Expert Recommendations & Patient Perspectives for Treating Relapsed/Refractory Multiple Myeloma

April 16, 2021

3 PM ET | 12 PM PT

LIVE WEBINAR

MYELOMA360
Changing the global paradigm

Expert Recommendations & Patient Perspectives for Treating Relapsed/Refractory Multiple Myeloma

Eric Low

Moderator

Faculty

Rafael Fonseca, MD
Interim Director
Mayo Clinic Cancer Center
Phoenix, AZ

Jack Aiello
Myeloma Survivor & Patient Advocate
San Jose, CA

James Berenson, MD
Founder & President
Institute for Myeloma & Bone Cancer Research
West Hollywood, CA

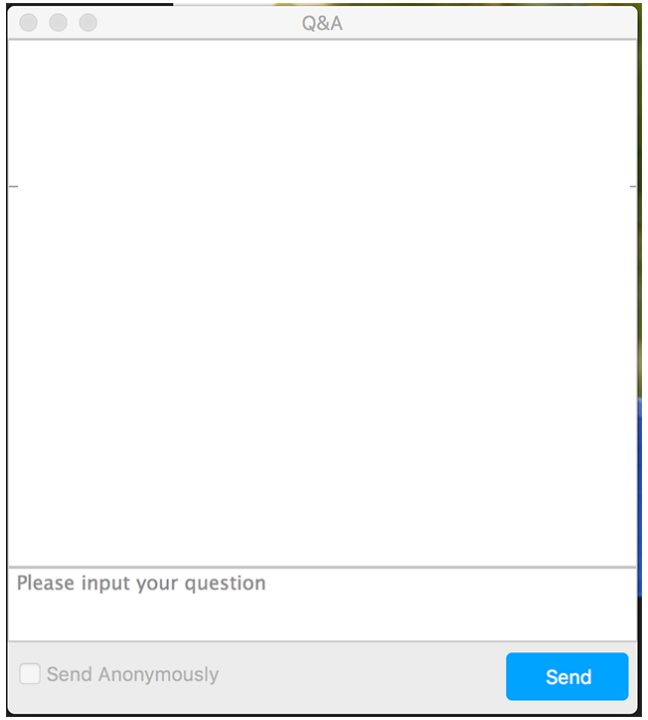
Agenda

12:00—12:05	**Introduction**
12:05—12:25	**Current Management of Patients with Relapsed/Refractory Multiple Myeloma** Rafael Fonseca, MD
12:25—12:45	**Patient's Perspective on Treatment Options and Living with Relapsed/Refractory Multiple Myeloma Myeloma** Jack Aiello
12:45—1:05	**Promising New Treatment Options for Patients with Relapsed/Refractory Multiple Myeloma** James Berenson, MD
1:05	**Additional Q&A**

How to Ask a Question

- Questions will be asked/answered at the end of each topic.
- Additional questions can be asked at the end of the program (time allowing)

Question & Answer : Open the Q&A window, allowing you to ask questions to the host and panelists. They can either reply back to you via text in the Q&A window or answer your question live.



To ask a question:

1.Type your question into the Q&A box. Click **Send**.

Note: Check **Send Anonymously** if you do not want your name attached to your question in the Q&A.

2.Most questions will be answered live by the faculty and questions not answered will be answered by follow up email after the program unless asked anonymously

Polling Questions

Current Management of Relapsed/Refractory Multiple Myeloma

Rafael Fonseca, MD

Interim Director, Mayo Clinic Cancer Center

MAYO CLINIC

Rafael Fonseca MD
Interim Executive Director Mayo Clinic Cancer Center

Relapse and Refractory Multiple Myeloma

Scottsdale, Arizona

Rochester, Minnesota

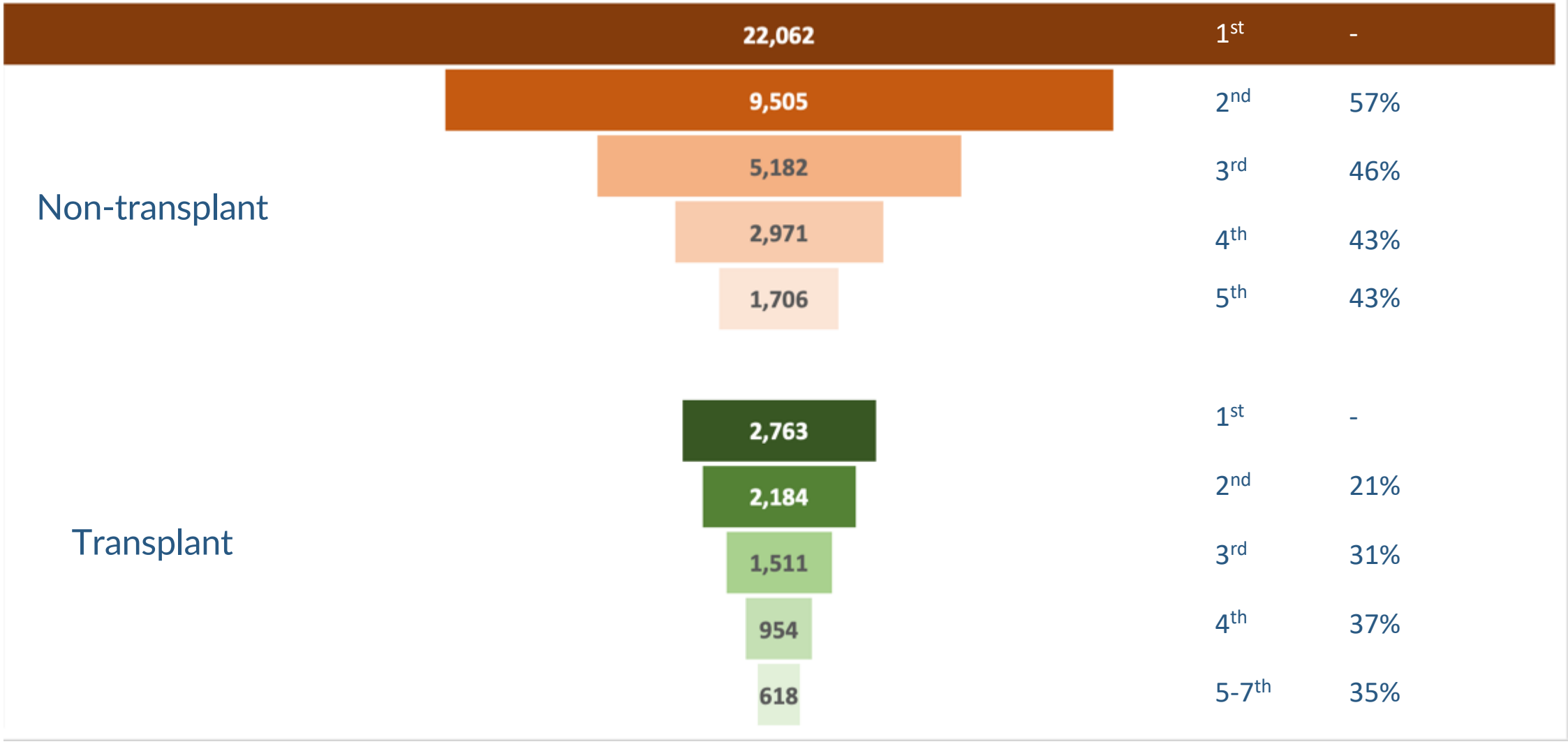
Jacksonville, Florida

MAYO CLINIC

Disclosures – Relaciones con la Industria

- Consulting: AMGEN, BMS, Celgene, Takeda, Bayer, Jansen, AbbVie, Pharmacyclics, Merck, Sanofi, Kite
- SAB: Adaptive Biotechnologies, Caris Life Sciences (stock options)
- Patent for FISH in MM: ~$2000/year
- Registered independent
- Believe in stem cell transplant

Attrition with Subsequent Treatment



Fonseca et al BMC 20: 1087 (2020)

ASPIRE—Len/Dex ± Carfilzomib

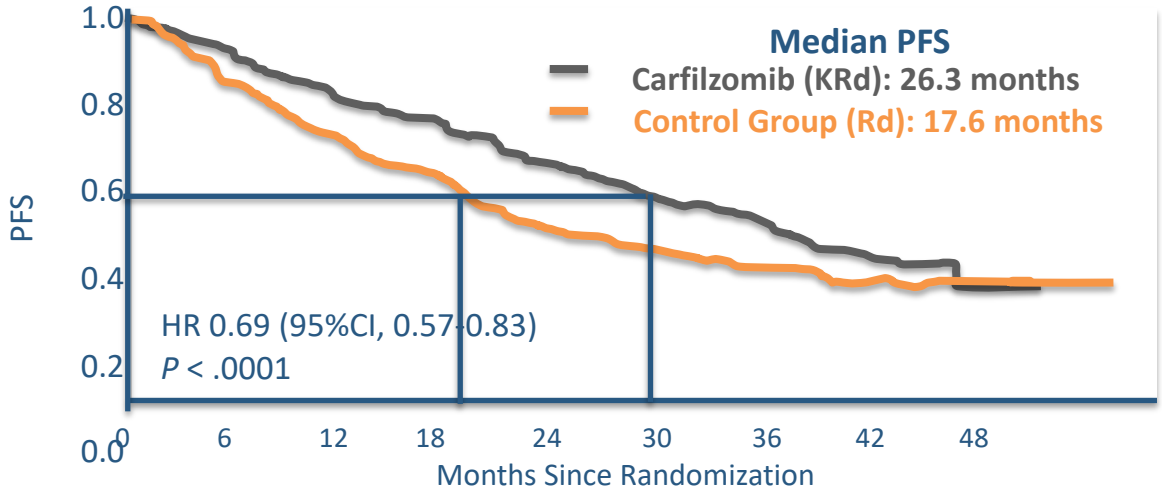
- **Carfilzomib 20mg/m² (27mg/m²)**
  - Cycle 1-12: d 1, 2, 8, 9, 15, 16
  - Cycles 13-18: d 1, 2, 15
- **Lenalidomide 25mg** d1-21
- **Dexamethasone 40mg** d1, 8, 15, 22

- **Lenalidomide** 25mg d1-21
- **Dexamethasone** d1, 8, 15, 22

After cycle 18, Len/Dex was continued until POD or toxicity

Primary End-Point: PFS

Secondary End-Points: OS, ORR, Duration of response, HRQoL, safety



Risk Group by FISH	KRd (n = 396)		Rd (n = 396)		HR	*P* Value
	n	Median PFS, Mos	n	Median PFS, Mos		
High	48	23.1	52	13.9	0.70	.083
Standard	147	29.6	170	19.5	*0.66*	.004

Stewart , et al. N Engl J Med. 2015;372:142-152.

Pollux Study

The NEW ENGLAND JOURNAL of MEDICINE

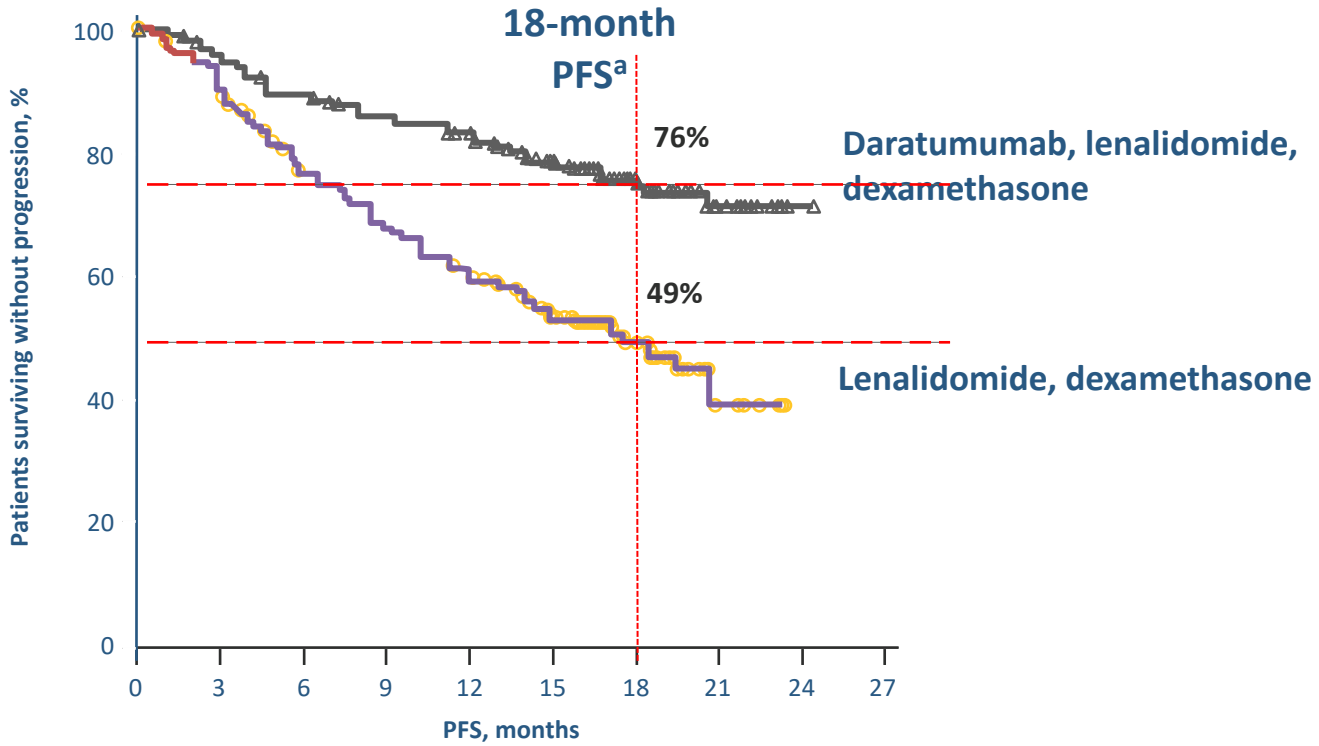
ESTABLISHED IN 1812 OCTOBER 6, 2016 VOL. 375 NO. 14

Daratumumab, Lenalidomide, and Dexamethasone for Multiple Myeloma

M.A. Dimopoulos, A. Oriol, H. Nahi, J. San-Miguel, N.J. Bahlis, S.Z. Usmani, N. Rabin, R.Z. Orlowski, M. Komarnicki, K. Suzuki, T. Plesner, S.-S. Yoon, D. Ben Yehuda, P.G. Richardson, H. Goldschmidt, D. Reece, S. Lisby, N.Z. Khokhar, L. O'Rourke, C. Chiu, X. Qin, M. Guckert, T. Ahmadi, and P. Moreau, for the POLLUX Investigators*

Dimopoulos et al. N Engl J Med 2016;375:1319-31.

