Lymphomas: the foundations

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DUBLIN · IRELAND

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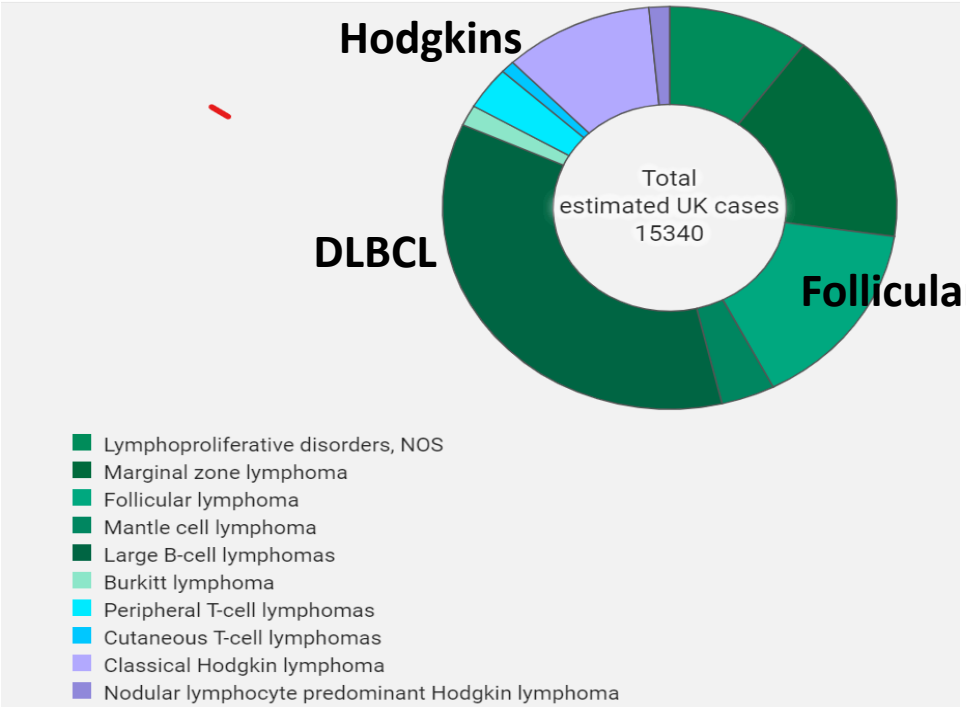
Topics to be covered

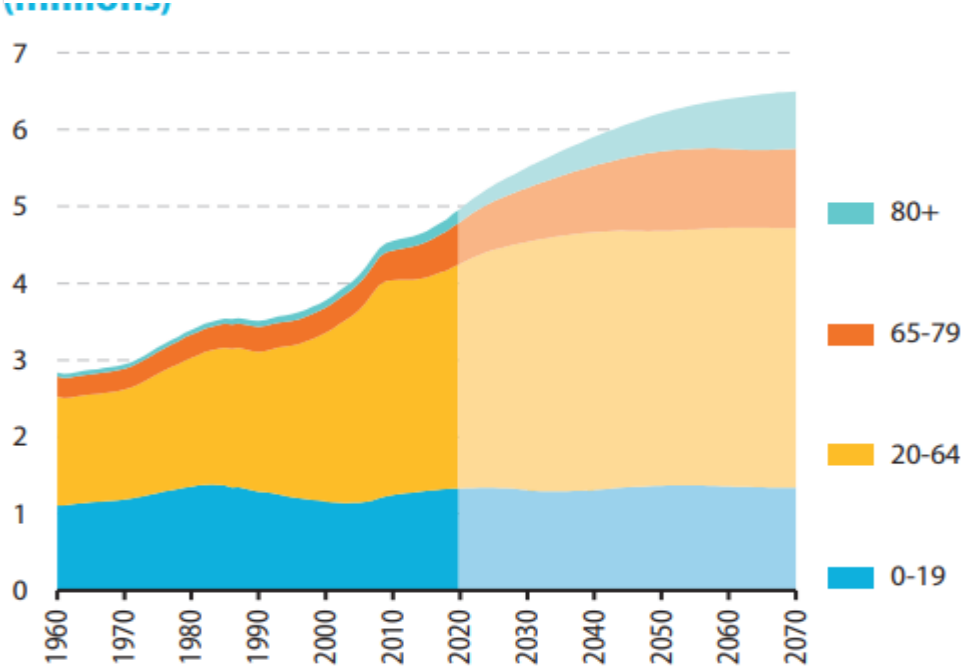
- Epidemiology
- Classification and Natural history
- Therapy grouping
- Hodgkins lymphoma – First line treatment; treatment evolution
- Follicular lymphoma – Pathogenesis
  Natural history
  Treatment pathway
- T-NHL/DLBCL/MCL The basics

Epidemiology of lymphomas

- **Incidence (Ireland)**
- NCRI 2020 1150
- HMRN (dynamic) 1175 (extrapolated) Exclude CLL, HCL, MM



