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# Indolent Lymphomas

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# What does indolent mean?

- Slow growth
- Often asymptomatic
- Chronic disease with periods of relapse (long natural history possible)
- Incurable with current standard therapy, but long remissions possible
- Goal of treatment is to maximize quality of life



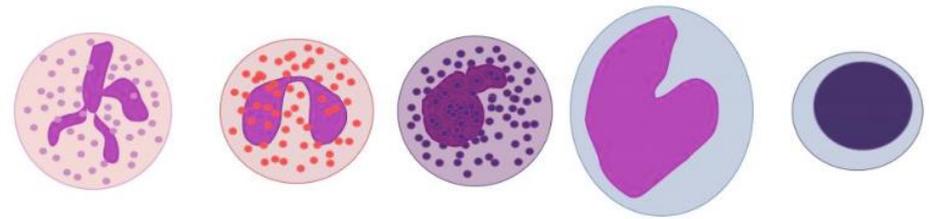
# Indolent lymphomas (NHL)

	Incidence (per 100,000)
• Follicular	3.4
• Marginal zone or MALT	1.8
• Mycosis fungoides	0.4
• Waldenstrom's macroglobulinemia	0.3
• Hairy cell leukemia	0.3
• Primary cutaneous	0.1

SEER Database Incidence 2011-12



# Lymphocytes



neutrophil eosinophil basophil monocyte lymphocyte

- **B cells** develop in the bone marrow
  - form antibodies against foreign bodies
    - 90% of all lymphomas
- **T cells** mature in the thymus gland
  - orchestrate the immune response
    - 10% of lymphomas
- **NK (natural killer) cells**
  - destroy viruses and cancers through direct attack
    - Very rare lymphomas, none indolent

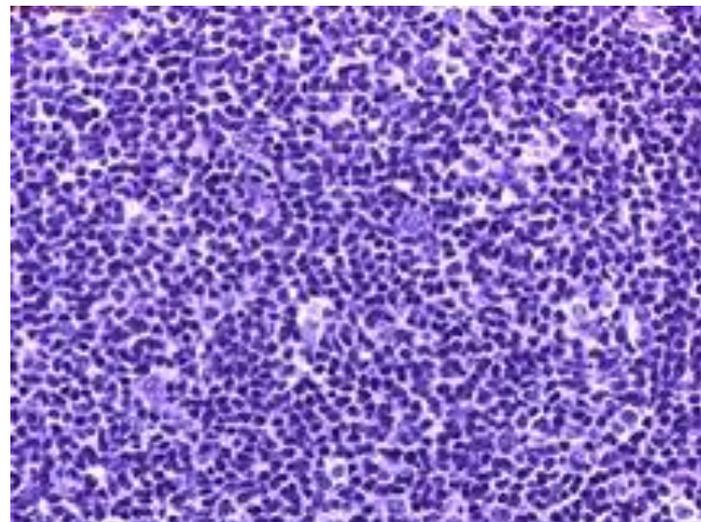
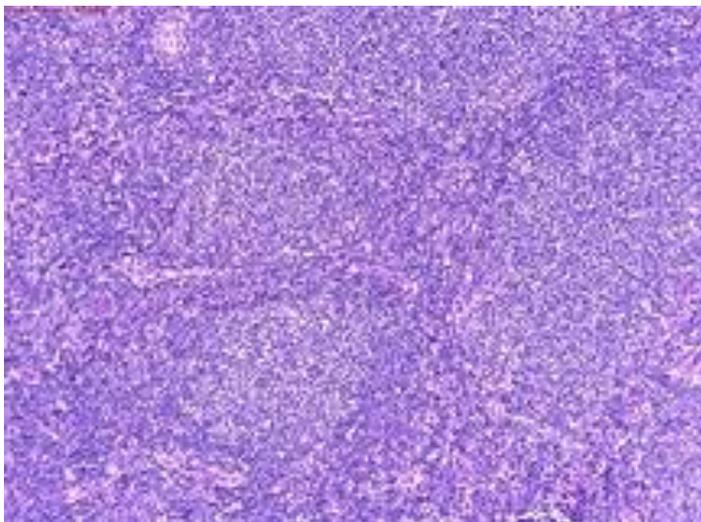


# How do we figure out which type you have?

- **Physical Exam**
  - Lymph nodes, spleen
- **Biopsy**
  - Core needle biopsy
  - Excisional biopsy
- **Laboratory**
  - CBC and differential
  - LDH (prognostic marker in NHL)
  - Bone marrow aspirate/biopsy
- **Imaging**
  - CT scans
  - PET scan

