Addressing the Challenges of Aggressive Lymphomas

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Katherine Byar: None

Learning Objectives

1. Assess the clinical significance of emerging data regarding management of aggressive lymphomas
2. Select optimal therapy for patients with aggressive lymphomas in accordance with evidence-based treatment recommendations
3. Manage adverse events associated with treatments for aggressive lymphomas

Non-Hodgkin Lymphoma (NHL)

- A heterogeneous group of neoplasms with differing patterns of growth and response to treatment
- New cases
  - Ranks 7th among men and women as the most frequently newly diagnosed cancer in the US
  - Estimated 74,200 new cases in 2019
- Deaths
  - 8th leading cause of cancer deaths in men and the 8th leading cause of cancer deaths in women
  - Estimated 19,970 deaths in 2019
  - Decline in death rates related to improvement in treatment of NHL

ACS 2019. Cancer Facts and Figures 2019. Atlanta: American Cancer Society.

Indolent vs Aggressive

Indolent (Low Grade)

Follicular (Grade 1-2), SLL/CLL, MZL, LPL, MCL?, Grade 3A FL?

- Slow disease progression
- 70% present with stage III or IV disease
- May not need treatment for years
  - High response rate to first treatment regimens
  - Invariably will relapse
  - After relapse, lower response rates, shorter duration of response
- Felt to be incurable to standard therapy
- Transform to aggressive lymphoma
- Presentation: Often asymptomatic

Aggressive (Intermediate/High Grade)

DLBCL, Most T-cells, MCL: FL , FL Grade 3B, TCL, FL Grade 3A?

Burkitt, Lymphoblastic, High Grade

- Aggressive progression of disease
- 50% present with stage III or IV disease
- Usually more sensitive to chemotherapy
- Higher response rates if treated
- 30% - 60% of patients can be cured
- Most relapses occur within first 2 years
- 1/3 have “B” symptoms
- Presentation: symptomatic

SLL/CLL = small lymphocytic lymphoma/chronic lymphocytic leukemia; MZL = marginal zone lymphoma; LPL = lymphoplasmacytic lymphoma; MCL = mantle cell lymphoma; DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma.

WHO Classification. 2016

Diffuse Large B-Cell Lymphoma

- Most common subtype of NHL
  - 30% to 40% of all cases
- Peak incidence in 6th decade of life
- May present as extranodal disease (lungs, CNS, testis, skin)
- Median survival: weeks to months if not treated

CNS = central nervous system

Diagnosis of DLBCL

- Adequate diagnostic tissue and extent of disease assessment is critical
- Adequate immunophenotyping is required to establish diagnosis
  - Germinal center B-cell (GCB) vs non-GCB origin (sometimes referred as activated B-cell, or ABC)—Hans or Choi algorithms often used
- GCB subtype has been associated with an improved outcome compared to non-GCB subtype
- Randomized clinical trials have explored whether the addition of novel targeted agents to R-CHOP will improve outcome in patients with non-GCB subtype
- Expression of MYC and either BCL2 or BCL6 by immunohistochemistry (IHC) should undergo FISH or karyotype testing for:
  - MYC, BLC2, and BCL6 gene rearrangements
- Findings of rearrangements of MYC plus either BCL-2 or BCL-6 rearrangements may lead to change in diagnosis and induction regimen
- Once the diagnosis of DLBCL is confirmed, treatment should be initiated promptly

NCCN. Clinical Practice Guidelines in Oncology: B-Cell Lymphomas (v.4.2019)

International Prognostic Index

Criteria ("APLES")

- Age (≤ 60 vs. > 60 years)
- Performance status (0 or 1 vs. ≥ 2)
- LDH (≤ 1 vs. > 1 times normal)
- Extranodal sites (≤ 1 vs. > 1)
- Stage (I or II vs. III or IV)

Risk group	Factors
Low	0-1
Low-intermediate	2
High-intermediate	3
High	4-5

Age-adjusted criteria (aaIPI; ≤ 60 years)

- Performance status (0 or 1 vs. ≥ 2)
- LDH (≤ 1 vs. > 1 times normal)
- Stage (I or II vs. III or IV)

Risk group	Factors
Low	0
Low-intermediate	1
High-intermediate	2
High	3

aaIPI = age-adjusted International Prognostic Index; LDH = lactate dehydrogenase.

The International Non-Hodgkin's Lymphoma Prognostic Factors Project. *N Engl J Med.* 1993;329(14):987-94.

Case Study

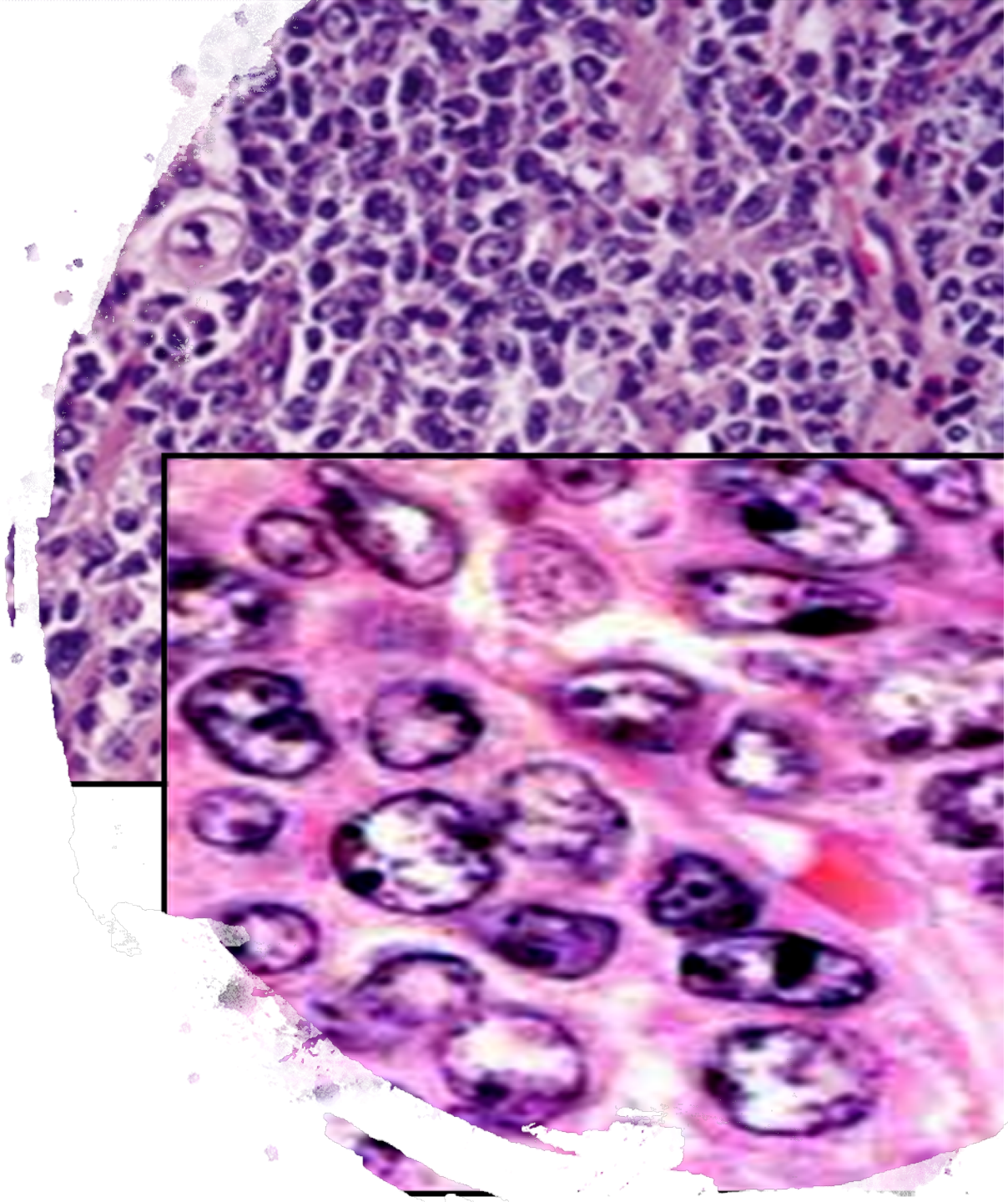
Patient is a 48-year-old male who presents to his PCP with an enlarged lymph node in his left axillary. Denies fevers, night sweats, or weight loss. Patient has felt fatigued over the past month but able to continue his normal activities (ECOG PS 0)

Laboratory Results			
WBC 14.7	Hgb 11.9	Platelets 420K	LDH 267 (98-192)

ECOG PS = Eastern Cooperative Oncology Group Performance Status; Hgb = hemoglobin; PCP = primary care provider; WBC = white blood cells

Case Study

- Excisional biopsy of the left axillary is performed and demonstrates a diffuse large B-cell lymphoma, germinal center B-cell subtype. FISH analysis was negative for MYC, BCL-2, and BCL-6.
- PET/CT scan demonstrates a left axillary mass of 5.3 x 6 cm with max SUV of 21.3, left supraclavicular lymphadenopathy 3.2 x 1.3 cm with SUV 10.4 and left iliac node 2.2 x 2.5 cm with SUV of 6.5.
- Bone marrow was deferred no bone lesions on PET/CT.
- Stage III with aaIPI: high-intermediate risk (2/3—elevated LDH and stage III).



First-Line Standard of Care for Aggressive Lymphomas

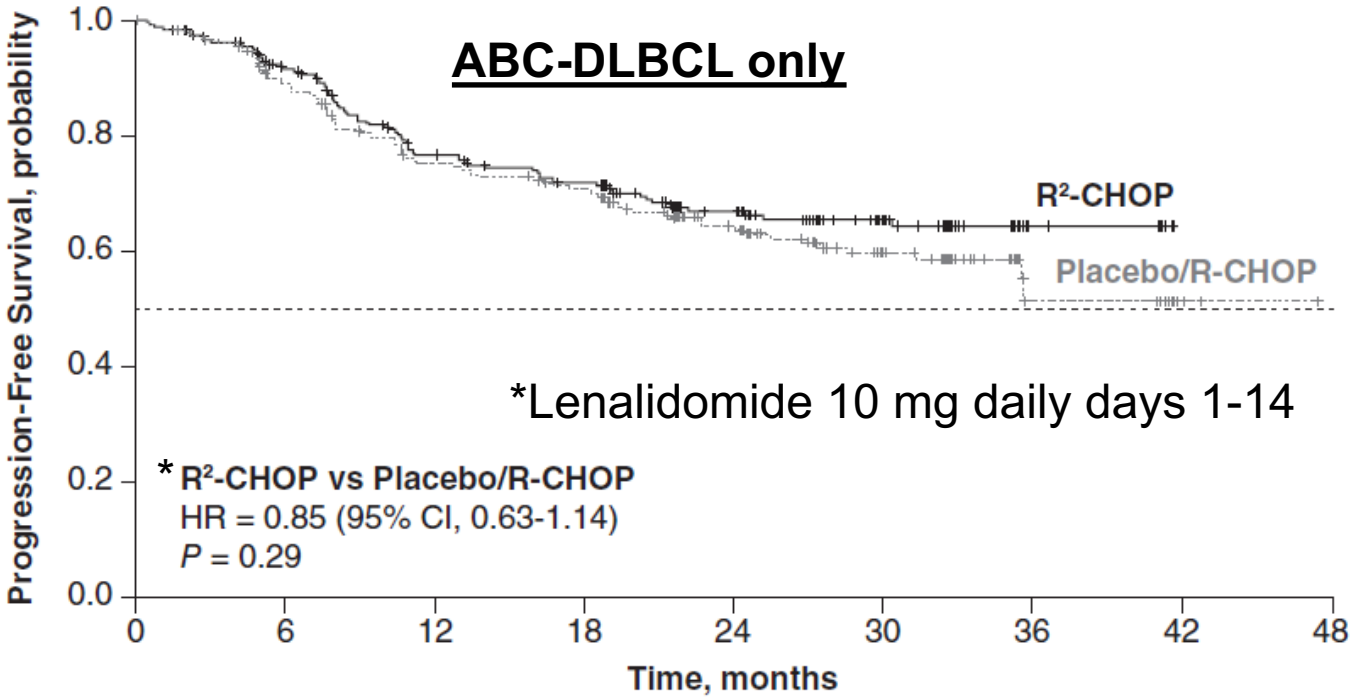
First-Line Treatment for DLBCL

- Stage I/II
  - Non-bulky (< 7.5 cm): R-CHOP for 3-4 cycles with radiotherapy or R-CHOP for 6 cycles with or without radiotherapy
  - Bulky (≥ 7.5 cm): R-CHOP for 6 cycles with or without radiotherapy
- Stage III/IV
  - R-CHOP for 6 cycles with or without radiotherapy

R-CHOP → rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone every 21 days

NCCN. Clinical Practice Guidelines in Oncology: B-Cell Lymphomas (v.4.2019)

