VIRTUAL CHALLENGING CASE CLINIC:

B-Cell Lymphomas

CAR T-Cell Therapy
Broadcast on May 12, 2021

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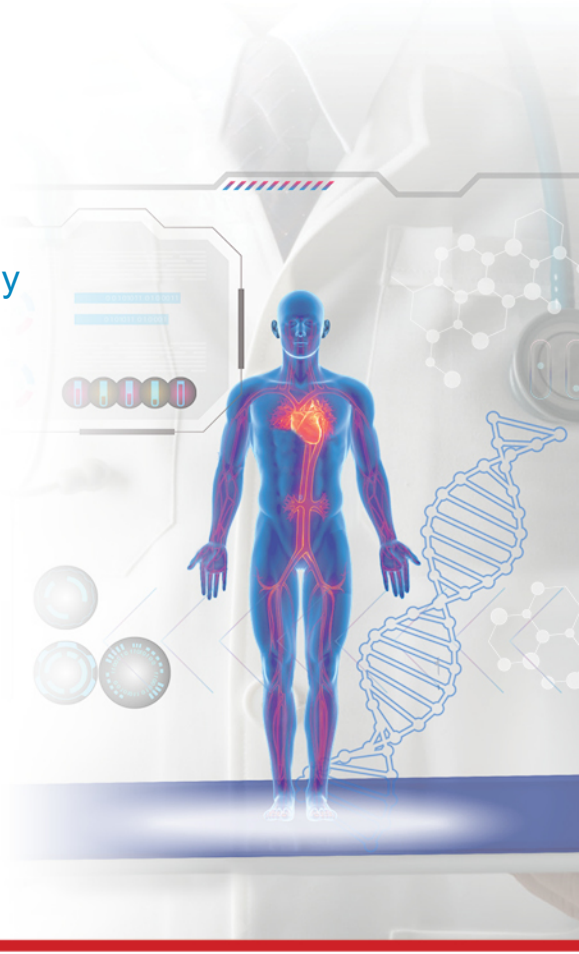

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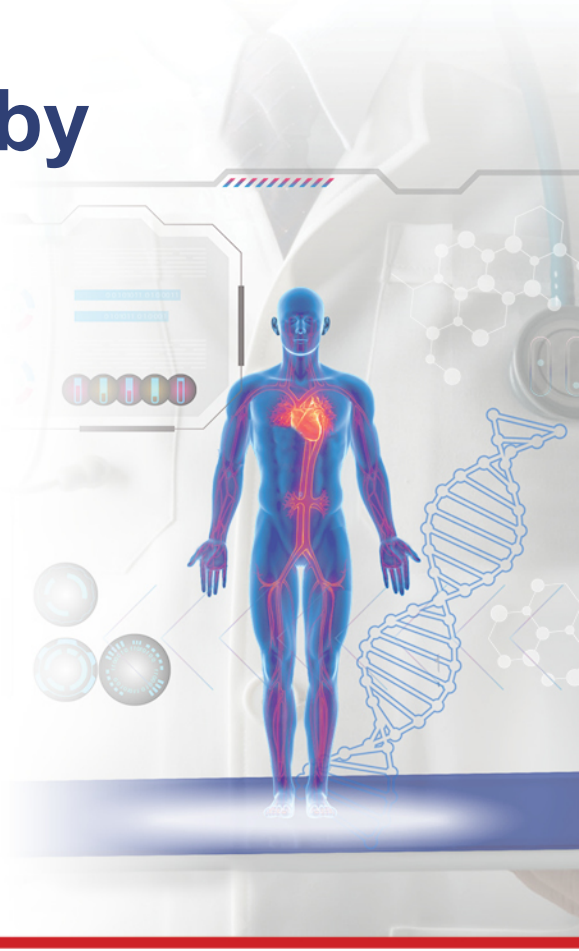

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Disclosures

John P. Leonard, MD

Consulting Fees: ADC Therapeutics, AstraZeneca, Bayer, Bristol-Myers Squibb Company, Epizyme, Kite, a Gilead Company, MEI Pharma, Miltenyi Biotec, Regeneron, Roche/Genentech, Sutro Biopharma

Mehdi Hamadani, MD

Consulting Fees: ADC Therapeutics, Celgene Corporation, Incyte Corporation, Janssen, Magenta Therapeutics, Omeros, Teneobio

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Planning Committee

The following planning committee members have nothing to disclose:
UNMC: Brenda Ram, CMP, CHCP

Bio Ascend: Patti Bunyasaranand, MS; Dru Dace, PhD; Lucja Grajkowska, PhD; Kraig Steubing

Learning Objectives

- Evaluate best available evidence regarding the CAR T-cell therapy for patients with lymphoma
- Assess the implications of emerging clinical trial data regarding CAR T cell treatment approaches
- Develop strategies to address complicated lymphoma cases using CAR T-cell therapy

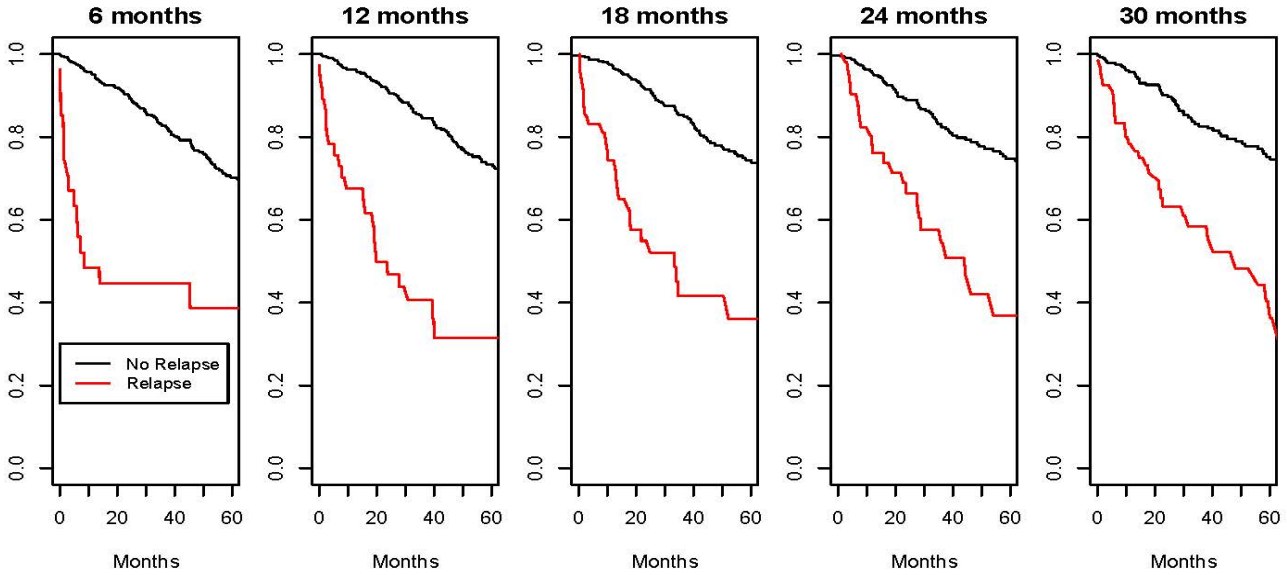
Clinical Case #1

- A symptomatic, stage IV MCL patient received R-CHOP/R-DHAP induction following by autoHCT consolidation. He relapsed 18 months post HCT & started ibrutinib/ixazomib (on trial). After ~1yr, the patient relapsed again (at current relapse = age 69; ECOG=1)

What would you do next?

