Holden Comprehensive Cancer Center

Multiple Myeloma Updates from ASCO 2022

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September 9th, 2022

CHANGING MEDICINE.
CHANGING LIVES.®

Disclosures

- Advisory board
  - Glaxo Smith Kline
- We will discuss off label / investigational uses

Acknowledgements

- Thank you to the abstract presenters for use of their slides:
  - Dr. Paul Richardson
  - Dr. Doris K Hanson
  - Dr. Cyrille Touzeau
  - Dr. Saad Usmani
  - Dr. Meera Mohan
  - Dr. Andrej Jakubowiak

What will we go over today?

Upfront Therapy

What changes are being made for treatment of newly diagnosed myeloma?

Transplant

What role does transplant play in 2022?

New Agents

What agents have been recently approved & what is coming down the road?

Pillars of Myeloma Chemotherapy

PIs:
- Bortezomib
- Carfilzomib
- Ixazomib

IMiDs©:
- Thalidomide
- Lenalidomide
- Pomalidomide

Anti-CD38:
- Daratumumab
- Isatuximab

High Dose Melphalan (Transplant)

CAR T cells:
Idecabtagene
Ciltacabtagene

Cyclophosphamide
Melphalan
Bendamustine

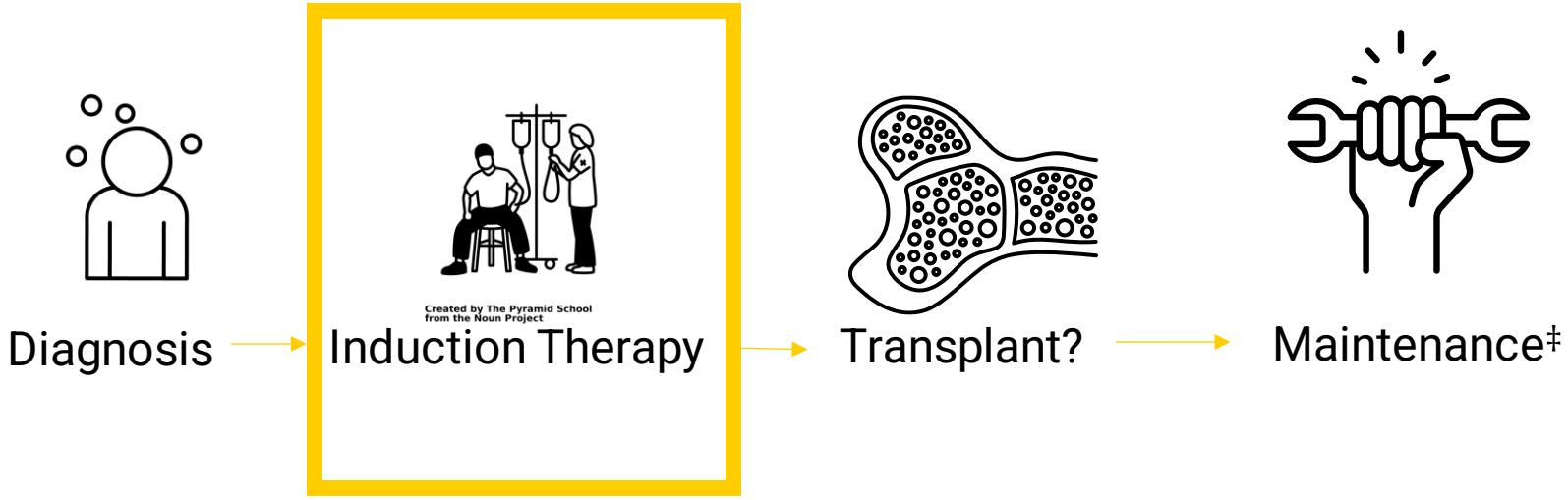
Anti-SLAM-F7:
- Elotuzumab

Selinexor

Belantamab

Venetoclax

Basic Initial Treatment Algorithm



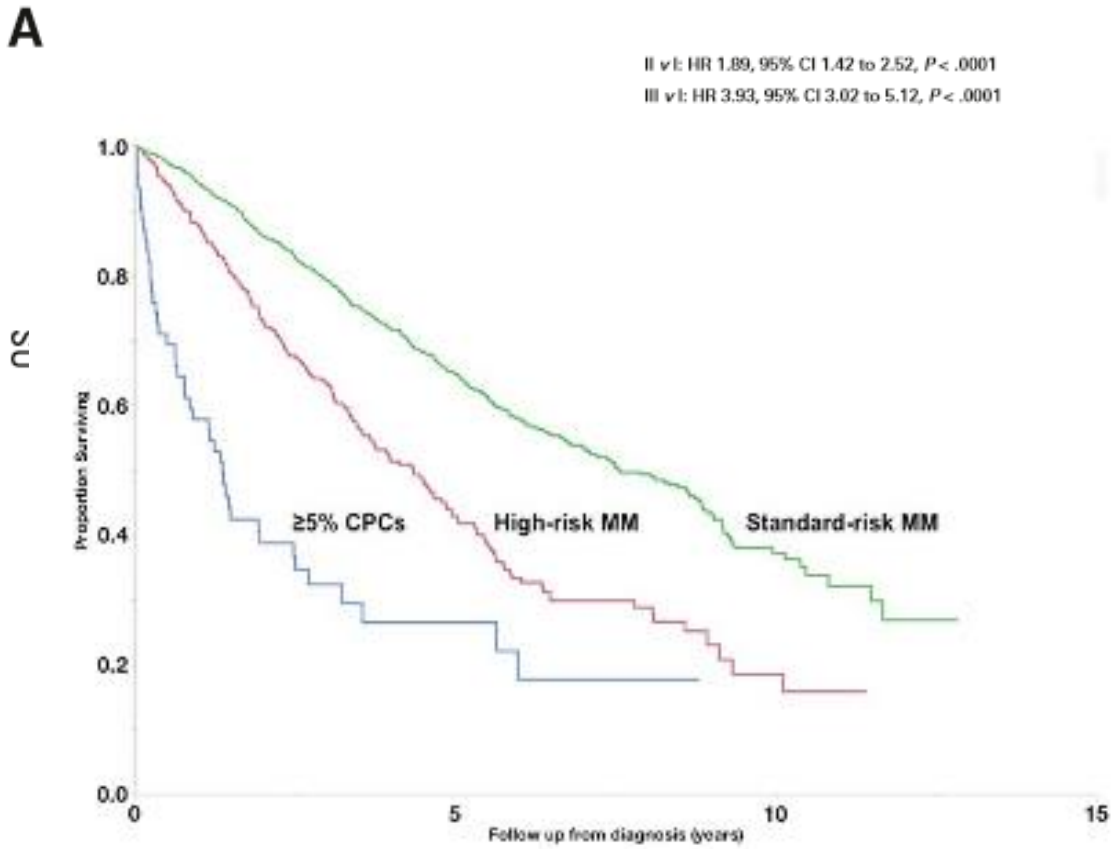
Current Status of Induction Therapy

- NCCN Category 1:
  - Bortezomib + Lenalidomide + Dexamethasone
    - Response in ~90% of patients
  - Daratumumab + Lenalidomide + Dexamethasone (non-transplant elig.)
- “Other Recommended”:
  - Carfilzomib + Lenalidomide + Dexamethasone
    - Useful if pre-existing neuropathy
  - Daratumumab + lenalidomide + bortezomib + dexamethasone
    - Useful if rapid, deep response is desired (skeletal pain, renal damage, high tumor burden)
  - Ixazomib + Lenalidomide + dexamethasone
    - All oral regimen

NCCN Guidelines: Multiple Myeloma v 5.2022

“High Risk” Myeloma, an area of need

- Cytogenetics (Perrot et al, JCO 2019)
  - +1q, -1p, +3, -17p, +21, t[4;14], t[14;16], t[14;20]
- R2-ISS staging (D’Agostino et al, JCO 2022)
  - Albumin, beta-2 macroglobulin, LDH, +1q, t[4;14], -17p
- Circulating plasma cells (Ravi et al, Blood Cancer Journal 2021
  - Poor survival if >5% circulating plasma cells
- Responsiveness to therapy
  - Persistence of MRD after X amount of therapy



New Ideas in Induction Therapy

- How can we better address high risk myeloma?
  - Deepen initial depth of response?
  - Combine mechanisms of action to minimize refractoriness?
  - Lengthy and intensive therapy?

IFM 2018-04 phase 2 study design

Key inclusion criteria:

- Age < 66
- **Newly diagnosed multiple myeloma**
- **Transplant-eligible**
- **High-risk FISH :** t(4;14), 17p del, t(14;16)
- ECOG 0-2

Objectives:

- **Primary Objective :**
  Feasibility (endpoint : >70% patients completed 2nd transplant)
- **Secondary Objectives:**
  Safety, ORR, PFS, OS, stem-cell collection

Induction Dara-KRd x 6	Stem cell collection	ASCT #1	Consolidation Dara KRd x 4	ASCT #2	Maintenance Dara Len 2 years
Dara : 16 mg/kg IV D1,8,15,22 (cycle 1 - 2) D1 D15 (Cycle 3 to 6) **K : (20)36 mg/m2 IV** D1-2, 8-9, 15-16 **Len : 25 mg** D1-21 **Dex** : **20 mg** D1-2,8-9,15-16,22-23 **28-day cycles**	Cyclo GCSF +/- Plerix	**Mel 200**	**Dara** : **16 mg/kg IV** D1 D15 **K** : **56 mg/m2 IV** D1, 8, 15 **Len** : **15 mg** D1-21 **Dex** : **40 mg** D1, 8, 15, 22 **28-day cycles**	**Mel 200**	**Dara** : 16 mg/kg IV every 8 weeks **Len** : 10 mg 21/28

Touzeau et al. ASCO Abstract #8002

Dara-KRd induction : Stem-cell collection

Stem-cell collection after 6 cycles (n=27) :

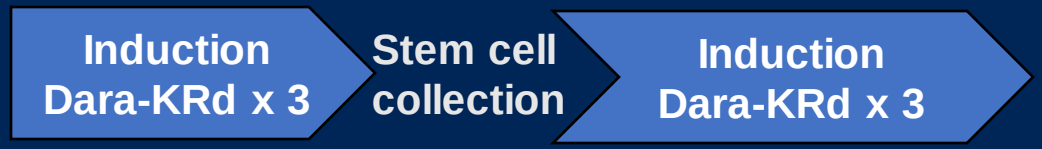
Stem cell collection

- median CD34+ (10^6/kg) : 6.1 (0-16)
- stem-cell collection failure (unable to proceed to double transplant) : n=6

6/27 = 22%

-> **<u>Study protocol was amended to collect stem-cell after Cycle 3</u>**

Stem-cell collection after 3 cycles (n=21) :

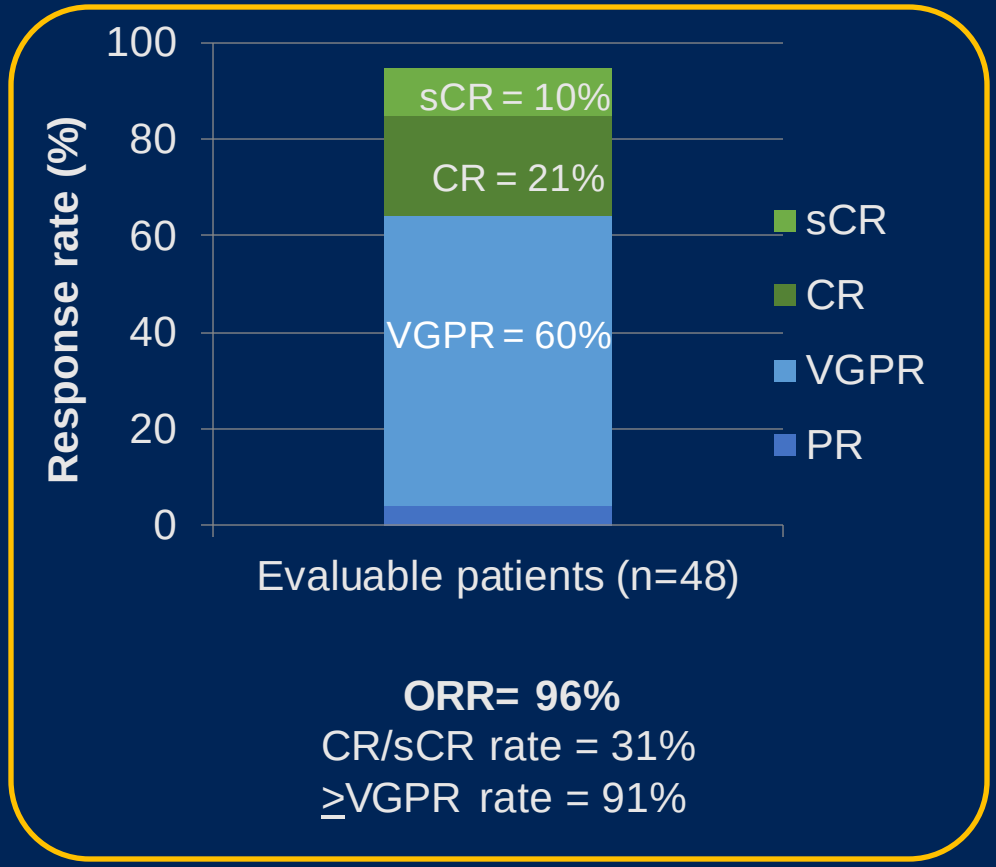


- median CD34+ (10^6/kg) : 8.3 (4.7-26)
- no stem-cell collection failure since protocole amendment

Touzeau et al. ASCO Abstract #8002

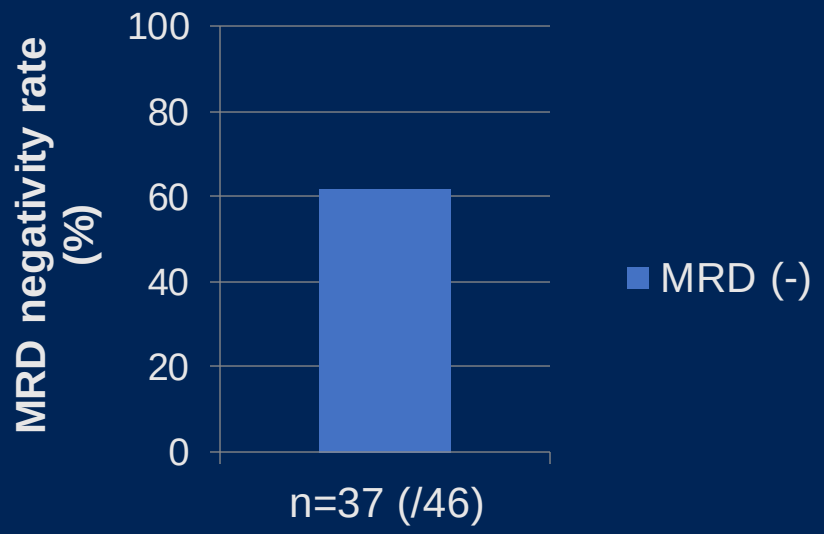
Dara-KRd induction : Response rates and MRD

