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Sequencing Therapy in Relapsed/Refractory Multiple Myeloma

19th New Orleans Summer Cancer Meeting

Session XII: Hematology Session III

12:35 pm – 12:50 pm

July 19-21, 2024 | The Roosevelt Hotel | New Orleans, LA

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Myeloma/ Amyloidosis Multidisciplinary Team

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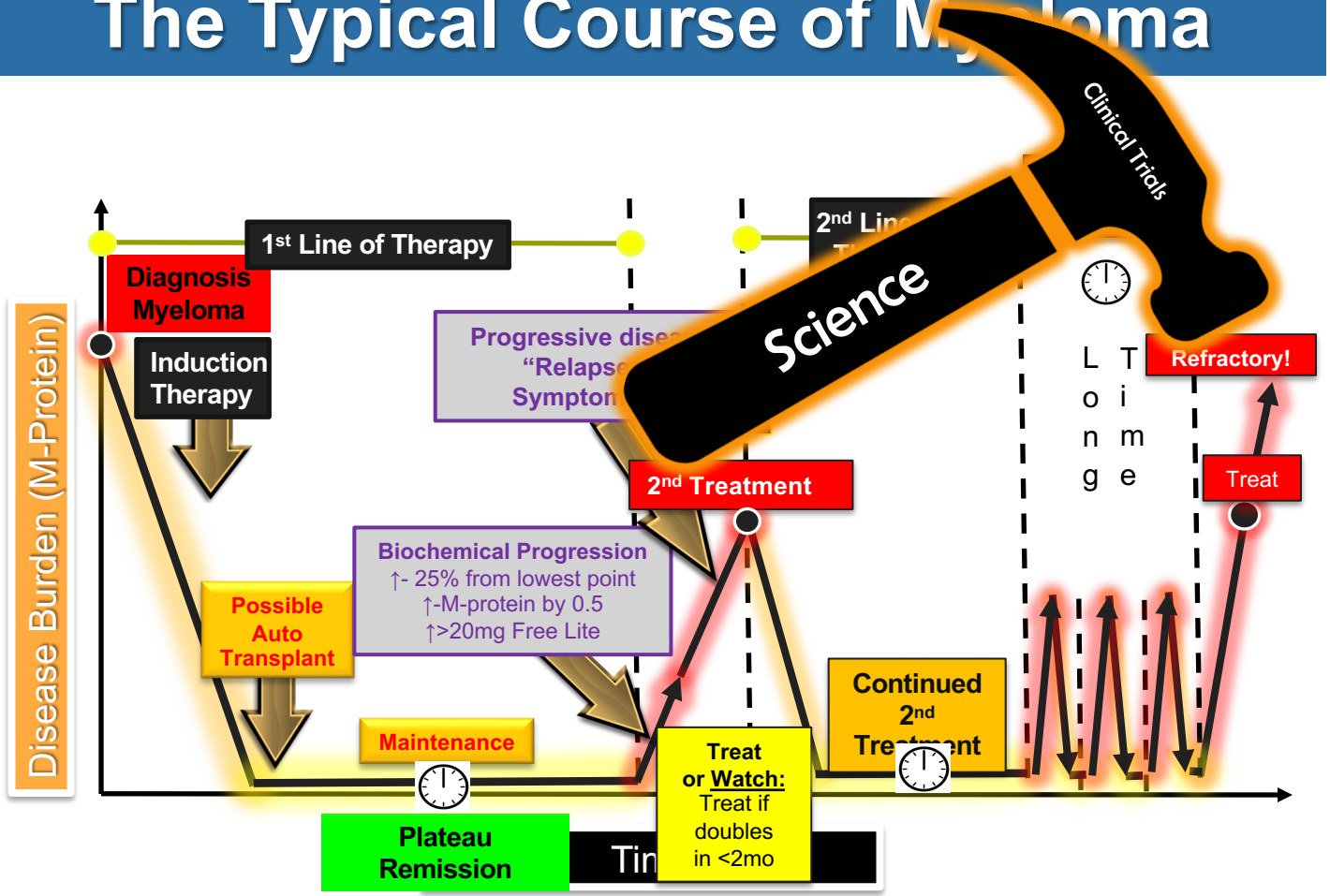
Outline of Discussion

- Definition of lines of therapy
- When to treat relapsed myeloma
- Tools of the trade
- Treating first relapse after induction therapy
  - Recent approval of CAR-T in earlier relpase
- Treating later relapses
  - Bispecifics
- Conclusions

Some discussion of regimens not approved by the FDA

The Typical Course of M[illegible]oma



When to Treat Relapsed MM

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- **Clinical relapse:**
  - Hypercalcemia(>11.5 g/dL)
  - Rise in serum creatinine by >2 mg/dL or more, due to myeloma
  - Decrease in hemoglobin of >2 g/dL, or to < 10g/dL
  - New bone lesions or soft-tissue plasmacytomas
  - Definite increase (>50%) in size of existing bone lesions or plasmacytomas

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International Myeloma Working Group 2016: Kumar S et al.Lancet Oncol. 2016 Aug;17(8):e328-e346.

When to Treat Relapsed MM

- **Significant biochemical relapse:**
  - Doubling of the M-component in <u>two consecutive</u> measurements separated by < 2 months with the reference value of 0.5 g/dL

    OR
  - <u>Two consecutive</u> measurements any of the following increases:
    - The absolute levels of serum M protein by >1g/dl

      or
    - An increase of urine M protein by >500mg/24h

      or
    - An increase of involved FLC level by >20mg/dl (plus an abnormal FLC ratio) or 25% increase

International Myeloma Working Group 2016: Kumar S et al.Lancet Oncol. 2016 Aug;17(8):e328-e346.

When to Treat Relapsed MM

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- **Significant biochemical relapse:**
  - Treatment should be considered at the stage of biochemical relapse in the presence of high-risk factors:
    - Original presentation was aggressive disease
    - Short treatment-free interval with a suboptimal response to the previous treatment line
    - Imminent risk for organ dysfunction (light chain-induced renal disease, amyloidosis, etc..)
    - High risk FISH cytogenetics as double hit, or del17p

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Ludwig H, et al.Oncologist. 2014;19(8):829–844

When to Treat Relapsed MM

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- **Remember:**
  - **Not all biochemical relapses need a change in treatment**
  - All relapse categories require 2 consecutive assessments before classification as relapse or disease progression and/or the institution of any new therapy.
  - Relapse from CR:
    - Reappearance of serum or urine M-protein by immunofixation or electrophoresis
    - Development of > 5% plasma cells in the bone marrow
    - Appearance of any other sign of progression (i.e., new plasmacytoma, lytic bone lesion, or hypercalcemia)

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International Myeloma Working Group 2016: Kumar S et al.Lancet Oncol. 2016 Aug;17(8):e328-e346.

