A Conversation with the Investigators: Chimeric Antigen Receptor T-Cell Therapy in Hematologic Cancers

Tuesday, July 13, 2021
5:00 PM – 6:00 PM ET

Faculty

Caron Jacobson, MD
David G Maloney, MD, PhD
Nikhil C Munshi, MD

Moderator

Neil Love, MD

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Faculty

Caron Jacobson, MD
Assistant Professor of Medicine
Harvard Medical School
Dana-Farber Cancer Institute
Boston, Massachusetts

Nikhil C Munshi, MD
Kraft Family Chair
Director of Basic and Correlative Science
Jerome Lipper Multiple Myeloma Center
Professor of Medicine
Harvard Medical School
Dana-Farber Cancer Institute
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David G Maloney, MD, PhD
Professor, Clinical Research Division
Medical Director, Cellular Immunotherapy
Leonard and Norma Klorfine Endowed Chair for Clinical Research
Fred Hutchinson Cancer Research Center
Professor of Medicine, Division of Oncology
University of Washington
Medical Director
Cellular Immunotherapy and Bezos Family Immunotherapy Clinic
Seattle Cancer Care Alliance
Seattle, Washington

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Commercial Support

This activity is supported by educational grants from Bristol-Myers Squibb Company and Janssen Biotech Inc, administered by Janssen Scientific Affairs LLC.

Dr Love — Disclosures

Dr Love is president and CEO of Research To Practice. Research To Practice receives funds in the form of educational grants to develop CME activities from the following companies: AbbVie Inc, Adaptive Biotechnologies Corporation, Agios Pharmaceuticals Inc, Alexion Pharmaceuticals, Amgen Inc, Array BioPharma Inc, a subsidiary of Pfizer Inc, Astellas, AstraZeneca Pharmaceuticals LP, Aveo Pharmaceuticals, Bayer HealthCare Pharmaceuticals, BeiGene Ltd, Blueprint Medicines, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, Clovis Oncology, Daiichi Sankyo Inc, Eisai Inc, Epizyme Inc, Exact Sciences Inc, Exelixis Inc, Five Prime Therapeutics Inc, Foundation Medicine, Genentech, a member of the Roche Group, Gilead Sciences Inc, GlaxoSmithKline, Grail Inc, Halozyme Inc, Helsinn Healthcare SA, ImmunoGen Inc, Incyte Corporation, Ipsen Biopharmaceuticals Inc, Janssen Biotech Inc, administered by Janssen Scientific Affairs LLC, Jazz Pharmaceuticals Inc, Karyopharm Therapeutics, Kite, A Gilead Company, Lilly, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, Merck, Novartis, Novocure Inc, Oncopeptides, Pfizer Inc, Pharmacyclics LLC, an AbbVie Company, Puma Biotechnology Inc, Regeneron Pharmaceuticals Inc, Sanofi Genzyme, Seagen Inc, Sumitomo Dainippon Pharma Oncology Inc, Taiho Oncology Inc, Takeda Oncology, Tesaro, A GSK Company, TG Therapeutics Inc, Turning Point Therapeutics Inc and Verastem Inc.

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Dr Jacobson — Disclosures

Consulting Agreements	AbbVie Inc, bluebird bio, Bristol-Myers Squibb Company, Celgene Corporation, Kite, A Gilead Company, Lonza, Novartis, Precision BioSciences
Contracted Research	Kite, A Gilead Company, Pfizer Inc, Precision BioSciences

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Dr Maloney — Disclosures

Advisory Committee	A2 Biotherapeutics
Consulting Agreements	Amgen Inc, BioLineRx, Bristol-Myers Squibb Company, Celgene Corporation, Genentech, a member of the Roche Group, Janssen Biotech Inc, Juno Therapeutics, a Celgene Company, Kite, A Gilead Company, Legend Biotech, MorphoSys, Novartis, Umoja Biopharma
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Dr Munshi — Disclosures

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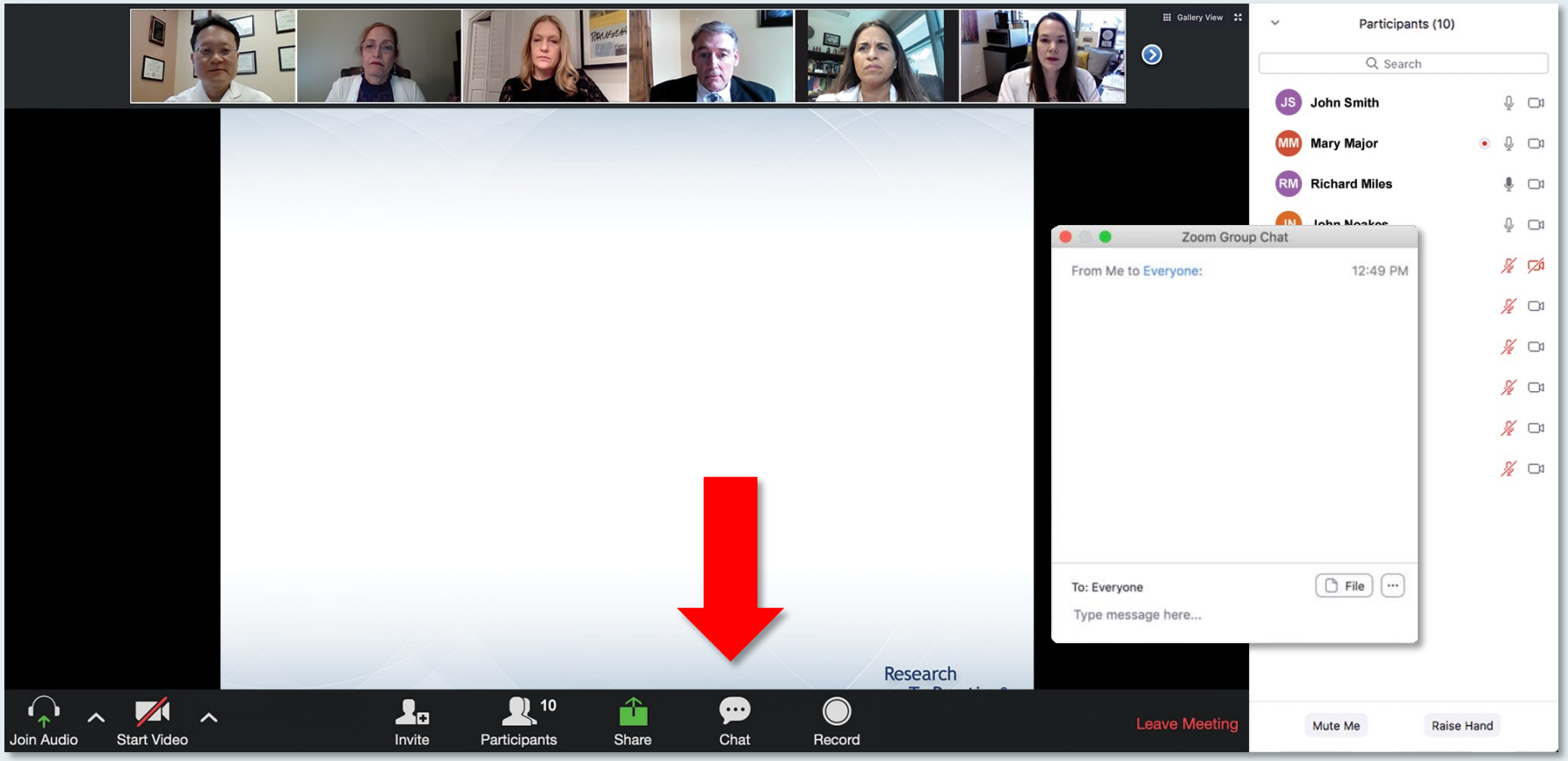

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Familiarizing Yourself with the Zoom Interface

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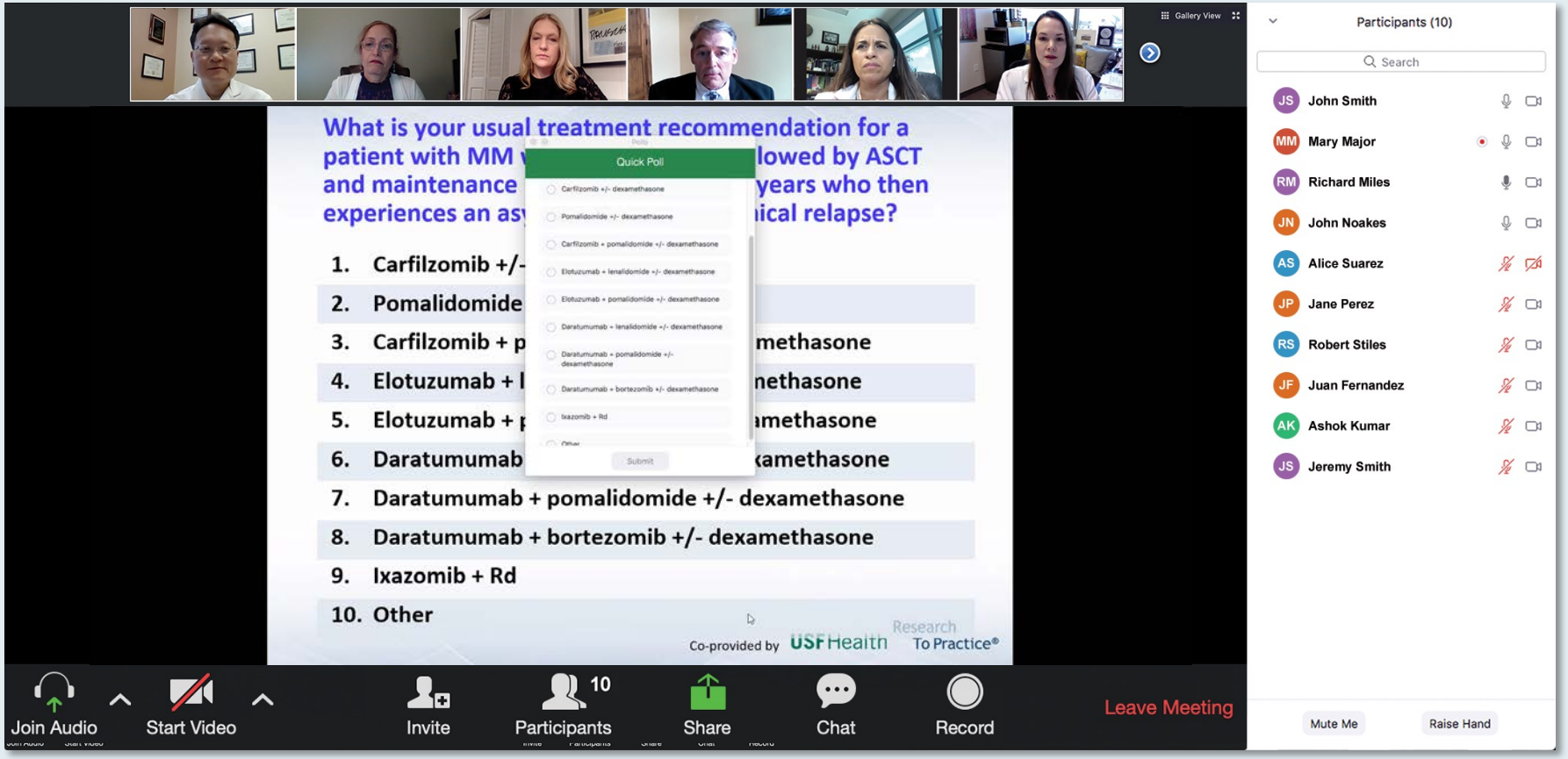

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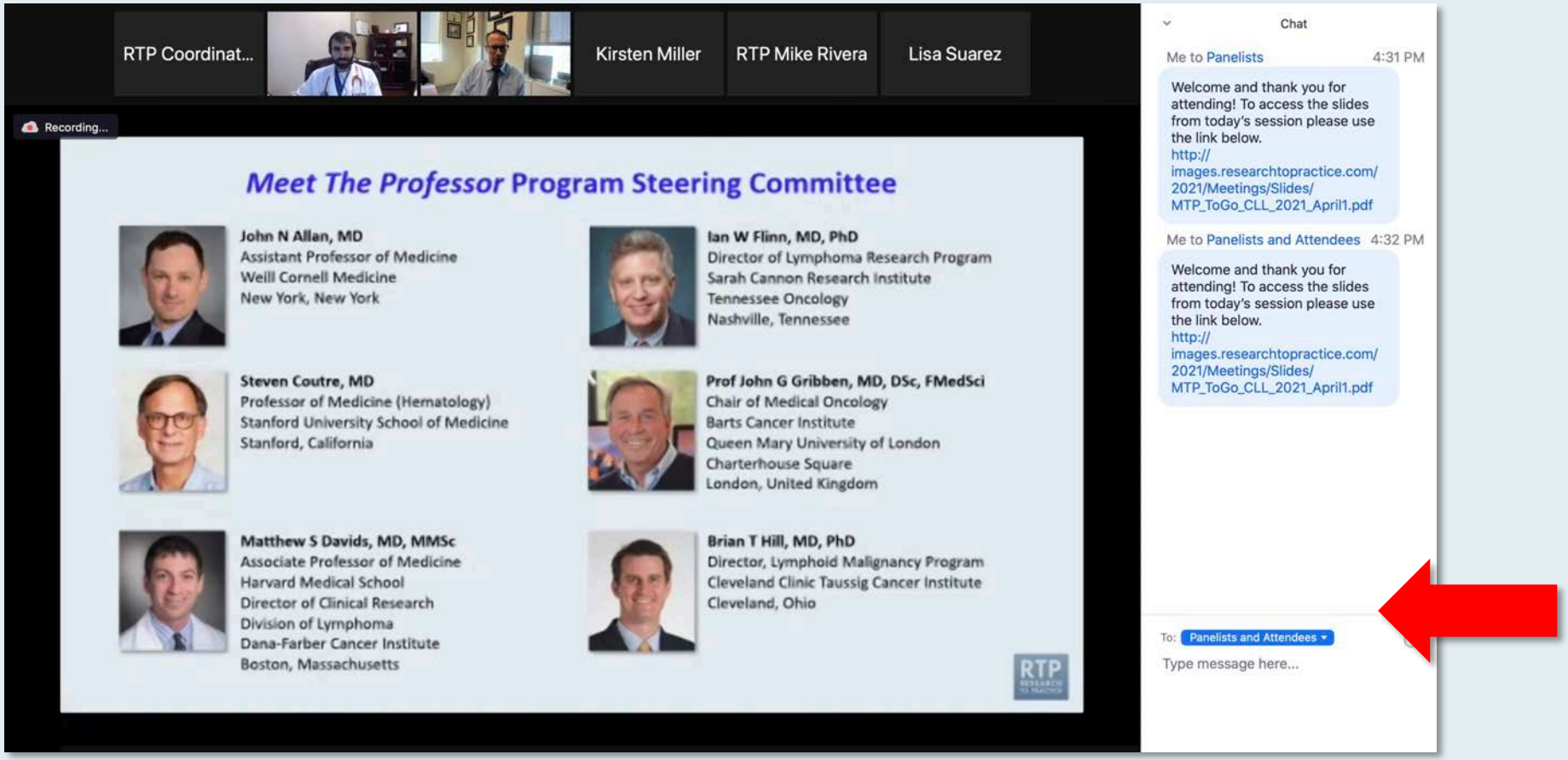
Familiarizing Yourself with the Zoom Interface

Expand chat submission box



Drag the white line above the submission box up to create more space for your message.

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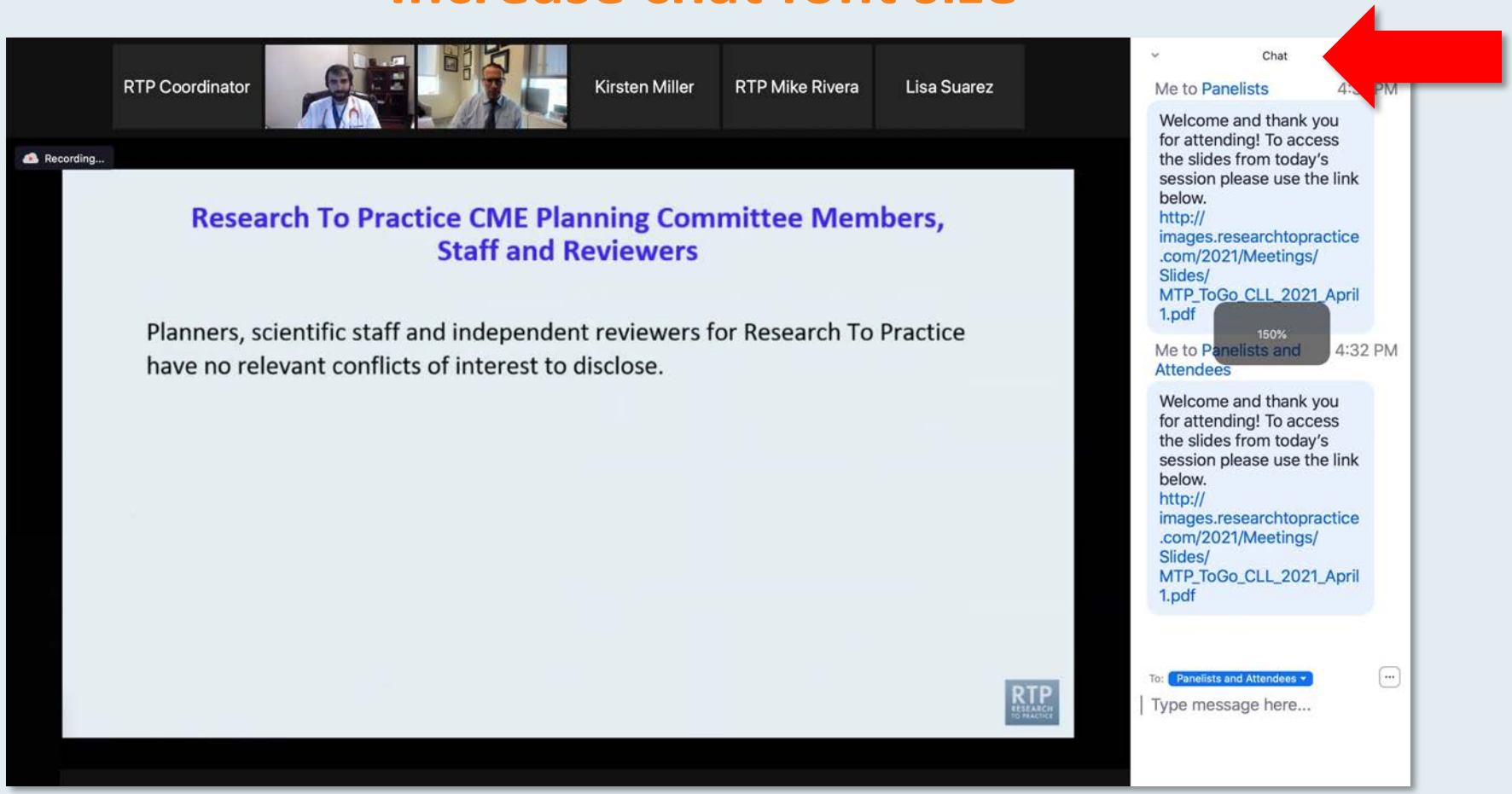

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WITH DR NEIL LOVE

CHIMERIC ANTIGEN RECEPTOR T-CELL THERAPY IN NON-HODGKIN LYMPHOMA

DR TANYA SIDDIQI

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Metastatic Castration-Resistant Prostate Cancer
Tuesday, July 20
5:00 PM – 6:00 PM ET

Bladder Cancer
Wednesday, July 21
5:00 PM – 6:00 PM ET

Endometrial and Cervical Cancers
Monday, July 26
5:00 PM – 6:00 PM ET

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Head and Neck Cancer
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RESEARCH TO PRACTICE

A Conversation with the Investigators: Acute Myeloid Leukemia and Myelodysplastic Syndromes

Wednesday, July 14, 2021
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Faculty

Courtney D DiNardo, MD, MSCE
Gail J Roboz, MD
Eytan M Stein, MD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Meet The Professor

Optimizing the Selection and Sequencing of Therapy for Patients with Advanced Gastrointestinal Cancers

Monday, July 19, 2021
5:00 PM – 6:00 PM ET

Faculty

Tanios Bekaii-Saab, MD

Moderator

Neil Love, MD

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A Conversation with the Investigators: Metastatic Castration-Resistant Prostate Cancer

Tuesday, July 20, 2021
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Johann de Bono, MBChB, MSc, PhD
Julie N Graff, MD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

A Conversation with the Investigators: Bladder Cancer

Wednesday, July 21, 2021
5:00 PM – 6:00 PM ET

Faculty

Petros Grivas, MD, PhD
Daniel P Petrylak, MD
Arlene Siefker-Radtke, MD

Moderator

Neil Love, MD

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Meet The Professor

Optimizing the Selection and Sequencing of Therapy for Patients with Renal Cell Carcinoma

Thursday, July 22, 2021
5:00 PM – 6:00 PM ET

Faculty

David F McDermott, MD

Moderator

Neil Love, MD

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A Conversation with the Investigators: Endometrial and Cervical Cancers

Monday, July 26, 2021
5:00 PM – 6:00 PM ET

Faculty

Mansoor Raza Mirza, MD
David M O'Malley, MD
Angeles Alvarez Secord, MD, MHSc

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

What General Medical Oncologists Want to Know About Targeted Therapy for Non-Small Cell Lung Cancer

Tuesday, July 27, 2021
5:00 PM – 6:00 PM ET

Faculty

Professor Solange Peters, MD, PhD
Zofia Piotrowska, MD, MHS
Gregory J Riely, MD, PhD

Moderator

Neil Love, MD

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RESEARCH
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What General Medical Oncologists Want to Know About Immunotherapy and Other Nontargeted Approaches for Lung Cancer

Wednesday, July 28, 2021
5:00 PM – 6:00 PM ET

Faculty

Mark Awad, MD, PhD
David R Spigel, MD
Heather Wakelee, MD

Moderator

Neil Love, MD

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Thank you for joining us!

CME and MOC credit information will be emailed to each participant within 2 to 3 business days.

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Seattle Cancer Care Alliance
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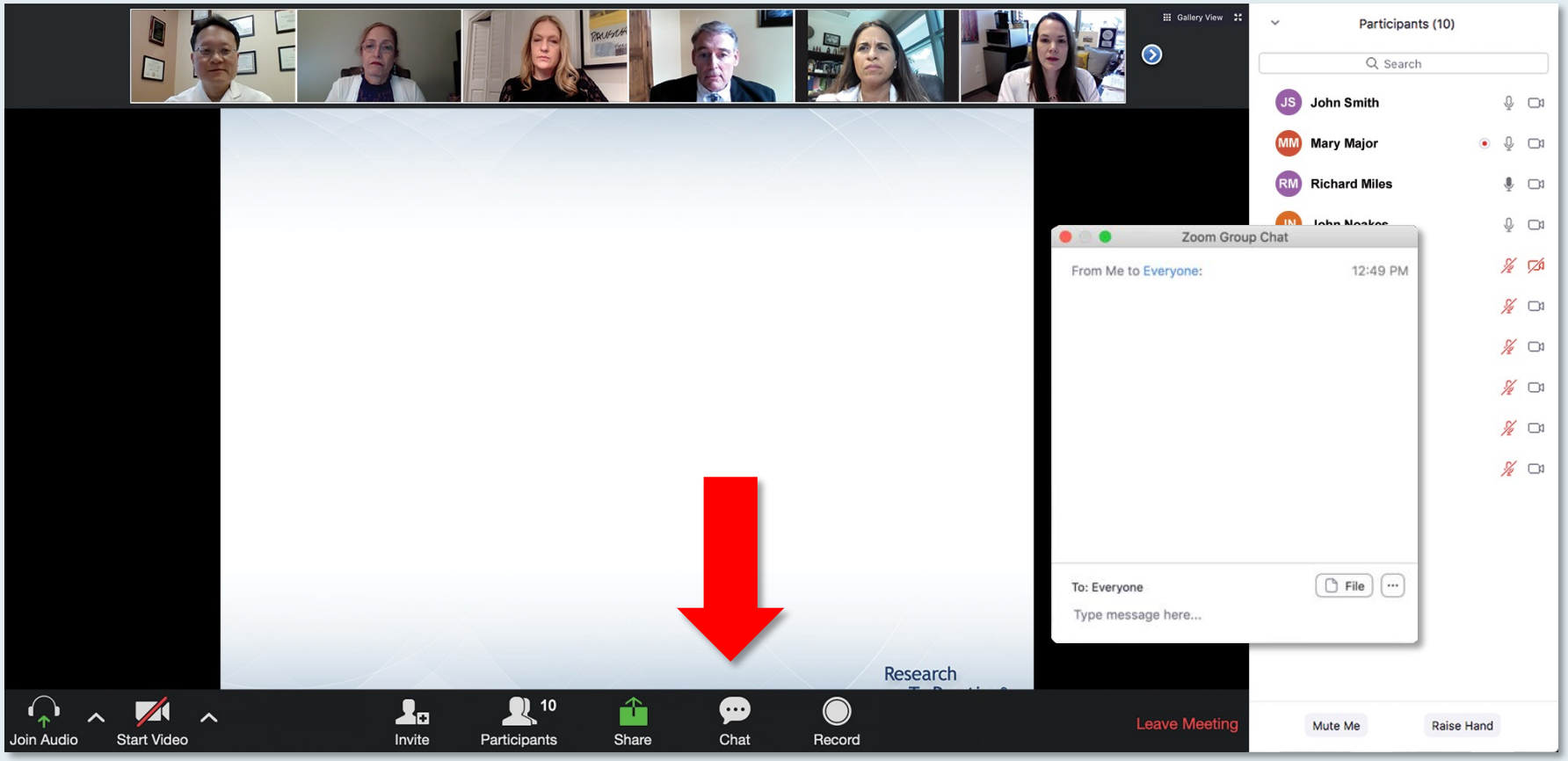

