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Aggressive NHL and Hodgkin Lymphoma

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November 10, 2017

What does aggressive mean?

- Shorter duration of symptoms
- Generally need treatment at time of diagnosis
 - Immediate, few days, few weeks
- Treatment generally given with the expectation of **remission**, goal of possible **cure**



Aggressive lymphomas

	Incidence (per 100,000)
• Diffuse large B cell	6.9
• Hodgkin	2.7
• T cell lymphomas	2.1
• Mantle cell lymphoma	0.8
• Burkitt lymphoma	0.4
• Gray zone lymphoma	<0.1

SEER Database Incidence 2011-12



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Not only in lymph nodes

Nodal

- Neck
- Supraclavicular
- Axillary
- Mediastinal
- Abdominal
- Groin
- Spleen

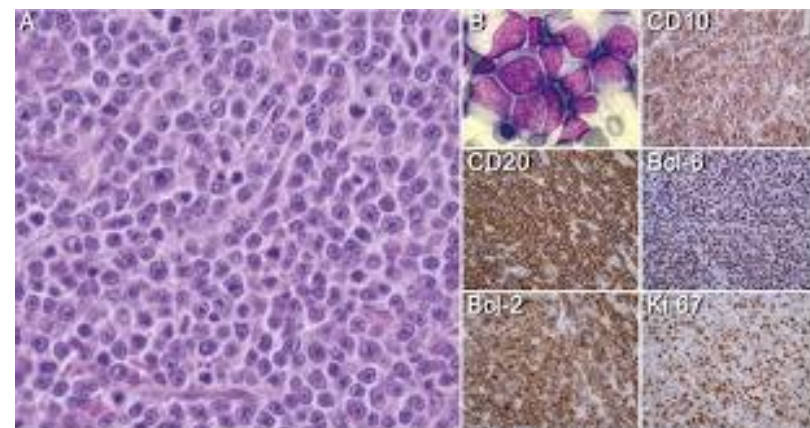
Extranodal

- GI tract (stomach, bowel)
- Bone marrow
- Liver
- Skin
- Head and neck
- Bone



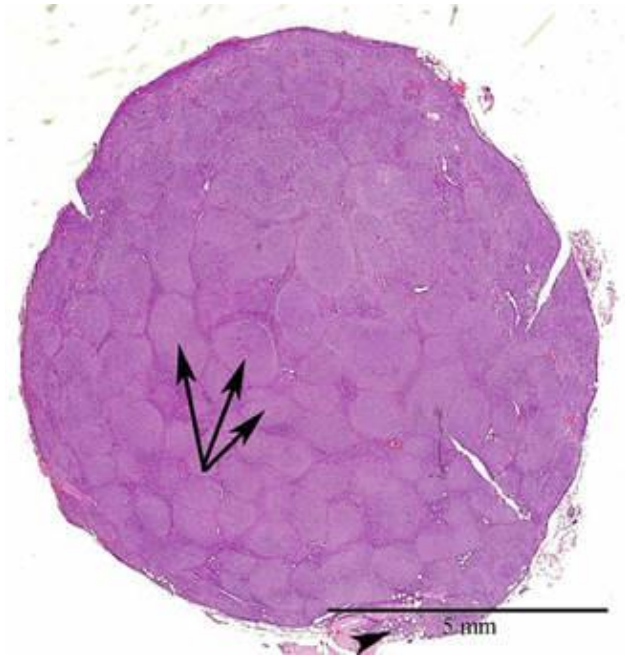
Diffuse large B cell (DLBCL)

- Most common type of NHL, 30-40% of cases
- Cancer cell appearance led to name – cells are large and spread out
- Approx. 50% of patients have organ involvement at diagnosis
- Average age diagnosis 64, but can affect any age group

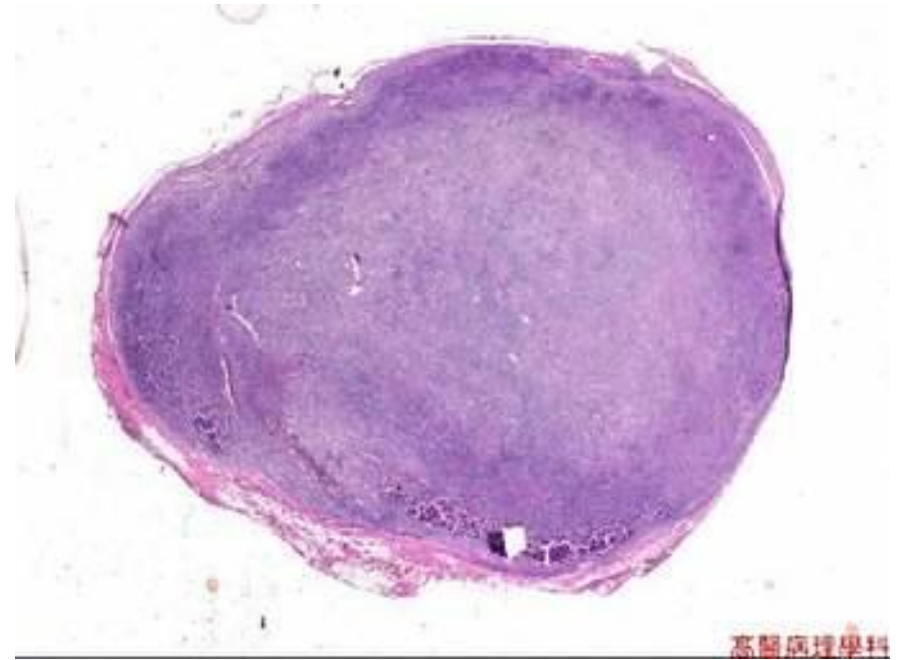


Lymph Node Architecture

Follicular NHL



Diffuse large B cell NHL



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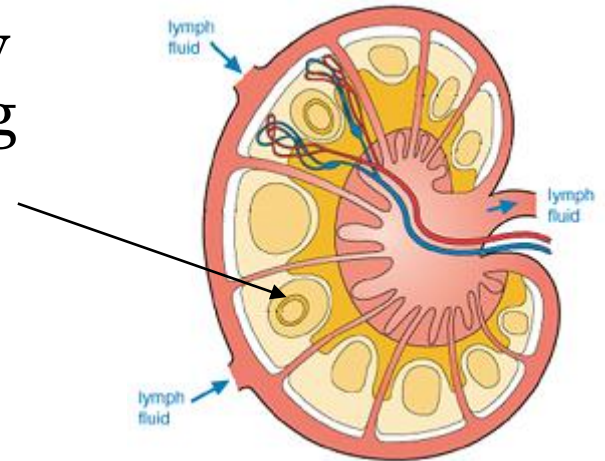


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Diffuse large B cell (DLBCL)

Germinal centre B cell (GCB)

DLBCLs get their name because they develop from lymphoid cells residing in the germinal centre of the lymph node. Patients with GCB-derived disease generally have better outcomes.



