Follicular and Other Indolent Lymphomas and Hodgkin Lymphoma

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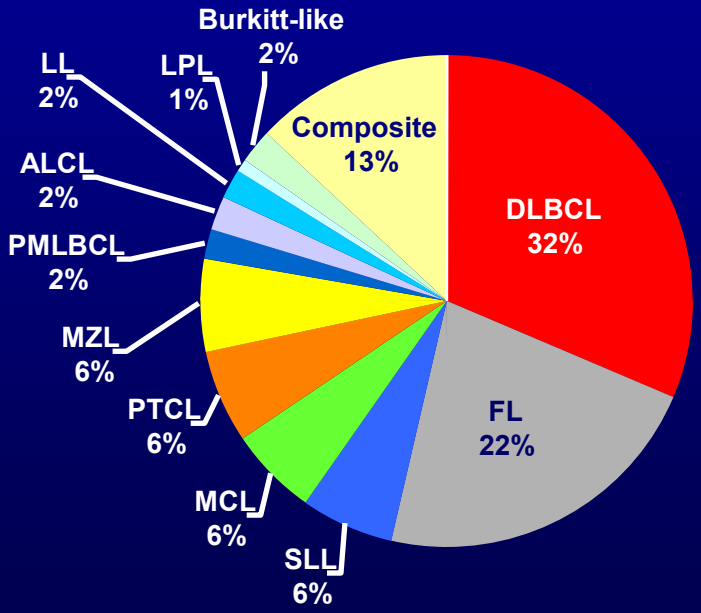
Relative Incidence of NHL Subtypes

>76,000 cases in US in 2020

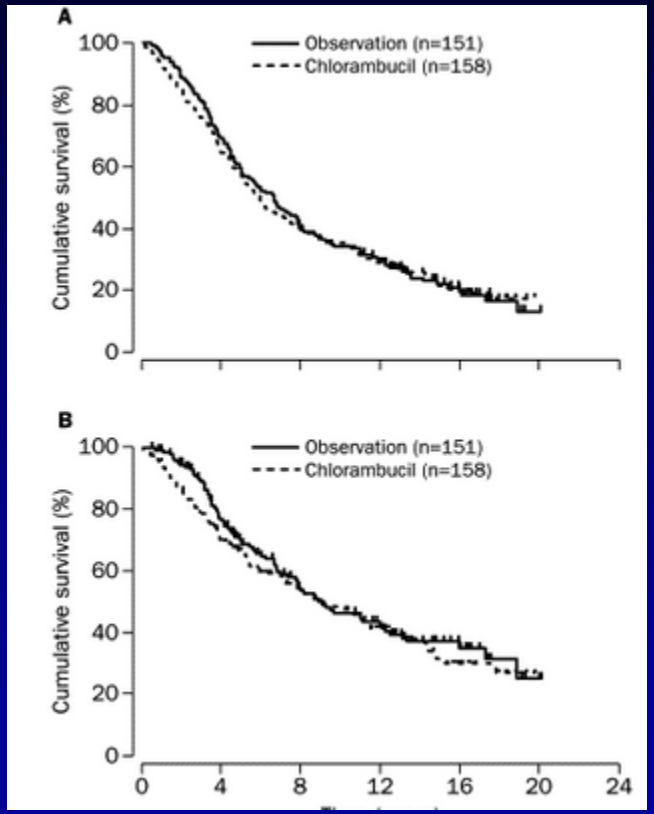


Armitage and Weisenburger. *J Clin Oncol.* 1998;16:2780.
Adapted from Jemal et al. *CA Cancer J Clin*. 2006;56:106.

Deferral of Treatment in Advanced Follicular Lymphoma

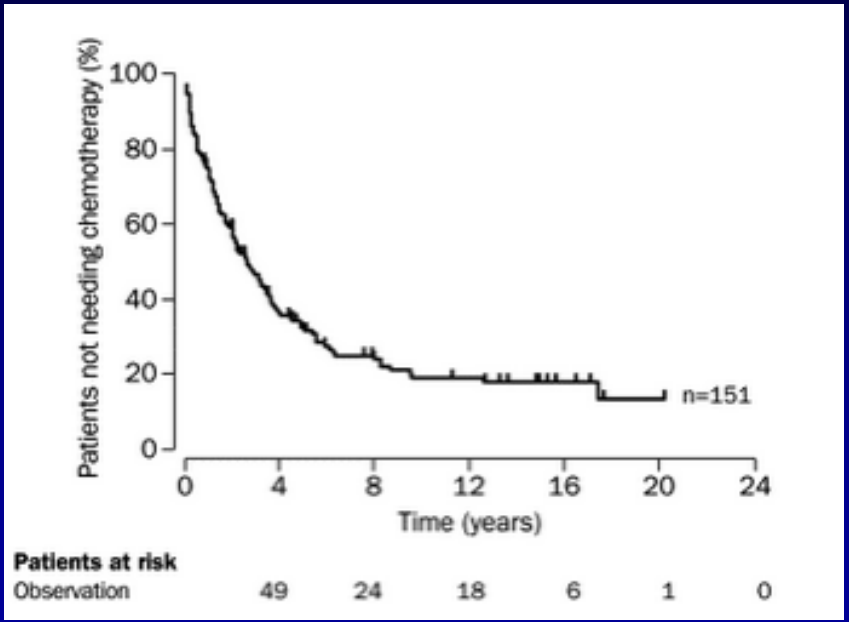
- Maximum diameter < 7 cm
- < 3 sites with a diameter of > 3 cm
- Absence of systemic symptoms
- No “substantial” spleen involvement
- No serious effusions
- No risk of local compression sx
- No circulating lymphoma cells
- No peripheral blood cytopenias