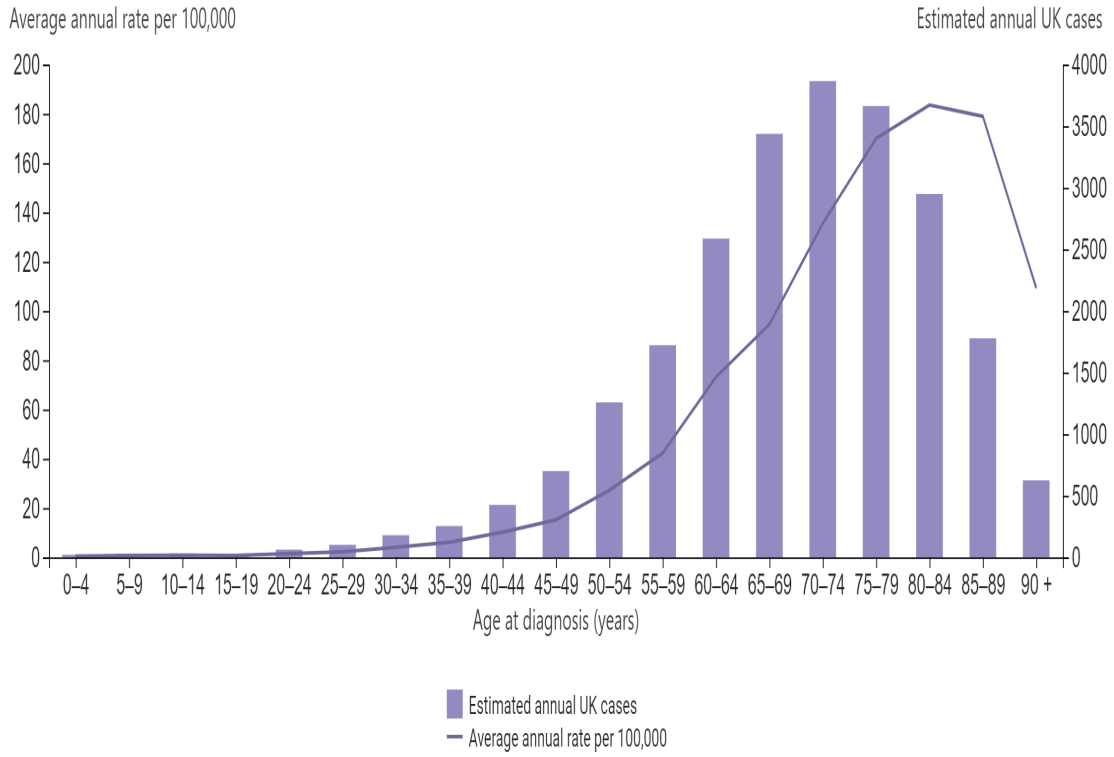
Irish population age 1960-2020



Epidemiology prevalence and age

Extrapolated prevalence of lymphoma in Ireland is 8000

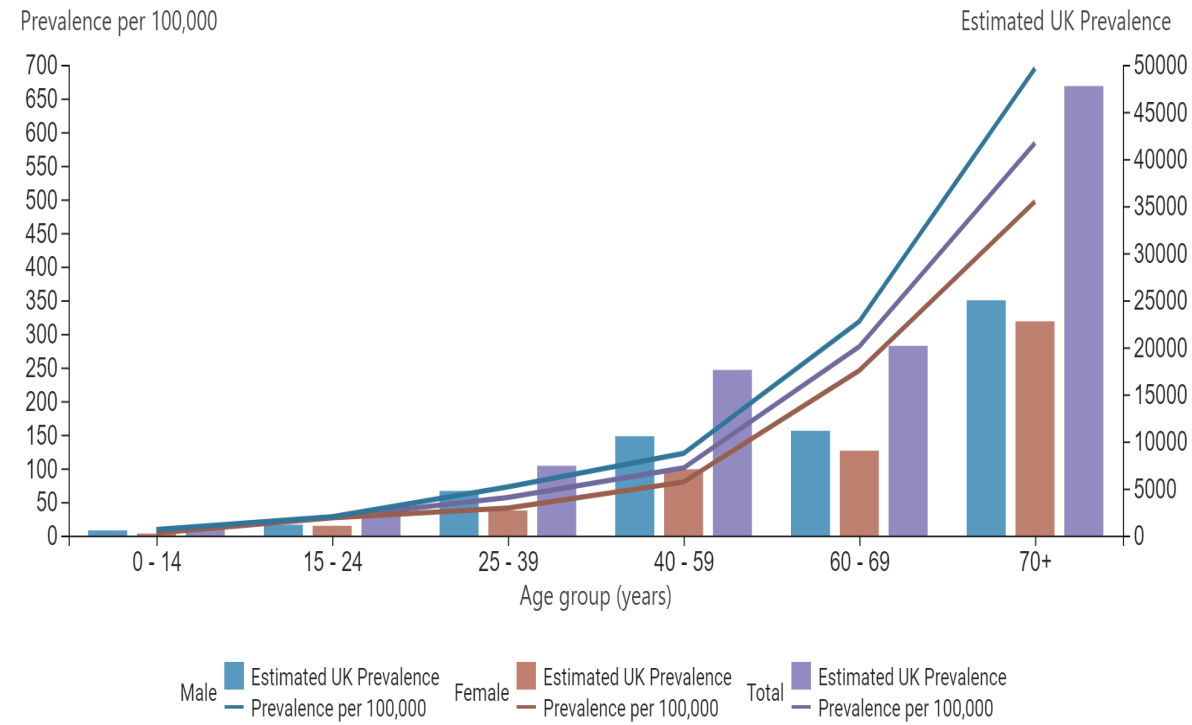
Incidence by age group



www.hmrn.org

Prevalence by age group

10-year limited-duration



www.hmrn.org

Classification: what is in a name

*2021: Indolent, classical, blastic
#2024: nnMCL, in situ, MCL

Leukemia

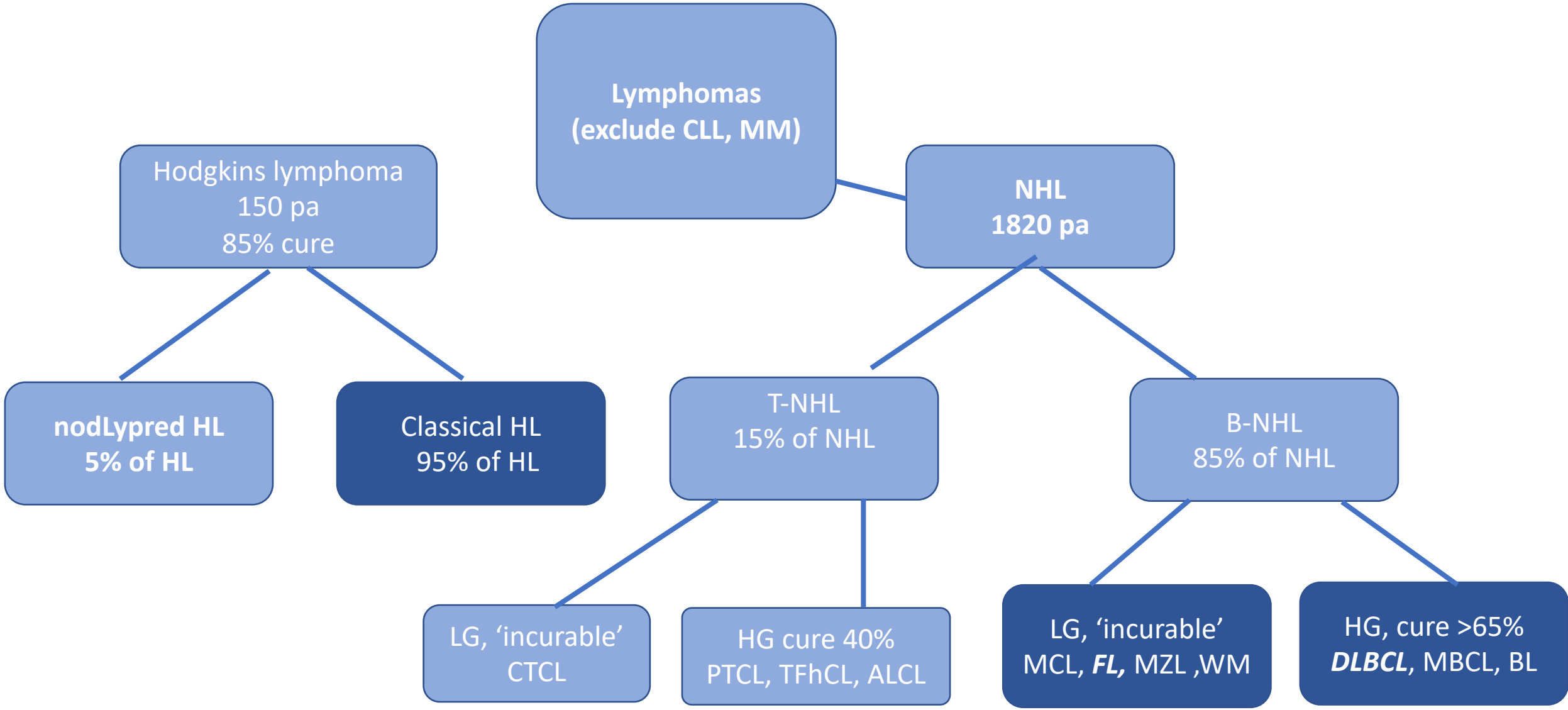
REVIEW ARTICLE OPEN

LYMPHOMA

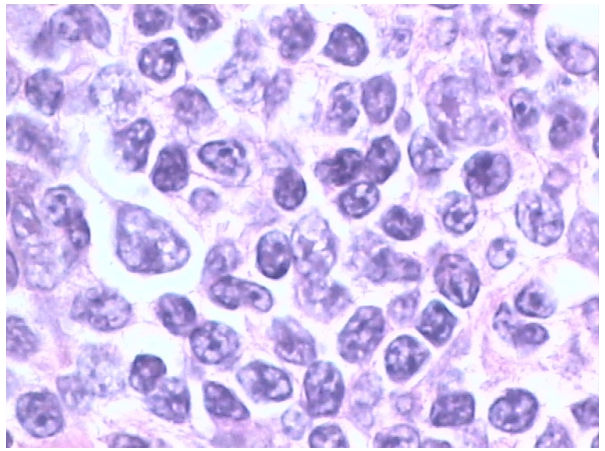
The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms

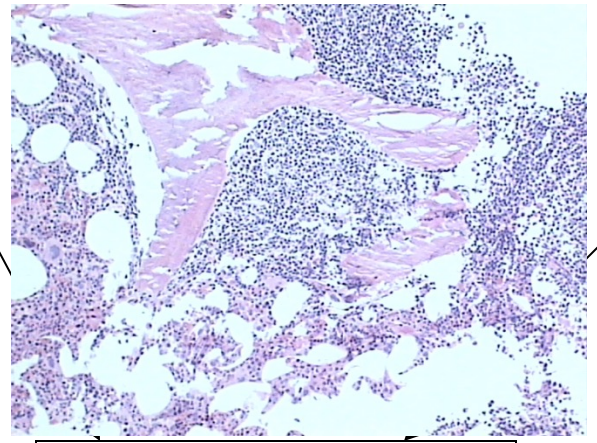
Pathogenesis
Traditional pathology
Genetics
Viral drivers
'precision pathology and treatment

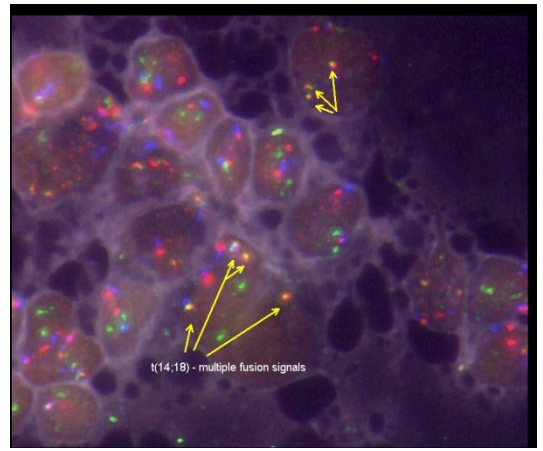
Classification: a simple/universal scaffold



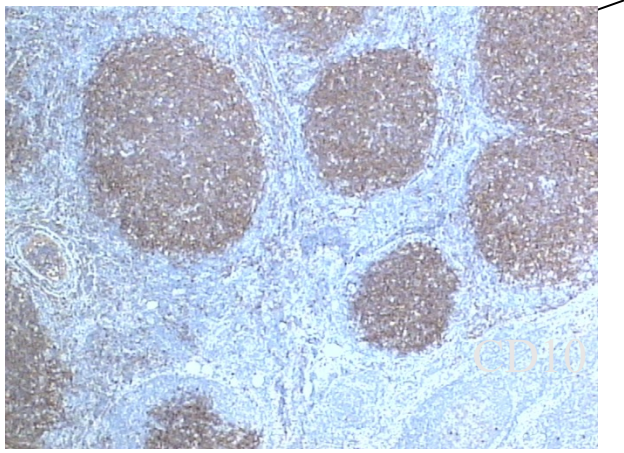
An Approach to Diagnosis Using the WHO Classification

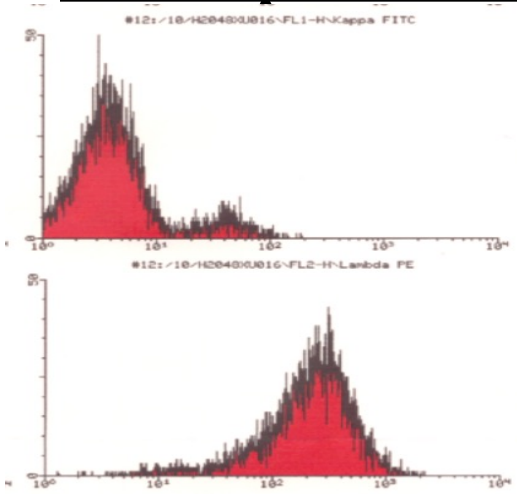


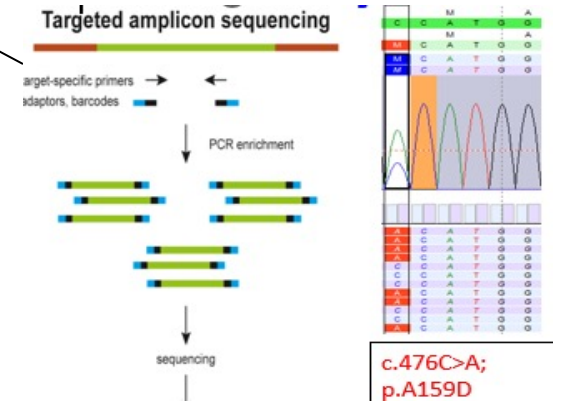




Follicular Lymphoma







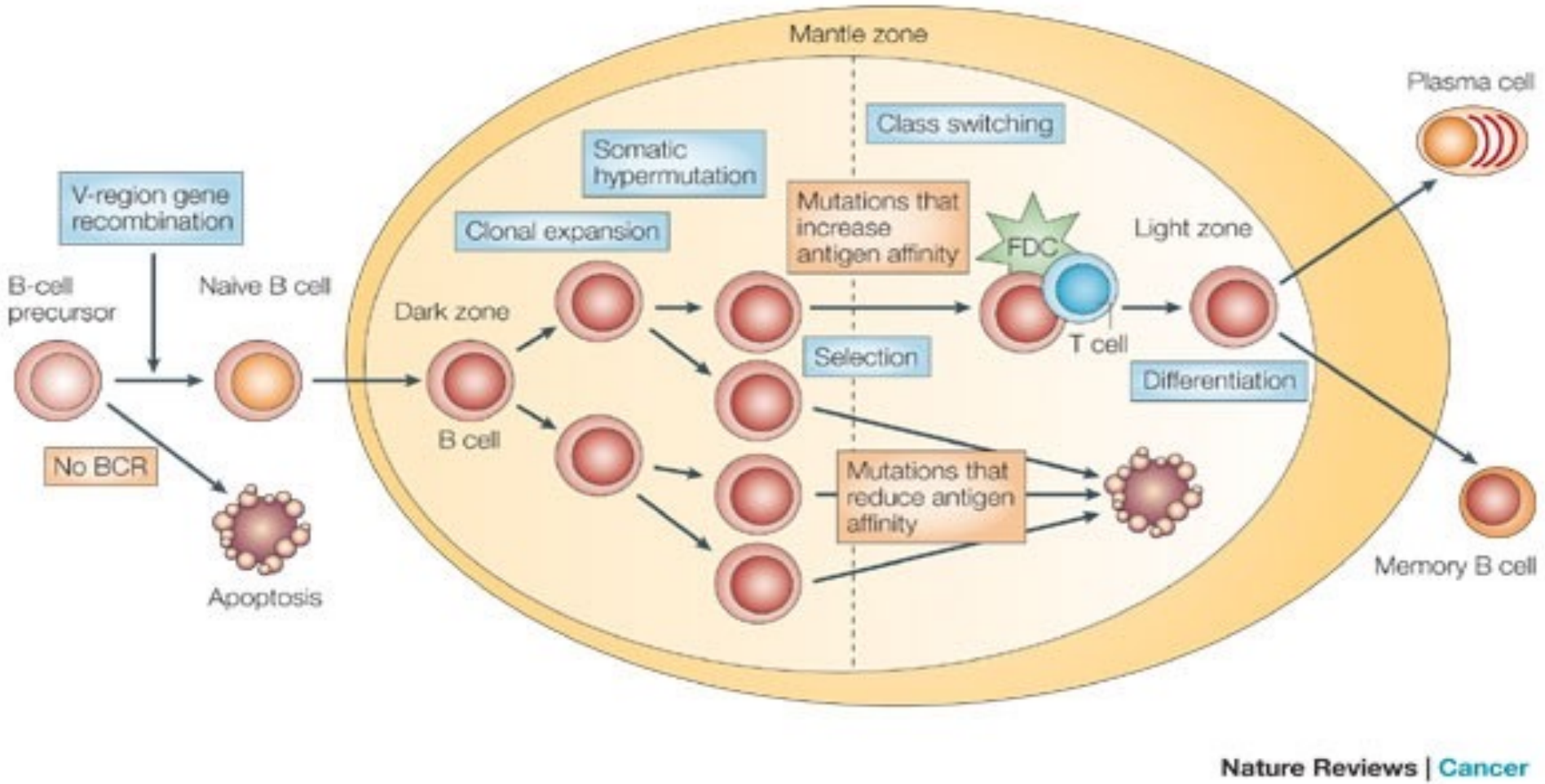
The frozen model approach to classification

- Each lymphoma subtype mimics a normal lymphocyte stage of differentiation’
- The genetic hit (if known) determines the differentiation block (FL)
- Concept of ‘Cancer stem cell’ rationale for RM
- Secondary abnormality determines subsequent behaviour (TP53)

‘Clonal evolution’

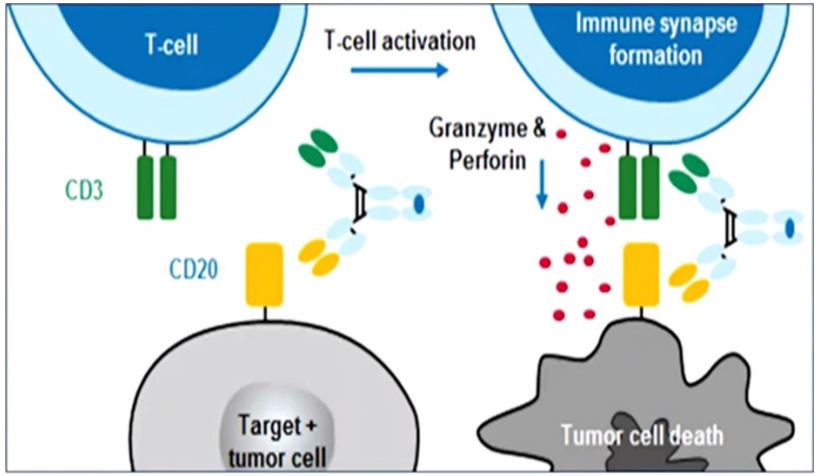
- Other determinants include: host,
  microenviroment
  epigenetics

