Aggressive B and T cell lymphomas: Treatment paradigms in 2018

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Disclosures

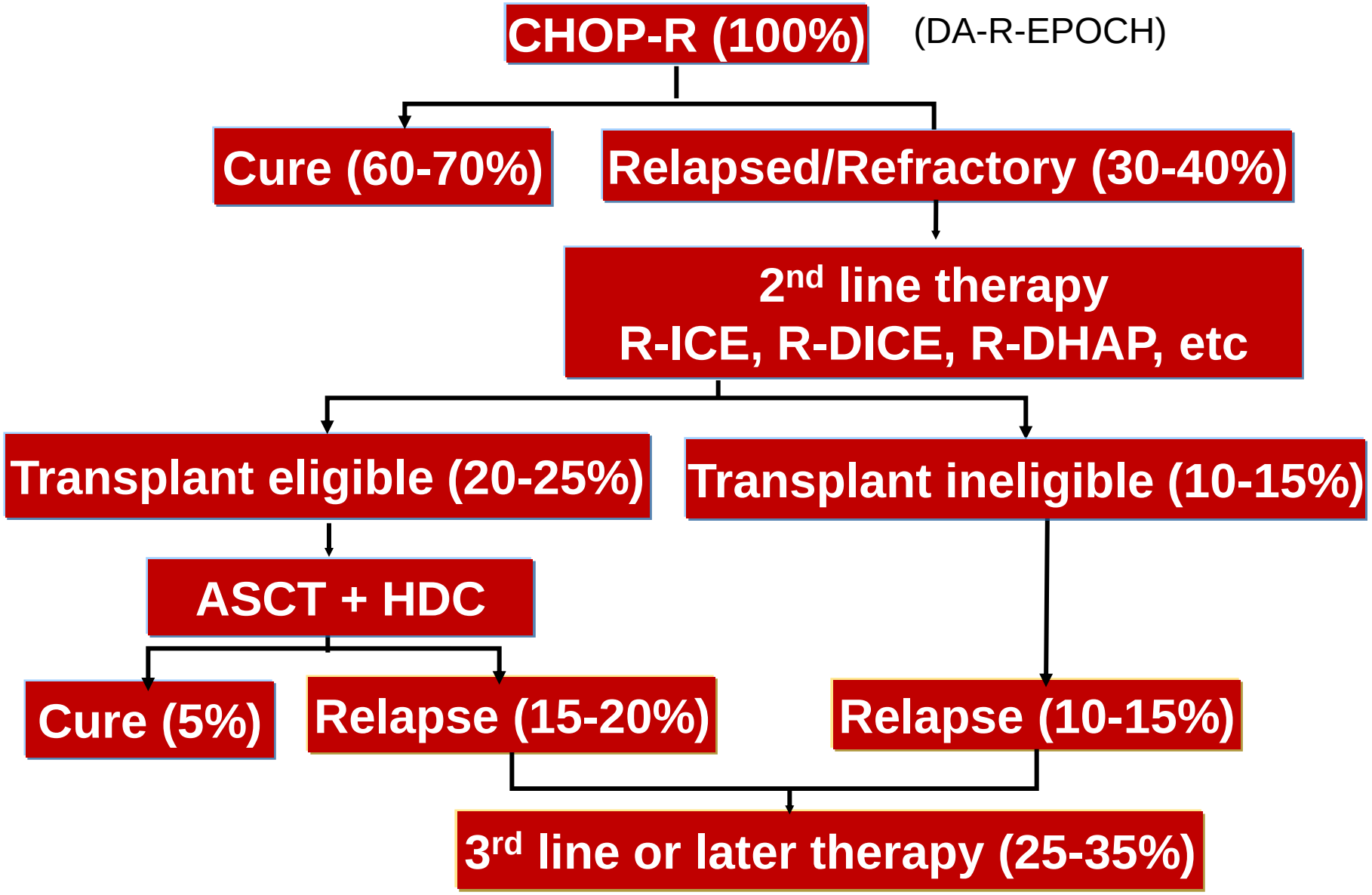
Consulting advice:

Gilead, Juno, Celgene, Sutro, BMS, Genentech/Roche, Pfizer, Bayer, ADC Therapeutics, AstraZeneca, United Therapeutics, Biotest, Karyopharm, MEI Pharma, Novartis

Diffuse large B cell lymphoma

- Median age 60, usually with advanced stage disease
  - LAN, extranodal disease, symptoms
- Practical objective of treatment – cure (70%)
- Reasonably good clinical prognostic tools
- Most patients treated same (R-CHOP)
- Unmet need – more cures, reduce toxicity
- Who should we treat differently?
- If refractory to second-line therapy, prognosis is poor

Treatment algorithm for DLBCL



Comparison of CHOP-R and EPOCH-R

R-CHOP

Rituximab 375 mg/m^2 d1
Cyclophosphamide 750 mg/m2 d1
Doxorubicin 50 mg/m^2 d1
Vincristine 1.4 mg/m^2 (2 mg cap) d1
Prednisone 40 mg/m^2 d1-5

q3w × 6

DA*-R-EPOCH

Rituximab 375 mg/m^2 d1
Etoposide 50 mg/m^2/d CI d1-4*
Doxorubicin 10 mg/m^2/d CI d1-4*
Vincristine 0.4 mg/m^2/d CI d1-4
Cyclophosphamide 750 mg/m^2 d5*
Prednisone 60 mg/m^2 bid d1-4
G-CSF 5 µg/kg d6-ANC recovery

q3w × 6

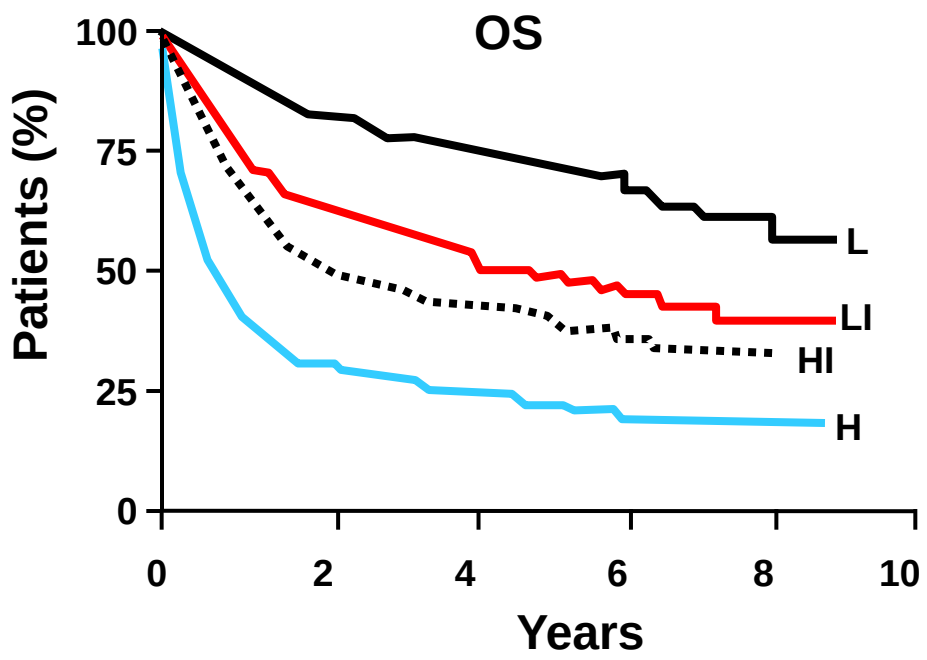
International Prognostic Index (IPI) in aggressive NHL

Prognostic factors (APLES)

- **A**ge >60 years
- **P**erformance status >1
- **L**DH >1× normal
- **E**xtranodal sites >1
- **S**tage III or IV

OR

Risk Category	Factors
Low (L)	0 or 1
Low intermediate (LI)	2
High intermediate (HI)	3
High (H)	4 or 5



International NHL Prognostic Factors Project. *N Engl J Med.* 1993;329:987.
Armitage. *CA Cancer J Clin.* 2005;55:368.

What does the physician need or want to know when approaching a new DLBCL patient?

- **Clinical features**
  - **International Prognostic Index**
  - **Primary mediastinal (R-EPOCH)**
  - **CNS, testicular (variations of rx)**
- **Pathological and molecular features**
  - **BM involvement (variations of rx)**
  - **Double hit (FISH) > Double protein (R-EPOCH)**
  - **Cell of origin (Germinal Center/Activated B Cell)**

When do I treat patients with DLBCL today with something other than R-CHOP x 6?

Double hit subtype

- **Data not robust in double protein subtype**

Primary mediastinal

HIV associated

Testicular

Limited stage (?)

CNS

Elderly

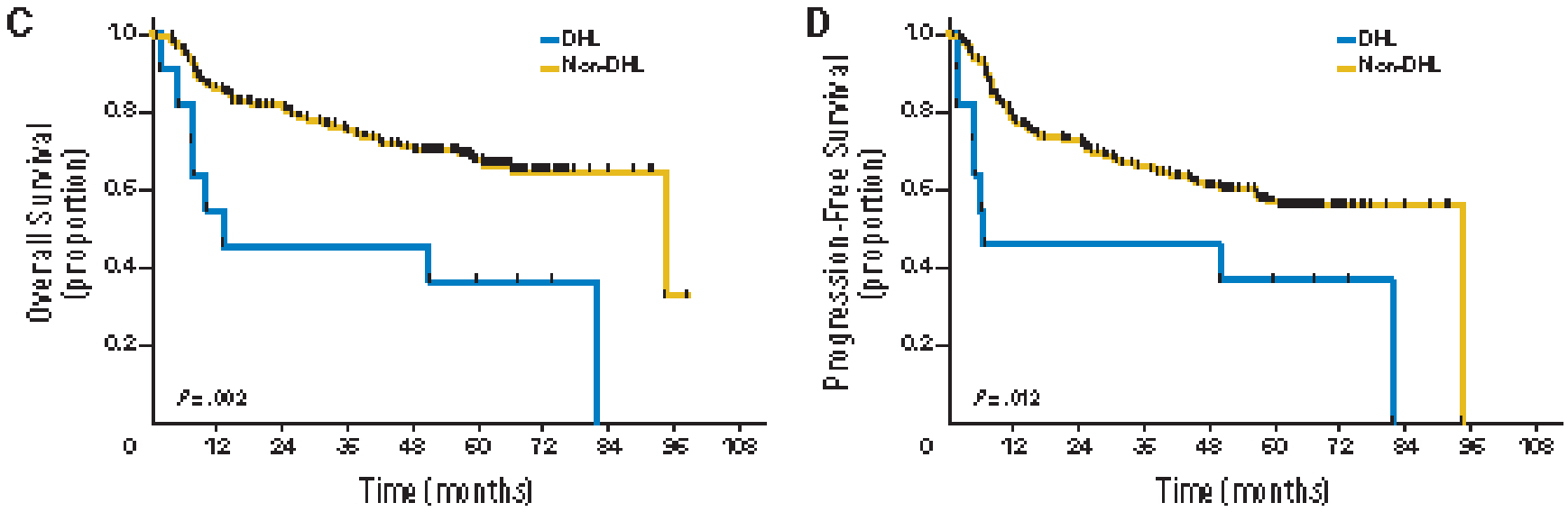
Double hit vs Double protein DLBCL
10-25% of DLBCL

- **Double-hit lymphoma: High-grade B-cell lymphoma with translocations of MYC as well as BCL2, BCL6, or both (“triple-hit”)**
  - **Histologically classified as DLBCL or B-cell lymphoma unclassifiable with intermediate features between DLBCL and Burkitt Lymphoma**
  - **Cell of origin: Virtually always germinal center subtype**
  - **Outcome poor with standard therapies**
- **Double-expressing lymphomas: DLBCL with dual immunohistochemical expression of MYC (≥40%) and BCL2 (≥70%) in the absence of translocations**
  - **Cell of origin: Usually activated B cell subtype**
  - **Outcome inferior to other DLBCLs, but not as poor as DHL**

Caveats in understanding clinical characteristics and outcomes in “double hit and double protein” lymphoma

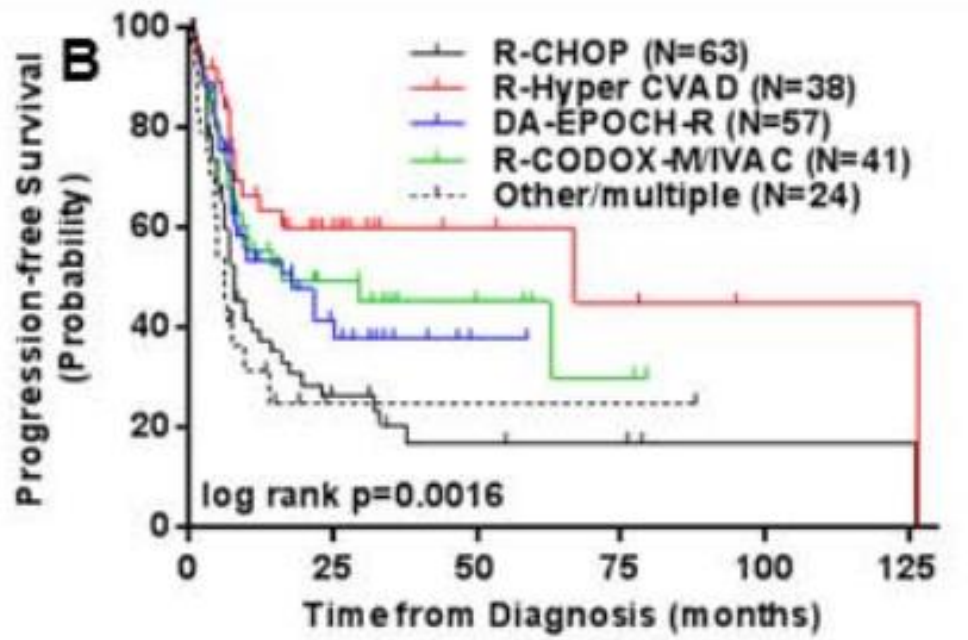
- Clinical features of the subtype are less favorable
- Selection biases of series
- Variability in molecular testing
- Challenges and changes in morphologic/pathologic classification
- Non-uniform therapy
- Single vs multicenter
- Retrospective

