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Myeloma Updates: Highlights from ASCO 2020

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ANNUAL MIDWEST REGIONAL ASCO REVIEW 2020 VIRTUAL CONFERENCE
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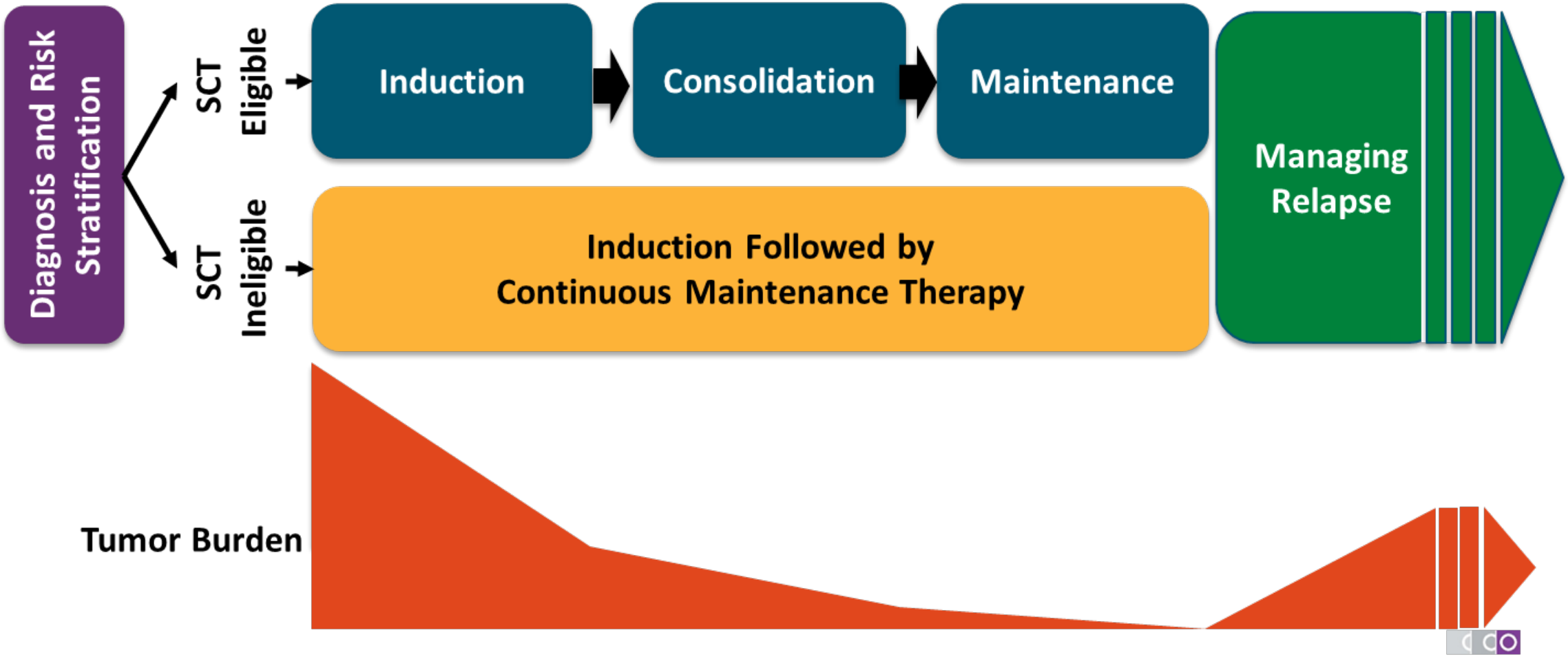
Disclosures

- Consulting/Advisory Boards: Celgene/BMS, Takeda, Janssen, Seattle Genetics, Kite Pharma, Oncopeptides, GlaxoSmithKline
- Research support: Novartis
- Intellectual property licensed by institution to: Novartis

Outline

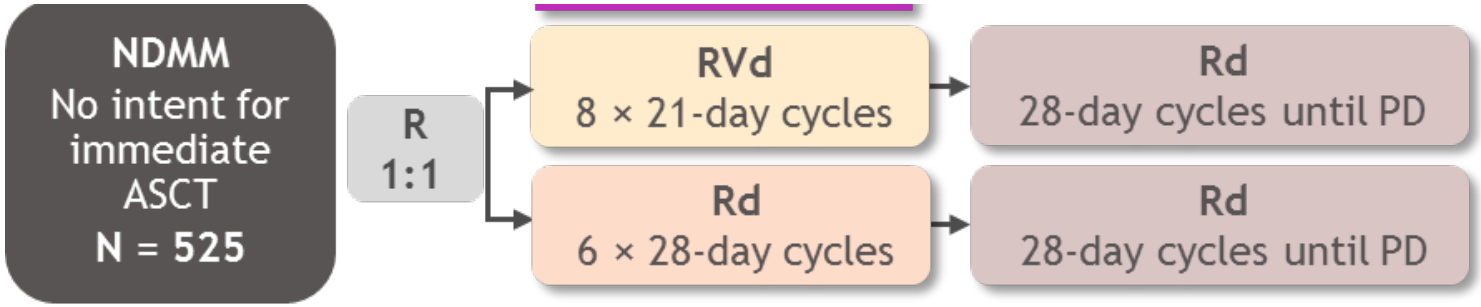
- Newly-diagnosed MM
  - #LBA3, ECOG E1A11/ENDURANCE (KRd vs VRd)
  - #8507, SWOG S1211 (Elotuzumab-VRd vs VRd for hi-risk)
  - #8508, GMMG CONCEPT (Isatuximab-KRd for hi-risk)
- Autologous stem cell transplant
  - #8506, BMT-CTN 0102/STAMINA long-term f/up
- Early relapsed MM
  - #8501, BOSTON (Selinexor-Vd vs Vd)
  - #8502, DREAMM6 (Belantamab-Vd)
- Relapsed/refractory MM
  - #8500, CC-92480 + dex
  - #100, Teclistamab (BCMA x CD3 bispecific Ab)
  - #8503, KARMMA study (ide-cel BCMA CAR T cells)
  - #8504, EVOLVE study (orva-cel BCMA CAR T cells)
  - #8505, CARTITUDE-1 (JNJ-4528 BCMA CAR T cells)

Treating newly-diagnosed myeloma



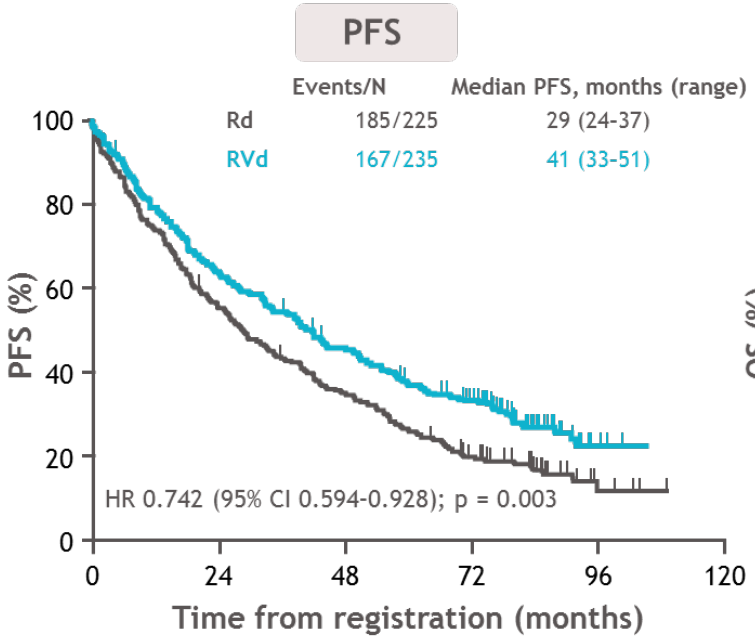
Slide credit: clinicaloptions.com

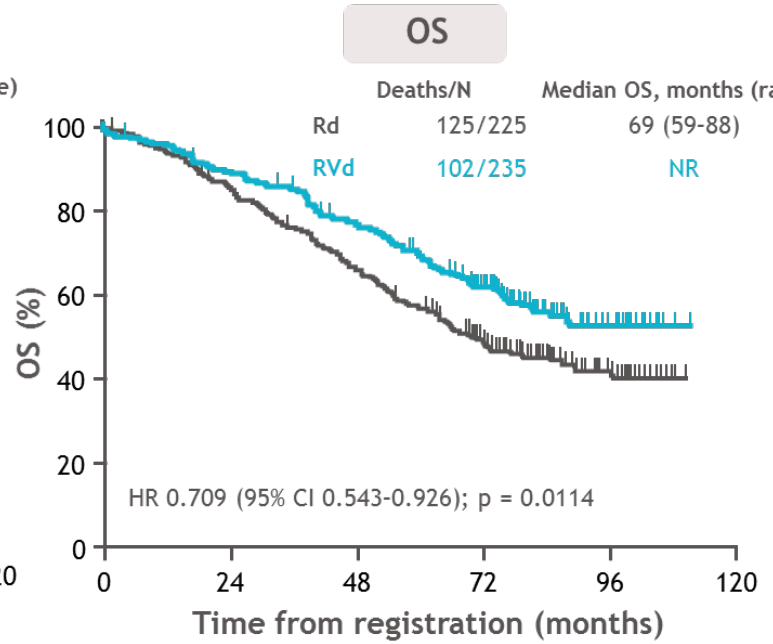
SWOG 0777: RVd superior to Rd for NDMM



Response	RVD	RD
ORR	81.5%	71.5%
PR	38%	39.7%
VGPR	27.8%	23.4%
CR	15.7%	8.4%
≥VGPR	43.5%	31.8%

Median follow-up: 84 months





Durie et al, Lancet 2017; updated ASH 2018, #1992

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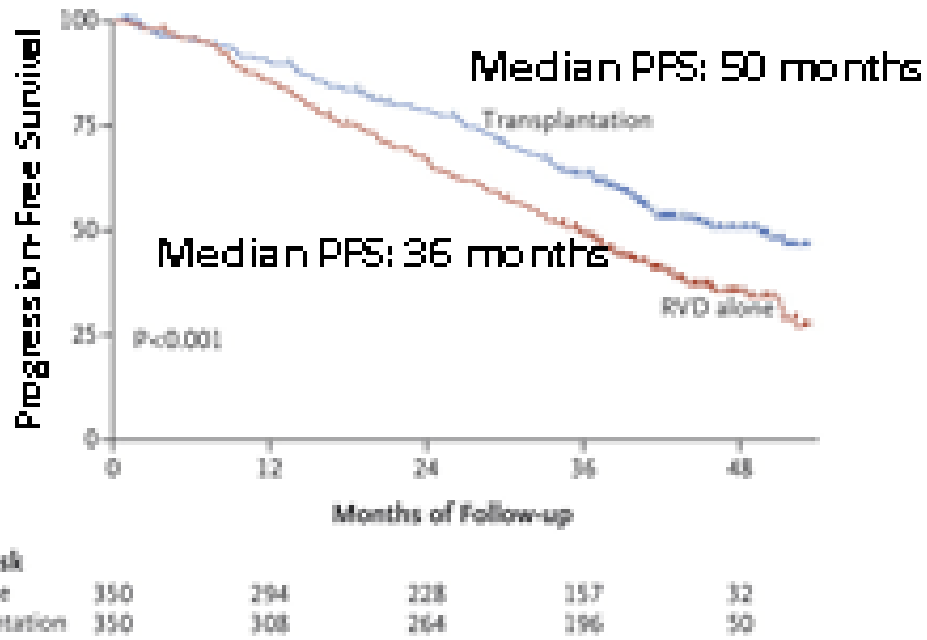
IFM 2009: RVd + ASCT prolongs PFS compared to RVd alone

Best Response	Deferred ASCT	Upfront ASCT	P Value
ORR	97%	99%	
PR	20%	11%	
VGPR	29%	29%	
CR	48%	59%	0.03
≥VGPR	77%	88%	0.001
MRD-[1]	65%	79%	<0.001

[1]MRD tested by flow cytometry in VGPR/CR pts

Median Follow-Up: 44 months for the deferred ASCT group, 43 months for the upfront ASCT group



Len maintenance given for 1 year

4-Year OS: 82% vs 81% for deferred and upfront ASCT, respectively

Attal et al, NEJM 2017

KRd (Carfilzomib, lenalidomide, dex) summary table

Trial	Pop	n	Induction	AutoSCT	Consol	Maint	ORR	≥VGPR	CR	PFS (mos)
MMRC 1	TE, TI	53	KRd x 8	MEL200 (n=7)	KRd x 16	R to PD	98%	81%	51% (sCR)	69% 4yrs
NCI	TE, TI	45	KRd x 8	-	-	R 2 yrs	98%	89%	67%	67 (TTP)
MMRC 2	TE	76	KRd x 4	MEL200	KRd x 4	KRd 1yr→R?	-	91%	78%	86% 3yrs
IFM	TE	46	KRd x 4	MEL 200	KRd x 4	R 1 yr	-	85%	61%	91% 2yrs
FORTE	TE	158	KRd x 4	MEL200	KRd x 4	KR vs R	-	89%	60%	-
FORTE	TE	157	KRd x 12	-	-	KR vs R	-	87%	61%	-

AutoSCT = autologous stem cell transplant; Consol = consolidation; CR = complete response; K = carfilzomib; Maint = maintenance; MEL200 = melphalan 200 mg/m2; ORR = overall response rate; Pop = population; PFS = progression-free survival; R = lenalidomide; TE = transplant-eligible; TI = transplant-ineligible; V = bortezomib; yr = year

Jakobowiak, Haematologica 2016, #S101; Kazandijan, JAMA Onc 2018; Jakubowiak, ASH 2017, #4533; Roussel, ASH 2016, #1142; Gay, ASCO 2019, #8002

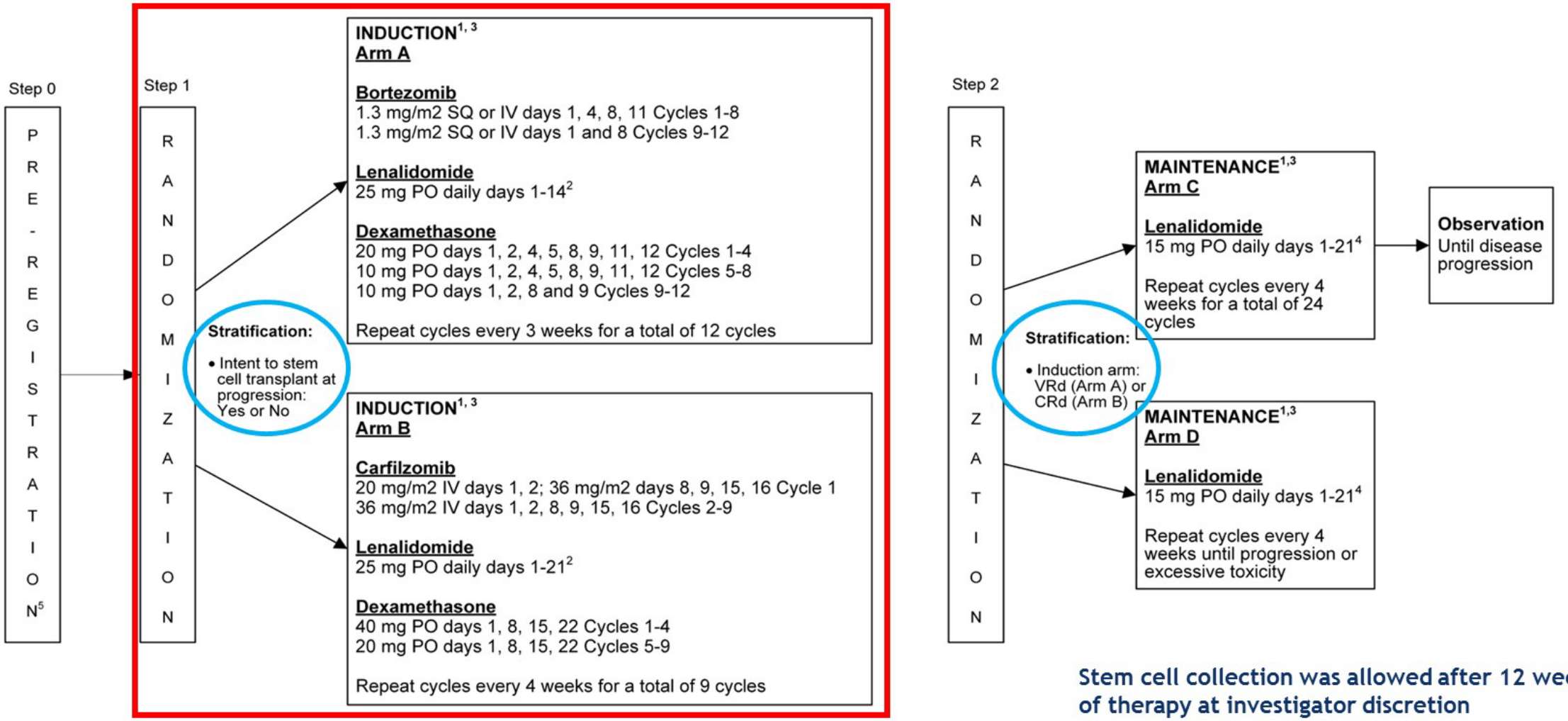
ECOG-ACRIN
cancer research group
Reshaping the future of patient care

Carfilzomib, lenalidomide, and dexamethasone (KRd) versus bortezomib, lenalidomide, and dexamethasone (VRd) for initial therapy of newly diagnosed multiple myeloma: results of ENDURANCE (E1A11) phase 3 trial

Shaji K. Kumar, Susanna J. Jacobus, Adam D. Cohen, Matthias Weiss, Natalie Scott Callander, Avina A. Singh, Terri L. Parker, Alexander Menter, Alex Yang, Benjamin Marshall Parsons, Pankaj Kumar, Prashant Kapoor, Aaron Seth Rosenberg, Jeffrey A. Zonder, Edward Anthony Faber, Sagar Lonial, Paul G. Richardson, Robert Z. Orlowski, Lynne I. Wagner, S. Vincent Rajkumar

Federally Funded Research

E1A11 (ENDURANCE): KRd vs VRd for standard-risk NDMM



Stem cell collection was allowed after 12 weeks of therapy at investigator discretion

Kumar et al, ASCO 2020, LBA3

E1A11 (ENDURANCE): KRd vs VRd for standard-risk NDMM

Baseline Demographics

Hi risk patients excluded: t(14;16), t(14;20), del17p, high risk GEP, LDH 2xULN

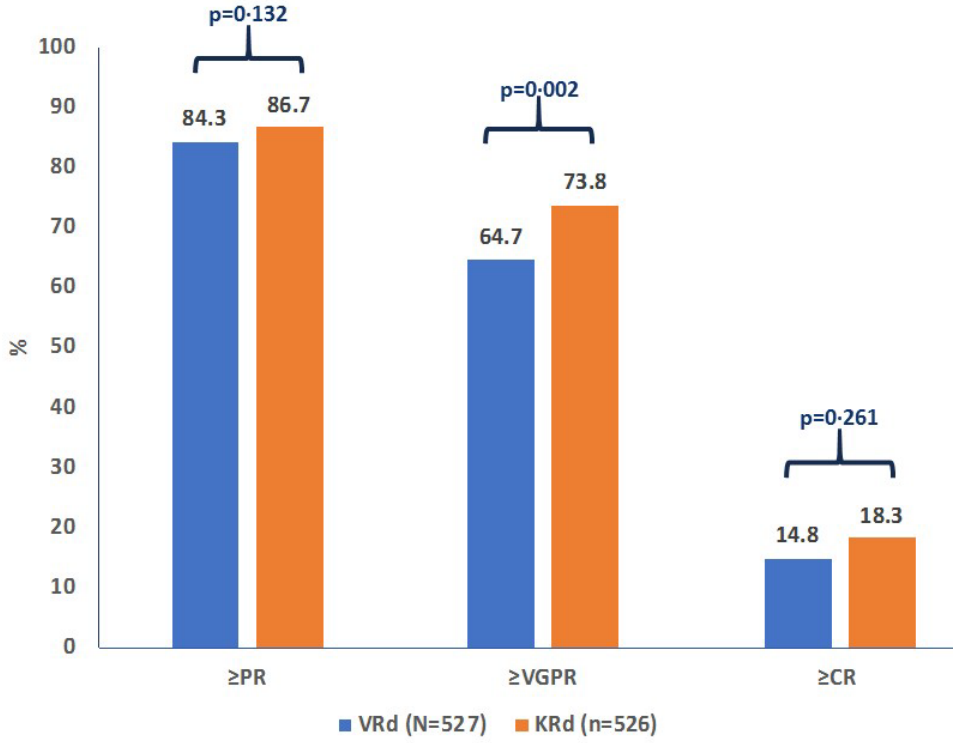
Variable	Category	VRd (n=542) N (%)	KRd (n=545) N (%)	Total (n=1087) N (%)
Age (y), median (range)		64 (32-88)	65 (35-86)	65 (32-88)
	>/=70 years	167 (30.8)	177 (32.5)	344 (31.6)
	>/=65 years	264 (48.7)	288 (52.8)	552 (50.8)
Gender	Male	315 (58.1)	327 (60.0)	642 (59.1)
Race	White	443 (84.5)	448 (86.3)	891 (85.4)
	Black	68 (13.0)	59 (11.4)	127 (12.2)
	Other	13 (2.5)	12 (2.3)	25 (2.4)
ECOG PS	PS0	212 (39.1)	241 (44.2)	453 (41.7)
	PS1	270 (49.8)	249 (45.7)	519 (47.8)
	PS2-3	60 (11.1)	55 (10.1)	115 (10.5)
ISS Stage	I	144 (30.6)	157 (32.5)	301 (31.6)
	II	203 (43.1)	207 (42.9)	410 (43.0)
	III	124 (26.3)	119 (24.6)	243 (25.5)
Measurable Disease Type	SPEP&UPEP	115 (21.2)	114 (20.9)	229 (21.1)
	SPEP	305 (56.3)	296 (54.3)	601 (55.3)
	UPEP	57 (10.5)	79 (14.5)	136 (12.5)
	FLC	58 (10.7)	51 (9.4)	109 (10.0)
	Bone Marrow	4 (0.7)	4 (0.7)	8 (0.7)
	Not Measurable	3 (0.6)	1 (0.2)	4 (0.4)