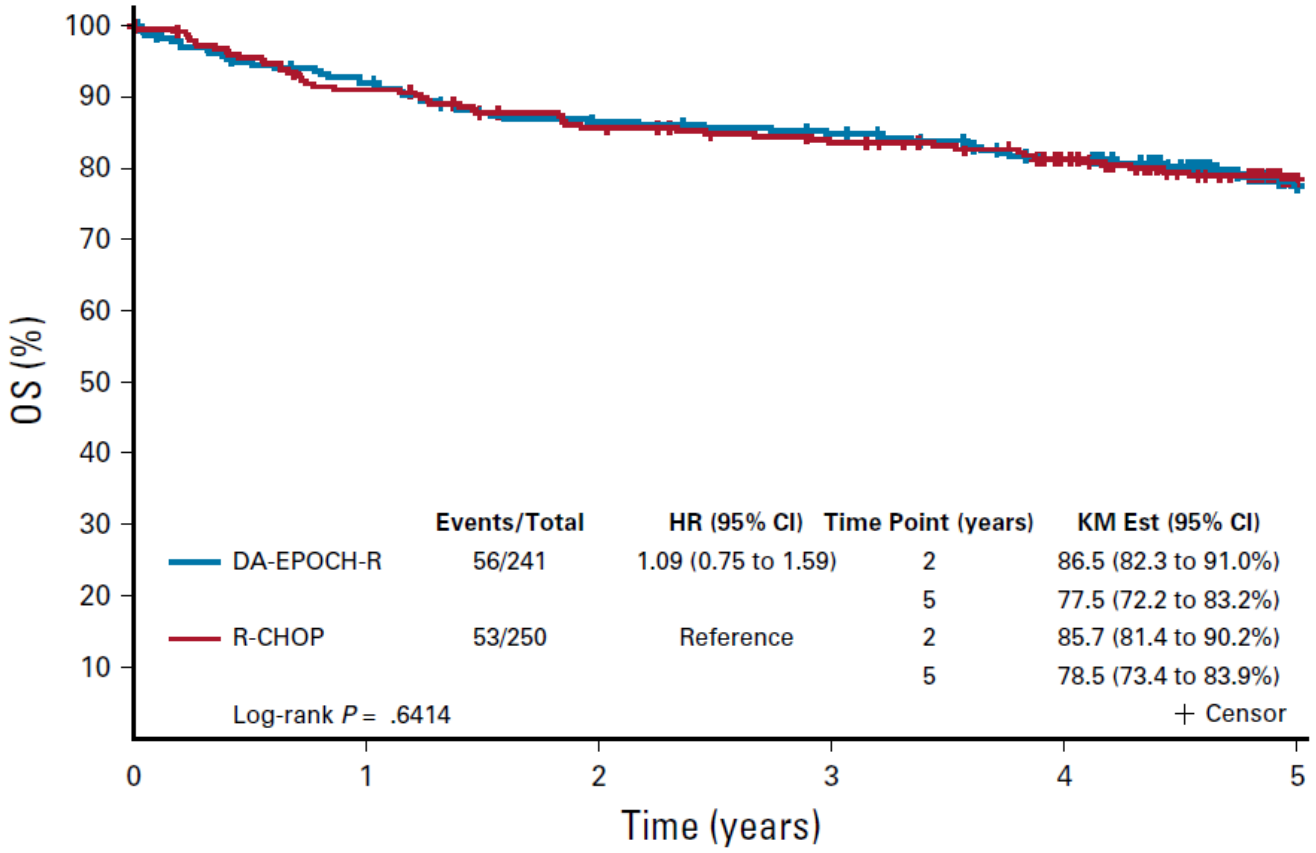
Challengers to R-CHOP: ROBUST



No. of patients at risk									
R²-CHOP	285	221	178	162	119	57	10	0	
Placebo/R-CHOP	285	229	187	173	111	55	10	3	0

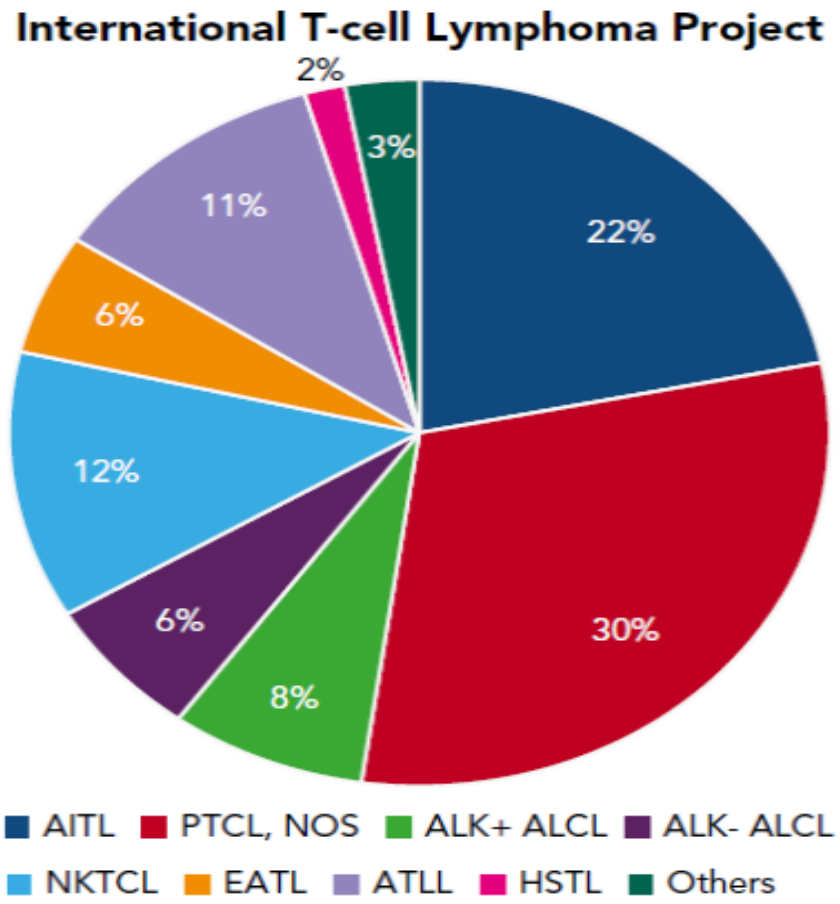
Vitolo U, et al. *Hematological Oncol.* 2019. https://doi.org/10.1002/hon.5_2629

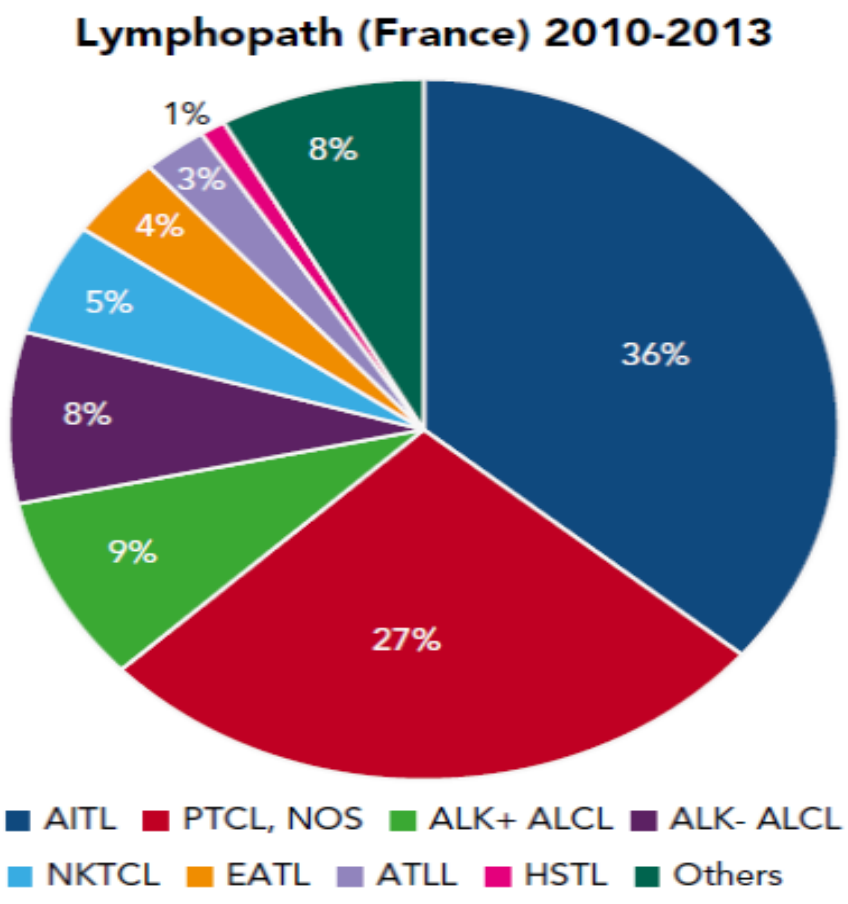
Challengers to R-CHOP: CALGB 50303



Bartlett NL, et al. *J Clin Oncol*. 2019;37(21):1790-99

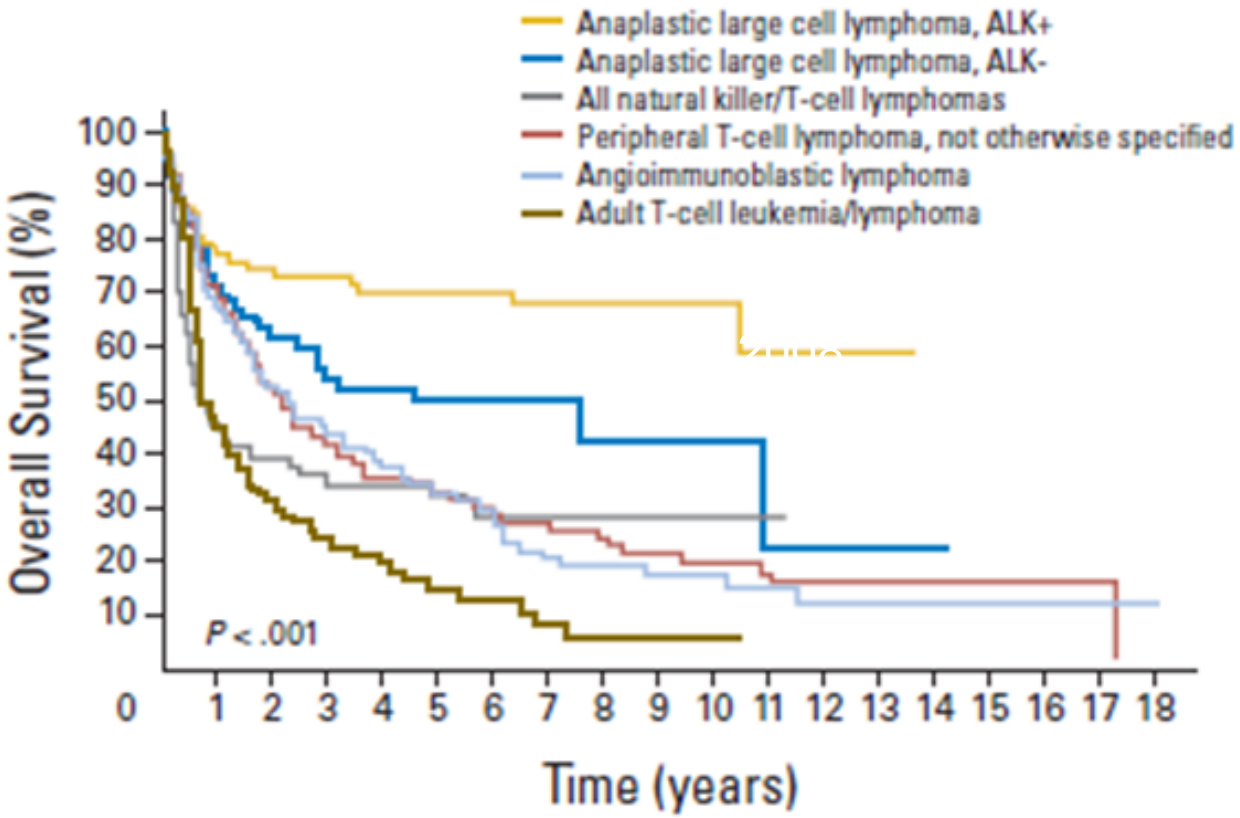
PTCL: The 10%





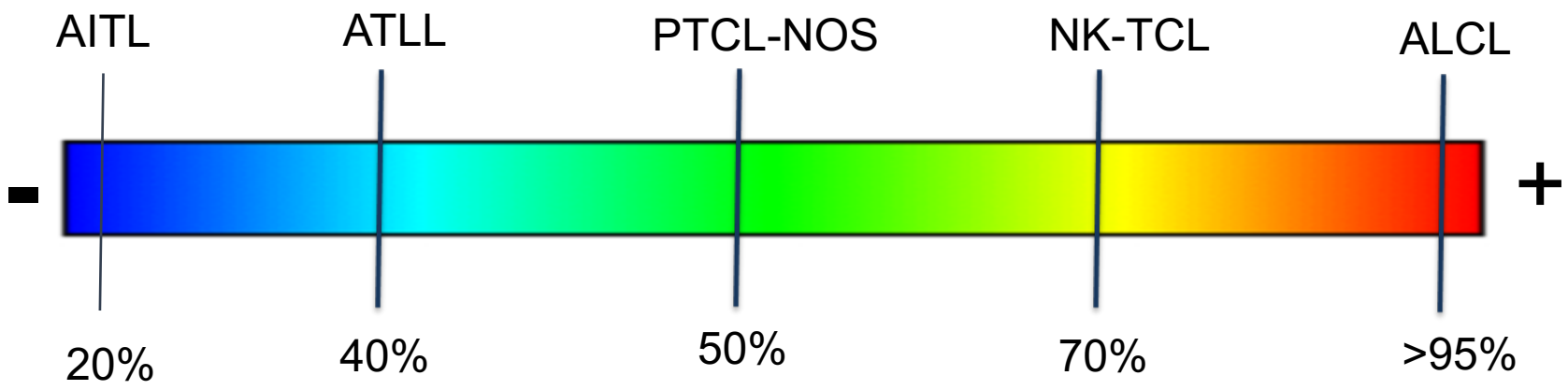
Vose J, et al. *J Clin Oncol*. 2008;26(25):4124-30; Laurent et al. *J Clin Oncol*. 2017;35(18):2008-17.

Outcomes in PTCL



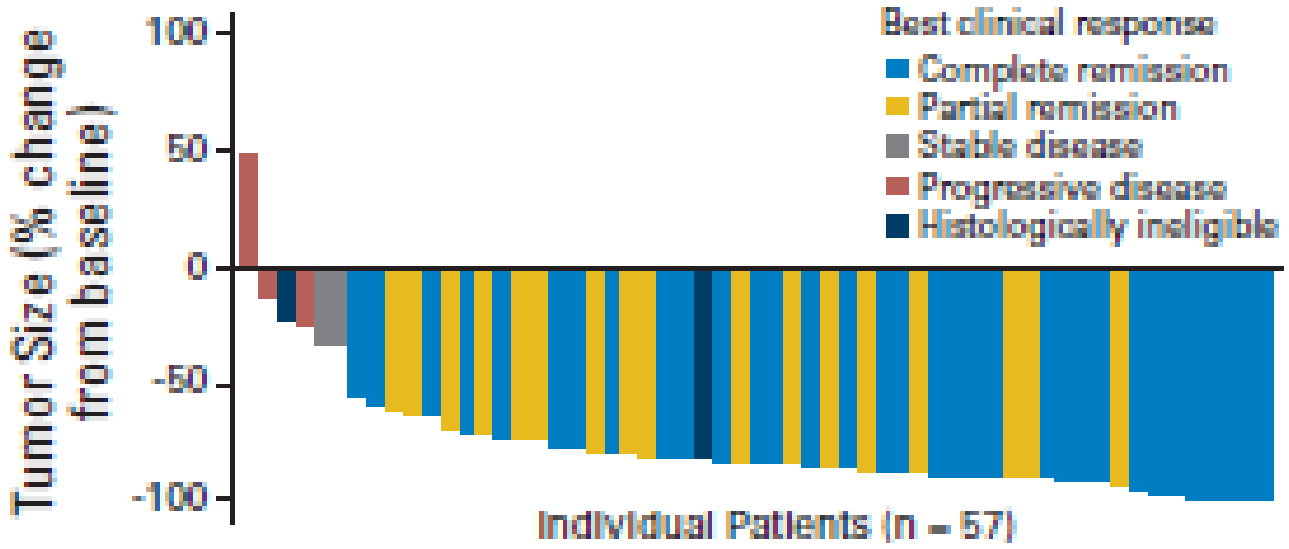
Vose J, et al. *J Clin Oncol*. 2008;26(25):4124-30.