Updated PFS for POLLUX Trial



HR, hazard ratio; CI, confidence interval.
[a]Kaplan-Meier estimates.
Clinical cut-off: June 30, 2016.

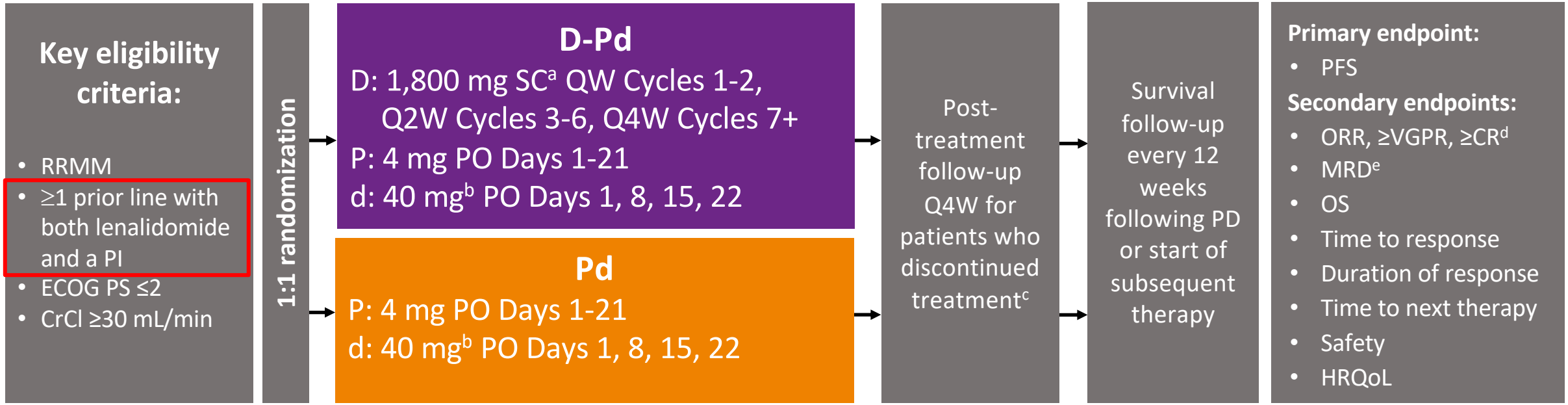
Median (range) follow-up:
17.3 (0-24.5) months

Median PFS

DRd: not reached; Rd: 17.5 months
HR: 0.37 (95% CI, 0.28-0.50; *P* <0.0001)

Dimopoulos et al. N Engl J Med 2016;375:1319-31.

APOLLO Dara-Pd



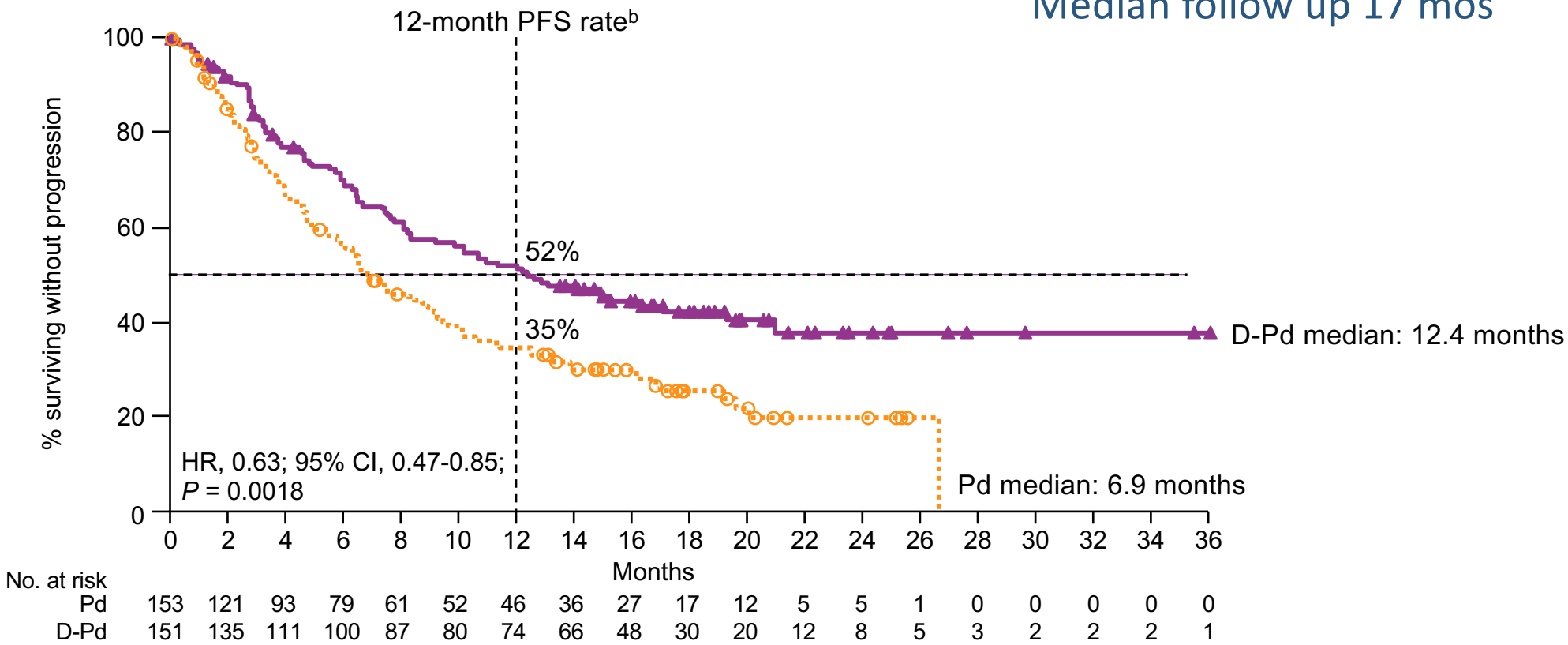
Stratification factors
- Number of lines of prior therapy (1 vs 2-3 vs ≥4)
- ISS disease stage (I vs II vs III)

Cycle duration: 28 days
Treatment until PD or unacceptable toxicity

Dimopoulos et al. ASH 2020

APOLLO Dara-Pd

Median follow up 17 mos

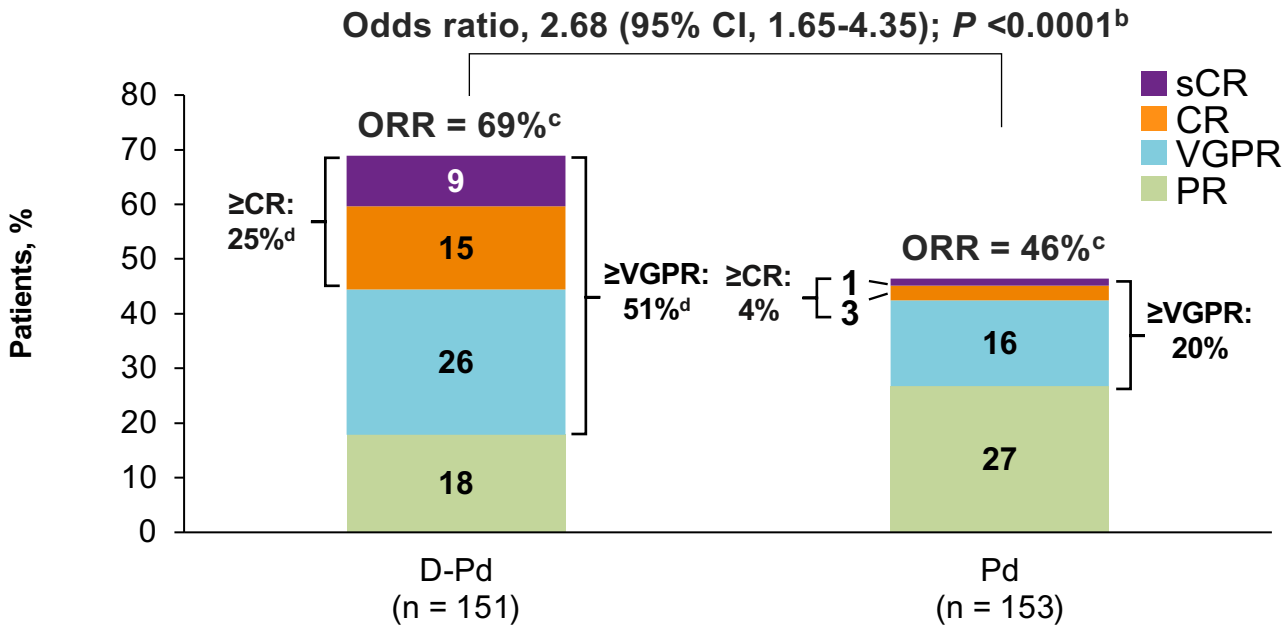


Median PFS among patients refractory to lenalidomide was 9.9 months for D-Pd and 6.5 months for Pd