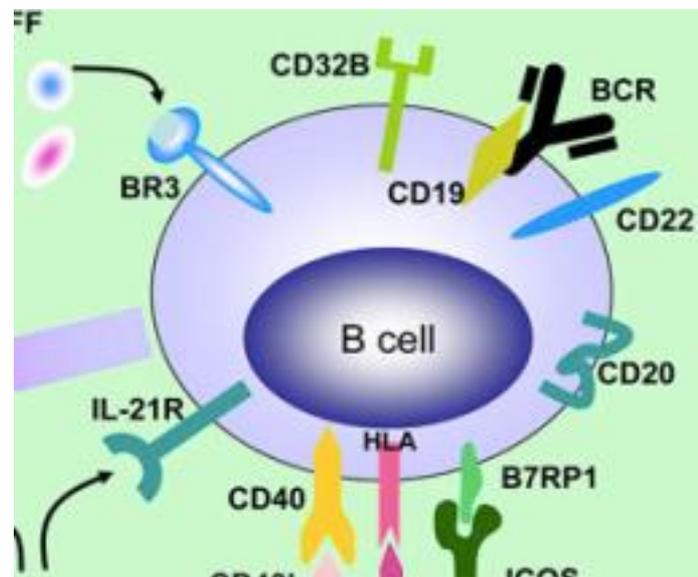


# Biopsies



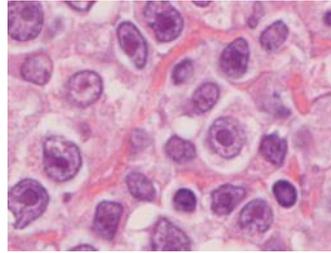
# Why is pathology important?

- Need to determine the most appropriate therapy
- Some of the criteria for diagnosis are very specific—and lead to specific treatment choices:
  - CD20 “positive” by immunohistochemistry: use of rituximab

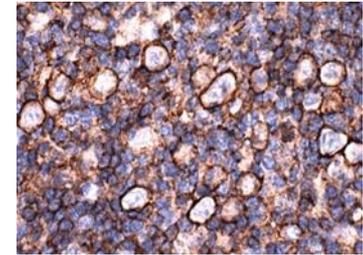


# Pathology

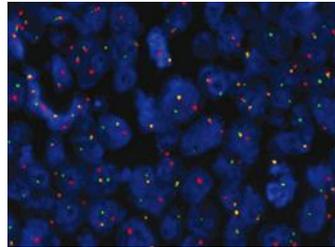
- Morphology



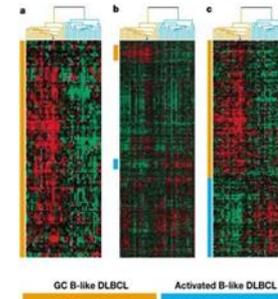
- Immunohistochemistry



- Cytogenetics



- Gene expression profiling



# Staging

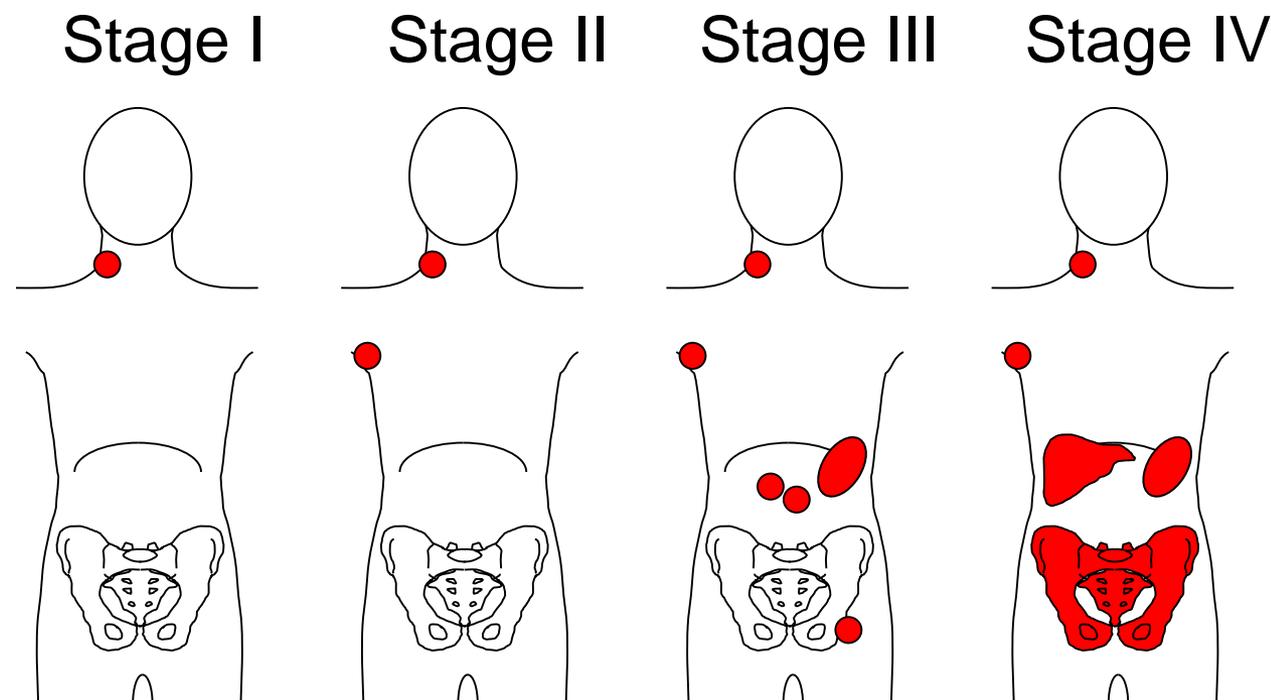
The # of staging investigations is dependent on the type of lymphoma and goals of therapy.

