MED TABLE TALK™ SPECIAL EDITION

NEW HORIZONS IN MULTIPLE MYELOMA TREATMENT:
THE PROMISE OF CAR-T FOR EARLY RELAPSED DISEASE

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Educational Objectives

- Evaluate the rationale and significance of CAR T-cell therapies in addressing an unmet need for response durability in early versus late RRMM.
- Explain the clinical implications for current and emerging evidence for the earlier use of CAR T-cell therapy in MM, particularly among those experiencing early relapse after first-line therapy or after triple-class exposure.
- Design practical approaches for the optimal use and timing of CAR T-cell therapies in practice, with considerations to promoting clinical trial enrollment and access to underrepresented communities.

Today's Discussion

- Risk stratification/prognosis to guide treatment selection
- Current guidelines and current indications for early vs. late MM
- Rationale for earlier use of CAR T-cell therapies
- Emerging clinical data for CAR T-cell therapies in TCE and/or early frontline relapse
- Early identification of optimal candidates for CAR T-cell therapy, including coordination of care strategies

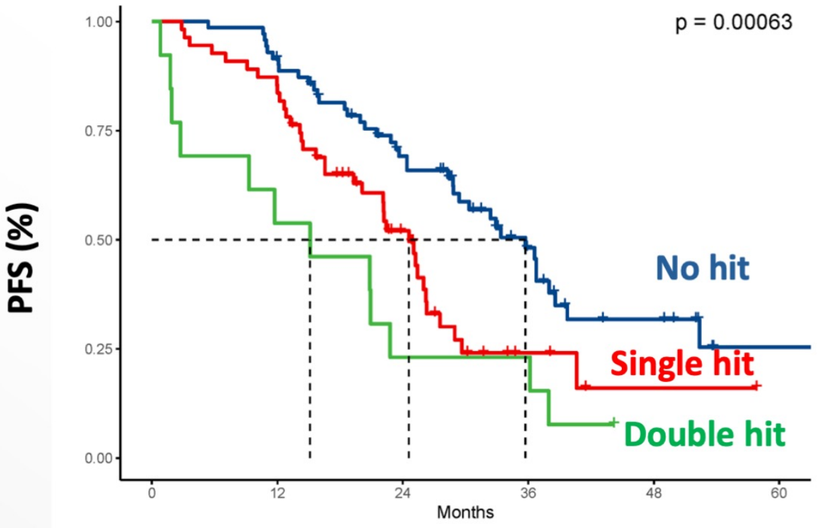
Identifying Patients at High-risk of Early Relapse following ASCT
Results from a Real-World Retrospective Study

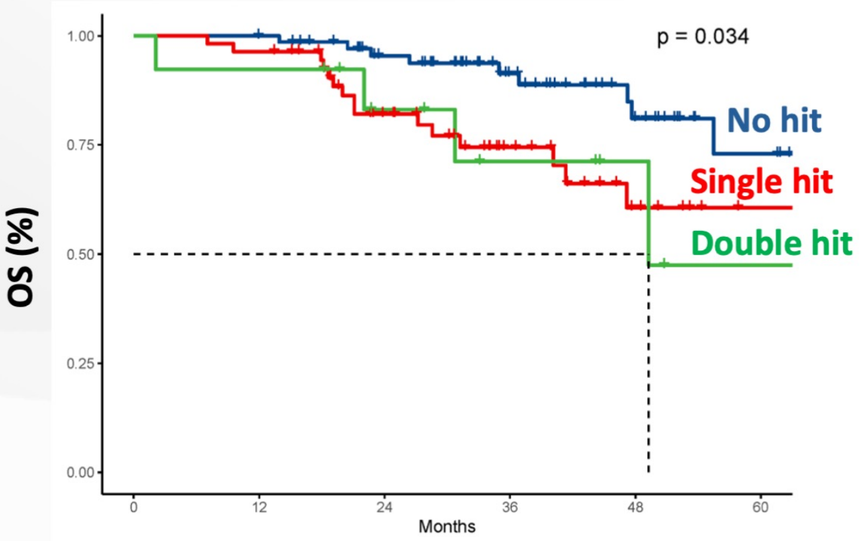
Results from a Real-World, Retrospective Study

- 139 newly diagnosed, transplant eligible MM patients stratified by mutational “hits"
  - “Hits” include mutations in t(4;14), t(14;16), t(14;20), gain(1q), and del(17p)

- Early relapse within 12 months post-ASCT has been associated with negative patient outcomes.

	Double hit	Single hit	No hit
mPFS (mo)	15.1	24.6	35.7
mOS (mo)	49.2	NR	NR
ER	46%	14.5%	9.9%
TTR	2.3 mo	6.4 mo	10.9 mo