W&W vs Clb in Advanced Stage, Asymptomatic, Untreated FL



Ardeshna et al, Lancet 362:516, 2003

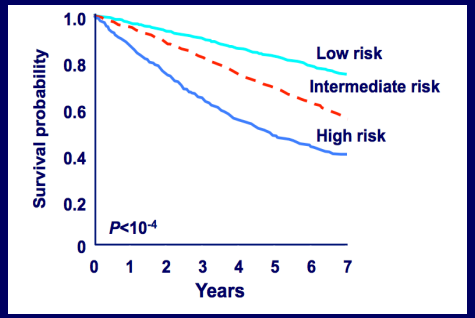
Long-term Follow-up of FL



Ardeshna et al, Lancet 362:516, 2003

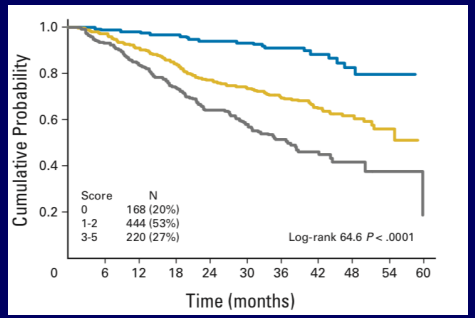
Prognostic Scoring Systems

FLIPI



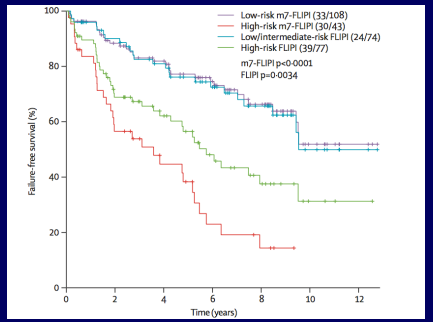
Nodes, LDH, Age, Stage, Hgb

F-2



β-2M, Hgb, Node size Age, BM

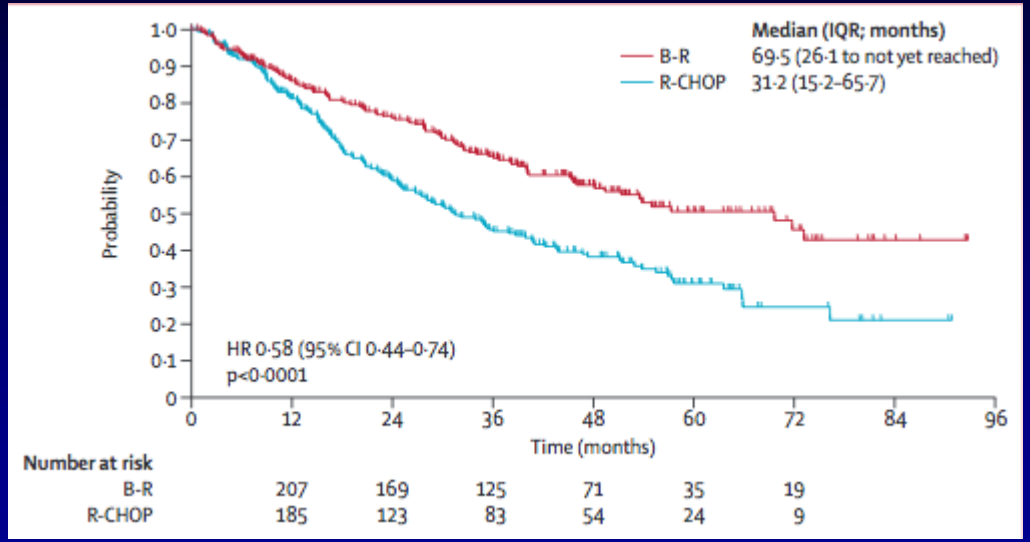
M7-FLIPI



Mutation of 7 genes, PS, F-2

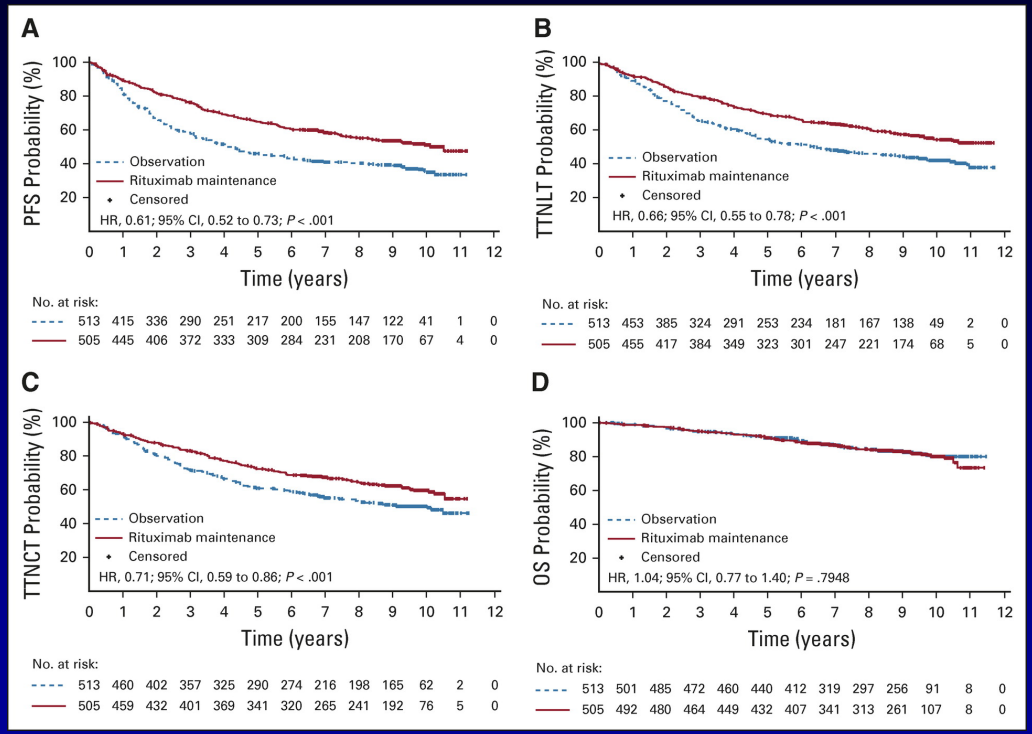
But what do you do with the information??

BR vs R-CHOP in Untreated iNHL



Rummel et al, Lancet 381:1203, 2013

Long-Term Outcome of PRIMA Study



Bachy et al, JCO 37:2815, 2019

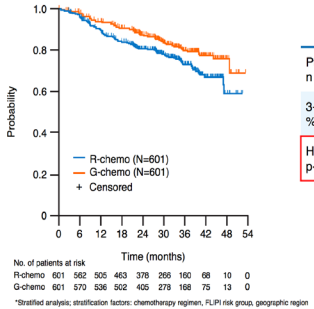
Final safety results

Safety Parameter	Observation N = 508	Rituximab Maintenance N = 501
Adverse events (includes Grade 3–5 toxicities, Grade 2–5 infections, and serious AEs)	194 (38%)	285 (57%)
Grade 3/4 adverse events	**86 (17%)**	**122 (24%) ***
Serious adverse events	**68 (13%)**	**106 (21%)**
Total deaths	83 (16%)	84 (17%)
Grade 5 AEs	3 (<1%)	8 (2%)

* Difference essentially represented by neutropenia and infections

GALLIUM Study: PFS and OS

INV-assessed PFS (FL; primary endpoint)



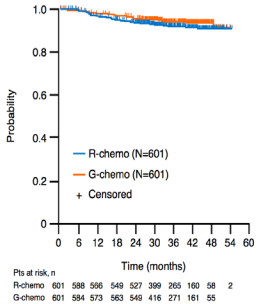
*Stratified analysis; stratification factors: chemotherapy regimen, FLIPI risk group, geographic region

	R-chemo, n=601	*G-chemo, n=601*
Pts with event, n (%)	144 (24.0)	101 (16.8)
3-yr PFS, % (95% CI)	73.3 (68.8, 77.2)	80.0 (75.9, 83.6)
HR (95% CI), p-value*	0.66 (0.51, 0.85), p=0.0012	

Median follow-up: 34.5 months

10

OS (FL)



*Stratified analysis; stratification factors: chemotherapy regimen, FLIPI risk group, geographic region

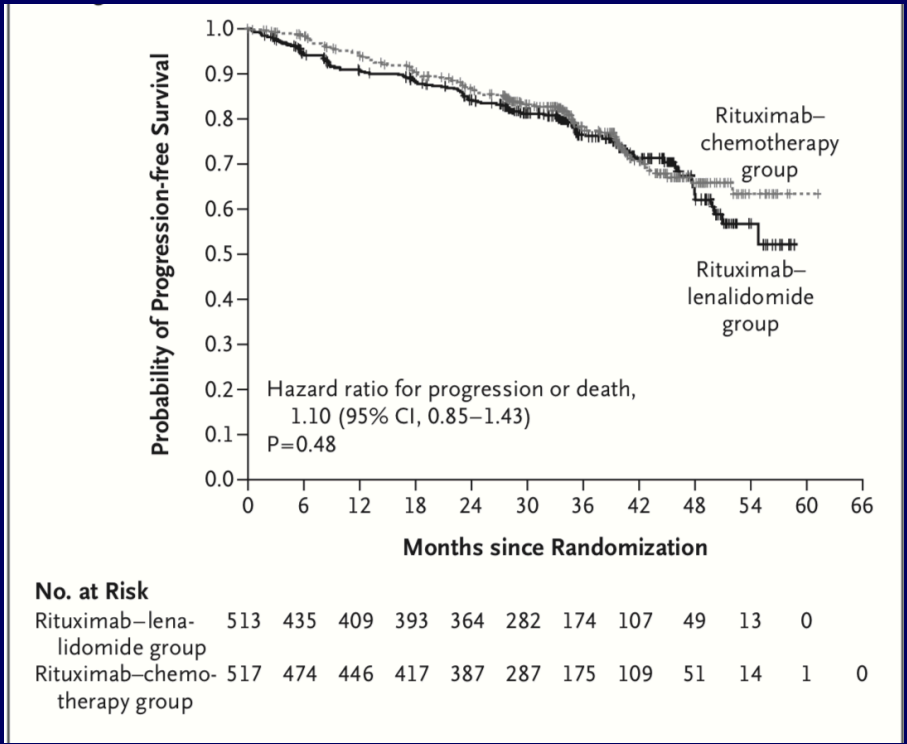
	R-chemo, n=601	*G-chemo, n=601*
Pts with event, n (%)	46 (7.7)	35 (5.8)
3-yr OS, % (95% CI)	92.1 (89.5, 94.1)	94.0 (91.6, 95.7)
HR (95% CI), p-value*	0.75 (0.49, 1.17), p=0.21	

