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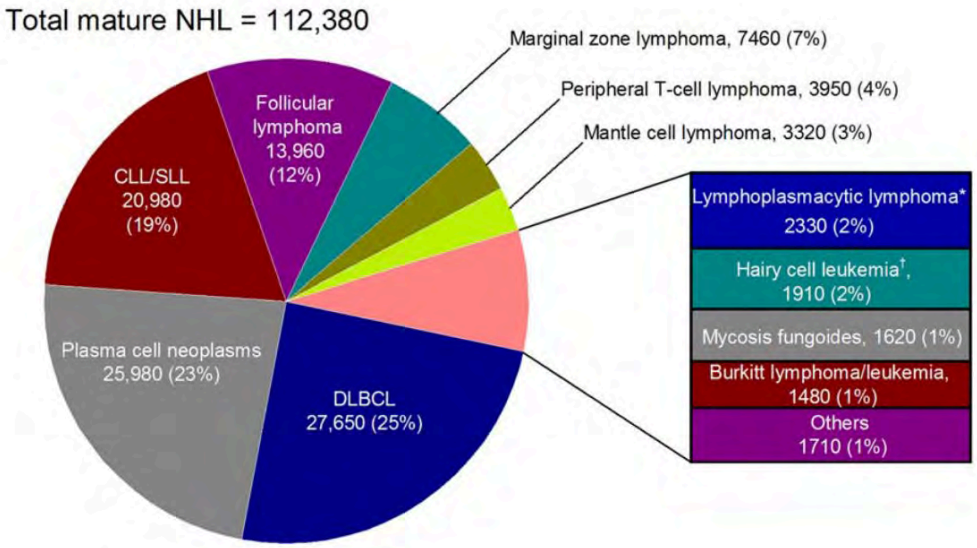
T. HOWARD LEE KEYNOTE LECTURE:

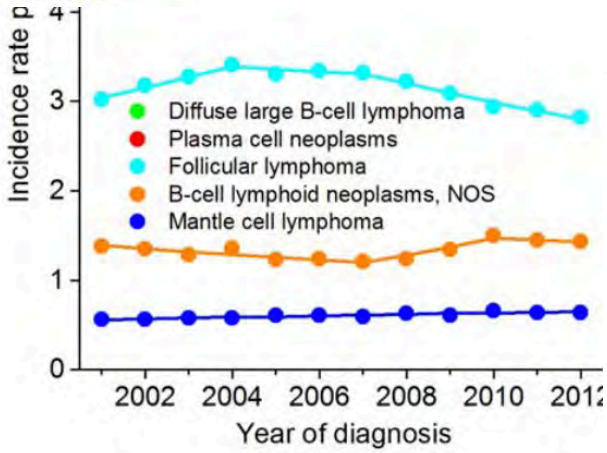
TARGETED AND CELLULAR THERAPY FOR DIFFUSE LARGE B-CELL LYMPHOMA: THE END OF A JOURNEY?

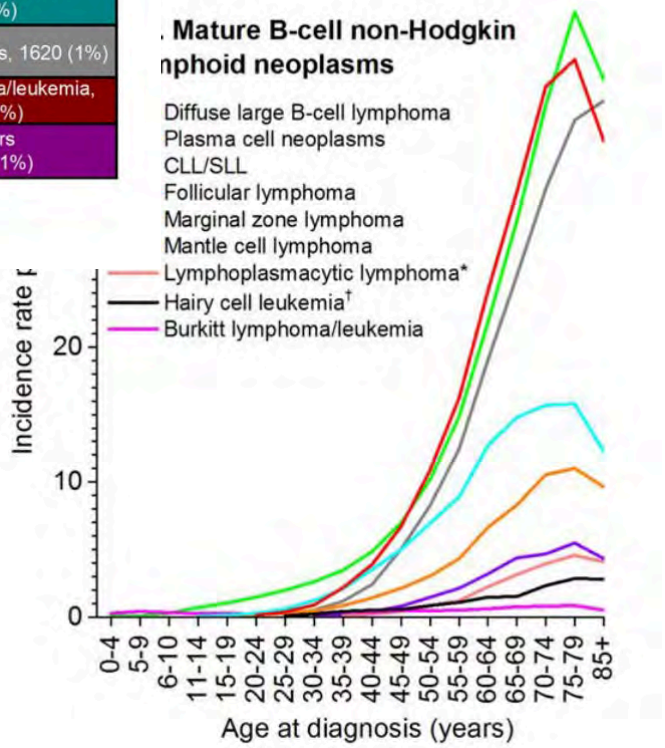
Sonali M. Smith, MD FASCO
Elwood V. Jensen Professor of Medicine
Chief, Section of Hematology/Oncology
Co-Leader, Cancer Service Line
The University of Chicago

DLBCL in context

- DLBCL is the most common lymphoid cancer
- ~27K new/year in US
- Increases with age
- Occurs in all age groups







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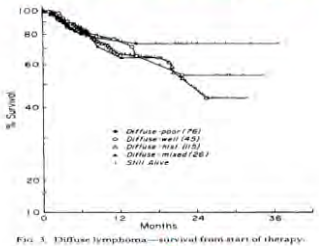
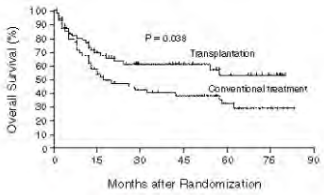
Teras CA Cancer J Clin 2016 Nov 12;66(6):443-459

The Journey: Major milestones in DLBCL Treatment

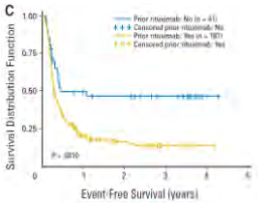
CHOP leads to cure in 54% of pts



HDC/ABMT in 2L chemosensitive disease has 53% long-term survival

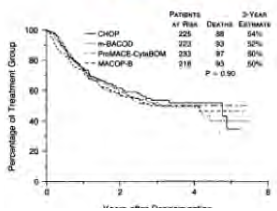


HDC/ASCT benefits fewer patients (~15-40% with long-term survival)

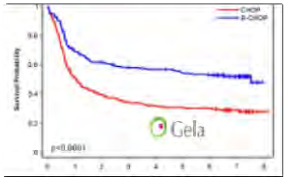


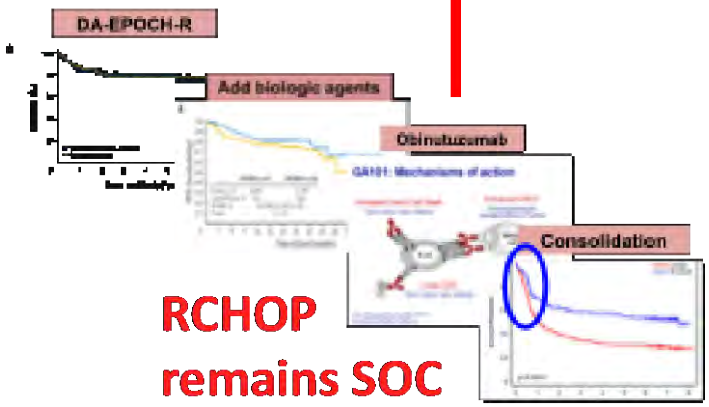
1976 — 1993 — 1995 — 2002 — 2010 — 2017

CHOP as effective and less toxic than intensive regimens



Rituximab plus CHOP improves OS





RCHOP remains SOC

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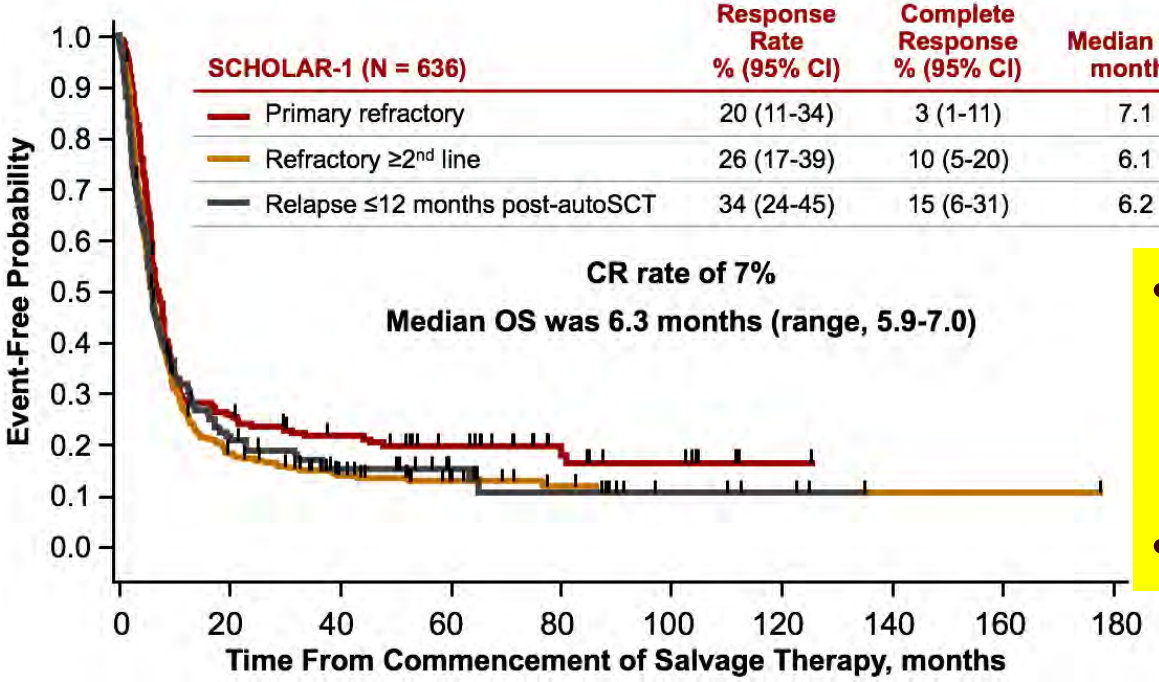
Expected survival for R/R DLBCL Treated with Salvage Chemotherapy

SCHOLAR-1 (N = 636)	Response Rate % (95% CI)	Complete Response % (95% CI)	Median OS, months
Primary refractory	20 (11-34)	3 (1-11)	7.1
Refractory ≥2nd line	26 (17-39)	10 (5-20)	6.1
Relapse ≤12 months post-autoSCT	34 (24-45)	15 (6-31)	6.2



- **SCHOLAR analysis included ~636 pts enrolled in clinical trials**
- **Median age 55y**

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

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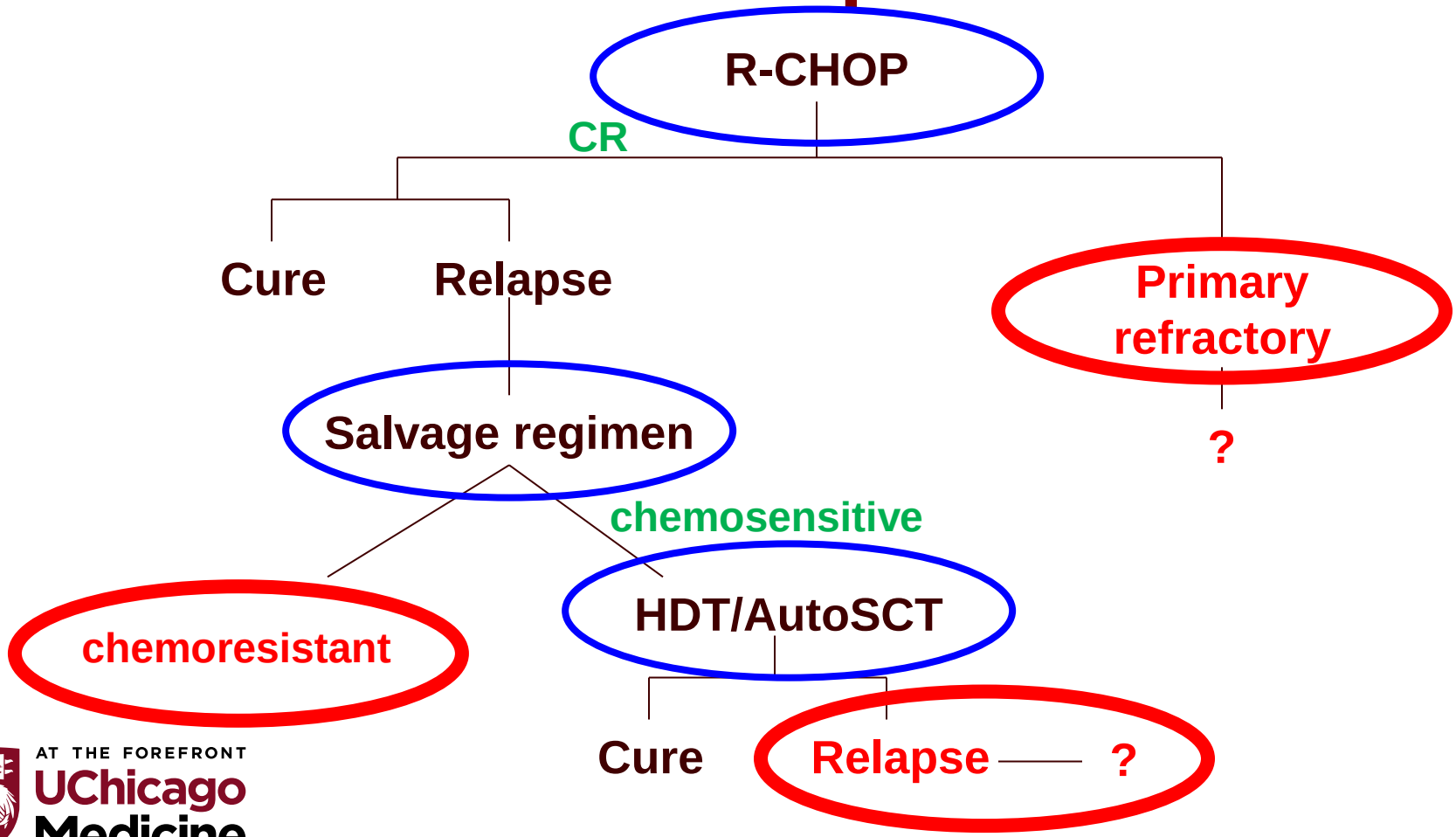
Crump M, et al. *Blood*. 2017;130:1800-1808

KEY QUESTIONS pre-2017:
1. Can we cure more patients in 1L?
2. What are the best options for 2L+?



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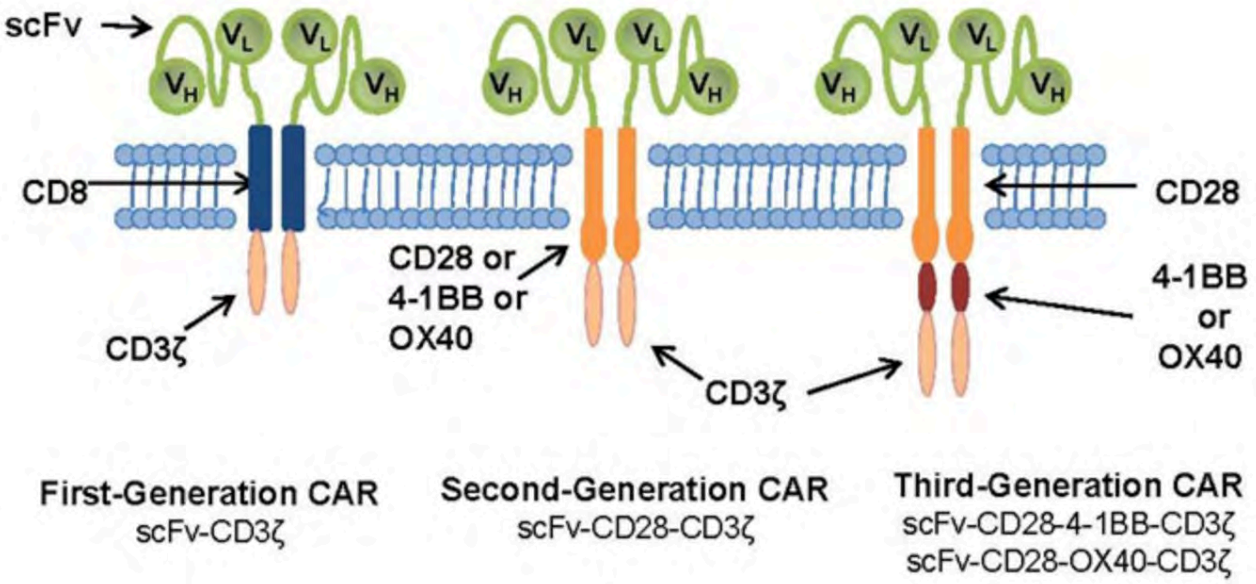
Anatomy of a chimeric antigen receptor



scFv
Single-chain variable fragment (scFv) allows direct activation of T cell by cancer cell antigens

Hinge region
Allows optimal antigen binding

Costimulatory Domain: CD28 or 4-1BB
Enhances CAR T cell proliferation, cytotoxicity and persistence

Signaling Domain: CD3-zeta chain
Proliferation & activation of CAR T cells
CAR T cell-mediated killing of tumor cells

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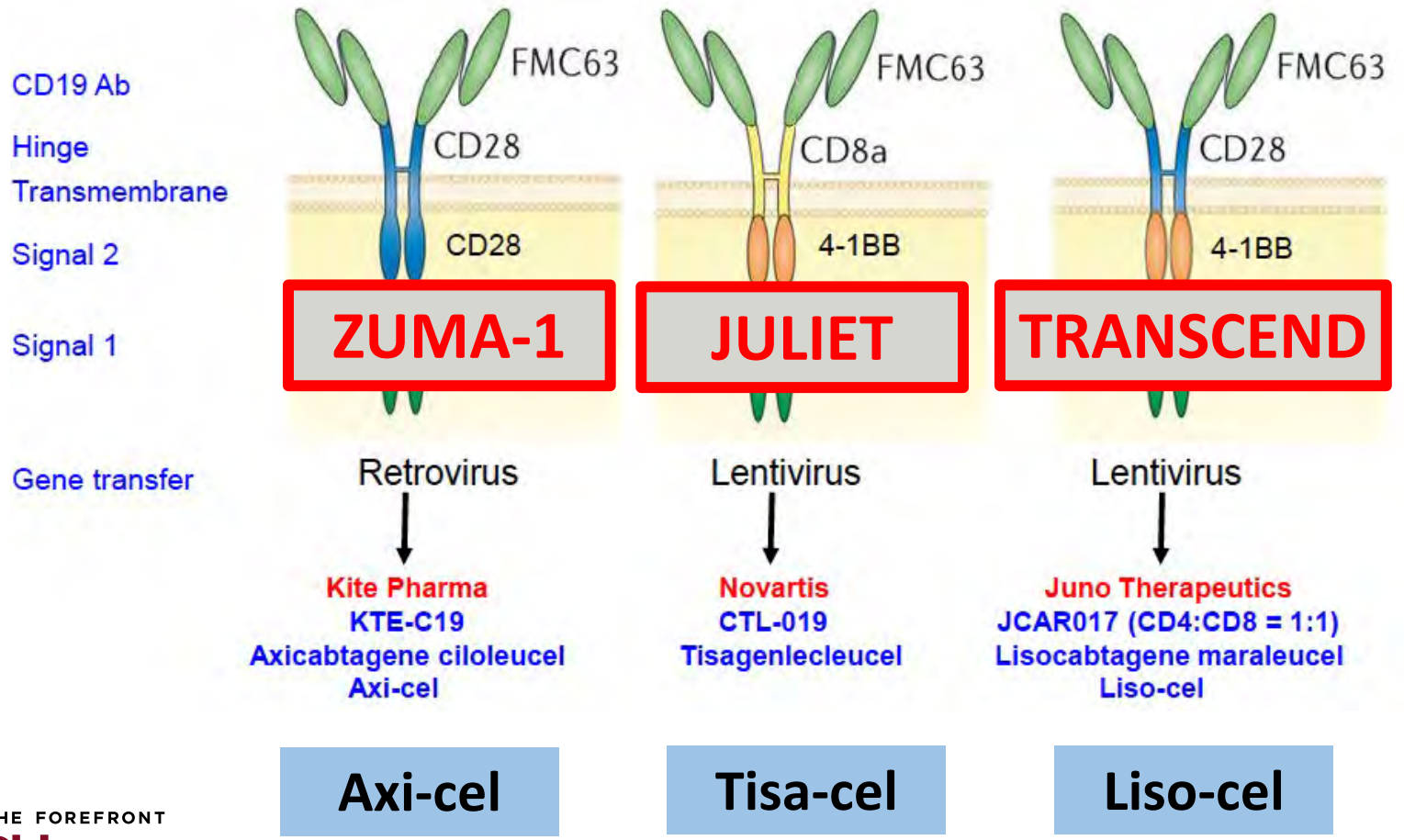
Park Discov Med 2010 Apr;9(47):277-88
Slide modified from Peter Riedell

