ASH Updates 2020

William Bensinger
Swedish Cancer Institute

Choosing Therapy for Patients With R/R MM

Chosen 1st-line Therapy

Chosen 2nd-line Therapy

Induction Therapy ± Consolidation → Len maintenance until PD

→

- **Anti-CD38 mAb/ Pomalidomide/Dex**
- **Daratumumab/PI/Dex**
- **Bortezomib/ Pomalidomide/Dex**
- **Carfilzomib/ Pomalidomide/Dex**

Treat until PD/toxicity

Clinical trial should be considered for all eligible patients

Choosing Therapy for Patients With R/R MM

Chosen 1st-line Therapy

Induction Therapy ± Consolidation → Len maintenance until PD

Chosen 2nd-line Therapy

Anti-CD38 mAb/ Pomalidomide/Dex

Daratumumab/PI/Dex

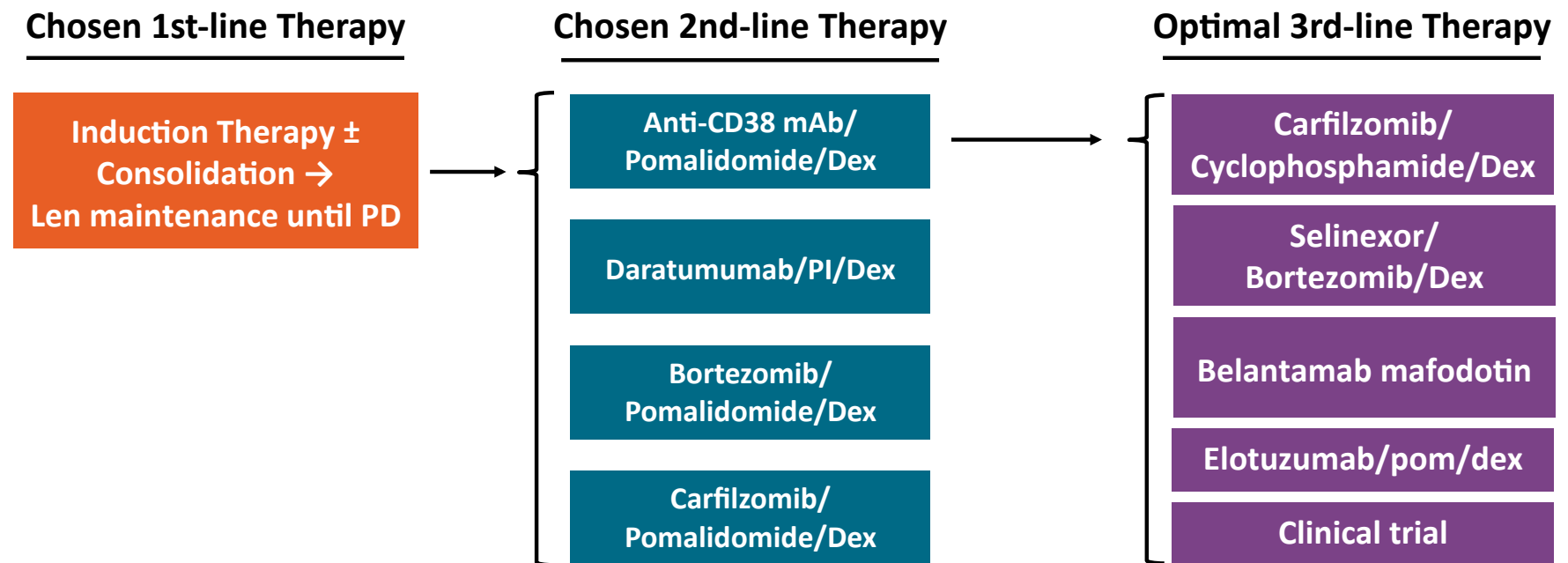Bortezomib/ Pomalidomide/Dex

Carfilzomib/ Pomalidomide/Dex

Optimal 3rd-line Therapy

Carfilzomib/ Cyclophosphamide/Dex

Selinexor/ Bortezomib/Dex

Belantamab mafodotin

Elotuzumab/pom/dex

Clinical trial

3rd-line treatment choice can largely be chosen based on prior therapy and previous resistance patterns
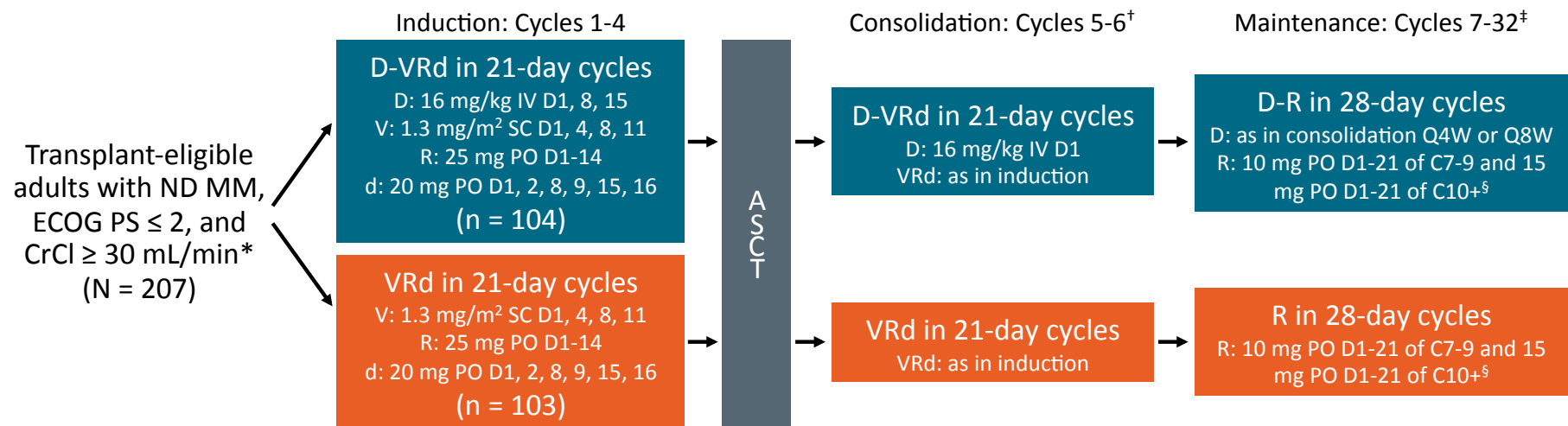
Clinical trial should be considered for all eligible patients

Contemporary Management of Multiple Myeloma

Frontline therapy is changing

GRIFFIN Maintenance Phase Update: Study Design

- Multicenter, open-label, randomized phase II trial

<div align="center">

Induction: Cycles 1-4   Consolidation: Cycles 5-6[†]   Maintenance: Cycles 7-32[‡]

</div>

Transplant-eligible adults with ND MM, ECOG PS ≤ 2, and CrCl ≥ 30 mL/min* (N = 207)

D-VRd in 21-day cycles
D: 16 mg/kg IV D1, 8, 15
V: 1.3 mg/m^2 SC D1, 4, 8, 11
R: 25 mg PO D1-14
d: 20 mg PO D1, 2, 8, 9, 15, 16
(n = 104)

VRd in 21-day cycles
V: 1.3 mg/m^2 SC D1, 4, 8, 11
R: 25 mg PO D1-14
d: 20 mg PO D1, 2, 8, 9, 15, 16
(n = 103)

ASCT

D-VRd in 21-day cycles
D: 16 mg/kg IV D1
VRd: as in induction

VRd in 21-day cycles
VRd: as in induction

D-R in 28-day cycles
D: as in consolidation Q4W or Q8W
R: 10 mg PO D1-21 of C7-9 and 15 mg PO D1-21 of C10+[§]

R in 28-day cycles
R: 10 mg PO D1-21 of C7-9 and 15 mg PO D1-21 of C10+[§]

*Lenalidomide dose was adjusted in patients with CrCl ≤ 50 mL/min. [†]Consolidation began 60-100 days after transplantation. [‡]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 α = .1

- Secondary endpoints: MRD, CR, ORR, ≥ VGPR

Kaufman. ASH 2020. Abstr 549.

Slide credit: clinicaloptions.com

GRIFFIN Maintenance Phase Update: Depth of Response Over Time

Depth of Response	D-VRd				VRd			
	End of Induction	End of ASCT	End of Consolidation	12 Mos of Maintenance Cutoff	End of Induction	End of ASCT	End of Consolidation	12 Mos of Maintenance Cutoff
sCR	12.1	21.2	42.4	63.6*	7.2	14.4	32.0	47.4*
CR	7.1	6.1	9.1	18.2*	6.2	5.2	10.3	13.4*
VGPR	52.5	59.6	39.4	14.1	43.3	46.4	30.9	18.6
PR	26.3	12.1	8.1	3.0	35.1	25.8	18.6	13.4
SD/PD/NE	2.0	1.0	1.0	1.0	8.2	8.2	8.2	7.2

*P = .0253 for comparison of sCR for D-VRd vs VRd. P = .0014 for comparison of ≥ CR.

- Median follow-up at 12-mo maintenance therapy cutoff: 27.4 mos
    - Entered maintenance phase: 87% D-VRd vs 68% VRd; discontinued during maintenance phase: 12% D-VRd vs 17% VRd

- End of induction, ASCT, consolidation data are from primary analysis (median follow-up: 13.5 mos)

GRIFFIN Maintenance Phase Update: MRD Status

MRD Status at 12-Mo-Maintenance Cutoff*	D-VRd	VRd	P Value‡
ITT population†	(n = 104)	(n = 103)	
▪ MRD negative, %	62.5	27.2	< .0001
▪ MRD negative and ≥ CR, %	59.6	24.3	< .0001
Patients with ≥ CR	(n = 81)	(n = 59)	
▪ MRD negative, %	76.5	42.4	< .0001
MRD evaluable in ITT patients§	(n = 83)	(n = 71)	
▪ MRD negative, %	78.3	39.4	< .0001
Durable MRD Negativity*	(n = 104)	(n = 103)	*P* Value‡
Sustained MRD negativity lasting ≥ 6 mos	37.5	7.8	< .0001
Sustained MRD negativity lasting ≥ 12 mos	28.8	2.9	< .0001

*MRD negativity threshold: 1 tumor cell/10^5 white cells using BM aspirates by NGS. †Patients with missing/inconclusive MRD assessment considered MRD positive. ‡Fisher's exact test. §Includes patients with baseline and post-baseline MRD samples.

- ▪ D-VRd improved sCR and MRD-negativity rates across most subgroups

GRIFFIN Maintenance Phase Update: Survival

- Median PFS and OS not reached in either study arm at median follow-up of 27.4 mos

PFS and OS in ITT Population	D-VRd	VRd
PFS rate, %		
▪ 12-mo PFS	96.9	94.0
▪ 24-mo PFS	94.5	90.8
OS rate, %		
▪ 12-mo OS	99.0	97.9
▪ 24-mo OS	94.7	93.3

Kaufman. ASH 2020. Abstr 549.

Recent New FDA Approvals for Novel Agents in R/R MM

Isatuximab-irfc

FDA approved Mar 2, 2020

In combination with pomalidomide/dex for patients with MM who have received ≥ 2 previous therapies, including lenalidomide and a PI

Belantamab Mafodotin

FDA approved Aug 5, 2020

For patients with R/R MM who have received ≥ 4 previous therapies including an anti−CD-38 mAb, a PI, and an IMiD

Selinexor + Vd

FDA approved Dec 18, 2020

In combination with bortezomib/dex for patients with R/R MM who have received ≥ 1 previous of therapy

Selinexor is also approved in combination with dex for patients with R/R MM who have received ≥ 4 previous therapies and whose disease is refractory to ≥ 2 PI, ≥ 2 IMiD, and an anti−CD-38 mAb

Melphalan Flufenamide (Melflufen)
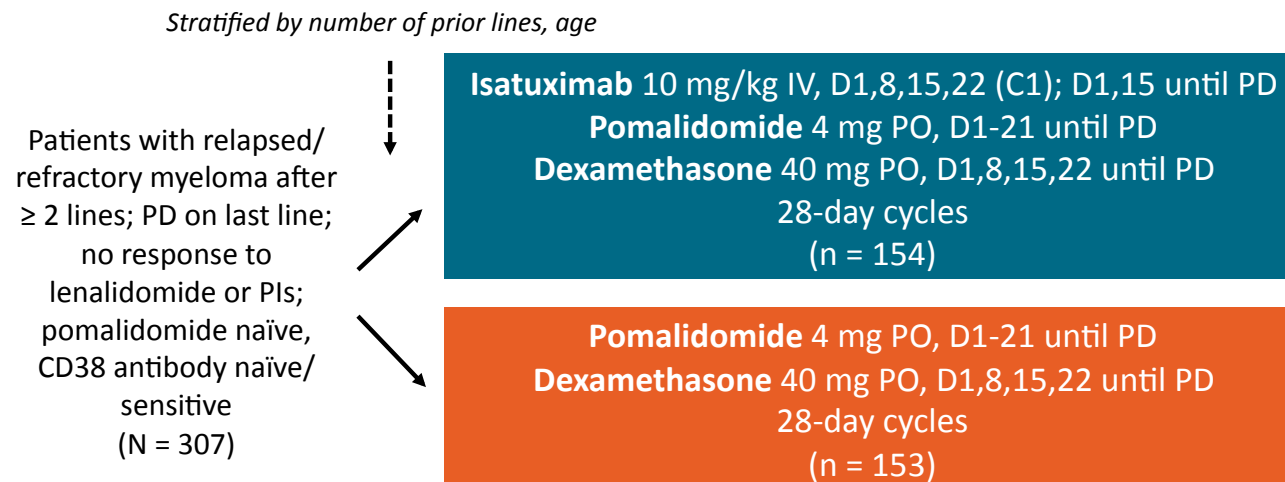
FDA approved Feb 26, 2021

In combination with dex for patients with R/R MM who have received ≥ 4 previous lines of therapy and whose disease is refractory to ≥ 1 PI, 1 IMiD, and 1 anti−CD-38 mAb

ICARIA-MM: Isatuximab/Pom/Dex vs Pom/Dex in R/R MM

- Prospective, open-label, randomized phase III trial in Europe, North America and Asia-Pacific

Stratified by number of prior lines, age

Patients with relapsed/ refractory myeloma after ≥ 2 lines; PD on last line; no response to lenalidomide or PIs; pomalidomide naïve, CD38 antibody naïve/ sensitive
(N = 307)