Post-Transplant Patterns of Relapse

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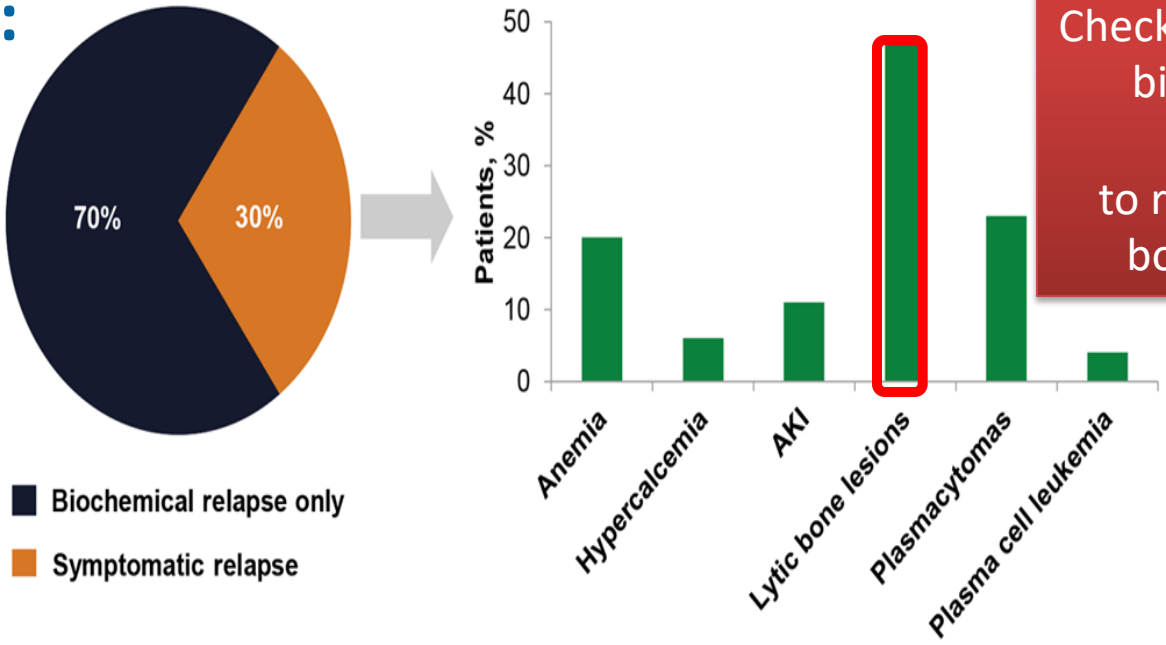
- **Remember:**



Check a PET scan at biochemical relapse to rule out new bone lesions

1. Gonsalves WI et al. *Bone Marrow Transplant*. 2016;51:1156-1158.

PeerView.com

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PeerView.com/QAJ910

Conditions Influencing the Selection of Treatment in Relapsed/Refractory Myeloma

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Goals of Treatment

- **Maximize response (MRD negativity) and maintain disease control**
- **Prolong PFS and OS**
- Delay or prevent disease progression
- Balance efficacy with tolerability and QoL

Disease-related

- Duration of response
- C.R.A.B. symptoms
- Kinetics of relapsed
  - Rapid progressi
    progression

Patient-r

- Age, frailty, perform
- Comorbidities (renal/ hepatic fx)

High Risk Relapse

- Secondary mutations
  - RAS, FGFR3, MYC, or loss or mutation in TP53
- Light chain escape

Treatment-Related

ors

- **l prior response**
- ff maintenance
- s of therapy
- class exposure
- ASCT > or < 3yrs
- ity
- e
- d toxicity of

- Expectations of the patient
- Available clinical trials

Reimbursement / Cost

- Availability/ access issues

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Munshi NS, et al. Blood Adv. 2020 Dec 8;4(23):5988-5999.

General Considerations

- A patient who is naïve to an agent (or a class of drugs) is typically treated with a regimen incorporating this agent (or any agent from the drug class)--**SWITCH DRUG CLASS**
  - Triplet regimen containing at least two new drugs that the patient is not refractory should be considered
- Patients are eligible for an ASCT should be considered for the procedure if they have never had one before
  - Or if they had a DOR with the first ASCT of at least 36 months or longer with maintenance
- **ALWAYS CONSIDER CLINICAL TRIALS**

Rajkumar SV. Am J Hematol. 2024 Jun 28. doi: 10.1002/ajh.27422. Epub ahead of print. Laubach, J. et al. Leukemia. 2016 30, 1005–1017

General Considerations

- A patient who previously responded to a particular agent with a DOR 6–9 months can be retreated at relapse with similar drugs used previously or in combination with other agents—
  - **Can recycle drugs if used in the past**
- Duration of therapy in relapsed MM is determined by the clinical context however most regimens require continuous therapy
  - Given the risk of disease to rapidly evolve into a more aggressive phenotype
- Zoledronic acid/Denosumab should be reinitiated at the time of clinical or biochemical relapse to reduce the risk of new bone events

Rajkumar SV. Am J Hematol. 2024 Jun 28. doi: 10.1002/ajh.27422. Epub ahead of print. Laubach, J. et al. Leukemia. 2016 30, 1005–1017.
Tepros E. Et al.Lancet Oncol. 2021 Mar;22(3):e119-e130

Tools of the Trade in Treating Relapsed Myeloma

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IMids
- Thalidomide (T)
- Lenalidomide (R)
- Pomalidomide (P)

Proteasome Inhibitor
- Bortezomib (V)
- Ixazomib (I)
- Carfilzomib (K)

Anti-CD38
- Daratumumab (D)
- Isatuximab (Isa)

Anti-SLAMF7
- Elotuzumab (E)

Chemotherapy
- Melphalan (ASCT)
- Cyclophosphamide (C)
- Bendamustine
- Anthracycline

Novel Agents

Exportin 1 inhibitors
- Selinexor (X)

BCL-2 Inhibitors
- Venetoclax for t(11;14)

BCMA-targeting
- Belantamab
- Teclistamab
- Elranatamab
- Ide-cel
- Cilta-cel

GPRC5D-targeting
- Talquetamab

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Suggested Options for the Treatment of Relapsed Multiple Myeloma in First Relapse

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Not Refractory to Lenalidomide

Not refractory to CD38 moAB

→ **DRd**

Dara-refractory or relapse while on CD38 moAB

→ **KRd (preferred)**
ERd, Ird, (Alternatives)

Refractory to Lenalidomide

Not refractory to CD38 moAB

→ **DKd or Isa-Kd**
Or
DPd or Isa-Pd

Dara-refractory or relapse while on CD38 moAB

→ **KCd or KPd (preferred)**
Vpd, VCd, Epd, XVd (Alternatives)

Consider cilta-cel if high risk and poor response to quadruplet based initial therapy

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Rajkumar SV. Am J Hematol. 2024 Jun 28. doi: 10.1002/ajh.27422.