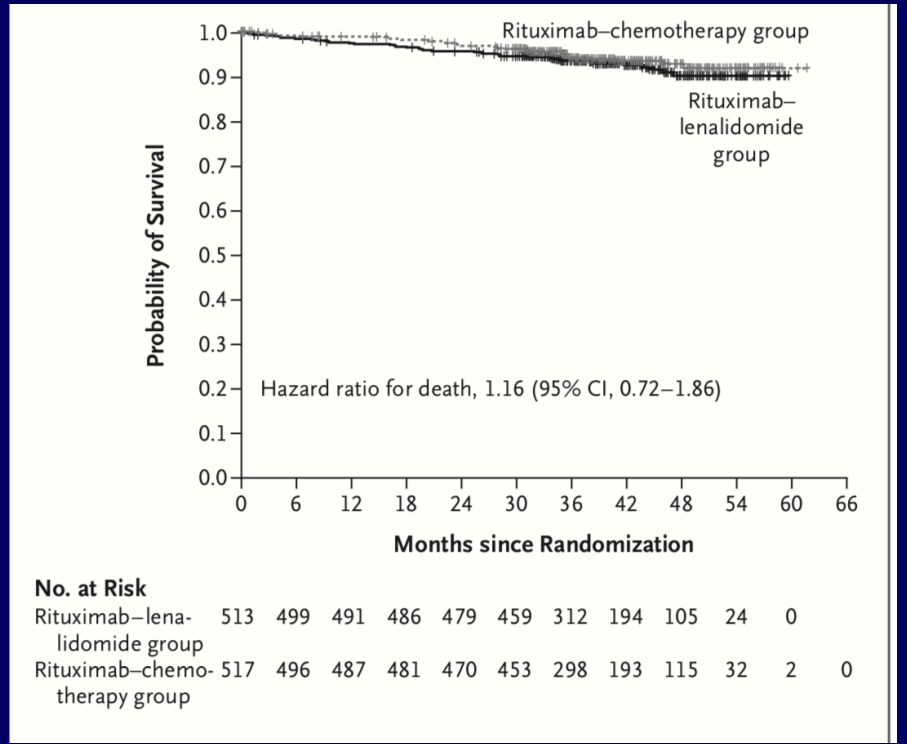
Median follow-up: 34.5 months

13

Marcus et al, NEJM 377:1331, 2017

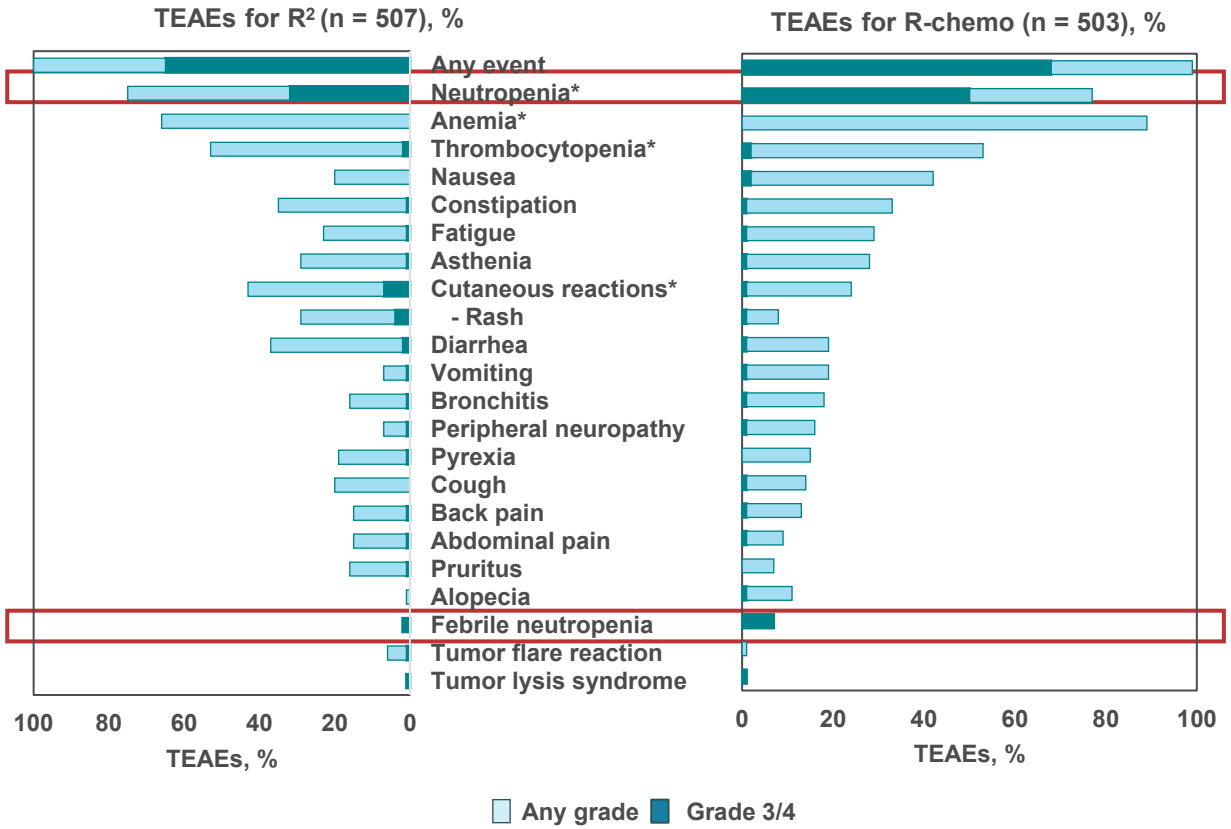
RELEVANCE – PFS and OS





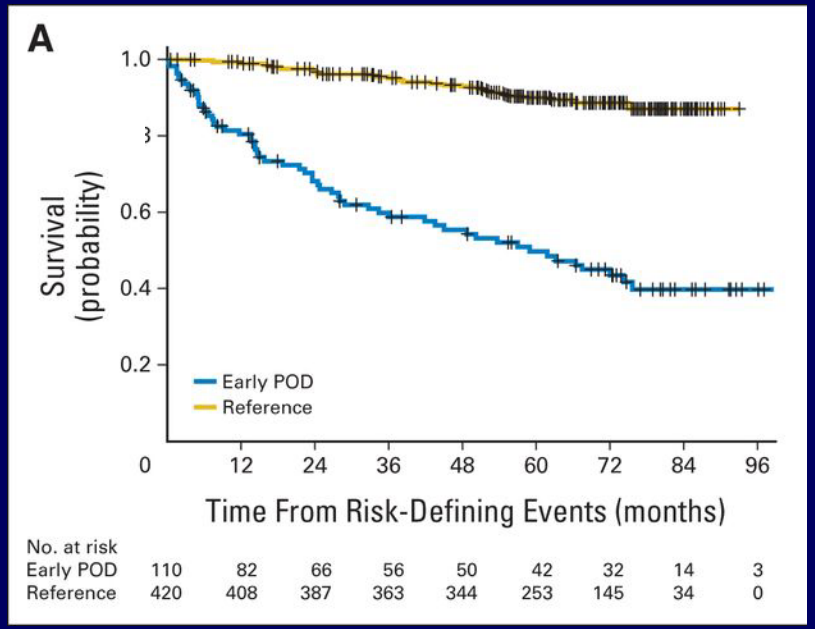
Morschhauser et al, NEJM 379:934, 2018

RELEVANCE: TREATMENT-EMERGENT ADVERSE EVENTS



Data cut-off 31May2017. Includes any-grade TEAEs (≥15%) and select AEs of interest as assessed per NCI CTCAE v4.03.
*Hematologic AEs were based on laboratory tests; all anemia events were grade 1. *Cutaneous reactions included preferred terms from skin and subcutaneous tissue disorders (including rash), gastrointestinal disorders, general disorders and administration site conditions, infections and infestations, and reproductive system and breast disorders.

