Seattle Cancer Care Alliance

Fred Hutch · Seattle Children's · UW Medicine

Indolent Non-Hodgkin Lymphoma: 2021

Solomon A Graf, MD

UW/FHCRC/VAPSHCS

Disclosures

Research Support

* TG Therapeutics
* BeiGene
* AstraZeneca / Acerta Pharma
* GlaxoSmithKline
* MorphoSys

Consulting / Advisory

* MorphoSys

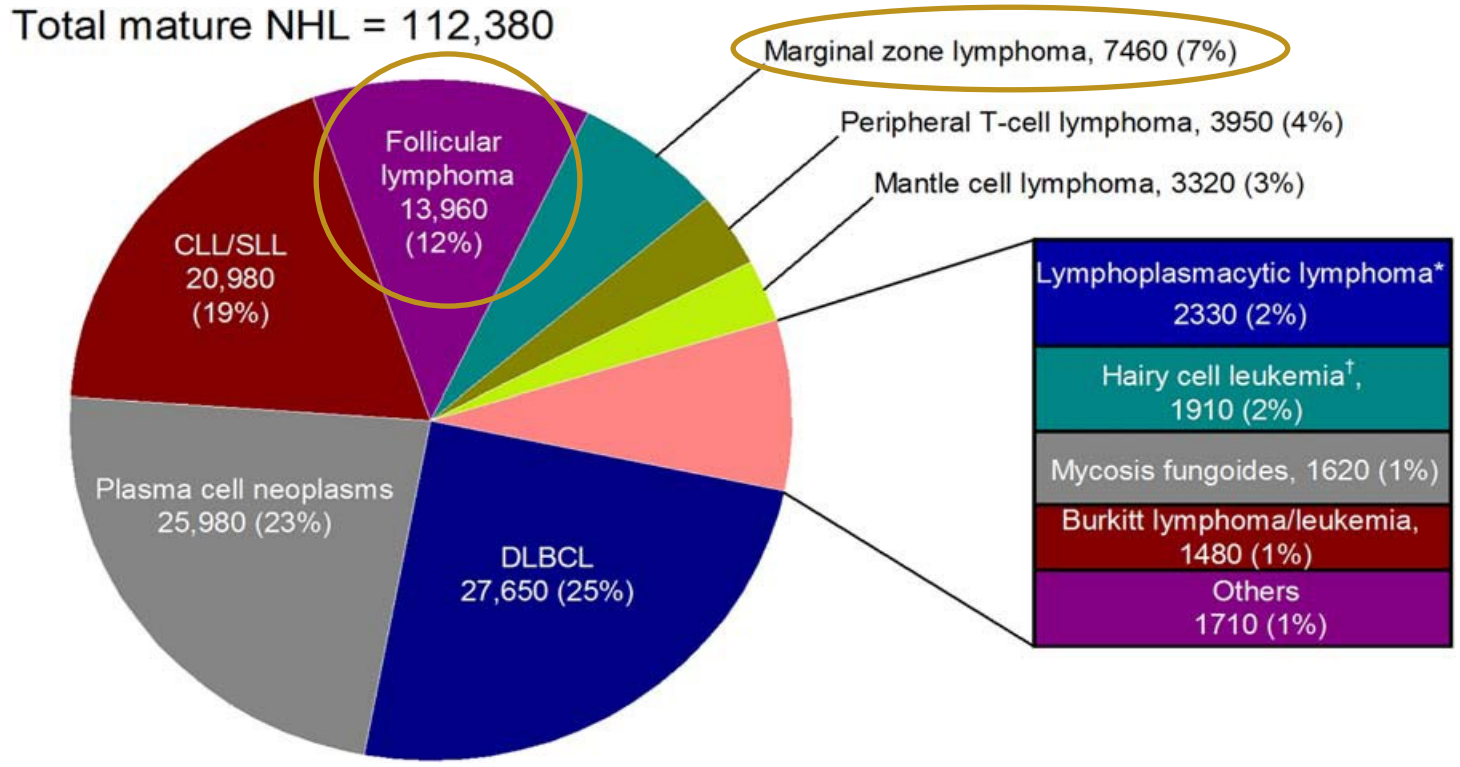
Objectives

- Review key epidemiology and pathology
- Management
  - Discuss indications for treatment, options for frontline and relapsed/refractory
- Highlight areas of unmet need and anticipated next steps
- Cover recent updates and approvals

Natural History

- Presents with advanced disease that usually progresses slowly
- Iterative treatment responses and relapses
- Generally considered incurable with conventional therapies
  - Exceptions include certain examples of limited stage disease treated with local therapies
- Most patients die from causes unrelated to lymphoma

Epidemiology



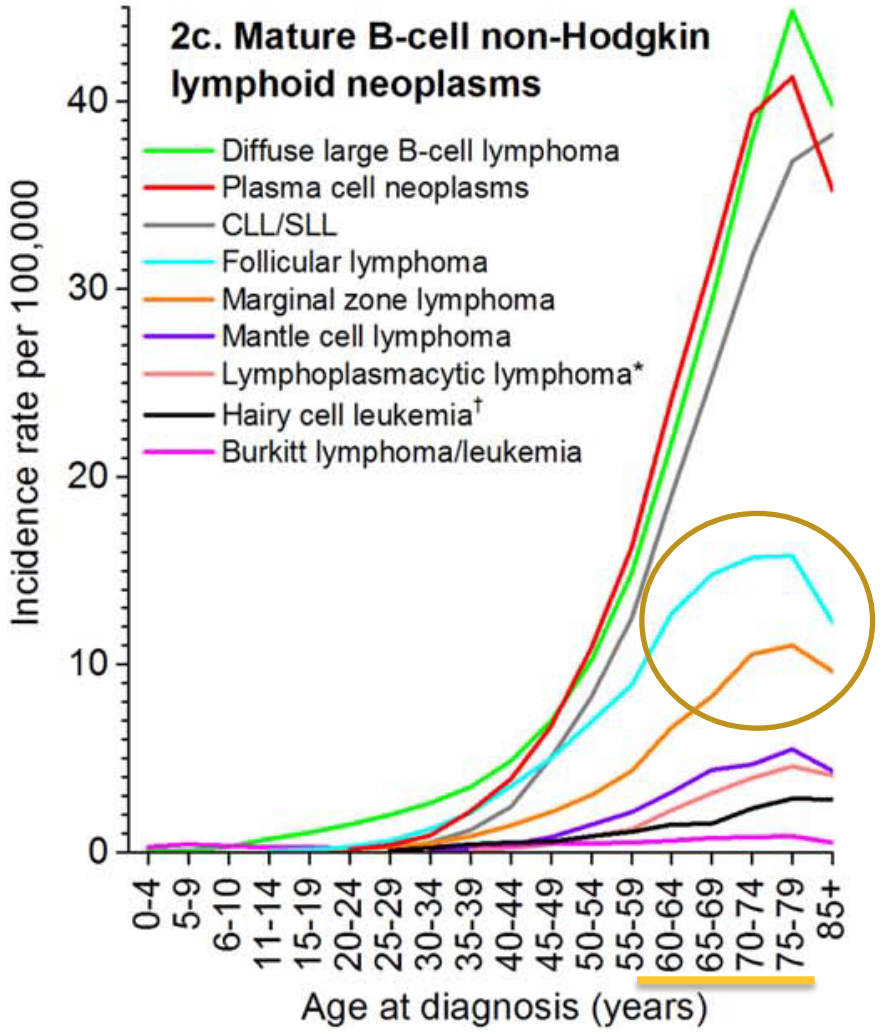
Estimated Cases and Distribution of Mature Non-Hodgkin Lymphoid Neoplasm Subtypes: US, 2016

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

Risk Factors

- Follicular lymphoma
  - Autoimmune conditions
  - Cigarette smoking (women)
  - Benzene, other solvents
  - Agent Orange, other herbicides

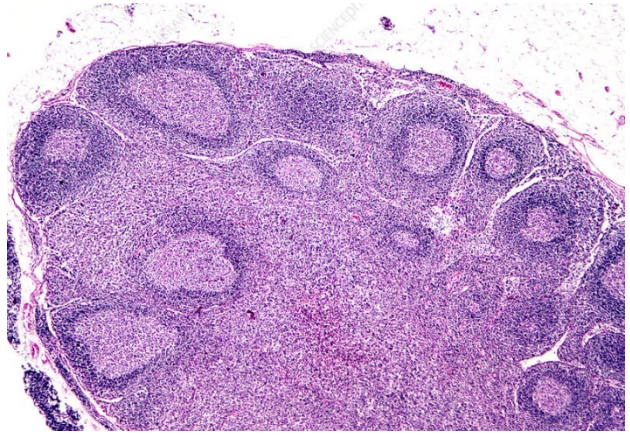
- Marginal zone lymphoma
  - As above, also specific infections (e.g. H pylori)

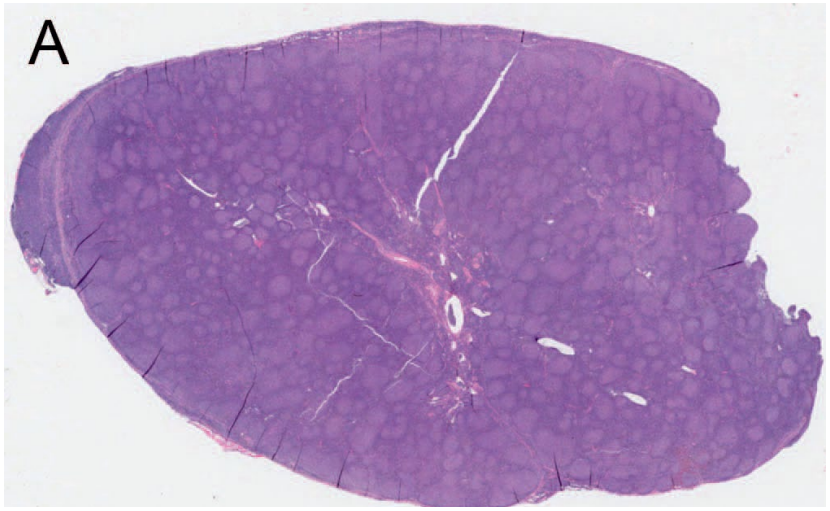


Teras et al. CA Cancer J Clin 2016;66:443–459
https://www.publichealth.va.gov/exposures/agentorange/conditions/nonhodgkinslymphoma.asp

Work-up

- Excisional or incisional biopsy preferred to core (FNA inadequate)
- Labs including LDH, hepatitis B
- Diagnostic CT, whole-body PET
- Marrow exam (clinical stage I-II disease)

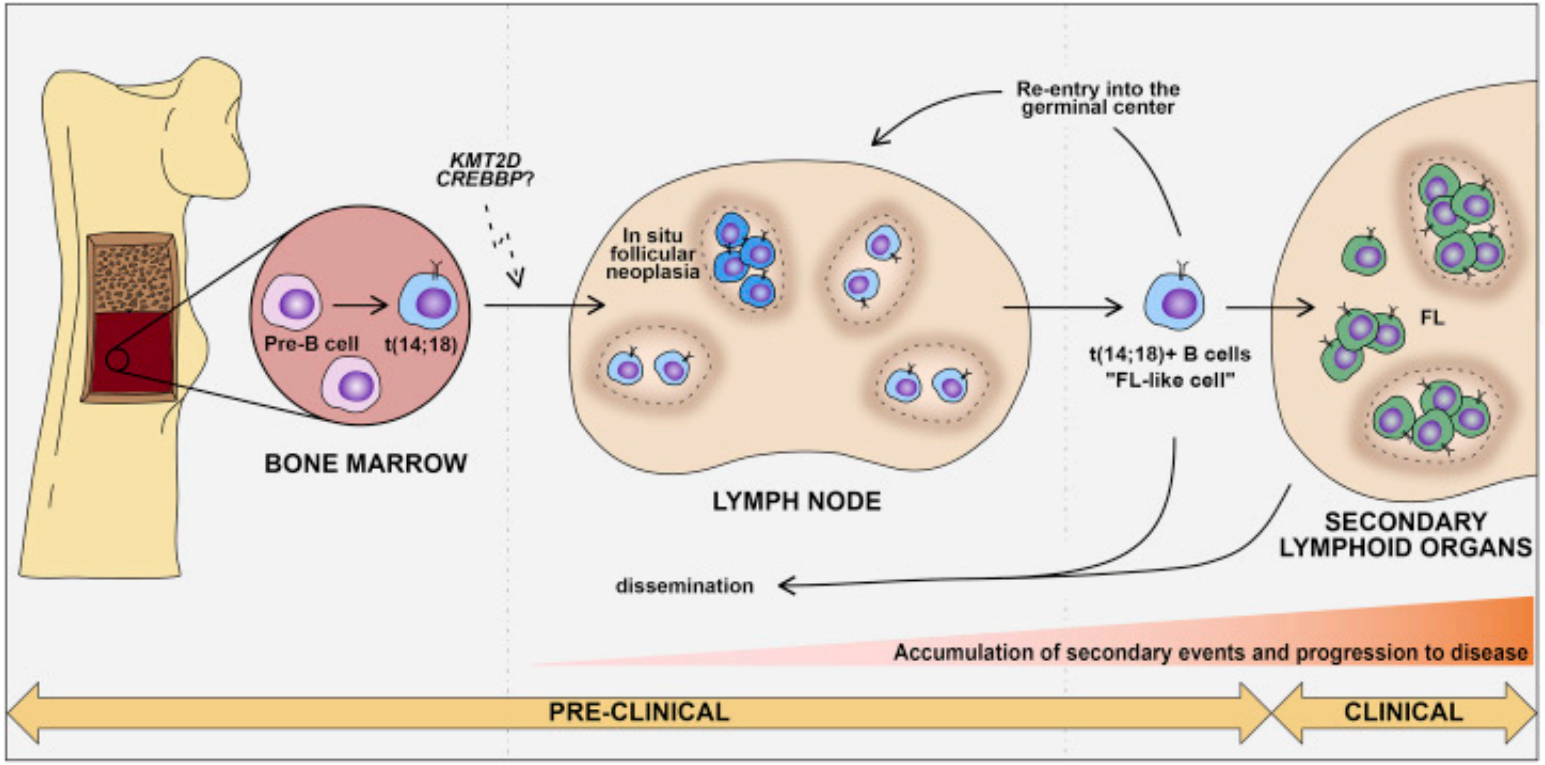




Choi et al. Arch Pathol Lab Med. 2018;142:1330-1340
https://www.sciencephoto.com/media/115304/view/normal-human-lymph-node

Typical Follicular Lymphomagenesis

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



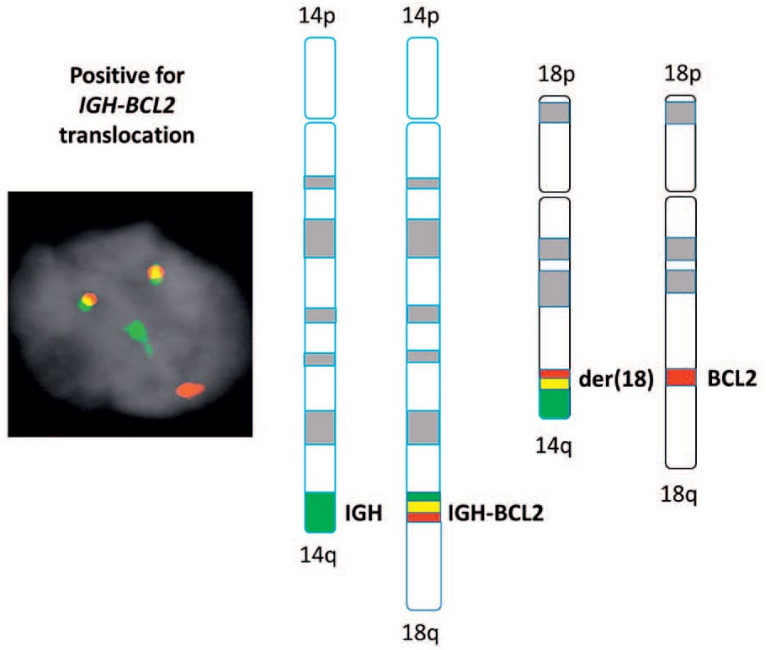
- 1st step: acquisition of t(14;18) that occurs in the bone marrow (pre-B cell stage)
  - Leads to constitutive expression of anti-apoptotic protein BCL-2
- B cells with t(14;18) that enter the germinal center (highly mutagenic environment) are at risk for developmental arrest leading to clonal expansion, new mutations, and ultimately FL

Lackraj et al Best Pract Res Clin Haematol. 2018 Mar;31(1):2-14.

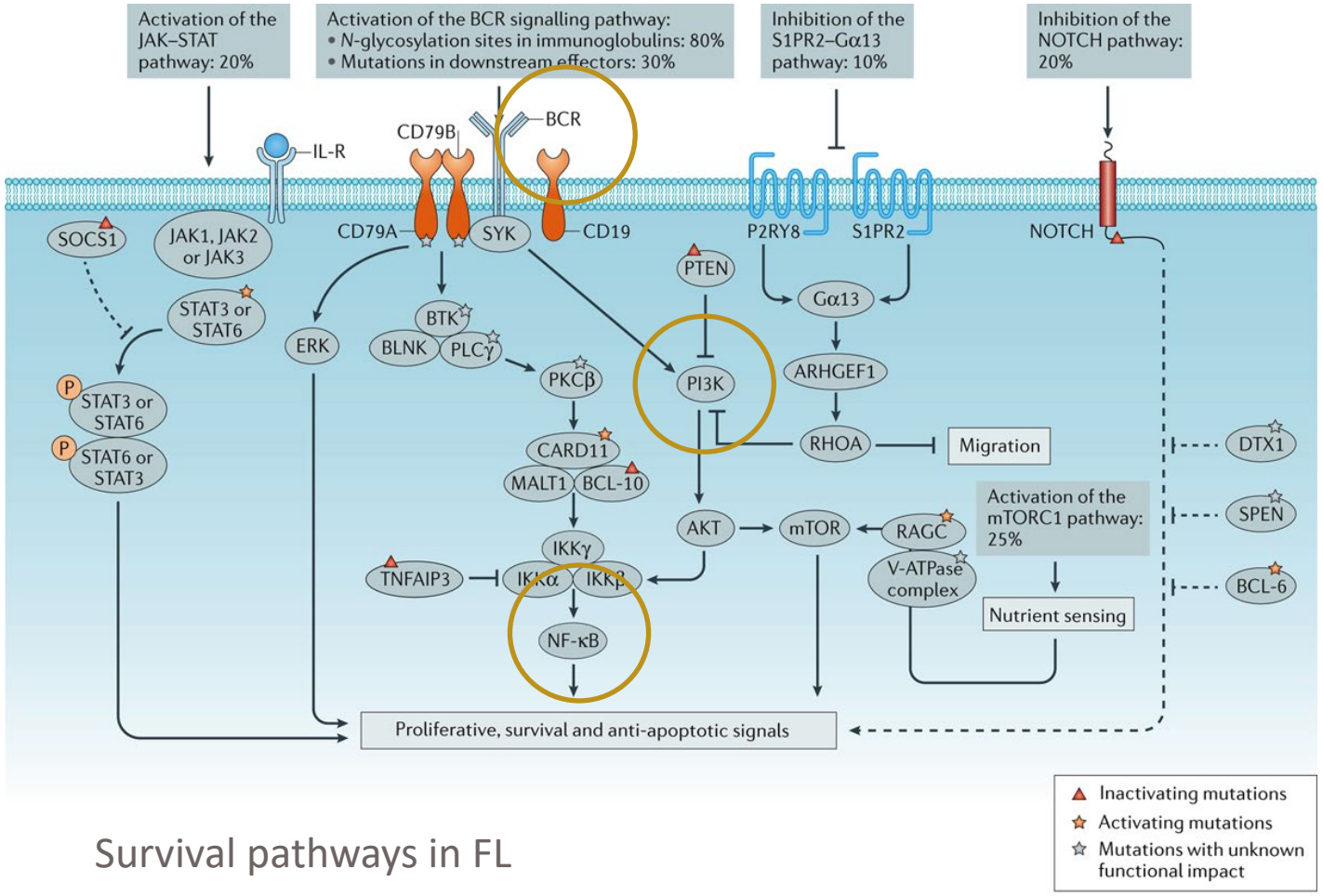
Molecular Characteristics: Typical FL

- Light chain restricted
- Pan B-cell markers (CD20+, CD19+)
- Arise from germinal center B-cells, thus CD10+ and BCL6+
- Also typically BCL2+ and CD5-