Isatuximab 10 mg/kg IV, D1,8,15,22 (C1); D1,15 until PD
Pomalidomide 4 mg PO, D1-21 until PD
Dexamethasone 40 mg PO, D1,8,15,22 until PD
28-day cycles
(n = 154)

Pomalidomide 4 mg PO, D1-21 until PD
Dexamethasone 40 mg PO, D1,8,15,22 until PD
28-day cycles
(n = 153)

- Primary endpoint: PFS

- Secondary endpoints: ORR, OS, DoR, QoL, safety

Phase III ICARIA-MM: Isatuximab/Pom/Dex vs Pom/Dex in R/R MM—Responses and PFS

Isa-Pd group
- 3 prior lines of therapy
- 94% len refractory (60% in last line)
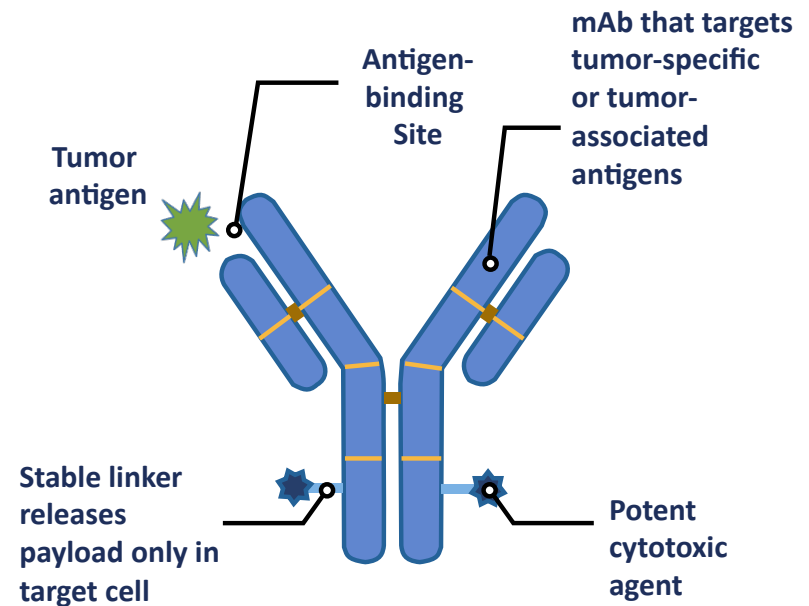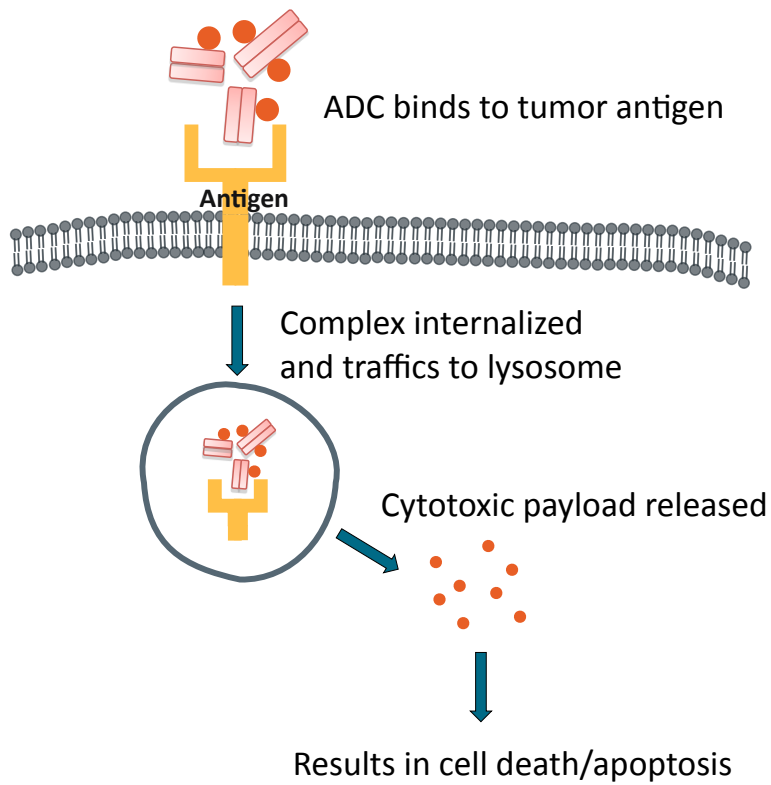- 77% PI refractory
- 72% double refractory

Response	Pd	Isa-Pd
ORR, %	35	60
▪ sCR	<1	0
▪ CR	1	5
▪ VGPR	7	27
▪ PR	27	29
Median DoR, mos	11.1	13.3

- Most frequent TRAEs with IsaPd vs Pd:
IRR (38% vs 0), upper respiratory tract infections (28% vs 17%), and diarrhea (26% vs 20%)
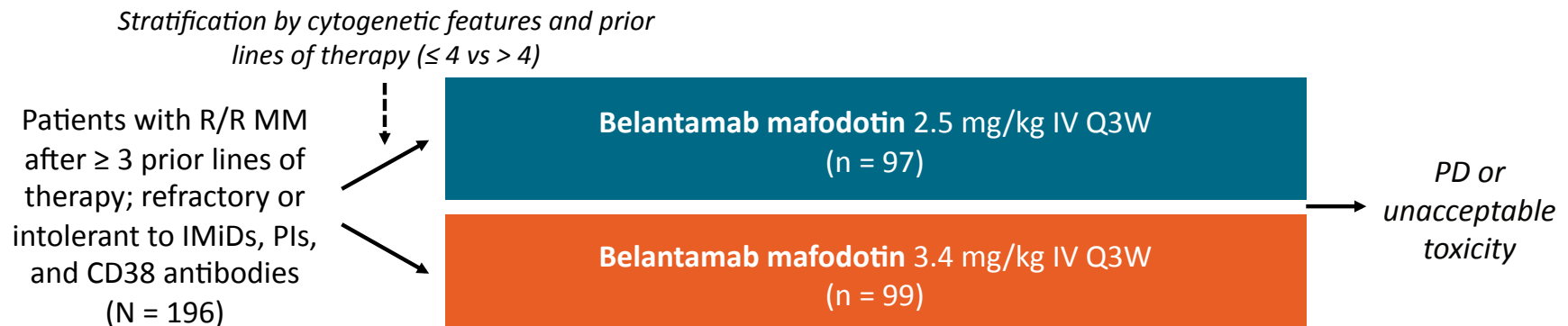
PFS (%) vs Mos

Median PFS: 11.53 mos

Median PFS: 6.47 mos

Isa-Pd (n = 154)

Pd (n = 153)

Median follow-up: 11.6 mos
HR: 0.596 (95% CI: 0.436-0.814; *P* = .001)

Patients at Risk, n

	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Isa-Pd	154		129		106		89		81		52		3-		14		1
Pd	153		105		80		63		51		33		17		5		0
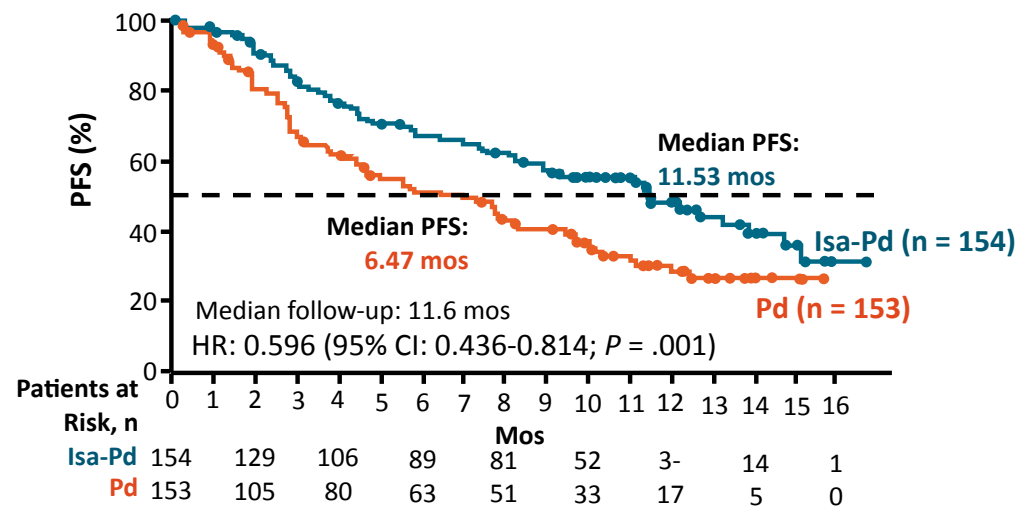
PFS HR (95% CI)
- Len refractory: 0.59 (0.43-0.82)
- Len refractory in last line: 0.50 (0.34-0.76)
- Len / PI refractory: 0.58 (0.40-0.84)

Attal. Lancet. 2019;394:2096.

BCMA-Targeted Antibody–Drug Conjugates

ADC binds to tumor antigen

Antigen

Complex internalized and traffics to lysosome

Cytotoxic payload released

Results in cell death/apoptosis

Tumor antigen

Antigen-binding Site

mAb that targets tumor-specific or tumor-associated antigens

Stable linker releases payload only in target cell

Potent cytotoxic agent

Tai. Blood. 2014;123:3128. Trudel. Lancet Oncol. 2018;19:1641. Trudel. Blood Cancer J. 2019;9:37.

Phase II DREAMM-2: Belantamab Mafodotin in R/R MM

- Open-label, randomized phase II trial

Stratification by cytogenetic features and prior lines of therapy (≤ 4 vs > 4)

Patients with R/R MM after ≥ 3 prior lines of therapy; refractory or intolerant to IMiDs, PIs, and CD38 antibodies (N = 196)

Belantamab mafodotin 2.5 mg/kg IV Q3W (n = 97)

Belantamab mafodotin 3.4 mg/kg IV Q3W (n = 99)

PD or unacceptable toxicity

- Primary Endpoint: ORR

- Key secondary endpoints: DoR, CBR, PFS, OS, TTBR, TTR, safety

DREAMM-2: Efficacy

Efficacy Endpoints	3-6 Prior Lines of Tx (n = 47)	≥ 7 Prior Lines of Tx (n = 50)	All Patients (n = 97)
ORR, % (97.5% CI)	34 (19.3-51.4)	30 (16.5-46.6)	31 (21.7-43.6)
OS, mos (95% CI)	13.7 (9.1-NR)	13.4 (8.7-NR)	13.7 (9.9-NR)
Median DoR, mos (95% CI)	11.0 (4.2-NR)	13.1 (4.0-NR)	11.0 (4.2-NR)
Probability of DoR ≥ 6 mos, % (95% CI)	63 (31-83)	73 (44-89)	68 (48-82)
Median PFS, mos (95% CI)	2.9 (1.5-5.7)	2.2 (1.2-3.6)	2.8 (1.6-3.6)
Probability of PFS at 6 mos, % (95% CI)	35 (20-50)	30 (17-43)	32 (22-42)

Response Rate

Patients With Response (%)

3-6 Prior Lines of Tx (n = 47):
- CR: 4%
- VGPR: 13%
- PR: 17%
- MR: 6%

≥ 7 Prior Lines of Tx (n = 50):
- sCR: 4%
- CR: 6%
- VGPR: 10%
- PR: 10%
- MR: 2%
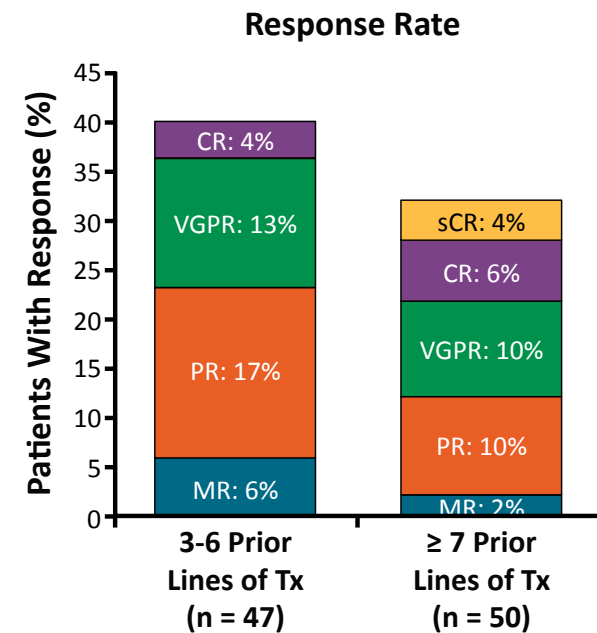
DREAMM-2: Common AEs Associated With Belantamab Mafodotin

AEs in > 10% of Patients, n (%)	3-6 Prior Lines of Therapy (n = 46)		≥ 7 Prior Lines of Therapy (n = 49)		All Patients (n = 95)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Any AE	44 (96)	36 (78)	49 (100)	43 (88)	93 (98)	79 (83)
Ocular AE						
▪ Keratopathy (MECs)	32 (70)	15 (33)	35 (71)	13 (27)	67 (71)	28 (29)
▪ Blurred vision	12 (26)	3 (7)	9 (18)	1 (2)	21 (22)	4 (4)
Hematologic AE						
▪ Thrombocytopenia	11 (24)	8 (17)	12 (24)	10 (20)	23 (24)	18 (19)
▪ Anemia	8 (17)	5 (11)	18 (37)	15 (31)	26 (27)	20 (21)
▪ Lymphocytopenia	6 (13)	5 (11)	7 (14)	7 (14)	13 (14)	12 (13)
▪ AST increased	11 (24)	0 (0)	9 (18)	2 (4)	20 (21)	2 (2)
Nonhematologic AE						
▪ Nausea	14 (30)	0 (0)	10 (20)	0 (0)	24 (25)	0 (0)
▪ Pyrexia	11 (24)	1 (2)	11 (22)	3 (6)	22 (23)	4 (4)

Managing Belantamab Mafodotin Toxicity

Keratopathy

- Conduct ophthalmic exams at baseline, prior to each dose, and promptly if symptoms (dry eye, blurred vision) occur
- Counsel patients to use preservative-free lubricant eye drops and avoid contact lenses unless directed by an ophthalmologist
  - However, prophylactic steroid eye drops DO NOT prevent or reduce risk of keratopathy
- Hold bela maf until improvement; resume or permanently discontinue based on severity