First relapse options in lenalidomide non-refractory

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Trial	Regimen	No. of patients	Overall response rate (%)	CR plus VGPR (%)	Progression-free survival (Median in mo)	*p* value for progression free survival	Overall survival (Median in months)	*p* value for overall survival
Stewart et al (ASPIRE)[1]	Rd	396	67	14	18	0.0001	40	0.04
	KRd	**396**	**87**	**32**	**26**		**48**	
Dimopoulos et al (POLLUX)[2]	Rd	283	76	44	18.4	<0.001	N/A; 87% at 1 year	NS
	DRd	**286**	**93**	**76**	**NR**		**N/A; 92% at 1 year**	
Lonial et al (ELOQUENT 2)[3]	Rd	325	66	28	15	<0.001	40	N/A
	Elo-Rd	**321**	**79**	**33**	**19**		**44**	
Moreau et al (TOURMALINE MM1)[4]	Rd	362	72	7	15	0.012	N/A	N/A
	IRd	**360**	**78**	**12**	**21**		**N/A**	

1.N Eng J Med. 2015; **372**(2): 142-152.
2.N Engl J Med. 2016; 375(14): 1319-1331.
3. N Engl J Med. 2015; 373(7): 621-631.
4. N Engl J Med. 2016; 374(17): 1621-1634.

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Rajkumar SV. Am J Hematol. 2024 Jun 28. doi: 10.1002/ajh.27422.

First relapse options refractory to Lenalidomide

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Trial	Regimen	No. of patients	Overall response rate (%)	CR plus VGPR (%)	Progression-free survival (Median in mo)	*p* value for progression free survival	Overall survival[a] (Median in months)	*p* value for overall survival
Dimopoulos et al (APOLLO)[1]	Pd	153	46	20	7	0.002	NR	N/A
	DPd	**151**	**69**	**51**	**12**		**NR**	
Attal et al (ICARIA)[2]	Pd	153	35	9	6.5	<0.001	NR; 63% at 1 year	0.06
	Isa-Pd	**154**	**60**	**32**	**11.5**		**NR; 72% at 1 year**	
Dimopoulos et al (CANDOR)[3]	Kd	154	75	49	16	0.003	74% at 18 months	NS
	DKd	**312**	**84**	**69**	**NR**		**80% at 18 months**	
Moreau et al (IKEMA)[4]	Kd	123	83	56	19	<0.001	NR	NR
	Isa-Kd	**179**	**87**	**73**	**NR**		**NR**	
Yong et al (MUKfive)[5]	VCd	91	68	31	6.6		28.1	
	KCd+ maint	**194**	**84**	**40**	**11.9**		**30.9**	
Palumbo et al (CASTOR)[6]	Vd	247	63	29	7.2	<0.001	N/A; 70% at 1 year	0.30
	DVd	**251**	**83**	**59**	**NR**		**N/A; 80% at 1 year**	

1. Lancet Oncol. 2021; 22(6): 801-812..
2. Lancet. 2019; 394(10214): 2096-2107..
3. Lancet. 2020; 396(10245): 186-197.
4. Lancet. 2021; 397(10292): 2361-2371.
5. Haematologica. 2021 Oct 1;106(10):2694-2706.
6. N Engl J Med. 2016; 375(8): 754-766.

Rajkumar SV. Am J Hematol. 2024 Jun 28. doi: 10.1002/ajh.27422.

Phase 1/2 study of carfilzomib, pomalidomide, and dexamethasone with and without daratumumab in RRMM

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Multicenter, open-label, phase Ib/II study in subjects with RRMM,within the Multiple Myeloma Research Consortium
≥1 prior LOT; LEN exposed/refractory; No prior Dara

KPd Phase I (N=42)

KPd Dose Level	No. of Patients Treated	Carfilzomib IV	Pomalidomide PO
1	Evaluable for DLT: 3	20 mg/m^2	2 mg
2	Evaluable for DLT: 26 Not evaluable: 3	20 mg/m^2	3 mg
3	Evaluable for DLT (Phase I): 13 Not evaluable (Phase I): 1	20/27 mg/m^2	4 mg
4	0*	20/36 mg/m^2	4 mg

KPd Phase II

Carfilzomib 20/27 mg/m2 on days 1, 2, 8, 9, 15, 16 (cycles 1-8) and then days 1, 2, 15, 16 cycle 9+; pomalidomide 4 mg on days 1-21; and dexamethasone 40 mg weekly in 28-day

(N=20)

Dara-KPd Phase II

N=28

Primary endpoints:
- Identification of a maximum tolerated dose (MTD) of KPd for phase 1
- Rates of ORR and nCR after 4 cycles of KPd and Dara-KPd, respectively, for phase 2

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Derman BA et al. Blood Adv. 2023 Oct 10;7(19):5703-5712.

Phase 1/2 study of carfilzomib, pomalidomide, and dexamethasone with and without daratumumab in RRMM