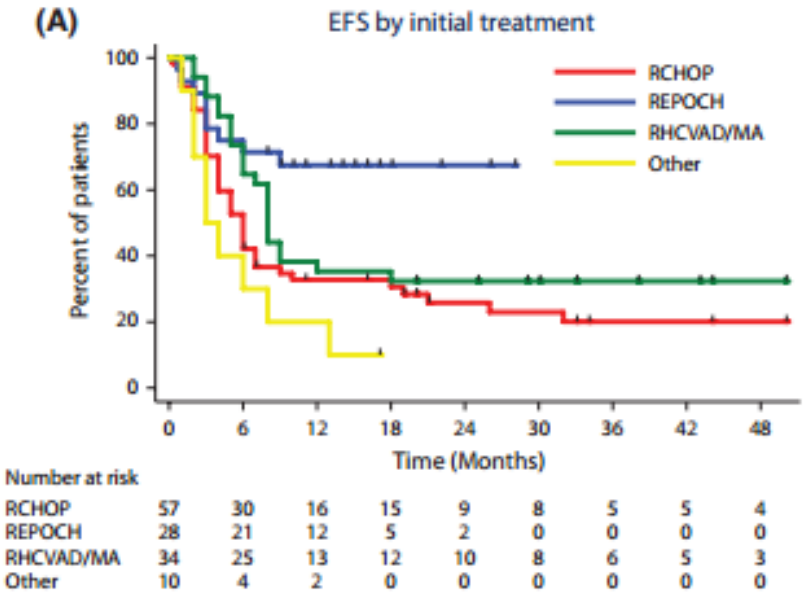
FISH DH DLBCL and treatment with R-CHOP



Green et al, JCO 2012

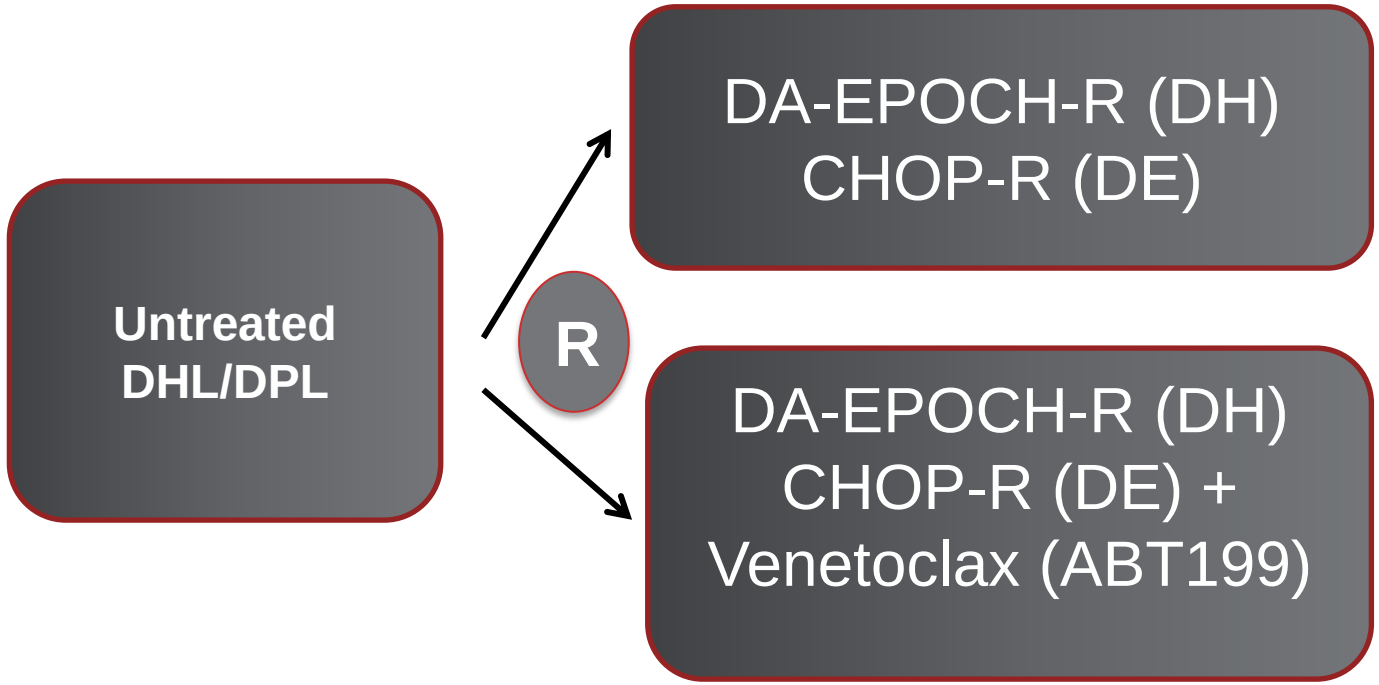
DA-EPOCH-R in double hit lymphoma





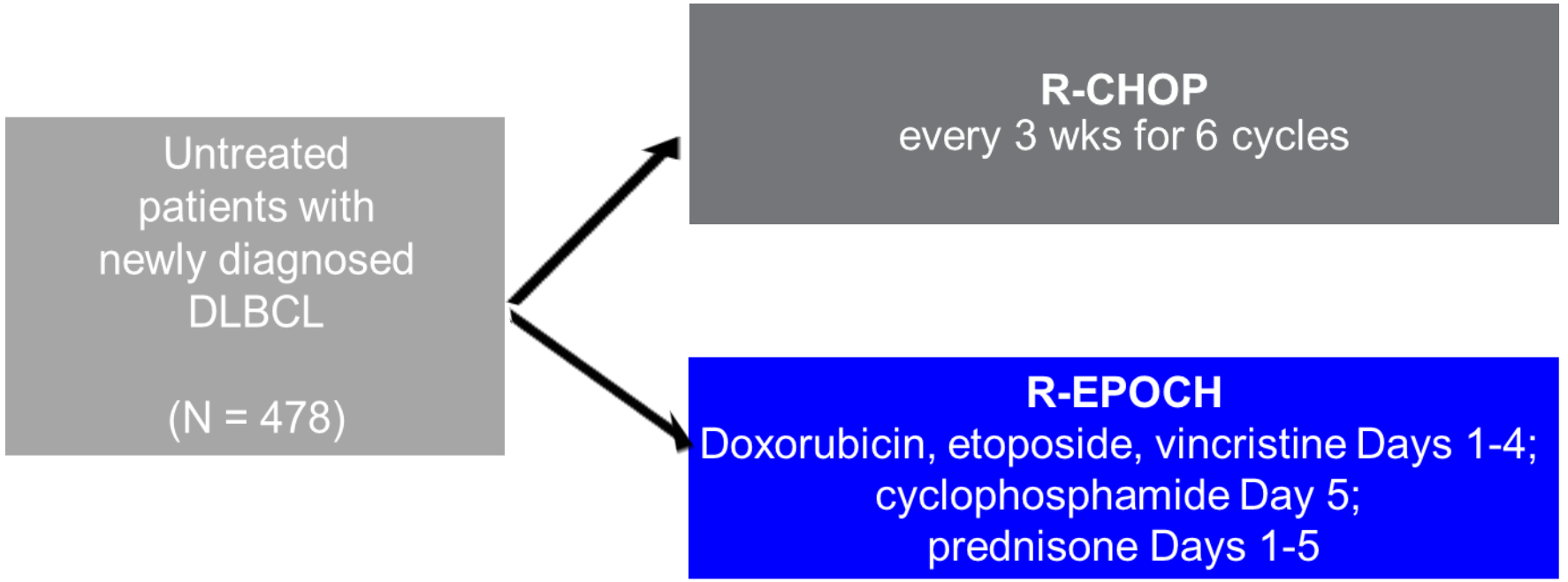
Petrich et al Blood 2014
Oki et al BJH 2014

Planned Intergroup Trial in DH/DE DLBCL
Phase I then Phase II-III
BCL-2 inhibitor Venetoclax



Ph I Investigator-initiated study (Alliance Foundation) WCM/NYP Coordinating Site (Rutherford)
Phase II/III NCI/Alliance/Intergroup (Abramson MGH)

Alliance/CALGB 50303: R-CHOP vs R-EPOCH in Newly Diagnosed DLBCL



- Primary endpoints: EFS, molecular predictors of outcome for each regimen
- Secondary endpoints: RR, OS, toxicity, use of molecular profiling

Bartlett et al, ASH 2016

Clinical Trials.gov. NCT00118209. http://www.clinicaltrials.gov

Alliance 50303: Design

- N = 524; enrolled 2005 – 2013; Data cutoff November 2016

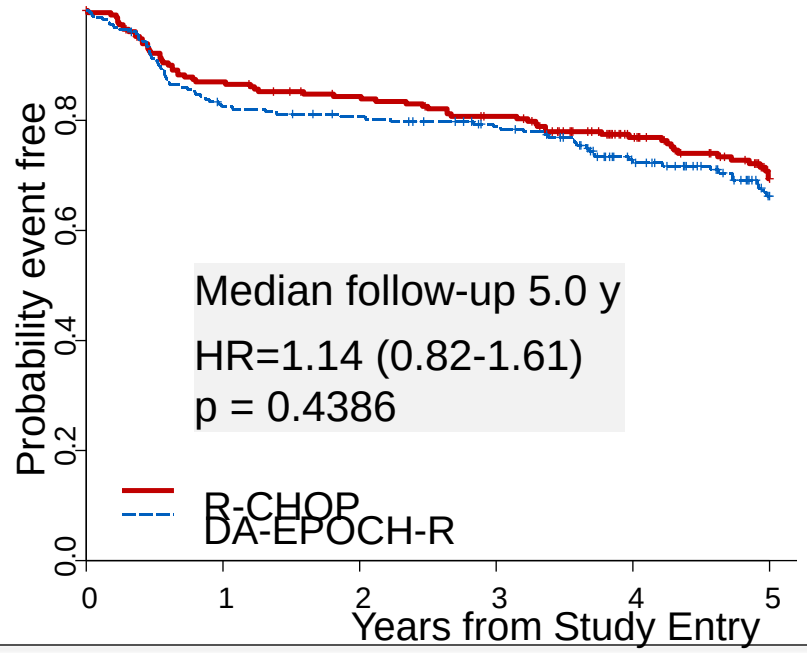
- Analysis planned after 242 events, but due to low event rate DSMB released data July 2016 with 167 events

Characteristic	R-CHOP (%)	DA-EPOCH R (%)	P-value
Median Age (range)	58 (18-86)	57 (19-84)	0.677
ECOG 0-1 vs. 2	88 vs. 12	87 vs. 13	0.518
Stage 3/4	73	77	0.641
IPI 0-2	65	61	0.405
GRADE ≥ 3 TOXICITY			
Treatment related deaths	2	2	0.975
Platelets	11	65	<0.001
Febrile neutropenia	17	35	<0.001
Infection	**11**	**14**	**0.169**
Neuropathy – sensory/motor	2/1	14/8	<0.001

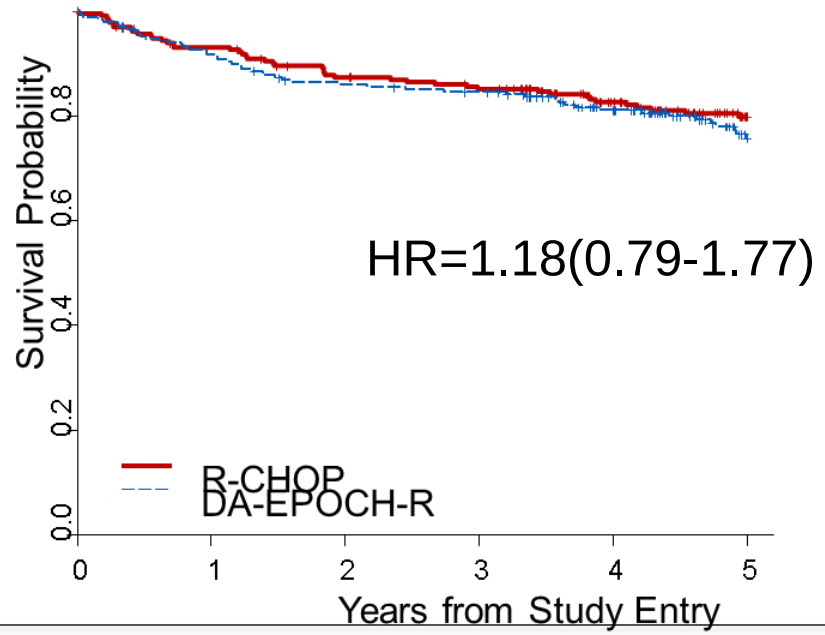
Alliance 50303: Outcomes

	R-CHOP	DA-EPOCH-R	P-value
ORR	**89%**	**89%**	**0.983**
CR/CRu	**62%**	**61%**	
PR	**27%**	**27%**	

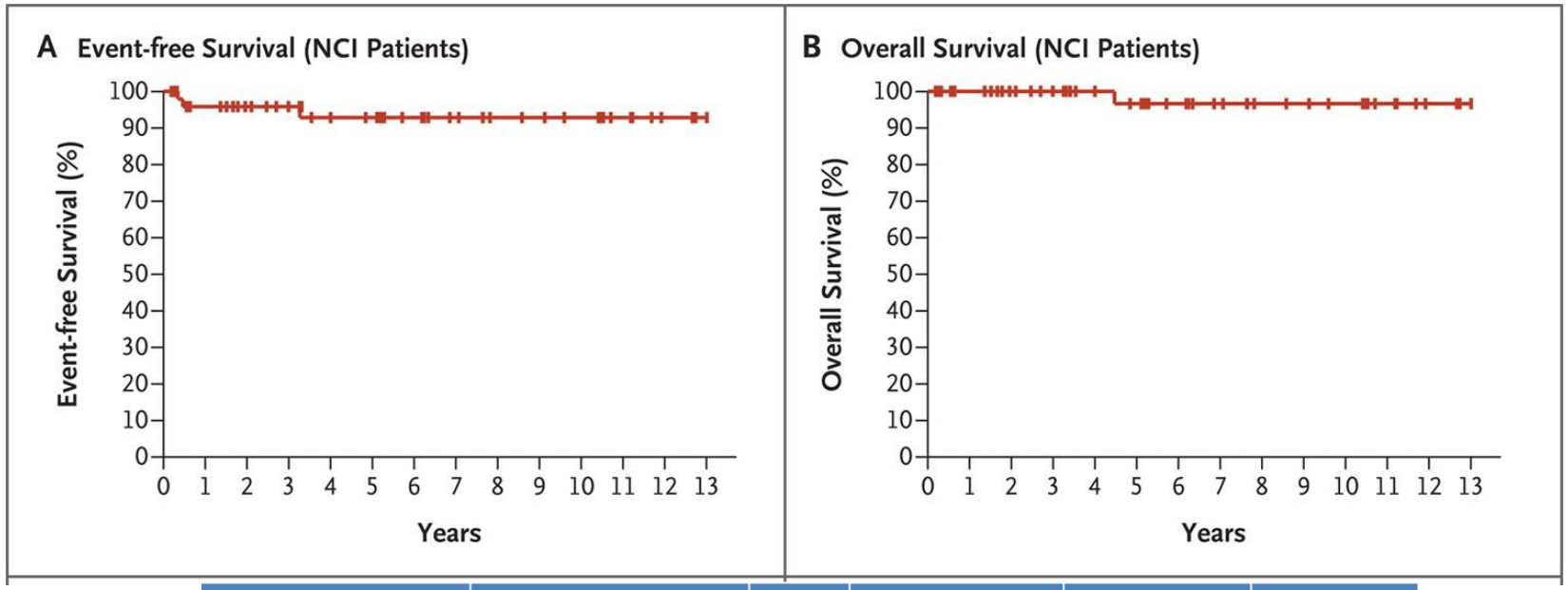
Event Free Survival



Overall Survival



DA-EPOCH-R without RT for PMBCL



Center	Study Type	n	Age median (range)	Median f/u	EFS
NCI [1]	prospective phase II	51	30y (19-52)	63 mo	93%
Stanford [1]	retrospective	16	33y (22-68)	37 mo	100%
MD Anderson [2]	retrospective	25	35y (19-70)	NR	approx. 85%