Response Rate



ORR= 96%
CR/sCR rate = 31%
≥VGPR rate = 91%

MRD negativity (NGS, 10-5)



MRD negativity rate (NGS, 10-5) : 62%

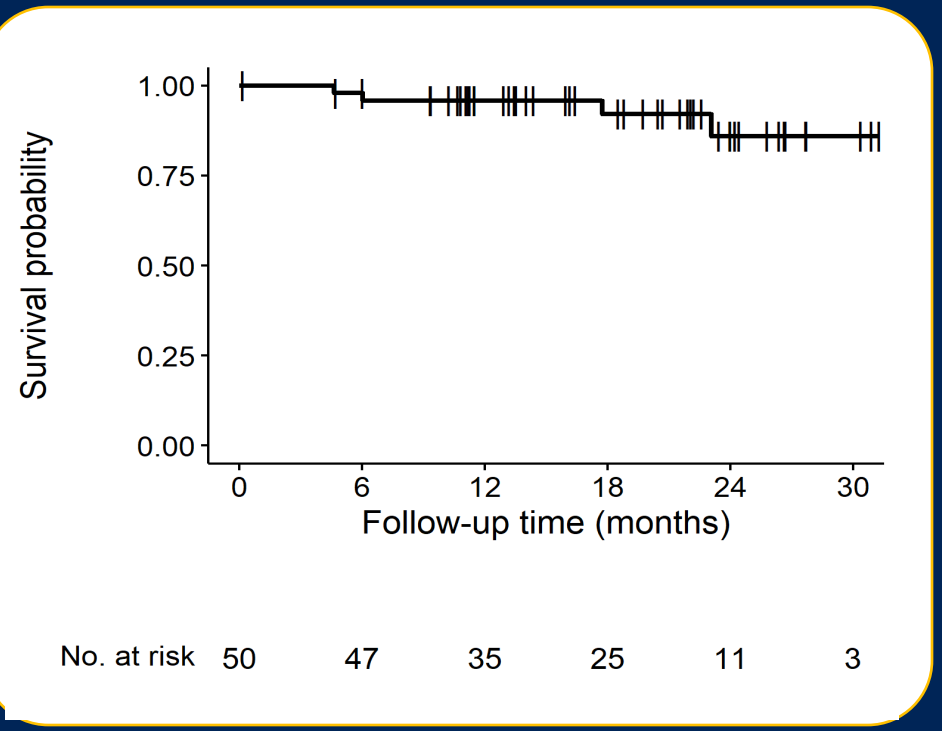
Touzeau et al. ASCO Abstract #8002

Progression-free and overall survival

Median follow-up : 19.4 months

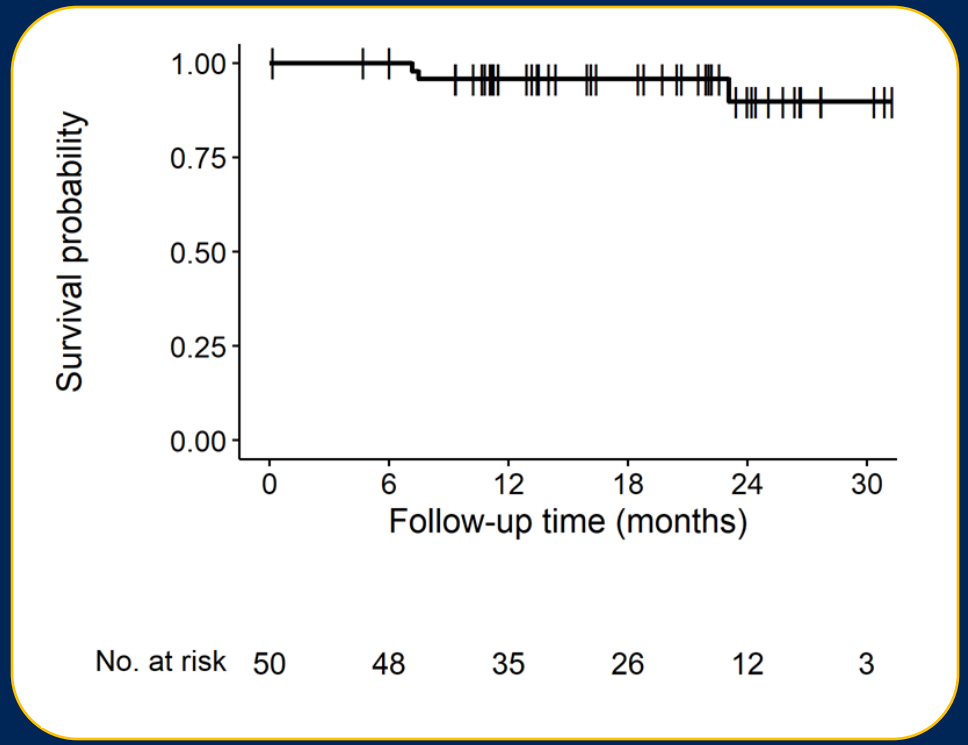
Data cut-off: april 25 2022

Progression-free survival



12-month PFS : 96% (90% - 100%)
18-month PFS : 92% (84% - 100%)

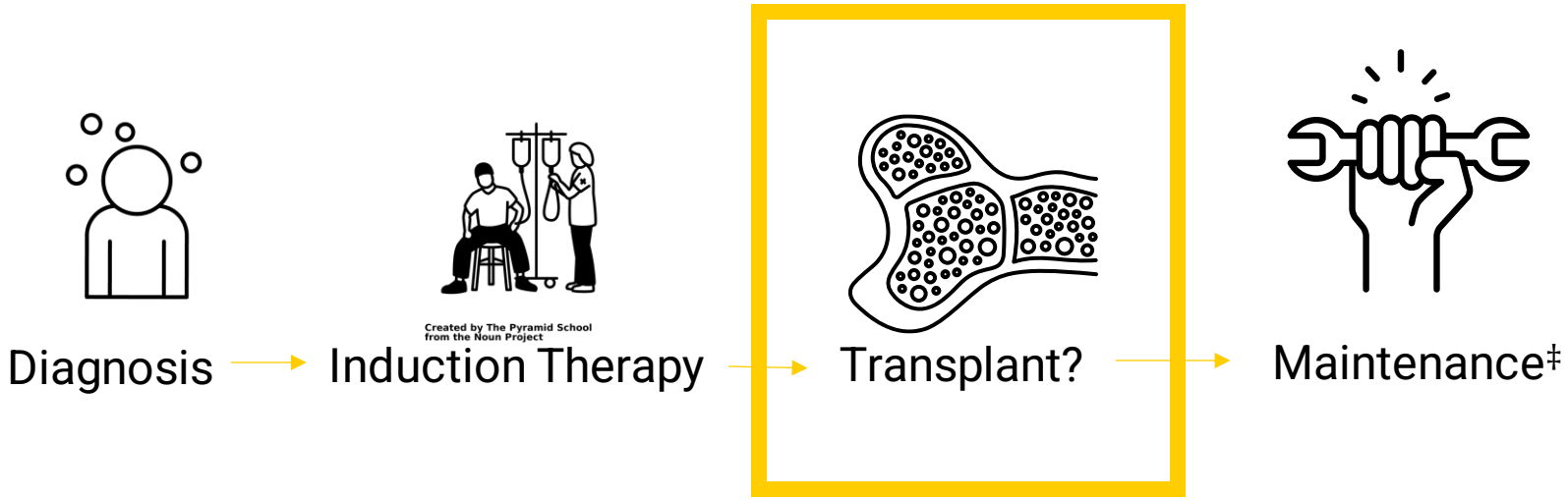
Overall Survival



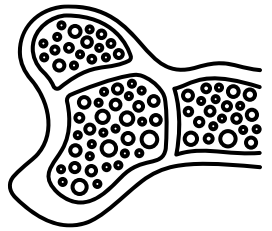
12-month OS : 96% (90% - 100%)
18-month OS : 96% (90% - 100%)

Touzeau et al. ASCO Abstract #8002

Basic Initial Treatment Algorithm



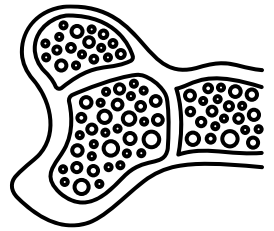
Update in Transplant



	N	Regimens	PFS (months, median)		OS	
			ASCT	Non-ASCT	ASCT	Non-ASCT
RV-MM-PI-209[1] 2007-2009	402	Rd x4 + MelPR vs. Rd x4 + ASCT	43†	22†	82% (4y)*	65% (4y)*
RV-MM-EMN-441[2] 2009-2011	256	Rd x4 + CyRd vs Rd x4 + ASCT	43†	29†	86% (4y)*	73% (4y)*
IFM 2009[3] 2010-2012	700	RVd x8 vs RVd x5 + ASCT	50†	36†	62% (8y)	60% (8y)
EMN02/HO95[4] 2011-2014	1493	VCd x3-4 + VMP x6 vs VCd x3-4 + ASCT x1-2	57†	42†	72% (5y)	75% (5y)
FORTE[5]	474	KRD x12 vs KRD x4 + ASCT + KRD x4	NR*	57*	90% (3yr)	90% (3yr)

1. Palumbo et al. NEJM 2014;371(10), 2. Gay et al. Lancet Oncol 2015;16(16), 3. Perrot et al. ASH 2021 Abstract #143
4. Cavo et al. Lancet Haematol. 2020;7(6), 5. Gay et al. Lancet Oncol 2021;22(12)

Update in Transplant (LBA4)



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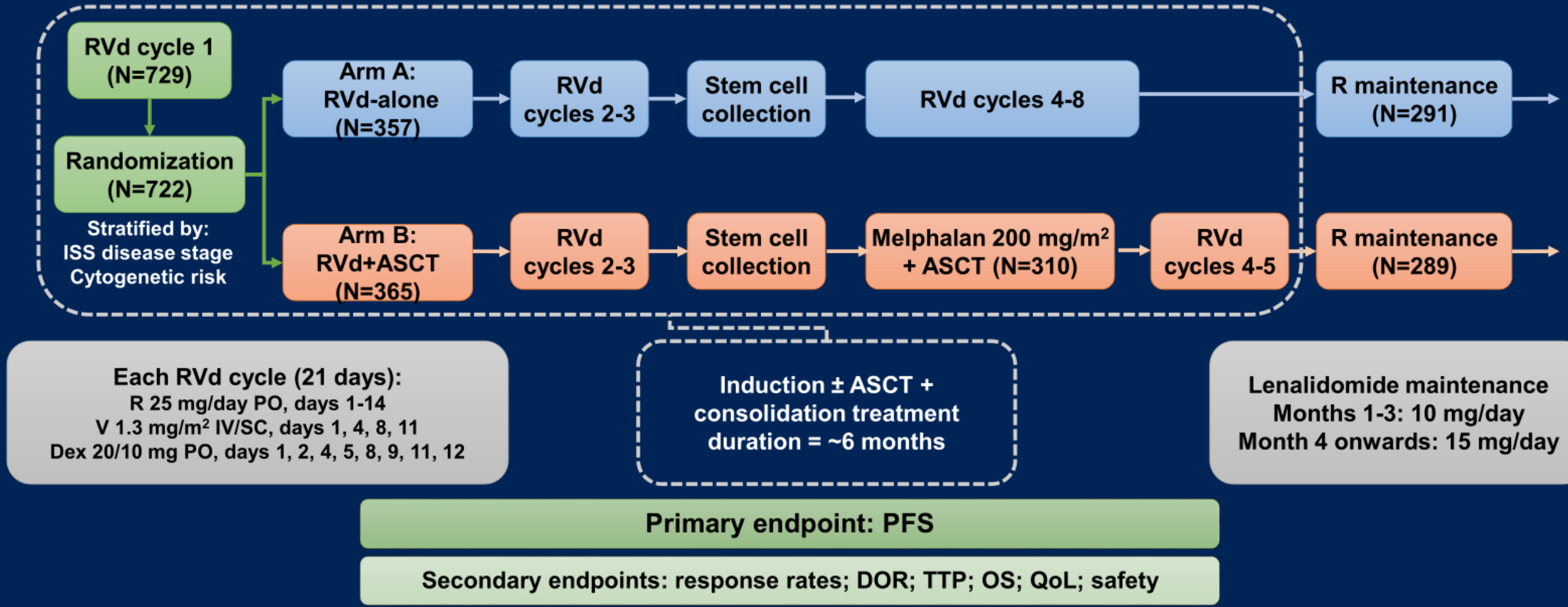
FORTE	474	KRD x12 vs KRD x4 + ASCT + KRD x4	NR*	57*	90% (3yr)	90% (3yr)
DETERMINATION 2010-2012	722	RVd x8 vs RVd x5 + ASCT	33†	51†	79% (5yr)	81% (5 yr)

DETERMINATION: study design and patient disposition

DETERMINATION: Delayed vs Early Transplant with Revlimid Maintenance and Antimyeloma Triple Therapy

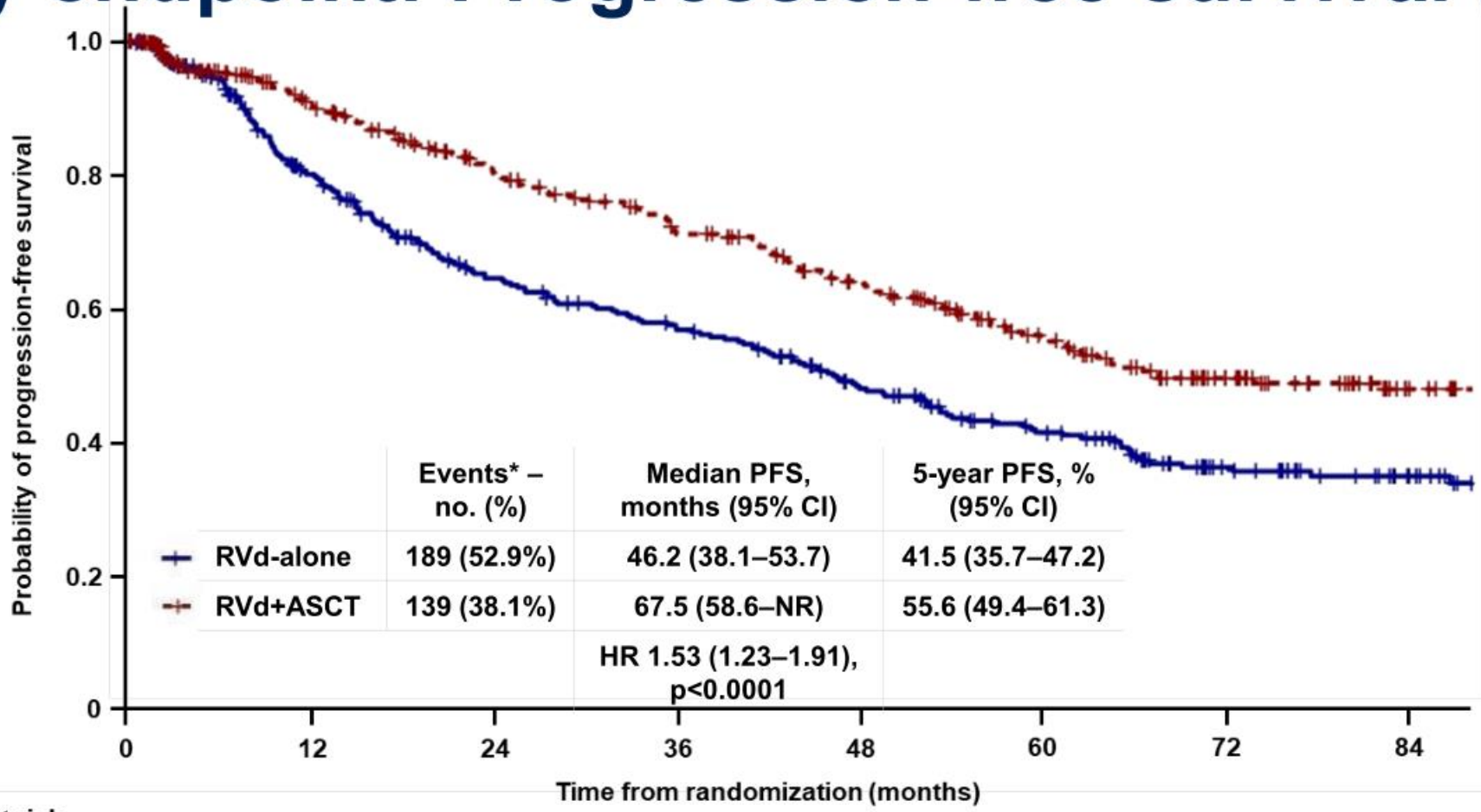


Primary endpoint: PFS

Secondary endpoints: response rates; DOR; TTP; OS; QoL; safety

d/Dex, dexamethasone; DOR, duration of response; ISS, International Staging System; IV, intravenous; PO, orally; R, lenalidomide; SC, subcutaneous; TTP, time to progression; V, bortezomib

