VCC

VIRTUAL Challenging Case Clinic

B-Cell Lymphomas SERIES

CAR T-cell Therapy

June 8, 2022

University of Nebraska Medical Center

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Continuing Education

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Disclosures

John Leonard, MD

Consulting Fees: AbbVie, Astellas, Beigene, Calithera, Celgene/BMS, Constellation, Eisai, Epizyme, Genmab, Grail, Incyte, Janssen, Karyopharm, Lilly, Merck, Mustang Bio, Pfizer, Roche/Genentech, Second Genome, Sutro

Mehdi Hamadani, MD

Research Support/Funding: Takeda Pharmaceutical Company, Sanofi, Spectrum Pharmaceuticals
Consulting Fees: Janssen, Incyte, ADC Therapeutics, Omeros, Kite/Gilead, Novartis, Genmab, Seattle Genetics, Kadmon
Speaker's Bureau: Sanofi Genzyme, AstraZeneca, BeiGene, ADC Therapeutics

Planning Committee

The following planning committee members have nothing to disclose:
UNMC: Brenda Ram, CMP, CHCP
Bio Ascend: Patti Bunyasaranand, MS; Jessica Davis; Tisheeka Graham-Steed, PhD; Kraig Steubing

Learning Objectives

- ✓ Evaluate best available evidence regarding the treatment of indolent and aggressive subtypes of B-cell lymphoma
- ✓ Assess the implications of emerging clinical trial data regarding B-cell lymphoma therapeutic approaches
- ✓ Develop strategies to optimize the outcomes of complicated B-cell lymphoma cases

Reminders!

- ✓ Visit www.OncologyCaseClinic.com to register for upcoming webinars

Virtual Challenging Case Clinic: CAR T-cell Therapy

Mehdi Hamadani, M.D.

Professor of Medicine

Medical College of Wisconsin

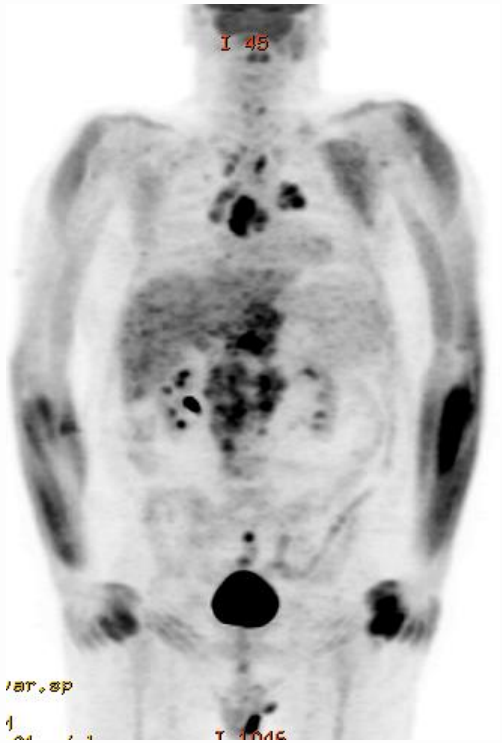
June 8th, 2022

@MediHumdani

Clinical Case #1(A)

- 70-year-old patient with PMH of HTN & CAD was diagnosed with stage IV DLBCL. Baseline EF 52%. Received R-CHOP x 6. EOT PET/CT shown below. Biopsy confirmed primary refractory disease. Repeat EF 49%

  - Salvage treatment ± auto transplant
  - CAR T-cell therapy
  - Bendamustine/polatuzumab/R
  - Tafa/lenalidomide



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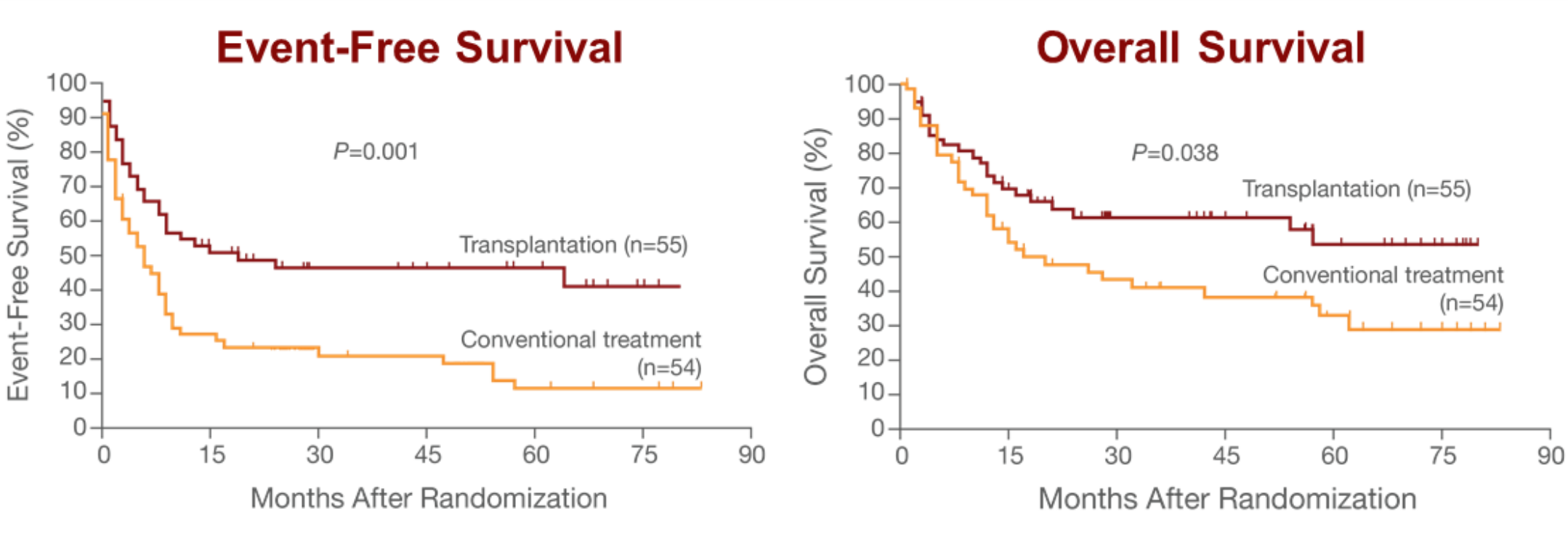
Autologous HCT for Relapsed but "Responding" DLBCL



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

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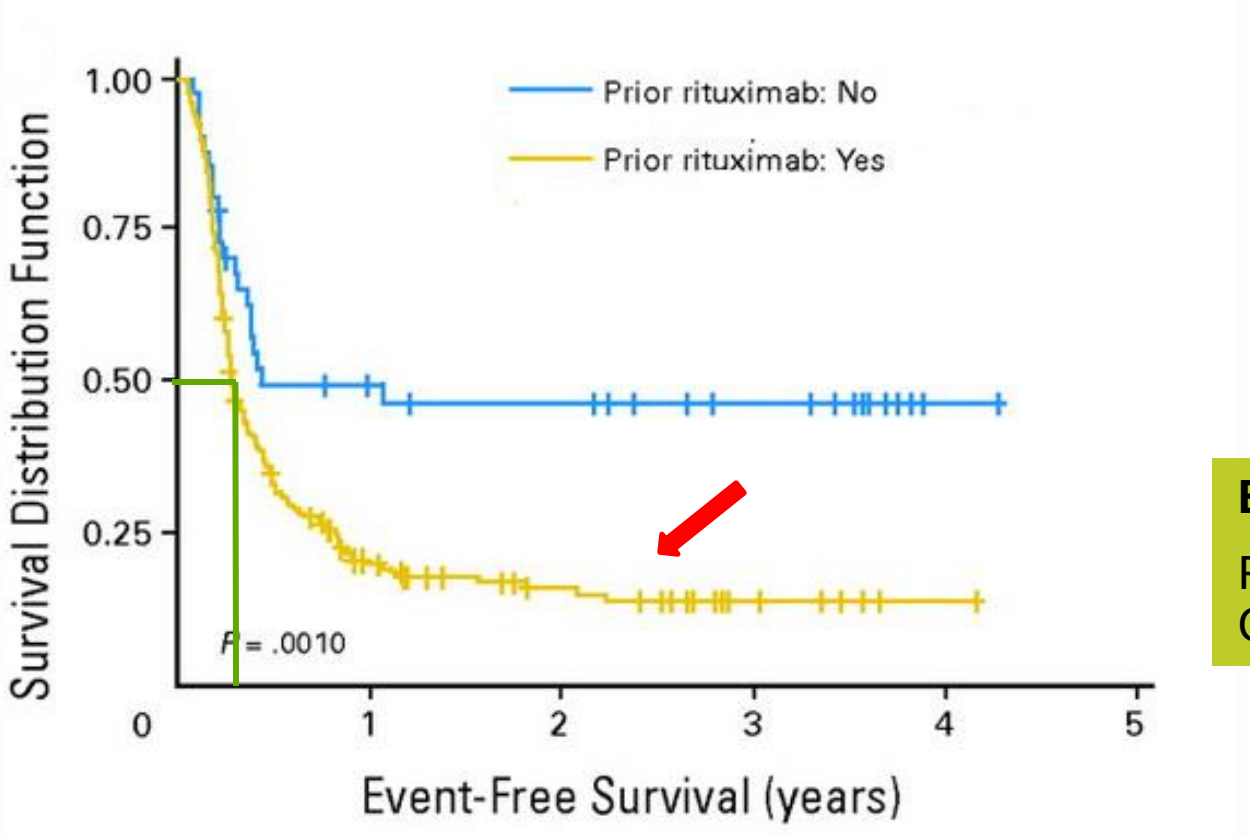
Philip & Chauvin. NEJM 1995;333:1540-1545.

Early Relapse Is BAD: DLBCL Is No Exception

Relapse within 1 year of "initial diagnosis"



Early Relapse

R + Chemotherapy
ORR = 46%

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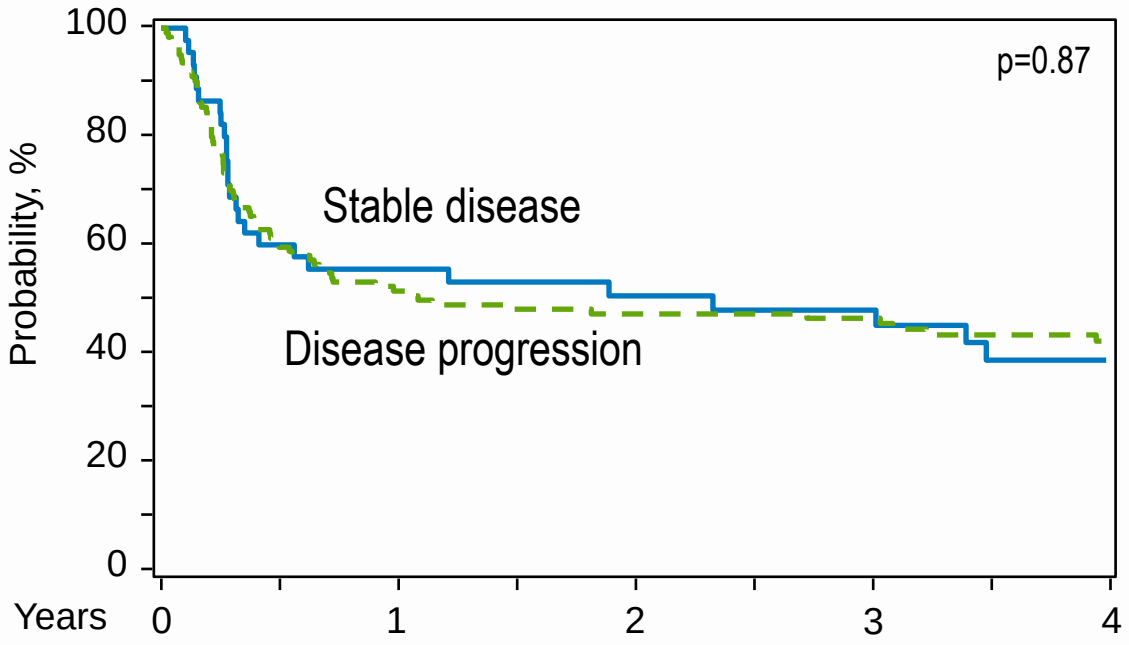
Gisselbrecht C & Schmitz N. JCO. 2010;28:4184-90.

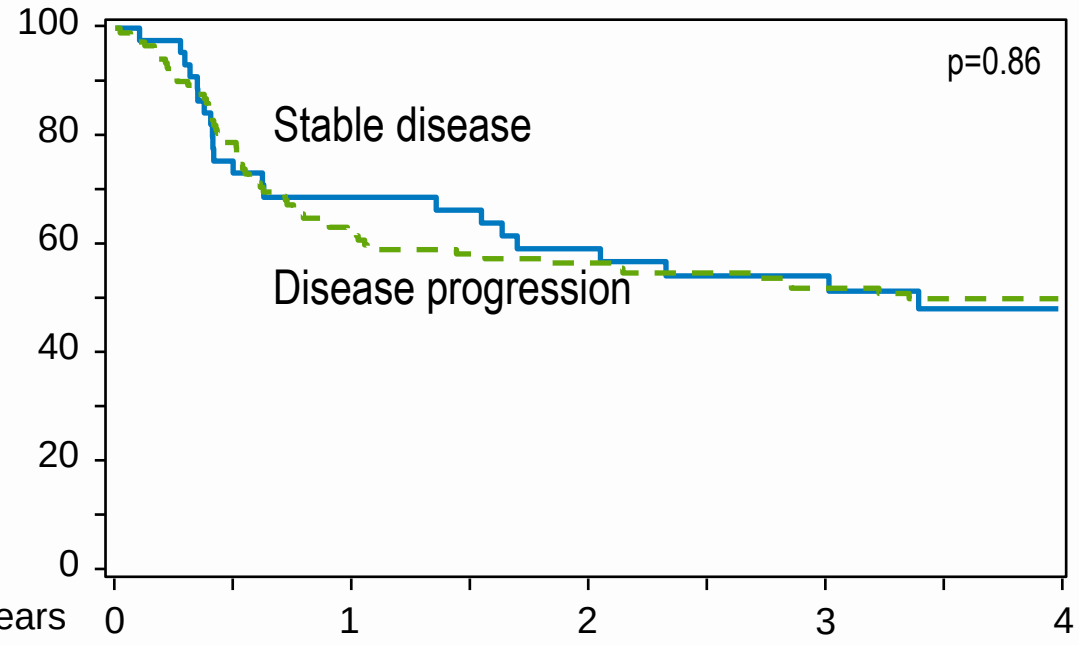
Are All SD or PD After R-CHOP Doomed?

