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

# THE FUTURE IS PROMISING

Dr. Claire Dearden

# Lymphoma

- Haematological malignancies are the 5th commonest cancer
- Lymphomas represent ≈50% of blood cancers
- Crude incidence rate of 20 cases per 100,000 of the population

In Canada

- 11,755 cases pa
  - NHL 8300
  - HL 990
  - CLL 2465
- Median age ~ 70 years
- Leading cancer in 15-29 age group
- 3rd Most common cancer in children 0-14
- Deaths from Lymphoma: 3448 pa
  - NHL 2700
  - HL 140
  - CLL 608

# Lymphomas are Heterogeneous and Complex: Biologically and Clinically

- WHO Classification is the 'dictionary' of blood cancers and defines more than 100 different distinct diseases and 60 Lymphoma subtypes
- Within any lymphoma sub-type there are numerous biological factors that define different prognostic groups
- New information- especially genomic- becoming available every week
- Some well established traditional therapies, with well known side effect profile
- A large, and ever increasing, number of novel treatments
- New therapy= new toxicities

This is challenging for the patients, their carers and the clinical team!

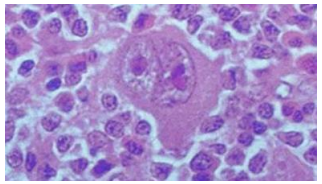
# WHO Classification

Lymphoma

Hodgkin Lymphoma

**Non-Hodgkin Lymphoma**

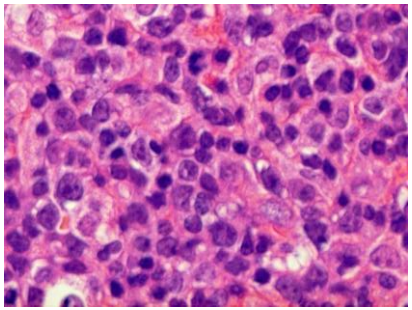
Classical Hodgkin Lymphoma



Nodular Lymphocyte Predominant Hodgkin Lymphoma

T-cell NHL

12%

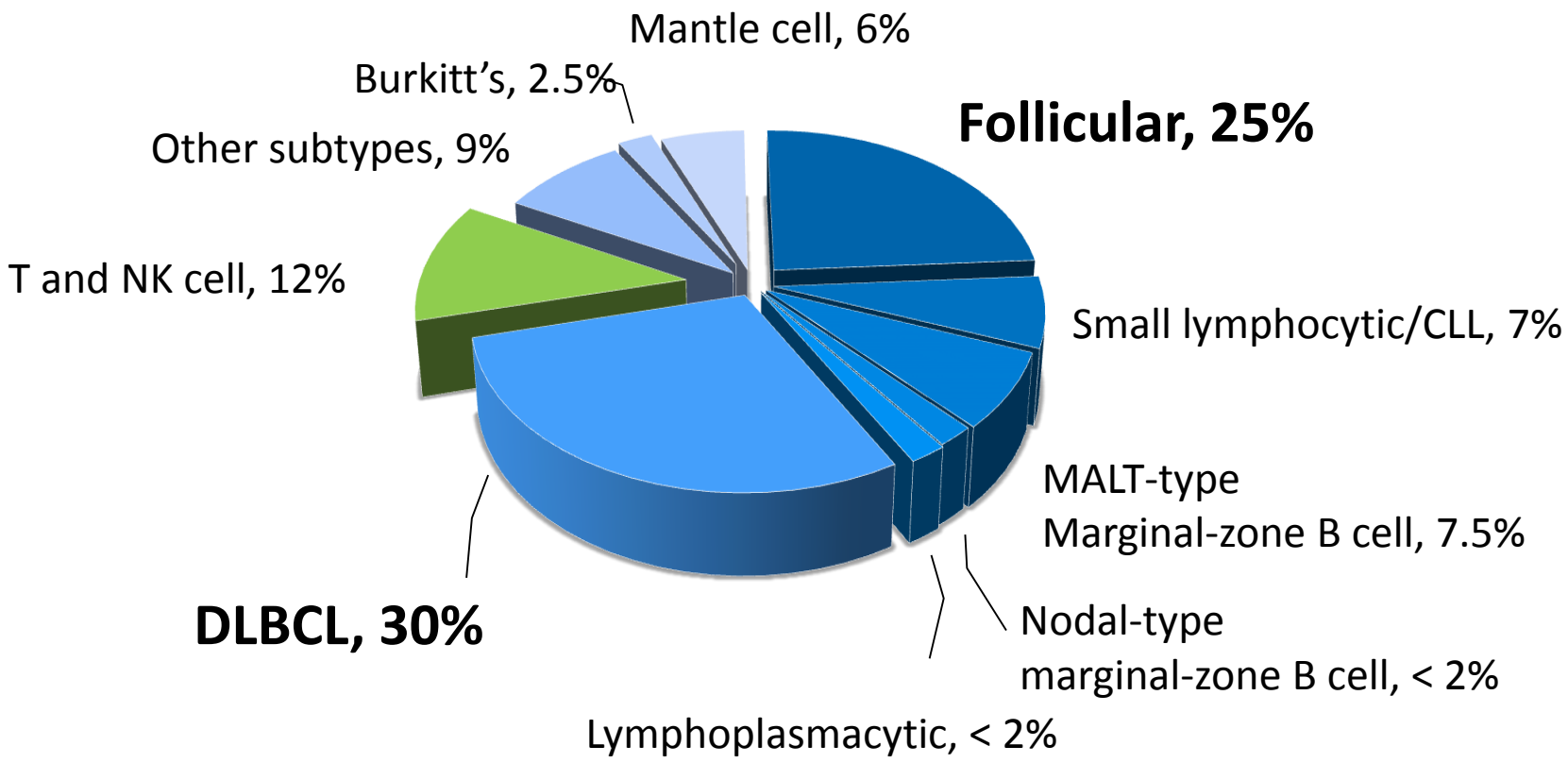


**B-cell NHL**

>80%

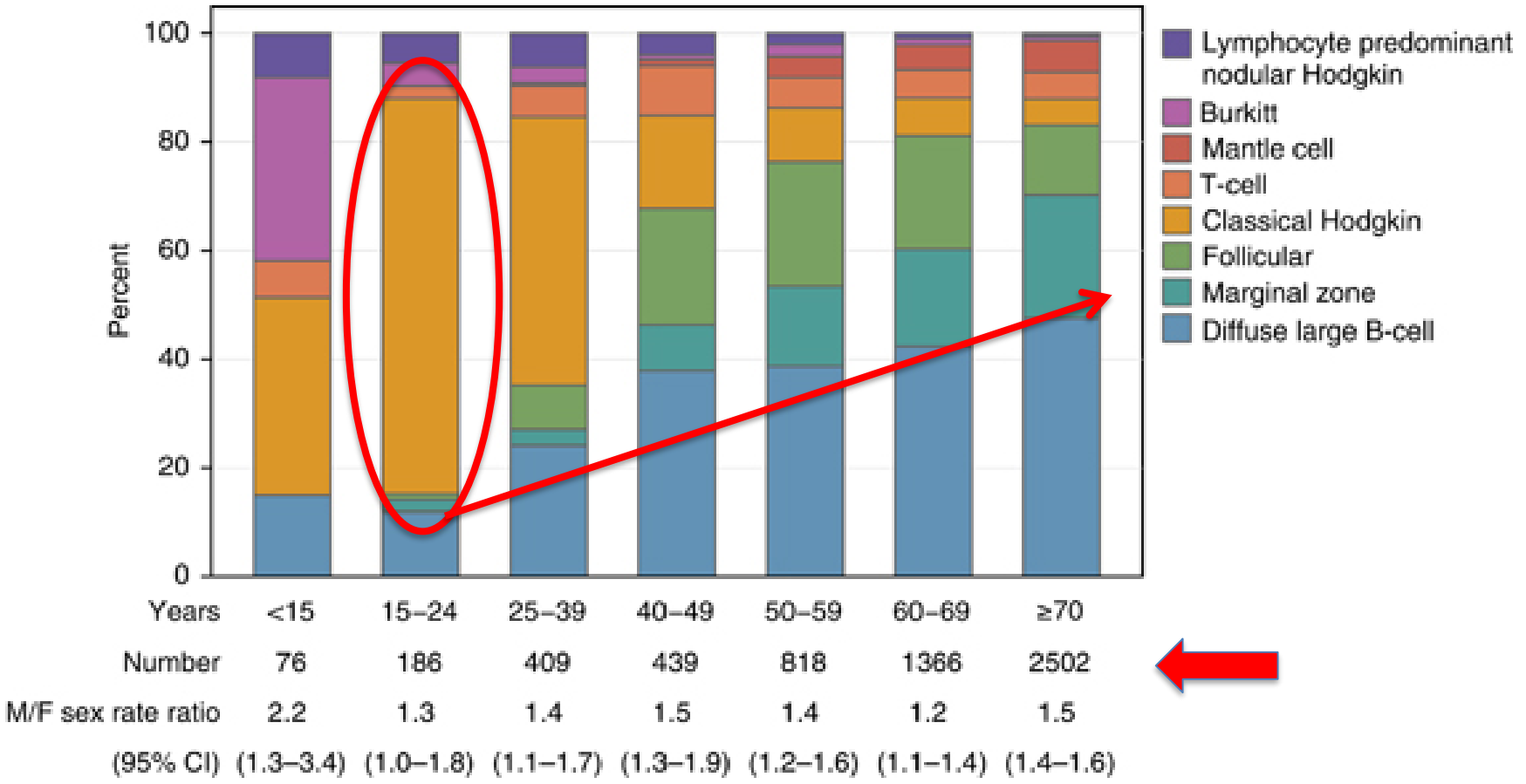
Low and High Grade

# Non-Hodgkin Lymphoma




Lichtman MA. *Williams Hematology*. 7th ed. New York, NY: McGraw Hill. 2006;1408

# Age distribution of lymphomas



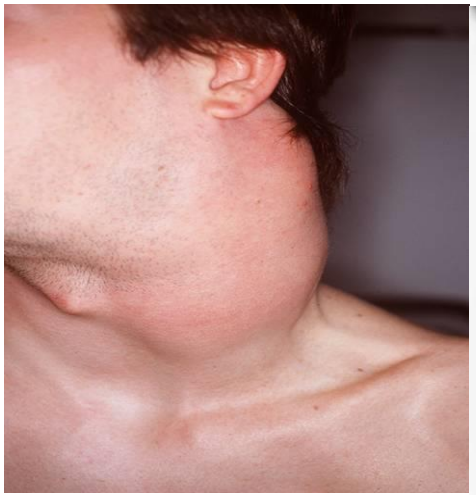
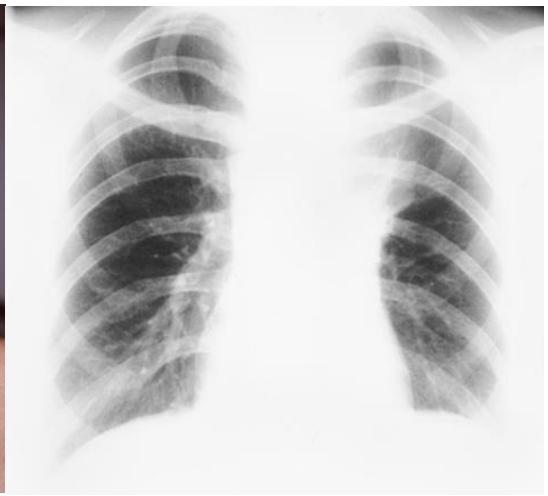
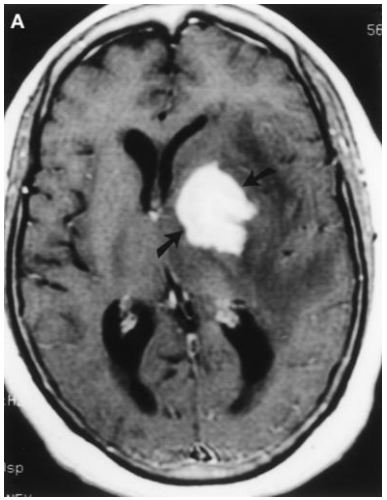

| Years | <15 | 15–24 | 25–39 | 40–49 | 50–59 | 60–69 | ≥70 |
|---|---|---|---|---|---|---|---|
| Number | 76 | 186 | 409 | 439 | 818 | 1366 | 2502 |
| M/F sex rate ratio | 2.2 | 1.3 | 1.4 | 1.5 | 1.4 | 1.2 | 1.5 |
| (95% CI) | (1.3–3.4) | (1.0–1.8) | (1.1–1.7) | (1.3–1.9) | (1.2–1.6) | (1.1–1.4) | (1.4–1.6) |

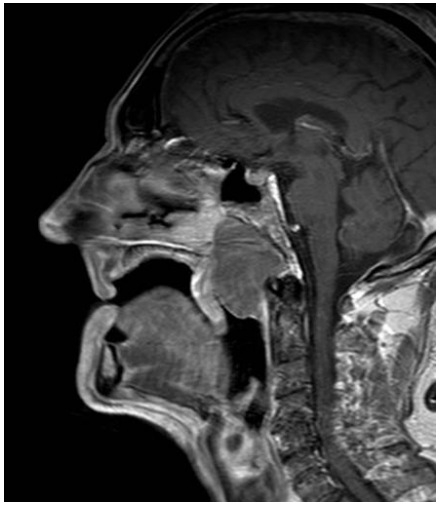
**Haematological Malignancy Research Network (HMRN) 2004–2012**

*British Journal of Cancer* (2015) **112**, 1575–1584

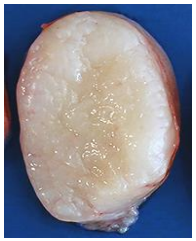
# Clinical presentation

- Very variable
  - Incidental lymphadenopathy to systemic illness
  - 15 to 20% of patients present with localised disease
  - LN is more common in neck / axillae than groin
  - Only around 10% will have B-symptoms
  - 20% have mainly extra-nodal disease