Activated B cell (ABC) DLBCLs develop from B cells that are in the process of differentiating from germinal centre B cells to plasma cells. ABC DLBCL is associated with a poorer outcome than GCB DLBC.



Diffuse large B cell (DLBCL) Subtypes

- Primary mediastinal B cell lymphoma (PMBL)
- Primary central nervous system (CNS) lymphoma
- EBV-positive DLBCL of the elderly
- T-cell/histiocyte-rich large B cell lymphoma
- Primary effusion lymphoma (PEL)
- Intravascular large B cell lymphoma (ILCL)
- ALK-positive large B cell lymphoma
- Double-expressor lymphomas (DEL)/Double hit



International Prognostic Index (IPI)

Evaluates 5 clinical variables:

- 1 Age (>60 years)
- 2 Stage (stage III,IV)
- 3 Performance status: what is the impact of lymphoma (or other medical problems) on daily life – how sick are you? (ECOG* ≥ 2)
- 4 Number of extranodal sites (≥ 2)
- 5 LDH (elevated)

ECOG – Eastern Co-operative Oncology Group*



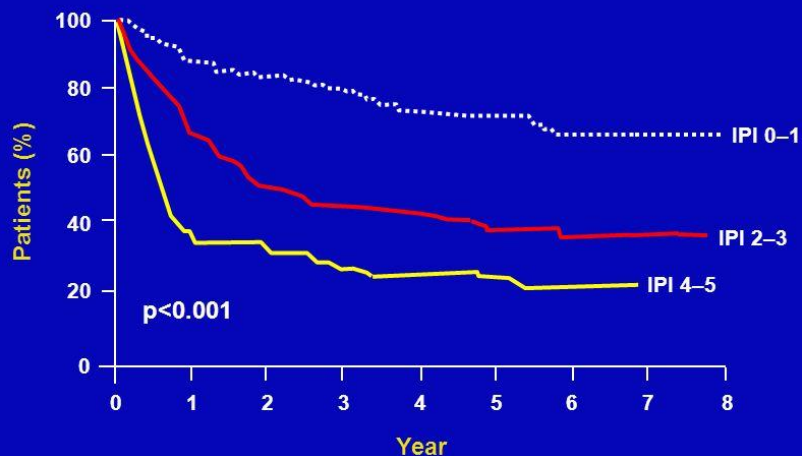
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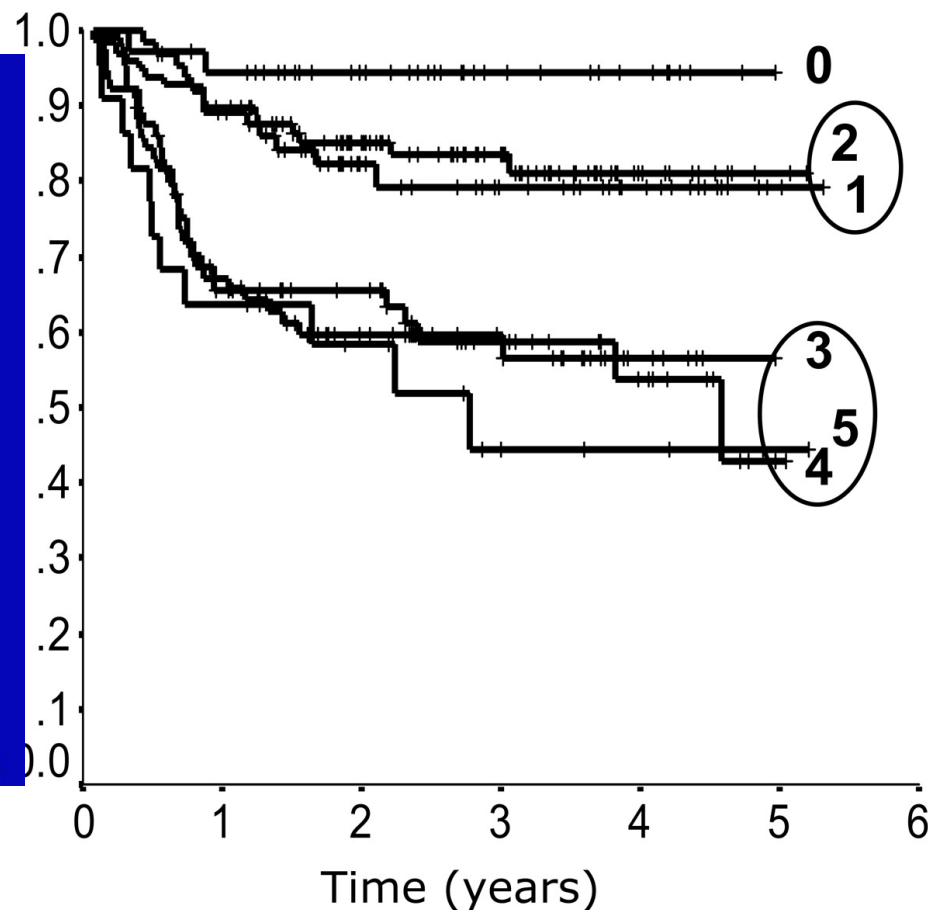
Outcome according to the IPI prior to Rituximab Era

DLBCL: overall survival



Adapted from Armitage and Weisenburger. *J Clin Oncol.* 1998;16:2780.

Outcome according the IPI in the Rituximab Era



Laurie H. Sehn et al. *Blood* 2007;109:1857-1861



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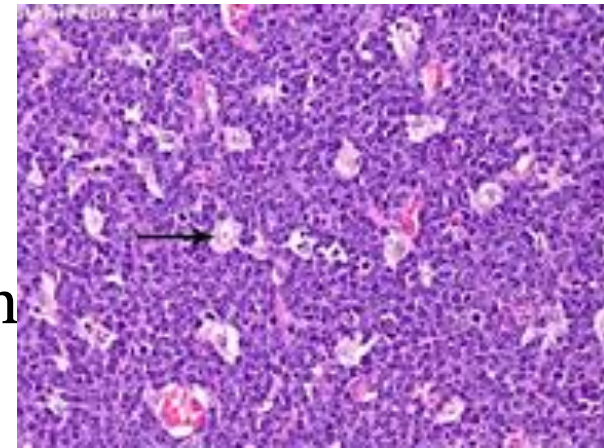


lymph



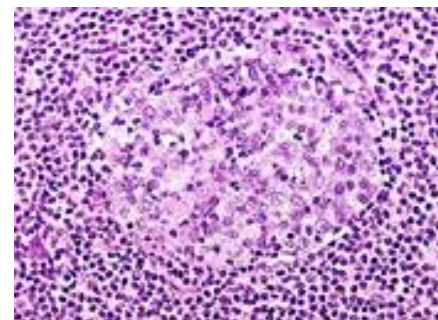
Burkitt lymphoma

- Most aggressive of all lymphomas
- Affects children (usually 5-10 yrs) and accounts for 30-40% of childhood lymphomas
- Affects adults (usually 30-50 yrs), often seen HIV+
- Can affect other organs like bowel, ovaries, kidneys, CNS or glandular tissues or jaw
- Treatment often includes intensive chemotherapy and CNS-directed therapy