Progression-Free Survival Mortality in SD and PD Cohort



# at Risk					
Stable Disease	45	24	22	18	12
Disease Prog.	124	64	55	51	37

Overall Survival Mortality in SD and PD Cohort



# at Risk					
Stable Disease	45	30	26	20	14
Disease Prog.	124	77	66	58	44

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Bal S. & Hamadani M. Transplant Cell Ther. 2021;27:55.e1.

CIBMTR Data Is, of Course, an Illusion Due to "Patient Selection"

- SCHOLAR-1 patient level data of refractory DLBCL
  - ORR of 26% (CR of 7%, PR of 19%)
  - Median OS of 6.6 months

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Crump & Gisselbrecht. Blood. 2017;130(16):1800-1808.

How Do We Improve Outcomes of High-Risk Patients in 2nd Line?

- Improved Salvage (CORAL, NCIC LY.12, ORCHHARD) 
- Improve autologous HCT (Radioimmunotherapy, R + HDT) 
- Replace 2nd Line with Novel Cell Therapies 

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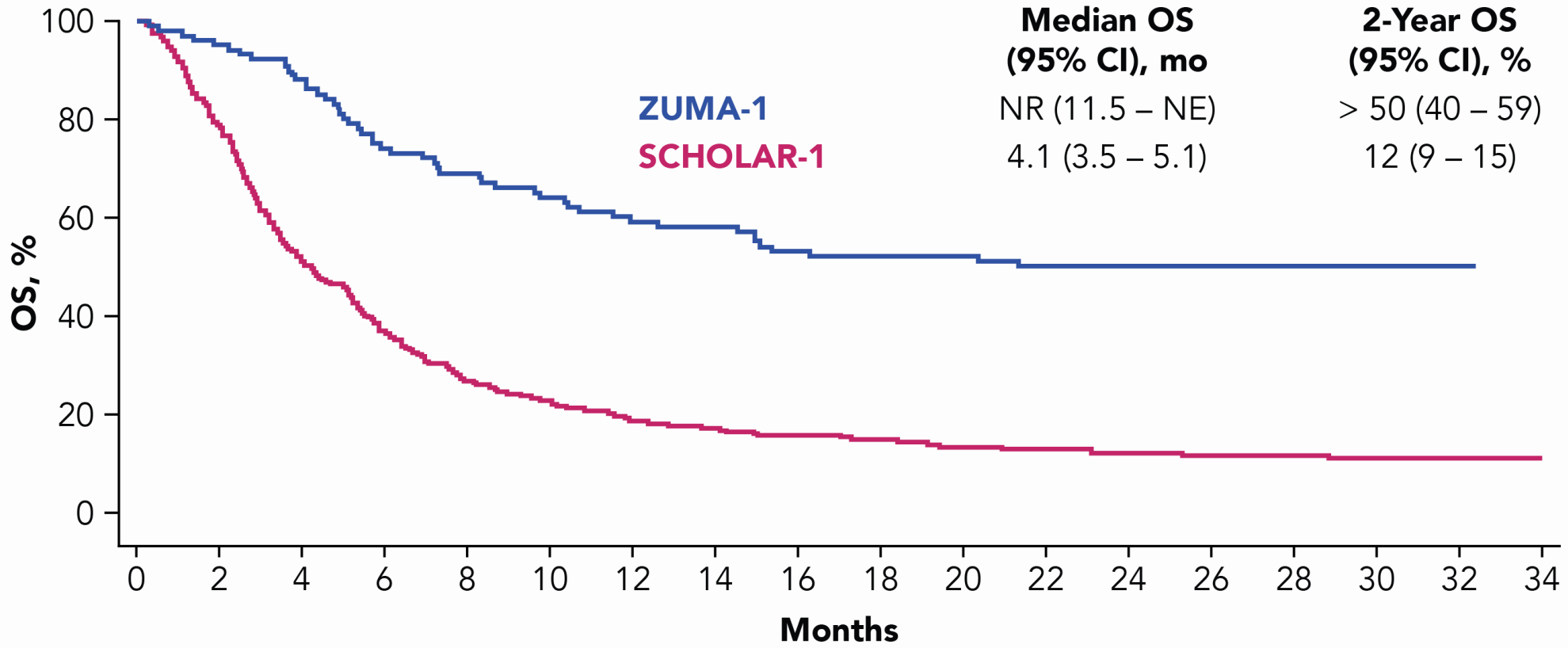
Simulation-Based Standardized OS Curves for ZUMA-1 and SCHOLAR-1



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)

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Neelapu, Locke, et al, ASH 2019

2nd Line CAR-T vs. Chemoimmunotherapy Trials (ZUMA-7; TRANSFORM; BELINDA)

Key eligibility
- Age 18+ years (capped at 75?)
- Aggressive NHL
- Refractory or **relapsed ≤ 12 months after finishing 1L treatment**
- ECOG PS ≤ 1
- Eligible for HCT
- Secondary CNS lymphoma allowed (Transform)
- Good organ function

Screening + leukapheresis

1:1 Randomization

Bridging therapy varied

CAR T cell arm (dose varied)

Stratification
- Refractory vs relapsed
- sAAIPI or IPI
- Region (BELINDA)

Standard Arm
salvage therapy (Belinda allowed 2nd salvage),
followed by HDT + autoHCT

Crossover specified?
- Liso-cel trial
- Tisa-cel trial

Initial Response assessments varied:
- Weeks 9 and 18 (Transform)
- Days 50 & 100 (ZUMA)
- Week 6 and 12 (Belinda)

Primary Endpoint EFS (definitions varied)

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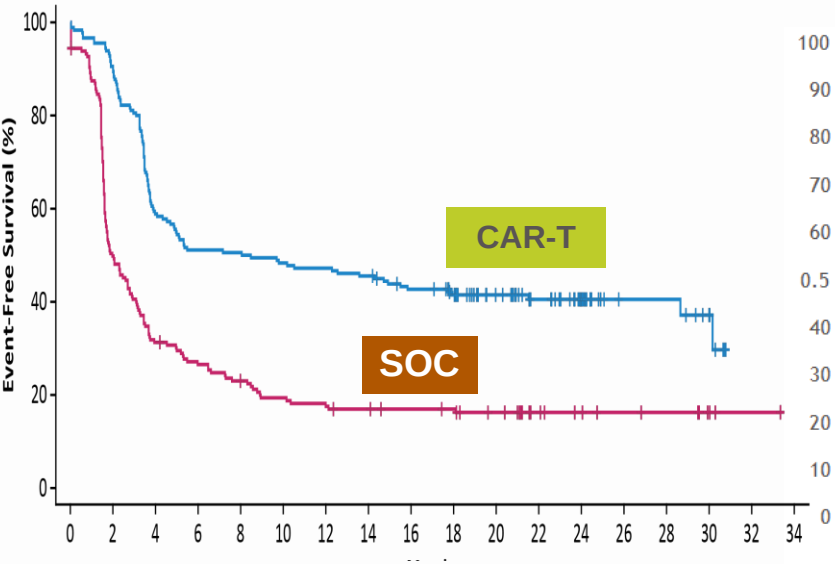
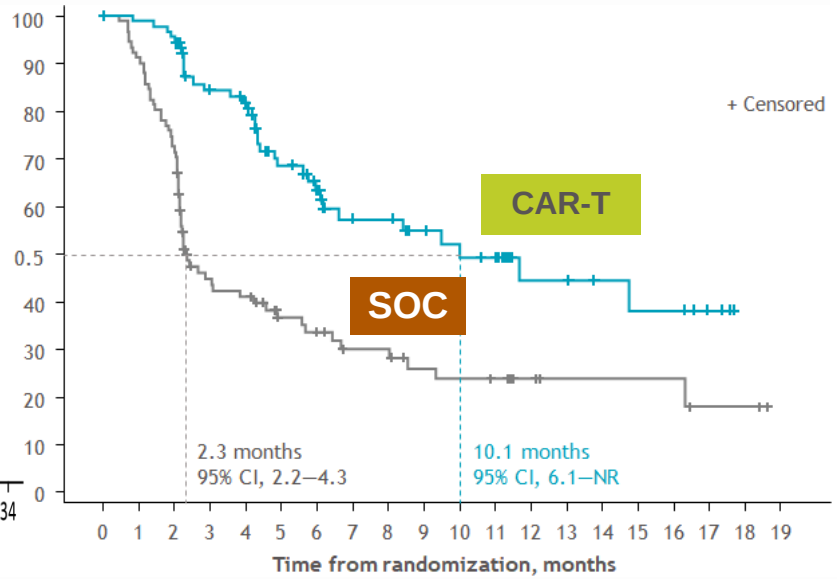
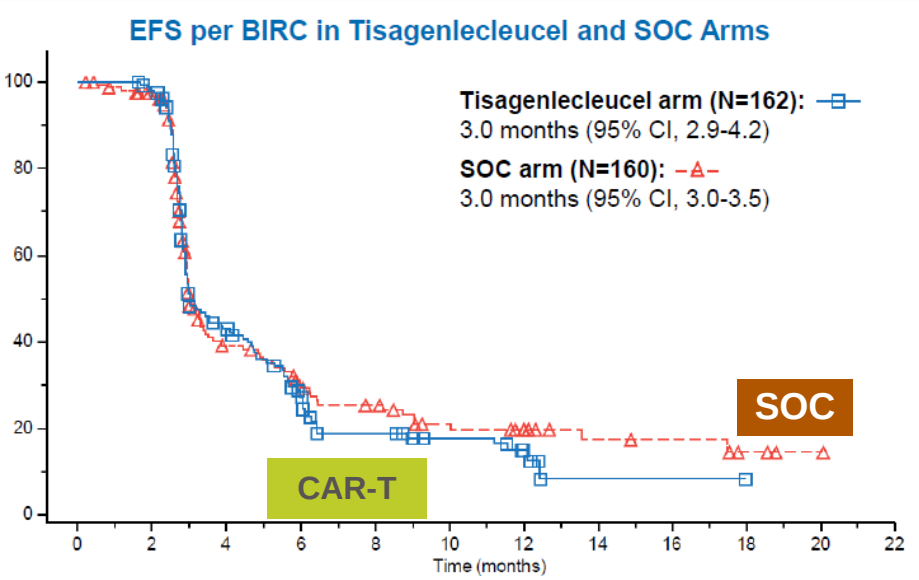
Locke & Westin. NEJM. 2022;386:640-654
Bishop & Westin. NEJM. 2022;386:629-639
Kamdar & Abramson. ASH 2021, abs #91