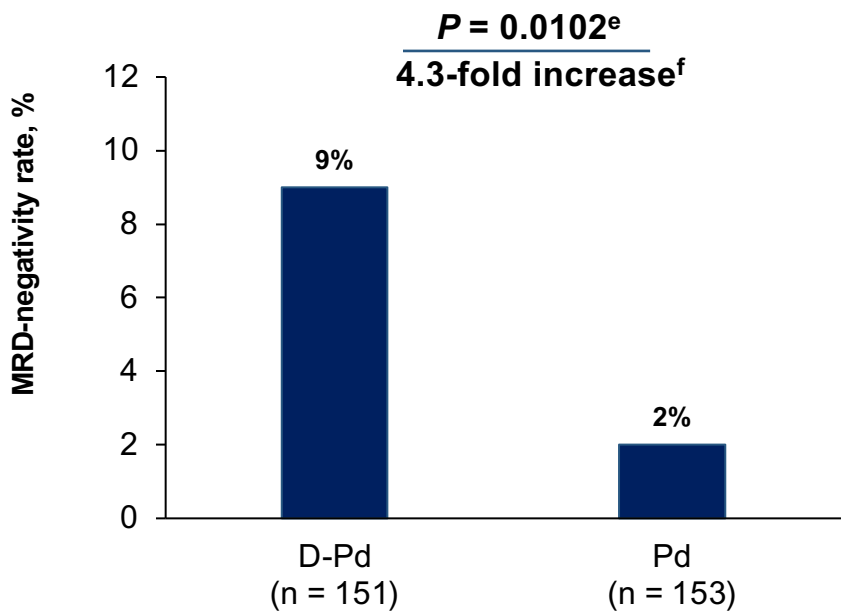
Dimopoulos et al. ASH 2020

APOLLO Dara-Pd

Hematologic response

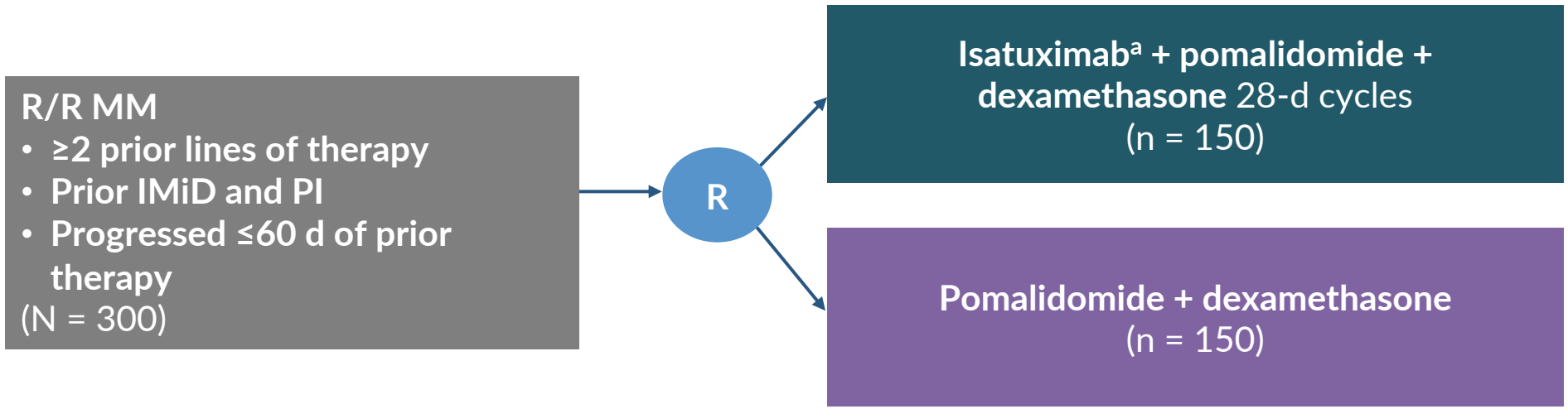


MRD negativity



Dimopoulos et al. ASH 2020

ICARIA: Isatuximab + Pd

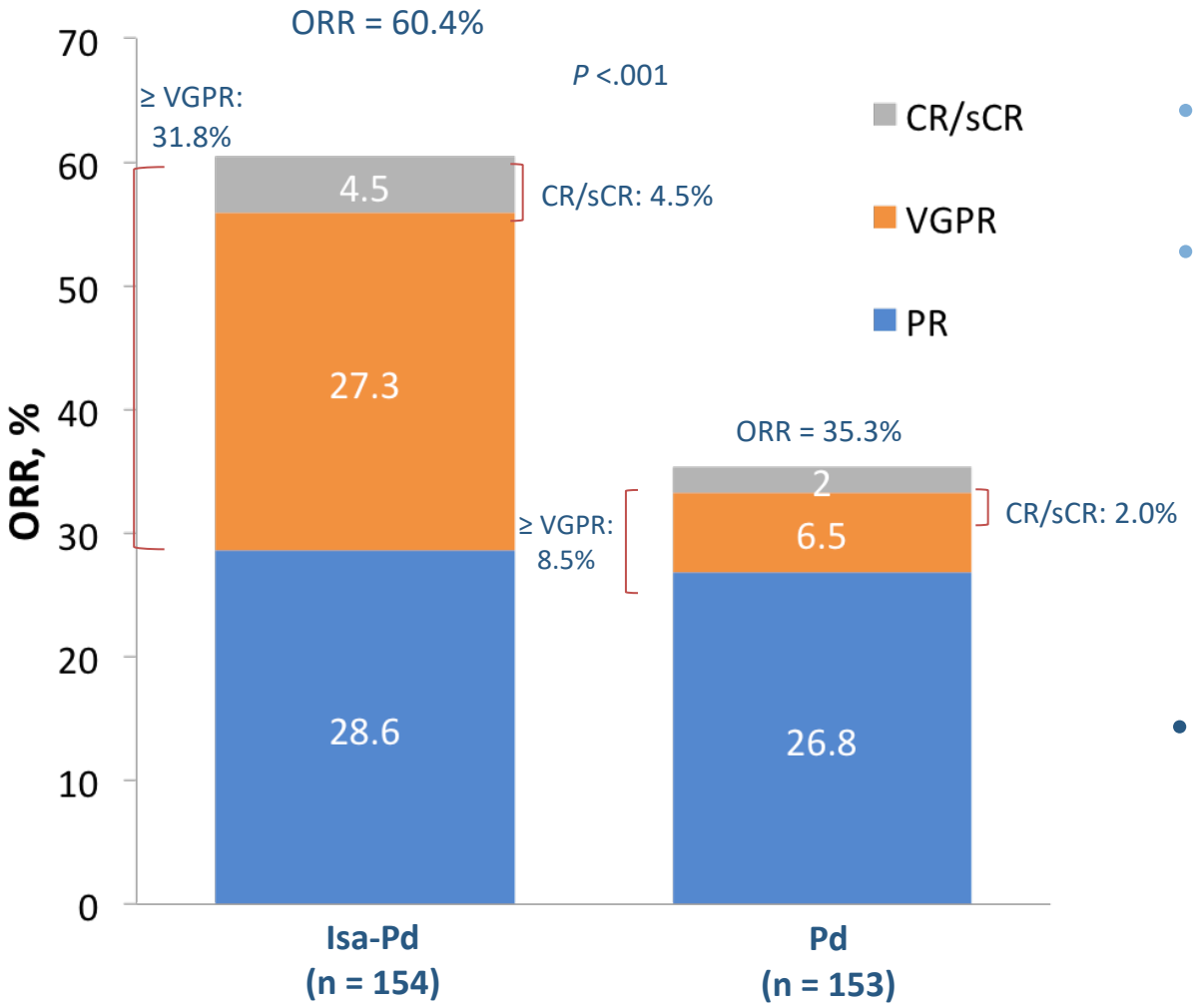


Until disease progression, occurrence of unacceptable AEs, or patient's decision to discontinue the study

- Primary endpoint: PFS
- Key secondary endpoints: ORR, OS, safety

Richardson PG, et al. ASCO 2019. Abstract 8004.

ICARIA-MM: Response



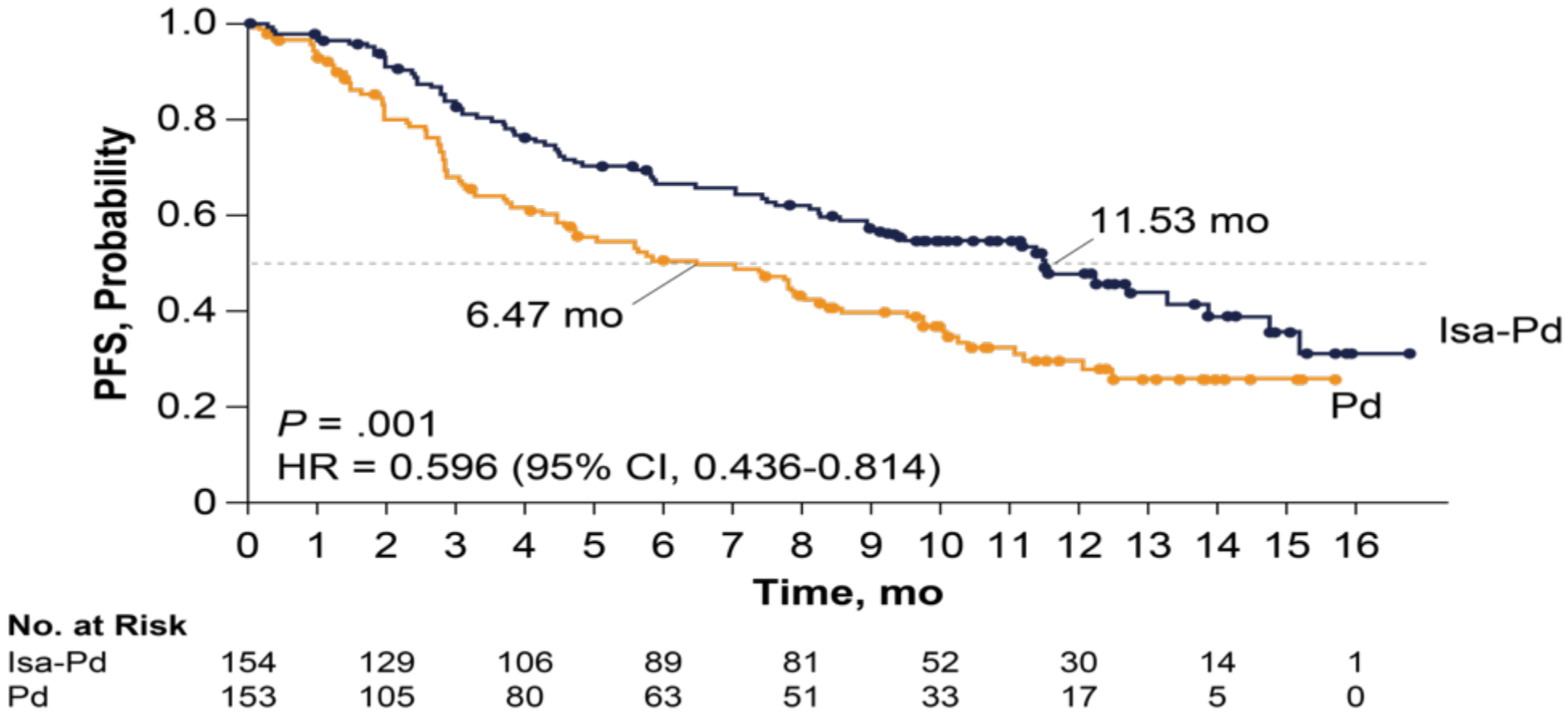
- Median time to first response: Isa-Pd = 35 days vs Pd = 58 days
- True CR rate in Isa-Pd underestimated because of isatuximab interference with M-protein measurement

	Isa-Pd (n = 154)	Pd (n = 153)
nCR, %	15.6	3.3

- MRD negativity at 10^{-5} (ITT): 5.2% for Isa-Pd vs 0% for Pd

Richardson PG, et al. ASCO 2019. Abstract 8004.

ICARIA-MM: PFS



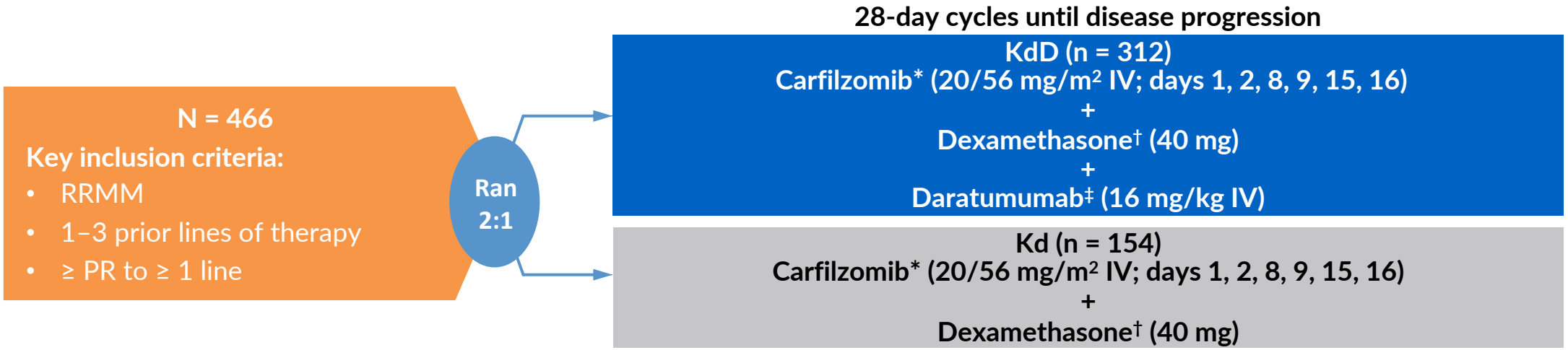
No. at Risk

Isa-Pd	154	129	106	89	81	52	30	14	1
Pd	153	105	80	63	51	33	17	5	0

Richardson PG, et al. ASCO 2019. Abstract 8004.

CANDOR (KdD vs Kd in RRMM)

- The CANDOR study previously demonstrated that KdD improved progression-free survival (PFS) vs Kd (HR 0.63, 95% CI 0.46–0.85) in patients with RRMM[1]
- This abstract reports updated efficacy and safety outcomes from CANDOR up to the data cut-off of ~36 months after enrollment of the first patient[2]



Primary endpoint: PFS[§]

Select secondary endpoints: ORR, MRD-negative CR at 12 months, OS, safety

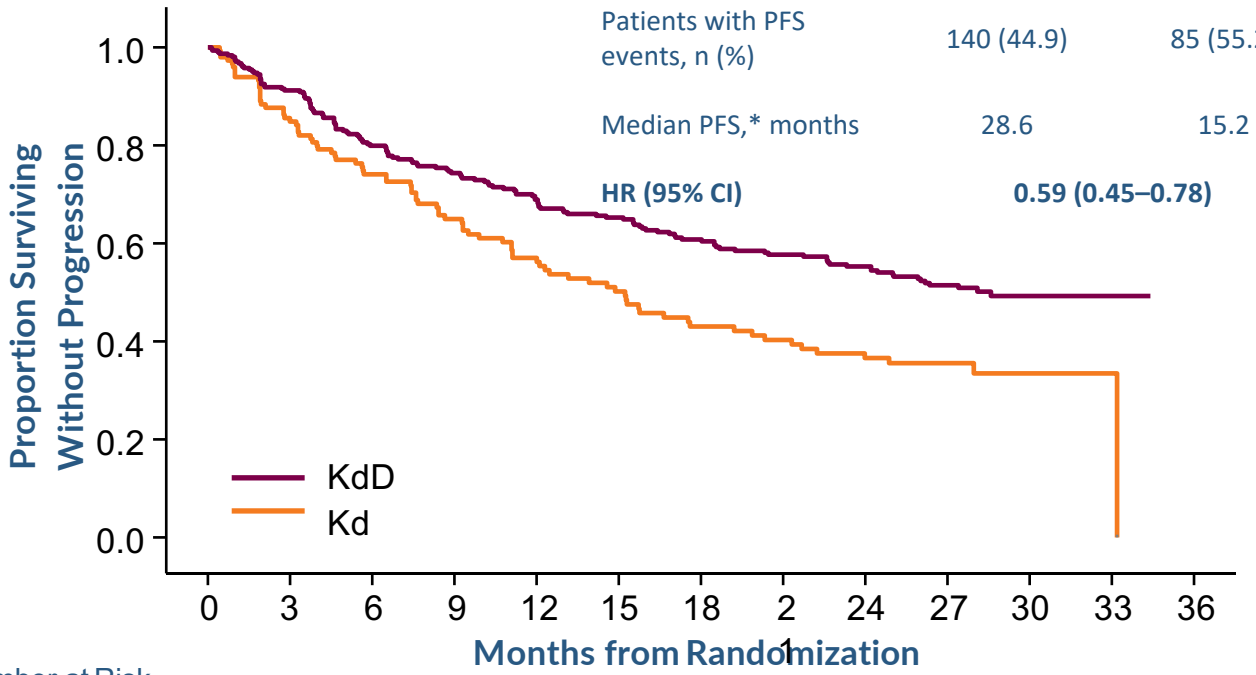
*Carfilzomib dose was 20 mg/m² on days 1 and 2 of cycle 1. †PO or IV weekly; 20 mg for patients > 75 years. ‡8 mg/kg on days 1 and 2 of cycle 1; 16 mg/kg weekly thereafter for cycles 1–2; Q2W for cycles 3–6; and Q4W thereafter. §Disease progression was determined locally by investigators in an unblinded manner and centrally by the sponsor using a validated computer algorithm (ORCA) in a blinded manner.