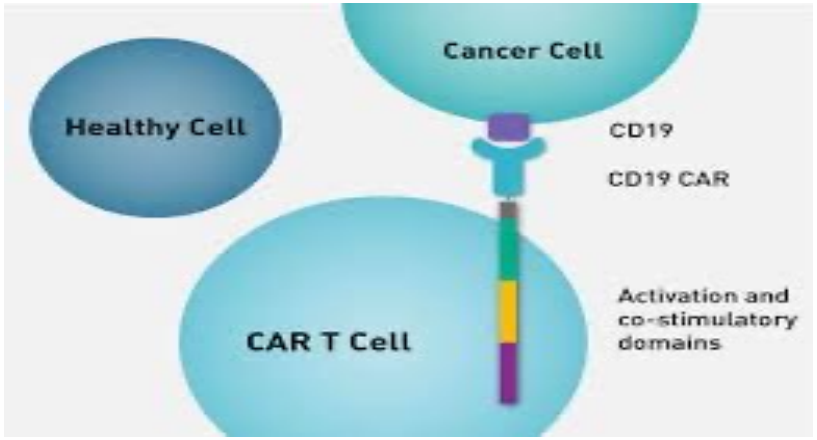
Lymphomagenesis: the frozen model



Therapy-snapshot

- Chemotherapy (pre-2000)
- Antibody based therapy
  - ‘naked’ ab
  - Conjugated ab (BV, Pola)
- Targeted therapy
  - BTKi, Pi3KI,
- Immune therapy
  - Allogeneic BMT
  - PD-1 inhibitor
  - CAR-T therapy
  - BiTE therapy
  - (IMIDs)





Personalised haematology

- Correct treatment, correct patient at correct time

OR

- Understanding the diagnosis/pathogenesis

Integrated diagnostics

Treatment defining versus prognosis defining (FL/tFL)

- Personalising ‘gold standard ‘therapy

Define aim of therapy

Consider co-morbidities, life-styles,

- Initiating treatment at the correct time

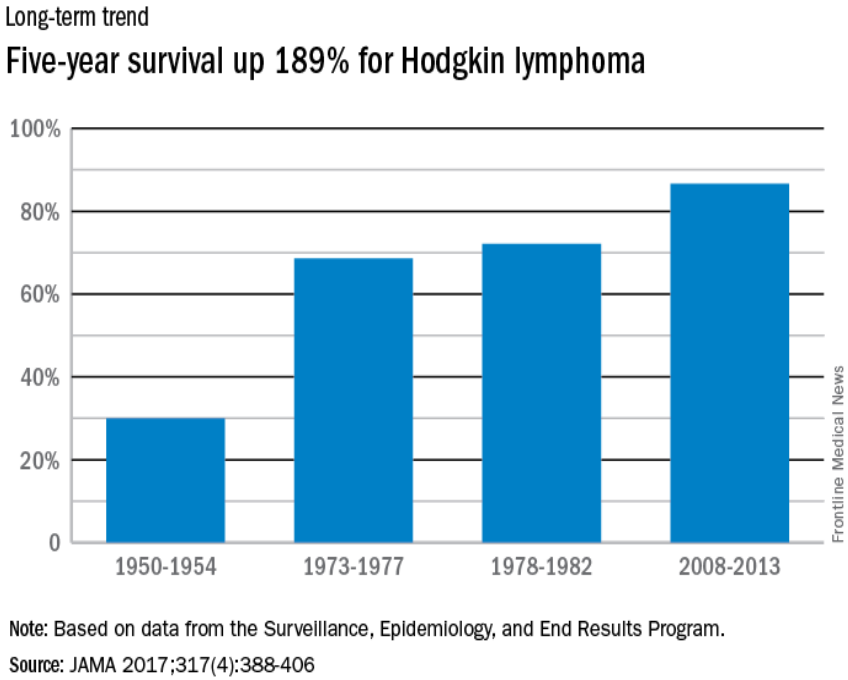
Burkitt, FL

Hodgkin's lymphoma

Peak incidence 20-29 years (2nd peak 60-70)
Cure 85% 1L, 50%-70% >1L

Pathogenesis
Classical Hodgkins lymphoma (95%)
'B lymphoid malignancey' without rearranged IgH
Genetic predisposition
EB virus implicated, but not universal

Ann Arbour Staging System
I, II, III, IV. A/B.
'E' Extranodal vs local extension
'X' Bulky > 10cm, med mass >33%



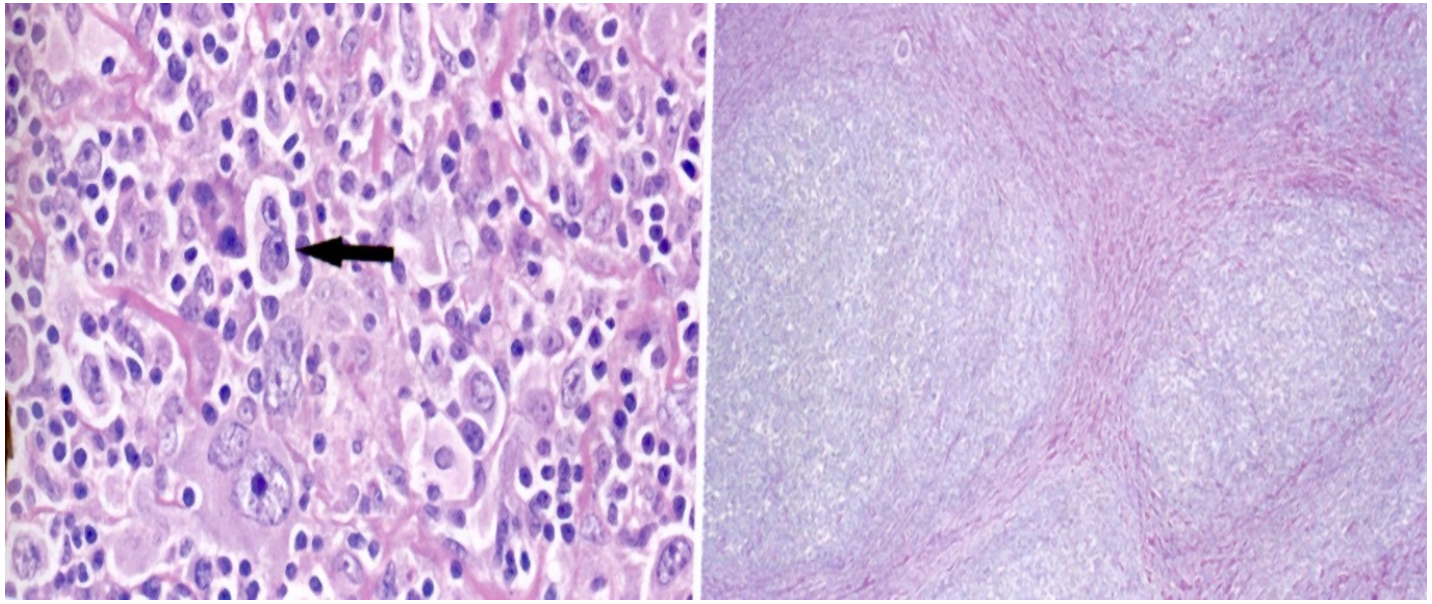
HL: Clinical features

- Mass in neck or axilla
- Mediastinal mass, cough /dyspnoea
- >60 yr atypical presentations (immune dysreg, MC)
- B symptoms (**tiredness)**
- Alcohol-induced bone pain
- Pruritus, no rash

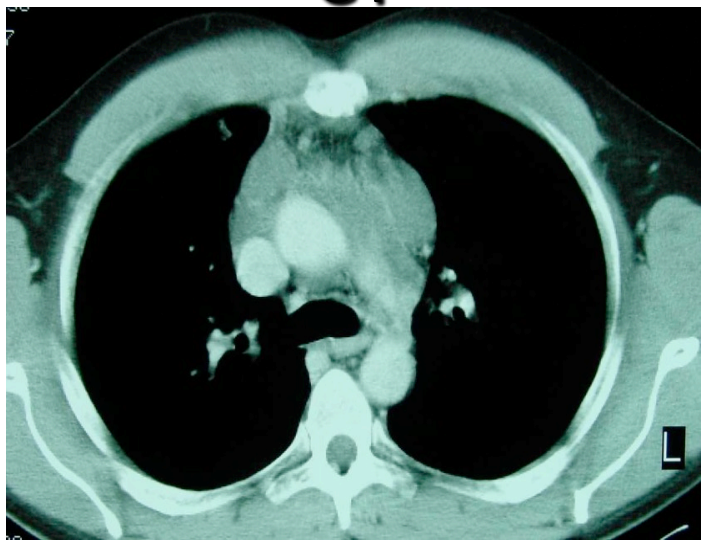
- International Prognostic Score (HC) for advanced disease
- Age>45, Male, Alb <40, Hb<105g/L, Stage, WCC>15, L<600

cHodgkins lymphoma

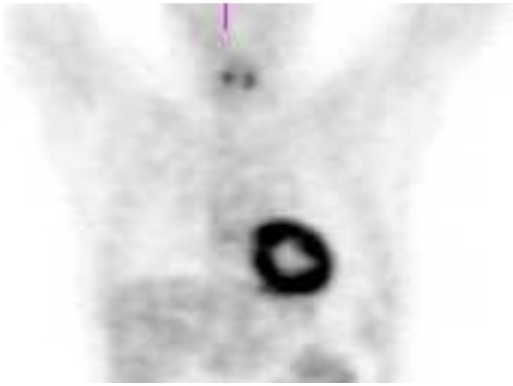
FBC, **ESR**, Biochemistry profile
PET scan
ECHO >45 years, or relevant history
Sperm banking (M)



CT



PET



Early stage HL

- Stage I/IIA (approx. 10% of HL)
- ABVD x 3/4 and IFRT
- Avoid RT Breast tissue <30 yrs, breast cancer risk

. Salivary glands, xerostomia

. Heart, small vessel disease

- However RT decreases relapse risk and local recurrence
- Expect to cure 98% of patients

Minimising toxicity in good risk patients

HD 10: reducing toxicity GSSLG

1370 pts 1998-2003
Early Favourable disease: I_A/II_A

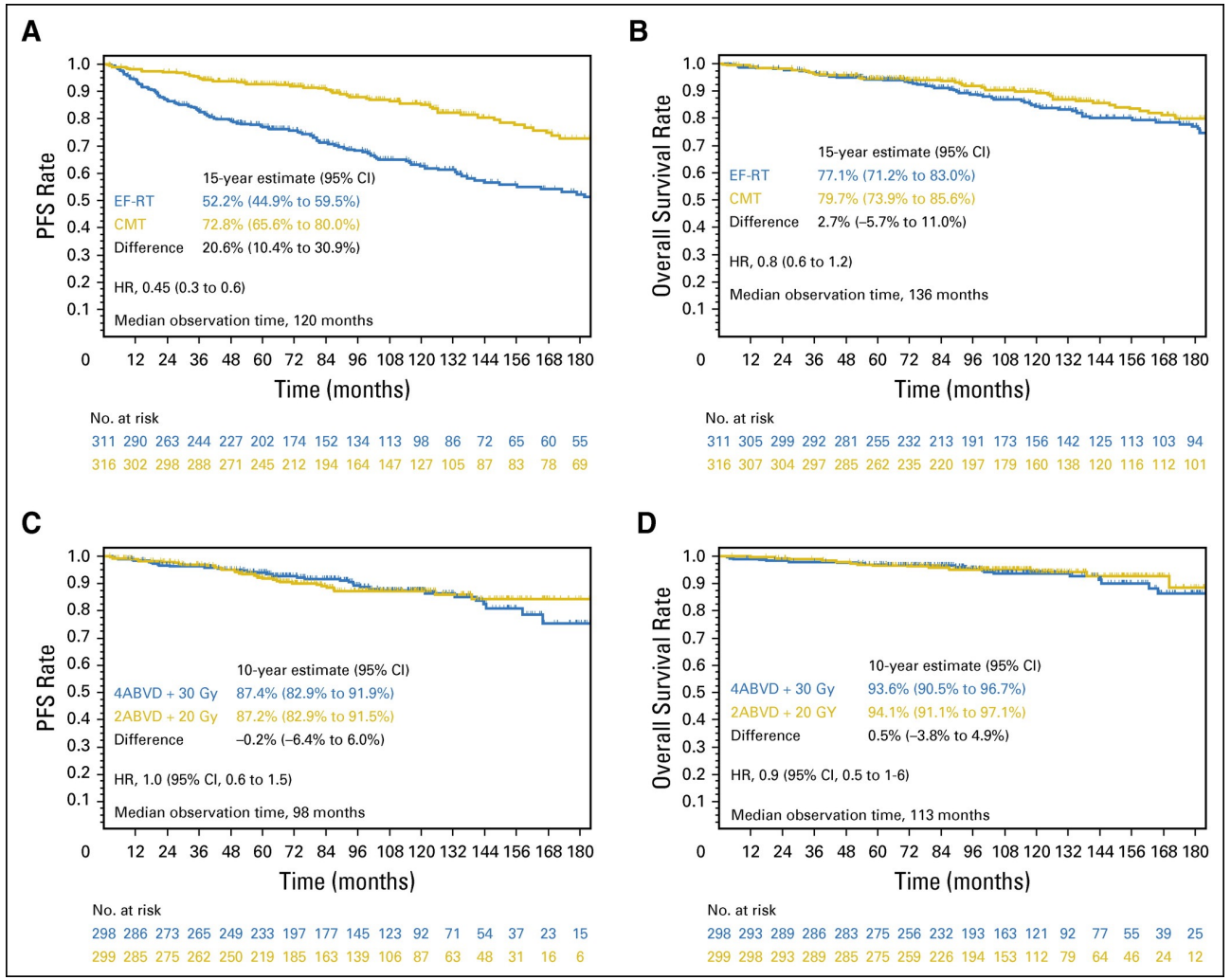
ABVD

2 cycles 4 cycles

Involved field RT

20 Gy 30 Gy

Results equivalent for all 4 arms:
5yr FFTF 92% OS 97%



Engert et al NEJM 2010

The ABVD versus escBEACOPP story

Advanced HL, Stage IIB, III, IV

ABVD,

- Developed in 1980's, Cures 85% of patients
- No alkylator
- Preserves fertility, reduces secondary cancer
- Increasing concern of dox associated breast cancer

