



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

INDOLENT LYMPHOMAS - FUTURE

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St. Michael's Hospital, Toronto ON

Objectives

- To understand treatment options in NHL
- To understand the molecular basis of chemotherapy and immunotherapy
- To appreciate what is ‘coming down the pipeline’ for therapy



Lymphoma: Basic Concepts

There are over 70 different types of lymphoma:

- 80% ' B ' cell; 20% ' T ' cell
- **Excisional Biopsies** > Core Biopsies
- Low Grade
 - Indolent but not curable (“chronic disease”)
- Intermediate Grade
 - Aggressive but curable in some cases
- High Grade
 - Very proliferative and often cured with aggressive treatment

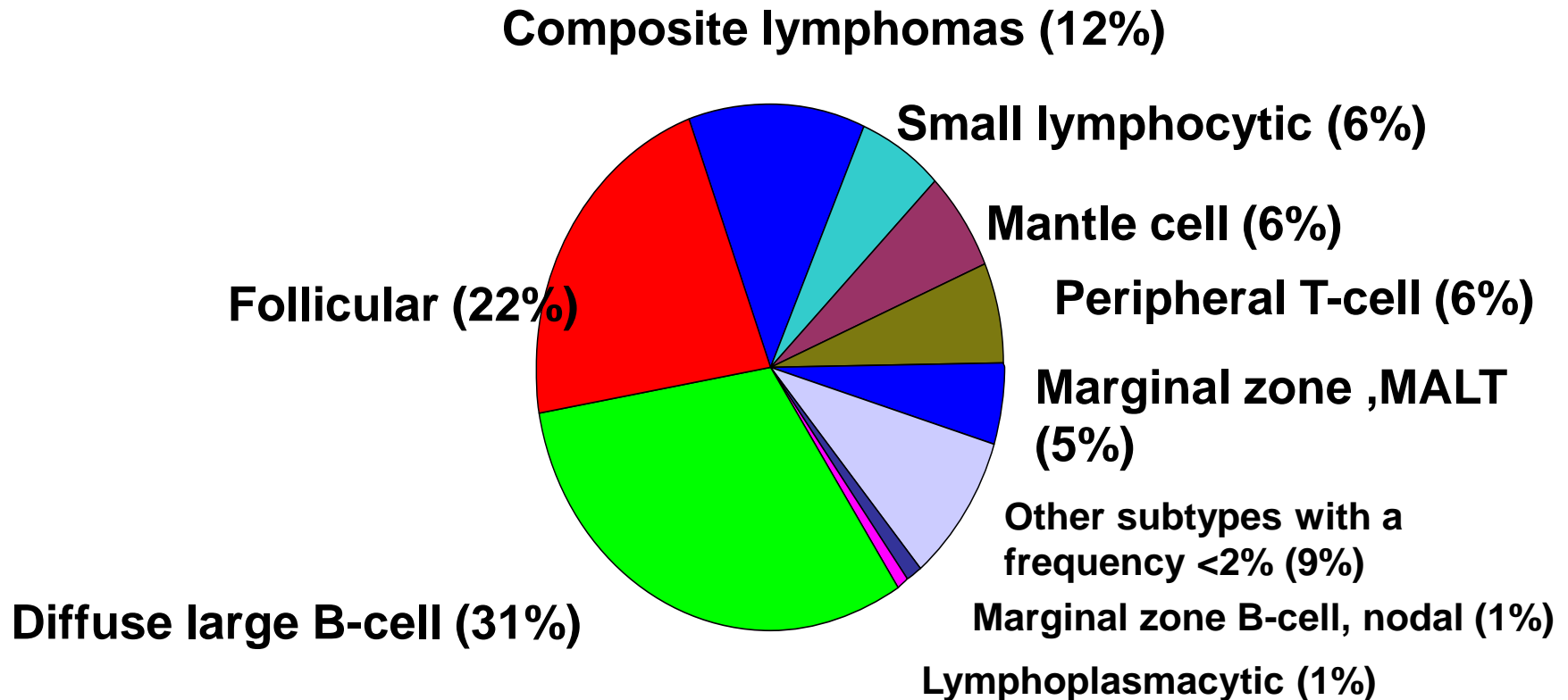


A practical way to think of lymphoma

Category		Survival of untreated patients	Curability	To treat or not to treat
Non-Hodgkin lymphoma	Indolent	Years	Generally not curable	Generally defer Rx if asymptomatic
	Aggressive	Months	Curable in some	Treat
	Very aggressive	Weeks	Curable in some	Treat
Hodgkin lymphoma	All types	Variable – months to years	Curable in most	Treat



Frequency of NHL Subtypes in Adults



Indolent Lymphomas

B Cell

- Follicular
- CLL/ SLL
- Lymphoplasmacytic
- Splenic marginal zone
- Hairy cell leukemia
- Extranodal marginal (MALT)
- Nodal marginal

T cell

- T cell LGL
- Mycosis fungoides
- Primary cutaneous CD30+



When to start treatment?

- “ABC”
 - Adenopathy – compromised organ function
 - Blood counts – drop
 - Constitutional Symptoms
- 20 to 30% may never need therapy in their lifetime
- Isolated disease: radiotherapy



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

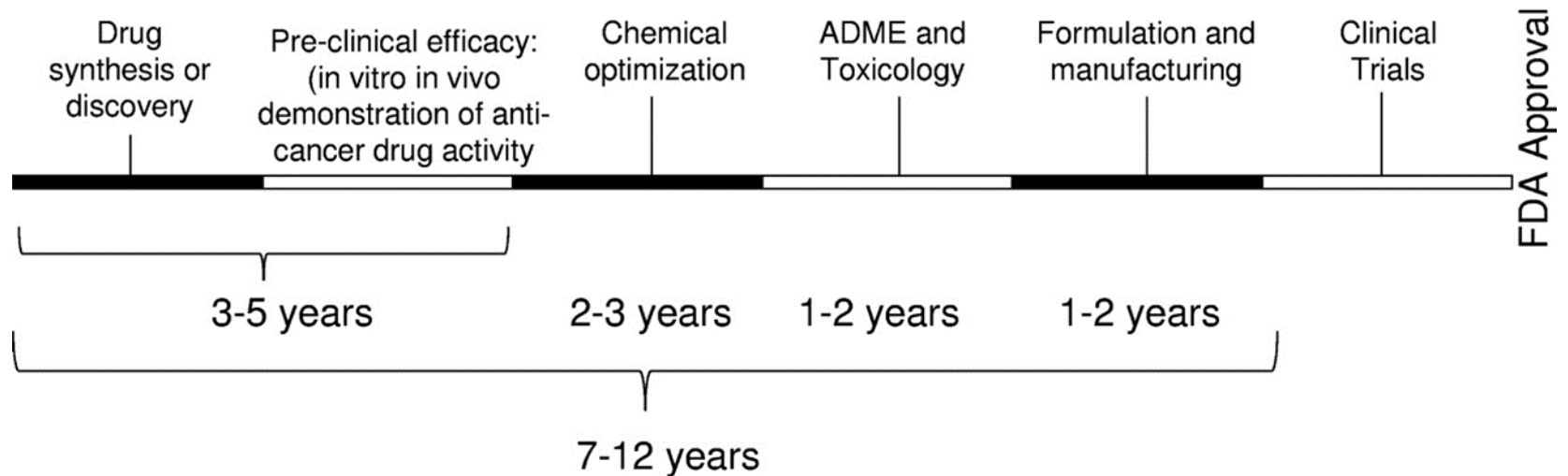
- Must be passed by REB and must meet rigorous Health Canada and medical standards.
- A large amount of detailed research is conducted on any new treatment or procedure before it reaches the stage where it is tested on patients.
- Healthcare professionals work very hard to minimize the risks of participating in a clinical trial.