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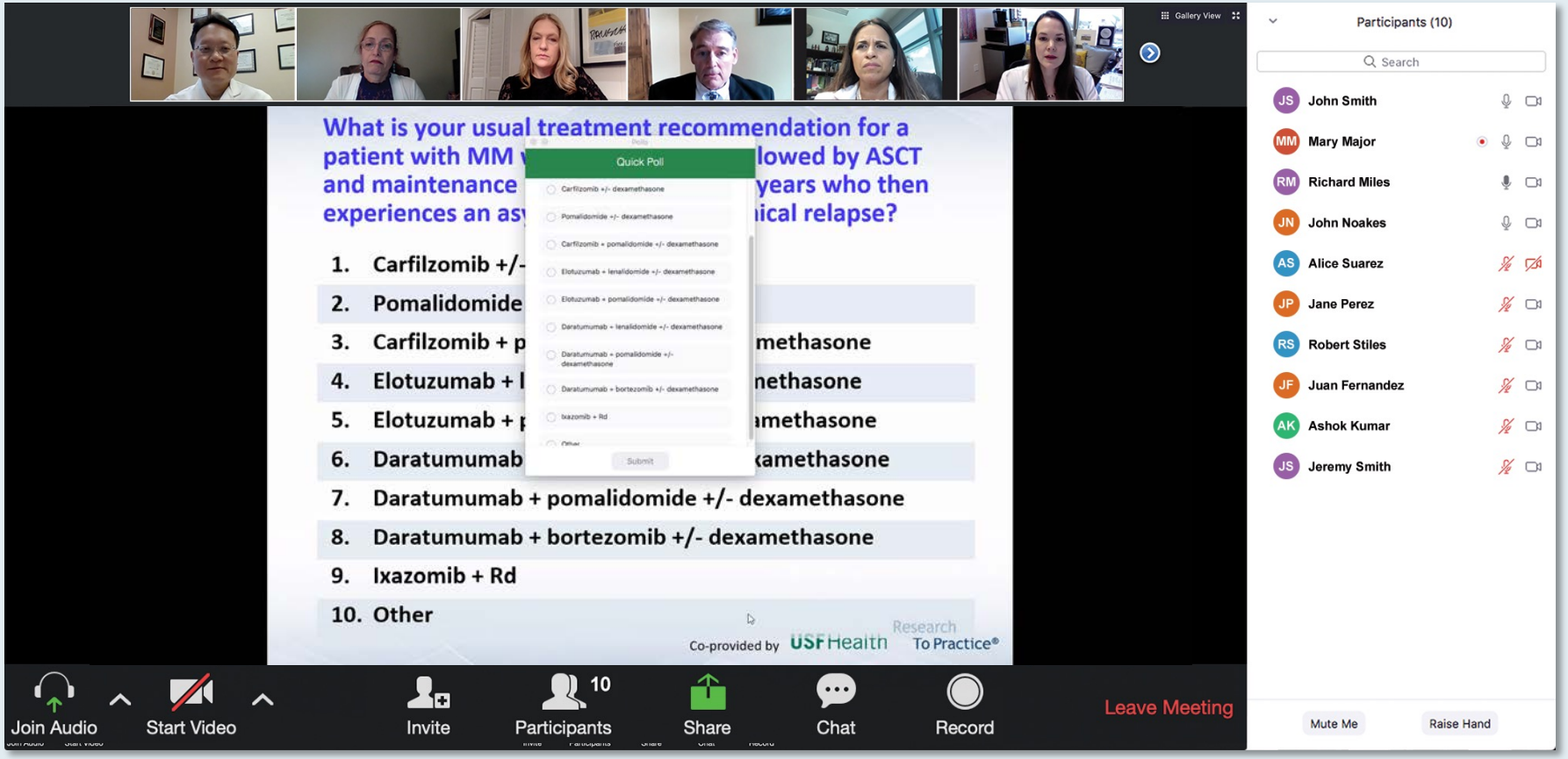

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ASCO 2021 CAR T-Cell Therapy Presentation Library

CAR T-Cell Therapy: Other Lymphoma Subtypes

Caron Jacobson, MD, MMSc

Download Slides

CD19 CAR T-Cell Therapy for Diffuse Large B Cell Lymphoma (DLBCL)

David G Maloney, MD, PhD

Download Slides

CAR T-Cell Therapy in Multiple Myeloma

Nikhil C Munshi, MD

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Agenda

Module 1: Diffuse Large B-Cell Lymphoma (DLBCL)

- Mechanistic similarities and differences between axicabtagene ciloleucel (axi-cel), tisagenlecleucel (tis-cel) and lisocabtagene maraleucel (liso-cel)
- Efficacy and safety of axi-cel, tis-cel and liso-cel in DLBCL
- Management of class-effect and other toxicities observed with CD19-directed CAR T-cell therapy
- Faculty cases

Module 2: Other Lymphoma Subtypes

- ZUMA-2: Brexucabtagene autoleucel (brex-cel) in relapsed/refractory (R/R) MCL
- ZUMA-5: Axi-cel for R/R follicular lymphoma
- ELARA: Tis-cel in patients with R/R indolent lymphomas
- Early efficacy and safety data with CD19-directed CAR T-cell therapy in patients with R/R CLL
- TRANSCEND CLL 004: Liso-cel in R/R CLL
- Faculty cases

Module 3: Multiple Myeloma (MM)

- KarMMa: Idecabtagene vicleucel (ide-cel) in patients with R/R MM; recent FDA approval
- CARTITUDE-1: Ciltacabtagene autoleucel (cilta-cel) for R/R MM
- Management of class-effect and other toxicities observed with BCMA-targeted CAR T-cell therapy
- Faculty cases

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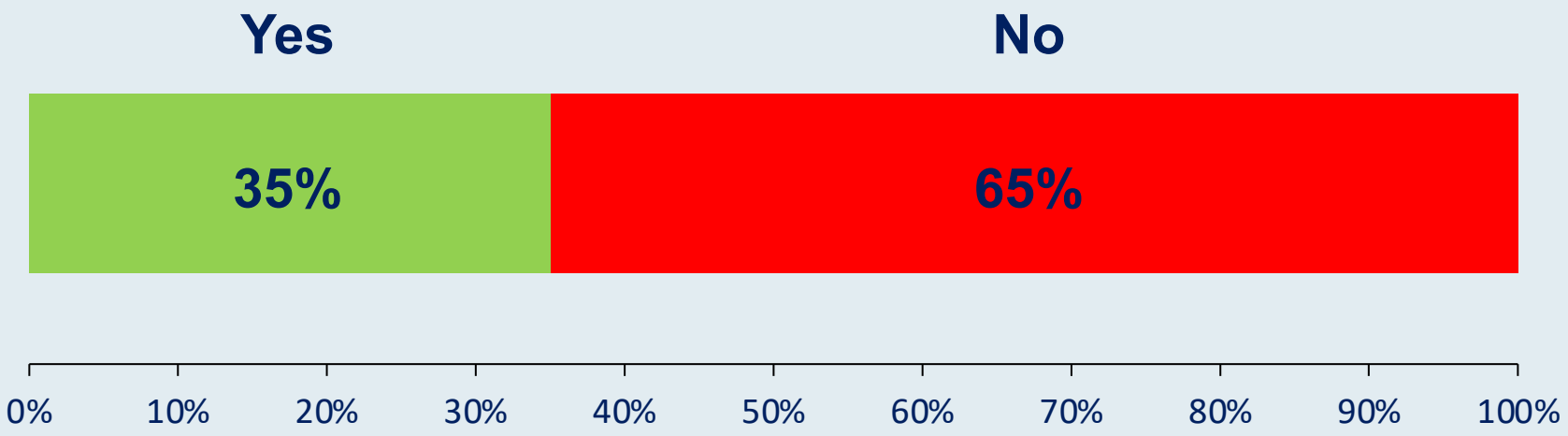

Premeeting survey: July 2021

If a live CME meeting was currently available for you to participate in person, would you likely attend?

1. Yes
2. Yes, if it is a smaller meeting with social distancing standards in place
3. No

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In the past 2 weeks, approximately how many hours did you spend conducting telemedicine visits with patients?

1. 0
2. 1-5 hours
3. 6-10 hours
4. 11-15 hours
5. More than 15 hours

Agenda

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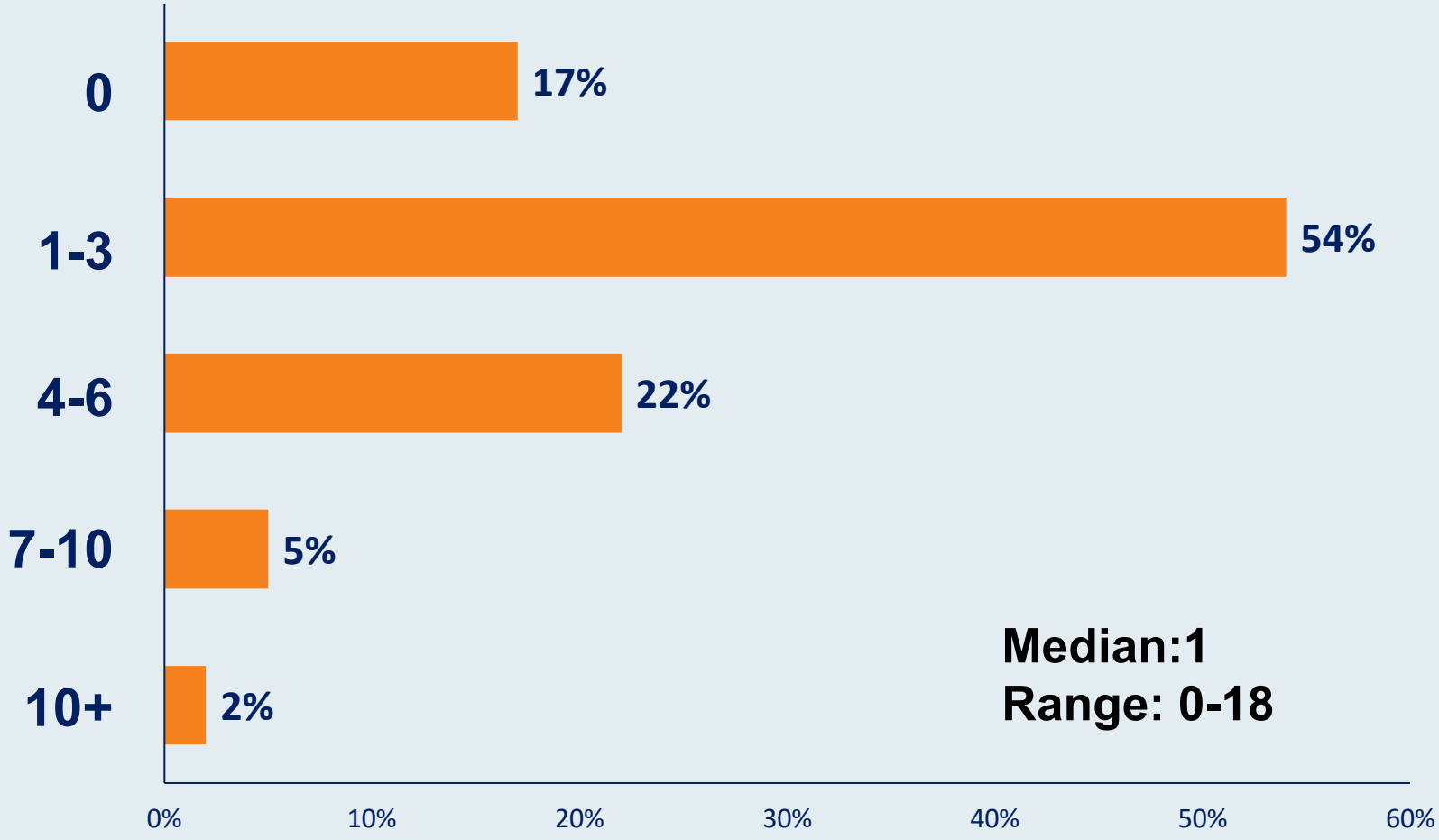
Approximately how many patients have you referred for chimeric antigen receptor (CAR) T-cell therapy?



Premeeting survey: July 2021

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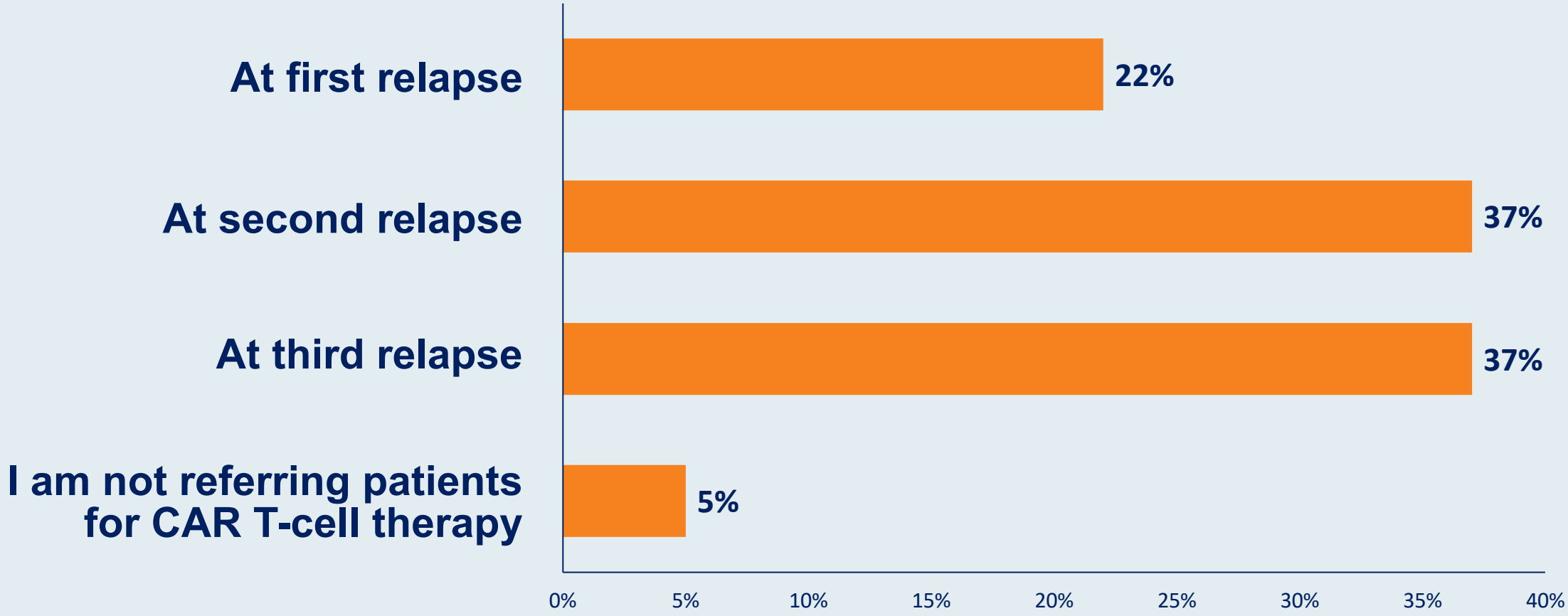
At what point in the treatment course are you referring patients with multiple regimen-relapsed diffuse large B-cell lymphoma (DLBCL) for consultation regarding CAR T-cell therapy?



Premeeting survey: July 2021

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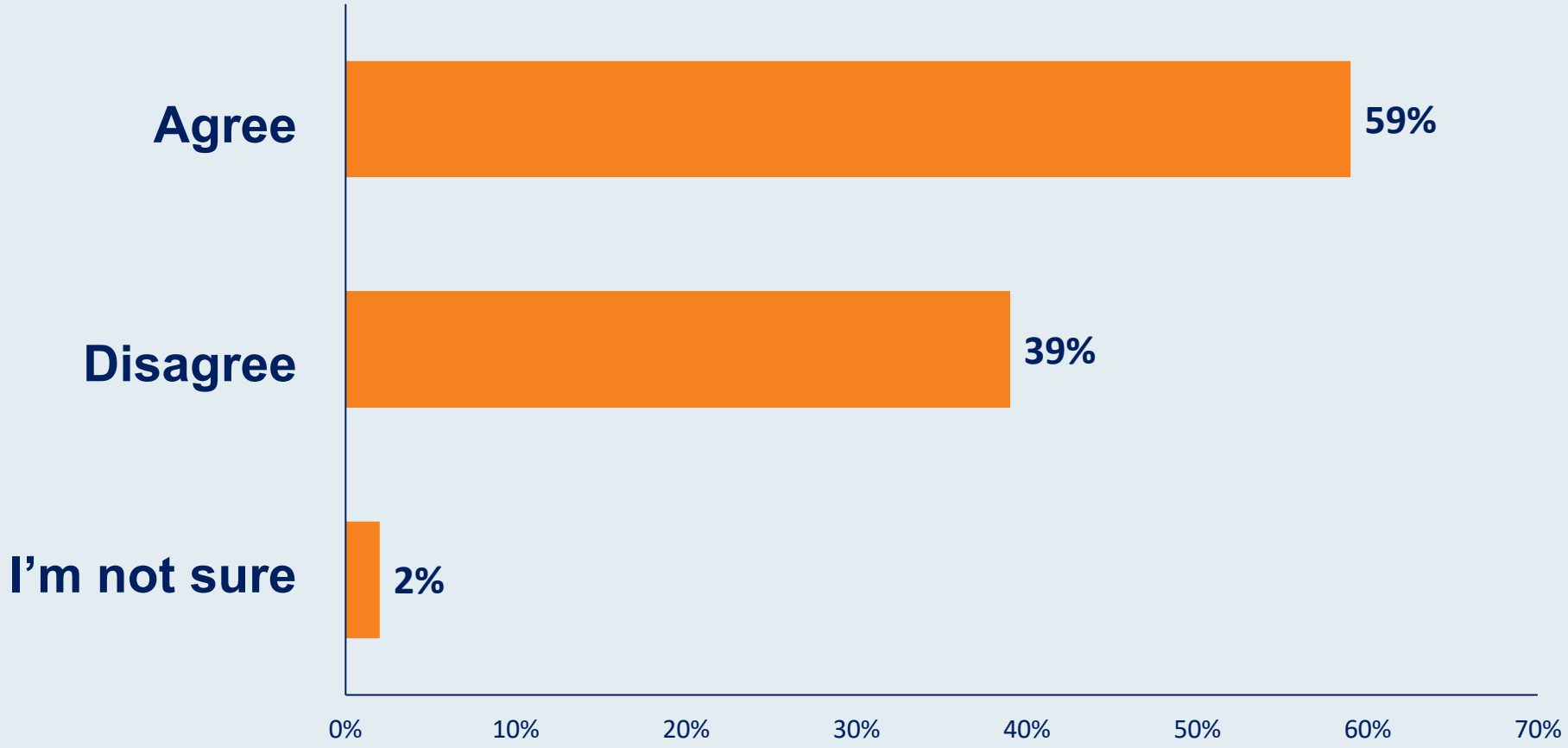
A patient with DLBCL should be in adequate physical condition to undergo ASCT to be a suitable candidate for CAR T-cell therapy.



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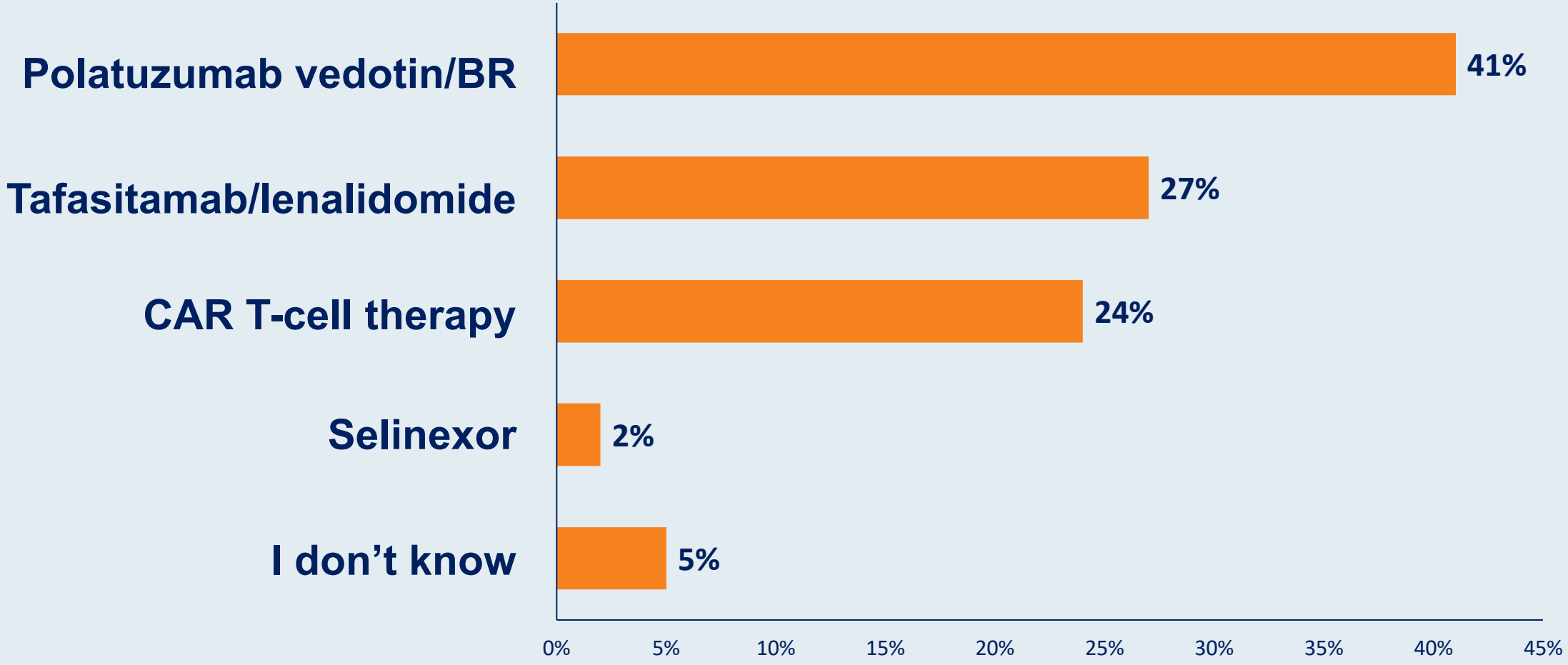
Which therapy would you generally recommend first for a patient with DLBCL who experiences disease progression on front-line R-CHOP and is not eligible for high-dose therapy or ASCT?



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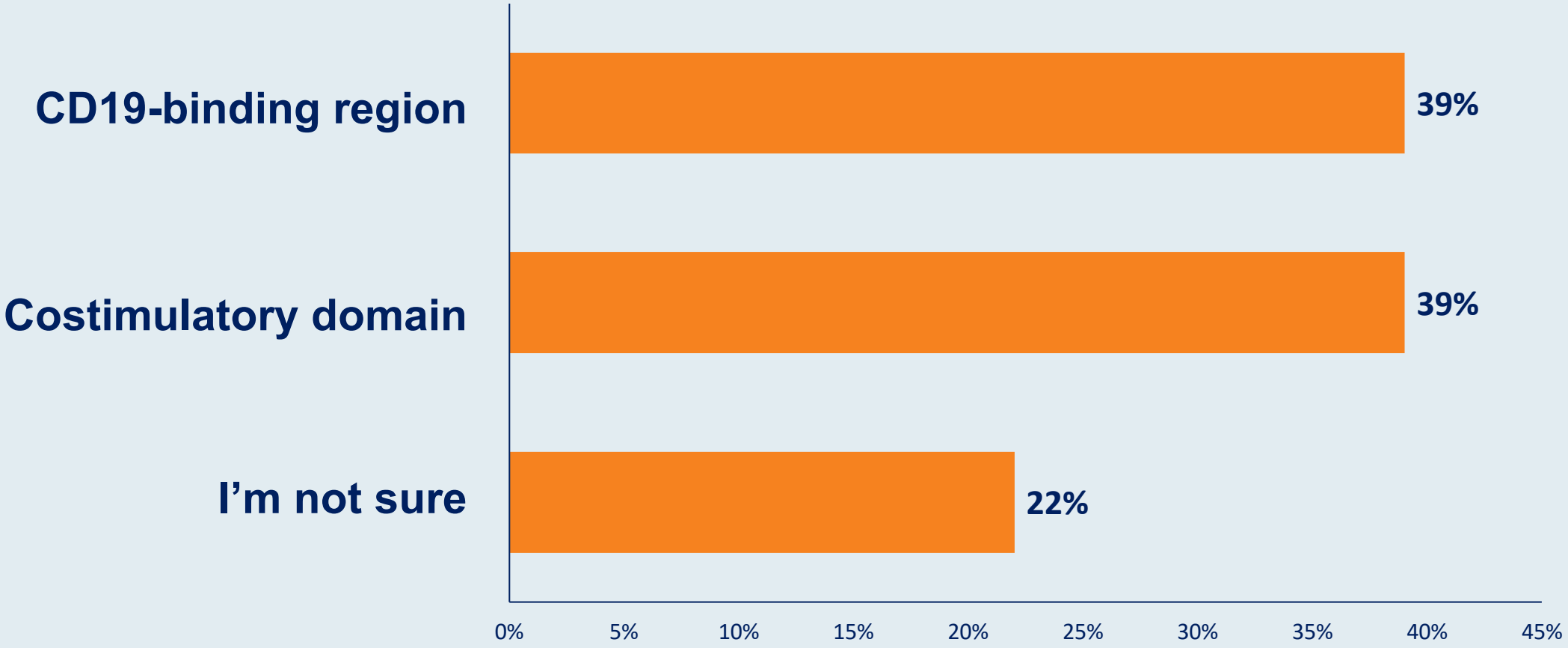
Currently approved CAR T-cell therapies for lymphoma differ significantly in which of their following components?



