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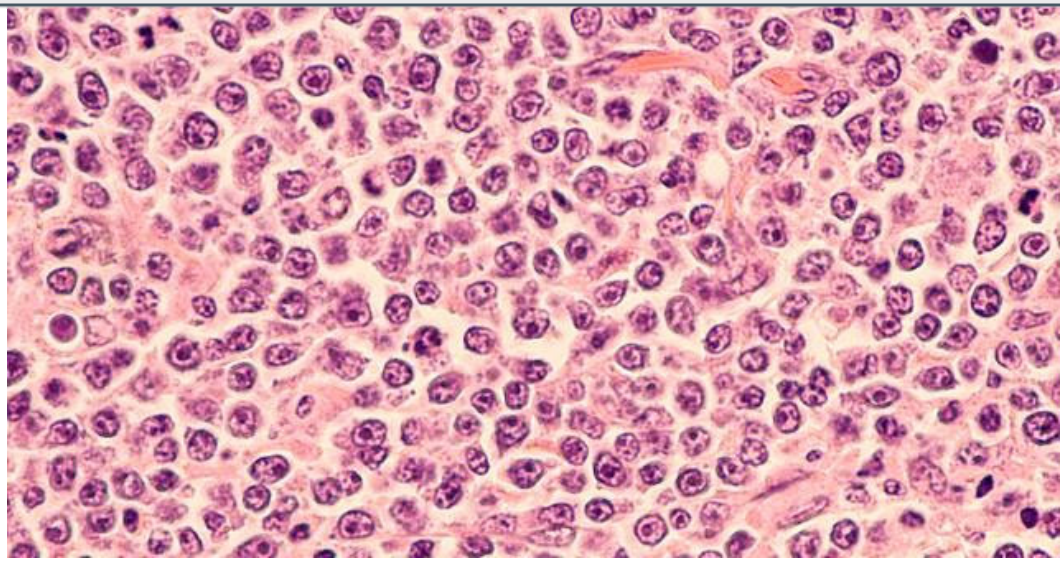
ONCOLOGY

Aggressive B-Cell Lymphomas: Clinical Application of New Advances in Community Practice

Saturday, September 10, 2022 | 4:00 PM PT
GLAONS 6th Annual Oncology Care Summit
Los Angeles, CA



Supported by educational grants from Bristol-Myers Squibb; Genentech, a member of the Roche Group; Genmab US, Inc. and AbbVie; Karyopharm Therapeutics; and Novartis Pharmaceuticals Corporation.

Faculty

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John Allan, MD, has disclosed that he has received consulting fees from AbbVie, ADC Therapeutics, AstraZeneca, BeiGene, Epizyme, Genentech, Janssen, Pharmacyclics, TG Therapeutics; funds for research support from AstraZeneca, Genentech, Janssen, and TG Therapeutics; and fees for non-CME/CE services from AbbVie, BeiGene, Janssen, and Pharmacyclics.

Let’s Start With a Few Questions

Poll: If you are a practicing health care provider, how many patients with lymphomas do you provide care for in a typical month?

A. <5

B. 5-10

C. 11-15

D. 16-20

E. >20

Poll: Which of the following patients with DLBCL do you test for the biomarkers *MYC*, *BCL2*, and *BCL6*?

1. Patients with DEL only
2. Patients with GCB only
3. Patients with GCB and DEL
4. All patients with DLBCL
5. I don’t test for these biomarkers

Patient Case 1: Stage III DLBCL

- 58-yr-old woman was diagnosed with stage IIIB DLBCL after presenting with increasing bilateral axillary adenopathy
  - PET/CT was FDG avid in cervical, axillary, and retroperitoneal lymph nodes; bone marrow was negative for involvement; LDH elevated at 288 U/L
- She received R-CHOP x 6 cycles and achieved a CR
- She relapsed 13 mo later with a biopsy-proven recurrence in a left axillary lymph node
  - Patient reports fatigue but PS = 0
- She received salvage R-ICE x 2 cycles
  - Assessment of disease status by PET/CT following cycle 2 of R-ICE demonstrated a 30% reduction in prior adenopathy but a new FDG-avid lesion in the liver
- Patient's organ functions and PS remain stable
- HLA typing of siblings reveals 1 match

Slide credit: clinicaloptions.com

Presurvey 1: Which of the following treatment options would you recommend for this patient?

1. An alternative chemoimmunotherapy regimen
2. An allogeneic stem cell transplant
3. An antibody–drug conjugate regimen
4. A CAR T-cell therapy
5. A nuclear export inhibitor
6. Uncertain

Presurvey 2: On Day 5 following an infusion of CAR T-cells, a patient becomes confused and increasingly disoriented and drowsy. The patient is assessed as having grade 2 immune effector cell–associated neurotoxicity syndrome. Which of the following treatment options would you recommend to manage this adverse event?

1. Anakinra
2. Cyclophosphamide
3. Siltuximab
4. Steroids
5. Tocilizumab
6. Uncertain

Presurvey 3: Which of the following novel therapies in combination with BR would you recommend as a treatment option for a patient with R/R DLBCL?

1. Loncastuximab tesirine
2. Polatuzamab vedotin
3. Selinexor
4. Tafasitamab
5. Tisagenlecleucel
6. Uncertain

Diffuse Large B-Cell Lymphoma

Most Common Lymphoid Neoplasms

B-Cell Neoplasms: 88%

B-Cell Neoplasm	%
DLBCL	31
FL	22
MALT lymphoma	8
CLL/SLL	7
MCL	6
Nodal MZL	2
Burkitt lymphoma	3
LPL	1
Splenic MZL	<1

T-Cell Neoplasms: 12%

T-Cell Neoplasm	%
PTCL NOS	12
ALCL	2
Precursor T-LBL	2
Nasal NK/T-cell lymphoma	1
AITL	1
Enteropathy-type T-cell lymphoma	<1
Adult T-cell lymphoma/leukemia	<1

NHLCP. Blood. 1997;89:3909.

Slide credit: clinicaloptions.com

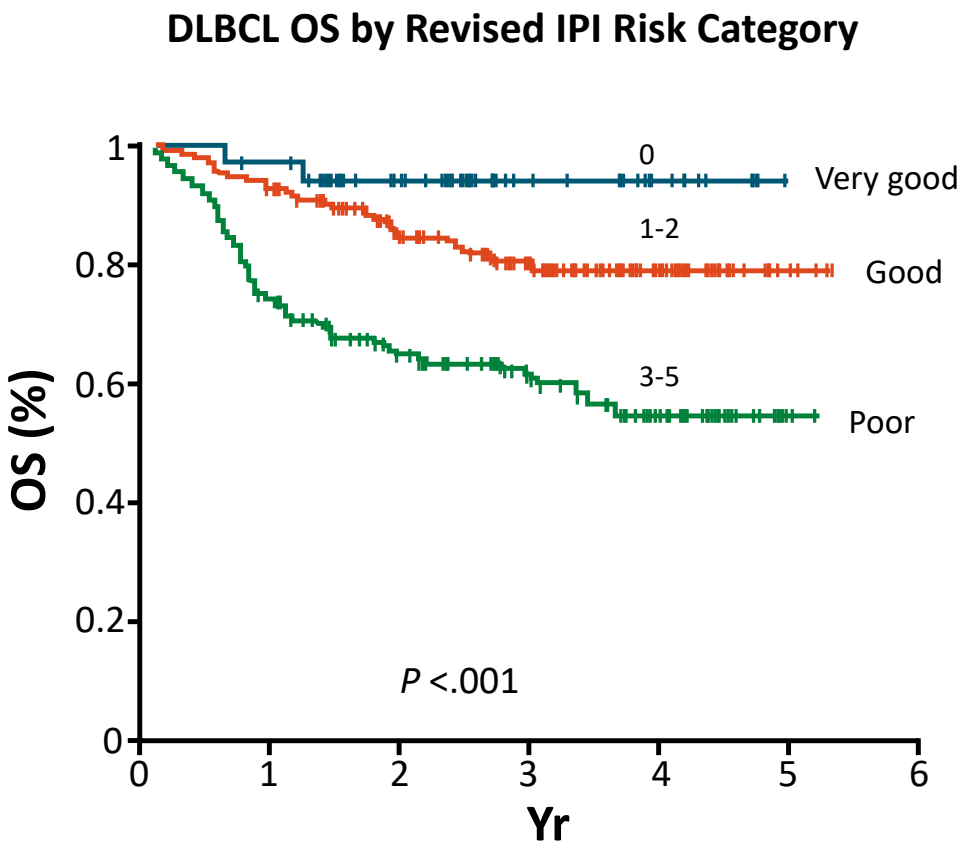
DLBCL: Clinical Features at Diagnosis

- Median age: 60-70 yr
- Male: 55%
- Presenting with advanced-stage disease: ~50%
- B symptoms: ~40%
- Elevated LDH: ~40%
- Any extranodal involvement: 40% to 70%
- Bone marrow involvement: 10% to 20%
- CNS involvement: <1% (~3% during entire course of disease)

Slide credit: clinicaloptions.com

International Prognostic Index

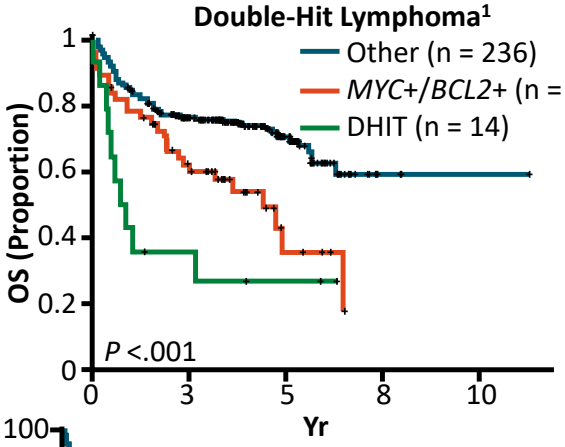
- Independent predictors of adverse outcome at diagnosis
  - Age >60 yr
  - Poor performance status (2-4)
  - Elevated LDH
  - Advanced Ann Arbor stage (III/IV)
  - Multiple extranodal sites
- Risk groups
  - Low (0-1)
  - Low-intermediate (2)
  - High-intermediate (3)
  - High (4-5)

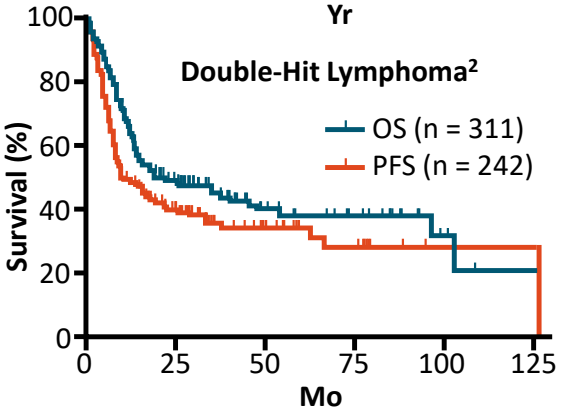


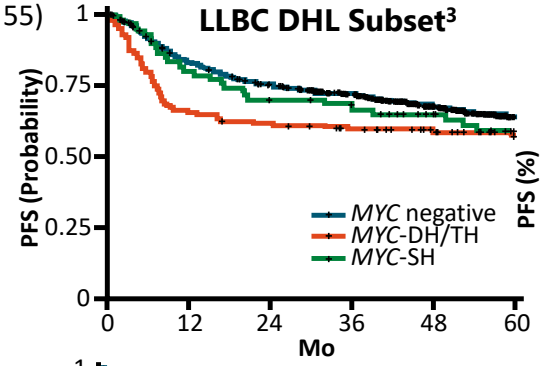
INHLPFP. NEJM. 1993;329:987. Sehn. Blood. 2007;109:1857.

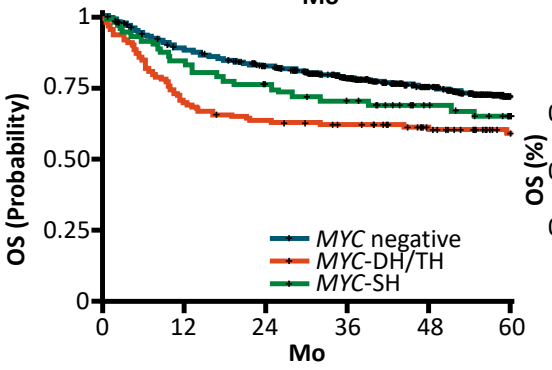
Slide credit: clinicaloptions.com

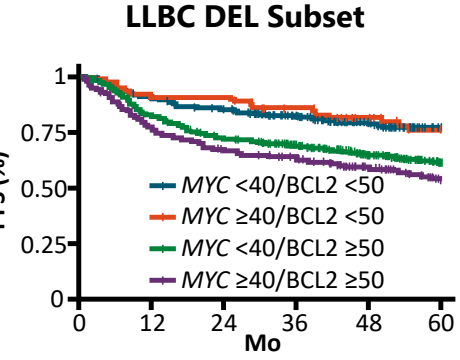
Lymphomas: "Double Hits" and "Double Expressers"

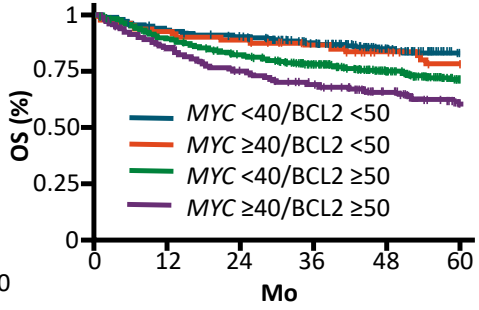


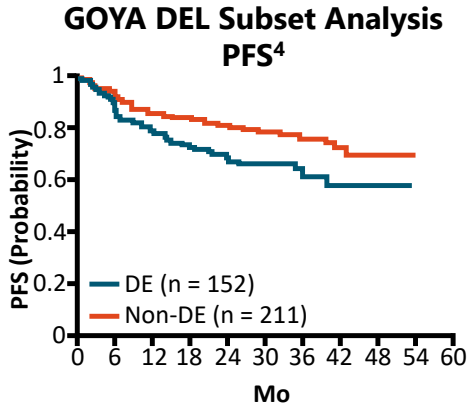










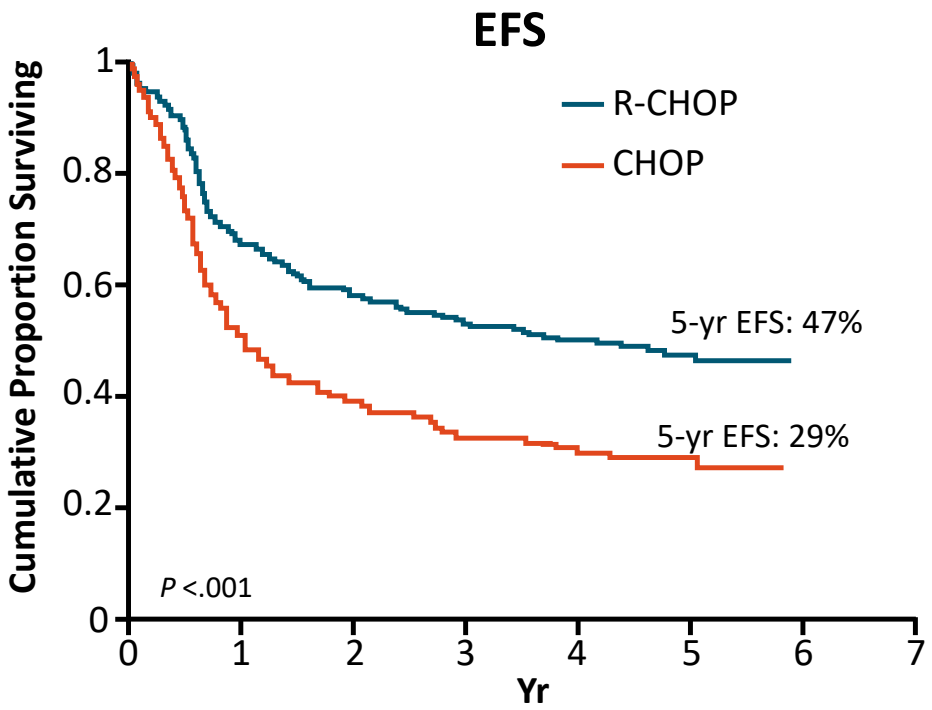


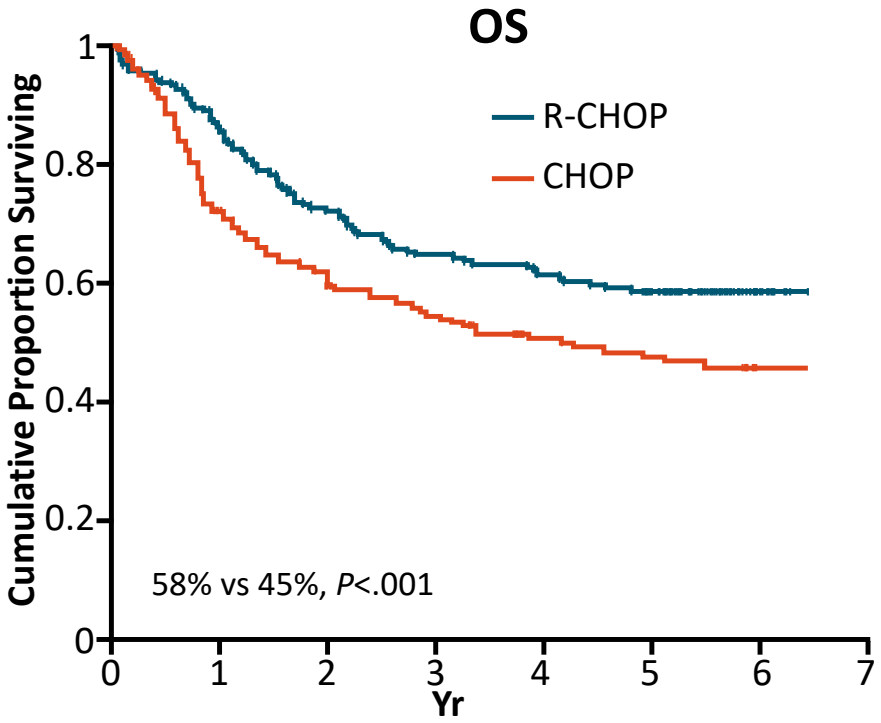
1. Johnson. JCO. 2012;30:3452. 2. Petrich. Blood. 2014;124:2354.
3. Rosenwald. JCO. 2019;37:3359. 4. Sehn. ICML. 2017.