CI, confidence interval; CR, complete response; HR, hazard ratio; IV, intravenous; Kd, carfilzomib, dexamethasone; KdD, carfilzomib, dexamethasone, daratumumab; MRD, minimal residual disease; ORCA, Onyx Response Computer Algorithm; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PO, per oral; PR, partial response; Q2W, once every 2 weeks; Q4W, once every 4 weeks; Ran, randomized; RRMM, relapsed or refractory multiple myeloma.

1. Dimopoulos M, et al. *Lancet*. 2020;396:186-97. 2. Dimopoulos M, et al. Presented at 62nd ASH Annual Meeting and Exposition; Dec 5–8, 2020; Virtual. Abstract 2325.

MAYO CLINIC
@rfonsi1, fonseca.rafael@mayo.edu

CANDOR (KdD vs Kd in RRMM)



	KdD (n = 312)	Kd (n = 154)
Patients with PFS events, n (%)	140 (44.9)	85 (55.2)
Median PFS,* months	28.6	15.2
HR (95% CI)	**0.59 (0.45–0.78)**	

Number at Risk

KdD	312	279	235	210	189	178	159	146	136	105	30	6	0
Kd	154	120	99	83	69	57	47	44	39	28	4	1	0

Safety	KdD (n = 312)	Kd (n = 154)
Grade ≥ 3 AEs, %	87.0	75.8
Fatal AEs,† %	8.8	4.6
Carfilzomib discontinuation due to AEs, %	26.0	22.2
Exposure-adjusted AE rates, per 100 patient-years:		
Grade ≥ 3 AEs	171.2	151.9
Fatal AEs	6.9	5.6

- Safety was consistent with previously reported results
- KdD continues to show a favorable benefit-risk profile

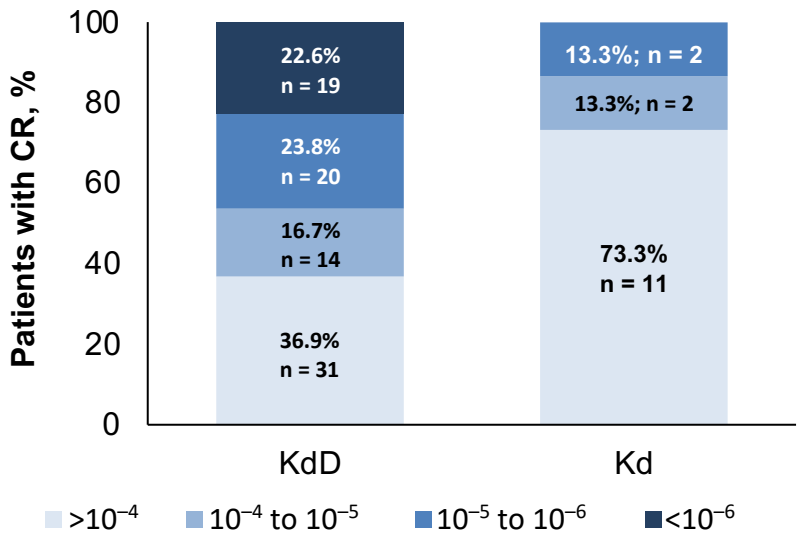
With ~11 months of additional follow-up, median PFS was improved in patients treated with KdD (28.6 months) versus Kd (15.2 months)

*By ORCA. †One fatal AE in the KdD arm (due to arrhythmia) and one fatal AE in the Kd arm (due to COVID-19 pneumonia) had occurred since the primary analysis.
AE, adverse event; CI, confidence interval; HR, hazard ratio; Kd, carfilzomib, dexamethasone; KdD, carfilzomib, dexamethasone, daratumumab; ORCA, Onyx Response Computer Algorithm; PFS, progression-free survival; RRMM, relapsed or refractory multiple myeloma.

Dimopoulos et al ASH 2020 Abstract 2325

CANDOR (KdD vs Kd in RRMM)

MRD in Patients with CR at 12-Month Landmark

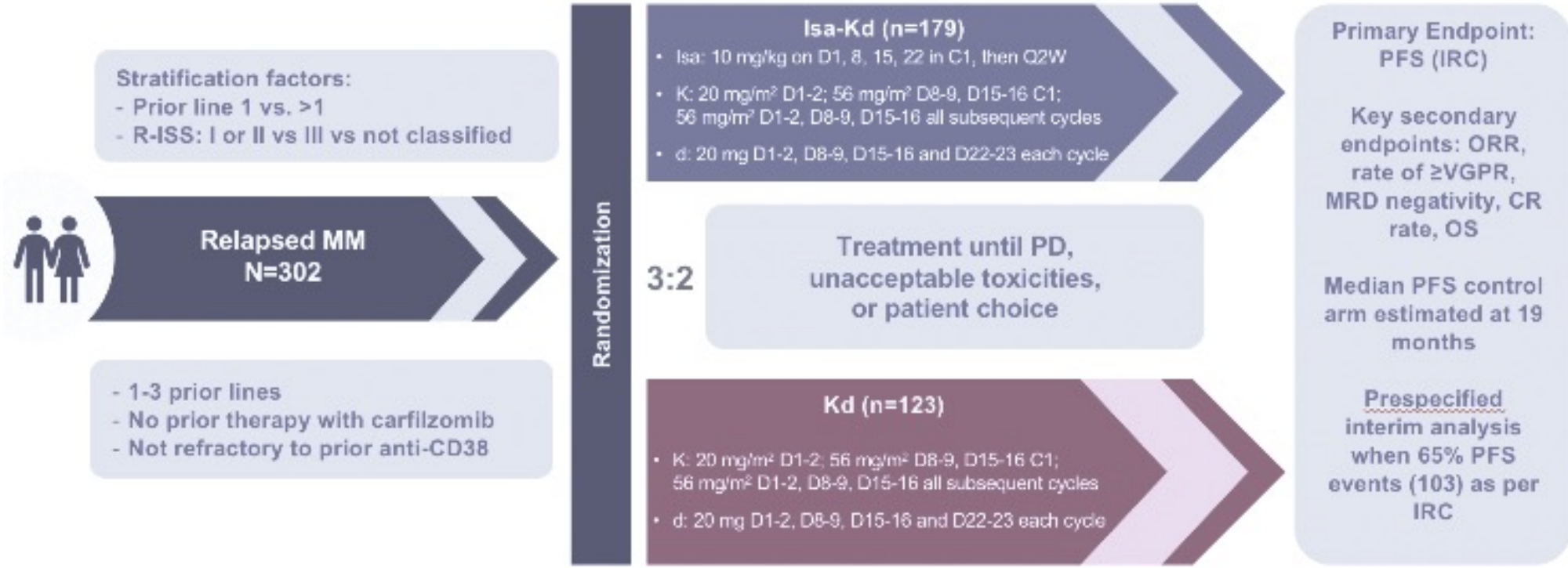


- At the 12-month landmark, patients treated with KdD had a greater proportion of CR rates (26.9% vs 9.7%) and deeper MRD responses than patients treated with Kd
- Among patients with CR, depth of response was deeper for KdD relative to Kd regardless of MRD sensitivity
- Within the KdD arm, prior lenalidomide exposure or refractoriness did not diminish the MRD-negative CR rate
- With a median of 6 months follow-up, no patient with MRD-negative CR progressed

Patients treated with KdD achieved significantly higher MRD-negative CR rates vs Kd at 12 months, which supports the efficacy of the KdD regimen as an effective treatment for RRMM including patients who have become refractory to lenalidomide

Landgren O, et al. ASH 2020

IKEMA



Sample size calculation: ~300 patients and 159 PFS events to detect 41% risk reduction in hazard rate for PFS with 90% power and one-sided 0.025 significance level

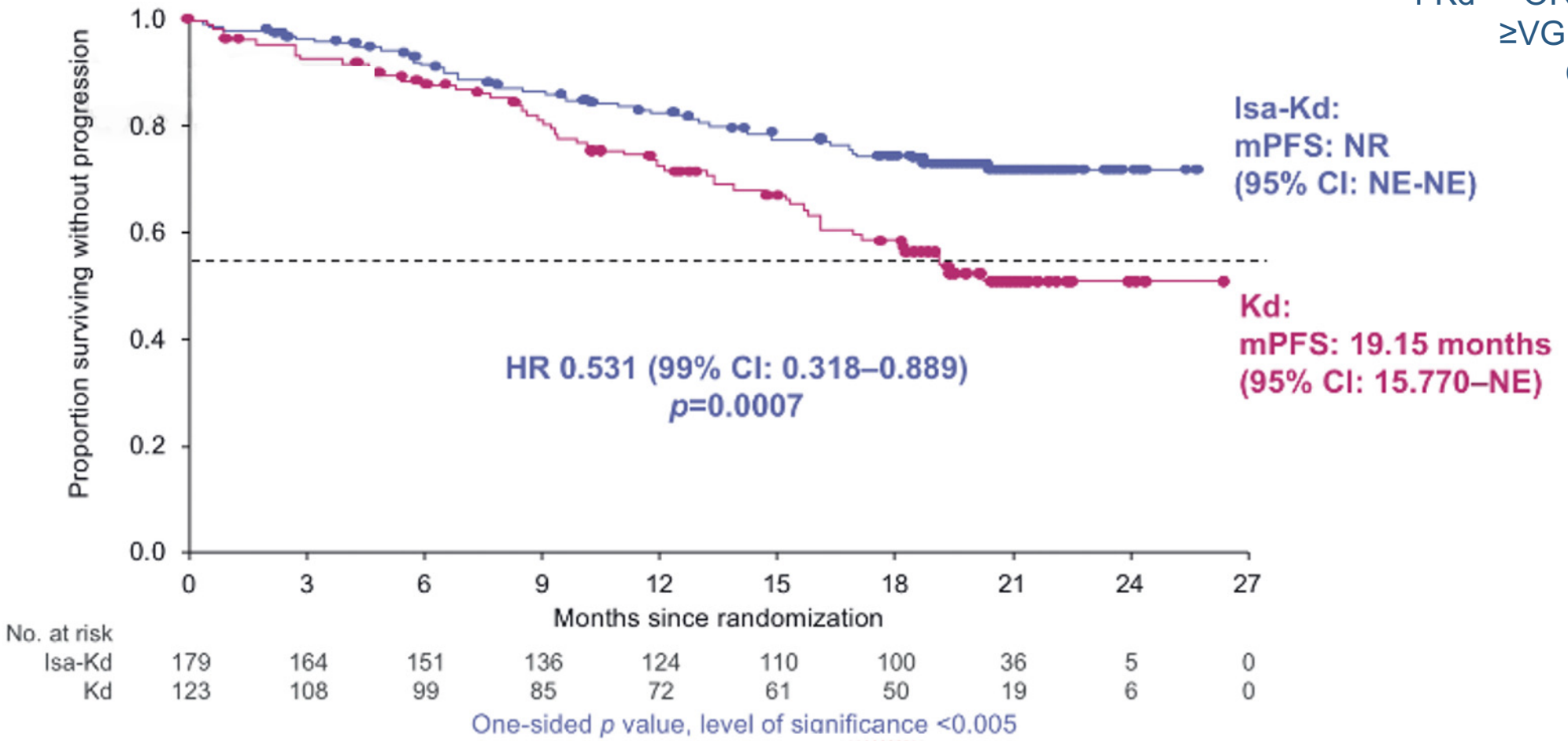
Patients refractory to, n (%)

IMiD	78 (43.6)	58 (47.2)
Lenalidomide	57 (31.8)	42 (34.1)
PI	56 (31.3)	44 (35.8)

