AT THE FOREFRONT
UChicago Medicine

Overview of Aggressive Lymphomas

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March 9, 2019

DISCLOSURES

Sonali M. Smith, MD

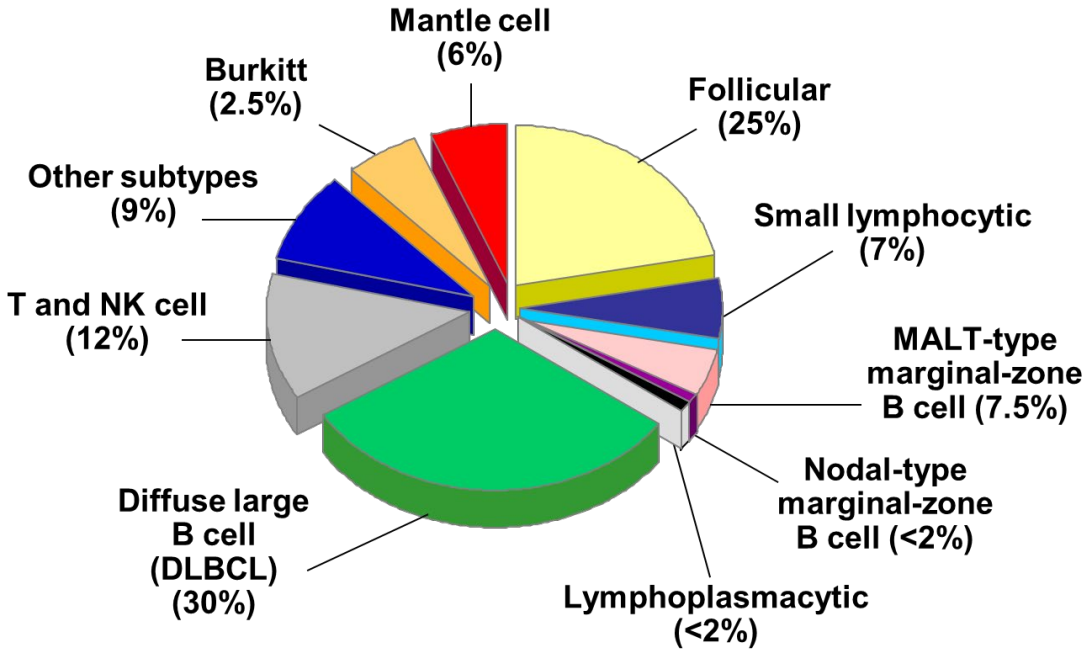
- I have the following relevant financial relationships to disclose:
  - Consultant for: Genentech, Bayer, TGTX, Kite, Seattle Genetics, Gilead
  - Speaker's Bureau for: none
  - Stockholder in: none
  - Honoraria from: none
  - Employee of: none

- • I will discuss the following off label use and/or investigational use in my presentation: lenalidomide, ibrutinib, acalabrutinib, venetoclax. I will disclose when they are being discussed in an off-label manner.

OBJECTIVES

- To discuss the historical and current treatment of diffuse large B-cell lymphoma
- To distinguish “double hit lymphoma” from aggressive lymphomas with “double protein expression”
- To understand risk stratification in diffuse large B-cell lymphoma
- To describe the treatment options for patients with relapsed disease

There are nearly 100 types of lymphoma



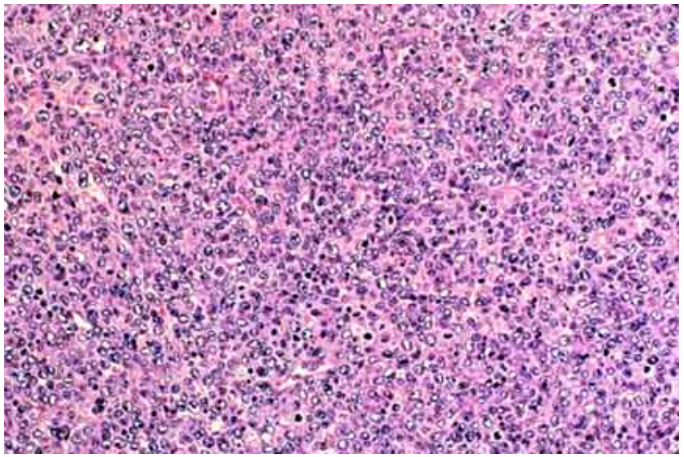
Goals of therapy vary by histology and expected clinical behavior:

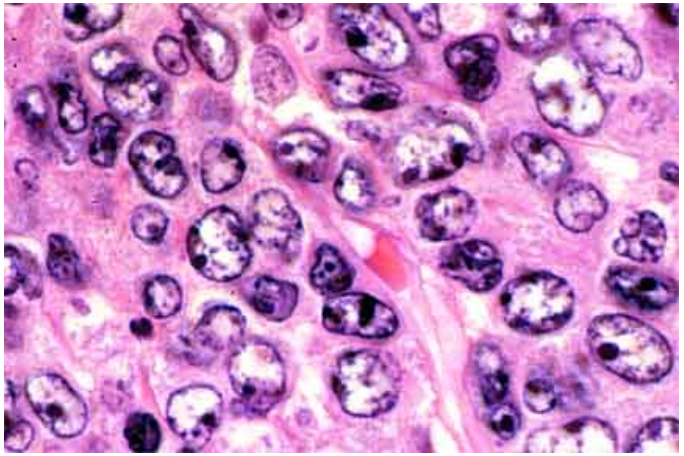
- ❑ **Curative intent**
- ❑ **Palliative intent**

Swerdlow Blood. 2016 May 19;127(20):2375-90. doi: 10.1182/blood-2016-01-643569.PMID: 2698072

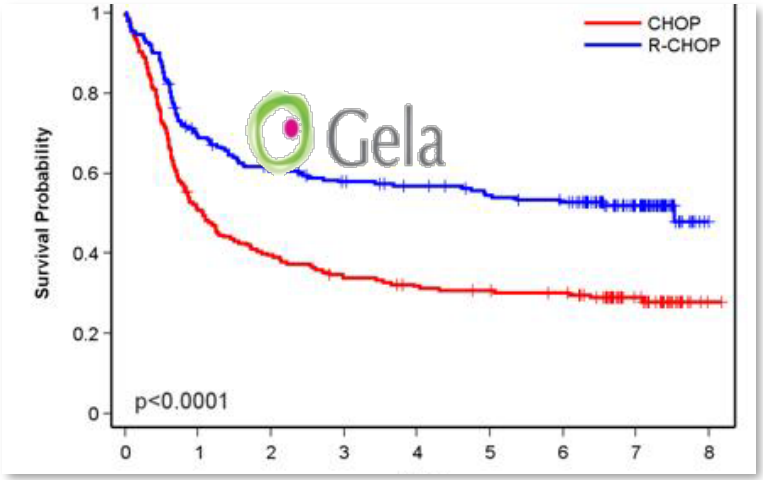
DLBCL

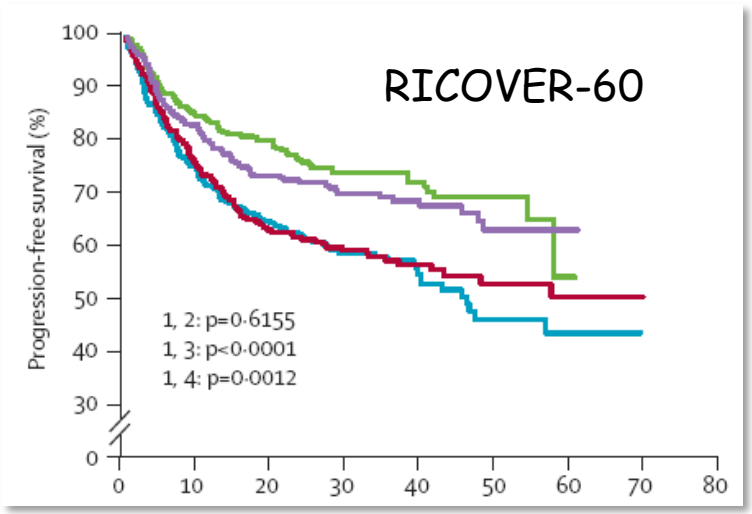
- Most common NHL, peak incidence 6th decade
- Large cells with loss of follicular architecture of node
- May present as extranodal disease (stomach, CNS, testis, skin)
- Median survival, weeks to months if not treated
- Immunophenotype: CD19+, CD20+, CD22+, CD79a+
- Cytogenetics: t(14;18) in 20-30%; 3q27 in 30%
- Curable in 30-90%