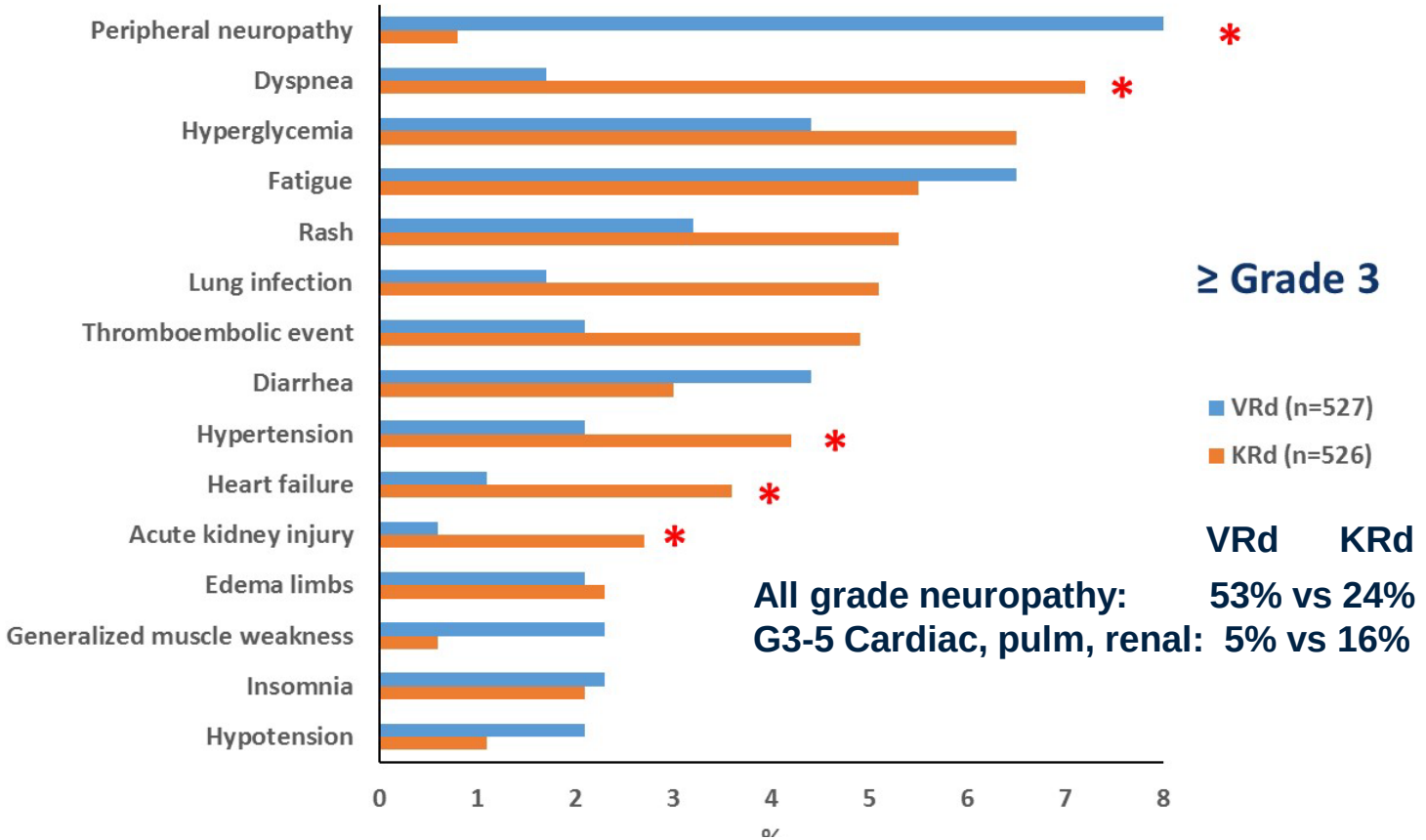
Variable	VRd (n=542) median (IQR)	KRd (n=545) median (IQR)	Total (n=1087) median (IQR)
Bone marrow plasma cell (%)	52 (30-75)	50.5 (30-72)	51 (30-75)
Albumin (g/dL)	3.8 (3.4-4.2)	3.8 (3.4-4.2)	3.8 (3.4-4.2)
Beta 2 microglobulin (ug/mL)	3.6 (2.6-5.6)	3.9 (2.8-6)	3.8 (2.6-5.8)
Hemoglobin (g/dL)	11 (9.6-12.4)	11.2 (9.8-12.6)	11.1 (9.7-12.5)
Calcium (mg/dL)	9.3 (8.9-9.8)	9.4 (8.9-9.8)	9.3 (8.9-9.8)
Serum M Spike (g/dL)	3 (1.8-4.2)	2.9 (1.8-4.2)	3 (1.8-4.2)
Urine M Spike (mg/24hr)	297.8 (64.9-1099)	257.1 (49.4-1312.4)	275 (56.4-1157)
Creatinine (mg/dL)	1 (0.8-1.3)	1 (0.8-1.3)	1 (0.8-1.3)
Lactate Dehydrogenase (U/L)	171 (136-222)	166 (135-203)	168 (136-209)

Variable	Category	VRd (n=542) N (%)	KRd (n=545) N (%)	Total (n=1087) N (%)
Cytogenetics	Normal	326 (71.8)	331 (72.3)	657 (72.0)
	Abnormal	128 (28.2)	127 (27.7)	255 (28.0)
	Missing	88	67	175
t(11;14)	Abnormal	87 (20.6)	80 (18.7)	167 (19.7)
t(4;14)	Abnormal	44 (10.4)	36 (8.4)	80 (9.4)

Kumar et al, ASCO 2020, LBA3

E1A11 (ENDURANCE): KRd vs VRd for standard-risk NDMM





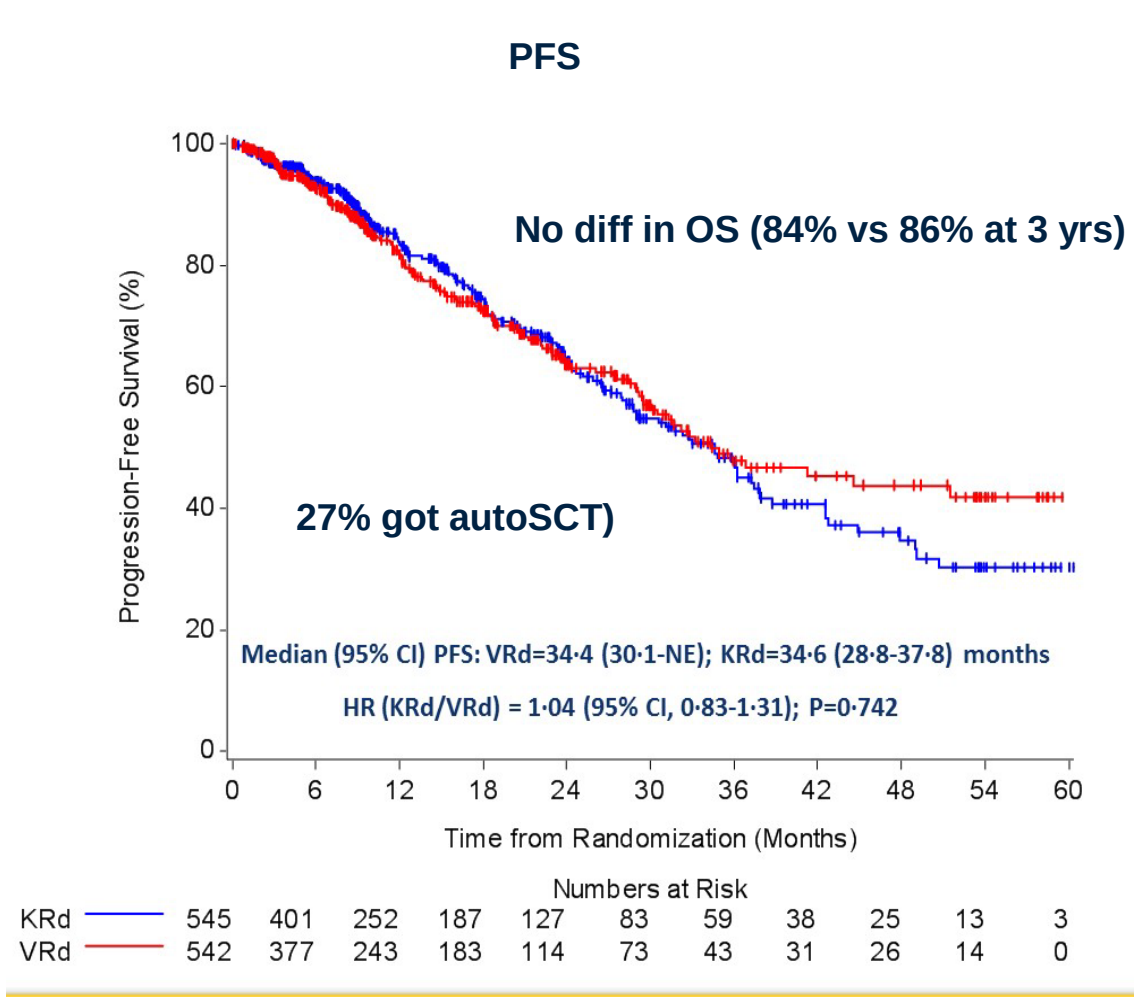
	VRd	KRd
All grade neuropathy:	53%	vs 24%
G3-5 Cardiac, pulm, renal:	5%	vs 16%

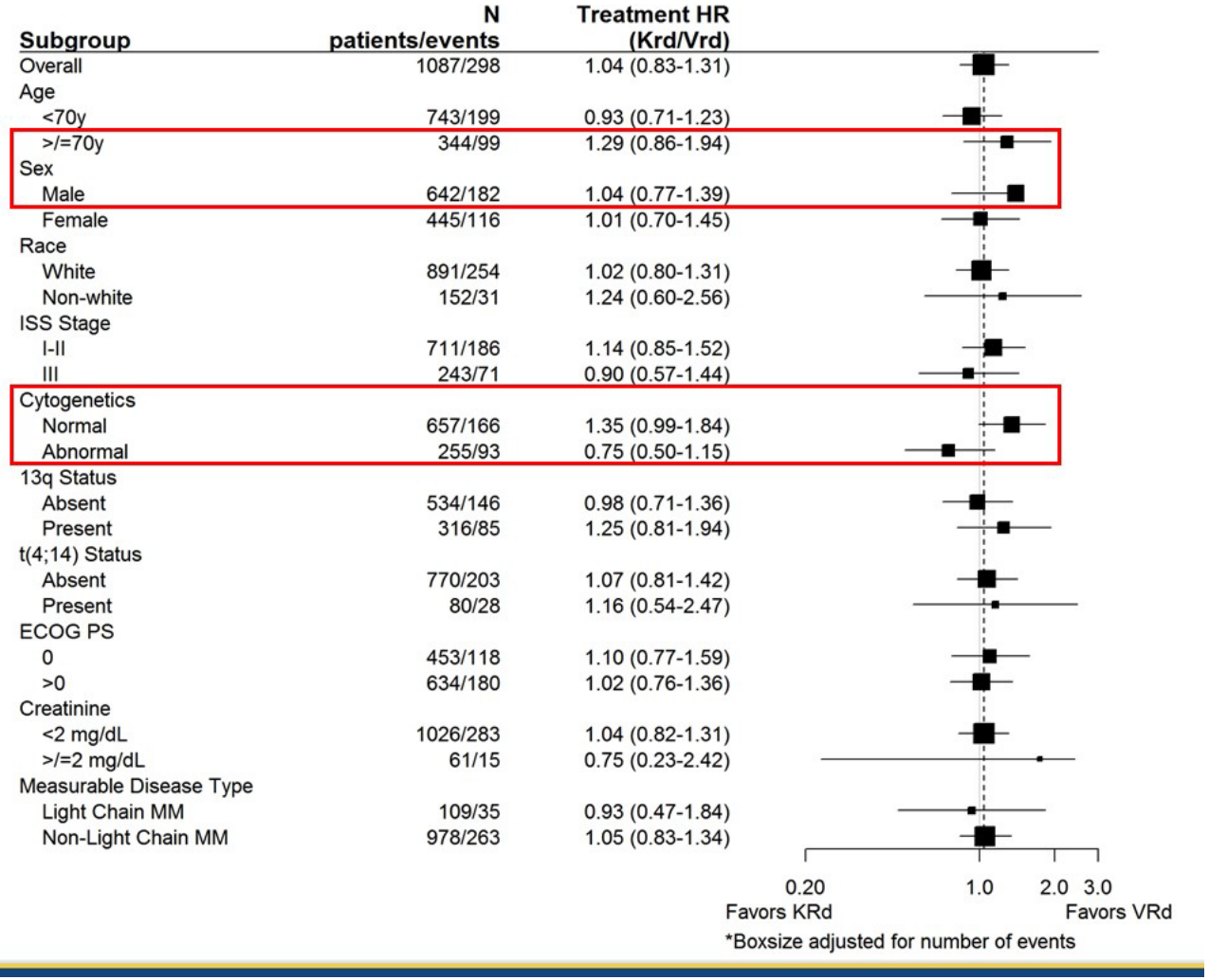
43% (VRd) vs 62% (KRd) completed planned 36 weeks induction

- **25% (VRd) vs 14% (KRd) d/c'd due to toxicity/patient withdrawal**

Kumar et al, ASCO 2020, LBA3

E1A11 (ENDURANCE): KRd vs VRd for standard-risk NDMM





Kumar et al, ASCO 2020, LBA3

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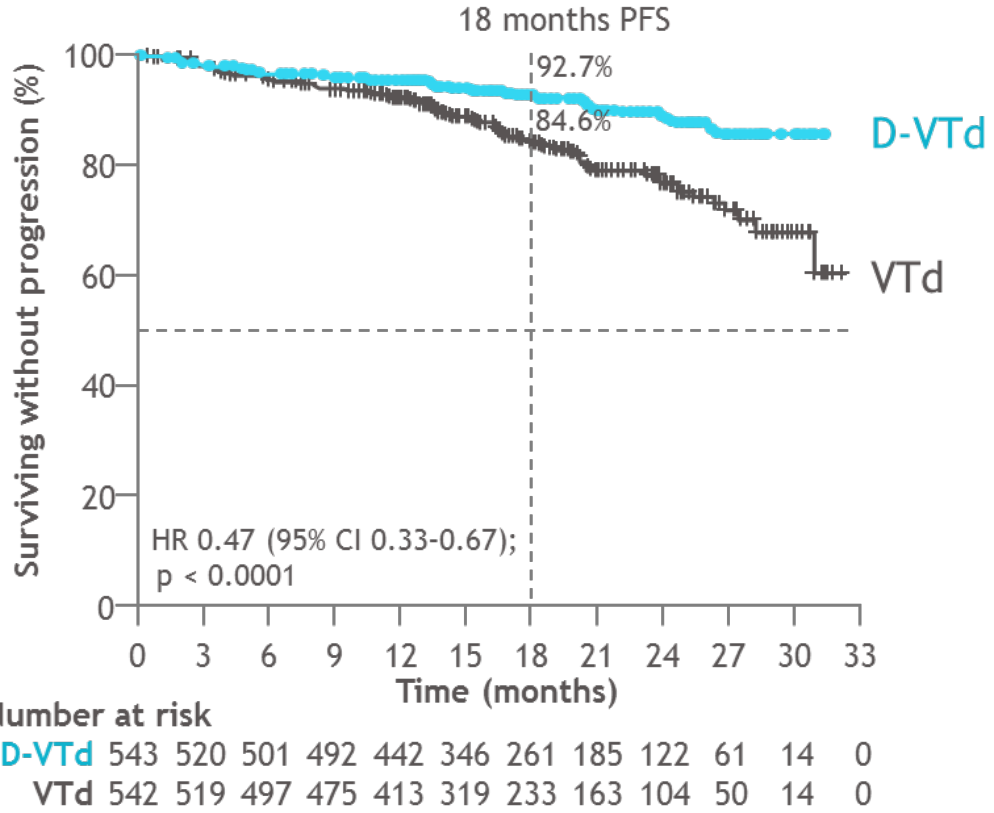
What about monoclonal antibodies? - Daratumumab

- DRd and D-VMP approved for non-SCT eligible
- D-VTd approved for SCT-eligible (CASSIOPEIA trial)

Median follow-up: 18.8 months

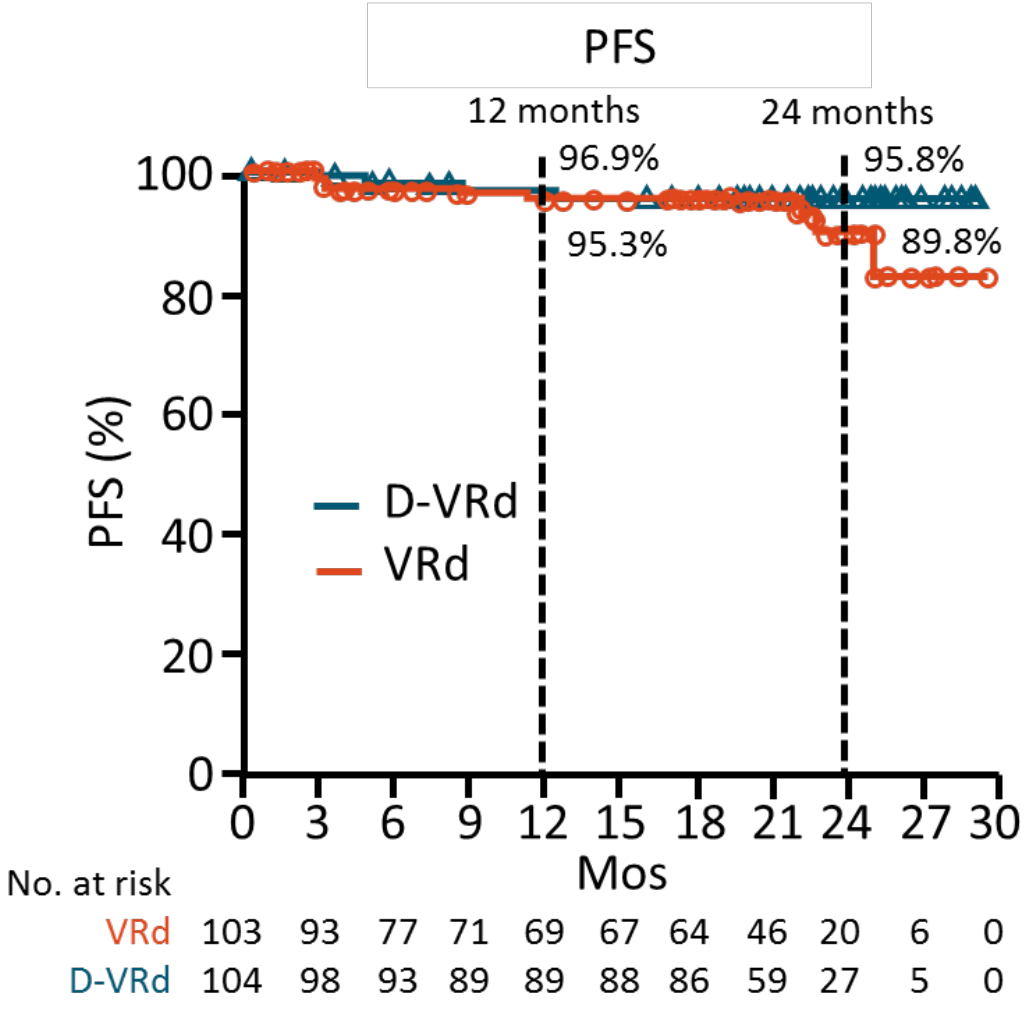


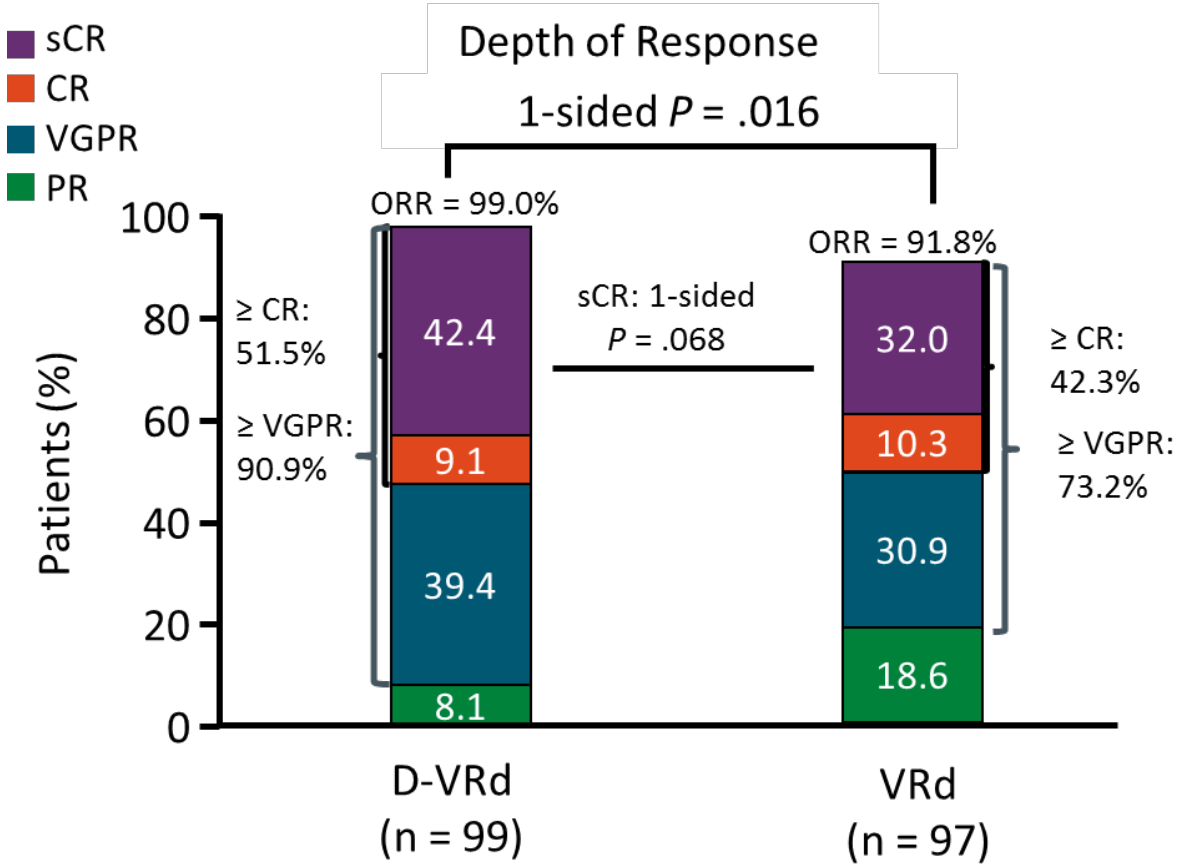
Response	D-VTd	VTd	OR (95% CI)	p value
sCR, %	29	20	1.60 (1.21-2.12)	0.0010
≥ CR, %	39	26	1.82 (1.40-2.36)	< 0.0001
≥ VGPR, %	83	78	1.41 (1.04-1.92)	0.0239
MRD negative (10^{-5}), %	64	44	2.27 (1.78-2.90)	< 0.0001
≥ CR + MRD negative (10^{-5}), %	34	20	2.06 (1.56-2.72)	< 0.0001

Grade 3 or 4 AEs of interest with D-VTd:
- Neutropenia (28%), thrombocytopenia (11%), lymphopenia (17%), peripheral neuropathy (9%), stomatitis (13%)

AE, adverse event; CI, confidence interval; HR, hazard ratio; OR, odds ratio; VGPR, very good partial response.
Moreau P, et al. Lancet. 2019;394:29-38.

