Consensus or Controversy? Multiple Myeloma

Wednesday, June 30, 2021
5:00 PM – 6:00 PM ET

Faculty

Natalie S Callander, MD
Shaji K Kumar, MD
Sagar Lonial, MD

Moderator

Neil Love, MD

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Faculty

Natalie S Callander, MD
Professor of Medicine
Director, Myeloma Clinical Program
Interim Director, Bone Marrow Transplant Program
University of Wisconsin Carbone Cancer Center
Madison, Wisconsin

Sagar Lonial, MD
Chair and Professor
Department of Hematology and Medical Oncology
Anne and Bernard Gray Family Chair in Cancer
Chief Medical Officer
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Emory University School of Medicine
Atlanta, Georgia

Shaji K Kumar, MD
Mark and Judy Mullins Professor of Hematological Malignancies
Consultant, Division of Hematology
Professor of Medicine
Mayo Clinic
Rochester, Minnesota

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Dr Love — Disclosures

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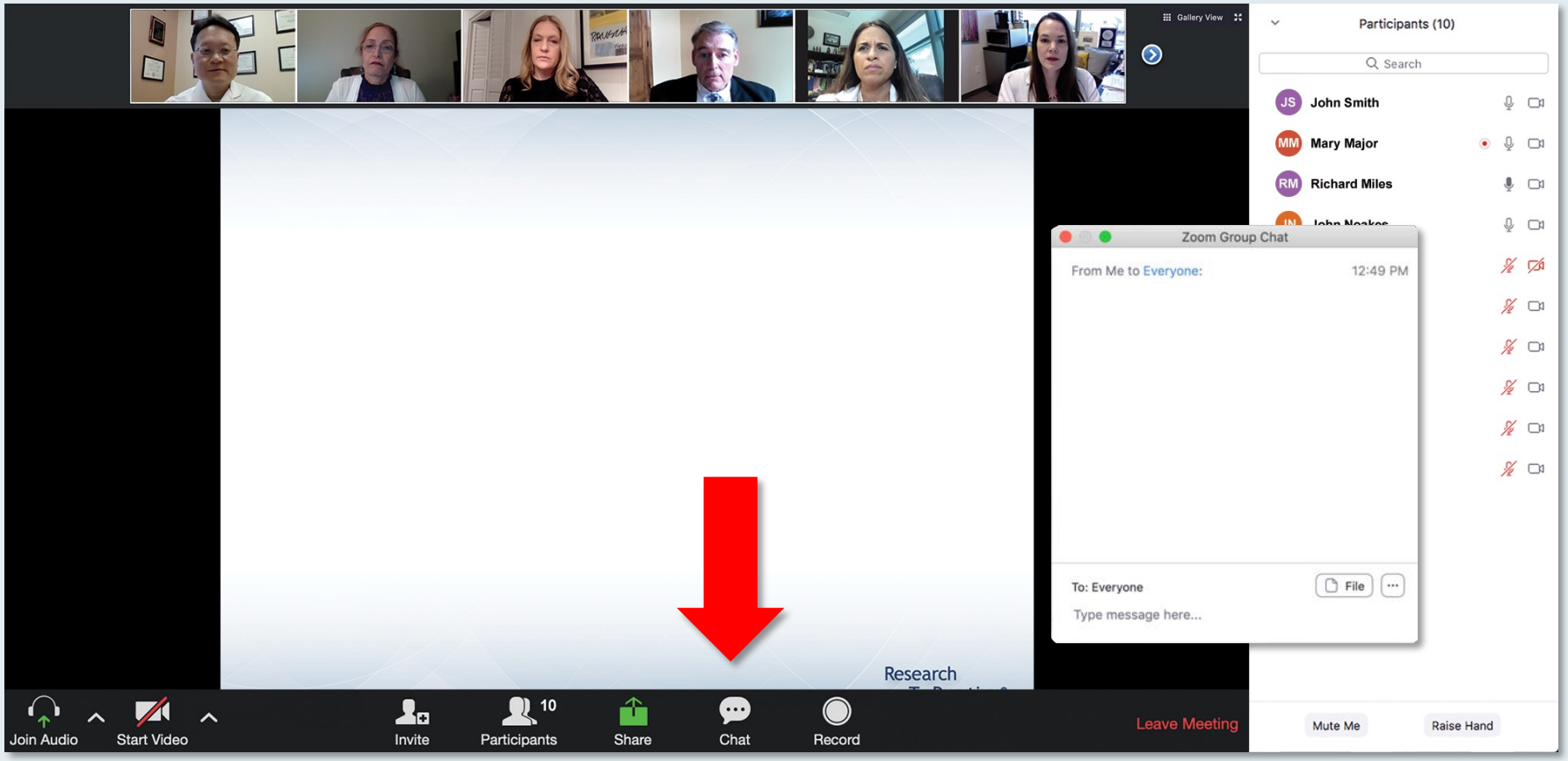

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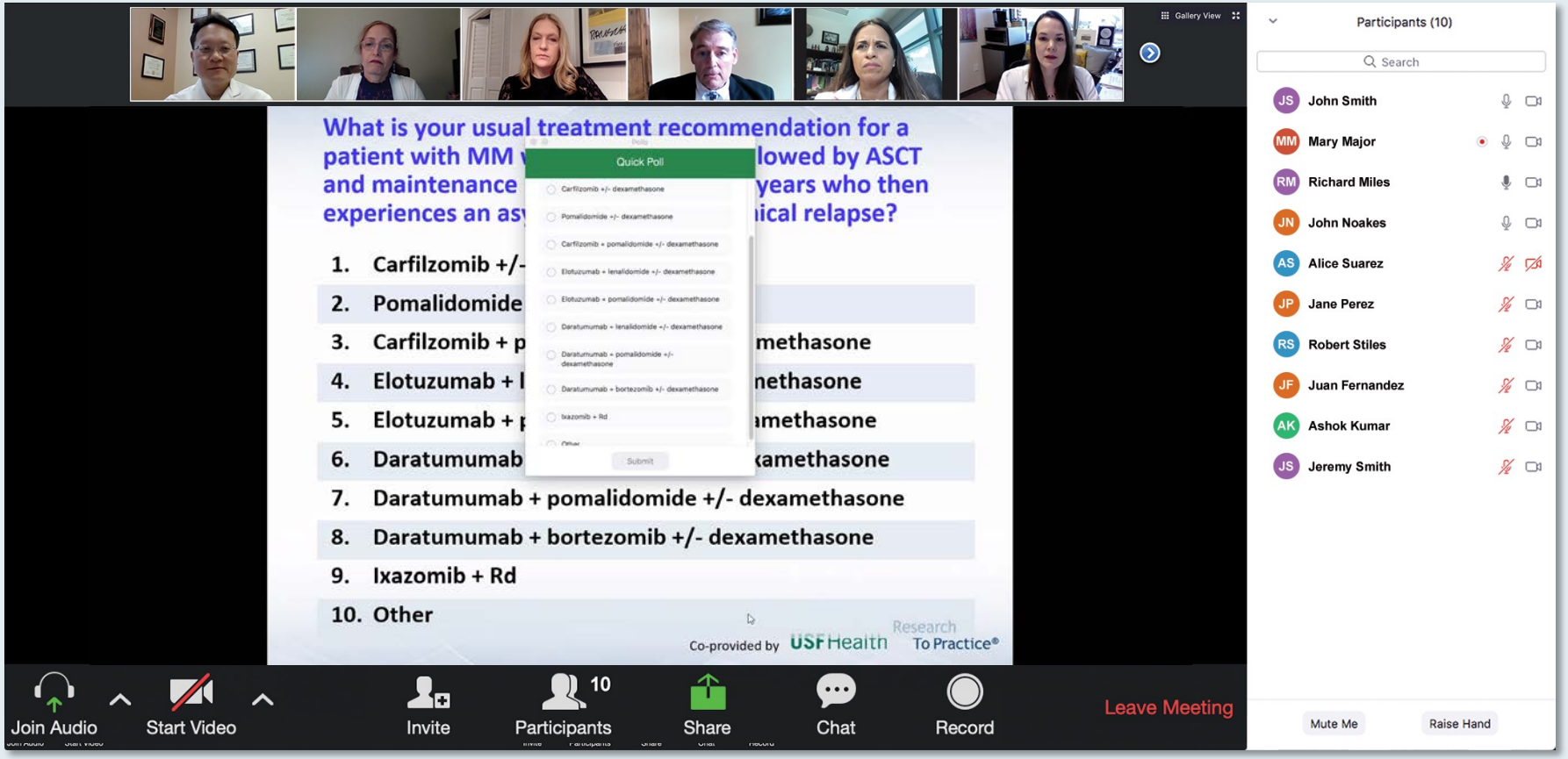
Familiarizing Yourself with the Zoom Interface

How to answer poll questions



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Familiarizing Yourself with the Zoom Interface

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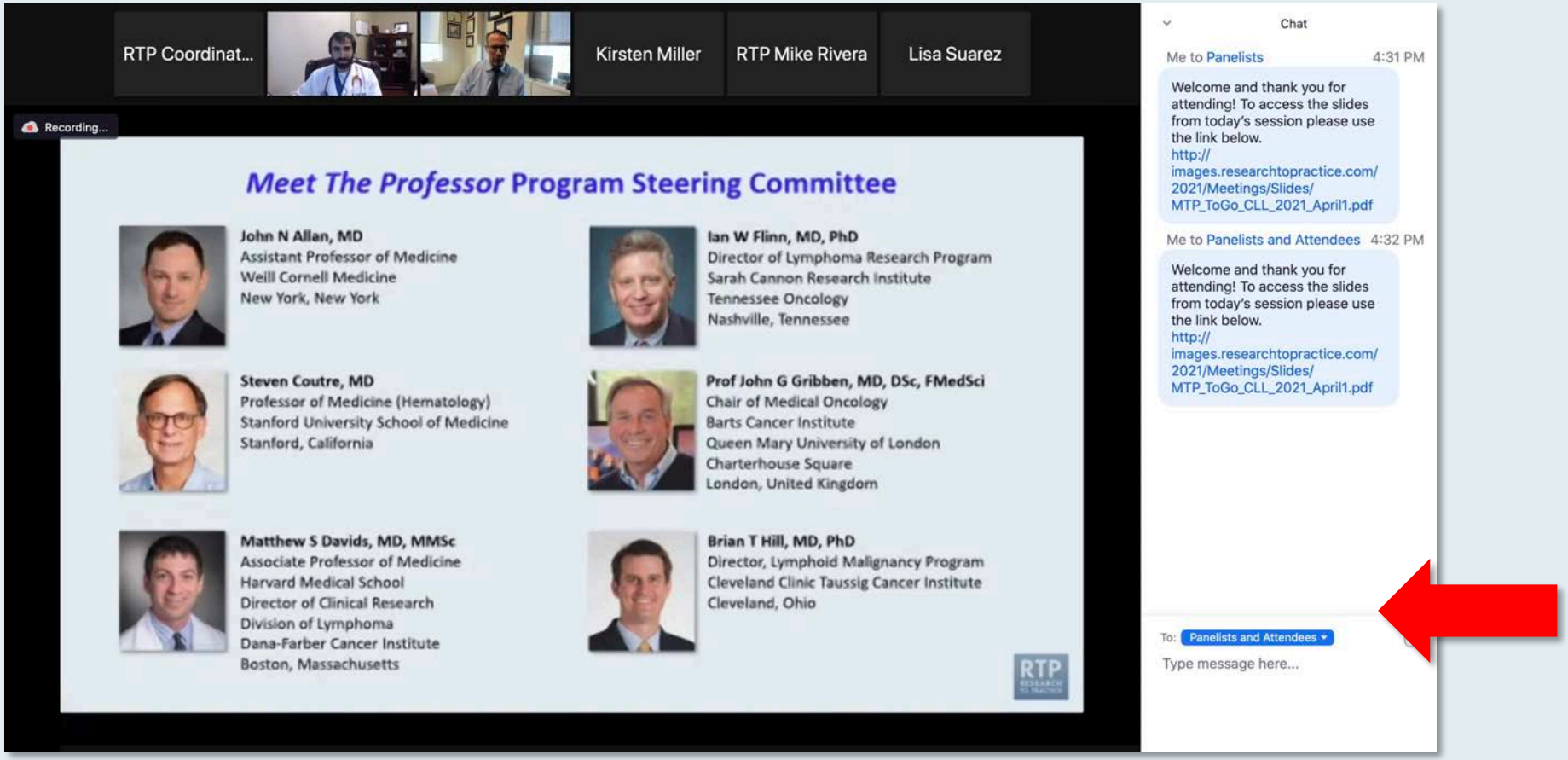

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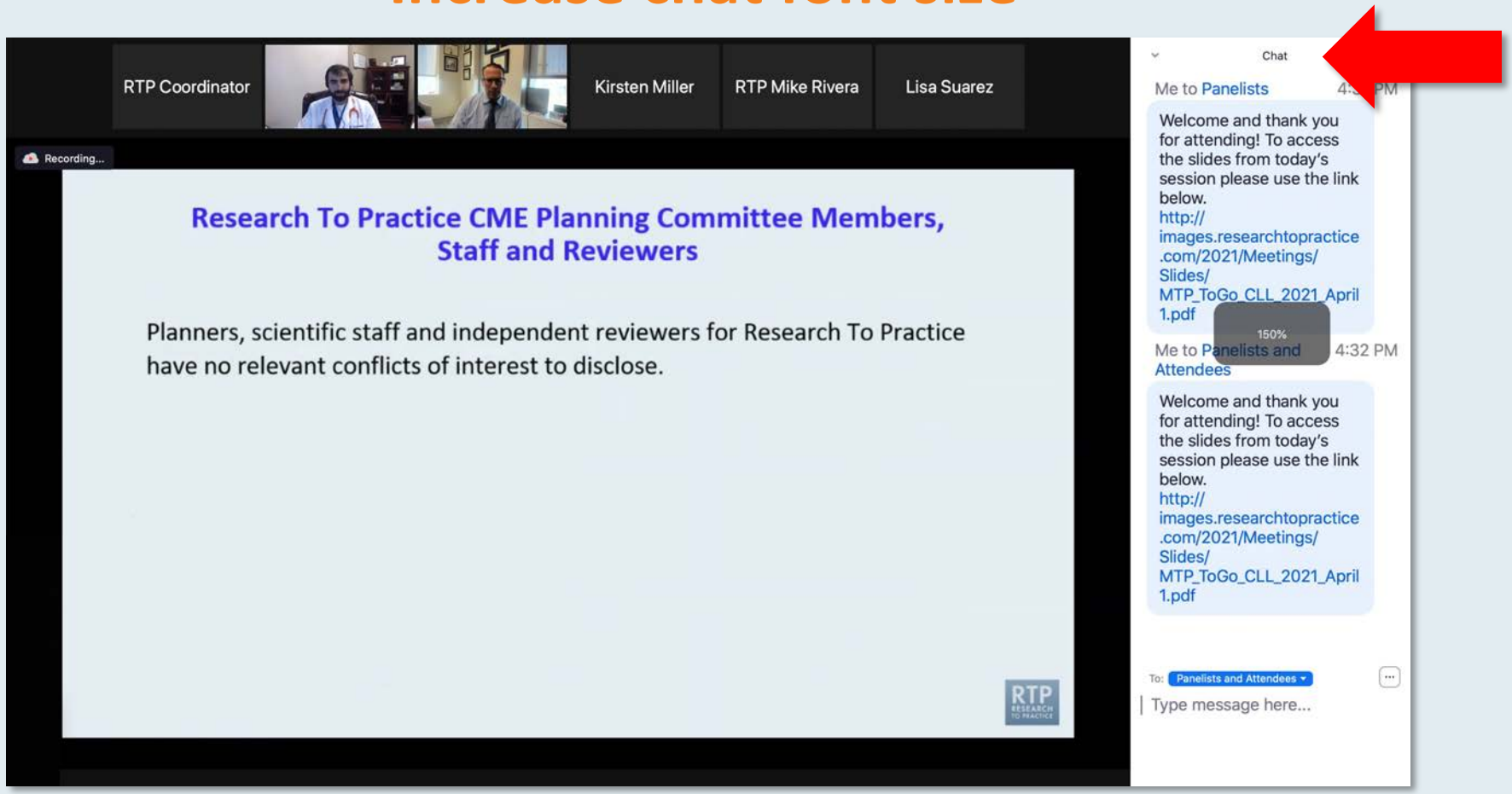

Press Command (for Mac) or Control (for PC) and the + symbol.
You may do this as many times as you need for readability.

