Overview of NHL, HL and CLL

Lymphoma Support Group December 7, 2021

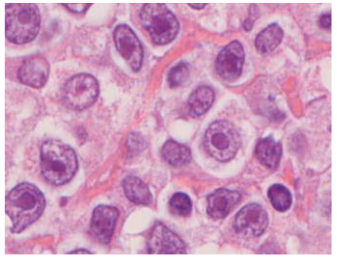
Dr. Carolyn Faught

Overview of NHL, HL, CLL

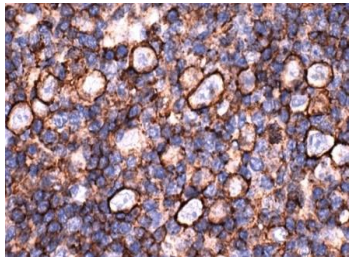
- Improving diagnostics
- Trends in Incidence
- Types of Lymphoma
- Evolving treatments
- Immunotherapy

Lymphoma Diagnosis – need tissue biopsy

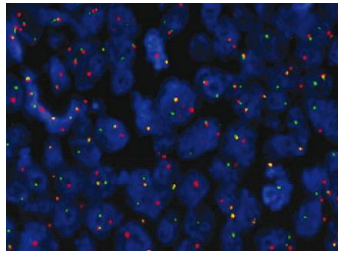
✓Morphology



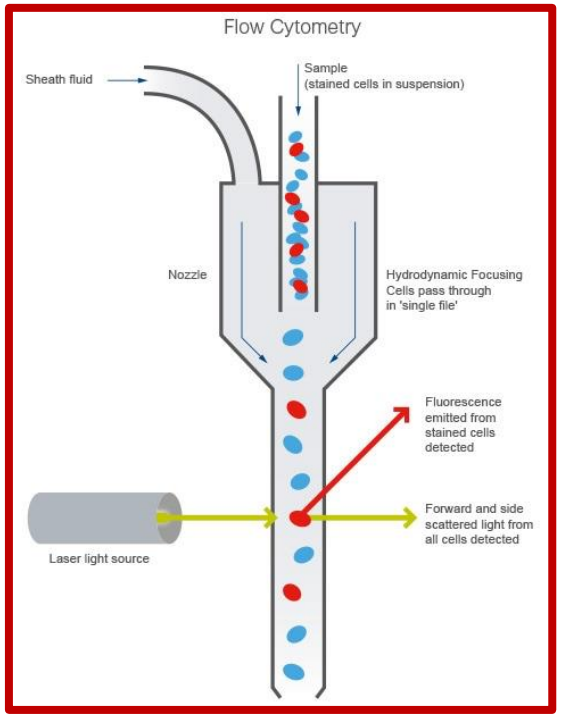
✓Immunohistochemistry



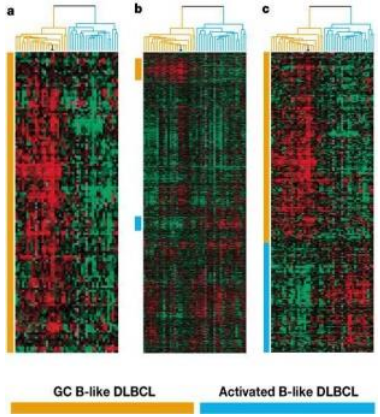
✓Cytogenetics/FISH



✓Flow cytometry



- gene expression profiling



Current Lymphoma Classification
WHO – 2016 Revision

There are over 60 types of lymphoma.

Hodgkin lymphoma

Mature B-cell neoplasms (41 types)

Mature T-cell & NK-cell neoplasms (27 types)

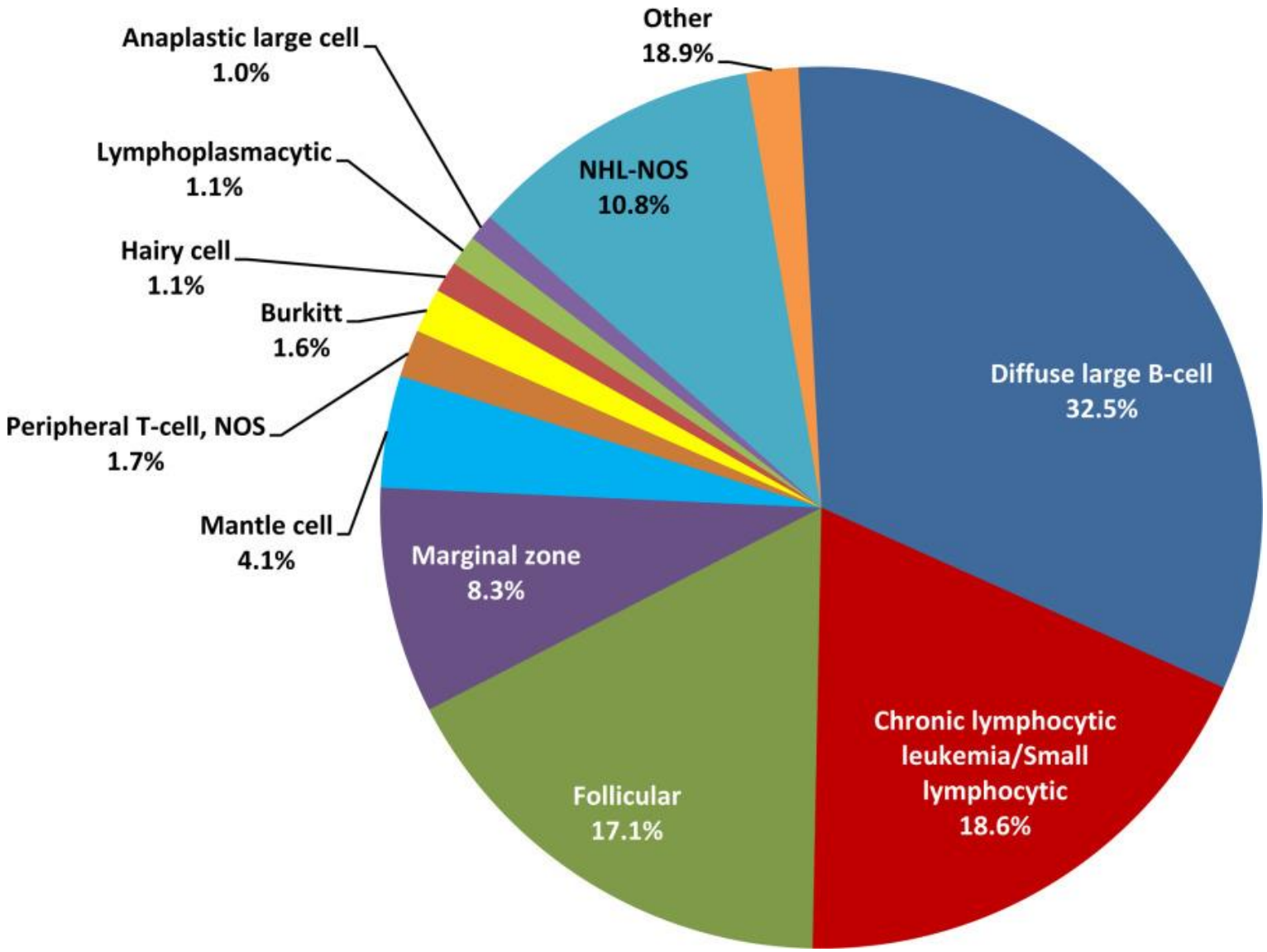
Non Hodgkin B Cell

- Chronic lymphocytic leukemia/small lymphocytic lymphoma
- Monoclonal B-cell lymphocytosis*
- B-cell prolymphocytic leukemia
- Splenic marginal zone lymphoma
- Hairy cell leukemia
    - Splenic B-cell lymphoma/leukemia, unclassifiable
    - Splenic diffuse red pulp small B-cell lymphoma
    - Hairy cell leukemia-variant
- Lymphoplasmacytic lymphoma
    - Waldenström macroglobulinemia
- Monoclonal gammopathy of undetermined significance (MGUS), IgM*
- μ heavy-chain disease
- γ heavy-chain disease
- α heavy-chain disease
- Monoclonal gammopathy of undetermined significance (MGUS), IgG/A*
- Plasma cell myeloma
- Solitary plasmacytoma of bone
- Extraosseous plasmacytoma
- Monoclonal immunoglobulin deposition diseases*
- Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
- Nodal marginal zone lymphoma
    - Pediatric nodal marginal zone lymphoma
- Follicular lymphoma
    - In situ follicular neoplasia*
    - Duodenal-type follicular lymphoma*
- Pediatric-type follicular lymphoma*
- Large B-cell lymphoma with IRF4 rearrangement*
- Primary cutaneous follicle center lymphoma
- Mantle cell lymphoma
- In situ mantle cell neoplasia*
- Diffuse large B-cell lymphoma (DLBCL), NOS
- Germinal center B-cell type*
- Activated B-cell type*
- T-cell/histiocyte-rich large B-cell lymphoma
- Primary DLBCL of the central nervous system (CNS)
- Primary cutaneous DLBCL, leg type
- EBV+ DLBCL, NOS*
- EBV+ mucocutaneous ulcer*
- DLBCL associated with chronic inflammation
- Lymphomatoid granulomatosis
- Primary mediastinal (thymic) large B-cell lymphoma
- Intravascular large B-cell lymphoma
- ALK+ large B-cell lymphoma
- Plasmablastic lymphoma
- Primary effusion lymphoma
- HHV8+ DLBCL, NOS*
- Burkitt lymphoma
- Burkitt-like lymphoma with 11q aberration*
- High-grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 rearrangements*
- High-grade B-cell lymphoma, NOS*
- B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma

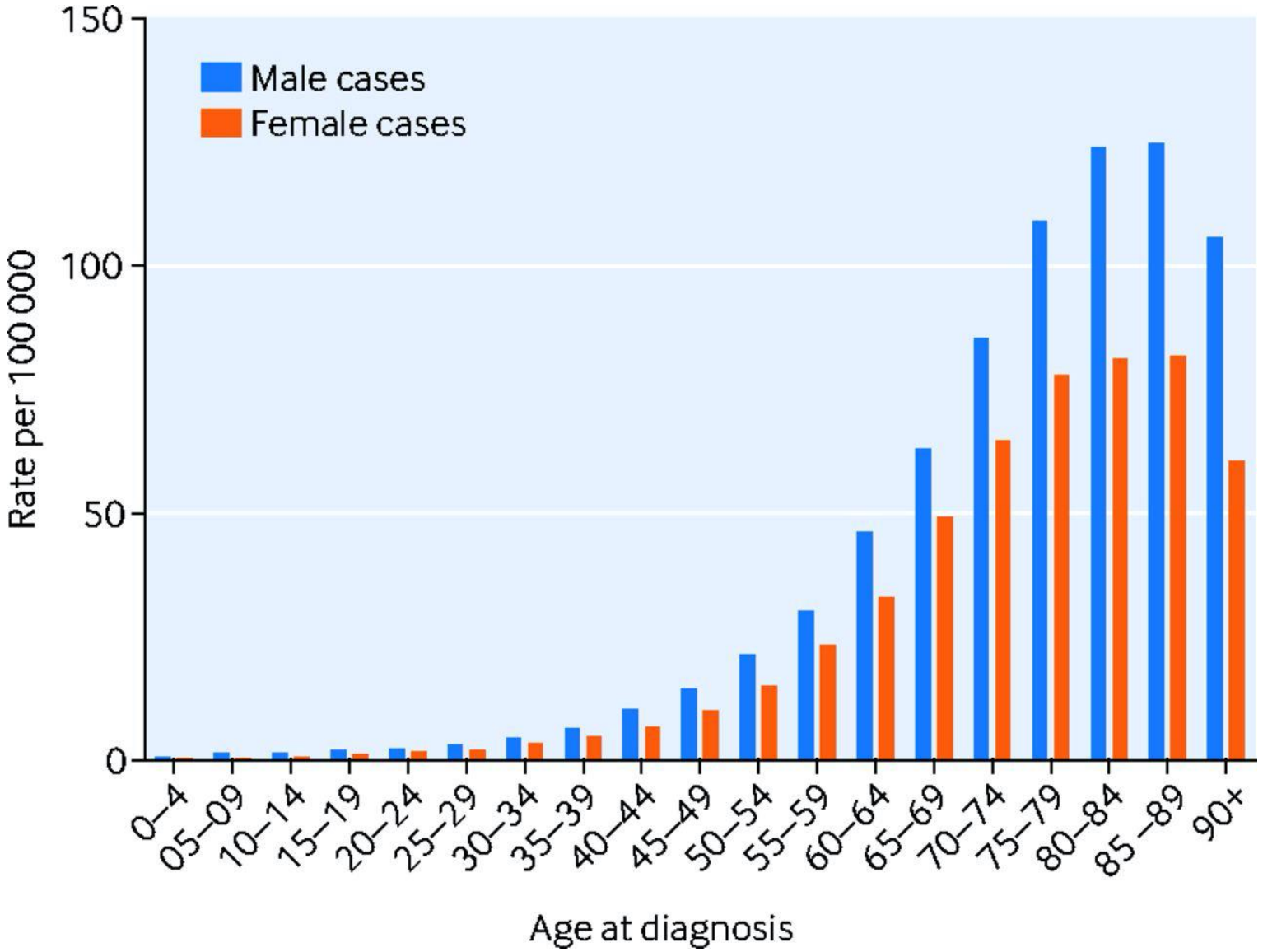
Non Hodgkin T Cell

- T-cell prolymphocytic leukemia
- T-cell large granular lymphocytic leukemia
- Chronic lymphoproliferative disorder of NK cells
- Aggressive NK-cell leukemia
- Systemic EBV+ T-cell lymphoma of childhood*
- Hydroa vacciniforme–like lymphoproliferative disorder*
- Adult T-cell leukemia/lymphoma
- Extranodal NK-/T-cell lymphoma, nasal type
- Enteropathy-associated T-cell lymphoma
- Monomorphic epitheliotropic intestinal T-cell lymphoma*
- Indolent T-cell lymphoproliferative disorder of the GI tract*
- Hepatosplenic T-cell lymphoma
- Subcutaneous panniculitis-like T-cell lymphoma
- Mycosis fungoides
- Sézary syndrome
- Primary cutaneous CD30+ T-cell lymphoproliferative disorders
    - Lymphomatoid papulosis
    - Primary cutaneous anaplastic large cell lymphoma
- Primary cutaneous γδ T-cell lymphoma
- Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma
- Primary cutaneous acral CD8+ T-cell lymphoma*
- Primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorder*
- Peripheral T-cell lymphoma, NOS
- Angioimmunoblastic T-cell lymphoma
- Follicular T-cell lymphoma*
- Nodal peripheral T-cell lymphoma with TFH phenotype*
- Anaplastic large-cell lymphoma, ALK+
- Anaplastic large-cell lymphoma, ALK−*
- Breast implant–associated anaplastic large-cell lymphoma*

