



Society for Immunotherapy of Cancer

Cancer Immunotherapy

GUIDELINES

Multiple Myeloma Webinar

Thursday, September 3, 2020

7:00-8:00 p.m. ET

Jointly provided by Postgraduate Institute for Medicine and the Society for Immunotherapy of Cancer

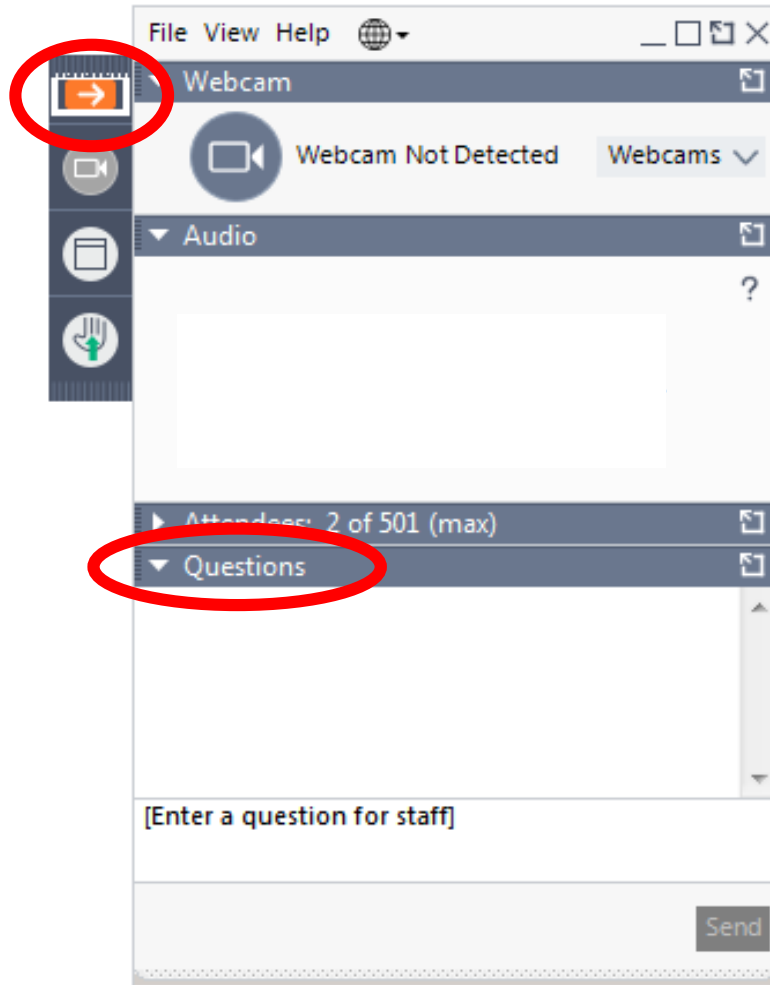
This webinar is supported, in part, by independent medical education grant funding from Amgen, AstraZeneca Pharmaceuticals LP, Celgene Corporation and Merck & Co., Inc.

Webinar Agenda

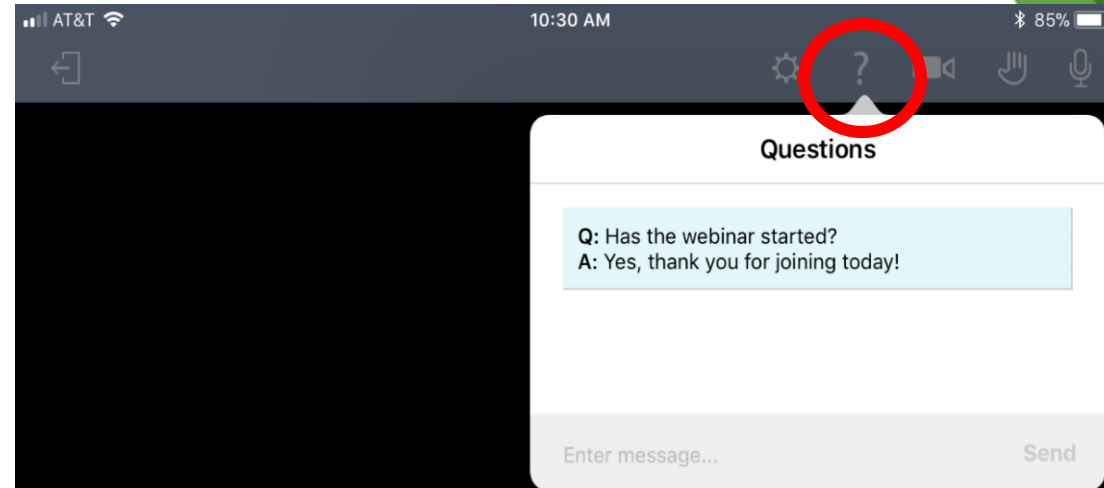
7:00–7:05 p.m. ET	Welcome, Introductions and Overview
7:05–7:40 p.m. ET	Presentation of SITC Cancer Immunotherapy Guideline – Multiple Myeloma
7:40-7:55 p.m. ET	Question and Answer Session
7:55–8:00 p.m. ET	Closing Remarks

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Webinar Faculty



Expert Panel Chair:
Nina Shah, MD –
*University of California
San Francisco Medical
Center*



Ajai Chari, MD – *Icahn
School of Medicine at
Mount Sinai*



Adam Cohen, MD –
*Abramson Cancer
Center at the
University of
Pennsylvania*

The Society for Immunotherapy of Cancer consensus statement on immunotherapy for the treatment of multiple myeloma

Nina Shah,¹ Jack Aiello,² David E Avigan,³ Jesus G Berdeja,⁴ Ivan M Borrello,⁵
Ajai Chari,⁶ Adam D Cohen,⁷ Karthik Ganapathi,⁸ Lissa Gray,⁹ Damian Green,¹⁰
Amrita Krishnan,¹¹ Yi Lin,^{12,13} Elisabet Manasanch,¹⁴ Nikhil C Munshi,¹⁵
Ajay K Nooka,¹⁶ Aaron P Rapoport,¹⁷ Eric L Smith,¹⁸ Ravi Vij,¹⁹
Madhav Dhodapkar²⁰

Development of clinical practice guidelines

- 19 participants – 17 medical oncologists, 1 nurse practitioner, 1 patient advocate
- Developed using the Institute of Medicine's Standards for Developing Trustworthy Clinical Practice Guidelines
- Panel participated in surveys and discussions to develop recommendations