GRIFFIN: Dara-VRd vs VRd pre- and post-SCT for NDMM





Phase 3 (PERSEUS) accruing (SQ dara)

Voorhees et al, Blood 2020

PRIMARY ANALYSIS OF THE RANDOMIZED PHASE II TRIAL OF BORTEZOMIB, LENALIDOMIDE, DEXAMTHASONE WITH/WITHOUT ELOTUZUMAB FOR NEWLY DIAGNOSED, HIGH RISK MULTIPLE MYELOMA (SWOG-1211)

Saad Z. Usmani[1], Sikander Ailawadhi[2], Rachael Sexton[3], Antje Hoering[3], Brea Lipe[4], Sandi Fredette[5], Jason Valent[6], Matthew Rosenweig[7], Jeffrey A. Zonder[8], Madhav Dhodapkar[9], Natalie Callander[10], Peter M. Voorhees[1], Brian Durie[11], S. Vincent Rajkumar[12], Paul G. Richardson[13], Robert Z. Orlowski[14], for the SWOG1211 Trial Investigators.

1. Levine Cancer Institute/Atrium Health, Charlotte, NC.
2. Mayo Clinic, Jacksonville, FL.
3. Cancer Research And Biostatistics, Seattle, WA.
4. University of Rochester Medical Center, Rochester, NY.
5. SWOG, Portland, Oregon
6. Cleveland Clinic Cancer Institute, Cleveland, OH.
7. City of Hope, Los Angeles, CA.
8. Karmanos Cancer Institute/Wayne State University, Detroit, MI.
9. Emory University Cancer Institute, Atlanta, GA
10. University of Wisconsin Cancer Center, Madison, WI.
11. Cedar-Sinai Medical Center, Los Angeles, CA.
12. Mayo Clinic, Rochester, MN.
13. Dana Farber Cancer Institute, Boston, MA.
14. MD Anderson Cancer Center, Houston, TX.

SWOG CANCER RESEARCH NETWORK

NCI National Clinical Trials Network | NCI Community Oncology Research Program

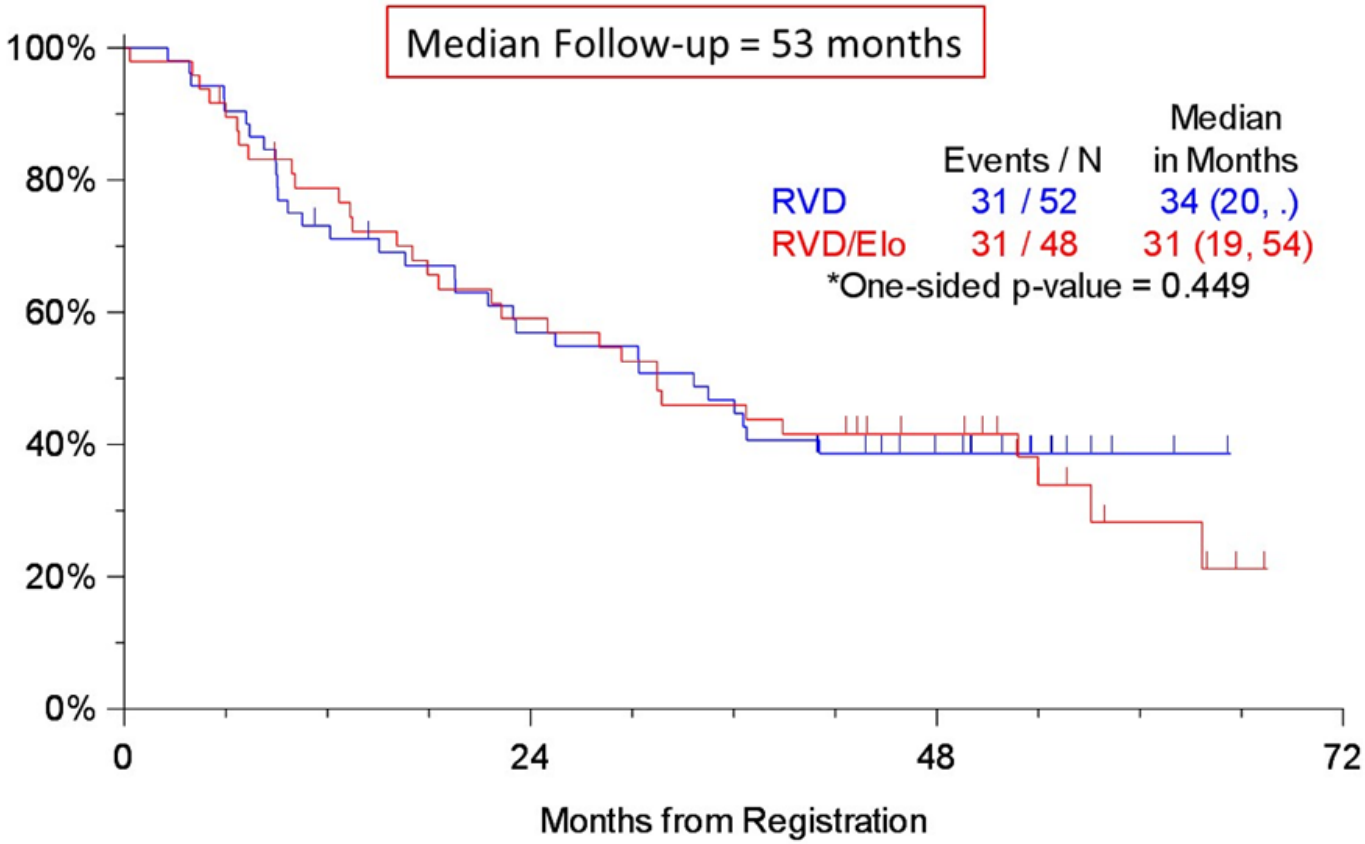
SWOG 1211 – Key Inclusion Criteria

- Newly diagnosed multiple myeloma

- Subjects had to meet one of the following high risk criteria:
  - ***Poor Risk Score by Gene Expression Profiling***
  - ***One or more of the following cytogenetic/FISH abnormalities:***
    - Translocation (14;20)(q32;q12)
    - Translocation (14;16)(q32.3;q23)
    - Deletion (17p)
    - Chromosome 1q21 amplification
  - ***Primary plasma cell leukemia (PPCL)***
  - ***Elevated serum LDH twice above the institutional ULN***

Usmani et al, ASCO 2020, #8507

SWOG 1211 Phase II– Progression Free Survival



SWOG CANCER RESEARCH NETWORK

NCI National Clinical Trials Network | NCI Community Oncology Research Program

Usmani et al, ASCO 2020, #8507

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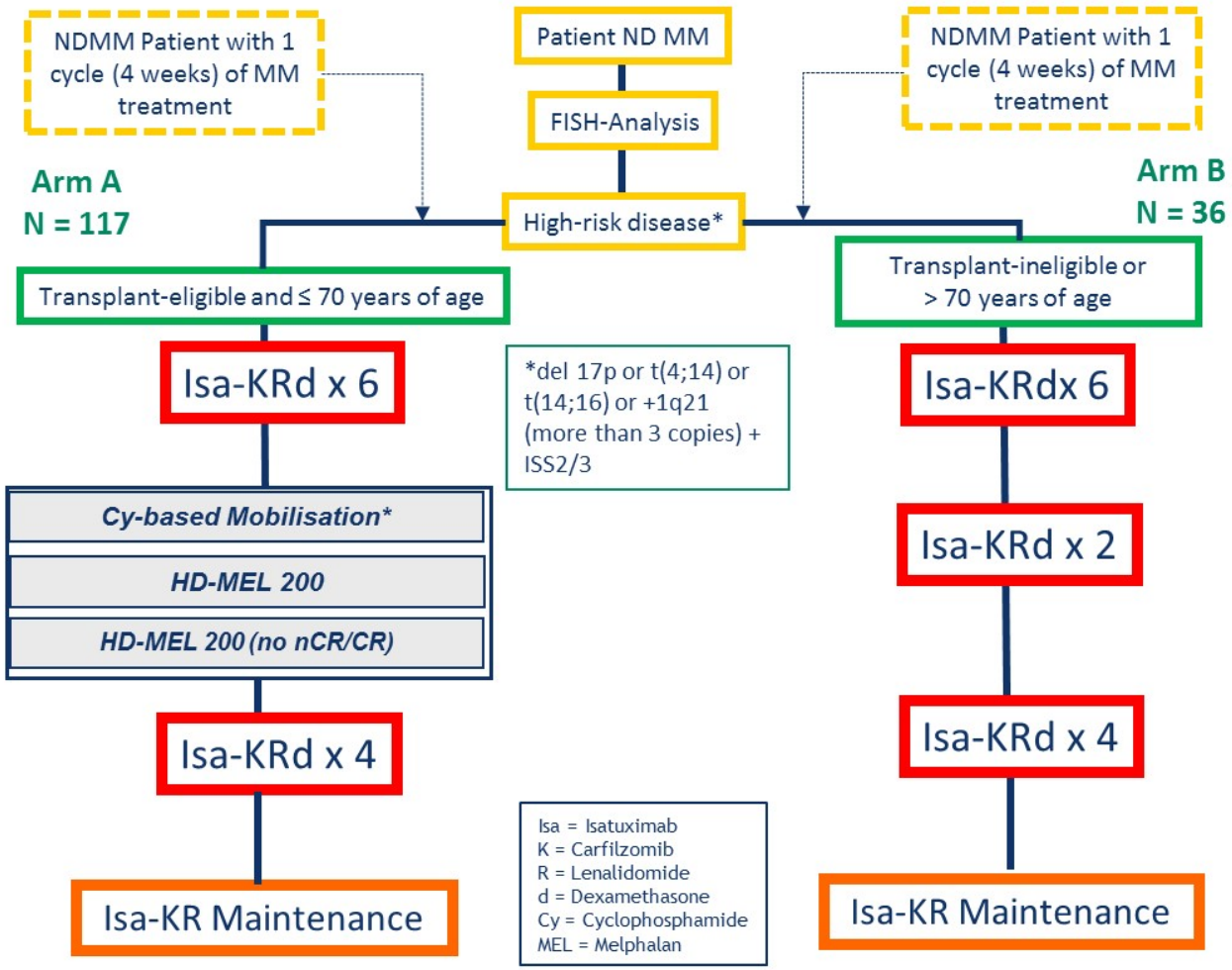
Depth of Response to Isatuximab, Carfilzomib, Lenalidomide and Dexamethasone (Isa-KRd) in front-line treatment of high-risk Multiple Myeloma: Interim Analysis of the GMMG-CONCEPT trial

Katja C. Weisel, Anne Marie Asemissen, Britta Besemer, Mathias Haenel, Wolfgang Blau, Martin Goerner, Yon-Dschun Ko, Jan Duerig, Peter Staib, Christoph Mann, Raphael Lutz, Markus Munder, Ullrich Graeven, Rudolf Peceny, Hans Salwender, Manola Zago, Axel Benner, Diana Tichy, Carsten Bokemeyer, Hartmut Goldschmidt

Weisel et al, ASCO 2020, #8508

Study Design – GMMG CONCEPT (NCT03104842)



Isa-KRd Induction
Cycle 1

Isatuximab	10 mg/kg	day 1, 8, 15, 22
Carfilzomib	20 mg/m²	day 1, 2
Carfilzomib	36 mg/m²	day 8, 9, 15, 16
Lenalidomide*	25 mg	day 1-21
Dexamethasone**	40 mg*	day 1, 8, 15, 22
28-day-cycle		

Isa-KRd Induction
Cycle 2-6

Isatuximab	10 mg/kg	day 1, 15
Carfilzomib	36 mg/m²	day 1, 2, 8, 9, 15, 16
Lenalidomide**	25 mg	day 1-21
Dexamethasone***	40 mg*	day 1, 8, 15, 22
28-day-cycle		

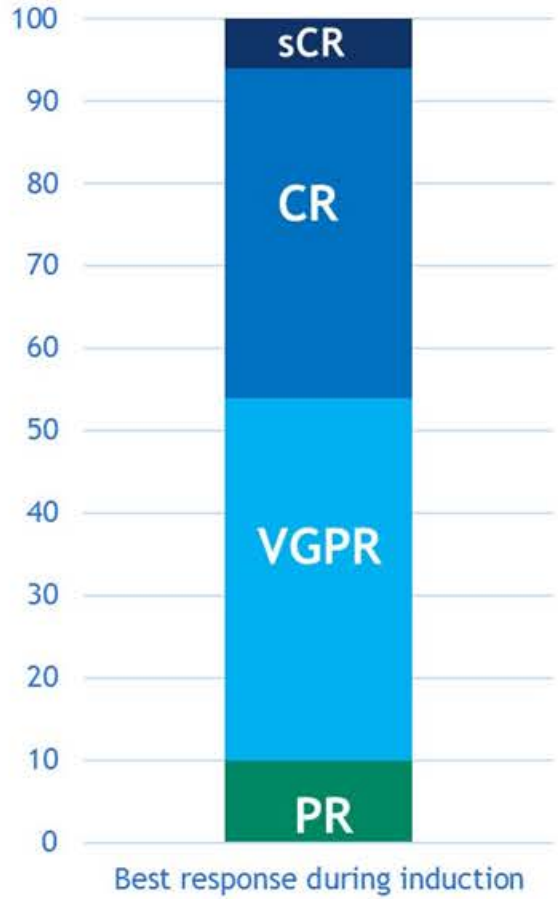
* Cy-based mobilisation was moved in an amendment to the time after 3 induction cycles
**Dose adaption of lenalidomide according to renal function
***20 mg in patients ≥75 years

Weisel et al, ASCO 2020, #8508

Results: Best response to therapy, 6 induction cycles

All evaluable patients: n = 50

- Overall response rate (ORR, ≥ PR): 100%
- ≥ VGPR : 90%; CR/sCR: 46%
  - Arm A: 41/46 ≥ VGPR
  - Arm B: all (n = 4) VGPR
- Arm A: MRD-assessment in 33 patients during induction
  - 20 patients MRD negative
  - 11 patients MRD positive
  - 2 not assessable



Results of MRD assessments after induction treatment are not reported and available yet

Weisel et al, ASCO 2020, #8508

Results: Safety, most common TEAE

Hematologic TEAEs, n = 50	Grade 3 or 4 N (%)
Leukopenia	13 (26%)
Neutropenia	17 (34%)
Lymphopenia	14 (28%)
Anemia	5 (10%)
Thrombocytopenia	7 (14%)

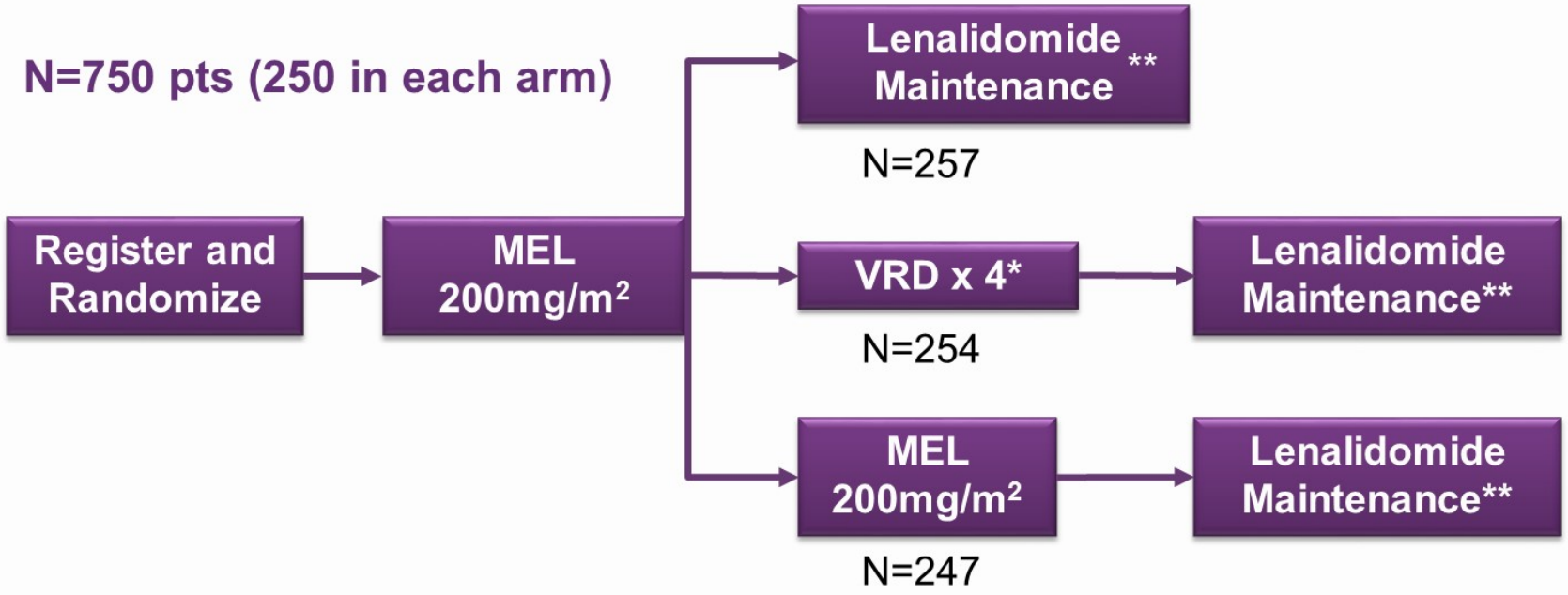
Non-Hematologic TEAEs, n = 50	Any Grade N (%)	Grade 3 or 4 N (%)
Upper respiratory tract Infection	9 (18%)	0
Pyrexia	6 (12%)	0
Rash	8 (16%)	0
Peripheral sensory neuropathy	8 (16%)	1 (2%)
Nasopharyngitis	5 (10%)	0
Hypertension	6 (12%)	6 (12%)
Cardiac failure	2 (4%)	2 (4%)
Infusion reaction	16 (32%)	0

- Low rates of peripheral neuropathy
- No death on study

For hematologic TAE, the following terms were summarized: Leukopenia and white blood cell count decreased, Lymphopenia and lymphocyte count decreased, Neutropenia and neutrophil count decreased, thrombocytopenia and platelet count decreased; AE observed during Cy-mobilization are partially included

Weisel et al, ASCO 2020, #8508

BMT CTN 0702 Stem Cell Transplantation for Multiple Myeloma Incorporating Novel Agents: SCHEMA



**Lenalidomide x 3years:
10mg/d for 3 cycles , then 15 mg/d (as tolerated)
Amendment in 2014 allowed Lenalidomide maintenance until disease progression (after CALGB 100104 was reported)

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Hari et al, ASCO 2020, #8506

07LT Schema

STaMINA Trial End

Progression Free at 38 mo.