Premeeting survey: July 2021

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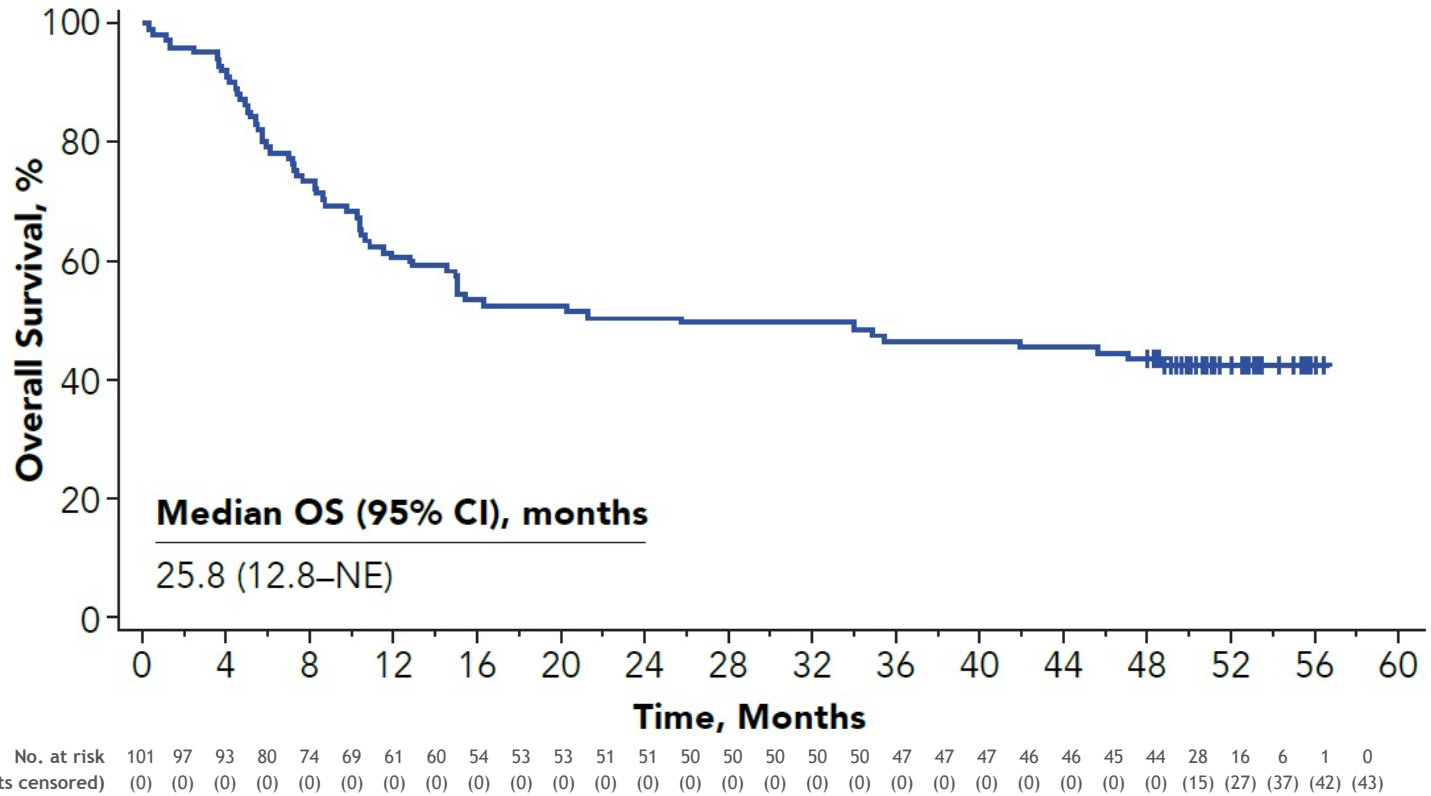
Aggressive lymphoma: commercial CD19 CAR T cell products

Feature	Tisagenlecleucel	Axi-cel	Liso-cel
Construct	FMC-63 murine scFv 4-1BB co-stimulatory domain	FMC-63 murine scFv CD28 co-stimulatory domain	FMC-63 murine scFv 4-1BB co-stimulatory domain
Viral transfer	Lentiviral	Gamma retroviral	Lentiviral
Collection	Resting state apheresis Cryopreserved Bulk cells	Resting state apheresis Fresh only Bulk cells	Resting state apheresis Fresh only Selection CD4 and CD8
Manufacture	CD3/CD28 stimulation	CD3/CD28 stimulation	CD4, CD8 selection CD3/CD28 stimulation
Dose administered	0.6–6.0 × 10^8 CAR T cells CoA based on cell recovery	2 × 10^6/kg Max. 200 × 10^6 No CoA	100 × 10^6 (CD4/CD8) in separate vials (1:1) Dose based on recovery
Histology	DLBCL tFL	DLBCL PMBCL tFL	DLBCL, HGBCL PMBCL tIndolent (FL, CLL, MZL)
CNS involvement	No	No	Secondary

Courtesy of David G Maloney, MD, PhD

ZUMA-1: durable responses with axi-cel in patients with R/R DLBCL

Updated long-term data (median follow-up: 51.1 months)



Patients, n (%)	Axi-cel (N = 111)
Deaths	66 (59)
Primary cause of death	
PD	52 (47)
Other	8[a] (7)
AEs	5[b] (5)
Secondary malignancy	1 (1)

Data cut-off date: August 11, 2020.

[a] Three events had no causal relationship (MDS, cardiac arrest), 4 events occurred post subsequent therapy (sepsis, infection, and pulmonary nocardiosis), and 1 event was unknown.

[b] One event was related to conditioning chemotherapy, 2 events had no causal relationship, and 2 events were related to axi-cel.

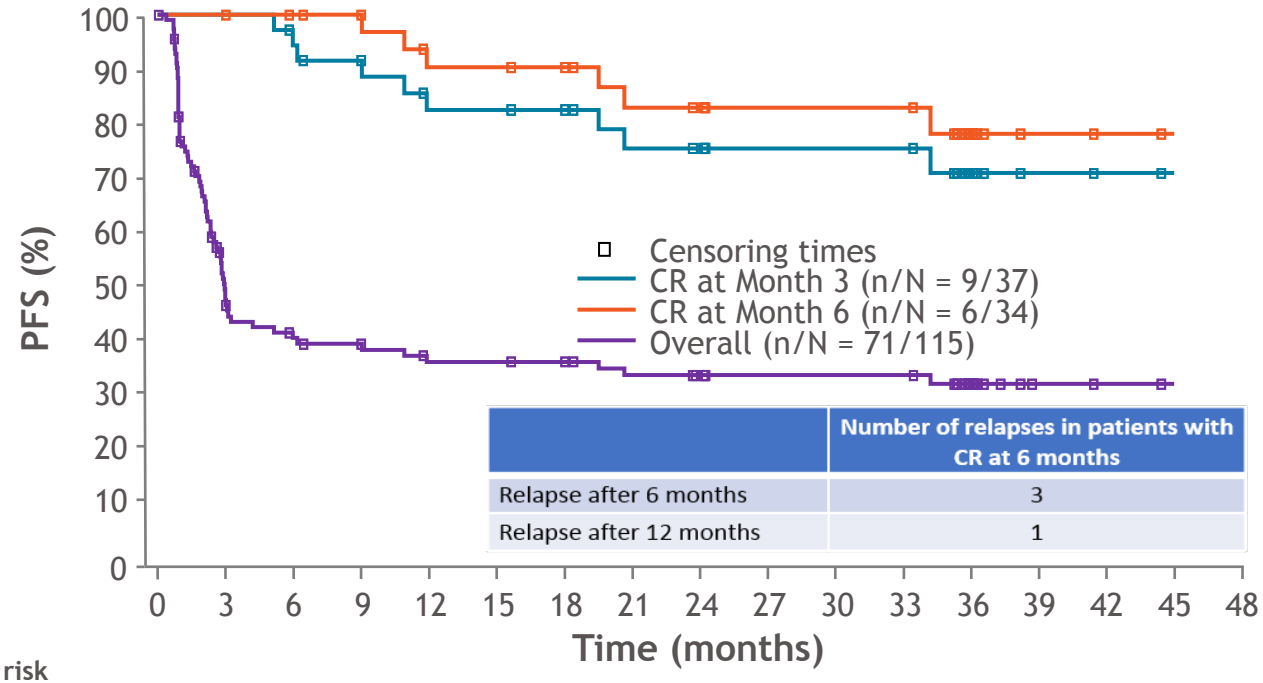
AE, adverse event; CI, confidence interval; MDS, myelodysplastic syndrome; NE, not estimable; PD, disease progression; RR, relapsed/refractory.

Jacobson C, et al. Long-term survival and gradual recovery of B cells in patients with refractory large B-cell lymphoma treated with axicabtagene ciloleucel. Poster presented at TCT 2021;abstract 494.

Courtesy of David G Maloney, MD, PhD

JULIET: sustained benefit of tisagenlecleucel in patients with R/R DLBCL

Updated long-term data (median follow-up: 40.3 months)[1]



	Number of relapses in patients with CR at 6 months
Relapse after 6 months	3
Relapse after 12 months	1

No. at risk																
CR at Month 3	37	37	33	31	26	26	25	21	20	17	17	17	7	2	1	0
CR at Month 6	34	34	33	32	27	27	26	22	21	18	18	18	8	2	1	0
Overall	115	47	38	36	31	31	30	26	24	21	21	21	11	2	1	0

- PFS at 24 and 36 months was 33% and 31%, respectively[1]
- Among responders, 60% were estimated to maintain response at 24 and 36 months[1]

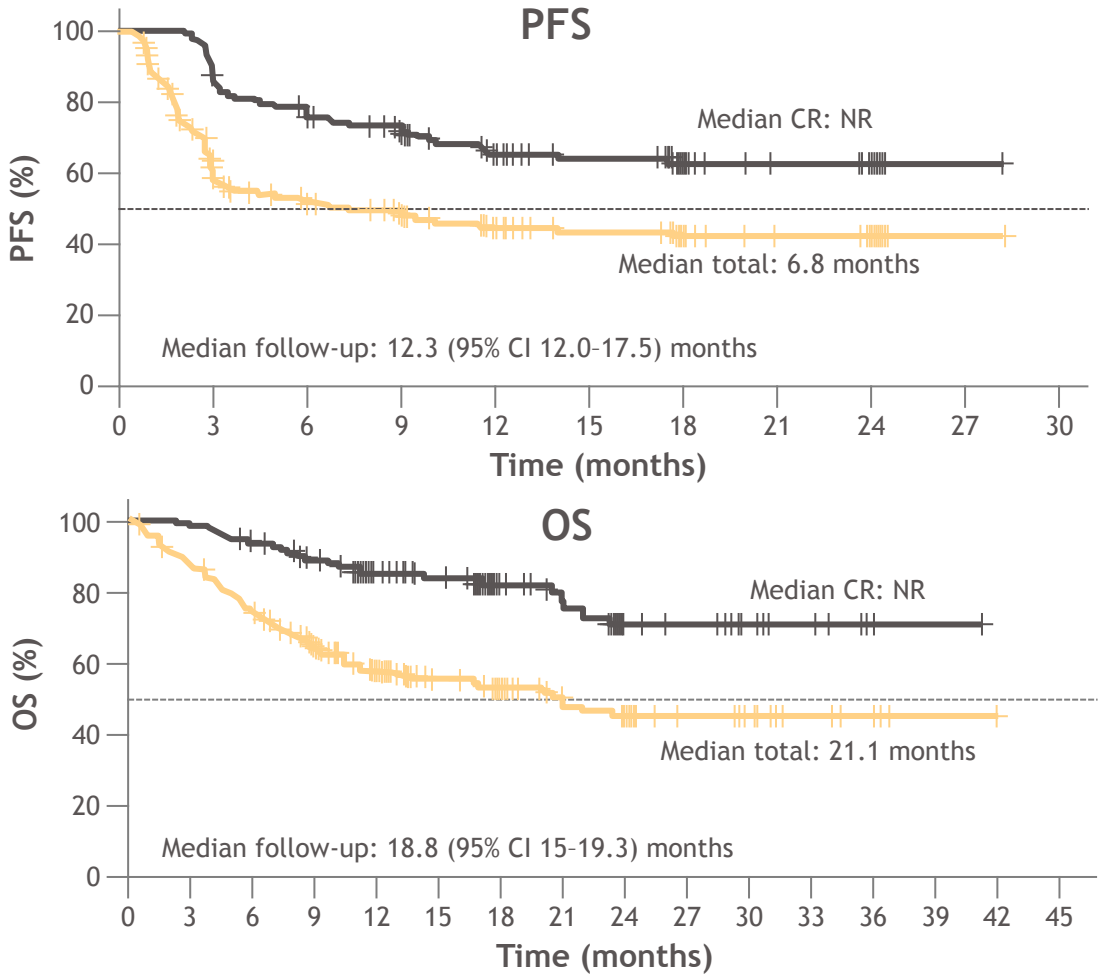
- With long-term follow-up, no new AEs were detected[1]
- Severe (Grade 3 or 4) CRS and neurologic events occurred in 23% and 11% of patients, respectively[2]
- No treatment-related deaths were reported

Data cut-off date: February 20, 2020.
Note: efficacy assessments were taken at Day 28, Month 3, 6, 9, 12, 18, 24, 36, 48, and 60, or as clinically indicated.
[a] Recorded during the first 8 weeks post infusion. [b] Lasting > 28 days. [c] Penn grading scale.
CR, complete response; PFS, progression-free survival, AE, adverse events

1. Jaeger U, et al. Myc expression and tumor-infiltrating T cells are associated with response in patients (pts) with relapsed/refractory diffuse large B-cell lymphoma (r/r DLBCL) treated with tisagenlecleucel in the Juliet trial. Presented at ASH 2020;abstract 1194. 2. Bachanova V, et al. Correlative analyses of cytokine release syndrome and neurologic events in tisagenlecleucel-treated relapsed/refractory diffuse large B-cell lymphoma patients. Presented at ICML 2019;abstract 254.

Courtesy of David G Maloney, MD, PhD

TRANSCEND NHL 001: efficacy and safety of liso-cel in patients with R/R LBCL



Characteristics	Patients (N = 269)
Median age, years (range)	63 (18-86)
Double-/triple-hit lymphoma, n (%)	36 (13)
CNS involvement, n (%)	7 (3)
Median prior lines of therapy, n (range)	3 (1-8)
Chemorefractory, n (%)	181 (67)
Best response	**Patients (N = 256)**
Best ORR, %	73
Best CR, %	53
12-month DOR, %	55
AEs	**Patients (N = 269)**
Any CRS, %	42
Median time to onset, days	5
CRS Grade ≥ 3, %	2
Any neurologic event, %	30
Neurologic event Grade ≥ 3, %	10

Data cut-off date: August 12, 2019.

Abramson JS, et al. Lisocabtagene maraleucel for patients with relapsed or refractory large B-cell lymphomas (TRANSCEND NHL 001): a multicentre seamless design study. Lancet. 2020;396:839-52.

Courtesy of David G Maloney, MD, PhD

Summary of CD19 CAR T cell therapies for aggressive lymphoma

Characteristics	Axi-cel	Tisagenlecleucel	Liso-cel
Lymphodepletion chemotherapy	Cy/Flu 500/30 mg/m^2 × 3 days	Cy/Flu 250/25 mg/m^2 × 3 days Bendamustine 90 mg/m^2 × 2 days	Cy/Flu 300/30 mg/m^2 × 3 days
Bridging therapy, %	Not allowed	92%	59%
Indication	DLBCL, High grade, PMBCL, tFL	DLBCL, High grade, tFL	DLBCL, HGBCL, PMBCL, tFL, tIND
ORR, %	82	53	73
CR, %	54	40	53
CRS overall/Grade 3/4, %	94/13	58/23[a]	42/2
Neurologic event overall/Grade 3/4, %	87/28	21/12	30/10
Outpatient treatment	No	Yes (26%)	Yes

Courtesy of David G Maloney, MD, PhD

Site and patient requirements for outpatient monitoring in TRANSCEND NHL 001, OUTREACH, and PILOT trials

Site requirements

- **University or non-university specialty oncology centers**
- HSCT or phase 1 trial capability
- Outpatient infusion center[a]
- Affiliated leukapheresis center
- Multidisciplinary medical team
  - Coordinates care between outpatient and inpatient setting
  - Standard operating procedures for outpatient monitoring and admission
  - 24/7 on-call oncologist

Hospital requirements

- **One designated hospital for CAR T cell patient care**
- CAR T cell AE management capability
  - Oncology ward, ICU, and ED medically staffed 24/7
  - Subspecialty care: neurology, cardiology, infectious disease
- Staff trained to manage CAR T cell toxicities (CRS, neurologic events, serious AEs)
- Tocilizumab available in pharmacy before liso-cel infusion

Patient and caregiver requirements

- **Caregiver support for the first 30 days after liso-cel infusion**
- Stay within 1 hour of site for 30 days
- Safety monitoring education to recognize early symptoms of CRS and neurologic events
- Commitment to return to site for immediate medical evaluation

Liso-cel has not yet obtained any regulatory approval outside of the USA and Japan. The safety and efficacy of this agent is still under investigation in other countries/regions. In the USA, liso-cel is indicated for r/r LBCL after two or more lines of therapy, including DLBCL NOS, HGBCL, PMBCL, and FL grade 3b. Prescribing Information may vary depending on local approval in each country or region. [a]CAR T cell therapy infusion could also be administered in the inpatient facility with subsequent discharge the same day at the end of the observation period. ED, emergency department; ICU, intensive care unit. Bachier C, et al. Outpatient treatment with lisocabtagene maraleucel (liso-cel) across a variety of clinical sites from three ongoing clinical studies in relapsed/refractory large B-cell lymphoma. Poster presented at EHA 2020; abstract EP1212.

Courtesy of David G Maloney, MD, PhD

Safety and efficacy of liso-cel in patients with R/R large B-cell NHL treated in the outpatient setting

Best overall response,[a] n (%)	All outpatients (N = 56)	TRANSCEND NHL 001 (n = 25)	OUTREACH (n = 19)[b]	PILOT (n = 12)[b]
ORR	47 (84)	20 (80)	16 (84)	11 (92)
CR	34 (61)	14 (56)	13 (68)	7 (58)
PR	13 (23)	6 (24)	3 (16)	4 (33)
SD	3 (5)	2 (8)	1 (5)	0
PD	6 (11)	3 (12)	2 (11)	1 (8)

Safety, n (%)	All outpatients (N = 59)	TRANSCEND NHL 001 (n = 25)	OUTREACH (n = 22)	PILOT (n = 12)
CRS any Grade	21 (36)	12 (48)	9 (41)	0
CRS Grade ≥ 3	1 (2)	1 (4)	0	0
Neurological event any Grade	17 (29)	11 (44)	6 (27)	0
Neurological event Grade ≥ 3	3 (5)	2 (8)	1 (5)	0
Tocilizumab alone	0	0	0	0
Steroid use	2 (3)	2 (8)	0	0
Tocilizumab and steroid use	4 (7)	1 (4)	3 (14)	0

Liso-cel has not yet obtained any regulatory approval outside of the US and Japan. The safety and efficacy of this agent is still under investigation in other countries/regions. In the US, liso-cel is indicated for r/r LBCL after two or more lines of therapy, including DLBCL NOS, HGBCL, PMBCL and grade 3b FL. Prescribing information may vary depending on local approval in each country or region.

[a] Per 2014 Lugano criteria.
[b] All patients with ≥ 1 efficacy assessment per protocol.
Bachier C, et al. Outpatient treatment with lisocabtagene maraleucel (liso-cel) across a variety of clinical sites from three ongoing clinical studies in relapsed/refractory large B-cell lymphoma. Poster presented at EHA 2020;abstract EP1212.

Courtesy of David G Maloney, MD, PhD

Progression of CAR T cell products to second line of therapy in LBCL?

- Various trials are ongoing

Axi-cel	Tisagenlecleucel	Liso-cel
ZUMA-7 trial	BELINDA trial	TRANSFORM trial
• Randomized, open label, phase 3 trial of second-line axi-cel versus standard of care in adult patients with r/r DLBCL	• Randomized, open label, phase 3 trial of second-line tisagenlecleucel versus standard of care in adult patients with r/r aggressive B-cell NHL	• Randomized, open-label, phase 3 trial of second-line liso-cel versus standard of care in adult patients with high-risk, transplant-eligible r/r aggressive B-cell NHL

Courtesy of David G Maloney, MD, PhD

Phase III ZUMA-7 Trial of Axi-Cel Meets Primary Endpoint

Press Release – June 30, 2021

"The ZUMA-7 trial (NCT03391466) demonstrated superiority of axicabtagene ciloleucel (axi-cel) compared with standard of care (SOC) autologous stem cell transplant (ASCT) after meeting the primary end point of event-free survival (EFS) improvement for patients with relapsed or refractory large B-cell lymphoma (LBCL), according to a press release from the company responsible for manufacturing the chimeric antigen receptor (CAR) T-cell therapy. A statistically significant EFS benefit (HR, 0.398; P <0.0001) was observed as well as improvement in the secondary end point of objective response rate (ORR).

The top-line results of the randomized ZUMA-7 trial paint the picture of a potential paradigm shift in the treatment of large B-cell lymphoma, Frederick L Locke, MD, ZUMA-7 lead principal investigator and co-leader of the Immuno-Oncology Program at Moffitt Cancer Center in Tampa, Florida, said in the press release. Investigators mentioned that these data are still immature and further analyses are planned for the future. The trial was conducted under a Special Protocol Agreement from the FDA where the trial design, end points, and statistical analysis were agreed in advance."

https://www.cancernetwork.com/view/zuma-7-trial-meets-event-free-survival-end-point-in-large-b-cell-lymphoma

RTP RESEARCH TO PRACTICE

Phase III TRANSFORM Trial of Liso-Cel Meets Primary Endpoint

Press Release – June 10, 2021

"Data from the Phase 3 TRANSFORM trial (NCT03575351) of the chimeric antigen receptor (CAR) T-cell therapy lisocabtagene maraleucel (liso-cel) as second-line therapy for patients with relapsed/refractory large B-cell lymphoma (LBCL) resulted in a statistically significant improvement in the primary end point of event-free survival versus therapy with the standard-of-care comparator arm, according to the company responsible for developing the agent.

Additionally, the toxicity profile observed with liso-cel was consistent with the safety data reported in the TRANSCEND NHL 001 trial (NCT02631044) which led to the FDA approving the CD19-directed therapy for patients with certain types of non-Hodgkin lymphoma, including diffuse large B-cell lymphoma (DLBCL), following 2 or more prior therapies. These data represent the first time a treatment for relapsed/refractory LBCL has demonstrated benefit over high-dose chemotherapy and hematopoietic stem cell transplant (HSCT).

Results regarding the primary end point will be evaluated and shared at an upcoming medical conference as well as with regulatory authorities."

https://www.cancernetwork.com/view/liso-cel-meets-primary-end-point-of-event-free-survival-improvement-in-phase-3-trial

RTP RESEARCH TO PRACTICE

Perspectives of moving CAR T cell therapy to the first line?

ZUMA-12: a phase 2, multicenter, open-label, single-arm study of axi-cel as part of first-line treatment in patients with high-risk LBCL

Eligibility criteria

- Age ≥ 18 years
- High-risk LBCL
  - HGBCL, with *MYC* and *BCL2* and/or *BCL6* translocations, or
  - LBCL with IPI score ≥ 3 any time before enrollment
- 2 cycles of anti-CD20 plus anthracycline-containing regimen
- Positive interim PET (DS 4 or 5)
- ECOG PS score 0 or 1

Enrollment/leukapheresis → Optional nonchemotherapy bridging therapy[a] →

Conditioning chemotherapy + axi-cel infusion

- Conditioning
  - Flu 30 mg/m^2 i.v. and Cy 500 mg/m^2 i.v. on Days −5, −4, and −3
- Axi-cel
  - Single i.v. infusion of 2 × 10^6 CAR T cells/kg on Day 0

Primary endpoint

- CR[b]

Key secondary endpoints

- ORR
- DOR
- EFS
- PFS
- OS
- Safety
- CAR T cells in blood and cytokine levels in serum

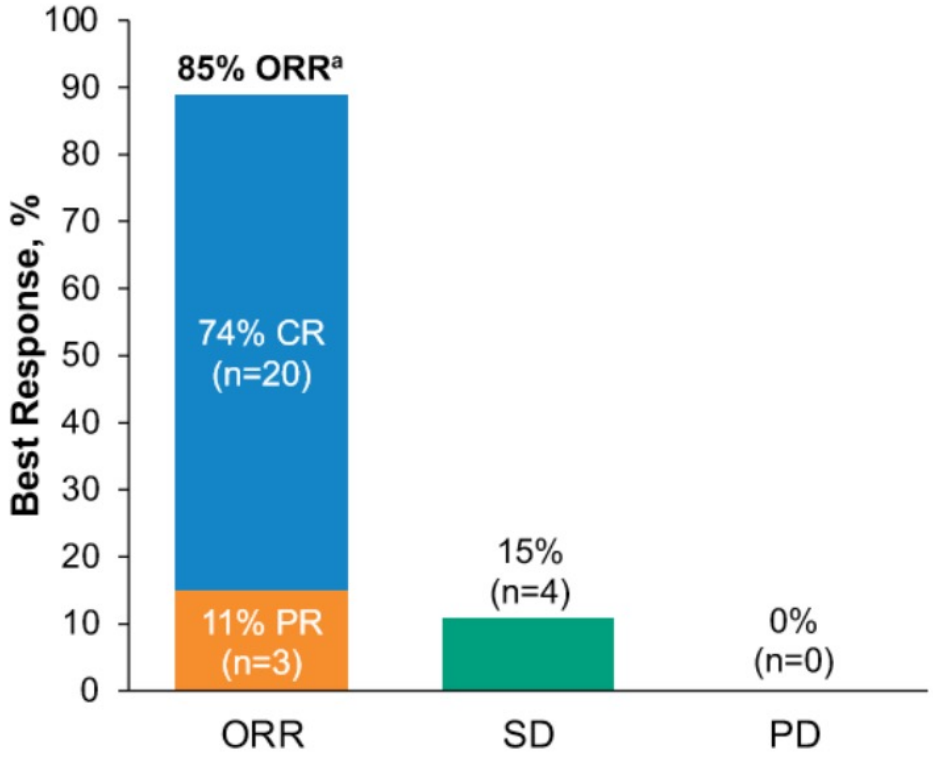
Courtesy of David G Maloney, MD, PhD

ZUMA-12: interim safety and efficacy results of axi-cel as first-line treatment

Baseline characteristics	Patients (N = 32)
Age	
Median (range), years	61 (23–86)
≥ 65 years, n (%)	13 (41)
Male, n (%)	23 (72)
Disease stage III or IV, n (%)	28 (88)
ECOG PS score ≥ 1, n (%)	21 (66)
1 prior line of systemic therapy, n (%)	32 (100)
Double-/triple-hit lymphoma, n (%)	17 (53)
IPI score ≥ 3, n (%)	23 (72)
DS 4, n (%)	16 (50)

Safety	CRS (N = 32)	Neurologic events (N = 32)
Any Grade, n (%)	32 (100)	22 (69)
Grade ≥ 3, n (%)	3 (9)	8 (25)
Grade 4, n (%)	0	2 (6)
Grade 5, n (%)	0	0
Most commonly associated any-Grade symptoms, n (%)	Pyrexia: 32 (100) Chills: 8 (25) Hypotension: 8 (25)	Encephalopathy: 10 (31) Confusional state: 9 (28)

ORR and CR in response-evaluable cohort[b] (N = 27)



Data cut-off date: July 15, 2020.

[a] In the safety-evaluable set (N = 32), the ORR was 88% and CR rate was 78%.

