LYMPHOME CANADA

Lymphoma 101

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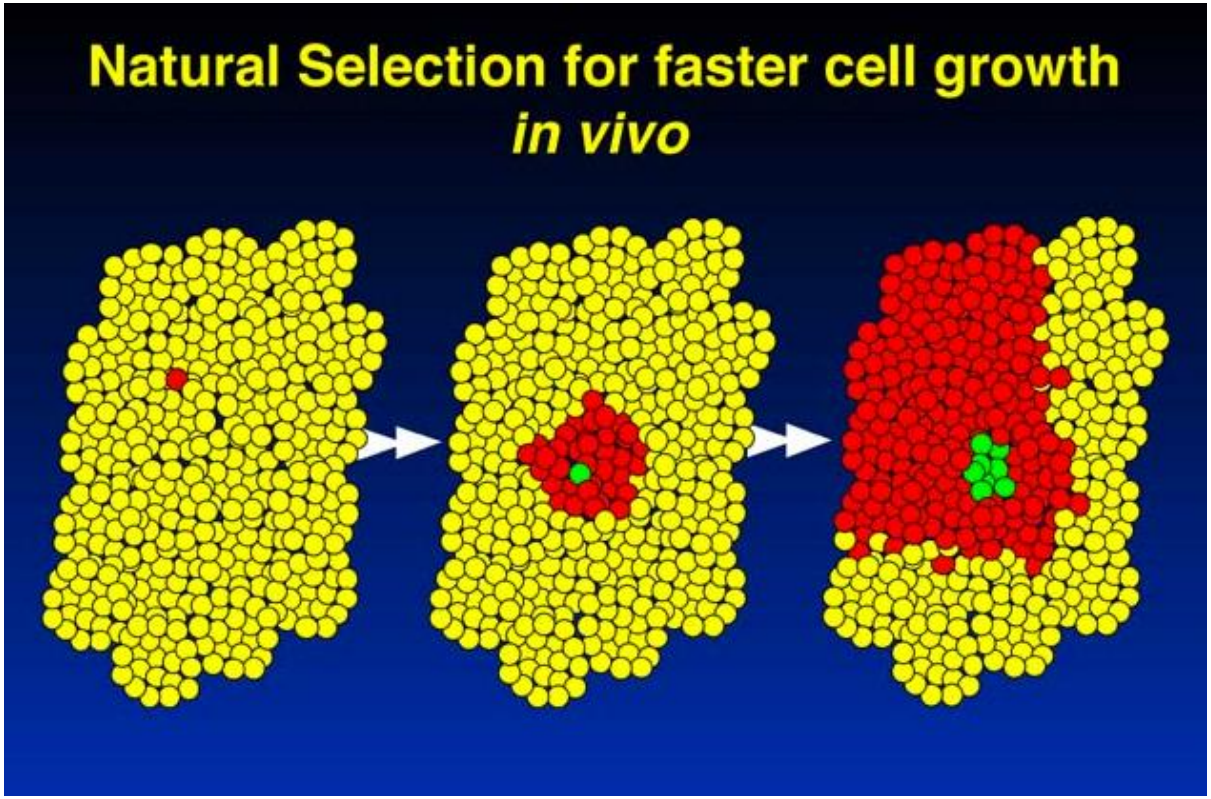
Disclosures

- Consultant and Advisory boards for multiple companies that make novel drugs
  - Roche
  - Abbvie
  - Gilead
  - Jansson
  - Lundbeck
  - Merck
- Research funding (Roche, Abbvie, Lundbeck)

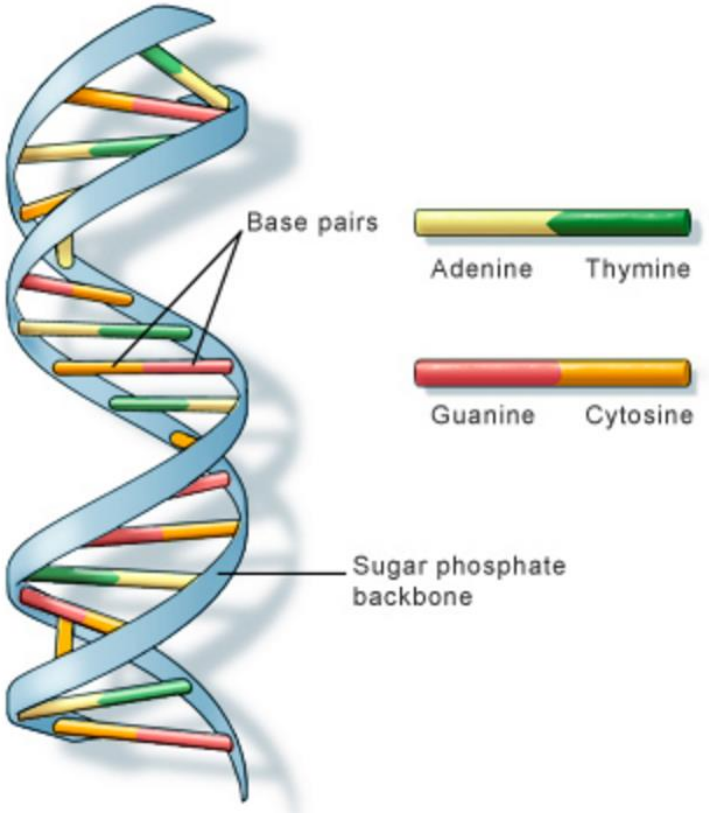
Outline

- Genetics of cancer
- Lymphoma subtypes
- Lymphoma treatments
- Novel therapies

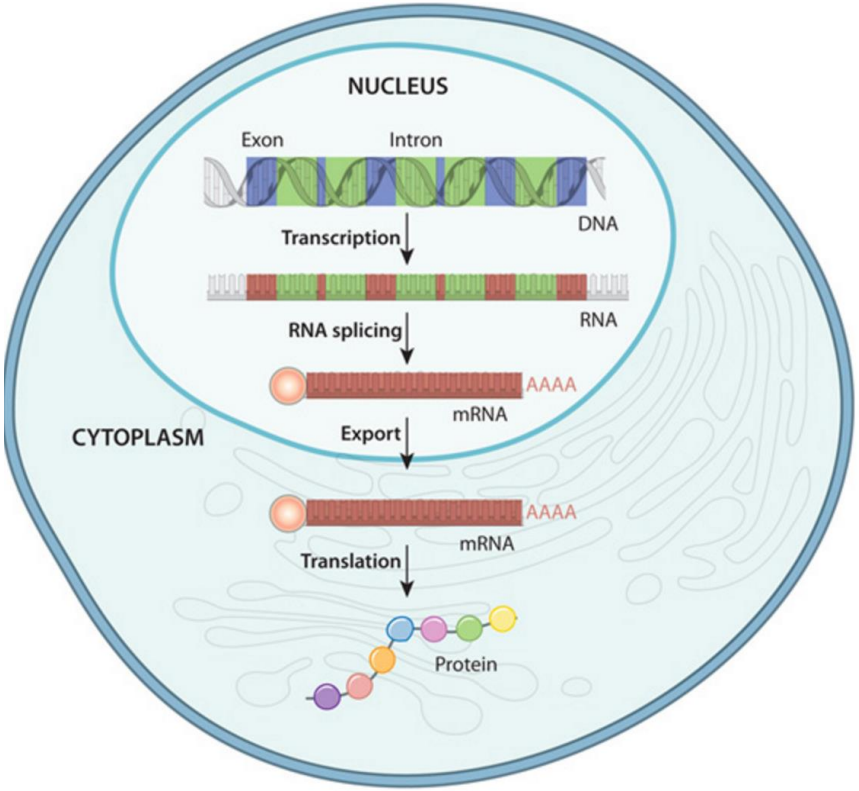
Cancer = uncontrolled cell growth of "clones" that are genetically different than normal cells



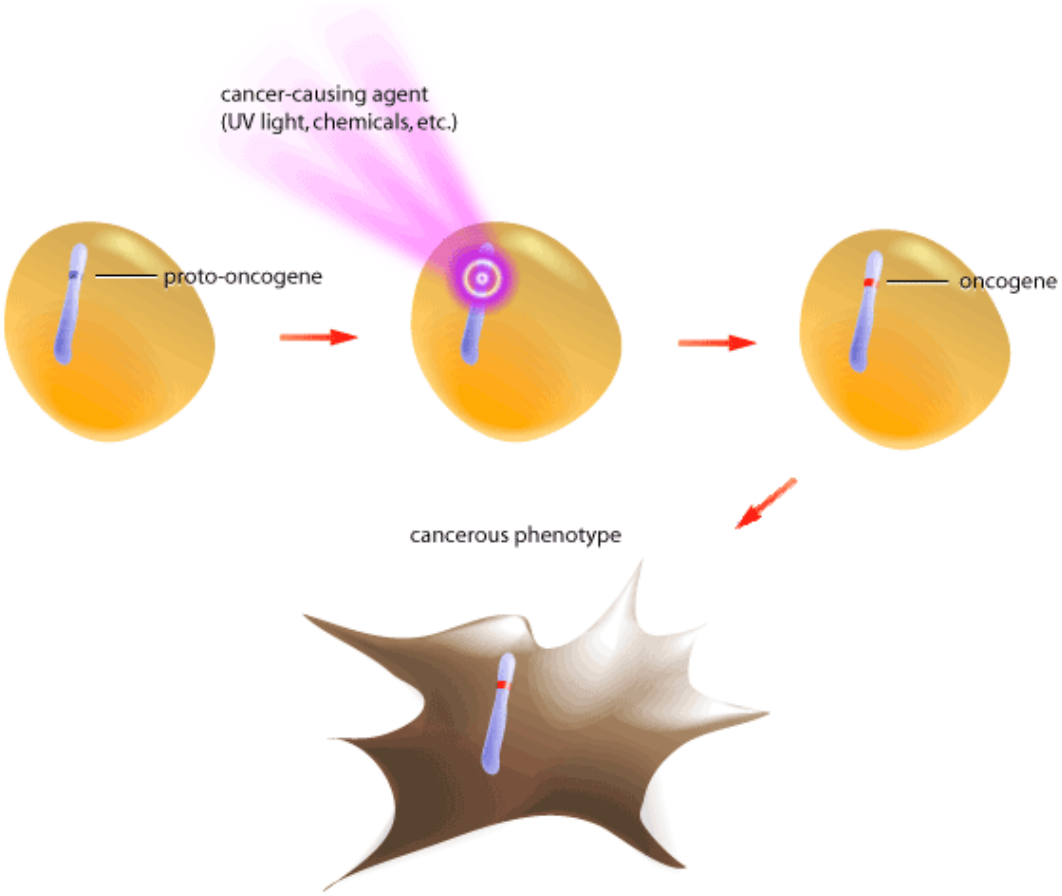
Growth is controlled by genes, made of DNA