On Len Maintenance

Within 4 years of F/up

N = 431

(143/148/140 across arms)

Enrolled in 07LT & eligible

N = 265

(95/85/85)

Lenalidomide Maintenance Continued at 38 mo

N=215

Pt and physician choice to enroll in 07LT Or start commercial Len

	Len Continued	Len Stopped
Treatment Arm (N)	63/79/71	80/66/67
High / Std Risk (N)	57/149	60/154

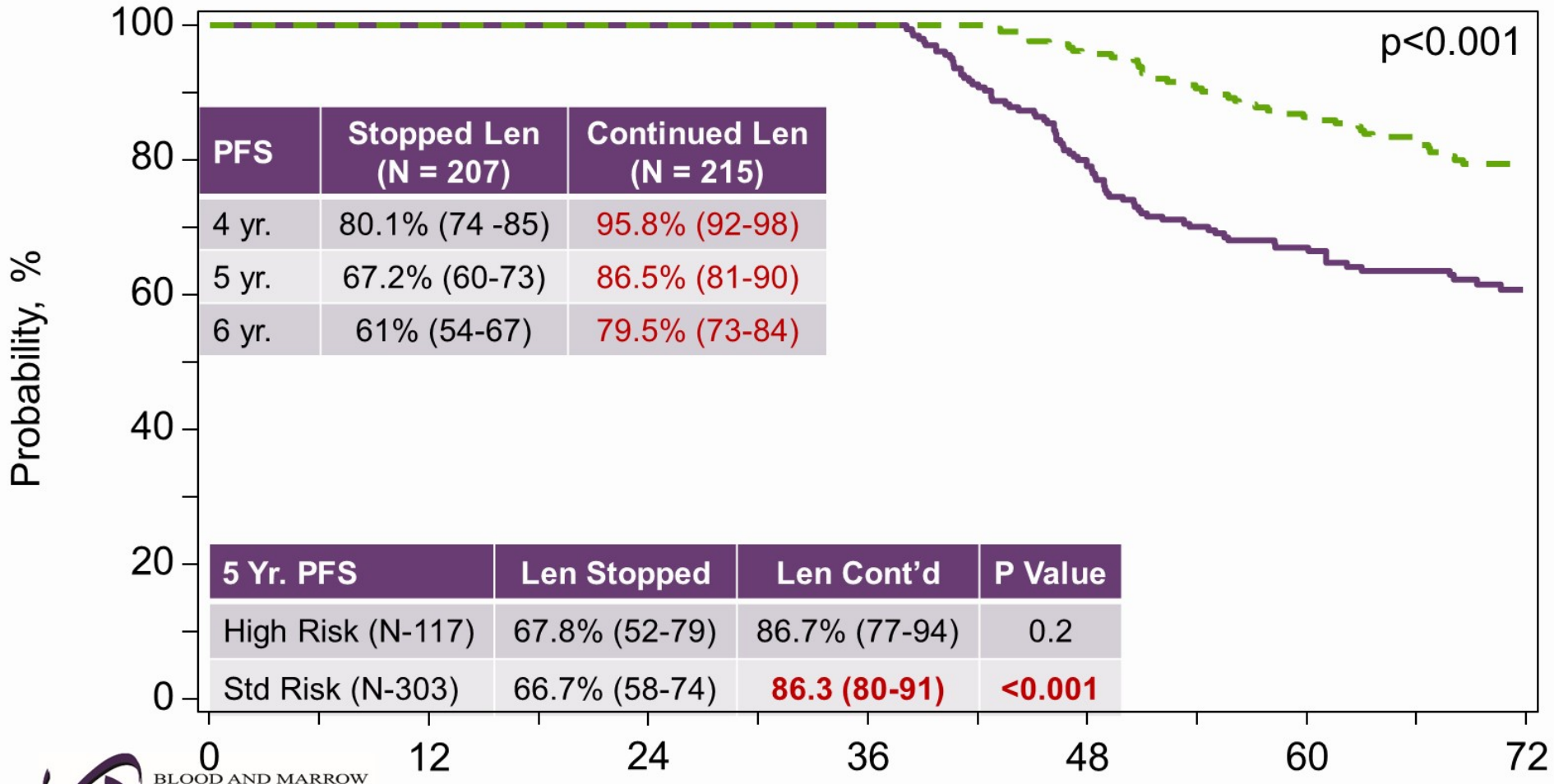
Progression Free at 38 mo. & Stopped Len

N = 207

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Hari et al, ASCO 2020, #8506

PFS Landmark Analysis: Len continued beyond 38 mo. vs. Not



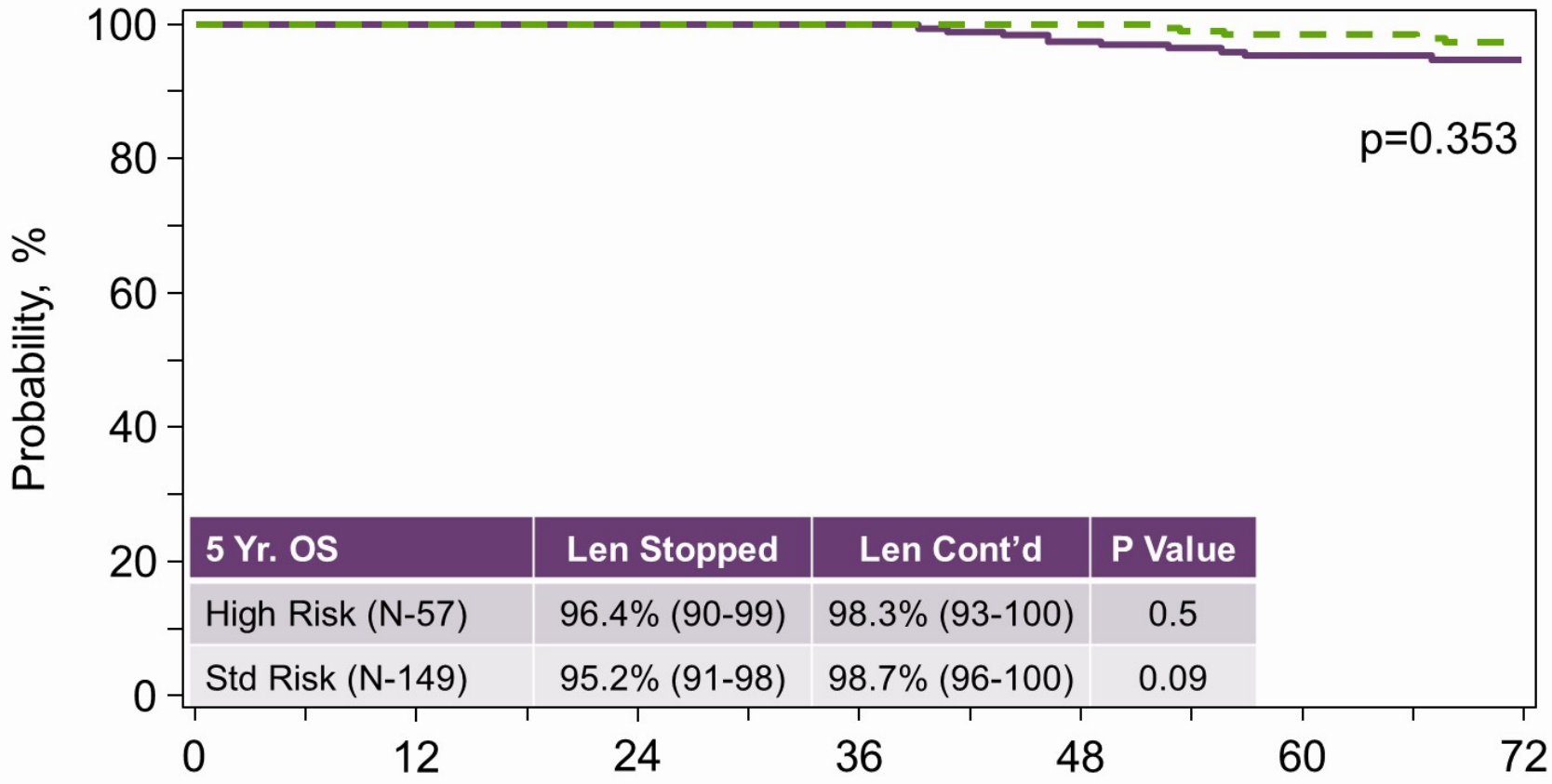
PFS	Stopped Len (N = 207)	Continued Len (N = 215)
4 yr.	80.1% (74 -85)	95.8% (92-98)
5 yr.	67.2% (60-73)	86.5% (81-90)
6 yr.	61% (54-67)	79.5% (73-84)

5 Yr. PFS	Len Stopped	Len Cont'd	P Value
High Risk (N-117)	67.8% (52-79)	86.7% (77-94)	0.2
Std Risk (N-303)	66.7% (58-74)	**86.3 (80-91)**	**<0.001**

MAJOR PFS BENEFIT FOR CONTINUATION

Hari et al, ASCO 2020, #8506

OS Landmark Analysis: Len continued beyond 38 mo. vs. Not



5 Yr. OS	Len Stopped	Len Cont'd	P Value
High Risk (N-57)	96.4% (90-99)	98.3% (93-100)	0.5
Std Risk (N-149)	95.2% (91-98)	98.7% (96-100)	0.09

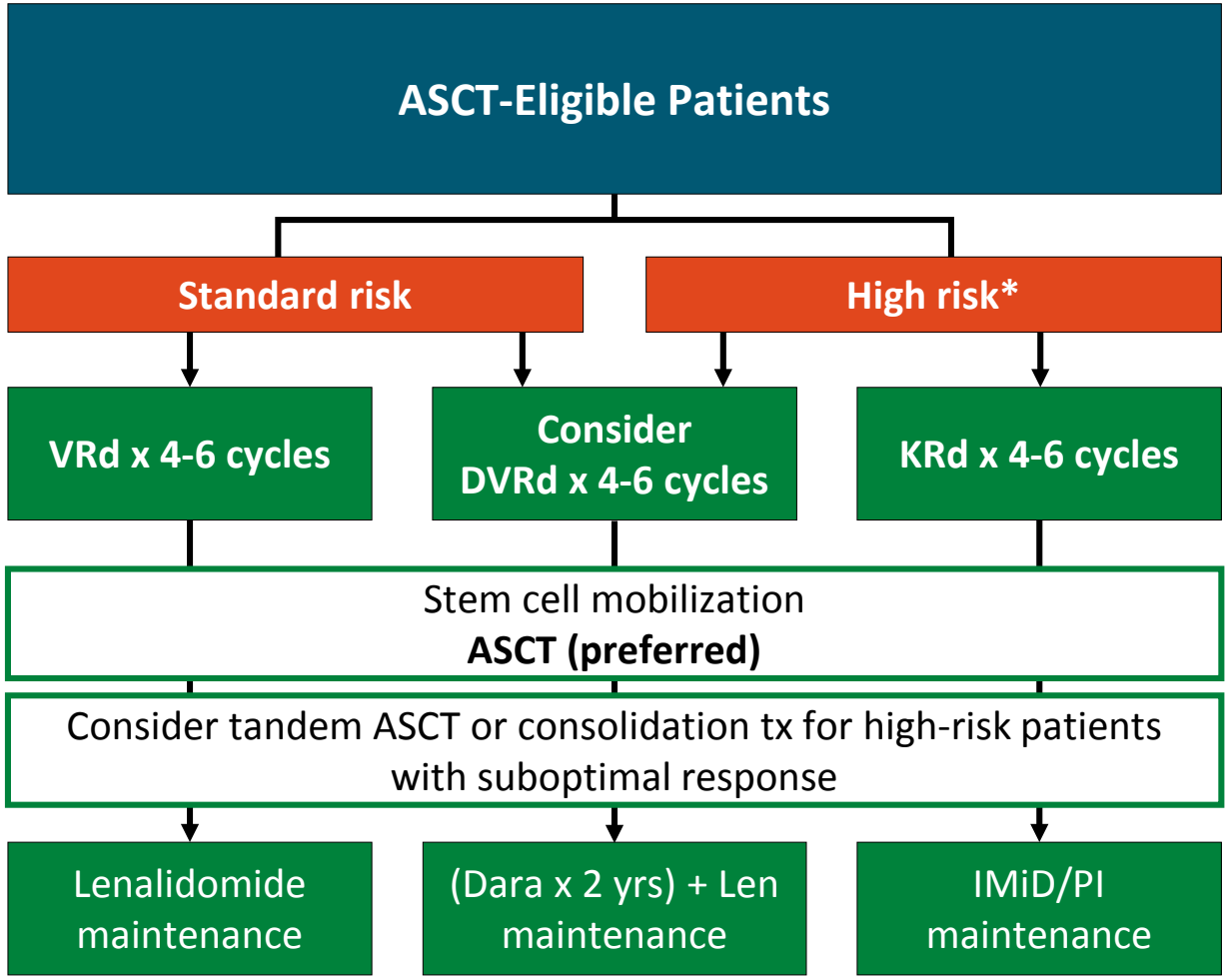
No difference in second primary malignancies at 6 years

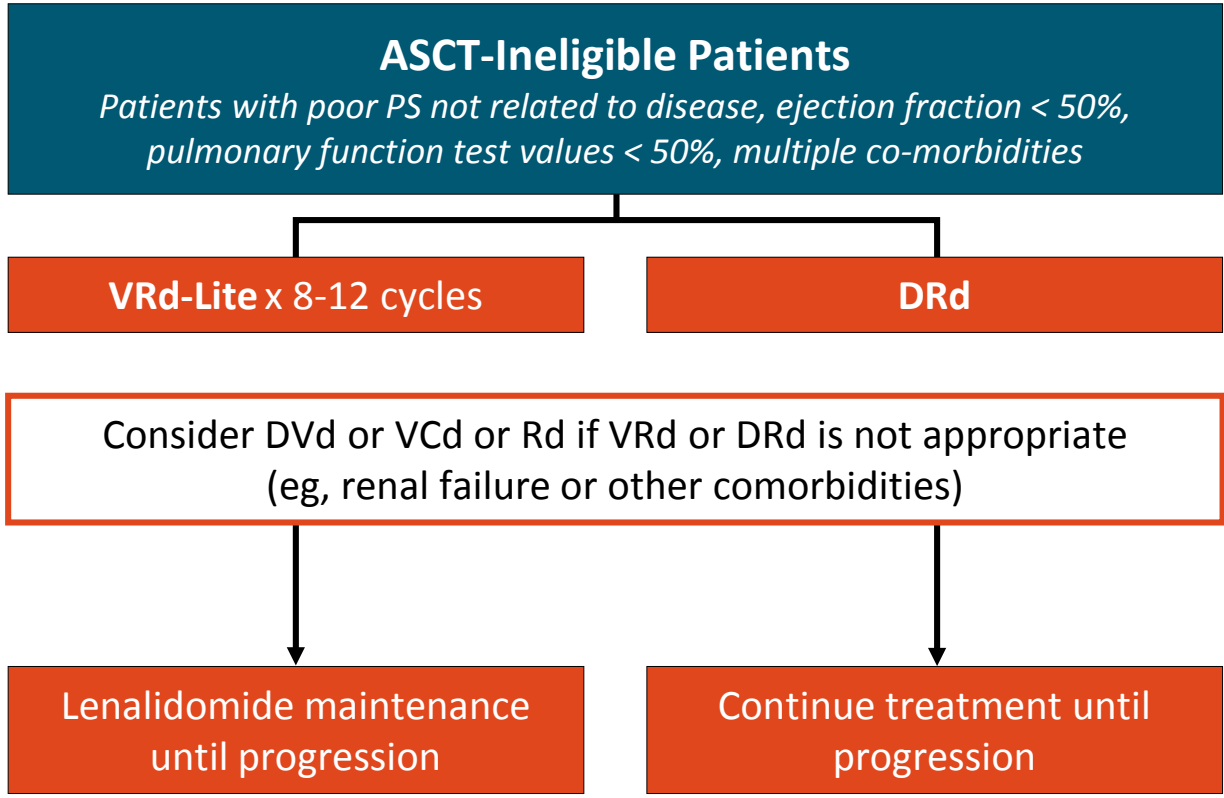
BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

NO OS DIFFERENCE FOR CONTINUATION vs. STOPPING

Hari et al, ASCO 2020, #8506

Proposed treatment of newly-diagnosed myeloma in USA



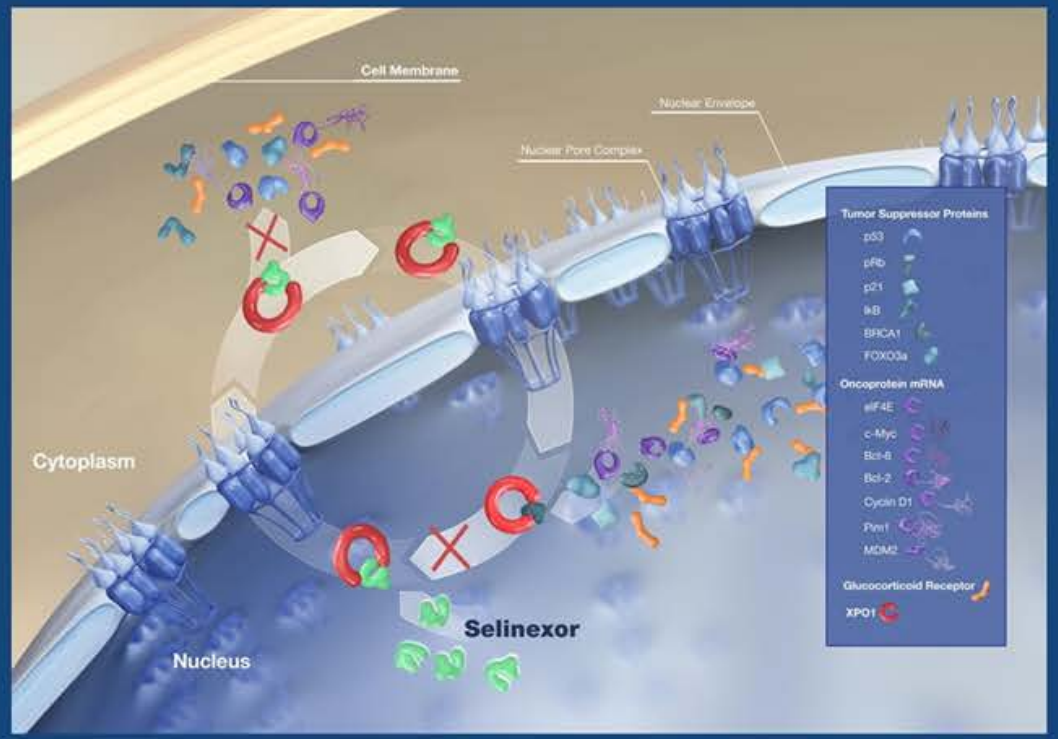


Adjust dosing of lenalidomide based on renal function. Consider empiric age-adjusted dose reductions for all regiments, as needed.[4]

What’s new in relapsed/refractory myeloma?

Selinexor:
First-in-Class, Oral Selective Inhibitor of Nuclear Export (SINE)[1-4]

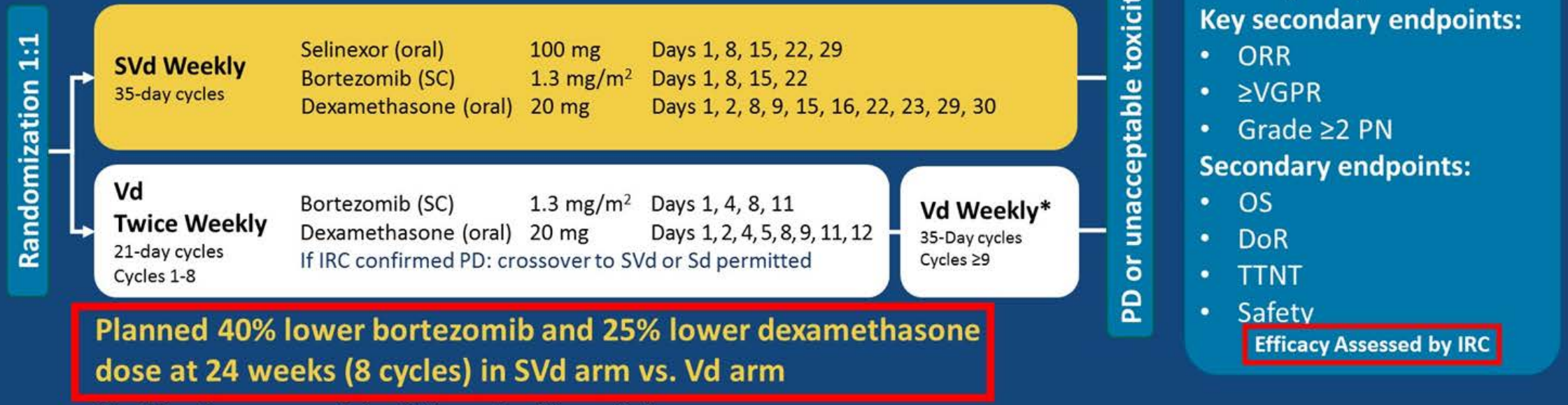
Demonstrates synergistic activity in combination with bortezomib *in vitro* and *in vivo*



- **Exportin 1 (XPO1) is the major nuclear export protein for**
  - Tumor suppressor proteins (TSPs, e.g., p53, IkB and FOXO)
  - eIF4E-bound oncoprotein mRNAs (e.g., c-Myc, Bcl-xL, cyclins)
  - Glucocorticoid receptor (GR)
- **XPO1 is overexpressed in multiple myeloma (MM)**
  - High XPO1 levels enable cancer cells to escape TSP-mediated cell cycle arrest and apoptosis
  - XPO1 levels correlate with poor prognosis and drug resistance
- **Selinexor is an oral selective XPO1 inhibitor that:**
  - Reactivates multiple TSPs by preventing nuclear export
  - Inhibits oncoprotein translation
  - Reactivates GR signaling in presence of dexamethasone
- **Selinexor + dexamethasone is approved in the US for MM refractory to ≥4 therapies including ≥2 PIs,≥2 IMiDs and an anti-CD38 mAb**

IMiD = immunomodulatory imide drug, mAb = monoclonal antibody, PI = proteasome inhibitor. 1. Gupta A, et al. Therapeutic targeting of nuclear export inhibition in lung cancer. J Thorac Oncol. 2017;12(9):1446-1450. 2. Sun Q, et al. Inhibiting cancer cell hallmark features through nuclear export inhibition. Signal Transduct Target Ther. 2016;1:16010. 3. Gandhi UH, et al. Clinical implications of targeting XPO1-mediated nuclear export in multiple myeloma. Clin Lymphoma Myeloma Leuk. 2018;18(5):335-345. 4. Gravina GL, et al. Nucleo-cytoplasmic transport as a therapeutic target of cancer. J Hematol Oncol. 2014;7:85.