Cellular Therapy: chimeric antigen receptor engineered T-cells (CAR-T)



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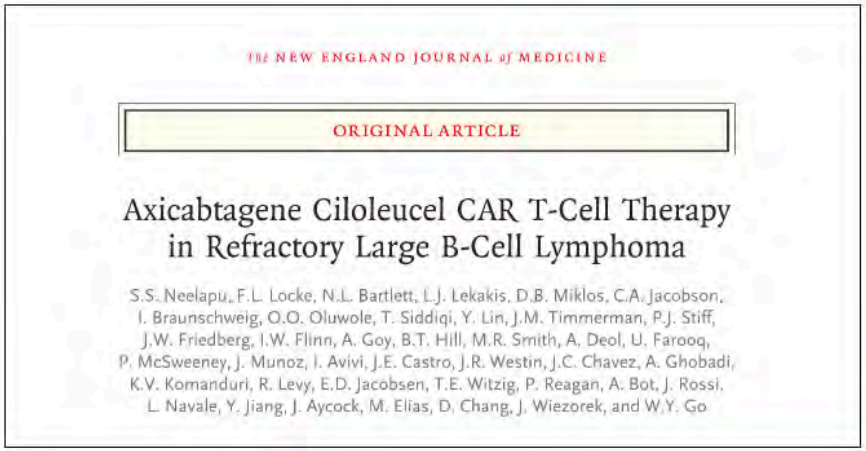
Adapted from van der Steegan et al. Nat Rev Drug Discov, 2015

Studies leading to FDA-approval

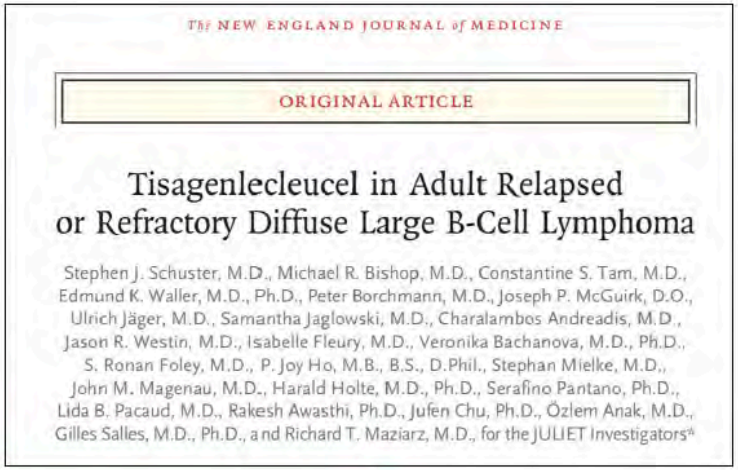


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma

S.S. Neelapu, F.L. Locke, N.L. Bartlett, L.J. Lekakis, D.B. Miklos, C.A. Jacobson, I. Braunschweig, O.O. Oluwole, T. Siddiqi, Y. Lin, J.M. Timmerman, P.J. Stiff, J.W. Friedberg, I.W. Flinn, A. Goy, B.T. Hill, M.R. Smith, A. Deol, U. Farooq, P. McSweeney, J. Munoz, I. Avivi, J.E. Castro, J.R. Westin, J.C. Chavez, A. Ghobadi, K.V. Komanduri, R. Levy, E.D. Jacobsen, T.E. Witzig, P. Reagan, A. Bot, J. Rossi, L. Navale, Y. Jiang, J. Aycock, M. Elias, D. Chang, J. Wiezorek, and W.Y. Go

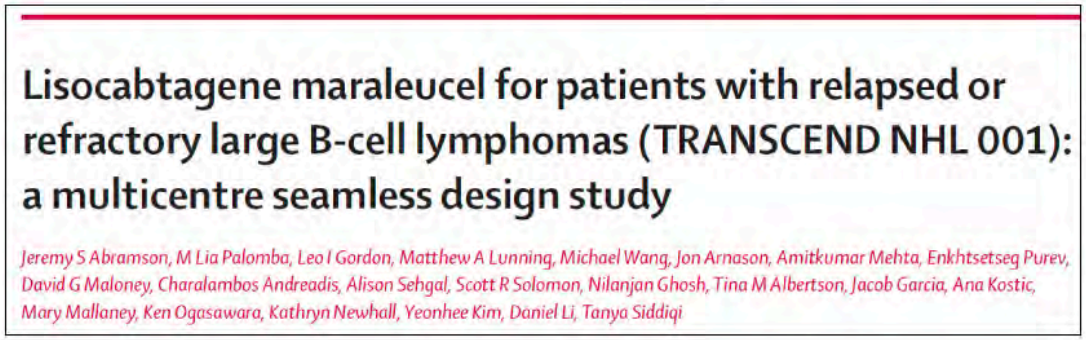


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tisagenlecleucel in Adult Relapsed or Refractory Diffuse Large B-Cell Lymphoma

Stephen J. Schuster, M.D., Michael R. Bishop, M.D., Constantine S. Tam, M.D., Edmund K. Waller, M.D., Ph.D., Peter Borchmann, M.D., Joseph P. McGuirk, D.O., Ulrich Jäger, M.D., Samantha Jaglowski, M.D., Charalambos Andreadis, M.D., Jason R. Westin, M.D., Isabelle Fleury, M.D., Veronika Bachanova, M.D., Ph.D., S. Ronan Foley, M.D., P. Joy Ho, M.B., B.S., D.Phil., Stephan Mielke, M.D., John M. Magenau, M.D., Harald Holte, M.D., Ph.D., Serafino Pantano, Ph.D., Lida B. Pacaud, M.D., Rakesh Awasthi, Ph.D., Jufen Chu, Ph.D., Özlem Anak, M.D., Gilles Salles, M.D., Ph.D., and Richard T. Maziarz, M.D., for the JULIET Investigators*



Lisocabtagene maraleucel for patients with relapsed or refractory large B-cell lymphomas (TRANSCEND NHL 001): a multicentre seamless design study

Jeremy S Abramson, M Lia Palomba, Leo I Gordon, Matthew A Lunning, Michael Wang, Jon Arnason, Amitkumar Mehta, Enkhtsetseg Purev, David G Maloney, Charalambos Andreadis, Alison Sehgal, Scott R Solomon, Nilanjan Ghosh, Tina M Albertson, Jacob Garcia, Ana Kostic, Mary Mallaney, Ken Ogasawara, Kathryn Newhall, Yeonhee Kim, Daniel Li, Tanya Siddiqi

Neelapu SS, et al. *N Engl J Med*. 2017;377:2531.
Schuster SJ, et al. *N Engl J Med*. 2019;380:45.
Abramson JS, et al. *Lancet*. 2019;396:839.

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Phase 2 trials leading to approval in 3L+ DLBCL: Patient and product details

	Axi-cel: ZUMA-1[13,37]	Tisa-cel: JULIET[16,17]	Liso-cel: TRANSCEND[11]
Disease type	▪ DLBCL: 76% ▪ Transformed follicular lymphoma: 16% ▪ Primary mediastinal B-cell lymphoma: 8%	▪ DLBCL: 79% ▪ Transformed follicular lymphoma: 19% ▪ Other: 2%	▪ DLBCL: 51% ▪ Transformed DLBCL: 29% ▪ High-grade B-cell lymphoma: 13% ▪ Primary mediastinal B-cell lymphoma: 6% ▪ Follicular lymphoma, grade 3: 1%
Median age, y (range)	58 (23-76)	56 (22-76)	63 (54-70)
Median No. of prior therapies	3	3	3
% patients with prior stem cell transplant	21%	49%	33%: autologous 3%: allogeneic
Lymphodepleting therapy	Fludarabine 30 mg/m^2 × 3 days and cyclophosphamide 500 mg/m^2 × 3 days	Fludarabine 125 mg/m^2 × 3 days and cyclophosphamide 250 mg/m^2 × 3 days (in 73% of patients) or bendamustine 90 mg/m^2 × 2 days (in 20% of patients)	Fludarabine 30 mg/m^2 × 3 days and cyclophosphamide 300 mg/m^2 × 3 days
CAR T-cell dose	2 × 10^6 cells/kg body weight	0.6-6.0 × 10^8 cells	Median dose 91 × 10^6 cells
Median time for CAR T-cell preparation	17 days (time from leukapheresis to delivery of axi-cel to treatment facility)	54 days (time from enrollment to infusion of tisa-cel)	37 days (time from leukapheresis to infusion of liso-cel)

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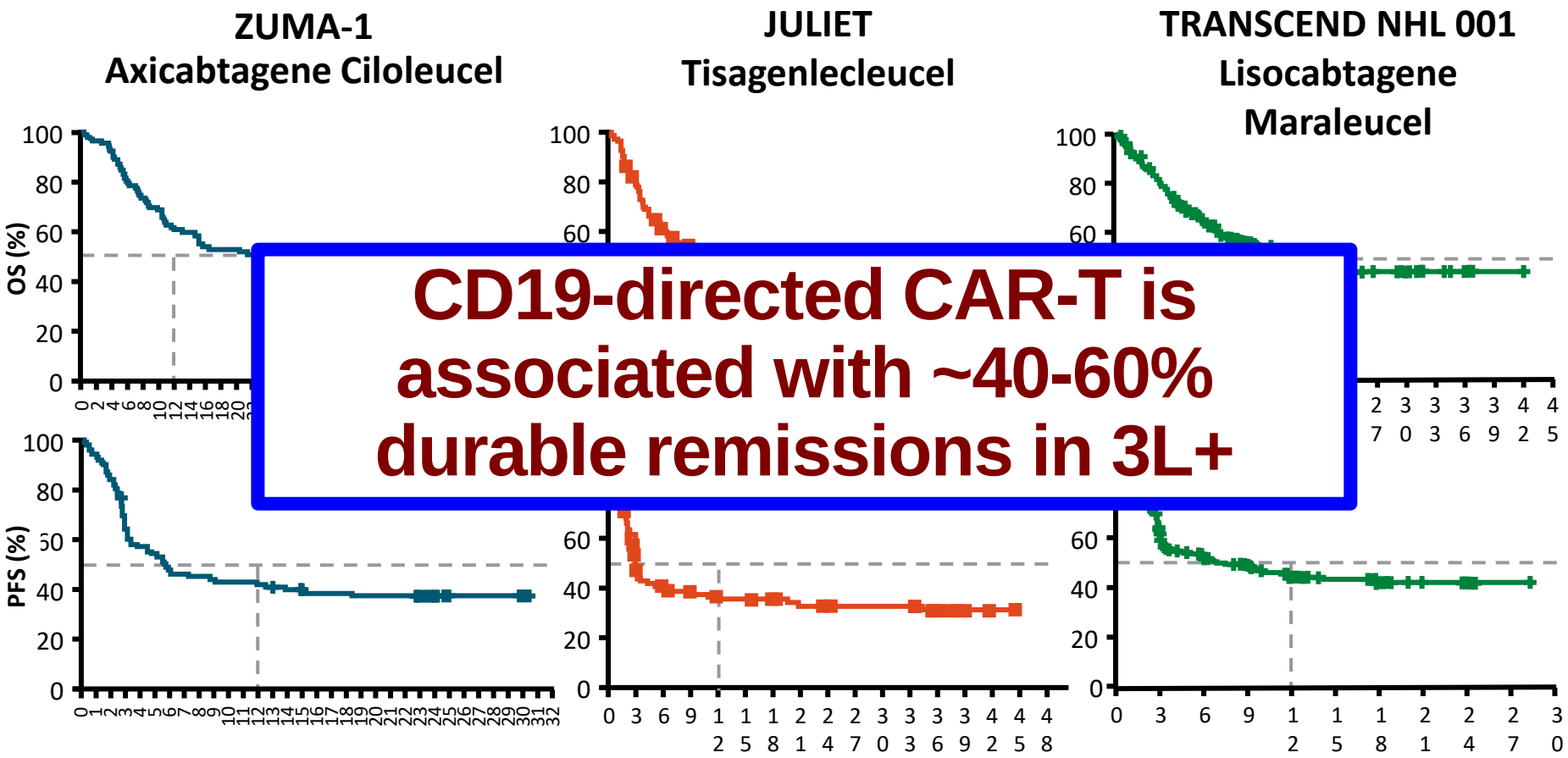
Kesireddy and Lunning Oncology 2022 Jun 10;36(6):366-375

Pivotal Anti-CD19 CAR T-Cell Therapy Trials: DLBCL



CD19-directed CAR-T is associated with ~40-60% durable remissions in 3L+

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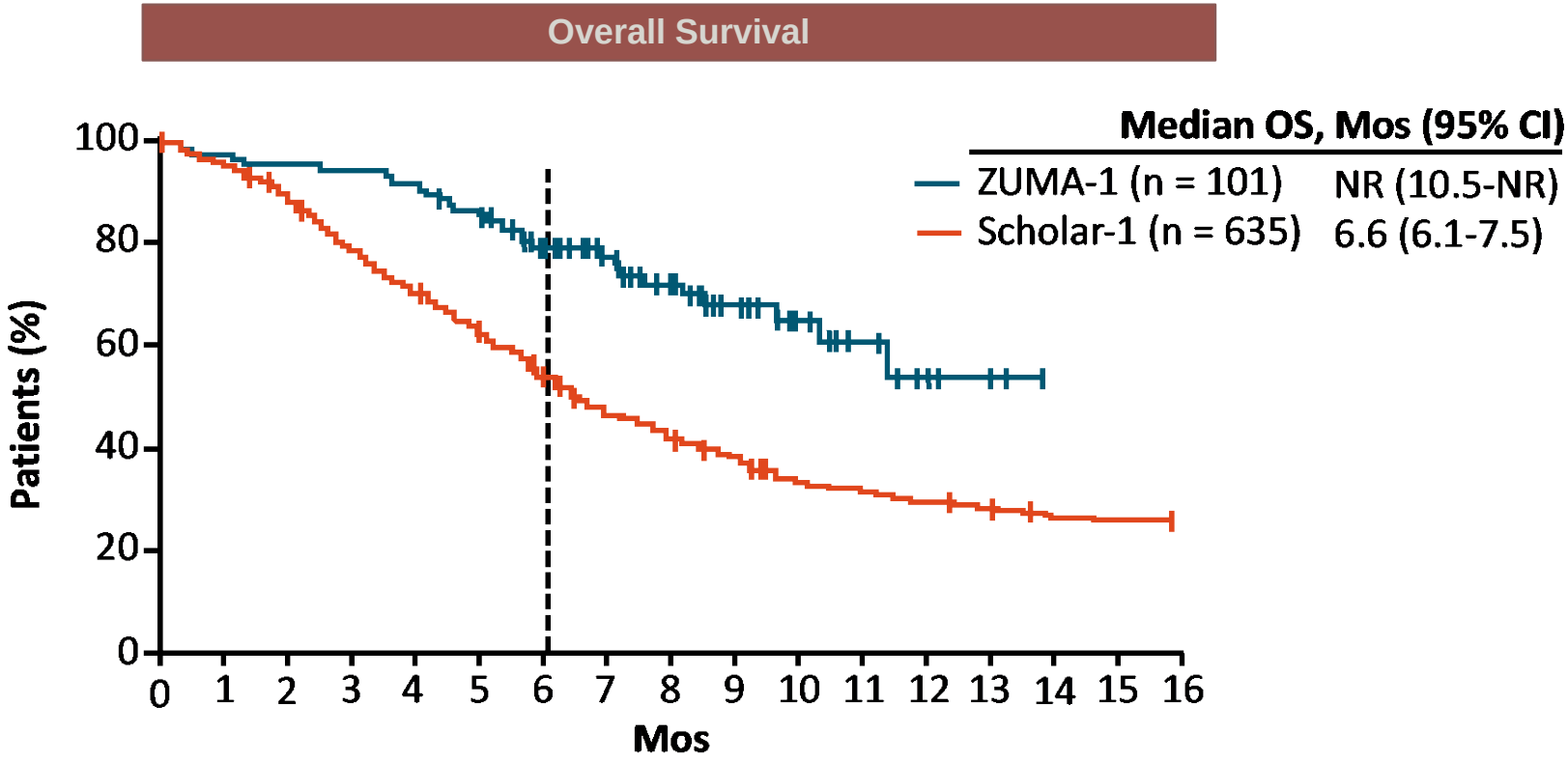
Slide courtesy of Michael Bishop

Locke. Lancet Oncol. 2019;20:31. Jacobson. ASH 2020. Abstr 1187. Jaeger. ASH 2020. Abstr 1194. Abramson. Lancet. 2020;396:839.

CD19 CAR T-cells for DLBCL Outpace Historical Controls



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- Neelapu, et al. *Blood.* 2018;132 (Supplement 1): 2967.

Toxicities of special interest: CRS and ICANS

	ZUMA-1	JULIET	TRANSCEND
CRS			
Grading Scale	Lee criteria	Penn grading scale	Lee criteria
Overall / ≥ Grade 3	93% / 13%	58% / 22%	42% / 2%
Median time to onset	2 days (range: 1-12)	3 days (range: 1-51)	5 days (range: 1-14)
Median duration	8 days	7 days (range: 2-30)	5 days (range: 1-17)
Neurologic Toxicities			
Grading Scale	CTCAE Criteria	CTCAE Criteria	CTCAE Criteria
Overall / ≥ Grade 3	64% / 28%	21% / 12%	30% / 10%
Median time to onset	5 days (range: 1-17)	6 days (range: 1-17)	9 days (range: 1-66)
Median duration	17 days	14 days	11 days (range: 1-86)

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Neelapu SS, et al. *N Engl J Med*. 2017;377:2531.
Schuster SJ, et al. *N Engl J Med*. 2019;380:45.
Abramson JS, et al. *Lancet*. 2019;396:839.