EFS: ZUMA-7 vs. TRANSFORM vs. BELINDA

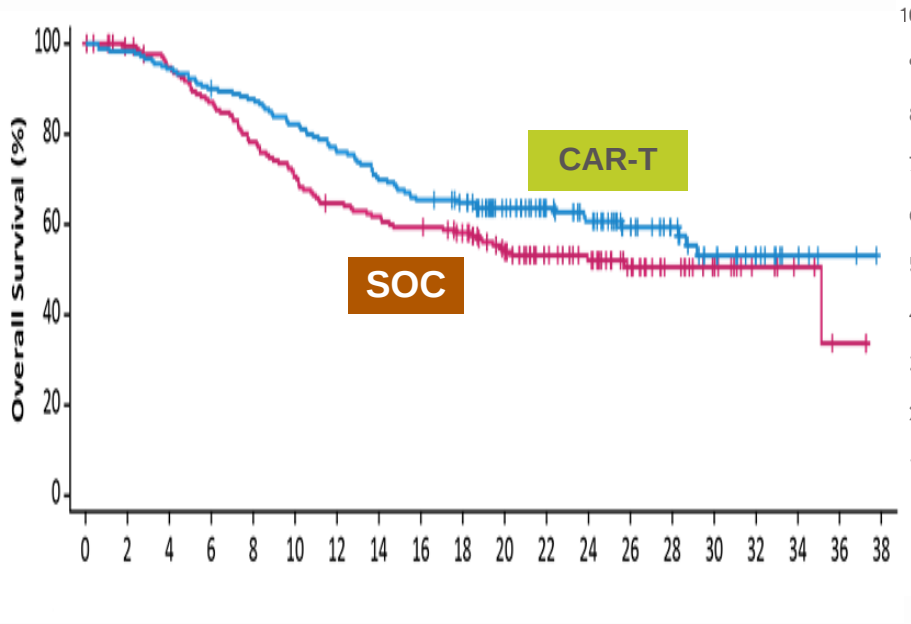


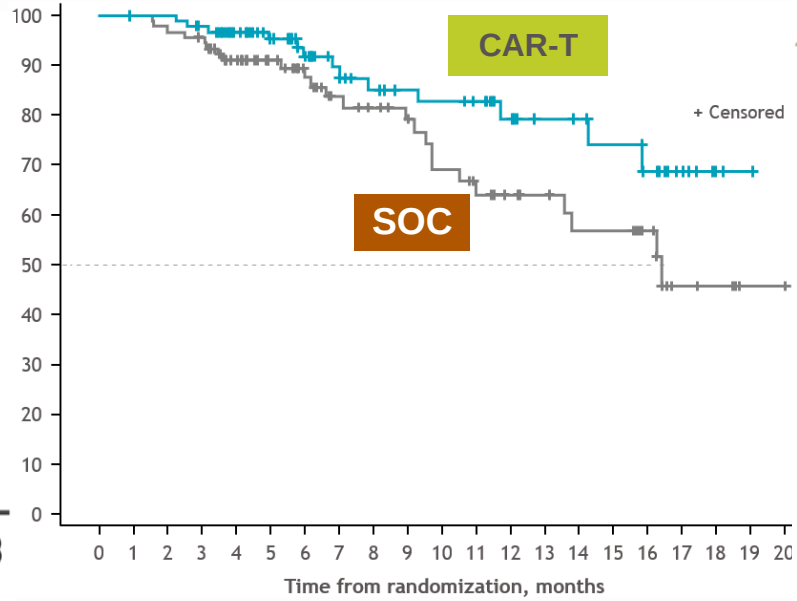


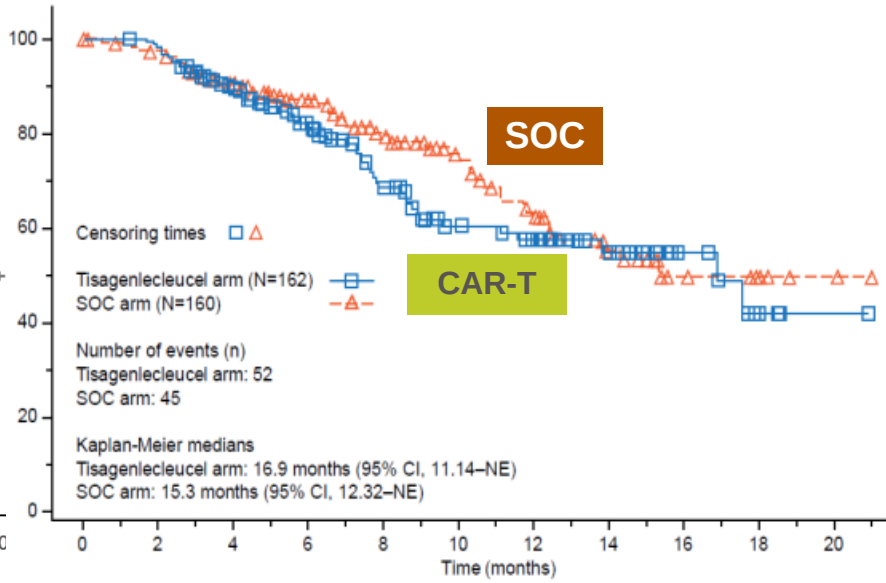


ZUMA-7	TRANSFORM	BELINDA
Median EFS = 8.3 vs. 2 mo	Median EFS = 10.1 vs. 2.3 mo	Median EFS = 3 vs. 3 mo
1. Progression or death 2. New treatment 3. No CR/PR by 150 days	1. Progression or death 2. New treatment 3. No CR/PR by 9 wks	1. Progression or death 2. SD/PD @/after 12 wks

OS: ZUMA-7 vs. TRANSFORM vs. BELINDA

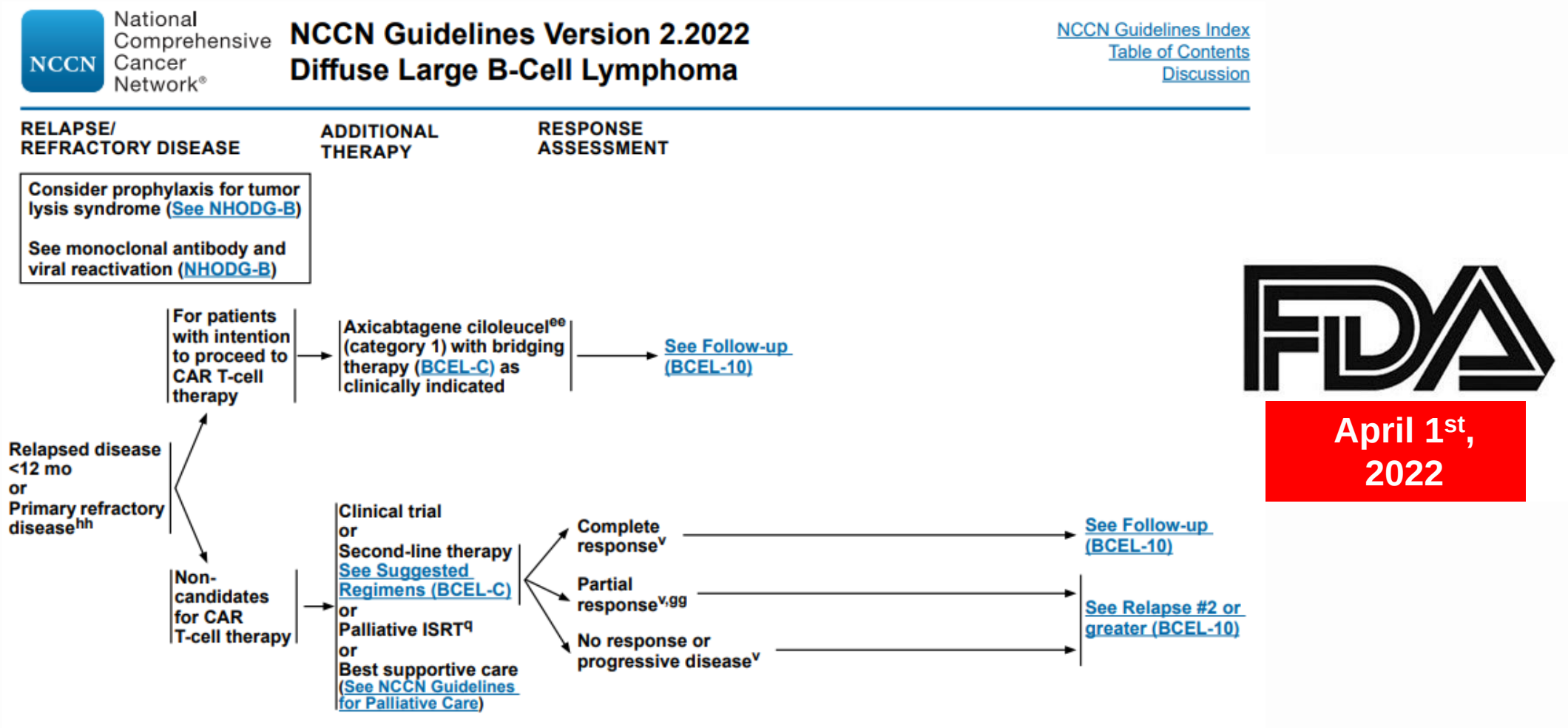






ZUMA-7	TRANSFORM	BELINDA
Not Reached vs. 35.1 mo	Not Reached vs 16.4 mo	19.9 mons vs. 15.3 mo

How to Apply These Results to Practice?



April 1st, 2022

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Clinical Case #1(A) [Is patient CAR eligible?]

- 70-yr-old patient with PMH of HTN & CAD was diagnosed with stage IV DLBCL. Baseline EF 52%. Received R-CHOP x 6. EOT PET/CT shown below. Biopsy confirmed primary refractory disease. Repeat EF 49%

  - Salvage treatment ± auto transplant
  - CAR T-cell Therapy
  - Bendamustine/polatuzumab/R
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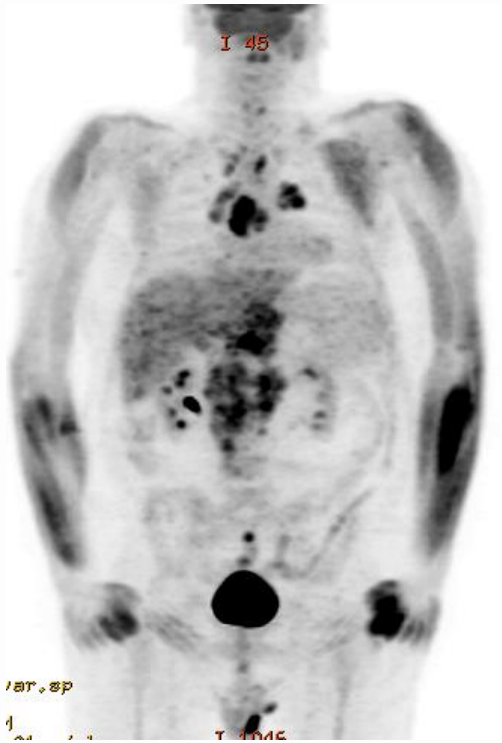

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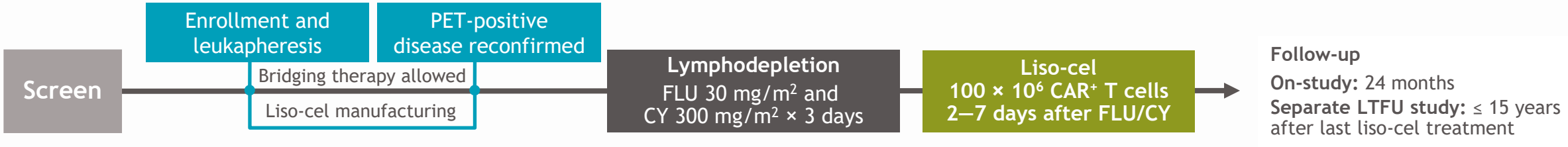
PILOT study design



Patient eligibility

- Age ≥ 18 years
- LBCL: DLBCL NOS (de novo; transformed from FL), HGBCL with (double/triple hit), or FL3B
- One prior line of therapy containing an anthracycline and a CD20-targeted agent
- Not intended for HSCT by investigator and met ≥ 1 of the following criteria: age ≥ 70 years, ECOG PS of 2, DLCO ≤ 60%, LVEF < 50%, CrCl < 60 mL/min (calculated using Cockcroft-Gault), and/or AST/ALT > 2 × ULN

Endpoints

- **Primary**
  - Overall response rate (ORR) by independent review committee (IRC) per Lugano 2014 criteria
- **Main secondary**
  - Adverse events (AE) and laboratory abnormalities
  - Complete response (CR) rate by IRC
  - Duration of response (DOR)
  - Progression-free survival (PFS)
  - Event-free survival (EFS)
  - Overall survival (OS)

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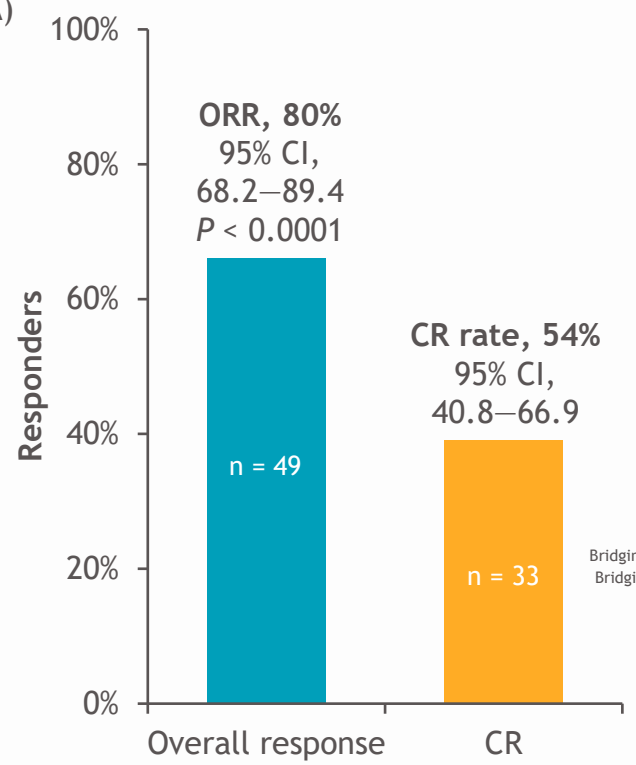
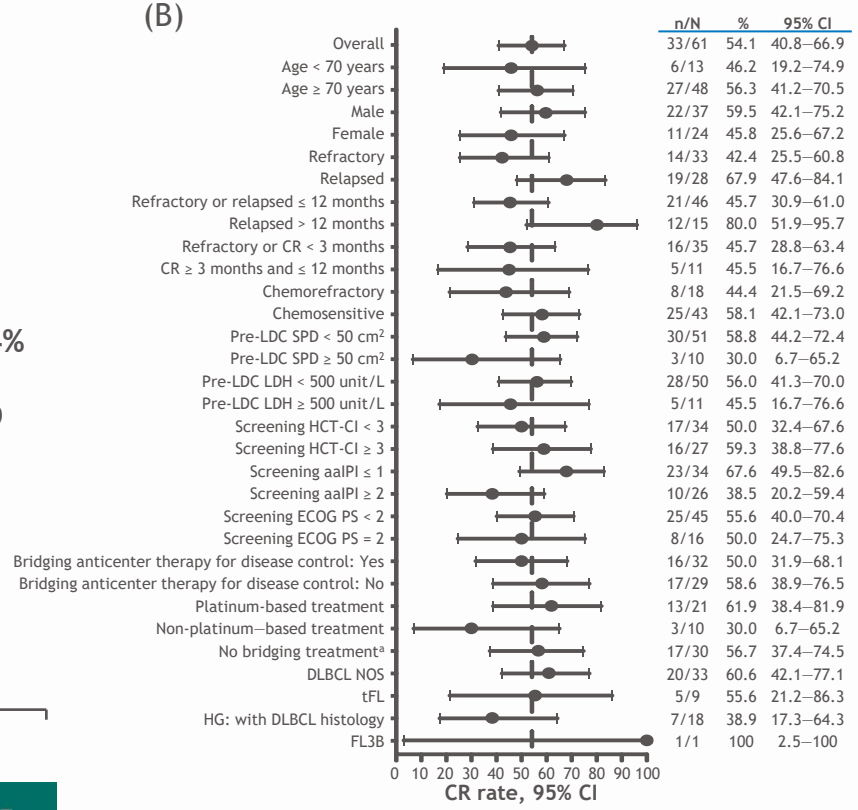
Efficacy Outcomes