Multiple myeloma by the numbers

32,270

Estimated new cases in
2020 in US

12,830

Estimated deaths in 2020
in US

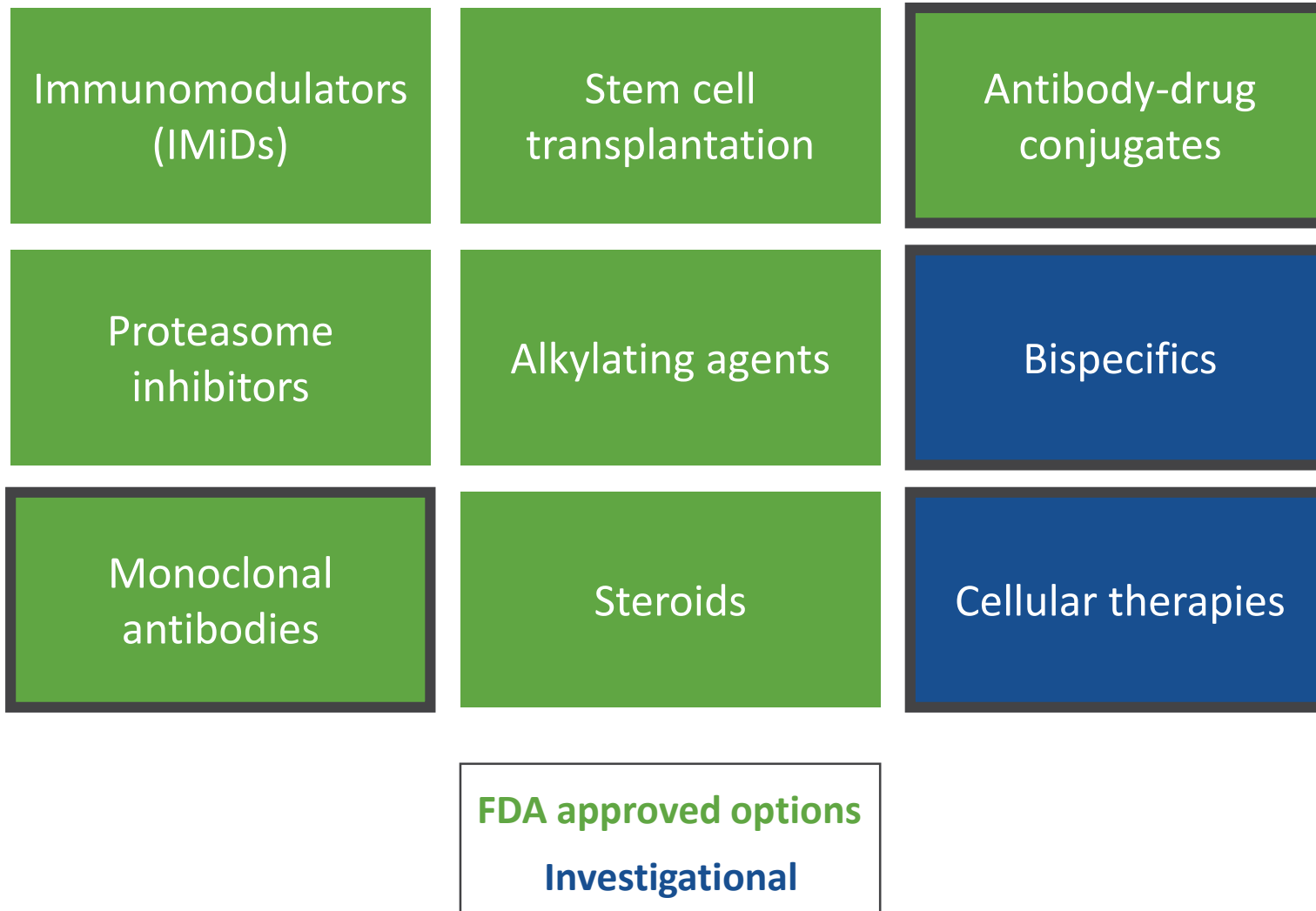
74%

Historical 5-year survival
if diagnosed at early
stage

51%

Historical 5-year survival
if diagnosed at late stage

Treatment options for MM



Outline

- Monoclonal antibodies
 - Daratumumab
 - Isatuximab
 - Elotuzumab
- Antibody-drug conjugates
- Bispecifics
- Cellular therapies

Daratumumab

- CD38-directed cytolytic antibody
- First monoclonal antibody approved for MM

Regimen	Indication
Daratumumab + bortezomib + dexamethasone	R/R MM after ≥ 1 prior therapy
Daratumumab + lenalidomide + dexamethasone	R/R MM after ≥ 1 prior therapy
Daratumumab + pomalidomide + dexamethasone	R/R MM after ≥ 2 prior therapies, including lenalidomide and proteasome inhibitor
Daratumumab + carfilzomib + dexamethasone	R/R MM after 1-3 prior therapies
Daratumumab	R/R MM after ≥ 3 prior therapies
Daratumumab + lenalidomide + dexamethasone	Newly diagnosed patients, ineligible for stem cell transplant
Daratumumab + bortezomib + melphalan + prednisone	Newly diagnosed patients, ineligible for stem cell transplant
Daratumumab + bortezomib + thalidomide + dexamethasone	Newly diagnosed patients, eligible for stem cell transplant

Daratumumab for relapsed/refractory MM

Trial	Phase	Treatment arms	N	ORR	Median PFS	PFS HR
POLLUX	3	Dara + lenalidomide + dexamethasone	286	93%	45.8 months	0.43
		Lenalidomide + dexamethasone	283	76%	17.5 months	
CASTOR	3	Dara + bortezomib + dexamethasone	251	82.9%	12-month: 60.7%	0.39
		Bortezomib + dexamethasone	247	63.2%	12-month: 26.9%	
EQUULEUS	1b	Dara + pomalidomide + dexamethasone	103	60%	8.8 months	-
CANDOR	3	Dara + carfilzomib + dexamethasone	466	84.3%	NR (>16.9 months)	0.63
		Carfilzomib + dexamethasone		74.7%	15.8 months	