Moreau P. et al. *Blood. 2020;136(suppl 1). Abstract 2316*

IKEMA

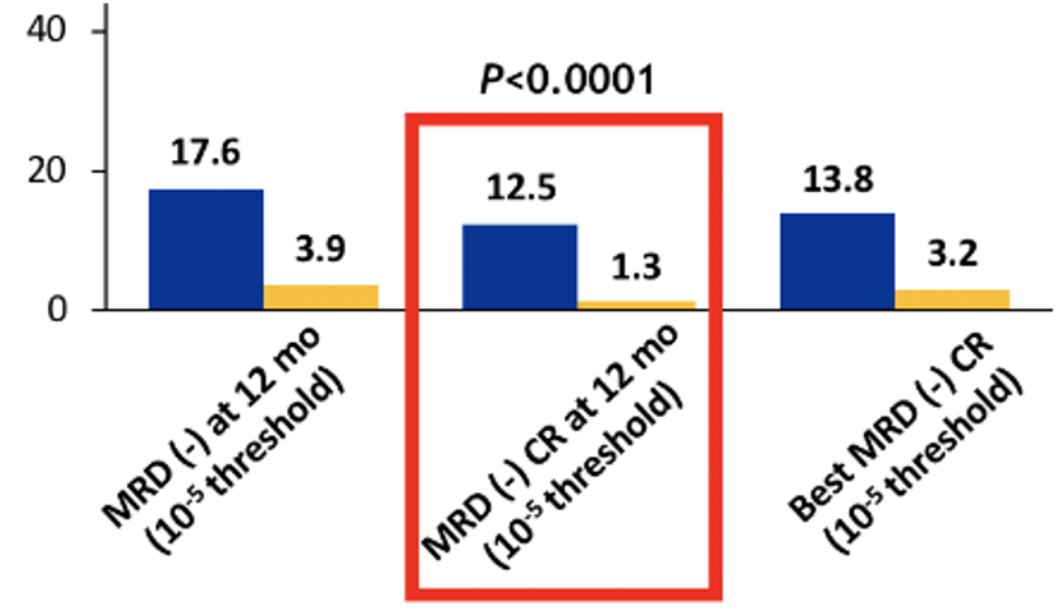
I-Kd ORR=86.6%
≥VGPR=72.6%
CR=39.7%



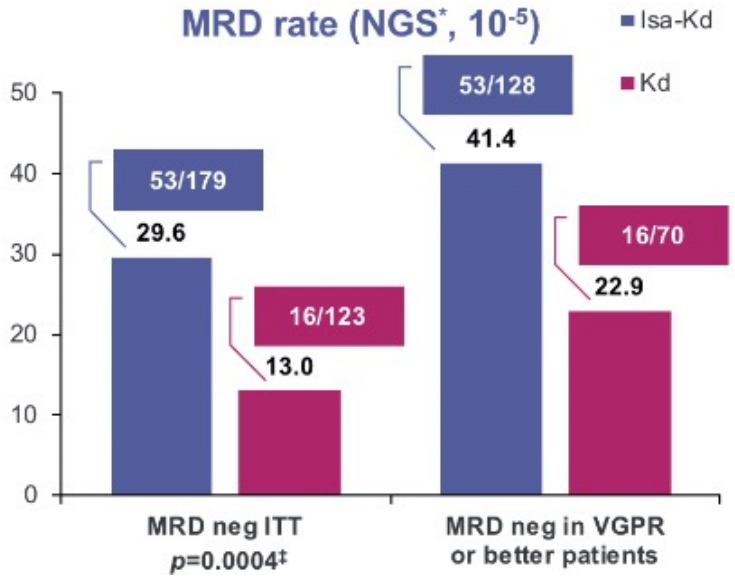
Moreau P. et al. *Blood. 2020;136(suppl 1). Abstract 2316*

MRD RESULTS

CANDOR



IKEMA



Moreau P. et al. *Blood. 2020;136(suppl 1). Abstract 2316*
Dimopoulos et al ASH 2020 Abstract 2325

ELOQUENT-3: Efficacy of Elotuzumab-PomDex vs PomDex in R/R MM

EPd Group

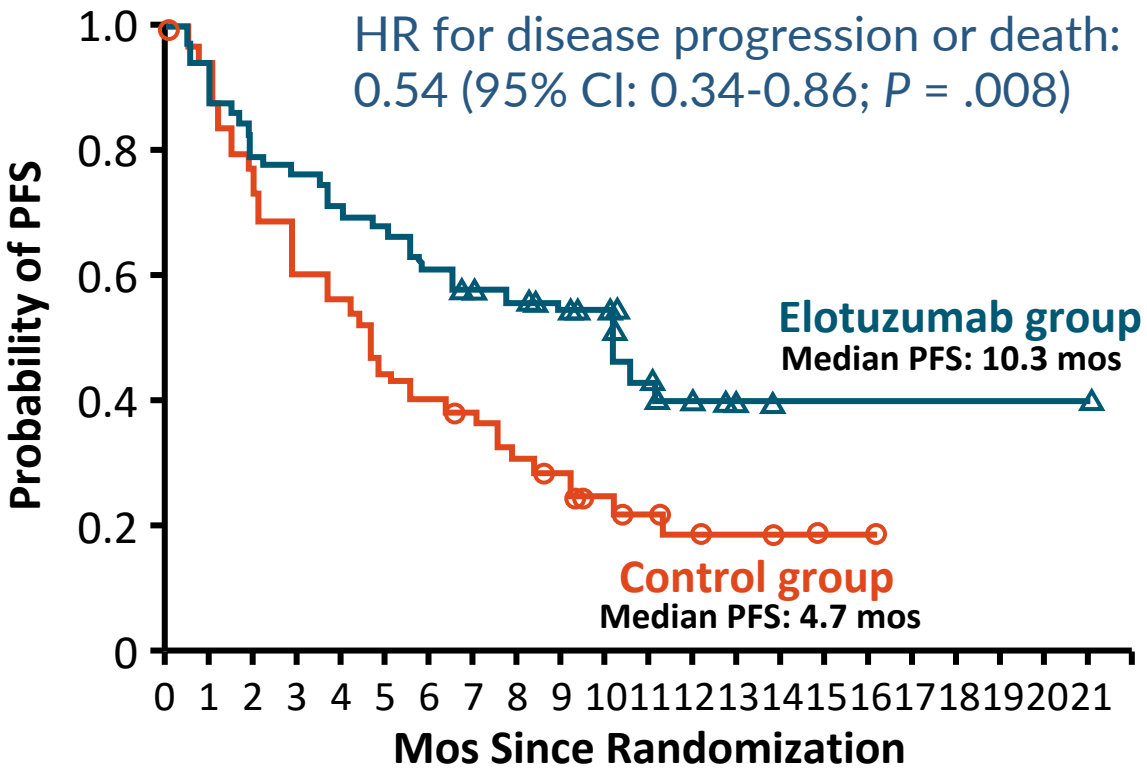
- ≥ 2 prior lines of therapy (40% with ≥ 4)
- 90% lenalidomide refractory (60% in last line)
- 78% PI refractory
- 68% double refractory

Response	Pd	EPd
ORR, %	26	53
▪ sCR	0	3
▪ CR	2	5
▪ VGPR	7	12
▪ PR	18	33
Median DoR, mos	8.3	Not reached

Minimum Follow-Up: 9.1 mos

PFS

HR for disease progression or death: 0.54 (95% CI: 0.34-0.86; *P* = .008)



HR for PFS with disease refractory to lenalidomide and PI: 0.56 (95% CI: 0.33-0.97)

Dimopoulos. NEJM. 2018;379:1811.

Selinexor: An Oral Selective Inhibitor of Nuclear Export

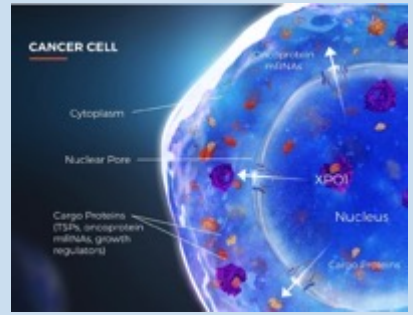
MOA[1-5]

Exportin-1: major nuclear export protein overexpressed in MM

- Removes tumor suppressor & growth regulatory proteins from nucleus
- Associated with poor outcomes and therapy resistance

Selinexor is a potent selective inhibitor of exportin-1

- Allows retention of tumor suppressor proteins in the nucleus
- Promotes cell-cycle arrest and apoptosis



FDA Approvals in MM[6]

- SVd: adults with RRMM after> 1 prior therapy (approved 2020)
- Selinexor/dexa: adults with RRMM after> 4 prior therapies, including >2 PIs, >2 IMDs, and an anti-CD38 mAb (approved 2019)

1. Gupta A, et al. J ThoracOncol. 2017.
2. Sun Q, et al. Signal TransductTarget Ther. 2016.
3. Gandhi UH, et al. Clin Lymphoma Myeloma Leuk. 2018.
4. GravinaGL, et al. J HematolOncol. 2014
5. Richter J, et al. Ther Adv Hematol. 2020;11:2040620720930629
6. Xpovio™ (selinexor) [PI]. 2020.

Selinexor BOSTON Trial: Phase 3 – Vd vs Xvd

Randomization 1:1

SVd Weekly 35-day cycles	Selinexor (oral)	100 mg	Days 1, 8, 15, 22, 29
	Bortezomib (SC)	1.3 mg/m^2	Days 1, 8, 15, 22
	Dexamethasone (oral)	20 mg	Days 1, 2, 8, 9, 15, 16, 22, 23, 29, 30
Vd **Twice Weekly** 21-day cycles Cycles 1-8	Bortezomib (SC)	1.3 mg/m^2	Days 1, 4, 8, 11
	Dexamethasone (oral)	20 mg	Days 1, 2, 4, 5, 8, 9, 11, 12
	If IRC confirmed PD: crossover to SVd or Sd permitted		

Vd Weekly*
35-Day cycles
Cycles ≥9

PD or unacceptable toxicity

Primary endpoint: PFS

Key secondary endpoints:
- ORR
- ≥VGPR
- Grade ≥2 PN

Secondary endpoints:
- OS
- DoR
- TTNT
- Safety

Efficacy Assessed by IRC

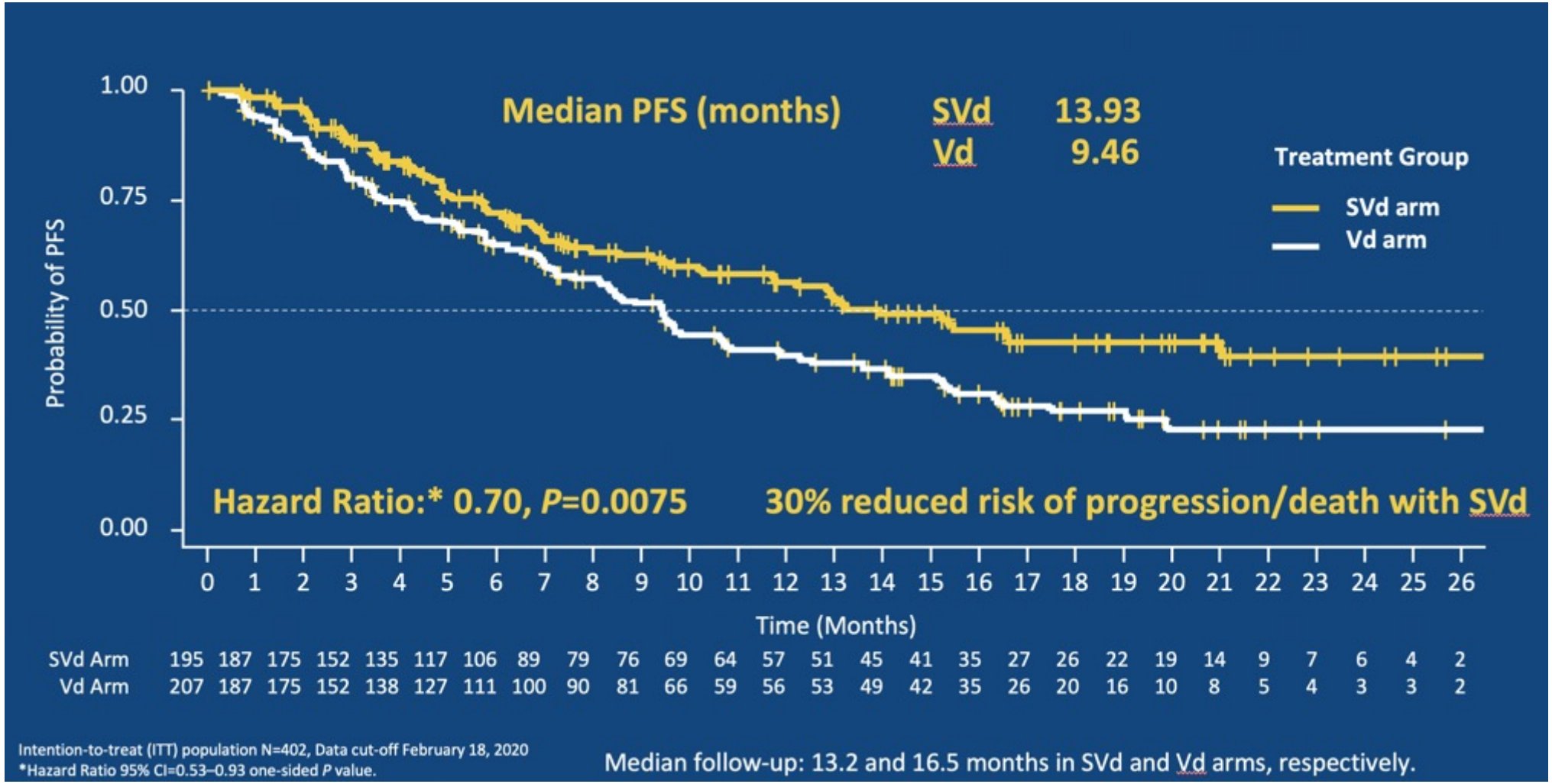
Planned 40% lower bortezomib and 25% lower dexamethasone dose at 24 weeks (8 cycles) in SVd arm vs. Vd arm