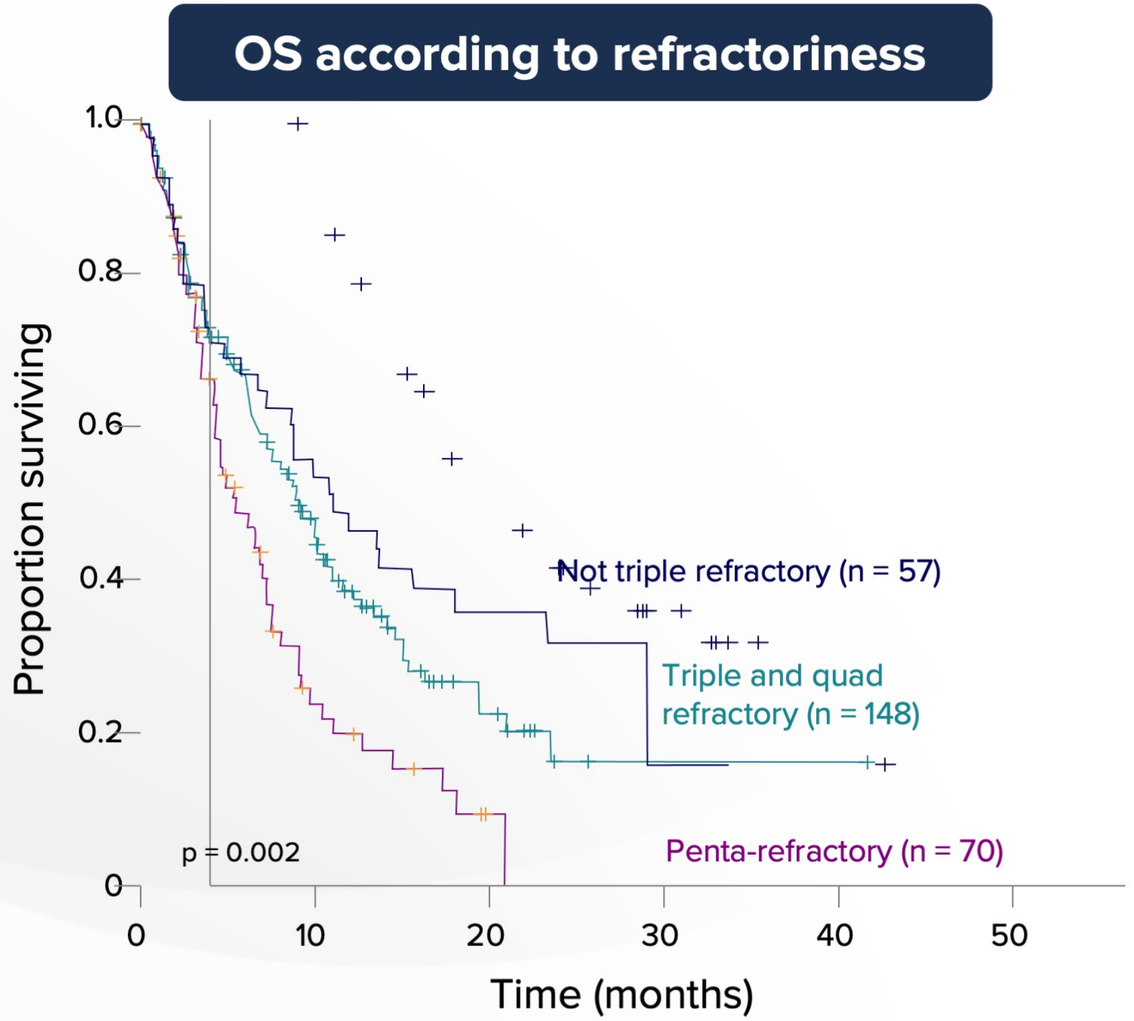


Panopoulou A, et al. *Hemasphere*. 2023.

Outcomes in Triple-Class Refractory Patients: MAMMOTH study

- 275 MM patients refractory to anti-CD38 mAbs
- mOS from refractoriness to CD38:
  - all patients: 8.6 months
  - non-triple-refractory[a]: 11.2 months
  - triple- and quad-refractory[b]: 9.2 months
  - penta-refractory[c]: 5.6 months

- 249 patients received further treatment:
  - mPFS: 3.4 months
  - mOS: 9.3 months



Slide Courtesy of Paula Rodriguez-Otero, MD

[a] Non-triple-refractory: refractory to 1 CD38 mAb, and not both PI and IMiD compound
[b] Triple- and quad-refractory: refractory to 1 CD38 mAb + 1 IMiD compound + 1 PI; or 1 CD38 mAb + 1 PI + 1 or 2 IMiD compounds; or 1 CD38 mAb + 1 or 2 PIs + 1 IMiD compound
[c] Penta-refractory: refractory to 1 CD38 mAb + 2 PIs + 2 IMiD compounds

mOS= median overall survival; mPFS= median progression-free survival

Gandhi UH, et al. *Leukemia*. 2019;33:2266-2275.

Guideline Recommendations – Early Relapsed Disease

THERAPY FOR PREVIOUSLY TREATED MULTIPLE MYELOMA[a-d,l-m]	
Preferred Regimens for Early Relapses (1–3 prior therapies) *Order of regimens does not indicate comparative efficacy*	
• If relapse is >6 months, the regimen used for primary therapy may be repeated. • For patients still sensitive to bortezomib and/or lenalidomide, any of the regimens listed on this page may be appropriate. • Ixazomib/lenalidomide/dexamethasone (category 1) • Bortezomib/lenalidomide/dexamethasone	
Bortezomib-Refractory	**Lenalidomide-Refractory**
• Daratumumab/lenalidomide/dexamethasone (category 1) • Daratumumab/carfilzomib/dexamethasone (category 1) • Carfilzomib/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) *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	• Daratumumab/carfilzomib/dexamethasone (category 1) • Daratumumab/bortezomib/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) *After two prior therapies including an IMiD and a PI and with disease progression on/within 60 days of completion of last therapy* ▸ Pomalidomide/bortezomib/dexamethasone (category 1) ▸ Ixazomib/pomalidomide/dexamethasone

NCCN Guidelines.

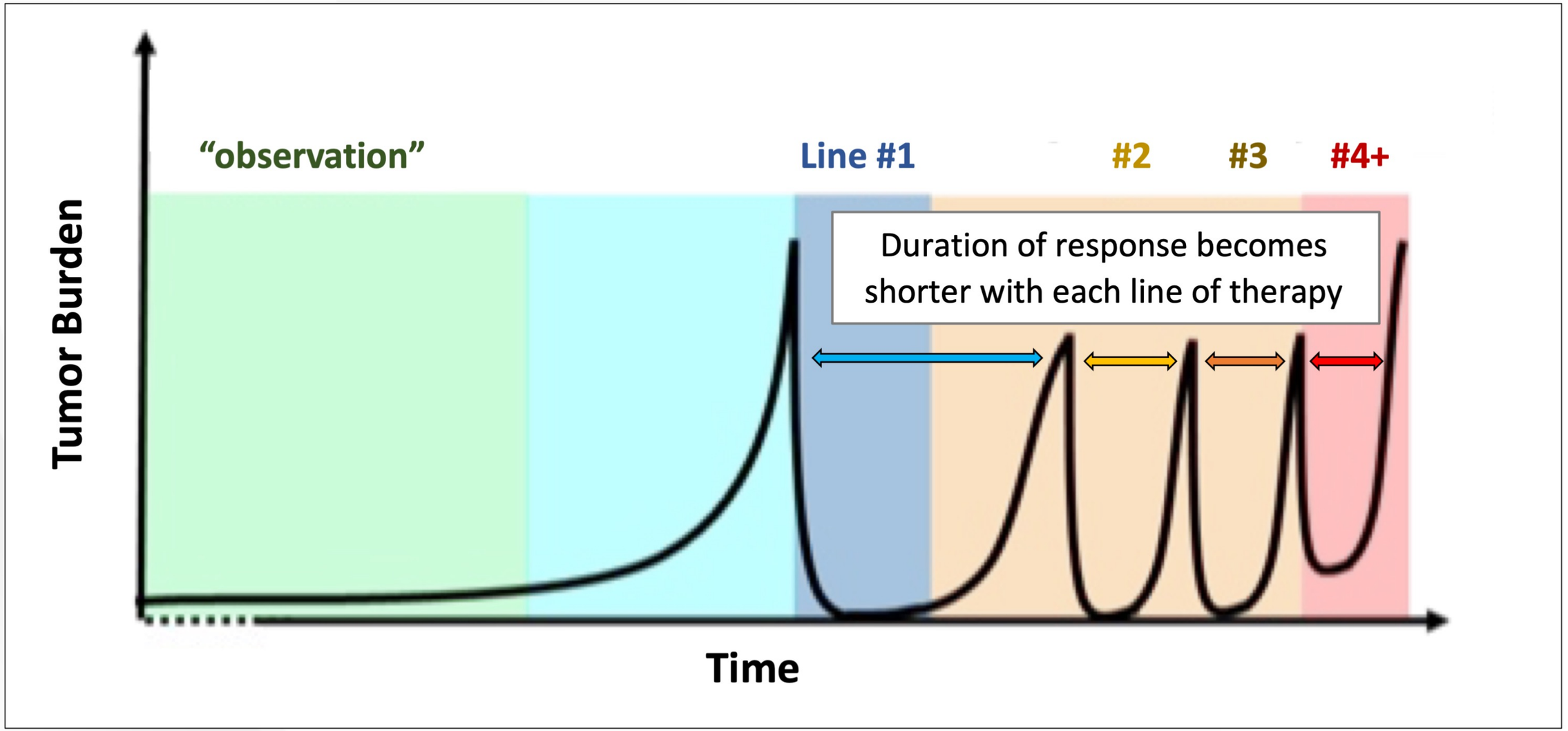
Guideline Recommendations – Late Relapsed Disease

