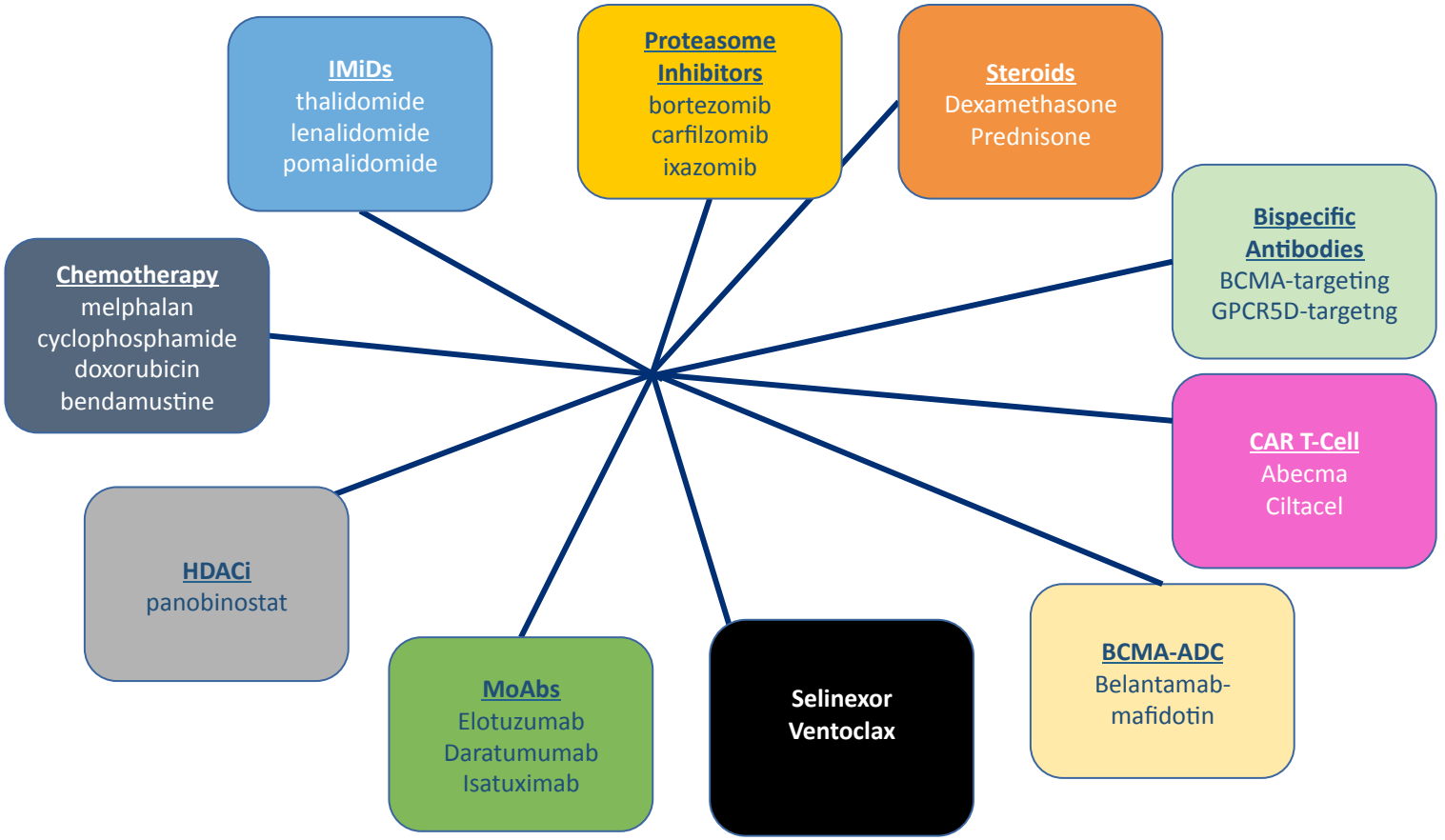
Best of ASH 2021 Myeloma abstracts

Mary Kwok, MD, FACP
Clinical Associate Professor, Hematology
University of Washington

What is new with induction therapy?

- What is the current standard of care?
- Should do you decide to treat with 3 drugs or 4 drugs?
- Can we use MRD to guide therapy decisions?

Myeloma Therapy: Currently Available Agents



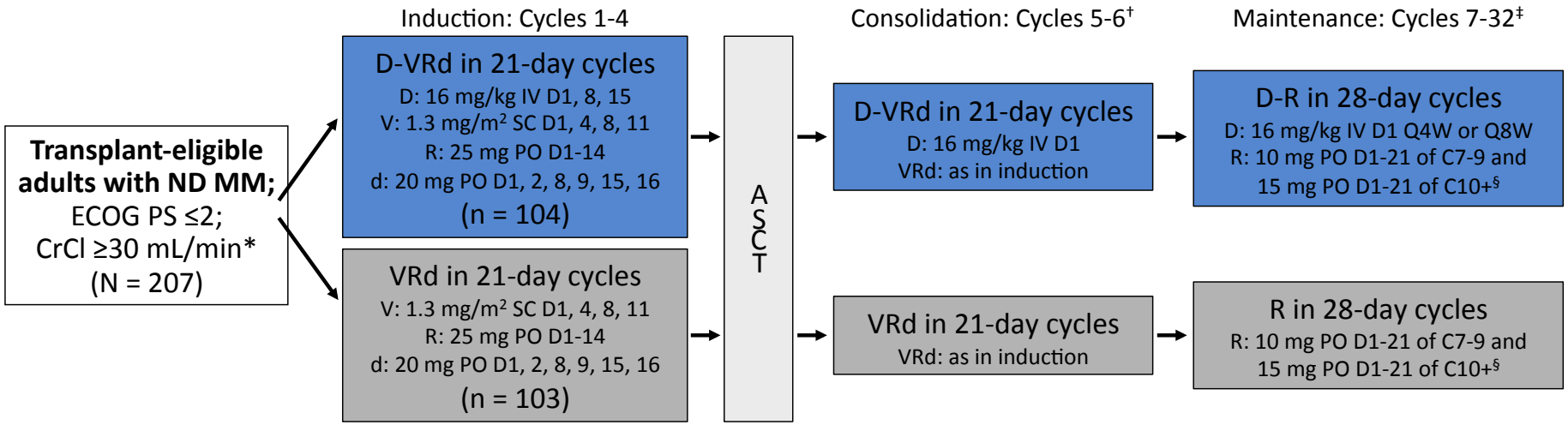
What is the current standard of care?

- Transplant eligible myeloma:
- RVD
- KRd?
- Dara-VRd?
- IRd?

- Transplant ineligible myeloma:
- Rd+daratumumab
- RVD-lite

Daratumumab + VRd for transplant-eligible newly diagnosed multiple myeloma: **the GRIFFIN trial**

- Multicenter, open-label, randomized phase II trial



*Lenalidomide dose was adjusted in patients with CrCl ≤50 mL/min. †Consolidation began 60-100 days after transplant. ‡Patients completing maintenance phase were permitted to continue single-agent lenalidomide. §15 mg administered only if tolerable.

Primary endpoint: sCR by end of consolidation with 1-sided $\alpha = 0.1$

Key secondary endpoints: rates of MRD negativity, ORR, ≥VGPR, CR, PFS, OS

Laubach. ASH 2021. Abstr 79.

Slide credit: clinicaloptions.com

GRIFFIN 2-Yr Maintenance Phase Update: Baseline Characteristics

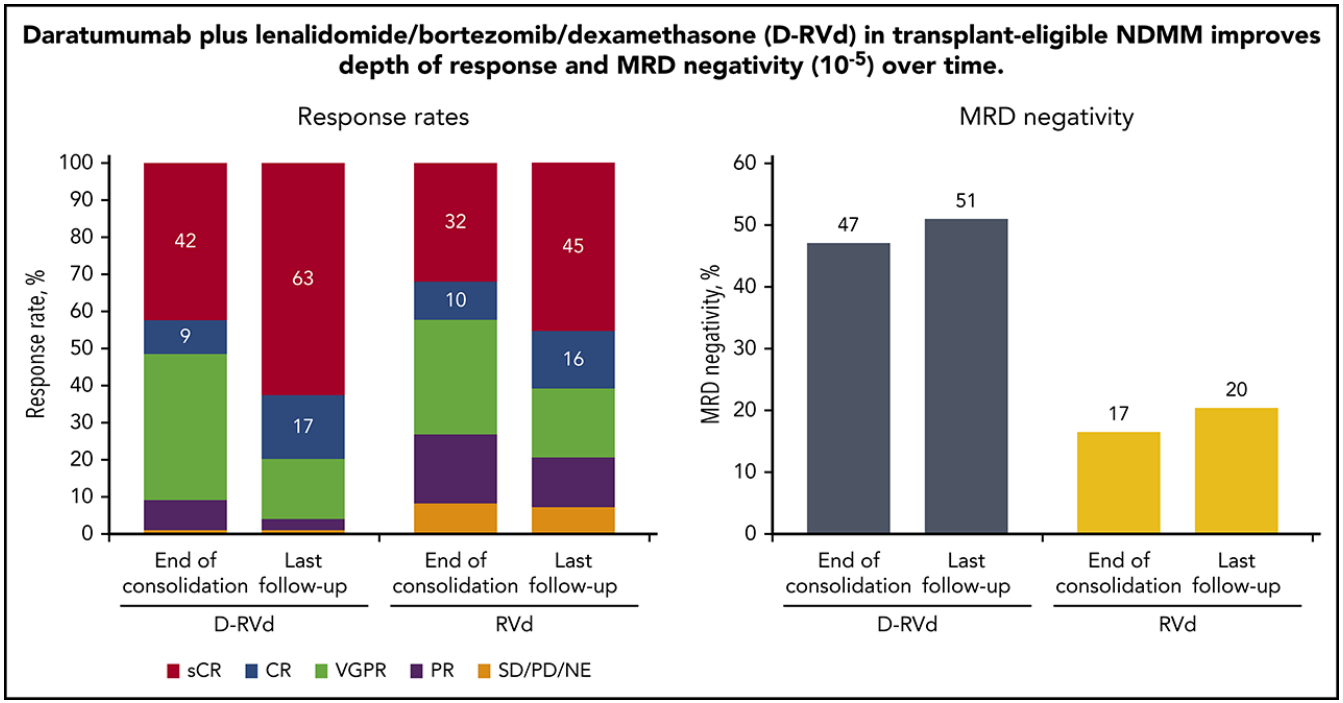
Characteristic	D-VRd (n = 104)	VRd (n = 103)
Median age, yr (range) ▪ ≥65 yr, n (%)	59 (29-70) 28 (27)	61 (40-70) 28 (27)
Male, %	58 (56)	60 (58)
ECOG PS, n (%) ▪ 0 ▪ 1 ▪ 2	(n = 101) 39 (39) 51 (50) 11 (11)	(n = 102) 40 (39) 52 (51) 10 (10)
Baseline CrCl, n (%) ▪ 30-50 mL/min ▪ >50 mL/min	 9 (9) 95 (91)	 9 (9) 94 (91)
Median time since MM diagnosis, mo	(n = 103) 0.7	(n = 102) 0.9

Characteristic	D-VRd (n = 104)	VRd (n = 103)
ISS stage, n (%) ▪ I ▪ II ▪ III ▪ Missing	 49 (47) 40 (38) 14 (13) 1 (1)	 50 (49) 37 (36) 14 (14) 2 (2)
Cytogenetic profile,* n (%) ▪ Standard risk ▪ High risk	(n = 98) 82 (84) 16 (16)	(n = 97) 83 (86) 14 (14)
Revised cytogenetic profile,† n (%) ▪ Standard risk ▪ High risk	(n = 98) 56 (57) 42 (43)	(n = 97) 60 (62) 37 (38)

Laubach. ASH 2021. Abstr 79.