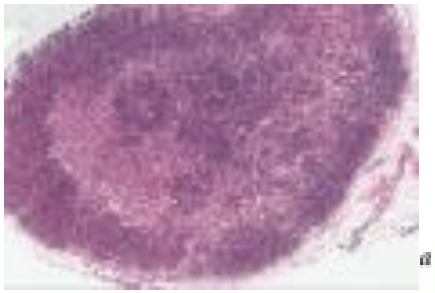






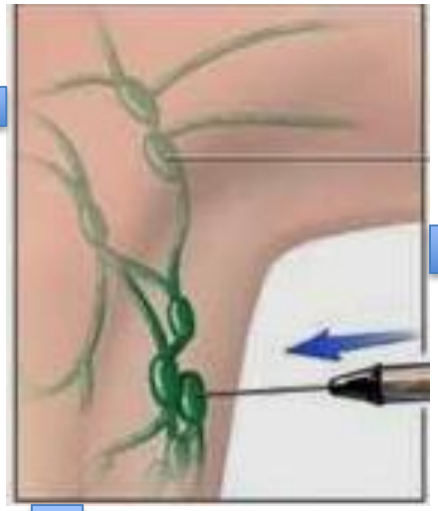
# Diagnosis = Tissue Biopsy



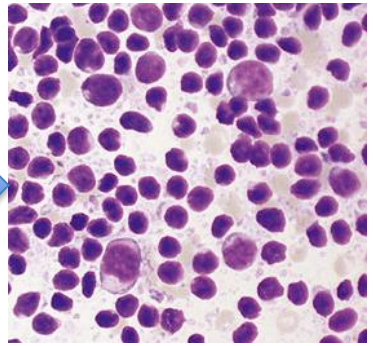
Cut, fixed and stained



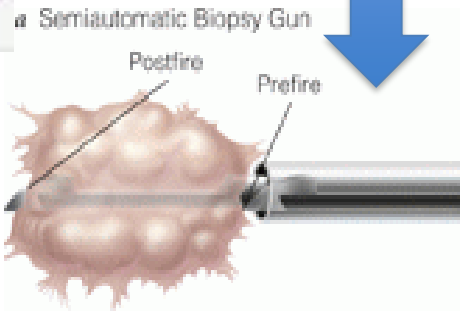
**Surgical excision**



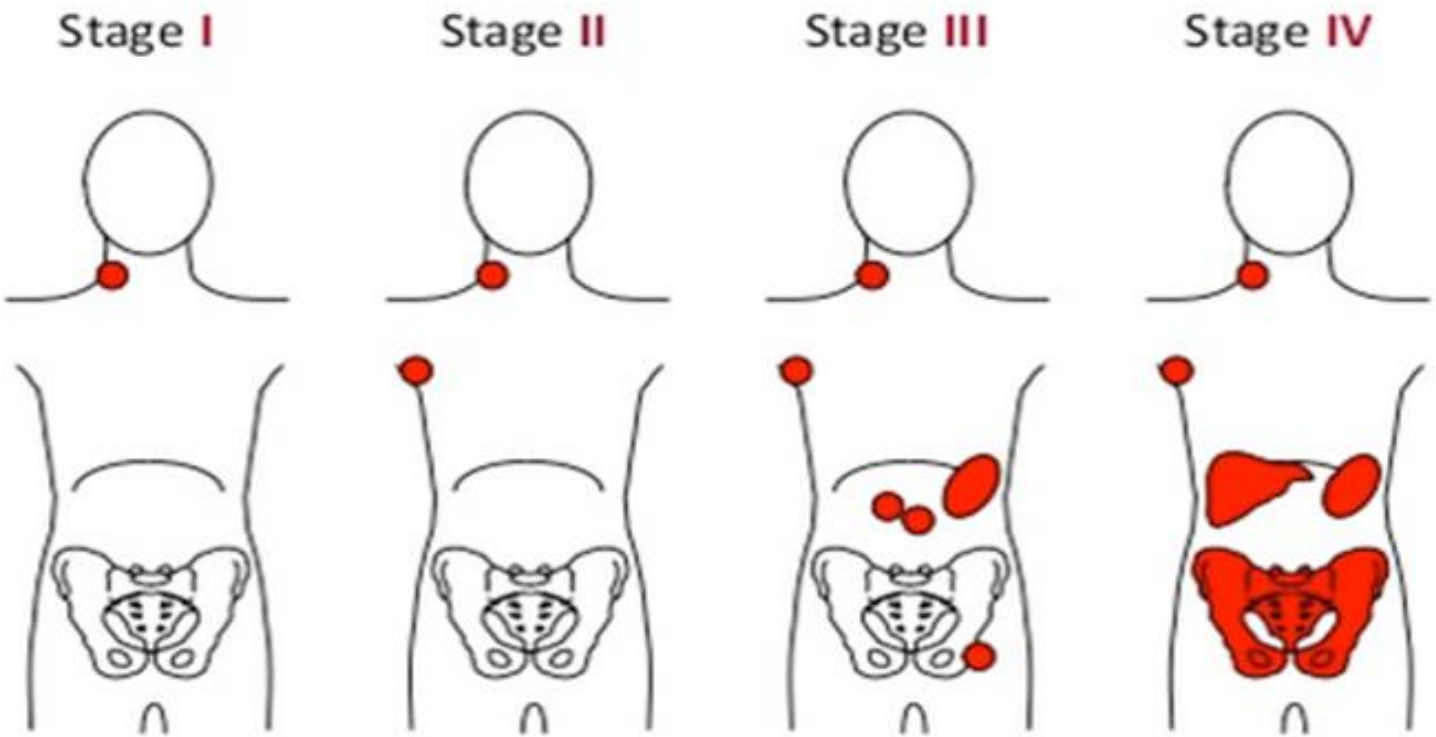
**FNA**



**Needle core biopsy**

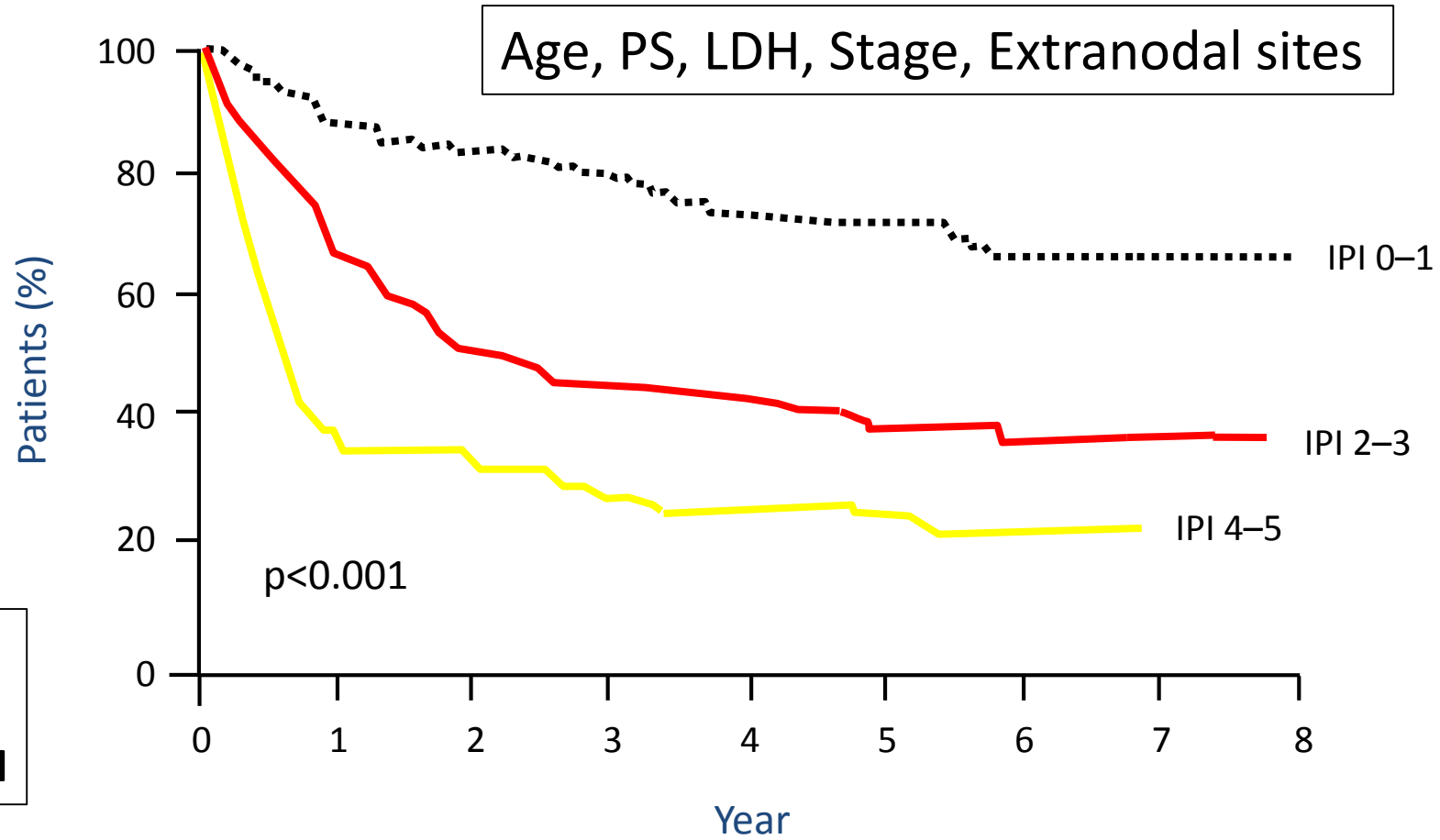



# Lymphoma staging




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

# Lymphoma Prognosis
# DLBCL: overall survival by International Prognostic Index (IPI)




**FLIPI**
**MIPI**
**CLLIPI**

Adapted from Armitage JO, and Weisenburger DD. J Clin Oncol. 1998;16:2780–95

# Lymphoma: Key Advances in the last decade

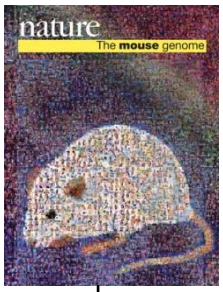
- Understanding the biology and genetics
  - Improved classification (WHO) and diagnosis
  - Risk stratification and prognosis
  - High tech staging and follow up
    - Imaging (PET)
    - MRD (minimal residual disease)
    - plasma cell-free DNA
  - Targeted therapy

# Genome Sequencing

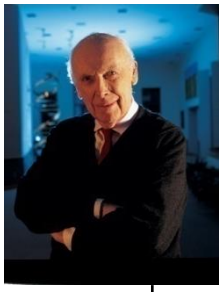
**Sanger (capillary) sequencing**

**Next generation sequencing**

Cancer Genomics





AML

Melanoma

Small-cell lung

Breast

Lung (NSS)

Hepatocellular

Myeloma

CLL

Mouse AML

**2000**
~10 years
~$ 3.5 billion

**2005**
~3 years
~$ 20million

**2008**
~4 months
~$ 1.5million

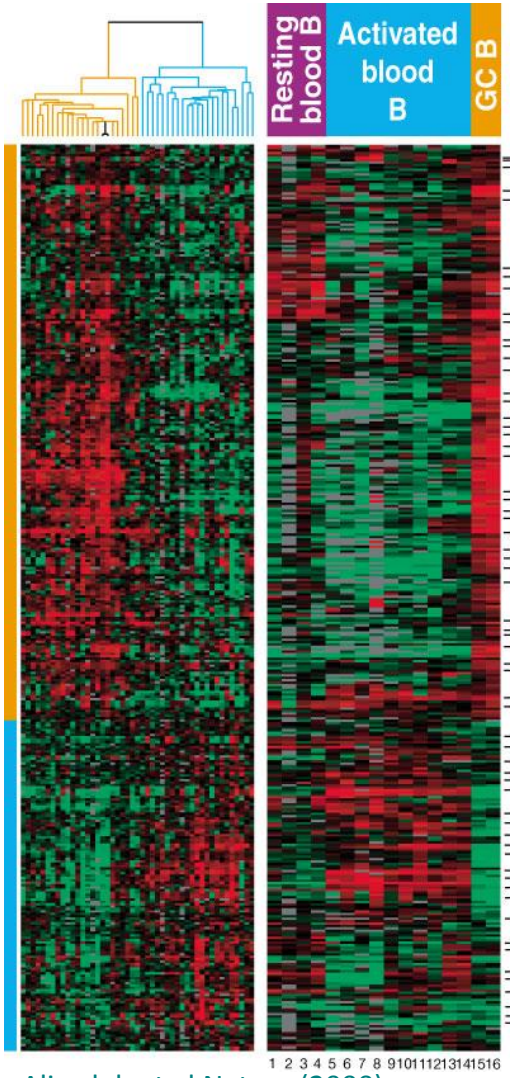
**2010**
~1month
$9,500
(Illumina)

**2015**
~1day
$100

# Gene sequencing- The Impact

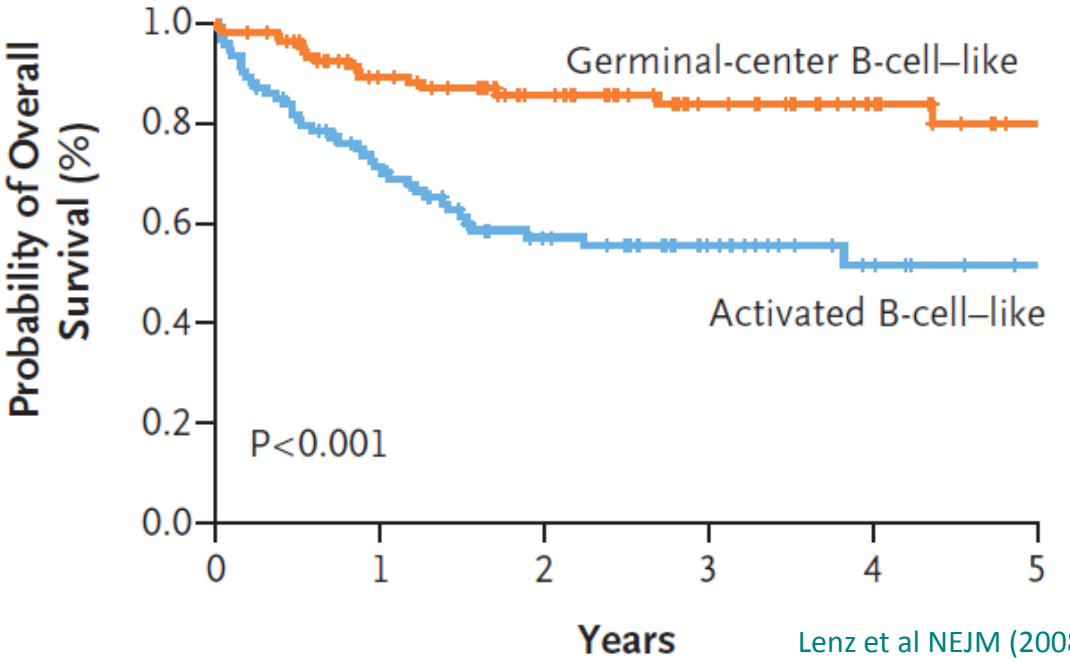
- Heritable risk-associated genes
- Diagnosis
- Prognosis
- Personalised therapy (targeted agents)
- Response assessment
- Disease monitoring

# DLBCL: not a single disorder




Alizadeh et al Nature (2000)

- Sub-classification of DLBCL into GCB/ABC type using GEP is widely reported.
- ABC has an inferior overall response rate which is independent of the use of Rituximab




Lenz et al NEJM (2008)