Dose Modifications
(see package insert for detailed instructions)

Starting Dose: 2.5 mg/kg IV every 3 wks
↳ Dose reduction: 1.9 mg/kg IV every 3 wks
Discontinue if unable to tolerate 1.9 mg/kg dosing

Grade	Description	Dose Modifications
1	**Exam findings**: mild superficial keratopathy **Change in BCVA**: decline of 1 line on Snellen Visual Acuity	Continue at current dose
2	**Exam findings**: moderate superficial keratopathy **Change in BCVA**: decline of 2-3 lines on Snellen Visual Acuity, not worse than 20/200	Hold until improvement in exam and BCVA to grade 1, then resume at current dose
3	**Exam findings**: severe superficial keratopathy **Change in BCVA**: decline of > 3 lines on Snellen Visual Acuity, not worse than 20/200	Hold until improvement in exam and BCVA to grade 1, then resume at reduced dose
4	**Exam findings**: corneal epithelial defect **Change in BCVA:** Snellen Visual Acuity worse than 20/200	**Consider permanent discontinuation** If continuing, follow grade 3 recommendations

Belantamab mafodotin is only available through REMS program

Phase III BOSTON Trial: Selinexor + Vd vs Vd in R/R MM

- Open-label, controlled, randomized phase III trial[1]

Patients with progressive measurable MM per IMWG criteria, 1-3 prior therapies, CrCl ≥ 20 mL/min, ECOG PS 0-2 with adequate hepatic and hematopoietic function*
(N = 402)

Selinexor 100 mg QW +
Bortezomib 1.3 mg/m^2 + **Dexamethasone** 20 mg
(n = 194) → PD

Bortezomib 1.3 mg/m^2 + **Dexamethasone** 20 mg
(n = 97) → PD

Crossover allowed
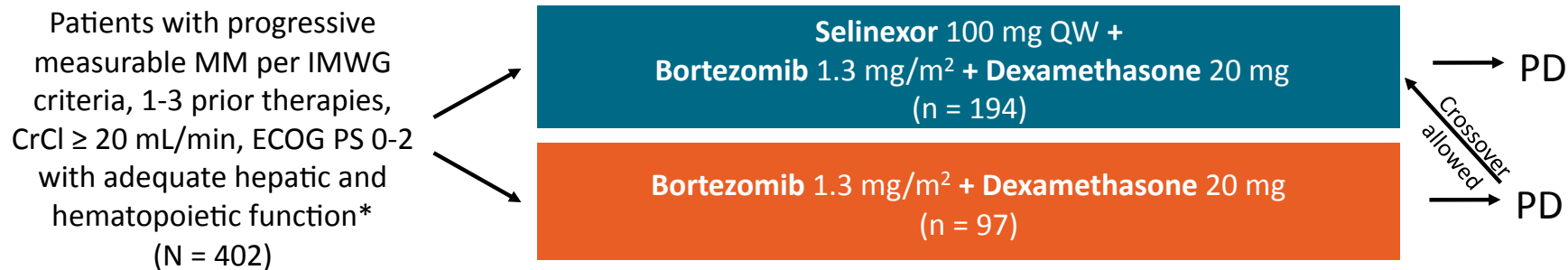
Vd Cycles 1-8: 21-day cycles with bortezomib on Days 1, 4, 8, 11 and dexamethasone on Days 1, 2, 4, 5, 8, 9, 11, 12; **Vd Cycles 9+:** 35-day cycles, bortezomib on Days 1, 8, 15, 22 and dexamethasone on Days 1, 2, 8, 9, 15, 16, 22, 23, 29, 30

- Primary Endpoint: PFS (per IRC)

- Key secondary endpoints: ORR, ≥ VGPR, grade ≥ 2 PN

Defined as ANC > 1000/μL and platelets > 75,000/μL.
†*Prophylactic 5HT-3 recommended in SVd arm.* ‡*Crossover to SVd or Sd permitted if IRC confirmed PD.*

Dimopoulos. ASCO 2020. Abstr 8501.

Phase III BOSTON Trial: PFS (Primary Endpoint) With Selinexor + Vd vs Vd in R/R MM

- Open-label, controlled, randomized phase III trial in R/R MM after 1-3 prior therapies (N = 402)

Median PFS, Mos
- SVd 13.93
- Vd 9.46

HR: 0.70 (P = .0075)

Patients at Risk, n																											
SVd	195	187	175	152	135	117	106	89	79	76	69	64	57	51	45	41	35	27	26	22	19	14	9	7	6	4	2
Vd	207	187	175	152	138	127	111	100	90	81	66	59	56	53	49	42	35	26	20	16	10	8	5	4	3	3	2
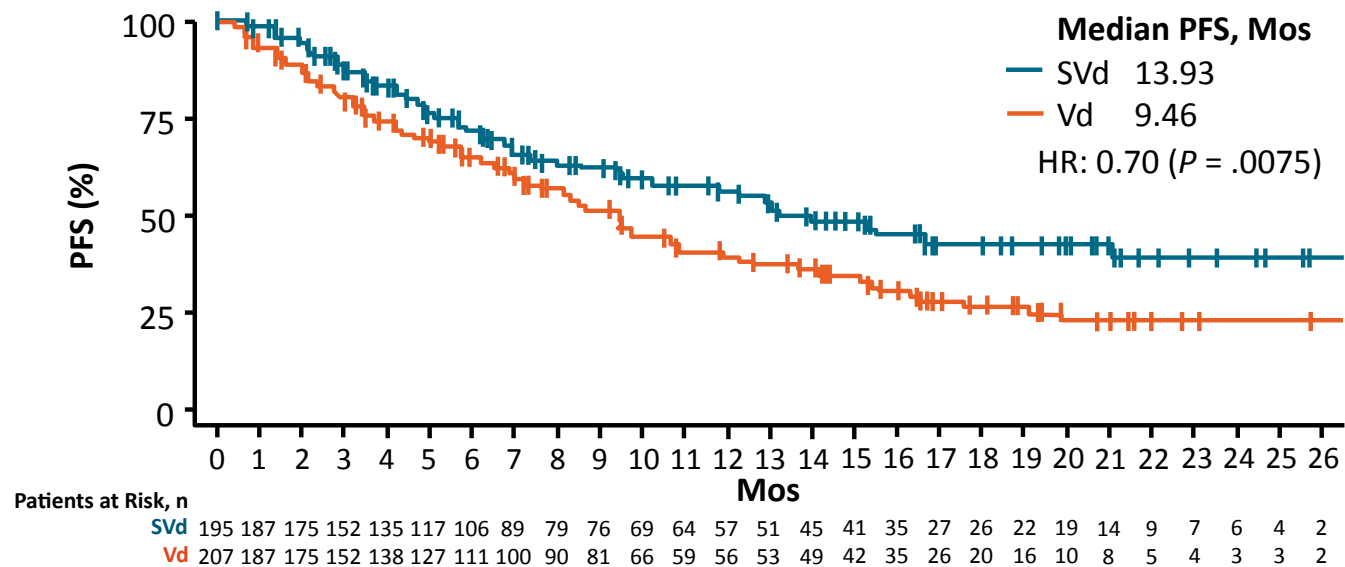
- SVD associated with benefit across subgroups; **in patients with del(17p) HR: 0.38**

- Rate of peripheral neuropathy lower with SVd vs Vd (32.3% vs 47.1%, respectively)

Management of Selinexor Toxicity

AE	Dose Modifications[1]	Preventative Measures
Thrombocytopenia	▪ **PLT 25,000 to < 75,000/μl:** reduce by 1 dose level ▪ **PLT 25,000 to < 75,000/μl with bleeding:** interrupt, then restart at 1 dose level lower after resolution of bleeding, give PLT transfusions as needed ▪ **PLT < 25,000/μl:** interrupt, monitor until PLT ≥ 50,000/μl, then restart at 1 dose level lower	▪ Prophylaxis at start of tx ▪ Romiplostim or eltrombopag given when selinexor held in STORM trial[2]
Nausea/vomiting	▪ **Grade 1/2 (vomiting: ≤ 5 episodes/day):** maintain dose, start additional antinausea medications ▪ **Grade 3 nausea/grade ≥ 3 vomiting (≥ 6 episodes/day):** interrupt, monitoring until resolved to grade ≤ 2 or baseline, start additional antinausea medications, then restart at 1 dose level lower	▪ Prophylaxis with 5-HT3 receptor antagonists at start of tx[1]
Anorexia/weight loss	▪ **Weight loss of 10% to < 20% *or* anorexia with significant weight loss/malnutrition:** interrupt, start supportive care, monitor until weight ≥ 90% of baseline, then restart at 1 dose level lower	▪ Prophylaxis at start of tx ▪ Consult dietitian[3]
Hyponatremia	▪ **Na+ ≤ 130 mmol/L:** interrupt and provide appropriate supportive care, monitor until Na+ > 130 mmol/L, then restart at 1 dose level lower	▪ Prophylaxis at start of tx ▪ Encourage salty foods/snacks, maintain fluid intake[3]
Fatigue	▪ **Grade 2 (lasting > 7 d)/grade 3:** interrupt, monitor until grade 1 or baseline, then restart at 1 dose level lower	▪ Prophylaxis at start of tx ▪ Encourage rest, hydration, exercise[3] ▪ Assess for other modifiable causes[3]
Anemia	▪ **Hg < 8 g/dL:** reduce by 1 dose level, administer blood transfusions as needed ▪ **Life-threatening consequences:** interrupt, monitor until Hg ≥ 8 g/dL, then restart at 1 dose level lower, administer blood transfusions as needed	▪ Prophylaxis at start of tx
Neutropenia	▪ **ANC 0.5 to 1 x 10⁹/L without fever:** reduce by 1 dose level ▪ **ANC < 0.5 x 10⁹/L *or* febrile neutropenia:** interrupt, monitor until ANC ≥ 1 x 10⁹/L, then restart at 1 dose level lower	▪ Prophylaxis at start of tx ▪ Consider antimicrobials and growth factors (eg, G-CSF)[1]

1. Selinexor PI. 2. Chari. ASH 2018. Abstr 598. 3. Mikhael. Clin Lymphoma, Myeloma and Leuk. 2020;20:351.

Phase II HORIZON: Melphalan Flufenamide + Dex in R/R MM Refractory to Pom and/or Anti-CD38 mAb

- Single-arm, open-label phase II trial of melphalan flufenamide

  – Melphalan flufenamide: first-in-class peptide-drug conjugate targeting aminopeptidases; rapidly taken up by MM cells due to high lipophilicity and immediately hydrolyzed by peptidases to release hydrophilic alkylator payload

Patients with MM; measurable disease with documented disease progression; ≥ 2 prior lines of therapy, including and IMiD and a PI and refractory to pom and/or daratumumab; ECOG PS 0-2 (N = 402)

→

Melphalan flufenamide (melflufen) 40 mg D1 + **Dexamethasone** 40 mg* D1, D8, D15, D22 of each 28-day cycle

*Dose reduced for patients ≥ 75 years of age.

- Primary Endpoint: ORR

- Key secondary endpoints: PFS, DoR, OS, Safety, QoL

Primary and Subgroup Analysis of Phase II HORIZON: Melflufen + Dex Activity in Triple-Class–Refractory MM

Population	OS Events, n (%)	Median OS, Mos	Median PFS, Mos	Median DoR, Mos
ITT (N = 157)	88 (56.1)	11.6	4.2	5.5
Triple-class refractory (n = 119)	72 (60.5)	11.2	3.9	4.4
Extramedullary disease (n = 55)	40 (72.7)	6.5	2.9	5.5
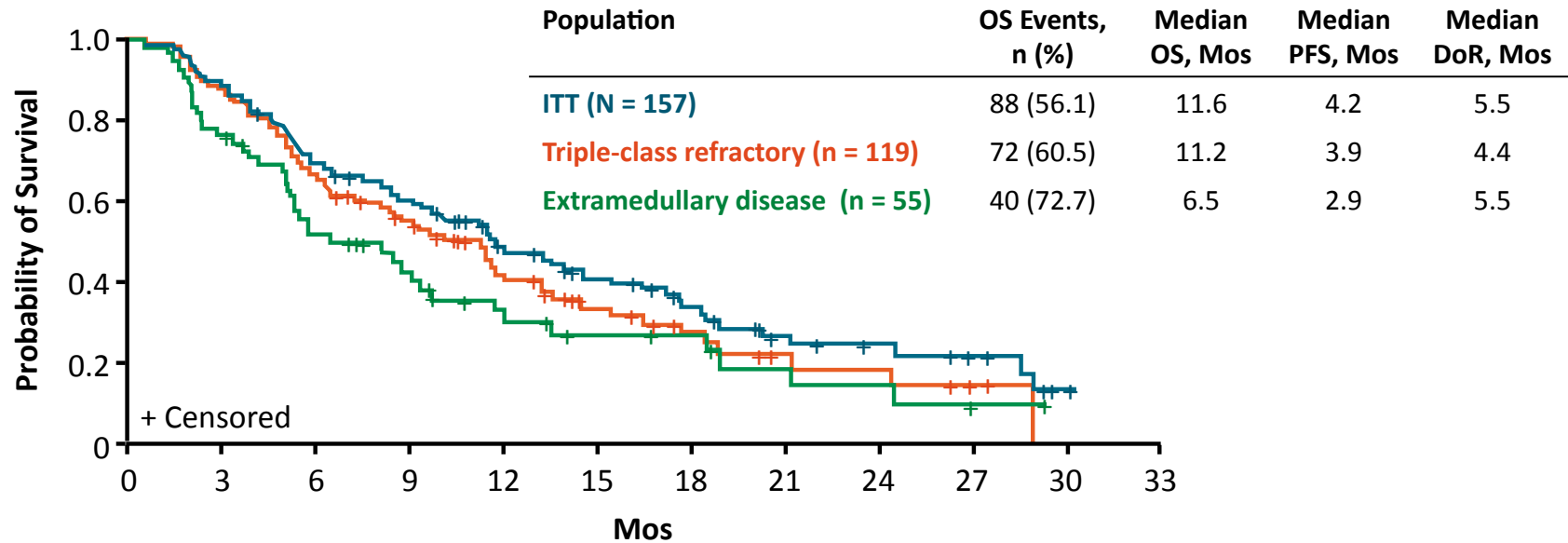
HORIZON: Adverse Events