BOSTON Trial: Phase 3, Global, Randomized, Open Label, Controlled Study in Patients With MM who Had Received 1–3 Prior Therapies



Planned 40% lower bortezomib and 25% lower dexamethasone dose at 24 weeks (8 cycles) in SVd arm vs. Vd arm

Stratification: Prior PI therapies (Yes vs No)
Number of prior anti-MM regimens (1 vs >1)
R-ISS stage at study entry (Stage III vs Stage I/II)

5HT-3 prophylactic recommended in SVd arm

CR= complete response, DoR = duration of response, IMWG = International Myeloma Working Group, IRC = Independent Review Committee, OS = overall survival, PD = progressive disease, PFS = progression free survival, PR = partial response, PN = peripheral neuropathy, sCR = stringent complete response, TTNT = time to next therapy, VGPR = very good partial response. PFS defined as: Time from date of randomization until the first date of progressive disease, per IMWG response criteria, or death due to any cause, whichever occurred first, as assessed by IRC. ORR: Any response ≥PR (ie, PR, VGPR, CR, or sCR) based on the IRC's response outcome assessments, according to IMWG response criteria (Kumar et al. Lancet oncology 2016). All changes in MM disease assessments were based on baseline MM disease assessments.
*Vd weekly dosing and schedule for cycles≥ 9 as per SVd arm description.

PRESENTED AT: 2020 ASCO ANNUAL MEETING #ASCO20

PRESENTED BY: Meletios A. Dimopoulos

Dimopolous et al, ASCO 2020, #8501

BOSTON Trial: Baseline Characteristics

Patient and Disease Characteristics Well Balanced Between Treatment Arms

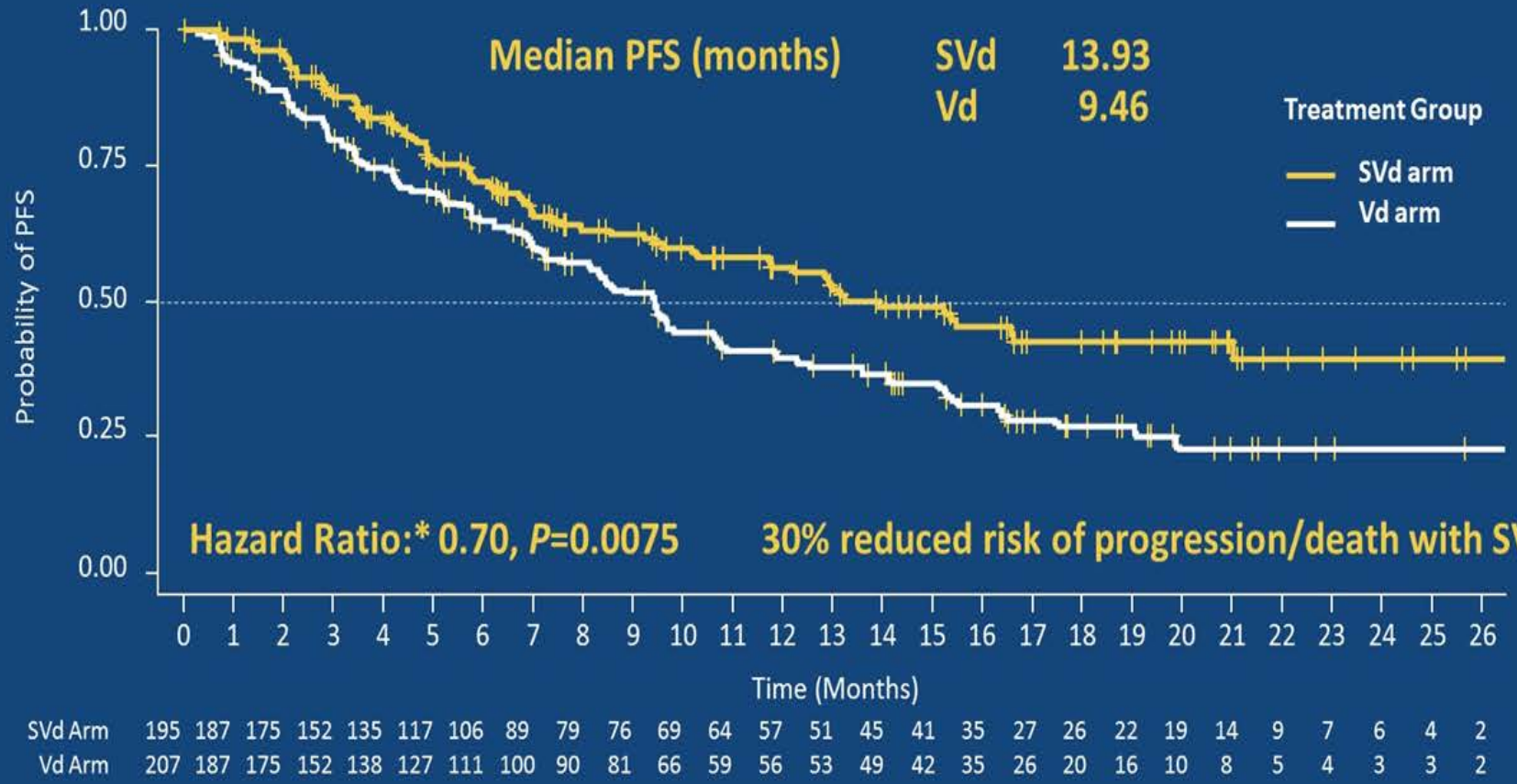
Characteristic	SVd arm (n=195)	Vd arm (n=207)
Median age, years (range)	66 (40, 87)	67 (38, 90)
≥75 years, n (%)	34 (17)	47 (23)
Male, n (%)	115 (59)	115 (56)
Creatinine clearance, mL/min, n (%)		
<30	3 (2)	10 (5)
30-60	53 (27)	60 (29)
Time since initial diagnosis, years, (range)	3.8 (0.4, 23.0)	3.6 (0.4, 22.0)
High risk cytogenetic, [del (17p) or t (14;16) or t (4;14) or amp 1q21] n (%)*	97 (50)	95 (46)
R-ISS disease stage at screening, n (%)		
I or II	173 (89)	177 (86)
III	12 (6)	16 (8)
Unknown	10 (5)	14 (7)
Number of prior lines of therapy, n (%)		
1	99 (51)	99 (48)
2	65 (33)	64 (31)
3	31 (16)	44 (21)
Prior therapies, n (%)		
Bortezomib	134 (68.7) } 80.0%	145 (70.0) } 80.1%
Carfilzomib	20 (10.3) }	21 (10.1) }
Daratumumab	11 (5.6)	6 (2.9)
Lenalidomide	77 (39.5)	77 (37.2)

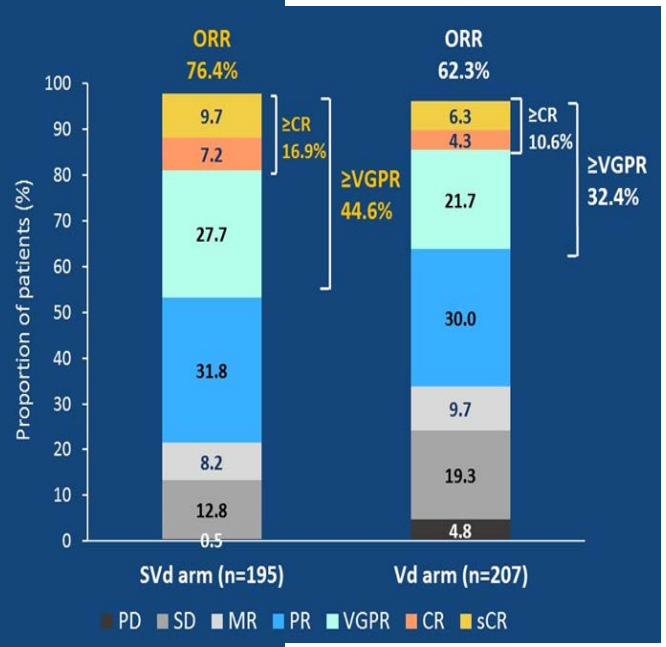
*Fluorescence in-situ hybridization was performed at a central laboratory and used to assess cytogenetic risk status. 1q21 required at least 3 copies.

Dimopolous et al, ASCO 2020, #8501

BOSTON Trial: PFS Significantly Longer With SVd Compared to Vd

Early and Sustained PFS Benefit (Assessed by IRC)





Intention-to-treat (ITT) population N=402, Data cut-off February 18, 2020
*Hazard Ratio 95% CI=0.53–0.93 one-sided *P* value.

Median follow-up: 13.2 and 16.5 months in SVd and Vd arms, respectively.

Dimopolous et al, ASCO 2020, #8501

BOSTON Trial: Safety – Selected Hematological TEAEs*

	SVd (n=195)		Vd (n=204)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Hematological (%)				
Thrombocytopenia	60.0†	39.5	27.0	17.2
Grade ≥3 bleeding		2.1		1.0
Anemia	36.4	15.9	23.0	9.8
Neutropenia	14.9	8.7	5.9	3.4
Febrile neutropenia		0.5		0.5

- **Thrombopoietin receptor agonists were used to mitigate thrombocytopenia in 35 patients on SVd and 2 patients on Vd, and reduced dose interruptions and reductions**
- **Twelve patients on SVd and 13 patients on Vd received platelet transfusions to manage thrombocytopenia**

*Shown are events that occurred in at least 10% of patients and had a >5% difference between treatment arms. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03. For patients who crossed over, adverse events that occurred after the crossover are not included.
†Includes 3 fatal events. Data cut-off February 18, 2020.

PRESENTED AT: 2020 ASCO ANNUAL MEETING #ASCO20

PRESENTED BY: Meletios A. Dimopoulos

Dimopolous et al, ASCO 2020, #8501

BOSTON Trial: Safety – Selected Non-Hematological TEAEs*

	SVd (n=195)		Vd (n=204)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Non-hematological (%)				
Nausea	50.3	7.7	9.8	0
Fatigue	42.1	13.3	18.1	1.0
Decreased Appetite	35.4	3.6	5.4	0
Diarrhea	32.3	6.2	25.0	0.5
Peripheral Neuropathy†	32.3	4.6	47.1	8.8
Upper Respiratory Tract Infection‡	29.2	3.6	21.6	1.5
Weight decreased	26.2	2.1	12.3	1.0
Asthenia	24.6	8.2	13.2	4.4
Cataract§	21.5	8.7	6.4	1.5
Vomiting	20.5	4.1	4.4	0

*Shown are events that occurred in at least 15% of patients and had a >5% difference between treatment arms. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03. For patients who crossed over, adverse events that occurred after the crossover are not included. †Includes high-level term Peripheral Neuropathies NEC. ‡Includes upper respiratory infection, nasopharyngitis, pharyngitis, respiratory syncytial virus infection, respiratory tract infection, rhinitis and viral upper respiratory tract infection. §Per Ophthalmology exam during 24% patients on the SVd arm versus 8.5% patients on the Vd arm had new-onset cataracts and worsening of cataracts on study was noted in 20.5% patients on the SVd arm versus 7.9% on the Vd arm. Data cut-off February 18, 2020.

Dimopolous et al, ASCO 2020, #8501

Novel immunotherapies for relapsed/refractory MM

CELMoD® agents

- Iberdomide (CC-220)
- CC-92480

mAbs

- Belantamab Mafodotin (GSK2857916)

CAR T

- Idecabtagene vicleucel (bb2121)
- Orvacabtagene autoleucel
- JNJ-4528

Bispecific Abs/T-cell engagers (TCE)

- AMG420
- CC-93269
- PF-06863135
- REGN 5458
- Teclistamab (JNJ-64007957)

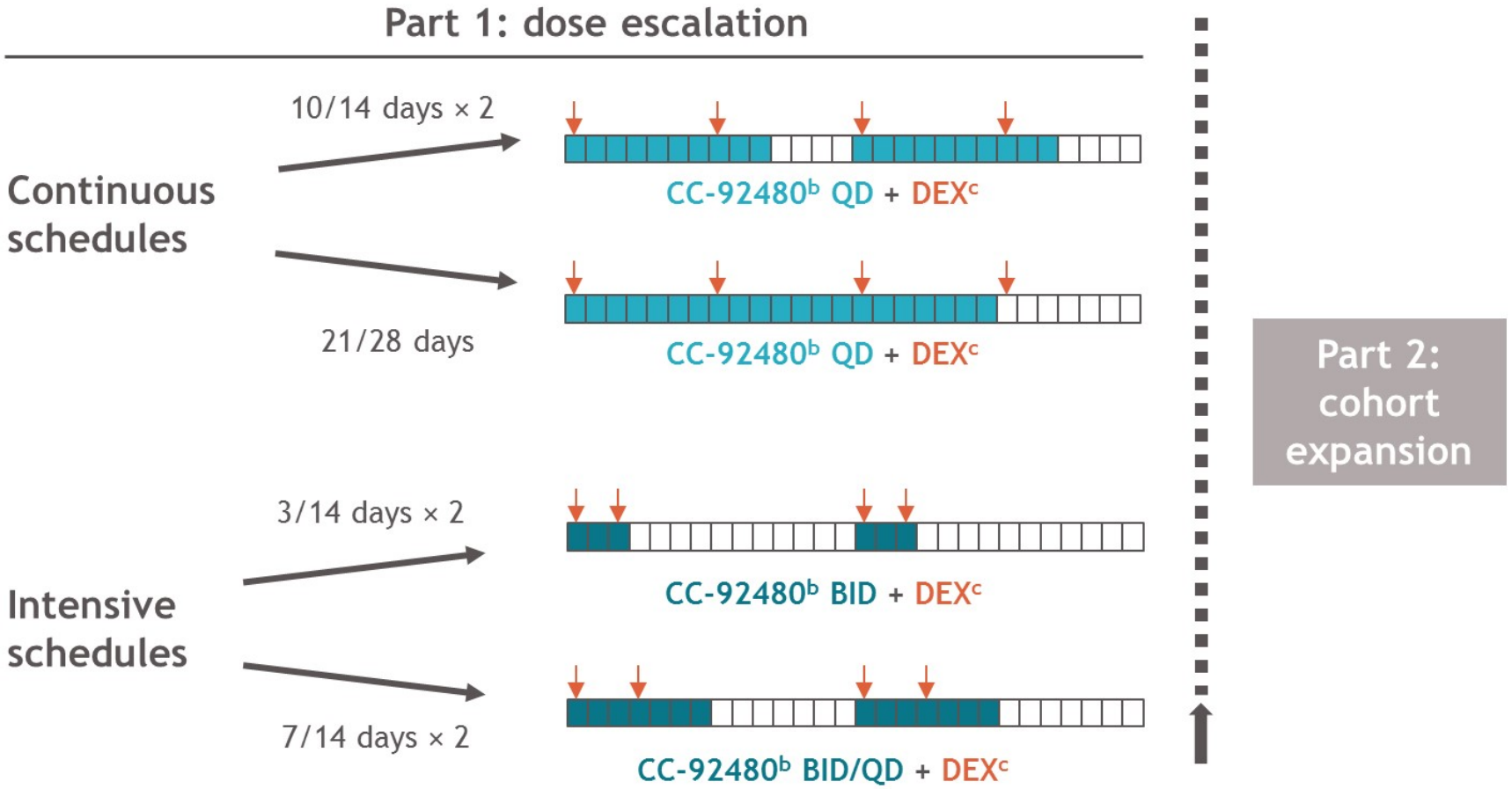
CC-92480-MM-001 phase 1 trial (NCT03374085): study design

Key eligibility criteria

- RRMM
- Resistant or intolerant to, or not otherwise candidates for currently available therapies[a]
- Progression on or within 60 days of last antimyeloma therapy

Study endpoints

- **Primary:** assess PK, safety, and define the MTD/RP2D
- **Secondary:** assess preliminary efficacy



[a]Including LEN, POM, a PI, a glucocorticoid, and/or anti-CD38 mAb, according to local availability; [b]Administered orally; [c]DEX given at a dose of 40 mg (20 mg in patients aged ≥ 75 years).

BID, twice daily; DEX, dexamethasone; LEN, lenalidomide; MTD, maximum tolerated dose; PD, pharmacodynamics; PK, pharmacokinetics; QD, once daily; RP2D, recommended phase 2 dose; RRMM, refractory/relapsed multiple myeloma.

Richardson et al, ASCO 2020, #8500

Prior therapies

Characteristics	Safety population[a] (N = 76)
Prior therapies, median (range), n	6 (2-13)
ASCT, n (%)	58 (76.3)
PI, n (%)	76 (100)
LEN, n (%)	74 (97.4)
POM, n (%)	70 (92.1)
Anti-CD38 mAb, n (%)	57 (75.0)
LEN-refractory, n (%)	56 (73.7)
POM-refractory, n (%)	60 (78.9)
IMiD-refractory,[b] n (%)	68 (89.5)
PI-refractory, n (%)	56 (73.7)
Anti-CD38 mAb-refractory, n (%)	53 (69.7)
Triple-class refractory,[c] n (%)	38 (50.0)

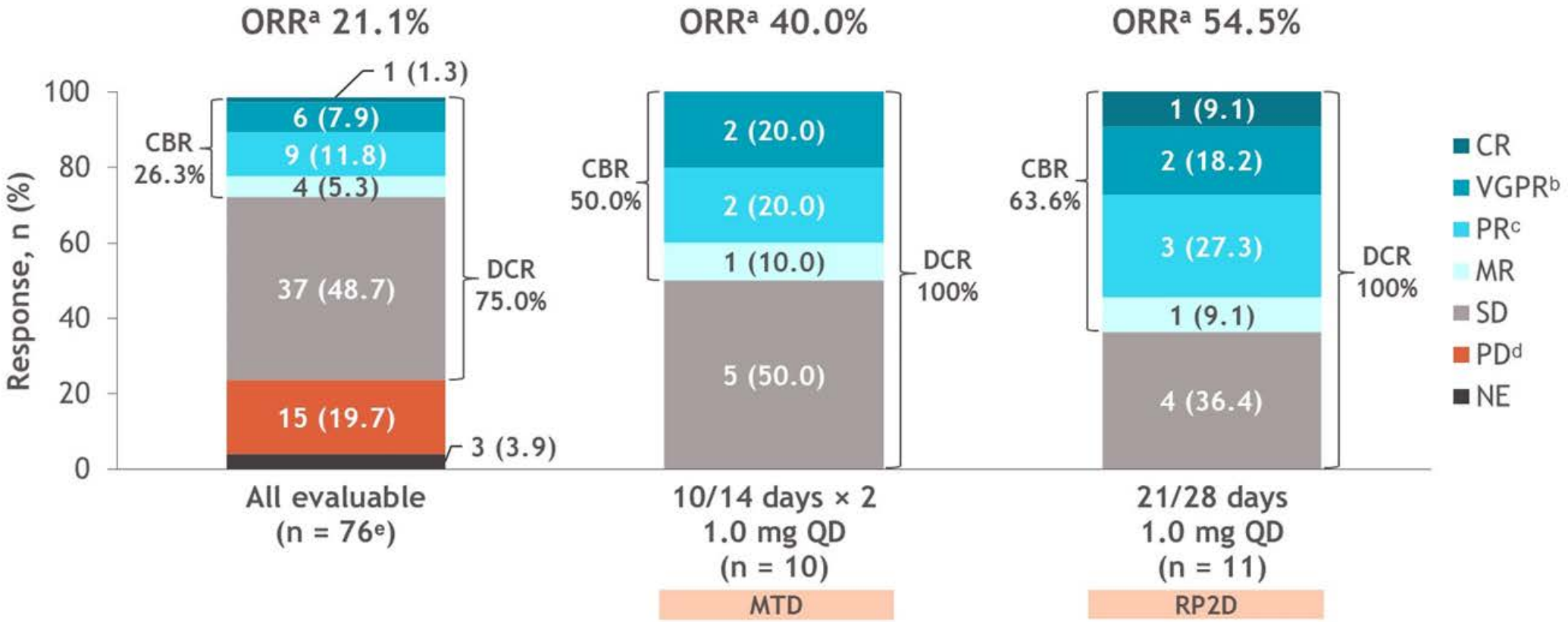
[a]Includes all enrolled patients who received ≥ 1 dose of CC-92480; [b]Defined as refractory to LEN or POM; [c]Defined as refractory to ≥ 1 IMiD agent, 1 PI, and 1 anti-CD38 mAb.

ASCT, autologous stem cell transplantation; BORT, bortezomib; IMiD, immunomodulary drug; LEN, lenalidomide; mAb, monoclonal antibody; PI, proteasome inhibitor; POM, pomalidomide.

7

Richardson et al, ASCO 2020, #8500

Best response



- At the RP2D 1.0 mg QD 21/28 days, 7 out of 11 patients were triple-class-refractory[f]
  - 1 patient had CR, 1 VGPR, 2 PR, and 1 MR

[a]PR or better; [b]1 patient in the 21/28-day 1.0 mg QD cohort had an unconfirmed VGPR as of the data cutoff date; [c]2 patients in the 21/28-day 0.8 mg QD cohort had an unconfirmed PR as of the data cutoff date; [d]1 patient in the 21/28-day 0.8 mg QD cohort had an unconfirmed PD as of the data cutoff date; [e]1 patient had a pending response assessment at data cutoff date; [f]Defined as refractory to ≥ 1 IMiD agent, 1 PI, and 1 anti-CD38 mAb.

CBR, clinical benefit rate; CR, complete response; DCR, disease control rate; MR, minimal response; MTD, maximum tolerated dose; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial response; QD, once daily; RP2D, recommended phase 2 dose; SD, stable disease; VGPR, very good partial response.