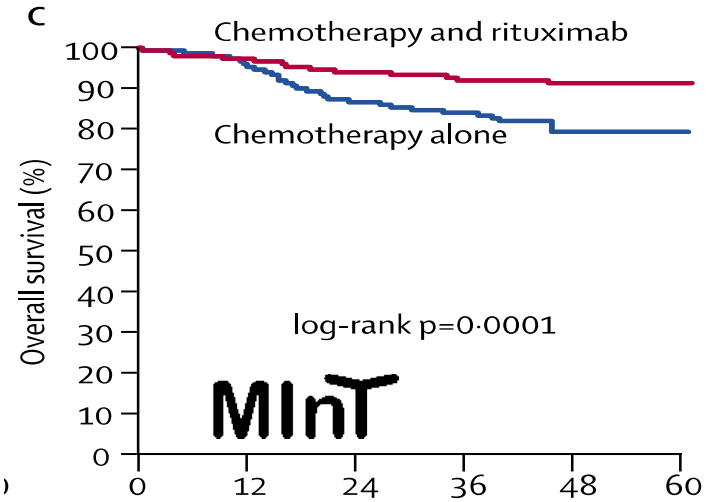


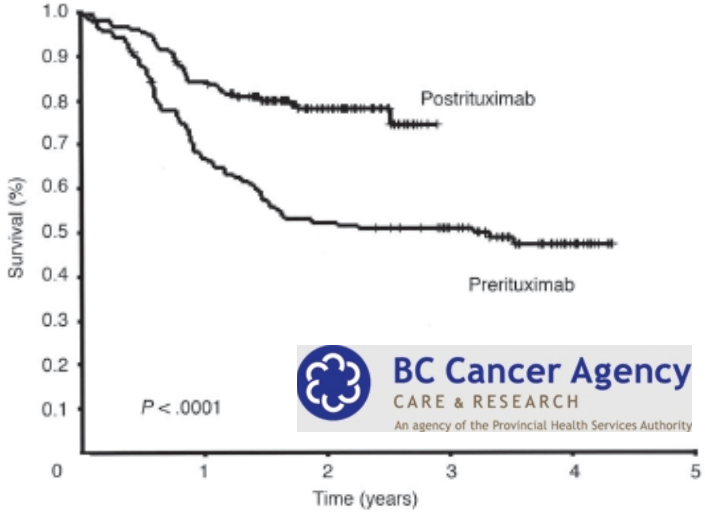


2002+: Rituximab plus CHOP-like regimens improves overall survival









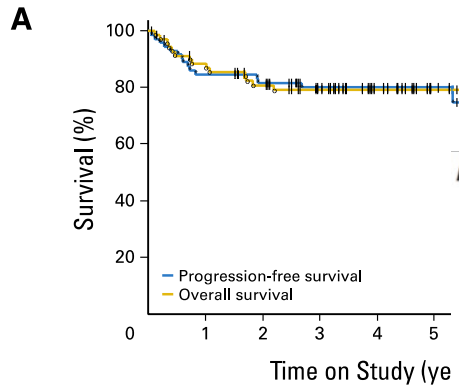
Pfreundschuh et al., Lancet Oncol. 2008; 9: 105. Pfreundschuh et al., Lancet Oncol. 2006; 7: 379. Habermann et al., JCO. 2006; 24: 3121. Feugier et al., JCO. 2005; 23: 4117.

CAN WE MOVE BEYOND R-CHOP?

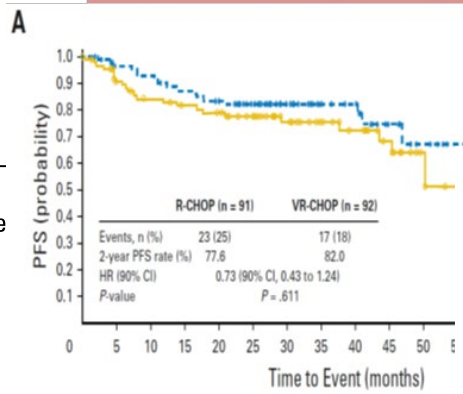
Challenging R-CHOP

e Large B-Cell

DA-EPOCH-R

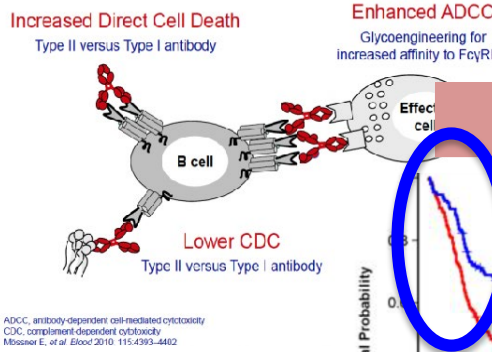


Add biologic agents

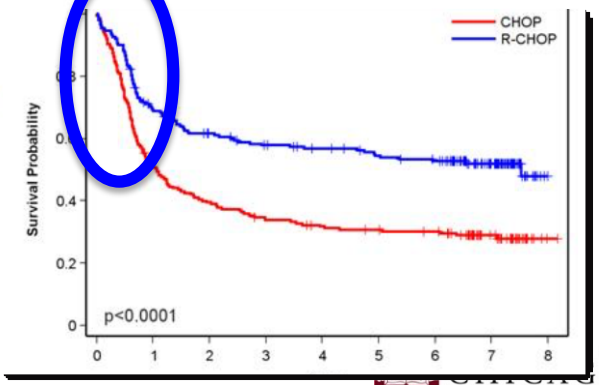


Obinutuzumab

GA101: Mechanisms of action



Consolidation



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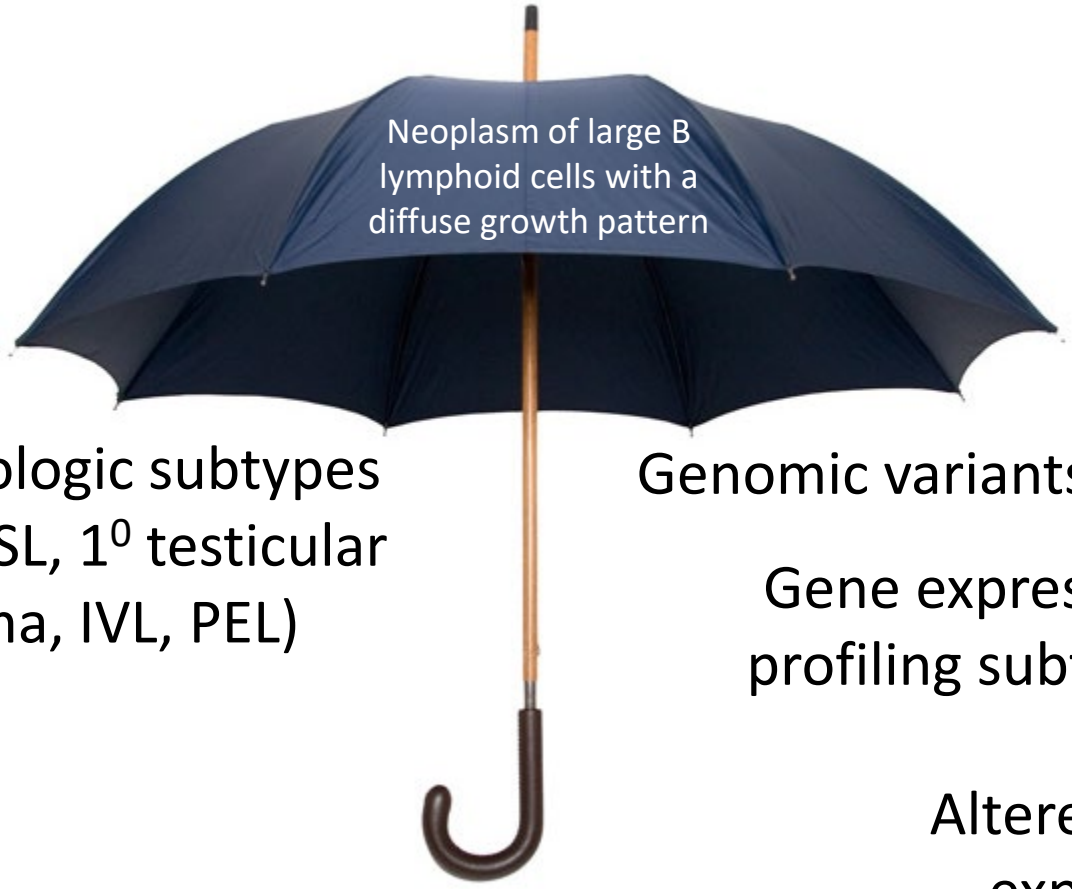
DLBCL: a study in clinical and biologic heterogeneity



Clinicopathologic subtypes (PMBL, PCNSL, 1^0 testicular lymphoma, IVL, PEL)