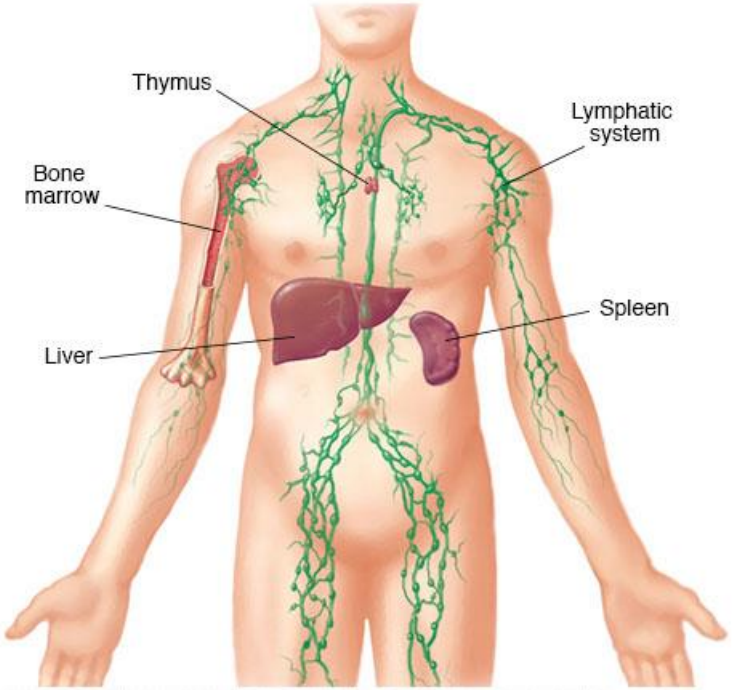
Genes control all functions of the cell

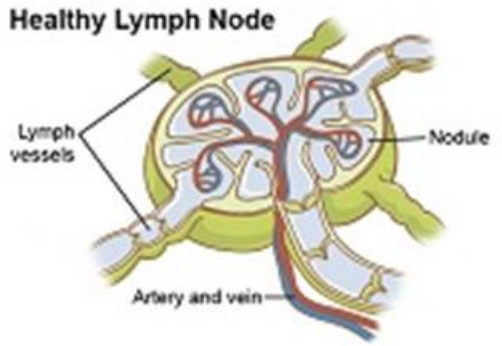


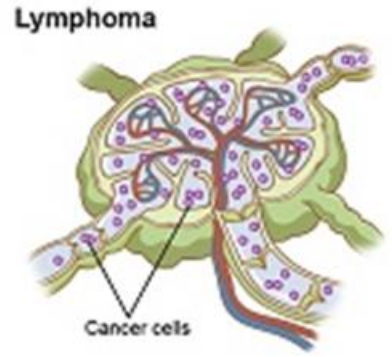
DNA damage can cause loss of growth control or prevent the cell from dying



Function of the Lymphatic System





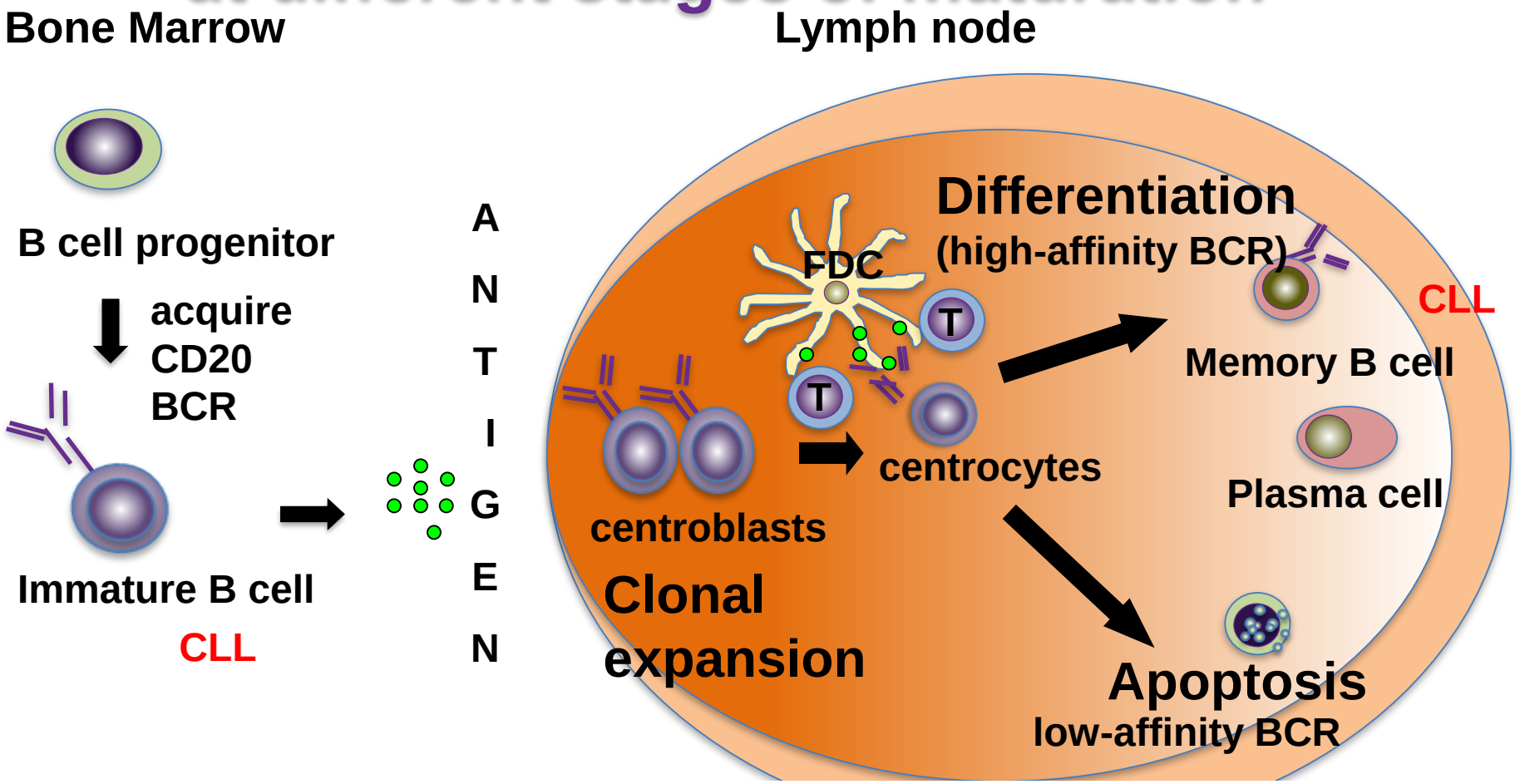


To defend the body against “intruders”

Lymphocytes

- B-cells develop in the bone marrow
  - form antibodies against foreign bodies
- T-cells develop and mature in the thymus gland
  - orchestrate the immune response
- NK (natural killer) cells
  - destroy viruses and cancers through direct attack

Lymphomas arise from normal lymphocytes at different stages of maturation



Most common lymphomas occur in the germinal center: DLBCL, Follicular Hodgkin and Burkitt lymphomas

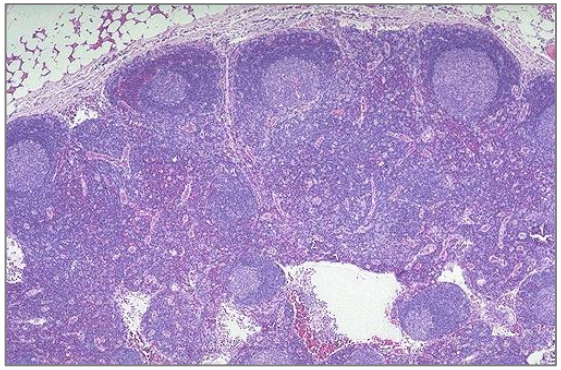
Lymphoma types

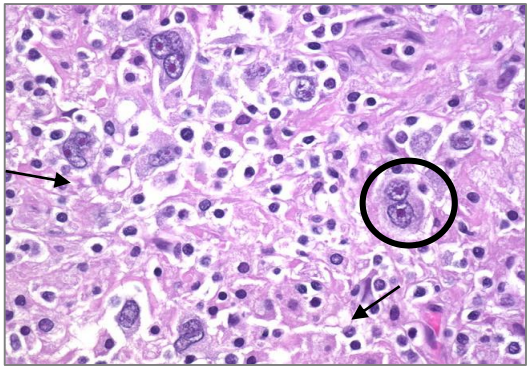
- Non-Hodgkin (NHL)
  - 85-90% of all lymphomas
  - ~50 subtypes
  - Indolent vs aggressive variants
- Hodgkin (HL)
  - 10-15% of all lymphoma
  - High cure rate

Hodgkin Lymphoma

- 1000 cases/year in Canada
- Two peaks: young adults and elderly
- Can be difficult to diagnose
  - Cancer cells represent 1% of cells in the biopsy
- > 80% curable with chemotherapy +/- radiation

Normal

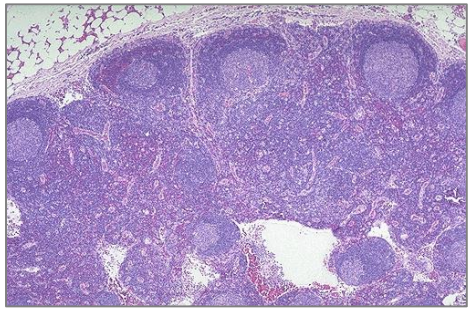




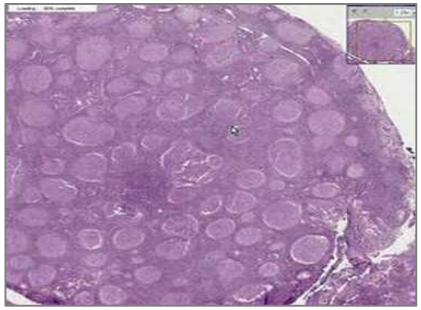
HL

Indolent Non-Hodgkin Lymphomas

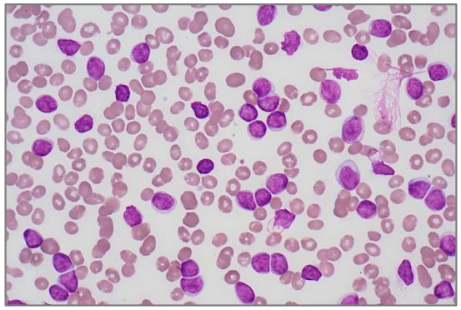
- 8200 cases per year in Canada: multiple subtypes
  - Follicular lymphoma and CLL most common
  - Less common: marginal zone lymphoma, mantle cell lymphoma, lymphoplasmocytic lymphoma
- Slow evolution, recurrent, unlikely curable
- Asymptomatic patients usually do not require treatment, but active monitoring



Normal



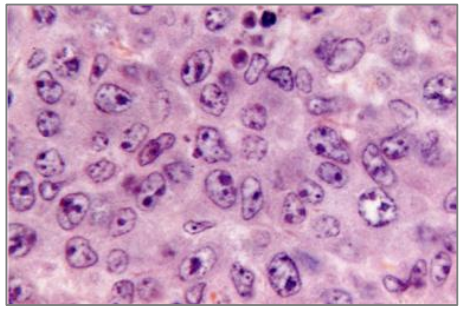
Follicular lymphoma



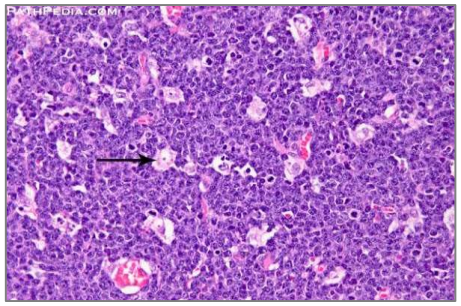
CLL

Aggressive Non-Hodgkin Lymphomas

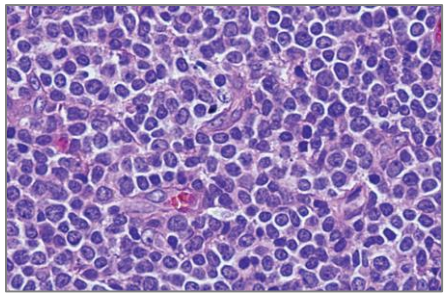
- **Diffuse large B-cell lymphoma**
  - Most common lymphoma 35-40% of cases of NHL
  - Often curable (65%)
- Very aggressive (e.g. Burkitt, lymphoblastic)
  - Often curable (>80%)(leukemia-like treatment)