Staging is used to determine:

- Extent of disease
- Bulk of tumour mass
- Potential for complications
- Type of treatment



# Ann Arbor Staging System



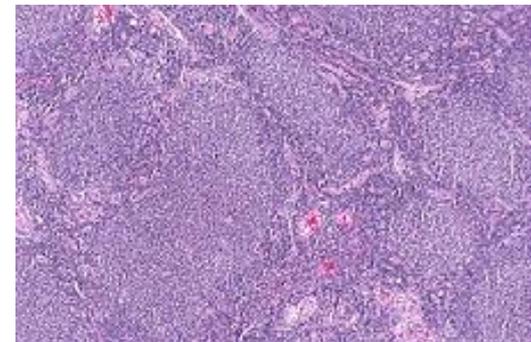
A – absence of any “B” symptoms

B – Unexplained fever, drenching sweats or weight loss



# Follicular lymphoma

- Typically affects middle-aged and older adults
- Abnormal follicles give disease its name
- Causes few symptoms in early stages
- Usually responds well to treatment, but can return
- Can transform into aggressive lymphoma



# FLIPI- Follicular Lymphoma International Prognostic Index

Parameter	Adverse factor	RR	95% CI
Age	$\geq 60$ y	2.38	2.04-2.78
Ann Arbor stage	III-IV	2.00	1.56-2.58
Hemoglobin level	$< 120$ g/L	1.55	1.30-1.88
Serum LDH level	$> \text{ULN}$	1.50	1.27-1.77
Number of nodal sites	$> 4$	1.39	1.18-1.64

Score	Prognosis	% Patients	OS (10 yr)
0-1	good	36	71
2	moderate	37	51
3-5	poor	27	36



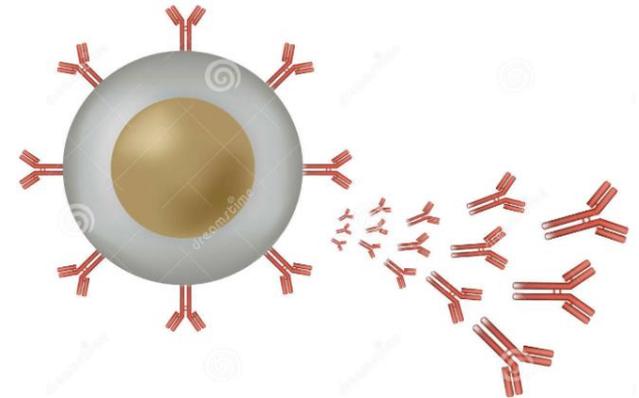
# Marginal zone lymphoma

- Accounts for ~10% of NHL
- Affects older adults usually
- 3 types:
  - **Extranodal marginal zone lymphoma or mucosa-associated lymphoid tissue (MALT)**
    - Occurs outside the lymph nodes in the stomach, small intestine, salivary glands, thyroid, eyes or lungs
  - **Nodal marginal zone lymphoma**
    - Occurs within lymph nodes
  - **Splenic marginal zone lymphoma**
    - Usually occurs in spleen and blood



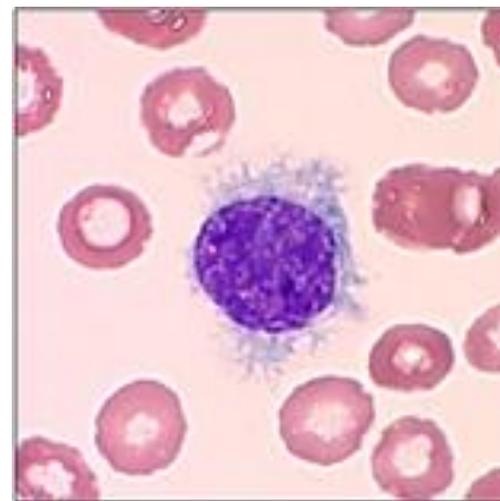
# Waldenstrom's macroglobulinemia

- Dr. Jan Waldenstrom first described the condition in 1948
- Rare, 1-2% of NHLs, usually affecting older adults
- Primarily found in bone marrow
- Overproduction of IgM protein, causing thickening of blood
- Plasmapheresis may temporarily reverse or prevent symptoms associated with blood thickening.



# Hairy cell leukemia

- Surface of cells look hairy under microscope
- Called 'leukemia' as cancerous lymphocytes can be found in the blood, though they mainly collect in the bone marrow and spleen
- Rare subtype usually found in middle-aged or older adults



# Cutaneous lymphoma



- Lymphoma in the skin
- Usually T cell, but can be B cell
- Most common subtype: mycosis fungoides
- Most common in those aged 50+, but can occur in younger adults
- Often small, raised, red patches on skin that may look like eczema or psoriasis
- Ulcerating tumours (open sores) can appear
- Treatment may include ultraviolet light



# Watch & wait

Randomized trial of “Watch and Wait” vs. early chemotherapy  
*British National Lymphoma Investigation Trial of 309 patients with indolent NHL*

Results	“Watch and Wait”	Early chemotherapy
Lymphoma-specific survival	No difference	
Overall Survival	No difference	

- On average, patients needed treatment ~2.5 years from diagnosis
- However, 1 in 5 participants did not require treatment by 10 years
- 2 in 5 over the age of 70 did not require treatment



# Coping with watch & wait

- Be gentle with yourself
- Talk it out
- Take care of yourself (healthy living)
- Learn about lymphoma (dispelling the myths)
- Ask for support