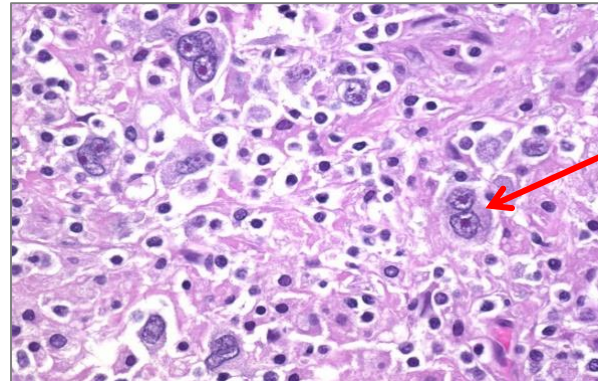
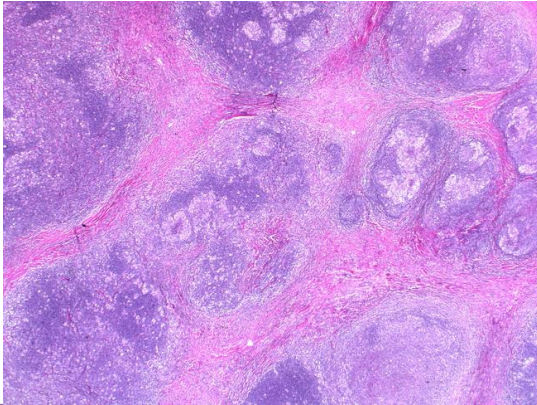
Mantle cell lymphoma (MCL)

- Develops in the outer edge of a lymph node called the mantle zone
- 6% of NHLs, usually affecting men over age 50
- Often have many lymph nodes, one or more organ (often GI tract) and bone marrow involved
- Often diagnosed late-stage
- Frequently relapses
- Mantle Cell Lymphoma International Prognostic Index (MIPI): low-, intermediate- and high-risk.



Hodgkin lymphoma

- Named after Dr. Thomas Hodgkin, who described the disease in 1832
- 1000 cases/year in Canada
- Two peaks: young adults and elderly
- Can be difficult to diagnose
 - Cancer cells are in minority in affected nodes
- > 80% curable with chemotherapy +/- radiation



HL
Reed-
Sternberg
cell is the
'malignant
cell'



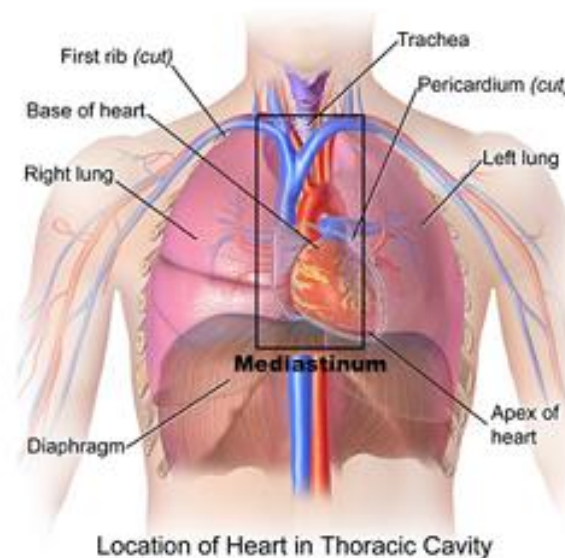
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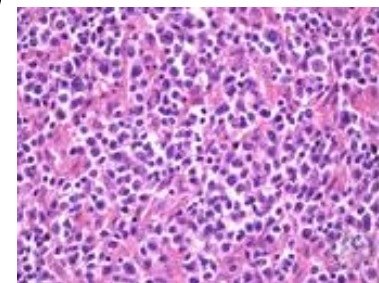
Gray zone lymphoma (GZL)

- Rare, but generally seen in teens & young adults
- Often presents with a large tumour in the chest area (mediastinum)
- Has features of both a large B cell lymphoma and Hodgkin, and is more aggressive
- Can spread to other organs



T Cell lymphoma

- Account for 10% of NHLs
- Peripheral T-cell lymphoma – general term referring to 10+ subtypes
 - Peripheral T-cell lymphoma not otherwise specified (PTCL-NOS)
 - Anaplastic large cell lymphoma (ALCL)
 - Angioimmunoblastic Lymphoma
 - Nasal NK/T-cell Lymphomas
- Lymphoblastic 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



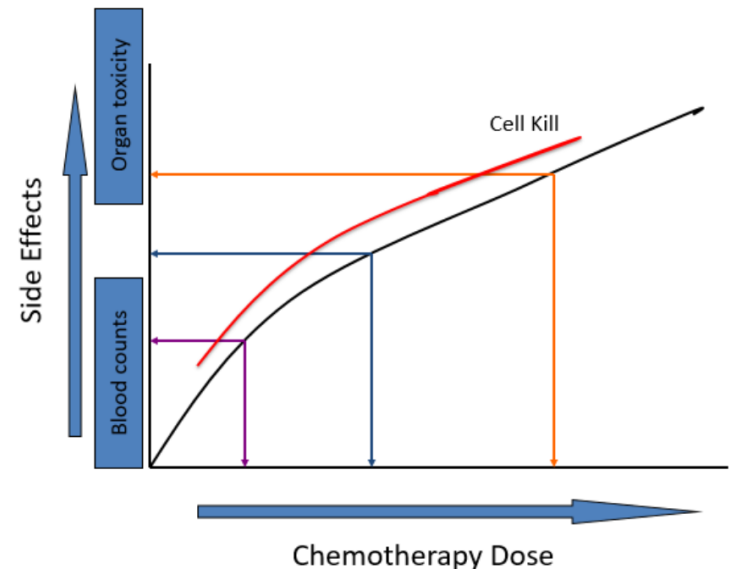
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Chemotherapy

- 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

CHOP - with or without R (Rituxan)