Richardson et al, ASCO 2020, #8500

TEAEs all cycles

Common (> 20 % all grade) TEAEs and events of interest, n (%)	All doses (N = 76)		
	All grade	Grade 3	Grade 4
Neutropenia	56 (73.7)	23 (30.3)	26 (34.2)
Febrile neutropenia	6 (7.9)	4 (5.3)	1 (1.3)
Anemia	42 (55.3)	24 (31.6)	-
Thrombocytopenia	33 (43.4)	5 (6.6)	7 (9.2)
Infections	54 (71.1)	25 (32.9)	2 (2.6)
Pneumonia[a]	13 (17.1)	11 (14.5)	-
Fatigue	29 (38.2)	7 (9.2)	-
Pyrexia	17 (22.4)	3 (3.9)	-
Peripheral sensory neuropathy	4 (5.3)	-	-
Diarrhea	18 (23.7)	1 (1.3)	-
Nausea	17 (22.4)	1 (1.3)	-
Deep vein thrombosis	1 (1.3)	-	-

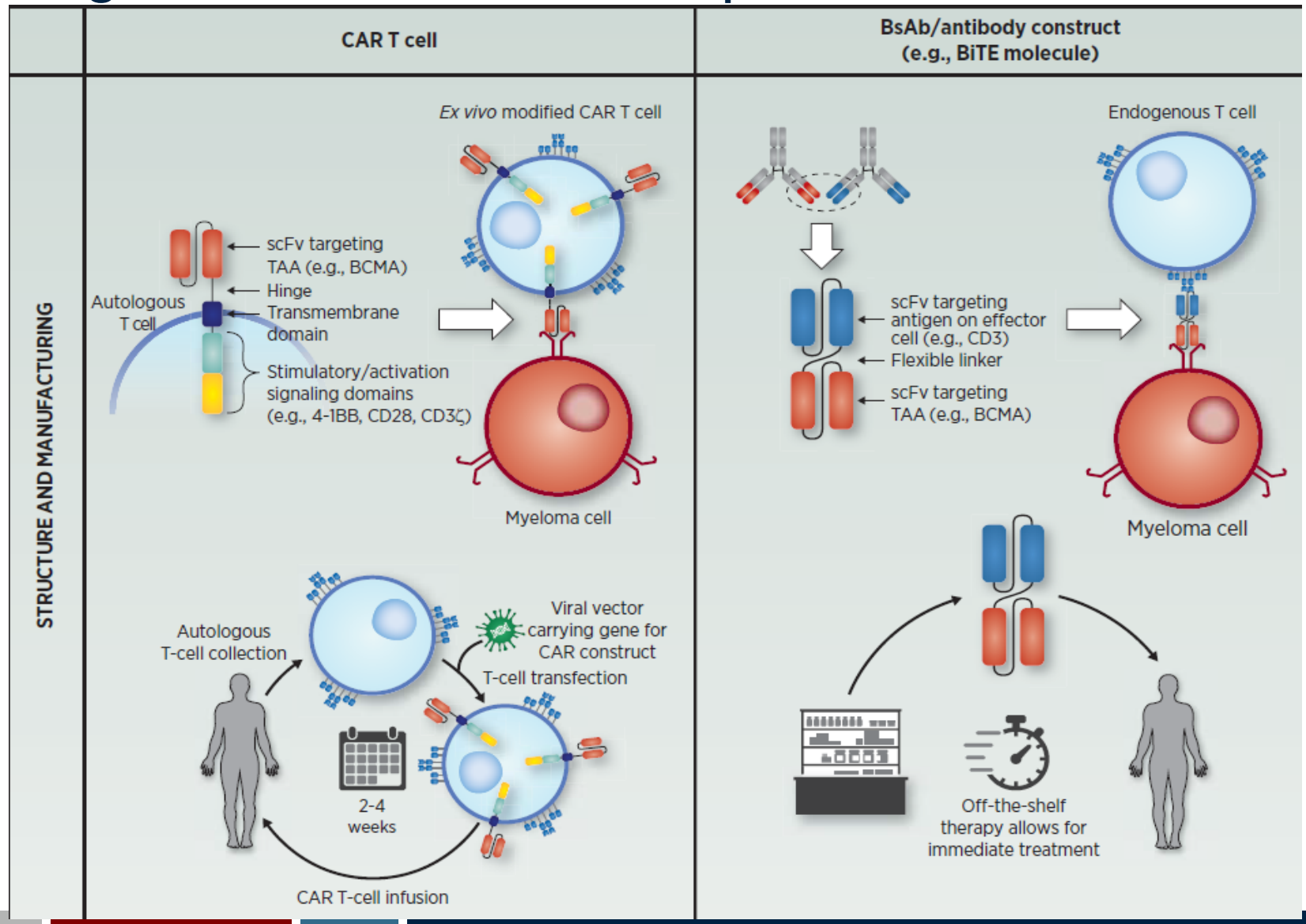
- Prophylactic G-CSF was not permitted during Cycle 1
- Neutropenia was managed with dose interruption/reduction and G-CSF
- Dose reductions of CC-92480 occurred in 17 (22.4%) patients
- No patients discontinued due to treatment-related AEs

[a]Includes Medical Dictionary for Regulatory Activities Terminology version 22.0 preferred terms pneumonia, pneumocystis jirovecii pneumonia, respiratory syncytial viral pneumonia, and staphylococcal pneumonia.

AE, adverse event; G-CSF, granulocyte colony-stimulating factor; MTD, maximum tolerated dose; TEAE, treatment-emergent adverse event.

Richardson et al, ASCO 2020, #8500

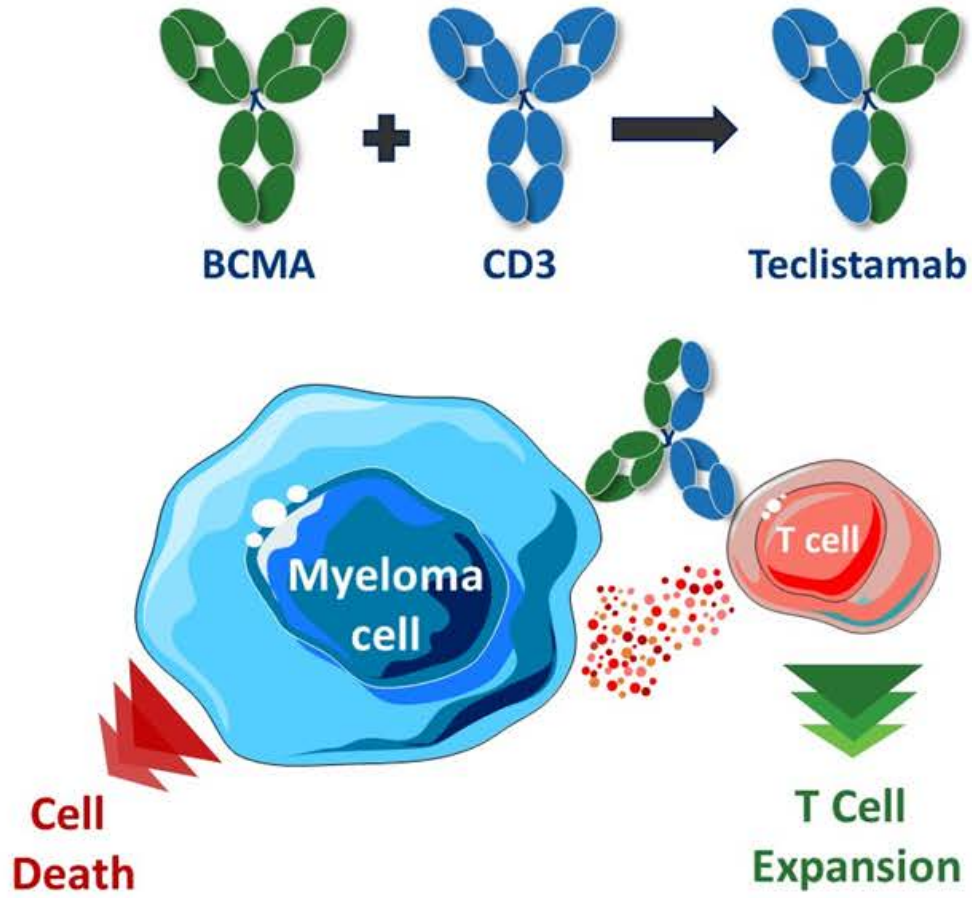
Redirecting T cells: CARs vs. Bispecific Antibodies/T-cell engagers



Cohen et al, Clin Can Res 2020

Teclistamab: BCMA x CD3 Bispecific DuoBody® Antibody

- Teclistamab (JNJ-64007957) is a humanized IgG-4 bispecific DuoBody® antibody that binds to BCMA and CD3
- Teclistamab redirects $CD3^+$ T cells to BCMA-expressing myeloma cells to induce cytotoxicity of the targeted cells in preclinical studies[1,2]
- Teclistamab potently kills myeloma cell lines and primary myeloma cells from heavily pretreated patients[2]
- A Phase 1 first-in-human study is underway to evaluate safety and antitumor activity of teclistamab in patients with RRMM (NCT03145181)



Teclistamab includes technology licensed from GenMab. [1]Labrijn AF et al. *Proc Natl Acad Sci USA*. 2013;110:5145. [2]Frerichs KA et al. *Clin Cancer Res*. 2020; doi: 10.1158/1078-0432.CCR-19-2299. BCMA=B-cell maturation antigen; MM=multiple myeloma; RR=relapsed or refractory

56th ASCO Annual Meeting 2020, Usmani SZ, et al. Abstract #100

Usmani et al, ASCO 2020, #100

Teclistamab: Phase 1 Study Design

Key Objectives

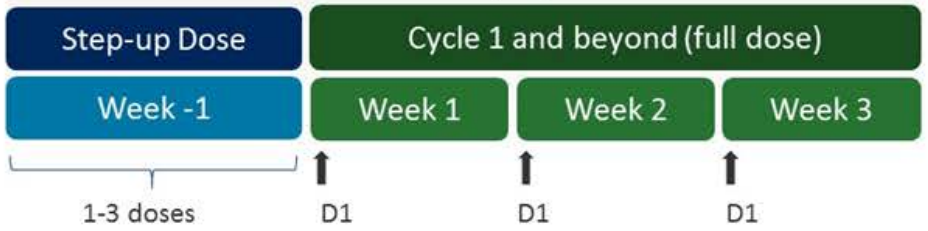
- Part 1: Identify RP2D
- Part 2: Safety and tolerability
- Antitumor activity, PK, PD

Key Eligibility Criteria

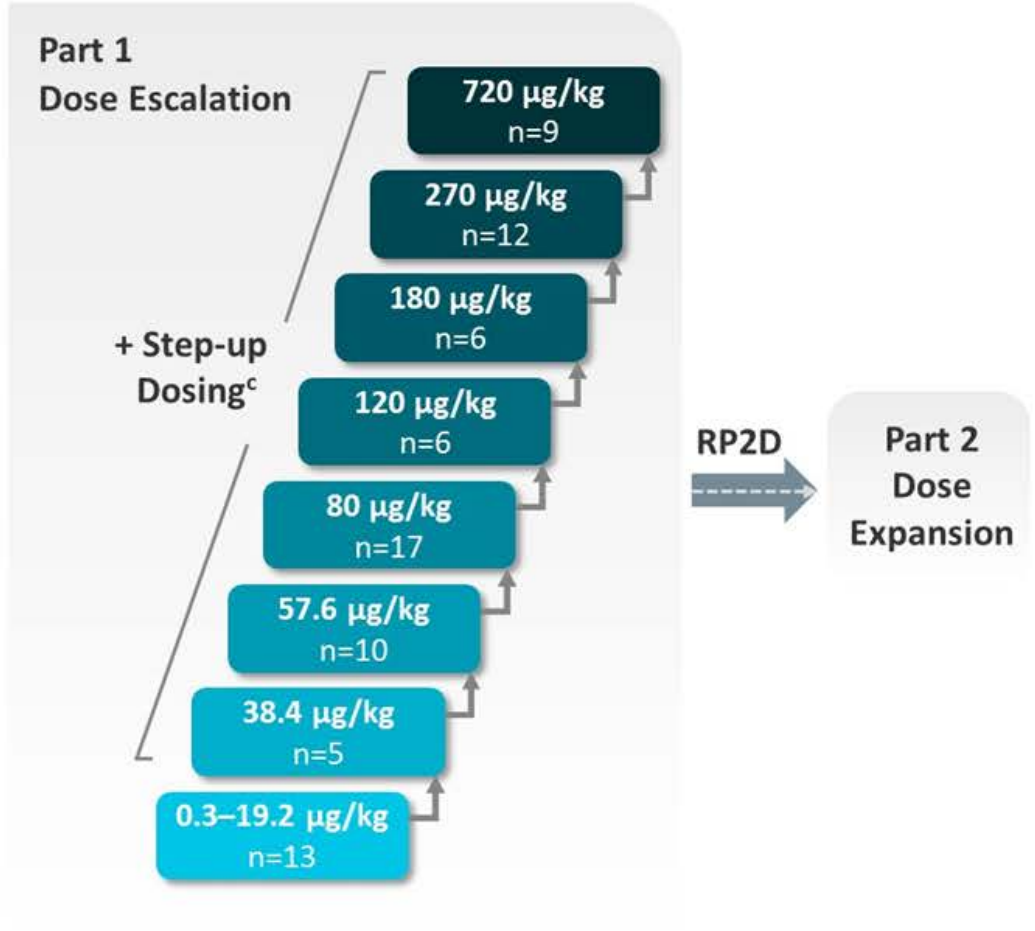
- Measurable MM
- RR or intolerant to established MM therapies
- Hb ≥8 g/dL, platelets[a] ≥75x10^9/L, ANC ≥1.0x10^9/L
- No prior BCMA-targeted therapy

Intravenous Dosing

- Initial Q2W dosing switched to weekly ± step-up dosing
- Pre-medications[b] limited to step-up doses and 1st full dose



- **Results from Part 1 intravenous dose escalation are presented**



Data cutoff: 30 Apr 2020. [a]≥50x10^9/L for patients with ≥50% bone marrow plasma cells, [b]Glucocorticoid, antihistamine, antipyretic, H_2-antagonist, and antiemetic, [c]1-3 step-up doses given within 1 week before full dose.
ANC=absolute neutrophil count; Hb=hemoglobin; PD=pharmacodynamics; PK=pharmacokinetics; Q2W=every 2 weeks; RP2D=recommended phase 2 dose

Usmani et al, ASCO 2020, #100

Teclistamab: Demographic and Disease Characteristics

Characteristic	Total (N = 78)
Median age (range), years	62 (24–82)
≥70 years, n (%)	16 (21)
Female, n (%)	41 (53)
ISS stage III, n (%)	21 (27)
≥1 Extramedullary plasmacytomas, n (%)	7 (9)
Bone marrow plasma cells ≥ 60%, n (%)	22 (30)
Median years from diagnosis (range)[a]	7 (1–26)
High-risk cytogenetics, n (%)[b]	19 (31)
Prior transplantation, n (%)	62 (80)

Characteristic	Total (N = 78)
Prior lines of therapy, median (range)	6 (2–14)
Triple-class exposed, n (%)[c]	72 (92)
Penta-drug exposed, n (%)[d]	51 (65)
Refractory status, n (%)	
Carfilzomib	48 (62)
Pomalidomide	56 (72)
Anti-CD38[e]	68 (87)
Triple-class refractory[c]	62 (80)
Penta-drug refractory[d]	32 (41)
Refractory to last line of therapy,[f] n (%)	67 (86)

[a]N=75, [b]Based on FISH or karyotype testing and includes del(17p), t(4;14), t(14;16); N=61, [c]PI, IMiD, and anti-CD38, [d]≥2 PIs, ≥2 IMiDs, and an anti-CD38, [e]Includes isatuximab (n=1), [f]Progressive disease within 60 days of last regimen. ISS=International Staging System

56th ASCO Annual Meeting 2020, Usmani SZ, et al. Abstract #100 5

Usmani et al, ASCO 2020, #100

Penn Medicine

Teclistamab: Safety Profile

AEs (≥20%), n (%)	N = 78	
	All Grade	Grade ≥3
Hematologic		
Anemia	45 (58)	28 (36)
Neutropenia	35 (45)	30 (38)
Thrombocytopenia	31 (40)	19 (24)
Leukopenia	22 (28)	10 (13)
Nonhematologic		
Cytokine release syndrome	44 (56)	0
Pyrexia	24 (31)	0
Cough	20 (26)	2 (3)
Diarrhea	18 (23)	1 (1)
Back pain	17 (22)	1 (1)
Headache	17 (22)	0
Fatigue	16 (21)	1 (1)

- 2 DLTs: Grade 4 delirium (n=1 at 20 µg/kg step-up dose) and grade 4 thrombocytopenia (n=1 at 180 µg/kg full dose)

SOC/AEs (≥10%), n (%)	N = 78	
	All Grade	Grade ≥3
Infections[a]	**51 (65)**	**16 (21)**
Upper respiratory tract infection	18 (23)	0
Respiratory tract infection	10 (13)	2 (3)
Urinary tract infections	10 (13)	2 (3)
Pneumonia	9 (12)	5 (6)

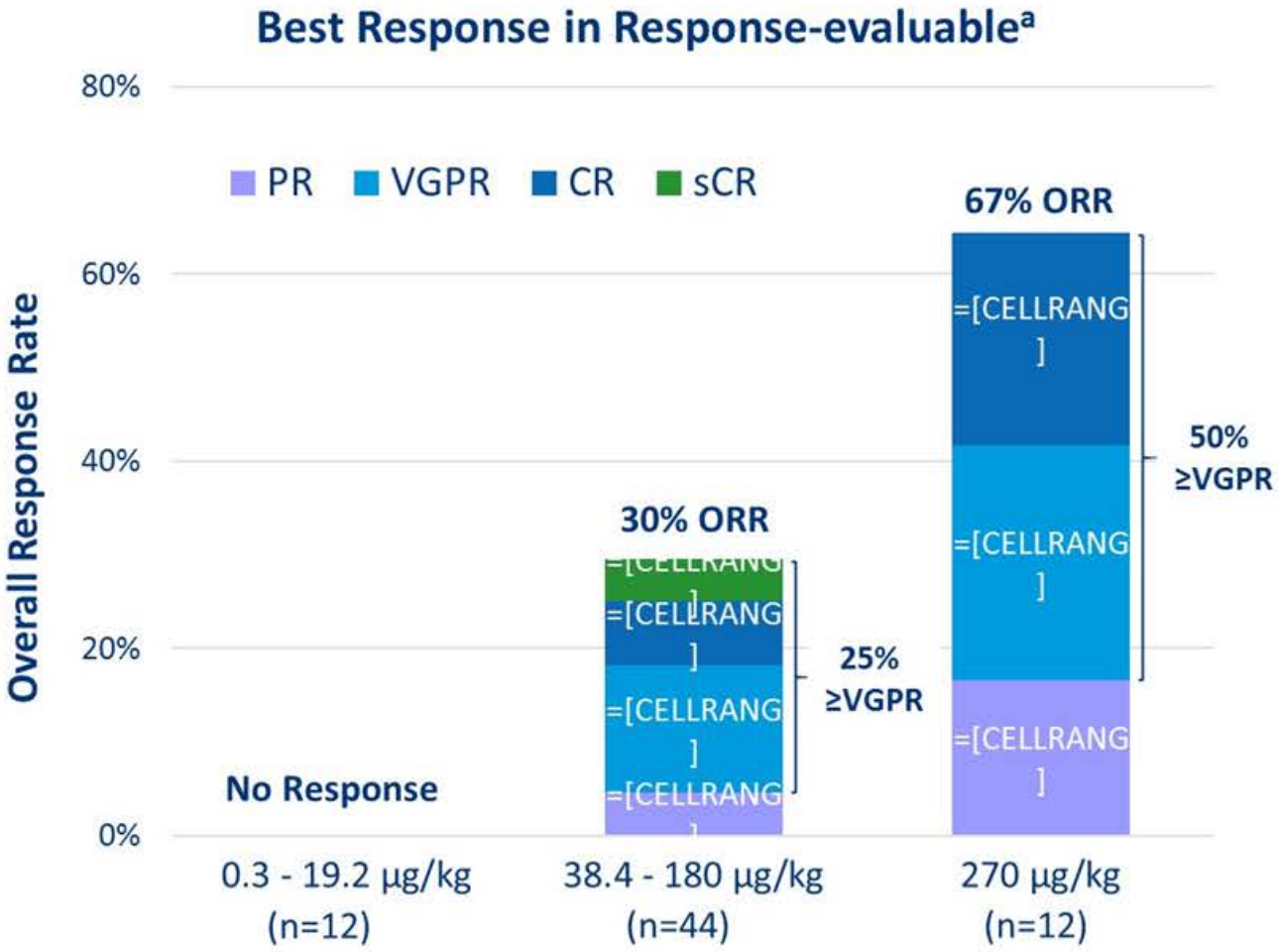
- 19% had infections considered treatment-related by the investigator; (3% of patients grade ≥3)

- Neurotoxic events were reported in 6 patients; 4 had grade 1-2 events
  - 1 DLT of grade 4 delirium, started the day after clinical signs of CRS resolved
  - 1 grade 3 mental status change, occurred in the setting of radiation therapy for new orbital plasmacytoma

26% got tocilizumab; 19% got steroids

Usmani et al, ASCO 2020, #100

Teclistamab: Overall Response Rate



- Efficacy data at 720 µg/kg dose are not mature
- At the 270 µg/kg dose, 7/8 responders were triple-class refractory; 5/8 were penta-drug refractory
- 4/5 evaluable-patients[b] were MRD-negative at 10^{-6}; 2 had MRD-negative CR
- 2/2 evaluable patients maintained MRD-negativity for 5 months (VGPR) and 14 months (CR)

16/21 responses ongoing

[a]Response-evaluable patients received at least one study treatment with at least 1-month follow-up or at least one response evaluation, [b]MRD-evaluable patients have suspected CR and identified baseline clone for assessment.
CR=complete response; MRD=minimal residual disease; ORR=overall response rate; PR=partial response; sCR=stringent complete response; VGPR=very good partial response