Hematologic TEAEs in ≥ 10% of Patients, %	ITT Population (N = 157)	
	Grade 3	Grade 4
Neutropenia	32	47
Thrombocytopenia	25	51
Anemia	42	< 1

Serious AE, %	Patients
Overall	49
▪ Pneumonia	9
▪ Febrile neutropenia	5

Emerging Therapies Targeting BCMA in R/R MM: Data on Efficacy and Management of AEs

Bispecific Antibodies vs CAR T-Cell Therapy
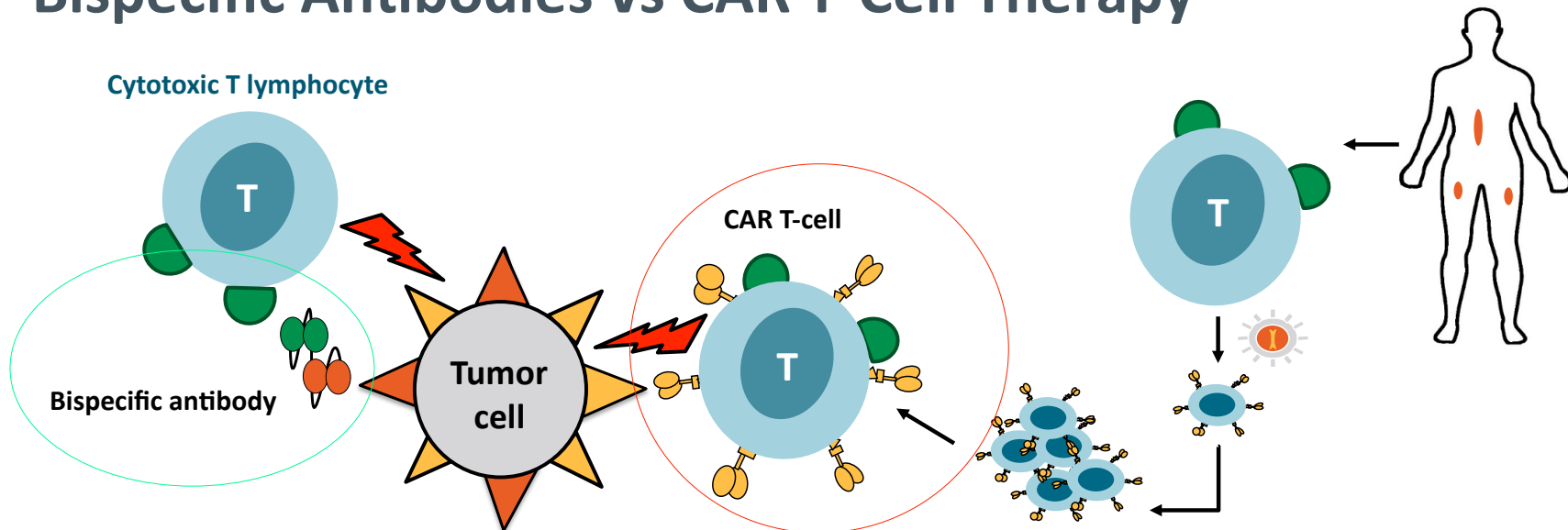
Characteristic	Bispecific Antibodies	CAR T-Cell Therapy
Preparation	"Off the shelf"	In vitro manufacturing (3-4 wks)
Dosing	Repetitive	Single (following lymphodepleting CT)
CRS incidence	Less	Greater

Slaney. Cancer Discov. 2018;8:924. Blinatumomab PI. Tisagenlecleucel PI.

Emerging Data on BMCA-Targeting CAR T-Cell Therapies in R/R MM

Agent	Trial	Prior Tx	N	Efficacy	Safety
Idecabtagene vicleucel	Phase II KarMMa[1]	≥ 3 prior tx; prior IMiD, PI, anti-CD38	158	▪ ORR: 73%; CR: 33% ▪ mTTR: 1.0 mo ▪ PFS: 8.8 mos	▪ CRS: 84% (gr 3: 4%, gr 4: < 1%, gr 5: < 1%) ▪ NT: 18% (gr 3: 3%)
Ciltacabtagene autoleucel (JNJ-4528)	Phase Ib/II CARTITUDE-1[2]	≥ 3 prior tx; prior IMiD, PI, anti-CD38 or double refractory to PI and IMiD	97	▪ ORR: 96.9% ▪ sCR: 67.0%	▪ CRS: 94.8% (gr ≥ 3: 4.1%) ▪ NT: 20.6% (gr ≥ 3: 9.3%)
Orvacabtagene autoleucel	Phase I/II EVOLVE[3]	≥ 3 prior tx; prior autoSCT, IMiD, PI, anti-CD38	62	▪ ORR: 92% ▪ sCR/CR: 36%	▪ CRS: 3% (gr ≥ 3: 3%) ▪ NT: 3% (gr ≥ 3: 3%)
bb21217	Phase I CRB-402[4]	≥ 3 prior tx; prior PI and IMiD or double refractory to PI and IMiD	69	▪ ORR: 43% to 83% ▪ sCR/CR: 14% to 42%	▪ CRS: 70% (gr ≥ 3: 4%) ▪ NT: 16% (gr ≥ 3: 4%)
P-BCMA-101	Phase I/II PRIME [5]	≥ 3 prior therapy lines (including PI + IMiD) or ≥ 2 prior therapy lines in patients refractory to both PI + IMiD	55	▪ ORR: 44% to 75%	▪ CRS: 17.0% (gr ≥ 3: 0%) ▪ NT: 3.8% (gr ≥ 3: 3.8%)
ALLO-715 CAR-T + ALLO-647 anti-CD52 mAb	Phase I UNIVERSAL[6]	≥ 3 prior therapy lines (including PI, IMiD, anti-CD38) and refractory to last tx	31	▪ ORR: 33% to 75%	▪ CRS: 45% (gr ≥ 3: 0%) ▪ NT: 0%

1. Munshi. ASCO 2020. Abstr 8503. 2. Madduri. ASH 2020. Abstr 177. 3. Mailankody. ASCO 2020. Abstr 8504.
4. Alsina. ASH 2020. Abstr 130. 5. Costello. ASH 2020. Abstr 134. 6. Mailankody. ASH 2020. Abstr 129.

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***

ide-cel manufacturing (99% success rate)

Leukapheresis

Bridging (≥14 before lymphodepletion)

CAR T Infusion†

1st Response Assessment (1 mo)

Flu (30 mg/m²) ||||
Cy (300 mg/m²) |||

Days -5,-4,-3   0

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

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.
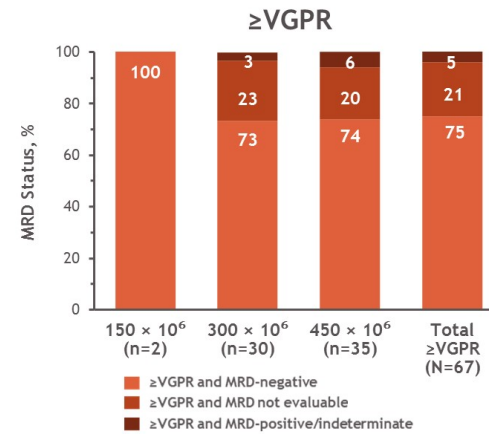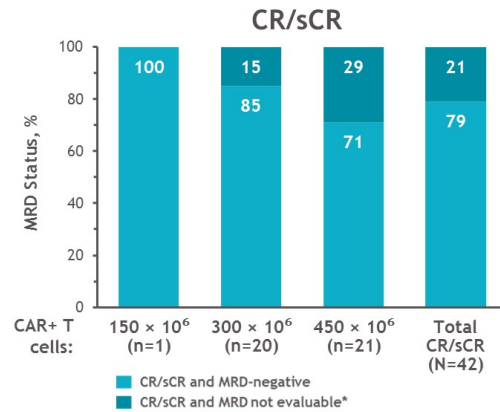
Best Overall Response
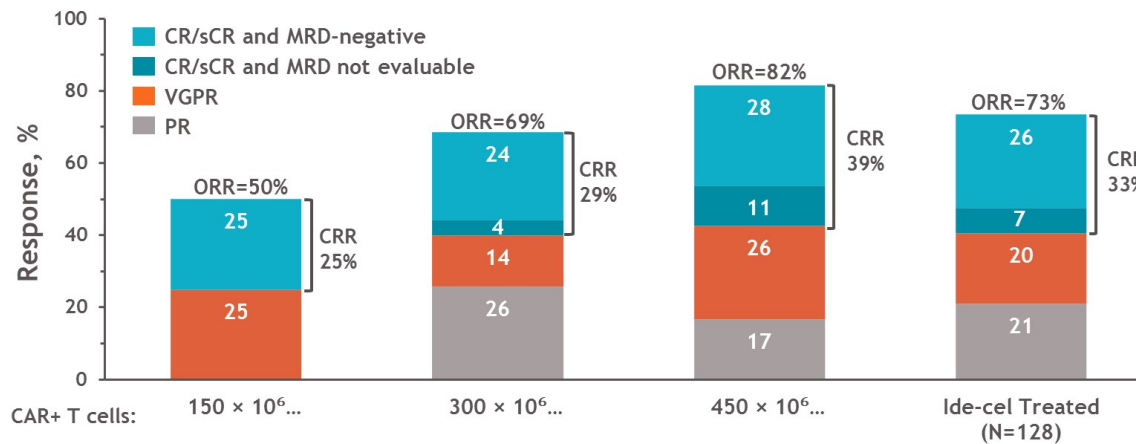
- Primary (ORR >50%) and key secondary (CRR >10%) endpoints met in the ide-cel treated population
  - *ORR of 73% (95% CI, 65.8–81.1; P<0.0001*)*
  - *CRR (CR/sCR) of 33% (95% CI, 24.7–40.9; P<0.0001)*
- Median time to first response of 1.0 mo (range, 0.5–8.8); median time to CR of 2.8 mo (range, 1.0–11.8)
- Median follow-up of 13.3 mo across target dose levels

MRD Negativity

Target Dose, CAR+ T cells	150×10^6	300×10^6	450×10^6	Total
All ide-cel treated	n=4	n=70	n=54	n=128
MRD-negative and ≥CR, n (%) [95% CI]	1 (25) [0.6–80.6]	17 (24) [14.8–36.0]	15 (28) [16.5–41.6]	33 (26) [18.5–34.3]
MRD-negative and ≥VGPR, n (%) [95% CI]	2 (50) [6.8–93.2]	22 (31) [20.9–43.6]	26 (48) [34.4–62.2]	50 (39) [30.6–48.1]

CR/sCR

- CR/sCR and MRD-negative
- CR/sCR and MRD not evaluable*

CAR+ T cells:
- 150×10^6 (n=1)
- 300×10^6 (n=20)
- 450×10^6 (n=21)
- Total CR/sCR (N=42)

≥VGPR

- ≥VGPR and MRD-negative
- ≥VGPR and MRD not evaluable
- ≥VGPR and MRD-positive/indeterminate

- 150×10^6 (n=2)
- 300×10^6 (n=30)
- 450×10^6 (n=35)
- Total ≥VGPR (N=67)

Clinically Meaningful Efficacy (ORR) Observed Across Subgroups

Subgroup		N	ORR, % (95% CI)
Age group, years	<65	83	
	≥65	45	
Sex	Male	76	
	Female	52	
Ide-cel target dose level, CAR+ T cells	150×10^6	4	
	300×10^6	70	
	450×10^6	54	
R-ISS stage at enrollment	I or II	104	
	III	21	
High-risk cytogenetics del(17p), t(4;14), t(14;16)	Yes	45	
	No	66	
Tumor burden at baseline, % BMPCs	≥50%	65	
	<50%	57	
Tumor BCMA expression	≥50%	109	
	<50%	3	
Extramedullary disease	Yes	50	
	No	78	
Triple-refractory*	Yes	108	
	No	20	
Penta-refractory†	Yes	33	
	No	95	
Bridging therapy	Yes	112	
	No	16	

(Forest plot x-axis: 0, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100)

CAR+ T Cell Expansion, Persistence, and Peak Exposure

CAR+ T Cell Expansion and Persistence

Legend:
- Total (n=127)
- 150 × 10^6 cells (n=4)
- 300 × 10^6 cells (n=69)
- 450 × 10^6 cells (n=54)
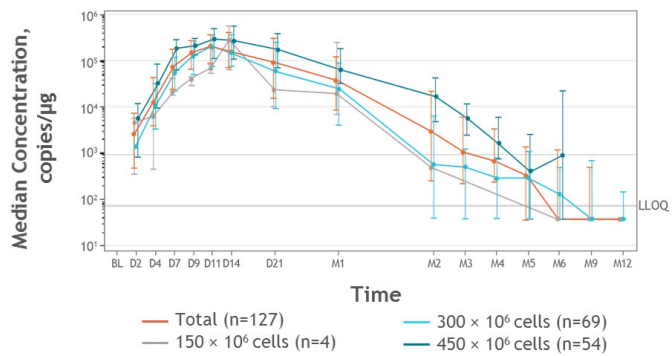
|	Mo 1	Mo 3	Mo 6	Mo 9	Mo 12
Evaluable patients, n	118	100	49	27	11
Patients with detectable vector, n (%)	117 (99)	75 (75)	29 (59)	10 (37)	4 (36)