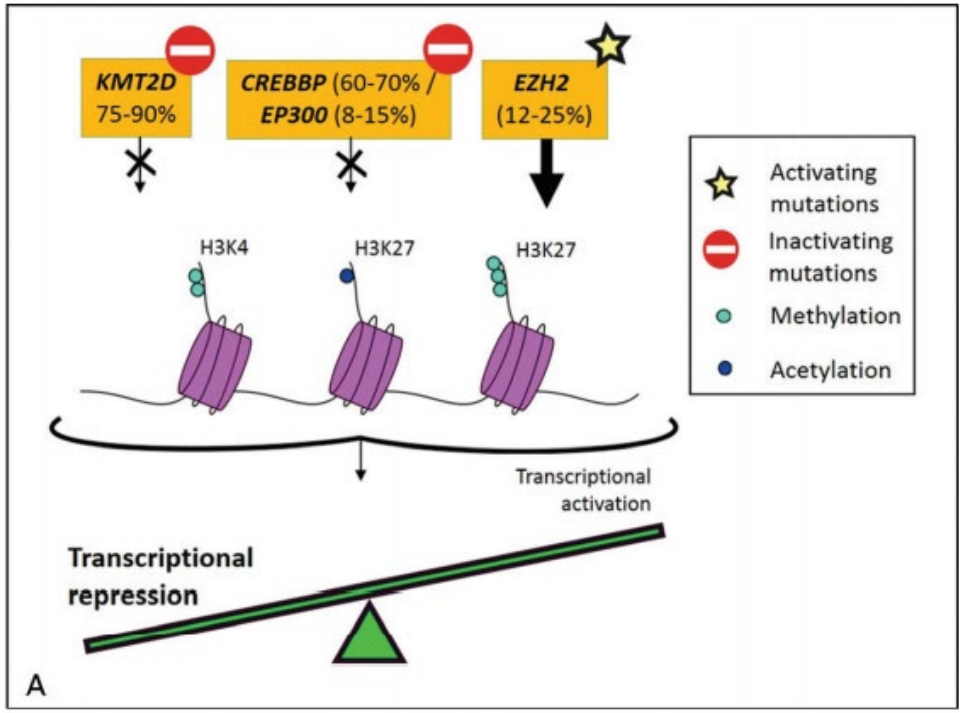
- [t(14;18)(q32;q21)] ~85% of cases
  - Juxtaposes Ig heavy chain promoter with *BCL-2*
  - Constitutive BCL-2 expression (anti-apoptosis)
  - Variants [t(2;18)] and [t18;22)]
    - Alternative *BCL-2* juxtapositions (kappa LC / lambda LC)



Pathways in Follicular Lymphomagenesis



Survival pathways in FL



Alterations in epigenetic modifiers occur >90% of cases of FL (most > 1)

*histone methyltransferases

*histone acetyltransferases

→ typically, early events

Huet et al. Nat Rev Cancer. 2018 Apr;18(4):224-239

Kumar and Okosun, HemaSphere 2019; 3(S2): 79-80

Pediatric-type FL (PTFL)

- Definitive entry in 2016 WHO Lymphoma Classification (testable!)

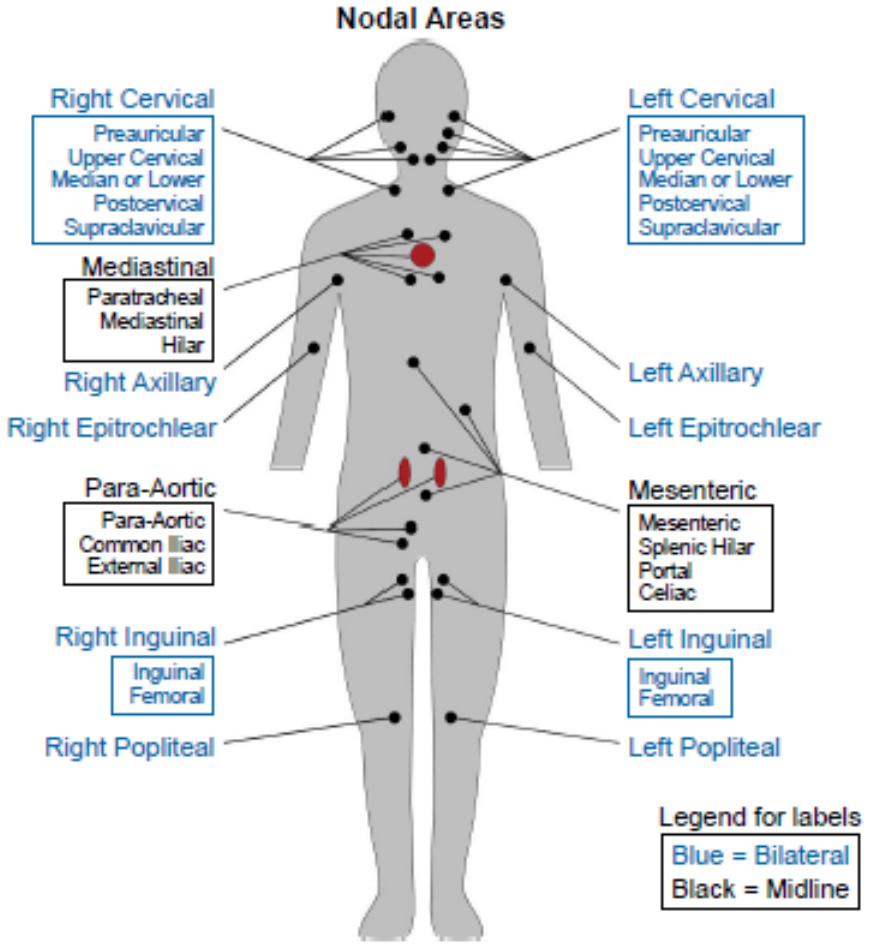
- Clinical presentation
  - Localized disease (H&N location common)
  - Males > Females
  - Younger age typical (though not necessary)

- Key pathologic/molecular features
  - High Ki67 (> 30%)
  - No t(14;18) on FISH (or rearrangements in *BCL6*, *IRF4/MUM1*)
  - (Epimutations less common)
  - (Low genetic complexity)

- Local therapy preferred: Excision > RT > Systemic therapy

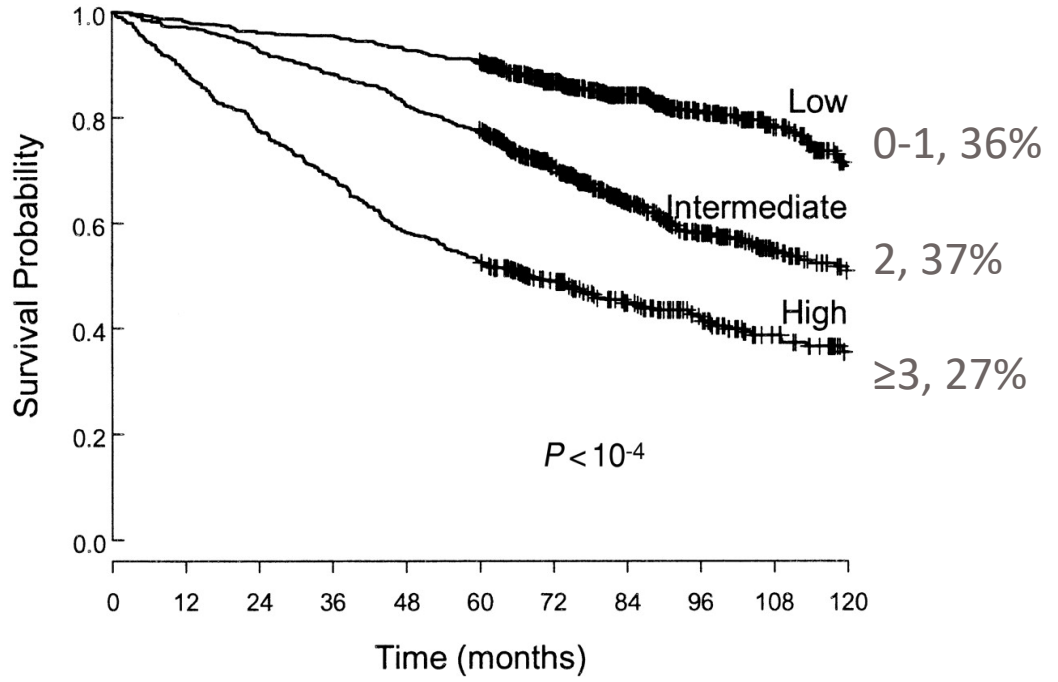
Clinical Characteristics of Follicular Lymphoma

- Median age at diagnosis approximately 65 years
- Multiple sites of waxing and waning adenopathy
- Approximately 25% present with B symptoms
- 65-70% stage III/IV



Follicular Lymphoma International Prognostic Index

- 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 Sep 1;104(5):1258-65

Next Generation FLIPIs

	FLIPI	FLIPI-2	PRIMA-PI	M7-FLIPI
Age	✔	✔		✔
Stage	✔			✔
Hemoglobin	✔	✔		✔
LDH	✔			✔
Nodal sites	✔			✔
B2M ≥ 3 gm/L		✔	✔	
Marrow inv		✔	✔	
Mass ≥ 6 cm		✔		
ECOG				✔
7-gene mutations				✔

Federico et al. J Clin Oncol 27: 4555-4562, 2009; Jurinovic et al. Blood 128: 1112-20;
Huet et al, ICML 2017; Salles et al. Blood. 2018 Jul 5;132(1):49-58.

Advanced Stage FL: Treatment Initiation

Table 2. Spontaneous Regressions in Initially Untreated Patients.*

	No. of Patients (%)	Months to Regression		Months of Regression	
		median	*range*	*median*	*range*
Total	19/83	8	2–120	>13	>4–>72
FSC/NLPD	13/44 (30)	7	2–120	15	>4–>72
FM/NM	3/18 (17)		2–23		>4–12
SL/DLWD	3/21 (14)		26–93		6–>72

FSC = Follicular small cleaved; FM = follicular mixed; SL = small lymphocytic; DLWD = diffuse well differentiated lymphocytic

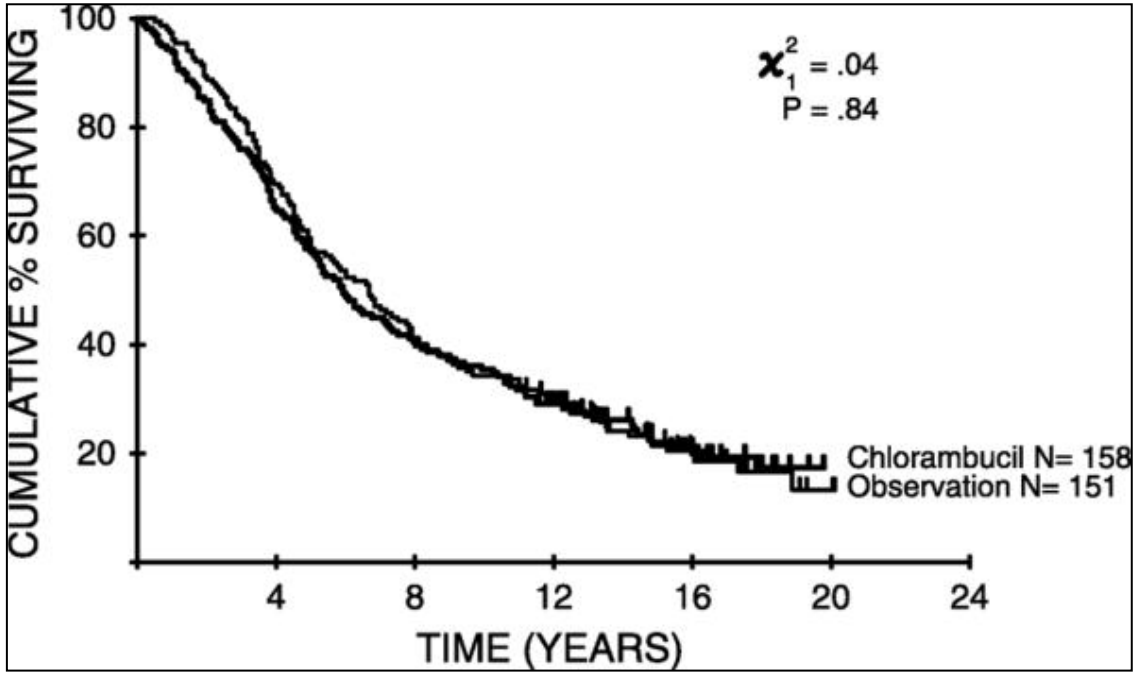
Hornig, NEJM 1984.

Advanced Stage Early Treatment (Chlorambucil)

Asymptomatic stage III/IV FL N = 309

RANDOMIZE

- Observation
- Chlorambucil

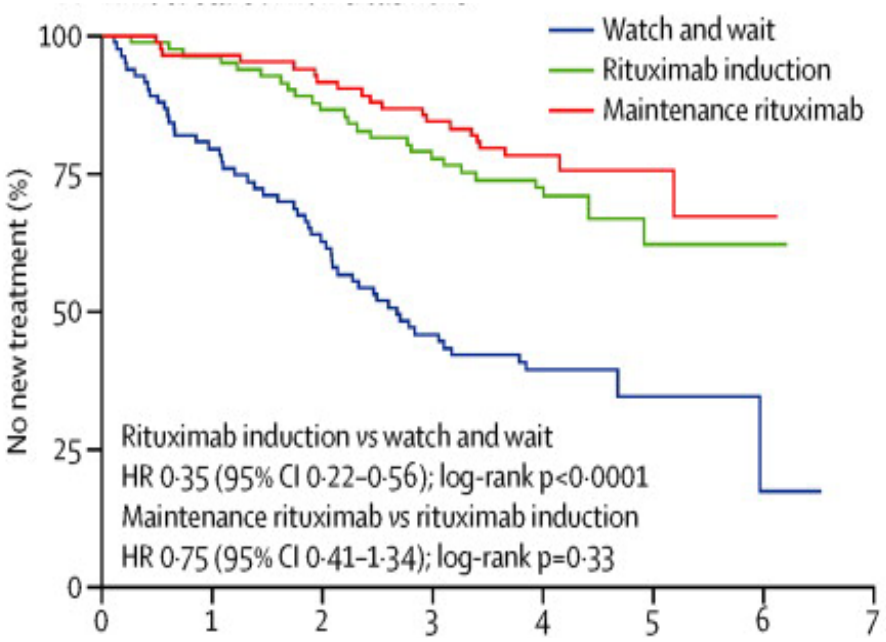


19% did not require treatment at 10 years

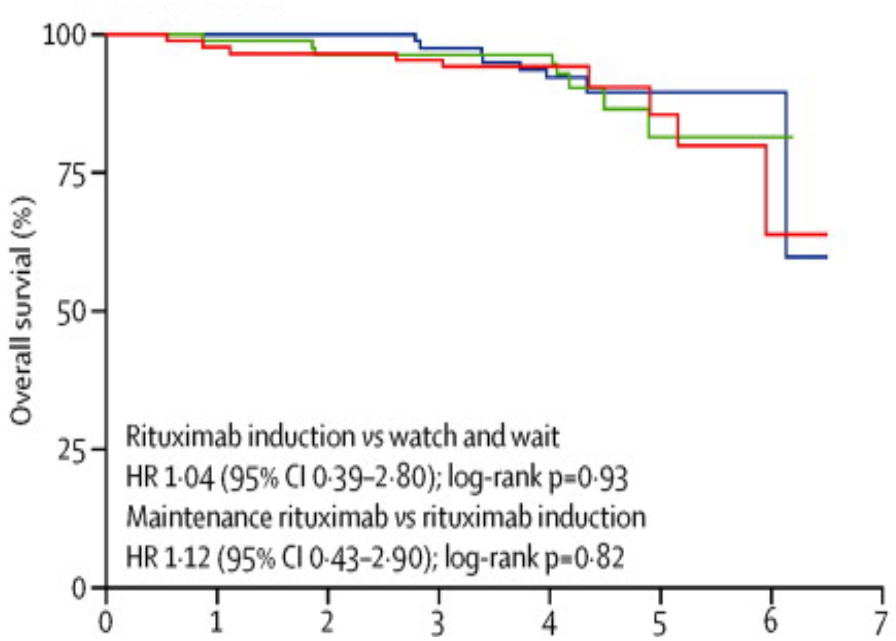
Ardeshna et al, Lancet. 2003 Aug 16;362(9383):516-22

Advanced Stage Early Treatment (Rituximab)

Time to Next Treatment



Overall Survival



- Those that received induction plus maintenance rituximab had some benefit related to anxiety
- Conversation on toxicities, costs, and potential for never requiring therapy

Ardeshna et al, Lancet Oncol. 2014 Apr;15(4):424-35

Groupe d'Etude des Lymphomes Folliculaires Criteria

- Involvement of ≥ 3 nodal sites, each ≥ 3 cm
- Any lesion ≥ 7 cm

} "Bulky"

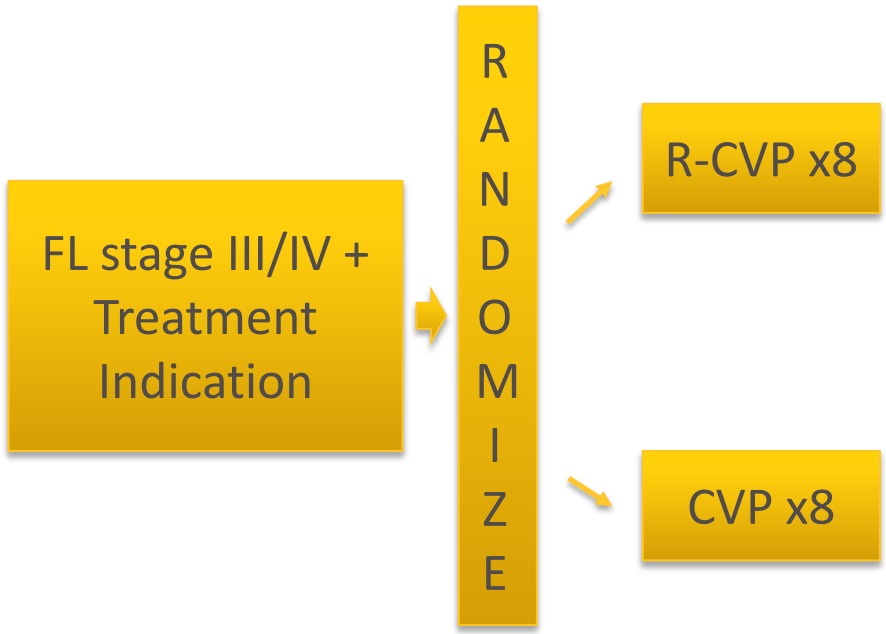
- B symptoms
- Splenomegaly
- Threatened organ function
- Pleural/peritoneal effusion
- Cytopenias (leukocytes < 1k or platelets < 100k) or leukemia