Slide credit: clinicaloptions.com

Daratumumab + Vrd improves depth of response and MRD negativity over time



Voorhees, P et al.Daratumumab, lenalidomide, bortezomib, and dexamethasone for transplant-eligible newly diagnosed multiple myeloma: the GRIFFIN trial, Blood, 2020,

GRIFFIN 2-Yr Maintenance Phase Update: Response

Depth of Response, %	D-VRd (n = 100)		VRd (n = 97)	
	End of Consolidation	24 Mo Maintenance	End of Consolidation	24 Mo Maintenance
sCR	42	66*	32	47*
CR	9	16†	10	13†
≥CR	52	82	42	61
VGPR	39	14	31	18
PR	8	3	19	14
SD/PD/NE	1	1	8	7

†*P* = .0013 for comparison of CR for D-

Laubach. ASH 2021. Abstr 79.

Slide credit: clinicaloptions.com

GRIFFIN 2-Yr Maintenance Phase Update: Response deepened with time

Response, %	D-VRd (n = 100)					VRd (n = 97)				
	Induction	ASCT	Consol	1-Yr Maint	2-Yr Maint	Induction	ASCT	Consol	1-Yr Maint	2-Yr Maint
sCR	12	21	42	63	66*	7	14	32	46	47*
CR	7	6	9	17	16†	6	5	10	13	13†
≥CR	19	27	52	80	82	13	19	42	60	61
VGPR	53	60	39	14	14	43	46	31	19	18
PR	26	12	8	4	3	35	26	19	14	14
SD/PD/NE	2	1	1	2	1	8	8	8	7	7

†*P* = .0013 for comparison of CR for D-

Laubach. ASH 2021. Abstr 79.

Slide credit: clinicaloptions.com

GRIFFIN 2-Yr Maintenance Phase Update: MRD Status

MRD Negativity After 24-Mo Maintenance, %	D-VRd (n = 104)	VRd (n = 103)	*P* Value
MRD at 10^{-5} threshold, %			
▪ ITT population	64	30	<.0001
▪ ≥CR	78	47	.0003
MRD at 10^{-6} threshold, %			
▪ ITT population	36	15	.0007
▪ ≥CR	43	22	.0121
Sustained MRD negativity lasting ≥12 mo, %	44.2	12.6	<.0001

Laubach. ASH 2021. Abstr 79.

Slide credit: clinicaloptions.com

GRIFFIN 2-Yr Maintenance Phase Update: MRD Status

MRD Negativity After 24-Mo Maintenance, %	D-VRd (n = 104)	VRd (n = 103)	*P* Value
MRD at 10^{-5} threshold, %			
▪ ITT population	64	30	<.0001
▪ ≥CR	78	47	.0003
MRD at 10^{-6} threshold, %			
▪ ITT population	36	15	.0007
▪ ≥CR	43	22	.0121
Sustained MRD negativity lasting ≥12 mo, %	44.2	12.6	<.0001

MRD Neg (10^{-5}) After 24-Mo Maintenance, n/N (%)		D-VRd (n = 104)	VRd (n = 103)	OR (95% CI)
Cytogenetic risk	▪ High risk	4/14 (28.6)	7/16 (43.8)	1.94 (0.42-8.92)
	▪ Standard risk	27/83 (32.5)	58/82 (70.7)	5.01 (2.59-9.71)
Revised cytogenetic risk	▪ High risk	12/37 (32.4)	23/42 (54.8)	2.52 (1.01-6.32)
	▪ Standard risk	19/60 (31.7)	42/56 (75.0)	6.47 (2.87-14.60)

Laubach. ASH 2021. Abstr 79.

Slide credit: clinicaloptions.com

GRIFFIN 2-Yr Maintenance Phase Update: PFS and OS

PFS*	D-VRd (n = 104)	VRd (n = 103)	HR (95% CI)
24-mo PFS, %	91.6	88.9	0.46 (0.21-1.01)
36-mo PFS, %	89.7	81.2	
OS	**D-VRd (n = 104)**	**VRd (n = 103)**	**HR (95% CI)**
24-mo OS, %	94.8	93.3	0.90 (0.32-2.57)
36-mo OS, %	92.6	92.2	

Slide credit: clinicaloptions.com

GRIFFIN : Common Treatment emergent adverse events

TEAE, %		D-VRd (n = 99)		VRd (n = 102)	
		Any	Grade 3/4	Any	Grade 3/4
Hematologic	▪ Neutropenia	64	46	40	24
	▪ Thrombocytopenia	44	15	35	9
	▪ Leukopenia	39	17	29	8
	▪ Anemia	37	9	32	6
	▪ Lymphopenia	31	23	28	23
Nonhematologic	▪ Fatigue	72	7	62	6
	▪ Upper respiratory tract infection	68	3	50	2
	▪ Diarrhea	67	7	55	5
	▪ Peripheral neuropathy	63	7	76	8
	▪ Cough	54	0	30	0
	▪ Nausea	52	2	50	1
	▪ Constipation	52	2	41	1
	▪ Pyrexia	48	3	32	3
	▪ Insomnia	45	2	30	1
	▪ Back pain	41	2	35	4
	▪ Arthralgia	37	1	37	2
	▪ Peripheral edema	36	2	36	3
	▪ Vomiting	32	3	28	0
	▪ Headache	32	5	24	1
	▪ Dyspnea	24	2	30	5
Infusion-related reactions		44	6	--	--

Laubach. ASH 2021. Abstr 79.

Slide credit: clinicaloptions.com

GRIFFIN 2-Yr Maintenance Phase Update: Key AEs With First Onset During Maintenance Therapy (Cycle 7+)

TEAE, %		D-VRd, D-R Maint (n = 89)		VRd, R Maint (n = 71)	
		Any	Grade 3/4	Any	Grade 3/4
Infection during maintenance		26	18	32	21
Most common infections	▪ Upper respiratory tract infection	53	2	41	3
	▪ Pneumonia	16	7	15	13
	▪ Urinary tract infection	11	0	3	0
	▪ Sinusitis	10	0	10	0
	▪ Influenza	10	0	7	0
	▪ Nasopharyngitis	10	0	3	0
	▪ Bronchitis	8	1	7	1
	▪ Cellulitis	8	1	3	1
Secondary primary malignancy		4	--	3	--
Type of secondary primary malignancy	▪ SCC of the skin	3		0	
	▪ Basal cell carcinoma	2		0	
	▪ Nasal cavity cancer	1		0	
	▪ SCC	1		0	
	▪ Breast cancer	1		0	
	▪ Malignant melanoma in situ	0		1	
	▪ Nodular melanoma	0		1	
	▪ Uterine cancer	0		1	

Laubach. ASH 2021. Abstr 79.

Slide credit: clinicaloptions.com

GRIFFIN 2-Yr Maintenance Phase Update: Conclusions

- D-VRd followed by D-R maintenance continued to show significant improvement in sCR and depth of response vs VRd followed by R maintenance[1]
  - **Patients with sCR after 24-mo maintenance: 66.0% vs 47.4% (*P* = .0096)**
  - **Patients with MRD negativity after 24-mo maintenance at 10^{-5} threshold: 64.4% vs 30.1% (*P* <.0001); at 10^{-6} threshold: 35.6% vs 14.6% (*P* = .0007)**
- Safety at 24 mo of maintenance cutoff was consistent with earlier analyses with no new safety concerns identified[2,3]
- **Investigators conclude results support use of D-VRd induction and consolidation with D-R maintenance in transplant-eligible patients with ND MM**
  - Phase III PERSEUS trial ongoing (NCT03710603)

1. Laubach. ASH 2021. Abstr 79. 2. Voorhees. Blood. 2020;136:936. 3. Kaufman. ASH 2020. Abstr 549.

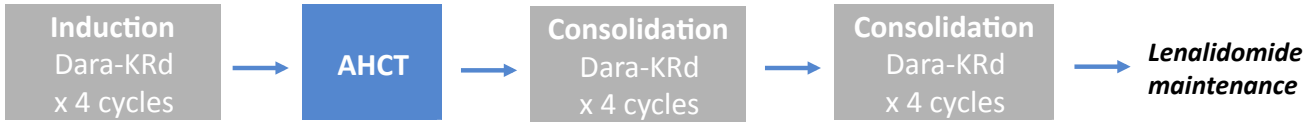
What else do we consider?

- Higher rates of neutropenia with 4 drug combinations
- Similar rates of grade 3 infection
- Financial toxicity
- Stem cell collection is impacted by daratumumab
  - Collect stem cells early if possible, after 4 cycles

MASTER trial: Daratumumab + KRd, with MRD Response-Adapted Therapy in Newly Diagnosed MM

- Multicenter, single-arm phase II trial, 5 US sites, median follow-up was 25.1 months

Untreated* patients with NDMM and measurable disease, ECOG PS 0-2, CrCl ≥ 40 mL/min, without significant cardiopulmonary disease or current/prior malignancy
(N = 123)



MRD assessment after each treatment phase; pts with confirmed (2nd) MRD-negative status (< 10^{-5}) entered treatment-free observation phase with MRD assessment at 24 and 72 wks after EOT.

Dara-KRd dosing: daratumumab 16 mg/m^2 on Days 1,8,15,22 (Days 1,15 of Cycles 3-6; Day 1 Cycle > 6); carfilzomib 56 mg/m^2 Days 1,8,15; lenalidomide 25 mg Days 1-21; dexamethasone 40 mg PO Days 1,8,15,22. *1 VCD cycle permitted.

- Primary endpoint: MRD-negative remission (< 10^{-5}) on NGS assay in pts receiving induction, AHCT, and response-adapted consolidation
- Secondary endpoints: safety, imaging frequency plus remission, MRD status post-AHCT, IMWG response, loss of MRD negativity in pts with no maintenance therapy
- Exploratory endpoint: MRD-negative rates on NGS assay (threshold < 10^{-6})

Costa. ASH 2019. Abstr 860.

Slide credit: clinicaloptions.com

MASTER: Baseline Characteristics

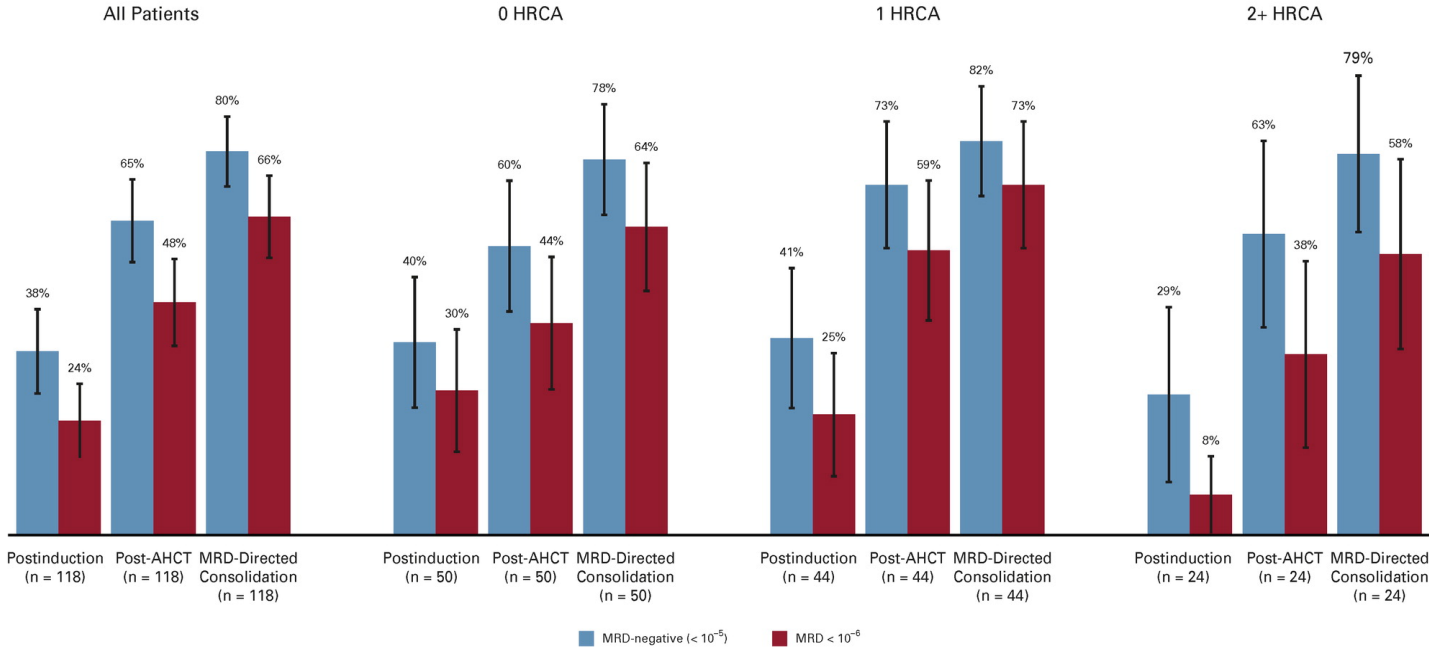
Parameter	≥ 2 Cycles of Induction (N = 81)	≥ Post AHCT (N = 42)
Male, n (%)	41 (51)	22 (52)
Median age, yrs (range) ▪ ≥ 70 yrs, %	61 (36-78) 18 (22)	61 (36-78) 10 (24)
Race/ethnicity, n (%) ▪ White ▪ Minority	 64 (79) 17 (21)	 31 (74) 11 (26)
ECOG PS, n (%) ▪ 0-1 ▪ 2	 64 (79) 17 (21)	 29 (69) 13 (31)
ISS, n (%) ▪ 1 ▪ 2 ▪ 3	 32 (40) 33 (41) 16 (20)	 14 (33) 18 (43) 10 (24)