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Key Presentations on Multiple Myeloma, Waldenström Macroglobulinemia and Amyloidosis from the 2020 ASH Annual Meeting

DR NATALIE CALLANDER

UNIVERSITY OF WISCONSIN CARBONE CANCER CENTER

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Ask the Expert: Clinical Investigators Provide Perspectives on the Management of Renal Cell Carcinoma

In Partnership with Project Echo® and Florida Cancer Specialists

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

Faculty

David I Quinn, MBBS, PhD

Moderator

Neil Love, MD

A Conversation with the Investigators: Ovarian Cancer

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5:00 PM – 6:00 PM ET

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Kathleen Moore, MD
Richard T Penson, MD, MRCP

Moderator

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Tanya B Dorff, MD
Matthew R Smith, MD, PhD

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Nikhil C Munshi, MD

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Thank you for joining us!

CME and MOC credit information will be emailed to each participant within 24 hours.

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Consensus or Controversy Consulting Investigators

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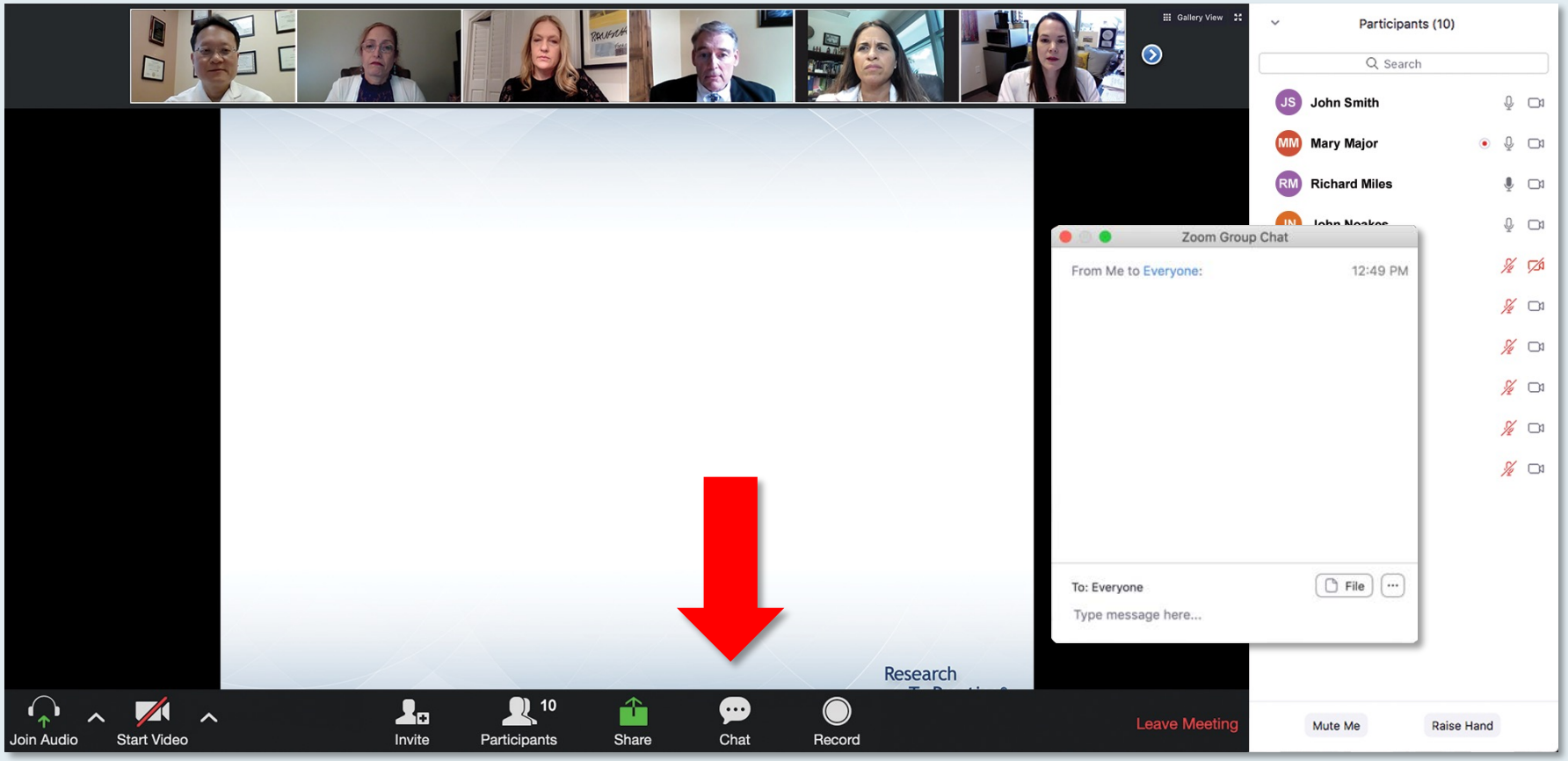

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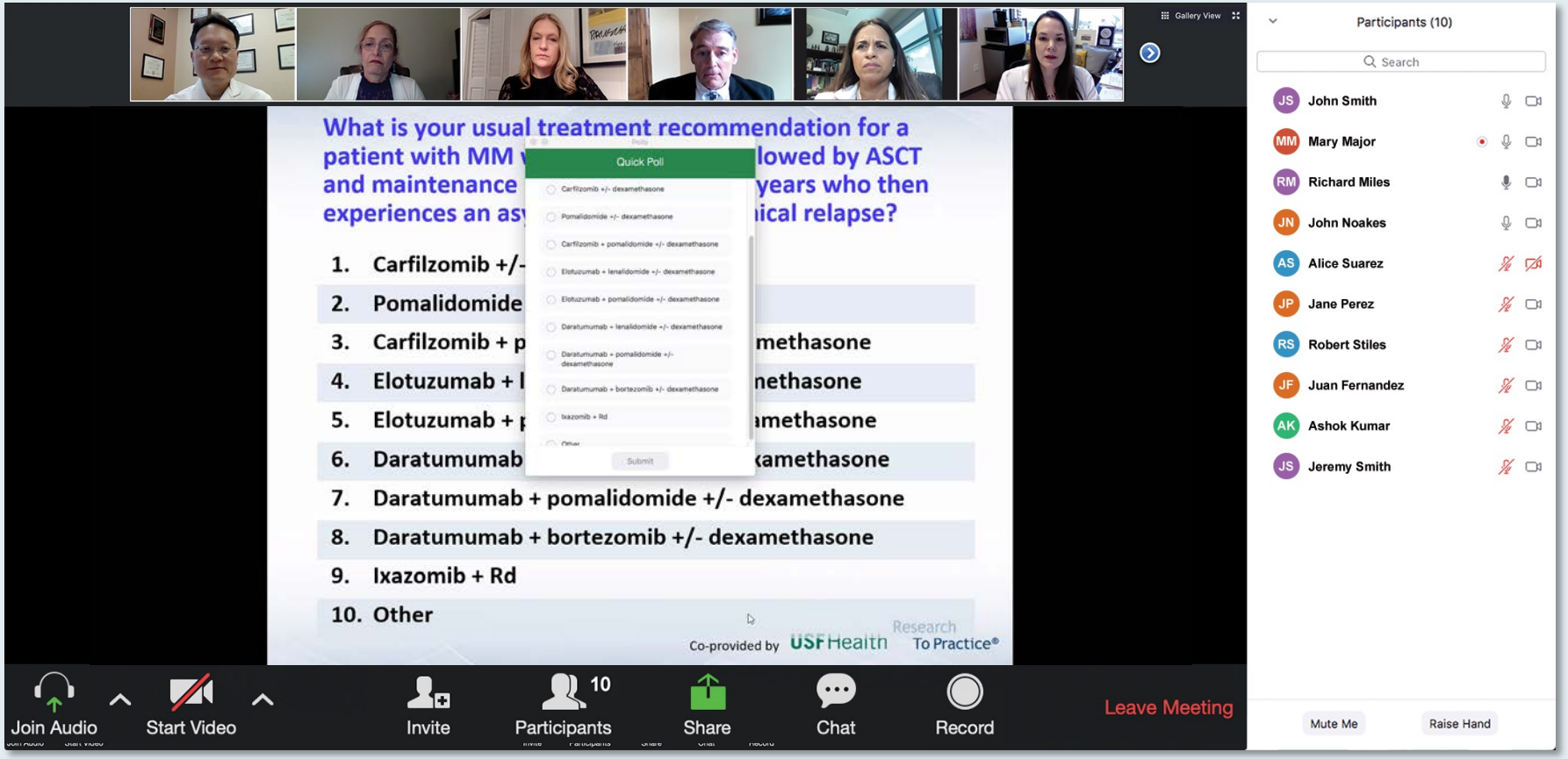

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Module 1: Newly Diagnosed Multiple Myeloma (MM)

- Induction therapy for transplant-eligible patients
- Up-front treatment for patients who are not transplant eligible
- Management of high-risk (del[17p]) MM
- Clinical role of minimal residual disease

Module 2: Relapsed/Refractory MM

- Initial relapse after RVd/transplant/maintenance therapy
- Novel agents and strategies for later-line relapse
  - Belantamab mafodotin
  - Anti-CD38 antibodies (eg, daratumumab, isatuximab)
  - Venetoclax
  - Melflufen
  - CELMoDs (eg, iberdomide, CC-92480)
  - CAR T-cell therapy

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Regulatory and reimbursement issues aside, what is your preferred pretransplant induction regimen for a younger, otherwise healthy patient with MM and no high-risk features?

1. RVd
2. KRd
3. CyBorD
4. Rd/daratumumab
5. RVd/daratumumab
6. KRd/daratumumab
7. MPV/daratumumab
8. Other

Regulatory and reimbursement issues aside, what is your preferred pretransplant induction regimen for a younger, otherwise healthy patient with MM and no high-risk features?

 Dr Callander	RVd	 Dr Richardson	RVd
 Dr Kumar	RVd	 Dr Shah	RVd
 Dr Lonial	RVd/daratumumab	 Dr Usmani	RVd/daratumumab
 Dr Hofmeister	RVd/daratumumab		

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Induction therapy: Transplant-eligible patients

Dr Craig Hofmeister

Dr Nina Shah

Dr Paul Richardson

Dr Saad Usmani

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What is the optimal first-line and maintenance therapy for a transplant-eligible patient with newly diagnosed average-risk MM?

- Multiple phase 3 trials, and meta-analyses have demonstrated the benefit of len alone as maintenance
- When used for standard risk following RVD induction and HDT, median PFS with continuous therapy has a PFS of 78 months (Joseph et al, JCO 2020)
- For patients who cannot tolerate Len maintenance, alternative considerations include ixazomib, which also demonstrated PFS benefit over observation
- Combinations with Carfilzomib or daratumumab (FORTE and GRIFFIN trials) suggest standard-risk gain/benefit from combo, but PFS benefit is unknown at this time

Regulatory and reimbursement issues aside, what is your preferred induction regimen for an 80-year-old patient with MM who is transplant ineligible with normal renal function and no high-risk features?

1. Rd
2. RVd or RVd lite
3. KRd
4. MPV/daratumumab
5. Rd/daratumumab
6. VTd (bortezomib/thalidomide/dexamethasone)/daratumumab
7. MPV, MPR or MPT
8. Other

Regulatory and reimbursement issues aside, what is your preferred initial regimen for an otherwise healthy 80-year-old patient with MM and no high-risk features?

 Dr Callander	Rd/daratumumab
 Dr Kumar	Rd/daratumumab
 Dr Lonial	Rd/daratumumab
 Dr Hofmeister	Rd/daratumumab
 Dr Richardson	Rvd or RVd lite
 Dr Shah	Rd/daratumumab
 Dr Usmani	Rd/daratumumab

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Up-front treatment: Transplant-ineligible patients

Dr Craig Hofmeister

Dr Nina Shah

Dr Paul Richardson

Dr Saad Usmani

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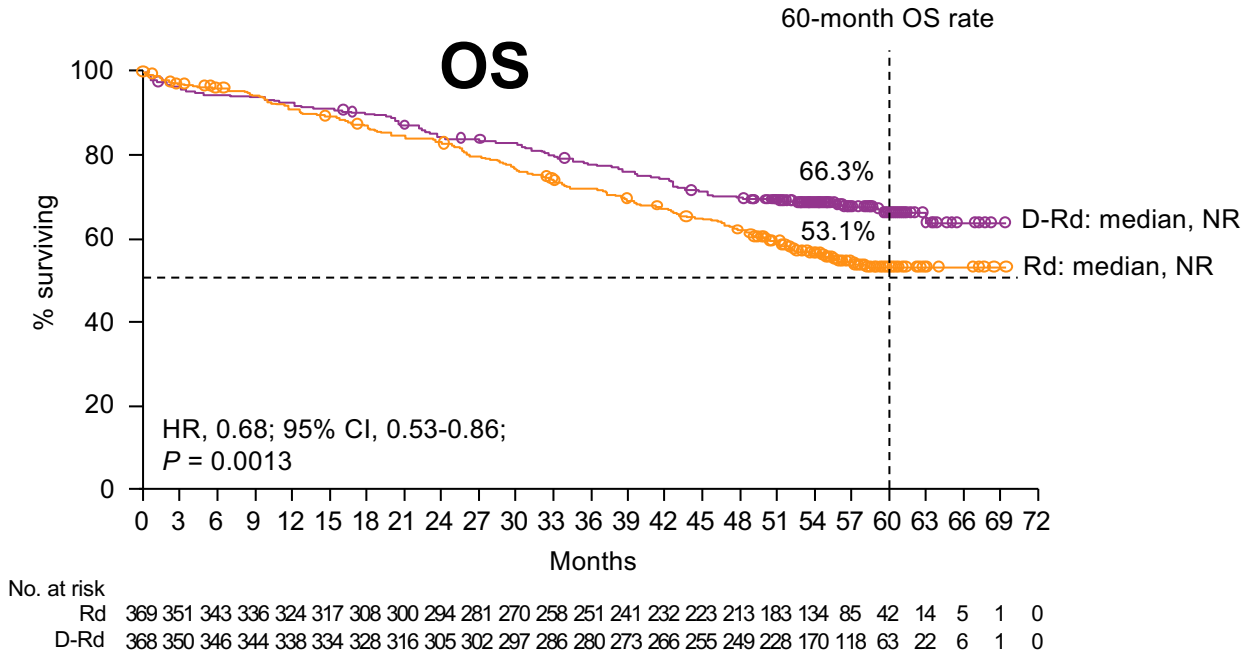
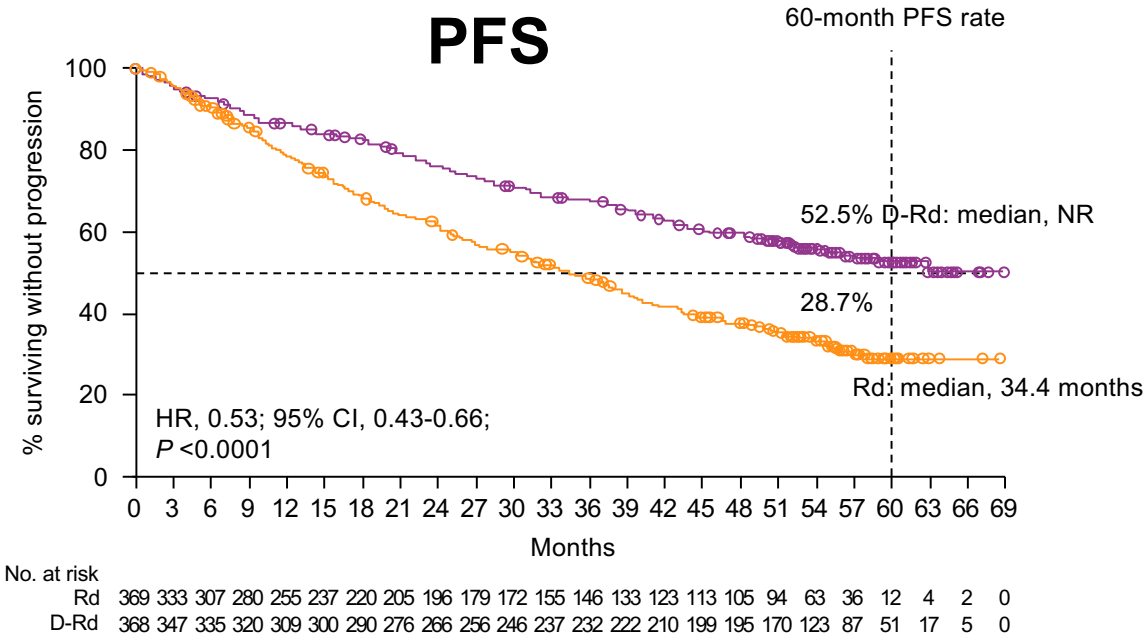
What is the optimal first-line and maintenance therapy for an otherwise healthy 80-year-old patient with standard-risk MM?