# Mutated vs Unmutated CLL – what is the difference?

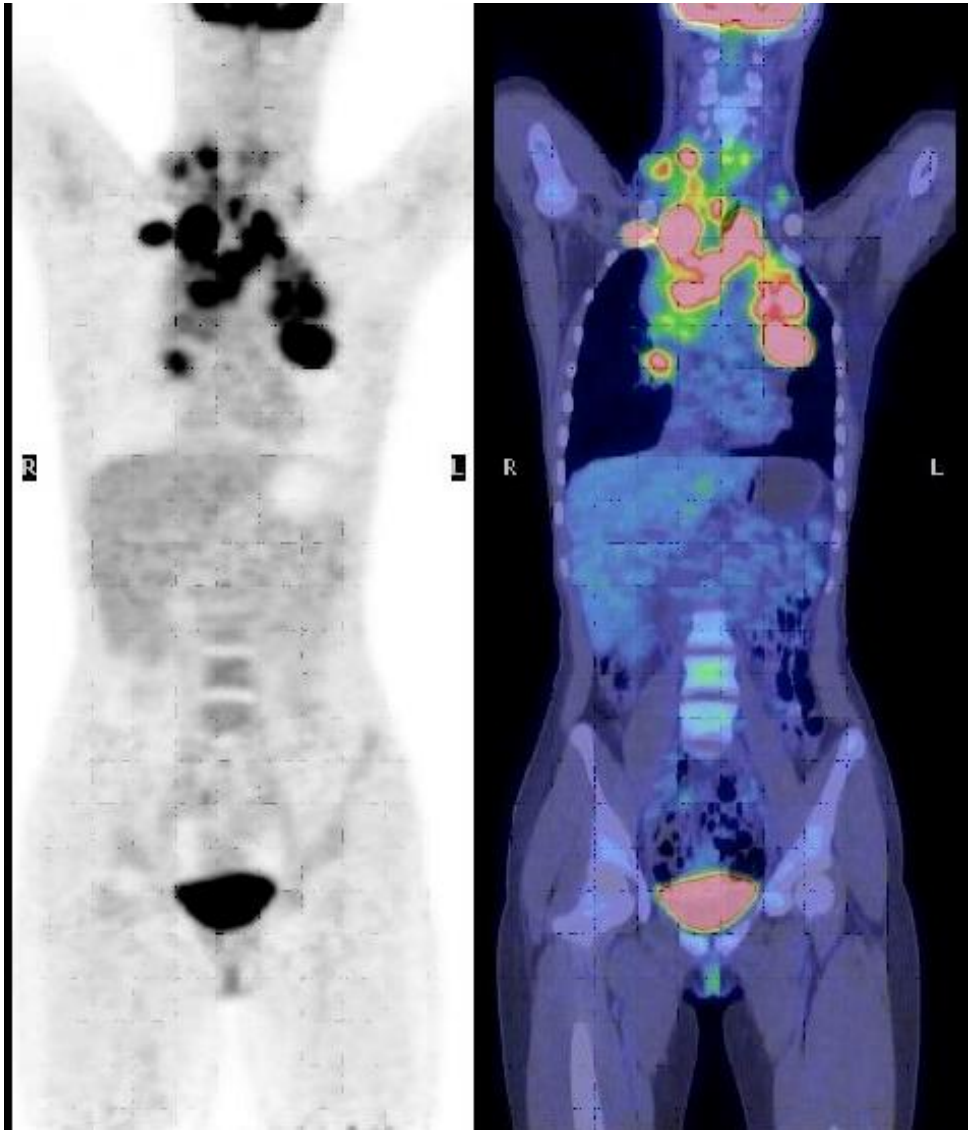
- Slower growing disease
- Many never need treatment
- Respond very well to FCR
- Less likely to develop other genetic change

- Faster pace of disease
- Usually need treatment
- Respond well to treatment but usually relapse
- More likely to develop other genetic change

# Important predictive gene alterations in CLL

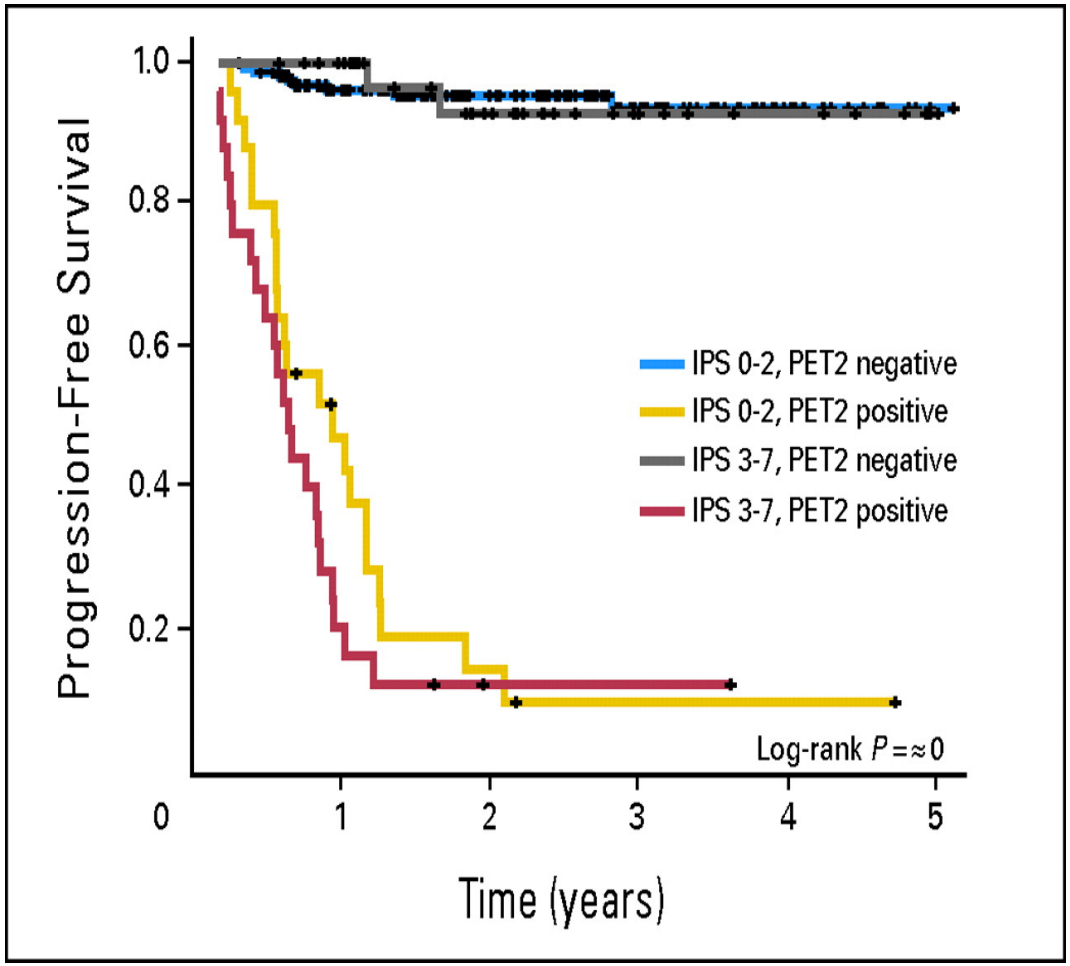
| Gene alteration | Affect on treatment outcome | References |
|---|---|---|
| IGHV mutated | Very good response to FCR | Rossi 2015, Fischer 2015, Thompson 2016 |
| TP53 del/mut | Resistance to chemo-immunotherapy | Hallek ,2012 |
| NOTCH1 | Resistance to anti-CD20 antibodies | Stilgenbauer 2014 |
| Complex Karyotype, BTK and PLCG2 mutations | Resistance to Ibrutinib | Woyach 2014, Thompson 2016, Burger 2016 |
| RPS15 | Poor response to FCR | Ljungstrom, 2016 |

# PET-CT in lymphoma




- Upstages 10% of cases compared to CT alone
- Useful to assess unusual sites eg bone
- Valuable in monitoring response
- Early response is highly prognostic in HL
- Negative PET at end of treatment is a good predictor of outcome for DLBCL
- Caution- numerous pitfalls in interpretation, false neg and pos

# PFS by PET result after 2 cycles of treatment (ABVD) in HL



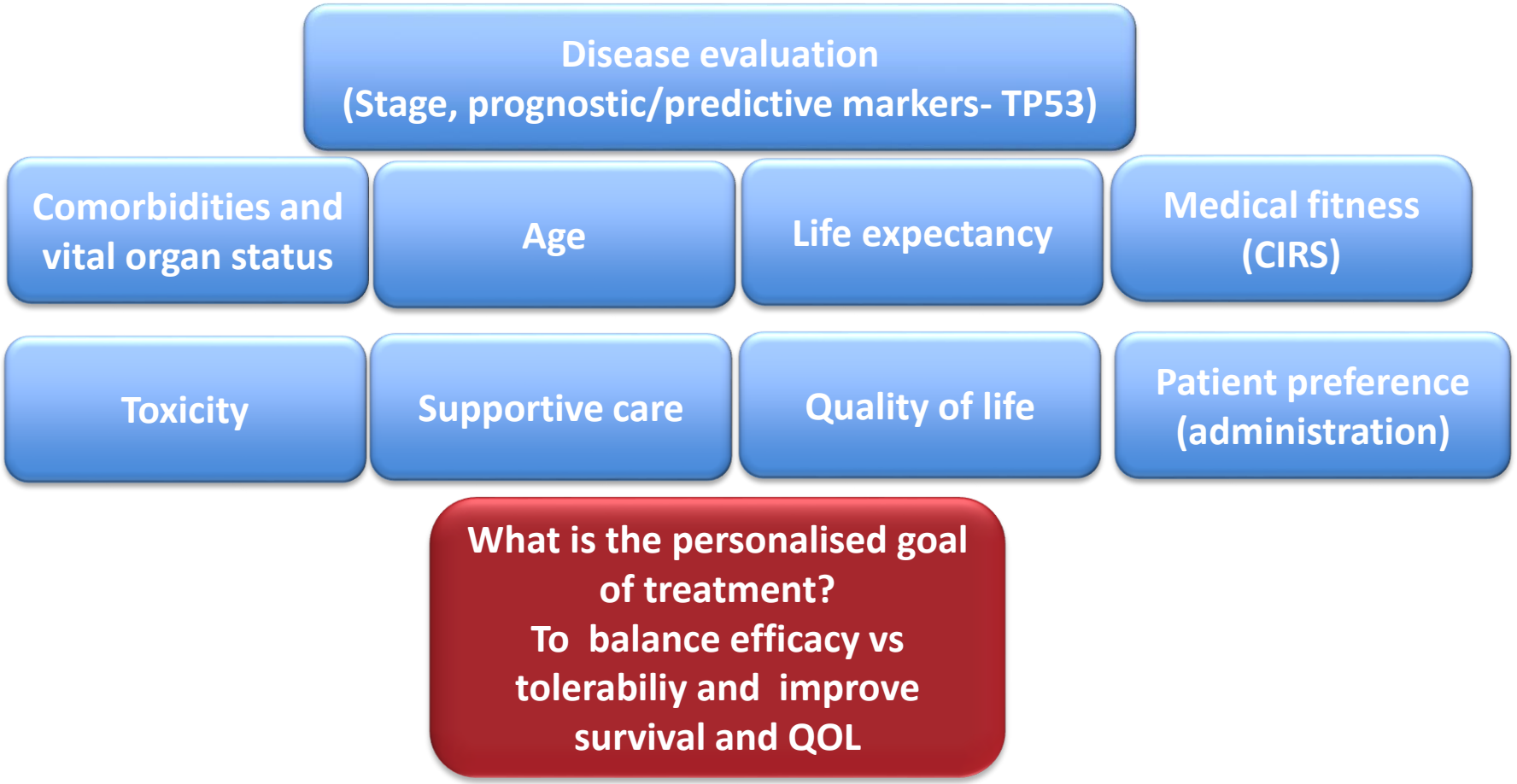

**Andrea Gallamini et al. JCO 2007;25:3746-3752**



JOURNAL OF CLINICAL ONCOLOGY ASCO

# Tailoring treatment for patients

Many factors must be considered in order to optimise management in patients with lymphoid malignancy



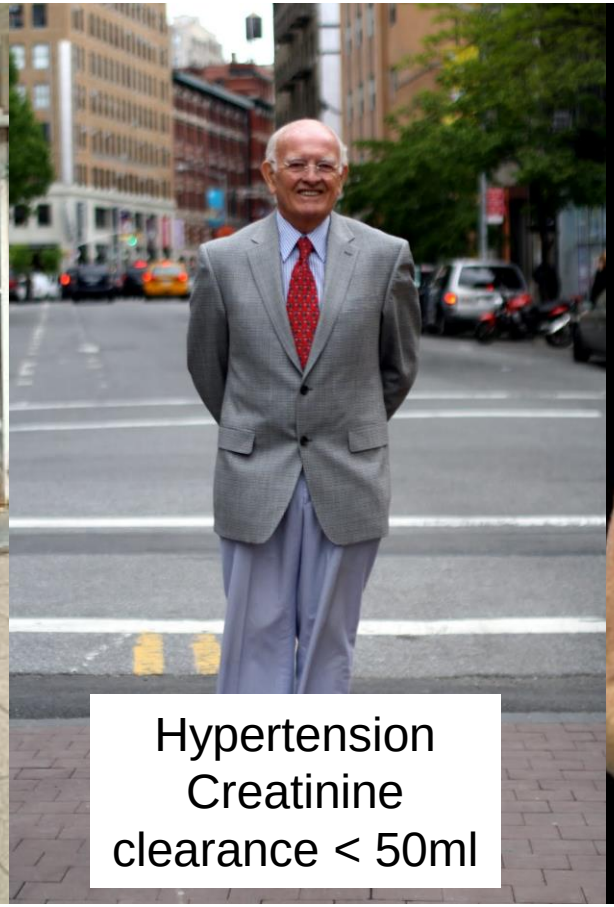
# What are the problems with current therapy?

- People still die from their cancer
- Older patient group with co-morbidities are ‘harder to treat (median age ~70 years)
- Non – selectivity of conventional cancer treatment
  i.e. drugs damage normal cells = Toxicity
- Drug resistance

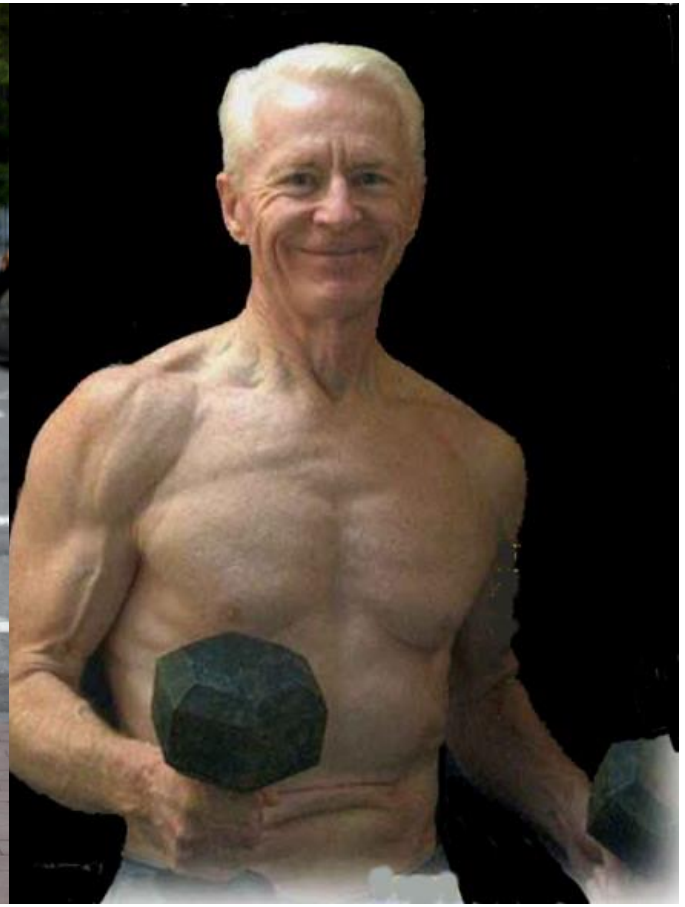
  i.e. cancer cells eventually stop responding to treatment

How can we improve the cure rate without increasing the damage to normal cells?

