Fred Hutch Cancer Center

Indolent Non-Hodgkin Lymphoma

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Disclosures

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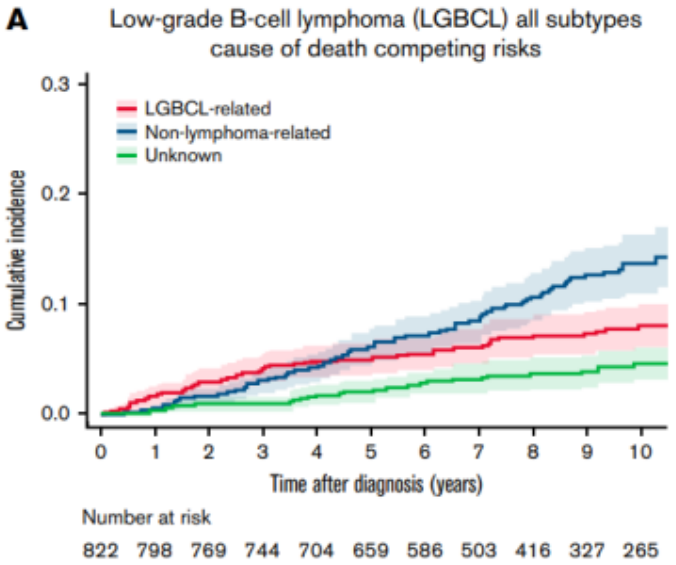
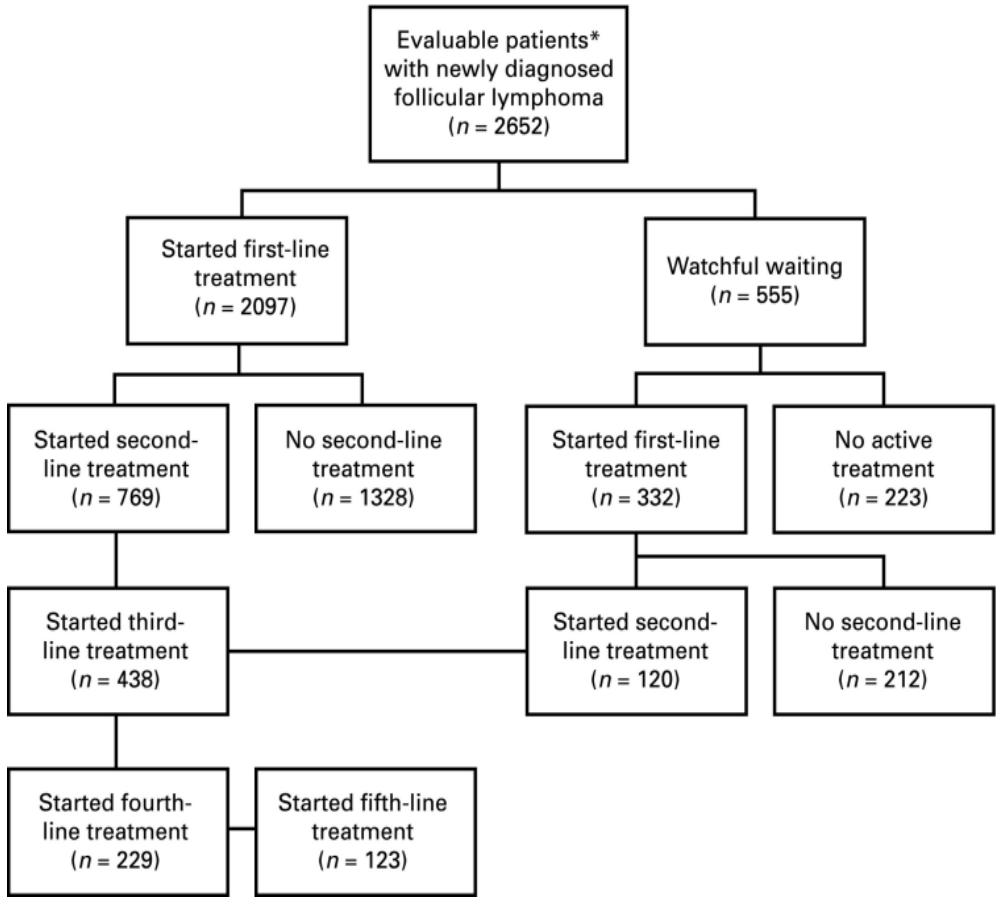
Outline

- Review key presenting and pathologic features of indolent non-Hodgkin B-cell lymphoma (iNHL)
- Management of iNHL in frontline and relapsed/refractory settings: newly gained (and lost) therapies for R/R disease
- Explore areas of unmet need in iNHL and anticipated next steps

iNHL Natural History

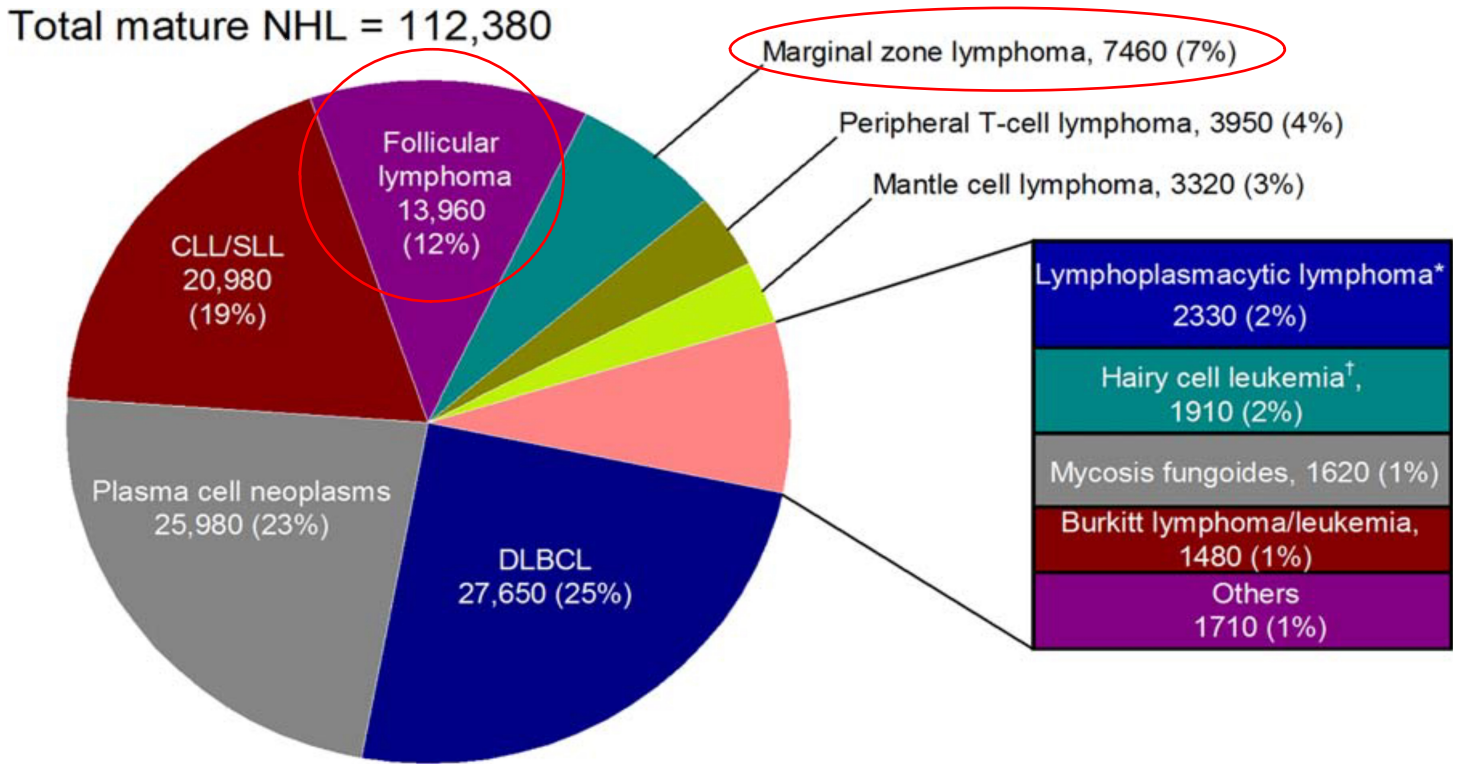
- Presents with advanced disease that progresses slowly
- Iterative treatment responses and relapses
- Incurable with conventional therapies
  - Possible exceptions? Limited stage disease, cellular therapies
- Often not life-limiting





Tun et al, Blood Advances Sep 2022; Link et al, BJH 2019

Epidemiology



Estimated Cases and Distribution of Mature Non-Hodgkin Lymphoid Neoplasm Subtypes: US, 2016

Teras et al. CA Cancer J Clin 2016;66:443–459

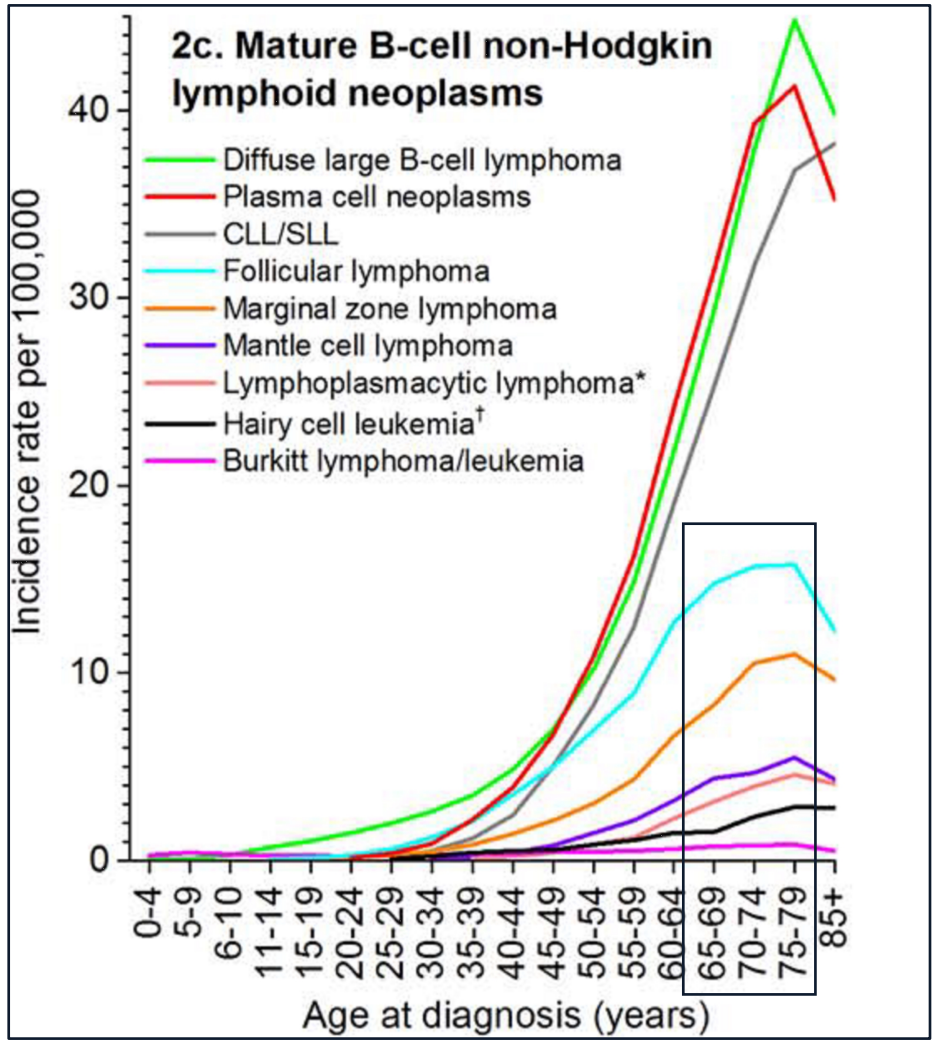
Risk Factors

Follicular lymphoma

- Autoimmune conditions
- Benzene, other solvents
- Agent Orange (herbicides)
- Radiation
- Burn pits
  - PACT Act Aug 2022 (presumptive conditions)

Marginal zone lymphoma

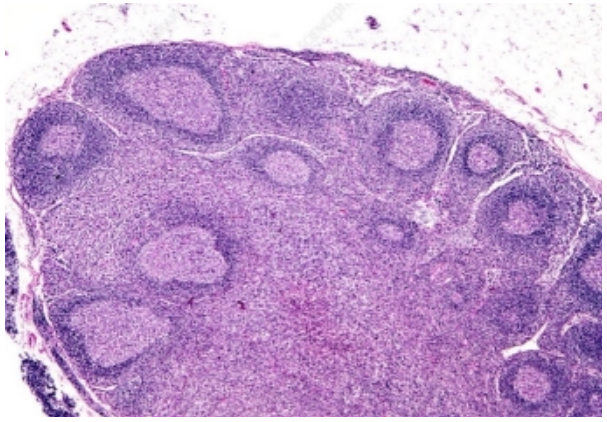
- As above, also certain infections (e.g. H pylori, C psittaci)



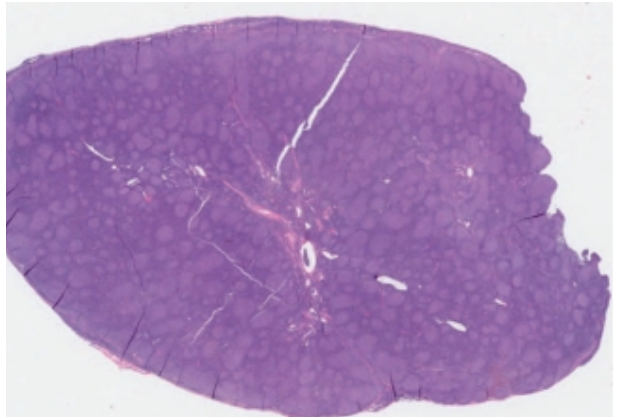
Teras et al. CA Cancer J Clin 2016;66:443–459
https://www.publichealth.va.gov/exposures

Work-up

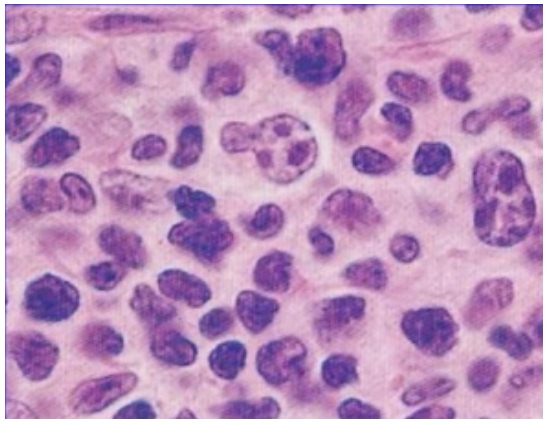
- Excisional or incisional biopsy preferable to core for morphology and architecture (FNA inadequate)
- Labs include LDH, hepatitis B; sometimes β2M and SPEP can be helpful
- Diagnostic CT, FDG-PET
- Marrow exam (consider if clinical stage I-II disease; not needed outside of clinical trials in known advanced stage)



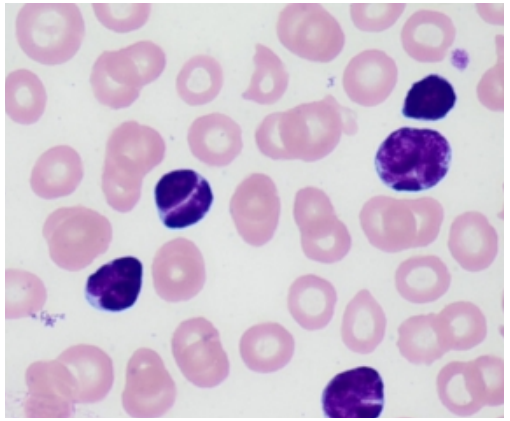
Normal



Follicular lymphoma



Centrocytes/Centroblasts



FL in PB (uncommon)

Choi et al. Arch Pathol Lab Med. 2018

Pathogenesis: Classic FL (cFL; > 85% of FL)

- Normal B cells differentiate in lymph node germinal centers
- Normal maturation occurs by random genetic modification followed by antigen driven selection