Choosing between the available products

	ZUMA-1	JULIET	TRANSCEND CORE
Product	Axi-cel	Tisa-cel	Liso-cel
# pheresed	111	165	344
# treated	101	111	269 (294*)
ORR (%)	82	52	73
CR (%)	54	40	53
6m ORR (%)	41	37	NR
mOS	25.8m	11.1m	21.1m
ITT ORR/CR	76/53	35/27	62/45
ITT OS	Median 17.5m, 4 year 41%	NR	NR
CRS (%)	93	58	42
Gr 3+ CRS (%)	13	NA	2
ICANS (%)	64	21	30
Gr 3+ ICANS (%)	28	12	10
Manufacturing Time (d)	17	22	24 (?)

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Neelapu SS, et al. *N Engl J Med*. 2017;377:2531.
Schuster SJ, et al. *N Engl J Med*. 2019;380:45.
Abramson JS, et al. *Lancet*. 2019;396:839.

Slide courtesy of Caron Jacobson

Patient Characteristics: Real-world vs. CAR-T cell trials

	Post-approval				
Characteristics	Jacobson et al.	Nastoupil et al.	Pasquini et al.	Pivotal trial ZUMA-1	Pivotal trial JULIET
Cellular therapy	Axi-cel	Axi-cel	Tisa-cel	Axi-cel	Tisa-cel
Number leukapheresed	104	295	NR	119	165
Number infused	91	274	63	108	111
Median age (range)	64 (21–80)	60 (21–83)	65 (18–81)	59 (23–76)	56 (22–76)
ECOG PS 0–1	90%	81%	82%	100%	100%
High risk IPI (≥3)	46%	55%	NR	44%	NR
Bridging therapy	40%	NR	NR	0%	92%
Double/triple hit	24%	23%	30%	11%[a]	27%
Prior autologous SCT	27%	33%	21%	23%	49%
Ineligible for pivotal trial	60%	43%	NR	NA	NA
Outcomes					
Median follow-up	5.6 months	3.9 months	4.5 months	27.1 months	14 months
Best ORR	71%	81%	66%	83%	52%
Best CR rate	44%	57%	42%	58%	40%
≥ Grade 3 CRS[b]	16%	7%	<5%	11%	22%
≥ Grade 3 neurotoxicity[c]	39%	33%	4%	32%	12%
Tocilizumab given	67%	63%	NR	43%	14%
Steroids given	64%	55%	NR	26%	NR

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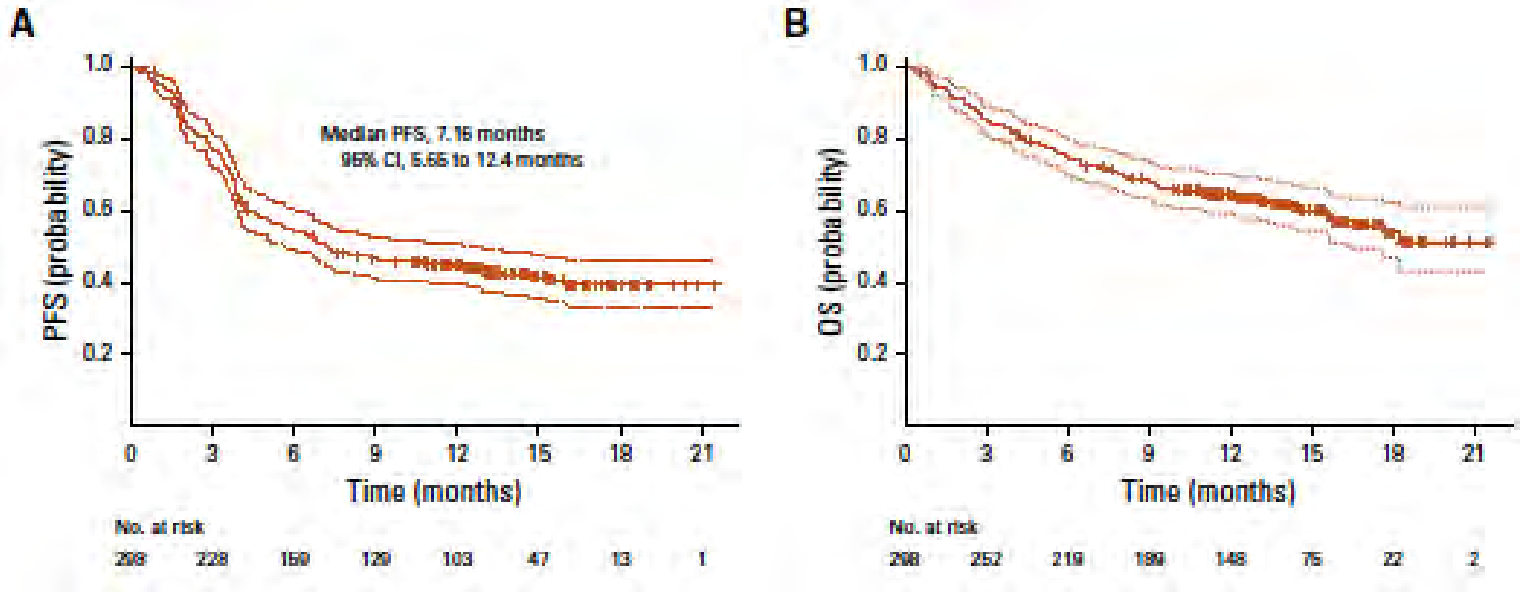
Cahill and Riedell Leuk Lymphoma 2020 Apr;61(4):799-807

Does CAR-T work in the “real world”? (Axi-cel analysis; n=298)



Yes…43% of patients would not have met criteria for the clinical trial poor PS, thrombocytopenia, recent VTE, CNS disease, renal insufficiency, cardiac dysfunction, other

…and no: median age 60y, and “real-world” remains limited to specialized centers

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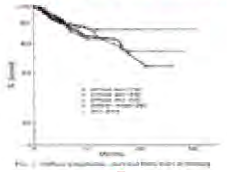
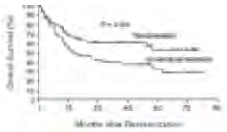
Nastoupil J Clin Oncol 2020 Sep 20;38(27):3119-3128

Major milestones in DLBCL Treatment

CHOP leads to cure in 54% of pts



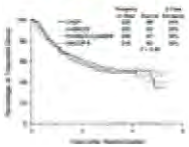
1976



HDC/ABMT in 2L chemosensitive disease has 53% long-term survival

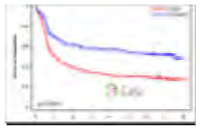
1993 1995

CHOP as effective and less toxic than intensive regimens

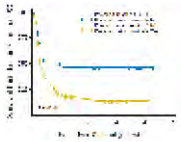


2002

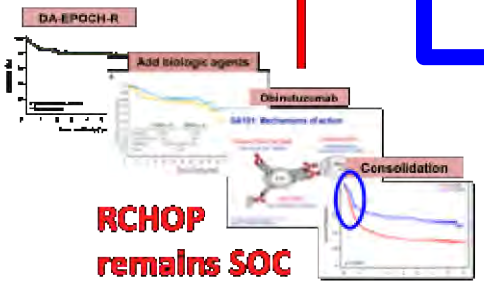
Rituximab plus CHOP improves OS



HDC/ASCT benefits fewer patients (~15-40% with long-term survival)



2010



RCHOP remains SOC

2017

November 2017: axi-cel is approved for 3L+ DLBCL followed soon by tisa-cel and liso-cel

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Treatment Algorithm for DLBCL post-2017

R-CHOP

1. *Can we cure more patients in 1L?*
2. What are options for CAR-T failure?
3. What can we offer non-CAR-T eligible patients (and who are they??)
4. **Can CAR-T be moved earlier in the algorithm?**

che

Cure **Relapse**

Pola-BR, selinexor, tafa-len, lonca-T, clinical trial

✓

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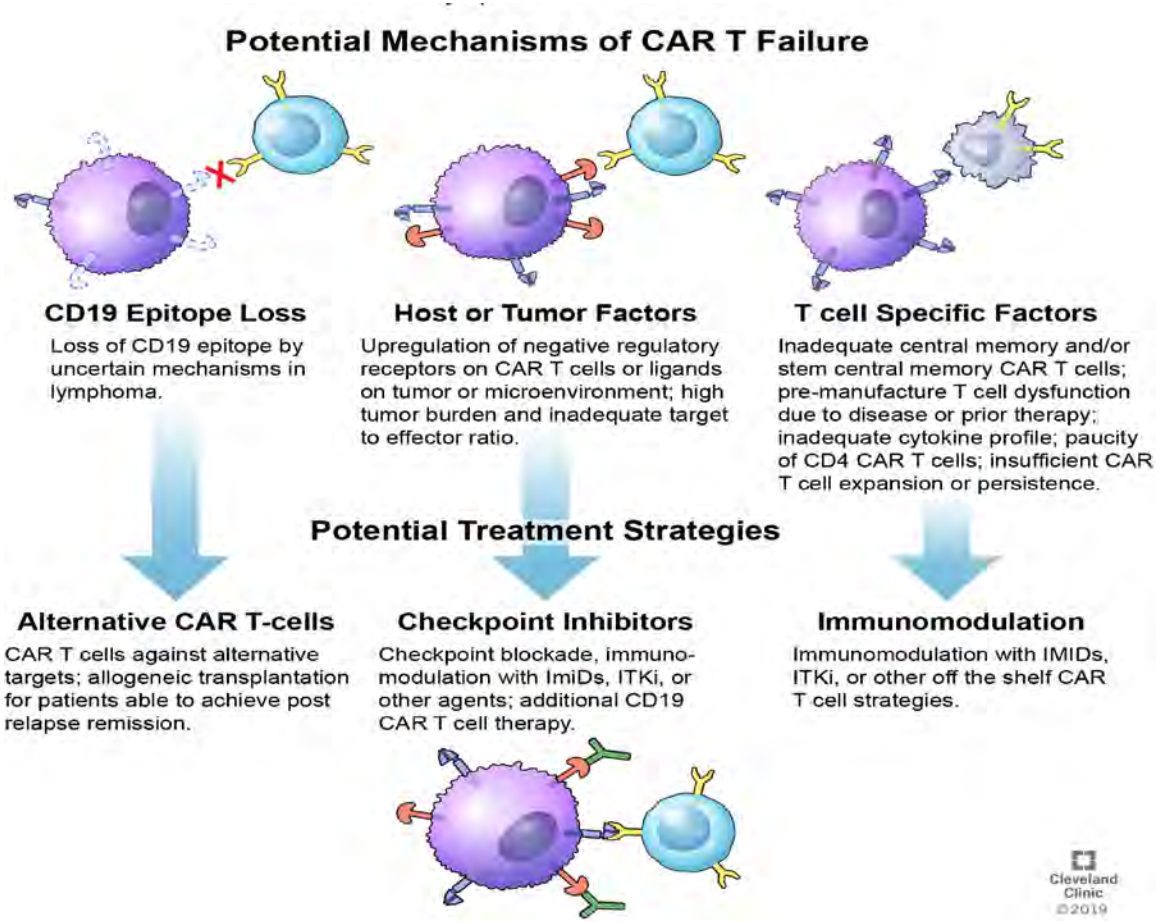
Post-CAR-T failure: potential mechanisms and mitigation strategies

Loss of CD19
Host or tumor factors
T-cell specific factors



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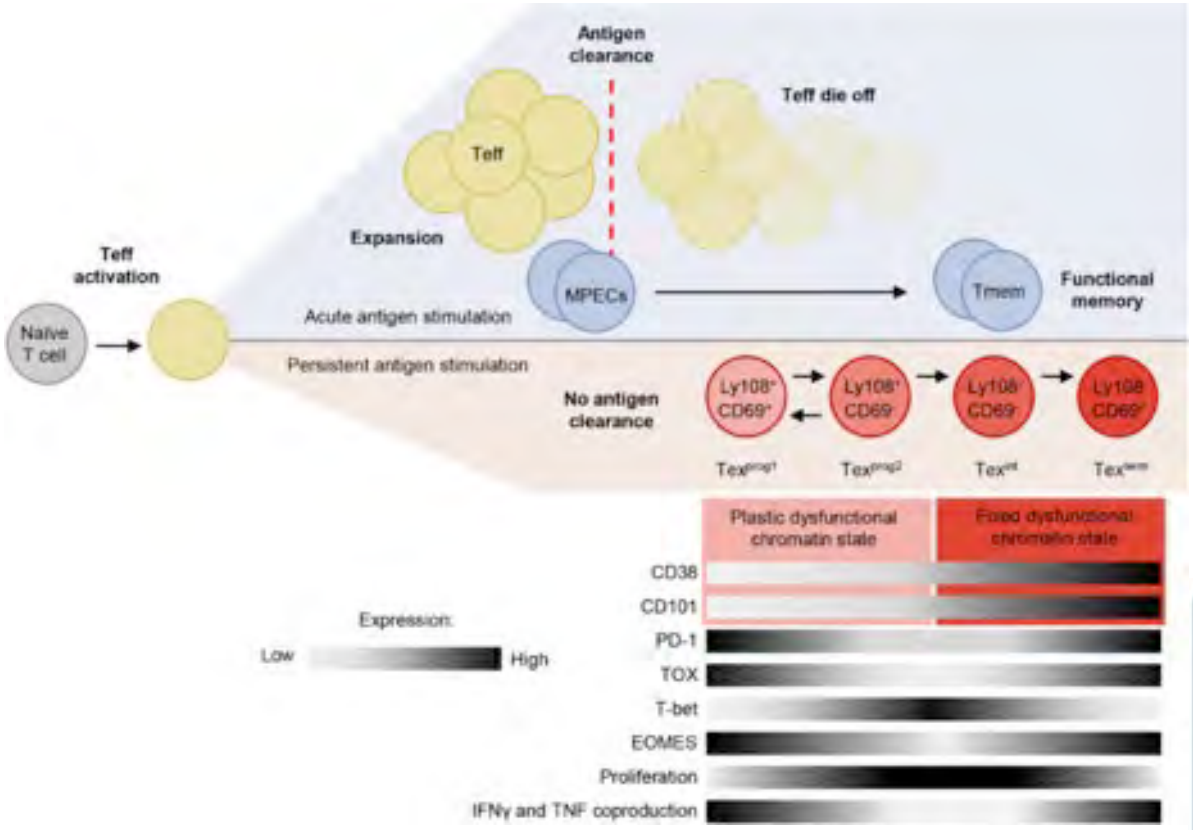
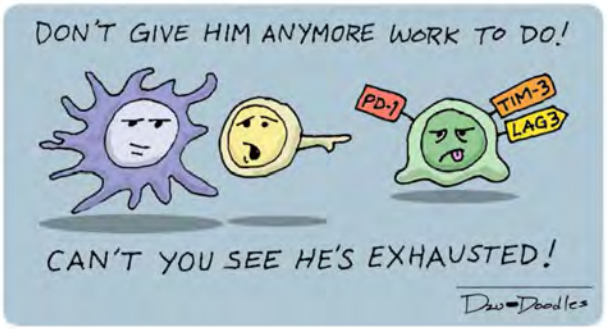
Biology of Blood and Marrow Transplantation 2019 25e344-e351DOI: (10.1016/j.bbmt.2019.06.036)

Can (and should) CAR-T be moved earlier?



- Drivers of T-cell fitness
  - Age, chronic infection, disease burden, prior treatment
- Markers of T-cell exhaustion:
  - PD-1, TIM-3, LAG-3, TIGIT, and CTLA-4



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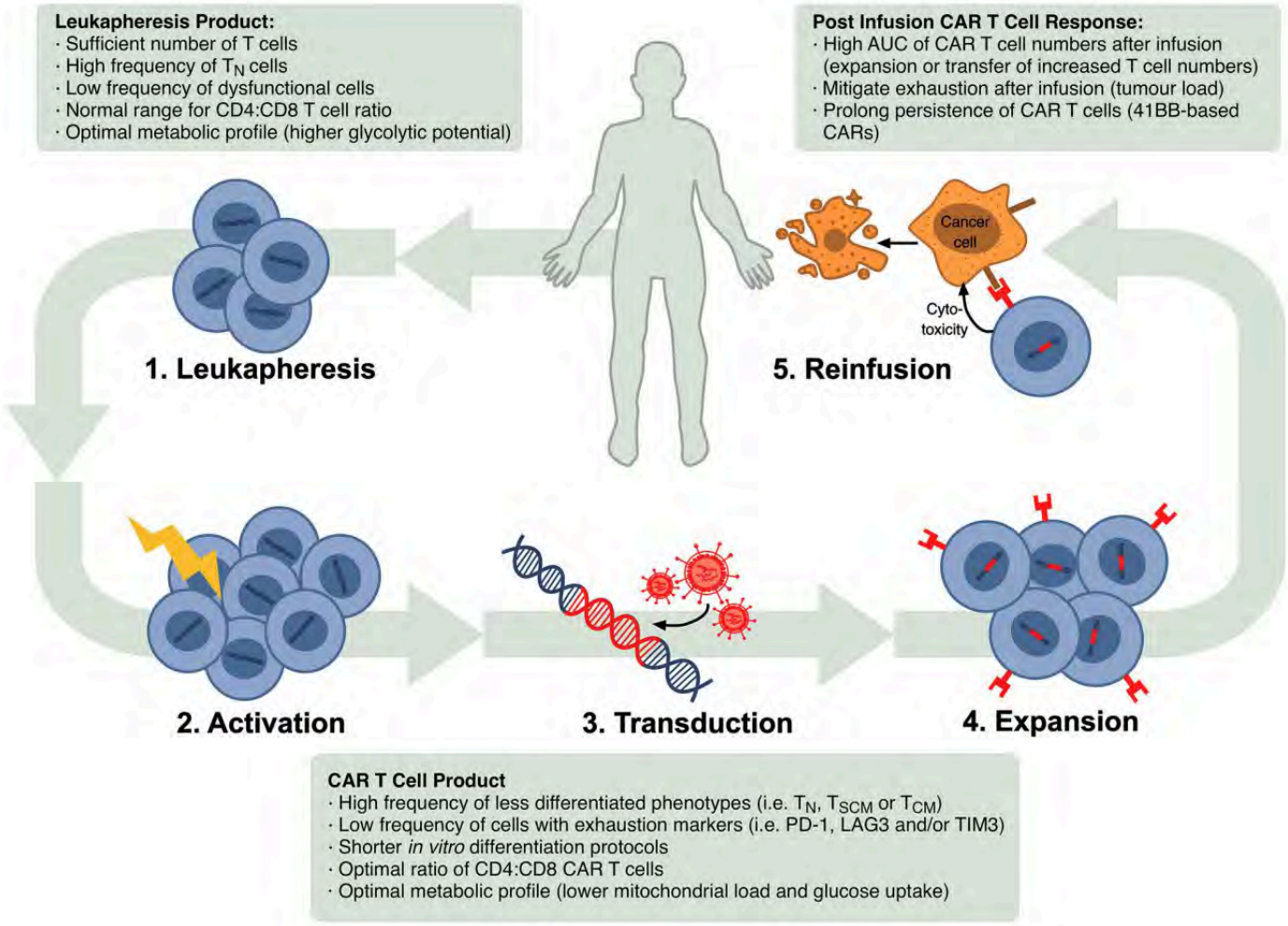
Mehta Front Immunol 2021 Nov 25;12:780442
Gumber and Wang EBioMedicine. 2022 Mar;77:103941

Impact of cancer and cancer treatment on T-cell fitness



Inflammatory state in cancer decreases T-cell fitness

Prior treatment and **lymphopenia** are associated with premature T-cell aging

Mehta Front Immunol 2021 Nov 25;12:780442

~~Ongoing~~ Phase III Clinical Trials in B-Cell Lymphomas: Will CD19 CAR T-Cell Therapy Replace Auto-transplant?