OS from a risk-defining event after diagnosis in FL patients who received R-CHOP in the National LymphoCare Study group.



Carla Casulo et al. JCO 2015;33:2516-2522

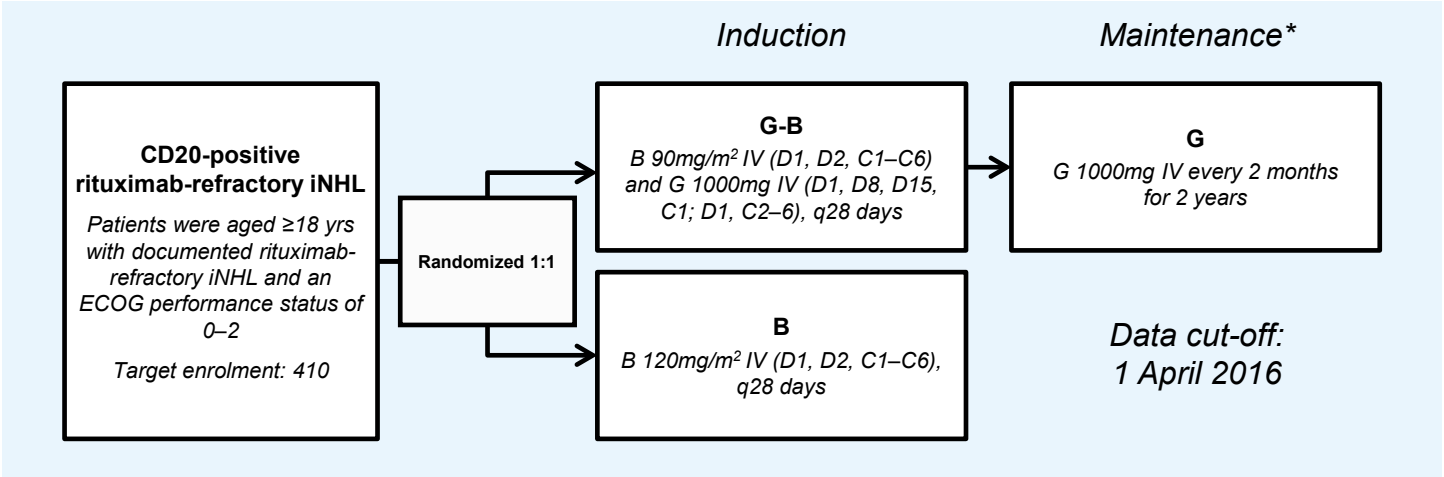
Targeted Agents for FL

Agent	Target
Obinutuzumab*/Ublituximab	CD20
Magrolimab	CD47
Ibrutinib, acalabrutinib	Btk
Idelalisib*, Copanlisib*, Duvelisib*, Umbralisib	PI3-K
Venetoclax Tazemetostat*	Bcl-2 EZH2
Lenalidomide/Rituximab*	Multiple
Nivolumab/Pembrolizumab	PD-1
Atezolizumab	PDL-1
CART-cell	CD19

* FDA approved

GADOLIN Trial: Study design

Open-label, multicenter, randomized, Phase III study in rituximab-refractory iNHL patients



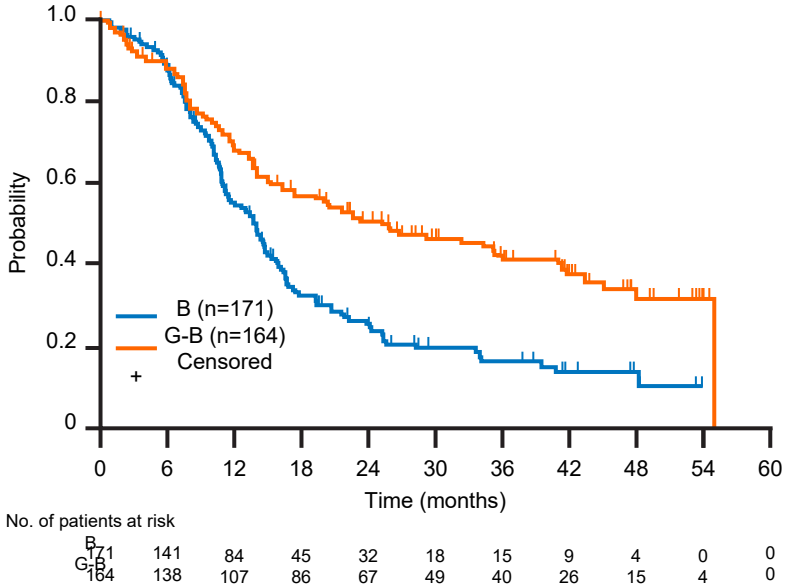
- **Rituximab-refractory definition:** Failure to respond to, or progression during any prior rituximab-containing regimen (monotherapy or combined with chemotherapy), or progression within 6 months of the last rituximab dose, in the induction or maintenance settings
- **Endpoints considered in current analysis:** PFS (INV), OS, TTNT, safety

*Patients in the G-B arm without evidence of progression following induction received G maintenance

Cheson et al, 36:2259-2266, 2018

INV-assessed PFS in the FL population

Kaplan-Meier plot of INV-assessed PFS by treatment arm (FL)



	G-B, n=164	*B, n=171*
Pts with event, n (%)	93 (56.7)	125 (73.1)
Median PFS (95% CI), mo	25.3 (17.4, 36.0)	14.0 (11.3, 15.3)
HR (95% CI), p-value*	0.52 (0.39, 0.69), p<0.0001	

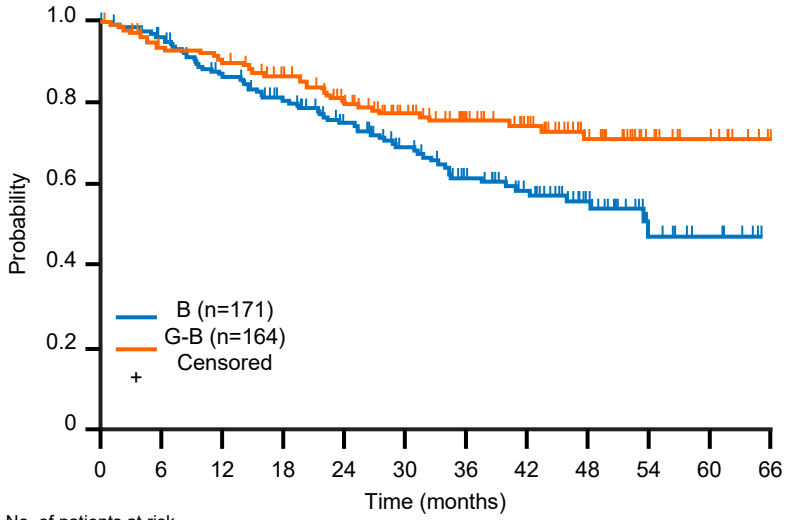
Median follow-up (FL): 31.2 months
(vs 21.1 months in primary analysis)

*Stratified analysis; stratification factors: prior therapies, refractory type, geographical region

Cheon et al, JCO 36:2259-2266, 2018 CC

OS in the FL population

Kaplan-Meier plot of OS by treatment arm (FL)



NR, not reached

*Stratified analysis; stratification factors: prior therapies, refractory type, geographical region

	G-B, n=164	B, n=171
Pts with event, n (%)	39 (23.8)	64 (37.4)
Median OS (95% CI), mo	NR (NR, NR)	53.9 (40.9, NR)
HR (95% CI), p-value*	0.58 (0.39, 0.86), p=0.0061	

Median follow-up (FL): 31.2 months
(vs 21.1 months in primary analysis)