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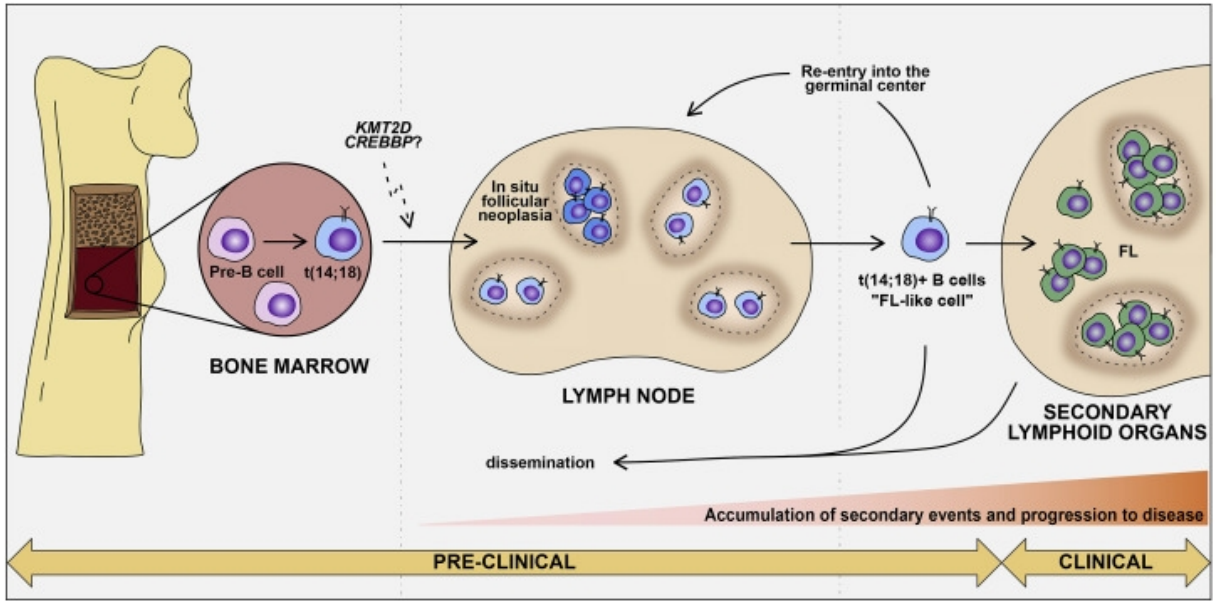
- 1st step: somatic rearrangement t(14;18) in bone marrow (pre-B cell)
  - Promotes expression of anti-apoptotic *BCL2*
  - Of note, can be identified in PB of > 50% of healthy individuals

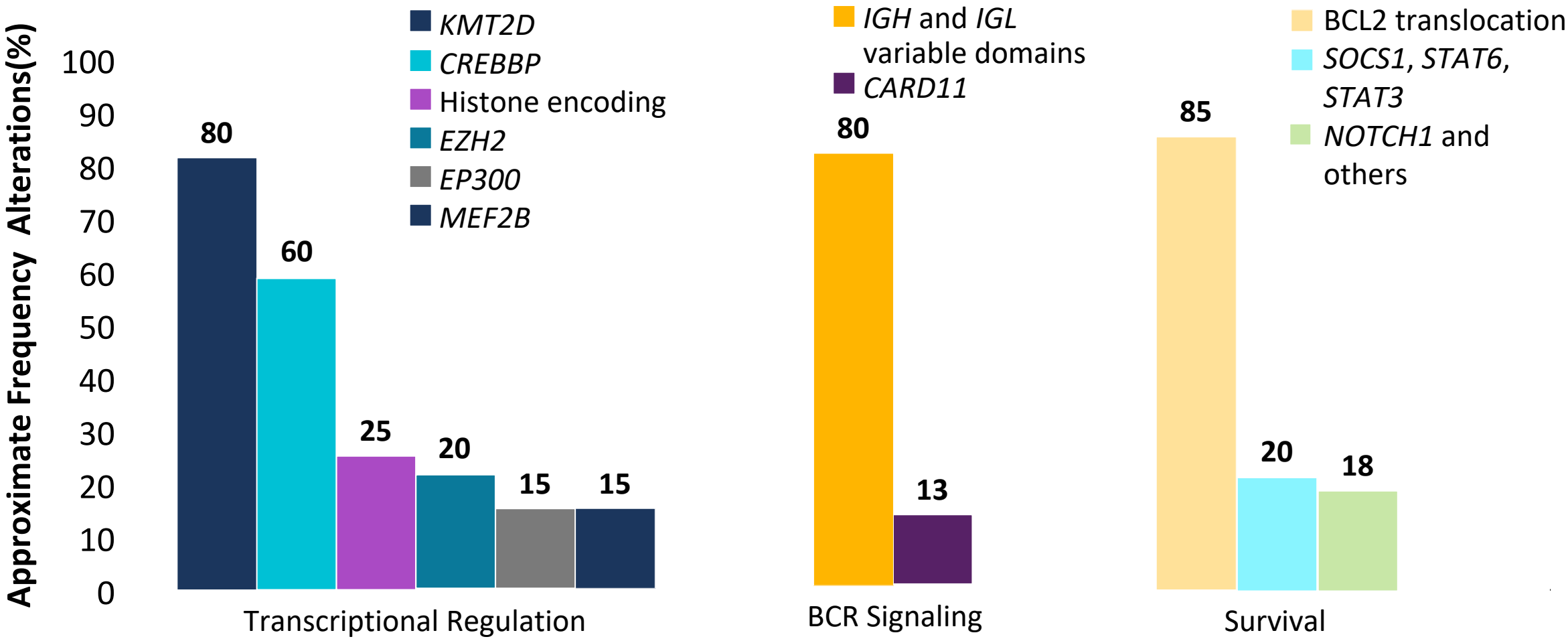
- B cells with t(14;18) enter the germinal center (highly mutagenic environment) → clonal expansion, further mutation mutations → classic FL

- Light chain restricted, CD20+, CD19+, CD10+
- CD5-



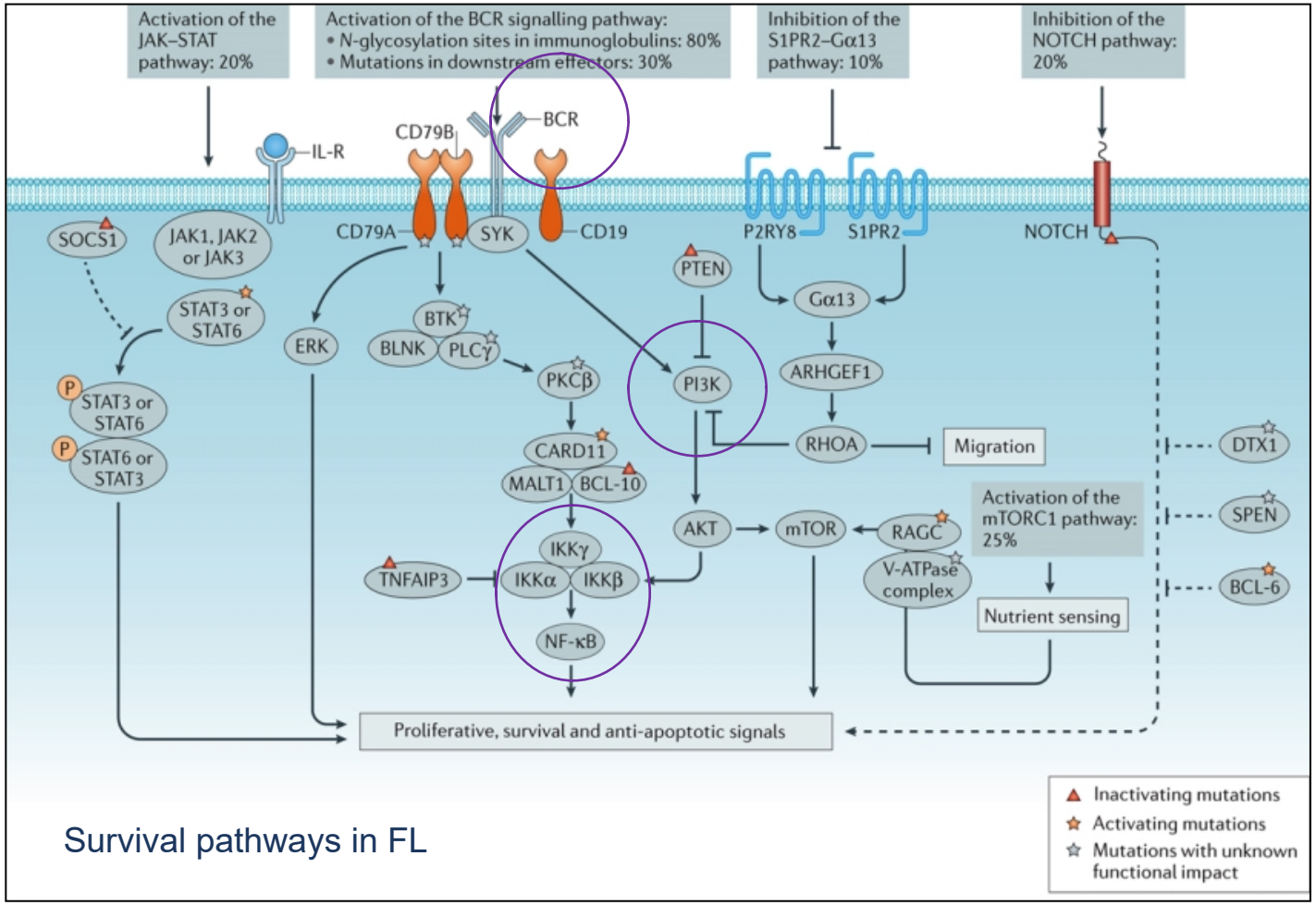
Lackraj et al Best Pract Res Clin Haematol 2018

FL Pathogenesis: Genetic Landscape



Huet. Nat Rev Cancer. 2018

FL Pathogenesis: Molecular Pathways



Survival pathways in FL

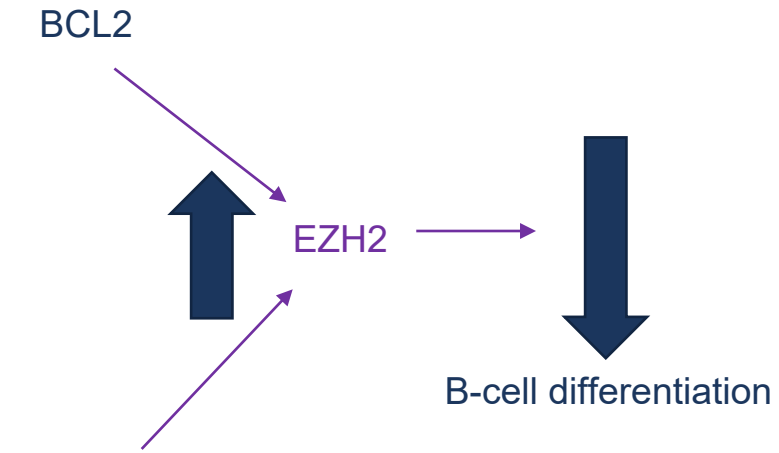
Epigenetics

Alterations in epigenetic modifiers occur > 90%

*histone methyltransferases

*histone acetyltransferases

Early events



Huet et al. Nat Rev Cancer. 2018

Other FL

WHO Revised 4th Edition	WHO 5th Edition	ICC 2022
Follicular lymphoma	Follicular lymphoma*	Follicular lymphoma**
- In situ follicular neoplasia	- In situ follicular B-cell neoplasm	- In situ follicular neoplasia
- Duodenal-type follicular lymphoma	- Duodenal-type follicular lymphoma	- Duodenal-type follicular lymphoma
Diffuse follicular lymphoma variant (not considered an entity)	FL with predominantly diffuse pattern (not considered an entity)	BCL2-R-negative, CD23-positive follicle center lymphoma (provisional entity)
Primary cutaneous follicle center lymphoma	Primary cutaneous follicle center lymphoma	Primary cutaneous follicle center lymphoma
Pediatric-type follicular lymphoma	Pediatric-type follicular lymphoma	Pediatric-type follicular lymphoma

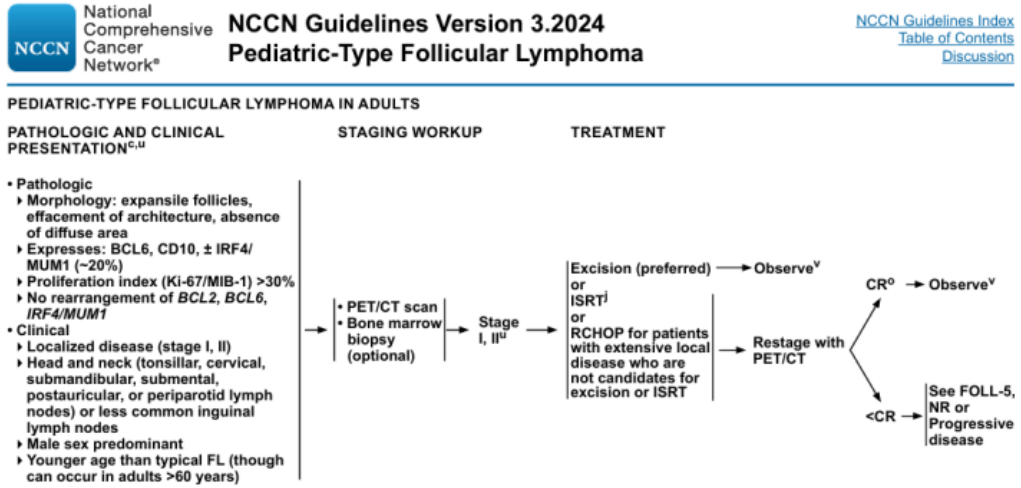
*Grading (1,2,3A) no longer required, citing poor reproducibility and limited significance; ** Grading persists

Falini et al, Leukemia 2023

Other FL

Pediatric-type FL

- Localized disease required (H&N location typical)
- Males > Females, younger age (though *not* required)
- Hi Ki67 (> 30%); no *BCL2-R* or BCL2 expression, and low genom
- Must distinguish from large B-cell lymphoma with *IRF4* rearrangement (subtype of DLBCL), FL grade 3B
- Preferred management: local therapy including excision, radiation



Duodenal-type FL

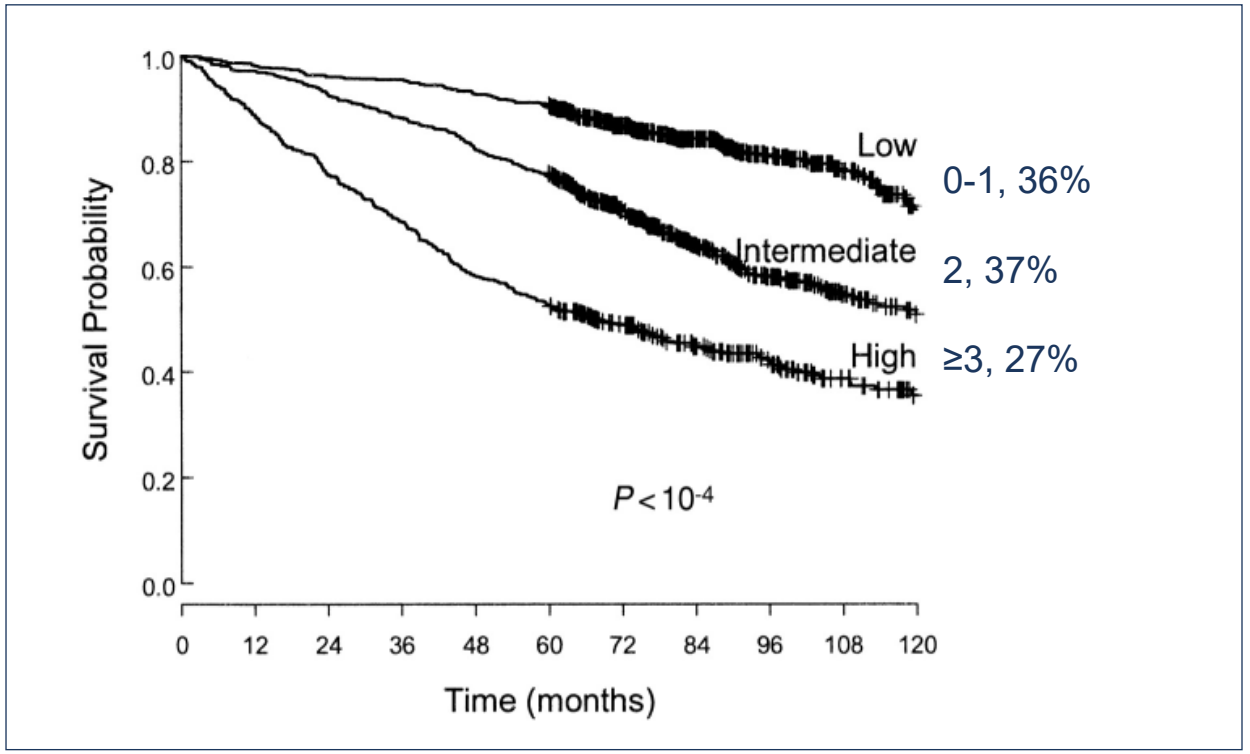
- Multiple small polyps
- Confined to mucosa: no infiltration of deeper structures or LN involvement
- Usually incidental finding, very indolent

BCL2-R negative, CD23-positive follicle center lymphoma (ICC entity only)

- Females > Males, favorable prognosis (manage as cFL)
- Common *STAT6* and *CREBBP* mutations along with 1p36 deletion or *TNFRSF14* mutation