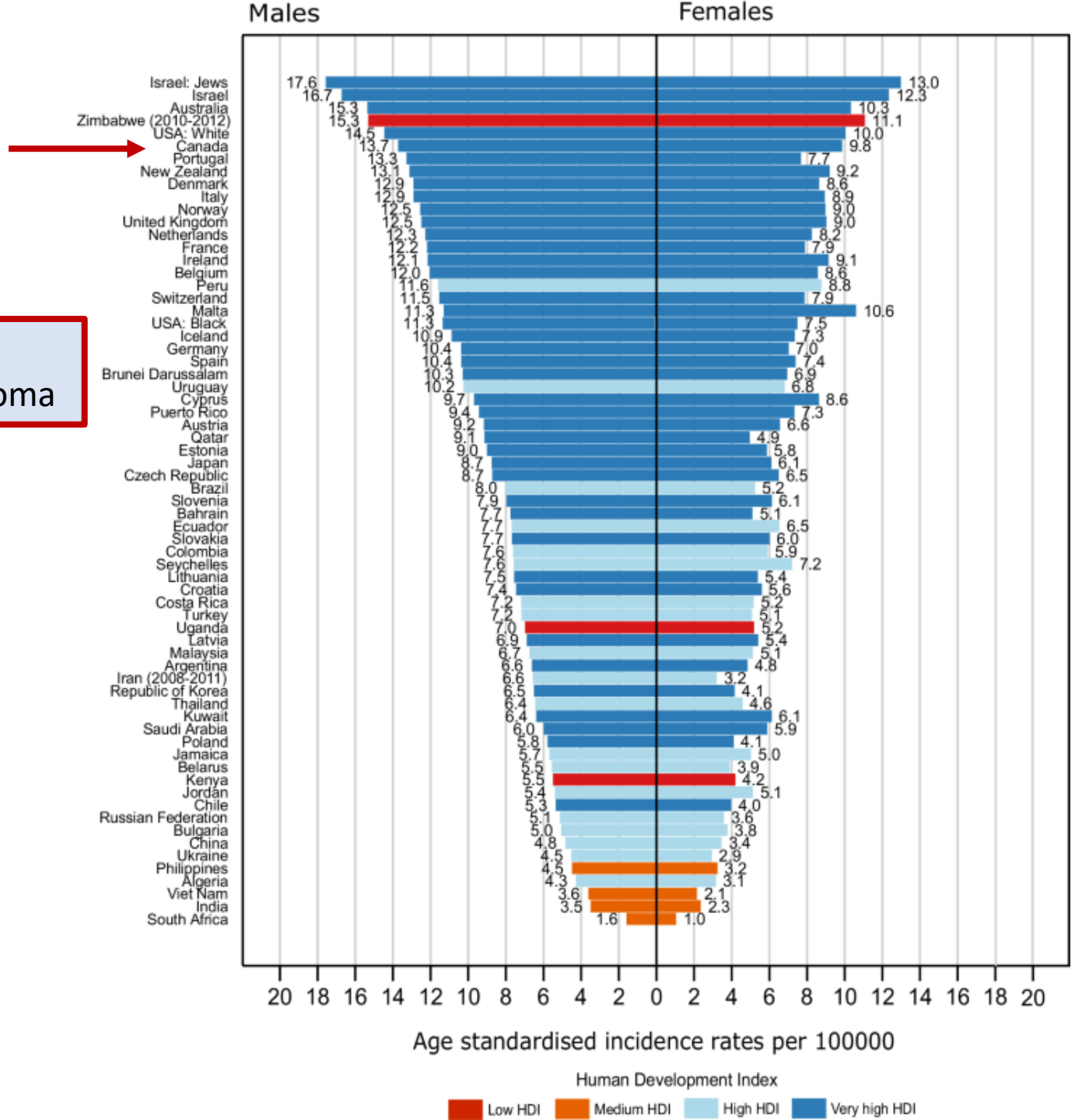
Non-Hodgkin Lymphoma Subtype Distribution

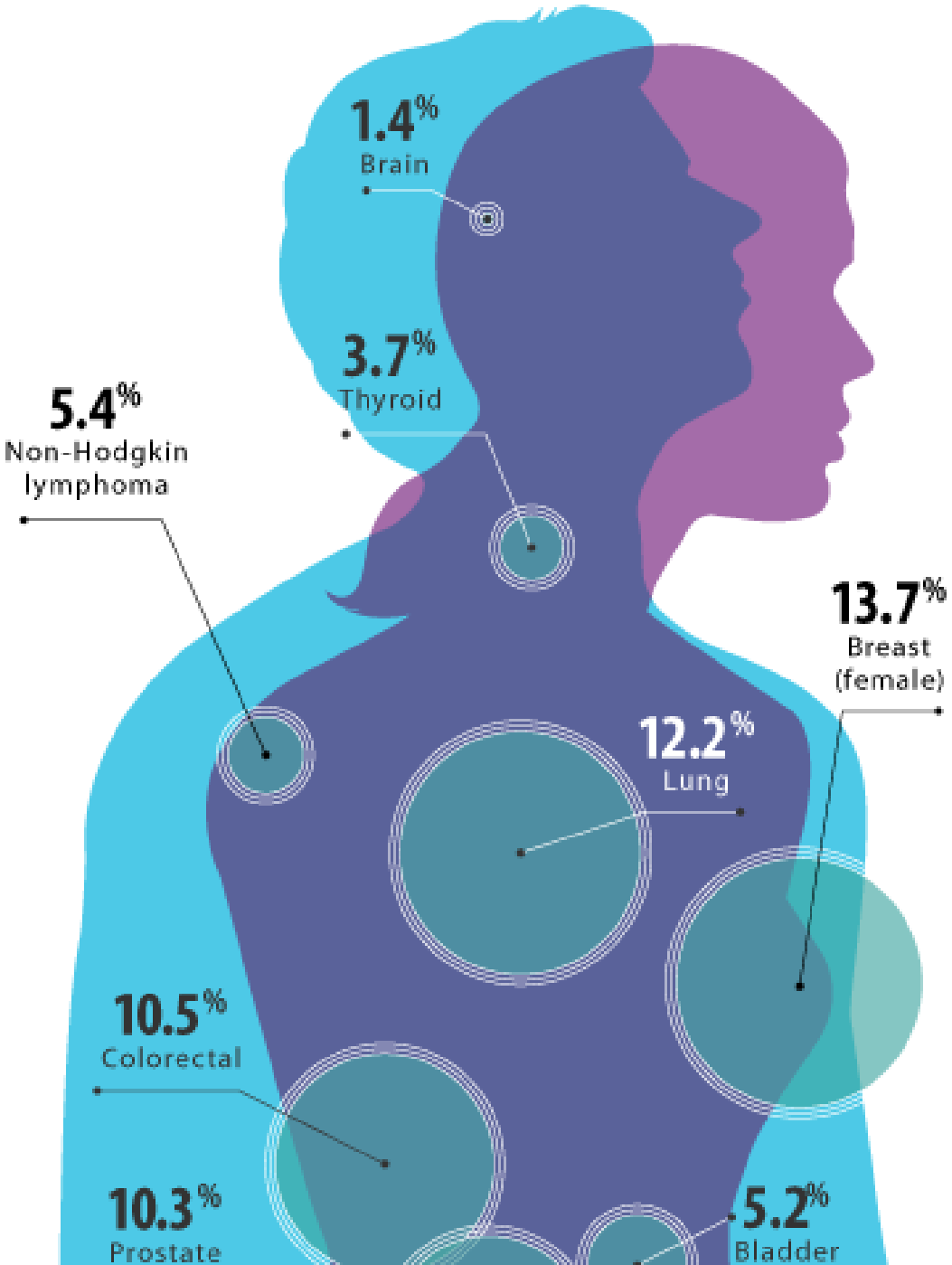


Increasing Age is a Risk Factor for NHL



Global Patterns and Trends in the Incidence of Non-Hodgkin's Lymphoma



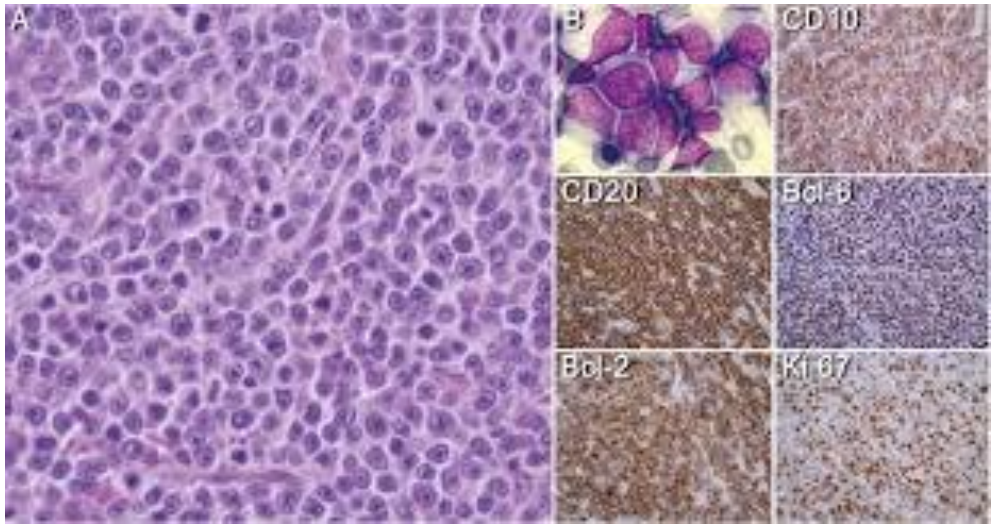


Cancer Incidence Rates – Cancer Care Ontario

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



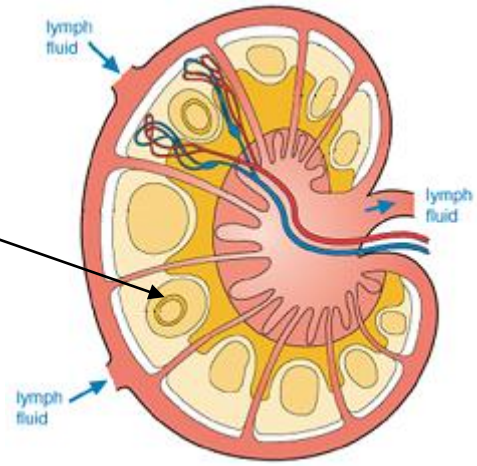
Diffuse large B cell (DLBCL) Subtypes

- 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*

* not treated with standard RCHOP

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 GBG-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.

All lymph nodes are signed out as GCB or non-GCB by using immunohistochemistry algorithm

Initial Work up for Aggressive NHL

- Blood work (CBC, liver, kidney function, glucose, hepatitis B)
- Echocardiogram
- CT neck/chest/abdo/pelvis for staging
- Pre-treatment PET CT – particularly good for extra-nodal disease. Also good as baseline to compare to final PET CT
- Bone marrow biopsy is now optional
- MRI brain/lumbar puncture for CSF analysis in specific cases

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 (became the global standard in 2002

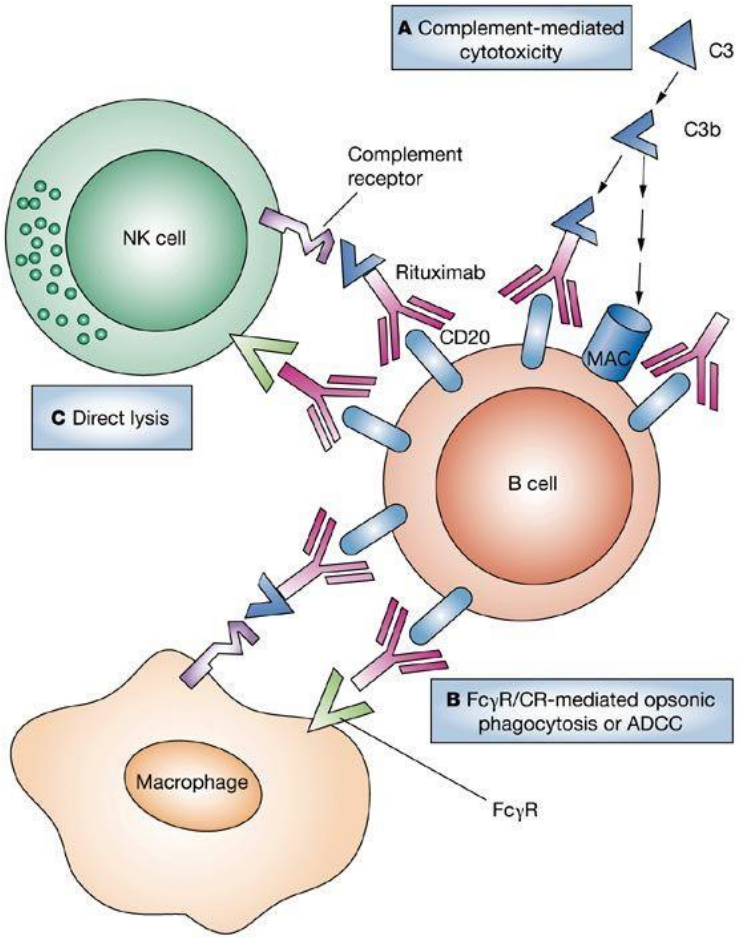
Regimen can be adjusted for the elderly (mini-RCHOP)
Ongoing trials trying to improve on RCHOP for the past 20 years

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
  - Now given subcutaneous



Benefit of RItuximab

Figure 1 – Overall survival RCHOP vs CHOP

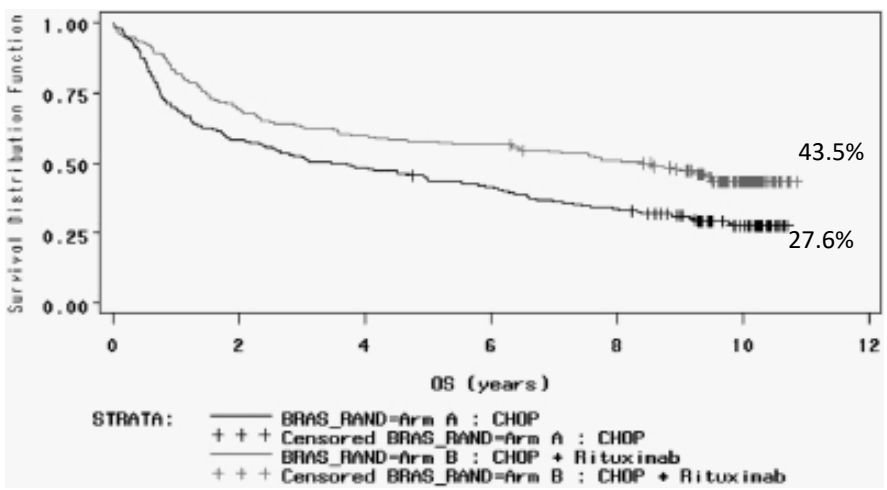
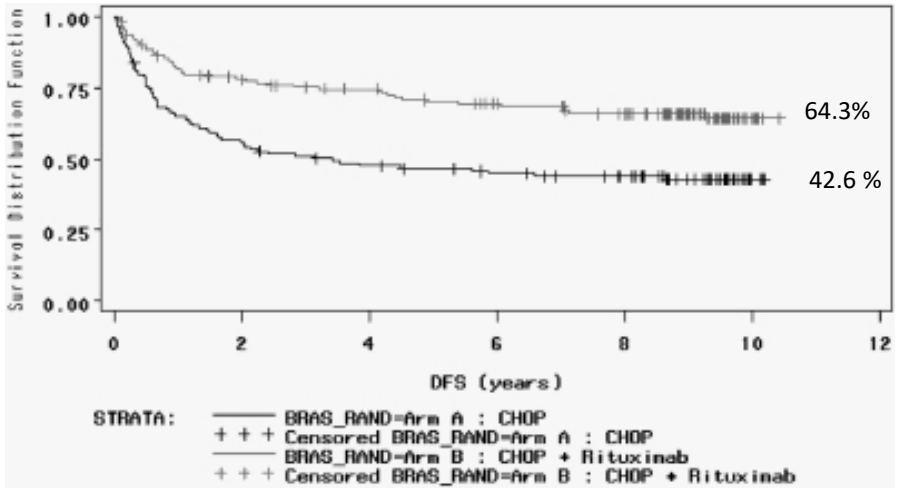