** Give full dose therapy on time**

escBEACOPP

- Improved PFS, increased toxicity, same OS
- Mitigate toxicity by
  - Reducing from 6 to 4 cycles (18 vs 12 weeks)
  - Substitute Dacarbazine escBEACOPPdac
  - Lack of clarity about fertility

** Offer to patients with IPS of 4-7**

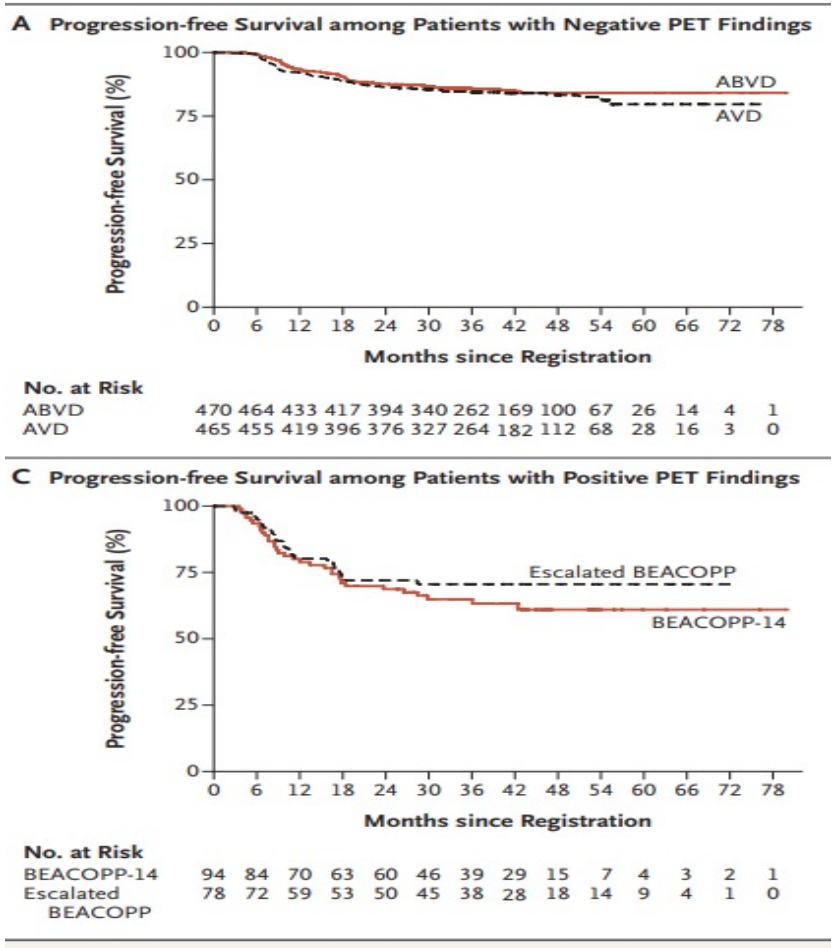
Risk adapted therapy: Rathl study

Phase 3 RCT of advanced HL
Role of interim PET scan in adapting treatment

1214 patients
ABVD primary therapy
Randomization at interim PET

Q1: PET-ve, omit Bleomycin- **proven**
Q2: PET+ve, all escalated to BEACOPP-like rx**-not proven**

Results
172 patients escalated
3 year PFS of 67%,
** personal view: individualise treatment**



Johnson et al NEJM 2016

The way forwards: Echelon 1 trial

BV-AVD versus ABVD

Stage III/IV disease

Stratified by IPS score

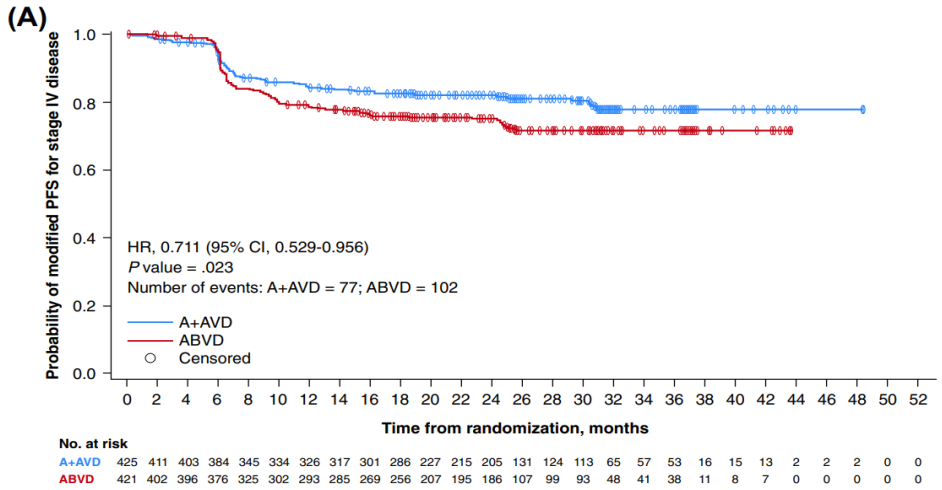
Pre-specified subset analysis

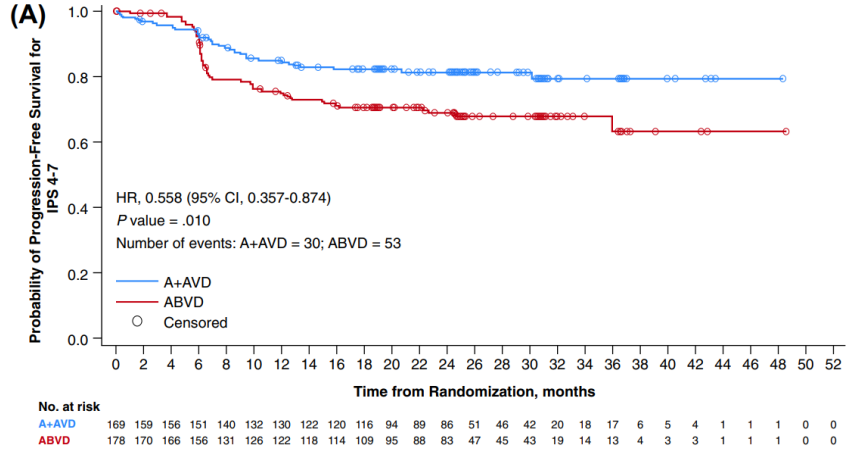
1384 patients randomised

Stage IV 64%

IPS 4-7 26%

Decrease pneumonitis, increase PN





Hutchings et al haem oncol2021

HL, more choice in 2024

escBEACOPP versus BRecaDD (PET-2 adapted)

1482 patients<60

Stage IIB, III, IV

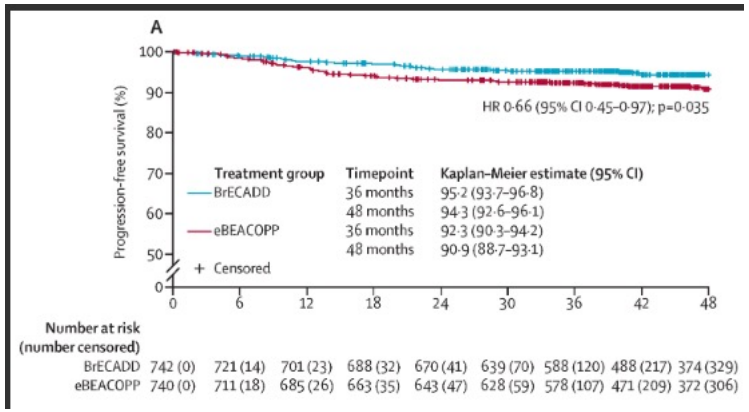
64% had 4 courses of chemo

Median FU 48m

PFS 94% vs 90%

RT for 15%

Borchmann et al Lancet 2024



N-AVD versus BV-AVD

970 patients, >12 years

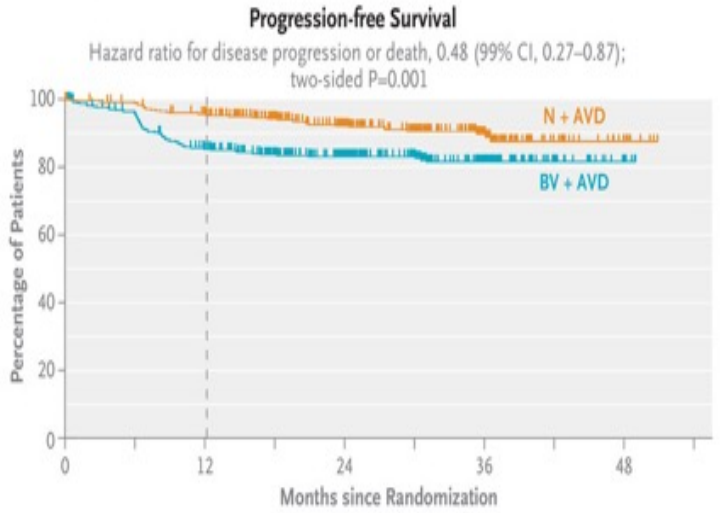
Stage III/IV only

Median follow up 12 months

PFS 92% vs 83%

RT for 7

Herrera et al NEJM 2024



Conclusion

Sifting the evidence to develop treatment pathways

Stage I/IIA

- HD10 if possible

Stage IIB, or high-risk features, III, IV

Standard therapy, (Rathl approach)

- ABVD/AVD for PET-ve patients, concern about escalation strategy

High risk patients IPS of 4-7

- escBEACOPDac, (BV-AVD, BRECADD, N-AVD)

Unanswered questions

- Optimal treatment of >60 years, 10 year OS of 40% (N-AVD?)
- Role of ct-DNA and TARC protein for MRD tracking

LG-NHL: Follicular lymphoma:
understanding pathogenesis clarifies management pathway

- 180 new cases pa in Ireland *(NCRI data*)
- Prevalence (B of E stats)
- Median age 60 (M>F)
- Geographic variation

- Present with painless lymphadenopathy
  - Rarely hepatosplenomegaly or B

- Usually stage IV disease, (Ann Arbour)

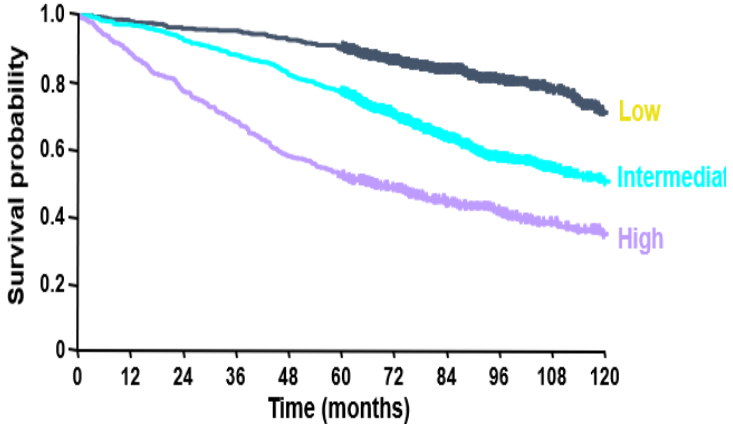
Follicular Lymphoma: Diagnosis and staging

- As for HL
  - SPEP, no ESR,
- Increasing use of PET (?)
- Decreasing BMA/Bx use, (PET)
- BM/PB: morphology, immunophenotype, +/- FISH/molecular

- Ann Arbour staging
- FLIPI index for **prognosis**
- **No px biomarkers/radiology**
- **Patient wish, co-morbidity**

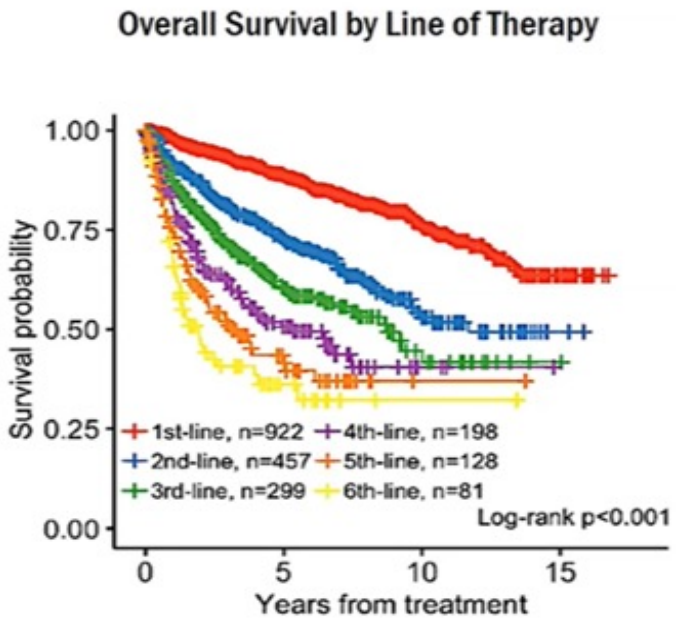
Predicting outcome in FL: clinical behaviour where are the biomarkers?