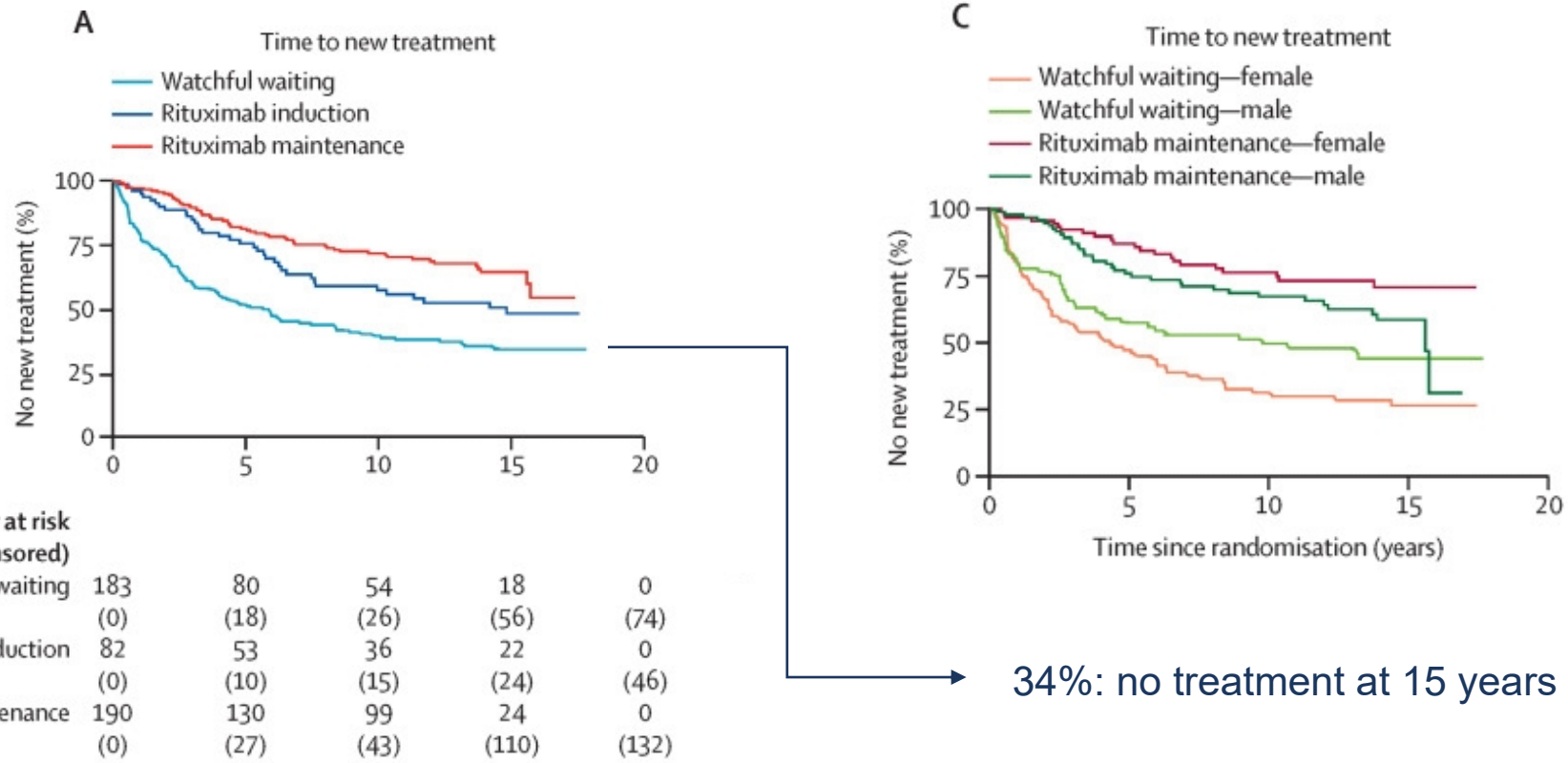
FL Risk Stratification: FLIPI

- N = 4,167 diagnosed 1985 - 1992
- Adverse factors
  - Nodal areas (> 4)
  - LDH (elevated)
  - Age (> 60)
  - Stage (III/IV)
  - Hemoglobin (< 12 g/dL)



Celigny et al Blood. 2004

Advanced Stage FL: Management (asymptomatic, low tumor burden)



34%: no treatment at 15 years

(For limited stage FL, ISRT can be considered but must be done so in clinical context)

Northend et al, Lancet Haematology 2025

Indications for Treating Advanced Stage* iNHL: GELF Criteria

- Any nodal or extranodal tumor mass >7 cm diameter
- Involvement of at least 3 nodal sites, each with diameter >3 cm
  View more nodal site information in the More Info section.
- Presence of any systemic or B symptoms
- Splenic enlargement with inferior margin below the umbilical line
- Compression syndrome (ureteral, orbital, gastrointestinal)
- Pleural or peritoneal serous effusion (irrespective of cell content)
- Leukemic phase (>5.0 x10^9/L circulating malignant cells)
- Cytopenia (granulocyte count <1.0x10^9/L and/or platelets <100x10^9/L)

If absent, recommend observation (NCCN cat 1)

↓

Regular H&P + labs; scans *up to* q6 mo x2 years then no more than annually

- NCCN: also, steady or rapid progression; candidate for trial
- Median time between diagnosis (no treatment indication) and start of treatment = 2 to 6 years

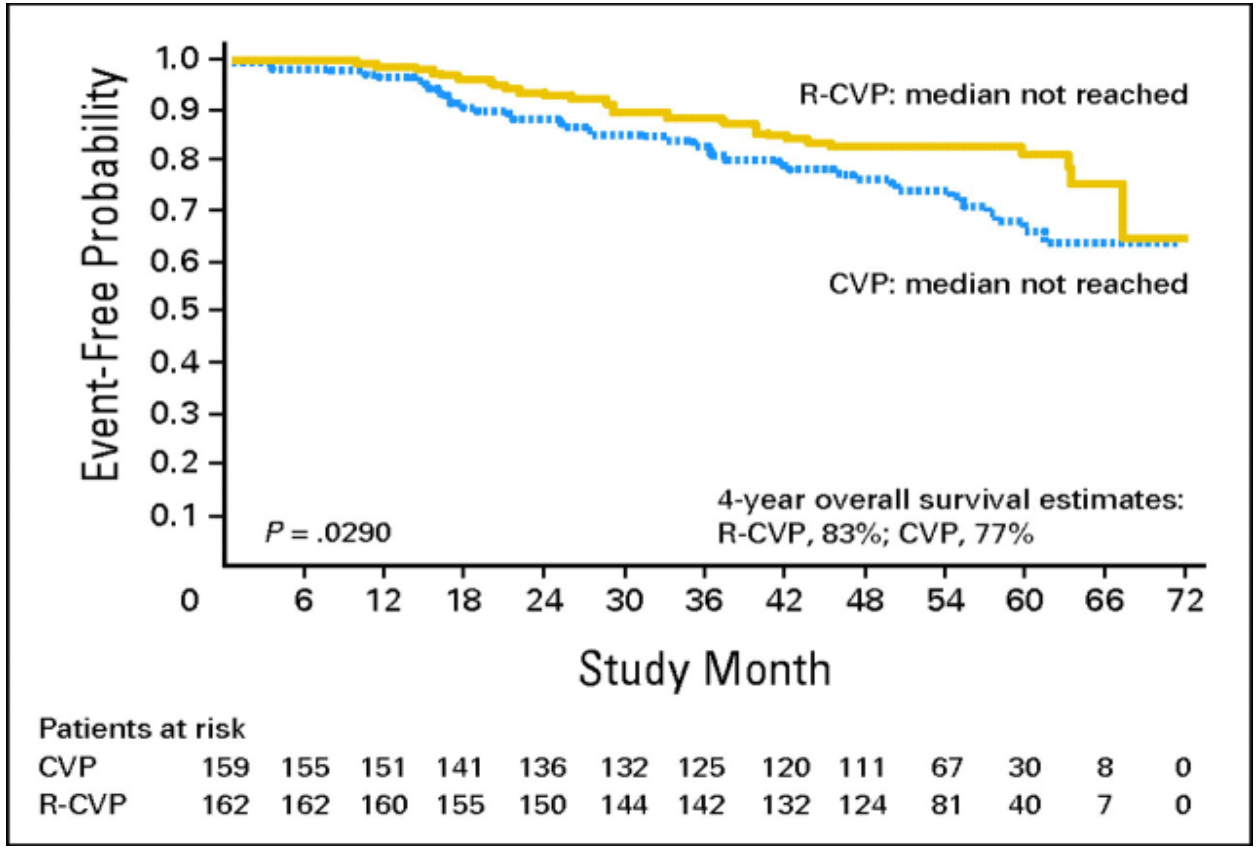
* Will circle back to early-stage management – less evidence basis

Solal-Celigny et al. J Clin Oncol. 1998
Nastoupil et al. Br J Haematol. 2016

FL 1L Treatment: Include anti-CD20

FL Stage III/IV +
Treatment Indication:

CVP x8 +/- R



Consistent benefit with addition of R to chemo shown across 4 randomized studies in PFS, OS and response rates

Marcus et al. J Clin Oncol. 2008

FL: Maintenance antiCD20?

Untreated FL, stage III/IV; grade 1-3a
High tumor burden

→ R-chemo

R-FCM (4%)
R-CVP (23%)
R-CHOP (74%)

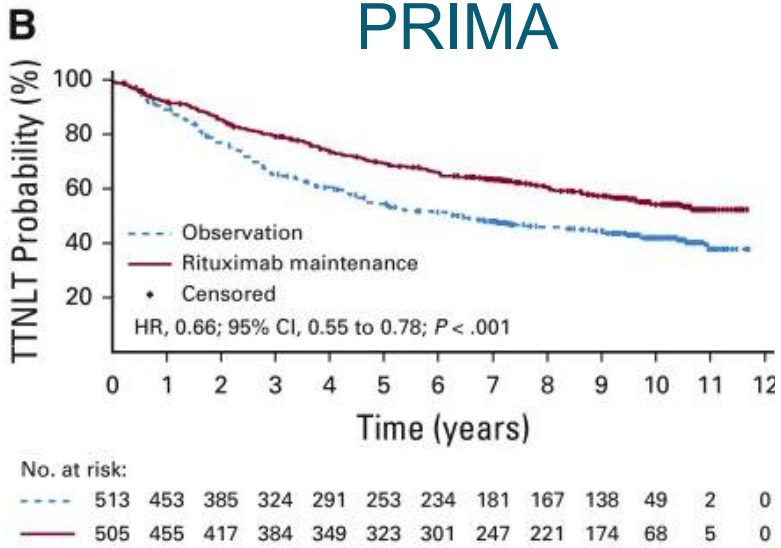
→ CR/PR
N = 1,018

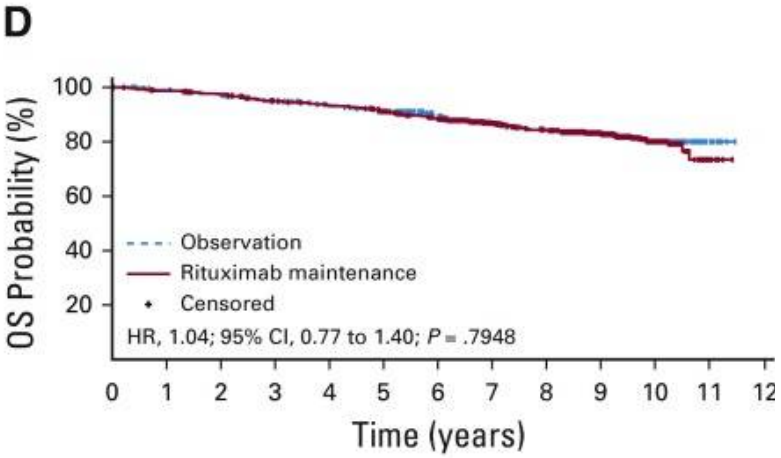
→ RANDOMIZE

→ Observation

→ R q2mo x2 yrs

PRIMA





Bachy et al, J Clin Oncol. 2019

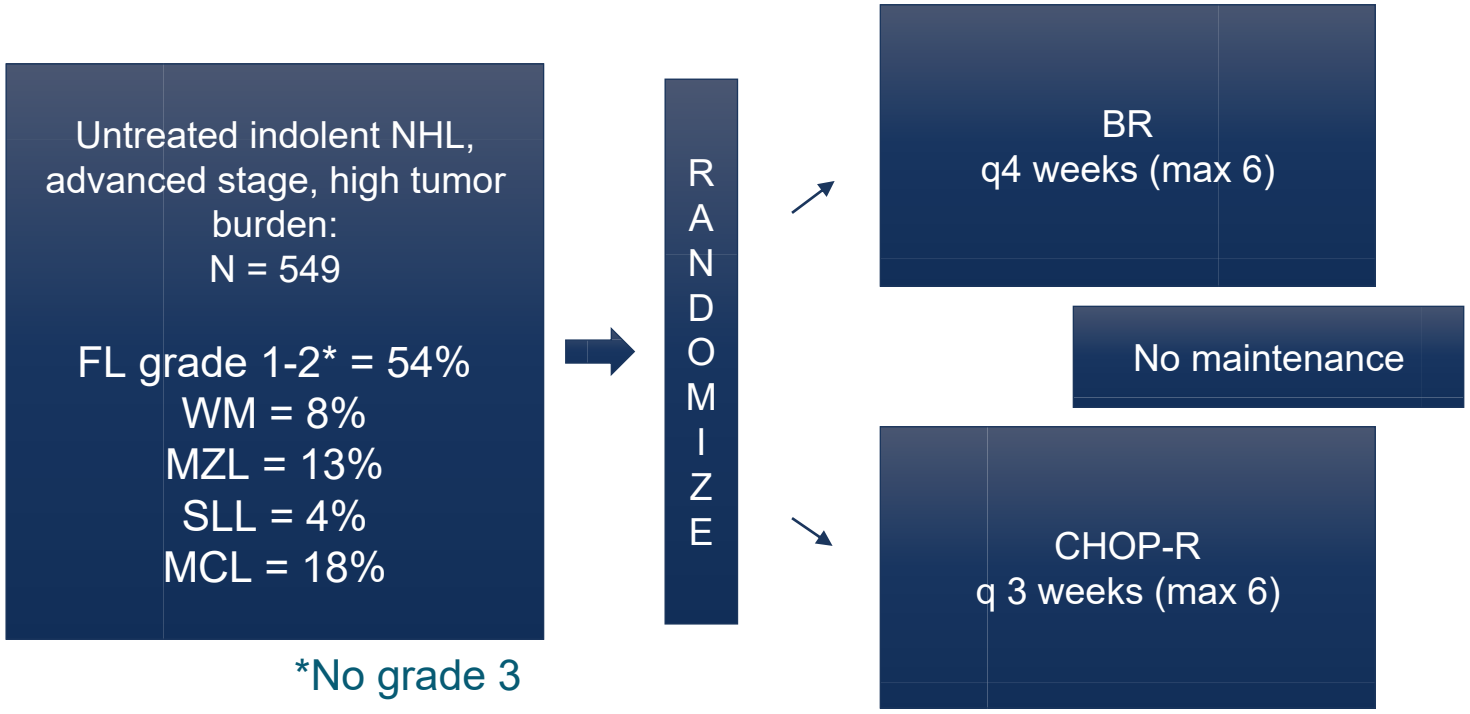
PRIMA: Toxicity

	Observation (n=508)		Rituximab maintenance (n=501)	
	Grade 3/4	Leading to treatment discontinuation	Grade 3/4	Leading to treatment discontinuation
All adverse events	84 (17%)	8 (2%)	121 (24%)	19 (4%)†
Neoplasia	17 (3%)	6 (1%)	20 (4%)	5 (1%)
Neutropenia	5 (1%)	0	18 (4%)	0
Febrile neutropenia	2 (<1%)	0	1 (<1%)	1 (<1%)
Infections	5 (1%)	0	22 (4%)	4 (1%)
CNS disorders	13 (3%)	0	10 (2%)	0
Cardiac disorders	5 (1%)	0	11 (2%)	1 (<1%)
Pregnancy	NA	2 (<1%)	NA	3 (1%)