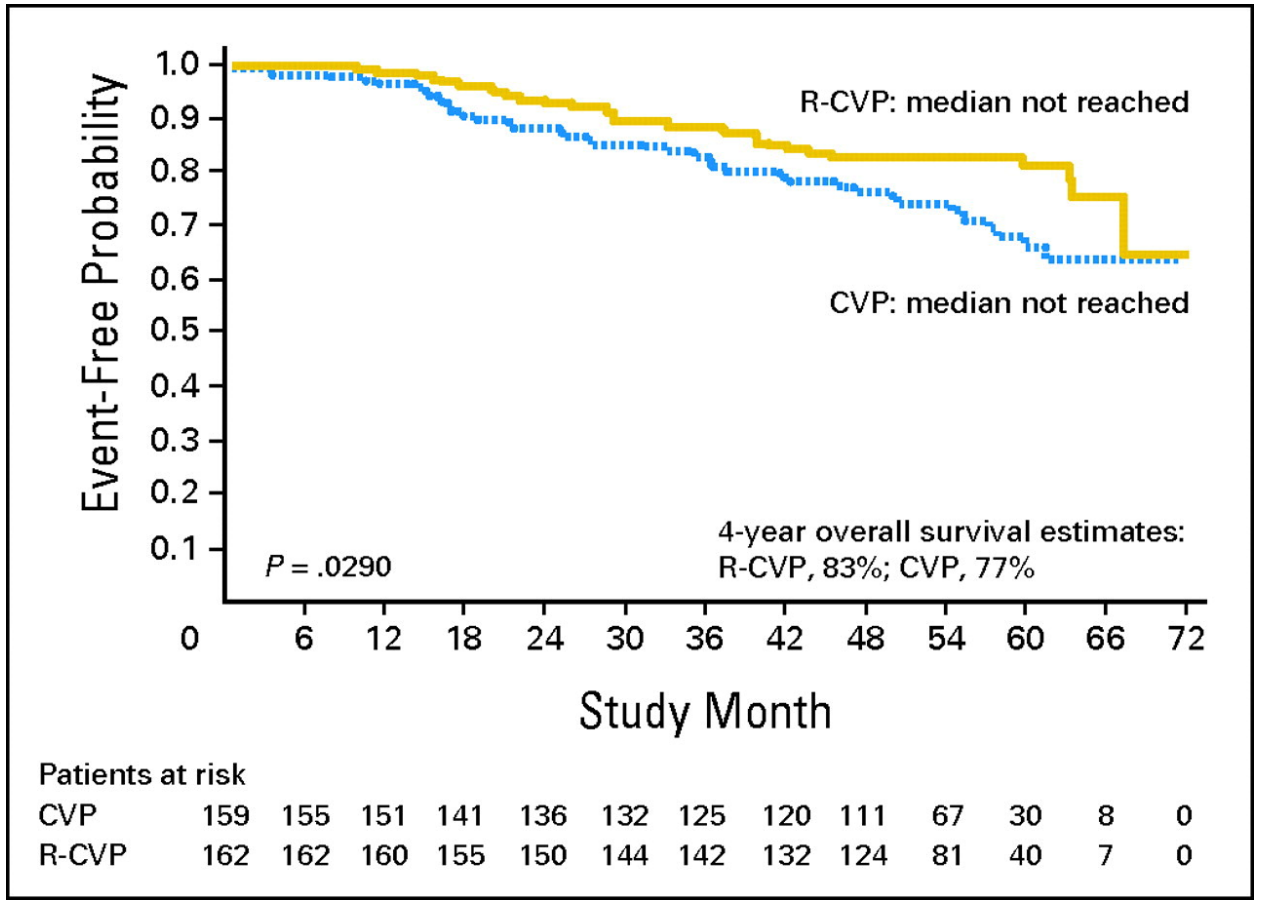
- NCCN: also, steady or rapid progression; candidate for trial

- Median time between diagnosis and start of treatment = 2 to 3 years

Solal-Celigny et al. J Clin Oncol 1998; 16:2332-2338
Nastoupil et al. Br J Haematol. 2016 Mar;172(5):724-34

Frontline Treatment: Addition of Rituximab





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 Oct 1;26(28):4579-86

Primary Rituximab and (Maintenance v Observation) PRIMA

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

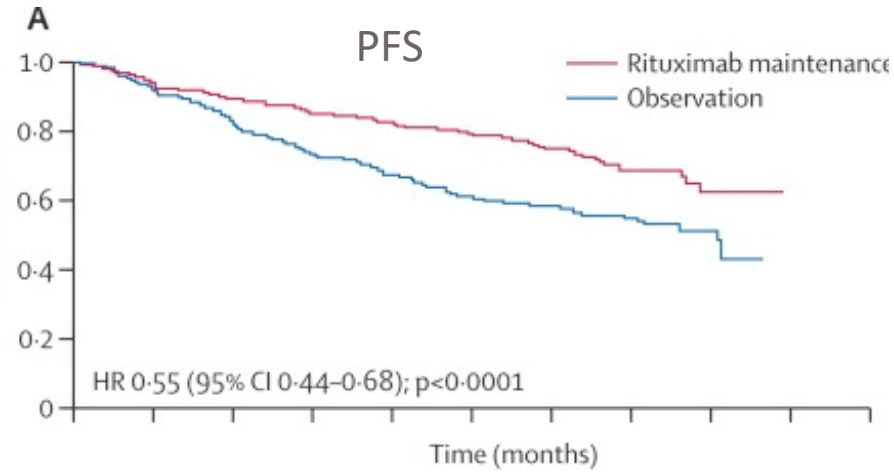
→ R-chemo

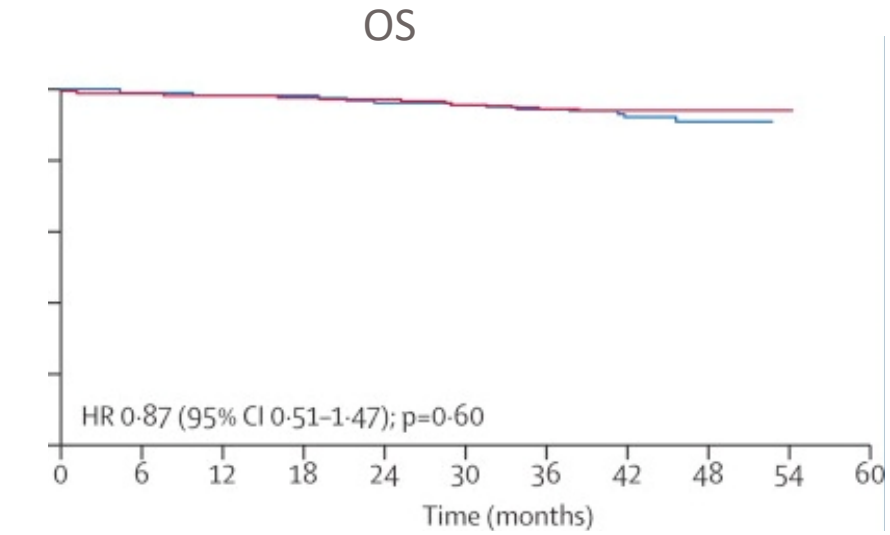
- R-FCM (4%)
- R-CVP (23%)
- R-CHOP (74%)

→ CR/PR
N = 1,018

→ RANDOMIZE

- → Observation
- → R q2mo x2 yrs





Salles et al. Lancet. 2011 Jan 1;377(9759):42-51.
Updated 2019 ASCO (9 years follow-up)

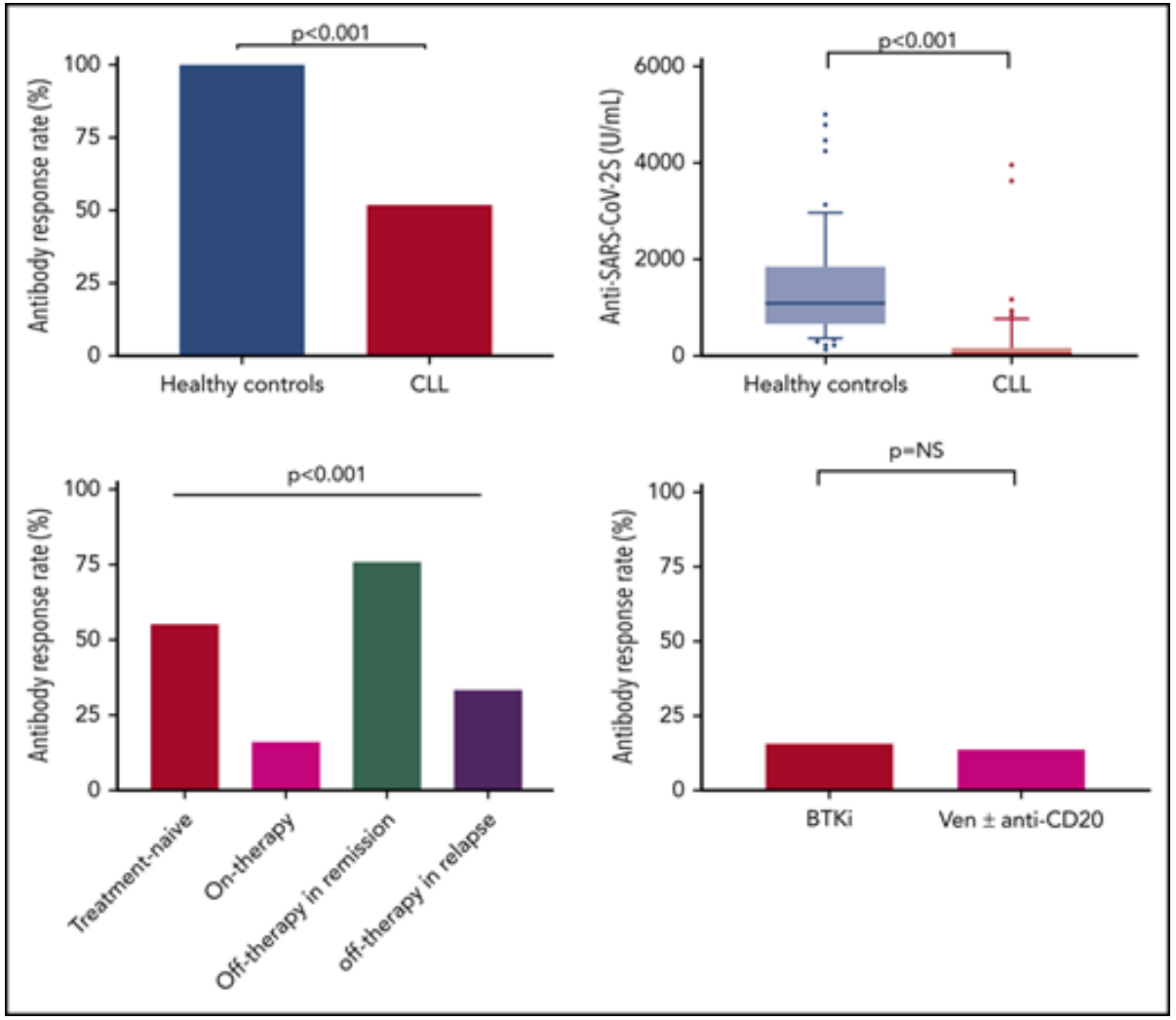
PRIMA: Toxicity

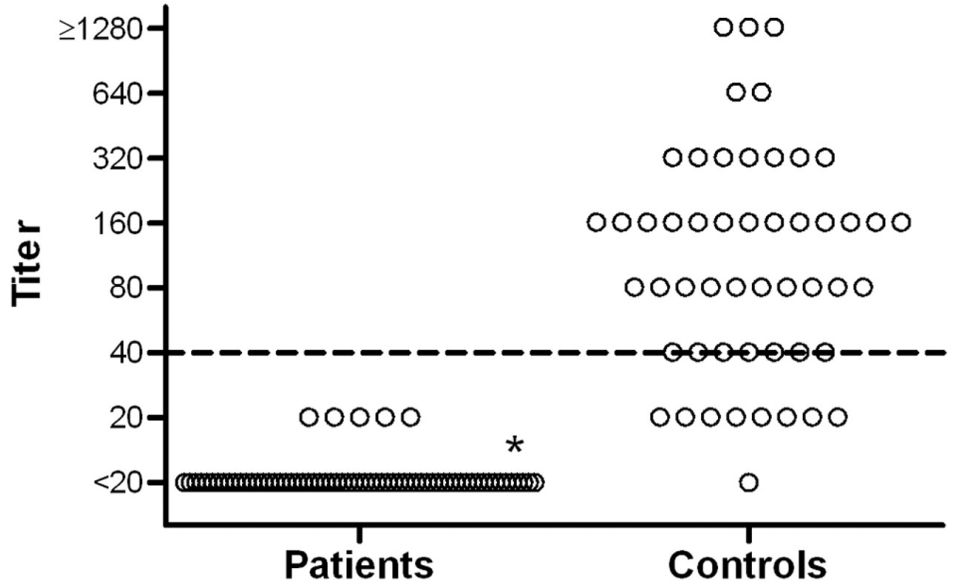
	Observation (n=508)		Rituximab maintenance (n=501)	
	Grade 3/4	Leading to treatment discontinuation	Grade 3/4	Leading to treatment discontinuation
All adverse events	84 (17%)	8 (2%)	121 (24%)	19 (4%)†
Neoplasia	17 (3%)	6 (1%)	20 (4%)	5 (1%)
Neutropenia	5 (1%)	0	18 (4%)	0
Febrile neutropenia	2 (<1%)	0	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 Jan 1;377(9759):42-51.

anti-CD20 antibody toxicity: 2021





Compared to 82% of adequate responses in control group, 0 or 67 patients with lymphoma receiving rituximab responded to H1N1 virus vaccine

Herishanu et al. Blood. 2021.
Yri et al. Blood, Nov 2011

Rituximab Extended Schedule or Re-treatement (RESORT)

Untreated FL: advanced stage, grade 1-2, **Low tumor burden**

→ R qweek x4

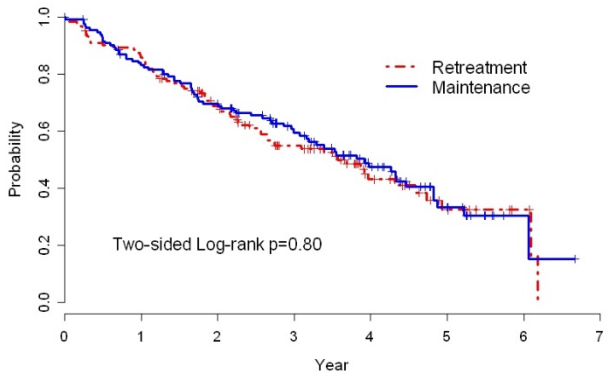
→ CR or PR

→ RANDOMIZE

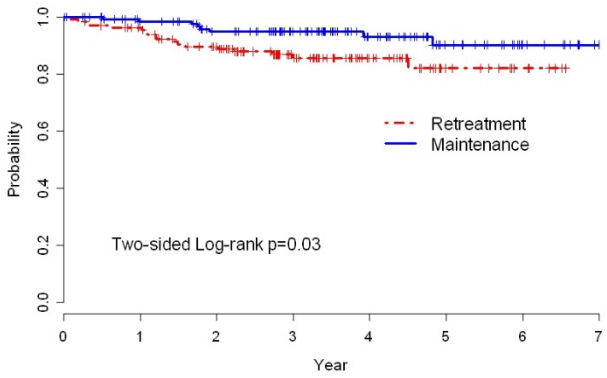
→ Observation → Repeat rituximab weekly x4 at progression (if TTP > 6 mo)

→ Rituximab q3 mo until progression

Time to treatment failure



Time to first cytotoxic chemo



Doses of Rituximab

	Min	Max	Median	Mean
Re-treat	4	16	4	4.5
Maint	5	31	15.5	15.8

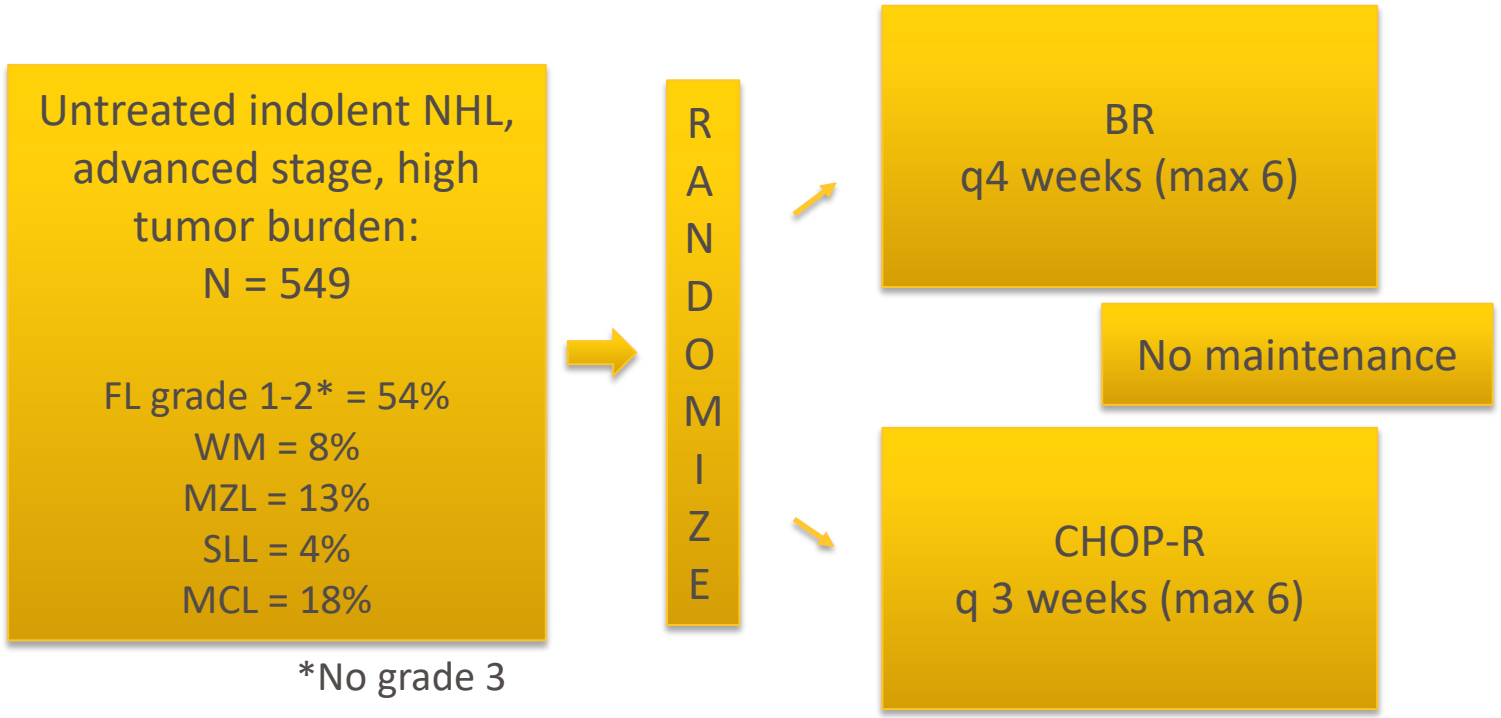
Kahl et al. J Clin Oncol. 2014 Oct 1;32(28):3096-102.

Rituximab Hyaluronidase

- Subcutaneous injection over ~ 5 minutes
- Efficacy and safety are similar to IV
- May be substituted after patients have received 1st full dose of IV rituximab
- Time-saving (for patients and infusion clinic) → monitor for 15 min post injection
- Injection-site erythema in 11%

eMPR.com accessed June 2020.