1. Lenalidomide +/- CD20 monoclonal antibody
2. Allogeneic transplant
3. Second autologous transplant
4. CAR-T Cell Therapy

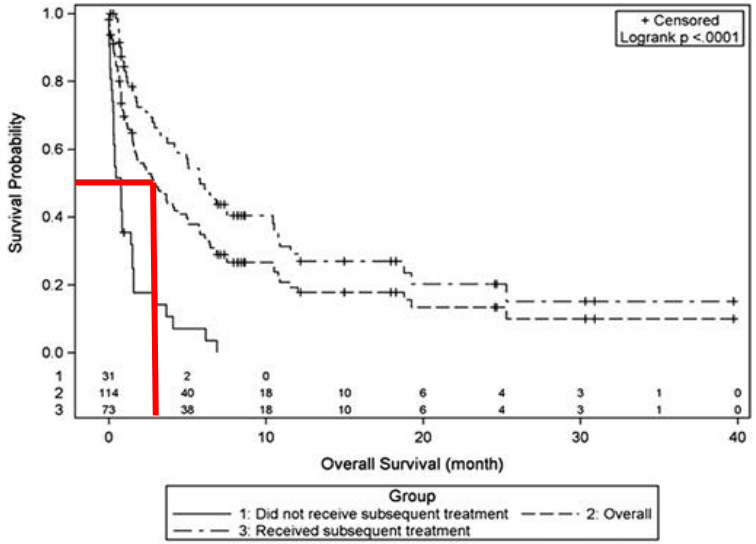
Simple Tools to Identify Poor-risk MCL at Relapse?



Time to relapse	6 months	12 months	18 months	24 months	30 months
Median OS	9 mons	24 mons	34 mons	44 mons	48 mons

CIBMTR Data (unpublished).

Simple Tools to Identify Poor-risk MCL at Relapse?

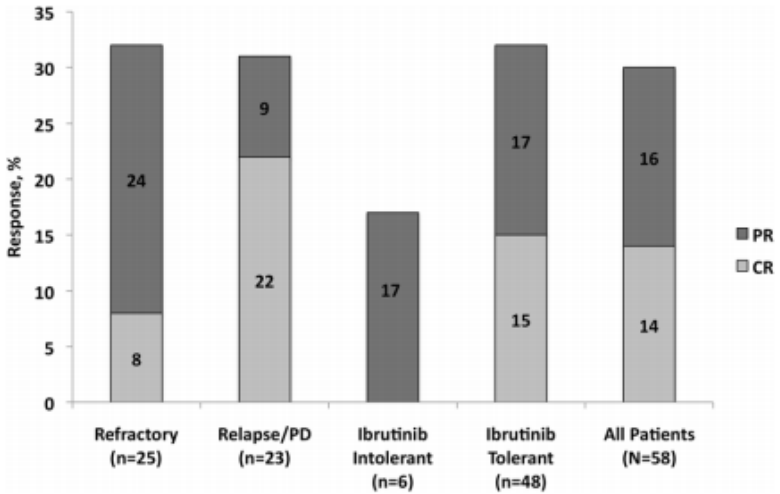


Survival after ibrutinib failure?

- Median post relapse OS in ibrutinib responders = 5months
- Median post relapse OS in ibrutinib non responders = 1month

Epperla & Hamadani. Hematol Oncol. 2017;35:528-35.

Targeted Agents Have Limited Efficacy After Ibrutinib Failure

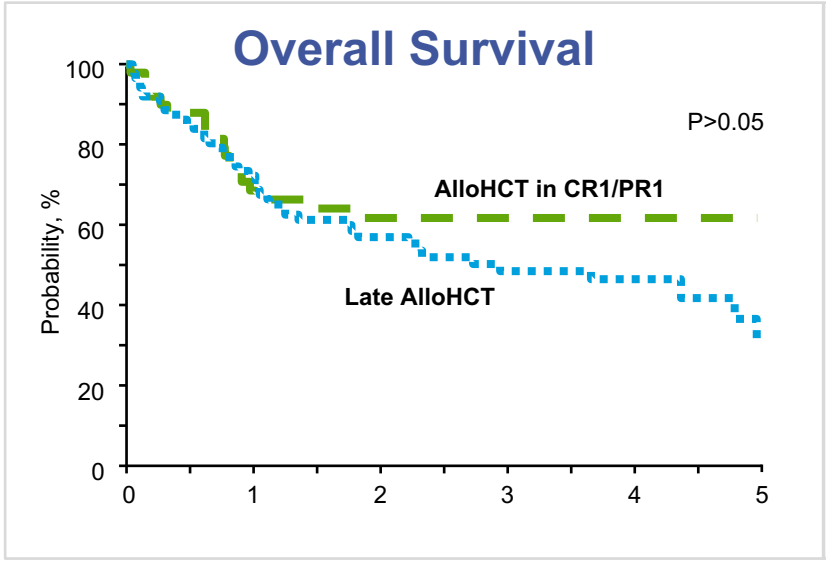


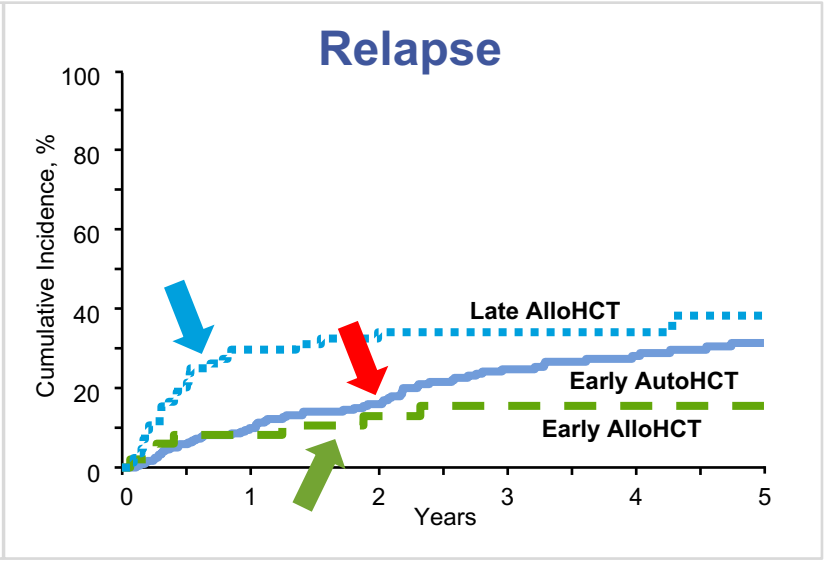
Lenalidomide after BTKi failure:

- 68 patients (lenalidomide based treatments)
- ORR in patients with relapsed/progressive disease after previous response to ibrutinib versus ibrutinib-refractory patients was 30% versus 32%
- Median DOR = 20 weeks

Wang M & Martin P. J Hematol Oncaol. 2017;10(1):171.

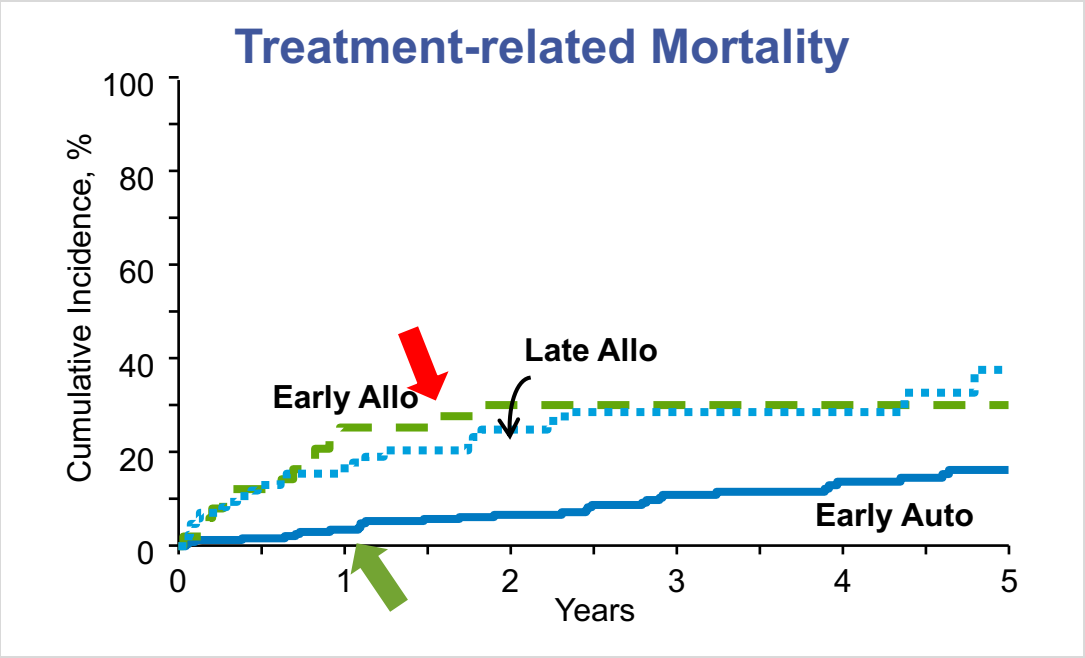
AlloHCT Exerts Meaningful Immune Effects in MCL





Fenske T & Hari P. J Clin Oncol. 2014;32:273-81.