Daratumumab for front-line MM

Trial	Phase	Patient population	Treatment arms	N	MRD-neg rate	PFS	PFS HR
GRIFFIN	2	Transplant-eligible	Dara + bortezomib + lenalidomide + dexamethasone	207	51.0%	24-month: 95.8%	-
			Bortezomib + lenalidomide + dexamethasone		20.4%	24-month: 89.8%	
CASSIOPEIA	3	Transplant-eligible	Dara + bortezomib + thalidomide + dexamethasone	1085	64%	18-month: 93%	0.47
			Bortezomib + thalidomide + dexamethasone		44%	18-month: 85%	
MAIA	3	Transplant-ineligible	Dara + lenalidomide + dexamethasone	737	24.2%	30-month: 70.6%	0.56
			Lenalidomide + dexamethasone		7.3%	30-month: 55.6%	
ALCYONE	3	Transplant-ineligible	Dara + bortezomib + melphalan + prednisone	706	28%	Median: 36.4 mo	0.55
			Bortezomib + melphalan + prednisone		7%	Median: 19.3 mo	

Panel recommendations

The panel recommends daratumumab for all FDA-approved indications:

Regimen	Indication
Daratumumab + bortezomib + dexamethasone	R/R MM after ≥ 1 prior therapy
Daratumumab + lenalidomide + dexamethasone	R/R MM after ≥ 1 prior therapy
Daratumumab + pomalidomide + dexamethasone	R/R MM after ≥ 2 prior therapies, including lenalidomide and proteasome inhibitor
Daratumumab + carfilzomib + dexamethasone	R/R MM after 1-3 prior therapies
Daratumumab	R/R MM after ≥ 3 prior therapies
Daratumumab + lenalidomide + dexamethasone	Newly diagnosed patients, ineligible for stem cell transplant
Daratumumab + bortezomib + melphalan + prednisone	Newly diagnosed patients, ineligible for stem cell transplant
Daratumumab + bortezomib + thalidomide + dexamethasone	Newly diagnosed patients, eligible for stem cell transplant

Panel recommendations

The panel recommends the following options based on emerging evidence, though not yet FDA-approved:

- Daratumumab + bortezomib + lenalidomide + dexamethasone as an induction regimen for newly diagnosed, transplant-eligible patients (GRIFFIN)
- Daratumumab + carfilzomib + dexamethasone for patients with R/R multiple myeloma (CANDOR)

The panel could not reach consensus on:

- Daratumumab + carfilzomib + lenalidomide + dexamethasone for newly-diagnosed, transplant-eligible patients

Dosing and administration of daratumumab

- Standard **pre-medication** to limit infusion-related reactions
 - Dexmethasone, acetaminophen, diphenhydramine, and montelukast
 - Steroids may be omitted after first infusion if no IRRs
 - For patients with severe IRRs or respiratory co-morbidities, administer oral corticosteroids on each of the two days following infusions
- **Subcutaneous dosing** is a feasible, patient-friendly option
- First dose may be **split** across two days (8 mg/kg, 4 hour infusion)
- For dose 4 and beyond, can be given over **90 minutes**
- **IVIG** should be administered to reduce infections following treatment

Monitoring responses to daratumumab

- In patients with IgG kappa myeloma, **serologic measurement** of response may be confounded by daratumumab
- In the presence of a measurable **M-spike**, daratumumab will have a minimal effect on disease measurement. When patients reach undetectable levels, however, mass spectrometry or other antibody interference testing methods should be considered.

Outstanding questions with daratumumab

- Use in patients with high-risk cytogenetics
- Re-treatment with daratumumab

Outline

- Monoclonal antibodies
 - Daratumumab
 - Isatuximab
 - Elotuzumab
- Antibody-drug conjugates
- Bispecifics
- Cellular therapies

Isatuximab

- CD38 antibody
- Like daratumumab, reduces Tregs and inhibits immunosuppressive cytokine production
- Can also directly kill MM cells (without cross-linking)
- Panel recommends isatuximab for its FDA-approved indication

Regimen	Indication
Isatuximab + pomalidomide + dexamethasone	R/R MM after ≥ 2 prior therapies

Clinical trials with isatuximab

Trial	Phase	Patient population	Treatment arms	N	ORR	PFS	PFS HR
ICARIA-MM	3	R/R multiple myeloma	Isatuximab + pomalidomide + dexamethasone	154	60%	Median: 11.53 mo	0.596
			Pomalidomide + dexamethasone	153	35%	Median: 6.47 mo	
GMMG-CONCEPT	2	Newly diagnosed MM	Induction: Isatuximab + carfilzomib + lenalidomide + dexamethasone Maintenance: Isatuximab + carfilzomib + lenalidomide	153	100%, 90% ≥ VGPR	<i>ongoing</i>	-
IKEMA	3	R/R multiple myeloma	Isatuximab + carfilzomib + dexamethasone	302	86.6%	NR	0.531
			Carfilzomib + dexamethasone		82.9%	Median: 19.15 months	
IMROZ	3	Newly diagnosed MM	Induction: isatuximab + bortezomib + lenalidomide + dexamethasone Maintenance: isatuximab + lenalidomide + dexamethasone	475	<i>Ongoing – anticipated December 2022</i>		-
			Induction: bortezomib + lenalidomide + dexamethasone Maintenance: lenalidomide + dexamethasone				

Dosing and administration of isatuximab

- Standard **pre-medications** to limit infusion-related reactions
- Initial infusion at 175 mg/hour over **2-7 hours**
- **Antibody interference testing** by mass spectrometry recommended for monitoring in Ig G kappa patients with m spike < 0.5 g/dl with suspected complete remission
- **IVIG** should be administered to manage infections

Outstanding questions with isatuximab

- Treating patients with prior daratumumab exposure

CD38 case study

- 78 yo Female with history of HTN, osteoporosis presents with hypercalcemia, anemia, lytic lesions and is diagnosed with IgG Kappa MM - ISS 2, LDH nl, FISH normal
- She is treated with Daratumumab Lenalidomide 15 mg and dexamethasone 20 mg with progressive improvement in her symptoms/improvement in quality of life and achieves a complete response
- She remains in remission 4 years since her diagnosis

Outline

- Monoclonal antibodies
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 - Elotuzumab
- Antibody-drug conjugates
- Bispecifics
- Cellular therapies