# Consider age and fitness

Hypertension
Creatinine clearance < 50ml

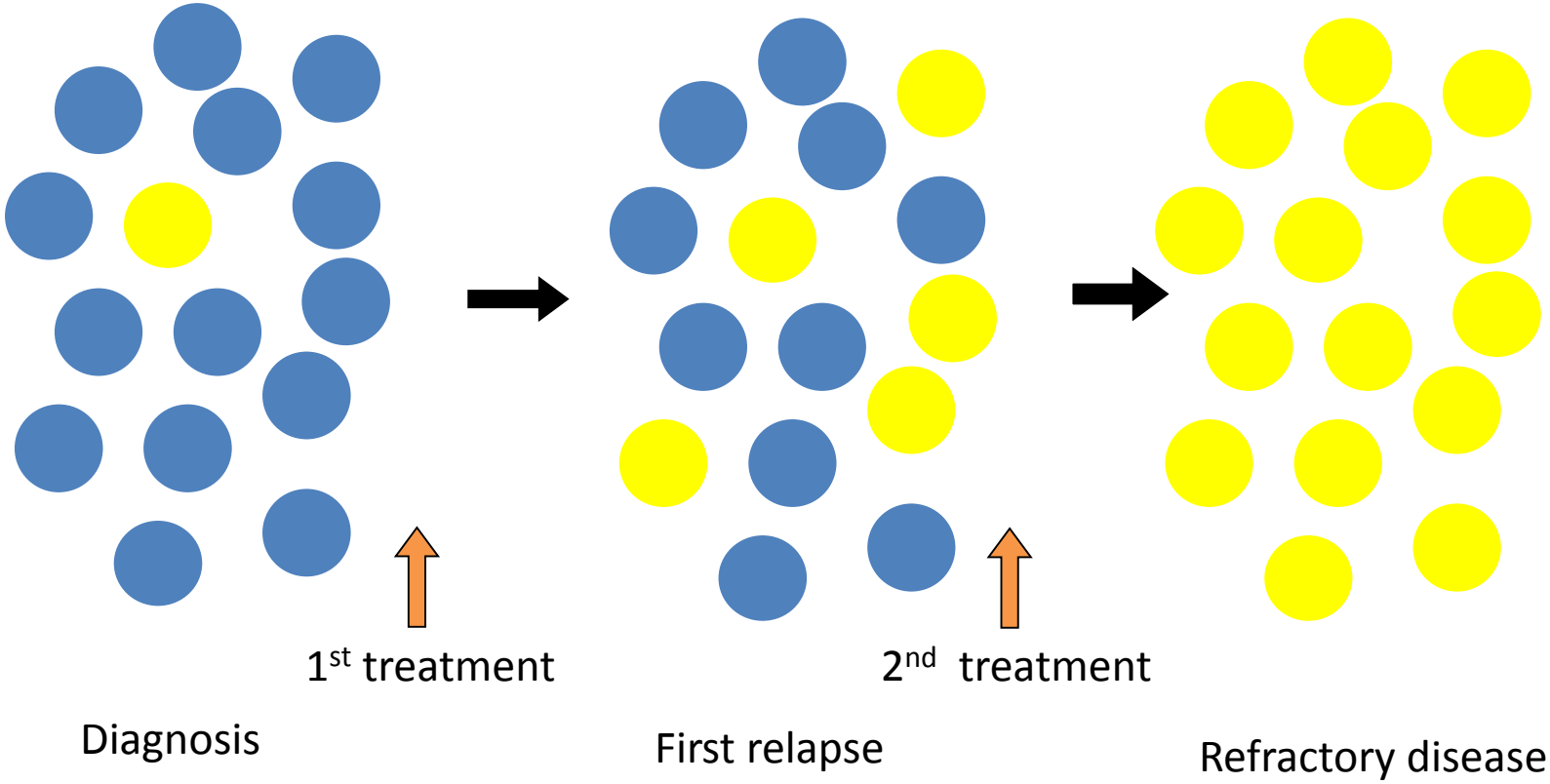


**SLOW-GO** **NOT–SO-GO-GO** **GO-GO**

Fitness is more important than age

# Toxicity

# Development of drug resistance




Clonal expansion of resistant cell to become the dominant population in refractory disease

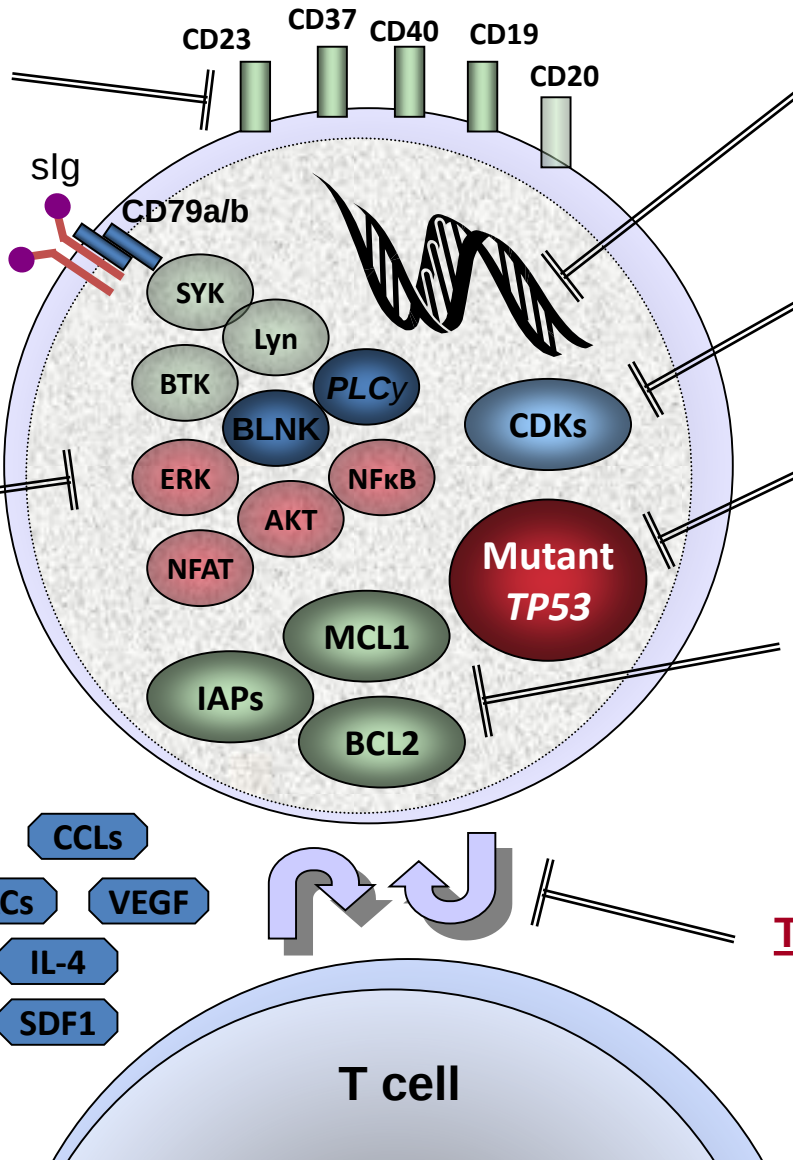
The dominant 'chemo-sensitive ' clone at diagnosis is subsequently replaced by the chemo-resistant subclone

# From Biology to Therapy: CLL as a Model

**Antibodies:**
Rituximab (CD20)
Obinutuzumab (CD20)
Ofatumumab (CD20)
Blinatumumab (CD19/CD3)

**Signal transduction inhibitors:**
Idelalisib (PI3K)
Ibrutinib (BTK)

**Microenvironment modulation:**
Lenalidomide (Imids)




**Classical treatment:**
Chemotherapy

**CDK inhibitors:**
Flavopiridol

**Aberrant p53:**
HDAC inhibitors

**Apoptosis machinery:**
Venetoclax (BCL2)

**T cell - CLL interaction:**
Lenalidomide (Imids)
CAR-T cells (CD19))
GvL effect (allo-SCT)

# Novel Treatment Targets

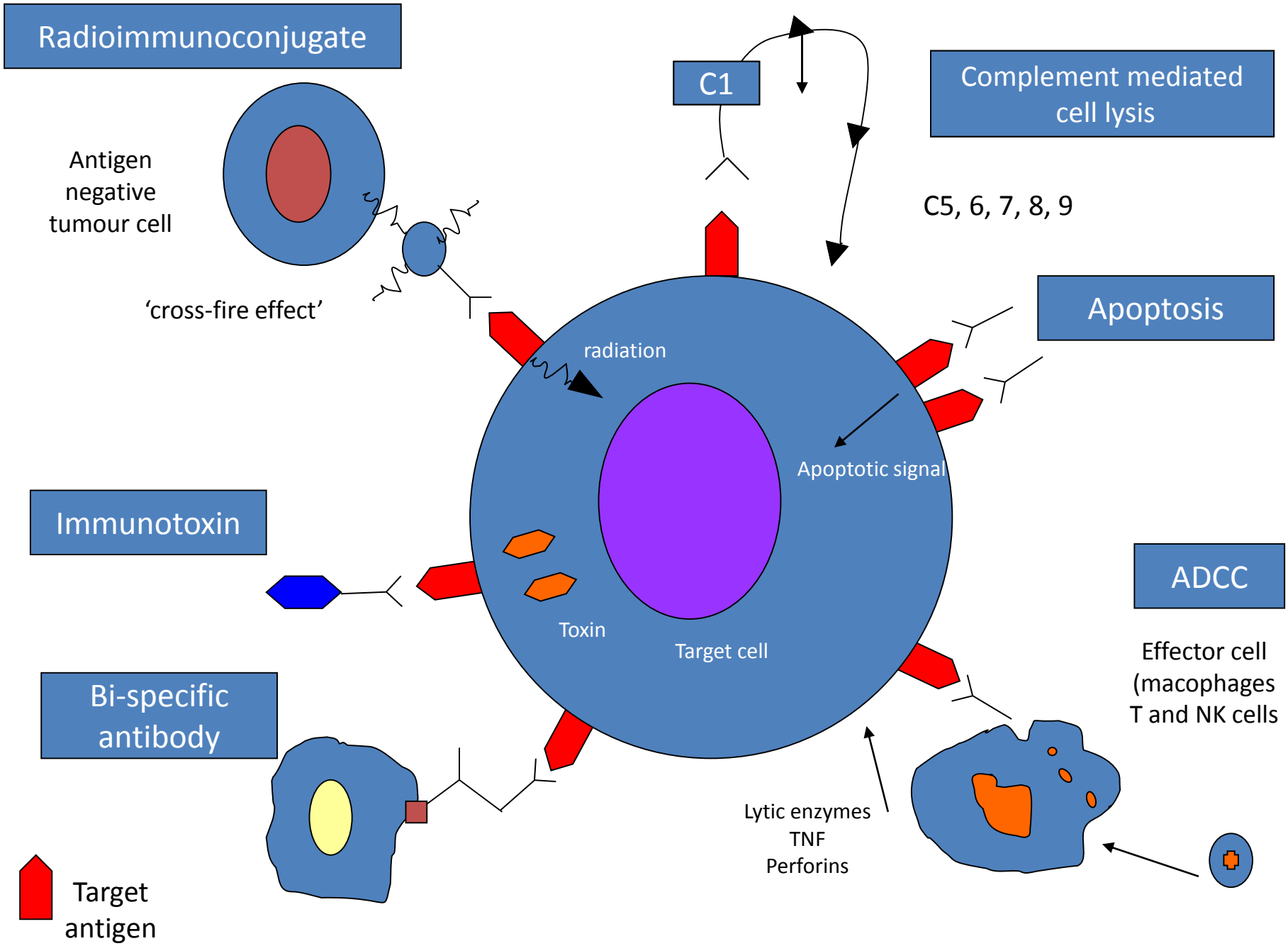
| Tumour cell target | Treatment |
| --- | --- |
| Surface molecules (antigens) | Monoclonal Antibodies |
| Cell signalling | Small inhibitory molecules |
| Cell micro-environment | Several agents |
| Gene mutations | Inhibit function |
| Gene products | Inhibition |
| Enhance Immune cell kill | Cellular therapies |

# Paul Ehrlich 1854-1915

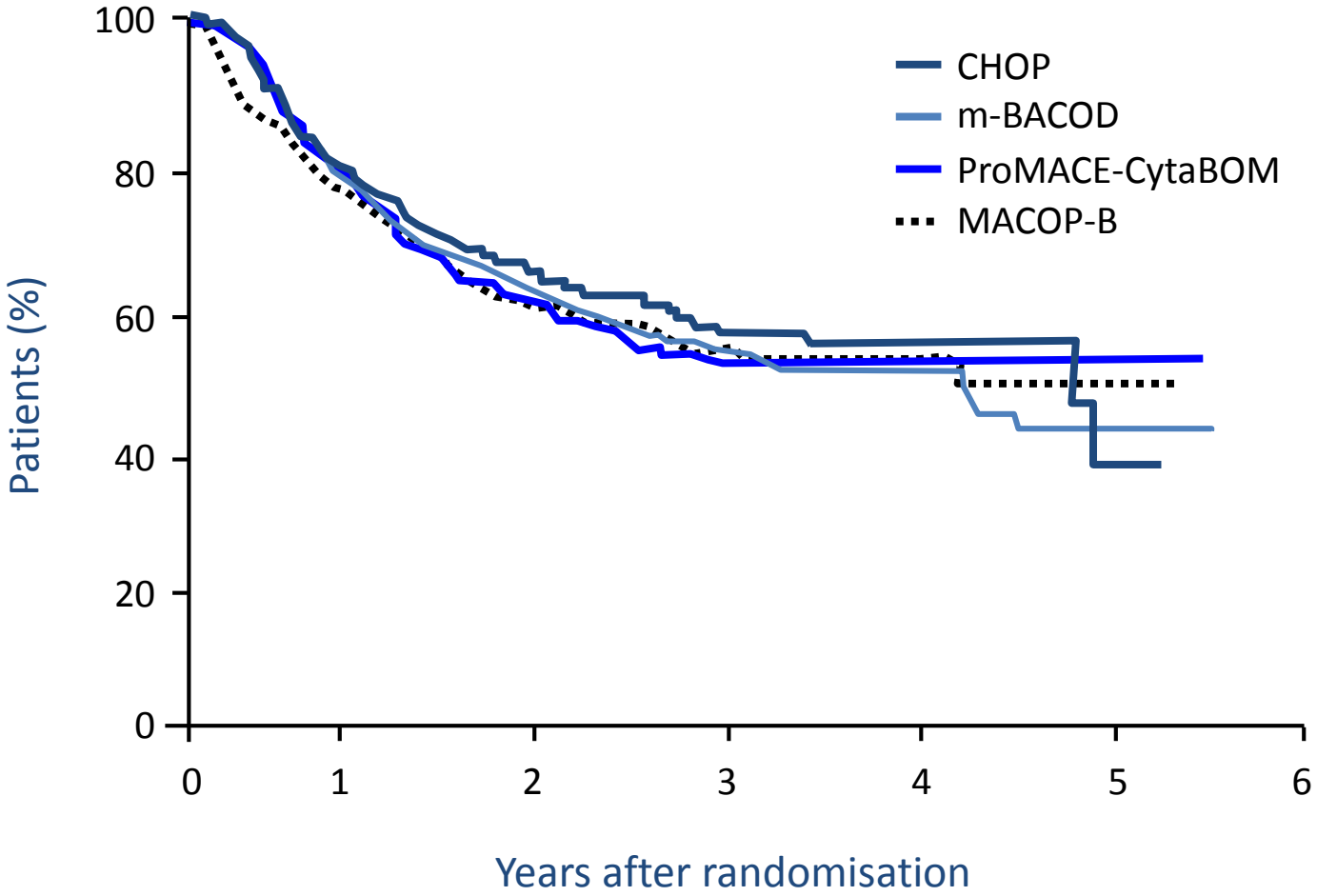
"You see we must take aim - aim by chemical variation! The marvellous effect of an antibody in the serum is due to the fact that in no case it has affinity for the body substances but flies straight onward without deviation, upon the parasites.