- Logistics, financial

Salles et al. Lancet. 2011

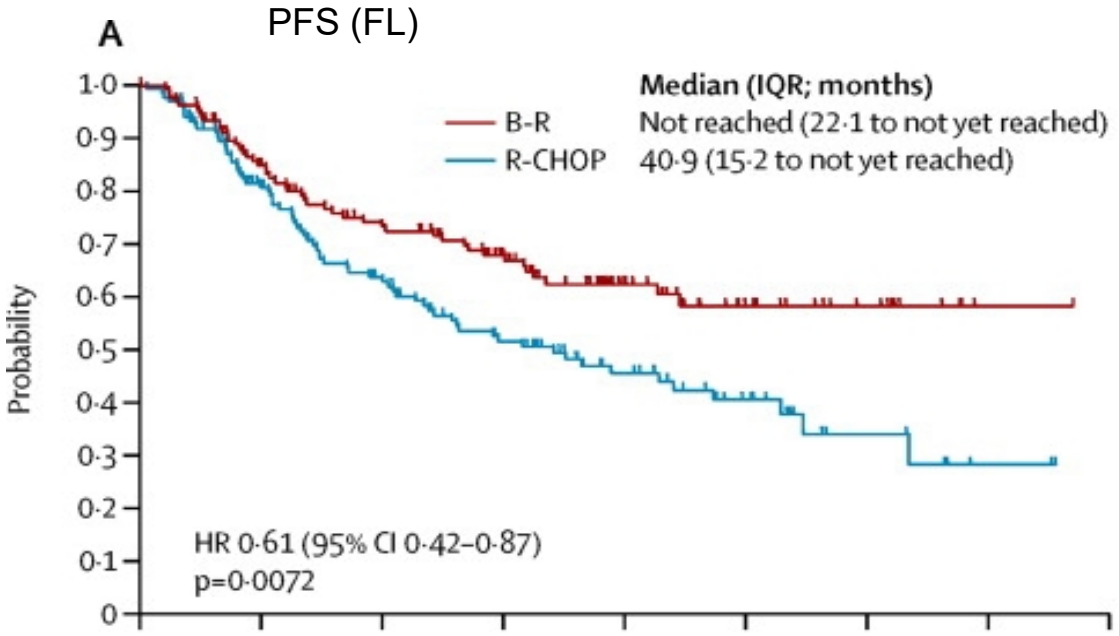
BR vs CHOP-R (StIL NHL1)



	B-R N = 260	CHOP-R N = 253	P
Alopecia	0	245	< 0.0001
Paresthesias	18	73	< 0.0001
Stomatitis	16	47	< 0.0001
Allergic reaction	40	15	0.0003
Infections	96	127	0.0025
Sepsis	1	8	0.0190
Neutropenia G3/4	11%	47%	

Rummel et al. Lancet. 2013

StIL NHL1

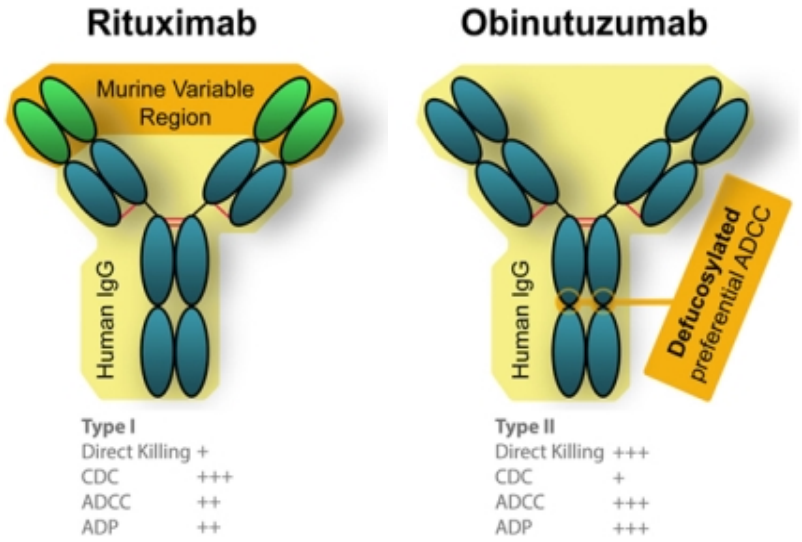


	BR	CHOP-R	P
ORR	93%	91%	NS
CR	40%	30%	0.03

- No difference in OS
- Comparable findings in North America “BRIGHT” study

Rummel et al. Lancet. 2013

FL 1L: R-Chemo vs O-Chemo: GALLIUM

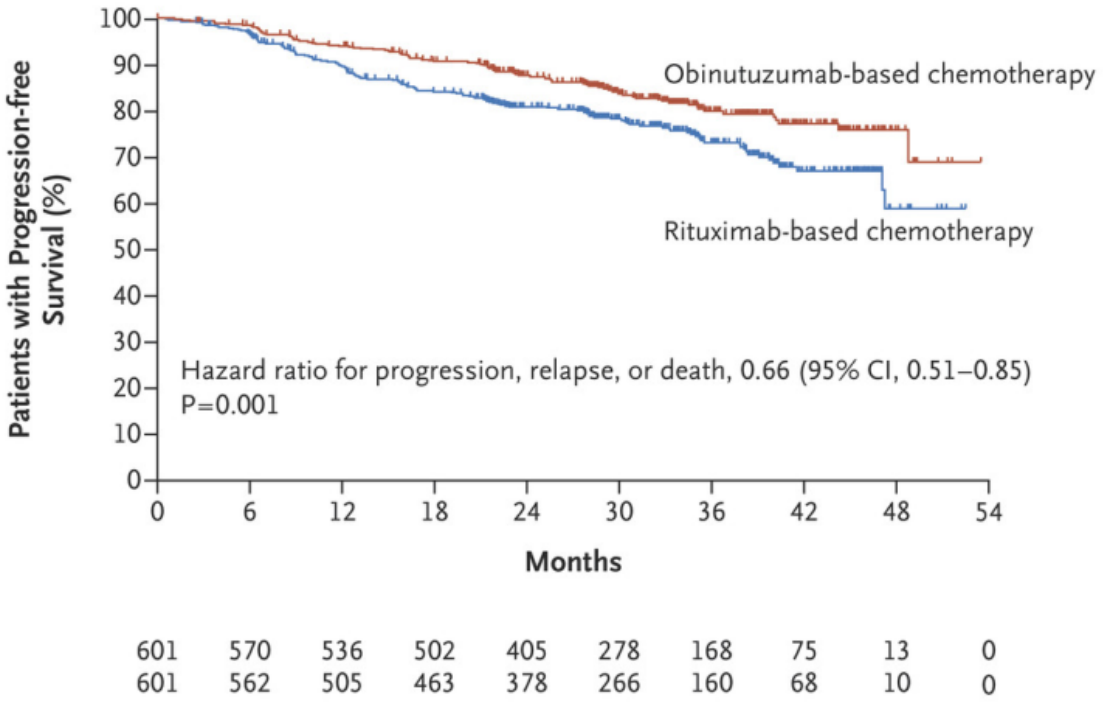


- FL meeting GELF criteria, grades 1 – 3A
- Maintenance antibody given q2 mo x2 years
- Dosing: obinutuzumab: 1000 mg days 1, 8, 15 of C1 then 1000 mg D1 subsequent cycles; rituximab: 375 mg/m2 on day 1 qcycle

- Obinu: binds overlapping epitope of CD20 (as R) but in different orientation
- Glycosylation manipulation → improved direct cell death and antibody dependent cell-mediated cytotoxicity
- Lower complement dependent cytotoxicity

Marcus et al. N Engl J Med. 2017
Pierpont et al. Front. Oncol. 2018

GALLIUM Results



- Most treated with bendamustine as chemo
- No difference in OS (5 yr OS 90.2% vs 89.4%)

Table 3. Adverse Events and Serious Adverse Events, According to Treatment Phase, and Treatment Phase in the Safety Population.*

Event	Overall Trial†	
	Obinutuzumab Group (N=595)	Rituximab Group (N=597)
No. of events	10,311	9343
Patients with ≥1 adverse event — no. (%)		
Any event	592 (99.5)	587 (98.3)
Event of grade 3 to 5	444 (74.6)	405 (67.8)
Event of grade 5‡	24 (4.0)	20 (3.4)§
Patients with ≥1 serious adverse event — no. (%)	274 (46.1)	238 (39.9)

Approximately 35% more O than R

Townsend et al, ASCO 2020

Bendamustine Toxicity in Older Patients

SEER Dataset, age > 65

Clinical Infectious Diseases

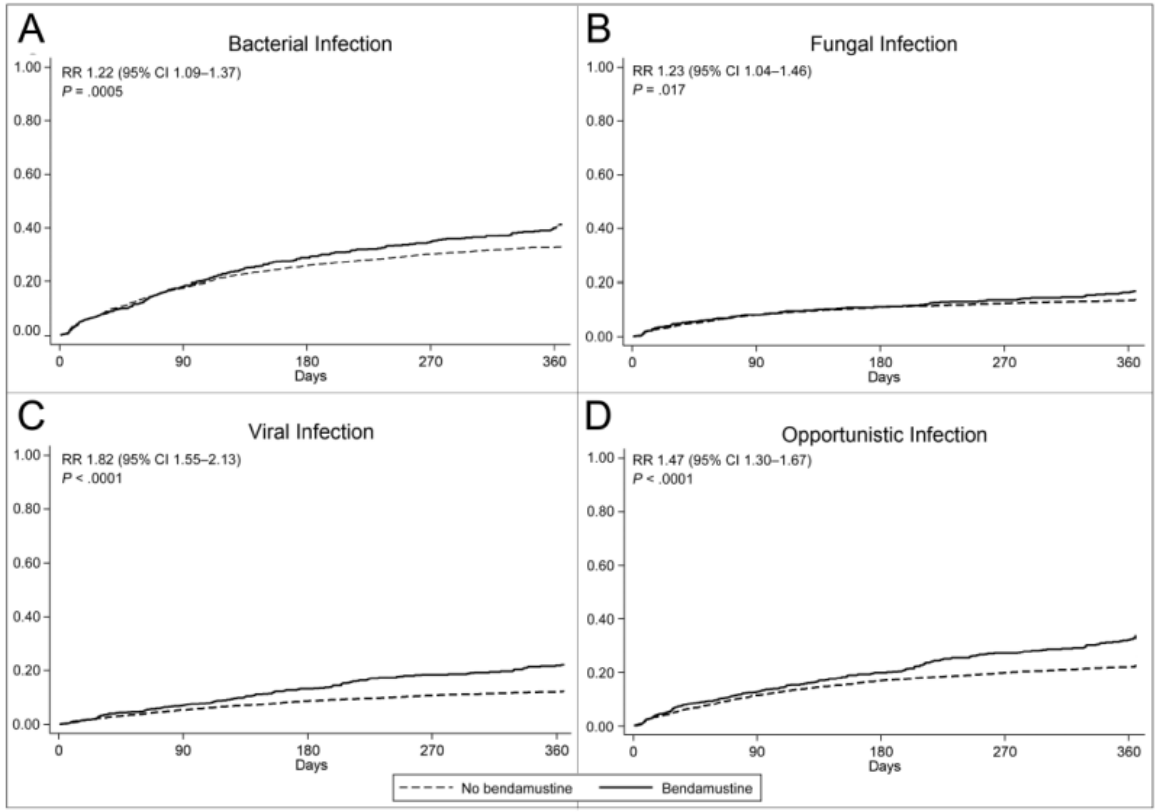
MAJOR ARTICLE

IDSA Infectious Diseases Society of America | hivma hiv medicine association | OXFORD

Increased Risk of Infectious Complications in Older Patients With Indolent Non-Hodgkin Lymphoma Exposed to Bendamustine

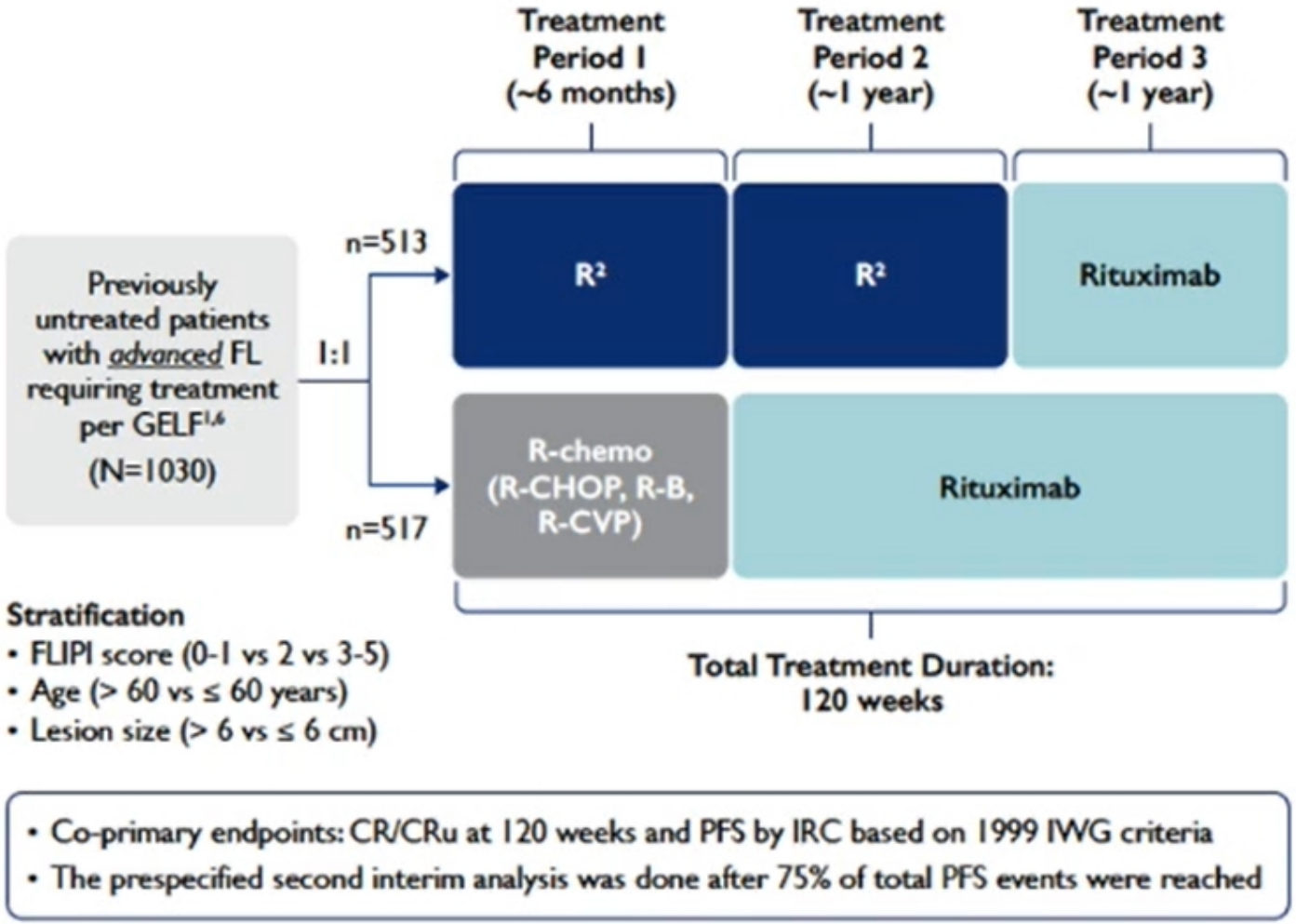
Monica Fung,[1] Eric Jacobsen,[2] Arnold Freedman,[2] Daniel Prestes,[3] Dimitrios Farmakiotis,[4] Xiangmei Gu,[3] Paul L. Nguyen,[5] and Sophia Koo[2,3]

- N = 9395 with iNHL
- 2006 – 2013
- 75% with FL
- Suspect prolonged CD4+ T-lymphopenia as culprit



NCCN advises prophylaxis for PJP and VZV if bendamustine given

FL 1L: R-Lenalidomide (R^2): RELEVANCE



- Co-primary endpoints: CR/CRu at 120 weeks and PFS by IRC based on 1999 IWG criteria
- The prespecified second interim analysis was done after 75% of total PFS events were reached

Lenalidomide: 20 mg PO daily days 2-22 (up to 18 cycles). Dose reduced to 10 mg daily in patients with CR/CRu after C6.