Genomic variants

Gene expression profiling subtypes

Altered protein expression

Morphologic variants

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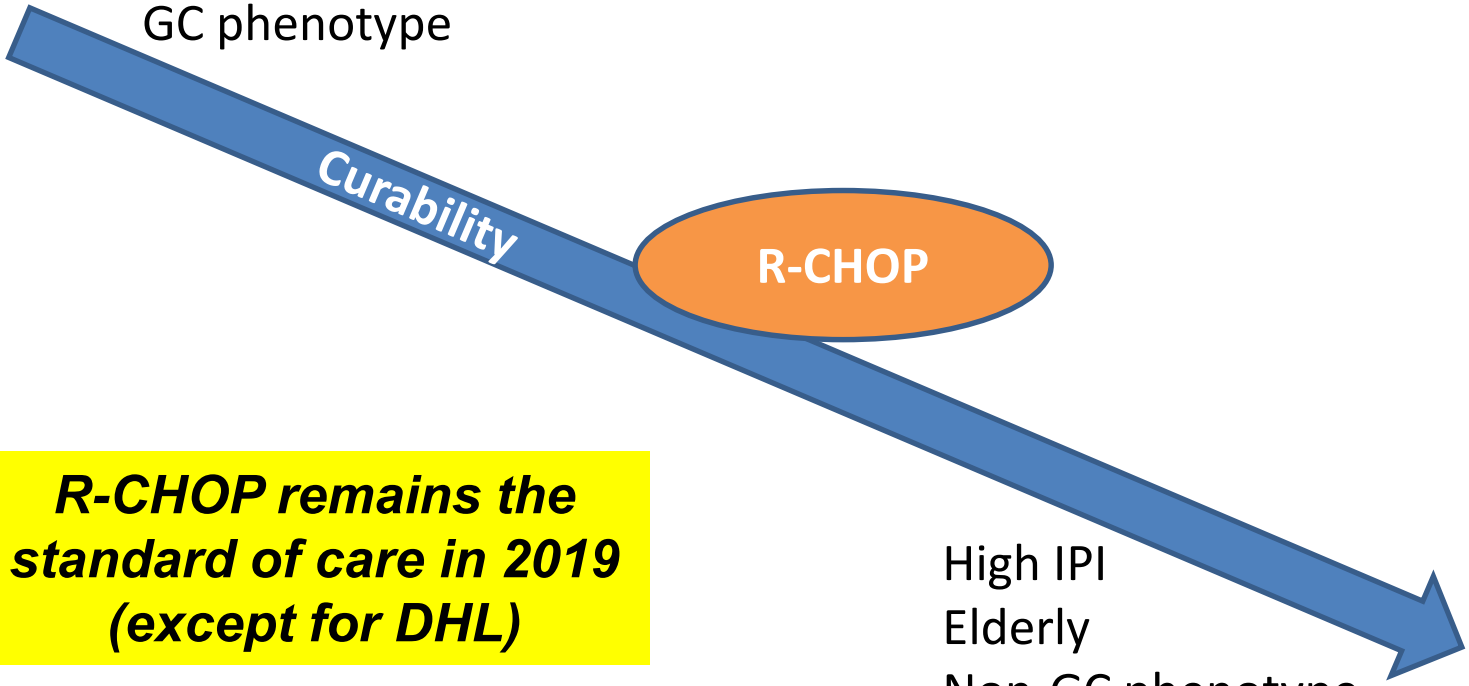
Clinical impact of heterogeneity on curative potential

Low IPI
Low stage
GC phenotype



R-CHOP remains the standard of care in 2019 (except for DHL)

High IPI
Elderly
Non-GC phenotype
Double hit lymphoma
Double protein lymphoma

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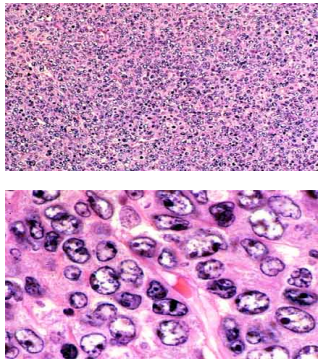
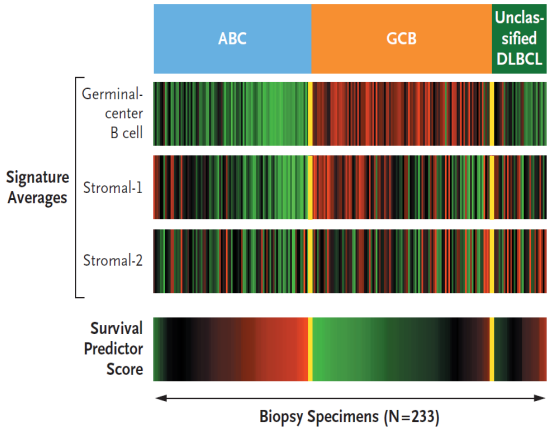
HETEROGENEITY AND RISK STRATIFICATION IN AGGRESSIVE B-NHL

Identifying high-risk subsets: 4 key approaches

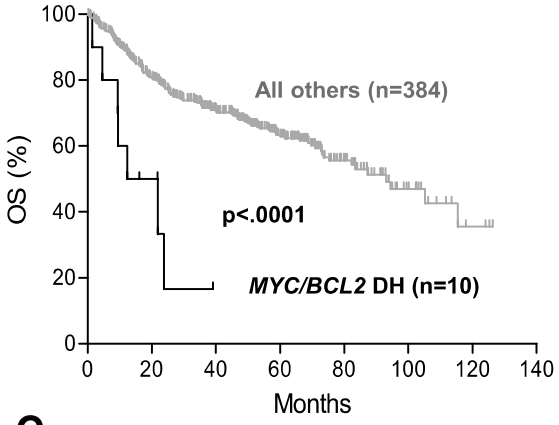
1 Histopathology



3 Cell-of-origin

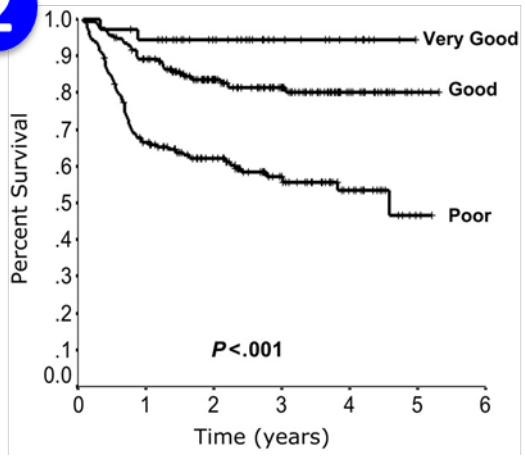


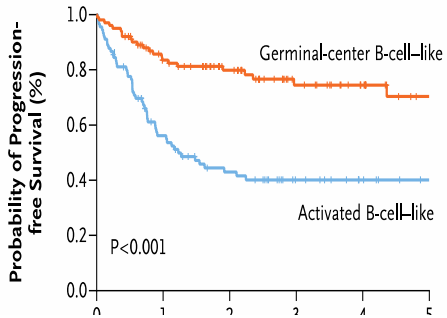
4 DHL, DEL, other

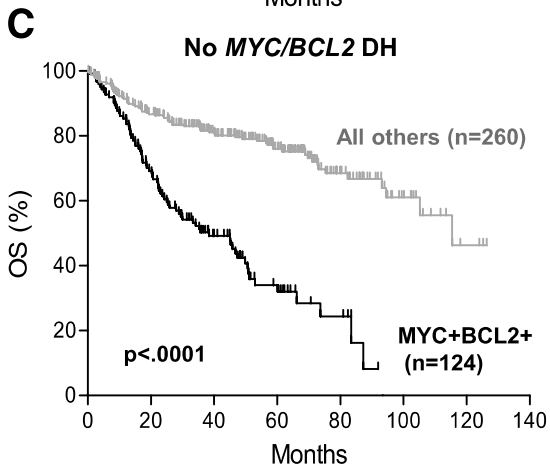


Clinical features/IPI

2







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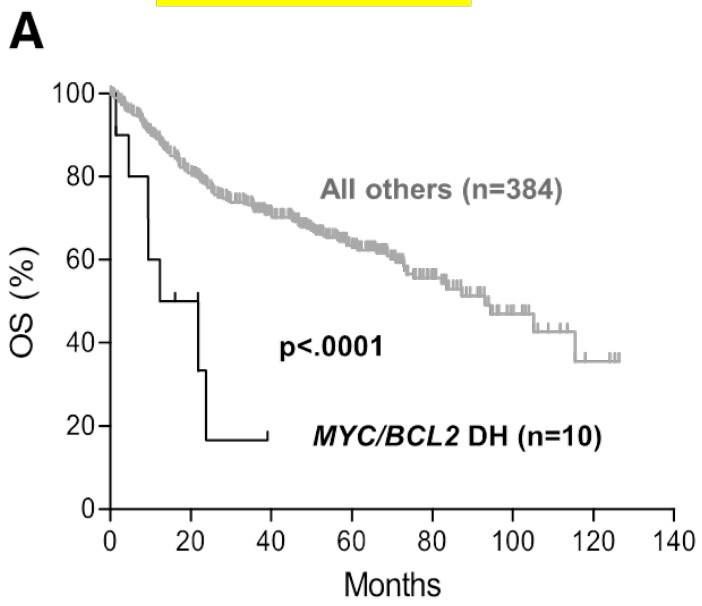
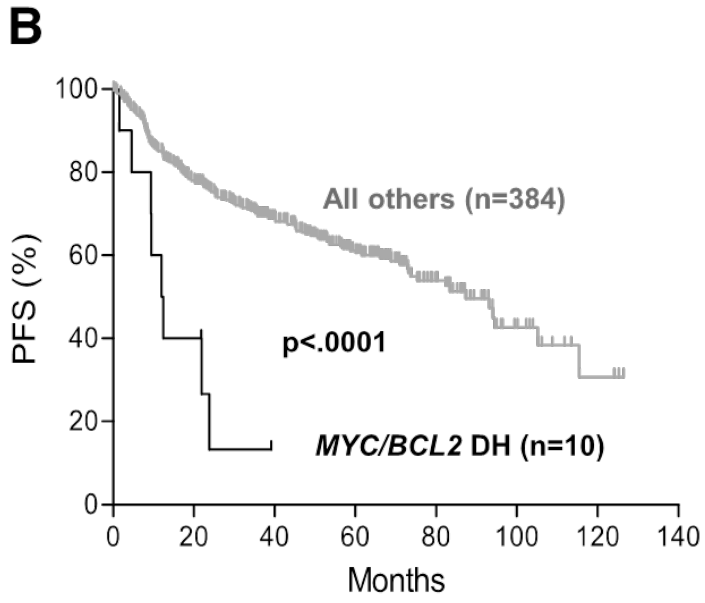
FOCUS ON HGBL-DHL/THL