DLBCL

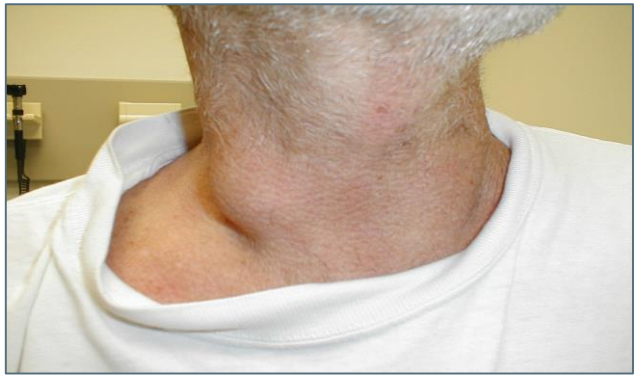


Burkitt



Lymphoblastic

Signs and symptoms of lymphoma



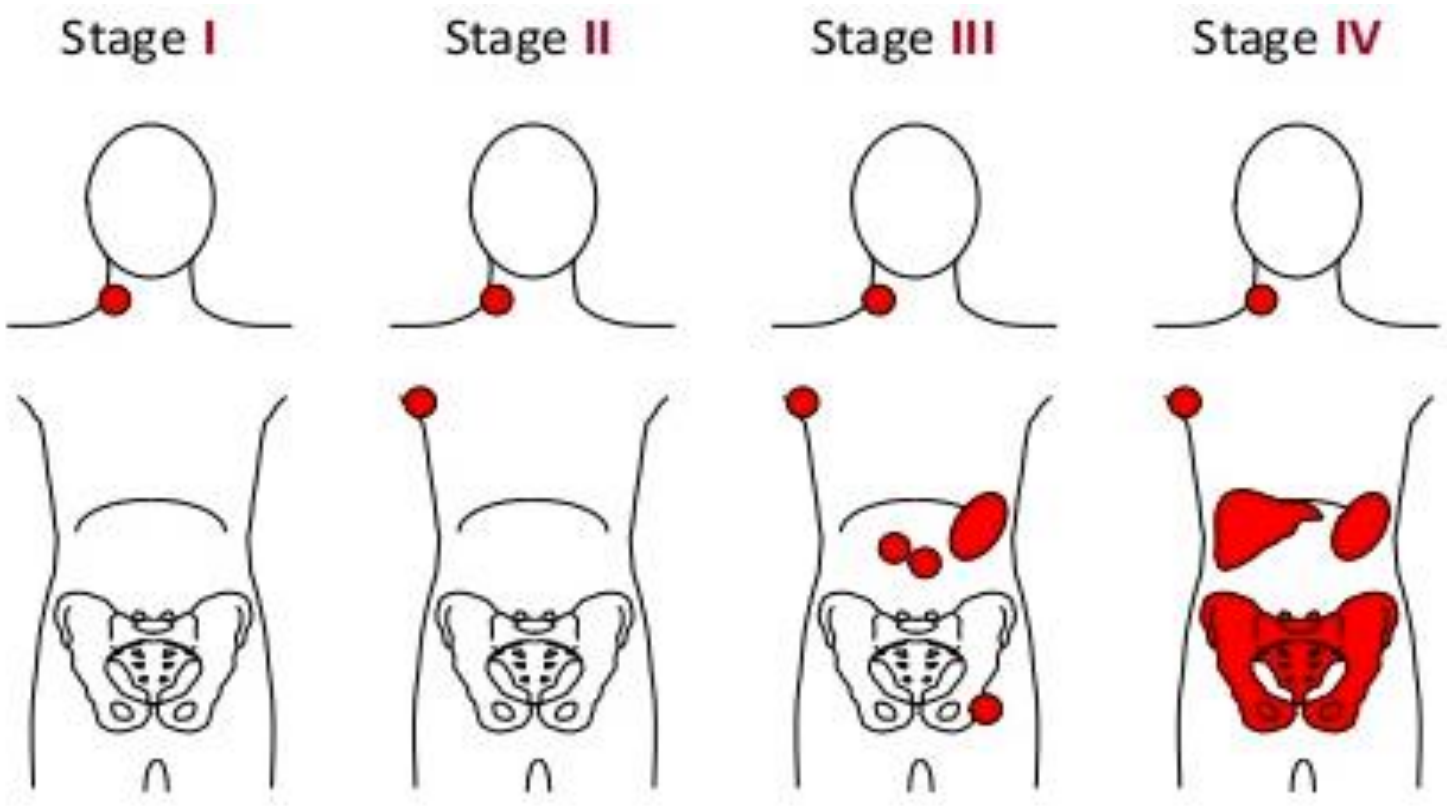
History:

- Fatigue
- Lumps/bumps
- Shortness of breath, abdominal pain/symptoms
- Rash or itching
- Constitutional (“B”) symptoms:
  - Fever
  - Drenching Night Sweats
  - Weight loss (>10% of baseline weight)

Evaluation of the lymphoma patient

- Examination of tumor sample (biopsy)
- Evaluation of spread (staging)
  - CT scans
  - PET scan
  - +/- Bone marrow biopsy
- “Know” the patient
  - State of health
  - Psychological state
  - Determination to fight
  - Support network

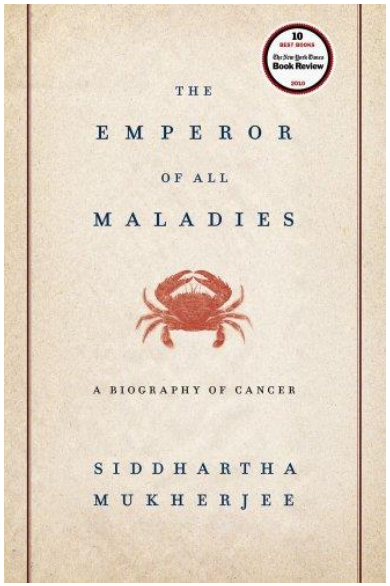
Staging of lymphoma



A: absence of B symptoms B: presence of fever, night sweats, weight loss

Treatment

- Most important is to establish goal of treatment
  - Curative intent versus a prolonged remission versus symptom control

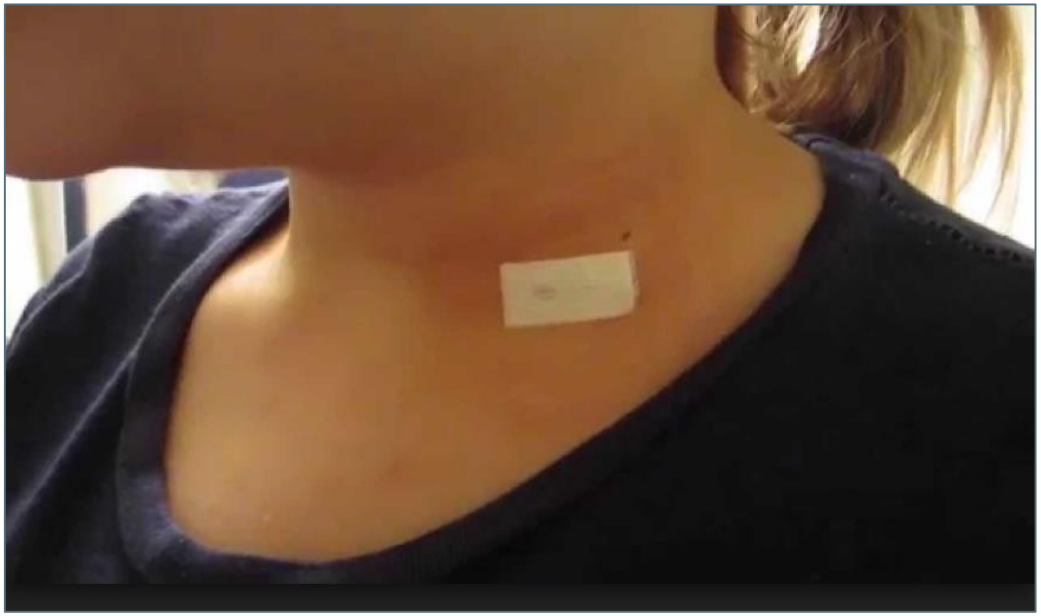


Factors affecting treatment

- Type of lymphoma
- Age
- Functional status
- Comorbidities (other diseases)
- Disease stage and “bulkiness”
- Prior therapies

Lymphoma treatment: generally not surgery

- Usually only indicated for diagnostic purposes (biopsy), not as a means of definitive treatment

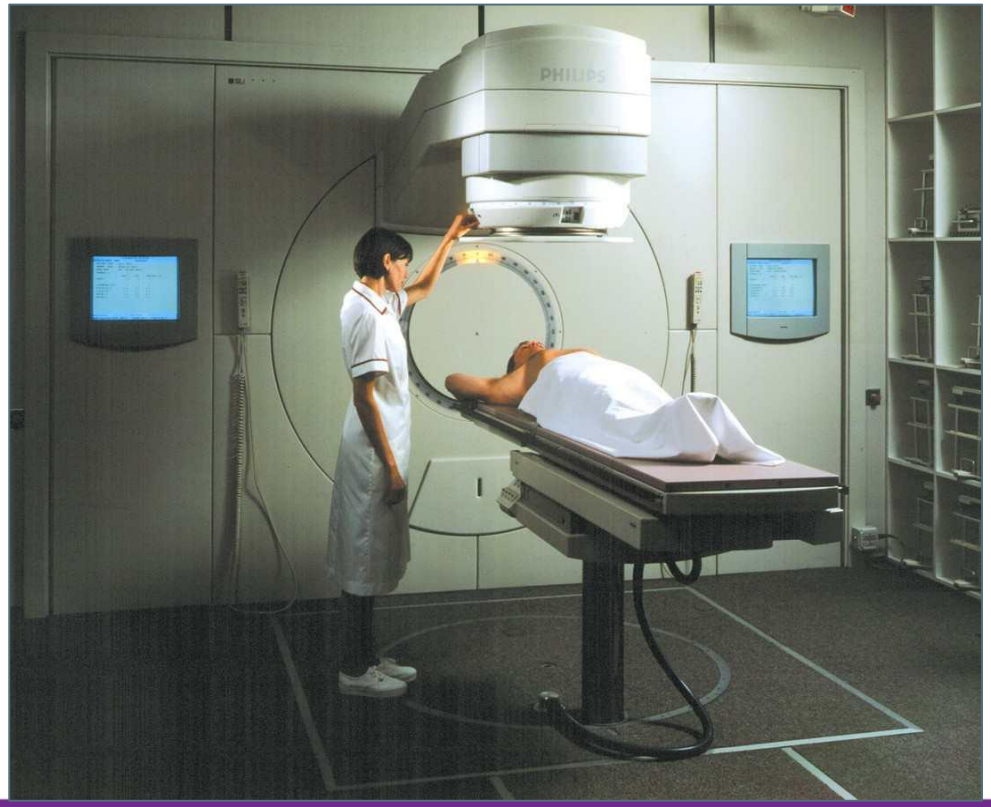


Observation for indolent lymphomas

- Watch and wait (watch and worry?)
- recommended for individuals without symptoms or organ compromise
- Many indolent lymphomas will never progress to a point where treatment becomes necessary
- Overall survival does not appear to be worse for patients whose iNHL is initially observed (vs treated at the time of diagnosis, even in the absence of symptoms)