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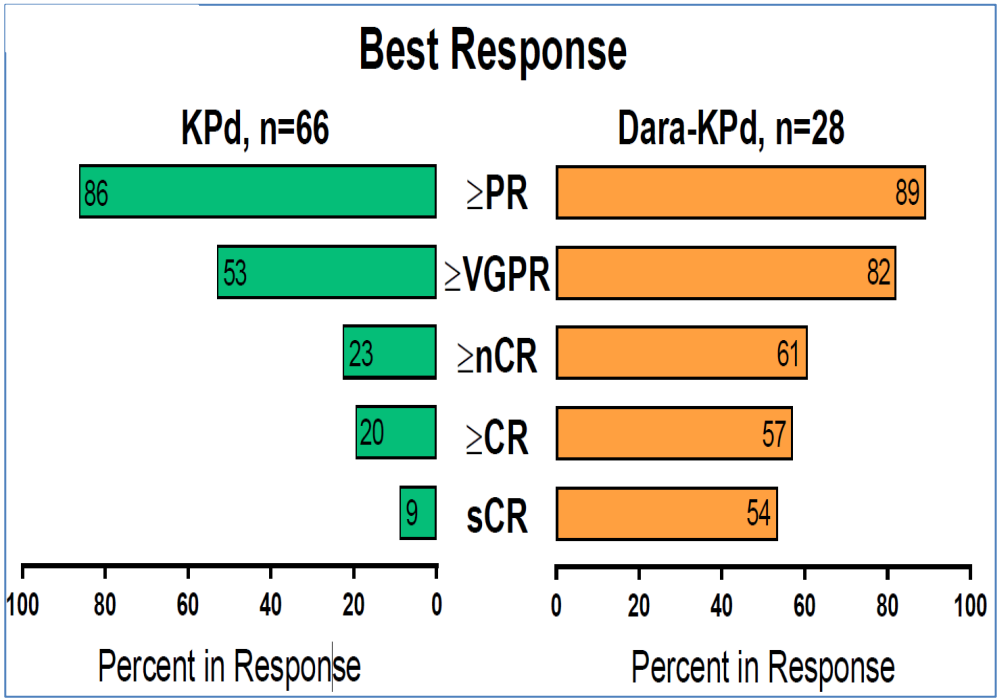
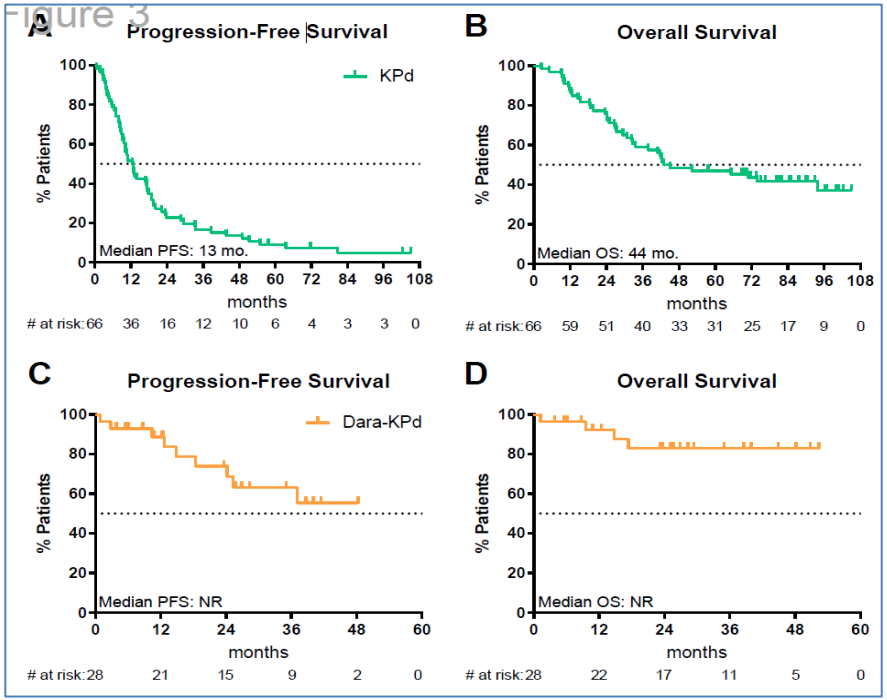
Figure 3





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Derman BA et al. Blood Adv. 2023 Oct 10;7(19):5703-5712.

April 16, 2024 the FDA approved CAR T-cell therapies cilta-cel (≥1 prior) and ide-cel (≥2 prior) lines of Tx in RRMM

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National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2024
Multiple Myeloma

NCCN Guidelines Index
Table of Contents
Discussion

THERAPY FOR PREVIOUSLY TREATED MULTIPLE MYELOMA[a-d,n-o,q]
Relapsed/Refractory Disease After 1–3 Prior Therapies

Preferred Regimens*
Order of regimens does not indicate comparative efficacy

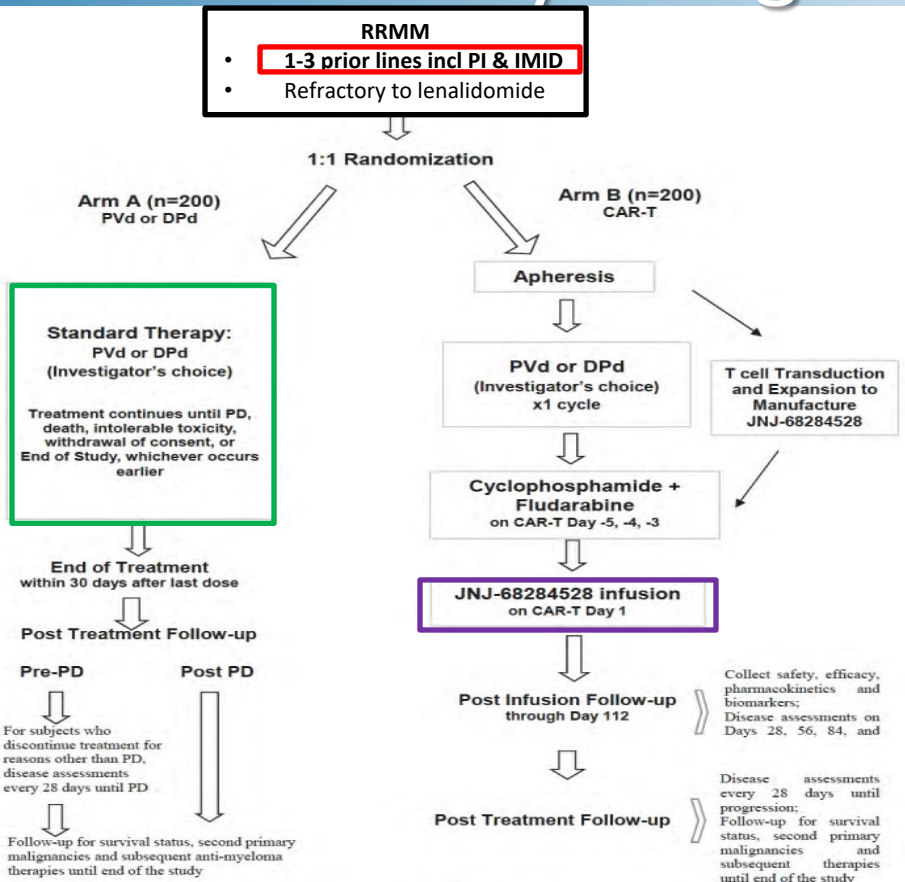
Bortezomib-Refractory[p]	Lenalidomide-Refractory[p]
• Carfilzomib/lenalidomide/dexamethasone (category 1) • Daratumumab/carfilzomib/dexamethasone (category 1) • Daratumumab/lenalidomide/dexamethasone (category 1) • Isatuximab-irfc/carfilzomib/dexamethasone (category 1) • Carfilzomib/pomalidomide/dexamethasone *After one prior therapy including lenalidomide and a PI* ‣ Daratumumab/pomalidomide/dexamethasone (category 1) *After two prior therapies including lenalidomide and a PI* ‣ Isatuximab-irfc/pomalidomide/dexamethasone (category 1)	• Daratumumab/bortezomib/dexamethasone (category 1) • Daratumumab/carfilzomib/dexamethasone (category 1) • Isatuximab-irfc/carfilzomib/dexamethasone (category 1) • Pomalidomide/bortezomib/dexamethasone (category 1) • Selinexor/bortezomib/dexamethasone (category 1) • Carfilzomib/pomalidomide/dexamethasone • Elotuzumab/pomalidomide/dexamethasone *After one prior therapy including lenalidomide and a PI* ‣ Daratumumab/pomalidomide/dexamethasone (category 1) *After two prior therapies including lenalidomide and a PI* ‣ Isatuximab-irfc/pomalidomide/dexamethasone (category 1) *After two prior therapies including an IMiD and a PI and with disease progression on/within 60 days of completion of last therapy* ‣ Ixazomib/pomalidomide/dexamethasone