The antibodies are therefore MAGIC BULLETS which find the targets themselves… we must therefore concentrate all our powers and abilities on making the aim as accurate as we can contrive, so as to strike the parasites as hard and the body cells as lightly as possible."

circa 1904


Radioimmunoconjugate
Antigen negative tumour cell
'cross-fire effect'
C1
Complement mediated cell lysis
C5, 6, 7, 8, 9
Apoptosis
radiation
Apoptotic signal
Immunotoxin
Toxin
Target cell
ADCC
Effector cell (macophages T and NK cells
Bi-specific antibody
Lytic enzymes
TNF
Perforins
Target antigen

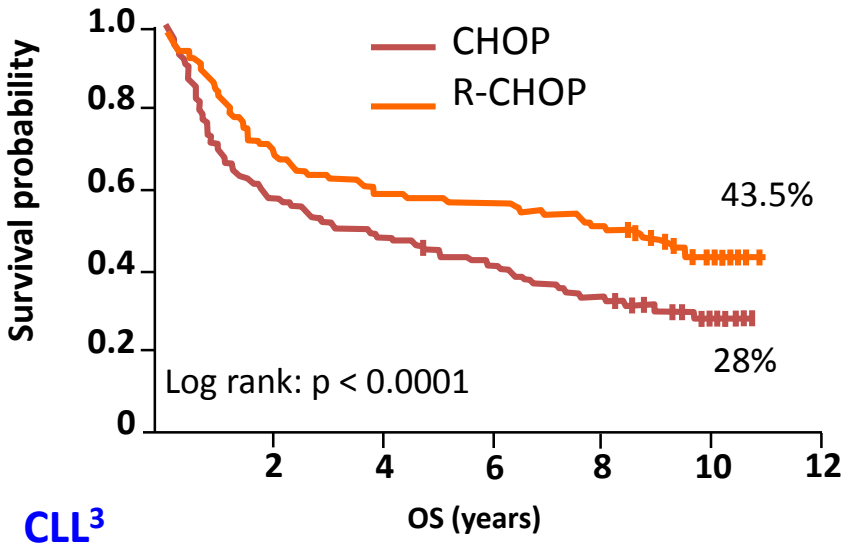
# Pre-rituximab – changing the chemo did not impact on OS



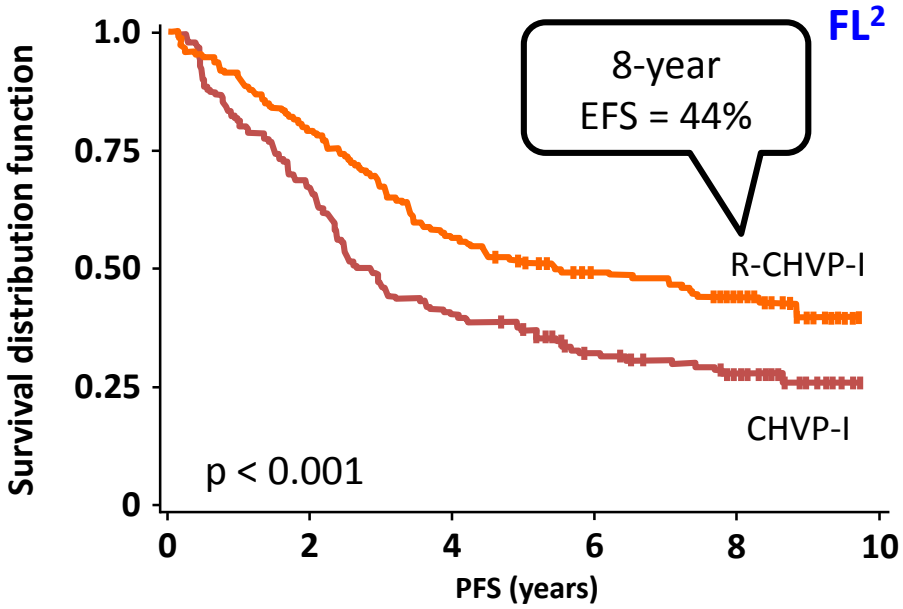

Fisher RI, et al. N Engl J Med 1993;328:1002–6

# Addition of rituximab to chemotherapy improves PFS and OS across B cell malignancies

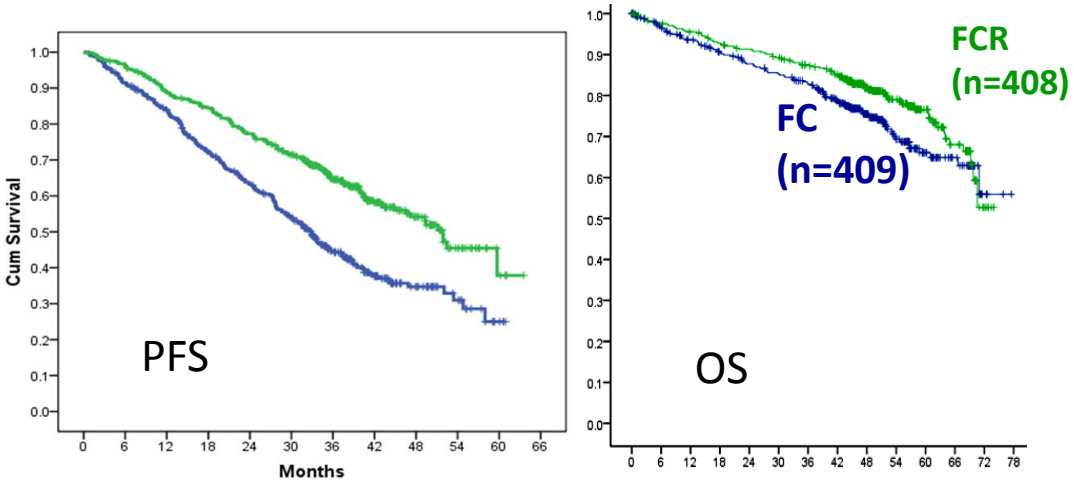
**DLBCL[1]**




**FL[2]**



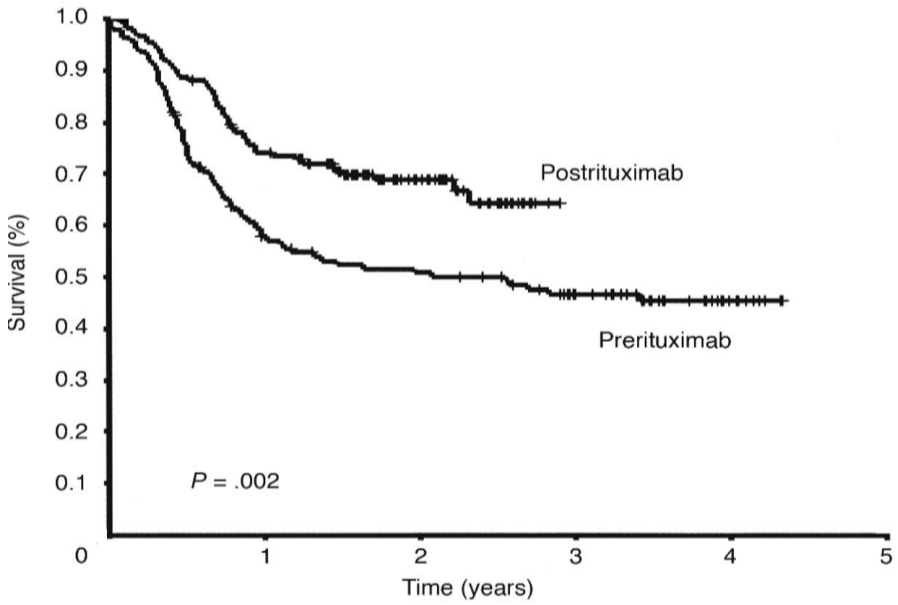

**CLL[3]**



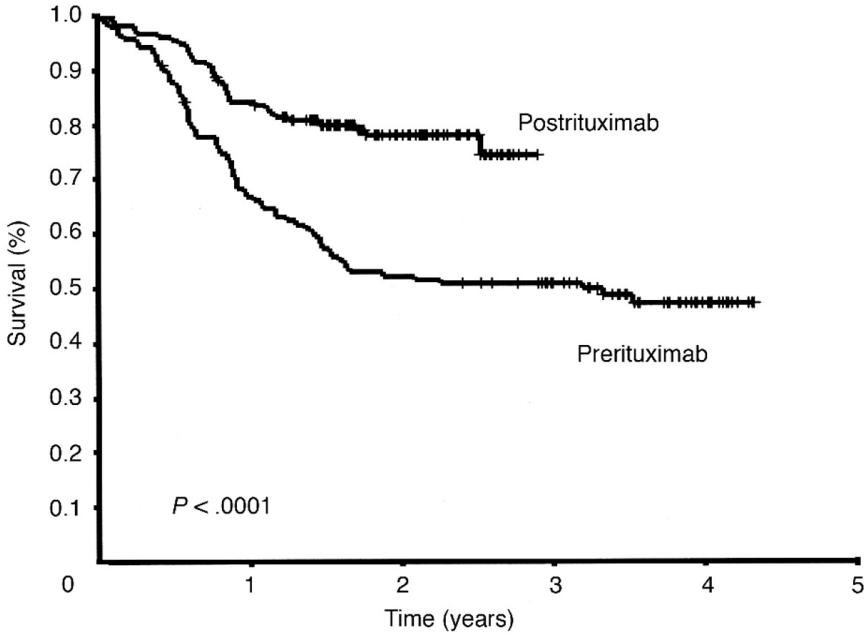


1. Coiffier B, et al. Blood. 2010;116:2040-5.
2. Bachy E, et al. Haematologica. 2013; epub May
3. Hallek et al, Lancet 2010

# Introduction of Combined CHOP Plus Rituximab Therapy Dramatically Improved Outcome of Diffuse Large B-Cell Lymphoma in British Columbia