Co-rearrangement of *MYC and BCL2*- in DLBCL

OS



PFS



MYC + **BCL2** = **"DOUBLE HIT LYMPHOMA"**

proliferation

Anti-apoptosis

Hu Blood. 2013 May 16;121(20):4021-31; quiz 4250. doi: 10.1182/blood-2012-10-460063. PMID: 23449635

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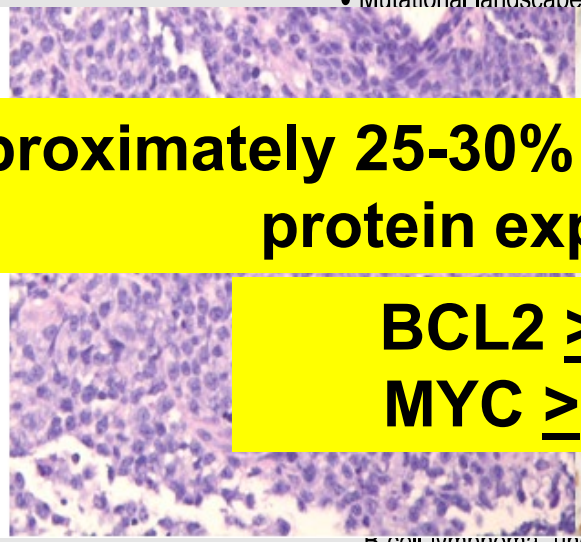
DHL ≠ Dual expression

Diffuse large B-cell lymphoma, NOS	• Distinction of GCB vs ABC/non-GC type required with use of immunohistochemical algorithm acceptable, may affect therapy. • Coexpression of MYC and BCL2 considered new prognostic marker (double-expressor lymphoma). • Mutational landscape better understood but clinical impact remains to be determined.
EBV$^+$ DLBCL, NOS	 ounger patients.
EBV$^+$ mucocutane	ic diagnosis. d
Burkitt lymphoma	
Burkitt-like lymphoma with 11	*MYC* rearrangement and has
High-grade B-cell lymphoma, and/or *BCL6* translocations	oblastic lymphomas.
High-grade B-cell lymphoma,	aces the 2008 category of B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and Burkitt lymphoma (BCLU). • Includes blastoid-appearing large B-cell lymphomas and cases lacking *MYC* and *BCL2* or *BCL6* translocations that would formerly have been called BCLU.

Approximately 25-30% of DLBCL have dual protein expression

BCL2 ≥50%
MYC ≥ 40%

Swerdlow, et al., BLOOD, 19 MAY 2016 x VOLUME 127, NUMBER 20

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DHL vs. DLBCL, NOS with DEL

Double-hit lymphoma

- High grade B-cell lymphoma with translocations of *MYC*, *BCL2*, +/- *BCL6*
- Accounts for 5-7% of all DLBCL
- New category:
  - 2016 WHO category: "High grade B-cell lymphoma, with rearrangements of *MYC* and *BCL2* and/or *BCL6*"
- Outcome poor with standard therapies

Majority are germinal center DLBCL

Double-expressing lymphomas

- DLBCL with immunohistochemical expression of MYC (≥40%) and BCL2 (≥50% recommended in 2016 WHO revision) ***in the absence of translocations***
- Accounts for 20-30% of all DLBCL
- Not a distinct entity but an adverse prognostic factor
- Outcome inferior to other DLBCLs treated with R-CHOP, but not as poor as DHL

Majority are non-germinal center DLBCL

Slide modified from Jeremy Abramson

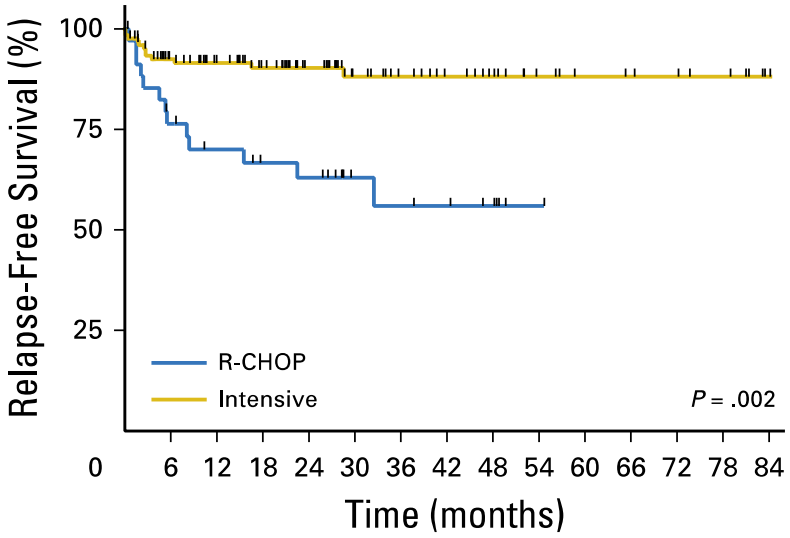
TREATMENT OF DHL

Management considerations

- All data to date is retrospective
- All data to date is on DHL and not DLBCL, NOS with DEL
- Role of intensified treatment
- Does achievement of CR matter?
- Impact of consolidative stem cell transplant
- Management of relapsed/refractory disease
- Need for CNS prophylaxis

R-CHOP is inferior to intensive therapy

C



No. at risk

R-CHOP	35	25	21	18	17	9	8	7	5	1	0	0	0	0	0
Intensive	124	96	79	67	52	38	32	26	22	16	13	12	11	9	3

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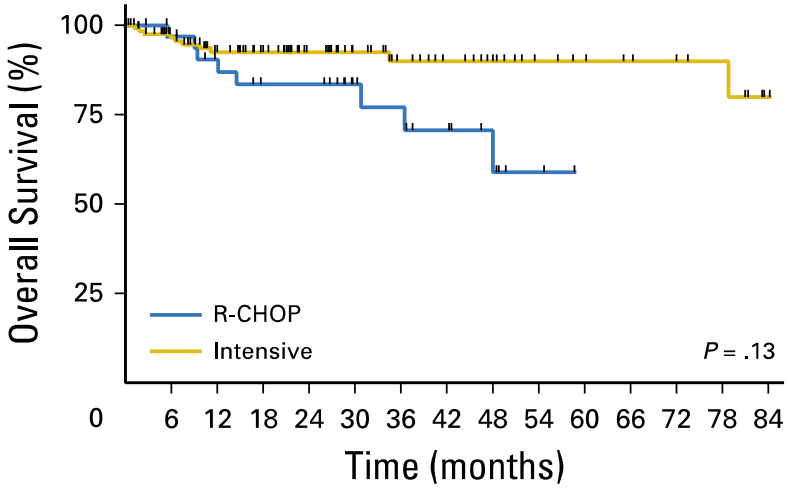
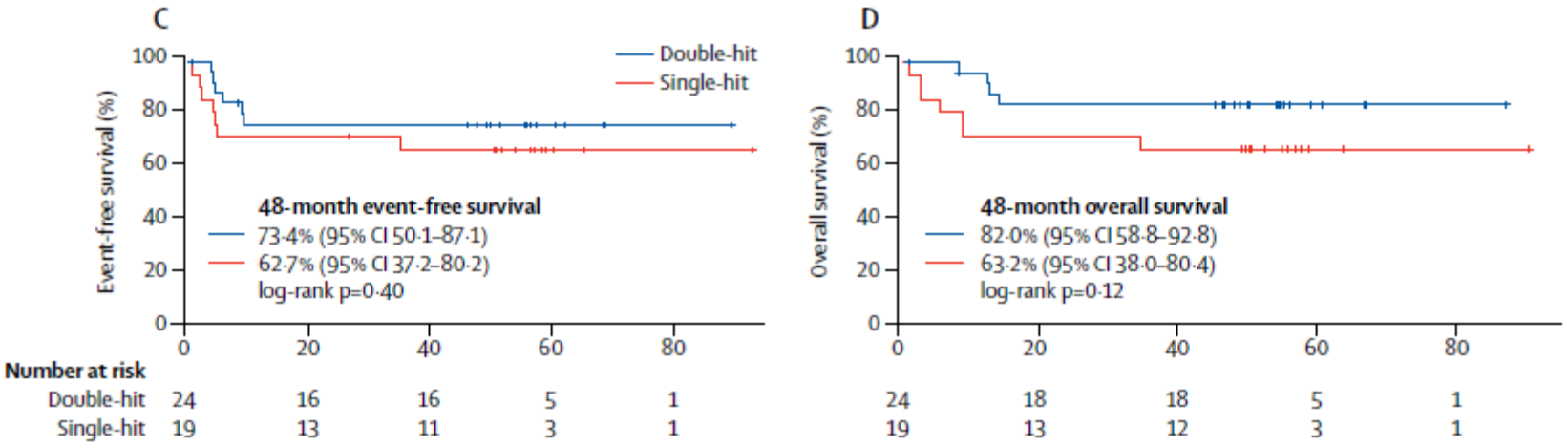