Clinical Trial Phases



Timeline for new drug discovery



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

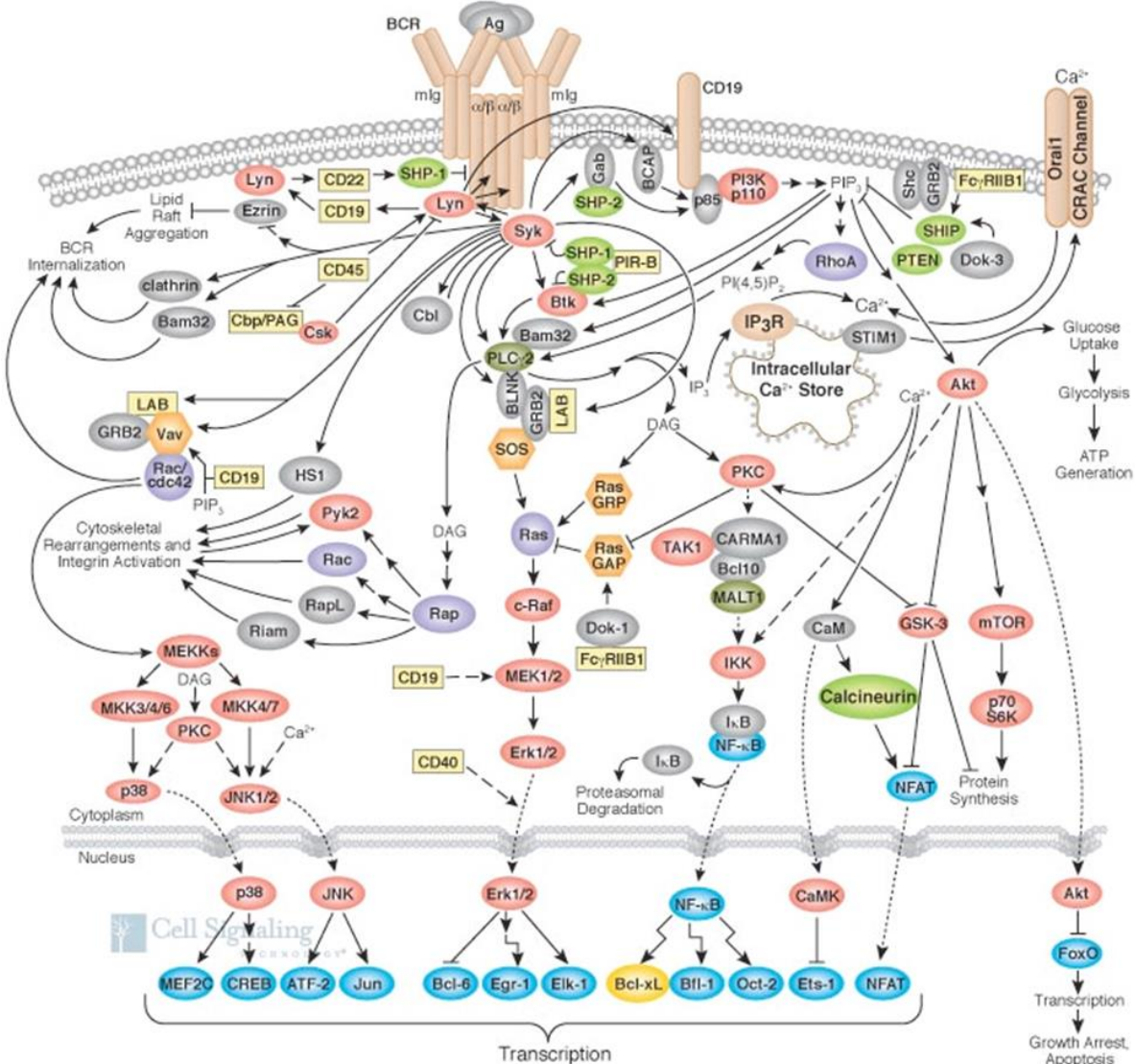


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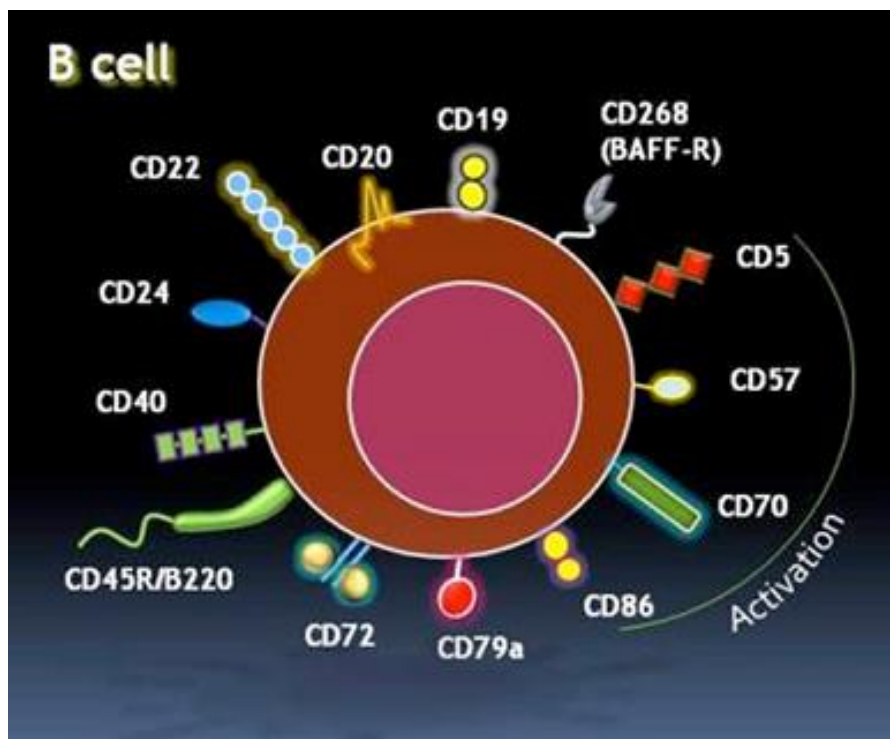


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Many targets...



Cell surface targets



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

www.myelomacinderella.net



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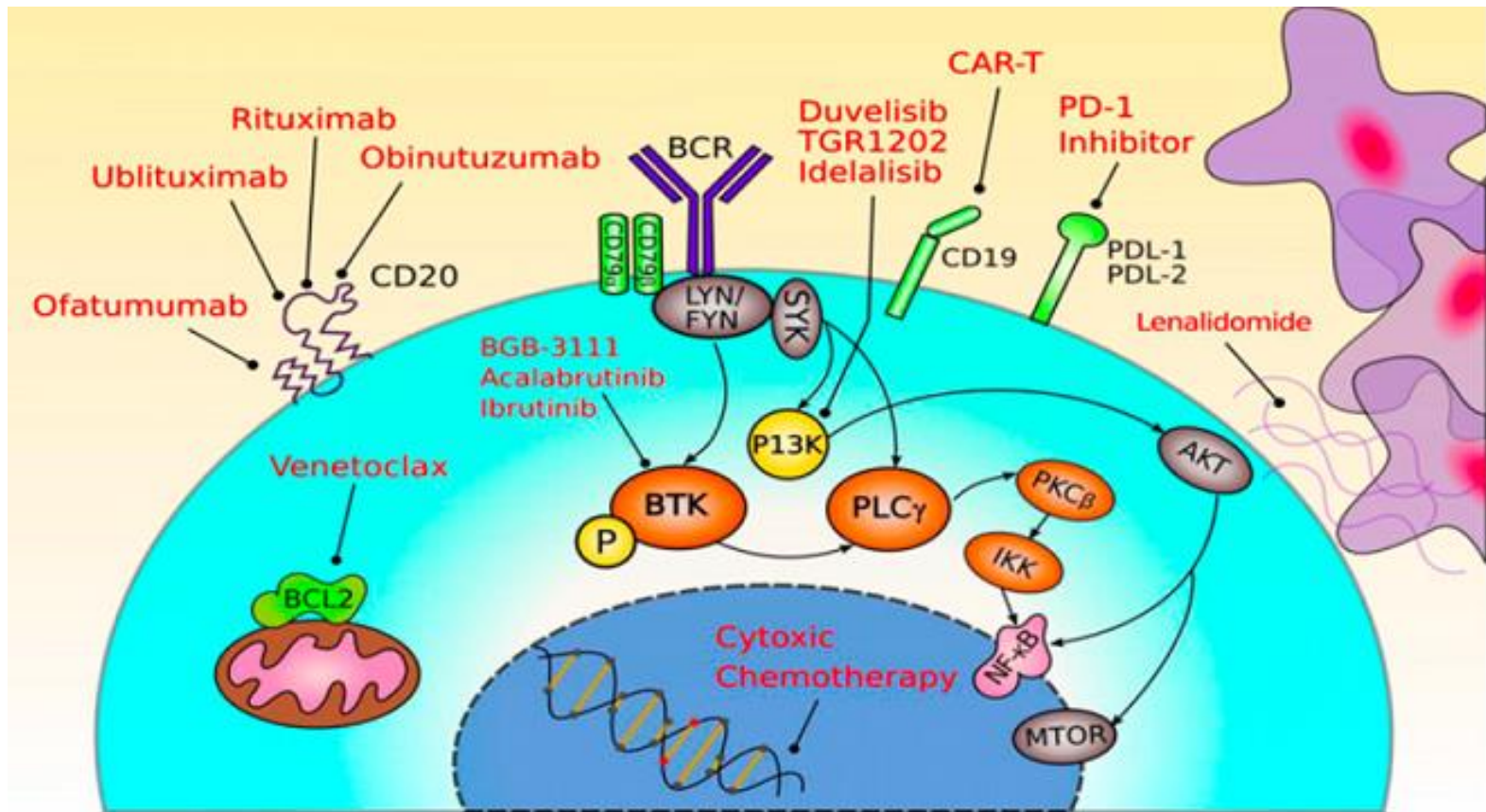