HCT Related Morbidity & Mortality



Fenske T & Hari P. J Clin Oncol. 2014;32:273-81.

Mantle Cell Lymphoma: Brexucabtagene Autoleucel

Phase 2

Enrollment/ Leukapheresis	Optional Bridging Therapy	Conditioning Chemotherapy	CAR T Cell Dose	**Follow-Up Period**
R/R MCL (1-5 prior line of therapy)	Dexamethasone 20 – 40 mg or equivalent PO or IV daily for 1 – 4 days, or ibrutinib 560 mg PO daily, or acalabrutinib 100 mg PO twice daily	Fludarabine 30 mg/m^2 IV and cyclophosphamide 500 mg/m^2 IV on Days −5, −4, −3	2×10^6 KTE-X19 cells/kg single IV infusion on Day 0	First tumor assessment on Day 28[b]

Primary Endpoint

- ORR (IRRC-assessed per the Lugano classification[1])

Key Secondary Endpoints

- DOR
- PFS
- OS
- AEs
- ORR (Investigator-assessed per revised IWG criteria[2])
- EQ-5D
- Levels of CAR T cells in blood and cytokines in serum

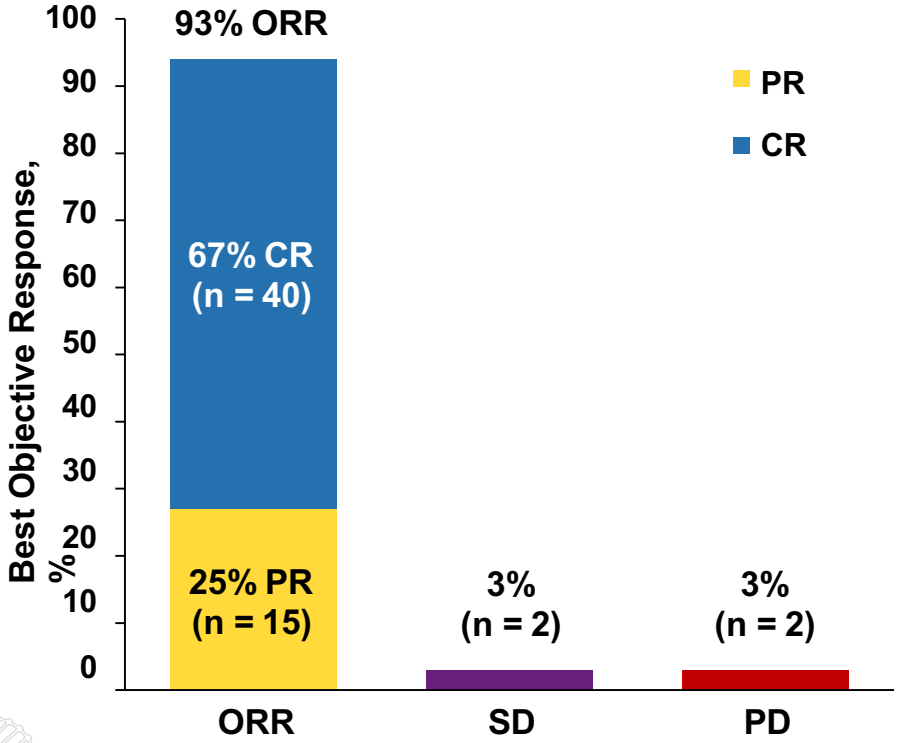
Wang M & Reagan P. NEJM. 2020;382(14):1331-1342.

CAR-T cells in MCL: ZUMA-2 (Brex-cel)

Characteristic	N = 68
Median age (range), years	65 (38 – 79)
ECOG 0 or 1, n (%)	100 (100)
Intermediate/high-risk MIPI, n (%)	38 (56)
Ki-67 proliferation index ≥ 50%, n/n (%)[a]	34/49 (69)
TP53 mutation, n/n (%)	6/36 (17)
Median no. of prior therapies (range)[a]	3 (1 – 5)
Relapsed after autologous HCT	29 (43)
BTKi, n (%)	68 (100)
BTKi refractory, n (%)	46 (68)

Wang M & Reagan P. NEJM. 2020;382(14):1331-1342.

CAR-T cells in MCL: ZUMA-2

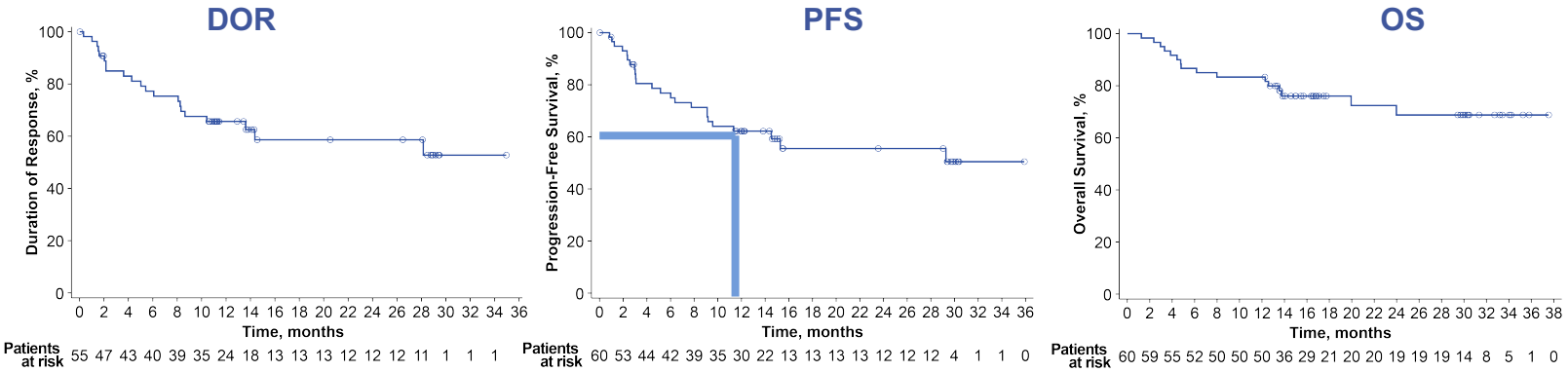


Parameter	N = 68
CRS, n (%)	
Any grade	62 (91)
Grade ≥ 3	10 (15)
Neurologic events, n (%)	
Any grade	43 (63)
Grade ≥ 3	21 (31)
AE management CRS, n (%)	
Tocilizumab	40 (59)
Corticosteroids	15 (22)
Median time to CRS onset (range), days	2 (1 – 13)
Median time to CRES onset (range), days	7 (1 – 32)

Wang M & Reagan P. NEJM. 2020;382(14):1331-1342.

CAR-T cells in MCL: ZUMA-2 (updated FU; 17.5 mons)

- The medians for DOR, PFS, and OS were not reached after a median follow-up of 17.5 months



	DOR		PFS		OS	
	Median (95% CI), mo	15-Mo Rate (95% CI), %	Median (95% CI), mo	15-Mo Rate (95% CI), %	Median (95% CI), mo	15-Mo Rate (95% CI), %
Evaluable pts (N=60)	NR (14–NE)[a]	59 (43–72)[a]	NR (10–NE)	59 (45–71)	NR (NE–NE)	76 (63–85)
Pts in CR (n=40)	NR (14–NE)	70 (49–83)	NR (15–NE)	75 (57–87)	NR (NE–NE)	92 (76–97)
Pts in PR (n=15)	2 (1–4)	24 (6–49)	3 (2–5)	24 (6–49)	13 (3–NE)	47 (21–69)

Wang M & Reagan P. NEJM. 2020;382(14):1331-1342.