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

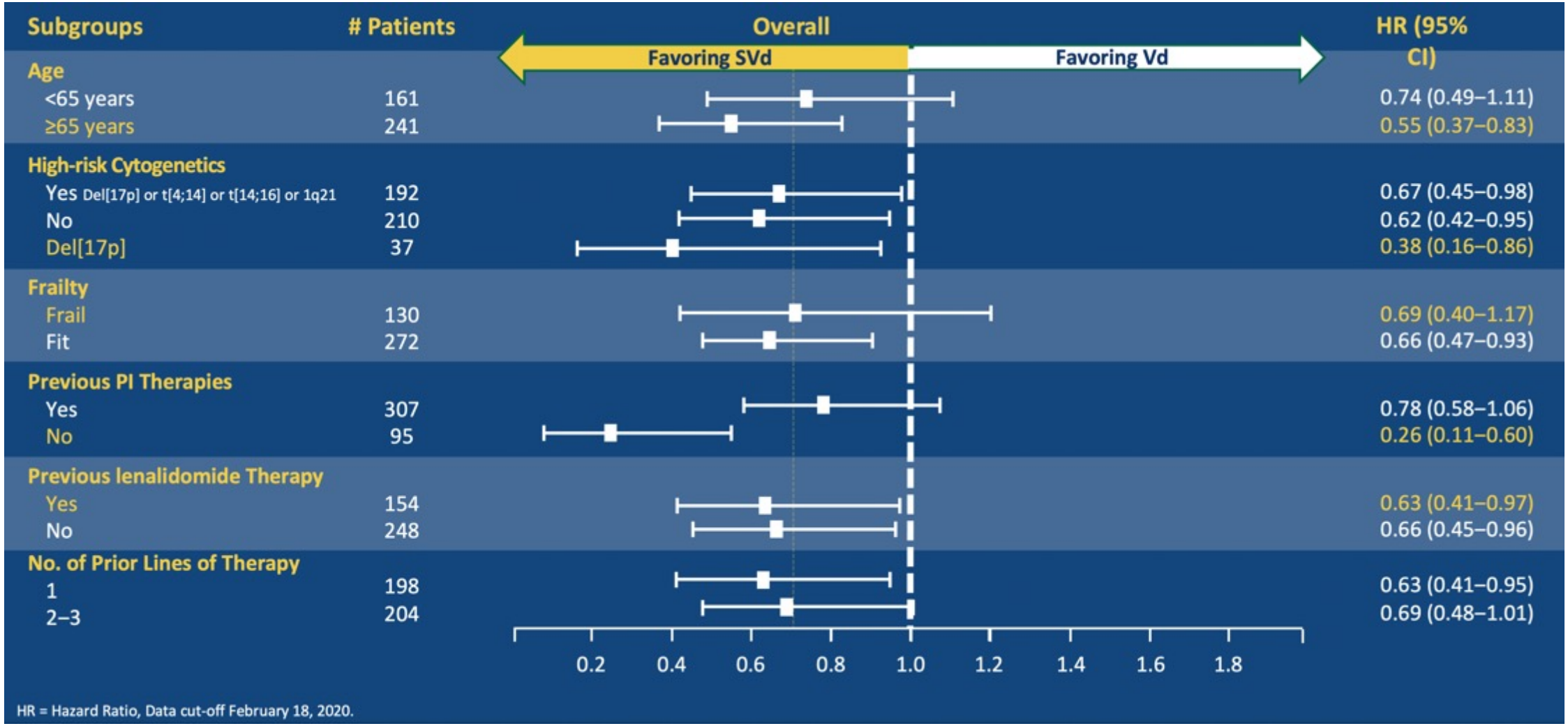
Meletios A. Dimopoulos ASCO 2020

Selinexor BOSTON Trial: PFS



Meletios A. Dimopoulos ASCO 2020

Selinexor BOSTON Trial: Forest Plot



Meletios A. Dimopoulos ASCO 2020

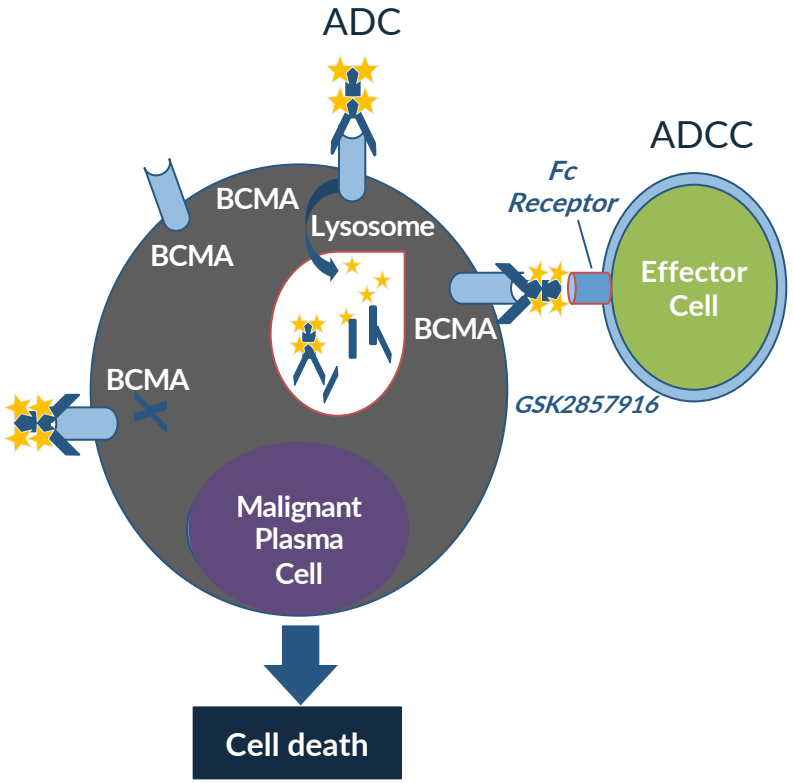
Managing Selinexor-induced Nausea/Vomiting

- Nausea is the most common AE (~68% of patients)[1]
- Antiemetic prophylaxis to prevent nausea/vomiting [1,2]
  - 5-HT3 receptor antagonist (e.g., ondansetron) 30 minutes before first dose and ongoing to provide 24-hour coverage (reassess in 8 weeks) [1]
  - Second antiemetic (e.g., olanzapine or NKl receptor antagonist) the night before therapy [1]
- IV fluids and electrolytes as needed for dehydration [2]
- Treatment interruption or dosage reduction steps per prescribing info [2]

1. Gavriatopoulou M, et al. Leukemia. 2020;34:2430-2440
2. Xpovio™ (selinexor) [PI]. 2020.

Belantamab Mafodotin: BCMA-Targeted ADC

- Belantamab mafodotin
  - Humanized, afucosylated IgG1 anti-BCMA antibody
  - Conjugated to a microtubule disrupting agent MMAF via a stable, protease-resistant maleimidocaproyl linker
- Preclinical studies demonstrate its selective and potent activity



Fc region of the antibody	• Target specific • Enhanced ADCC
Linker	• Stable in circulation
Drug	• MMAF (non—cell-permeable, highly potent auristatin)

Mechanisms of Action:
1. ADC mechanism
2. ADCC mechanism
3. Immunogenic cell death

Tai YT, et al. Blood. 2014;123: Abstract 3128.

Belantamab Mafodotin – DREAMM-2

ORR

- 30/97 patients (31%) in the 2.5-mg/kg cohort
- 34/99 patients (34%) in the 3.4-mg/kg cohort

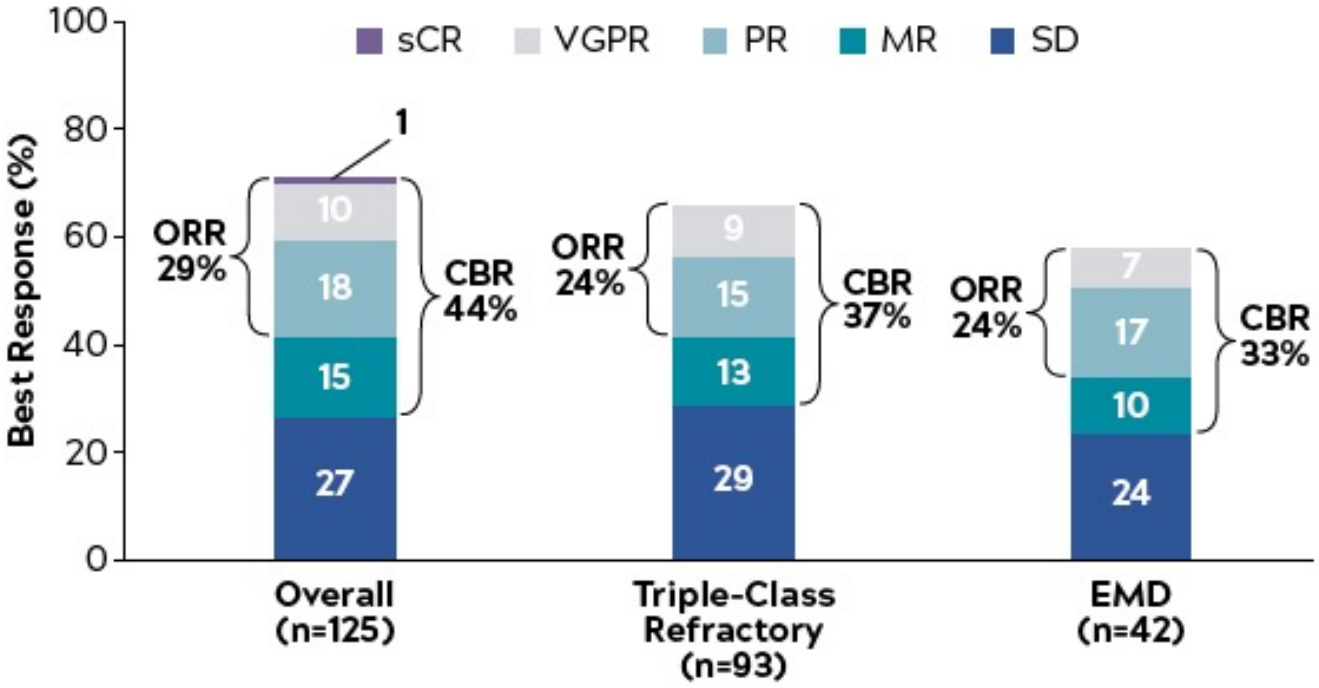
Adverse events

- Most common grade 3/4 AE
  - Keratopathy (27% in the 2.5-mg/kg cohort; 21% 3.4-mg/kg cohort)
  - Thrombocytopenia (20% and 33%)
  - Anemia (20% and 25%)
- Serious AE in 40% in 2.5-mg/kg cohort and 47% in the 3.4-mg/kg cohort
- 2 deaths were potentially treatment related
  - Sepsis in the 2.5-mg/kg cohort and hemophagocytic lymphohistiocytosis in the 3.4-mg/kg cohort

Lonial S, et al. Lancet Oncol. 2019;21(2):207-221.

HORIZON Melflufen

- Patients with RRMM refractory to pomalidomide or anti-CD38 mAb or both
- ≥ 2 prior lines of therapy including an IMiD and a PI
- ECOG PS ≤ 2



TEAE	Grade 3, n (%)	Grade 4, n (%)
Anemia	56 (36)	1 (1)
Neutropenia	47 (31)	54 (35)
Thrombocytopenia	32 (21)	74 (48)
↓ WBC	13 (8)	15 (10)
Pneumonia	11 (7)	2 (1)
Febrile neutropenia	6 (4)	2 (1)
Lymphopenia	6 (4)	2 (1)
Leukopenia	4 (3)	6 (4)

Mateos MV, et al. ASH 2019. Abstract 1883.

Melflufen Plus Dexamethasone and Daratumumab

Subgroup	Best Confirmed Response, Patients, n							Patients, %	
	>CR	VGPR	PR	MR	SD	PD	NA	ORR	CBR
Melflufen 30 mg (n=6)	0	4	1	0	0	0	1[a]	83	83
Melflufen 40 mg (n=27)	2	6	11	1	2	1	4[b]	70	74
Total (N=33)	**2**	**10**	**12**	**1**	**2**	**1**	**5**	**73**	**76**

[a]One patient had an unconfirmed PD in 30-mg dose cohort.
[b]Four patients had unconfirmed responses in the 40-mg dose cohort: 2 PD, 1 SD, and 1 PR.

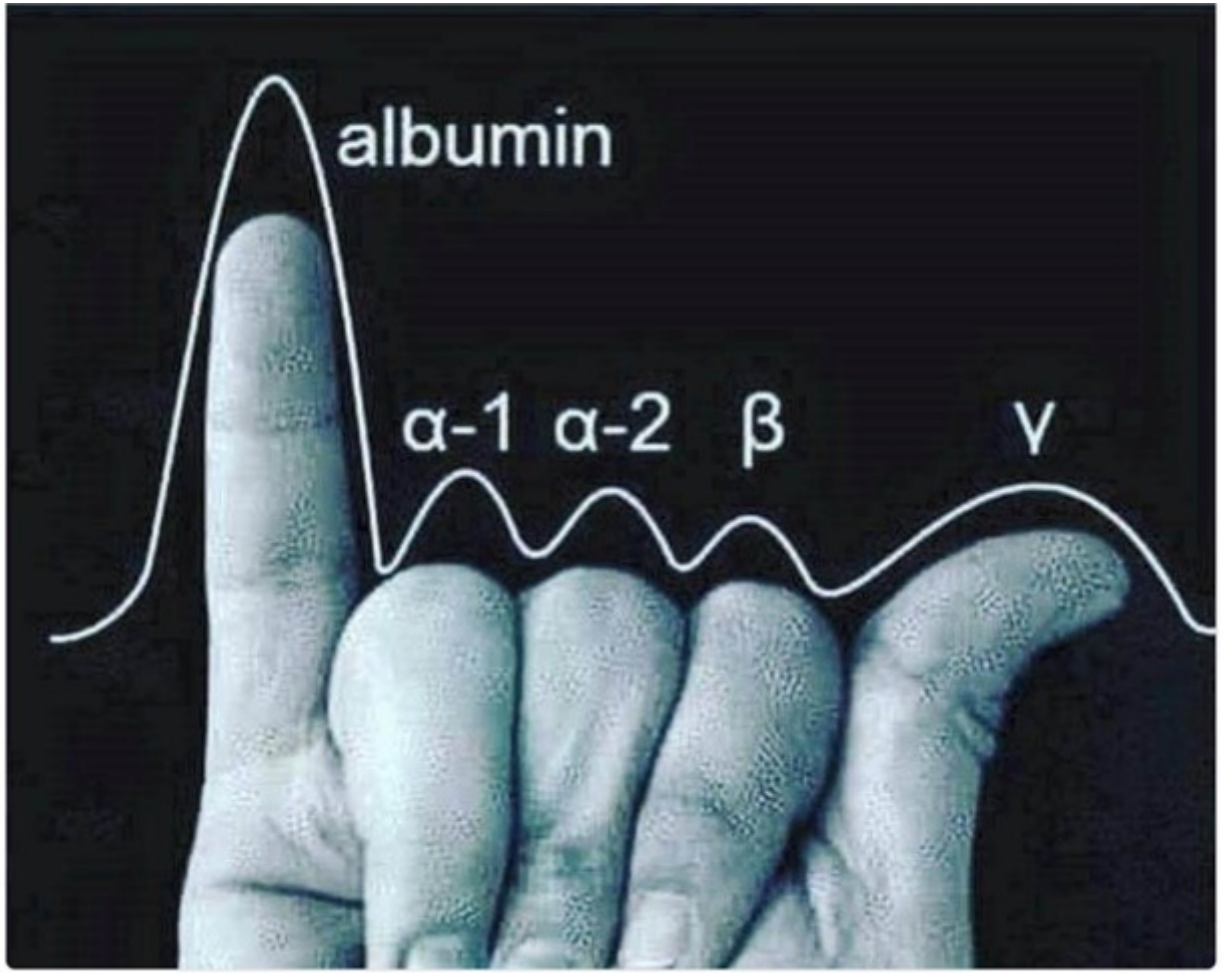
- ORR in patients was similar for both cohorts
  - 30 mg: 83%
  - 40 mg: 70%
  - 30 + 40 mg: 73%

Mateos MV, et al. ASH 2019. Abstract 1883.