Elotuzumab

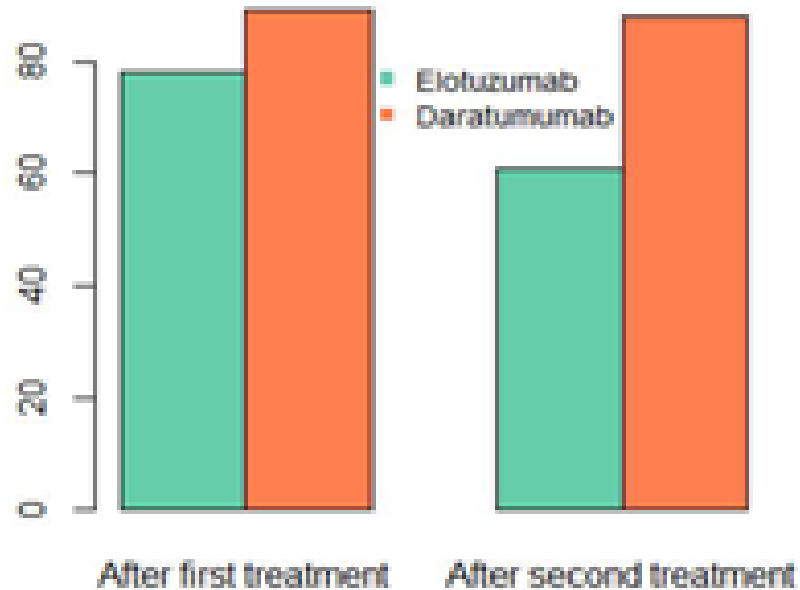
- Antibody targeting SLAMF7
- Anti-tumor effects through ADCC and direct activation of NK cells
- Panel recommends use of elotuzumab for FDA-approved indications

Regimen	Indication
Elotuzumab + lenalidomide + dexamethasone	R/R MM after 1-3 prior therapies
Elotuzumab + pomalidomide + dexamethasone	R/R MM after ≥ 2 prior therapies

Clinical trials with elotuzumab

Trial	Phase	Patient population	Treatment arms	N	ORR	PFS
ELOQUENT-2	3	R/R MM after 1-3 prior treatments	Elotuzumab + lenalidomide + dexamethasone	321	79%	5-year: 18%
			Lenalidomide + dexamethasone	325	66%	5-year: 12%
ELOQUENT-3	2	R/R MM after lenalidomide and PI	Elotuzumab + pomalidomide + dexamethasone	60	53%	Median: 10.3 mo
			Pomalidomide + dexamethasone	57	26%	Median: 4.7 mo
GMMG-HD6	3	Newly diagnosed, transplant-eligible MM	Elotuzumab + bortezomib + lenalidomide + dexamethasone	564	≥PR: 82.4%	<i>Ongoing</i>
			Bortezomib + lenalidomide + dexamethasone		≥PR: 85.6%	
SWOG 1211	1/2	Newly diagnosed, high risk MM	Elotuzumab + bortezomib + lenalidomide + dexamethasone	134	83%	Median: 31 months
			Bortezomib + lenalidomide + dexamethasone		88%	Median: 34 months
ELOQUENT-1	3	Newly diagnosed, transplant-ineligible MM	Elotuzumab + lenalidomide + dexamethasone	68	<i>Ongoing – anticipated September 2020</i>	

Sequencing elotuzumab and anti-CD38 agents



MDACC, n=50

32 elo first, 18 dara first

	Dara-first (n = 23)	Elo-first (n = 14)	p-value
ORR to first antibody, n (%)	13 (56.5%)	9 (64.3%)	.641
ORR to second antibody, n (%)	8 (34.8%)	9 (64.3%)	.081

Michigan, n=37

14 elo first, 23 dara first

Retrospective analyses

“Response rates to daratumumab may be preserved irrespective of sequence. However, response rates to elotuzumab may diminish with prior daratumumab exposure.”

Panel recommendations for elotuzumab

- The panel recommends use of elotuzumab for its **FDA-approved** indications.
- Patients with **high-risk cytogenetics** may benefit from elotuzumab.
- At present, there is no approved indication for the use of elotuzumab in the **initial management** of myeloma.
- *By consensus, elotuzumab-containing regimens may be considered for patients who have **progressed on dara-containing** regimens.*
- Elotuzumab should not be used as a **single agent**.
- Prior treatment with elotuzumab is **not a contraindication** for treatment with anti-CD38 antibodies.
- *By consensus, elotuzumab-containing regimens are not recommended for patients with a **rapidly growing disease burden**.*