Figure 2. Disease-free survival in folks achieving CR RCHOP vs CHOP



Coiffier. *Blood* 2010 Sept 23 10 year follow up

Dose Adjusted R-EPOCH

- Used for double hit lymphoma, PMBCL
- 5 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

- -randomized controlled trial comparing to RCHOP showed no advantage in DLBCL

Double Hit Aggressive B cell Lymphoma

a) morphology

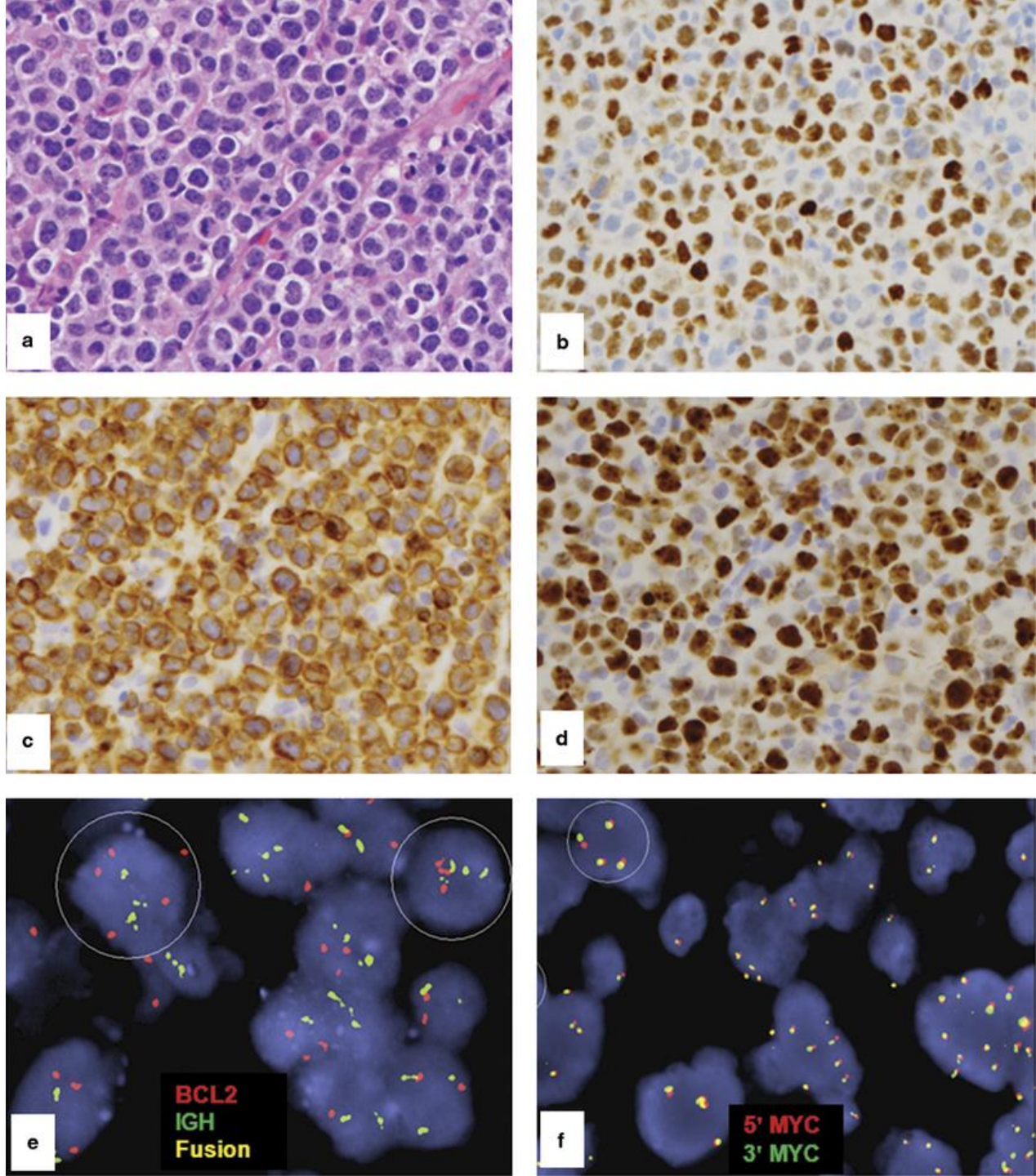
b) C-MYC

c) BCL-2

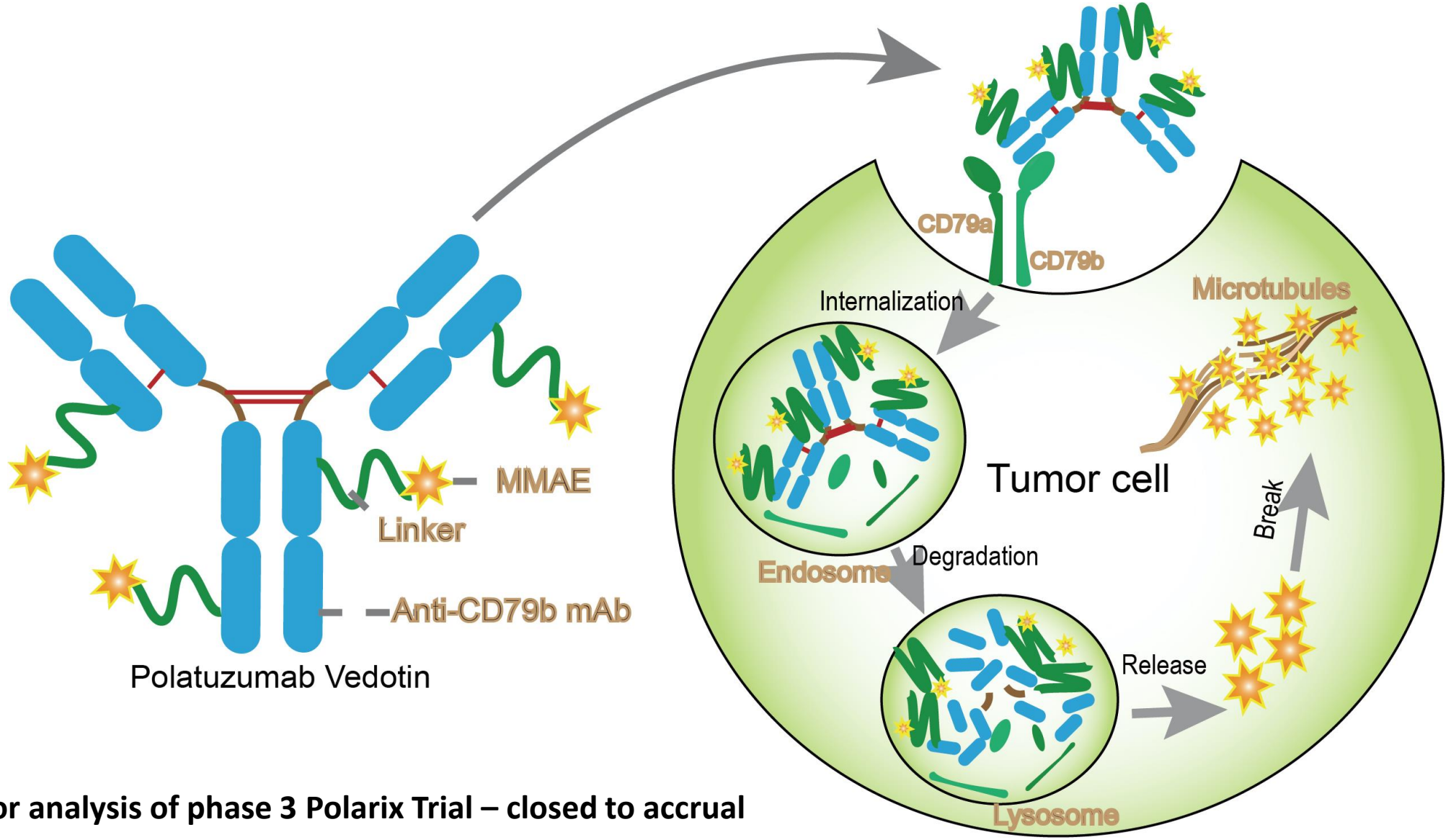
d) Proliferation index

e) FISH for BCL-2

f) FISH for CMYC

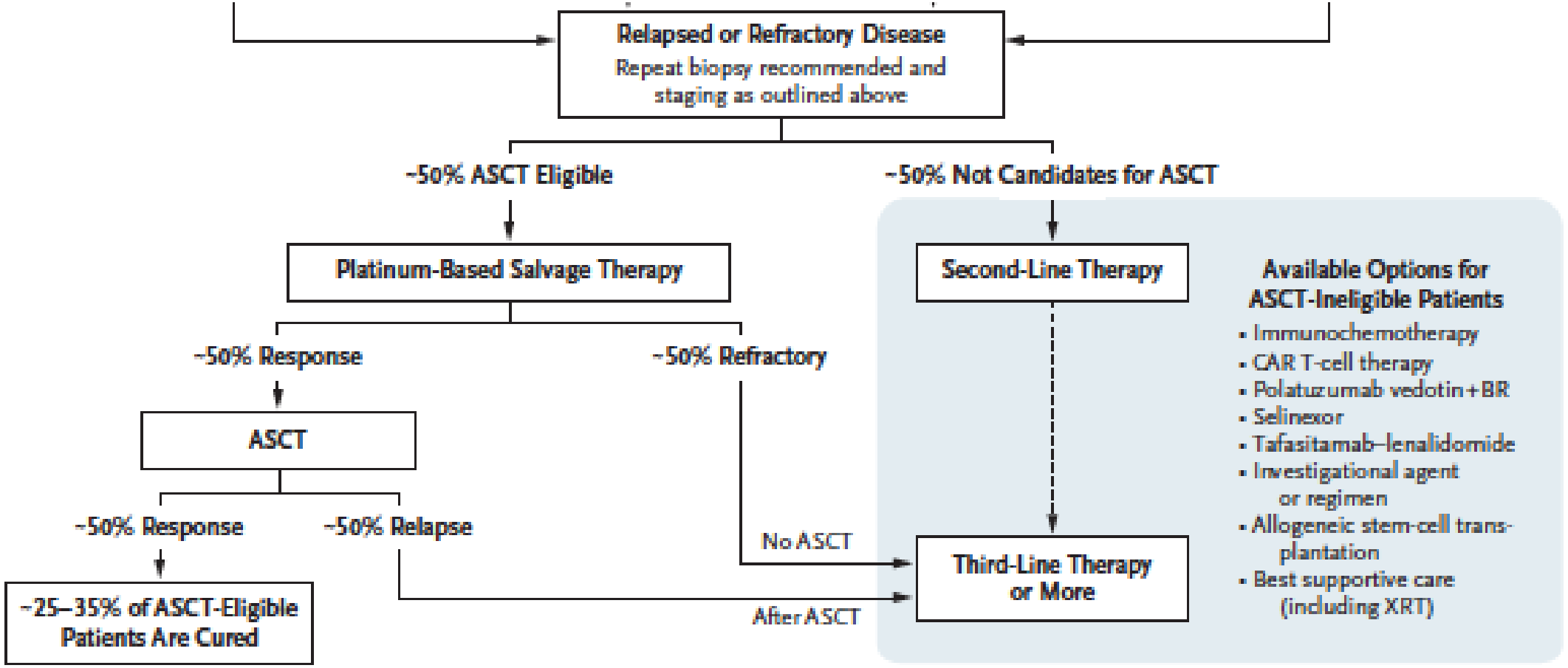


Polatuzumab for NHL



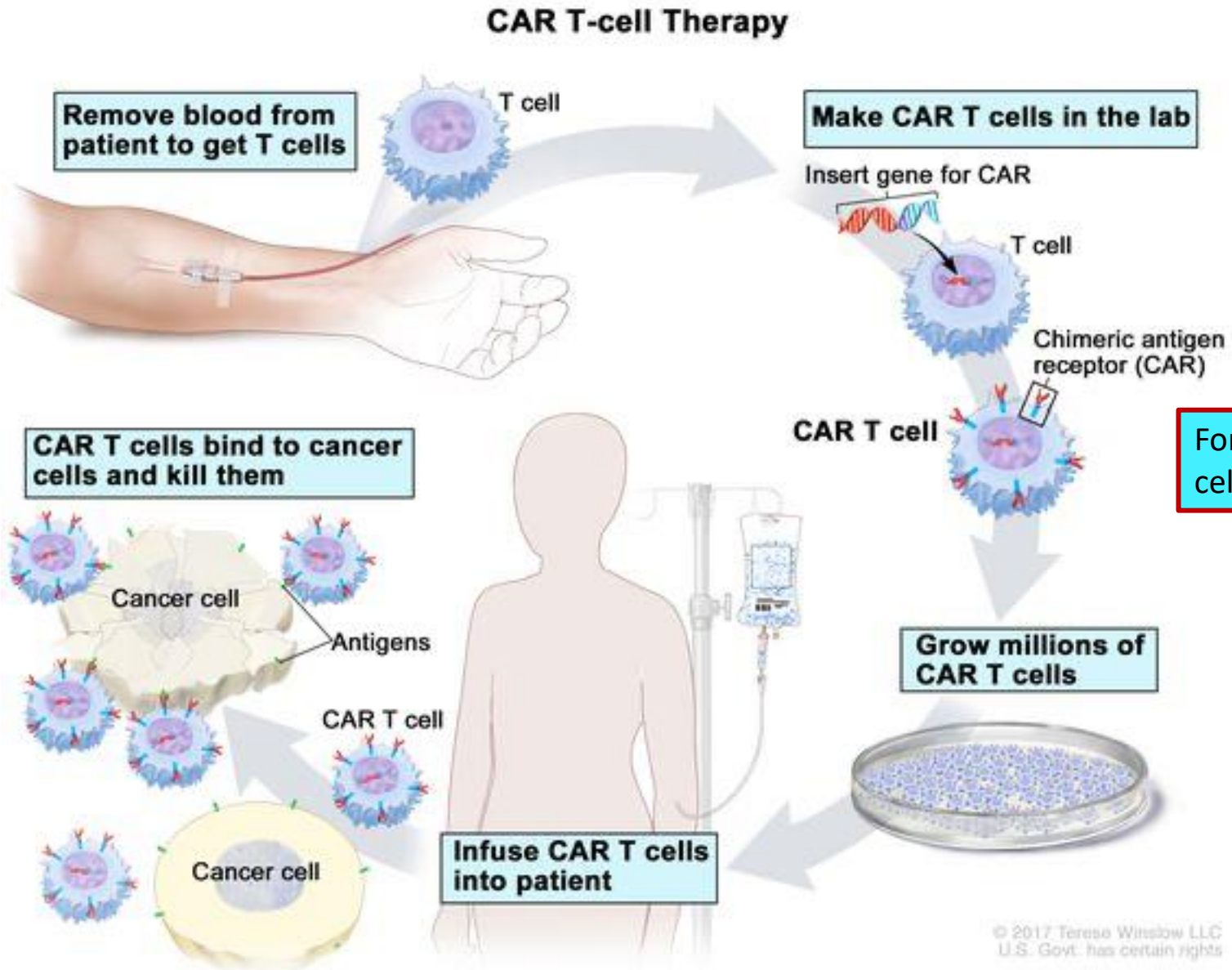
Waiting for analysis of phase 3 Polarix Trial – closed to accrual

Management of Relapsed or Refractory DLBCL



Car-T cell therapy for relapsed/refractory DLBCL

- Car-T cell therapy currently may be offered to patients who fail 2 lines of therapy
- No absolute age cut-off
- Includes patients:
    1) who do not respond to salvage chemotherapy
    2) those not eligible for stem cell transplant
    3) those who relapse after stem cell transplant
- Currently 4-5 Car-T cell therapies per month in Ottawa



For NHL and B cell ALL Car-T cell expresses CD19

Currently 3 CD19 Car-T cell products commercially available
Positioned as third line treatment for aggressive B cell lymphoma

What else can we offer?