Conclusions

- Many new therapies have received FDA approval for MM
- Monitor patients for toxicities and manage AEs proactively
- Different treatments have different AEs
  - Ocular toxicities with belantamab mafodotin
  - Nausea, vomiting, and diarrhea with Selinexor
  - Peripheral neuropathy with bortezomib
- Follow guidelines or prescribing information for managing toxicity
  - Is a dose adjustment, treatment interruption, or discontinuation required?
  - Are any prophylactic regimens recommended?
  - What monitoring steps should be taken?

Thank you!



Patient's Perspective on living with Relapsed/Refractory Multiple Myeloma

Jack Aiello

Myeloma Survivor & Patient Advocate

My Journey with Myeloma

- ’95: Dx’d Stage 3 MM, VAD treatment
- ’96: Tandem auto transplant
- Late ’97: Relapse after 18 mos.
- Early ’98: Thalidomide Clinical Trial, up to 800 mg; Refractory
- Mid’98: Other chemo combos, CDEP, Dex-only; Refractory
- Late’98: TBI followed by full myeloablative allo transplant
- ’99-’01: GVHD required immunosuppressants, 3 extramedullary plasmacytomas, each requiring radiation.
- ’02: Remission but medical disability due to progressive neuropathy and fibrosis.
- ’02-current: No treatment but graduated to cane for short walks and electric scooter for conferences.

Note: Worked as VP Marketing ’95-’02 in Hi-Tech but reduced travel and responsibilities. Retired ’02 and became more involved in advocacy work.

My Tips and Recommendations

- Get 2nd and 3rd opinions from MM experts
- Be your own best advocate
- Avoid emotional highs and lows
- Accept help
- Tell all regarding side effects
- Understand your priorities and share them with your physician

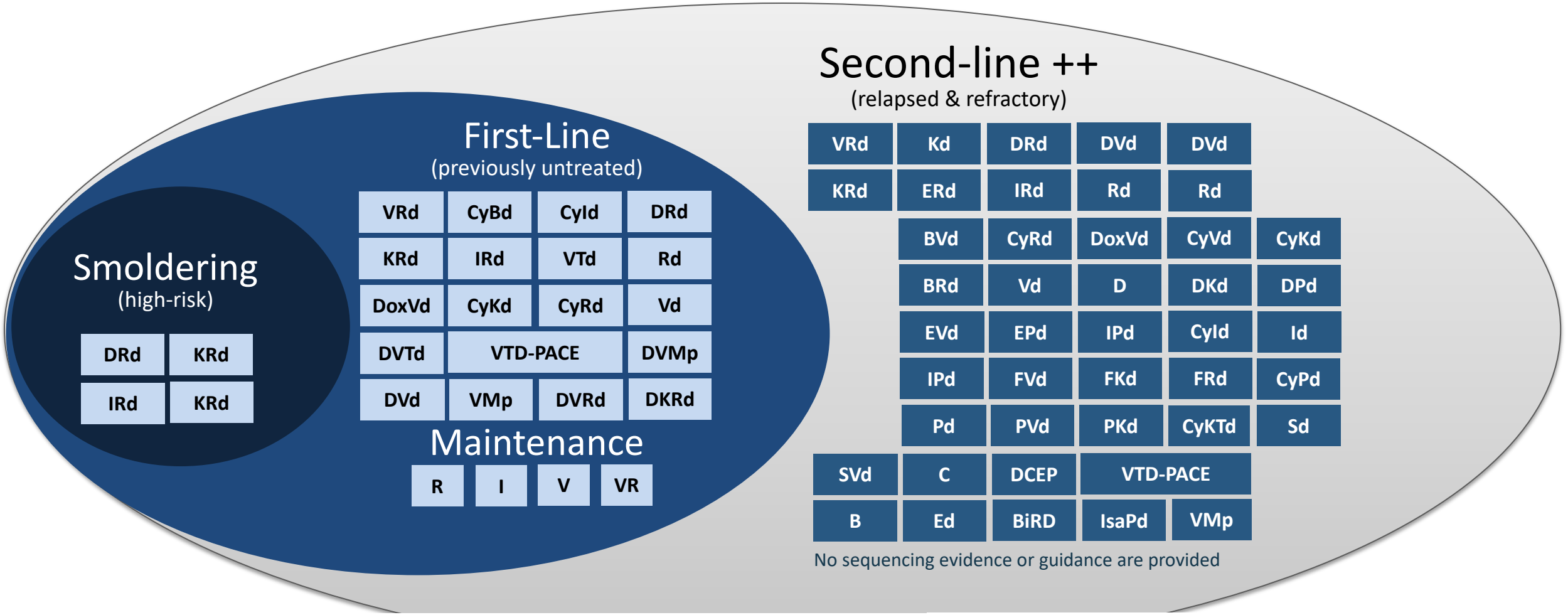
Knowledge can be your best medicine

Promising New Treatment Options for Patients With Relapsed / Refractory Multiple Myeloma

James Berenson, MD

Founder & President, Institute for Myeloma & Bone Cancer Research

Vast and Complex Menu of Treatment Options



D – Daratumumab
Isa - Isatuximab
E - Elotuzumab

R - Lenalidomide
P – Pomalidomide
T – Thalidomide

V – Bortezomib
K – Carfilzomib
I – Ixazomib

Cy – Cyclophosphamide
M – Melphalan
Dox – Lipo-doxorubicin

S – Selinexor
F – Panobinostat

B- Bendamustine
Eto - Etoposide
Cis - Cisplatin

p – prednisone
d – dexamethasone

Recent FDA Approvals for Novel Agents in R/R MM

An Ever-Changing Landscape Expected to Continue

Isatuximab-irfc

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

Belantamab Mafodotin

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

In combination with bort/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

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

idecabtagene vicleucel

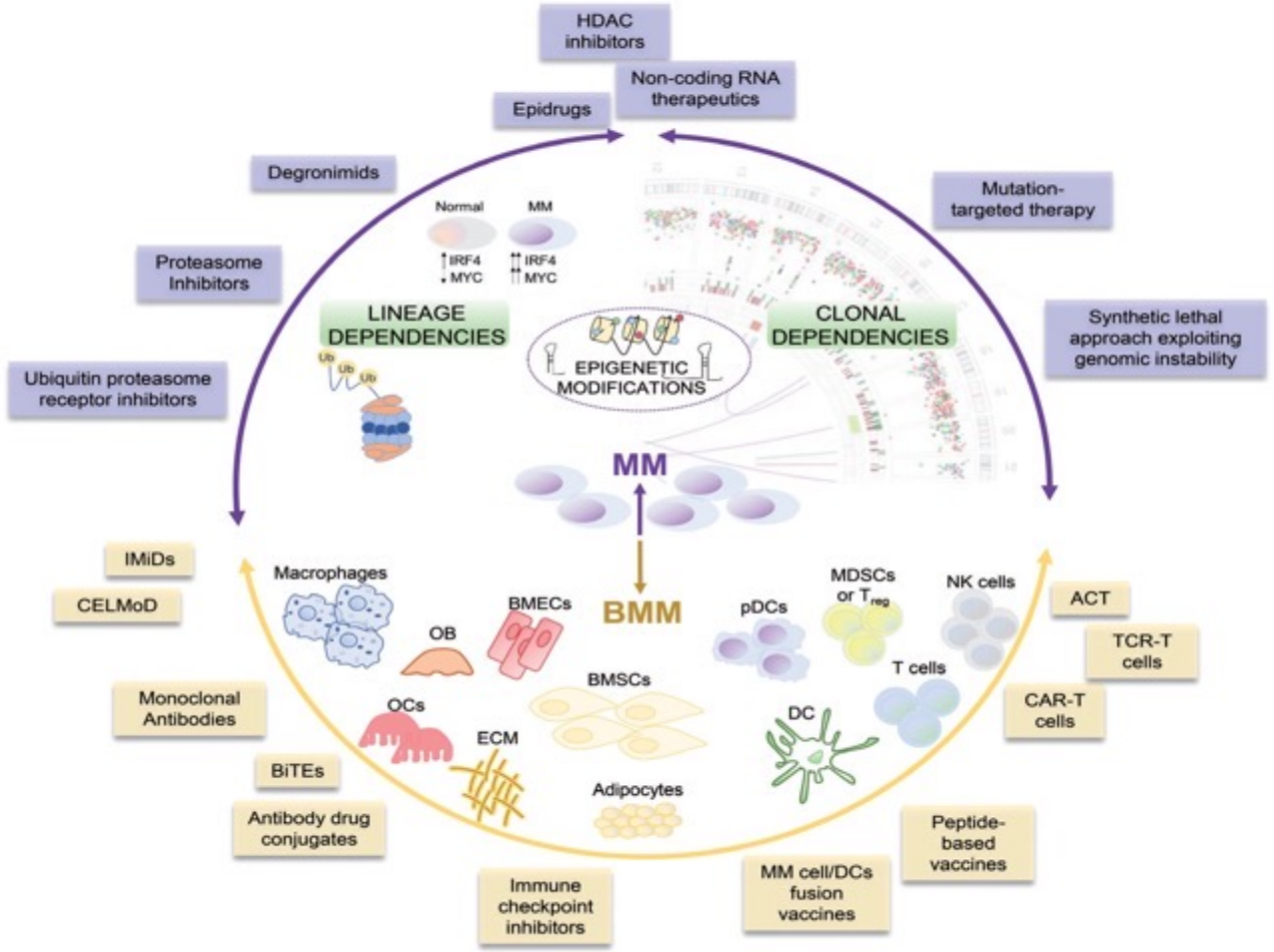
First CAR T-cell (ide-cel) approved for patients with relapsed or refractory multiple myeloma after four or more prior lines of therapy, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody.

Isatuximab

In combination with carfilzomib and dexamethasone (Kd), for the treatment of adult patients with relapsed or refractory multiple myeloma (RRMM) who have received one to three prior lines of therapy.

Emerging Therapies for Relapsed/Refractory Myeloma

- ADCs[1]
  - Targeting BCMA, CD56, CD38, and CD74
- Alkylator peptides[2]
- CAR-T cell therapies [1]
- Other BCMA-targeted drugs[1]
- Immune checkpoint inhibitors[1]
- Vaccines[1]
- Bispecific antibodies and T-cell engagers[1]
- CRBN E3 ligase modulators[2]
- JAK inhibitors[3]

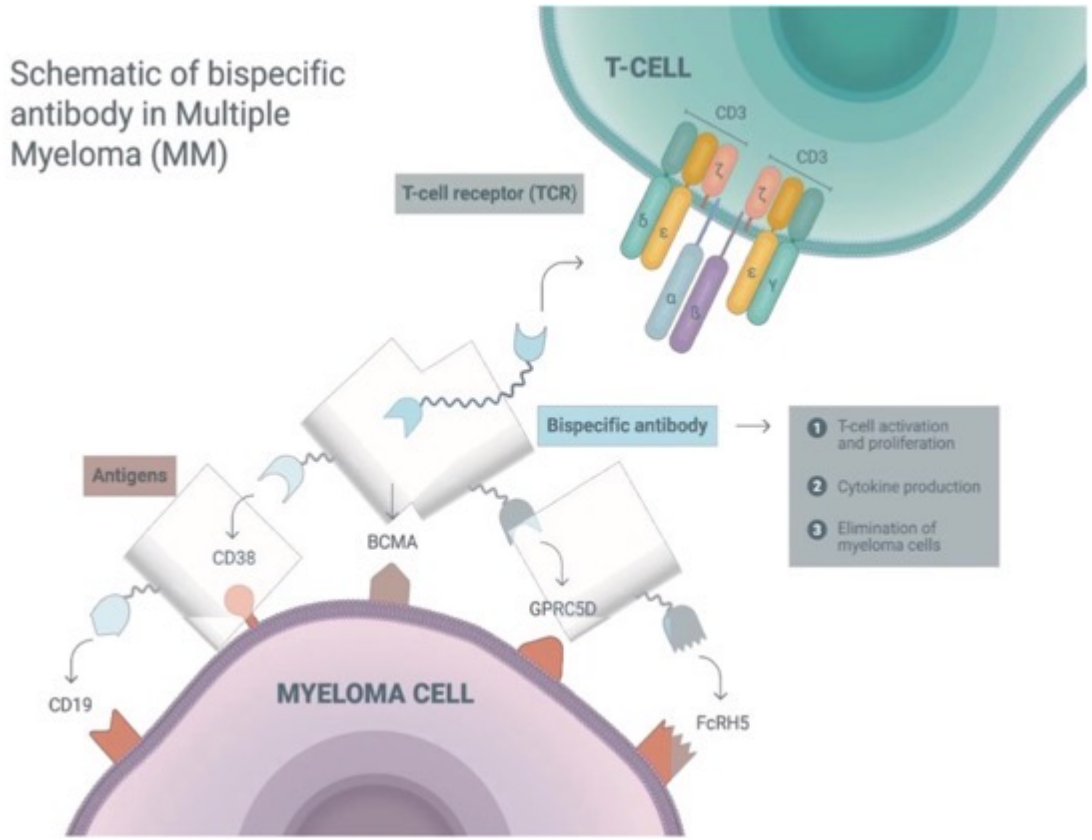


1. Yang Y, et al. J Hematol Oncol. 2020;13:150. Creative Commons 4.0 International Li
2. Hansen JD, et al. J Med Chem. 2020;63:6648-6676.
3. Ghermezi M. et al. Clin Adv Hematol Oncol. 2019 Sep;17(9):500-505
4. 4. Gulla A., Anderson K. Haematologica 2020 Volume 105(10):2358-2367

Bispecific Antibodies and T-cell Engagers

- Bispecific antibodies facilitate an immune synapse between T-cell and myeloma cell via recognizing and binding the surface antigens on both cells.
- T-cells are activated, and this leads
  - T-cell proliferation
  - cytokine production
  - immune regulation
  - induction of cellular lysis
  - tumor cell elimination

G-protein coupled receptor family C group 5 member D (GPRC5D); Fc receptor-homolog 5 (FcRH5); B-cell maturation antigen (BCMA).