Cheson et al, JCO :2259-2266, 2018

C

FL Response Rates for Approved and Emerging Single-Agent PI3K Inhibitors*

	Copanlisib[1–3]	Idelalisib[4,5]	Duvelisib[6–8]	Umbralisib (TGR1202)[10–13]
Current indication(s)	3rd-line FL	3rd-line FL; 3rd-line SLL; 2nd-line CLL	N/A	N/A
Future indication(s)	2nd-line NHL	2nd-line CLL	2nd-line CLL; 3rd-line FL; 2nd-line PTCL	CLL; ≥2nd-line NHL
MoA	PI3Ki (α,δ)	PI3Ki (δ)	PI3Ki (δ,γ)	PI3Ki (δ), cMyc
Administration	IV	Oral	Oral	Oral
Dosing schedule	60 mg Day 1, 8, 15 (28-day cycle)	150 mg, twice daily	25 mg, twice daily	Once daily
Study population	≥3rd line[b] (FL, n=104)	≥3rd line[b] (FL, n=72)	≥3rd line[b] (FL, n=83)	≥2nd line (FL, n=12)
ORR (FL)	59%	54%	41%	53%
PFS (FL)	12.5 months	11 months	8.3 months	16
CR (FL)	20%	8%	1.2%	12

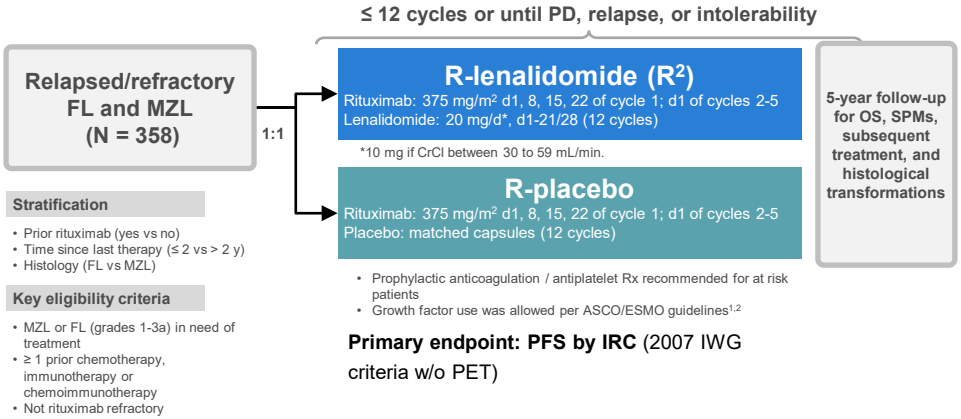
[b]Prior rituximab and alkylating agent.

1. Aliqopa® (copanlisib) Injection [Prescribing Information]. Whippany, NJ. Bayer HealthCare Pharmaceuticals, November 2017 **2.** Bayer. 2017. CHRONOS Trials. Available at: http://www.chronostrials.com/. **3.** Dreyling M *et al. Am J Hematol* 2019;. **4.** Zydelig® (idelalisib) [Prescribing Information]. Gilead. 2016. Available at: http://www.gilead.com/~/media/Files/pdfs/medicines/oncology/zydelig/zydelig_pi.pdf. **5.** Barrientos JC, *OncoTargets and Therapy* 2016;9:2945–2953. **6.** Duvelisib. Verastem Inc. 2016. Available at: http://www.verastem.com/products/duvelisib.aspx. **7.** Zinzani P *et al. Hematol Oncol* 2017;35(S2):69–70. **8.** Flinn I *et al.* Presented at: ASH Annual Meeting; December 3–6, 2016; San Diego, CA, USA. **9.** Batlevi C *et al.* Presented at: International Conference on Malignant Lymphoma; June 14–17, 2017; Lugano, Switzerland. **10.** ClinicalTrials.gov: NCT02793583. **11.** ClinicalTrials.gov: NCT02612311. **12.** TGR1202. TG Therapeutics. 2016. Available at: http://www.tgtherapeutics.com/pipeline/TGR-1202.cfm. **13.** O'Connor OA *et al.* Presented at American Society of Hematology, December 5–8, 2015, Orlando, Florida, USA.

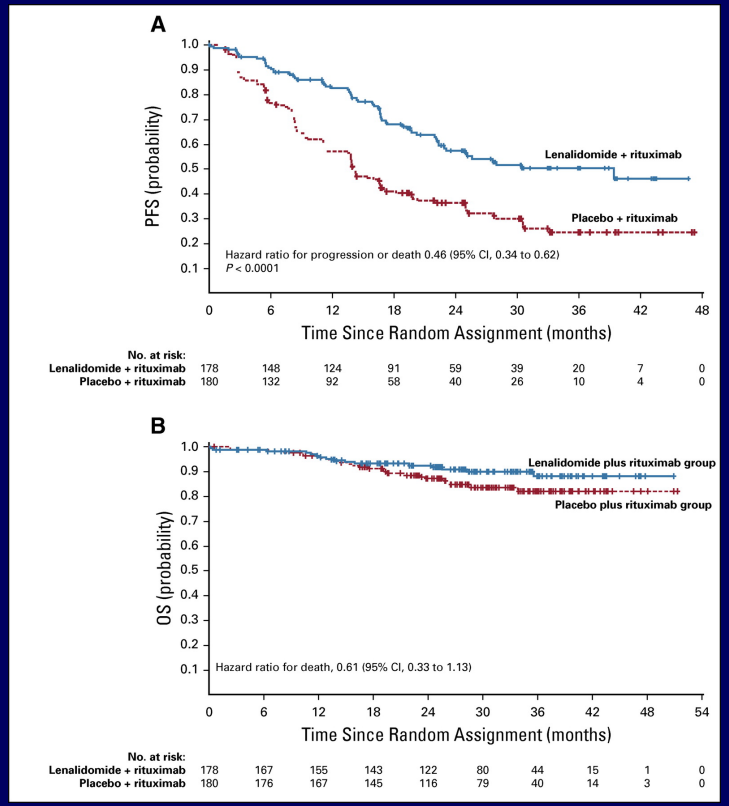
Warnings and Grade ≥3 AEs for Approved and Emerging PI3K Inhibitors for Indolent NHL*

	Copanlisib[1,2]	Idelalisib[3]	Duvelisib[5]	Umbralisib (TGR1202)[4]
Black box warning	None	Fatal and/or serious toxicities: • Hepatotoxicity (11–18%) • Severe diarrhea or colitis (14–19%) • Pneumonitis (4%) • Infections (21–36%) • Intestinal perforation	N/A	N/A
Grade ≥3 AEs (in FL patients unless otherwise noted)[b]				
Hyperglycemia	41% (infusion-related)	N/A	N/A	N/A
Hypertension	26% (infusion-related)	N/A	N/A	N/A
Pneumonitis	1%	16%[d]	2%	<1.5%[a]
Lung infection	16%		9%[e]	5%[e]
Diarrhea	5%	14%	15%	3%
Colitis	1%[c]		5%	<1.5%[a]
ALT increased	1.4%	18%	6%	3%
AST increased	1.4%	12%	N/A	3%

AUGMENT: Study Design: Randomized double blind phase III trial



PFS and OS From the AUGMENT Trial

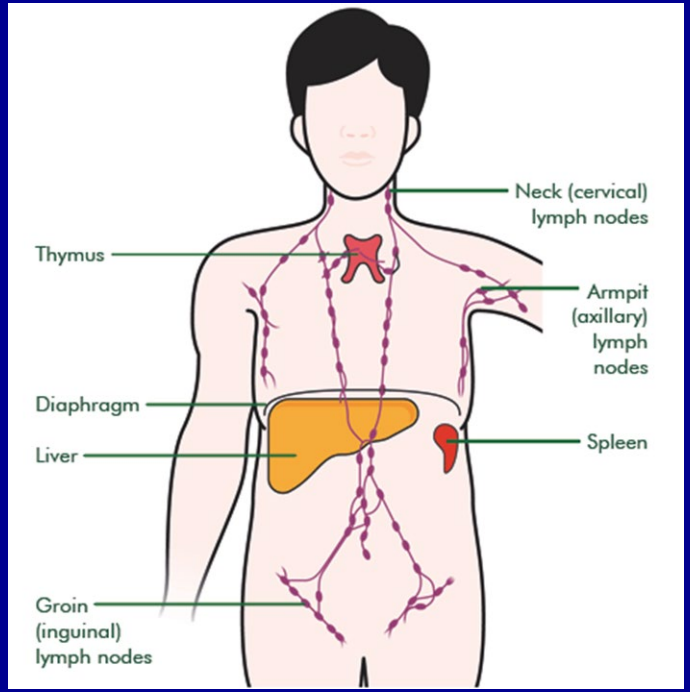


Leonard, et al; *JCO* 2019 371188-1199

Types of Marginal Zone Lymphoma

- Nodal
- Splenic
- Extranodal of MALT

  (mucosa-associated lymph tissue)