Lymphoma treatment: radiotherapy

- Lymphomas that have limited spread can sometimes be treated (and even cured) by radiation alone



Lymphoma treatment: chemotherapy

- Lymphoma that has spread within the body, or is aggressive in nature, is usually treated with chemo(immuno)therapy

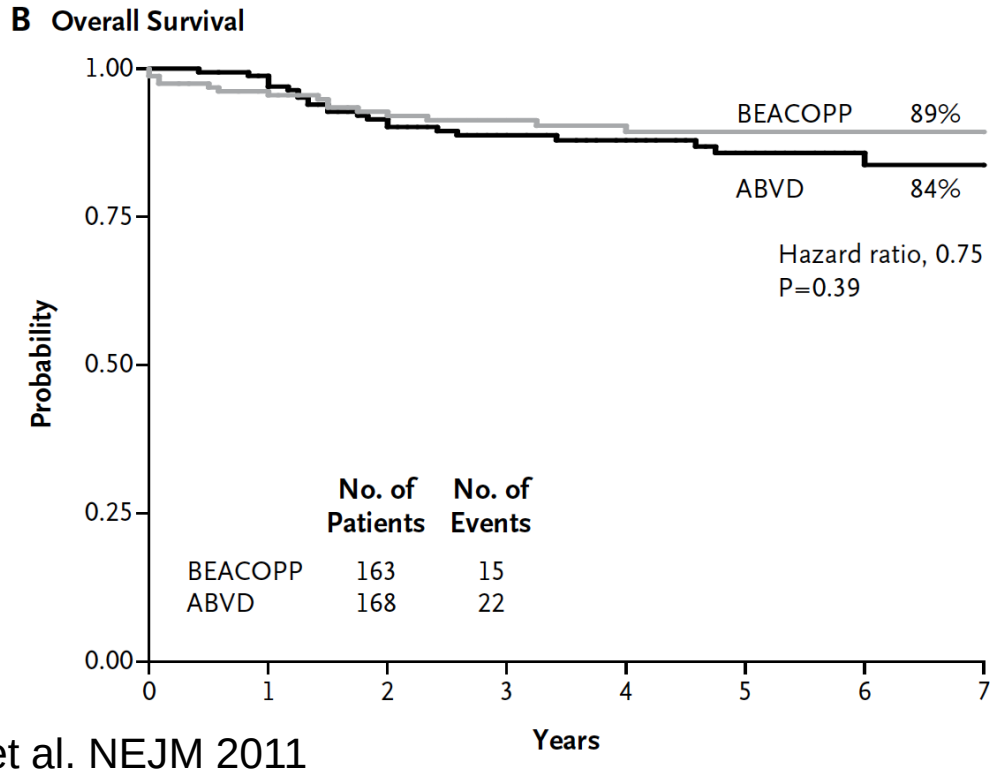
Chemotherapy regimens for lymphoma developed after World War II

Mustard Gas in WWII

Veterans exposed to mustard gas had decreased white blood cell counts

- 1965: MOPP (before ABVD and CHOP)
  - M: nitrogen mustard (mechlorethamine)
  - O: oncovin
  - PP: prednisone and procarbazine
  - Side effects: **++ nausea, sterility, leukemia**
- 1975: **ABVD in Hodgkin Lymphoma**
  - Adriamycin (cardiac toxicity)
  - **Bleomycin (lung and skin toxicity ~3%)**
  - Vinblastine (neuro toxicity)
  - Dacarbazine (nausea, pain)
- 1976: "**CHOP" in non-Hodgkin lymphoma**
  - Cyclophosphamide, hydroxyrubicin,
  - oncovin, prednisone
  - Cardiac, neuro, nausea, **leukemias (2%)**

Advanced Stage Hodgkin
> 80 % are cured with ABVD



Viviani et al. NEJM 2011

Survival at 7 years =
84% (ABVD)
89% (BEACOPP), p>0.05

Thus need to minimize toxicities for survivors

CHOP the standard chemotherapy backbone for DLBCL: cured 40% of patients

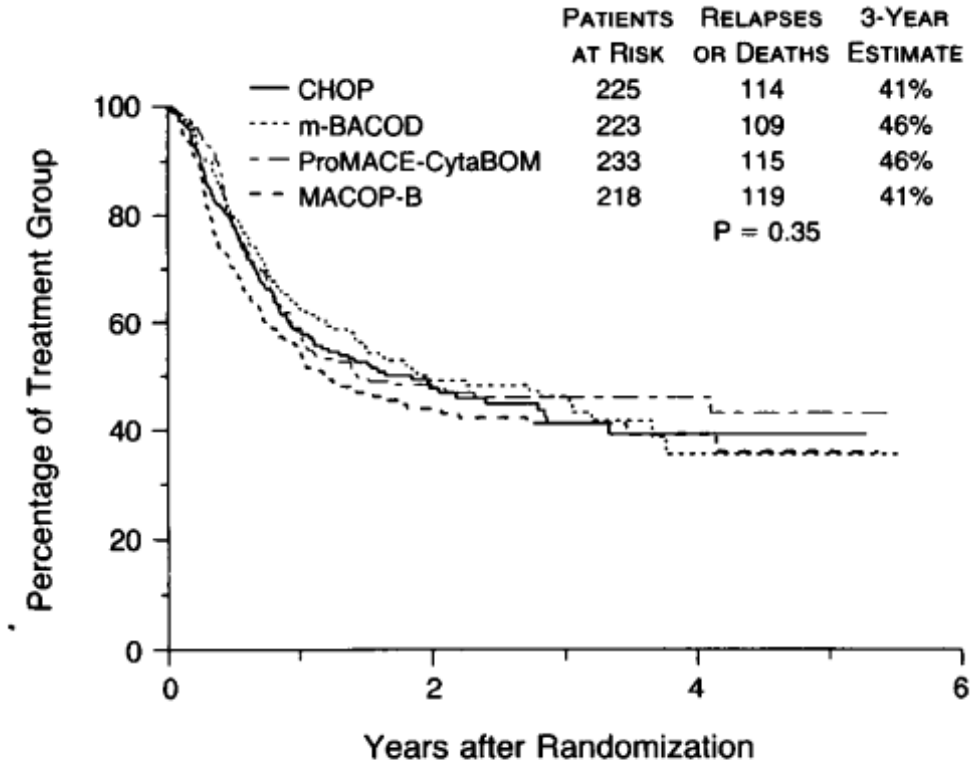
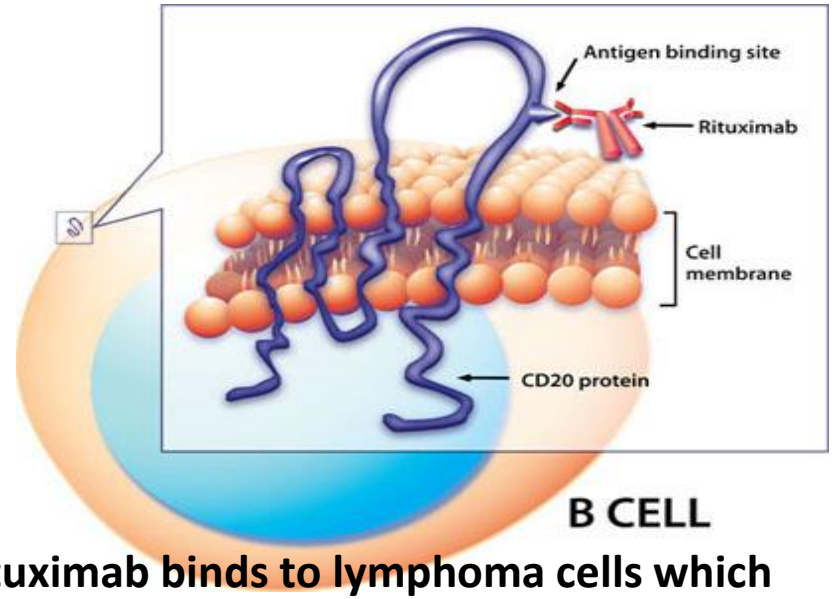


Figure 1. Time to Treatment Failure in the Treatment Groups. The three-year estimate is of survival without disease.

Fisher et al. NEJM 1993, 328: 1002-1006

Success of immunotherapy in DLBCL: Rituximab-CHOP standard of care

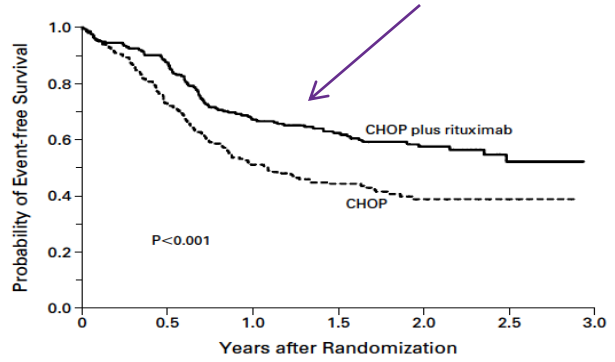
Rituximab: antibody targeting the CD20 protein on B cells



Rituximab binds to lymphoma cells which will be targeted for destruction by other immune cells

R-CHOP is better than CHOP

~50% improvement in survival



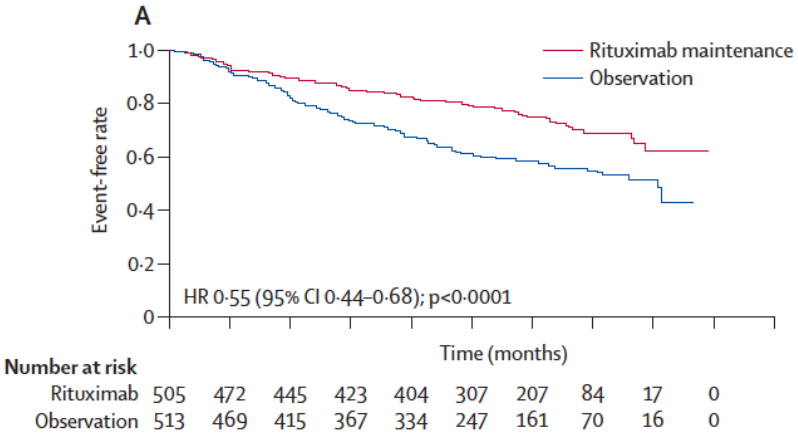
No. at Risk						
CHOP plus rituximab	202	177	137	108	63	19
CHOP	197	144	101	72	42	17

Figure 1. Event-free Survival among 399 Patients Assigned to Chemotherapy with Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone (CHOP) or with CHOP plus Rituximab.