Peak Vector Copies in Responders (≥PR) vs Nonresponders (<PR)
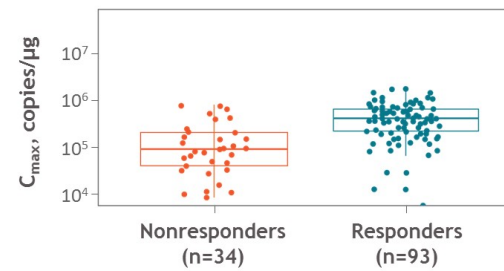
- Median peak CAR+ T cell expansion was at 11 d
- Median expansion increased at higher target doses with overlapping profiles
- Peak exposure higher in responders than nonresponders
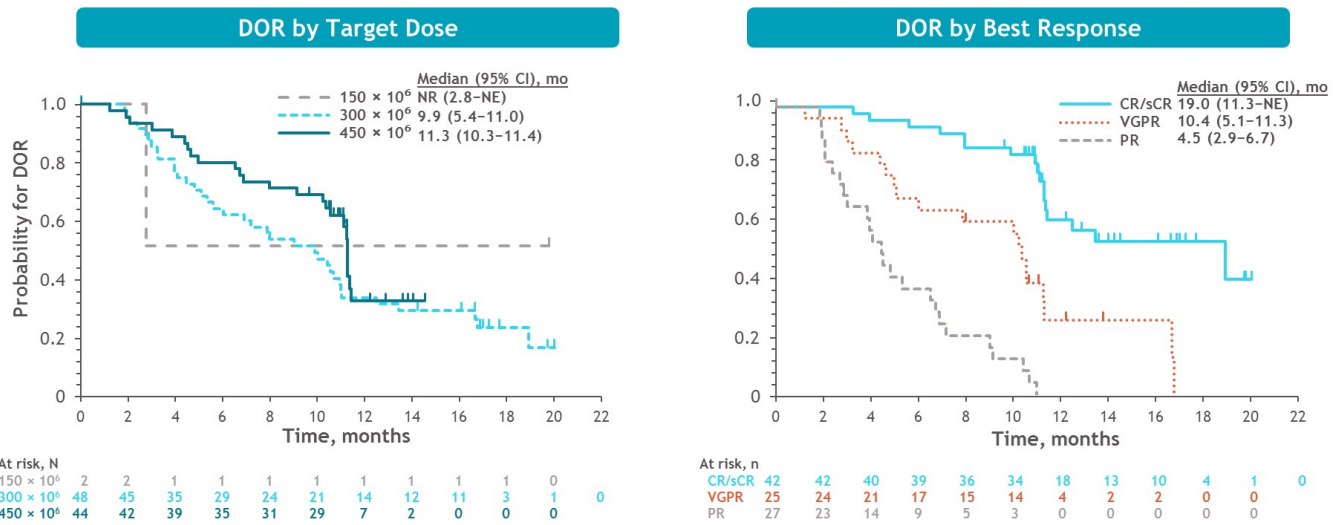- Durable persistence was observed up to 1 y

Data cutoff: 19 April 2019. Pharmacokinetic (PK) analysis population (N=127). One patient died on day 4 and had no evaluable PK samples and was therefore excluded. Error bars represent interquartile range. BL, baseline; C_{max}, maximum concentration; LLOQ, lower limit of quantitation; M, month.

8

Duration of Response

Median (95% CI): 10.7 mo (9.0–11.3)

At risk, N: 94 89 75 65 56 51 22 15 12 4 1 0
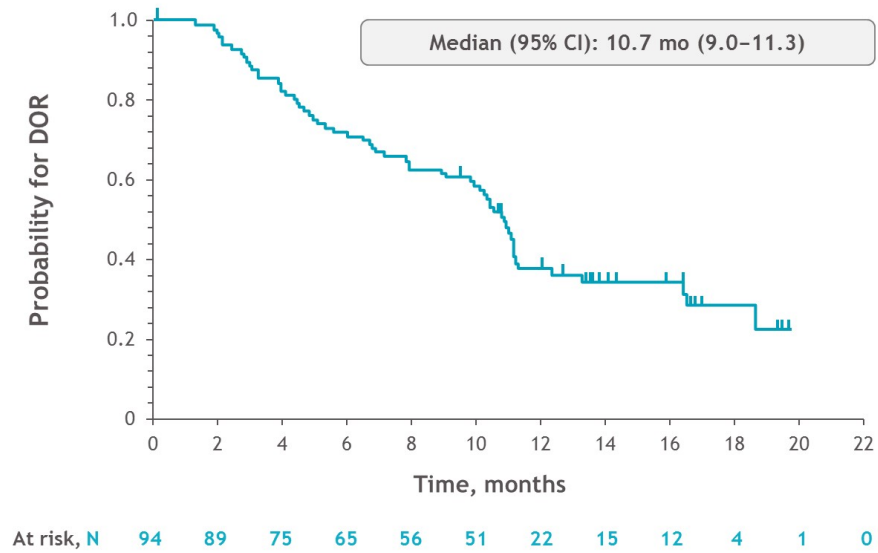
Data cutoff: 14 Jan 2020. DOR is measured from the start of first partial response or better. DOR, duration of response.

Duration of Response By Target Dose and Best Response

KarMMa™

DOR by Target Dose

	Median (95% CI), mo
150 × 10^6	NR (2.8–NE)
300 × 10^6	9.9 (5.4–11.0)
450 × 10^6	11.3 (10.3–11.4)

Probability for DOR vs **Time, months**

At risk, N

	0	2	4	6	8	10	12	14	16	18	20
150 × 10^6	2	2	1	1	1	1	1	1	1	1	0
300 × 10^6	48	45	35	29	24	21	14	12	11	3	1	0
450 × 10^6	44	42	39	35	31	29	7	2	0	0	0

DOR by Best Response

	Median (95% CI), mo
CR/sCR	19.0 (11.3–NE)
VGPR	10.4 (5.1–11.3)
PR	4.5 (2.9–6.7)

Time, months

At risk, n

	0	2	4	6	8	10	12	14	16	18	20
CR/sCR	42	42	40	39	36	34	18	13	10	4	1	0
VGPR	25	24	21	17	15	14	4	2	2	0	0
PR	27	23	14	9	5	3	0	0	0	0	0

- Durable responses were observed across all target doses; median DOR of 11.3 mo at 450 × 10^6 CAR+ T cells
- DOR increased with depth of response; median DOR of 19 mo in patients achieving CR/sCR

Data cutoff: 14 Jan 2020. CR/sCR, complete response/stringent CR; DOR, duration of response; NE, not estimable; NR, not reached; PR, partial response; VGPR, very good PR.
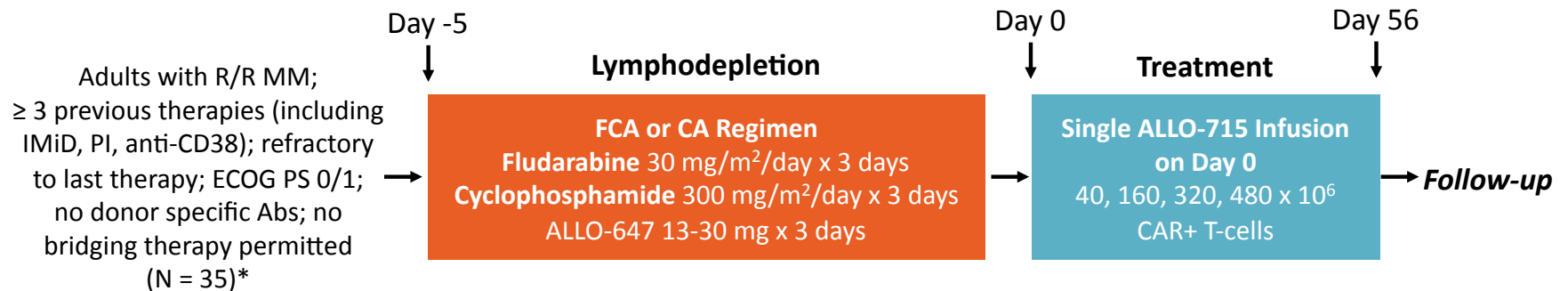
Progression-Free Survival

Median (95% CI): 8.8 mo (5.6–11.6)

At risk, N: 128 102 83 70 64 56 35 19 13 8 4 0
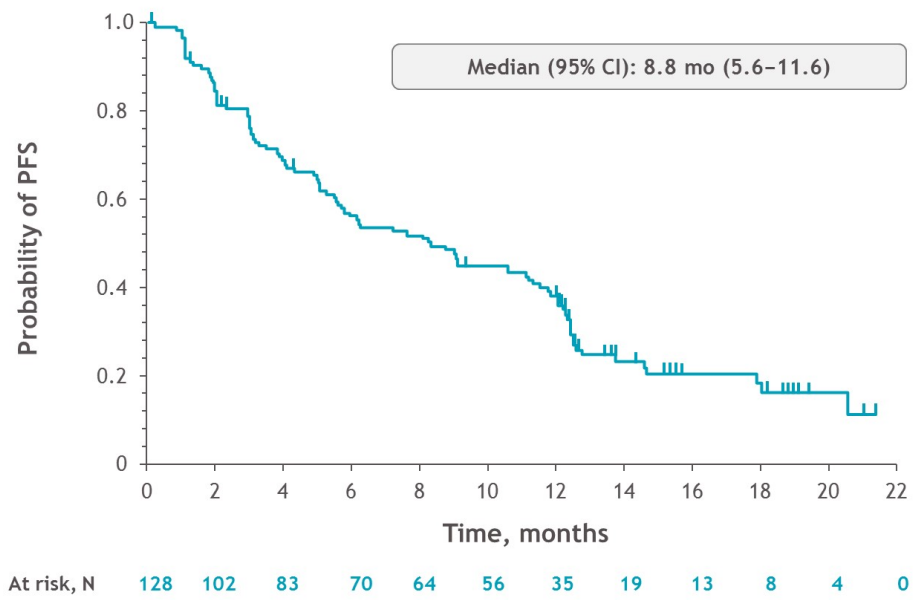
Phase I UNIVERSAL: Allogeneic CAR T-Cell Therapy With ALLO-715 (Anti-BCMA) in R/R MM

- Multicenter, open-label, dose-escalation phase I study

Day -5   Day 0   Day 56

Adults with R/R MM;
≥ 3 previous therapies (including IMiD, PI, anti-CD38); refractory to last therapy; ECOG PS 0/1; no donor specific Abs; no bridging therapy permitted (N = 35)*

Lymphodepletion

FCA or CA Regimen
Fludarabine 30 mg/m^2/day x 3 days
Cyclophosphamide 300 mg/m^2/day x 3 days
ALLO-647 13-30 mg x 3 days

Treatment

Single ALLO-715 Infusion on Day 0
40, 160, 320, 480 x 10^6 CAR+ T-cells

→ *Follow-up*

*4 patients ineligible due to organ failure from PD; 31 patients evaluated in safety analysis; 26 patients reached assessment point and included in efficacy analysis.

- Primary endpoint: safety and tolerability

- Secondary endpoints: lymphodepletion regimen and recommended ALLO-715 phase II dose; anti-tumor activity (ORR, DoR, PFS, MRD); ALLO-715 cellular kinetics; ALLO-647 PK data
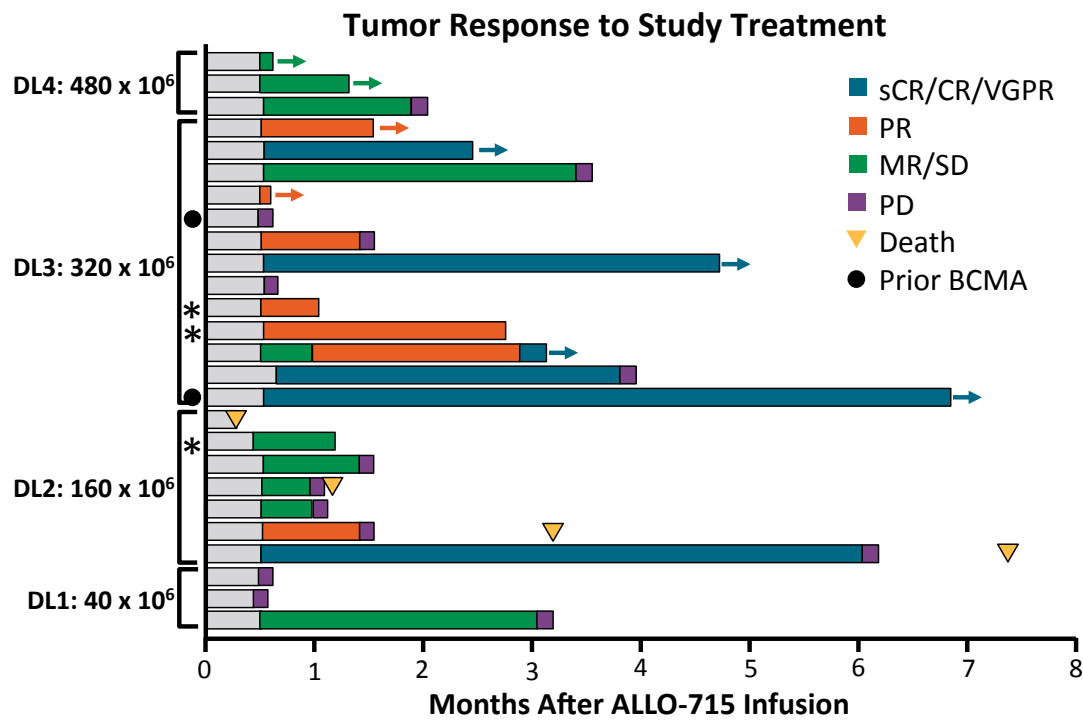
UNIVERSAL: Response Rate

- 60% of patients in FCA plus 320 x 10^6 dose of ALLO-715 cohort responded to treatment; 40% achieved ≥ VGPR[1]

- 5/6 patients assessed with ≥ VGPR had negative MRD status[1]

Cell Dose and LD Regimen	FCA Cohort						CA Cohort	
ALLO-715	40	160	320	320	320	480	160	320
ALLO-647	Low (n = 3)	Low (n = 4)	Low (n = 6)	High (n = 4)	All (n = 10)	Low (n = 3)	Low (n = 3)	Low (n = 3)
ORR, n (%)	--	2 (50)	3 (50)	3 (75)	6 (60)	1 (33)	--	2 (67)
≥ VGPR, n (%)	--	1 (25)	3 (50)	1 (25)	4 (40)	--	--	1 (33)

*Clinical response evaluation based on IMWG response criteria.[2] ≥ VGPR defined as sCR, CR or VGPR.

1. Mailankody. ASH 2020. Abstr 129. 2. Kumar. Lancet Oncol. 2016;17:e328.

UNIVERSAL: Duration of Response

Tumor Response to Study Treatment

- DL4: 480 x 10^6
- DL3: 320 x 10^6
- DL2: 160 x 10^6
- DL1: 40 x 10^6

Legend:
- ■ sCR/CR/VGPR
- ■ PR
- ■ MR/SD
- ■ PD
- ▼ Death
- ● Prior BCMA

X-axis: **Months After ALLO-715 Infusion** (0 to 8)

*Discontinued follow-up on study before disease progression occurred.

Mailankody. ASH 2020. Abstr 129. Reproduced with permission.