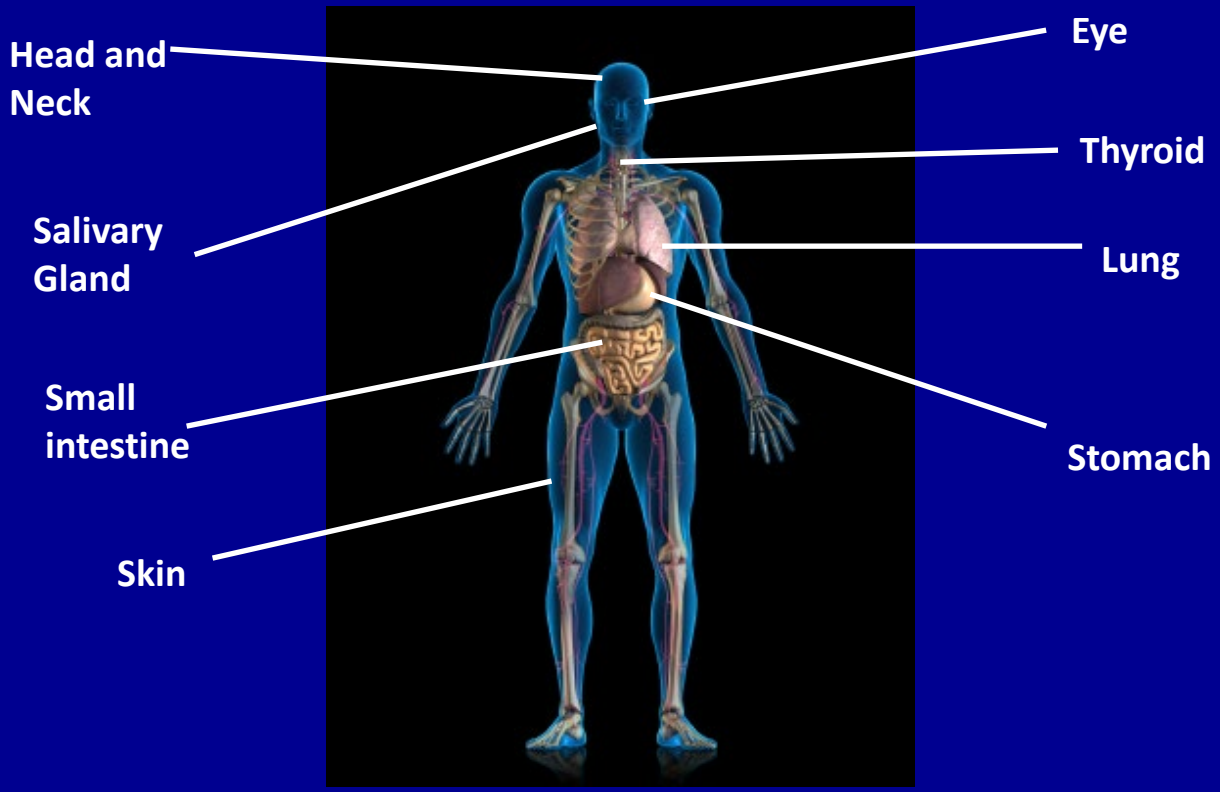


Risk Factors

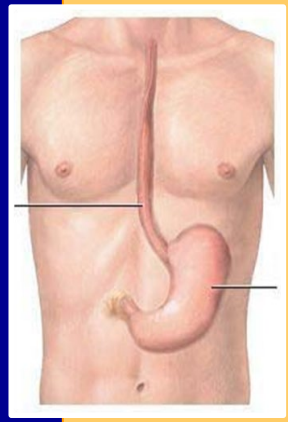
- Chronic Infections
  - Helicobacter pylori
  - Hepatitis C
  - Borrelia burgdorferi
  - Chlamydia psittaci
- Autoimmune disorders
  - Hashimoto's disease
  - Sjögren's disease

Picture Courtesy of Davidson College

Locations of MALT Lymphomas



Treatment



Gastric MALT

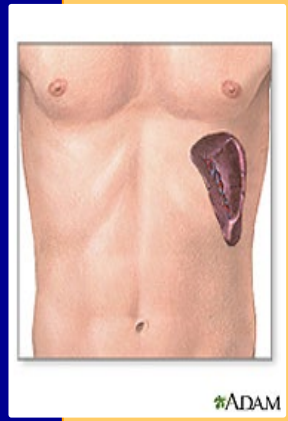
- Treat the H. Pylori
- Radiation
- Rituximab
- Rituximab + Chemo

Treatment

Non-gastric MALT

- Treat the infection
- Radiation
- Surgery
- Topical steroids
- Rituximab +/- Chemo

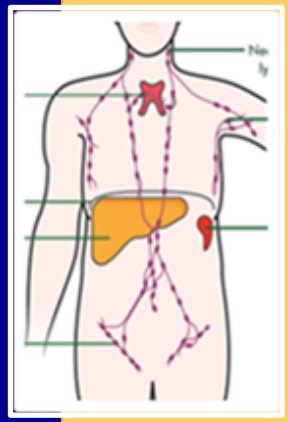
Treatment



Splenic

- Treat the Hepatitis C
- Rituximab +/- Chemo
- PI3K inhibitors
- Surgery

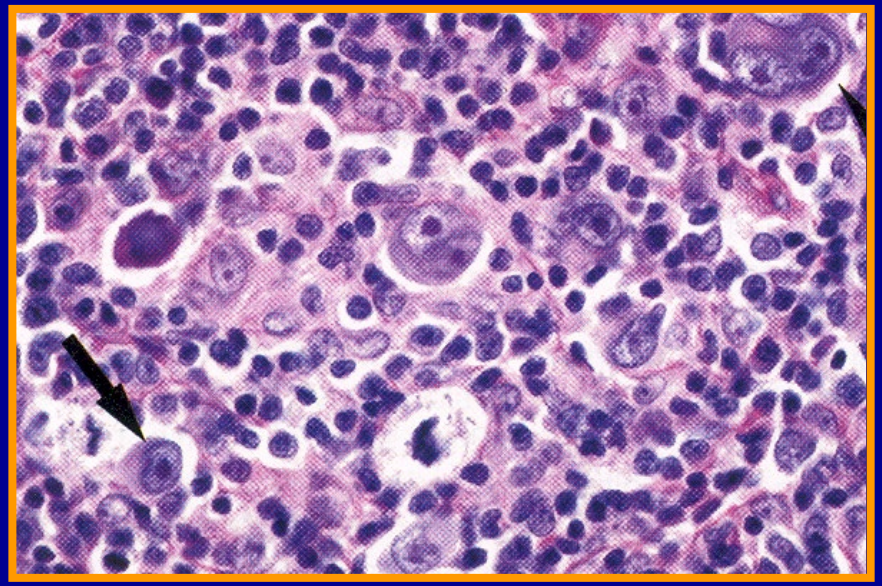
Treatment



Nodal

- Rituximab + Chemo
  - Bendamustine
  - CHOP
- Ibrutinib, acalabrutinib
- Idelalisib, Copanlisib, Duvelisib