THERAPY FOR PREVIOUSLY TREATED MULTIPLE MYELOMA[a-d,l-n]
Therapies for Patients with Late Relapses (>3 prior therapies)
• **Bendamustine** • **Bendamustine/bortezomib/dexamethasone** • **Bendamustine/carfilzomib/dexamethasone** • **Bendamustine/lenalidomide/dexamethasone** • **High-dose or fractionated cyclophosphamide** *After at least four prior therapies, including an anti-CD38 monoclonal antibody, a PI, and an IMiD* ▸ **Idecabtagene vicleucel** ▸ **Ciltacabtagene autoleucel** ▸ **Teclistamab-cqyv** ▸ **Useful in certain circumstances:** ◊ **Belantamab mafodotin-blmf (if available through compassionate use program)** *After at least four prior therapies and whose disease is refractory to at least two PIs, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody* ▸ **Selinexor/dexamethasone**

- BCMA-directed genetically modified autologous T cell immunotherapy
- Indicated for the treatment of RRMM after ≥4 prior lines of therapy, including an IMiD, PI, and anti-CD38 mAb.

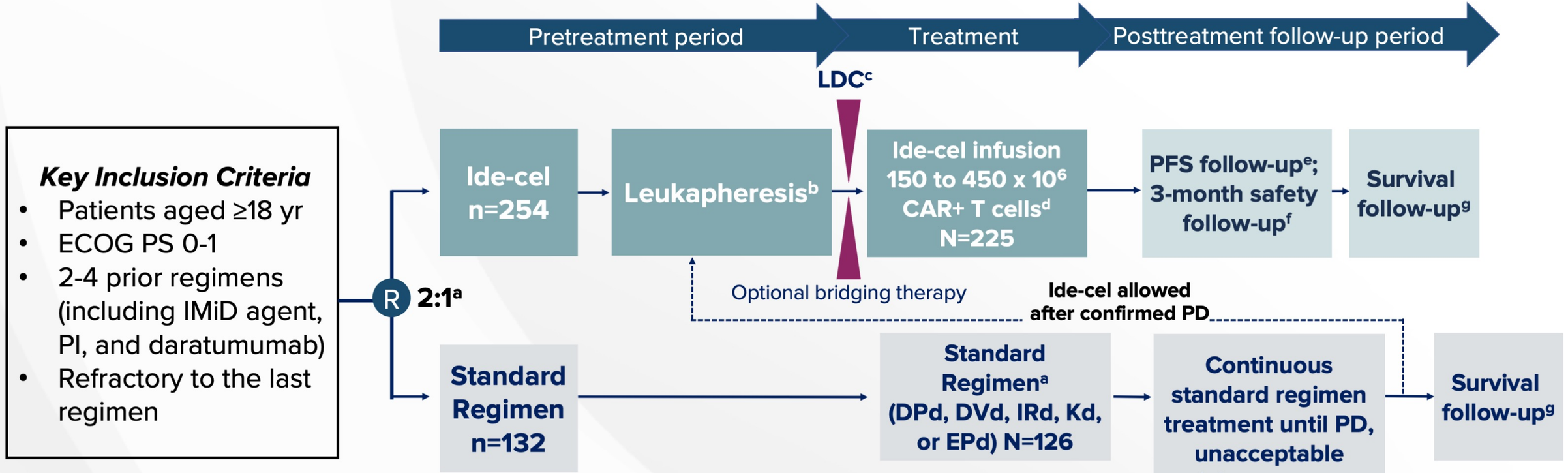
FDA Prescribing Information; NCCN Guidelines.

Multiple Myeloma Disease Progression with Each Subsequent Line of Therapy



https://lab.moffitt.org/silva/current-projects/.

Phase III KarMMA-3 : Ide-cel in MM



- **Primary endpoint:** PFS (by IRC)
- **Secondary endpoints:** ORR (by IRC), OS
- **Other secondary endpoints:** CR rate,[h] DOR,[h] TTR, MRD, safety

[a]Based on most recent treatment regimen and investigator discretion;
[b]Up to 1 cycle of DPd, DVd, IRd, or EPd may be given;
[c]3days fludarabine 30 mg/m^2 and cyclophosphamide 300 mg/m^2;
[d]Doses ≤540 x 106 cells permitted;
[e]Monthly for patients randomized to ide-cel for 24 months, then every 3 months until PD;
[f]Patients randomized to standard regimens and received subsequent ide-cel therapy;
[g]Every 3 months after PD until end of trial; 5 years after last patient randomized;
[h]By IRC; DPd, daratumumab/pomalidomide/dexamethasone; DVd, daratumumab/bortezomib/ dexamethasone; EPd, elotuzumab/pomalidomide/dexamethasone; IRd, ixazomib/lenalidomide/dexamethasone; Kd, carfilzomib/dexamethasone; LDC, lymphodepleting chemotherapy.