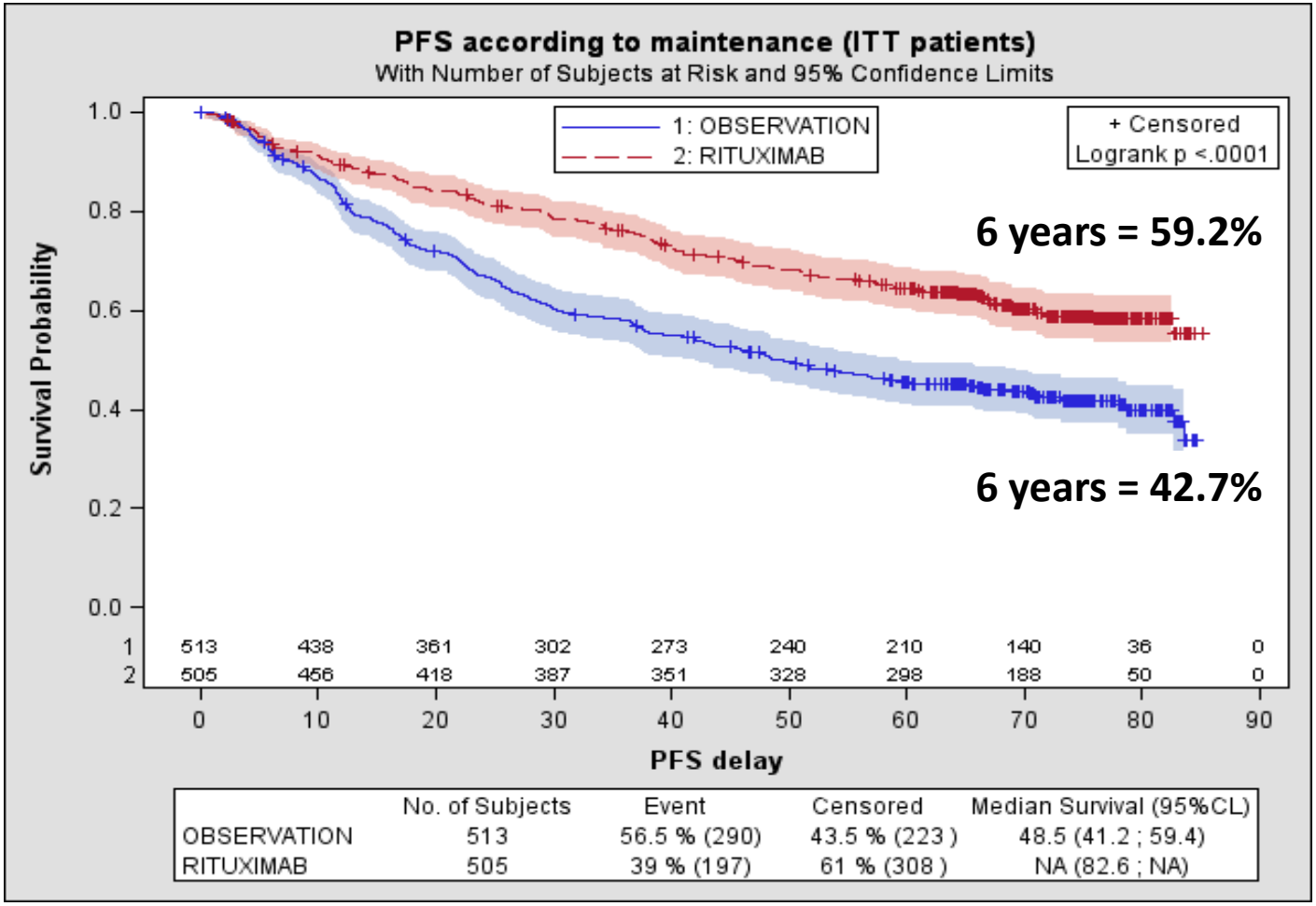

**PFS**




**OS**

Sehn et al J Clin Oncol 2005 23(22): 5027-33

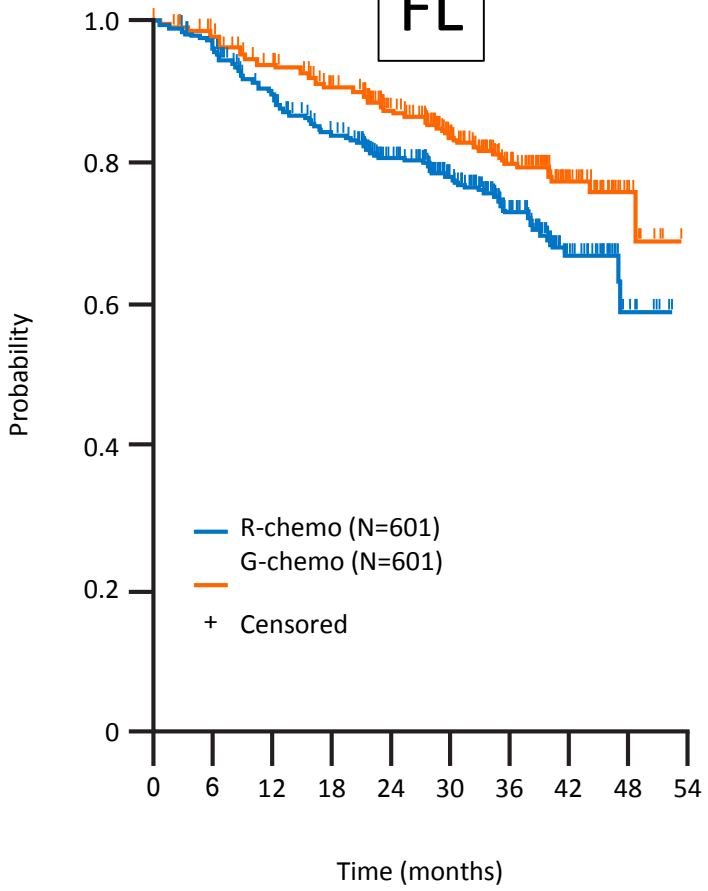
# Rituximab maintenance in FL



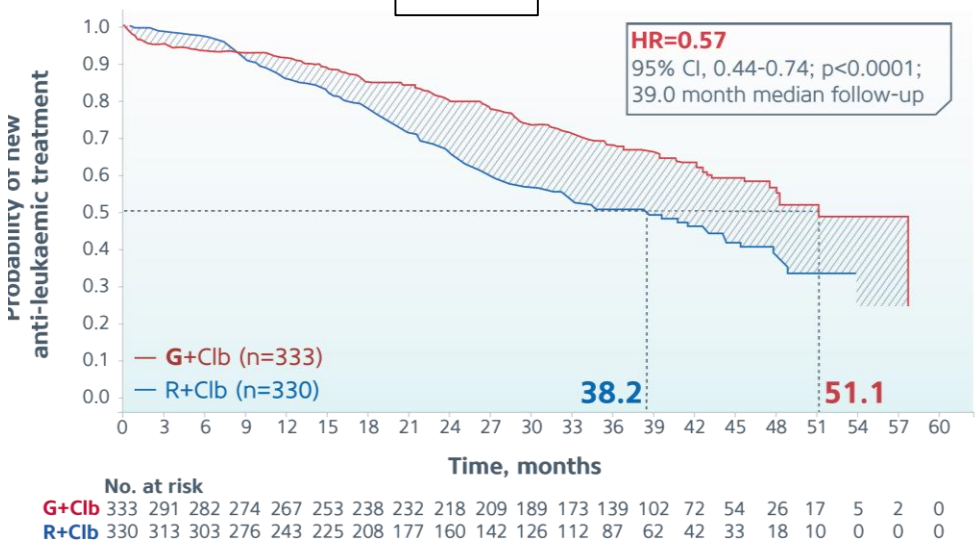

Median follow-up since randomization : 73 months

# New generation Anti-CD20 antibodies may be more effective

FL




CLL

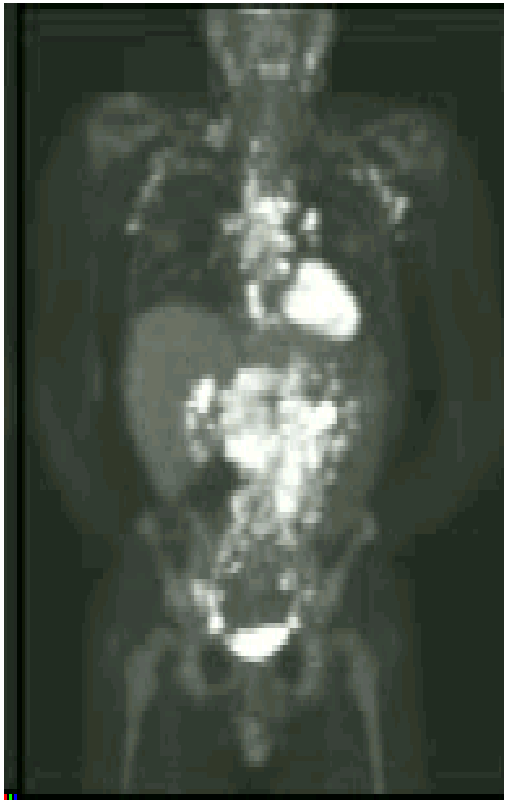


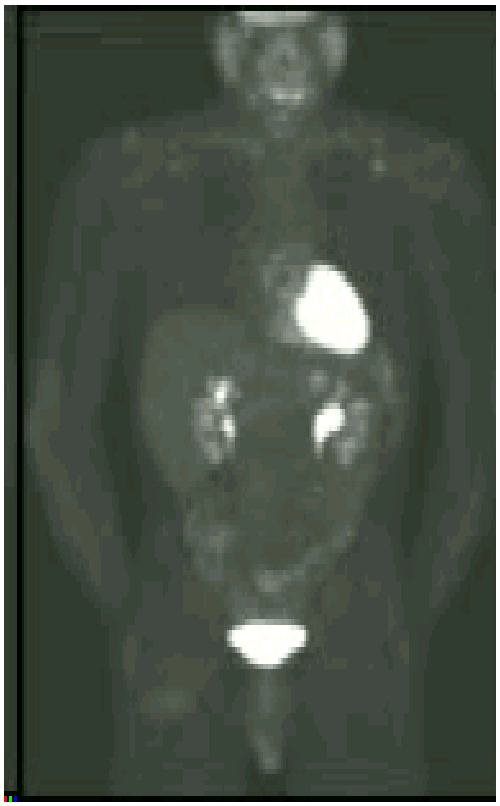

G-CHEMO superior to R-CHEMO in CLL and FL

*Marcus et al NEJM 2017*

*Goede et al NEJM 2013*

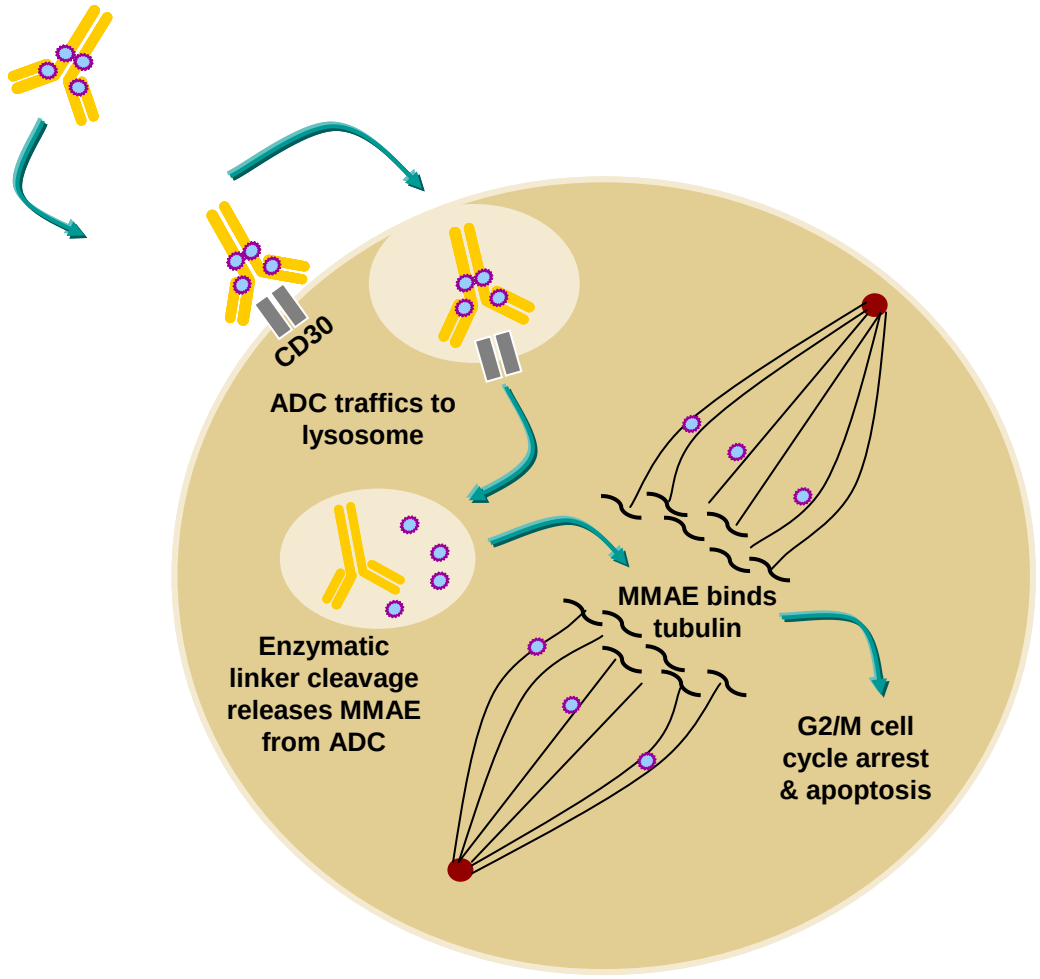
# Radio-Immunotherapy
# Tumour Response with Zevalin®





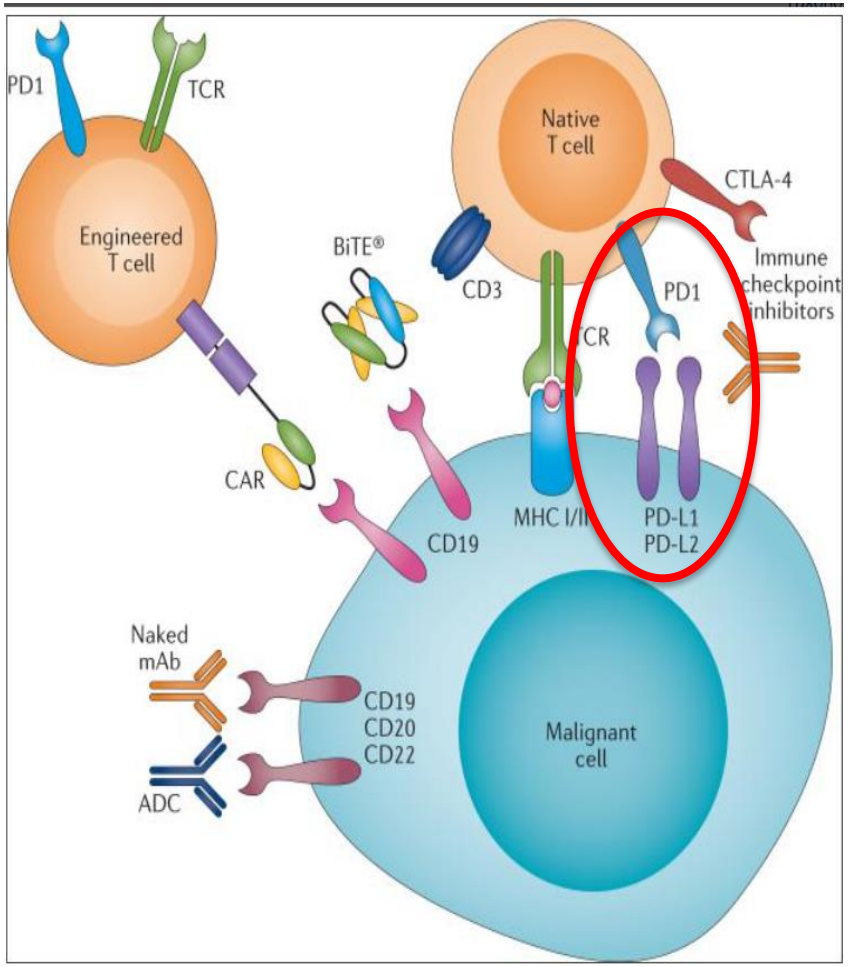
# Immuno-conjugates
# Brentuximab Vedotin

- SGN-35 antibody-drug conjugate
  - CD30-targeted antibody (cAC10) conjugated to an auristatin (MMAE), an anti-tubulin agent
  - Binds to CD30
  - Becomes internalized
  - Releases MMAE
- Effective in HL and ALCL



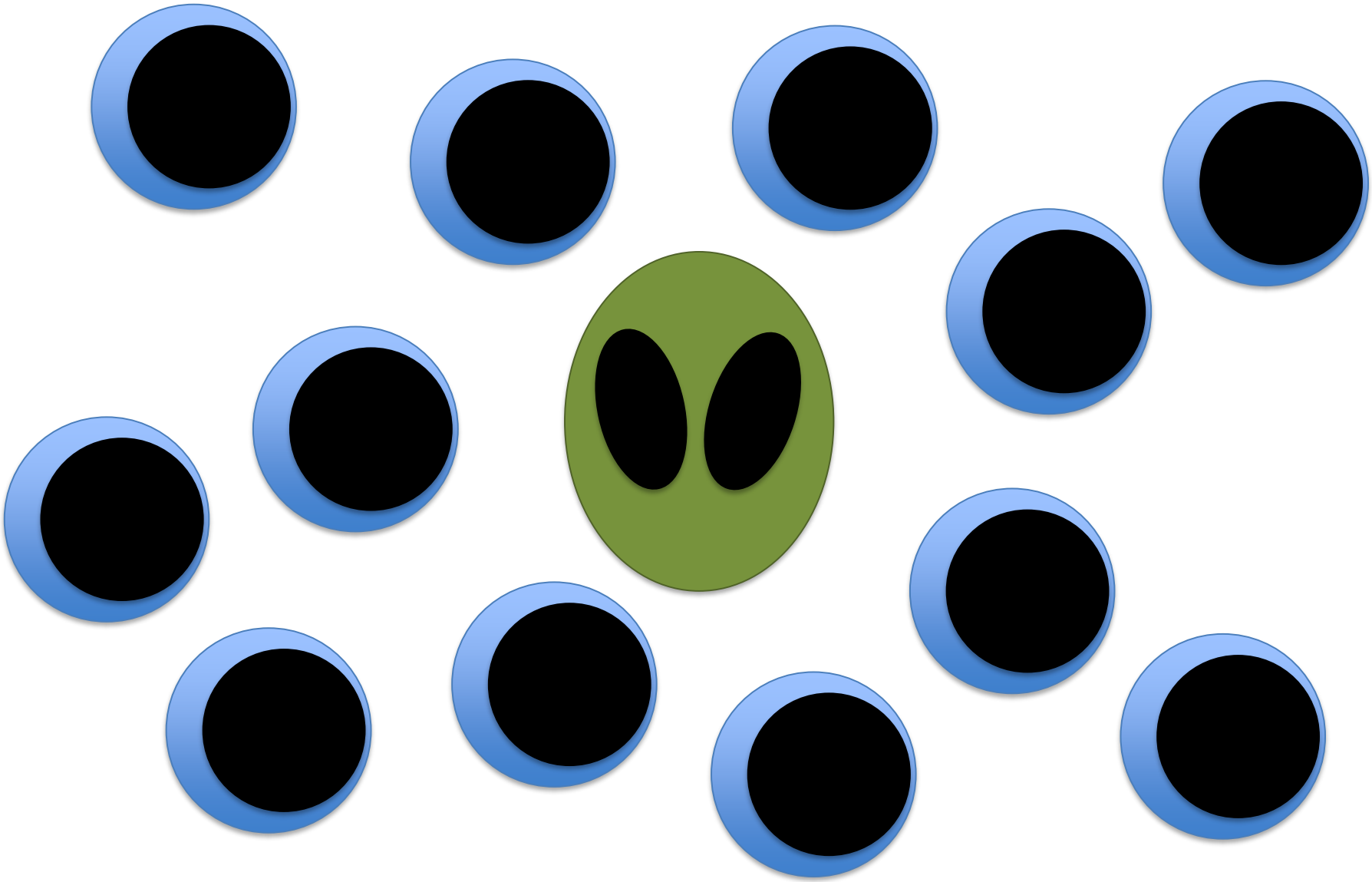
# Targeting the Immune System

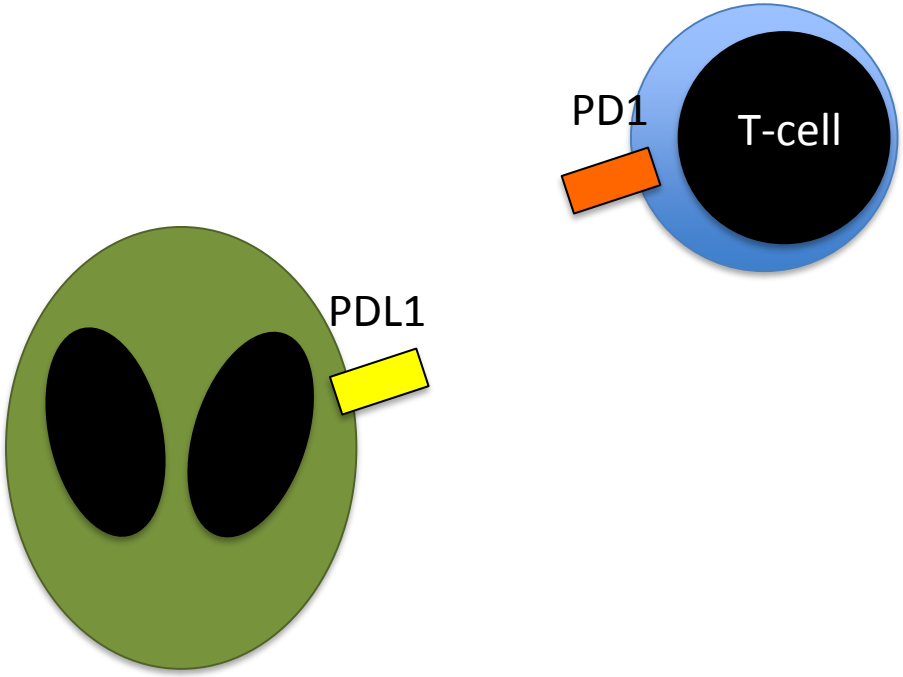
- Antibodies which target key immune interactions
- PD1 is an immune checkpoint protein and signalling via this pathway leads to T-cell exhaustion and limits the immune response
- Tumour cells avoid immune destruction by expressing PD1-ligands on the surface
- PD1/ PDL1 'check-point' inhibitors render cells sensitive to a T-cell immune response
  - Nivolumab
  - Pembrolizumab
- Highly active in HL, less so as monotherapy for other lymphomas
- Useful for rare types: Primary CNS lymphoma, PMBCL, NK/T cell