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Immuno-oncology

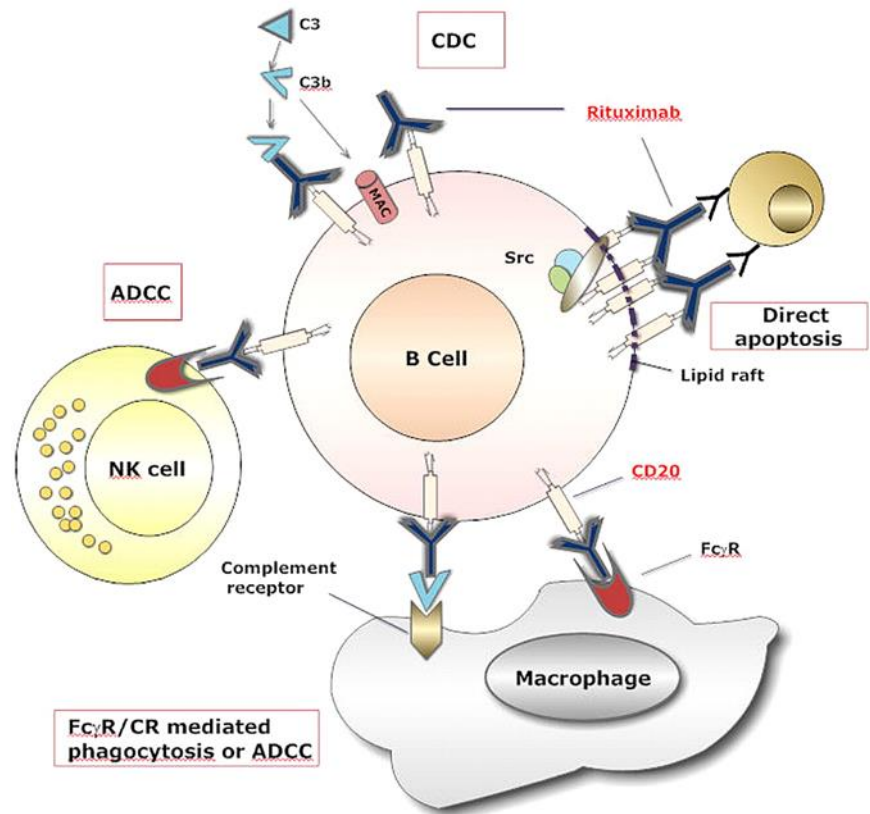
- "Immuno" in Immuno-Oncology (I-O) refers to your immune system
- I-O uses drugs known as immunotherapies that target your body's immune system to help fight cancer.



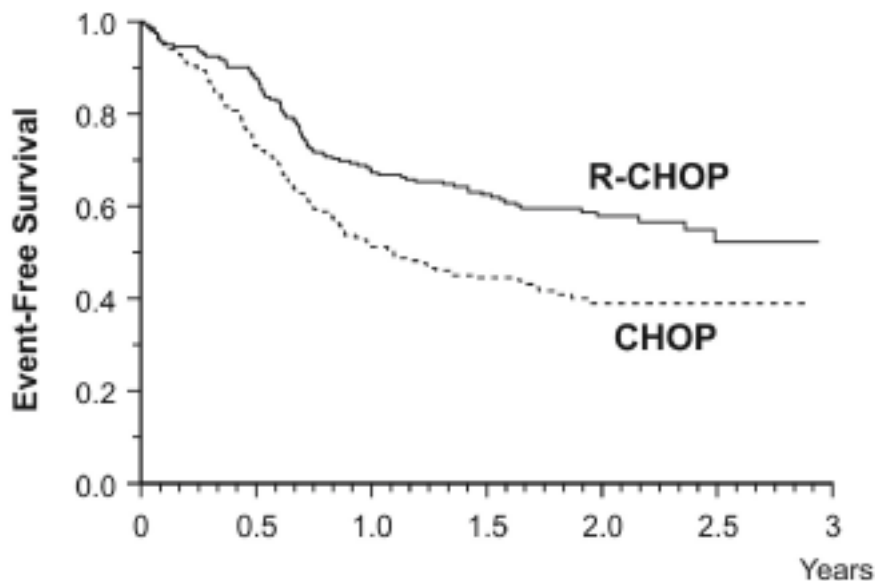


Monoclonal antibodies

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



Treatment of DLBCL = R-CHOP



Rituximab: 375 mg/m²

Cyclophosphamide 750 mg/m²

Doxorubin 50 mg/m²

Vincristine 1.4 mg/m²

Prednisone 100 mg po od x 5d

Event-free survival of 399 patients comparing CHOP to R-CHOP (P<0.001)

Coiffier et al. **N Engl J Med** 2002; 346: 235-242



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Rituximab subcutaneous

- Flat dose of 1400 mg s.c. = 375 mg/m² iv

Subcutaneous rituximab



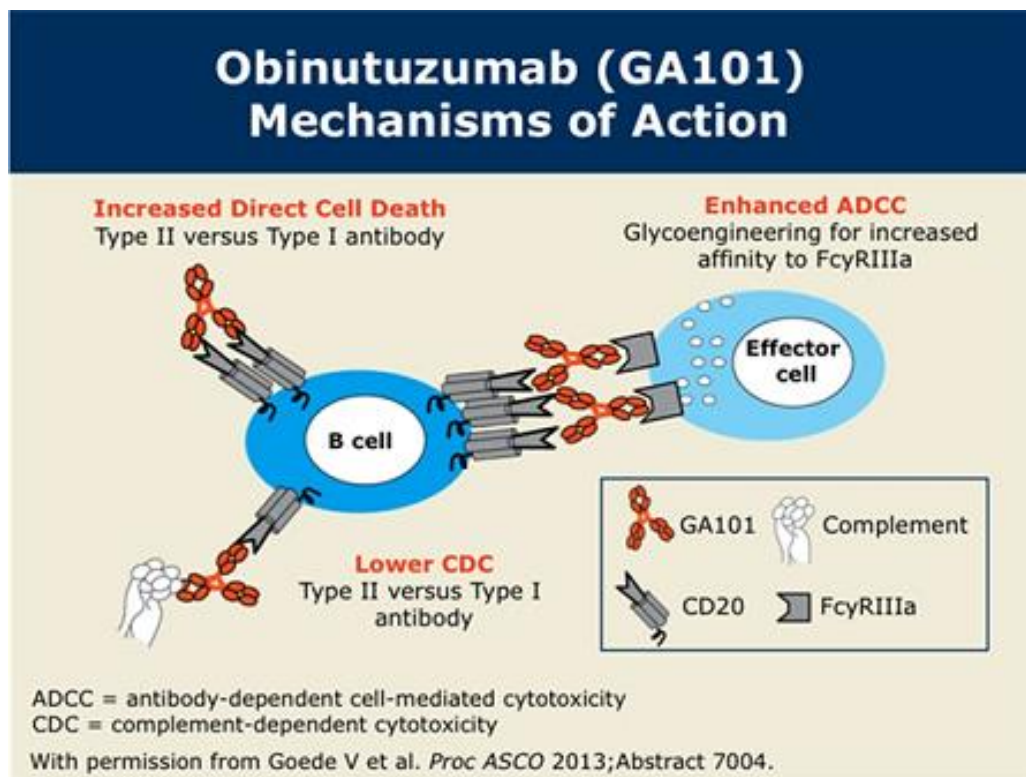
- To simplify treatment, especially for maintenance therapy
- Drug together with hyaluronidase
- Rash, erythema, mild discomfort, no general reactions



Obinutuzumab

Phase III GALLIUM trial:

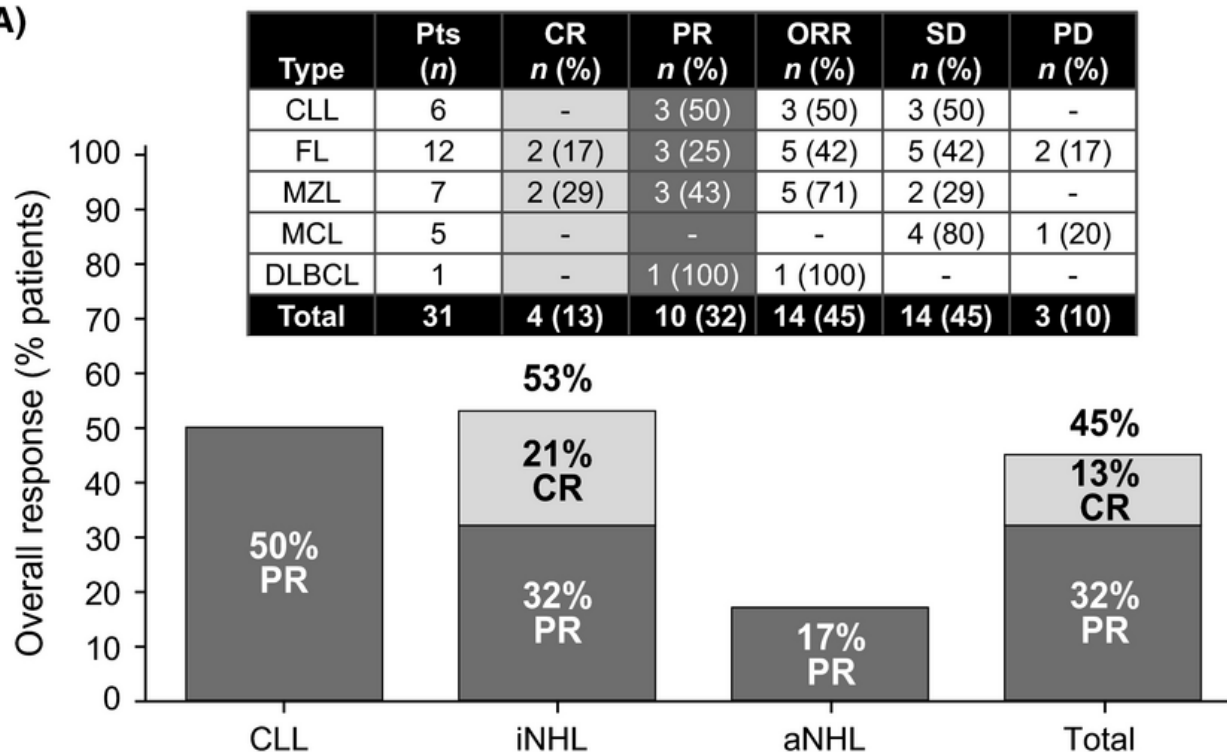
- > 40 months follow up
- 1st line FL patients
- O + chemo vs R + chemo
- Reduced the risk of disease progression or death by 34% versus rituximab (Rituxan)
- 80% of patients in remission at 3 years
- Maintenance tx given every 2 months x 2 years



Ublituximab (TG-1101)

- Type I, chimeric, anti-CD20 MAb that targets CD20 antigen
- Greater antibody-dependent cellular cytotoxicity (ADCC) activity
- Phase 1/2 trial in a highly treated rituximab population

(A)



Ahmed Sawas, et al. *Br J Haematol*. 2017 Apr; 177(2): 243–253



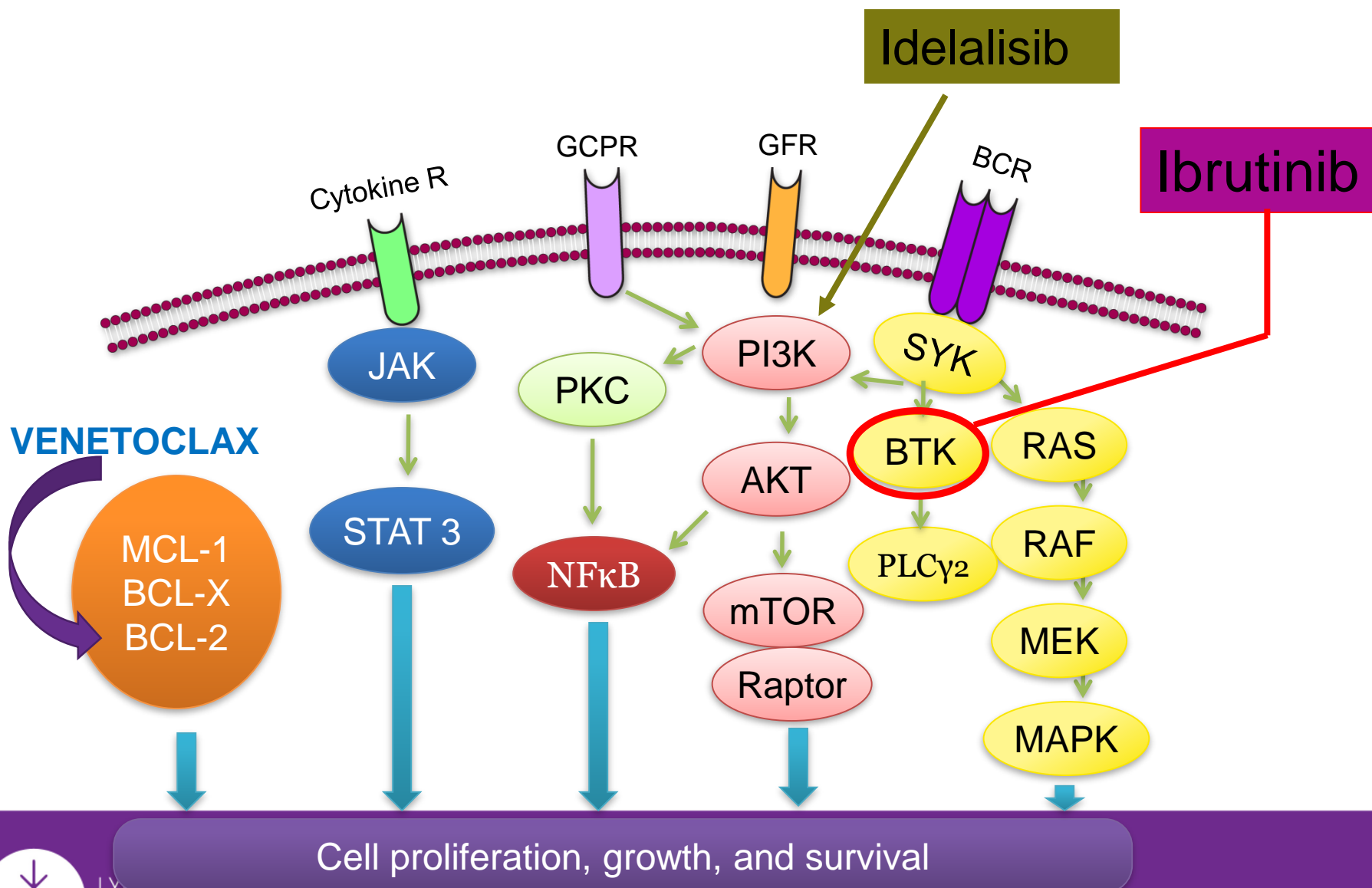
Targeted Therapies

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



Targetted Agents in CLL



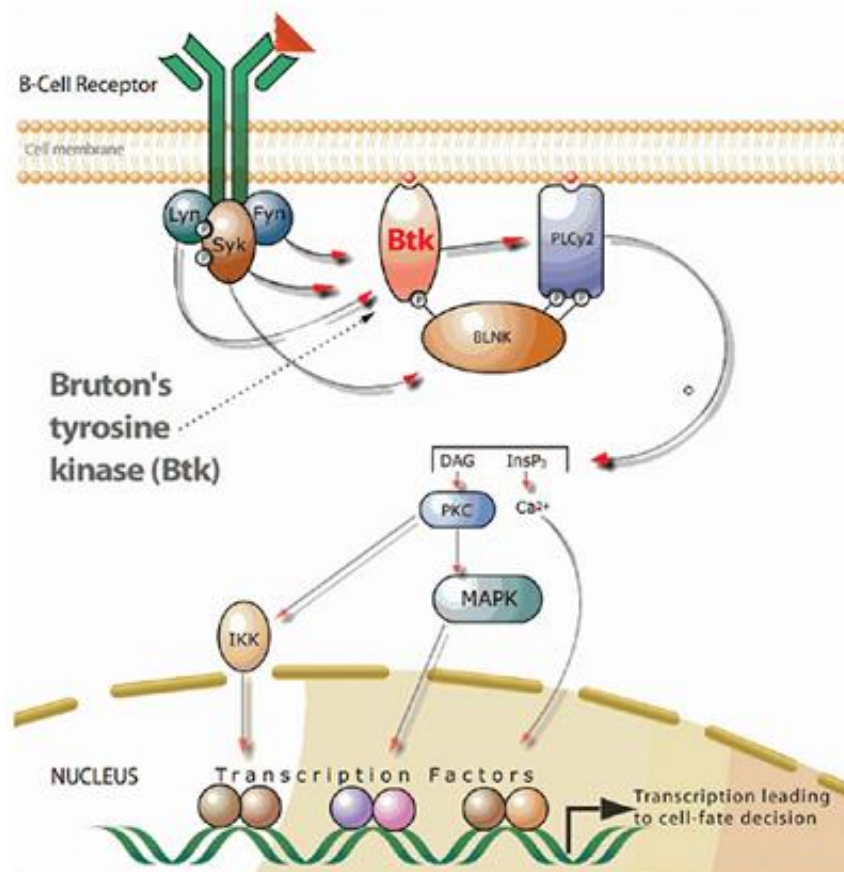
Bruton's Tyrosine Kinase (BTK) Inhibitors