Rodriguez-Otero P, et al. *N Engl J Med*. 2023.

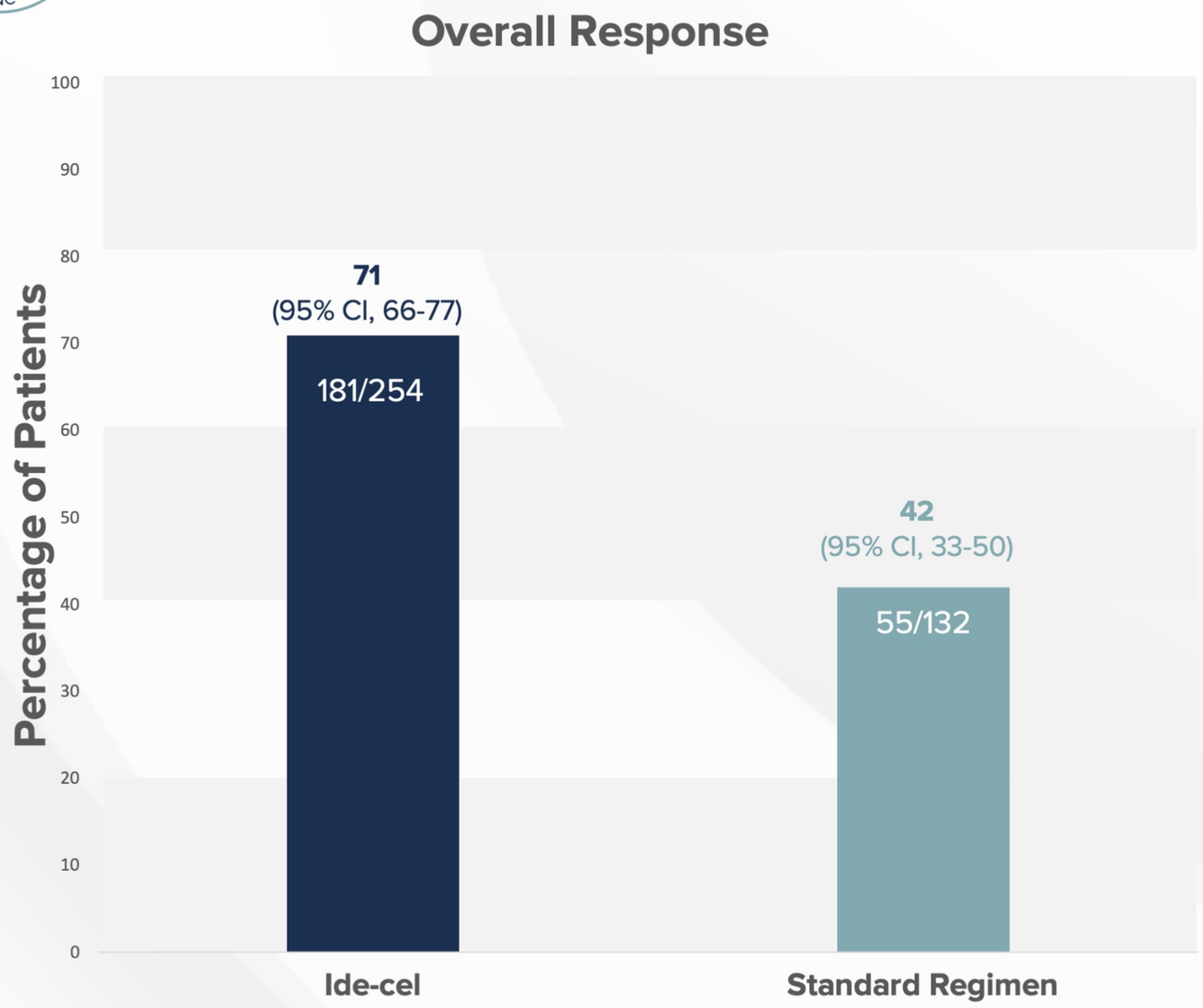
Phase III KarMMA-3: Ide-cel in MM

Characteristic	Ide-cel (n=254)	Standard Regimen (n=132)
Median age, yr (range)	63 (30-81)	63 (42-83)
Male, n (%)	156 (61)	79 (60)
Race, n (%)		
▪ White	172 (68)	78 (59)
▪ Black	18 (7)	18 (14)
▪ Asian	7 (3)	5 (4)
▪ Other/unknown	3 (1)	4 (3)
ECOG PS 0, n (%)	120 (47)	66 (50)
Median time from initial diagnosis to screening, yr (IQR)	4.1 (0.6-21.8)	4.0 (0.7-17.7)
R-ISS stage, n (%)		
▪ I	50 (20)	26 (20)
▪ II	150 (59)	82 (62)
▪ III	31 (12)	14 (11)
▪ Unknown	23 (9)	10 (8)
Extramedullary disease, n (%)	61 (24)	32 (24)
High tumor burden, n (%)	71 (28)	34 (26)

Characteristic	Ide-cel (n=254)	Standard Regimen (n=132)
High-risk cytogenetics, n (%)	42%	46%
▪ del(17p)	26%	32%
▪ t(4;14)	17%	14%
▪ t(14;16)	3%	3%
Other cytogenetic abnormalities, n (%)		
▪ 1q gain or amplification	49%	39%
▪ 13q14del	33%	30%
▪ 1pdel	7%	6%
▪ 13q34 monosomy	20%	20%
▪ t(14;20)	1%	2%
Mean previous regimens, no. (range)	3 (2-4)	3 (2-4)
Refractory status, n (%)		
▪ IMiD agent	88%	94%
▪ PI	74%	72%
▪ Anti-CD38 mAb	95%	94%
Triple-class-refractory disease	65%	67%
Penta-refractory disease	6%	4%

Rodriguez-Otero P, et al. N Engl J Med. 2023.

Phase III KarMMA-3: Ide-cel in MM



Efficacy Outcome	All Patients (N = 37)
Median PFS, mo (95% CI)	11.4 (5.6-19.6)
Median OS, mo (95% CI) ▪ 12-mo OS rate, % (SE) ▪ 24-mo OS rate, % (SE)	Not reached 88.0 (5.64) 84.7 (6.31)

Rodriguez-Otero P, et al. *N Engl J Med*. 2023.