CAR T-Cell Therapy
After one prior therapy including IMiD and a PI, and refractory to lenalidomide
‣ Ciltacabtagene autoleucel (category 1)

After two prior therapies including an IMiD, an anti-CD38 monoclonal antibody and a PI
‣ Idecabtagene vicleucel (category 1)

* For Other Recommended Regimens and for regimens Useful in Certain Circumstances for Relapsed/Refractory Disease After 1–3 Prior Therapies, see MYEL-G 4 of 5

Cilta-cel CAR-T
Phase 3 CARTITUDE-4: Study Design



San-Miguel J, et al. *NEJM*. 2023;389:335-347.

Cilta-cel CAR-T CARTITUDE-4: Progression Free Survival and Response

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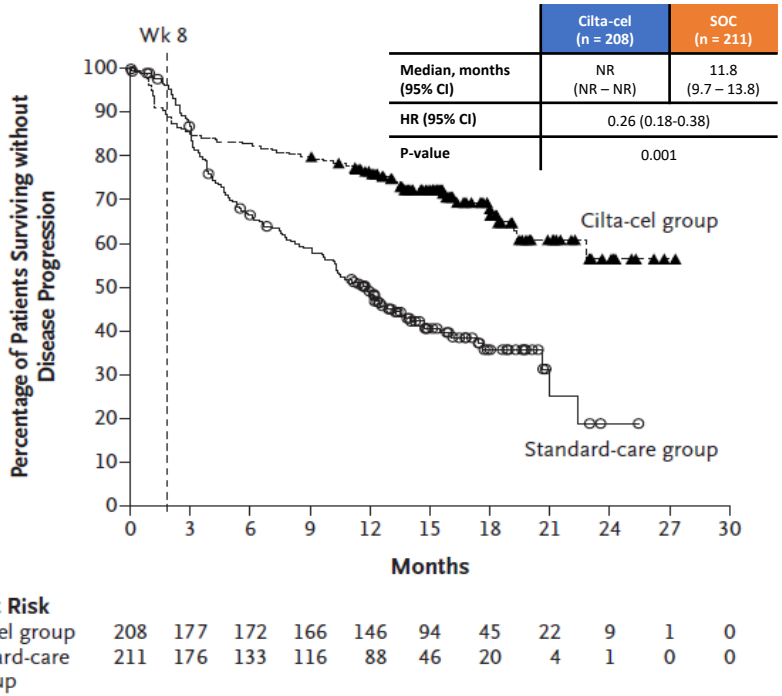
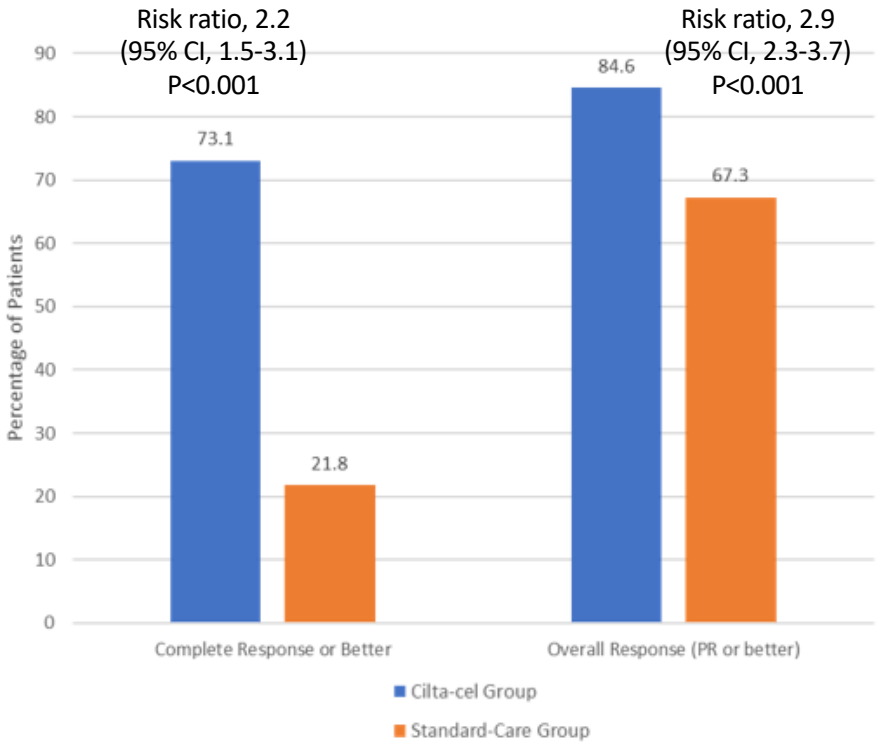


	Cilta-cel (n = 208)	SOC (n = 211)
Median, months (95% CI)	NR (NR – NR)	11.8 (9.7 – 13.8)
HR (95% CI)	0.26 (0.18-0.38)	
P-value	0.001	