- The primary endpoint of ORR was 80%
- Responses were durable in patients with CR (median, 21.7 months; 95% CI, 12.1—NR)

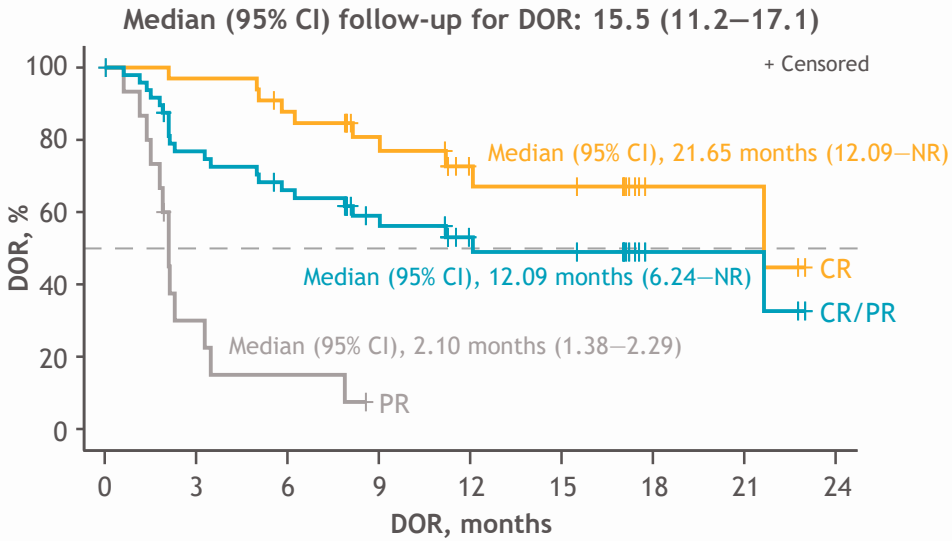
(A)



(B)



(C)



No. at risk (censored)

CR 33 (0)	32 (0)	28 (1)	21 (5)	13 (6)	12 (0)	3 (9)	3 (0)	0 (2)
PR 16 (0)	4 (2)	2 (0)	0 (1)					
CR/PR 49 (0)	36 (2)	30 (1)	21 (6)	13 (6)	12 (0)	3 (9)	3 (0)	0 (2)

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Clinical Case #1(A)……Answer

- 70-year-old patient with PMH of HTN & CAD was diagnosed with stage IV DLBCL. Baseline EF 52%. Received R-CHOP x 6. EOT PET/CT shown below. Biopsy confirmed primary refractory disease. Repeat EF 49%

  - Salvage treatment ± auto transplant
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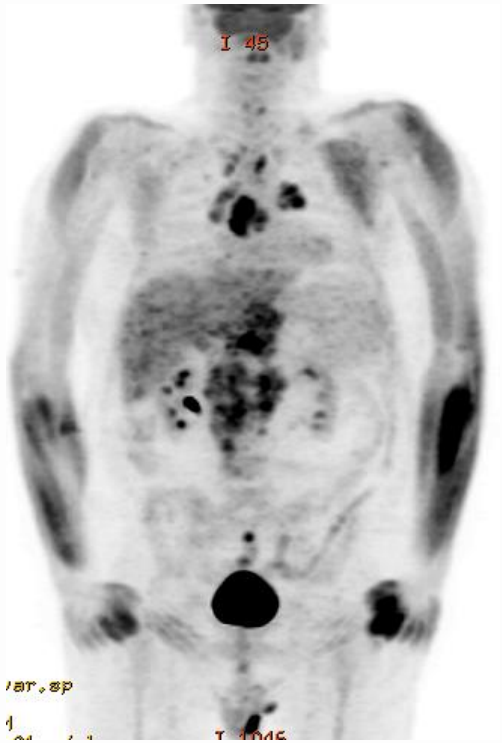
  - Loncastuximab tesirine



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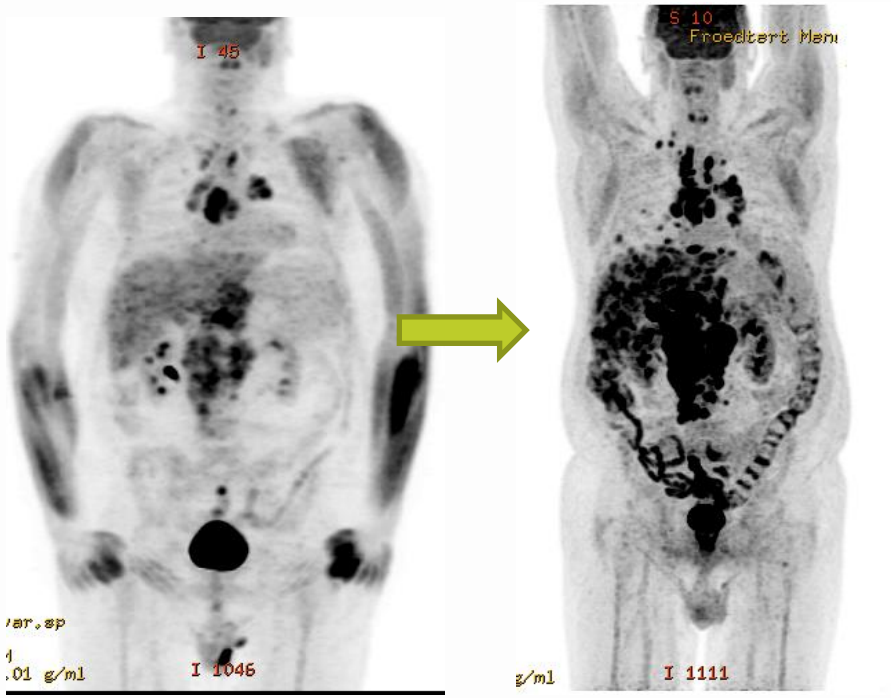
Clinical Case #1(B)

- The patient in case 1(A), underwent CD19 directed CAR-T cell therapy. A PET/CT scan performed ~30 days post CAR treatment is shown below. What is next best step ± treatment option? [*Select all that apply*]
  - Repeat PET/CT in 1-2 months
  - Biopsy to assess CD19 expression
  - polatuzumab ± BR
  - Tafa/lenalidomide
  - Loncastuximab tesirine
  - Clinical trial



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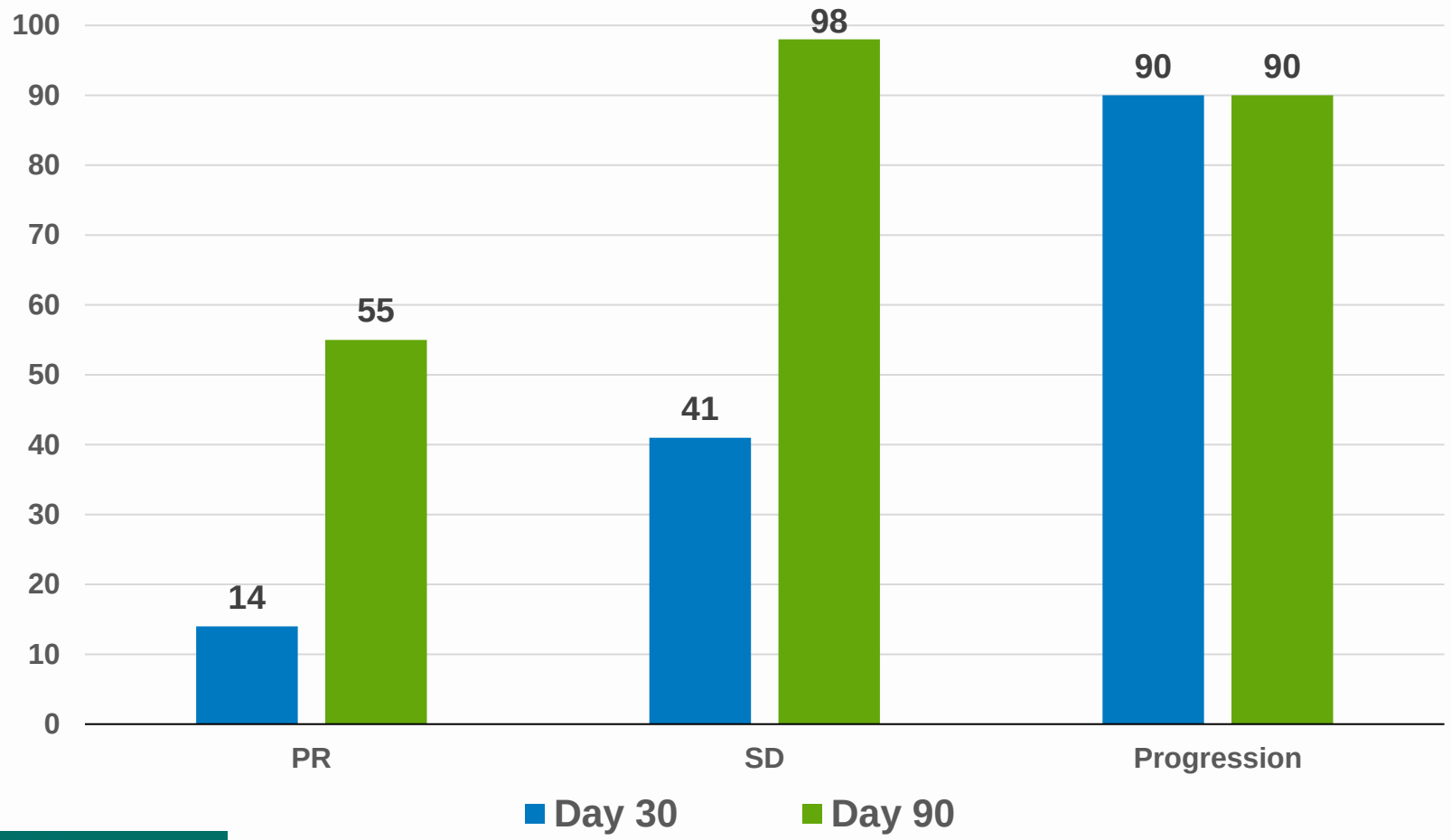
When Do Cell Therapists Consider CAR-T Failure? *ASTCT Physician Survey*