BR vs CHOP-R (StIL NHL1)



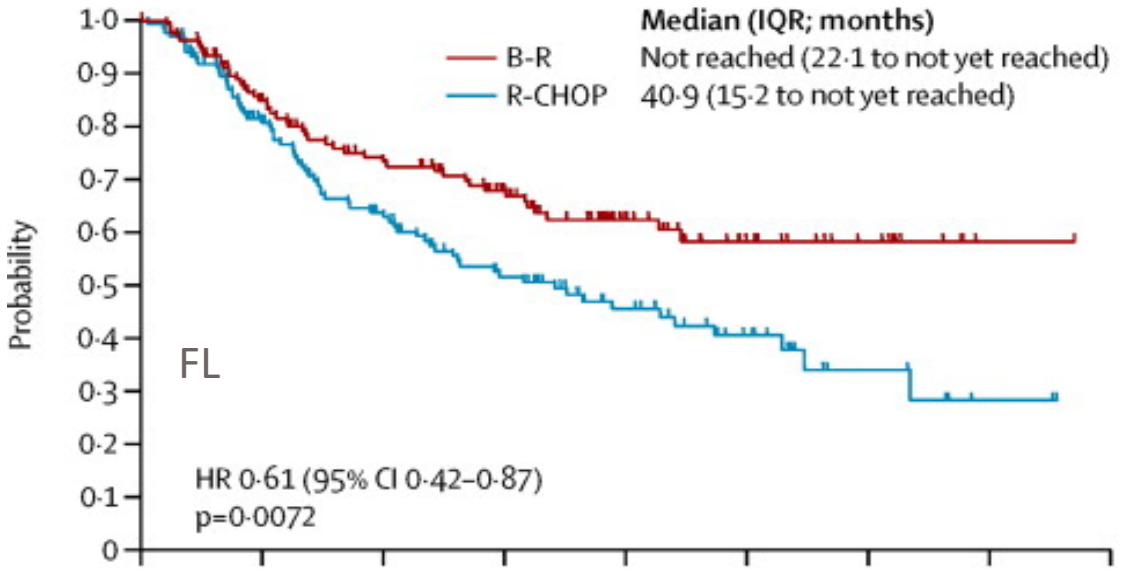
	B-R N = 260	CHOP-R N = 253	P
Alopecia	0	245	< 0.0001
Paresthesias	18	73	< 0.0001
Stomatitis	16	47	< 0.0001
Allergic reaction	40	15	0.0003
Infections	96	127	0.0025
Sepsis	1	8	0.0190
Neutropenia G3/4	11%	47%	

Rummel et al. Lancet. 2013 Apr 6;381(9873):1203-10.

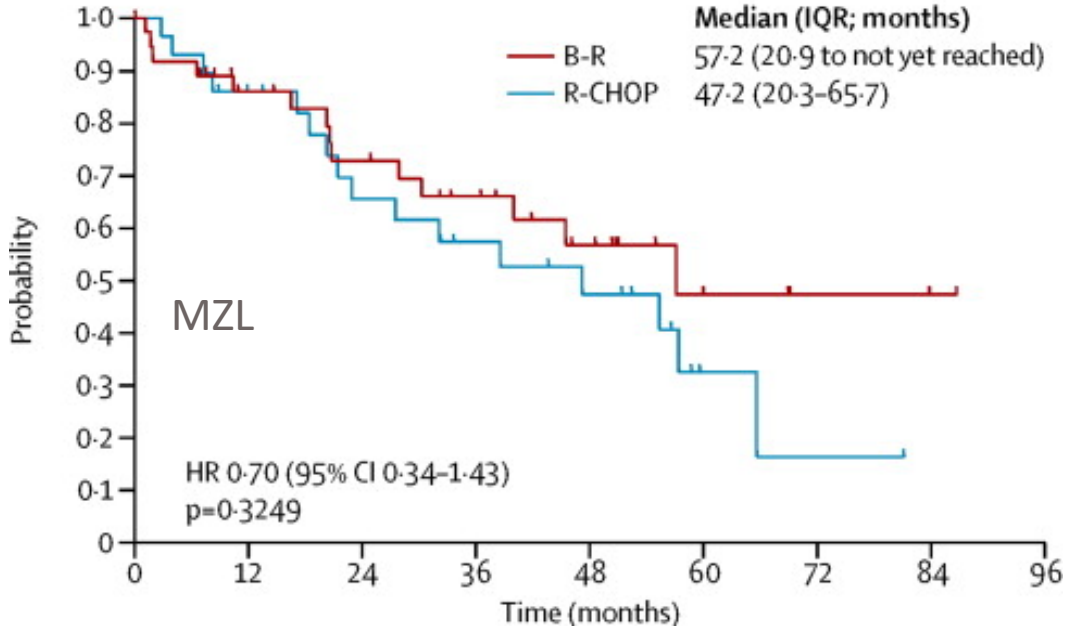
StIL NHL1

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

PFS A



PFS C



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

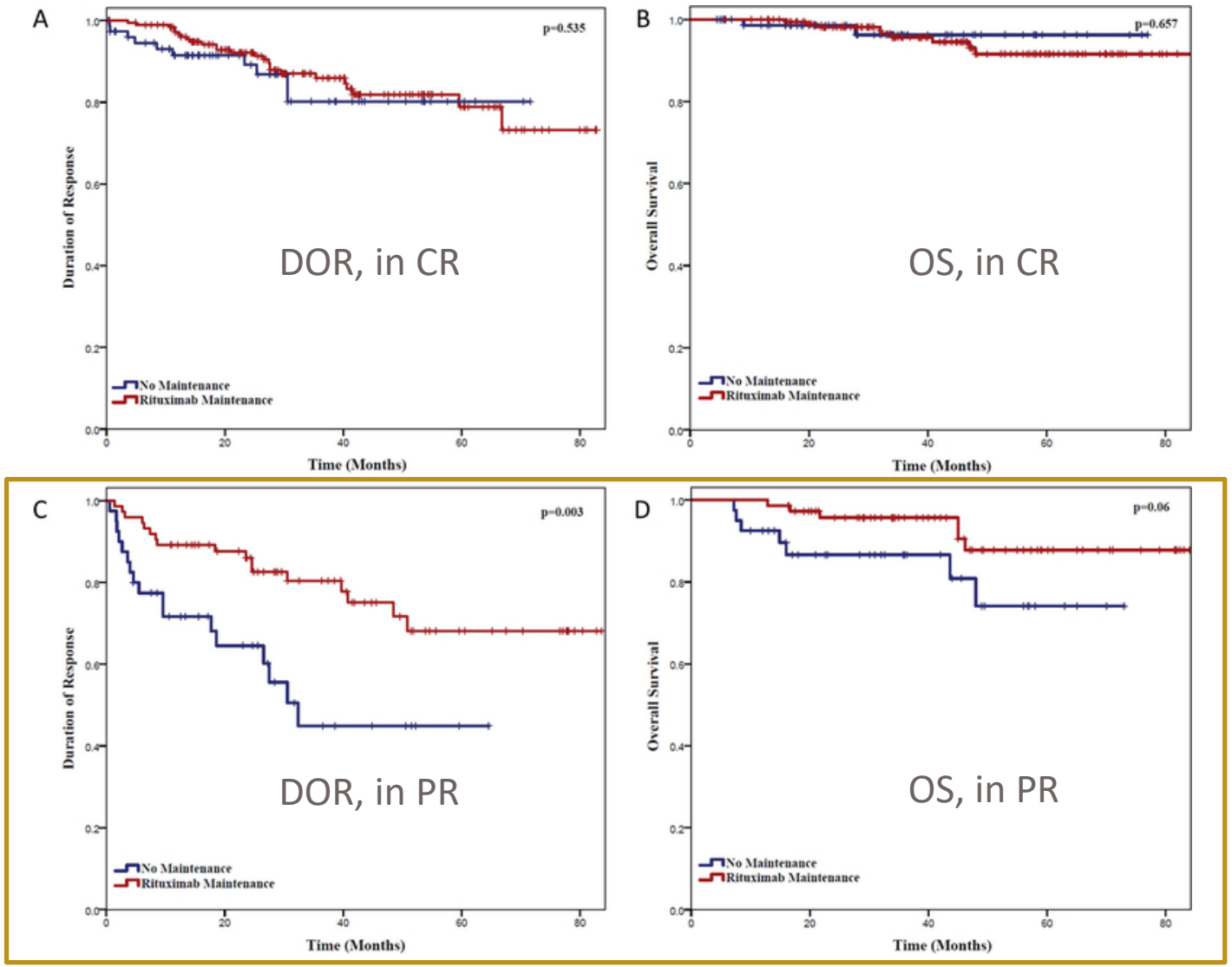
Rummel et al. Lancet. 2013 Apr 6;381(9873):1203-10.

Maintenance Rituximab after BR

- Retrospective, limited to patients in CR or PR after induction BR (at least 4 cycles)
- Findings comparable to other, cross-trial analyses

Maintenance Rituximab after R-chemo

For	Neutral/Against
PR	CR
Concern for toxicity from 2nd line	Toxicity
	Cost, time

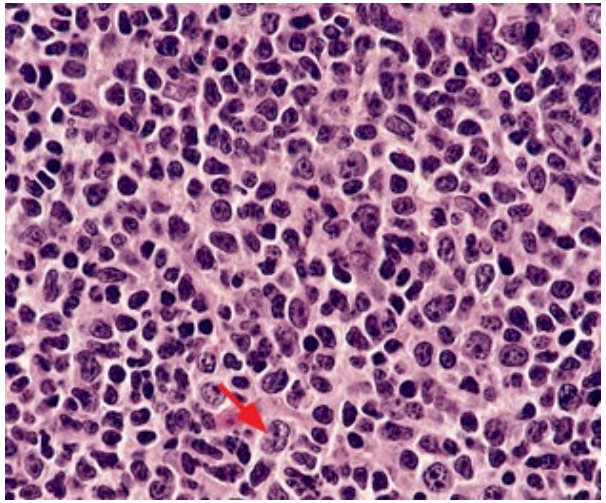


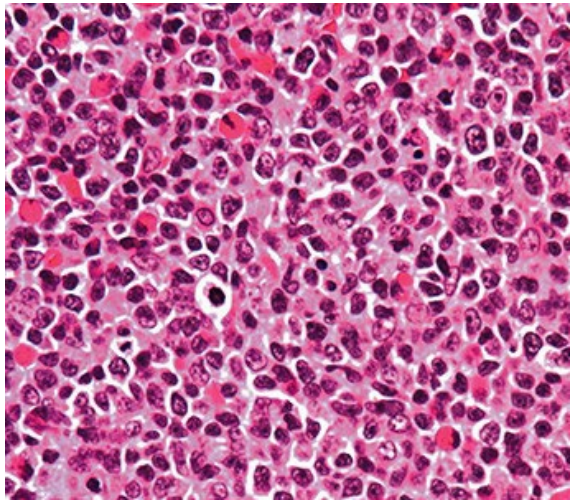
Hill et al. Br J Haematol. 2019 Feb;184(4):524-535.

BR for Frontline Treatment of FL

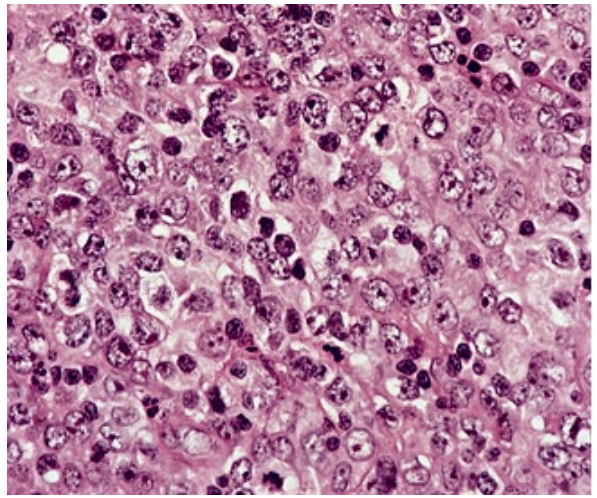
https://substance.etsmtl.ca accessed July 2020

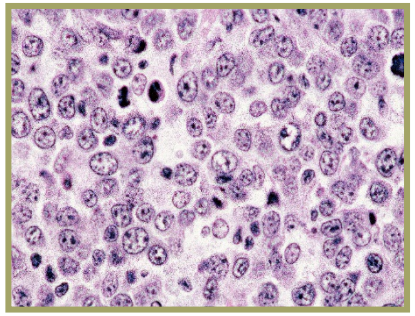
FL Histologic Grade





25-30% of FL

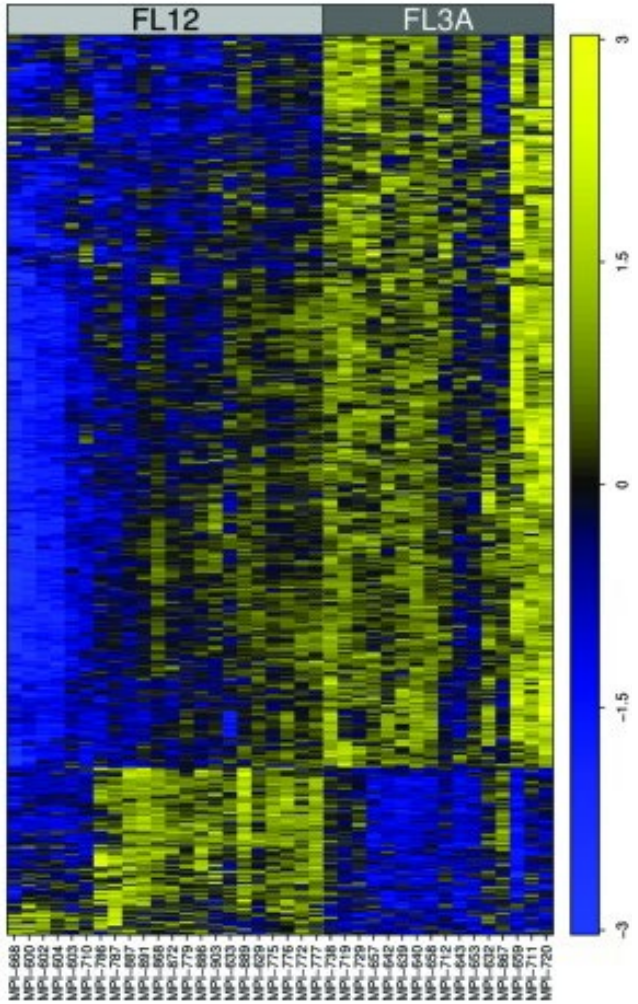


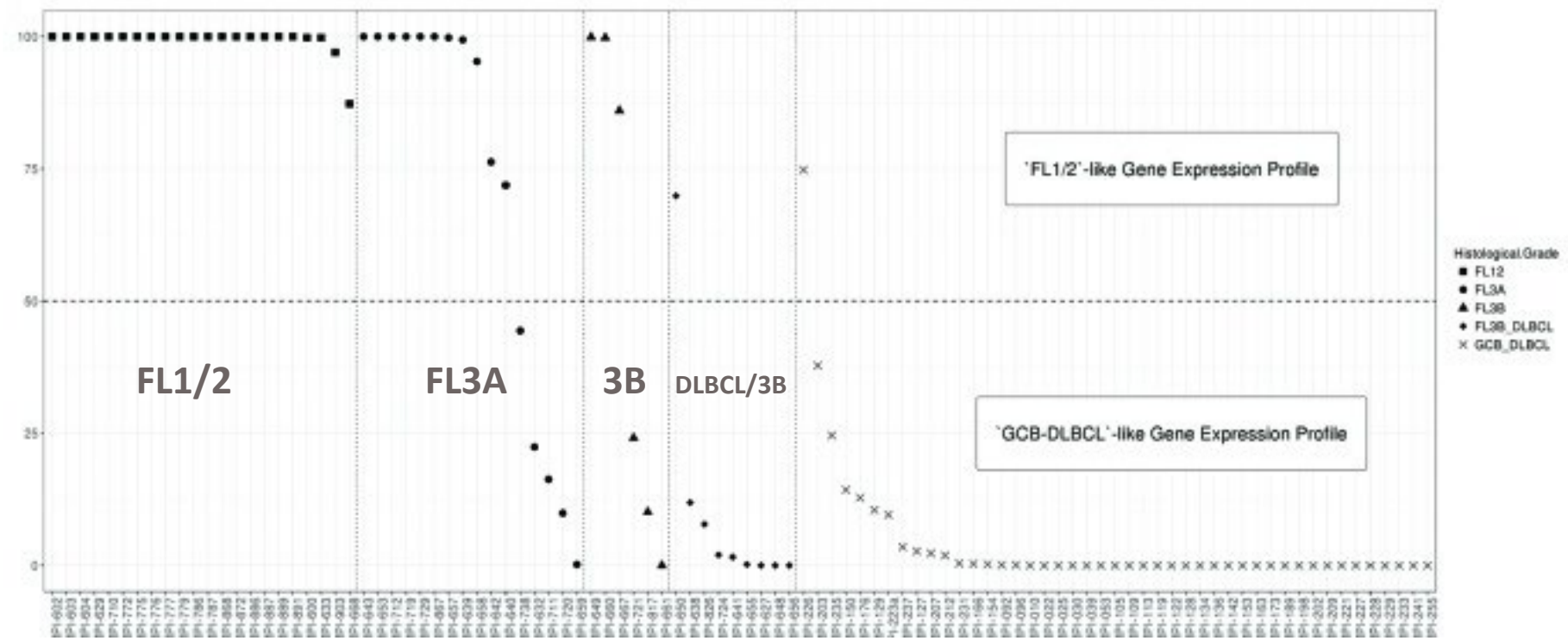


	1/2	3A	3B
Diffuse areas	Absent	Absent	Present
Centrocytes	Present	Present	Absent
Marrow invasion	Frequent	Frequent	Uncommon
CD10+	100%	83%	43%
***BCL2* break**	88%	58%	9%