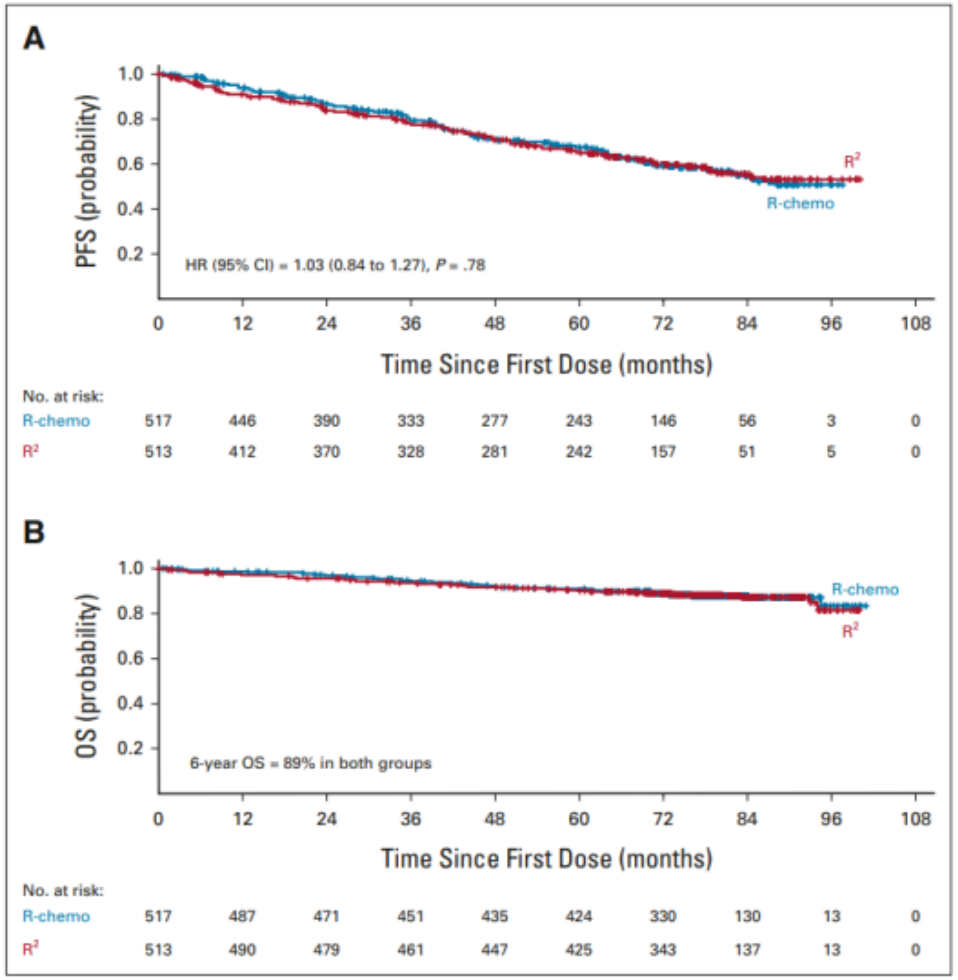
RCHOP = 372
RB = 117
RCVP = 28

Morschhauser et al. NEJM. 2018

RELEVANCE: Results

- N = 1,030
- CR/CRu at 24 mo
  - R2 = 48%
  - R-chemo = 53% (P = 0.13)

- Toxicities
  - Overall, comparable frequencies
  - R2 = less nausea, febrile neutropenia
  - R2 = more rash, diarrhea
  - R2 = toxicities drawn out



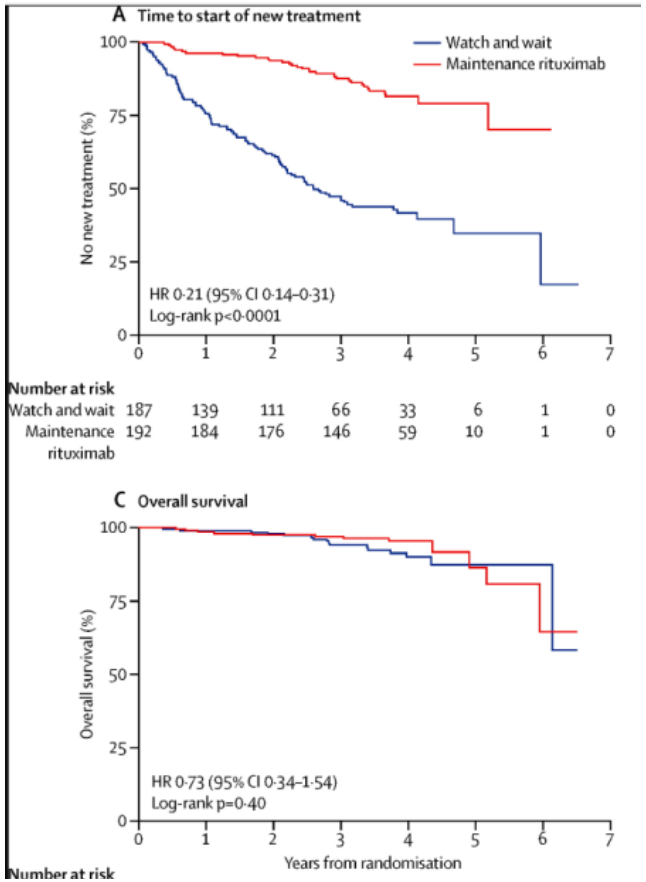
No FDA approval

NCCN listed as a preferred option (BR, BO, RCHOP, OCHOP, RCVP, OCVP)

Morschhauser et al. J Clin Onc. 2022

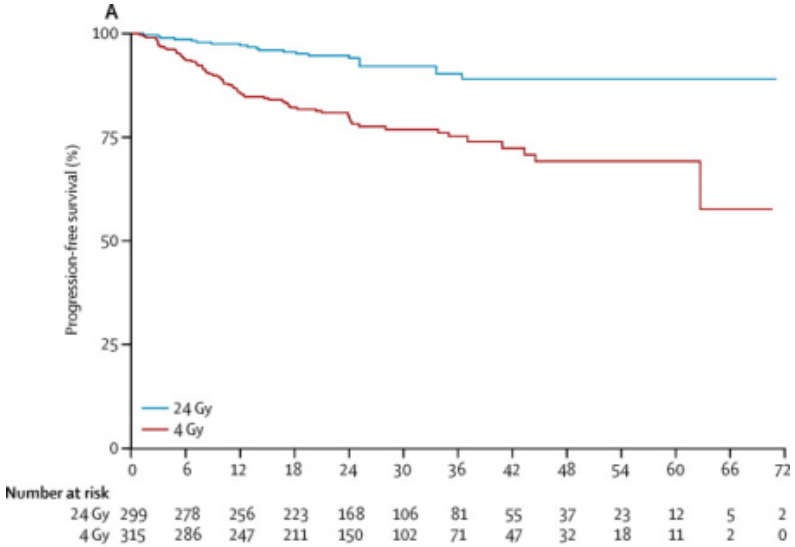
FL 1L: Special Circumstances

Frail/Elderly/Low Tumor Burden



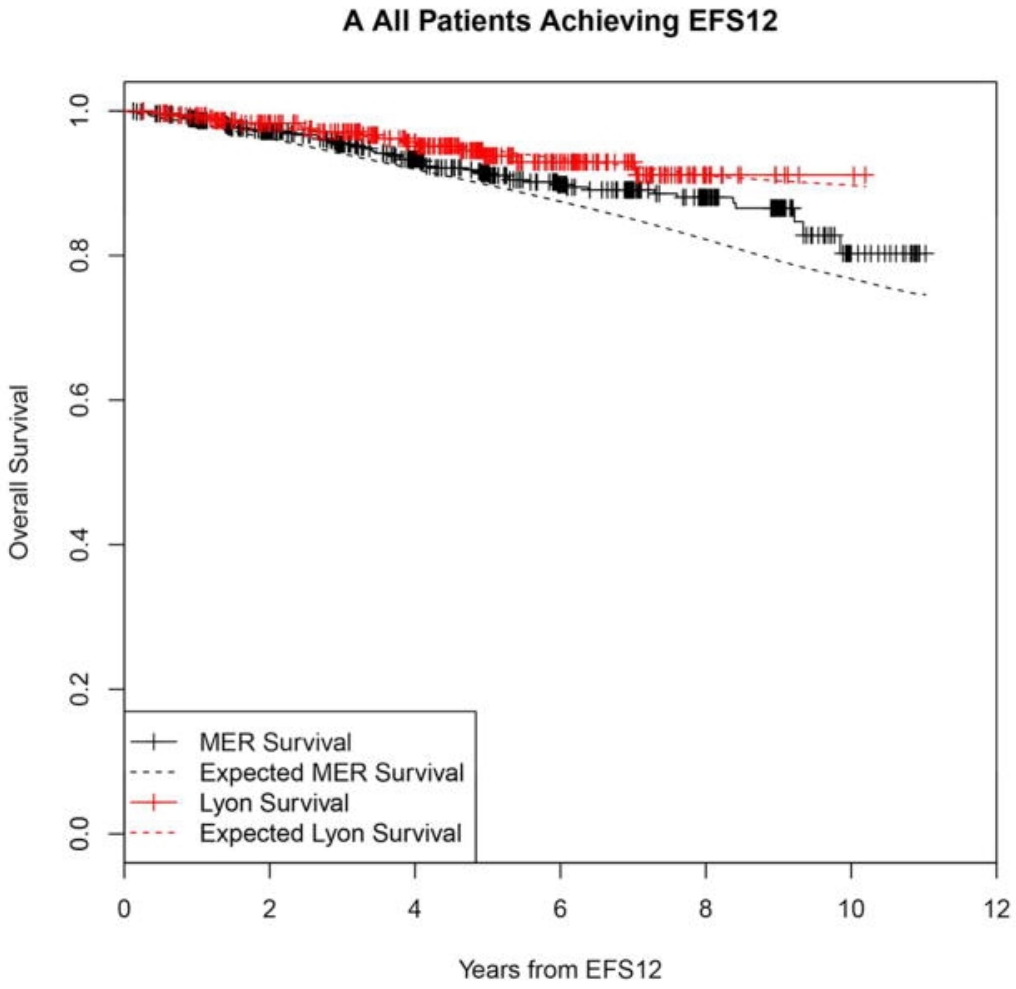
Confirmed Limited Stage

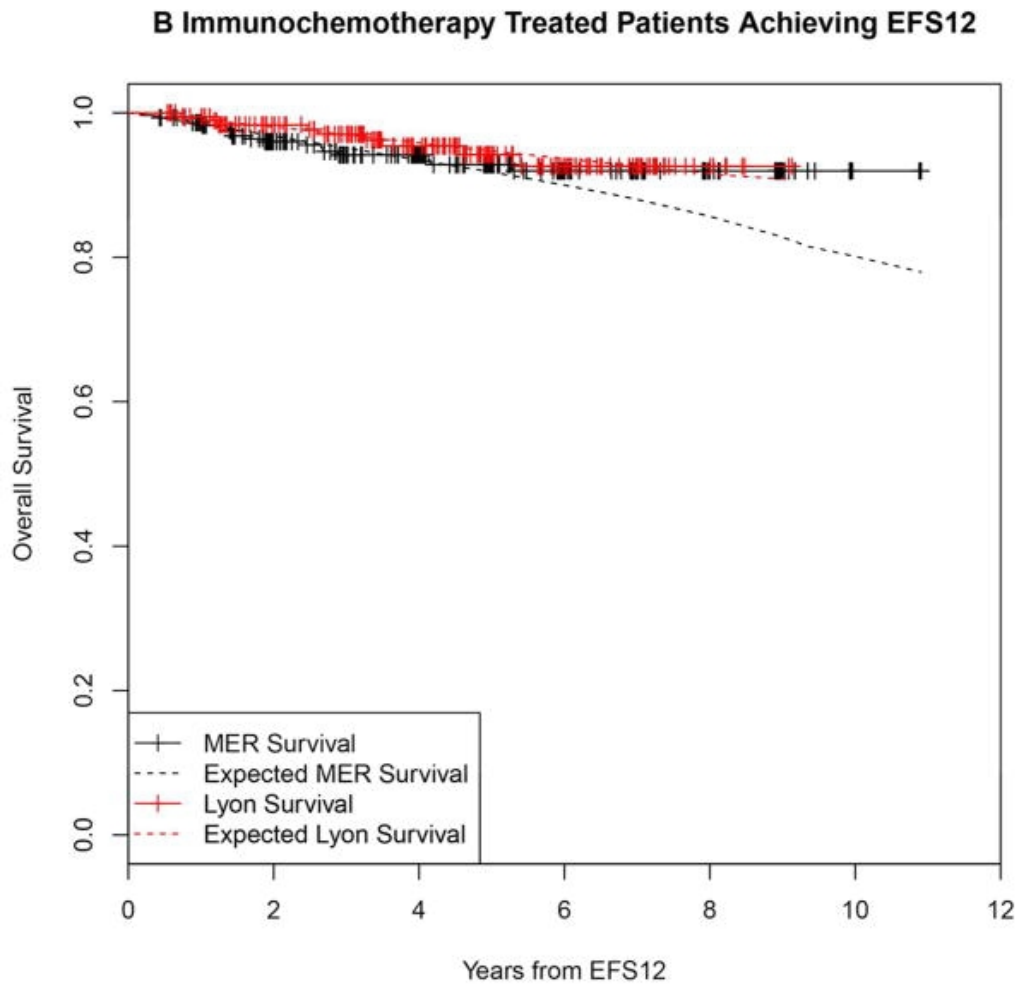
- ISRT
- Consider volume to encompass adjacent LNs
- Definitive RT dose of 24-30 Gy
  - 4 Gy (2 + 2) inferior but effective (eg palliative)



Ardeshna et al, Lancet Oncol 2014.
Hoskin et al, Lancet Oncol 2014.