Primary endpoint: Progression-free survival (PFS)

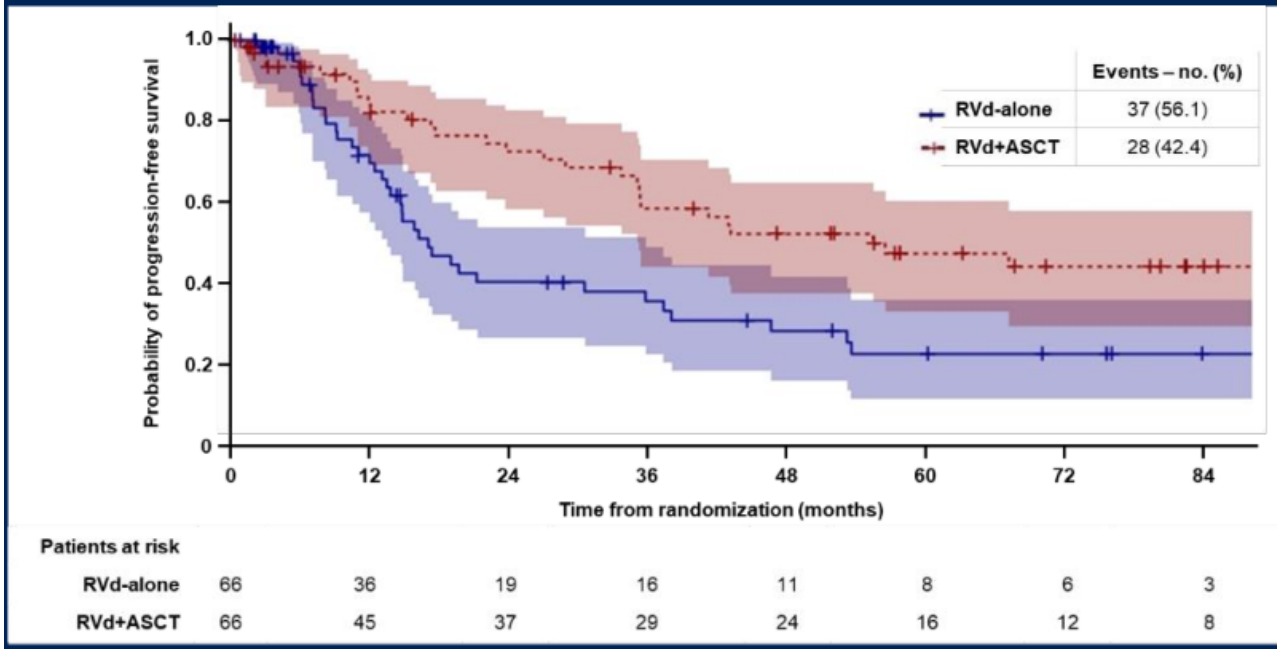


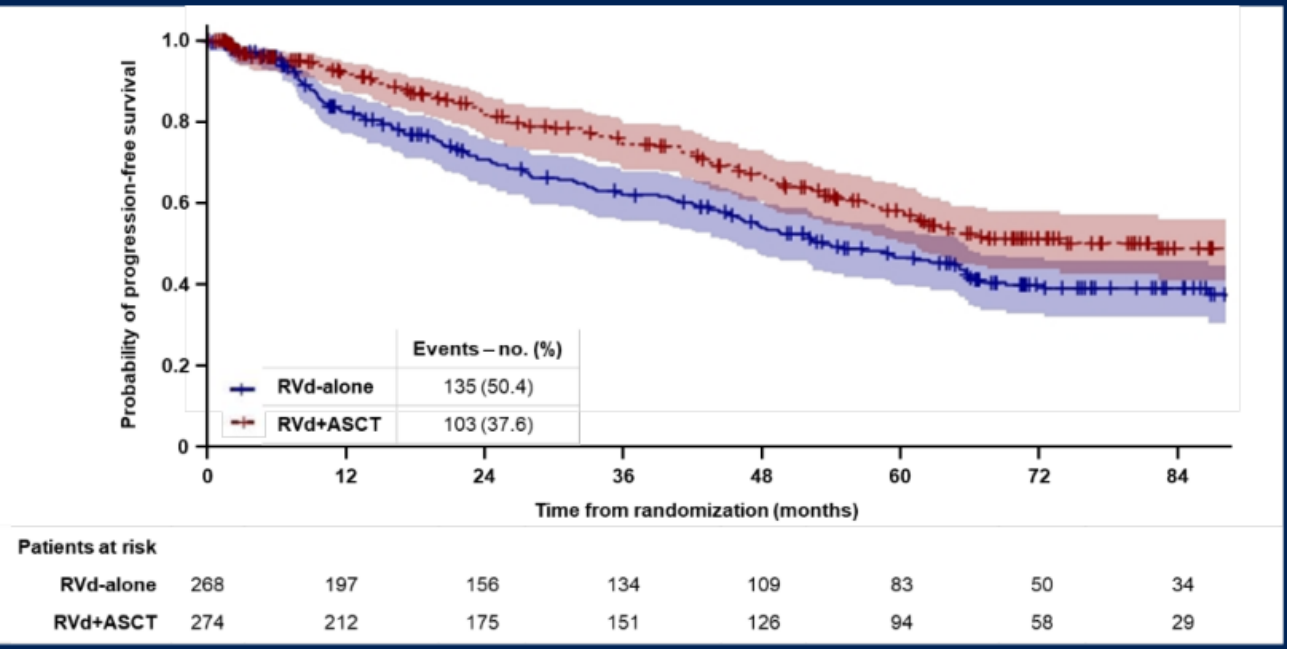
	Events* – no. (%)	Median PFS, months (95% CI)	5-year PFS, % (95% CI)
RVd-alone	189 (52.9%)	46.2 (38.1–53.7)	41.5 (35.7–47.2)
RVd+ASCT	139 (38.1%)	67.5 (58.6–NR)	55.6 (49.4–61.3)
		HR 1.53 (1.23–1.91), p<0.0001	

Patients at risk								
RVd-alone	357	250	187	160	126	96	60	40
RVd+ASCT	365	276	226	191	160	118	77	42

CI, confidence interval; HR, hazard ratio; Data cutoff: 12/10/21. *PFS events: disease progression or death.

PFS by stratification factor – cytogenetic risk





Shaded areas indicate 95% CIs

Median PFS, months	RVd-alone	RVd+ASCT
High-risk	17.1	55.5
	HR 1.99 (95% CI 1.21–3.26)	

Median PFS, months	RVd-alone	RVd+ASCT
Standard-risk	53.2	82.3
	HR 1.38 (95% CI 1.07–1.79)	

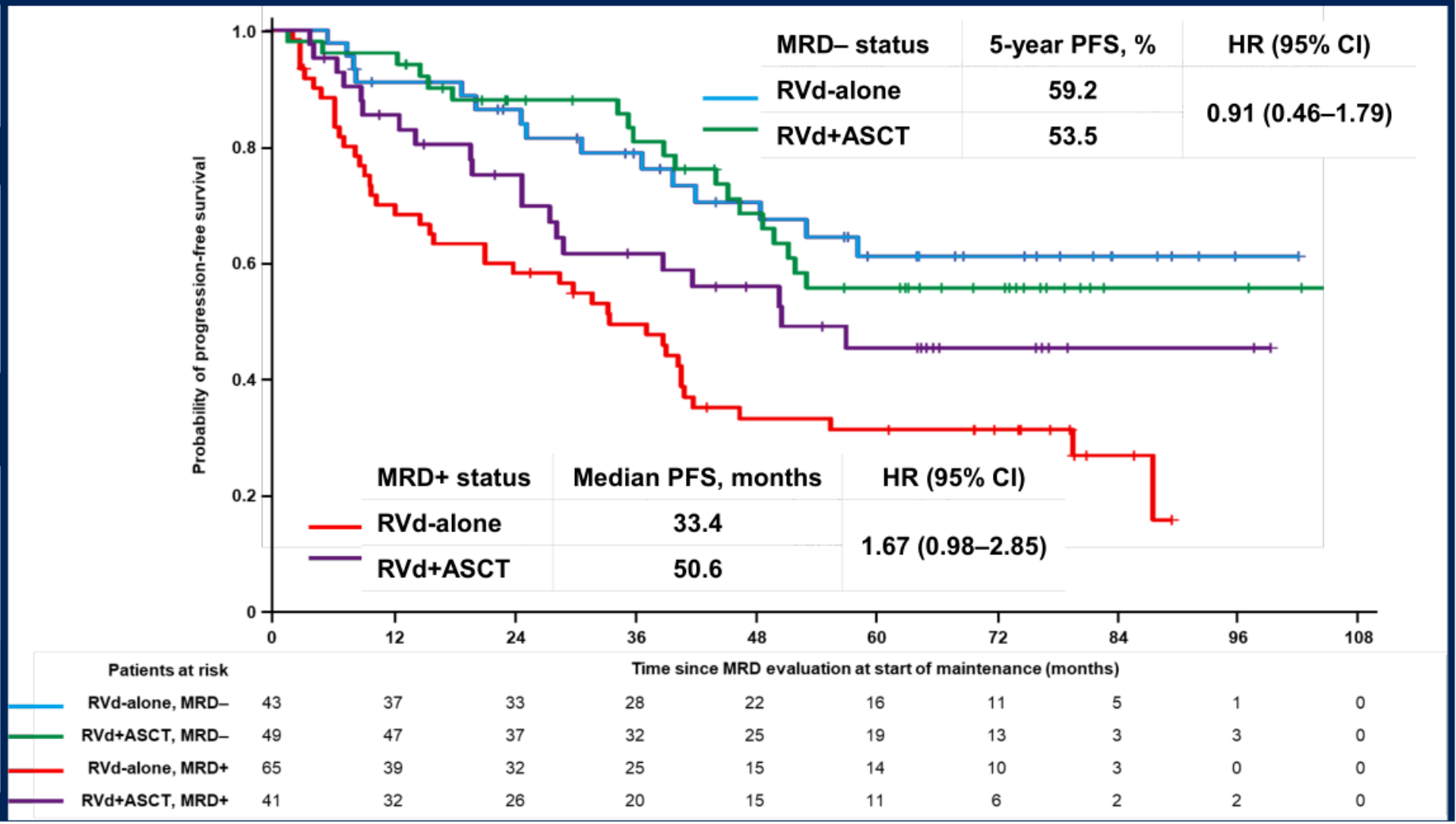
MRD / PFS by MRD status

Preliminary analysis

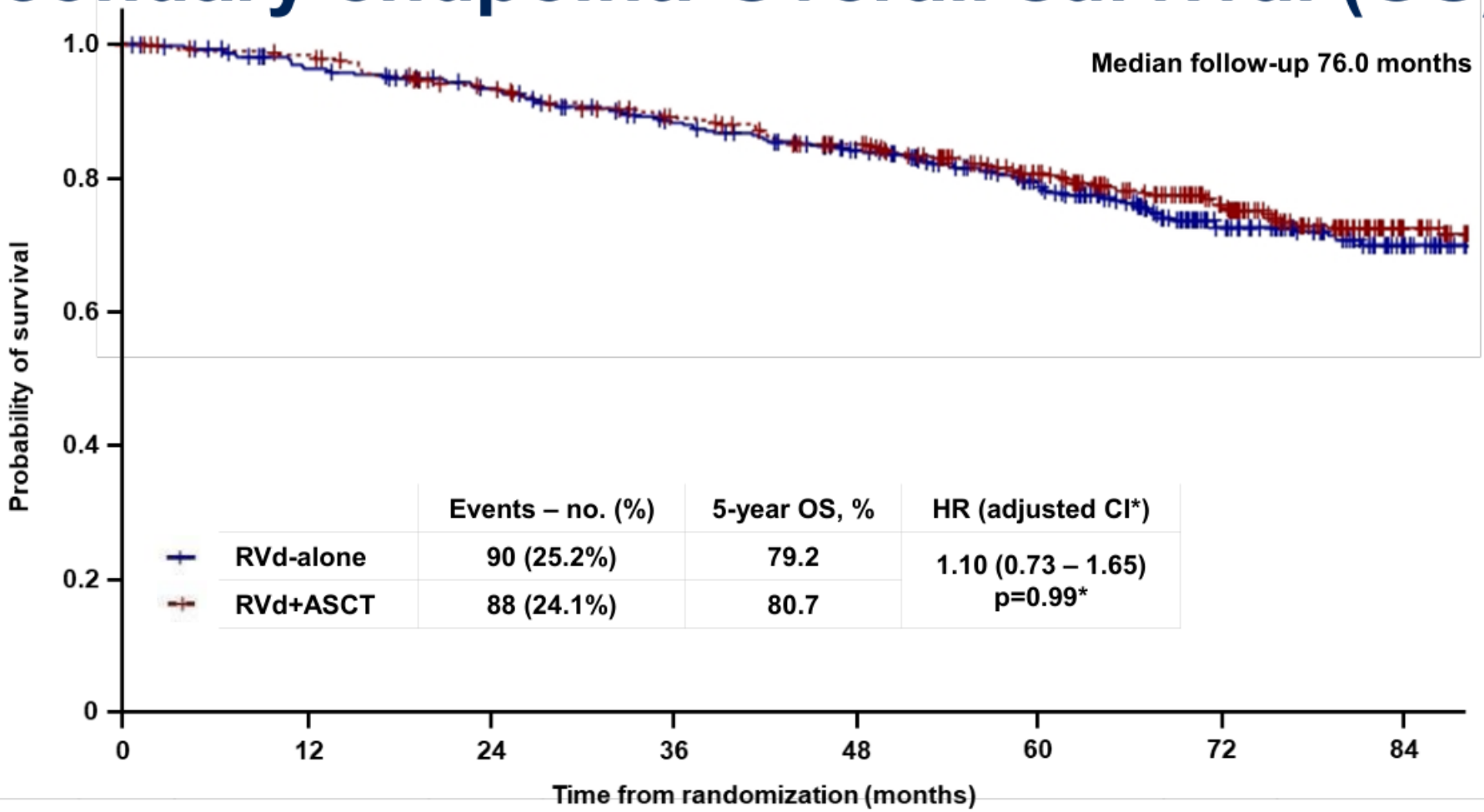
108 RVd-alone, 90 RVd+ASCT patients with samples from start of maintenance

Rate of MRD-negative status (NGS, 10^{-5}):
39.8% vs 54.4%

Odds ratio 0.55 (unadjusted 95% CI 0.30–1.01)



Key secondary endpoint: Overall survival (OS)



	Events – no. (%)	5-year OS, %	HR (adjusted CI*)
RVd-alone	90 (25.2%)	79.2	1.10 (0.73 – 1.65) p=0.99*
RVd+ASCT	88 (24.1%)	80.7	

Patients at risk								
RVd-alone	357	332	313	285	258	214	143	88
RVd+ASCT	365	353	324	300	275	228	165	95

*CIs and p-value adjusted using Bonferroni's correction to control overall family-wise error rate for secondary outcomes. Therefore, CIs use an α level of 0.05/7.