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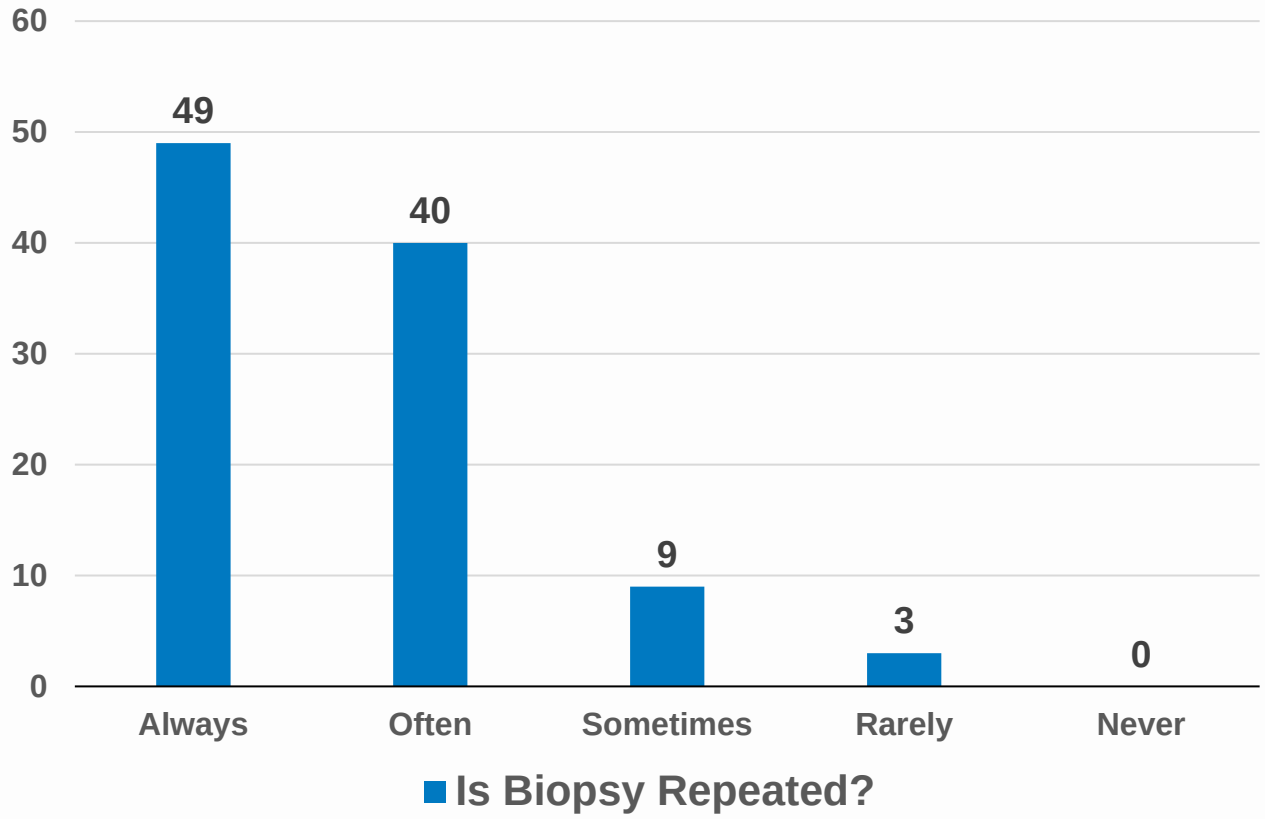
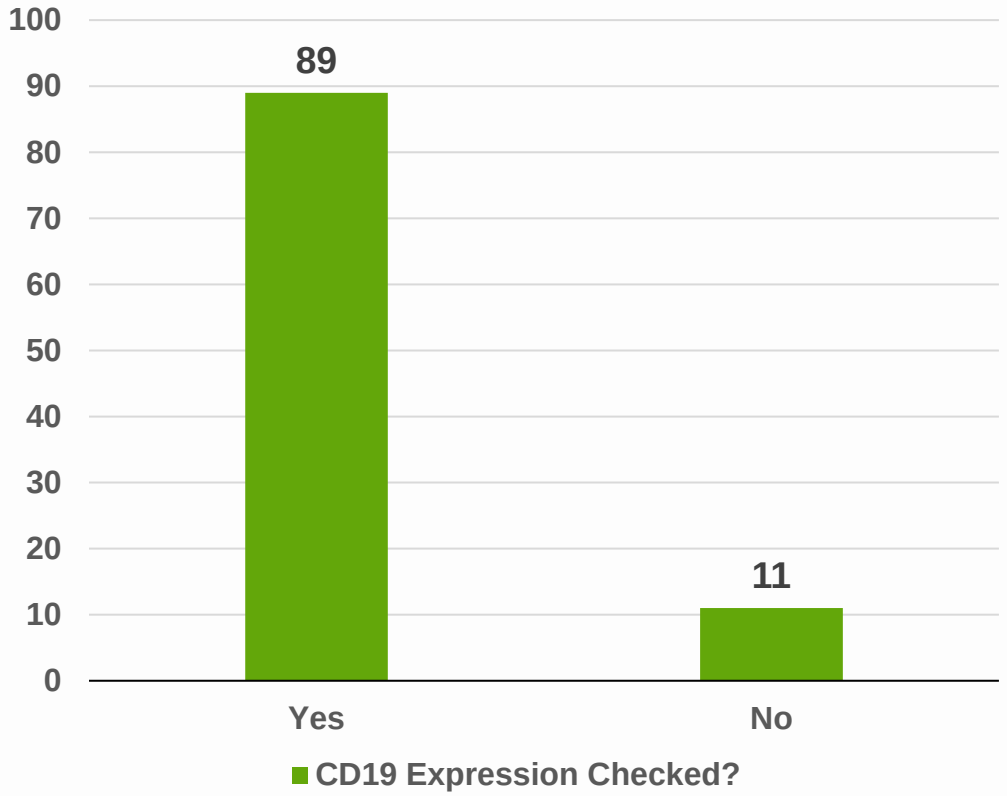
Ahmed & Hamadani: ASTCT CoPG Manuscript Submitted

Do Centers Confirm Relapse With Biopsy and Assess CD19 Expression? *ASTCT Survey*





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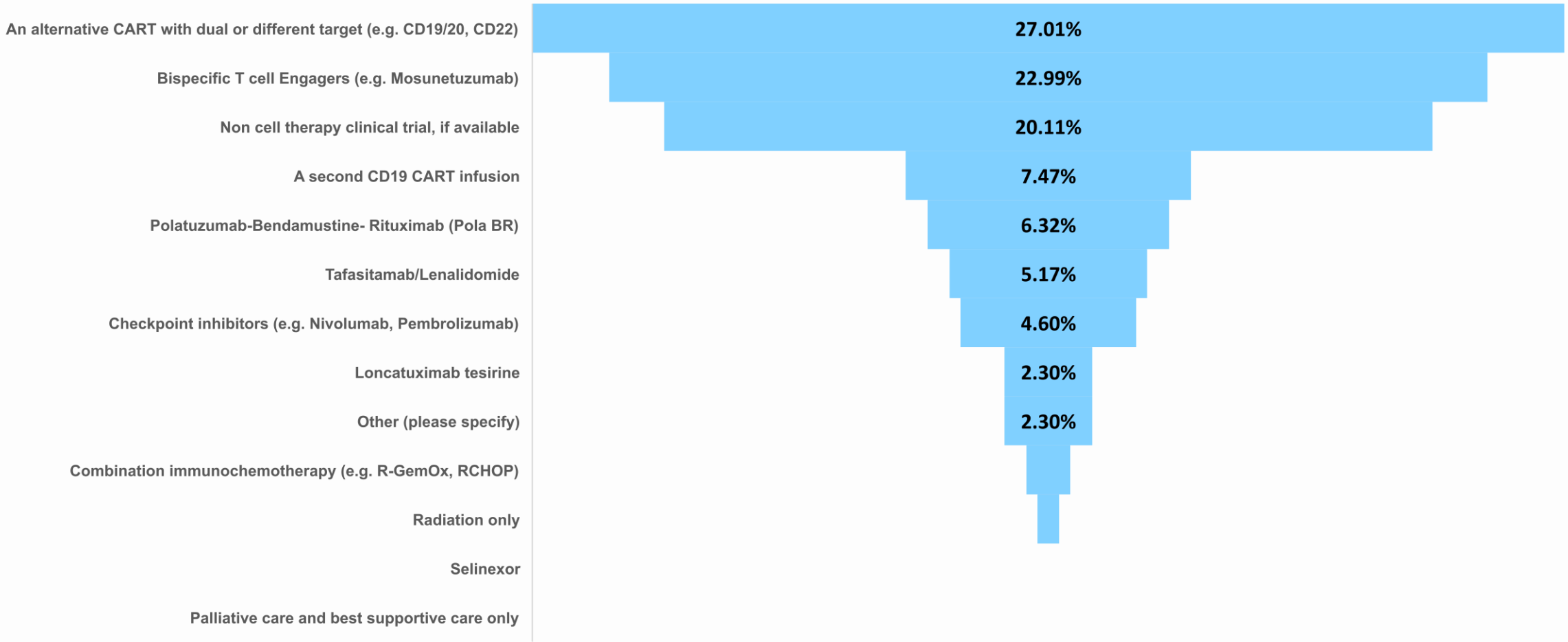
Ahmed & Hamadani: ASTCT CoPG Manuscript Submitted

First Choice for Failure Post CD19 CAR-T & CD19+ disease? *ASTCT Survey*



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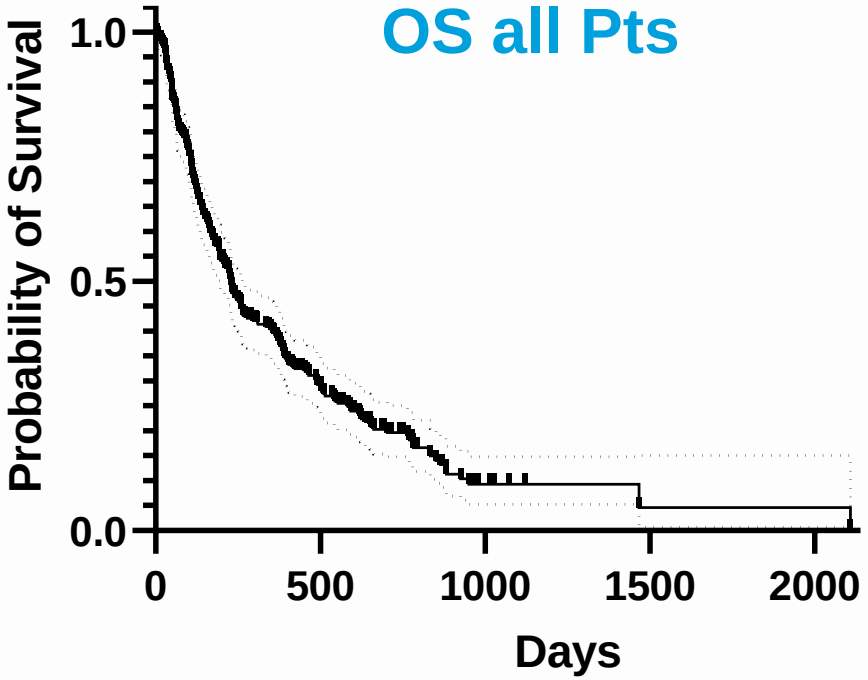
Ahmed & Hamadani: ASTCT CoPG Manuscript Submitted

US Retrospective Analysis of Patients Failing CAR-T Therapy, n=284

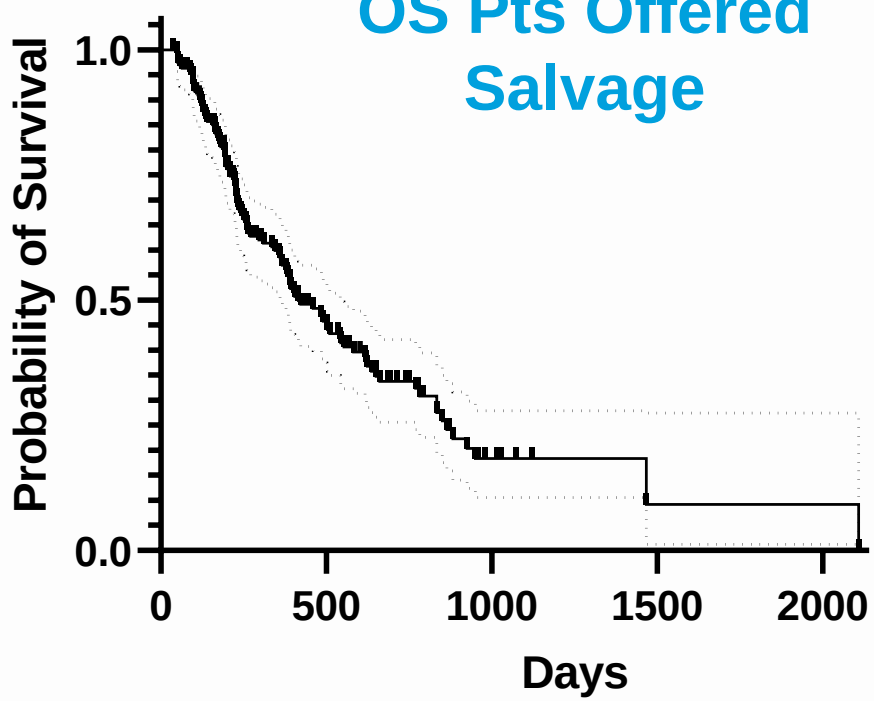
- From time of progression post-CAR-T
  - Median OS all pts with PD: **7.5 mo**
  - Median OS pts who received salvage: **13.6 mo**

*Median f/u surviving pts: **15.9 mo** (range: 2.6-36.9)

OS all Pts



OS Pts Offered Salvage



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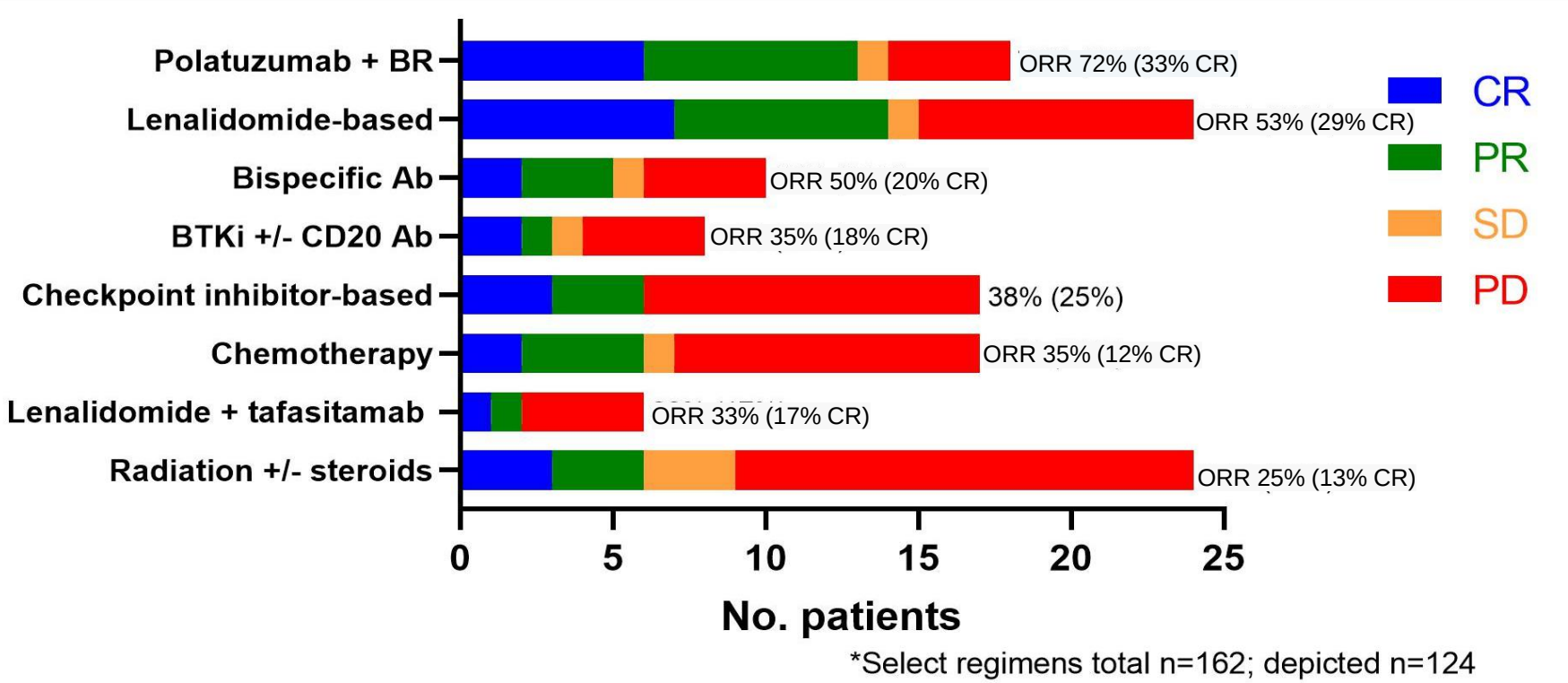
Zurko & Karmali. ASH 2021 Oral Abs.