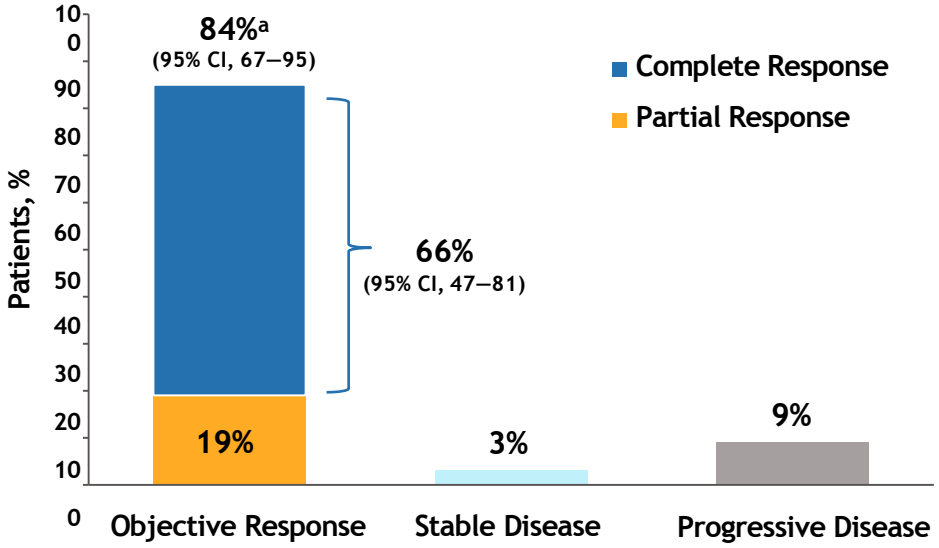
TRANSCEND NHL 001: Patient Characteristics

	All liso-cel— Treated Patients (N = 32)
Age, median (range), y	67 (36—80)
≥65 y, n (%)	21 (66)
Male, n (%)	27 (84)
ECOG PS at screening, n (%)	
0	16 (50)
1	16 (50)
Blastoid morphology, n (%)	13 (41)
Ki67 ≥30%, n (%)	23 (72)
TP53 mutations, n (%)	7 (22)
SPD ≥50 cm^2 prior to LDC,[a] n(%)	5 (17)
LDH >ULN prior to LDC, n (%)	16 (50)
CRP ≥20 mg/L at baseline,[b] n(%)	17 (55)
Secondary CNS lymphoma at time of liso-cel administration, n (%)	1 (3)

	All liso-cel— Treated Patients (N = 32)
Bone marrow involvement at infusion,[c] n (%)	8 (25)
No. of prior therapies, median (range)	3 (1—7)
≥3 prior therapies, n (%)	22 (69)
Prior HSCT, n (%)	11 (34)
Allogeneic	3 (9)
Autologous	10 (31)
Refractory,[d] n (%)	26 (81)
Prior BTK inhibitor, n (%)	28 (88)
Prior ibrutinib	24 (75)
Refractory to prior ibrutinib[e]	10 (31)
Prior venetoclax, n (%)	8 (25)
Refractory to prior venetoclax[e]	5 (16)
Bridging therapy, n (%)	17 (53)
Systemic treatment only	12 (37.5)
Radiotherapy only	1 (3)
Systemic treatment and radiotherapy	4 (12.5)

Palomba & Wang. ASH 2020 Abstract

Response Rates & Toxicity



	All liso-cel— Treated Patients (N = 32)
CRS or NE, n (%)	
Any grade	19 (59)
Grade ≥3	5 (16)
CRS	
Any grade, n (%)	16 (50)
Grade ≥3, n (%)	1 (3)
Time to onset, median (range), days	6 (2—10)
Time to resolution, median (range), days	4 (2—9)
NE	
Any grade, n (%)	11 (34)
Grade ≥3, n (%)	4 (12.5)
Time to onset, median (range), days	8 (2—25)
Time to resolution, median (range), days	4 (1—27)
ICU admissions, n (%)	3 (9)
CRS and/or NE	3 (9)
Other reasons	0

Palomba & Wang. ASH 2020 Abstract

Clinical Case #1

ANSWER

- A symptomatic, stage IV MCL patient received R-CHOP/R-DHAP induction following by autoHCT consolidation. He relapsed 18 months post HCT & started ibrutinib/ixazomib (on trial). After ~1yr, the patient relapsed again (at current relapse = age 69; ECOG=1)

1. Lenalidomide +/- CD20 monoclonal antibody
2. Allogeneic transplant
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4. **CAR-T Cell Therapy**

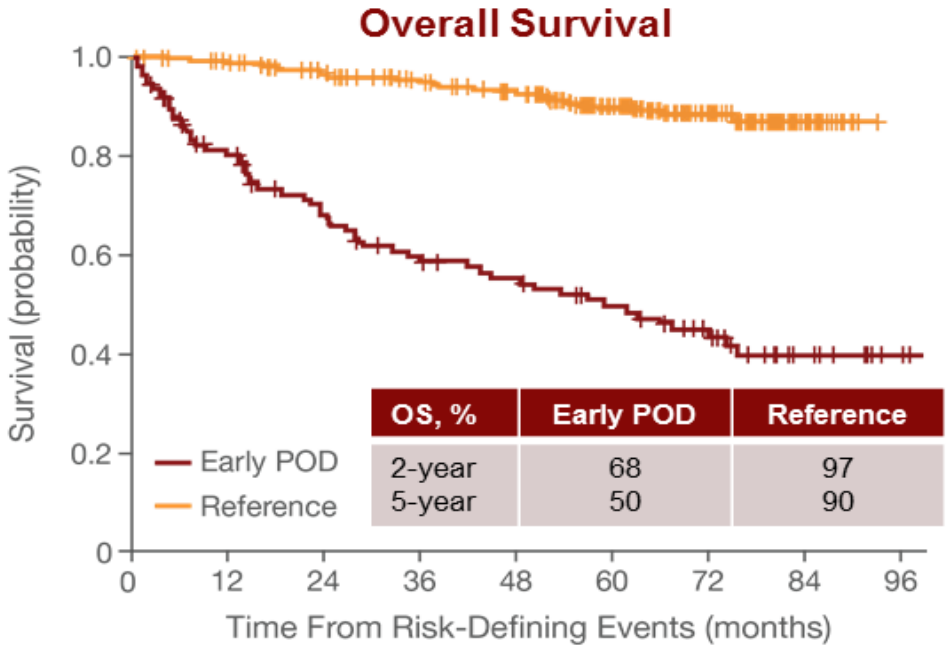
Clinical Case #2

- 57-year-old female, with advanced stage follicular lymphoma (grade 3A), received first therapy with R-CHOP followed by rituximab maintenance. ~1.5 year after diagnosis patient relapsed (biopsy ruled out transformation). She achieved a CR with 2nd line treatment with bendamustine/obinutuzumab

What would you do next?

1. CAR T-cell therapy
2. Autologous transplant
3. Watch & wait
4. Allogeneic transplantation

Early failure (POD24) of R-Chemo Identifies a High-risk FL



- National LymphoCare Study

Casulo C & Friedberg J. JCO. 2015;33:2516-22.