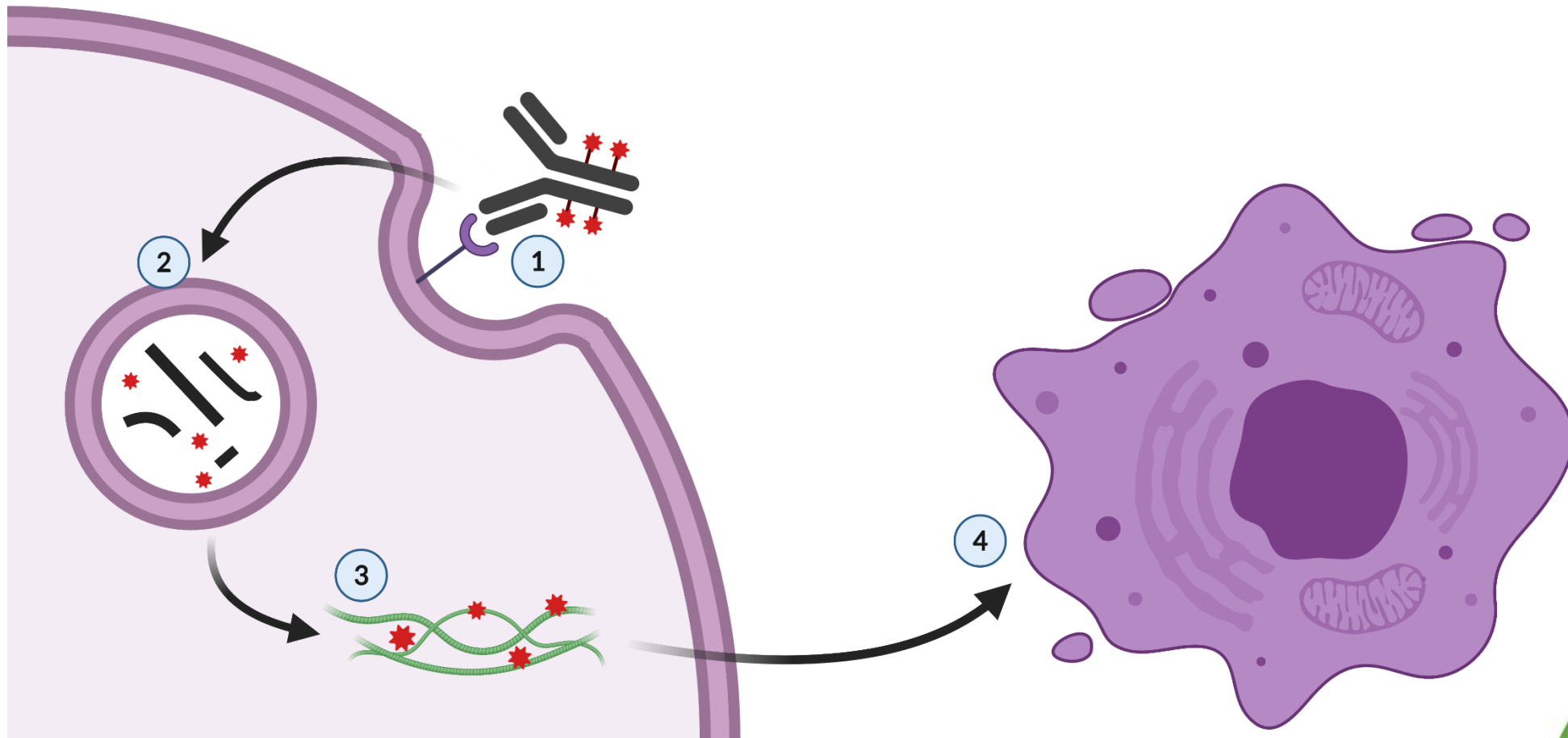
Outstanding questions for elotuzumab

- Front-line applications
- Use in patients with hepatic impairment or plasma cell leukemia
- Biomarkers of response and resistance

Outline

- Monoclonal antibodies
 - Daratumumab
 - Isatuximab
 - Elotuzumab
- **Antibody-drug conjugates**
- Bispecifics
- Cellular therapies

Antibody-drug conjugates



Belantamab mafodotin

- FDA-approved August 2020 (this guideline published July 2020)
- Anti-BCMA humanized antibody conjugated to MMAF

Regimen	Indication
Belantamab mafodotin	R/R MM after ≥ 4 prior therapies, including anti-CD38, PI, and IMiD.

Clinical trials of belantamab mafodotin

Trial	Phase	Patient population	N	Treatment arm(s)	ORR	Median PFS
DREAMM-1	1	R/R MM after ASCT, alkylators, PI, and IMiD	35	3.4 mg/kg belantamab mafodotin Q3W	60%	12 months
DREAMM-2	2	R/R MM after IMiD, PI, and anti-CD38	196	2.5 mg/kg belantamab mafodotin Q3W	31%	2.9 months
				3.4 mg/kg belantamab mafodotin Q3W	34%	4.9 months

Administration of belantamab mafodotin

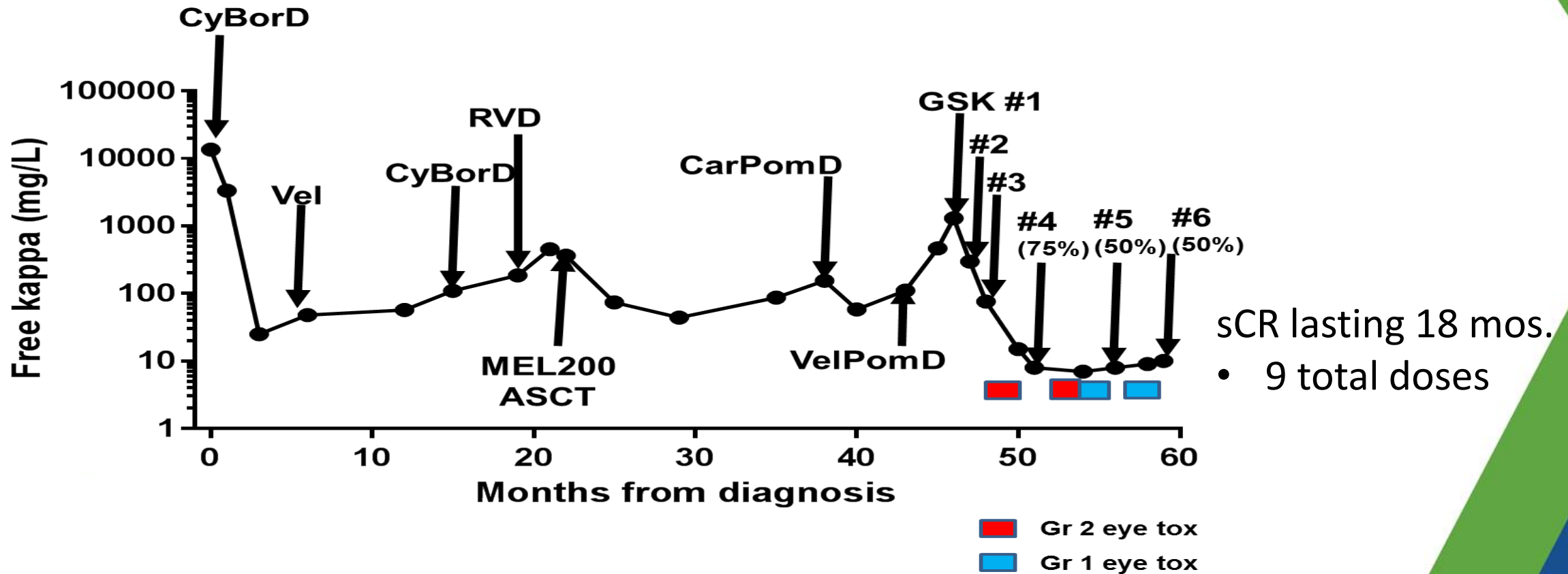
- Patients with severe **cytopenias** or pre-existing **corneal disease** may not be suitable for treatment
- Corneal toxicity can **be managed** through lubricating eye drops, holding therapy until grade 1 or less, or dose reductions
- Co-management with an **eye healthcare professional** required
- Based on MOA of belantamab mafodotin, patients with **prior allo-HSCT** may be considered for treatment

Other ADCs in development for myeloma

Target	Agent	Type (toxin)	Clinicaltrials.gov #
CD38	TAK-079	Naked	NCT03439280
CD38	TAK-573	ADC (IFN α)	NCT03215030
CD38	TAK-169	ADC (shiga-like toxin A subunit)	Pre-clinical
BCMA	SEA-BCMA	Naked	NCT03582033
BCMA	MEDI-2228	ADC (PBD)	NCT03489525
BCMA	HDP-101	ADC (Amanatin)	Pre-clinical
BCMA	CC-99712	ADC (maytansinoid)	NCT04036461
CD46	FOR46	ADC (MMAF)	NCT03650491
CD56	IMGN901	ADC (DM1)	NCT00346255
CD74	STRO-001	ADC (SC236)	NCT03424603