Parameter	≥ 2 Cycles of Induction (N = 81)	≥ Post AHCT (N = 42)
High-risk FISH [t(4;14), t (14;16) or del17p]	23 (28)	12 (29)
High-risk FISH +1q [+1q, t (4;14), t(14;16), del17p]	42 (52)	22 (52)
LDH > ULN	15 (19)	9 (21)
R-ISS, n (%) ▪ 1 ▪ 2 ▪ 3	 25 (31) 43 (53) 13 (16)	 12 (29) 21 (50) 9 (21)

Costa. ASH 2019. Abstr 860.

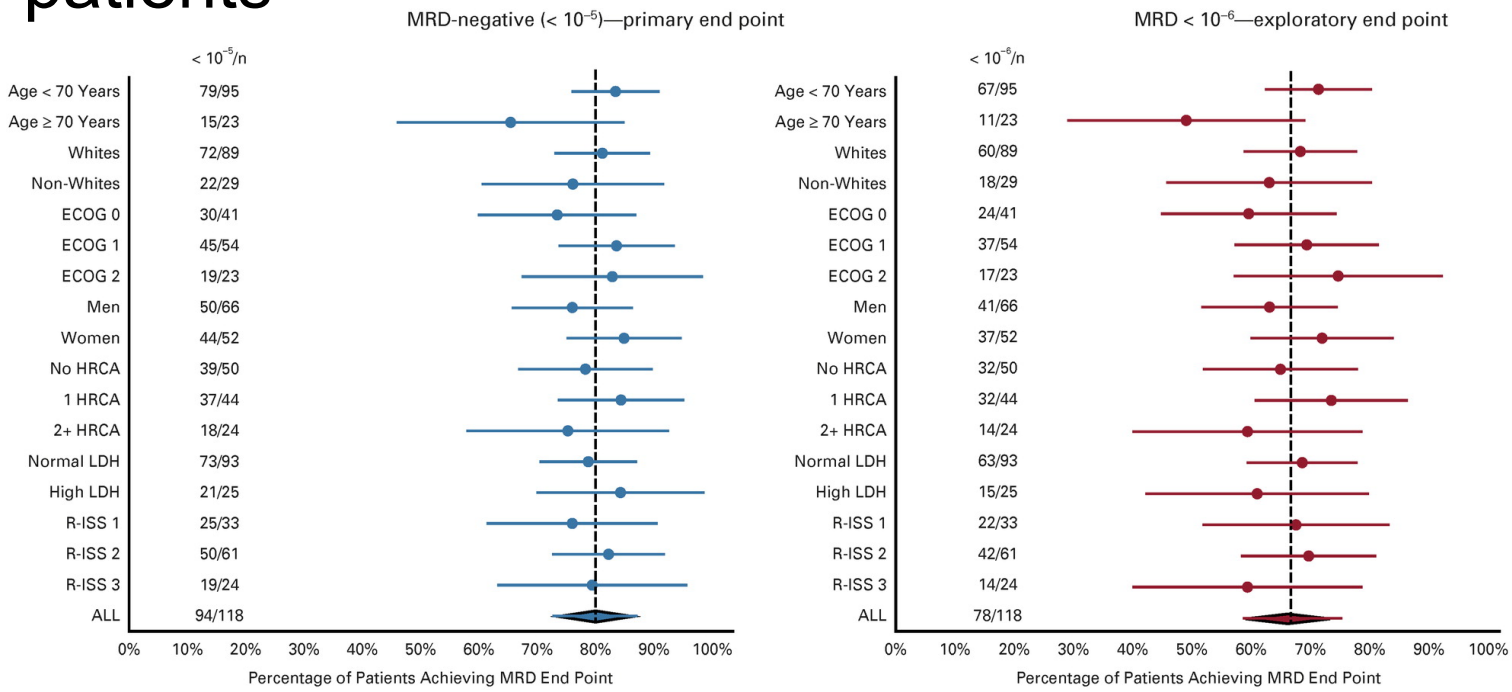
Slide credit: clinicaloptions.com

MRD negativity according to phase of therapy and # of high risk cytogenetic abnormalities



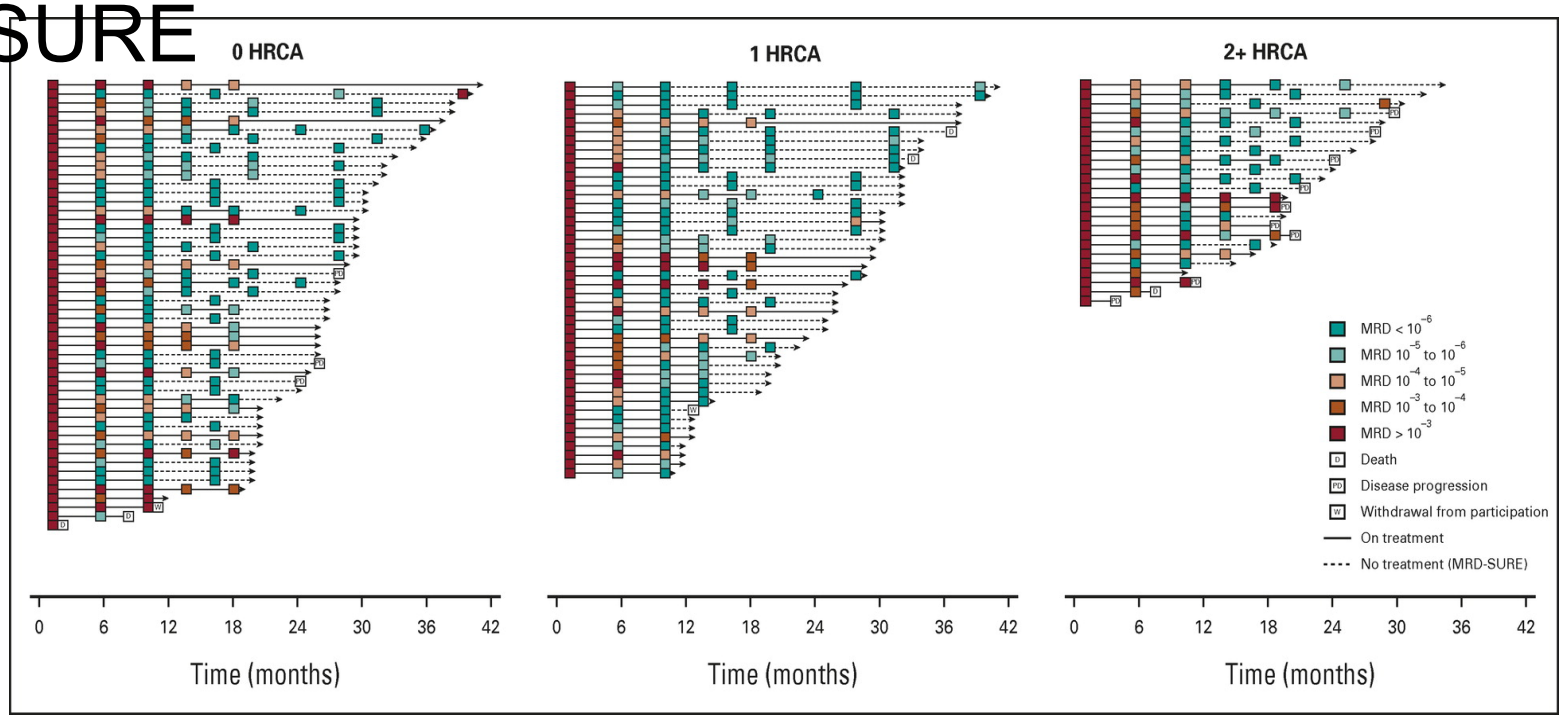
Published in: Luciano J. Costa; Saurabh Chhabra; Eva Medvedova; Bhagirathbhai R. Dholaria; Timothy M. Schmidt; Kelly N. Godby; Rebecca Silbermann; Binod Dhakal; Susan Bal; Smith Giri; Anita D'Souza; Aric Hall; Pamela Hardwick; James Omel; Robert F. Cornell; Parameswaran Hari; Natalie S. Callander; *Journal of Clinical Oncology* Ahead of Print
DOI: 10.1200/JCO.21.01935

Forest plot of MRD end points by subsets of patients



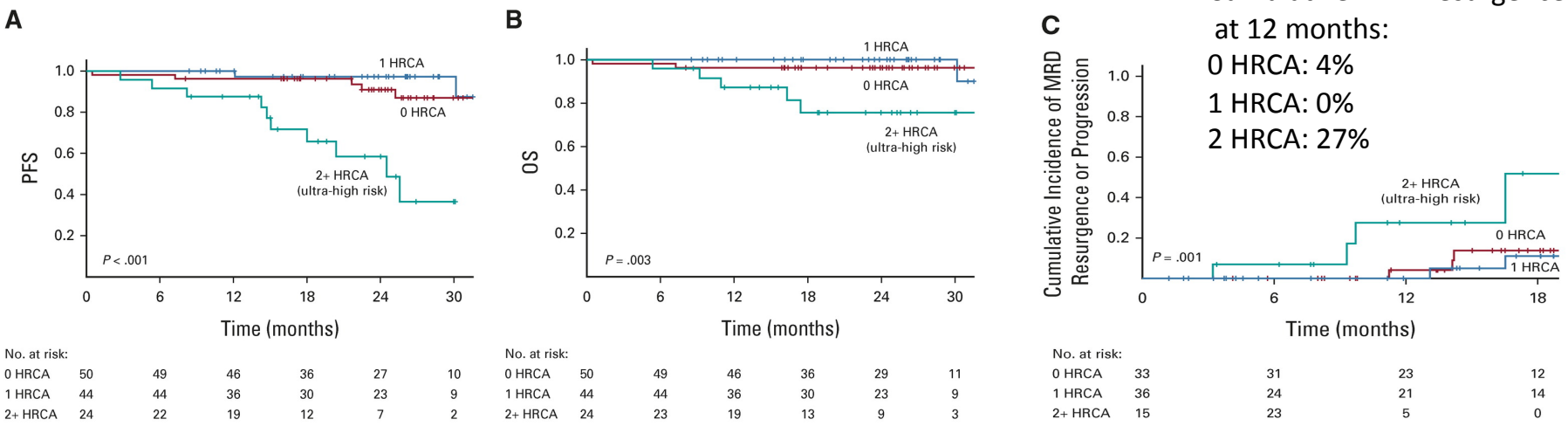
Published in: Luciano J. Costa; Saurabh Chhabra; Eva Medvedova; Bhagirathbhai R. Dholaria; Timothy M. Schmidt; Kelly N. Godby; Rebecca Silbermann; Binod Dhakal; Susan Bal; Smith Giri; Anita D'Souza; Aric Hall; Pamela Hardwick; James Omel; Robert F. Cornell; Parameswaran Hari; Natalie S. Callander; *Journal of Clinical Oncology* Ahead of Print
DOI: 10.1200/JCO.21.01935