Horn et al. Haematologica. 2011 Sep;96(9):1327-34

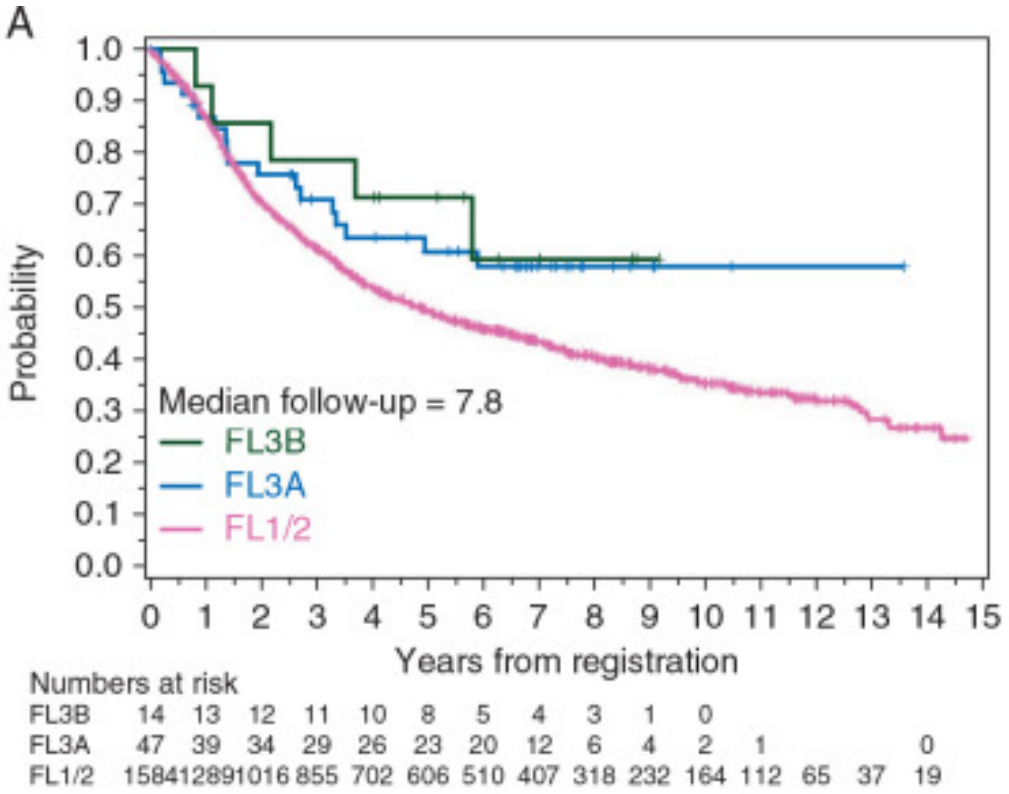
FL Histologic Grade

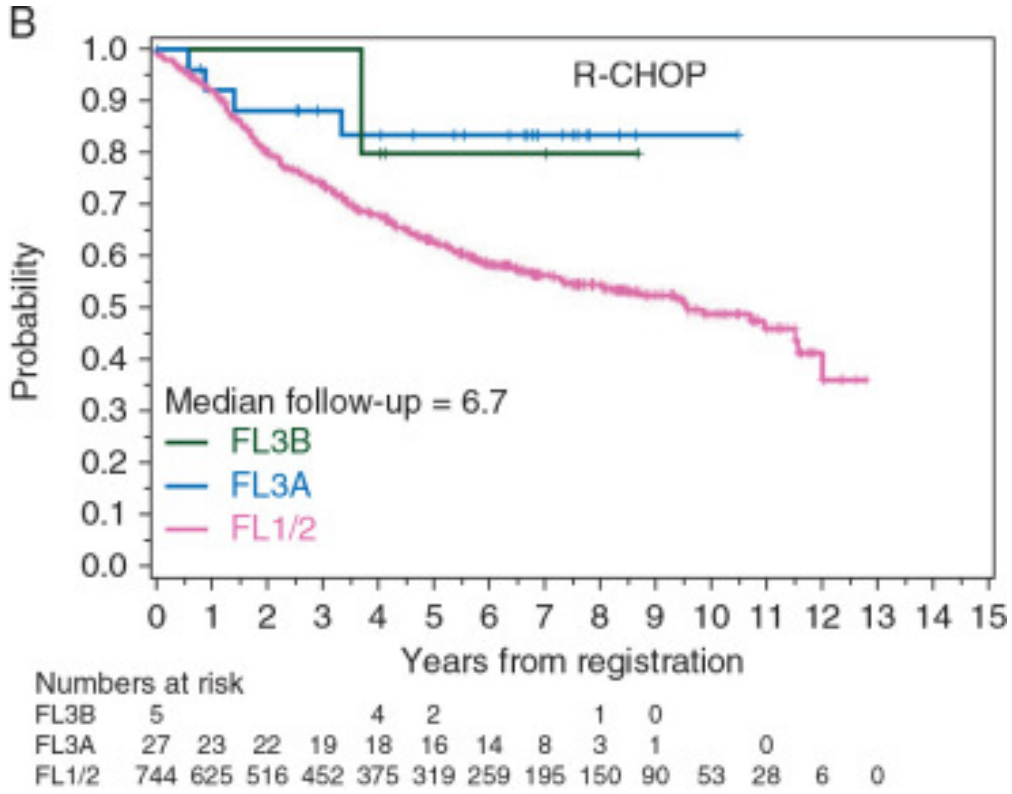




Horn et al. Haematologica. 2018 Jul;103(7):1182-1190

FL PFS by Grade





Koch et al. Ann Oncol. 2016 Jul;27(7):1323-9

R-Chemo Frontline for Advanced FL: Conclusions

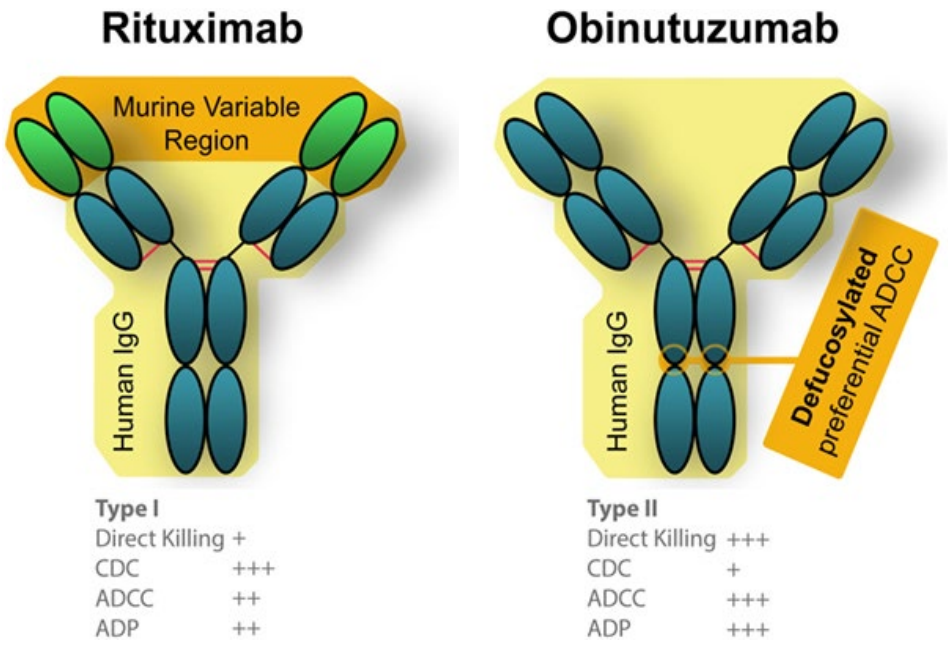
- BR a preferred standard for bulky disease, treatment indication
- R-CHOP perfectly acceptable alternative considering no difference in OS
  - Deserves particular consideration in case of 3A grade

- Maintenance rituximab can be offered
  - Benefit and limitations in shared-decision making

Alternatives to R-Chemo: #1, O-Chemo

- Obinutuzumab binds overlapping epitope of CD20 (as rituximab) but in different orientation: results in different CD20 arrangement in cell membrane and increased apoptosis (type II)

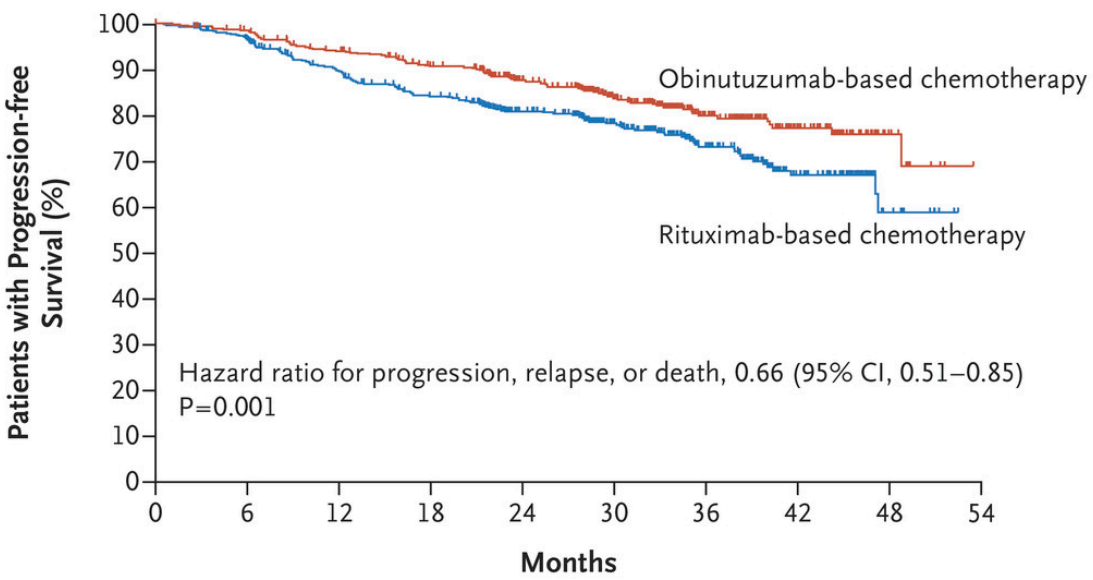
- By manipulating glycosylation of cells that produce obinutuzumab, improvement in direct cell death and higher antibody dependent cell-mediated cyto-toxicity (via NK cell recruitment) is achieved

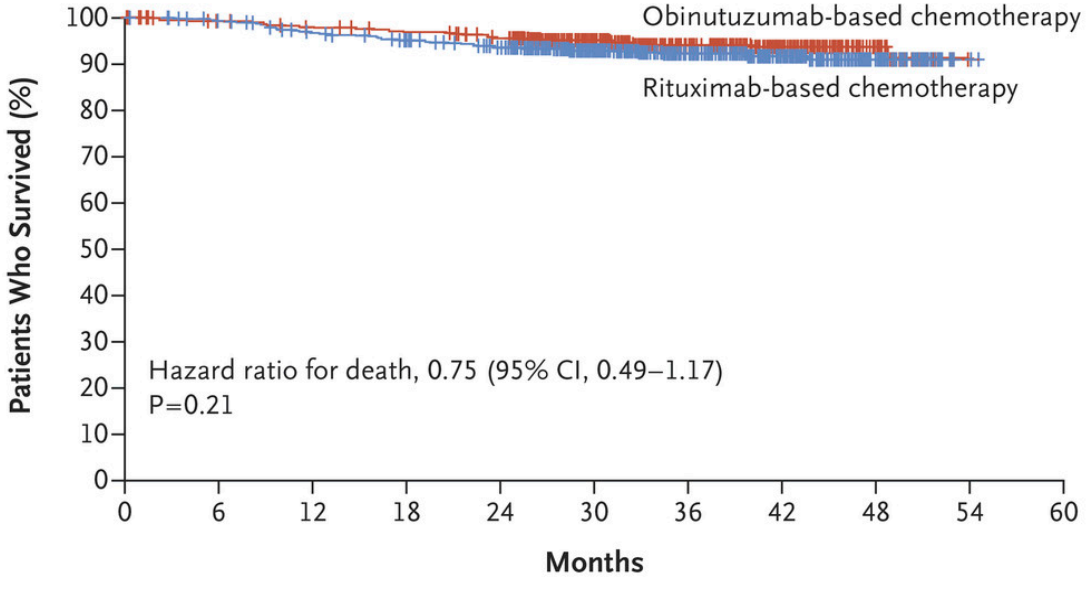


Pierpont et al. Front. Oncol., 04 June 2018

GALLIUM: R-Chemo vs O-Chemo, Frontline FL

- High tumor burden FL only, 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





Approximately 35% more O than R

Marcus et al. N Engl J Med. 2017 Oct 5;377(14):1331-1344

GALLIUM: Higher Toxicity with O-Chemo, Bendamustine

Table 3. Adverse Events and Serious Adverse Events, According to Treatment Phase, and Selected Grade 3 to 5 Adverse Events during Treatment, According to Chemotherapy Agent and Treatment Phase in the Safety Population.*

Event	Overall Trial†		Induction Phase		Maintenance and Observation Phases		Follow-up	
	Obinutuzumab Group (N=595)	Rituximab Group (N=597)	Obinutuzumab Group (N=595)	Rituximab Group (N=597)	Obinutuzumab Group (N=548)	Rituximab Group (N=535)	Obinutuzumab Group (N=427)	Rituximab Group (N=428)
No. of events	10,311	9343	7012	6533	3002	2578	295	230
Patients with ≥1 adverse event — no. (%)								
Any event	592 (99.5)	587 (98.3)	580 (97.5)	577 (96.6)	501 (91.4)	458 (85.6)	130 (30.4)	106 (24.8)
Event of grade 3 to 5	444 (74.6)	405 (67.8)	357 (60.0)	336 (56.3)	205 (37.4)	169 (31.6)	56 (13.1)	33 (7.7)
Event of grade 5‡	24 (4.0)	20 (3.4)§	4 (0.7)	3 (0.5)	10 (1.8)	10 (1.9)	10 (2.3)	7 (1.6)
Infection¶	—	—						
Bendamustine	—	—	27/338 (8.0)	26/338 (7.7)	52/312 (16.7)	39/305 (12.8)	25/270 (9.3)	6/263 (2.3)
CHOP	—	—	14/193 (7.3)	13/203 (6.4)	7/179 (3.9)	11/187 (5.9)	2/128 (1.6)	2/143 (1.4)
CVP	—	—	3/61 (4.9)	4/56 (7.1)	5/57 (8.8)	1/43 (2.3)	1/44 (2.3)	2/45 (4.4)

- Bendamustine associated OIs: PJP and VZV prophylaxis, especially with B-O

Marcus et al. N Engl J Med. 2017 Oct 5;377(14):1331-1344

Bendamustine toxicities, cont (age > 65 yrs)

Clinical Infectious Diseases

MAJOR ARTICLE

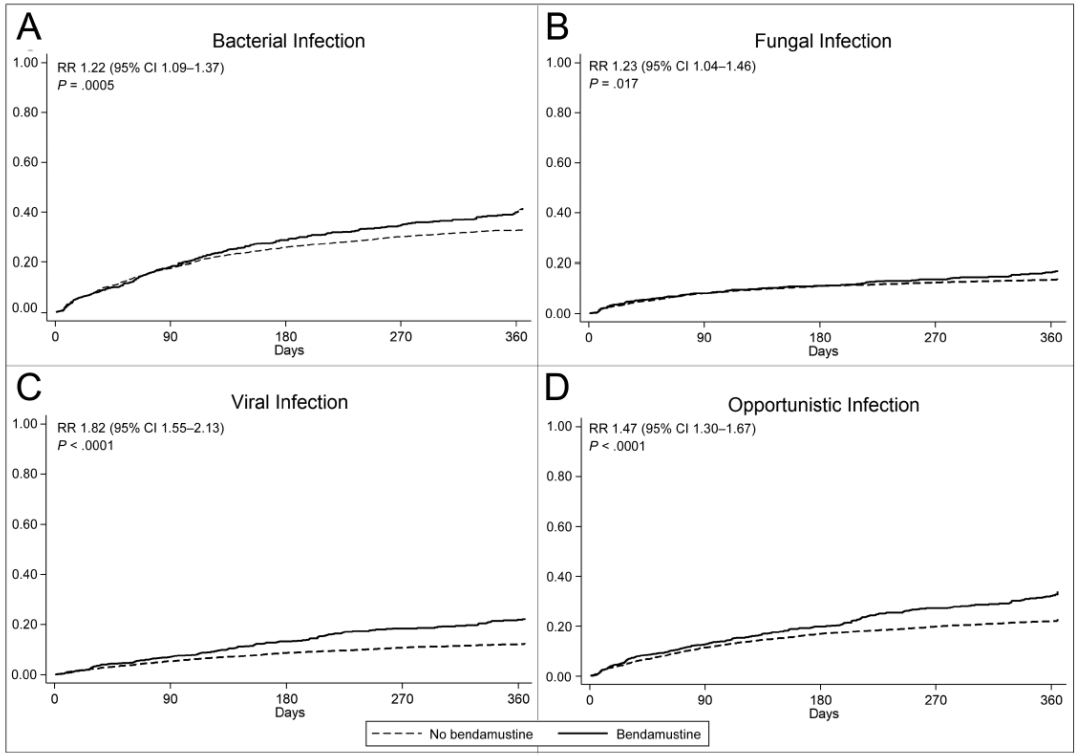
Increased Risk of Infectious Complications in Older Patients With Indolent Non-Hodgkin Lymphoma Exposed to Bendamustine

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 indolent NHL from SEER
2006 - 2013
75% with FL

Prolonged CD4+ T-lymphopenia = presumed culprit
→ May persist even 3 years after treatment

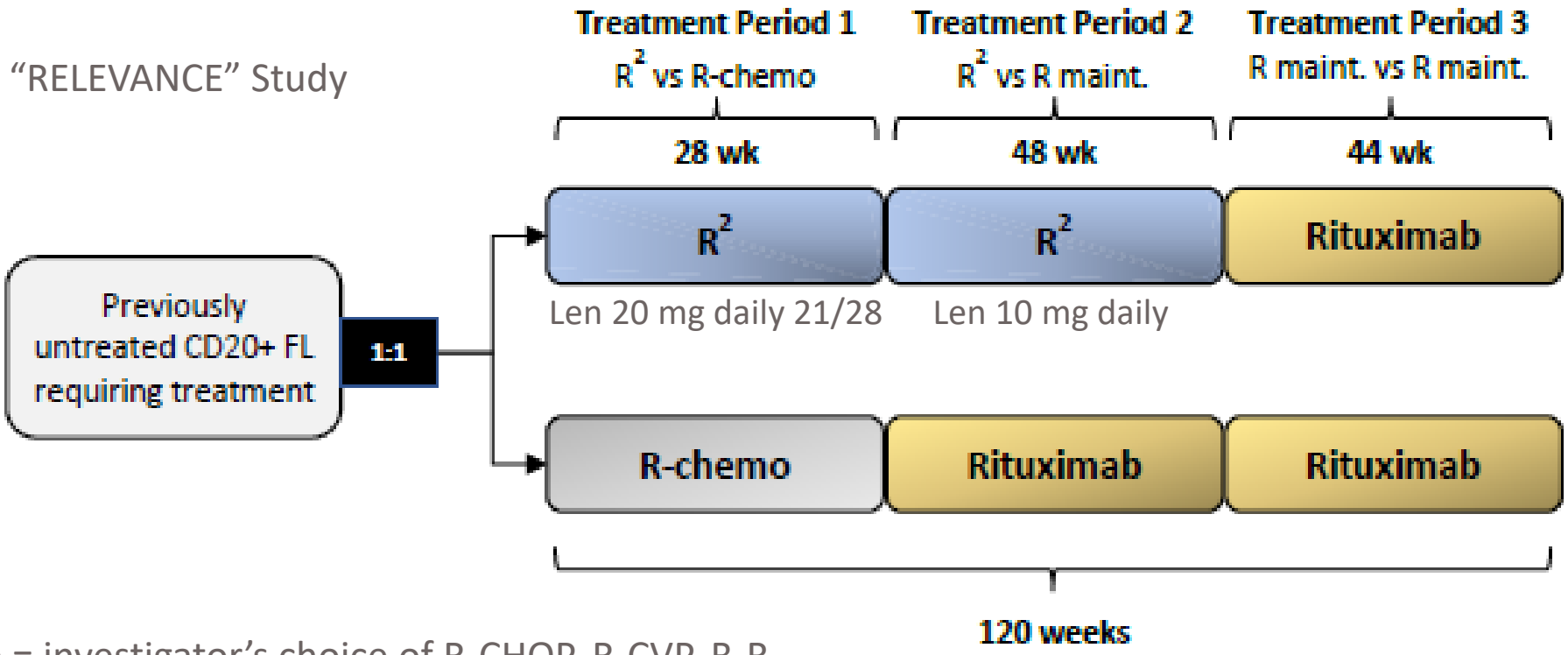
(This is not observed after, e.g., R-CHOP)



NCCN advises prophylaxis for PJP and VZV if bendamustine given

Alternatives to R-Chemo: #2, R-Lenalidomide

- Lenalidomide: immune-mediated inflammatory disease immunomodulatory agent
- Combined with rituximab: enhanced antibody-dependent cellular cytotoxicity and direct cytotoxicity



R-chemo = investigator's choice of R-CHOP, R-CVP, B-R

Morschhauser et al. NEJM. 2018 Sep 6;379(10):934-947

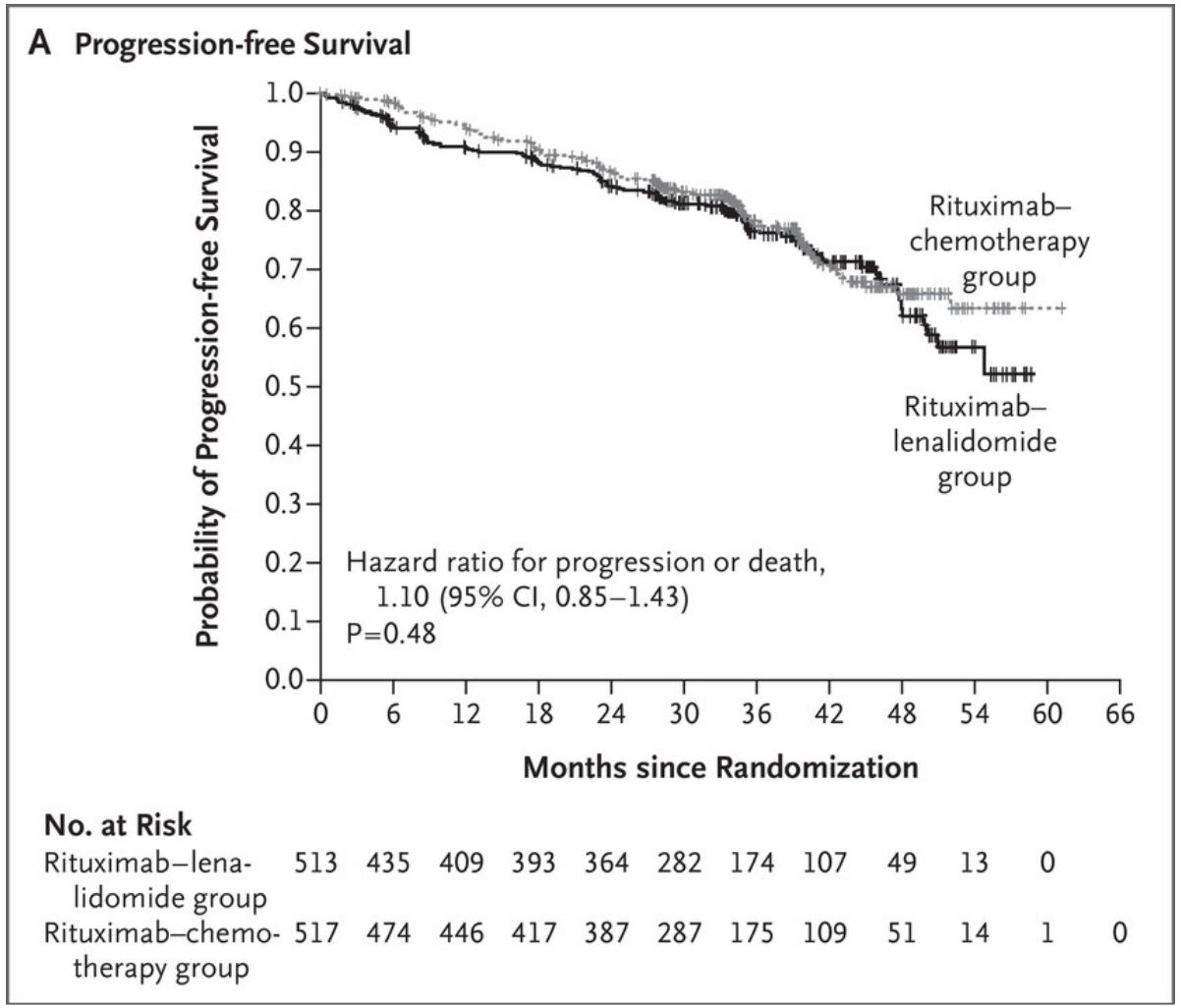
Ito et al. Int J Hem. 2016 Sep;104(3):293-299

RELEVANCE: “Inferior” Primary End-Point?