- 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 (Acalabrutinib)
 - ONO/GS-4059
 - BGB-3111, CC-292



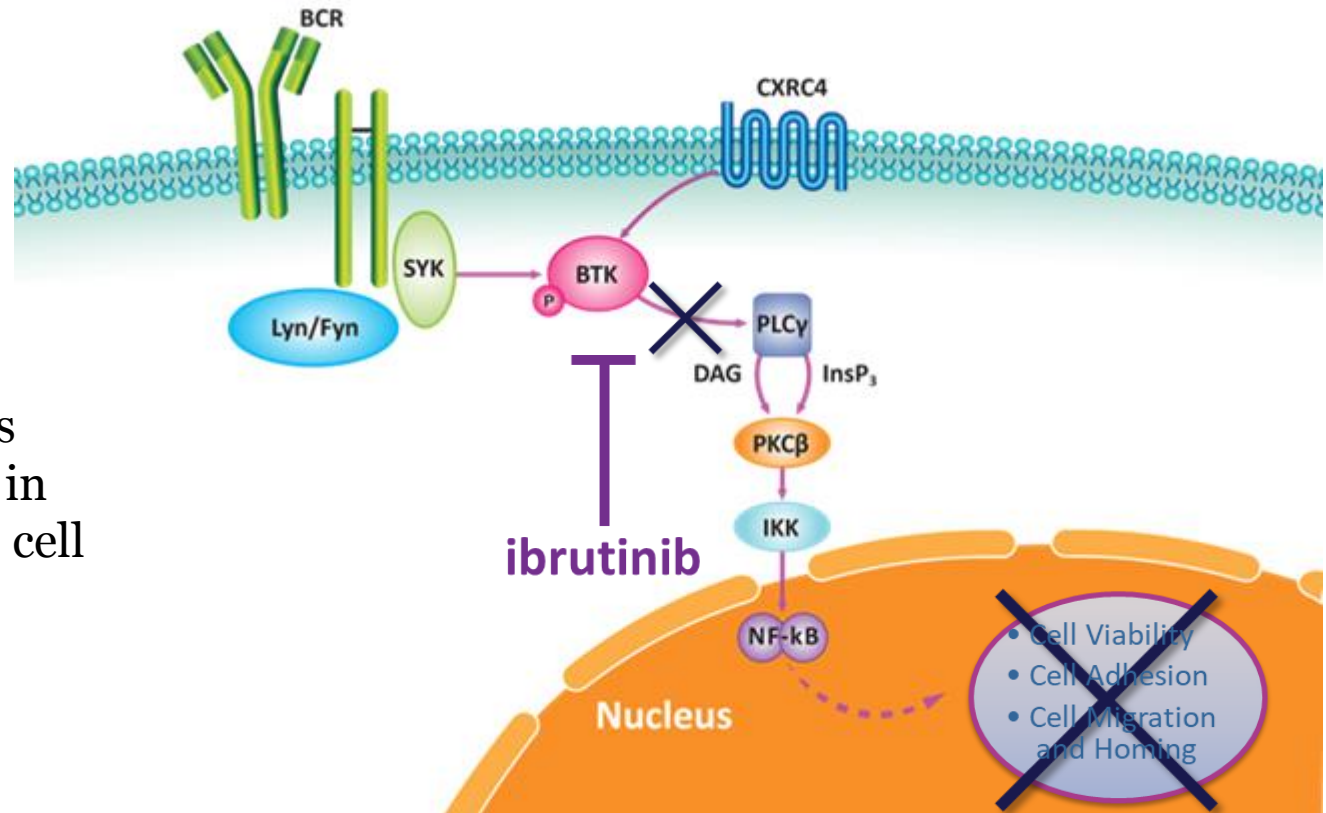
Ibrutinib

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



Ibrutinib

- First in class, potent, irreversible BTK inhibitor



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



IBRUTINIB SIDE EFFECT PROFILE

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Atrial fibrillation (5%)	E
Dermatological	Rash (24%)	E
Gastrointestinal	Constipation (15%)	E
	<u>Diarrhea (48%) (4% severe)</u>	E
	Mucositis (17%)	E
	Nausea, vomiting (26%)	I E
Hematological	<u>Hemorrhage (3%) (severe)</u>	E
	Leukocytosis (rare)	E
	<u>Myelosuppression ± infection, bleeding (23%) (grade 3/4)</u>	E
Musculoskeletal	Musculoskeletal pain (28%)	E
Neoplastic	Secondary malignancy (8%) (skin and other cancers)	L

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CCO Formulary - January 2015

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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
- 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
- Less bleeding risk: no clinically significant diarrhea, cardiac dysrhythmias or arthralgia were observed

[Oncotarget](#). 2017 Jan 24; 8(4): 7201–7207



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BGB-3111

- Highly specific BTK inhibitor
- Active in patients with LPL/ WM
- 42 patients - best objective response rate (ORR) of 90%

Number of Patients	Response
18 (43%)	VGPR
14 (33%)	PR
6 (14%)	Minor response
4 (10%)	SD
IgM	33 g/L down to 6 g/L
Hemoglobin	100 g/L up to 140 g/L

Trotman J et al. Hematol Oncol. June 7, 2017

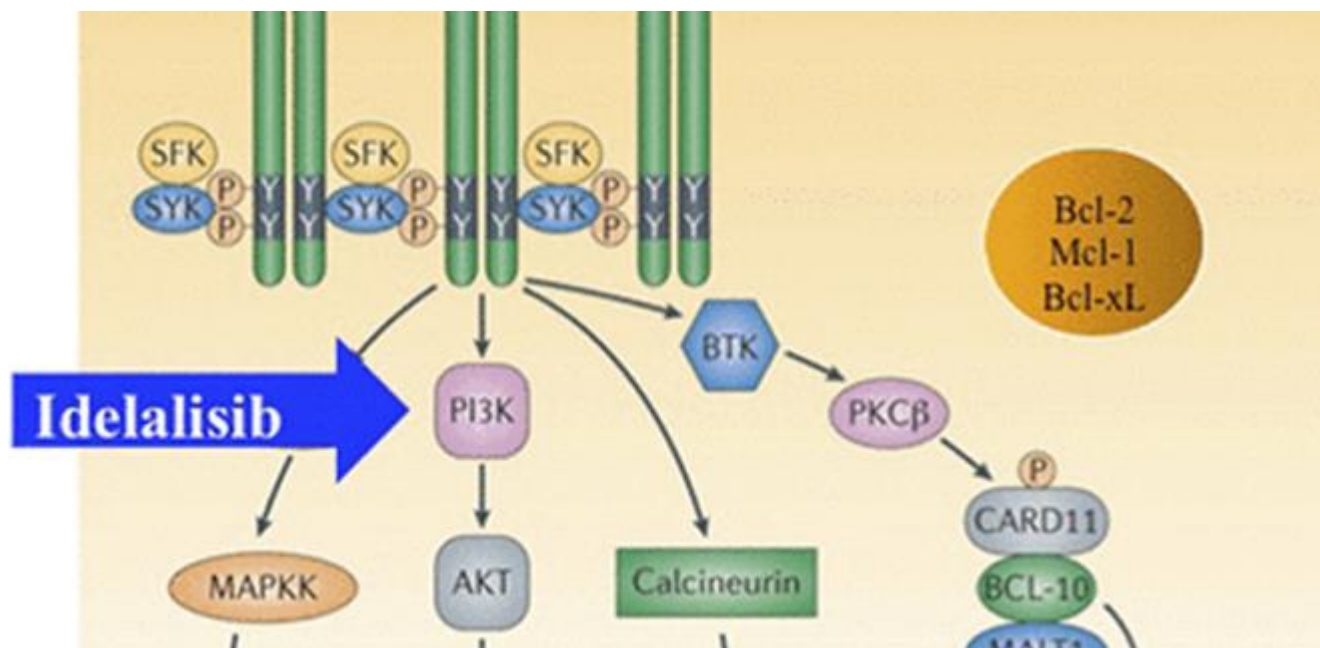


PI3K inhibitor

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



Idelalisib



Toxicity:

- Diarrhea
- Pneumonia/
Pneumonitis
- Hepatitis
- Infections
(CMV)
- Collitis



Umbralisib (TGR-1202)

- Unique structure and improved tolerability
- Monotherapy, oral
- Combined ublituximab (anti-CD20), 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



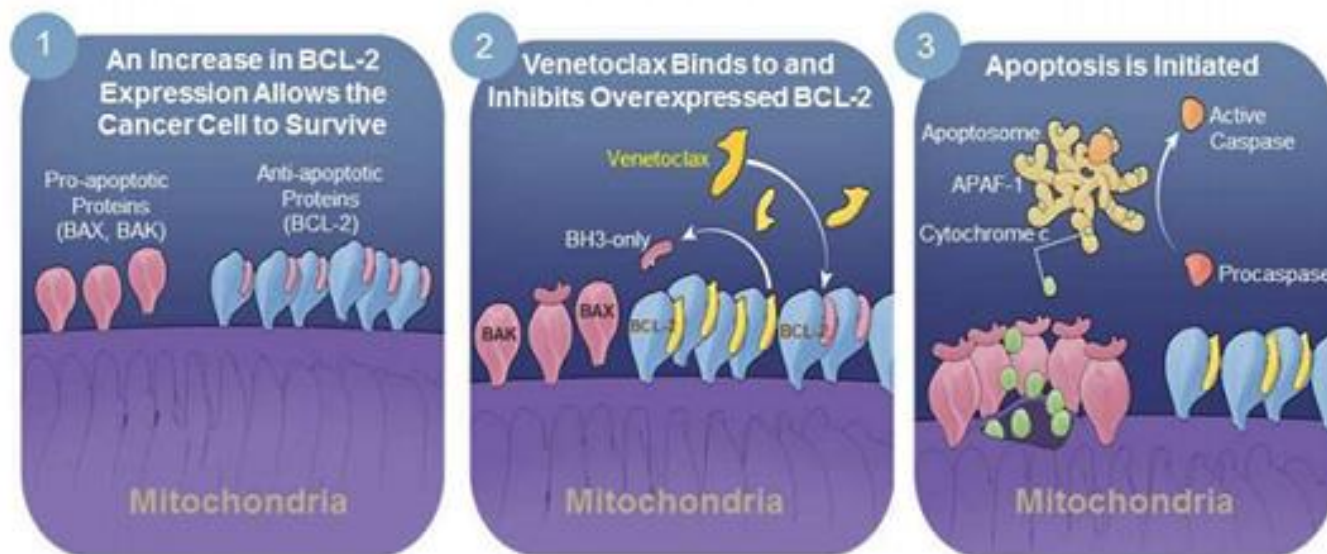
Copanlisib

CHRONOS-1 Study

- Phase 2 trial in RR B-cell iNHL
- ORR of 59.2% without inducing major colitis events or elevation of hepatic transaminases 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
- **Sept 14:** The FDA has granted an accelerated approval to copanlisib (Aliqopa) as a treatment for patients with relapsed follicular lymphoma who have received at least 2 least prior systemic therapies



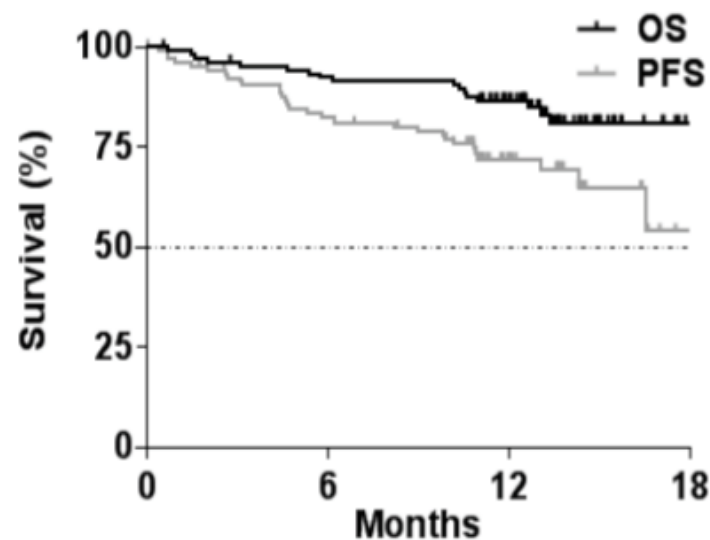
Bcl-2 Inhibitor: Venetoclax



Venetoclax Response Rates Relapsed CLL and 17p del CLL

Variable	No. of Patients	Complete Response Rate* <i>percent of patients (95% CI)</i>	Overall Response Rate
All patients	116	20 (13–28)	79 (71–86)
Dose-escalation cohort	56	30 (19–44)	77 (64–87)
Expansion cohort	60	10 (4–21)	82 (70–91)
Age			
≥70 yr	34	21 (9–38)	71 (53–85)
<70 yr	82	20 (12–30)	83 (73–90)
No. of previous therapies			
≥4	56	16 (8–28)	73 (60–84)
<4	60	23 (13–36)	85 (73–93)
Fludarabine resistance			
Yes	70	16 (8–26)	79 (67–88)
No	44	27 (15–43)	82 (67–92)
Bulky nodes of >5 cm			
Yes	67	8 (3–17)	78 (66–87)
No	48	38 (24–53)	83 (70–93)
Chromosome 17p deletion			
Yes	31	16 (6–34)	71 (52–86)
No	60	18 (10–30)	80 (68–89)
Chromosome 11q deletion			
Yes	28	11 (2–28)	82 (63–94)
No	62	21 (12–33)	76 (63–86)

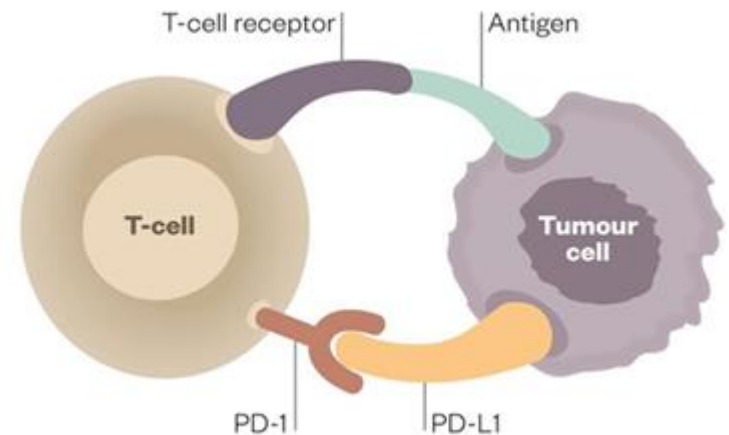
PFS and OS (N=107)



- 12-month estimates (95% CI):
PFS: 72.0% (61.8, 79.8)
OS: 86.7% (78.6, 91.9)

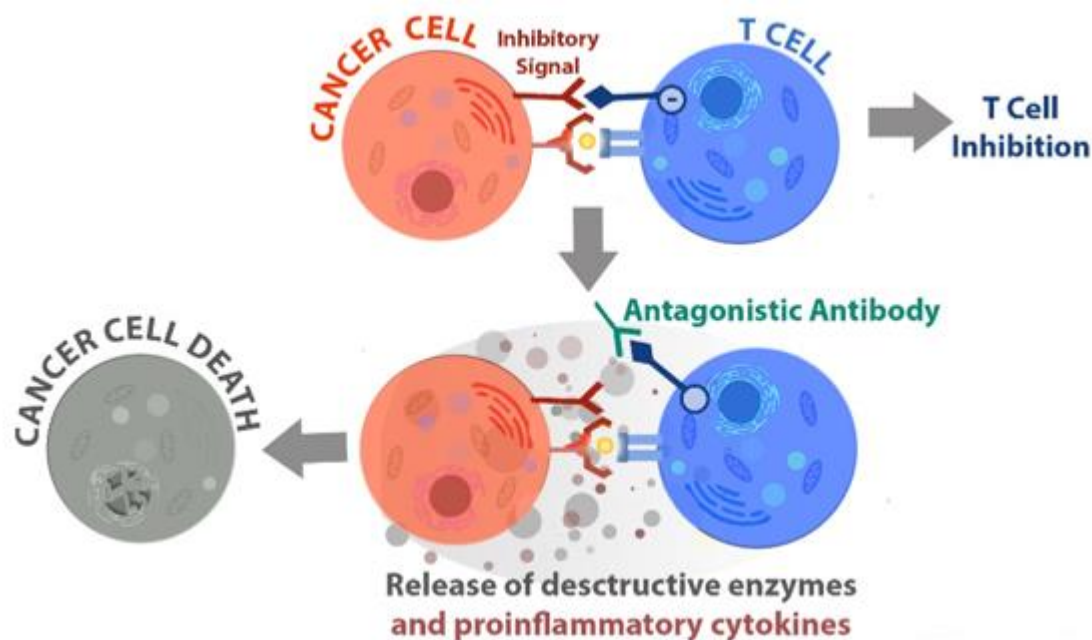
Immune checkpoint inhibitors

- PD = Programmed Cell Death protein
- PD-1 and PD-L1 turn off T-cell activation, preventing T cells from attacking the cancer.
- Binding of T-cells to PD-L1/2 inhibits T-cell function and blunts the normal immune response
- By preventing this ‘turn off’ switch, the T cell can be activated to kill the cancer