1. Dunleavy K et al. N Engl J Med 2013.
2. Pinnix CC et al, Int J Radiat Oncol Biol Phys 2015.

DA-EPOCH-R in children and adults with PMBCL: A retrospective multicenter analysis

Objectives:

- Describe outcomes in a large number of patients with PMBCL treated with DA-EPOCH-R
- Compare pediatric and adult experience

Methods:

- Collected data from 24 academic medical centers on patients treated from 2005-2015
- No age restriction
- Excluded pediatric patients enrolled on ANHL1131

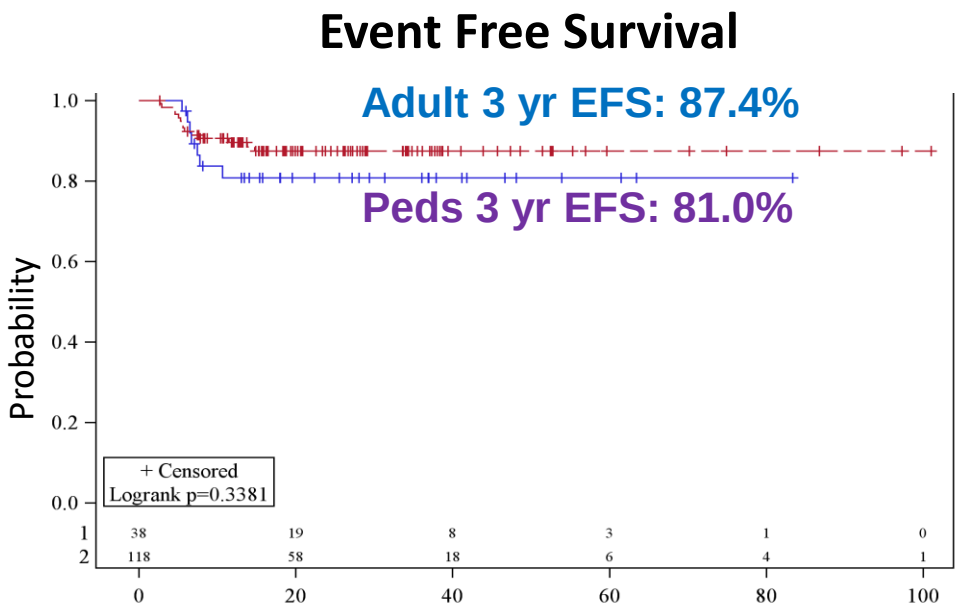
Roth et al. BJH 2017

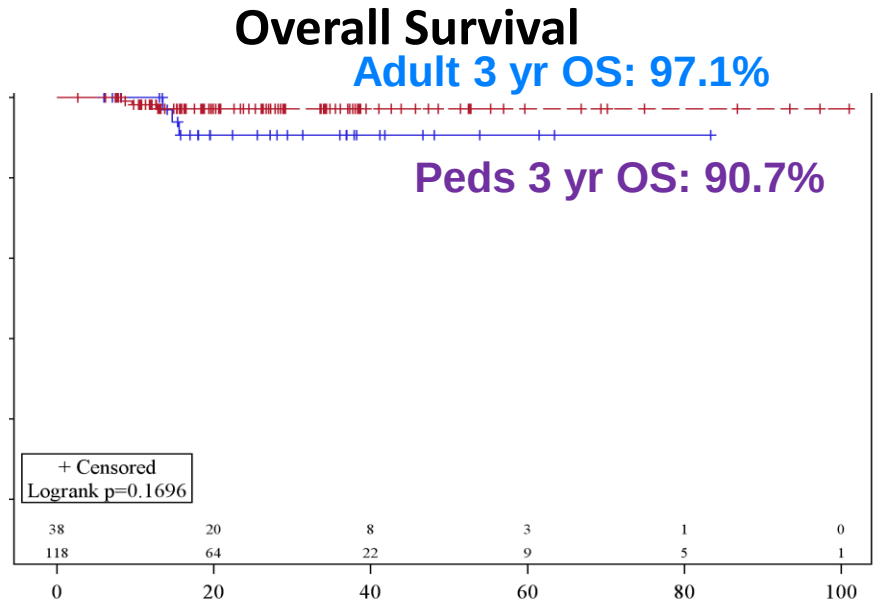
Patient Characteristics

		Total Cohort n=156	Pediatrics (age <21) n=38	Adult (age ≥21) n=118	p value peds vs. adult
Age in yrs: median (range)		31y (9-70)	16y (9-20)	34y (21-70)	**<0.01**
Female sex: number (%)		100 (64.1%)	21 (55.3%)	79 (66.9%)	0.243
ECOG performance status: median (range)		1 (0-4)	N/A	1 (0-4)	N/A
Stage: number (%)	I	26 (16.8%)	1 (2.6%)	25 (21.4%)	N/A*
	II	68 (43.9%)	9 (23.7%)	59 (50.4%)	
	III	30 (19.4%)	23 (60.5%)	7 (6.0%)	
	IV	31 (20.0%)	5 (13.2%)	26 (22.2%)	
B symptoms: number (%)		61 (39.9%)	11 (30.6%)	50 (42.7%)	0.244
Bulky tumor >10cm: number (%)		95 (62.9%)	29 (78.4%)	66 (57.9%)	**0.031**
LDH > ULN: number (%)		125 (82.8%)	30 (85.7%)	95 (81.9%)	0.799
Extranodal disease: number (%)		51 (32.9%)	15 (39.5%)	36 (30.8%)	0.328
Pleural effusion: number (%)		73 (48.0%)	20 (58.8%)	53 (44.9%)	0.176
Pericardial effusion: number (%)		82 (53.9%)	19 (55.9%)	63 (53.4%)	0.847
CD20+ malignant cells: number (%)		146 (98.6%)	30 (100%)	116 (98.3%)	1.000

Roth et al, BJH 2017

DA-R-EPOCH in PMBCL

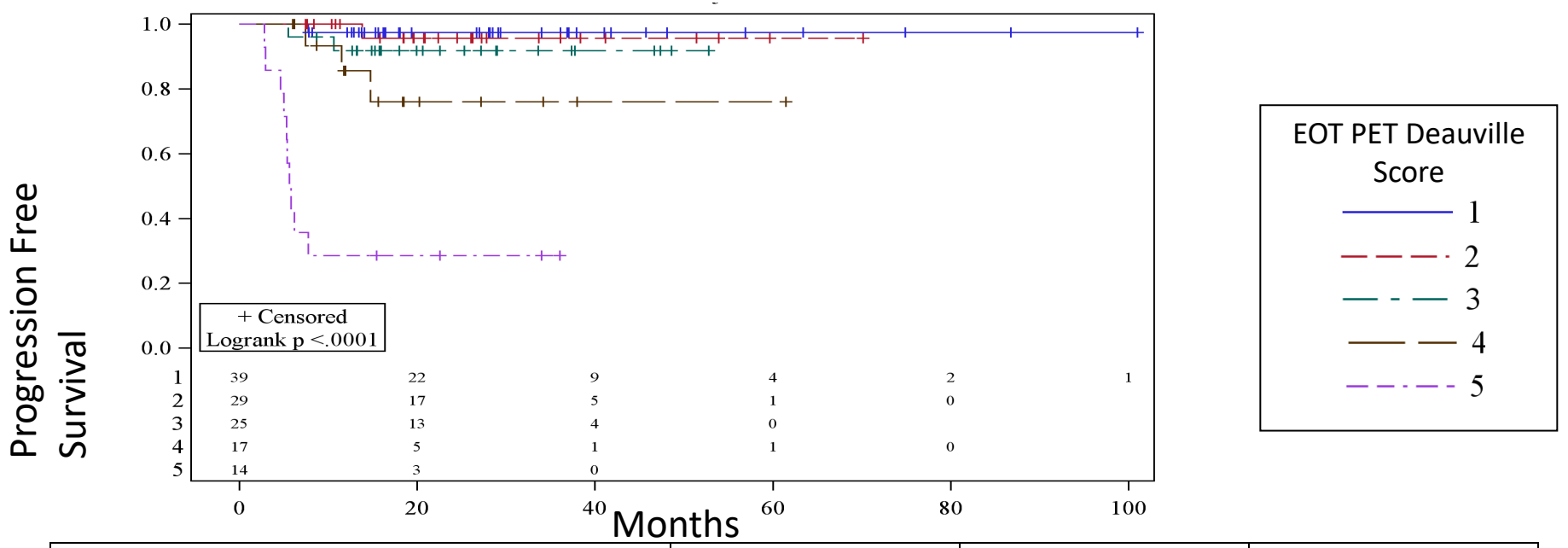




	Total Cohort n=156	Pediatrics (age<21) n=38	Adult (age ≥ 21) n=118	P value for peds vs. adult
3 yr EFS (95% CI)	85.9 (80.3-91.5)	81.0 (68.3-93.7)	87.4 (81.2-93.6)	0.338
3 yr OS (95% CI)	95.4 (91.8-99.0)	90.7 (80.6-100.0)	97.1 (94.0-100.0)	0.170
Follow up in mo: Median (range)	22.6 (2.1-101.0)	24.0 (6.0-83.3)	22.6 (2.7-101.0)	0.780

Roth et al, BJH 2017

Outcome by end of therapy FDG-PET

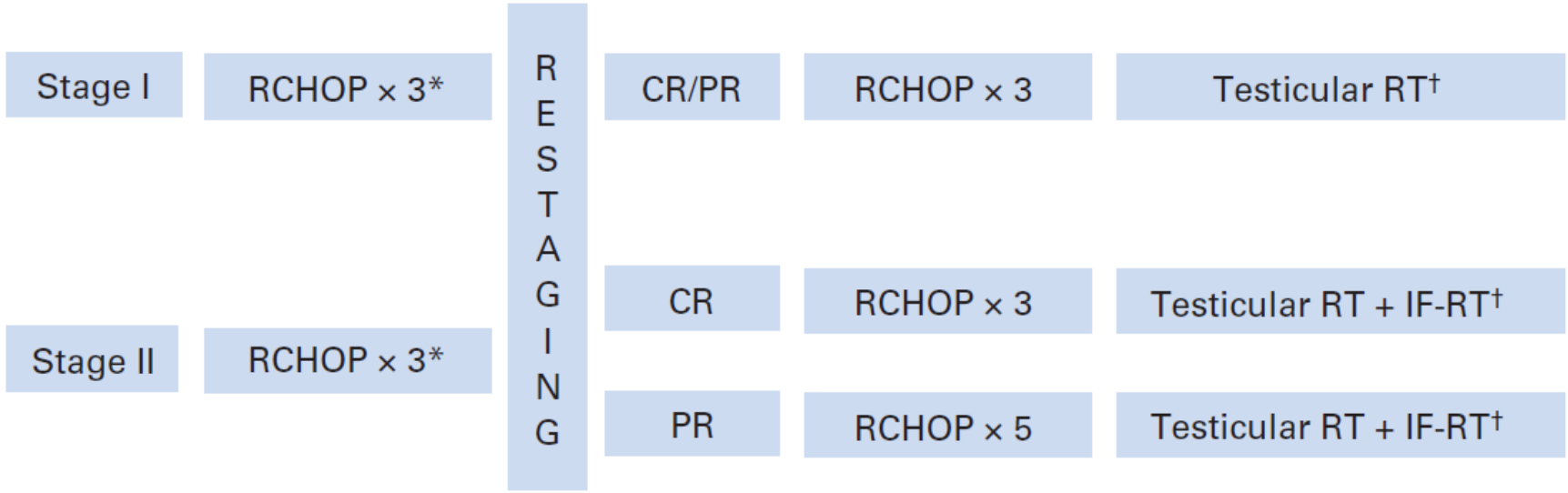


		Total Cohort n=156	EFS	OS
Patients evaluated by PET or PET/CT at end of therapy:		149 (96.1%)		
Deauville score : number (%)	≤3	94 (75.2%)	95.4%	96.2%
	4	17 (13.6%)	75.4%	100%
	5	14 (11.2%)	28.6%	74.1%

Roth et al, BJH 2017

Approach to testicular DLBCL

IELSG10 – 53 patients

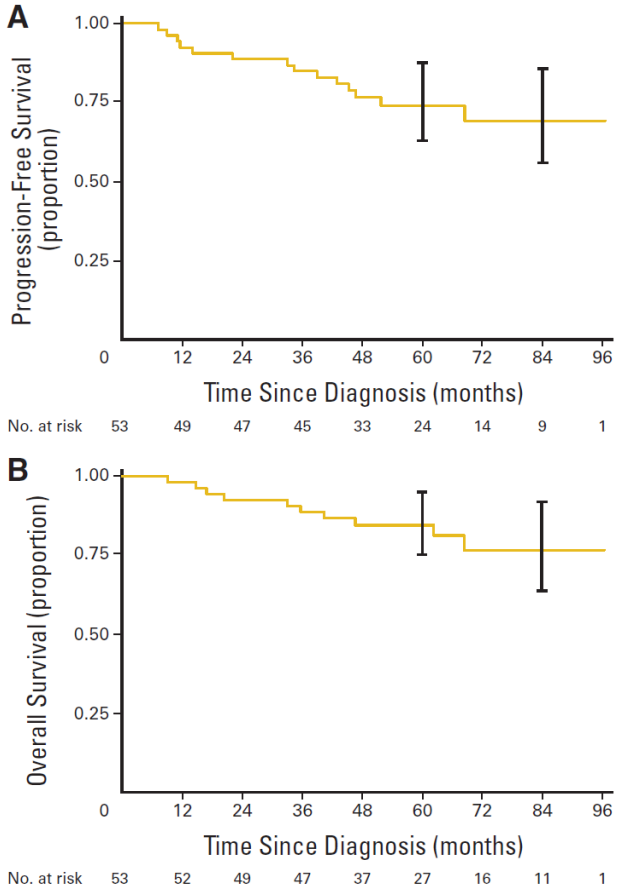


+ 4 doses IT MTX

Vitolo et al, JCO 2011

Approach to testicular DLBCL

IELSG10 – 53 patients



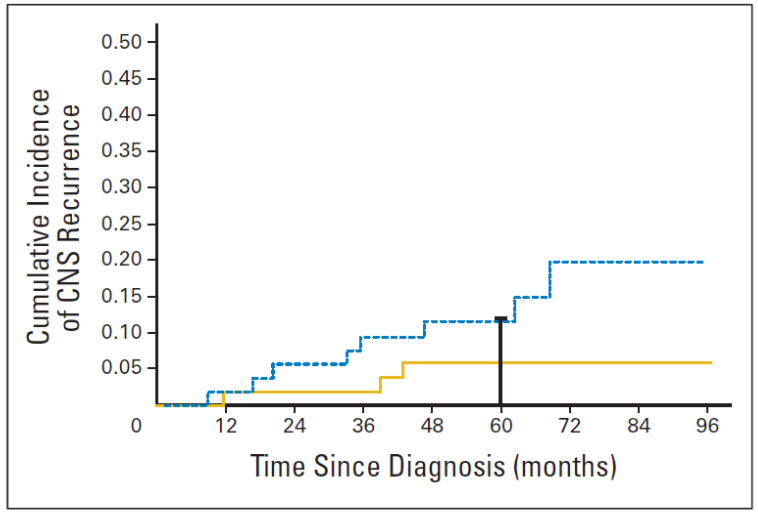


Fig 4. Cumulative incidence of CNS recurrence (solid gold line) and cumulative mortality without CNS involvement (dashed blue line); 5-year CNS cumulative incidence, 5.9% (95% CI, 0% to 12%). Vertical bar represents 95% CI.