Flipi index

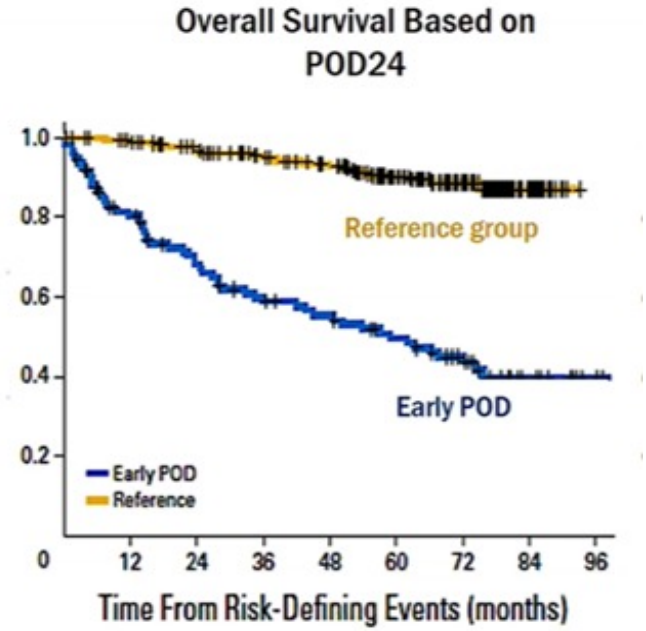


Solal-Céligny P, et al. Blood 2004

Age >60
PS 2-4
Stage III/IV
Elevated LDH
No of nodal sites >3



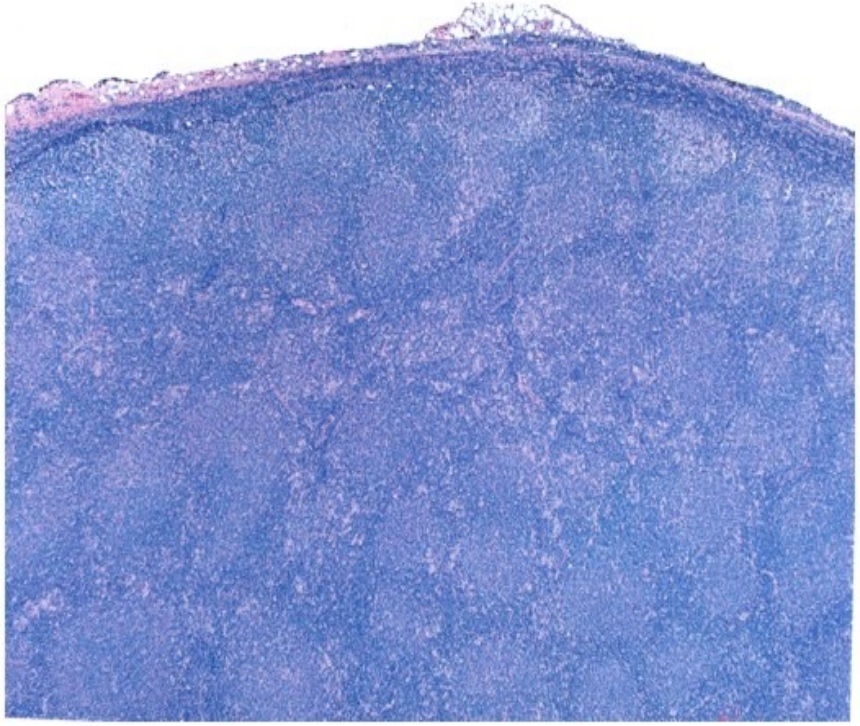
Batlevi et al
Blood Can Jour, 2020

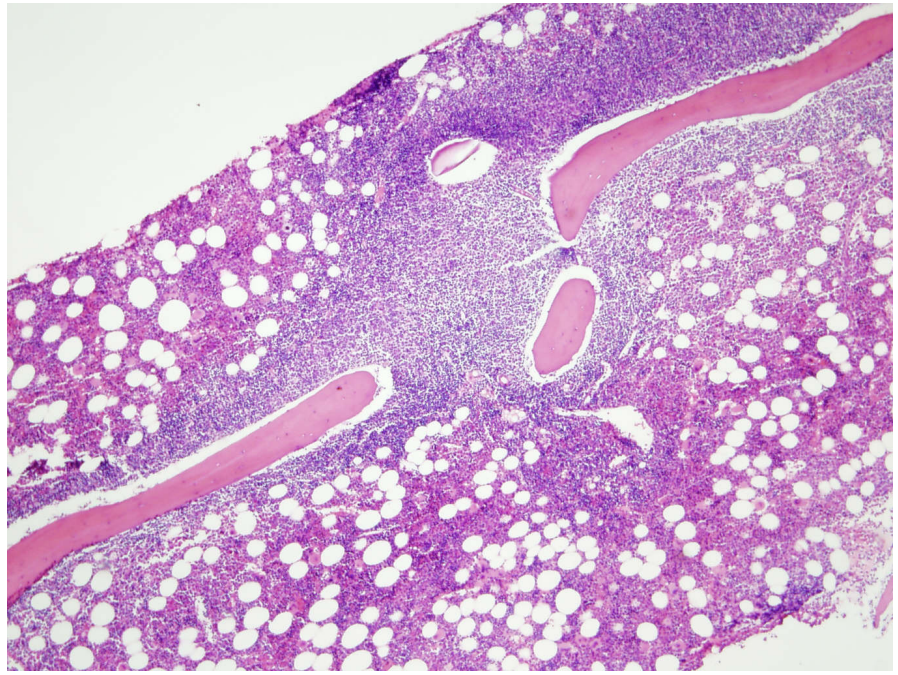


Casulo et al
Jour Clin Oncol, 2020

Predictive markers
PET at end of primary therapy
Pathology of microenv (TI rich versus macrophage)
Secondary mutations
MRD/Kinetics

FL lymphoma
A BM and GC based disease





Typical immunophenotype
CD20, CD10, CD5-ve, t(14;18)(q13;q32)
Results in upregulation of the anti-apoptotic BCL2

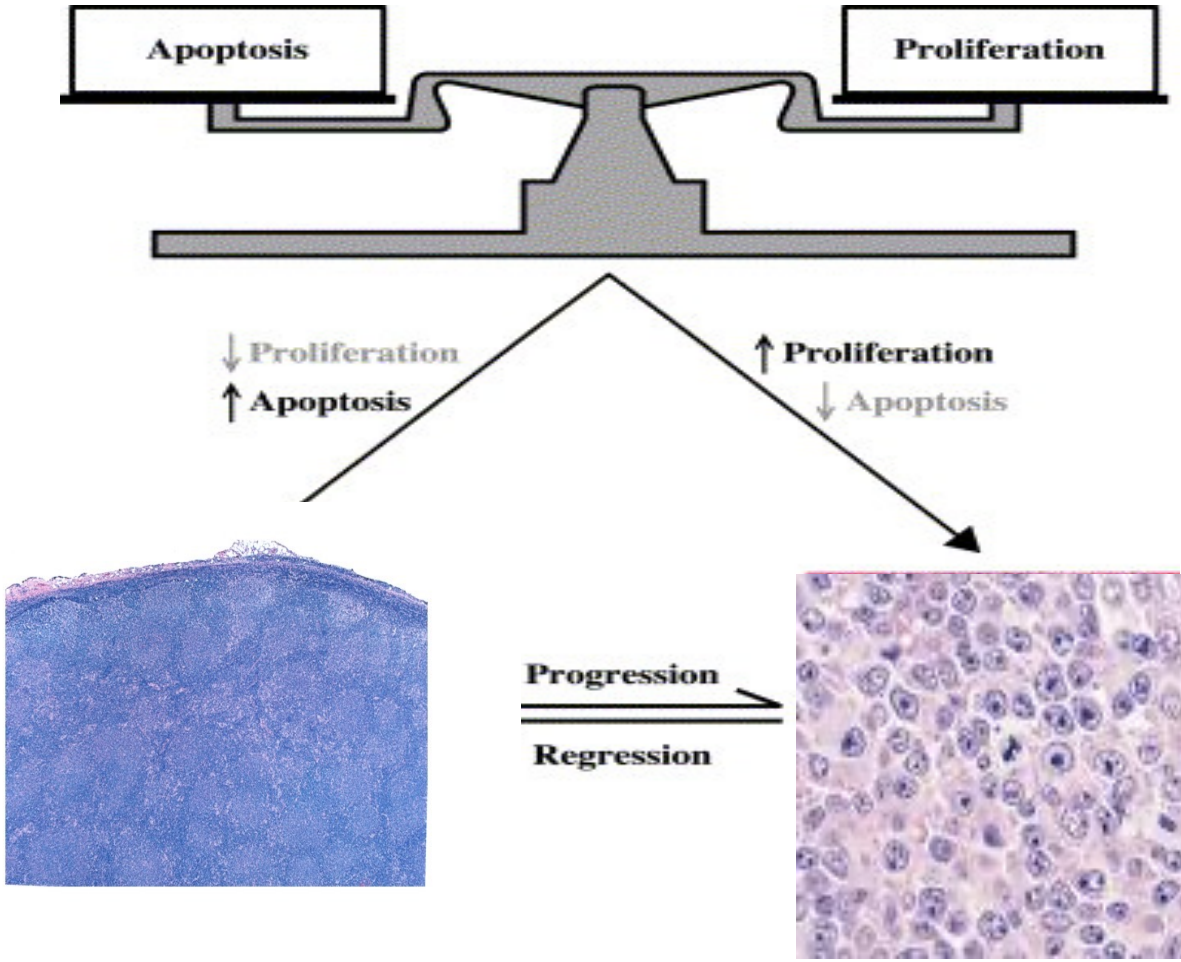
WHO 5 classification
Classical FL replaces grade 1, 2 and 3a
Follicular Large B cell Lymphoma replaces Grade3b
Some unusual subtypes
Grading reproducible within unit

Most cancers are proliferative: follicular lymphomas based on failure of apoptosis

What is happening in GC

Isotype switch from M to G
Hypermutation in CDR3 increases diversity

Proliferation if good fit
Apoptosis if bad fit
Persistence if BCL2 upregulated



Think in terms of lifetimes, not disease episodes

The future therapeutic landscape is not clear

Do no harm

Bendamustine and BITE/CAR-T
Ritux Maintenance and Covid

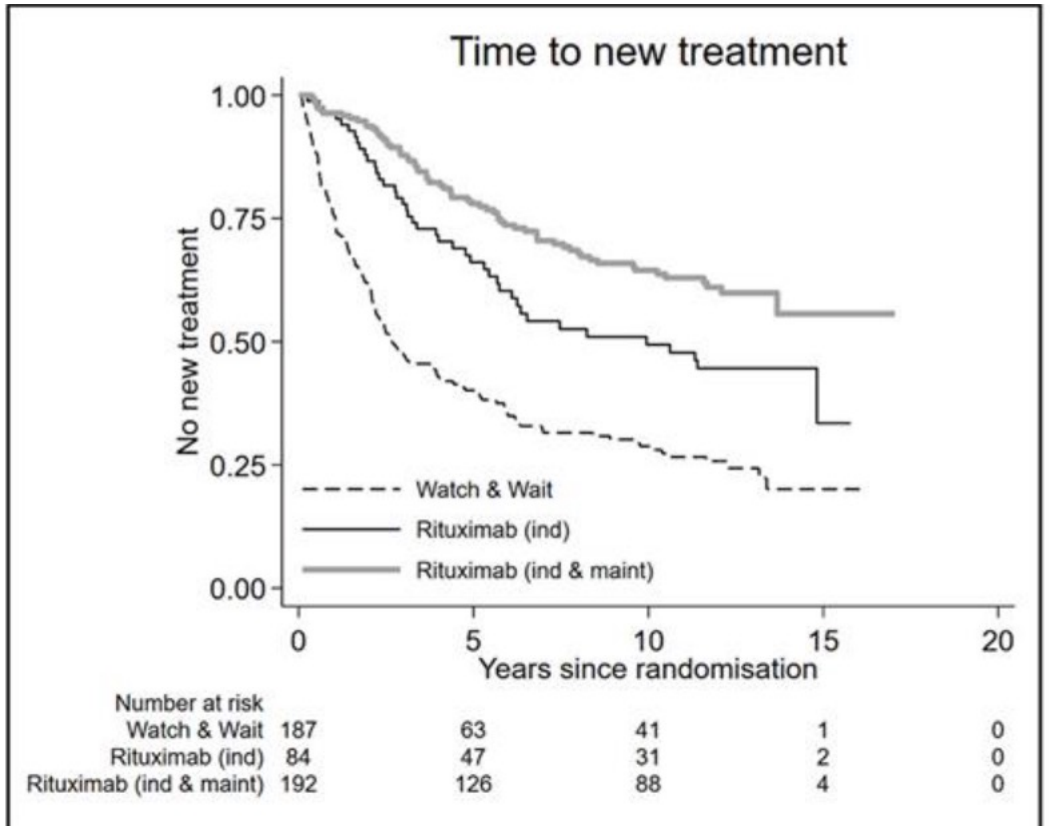
Follicular Lymphoma: Treatment

Stage I (II):