Slide credit: clinicaloptions.com

R-CHOP Has Been the Standard Initial Therapy for DLBCL for More Than 20 Years

- Long-term outcomes from randomized study of 399 previously untreated patients with DLBCL



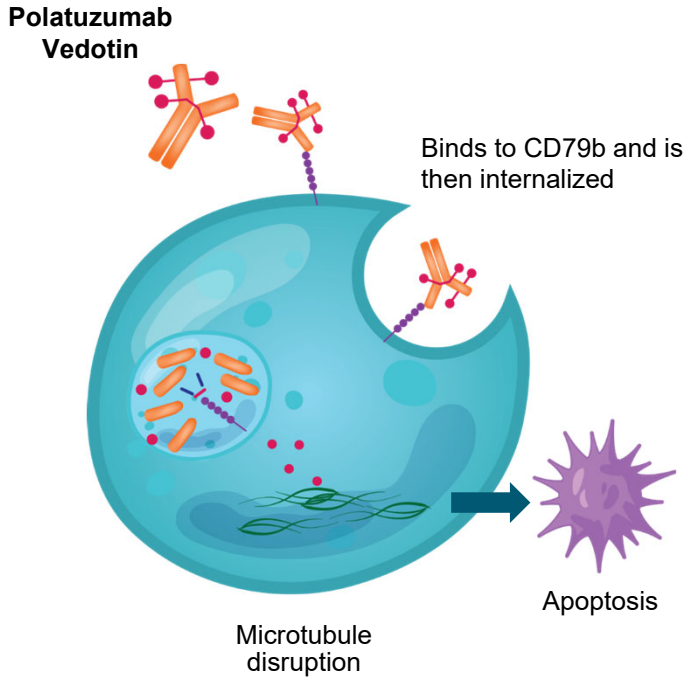


Coiffier. NEJM. 2002;346:235. Feugier. JCO. 2005;23:4117.

Slide credit: clinicaloptions.com

Polatuzumab Vedotin in DLBCL: Background

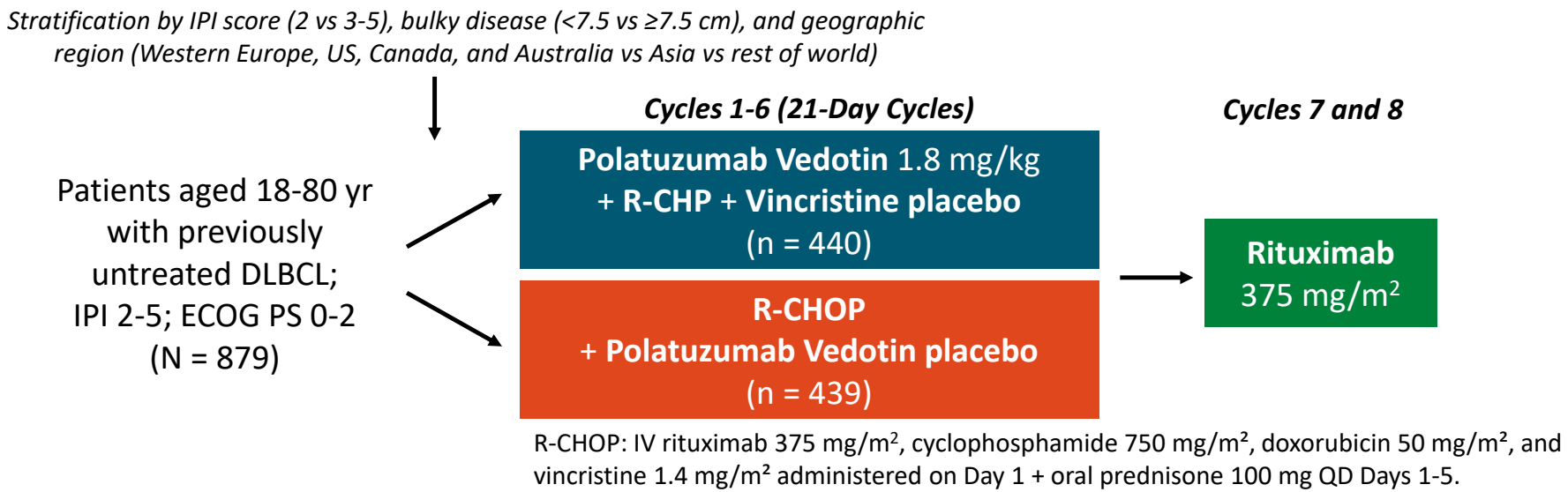
- R-CHOP well established as standard frontline therapy for DLBCL[1]
- Polatuzumab vedotin, ADC targeting CD79b[2]
  - CD79b expressed on mature B-cell lymphomas including DLBCL
- Polatuzumab vedotin + R-CHP or G-CHP demonstrated activity and manageable safety in untreated DLBCL in phase II trial[3]
- Current phase III POLARIX trial compared safety and efficacy of polatuzumab vedotin + R-CHP vs R-CHOP in previously untreated DLBCL[4,5]



1. Vitolo. JCO. 2017;35:3529. 2. Dornan. Blood. 2009;114:2721.
3. Tilly. Lancet Oncol. 2019;20:998. 4. Tilly. ASH 2021. Abstr LBA1. 5. Tilly. NEJM. 2021;[Epub].

POLARIX: Polatuzumab + R-CHP vs R-CHOP in Previously Untreated DLBCL

- Multicenter, double-blind, placebo-controlled phase III trial



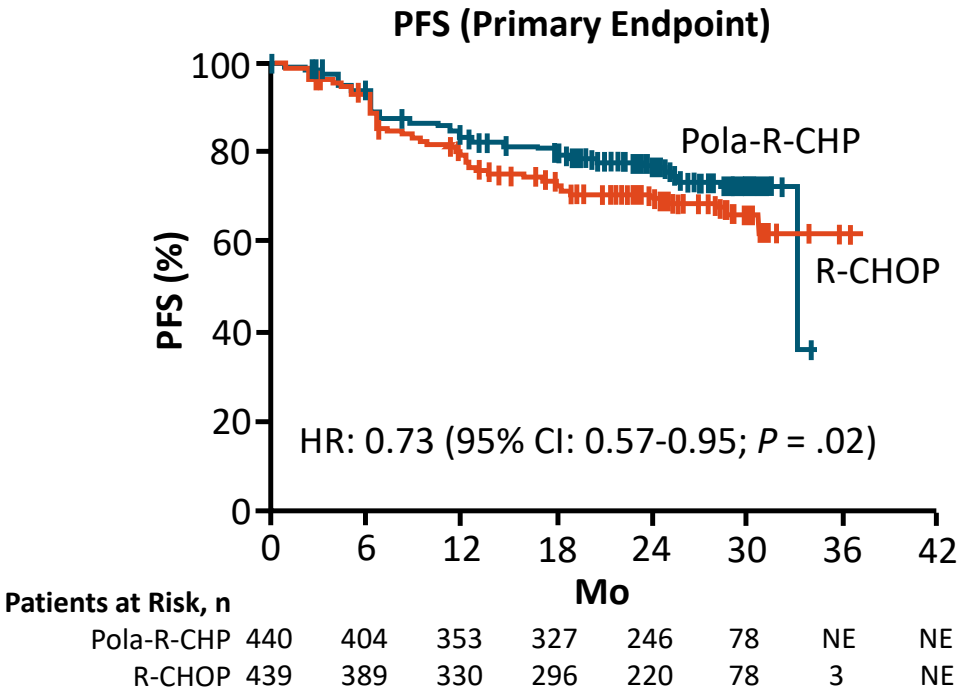
R-CHOP: IV rituximab 375 mg/m², cyclophosphamide 750 mg/m², doxorubicin 50 mg/m², and vincristine 1.4 mg/m² administered on Day 1 + oral prednisone 100 mg QD Days 1-5.

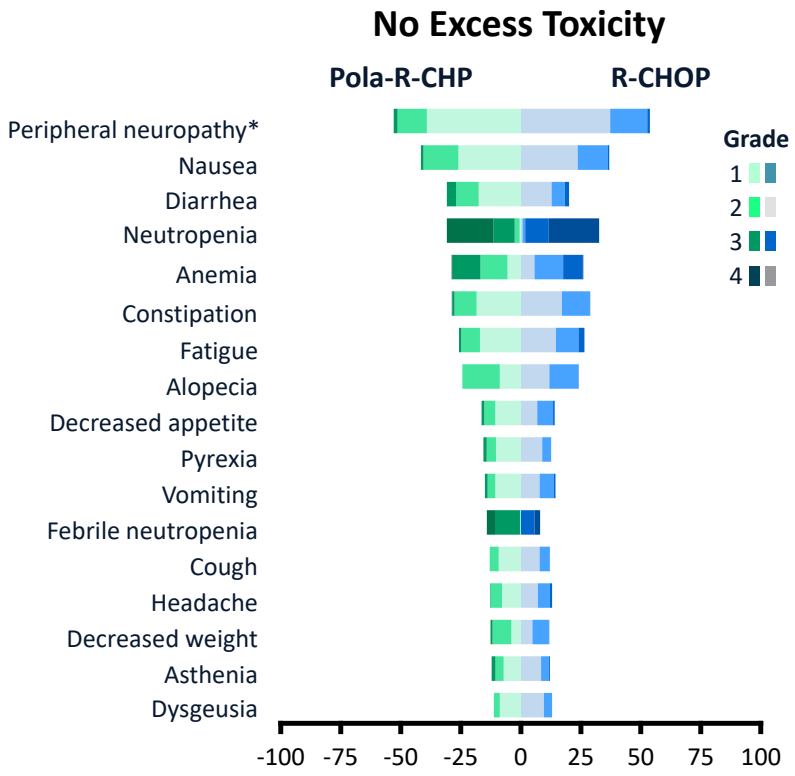
- **Primary endpoint:** investigator-assessed PFS
- **Secondary endpoints:** EFS, CRR at end of treatment, DFS, OS, safety

Tilly. ASH 2021. Abstr LBA1. Tilly. NEJM. 2021;[Epub].

Slide credit: clinicaloptions.com

POLARIX: Polatuzumab Vedotin + R-CHP vs R-CHOP PFS and Safety





- Median follow-up: 28.2 mo
- 24-mo PFS: 76.7% polatuzumab vedotin + R-CHP vs 70.2% R-CHOP

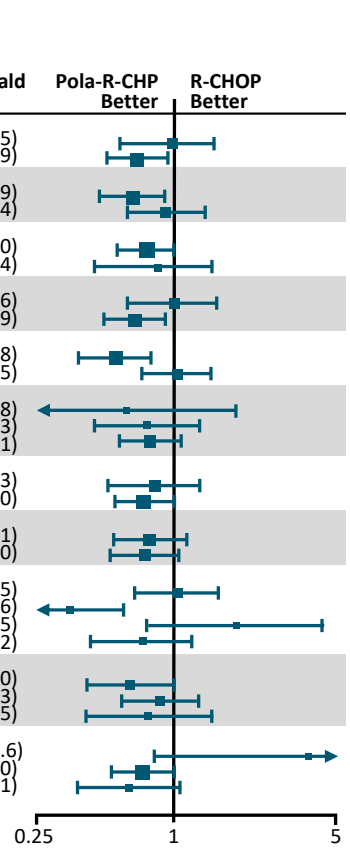
Tilly. ASH 2021. Abstr LBA1. Tilly. NEJM. 2021;[Epub].

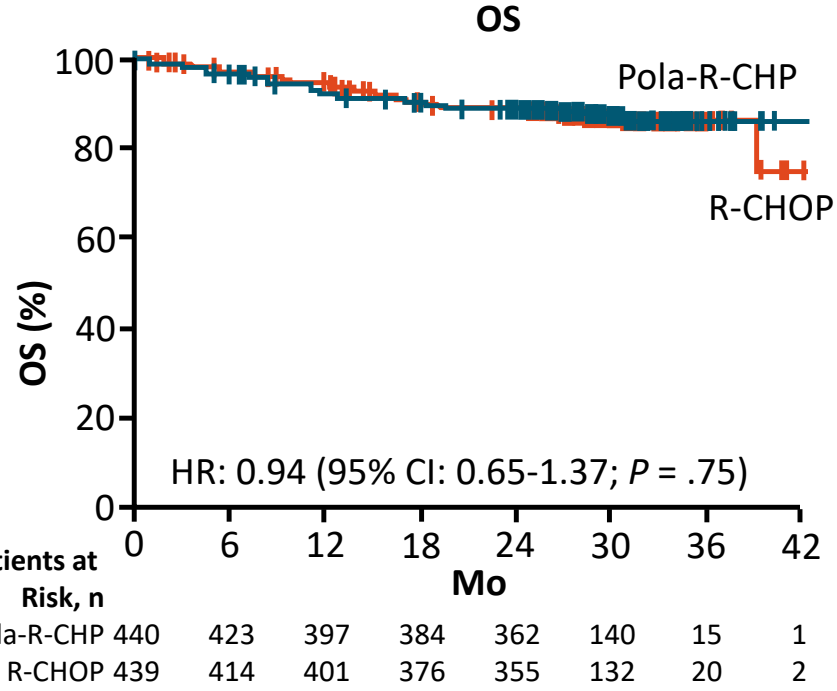
Slide credit: clinicaloptions.com

POLARIX: Polatuzumab Vedotin + R-CHP vs R-CHOP PFS Subset Analysis and OS

PFS

Baseline Risk Factors	Total N	Pola-R-CHP (N = 440) n	Pola-R-CHP (N = 440) 2-Yr Rate	R-CHOP (N = 439) n	R-CHOP (N = 439) 2-Yr Rate	HR	95% Wald CI
Age Group							
<60	271	140	74.1	131	71.9	0.9	(0.6-1.5)
>60	608	300	77.9	308	69.5	0.7	(0.5-0.9)
Sex							
Male	473	239	75.9	234	65.9	0.7	(0.5-0.9)
Female	406	201	77.7	205	75.2	0.9	(0.6-1.4)
ECOG PS							
0-1	737	374	78.4	363	71.2	0.8	(0.6-1.0)
2	141	66	67.2	75	65.0	0.8	(0.5-1.4)
IPI score							
IPI 2	334	167	79.3	167	78.5	1.0	(0.6-1.6)
IPI 3-5	545	273	75.2	272	65.1	0.7	(0.5-0.9)
Bulky disease							
Absent	494	247	82.7	247	70.7	0.6	(0.4-0.8)
Present	385	193	69.0	192	69.7	1.0	(0.7-1.5)
Ann Arbor stage							
I-II	99	47	89.1	52	85.5	0.6	(0.2-1.8)
III	232	124	80.7	108	73.6	0.8	(0.5-1.3)
IV	548	269	72.6	279	66.1	0.8	(0.6-1.1)
Baseline LDH							
≤ ULN	300	146	78.9	154	75.6	0.8	(0.5-1.3)
> ULN	575	291	75.4	284	67.2	0.7	(0.5-1.0)
Extranodal sites, n							
0-1	453	227	80.2	226	74.5	0.8	(0.5-1.1)
≥2	426	213	73.0	213	65.8	0.7	(0.5-1.0)
Cell of origin							
GCB	352	184	75.1	168	76.9	1.0	(0.7-1.5)
ABC	221	102	83.9	119	58.8	0.4	(0.2-0.6)
Unclassified	95	44	73.0	51	86.2	1.9	(0.8-4.5)
Unknown	211	110	73.8	101	64.3	0.7	(0.4-1.2)
Double expressor by IHC							
DEL	290	139	75.5	151	63.1	0.6	(0.4-1.0)
Non-DEL	438	223	77.7	215	75.7	0.9	(0.6-1.3)
Unknown	151	78	76.0	73	69.8	0.8	(0.4-1.5)
Double- or triple-hit lymphoma							
Yes	45	26	69.0	19	88.9	3.8	(0.8-17.6)
No	620	305	76.8	315	70.3	0.7	(0.5-1.0)
Unknown	214	109	78.5	105	66.4	0.6	(0.4-1.1)





Patients at Risk, n								
Pola-R-CHP	440	423	397	384	362	140	15	1
R-CHOP	439	414	401	376	355	132	20	2

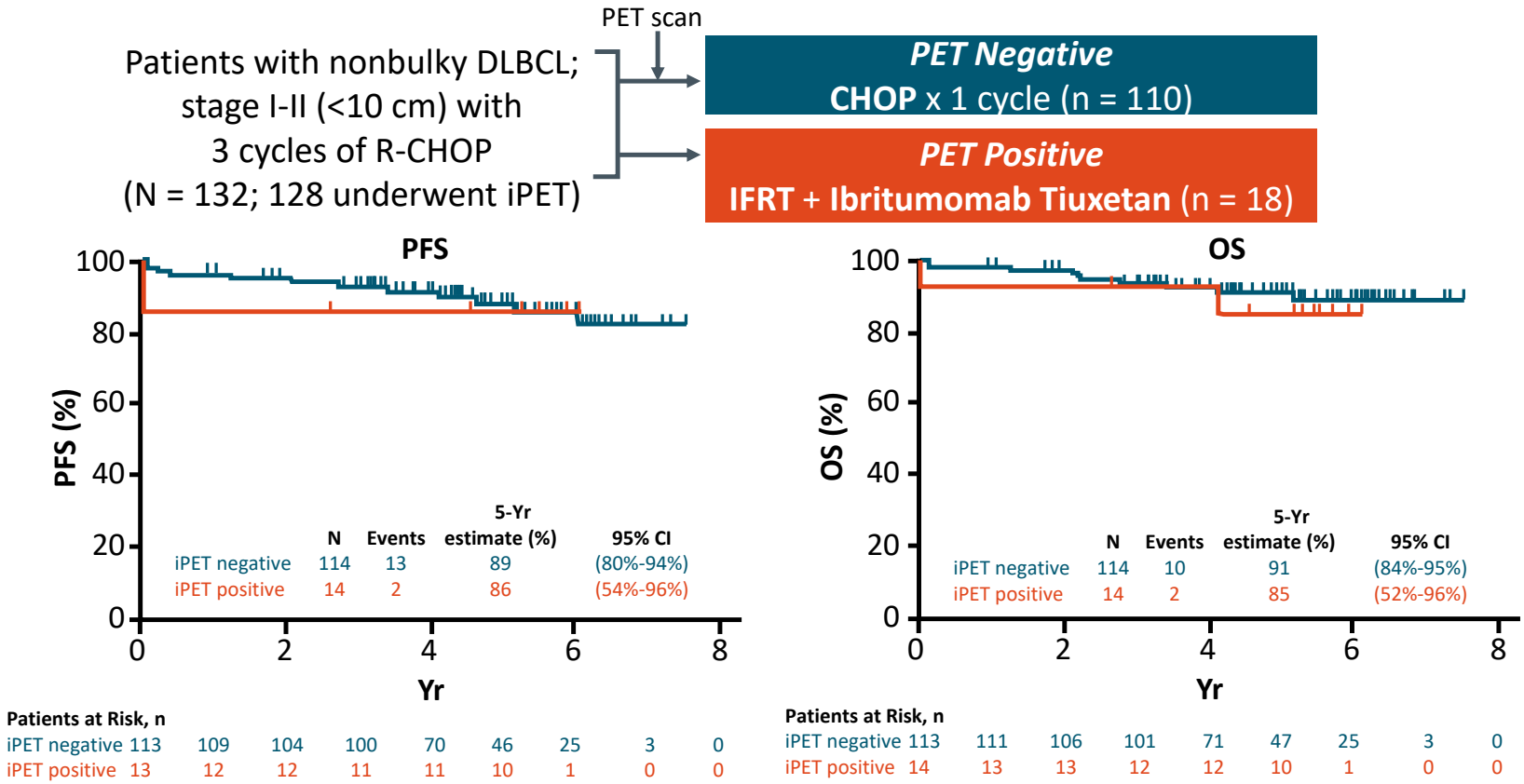
Tilly. ASH 2021. Abstr LBA1. Tilly. NEJM. 2021;[Epub].