- Historic data for this group of patients has been MP or MP + novel agent
- FIRST trial demonstrated the benefit of Rd over MP combo
- SWOG-S0777 trial demonstrated the benefit of RVD over Rd for this same group, though some were younger and would have been transplant eligible in the US
- MAIA trial has now demonstrated superiority of Rd and looks very promising with PFS benefit around 5.5 years and suggested OS benefit

MAIA: OS and PFS with D-Rd and Rd





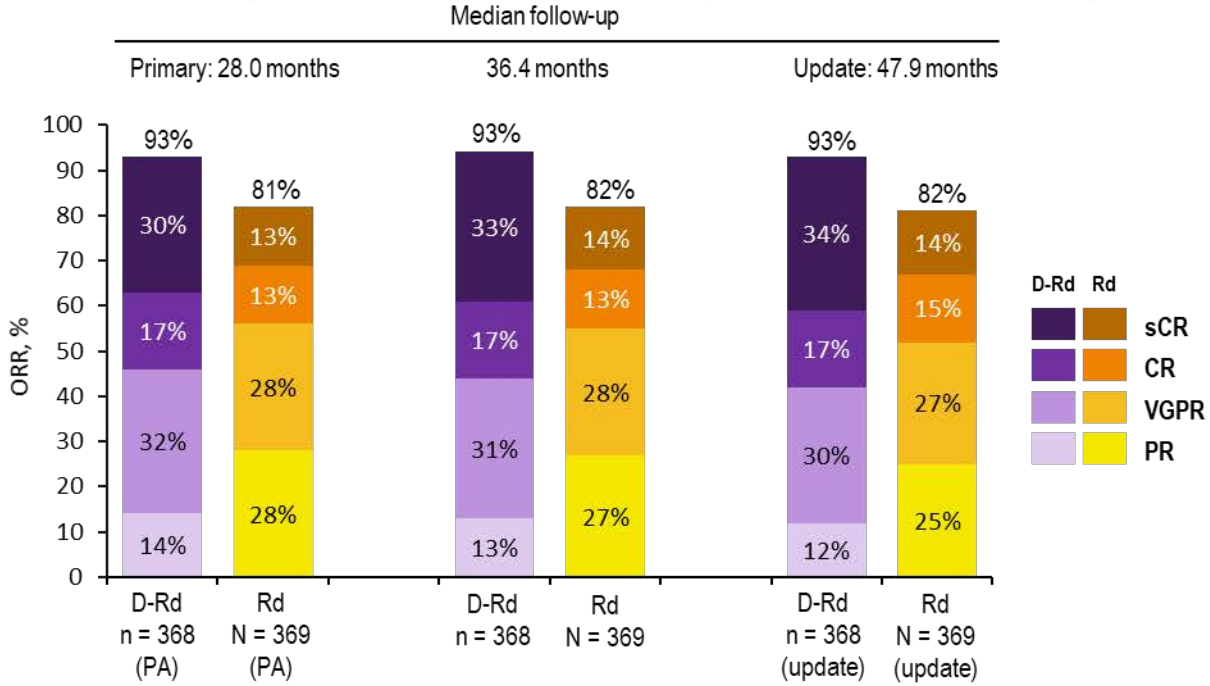
D-Rd, daratumumab plus lenalidomide and Dexamethasone; Rd, lenalidomide and Dexamethasone; HR, hazard ratio; CI, confidence interval; NR, not reached.

Facon T, et al. EHA (abstr LB1901)

Courtesy of Sagar Lonial, MD

Phase 3 MAIA Study: Updated Response

- Most common grade 3/4 AEs: neutropenia (50.0% vs 35.3%), anemia (11.8% vs 19.7%), lymphopenia (15.1% vs 10.7%), and pneumonia (13.7% vs 7.9%)



Adding DARA to Rd resulted in deeper responses with higher rates of ≥CR and ≥VGPR, compared with Rd alone

Kumar S et al, ASH 2020; abstract 2276

Courtesy of Sagar Lonial, MD

Regulatory and reimbursement issues aside, what is your preferred pretransplant induction regimen for a younger, otherwise healthy patient with MM and del(17p)?

1. RVd
2. KRd
3. CyBorD
4. Rd/daratumumab
5. RVd/daratumumab
6. KRd/daratumumab
7. MPV/daratumumab
8. Other

Regulatory and reimbursement issues aside, what is your preferred pretransplant induction regimen for a 65-year-old patient with MM and del(17p)?

 Dr Callander	KRd
 Dr Richardson	RVd/daratumumab
 Dr Kumar	RVd/daratumumab
 Dr Shah	KRd
 Dr Lonial	KRd
 Dr Usmani	KRd or KRd/daratumumab
 Dr Hofmeister	KRd

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High-risk disease (eg, del[17p])

Dr Craig Hofmeister

Dr Nina Shah

Dr Paul Richardson

Dr Saad Usmani

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What is the optimal first-line and maintenance therapy for a transplant-eligible patient with newly diagnosed high-risk (eg, del[17p]) MM?

- High risk data needs more than len alone
- Data from our group (Nooka et al, Leukemia 2013) suggested that RVD consolidation for 3 years offers benefit over len or Bz alone
- 2 years ago, our group switched to KRD maintenance and consolidation in order to reduce toxicity of treatment
- FORTE trial demonstrated better sustained MRD negativity for KR maintenance, supporting our group's use of KRD consolidation

In what situations, if any, do you employ ixazomib instead of a parenteral proteasome inhibitor as part of maintenance therapy?

- Patients who are unable to tolerate len maintenance and are in standard risk
  - Typically have received <1yr of len
- Patients with high-risk disease who are unable to come in for weekly dosing of Bz or carfilzomib
- Patients with high-risk disease who wish to consider less frequent visits to clinic after a period of VRD or KRD maintenance

Are there situations in which you believe community-based oncologists/hematologists should be ordering minimal residual disease assessment to guide treatment decision-making for patients with MM?

1. Yes
2. No

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Are there situations in which you believe community-based oncologists/hematologists should be ordering minimal residual disease assessment to guide treatment decision-making for patients with MM?

 Dr Callander	No	 Dr Richardson	No
 Dr Kumar	No	 Dr Shah	No
 Dr Lonial	No	 Dr Usmani	No
 Dr Hofmeister	Yes – to balance toxicity vs benefit of len maintenance		

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Minimal residual disease (MRD)

Dr Craig Hofmeister

Dr Nina Shah

Dr Paul Richardson

Dr Saad Usmani

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Are there situations in which you believe community-based oncologists/hematologists should be ordering MRD assessment to guide treatment decision-making for patients with MM?

- MRD assessments are prognostic, just like achieving CR or sCR
- It may provide information but should not guide therapy
- No evidence that changing therapy based on MRD status changes outcomes
- For patients who are MRD-negative at a single time point, this does not have the same impact as sustained MRD status over 6-12 months
- In situations where taking len maintenance is difficult, can use MRD status as a way to inform decisions about continued therapy vs stopping

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What is your usual treatment recommendation for a 65-year-old patient with MM treated with RVd → ASCT and maintenance lenalidomide for 1.5 years who then experiences asymptomatic biochemical relapse?

1. Carfilzomib + dexamethasone (dex)
2. Pomalidomide + dex
3. Carfilzomib + pomalidomide + dex
4. Elotuzumab + lenalidomide + dex
5. Elotuzumab + pomalidomide + dex
6. Daratumumab + lenalidomide + dex
7. Daratumumab + pomalidomide + dex
8. Other

What is your usual treatment recommendation for a 65-year-old patient with MM treated with RVd → ASCT and maintenance lenalidomide for 1.5 years who then experiences an asymptomatic biochemical relapse?

 Dr Callander	Dara/pom/dex	 Dr Richardson	Elo/pom/dex
 Dr Kumar	Dara/pom/dex	 Dr Shah	Dara/pom/dex
 Dr Lonial	Observe tempo of progression, obtain PET before starting salvage therapy	 Dr Usmani	Dara/pom/dex *OR* Dara/carfilzomib/dex
 Dr Hofmeister	Dara/pom/dex		

Dara/pom/dex = daratumumab + pomalidomide + dexamethasone; elo/pom/dex = elotuzumab + pomalidomide + dexamethasone

Initial relapse after RVd/transplant/maintenance therapy

Dr Craig Hofmeister

Dr Nina Shah

Dr Paul Richardson

Dr Saad Usmani

RTP
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TO PRACTICE

Which of the following strategies 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?

1. Isatuximab-based combination
2. Selinexor
3. Belantamab mafodotin
4. Melflufen
5. BCMA-directed CAR T-cell therapy
6. Venetoclax
7. I would not recommend any of these

Which of the following strategies 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?

 Dr Callander	Belantamab mafodotin	 Dr Richardson	Belantamab mafodotin
 Dr Kumar	BCMA-directed CAR T-cell therapy	 Dr Shah	BCMA-directed CAR T-cell therapy
 Dr Lonial	Belantamab mafodotin	 Dr Usmani	BCMA-directed CAR T-cell therapy
 Dr Hofmeister	BCMA-directed CAR T-cell therapy		

RTP RESEARCH TO PRACTICE

Belantamab mafodotin

Dr Craig Hofmeister

Dr Nina Shah

Dr Paul Richardson

Dr Saad Usmani

RTP
RESEARCH
TO PRACTICE

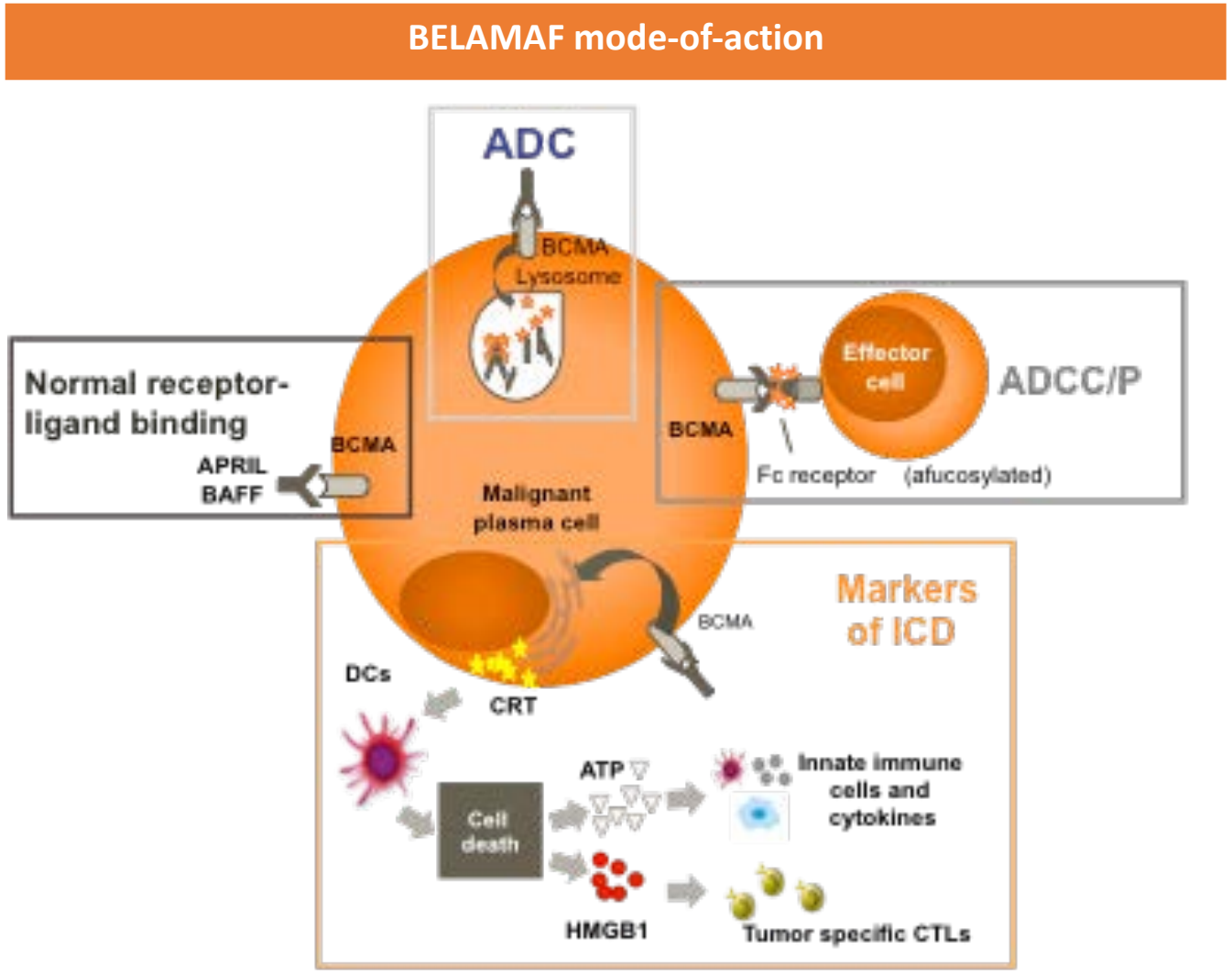
When in the treatment course is the optimal time to recommend belantamab mafodotin?