Patient level depth of response during therapy and treatment cessation with MRD-SURE



Published in: Luciano J. Costa; Saurabh Chhabra; Eva Medvedova; Bhagirathbhai R. Dholaria; Timothy M. Schmidt; Kelly N. Godby; Rebecca Silbermann; Binod Dhakal; Susan Bal; Smith Giri; Anita D'Souza; Aric Hall; Pamela Hardwick; James Omel; Robert F. Cornell; Parameswaran Hari; Natalie S. Callander; *Journal of Clinical Oncology* Ahead of Print
DOI: 10.1200/JCO.21.01935

PFS, OS and MRD resurgence by # of HRCA



Cumulative MRD resurgence at 12 months:

0 HRCA: 4%

1 HRCA: 0%

2 HRCA: 27%

Published in: Luciano J. Costa; Saurabh Chhabra; Eva Medvedova; Bhagirathbhai R. Dholaria; Timothy M. Schmidt; Kelly N. Godby; Rebecca Silbermann; Binod Dhakal; Susan Bal; Smith Giri; Anita D'Souza; Aric Hall; Pamela Hardwick; James Omel; Robert F. Cornell; Parameswaran Hari; Natalie S. Callander; *Journal of Clinical Oncology* Ahead of Print
DOI: 10.1200/JCO.21.01935

MASTER: Safety

Most Common Hematologic TRAEs, n (%)	All Grades	Grade ≥ 3
Lymphopenia	31 (38)	19 (23)
Neutropenia	28 (35)	20 (25)
Thrombocytopenia	16 (20)	4 (5)
Anemia	15 (19)	9 (11)

Most Common Nonhematologic TRAEs, n (%)	All Grades	Grade ≥ 3
Musculoskeletal pain	50 (62)	0 (0)
Infections	47 (58)	10 (12)
Fatigue	45 (56)	1 (1)
Rash/cutaneous AE	45 (56)	3 (4)
Nausea/vomiting	41 (51)	0 (0)
Infusion-related reaction	31 (38)	2 (2)
Constipation	26 (32)	0 (0)
Peripheral neuropathy	23 (28)	2 (2)
Dyspnea	19 (23)	1 (1)
Hypertension	16 (20)	3 (4)
Venous thromboembolism	7 (9)	1 (1)

- 18 SAEs: pneumonia (n = 5), fever and neutropenia (n = 2), pulmonary embolism (n = 1), aHUS (n = 1), IRR (n = 1), atrial fibrillation (n = 1), other (n = 7)
- 2 deaths: metapneumovirus pneumonia 9 days pos AHCT, unwitnessed sudden death 58 days post AHCT
- No other d/c's due to toxicity

Costa. ASH 2019. Abstr 860.

Slide credit: clinicaloptions.com

MASTER trial: conclusions

- Treatment with Dara-KRd, AHCT and MRD response adapted consolidation leads to high rates of MRD negative in NDMM
- 80% of patients achieved MRD negativity
- 66% of patients achieved MRD $<10^{-6}$
- 71% of patients achieved two consecutive MRD negative assessments and began treatment-free MRD surveillance (MRD-SURE)
  - MRD resurgence at 12 months was 6.4%
    - 4% for 0 HRCA
    - 0% for 1 HRCA
    - 27% for >1 HRCA
- For patients with 0-1 HRCA, this creates an opportunity for MRD surveillance as an alternative to indefinite maintenance

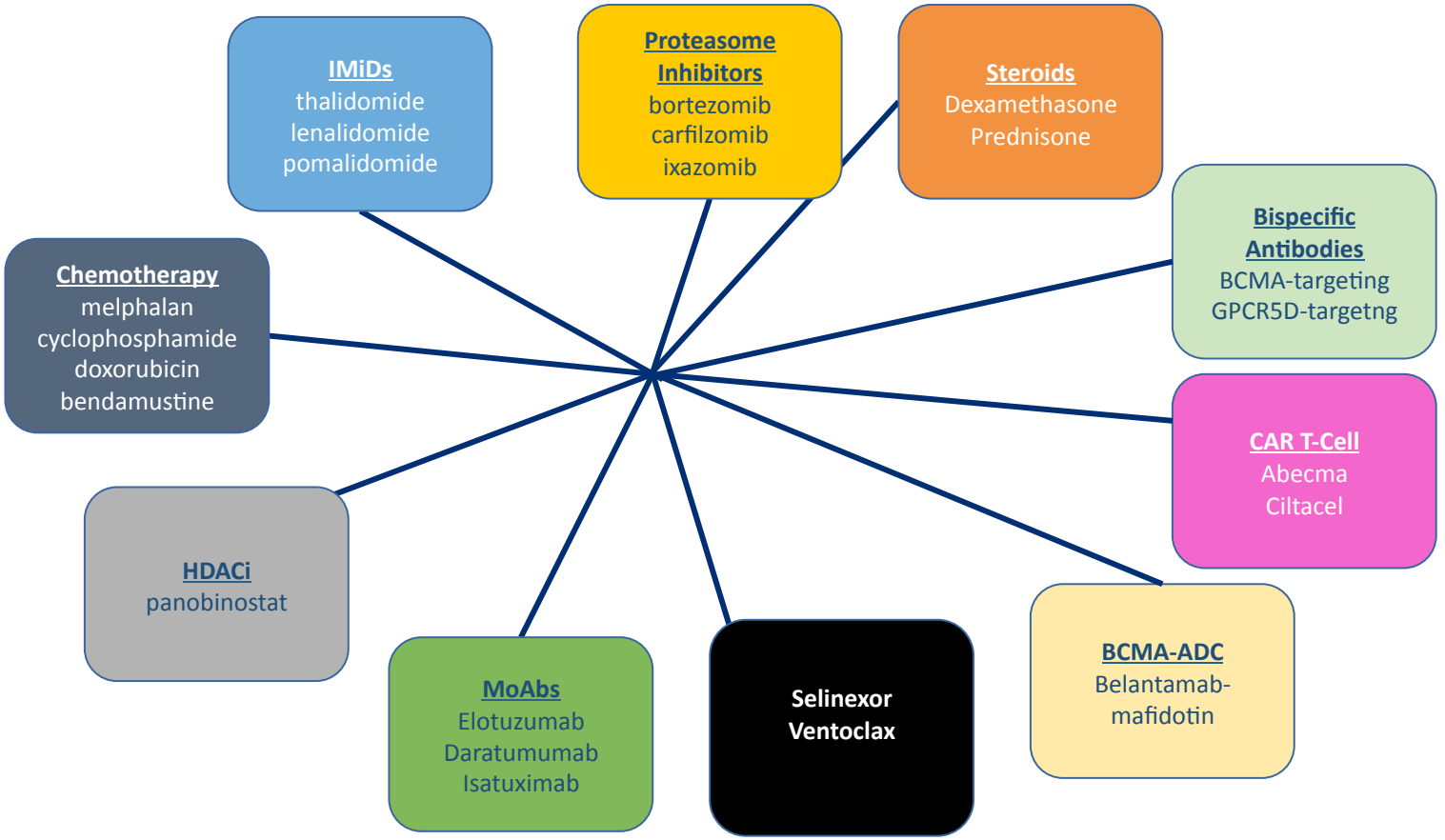
Relapsed/Refractory Myeloma

New triplets

Bispecific antibodies

CAR T-cell therapies

Myeloma Therapy: Currently Available Agents



- What options are available to patients who progresses after initial therapy?

Triplets are still better than doublets in the R/R setting

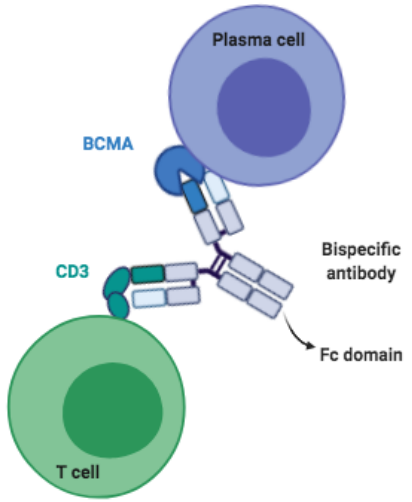
- CASTOR study:
  - Daratumumab + Vd has super PFS compared to Vd
- POLLUX study:
  - Daratumumab + Rd has superior PFS compared to Rd
- APOLLO study:
  - Daratumumab + Pd has superior PFS compared to Pd
- **CANDOR study:**
  - **Daratumumab + Kd has superior PFS compared to Kd**

- ICARIA study
  - Isatuximab + Pd has superior PFS compared to Pd
- IKEMA study
  - Isatuximab + Pd has superior PFS compared to Kd

Bispecific antibodies

- BCMA-targeting Bispecific antibodies
  - Teclistamab
  - GSK2857916
  - REGN5458
  - CC-93269

- GPRC5D
  - Talquetamab



Updated Results From Phase I/II MajesTEC-1 Study: Teclistamab, a BCMA x CD3 Bispecific Antibody, in Relapsed/Refractory Multiple Myeloma

CCO Independent Conference Coverage Highlights*

of the *2021 ASH Annual Meeting, December 11-14, 2021*

Atlanta, Georgia

*CCO is an independent medical education company that provides state-of-the-art medical information to healthcare professionals through conference coverage and other educational programs.

This program is supported by educational grants from AbbVie; AstraZeneca; Daiichi Sankyo, Inc.; GlaxoSmithKline; Incyte Corporation; Jazz Pharmaceuticals; Merck Sharp & Dohme Corp.; and Novartis Pharmaceuticals Corporation.

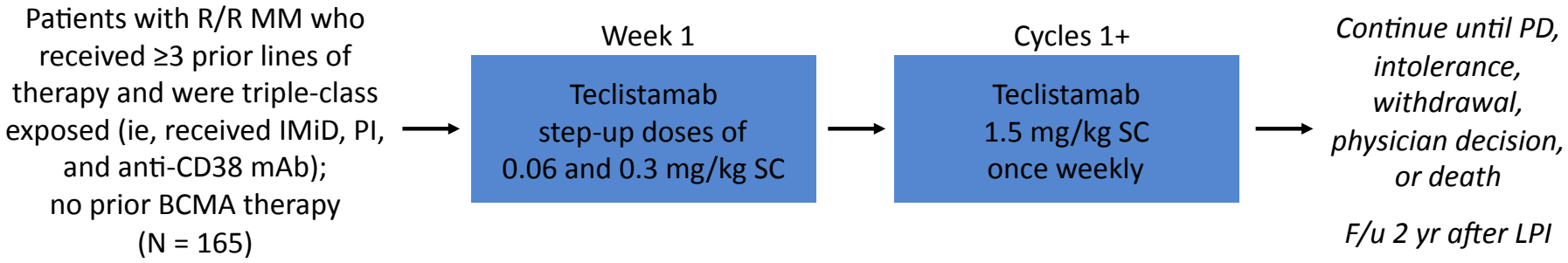
MajesTEC-1: Background

- Triple class–exposed patients with R/R MM still in need of novel therapies despite newly approved agents[1,2]
- Teclistamab (JNJ-64007957): off-the-shelf, investigational BCMA x CD3 bispecific antibody[3,4]
  - Engineered to enhance the immune response against tumor cells by binding to CD3 on T-cells and BCMA on plasma cells, promoting T-cell–mediated killing of BCMA-positive myeloma cells
- Phase I/II MajesTEC-1: first-in-human, dose-escalation/dose-expansion trial of teclistamab SC in patients with R/R MM[3,4]
  - Initial phase I results identified RP2D as 1.5 mg/kg QW with step-up doses of 0.06 and 0.3 mg/kg[3]
- Current analysis reports updated phase I/II MajesTEC-1 data for teclistamab SC in patients with R/R MM at 1.5-mg/kg dose[4]

1. Mateos. ASCO 2021. Abstr 8041. 2. Costa. ASCO 2021. Abstr 8030. 3. Usmani. Lancet. 2021;398:665. 4. Moreau. ASH 2021. Abstr 896.