Slide credit: clinicaloptions.com

Limited-Stage DLBCL

Number of Cycles and Role of Radiation

NCTN S1001: PET-Adapted Therapy for Early-Stage DLBCL

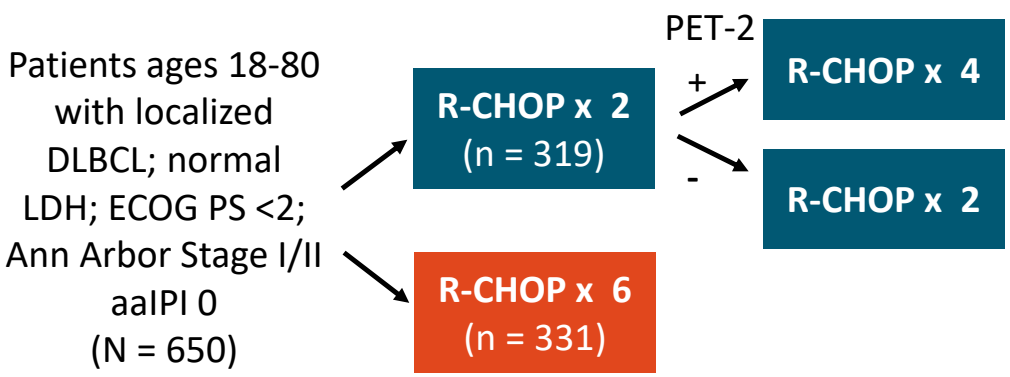


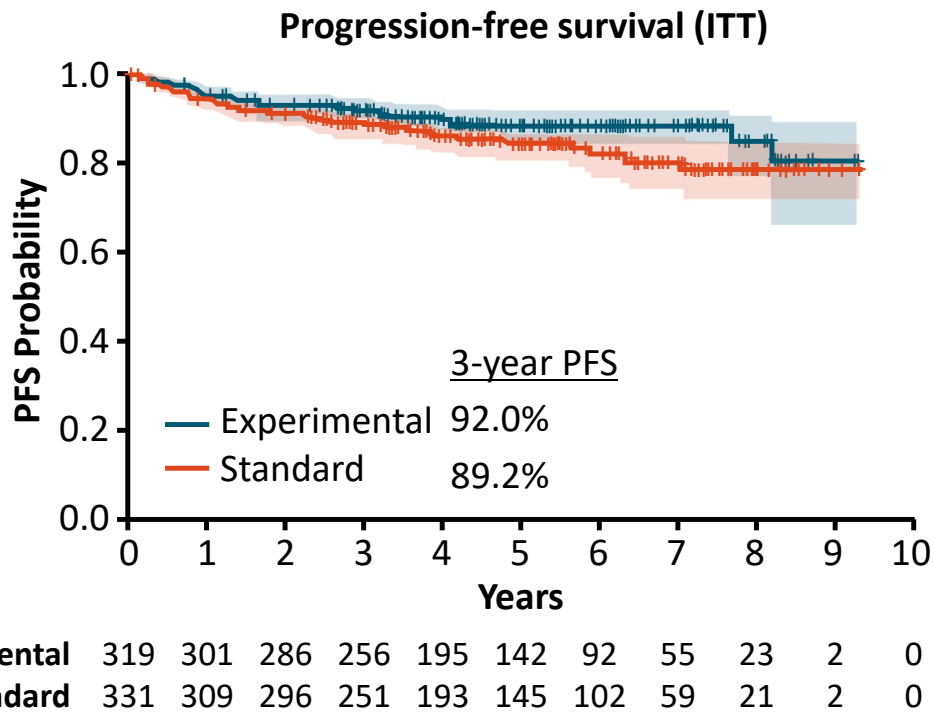
Persky. JCO. 2020;38:3003.

Slide credit: clinicaloptions.com

LNH 09-1B Trial: R-CHOP Treatment Adapted to the PET Response vs Standard Treatment

- Randomized open-label phase III trial





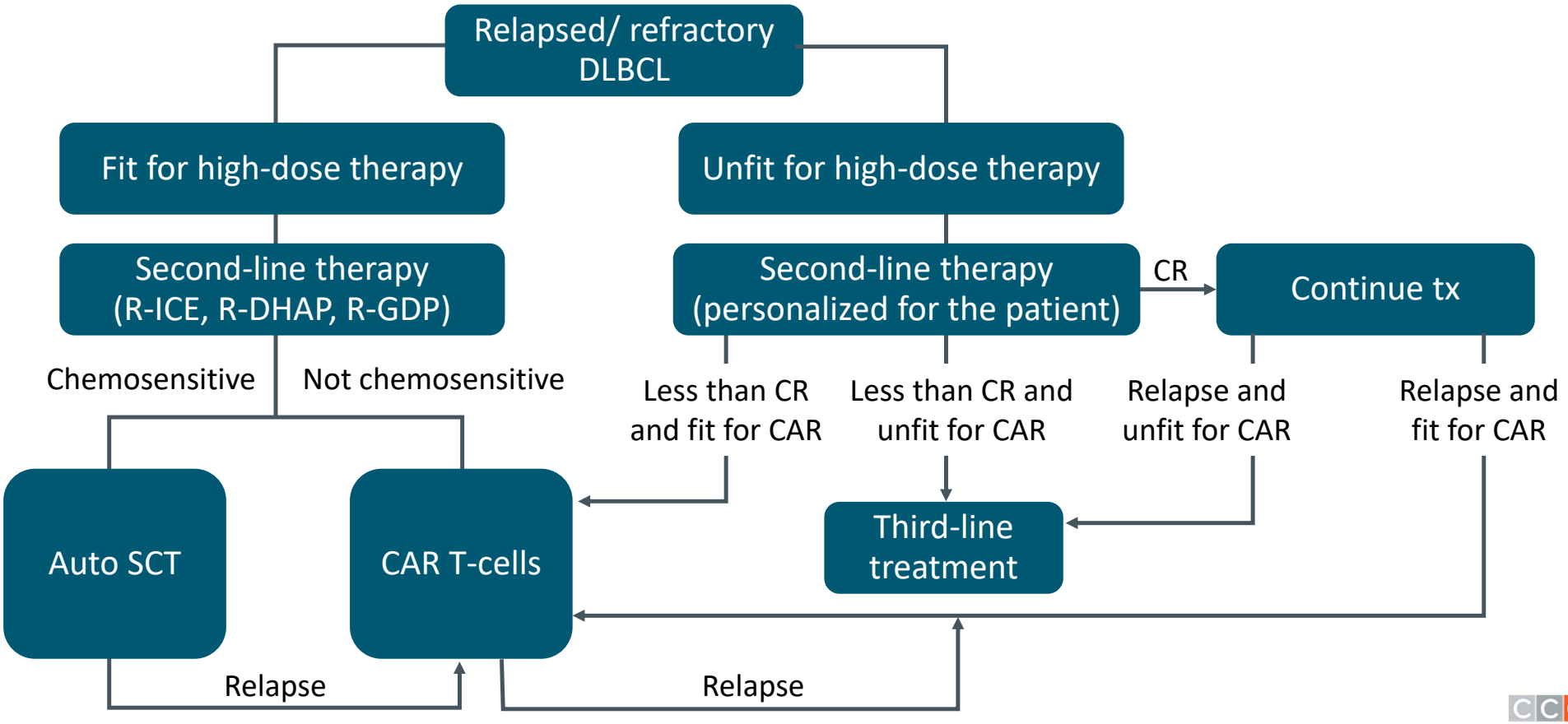
- **Primary endpoint:** PFS at 3 years

Bologna. Proc ICML. 2021. Abstract 2879. NCT01285765.

Slide credit: clinicaloptions.com

Relapsed Disease

Relapsed DLBCL: Current Treatment Paradigm



Slide credit: clinicaloptions.com

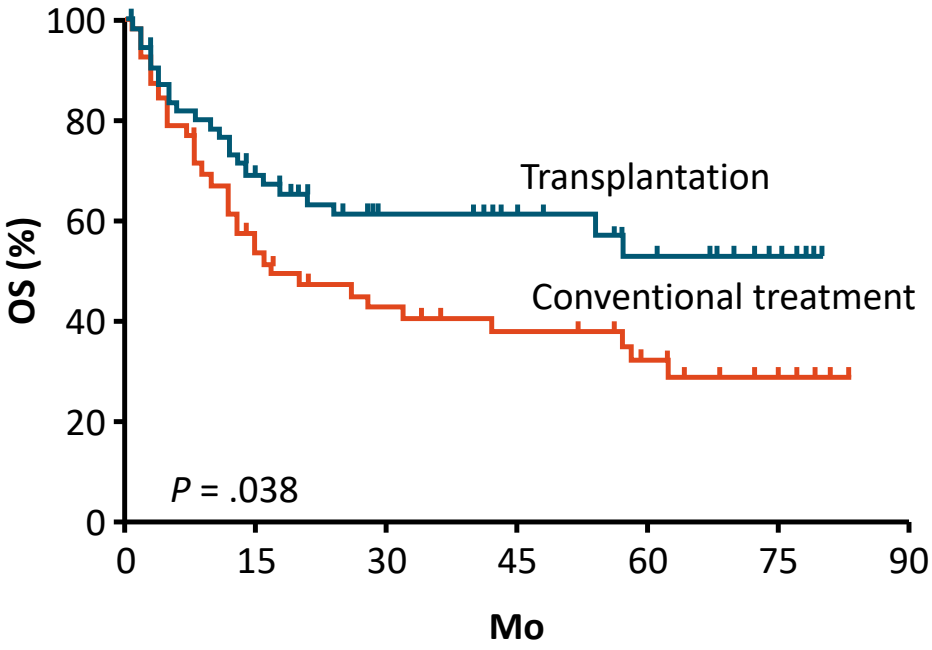
3 Approved CD19-Targeted T-Cell Therapies for DLBCL and Other Large B-Cell Lymphomas in Third-line or Later Setting

	Axicabtagene Ciloleucel (ZUMA-1)[1,2]	Tisagenlecleucel (JULIET)[3,4]	Lisocabtagene Maraleucel (TRANSCEND)[5,6]
Construct	Anti-CD19/CD28/CD3z	Anti-CD19/4-1BB/CD3z	Anti-CD19/4-1BB/CD3z
T-cell manufacturing	Bulk	Bulk	Defined doses: CD4+, CD8+
ORR/CRR, %	82/54	52/40	73/53
2-yr PFS, %	41	30	41
CRS (any/severe), %	93/13	58/22	42/2
NT (any/severe), %	64/28	21/12	30/10
FDA/EMA-approved indications	DLBCL, high-grade BCL, transformed FL, PMBCL	DLBCL, high-grade BCL, B-ALL (age 3-25 yr), transformed FL	DLBCL (incl transformed iNHL), high-grade BCL, PMBCL, grade 3B FL

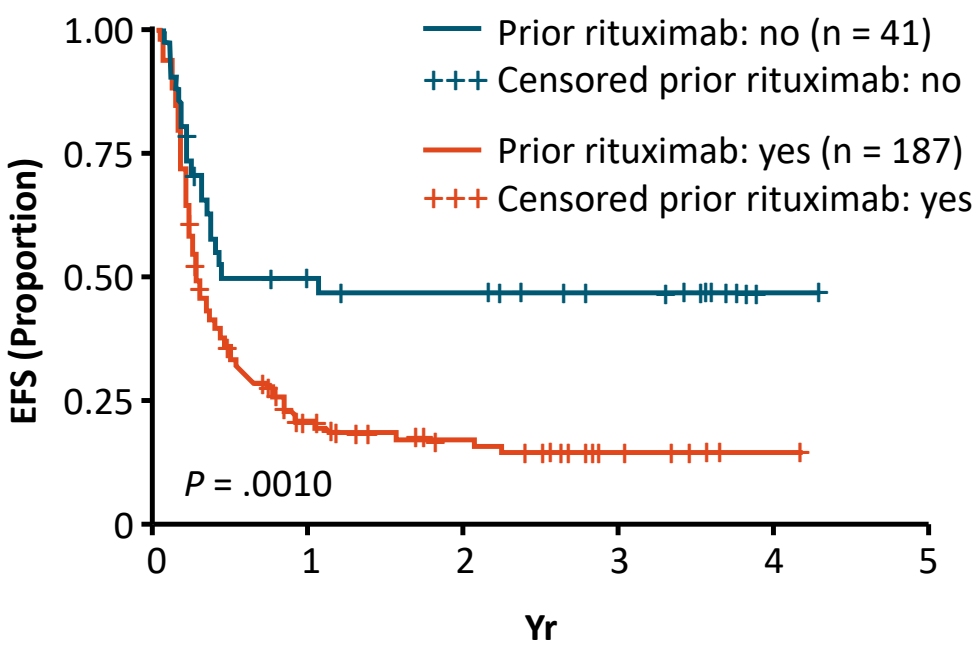
1. Neelapu. NEJM. 2017;377:2531. 2. Axicabtagene ciloleucel PI. 3. Schuster. NEJM. 2019;380:45.
4. Tisagenlecleucel PI. 5. Abramson. Lancet. 2020;396:839. 6. Lisocabtagene maraleucel PI.

High-Dose Chemotherapy + ASCT in Relapsed NHL

Pre-Rituximab Era[1]



CORAL Trial[2]



1. Philip. NEJM. 1995;333:1540. 2. Gisselbrecht. JCO. 2010;28:4184.

Slide credit: clinicaloptions.com

ZUMA-7: Axicabtagene Ciloleucel vs SoC in R/R Large B-Cell Lymphoma

- Global, multicenter, randomized phase III trial

Stratified by 1L treatment response, 2L age-adjusted IPI

Patients ≥18 yr with LBCL; ECOG PS 0-1; R/R disease with ≤12 mo of adequate 1L CIT (including anti-CD20 mAb and an anthracycline); intent to proceed to HDT-ASCT (N = 359)

Axi-cel 2 x 10^6 CAR T-cells/kg after conditioning chemotherapy (n = 180)

Conditioning regimen: cyclophosphamide 500 mg/m^2/day + fludarabine 30 mg/m^2/day on Days 5, 4, and 3 prior to CAR T-cell infusion. Optional bridging therapy limited to corticosteroids (no CIT).

SoC*
(2-3 cycles of investigator-selected, protocol defined, platinum-based CIT)
(n = 179)

CR/PR → **HDT-ASCT** (n = 64)

No CR/PR → **Off-Protocol Tx**†

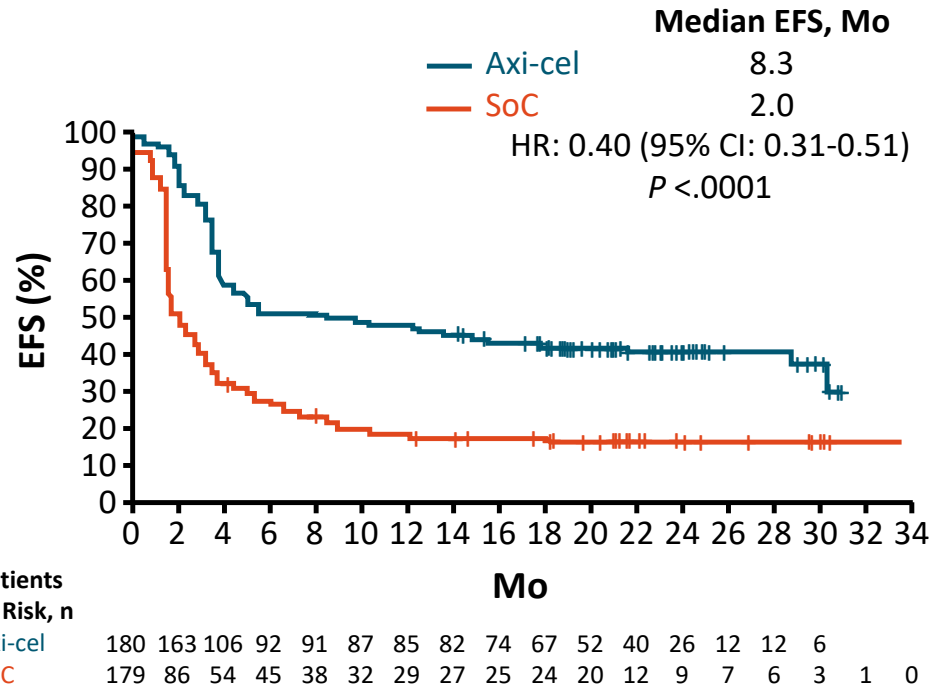
*SoC included R-GDP, R-DHAP, R-ICE, or R-ESHAP. †56% received subsequent cellular immunotherapy.