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

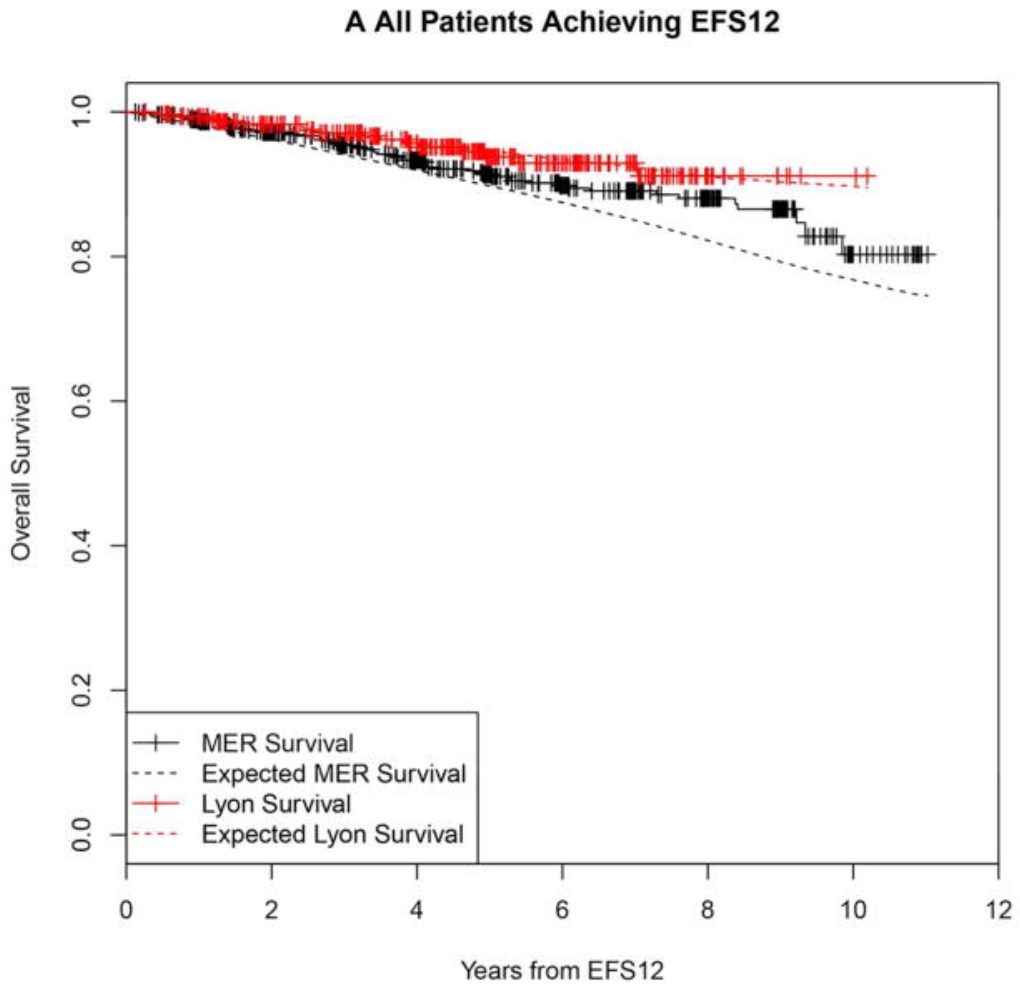
- Toxicity
  - Overall, comparable frequencies
  - R2 = less nausea, febrile neutropenia
  - R2 = more rash, diarrhea
  - R2 = toxicities drawn out

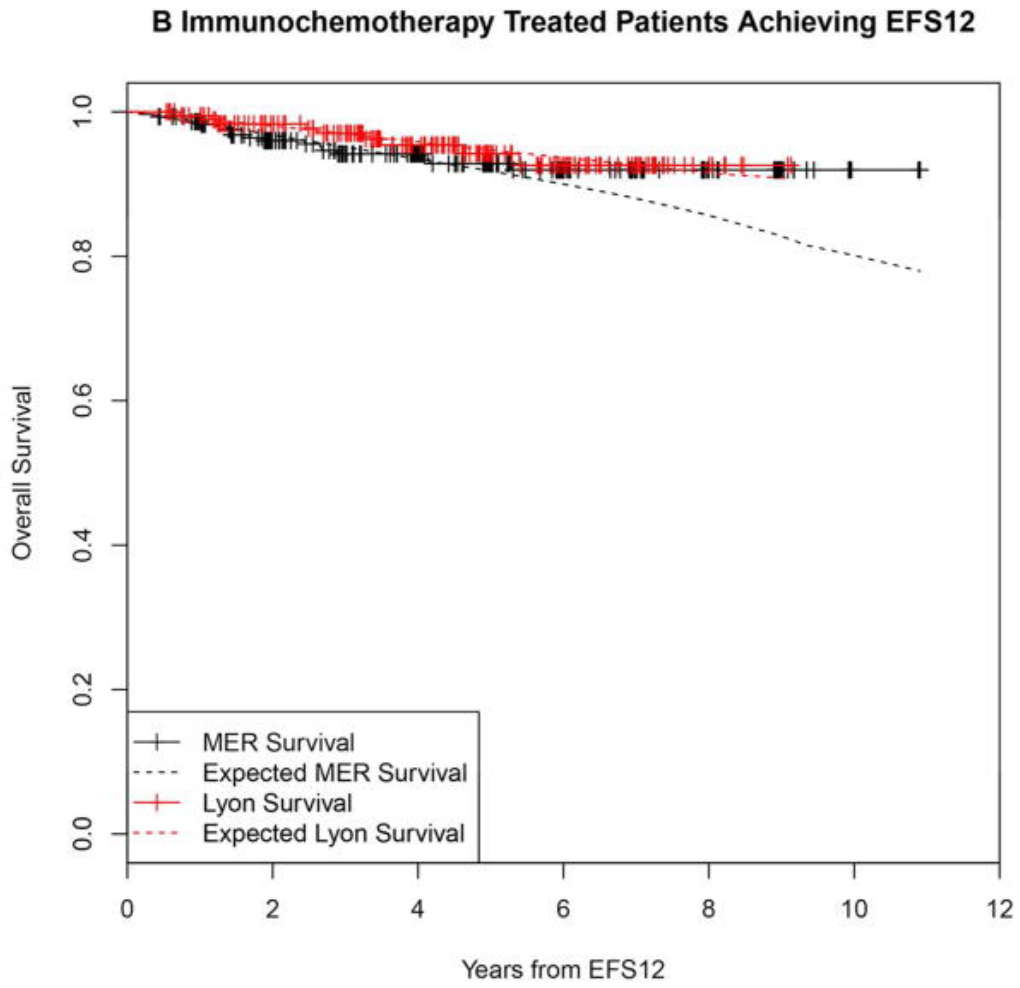
- No FDA approval (though NCCN listed)



Morschhauser et al. NEJM. 2018 Sep 6;379(10):934-947

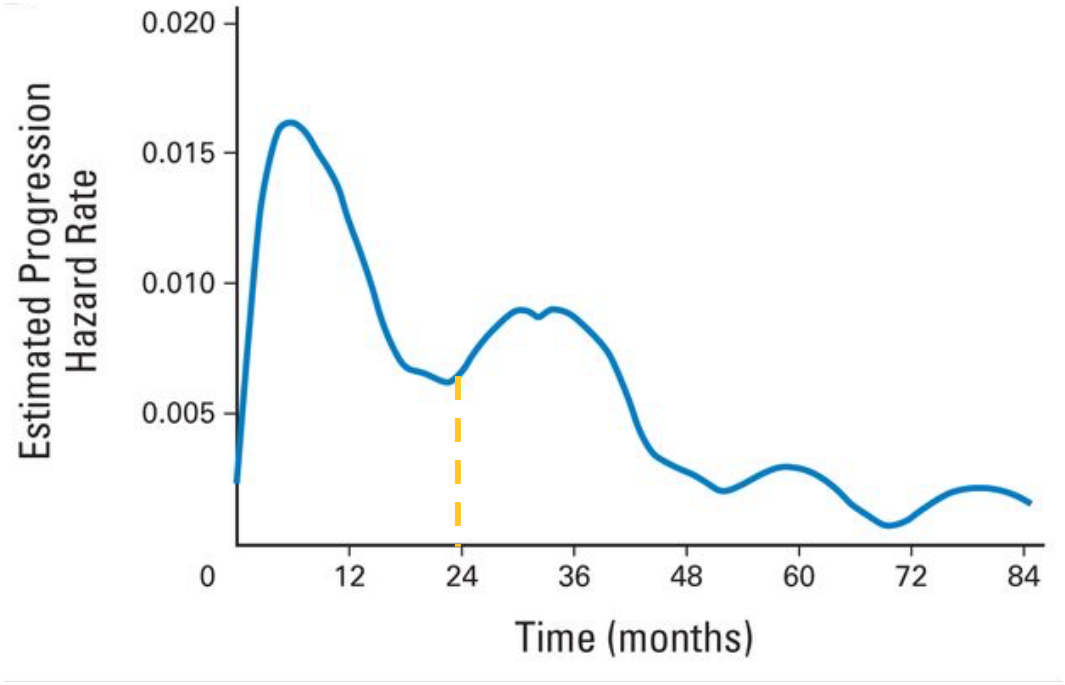
Outcomes of Patient with FL and “EFS12”

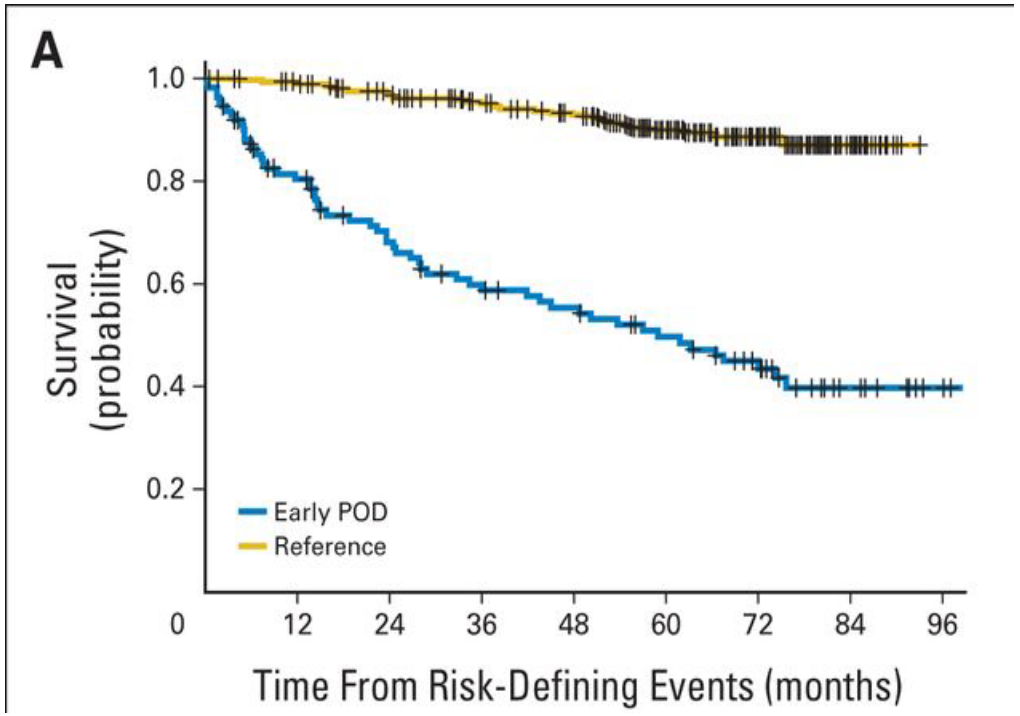




Maurer et al. Am J Hematol. 91: 1096-1101, 2016

Follicular Lymphoma: Relapse





- Risk of progression highest in 24 months after R-CHOP
- In the 20% with "early" (< 24 mo) progression, survival markedly worse (independent of FLIPI)
- To date, no reliable marker for early POD or preferred treatment
- Data have been recapitulated in e.g. BR-treated, MZL

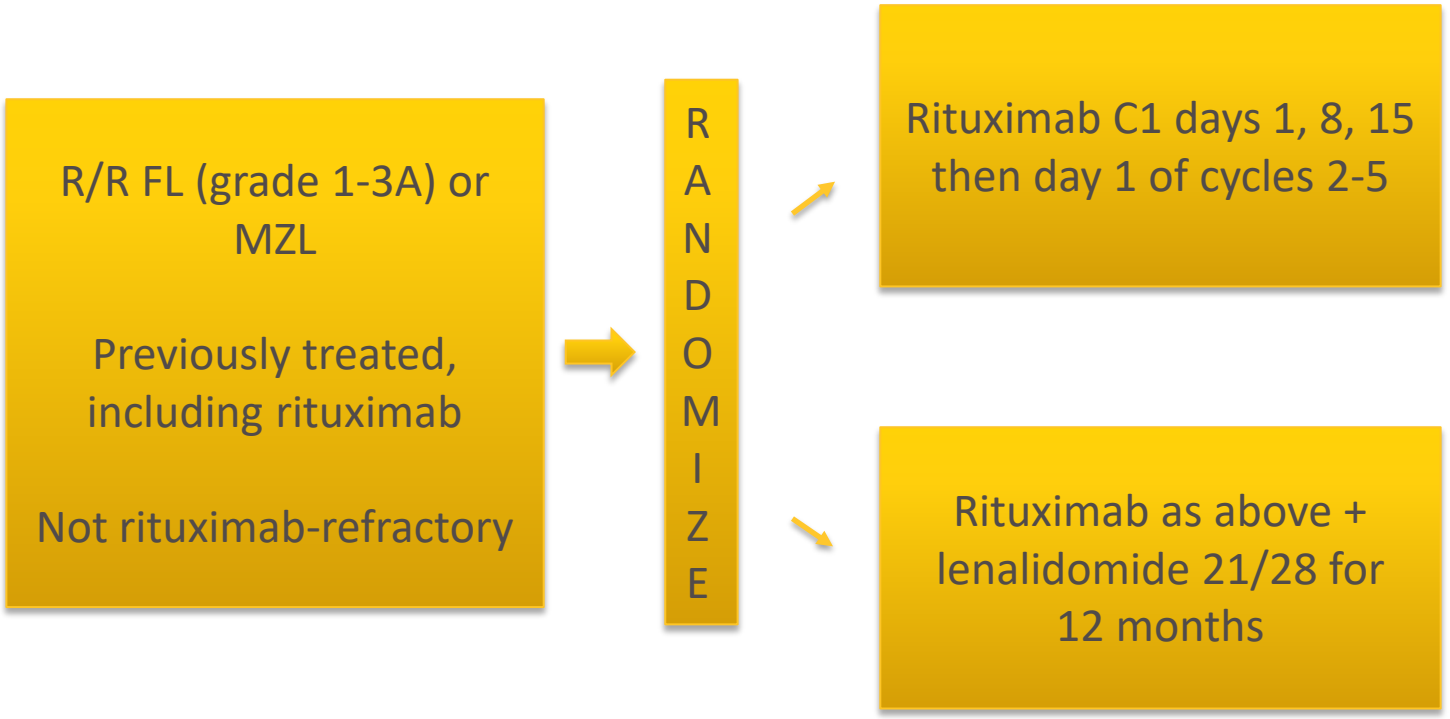
Casulo et al. J Clin Oncol. 2015 Aug 10;33(23):2516-22

Relapsed FL: Treatment

- Treatment indication?