ADC case study

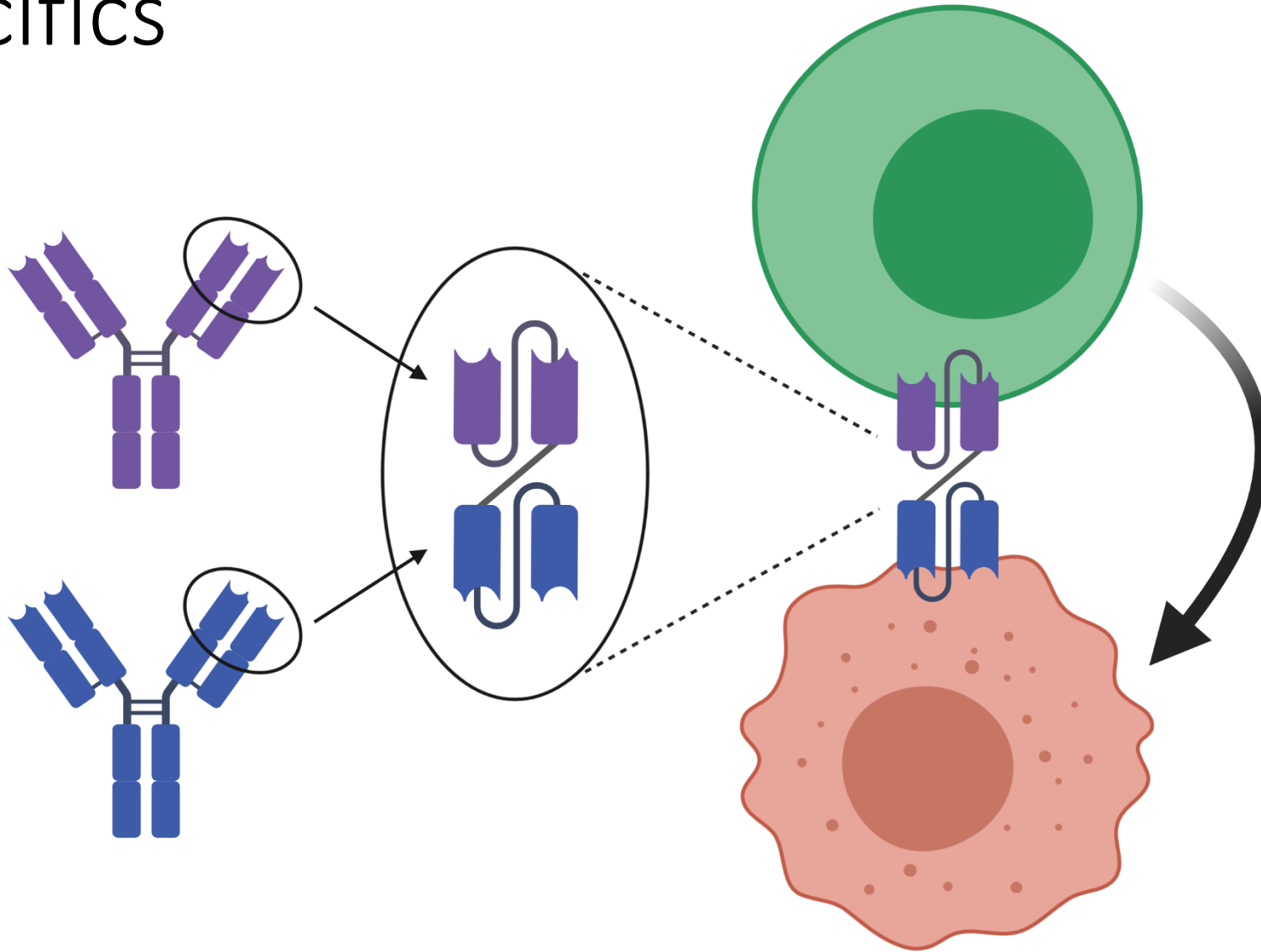
- 44M, Kappa LC MM dx'd 2012, FISH -14. 6 prior therapies
- Enrolled on GSK2857916 (belantamab mafadotin) phase 1 in April 2016



Outline

- Monoclonal antibodies
 - Daratumumab
 - Isatuximab
 - Elotuzumab
- Antibody-drug conjugates
- **Bispecifics**
- Cellular therapies

Bispecifics

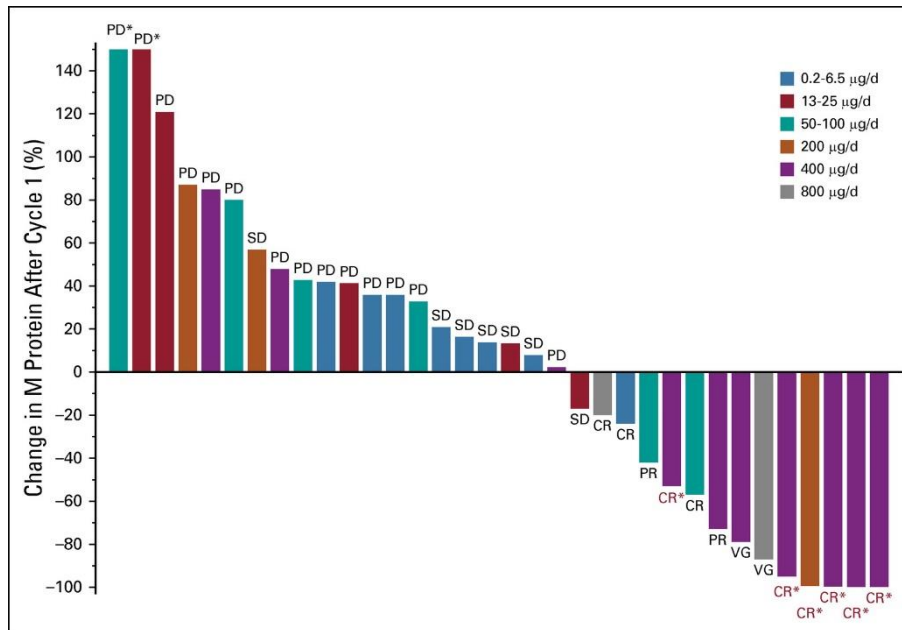


Ongoing trials of bispecifics for MM

Agent name	Target antigen	Phase	Clinical trials number
AMG-420	BCMA	1	NCT02514239
AMG-701	BCMA	1/2	NCT03287908
CC-93269	BCMA	1	NCT03486067
PF-06863135	BCMA	1	NCT03269136
REGN-5458	BCMA	1/2	NCT03761108
TNB-383B	BCMA	1	NCT03933735
JNJ-64007957	BCMA	1	NCT03145181
JNJ-64007564	GPRC5d	1	NCT03399799
GBR-1342	CD38	1/2	NCT03309111
BCFR4350A	FCRH5	1	NCT03275103