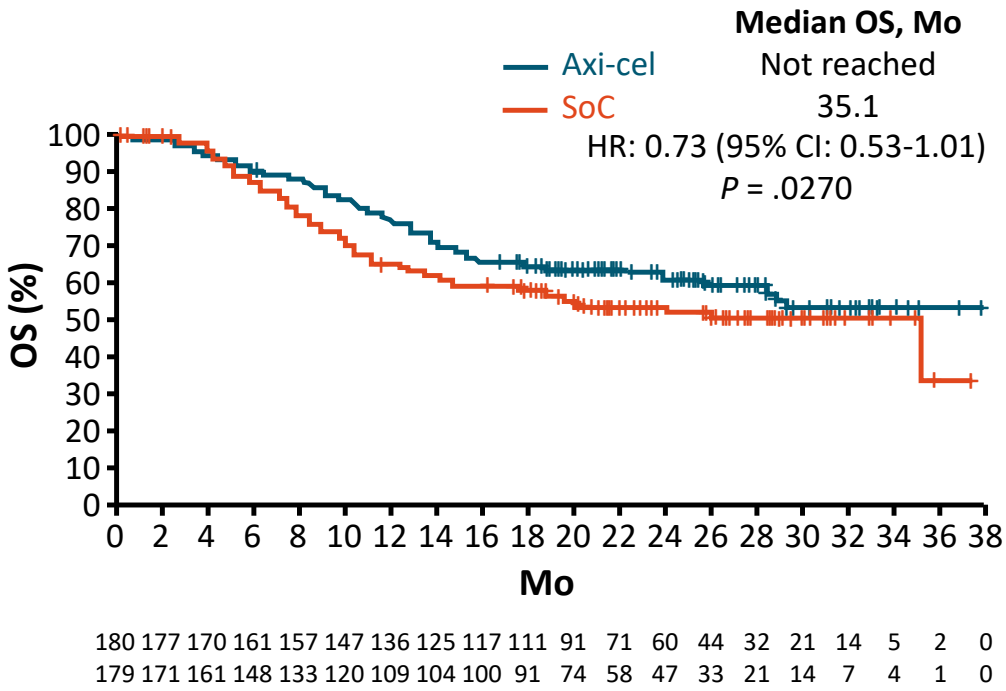
- Primary endpoints: EFS (BICR)
- Key secondary endpoints: ORR and OS (tested hierarchically)
- Other secondary endpoints: PFS, safety, PROs
- Median follow-up: 24.9 mo

Locke. ASH 2021. Abstr 2.

Slide credit: clinicaloptions.com

ZUMA-7 Axicabtagene Ciloleucel vs SoC: EFS and OS





Patients at Risk, n																				
Axi-cel	180	163	106	92	91	87	85	82	74	67	52	40	26	12	12	6				
SoC	179	86	54	45	38	32	29	27	25	24	20	12	9	7	6	3	1	0		

Axi-cel	180	177	170	161	157	147	136	125	117	111	91	71	60	44	32	21	14	5	2	0
SoC	179	171	161	148	133	120	109	104	100	91	74	58	47	33	21	14	7	4	1	0

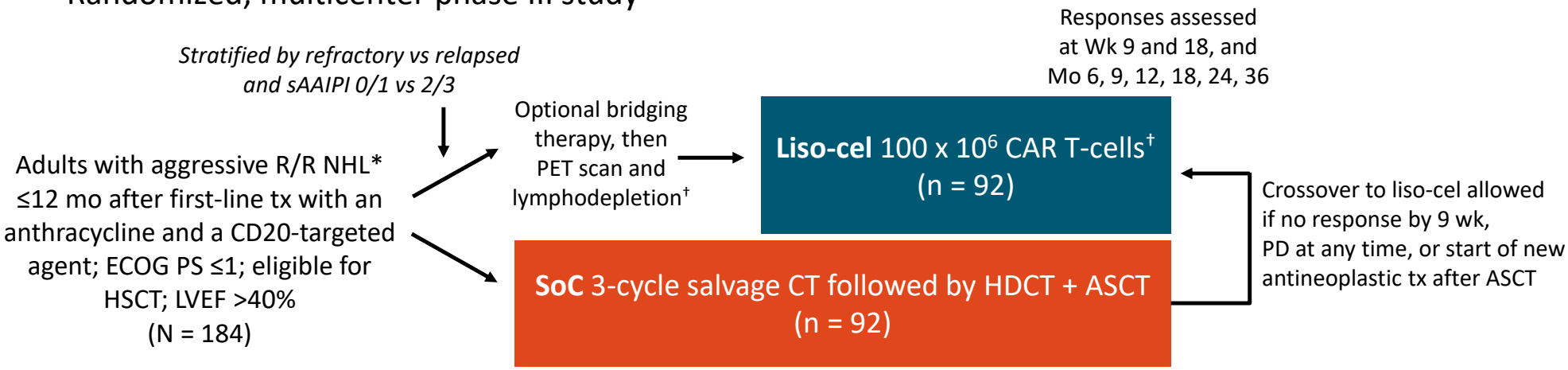
- CR rate: 65% with axi-cel vs 32% with SoC
- Median follow-up: 24.9 mo

Locke. ASH 2021. Abstr 2. Locke. NEJM. 2021;[Epub].

Slide credit: clinicaloptions.com

TRANSFORM: Lisocabtagene Maraleucel vs Salvage Chemo + ASCT in Relapsed/Refractory Aggressive NHL

- Randomized, multicenter phase III study



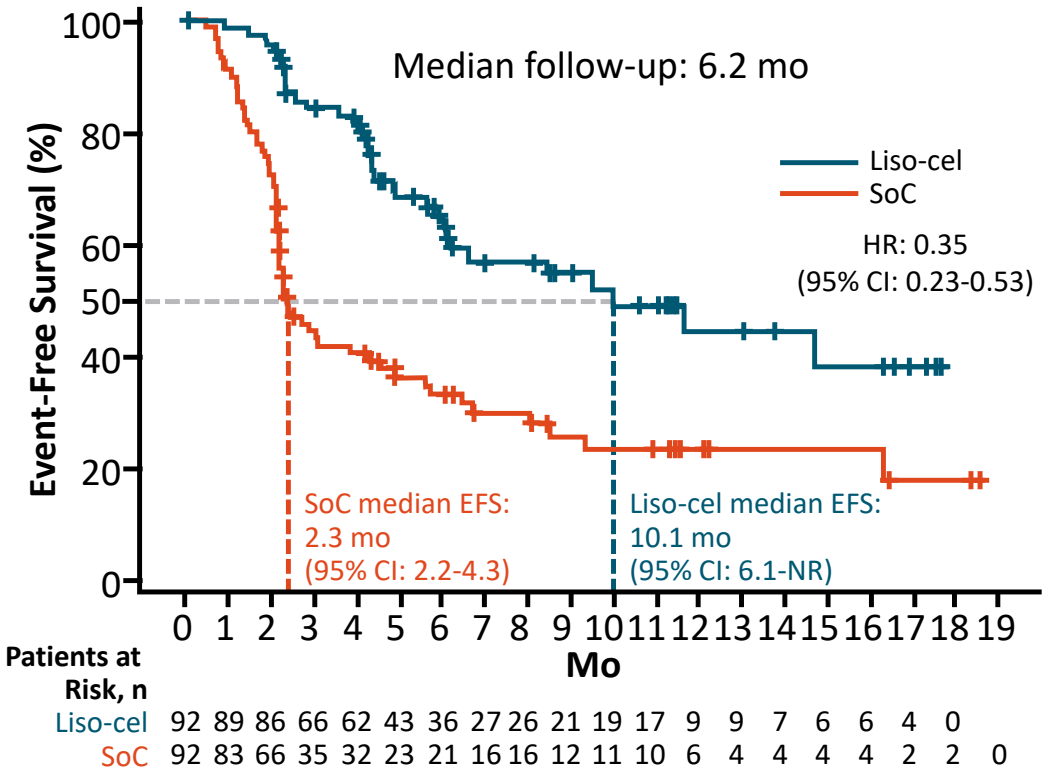
*DLBCL NOS, HGBCL (double/triple hit) with DLBCL histology, FL3B, PMBCL, THRBCL.
†Fludarabine 30 mg/m^2 + cyclophosphamide 300 mg/m^2 x 3 days.

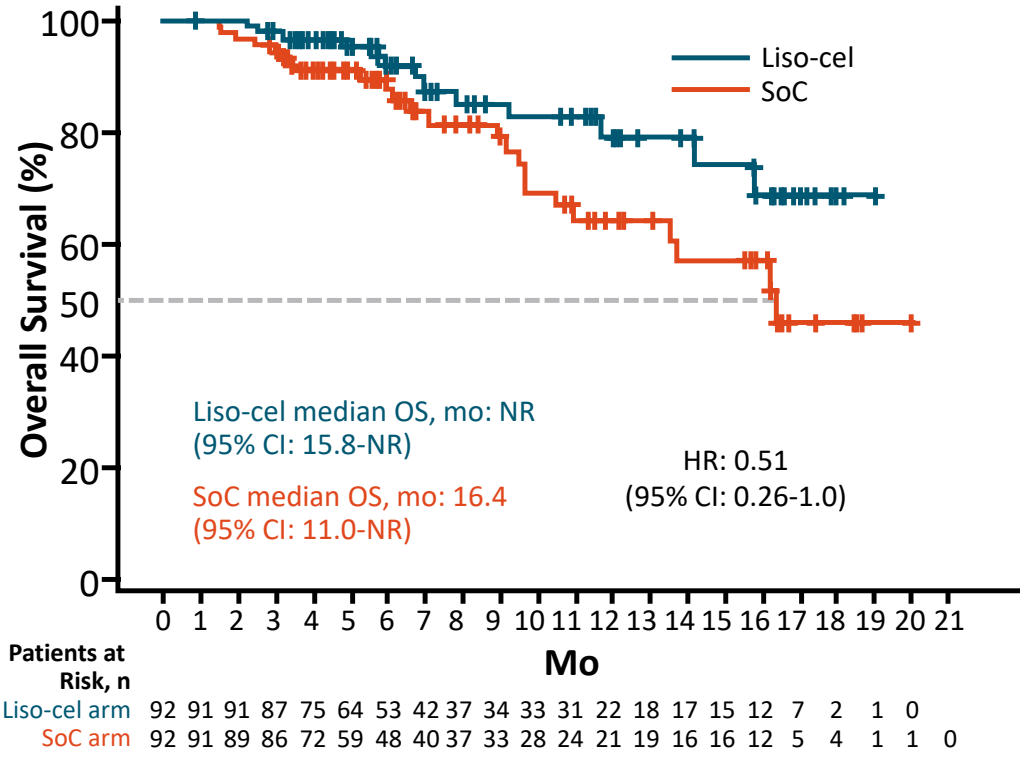
- Primary endpoint: EFS per IRC
- Key secondary endpoints: CR, PFS, OS
- Exploratory endpoints: cellular kinetics, B-cell aplasia
- Primary refractory: 75% in both arms
- Double- or triple-hit lymphoma: 24%

Kamdar. ASH 2021. Abstr 91. NCT03575351.

Slide credit: clinicaloptions.com

TRANSFORM Liso-cel vs SoC: EFS and OS





Kamdar. ASH 2021. Abstr 91.

Slide credit: clinicaloptions.com

CAR T-Cells vs SoC as Second-line Therapy in Aggressive B-Cell NHL: Recent Data From ASH 2021

	Axicabtagene Ciloleucel (ZUMA-7)[1]	Lisocabtagene Maraleucel (TRANSFORM)[2]	Tisagenlecleucel (BELINDA)[3]
N	359	184	322
Proceeded to CAR-T/ASCT, %	94/36	97/46	96/32
Median days from registration to CAR	29	34	52
Bridging therapy allowed	Steroids only	1 cycle salvage chemo (63%)	>1 cycle salvage chemo (84%)
Crossover	Not allowed	Allowed (51%)	Allowed (51%)
Median F/U, mo	25	6.1	10
Median EFS, mo	8.3 vs 2.0	10.1 vs 2.3	3.0 vs 3.0
HR	0.40 (*P* <.0001)	0.35 (*P* <.0001)	1.07 (*P* = .69)
CR, %	65 vs 32	66 vs 39	28 vs 28
Grade ≥3 CRS/NE, %	6 / 21	1 /4	5 / 3

1. Locke. ASH 2021. Abstr 2. 2. Kamdar. ASH 2021. Abstr 91. 3. Bishop. ASH 2021. Abstract LBA6.

Slide credit: clinicaloptions.com

Class Effects of the Cell-Mediated Immune Response: CRS and Neurotoxicity

	B-ALL		DLBCL			MCL	MM
	ELIANA[1]	ZUMA-3[2]	JULIET[3]	ZUMA-1[4]	TRANSCEND[5]	ZUMA-2[6]	KarMMa[7]
CAR T-cell agent	Tisagenlecleucel	Brex. autoleucel	Tisagenlecleucel	Axicabtagene ciloleucel	Lisocabtagene maraleucel	Brex. autoleucel	Idecabtagene vicleucel
Construct	Anti–CD19-**41BB**-CD3z	Anti–CD19-**CD28**-CD3z	Anti–CD19-**41BB**-CD3z	Anti–CD19-**CD28**-CD3z	Anti–CD19-**41BB**-CD3z	Anti–CD19-**CD28**-CD3z	Anti-BCMA
N treated	75	55	111	101	269	68	128
CRS, %	77*	89†	58*	93†	42†	91†	84†
Grade ≥3 CRS, %	46*	24†	22*	13†	2†	15†	5†
NT, %	40	60	21	64	30	63	18
Grade ≥3 NT, %	13	25	12	28	10	31	3

*Per Penn scale. †Per Lee Scale.

1. Maude. NEJM. 2018;378:439. 2. Shah. Lancet. 2021;[Epub]. 3. Schuster. NEJM. 2019;380:45. 4. Neelapu. NEJM. 2017;377:2531.
5. Abramson. Lancet. 2020;396:839. 6. Wang. NEJM. 2020;382:1331. 7. Munshi. NEJM. 2021;384:705.

Principles of Toxicity Management by Grade

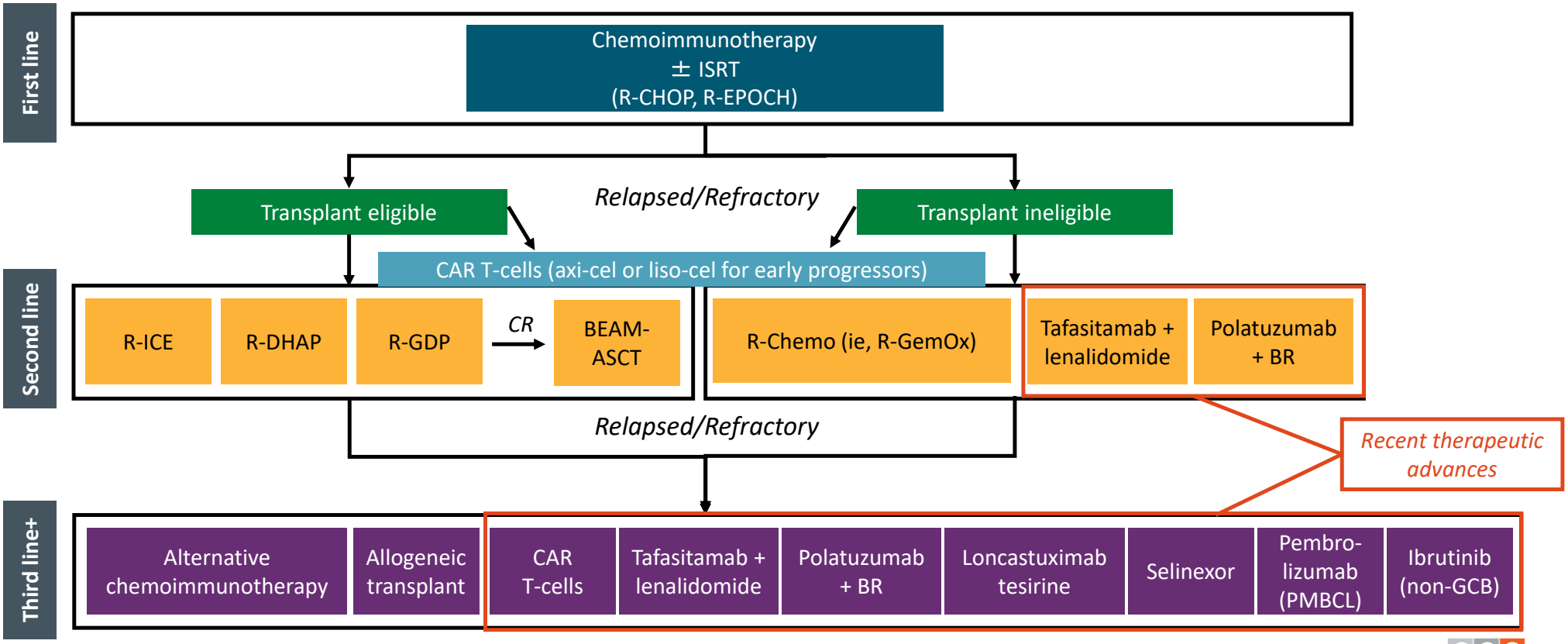
Grade	CRS	Neurotoxicity	CRS + Neurotoxicity
1	Supportive care (+/- toci)*	Supportive care (+/- steroid)*	Supportive care
2	Tocilizumab	Steroids (dexamethasone or methylprednisolone)	Tocilizumab + steroids (dexamethasone)
3	Tocilizumab	Steroids (dexamethasone)	Tocilizumab + steroids (dexamethasone)
4	Tocilizumab + high-dose steroids ICU/critical care	High-dose steroids (methylprednisolone) ICU/critical care	Tocilizumab + high-dose steroids (methylprednisolone) ICU/critical care

- Always rule out/treat alternative causes
- If tocilizumab refractory, consider corticosteroids
- Patients with neurotoxicity should receive AEDs and appropriate CNS imaging, EEG monitoring
- Steroid dosing for neurotoxicity may vary among products
- Patients receiving steroids should receive appropriate fungal prophylaxis

*High-burden, high-risk products, older, comorbidities, etc.