- ISRT, 24Gy cure 50%, PET stage

Stage II-IV

- Watch and wait: inactive, genetically unstable lymphoid population
- Rituximab single agent may increase PFS

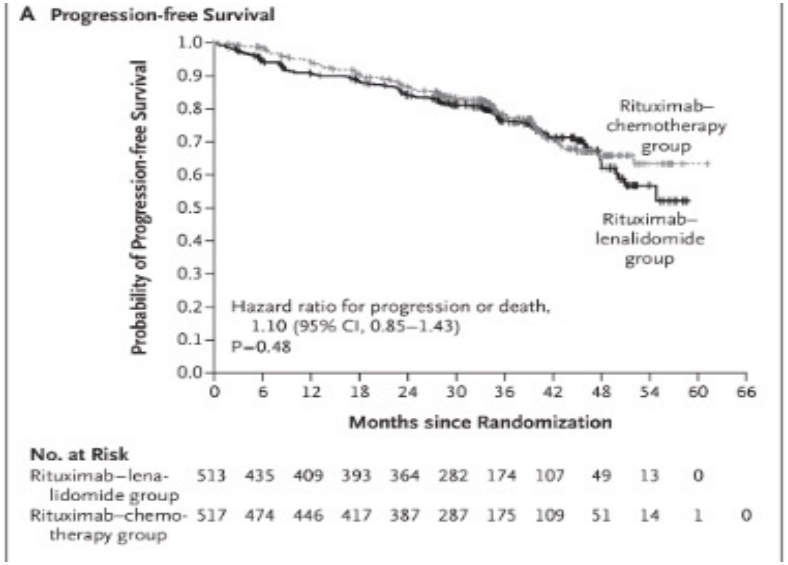


Northend et al Blood 2022

Follicular Lymphoma: Treatment

Progressive or symptomatic disease

- R/O-CVP / R/O-CHOP (R-Benda)
- R2 (Relevance trial)
- R maintenance never over 80 years
  should everyone get it (
  2 or 3 monthly
  limited evidence after Benda



Relapse 1

- R/O-Chemo,
- Immunotherapy (antibody+micro-envrioment R2)
- Obin-Zan (median PFS 28m)
- **Consider POD24,** Exclude transformation
- Auto SCT

BiTES, CART, BMT- chemorefractory disease

Allo-BMT, available

- Long term OS is about 70% (SJH)
- TRM is main cause of death. QOL

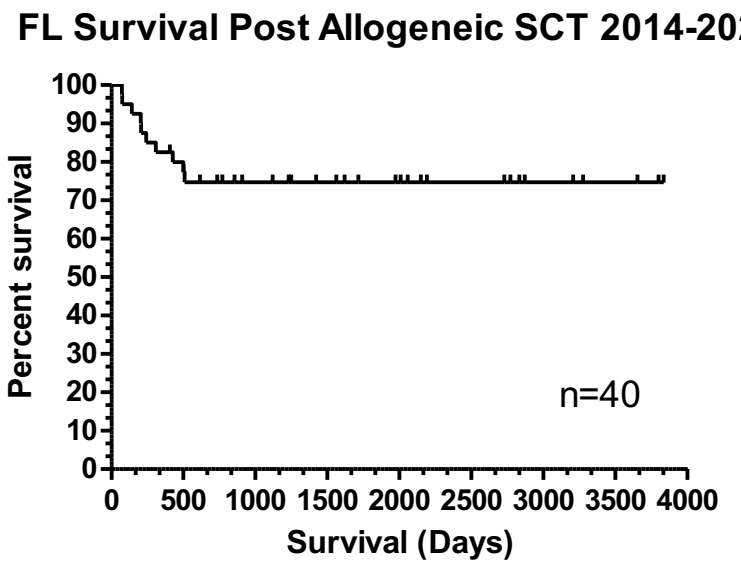
CART, not available

- Axi-cel (53m)
- CR rate 79%, Median PFS is 57m

BITES, CUP for Mosentuzamab and Epco

- CR rates 60-70% (30%), Median PFS is 24m and 15m
- Short follow up
- Induction strategy and time defined treatment

FL Allogeneic SCT 2014-2023 (SJH)



- N=40
- 24M and 16F, median age 53 years (34-63)
- 8 patients post-auto
- OS at 1 and 5 years 82.5% and 75%

Follicular lymphoma: auto vs allo in early relapse: CIBMTR data

N= 440 with ETF	ASCT N=240	Matched sibling N=105	Matched unrelated N=95
Median Prior Therapies	2 (1-6)	3 (1-9)	3 (1-8)
5 year OS	70%	73%	49%
5 year NRM	5%	17%	33%
5 year relapse rate	58%	31%	23%

Personal view: SJH results

Auto vs allo is not a fair comparison

Auto-SCT: older patients, lower risk disease, no sib donor, OS of 50%

Allo-SCT: younger patients, chemo-insensitive, sib donor, OS of 70% pre-covid

Smith et al Cancer 2018

FL: Bi-specific antibodies in

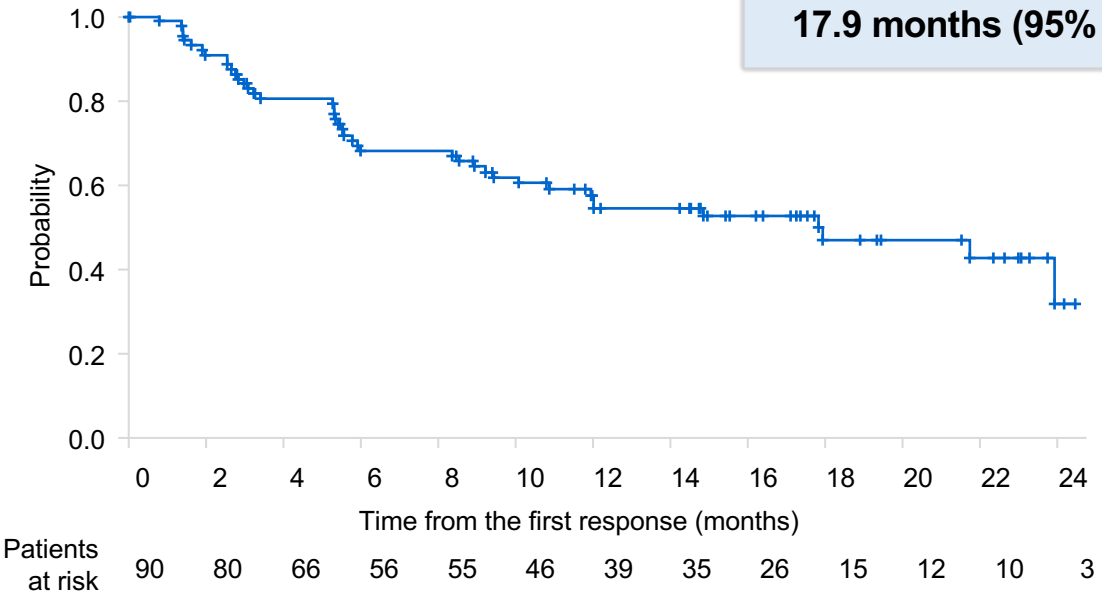
Agent	Mosunetuzumab[1]	Odronextamab (REGN1979)[2]	Epcoritamab (GEN3013)[3]
Phase	I/II (NCT02500407)	II (NCT02290951)	I/II (NCT03625037)
Population	R/R indolent NHL after ≥ 2 prior regimens	R/R B-NHL after 2 prior regimens	R/R B-NHL after prior anti-CD20 mAbs
N (efficacy/safety)	90 (FL cohort)	30/136	16/68 (5 at ≥12 mg level)
Efficacy (with FL/iNHL), %	▪ ORR: 80 ▪ CR: 60	▪ ORR: 90 ▪ CR: 70	▪ ORR: 80 ▪ CR: 60
Safety (all patients), %	▪ CRS: All grade: 44 Grade ≥ 3: 2 ▪ Neurotoxicity[a]: – All grade: 4 – Grade ≥ 3: 0	▪ CRS: – All grade: 61 – Grade ≥ 3: 7.4 ▪ Neurotoxicity: – All grade: NR – Grade 3: 1.5	▪ CRS: – All grade: 59 – Grade ≥ 3: 0 ▪ Neurotoxicity: – All grade: 5.9 – Grade 3: 2.9

[a]Data from abstract

1. Budde et al. ASH 2021. Abstract 127
2. Bannerji et al. ASH 2020. Abstract 400.
3. Hutchings et al. ASH 2020. Abstract 402.

- **T cell engagement, activation and delivery of cytotoxic granules at T cell-Tumour cell synapse**
- **T cell expansion at site of activation**
- **Cytokine recruitment of additional T cells**

Mosunetuzumab: bispecific antibody
Phase 2 study >2 or more prior lines, 90 patients



- **Median PFS: 17.9 months (95% CI: 10.1, NE)**

- **60% CR rate significantly greater (p<0.0001)* than 14% historical control CR rate[2]**

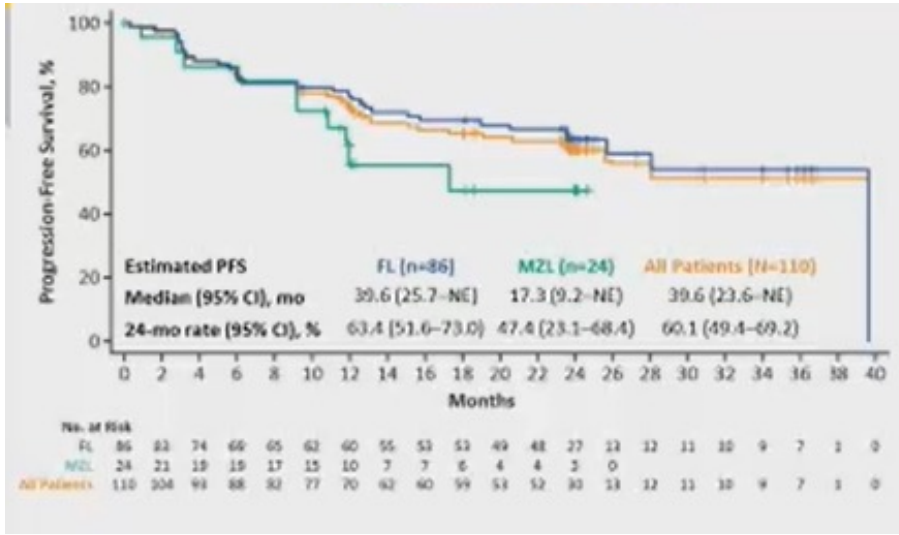
1. Cheson et al. J Clin Oncol 2007;25:579–86
2. Dreyling et al. J Clin Oncol 2017;35:3898–905

Budde et al ASH 2021

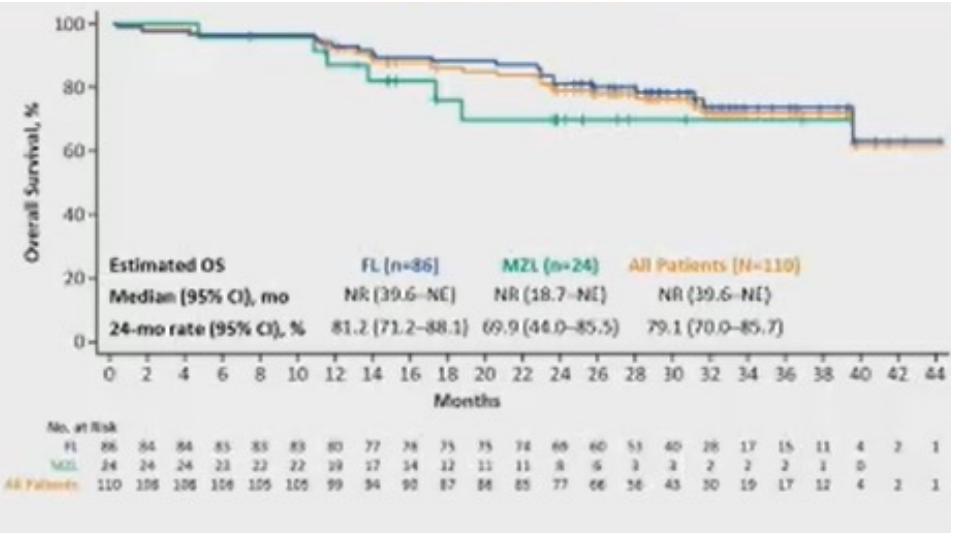
Follicular lymphoma: CAR-T ZUMA 5 trial: 2 year follow up