No. at risk

R-CHOP	35	31	26	22	22	14	12	9	6	2	0	0	0	0	0
Intensive	124	101	81	69	54	41	32	26	22	16	14	12	11	9	3

Landsburg J Clin Oncol. 2017 Jul 10;35(20):2260-2267. doi: 10.1200/JCO.2017.72.2157. PMID: 28475457

DA-EPOCH-R in MYC-R NHL (n=43)



Dunleavy Lancet Haem 2018

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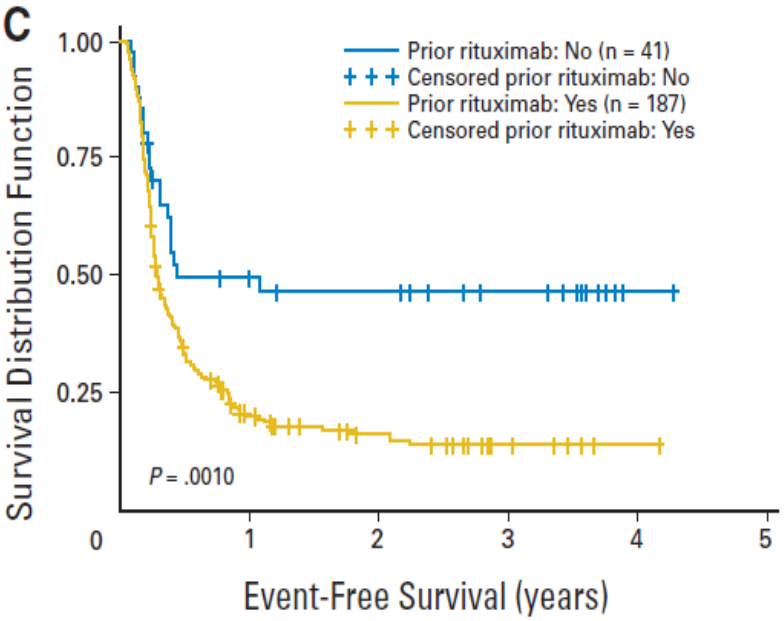
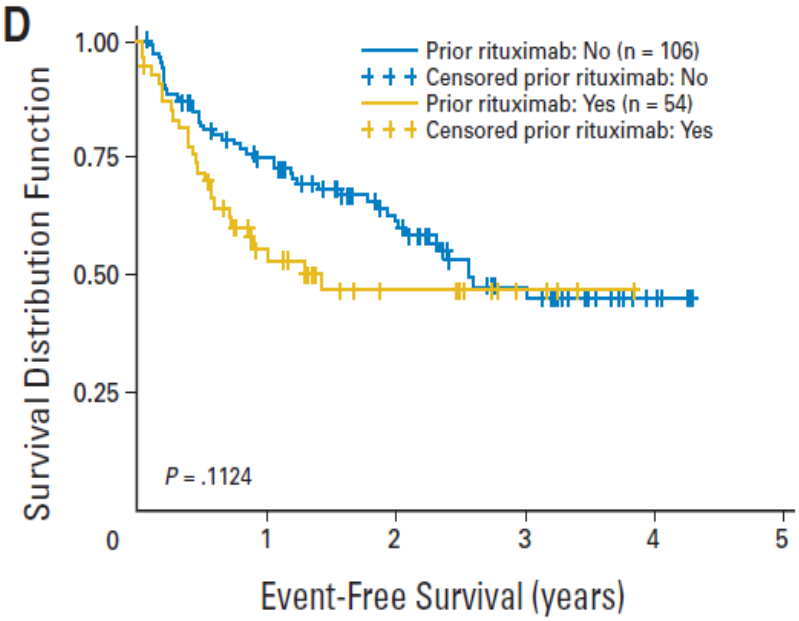
MANAGEMENT OF RELAPSED DLBCL

Autologous transplant in modern era: outcome by prior rituximab exposure and time to relapse



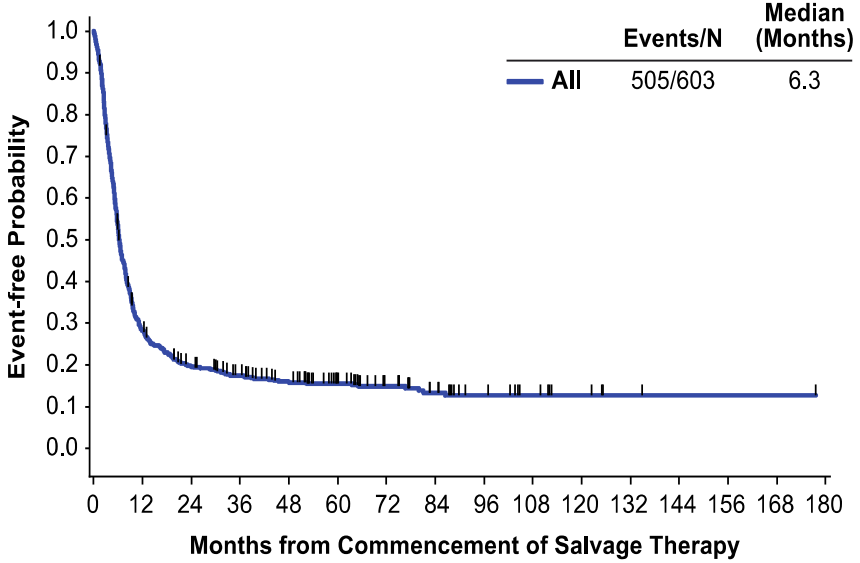


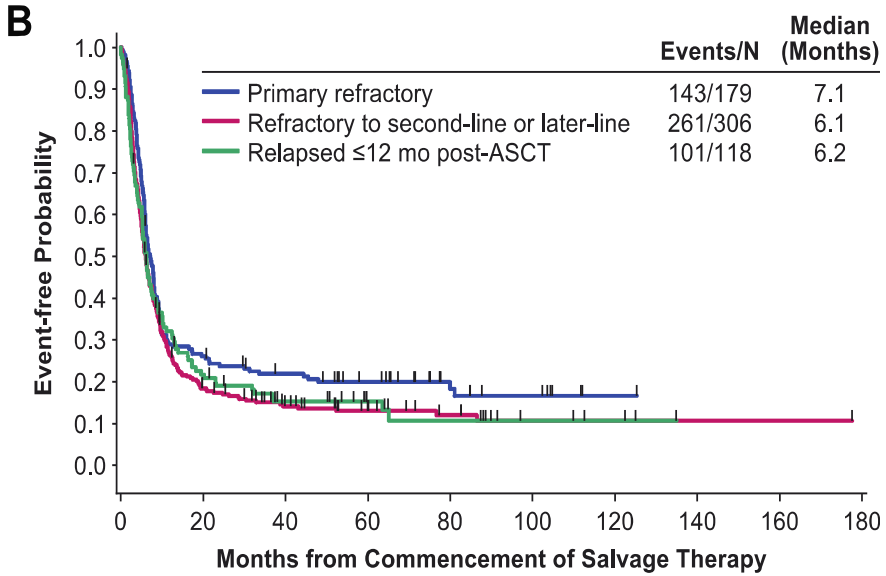
Outcome by prior rituximab AND relapse < 12 months

Outcome by prior rituximab AND relapse > 12 months

Gisselbrecht J Clin Oncol. 2010 Sep 20;28(27):4184-90. doi: 10.1200/JCO.2010.28.1618. PMID: 20660832