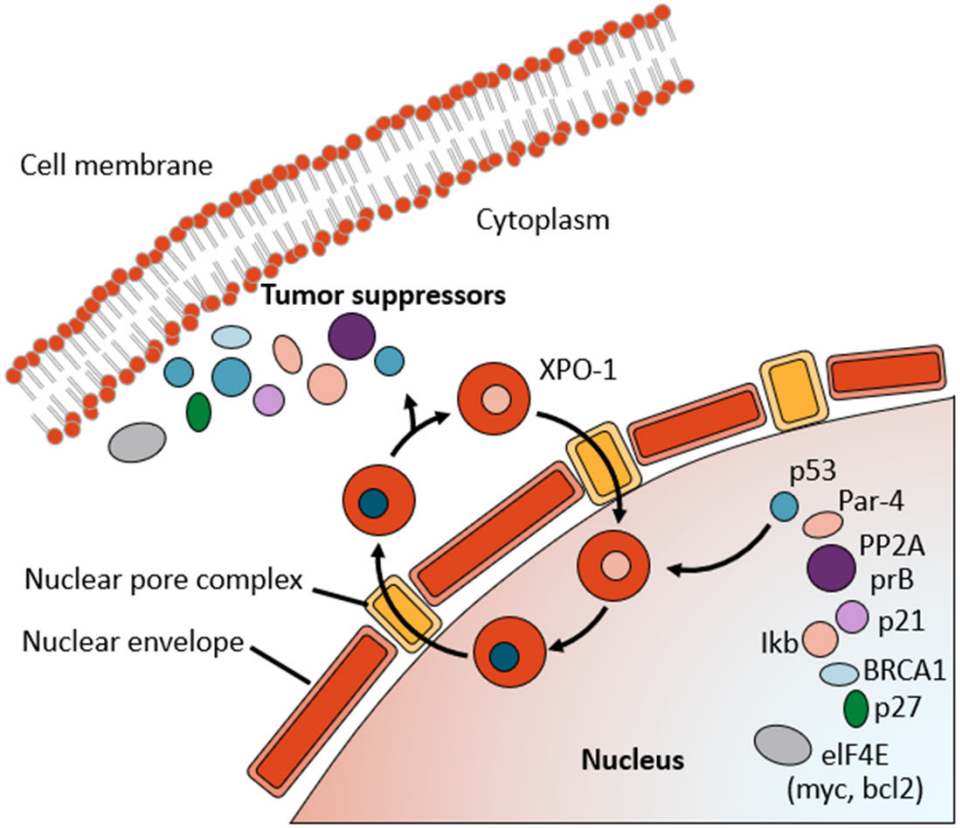
MD Anderson. CAR cell therapy toxicity assessment and management. 2017. Neelapu. Nat Rev Clin Oncol. 2018;15:47.

The Current DLBCL Treatment Landscape



Slide credit: clinicaloptions.com

Selinexor—Third-line Relapsed DLBCL: Mechanism of Action



- XPO1 is the major nuclear export protein for:
  - TSPs (eg, p53, IkB, and FOXO)
  - eIF4E-bound oncoprotein mRNAs (eg, c-Myc, Bcl-xL, cyclins)
- Selinexor is an oral selective XPO1 inhibitor; preclinical data support that XPO1 inhibition:
  - Reactivates multiple TSPs relevant to NHL, including p53, p21, IkB, and FOXO
  - Promotes nuclear localization of eIF4e, which is overexpressed in most B-cell lymphomas
  - Reduces c-Myc, Bcl-2, and Bcl-6 levels
  - Toxicities: GI toxicities may be prohibitive

Theodoropoulos. Target Oncol. 2020;15:697.

Slide credit: clinicaloptions.com

L-MIND: Phase II Study of Tafasitamab + Len in R/R DLBCL

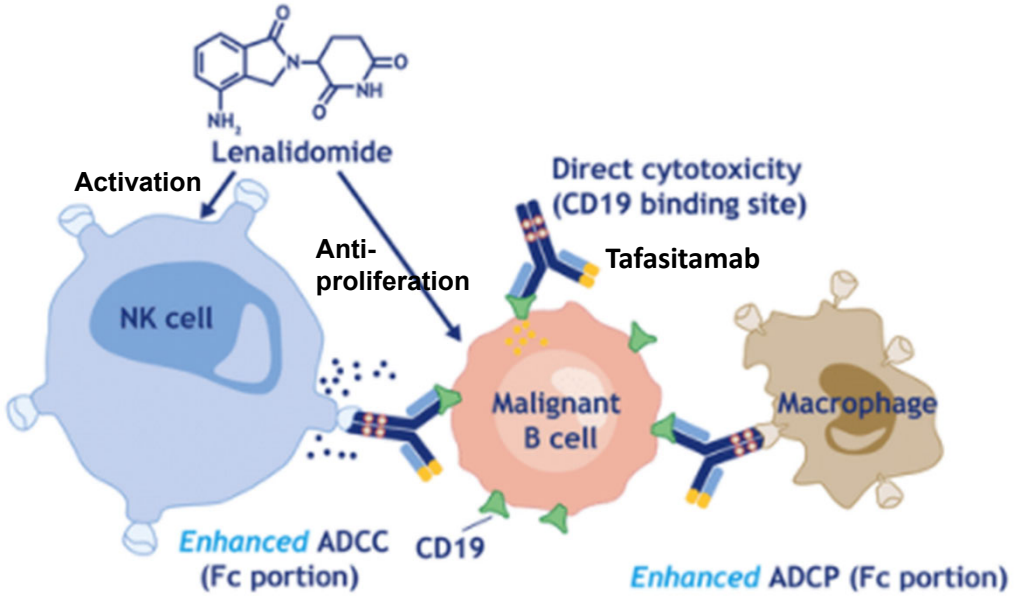
Patients with R/R DLBCL;
1-3 prior regimens
(≥1 anti-CD20); ECOG PS 0-2;
ineligible for HDT/ASCT;
primary refractory excluded
(N = 81)

→ **Lenalidomide** 25 mg/d PO, D1-21 x ≤12 28-d cycles
Tafasitamab 12 mg/kg/wk IV, cycles 1-3 (Q4W; D1,8,15,22)
(+ additional loading dose C1, D4) and C4-12 (Q4W, D1,15)

If no PD after 12 cycles →

Tafasitamab
12 mg/kg/wk
D1,15 until PD

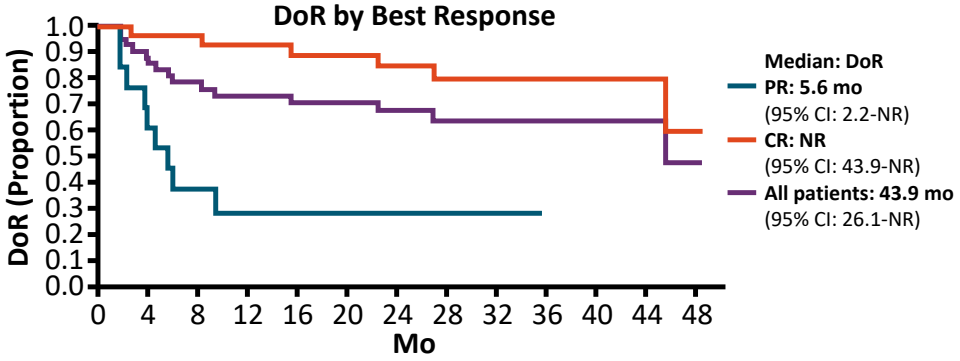
Baseline Characteristics	N = 81
Median age, yr (range)	72 (41-87)
IPI 3-5, n (%)	42 (52)
Median prior tx, n (range)	2 (1-4)
Refractory to previous line, n (%)	34 (42)

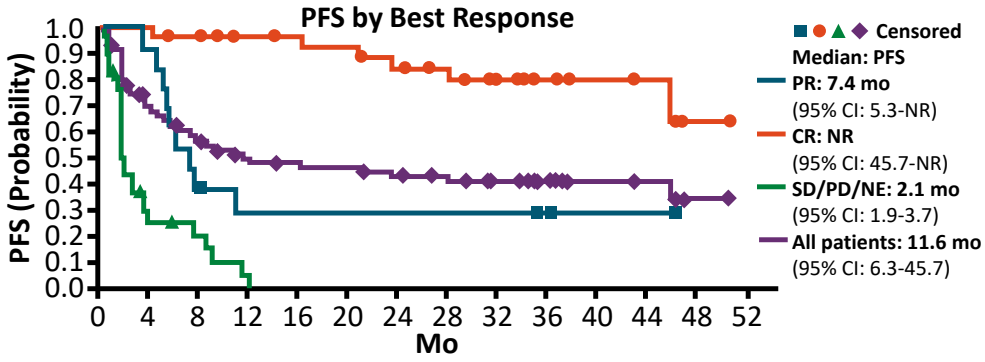


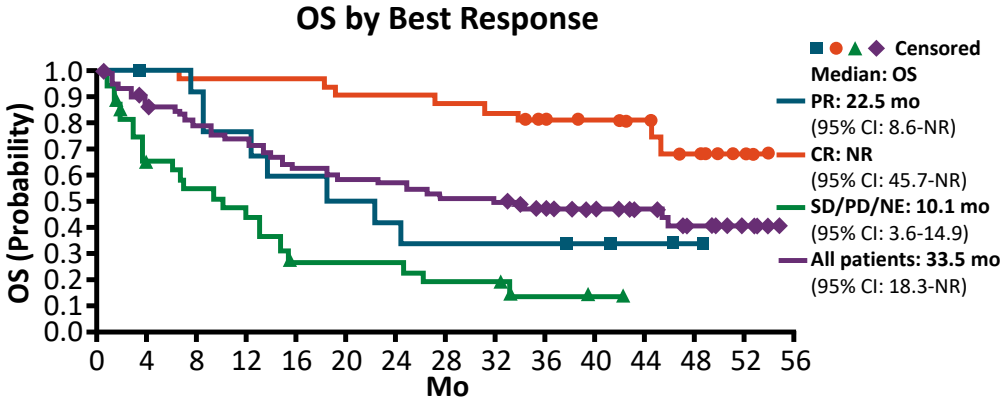
Salles. Lancet Oncol. 2020;21:978.

Slide credit: clinicaloptions.com

L-MIND 3-Yr Update: Tafasitamab + Lenalidomide in R/R DLBCL







- ORR: 58% (40% CRs)
  - Median DoR: 43.9 mo
- Median PFS: 11.6 mo
- Median OS: 33.5 mo

Remaining Questions

- Can this be given before an anti-CD19 CAR T-cell?
- Will it work after failing CAR T-cells?

Dull. ASCO 2021. Abstract 7513.

Slide credit: clinicaloptions.com

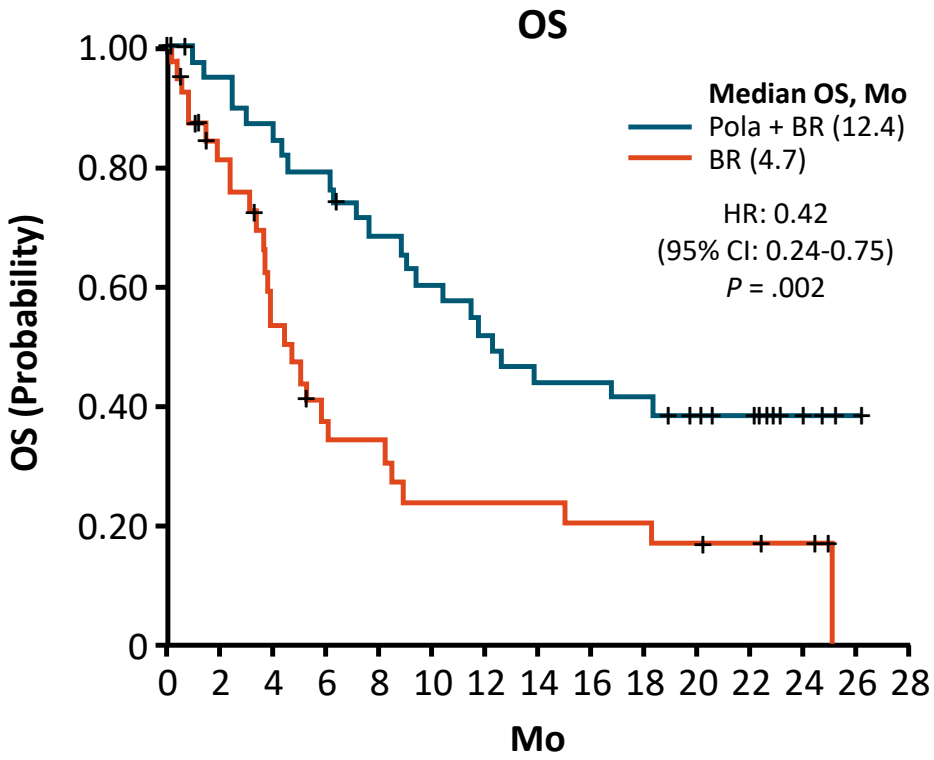
Polatuzumab Vedotin + BR vs BR in R/R DLBCL: Efficacy

Phase II Trial

Baseline Characteristic	BR (n = 40)	Pola + BR (n = 40)
Median age, yr (range)	71 (30-84)	67 (33-86)
IPI ≥3, n (%)	29 (73)	22 (55)
Median prior tx, no (range)	2 (1-5)	2 (1-7)
Prior BMT, n (%)	6 (15)	10 (25)

Response, %	BR (n = 40)	Pola + BR (n = 40)
CR	17.5	40.0
Median PFS, mo	3.7	9.5

- Consider in:
  - Nontransplant/non–CAR-T patient
  - Bridging therapy prior to CAR-T (caution with bendamustine)
  - Post CAR-T failure (caution with bendamustine)



Sehn. JCO. 2020;38:155.

Slide credit: clinicaloptions.com

LOTIS-2 Phase II Study of Loncastuximab Tesirine (Anti-CD19 ADC) in R/R Aggressive DLBCL

Patients with relapsed/refractory DLBCL (N = 145)

Treat for ≤1 yr

Loncastuximab tesirine 150 µg/kg Q3W (C1-2) then 75 µg/kg (C3+); 30-min infusion

Responders

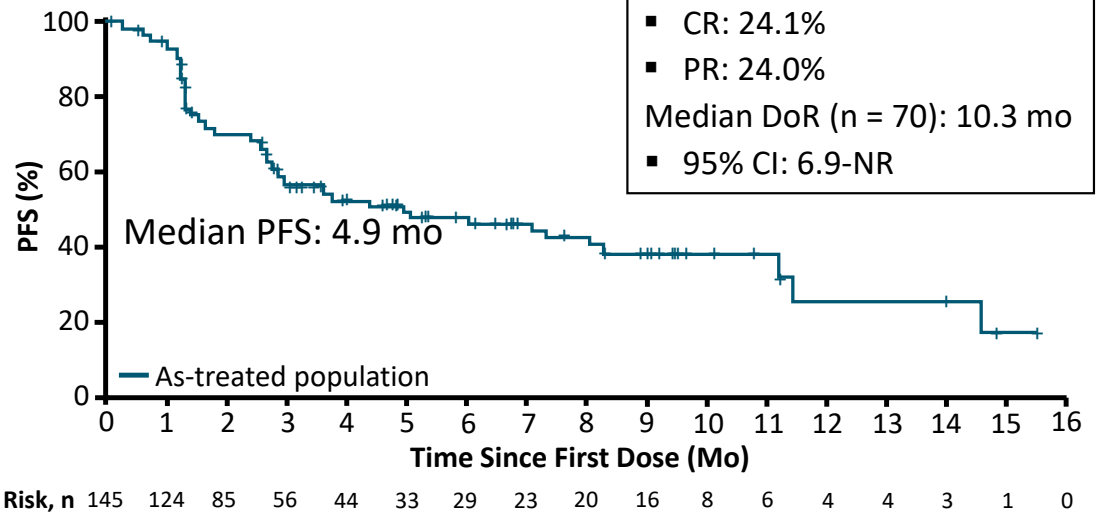
Treat for ≤3 yr

Loncastuximab tesirine Q3W

Baseline Characteristic	N = 145
Median age, yr (range)	66 (23-94)
Histology, n (%)	
▪ DLBCL NOS	127 (88)
▪ HGBCL	11 (8)
▪ PMBCL	7 (5)
Median prior tx (IQR)	3 (2-4)
Relapsed to prior tx, n (%)	43 (30)
Refractory to prior tx, n (%)	84 (58)
Prior CAR T-cells, n (%)	13 (9)

ORR: 48.3%
- CR: 24.1%
- PR: 24.0%

Median DoR (n = 70): 10.3 mo
- 95% CI: 6.9-NR



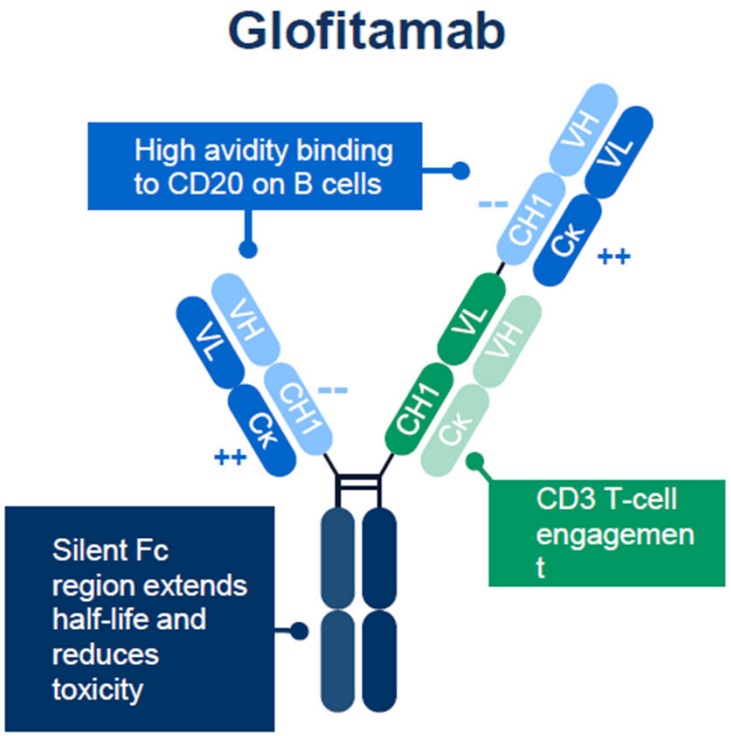
- Key toxicities: GGT increase, cytopenias, fatigue, nausea/vomiting, edema (requires dex x 3 days, starting day prior)

Caimi. Lancet Oncol. 2021;22:790.