Data cutoff:12/10/21

Subsequent therapy and rate of ASCT in RVD-alone arm (delayed ASCT)

279 RVd-alone and 276 RVd+ASCT patients were off protocol therapy

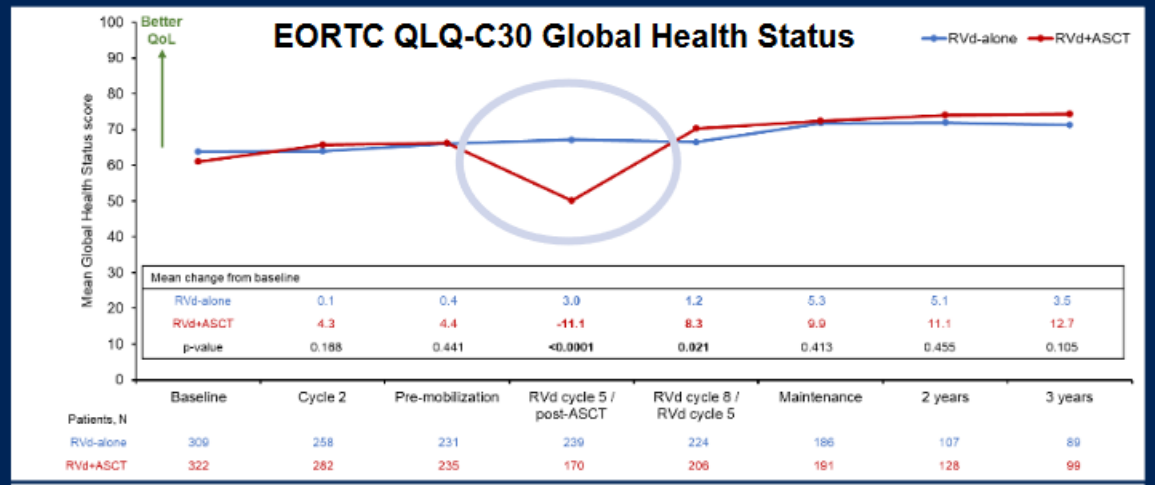
- 222 (79.6%) and 192 (69.6%) had received subsequent therapy (table)

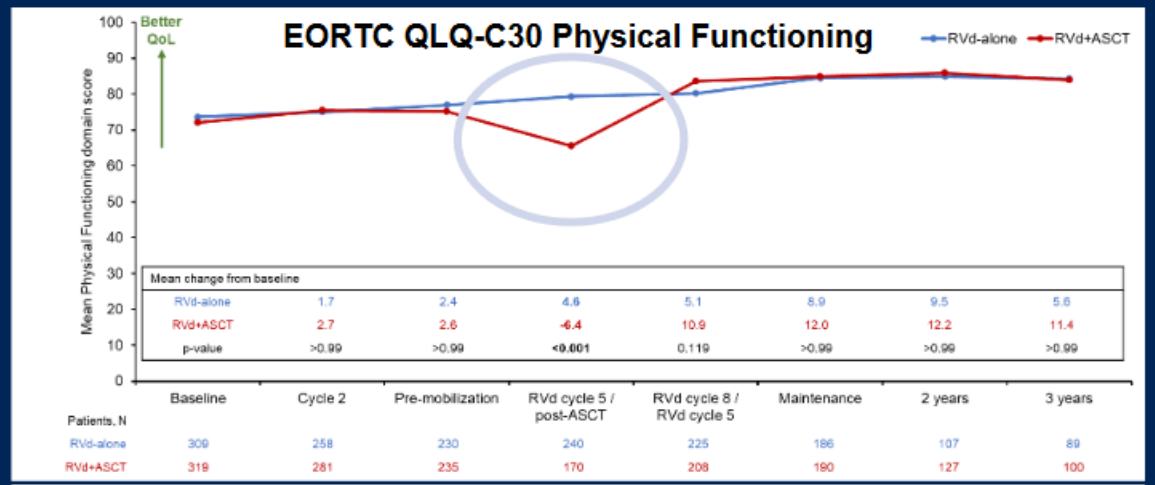
Only 78 (28.0%) of 279 RVd-alone patients had received ASCT at any time following end of study treatment

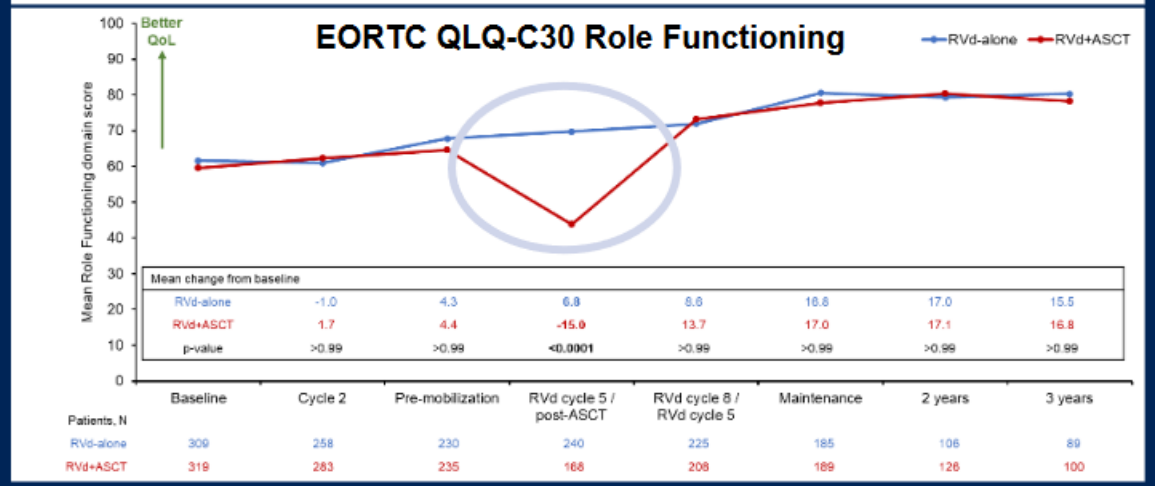
Subsequent therapy in patients off protocol therapy, %	RVd-alone (N=279)	RVd+ASCT (N=276)
Any treatment *	79.6	69.6
Subsequent therapy	n=222	n=192
Any immunomodulatory drug	55.9	58.3
Pomalidomide	30.2	29.2
Lenalidomide	25.7	29.2
Any proteasome inhibitor	55.9	50.0
Bortezomib	27.5	25.5
Carfilzomib	21.2	16.7
Ixazomib	8.1	7.8
Marizomib	0	0.5
Any monoclonal antibody	16.2	27.6
Daratumumab	11.3	21.4
Elotuzumab	4.5	6.3
Isatuximab	0.5	0

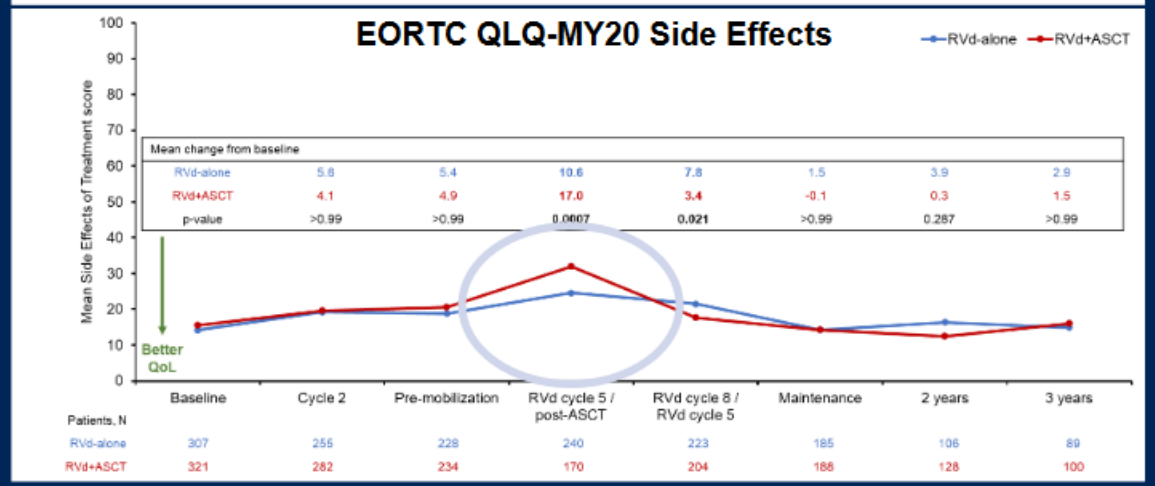
*Including IMiDs, PIs, mAbs, HDACi (panobinostat), ASCT, chemotherapy, RT, steroids, other

QoL over the course of treatment with RVd-alone vs RVd+ASCT (baseline N >300 patients per arm)







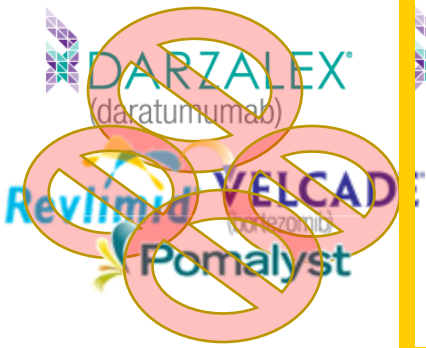


DETERMINATION Takeaways

- Deferred Transplant is a reasonable option
  - Inconvenient for patient's career (waiting to retire?)
  - Need to maintain income
  - Need to care for dependents
  - Wish to maintain current quality of life
- Unclear if MRD status should be used to identify patients for transplant
  - MRD samples were obtained post transplant
- QOL impact of transplant is substantial, but recovers rapidly

Basic Relapsed Therapy Algorithm

No Known Refractoriness



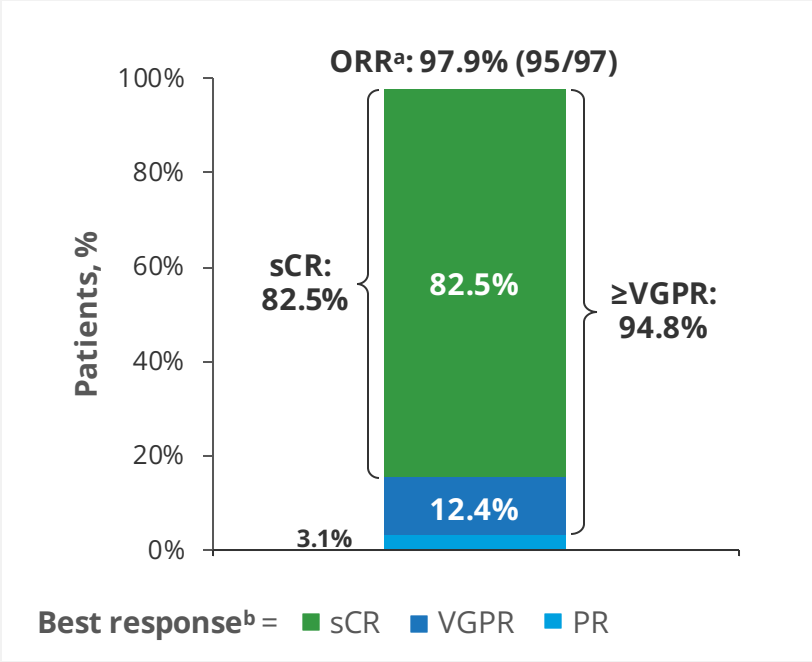
Rd	DVd	DPd	KPd	Selinexor-Kd	**Idecabtagene/Ciltacabtagene**
VRd	DPd	DKd	KCd	Bendamustine	Belantamab Mafodotin
DRd	DKd	Elo-Pd	Selinexor-Pd	KTd-PACE	Selinexor
Transplant?	Elo-Pd	KPd	Transplant?	K-Cyclo-D	Bendamustine
	Transplant?	Transplant?		Transplant?	KTd-PACE
					Transplant?