- Clinical trials ongoing for upfront and relapsed DLBCL
- Newly diagnosed patients with non-GCB phenotype
  - Randomized to RCHOP+ acalabrutinib vs RCHOP+placebo
- Current trial in relapsed refractory:
  - Lenalidomide + rituximab + brentuximab

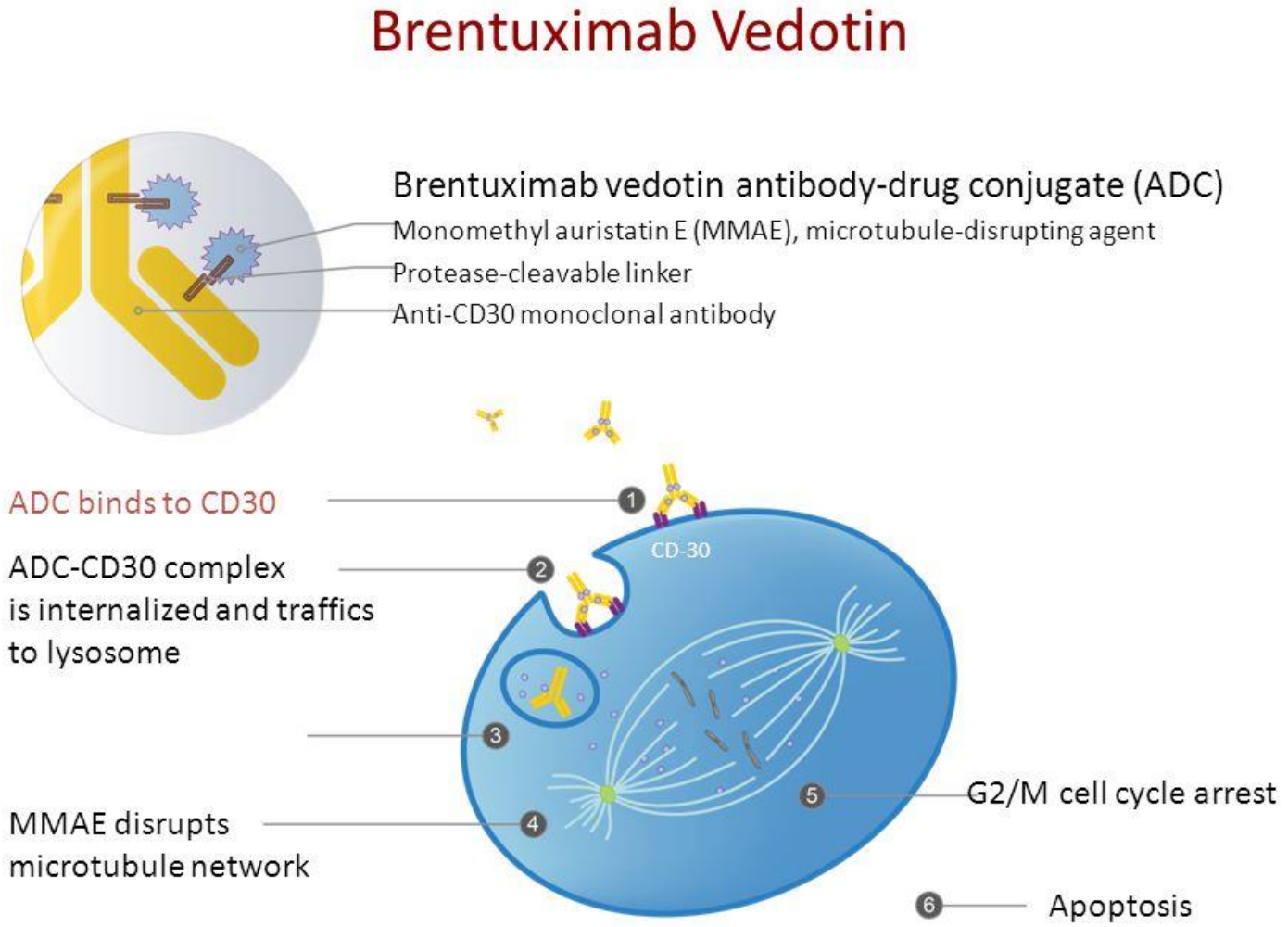
T Cell lymphoma

- 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
- Overall more aggressive and less curable than B cell lymphomas

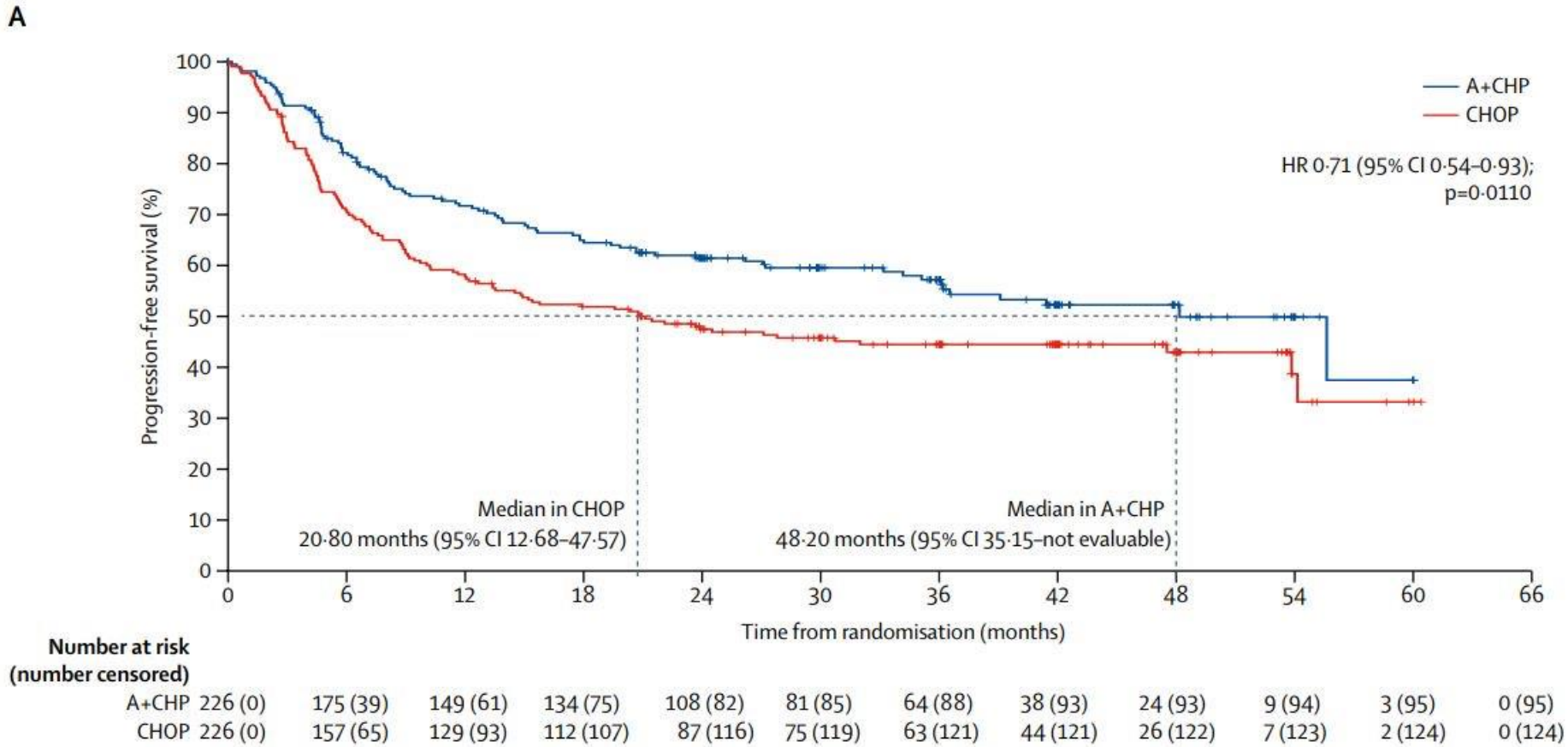
Treatment

- Very little improvement over 20 years
- CHOP vs CHOEP
- Addition of Brentuximab in CD30+ lymphomas has improved outcomes, particularly in Anaplastic Large Cell Lymphoma
- **CCO approved Brentuximab for T cell lymphoma upfront early in 2021**
- Car-T cell therapy still experimental stage
- Role for upfront stem cell transplant

CD30 present on some T cell NHL cells, not many normal cells



Brentuximab substituted for Vincristine in T cell Lymphomas expressing CD30



Lancet December 2018

Follicular Lymphoma

- Very excellent first line treatment with Bendamustine/rituximab followed by maintenance rituximab
- Approximately 15% of patients progress early after first line treatment
- What will be the role for Car-T cell therapy in follicular lymphoma?
- Will it replace stem cell transplant for high risk patients?
- We are waiting final publication of the Zuma-5 trial first presented at ASH December 2020
- Patients had >/= 2 lines of therapy, many had “POD24”. High CR rates but don’t have long term follow up yet

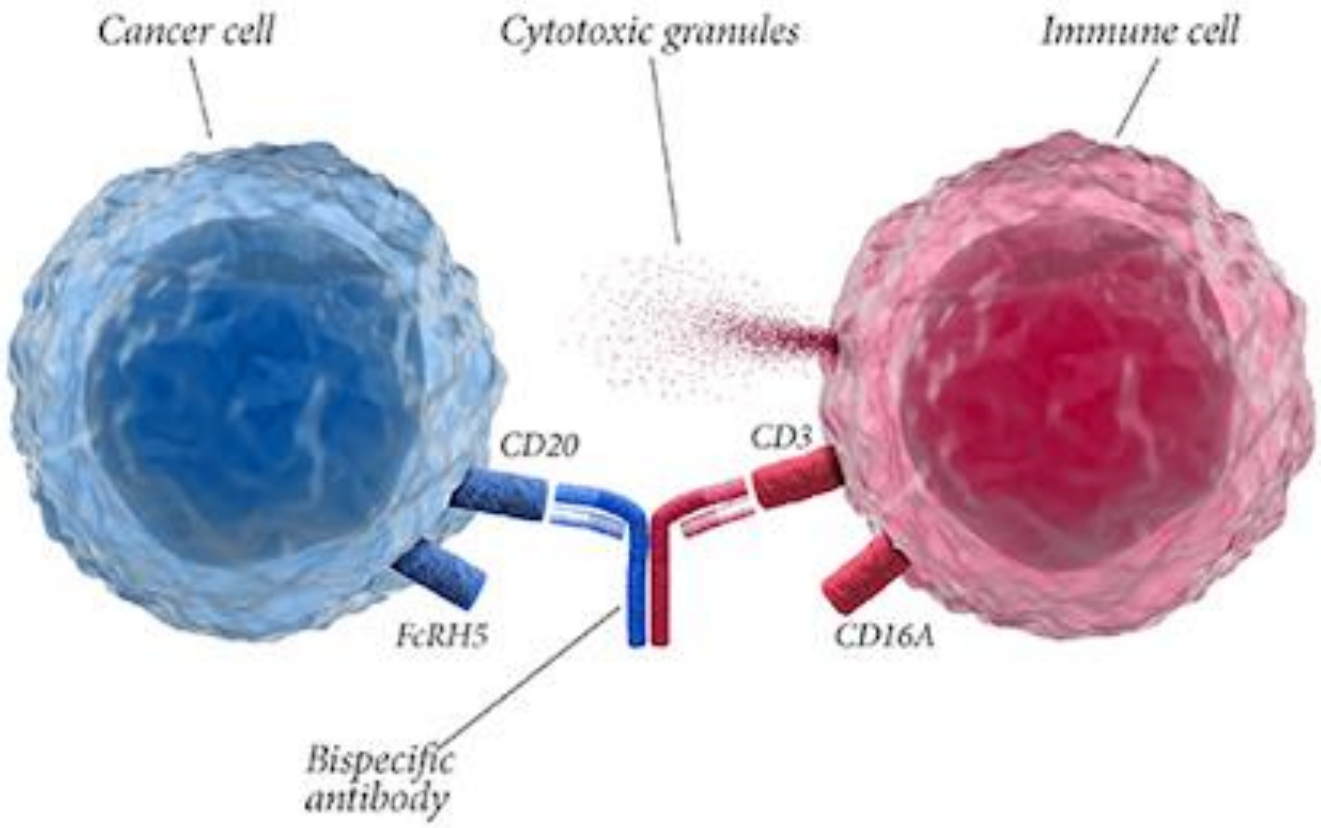
ORIGINAL ARTICLE

Rituximab plus Lenalidomide in Advanced Untreated Follicular Lymphoma

F. Morschhauser, N.H. Fowler, P. Feugier, R. Bouabdallah, H. Tilly, M.L. Palomba, C. Fruchart, E.N. Libby, R.-O. Casasnovas, I.W. Flinn, C. Haioun, H. Maisonneuve, L. Ysebaert, N.L. Bartlett, K. Bouabdallah, P. Brice, V. Ribrag, N. Daguindau, S. Le Gouill, G.M. Pica, A. Martin Garcia-Sancho, A. López-Guillermo, J.-F. Larouche, K. Ando, M. Gomes da Silva, M. André, P. Zachée, L.H. Sehn, K. Tobinai, G. Cartron, D. Liu, J. Wang, L. Xerri, and G.A. Salles, for the RELEVANCE Trial Investigators*

Bi-specific antibody targeting CD20 and CD3

B cell NHL cell



T cell

Mosunetuzumab

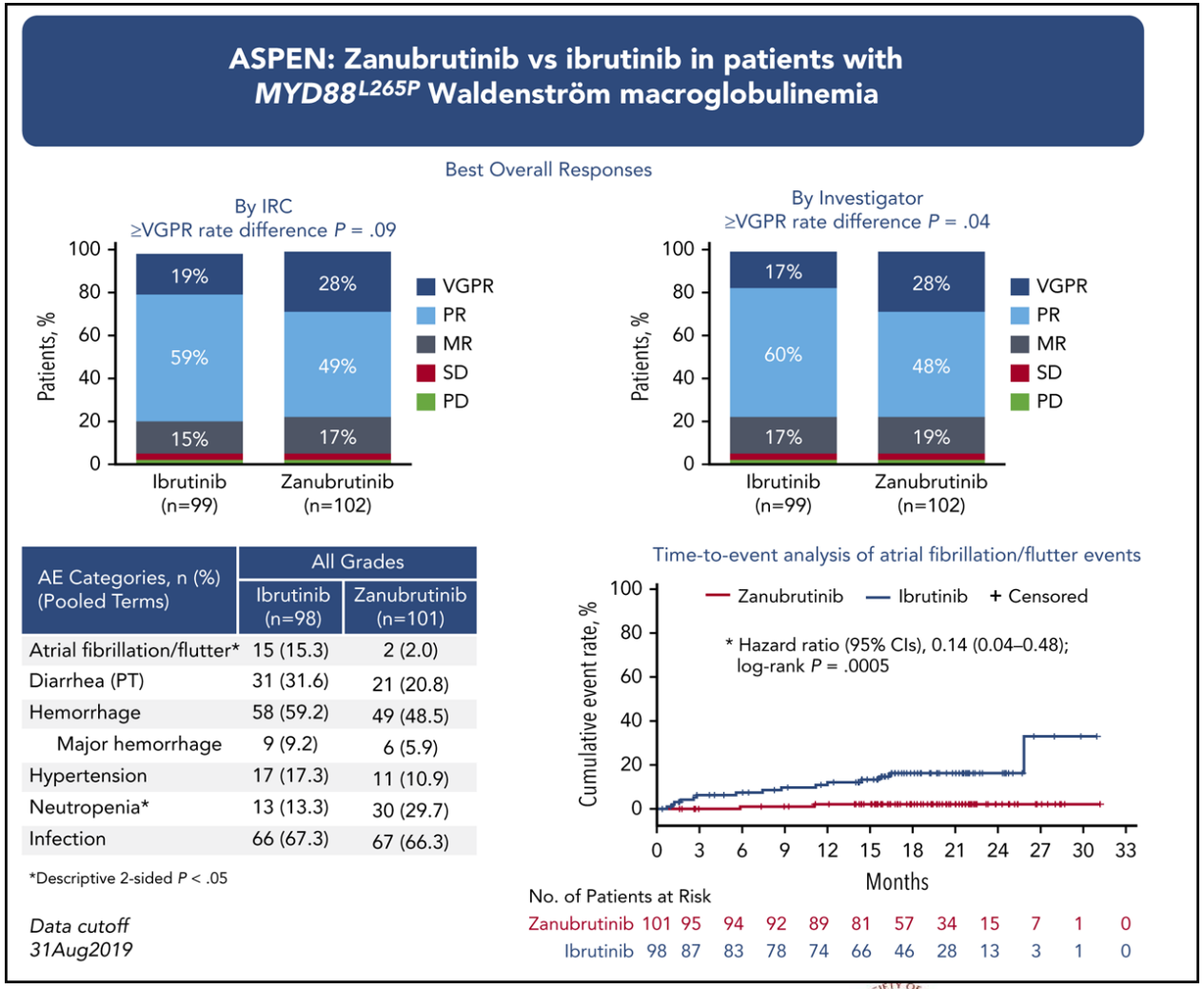
Waldenstrom's Macroglobulinemia

- Mature B cell NHL, IgM secreting
- MYD88 may be considered first genetic hit in WM that promotes NFkB and JAK-STAT signalling
- Over 90% of cases have the MYD88 mutation
- MYD88 PCR available in Ottawa
- Targets for these genes in ongoing clinical trials