Slide credit: clinicaloptions.com

Glofitamab: A Bispecific Antibody Targeting CD3 and CD20 in 2:1 Ratio

- **CD3/CD20 bispecific antibody for DLBCL**
- Unique 2:1 molecular configuration allows "double binding" to CD20 (highlighted in the blue zones)
- Advantages of the 2:1 design
  - Associated with superior potency under experimental conditions compared with 1:1 binding bispecifics
  - Allows concomitant treatment with anti-CD20 antibodies—predosing

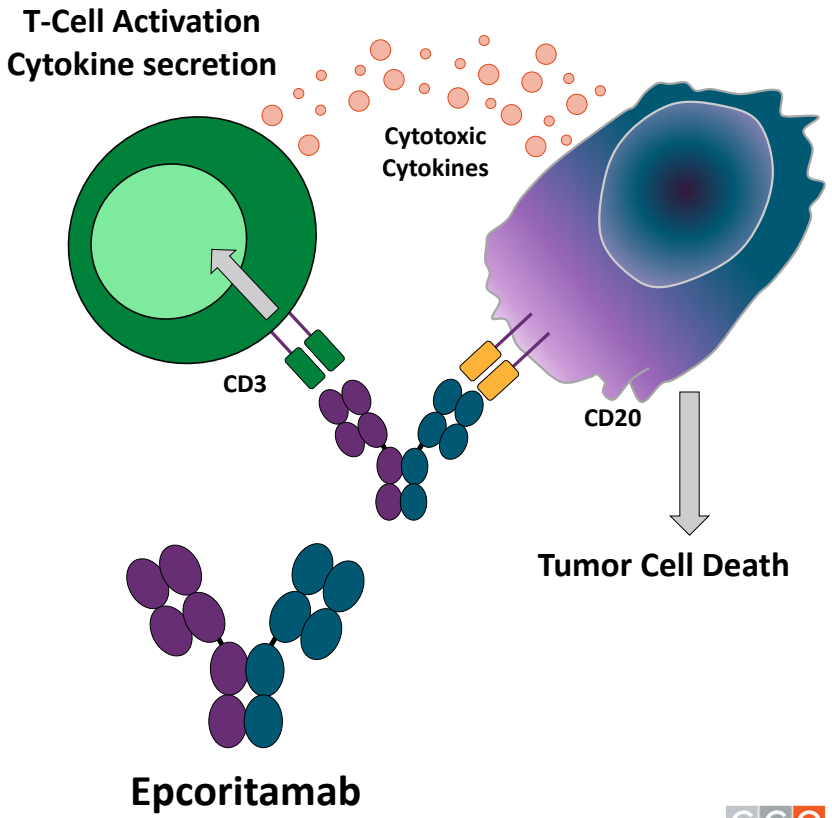


Dickinson. EHA 2020. Abstr S241.

Slide credit: clinicaloptions.com

Epcoritamab: Subcutaneously Administered CD3 x CD20 Bispecific Antibody

- Epcoritamab: novel subcutaneously administered CD3 x CD20 bispecific antibody
  - Induces T-cell activation by binding to CD3 on T-cells and CD20 on malignant B-cells
  - Promotes immunologic synapse between bound cells, resulting in apoptosis of B-cells
  - Binds to a distinct epitope on CD20 differently from epitopes of rituximab or obinutuzumab
  - Retains activity in the presence of CD20 mAbs



Huchings. ASH 2020. Abstr 402. Engelberts. EBioMedicine. 2020;52:102625. Chiu. EHA 2020. Abstr EP1330.

Slide credit: clinicaloptions.com

The Rapidly Evolving Landscape of DLBCL Therapy: Summary

- DLBCL is a clinically and biologically heterogeneous disease that is treated with curative intent in most patients
- Polatuzumab vedotin will be moving into frontline with R-CHP based on modestly improved efficacy over R-CHOP
- CAR T-cells have emerged as the treatment of choice in third-line and later DLBCL for eligible patients and are poised to move into second line for primary refractory and early progressing patients
- Other second-line therapies include tafasitamab/lenalidomide, polatuzumab/BR, or chemoimmunotherapy (ie, R-GemOx)
- Available third-line+ options after CAR T-cells or for patients ineligible for CAR T-cells include tafasitamab/lenalidomide, polatuzumab/BR, loncastuximab tesirine, and selinexor

CCO

Slide credit: clinicaloptions.com

Let’s Revisit Our Questions

Patient Case 1: Stage III DLBCL

- 58-yr-old woman was diagnosed with stage IIIB DLBCL after presenting with increasing bilateral axillary adenopathy
  - PET/CT was FDG avid in cervical, axillary, and retroperitoneal lymph nodes; bone marrow was negative for involvement; LDH elevated at 288 U/L
- She was treated with R-CHOP x 6 cycles and achieved a CR
- She relapsed 13 mo later with a biopsy-proven recurrence in a left axillary lymph node
  - Patient reports fatigue but PS = 0
- The patient was treated with salvage R-ICE x 2 cycles
  - Assessment of disease status by PET/CT following cycle 2 of R-ICE demonstrated a 30% reduction in prior adenopathy but a new FDG-avid lesion in the liver
- The patient's organ functions and PS remain stable
- HLA typing of siblings reveals 1 match

Assessment 1: After the previous discussion, now which of the following treatment options would you recommend for this patient?

1. An alternative chemoimmunotherapy regimen
2. An allogeneic stem cell transplant
3. An antibody-drug conjugate regimen
4. A CAR T-cell therapy
5. A nuclear export inhibitor
6. Uncertain

Assessment 2: On Day 5 following an infusion of CAR T-cells, a patient becomes confused and increasingly disoriented and drowsy; the patient is assessed as having grade 2 immune effector cell–associated neurotoxicity syndrome. Now which of the following treatment options would you recommend to manage this adverse event?

1. Anakinra
2. Cyclophosphamide
3. Siltuximab
4. Steroids
5. Tocilizumab
6. Uncertain

Assessment 3: After the previous discussion, now which of the following novel therapies in combination with BR would you recommend as a treatment option for a patient with R/R DLBCL?

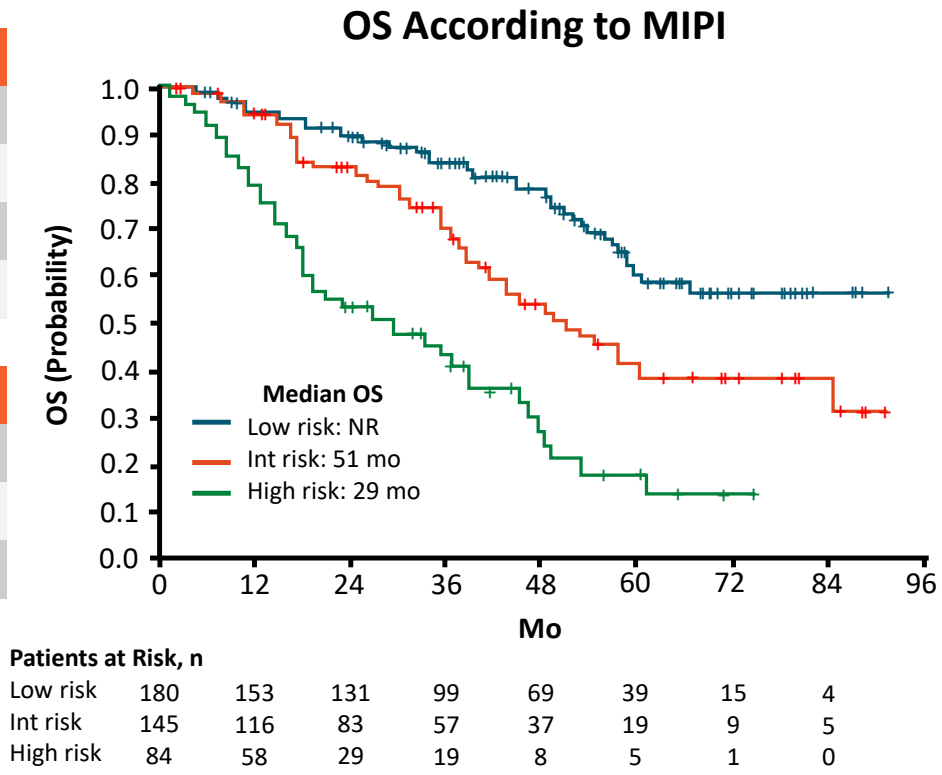
1. Loncastuximab tesirine
2. Polatuzamab vedotin
3. Selinexor
4. Tafasitamab
5. Tisagenlecleucel
6. Uncertain

Mantle Cell Lymphoma

MCL: Prognostic Factors for Overall Survival

Points	Age, Yr	ECOG PS	LDH/ULN, IU/L	WBC x 10^9/L
0	<50	0-1	<0.67	<6.7
1	50-59	--	0.67-0.99	6.7-9.99
2	60-69	2-4	1.00-1.49	10.0-14.99
3	≥70	--	≥1.50	≥15.0

Total Points	Risk	Patients, %
0-3	Low	44
4-5	Intermediate	35
6-11	High	21



Hoster. Blood. 2008;111:558-565.

Slide credit: clinicaloptions.com

MCL: Other Risk Factors

- Risk factors are heterogeneous within a patient and between patients
- MCL is biologically heterogeneous, and risk stratification incorporates multiple biologic factors

Low Risk

- Low KI-67 (≤10%)
- SOX-11 negative
- IGHV hypermutated
- Stable karyotype

High Risk

- Blastic/blastoic/pleomorphic
- High KI-67 (>30%)
- Complex karyotype
- *TP53* alterations

Indolent MCL

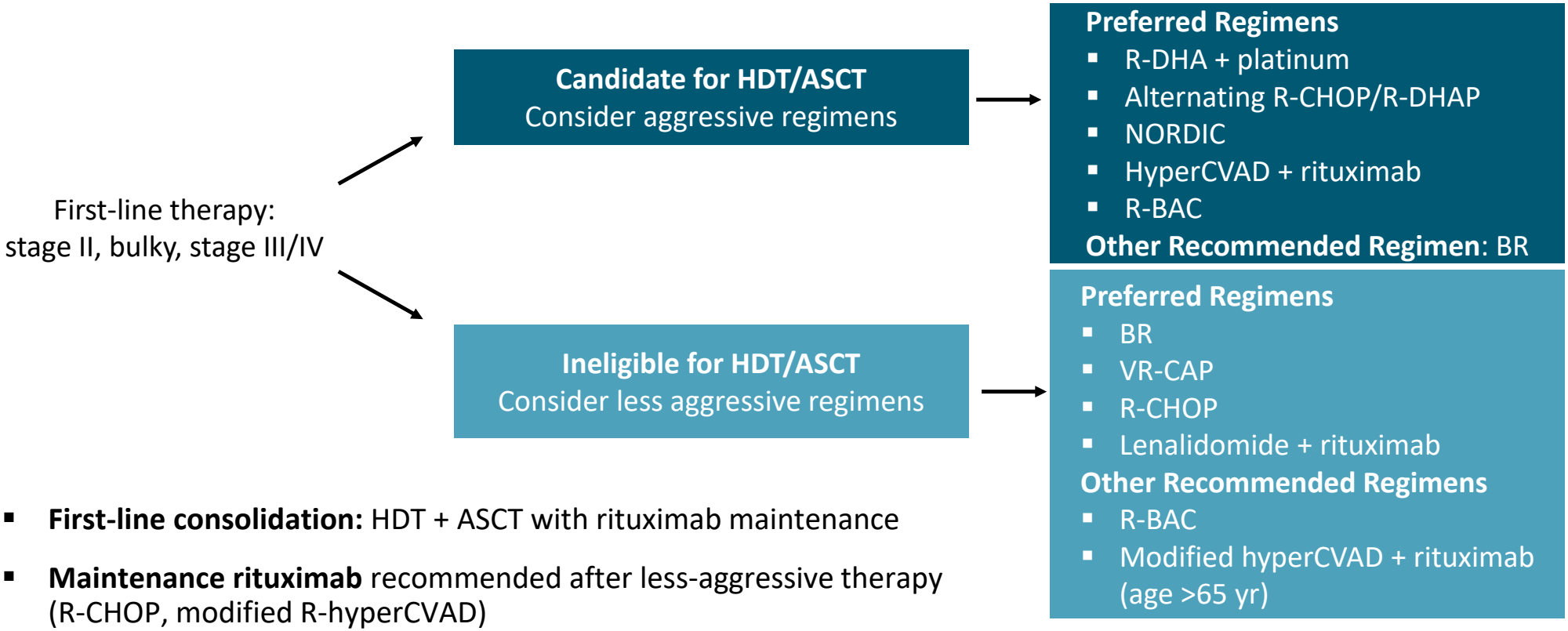
Classic MCL

Blastic MCL

Hoster. Blood. 2008;111:558-565.

Slide credit: clinicaloptions.com

First-line MCL Treatment Recommendations Still Center on Chemoimmunotherapy

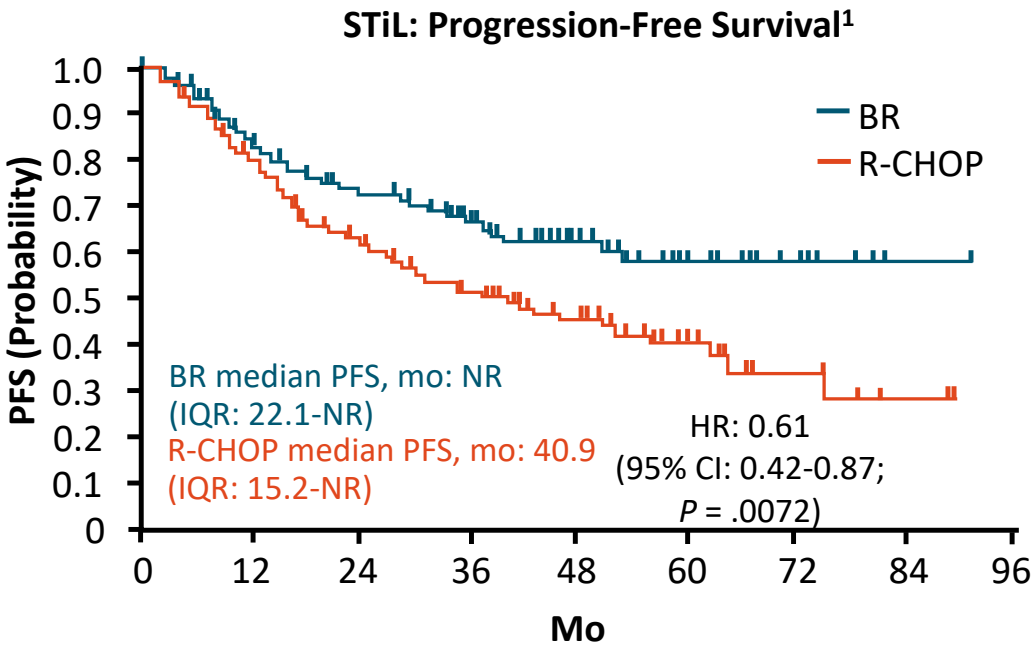


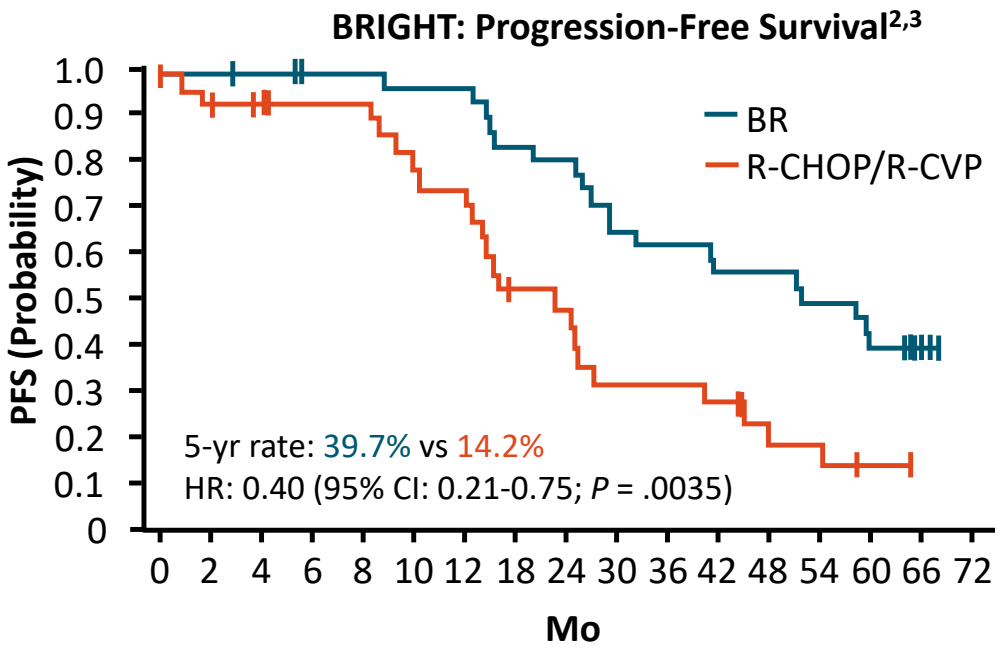
- **First-line consolidation:** HDT + ASCT with rituximab maintenance
- **Maintenance rituximab** recommended after less-aggressive therapy (R-CHOP, modified R-hyperCVAD)

NCCN. Clinical practice guidelines in oncology: B-cell lymphomas. v.1.2022. nccn.org

Slide credit: clinicaloptions.com

STiL and BRIGHT Phase III Trials: PFS With BR Superior to R-CHOP in MCL Cohorts





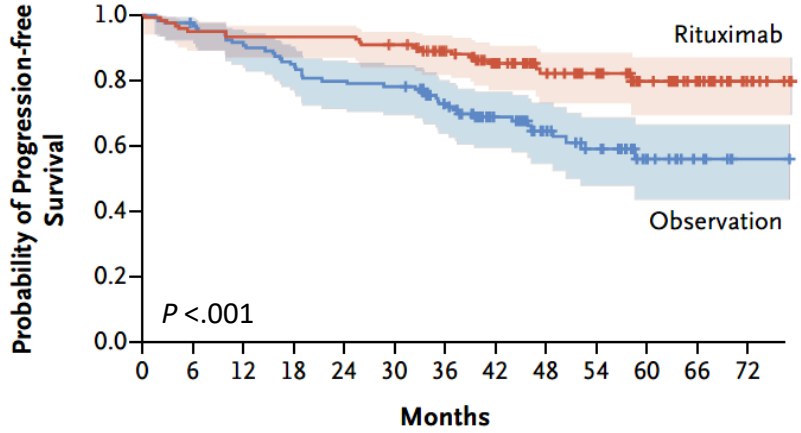
1. Rummel. Lancet. 2013;381:1203. 2. Flinn. ASCO 2017. Abstract 7500. 3. Flinn. JCO. 2019;37:984.