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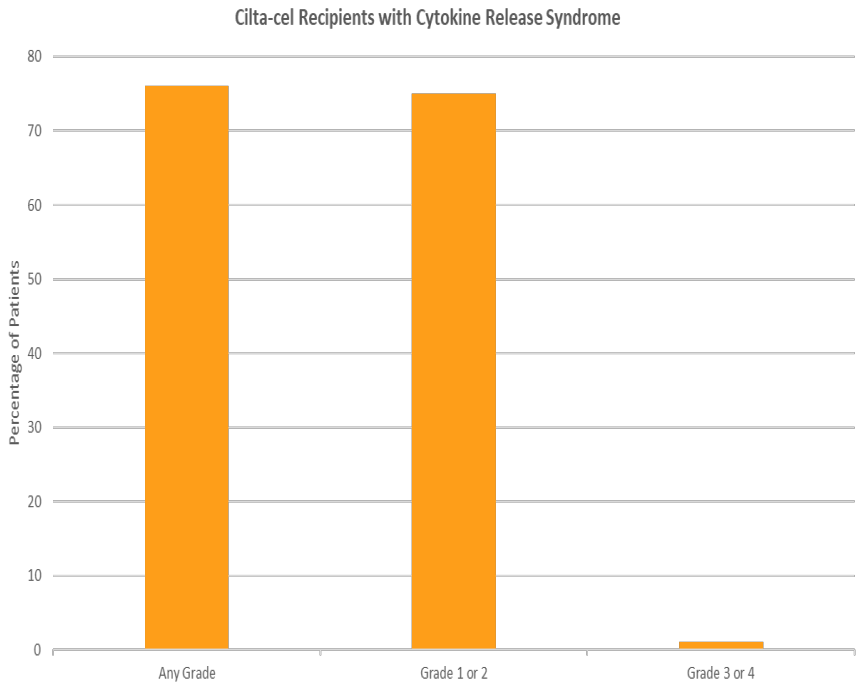
Median follow-up 15.9 months

San-Miguel J, et al. NEJM. 2023;389:335-347.

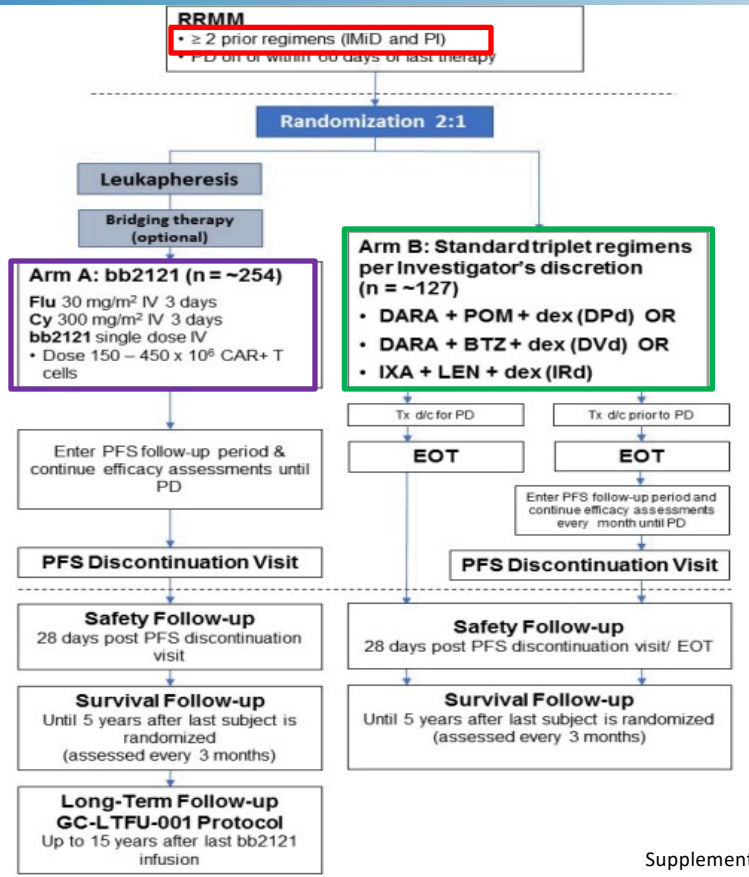
Cilta-cel CAR-T
CARTITUTE-4: Adverse Events



Adverse Event	Cilta-cel (N=208)		Standard Care (N=208)	
	All	Grade 3 or 4	All	Grade 3 or 4
Any adverse event — no. (%)	208 (100.0)	201 (96.6)	208 (100.0)	196 (94.2)
Hematologic event — no. (%)	197 (94.7)	196 (94.2)	185 (88.9)	179 (86.1)
Neutropenia	187 (89.9)	187 (89.9)	177 (85.1)	171 (82.2)
Thrombocytopenia	113 (54.3)	86 (41.3)	65 (31.2)	39 (18.8)
Anemia	113 (54.3)	74 (35.6)	54 (26.0)	30 (14.4)
Lymphopenia	46 (22.1)	43 (20.7)	29 (13.9)	25 (12.0)
Infection — no. (%)	129 (62.0)	56 (26.9)	148 (71.2)	51 (24.5)
Upper respiratory tract†	39 (18.8)	4 (1.9)	54 (26.0)	4 (1.9)
Covid-19‡	29 (13.9)	6 (2.9)	55 (26.4)	12 (5.8)
Lower respiratory tract or lung§	19 (9.1)	9 (4.3)	36 (17.3)	8 (3.8)
Other — no. (%)				
Nausea	101 (48.6)	0	38 (18.3)	2 (1.0)
Hypogammaglobulinemia	88 (42.3)	15 (7.2)	13 (6.2)	1 (0.5)
CAR-T–associated adverse event — no./total no.¶				
Cytokine release syndrome	134/176 (76.1)	2/176 (1.1)	—	—
Neurotoxicity‖	36/176 (20.5)	5/176 (2.8)	—	—
Immune effector cell–associated neurotoxicity syndrome and associated symptoms	8/176 (4.5)	1/176 (0.1)	—	—
Other	30/176 (17.0)	4/176 (2.3)	—	—
Movement or neurocognitive	1/176 (0.6)	0	—	—

San-Miguel J, et al. NEJM. 2023;389:335-347.

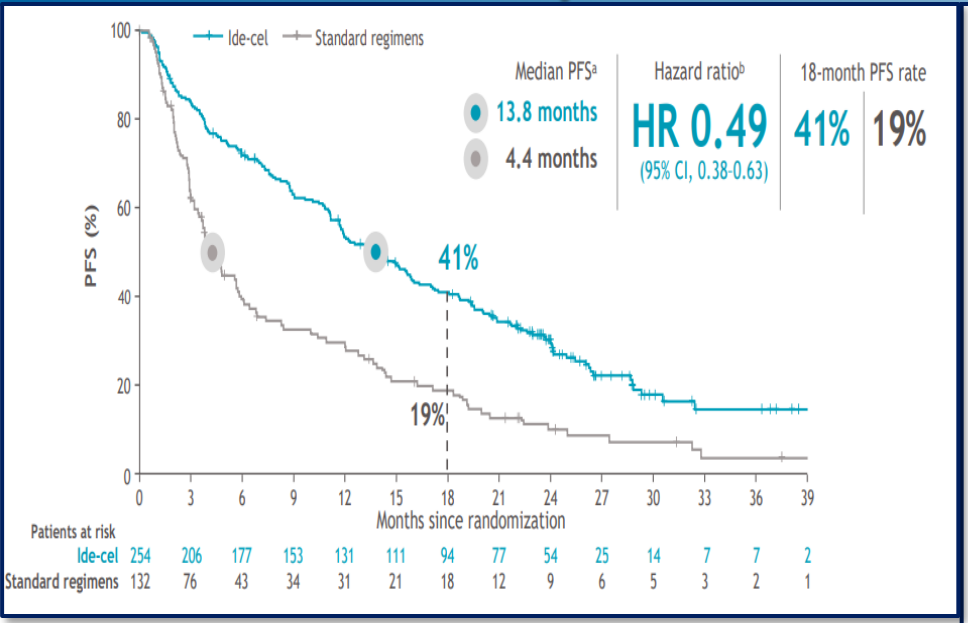
Ide-cel Phase 3 KarMMa-3 Trial: Study Design