Phase III KarMMA-3: Ide-cel in MM

AEs, n (%)	Ide-cel (N=250)		Standard Regimen (N=126)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Any	248 (99)	233 (93)	123 (98)	94 (75)
Neutropenia	195 (78)	189 (76)	55 (44)	50 (40)
CRS	197 (88)	9 (4)	0	0
Anemia	165 (66)	127 (51)	45 (36)	23 (18)
Infections and infestations	146 (58)	61 (24)	68 (54)	23 (18)
Thrombocytopenia	136 (54)	106 (42)	36 (29)	22 (17)
Nausea	112 (45)	4 (2)	34 (27)	0
Diarrhea	85 (34)	4 (2)	30 (24)	4 (3)
Hypokalemia	78 (31)	12 (5)	14 (11)	1 (1)
Hypophosphatemia	78 (31)	50 (20)	10 (8)	3 (2)
Leukopenia	72 (29)	71 (28)	15 (12)	11 (9)
Headache	59 (24)	0	24 (19)	1 (1)
Neurotoxic event	24 (15)	7 (3)	0	0

Rodriguez-Otero P, et al. *N Engl J Med.* 2023.

Cilta-cel: CARTITUDE-4 (MMY3002) Study Design

Patients:

- Measurable disease
- Documented evidence of PD by IMWG criteria
- 1-3 prior lines of therapy including PI and IMiD
- Refractory to lenalidomide
- No prior treatment with BCMA or CAR-T therapy
- No monoclonal antibody treatment within 21 days
- N-419

Randomization 1:1

PVd

Pomalidomide PO 4 mg on days 1-14
Bortezomib 1.3 mg/m²SC
Cycles 1-8: days 1, 4, 8, 11
Cycles 9+ days 1 and 8
Dexamethasone 20 mg* PO
Cycles 1-8: days 1, 2, 4, 5, 8, 9, 11, 12
Cycles 9+ days 1, 2, 8, 9

Cycle: 21 days
*Dexamethasone 10mg/day for participants > 75 years of age

Or

DPd

Daratumumab SC 1800 mg
Cycles 1-2: QW; Cycles 3-6: Q2W;
Cycles 7+: Q4W
Pomalidomide PO 4 mg
on days 1-21
Dexamethasone 20 mg⁺ PO or IV
on days 1, 8, 15, 22

Cycle: 28 days
⁺Dexamethasone 20mg/day for participants > 75 years of age

Cilta-cel

Cilta-cel infusion at a target dost of $0.75x10^5$ CAR-positive viable T-cells/kg

Participants will receive 1 cycle of bridiging therapy (PVd or DPd)
a second cycle of PVd or DPd may be administered per investigator discretion along with conditioning regimen (cyclophosphamide and fludarabine)

Primary Outcomes:	Secondary Outcomes:	
• Progression –free survival	• CR or sCR • MRD negativity status • Sustained MRD negative rate	• HRQoL • OS, ORR, PFS2 • Safety

Primary endpoint of PFS has been met (January 2022)[2]

1. https://clinicaltrials.gov/ct2/show/NCT04181827
2. https://www.prnewswire.com/news-releases/janssen-announces-unblinding-of-phase-3-cartitude-4-study-of-carvykti-cilta-cel-as-primary-endpoint-met-in-treatment-of-patients-with-relapsed-and-refractory-multiple-myeloma-301732398.html

Phase II KarMMA-2 Cohort 2: Ide-cel in Clinical High-Risk MM

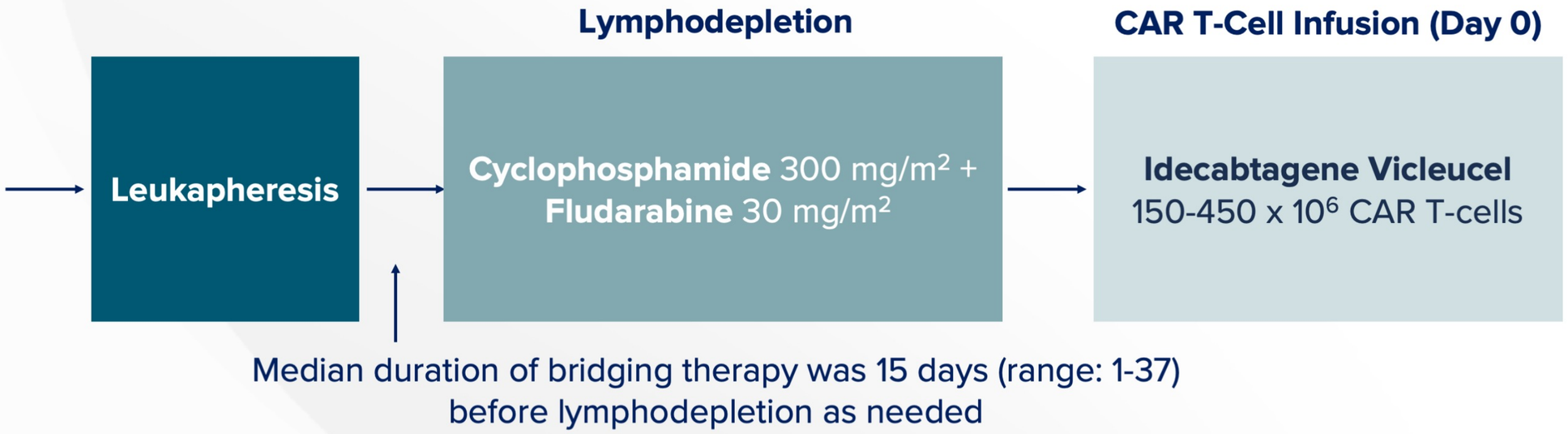
The phase II KarMMa-2 trial is a multicohort trial investigating the efficacy and safety of ide-cel in patients with R/R MM and those with clinical high-risk MM (NCT03601078)

Cohort 2 (N=99) **Clinical high-risk MM (1 regimen)**
Cohort 2a (n=37) Early relapse – PD <18 months from initiation of frontline therapy containing induction, ASCT (single or tandem and lenalidomide containing maintenance)
Cohort 2b (n=31) Early relapse – PD <18 months from frontline therapy without ASCT
Cohort 2c (n=31) Inadequate response (<VGPR) post-ASCT

Usmani S, et al. *ASH. 2022*. Abstract 361.

Phase II KarMMA-2 Cohort 2: Ide-cel in MM with Early Relapse After Frontline ASCT

Cohort 2a:
Patients aged ≥18 yr with clinical high-risk MM; PD <18 mo from start of 1L induction, ASCT (single or tandem), and LEN-containing maintenance; measurable disease; ECOG PS 0-1
(N = 37)



- **Primary endpoint:** CR rate (CR and sCR) per IMWG criteria
- **Secondary endpoints:** ORR, TTR, DoR, PFS, TTP, OS, safety, PK, immunogenicity, health-related QoL
- **Exploratory endpoints:** MRD negativity, biomarker status (soluble BCMA level)

Usmani S, et al. *ASH. 2022*. Abstract 361.