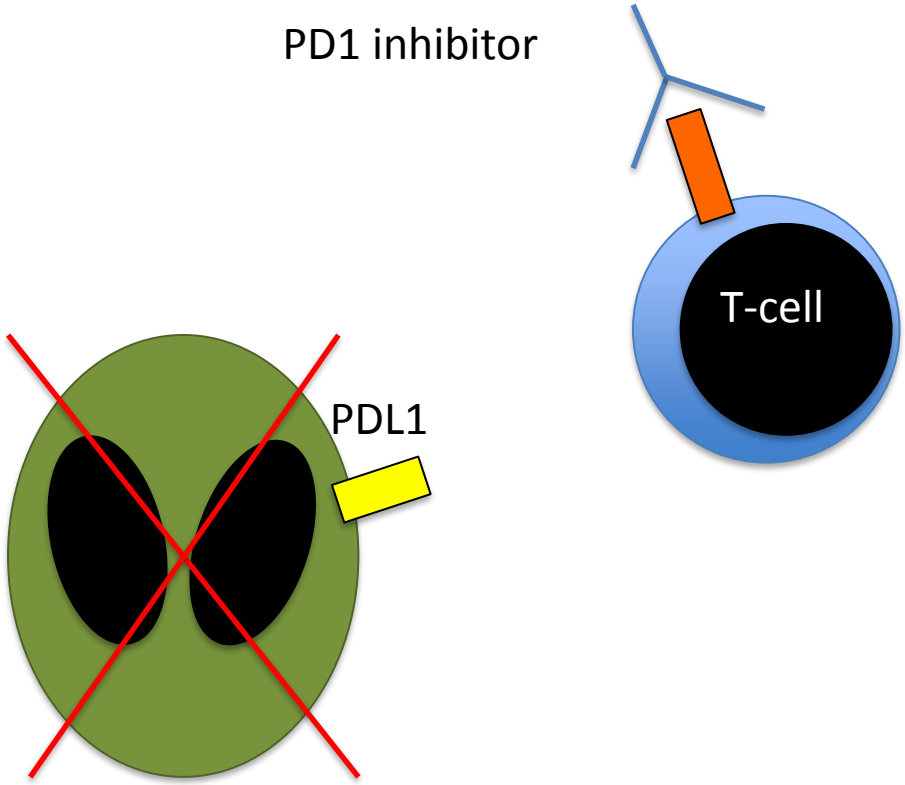

Batlevi et al. Nat Rev Clin Oncol. 2016 Jan; 13( 40.

# Hodgkin lymphoma




PD1
T-cell
PDL1

# Enter PD1 inhibitors



# Monoclonal Antibodies: Summary

- Activity as single agents
- Increased efficacy when combined with chemotherapy
- Immuno-chemotherapy combinations superior to chemotherapy alone
- Prolonged use may improve remisssion duration
- May be active against high risk/ chemo-resistant cases
- Can be used to ‘deliver’ a payload (radiotherapy, toxins)
- Can be used to ‘target’ non-malignant cells in order to ‘activate’ the immune system

# New treatment paradigms

- Effective in all patient subgroups
  - Those with co-morbidities (older)
  - Those with genetic abnormalities that confer resistance
  - Those refractory to standard therapy
- Selective targeted treatment
  - Able to identify specific patients who will most benefit
  - Able to enhance existing therapies
- Non-toxic/ tolerable
- Easy to administer (oral)
- Mechanisms of resistance understood
- Cost-effective

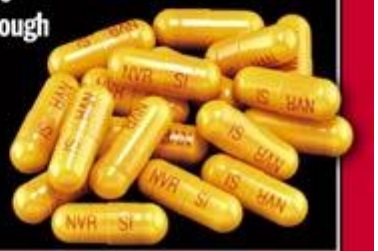
# Small molecule Inhibitors

MAY 28, 2001 www.time.com AOL Keyword: TIME

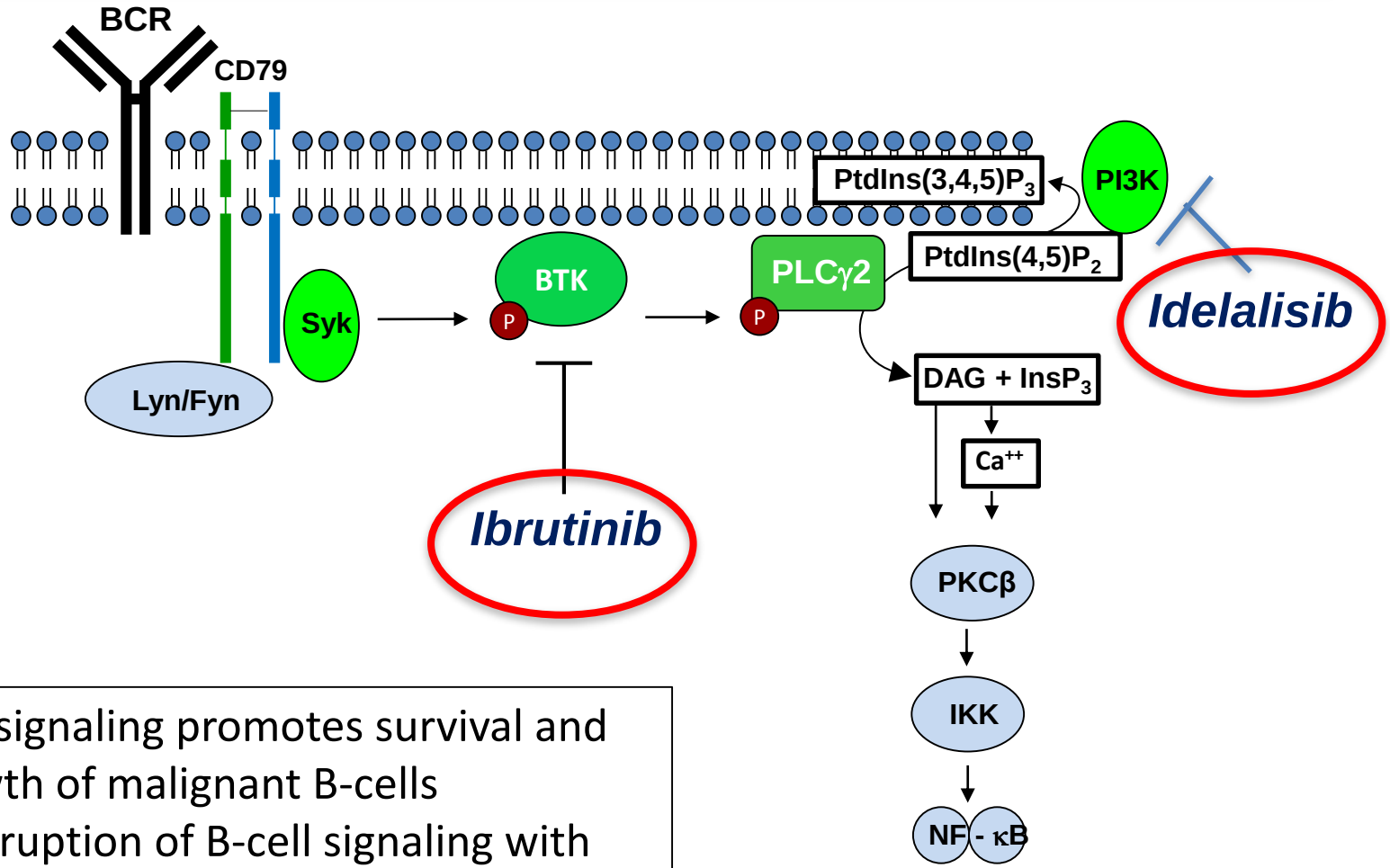
# TIME

## THERE IS NEW AMMUNITION IN THE WAR AGAINST CANCER. THESE ARE THE BULLETS.

Revolutionary new pills like GLEEVEC combat cancer by targeting only the diseased cells. Is this the breakthrough we've been waiting for?

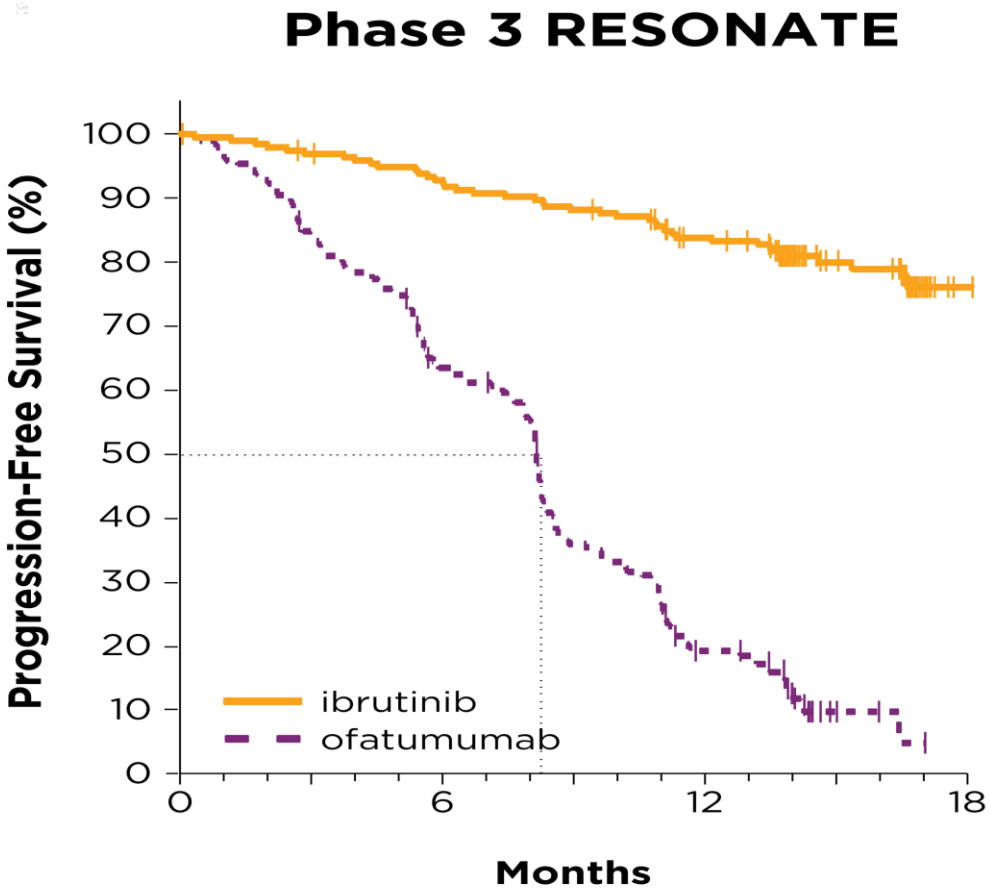


# Targeting B-Cell Signaling
# A Simplified BCR Signaling Pathway




- BCR signaling promotes survival and growth of malignant B-cells
- Interruption of B-cell signaling with oral inhibitors can cause cell death

# Treatment for Relapsed/Refractory CLL Resonate Trial : Ibrutinib vs Ofatumumab- PFS




- 16 months median follow-up for ibrutinib vs. 12 months for ofatumumab
- 12-month PFS rate significantly improved for ibrutinib vs. ofatumumab (84% vs. 18%, *P*<0.001)
- 12-month OS rate was 90% for ibrutinib

| | ofatumumab N=196 | ibrutinib N=195 |
|---|---|---|
| Median PFS (mo) | 8.1 | NR |
| Hazard ratio | 0.106 | |
| (95% CI) | (0.073-0.153) | |
| *P* value | <0.001 | |