CD30+ Spectrum in PTCL



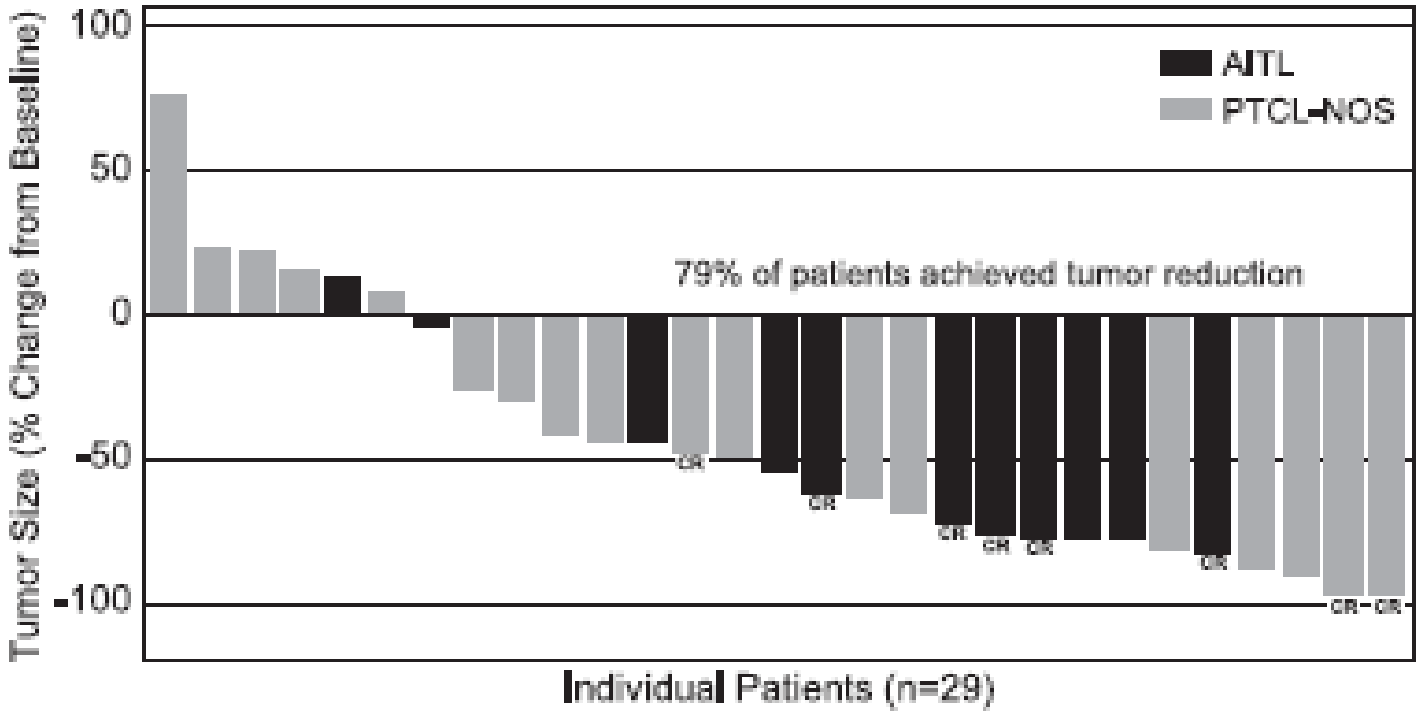
Sabattini E, et al. *Hematologica*. 2013;98(8):e81-e82.

Brentuximab Vedotin (BV) in ALCL



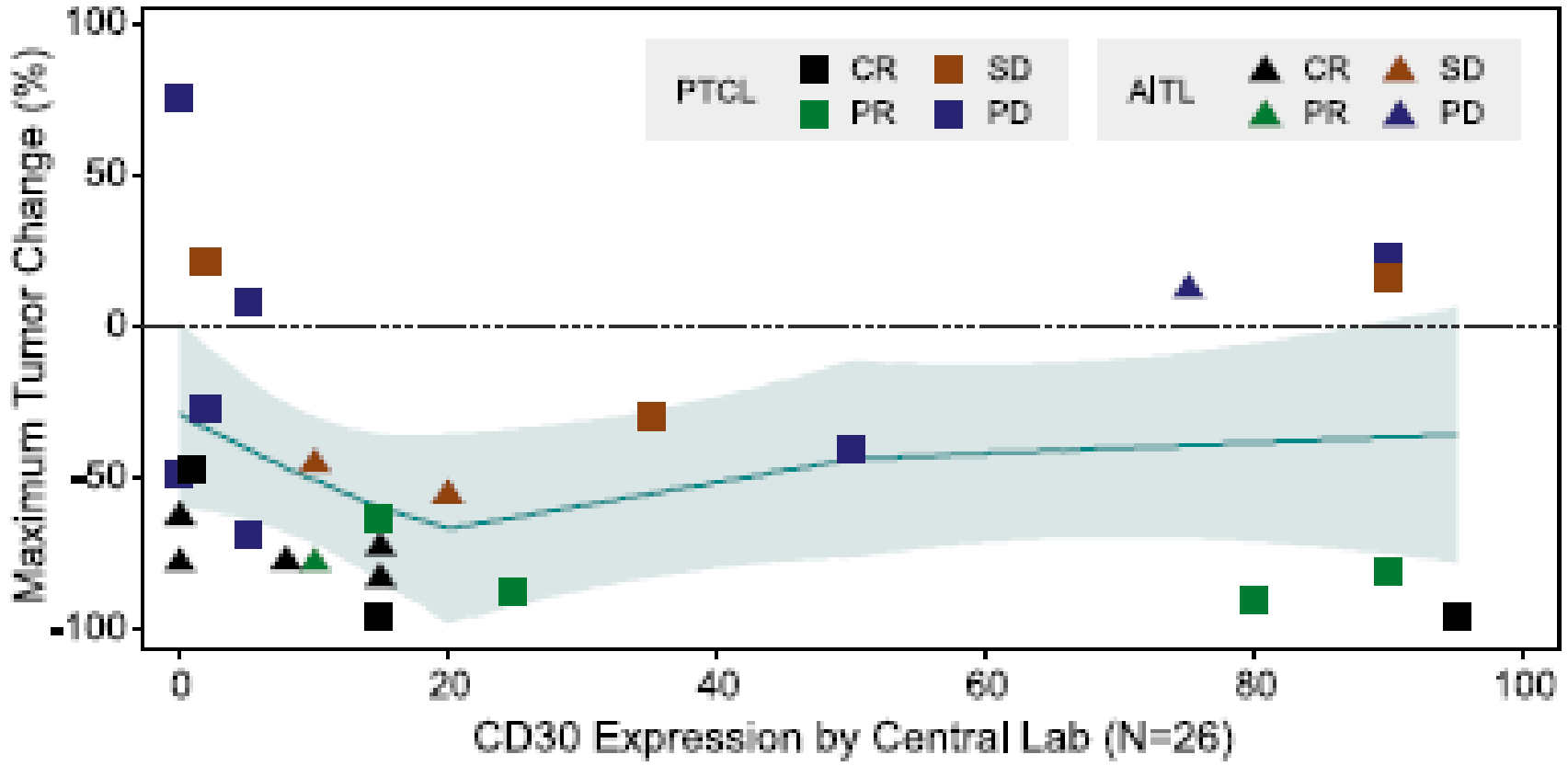
Pro B, et al. *J Clin Oncol*. 2012;30(18):2190-6.

Targeting Other PTCL Subtypes With BV



Horwitz SM, et al. *Blood*. 2014;123(20):3095-100.

Targeting Other PTCL Subtypes With BV



Horwitz SM, et al. *Blood*. 2014;123(20):3095-100.

BV + CHP in PTCL

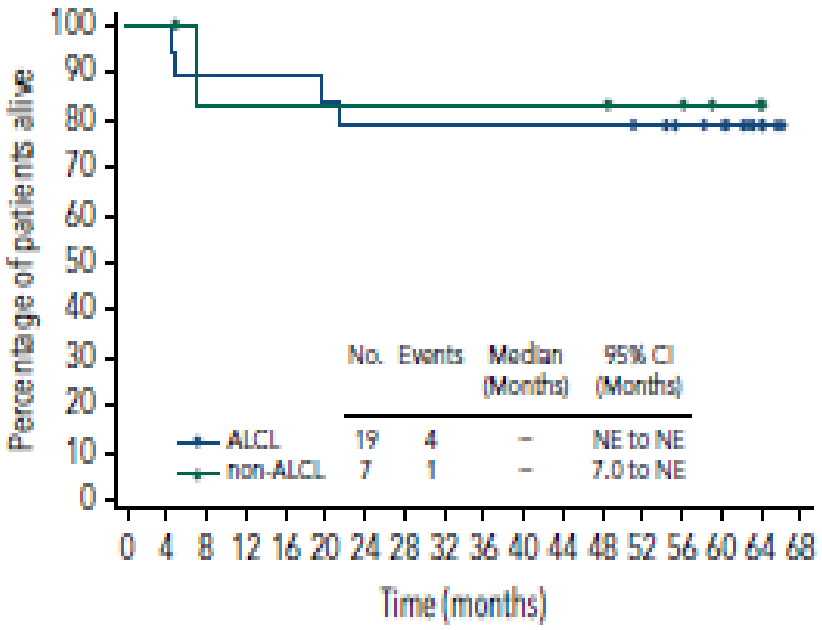
	Sequential ALCL (n = 13)		Combination					
			ALCL (n = 19)		Non-ALCL (n = 7)		Total (n = 26)	
Response	No.	%	No.	%	No.	%	No.	%
Objective response	11	85	19	100	7	100	26	100
Complete remission	8	62	16	84	7	100	23	88
Partial remission	3	23	3	16	0		3	12
Stable disease	0		0		0		0	
Progressive disease	2	15	0		0		0	

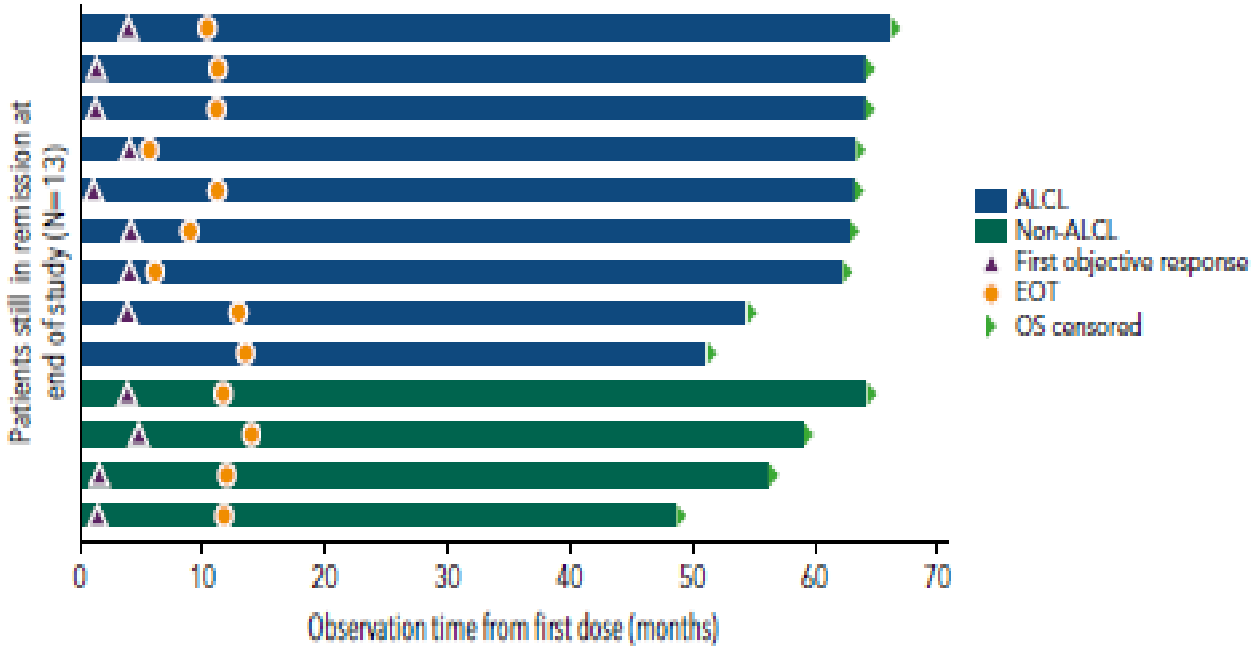
Table 2. CD30 Expression by IHC in Tumor Biopsies, Clinical Response, and Progression-Free Survival for Patients Without ALCL (n = 7)

Diagnosis	CD30+ Cells (%)*	Tumor H-Score†	Stage at Diagnosis	IPI Score	Response‡	PFS (months)
Adult T-cell leukemia/lymphoma	25	60	IV	3	CR	7.1
Adult T-cell leukemia/lymphoma	98	291	IV	5	CR	22.8§
Angioimmunoblastic T-cell lymphoma	20	38	IV	2	CR	17.6§
Angioimmunoblastic T-cell lymphoma	25	50	III	2	CR	4.1§
Enteropathy-associated T-cell lymphoma	60	165	IV	2	CR	7.0
Peripheral T-cell lymphoma NOS	50	150	IV	2	CR	22.2§
Peripheral T-cell lymphoma NOS	90	200	III	3	CR	19.4§

Fanale MA, et al. *J Clin Oncol*. 2014;32(28):3137-43.