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



By IV every
3 weeks

R-CHOP for CD20+ NHL like DLBCL



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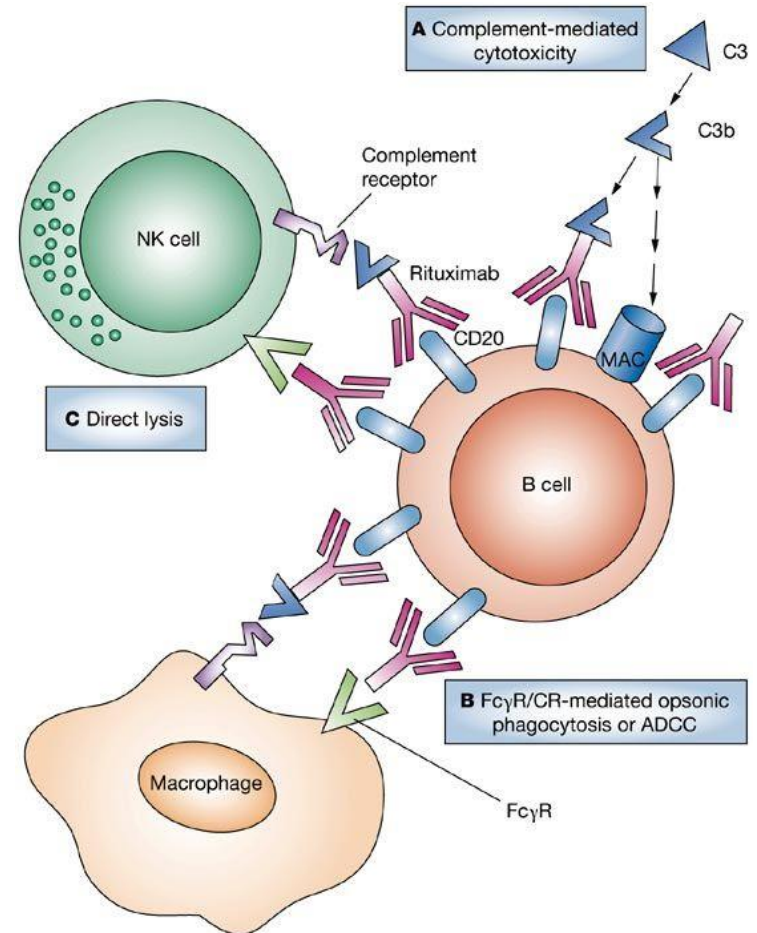


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Immunotherapy = Monoclonal antibodies

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

- Examples:
 - **Rituximab**
 - Obinutuzumab
- Only used in B cell lymphomas



Why add rituximab?

Figure 1 – Overall survival RCHOP vs CHOP

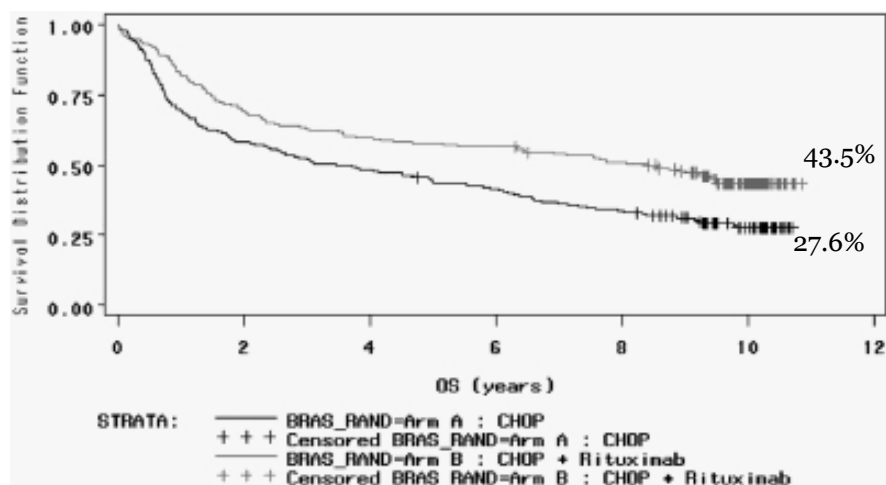
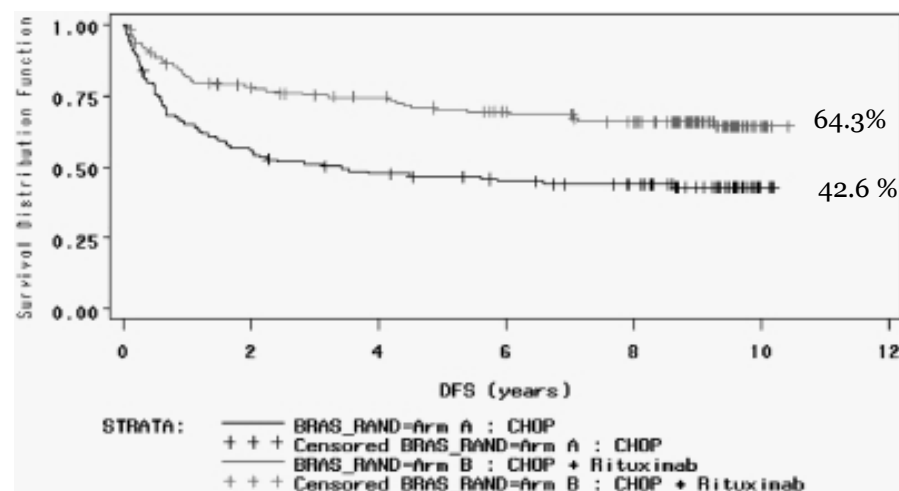


Figure 2. Disease-free survival in folks achieving CR RCHOP vs CHOP



Coiffier. *Blood* 2010 Sept 23



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Dose Adjusted R-EPOCH

- Used for double hit lymphoma, other subtypes of DLBCL
- 4 day continuous infusion of chemotherapy
- Blood counts done twice a week and doses are adjusted to WBC and platelet counts
 - R=rituximab
 - E= etoposide
 - P = prednisone
 - O=vincristine
 - C=cyclophosphamide
 - H=doxorubicin

6 cycles every 21 days
more toxic than RCHOP



Hyper-CVAD-R Regimen

Regimen used locally for mantle cell lymphoma

Part A – outpatient (CHOP-like)

Part B – inpatient (high dose methotrexate, high dose Ara-C)