Contemporary Status with CAR T cells

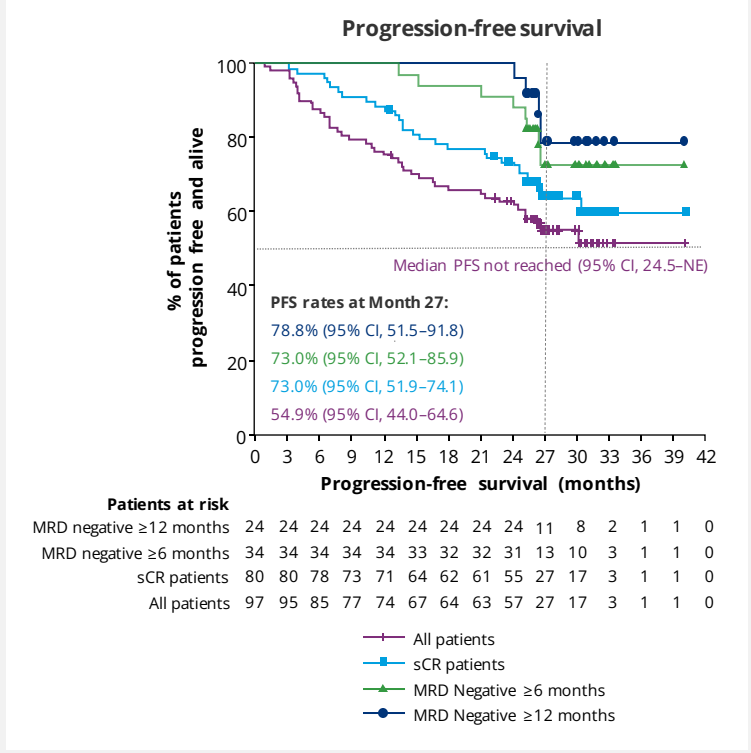
FDA Approved Products	n	ORR	>CR	CRS any	CRS > gr3	Neurotox	Neurotox >gr3	PFS (2-year)
Ciltacabtagene[1] CARTITUDE-1 (**8028**)	113 leukapheresed (97 infused)	83% (98%)	(83%)	95%	5%	21%	10%	61%
Idecabtagene[2] KARMMA-1	140 enrolled (128 infused)	64% (72%)	(33%)	85%	5%	18%	3%	<25%
Idecabtagene “Real World” (**8042**)[3]	138 leukapheresed (108 infused)	65% (83%)	(64%)	82%	4%	15%	5%	NR

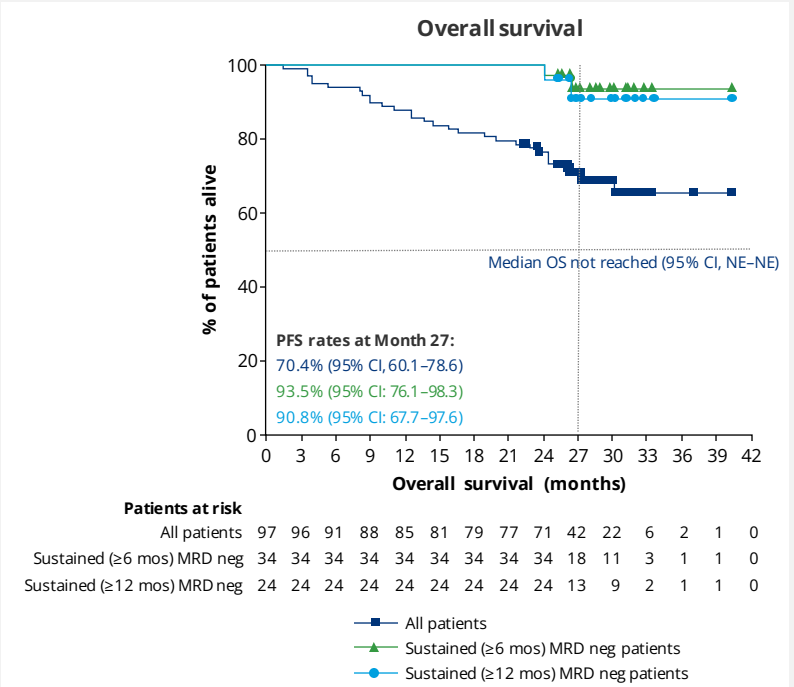
1. Usmani et al. ASCO 2022 Abstract 8028, 2. Munshi et al. NEJM 2021; 384, 3. Hansen et al. ASCO 2022 Abstract 8042

CARTITUDE-1: Efficacy



- Responses deepened over time from the 12-month follow-up
- Median DOR was not estimable
- Most patients in high-risk subgroups responded (ORR range 95.1–100%), including those with high-risk cytogenetics, high tumor burden, or baseline plasmacytomas
  - DOR, PFS, and/or OS were shorter in subgroups with high-risk cytogenetics, ISS stage III, high tumor burden, or plasmacytoma
- High efficacy was achieved despite a lack of detectable CAR-T cell persistence over time





- Median PFS and OS were not reached
- Patients who achieved sCR had improved PFS compared with the overall population
- Of 61 patients evaluable for MRD, 91.8% were MRD-negative at (10^{-5})
- Patients with sustained MRD negativity (10^{-5}) for ≥6 and ≥12 months had improved PFS and OS compared with the overall population

[a]ORR assessed by independent review committee. [b]No patient had CR or stable disease. CAR, chimeric antigen receptor; DOR, duration of response; ISS, International Staging System; MRD, minimal residual disease; NE, not estimable; ORR, overall response rate; OS, overall survival; PR, partial response; PFS, progression-free survival; sCR, stringent CR; VGPR, very good partial response

CARTITUDE-1: Safety

1. Usmani et al. ASCO 2022 Abstract 8028

- **No new treatment-related deaths**
- **A total of 20 SPMs were reported in 16 patients**
  - Nine patients with hematologic malignancies (1 low-grade B-cell lymphoma, 6 MDS, 3 fatal AML[one patient had both MDS and fatal AML])
  - One patient each with malignant melanoma, adenocarcinoma, myxofibrosarcoma, and prostate cancer
  - Six non-melanoma skin cancers
- **One new case of signs and symptoms of parkinsonism (also referred to as movement and neurocognitive TEAEs) (total n=6)**
  - On day 914, patient experienced cognitive slowing, gait instability, and neuropathy (all grade 1), and tremor (grade 3); he is currently stable and functioning, and remains in sCR with no steroids or anticytokine therapies given
  - Work-up is ongoing, including a differential diagnosis as post-encephalitis syndrome
  - Had 2 risk factors for parkinsonism (grade 2 CRS and grade 3 ICANS) after cilta-cel[5,6]
- **Outcomes in the previously reported 5 patients with parkinsonism[1,2]**
  - 3 have died (two from other underlying causes [sepsis and lung abscess] and one related to parkinsonism)
  - One patient has recovered, and one is recovering (ongoing grade 2 symptoms) at the time of the data cut
- **Following implementation of patient management strategies, the incidence of movement and neurocognitive disorders (parkinsonism) has decreased from 6% in CARTITUDE-1 to <0.5% across the CARTITUDE program**

Deaths

	Total (N=97)	Time of death post cilta-cel infusion (days)
Total deaths during the study	30	45–917
Due to progressive disease	14	253–746
AEs unrelated to treatment (n=9)		
Pneumonia	1	109
Acute myeloid leukemia[a]	3	418, 582, 718
Ascites[b]	1	445
Myelodysplastic syndrome	1	803
Respiratory failure	3	733, 793, 829
Septic shock	1	917
AEs related to treatment (n=6)		
Sepsis and/or septic shock	2	45, 162
CRS/HLH	1	99
Lung abscess	1	119
Respiratory failure	1	121
Neurotoxicity	1	247

[a]One patient with AML also had MDS and a cytogenetic profile consistent with MDS (del20q [present before cilta-cel infusion], loss of 5q); another patient who died from AML had both prostate cancer and squamous cell carcinoma of the scalp. [b]Patient died from ascites unrelated to cilta-cel as assessed by the investigator due to noncirrhotic portal fibrosis and nonalcoholic steatosis that was present for many years preceding the study. AML, acute myelogenous leukemia; AEs, adverse events; CRS, cytokine release syndrome; HLH, hemophagocytic lymphohistiocytosis; ICANS, immune effector cell-associated neurotoxicity syndrome; MDS, myelodysplastic syndrome; sCR, stringent complete response; SPM, secondary primary malignancies; TEAE, treatment-emergent AE

1. Berdeja JG, et al. *Lancet* 2021; 398:314-24. 2. Cohen AD, et al. *Blood Cancer J* 2022; 12:32.

Idecabtagene Vicleucel for Relapsed/Refractory Multiple Myeloma: Real-World Experience

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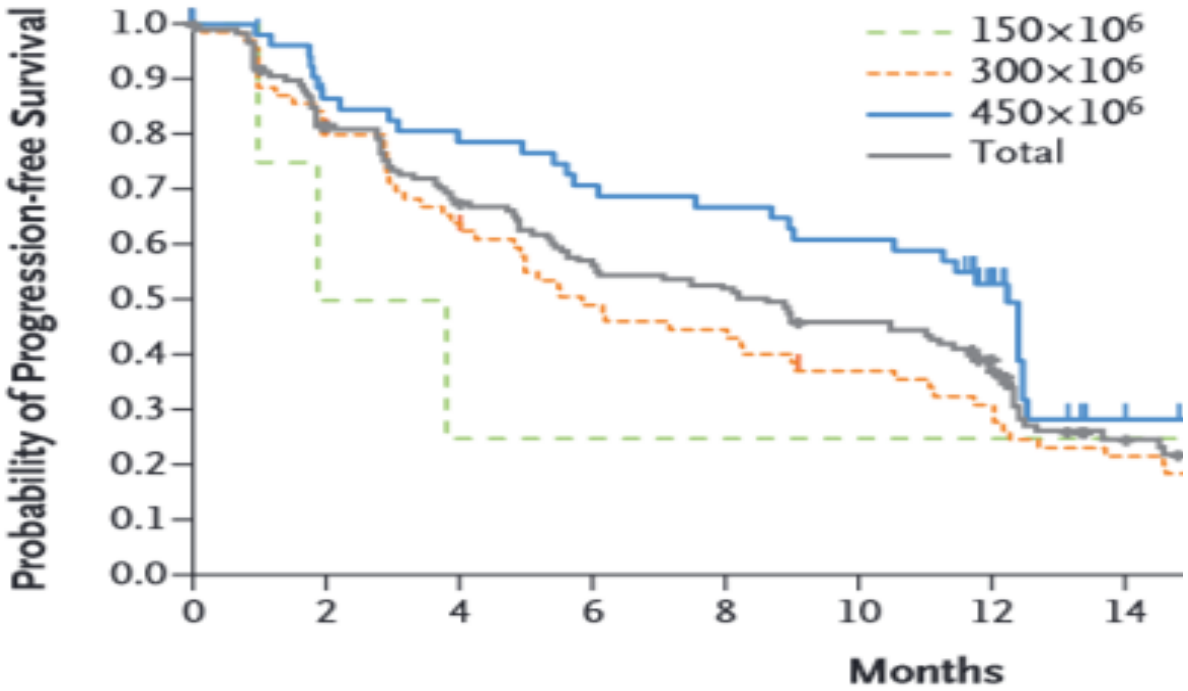
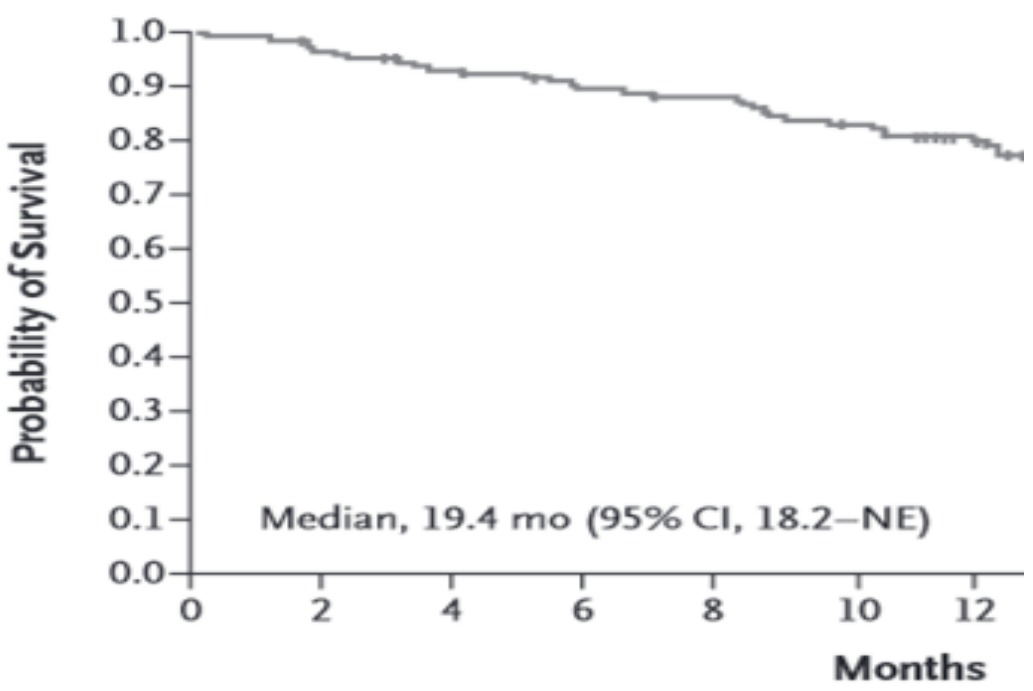
[*]DKH and SS are co-first authors. [**]JM, FLL, and KKP are co-senior authors

[1] H. Lee Moffitt Cancer Center & Research Institute; [2]Stanford University; [3]The University of Kansas Medical Center; [4] The University of Utah Huntsman Cancer Institute; [5]Medical University of South Carolina; [6]University of Maryland Marlene and Stewart Greenebaum Comprehensive Cancer Center; [7]Levine Cancer Institute; [8]Virginia Commonwealth University Massey Cancer Center; [9]The University of Texas MD Anderson Cancer Center; [10]UT Southwestern Harold C. Simmons Comprehensive Cancer Center; [11]Cleveland Clinic Taussig Cancer Center

KARMMA-1 PFS



KARMMA-1 OS



Safety of Ide-cel in the Real World

Characteristic	SOC Ide-cel (N=159)	KarMMa[1] (N=128)
Any CRS*, n (%)	131 (82)	107 (84)
Grade ≥ 3	5 (3)	7 (5)
Any neurotoxicity (NT), n (%)**	29 (18)	23 (18)
Grade ≥ 3	9 (6)	4 (3)
Tocilizumab use, n (%)	113 (71)	67 (52)
Steroid use, n (%)	42 (26)	19 (15)

Total of 21 (13%) deaths in SOC population:

- **N=13 due to myeloma progression**
- **N=8 due to NRM after SOC ide-cel**
  - **Toxicity (N=3)**
  - **Infection (N=3; COVID-19)**
  - **HLH (N=2)**
  - **Cardiomyopathy (N=1)**

***Concomitant grade 5 CRS/HLH (N=1)**

*Lee criteria used for grading CRS. **CTCAE or CARTOX criteria used for grading neurotoxicity

[1]Munshi et al, NEJM 2021; 384:705-716

Baseline Characteristics: 77% KarMMa Ineligible

Characteristic	SOC Ide-cel (N=196)	KarMMa (N=128)
Age, median (range)	64 (36,83)	61 (33,78)
Male Sex, n (%)	113 (53)	76 (59)
Extramedullary disease, n (%)	92 (47)	50 (39)
ECOG PS, n (%)		
0-1	132 (80)	125 (98)
2-4	33 (20)	3 (2)
R-ISS, n (%)		
I	25 (18)	14 (11)
II	73 (54)	90 (70)
III	38 (28)	21 (16)
Unknown	60	3
High-risk cytogenetics, n (%)		
Any high-risk cytogenetics	64 (38)	45 (35)
del (17p)	43 (25)	23 (18)
t(4;14)	25 (15)	23 (18)
t(14;16)	9 (5)	6 (5)
Bridging therapy, n (%)	150 (77)	112 (88)
Prior BCMA therapy, n (%)	43 (22)	0
Prior lines of therapy, median (range)	7 (4,19)	6 (3,16)
Autologous HCT, n (%)	164 (84)	120 (94)
Refractory status, n (%)		
Double-refractory	171 (87)	114 (89)
Triple-refractory	163 (83)	108 (84)
Penta-refractory	86 (44)	33 (26)

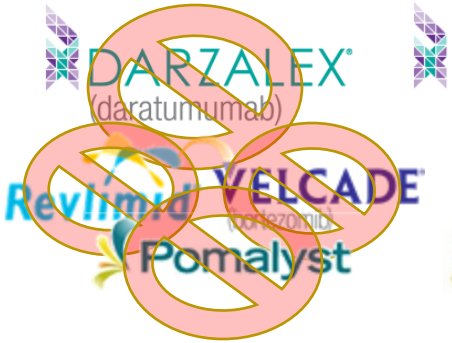
*Patients with unknown ECOG PS and cytogenetics are not included in the table

Contemporary Issues with CAR T cells

- Access
  - Manufacturing capacity is much lower than demand
  - FDA indication requires 4 prior lines of therapy
- Infections
- Post BCMA outcomes
  - No plateau so far

Basic Relapsed Therapy Algorithm

No Known Refractoriness



Rd
VRd
DRd
Transplant?