BV + CHP in PTCL





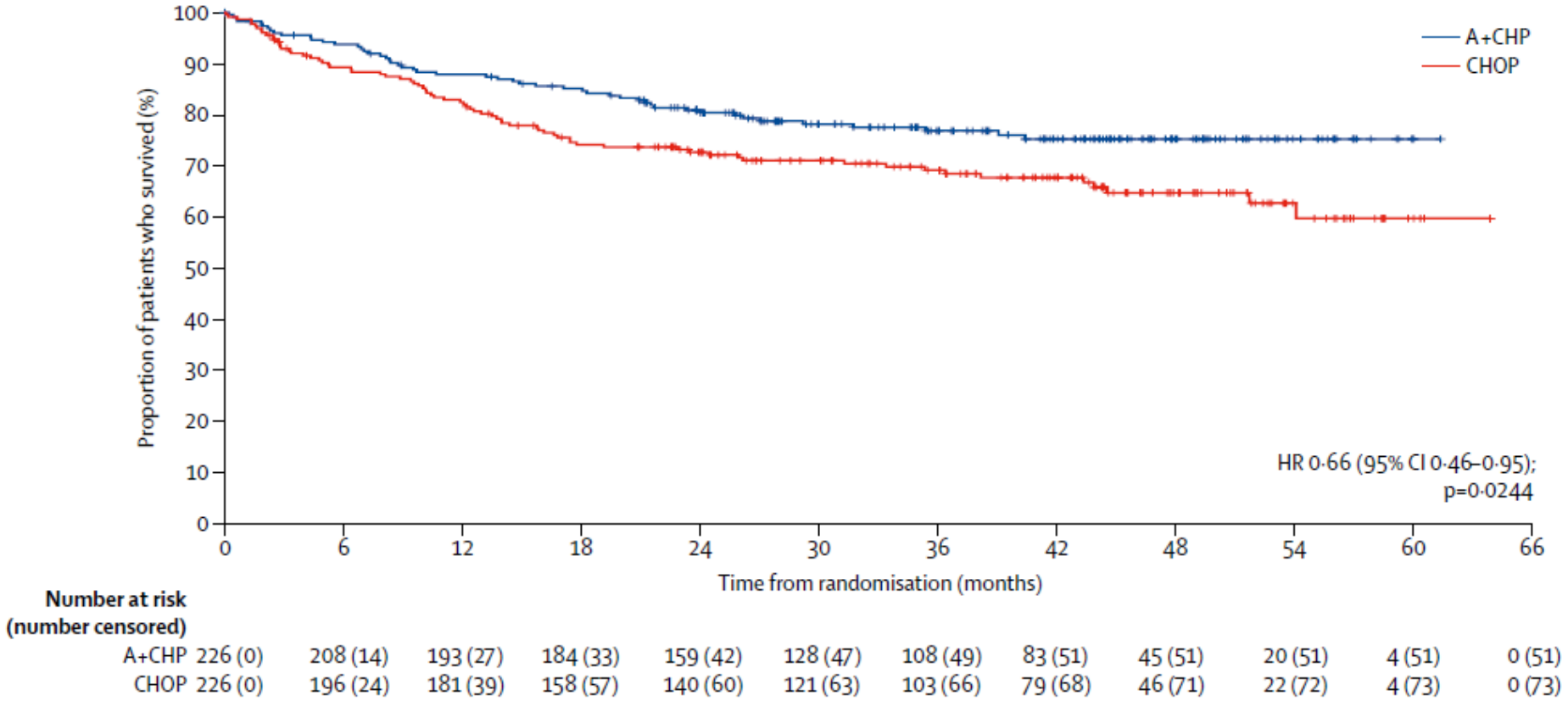
Fanale MA, et al. *J Clin Oncol*. 2014;32(28):3137-43.

ECHELON-2

- International
  - 144 sites
- Double blind
- Randomized
- Enrollment→ N = 452 patients
- BV + CHP vs CHOP
- Primary endpoints: PFS by independent review
- Secondary endpoints: PFS in patients with ALCL, complete remission rate, overall survival and objective response rate
- Approximately 75% ALCL
- Approximately 25% PTCL with ≥ 10% CD30

Horwitz S, et al. *Lancet*. 2019;393:229-40.

ECHELON-2

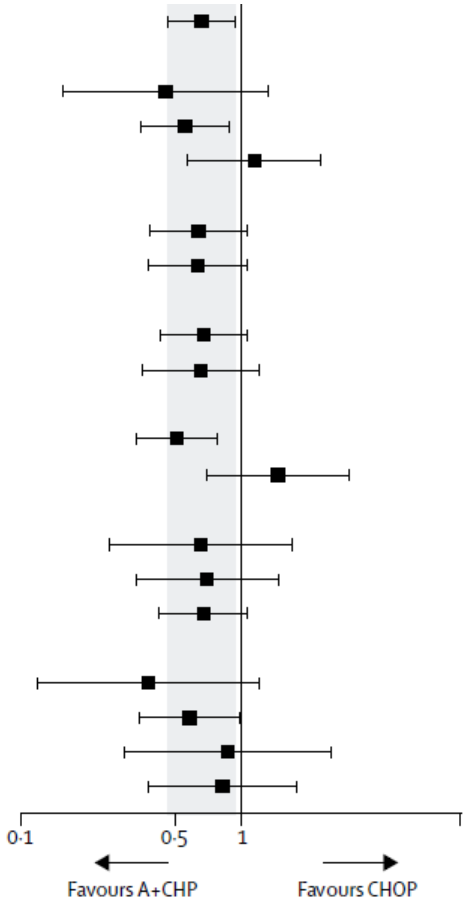


Number at risk (number censored)												
A+CHP	226 (0)	208 (14)	193 (27)	184 (33)	159 (42)	128 (47)	108 (49)	83 (51)	45 (51)	20 (51)	4 (51)	0 (51)
CHOP	226 (0)	196 (24)	181 (39)	158 (57)	140 (60)	121 (63)	103 (66)	79 (68)	46 (71)	22 (72)	4 (73)	0 (73)

Horwitz S, et al. *Lancet*. 2019;393:229-40.

Forest Plot

Overall	51/226	73/226	0·66 (0·46–0·95)
IPI Score			
0–1	5/52	10/48	0·46 (0·16–1·33)
2–3	29/141	48/145	0·56 (0·35–0·89)
4–5	17/33	15/33	1·15 (0·58–2·31)
Age			
<65 years	26/157	37/156	0·64 (0·39–1·06)
≥65 years	25/69	36/70	0·64 (0·38–1·08)
Sex			
Male	32/133	49/151	0·68 (0·43–1·06)
Female	19/93	24/75	0·66 (0·36–1·22)
Baseline ECOG status			
0–1	34/174	61/179	0·51 (0·34–0·78)
2	17/51	12/47	1·48 (0·70–3·11)
Disease stage			
1–2	7/42	12/46	0·66 (0·25–1·71)
3	13/57	17/67	0·71 (0·33–1·49)
4	31/127	44/113	0·68 (0·43–1·07)
Disease indication			
ALK-positive sALCL	4/49	10/49	0·38 (0·12–1·22)
ALK-negative sALCL	25/113	34/105	0·58 (0·35–0·98)
AITL	8/30	6/24	0·87 (0·29–2·58)
PTCL-NOS	11/29	20/43	0·83 (0·38–1·80)



Horwitz S, et al. *Lancet*. 2019;393:229-40.

Emerging Agents for Relapsed/Refractory Aggressive B-cell NHL

Case Study (Follow-up)

- Treated with R-CHOP x 6 cycles (Refractory; Deauville 5)
- Received R-ICE x 3 for salvage treatment in preparation for autologous stem cell transplant and remains with refractory disease (Deauville 5)

How would you treat him?

R-ICE = rituximab, ifosfamide, carboplatin, etoposide

Polatuzumab

	Diffuse large B-cell lymphoma (n=40)	Indolent NHL (n=30)	Mantle-cell lymphoma (n=7)	Chronic lymphocytic leukaemia (n=18)*
Age (years)	67 (20–81)	67 (41–86)	71 (60–85)	69 (54–74)
Sex				
Men	25 (63%)	22 (73%)	7 (100%)	13 (72%)
Women	15 (38%)	8 (27%)	0	5 (28%)
ECOG performance status				
0	11 (28%)	13 (43%)	2 (29%)	7 (39%)
1	19 (48%)	15 (50%)	4 (57%)	10 (56%)
2	10 (25%)	2 (7%)	1 (14%)	1 (6%)
Number of previous systemic therapies				
1	2 (5%)	2 (7%)	0	1 (6%)
2	3 (8%)	7 (23%)	4 (57%)	0
≥ 3	35 (88%)	21 (70%)	3 (43%)	17 (94%)
Previous stem-cell transplantation	13 (33%)	3 (10%)	2 (29%)	0
Refractory to last therapy†	31 (78%)	16 (53%)	4 (57%)	9 (50%)
Previous radiotherapy	21 (53%)	7 (23%)	1 (14%)	1 (6%)
Previous rituximab therapy (at any timepoint)	39 (98%)	28 (93%)	7 (100%)	17 (94%)

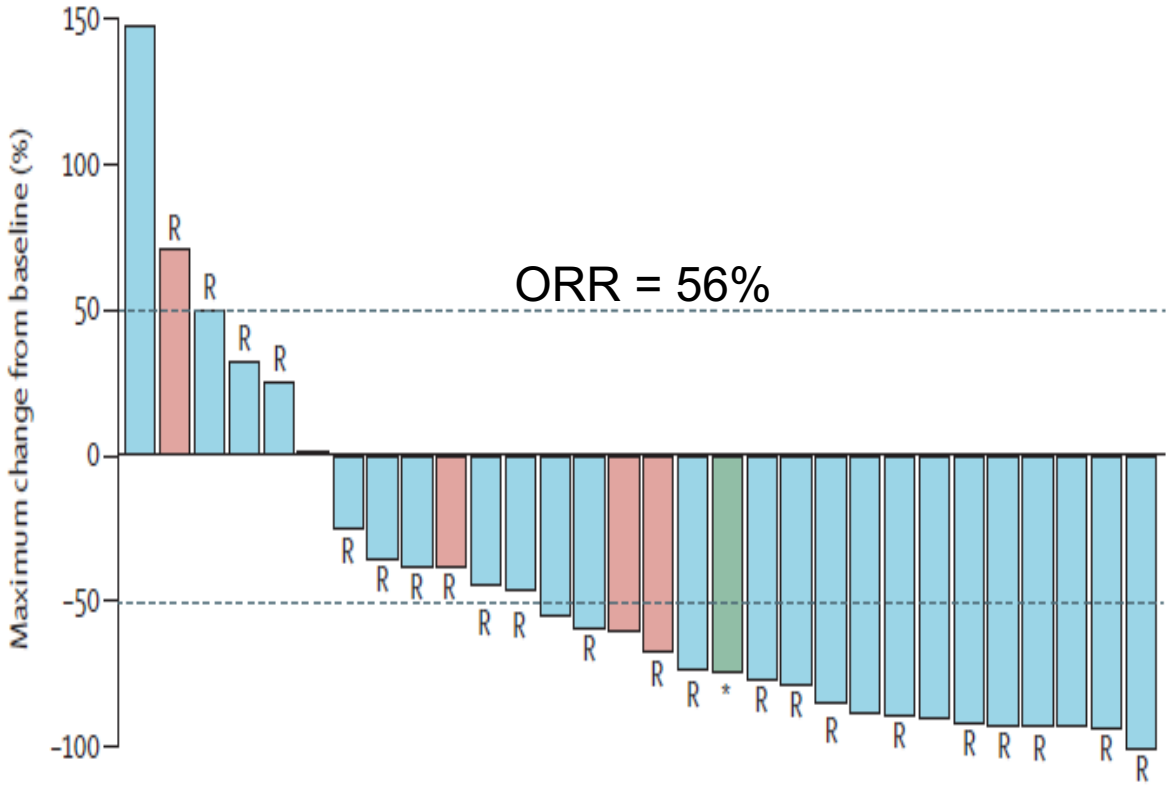
Palanca-Wessels, MCA, et al. *Lancet Oncol.* 2015;16(6):704-15.

Polatuzumab

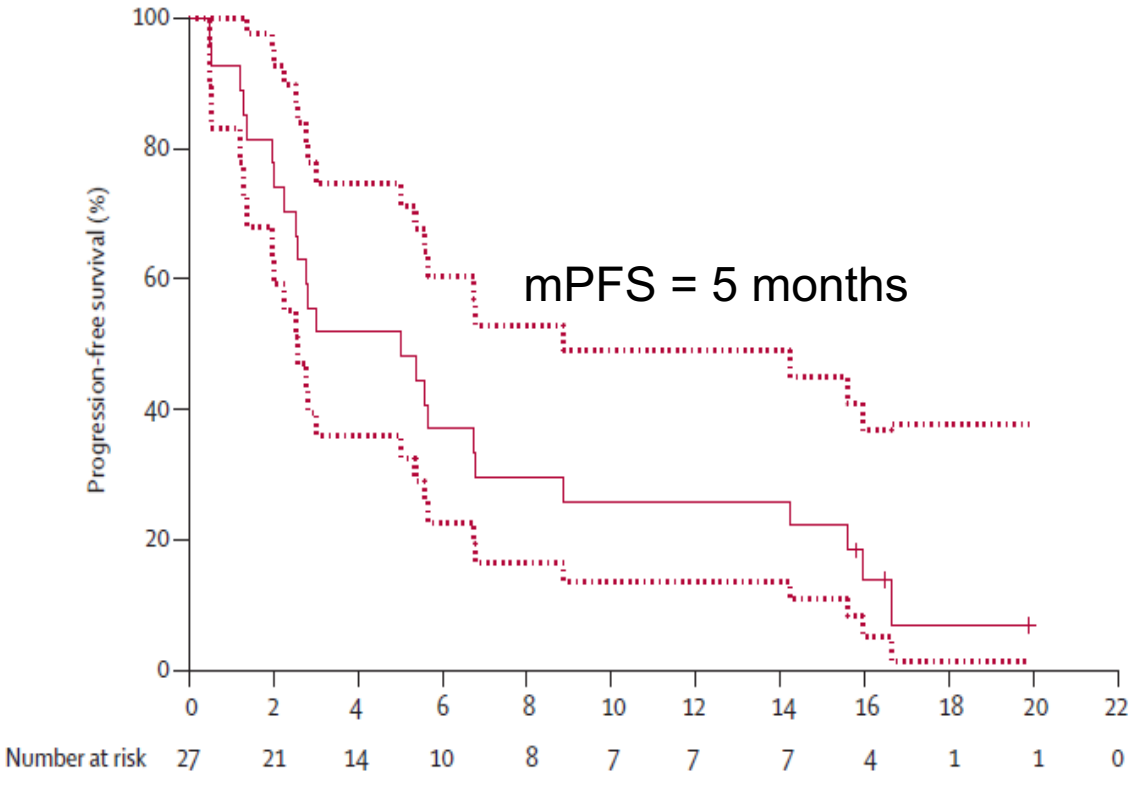
	Indolent B-cell lymphoma*		Diffuse large B-cell lymphoma			Mantle-cell lymphoma	
	<1·8 mg/kg (n=9)	2·4 mg/kg (n=16)	<1·8 mg/kg (n=8)	1·8 mg/kg (n=4)	2·4 mg/kg (n=27)	1·8 mg/kg (n=2)	2·4 mg/kg (n=2)
Complete response	0	3	0	0	4	0	0
Partial response	0	4	1	2	10	2	2
Stable disease	3	5	0	1	4	0	0
Progressive disease	5	3	7	1	7	0	0
Unable to evaluate†	0	0	0	0	1	0	0
Missing‡	1	1	0	0	1	0	0

Palanca-Wessels MCA, et al. *Lancet Oncol.* 2015;16(6):704-15.