# Indications for starting treatment

- Symptoms attributable to the lymphoma
- Low blood counts because of bone marrow involvement
- Threat to organ function
- Bulky disease or spleen
- Disease that has transformed to an aggressive lymphoma



# Overview of primary treatment options

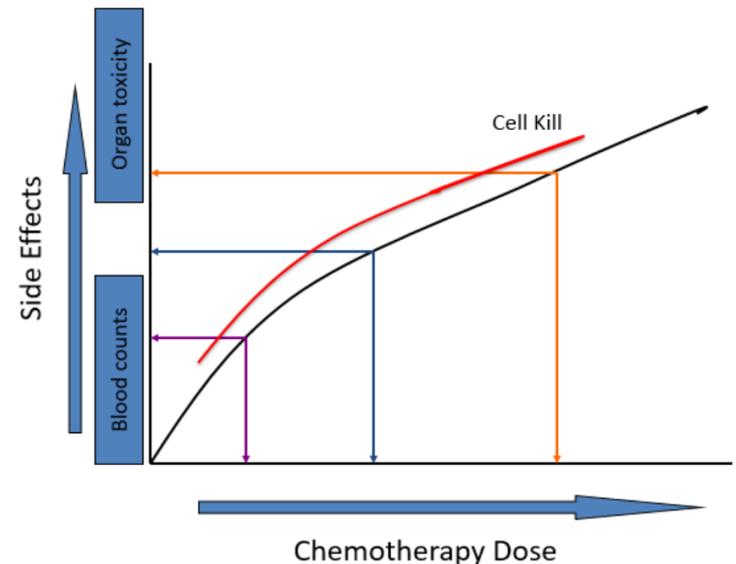
Treatment Option	Description
Chemotherapy	Use of drugs to kill lymphoma cells
Radiation Therapy	Use of high-energy rays to kill lymphoma cells or slow their growth
Immunotherapy	Use of agents designed to target and destroy lymphoma cells
Transplantation	Infusion of healthy stem cells/bone marrow to help the body restore its supply of healthy blood cells

**Balance potential toxicity against effectiveness**



# Chemotherapy

- Backbone of many cancer treatments
- Damages DNA, leading to cell death
- Systemic
- Affects all growing cells
  - Cancer cells
  - Blood cells
  - Lining of GI tract
  - Hair



# Common chemotherapy regimens

## **Bendamustine** – with R (Rituximab)

- IV, days 1 and 2, 28-day cycles
- Usually 6 cycles total
- In Ontario – since 2013
- Progression-free survival ~70 months
- Side effects:
  - No hair loss
  - Nausea/vomiting
  - Suppression of immune system
  - Rashes, constipation/diarrhea



# Common chemotherapy regimens

**CHOP** - with or without R (Rituximab)

- ✓ Cyclophosphamide
- ✓ Doxorubicin
- ✓ Vincristine
- ✓ Prednisone— pills daily x 5 days



By IV every  
3 weeks

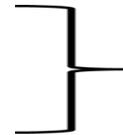
Usually 6 cycles



# Common chemotherapy regimens

**CVP** – with or without R (Rituximab)

- Cyclophosphamide
- Vincristine
- Prednisone — pills daily x 5 days



By IV every  
3 weeks

Usually 6 cycles

Even more gentle option = rituximab alone



# Immunotherapy

- Also called biologic therapy
- Drugs designed to boost the body's natural defenses against cancer
- Generally fewer side effects than traditional chemotherapy

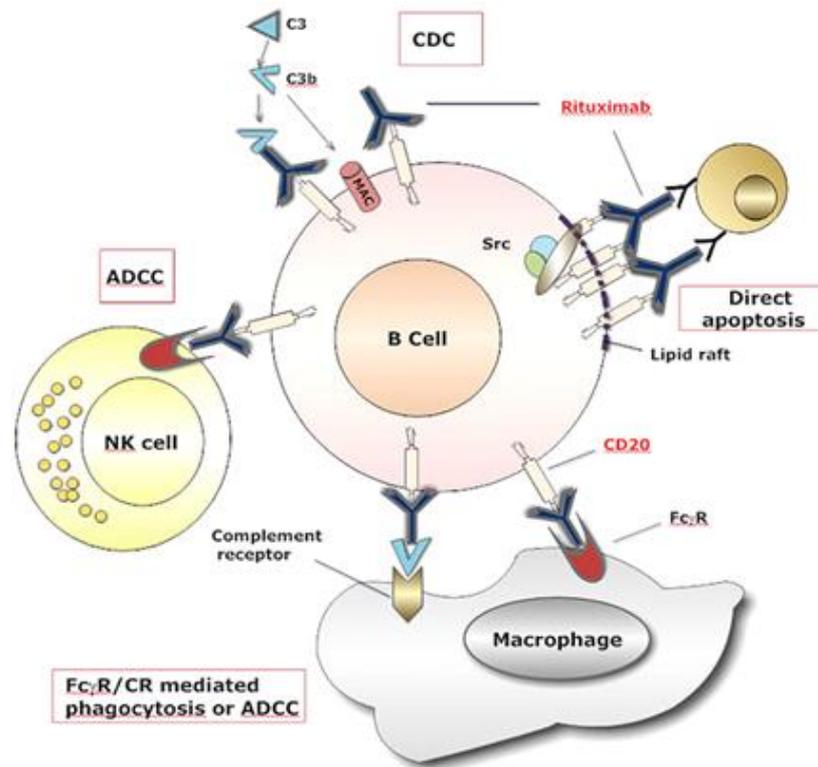


# Monoclonal antibodies

Antibodies developed against cancer cells can be administered to patients to destroy the tumour