Waldenstrom's Macroglobulinemia

- First line treatment generally bendamustine/rituximab with good response rates and durable remission
- BTK inhibitors approved at relapse and are very effective
- Zanabrutinib now available (not funded), recently approved, FDA approved front line based on the recent ASPEN trial (head to head comparison of Zanabrutinib with Ibrutinib for treatment-naïve WM))
- Clinical trial using Acalabrutinib + bendamustine + rituximab

A randomized phase 3 trial of zanubrutinib vs ibrutinib in symptomatic Waldenström macroglobulinemia: the ASPEN study



AE Categories, n (%) (Pooled Terms)	All Grades	
	Ibrutinib (n=98)	Zanubrutinib (n=101)
Atrial fibrillation/flutter*	15 (15.3)	2 (2.0)
Diarrhea (PT)	31 (31.6)	21 (20.8)
Hemorrhage	58 (59.2)	49 (48.5)
Major hemorrhage	9 (9.2)	6 (5.9)
Hypertension	17 (17.3)	11 (10.9)
Neutropenia*	13 (13.3)	30 (29.7)
Infection	66 (67.3)	67 (66.3)

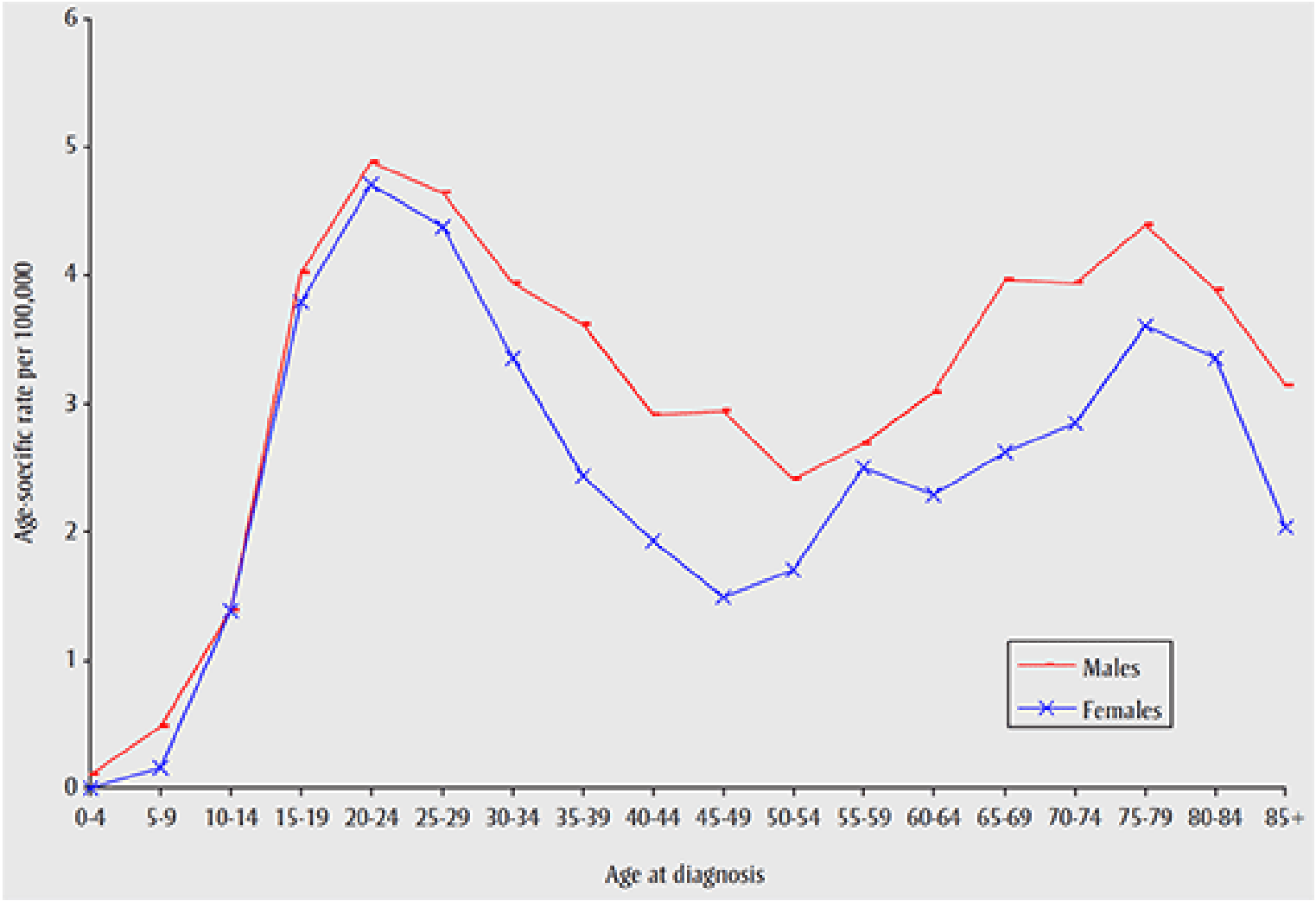
*Descriptive 2-sided $P < .05$

Data cutoff 31Aug2019

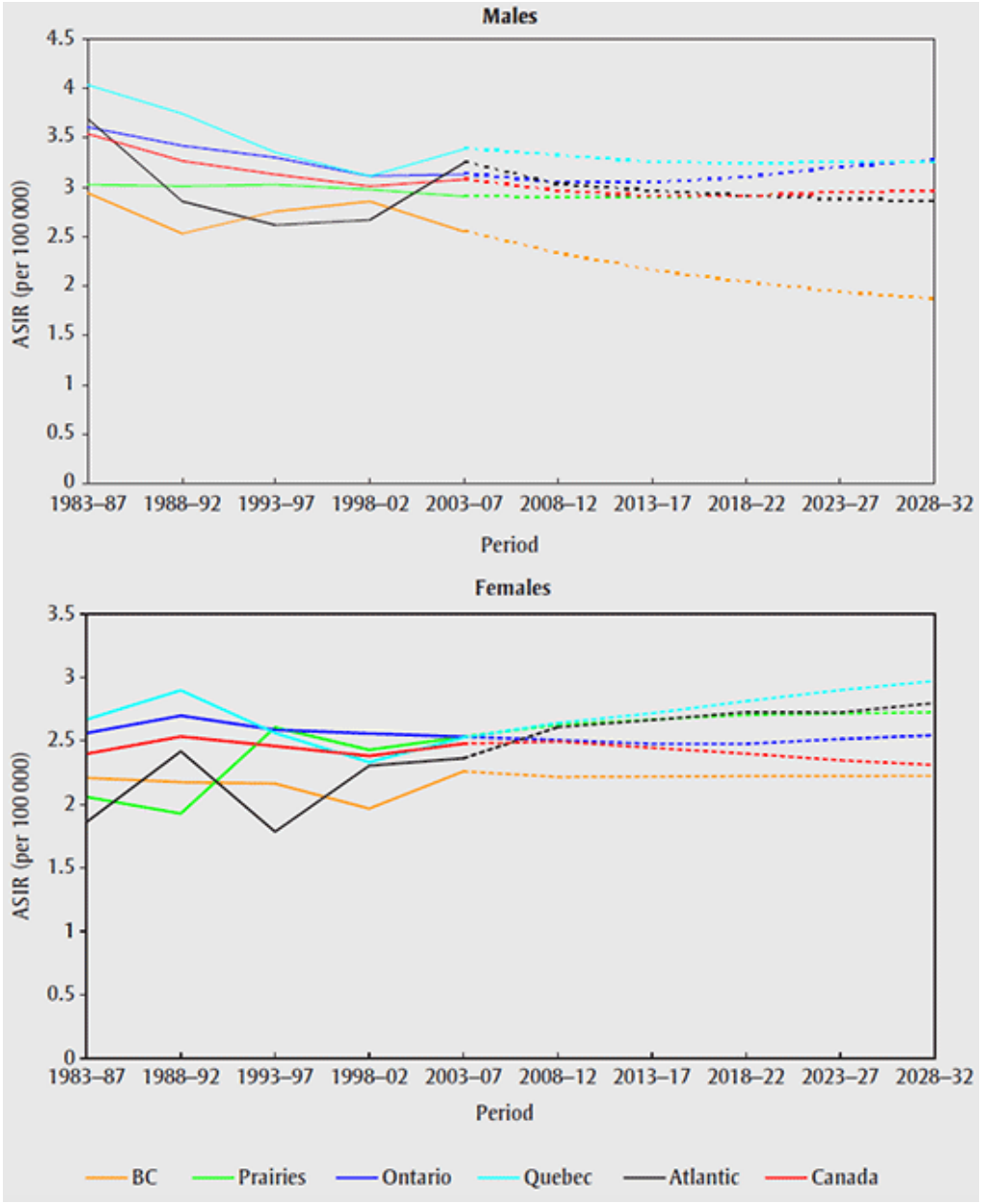
Hodgkin lymphoma

- 1000 cases/year in Canada
- 4 subtypes but most important factor is the stage
- Can be difficult to diagnose
  - Cancer cells are in minority in affected nodes
- Use of PET CT used for many years and help guide therapy
- Use of newer therapies being increasingly incorporated in upfront management
- Highly curable

Age-specific incidence rates of Hodgkin lymphoma, Canada, 2003–2007 (from average annual counts)



Age-standardized incidence rates (ASIRs) by region, Hodgkin lymphoma, 1983–2032



Relapsed/Refractory Hodgkin's Lymphoma

Over 85% limited stage cured

~ 75% advanced stage cured

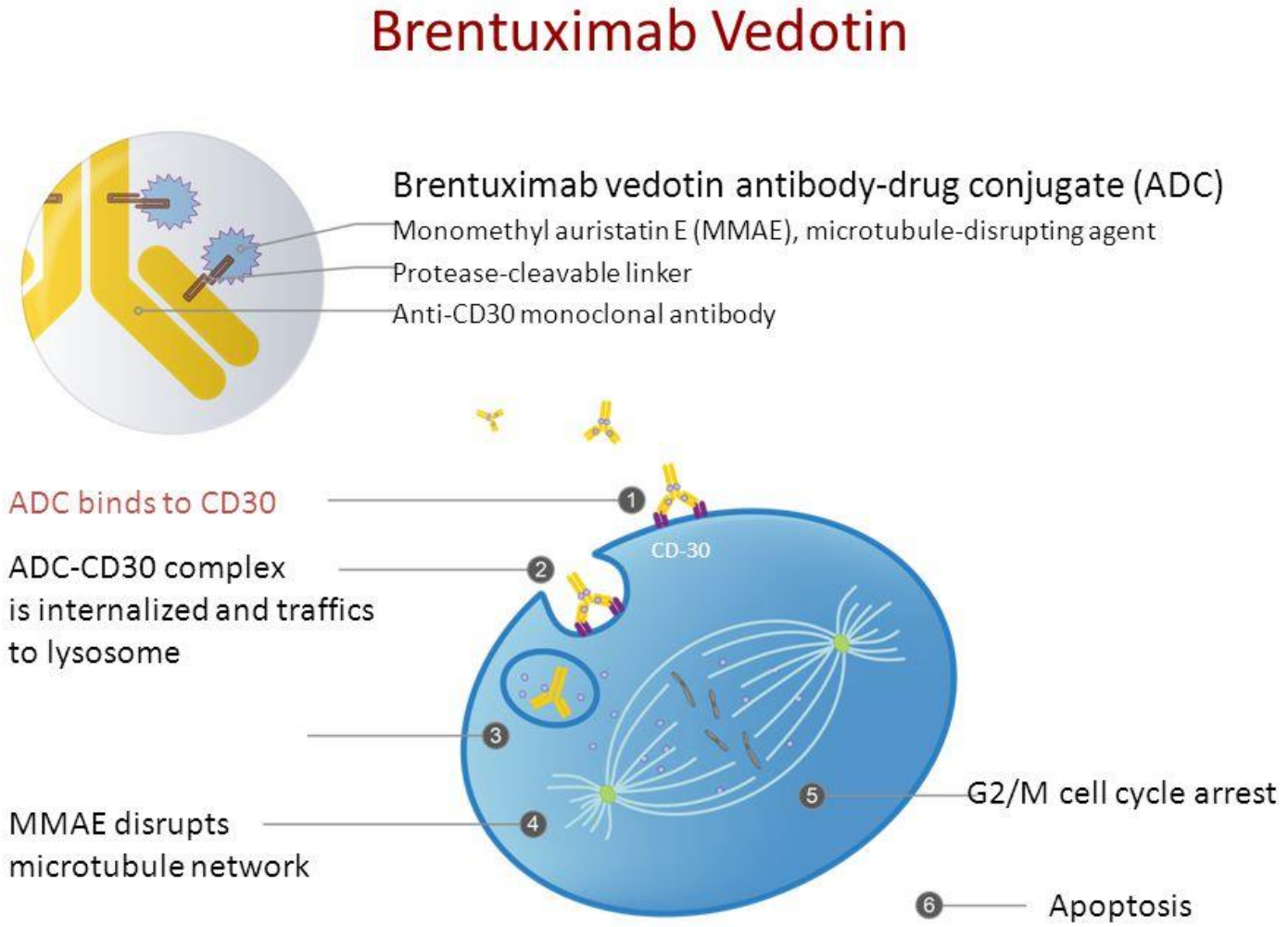
Standard salvage with chemotherapy followed by autologous stem cell transplant

Brentuximab post transplant for high risk individuals

Checkpoint inhibitors (Nivolumab or Pembrolizumab) for Brentuximab or Transplant failures