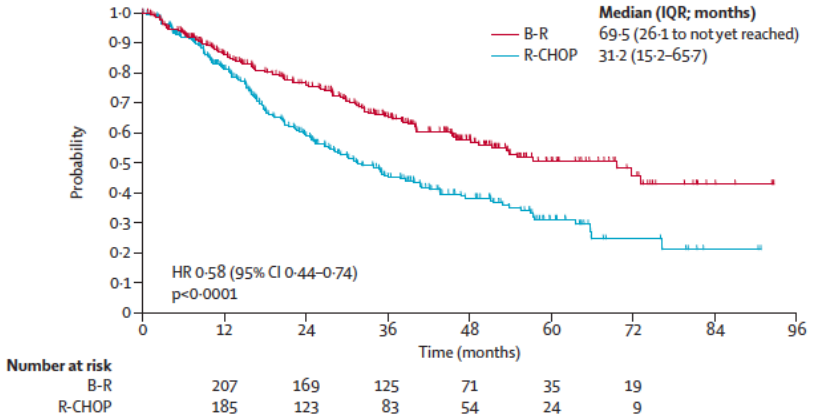
Coiffier et al. NEJM 2002, 328: 1002-1006

Follicular lymphoma

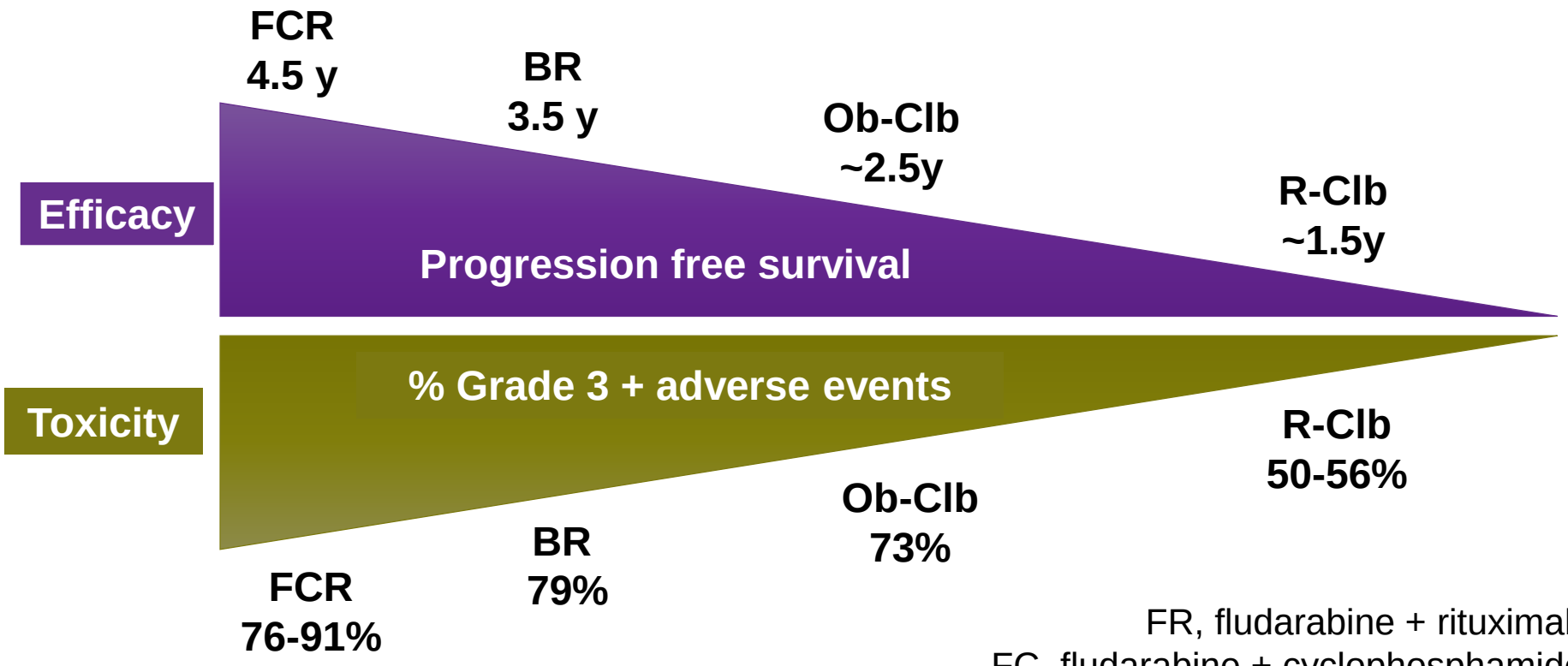
<u>Prima trial:</u> RCHOP x 6 cycles followed by 2 years of rituximab maintenance



<u>STiL trial:</u> Bendamustine and rituximab (BR) x 6 cycles
no rituximab maintenance



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.

Life after primary chemotherapy

- What is response? PET scan
  - Progression
  - Stable disease
  - Partial response

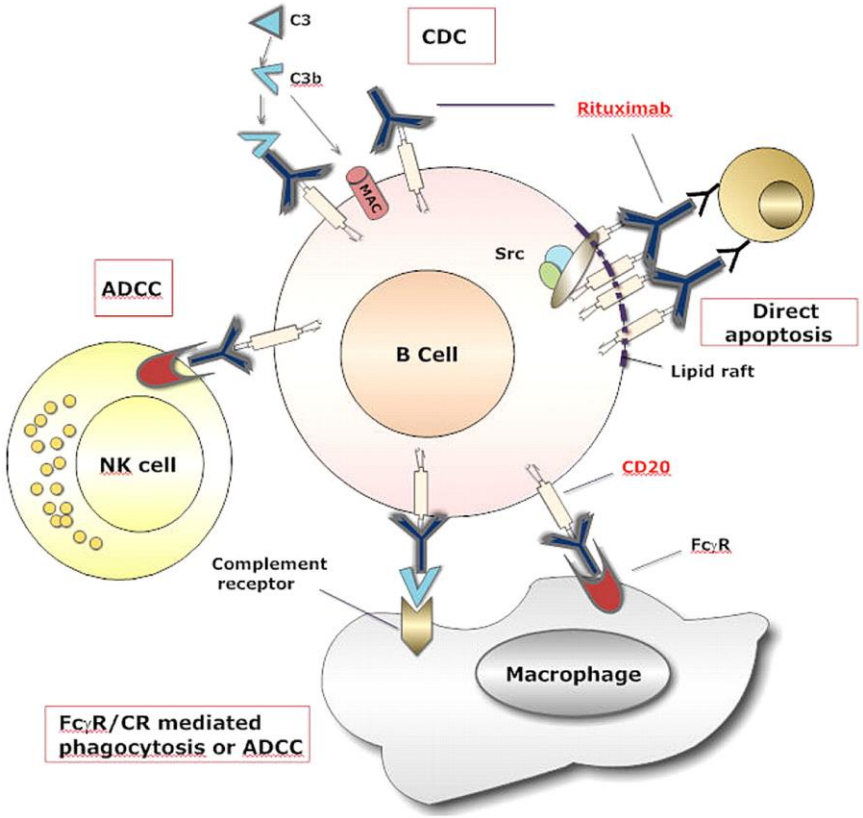
  → Biopsy, salvage chemo and transplant
  → Residual PET avid nodes within a radiation field may get radiation therapy

  - Complete response → No further therapy or scans

- Monitoring patients in remission: most relapses occur < 2 years of completing chemotherapy (20-40% Hodgkin and 25-50% DLBCL)
  - every 3 months x 2 years, then every 6 months x 3 years then every year to monitor for relapse and long term toxicity
- No pregnancies within first 2 years
- Goal: “return to normal”
  - Issues: Anxiety, Depression, Fatigue

New cancer treatments: monoclonal antibodies

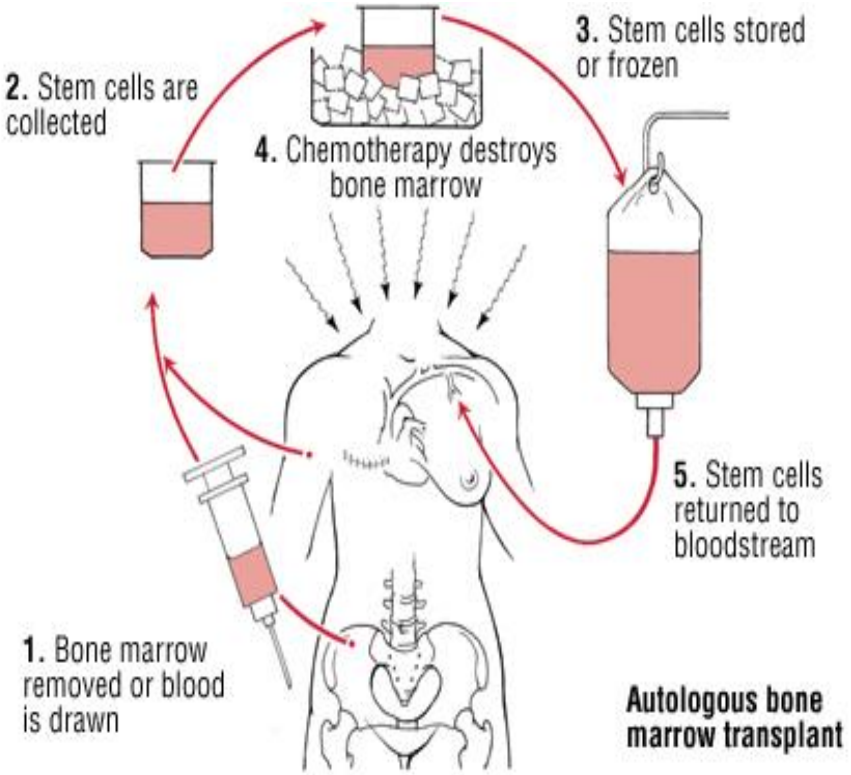
- Antibodies developed against cancer cells can be administered to patients to destroy the tumor
- Examples:
  - CD20: Obinutuzumab and Ofatumumab
  - CD52: Alemtuzumab
  - CD30: Brentuximab vedotin



Samantha M. Jaglowski et al. Blood 2010;116:3705-3714

Stem cell transplantation (SCT)