Results: ORR of 1st-line Salvage Regimens, (n=165)

- 165 pts (**57%**) received further therapies after failure of CAR-T (162 pts evaluable for response)



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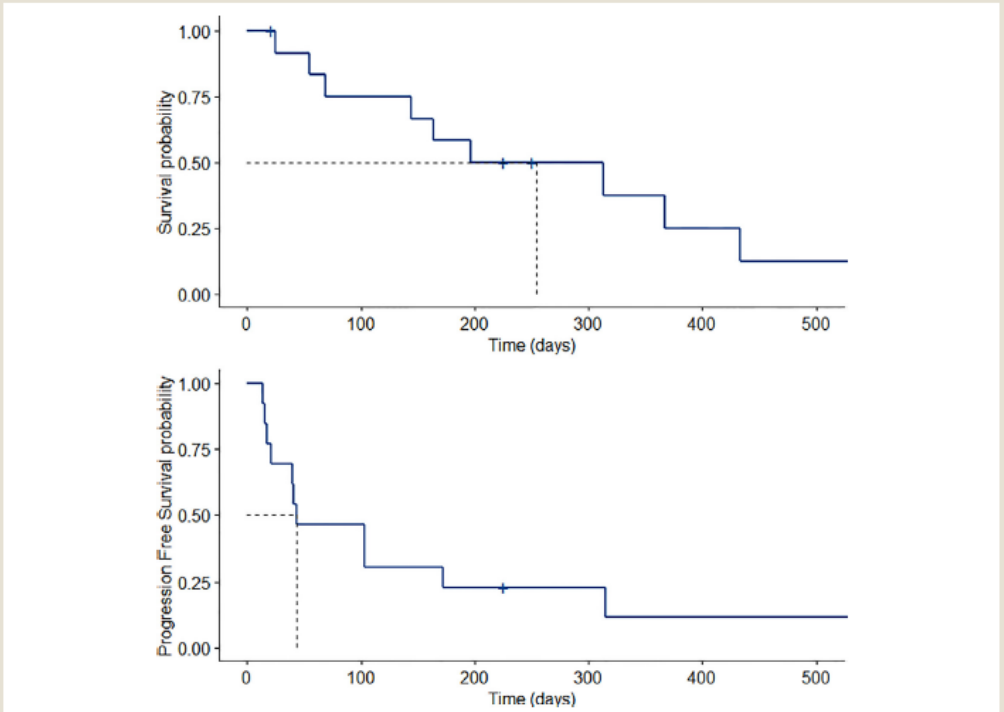
Zurko & Karmali. ASH 2021 Oral Abs.

Can a CD19-Directed Agent Work After Anti-CD19 CAR-T?

Figure 1 (A) Kaplan Meier estimate of overall survival of patients treated with loncastuximab tesirine after CAR-T cell therapy. (B) Kaplan Meier estimate of progression free survival of patients treated with loncastuximab tesirine after CAR-T cell therapy.



Lonca After CAR T-Cell Therapy Relapse[2]

		n=13
Best response to CAR T-cell therapy, n (%)	CR	7 (54)
	PR	2 (15)
	No response	4 (31)
Best response to Lonca post CAR T-cell therapy[a], n (%)	CR	2 (15)
	PR	4 (31)
	SD	1 (8)
	PD	2 (15)

CAR T-Cell Therapy After Lonca Failure[3]

		n=14
Best response to Lonca, n (%)	CR	1 (7)
	PR	5 (36)
	Refractory	8 (57)
Best response to CAR T-cell therapy post Lonca, n (%)	CR	6 (43)
	PR	1 (7)
	Refractory	7 (50)

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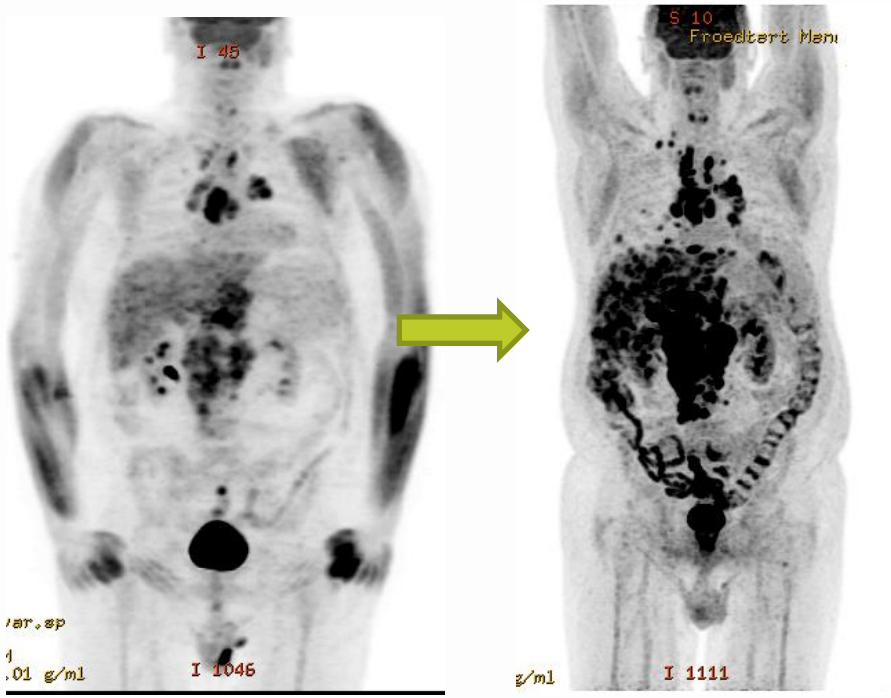
[a] 4 patients were not evaluable (30.8%).

Caimi PF, et al. *Clin Lymphoma Myeloma Leuk*. 2021 Nov 12:S2152-2650(21)02437-X. Online ahead of print. 3. Thapa et al. *Blood Adv*. 2020;4(16):3850-3852.

Clinical Case #1(B)…….Answer

- The patient in case 1(A), underwent CD19 directed CAR-T cell therapy. A PET/CT scan performed ~30 days post CAR treatment is shown below. What is next best step ± treatment option? [*Select all that apply*]
  - Repeat PET/CT in 1-2 months
  - Biopsy to assess CD19 expression
  - polatuzumab ± BR
  - Tafa/lenalidomide
  - Loncastuximab tesirine
  - **Clinical trial**



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Clinical Case #2

- 57-year-old female, with advanced stage follicular lymphoma (grade 1-2), received first therapy with BR. EOT = CR. ~23 months after diagnosis patient relapsed (biopsy ruled out transformation). She achieved a ‘rapid’ CR with 2nd-line treatment with lenalidomide/rituximab

  - CAR T-cell therapy
  - Autologous transplantation
  - Watch & wait
  - Allogeneic transplantation

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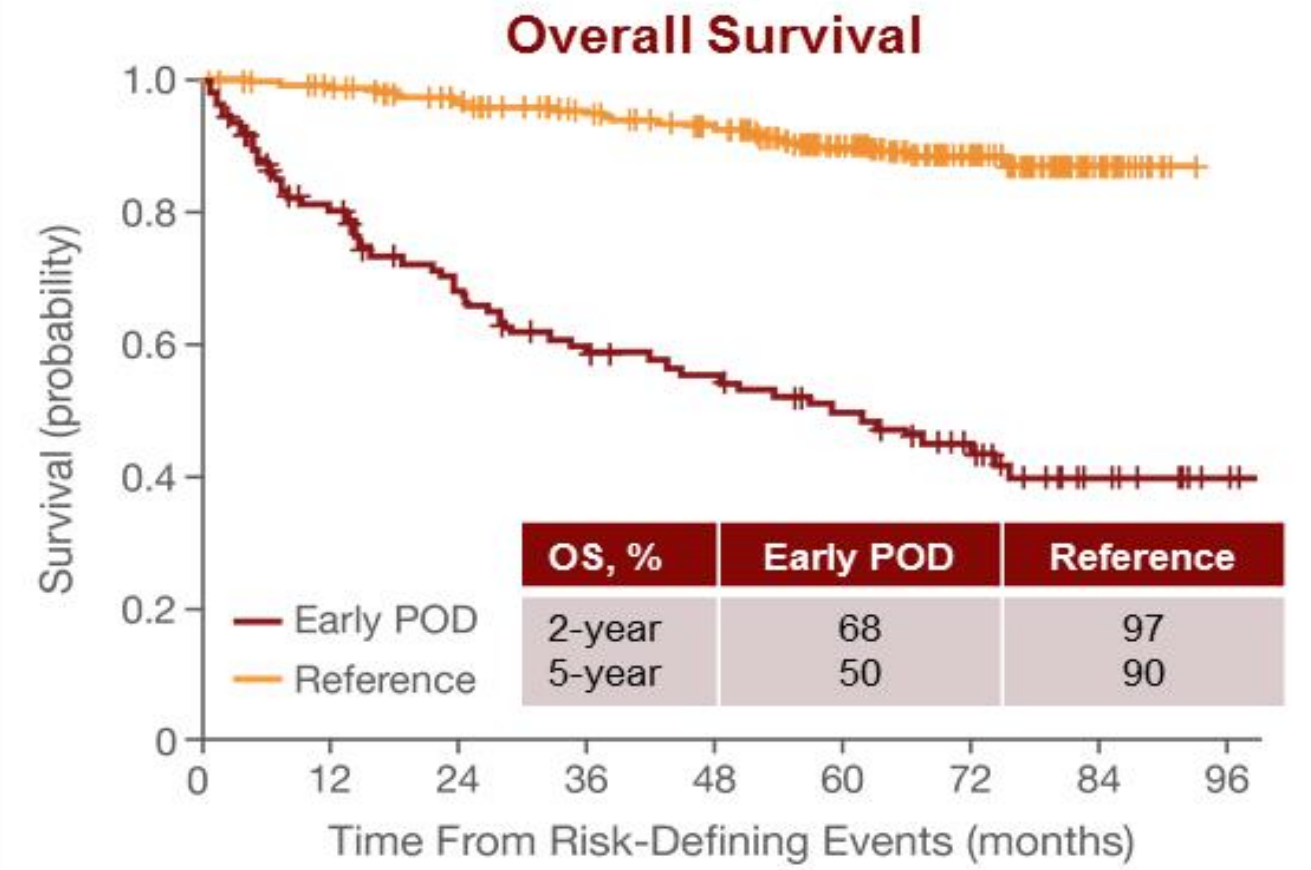
Early Failure (POD24) of R-Chemo Identifies a High-Risk FL

National LymphoCare Study



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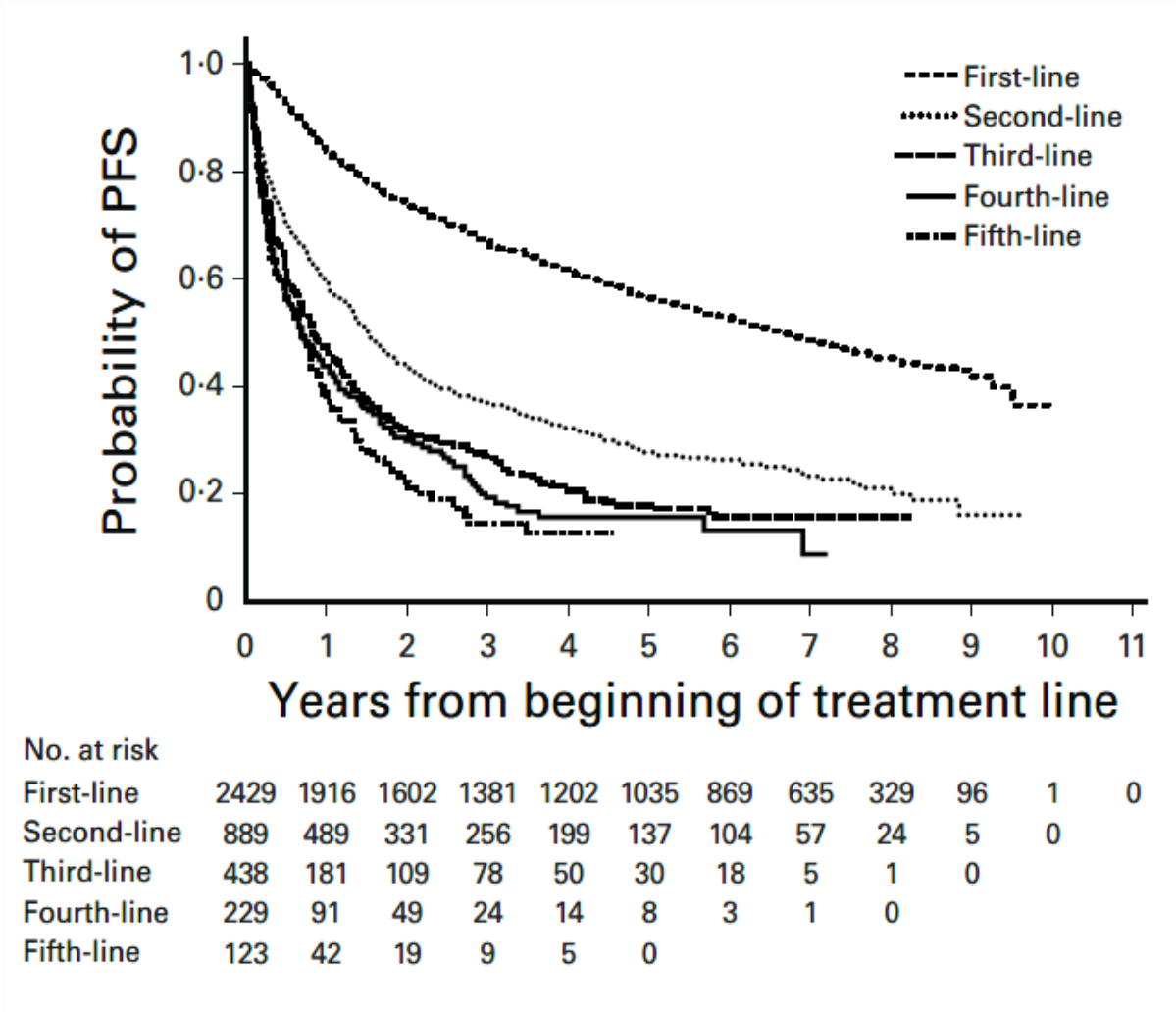
Casulo C & Friedberg J. JCO. 2015;33:2516-22.