Expected survival for rel/ref DLBCL

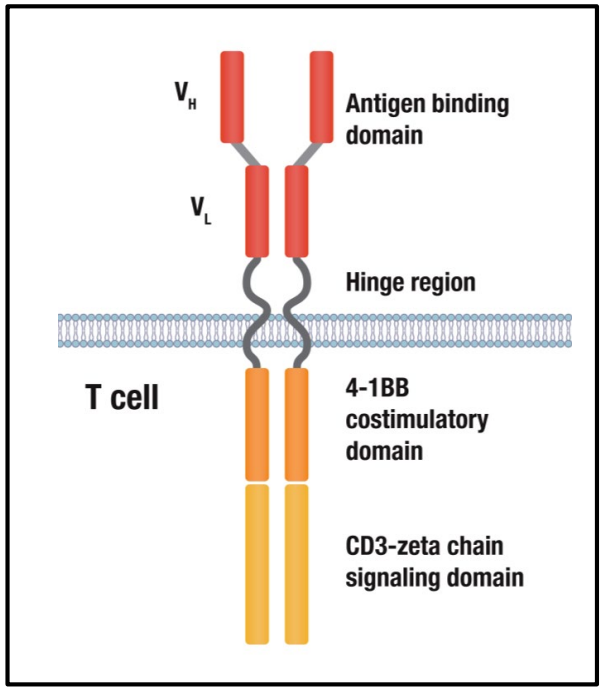




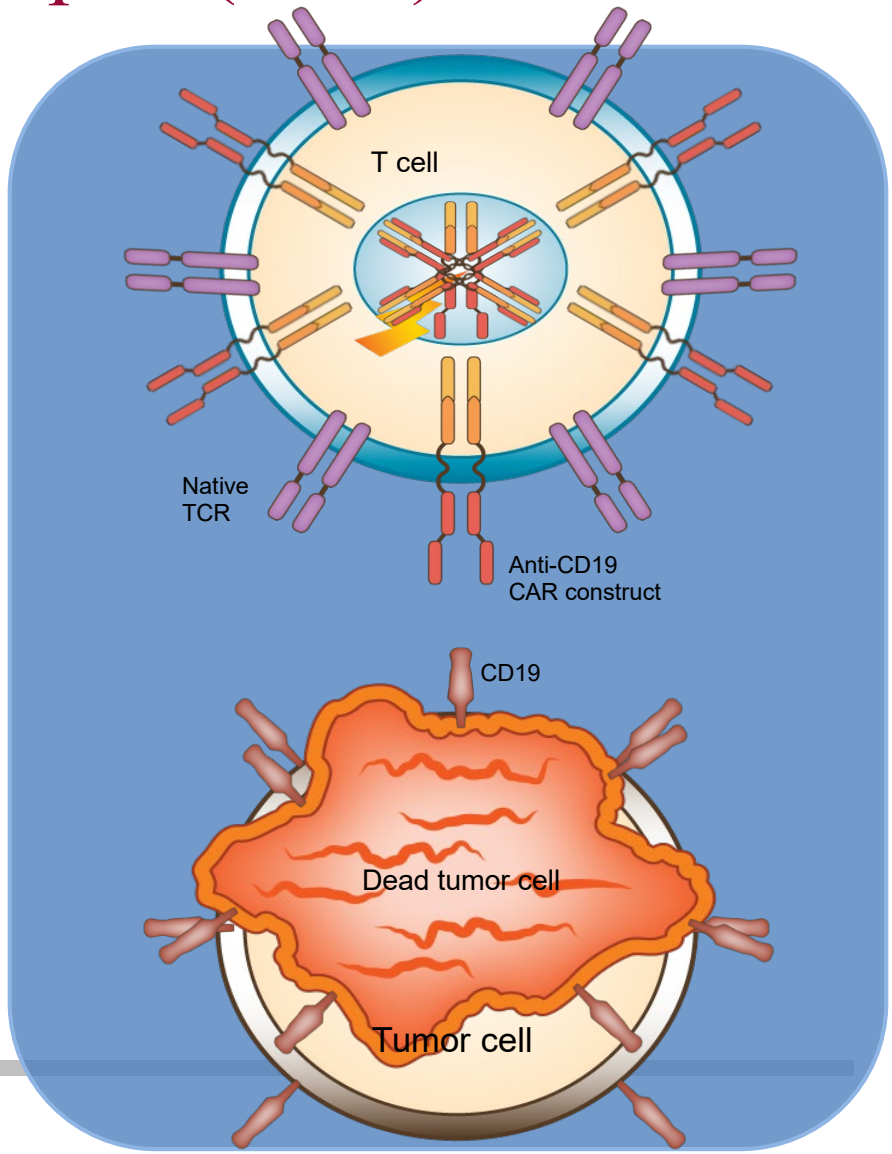
Patients unable to undergo autologous stem cell transplant have median survivals < 1 year

Crump Blood. 2017 Oct 19;130(16):1800-1808. doi: 10.1182/blood-2017-03-769620. PMID: 28774879

Chimeric Antigen Receptor (CAR) T-cells



- **Uses patients own cells**
- **Tumor specific**
- **Can be applied to multiple malignancies**



Courtesy N. Frey

Slide courtesy of Dr. Michael Bishop, University of Chicago

Patient Characteristics in CAR-T trials

Patient characteristics in the three largest anti-CD19 multicenter studies CAR T-cells in aggressive B-cell NHLs.

Patients Characteristics	ZUMA-1 (Neelapu, 2017)	JULIET (Schuster, 2017)	TRANSCEND (Abramson, 2017)
No of patients enrolled	111 (101)	141 (85)	91 (67)
Median age, range	58 (23–76)	56 (24–75)	61 (29–82)
Age ≥ 65	24%	21%	17%
Lymphoma subtypes	DLBCL, TFL, PMBCL	DLBCL, TFL	DLBCL, TFL (CORE)[a]
Double hit lymphomas	NR	27%	27%
≥3 lines of therapy	69%	50%	50%
Primary refractoriness	26%	NR	NR
Refractory to > 2nd line	77%	NR	76%
Relapse post ASCT	21%	51%	44%

Chavez and Locke Best Prac and Res Clin Haem 2018

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Initial results of CAR-T trials

Study	ZUMA-1 (Neelapu, 2017)	JULIET (Schuster, 2017)	TRANSCEND (Abramson, 2017)
No of patients enrolled (treated)	111 (101)	141 (99)	NR (91) 67 in CORE
Median age, range	58 (23–76)	56 (24–75)	61 (29–82)
Median follow-up	15.4 months	5.6 months	6.3 months
Costimulatory domain	CD28	4-1BB	4-1BB
Bridging chemotherapy	Not allowed	Allowed	Allowed
CART dose	2.0×10^6 cells/kg	Median, 3.1×10^8	DL1 5.0×10^7 cells[a] DL2 1.0×10^8 cells
Conditioning regimen	Flu 30 mg/m^2 x3d Cy 500 mg/m^2 x3d	Flu 25/m^{2}x 3d Cy 250 mg/m^2 x3d or B 90 mg/m^2 x 2d	Flu 30 mg/m^2 x3d Cy 300 mg/m^2 x3d
Efficacy			
%ORR (%CR)	82 (54)	59 (43)	84 (61)
3-mo %ORR (%CR)	44 (39)	45 (37)	65 (53)
mDOR	11.1 months	NR	9.2 months

Chavez and Locke Best Prac and Res Clin Haem 2018

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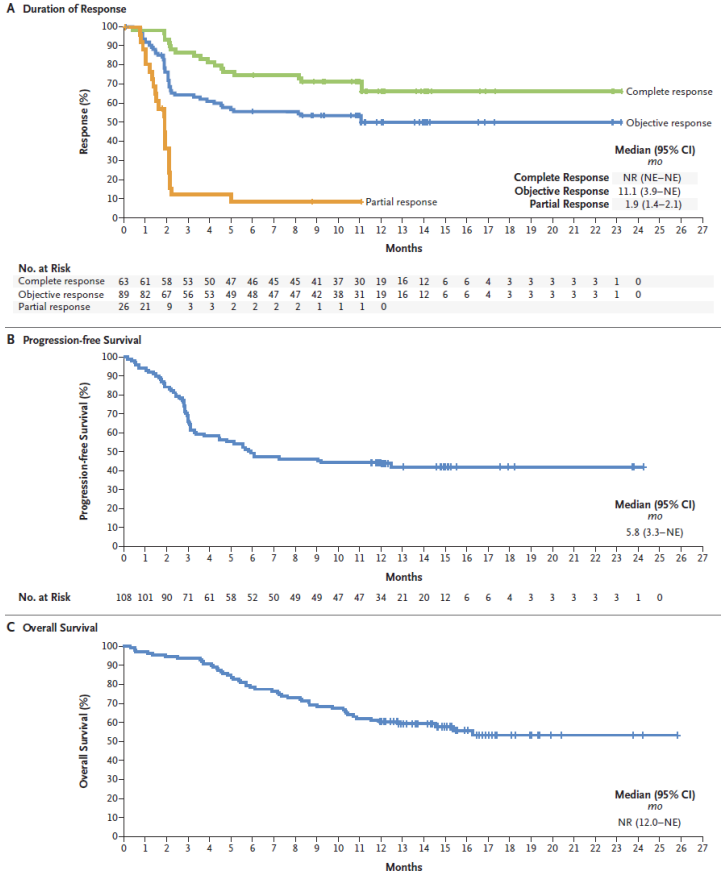
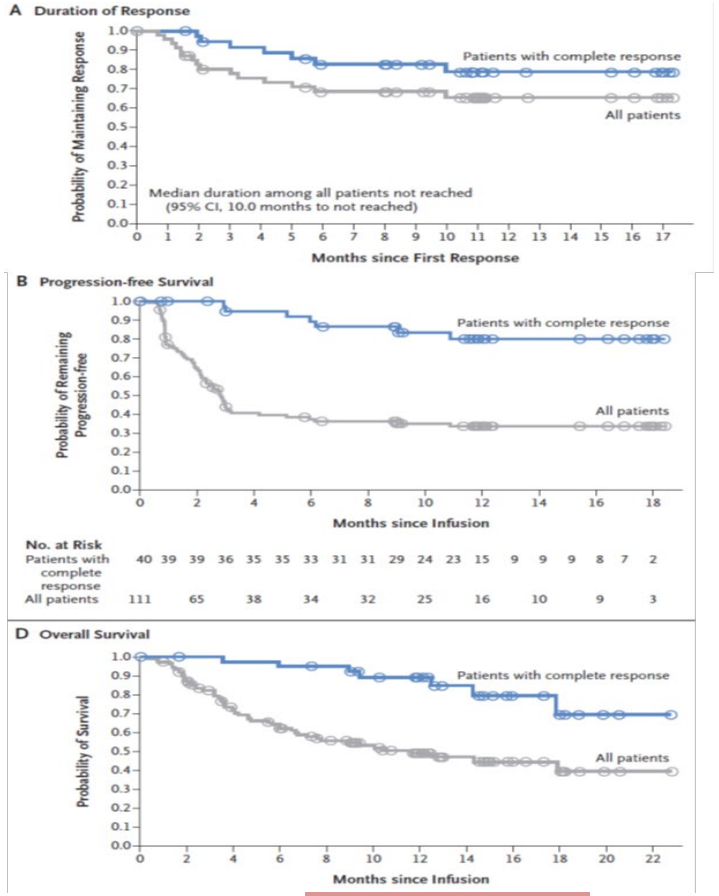
Published CAR-T results