- BCMA targeted ADC: effective as a single agent
- Indicated for the treatment of relapsed myeloma after at least 4 prior therapies, including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent
- Typically, would be used after patients have used up IMIDs, PIs and anti-CD38 Mabs
- So late relapse, adequate heme function and no eye problems
- Need to carefully observe for eye toxicity

Belantamab Mafodotin

- B cell maturation antigen (BMCA)
  - ✓ Selectively expressed on plasmablasts and plasma cells[1]
  - ✓ Requisite for long-lived plasma cell survival[1]
- Belantamab mafodotin (BELAMAF)
  - ✓ Humanized, afucosylated IgG1, antibody drug conjugate (ADC)

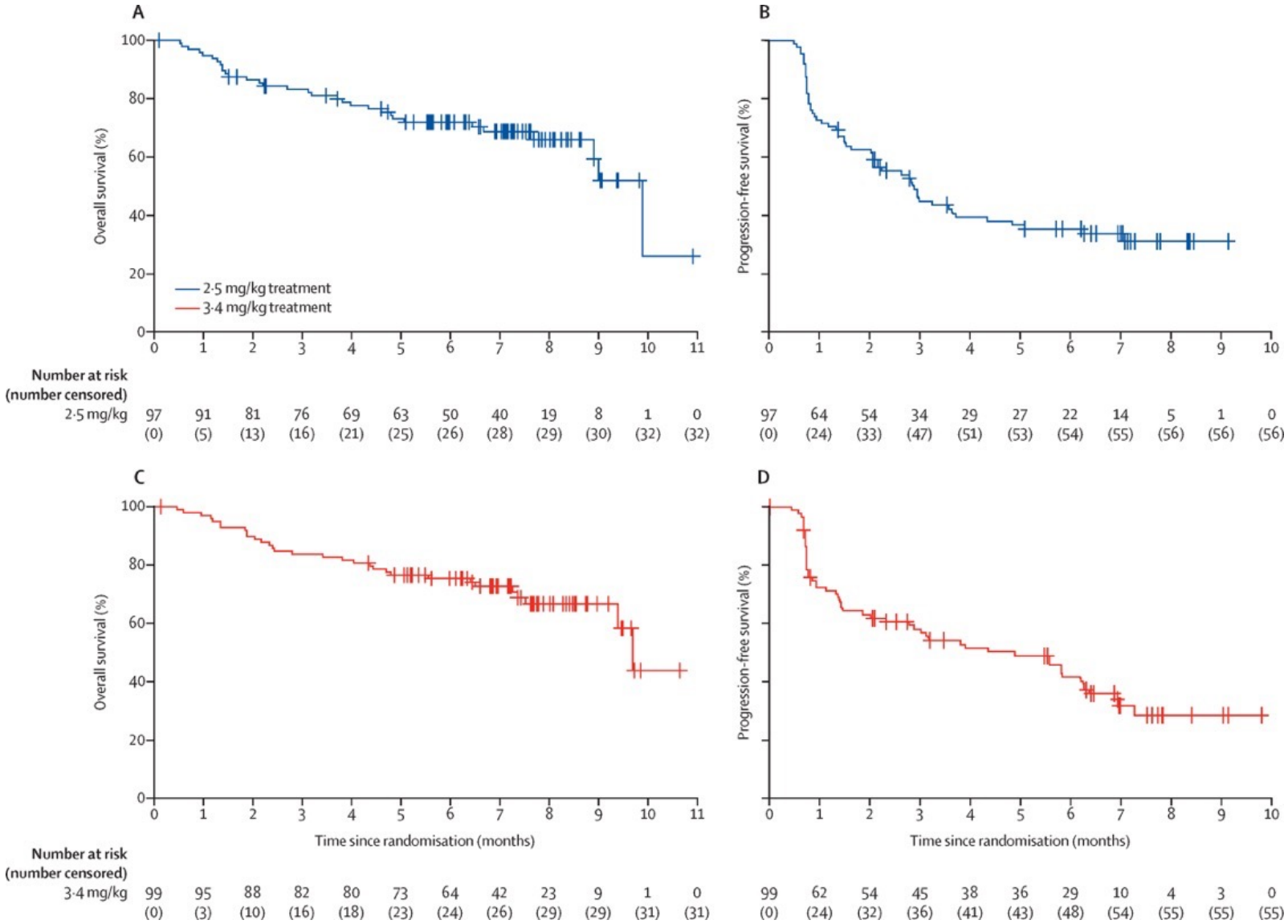
  targeting BMCA[2]
  - ✓ Multimodal mechanisms of action (MoA)[2]
  - ✓ Convenient IV 0.5-1 h outpatient infusion



[1]Cho, Front Immunol. 2018;9:1821; [2]Sheikh, Future Oncol. 2020; [3]Carral, J Immunol, 1999:163:380.

Courtesy of Shaji K Kumar, MD

DREAMM2: Single agent Belantamab



The Lancet Oncology 2020 21207-221DOI: (10.1016/S1470-2045(19)30788-0)

Courtesy of Shaji K Kumar, MD

In the relapsed/refractory setting do you consider daratumumab and isatuximab to be essentially equivalent therapeutic options (when combined with the same agents)?

1. Yes
2. No

In the relapsed/refractory setting do you consider daratumumab and isatuximab to be essentially equivalent therapeutic options (when combined with the same agents)?

Anti-CD38 antibodies (eg, daratumumab, isatuximab)

Dr Craig Hofmeister

Dr Nina Shah

Dr Paul Richardson

Dr Saad Usmani

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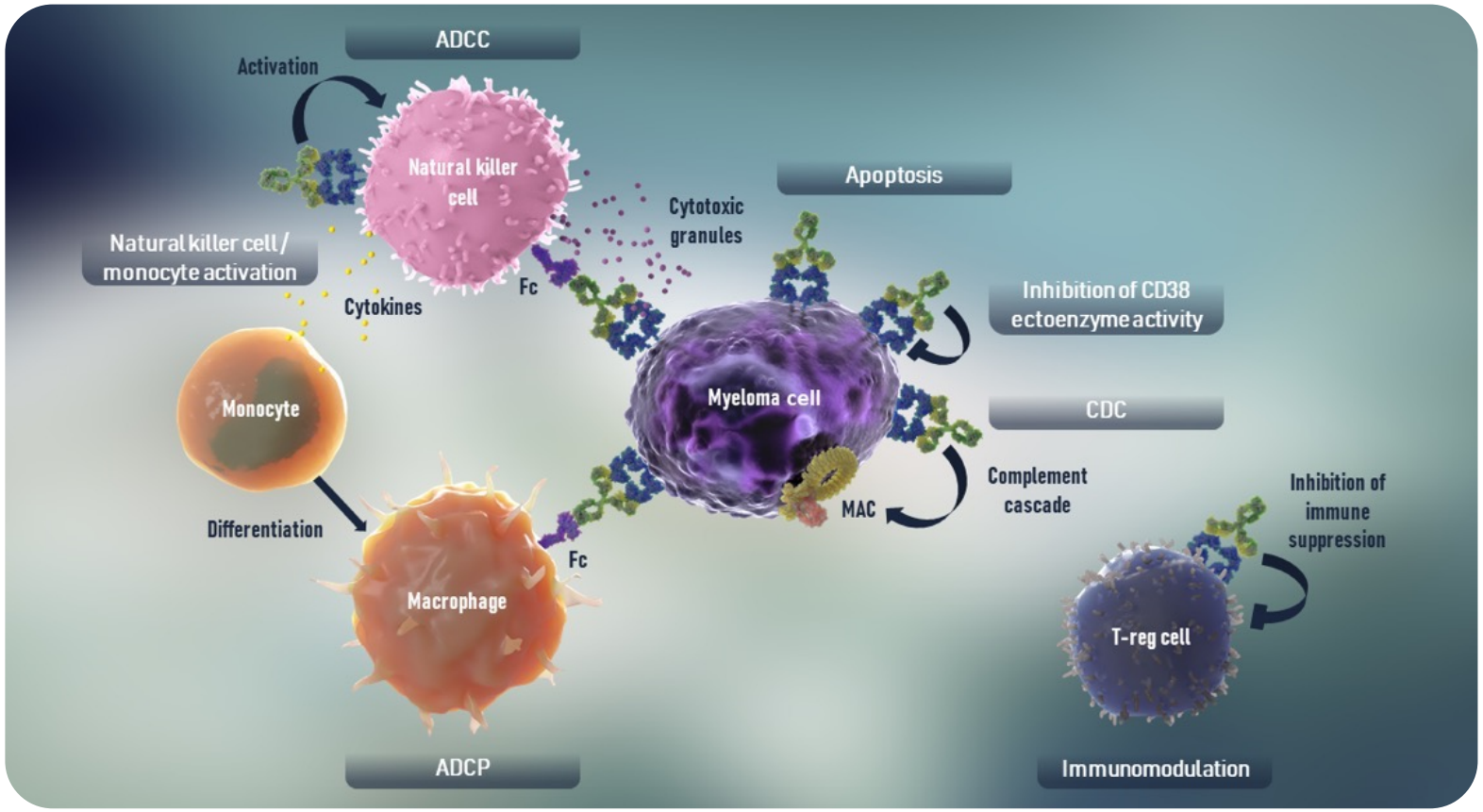
In the relapsed/refractory setting do you consider daratumumab and isatuximab to be essentially equivalent therapeutic options (when combined with the same agents)? Is it reasonable to employ isatuximab for a patient whose disease has progressed on daratumumab?

- Both targets CD38, overall mechanisms of action similar
- Daratumumab is IV and SQ, Isatuximab is IV
- Overall adverse event profiles appear similar, when IVs are compared, isatuximab may be associated with less infusion reactions
- Both carfilzomib and pomalidomide combinations have been studied in phase 3 trials with relatively similar results
- No data to support that isatuximab will work when patient is refractory to daratumumab or vice versa

Isatuximab: Targets a specific epitope on CD38



CD38 functions as a receptor and an ectoenzyme, uniformly expressed on multiple myeloma (MM) cells[1–5]

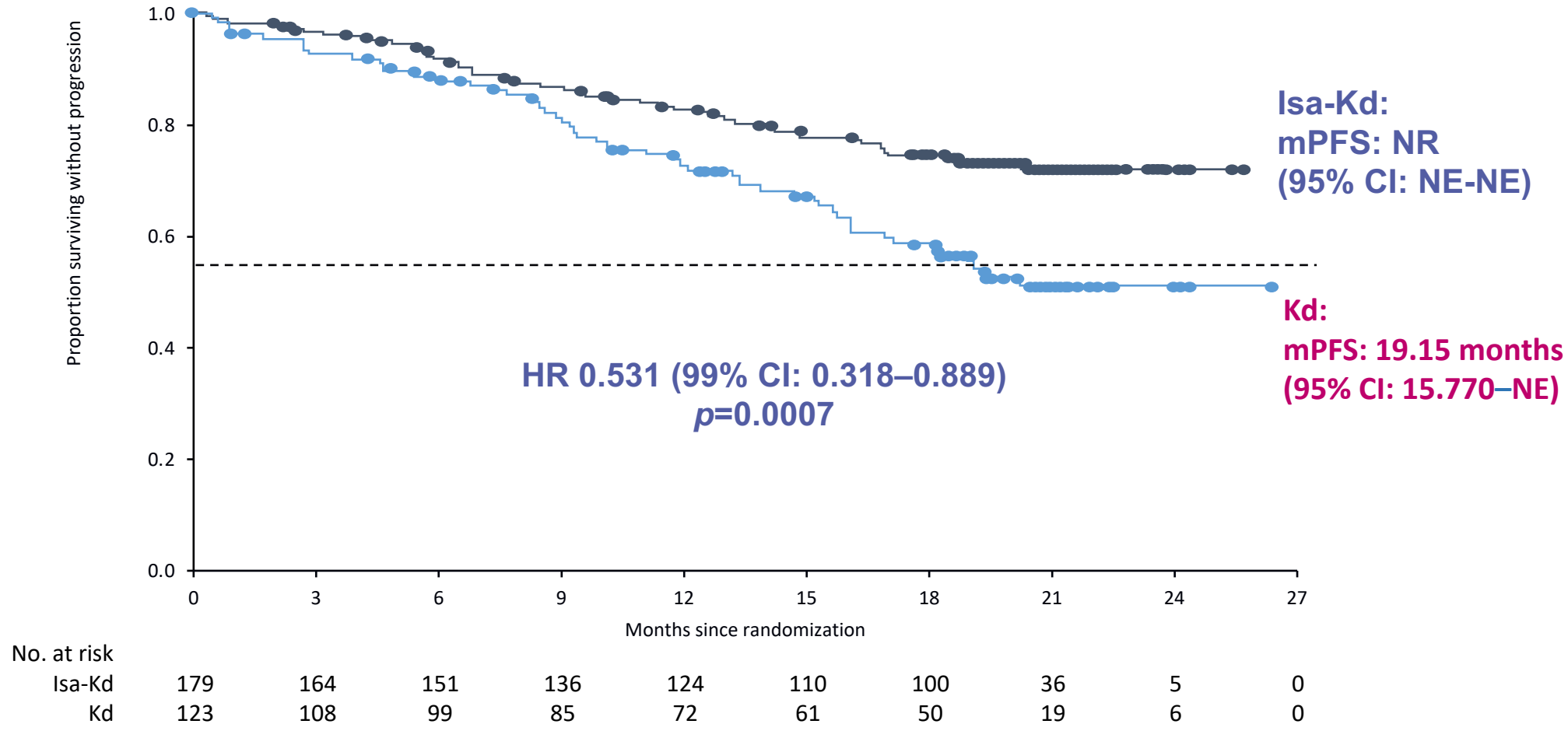
Isatuximab: IgG1 monoclonal antibody targeting a CD38 transmembrane glycoprotein in MM with multiple modes of action:[6]

- **ADCC, CDC, and ADCP**
- **Direct apoptosis**
- **Immunomodulation**
- **Inhibition of ectoenzyme activity**

1. Lin P, et al. Am J Clin Pathol. 2004;121:482–488. 2. Angelopoulou MK, et al. Eur J Haematol. 2002;68:12–21.
3. Schwonzen M, et al. Br J Haematol. 1993;83:232–239. 4. Keyhani A, et al. Leuk Res. 2000;24:153–159.
5. Domingo-Domènech E, et al. Haematologica. 2002;87.1021–1027. 6. Jiang H, et al. Leukemia. 2016;30:399–408 7. Sanofi. Isatuximab [Package Insert]. Bridgewater, NJ 2020.