R2 in the R/R Setting: AUGMENT

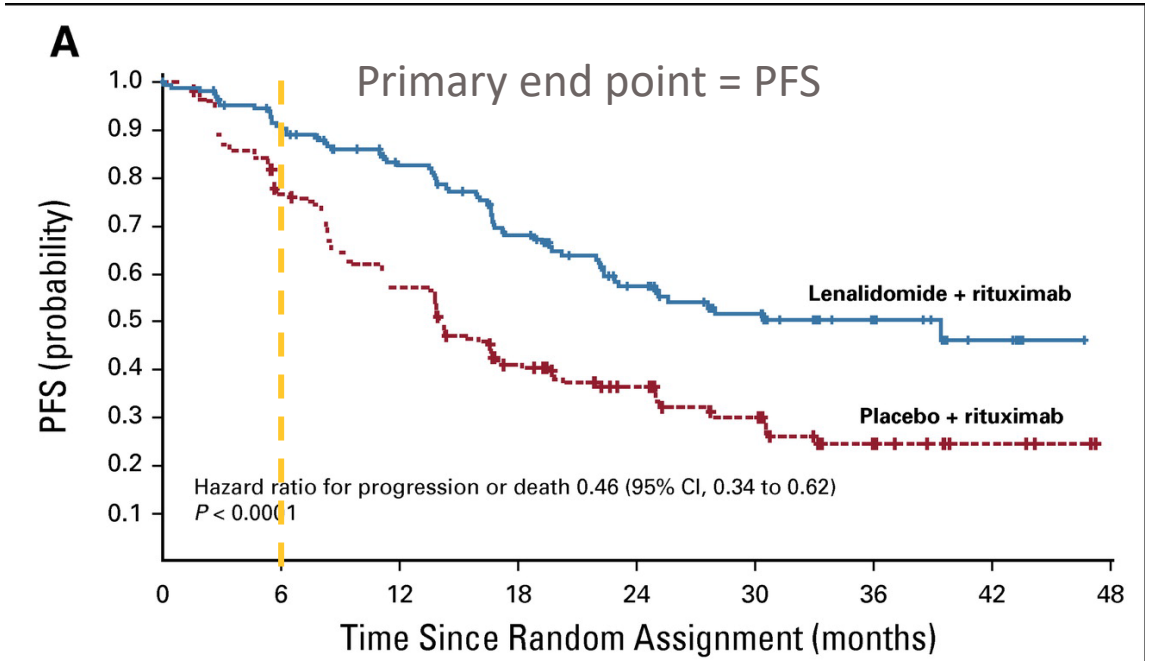
- FL grade 1 – 3A or MZL, previously treated, and in need of treatment for relapse. Prior treatment necessarily included rituximab, though cannot be considered rituximab-refractory

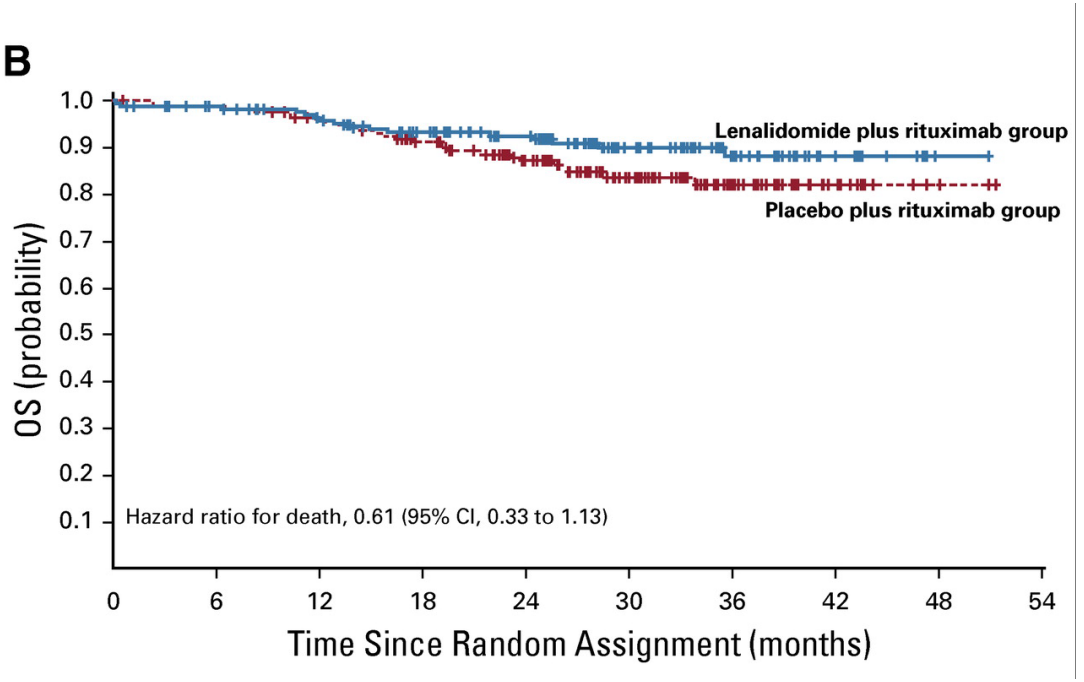


- ORR 78 vs 53% (P < 0.001)
- CR 34 vs 18% (P = .001)

Leonard et al. J Clin Oncol. 2019 May 10;37(14):1188-1199.

AUGMENT: Results





Leonard et al. J Clin Oncol. 2019 May 10;37(14):1188-1199.

Other Oral Oncolytics for R/R iB-NHL

	FL	MZL
BTK inhibitors		Ibrutinib
PI3K inhibitors	Idelalisib Copanlisib Duvelisib Umbralisib	Umbralisib

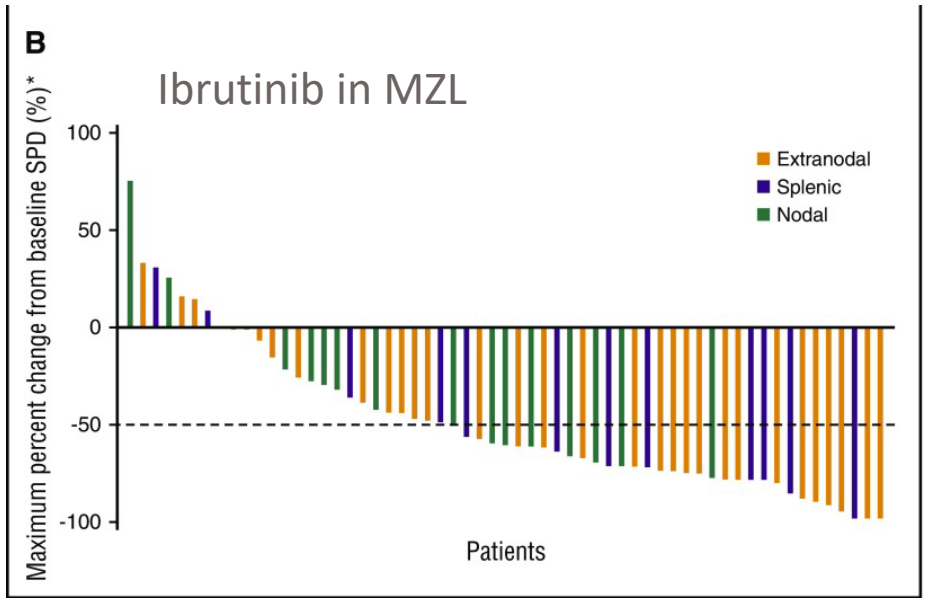
	Setting	ORR	CR	mPFS
Idelalisib (δ)	Double refractory (R, alkylator) FL	56%	6%	11.0 mo
Duvelisib (γ,δ)	Double refractory (R, alkylator) FL	47%	2%	9.5 mo
Copanlisib* (α,δ)	≥2 prior lines of therapy for FL	59%	12%	11.0 mo
Umbralisib (δ+ casein kinase-1ε**)	≥3 prior lines of therapy for FL; ≥1 prior anti-CD20 therapy in MZL	45% (FL) 49% (MZL)	5% (FL) 16% (MZL)	10.6 mo (FL) NR (MZL)
Ibrutinib	≥1 prior anti-CD20 therapy in MZL	48%	3%	14.2 mo

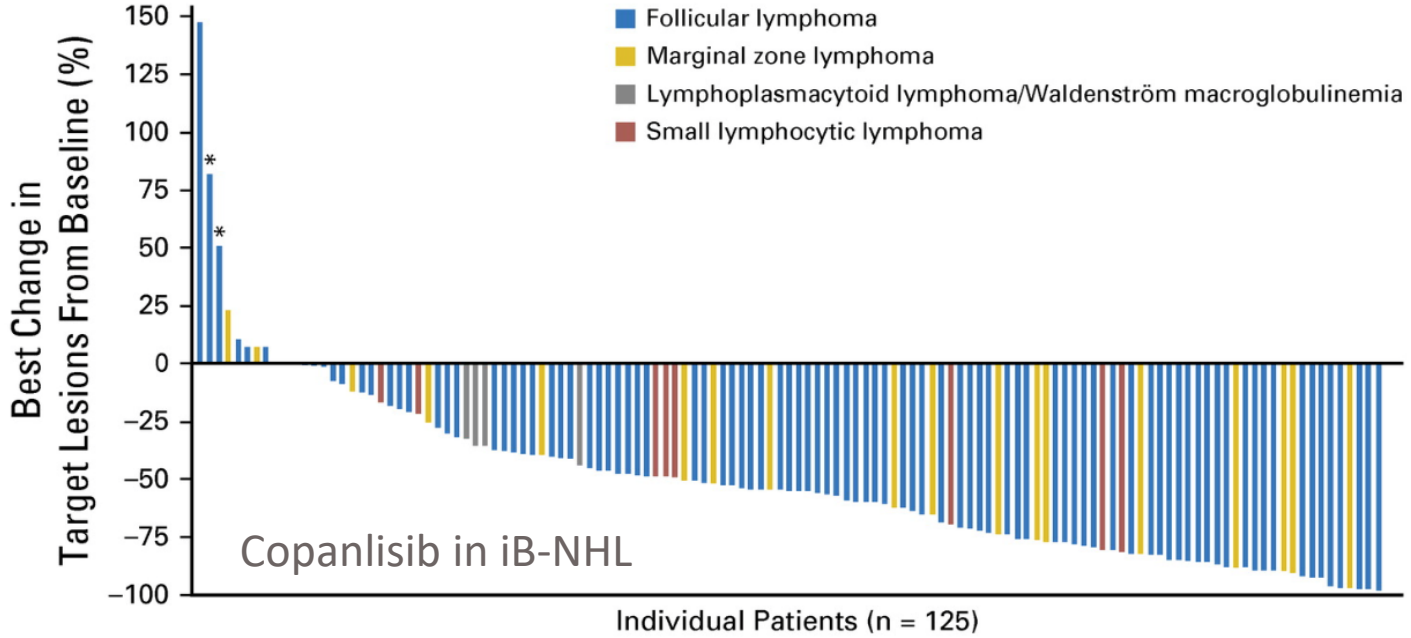
*IV on days 1, 8, 15 q28
** Targeting CK-1ε to stimulate immunomodulatory activity of T-reg cells

Gopal et al. N Eng J Med. 2014 Mar 13;370(11):1008-18
Dreyling et al. J Clin Oncol. 2017 Dec 10;35(35):3898-3905
Flinn et al. J Clin Oncol. 2019 Apr 10;37(11):912-922
Noy et al. Blood. 2017 Apr 20;129(16):2224-2232
Zinzani et al. J Clin Oncol. 2021 May 20;39(15):1609-1618

Single Arm Phase 2 Studies of Oral Oncolytics for R/R iBNHL

- Primary endpoint = ORR

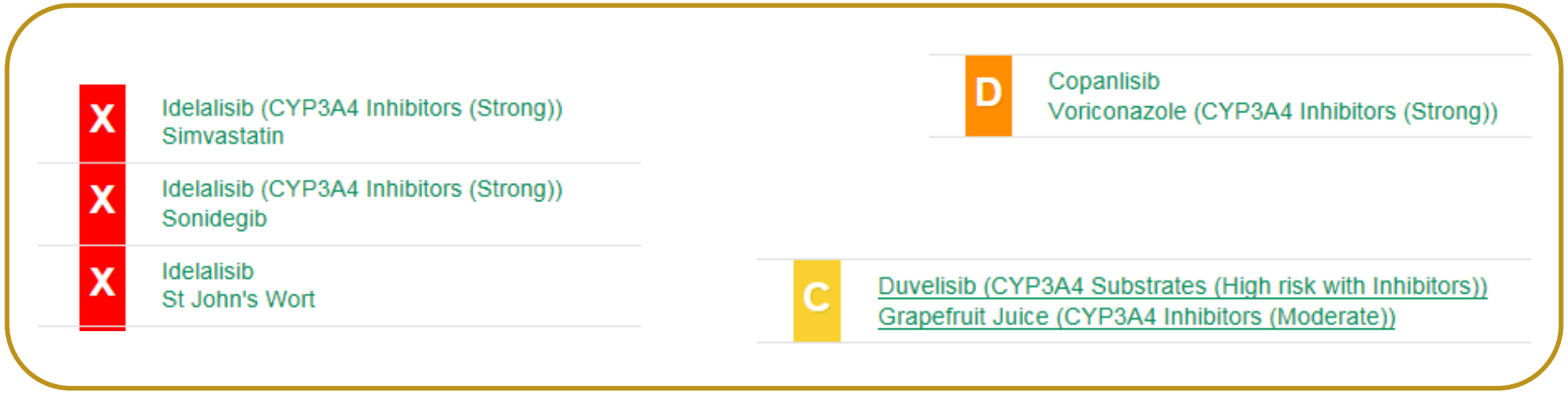




Dreyling et al. J Clin Oncol. 2017 Dec 10;35(35):3898-3905
Noy et al. Blood. 2017 Apr 20;129(16):2224-2232

Toxicities of Targeted Oral Oncolytics

	Key Toxicities	Recommended prophylaxis
Idelalisib Duvelisib	Opportunistic infections, transaminitis, diarrhea/colitis, pneumonitis, intestinal perforation, dermatologic events	PJP; CMV monitoring
Copanlisib	OI's, Hyperglycemia (short-lived), hypertension	PJP
Ibrutinib	Atrial fibrillation, hemorrhage	
Umbralisib	**? Better tolerated** (no TRM reported)	PJP; consider CMV

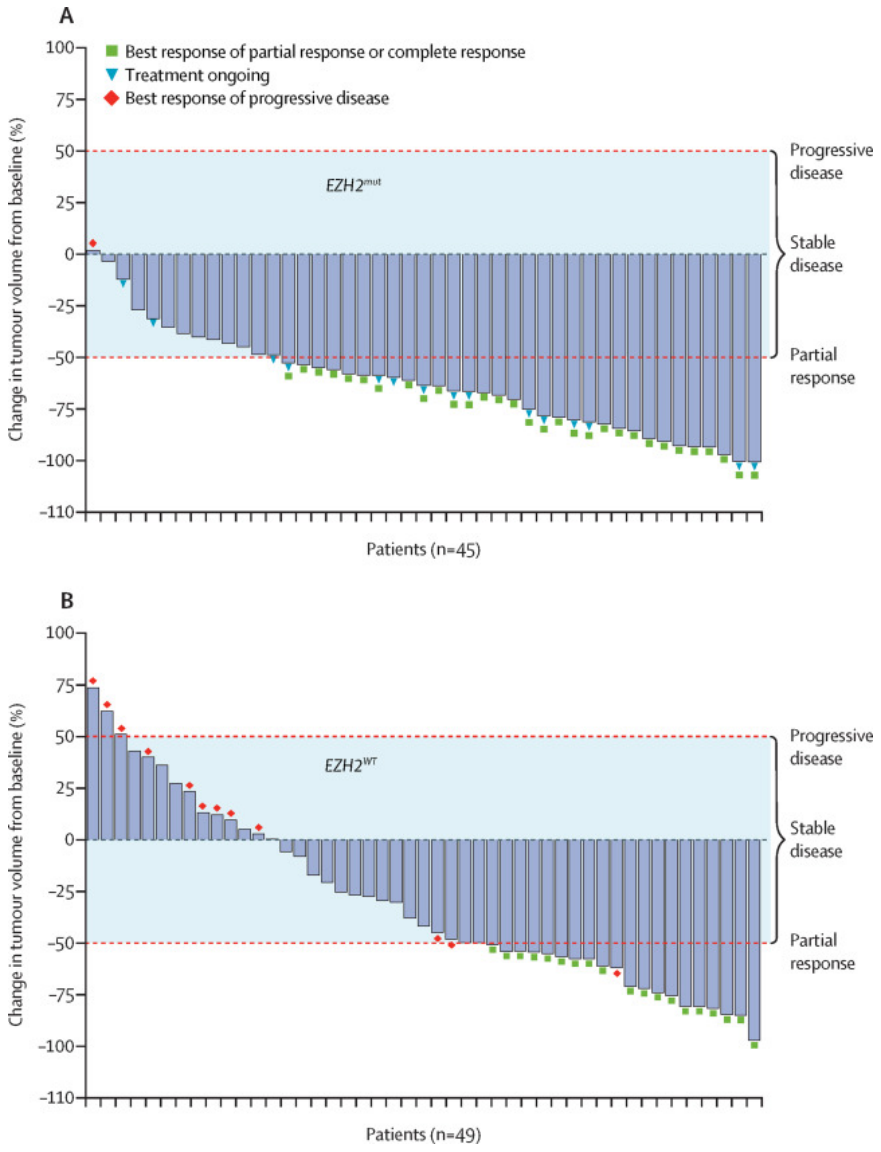


Zeste Homolog 2 (EZH2)

- Genetic lesions that disrupt histone-modifying enzymes occur in nearly all cases of FL
- Gain of function mutation to *EZH2* found in ~20% of FL
  - Results in epigenetic silencing and B cell proliferation
  - WT EZH2 also supports B cell proliferation in germinal centers (lesser degree)
- Reduction in histone methyltransferase EZH2 activity → B cell differentiation

Huet et al. Nat Rev Cancer. 2018 Apr;18(4):224-239
Morschhauser et al. ASH Congress 2019.

Zeste Homolog 2 (EZH2) Inhibitor: Tazemetostat



- ORR in N = 45 *EZH2* mutant FL = 69% (13% CR); mPFS = 13 mo
- ORR in N = 54 *EZH2* WT FL = 34% (4% CR); mPFS = 11 mo
- AEs = fatigue, URI, MSK pain, nausea, abdominal pain. **Only 4% serious TRAEs and zero TRM**.
  - FDA approval: *EZH2* mutant FL: 2 prior therapies; *EZH2* WT FL: no satisfactory alternatives

Morschhauser et al. Lancet Oncol. 2020 Nov;21(11):1433-1442.

Topics of Special Interest in iB-NHL: 2021

- **Early relapse**
  - Prediction

	High risk FLIPI*, %	High risk m7-FLIPI, %	High risk POD24-PI, %
Sensitivity	70-78	43-61	61-78
Specificity	56-58	79-86	67-73

*High-risk pre-treatment FLIPI found in 75% of patients with POD24 and 40% of patients without POD24

    - Bottom line: ongoing research into clinical, molecular, radiographic factors

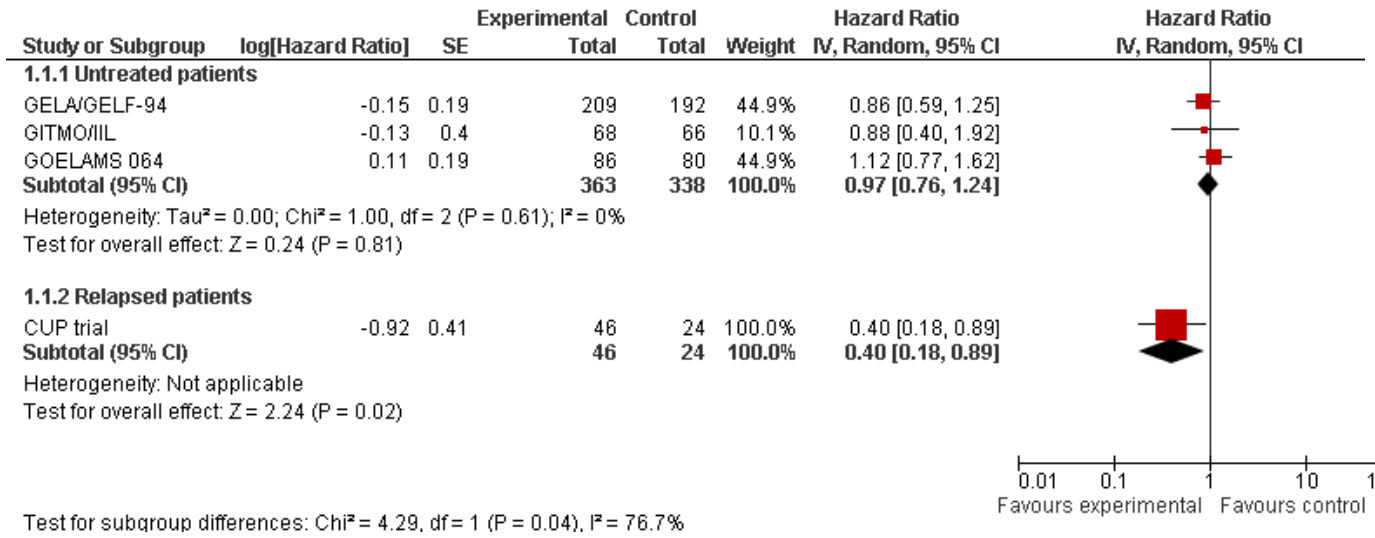
  - Management
    - Biopsy if possible: HT identified in 20% - 75% of cases of early relapse