"Axi-cel"

"Tisa-cel"

Schuster N Engl J Med. 2019 Jan 3;380(1):45-56. doi: 10.1056/NEJMoa1804980. PMID: 30501490
Neelapu N Engl J Med. 2017 Dec 28;377(26):2531-2544. doi: 10.1056/NEJMoa1707447. PMID: 29226797

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CAR-T IN DLBCL: ONE YEAR LATER…

"Real-world" Axi-cel

Table 1. Patient characteristics and outcomes: comparison between ZUMA-1 (Neelapu and Locke et al. NEJM 2017) and commercial standard of care axi-cel treatment at 17 US centers.

	ZUMA-1	This Study
N infused pts	108	165
% meeting ZUMA-1 eligibility criteria	100%	51%
Age, median (range)	58 (23-76)	59 (21 – 82)
ECOG 0 or 1	100%	84%
Prior autologous transplant	23%	31%
DLBCL including HGBCL, not tFL or PMBCL	78%	61%
ORR/CR	82%/58% (Best)	79%/50% (Day 30)
Grade 3 or higher toxicity	CRS 13%/NEs 31%	CRS 7%/NEs 31%

- Seventeen US academic
- N= 165 with 78% pts completing axi-cel infusion
- Grade 3 CRS in 7%
- Grade 3 NE in 31%
- ORR at Day 30 in 112 evaluable pts was 79% with 50% CR
- PFS and OS data to be presented

Nastoupil ASH 2018 Abstract 91 Saturday, December 1, 2018: 9:30 AM
Pacific Ballroom 20 (Marriott Marquis San Diego Marina)

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"Real-world" Axi-cel

- N=73 evaluable patients
- At 4m median f/u, best ORR and CRR was 64% and 41% among those treated.
- Predictors of poor outcome:
  - Poor PS, tumor bulk, high IPI, baseline CRP, prior ibrutinib
- 96% all-grade CRS, 17% grade 3-4 CRS

AUTHORS' CONCLUSION: "The ORR and CR rate are lower than the 82% and 54% reported on ZUMA-1. This may reflect inclusion of sicker patients with a poorer PS, and/or with different histologies (ie transformation from non-FL). Outcomes were significantly worse in high risk lymphomas, reflected by IPI, PS, tumor bulk, and baseline CRP. Rates of CRS and NT were similar to ZUMA-1"

Jacobsen ASH 2018 Abstract 92 Saturday, December 1, 2018: 9:45 AM
Pacific Ballroom 20 (Marriott Marquis San Diego Marina)

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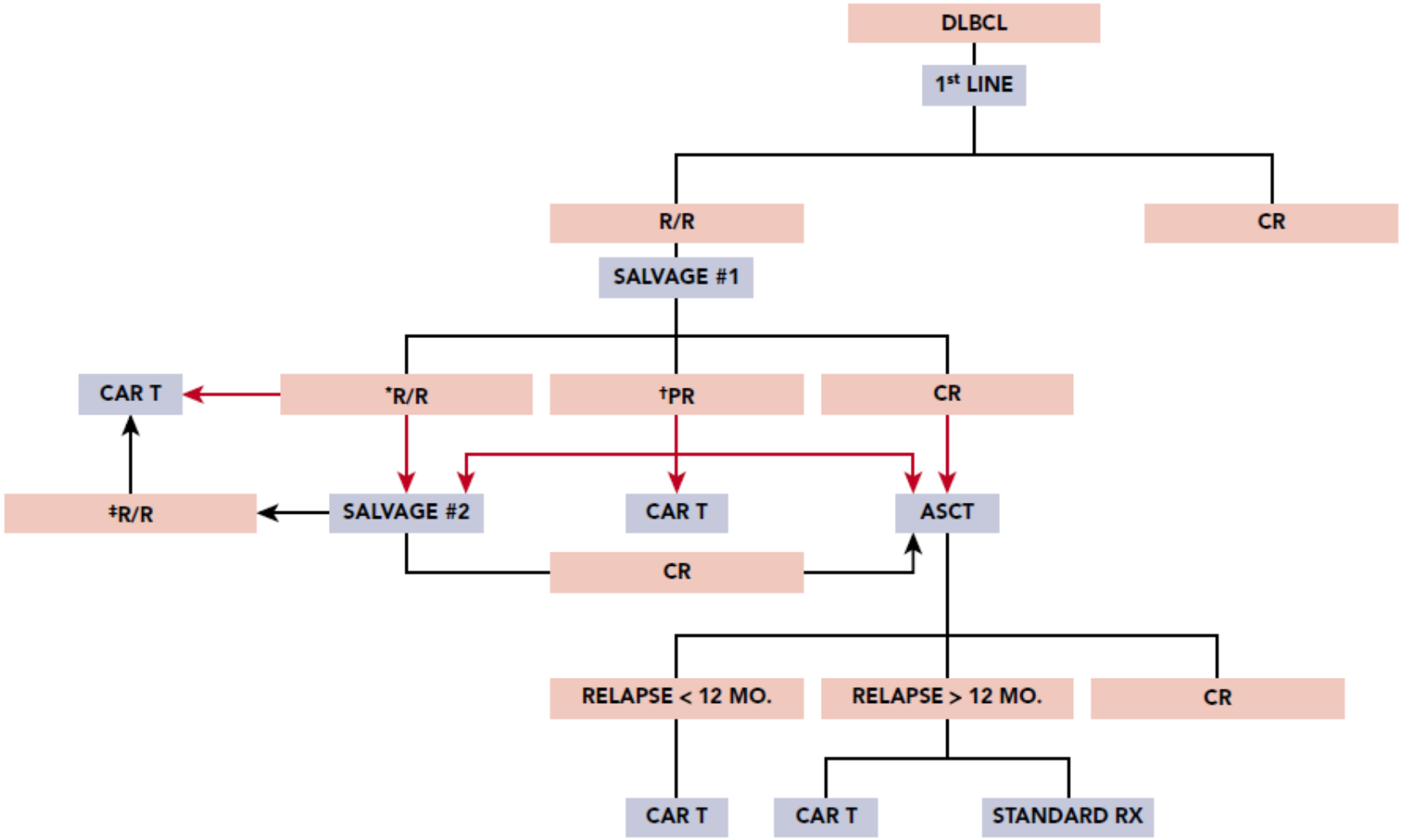
New relapsed DLBCL algorithm



Chow Blood 2018

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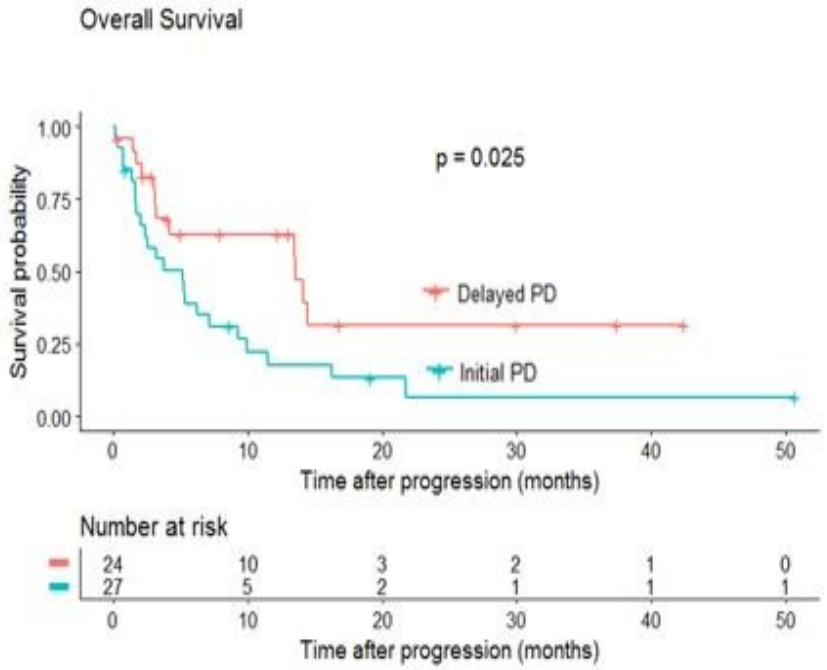
If CAR-T doesn't work…