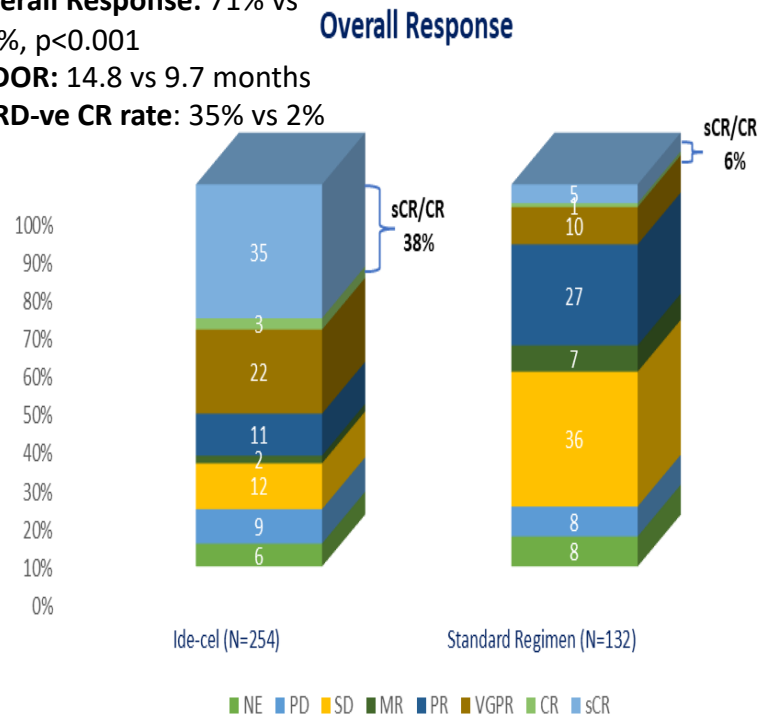
Crossover from standard regimens to ide-cel was allowed: 74 patients (56%)

Supplement to Rodriguez-Otero P, et al. N Engl J Med. 2023; 388:1002-1014.

Ide-cel KarMMa-3: PFS – ITT Population



Overall Response: 71% vs 42%, p<0.001
mDOR: 14.8 vs 9.7 months
MRD-ve CR rate: 35% vs 2%



Rodriguez-Otero P, et al. N Engl J Med. 2023; 388:1002-1014.

Ide-cel KarMMa-3: PFS – Adverse Events

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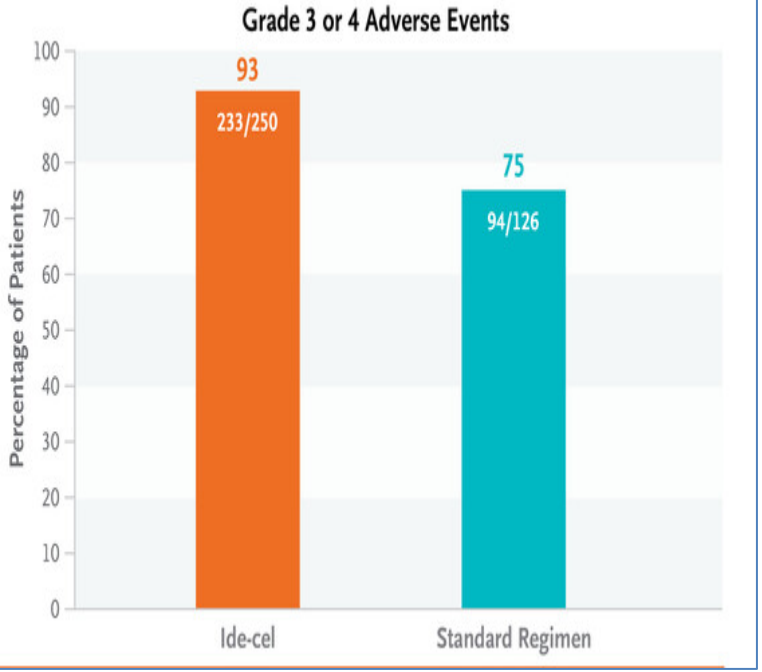

Event	Ide-cel (N=250)			Standard Regimen (N=126)		
	Any Grade	Grade 3 or 4	Grade 5	Any Grade	Grade 3 or 4	Grade 5
Any adverse event — no. (%)*	248 (99)	233 (93)	36 (14)†	123 (98)	94 (75)	8 (6)†
Hematologic event	224 (90)	218 (87)	0	90 (71)	75 (60)	0
Neutropenia	195 (78)	189 (76)	0	55 (44)	50 (40)	0
Anemia	165 (66)	127 (51)	0	45 (36)	23 (18)	0
Thrombocytopenia	136 (54)	106 (42)	0	36 (29)	22 (17)	0
Lymphopenia	73 (29)	70 (28)	0	25 (20)	23 (18)	0
Leukopenia	72 (29)	71 (28)	0	15 (12)	11 (9)	0
Gastrointestinal event	182 (73)	13 (5)	0	65 (52)	5 (4)	0
Nausea	112 (45)	4 (2)	0	34 (27)	0	0
Diarrhea	85 (34)	4 (2)	0	30 (24)	4 (3)	0
Constipation	67 (27)	0	0	9 (7)	0	0
Vomiting	51 (20)	0	0	11 (9)	0	0
Other adverse event						
Infection	146 (58)	61 (24)	11 (4)	68 (54)	23 (18)	3 (2)
Hypophosphatemia	78 (31)	50 (20)	0	10 (8)	3 (2)	0
Hypokalemia	78 (31)	12 (5)	0	14 (11)	1 (1)	0
Fatigue	69 (28)	4 (2)	0	44 (35)	3 (2)	0
Pyrexia	69 (28)	2 (1)	0	22 (17)	1 (1)	0
Headache	59 (24)	0	0	24 (19)	1 (1)	0
Hypomagnesemia	52 (21)	2 (1)	0	6 (5)	1 (1)	0
Dyspnea	44 (18)	4 (2)	0	27 (21)	2 (2)	0
Cytokine release syndrome — no./total no. (%)‡	197/225 (88)	9/225 (4)	2/225 (1)§	0/126	0/126	0/126
Neurotoxic event — no./total no. (%)¶	34/225 (15)	7/225 (3)	0/225	0/126	0/126	0/126

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Rodriguez-Otero P, et al. *N Engl J Med.* 2023; 388:1002-1014.