- Examples:
  - Rituximab
  - Obinutuzumab

*Only work for B cell lymphomas*



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



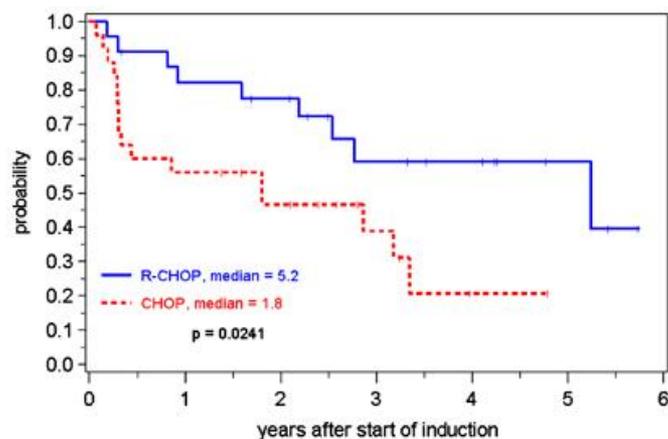
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# Why add rituximab?

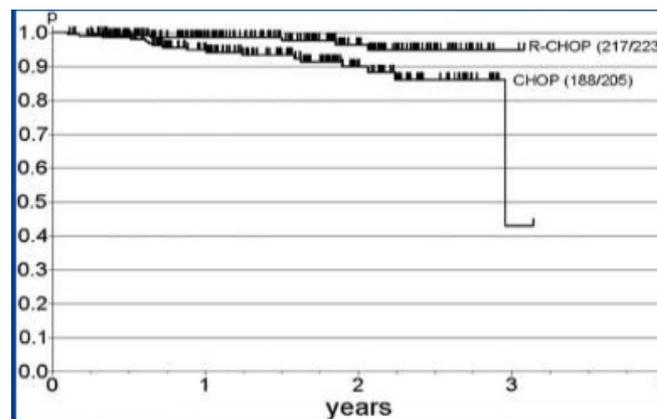
Addition of anti-CD20 antibody rituximab to chemotherapy: improvement in survival.



numbers of patients at risk

R-CHOP	23	18	16	9	7	3	0
CHOP	25	14	10	5	1	0	

Waldenstrom's Macroglobulinemia CHOP vs R-CHOP, German Low Grade Lymphoma Study Group, Phase III Trial Results



Follicular Lymphoma CHOP vs R-CHOP, Hiddemann et al, 2005



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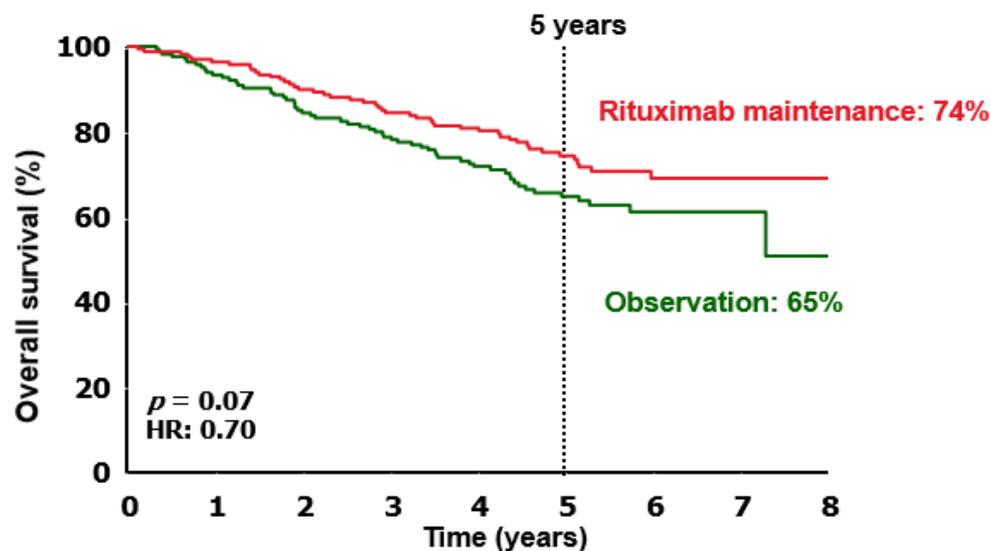


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# Rituximab maintenance

- Rituximab maintenance for 2 years
- Administered every 3 months, 8 cycles

FL



van Oers MHJ, et al. *J Clin Oncol* 2010; 28:2853–2858.



# Targeted therapies

Drugs that target specific molecules on the surface of cancer cells or cell pathways.

## **Bortezomib**

## **Ibrutinib**

- Pill, taken as directed until disease progression or intolerance to drug develops



# Radiation

Medical uses of radiation:

1. **Diagnostic:** low doses of radiation to take images of internal body structure i.e. chest x-ray
2. **Therapeutic:** higher doses of radiation to kill cancer cells

Difference between the two is the amount of energy. Therapeutic radiation can use up to 1,000 times the energy of diagnostic radiation.