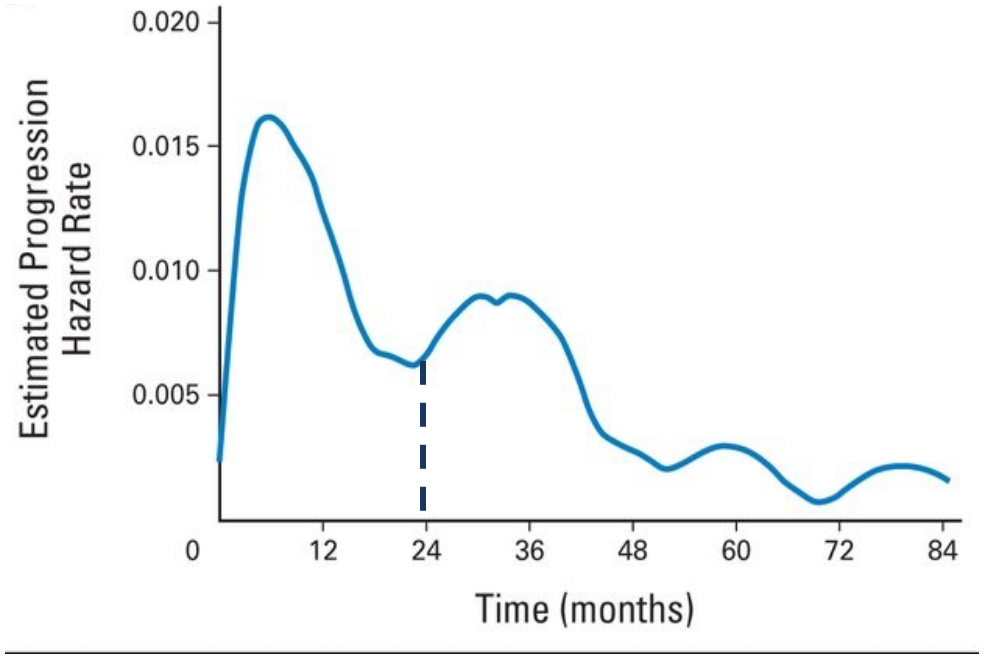
FL: After 1L Treatment

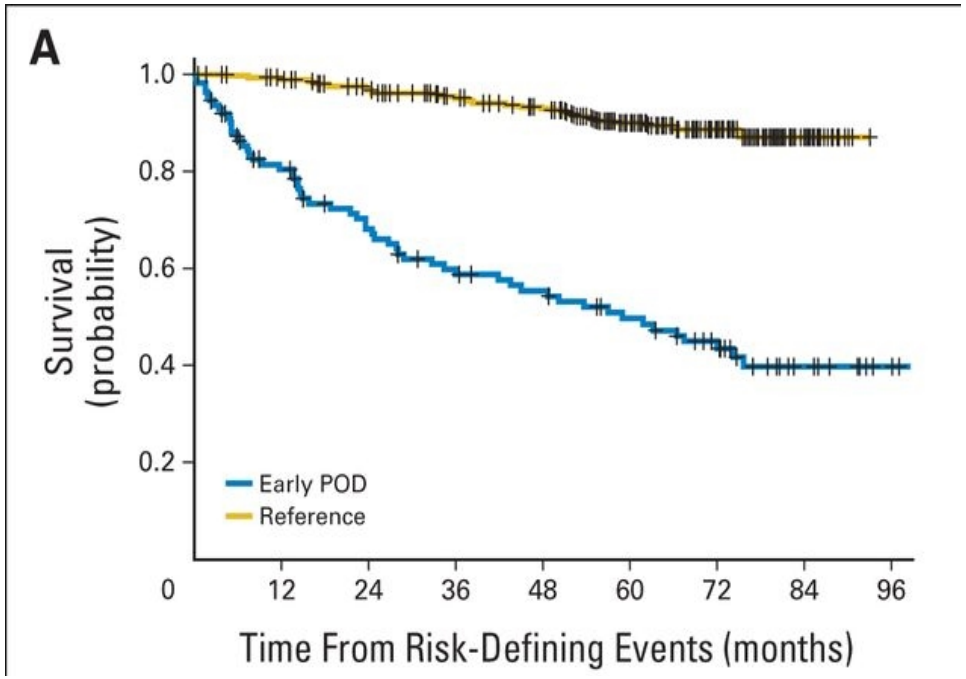




Maurer et al. Am J Hematol, 2016

FL: Relapse



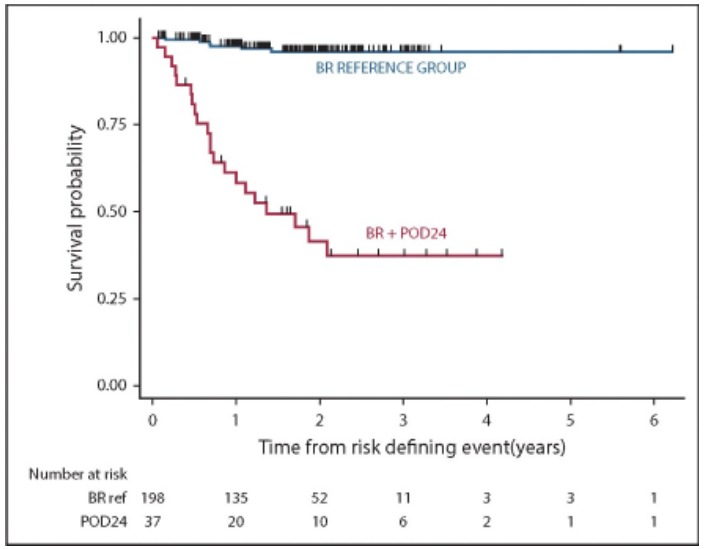


- In the 20% with "early" (< 24 mo) progression, survival markedly worse

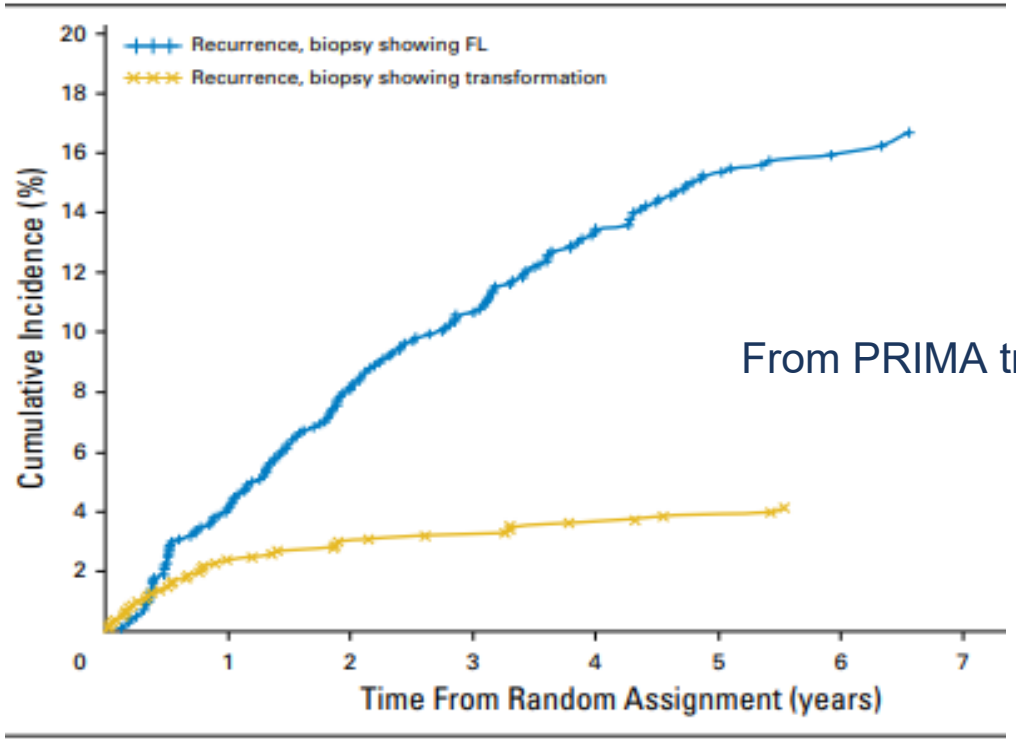
- **RFs for early POD: male (OR 1.3); PS > 1 (OR 1.6); High B2M (OR 1.4); High FLIPI (OR 3.1)**

Casulo et al. J Clin Oncol. 2015
Casulo et al. Blood 2022

FL POD24



	POD		noPOD	
Landmark	OS (%) at 2 years post-landmark	95% CI	OS (%) at 2 years post-landmark	95% CI
6 months	20	2.5-37.5	95.8	94.6-97.0
12 months	58.4	45.5-71.3	97.6	96.7-98.6
18 months	76.5	67.0-86.0	97.8	97.0-98.9
24 months	82.4	74.2-91.34	98.2	97.1-99.2



From PRIMA trial

→ HT occurring after 1L treatment tends to occur early

Freeman et al. Blood 2019
Sarkozy et al, J Clin Onc 2016
Seymour et al, Haematologica. 2019

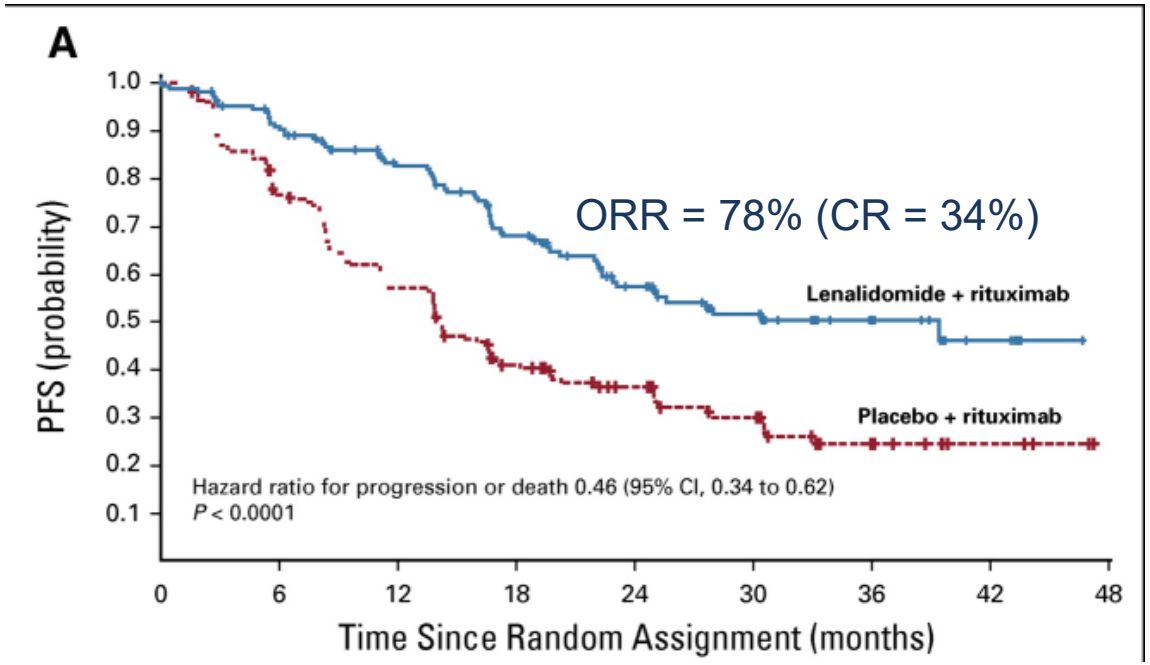
Relapsed FL: Treatment

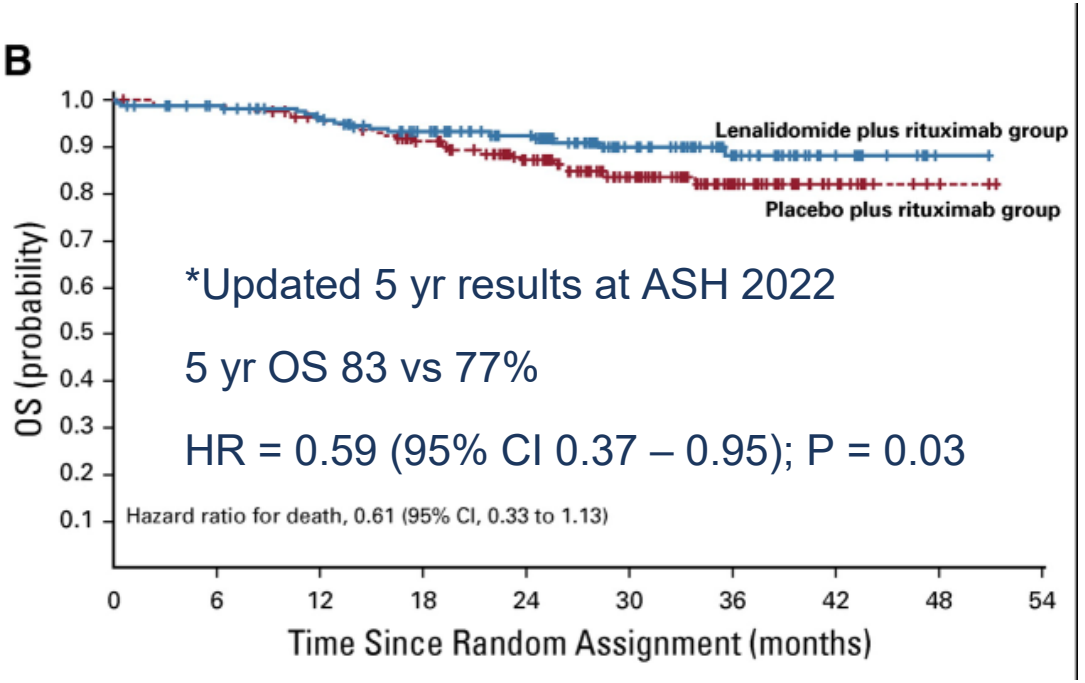
Evaluate for indication

R^2 for Relapsed iNHL: AUGMENT

FL grade 1 – 3A or MZL, previously treated, and in need of treatment for relapse. Prior treatment includes rituximab; cannot be considered rituximab-refractory.

Lenalidomide: 20 mg daily, days 1-21 of 28, up to 12 cycles. Prophylactic AC rec'd for at-risk patients.





Leonard et al. J Clin Oncol. 2019;
Leonart et al. ASH 2022

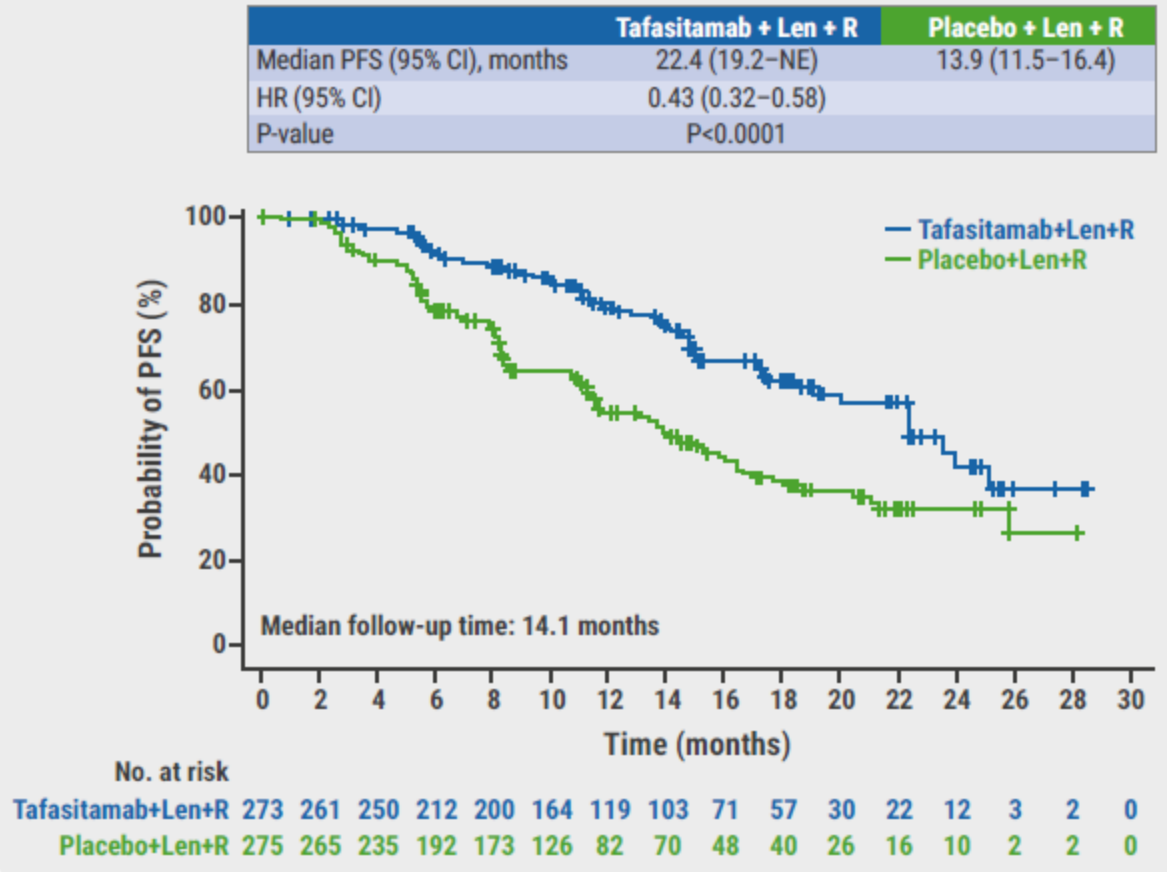
Addition of tafasitamab: inMIND

Presented at ASH 2024. FDA approval June 2025. Full manuscript pending.

- 548 patients with R/R FL relapsed 1:1 to R2 + tafasitamab or placebo
- Median 1 prior line; 25% had 2 and 20% had 3 or more prior lines
- At median follow-up of 14.1 mo, HR for PFS = 0.43 [0.32 – 0.58]; PFS 22.4 vs 13.9 mo
- No OS benefit, though “trend” to improvement

- Well tolerated: discontinued due to AEs in 11% vs 7%

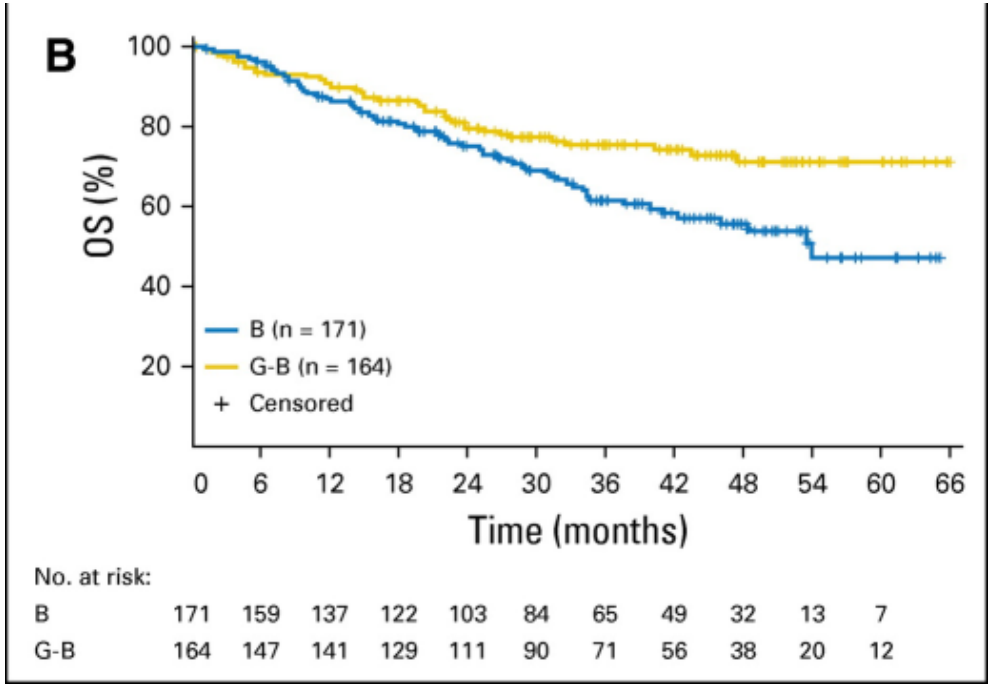
- Schedule: standard R2, with tafa dosed 12 mg/kg iv or pbo weekly x12 weeks then qow through cycle 12



Sehn et al, ASH 2024 LBA

Relapsed FL, Rituximab “Refractory”: GADOLIN

Defined as nonresponse to or progression during prior rituximab or PD within 6 months of last R