DVd
DPd
DKd
Elo-Pd
Transplant?

DPd
DKd
Elo-Pd
KPd
Transplant?

KPd
KCd
Selinexor-Pd
Transplant?

Selinexor-Kd
Bendamustine
KTd-PACE
K-Cyclo-D
Transplant?

Idecabtagene/Ciltacabtagene
Bispecific Antibody (Soon)
Belantamab Mafodotin
Selinexor
Bendamustine
KTd-PACE
Transplant?

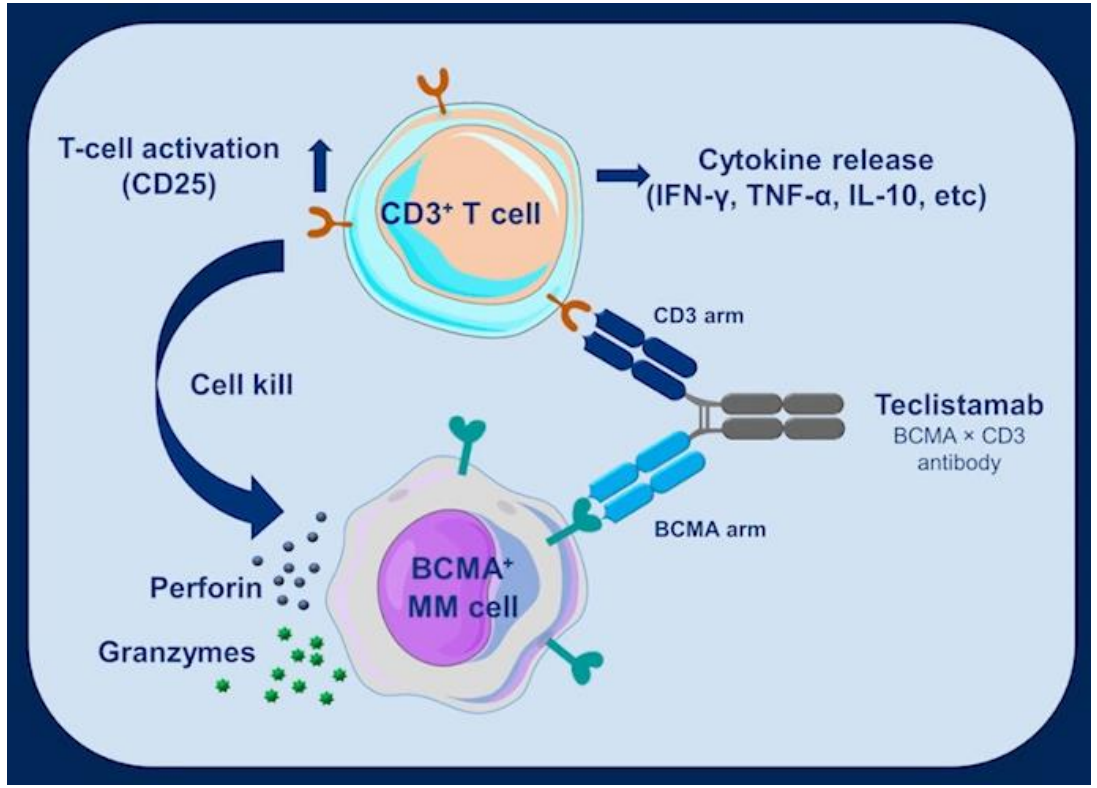
Bispecific Antibodies in Myeloma

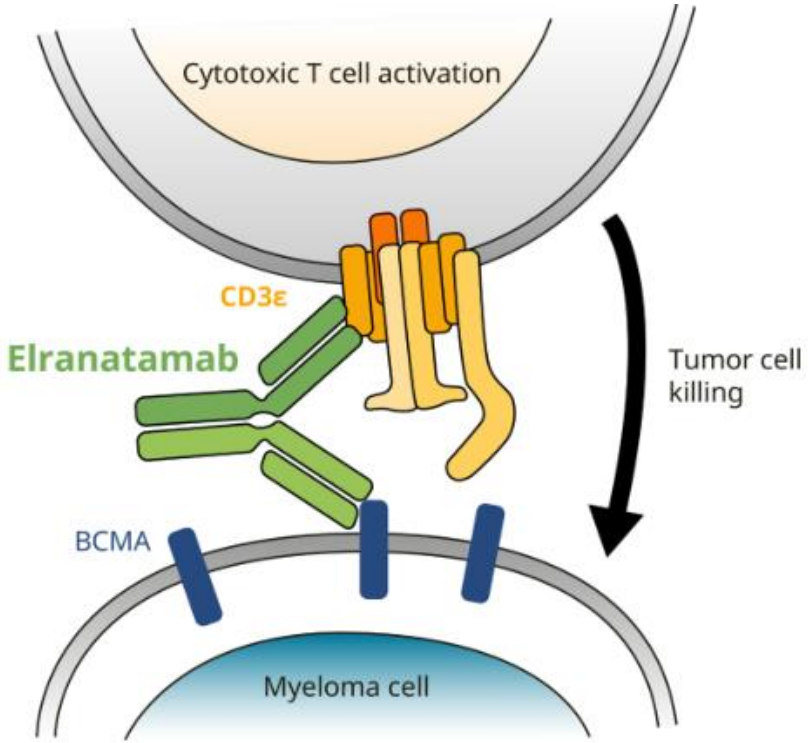
Agent	Abstract	N	Prior LOT (median)	CR/ sCR	ORR, %	Duration of response, months	Median follow up, months	Target
REGN5458[1]		75	5	48%	75%	NR	3	BCMA
Elranatamab[2]	**8014**	94	6		61%	EFS = 90% (6 mo)	8.1	BCMA
Teclistamab[3]	**8007**	165	5	39%	63%	EFS = 68% (12 mo)	18	BCMA
ABBV-383[4]		114	5	38%	81%	NR	NR	BCMA
Cevostamab[5]		160	6	9%	57%	12	NR	FcRH5
Talquetamab[6]	**8015**	184	6	19%	70%	NR	12	GPRC5D

1. Zonder et al. ASH 2021 pg160, 2. Lesokhin et al. ASCO 2022 Abstract 8008, Abstract 3. Nooka et al. ASCO Abstract 8007, 4. Kumar et al. ASH 2021 pg900, 5. Trudel et al. ASH 2021 pg157, 6. Minnema et al. ASCO abstract 8015

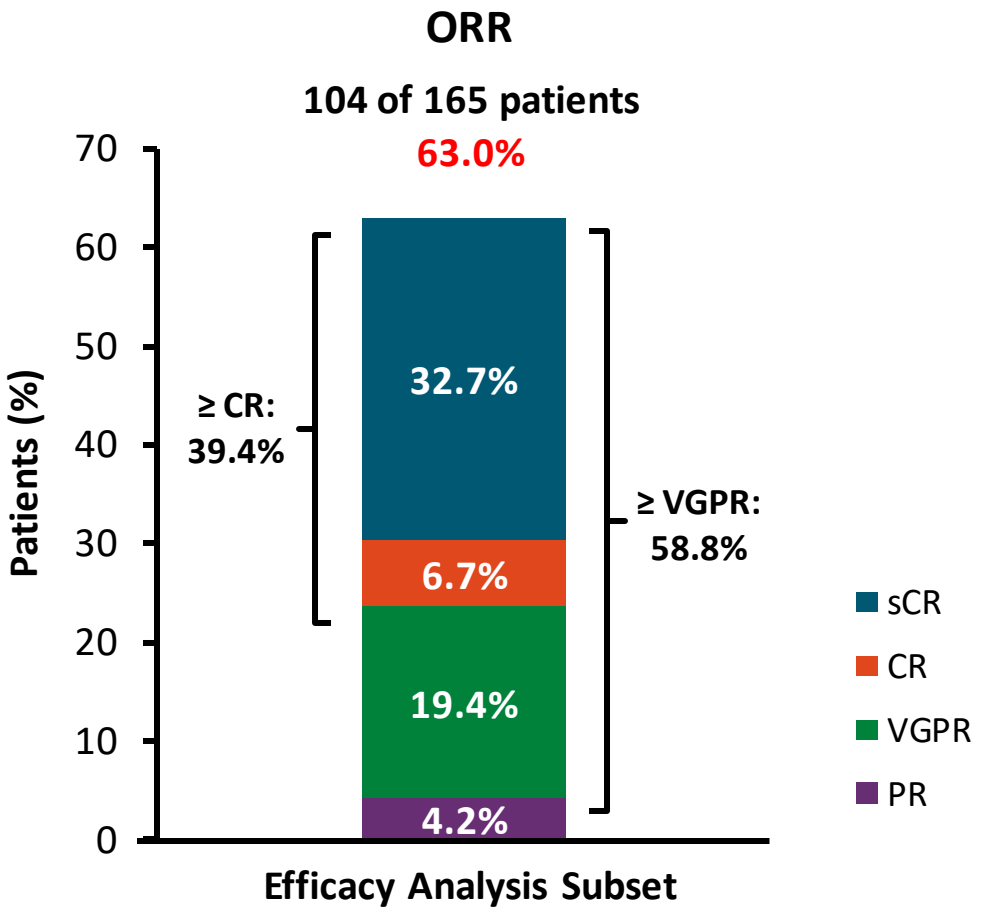
Elranatamab/Teclistamab (8014 / 8007)

- Tested in R/R MM, “triple class exposed”





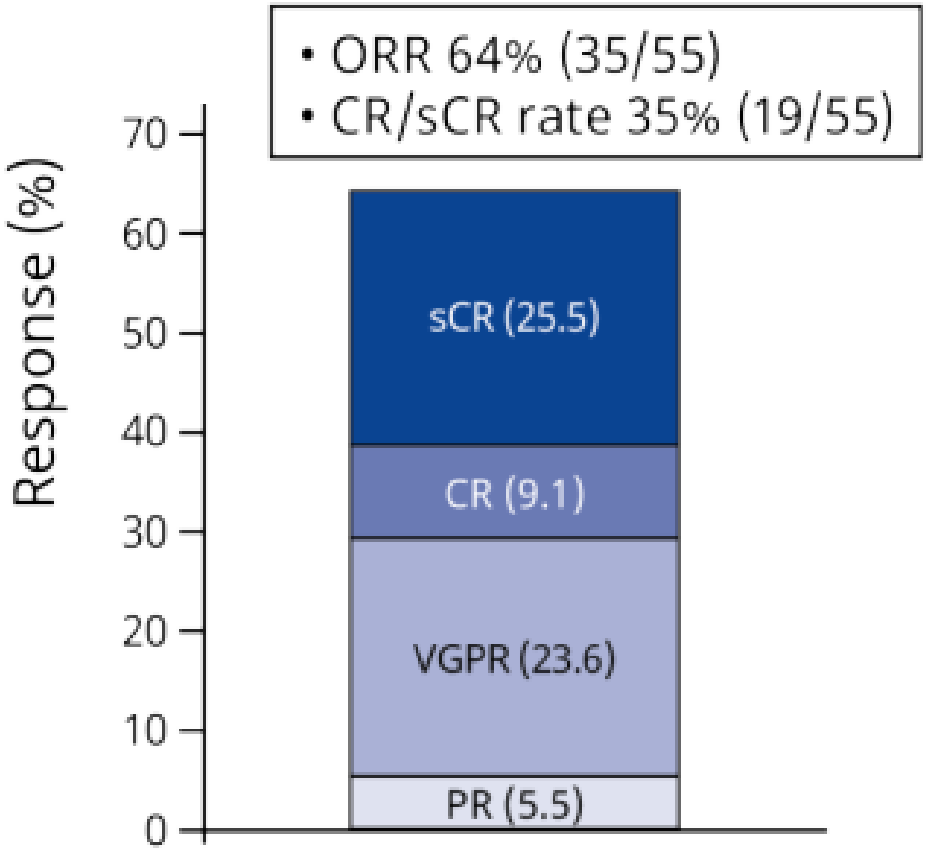
Teclistamab: Response



Median DoR, mo (95% CI)	18.4 (14.9-NE)

Nooka. ASCO 2022. Abstr 8007. Moreau. NEJM. 2022;[Epub].

Elranatamab: Response



Median DoR, mo (95% CI)	Not Reported

Jakubowiak. ASCO 2022. Abstr 8014

Teclistamab: Safety

AEs in ≥20% of Patients, n (%)	All Patients (N = 165)	
	Any Grade	Grade 3/4
Hematologic		
▪ Neutropenia	117 (70.9)	106 (64.2)
▪ Anemia		
▪ Thrombocytopenia		
▪ Lymphopenia		
Nonhematologic		
▪ CRS		
▪ Diarrhea		
▪ Fatigue		
▪ Nausea		
▪ Pyrexia		
▪ Injection site erythema	43 (26.1)	0 (0)
▪ Headache	39 (23.6)	1 (0.6)
▪ Arthralgia	36 (21.8)	1 (0.6)
▪ Constipation	34 (20.6)	0 (0)
▪ Cough	33 (20.0)	0 (0)

	Teclistamab	Elranatamab
ICANS (any)	3%	2.2%
Infection (any)		52%
Infection (gr ≥ 3)	13% +	25%
Hypo-γ-globulin	75%	
COVID-19 death	12 / 165 (7%)	

Nooka. ASCO 2022. Abstr 8007. Moreau. NEJM. 2022;[Epub].