Vitolo et al, JCO 2011

Approach to limited stage DLBCL

S0014 – R-CHOP x 3 + IFRT

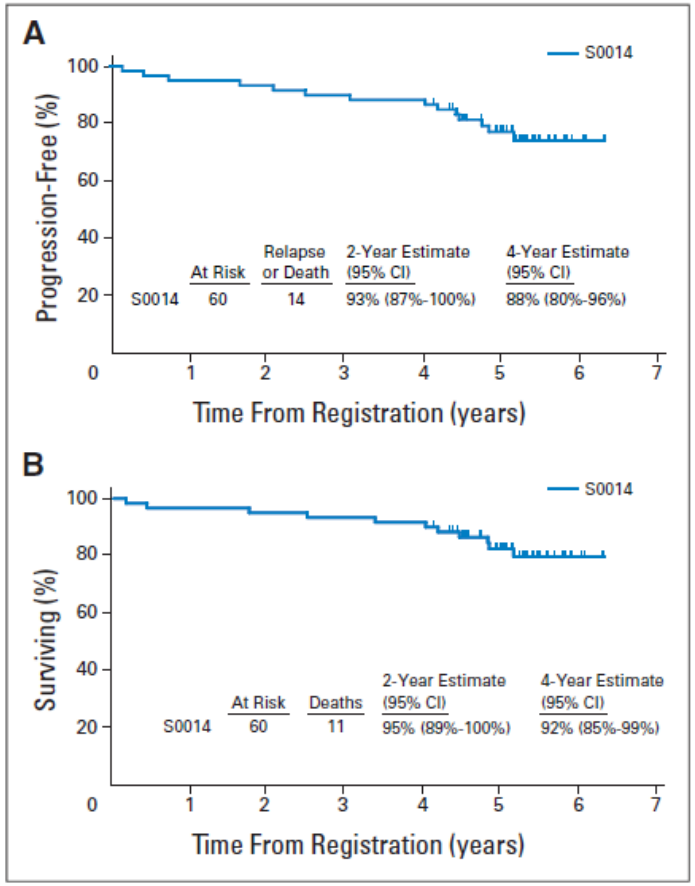
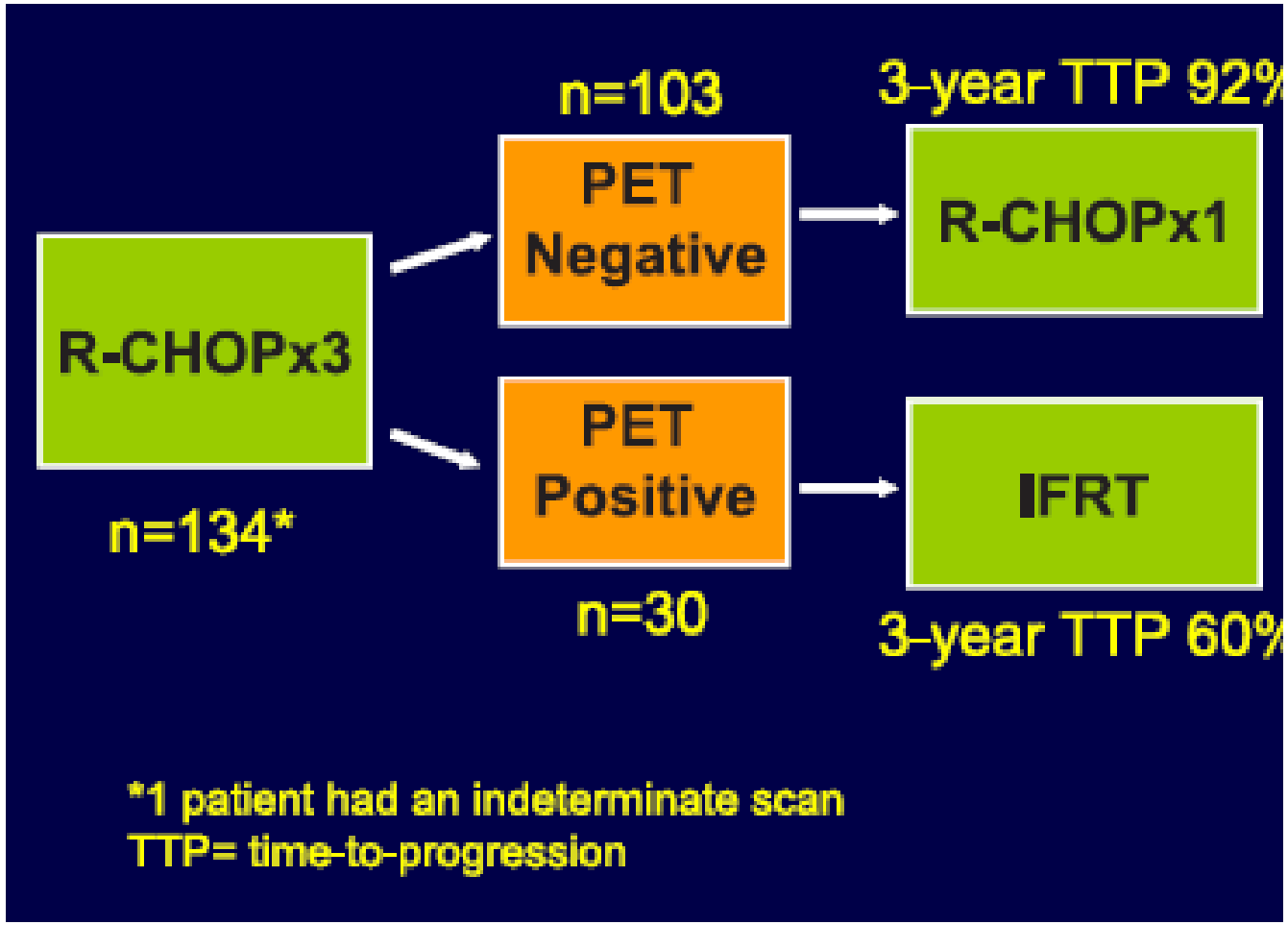


Fig 1. (A) Progression-free and (B) overall survival of 60 eligible patients enrolled in a Southwest Oncology Group (SWOG) trial of three cycles of R-CHOP followed by involved-field radiation therapy. R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone.

Persky et al, JCO 2008

Approach to limited stage DLBCL

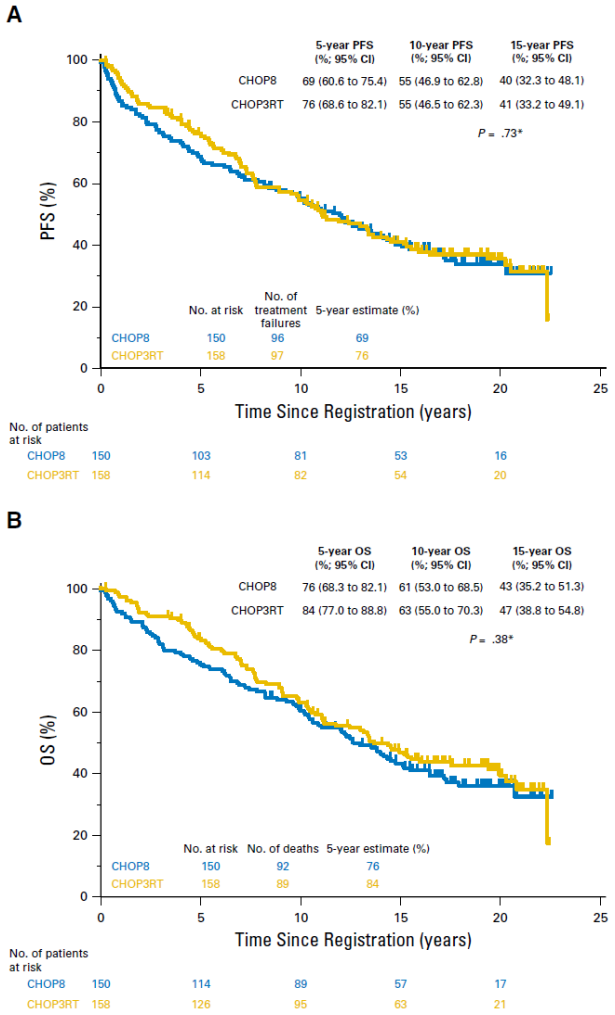
Is RT needed?



Sehn, Cancer Journal, 2012

Long term F/U limited stage DLBCL

S8736 – CHOP x 3 + IFRT vs CHOP x 8



Stephens et al, JCO 2016

Weill Cornell Medicine NewYork-Presbyterian

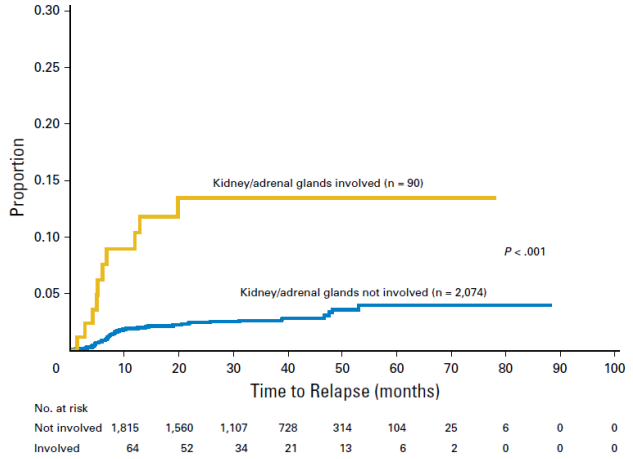
Who is at risk for CNS involvement in DLBCL?

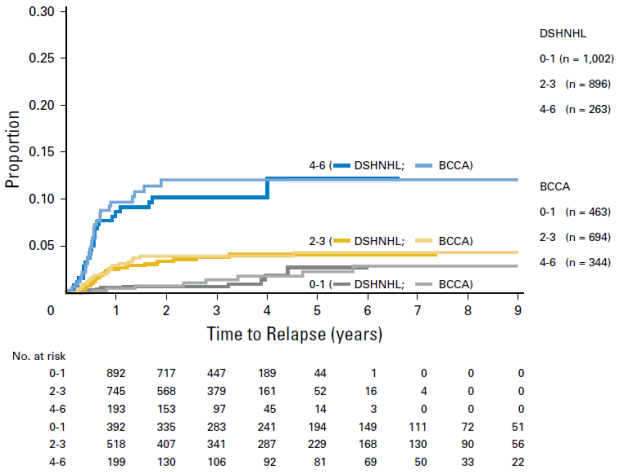
CNS-IPI

Table 2. Factors Defining the CNS International Prognostic Index: Results of Multivariable Analysis

Factor	Hazard Ratio	95% CI	*P*
Kidney and/or adrenal glands involved	2.8	1.3 to 5.8	.006
Age > 60 years	2.5	1.3 to 4.5	.001
LDH > normal	2.4	1.3 to 4.5	.005
ECOG PS > 1	2.2	1.3 to 3.9	.006
Stage III/IV disease	2.0	1.0 to 3.8	.039
Extranodal involvement > 1	1.0	0.5 to 1.8	.935

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase.





Schmitz et al, JCO 2016

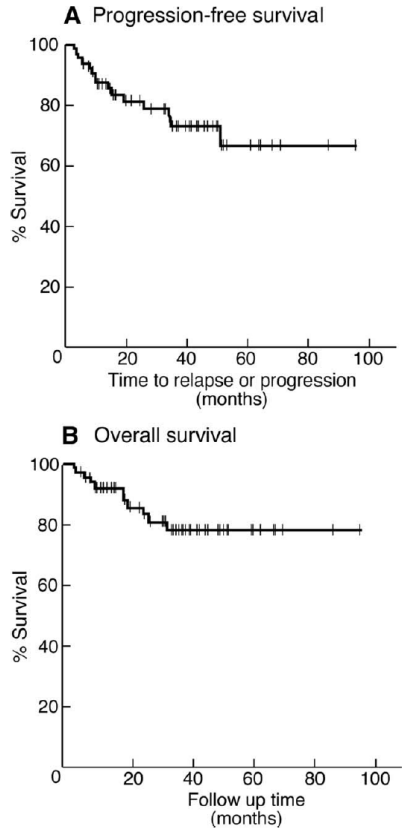
What CNS prophylaxis or treatment do I use in high risk patients?

R-CHOP + d14 MTX 3.5 g/m2 x 3-4 cycles

Retrospective analysis
65 “high risk” patients
2 CNS recurrences

CNS Risk Factor	No.	%
>1 extranodal site	40	62
>1 extranodal site and elevated LDH	30	46
Hollender score of 4-5	11	17
High-risk sites		
Bone marrow	14	22
Testis	5	8
Paranasal sinus	6	9
Orbit	9	14
Breast	1	2
Renal/adrenal	9	14
Liver	8	12
Epidural disease	14	22

CNS indicates central nervous system; LDH, lactate dehydrogenase.