Consolidation with autologous stem cell transplant

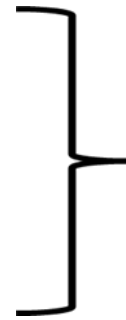
Higher infection rates than CHOP-R



Chemotherapy treatment for Hodgkin Lymphoma

ABVD

- Adriamycin
- Bleomycin
- Vinblastine
- Dacarbazine



1 cycle = 2
treatments and is
given over 4 weeks

ABVD is given every 2 weeks (A and B parts)
4-6 cycles +/- radiation



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

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



Treatment outcomes

- PET CT often used to assess remission status
- Variable, depend on many things....
- Favourable group (IPI score): 90% relapse-free
- Intermediate prognosis: 60-70%
- Unfavourable: 40-50% relapse-free
- Long-term remission rates lower for elderly, T cell lymphoma, certain subtypes of B cell NHL



Relapse/refractory

- Many other treatments available, goals of therapy change
- Single agent chemotherapy drugs
- Combinations (occasionally)
- Radiation to local areas causing symptoms
- Clinical trials of new agents
- Clarification of goals with your oncologist is very important



Relapse/refractory

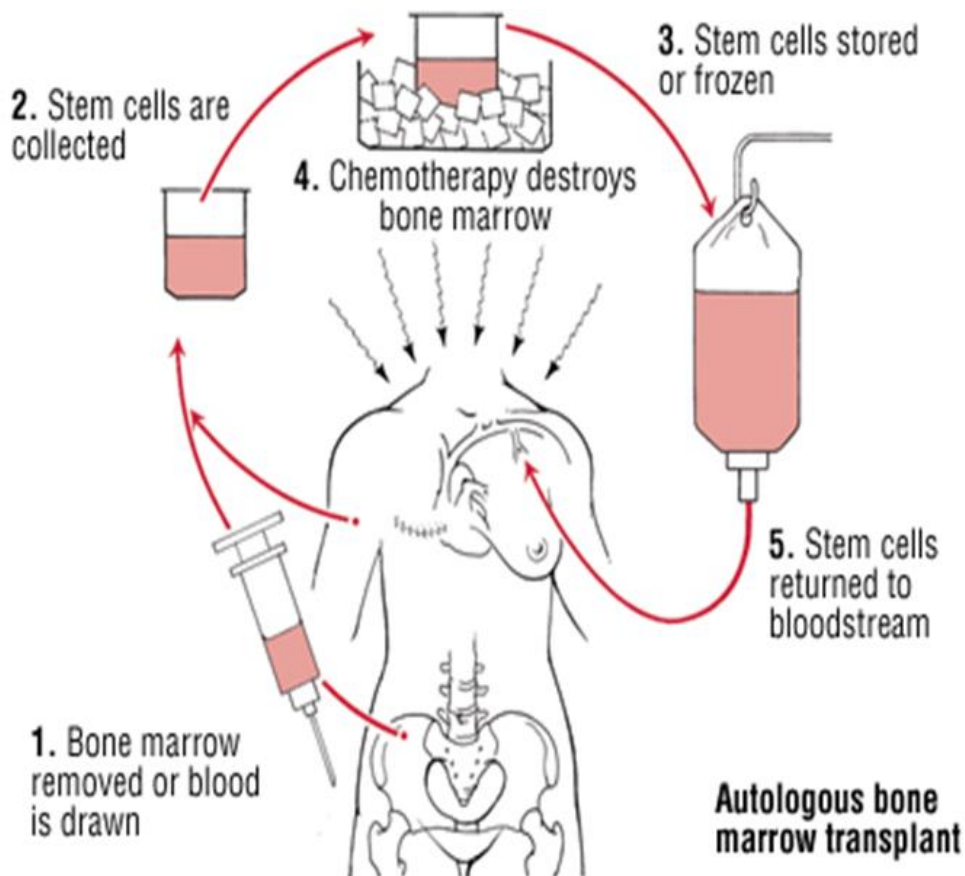
- For younger patients: stem cell transplantation considered best option
- Autologous stem cells (patients own)
- Uses very high dose of chemotherapy to try to eliminate resistant lymphoma cells
- Only beneficial if lymphoma responds to a second chemotherapy regimen



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





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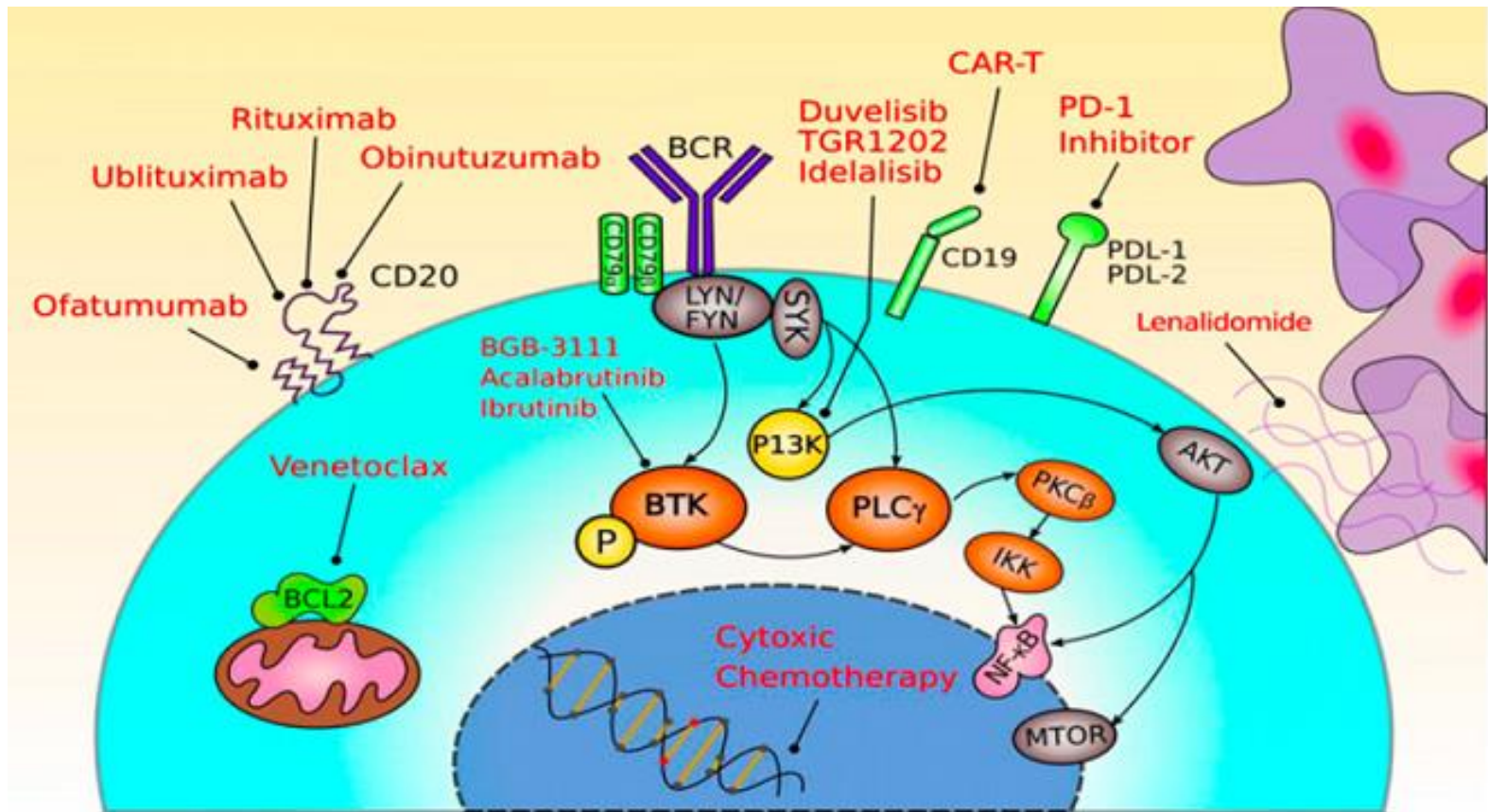
What about Targeted therapies?