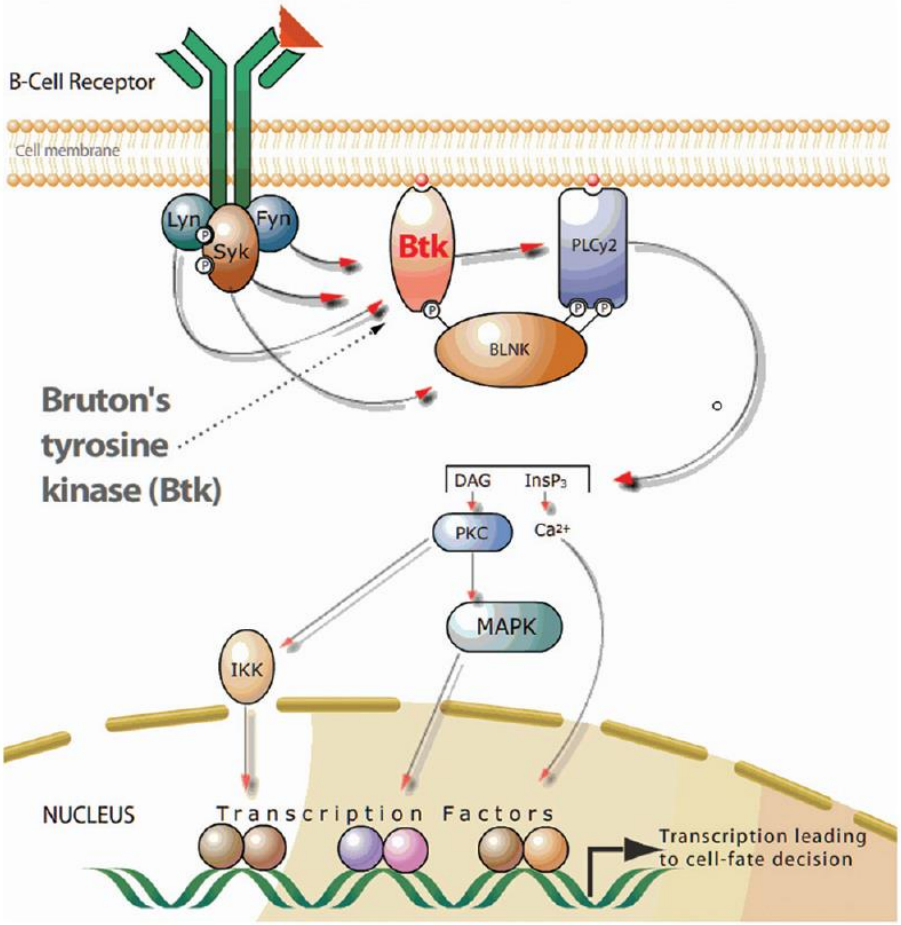
- When lymphoma can no longer be managed by conventional chemotherapy, it can sometimes be controlled or cured through high dose chemo and stem cell rescue
- Rarely, allogeneic stem cell transplants may be employed



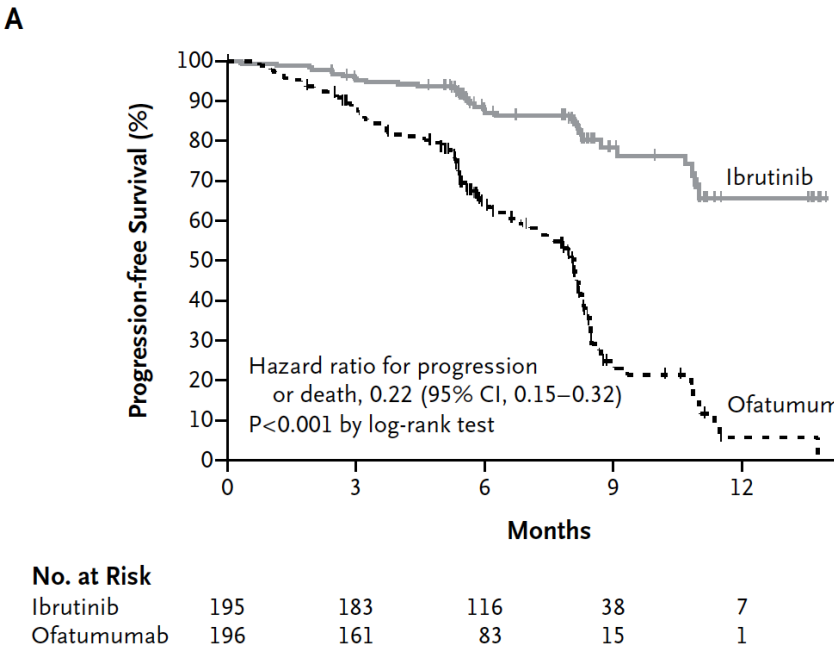
Lymphoma treatment: the “designer” drugs

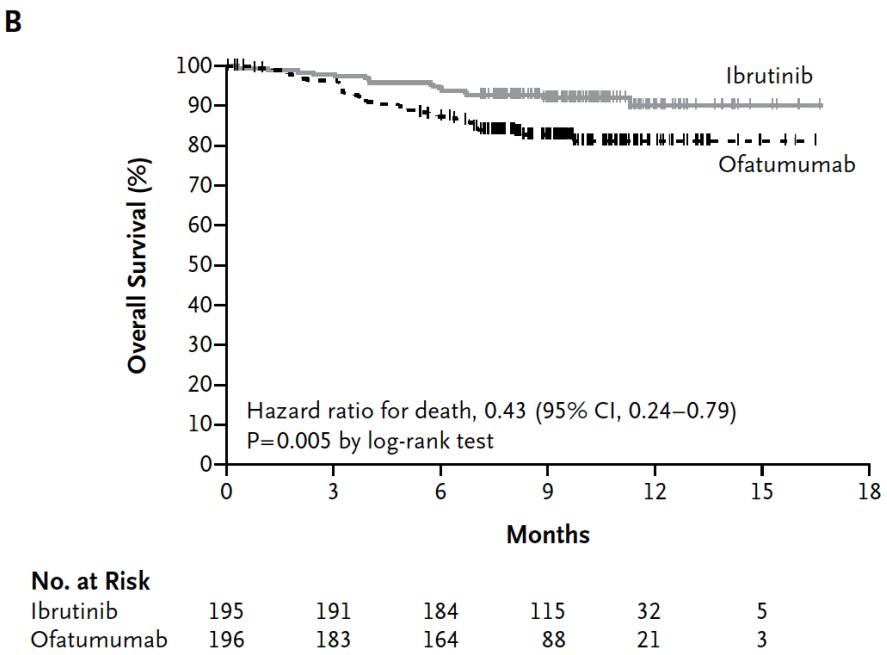
- Drugs are being developed to interfere specifically with the abnormal “gene products” of cancer cells with minimal effect on normal cells, e.g.:
  - Ibrutinib (CLL, relapsed MCL)
  - Idelalisib (relapsed CLL, relapsed iNHL)
  - Venetoclax (relapsed CLL)