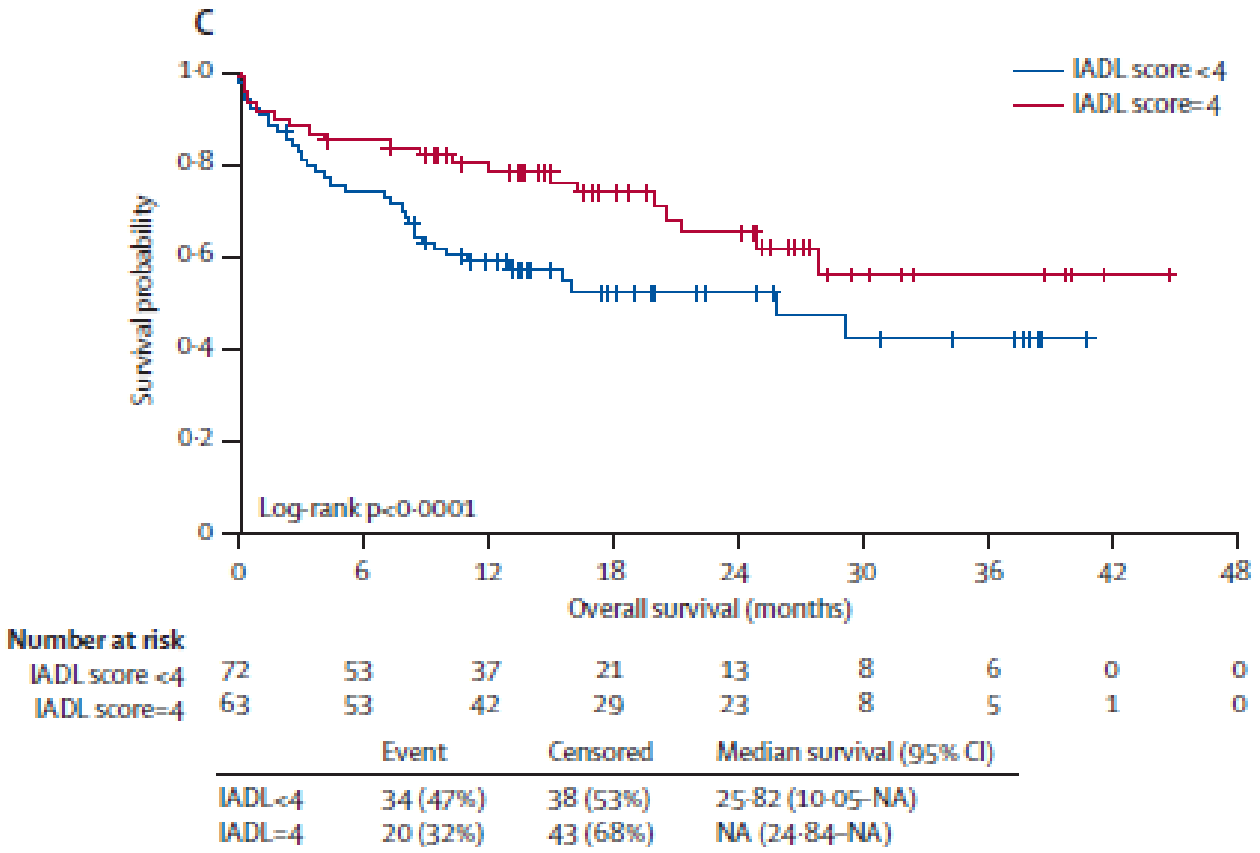
Abramson et al, Cancer 2010

R-mini CHOP for age 80 and over

- **Rituximab 375 mg/m2 day 1**
- **Cyclophosphamide 400 mg/m2 day 1**
- **Doxorubicin 25 mg/m2 day 1**
- **Vincristine 1 mg day 1**
- **Prednisone 40 mg/m2 days 1-5**

Peyrade et al: Lancet Oncol 12: 460-68, 2011

R-mini CHOP for age 80 and over



	Event	Censored	Median survival (95% CI)
IADL<4	34 (47%)	38 (53%)	25·82 (10·05–NA)
IADL=4	20 (32%)	43 (68%)	NA (24·84–NA)

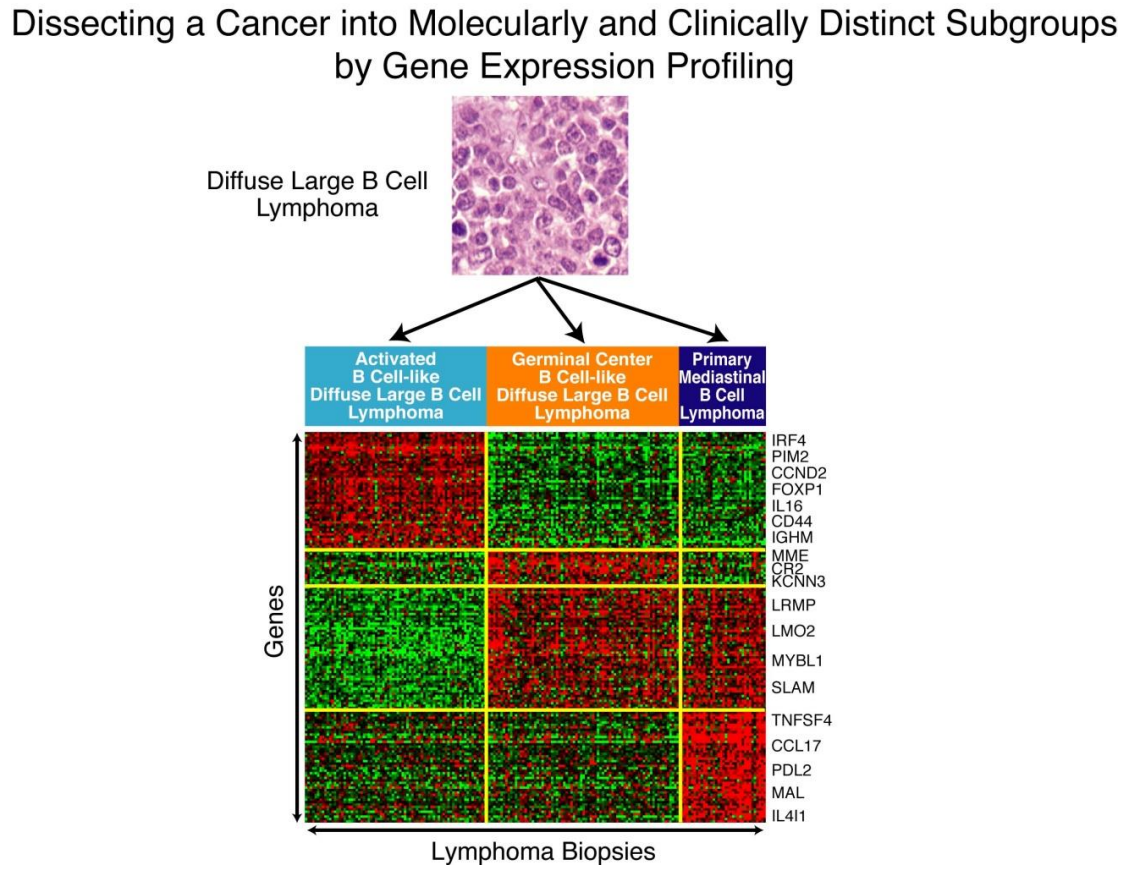
Peyrade et al: Lancet Oncol 12: 460-68, 2011

What about new approaches in DLBCL?

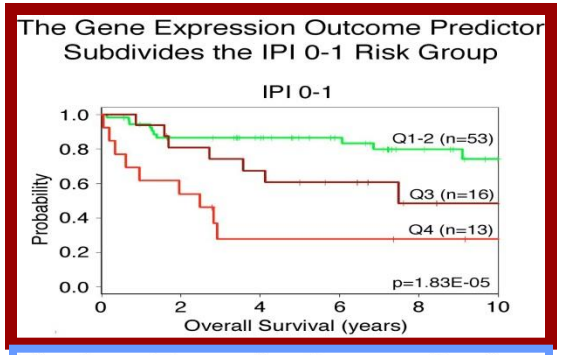
- **Strategies under investigation independent of cell of origin**

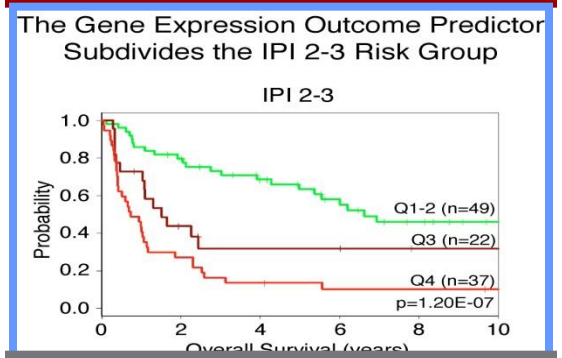
- **Strategies targeting specific cell of origin subtype**

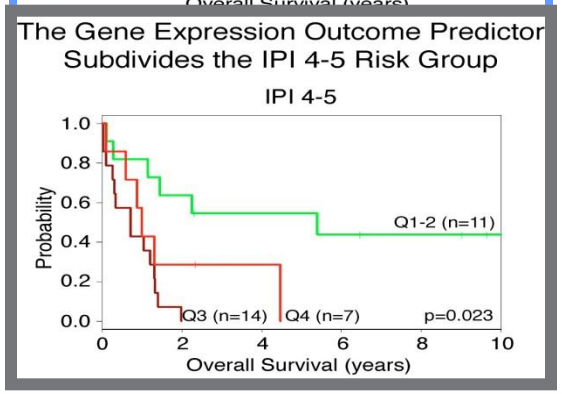
Germinal Center vs Activated B Cell DLBCL



Rosenwald A et al. N Engl J Med. 2002;346:1937-1947



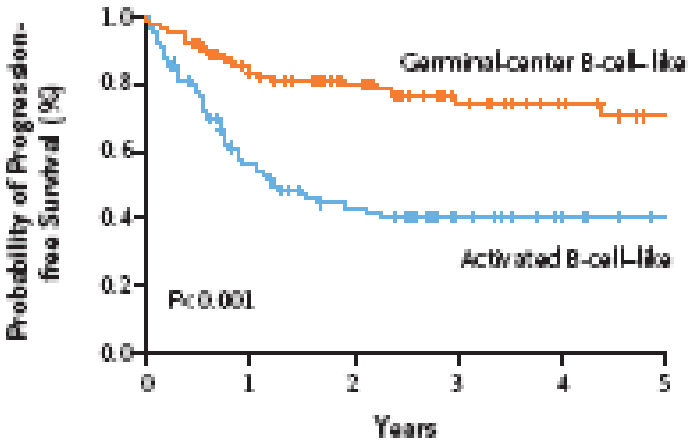




IHC surrogate (Hans) - CD10, bcl-6, MUM-1
GCB vs "non-GCB"

Outcome by GCB vs ABC gene signatures in DLBCL
N=233 patients treated with R-CHOP

PFS



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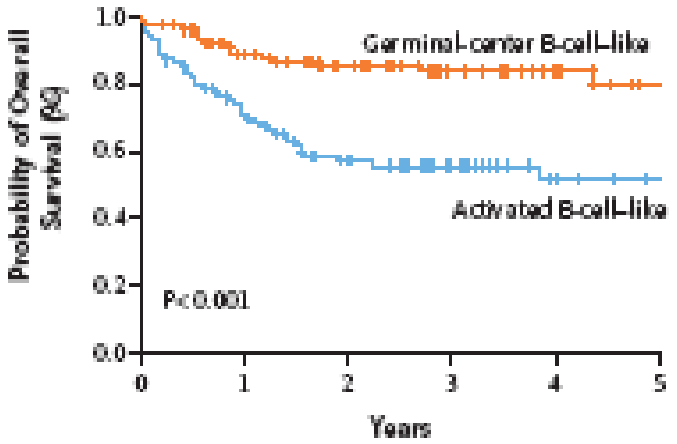


No. at Risk												
Germinal-center B-cell–like	107	82	61	39	27	15	101	74	56	35	24	14
Activated B-cell–like	93	60	38	23	11	6	90	45	30	17	10	5

Lenz G, et al, NEJM 2008

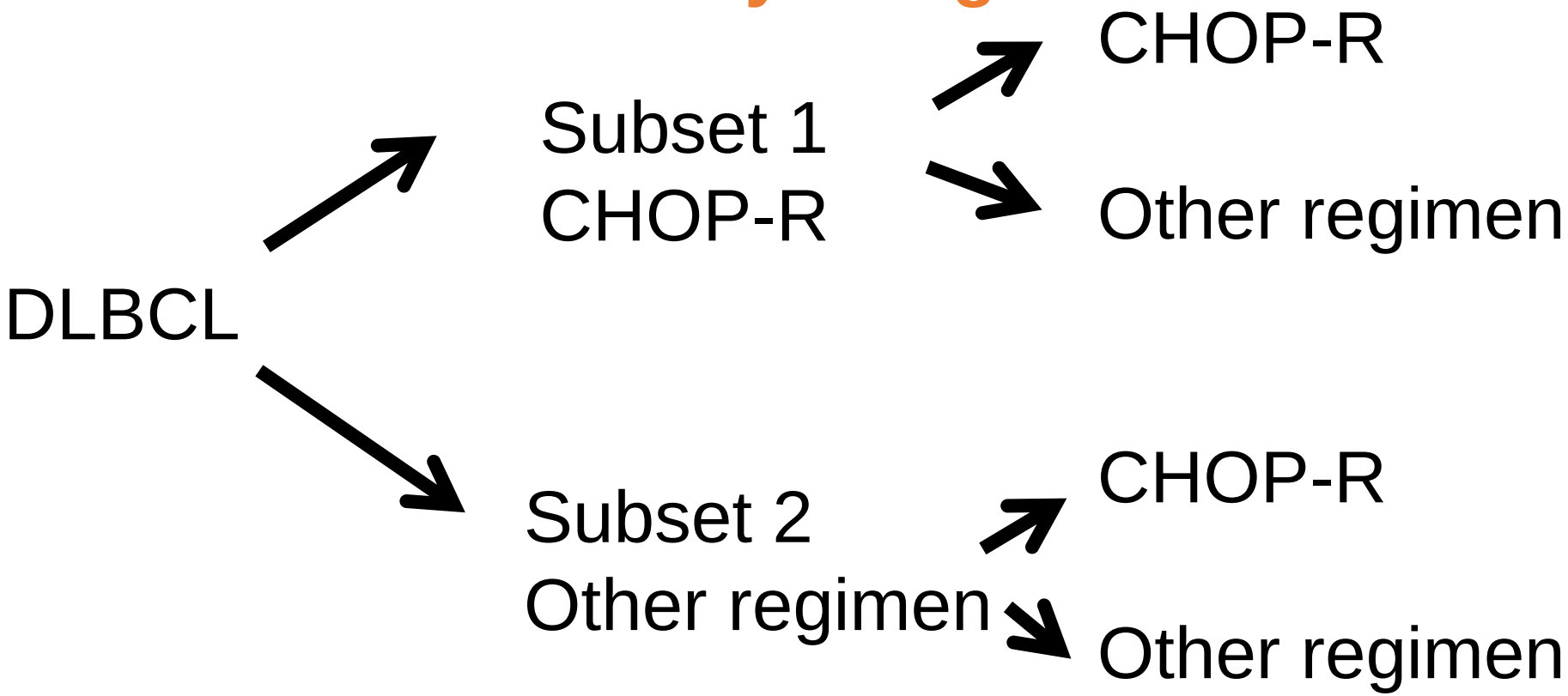
Oncogenic mechanisms and potential therapeutic targets in GCB and ABC DLBCLs

DLBCL subtype	Cell of origin	Oncogenic mechanisms	Potential targets
GCB	Germinal centre B-cell	*BCL2* translocation* *EZH2* mutations‡ *PTEN* deletions§ Loss of PTEN expression	BCL6 EZH2 PI3K/Akt
ABC	Post-germinal centre B-cell	NF-κB activation‖ *CARD11* mutations *MYD88* mutations *CD79B* mutations *A20* deletions	BCR CBM complex IRAK-4 JAK–STAT

Roschewski M. et al. *Nat. Rev. Clin. 2013;*11:12-23.