Courtesy of Shaji K Kumar, MD

IKEMA: Progression Free Survival

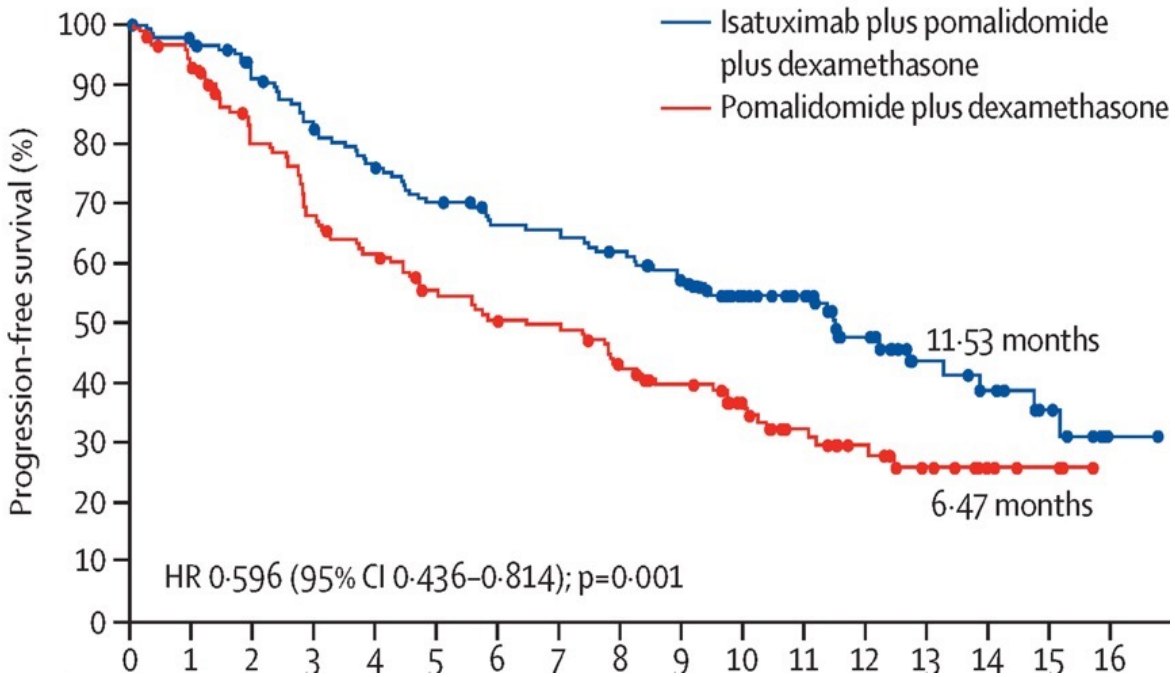


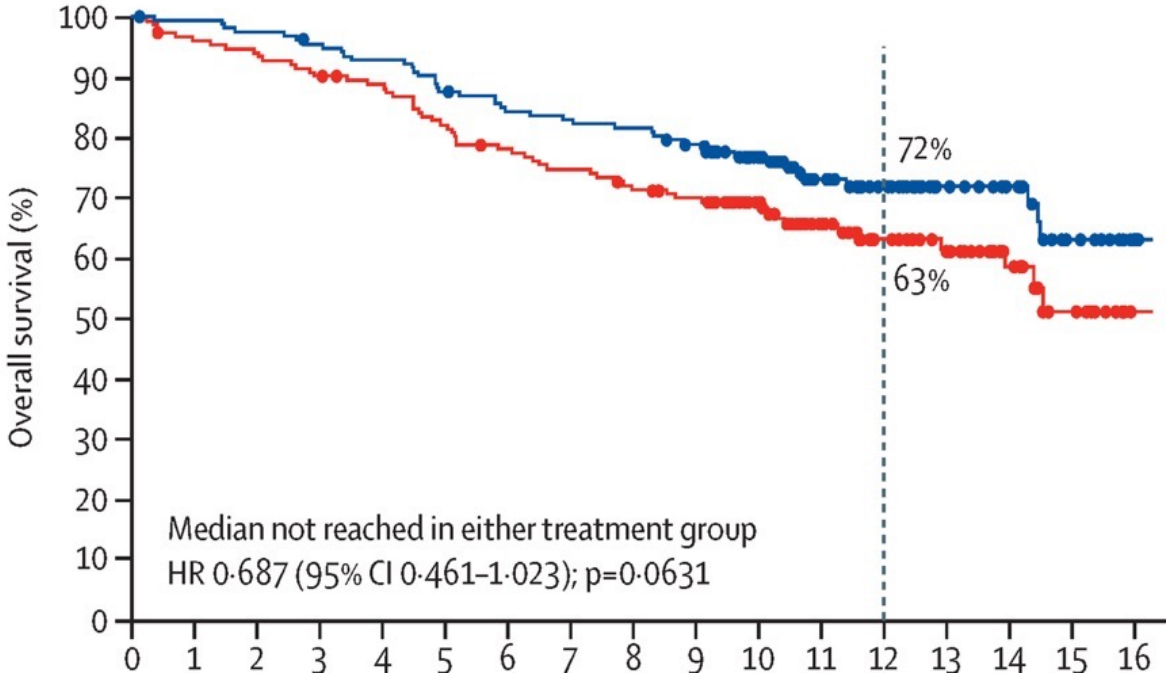
One-sided *p* value, level of significance <0.005

Moreau et al

Courtesy of Shaji K Kumar, MD

ICARIA-MM Survival





Lancet 2019; 394: 2096-107

Courtesy of Shaji K Kumar, MD

Are there situations in which you would attempt to use venetoclax outside a trial setting for relapsed/refractory MM?

1. Yes
2. Yes, but only for patients with t(11;14) or high Bcl-2 expression
3. No

Are there situations in which you would attempt to use venetoclax outside a trial setting for relapsed/refractory MM?

Dr Callander

Yes, but only in patients with t(11;14)

Dr Kumar

Yes, but only in patients with t(11;14)

Dr Lonial

Yes, but only in patients with t(11;14)

Dr Hofmeister

Yes, but only in patients with t(11;14)

Dr Richardson

Yes, but only in patients with t(11;14) or high Bcl-2 expression

Dr Shah

Yes, but only in patients with t(11;14) or high Bcl-2 expression

Dr Usmani

Yes, but only in patients with t(11;14) or high Bcl-2 expression

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Reimbursement and regulatory issues aside, at what point, if any, would you attempt to access venetoclax for a patient with MM and t(11;14)?

 Dr Callander	Beyond third line	 Dr Richardson	Second line
 Dr Kumar	Beyond third line	 Dr Shah	Second line
 Dr Lonial	Second line	 Dr Usmani	Up front
 Dr Hofmeister	Second line		

RTP RESEARCH TO PRACTICE

Venetoclax

Dr Craig Hofmeister

Dr Nina Shah

Dr Paul Richardson

Dr Saad Usmani

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TO PRACTICE

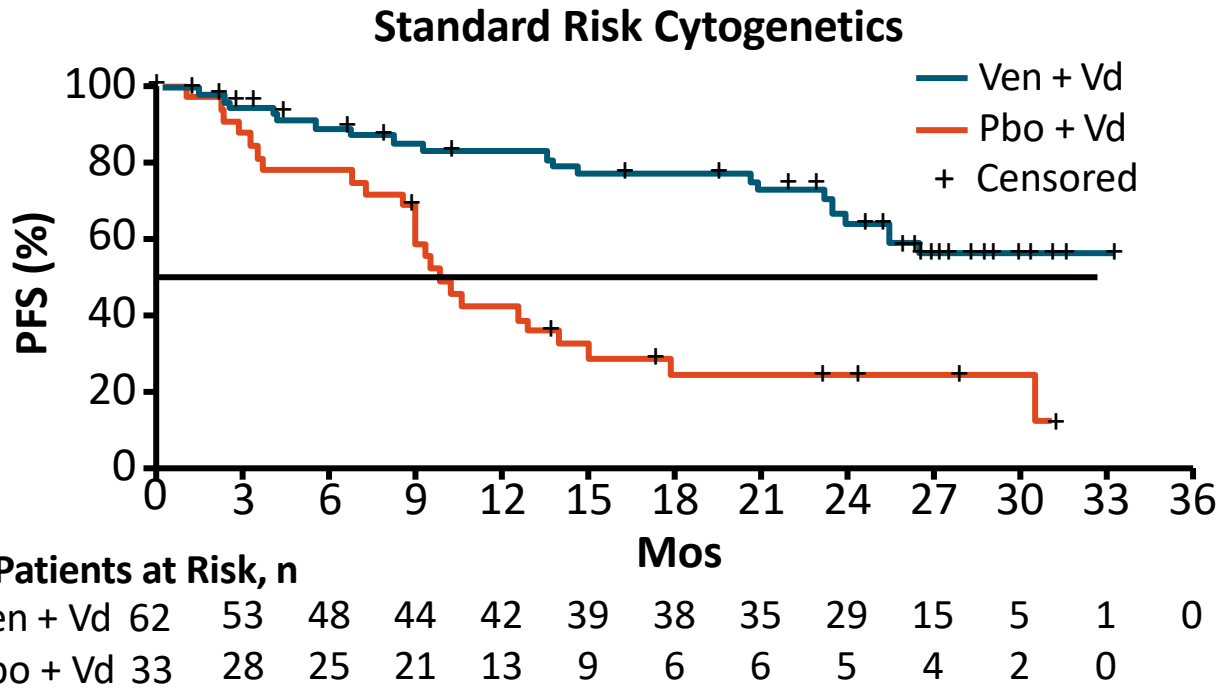
Is it reasonable to use venetoclax in a patient with t(11;14) and would you do so with dexamethasone or as part of another regimen?

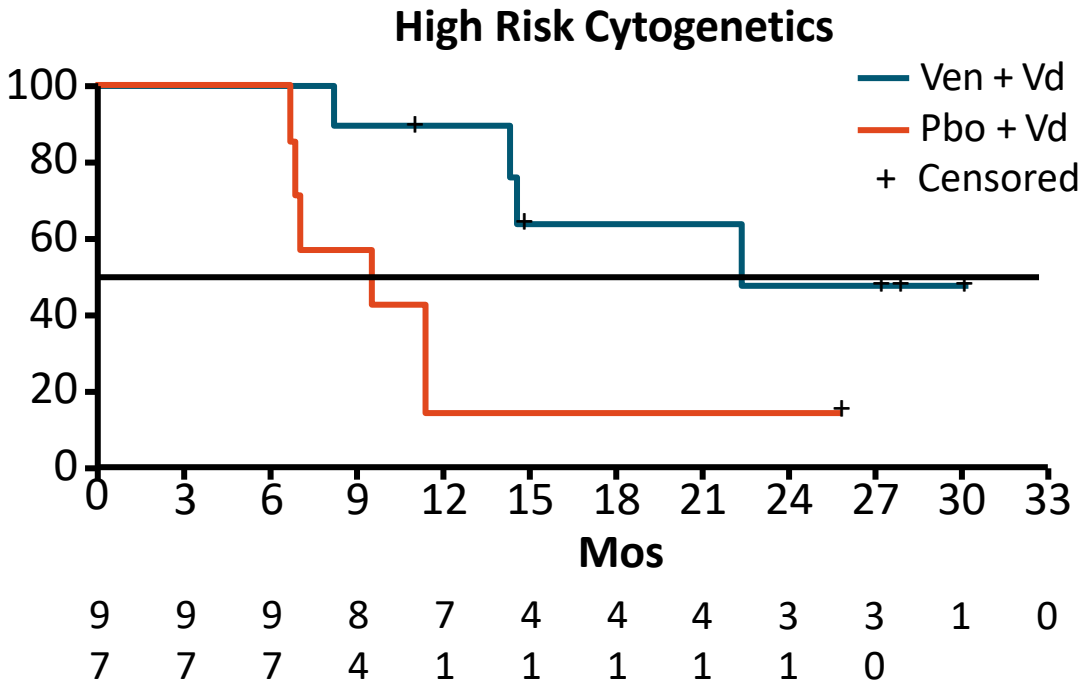
- YES! Either with dex or bortezomib/dex with ***careful*** monitoring
- 75 year old male with stage II MM, dx 8 years ago FISH: del 13 and t(11;14), 63% PCs
- CyBorD X 6, auto transplant-no maintenance
- Relapsed 3 years later and received daratumumab, len, dex with 2nd CR
- Progressed after 1 year; changed to DVD, no response
- Pom/Cy/Dex no response
- Significant cardiac history- did not want to use carfilzomib
- Started venetoclax/dexamethasone with sustained PR, no TLS

What is the optimal dose and schedule of venetoclax in MM, and is tumor lysis syndrome prophylaxis necessary?

- Unlike in CLL, TLS occurs rarely in myeloma patients (1 pt. in KVenD study with mild TLS, no TLS in original Ven study)
- Start at 50 mg daily and increase weekly
- Monitor labs weekly during first month
- Routine admission not necessary
- Some patients do not tolerate 800 mg (thrombocytopenia)
- Do start allopurinol for first week if creatinine acceptable

BELLINI: PFS and OS in t(11;14)-Positive or BCL2^{high} MM





Patients at Risk, n

Ven + Vd	62	53	48	44	42	39	38	35	29	15	5	1	0
Pbo + Vd	33	28	25	21	13	9	6	6	5	4	2	0	

9	9	9	8	7	4	4	4	3	3	1	0
7	7	7	4	1	1	1	1	1	0		

Kumar. ASCO 2020. Abstr 8509.

Courtesy of Natalie S Callander, MD

Melflufen

Dr Craig Hofmeister

Dr Nina Shah

Dr Paul Richardson

Dr Saad Usmani

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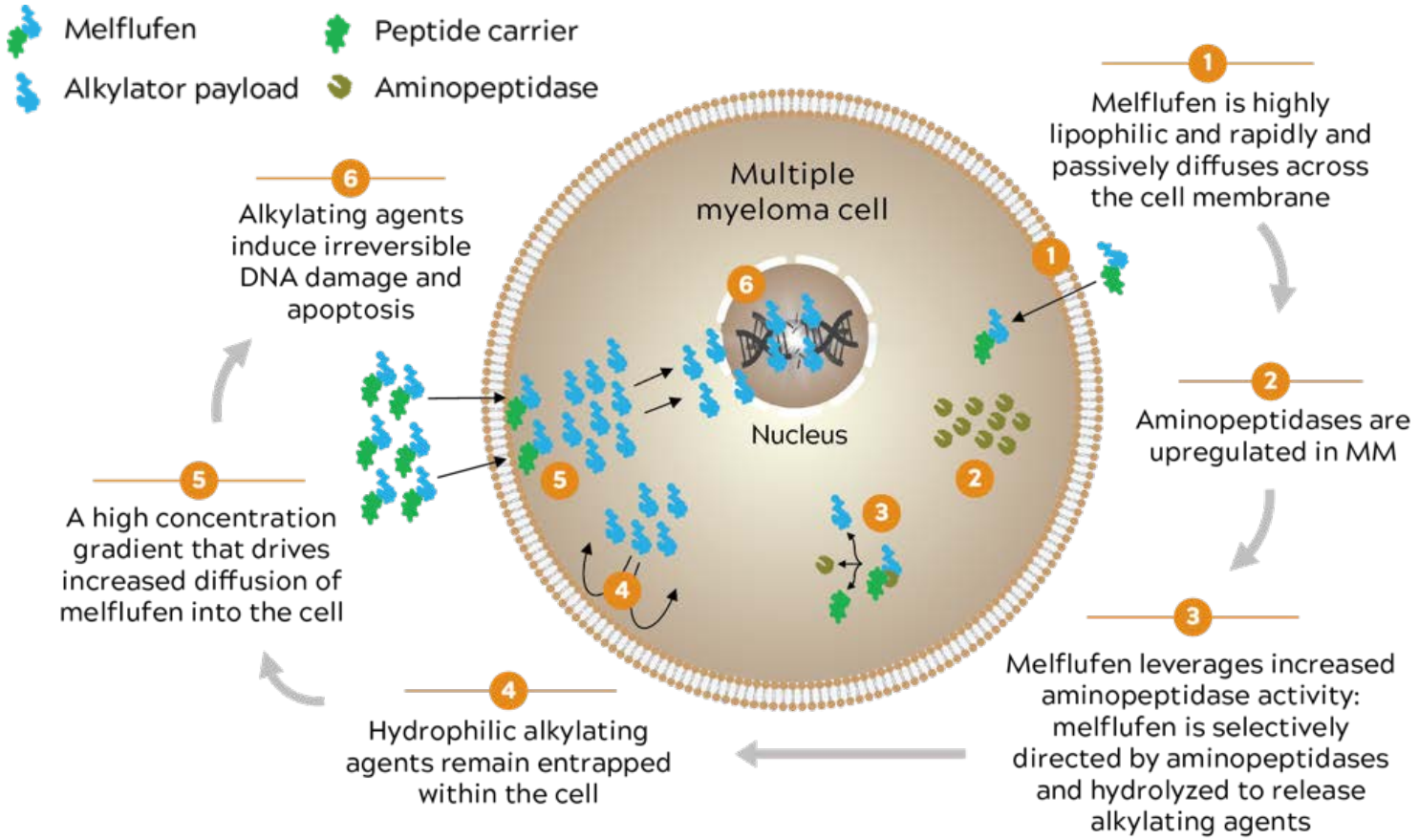
Melphalan Flufenamide (Melflufen)