MajesTEC-1: Study Design

- First-in-human, open-label, dose-escalation/dose-expansion phase I/II trial
  - Median follow-up: 7.8 mo (range: 0.5+ to 18); data cutoff: September 7, 2021



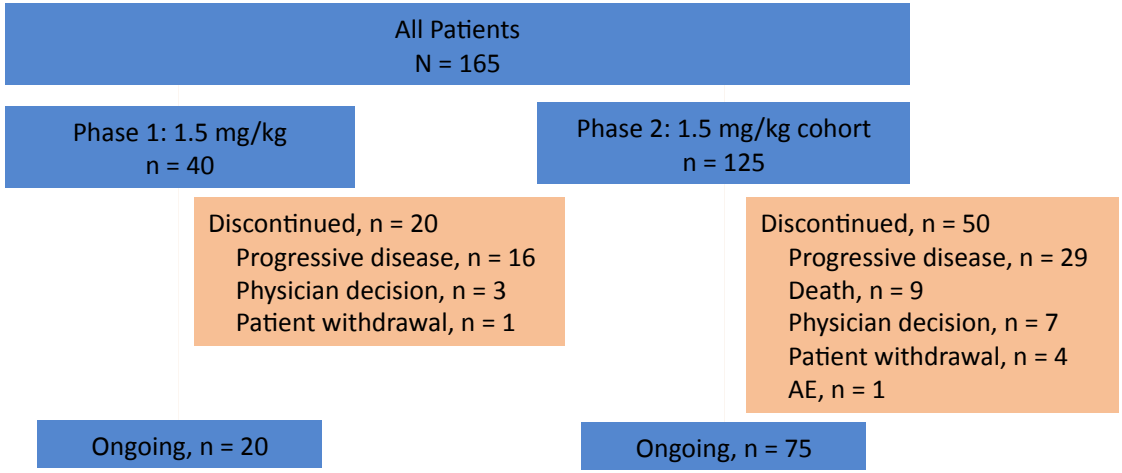
Primary endpoint: ORR

Key secondary endpoints: DoR, ≥VGPR, ≥CR, sCR, TTR, MRD status, PFS, OS, safety, PK, immunogenicity, PROs

Moreau. ASH 2021. Abstr 896. NCT03145181. NCT04557098.

Slide credit: clinicaloptions.com

MajesTEC-1: Treatment Disposition



Patients, n	Phase I Cohort	Phase II Cohort	Total Patients
Primary efficacy analysis*	40	110	150
Primary safety analysis†	40	125	165

*Includes all patients who received ≥1 dose before March 18, 2021.
†Includes all patients enrolled before data cutoff of September 7, 2021.

- Median treatment duration for patients in primary safety analysis: 5.9 mo (range: 0.2-18.0)
  - 46.7% received ≥6 mo of treatment
  - 16.4% received ≥9 mo of treatment
- No dose reductions

Moreau. ASH 2021. Abstr 896.

Slide credit: clinicaloptions.com

MajesTEC-1: Baseline Characteristics

Characteristic	All Patients (N = 165)
Median age, yr (range)	64.0 (33-84)
▪ Age ≥75 yr, n (%)	24 (14.5)
Male, n (%)	96 (58.2)
Race, n (%)	
▪ White	134 (81.2)
▪ Black	21 (12.7)
▪ Other	10 (6.1)
BM plasma cells ≥60%, n (%)*	18 (11.3)
Extramedullary plasmacytomas ≥ 1, n (%)†	28 (17.0)
High-risk cytogenetics, n (%)‡	38 (25.9)
ISS stage at BL, n (%)§	
▪ I	85 (52.5)
▪ II	57 (35.2)
▪ III	20 (12.3)

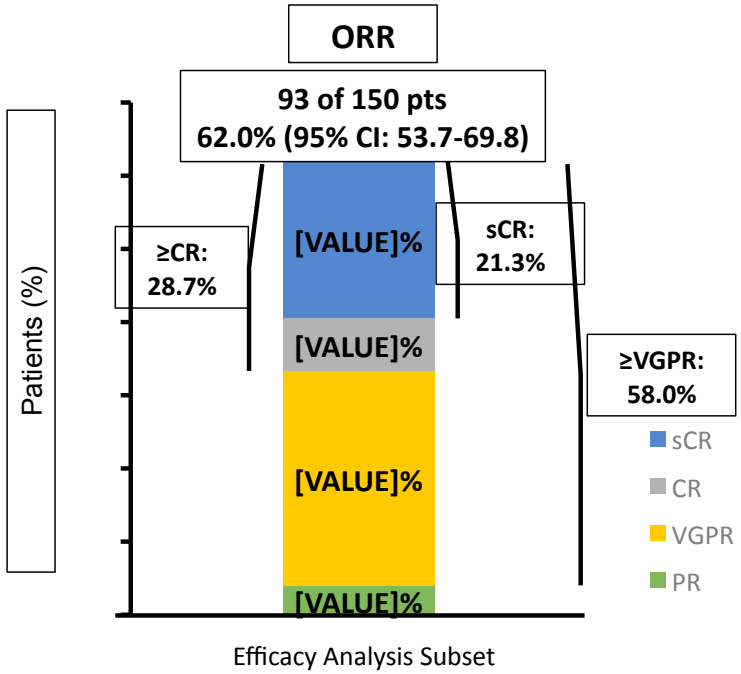
Characteristic	All Patients (N = 165)
eGFR < 60 mL/min/1.73 m^2, n (%)	44 (26.7)
Median time since dx, yr (range)	6.0 (0.8-22.7)
Median prior lines of therapy, n (range)	5 (2-14)
Prior SCT, n (%)	135 (81.8)
Exposure status, n (%)	
▪ Triple class exposed‖	165 (100)
▪ Penta drug exposed¶	116 (70.3)
▪ Selinexor	6 (3.6)
Refractory status, n (%)	
▪ Triple class refractory‖	128 (77.6)
▪ Penta drug refractory¶	50 (30.3)
▪ Refractory to last line of therapy	148 (89.7)

*n = 160; includes bone marrow biopsy and aspirate. †Included soft-tissue plasmacytomas not associated with bone. ‡n = 147; del(17p), t(4:14), and/or t(14;16). §n = 162. ‖≥1 PI, ≥1 IMiD, ≥1 anti-CD38 mAb. ¶≥2 PI, ≥2 IMiD, ≥1 anti-CD38 mAb.

Moreau. ASH 2021. Abstr 896.

Slide credit: clinicaloptions.com

MajesTEC-1: Efficacy Outcomes



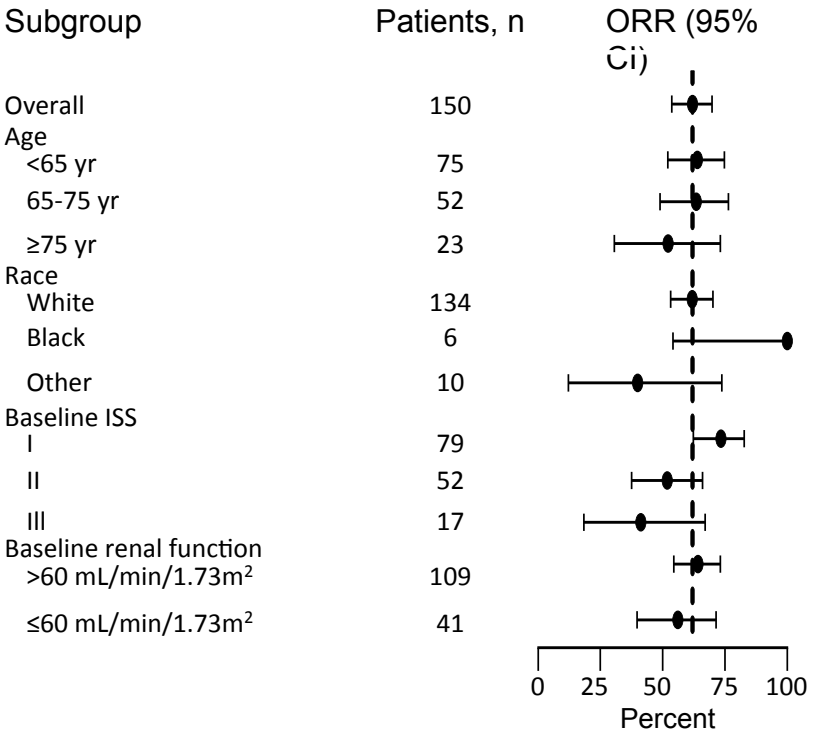
Median follow-up: 7.8 mos (range: 0.5+ to 18)

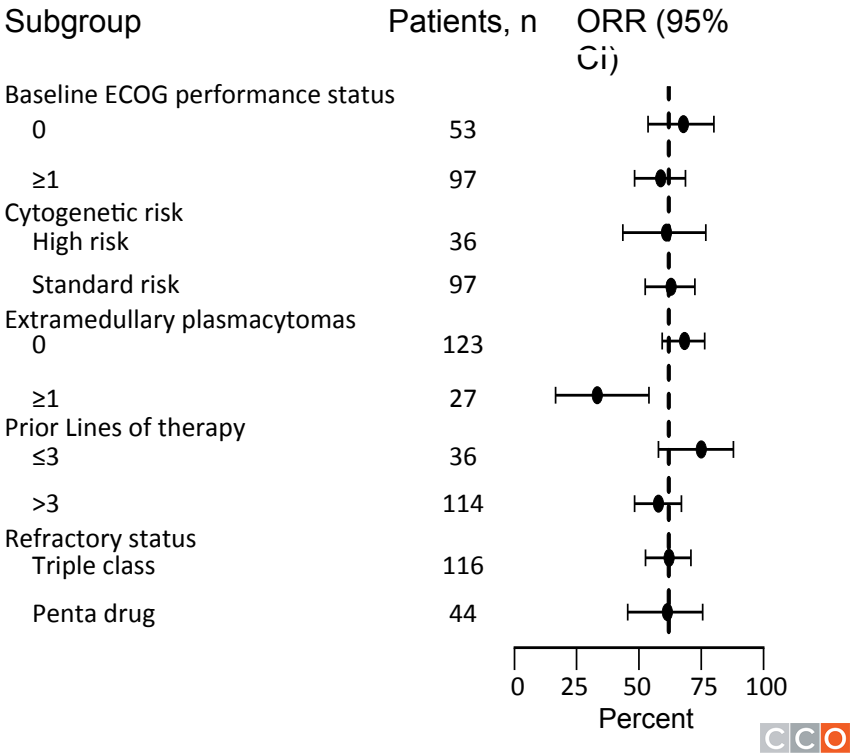
Event	All Patients (N = 165)
MRD negativity, n (%, 95% CI)	(n = 150)
▪ At 10^{-5}	37 (24.7; 18.0-32.4)
▪ At 10^{-6}	25 (16.7; 11.1-23.6)
MRD negativity with ≥CR, %	41.9
Median TTR, mo (range)	1.2 (0.2-5.5)
Median DoR, mo	Not yet reached
EFS rates, % (95% CI)	
▪ 6-Mos	92.5 (80.6-97.2)
▪ 9-Mos	85.9 (70.0-93.7)
PFS rates, % (95% CI)	
▪ 6-Mos	64.4 (56.0–71.7)
▪ 9-Mos	58.5 (48.8–67.0)
Median OS	Not yet reached

Moreau. ASH 2021. Abstr 896. Reproduced with permission.