- Median TTR: 16 days

- Response rates appear dose dependent

- 6 of 9 patients treated with 320 x 10^6 or 480 x 10^6 cell dosing who responded remain in response

Bispecific Antibodies and T-Cell Engager Antibody Constructs in Clinical Evaluation
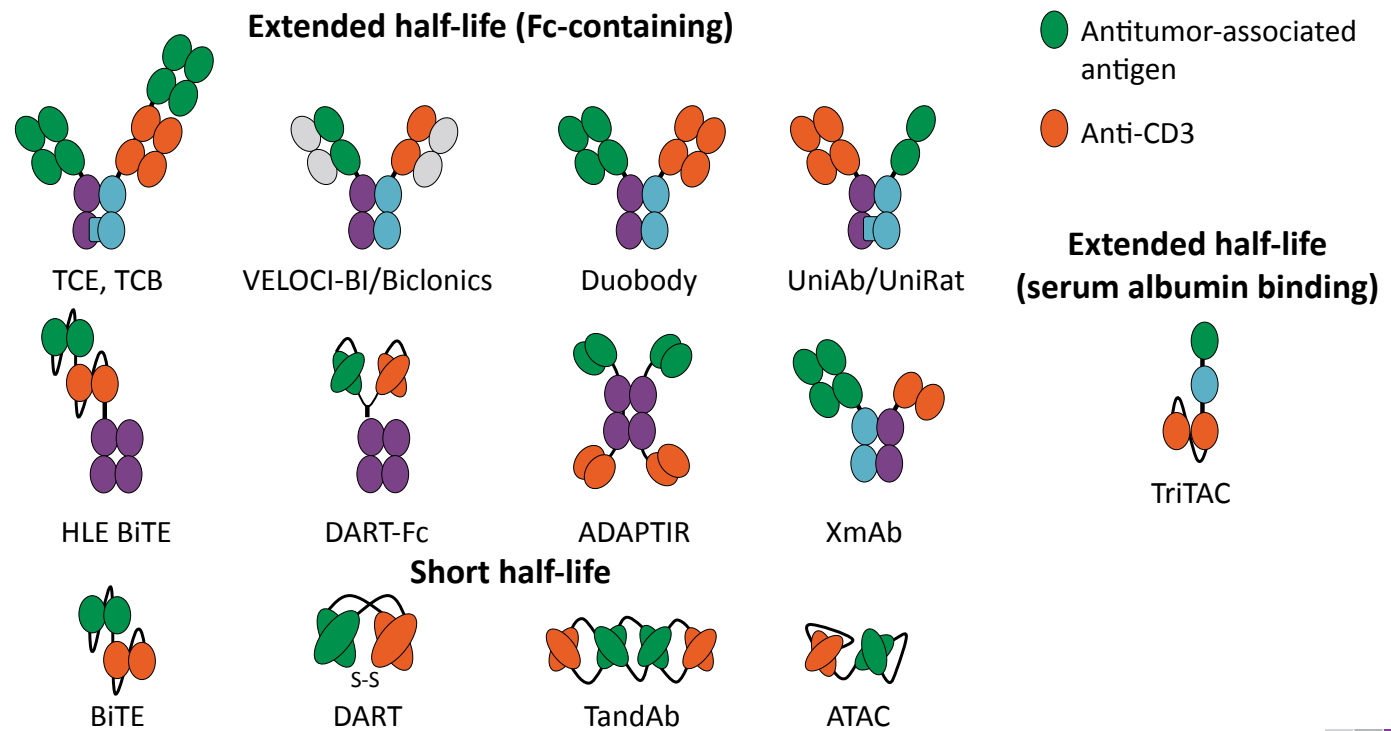
Kontermann. Drug Discov Today. 2015;20:838. Ellergman. Methods. 2019;154:102.
Strohl. Antibodies (Basel). 2019;8:41. Suurs. Pharmacol Ther. 2019;201:103. Costa. ASH 2019. Abstr 143.

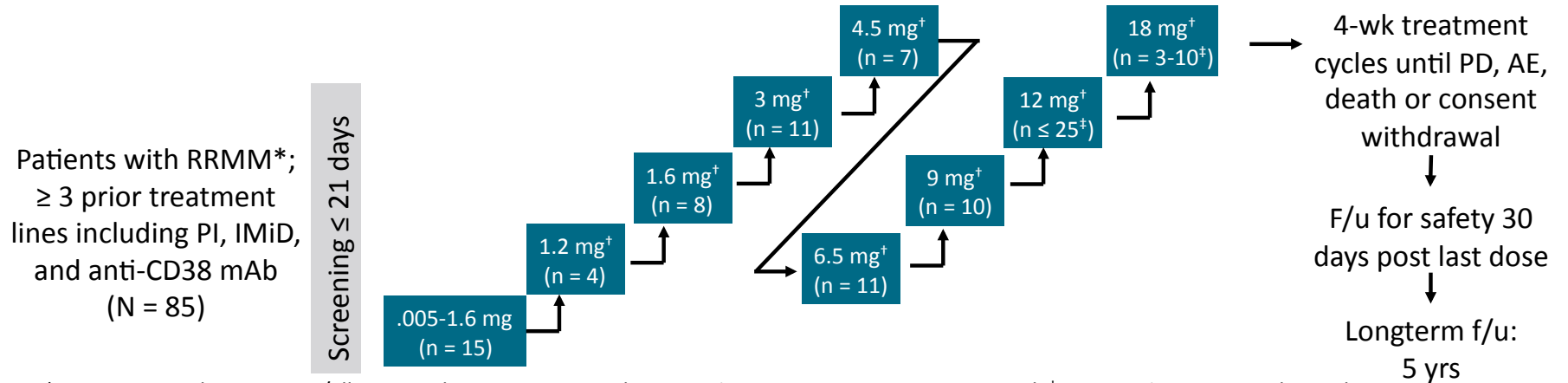# Emerging Data on BMCA-Targeting Bispecific T-Cell Engagers in R/R MM

Agent	Trial	Prior Tx	N	Efficacy	Safety
CC-93269 (CD3ε x BCMA)	Phase I (NCT03486067)[1]	≥ 3 prior tx; no prior anti-BCMA	30	▪ ORR: 43.3%; sCR/CR: 16.7% ▪ mTTR: 4.1 wks	▪ CRS: 76.7% (gr ≥ 3: 3.3%) ▪ No encephalopathy
Teclistamab	Phase I (NCT03145181)[2]	Refractory to std therapies	149	▪ At RP2D, ORR: 73%; ≥ VGPR: 55%	▪ CRS: 55% (no gr ≥ 3) ▪ NT: 5% (gr ≥ 3: 1%)
Pavurutamab (AMG 701)	Phase I (NCT03287908)[3]	≥ 3 prior treatment lines including PI, IMiD, and anti-CD38 mAb	85	▪ ORR: 26%; ≥ VGPR: 17%	▪ CRS: 65% (gr 3: 9%)
REGN5458	Phase I (NCT03761108)[4]	≥ 3 lines of prior therapy (including IMiD, PI, anti-CD38) or double-refractory to an IMiD/PI combo and to an anti-CD38 Ab	49	▪ ORR: 29.2% to 62.5%	▪ CRS: 39% (no gr ≥ 3) ▪ NT: 12% (no gr ≥ 3)

1. Cortes. ASH 2019. Abstr 143. 2. Garfall. ASH 2020. Abstr 180. 3. Harrison. ASH 2020. Abstr 181. 4. Madduri. ASH 2020. Abstr 291.

First-in-Human Study of Pavurutamab (AMG 701): Anti-BCMA Bispecific Antibody in Patients with R/R MM

- Ongoing phase I dose-escalation study with pavurutamab (weekly IV infusions); premedication with dexamethasone 8 mg (or equivalent) given in first 2 cycles
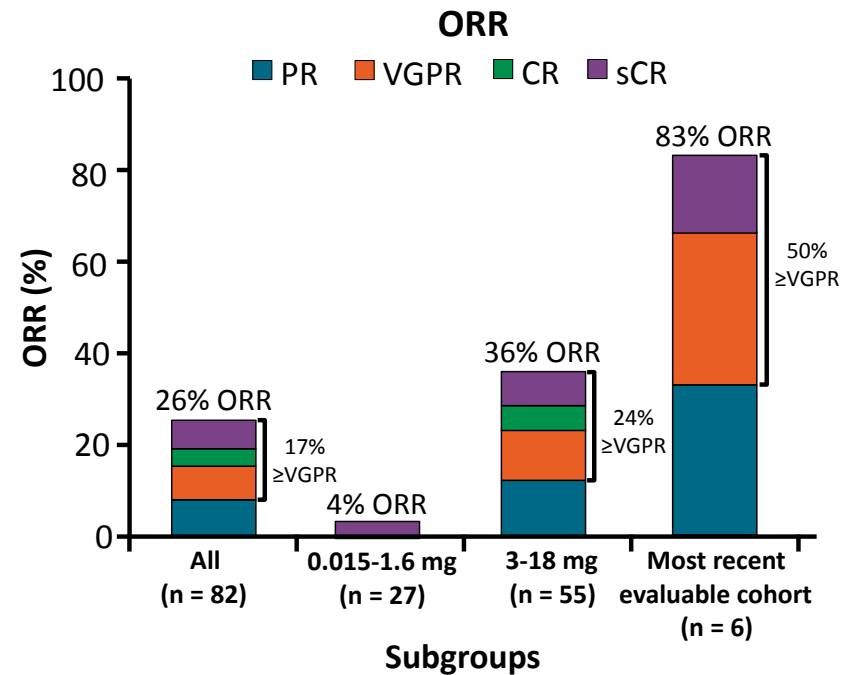
Patients with RRMM*;
≥ 3 prior treatment lines including PI, IMiD, and anti-CD38 mAb
(N = 85)

Screening ≤ 21 days

.005-1.6 mg (n = 15)

1.2 mg† (n = 4)

1.6 mg† (n = 8)

3 mg† (n = 11)

4.5 mg† (n = 7)

6.5 mg† (n = 11)

9 mg† (n = 10)

12 mg† (n ≤ 25‡)

18 mg† (n = 3-10‡)

4-wk treatment cycles until PD, AE, death or consent withdrawal

F/u for safety 30 days post last dose

Longterm f/u: 5 yrs

*Nonsecretory disease, auto/allo SCT within 3 to 6 mos, and prior anti-BCMA treatment not permitted. †Some patients received step dosing. ‡Planned enrollment.
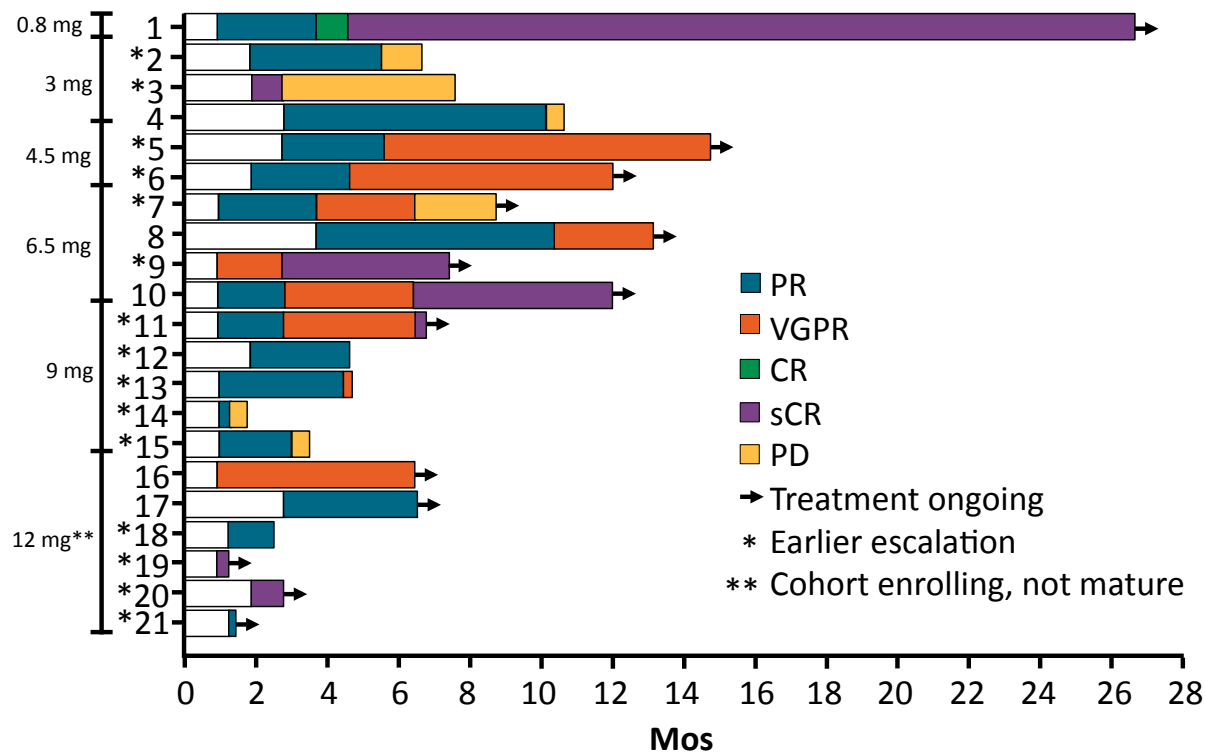
- **Primary objectives: safety/tolerability, estimate active dose**

- **Secondary objectives: PK, ORR**

Pavurutamab Phase I: ORR

- Responses to date in 82 evaluable patients include 5 sCR, 3 CR, 6 VGPR, 7 PR

- ORR: 83% in most recent evaluable cohort (5/6 responses)
  - 4 of 5 patients triple refractory

- 6 of 7 patients (86%) with ≥ VGPR tested for MRD were negative by NGS ($\leq 10^{-5}$ per IMGW) or flow cytometry ($\leq 3 \times 10^{-5}$)
  - All 6 patients have ongoing responses; 22-month MRD-negative response in 1 patient

ORR

Legend: ■ PR ■ VGPR ■ CR ■ sCR

Chart — ORR (%) by Subgroups:
- All (n = 82): 26% ORR, 17% ≥VGPR
- 0.015-1.6 mg (n = 27): 4% ORR
- 3-18 mg (n = 55): 36% ORR, 24% ≥VGPR
- Most recent evaluable cohort (n = 6): 83% ORR, 50% ≥VGPR

X-axis: Subgroups
Y-axis: ORR (%)

Pavurutamab Phase I: DOR

- Median treatment duration: 7.6 weeks (quartile 1, 3: 4.1, 15.1)

- Median follow-up for responding patients: 6.5 months (range: 1-27)

  - Median DoR: not reached

  - Responses ongoing in 17/21 patients at last assessment

- Interim median response: 5.6 months (quartile 1, 3: 2.1, 7.8)

  - Mean response: 6 months

  - Max DoR: 26 months

Legend:
- PR
- VGPR
- CR
- sCR
- PD
- ➜ Treatment ongoing
- * Earlier escalation
- ** Cohort enrolling, not mature

REGN5458 in R/R MM: Study Design

- Open-label phase I study with step-up dosing followed by QW, then Q2W infusions

Step-up Dosing Schema	Wk1 Dosing, Split: W1D1, W1D2	Wk2 Dosing, Split: W2D1, W2D2	Wk3-15 Dosing, Single: QW infusions	Wk16+ Dosing, Single: Q2W infusions

Patients with R/R MM and ≥ 3 lines of prior therapy including an IMiD, a PI, and an anti-CD38 Ab; or double-refractory to an IMiD/PI combo and to an anti-CD38 Ab; non-secretory MM allowed (N = 49) →

Part 1: REGN5458 IV Dose Escalation*					
DL1: 3 mg (n = 4)	DL2: 6 mg (n = 10)	DL3: 12 mg (n = 10)	DL4: 24 mg (n = 10)	DL5: 48 mg (n = 7)	DL6: 96 mg (n = 8)

RP2D → Part 2: Dose Expansion

*4 + 3 design.