Upfront DLBCL – Novel agent/regimen in specific clinical or molecular patient subsets

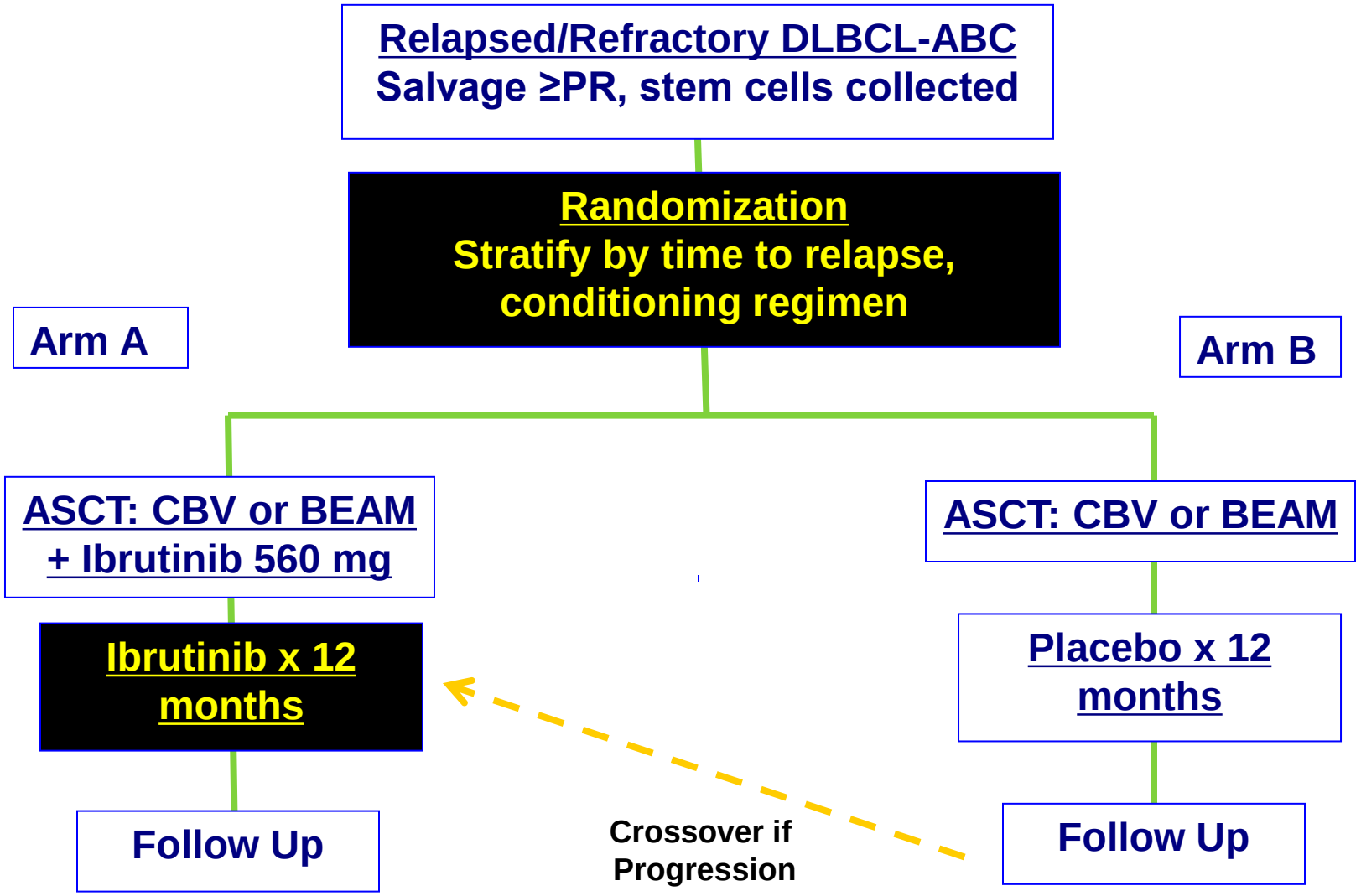
Study design



Agents under evaluation based on cell of origin

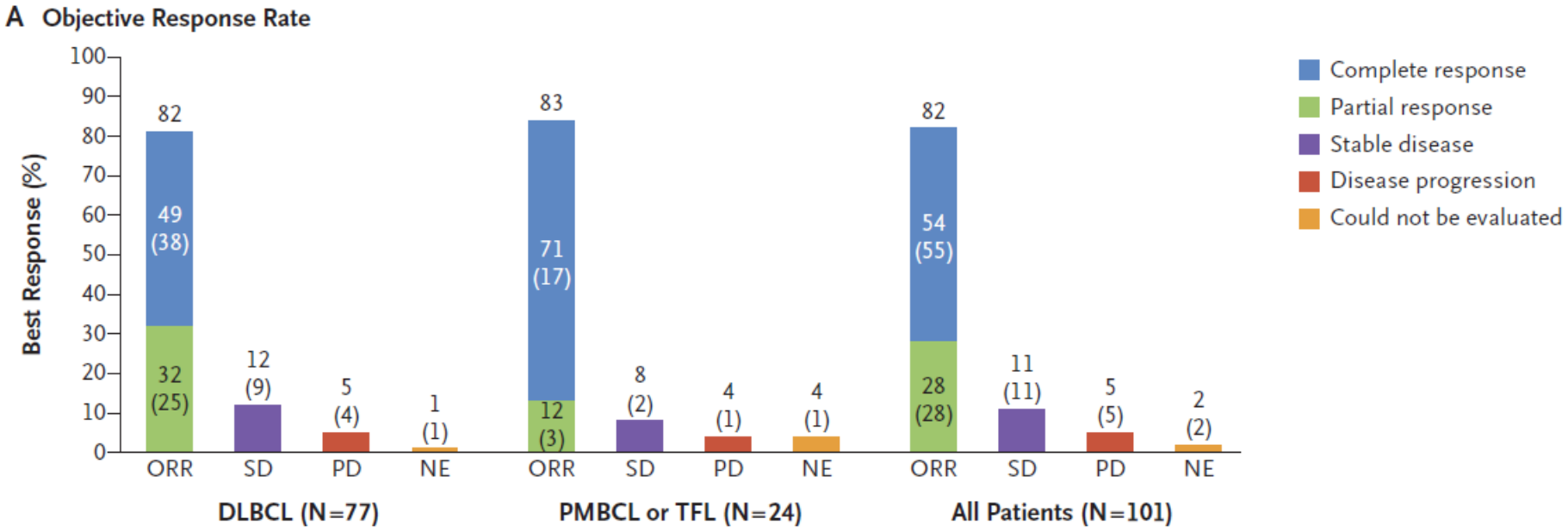
- **Bortezomib**
- **Ibrutinib**
- **Lenalidomide**

Alliance 51301 Study Schema



Axicabtagene Ciloleucel CAR T-Cell in refractory DLBCL

111 enrolled, 101 received drug



Neelapu et al; NEJM 377;26:2531-44, 2017

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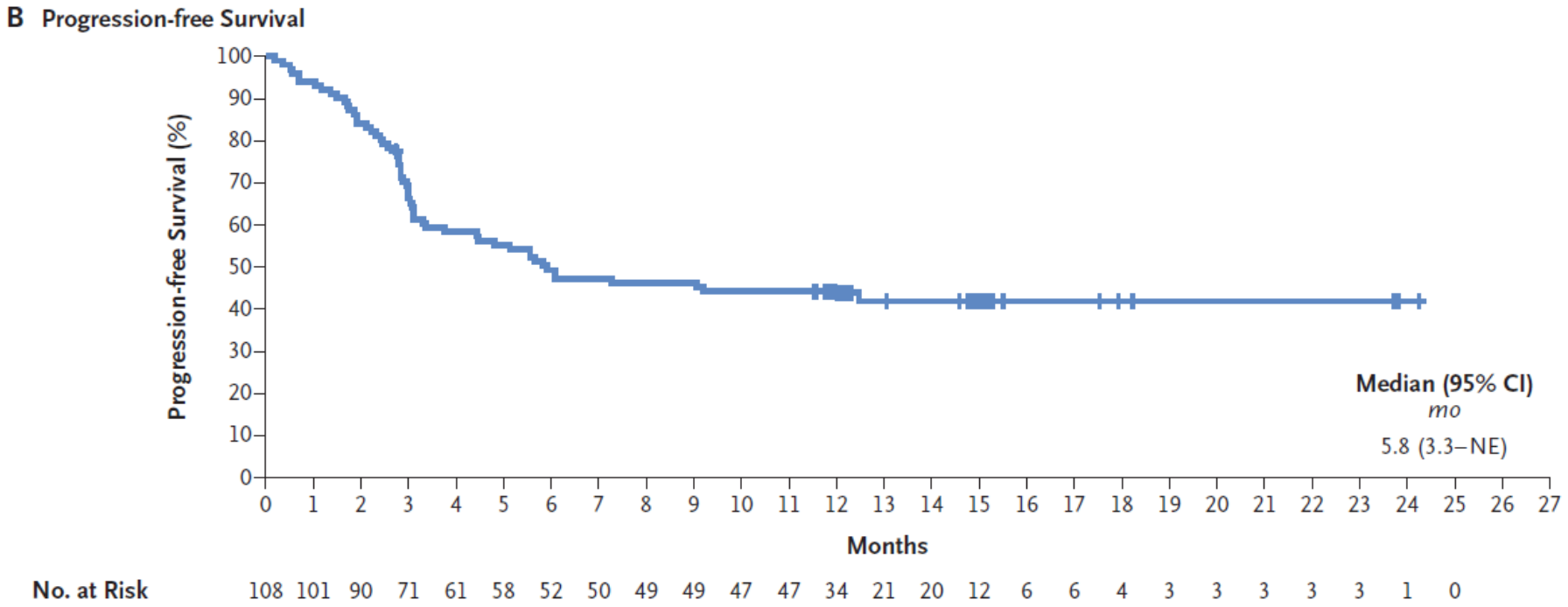


Neelapu et al; NEJM 377;26:2531-44, 2017

Axicabtagene Ciloleucel CAR T-Cell in refractory DLBCL

Event	Any Grade	Grade 1 or 2	Grade ≥3
		number of patients (percent)	
Neurologic event			
Any	65 (64)	37 (37)	28 (28)
Encephalopathy	34 (34)	13 (13)	21 (21)
Confusional state	29 (29)	20 (20)	9 (9)
Tremor	29 (29)	28 (28)	1 (1)
Aphasia	18 (18)	11 (11)	7 (7)
Somnolence	15 (15)	8 (8)	7 (7)
Agitation	9 (9)	5 (5)	4 (4)
Memory impairment	7 (7)	6 (6)	1 (1)
Mental-status change	6 (6)	4 (4)	2 (2)
Cytokine release syndrome			
Any	94 (93)	81 (80)	13 (13)
Pyrexia	77 (76)	66 (65)	11 (11)
Hypotension	41 (41)	32 (32)	9 (9)
Hypoxia	22 (22)	13 (13)	9 (9)
Tachycardia	21 (21)	20 (20)	1 (1)

Neelapu et al; NEJM 377;26:2531-44, 2017

CTCL: Background

- **Chronic T-cell lymphoma primarily involving skin**
- **Mycosis fungoides (MF) and primary cutaneous anaplastic large cell lymphoma (pcALCL) are the most common CD30 expressing CTCL**
- **Brentuximab vedotin, a CD30 targeting antibody-drug-conjugate, has clinical activity in CTCL**
  - **Duvic et al. ORR, MF 54%, pcALCL 100%;**
  - **Kim et al. ORR, MF/Sézary syndrome 70%**

Swerdlow SH, et al. Blood 2016;127:2375–90 Willemze R, et al. Ann Oncol 2013;24 Suppl 6:vi149–54

Jawed SI, et al. J Am Acad Dermatol 2014;70:223e1–17 Duvic M, et al. J Clin Oncol 2015;33:3759–65

Kim YH, et al. J Clin Oncol 2015;33:3750–8

Brentuximab Vedotin vs Investigator Choice in CD30+ CTCL (Alcanza study)

	Brentuximab vedotin (n=64)	Physician's choice of methotrexate or bexarotene (n=64)	Overall (N=128)
Age (years)	62 (51–70)	59 (48–67)	60 (48–69)
Sex			
Male	33 (52%)	37 (58%)	70 (55%)
Female	31 (48%)	27 (42%)	58 (45%)
Race			
White	56 (88%)	53 (83%)	109 (85%)
Other	5 (8%)	10 (16%)	15 (12%)
Not reported	3 (5%)	1 (2%)	4 (3%)
ECOG PS			
0	43 (67%)	46 (72%)	89 (70%)
1	18 (28%)	16 (25%)	34 (27%)
2	3 (5%)	2 (3%)	5 (4%)
Median CD30 expression*	32·5% (12·5–67·5)	31·3% (12·0–47·5)	31·3% (12·5–60·0)
Time since initial diagnosis (months)	42·2 (12·8–87·4)	37·0 (12·3–102·7)	40·9 (12·7–96·8)
Time since progression on last therapy† (months)	2·4 (1·4–7·9)	1·3 (0·9–3·7)	1·9 (1·1–3·8)
Lines of previous therapy			
Total	4·0 (2·0–7·0)	3·5 (2·0–5·5)	4·0 (2·0–6·0)
Skin-directed	1·0 (1·0–2·0)	1·0 (1·0–2·0)	1·0 (1·0–2·0)
Systemic	2·0 (1·0–4·0)	2·0 (1·0–3·0)	2·0 (1·0–4·0)
Mycosis fungoides	48 (75%)	49 (77%)	97 (76%)