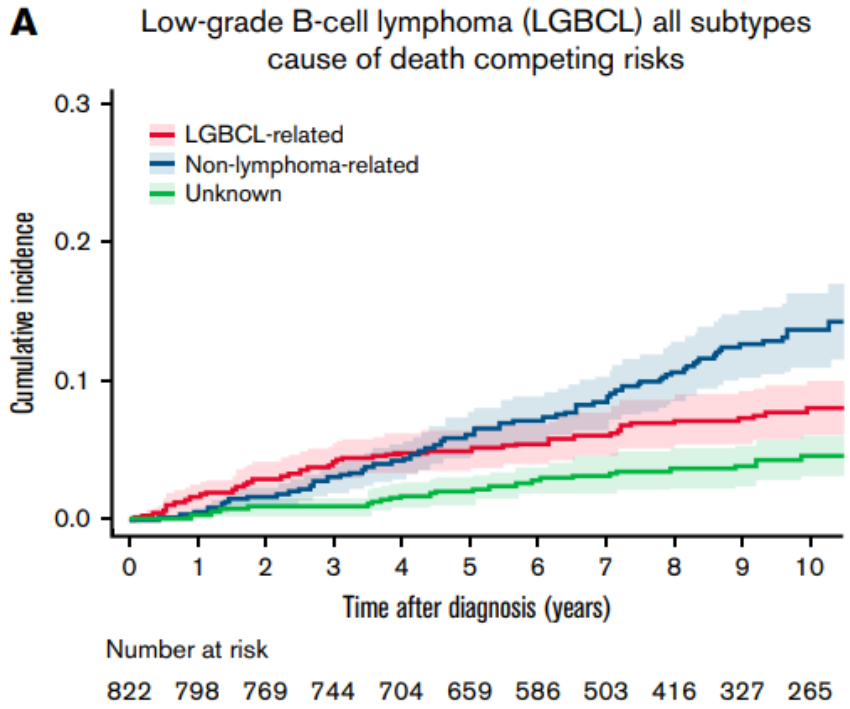
BO + Maintenance O

B dosed at 90 mg/m2 with O and 120 mg/m2 alone

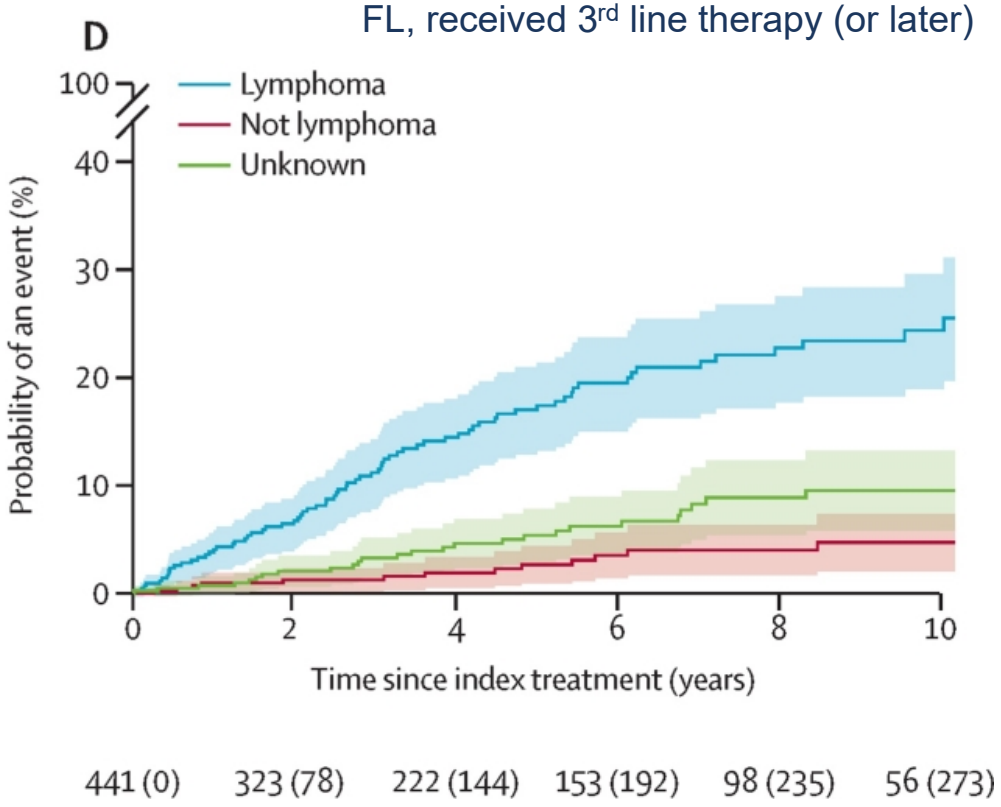
Cheson et al. J Clin Oncol. 2018

Multiply Relapsed FL

Area of need and significant recent advances



FL, received 3rd line therapy (or later)



Tun et al, Blood Advances 2022
Casulo et al, Lancet Haematol 2022

Multiply Relapsed FL: Small Molecule Inhibitors

PI3K inhibitors: several early successes led to accelerated approvals, subsequently withdrawn

	Setting	ORR	CR	mPFS
Idelalisib (δ)	Double refractory (R, alkylator) FL	56%	6%	11.0 mo
Duvelisib (γ,δ)	Double refractory (R, alkylator) FL	47%	2%	9.5 mo
Copanlisib* (α,δ)	≥2 prior lines of therapy for FL	59%	12%	11.0 mo
Umbralisib (δ+ casein kinase-1ε**)	≥3 prior lines of therapy for FL; ≥1 prior anti-CD20 therapy in MZL	45% (FL) 49% (MZL)	5% (FL) 16% (MZL)	10.6 mo (FL) NR (MZL)

Matasar et al, Lancet Oncol. 2021

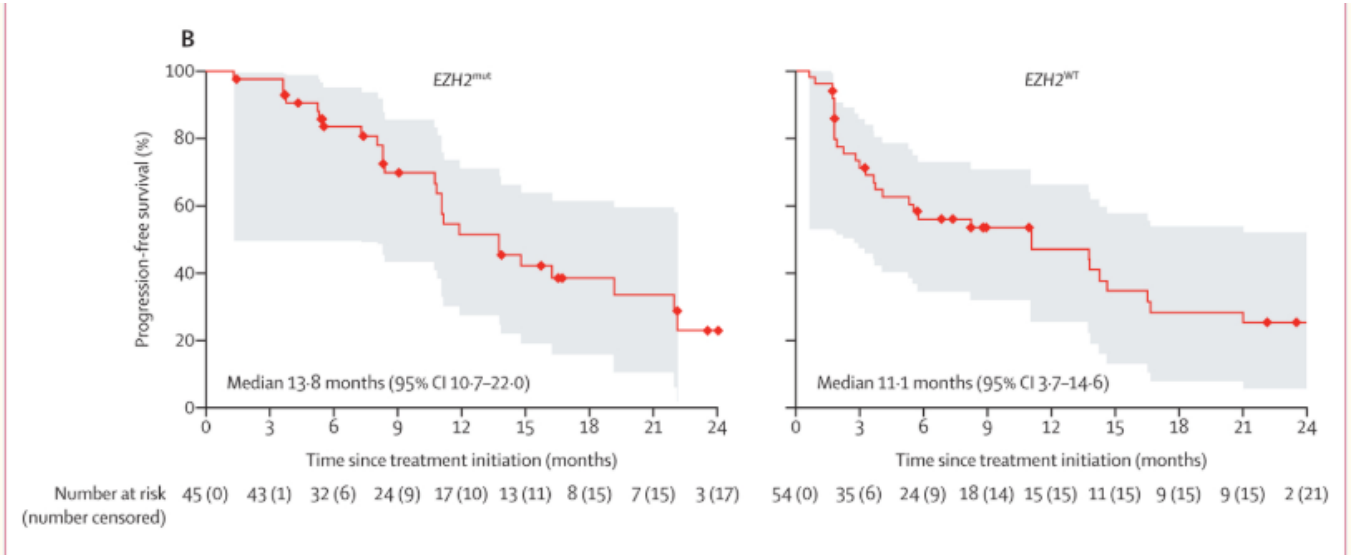
Multiply Relapsed FL: Small Molecule Inhibitors

	Setting	ORR, mPFS
Tazemetostat	R/R after at least 2 prior systemic therapies (single arm) *EZH2* mutated (gain of function, found in ~20%), N = 45 *EZH2* WT, N = 54	 69%, 13.8 mo 35%, 11.1 mo

* PO administration BID continuous

* Very well tolerated

FDA acc approval: *EZH2* mutant FL: ≥2 prior systemic therapies; *any* FL: no satisfactory alternatives



Morschhauser et al. Lancet Oncol. 2020

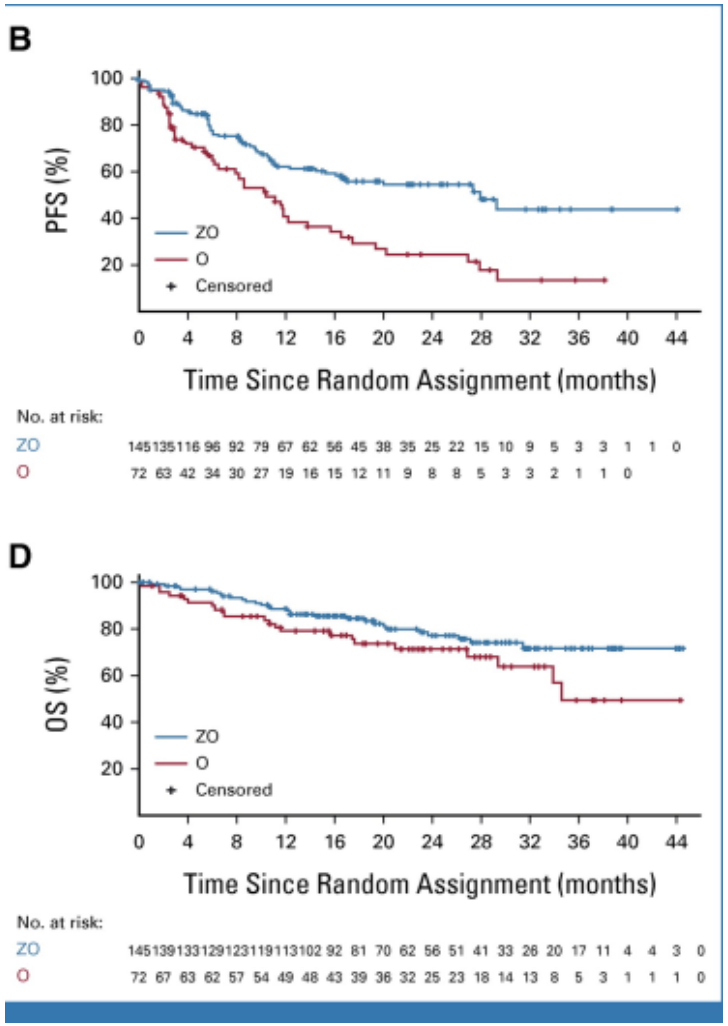
Multiply Relapsed FL: Small Molecule Inhibitors

DAWN: Single arm phase 2 study showed only modest activity of single agent ibrutinib: ORR 21%, median PFS 4.6 mo: “negative” trial; no approval

Rosewood: Randomized phase 2 showed improvement with addition of zanubrutinib to obinutuzumab monotherapy. AEs as expected: modest signals for marrow suppression, GI symptoms, infectious, cardiovascular complications

ORR: 69 vs 46%; CR 39 vs 19%; mPFS 28 vs 10 mo (HR 0.5)

FDA acc approval 2024: ZO for FL R/R after ≥2 lines of systemic therapy



Zinzani et al, J Clin Oncol 2023
Gopal et al, J Clin Oncol 2018

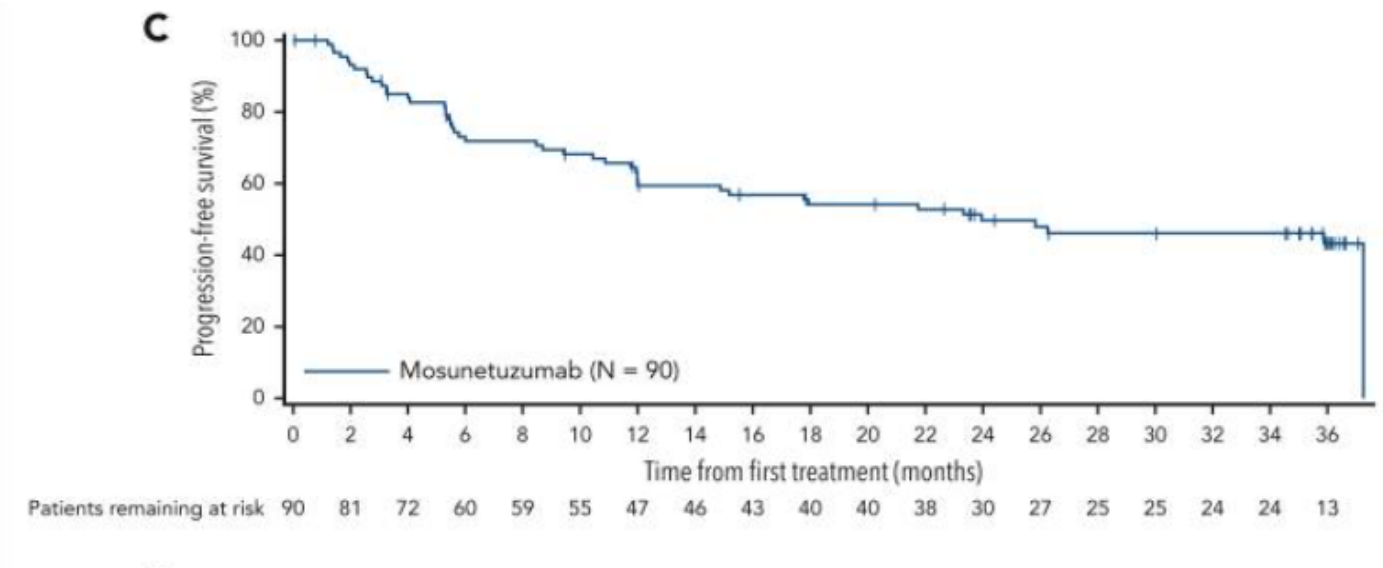
Multiply Relapsed FL: Bispecific T-cell Engagers

Mosunetuzumab-axgb

- Single arm phase 2
- R/R to ≥ 2L (antiCD20, alkylator)
- Ramp up C1 then q21 days (IV) to total of 8 or 17 cycles, depending on response (ie, fixed duration)
- CRS in 44% (G3+ in 2%); no correlation with ORR
- ICANS 4.4%, no G3+

- ORR 78% (CR 60%)
- Median PFS = 24 mo

FDA acc. approval 2022: FL R/R after ≥2 lines of systemic therapy



Sehn et al, Blood 2025

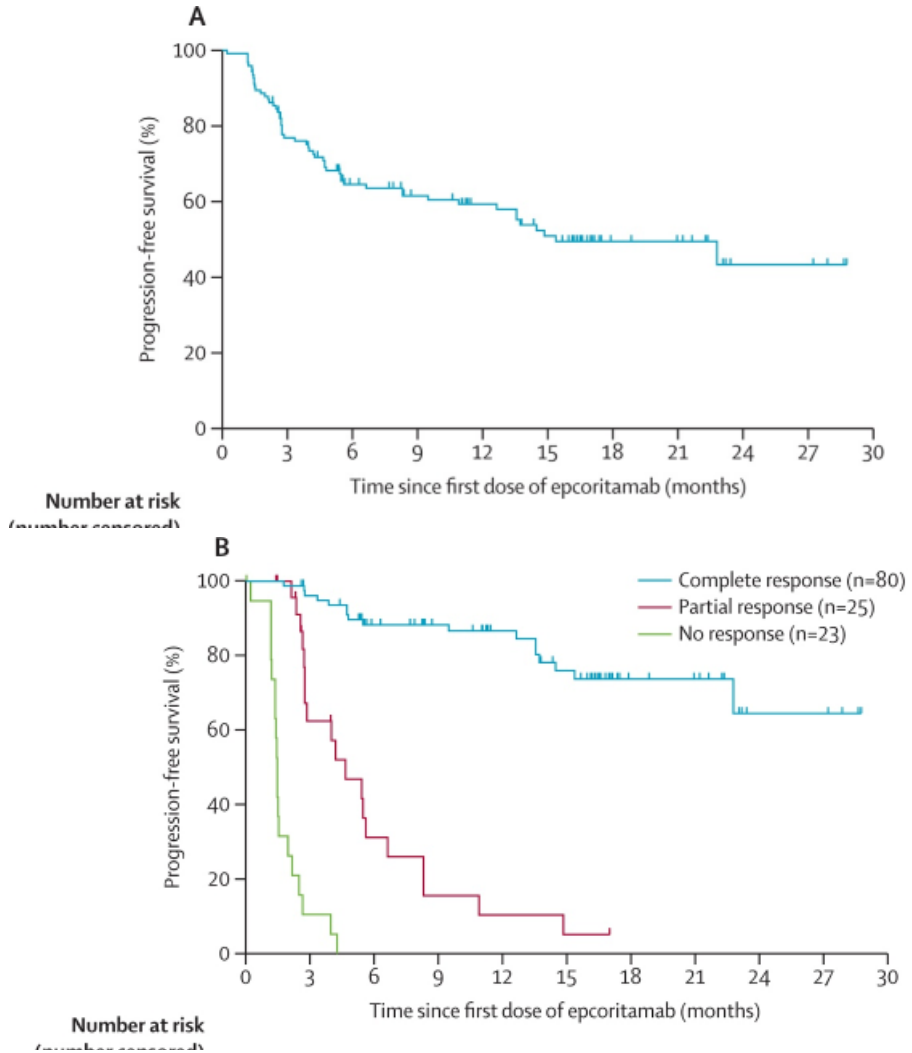
Multiply Relapsed FL: Bispecific T-cell Engagers

Epcoritamab-bysp

- Single arm phase 2 (N = 127 + 86 dose optimization with extra step-up dose)
- Administered subcutaneously
- R/R to ≥ 2L (antiCD20, alkylator)
- Ramp up C1, weekly C2 and 3, biweekly C4-9, q4w C10+
- CRS in 49% (no G3+)
- ICANS 6.0%, no G3+
- Serious infections in 40%