PD-L1 Inhibitors

- Act to inhibit the association of the programmed death-ligand 1 (PD-L1) with its receptor, programmed cell death protein 1 (PD-1)



- Advanced melanoma
- Non-small cell lung cancer
- Renal cell carcinoma
- Bladder cancer
- Hodgkin Lymphoma
- NHL

https://www.google.ca/search?q=PD1+inhibitors&source=lnms&tbm=isch&sa=X&ved=oahUKEwiis8SL4MjWAhXliVQKHcuaAHEQ_AUICigB&biw=1280&bih=899#imgrc=ZKyz02lQ_IVDqM:&spf=1506631603448



Pembrolizumab + Rituximab

Phase II RR Trial

- Follicular lymphoma tumors are infiltrated with anti-tumor T cells
 - Their function is impaired by immune checkpoints, such as PD-1
 - Blocking PD-1 could enhance antitumor T cells' activity that could be further enhanced by inducing ADCC using an anti-CD20 antibody
- 20 patients, Overall response rate (ORR) = 65%
 - Complete response rate of 50%

Nastoupil LJ et al Hematological Oncology, 35(S2): 120-121. doi:10.1002/hon.2437_108

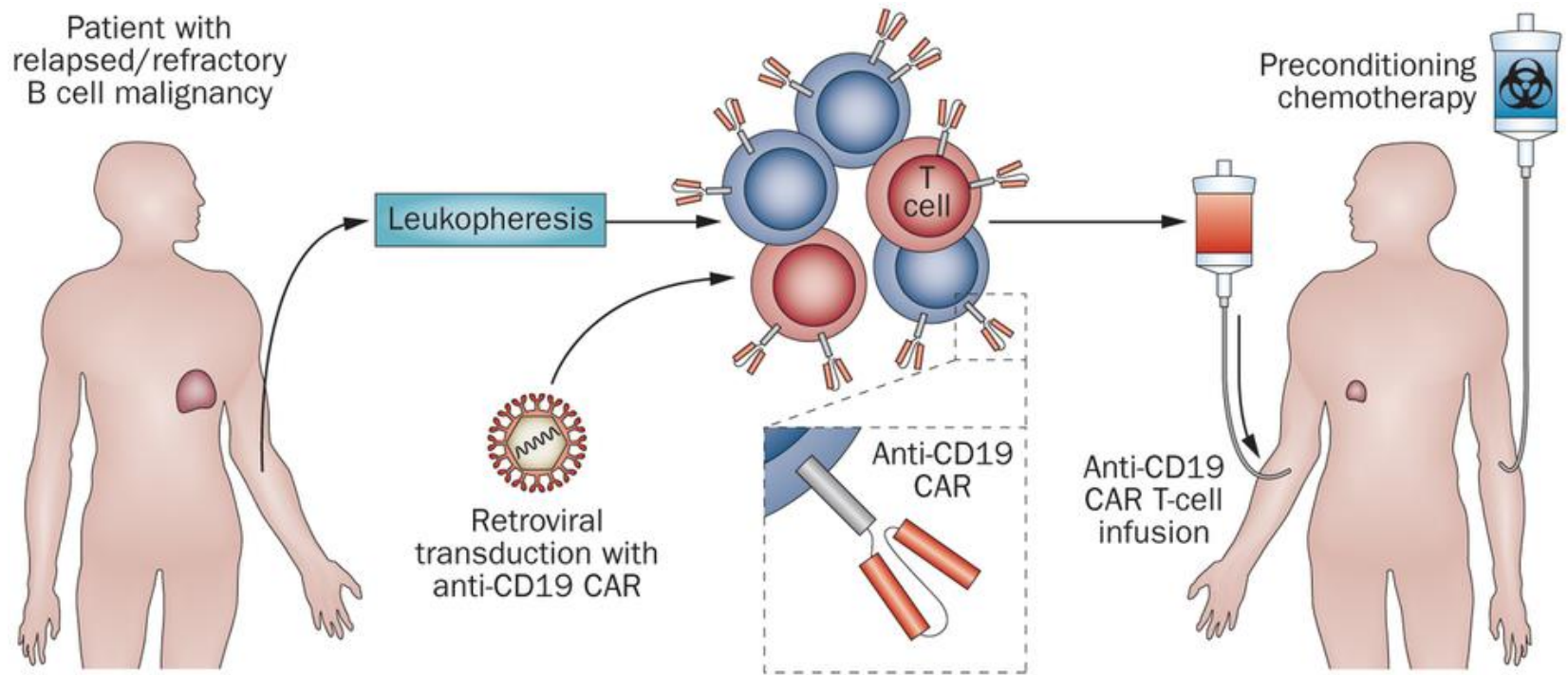


Nivolumab

- 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)



<http://www.nature.com/nrclinonc/journal/v11/n12/images/nrclinonc.2014.190-f1.jpg>



Differences between small molecules and biologics

- Small Molecules:

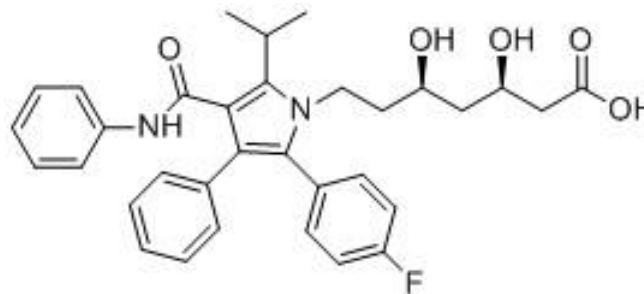
- made via chemical synthesis *in vitro*

- 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

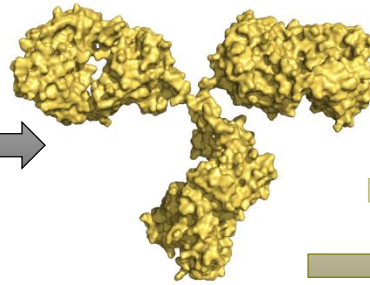
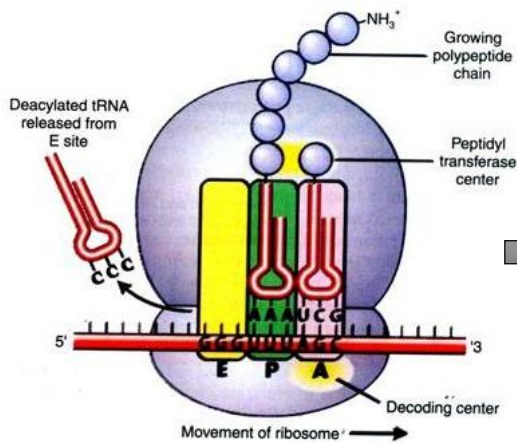