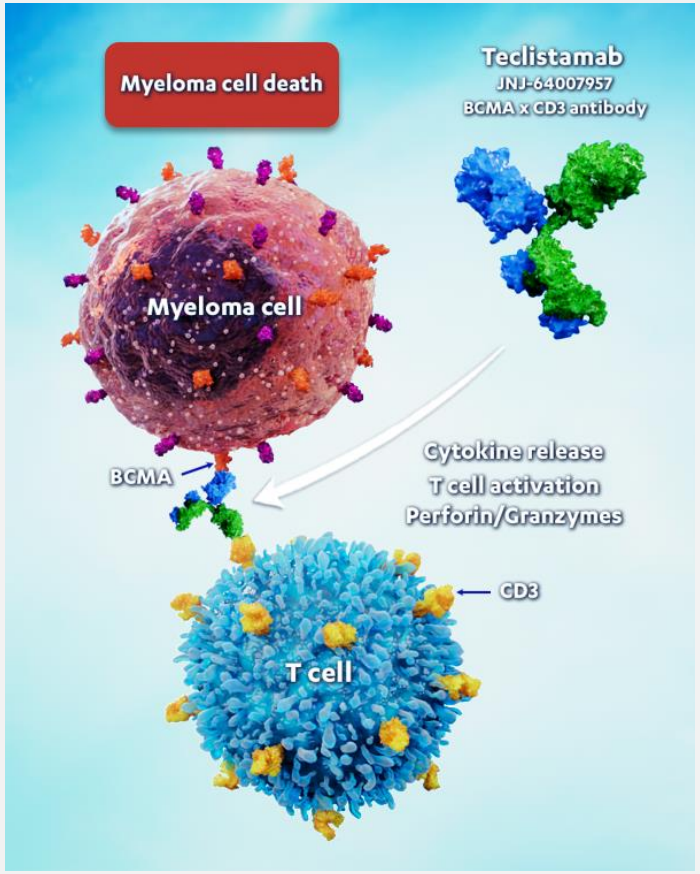
Elranatamab: Safety

Adverse event, n (%)	Total (N=55)	Grade 3	Grade 4
Hematologic			
Neutropenia	41 (74.5)	14 (25.5)	25 (45.5)
	36 (65.5)	26 (47.3)	0
	29 (52.7)	3 (5.5)	26 (47.3)
	28 (50.9)	5 (9.1)	10 (18.2)
	48 (87.3)	0	0
	31 (56.4)	0	0
	22 (40.0)	2 (3.6)	0
Fatigue	22 (40.0)	3 (5.5)	0
Dry skin	20 (36.4)	0	0
Hypophosphatemia	20 (36.4)	13 (23.6)	1 (1.8)
Decreased appetite	19 (34.5)	1 (1.8)	0

Jakubowiak. ASCO 2022. Abstr 8014

Teclistamab Treatment After Other BCMA-Targeted Agents

- **BCMA** represents an established target for treatment of patients with MM
- **Three classes of BCMA-targeted agents** have emerged in recent years, including CAR-T, ADCs (eg, belantamab mafodotin), and bispecific antibodies[1]
- **Teclistamab (JNJ-64007957)** is a full size, fully humanized, off-the-shelf, BCMA x CD3 bispecific antibody that redirects CD3+ T cells to mediate T-cell activation and subsequent lysis of BCMA-expressing myeloma cells[2]
- The multicohort **phase 1/2 MajesTEC-1 study** is investigating teclistamab in patients with RRMM who previously received ≥3 lines of therapy[3,4]
- In Cohort A (patients without prior BCMA-targeted treatment), weekly teclistamab (following step-up doses) was well tolerated with a high response rate[4]
- **Here we present efficacy and safety results from Cohort C of MajesTEC-1, which enrolled patients previously exposed to BCMA-targeted treatment**



ADC, antibody drug conjugate; BCMA, B-cell maturation antigen; CAR-T, chimeric antigen receptor T cell; MM, multiple myeloma; RRMM, relapsed/refractory MM

1. Strassl I, et al. *Cancers* 2021; 13(18):4701. 2. Pillarisetti K, et al. *Blood Adv* 2020; 4(18):4538. 3. Usmani SZ, et al. *Lancet* 2021; 398(10301):665. 4. Moreau P, et al. 63rd ASH Annual Meeting and Exposition 2021. Abstract #896.

Patients

Characteristic		N=40
Age (years), median (range)		63.5 (32–82)
Male, n (%)		25 (62.5)
Race, n (%)	White	35 (87.5)
	African American/Black	3 (7.5)
	Asian	1 (2.5)
	Not reported	1 (2.5)
Bone marrow plasma cells ≥60%[a], n (%)		4 (10.0)
Extramedullary plasmacytomas ≥1[b], n (%)		12 (30.0)
High-risk cytogenetics[c], n (%)		12 (33.3)
ISS stage, n (%)	I	21 (52.5)
	II	9 (22.5)
	III	10 (25.0)
Time since diagnosis (years), median (range)		6.5 (1.1–24.1)

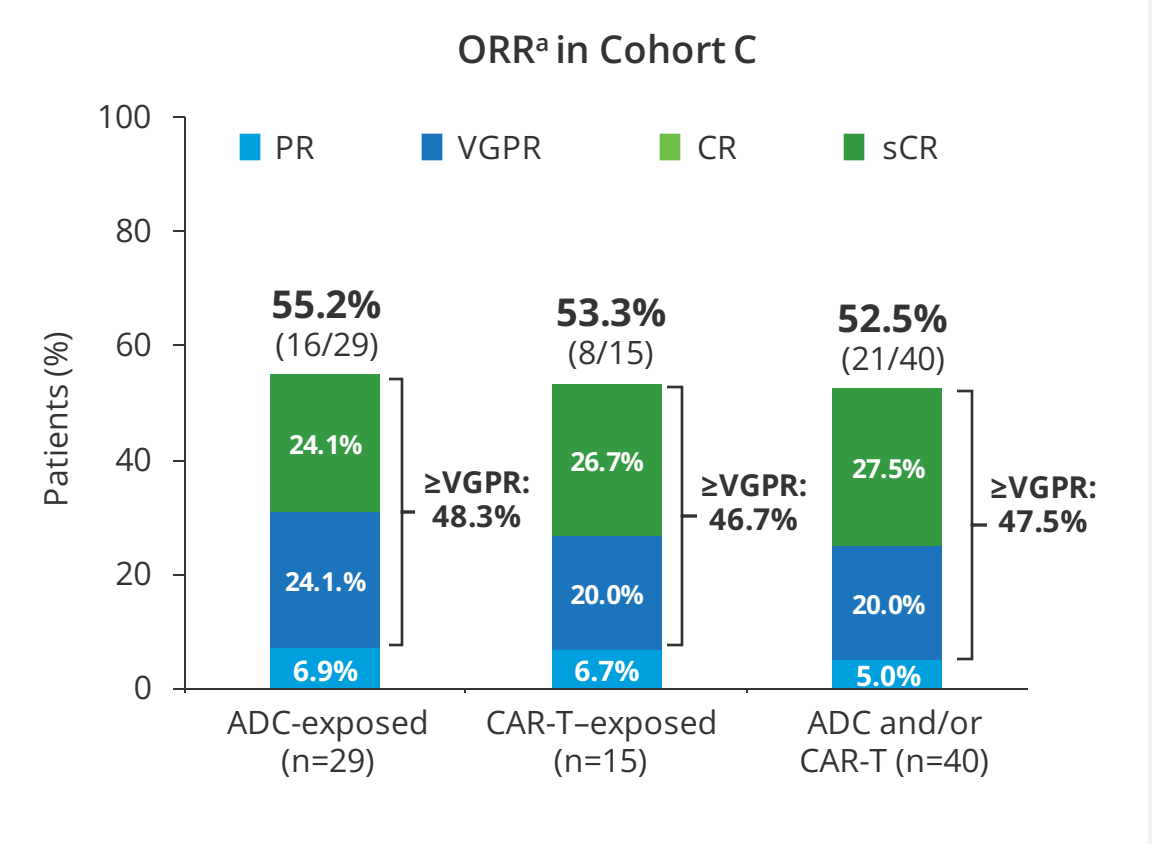
Characteristic	N=40
Prior lines of therapy, median (range)	6 (3–14)
Prior stem cell transplantation, n (%)	36 (90.0)
Exposure status, n (%)	
Triple-class[d]	40 (100)
Penta-drug[e]	32 (80.0)
BCMA-targeted treatment	40 (100)[f]
ADC	29 (72.5)
CAR-T	15 (37.5)
Refractory status, n (%)	
Triple-class[d]	34 (85.0)
Penta-drug[e]	14 (35.0)
To last line of therapy	34 (85.0)

- **Median follow-up** was 12.5 months (range: 0.7–14.4); 17 of 40 patients (42.5%) remain on treatment
- Median duration of treatment was 5.2 months (range: 0.2–13.6)
- Baseline BCMA expression and soluble BCMA levels were comparable in patients with and without prior BCMA-targeted treatment

Data analysis cutoff date: March 16, 2022.
[a]Includes bone marrow biopsy and aspirate. [b]Soft-tissue plasmacytomas not associated with bone were included. [c]del(17p), t(4:14), and/or t(14;16) (n=36). [d]≥1 PI, ≥1 IMiD, and ≥1 anti-CD38 antibody. [e]≥2 PIs, ≥2 IMiDs, and ≥1 anti-CD38 mAb. [f]4 patients had received both ADC and CAR-T.
ADC, antibody drug conjugate; BCMA, B-cell maturation antigen; CAR-T, chimeric antigen receptor T cell; IMiD, immunomodulatory drug; ISS, International Staging System; PI, proteasome inhibitor

Overall Response Rate

- The ORR was **52.5%** (21/40; 95% CI: 36.1–68.5) in patients with prior exposure to either class of BCMA-targeted treatment
  - ADC-exposed patients: **55.2%**
  - CAR-T–exposed patients: **53.3%**
  - Both ADC and CAR-T: 3 of 4 patients responded
- MRD negativity (10^{-5}) rate was 17.5%
  - Among ≥CR patients: **63.6%** (7/11)

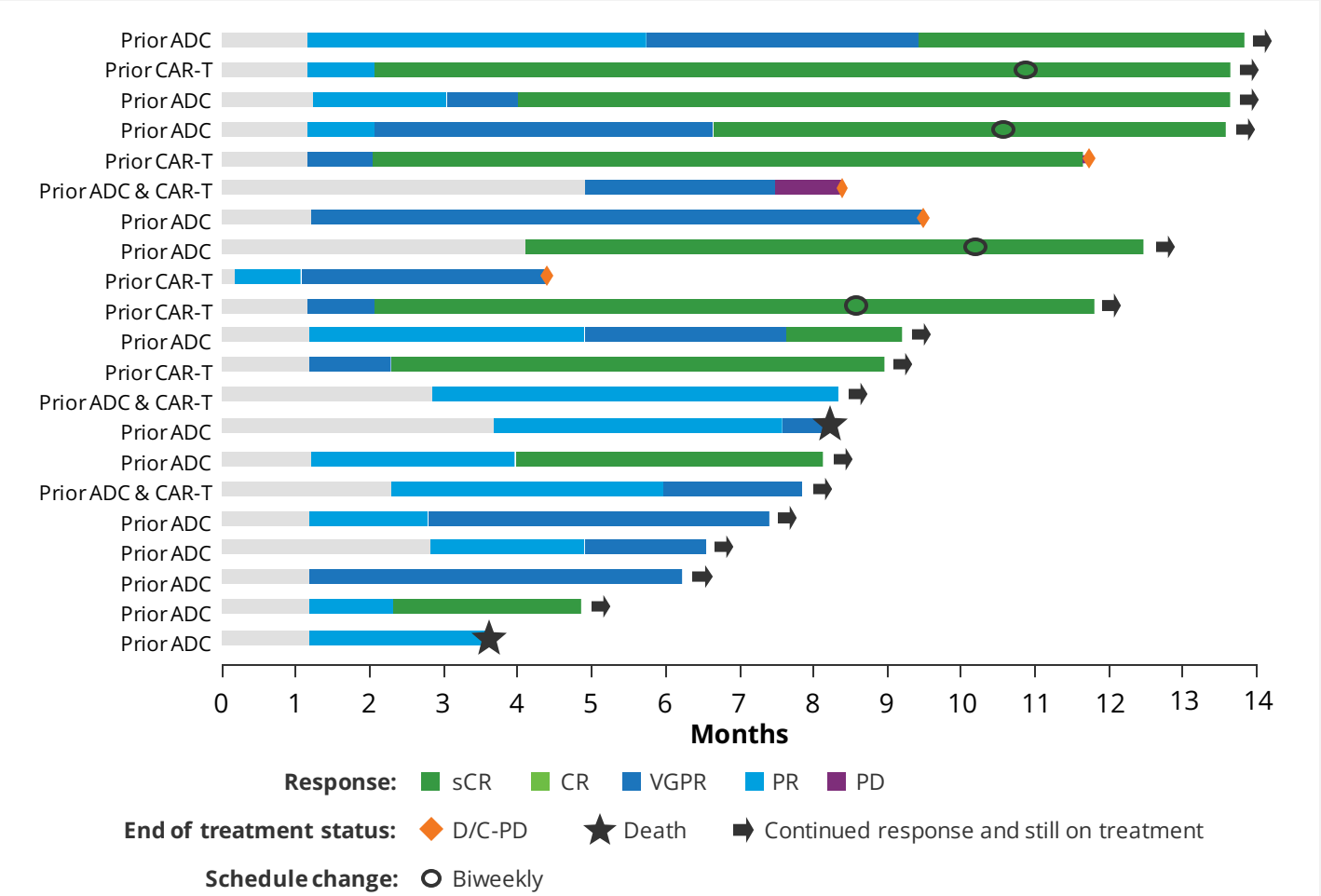


Data analysis cutoff date: March 16, 2022.

[a]PR or better, IRC assessed, per IMWG 2016 criteria.

ADC, antibody drug conjugate; BCMA, B-cell maturation antigen; CAR-T, chimeric antigen receptor T cell; CR, complete response; IMWG, International Myeloma Working Group; IRC, independent review committee; MRD, minimal residual disease; ORR, overall response rate; PR, partial response; sCR, stringent complete response; VGPR, very good partial response

Durability of Response



- Responses occurred early, deepened over time, and were durable
- Median time to first response was 1.2 months (range: 0.2–4.9)
- Median time to best response was 2.9 months (range: 1.1–9.5)
- 15 (71.4%) of the 21 responders had responses that deepened over time
- Median DOR was not reached (95% CI: 10.5 months to NE)
- With a median follow-up of 11.8 months (range: 3.6–13.8) in responders, 71.4% of responders (15/21) maintained their response

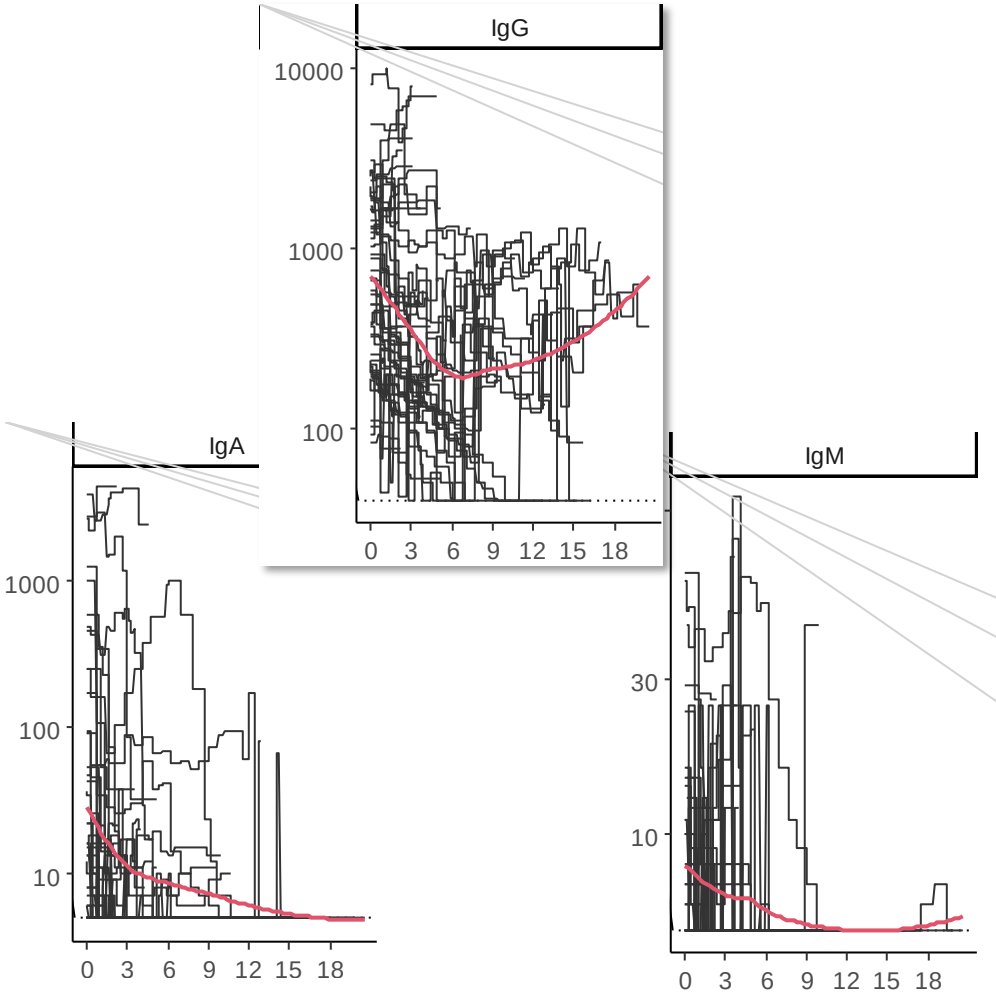
Data analysis cutoff date: March 16, 2022.
ADC, antibody drug conjugate; CAR-T, chimeric antigen receptor T cell; CR, complete response; D/C, discontinued; DOR, duration of response; NE, not estimable; PD, progressive disease; PR, partial response; sCR, stringent complete response; VGPR, very good partial response