# Radiation

- X-ray beams interact with atoms, creating a reaction that leads to cell DNA damage
- Damage prevents the cells from dividing and growing
- Lymphocytes are the most sensitive cells in the body to radiation, so can use lower doses of radiation compared to what is used to treat solid tumours.



# Radiation



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# Radiation

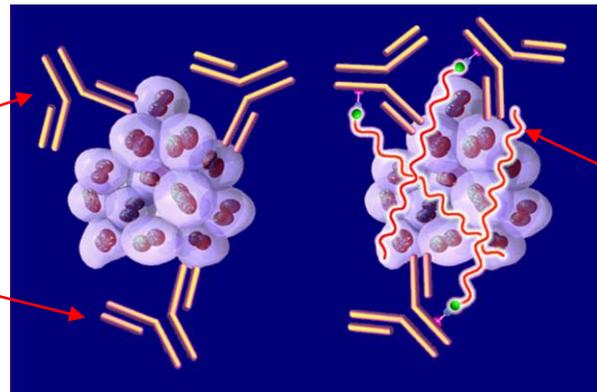
- Applies to localized disease, or for palliative purposes (to relieve symptoms)
- May not be used in all types of indolent NHL
- Generally treatment is given daily for 4 weeks (Monday to Friday X 4 weeks = 20 treatments or “fractions”)
- Side effects based on the area that is being radiated (skin and tissue beneath it)



# Combination therapy

- Chemotherapy + radiation
- Chemotherapy + immunotherapy = chemoimmunotherapy
- Radiation (radioactive isotopes) + immunotherapy = radioimmunotherapy

Monoclonal antibody alone



With radioactive isotopes



# Side effects of treatment

## Short term:

- Hair loss
- Mouth sores
- Nausea, vomiting: controllable with medication
- Fatigue
- Fever: need a thermometer! If  $\geq 38.3$  get a blood test (even Sunday afternoon...)
- Low blood counts



# Other possible issues

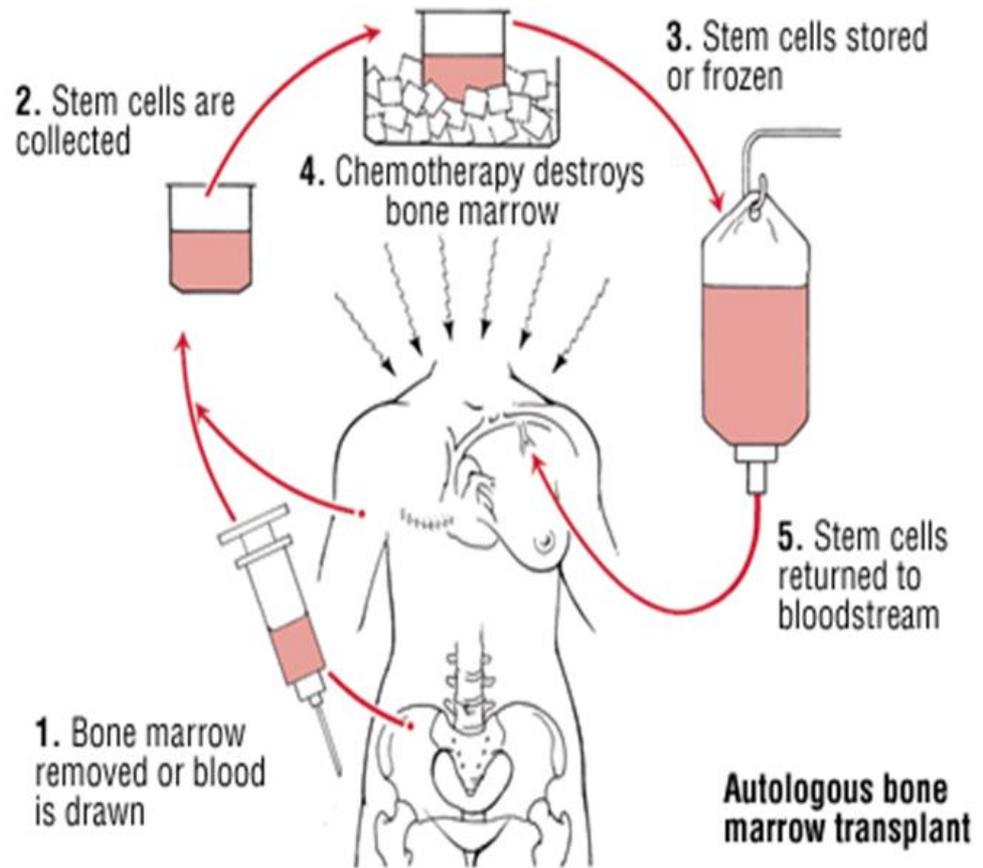
- Heart function: may need monitoring
- Peripheral neuropathy (numb hands, feet)
- Difficulty with memory, concentration (multi-tasking)– “chemobrain”
- Fertility



# Stem cell transplant (SCT)

## Autologous

- Use own cells
- Low treatment related mortality
- High rates of remission
- Transplant strategies vary centre-to-centre



# Stem cell transplant (SCT)

## **Allogeneic**

- Rare
- HLA matched sibling or matched unrelated donor
- 1 in 4 chance of sibling being a match
- Graft versus lymphoma: good!
- Graft versus host disease: can be very bad, including fatal, and life long
- Higher treatment related mortality