Follicular Lymphoma: ZUMA-5

Phase 2 (N=151 enrolled)

R/R iNHL	N=146 Treated (124 FL, 22 MZL)

Key Eligibility Criteria

- R/R FL (Grades 1–3a) or MZL (nodal or extranodal)
- ≥2 Prior lines of therapy—must have included an anti-CD20 mAb combined with an alkylating agent

Conditioning Regimen

- Fludarabine 30 mg/m^2 IV and cyclophosphamide 500 mg/m^2 IV on Days −5, −4, −3

Axi-Cel: 2×10^6 CAR+ cells/kg

Primary Endpoint

- ORR (IRRC-assessed per the Lugano classification)

Key Secondary Endpoints

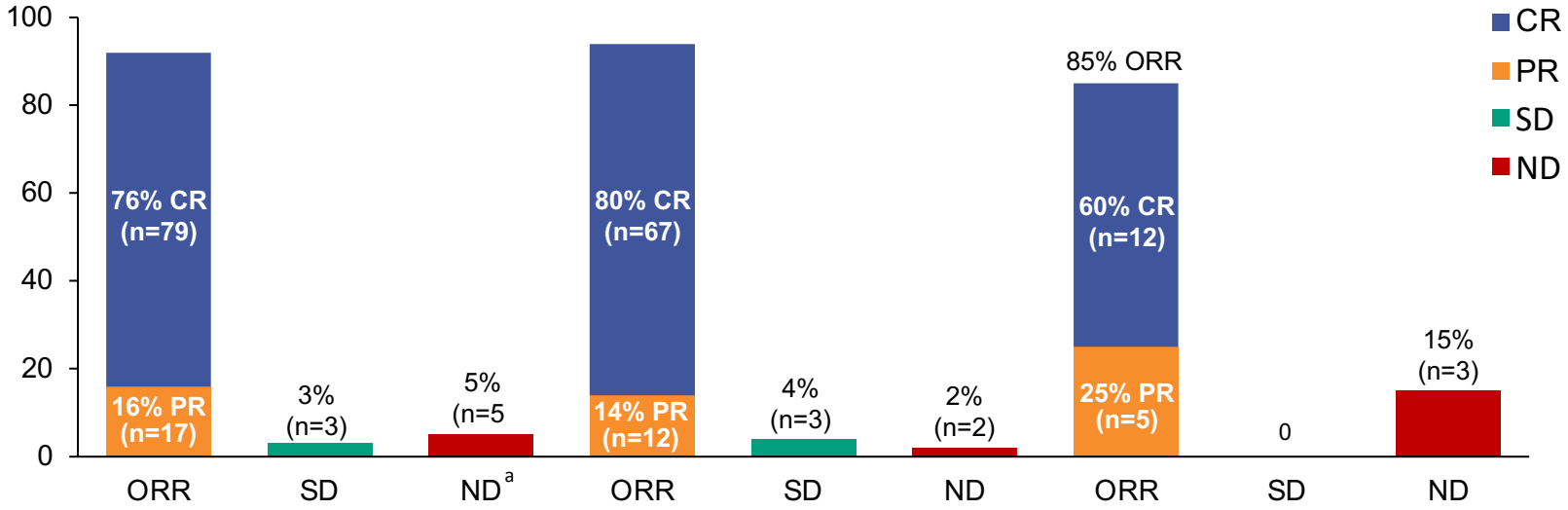
- CR rate (IRRC-assessed)
- Investigator-assessed ORR
- DOR, PFS, OS
- AEs
- CAR T cell and cytokine levels

Baseline Disease Characteristics

Characteristic	FL (n=124)	MZL (n=22)	All Patients (N=146)
Median age (range), years	60 (34–79)	66 (48–77)	61 (34–79)
≥65 years, n (%)	38 (31)	13 (59)	51 (35)
Male, n (%)	73 (59)	10 (45)	83 (57)
ECOG 1, n (%)	46 (37)	9 (41)	55 (38)
Stage III-IV disease, n (%)	106 (85)	20 (91)	126 (86)
≥3 FLIPI, n (%)	54 (44)	14 (64)	68 (47)
High tumor bulk (GELF criteria), n (%)[a]	64 (52)	8 (36)	72 (49)
Median no. of prior therapies (range)	3 (1–10)[b]	3 (2–8)	3 (1–10)[b]
≥3, n (%)	78 (63)	15 (68)	93 (64)
Prior PI3Ki therapy, n (%)	34 (27)	9 (41)	43 (29)
Refractory disease, n (%)[c]	84 (68)	16 (73)	100 (68)
POD24 from first anti-CD20 mAb-containing therapy, n (%)[d]	68 (55)	11 (52)	79 (55)
Prior autologous SCT, n (%)	30 (24)	3 (14)	33 (23)

[a] Disease burden, as defined by GELF criteria: involvement of ≥3 nodal sites (≥3 cm diameter each); any nodal or extranodal tumor mass with ≥7 cm diameter; B symptoms; splenomegaly; pleural effusions or peritoneal ascites; cytopenias; or leukemia. [b] Enrollment of 3 patients with FL who had 1 prior line of therapy occurred before a protocol amendment requiring ≥2 prior lines of therapy. [c] Patients with iNHL who progressed within 6 months of completion of the most recent prior treatment. [d] POD24 defined as <24 months from initiation of the first line of anti-CD20–containing immunochemotherapy to progression. Percentages are based on the number of patients who ever received anti-CD20–chemotherapy combination therapy.

Follicular Lymphoma: ZUMA-5

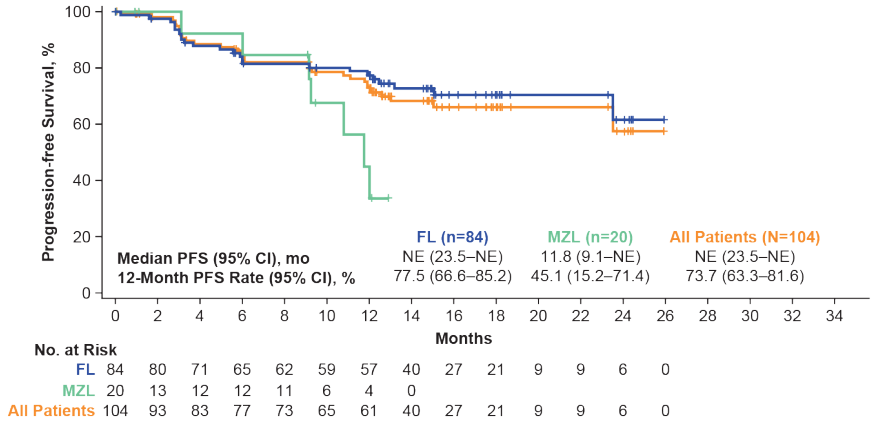


- The median time to first response was 1 month (range, 0.8–3.1)
- Among the 25 patients with FL who initially had a PR, 13 (52%) subsequently converted to a CR

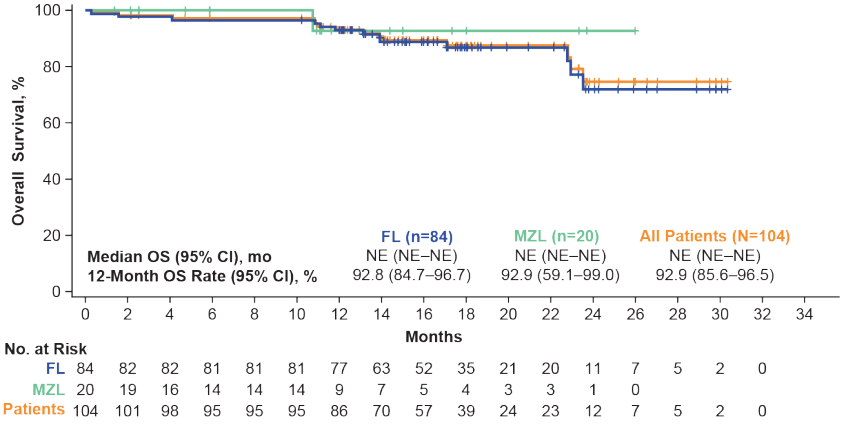
Jacobson & Neelapu. TCTM 2021. Abstract #69.

Follicular Lymphoma: ZUMA-5

Progression-Free Survival



Overall Survival



- With a median follow-up of 17.5 months, median PFS and median OS were not reached
  - The 12-month PFS rate was 73.7% (95% CI, 63.3–81.6) for all patients
  - The 12-month OS rate was 92.9% (95% CI, 85.6–96.5) for all patients

Jacobson & Neelapu. TCTM 2021. Abstract #69.