Polatuzumab



ORR = 56%



mPFS = 5 months

mDOR = 5.7 months

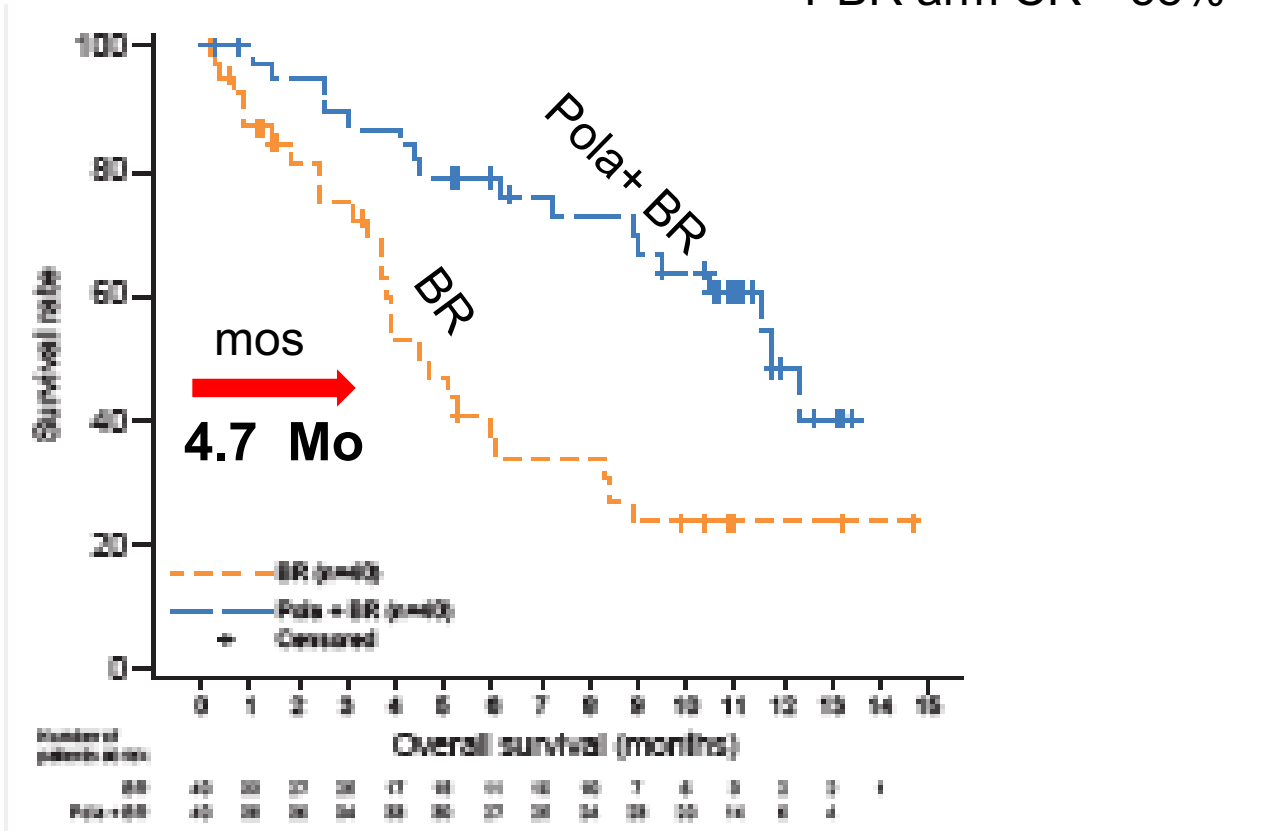
ORR = overall response rate; mPFS = median progression-free survival; mDOR = median duration of response.

Palanca-Wessels MCA, et al. *Lancet Oncol.* 2015;16(6):704-15.

Polatuzumab + BR

BR arm ORR 33%
BR arm CR—20%

PBR arm ORR 70%
PBR arm CR—58%

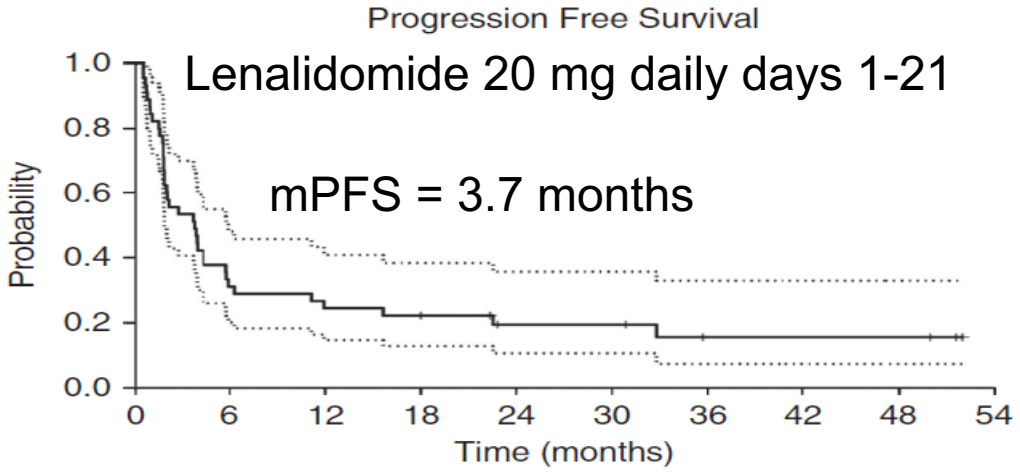


CR = complete response; BR = bendamustine-rituximab.

Sehn LH, et al. ASH 2017, abstract #2821.

Lenalidomide-Rituximab

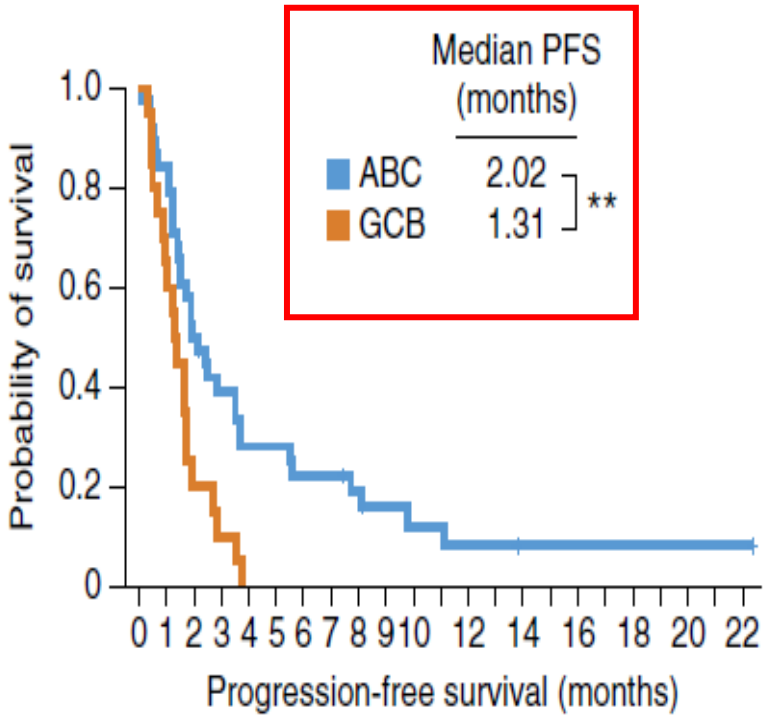
	All (n = 45)	*DLBCL* (n = 32)	*FLG3* (n = 4)	*Transformed* (n = 9)
Complete remission	10 (22%)	7 (22%)	0 (0%)	3 (33%)
Partial remission	5 (11%)	2 (6%)	1 (25%)	2 (22%)
Overall response	15 (33%)	9 (28%)	1 (25%)	5 (56%)
Stable disease	11 (24%)	9 (28%)	0 (0%)	2 (22%)
Progressive disease	15 (33%)	12 (37%)	3 (75%)	0 (0%)
Unevaluable patients	4 (9%)	2 (6%)	0 (0%)	2 (22%)
Progression-free survival (months)	3.7 (1.8–5.9)	2.8 (1.8–11.1)	2.0 (1.7–NR)	4.3 (3.9–NR)
Overall survival (months)				11.5 (6.3–NR)



Wang M, et al. *Leukemia & Lymphoma*. 2013;27(9):1902-9.

Ibrutinib

Characteristics	ABC (*N* = 38)	GCB (*N* = 20)	Unclassified (*N* = 17)	Unknown (*N* = 5)
Median age, years (range)	60 (34–89)	65 (28–92)	63 (44–85)	65 (58–78)
Sex (male)	66%	70%	82%	60%
ECOG performance score ≥ 2	5%	20%	24%	40%
RIPI (poor)	63%	59%	50%	60%
Median time from diagnosis, months (range)	19 (4–118)	17 (11–104)	21 (7–332)	19 (9–57)
Median number of prior regimens (range)	3 (1–7)	3.5 (1–7)	3 (1–4)	3 (1–3)
Prior ASCT	13%	30%	24%	40%
Chemotherapy-refractory disease	66%	65%	59%	50%

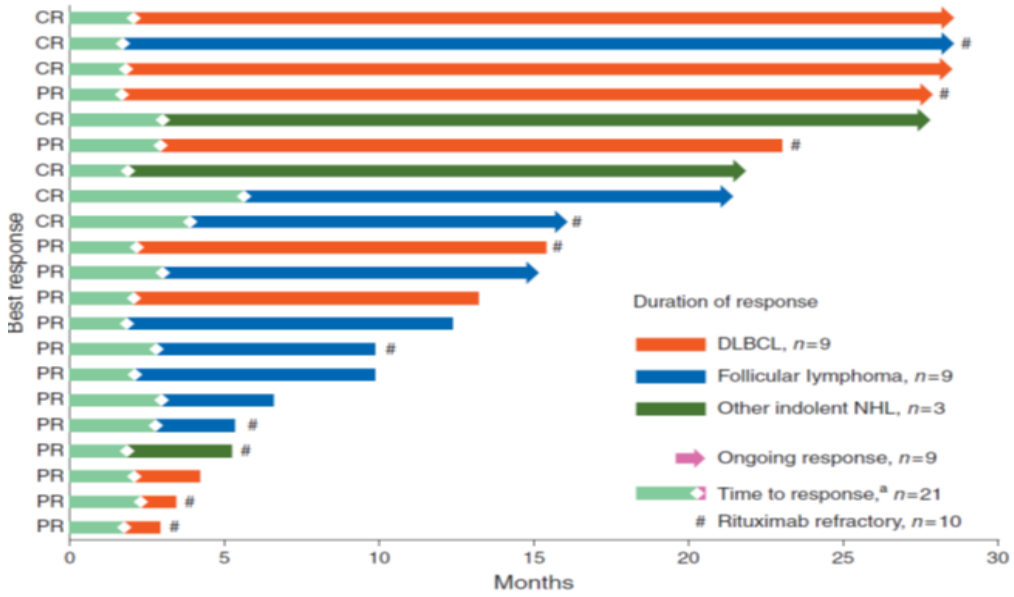


Wilson WH, et al. *Nat Med*. 2015;21:922-6.

Tarasitamab (MOR208)

Humanized, CD19 monoclonal antibody

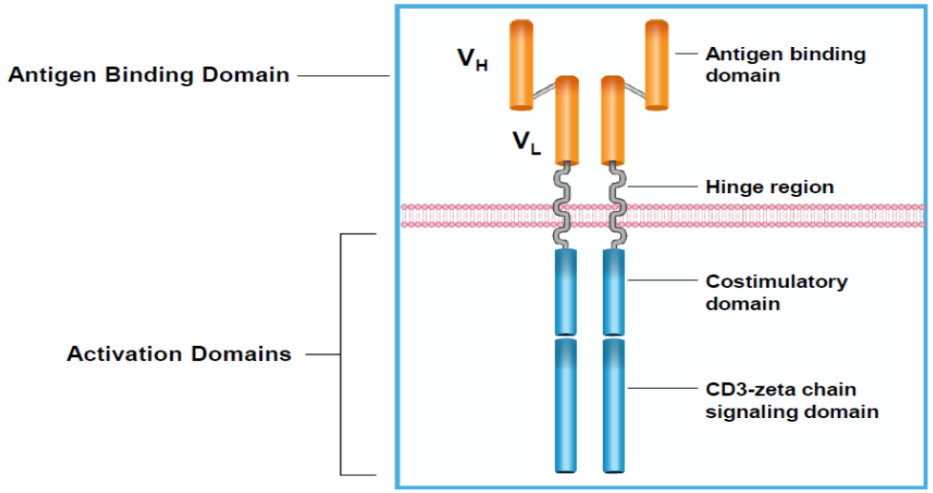
	DLBCL N = 35	FL N = 34	Other iNHL N = 11	MCL N = 12	Total N = 92
Best overall response					
Complete response	2 (6)	3 (9)	2 (18)	0	7 (8)
Partial response	7 (20)	7 (21)	1 (9)	0	15 (16)
Stable disease	5 (14)	16 (47)	4 (36)	6 (50)	31 (34)
Progressive disease	11 (31)	4 (12)	3 (27)	5 (42)	23 (25)
Not evaluable[a]	10 (29)	4 (12)	1(9)	1 (8)	16 (17)
ORR (all patients)	9 (26)	10 (29)	3 (27)	0	22 (24)
ORR (assessable patients only[b])	9 (36)	10 (33)	3 (30)	0	22 (29)
DCR (all patients)	14 (40)	26 (76)	7 (64)	6 (50)	53 (58)



- The Fc region is enhanced to potentiation of ADCC and antigen-dependent cell mediated phagocytosis
- MOR208 also directly induces cytotoxicity and is postulated to disrupt B-cell antigen receptor signaling.