# After treatment is completed

- Repeat staging tests to determine if the lymphoma is “in remission”
  - Hope that we have attained a long period of disease control before we have to re-treat the lymphoma
- Follow-up with your family MD (~annually)
  - Screening for secondary cancers
  - Vaccines
- Follow-up with your oncologist (~3 months)

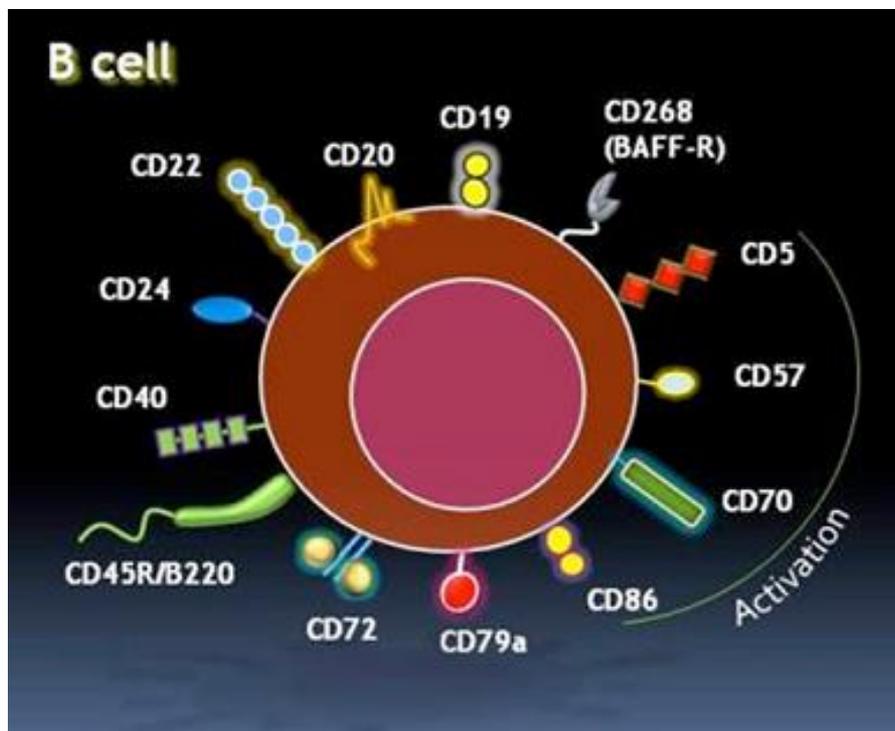


# Relapse/refractory

- Many other treatments available
- Goals of therapy may change
- Clarification of goals with your oncologist is very important
- Clinical trials of new agents



# Cell surface targets



[www.myelomacinderella.net](http://www.myelomacinderella.net)