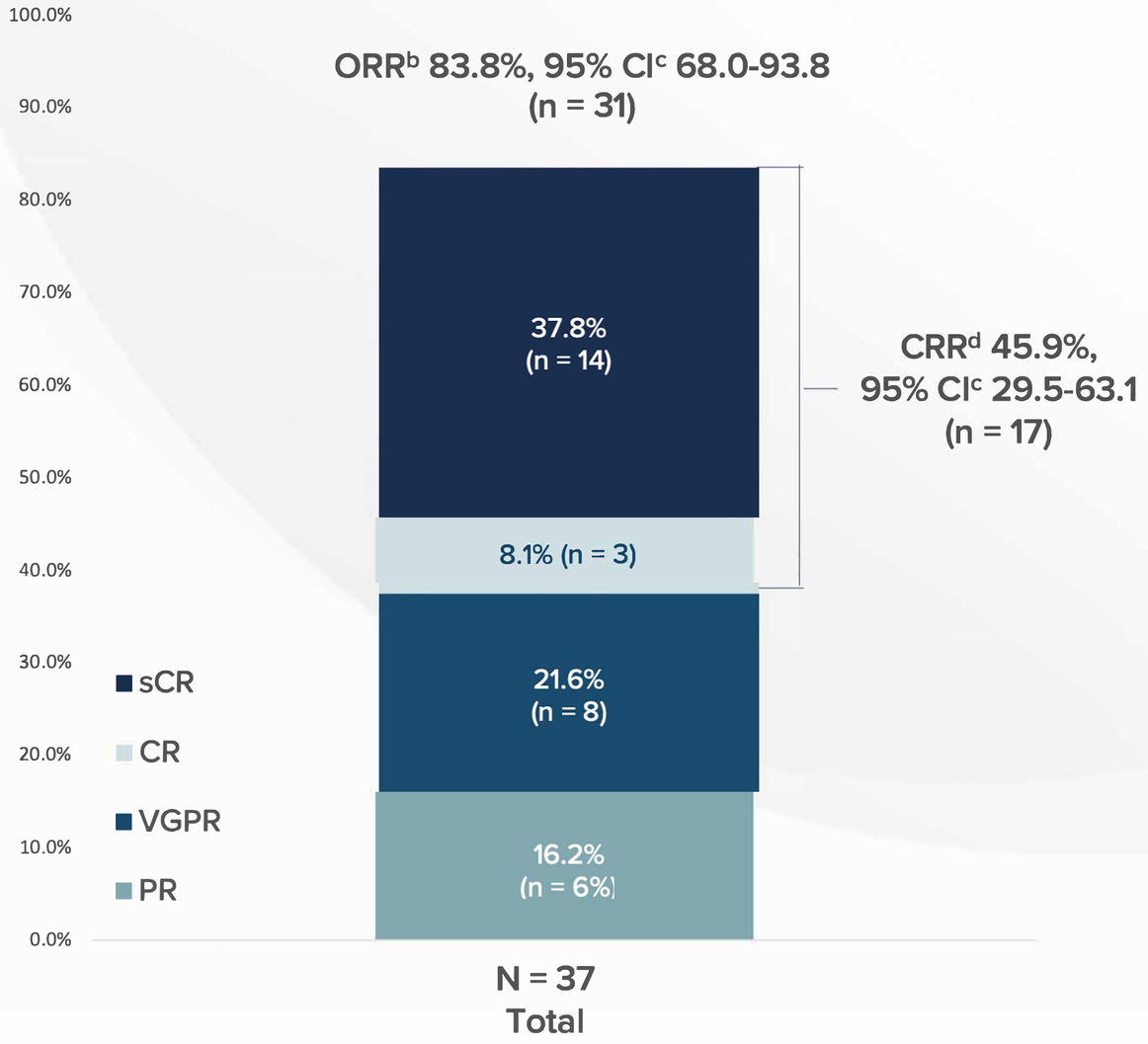
Phase II KarMMA-2 Cohort 2a: Ide-cel in MM with Early Relapse After Frontline ASCT

Characteristic	All Patients (N = 37)
Median age, yr (range)	57 (36-77)
Male, n (%)	21 (56.8)
Race, n (%) ▪ White ▪ Black ▪ Asian ▪ Other/unknown	 29 (78.4) 4 (10.8) 1 (2.7) 3 (8.1)
ECOG PS 0, n (%)	23 (62.2)
Median time from initial diagnosis to screening, yr (IQR)	1.6 (1.3-1.8)
R-ISS stage, n (%) ▪ I ▪ II ▪ III	 5 (13.5) 19 (51.4) 2 (5.4)
Extramedullary disease, n (%)	3 (8.1)
High tumor burden (≥50% BM CD138+ BMPCs), %	7 (18.9)

Characteristic	All Patients (N = 37)
High-risk cytogenetics, n (%) ▪ Any (del[17p], t[4;14], t[14;16]) ▪ Missing	 12 (32.4) 15 (40.5)
Ultra high–risk cytogenetics (≥2 features of del[17p], t[4;14], t[14;16], t[14;20], 1q amp), n (%)	4 (10.8)
LEN post ASCT as maintenance therapy, n (%)	30 (81.1)
Best response to 1L therapy (including ASCT), n (%) ▪ CR/sCR ▪ VGPR ▪ PR ▪ PD	 9 (24.3) 19 (51.4) 8 (21.6) 1 (2.7)
Time of PD, n (%) ▪ <12 mo after initiation of 1L therapy ▪ <12 mo after ASCT	 11 (29.7) 33 (89.2)
Refractory status, n (%) ▪ IMiD agent ▪ PI ▪ Anti-CD38 mAb	 32 (86.5) 33 (89.2) 0

Usmani S, et al. *ASH. 2022.* Abstract 361.

Phase II KarMMA-2 Cohort 2a: Ide-cel in MM with Early Relapse After Frontline ASCT



Usmani S, et al. *ASH. 2022.* Abstract 361.

