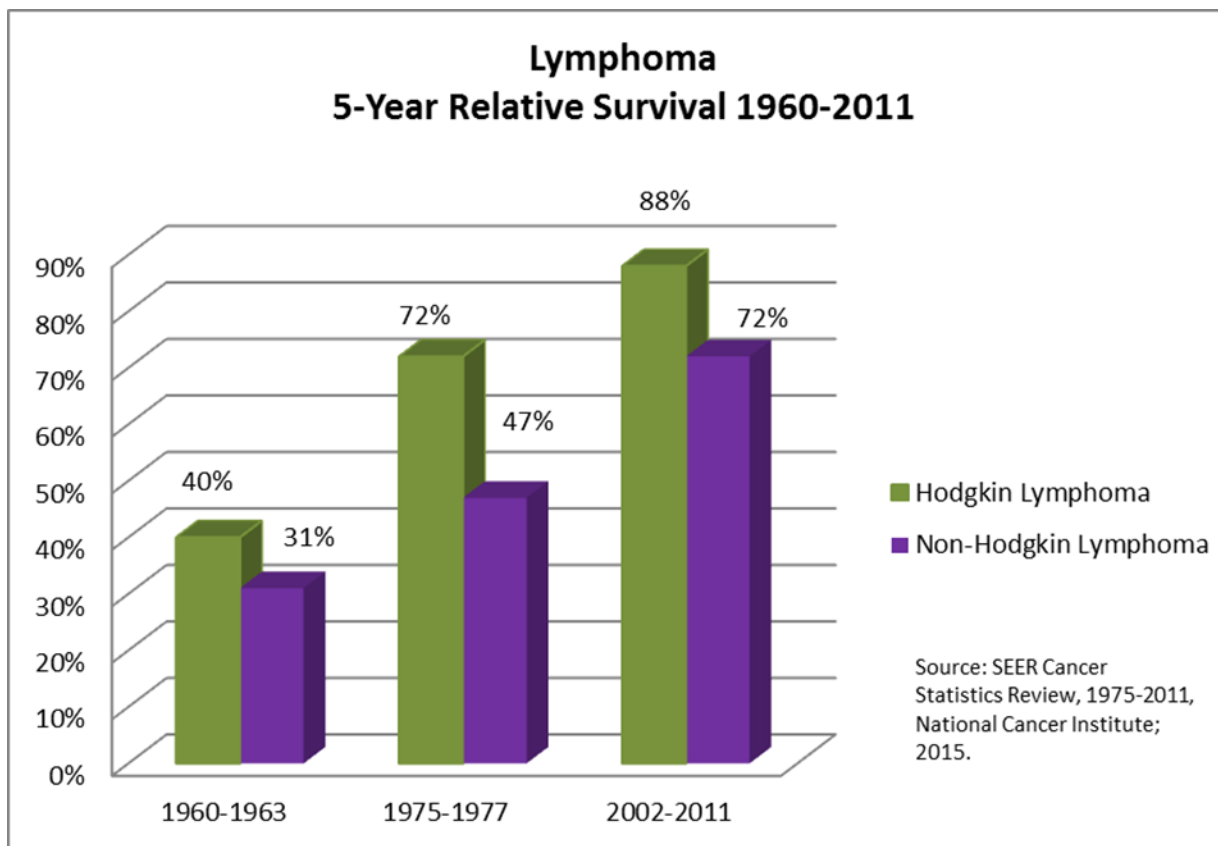


Is research working?

- Yes!!!!
- Improved depth of remissions, longer remissions and improved survivals since introduction of rituximab
 - In combination with chemotherapy
 - As maintenance therapy
- Better understanding of cancer cell signaling and pathways
- Newer targeted agents



Is research working?



LYMPHOMA
CANADA | LYMPHOME
CANADA



lymphoma.ca · lymphome.ca



LYMPHOMA
CANADA | LYMPHOME
CANADA



lymphoma.ca · lymphome.ca