Slide credit: clinicaloptions.com

Phase III LYSA: PFS and OS w/Rituximab vs Observation as Maintenance in MCL Following ASCT

- N = 240 patients with MCL <66 yr of age at diagnosis after 4 courses of R-DHAP and ASCT
- Rituximab maintenance: 375 mg/m^2 Q2M x 3 yr

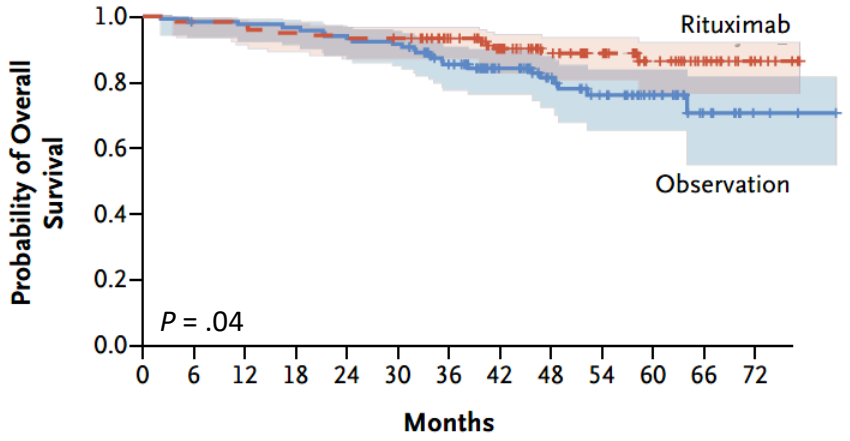
Agent	n	Patients w/Event, n (%)	Pts w/Censored Data, n (%)	Median PFS
Rituximab	120	20 (17)	100 (83)	NR
Observation	120	43 (36)	77 (64)	NR



No. at Risk

Rituximab	120	114	112	112	112	108	96	75	55	44	29	20	7
Observation	120	116	109	101	95	93	77	57	37	29	13	6	1

Agent	n	Patients w/Event, n (%)	Pts w/Censored Data, n (%)	Median OS
Rituximab	120	13 (11)	107 (89)	NR
Observation	120	24 (20)	96 (80)	NR



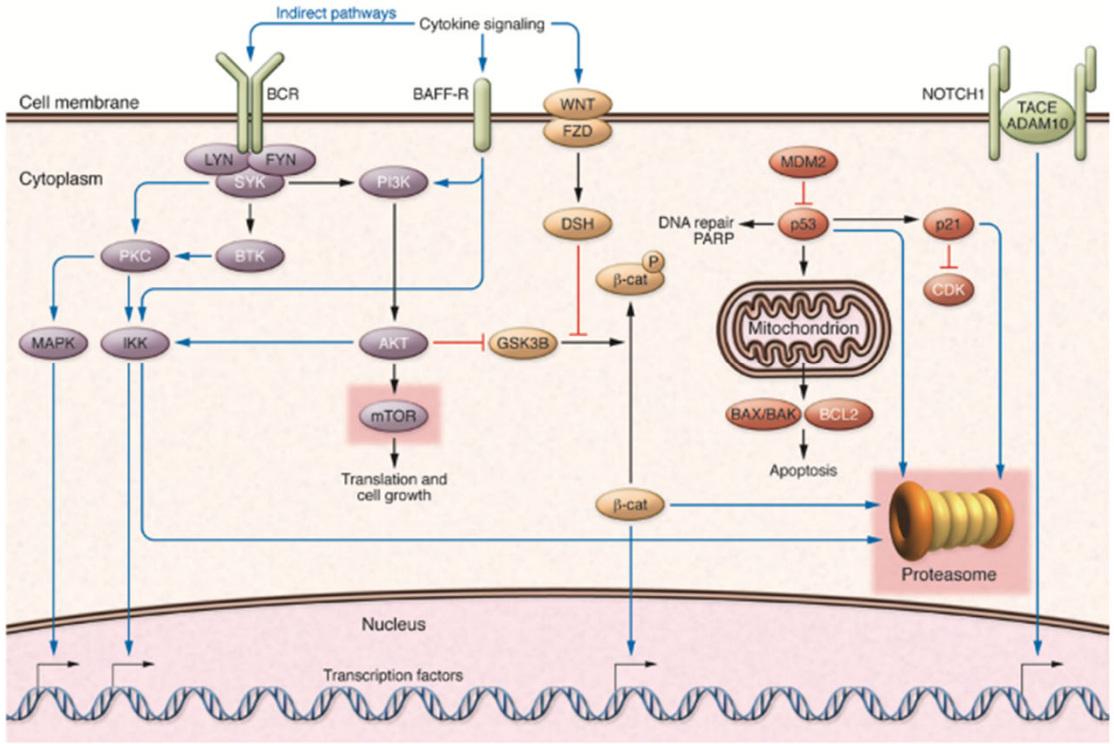
No. at Risk

Rituximab	120	118	116	114	112	111	100	79	60	48	32	20	7
Observation	120	117	116	115	111	109	90	71	50	39	23	10	3

Le Gouill. NEJM. 2017;377:1250.

Slide credit: clinicaloptions.com

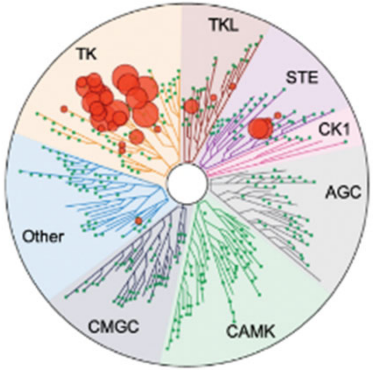
How Do We Approach R/R MCL?



- **Better understanding of biology of MCL has led to shift away from chemotherapy**
  - **BTK:** covalent inhibitors ibrutinib, acalabrutinib, zanubrutinib; noncovalent inhibitors pirtobrutinib,* nemtabrutinib*
  - **IMiDs:** lenalidomide
  - **BCL2:** venetoclax*

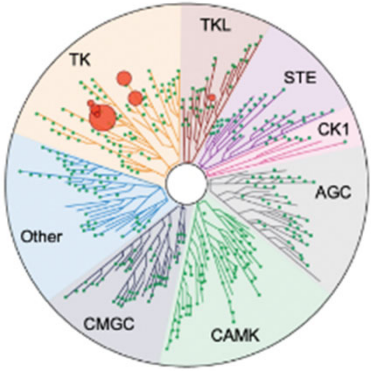
*Not approved by FDA for R/R MCL.

FDA-Approved BTK Inhibitors in R/R MCL



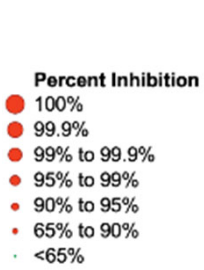
Ibrutinib

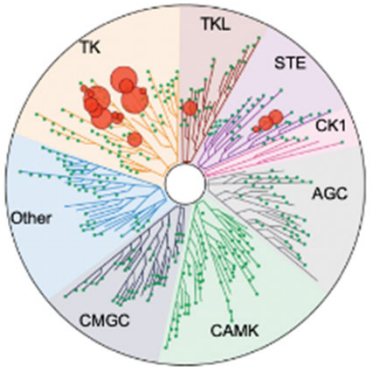
Once-daily oral treatment



Acalabrutinib

Twice-daily oral treatment





Zanubrutinib

Once- or twice-daily oral treatment

- All 3 FDA-approved covalent BTK inhibitors are efficacious but are not curative therapies
- Differing selectivity of these agents may account for differences in AE profiles (acalabrutinib and zanubrutinib more selective)

Kaptein. ASH 2018. Abstr 1871.

CCO

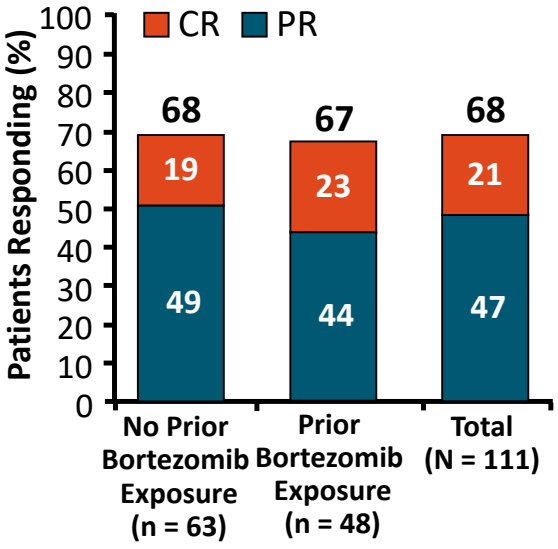
Slide credit: clinicaloptions.com

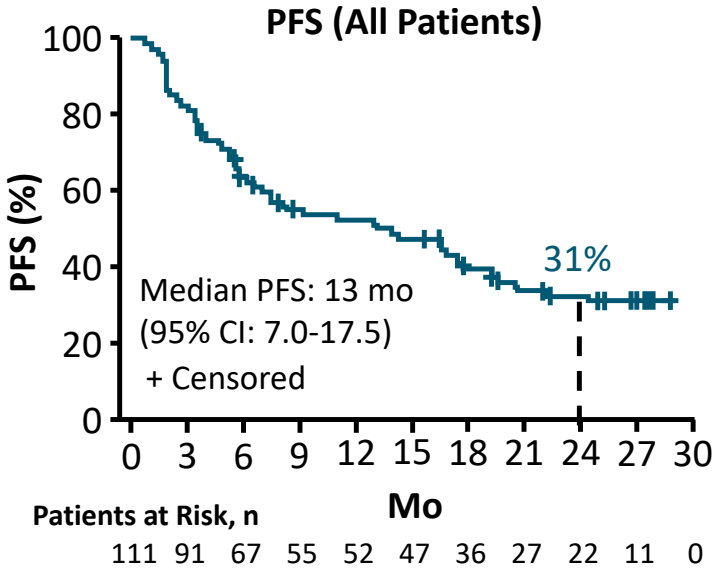
Phase II PCYC-1104: Ibrutinib in R/R MCL

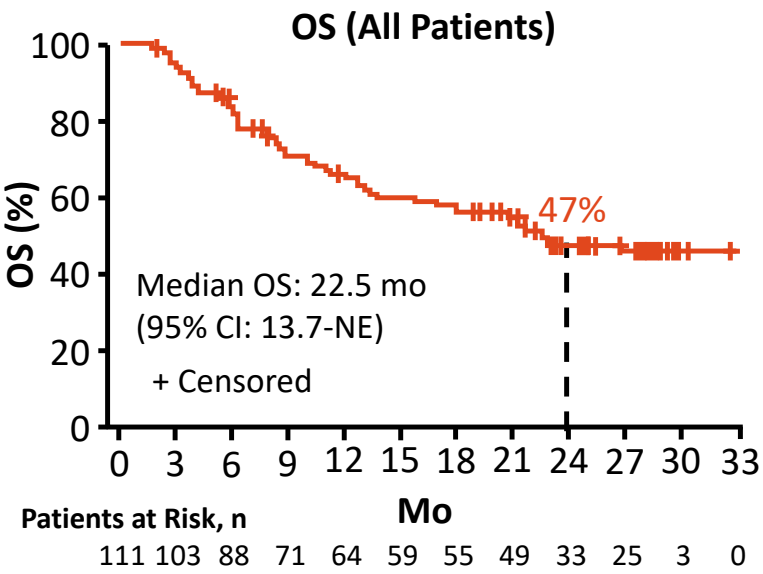
Patients with MCL and measurable disease (LN diameter ≥2 cm); 1-5 previous lines of tx; no <PR to the most recent tx or PD after the most recent tx; adequate organ function (N = 111)

→ **Ibrutinib** 560 mg PO daily →

Continue until PD or unacceptable AE occurred







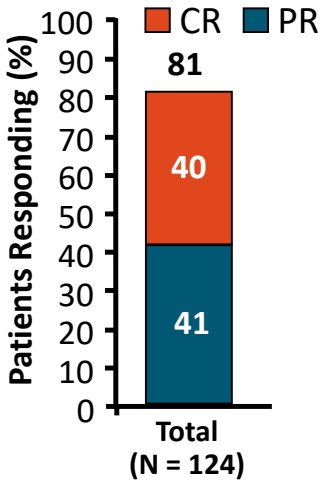
Wang. NEJM. 2013;369:507. Wang. Blood. 2015;126:739.

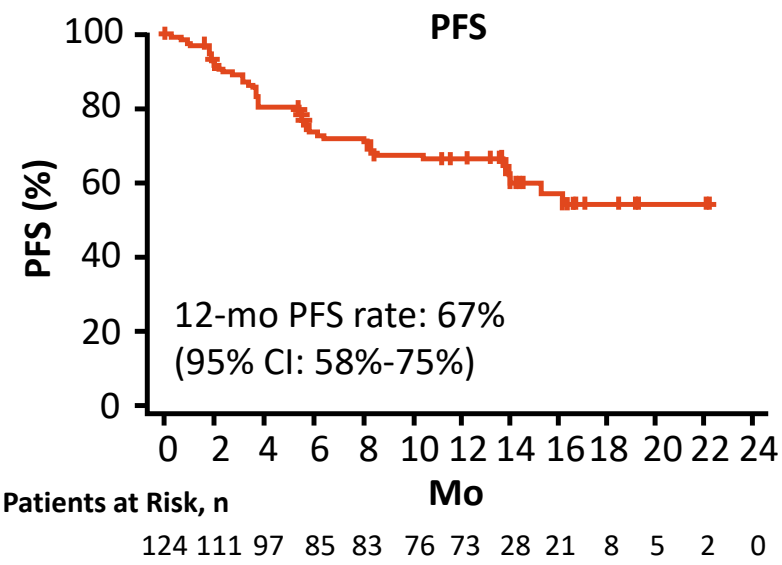
Slide credit: clinicaloptions.com

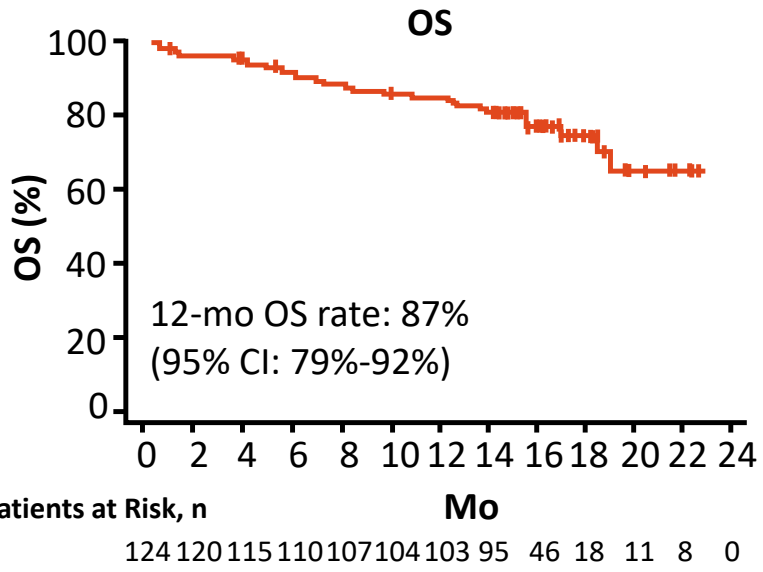
Phase II ACE-LY-004: Acalabrutinib in R/R MCL

Adult patients with MCL;
1-5 prior lines of tx; ECOG PS 0-2; no notable CVD*;
no concurrent use of warfarin/equivalent vitamin K antagonists; no prior BTK inhibitors
(N = 124)

→ **Acalabrutinib** 100 mg PO BID in 28-day cycles → *Until PD*







*Includes: class 3/4 cardiac disease per NYHA Functional Classification; CHF or MI within 6 mo of screening; QTc >480 ms; uncontrolled/symptomatic arrhythmias.