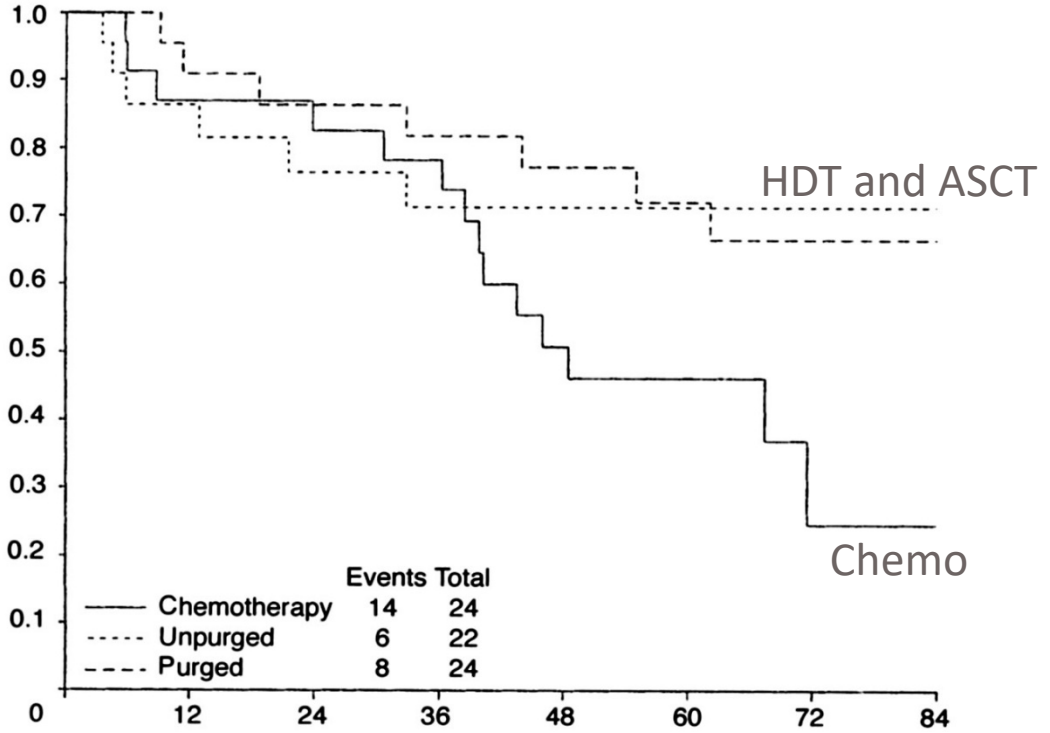
- **Cellular therapy**
  - Autologous SCT
  - CAR-T
  - Bi-specifics

Casulo et al. Blood . 2019 Apr 4;133(14):1540-1547

High Dose Therapy and Autologous SCT in FL

- CUP trial (2003, pre-rituximab)
- Randomized 70 patients with at least PR to 3 cycles of R-CHOP(like) for relapsed FL to HDT and autoSCT or 3 more cycles

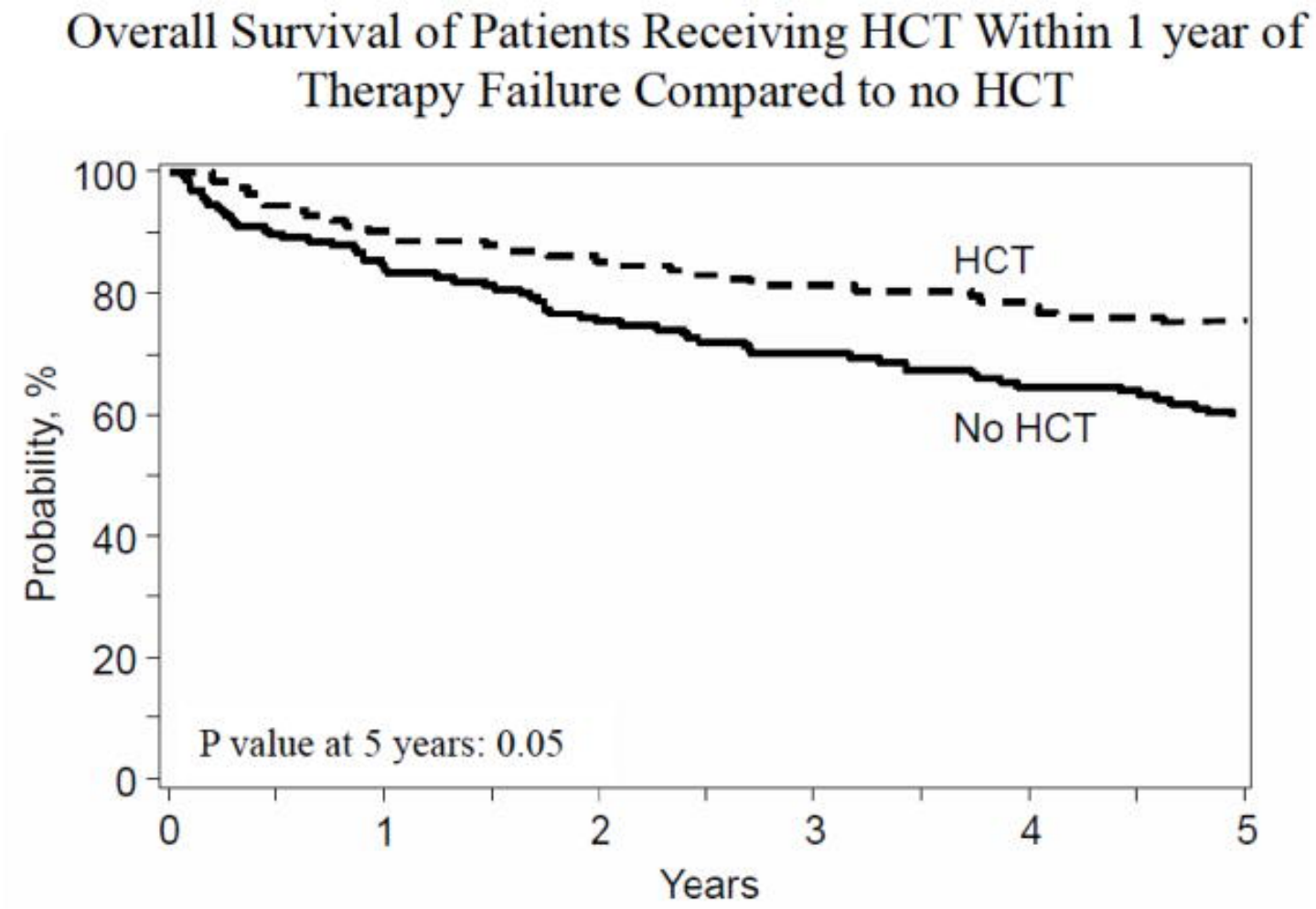




Schouten et al. JCO 21: 3918, 2003
Schaaf et al. Cochrane Database of Systematic Reviews 2012

HDT and ASCT for Early Relapse FL

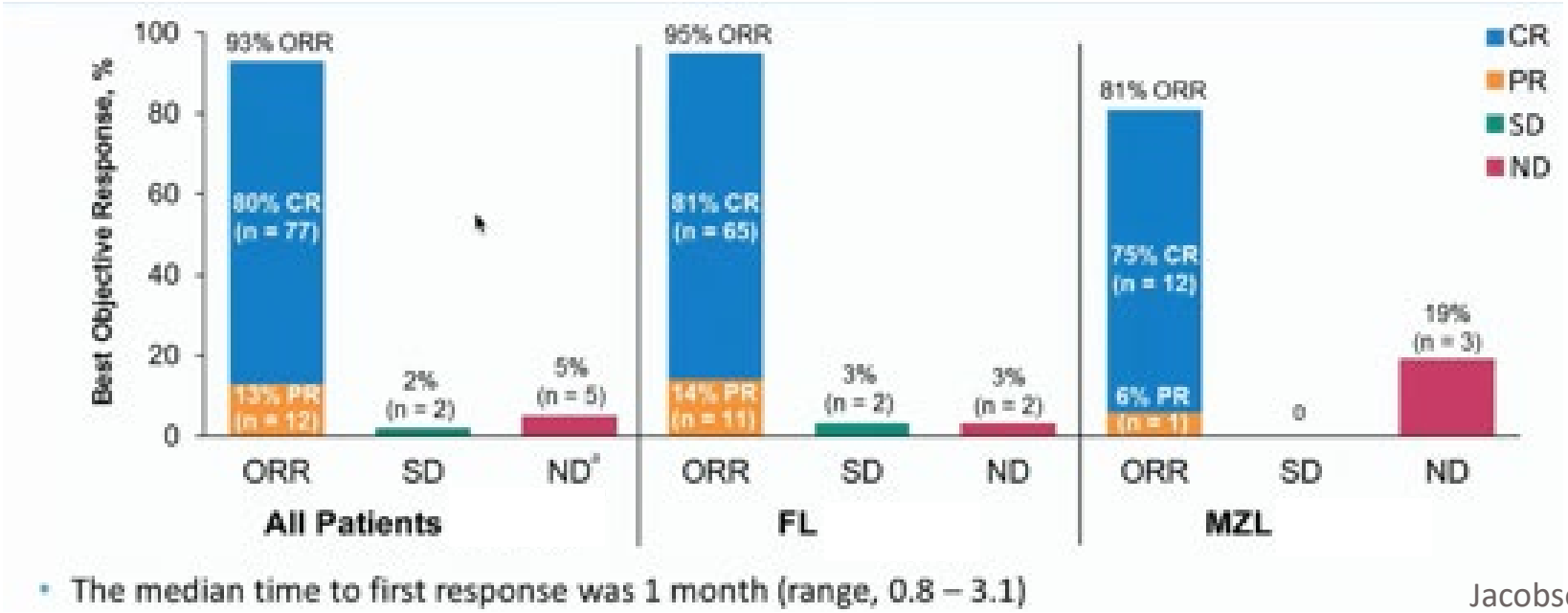
- Retrospective analysis of CIBMTR and NLCS (N = 174 + 175)
- Overall, no significant improvement in OS with ASCT
- Planned subgroup: OS benefit if early ASCT (within 1 year of ETF), 73 vs 60% at 5 years



Casulo et al., Biol Blood Marrow Transplant. 2018 Jun;24(6):1163-1171

CAR-T for iB-NHL

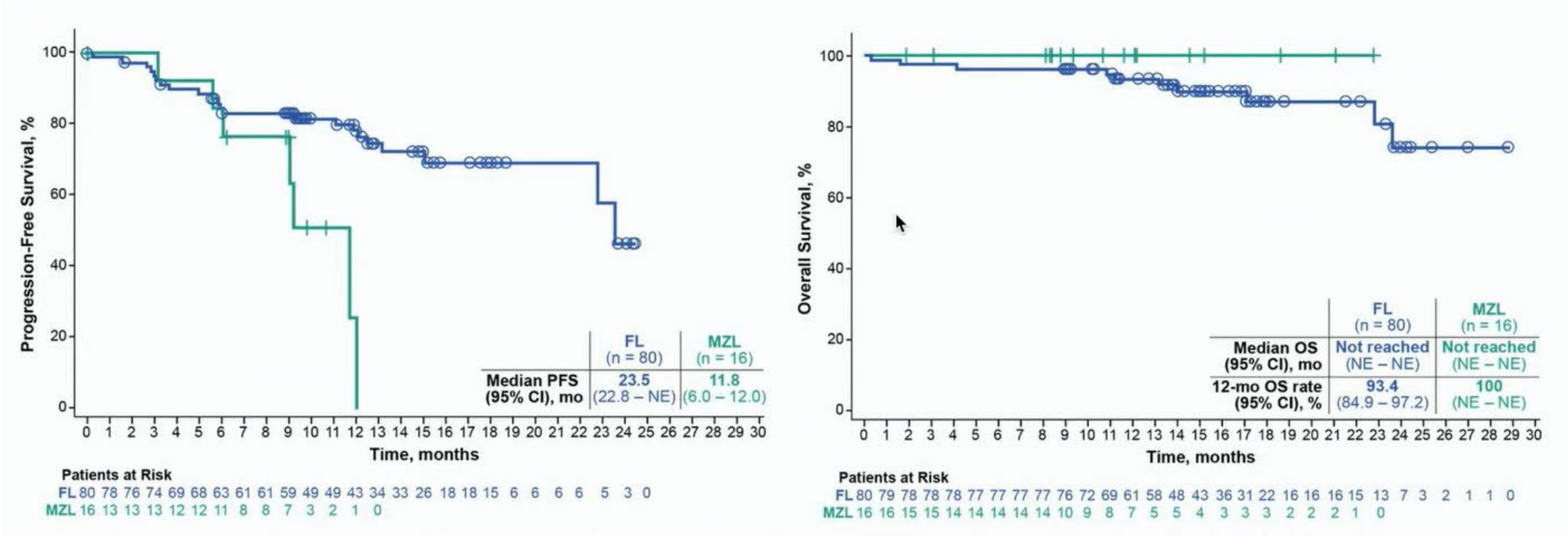
- ZUMA-5: R/R iB-NHL: axicabtagene ciloleucel (axi-cel)
  - N = 129 (108 FL, 21 MZL)
  - 63% with POD24
  - ORR 92% in 98 evaluable patients



- The median time to first response was 1 month (range, 0.8 – 3.1)

Jacobson et al. ASCO 2020
Jacobson et al. ASCO 2021

CAR-T for iB-NHL



- With 23.3 months follow-up: ORR equal across POD24
- 52% with POD24 and 70% without POD24 had ongoing responses
- **Estimated 18-month PFS 55% (with POD24) vs 84% (without POD24)**

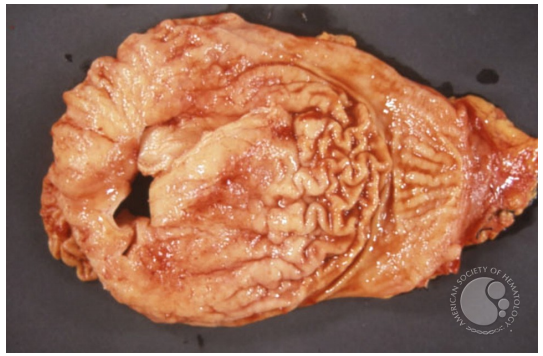
FDA approved
R/R FL ≥ 2 lines therapy

Jacobson et al. ASCO 2020
Jacobson et al. ASCO 2021

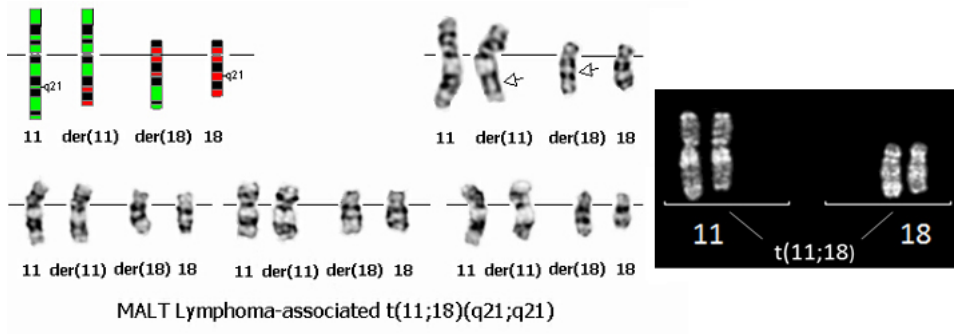
Marginal Zone Lymphomas

- Extranodal MZL of mucosa-associated lymphoid tissue (e.g. gastric MALT); nodal MZL; splenic MZL
- Immunophenotype: typically negative for CD10, CD5, and BCL2
- Limited stage: observe vs treat definitively (RT or surgery +/- RT in certain cases e.g. pulmonary MALT)
- Advanced stage: generally apply FL principles and management

Marginal Zone Lymphoma: gastric MALT



if +



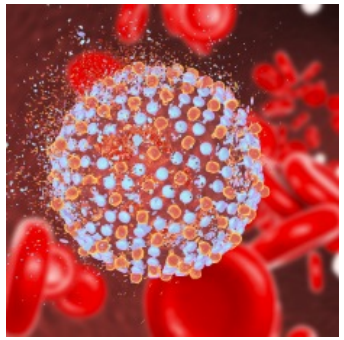
* Presence of t(11;18) predicts lack of CR to H. pylori eradication

Site	Putative pathogen	Treatment	ORR
Gastric MALT	Heliobacter pylori	PPI + triple antibiotics	~75%
Ocular adnexal MALT	Chlamydia psittaci	Doxycycline	~50%
Splenic MZL	Hepatitis C	IFN, DAA's	~75%

Zucca et al. Clin Cancer Res 2014;20:5207-5216
ASH Image Bank 05/02/2003
https://www.hopkinsmedicine.org/health/conditions-and-diseases/helicobacter-pylori
http://atlasgeneticsoncology.org/Anomalies/t1118ID2022.html

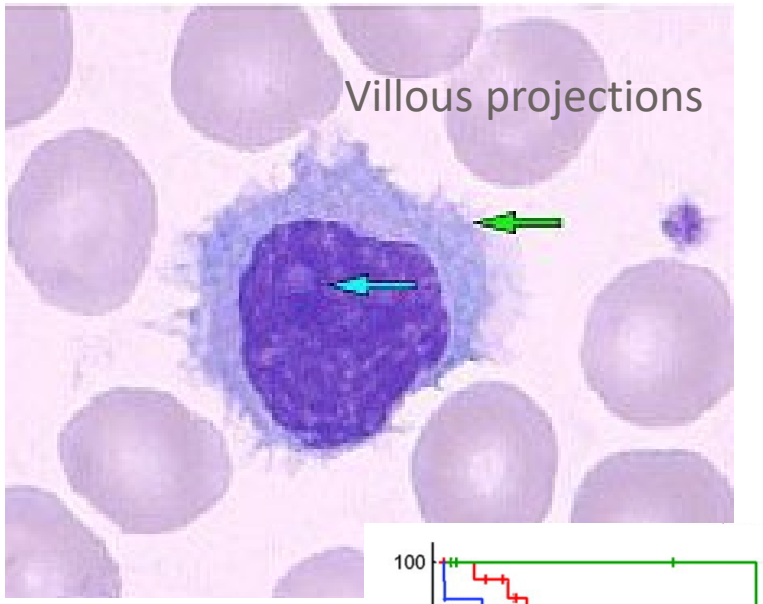
Marginal Zone Lymphoma: splenic MZL

- Observe if asymptomatic and no splenomegaly
- If splenomegaly:

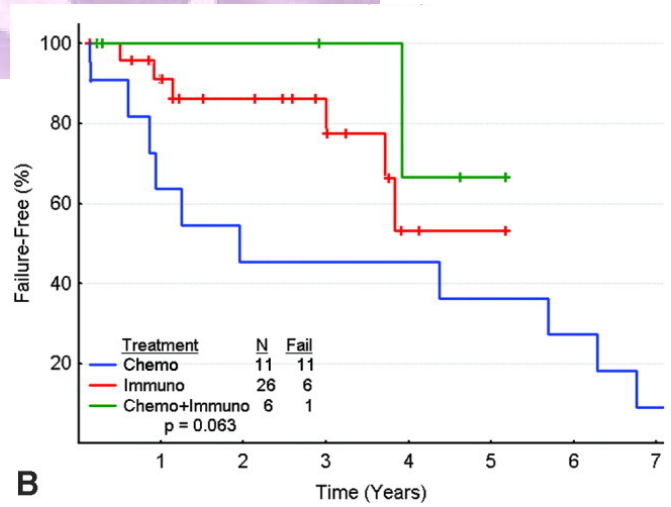


Hepatitis C?

Treat hepatitis C or
Give rituximab (or
Splenectomy or
Observe)



Excellent results (> 90% resolution of splenomegaly) possible with rituximab alone



https://medlineplus.gov/hepatitisc.html

https://www.leukemia-cell.org/atlas/index.php?pg=images--mature-b-cell-neoplasms--splenic-marginal-zone-lymphoma#2

Tsimberidou et al, Cancer. 2006 Jul 1;107(1):125-35

Summary

- iB-NHL often not a life-limiting diagnosis
- Clinical variables
  - remain standard for prognostic stratification
  - inform treatment initiation and follow-up
- New options in frontline and relapsed settings allow better precision fitting of treatment to patient
- Oral targeted oncolytics associated with important limitations and toxicities
- Cellular therapies likely to have a growing role in certain iB-NHL, e.g. early relapse

Questions

grafsa@uw.edu