Ibrutinib mechanism of action



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



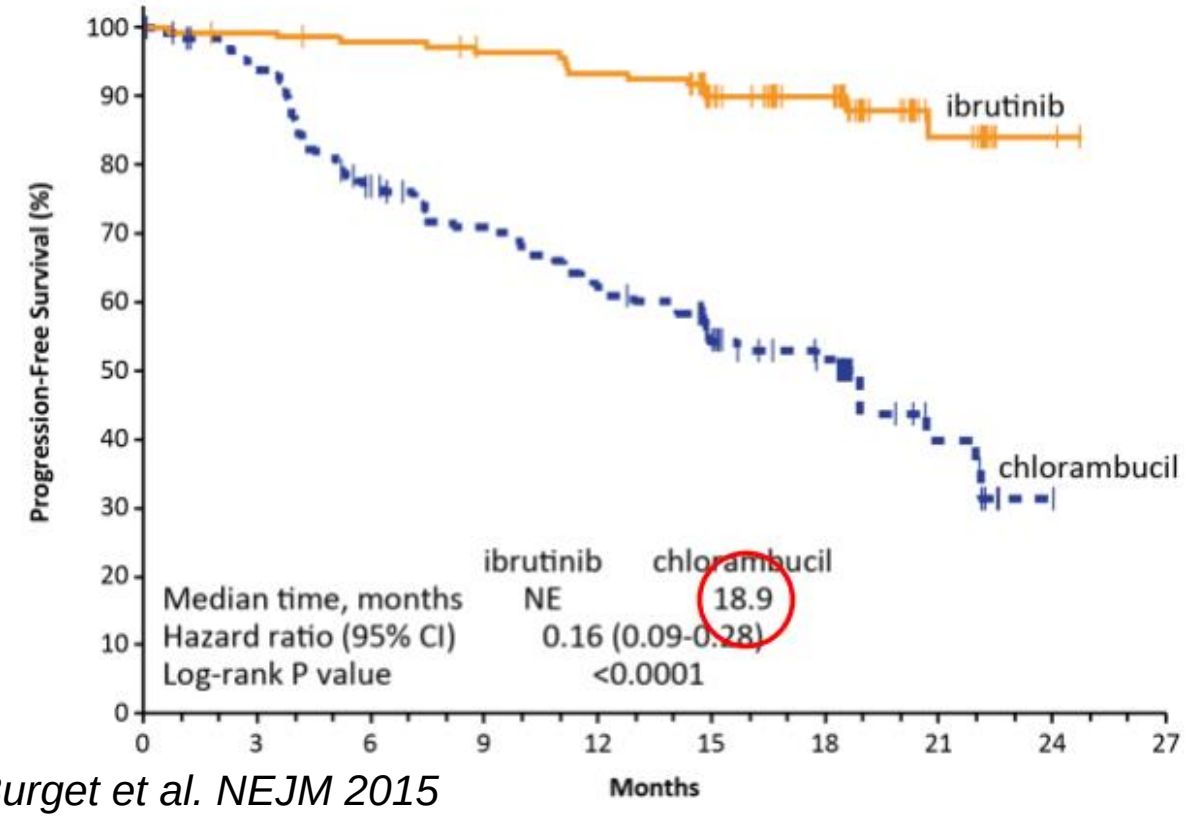


Byrd et al. NEJM 2014

Overall response: 40% Ibru vs 4% Ofa

No difference in response based on 17p del status

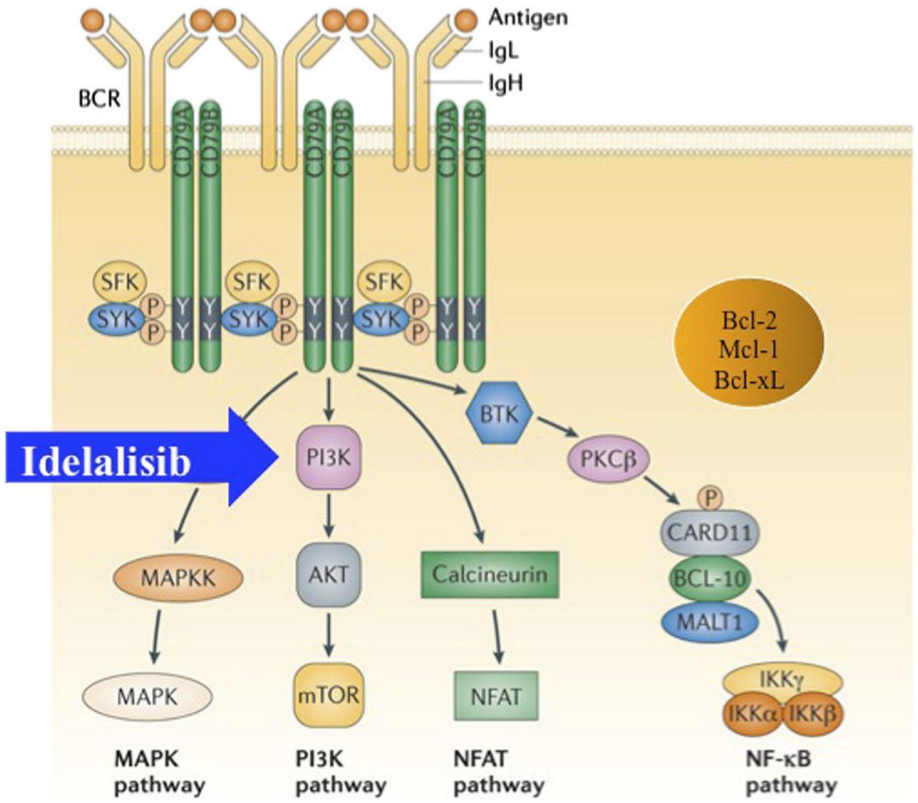
Ibrutinib for front-line CLL



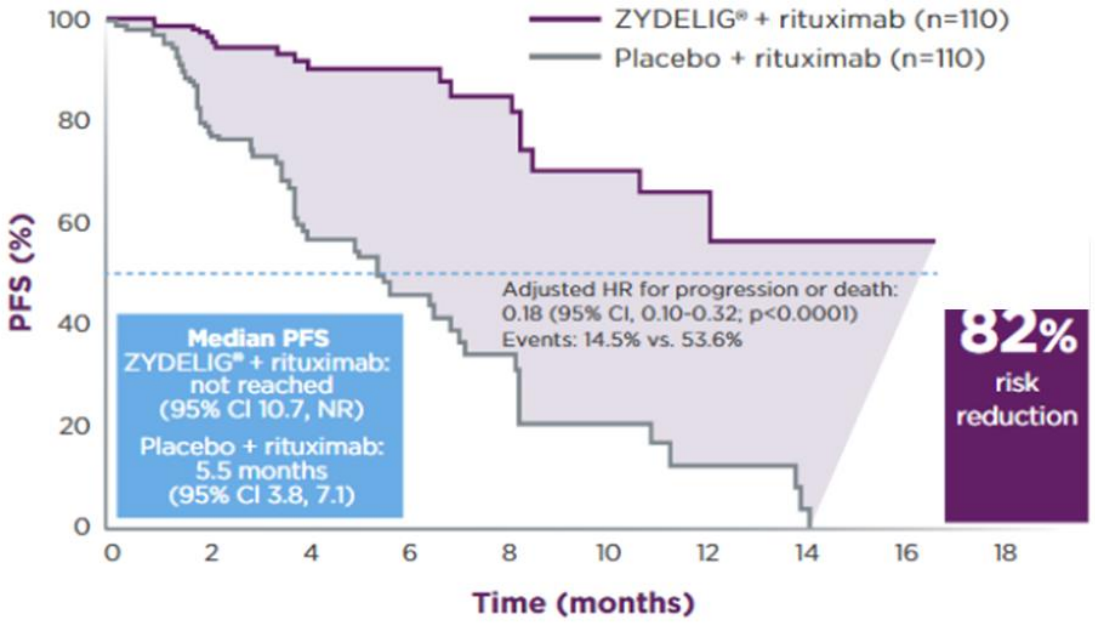
Burget et al. NEJM 2015

- 84% reduction in risk of progression or death with Ibrutinib
- 18-month PFS rate: 90% with Ibrutinib vs. 52% with Chlorambucil

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



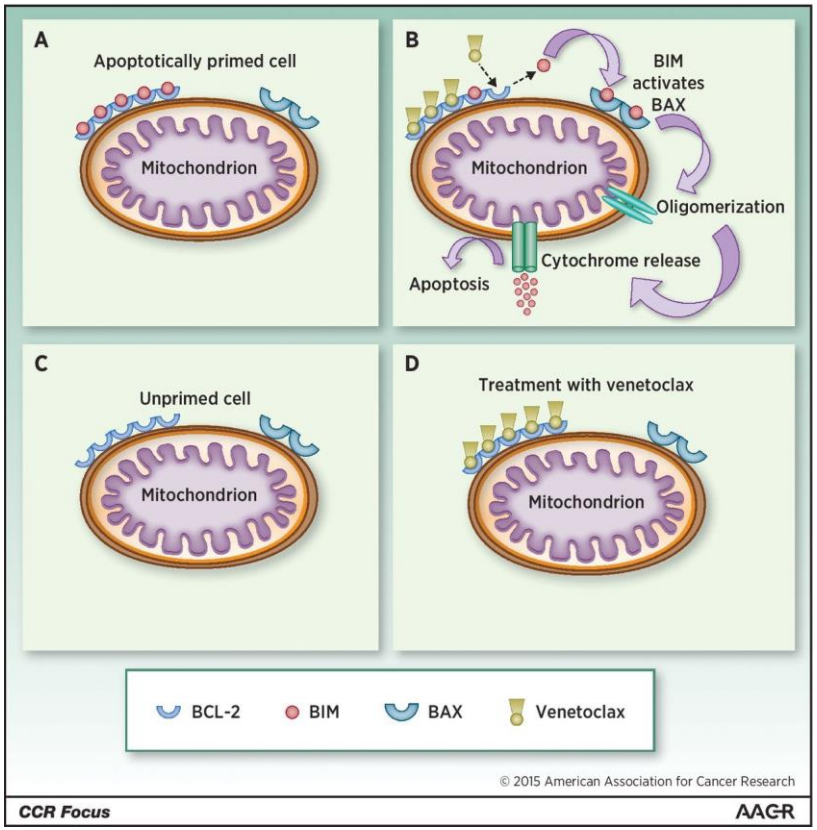
Idelalisib & rituximab is superior to rituximab



	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)

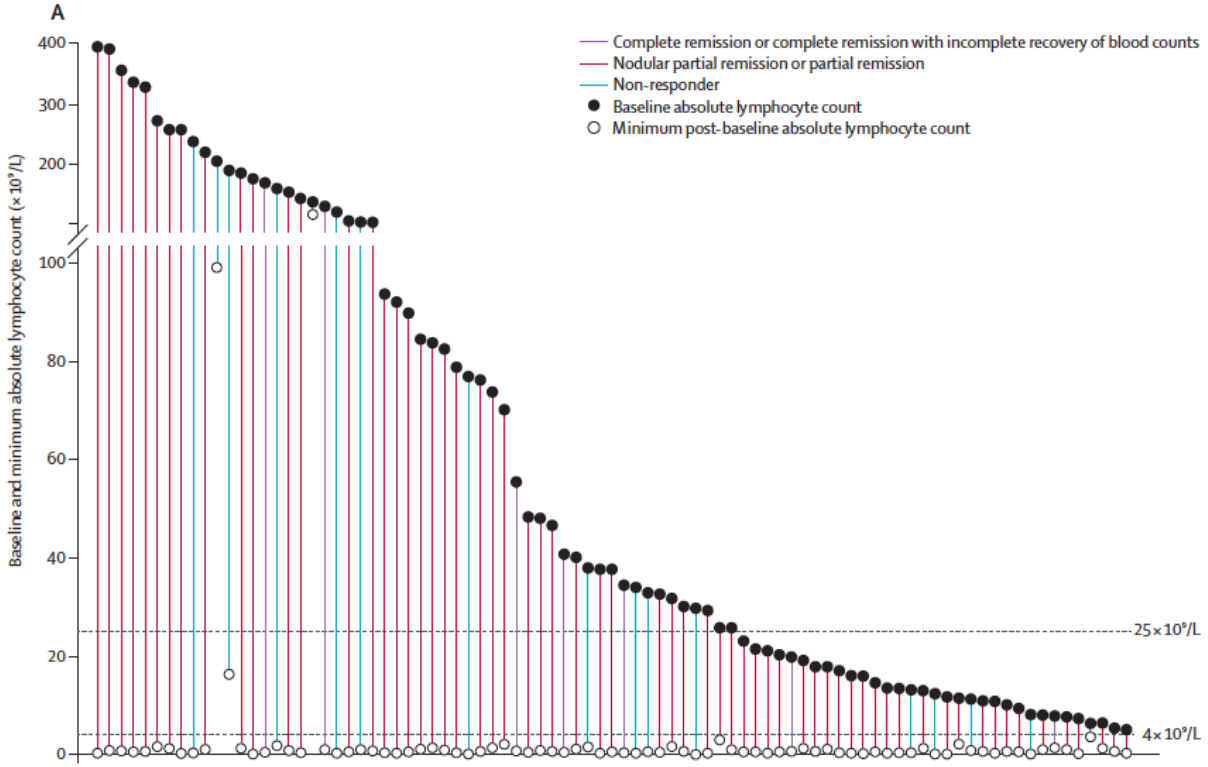
At 24 weeks, disease progression occurred in 12 patients (10.9%) with Zydelig + rituximab vs 53 patients (48.2%) with placebo[1]