[b] Includes all treated patients with centrally confirmed disease type (double-/triple-hit lymphomas) or IPI score ≥ 3 who received ≥ 1×10^6 CAR T cells/kg and had ≥ 1 month of follow-up

Neelapu SS, et al. Interim analysis of ZUMA-12: A phase 2 study of axicabtagene ciloleucel (axi-cel) as first-line therapy in patients (Pts) with high-risk large B cell lymphoma (LBCL). Oral presentation at ASH 2020;abstract 405.

Courtesy of David G Maloney, MD, PhD

Case Presentation – Dr Maloney: A 57-year-old man with refractory Primary Mediastinal B-cell Lymphoma (PMBCL)

57 year old man with refractory PMBCL with massive chest disease as well as nodules in lungs and abdomen. Presented in 12/2015 with neck swelling and early SVC syndrome.

PATH: Biopsy showed PMBCL, CD20 positive 11 x 7 cm mass.

Prior treatments:

R-EPOCH x 6 with good, but not complete response on PET.

PD 2 months later- treated with XRT.

11/2016 PET showed CR

Relapsed 4/2017, 11 x 10 cm mass, SUV 18.9.

Bx: PMBCL, CD19 positive

5/2017 R-ICE x 1 mixed response

Lenolidomide- PD

R- Gem/dex - PD

Referred to Fred Hutch IMTX service for clinical trial with JCAR-017 (Lisocabtagene Maraleucel)

Cells collected

Required R-gem/dex bridging

PET pre (see image) 11 x 7.4 cm mass (SUV 16.7), encasing pulmonary vessels

Cy/Flu lymphodepletion

Courtesy of David G Maloney, MD, PhD

Case Presentation – Dr Maloney: A 57-year-old man with refractory PMBCL (continued)

CAR-T cells infused (outpatient)

Day 4- Admitted overnight with low grade fever and discharged.

No significant CRS and no NT.

PET/CT day 30 showed PR that continued to improve.

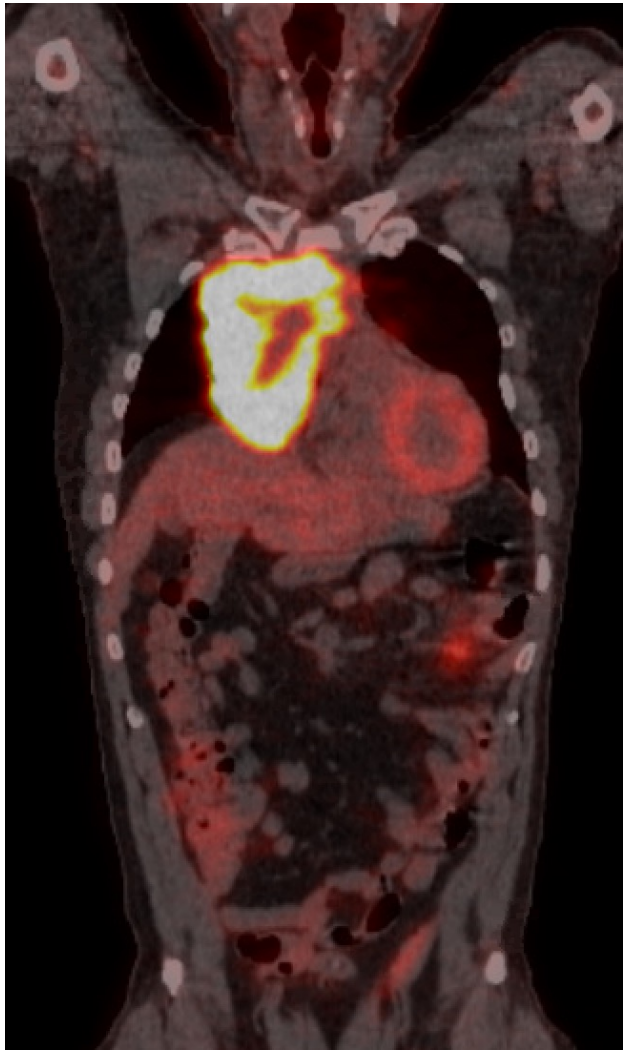
Month 9 and 12 PET showed CR (see image from 1 year)

Continues in CR to date.

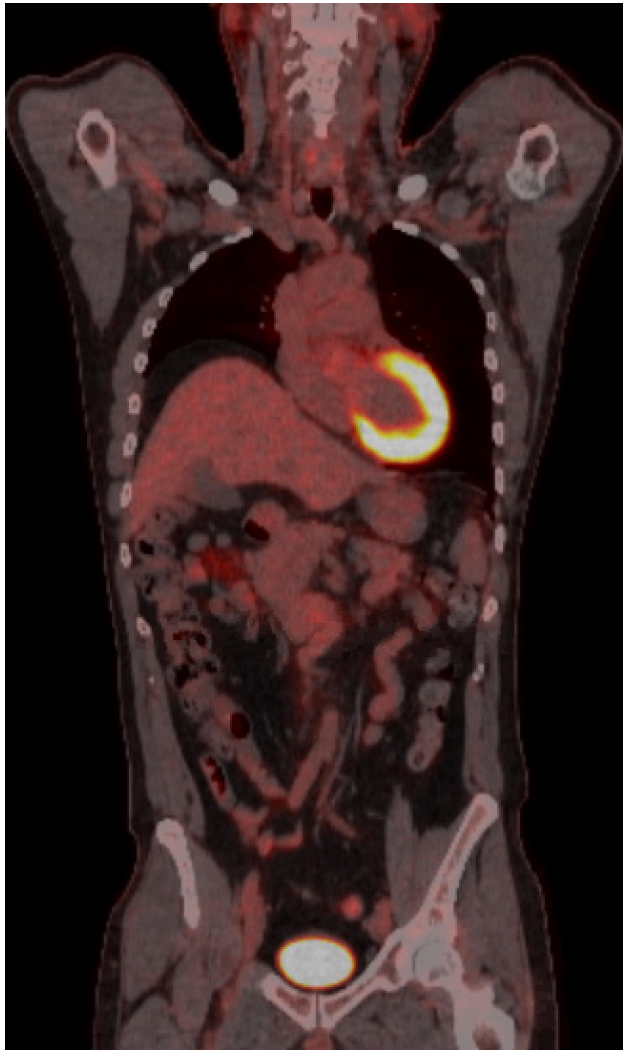
Courtesy of David G Maloney, MD, PhD

Case Presentation – Dr Maloney: A 57-year-old man with refractory PMBCL (continued)

Pre Lisocabtagene Maraleucel



1 year post Lisocabtagene Maraleucel



Courtesy of David G Maloney, MD, PhD

Case Presentation – Dr Maloney: A 61-year-old man with double-hit DLBCL

5/2017. 61 year old man with double hit DLBCL with widespread abdominal disease. Presented with NS, weight loss, abdominal pain. Stage IVB disease. Negative bone marrow and CNS.

PATH: Double hit (myc/bcl2) DLBCL, CD10 positive, GC like.

Prior treatments:

DA-EPOCH-R x 6 cycles, Dose escalation to dose level 4 with IT MTX x 4

PET PR (Primary refractory)

Rapidly presented with bowel obstruction requiring surgery- Path:DLBCL

R-ICE x 2 PD

Referred to Fred Hutch IMTX service for commercial CAR-T (axicabtagene ciloleucel)

1/2018 cells collected

Rapidly progressive disease required DA-EPOCH-R with Flu as bridging

PET/CT pre (see image) PD, Deauville score =5

2/28 Cy/flu lymphodepletion and commercial CAR-T infusion

-CRS grade 2- treated with Toci x 1, dex, 10 mg x 2

-NT grade 2

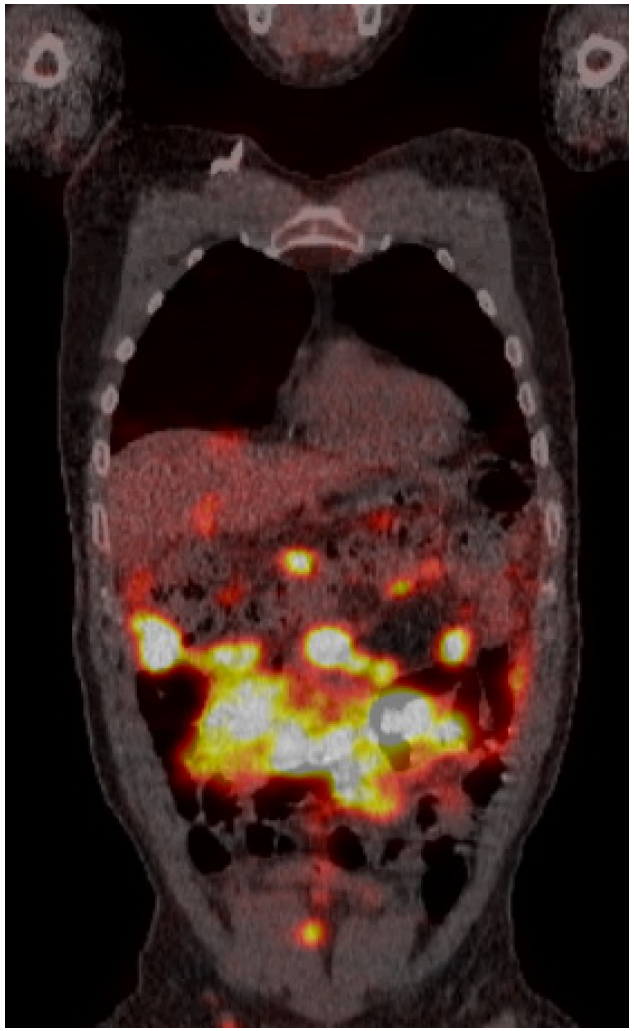
Day 30 PET/CT- (see image) CR, Deauville score of 2.

Had some persistent cytopenias that resolved, requires IVIG. Continues in CR to date.

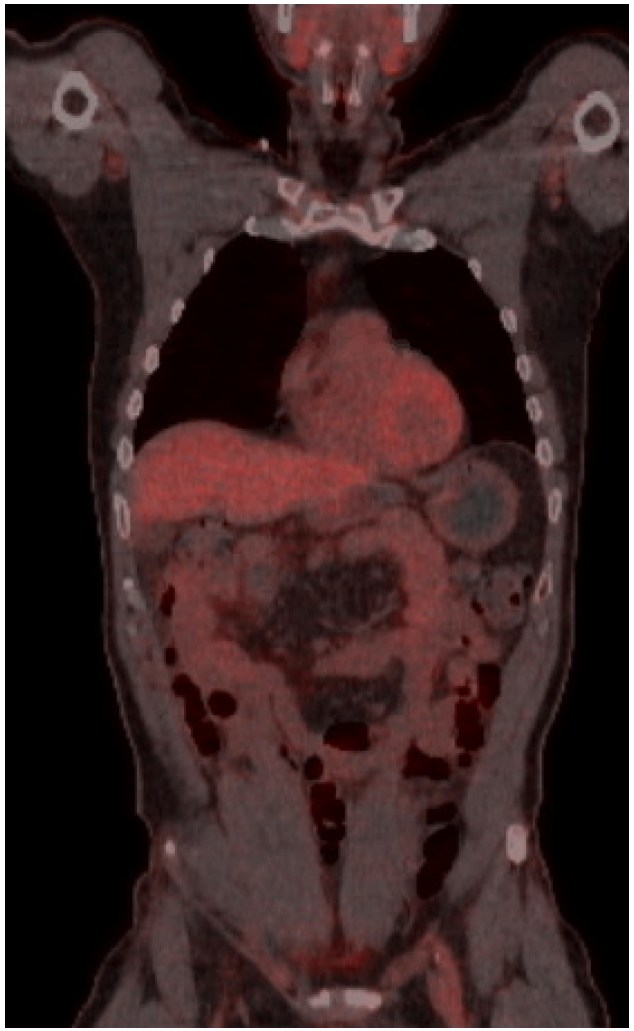
Courtesy of David G Maloney, MD, PhD

Case Presentation – Dr Maloney: A 61-year-old man with double-hit DLBCL (continued)

Pre axicabtagene ciloleucel



1 month Post axicabtagene ciloleucel



Courtesy of David G Maloney, MD, PhD

Agenda

Module 1: Diffuse Large B-Cell Lymphoma (DLBCL)

- Mechanistic similarities and differences between axicabtagene ciloleucel (axi-cel), tisagenlecleucel (tis-cel) and lisocabtagene maraleucel (liso-cel)
- Efficacy and safety of axi-cel, tis-cel and liso-cel in DLBCL
- Management of class-effect and other toxicities observed with CD19-directed CAR T-cell therapy
- Faculty cases

Module 2: Other Lymphoma Subtypes

- ZUMA-2: Brexucabtagene autoleucel (brex-cel) in relapsed/refractory (R/R) MCL
- ZUMA-5: Axi-cel for R/R follicular lymphoma
- ELARA: Tis-cel in patients with R/R indolent lymphomas
- Early efficacy and safety data with CD19-directed CAR T-cell therapy in patients with R/R CLL
- TRANSCEND CLL 004: Liso-cel in R/R CLL
- Faculty cases

Module 3: Multiple Myeloma (MM)

- KarMMa: Idecabtagene vicleucel (ide-cel) in patients with R/R MM; recent FDA approval
- CARTITUDE-1: Ciltacabtagene autoleucel (cilta-cel) for R/R MM
- Management of class-effect and other toxicities observed with BCMA-targeted CAR T-cell therapy
- Faculty cases

RTP
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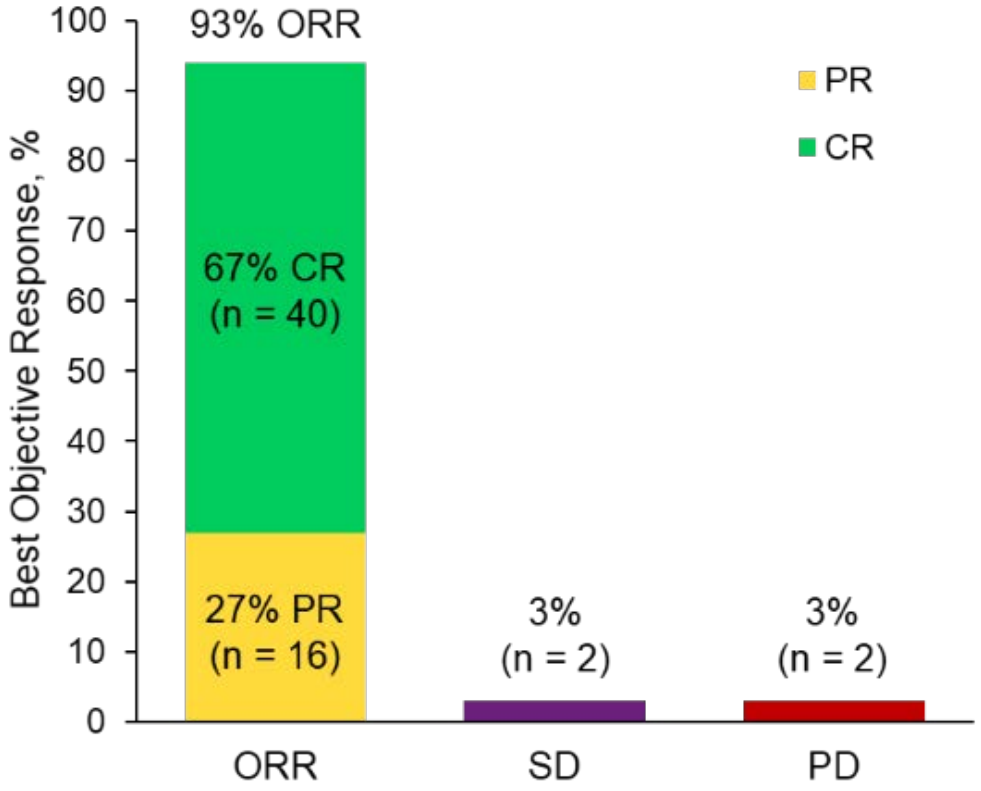
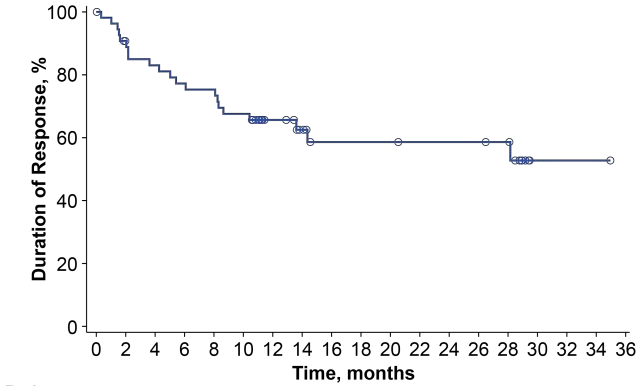
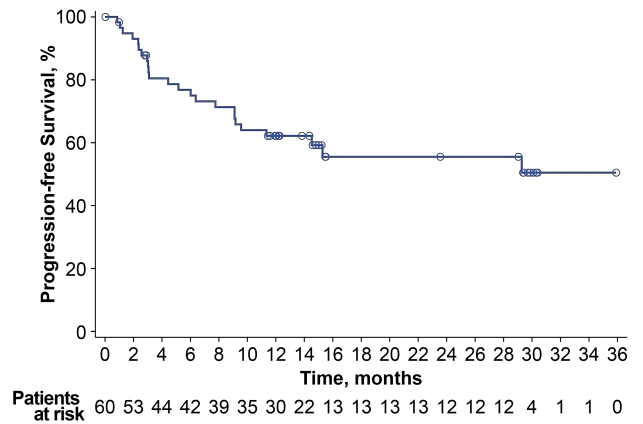
ZUMA-2: Brexucabtagene autoleucel in MCL



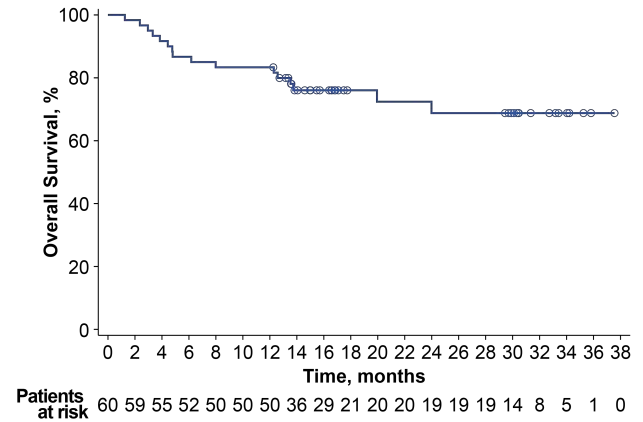
DOR



PFS



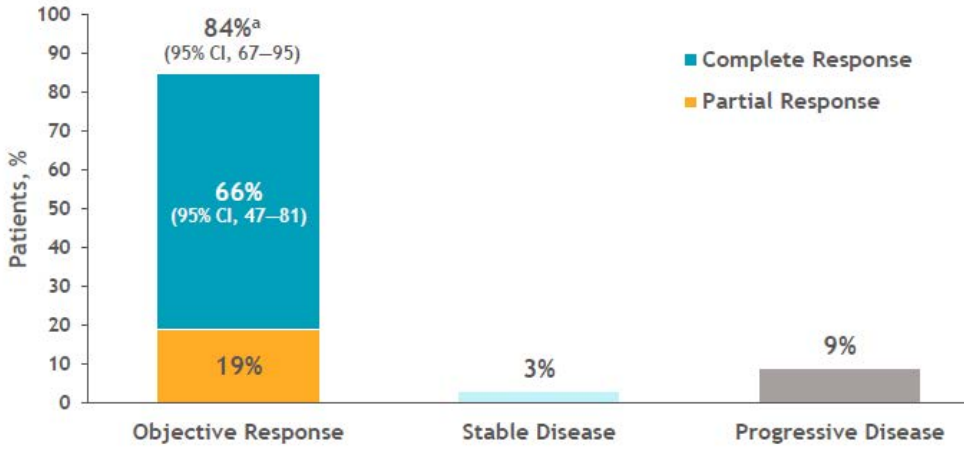
OS



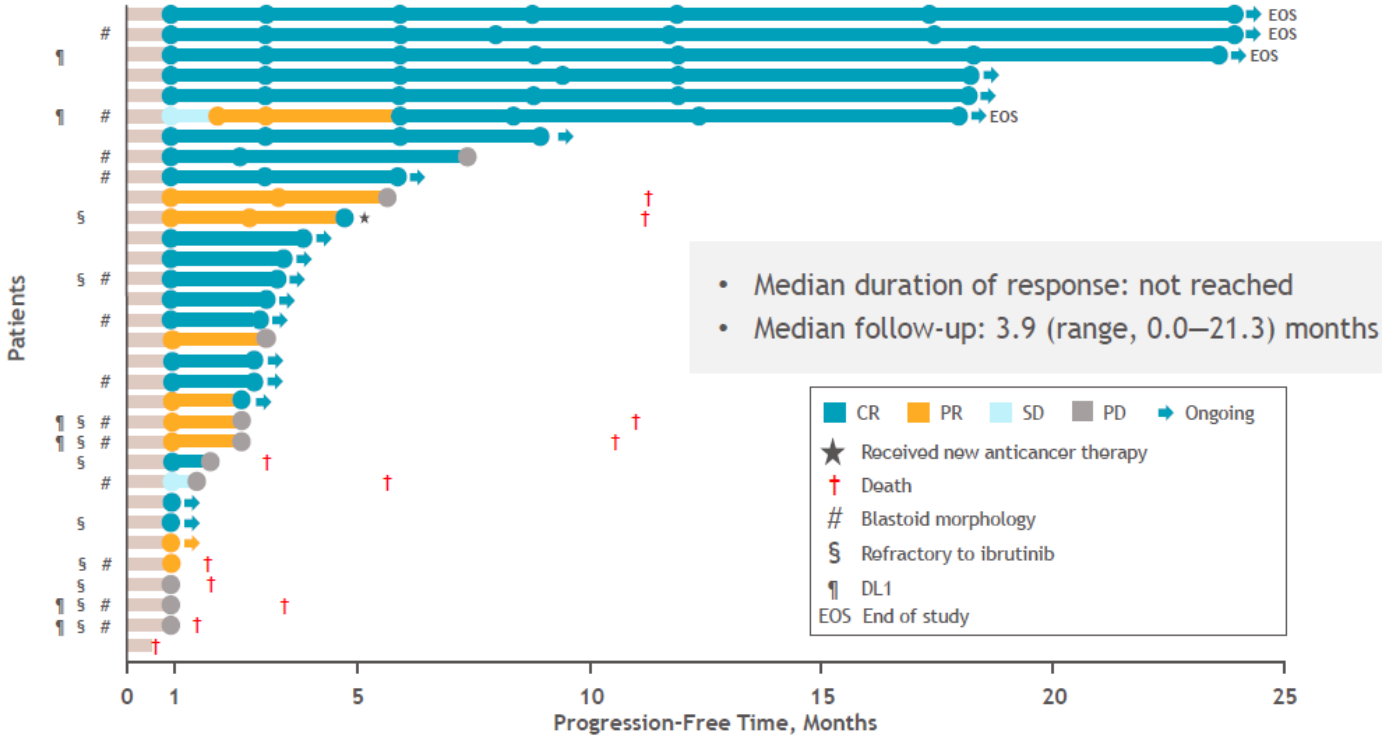
Wang M, et al. N Engl J Med. 2020;382:1331–42; Wang et al ASH 2020.

Courtesy of Caron Jacobson, MD

TRANSCEND NHL 001 Outcomes



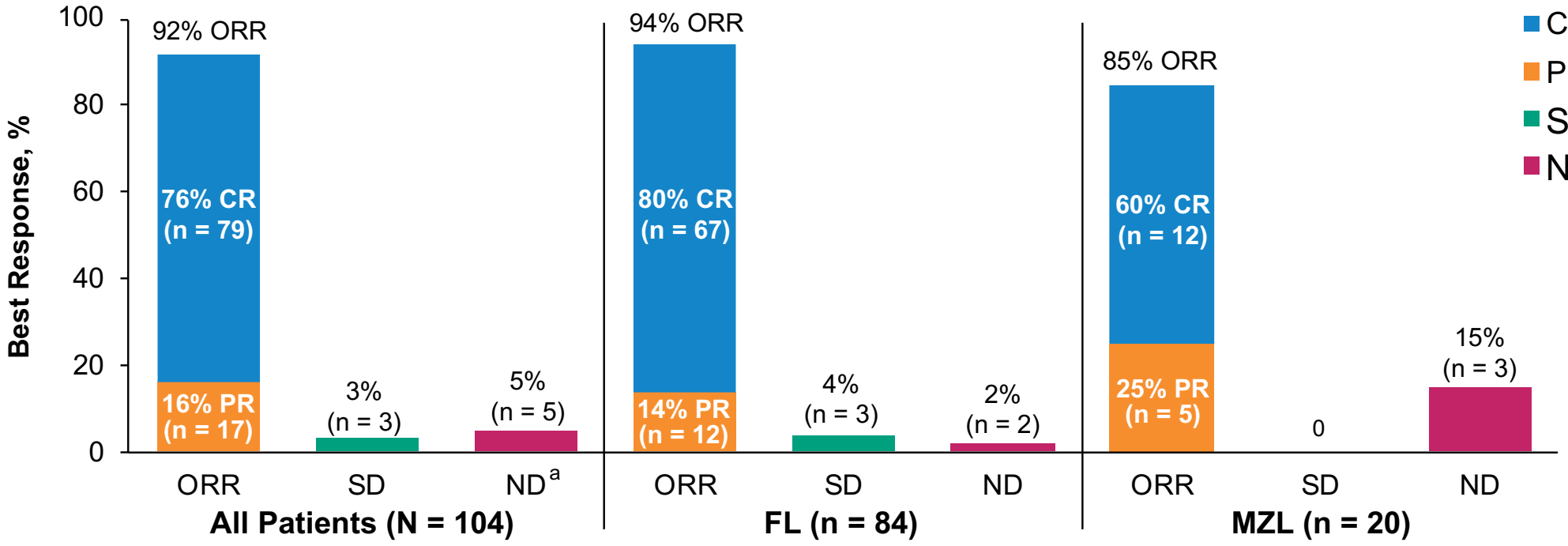
	All liso-cel–Treated Patients (N = 32)
CRS or NE, n (%)	
Any grade	19 (59)
Grade ≥3	5 (16)
CRS	
Any grade, n (%)	16 (50)
Grade ≥3, n (%)	1 (3)
Time to onset, median (range), days	6 (2–10)
Time to resolution, median (range), days	4 (2–9)
NE	
Any grade, n (%)	11 (34)
Grade ≥3, n (%)	4 (12.5)
Time to onset, 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



Courtesy of Caron Jacobson, MD

Palomba et al. ASH 2020;Abstract 118.