ASH 2021

ASH Presentation

ZUMA-7
Axicabtagene ciloleucel

TRANSFORM
Lisocabtagene maraleucel

BELINDA
Tisagenlecleucel

High-risk DLBCL/
B-cell lymphomas:
- Refractory to first-line tx
- Relapsed after first-line tx

CAR T-cell therapy → Locke, Abstr 2, Sunday, 12/12, 2:00 PM

Salvage therapy/ auto-transplant → Kamdar, Abstr 91, Saturday, 12/11, 9:30 AM; Bishop, Abstr LBA-6, Tuesday, 12/14, 9:00 AM

NCT03391466. NCT03570892. NCT03575351.

Slide credit: clinicaloptions.com

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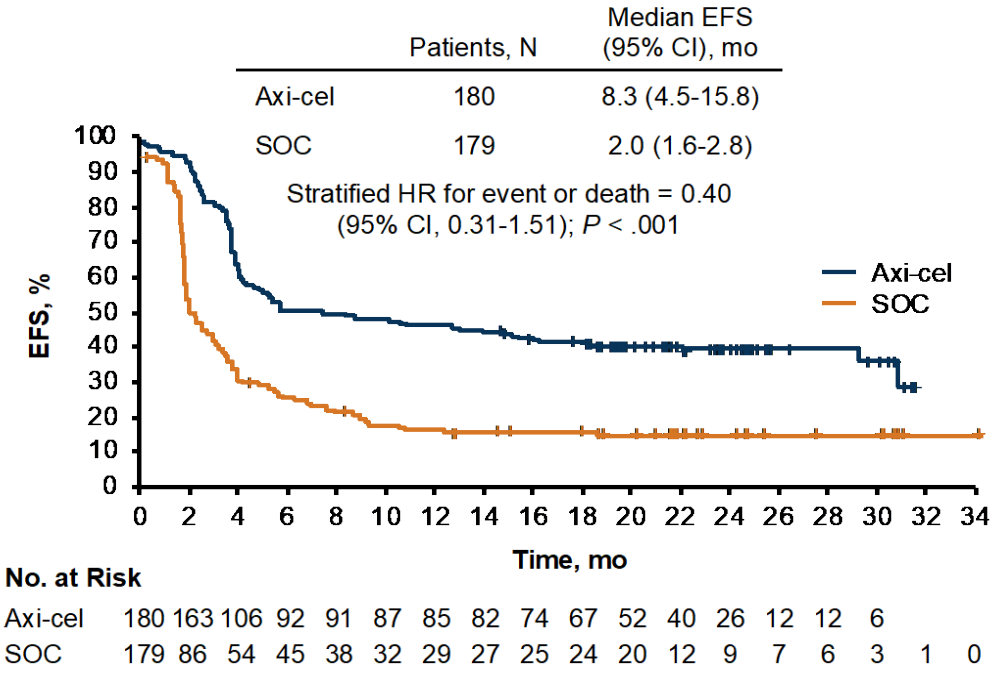
Slide courtesy of Michael Bishop

Phase 3 ZUMA-7: Axi-Cel Versus SOC as 2L Treatment for R/R LBCL[1]

At a medium follow-up of 24.9 months:

- The primary endpoint of EFS was met with axi-cel vs SOC in patients with R/R LBCL
- 24-mo EFS rates were 41% vs 16%, respectively
- ORR and CR rates were higher with axi-cel vs SOC (ORR: 83% vs 50%; *P* < .0001; CR: 65% vs 32%)
- Median OS favored axi-cel vs SOC, although it did not meet statistical significance



April 2022: Axi-cel was FDA approved for patients with R/R LBCL refractory to 1L chemoimmunotherapy or that relapses within 12 months of 1L chemoimmunotherapy

1. Locke FL et al. *N Engl J Med*. 2022;386:640-654.

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Slide courtesy of Michael Bishop

Phase 3 TRANSFORM: liso-cel vs. SOC in 2L DLBCL (med f/u 6m)

Efficacy, IRC assessed[a]	SOC Arm A (ITT; n = 92)	Liso-Cel Arm B (ITT; n = 92)
EFS, median [95% CI], mo	2.3 [2.2-4.3]	10.1 (6.1-NR)
	HR = 0.349 (0.229-0.530); *P* < .0001	
EFS rate at 6 mo, %	33.4	63.3
EFS rate at 12 mo, %	23.7	44.5
ORR, n (%) [95% CI]	44 (48) [37.3-58.5]	79 (86) [77.0-92.3]
CR rate	36 (39) [29.1-49.9]	61 (66) [55.7-75.8]
PFS, median [95% CI], mo	5.7 [3.9-9.4]	14.8 [6.6-NR]
	HR = 0.406 (0.250-0.659); *P* = .0001	
OS, median [95% CI], mo	16.4 [11-NR]	NR [15.8-NR]
	HR = 0.509 (0.258-1.004); *P* = .0257	

[a] Lugano 2014 criteria.

1. Kamdar M, et al. ASH 2021. Abstract 91.

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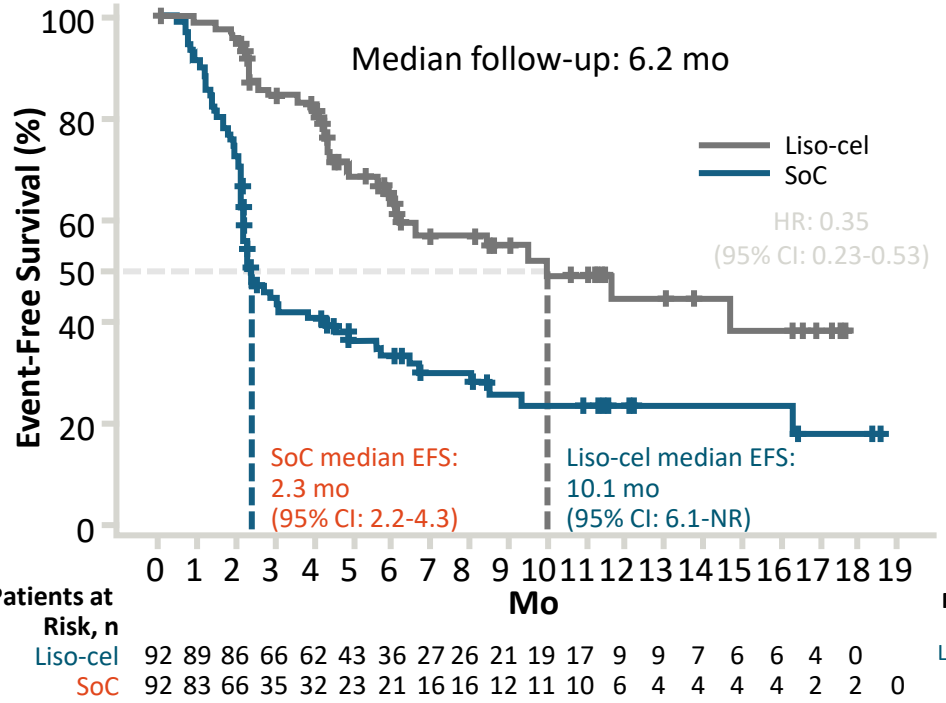
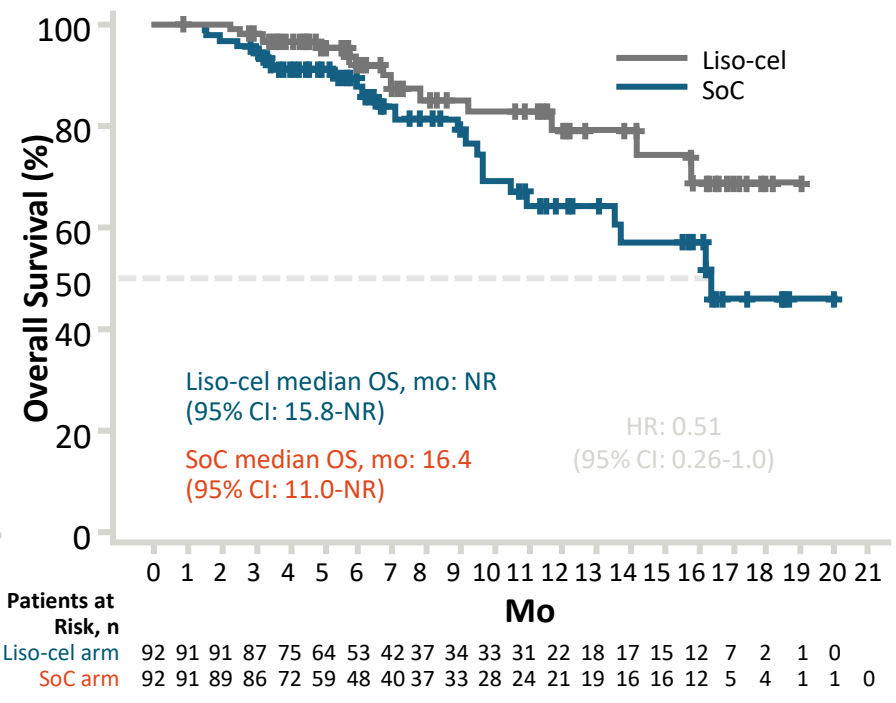
Slide courtesy of Michael Bishop

TRANSFORM Liso-cel vs SoC: EFS and OS





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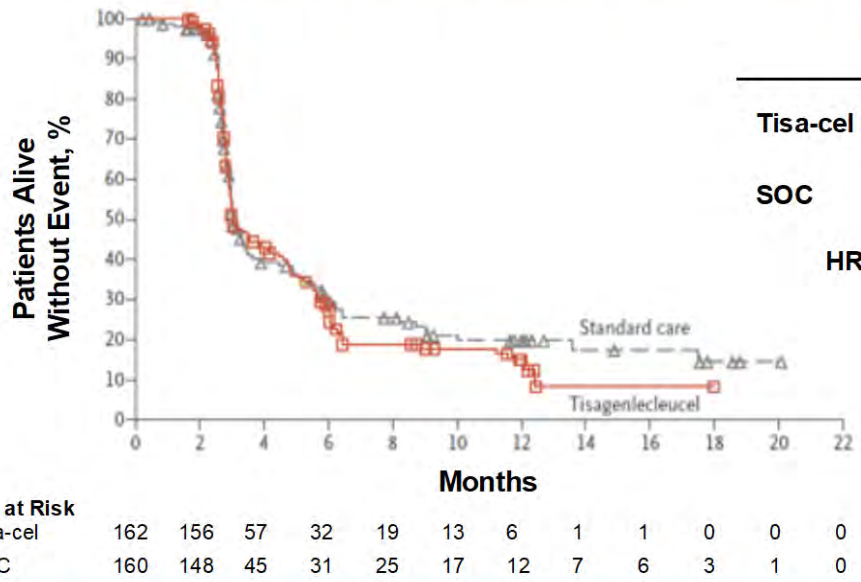
Improved EFS

No new safety concerns

Kamdar. ASH 2021. Abstr 91.

Phase 3 BELINDA: Tisa-Cel Versus SOC as 2L Treatment for R/R Aggressive NHL[1]



	Patients, N	Events, N	Median EFS (95% CI), mo
Tisa-cel	162	117	3.0 (2.9-4.2)
SOC	160	104	3.0 (3.0-3.5)

HR for event or death (tisa-cel vs SOC) = 1.07 (95% CI, 0.82-1.40); *P* = .61

EFS was not significantly different between tisa-cel and SOC as 2L treatment in patients with R/R aggressive NHL; additional studies are needed to assess which patients may obtain the most benefit from each approach

1. Bishop MR et al. *N Engl J Med*. 2022;386:629-639.

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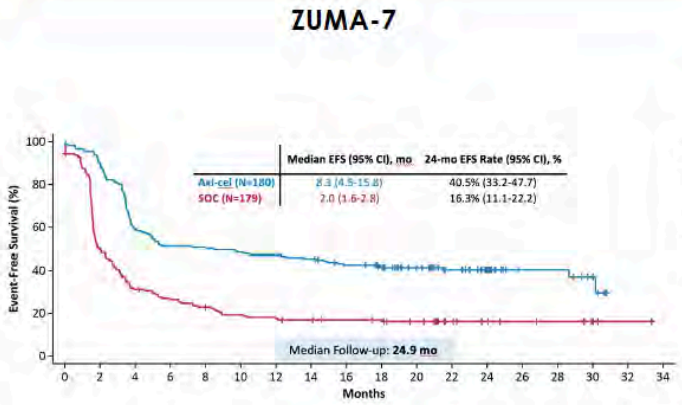
Slide courtesy of Michael Bishop

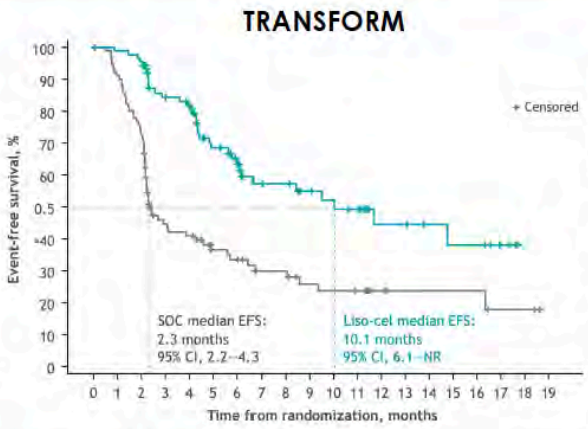
So Why Did BELINDA Not Succeed?

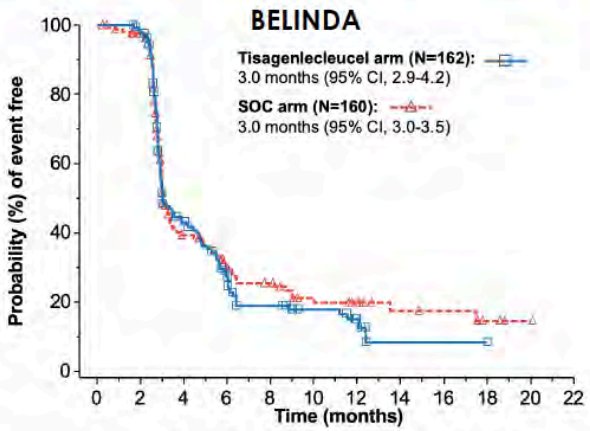
- Flawed Study Design:
  - EFS definition
  - Permission of too much or any bridging therapy
  - Inadequate lymphodepleting chemotherapy
- More difficult patient population
  - A high proportion of patients had PD at week 6
  - Low response rate in SOC arm
- Delay in infusion (med 53d to infusion)
- Inadequate expansion relative to lymphoma proliferative rate and burden
- Construct (4-1BB)/Product

Slide courtesy of Michael Bishop

CAR-T cell therapy in 2L DLBCL







	Trial	Median EFS, m		CR rate		2-yr OS		Median f/u, m
		CAR-T	SOC	CAR-T	SOC	CAR-T	SOC	
-	BELINDA	3	3	28%	28%	Not reached		10
+	ZUMA-7	8.3	2	65%	32%	61%	52%	24.9
+	TRANSFORM	10.1	2.3	66%	39%	Not reached		6.2

Locke FL, et al. *N Engl J Med*. 2021; Dec 11.
Kamdar M, et al. *Blood*. 2021;138(suppl 1):91.
Bishop MR, et al. *N Engl J Med*. 2021;Dec 14.