Can Autologous HCT Improve Outcomes of POD24 Follicular Lymphoma?

Inclusion criteria

AHCT cohort:

- FL diagnosed between 2002-2009 in **CIBMTR**
- Meet criteria for POD24 per the NLCS

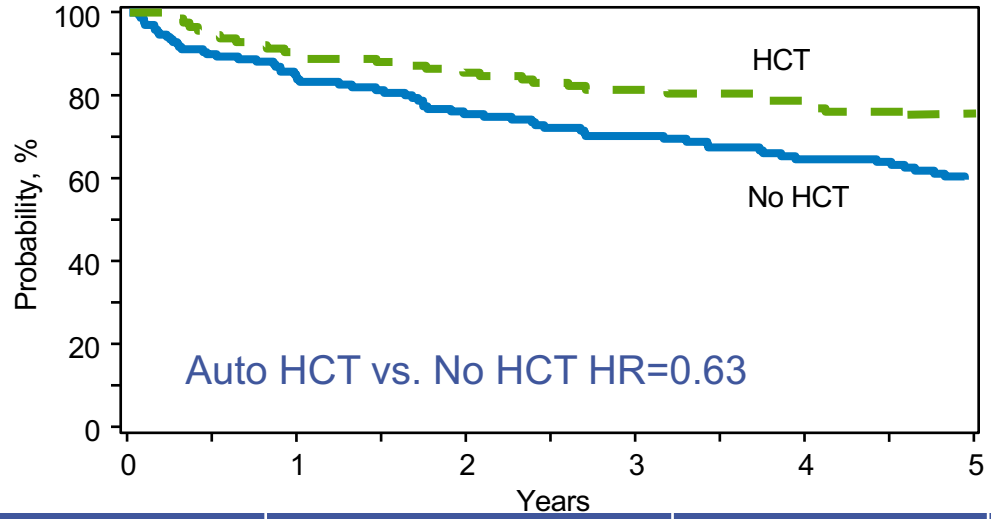
Non AHCT Cohort:

- FL in the **NLCS** with POD24
- No AHCT

Exclusion criteria

- Age >70 at time of diagnosis
- No watchful waiting, progression or transformation prior to therapy
- Death within 4 months of POD24

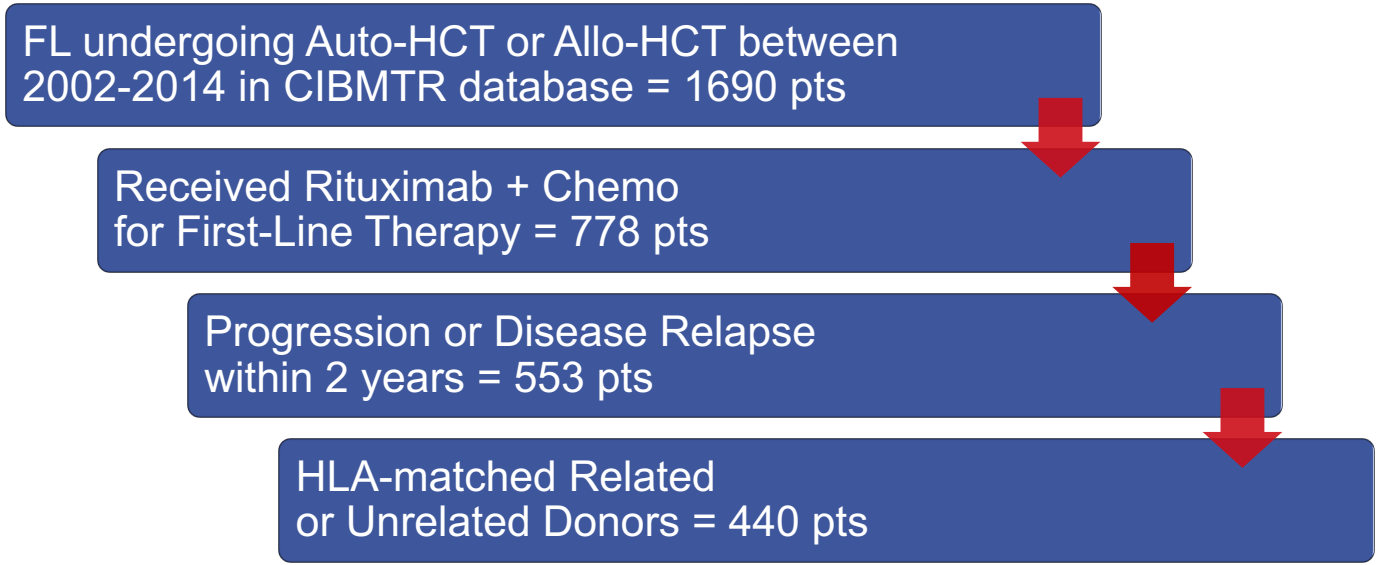
Autologous HCT Improves OS in POD24 Follicular Lymphoma



Early AHCT	Non-AHCT cohort	AHCT cohort	P-value
5-year OS	60%	73%	0.02

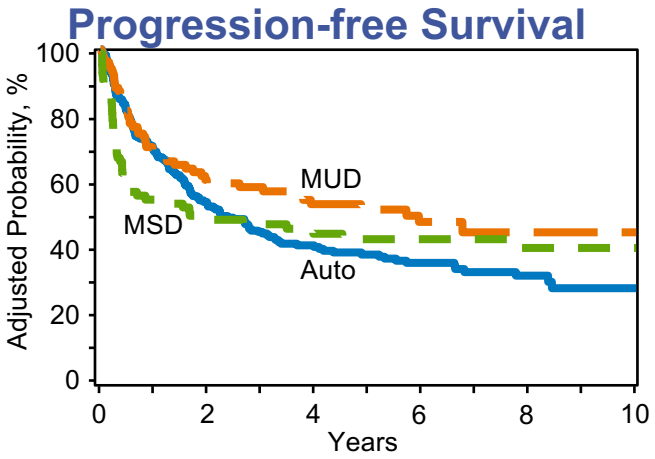
Casulo C. & Hamadani M. BBMT 2018;24:1163-71.

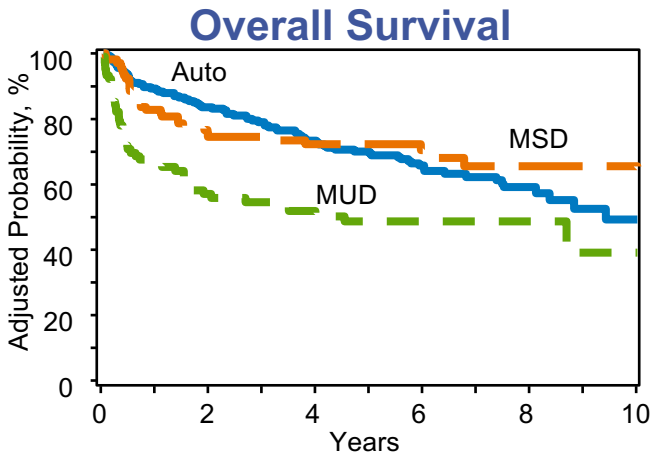
Autologous vs. Allogeneic HCT for POD24 Follicular Lymphoma?



Smith S. & Hamadani M. Cancer. 2018;124:2541-51

Autologous vs. Allogeneic HCT for POD24 Follicular Lymphoma?