ZUMA-5 Outcomes: ORR and CR



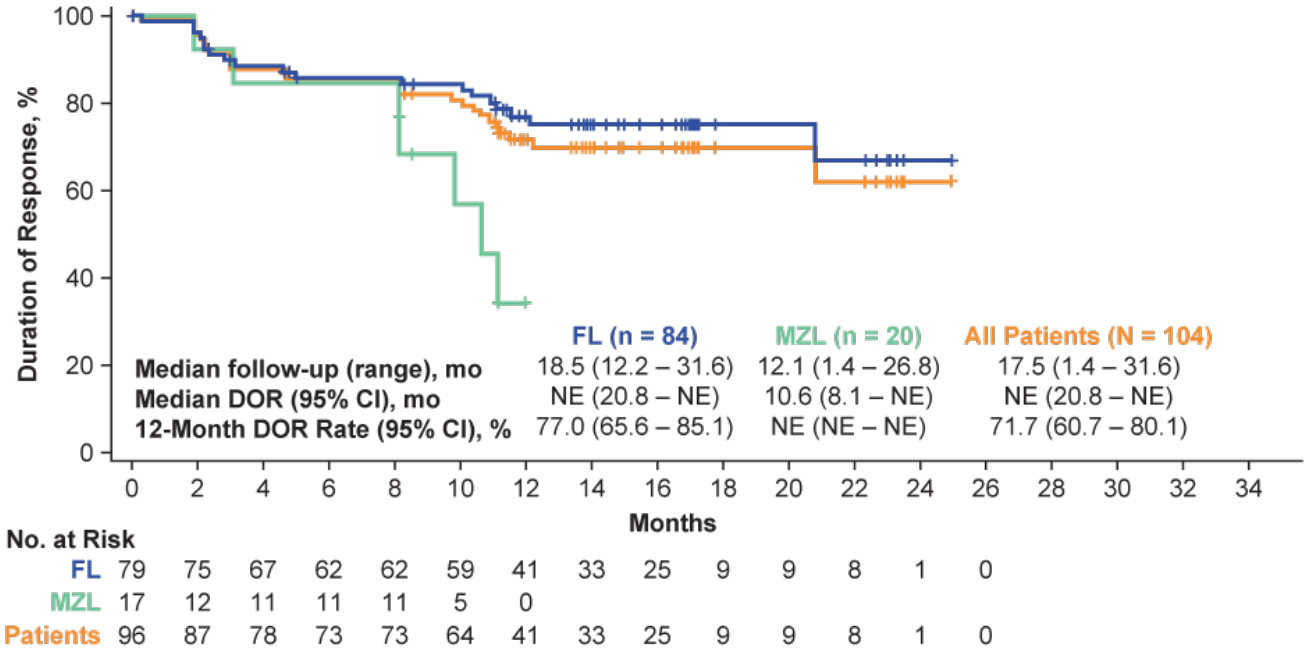
- The median time to first response was 1 month (range, 0.8 – 3.1)
- Among the 25 patients with FL who initially had a PR, 13 (52%) subsequently converted to a CR after a median of 2.2 months (range, 1.9 – 11.2)

Jacobson et al. ASH 2020;Abstract 700.

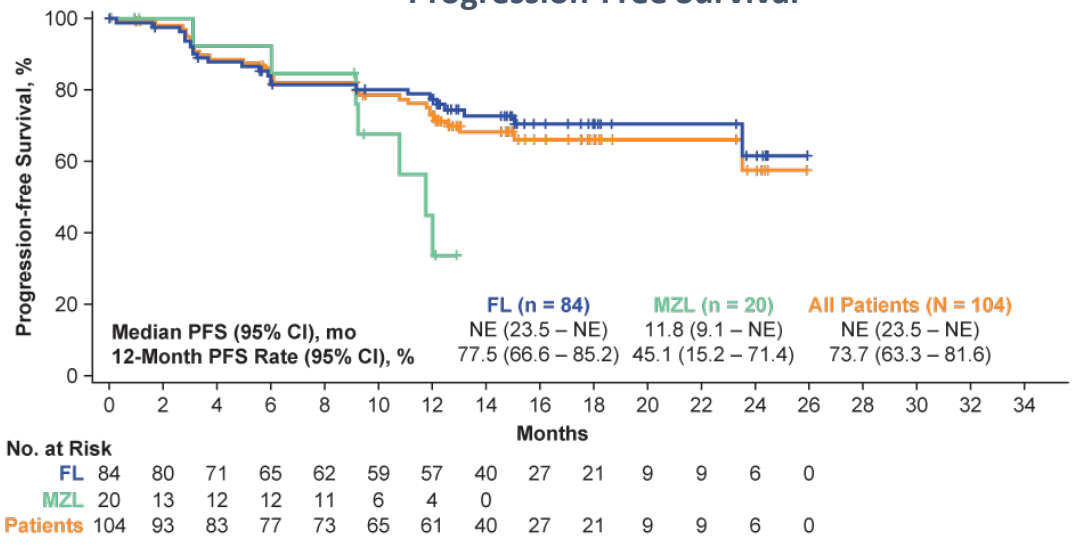
Courtesy of Caron Jacobson, MD

ZUMA-5 Outcomes: DOR, PFS, OS

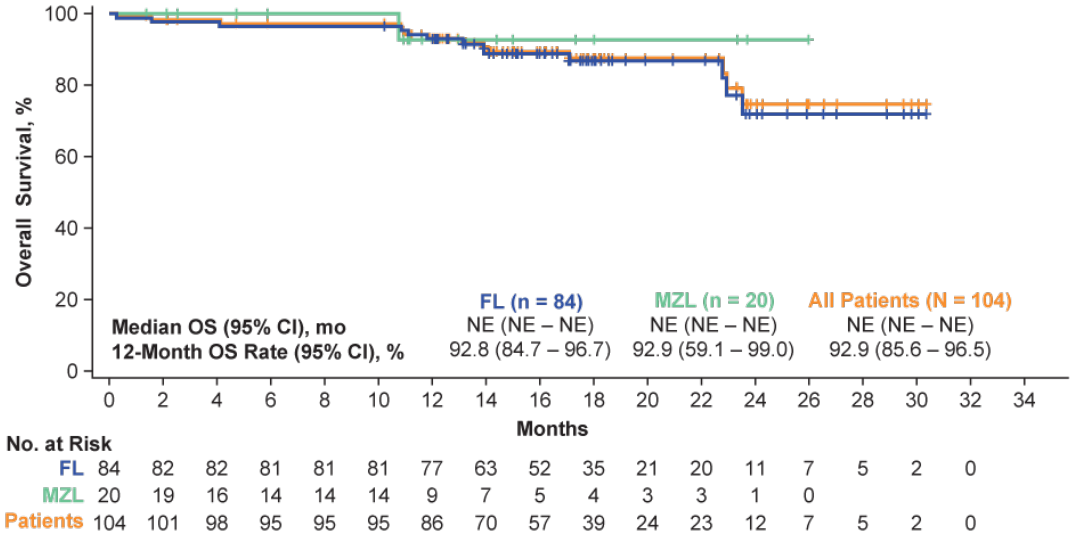
Duration of Response



Progression-Free Survival



Overall Survival



Jacobson et al. ASH 2020;Abstract 700.

Courtesy of Caron Jacobson, MD

FDA Approvals in MCL and FL: Who Should be Referred for CAR T-cells?

- FDA label very broad:
  - **Relapsed/refractory MCL** (no restrictions on prior lines of therapy)
  - **Relapsed/refractory FL** after 2 lines of systemic therapy
  - **No upper age limit**
  - No evidence that tumor must demonstrate CD19+
- We have learned from aggressive lymphoma that referral timing matters! Best to refer as early as possible!
- For MCL, best to refer when the patient starts a BTK inhibitor or refer all patients with high-risk features
- For FL, there is generally more time and it is challenging to identify high-risk patients but would consider referral for any patient who has relapsed within 24m of initial therapy or who requires 3rd line therapy
- Same special considerations/lessons from DLBCL remain:
  - i.e. Disease pace and burden, ECOG PS, organ dysfunction, underlying autoimmune and neurologic conditions
  - Refer everyone! Allow CAR T-cell center to assess eligibility as criteria differ between centers

Courtesy of Caron Jacobson, MD

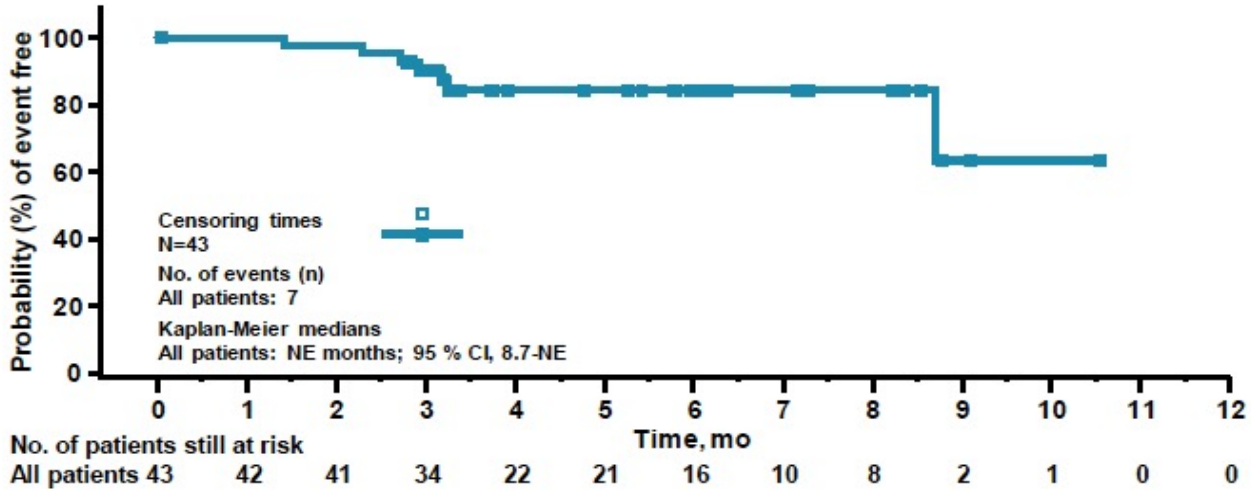
Tisa-cel in R/R FL: ELARA ORR, DOR, Safety

Best Overall Response Rate

Response Rate, %	Patients Evaluable for Efficacy[a] (n=52)
CR	65.4[a]
PR	17.3
ORR (CR + PR)	82.7

- Investigator-assessed CR rate was 67.3%[b] (ORR 88.5%)
- ORR was consistent across subgroups, including prior SCT, disease status, and high-risk features

At 10 Months Median Follow-up for Efficacy, Median DOR Not Reached



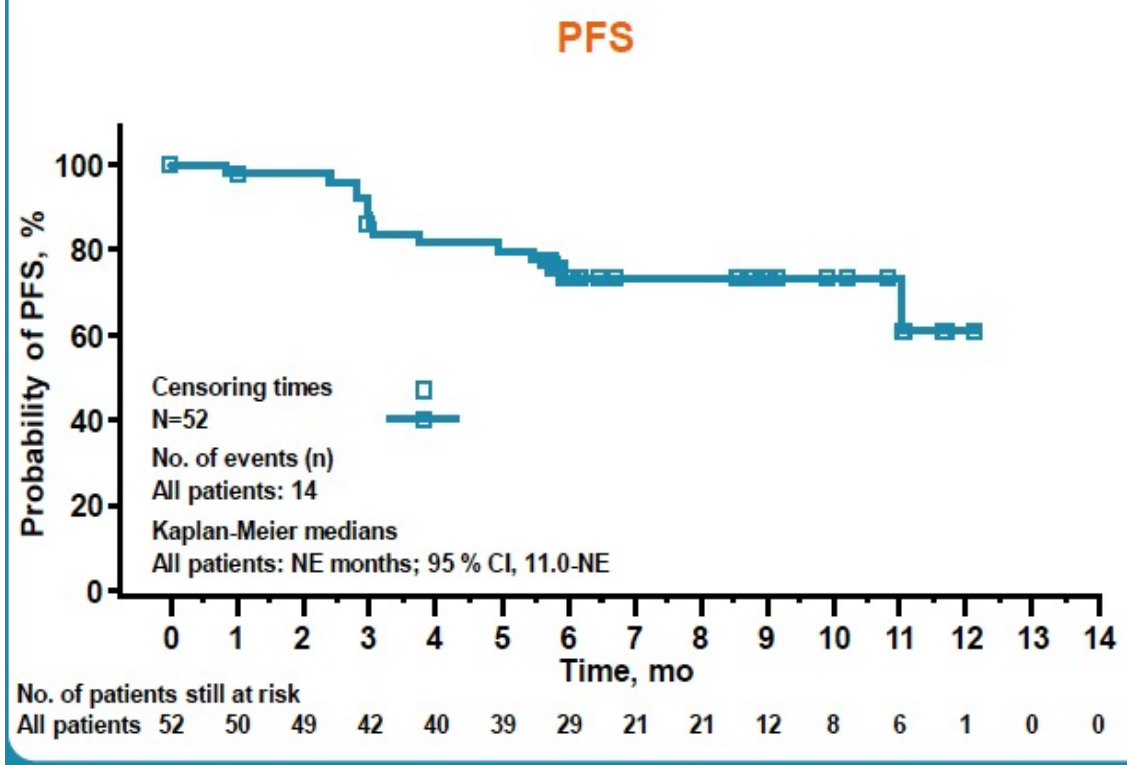
- Median follow-up for efficacy (n=52): 9.9 months (6.0-15.6)
- Probability for a responding patient to remain in response ≥6 months was 84.4%
- 8 of 18 PRs (44%) converted to CRs; all but 1 occurred between Month 3 and Month 6
- Median time to next antilymphoma treatment was not reached
- 69% (36/52) had ongoing responses at the time of data cutoff

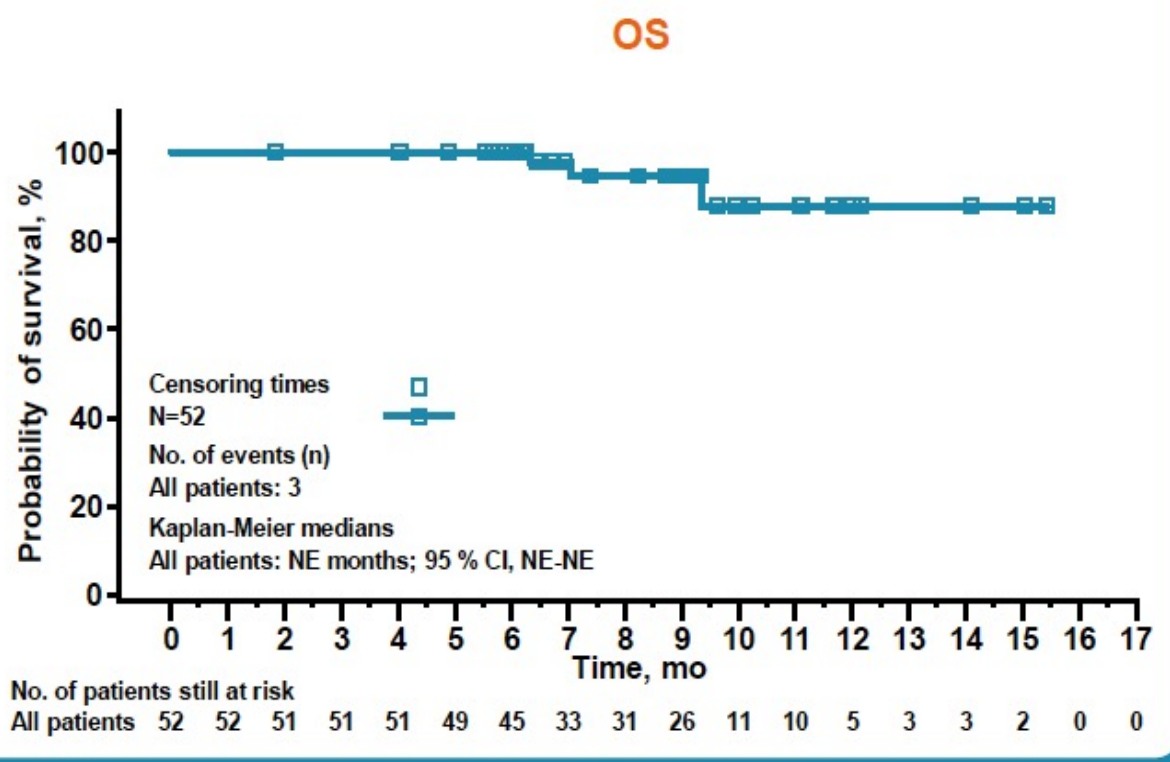
First efficacy assessment conducted at Month 3.
[a]$P<0.0001$; indicates statistical significance (1-sided) at the 0.0025 level so that the null hypothesis CRR≤0.15 is rejected. [b]95% CI, 52.9-79.7.
CI, confidence interval; CR, complete response; DOR, duration of response; PR, partial response; ORR, overall response rate; SCT, stem cell transplant.

Fowler et al. ASH 2020;Abstract 1149.

Courtesy of Caron Jacobson, MD

ELARA: PFS and OS





- Median PFS and median OS were not reached, 95% CI (11-NE) and 95% CI (NE-NE), respectively
- 6-month PFS was 73.2% (95% CI, 58.2-83.5)

Fowler et al. ASH 2020;Abstract 1149.

Courtesy of Caron Jacobson, MD

Ongoing Studies

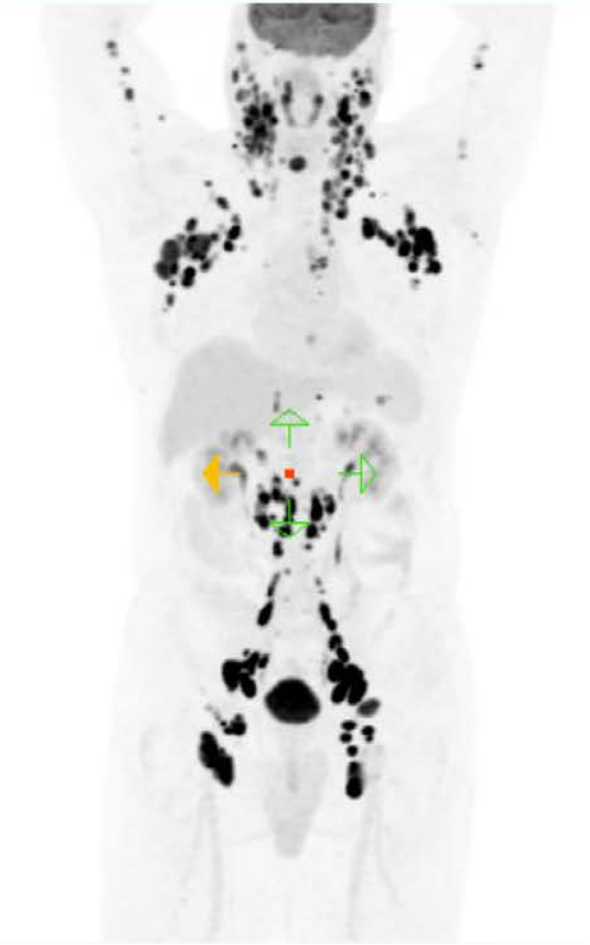
- Mantle-cell lymphoma
  - TRANSCEND NHL 001 (Liso-cel)
  - ZUMA-2 Cohort 2: relapsed MCL pre-BTK inhibition (Brexu-cel)
- Indolent B-NHL
  - ZUMA-5 in marginal zone lymphoma (Axi-cel)
  - ELARA (Tisa-cel)
  - TRANSCEND FL (Liso-cel)
- CLL
  - TRANSCEND CLL 004 (Liso-cel)
  - ZUMA-8 (Brexu-cel)
- Phase 1/2 studies of new products: allo and NK CAR, dual antigen targeting CARs

Courtesy of Caron Jacobson, MD

Case Presentation – Dr Jacobson: A 55-Year-Old Man with Refractory Mantle-Cell Lymphoma

55 year-old man with relapsed TP53 mutated MCL, blastoid variant, Ki67 80%

- Diagnosed 11/2017 with weight loss and fatigue; CT scans showed LAD and splenomegaly. Biopsy blastoid MCL with a TP53 mutation
- 1/2018-2/2018: cycles 1-3 BR
  - PET with SD
- 3/2018-5/2018: cycles 1-3 R-araC
  - PET with SD
- 6/2018-9/2018: acalabrutinib
  - PET with PD
- Received CAR T-cells on a clinical trial on 11/13/2018
  - Course c/b grade 1 CRS and no ICANS. Neither Toci nor dex were given
  - Discharged home on day +8



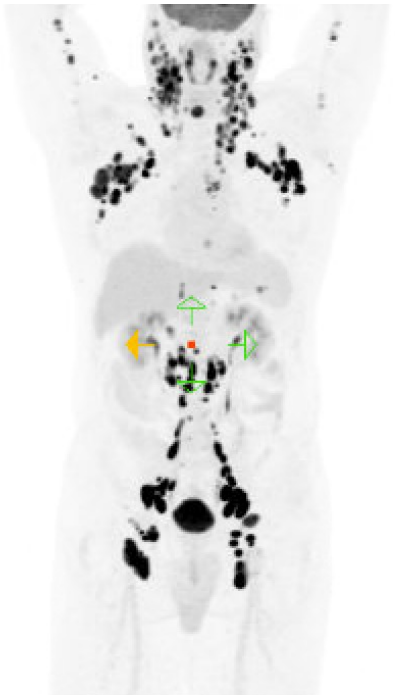
Courtesy of Caron Jacobson, MD

Case Presentation – Dr Jacobson: A 55-Year-Old Man with Refractory Mantle-Cell Lymphoma (continued)

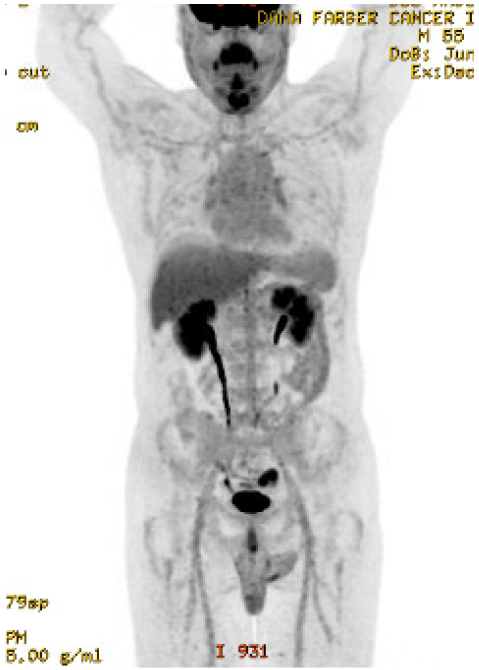
Dana-Farber Cancer Institute

The Jimmy Fund

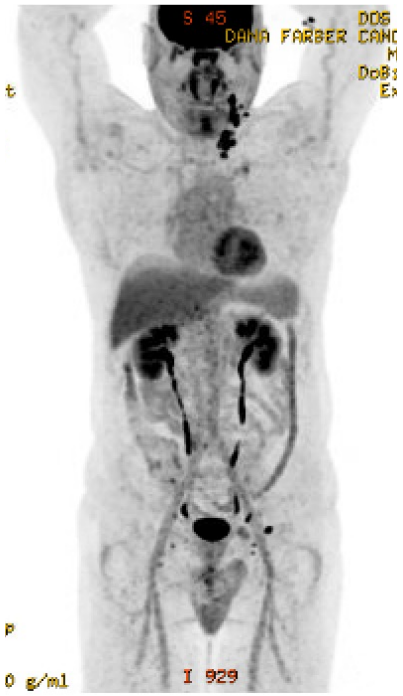
Pre-treatment



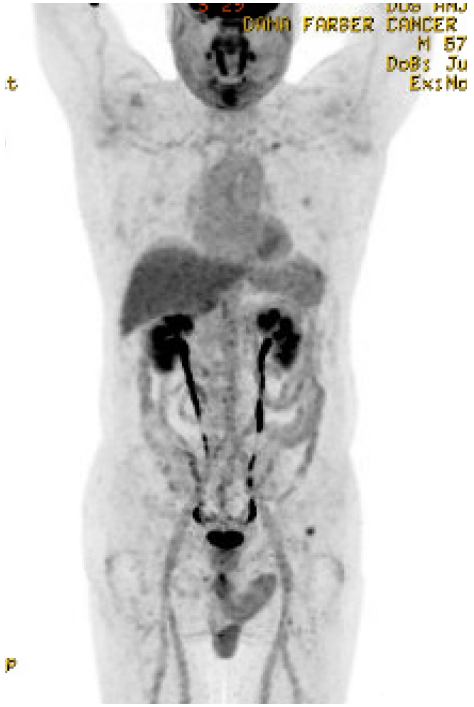
1 month



1 year



2 years

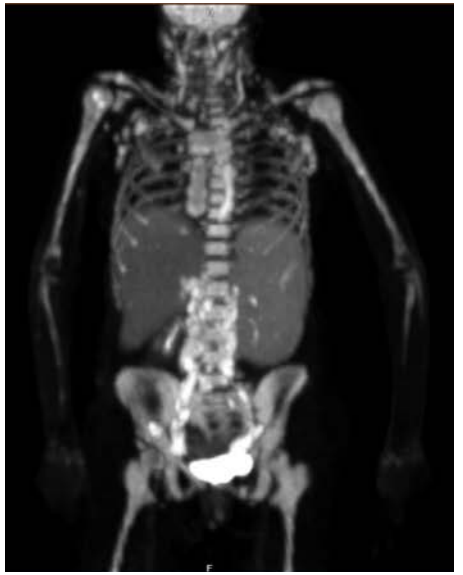


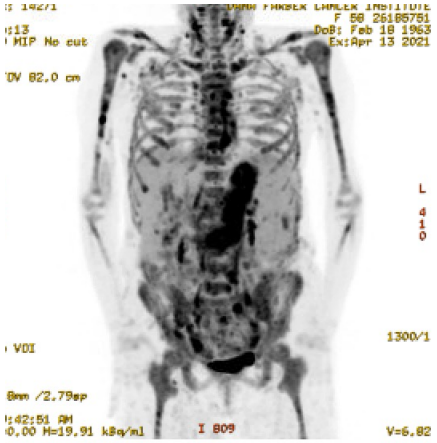
Courtesy of Caron Jacobson, MD

Case Presentation – Dr Jacobson: A 58-Year-Old Woman with Refractory Follicular Lymphoma