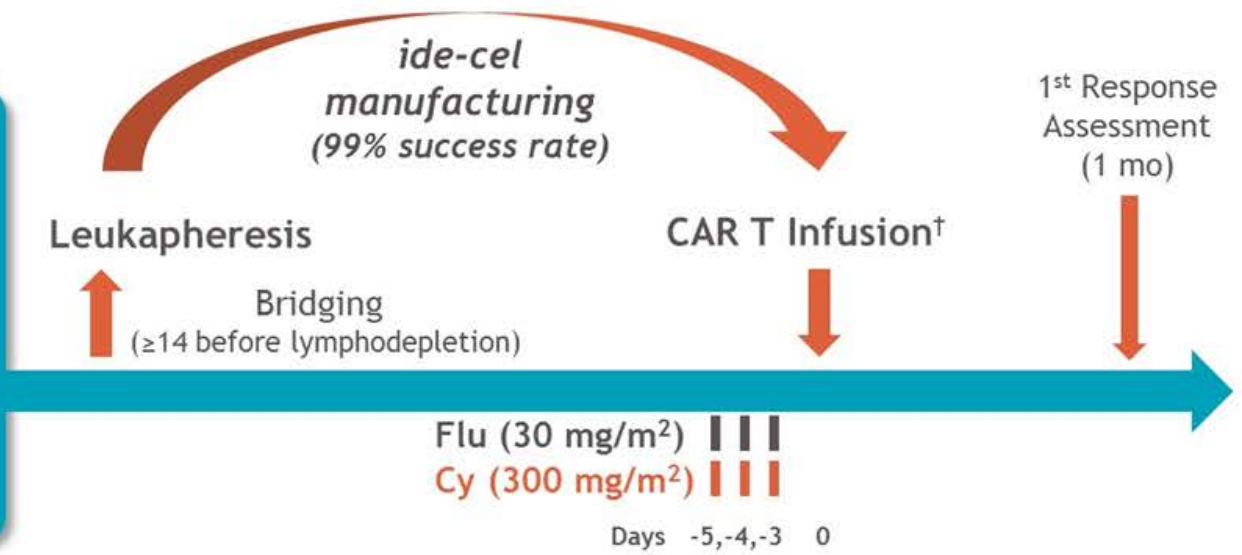
56th ASCO Annual Meeting 2020, Usmani SZ, et al. Abstract #100

Usmani et al, ASCO 2020, #100

Phase II Pivotal KarMMa Study

KarMMa™

- RRMM
- ≥3 prior regimens with ≥2 consecutive cycles each (or best response of PD)
- Previously exposed to:
  - IMiD agent
  - Proteasome inhibitor
  - Anti-CD38 antibody
- Refractory to last prior therapy per IMWG*



Endpoints

- **Primary**: ORR (null hypothesis ≤50%)
- **Secondary**: CRR (key secondary; null hypothesis ≤10%), Safety, DOR, PFS, OS, PK, MRD‡, QOL, HEOR
- **Exploratory**: Immunogenicity, BCMA expression/loss, cytokines, T cell immunophenotype, GEP in BM

Study Status as of Jan 14, 2020

Screened N=158

Leukapheresed N=140

Treated N=128 (Target Dose CAR+ T cells)

150 × 10⁶	n=4
300 × 10⁶	n=70
450 × 10⁶	n=54

Median Follow-up (mo)

150 × 10⁶	18.0
300 × 10⁶	15.8
450 × 10⁶	12.4
Total	13.3

CRR, complete response rate; Cy, cyclophosphamide; DOR, duration of response; Flu, fludarabine; GEP in BM, gene expression profile in bone marrow; HEOR, health economics and outcomes research; IMiD, immunomodulatory drug; IMWG, International Myeloma Working Group; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PK, pharmacokinetics; QOL, quality of life.
*Defined as documented disease progression during or within 60 d from last dose of prior antimyeloma regimen. †Patients were required to be hospitalized for 14 d post-infusion. Ide-cel retreatment was allowed at disease progression for best response of at least stable disease. ‡By next-generation sequencing.

EudraCT: 2017-002245-29
ClinicalTrials.gov: NCT03361748

Munshi et al, ASCO 2020, #8503

Penn Medicine

Baseline Demographics and Clinical Characteristics

Characteristics		Ide-cel Treated (N=128)
Age, median (range), y		61 (33–78)
Male, %		59
ECOG PS, %	0	45
	1	53
	2	2
R-ISS Stage,* %	I	11
	II	70
	III	16
High-risk cytogenetics [del(17p), t(4;14), t(14;16)],† %		35
High tumor burden (≥50% BMPCs), %		51
Tumor BCMA expression (≥50% BCMA+),‡ %		85
Extramedullary disease, %		39
Time since initial diagnosis, median (range), y		6 (1–18)
No. of prior anti-myeloma regimens, median (range)		6 (3–16)
Prior autologous SCT, %	1	94
	>1	34
Any bridging therapies for MM, %		88
Refractory status, %	Anti-CD38 Ab-refractory	94
	Triple-refractory	84

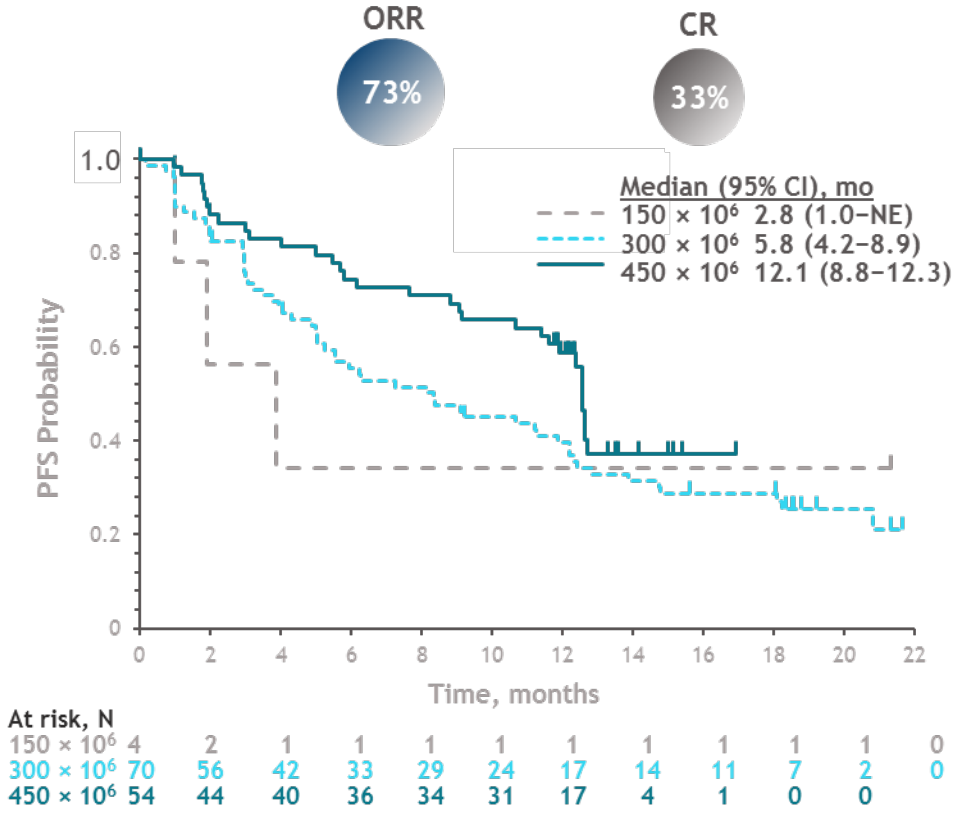
- Patients were heavily pretreated, refractory to last line per IMWG criteria, and mostly refractory to all 3 major MM drug classes
- The majority had high tumor burden and more than one third had extramedullary disease and high-risk cytogenetics
- Tumor BCMA expression identified by IHC in all patients
- Most patients (88%) received bridging therapy during CAR T cell manufacturing
  - Only 4% of patients responded (4 PR, 1 VGPR) to bridging therapy

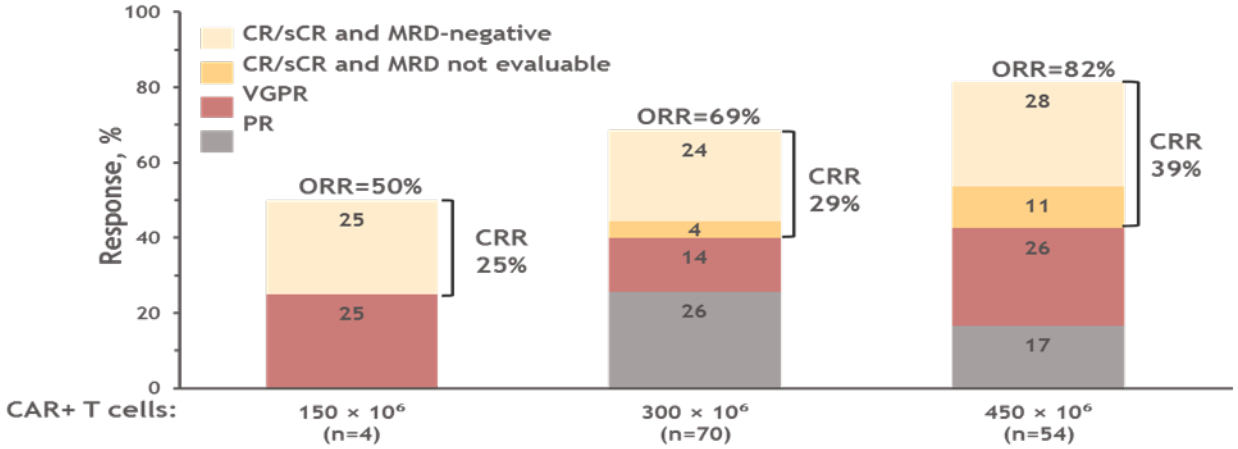
Data cutoff: 14 Jan 2020. Ab, antibody; BCMA, B-cell maturation antigen; BMPC, bone marrow plasma cells; ECOG PS, Eastern Cooperative Oncology Group performance status; IMWG, International Myeloma Working Group; MM, multiple myeloma; PR, partial response; R-ISS, revised International Staging System; SCT, stem cell transplant; VGPR, very good PR.
*R-ISS stage was assessed at enrollment; unknown for 3 patients. †Baseline cytogenetics not evaluable/missing for 17 patients; 45 patients (35%) had 1q amp abnormality. ‡No minimum tumor BCMA expression required for study entry.

Munshi et al, ASCO 2020, #8503

KarMMa Phase 2 study: summary key findings

Efficacy





Adverse events of interest

Target Dose, × 10⁶ CAR+ T cells	150 (n=4)	300 (n=70)	450 (n=54)	Ide-cel Treated (N=128)
≥1 CRS event, n (%)	2 (50)	53 (76)	52 (96)	107 (84)
Grade ≥ 3 (Lee Criteria)[a]	0	4 (6)	3 (6)	7(5)
≥1 NT event, n (%)	0	12 (17)	11 (20)	23 (18)
Grade 3 (CTCAE)[a]	0	1 (1)	3 (6)	4 (3)

52% got toci

Primary (ORR >50%) and key secondary (CRR >10%) endpoints met
PFS increased with higher target dose; median PFS was 12.1 mo at 450 × 10⁶ CAR+ T cells

Munshi et al, ASCO 2020, #8503

Penn Medicine

Orvacabtagene autoleucel (orva-cel)

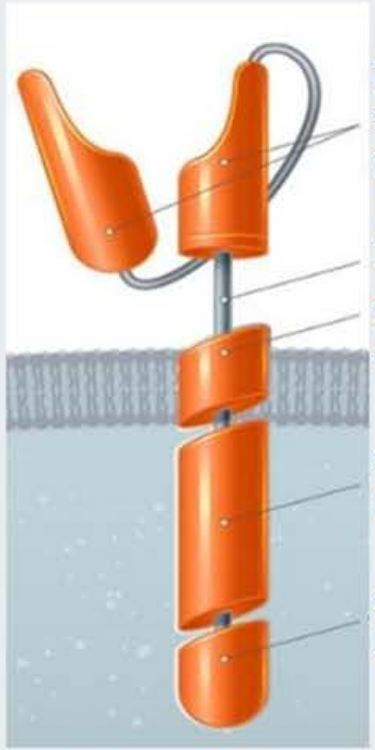
Design and manufacturing features

Construct

- Fully human binder with low affinity for soluble BCMA (sBCMA)
- Active on target cells that express low BCMA density
- Minimized tonic signaling to reduce antigen-independent exhaustion[1]
- Spacer is designed to enhance binding to BCMA on target cells

Manufacturing process

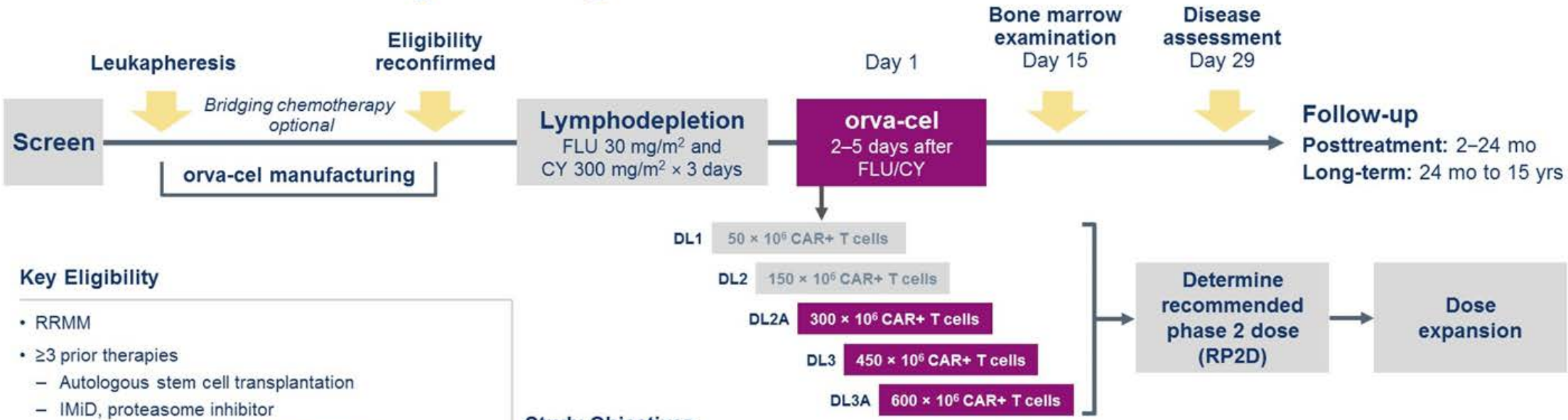
- Designed to deliver a product comprising purified CD4+ and CD8+ CAR+ T cells enriched for central memory phenotype, potentially increasing persistence and durability
- To date, orva-cel has been successfully manufactured for all patients



1. Long et al. *Nat Med*. 2015;21(6):581–590.

Mailankody et al, ASCO 2020, #8504

EVOLVE: Study Design



Key Eligibility

- RRMM
- ≥3 prior therapies
  - Autologous stem cell transplantation
  - IMiD, proteasome inhibitor
  - Anti-CD38 (combination or monotherapy)
- Refractory to last line of therapy
- ECOG performance status 0–1
- CrCl ≥60 ml/min, ANC ≥1000 cells/mm^3, PLT ≥50/mm^6, Hb ≥8 g/dL
- No selection based on BCMA expression
- BCMA cohort: relapse after prior anti-BCMA directed therapy at any time

Study Objectives

Phase 1

Primary

- To evaluate safety and tolerability (DLTs, adverse events)
- To determine a recommended phase 2 dose (RP2D)

Secondary

- To determine orva−cel pharmacokinetics (C_{max}, T_{max}, AUC)
- To evaluate preliminary antitumor activity

Phase 2

Primary

- To evaluate the antitumor activity of orva−cel, as determined by ORR, at the RP2D

ANC, absolute neutrophil count; AUC, area under the curve; BCMA, B-cell maturation antigen; C_{max}, maximum concentration; CrCl, creatinine clearance; CY, cyclophosphamide; DL, dose level; DLT, dose-limiting toxicity; FLU, fludarabine; Hb, hemoglobin; IMiD, immunomodulatory agent; MRD, minimal residual disease; ORR, objective response rate; PLT, platelet; T_{max}, time to maximum concentration.

Mailankody et al, ASCO 2020, #8504

EVOLVE: Treatment History

	300 × 10^6 CAR+ T cells (n=19)	450 × 10^6 CAR+ T cells (n=19)	600 × 10^6 CAR+ T cells (n=24)	Total (N=62)
Number of prior treatment regimens				
Median (min–max)	7 (3–14)	6 (3–18)	6 (3–12)	6 (3–18)
Prior ASCT, n (%)	**19 (100)**	**16 (84)**	**23 (96)**	**58 (94)**
≥2 ASCT	7 (37)	1 (5)	3 (13)	11 (18)
Penta-exposed, n (%) (Prior 2 IMiD agents, 2 PIs, and anti-CD38 agent)	17 (89)	18 (95)	23 (96)	58 (94)
Refractory to last regimen, n (%) (PD within 60 days from the last anti-MM tx)	19 (100)	19 (100)	24 (100)	62 (100)
Triple-refractory, n (%) (Refractory to PI, IMiD, and anti-CD38)	19 (100)	18 (95)	21 (88)	58 (94)
Penta-refractory, n (%) (Refractory to 2 IMiD, 2 PIs, and anti-CD38 agent)	10 (53)	11 (58)	9 (38)	30 (48)
Received bridging chemotherapy, n (%)	**9 (47)**	**13 (68)**	**17 (71)**	**39 (63)**
Refractory to bridging chemotherapy, n (%)	6 (75)	11 (85)	11 (65)	28 (74)

ASCT, autologous stem cell transplant; IMiD, immunomodulatory agent; PI, proteasome inhibitor.

Data cutoff: 01 May 2020

Mailankody et al, ASCO 2020, #8504

EVOLVE: Safety Summary

	300 × 10^6 CAR+ T Cells (n=19)	450 × 10^6 CAR+ T Cells (n=19)	600 × 10^6 CAR+ T Cells (n=24)	Total (N=62)
Any SAE, n (%)	**4 (21)**	**5 (26)**	**8 (33)**	**17 (27)**
AEs of special interest grade ≥3, n (%)				
Neutropenia	15 (79)	19 (100)	22 (92)	56 (90)
Anemia	8 (42)	8 (42)	14 (58)	30 (48)
Thrombocytopenia	6 (32)	10 (53)	13 (54)	29 (47)
Infections	3 (16)	4 (21)	1 (4)	8 (13)
Cytokine release syndrome (CRS)	0	1 (5)	1 (4)	2 (3)
Neurological events (NE)	1 (5)	1 (5)	0	2 (3)
MAS/HLH	0	2 (11)	1 (4)	3 (5)

All grade
89%
13%

Tocilizumab 76%, Steroids 52%

Two deaths within 90 days of orva-cel infusion

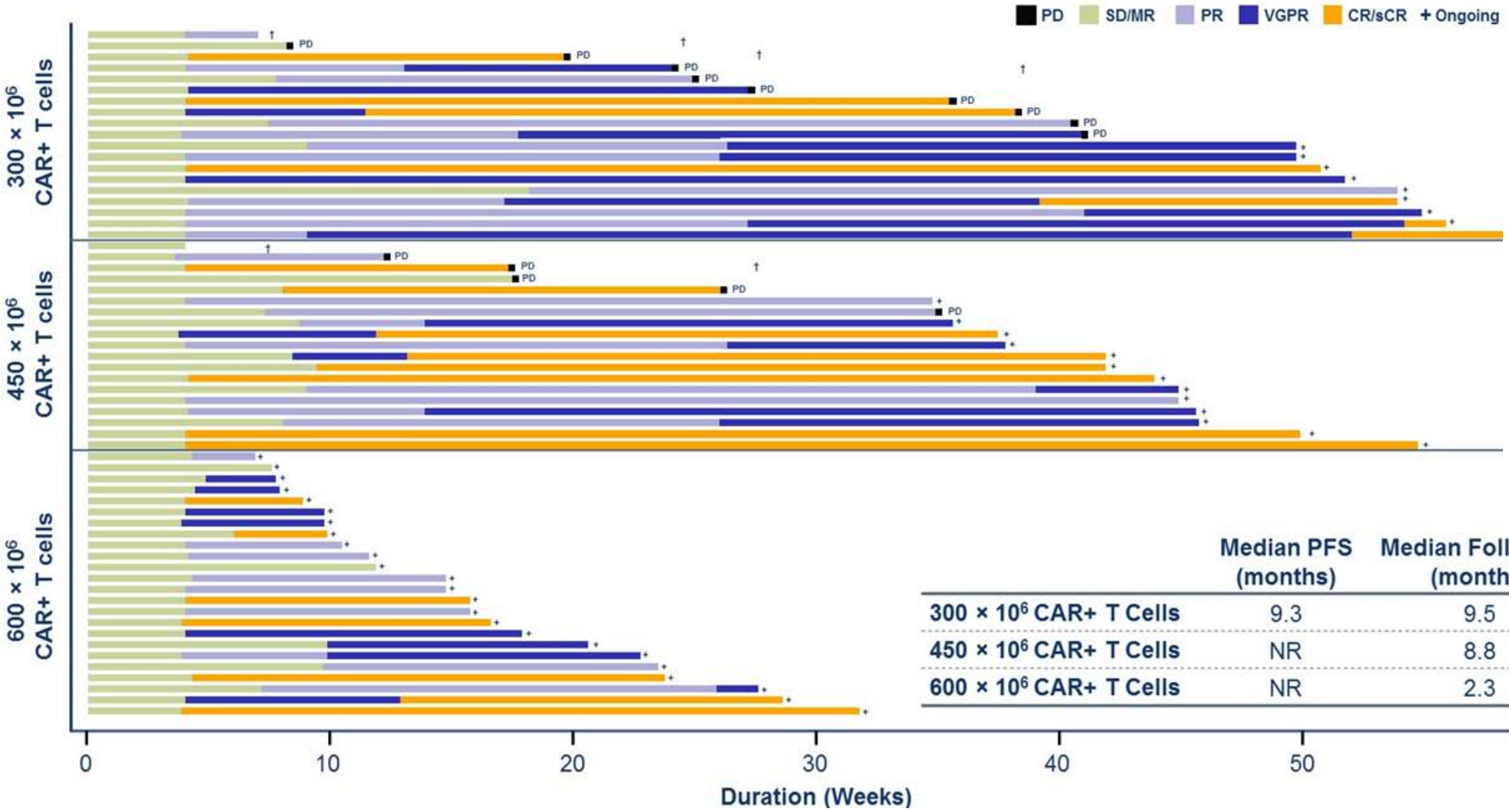
- 1 patient infused with 300 × 10^6 CAR+ T cells was experiencing several comorbidities including pneumonia, GI bleeding, and steroid-induced myopathy; patient withdrew consent and died at home on day 53 due to cardiac arrest
- 1 patient with 3% circulating plasma cells before infusion; infused with 450 × 10^6 CAR+ T cells; died on day 51 due to grade 5 MAS/HLH; patient developed grade 1 CRS and grade 3 MAS/HLH

SAE, serious adverse event; AE, adverse event; CRS, cytokine release syndrome; NE, neurological event; MAS, macrophage activation syndrome; HLH, hemophagocytic lymphohistiocytosis; ASCT, autologous stem cell transplant; URI, upper respiratory infection; GI, gastrointestinal.