Median PFS 40 months and OS not reached

PFS



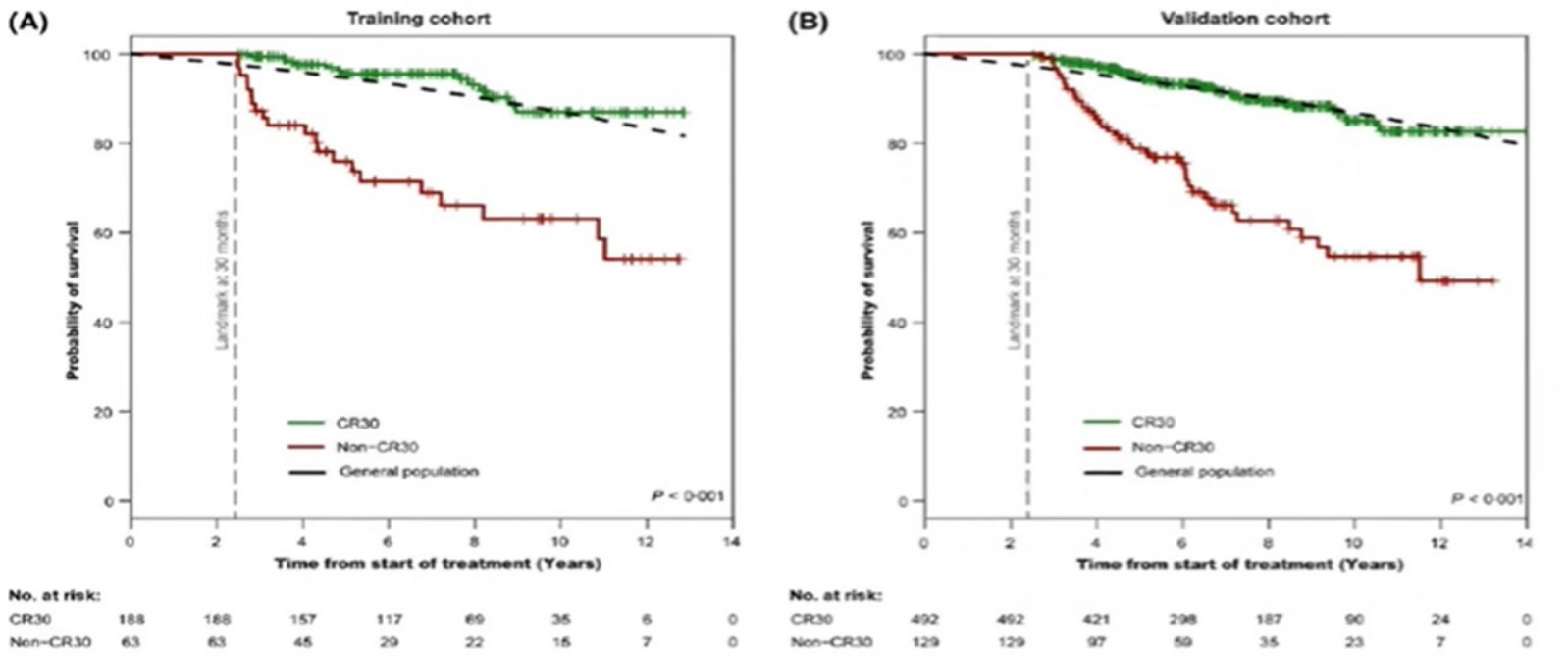
OS



Median duration of response: 39 months

Neelapu et al ASH 2021

Patients in CR1 at 30 months have a similar OS to a matched population



10 yr OS;
53% non CR30 pts (red line)
87% CR 30pts (green line)
Matched population blue broken line

Magnano et al BJH 2019

Conclusion

- Predictive biomarkers needed at dx/EO first line therapy
- MRD strategy following first line therapy

Good risk patients

- CR1; discharge at 10 years (1% risk of relapse)

Bad px patients

- Sequencing of new treatments, eg

CIT and risk stratified RM (chemo-free),

Bispecific antibody

CAR-T or allogeneic SCT

High grade lymphoma
'DLBCL' is commonest type

- Median age is 65 years, M>F
- Incidence of 380 pa in Ireland *(NCRI)*
- Clinical features
  - Painless lump
  - Atypical presentations common,
  - Varied referral route; EWS at SJH via pathology
- Staging
  - Std, LDH
  - BMA/Bx – yes but discussion
  - PET scan (but don't delay treatment)
  - IPI and ECOG

How can pathology help

The basics

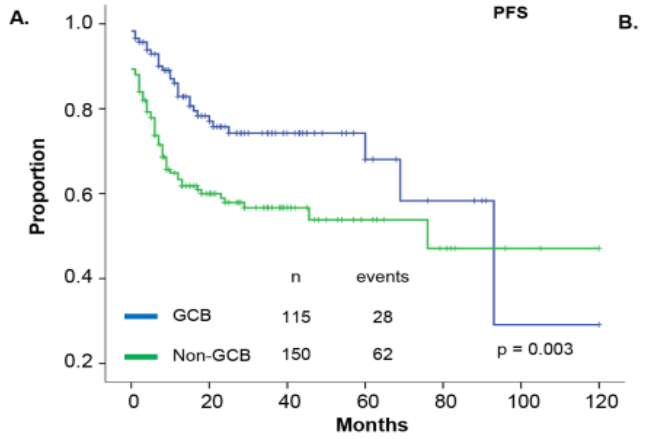
IHC

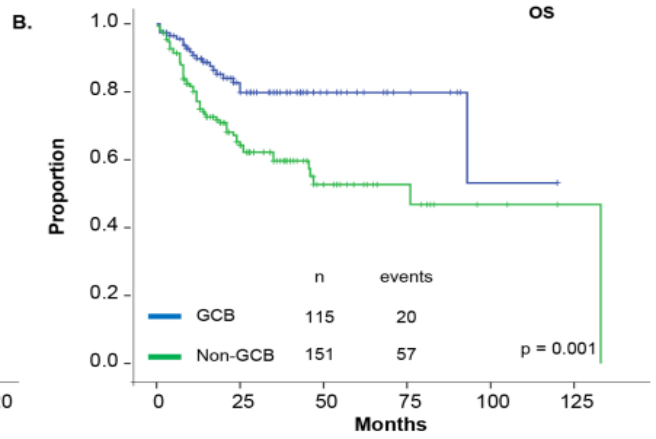
- GCB vs non-GCB
- Ki67
- Double expressor
- P53 expression

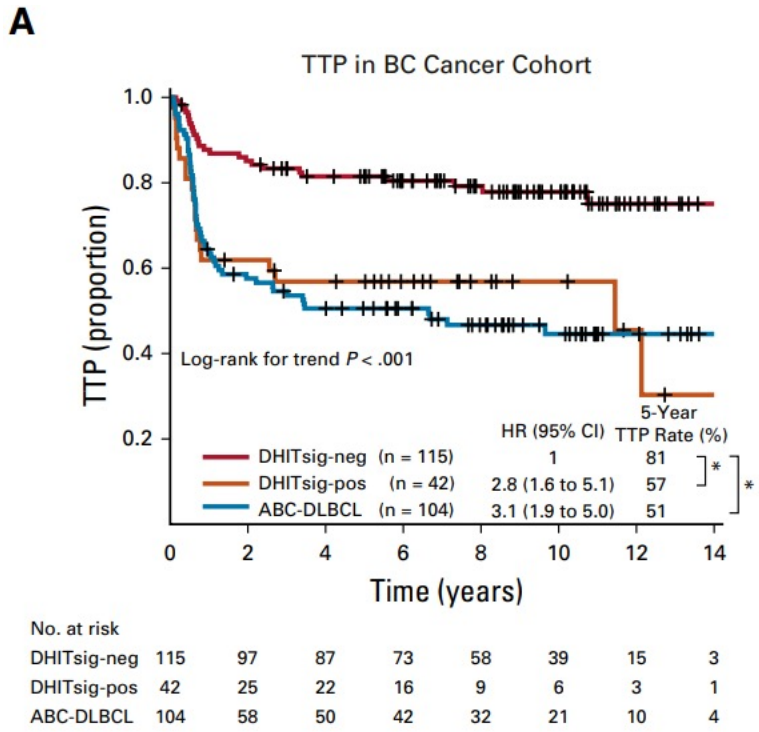
FISH

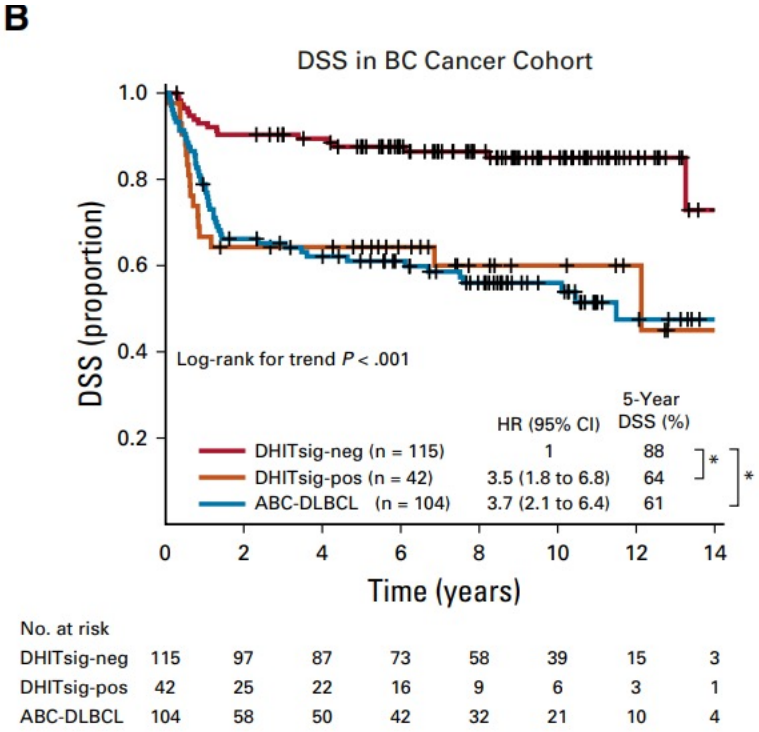
- t(14;18)
- T(8;14) and variants
- ***BCL6 break apart***

Molecular subtyping

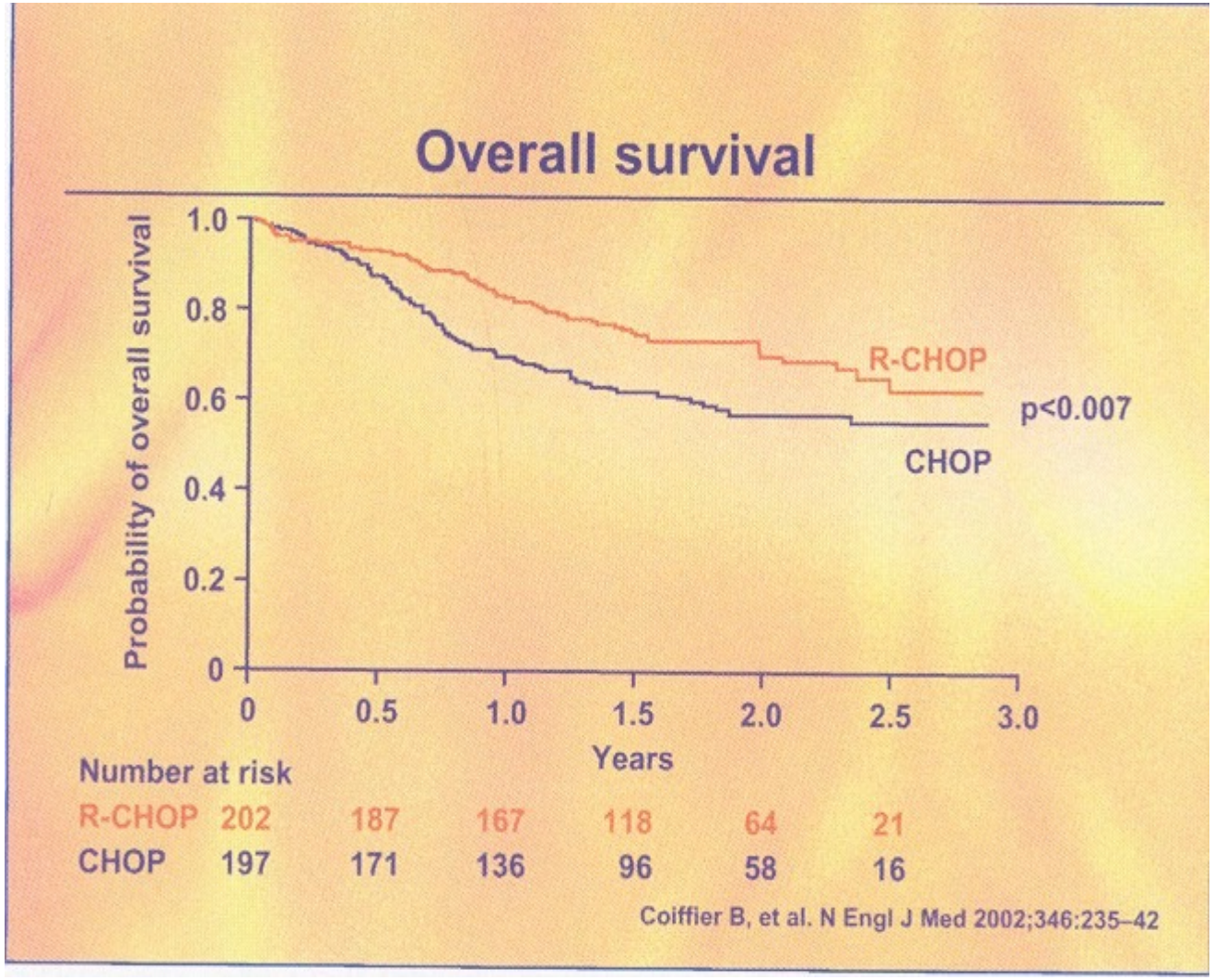








First line treatment is still R-CHOP



The add ons

- 2 week wait
- t(FL); role of RM
- CNS: EOT iv MTX
- **Clinical assessment for early progressors**
- Intensify treatment
- IFRT