Relapsed/Refractory FL

- Patients with FL will experience multiple relapses
- Sharply decreasing length of PFS after 1st relapse

Treatment Line	Median PFS, Years (95% CI)
First	6.62 (6.10-7.20)
Second	1.50 (1.35-1.70)
Third	0.83 (0.68-1.09)
Fourth	0.69 (0.50-0.97)
Fifth	0.68 (0.43-0.88)



Link and Friedberg. Br J Haematol. 2019;184:660.

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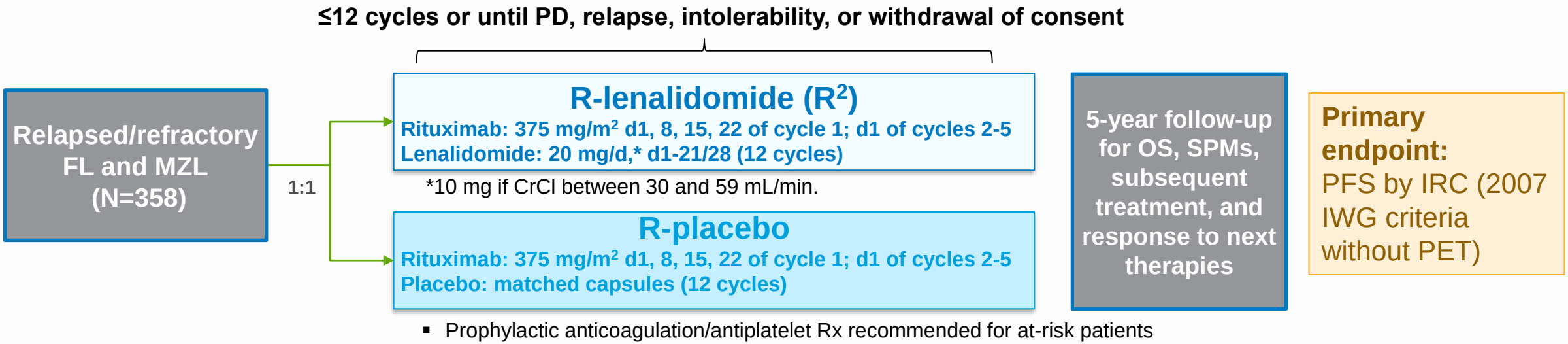
AUGMENT: Phase 3 Study of R^2 vs R in R/R FL and MZL



Key eligibility criteria

- R/R MZL or FL (grades 1-3a) in need of treatment
- ≥1 prior chemotherapy, immunotherapy, or chemoimmunotherapy and ≥2 previous doses of rituximab
- Not rituximab-refractory

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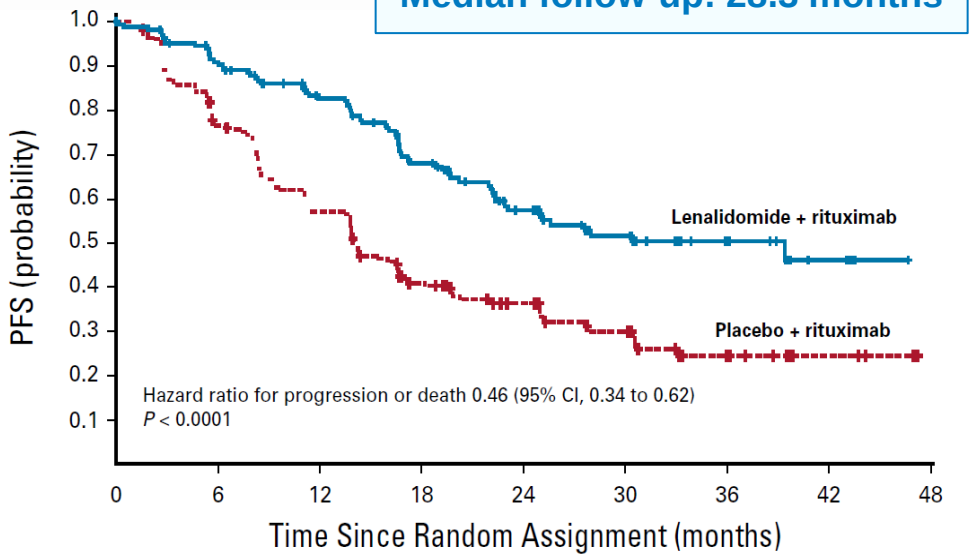
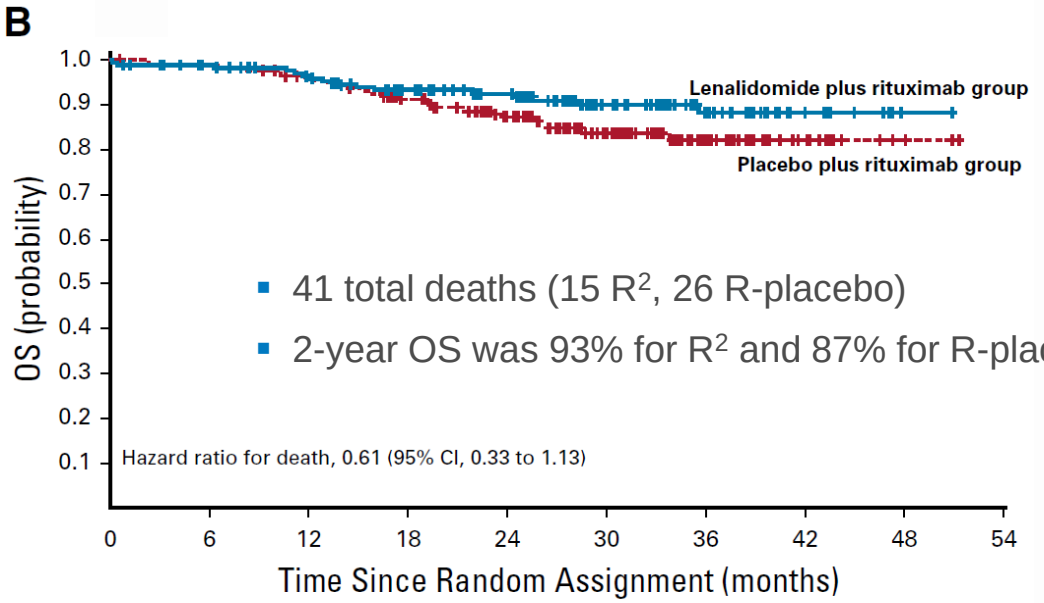
Leonard J & Gribben J. JCO. 37:1188-1199.

R^2 vs R: Survival Outcomes

Median follow-up: 28.3 months



No. at risk:									
Lenalidomide + rituximab	178	148	124	91	59	39	20	7	0
Placebo + rituximab	180	132	92	58	40	26	10	4	0



No. at risk:										
alidomide + rituximab	178	167	155	143	122	80	44	15	1	0
Placebo + rituximab	180	176	167	145	116	79	40	14	3	0

- 41 total deaths (15 R^2, 26 R-placebo)
- 2-year OS was 93% for R^2 and 87% for R-placebo

Median PFS	R^2 (n=178)	R-Placebo (n=180)	HR	*P* Value
By IRC, mo (95% CI)	39.4 (22.9-NE)	14.1 (11.4-16.7)	0.46 (0.34-0.62)	<0.0001
By INV, mo (95% CI)	25.3 (21.2-NE)	14.3 (12.4-17.7)	0.51 (0.38-0.69)	<0.0001

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Leonard J & Gribben J. JCO. 37:1188-1199.

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

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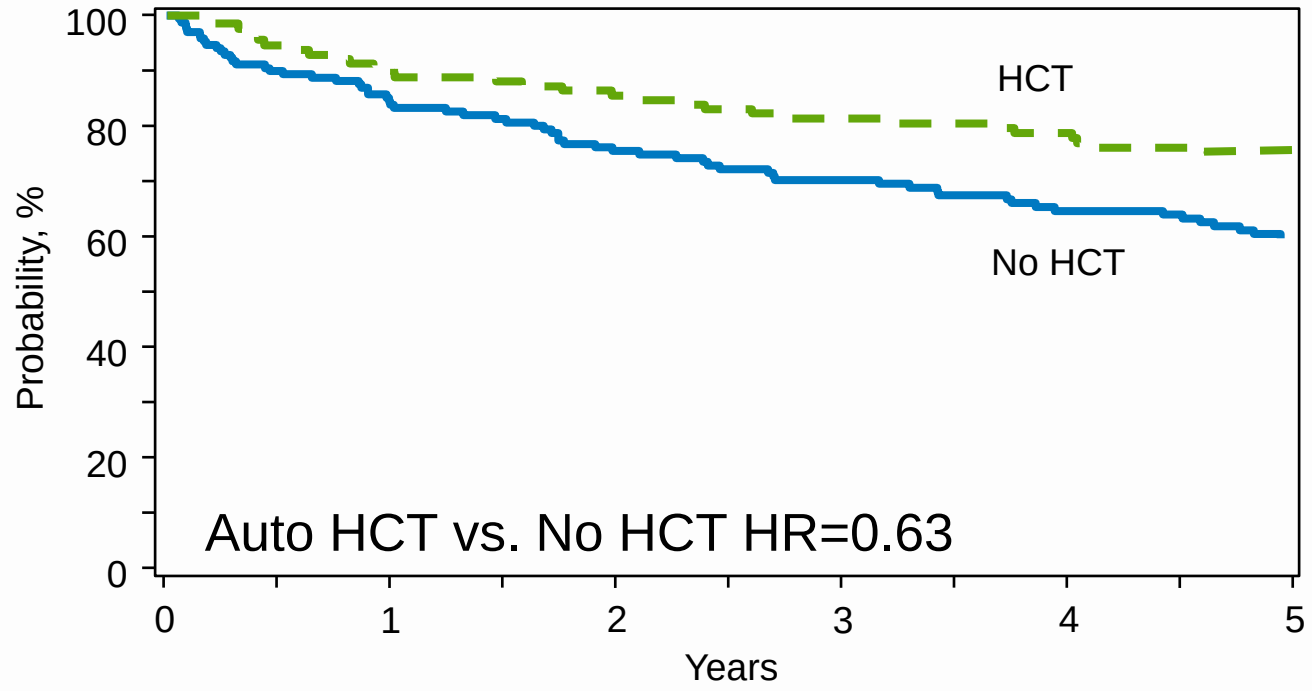
Casulo C. & Hamadani M. BBMT 2018;24:1163-71.

Autologous HCT Improves OS in POD24 Follicular Lymphoma



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

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

Follicular Lymphoma: ZUMA-5

R/R iNHL — **N=149 Treated (124 FL, 25 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

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Jacobson & Neelapu. Lancet Oncol. 2022;23:91-103.

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.