Gap in how to treat elderly who relapse

CD30 present on Hodgkin lymphoma cells, not many normal cells

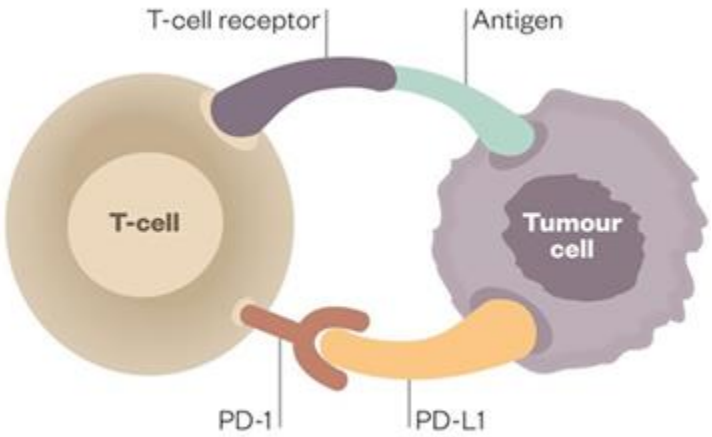


2010 first publication in NEJM showing good response in post-ASCT patients

Immune checkpoint inhibitors

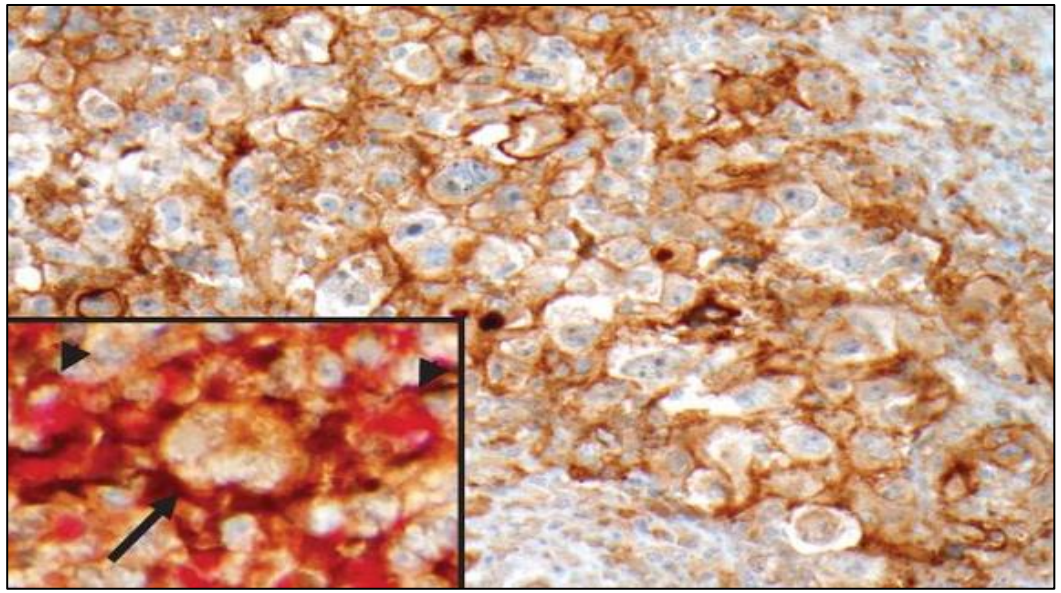
- Cells of the immune system have “checkpoints”-molecules on immune cells that need to be activated or inactivated to start an immune response
- PD = Programmed Cell Death protein
- PD-1 and PD-L1 turn off T-cell activation, preventing T cells from attacking the cancer.

- 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



Classical Hodgkin lymphoma – The 'Poster Child' for the biologic basis of PD1 inhibitor therapy

- **Classical Hodgkin lymphoma (cHL) is characterized by expression of PD-L1 and PD-L2 on HRS cells and on tumor infiltrating macrophages**



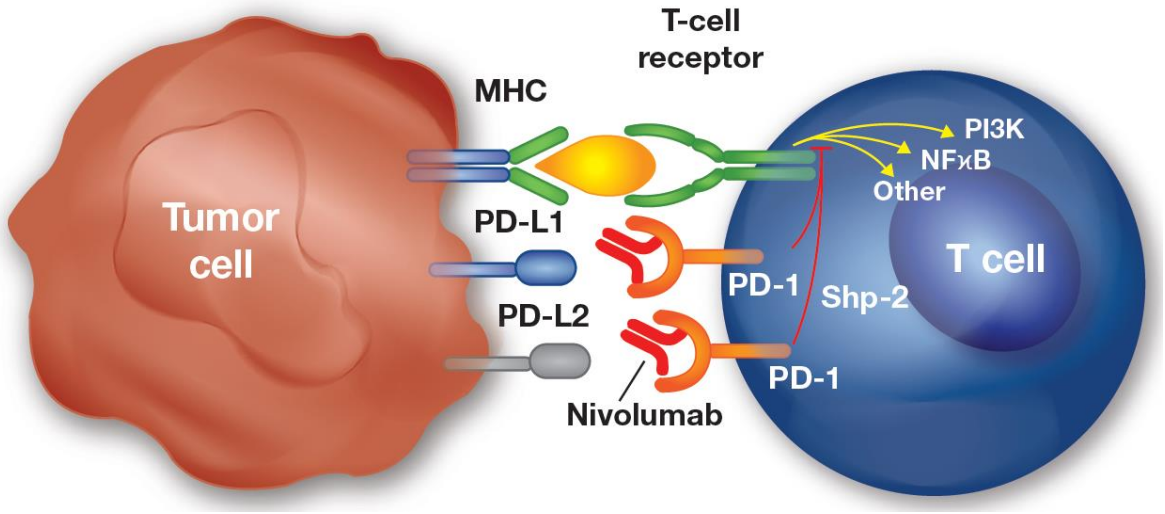
PD-L1 expression in cHL

Chen BJ, et al. *Clin Cancer Res.* 2013;19:3462–3473.
Ansell SM, et al. *N Engl J Med*. 2015;372:311–319.

- **Once PD1 inhibitors became available, cHL was a 'no brainer' to test them in**

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

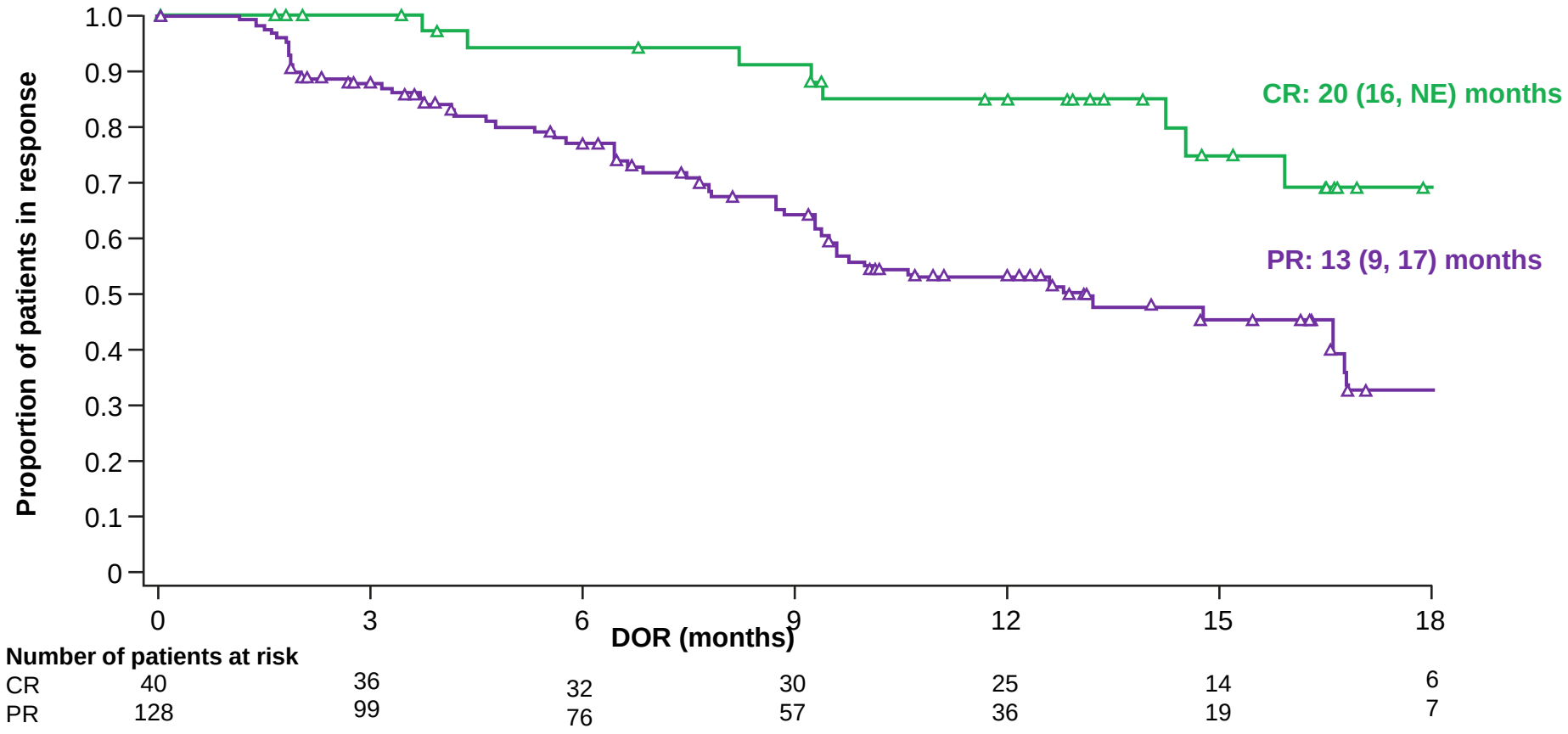


Nivolumab blocks signalling through the PD-1 receptor and activates the immune system to kill the cancer cells

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

Responses are durable with PD1 inhibitors



Response rate ~ 70%

Relapsed Hodgkin's Lymphoma

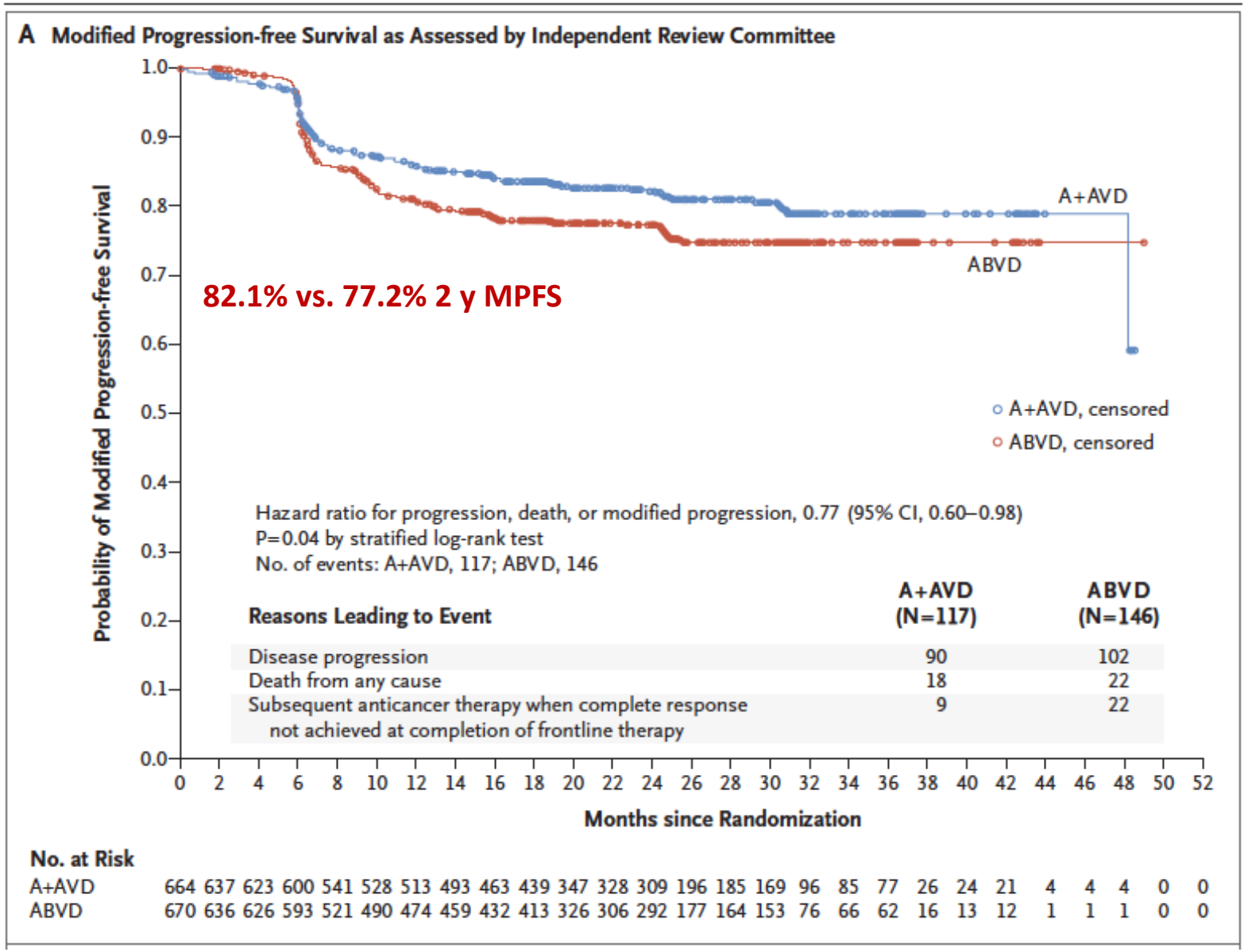
All values are medians (95% CI); NE = not evaluable

What's New

- CCO funding November 2021 for upfront Brentuximab in stage IV Hodgkin's Lymphoma
- Brentuximab = brand name **Adcedris**
- A+AVD replacing ABVD (Bleomycin dropped)

Brentuximab Vedotin with Chemotherapy for stage III/IV Hodgkin's Lymphoma

NEJM 25 January 2018



Clinical Trial

- Opening December 2021
- NCIC trial
- Stage III/IV Hodgkin's Lymphoma
- A+AVD (standard arm) vs Nivolimab+ AVD
- Predicting a progression-free survival rate of 90% in the Nivolimab arm

Chronic Lymphocytic Leukemia

Prolonged clinical course

"**C**hronic"

A particular type of white blood cell – B lymphocyte

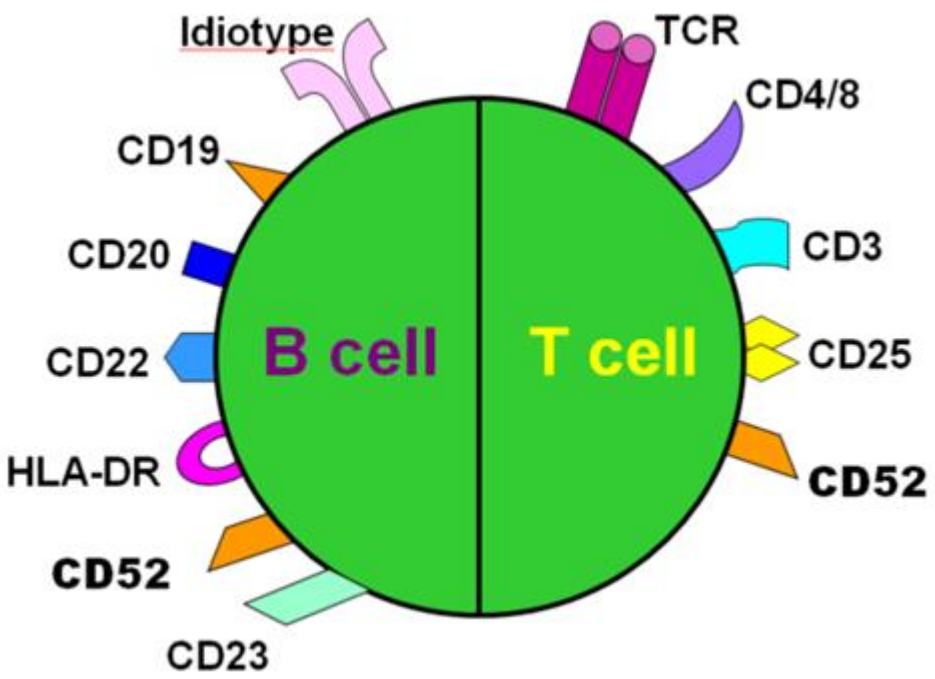
"**L**ymphocytic"