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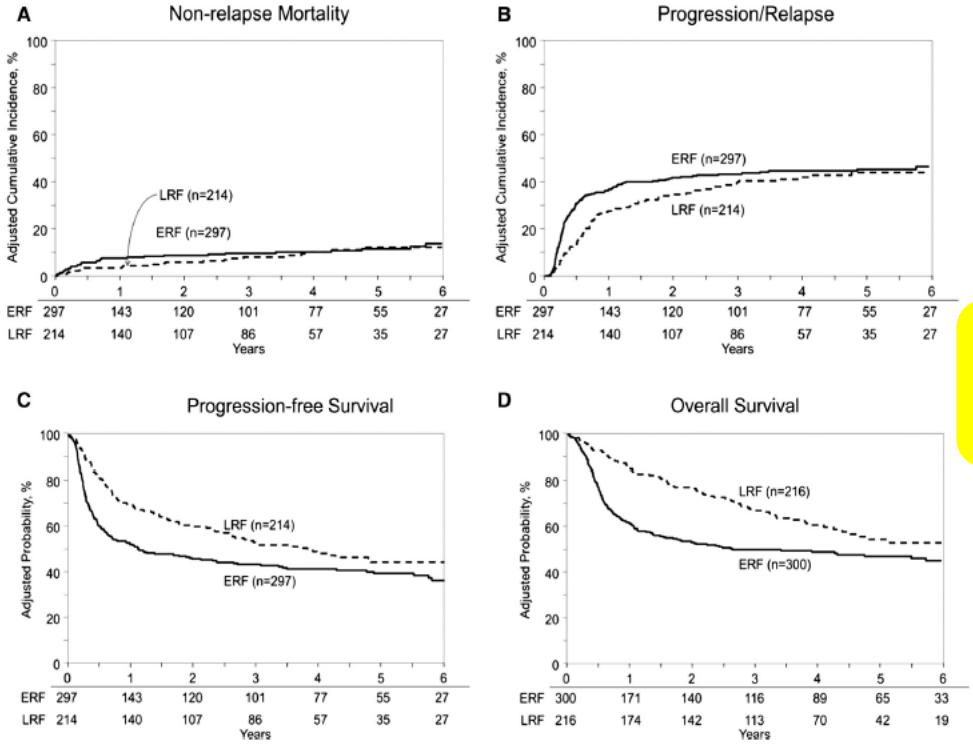
Slide courtesy of Peter Riedell

Autologous stem cell transplant still has a role in the relapsed setting

CIBMTR Analysis: Early relapse versus late relapse following rituximab-containing initial therapy

- Med age 58y (ERF) and 62y (LRF)
- No CNS disease
- KPS >90% in 2/3 of patients
- 15-20% with marrow involvement



…for selected pts

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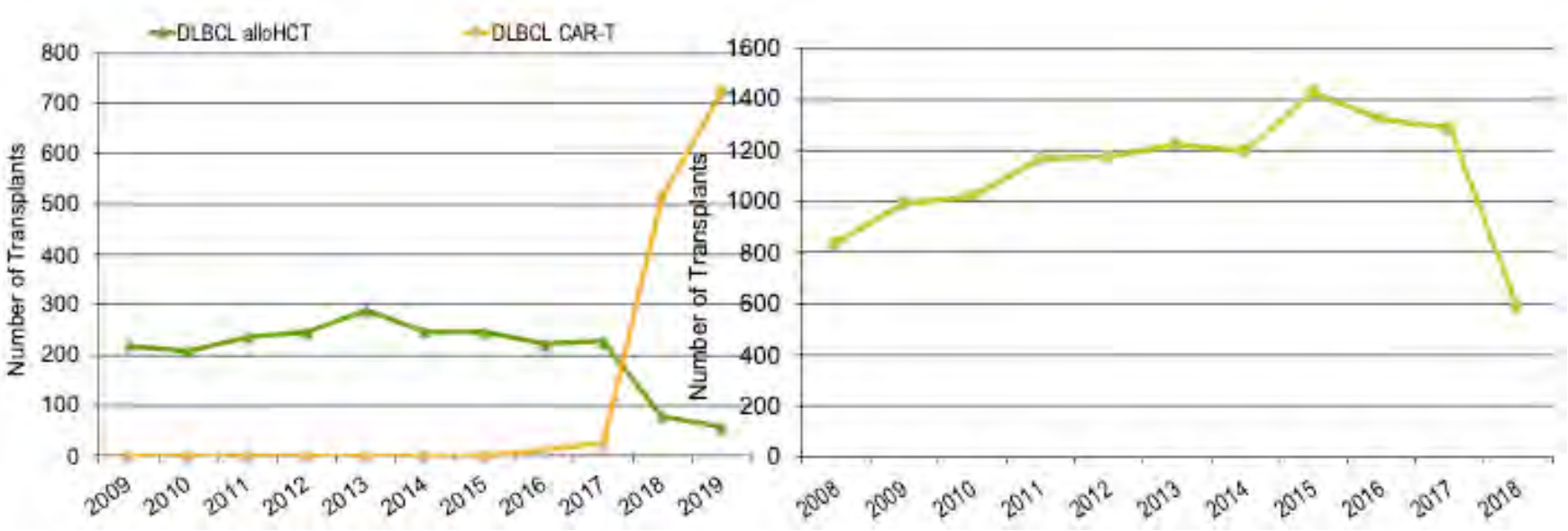
Hamadani Biol Blood Marrow Transplant 2014 Nov;20(11):1729-36

Speaking with their feet—transplant trends in the US (CIBMTR data)

Allo vs. CAR-T in DLBCL

AutoHCT for DLBCL



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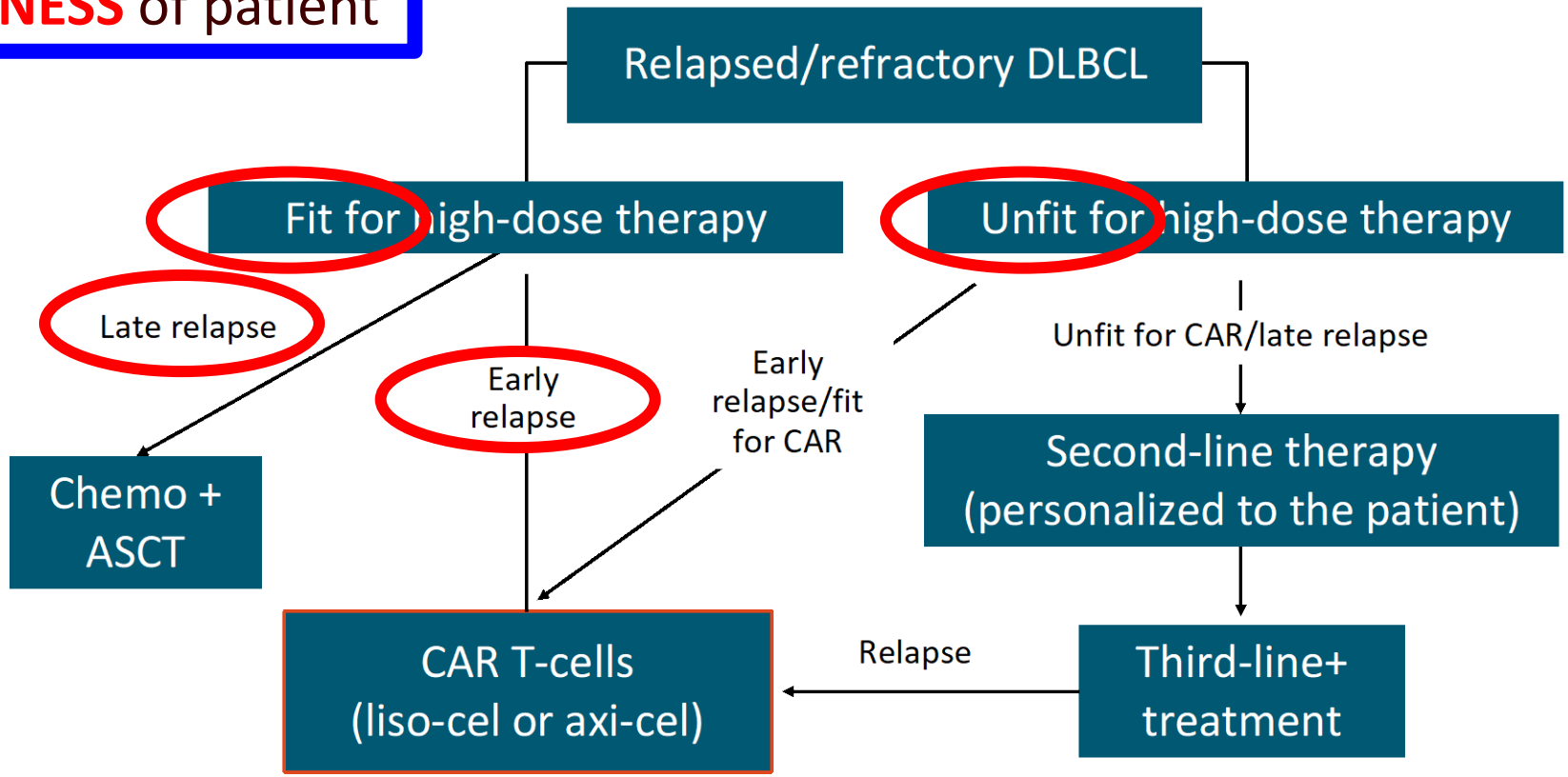
Data courtesy of Mehdi Hamadani

A new algorithm for 2022 and beyond

TIMING of relapse
FITNESS of patient



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IF CAR-T IS NOT AN OPTION

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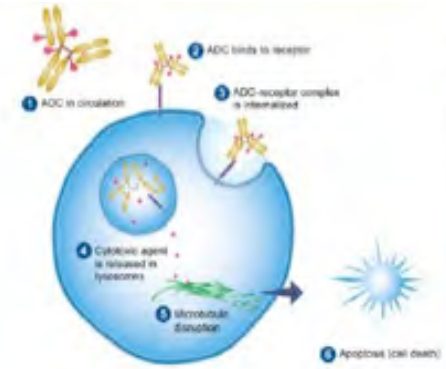
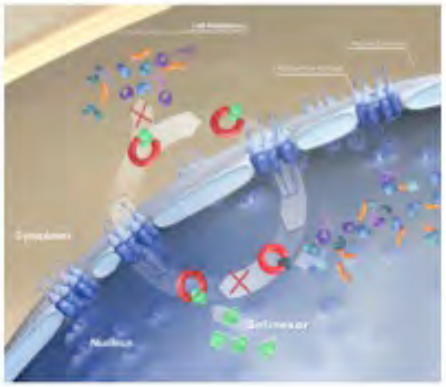
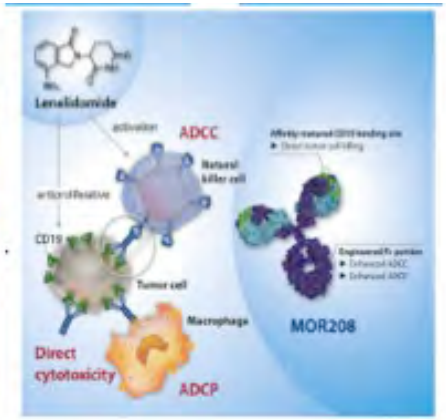
Recently approved agents/regimens



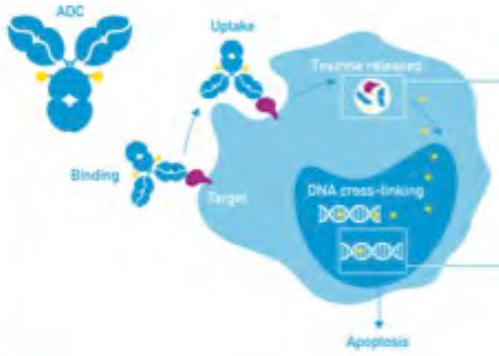
Polatuzumab vedotin (antiCD79 ADC)



Selinexor (XPO1 inhibitor)



Tafasitamab (enhanced anti-CD19 moAb)



Loncastuximab teserine (anti-CD19 ADC with PBD dimer payload)

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ADC: antibody drug conjugate

Recently approved agents/regimens for RR DLBCL

Agent/ Regimen	No. pts	Key pt features	ORR/CR	PFS/OS/DR
Pola-BR	40	Med age 67y Med 2 prior Rx 75% ref	63/50	9.5m/12.4m/12.6m (v. BR with med DR 7.7m)
Selinexor	127	Med age 67y 45% ≥ 70y Med 2 prior Rx 72% ref	28/12	2.6m/9.1m/9.3m
Tafa-len	81	Med age 72y 50% 2L 44% ref	48/34	12.1m/NR/DR 22m (NR for CR pts)
Lonca-T	145	Med age 66y 55% ≥ 54y Med 3 prior Rx 20% ref	48/25	4.9m/9.9m/10.3m

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Caimi Lancet Oncol 2021 Jun;22(6):790-800 Sehn J Clin Oncol 2020 Jan 10;38(2):155-165; Kalakonda Lancet Haematol. 2020 Jul;7(7):e511-e522; Salles Lancet Oncol 2020 Jul;21(7):978-988

Ease of administration

Agent/ Regimen	Administration route	Treatment duration	Selected Toxicities
Pola-BR	Pola over 90 min (can shorten to 30min) on D1 of C1-6 BR	6 months	Peripheral neuropathy, cytopenias
Selinexor	Take on D1 and D3 weekly (*60mg)	Until progression	Asthenia, nausea
Tafa-len	Tafa over 2h on C1 D1, 4, 8, 15, 22 Tafa over 2h on C2-3 D1, 8, 15, 22 Tafa over 2h on C4-12 D1 and D15	12 cycles	Cytopenias, rash
Lonca-T	30 min infusion q3 weeks	Up to 1 year	Cough, peripheral edema, rash

All are generally well-tolerated, have outpatient administration

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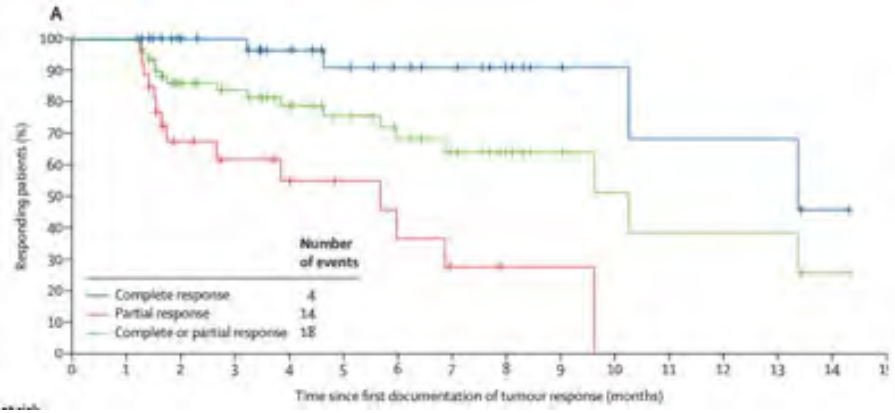
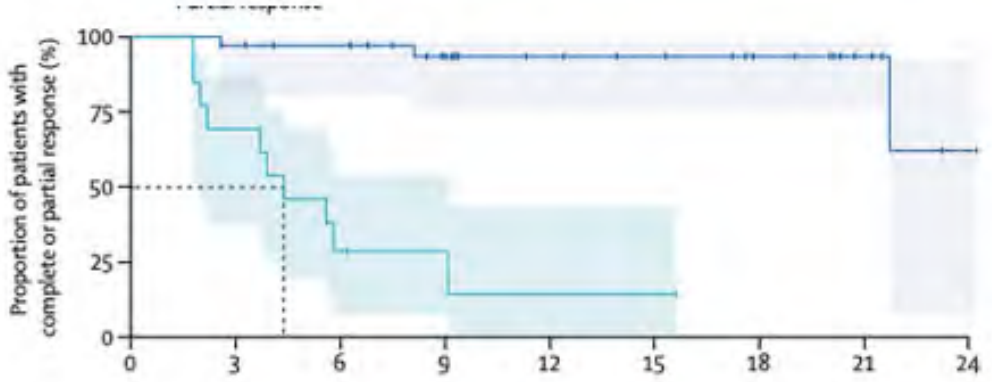
Caimi Lancet Oncol 2021 Jun;22(6):790-800 Sehn J Clin Oncol 2020 Jan 10;38(2):155-165; Kalakonda Lancet Haematol. 2020 Jul;7(7):e511-e522; Salles Lancet Oncol 2020 Jul;21(7):978-988

Some complete responders and less heavily pretreated pts can have long duration of response



Lonca-T



Tafa-len

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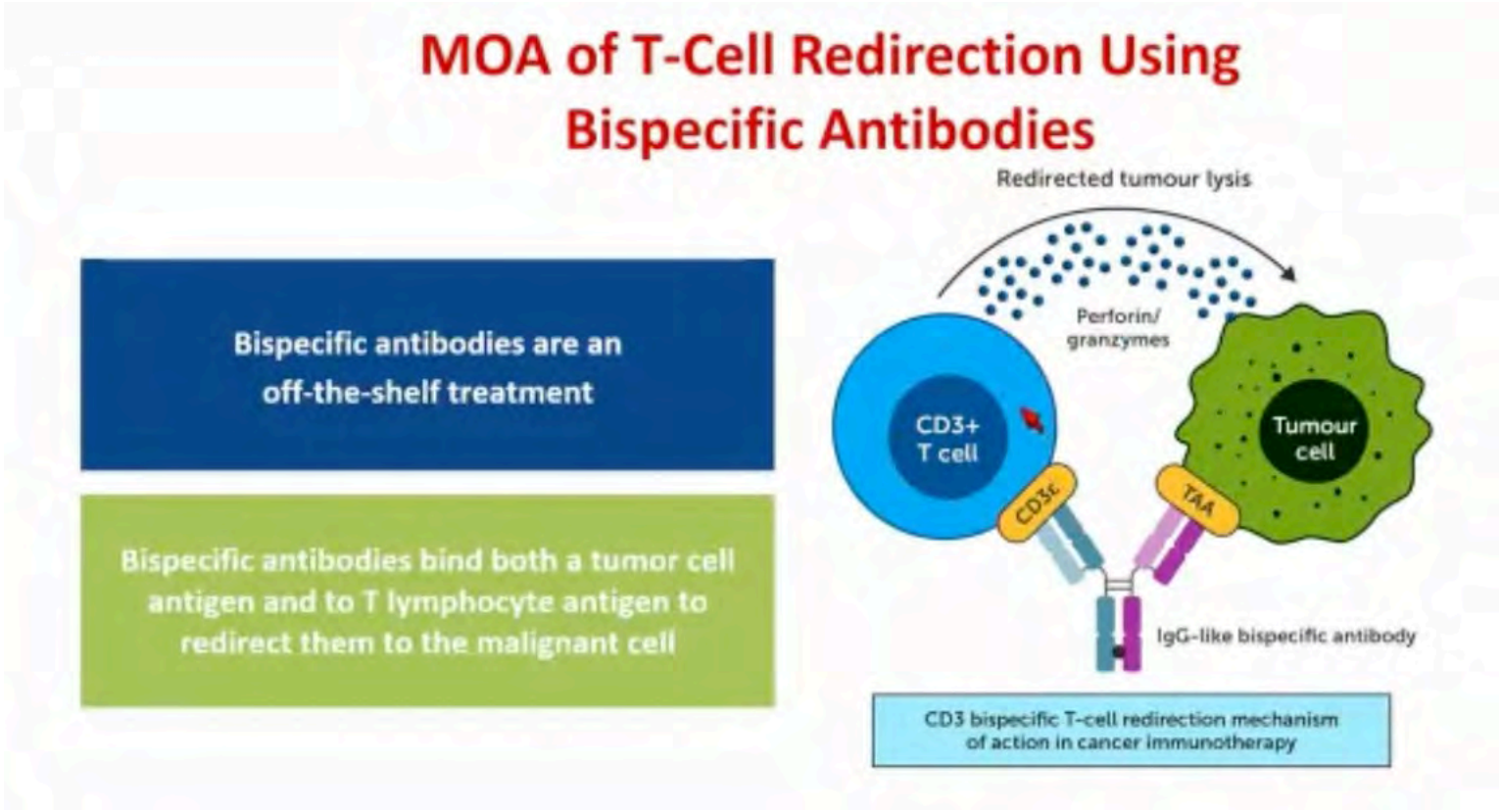
Caimi Lancet Oncol 2021 Jun;22(6):790-800
Salles Lancet Oncol 2020 Jul;21(7):978-988

Tafa-len and Lonca-T: Can anti-CD19 directed treatment be given in the era of CAR-T?...probably

- Lonca-T: 15 pts had subsequent CD19-directed CAR-T with ORR 47% and 40% with CR
- Tafa-len: case reports of durable remission

Bispecific antibodies: an alternative T-cell engaging therapy



- Engineered antibodies to prolong half-life
- Target CD3 (on T-cells) and CD20 (on B-cells)
- Induces T-cell mediated cytotoxic activity against CD20 expressing B-cells

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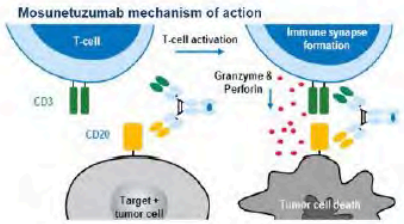
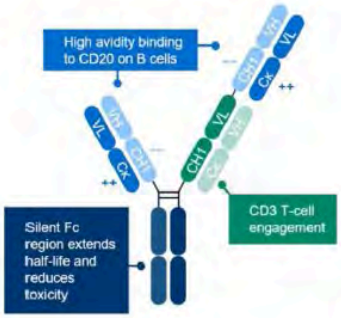
CD20 x CD3 bispecific antibodies in development