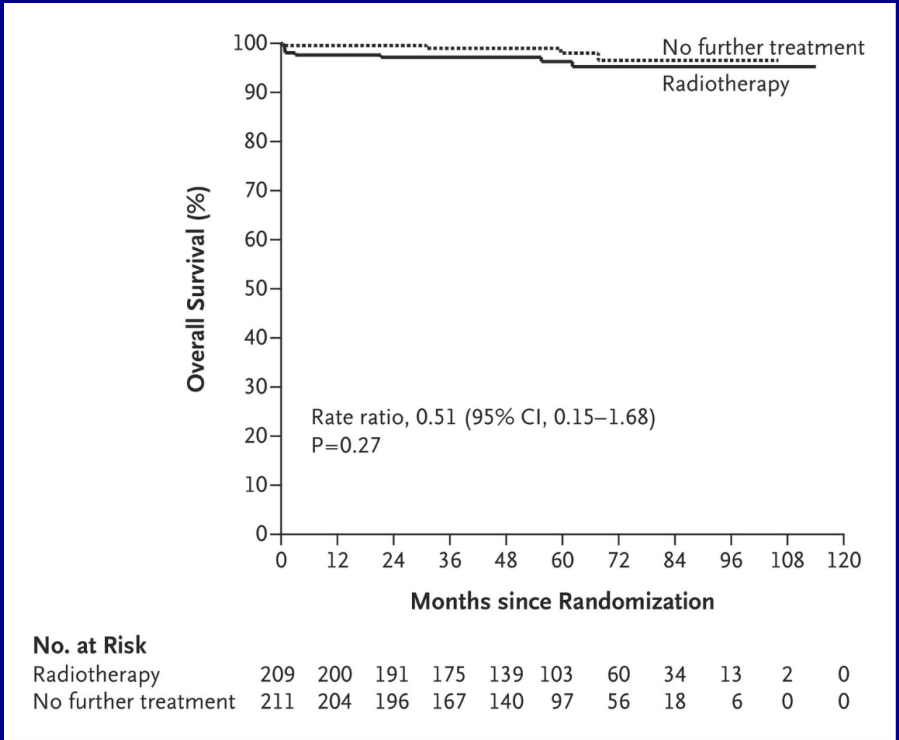
Hodgkin Lymphoma



Hodgkin's Disease: Standard Initial Treatment

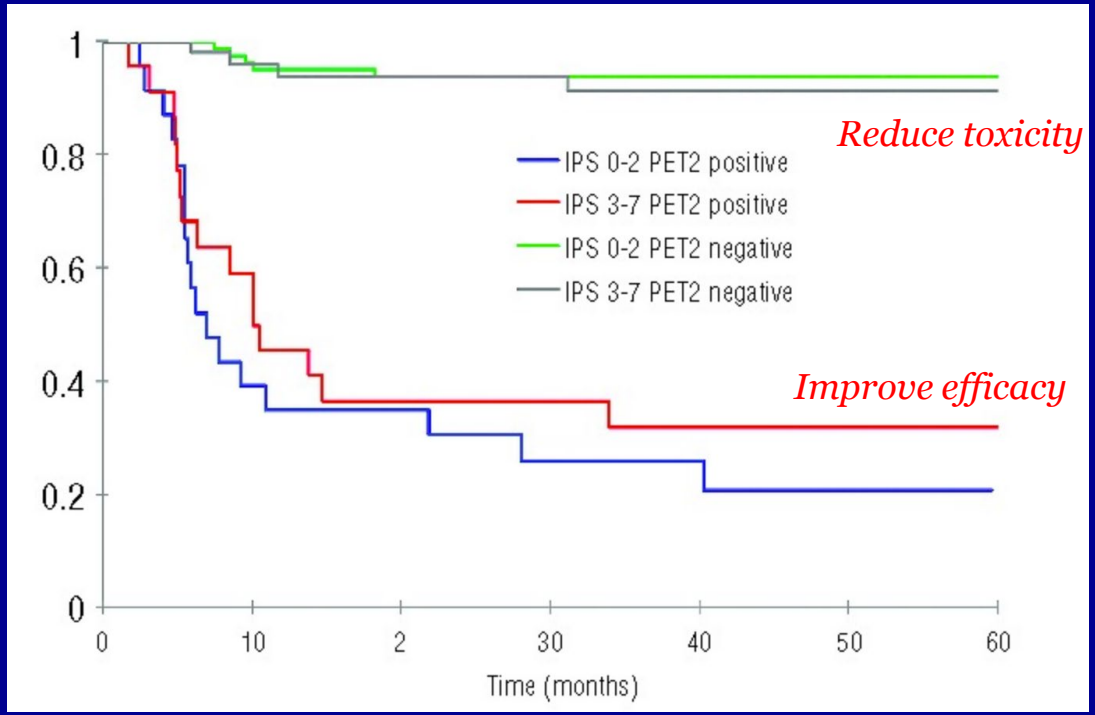
Stage	Bulk	Treatment
IA/IIA	Non-bulky	ABVD x 3-4 or ABVD x 2 ➔ INRT
IIB, III/IV	Non-bulky	ABVD x 6; AVD-BV x 6
Any	Bulky	ABVD x 6