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Rituximab/hyaluronidase

- Subcutaneous (under the skin) injection
- Same monoclonal antibody as intravenous Rituxan® (rituximab) and hyaluronidase, a molecule that helps to deliver medicine under the skin
- Administered in 5-7 minutes compared to 90 minutes+ for intravenous Rituxan



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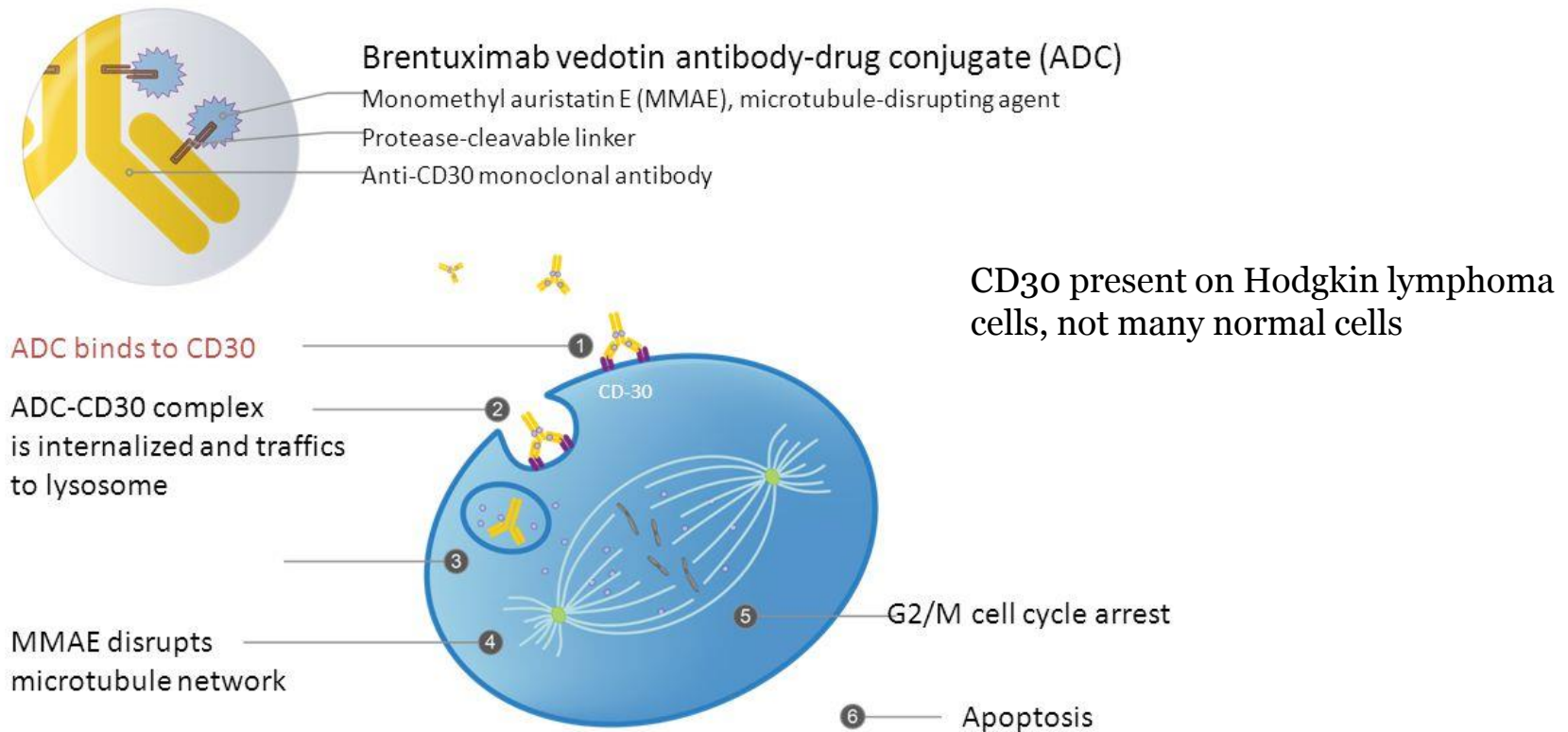
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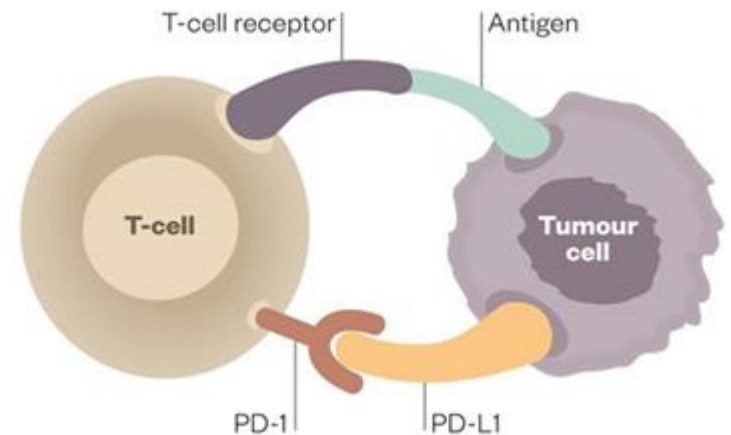
Relapsed Hodgkin Lymphoma Anaplastic Large Cell Lymphoma (CD30)