Jurzcak W, et al. *Ann Oncol*. 2018;29(5):1266-72.

Chimeric Antigen Receptor (CAR) T-cell Therapy



CAR-T Product	Viral Vector	Costimulatory
Axi-Cel (KiTE/Gilead)	Gamma-retrovirus	CD28
Tisagenlecleucel (Novartis)	Lentivirus	41BB
Liso-Cel (JUNO/Celgene)	Lentivirus	41BB

Axi-Cel

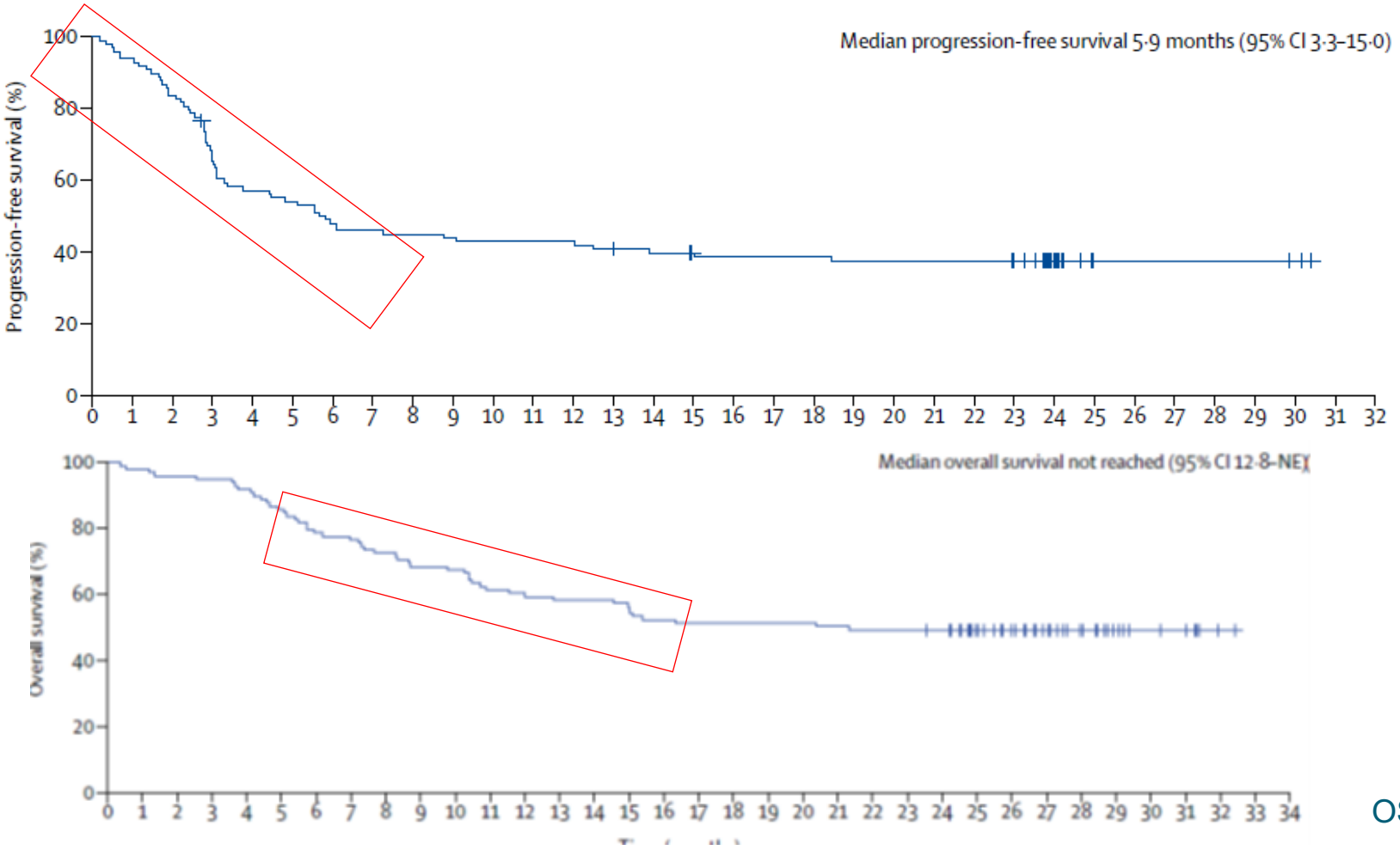
CAR-T Product	Viral Vector	Costimulatory
Axi-Cel (KiTE/Gilead)	Gamma-retrovirus	CD28
Tisagenlecleucel (Novartis)	Lentivirus	41BB
Liso-Cel (JUNO/Celgene)	Lentivirus	41BB

State of Axi-Cel

	N=101	
Median follow-up (months)	27.1	
	ORR	**CR**
Best overall response rate (ORR; %)	**83%**	**58%**
Refractory > /+ 2 lines		**53%**
Relapse within 12 months post auto txp		**72%**
Double expressers (MYC, BCL2, and BCL6)		**68%**
Duration of response (DOR; months)	11.1 (4.2 to NE)	
Median progression-free survival (PFS; months)	5.9 (95% CI, 3.3 to 15)	

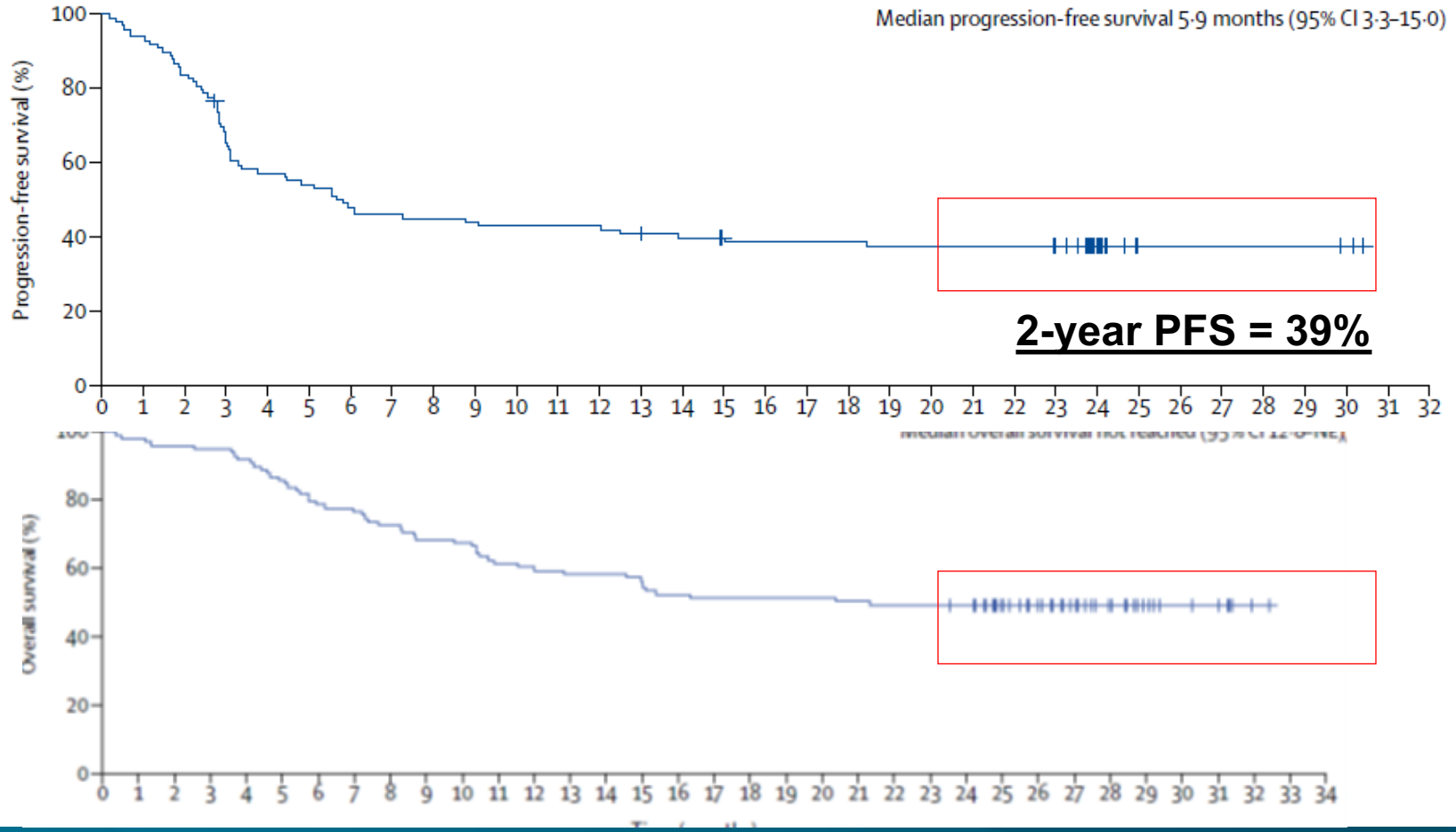
Neelapu SS, et al. *NEJM*. 2018;377:2531-44; Neelapu SS, et al. *Lancet Oncol*. 2018.

Efficacy of Axi-Cel



OS = overall survival

The Durability of Axi-Cel



Neelapu SS, et al. *Lancet Oncol* 2019

Tisagenlecleucel

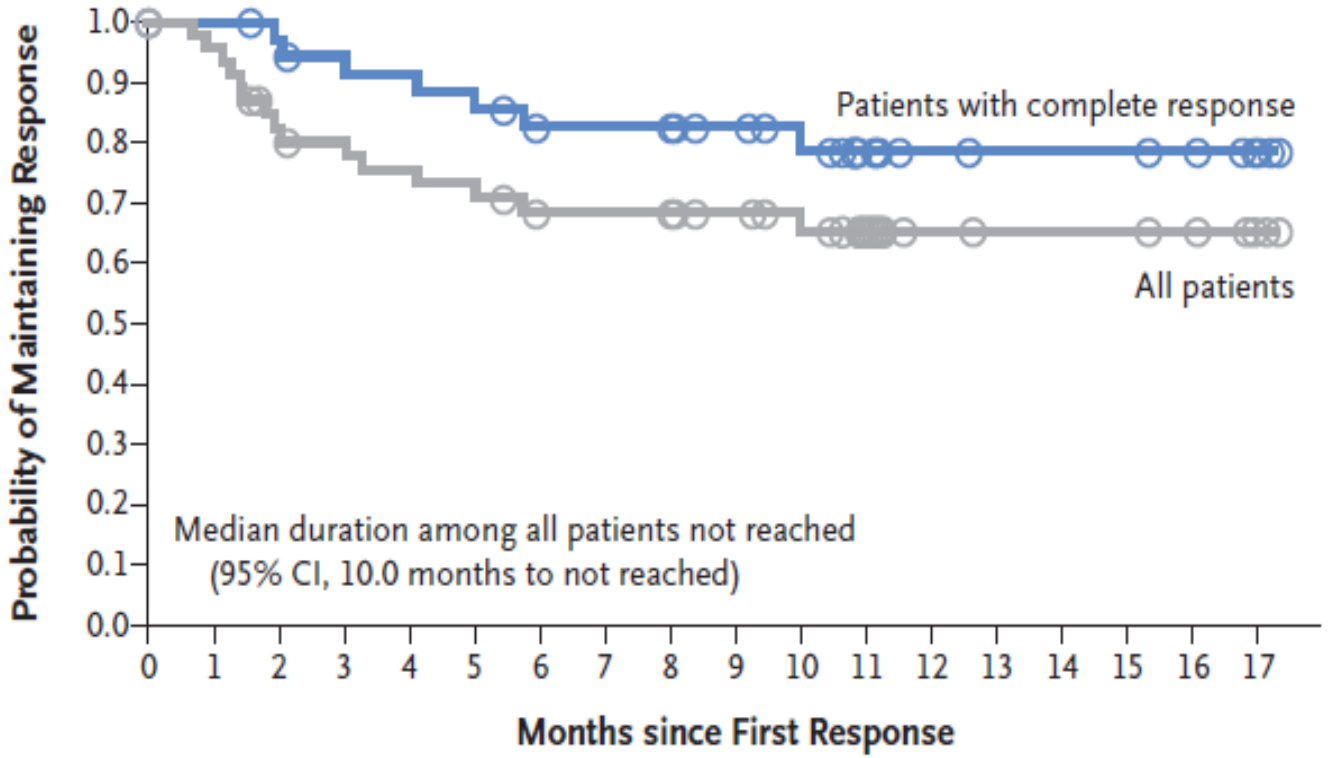
CAR-T Product	Viral Vector	Costimulatory
Axi-Cel (KiTE/Gilead)	Gamma-retrovirus	CD28
Tisagenlecleucel (Novartis)	Lentivirus	41BB
Liso-Cel (JUNO/Celgene)	Lentivirus	41BB

State of Tisagenlecleucel

	N=93	
Median Follow-up (Months)	14.0	
	ORR	**CR**
Best ORR (%) within 3 months of infusion	**52%**	**40%**
< 65	**49%**	
> 65	**59%**	
12 months post response (%)		
Relapse-free survival	**65%**	
Relapse-free in CR	**79%**	

Schuster SJ, et al. *NEJM*. 2019;380:45-56.

Duration of Remissions of Tisagenlecleucel



Schuster SJ, et al. *NEJM*. 2019;380:45-56.