Phase II KarMMA-2 Cohort 2a: Ide-cel in MM with Early Relapse After Frontline ASCT

AEs, n (%)	Ide-Cel (N = 37)	
	Any Grade	Grade 3/4
Any	37 (100)	37 (100)
Neutropenia	35 (94.6)	35 (94.6)
CRS	31 (83.8)	1 (2.7)
Infections and infestations	22 (59.5)	8 (21.6)
Anemia	21 (56.8)	17 (45.9)
Thrombocytopenia	19 (51.4)	14 (37.8)
Hypophosphatemia	14 (37.8)	9 (24.3)
Headache	14 (37.8)	1 (2.7)
Leukopenia	12 (32.4)	12 (32.4)
Diarrhea	11 (29.7)	0
Hypokalemia	9 (24.3)	0
Nausea	9 (24.3)	0
Hypocalcemia	8 (21.6)	2 (5.4)

AEs (N = 37), n (%)	Any Grade	Grade 3/4
Constipation	8 (21.6)	0
Pyrexia	8 (21.6)	0
Cough	8 (21.6)	0
Insomnia	8 (21.6)	0

- Median time to recovery of selected AEs
  - Grade ≥3 neutropenia: 1.45 mo (95% CI: 1.45-1.87)
  - Grade ≥3 thrombocytopenia: 1.87 mo (95% CI: 1.45-NE)
- 2 patients died due to AEs, both from infections
  - 1 due to pneumonia (67 days post ide-cel)
  - 1 due to pseudomonal sepsis (91 days post ide-cel)

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Phase II KarMMA-2 Cohort 2a: Ide-cel in MM with Early Relapse After Frontline ASCT

All Patients (N = 37)	CRS	Neurotoxicity
≥1 event of any grade, n (%) ▪≥1 grade 3/4 event	31 (83.8) 1 (2.7)	8 (21.6) 0
Median time to first onset, days (range)	2.0 (1-15)	3.0 (1-12)
Median duration, days (range)	3.0 (1-11)	3.5 (2-7)
Tocilizumab use, n (%) ▪1 dose ▪>1 dose	21 (56.8) 11 (29.7) 10 (27.0)	0 0 0
Glucocorticoid use, n (%)	6 (16.2)	3 (8.1)

- CRS was primarily managed with tocilizumab and glucocorticoids
  - 1 patient received anakinra
- Neurotoxicity was solely managed with glucocorticoids, when necessary

Usmani S, et al. *ASH. 2022*. Abstract 361.

Phase II KarMMA-2 Cohort 2c: Ide-cel in MM with Inadequate Response (<VGPR) Post-ASCT

Efficacy Outcome	All Patients (N = 31)
Best overall response	
ORR, % (95% CI)	87.1 (70.2-96.4)
VGPRR, % (95% CI)	83.9 (66.3-94.5)
CRR, % (95% CI)	74.2 (55.4-88.1)
Stringent CR, n (%)	15 (48.4)
CR, n (%)	8 (25.8)
VGPR, n (%)	3 (9.7)
PR, n (%)	1 (3.2)
Minimal response, n (%)	2 (6.5)
Stable disease, n (%)	2 (6.5)
Progressive disease, n	0

Time to event rates	All Patients (N = 31)
12 mo DOR rate, % (SE)	92.1 (5.4)
24 mo DOR rate, % (SE)	
12 mo PFS rate, % (SE)	90.1 (5.4)
24 mo PFS rate, % (SE)	83.1 (6.9)
12 mo OS rate, % (SE)	100 (0)
24 mo OS, % (SE)	100 (0)

Dhodapkar M, et al. *ASH. 2022*. Abstract 704.

Phase II KarMMA-2 Cohort 2c: Ide-cel in MM with Inadequate Response (<VGPR) Post-ASCT

AEs of special interest	All Patients (N = 31)	
	Cytokine release syndrome	Neurotoxicity
Number of pts with at least one event of any grade, n (%)	18 (58.1)	2 (6.5)
Number of pts with at least one grade 3/4 event, n (%)	0	1 (3.2)
Time to first onset, median, days (range)	2 (1-4)	10 (2-18)
Duration of event, median, days (range)	3 (1-7)	3.5 (2-5)

Dhodapkar M, et al. *ASH. 2022*. Abstract 704.

Phase II CARTITUDE-2: Cilta-cel in MM

Cohort A (n=40) 1-3 prior lines of therapy
Cohort B (n=20) Early relapse: < 12 mo after front line therapy or <12 mo after ASCT
Cohort C (n=20) RRMM after PI, IMiD, anti-CD38, and BCMA-targeting therapy
Cohort D (n=20) <CR after ASCT with or without consolidation in NDMM + lenalidomide
Cohort E (n=20) NDMM with no prior therapy and high-risk per ISS stage III criteria
Cohort F (n=40) NDMM with standard risk per ISS stage I & II criteria, and after initiation of therapy

Screening (1 to ≤28 days)

Induction if applicable

Cohort E
D-VRd

Apheresis

Lymphodepletion
Cy/Flu
(Day -5 to -3)

Cilta-cel infusion
(Target: 0.75 x 10^4 CAR+ T cells)

Follow-up

T-cell transduction and expansion to manufacture cilta-cel

Bridging therapy as needed

Consolidation

Cohort D + Len (2 years)

Cohort E + Len Dara (2 years)

Van de donk N, et al. *ASH. 2022*. Abstract 3354.