Slide credit: clinicaloptions.com

MajesTEC-1: ORR Across Subgroups

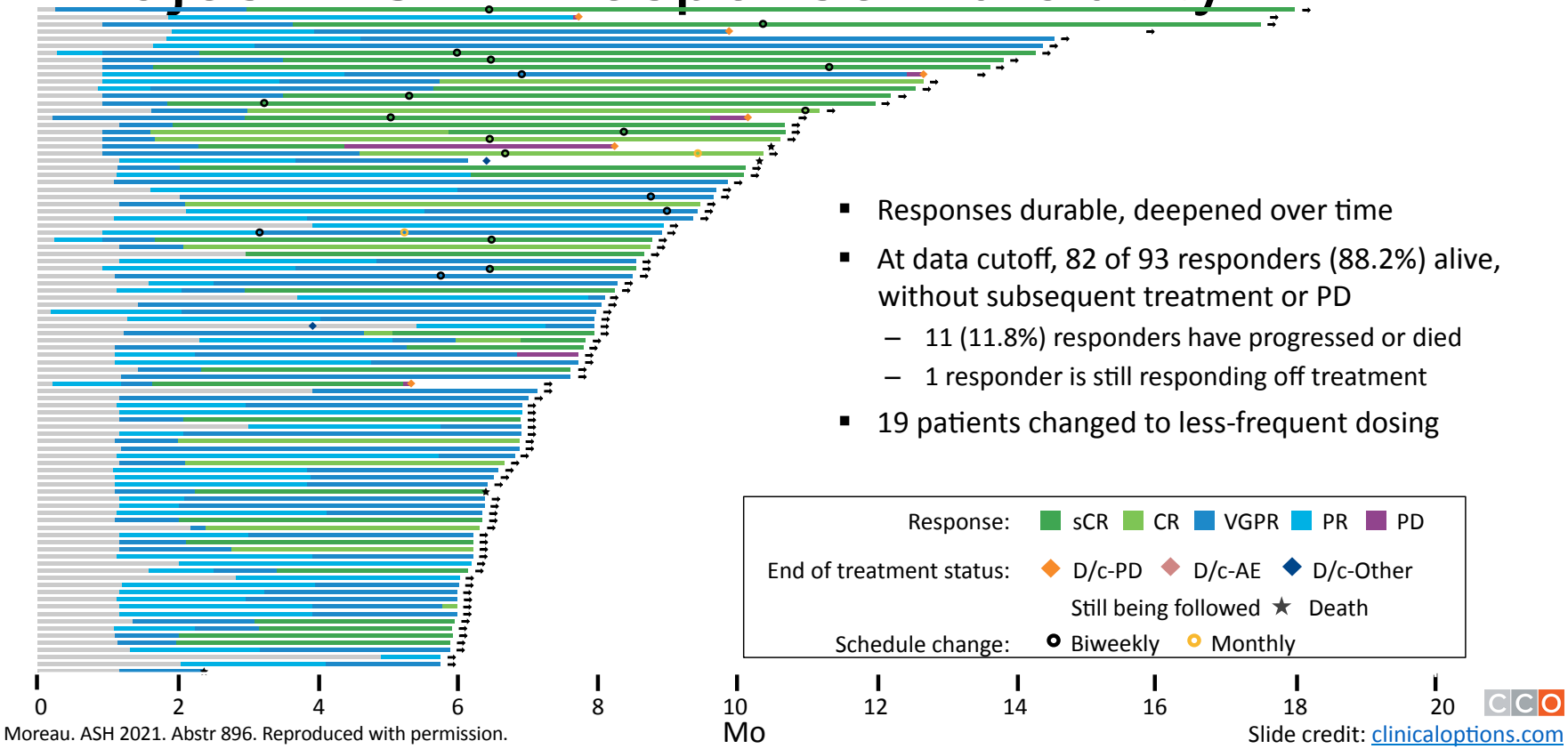




Moreau. ASH 2021. Abstr 896. Reproduced with permission.

Slide credit: clinicaloptions.com

MajesTEC-1: Response Durability



- Responses durable, deepened over time
- At data cutoff, 82 of 93 responders (88.2%) alive, without subsequent treatment or PD
  - 11 (11.8%) responders have progressed or died
  - 1 responder is still responding off treatment
- 19 patients changed to less-frequent dosing

Moreau. ASH 2021. Abstr 896. Reproduced with permission.

Slide credit: clinicaloptions.com

MajesTEC-1: Safety

- No patients required teclistamab dose reduction; only 1 patient discontinued due to AE (adenoviral pneumonia)
- Serious AEs: 88 (53.3%)
  - Teclistamab-related per investigator: 33 (20.0%)
- Injection-site reactions (all grade 1/2): 58 (35.2%)
- Infections: any grade, 104 (63.0%); grade 3/4: 35.2%
  - Opportunistic infections: 9 (5.5%)
- Hypogammaglobulinemia: 119 (72.1%)
  - 41 patients received IVIG at any time during the study (at physician discretion)
- 9 deaths due to AEs; none related to teclistamab
  - 7 COVID-19, 1 pneumonia, 1 hemoperitoneum

AEs in ≥20% of Patients, n (%)	All Patients (N =165)	
	Any Grade	Grade 3/4
Hematologic		
▪ Neutropenia	108 (65.5)	94 (57.0)
▪ Anemia	82 (49.7)	57 (34.5)
▪ Thrombocytopenia	63 (38.2)	35 (21.2)
▪ Lymphopenia	56 (33.9)	53 (32.1)
Nonhematologic		
▪ CRS	118 (71.5)	1 (0.6)
▪ Injection site erythema	42 (25.5)	0
▪ Fatigue	41 (24.8)	3 (1.8)
▪ Nausea	40 (24.2)	1 (0.6)
▪ Headache	36 (21.8)	1 (0.6)
▪ Diarrhea	34 (20.6)	4 (2.4)

Moreau. ASH 2021. Abstr 896.

Slide credit: clinicaloptions.com

MajesTEC-1: CRS

- All CRS events grade 1 (49.7%) or grade 2 (21.2%), except for 1 transient grade 3 CRS event (0.6%) that fully resolved
- 97% of events confined to step-up and cycle 1
- All CRS events resolved without the need for treatment discontinuation
- 2.4% of patients received >1 dose of tocilizumab for a single CRS event

CRS Parameter	All Patients (n = 165)
CRS, n (%)	118 (71.5)
≥2 CRS events, n (%)	54 (32.7)
Median time to onset, days (range)	2 (1-6)
Median duration, days (range)	2 (1-9)
Supportive measures, n (%)*	109 (66.1)
▪ Tocilizumab	60 (36.4)
▪ Low-flow oxygen by nasal cannula†	21 (12.7)
▪ Steroids	13 (7.9)
▪ Single vasopressor	1 (0.6)

Moreau. ASH 2021. Abstr 896.

Slide credit: clinicaloptions.com

MajesTEC-1: Neurotoxicity

- No treatment discontinuations or dose reductions due to neurotoxicity
- 5 patients had ICANS events at RP2D, all grade 1/2
- Most (7/9) ICANS events occurred concurrently with CRS
  - All resolved

Neurotoxicity Parameter	All Patients (n = 165)
Neurotoxicity, n (%)	21 (12.7)
▪ Grade ≥3	0
Specific event, n (%)	
▪ Headache	14 (8.5)
▪ ICANS	5 (3.0)
▪ Encephalopathy	2 (1.2)
▪ Tremor	2 (1.2)
Median time to onset, days (range)	2.5 (1-7)
Median duration, days (range)	3 (1-37)
Supportive measures, n (%)	12 (7.3)
▪ Tocilizumab	3 (1.8)
▪ Dexamethasone	3 (1.8)
▪ Levetiracetam	1 (0.6)

Moreau. ASH 2021. Abstr 896.

Slide credit: clinicaloptions.com

MajesTEC-1: Conclusions

- In the phase I/II MajesTEC-1 trial, teclistamab achieved deep and durable responses in patients with triple-class–exposed R/R MM
  - **ORR: 62%**
- Teclistamab was well tolerated with manageable safety profile
  - No patients required dose reduction
  - Most common AEs: CRS (mostly low grade) and hematologic events
  - ICANS events rare and low grade, all resolved without discontinuation
- Investigator's concluded that teclistamab is a promising new, off-the-shelf, T-cell redirecting, BCMA-targeting therapy for patients with R/R MM
  - Ongoing studies are evaluating teclistamab in earlier-line settings and in combination with other agents (NCT04722146, NCT04586426, NCT04108195)
  - Phase III MajesTEC-3 underway in patients with R/R MM and prior BCMA exposure (NCT05083169)

Moreau. ASH 2021. Abstr 896.

Phase I MonumenTAL-1: GPCR5D x CD3 Bispecific Antibody Talquetamab in Relapsed/ Refractory Multiple Myeloma

CCO Independent Conference Coverage Highlights*

of the *2021 ASH Annual Meeting, December 11-14, 2021*

Atlanta, Georgia

*CCO is an independent medical education company that provides state-of-the-art medical information to healthcare professionals through conference coverage and other educational programs.

This program is supported by educational grants from AbbVie; AstraZeneca; Daiichi Sankyo, Inc.; GlaxoSmithKline; Incyte Corporation; Jazz Pharmaceuticals; Merck Sharp & Dohme Corp.; and Novartis Pharmaceuticals Corporation.

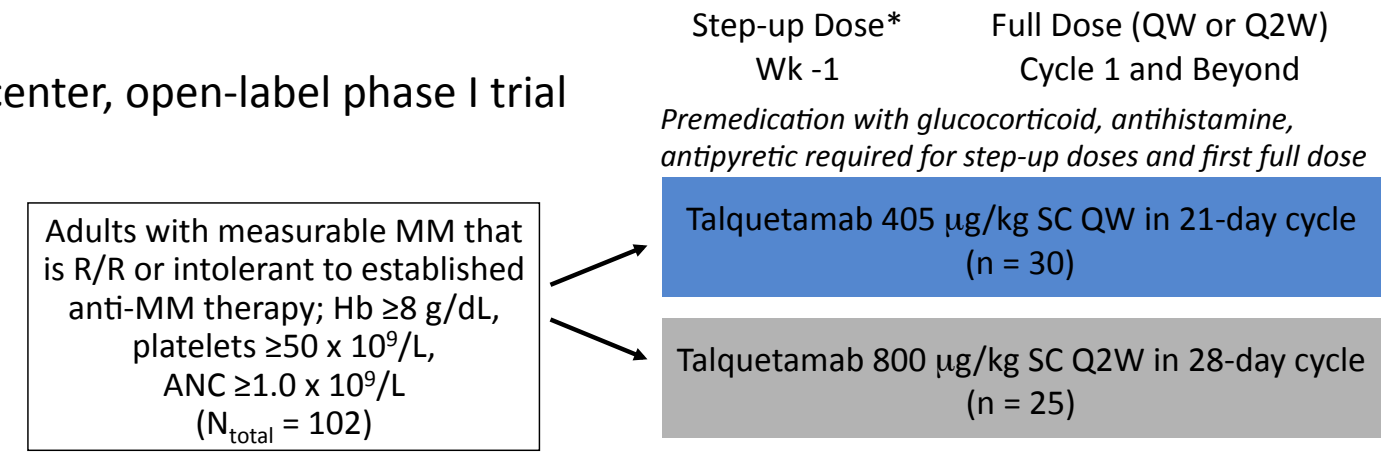
Talquetamab in MM: Background

- GPCR5D: orphan receptor highly expressed on MM cells relative to normal cells[1]
- Talquetamab: first-in-class bispecific IgG4 antibody binding GPCR5D and CD3 receptors
  - Recruits CD3+ cells to GPCR5D+ myeloma cells and induces tumor cell death in preclinical cell and xenograft models[2]
- Ongoing phase I trial evaluating talquetamab in heavily pretreated patients with R/R MM identified 2 doses—405 µg/kg SC QW and 800 µg/kg SC Q2W—as initial R2PD and second R2PD[3]
  - Current analysis reports updated data from phase I study[4]

1. Verkleij. Blood Adv. 2021;5:2196. 2. Pillarisetti. Blood. 2020;135:1232.
3. Chari. ASH 2020. Abstr 290. 4. Krishnan. ASH 2021. Abstr 158.