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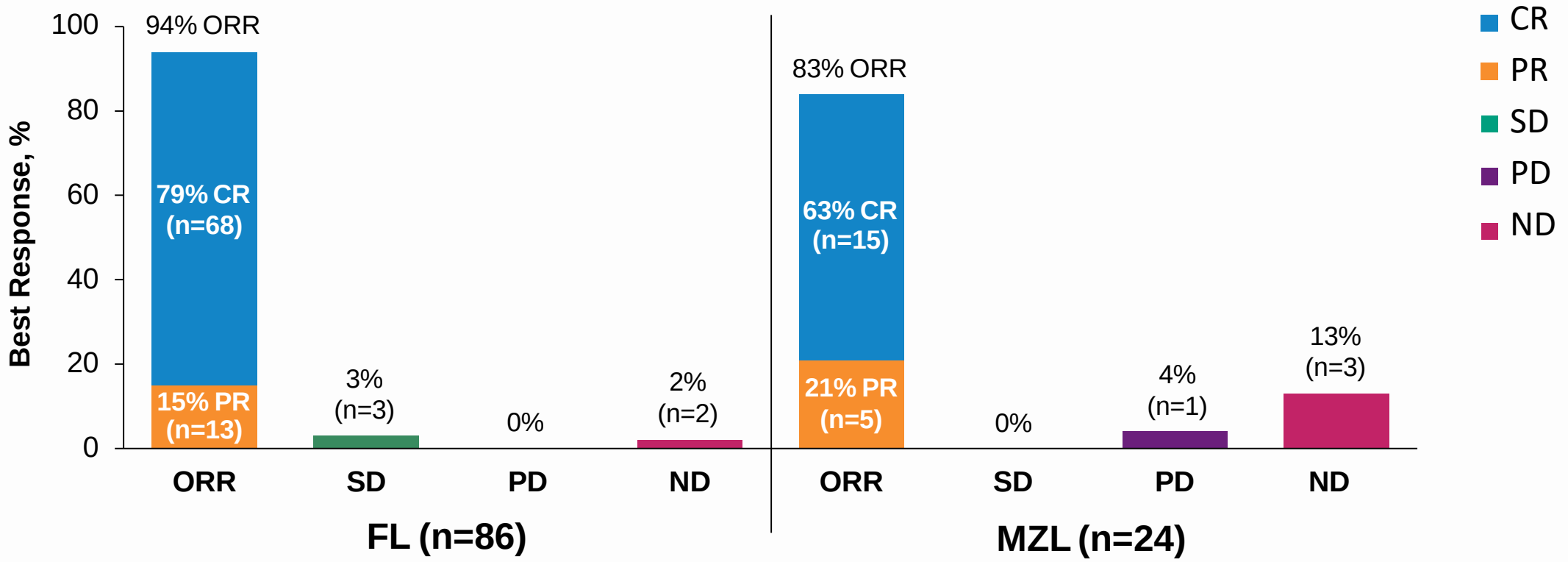
Follicular Lymphoma: ZUMA-5



- Among efficacy-eligible patients with iNHL (n=110), the ORR was 92% (95% CI, 85–96), with a 75% CR rate
- Among all treated patients with iNHL (n=149), the ORR was 92% (95% CI, 86–96), with a 77% CR rate

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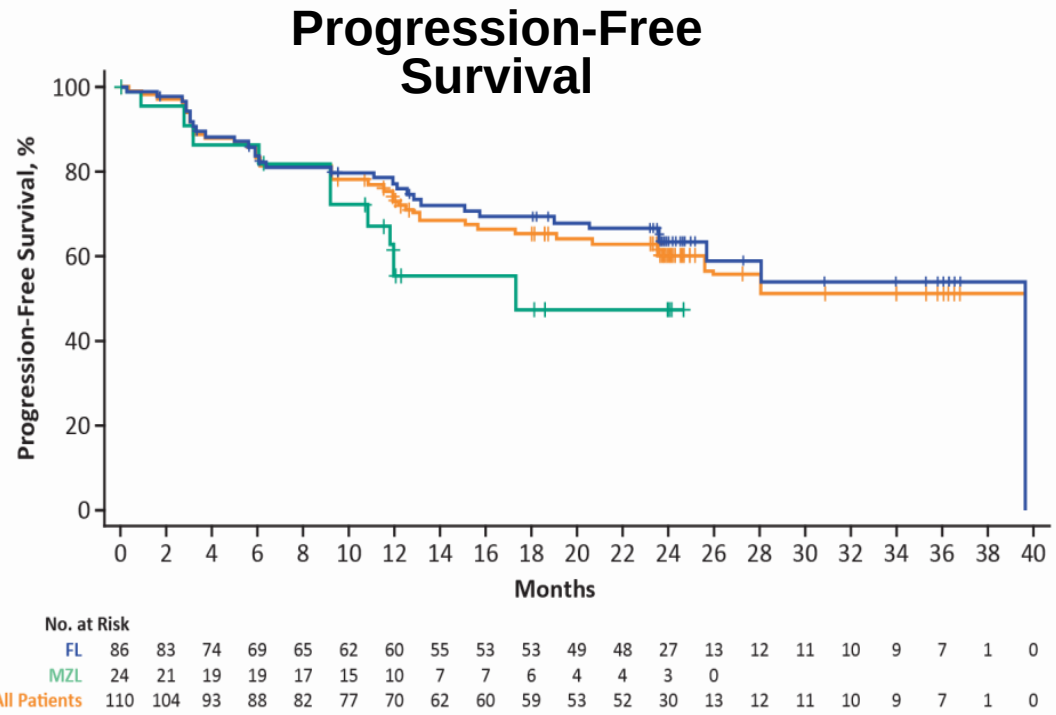
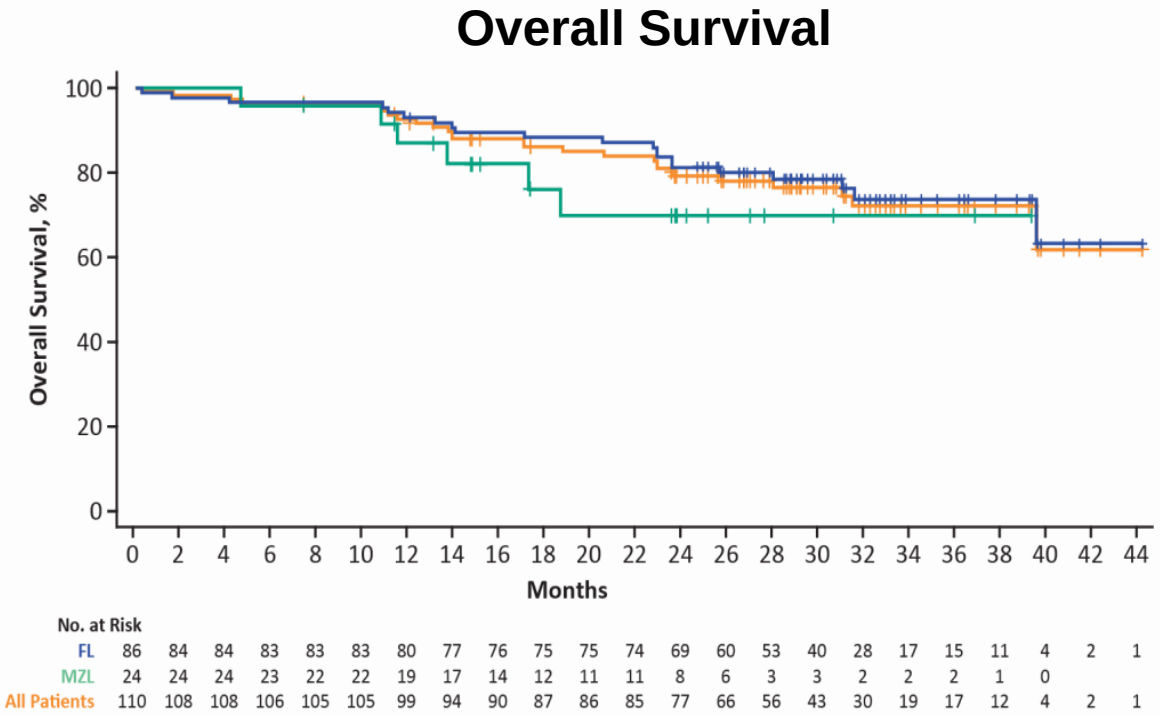
Neelapu et al. ASH 2020. Abstract #93

Follicular Lymphoma: ZUMA-5





With a median follow-up of “efficacy eligible” FL patients (N=110) ~31 months

- The 24-month PFS rate was 57% vs. 73% for those with or without POD24 FL
- The 24-month OS rate was 78% vs. 86% for those with or without POD24 FL

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Neelapu et al. ASH 2020. Abstract #93

Efficacy Outcomes in Patients With FL by POD24 Status

Parameter (95% CI)	Follicular Lymphoma (n=78)	
	With POD24 (n=49)	Without POD24 (n=29)
Median PFS, months	39.6 (13.1–NE)	NR (25.7–NE)
24-month rate, %	57.3 (41.2–70.4)	73.0 (51.1–86.2)
Median OS, months	NR (39.6–NE)	NR (NE–NE)
24-month rate, %	77.6 (63.1–86.9)	85.9 (66.7–94.5)

- Patients with FL who had POD24 benefitted from axi-cel, but didn't respond as well as patients without POD24
  - Median PFS among patients without POD24 were not yet reached at data cutoff

POD24, progression of disease <24 months from initiating the first anti-CD20–containing chemoimmunotherapy.

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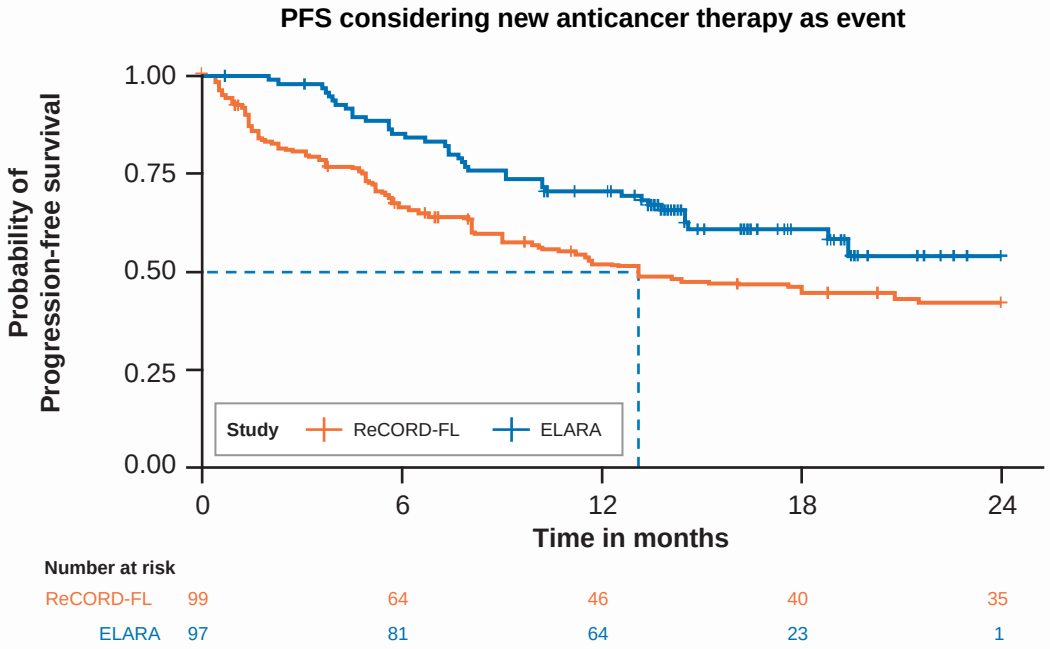
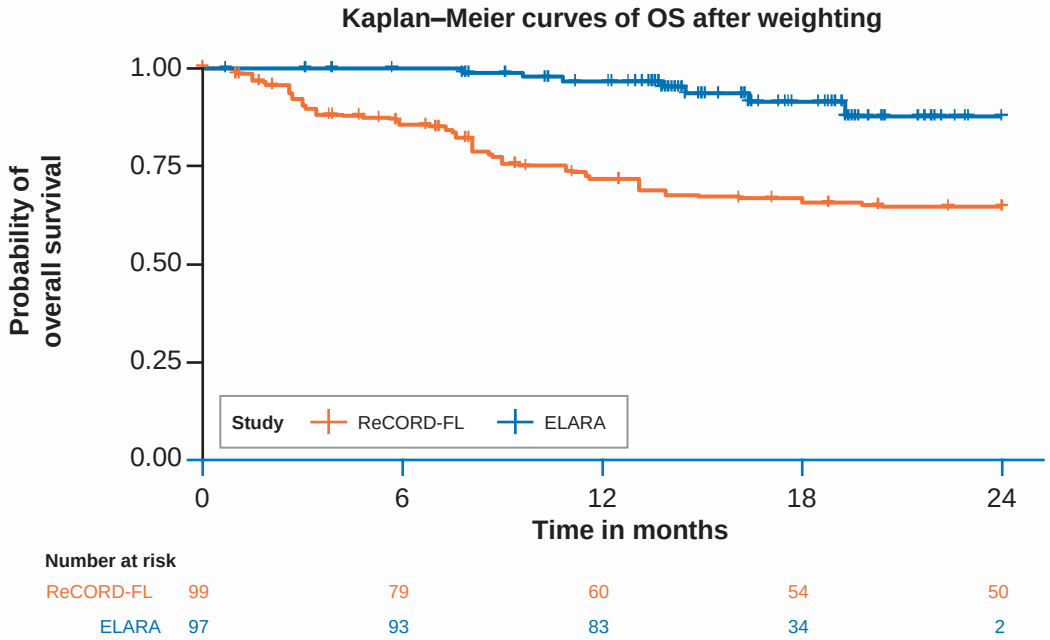
Is CAR-T Superior to Standard Options?
ELARA vs. ReCORD-FL99 Analysis





ELARA Trial evaluated tisa-cel in patients with R/R FL

ReCORD-FL, a global retrospective cohort study of clinical outcomes in patients with R/R FL who meet the ELARA eligibility criteria

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Presented by Salles G, et al. ASH 2021. Poster 3528.

Clinical Case #2…… Answer

- 57-year-old female, with advanced stage follicular lymphoma (grade 1-2), received first therapy with BR. EOT = CR. ~23 months after diagnosis patient relapsed (biopsy ruled out transformation). She achieved a “rapid” CR with 2nd-line treatment with lenalidomide/rituximab

  – CAR T-cell therapy
  – Autologous transplantation
  – Watch & wait
  – Allogeneic transplantation

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Thank you for your kind attention!

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Next presentation: Wednesday, July 13, 2022
Updates from ASCO and EHA
Gilles Salles, MD, PhD