Characteristic	Total (N=51)	Initial PD (N=27)	Delayed PD (N=24)
Gender			
Female	17 (33.3%)	8 (29.6%)	9 (37.5%)
Male	34 (66.7%)	19 (70.4%)	15 (62.5%)
Histology			
HGBCL	11 (21.6%)	3 (11.1%)	8 (33.3%)
DLBCL	29 (56.9%)	18 (66.7%)	11 (45.8%)
PMBCL	3 (5.9%)	2 (7.4%)	1 (4.2%)
tFL	8 (15.7%)	4 (14.8%)	4 (16.7%)
Median age (range)	60 (26-75)	60 (29-70)	59 (26-75)
Additional therapy after progression	39 (76.5%)	17 (63.0%)	22 (91.7%)
Next line of therapy			
Allogeneic Transplant	1 (2.6%)	0 (0.0%)	1 (4.5%)
CAR T	14 (35.9%)	6 (35.3%)	8 (36.4%)
Chemotherapy	7 (17.9%)	5 (29.4%)	2 (9.1%)
Immunotherapy	3 (7.7%)	1 (5.9%)	2 (9.1%)
Intrathecal	1 (2.6%)	0 (0.0%)	1 (4.5%)
Radiation	3 (7.7%)	1 (5.9%)	2 (9.1%)
Targeted	10 (25.6%)	4 (23.5%)	6 (27.3%)
Next treatment on clinical trial	5 (9.8%)	3 (11.1%)	2 (8.3%)
Allogeneic transplant after progression	4 (7.8%)	1 (3.7%)	3 (12.5%)

- N=51
- Initial progression did worse than delayed progression
  - Med OS 5.1 m vs. 13.6m

Chow ASH Abstract 94 Saturday, December 1, 2018: 10:15 AM
Pacific Ballroom 20 (Marriott Marquis San Diego Marina)

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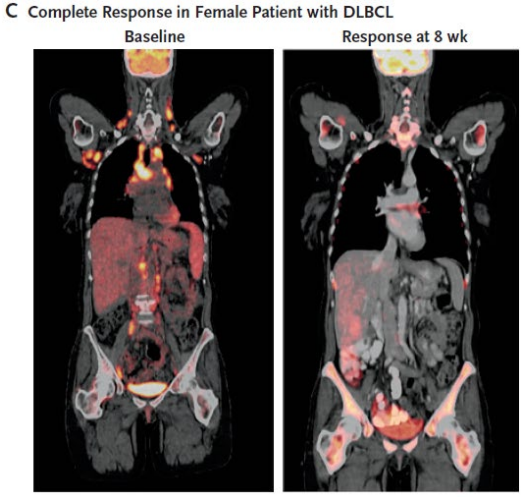
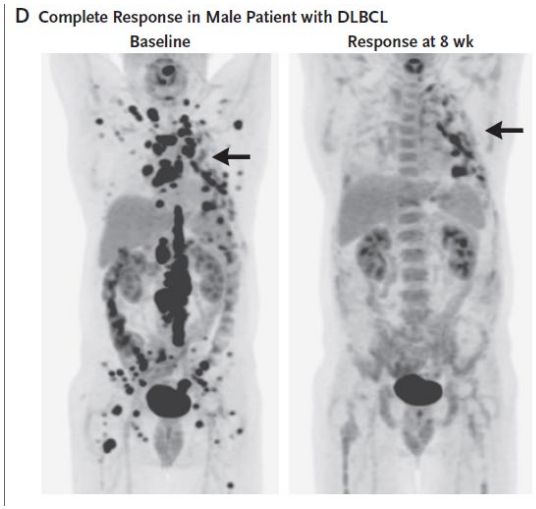
What if transplant and/or CAR-T are not options?

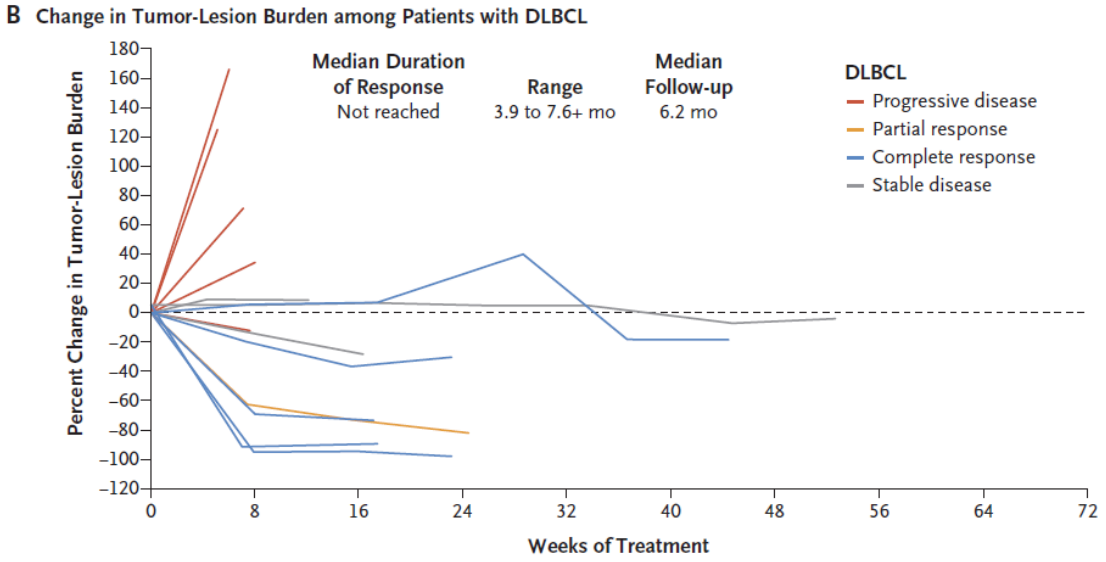
- Chemoimmunotherapy
  - Gemcitabine-based regimens
  - BR
- Non-chemotherapy agents include:
  - Ibrutinib (for non-GCB only and if insurance allows)
  - Len/rituximab
- Best supportive care

Clinical trials

Targeting the macrophage checkpoint: 5F9 plus rituximab







- Favorable toxicity profile
- No chemotherapy

Advani NEJM 2019

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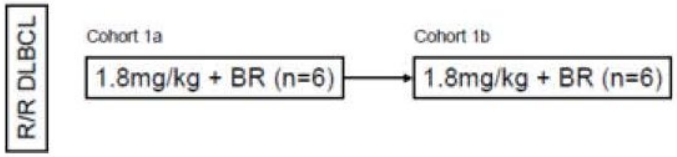
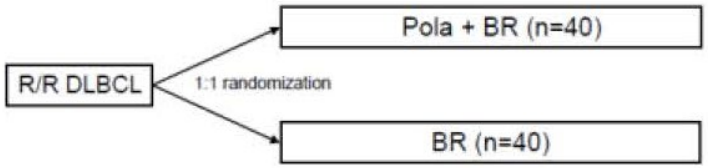
Polatuzumab plus BR in rel/ref DLBCL

Ph Ib safety run-in: Pola + BR or BG



Ph II randomization: Pola + BR versus BR



Ph II expansion: Pola + BG

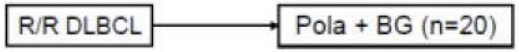
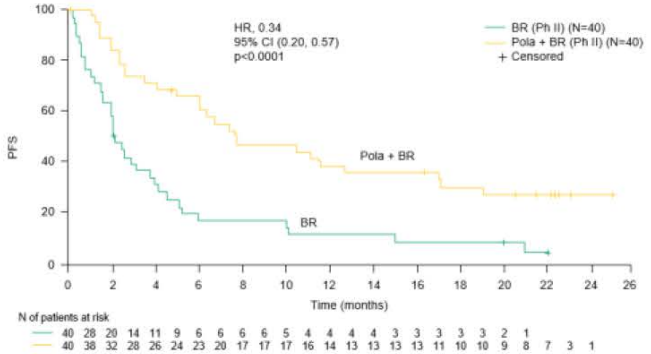
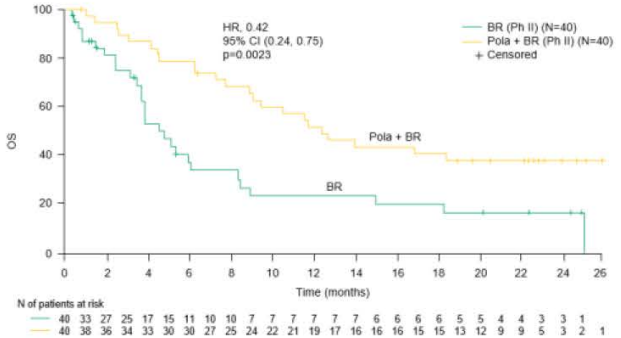


Figure 2a. Randomized DLBCL cohort: Kaplan Meier curves for PFS



B, bendamustine; CI, confidence interval; DLBCL, diffuse large B-cell lymphoma
vedotin;
R, rituximab

Figure 2b. Randomized DLBCL cohort: Kaplan Meier curves for OS



B, bendamustine; CI, confidence interval; DLBCL, diffuse large B-cell lymphoma; N, n

Sehn ASH Abstract 1683 Saturday, December 1, 2018, 6:15 PM-8:15 PM
Hall GH (San Diego Convention Center)

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