- ORR 82% (CR 60%)
- 12 mo DOR 68%

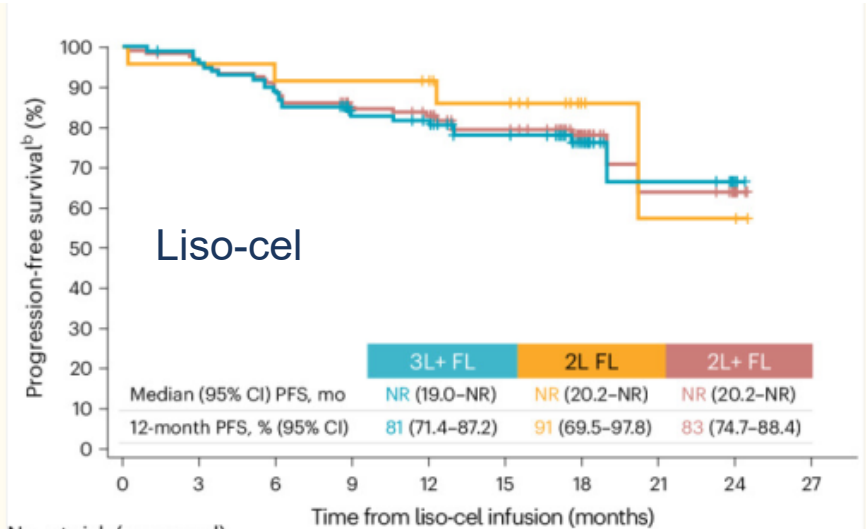
FDA acc. approval 2024: FL R/R after ≥2 lines of systemic therapy



Linton et al, Lancet Haematol 2024

Multiply Relapsed FL: Anti-CD19 CAR-T cells

	Axicabtagene	Lisocabtagene	Tisagenlecleucel
Study	ZUMA-5	TRANSCEND-FL	ELARA
N	81	94	90
ORR	94%	97%	86%
CR	60%	94%	68%
mPFS	40.2 mo	NR	NR
CRS (G3+)	78% (7%)	58% (1%)	49% (0%)
Neurological events	59% (15%)	15% (2%)	37% (3%)
FDA acc approval	2021	2024	2022

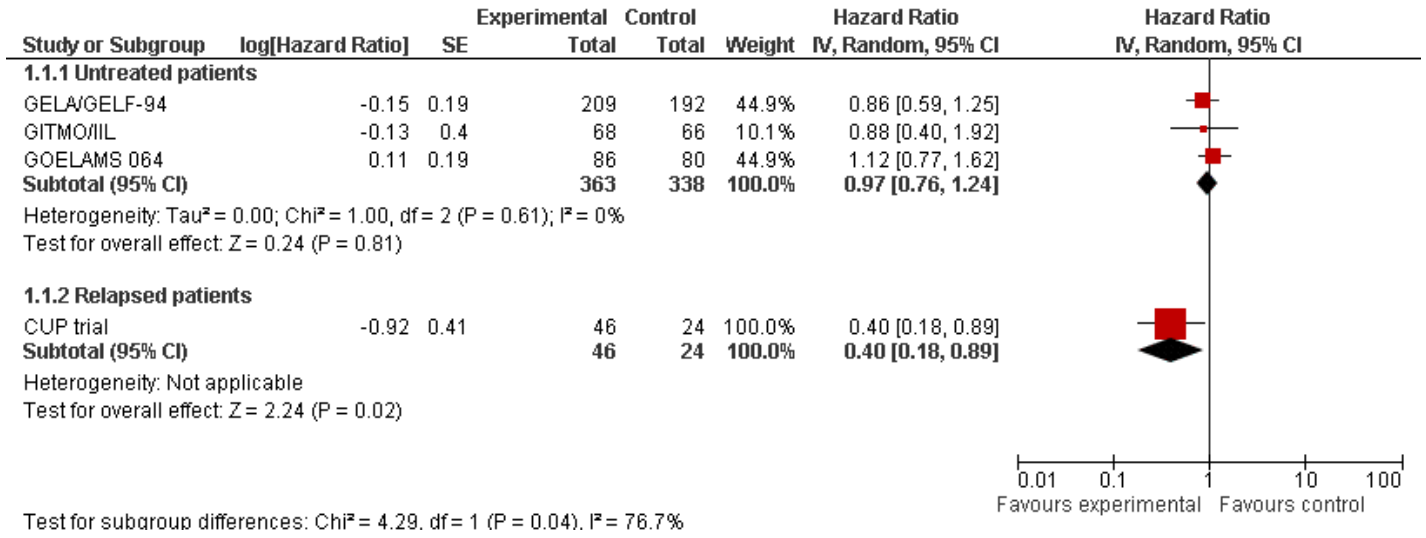


Neelapu et al, Blood 2024
Morschhauser et al, Nat Med 2024
Fowler et al, Nat Med 2022

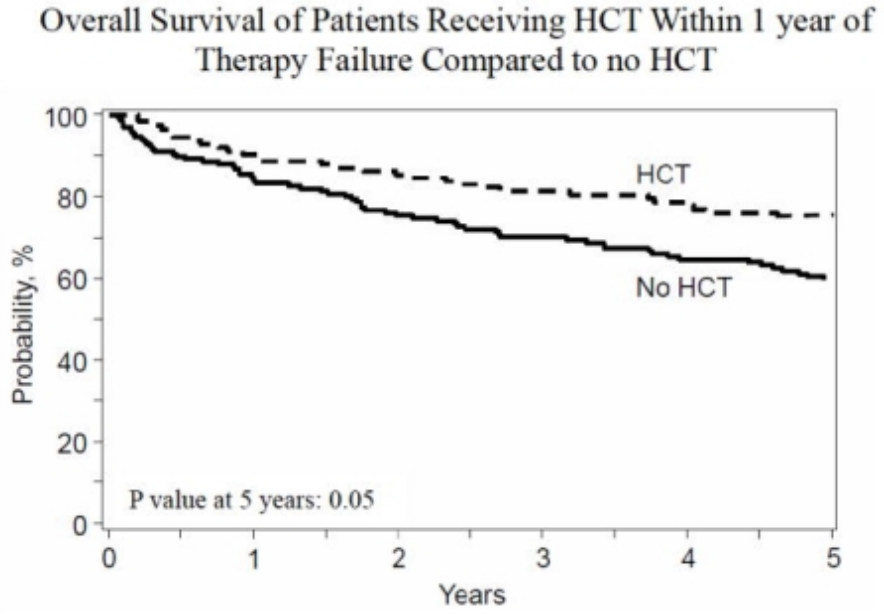
High Risk FL: Auto SCT?

CUP trial (2003, pre-rituximab)

- Randomized 70 patients with at least PR to 3 cycles of CHOP for relapsed FL to HDT and autoSCT or 3 more cycles



Retrospective analysis of CIBMTR and NLCS (N = 350)



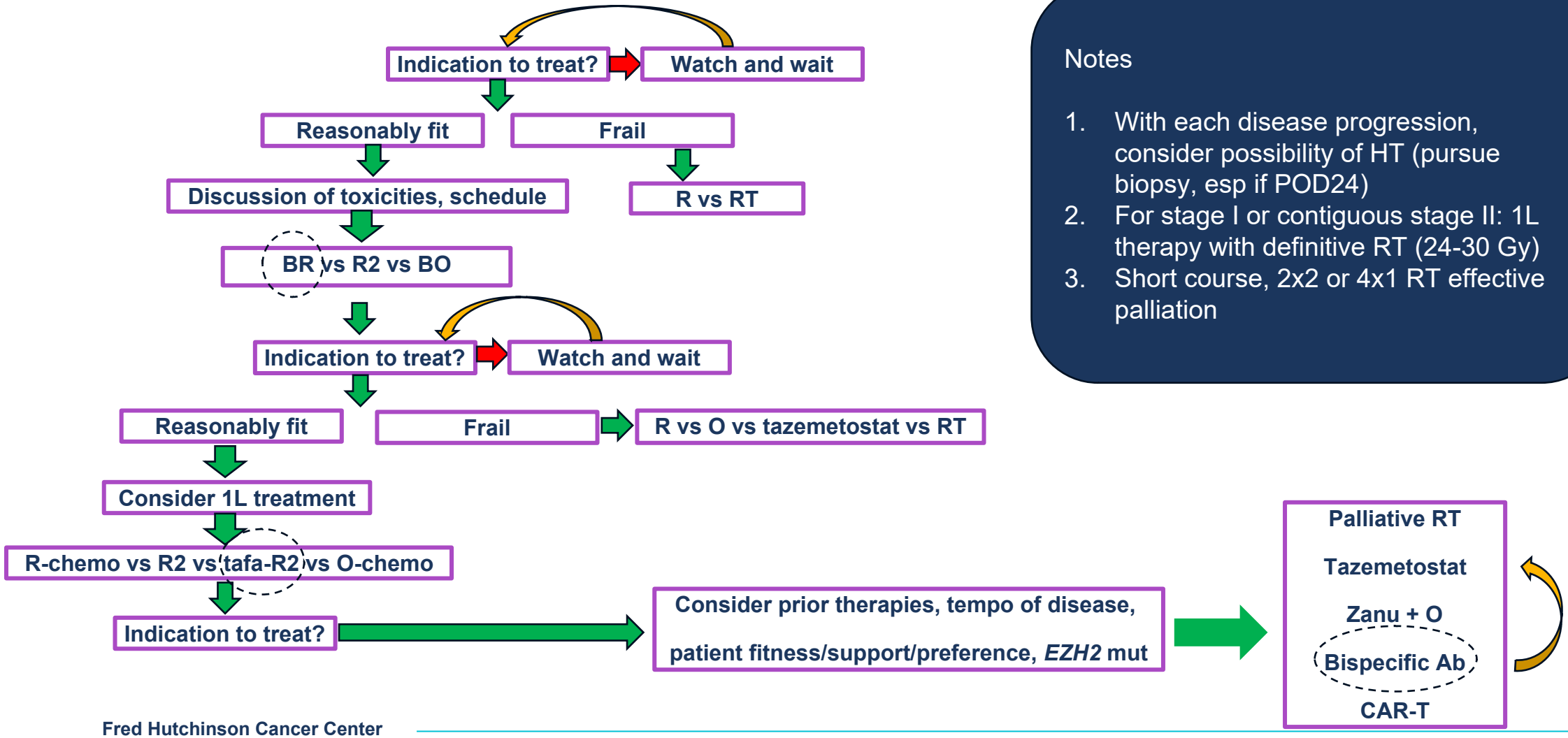
Casulo et al., Biol Blood Marrow Transplant. 2018
Schaaf et al. Cochrane Database of Systematic Reviews 2012

Applying HCT and CAR-T in FL: ASTCT + ESBMT

- Auto SCT: an option for consolidation in patients with POD24, no evidence of HT, and achieve CR or PR to salvage 2nd line therapy (70% agreement)
- CAR-T: considered a treatment option for patients not achieving CR or PR after 2nd or later lines of therapy (96% agreement)
- Allo SCT: considered for consolidation in select cases of relapsed chemosensitive FL after 3+ lines therapy and are post CAR-T failure or lack access to CAR-T or have a concurrent marrow disorder (81% agreement)
- CAR-T versus bispecifics: known differences and unknowns including comparison of efficacy, toxicity, logistics, duration of therapy

Iqbal et al, Transplantation and Cellular Therapy Sep 2024

Management of FL, 2025



Notes

1. With each disease progression, consider possibility of HT (pursue biopsy, esp if POD24)
2. For stage I or contiguous stage II: 1L therapy with definitive RT (24-30 Gy)
3. Short course, 2x2 or 4x1 RT effective palliation

Marginal Zone Lymphomas

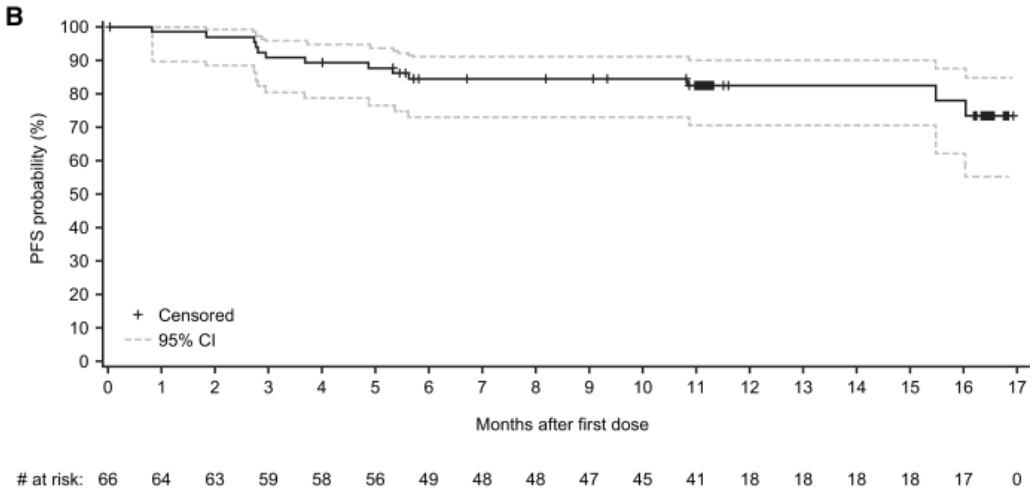
Nodal MZL and Extranodal nongastric MZL

- Immunophenotype typically positive for CD20, CD19 and negative for CD10, CD5
- Principles for management of FL broadly apply
- Caveat 1: No established role for obinutuzumab in 1L
- Caveat 2: Preferred options in 2L include covalent BTK inhibitors (zanubrutinib = FDA acc approved 2021)

MAGNOLIA

→ N = 68, R/R MZL

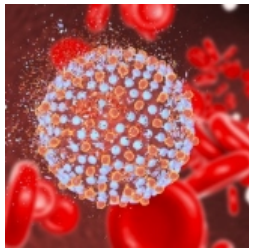
→ ORR 68%, CR 26%



Opat et al, Clin Cancer Res. 2021

Marginal Zone Lymphomas

Splenic MZL

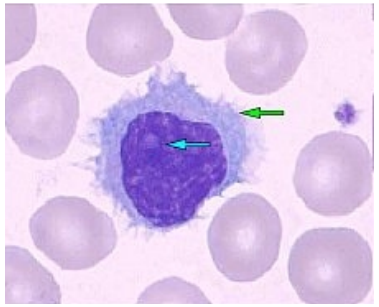


Hepatitis C+?

ORR up to 75% with antiviral therapy

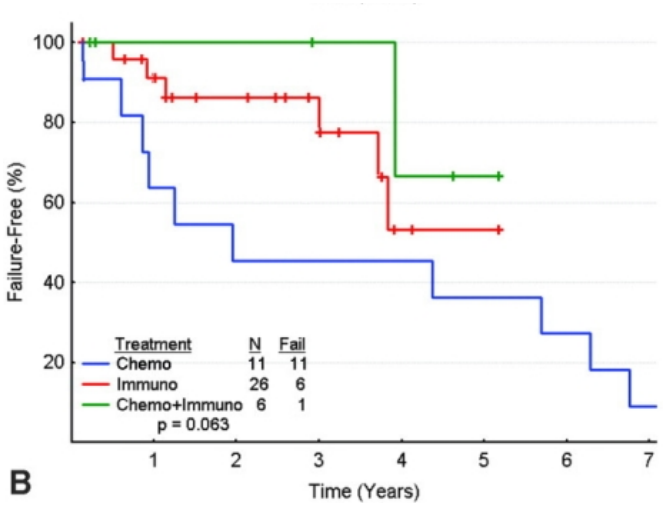
Typical presentation = splenomegaly, lymphocytosis

Cytopenias often indication for Rx



Otherwise, excellent, durable results (> 90% resolution of splenomegaly) possible with rituximab alone;

Splenectomy can also be considered



Tsimberidou et al, Cancer. 2006

Marginal Zone Lymphomas

Extranodal MZL of Stomach (gastric MALT)

- Complete staging: if localized (IE or II)*, determine *H. pylori* status
  - If negative by histopathology conduct stool antigen or urea breath test
  - If H. pylori positive, can check for t(11;18) as it predicts poor response to *H. pylori* eradication
  - *H. pylori* eradication alone if positive and t(11;18) negative
  - *H. pylori* eradication + ISRT of *H. pylori* positive and t(11;18) positive
  - ISRT if *H. pylori* negative
    - 24–30 Gy in 20 fractions
  - Rituximab monotherapy if ISRT contraindicated

*Stage I: confined to GI tract

Stage II: nodal involvement

- Note, response after *H. pylori* eradication, radiation can take several months (restage at 6 mo)

- Higher stage (distant nodal/organ, invasion): manage as per advanced stage EMZL

Summary

- Careful consideration of indication for treatment, avoid excessive toxicity
- Early relapse and multiply relapsed disease remains area of unmet need but rapidly evolving
- Growing list of T-cell engaging therapies, anticipate movement to earlier lines as toxicity mitigated