Phase II CARTITUDE-2 Cohort b: Cilta-cel in MM

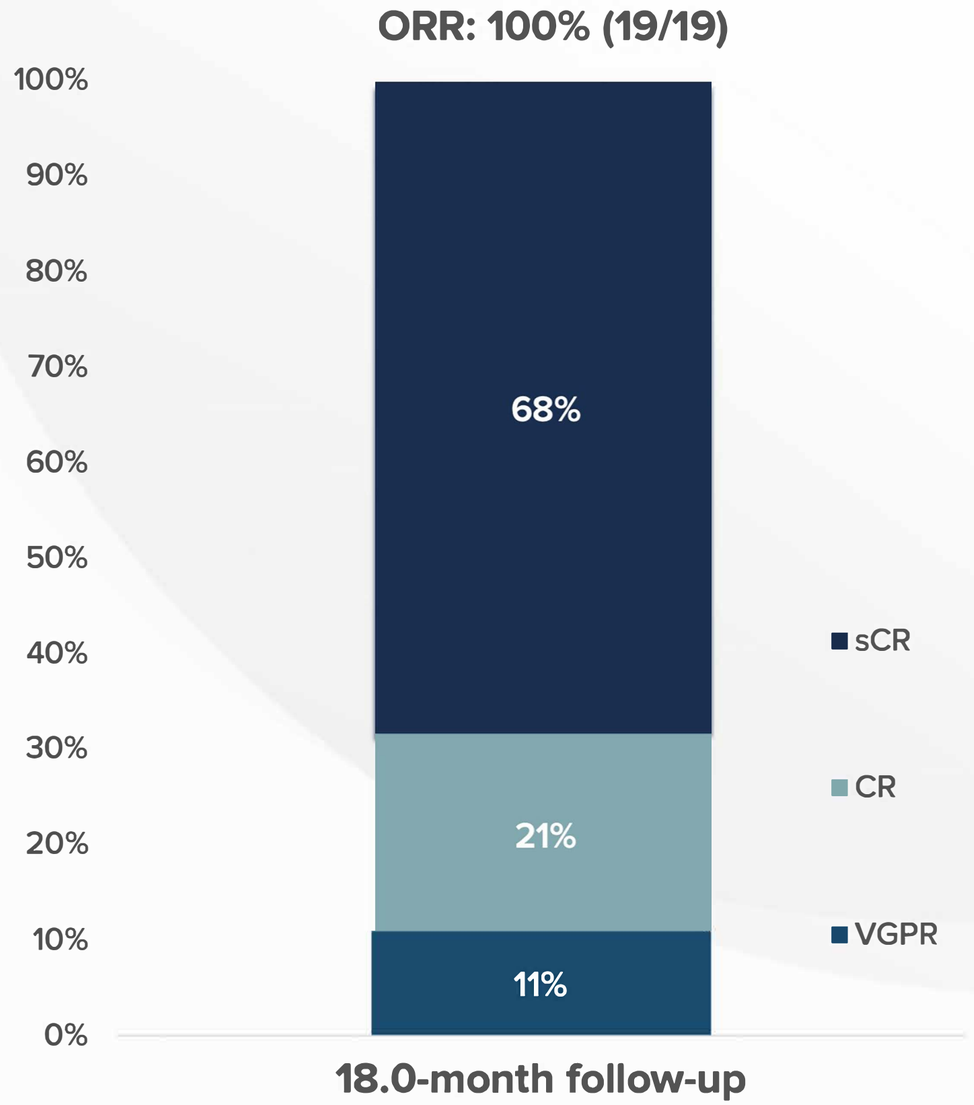
Characteristic	Total (N=20)
Median age, yr (range)	58 (44-67)
Male, n (%)	14 (74)
Race, n (%) ▪ White ▪ Black	 14 (74) 2 (11)
Extramedullary plasmacytomas, n (%)	3 (16)
Bone marrow plasma cells ≥60%, n (%)	4 (21)

Characteristic	Total (N=20)
High-risk cytogenetics, n (%) ▪ del(17p)	3 (20)
Mean previous regimens, no. (range)	1 (1-1)
Prior stem cell transplantation, n (%) ▪ Autologous ▪ Allogenic	 15 (79) 0
Triple-class-exposed disease	4 (21)
Triple-class-refractory disease	3 (16)
Penta-class-exposed disease	0
Penta-refractory disease	0
Refractory to last line of therapy, n (%)	15 (79)

Van de donk N, et al. *ASH. 2022*. Abstract 3354.

CARTITUDE-2: Response and Safety

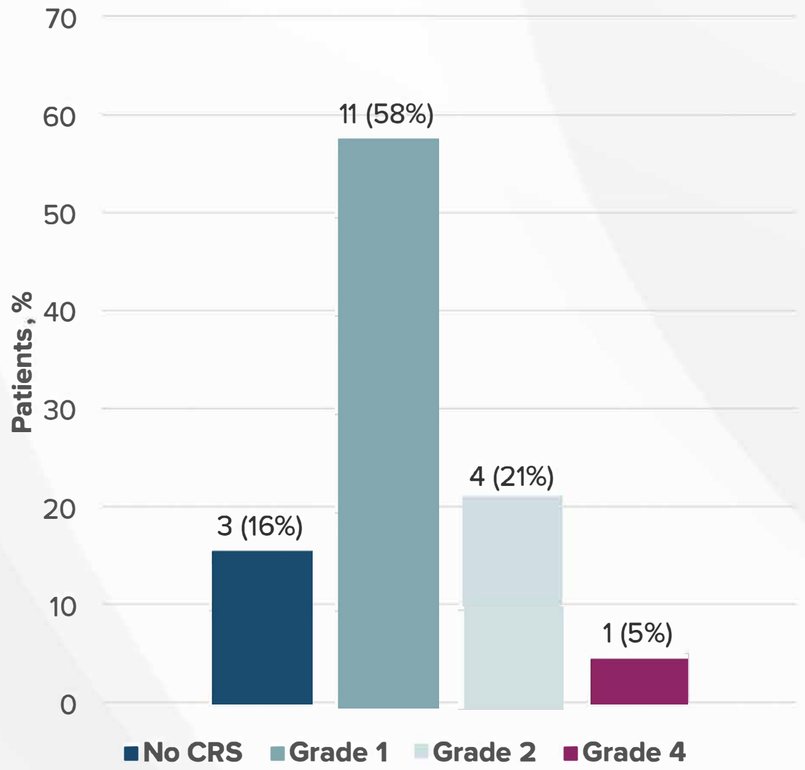
Cohort B – Relapse within 12 Months after ASCT or Start of Therapy



Van de donk N, et al. *ASH. 2022*. Abstract 3354.

CARTITUDE-2: CRS Cohort B – Relapse within 12 months after ASCT or Start of Therapy

Maximum CRS grade



- **Median time to CRS onset:** 8 days
- **Median duration of CRS:** 3.5 days

Management strategies for Parkinsonism

Parkinsonism risk factors (≥2)

- High tumor burden at baseline[a]
- Grade ≥2 CRS
- ICANS
- High CAR0T cell expansion and persistence

Implementation of patient management strategies

- More effective bridging therapy to reduce tumor burden
- Early and aggressive treatment of CRS and ICANS
- Handwriting assessments and extended monitoring

CARTITUDE program level

Approximately 250 patients have been diagnosed since implementation

- Implementation of patient management strategies in new and ongoing cilta-cel studies reduced incidence of parkinsonism from 6% to <0.5%

[a]Defined as high tumor burden when any of the following parameters were met: bone marrow plasma cells ≥80%, serum M-protein spike ≥5 g/dL, serum free light chain level ≥5000 mg/L

ASCT, autologous stem cell transplant; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome

Van de donk N, et al. *ASH. 2022*. Abstract 3354.