58 year-old woman with multiply relapsed and refractory FL

- Diagnosed 7/2011 with asymptomatic LAD and observed for 3 years off treatment
- 3/2014-8/2014 cycles 1-6 **BR** due to paraneoplastic rash with **CR**
- 2/2019: recurrence of rash prompting CT scans that showed low volume recurrent disease, confirmed on biopsy
- 2/2019-3/2019: **single agent rituximab** with **PD**
- 6/2019-9/2019: **O-CVP x4** with **PD**, rebiopsy c/w FL (CD20 negative)
- 10/2019-12/2019: **clinical trial** of combination immunotherapy with **PD**
- 1/2020-8/2020: **lenalidomide** with initial PR but then **PD**
- 8/2020-10/2020: **copanlisib** with mixed response but ultimate **PD** in marrow and spleen; bone marrow biopsy c/w FL (still CD20 negative)
- 10/2020-11/2020: dose reduced **ICE** with **PD**
- 12/2020-1/2021: **polatuzumab** with **SD** but c/b cytopenias, bleeding and DIC
- 2/2021-4/2021: **venetoclax** with **SD** by marrow and imaging but good clinical response





Courtesy of Caron Jacobson, MD

Case Presentation – Dr Jacobson: A 58-Year-Old Woman with Refractory Follicular Lymphoma (continued)

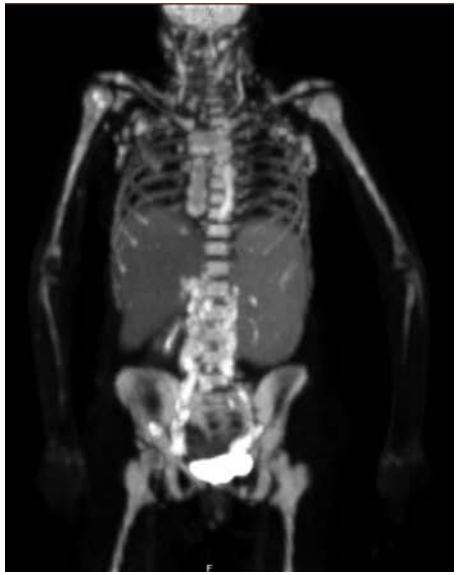
58 year-old woman with multiply relapsed and refractory FL

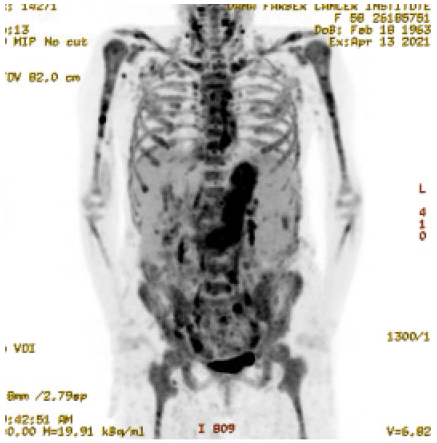
- Diagnosed 7/2011 with asymptomatic LAD and observed for 3 years off treatment
- 3/2014-8/2014 cycles 1-6 **BR** du
- 2/2019: recurrence of rash prom
  disease, confirmed on biopsy
- 2/2019-3/2019: **single agent ritu**
- 6/2019-9/2019: **O-CVP x4** with **R**
- 10/2019-12/2019: **clinical trial** c
- 1/2020-8/2020: **lenalidomide** w
- 8/2020-10/2020: **copanlisib** with
  spleen; bone marrow biopsy c/w
- 10/2020-11/2020: dose reduced **ICE** with **PD**
- 12/2020-1/2021: **polatuzumab** with **SD** but c/b cytopenias, bleeding and DIC
- 2/2021-4/2021: **venetoclax** with **SD** by marrow and imaging but good clinical response

Treated with CD19 CAR T-cells on 4/21/2021

Course complicated by grade 1-2 CRS (fevers and mild transaminitis) treated with tocilizumab

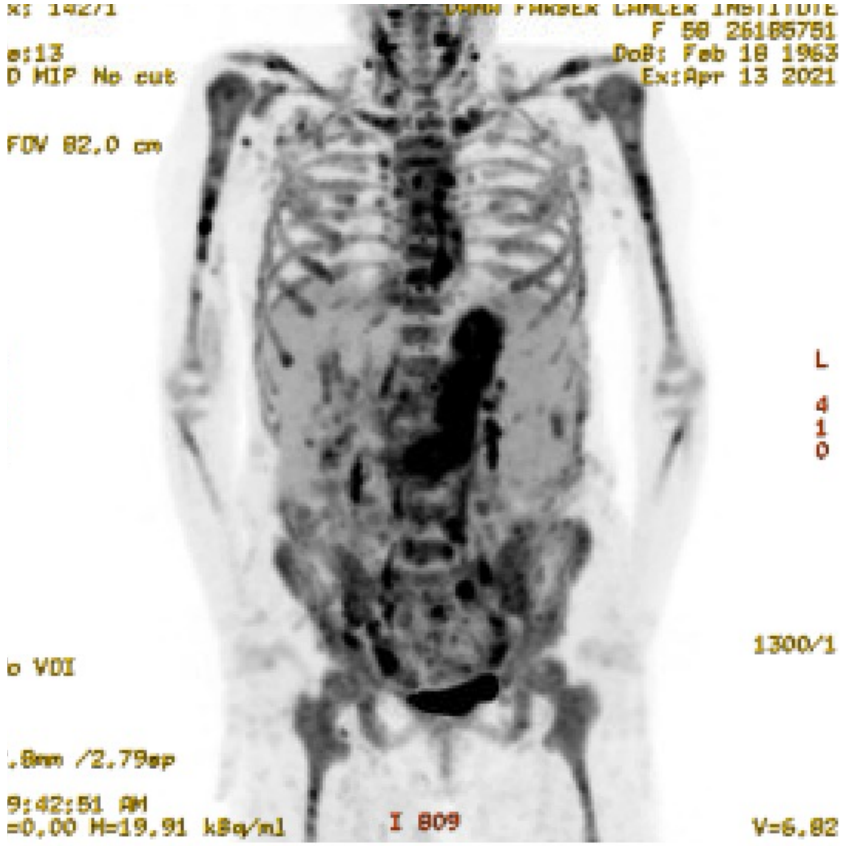
Discharged home on day +10

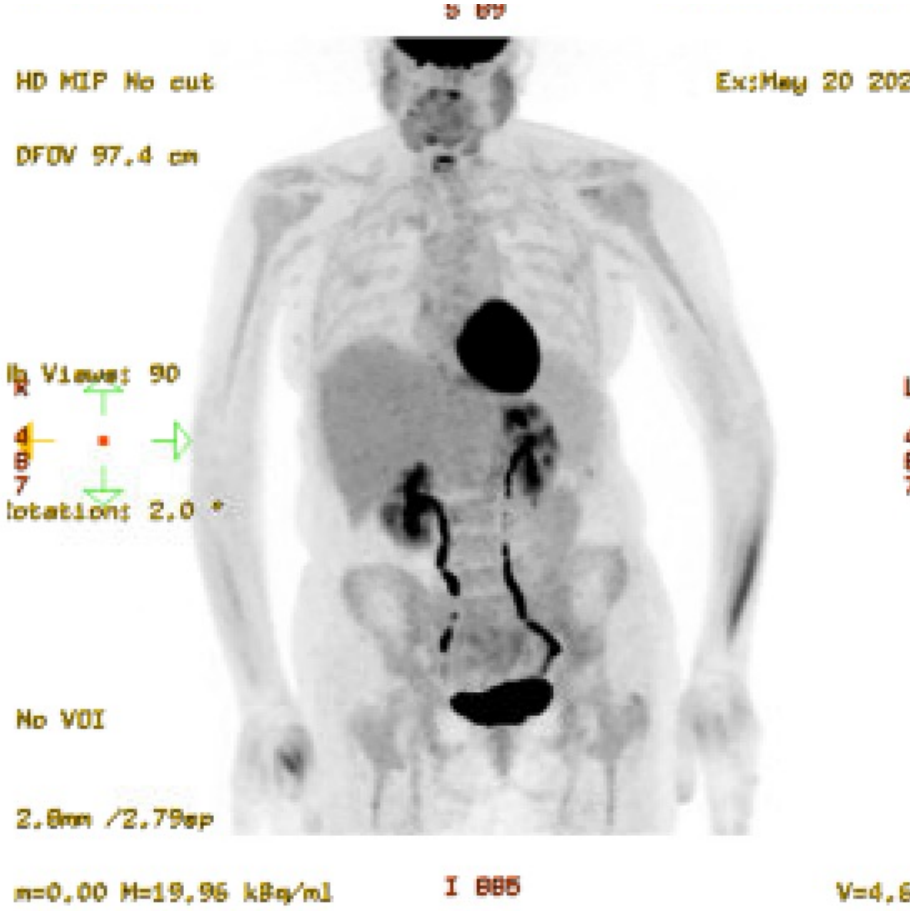




Courtesy of Caron Jacobson, MD

Case Presentation – Dr Jacobson: A 58-Year-Old Woman with Refractory Follicular Lymphoma (continued)





Courtesy of Caron Jacobson, MD

Agenda

Module 1: Diffuse Large B-Cell Lymphoma (DLBCL)

- Mechanistic similarities and differences between axicabtagene ciloleucel (axi-cel), tisagenlecleucel (tis-cel) and lisocabtagene maraleucel (liso-cel)
- Efficacy and safety of axi-cel, tis-cel and liso-cel in DLBCL
- Management of class-effect and other toxicities observed with CD19-directed CAR T-cell therapy
- Faculty cases

Module 2: Other Lymphoma Subtypes

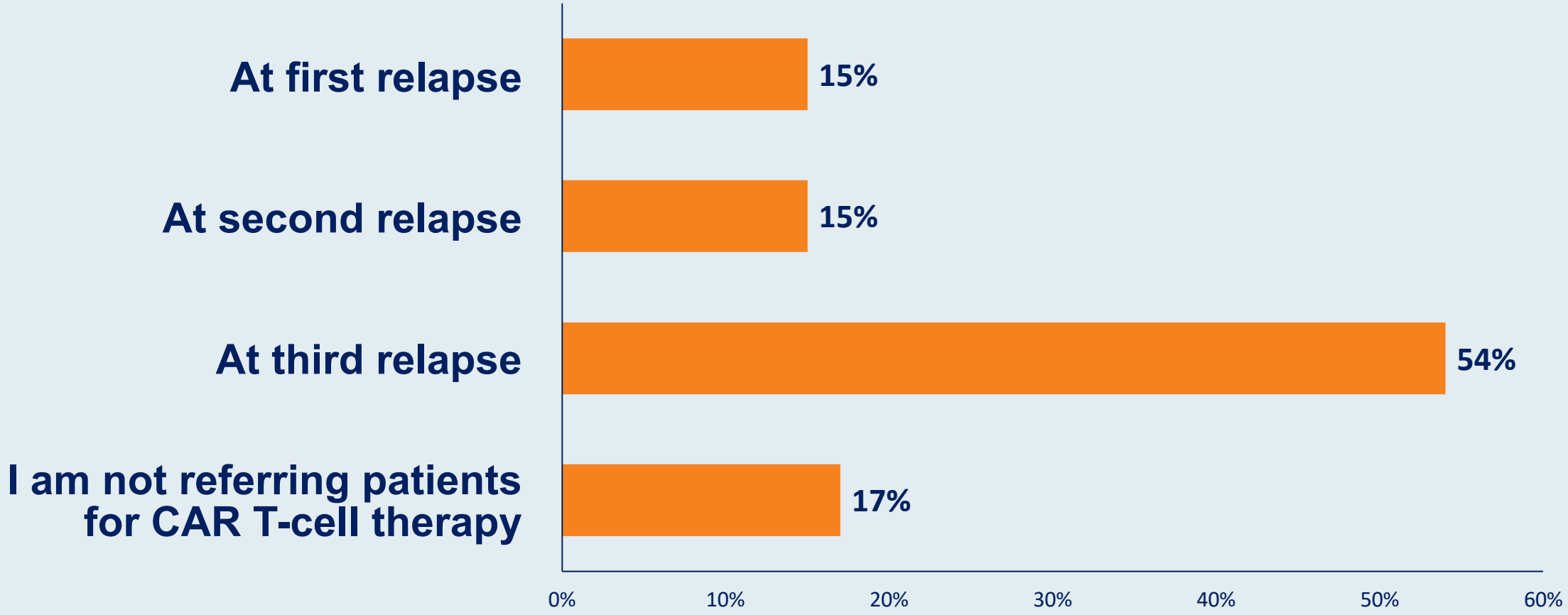
- ZUMA-2: Brexucabtagene autoleucel (brex-cel) in relapsed/refractory (R/R) MCL
- ZUMA-5: Axi-cel for R/R follicular lymphoma
- ELARA: Tis-cel in patients with R/R indolent lymphomas
- Early efficacy and safety data with CD19-directed CAR T-cell therapy in patients with R/R CLL
- TRANSCEND CLL 004: Liso-cel in R/R CLL
- Faculty cases

Module 3: Multiple Myeloma (MM)

- KarMMa: Idecabtagene vicleucel (ide-cel) in patients with R/R MM; recent FDA approval
- CARTITUDE-1: Ciltacabtagene autoleucel (cilta-cel) for R/R MM
- Management of class-effect and other toxicities observed with BCMA-targeted CAR T-cell therapy
- Faculty cases

RTP
RESEARCH
TO PRACTICE

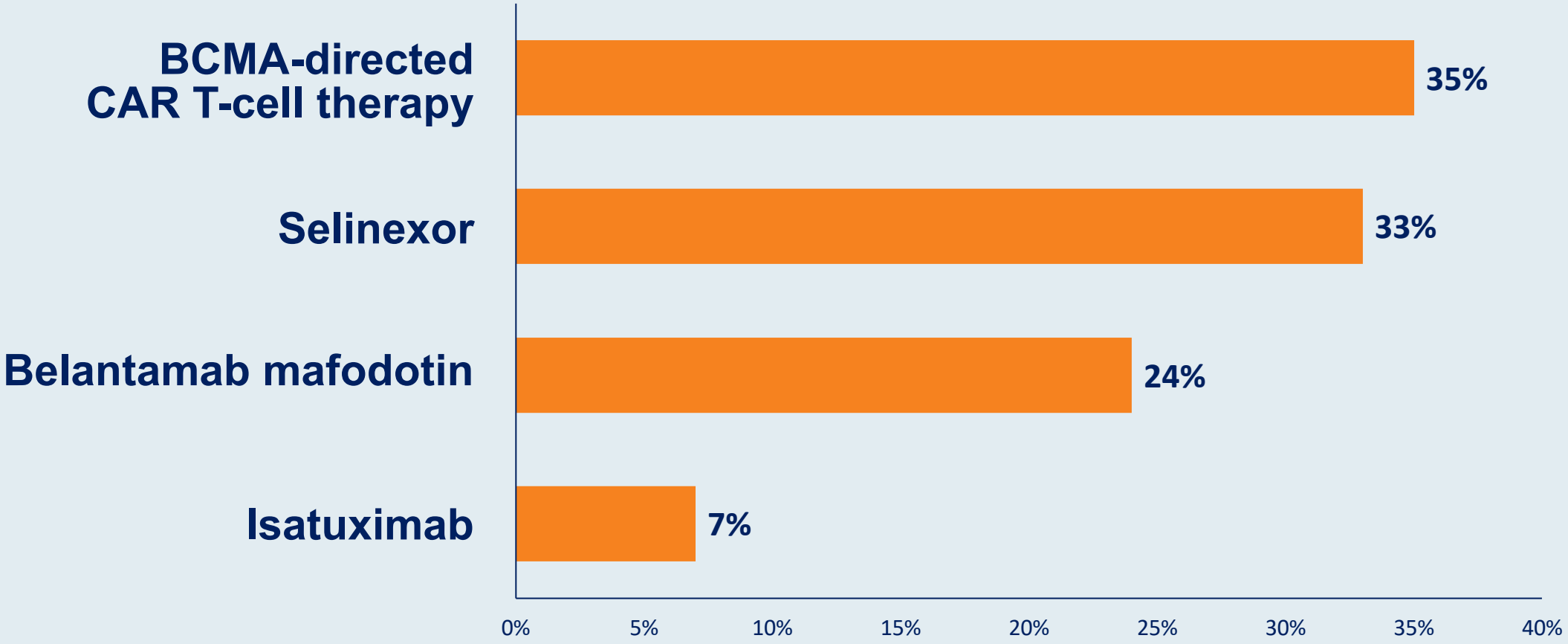
At what point in the treatment course are you referring patients with multiple regimen-relapsed multiple myeloma (MM) for consultation regarding CAR T-cell therapy?



Premeeting survey: July 2021

RTP RESEARCH TO PRACTICE

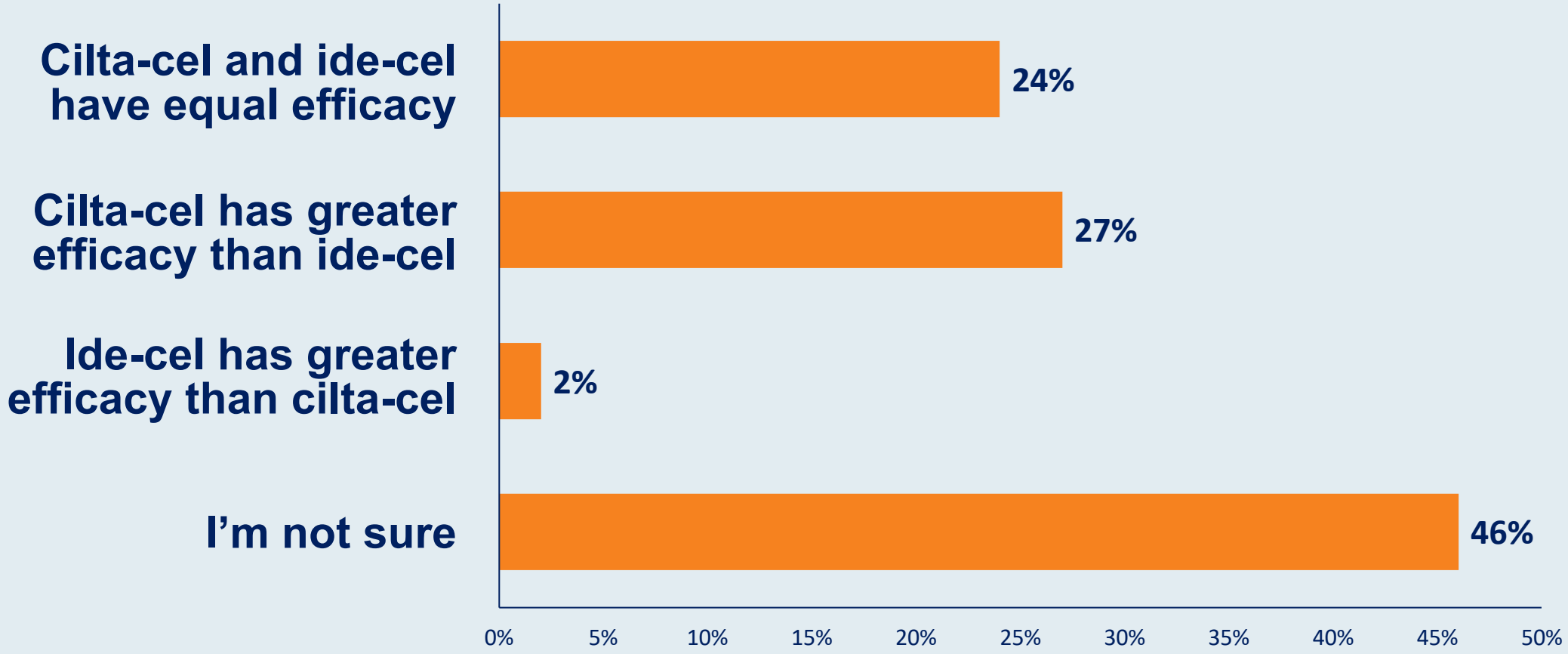
Which of the following agents would you generally use first for a patient with relapsed MM who has experienced disease progression on multiple prior therapies, including daratumumab, proteasome inhibitors and IMiDs?



Premeeting survey: July 2021

RTP RESEARCH TO PRACTICE

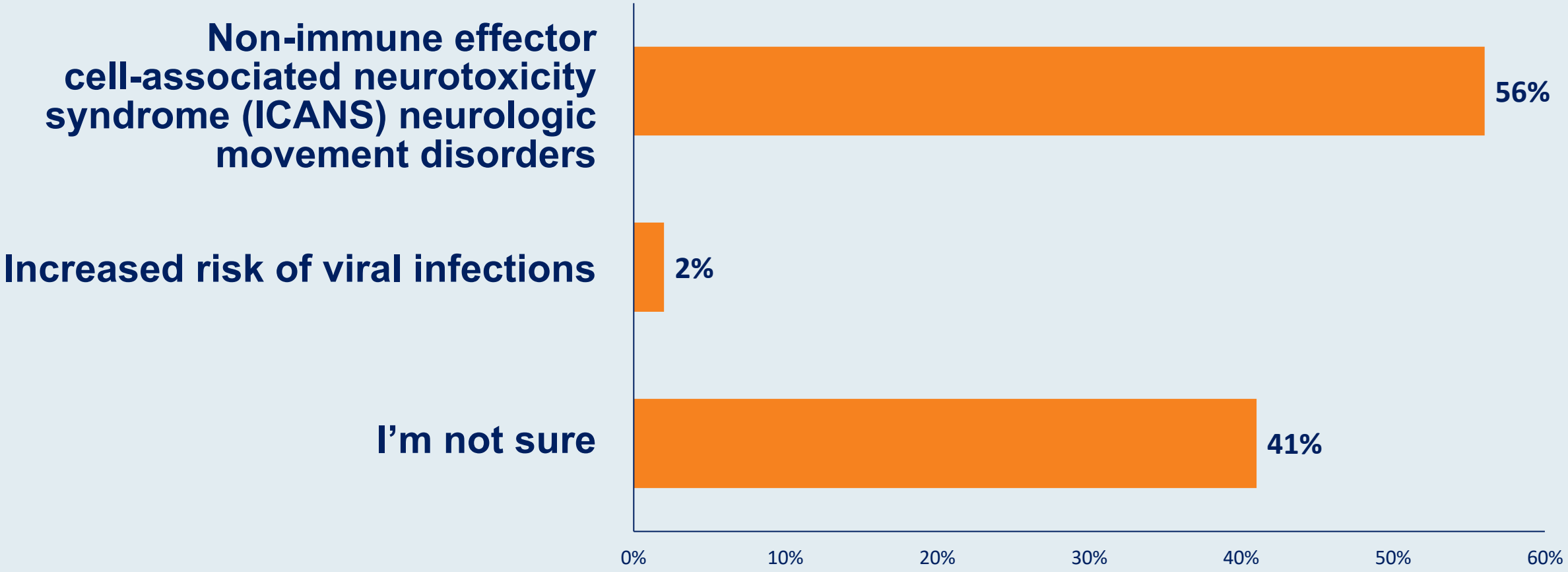
Indirect comparison of the efficacy data from the KarMMa and CARTITUDE-1 studies in patients with R/R MM suggests which of the following regarding ide-cel and ciltacabtagene autoleucel (cilta-cel)?



Premeeting survey: July 2021

RTP RESEARCH TO PRACTICE

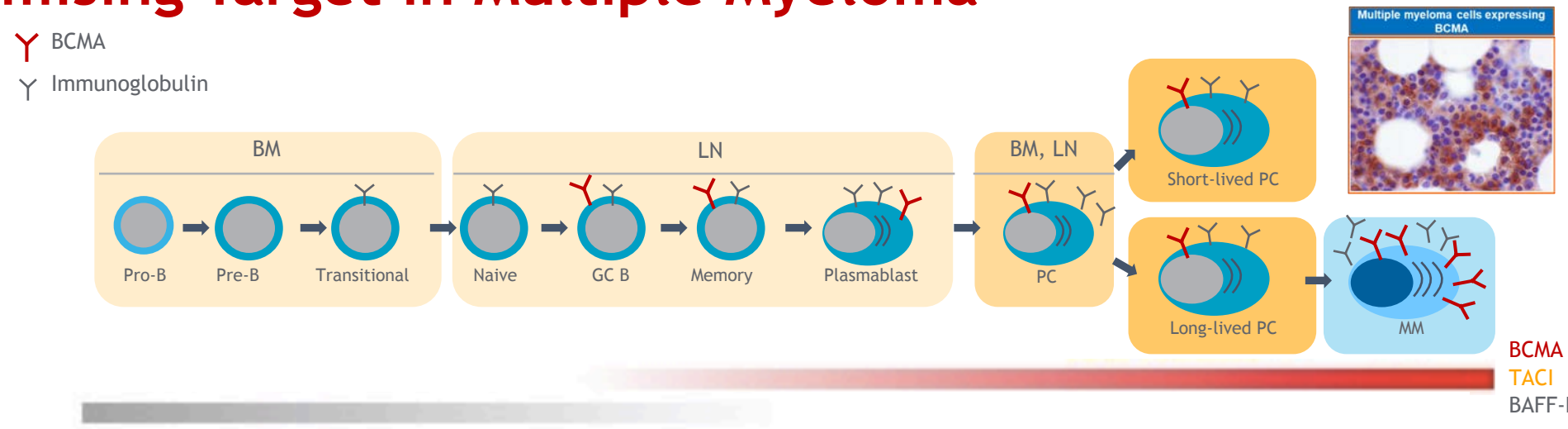
Treatment with cilta-cel has been associated with which of the following?