Brentuximab Vedotin



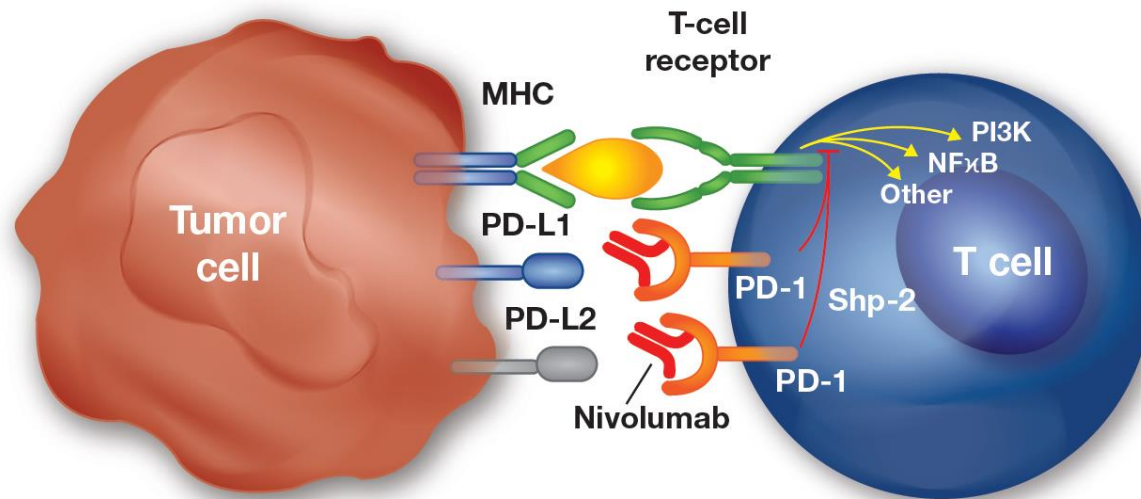
Immune checkpoint inhibitors

- Cells of the immune system have “checkpoints”-molecules on immune cells that need to be activated or inactivated to start an immune response
- 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
- Certain tumors have high expression of PD-L1 and so evade immune attack



Nivolumab for Classical Hodgkin Lymphoma

- Patients with cHL show overexpression of **PD-L1** and **PD-L2**¹ (**programmed cell death protein**)
- Nivolumab is a fully human immunoglobulin G4 monoclonal antibody targeting the programmed death-1 (PD-1) receptor immune checkpoint pathway



Nivolumab blocks signalling through the PD-1 receptor and activates the immune system to kill the cancer cells



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cHL = classical Hodgkin lymphoma; MHC = major histocompatibility complex; NFκB = nuclear factor kappa B; PD-L1/2 = programmed death ligand 1/2; PI3K = phosphoinositide-3-kinase; Shp-2 = Src homology region 2-containing protein tyrosine phosphatase 2

1. Roemer MGM, et al. *J Clin Oncol* 2016;34:2690–2697

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PD-1 Blockade with Nivolumab in Relapsed or Refractory Hodgkin's Lymphoma

Stephen M. Ansell, M.D., Ph.D., Alexander M. Lesokhin, M.D., Ivan Borrello, M.D., Ahmad Halwani, M.D., Emma C. Scott, M.D., Martin Gutierrez, M.D., Stephen J. Schuster, M.D., Michael M. Millenson, M.D., Deepika Cattray, M.S., Gordon J. Freeman, Ph.D., Scott J. Rodig, M.D., Ph.D., Bjoern Chapuy, M.D., Ph.D., Azra H. Ligon, Ph.D., Lili Zhu, M.S., Joseph F. Grosso, Ph.D., Su Young Kim, M.D., Ph.D., John M. Timmerman, M.D., Margaret A. Shipp, M.D., and Philippe Armand, M.D., Ph.D.

ABSTRACT



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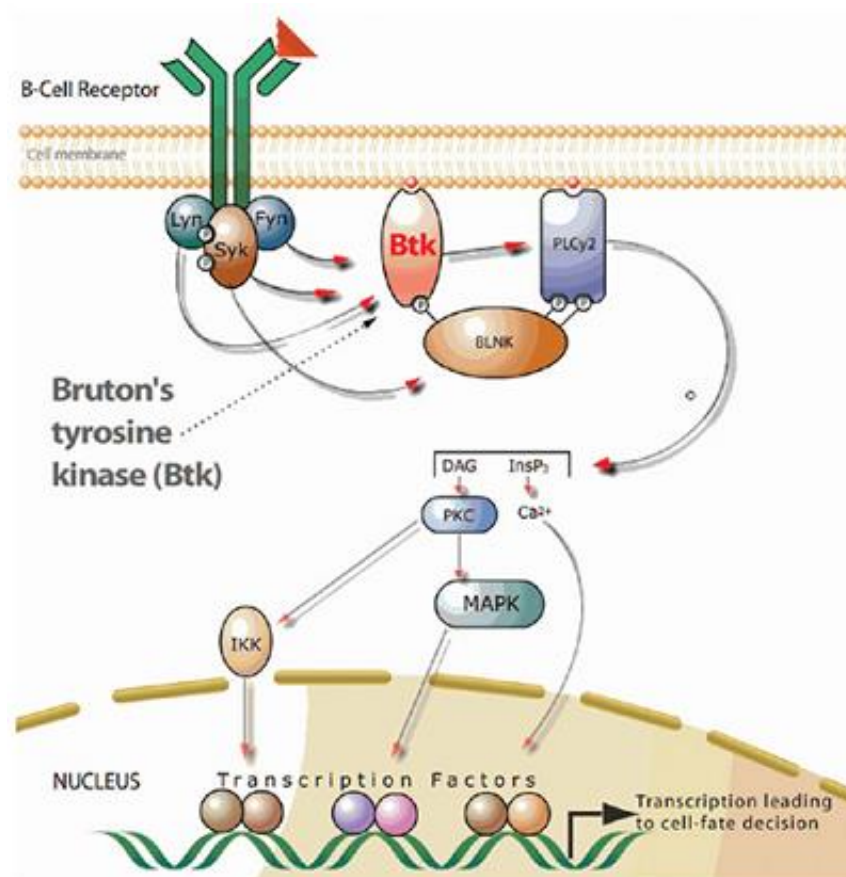
Bruton's Tyrosine Kinase (BTK) Inhibitors