Mosunetuzumab

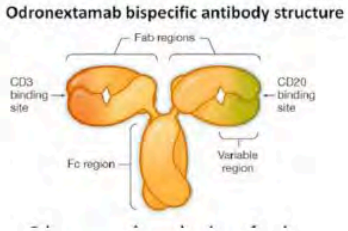


Glofitamab



Epcoritamab

Odronextamab



Plamotamab

- "Off the shelf" therapy
- Route of administration: IV or SC
- Being explored in various subtypes of B-NHL

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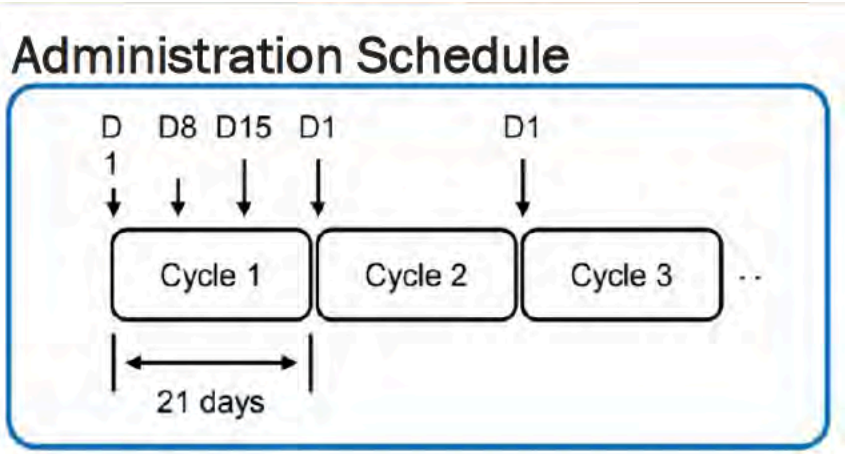
Olszewski ASH 2020 #401
Matasar ASH 2020 #2096
Philips ASH 2020 #1184

REGN1979 Bannerji ASH 2020 #400;
Glofitamab Hutchings ASH 2020 #403
Epcoritamab Hutchings ASH 2020 #402

Mosunetuzumab administration



- IV **outpatient** administration
- Cycle 1 step-up dosing followed by fixed dosing
- Key inclusion:
  - RR B-NHL after > 1 prior regimen
  - ECOG 0-1
  - No viable treatment options

Characteristic	Aggressive NHL[a] (n = 129)
Age, years	
Median	63.0
Range	19-91
Prior systemic therapies, No.	
Median	3
Range	1-14
Prior CAR-T therapy, No. (%)	15 (11.6)
Prior autologous stem-cell transplant, No. (%)	44 (34.1)
Refractory to last therapy, No. (%)[d]	106 (82.2)
Refractory to prior anti-CD20 therapy, No. (%)[d]	100 (77.5)

- Initial treatment = 8 cycles; if CR, stop (if PR/SD, continue to up to 17 cycles)

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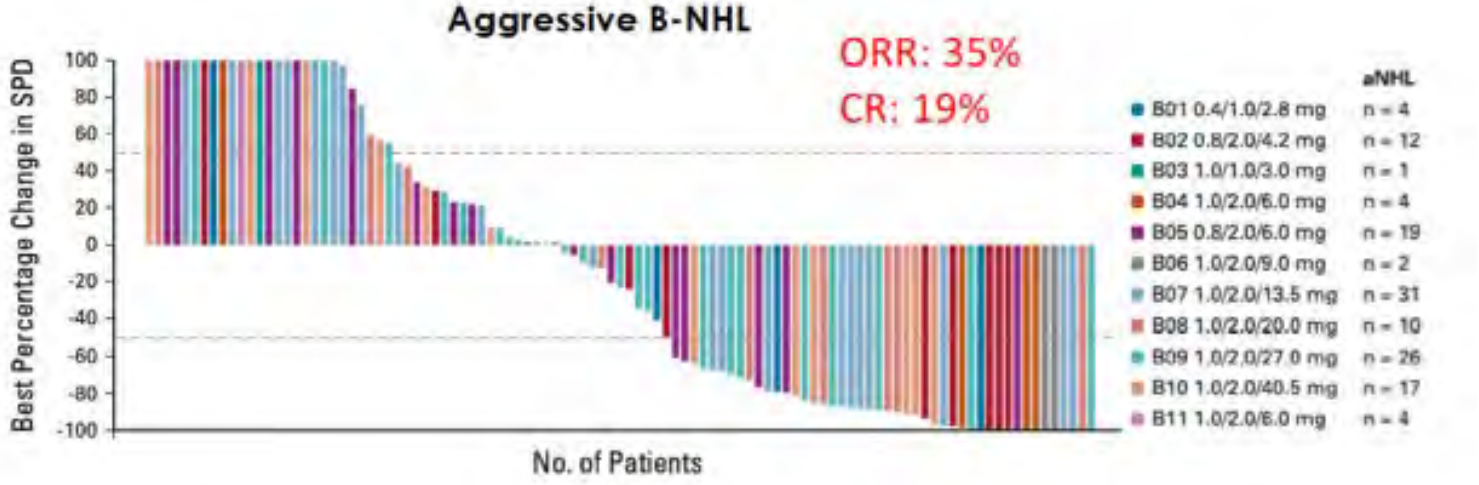
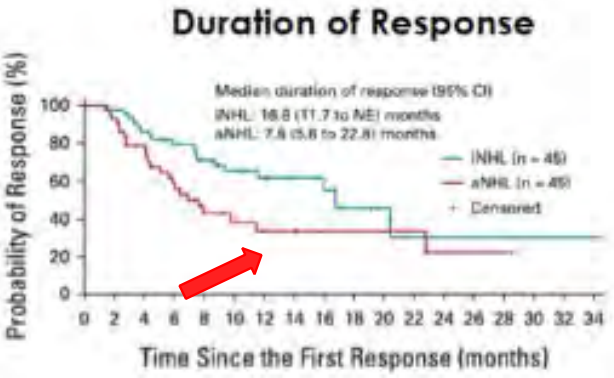
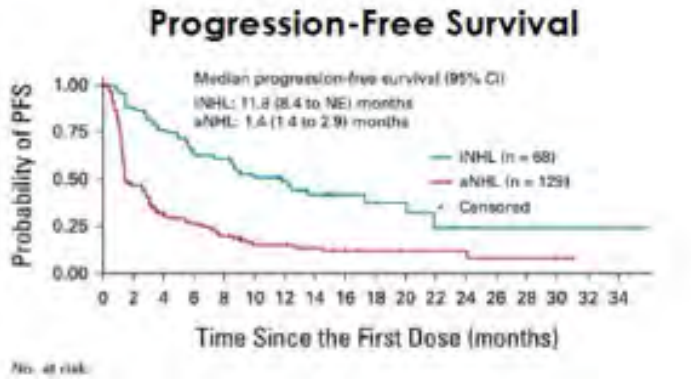
Budde J Clin Oncol. 2022 Feb 10;40(5):481-491.

Mosunetuzumab monotherapy in RR aNHL







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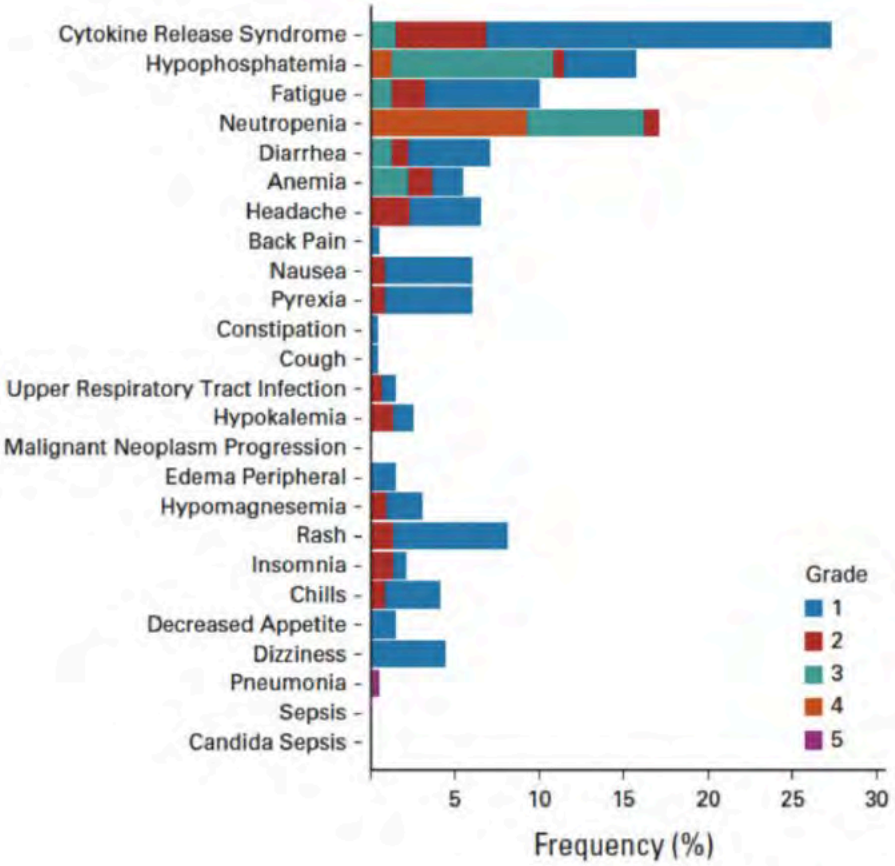
Budde J Clin Oncol. 2022 Feb 10;40(5):481-491.

Toxicity Profile: mosunetuzumab



- CRS:
  - All Grade: 27%
  - Grade 1: 21%
  - Grade 2: 6%
  - **Grade 3: 1%**
- Tocilizumab used in 3 patients

- Neurologic toxicity:
  - Headache: 18%
  - Insomnia: 11%
  - Dizziness: 10%
  - **Grade 3: 1%**

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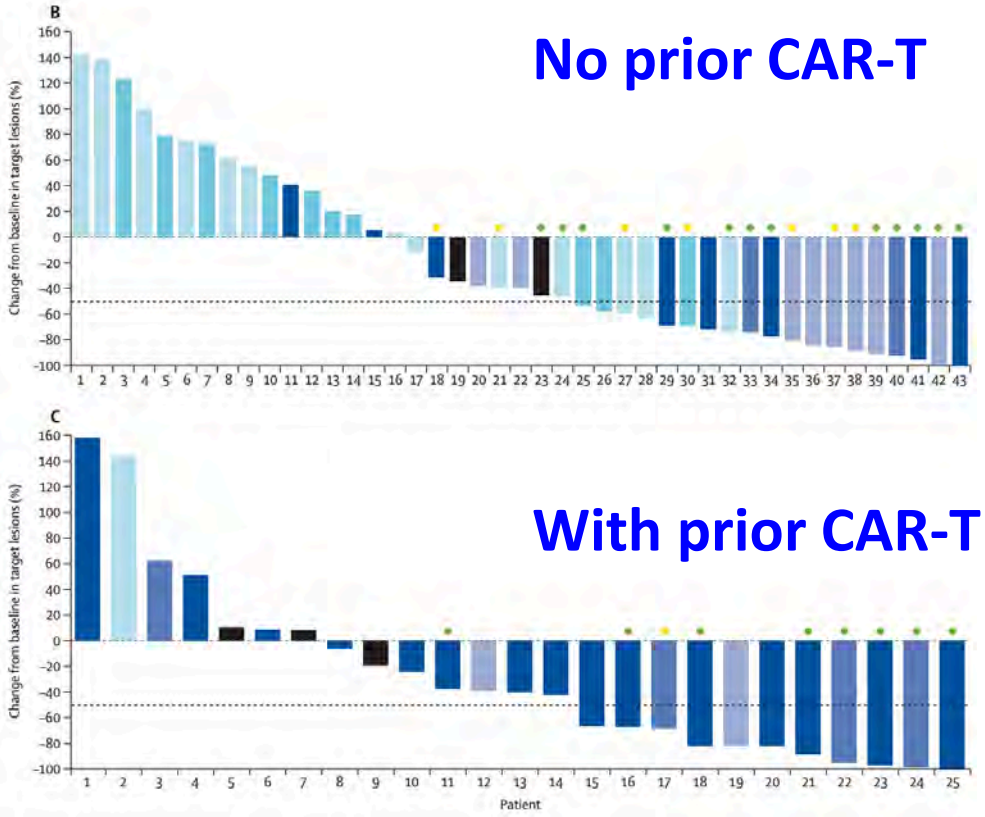
Budde J Clin Oncol. 2022 Feb 10;40(5):481-491.

Odrenextumab: impact of prior CAR-T

	Relapsed or refractory diffuse large B-cell lymphoma without previous CAR T-cell therapy (n=49)	Relapsed or refractory diffuse large B-cell lymphoma with previous CAR T-cell therapy (n=33)
Objective response (complete or partial)	19 (39%; 25·2–53·8)	11 (33%; 18·0–51·8)
Best overall complete tumour response	12 (24%; 13·3–38·9)	8 (24%; 11·1–42·3)
Best overall partial tumour response	7 (14%; 5·9–27·2)	3 (9%; 1·9–24·3)
Time to first response, months	1·4 (1·0–2·6)	1·1 (0·8–2·5)
Estimated duration of response, months	4·4 (95% CI 2·9–NE)	NR (95% CI 1·6–NE)
Observed duration of response, months	4·4 (2·8–21·0)†	6·7 (1·6–12·8)‡
Time to first complete response, months	2·3 (1·0–2·8)	1·5 (0·8–2·6)
Estimated duration of complete response, months	NR (95% CI 4·0–NE)	NR (95% CI NE–NE)
Observed duration of complete response, months	10·3 (4·2–21·4)	7·4 (2·6–15·8)



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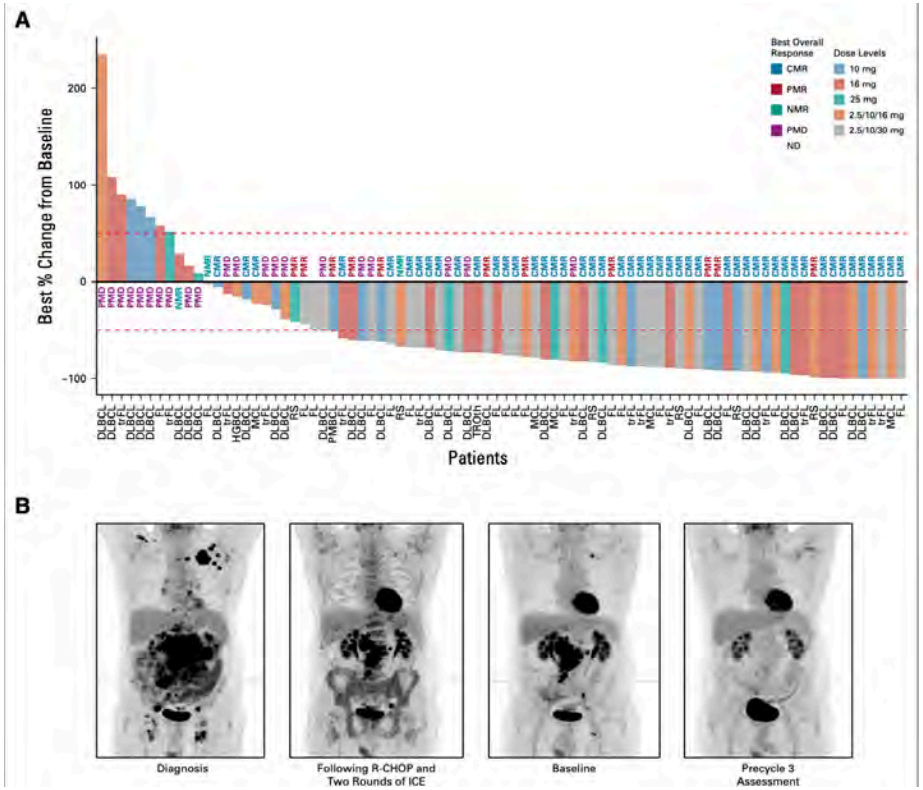
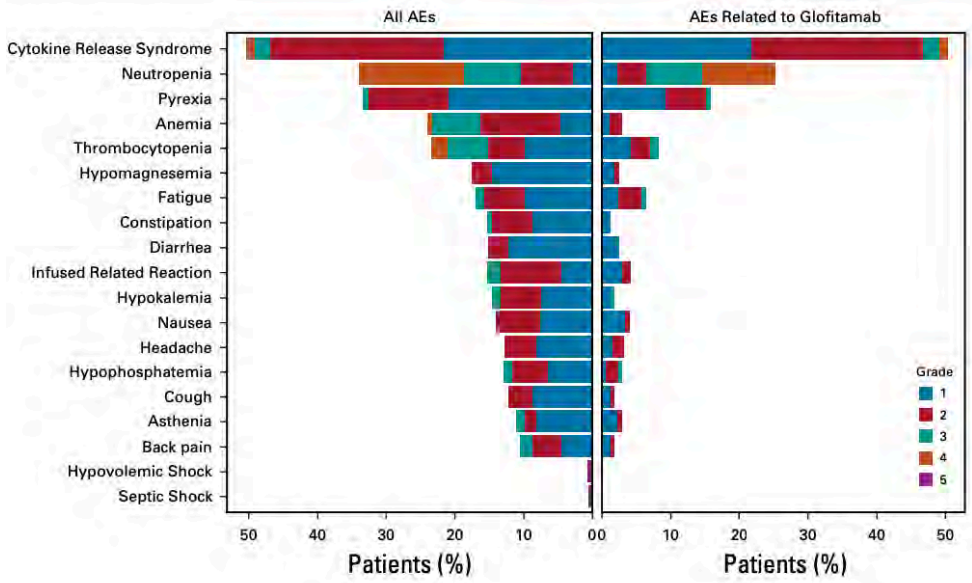
Bannerji Lancet Haematol 2022 May;9(5):e327-e339