	AutoHCT	MSD	MUD	Auto vs MSD	Auto vs MUD	MSD vs MUD
5-yr PFS	38 (32-45)%	52 (41-62)%	43 (32-54)%	p=0.03	p=0.47	p=0.24
5-yr OS	70 (64-76%)	73 (64-81)%	49 (39-60)%	p=0.60	p<0.0007	p<0.0005

Smith S. & Hamadani M. Cancer. 2018;124:2541-51

Clinical Case #2

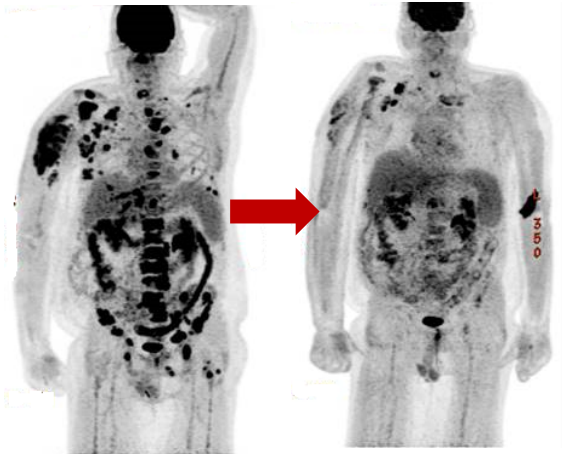
ANSWER

- 57-year-old female, with advanced stage follicular lymphoma (grade 3A), received first therapy with R-CHOP followed by rituximab maintenance. ~1.5 year after diagnosis patient relapsed (biopsy ruled out transformation). She achieved a CR with 2nd line treatment with bendamustine/obinutuzumab

1. CAR T-cell therapy
2. **Autologous transplant**
3. Watch & wait
4. Allogeneic transplant

Clinical Case #3

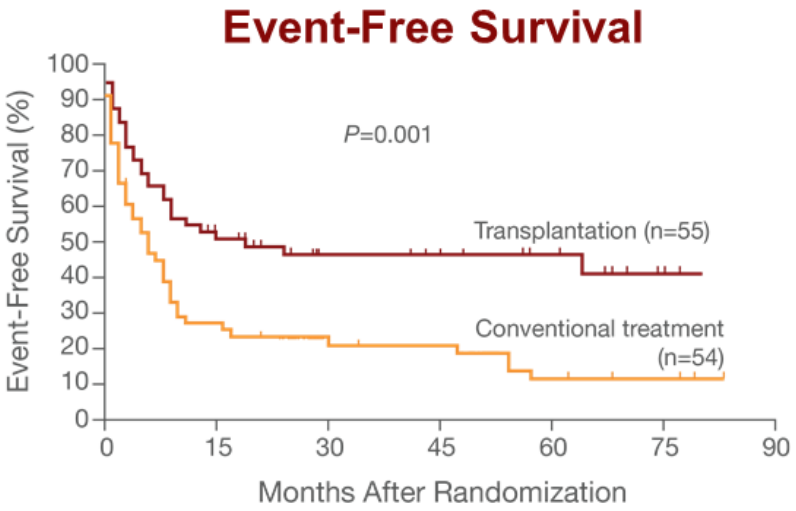
- 54-year-old DLBCL patient relapsed 2 years after achieving CR with R-CHOP treatment. Patient started salvage with R-ICE and obtained >50% reduction in tumor burden on PET/CT

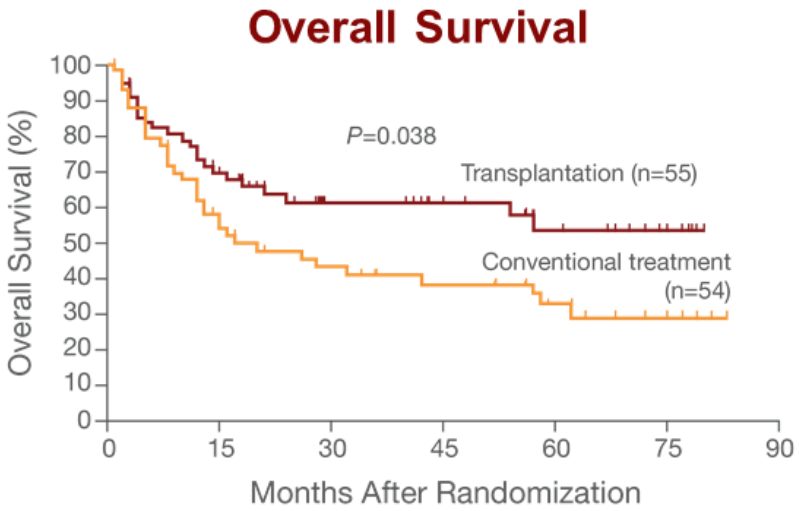


What would you do next?

1. CAR-T Cell Therapy
2. Autologous Transplant
3. Bendamustine/polatuzuamb
4. Allogeneic Transplant

Autologous HCT for relapsed DLBCL

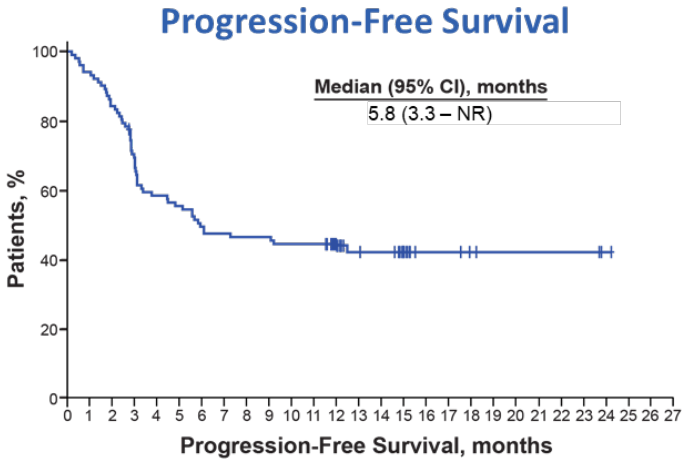




- In **relapsed** DLBCL, responding to salvage chemotherapy, autologous HCT remains standard-of-care

Philip & Chauvin. NEJM 1995;333:1540-1545.

What about CAR-T cell therapy?



Landmark	PFS
6-month	49
12-month	44
18-month	41

NR, not reached; OS, overall survival; PFS, progression-free survival.

Neelapu & Go. NEJM. 2017;377:2531-44.

- October 18, 2017: Axicabtagene ciloleucel was FDA approved for adults with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy

Durability Across CAR-T studies

Study	Lymphodepletion details	Dose	FDA Approval
Zuma-1 Axi-Cel	Flu/Cy 30/500 x 3 days	2 million /kg (max 2 x 10^8)	R/R DLBCL FL transforming to DLBCL PMLBCL
JULIET Tisa-Cel	Flu/Cy 25/250 x 3 days Or bendamustine x 2 days	0.6 – 6 x 10^8/kg	R/R DLBCL FL transforming to DLBCL
JCAR- 017 Liso-Cel	Flu/Cy 30/300 x 3 days	50-150 x 10^6	R/R DLBCL FL transforming to DLBCL PMLBCL FL grade 3B

Neelapu S. NEJM. 2017;377:2531-44. Schuster S. NEJM. 2019;380:45-56. Abramson J. Lancet. 2020;396:839-852.

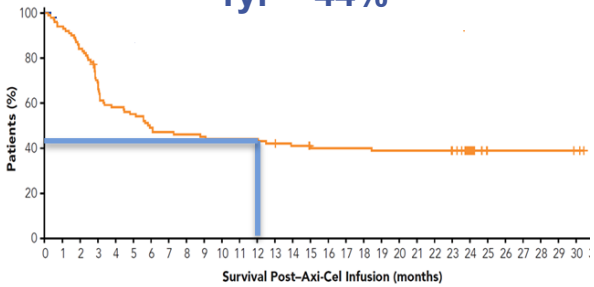
Durability Across CAR-T studies

Study	Number & lympho-depletion	Construct	ORR / CR	1-yr PFS	Grade 3-4 CRS/CRES
Zuma-1 Axi-Cel	111 (101) / Flu/CY / bridge not allow	Retrovirus / CD3ζ / CD28	82% / 54%	44%	13% / 28%
JULIET Tisa-Cel	165 (111) / various LD regimens / 92% bridged	Lentiviral / CD3ζ / 4-1BB	52% / 40%	~35%	22% / 12%
JCAR- 017 Liso-Cel	344 (269) / Flu/CY / 59% bridged	Lentiviral / CD3ζ / 4-1BB	73% / 53%	44%	2% / 10%

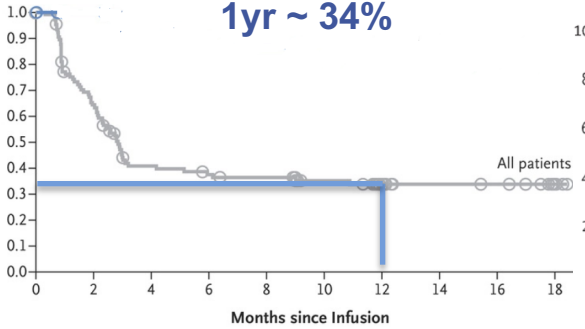
Neelapu S. NEJM. 2017;377:2531-44. Schuster S. NEJM. 2019;380:45-56. Abramson J. Lancet. 2020;396:839-852.