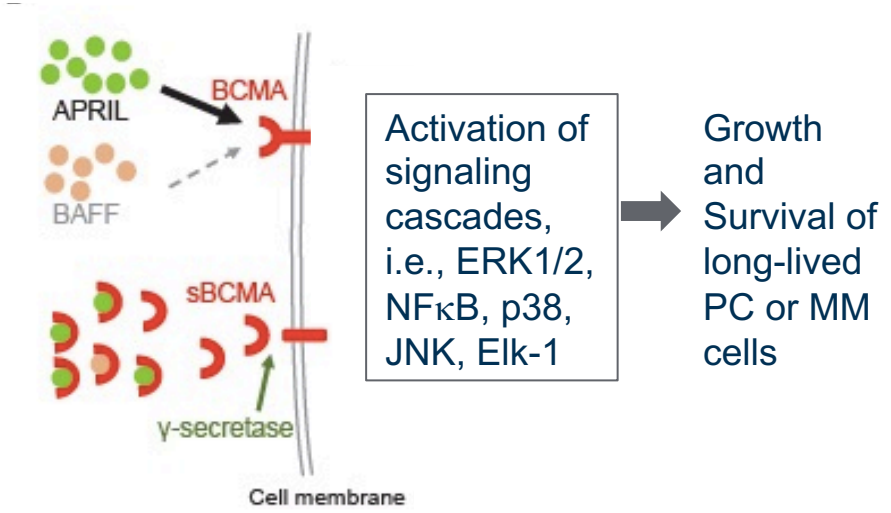


Premeeting survey: July 2021

RTP RESEARCH TO PRACTICE

B-Cell Maturation Antigen (BCMA)
A Promising Target in Multiple Myeloma





Activation of signaling cascades, i.e., ERK1/2, NFκB, p38, JNK, Elk-1

→ Growth and Survival of long-lived PC or MM cells

- **BCMA is member of the TNF receptor superfamily**
  - Expressed nearly universally on MM cells
  - Expression largely restricted to plasma cells and some mature B cells
- **BCMA support survival of long-lived PCs, Ig Class switch and antibody production**
- **Promotes proliferation, survival and associated with immunosuppressive BM microenvironment.**

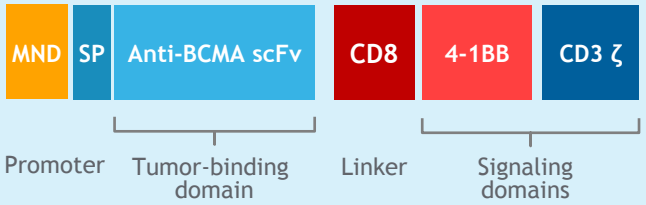
APRIL, a proliferation-inducing ligand; BAFF-R, B-cell activating factor receptor; BM, bone marrow; GC, germinal center; LN, lymph node; MGUS, monoclonal gammopathy of unknown significance; sBCMA, soluble BCMA; TACI, transmembrane activator and CAML interactor.

1. Cho SF, et al. Front Immunol. 2018;9:1821. 2. Moreaux J, et al. Blood. 2004;103:3148-57. 3. Sanchez E, et al. Br J Haematol. 2012;158:727-38.

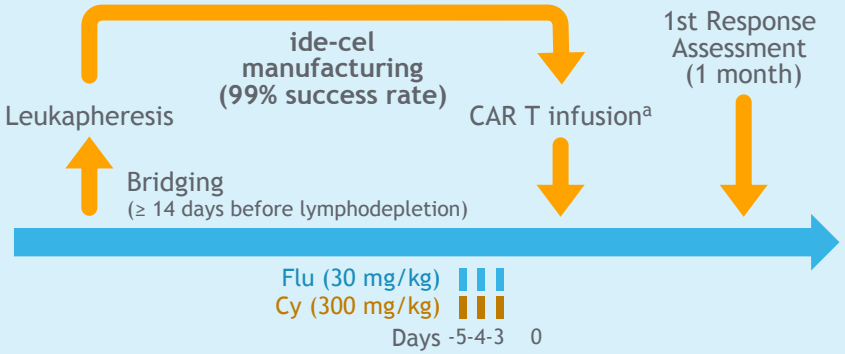
Courtesy of Nikhil C Munshi, MD

The phase 2 pivotal KarMMa study assessed the efficacy and safety of idecabtagene vicleucel (ide-cel; bb2121)

Ide-cel CAR design[1,2]



- RRMM
- ≥ 3 prior regimens
- Previously exposed to:
  - IMiD® agent
  - Proteasome inhibitor
  - Anti-CD38 antibody
- Refractory to last prior therapy per IMWG[b]



Study status as of 14 January 2020

Screened N = 158

↓

Leukapheresed N = 140

↓

Treated N = 128 (Target dose CAR T cells)

150 × 10⁶	n = 4
300 × 10⁶	n = 70
450 × 10⁶	n = 54

↓

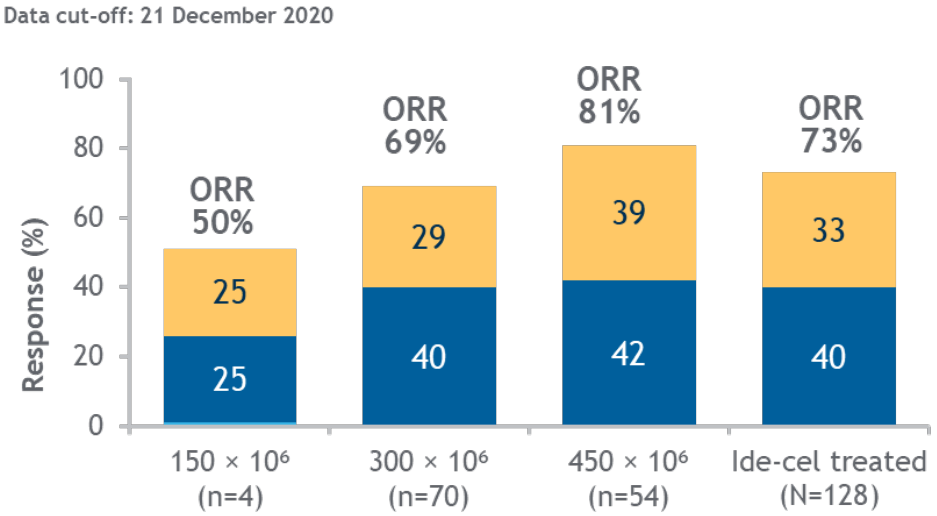
Median follow-up (months)

150 × 10⁶	18.0
300 × 10⁶	15.8
450 × 10⁶	12.4
Total	13.3

EudraCT: 2017-002245-29
ClinicalTrials.gov: NCT03361748

Patient characteristics[2]

Time since initial diagnosis, median (range)		6 (1–18)
No. of prior anti-myeloma regimens, median (range)		6 (3–16)
Prior autologous SCT, %	1	94
	> 1	34
Any bridging therapies for MM, %		88
Refractory status, %	Anti-CD38 Ab-refractory	94
	Triple-refractory	84



Courtesy of Nikhil C Munshi, MD

Ide-cel efficacy (KarMMa): longer follow-up (median 24.8 months)
Patients treated at 450 × 10^6 cells target dose had an ORR of 81% and a CR/sCR of 39%

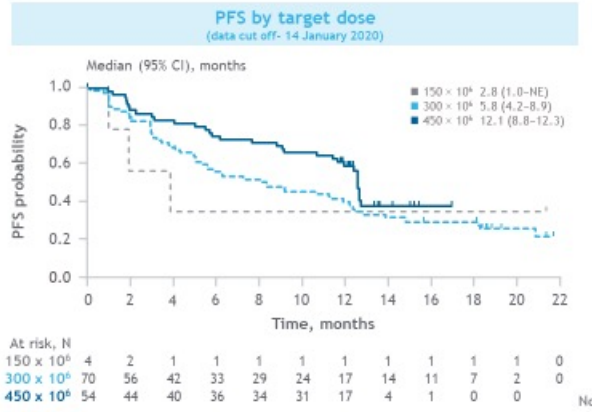
Target dose, CAR T cells	150 x 10^6 n = 4	300 x 10^6 n = 70	450 x 10^6 n = 54	Total n = 128
MRD-negative and ≥CR, n (%) [95% CI]	1 (25) [0.6–80.6]	17 (24) [14.8–36.0]	15 (28) [16.5–41.6]	33 (26) [18.5–34.3]
MRD-negative and ≥VGPR, n (%) [95% CI]	2 (50) [6.8–93.2]	22 (31) [20.9–43.6]	26 (48) [34.4–62.2]	50 (39) [30.6–48.1]

- Median PFS was 8.6 months and median OS was 24.8 months in all ide-cel treated patients
- Median time to first response of 1.0 month (range 0.5–8.8); median time to CR of 2.8 months (range 1.0–15.8)
- 79% of patients in CR were MRD negative

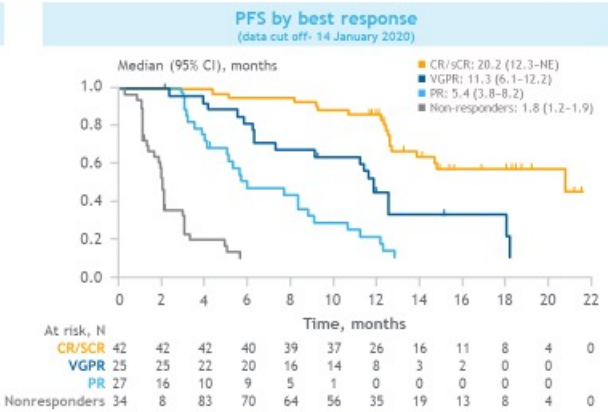
TOXICITIES

- CRS – 84%, with 5% grade 3-5
- Time to CRS 1 (1-12) day; Duration – 5 (1–63) days
- Neurotoxicity - 18% of all patients treated with ide-cel
  - No grade 4 or 5 NT occured
- All neurotoxicity was proximal to CRS

Ide-cel efficacy: Median PFS increased with higher target dose and greater depth of response



PFS increased with higher target dose; median PFS was 12 months at 450 × 10^6 CAR T cells



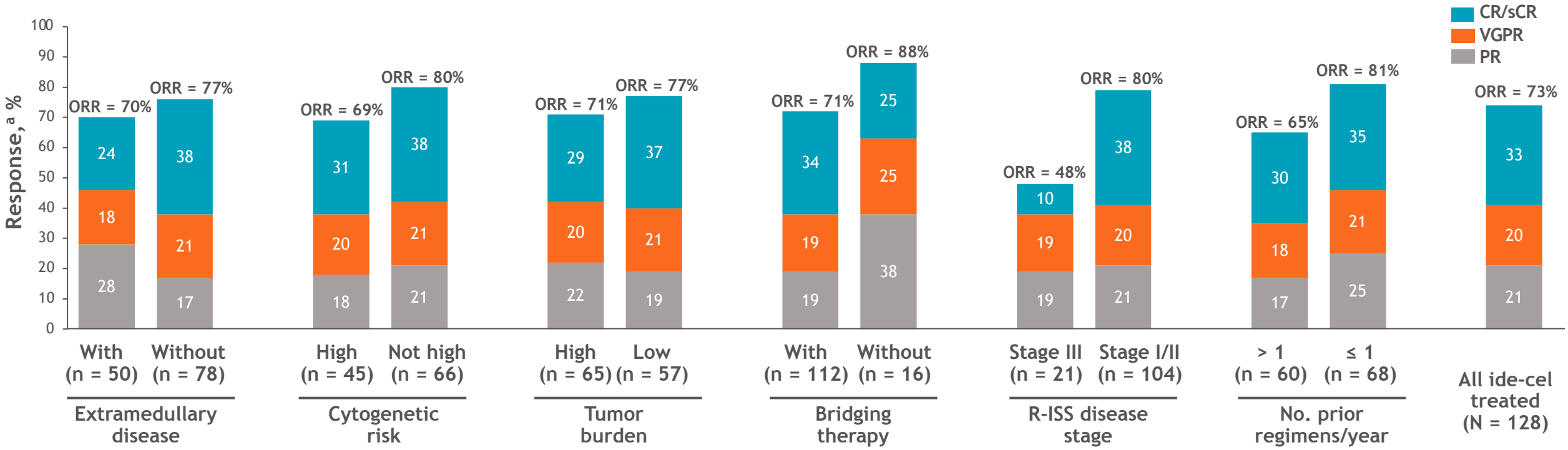
PFS increased with depth of response; median PFS of 20 months in patients achieving CR/sCR

Ide-cel is currently approved by the FDA. The safety and efficacy of ide-cel is still under investigation by other regulatory authorities.
CI, confidence interval; PFS, progression-free survival.
Munshi NC, et al. New Engl J Med. 2021;384:705-15.

Dana-Farber Cancer Institute 11

Courtesy of Nikhil C Munshi, MD

KarMMa Trial of Ide-cel in R/R MM: Response rate by subgroup



- ORR was ≥ 65% and CR rate was ≥ 20% across all high-risk subgroups except R-ISS disease stage III
- Presence of extramedullary disease and baseline tumor burden did not substantially affect ORR
- Among high-risk subgroups treated with the highest target dose of 450 × 10^6 CAR+ T cells, ORR and CR rate were ≥ 75% and ≥ 19%, respectively, across all subgroups except R-ISS disease stage III

Data cutoff date: 14 Jan 2020.
CR, complete response; ORR, overall response rate; PR, partial response; R-ISS, revised International Staging System; sCR, stringent CR; VGPR, very good PR.
[a] Sum of CR/sCR, VGPR, and PR rates may differ from the ORR rate due to rounding.

Raje N, et al. ASH 2020. Abstract 3234.

Courtesy of Nikhil C Munshi, MD

KarMMa: Summary of adverse events in high-risk subgroups

n (%)	Extramedullary disease (n = 50)	High-risk cytogenetics (n = 45)	High tumor burden (n = 65)	Received bridging therapy (n = 112)	R-ISS disease stage III (n = 21)	> 1 prior regimens/year (n = 60)	All ide-cel treated (N = 128)
Any-grade TEAE	50 (100)	45 (100)	65 (100)	112 (100)	21 (100)	60 (100)	128 (100)
Grade 3/4 TEAE	50 (100)	45 (100)	64 (99)	111 (99)	21 (100)	60 (100)	127 (99)
SAE	36 (72)	32 (71)	50 (77)	78 (70)	15 (71)	41 (68)	86 (67)
≥ 1 CRS event	41 (82)	41 (91)	57 (88)	94 (84)	16 (76)	49 (82)	107 (84)
Max. grade (Lee criteria),[a,b]							
1	24 (48)	21 (47)	31 (48)	55 (49)	8 (38)	27 (45)	61 (48)
2	14 (28)	18 (40)	23 (35)	32 (29)	7 (33)	20 (33)	39 (31)
≥ 3	3 (6)	2 (4)	3 (5)	7 (6)	1 (5)	2 (3)	7 (5)

- No new safety signals were identified in the subgroups examined
- Across all high-risk subgroups, the incidence of CRS was comparable with that of the overall ide-cel treated population
- Median time to onset of CRS was 1 day in all subgroups and in the overall ide-cel treated population; median duration of CRS ranged from 5 to 7 days

Data cutoff date: 14 Jan 2020.
CRS, cytokine release syndrome; R-ISS, revised International Staging System; SAE, serious adverse event; TEAE, treatment-emergent adverse event.
[a] Sum of percentages may differ from the total due to rounding. [b] CRS graded according to Lee criteria (Lee DW, et al. *Blood*. 2014;124:188-195).

Raje N, et al. ASH 2020. Abstract 3234.

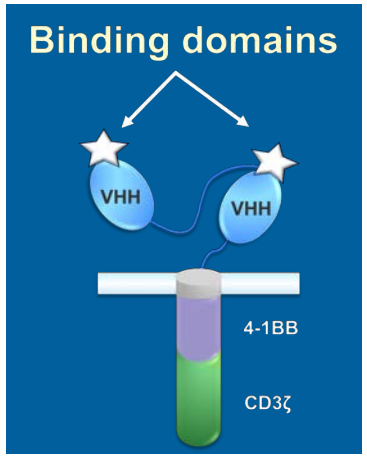
Courtesy of Nikhil C Munshi, MD

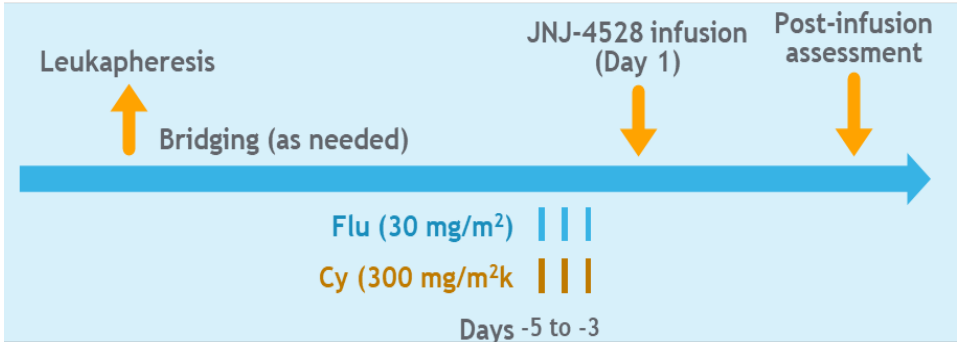
Ide-Cel Studies

	Ide-cel KarMMa-1 N = 128	Ide-cel KarMMa-1-450x10⁶ dose N = 54	Ide-Cel CRB-401 N = 62	Ide-cel CRB-401 450x10⁶ dose N = 38
RESPONSE				
ORR	73%	82%	75.8 %	89.5 %
CR	33%	39%	38.7%	36.8 %
RESPONSE				
Median f/p	13.3 mo	12.4 mo	18.1 mo	NA
Median DOR	10.7 mo	Not reported	10.3 mo	10.0 mo
Median PFS	8.8 mo	12.1 mo	8.8 Mo.	9.0 Mo
Median OS	19.4 mo	NA	34.2 mo.	34.2 mo.
CYTOKINE RELEASE SYNDROME				
All grades (≥3) %	84% (6%)	96% (6%)	76 % (6.5 %)	92 % (7.9 %)
NEUROTOXICITY				
All grades (≥3) %	18% (3%)	20% (6%)	43 % (3.2 %)	52.6% (5.2 %)

Courtesy of Nikhil C Munshi, MD

CARTITUDE-1: a phase1b/2 trial of cilta-cel (JNJ-4528) BCMA CAR T cell therapy[1,2]





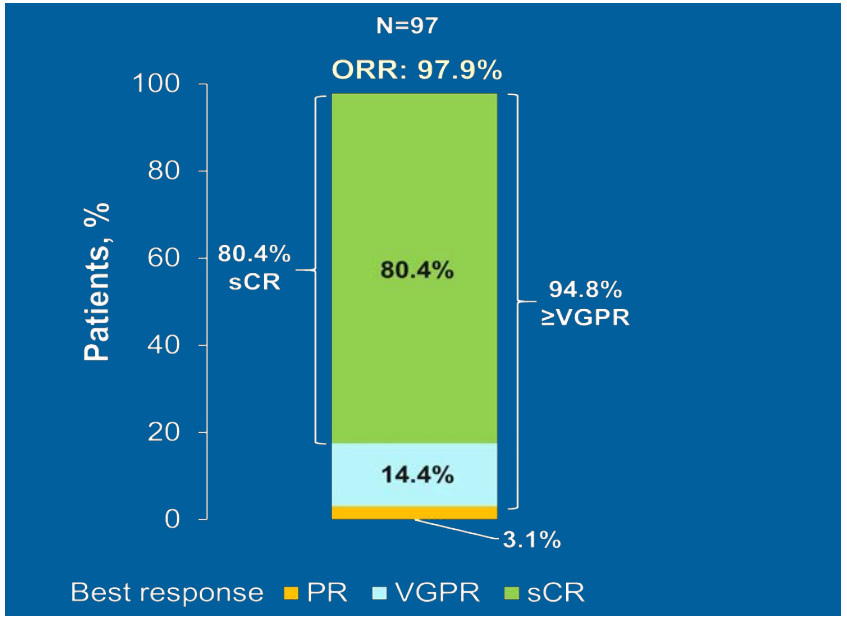
Median administered dose:
$0.71x10^6$ ($0.51–0.95x10^6$) CAR+ viable T cells/kg

Eligibility criteria

- PD MM with 3 prior therapies or double-refractory
- Prior PI, IMiD, and anti-CD38 mAb
- Measurable disease

Patient characteristics (N = 97)[1]		
Years since initial diagnosis, median (range)		5.9 (1.6–18.2)
No. of prior lines of therapy, median (range)		6 (3–18)
Prior autologous SCT, n (%)		87 (89.7)
Any bridging therapies for MM, n (%)		73 (75)
Refractory status, n (%)	Triple-refractory Penta-refractory	85 (87.6) 41 (42.3)

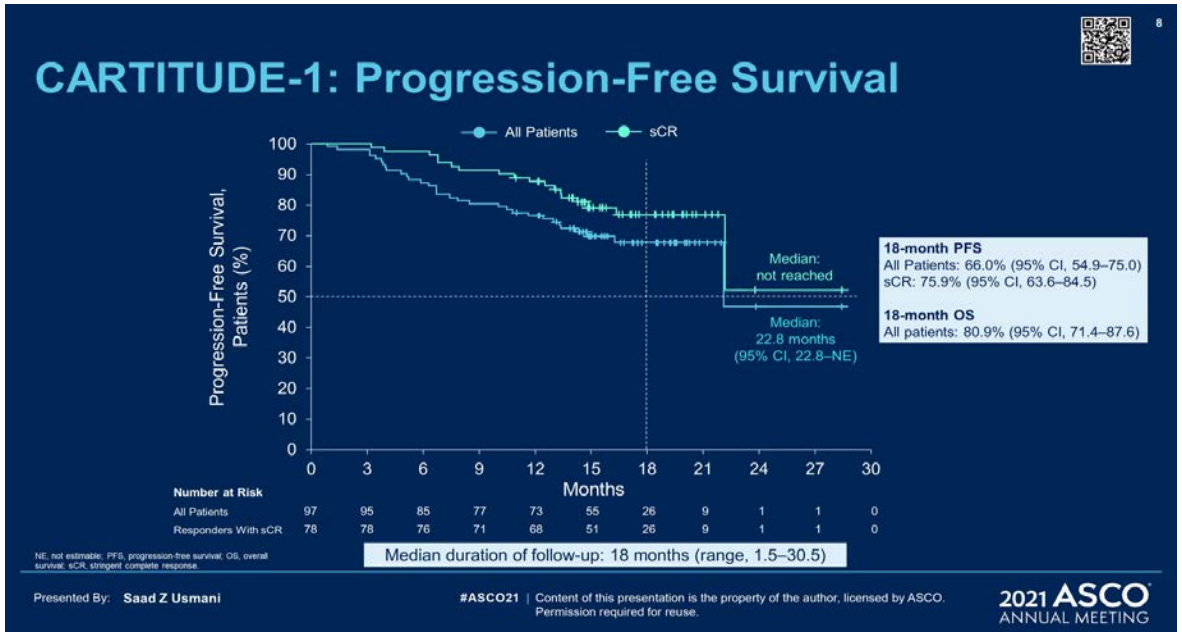
OVERALL RESPONSE



Courtesy of Nikhil C Munshi, MD

CARTITUDE-1: Progression-free survival with cilta-cel

PFS All Pts and by sCR



- Median duration of response: 21.8 months
- At 12 months 73% of responders have not progressed or died
- Median DOR not reached in patients with sCR
- Median time to first response of 1.0 month (range 0.9–10.7); median time to CR of 2.6 months (range 0.9–15.2)
- Of 16 evaluable patients in CR were MRD negative:
  - 81% were MRD- at 10^{-5} or 10^{-6}; 69% were MRD- at 10^{-6}

Toxicities

- Total CRS -94.8%
- Time to CRS 7 (1-12) days
- Duration 4 (1-97) days

Neurotoxicities[a]

- Total CAR T cell neurotoxicities
  - Any grade: 20 patients (20.6%)
  - Grade ≥3: 10 patients (10.3%)
- Other neurotoxicities - Occurring after resolution of CRS and/or ICANS – 12.4%
  - 9.3% grade ≥3
  - 5 AEs including movement and/or neurocognitive changes; 7 including nerve palsy, peripheral motor neuropathy
  - Mitigating measures

Courtesy of Nikhil C Munshi, MD

Select Ongoing Trials of CAR T-Cell Therapies in MM

Trial Name or NCT#	Phase	Agent	Target	Setting	Estimated 1º completion date
KarMMa-3	III	Ide-cel	BCMA	R/R (3 or 4 prior lines)	May 2022
CARTITUDE-4	III	Cilta-cel	BCMA	R/R (1-3 prior lines)	April 2026
CARTITUDE-5	III	Cilta-cel	BCMA	NDMM not undergoing HSCT	June 2026
CARTITUDE-2	II	Cilta-cel	BCMA	R/R (1-3 prior lines)	April 2022
NCT03448978	I/II	Descartes-08	CD8/BCMA	R/R (≥2 prior lines)	December 2021
NCT04499339	I/II	SLAM7 CAR-T	SLAM7	R/R (≥2 prior lines)	March 2024
NCT04555551	I	MCARH109	GPRC5D	R/R (≥3 prior lines)	August 2023
KarMMa-4	I	Ide-cel	BCMA	NDMM	January 2025
NCT03274219	I	bb21217	BCMA	R/R (≥3 prior lines)	October 2025
MELANI-01	I	UCART	CS1	R/R (≥2 prior lines)	December 2021
LUMMICAR STUDY 2	I	CT053	CD137/BCMA	R/R	August 2021

Clinicaltrials.gov; Accessed June 2021

Courtesy of Nikhil C Munshi, MD

CARTITUDE-2: Initial Results with Cilta-Cel in Progressive MM

- As of Jan 2021 data cut-off, median follow-up was 5.8 months, median age 60 years; 65% were male
- One patient was treated in an outpatient setting
- All patients were exposed to PI, IMiD, and dexamethasone, 95% to alkylating agents, and 65% to daratumumab

Characteristics	N=20
Years since diagnosis, median (range)	3.5 (0.7–8.0)
Prior lines of therapy, median (range)	2 (1–3)
Previous autologous stem cell transplantation, n (%)	17 (85)
Triple-class exposed,[a] n (%)	13 (65)
Triple-class refractory,[a] n (%)	8 (40)
Penta-drug exposed,[b] n (%)	4 (20)
Penta-drug refractory,[b] n (%)	1 (5)
Refractory status, n (%)	
Bortezomib	8 (40)
Carfilzomib	2 (10)
Pomalidomide	7 (35)
Daratumumab	12 (60)
Refractory to last line of therapy, n (%)	19 (95)

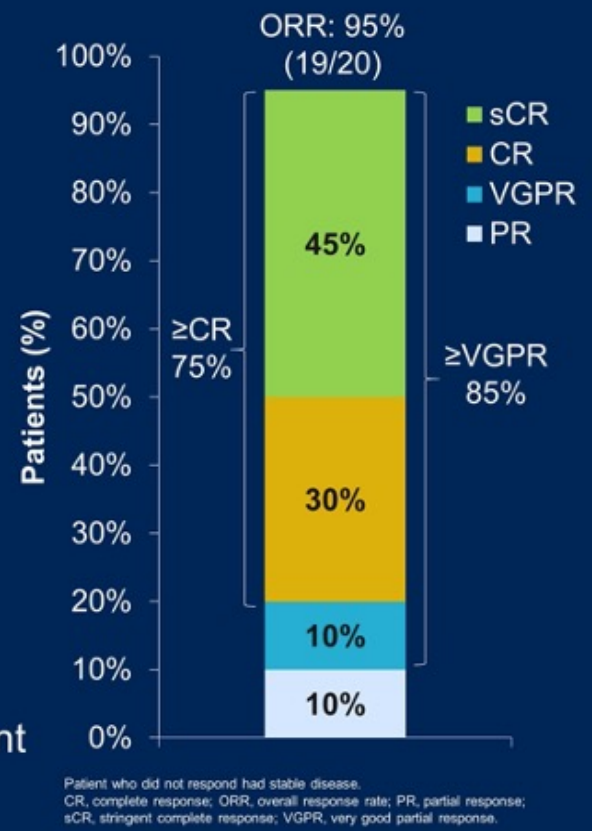
[a]≥1 PI, ≥1 IMiD, and 1 anti-CD38 antibody; [b]≥2 PIs, ≥2 IMiDs, and 1 anti-CD38 antibody.
AE, adverse event; IMiD, immunomodulatory drug; MRD, minimal residual disease; PI, proteasome inhibitor.