Melflufen is a first-in-class peptide-drug conjugate (PDC) that **targets aminopeptidases and rapidly releases alkylating agents into tumor cells.**[1-5]



Courtesy of Shaji K Kumar, MD

OCEAN: Positive Topline Results Reported from Phase III Head-to-Head Trial of Melflufen versus Pomalidomide for R/R MM

Press Release: May 25, 2021

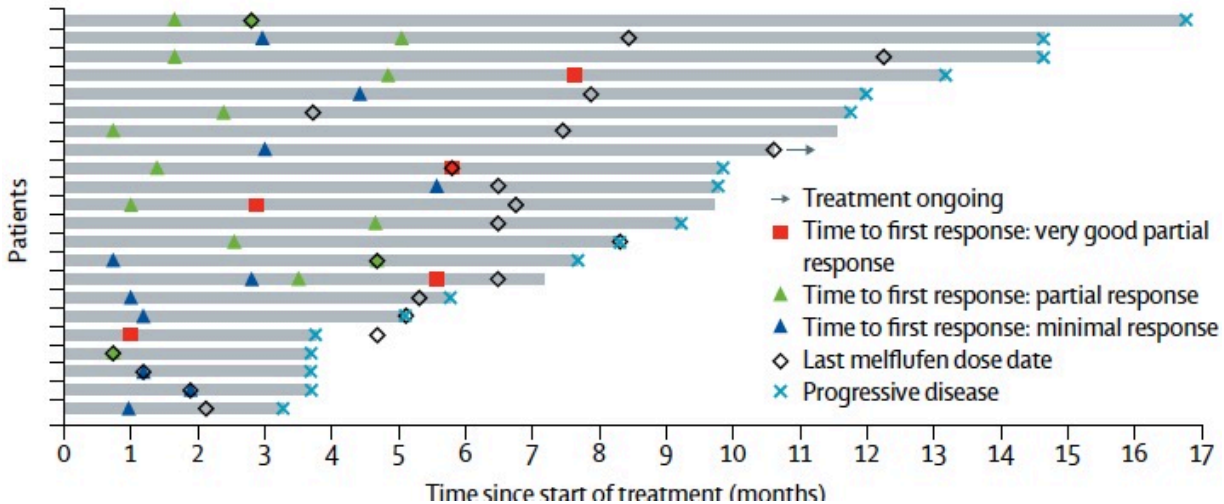
"Today positive topline results [were announced] from the head-to-head Phase III OCEAN study evaluating the efficacy and safety of melflufen (melphalan flufenamide) versus pomalidomide in patients with relapsed refractory multiple myeloma (RRMM). The randomized study was initiated in 2017 and includes 495 patients from more than 100 hospitals in 21 countries around the world. Following the accelerated approval of melflufen in combination with dexamethasone in the US earlier this year, the positive topline results from the OCEAN study mark another major milestone.

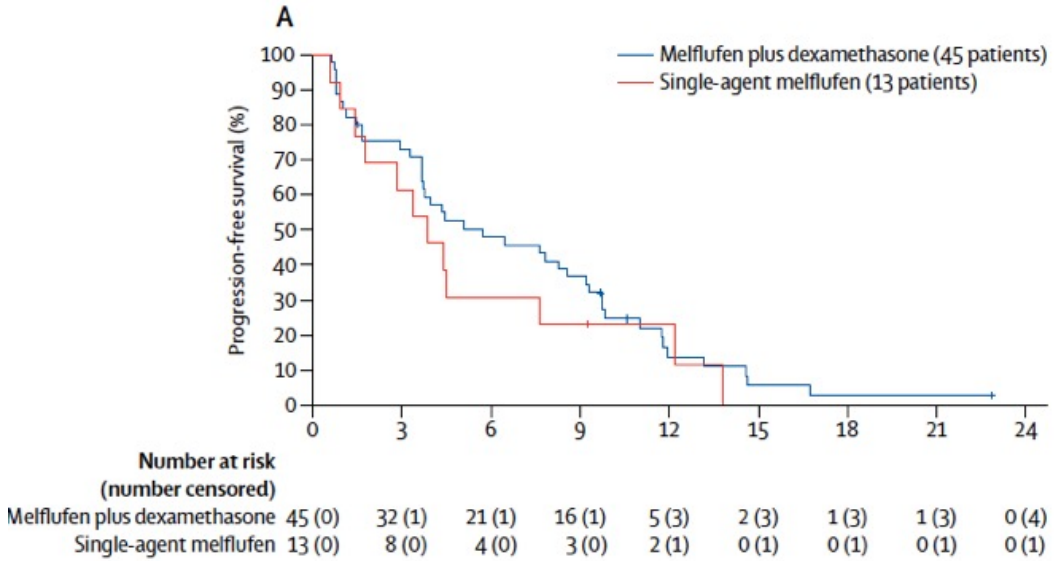
The PFS, as assessed by the independent review committee, demonstrated a Hazard Ratio favoring melflufen of 0.817 (p=0.0640) for the primary endpoint and shows that melflufen is non-inferior to pomalidomide. The Hazard Ratio for PFS as per investigator assessment was 0.790. In both assessments, the median PFS for the melflufen arm was more than 40% higher than for the pomalidomide arm. The Overall Response Rate for melflufen was 32.1% vs 26.5% for pomalidomide. Melflufen and pomalidomide had similar discontinuation rates for adverse events, and the safety profile of melflufen was in line with previous studies and consistent across age subgroups."

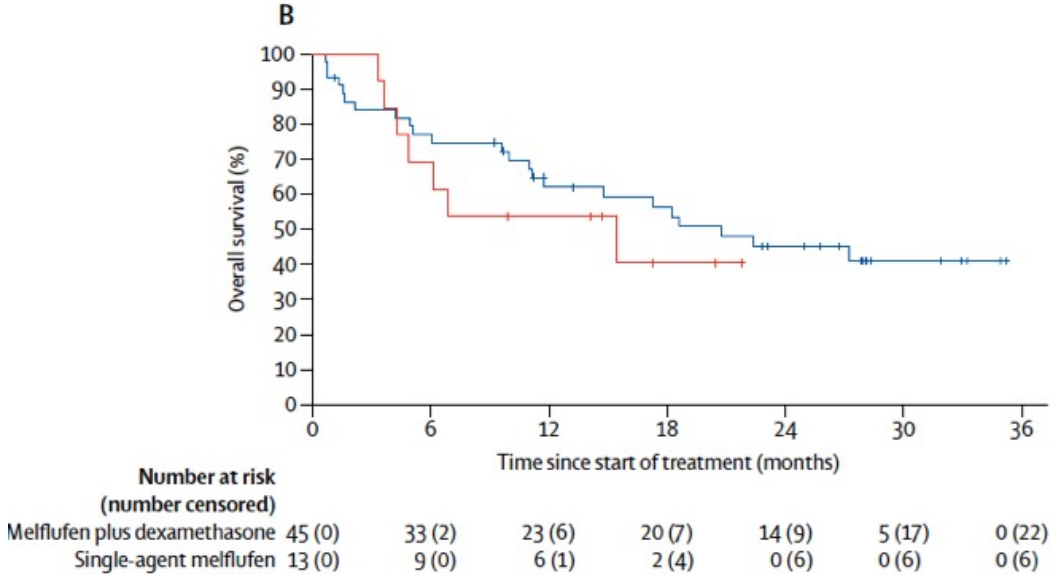
https://www.oncopeptides.com/en/media/press-releases/phase-3-ocean-study-demonstrates-that-melflufen-is-at-least-as-efficacious-as-pomalidomide-the-most-used-medicine-in-relapsed-refractory-multiple-myeloma

HORIZON: Melflufen – with or without Dex

	Melflufen plus dexamethasone group (n=45)	Melflufen group (n=13)
Overall response rate	14 (31%; 18·2–46·6)	1 (8%; 0·2–36·0)
Clinical benefit rate	22 (49%; 33·7–64·2)	3 (23%; 5·0–53·8)
Complete response	0 (0·0–7·9)	0 (0·0–24·7)
Very good partial response	5 (11%; 3·7–24·1)	0 (0%; 0·0–24·7)
Partial response	9 (20%; 9·6–34·6)	1 (8%; 0·2–36·0)
Minimal response	8 (18%; 8·0–32·1)	2 (15%; 1·9–45·4)
Stable disease	12 (27%; 14·6–41·9)	9 (69%; 38·6–90·9)
Progressive disease	7 (16%; 6·5–29·5)	1 (8%; 0·2–36·0)

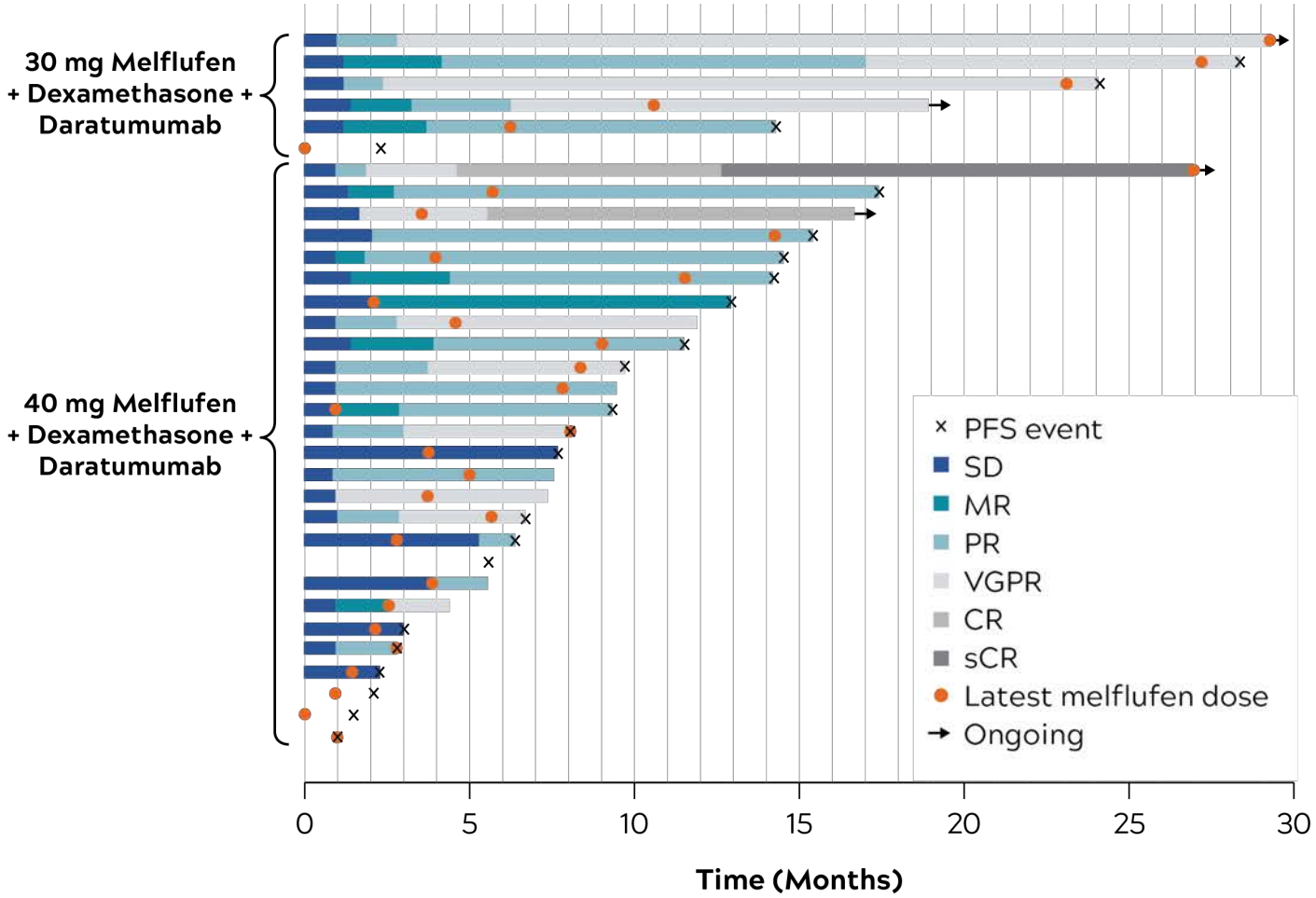


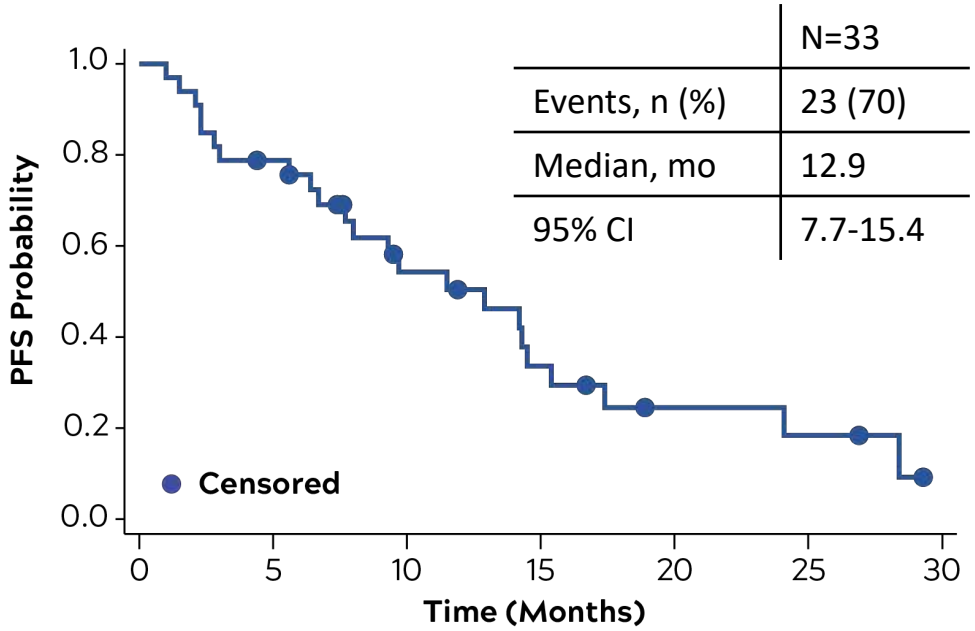




Courtesy of Shaji K Kumar, MD

ANCHOR: Melflufen Plus Dexamethasone and Daratumumab





	N=33
Events, n (%)	23 (70)
Median, mo	12.9
95% CI	7.7-15.4

- Median DOR was 12.6 months (95% CI, 7.6-24.2), with 5 of 33 patients still ongoing at the time of data cutoff (2 patients on melflufen 30 mg and 3 patients on melflufen 40 mg)
- At a median follow-up of 18.9 months, median PFS was 12.9 months (95% CI, 7.7-15.4)
- The OS data were immature at the median follow-up of 18.4 months

Data cutoff date: 19 October 2020.

CR, complete response; DOR, duration of response; MR, minor response; OS, overall survival; PFS, progression-free survival;
PR, partial response; sCR, stringent CR; SD, stable disease; VGPR, very good PR.