- Primary objectives: safety, tolerability, DLTs, RP2D

- Secondary objectives: ORR, DoR, PFS, MRD status, OS

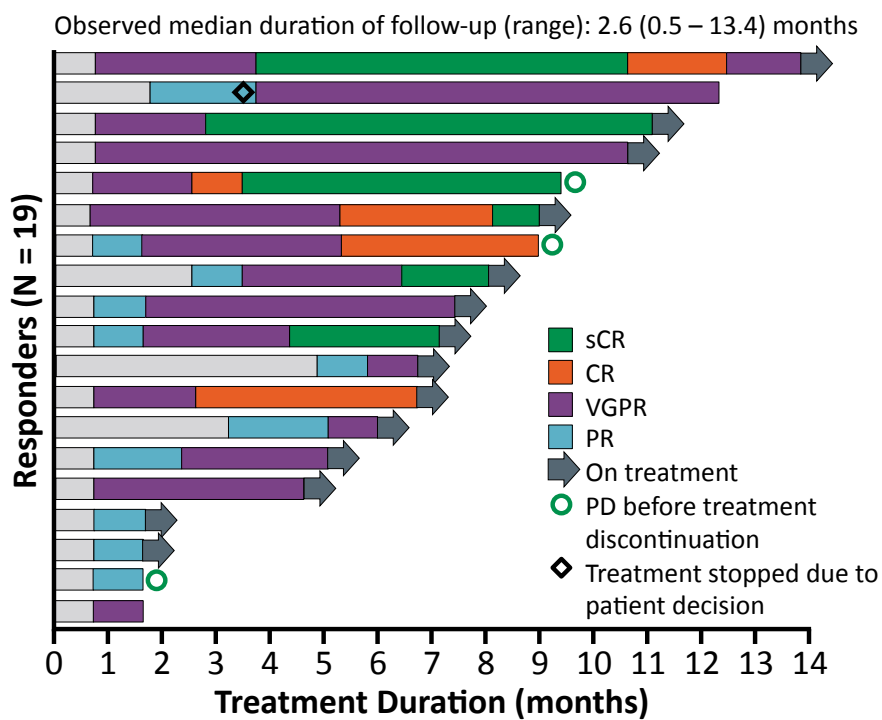# REGN5458 in R/R MM: Response (ITT Analysis)
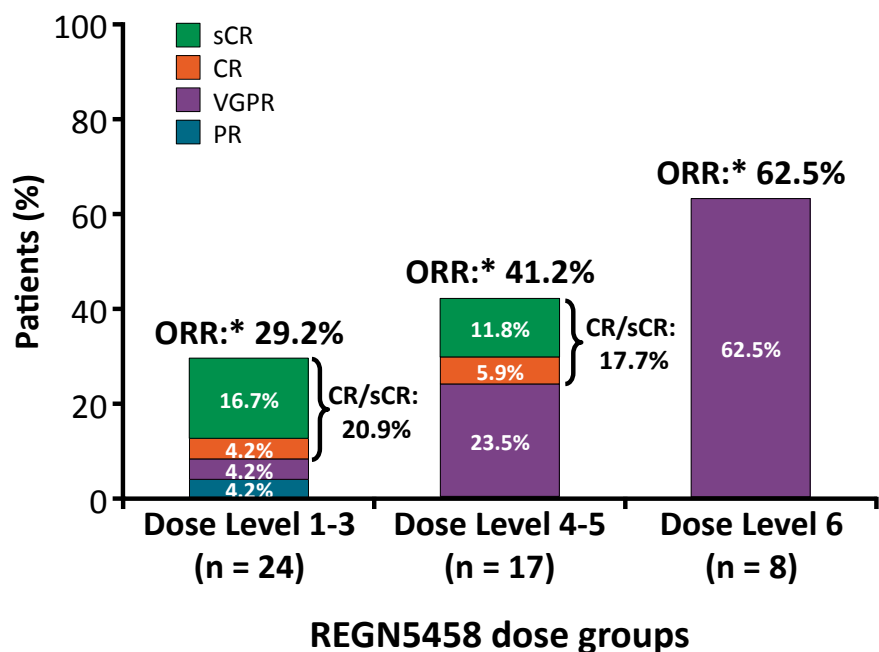
Median duration of follow-up: 2.6 mos (range: 0.5-13.4).
*Includes patients with opportunity for response assessment at 4 wks.

- Responders
  - 95% (18/19) with VGPR or better
  - 42% (8/19) with CR or sCR

- Among patients with CR or sCR and MRD testing, 57% (4/7) were MRD negative (at 10^{-5})

- IHC-assessed core biopsy showed no effect of BCMA expression level on response
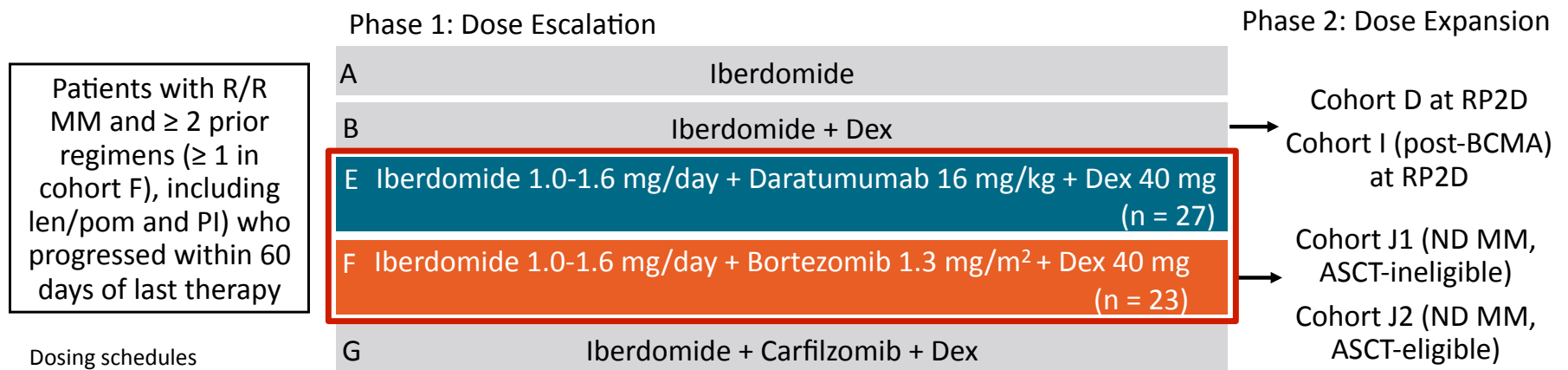
REGN5458 in R/R MM: DoR

Observed median duration of follow-up (range): 2.6 (0.5 – 13.4) months

Legend:
- sCR
- CR
- VGPR
- PR
- On treatment
- ○ PD before treatment discontinuation
- ◇ Treatment stopped due to patient decision

Y-axis: Responders (N = 19)
X-axis: Treatment Duration (months)

- **Median DoR: 6.0 mos (range: 1.0-13.1)**
  - Responses typical by Wk 4, deepened over time

- **Responders**
  - 37% with response ≥ 8 mos (data currently maturing)
  - 74% receiving ongoing REGN5458 therapy

Other Novel Agents and New Targets

Iberdomide Plus Dd or Vd in R/R MM: Phase I/II Study Design

- Open-label, dose-escalation/dose-expansion trial

Patients with R/R MM and ≥ 2 prior regimens (≥ 1 in cohort F), including len/pom and PI) who progressed within 60 days of last therapy

Phase 1: Dose Escalation

A	Iberdomide
B	Iberdomide + Dex
E	Iberdomide 1.0-1.6 mg/day + Daratumumab 16 mg/kg + Dex 40 mg (n = 27)
F	Iberdomide 1.0-1.6 mg/day + Bortezomib 1.3 mg/m² + Dex 40 mg (n = 23)
G	Iberdomide + Carfilzomib + Dex

Phase 2: Dose Expansion

Cohort D at RP2D
Cohort I (post-BCMA) at RP2D

Cohort J1 (ND MM, ASCT-ineligible)
Cohort J2 (ND MM, ASCT-eligible)

Dosing schedules
Cohort E (28-day cycles)
Iberdomide D1-21
Dexamethasone D1,8,15,22
Daratumumab C1-2: D1,8,15,22; C3-6: D1,15; C7+: D1
Cohort F (21-day cycles)
Iberdomide D1-14
Dexamethasone D1,8,15
Bortezomib C1-8: D1,4,8,11; C9+: D1,8

- Primary endpoints: identify MTD and RP2D, efficacy

- Secondary endpoint: safety

- RP2D of 1.6 mg/day determined for iberdomide with dex; cohorts E, F continuing enrollment with 1.6-mg/day dose

Van De Donk. ASH 2020. Abstr 724.

Iberdomide Plus Dd or Vd in R/R MM: Safety

Treatment-Emergent AE, n (%)	Iber + Dd (n = 27)		
	All Gr	Gr 3	Gr 4
Hematologic			
▪ Neutropenia	19 (70.4)	4 (14.8)	14 (51.9)
• Febrile neutropenia	1 (3.7)	0	1 (3.7)
▪ Thrombocytopenia	11 (40.7)	3 (11.1)	1 (3.7)
▪ Anemia	10 (37.0)	7 (25.9)	1 (3.7)
Nonhematologic			
▪ Fatigue	9 (33.3)	0	0
▪ Diarrhea	6 (22.2)	1 (3.7)	0
▪ Constipation	6 (22.2)	0	0
▪ Rash	3 (11.1)	0	0
▪ Peripheral neuropathy	2 (7.4)	0	0
▪ Infusion-related reactions	1 (3.7)	0	0
Infections	21 (77.8)	3 (11.1)	2 (7.4)
▪ Upper respiratory tract	10 (37.0)	0	0

Treatment-Emergent AE, n (%)	Iber + Vd (n = 23)		
	All Gr	Gr 3	Gr 4
Hematologic			
▪ Neutropenia	8 (34.8)	5 (21.7)	1 (4.3)
• Febrile neutropenia	0	0	0
▪ Thrombocytopenia	8 (34.8)	1 (4.3)	5 (21.7)
▪ Anemia	5 (21.7)	3 (13.0)	0
Nonhematologic			
▪ Peripheral neuropathy	7 (30.4)	0	0
▪ Diarrhea	7 (30.4)	1 (4.3)	0
▪ Decreased appetite	7 (30.4)	0	0
▪ Fatigue	6 (26.1)	0	0
▪ Rash	6 (26.1)	1 (4.3)	0
▪ Myalgia	5 (21.7)	0	0
▪ Insomnia	5 (21.7)	0	0
▪ Pruritus	5 (21.7)	0	0
▪ Constipation	5 (21.7)	0	0
Infections	14 (60.9)	13.0	0
▪ Upper respiratory tract	7 (30.4)	8.7	0

- ▪ No incidence of thrombotic events (including pulmonary embolism or deep vein thrombosis) reported in either cohort

Iberdomide Plus Dd or Vd in R/R MM: Efficacy

Best Response, n (%)	Iber + Dd (n = 27)	Iber + Vd (n = 23)
ORR	11 (42.3)	14 (60.9)
▪ sCR	1 (3.8)	0
▪ CR	2 (7.7)	1 (4.3)
▪ VGPR	2 (7.7)	5 (21.7)
▪ PR	6 (23.1)	8 (34.8)
MR	2 (7.7)	2 (8.7)
SD	10 (38.5)	4 (17.4)
PD	3 (11.5)	2 (8.7)
NE	0	1 (4.3)
CBR (MR or better)	13 (50)	16 (69.6)
DCR (SD or better)	23 (88.5)	20 (87.0)
Median time to response, wks (range)	4.1 (4.0-12.0)	3.6 (3.0-13.1)

- High response rates in heavily exposed and highly refractory patient population

  - Among 27 patients in daratumumab cohort, 26 were IMiD refractory, 15 daratumumab refractory, 13 triple-class refractory; 4 patient refractory to daratumumab achieved PR

  - Among 23 patients in bortezomib cohort, 18 were IMiD refractory, 15 PI refractory, 9 bortezomib refractory, 9 triple class refractory; durable responses achieved in patients refractory or with prior exposure to bortezomib