OS Early Stage HL



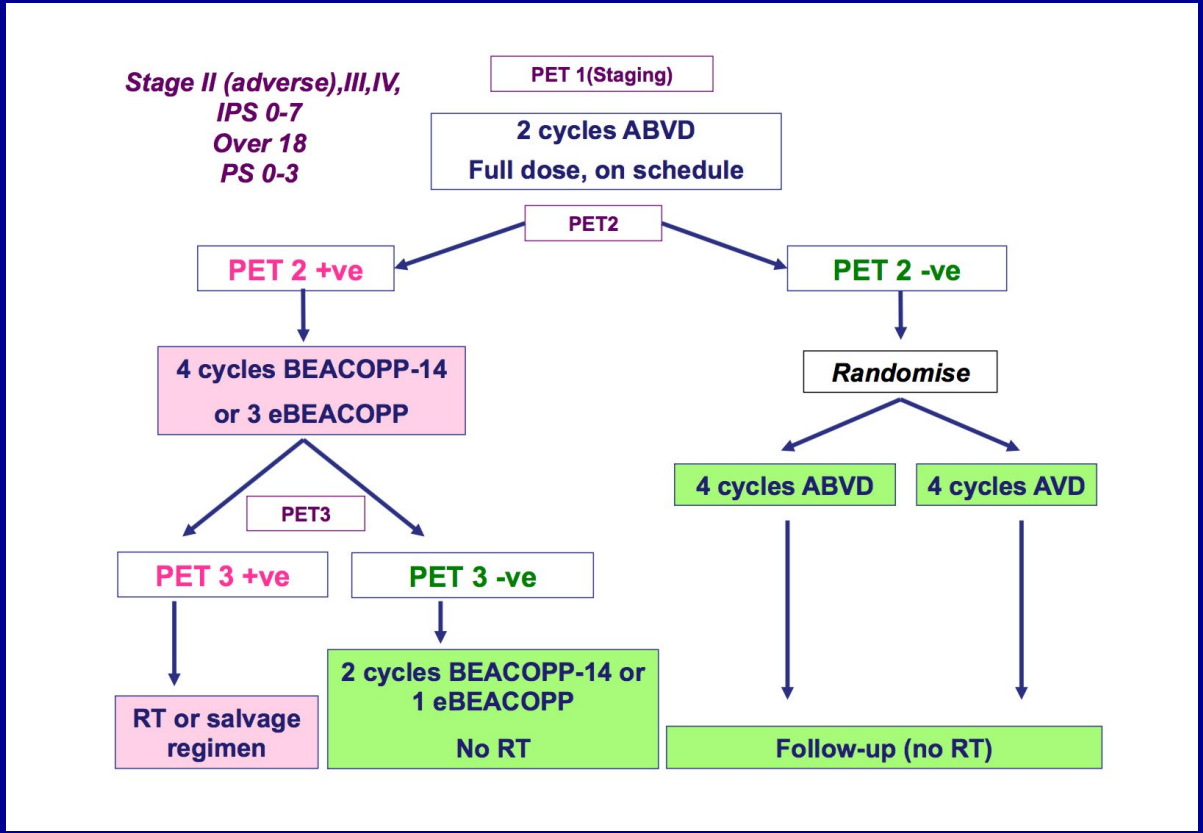
Radford et al, NEJM 372:1598, 2015

Interim PET Following ABVD in HL Using the Deauville 5-PS



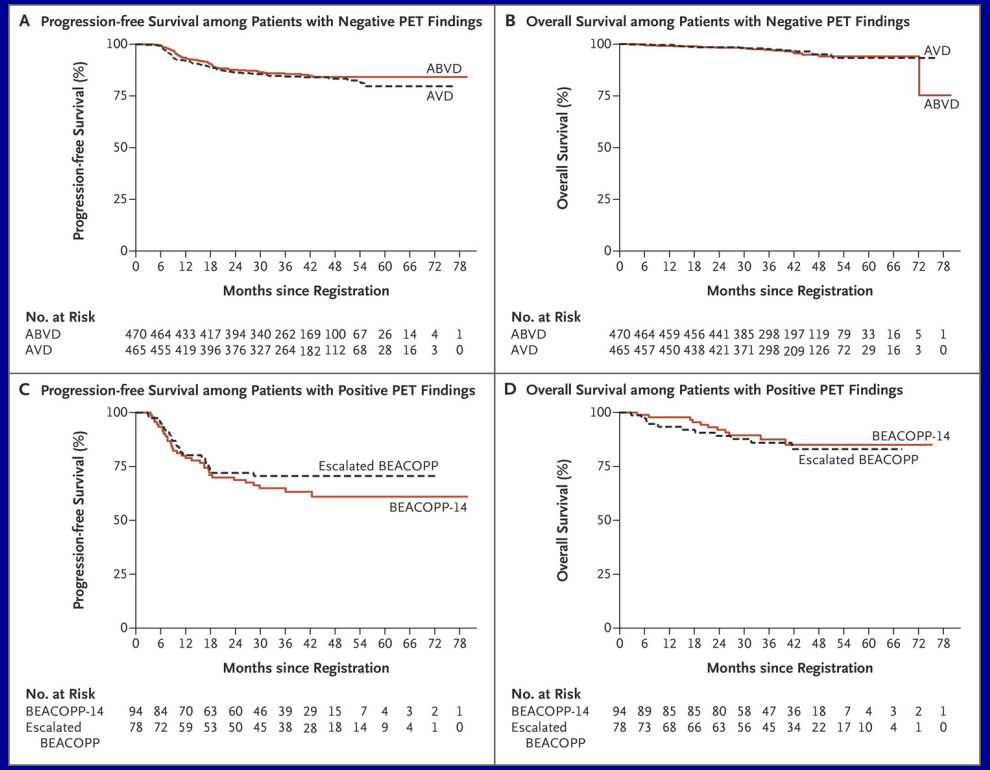
Gallamini, et al, Haematologica 99:1107, 2014

RATHL: Schema



Johnson et al, NEJM 374:2419, 2016

RATHL - Progression-free and Overall Survival



Johnson P et al. N Engl J Med 2016;374:2419-2429.

Toxicity of therapy: ABVD vs AVD

% of patients experiencing grade 3-4 events

	ABVD cycles 1-2	ABVD cycles 3-6	AVD cycles 3-6	P-value
Neutropenia	57.3	58.4	57.5	0.78
Thrombocytopenia	1.3	1.3	3.2	0.045
Neutropenic fever	2.1	4.7	2.2	0.032
Infection	6.3	14.5	10.1	0.040
Thrombo-embolism	1.4	4.9	2.6	0.061
Respiratory AEs	0.7	3.6	0.6	0.002
Any non-haematological toxicity	16	31	21	<0.001

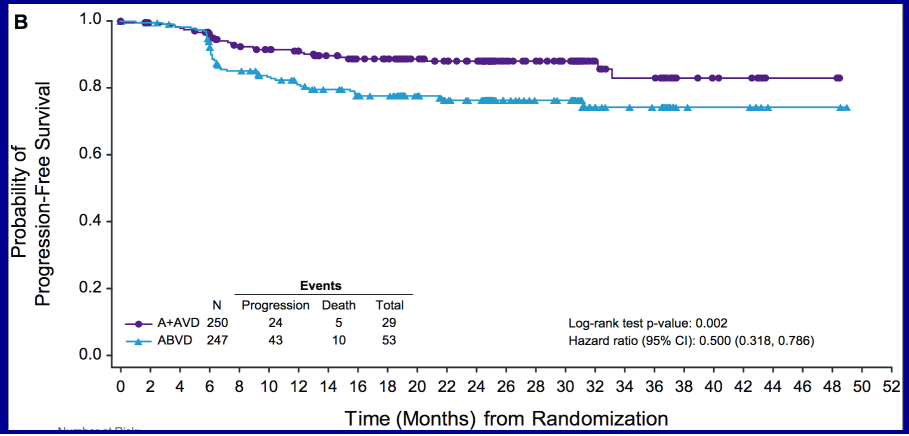
Johnson et al NEJM 374:2419, 2016

Brentuximab Vedotin in HL: Response Results

	N=102	
	IRF	Investigator
Overall response rate (95% CI)	75% (65, 83)	72% (62, 80)
Complete remission	34%	33%
Partial remission	40%	38%
Stable disease	22%	27%
Progressive disease	3%	0%
Not evaluable	1%	1%

Younes et al, JCO. 30:2183, 2012

ECHELON-1 in US



Adverse event category, n (%)	A+AVD (N=249)	ABVD (N=240)
Neutropenia[a]		
Incidence of neutropenia (any grade)	154 (62)	130 (54)
Grade 3 or higher neutropenia	146 (59)	109 (45)
Incidence of febrile neutropenia[b]	51 (20)	22 (9)
Peripheral neuropathy[c]		
Incidence of peripheral neuropathy (any grade)	198 (80)	134 (56)
Grade 1 peripheral neuropathy	102 (41)	104 (43)
Grade 2 peripheral neuropathy	53 (21)	28 (12)
Grade 3 peripheral neuropathy	43 (17)	2 (<1)
Pulmonary toxicity[d]		
Incidence of pulmonary toxicity (any grade)	7 (3)	25 (10)
Grade 3 or higher pulmonary toxicity	4 (2)	14 (6)

Ramchandren et al Clin Cancer Res e-pub, 2019

Nivo in R/R HL

Response	Protocol-Specified Analysis by Cohort: BV Naïve: Cohort A (n = 63)	BV After Auto-HCT: Cohort B (n = 80)	BV Before and/or After Auto-HCT: Cohort C (n = 100)	All patients (N = 243)
ORR, % (95% CI)	65 (52-77)	68 (56-78)	73 (63-81)	69 (63-75)
Best overall response				
Complete remission	18 (29)	10 (13)	12 (12)	40 (16)
Partial remission	23 (37)	44 (55)	61 (61)	128 (53)
Stable disease	15 (24)	17 (21)	15 (15)	47 (19)
Progressive disease	7 (11)	6 (8)	10 (10)	23 (9)
Unable to determine	0	3 (4)	2 (2)	5 (2)

	Exploratory Analyses by Refractory Status (all patients): To First Line (n = 142)	To Last Line (n = 114)	To BV After Auto-HCT (n = 75)
ORR	73	68	68
Best overall response			
Complete remission	25 (18)	15 (13)	5 (7)
Partial remission	78 (55)	62 (54)	46 (61)
Stable disease	25 (18)	22 (19)	13 (17)
Progressive disease	12 (8)	12 (11)	8 (11)
Unable to determine	2 (1)	3 (3)	3 (4)

Armand et al JCO 36:1428, 2018

Wine Spectator

Wine & Healthy Living

Breaking News

Long-Term Wine Drinking Linked to Low Lymphoma Death Rates

While scientists struggle to find common ground on alcohol consumption and its relationship to breast cancer, moderate wine drinkers may find comfort in a new study that links the beverage to lower death rates among female non-Hodgkin's lymphoma sufferers.

According to an unpublished epidemiology study presented at the American Association for Cancer Research 100th Annual Meeting, held April 18–22 in Denver, those stricken with the ailment who drank wine regularly for 25 years before diagnosis enjoyed better survival rates five years after being diagnosed compared to nondrinkers. Wine drinkers were also more likely to be disease-free after five years.

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