Courtesy of Shaji K Kumar, MD

Given its recent FDA approval, where in the treatment sequence are you planning to integrate melflufen?

- Majority of patients are alkylator naive outside of high dose therapy given increased use of IMiDs, PI, and anti—CD38 in the first 3-4 lines of therapy.
- Indicated in combination with dexamethasone for relapsed myeloma with
  - at least four prior lines of therapy and
  - refractory to at least one proteasome inhibitor, one immunomodulatory agent, and one CD38-directed monoclonal antibody
- Current goal would be to integrate in the later lines of therapy as per label.

If CELMoDs were available, would you use them in a patient who has previously experienced disease progression on standard IMiDs (eg, lenalidomide, pomalidomide)?

CELMoDs (eg, iberdomide, CC-92480)

Dr Craig Hofmeister

Dr Nina Shah

Dr Paul Richardson

Dr Saad Usmani

RTP
RESEARCH
TO PRACTICE

Based on your experience and/or clinical trial data, how would you compare the global efficacy and tolerability of CELMoD agents (eg, iberdomide, CC-92480) to that of standard IMiDs (eg, lenalidomide, pomalidomide) in MM? If CELMoDs were available, would you use them in a patient who has previously experienced disease progression on an IMiD?

- IMID drugs (thalidomide, lenalidomide, pomalidomide) fundamentally changed treatment for patients with myeloma
- Preliminary data from CelMODs looks very exciting with responses in both lenalidomide and pomalidomide refractory patients
- More clinical trial experience may lead to ability to select patients appropriately
- Combinations and use as maintenance also likely very efficacious
- Oral administration always attractive
- Given side effects appear to be cytopenias, suspect use in older MM patients will be feasible

Iberdomide (CC-220)

CELMOD-binds with higher affinity to cereblon, part of the E3 Ubiquitin ligase complex.

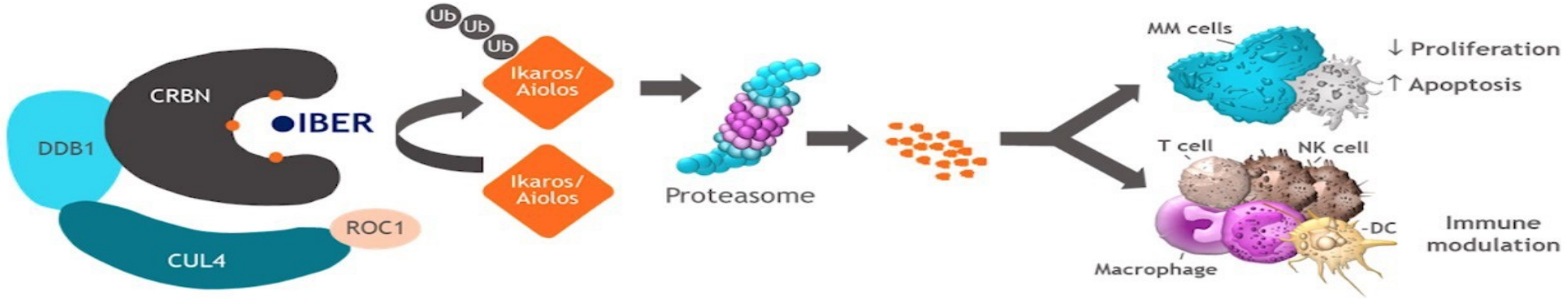
Binding leads to more rapid degradation of Ikaros and Aiolos (5 min versus 30+ min for pom and len)

Leads to greater apoptosis in MM cell lines than pomalidomide

Active in myeloma cells lines resistant to lenalidomide and pomalidomide

Preclinical synergism with bortezomib and daratumumab

Induces NK cell proliferation and may rescue NK cell depletion by daratumumab



Lonial. ASCO 2019. Abstr 8006. Van de Donk ASH 2020 Abstract 724

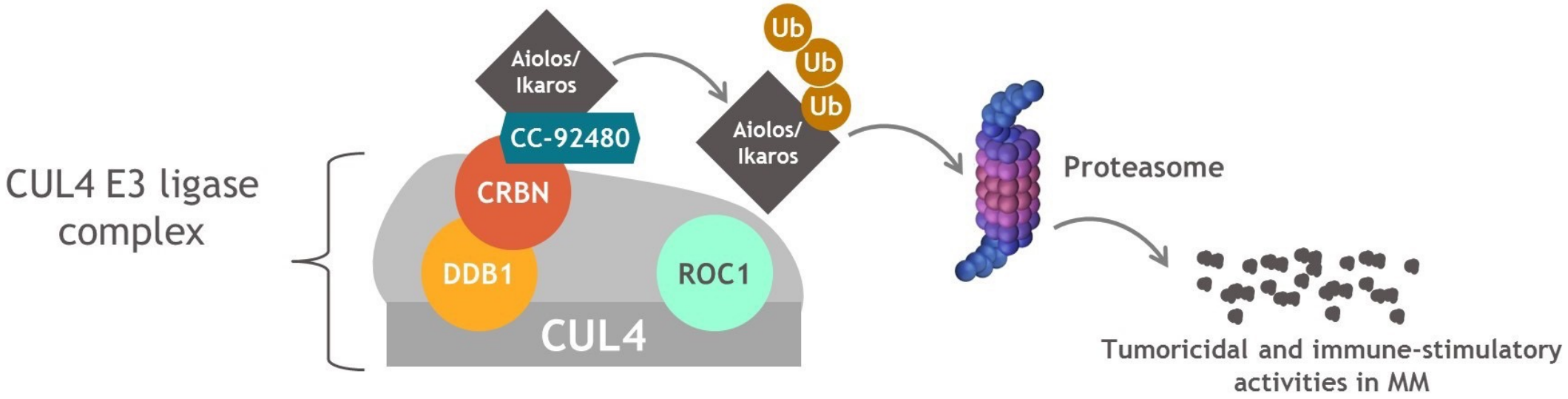
Courtesy of Natalie S Callander, MD

CC-92480: Background

CC-92480: cereblon E3 ligase modulator (CELMoD) that rapidly degrades target proteins (including Aiolos and Ikaros)[1]

Potent anti-MM activity in cell lines, including lenalidomide- and pomalidomide-resistant[1,2]

Synergy with other therapies, including dexamethasone, PIs, and monoclonal antibodies[3]



1. Hansen. J Med Chem. 2020. 2. Lopez-Garona. Blood. 2019;134. Abstr 1812. 3. Wong. Blood. 2019;134. Abstr 1814.

Courtesy of Natalie S Callander, MD

Is it reasonable to administer BCMA-directed CAR T-cell therapy to a patient who has previously received belantamab mafodotin and vice versa?

Dr Callander

Yes

Dr Kumar

I don’t know

Dr Lonial

Yes

Dr Hofmeister

I don’t know

Dr Richardson

No

Dr Shah

Yes

Dr Usmani

No

RTP
RESEARCH TO PRACTICE

CAR T-cell therapy

Dr Craig Hofmeister

Dr Nina Shah

Dr Paul Richardson

Dr Saad Usmani

RTP
RESEARCH
TO PRACTICE

Is it reasonable to use BCMA-directed CAR T-cell therapy in a patient who has previously received belantamab mafodotin and vice versa?

- Three different platforms targeting BCMA: ADC, CART and Bispecific antibodies
- Clinical trials excluded patients relapsing on another BCMA targeted agent, so no data
- Can consider using ADC after CART or bispecific since approved
- Also, Idecel can be given since the label does not specifically contraindicate, but would prefer to have data
- Future studies warranted

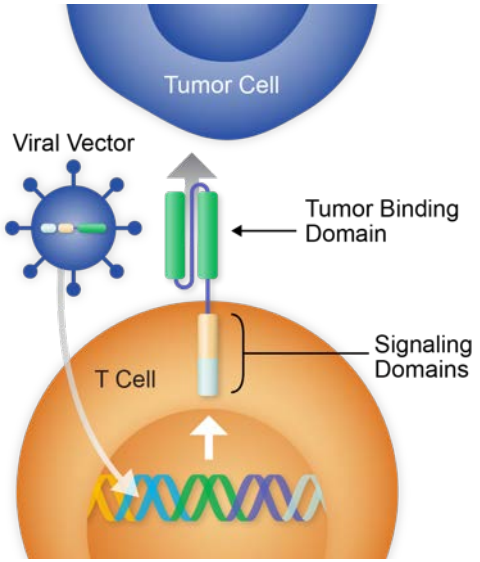
Do you believe there are significant differences between ide-cel and the investigational CAR T-cell platforms (eg, ciltacabtagene autoleucel, bb21217) in MM that will ultimately result in superior efficacy or safety for one over the others?

- Data is still quite young, although JNJ seems to have highest response rate
- Populations are not identical in each study and small
- Results incorporating CAR-T as earlier line of therapy will be critical
- There may be some real differences in toxicity—that may be as important as responses in selecting drugs
- Additional data from “real world” use should be quite helpful (as it has been in DLBCL)

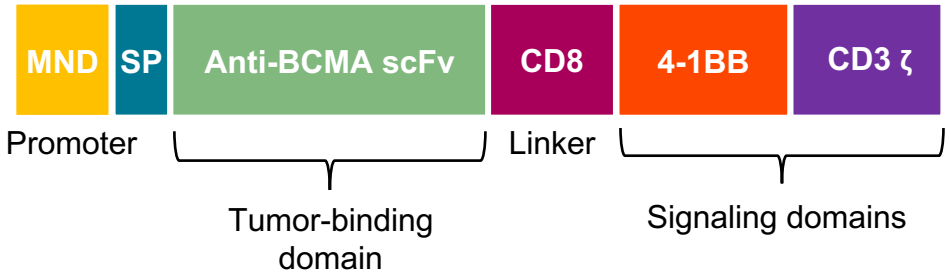
What other novel agents and strategies do you believe are most promising for patients with MM?

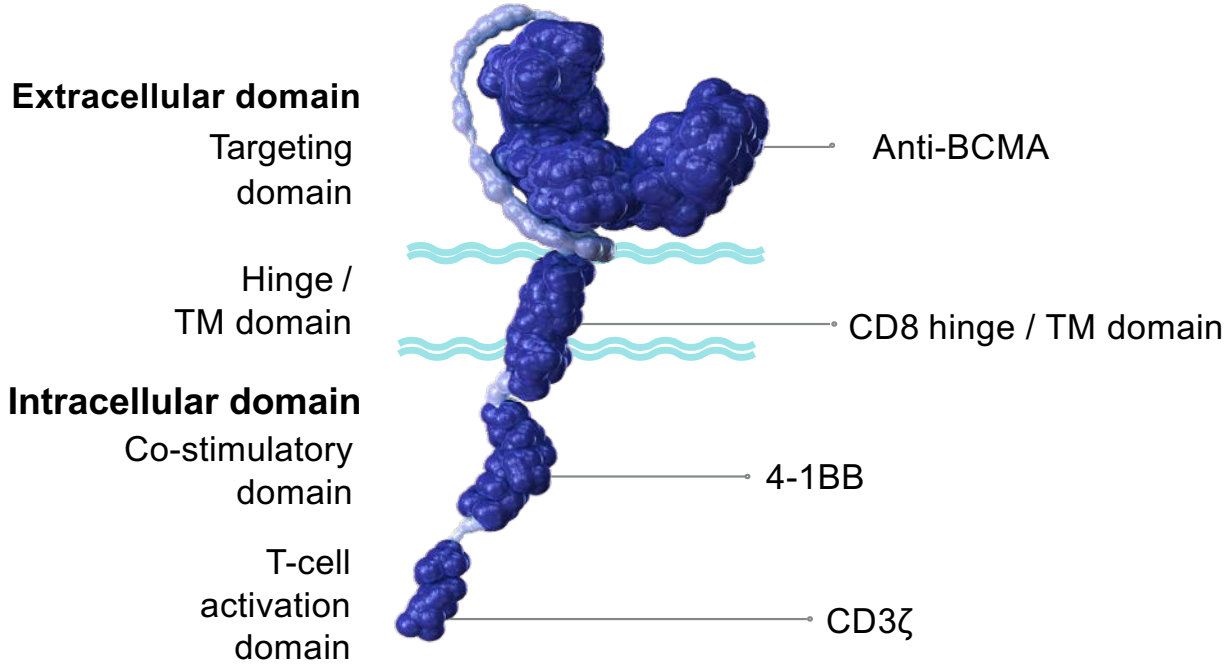
- “off the shelf” Allogeneic CAR-Ts appear promising (ALLO-715 from ASH)
- CAR-T as adjuvant therapy, e.g. high risk MM, inadequate response, earlier relapse
- CAR-T directed at other cell types
- Drug antibody conjugates appealing due to ease of use and effective in some patients, waiting for combinations
- MRD directed therapy—ability to stop and/or restart therapy based on MRD before organ damage occurs

Idecabtagene vicleucel (bb2121): BCMA CAR T-cell



Ide-cel CAR design





Ide-cel is a 2nd-generation CAR construct

- **Autologous** T cells transduced with a lentiviral vector encoding CAR specific for BCMA
- Targeting domain: **anti-BCMA**
- Co-stimulatory domain: **4-1BB**
- T-cell activation domain: **CD3 ζ**

4-1BB associated with less toxicity and more durable CAR T-cell persistence than CD28 costimulatory domain

Raje NS, et al. *J Clin Oncol* 2018;36:8007. Presented at ASCO 2018.