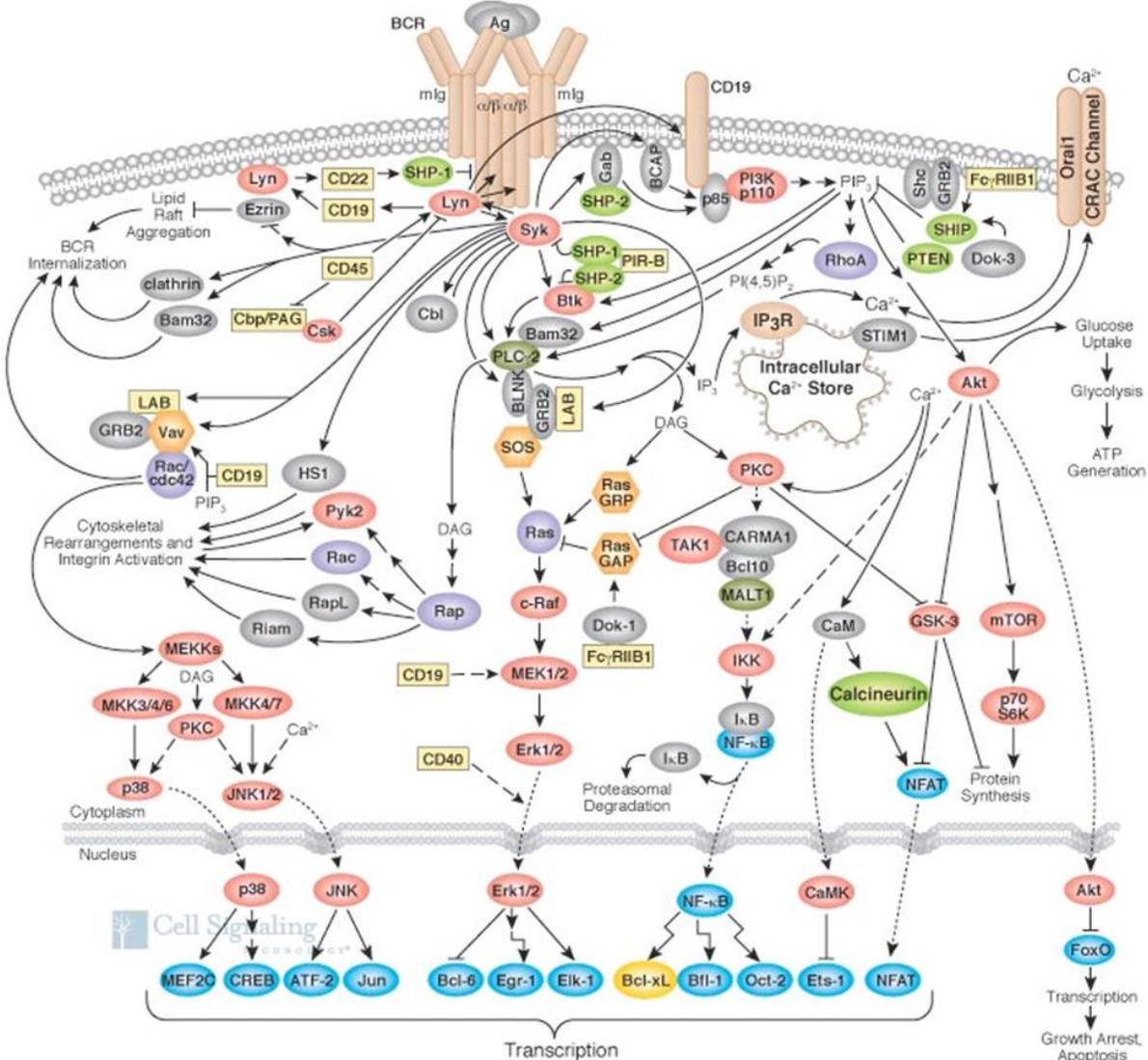


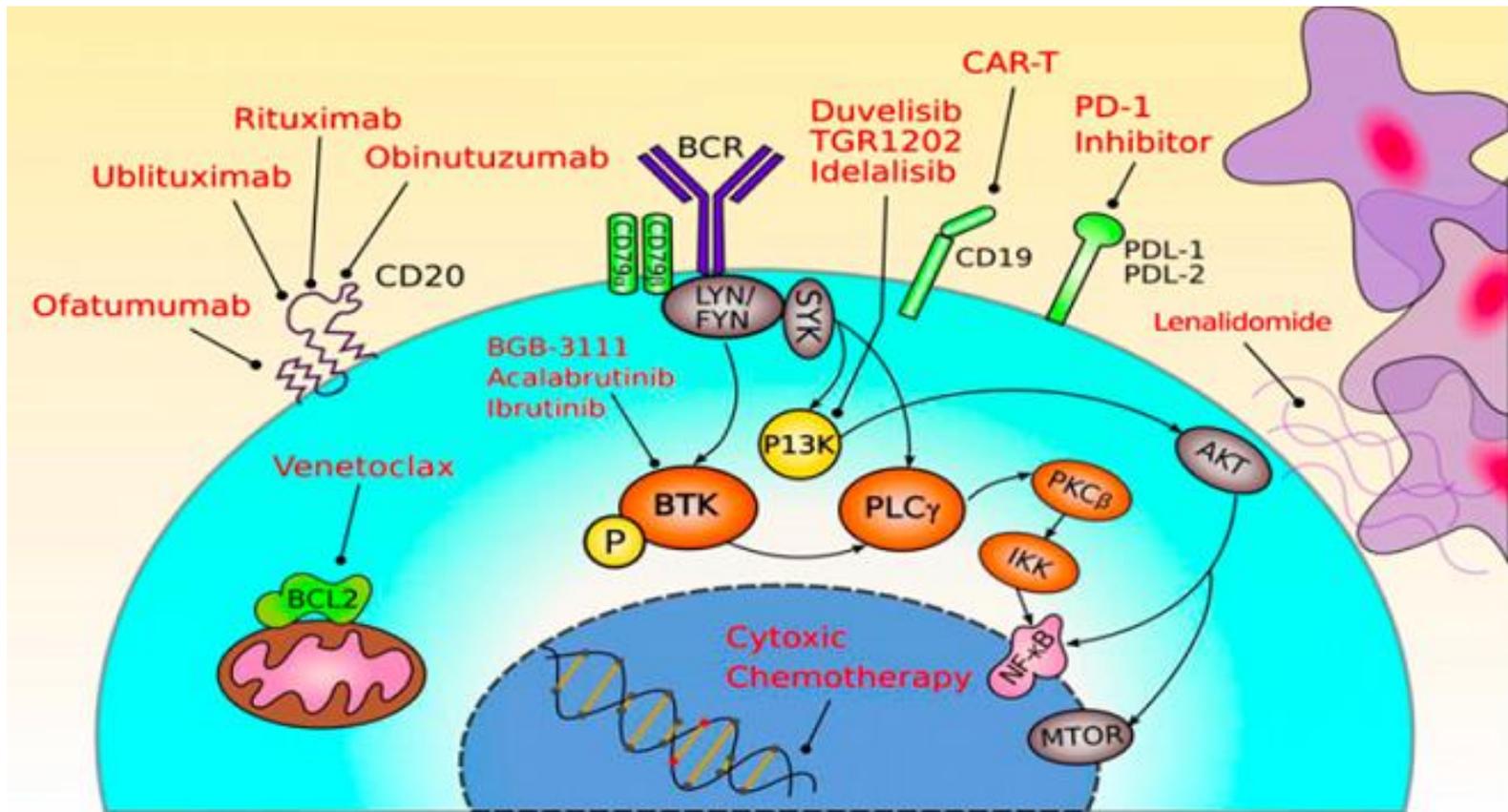
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Many targets...







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