Liso-Cel

CAR-T Product	Viral Vector	Costimulatory
Axi-Cel (KiTE/Gilead)	Gamma-retrovirus	CD28
Tisa-Cel (Novartis)	Lentivirus	41BB
Liso-Cel (JUNO/Celgene)	Lentivirus	41BB

Efficacy of Liso-cel
Liso-cel (not FDA approved)

- Individually formulated CD4 and CD8 suspensions through lentiviral transduction
- Low ALC requirement
- Flat dosing
  - 1:1 ratio of CD4:CD8
- 41BB costimulatory
  - CD8-→ Target tumor
  - CD4 → T-cell persistence and target tumor

Abramson J, et al. EHA 2018

Design of TRANSCEND

Core group

- DLBCL-NOS
- Transformed FL
- High grade B-cell lymphoma (DH/TH)

- ECOG 0-1
- No ALC minimum

Dosing levels

- 5 x 10^7 cells single dose (DL1S)
- 5 x 10^7 cells double dose (DL1D)
- 1 x 10^8 cells single dose (DL2S)

Abramson J, et al. EHA 2018

Efficacy of Liso-cel

Pivotal Cohort

Core & DLS2	N=37
Best ORR	80%
Best CR	55%
ORR @ 6 months	50%
CR @ 6 months	50%

Abramson J, et al. EHA 2018

Axi-Cel Toxicities

	CRS	NT
All grades	93%	64%
Grade ≥ 3	13%	28%
Median time to onset (range) in days	2 (1-12)	5 (1-17)
Median time to resolution	8 days	17 days
Tocilizumab usage	43%	
Dexamethasone usage	27%	

CRS Grading per Lee et al; Neurotoxicity (NT) Grading = CTAE 4.03

CRS = cytokine release syndrome

Neelapu SS, et al. NEJM. 2018; Neelapu SS, Lancet Oncol 2019.

Tisagenlecleucel Toxicities

	CRS*	NT
All grades	58%	21%
Grade ≥ 3	22%	12%
Median time to onset (range) in days	3	6
Median time to resolution	7	14
Tocilizumab usage	14%	
Dexamethasone usage	10%	

*CRS = UPENN criteria; NT = CTAE 4.03

Schuster SJ, et al. *NEJM*. 2019;380:45-56.

Liso-Cel Toxicities

Core & DL2S or Full	CRS	NT
All grades	37%	25%
Grade ≥ 3	3%	15%
Median time to onset (range) in days	5	10
Median time to resolution	NR	NR
Tocilizumab usage (FULL)	17%	
Dexamethasone usage	21%	

CRS Grading per Lee et al; NT = CTAE 4.03; NR = not reported

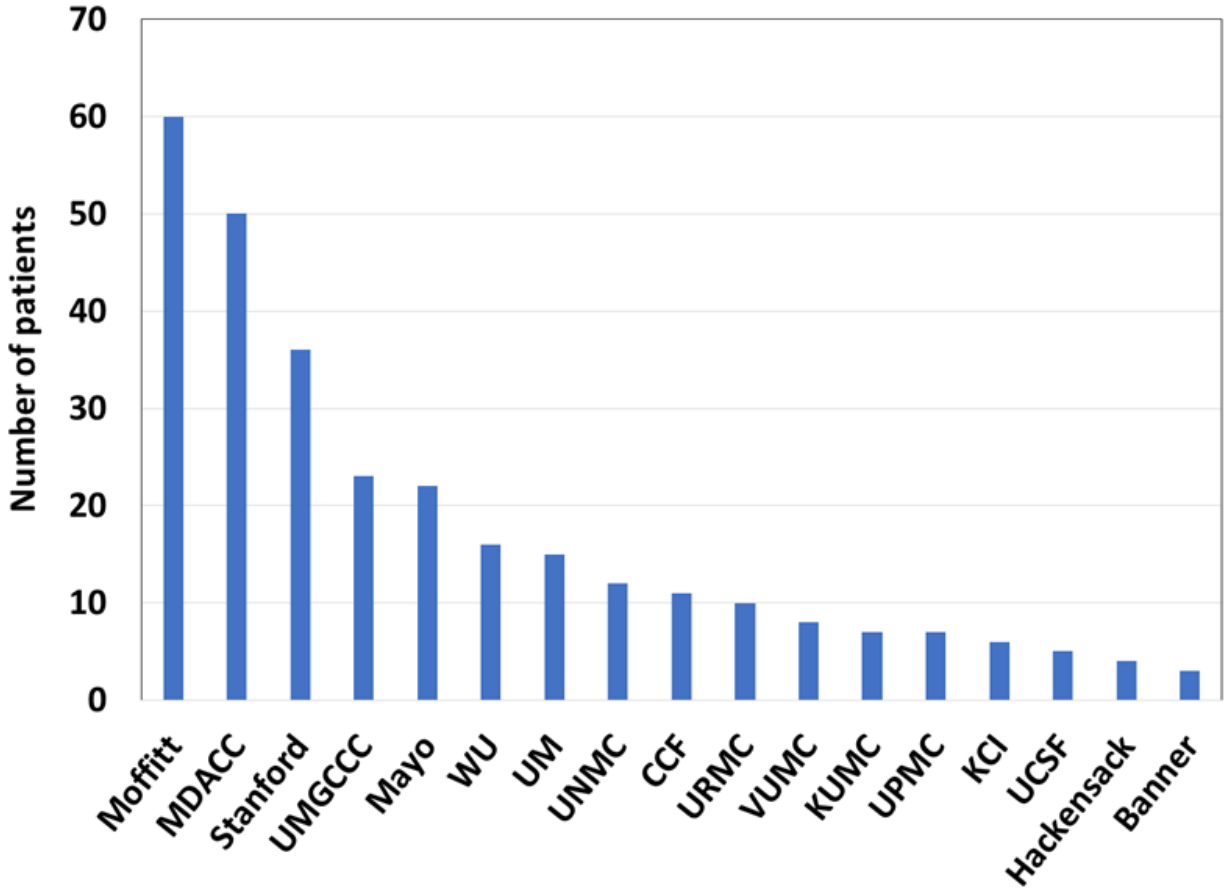
Abramson J, et al. EHA 2018

State of CAR-T

Clinical Trials

Real World

Fighting DLBCL as One



Nastoupil LJ, et al. ASH 2018

Real-World Experience

Criteria Excluded from ZUMA-1	N=124 N (%)
Platelets < 75	37 (13)
Active DVT/PE	27 (9)
Prior CD19 or CAR T cell therapy	24 (8)
GFR < 60	22 (8)
History of CNS lymphoma	22 (8)
Symptomatic pleural effusion	11 (4)
LVEF < 50%	10 (4)
Prior allogeneic SCT	7 (2)

DVT = deep vein thrombosis; PE = pulmonary embolism; GFR = glomerular filtration rate; LVEF = left ventricular ejection fraction; SCT = stem cell transplant.

Nastoupil LJ, et al. ASH 2018

Outcomes

	SOC Axi-cel Evaluable	SOC Axi-Cel	ZUMA-1[1] N=108
Median follow up, months		3.9	15.4
Day 30 ORR, N (%)	238	191 (80)	N/A
Day 30 CR, N (%)		113 (47)	N/A
Best ORR at Day 90, N (%)	248[a]	201 (81)	89 (82)
Best CR at Day 90, N (%)		142 (57)	63 (58)

Nastoupil LJ, et al. ASH 2018

Too Sick to CAR?

Characteristic	CR at 3 months*, N (%)	P-value
Age <60 vs. ≥60	37 (51) vs. 52 (64)	0.11
DLBCL vs. PMBCL vs. TFL	59 (58) vs. 4 (40) vs. 26 (63)	0.41
COO GCB vs. ABC	50 (62) vs. 30 (53)	0.29
DHL/THL vs. Not	19 (59) vs. 65 (57)	0.77
IPI 0-2 vs. 3-5	45 (58) vs. 43 (58)	0.96
Bridging therapy Yes vs. No	40 (53) vs. 49 (64)	0.17
Tocilizumab Yes vs. No	51 (58) vs. 38 (59)	0.86
Steroids Yes vs. No	49 (58) vs. 40 (61)	0.71
ICU Admission Yes vs. No	26 (52) vs. 63 (61)	0.28

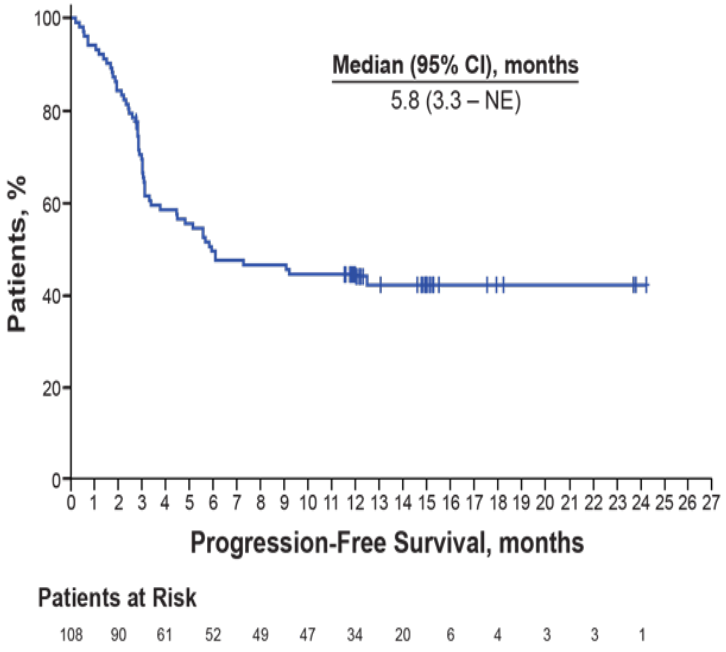
Nastoupil LJ, et al. ASH 2018

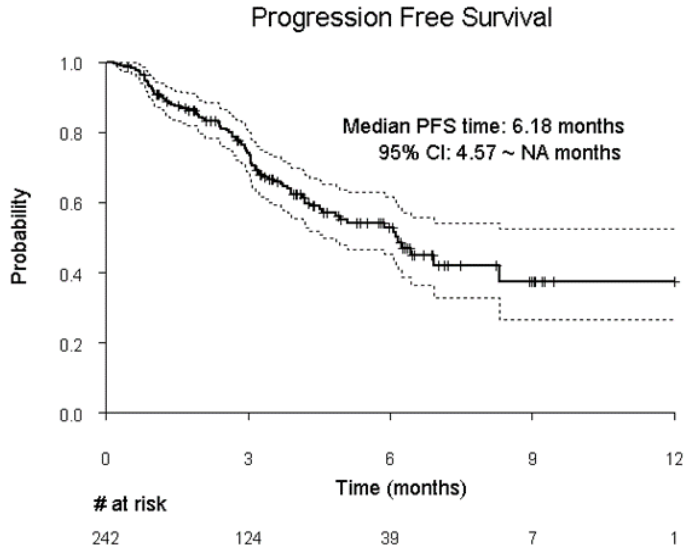
Fittest Patients?

Characteristic	CR at 3 months*, N (%)	P-value
Female vs. male	39 (72) vs. 50 (51)	0.009
ECOG 0-1 vs. ≥ 2	82 (62) vs. 7 (35)	0.024
Relapsed vs. primary refractory/refractory	27 (79) vs. 24 (47)/38 (56)	0.011
Non-bulky vs. bulky (≥ 10cm)	76 (62) vs. 13 (42)	0.040
Met eligibility for ZUMA-1 vs. not	62 (65) vs. 27 (47)	0.037

Nastoupil LJ, et al. ASH 2018

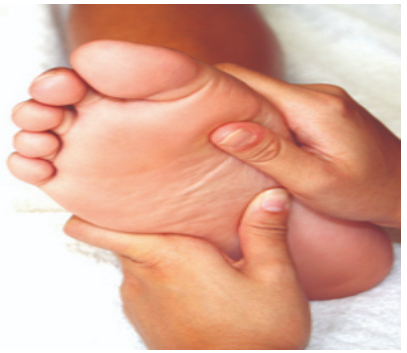
Should We Keep Going With CAR-T?





Nastoupil LJ, et al. ASH 2018; Neelapu S, et al. *Lancet Oncol* 2019.

Antibody Drug Conjugates



	Brentuximab vedotin	Polatuzumab vedotin
Indications (aggressive NHL) summary	• Systemic anaplastic large cell lymphoma (ALCL) after failure of at least 1 prior multiagent regimen	• Relapsed/refractory diffuse large B-cell lymphoma, not otherwise specified, after at least 2 prior therapies
Dose	• 1.8 mg/kg IV over 30 minutes every 3 weeks (max dose 180 mg) • Continue treatment until a maximum of 16 cycles, disease progression, or unacceptable toxicity	• 1.8 mg/kg IV over 90 minutes every 21 days for 6 cycles in combination with BR • Subsequent infusions may be administered over 30 minutes if previous tolerated
Cautions	Peripheral neuropathy, infusion reactions, neutropenia, tumor lysis syndrome, Stevens-Johnson syndrome	Peripheral neuropathy, infusion reactions, myelosuppression, infections, progressive multifocal leukoencephalopathy, tumor lysis syndrome, hepatoxicity
Most common adverse events (≥20%)	Anemia, cough, diarrhea, fatigue, nausea, neutropenia, peripheral neuropathy (sensory), pyrexia, rash, thrombocytopenia, upper respiratory infection, vomiting	Neutropenia, thrombocytopenia, anemia, peripheral neuropathy, fatigue, diarrhea, pyrexia, decreased appetite, pneumonia

BR = bendamustine/rituximab

Matasar M, et al, EHA 2017

Management of Common Lenalidomide Toxicities

Symptom	Description	Intervention
GI complaints	• Usually mild/intermittent cramping and/or diarrhea • Decreased appetite	• Diet control • Dose reduction
Myelosuppression (neutropenia, thrombocytopenia)	• Predominant toxicity • Occurs most often with higher doses • More common in combination with dexamethasone/steroids	• Monitor CBC bi-weekly for first 12 weeks of treatment and monthly thereafter • Hold drug or reduce dose • Transfusions, growth factors
Rash	• Usually resolves within 1 week	• Antihistamine Q4-6 hours • Discontinue if any signs of toxic epidermal necrosis
Thromboembolic events (DVT, PE)	• More common in combination with dexamethasone/steroids	• Anticoagulation recommended • Monitor coagulation assays