Courtesy of Shaji K Kumar, MD

Best response

KarMMA-1 UPDATED 6/2021

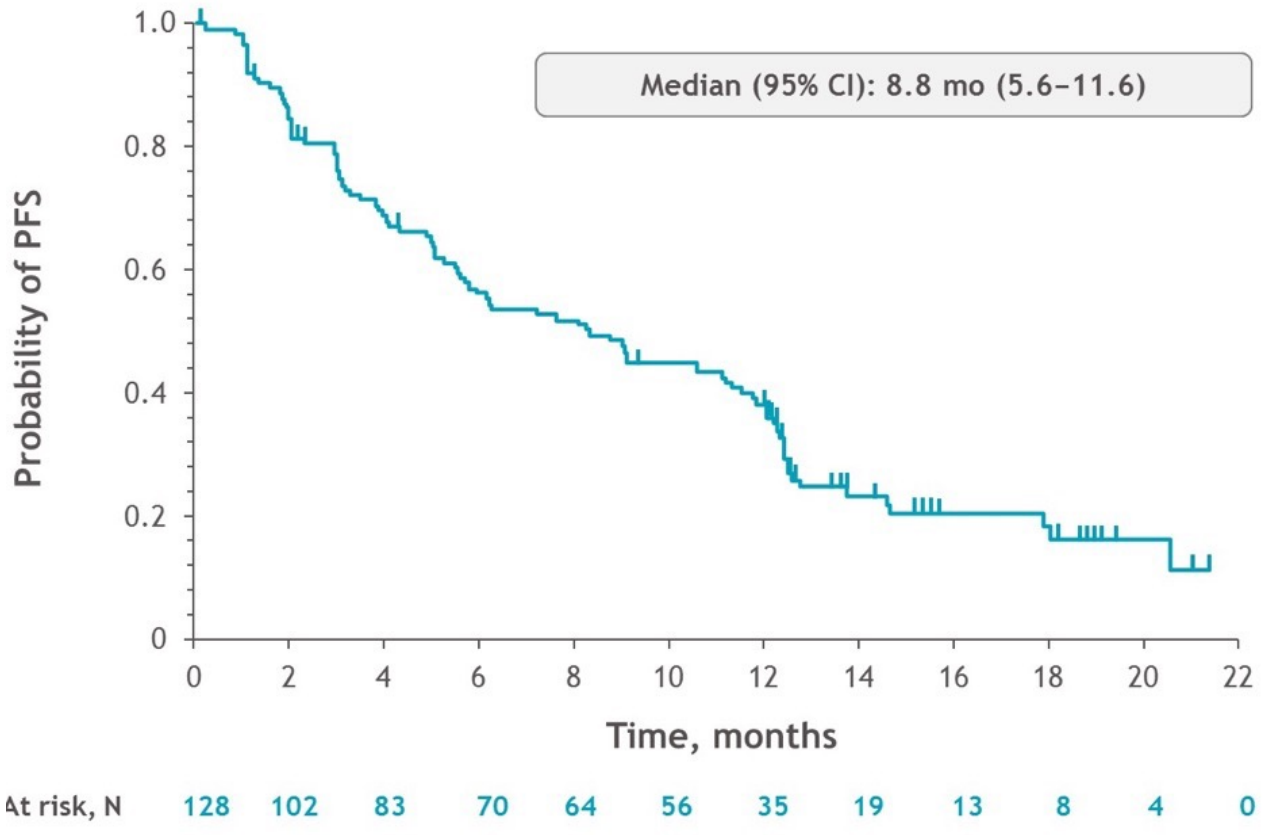
All 15 patients with ≥ CR who had a qualified assessment were MRD negative by NGS[a]

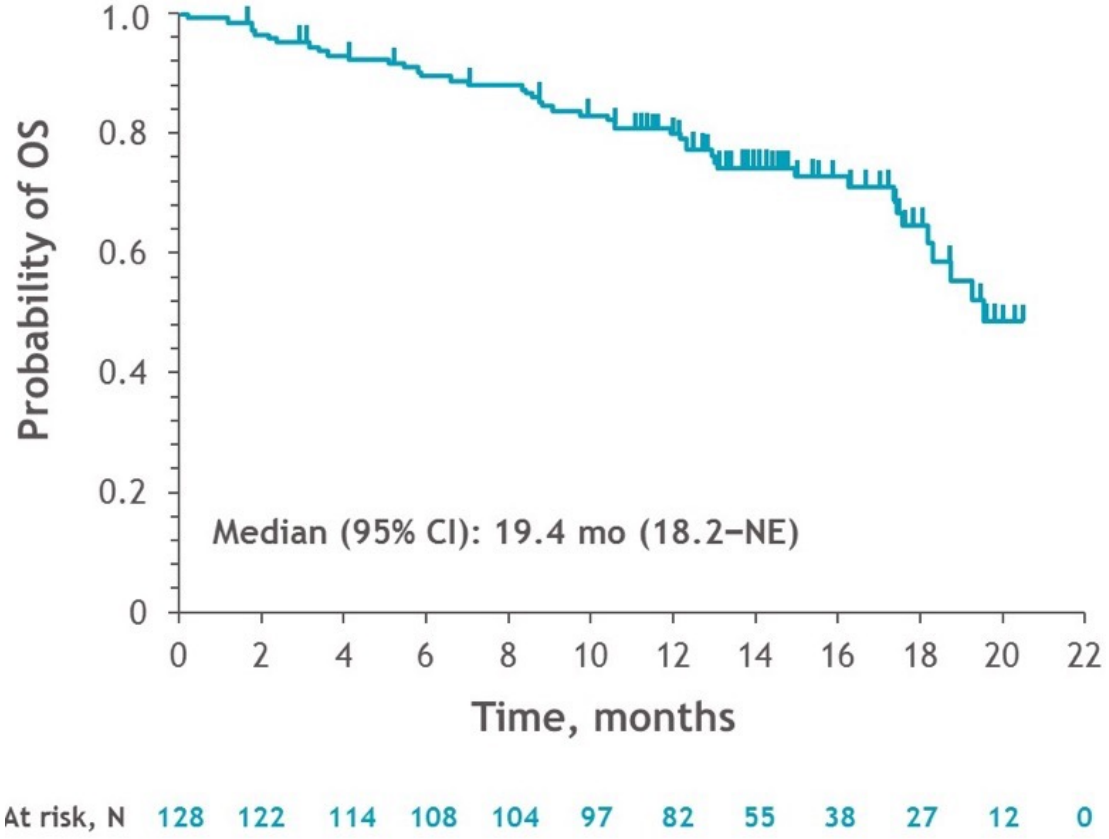
Median PFS 10.3 mo.; median OS 34 mo. Median DOR 10.9 mo.; 21.5 mo. if CR obtained

[a]Of 24 patients with ≥ CR, 8 had no MRD assessment and 1 had an assessment outside of the 3-month window; 10^{-4} sensitivity.

Courtesy of Natalie S Callander, MD

KarMMa: Survival

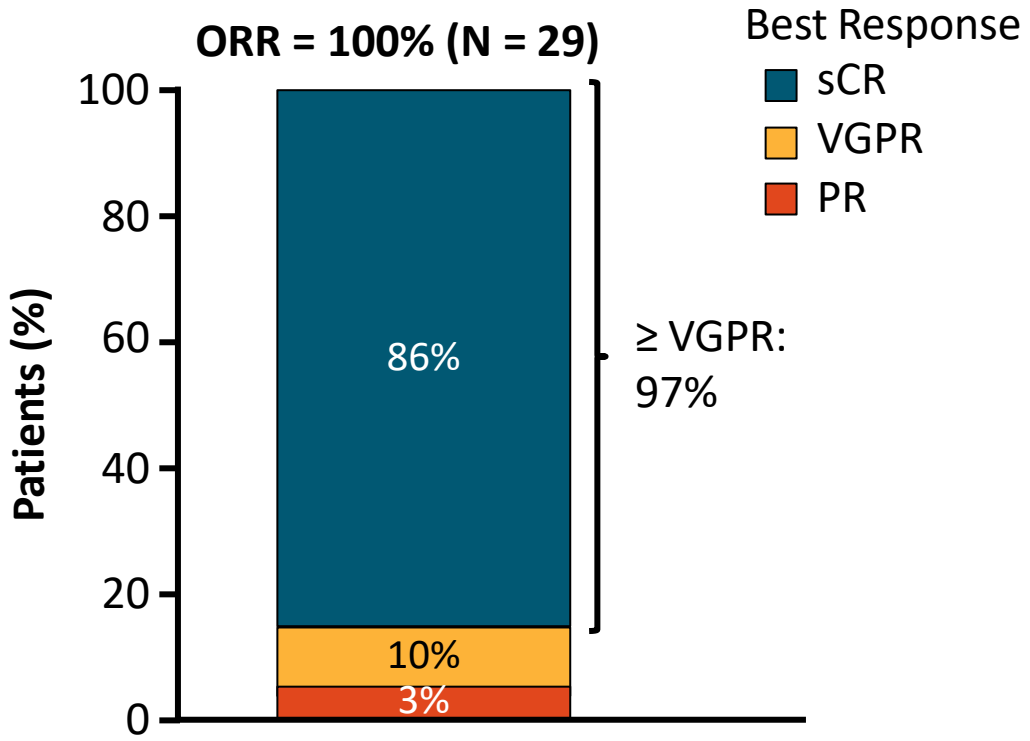


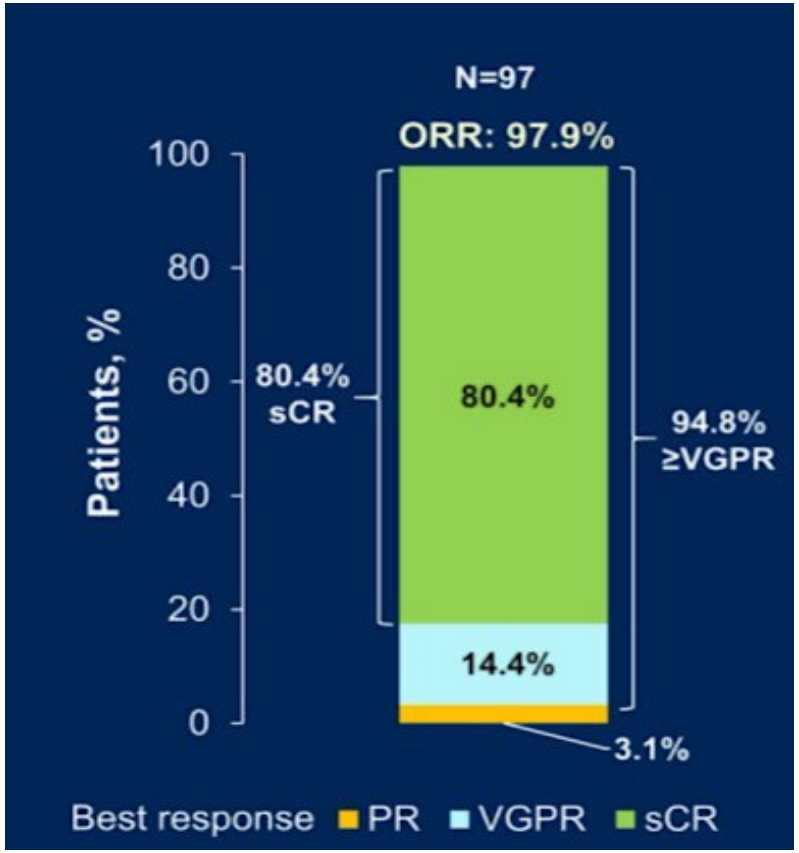


Presented By Nikhil Munshi at TBD

Courtesy of Shaji K Kumar, MD

CARTITUDE-1: Response with ciltacabtagene autoleucel (JNJ-4528): update sustains high response rate





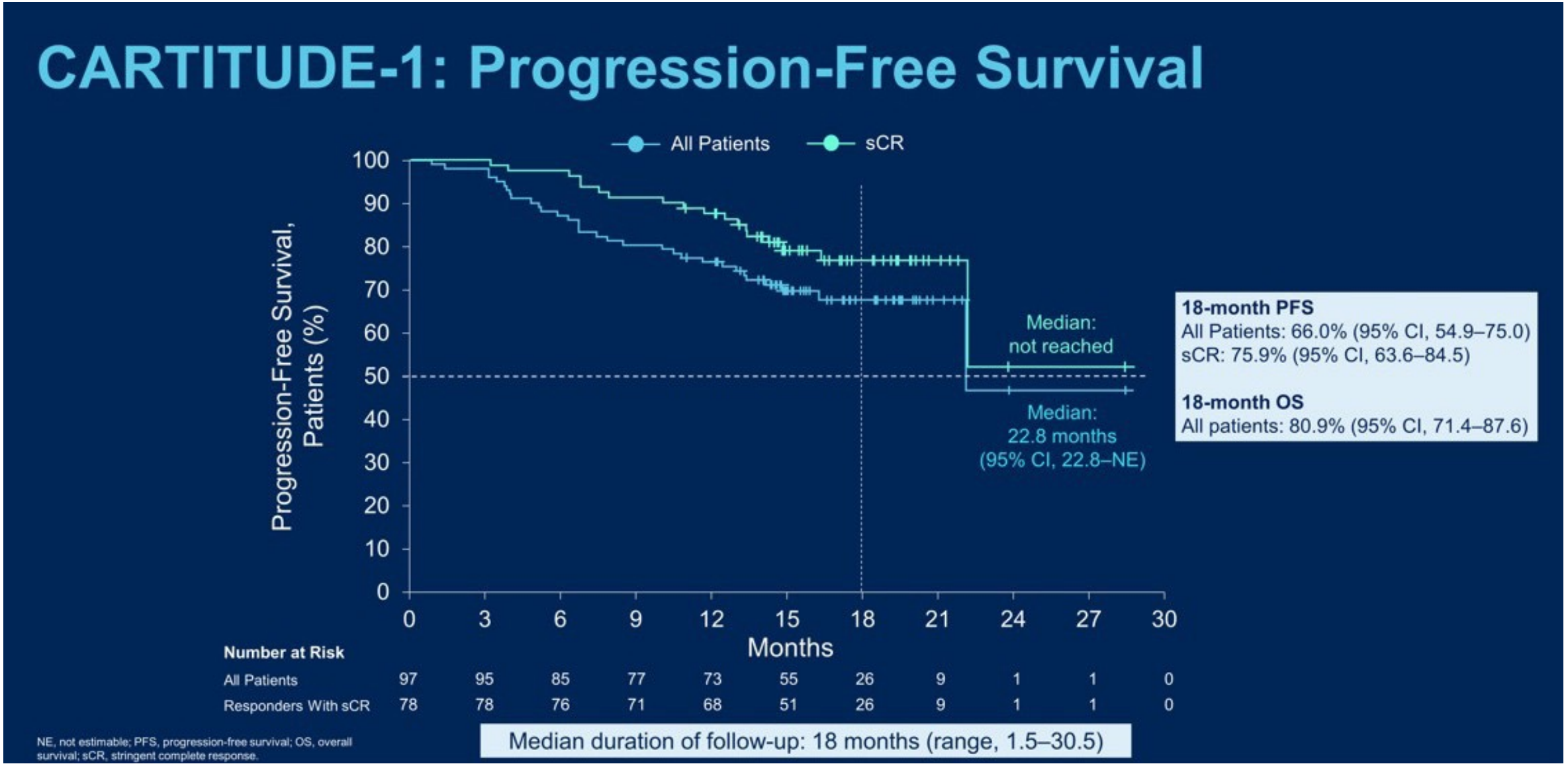
Median TTR: 1 mo (range, 1-3 mos)

Median time to ≥ CR: 3 mos (range, 1-13 mos)

Berdeja. ASCO 2020. Abstr 8505 Usmani ASCO 2021 Absract 8005.

Courtesy of Natalie S Callander, MD

18 mo. PFS 66%, 18 mo. OS 80.9%



Usmani ASCO 2021 Abstr 8005

Courtesy of Natalie S Callander, MD

BISPECIFIC T CELL ENGAGERS

Agent	Target	Route of	Previous BCMA rx	ORR	CR	AEs	Other
Elranatamab n=30[1]	BCMA	IV now SQ	23%	75%	20%	↓plts, WBC (40%)	**FDA hold for neurotoxicity**
Talquetamab[2] N=174	GPRC5D	IV or SQ	27%	63%		**Cytopenias, rash, nail disorders, dysgeusia**	CRS 73%
Teclistamab[3] N= 157	BCMA	IV/SQ	Not stated	65%	19%	CRS 70% cytopenias	
REGN 5458[4] N=45	BCMA	IV	Not stated	39%			
Cevostamab[5]	FcRHC	IV	21%	61%	17%	CRS,	
AMG 701[6] N=75	BCMA	IV	Excluded	36% (83% at highest dose)		CRES 9%	

[1]Bahlis ASCO 2021 # 8006; [2]Berdeja ASCO 2021 #8008; [3]Garfall, ASH 2020 Abstract #180; [4]Madduri ASH 2020, Abstract #; [5]Krishnan ASCO 2021 #8007; [6]Harrison ASH 2020 Abstract #183

Courtesy of Natalie S Callander, MD

Consensus or Controversy Consulting Investigators

Dr Craig Hofmeister

Dr Nina Shah

Dr Paul Richardson

Dr Saad Usmani

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TO PRACTICE

Ask the Expert: Clinical Investigators Provide Perspectives on the Management of Renal Cell Carcinoma

In Partnership with Project Echo® and Florida Cancer Specialists

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

Faculty

David I Quinn, MBBS, PhD

Moderator

Neil Love, MD

Thank you for joining us!

CME and MOC credit information will be emailed to each participant within 24 hours.

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