- Addition of daratumumab or bortezomib to iberdomide + dexamethasone shows minimal effect on pharmacodynamics
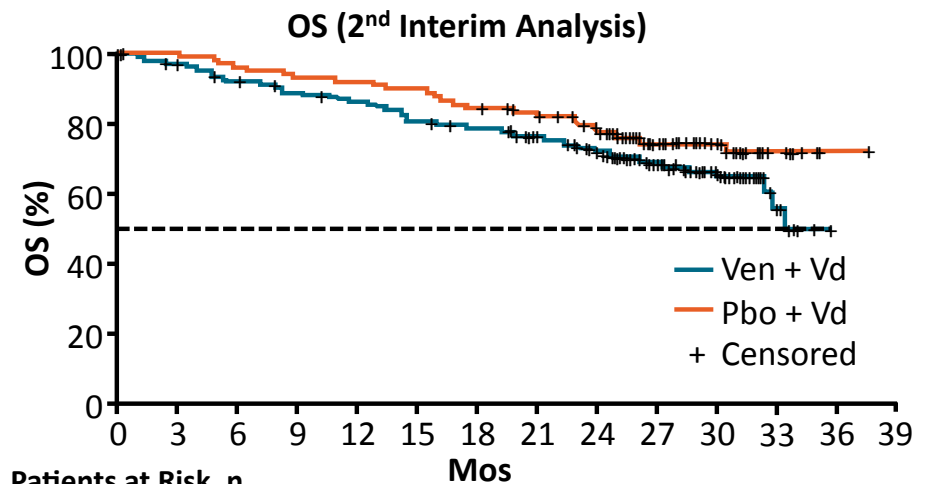
Phase III BELLINI in RRMM After 1-3 Prior Lines: PFS and OS in Unselected Patients (ITT Patient Population)

Investigator-Assessed PFS

OS (2nd Interim Analysis)
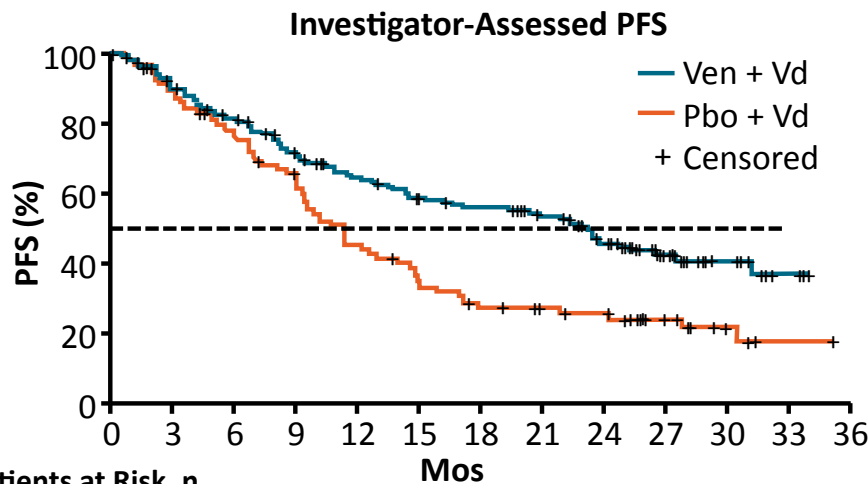
Patients at Risk, n

Ven + Vd	194	163	140	118	101	89	84	79	64	44	21	6	0
Pbo + Vd	97	83	69	57	39	30	22	20	18	12	6	1	0

Patients at Risk, n

194	186	174	165	159	150	144	140	125	95	47	10	0
97	95	91	88	87	85	80	79	70	53	25	7	1	0

Endpoint	Ven + Vd	Placebo + Vd
Median PFS, mos	23.2	11.4
HR	0.60 (95% CI: 0.43-0.82; *P* = .0013)	

Endpoint	Ven + Vd	Placebo + Vd
Median OS, mos	33.5	NR
HR	1.460 (95% CI: 0.912-2.337; *P* = .112)	

Kumar. ASCO 2020. Abstr 8509.

BELLINI: PFS With Venetoclax + Vd vs Placebo + Vd by t (11;14) and *BCL2* Status in MM

t(11;14) or *BCL2*high*
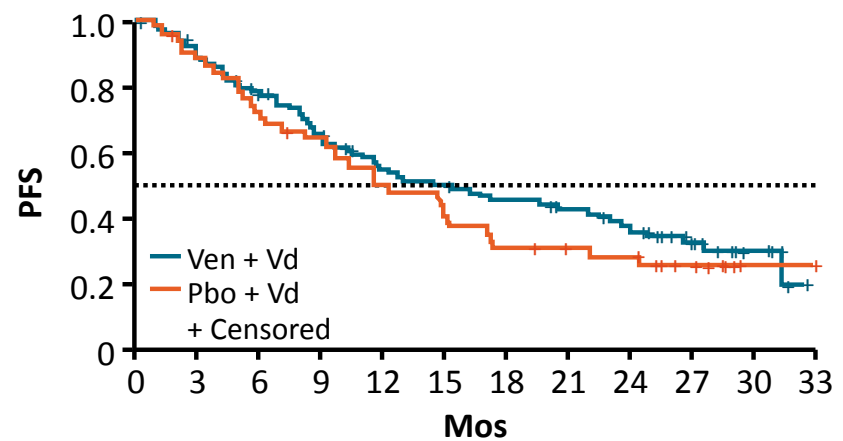
Median PFS, Mos	Ven + Vd	Pbo + Vd	HR (95% CI)
Interim analysis*	NR	9.9	0.30 (0.17-0.53); *P* < .001
Updated analysis†	NR	9.9	0.31 (0.18-0.53)

Data cutoff: *July 15, 2019; †September 13, 2019.

Non-t(11;14) or *BCL2*low*

Median PFS, Mos	Ven + Vd	Pbo + Vd	HR (95% CI)
Interim analysis*	15.3	11.5	0.85 (0.56-1.30); *P* = .451
Updated analysis†	15.3	11.5	0.84 (0.55-1.28)

Kumar. ASCO 2020. Abstr 8509. Harrison. ASH 2019. Abstr 142.

BELLINI: OS With Venetoclax + Vd vs Placebo + Vd by t (11;14) and *BCL2* Status in MM

t(11;14) or *BCL2*high*
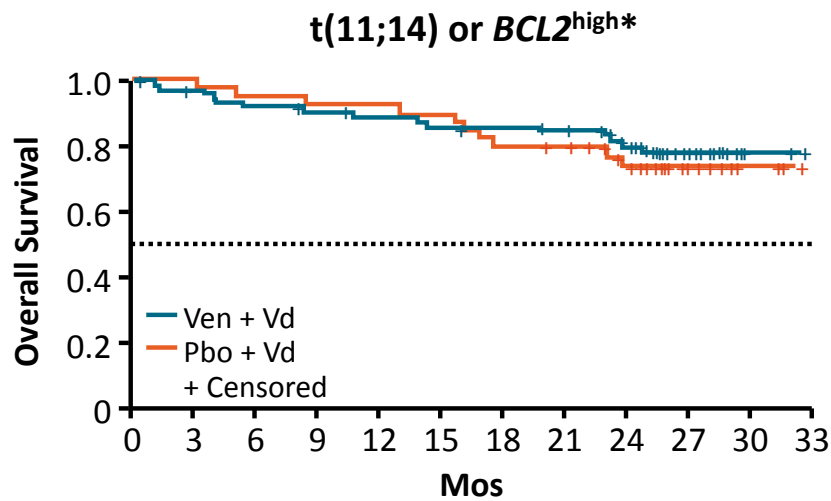
Median OS, Mos	Ven + Vd	Pbo + Vd	HR (95% CI)
Interim analysis*	NR	NR	0.92 (0.41-2.08) *P* = .843
Updated analysis†	NR	NR	0.97 (0.43-2.17)

Non-t(11;14) or *BCL2*low*
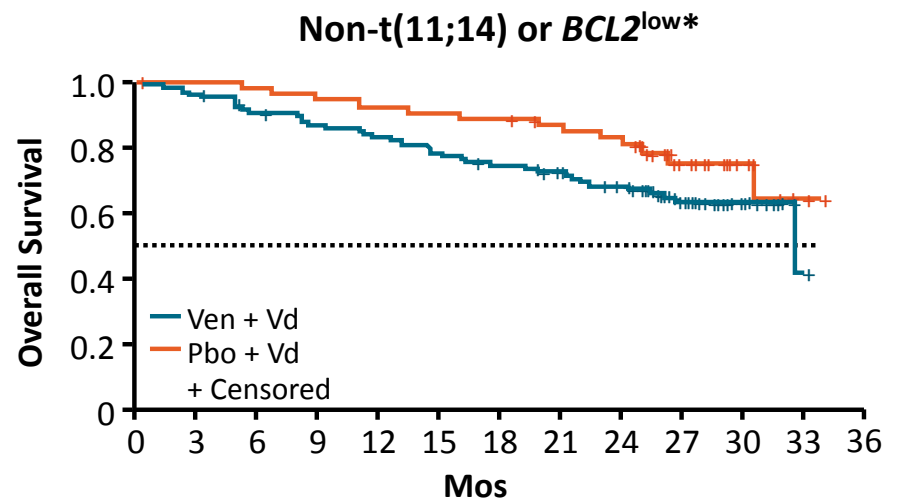
Median OS, Mos	Ven + Vd	Pbo + Vd	HR (95% CI)
Interim analysis*	32.4	NR	1.52 (0.81-2.88) *P* = .194
Updated analysis†	32.8	NR	1.74 (0.93-3.25)

Data cutoff: *July 15, 2019; †September 13, 2019.

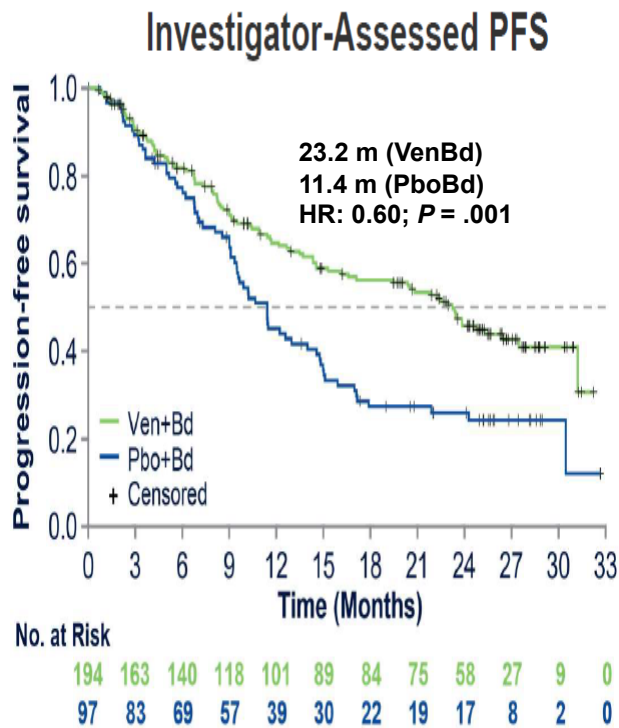Kumar. ASCO 2020. Abstr 8509. Harrison. ASH 2019. Abstr 142.
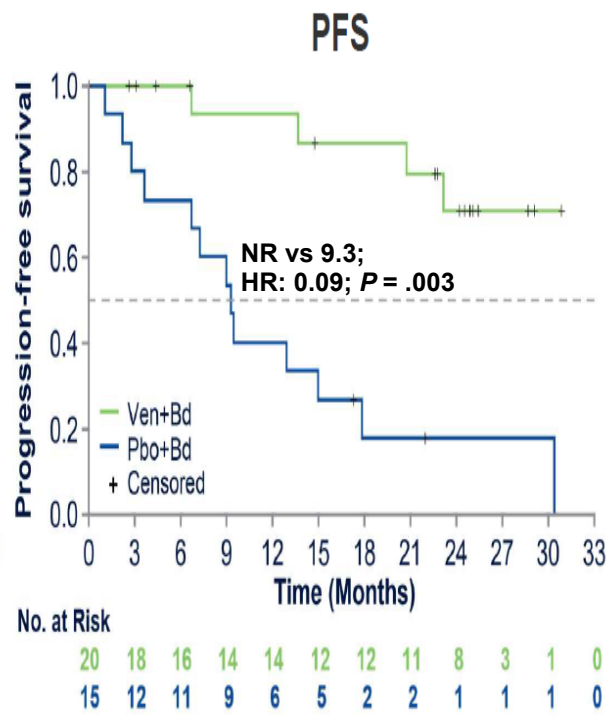
Slide credit: clinicaloptions.com

VENETOCLAX+ BortDex vs BortDex (291 patients, 2:1 random) BELLINI Study

Venetoclax is a small molecule BCL-2 inhibitor[1,] induces cell death in MM cell, particularly t(11;14) & high *BCL2....ORR: 21%...60%,*
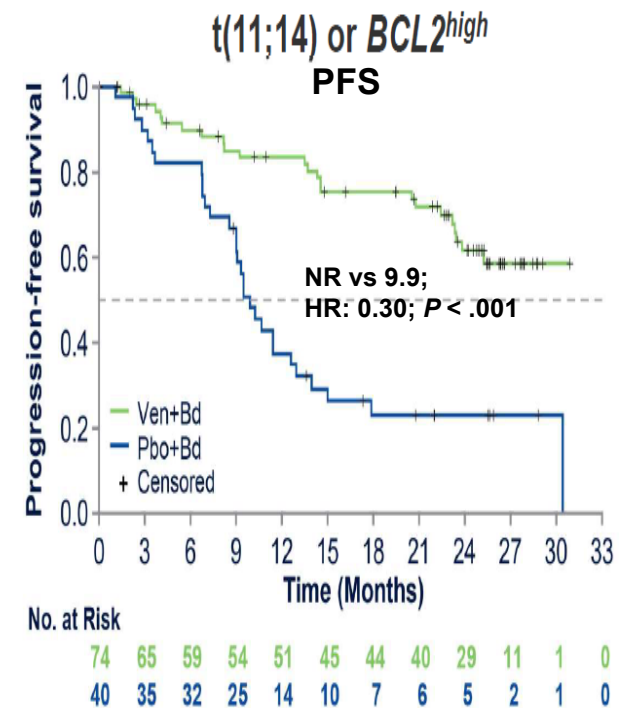
PFS in all patients

Investigator-Assessed PFS

23.2 m (VenBd)
11.4 m (PboBd)
HR: 0.60; *P* = .001

PFS in patients with t(11;14)

PFS

NR vs 9.3;
HR: 0.09; *P* = .003

PFS by t(11;14) and *BCL2* status

t(11;14) or *BCL2*^{high}
PFS

NR vs 9.9;
HR: 0.30; *P* < .001

Venetoclax: 800mg QD; BtzDex: C1-8 /21d....C9/35d ....until progression

ASH Updates

- 4 drug combination of daratumumab, bortezomib, lenalidomide, dex emerging as new standard for fit patients with ND MM

- newly approved drugs for RR MM with unique mechanisms of action

- First in class newly approved Car T cell product for RR MM