Cancer of white blood cells

"**L**eukemia" – white blood

Flow cytometry (a blood test)

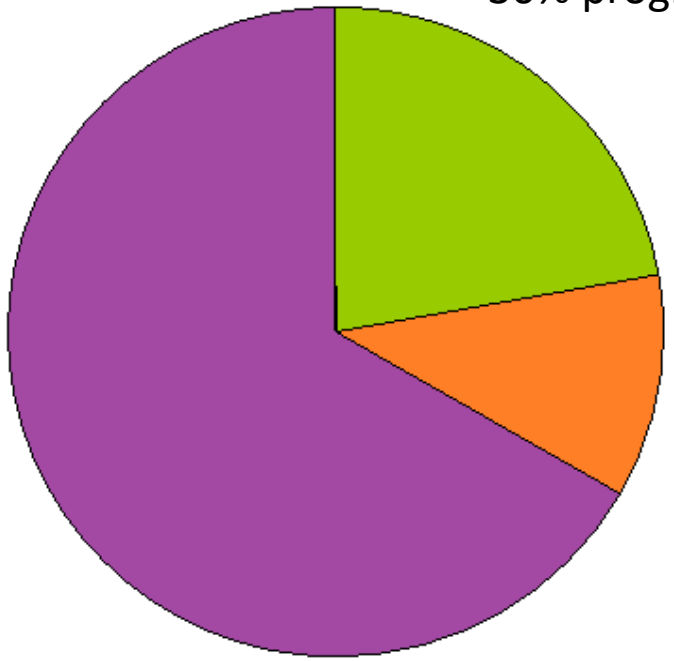
- Diagnostic tool for diagnosing CLL
- Reads the cell's surface like a barcode
- Detects extremely low levels of CLL in blood (or marrow)
- CLL: CD19+, CD20+, CD23+, CD5+



How CLL may progress over time

30% progression-free for years and years

Majority → Median of 5 years without symptoms followed by progression and complications

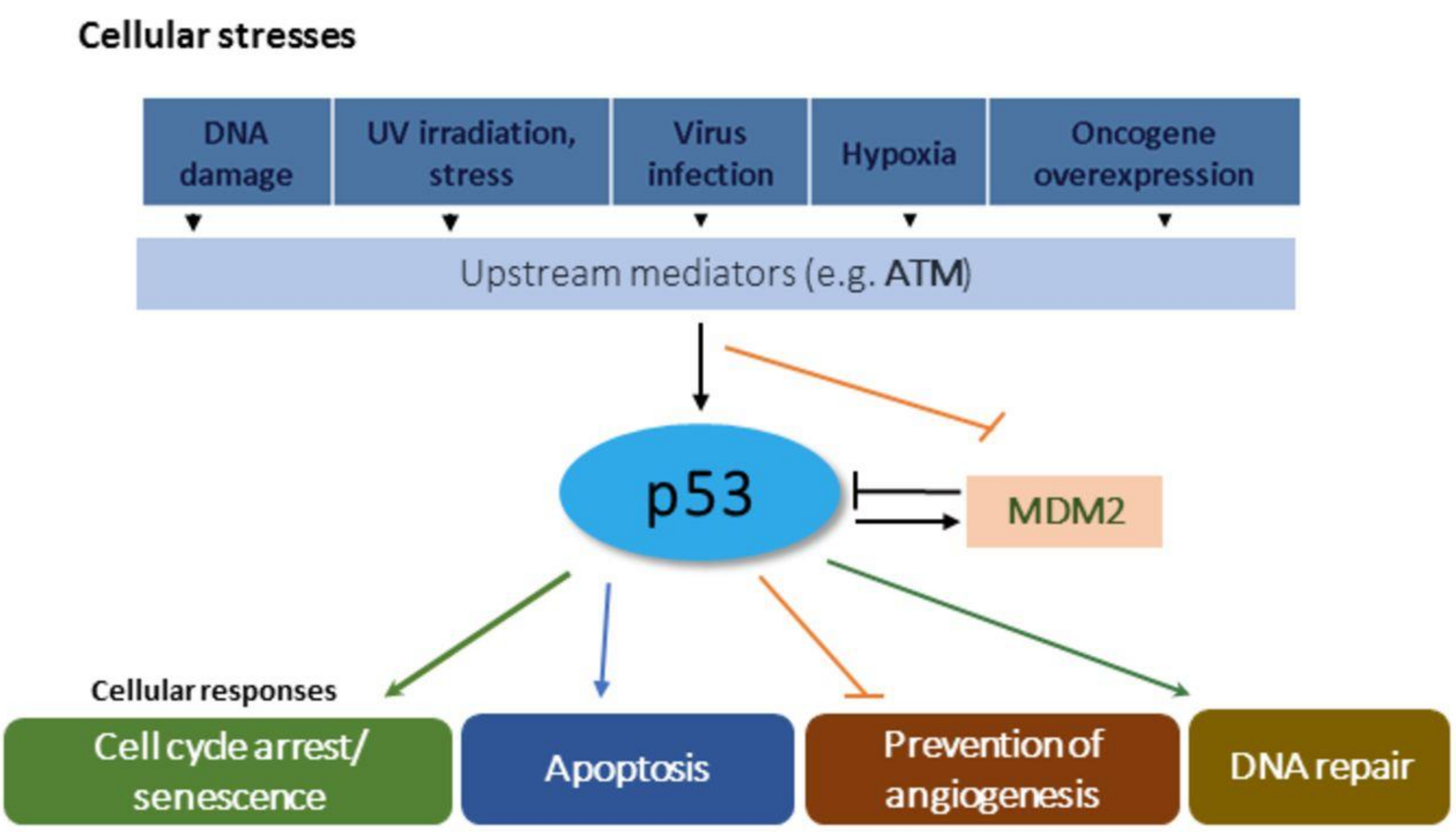


15 % → Aggressive disease from onset

CLL International Prognostic Index (2016)

	Adverse Factor	Grade
Age	>65 years	1
Clinical Stage	Rai I-IV or Binet B-C	1
β_2-microglobulin level	>3.5 mg/L	2
IGHV mutation status	Unmutated (>98% homology with germline)	2
Del(17p) and/or *TP53* mutation	Present	4

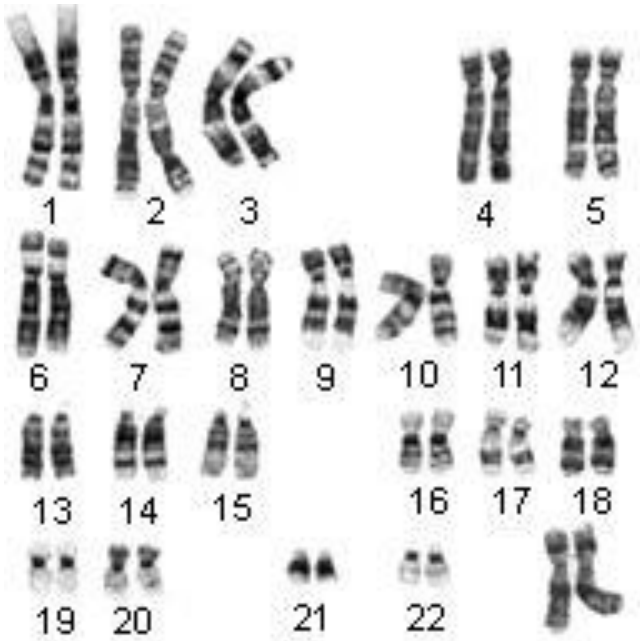
Risk	Score	5-year Overall Survival (p<0.001 for all)
Low	0-1	93%
Intermediate	2-3	79%
High	4-6	63%
Very High	7-10	23%


Cellular stresses
DNA damage
UV irradiation, stress
Virus infection
Hypoxia
Oncogene overexpression
Upstream mediators (e.g. ATM)
p53
MDM2
Cellular responses
Cell cycle arrest/ senescence
Apoptosis
Prevention of angiogenesis
DNA repair

Immunoglobulin gene mutation status

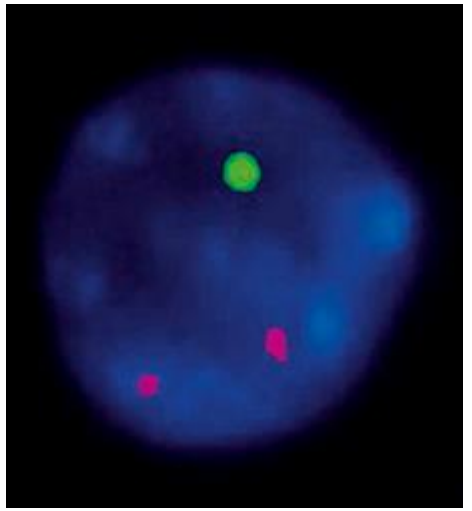
-Also called V-gene mutational status (IGVH status)
-A given patient's CLL can have a mutated or unmutated V gene test result
-It stays the same way throughout the years
-The CLL may behave more aggressively if it is unmutated
-now part of routine clinical practice for anyone requiring treatment
-molecular test done in reference lab (Sudbury in Ontario)

FISH status:
chromosome abnormalities can be predictors of response to some treatments



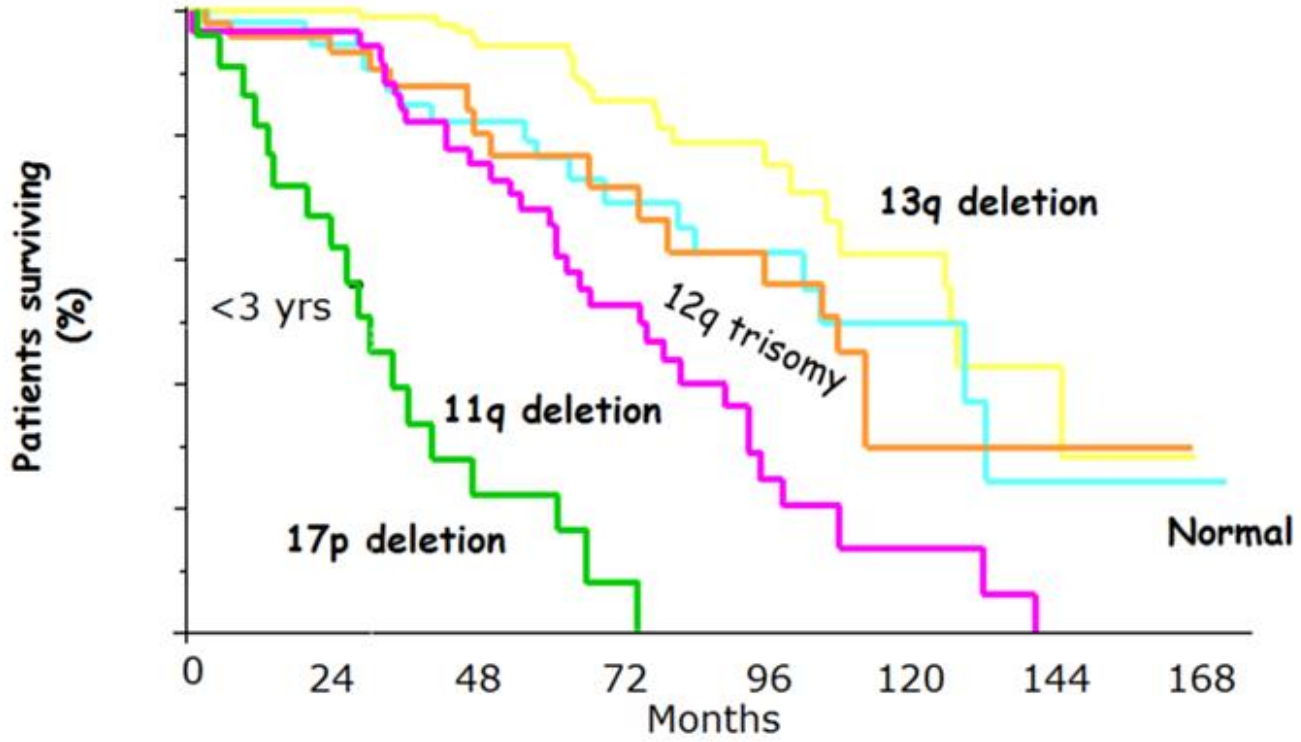
Normal karyotype: 46 chromosomes

Missing one green signal:
"deletion" of a chromosome arm



Fluorescence in situ hybridization

Deletion in chromosome 17p (TP53 gene) is the most important predictor of response – but we now have effective therapies for this



Döhner H, et al. *N Engl J Med*. 2000;343:1910-1916.

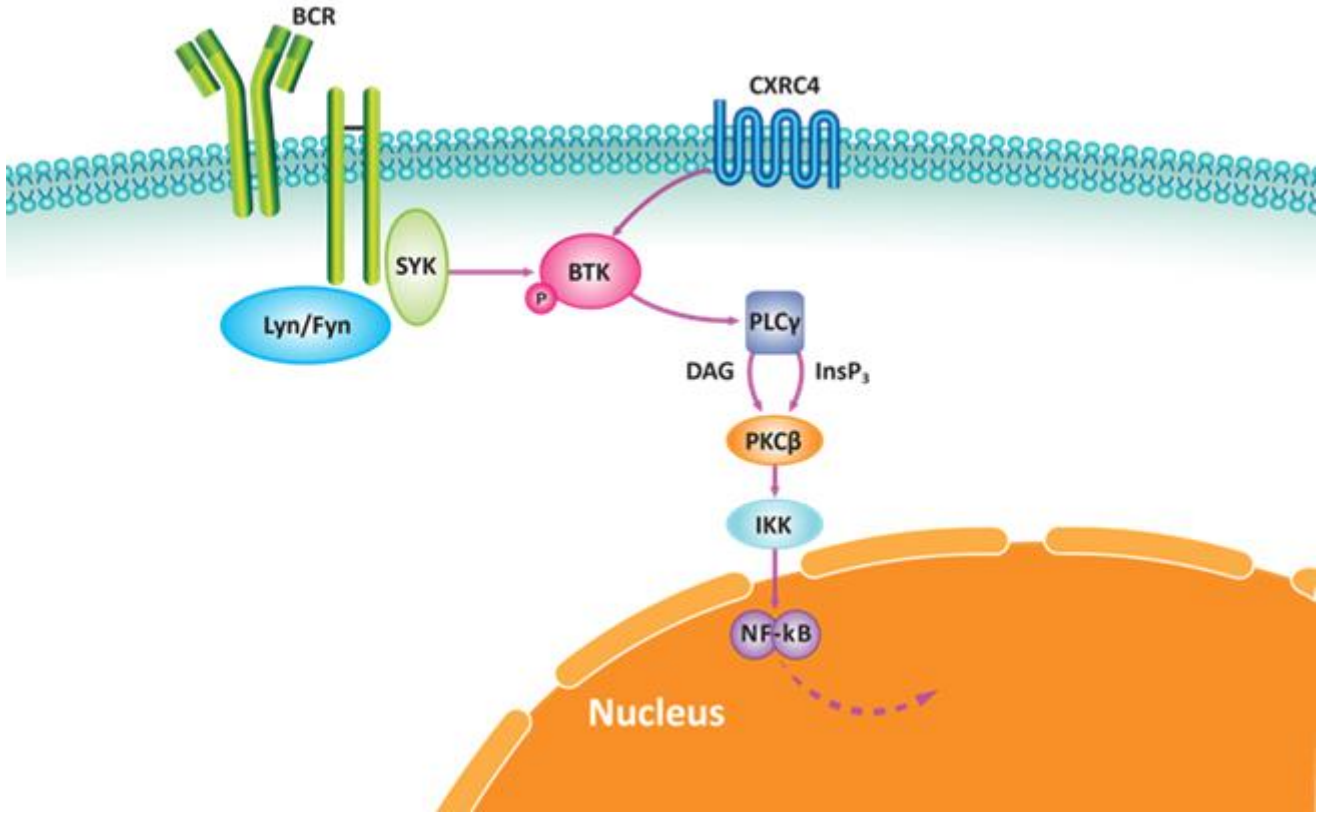
Principles of CLL treatment

- Establish treatment goals
- Establish prognostic factors
  - ➢IVGH status (molecular)
  - ➢FISH (most important are 17 p and 11q), p53 mutation (molecular)
- Decide on
  - standard therapy: based on consensus guidelines from published Phase 3 randomized clinical trials and availability of drugs
  - clinical trials: novel therapies or novel combination therapies not otherwise available as standard of care