CAR T Options: Can Efficacy Inform a Winner?

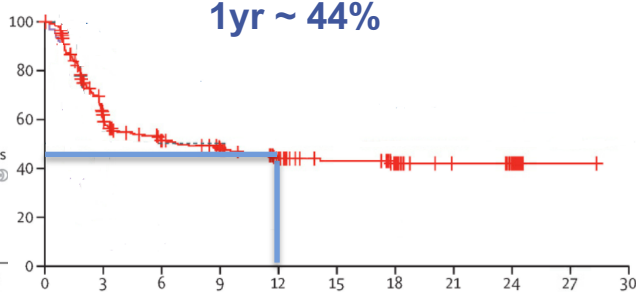
Axi-cel
1yr = 44%



Tisa-cel
1yr ~ 34%

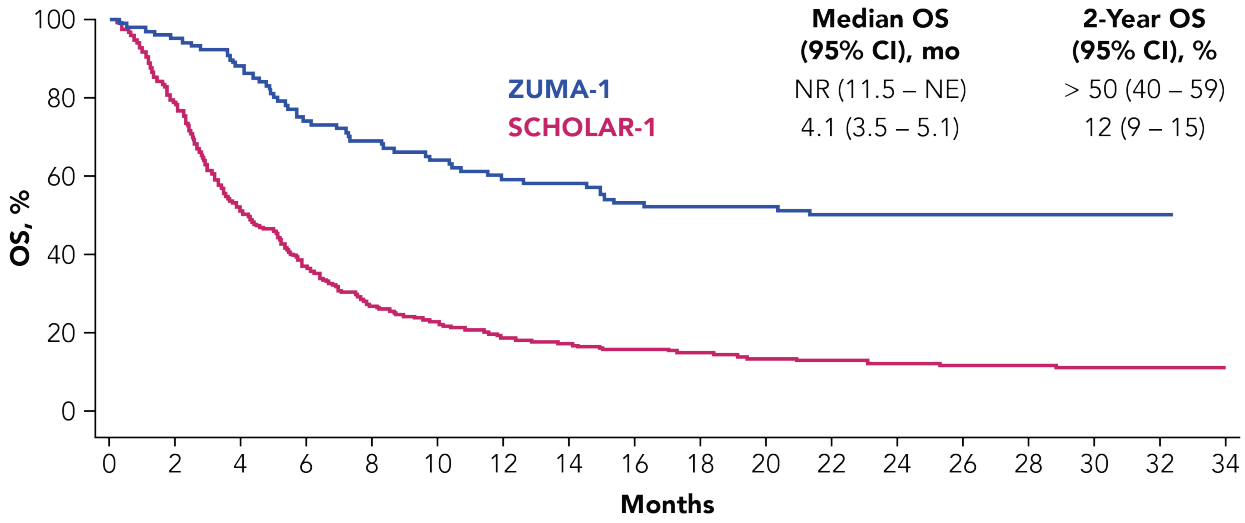


Liso-cel
1yr ~ 44%



Neelapu S. NEJM. 2017;377:2531-44.
Schuster S. NEJM. 2019;380:45-56.
Abramson J. Lancet. 2020;396:839-852.

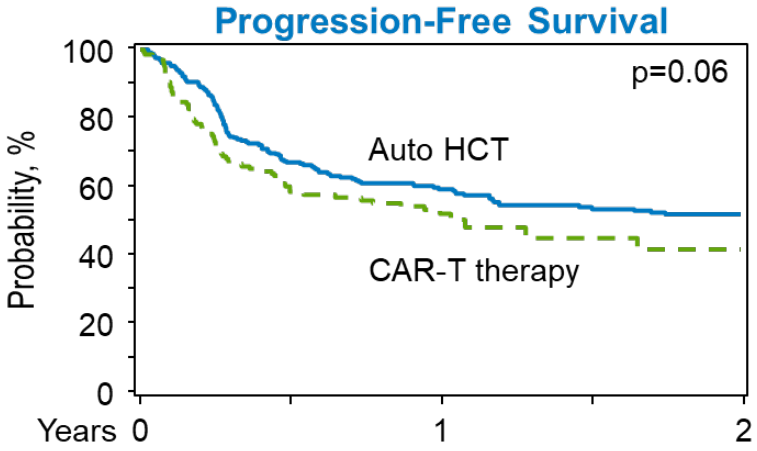
Simulation-Based Standardized OS Curves for ZUMA-1 and SCHOLAR-1

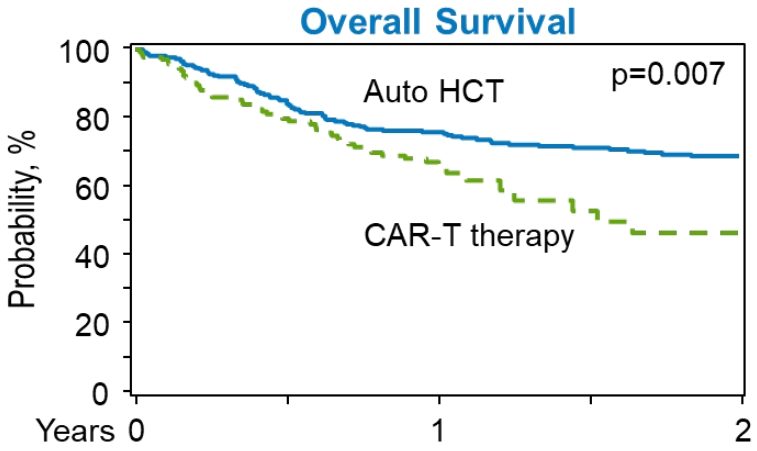


- A stratified Cox proportional hazards model indicated a 73% reduction in the risk of death in ZUMA-1 relative to SCHOLAR-1 (hazard ratio, 0.27, 95%CI 0.2-0.38; *P* < .0001)

Neelapu, Locke, et al, ASH 2019

Autologous HCT vs. CAR T-cell Therapy for DLBCL Patients in a PR following Salvage?



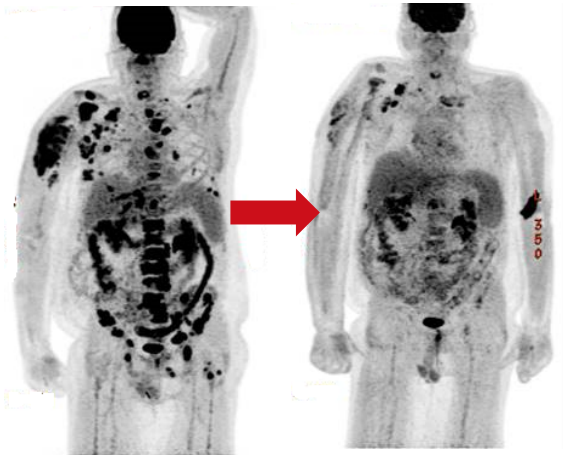


Shadman & Hamadani. Manuscript Submitted

Clinical Case #3

ANSWER

- 54-year-old DLBCL patient relapsed 2 years after achieving CR with R-CHOP treatment. Patient started salvage with R-ICE and obtained >50% reduction in tumor burden on PET/CT



1. **CAR-T Cell Therapy**
2. **Autologous Transplant**
3. Bendamustine/polatuzuamb
4. Allogeneic Transplant

Thank you for your kind attention!

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@MediHumdani

Thank You!

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Hodgkin's Lymphoma
Presented by Ann LaCasce, MD