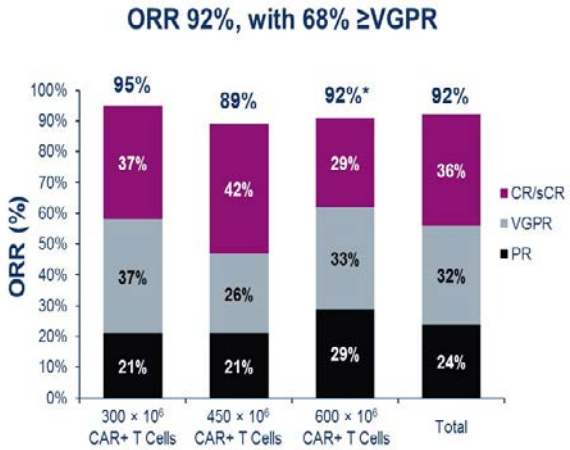
Data cutoff: 01 May 2020

Mailankody et al, ASCO 2020, #8504

EVOLVE: Response Over Time

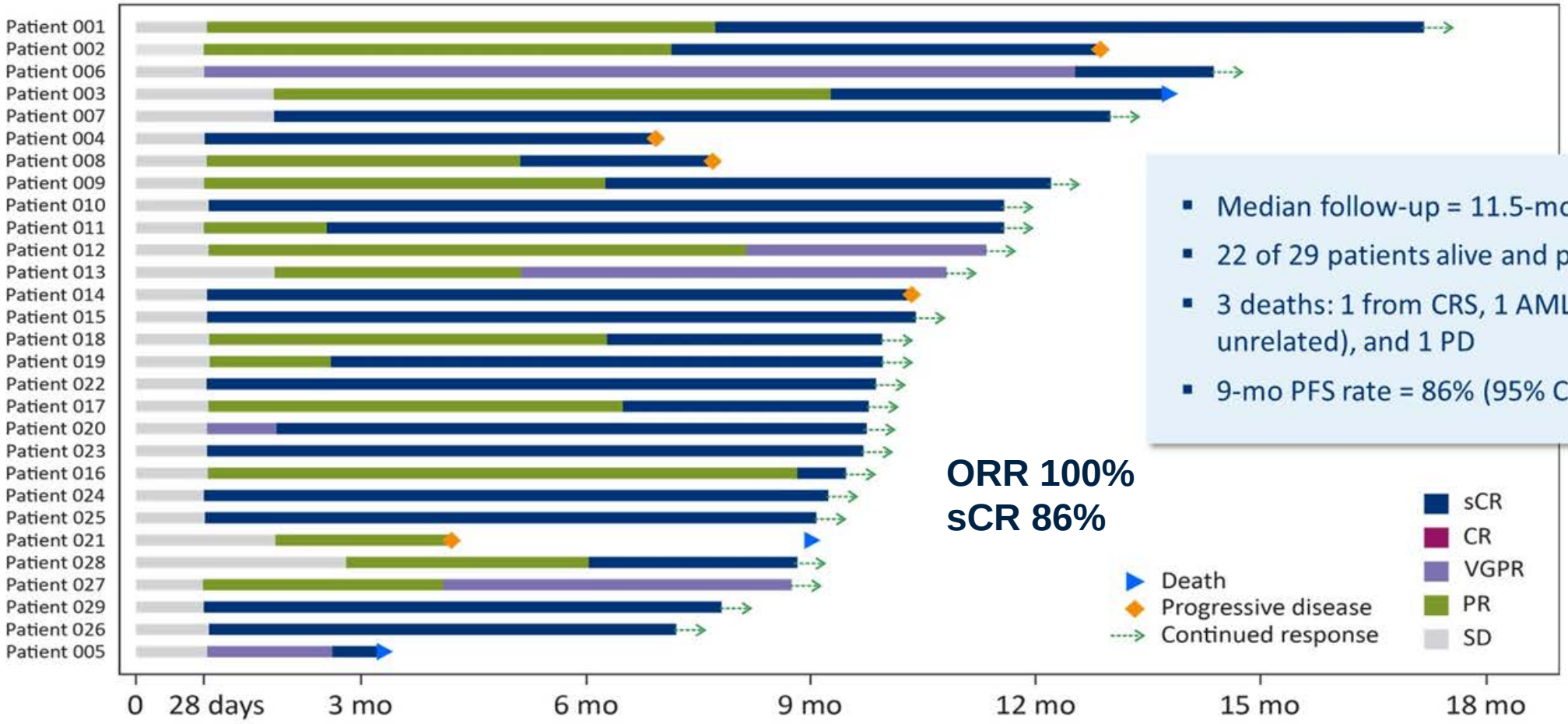


	Median PFS (months)	Median Follow-up (months)
300 × 10^6 CAR+ T Cells	9.3	9.5
450 × 10^6 CAR+ T Cells	NR	8.8
600 × 10^6 CAR+ T Cells	NR	2.3



Mailankody et al, ASCO 2020, #8504

JNJ-4528: CARTITUDE-1: Duration of Response



- Median follow-up = 11.5-mo (3 – 17)
- 22 of 29 patients alive and progression-free
- 3 deaths: 1 from CRS, 1 AML (treatment unrelated), and 1 PD
- 9-mo PFS rate = 86% (95% CI, 67 – 95)

ORR 100%
sCR 86%

AML=acute myeloid leukemia (biphenotypic); PD=progressive disease; PFS=progression-free survival

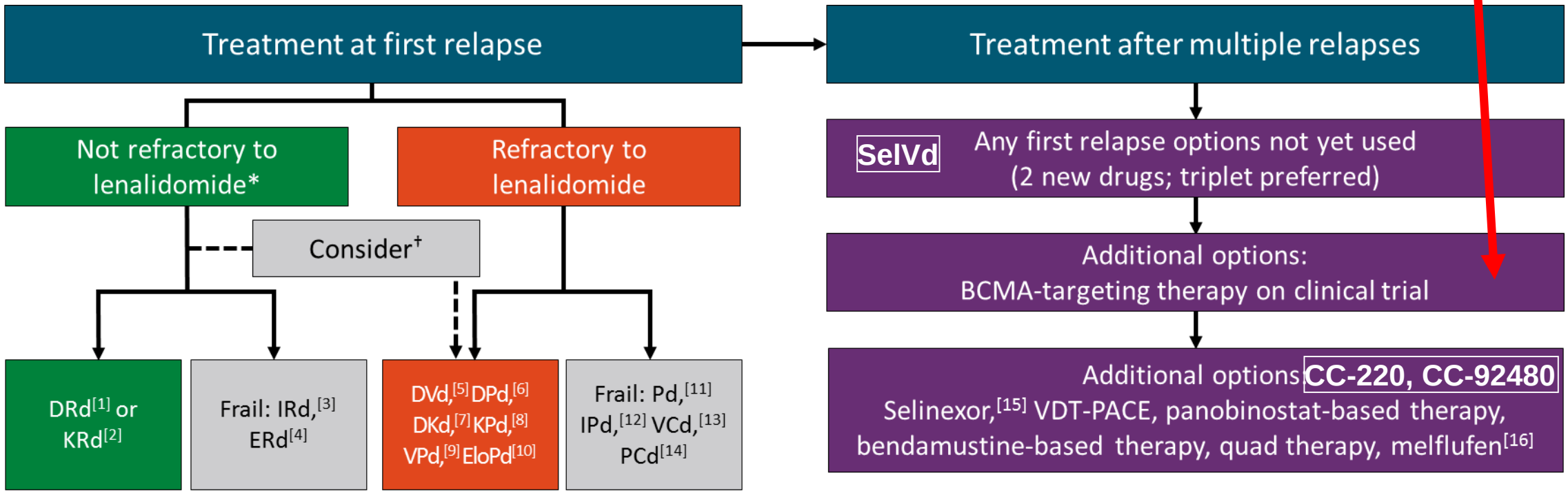
56th ASCO Annual Meeting 2020, Berdeja et al. Abstract #8505 9

Berdeja et al, ASCO 2020, #8505

Treatment of relapsed/refractory myeloma in USA

Belantamab
Ide-cel
Orva-cel
JNJ-4528

Teclistamab
AMG420
CC-93269



*Relapse occurring while off all therapy, while on small doses of single-agent lenalidomide, or on bortezomib maintenance.

†For those intolerant to lenalidomide, with aggressive relapse, or with high-risk disease.

‡Consider salvage ASCT in eligible patients if first PFS > 2 yrs off maintenance or > 4 yrs with maintenance or for patients with pan-cytopenias and heavy bone marrow involvement.

1. Dimopoulos. Haematologica. 2018;103: 2088. 2. Stewart. ASH 2017. Abstr 743. 3. Moreau. NEJM. 2016;374:1621. 4. Lonial. ASCO 2018. Abstr 8040. 5. Lentzsch. ASCO 2017. Abstr 8036. 6. Chari. Blood. 2017;130:974. 7. Chari. ASCO 2018. Abstr 8002. 8. Bringhen. Leukemia. 2018;32:1803. 9. Richardson. ASCO 2018. Abstr 8001. 10. Dimopoulos. EHA 2018. Abstr LBA2606. 11. San Miguel. Lancet Oncol. 2013;14:1055. 12. Krishnan. Leukemia. 2017;[Epub]. 13. Rajkumar. Am J Hematol. 2014;89:999. 14. Baz. Blood. 2016;127:2561. 15. Vogl. JCO. 2018;36:859. 16. Richardson. ASH 2018. Abstr 600.

Conclusions:

- VRd and KRd with similar ORR, PFS, different toxicities for standard-risk new MM
  - VRd neuropathy; KRd cardio-pulm-renal tox
- Adding Elotuzumab (anti-SLAMF7) to VRd for high-risk MM not beneficial
- Adding Isatuximab (anti-CD38) to KRd feasible for high-risk MM
- Prolonged Len maint post-SCT assoc. with improved PFS
- Adding Selinexor to bortez-dex for early relapsed (1-3 priors) MM improves ORR, PFS (HR 0.7)
  - More GI tox, cytopenias, fatigue
- CC-92480 (novel CELmoD) + dex with 30% ORR in rel/ref MM
- Multiple BCMA-targeted immunotherapies highly active in rel/ref MM
  - Teclistamab (bispecific Ab), ide-cel (CAR T), orva-cel (CAR T), JNJ-4528 (CAR T)
  - ORR 80-100%, CR 33-86%, MRD-negative responses seen
  - Response durability variable
  - Challenges: CRS (cytokine release syndrome), neurotoxicity, prolonged cytopenias,
  - Need biomarkers of response/resistance

Extra slides

Bortezomib, Lenalidomide, dex (VRd) vs Carfilzomib, Lenalidomide, Dex (KRd) for Newly-diagnosed Myeloma

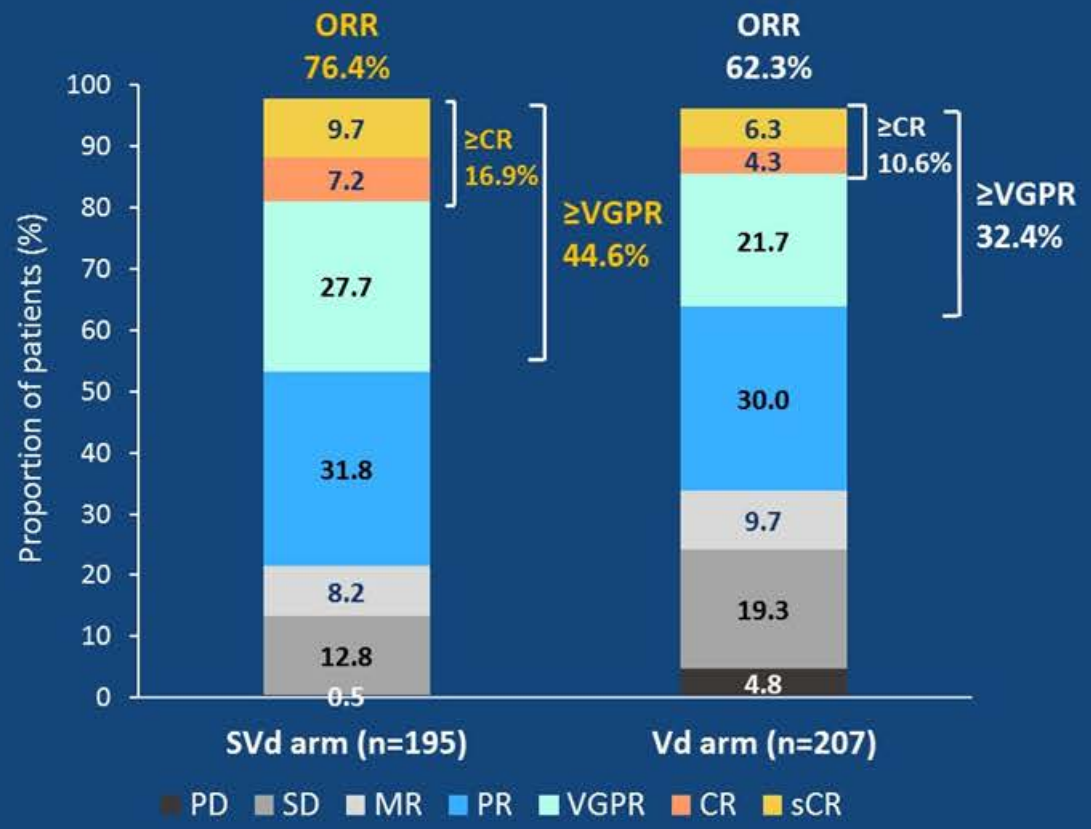
Trial	Pop	n	Induction	AutoSCT	Consol	Maint	ORR	≥VGPR	CR	PFS (mos)
S0777	TE, TI	235	VRd x 8	-	-	Rd to PD	82%	44%	16%	41
IFM2009	TE	350	VRd x 3	MEL200	VRd x 2	R 1 yr	99%	88%	59%	50
IFM2009	TE	350	VRd x 8	-	-	R 1 yr	97%	77%	48%	36
GEM2012	TE	458	VRd x 6	MEL200 vs BuMEL	VRd x 2	-	81%	75%	44%	-

AutoSCT = autologous stem cell transplant; BuMEL = busulfan + melphalan; Consol = consolidation; CR = complete response; K = carfilzomib; Maint = maintenance; MEL200 = melphalan 200 mg/m2; ORR

transplant-eligible; TI = transplant-ineligible; V = bortezomib; yr = year

Durie, Lancet 2017, ASH 2018, #1992; Attal, NEJM 2017; Rosinol, Blood 2019; Jakobowiak, Haematologica 2016, #S101; Kazandijan, JAMA Onc 2018; Jakubowiak, ASH 2017, #4533; Roussel, ASH 2016, #1142; Gay, ASCO 2019, #8002

SVd: Significantly Higher Rate of Deep Responses (≥VGPR, *P*=0.0082)



Longer duration of response with SVd

	SVd arm (n=149)	Vd arm (n=129)
Median Time to Response (months)†	1.1	1.4
Median Duration of Response (months)*	20.3	12.9

Fewer patients with progressive disease: SVd (n=1, 0.5%) vs Vd (n=10, 4.8%)

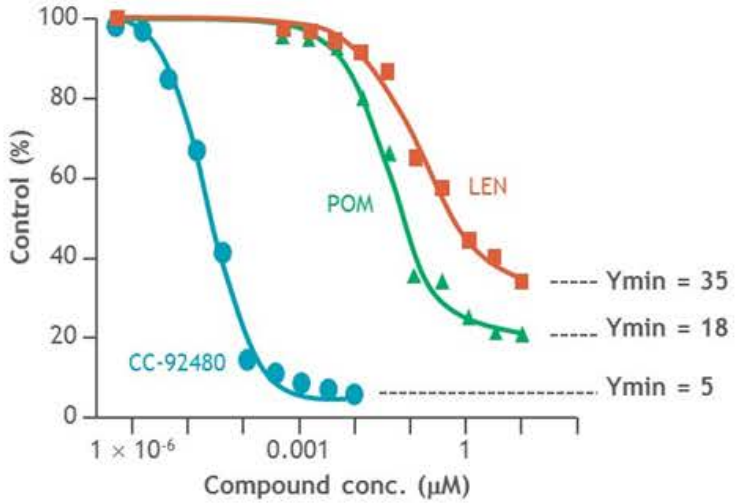
CR= complete response, MR = minimal response, PD = progressive disease, PR = partial response, sCR = stringent complete response, SD = stable disease, VGPR = very good partial response. All Responses assessed by an Independent Review Committee (IRC), according to the IMWG criteria (Kumar et all. Lancet Oncology 2016) †Unadjusted Time from date of randomization until first response per IMWG response criteria.
*Duration of the time interval between the first IRC-confirmed PR or better response and the first IRC-confirmed PD or death due to any cause, whichever occurred first. Data cut-off February 18, 2020.

Dimopolous et al, ASCO 2020, #8501

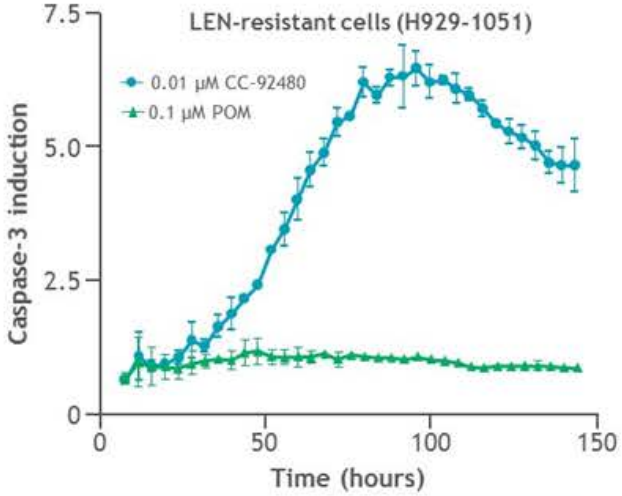
CC-92480

- Efficient substrate degradation leading to apoptosis and potent antiproliferative activity in LEN and POM resistance

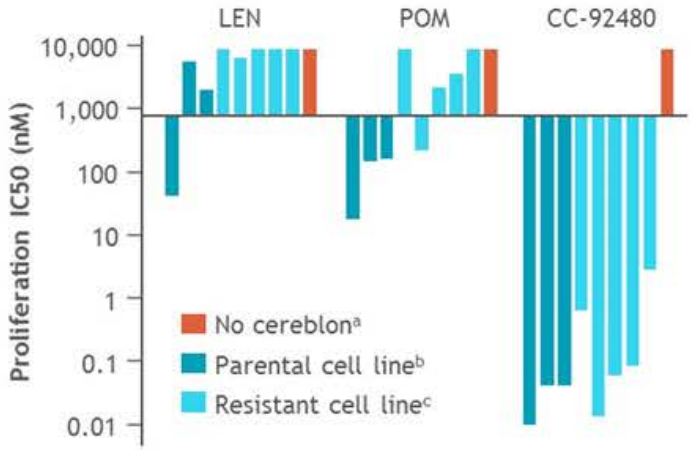
Aiolos degradation efficiency

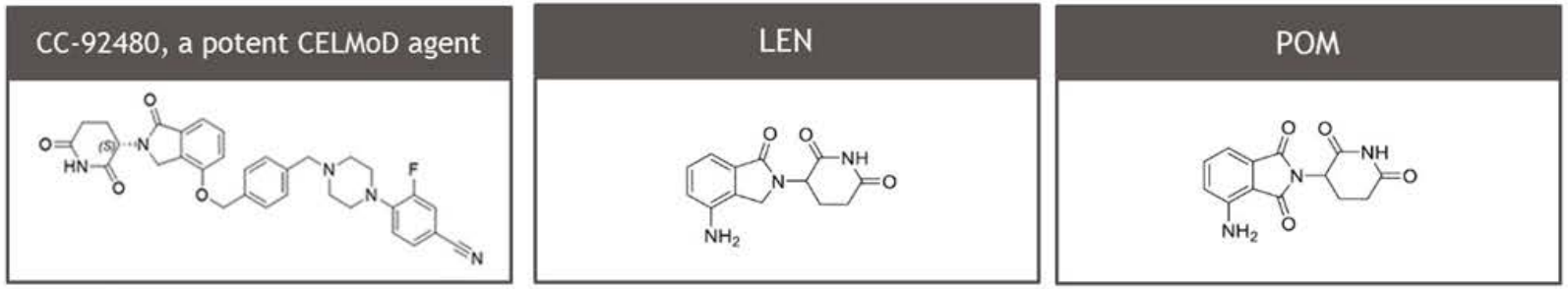


Apoptosis induction kinetics



Antiproliferative activity in LEN/POM resistance





[a]DF15R; [b]DF15, H929, and OPM-2; [c]H929R1, H929R2, OPM-2R1, OPM-2R2, and OPM-2R3.

CELMoD, cereblon E3 ligase modulator; IC50, 50% inhibitory concentration; LEN, lenalidomide; POM, pomalidomide; Ymin, maximum degradation point.

Richardson et al, ASCO 2020, #8500