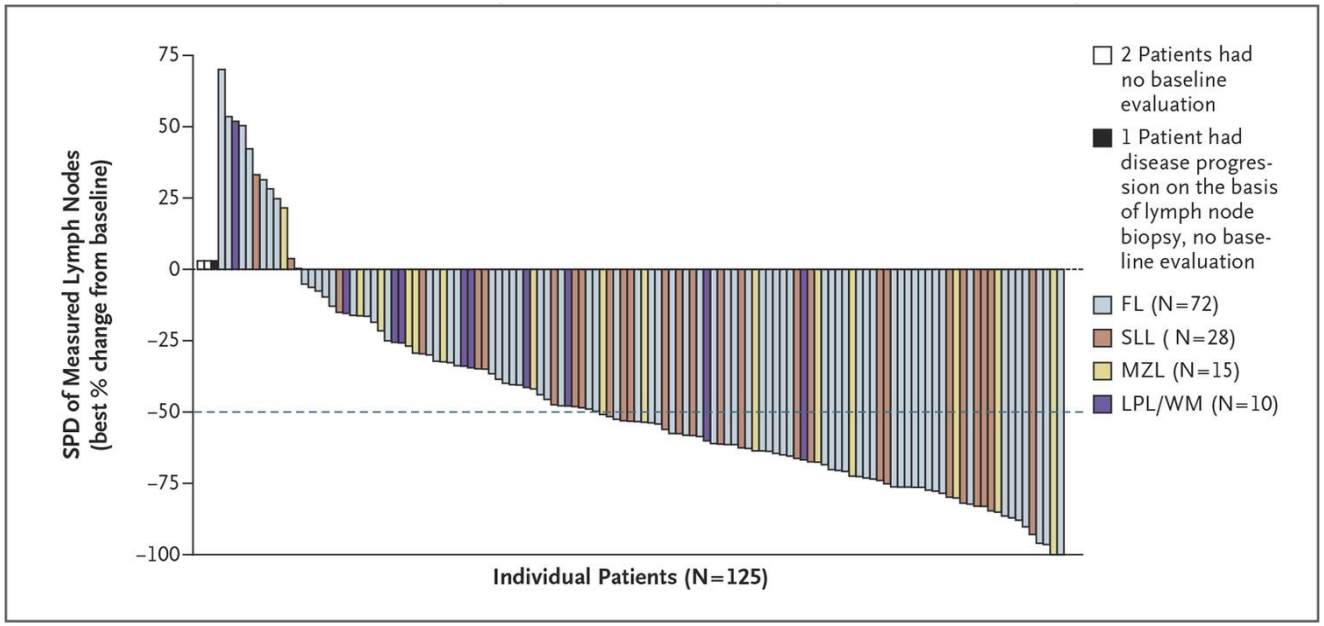
Byrd et al NEJMed 2013

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

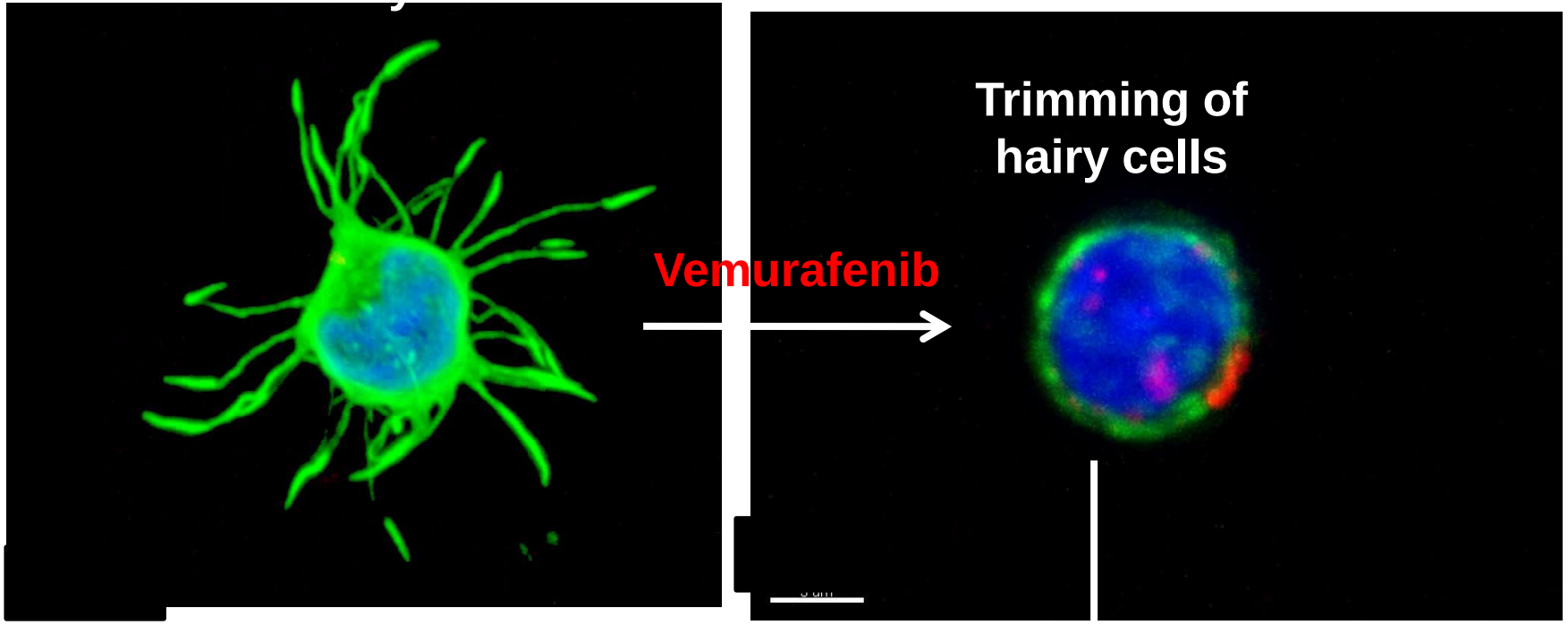
# PI3Kδ Inhibition by Idelalisib in Patients with Relapsed Indolent Lymphoma

Ajay K. Gopal, M.D., Brad S. Kahl, M.D., Sven de Vos, M.D., Ph.D., Nina D. Wagner-Johnston, M.D., Stephen J. Schuster, M.D., Wojciech J. Jurczak, M.D., Ph.D., Ian W. Flinn, M.D., Ph.D., Christopher R. Flowers, M.D., Peter Martin, M.D., Andreas Viardot, M.D., Kristie A. Blum, M.D., Andre H. Goy, M.D., Andrew J. Davies, M.R.C.P., Ph.D.,

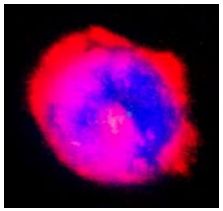


# Targeting Genes
# BRAF Mutations and Inhibition in HCL

Virtually all patients with Hairy cell leukaemia have BRAF mutation and respond to BRAF inhibitors



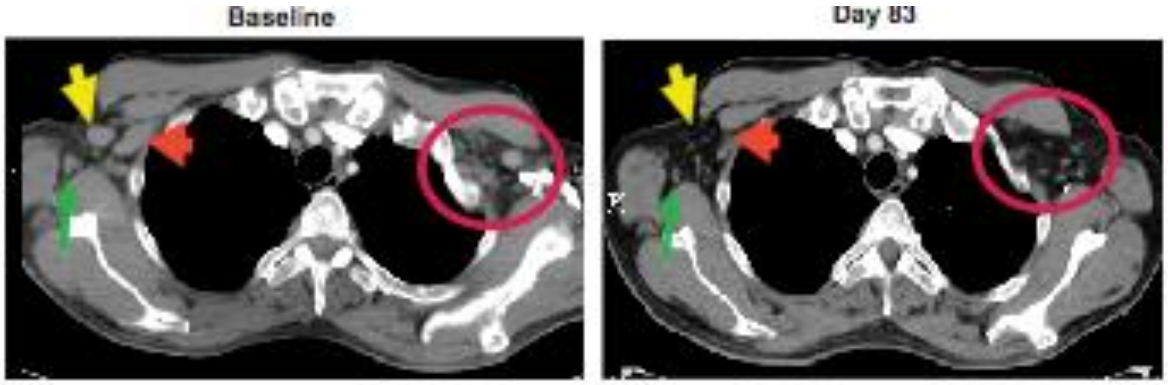

**Cell death**

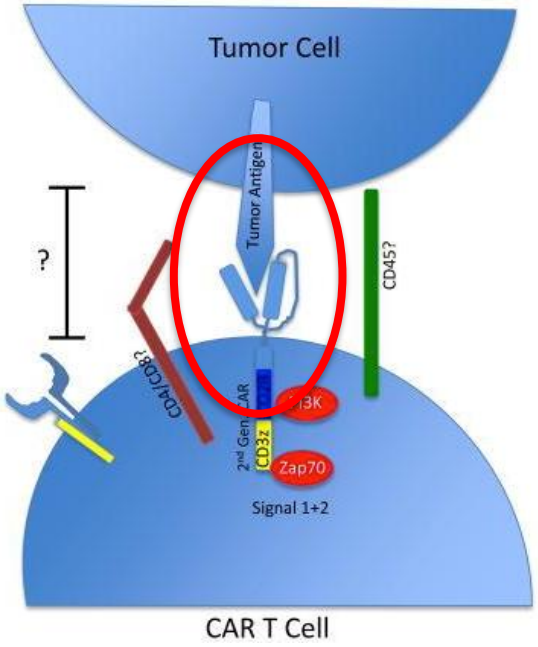


# Cellular therapies

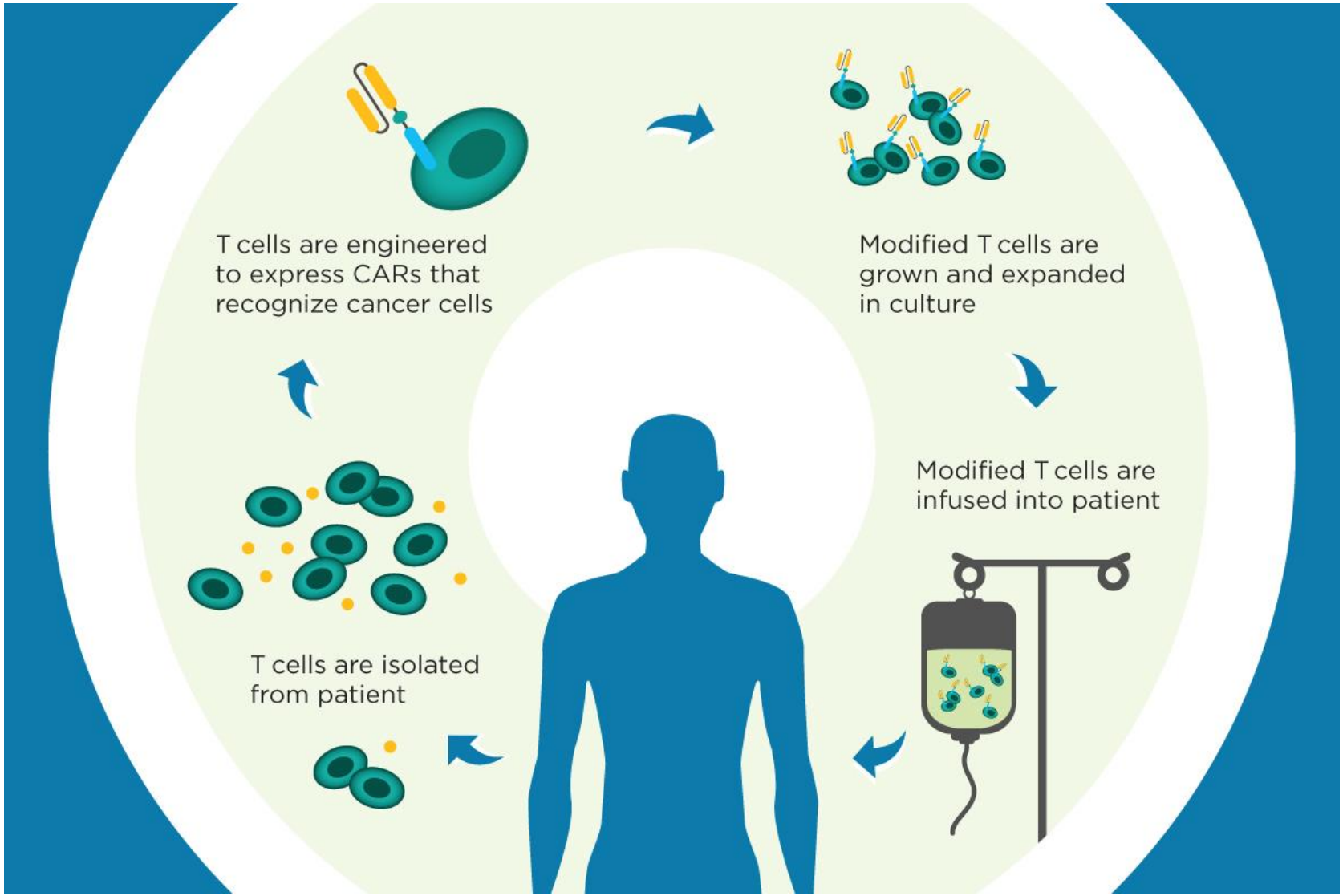
# Chimeric Antigen Receptor (CAR)–Modified T Cells ‘A drug for life’

- CAR-T cells are autologous or allogeneic T-cells genetically engineered to express a chimeric antigen receptor (CAR) targetted to a specific tumour associated antigen expressed on the cancer cell surface
- CAR-T combine advantages of:
  - Antibody therapy (specificity)
  - Cellular therapy (amplification)
  - Vaccine therapy (persistence)



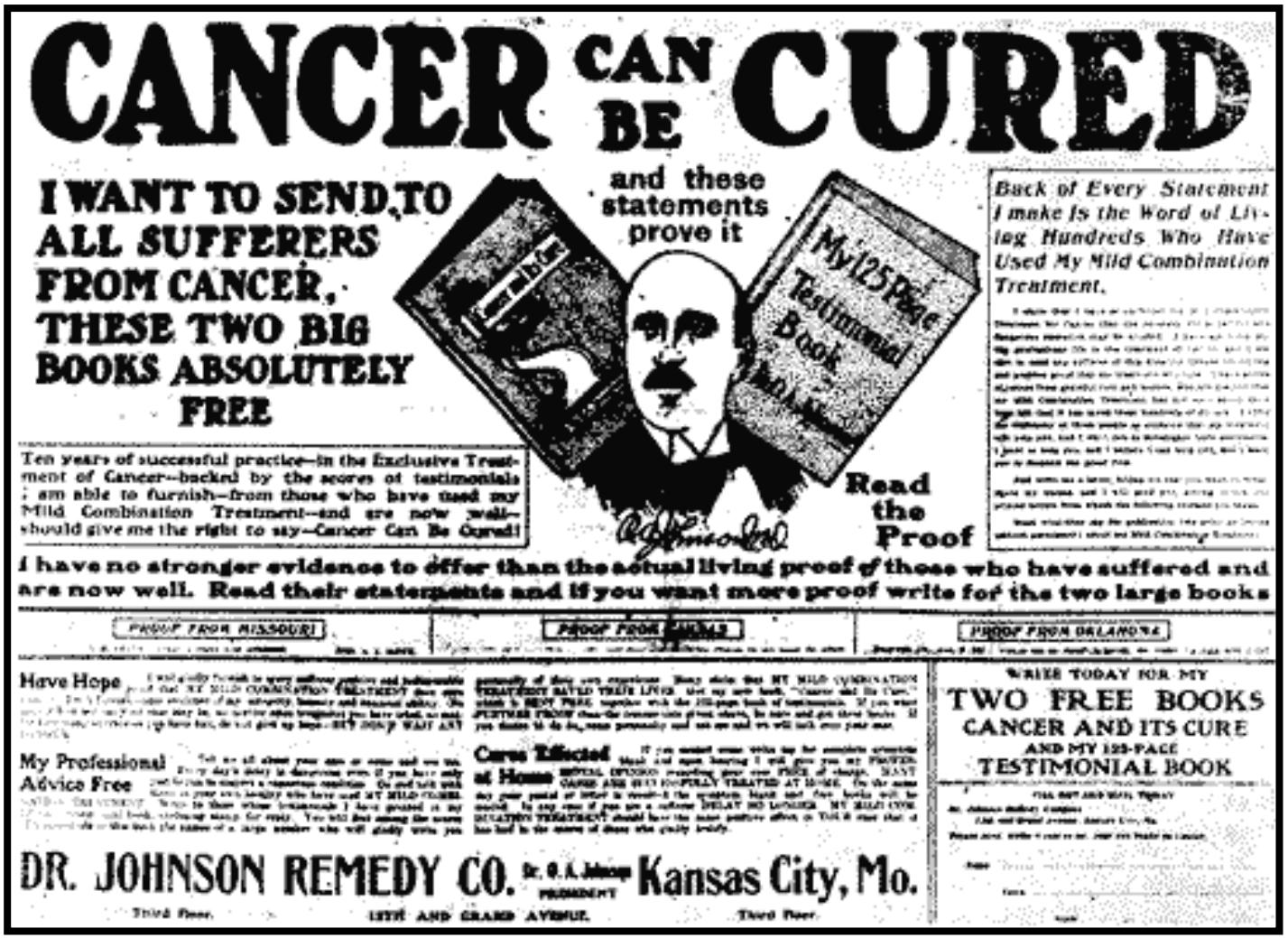



# CAR-T cell Immunotherapy in lymphoma



# Beyond 2017

- There has been a staggering improvement in survival for patients with lymphoid malignancies over the past 15 years
- There are remaining questions to address in the future:
  - How do the new drugs compare to current standard therapies?
  - How can they be combined?
  - Can small molecule inhibitors ever be stopped and if so after how long?
  - What are the immediate and long-term side effects of these new therapies and how do we prevent and manage them?
  - Will patients become resistant to these therapies?
  - How do we afford them?!




**With thanks to all the patients and their carers who have made these advances possible by entering into clinical studies, raising money for research and being advocates within the community**