1. Wang. Lancet. 2018;391:659. 2. Cheson. JCO. 2014;32:3059. 3. Cheson. JCO. 2007;25:579.

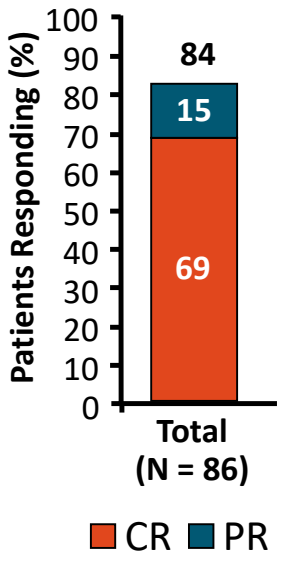
Slide credit: clinicaloptions.com

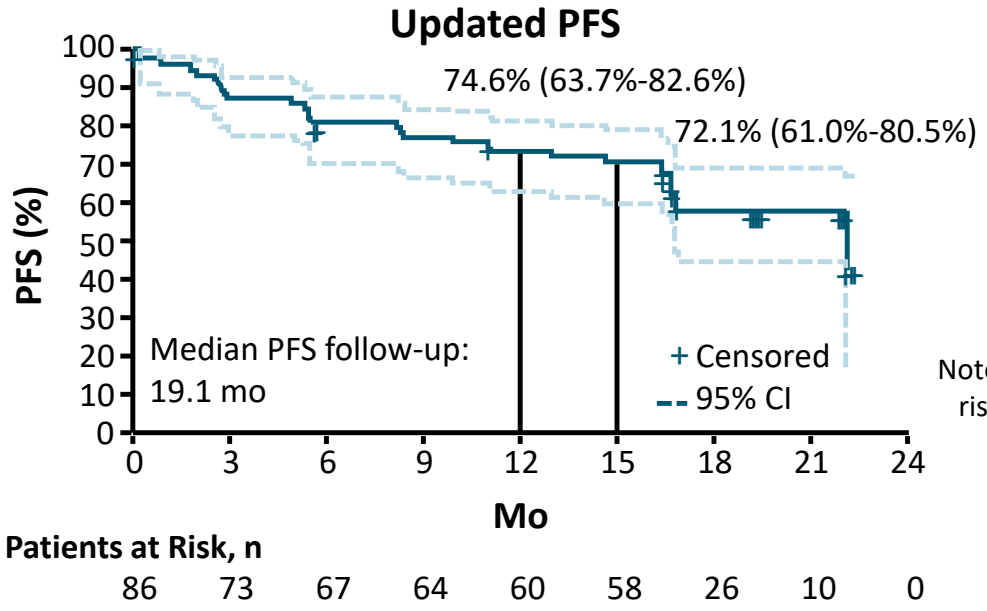
Phase II BGB-3111-206: Zanubrutinib in R/R MCL

Patients with MCL and ≥1 prior lines of tx; ECOG PS 0-2; no notable CVD; no prior BTK inhibitors (N = 86)

→ **Zanubrutinib** 160 mg PO BID →

Up to 3 yr or until PD, unacceptable toxicity, or death





Note: Only 4 patients were at risk at the last event time.

Song. Clin Canc Res. 2020;26:4216

Slide credit: clinicaloptions.com

R-Lenalidomide Combination Highly Effective for MCL in Frontline and Relapsed Settings

Phase II Study[1]

Patients with untreated MCL; tumor ≥1.5 cm; low/int-risk MIPI or high-risk MIPI if ineligible for chemo (N = 38)

Induction (C1-12)

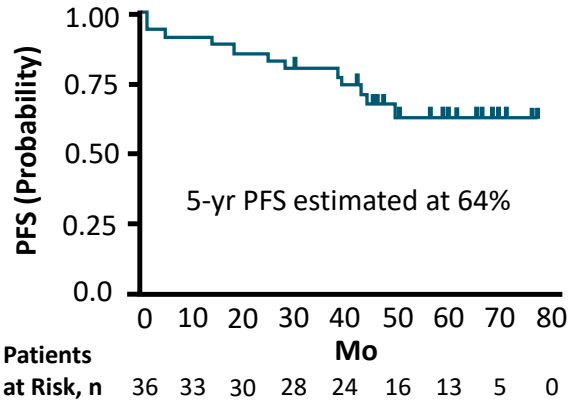
Rituximab 375 mg/m^2 IV QW x 4, then every 2 cycles
Lenalidomide PO 20 mg/d, D1-21, Q28D

Maintenance (C13-PD)

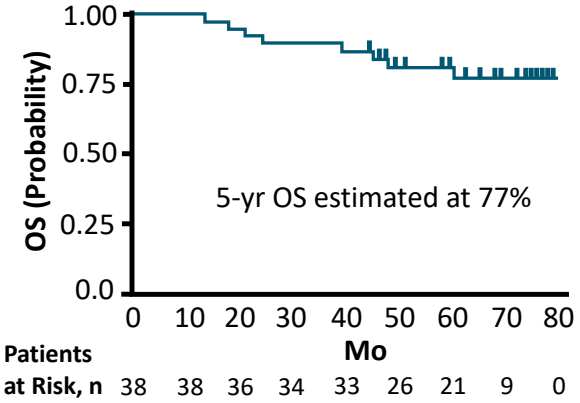
Rituximab 375 mg/m^2 every 2 cycles
Lenalidomide PO 15 mg/d, D1-21, Q28D

- Primary endpoint: ORR
- Secondary endpoints: survival, safety
- Exploratory endpoints: MRD, cytokine/chemokine

PFS

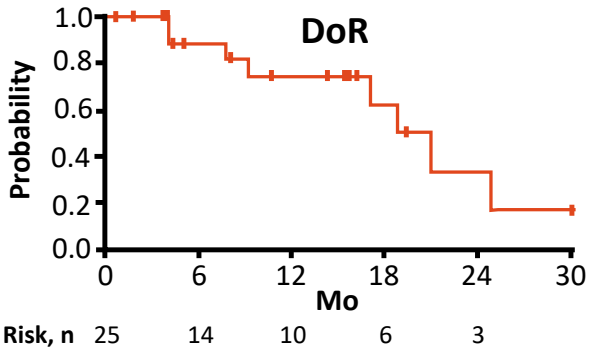


OS

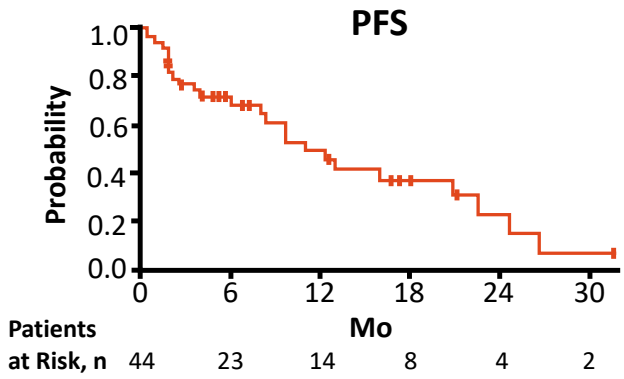


Phase I/II Study in R/R MCL (N = 52)[2]

DoR



PFS

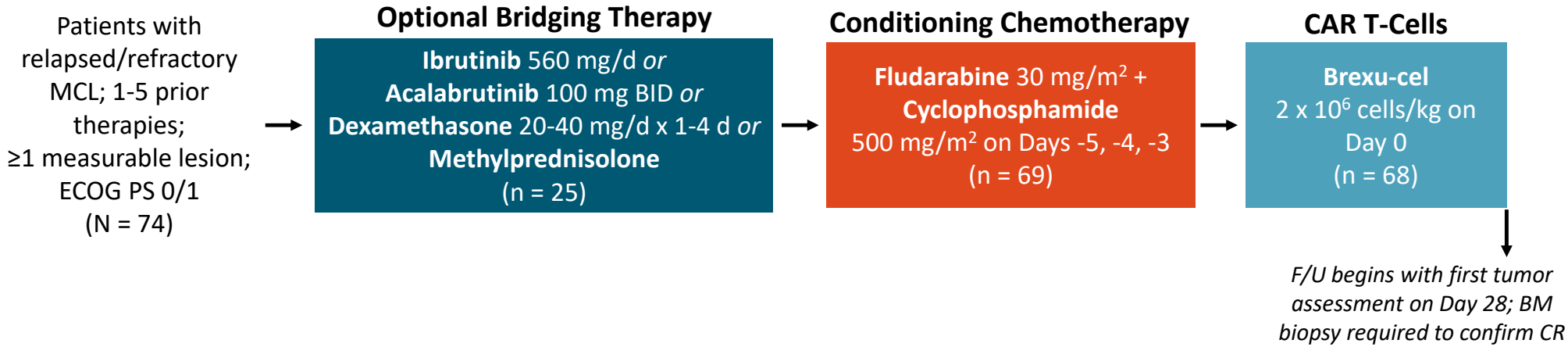


1. Ruan. Blood. 2018;132:2016. 2. Wang. Lancet Oncol. 2012;13:716.

Slide credit: clinicaloptions.com

ZUMA-2: Brexucabtagene Autoleucel in R/R MCL

- International, open-label phase II trial

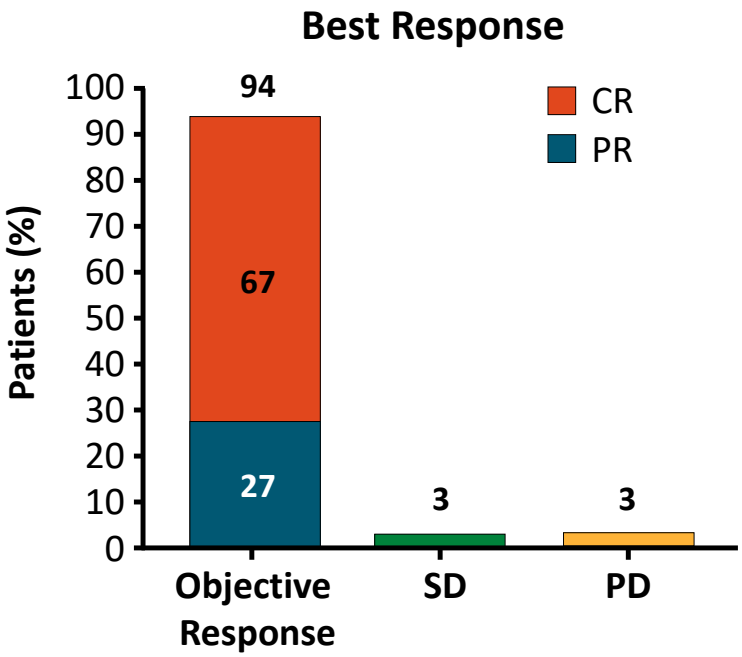


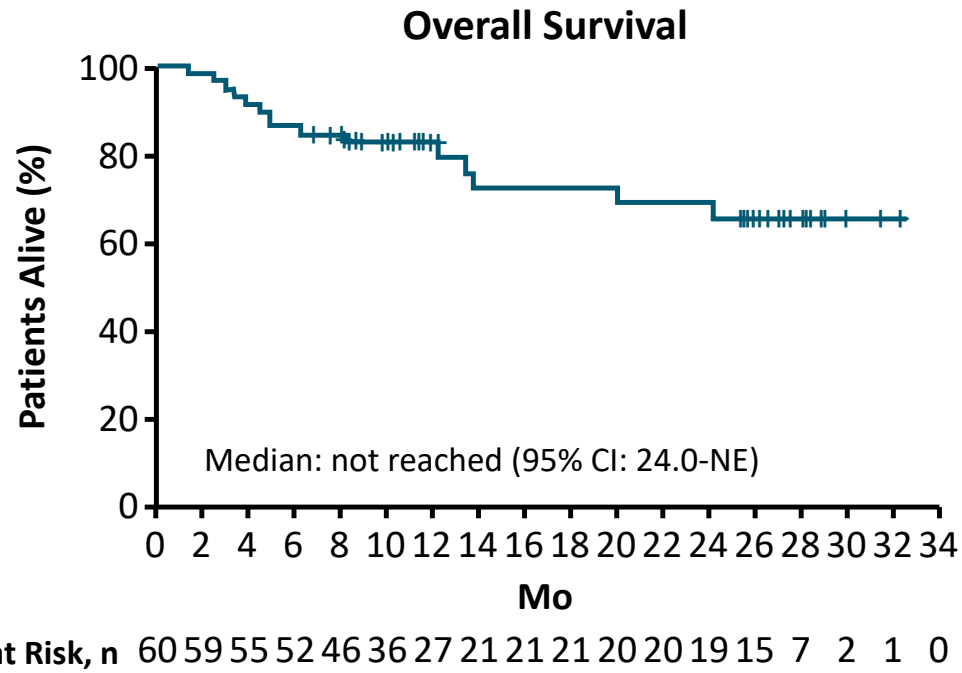
- **Primary endpoint:** ORR (IRRC assessed per Lugano classification)
- **Secondary endpoints:** DoR, PFS, OS, safety, ORR (investigator assessed), QoL (EQ-5D), CAR T-cell levels in blood, cytokines in serum

- Brexu-cel was successfully manufactured in 96% of patients and administered to 92% of patients
- Median time from leukapheresis to brexu-cel delivery was 16 days

Wang. NEJM. 2020;382:1331. Wang. ASH 2019. Abstr 759.

ZUMA-2: Brexucabtagene Autoleucel Efficacy in R/R MCL





- Most common grade ≥3 AEs were cytopenias (94%) and infections (32%)
- CRS occurred in 91% of patients, but 76% were grade 1/2

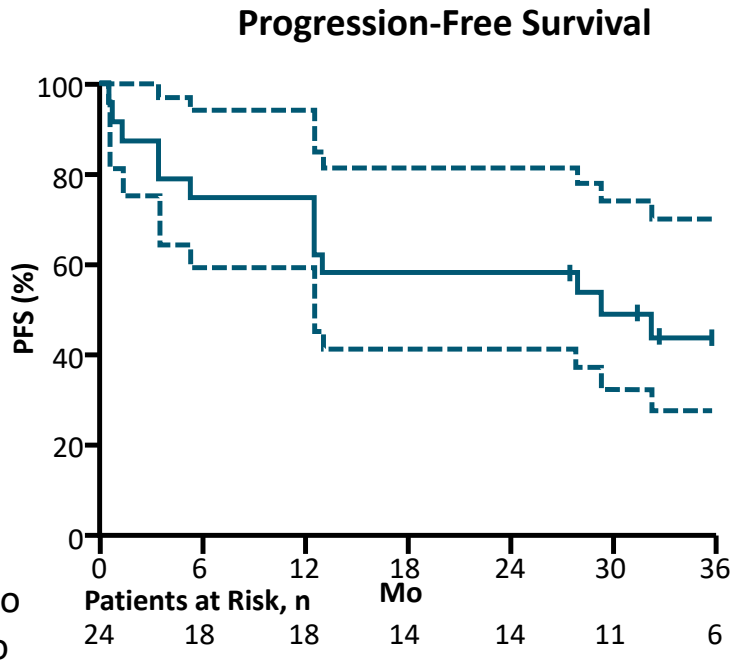
Wang. NEJM. 2020;382:1331.

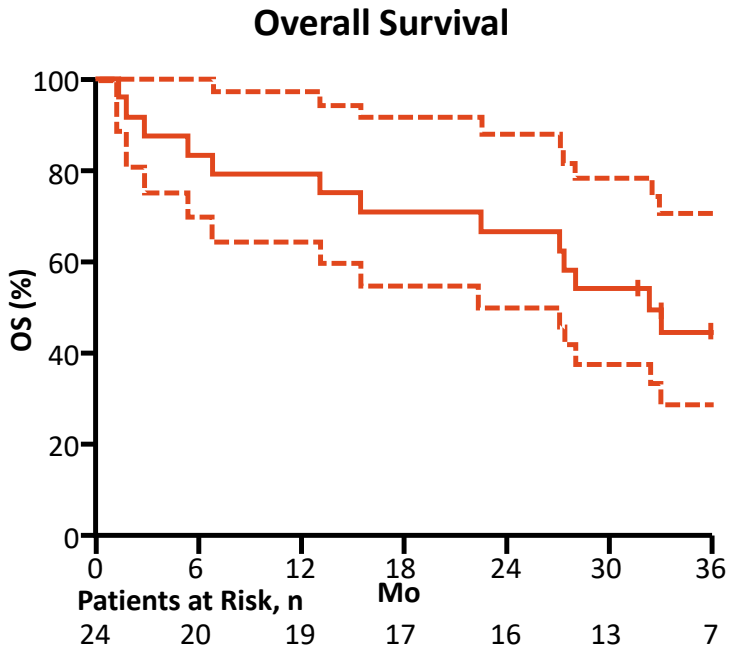
Slide credit: clinicaloptions.com

AIM: 3-Yr Update of Ibrutinib + Venetoclax in R/R MCL—PFS and OS

Patients with R/R MCL after ≥1 line of prior therapy (N=23)

Treatment:
Ibrutinib 560 mg x 4 wk
Venetoclax ramp-up x 5 wk
I + V until PD or tox





- Median PFS: 29 mo
- Median OS: 32 mo
- *TP53* abnormal (n = 12): ORR, 50%; CR, 50%
- *TP53* wild type (n = 10): ORR, 90%; CR, 90%
- Proof of concept for deep responses with combination BTKi and BCL2i

Handunnetti. ASH 2019. Abstr 756.

Slide credit: clinicaloptions.com

Conclusions: Mantle Cell Lymphoma

- Chemoimmunotherapy with /without consolidation with high dose therapy and autologous PBSCT most common frontline therapy
- Efficacy and safety profile of BTK inhibitors has made BTK inhibitors therapy of choice in second-line MCL
- Novel combinations with BTK inhibitors under investigation
- CAR T-cells are important therapeutic choice in relapsed MCL

Go Online for More CCO Coverage of B-Cell Malignancies!

CME-certified on-demand webcast of a live workshop (*coming soon*)

Downloadable slideset with slides from today's presentation and updated throughout the course of the live meeting series

Additional programs on the management of B-cell lymphomas

Clinical Summary Resources for each class of agent discussed in this activity

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