Second and Subsequent Relapses

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Second Relapse

Consider one of the options listed for first relapse that contains two drugs that the patient is not refractory to

Additional Options

- CAR-T
- Bispecific antibody
- Belantamab (combinations)
- Selinexor-based regimen
- Venetoclax for t(11;14) myeloma
- Bendamustine-based regimens
- Anthracycline-containing regimen

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Rajkumar SV. Am J Hematol. 2024 Jun 28. doi: 10.1002/ajh.27422.

	Bispecific T-cell engagers	CAR T-cell therapy
Advantages	Off-the-shelf therapy (no delays)	-
	-	One time treatment Vacation from continuous therapy
	Deep responses	**Deep responses**
	Mostly grade 1-2 CRS/ICANS	-
	Only initial dosing as inpatient(?)	Only initial dosing as inpatient
Disadvantages	-	Administration delays due to manufacturing time
	Continuous therapy until progression	-
	Weekly or biweekly dosing	-
	Significant immunosuppression	Significant immunosuppression
	-	Potential for severe CRS/ICANS; prolonged cytopenias
	Specialized centers required (?)	Complex infrastructure required
	Cost ($$)	Cost ($$$)

Adapted from Hematology Am Soc Hematol Educ Program 2022; 2022 (1): 163–172

FDA approved Bispecifics in RRMM

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Agent	Teclistamab[1]
Myeloma Target	BCMA
Median Prior Lines	5
Median Age, Y	64
Triple-Class Refractory (%)	77.6
Penta-Drug Refractory (%)	30.3
ORR,%	63
MRD- Rate ($\geq 10^{-5}$), in pts who achieved ≥CR, %	46 (n=30)
DOR, months	18.4
mPFS, months	11.3
mOS, months	18.3
CRS, ≥grade 3 (%)	76.4, 44.8
ICANS, ≥grade 3 (%)	3,0
Infections, ≥grade 3 (%)	76.4, 44.8

1. N Engl J Med. (2022) 387:495–505. doi: 10.1056/NEJMoa2203478

2. Nat Med. (2023) 29:2259–67. doi: 10.1038/s41591-023-02528-9

3. N Engl J Med. (2022) 387:2232–44. doi: 10.1056/NEJMoa2204591

Front Oncol. 2024 Apr 10;14:1394048. doi: 10.3389/fonc.2024.1394048.

Tocilizumab as Prophylaxis for CRS Associated with Bispecifics

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- 53 patients admitted to the Emory for teclistamab step-up dosing
  - 38 pts were given tocilizumab 8 mg/kg IV (max dose of 800 mg) prophylactically at 44 h (4 h prior to the second step-up dose level)
  - CRS occurred in 26.3% (10/38) in the prophylactic tocilizumab cohort, compared to 73.3% (11/15) without toci
    - 5 of the 10 patients in the prophylaxis cohort experienced CRS after step-up dose 1
  - No evidence of impact on response to teclistamab
- 14 patients treated with teclistamab in MajesTEC-1 were given tocilizumab (single 8 mg/kg IV dose) ≤4 hours before the first teclistamab step-up dose
  - CRS occurred in 4 pts (29%; no gr ≥3 CRS); 1 had a subsequent CRS event
  - No evidence of impact on response to teclistamab

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Scott, S.A. et al. Blood Cancer J.2023 13, 191; van de Donk, N et al. JCO 2023 41(16)-Abstract#8033

Conclusions

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- The treatment landscape for RRMM patients is rapidly changing
- At biochemical relapse, reassess disease for symptomatic progression
- Treatment at relapse should be individualized: type of relapse, previous therapies, comorbidities, side-effects, cost, etc.
- The increased use of lenalidomide and CD38 antibodies as part of first-line regimens has major impact on treatment of first relapse
- BCMA-targeted therapies (Ide-cel, Cilta-cel) show favorable profile post 1st relapse(KarMMA-3, CARTITUDE-4).
- Bispecifics (teclistamab, elranatamab, talquetamab) are also very effective, immediately available, and potentially also soon to be seen used in early relapse

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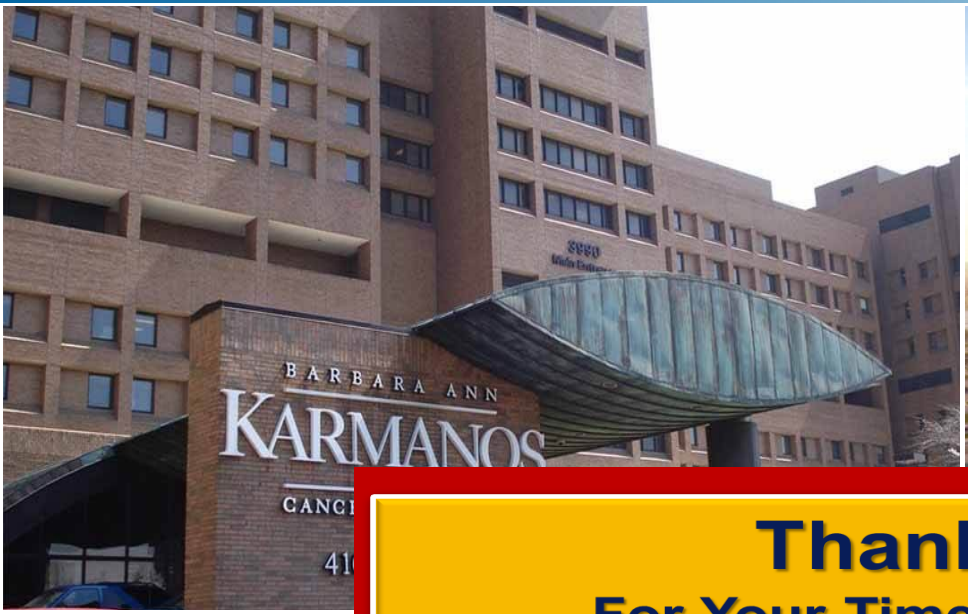

Thank You!

For Your Time and Attention

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