Efficacy

- Median time to first response: 1.0 month
- Median time to best response: 1.9 months
- Median duration of response: not reached
- All patients (n=4) with MRD-evaluable samples at the 10^{-5} threshold were MRD negative at data cut-off

Safety

- Cilta-cel safety profile was manageable, including in the patient treated in an outpatient setting
- No movement and neurocognitive treatment-emergent AEs were observed in patients of Cohort A



Patient who did not respond had stable disease.
CR, complete response; ORR, overall response rate; PR, partial response; sCR, stringent complete response; VGPR, very good partial response.

Presented By: Mounzer Agha, UPMC Hillman Cancer Center, Pittsburgh, PA, USA

2021 ASCO ANNUAL MEETING

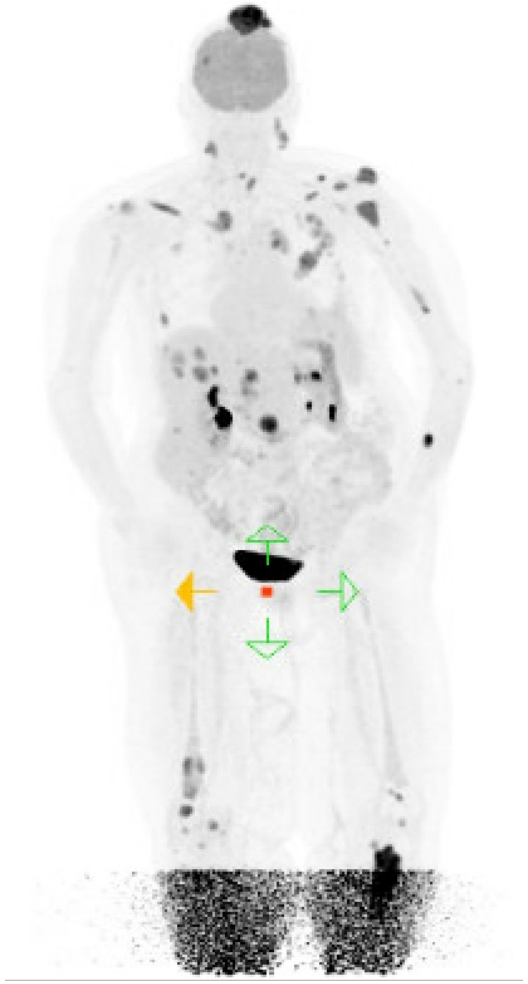
Courtesy of Nikhil C Munshi, MD

Case Presentation – Dr Munshi: A 65-year-old woman with multiple myeloma

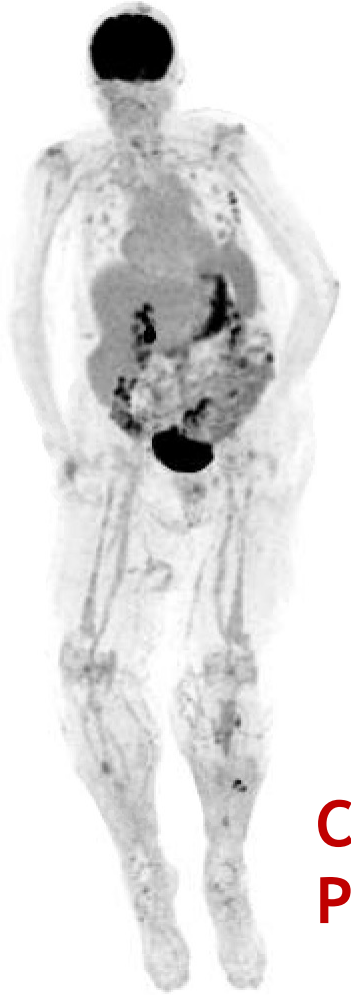
- 65 year old lady with IgG kappa multiple myeloma, BM plasma cells 45% with ISS stage I with a 1q amplification and 13q deletion diagnosed in 2016.
- Induction therapy with KRD. Excellent response but developed PE and on Rivaroxaban
- 09/2016 – HDT and ASCT – Maintenance with weekly Bortezomib + Lenalidomide
- 01/2018 – Progression on PET/CT – Started on DaraPD
- 04/2018 – A localized head mass – changed to DaraPVD
- 06/2018 – Progression on PET/CT – KCD
- 10/2018 – anti-BCMA CAR T-cell therapy

Courtesy of Nikhil C Munshi, MD

10/2018



03/2019



Case Presentation – Dr Munshi: A 65-year-old woman with multiple myeloma

- Cytokine release syndrome Day +1 with fevers and fluid-responsive hypotension (grade 2 CRS) on day +2,
- Resolved with a single dose of tocilizumab.
- She was treated with empiric ceftazidime for neutropenic fever

COVID Pandemic

Patient gets COVID-19

	10/2018	11/2018	12/2019	2/2020	3/2020	05/2020	7/2020
Kappa FLC (mg/L)	436.7	1.9	40.2	72.9	125.2	----	5,368.9

Courtesy of Nikhil C Munshi, MD

Case Presentation - Dr Munshi: A 63-year-old man with t(11;14) myeloma

- 63 year old man. Very healthy. He has run a number of Boston marathons; however, April 2017, while running the Boston marathon he felt extremely exhausted and almost had a syncopal attack.
- Dx Myeloma with t(11;14)
- Complex cytogenetics – 7 with complex karyotype including an unbalanced **t(11;14)(q13;q32), monosomy 13, and loss of 17p.**

- **43,X-Y, -1,add(3)(q27),del(4)(p14p16),add(6)(q25), add(7)(p22),13,der(14)t(11;14)(q13;q32),der(15) t(1;15)(q12;q26.1),i(17)(q10)[7]/46,XY[13]**

Courtesy of Nikhil C Munshi, MD

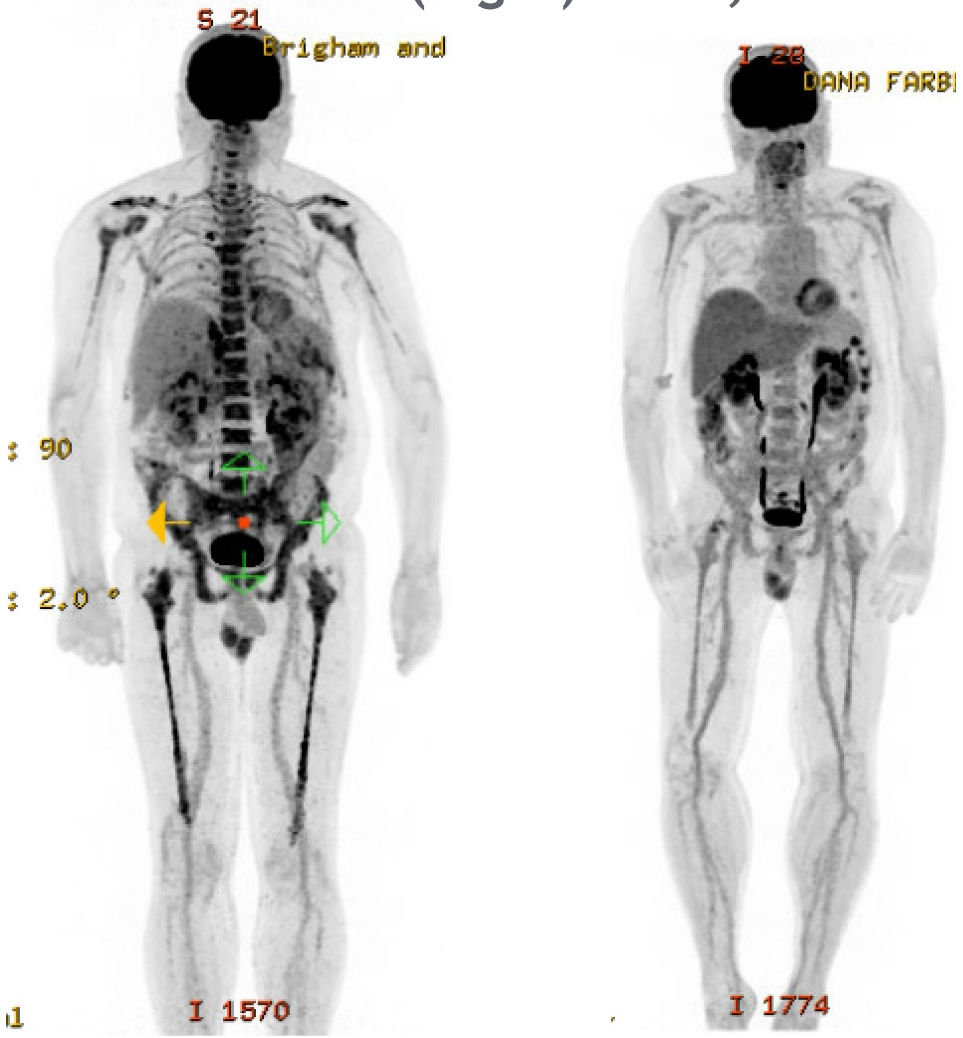
Case Presentation – Dr Munshi: A 63-year-old man with t(11;14) myeloma (continued)

- 07/2017 - RVDx6 followed by HDT and ASCT – PR and RD maintenance
- 02/2018 - relapsed- Daratumumab with PD
- 05/2018 - Venetoclax with carfilzomib and Dex.
- 07/2019 - progressive disease – eligible for CAR-T protocol
- Following lymphodepletion CAR-T infusion was postponed due to high grade fever with High CRP.
- Fever eventually considered due to aggressive myeloma
- He did develop CRS and required one infusion of Toci

Courtesy of Nikhil C Munshi, MD

Case Presentation – Dr Munshi: A 63-year-old man with t(11;14) myeloma (cont)

	Ref. Range 11/2019	7/02/19	7/19/19	8/2019		9/2019	10/2019
Lambda FLC(mg/L)		10,079.8	752.8	24.9	11.8	34.6 (H)	117.7 (H)



07/03/2019

08/08/2019

7/10/2019
CAR-T
Infusion

- Started on Elotuzumab, Thalidomide and Dex
- Excellent response sustained over 15 months

Courtesy of Nikhil C Munshi, MD

Faculty Case Appendix

Case Presentation - Dr Maloney: A 50-year-old man with non-GCB type, double-hit DLBCL

50 year old man with bilateral cervical LN in 5/2017.

PATH: DLBCL, non GCB type, not double hit, CD19 positive

Prior treatments:

R-CHOP x 6 through 10/2017.

PET: good response but slight FDG uptake in cervical nodes that progressed 1 mo

R-ICE x 2 and referred to Fred Hutch BMT program for Autologous HCT.

Staging: showed new cervical and inguinal LN and referred to IMTX.

Cells collected for axicabtagene ciloleucel.

Bridging not required.

PET/CT (see scan) showed minimal cervical and inguinal LN

Cy/Flu lymphodepletion.

Admitted for CAR-T infusion 3/21

Day 6- grade 3 NT with global aphasia

Day 7- CRS grade 2

Toci x 1, Dex (10 mg) x 9 with resolution.

Discharged back to outpatient on Day +12.

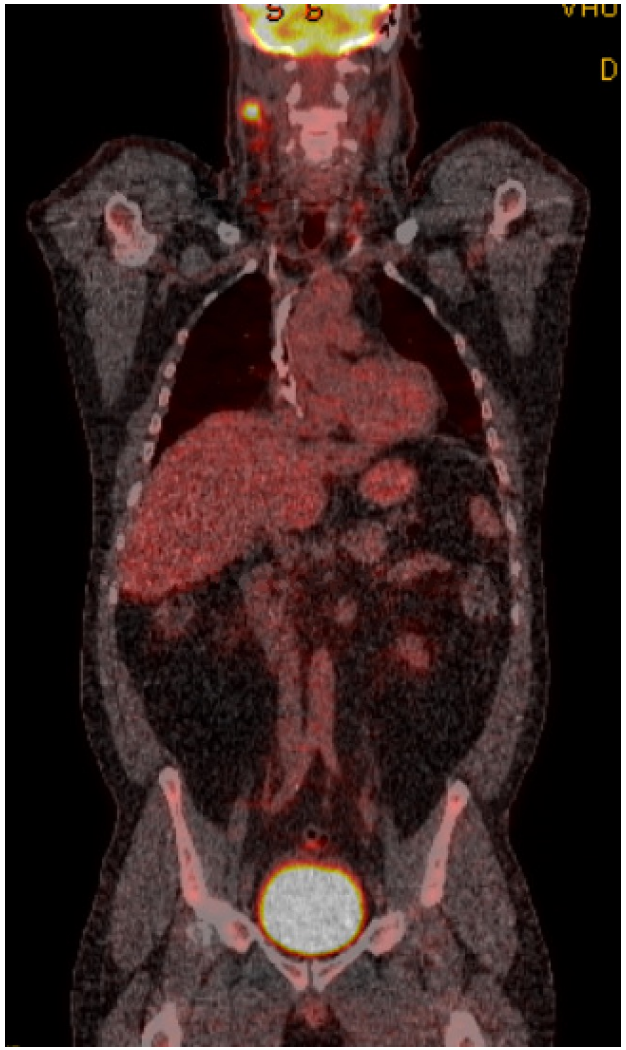
Day 30 PET/CT showed CR- (see image) Deauville score 2.

Remains in CR to date.

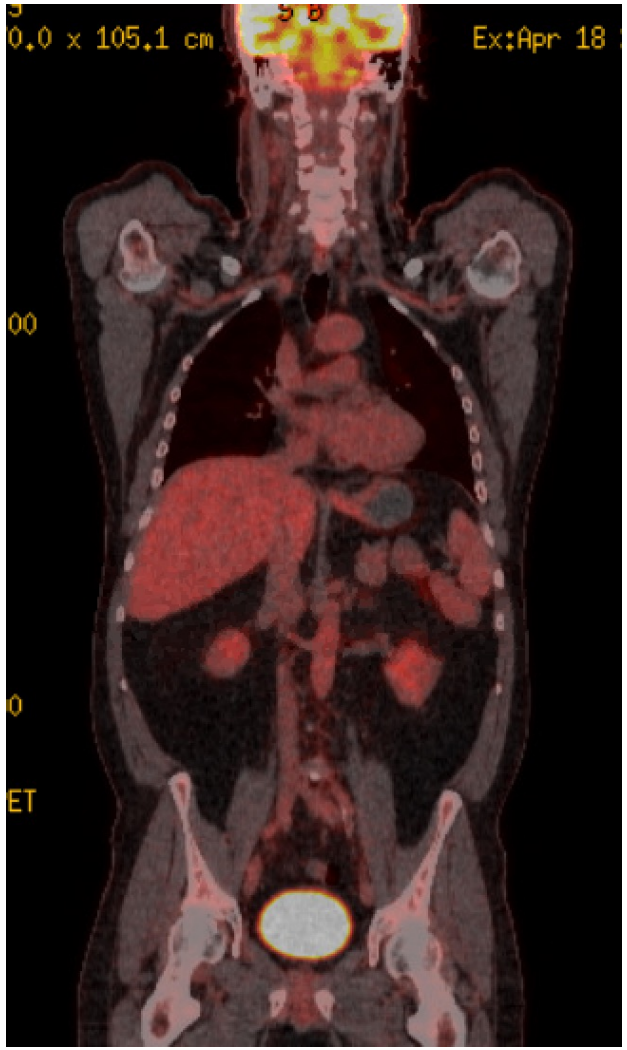
Courtesy of David G Maloney, MD, PhD

Case Presentation – Dr Maloney: A 50-year-old man with non-GCB type, double-hit DLBCL (continued)

Pre axicabtagene ciloleucel



Post axicabtagene ciloleucel

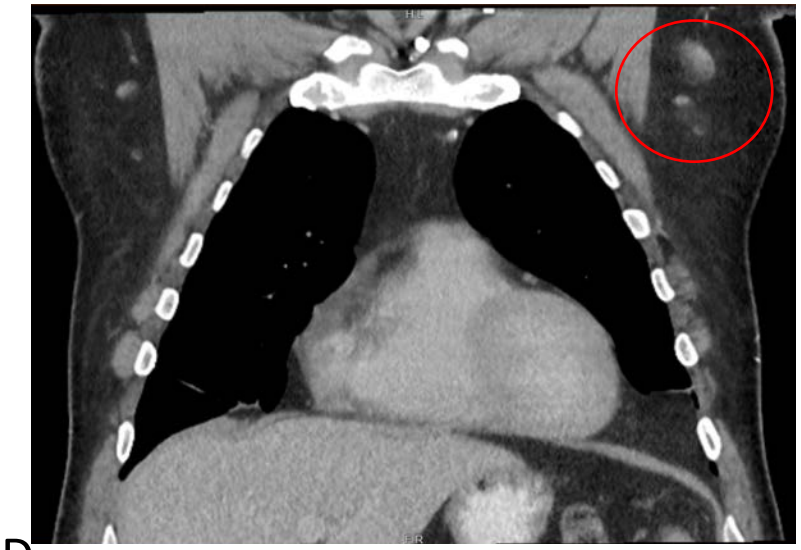


Courtesy of David G Maloney, MD, PhD

Case Presentation – Dr Jacobson: A 66-Year-Old Man with Refractory Chronic Lymphocytic Leukemia

66 year-old man with refractory del17p CLL c/b Richter's transformation

- Diagnosed 8/2018 with abdominal pain, bulky LAD, cytopenias and a lymphocytosis; flow c/w CLL; IGVH unmutated; FISH with del17p
- 8/2018-11/2018: ibrutinib monotherapy with PD
- 12/2018-2/2019: venetoclax with SD
- 2/2019-4/2019: venetoclax and ibrutinib with no response



- Enrolled to receive CAR T-cells on a clinical trial when optional LN biopsy revealed evidence of Richter's transformation
- 6/10/19: received CAR T-cells under a single patient compassionate use IND
  - Course c/b grade 3 CRS (hypotension requiring pressors) but no ICANS. Toci and dex were given for CRS
  - Discharged home on day +13

Courtesy of Caron Jacobson, MD

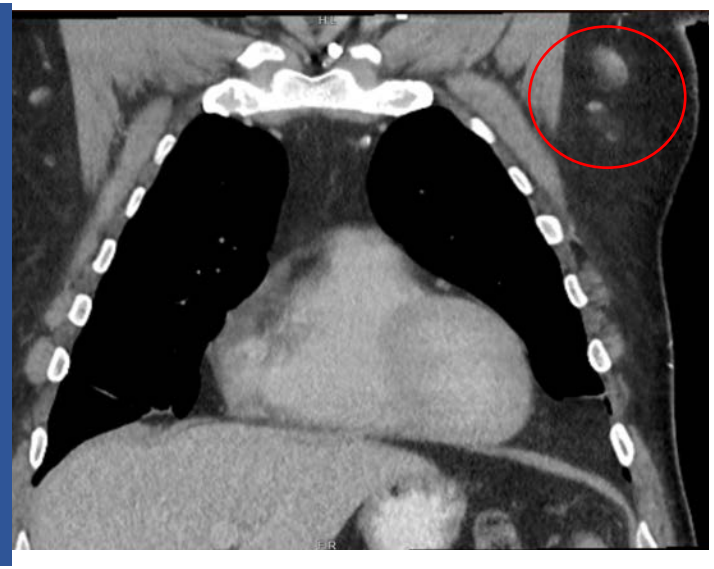
Case Presentation – Dr Jacobson: A 66-Year-Old Man with Refractory Chronic Lymphocytic Leukemia (continued)

66 year-old man with refractory del17p CLL c/b Richter's transformation

- Diagnosed 8/2018 with abdominal pain, bulky LAD, cytopenias and a lymphocytosis; flow c/w CLL
- 8/2018-11/2018: ibrutinib
- 12/2018-2/2019: venetoclax
- 2/2019-4/2019: venetoclax
- Enrolled to receive CAR T-ce
  revealed evidence of Richte
- 6/10/19: received CAR T-cells under a single patient compassionate use IND
  - Course c/b grade 3 CRS (hypotension requiring pressors) but no ICANS. Toci and dex were given for CRS
  - Discharged home on day +13

Day 30 bone marrow and CT assessment consistent with a CR in the marrow and a PR by CT

At 24 months, CBCD remains within normal limits and CT scans show further decrease in LAD c/w an ongoing PR



Courtesy of Caron Jacobson, MD

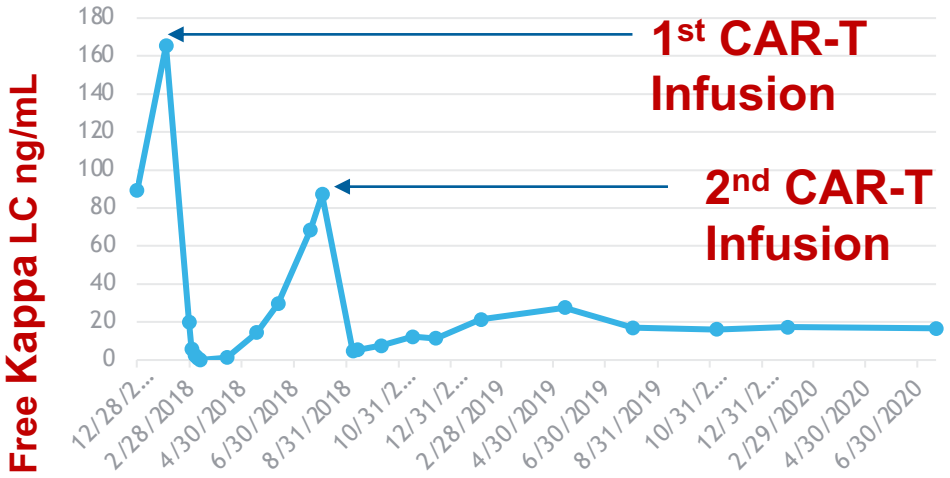
Case Presentation – Dr Munshi: A patient with multiple myeloma

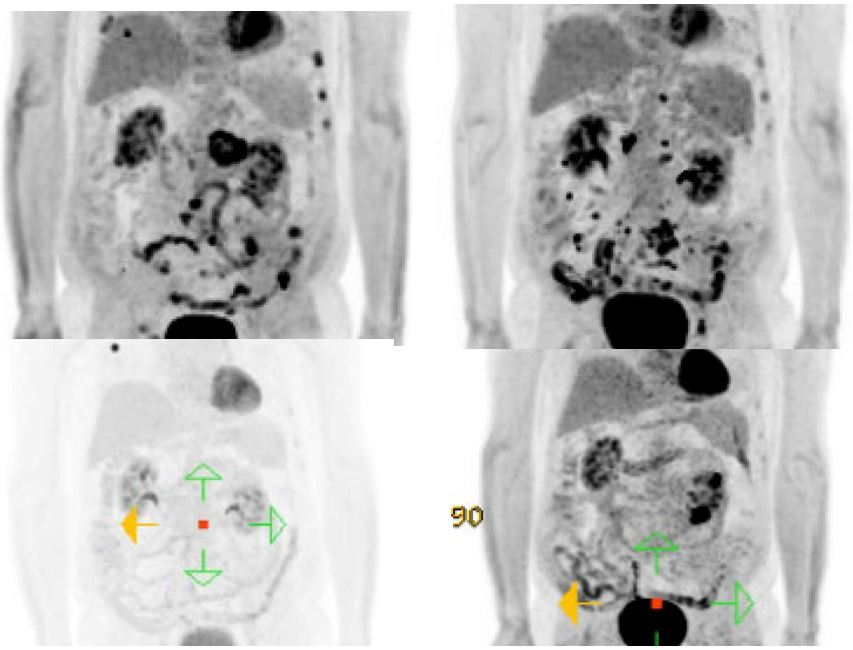
5/8/2015	**Initial Diagnosis**
	IgG Kappa Multiple myeloma
5/12/2015 - 9/8/2016	RVD -> RD maintenance
10/2016 - 1/2017	Carfilzomib+Pomalidomide+Dexamethasone
1/23/2017 - 4/5/2017	Daratumumab+Pomalidomide+Dexamethasone
4/5/2017 - 8/2017	Elotuzumab+Pomalidomide+Dexamethasone
8/2017 - 8/30/2017	**Radiation -** XRT to Pancreas
8/2017 - 12/23/2017	Carfilzomib+Pomalidomide+Dexamethasone

Courtesy of Nikhil C Munshi, MD

Case Presentation – Dr Munshi: A patient with multiple myeloma (continued)

Response to Retreatment





01/2018 08/08/2019

	1st Resp	2nd Resp	1st PFS	2nd PFS	1st CRS	2nd CRS	1st Dose	2nd Dose	1st CRP-Day	2nd CRP-Day	1st Ferritin	2nd Ferritin
2	SD	VGPR	6 mos	12mos	None	1- D4	150	360	45 - D6	216 - D6	23	1693

Courtesy of Nikhil C Munshi, MD

A Conversation with the Investigators: Acute Myeloid Leukemia and Myelodysplastic Syndromes

Wednesday, July 14, 2021
5:00 PM – 6:00 PM ET

Faculty

Courtney D DiNardo, MD, MSCE
Gail J Roboz, MD
Eytan M Stein, MD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Thank you for joining us!

CME and MOC credit information will be emailed to each participant within 2 to 3 business days.

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