Differences between small molecules and biologics

- Proteins

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

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

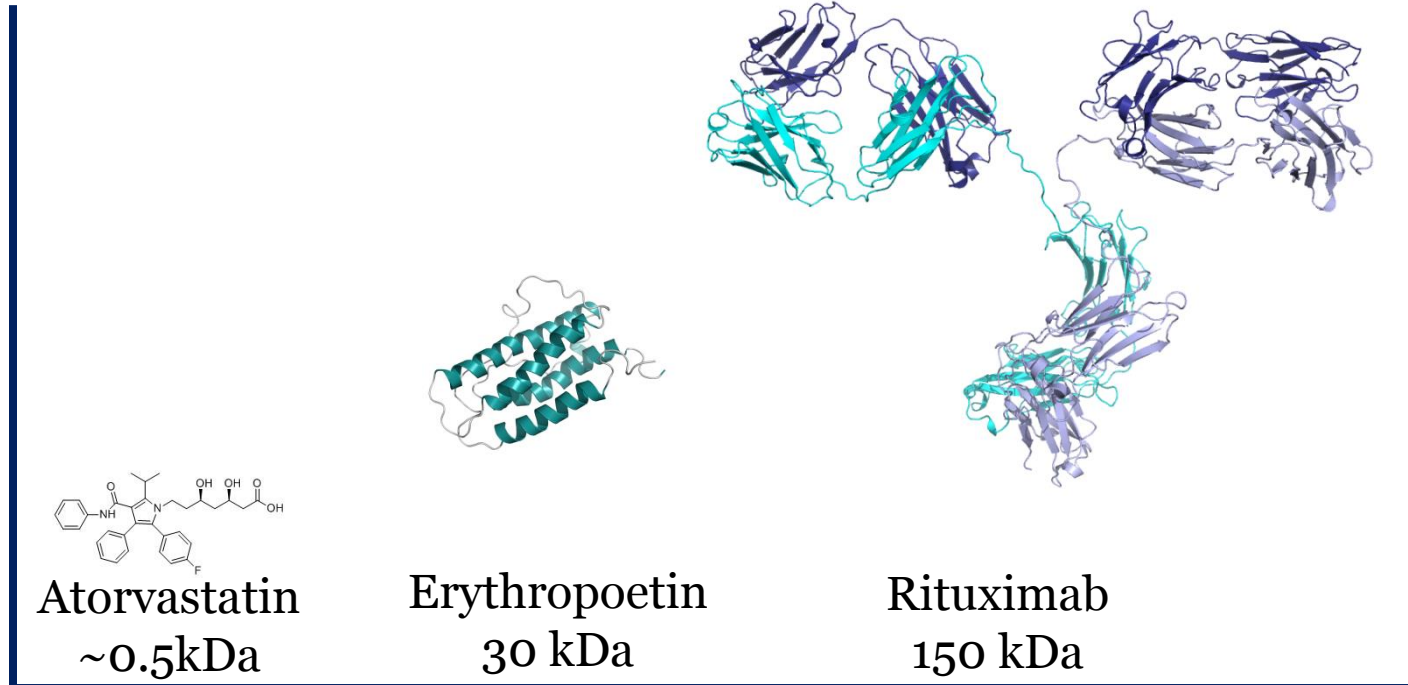


The final protein product may be subject to numerous post-translational modifications that can alter the chemistry of the molecule

These modifications can have a number of important implications



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

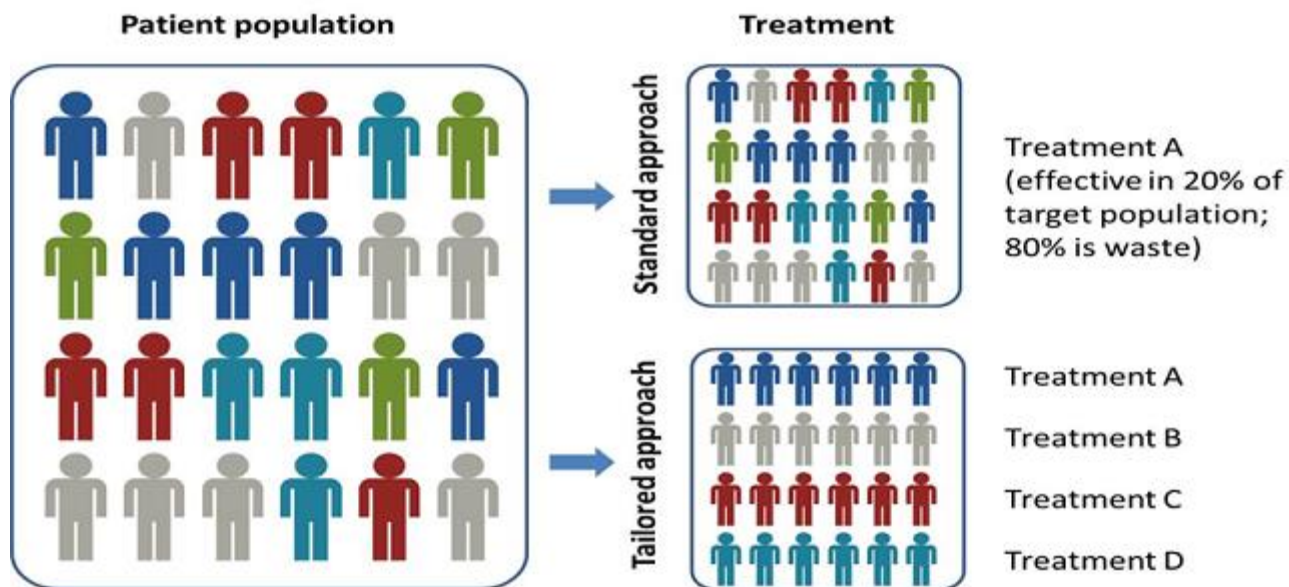


Biosimilars in lymphoma

- Subsequent Entry Biologics (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

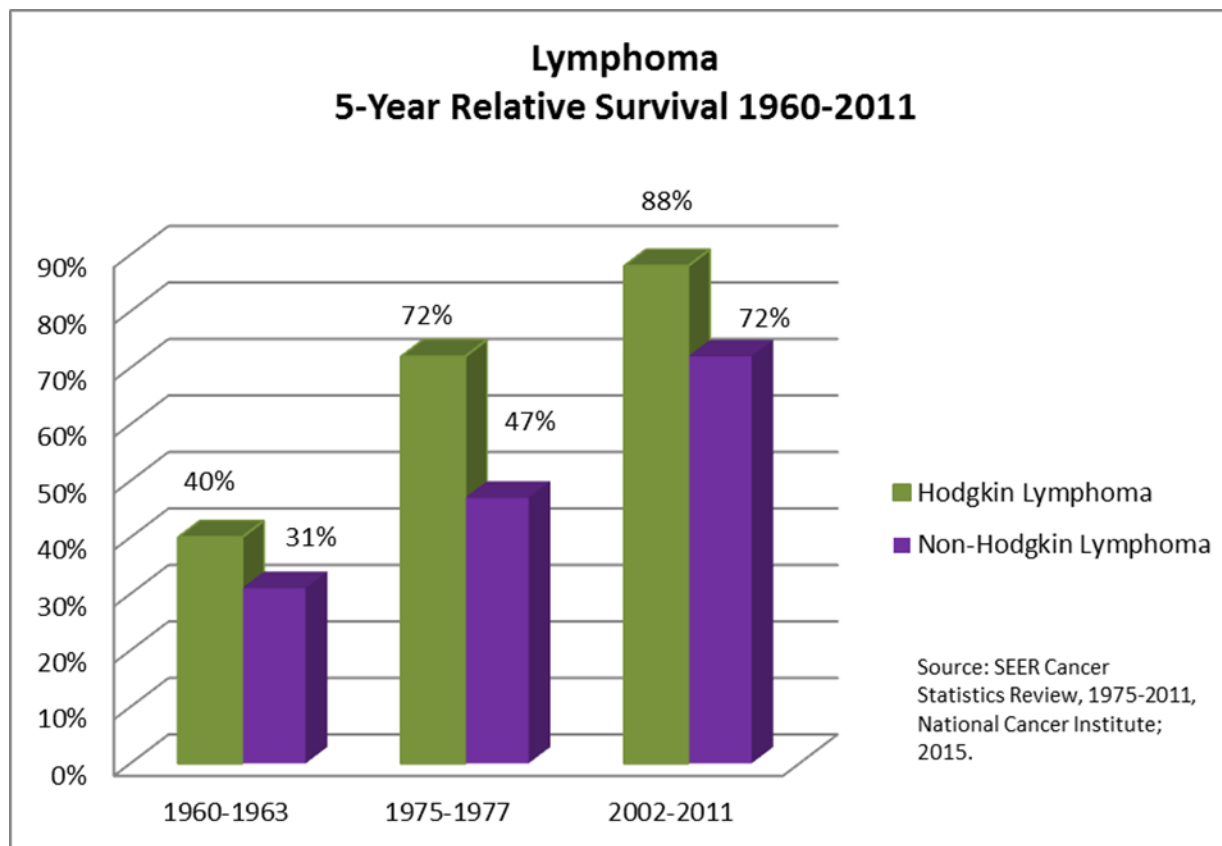


Is research working?

- 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?





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