Indications for treatment

- **Symptoms**
  - Severe fatigue, fevers, night sweats, pain from enlarged nodes
- **Organ dysfunction**
  - Bone marrow dysfunction (low blood counts), nodes compressing organs
- **(Rapid lymphocyte doubling time < 6 months)**
- **Complications of CLL not responding to therapy**
  - Auto-immune hemolytic anemia or ITP (very low platelets)

Ibrutinib: inhibits BTK (Bruton's tyrosine kinase)

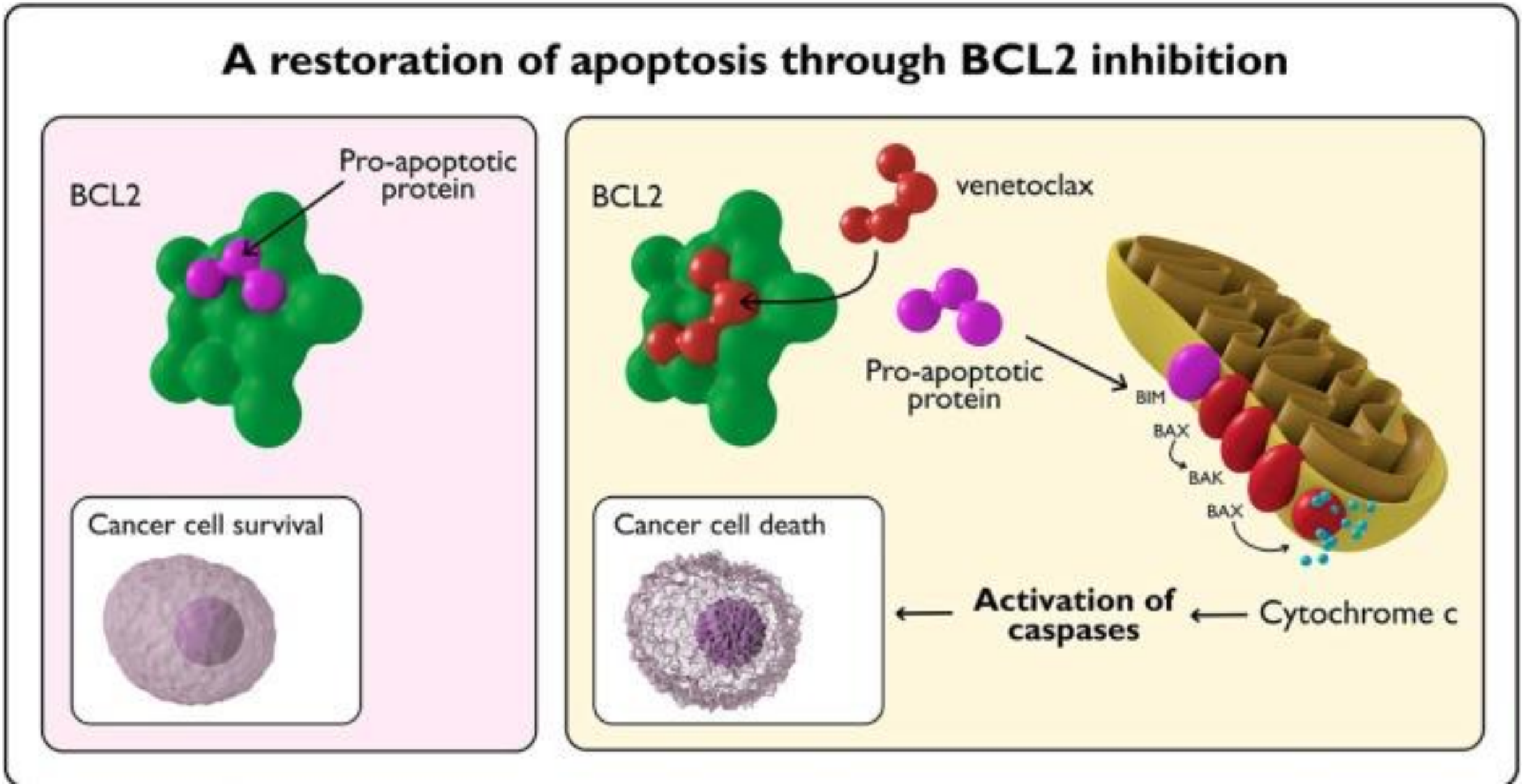


CLL B cell

CLL cells depend on extra-cellular signals that are transmitted by the B cell receptor

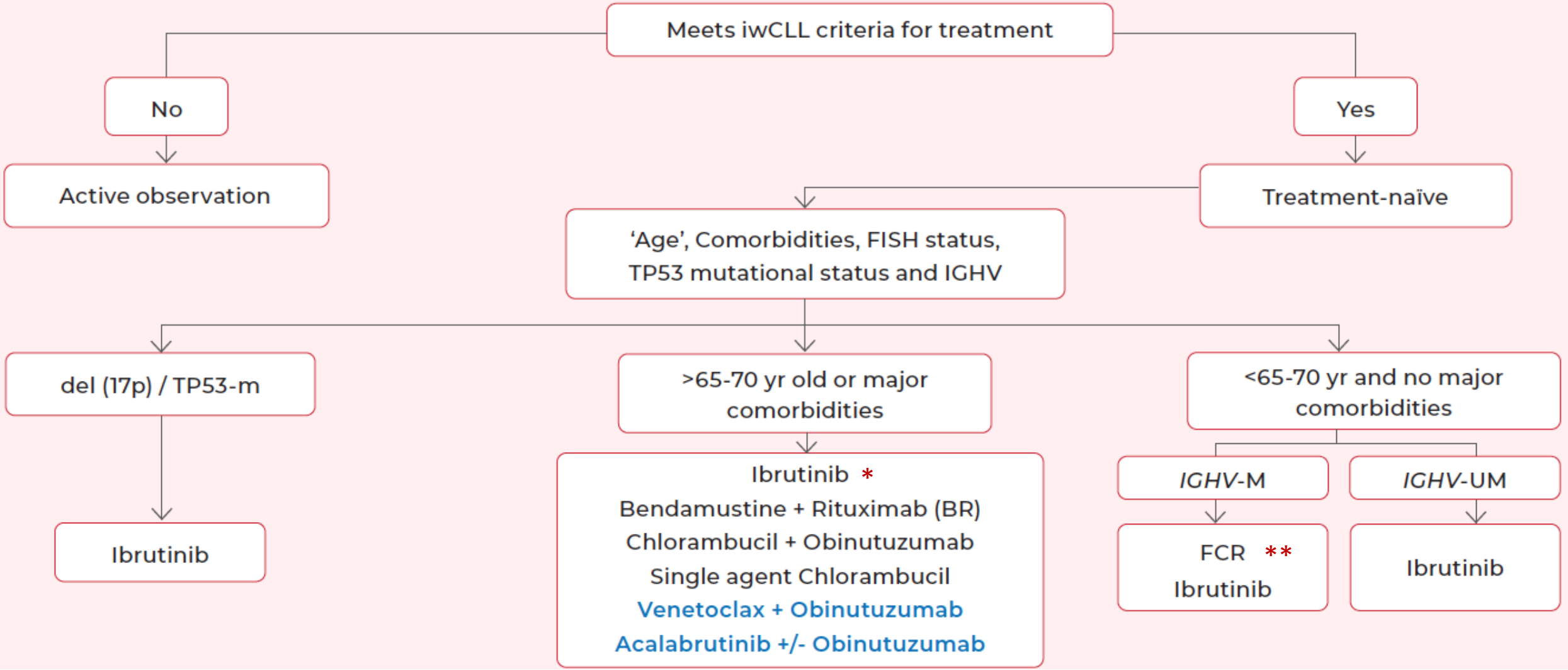
Binding to the BCR provides a survival signal "feed me"

Venetoclax - a BCL2 specific inhibitor



CARE™ FRONTLINE CLL ALGORITHM

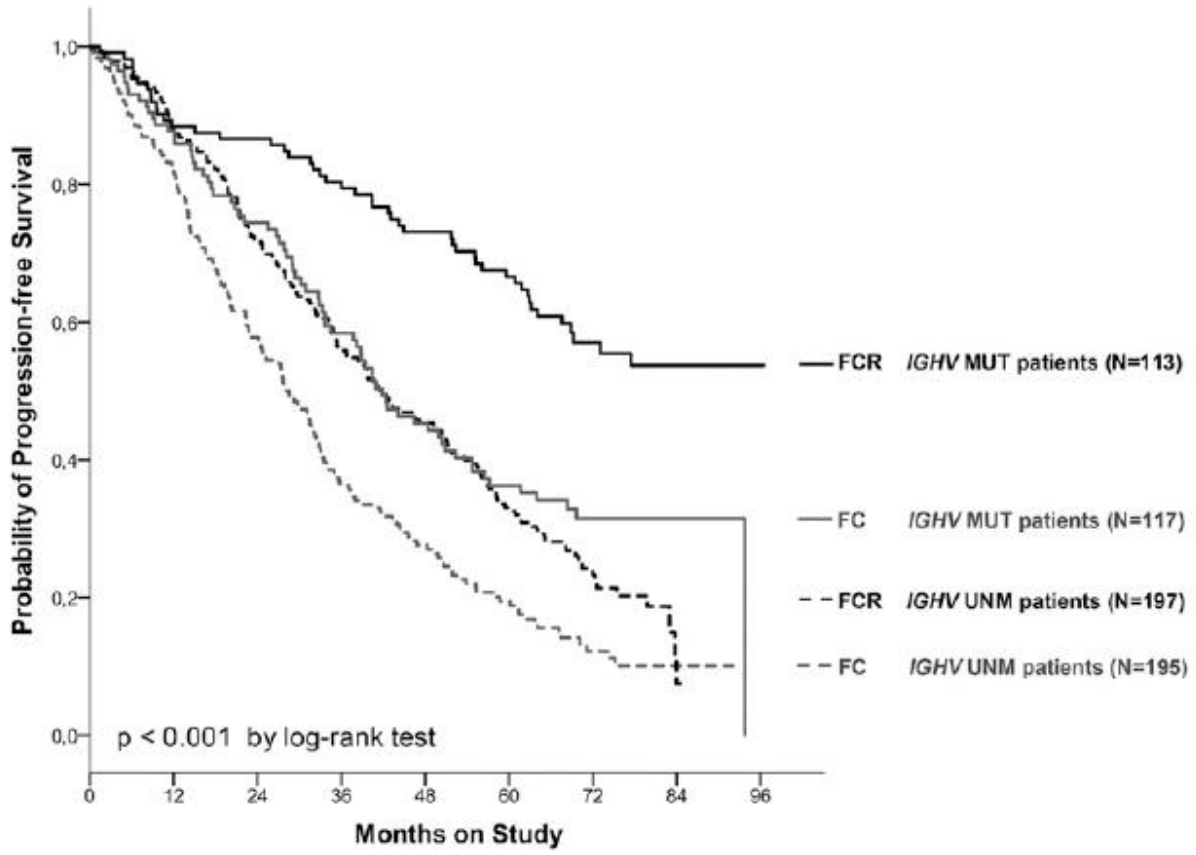
VERSION 3.0



* Upfront BTK inhibitor if IGHV-UM or 17p/p53 mutation

**Recent RCT shows no difference in FCR vs Ibrutinib in IGHV-M group

Long-term survival with FCR: If IGVH is mutated, ~60% still in remission after 8 years

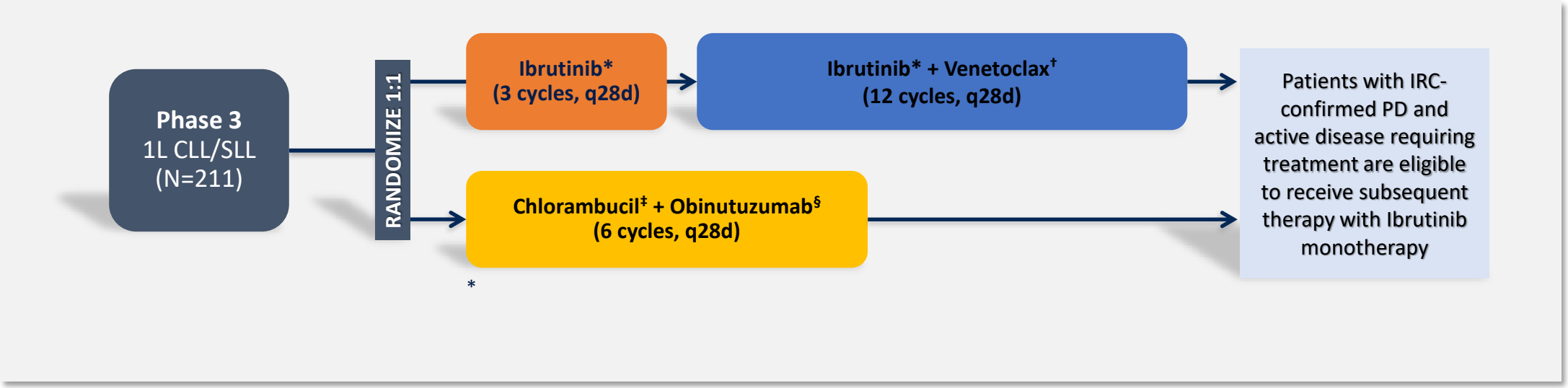


Fisher et al. Updated results from the CLL8 trial. Blood 2016

Moving Forward

- Future strategies for CLL therapy are expected to include:
  - ➢Combination therapies (BTKi and BCL2i +/- monoclonal antibodies)
  - ➢Selective, non-covalent BTKI (ie. LOXO-305)
  - ➢Car-T cells (ie Liso-cel)
  - ➢Use of uMRD to direct treatment decisions in routine clinical practice

GLOW – Study Design



INCLUSION CRITERIA

- 1L active CLL or SLL requiring treatment per iwCLL criteria
- ≥65 years or <65 years with comorbidities
- ECOG PS ≤2

EXCLUSION CRITERIA

- del(17p) or *TP53* mutations
- CNS involvement or suspected Richter's syndrome

ACE-CLL 311 Trial

RCT, 3 arms, first line, 17p, p53 excluded, no age exclusion

ARM A: Acalabrutinib + Venetoclax

ARM B: Acalabrutinib + Venetoclax + Obinutuzumab

Arm C: FCR or BR (investigator’s choice of chemotherapy)

QUESTIONS