Venetoclax kills CLL cells that are “primed” to die



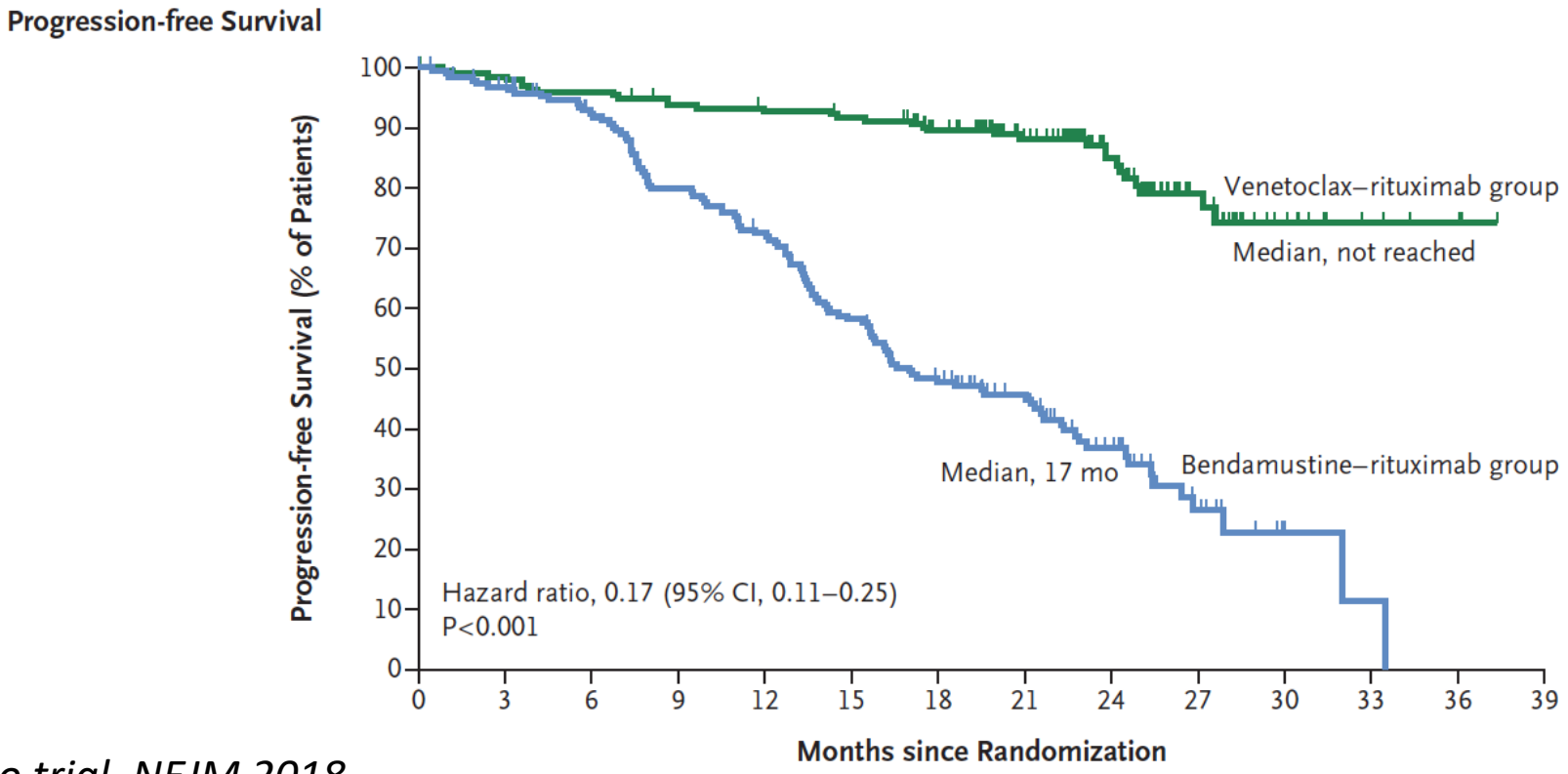
Concept by Antony Letai

Venetoclax induces rapid clearance of peripheral blood lymphocytes



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

Venetoclax and rituximab in relapsed CLL



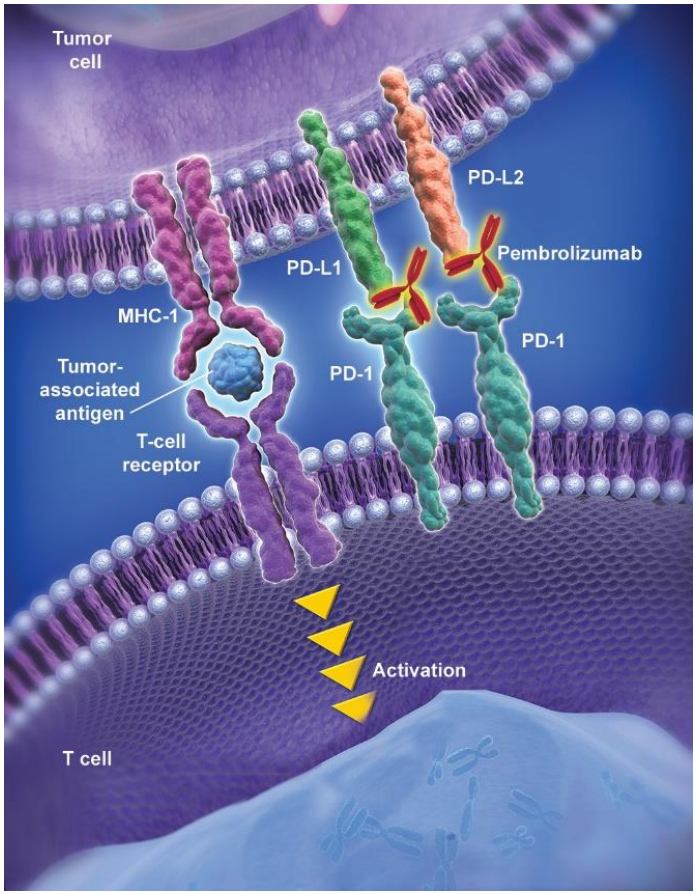
Murano trial, NEJM 2018

Lymphoma treatment: immunotherapy

- Drugs that activate the immune system to kill lymphoma cells e.g.:
  - PD1 inhibitors for Hodgkin lymphoma
  - CAR-T cells for DLBCL

Immune checkpoint inhibitors

- PD-L1/2 is highly expressed on some tumor cells
- Binding of T-cells to PD-L1/2 inhibits T-cell function and blunts the normal immune response
- PD-1 inhibitors have been shown to be very effective in relapsed HL, among other cancer types



Immunotherapy with PD1 inhibitors: 70% response in relapsed Hodgkin lymphoma

ASCT failure and brentuximab failure

No ASCT and brentuximab failure

No brentuximab

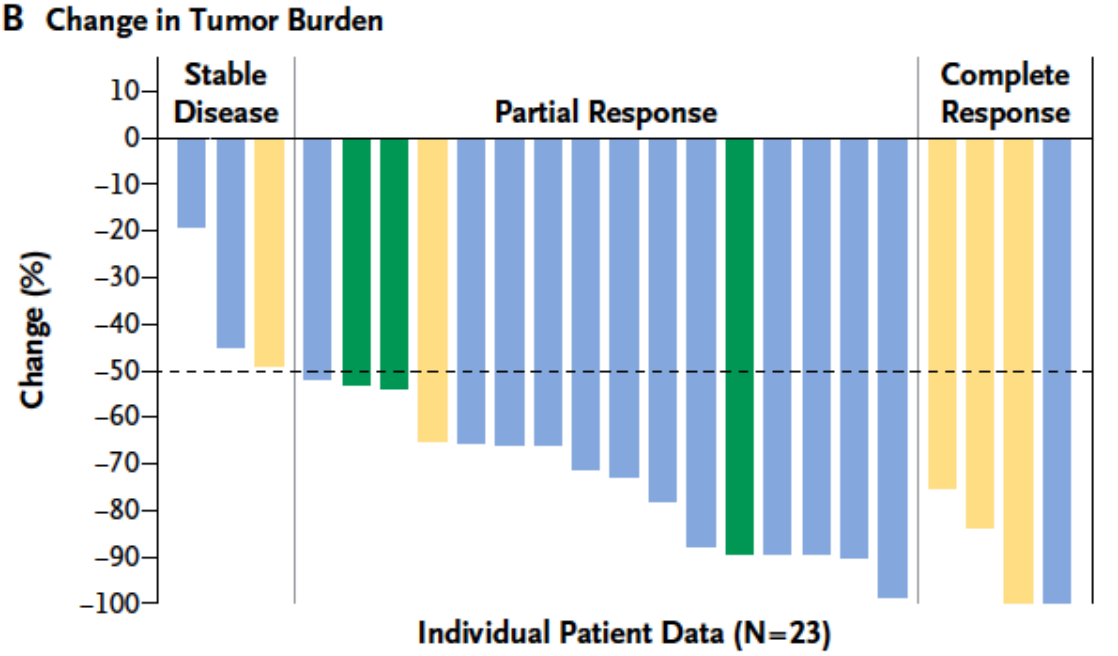
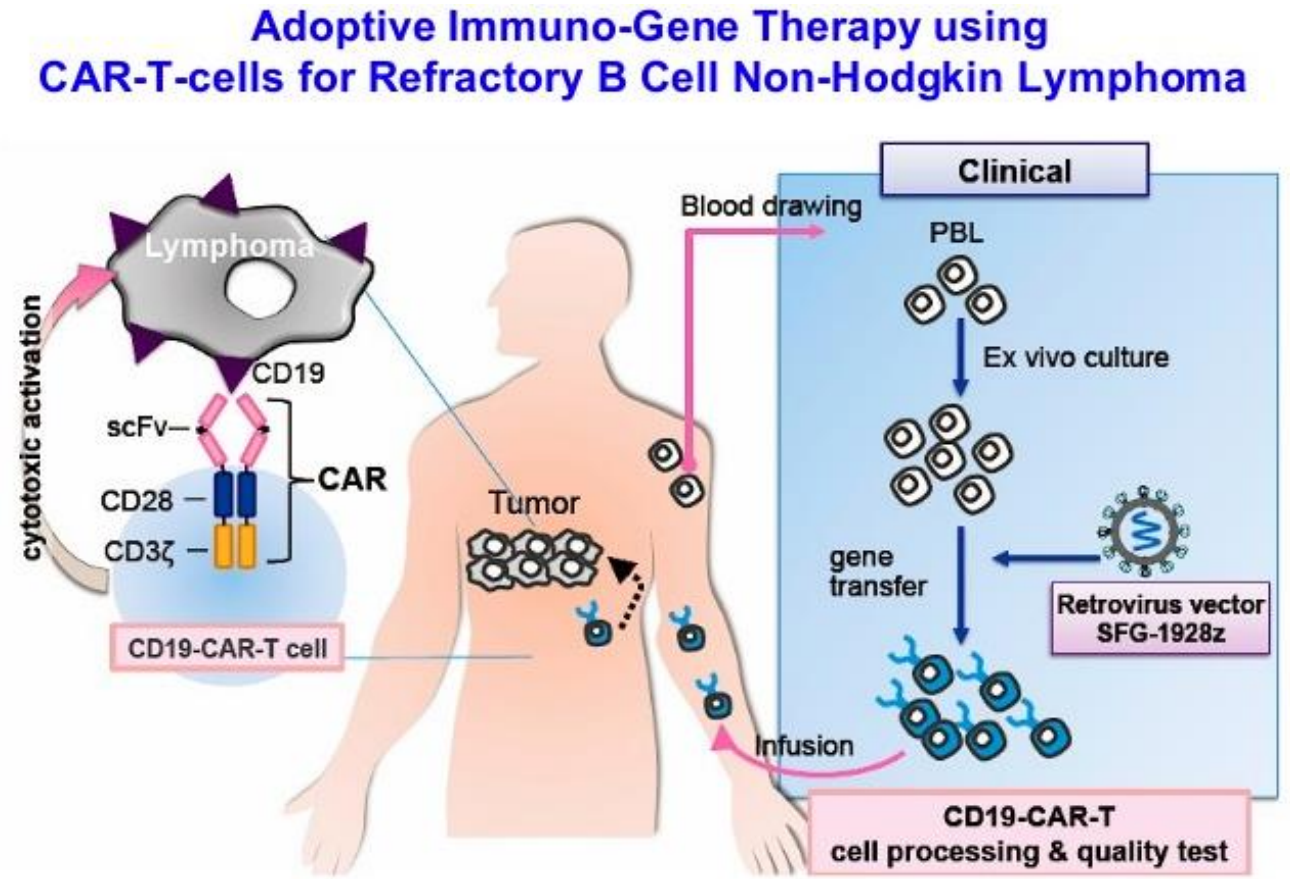


Figure 1. Response Characteristics and Changes in Tumor Burden in Patients with Hodgkin's Lymphoma Receiving Nivolumab.

Ansell et al. NEJM 2015

Experimental therapy: chimeric antigen receptor gene therapy



Summary: frontline therapies used in 2019

- **Diffuse large B-cell lymphoma (curative)**
  - **R-CHOP**
- **Hodgkin Lymphoma (curative)**
  - **ABVD**

- iNHL (Follicular lymphoma) (prolonged remission)
  - R-CVP or RCHOP followed by maintenance R
  - R-Bendamustine +/- maintenance R
- Chronic Lympocytic leukemia (prolonged remission)
  - FCR
  - R-Bendamustine
  - Obinutuzumab and chlorambucil
  - Ibrutinib likely will be approved frontline for everyone based on recent data

Novel therapies

- Ibrutinib (CLL, MZL, LPL)
- Idelalisib (CLL and FL)

- Venetoclax (CLL)

- Immunotherapies: PD1 inhibitors (Hodgkin) and CAR-T (DLBCL)

Side effects of novel therapies

- **Ibrutinib**
  - Neutropenia
  - Cardiac Arrythmias
  - Bleeding

- **Idelalisib**
  - Opportunistic infections
  - Colitis/diarrhea

- **Venetoclax**
  - Neutropenia
  - Nausea
  - Tumor lysis

<u>Immunotherapies:</u>
Autoimmune side effects
Neurological and cytokine release syndrome with CART-T

<u>Advantage:</u> oral medications, kills cells in a different way than chemotherapy

<u>Disadvantages:</u>
Some have low complete responses
use indefinitely until progression
Cost (~$8,000 to 12,000/month and ~$~500,000 for CAR-T)

Conclusion

- Lymphomas constitute a large group of disorders having highly variable natural histories, treatments and outcomes
- Almost all lymphomas are treatable
- Many lymphomas are curable
- Research allows us to continuously expand treatment options, with the goal of improving treatment outcomes and quality of life

Questions?