Clinical data for bispecifics in MM: AMG-420

- Targeting BCMA and CD3
- No correlation of response and BCMA levels
- Development stopped for this agent in favor of one with longer half-life

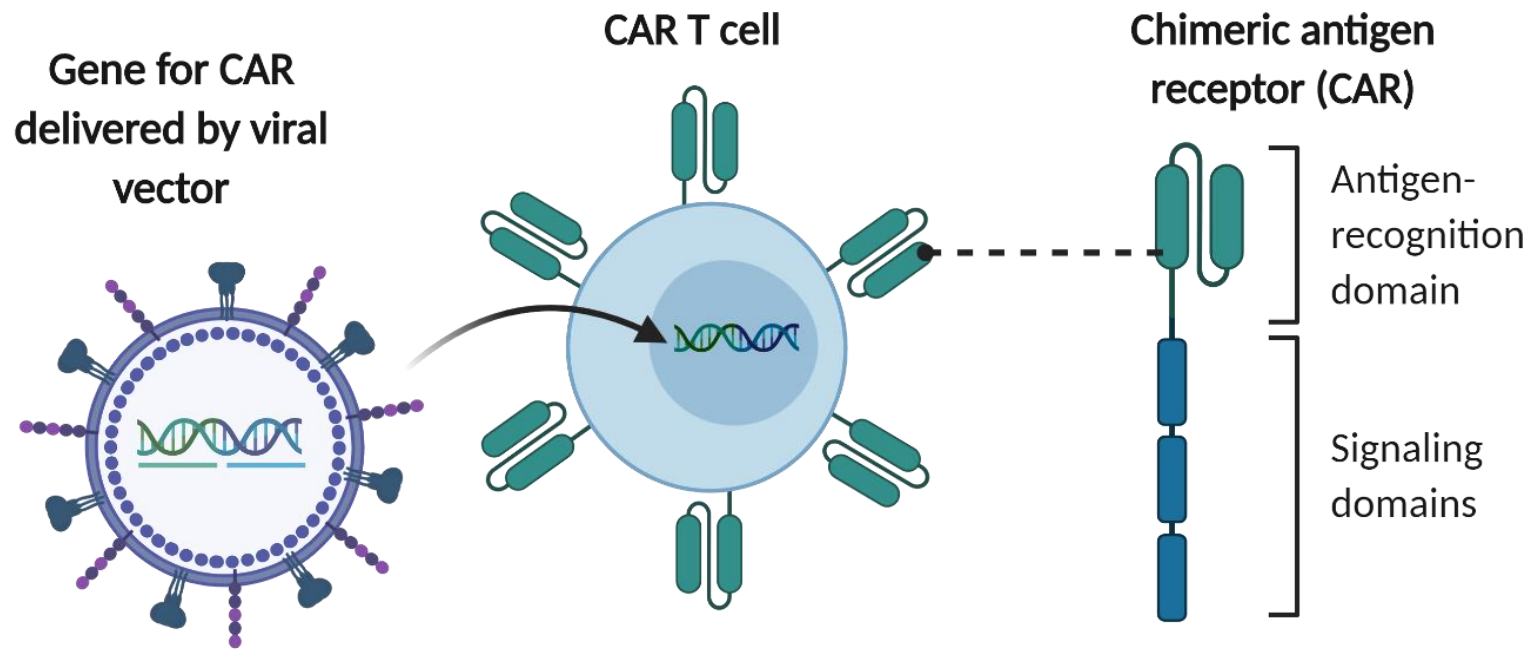


Variable	No. (%)	No. of Patients With AEs at Each Grade				
		1	2	3	4	5
No. of patients	42					
Infections serious AEs						
All	14 (33)	—	4	8	—	2 ^b
Pulmonary ^a	6 (14)	—	3	3	—	—
Central line/port infections	5 (12)	—	—	5	—	—
Adenovirus ^{b,c}	1 (2)	—	—	—	—	1
Aspergillosis/influenza ^b	1 (2)	—	—	—	—	1
Infection of unknown origin (fever) ^d	1 (2)	—	1	—	—	—
Treatment-related serious AEs						
Peripheral polyneuropathy	2 (5)	—	—	2	—	—
Edema	1 (2)	—	—	1	—	—
Cytokine release syndrome						
All treatment related, maximum grade	16 (38)	13	2	1	—	—

Outline

- Monoclonal antibodies
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Cellular therapies – CAR T cells



Ongoing trials of CAR T cells for MM

Agent name	Target antigen	Clinical trials number
bb2121	BCMA	NCT03651128
JNJ-682684528	BCMA	NCT04181827
JCARH125	BCMA	NCT03430011
P-BCMA-101	BCMA	NCT03288493
CT053	BCMA	NCT03915184
CART-BCMA \pm huCART19	BCMA; CD19	NCT03549442
Anti-SLAMF7 CAR T	SLAMF7	NCT03958656

BCMA CAR-T Cells ASCO 2020

Safety

	KarMMa	EVOLVE	CARTITUDE-1
↓ ANC \geq G3, %	89	90	100
↓ Plts \geq G3, %	52	47	69
CRS: all, \leq G3, %	84, 6	89, 3	93, 7
Med. Time to CRS, duration, days	1 (1-12) 5 (1-63)	2 (1-4) 4 (1-10)	7 (2-12) 4 (2-64)
ICANS: all, \leq G3, %	17, 3	13, 3	10, 3
HLH/MAS, %	--	5	? 7 (lfts)
Infections: all, \geq G3 %	69, --	40, 13	--, 19
Toci / steroid / anakinra use, %	52/15/0	76/52/23	79/21/21

Efficacy

	KarMMa (n = 128)	EVOLVE (n = 62)	CARTITUDE-1 (n = 29)
ORR, %	73 (66-82)	92	100
sCR/CR, %	33	36	86
MRD neg $\geq 10^{-5}$, % evaluable	94	84	81
PFS/DoR, months	8.8/10.7	NR	NR
Screened	150		35
Apheresed	140	--	35
Treated	128		29

Panel recommendations for CAR T administration

- Patients should be **re-evaluated & re-staged** if they received bridging therapy or >30 days have passed since lymphodepletion
- *If bridging therapy induces a CR, CAR T therapy should **still proceed** (even though data are currently limited)*
- Patients with appropriate characteristics may receive CAR T therapy as **outpatient infusion**