- 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

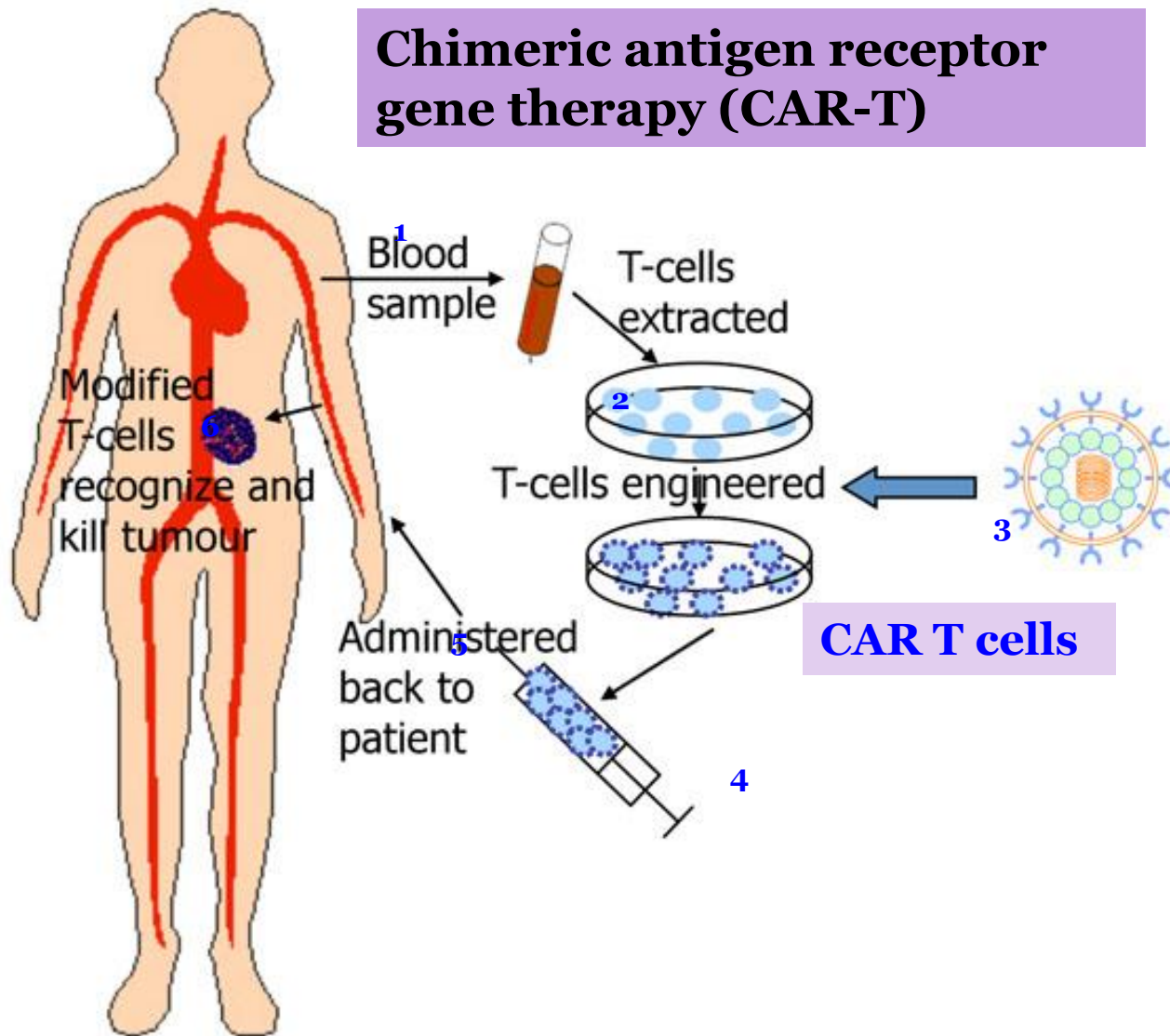


Ibrutinib

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



Chimeric antigen receptor gene therapy (CAR-T)



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

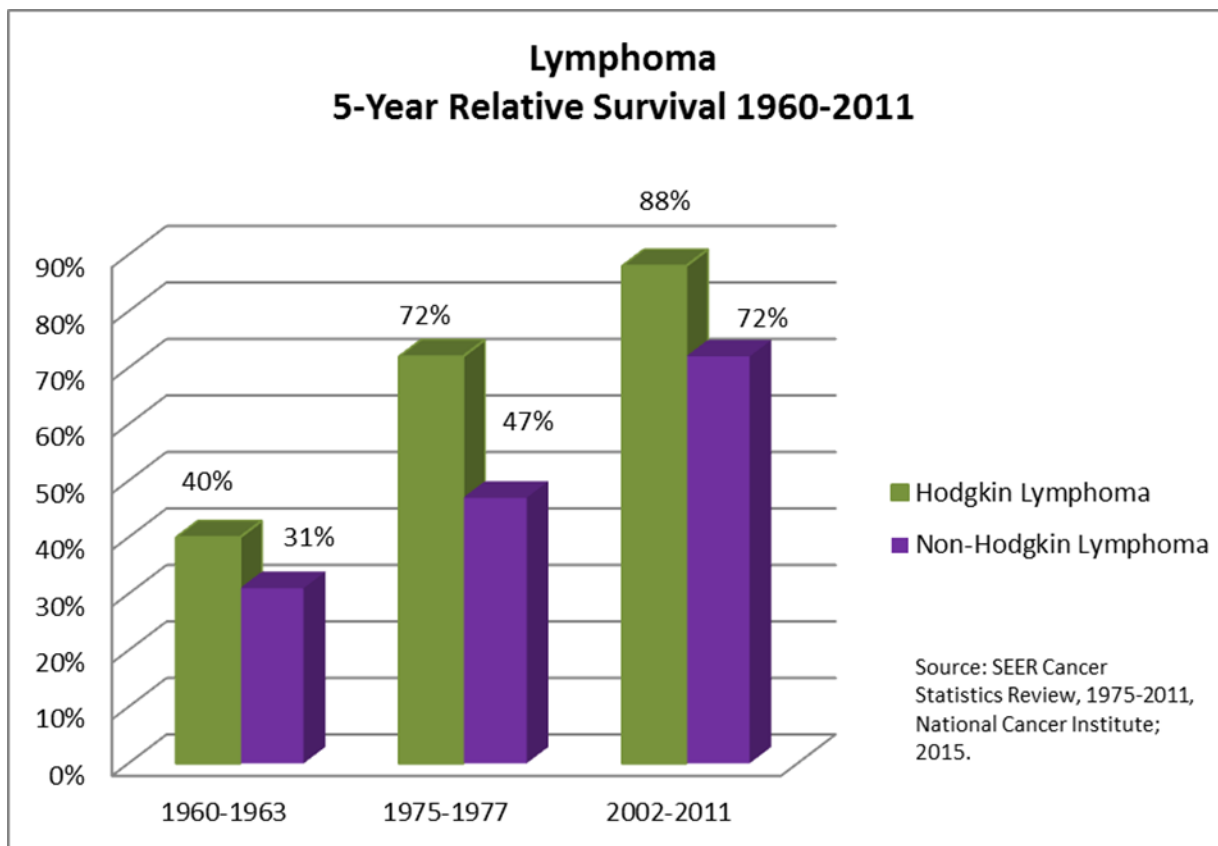


Is research working?

- 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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