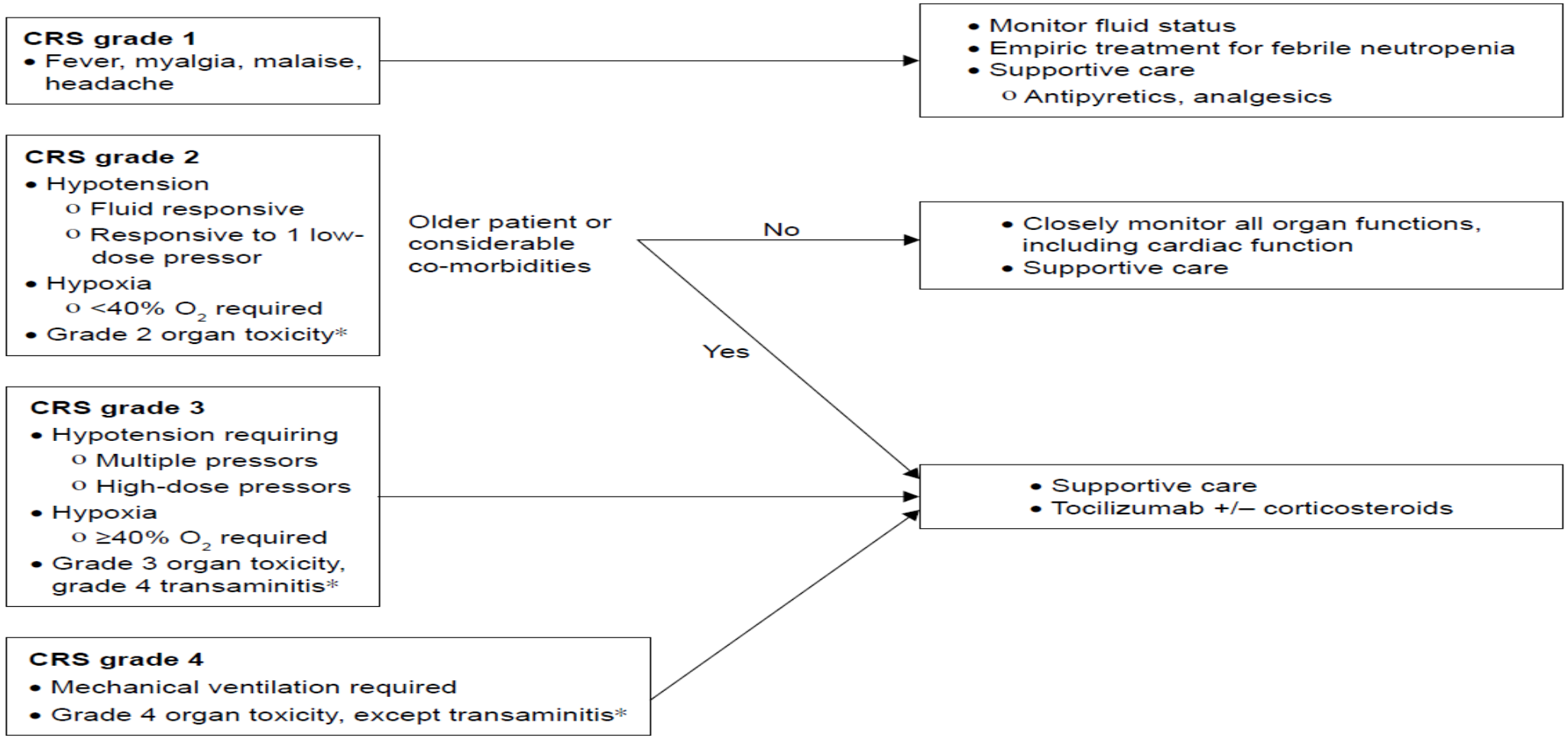
Revlimid (lenalidomide) prescribing information.

BTK Inhibitors

	Ibrutinib	Acalabrutinib	Zanubritinib
Indications (aggressive NHL summary) and Dose	Mantle cell lymphoma (MCL) who have received at least one prior therapy. *Accelerated approval was granted for this indication based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial • 560 mg PO once daily	Mantle cell lymphoma (MCL) who have received at least one prior therapy. *This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. • 100 mg PO every 12 hours	Breakthrough therapy designation from the FDA for the treatment of adult patients with mantle cell lymphoma (MCL) who have previously received at least 1 prior therapy • 160 mg twice daily
Common AEs (>20%) in B-cell malignancies:	Thrombocytopenia, diarrhea , anemia, neutropenia, musculoskeletal pain, rash, bruising, nausea, fatigue, hemorrhage, pyrexia	Anemia, thrombocytopenia, head ache, neutropenia, diarrhea, fatigue, myalgia, bruising	Neutropenia, upper respiratory tract infection, rash, thrombocytopenia

FDA Prescribing Information; Rogers B, et al. *J Adv Pract Oncol.* 2017

Post-Infusion CRS Management



Riegler LL, et al. *Ther Clin Risk Manag*. 2019;15:323-35; Adkins S. *J Adv Pract Oncol*. 2019.

Grading of Neurologic Events With the ASBMT ICANS Tool

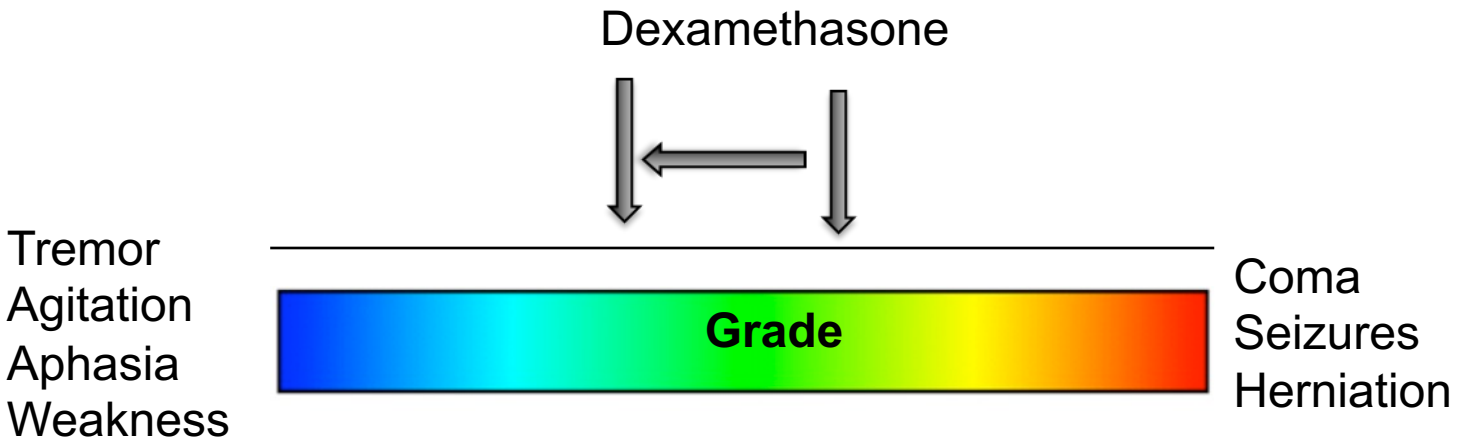
Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score*	7-9	3-6	0-2	0 (patient is unarousable and unable to perform ICE)
Depressed level of consciousness†	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 min); or Repetitive clinical or electrical seizures without return to baseline in between
Motor findings‡	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP/cerebral edema	N/A	N/A	Focal/local edema on neuroimaging§	Diffuse cerebral edema on neuroimaging; Decerebrate or decorticate posturing; or Cranial nerve VI palsy; or Papilledema; or Cushing's triad

ICANS: immune effector cell (IEC) associated neurotoxicity syndrome

Lee D, et al. *BBMT*. 2019;25(4):625-38.

Management of ICANS

"Shake of the Hand"



Other considerations during ICANS:

- Keppra
- MRI
- EEG
- LP

Adkins S. *J Adv Pract Oncol.* 2017; Perrinjaquet C, et al. *Curr Opin Neurol.* 2019;32:500-10.

Case Study

- Received CAR T-cell therapy with axicabtagene ciloleucel (Axi-cel)
- While inpatient the APP on-call was called to the patient's room on Day +3 developed fever of 39.5 C with rigors/chills. Ox saturation 88% on room air; HR 135 BPM; BP 80/50 mm/Hg but improved with 500 cc bolus of NaCl. Blood and urine cultures were obtained. CXR was negative.
  - Started on cefepime IV (neutropenic). His CRP and ferritin levels were trending up.
  - His neurologic exam was normal with ICE score 10/10.
  - He was found to have a grade 2 CRS (due to fever and hypotension).
    - He was given tocilizumab at 8 mg/kg x1 dose and his fever resolved.
  - The following day he maintained his oxygen saturation and vitals remained stable except for a fever of 39.2 C which improved with intermittent acetaminophen.
  - The attending physician and APP were on continuous interaction regarding the patient's status.

Case Study

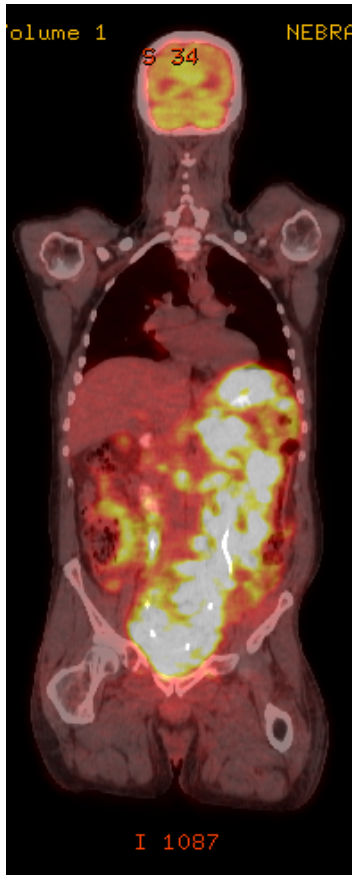
On day +5 his C-reactive protein and ferritin levels continued to trend up. In the evening, he developed altered mental status changes. He was not able to state the year or month or the follow a simple command and his handwriting and deteriorated.

- An electroencephalogram was negative and CT of brain showed no evidence of cerebral edema.
- An LP was also negative.
- The patient was determined to have a grade 3 neurologic event (ICE score 2).
- He was started on dexamethasone 10 mg IV every 6 hours.
- His mental status improved within 24 hours and the drug was tapered.

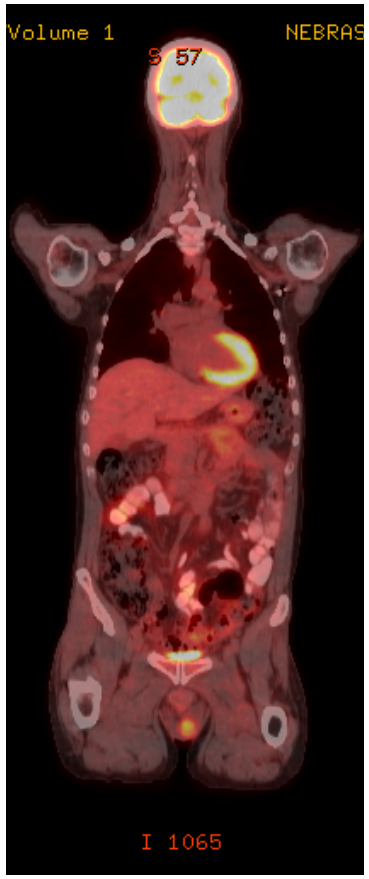
His C-reactive protein and ferritin levels started trending down, and he was discharged on day +14.

Case Study

Pre-CAR-T

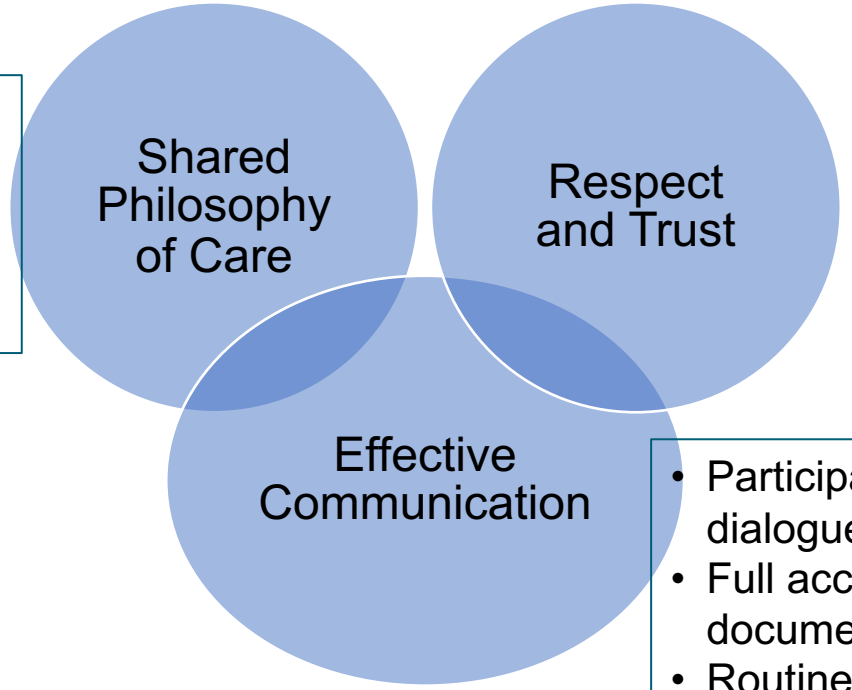


D+100



APP/Physician Collaborative Model

- Method to resolve conflicting opinions
- Clinical alignment
- Similar work ethic
- Mutual goals for patient care
- Agreement on rationale for care plan



- Clear understanding of roles and expectations
- Knowledge of each other's care management expertise
- Mutual respect of disciplines
- Trust of each other's care decision

- Participate in open and respectful dialogue
- Full access to each other's patient care documentation
- Routine multidisciplinary team meetings
- Mutual medical language

Adapted from Am Fam May/June 2018

Clinical Pearls

- R-CHOP remains a standard of care for aggressive B-cell lymphoma, but other novel therapies such as antibody drug conjugates and immunomodulators show promise for relapsed or refractory disease.
- CAR T-cell therapy for relapse/refractory aggressive B-cell lymphoma have demonstrated activity with evidence of durable responses.
- Prompt recognition of CRS and neurological events post CAR-T are crucial.
- APPs play a vital role in the management of adverse events associated with these new novel agents including CAR-T in the treatment of aggressive lymphomas.
- Close collaboration with the multidisciplinary team is essential for positive patient outcomes and successful implementation of this therapy.

More Questions?

Come see Katherine Byar at Booth #829 (next to the APSHO booth) in the Exhibit Hall from **10:15** to **11:15 am** tomorrow.

SMARTIE

This has been a SMARTIE presentation.

To access your post-session questions, you can:

- Click on the link that was sent to you via email
- Visit the SMARTIE station
- Go to jadprolive.com/smartie2019