MonumenTAL-1: Study Design

- Multicenter, open-label phase I trial



- Key objectives: assess safety and tolerability of RP2D(s), antitumor activity, PK, PD

*With 2-3 step-up doses given prior to first full dose.

Krishnan. ASH 2021. Abstr 158.

Slide credit: clinicaloptions.com

MonumenTAL-1: Baseline Characteristics

Characteristic	405 µg/kg SC QW* (n = 30)	800 µg/kg SC Q2W* (n = 25)
Median age, yr (range)	61.5 (46-80)	64.0 (47-84)
▪ ≥70 yr	7 (23)	9 (36)
Male, n (%)	19 (63)	11 (44)
BM plasma cells ≥60%, n (%)	(n = 29) 6 (21)	(n = 24) 2 (8)
Extramedullary plasmacytomas, n (%)	10 (33)	9 (36)
High-risk cytogenetics,† n (%)	(n = 27) 3 (11)	(n = 23) 3 (13)
ISS stage, n (%)	(n = 28)	(n = 24)
▪ I	12 (43)	7 (29)
▪ II	13 (46)	12 (50)
▪ III	3 (11)	5 (21)
Median time since diagnosis, yr	5.6 (1.7-19.6)	5.9 (0.8-14.9)
Median prior lines of therapy, n (range)	6.0 (2-14)	5.0 (2-17)

Characteristic, n (%)	405 µg/kg SC QW* (n = 30)	800 µg/kg SC Q2W* (n = 25)
Prior SCT	27 (90)	18 (72)
Exposure status		
▪ Prior BCMA therapy	8 (27)	4 (16)
▪ Triple class‡	30 (100)	23 (92)
▪ Penta drug§	24 (80)	17 (68)
Refractory status		
▪ PI	25 (83)	20 (80)
• Carfilzomib	19 (63)	16 (64)
▪ IMiD	28 (93)	21 (84)
• Pomalidomide	26 (87)	18 (72)
▪ Anti-CD38 mAb	30 (100)	21 (84)
▪ Triple class	23 (77)	19 (76)
▪ Penta drug	6 (20)	6 (24)

† ‡

Krishnan. ASH 2021. Abstr 158.

Slide credit: clinicaloptions.com

MonumenTAL-1: Overall Safety and Hematologic Safety

Hematologic AEs in ≥20% of Total SC Population, n (%)	405 µg/kg SC QW* (n = 30)		800 µg/kg SC Q2W* (n = 25)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Neutropenia	20 (67)	18 (60)	11 (44)	9 (36)
Anemia	18 (60)	8 (27)	9 (36)	2 (8)
Lymphopenia	12 (40)	12 (40)	6 (24)	6 (24)
Thrombocytopenia	11 (37)	7 (23)	5 (20)	2 (8)
Leukopenia	12 (40)	9 (30)	4 (16)	4 (16)

Krishnan. ASH 2021. Abstr 158.

Slide credit: clinicaloptions.com

MonumenTAL-1: Nonhematologic AEs

- Infections: 18/55 (33%)
  - 3 (5%) with grade 3/4
- **Skin and nail AEs: 75%**
  - **7.5% with grade 3 rashes**
- ISR: 9/55 (16%); all grade 1/2
- No toxicity-related deaths

Nonhematologic AEs in ≥20% of Total SC Population, n (%)	405 µg/kg SC QW* (n = 30)		800 µg/kg SC Q2W* (n = 25)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
CRS	23 (77)	1 (3)	18 (72)	0 (0)
Dysgeusia	18 (60)	NA	9 (36)	NA
Dysphagia	11 (37)	0 (0)	4 (16)	0 (0)
Skin exfoliation	11 (37)	0 (0)	9 (36)	0 (0)
Fatigue	9 (30)	1 (3)	7 (28)	0 (0)
Weight decreased	9 (30)	0 (0)	6 (24)	0 (0)
Nail disorder	9 (30)	NA	5 (20)	NA
Pyrexia	6 (20)	0 (0)	4 (16)	0 (0)
Dry mouth	8 (27)	0 (0)	10 (40)	0 (0)
Diarrhea	8 (27)	0 (0)	3 (12)	0 (0)
Nausea	7 (23)	0 (0)	3 (12)	0 (0)
ALT increased	6 (20)	1 (3)	8 (32)	1 (4)

Krishnan. ASH 2021. Abstr 158.

Slide credit: clinicaloptions.com

MonumenTAL-1: CRS

Parameter, n (%)	405 µg/kg SC QW* (n = 30)	800 µg/kg SC Q2W* (n = 25)
Patients with CRS, n (%)	23 (76.7)	18 (72.0)
Maximum grade CRS, n (%)		
▪ Grade 1	18 (60.0)	12 (48.0)
▪ Grade 2	4 (13.3)	6 (24.0)
▪ Grade 3	1 (3.3)	0 (0)
Median time to onset, days (range)	2 (1-22)	2 (1.4)
Median duration, days (range)	2 (1-3)	2 (1-5)
Patients who received supportive measures, n (%)	23 (76.7)	18 (72.0)
▪ Tocilizumab†	19 (63.3)	15 (60.0)
▪ Steroids	1 (3.3)	1 (4.0)
▪ Low-flow oxygen by nasal cannula	0 (0)	1 (4.0)
▪ High-flow oxygen by face mask	1 (3.3)	0 (0)
▪ Single vasopressor	1 (3.3)	0 (0)

Krishnan. ASH 2021. Abstr 158.

Slide credit: clinicaloptions.com

MonumenTAL-1: Response

Response, %	405 µg/kg SC QW*	800 µg/kg SC Q2W*
ORR, n/N (%)	21/30 (70.0)	14/21 (66.7)
sCR	10	9.5
CR	3.3	9.5
VGPR	40	33.3
≥VGPR (sCR + CR + VGPR)	53.3	52.4
PR	16.7	14.3

Response	405 µg/kg SC QW* (n = 30)	800 µg/kg SC Q2W* (n = 25)
Median follow-up, mo (range)	9.0 (0.9-17.1)	4.8 (0.4-11.1)
Response-evaluable patients, n	30	21
ORR, n (%)	21 (70.0)	14 (66.7)
▪ Triple-class-refractory patients, n/N (%)	15/23 (65.2)	12/18 (66.7)
▪ Penta-drug refractory patients, n/N (%)	5/6 (83.3)	5/6 (83.3)
Median time to first confirmed response, mo (range)	0.9 (0.2-3.8)	1.2 (0.2-6.8)

- Median DoR not reached in either arm
- QW arm: 11/21 (52%) responders still receiving treatment at median 10.1-mo follow-up
- Q2W arm: 12/14 (86%) responders still receiving treatment at median 7.9-mo follow-up

Krishnan. ASH 2021. Abstr 158.

Slide credit: clinicaloptions.com

Investigators' Conclusions

- In this phase I trial, talquetamab was tolerable in heavily pretreated patients with R/R MM
  - Efficacy and safety of 405 µg/kg SC QW and 800 µg/kg SC Q2W similar
  - No new safety concerns
- Data suggest promising ORR of 67% to 70% in triple- and penta-refractory patients
- PK support QW and Q2W dosing
- Evaluation of talquetamab in phase II trial in R/R MM ongoing (NCT04634552), and additional trials are exploring combination therapy with talquetamab (NCT04586426, NCT04108195, NCT05050097)

Krishnan. ASH 2021. Abstr 158.

CAR T-cell therapies

- Currently available: Abecma (idecabtagene vicleucel)
  - FDA approved March 27, 2021
  - Based on multicenter study of 127 patients with relapsed/refractory myeloma
  - 3 prior lines of therapy (88% had 4 or more lines)
  - **Overall response rate was 72%**
  - **CR rate of 28%** -- 65% of patients who achieved CR remained in CR for at least 12 months
  - KarMMa-1 study:
    - MRD negative status in 33 patients
    - Median Progression Free Survival was **8.8 months**

CARTITUDE-1 Phase Ib/II Study of Ciltacabtagene Autoleucel in Patients With R/R MM: 2-Yr Update

CCO Independent Conference Coverage Highlights*

of the *2021 ASH Annual Meeting, December 11-14, 2021*

Atlanta, Georgia

*CCO is an independent medical education company that provides state-of-the-art medical information to healthcare professionals through conference coverage and other educational programs.

This program is supported by educational grants from AbbVie; AstraZeneca; Daiichi Sankyo, Inc.; GlaxoSmithKline; Incyte Corporation; Jazz Pharmaceuticals; Merck Sharp & Dohme Corp.; and Novartis Pharmaceuticals Corporation.

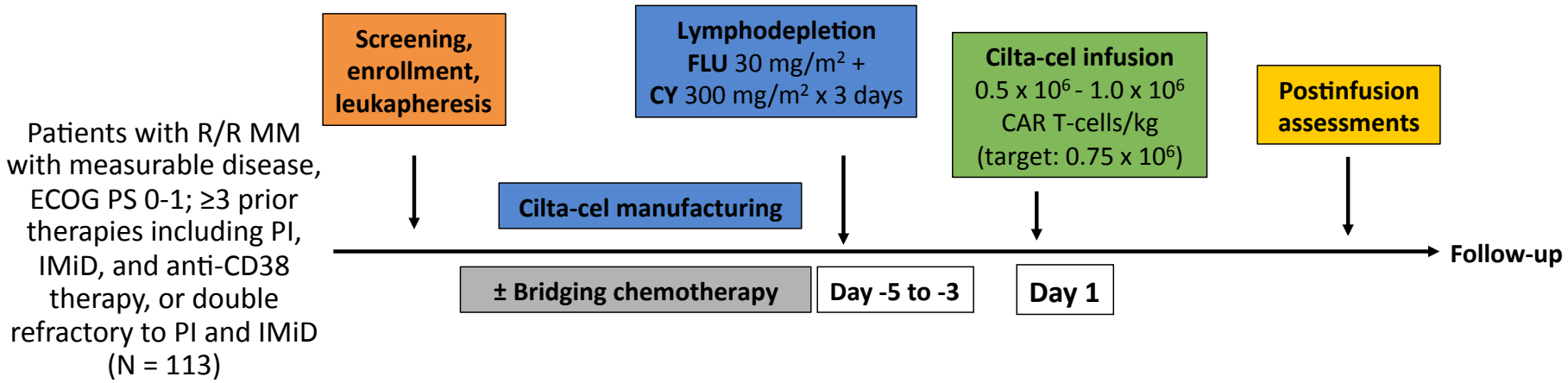
CARTITUDE-1: Background

- Ciltacabtagene autoleucel: investigational CAR T-cell therapy comprising 2 BCMA-targeting single-domain antibodies intended to boost avidity plus a 4-1BB costimulatory domain[1]
- Cilta-cel demonstrated early, deep, and durable responses in the phase Ib/II CARTITUDE-1 study in heavily pretreated patients with R/R MM[1]
  - After a median follow-up of 12.4 mo, ORR (by IRC) was 97%, with 67% sCR rate
  - 12-mo PFS and OS rates: 77% and 89%, respectively
- Current analysis reports updated results from CARTITUDE-1 with longer duration of patient follow-up (median: ~2 yr)[2]

1. Berdeja. Lancet. 2021;398:314. 2. Martin. ASH 2021. Abstr 549.

CARTITUDE-1: Study Design

- Phase Ib/II trial conducted in the United States



- Of 113 patients enrolled, 97 received cilta-cel; median administered dose: 0.71 x 10^6 (0.51-0.95 x 10^6) CAR+ viable T-cells/kg
- **Primary endpoint:** safety and RP2D (phase Ib), efficacy (phase II)

Martin. ASH 2021. Abstr 549.