Glofitamab: activity and adverse effects





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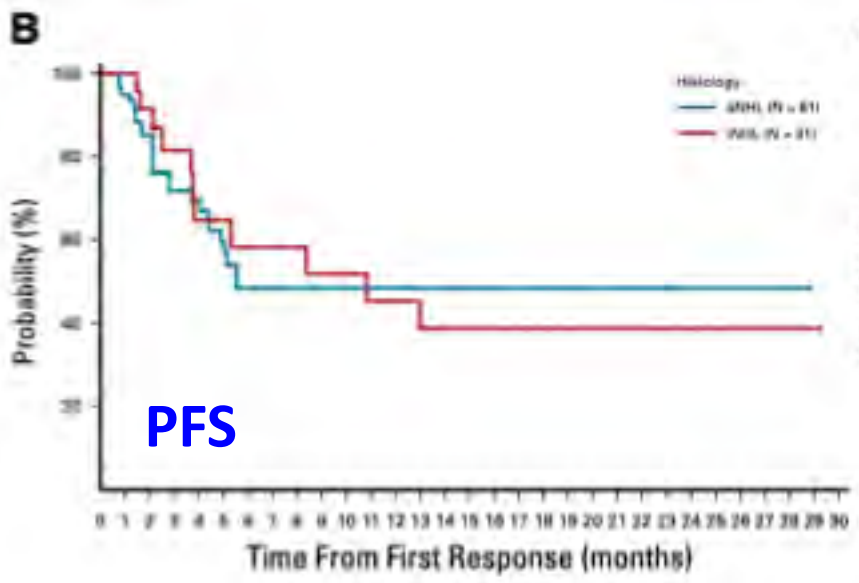
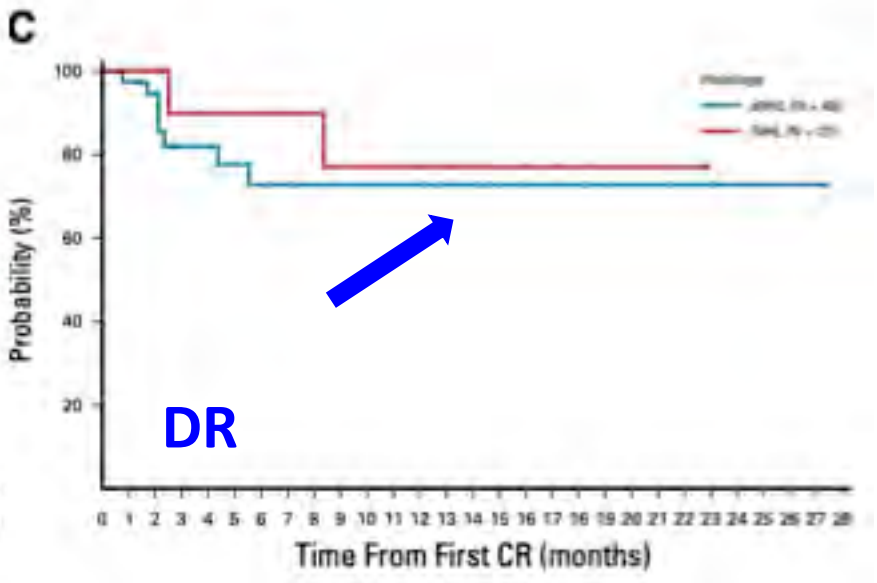
Hutchings J Clin Oncol 2021 Jun 20;39(18):1959-1970

Glofitamab: efficacy





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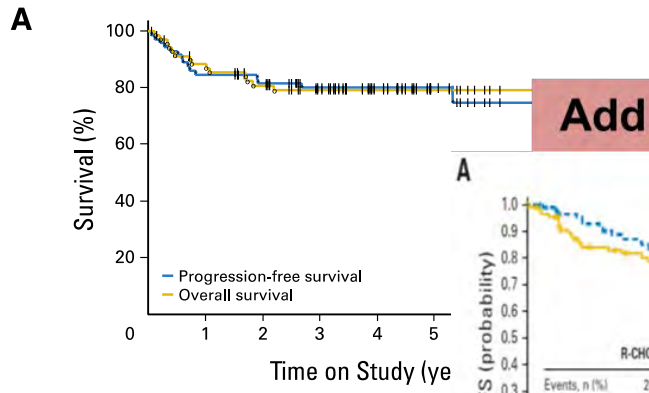
Hutchings J Clin Oncol 2021 Jun 20;39(18):1959-1970

BACK TO THE BEGINNING: ARE THERE OPPORTUNITIES FOR TARGETED THERAPY IN 1L?

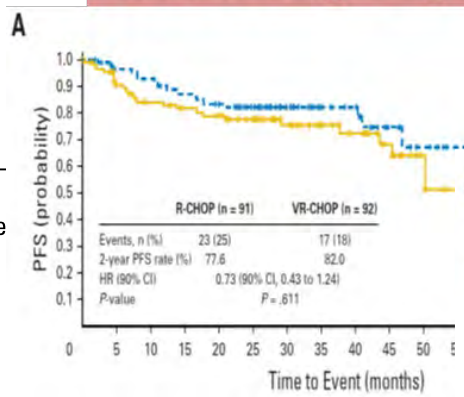
Challenging R-CHOP

se Large B-Cell

DA-EPOCH-R

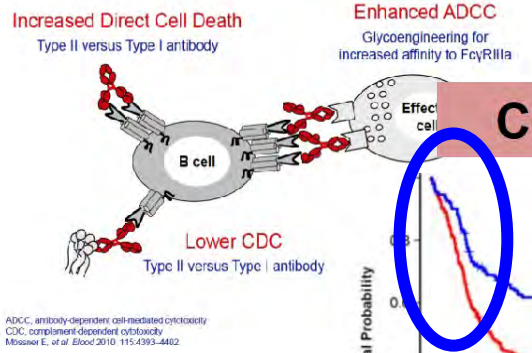


Add biologic agents

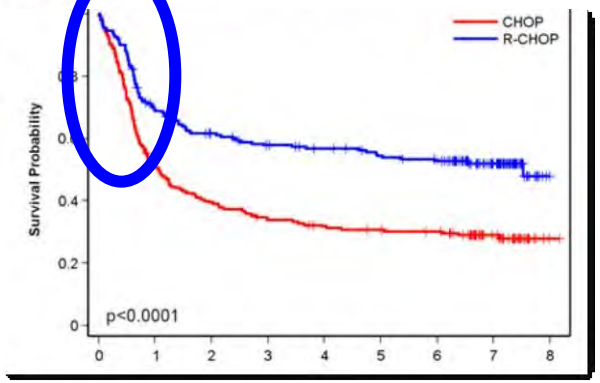


Obinutuzumab

GA101: Mechanisms of action



Consolidation



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Evolution of CHOP-like regimens for aggressive B-NHL

- m-BACOD = ProMACE-cytaBOM= CHOP21
- CHOP14 > CHOP21
- CHOEP-14/21 >CHOP21 (younger pts)
- R-CHOP21 > CHOP21
- R-CHOEP=R-CHOP
- R-CHOP14 x 8 = R-CHOP14 x 6 + R2
- R-CHOP14=RCHOP21

R-CHOP-21 has been the standard of care for the past 20 years

Pfreundschuh Lancet Oncology 2008; Pfreudschuh Blood 2004;
Coiffier NEJM 2002, Fisher NEJM 1995; Cunningham Lancet 2013

Can we improve upon R-CHOP with targeted approaches?

R-CHOP + X	**Negative trials**: ibrutinib, bortezomib, lenalidomide*
R-CHOP → X	**Negative trials**: rituximab, enzastaurin, lenalidomide, everolimus
Response adapted R-CHOP	**Negative trials**: PET-adapted ? PET-adapted CAR-T ? ctDNA driven

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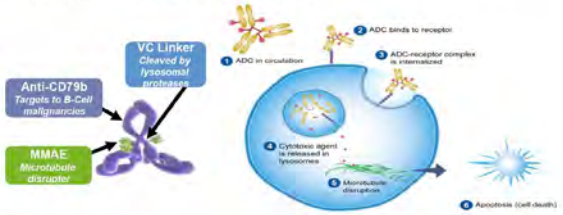
Slide adapted from Laurie Sehn

POLARIX: a randomized double blind phase 3 trial

- Microtubule inhibitor MMAE conjugated to CD79b monoclonal antibody via a protease-cleavable peptide linker



Patients

- Previously untreated DLBCL
- Age 18–80 years
- IPI 2–5
- ECOG PS 0–2

Stratification factors

- IPI score (2 vs 3–5)
- Bulky disease (<7.5 vs ≥7.5cm)
- Geographic region (Western Europe, US, Canada, & Australia vs Asia vs rest of world)

R 1:1

Pola-R-CHP

Polatuzumab vedotin (1.8mg/kg)*
R-CHP + vincristine placebo

Cycles 1–6
(1 cycle=21 days)

R-CHOP

R-CHOP† +
polatuzumab vedotin placebo

Rituximab
375mg/m²

Cycles 7 & 8

PRIMARY ENDPT: PFS
Med f/u 28.2m

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Tilly N Engl J Med. 2022 Jan 27;386(4):351-363

POLARIX: toxicity

AEs, %	Pola + R-CHP (n = 435)		R-CHOP (n = 438)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Peripheral neuropathy	52.9	1.6	53.9	1.1
Nausea	41.6	1.1	36.8	0.5
Neutropenia	30.8	28.3	32.6	30.8
Diarrhea	30.8	3.9	20.1	1.8
Anemia	28.7	12.0	26.0	8.4
Constipation	28.7	1.1	29.0	0.2
Fatigue	25.7	0.9	26.5	2.5
Alopecia	24.4	0	24.0	0.2
Dec appetite	16.3	1.1	14.2	0.7

AEs, %	Pola + R-CHP (n = 435)		R-CHOP (n = 438)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Pyrexia	15.6	1.4	12.6	0
Vomiting	14.9	1.1	14.4	0.7
Febrile neutropenia	14.3	13.8	8.0	8.0
Headache	12.9	0.2	13.0	0.9
Cough	12.9	0	12.1	0
Dec weight	12.6	0.9	11.9	0.2
Asthenia	12.2	1.6	12.1	0.5
Dysgeusia	11.3	0	13.0	0

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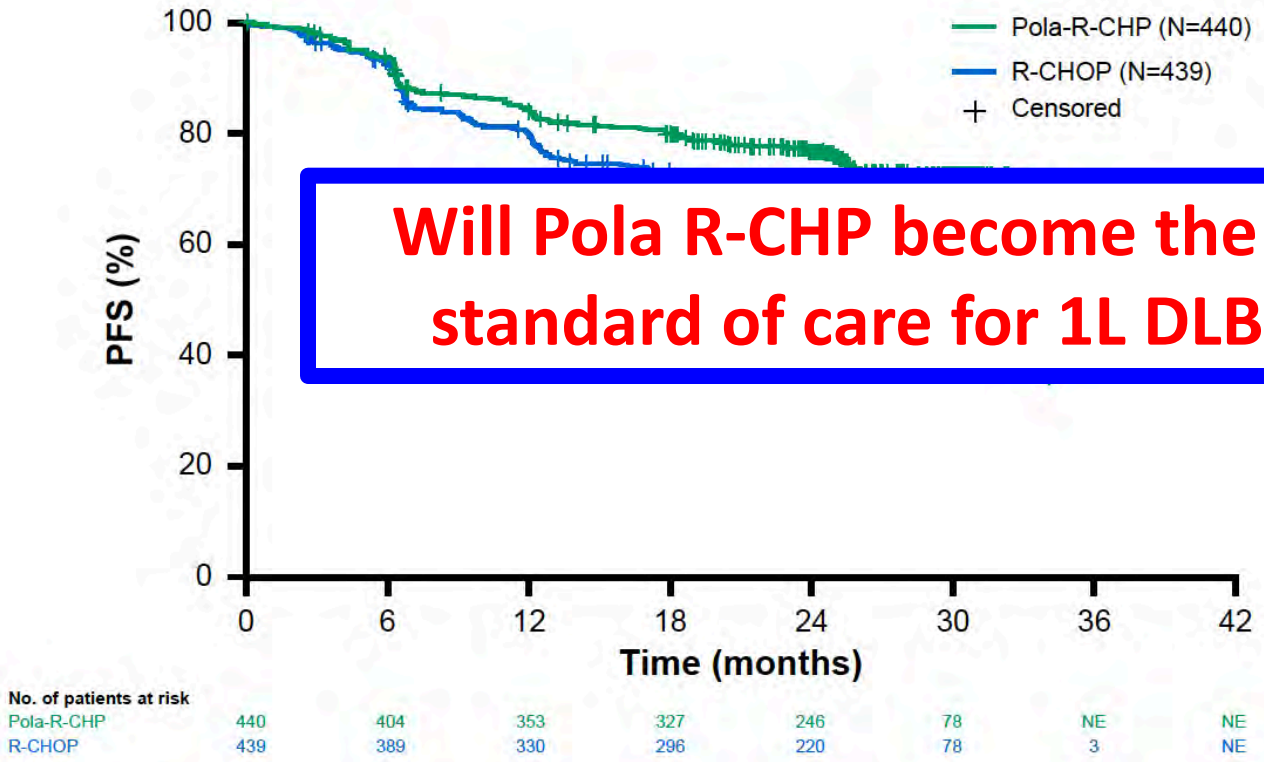
Tilly N Engl J Med. 2022 Jan 27;386(4):351-363

POLARIX: primary endpoint was met



Will Pola R-CHP become the new standard of care for 1L DLBCL?

HR 0.73 (P<0.02)
l: 0.57, 0.95

HP demonstrated a 27%
n in the relative risk of disease progression, relapse, or death versus R-CHOP

- **24-month PFS:**
  76.7% with Pola-R-CHP versus
  70.2% with R-CHOP (**Δ=6.5%**)

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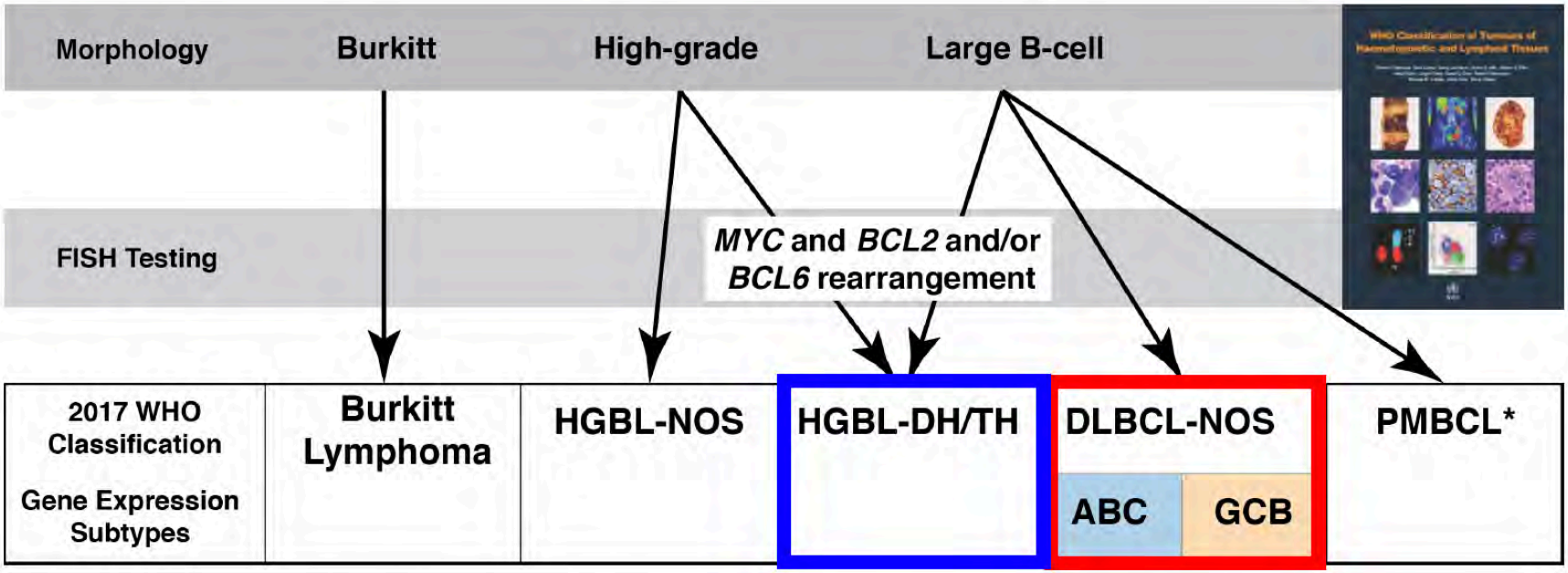
No difference in overall survival

Tilly N Engl J Med. 2022 Jan 27;386(4):351-363

TARGETED VS. PRECISION APPROACHES

Heterogeneity of aggressive B-cell lymphomas



HGBL-NOS: high-grade B-cell lymphoma NOS
HGBL-DH/TH: high-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements
PMBCL: Primary mediastinal B-cell lymphoma

Swerdlow et al WHO revised 4th Edition 2017

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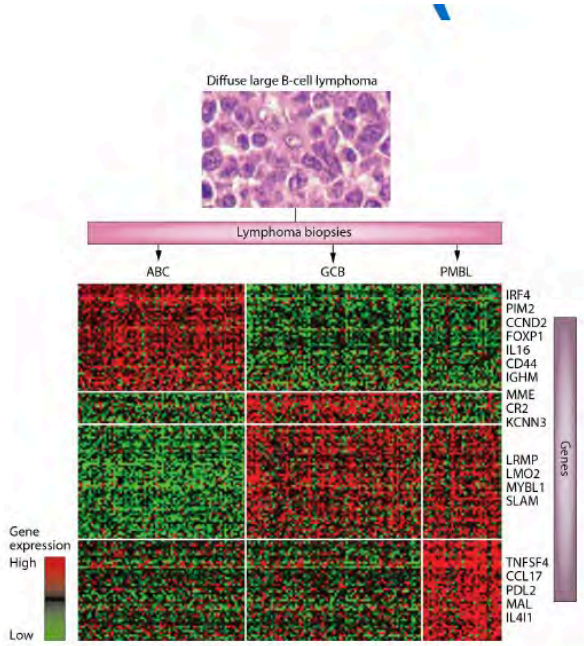
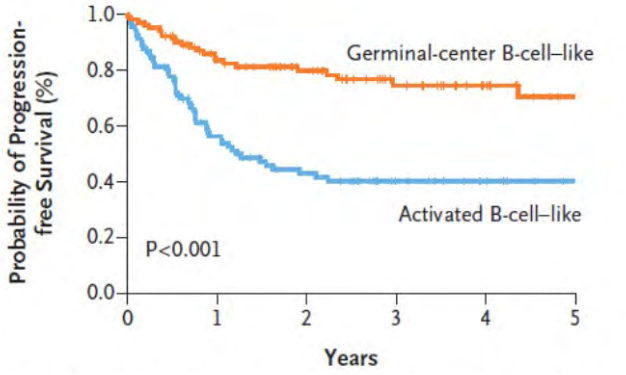
Slide adapted from Laurie Sehn

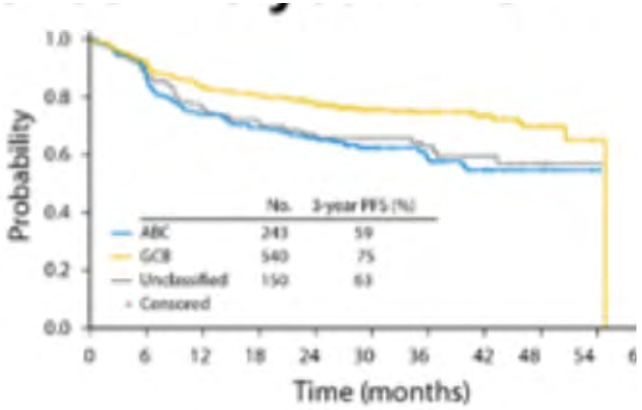
Cell-of-origin (COO) model as a *prognostic* tool in DLBCL



Alizadeh et al Nature 2000
Rosenwald et al, NEJM 2002
Lenz et al, NEJM 2008



Lenz et al. *N Engl J Med.* 2008;359:2313-2323.