Relapsed Refractory setting

- Salvage + ASCT (25% cure)
- Salvage + allo
  - The sequencing challenge
  - Need to have an effective bridge
  - 50% cure
- BiTE: Glofitamab, Epco (CUP) (3rd line)
- CIT: Pola/tafasitamb
- CART: tisacel/axicel (3rd line) (50% OS at 2 years)

- Risk of relapse after 24 months low: discharge
- No role for surveillance scanning

Unmet need

- DLBCL risk stratification
  - Use current tools more effectively
  - Molecular subgroups may direct therapy

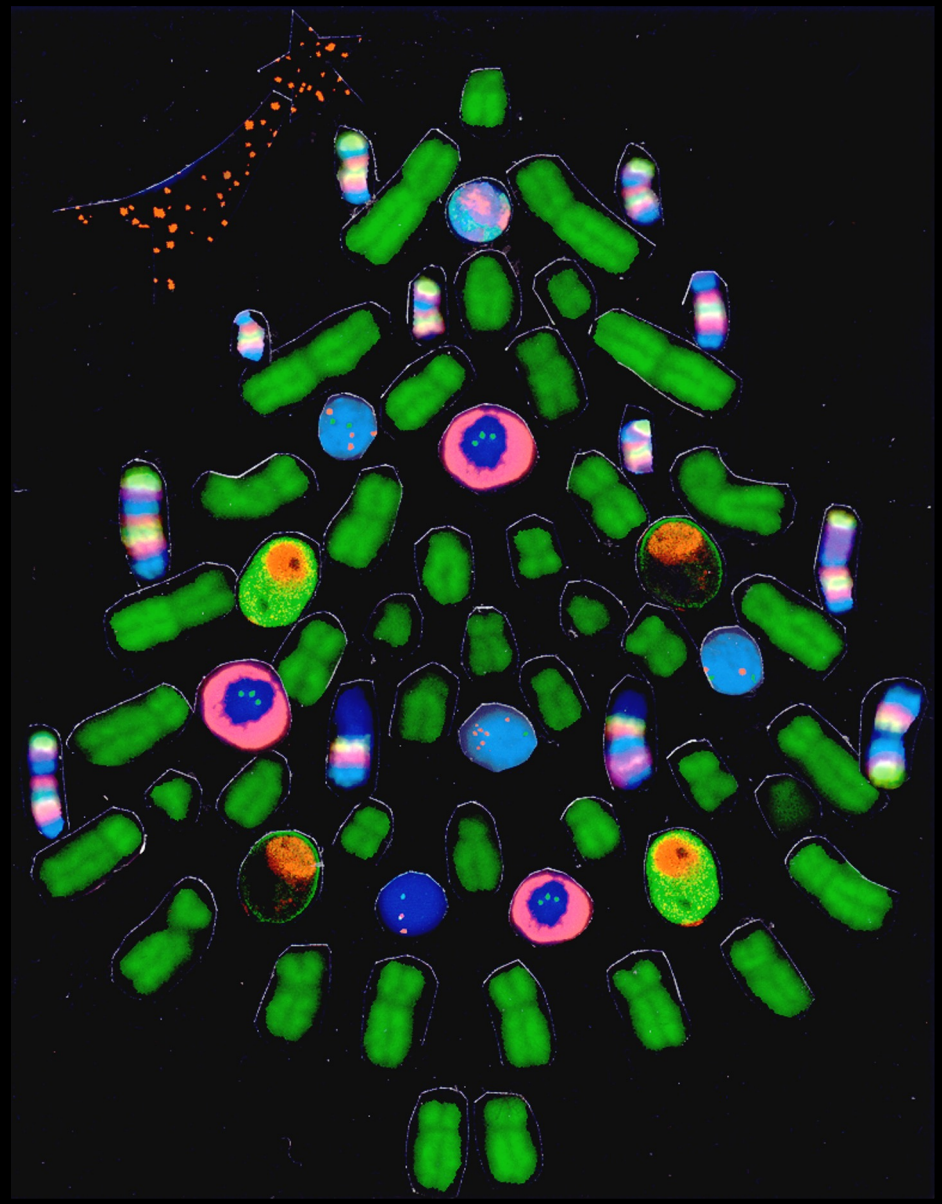
- Improving first line therapy
  - Study design flaws, academic versus industry sponsored
  - Incorporation of translational research in CT
  - Delayed treatment decreases survival
  - Addition of novel therapy (bi-specific or conjugated ab)
  - Older patients not eligible for R-CHOP

Take home messages – Changes in practise

- **Staging**
- (HL, FL, DLBCL)
- Methodology, Prognostic factors, Directing therapy

- **Treatment**
- Treatment classes
- Precision medicine, the softer end!
- Role of allo/CAR-T

- **Follow up**
- FL



Merry Christmas and Happy 2003 Year!

Iwona & company

- The central role of the germinal centre

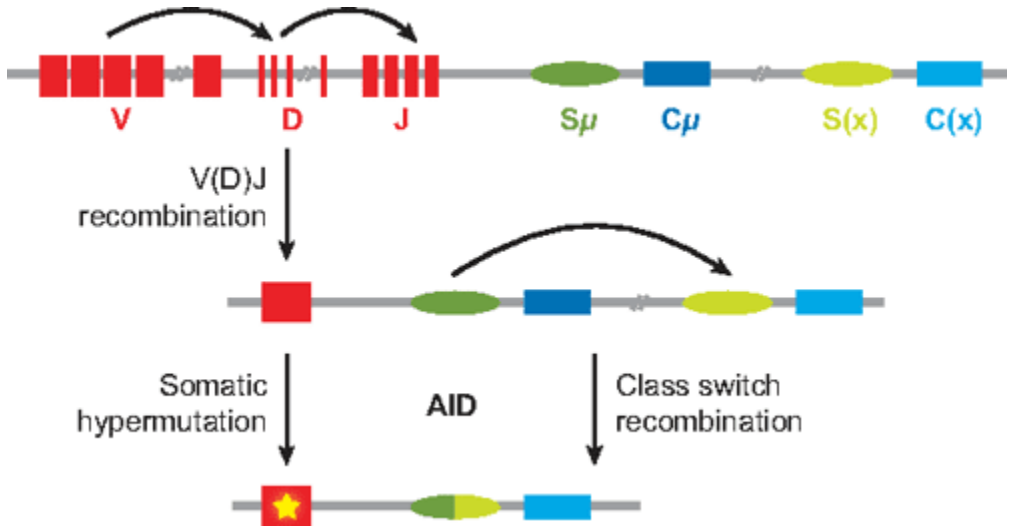
- Refine and educate the CDR3 region of the Ig gene (isotype switch, SHM)
- Pre GC are under less control then post GC

- GC associated lymphomas are the commonest type and include

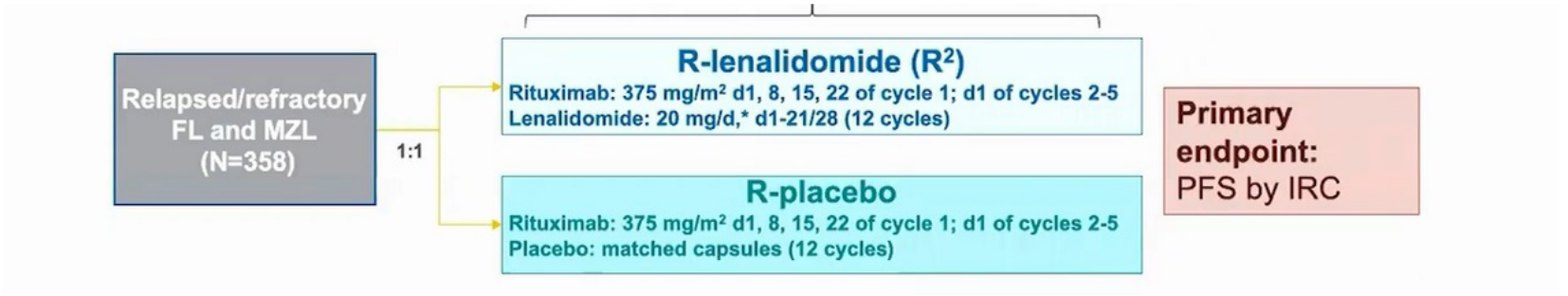
  FL, DLBCL (GC subtype), tFL, DH DLBCL, Burkitt lymphomas

Molecular tracking of lymphocyte

Productive IG rearrangement:	transition to mature B lymphocyte (BM)
Class switch recombination:	transition from ag naïve cell (MZ)
Somatic Hypermuation:	transition to high affinity IgG antibody (FC)

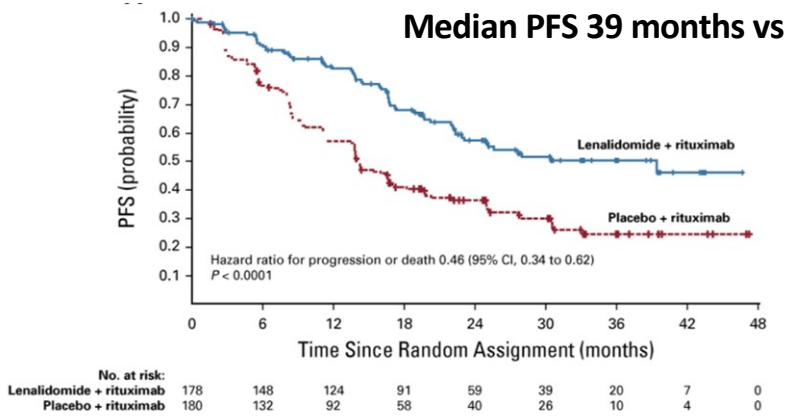


Relapse/Refractory FL/MZL
AUGMENT; rituximab lenalidomide compared to rituximab

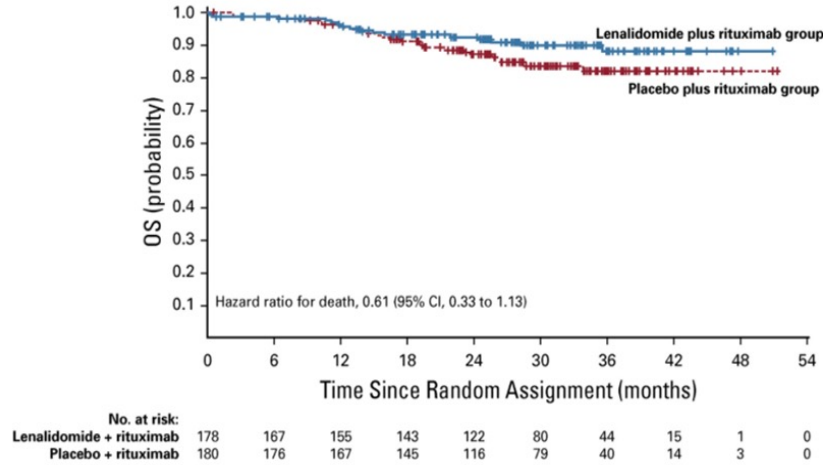


PFS

Median PFS 39 months vs 14 months



OS



90 patients!
57% pts 1 prior line in ritux len arm
83% FL pts and 17% MZL
Ritux refractory patients excluded

2 yr OS 95% Rlen vs 86% R

Leonard et al J Clin Oncol. 2019

Follicular lymphoma: CART results

Patient features Tis-a-cel

- 29% pts => 5 lines therapy
- 37% pts had ASCT
- 65% pts were POD 24
- Grade 3/4 CRS 0%, ICANS 1%

- **Patient features Axi-cel**
- >2 years follow up
- 50%=> lines 3
- 24% had aSCT
- 55% were POD 24:
- Grade 3/4 CRS 6% and ICANS 15%

Thieblemont et al 131 ASH 2021