Panel recommendations for CAR T toxicity management

- **ASTCT grading** for CRS and ICANS
- Grade 2+ CRS requires **prompt tocilizumab** treatment
- Tocilizumab may be considered for **grade 1 CRS** in elderly patients, those with comorbidities, or for prolonged high fevers
- **ICANS should be managed** with supportive care, escalating to steroids and possible use of levetiracetam
- For persistent (>3 months) cytopenia, evaluate for **alternative causes** like infections and MDS
- *Panel **does not recommend CAR T** therapy for patients with renal failure or hepatic impairment*

Outstanding questions for bispecifics and cell therapies

- Interpretation of MRD status
- Management of steroid and tocilizumab-refractory CRS (anakinra vs siltuximab)
- Impact of prior ADC or bispecific exposure on CAR T efficacy

Cell therapy case study

- 65 yo pt with MM, R-ISS stage II
- Initially treated with VRD → ASCT → lenalidomide maintenance x 30 months (stopped d/t side effects)
- Progressed 6 mo later → received KRD → VGPR, 13 months
- Progressed → DPD → PR x 8 months
- Progressed with new sacral plasmacytoma and increase in M protein
- ECOG 0, mild neuropathy from treatment
- Wants to be considered for CAR T therapy

Patient quality of life and education

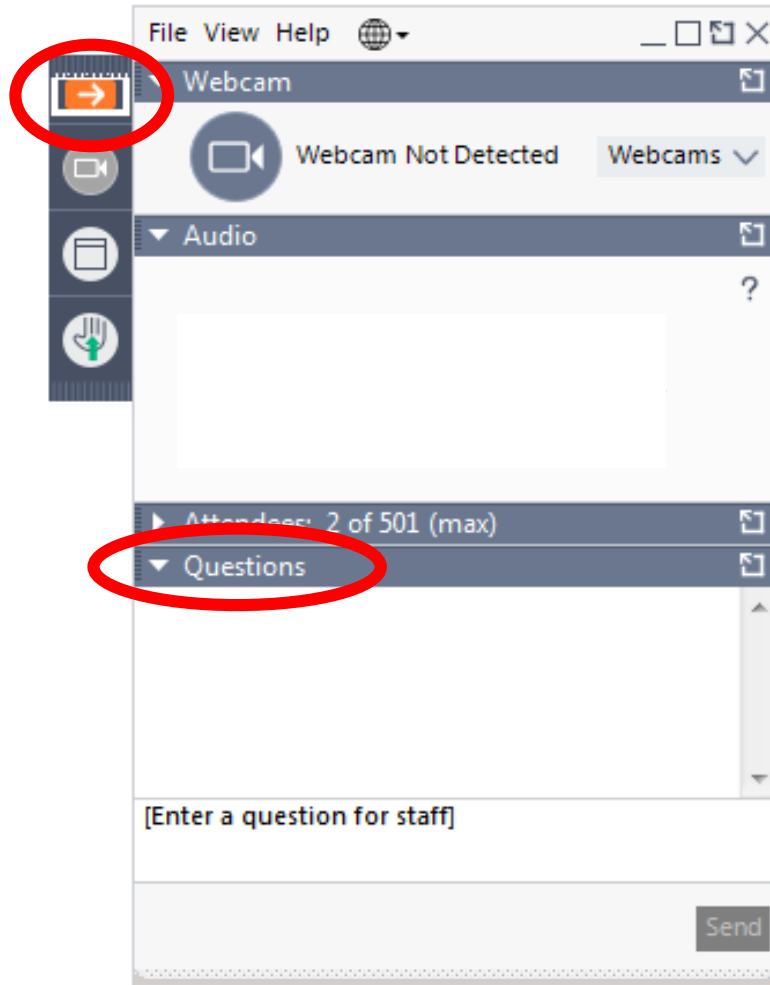
- Patients and caregivers should be informed about **potential side effects** and when to contact their provider
- Recommend patient referral to **support groups**, advocacy organizations, and survivorship programs
- Utilize validated tools like EORTC QLQ-C30 and PROMIS to evaluate **quality of life impacts**

Conclusions

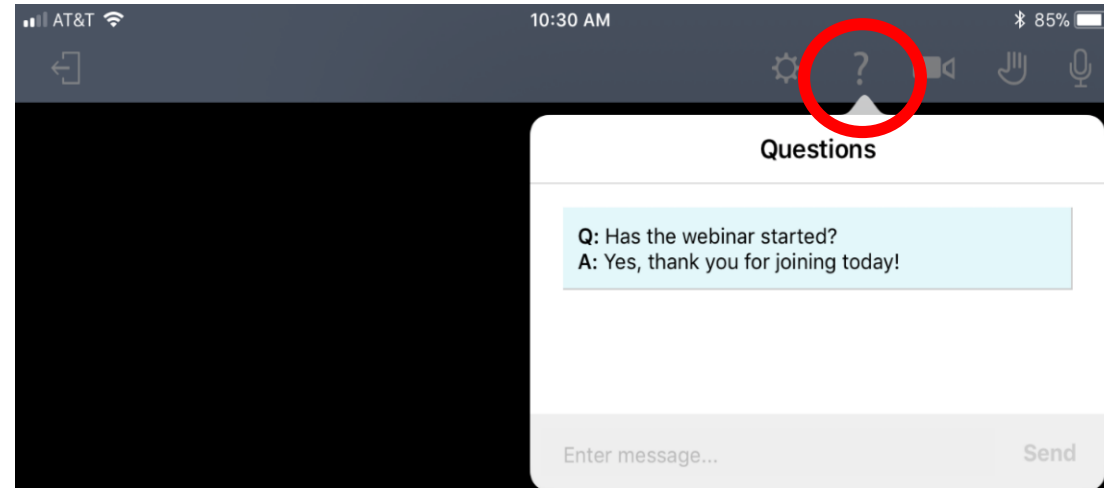
- Immunotherapies are impacting the management of multiple myeloma
- There is potential for these options to move into earlier stages of disease management
- Combinations of immunotherapies are likely in the future
- Evaluation of response is still complicated

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Upcoming Advances in Cancer Immunotherapy™ Webinar: Clinical Updates from ASCO20 Virtual

Thursday, September 10, 2020, 5:00-6:00 p.m. ET

Faculty:

Michael Atkins, MD – *Georgetown-Lombardi Comprehensive Cancer Center*

Shailender Bhatia, MD – *University of Washington*

Stephan Grupp, MD, PhD – *University of Pennsylvania*

Jose Lutzky, MD, FACP – *University of Miami Sylvester Cancer Center*

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