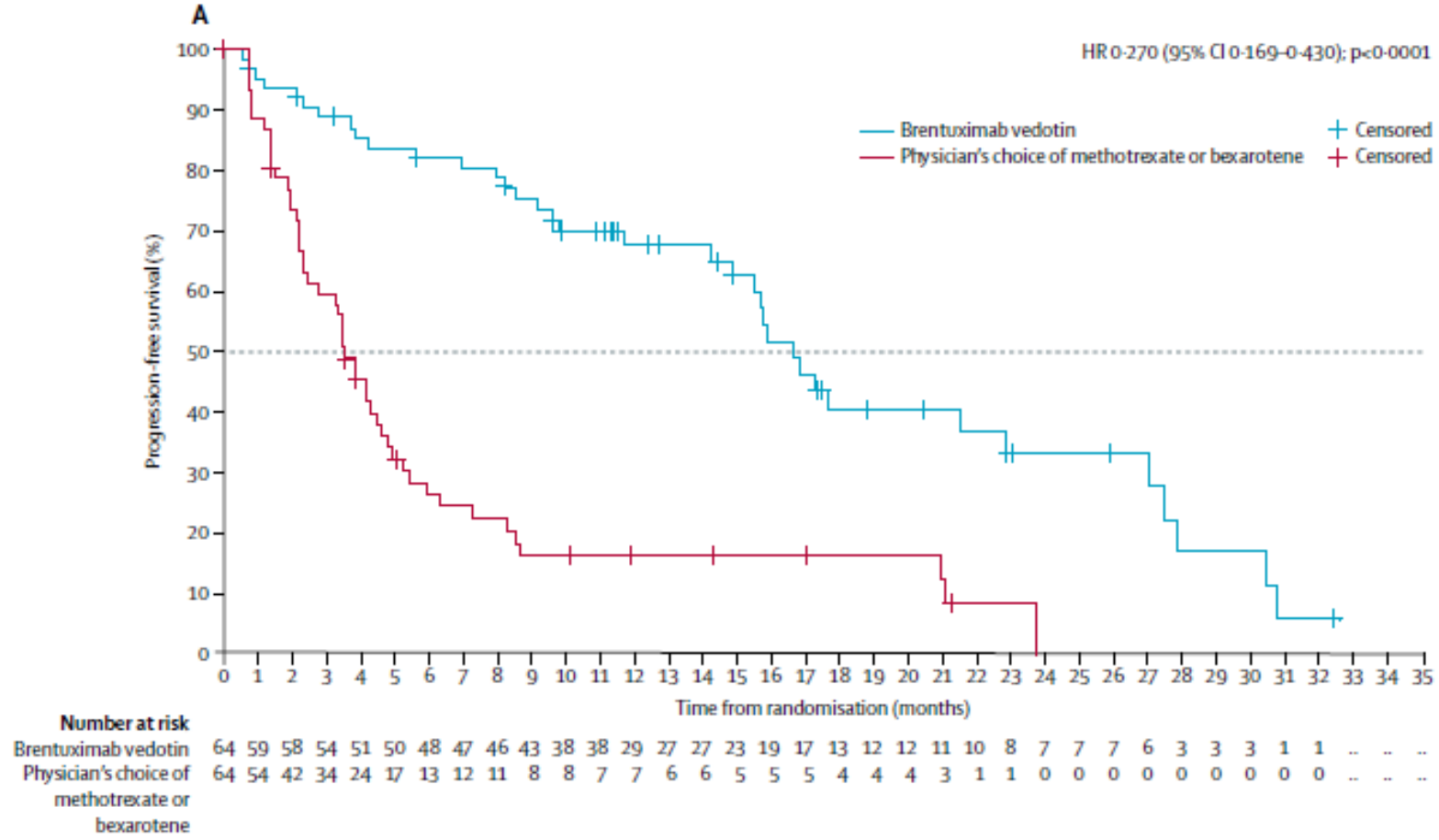
Prince et al; Lancet 390: 555-66, 2017

Brentuximab Vedotin vs Investigator Choice in CD30+ CTCL (Alcanza study)

	Brentuximab vedotin				Physician's choice of methotrexate or bexarotene			
	Total (n=64)	ORR4	ORR	CR	Total (n=64)	ORR4	ORR	CR
ITT population	64 (100%)	36 (56%)*	43 (67%)	10 (16%)	64 (100%)	8 (13%)†	13 (20%)	1 (2%)
Mycosis fungoides	48 (75%)	24 (50%)	31 (65%)	5 (10%)	49 (77%)	5 (10%)	8 (16%)	0
Stage‡§								
IA–IIA	15 (31%)	6 (40%)	8 (53%)	1 (7%)	18 (37%)	4 (22%)	5 (28%)	0
IIB	19 (40%)	12 (63%)	13 (68%)	3 (16%)	19 (39%)	1 (5%)	3 (16%)	0
IIIA–IIIB	4 (8%)	2 (50%)	3 (75%)	0	2 (4%)	0	0	0
IVA	2 (4%)	2 (100%)	2 (100%)	1 (50%)	9 (18%)	0	0	0
IVB	7 (15%)	2 (29%)	4 (57%)	0	0	NA	NA	NA
pcALCL	16 (25%)	12 (75%)	12 (75%)	5 (31%)	15 (23%)	3 (20%)	5 (33%)	1 (7%)

Prince et al; Lancet 390: 555-66, 2017

Brentuximab Vedotin vs Investigator Choice in CD30+ CTCL (Alcanza study)



Prince et al; Lancet 390: 555-66, 2017

Mantle cell lymphoma (10%)

Incurable, median survival 5-10 years

Key focus:

- **More vs less intensive initial therapies**
  - **Bendamustine based rx in older pts standard**
  - **Does SCT improve survival in younger patients?**
  - **Role of MRD?**
- **Development of novel agents and translational studies to understand resistance and advance rational combinations**

MCL “standard” initial treatment options

Observation

R-CHOP

Modified R-HyperCVAD

Bortezomib-R-CAP

R-Bendamustine

Less intensive

vs

R-CHOP/DHAP/ASCT

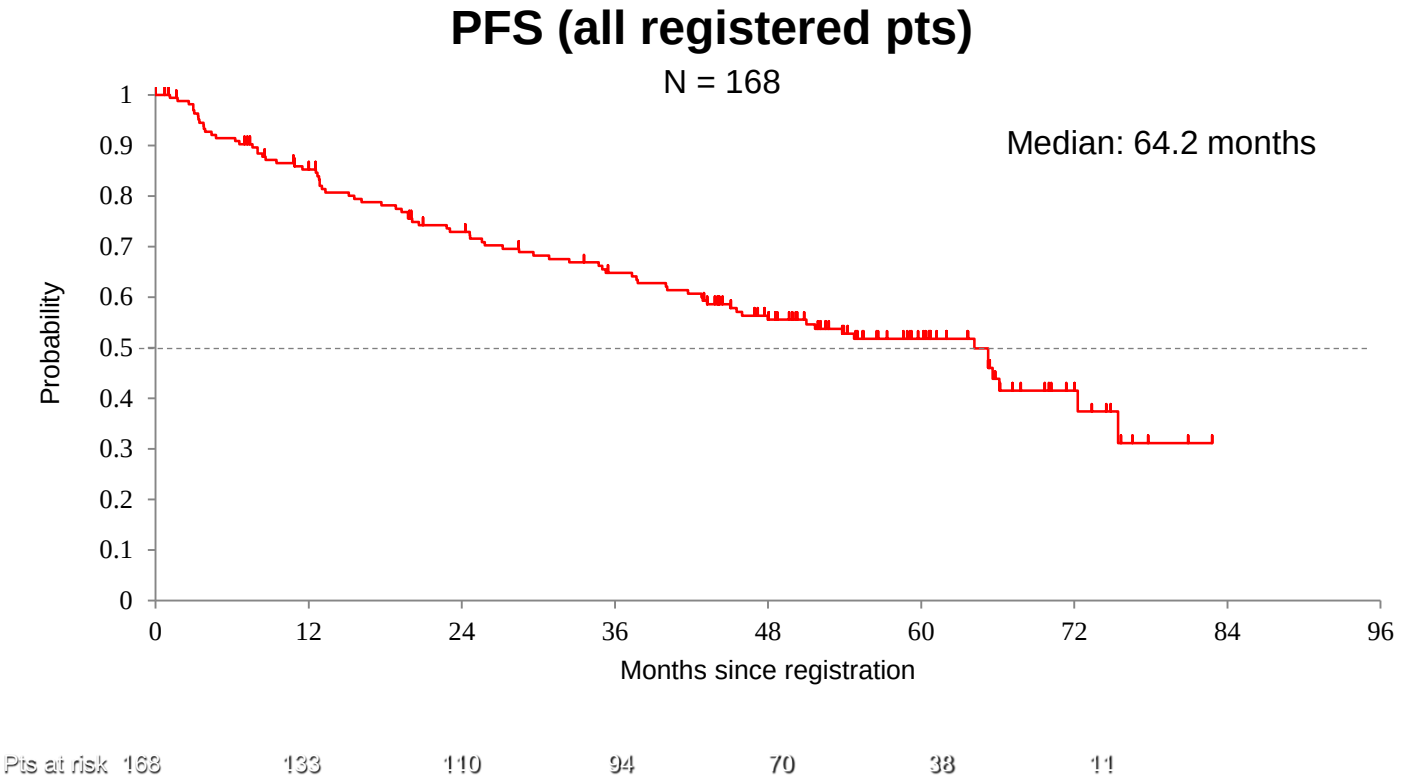
R-HyperCVAD/MTX/Ara-C

R-HyperCVAD/MTX/Ara-C/ASCT

Nordic

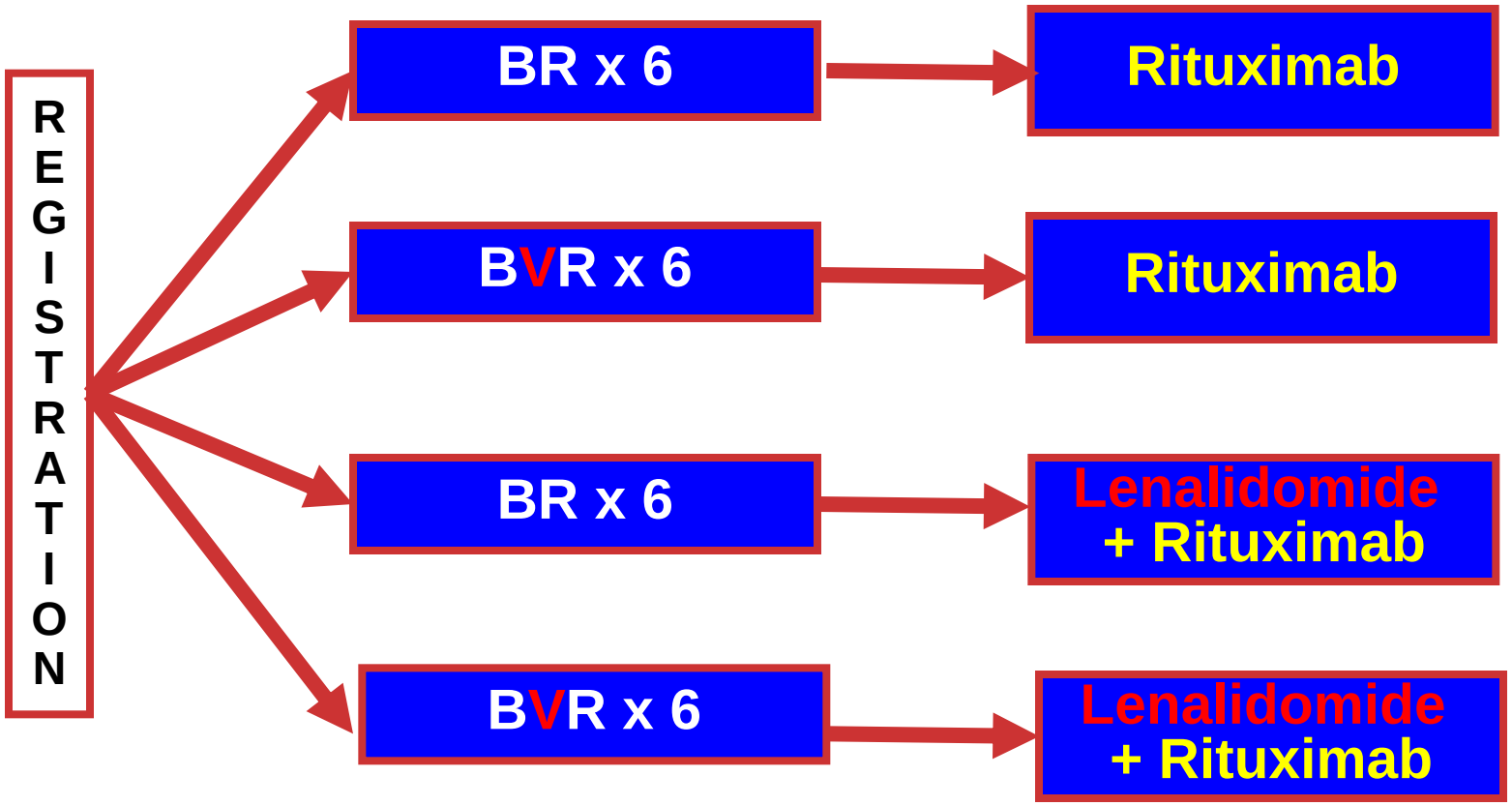
More intensive

Bendamustine + Rituximab (+/- maint R) upfront MCL
Median age 71, 84% MIPI int/high risk