GOYA Trial
R-CHOP v G-CHOP
PFS including both arms

Vitolo et al J Clin Oncol 2017

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Cell-of-origin (COO) model as a *predictive* tool in DLBCL

Putative targets may differ between GC and non-GC DLBCL

PI3K

BCL6

BCR signaling

SYK

…and MANY more

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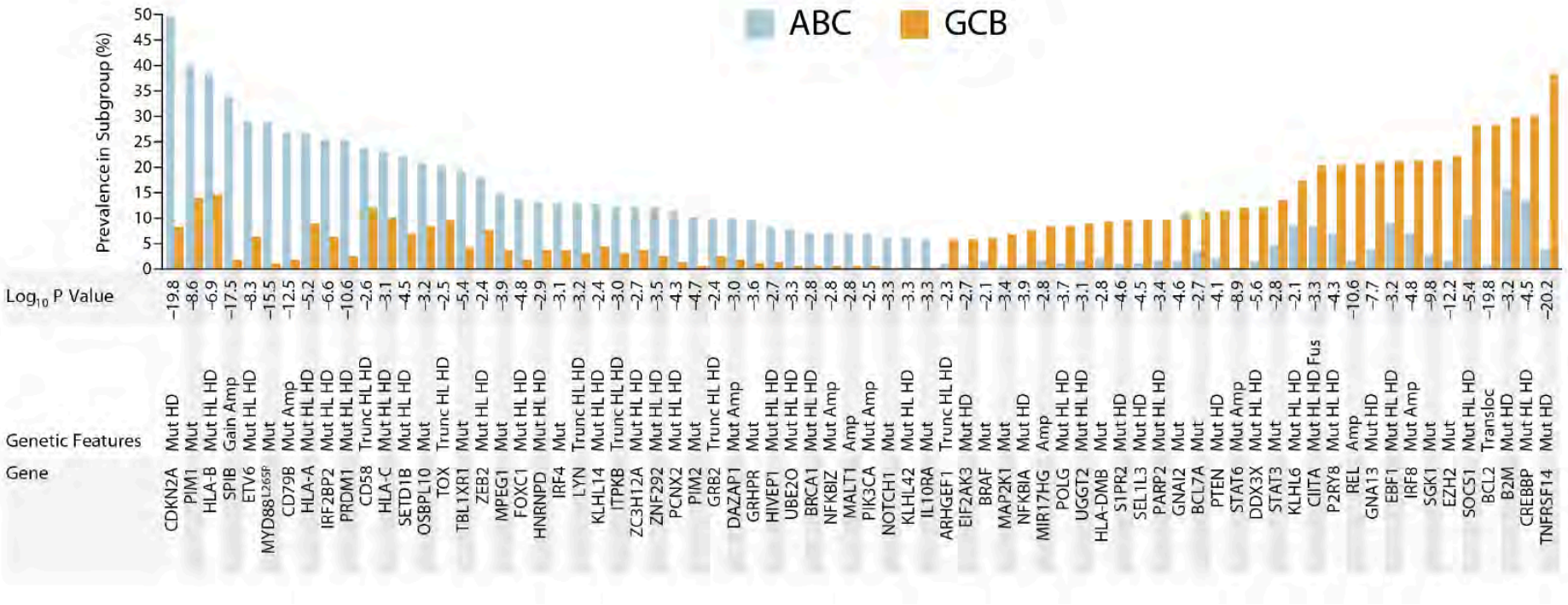
Monti Blood. 2005 Mar 1;105(5):1851-61; Alizadeh Nature. 2000 Feb 3;403(6769):503-11

Cell-of-origin is not a dichotomous distinction



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Schmitz N Engl J Med. 2018 Apr 12;378(15):1396-1407

Rethinking biologic heterogeneity in DLBCL

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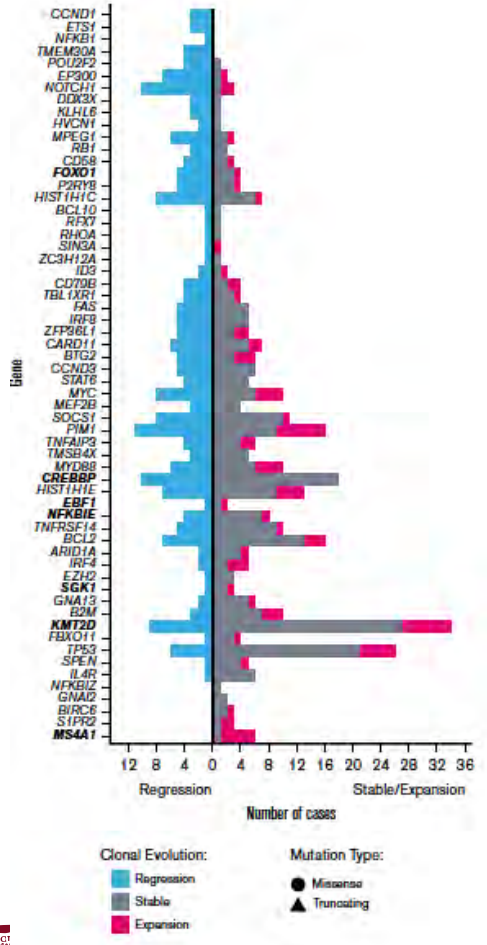
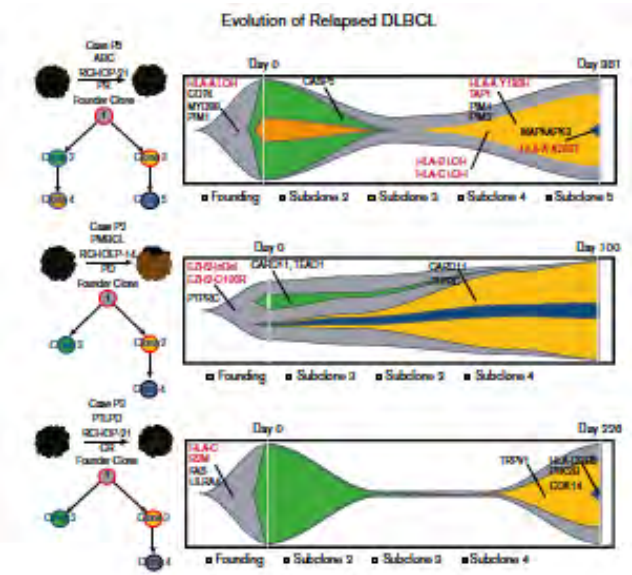
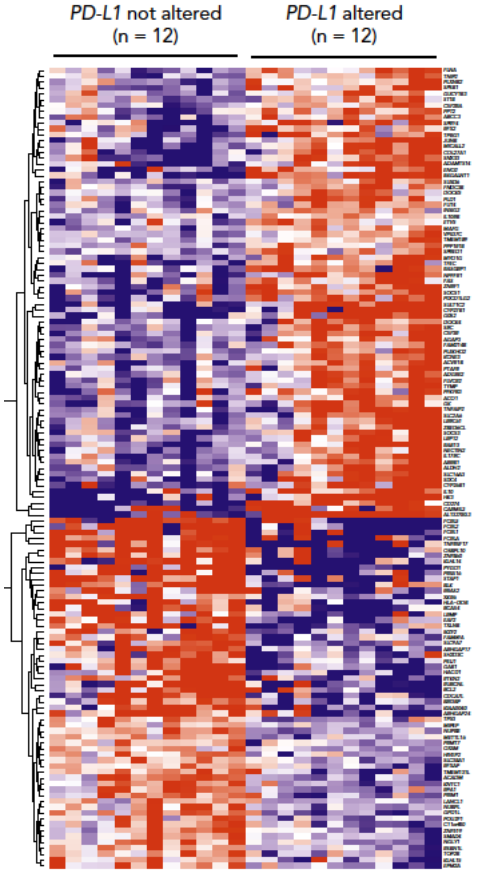
Wright Cancer Cell 2020 Apr 13;37(4):551-568.e14

Can biology direct treatment in rel/ref DLBCL?



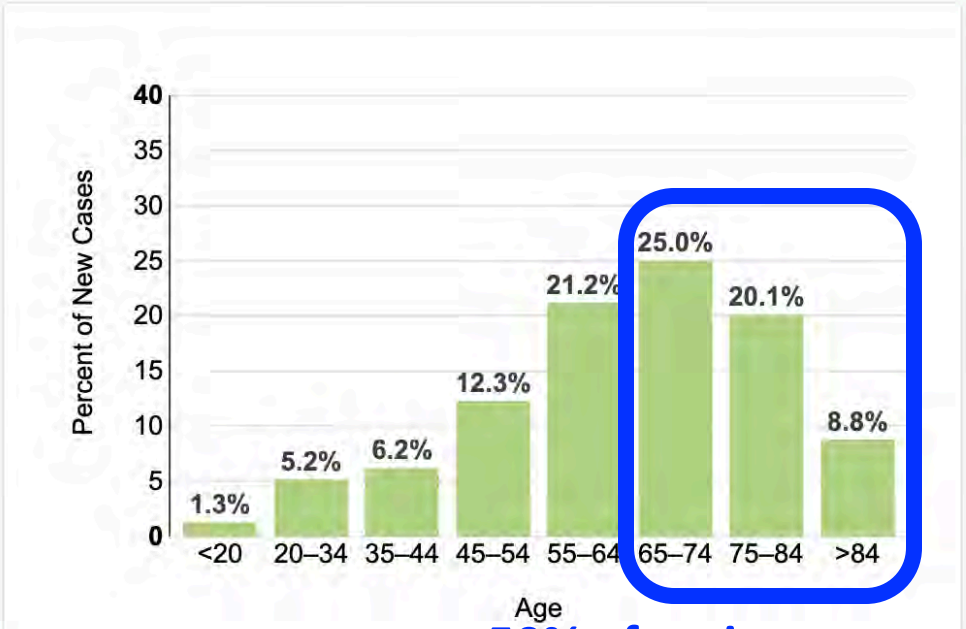




Godfrey Blood 2019 May 23;133(21):2279-2290; Rushton Blood Adv 2020 Jul 14;4(13):2886-2898; Wise Blood Adv 2020 May 12;4(9):1859-1866

What about clinical heterogeneity? Most patients are older

Percent of New Cases by Age Group: Diffuse Large B-Cell Lymphoma



Diffuse large B-cell lymphoma is most frequently diagnosed among people aged 65–74.

Median Age At Diagnosis
66

- **~50% of patients are ≥ 65y**
- **~30% of patients are ≥ 75y**

SEER 21 2013–2017, All Races, Both Sexes

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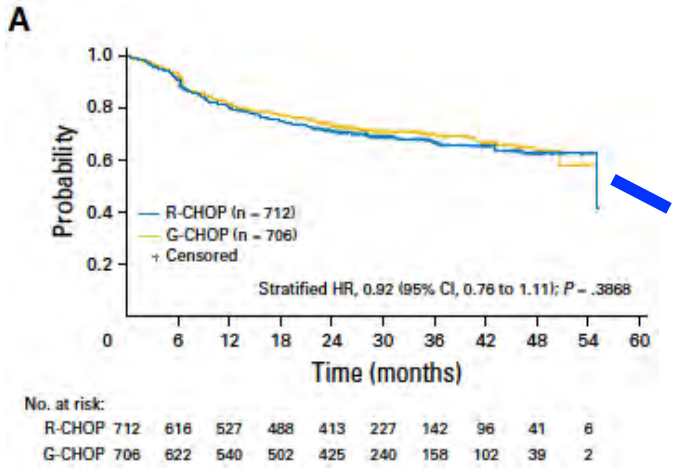
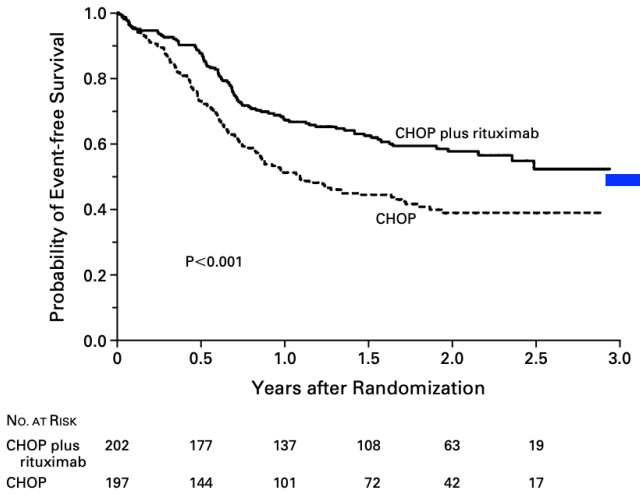
Cancer.gov

Relapse risk by age group

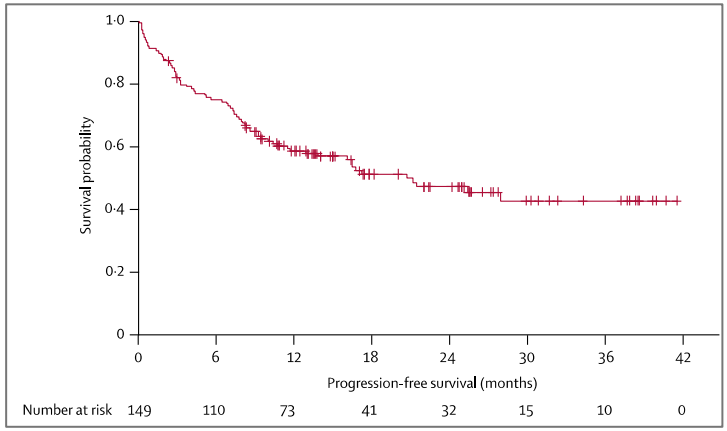
And these are just trial-eligible patients!!



GOYA trial:
Med age 62y
PFS @3y 70%



LNH98.5 trial:
Med age 69y
EFS @2y 57%



R-miniCHOP trial:
Med age 83y
EFS @2y 47%

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Vitolo J Clin Oncol. 2017 Nov 1;35(31):3529-3537; Coiffier N Engl J Med 2002 Jan 24;346(4):235-42; Peyrade Lancet Oncol. 2011 May;12(5):460-8

S1918: First US Intergroup Study in older adults with DLBCL

Available to you via NCTN!!

TN DLBCL
Age ≥ 75y with comorbidities or ≥ 80 yrs

- **RminiCHOP**
- **RminiCHOP + oral azacitidine**

- All patients have baseline frailty assessment
- Serial comprehensive geriatric assessment
- Primary endpoint of phase II: PFS and go/no-go for phase III
- Primary endpoint of phase III: OS

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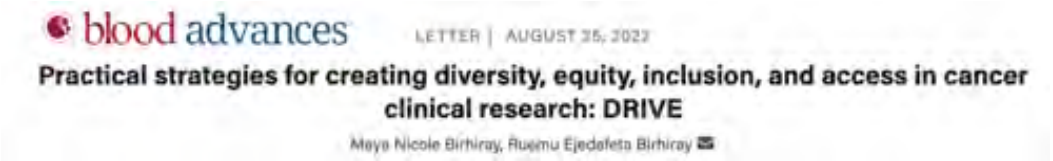
NCT04799275
clinicaltrials.gov

TARGETED AND CELLULAR THERAPY FOR DIFFUSE LARGE B-CELL LYMPHOMA: THE END OF A JOURNEY? *NOT YET…*

- Aim for **precision** therapy
  - Matching patients to the best treatment
  - We have yet to capitalize on the genomic and transcriptomic features of DLBCL
- Populations with **unmet needs**
  - Older patients
  - CNS recurrence
  - Patients with comorbidities
- Ensure **equitable** inclusion and access of treatment advances
  - Enroll ALL patient groups who reflect our country



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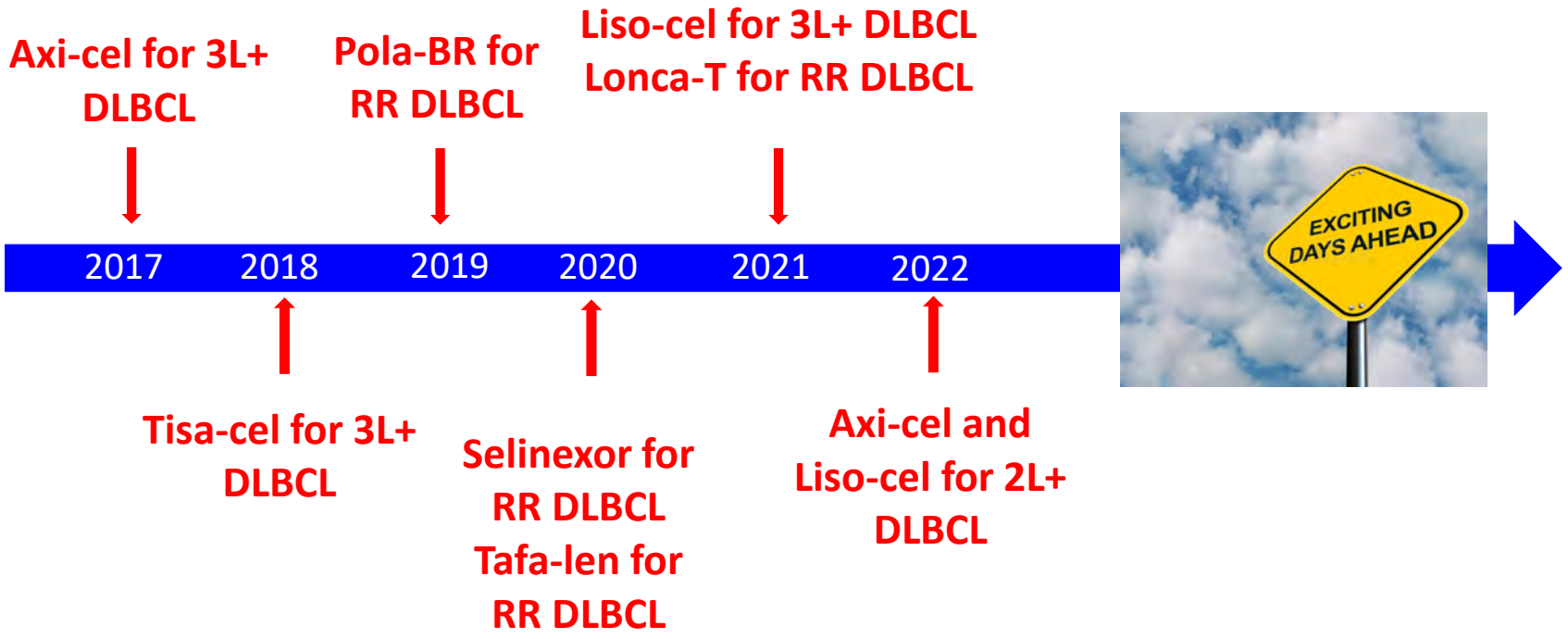
Major milestones in DLBCL Treatment



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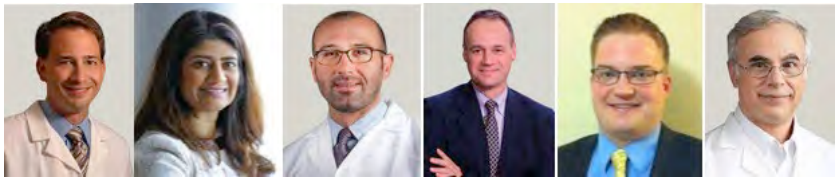

LYMPHOMA PROGRAM:
The University of Chicago
cancer@uchospitals.edu

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