Humoral Immunodeficiency Kinetics (8049)

- BCMAxCD3 Bispecific antibodies induce Profound and Prolonged hypogammaglobulinemia
  - Teclistamab study: 75% prevalence of hypogammaglobulinemia
  - Teclistamab/Elranatamab: 13-25% Gr 3+ infections
- Hammons et al. reported their experience with these agents

Humoral Immunodeficiency Kinetics (8049)

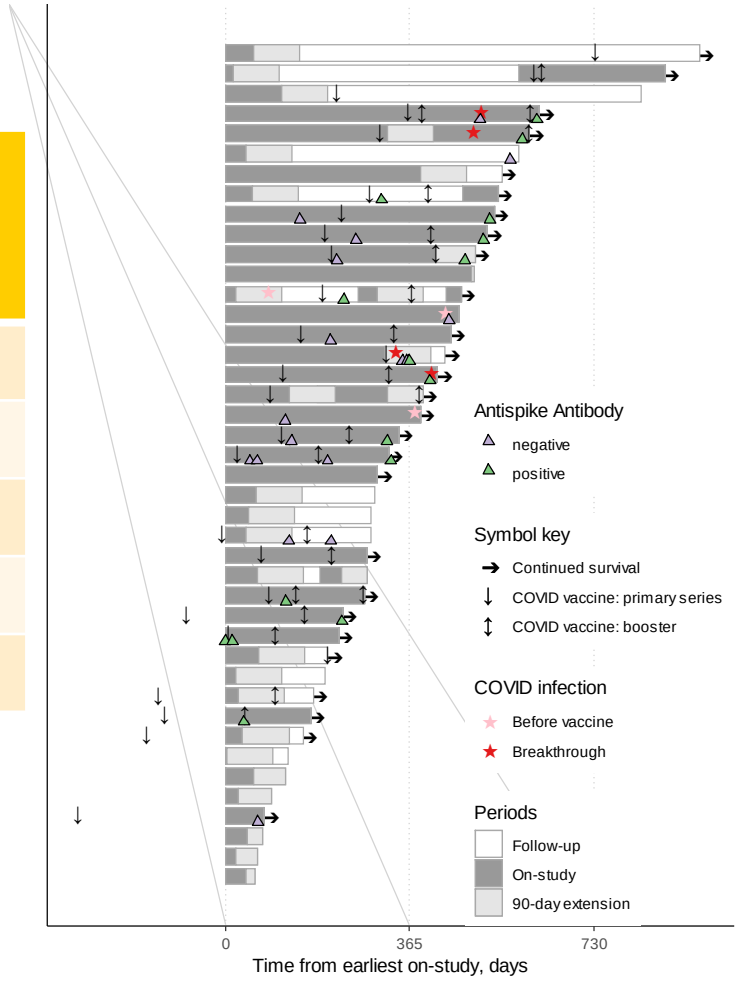
- N=49 patients treated with BCMAxCD3 bispecific antibodies
- At start, Median IgG = 560 mg/dl
- Nadir, Median IgG = 159 mg/dl
  - IgG Undetectable (<40mg/dl) in 28% at some point in therapy.
- Median time to nadir = 3 months
- Median nadir IgA/IgM both <5 mg/dl



Humoral Immunodeficiency Kinetics (8049)

- Infectious event: 71% of patients
  - Increasing incidence with time
- No response to COVID19 immunization series in 57%

Months s/p BCMAxCD3 BisAB	Cumulative Risk of Infection
3	41%
6	57%
9	64%
12	67%
15	70%

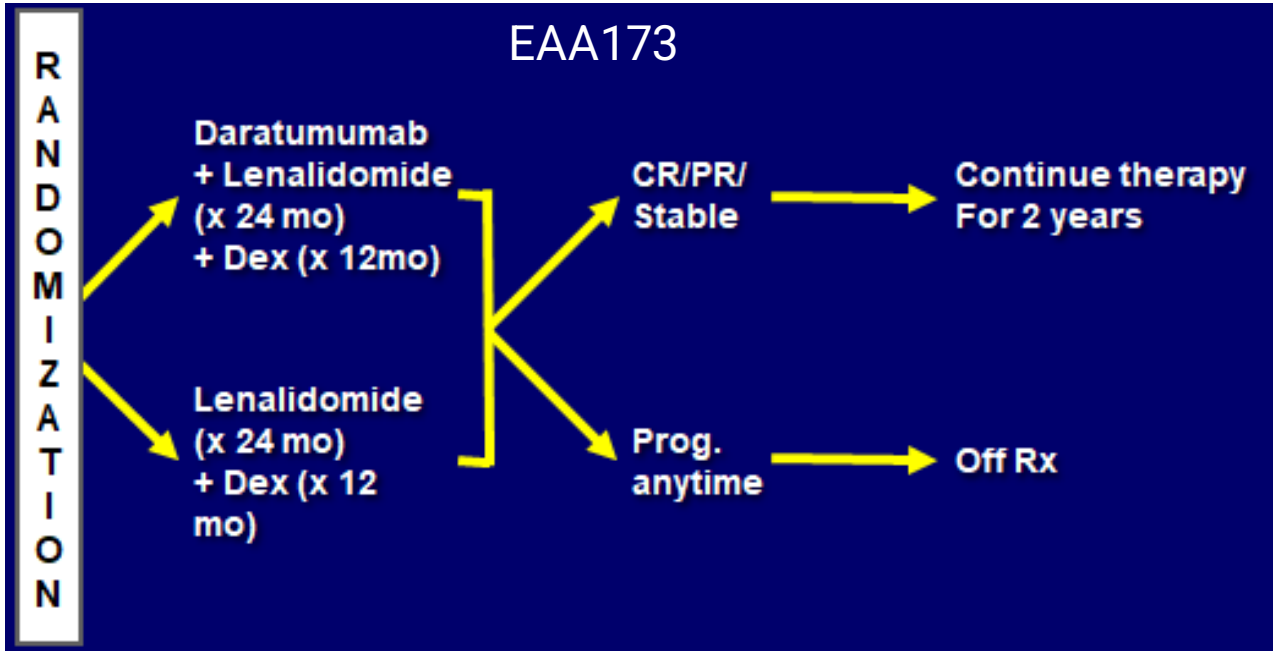


Summary ASCO 2022

- Overall Survival is not different in initial vs deferred transplant strategy in all comers
  - Deferred strategy is a reasonable option
- CAR T cells offer high response rates
  - Real world experience similar to that of studies
- BCMA x CD3 bispecific antibodies are also efficacious
  - Frequent low grade CRS necessitates step up dosing, hospitalization to start
- Infectious complications are common s/p BCMA targeted therapies

Myeloma Clinical Trials @ Iowa

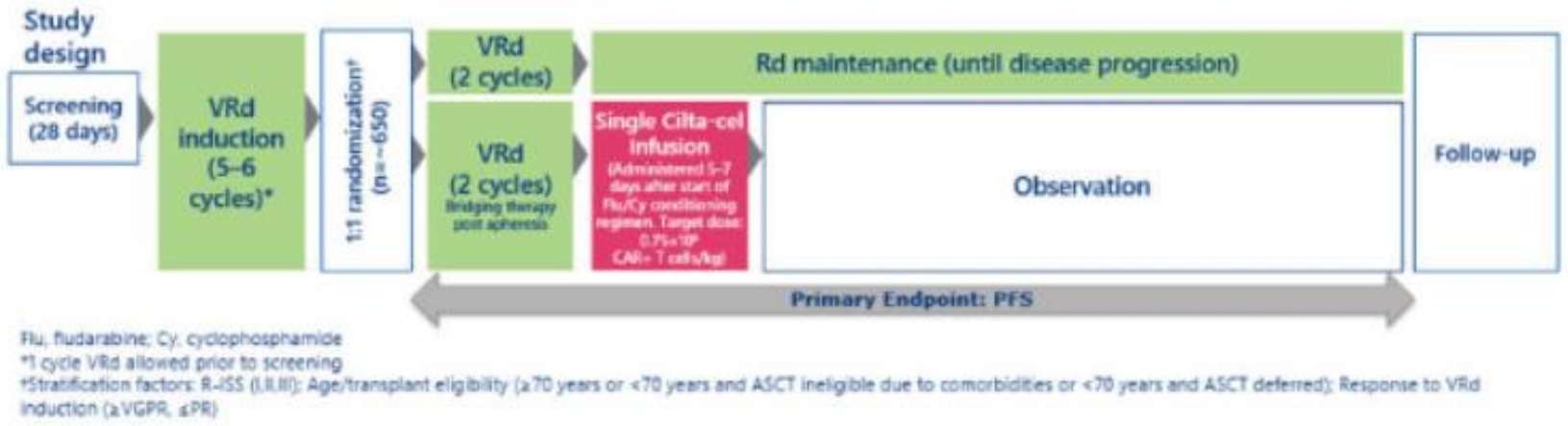
- High risk smoldering myeloma
  - High risk cytogenetics
  - Marrow plasma cells >20%
  - Light chain ratio > 20:1
  - M protein > 2.0 g/dl



Myeloma Clinical Trials @ Iowa

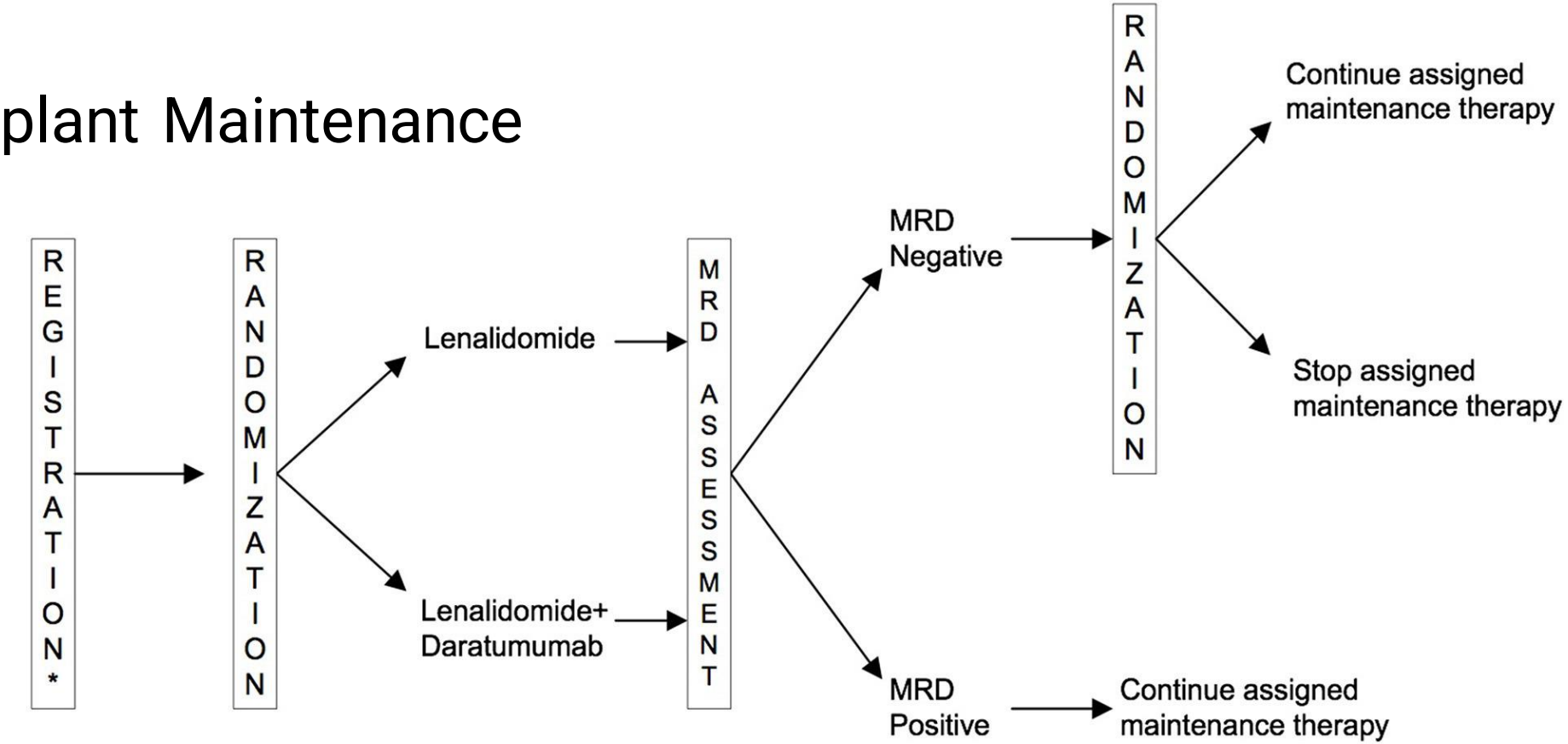
- Newly Diagnosed Myeloma
  - CARTITUDE 5
  - CARTITUDE 6
    - Likely 2023

Figure: CARTITUDE-5 study design



Myeloma Clinical Trials @ Iowa

- Post-transplant Maintenance
  - S1803



*Patients may register any time following induction therapy.

Myeloma Clinical Trials @ Iowa

- Relapsed/Refractory
  - TAK173
    - CD38-INFa conjugate
    - R/R myeloma, 1-3+ prior lines
  - MagnitisMM 4 (Elranatamab)
    - BCMAxCD3 bispecific combos
    - R/R myeloma, 1-3 prior lines
  - SEA-BCMA
    - Anti-BCMA antibody
    - R/R myeloma, 3+ prior lines
  - Melphalan + Vitamin C