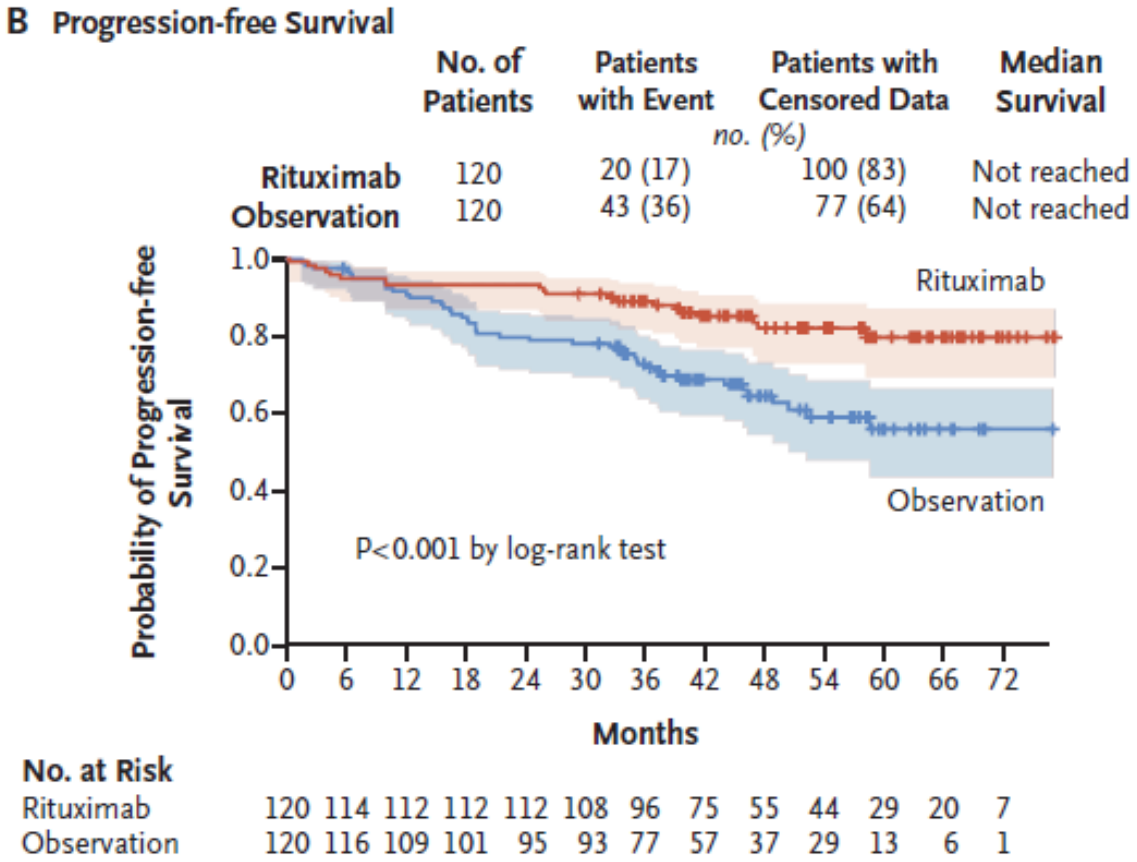


Rummel et al, ASCO 2016

E1411: Randomized Phase 2 Intergroup Trial: Initial Therapy of Mantle Cell Lymphoma

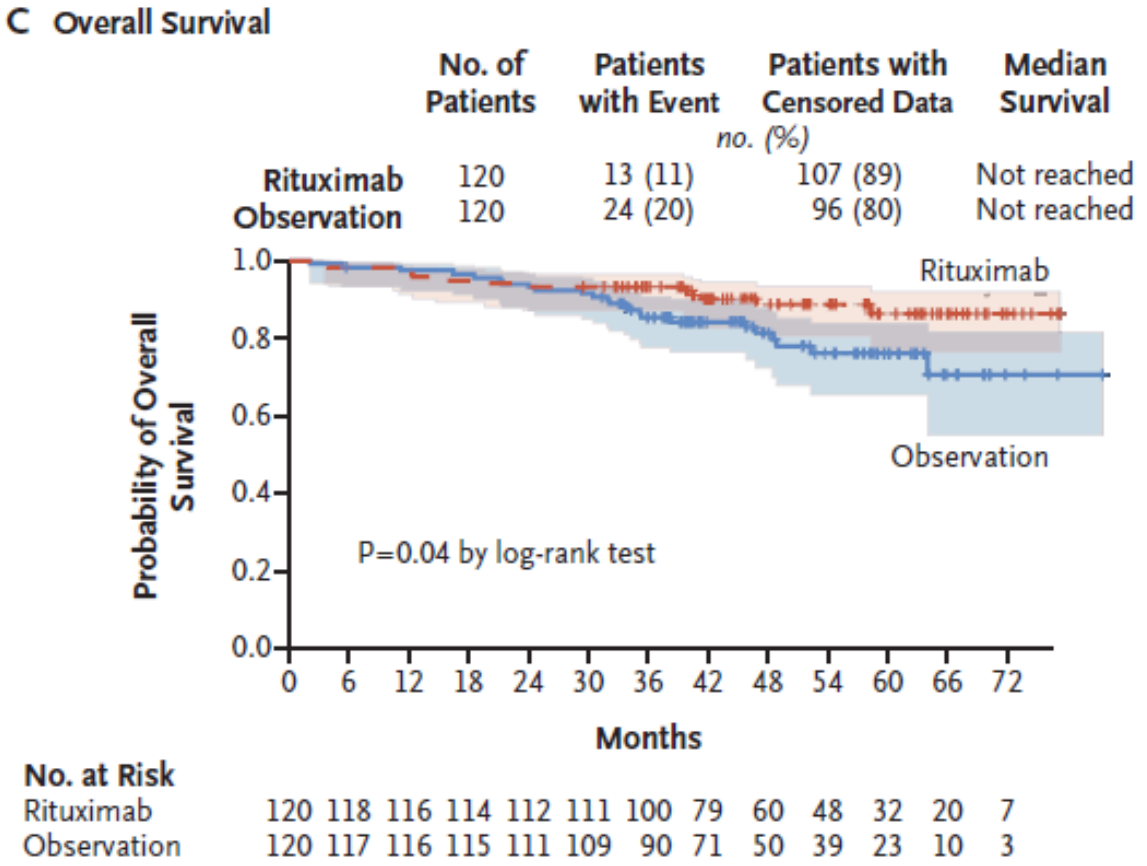


Maintenance Rituximab after AuSCT in Mantle Cell Lymphoma



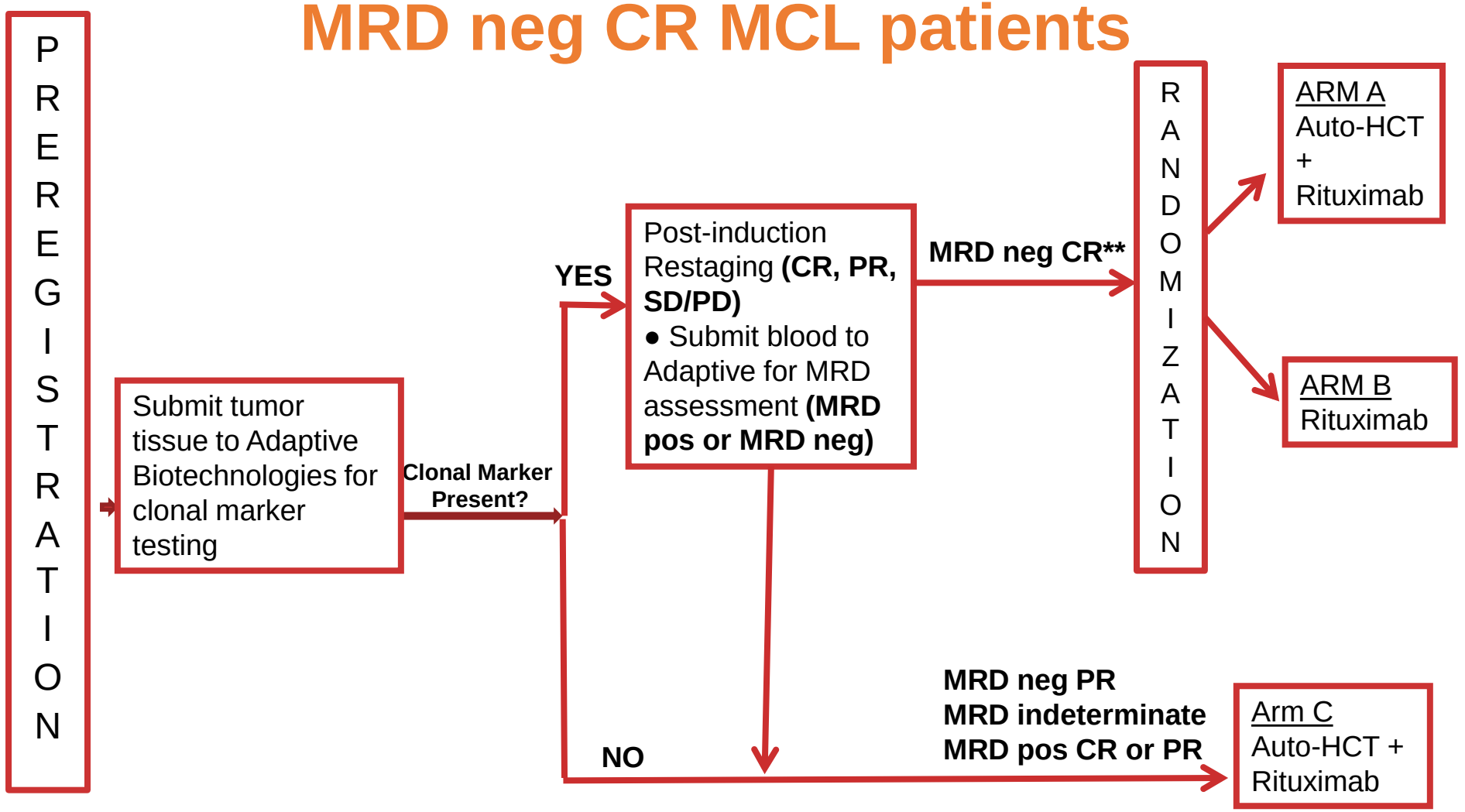
Le Gouill et al; NEJM 377;13:1250-60, 2017

Maintenance Rituximab after AuSCT in Mantle Cell Lymphoma



Le Gouill et al; NEJM 377;13:1250-60, 2017

E4151: Randomized trial of SCT/R vs R in MRD neg CR MCL patients



Acalabrutinib in Relapsed/Refractory Mantle Cell Lymphoma

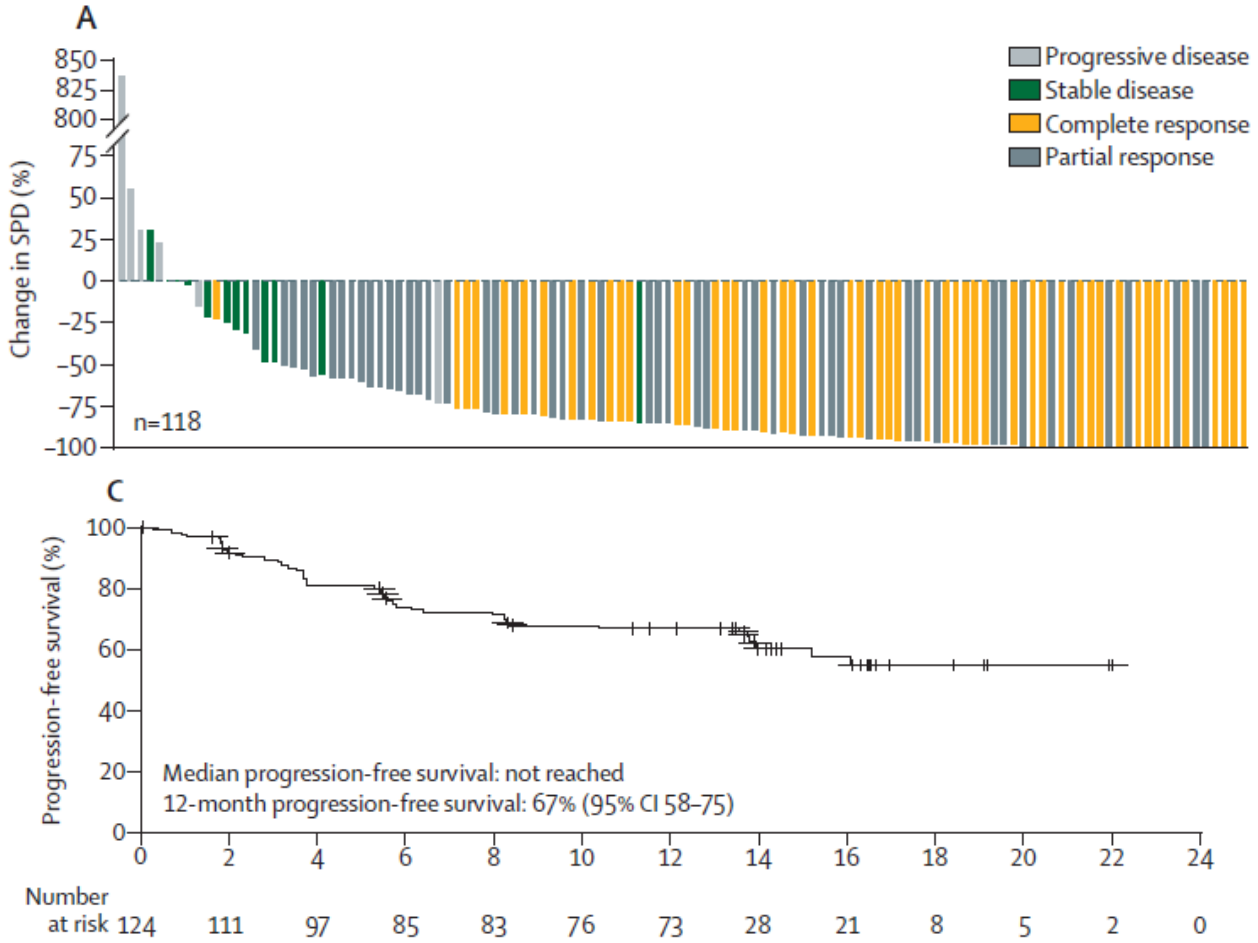
124 pts, median 2 prior rx
81% ORR, 40% CR

	All grades	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5*
Most common events†						
Headache	47 (38%)	30 (24%)	15 (12%)	2 (2%)	0	0
Diarrhoea	38 (31%)	21 (17%)	13 (10%)	4 (3%)	0	0
Fatigue	34 (27%)‡	24 (19%)	8 (6%)	1 (1%)	0	0
Myalgia	26 (21%)	19 (15%)	6 (5%)	1 (1%)	0	0
Cough	24 (19%)	21 (17%)	3 (2%)	0	0	0
Nausea	22 (18%)	12 (10%)	9 (7%)	1 (1%)	0	0
Pyrexia	19 (15%)	14 (11%)	5 (4%)	0	0	0
Most common grade 3 or worse events§						
Anaemia	15 (12%)	1 (1%)	3 (2%)	10 (8%)	1 (1%)	0
Neutropenia	13 (10%)	0	0	6 (5%)	7 (6%)	0
Pneumonia	7 (6%)	0	1 (1%)	6 (5%)	0	0

Data are n (%). *Only one grade 5 event (aortic stenosis) was reported. †Reported in ≥15% of all treated patients. ‡Includes one case of fatigue without grading. §Reported in ≥5% of all treated patients.

Wang et al; Lancet 2017

Acalabrutinib in Relapsed/Refractory Mantle Cell Lymphoma



Wang et al; Lancet 2017

Key take home points for aggressive lymphoma

- **DLBCL**
  - **Modifications to R-CHOP currently based on clinical features, COO/molecular directed rx under evaluation**
  - **CAR-T cell rx available, undergoing further optimization**
- **T cell**
  - **CD30-directed therapy of value**
- **MCL**
  - **Maintenance rituximab, role of MRD-directed therapy**
  - **Novel BTK inhibitors**