Slide credit: clinicaloptions.com

CARTITUDE-1: Baseline Characteristics

Characteristic	All Patients (N = 97)
Median age, yr (range)	61 (43-78)
Male, n (%)	57 (58.8)
Black race, n (%)	17 (17.5)
Extramedullary plasmacytomas, n (%)	13 (13.4)*
Bone marrow plasma cells ≥60%, n (%)	21 (21.9)
Any high-risk cytogenetics, n (%) ▪ del(17p) ▪ t(14;16) ▪ t(4;14)	23 (23.7) 19 (19.6) 2 (2.1) 3 (3.1)
≥50% tumor BCMA expression, n (%)	57 (91.9)†
Median prior lines of therapy, n (range)	6 (3-18)
Median previous lines of therapy, n (range)	6.0 (3-18)

Characteristic, n (%)	All Patients (N = 97)
≥5 prior lines of therapy	64 (66.0)
Previous SCT ▪ Autologous ▪ Allogeneic	87 (89.7) 8 (8.2)
Triple-class exposed‡	97 (100)
Penta-drug exposed§	81 (83.5)
Triple-class refractory‡	85 (87.6)
Penta-drug refractory	41 (42.3)
Refractory to: ▪ Carfilzomib ▪ Pomalidomide ▪ Anti-CD38 Ab	 63 (64.9) 81 (83.5) 96 (99.0)
Refractory to last line of therapy	96 (99.0)

†Number of evaluable samples = 62.

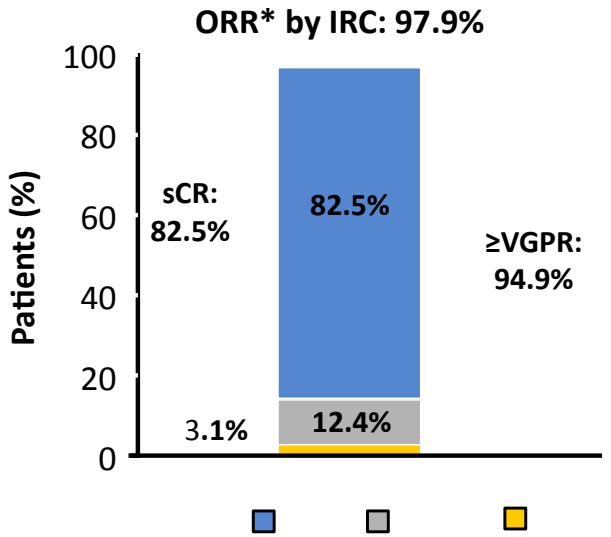
Martin. ASH 2021. Abstr 549.

Slide credit: clinicaloptions.com

CARTITUDE-1: Responses

- sCR rates deepened over time
  - 67% at median 1-yr follow-up
  - 83% at median 2-yr follow-up
- Median time to first response: 1 mo (range: 0.9-10.7)
- Median time to best response: 2.6 mo (range: 0.9-17.8)
- Median time to ≥CR: 2.9 mo (range: 0.9-17.8)
- Median DoR: NE (range: 21.8-NE)
- Percentage of patients remaining progression-free at 2 yr was 60.5%

- No patient had CR or SD as best response

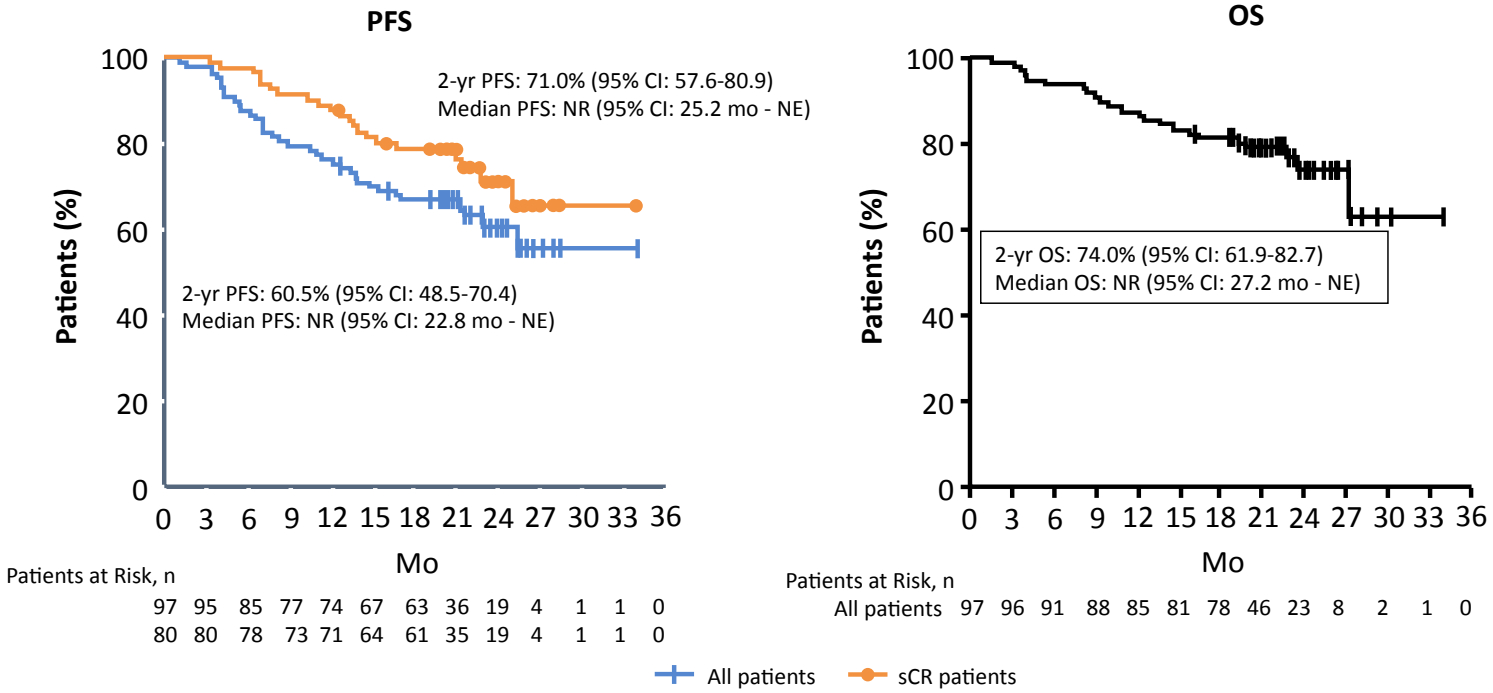


*ORR assessed by independent review committee.

Martin. ASH 2021. Abstr 549. Reproduced with permission.

Slide credit: clinicaloptions.com

CARTITUDE-1: PFS and OS

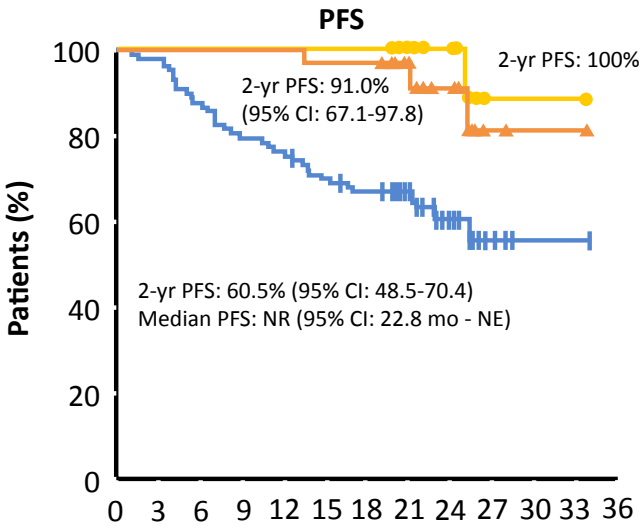


Martin. ASH 2021. Abstr 549. Reproduced with permission.

Slide credit: clinicaloptions.com

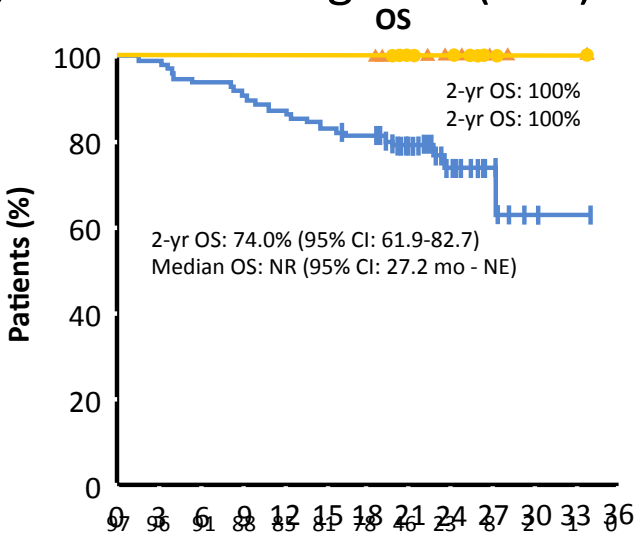
CARTITUDE-1: PFS and OS by MRD Status

- 92% of 61 patients evaluable for MRD, were MRD negative (10^{-5})



Patients at Risk, n

All patients	97	95	85	77	74	67	63	36	19	4	1	1	0
MRD negativity ≥6 mo	30	30	30	30	30	29	29	17	12	2	1	1	0
MRD negativity ≥12 mo	18	18	18	18	18	18	18	12	10	2	1	1	0



Patients at Risk, n

All patients	97	96	91	88	85	81	78	46	25	8	2	1	0
MRD negativity ≥6 mo	30	30	30	30	30	30	30	17	13	3	1	1	0
MRD negativity ≥12 mo	18	18	18	18	18	18	18	12	11	2	1	1	0

All patients MRD negativity sustained ≥6 mo MRD negativity sustained ≥12 mo

Martin. ASH 2021. Abstr 549. Reproduced with permission.

Slide credit: clinicaloptions.com

CARTITUDE-1: Safety Update

- No new safety signals observed with median follow-up of ~2 yr[1]
- Since median ~1 yr follow-up[1]
  - No new neurotoxicity events or neurocognitive TEAEs reported
    - ~200 patients have been dosed with cilta-cel across CARTITUDE clinical development program since implementation
    - After implementation of management strategies, neurocognitive TEAEs decreased to 0.5%
  - No new treatment-related deaths since previous 1-yr follow-up[2,3]
- 15 SPMs reported in 11 patients over median follow-up of ~2 yr[1]
  - All determined to be unrelated to cilta-cel[1]
  - 6 new events of SPMs since the median ~1-yr follow-up[1]
  - SPM rate consistent with published data for similar patient populations[2,3]

1. Martin. ASH 2021. Abstr 549. 2. Stadmauer. JCO. 2019;37:589. 3. Palumbo. Lancet Oncol. 2014;15:333.

CARTITUDE-1: Investigators' Conclusions

- After a median of ~2 yr of follow-up of the phase Ib/II CARTITUDE-1 trial of cilta-cel, patients with R/R MM showed durable and deepening responses
  - ORR remained at 98%; sCR rates increased from 67% at ~1 yr to 83% at ~2 yr
  - 2-yr PFS and OS were 60.5% and 74.0%, respectively
  - 92% of evaluable pts achieved MRD negativity (10^{-5}), and individuals who sustained negative MRD attained improved PFS and OS outcomes
- Cilta-cel showed a manageable safety profile with no new safety signals with longer follow-up
- Investigators conclude that these encouraging data suggest cilta-cel will be an important treatment option for patients with MM
  - Studies ongoing to evaluate cilta-cel in earlier-line settings for other populations of patients with MM, including assessment of outpatient administration
  - These studies include CARTITUDE-2 (NCT04133636), CARTITUDE-4 (NCT04181827), and CARTITUDE-5 (NCT04923893)

Martin. ASH 2021. Abstr 549.

Takeaways

- Triplets or Quadruplets for induction
- New options for future therapies including BCMA targets and GPRC5D
  - Bispecific antibodies
  - CAR T-cell therapy

Thank you for joining today!

marykwok@uw.edu