Zhou X, et al. J Clin Med. 2020 Jul; 9(7): 2166.

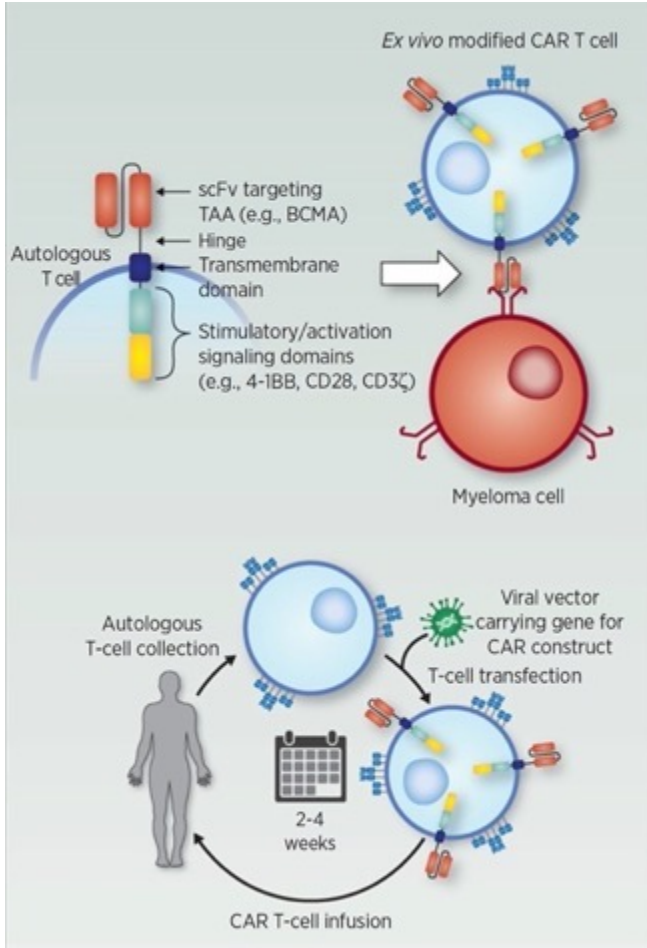
Bispecific Antibody Therapies and T-cell Engagers

Agent	Trial	N	Efficacy	Safety
Talquetamab (JNJ-64407564) [1]	Phase 1 NCT03399799	102 (IV) 55 (SC)	ORR ▪ 69% for RP2D 405 µg/kg SC	▪ CRS 54% (gr ≥ 3: 3%) ▪ G3/4 AEs: Lymphopenia, Anemia, Neutropenia ▪ NT: 6% (gr ≥ 3: 2%)
Cevostamab (BFCR4350A)[2]	Phase 1 GO39775 NCT03275103	53	ORR ▪ 53% at> 3.6/20 mg dose	▪ CRS 76% ▪ G3/4 AEs: Lymphopenia, Neutropenia, Anemia, Thrombocytopenia. NT not reported.
Teclistamab[3] (JNJ-64007957)	Phase 1 NCT03145181 (Phase 2 Planned)	149	ORR ▪ 73% at RP2D of 1500 µg/kg	▪ CRS 55% ▪ G3/4 AEs: Lymphopenia, Neutropenia, Anemia, Thrombocytopenia
REGN5458[4]	Phase 1 NCT03761108 (Phase 2 recruiting)	49	ORR ▪ 29.2% to 62.5%	▪ CRS 39% ▪ G3/4 AEs: Anemia, Lymphopenia,
TNB-383B[5]	Phase 1 NCT03933735	38	ORR ▪ 52%	▪ CRS 21% ▪ G3/4 AEs: Anemia, Thrombocytopenia, Neutropenia
Pavurutamab AMG 701[6]	Phase 1 NCT03287908	85	ORR (82 pts evaluable) ▪ 26% ▪ 36% at doses of 3-12 mg	▪ CRS 61% ▪ G3/4 AEs: infections , asymptomatic pancreatic enzyme rise
PF-3135[7] (PF-06863135)	Phase 1 NCT03269136 (Phase 2 MagnetisMM-3 started Feb. 17/21)	30	ORR ▪ 80% at 215 - 1000 µg/kg (20 pts)	▪ CRS 73.3% ▪ G3/4 AEs: Lymphopenia, Neutropenia, Thrombocytopenia, Anemia
CC-93269 (CD3ε x BCMA) [8]	Phase 1 (NCT03486067)[8]	30	ORR ▪ 43.3%; sCR/CR: 16.7%	▪ CRS: 76.7% ▪ G3/4 AEs: Neutropenia, Anemia, Infections, Thrombocytopenia, -No encephalopathy

1. Chari A. et al. ASH 2020. Abstract 290
2. Cohen AD. et al. ASH 2020. Abstract 292;
3. Garfall A. et al. ASH 2020. Abstract 180
4. Madduri D. et al. ASH 2020 Abstract 291
5. Rodriguez C et al. ASH 2020. Abstract 293
6. Harrison S. et al. ASH 2020 Abstract 181
7. Lesohkin A. et al. ASH 2020. Abstract 3206
8. Cortes. ASH 2019. Abstr 143

CAR T-cells

- Genetically modified T cells from a patient's own cells
- Designed to recognize & bind to specific proteins on MM cells
- CAR T cells are then expanded for clinical use and infused back into the patient's body to attack and destroy chemotherapy-resistant cancer



1. Feins S. et al. Am J Hematol. 2019 May;94(S1):S3-S9.
2. Cohen A. et al. Clin Cancer Res April 1 2020 (26) (7) 1541-1554

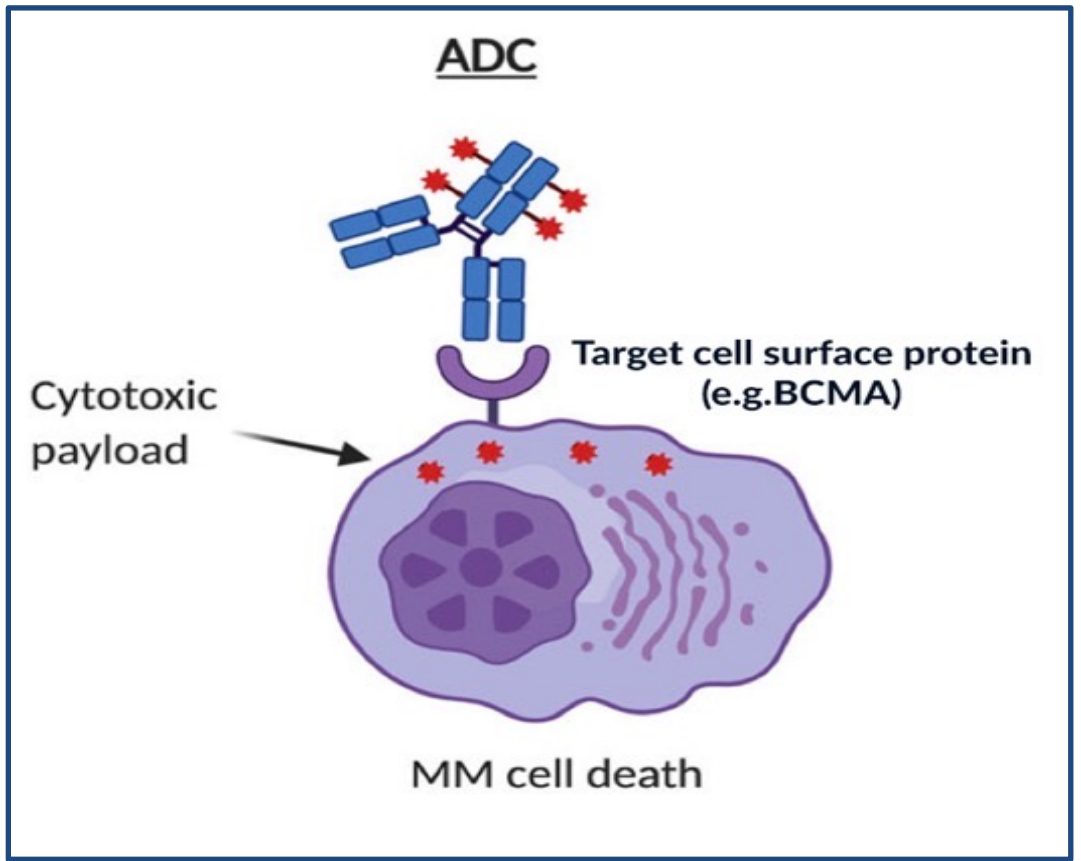
Emerging Data on CAR T-Cell Therapies in R/R MM

Agent	Trial	Prior Tx	N	Efficacy	Safety
Ciltacabtagene autoleucel (JNJ-4528)	Phase Ib/II CARTITUDE-1[1]	≥ 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 (JCARH125)	Phase I/II EVOLVE[2]	≥ 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[3]	≥ 3 prior tx; prior PI and IMiD or double refractory to PI and IMiD	69	▪ ORR: 68% (43% to 83%) ▪ sCR/CR: 29% (14% to 42%)	▪ CRS: 70% (gr ≥ 3: 4%) ▪ NT: 16% (gr ≥ 3: 4%)
P-BCMA-101	Phase I/II PRIME[4]	≥ 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[5]	≥ 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%
Idecabtagene vicleucel* (bb2121)	Phase 2 KarMMa *FDA approved March 26, 2021	≥ 3 prior therapy lines	128	▪ ORR: 72% ▪ 82% at highest dose level	▪ CRS: 84% (gr ≥ 3: 6%) ▪ NT: 0%
CT053	Phase 1b/2 Lummicar-2[7]	≥ 3 prior therapy lines (including PI, IMiD, anti-CD38)	20	▪ ORR: 94%	▪ CRS: 79% (gr ≥ 3: 0%) ▪ NT: 0%
BM38 CAR	Phase 1 (ChiCTR1800018143)[8]	≥ 2 prior therapy lines (including PI)	22	▪ ORR: 90.9%	▪ CRS: 62.5% (gr ≥ 3: 12%) ▪ NT: 0%

1. Madduri. ASH 2020. Abstr 177.
2. Mailankody. ASCO 2020. Abstr 8504.
3. Alsina. ASH 2020. Abstr 130.
4. Costello. ASH 2020. Abstr 134.
5. Mailankody. ASH 2020. Abstr 129.
7. Kumar S. et al. ASH 2020. Abstract 133
8. Li C et al. Blood (2019) 134 (Supplement_1): 930.

Antibody–Drug Conjugates

- Antibody-drug conjugates (ADCs) are cytotoxic drugs linked to antibodies via specialized chemical linkers.
- ADCs provide a means to target cytotoxic drugs to neoplastic cells, reducing the nonspecific systemic effects of the cytotoxic drug while retaining any efficacy of the antibody.



Upon binding to the surface of multiple myeloma (MM) cells, the ADC is internalized first, and then the linker is hydrolyzed inside of the lysosomes or endosomes, releasing the cytotoxic payloads that lead to cell death.

1. Yu, B. et al. J Hematol Oncol 13, 125 (2020)
2. Elkins K et al. Mol Cancer Ther; 11(10) October 2012

Phase I MEDI2228: Study Design

- A first-in-human, open-label, phase I study
- Dose-escalation design (Figure 1)
- Eligibility criteria:
  - Aged ≥ 18 years
  - Confirmed and measurable RRMM
  - European Cooperative Oncology Group (ECOG) performance status ≤ 1
  - Disease progression following treatment with proteasome inhibitors (PIs), immunomodulatory drug (IMIDs), and monoclonal antibodies (mAbs)
- Primary endpoints included safety and tolerability
- Secondary endpoints were preliminary efficacy, pharmacokinetics, and immunogenicity

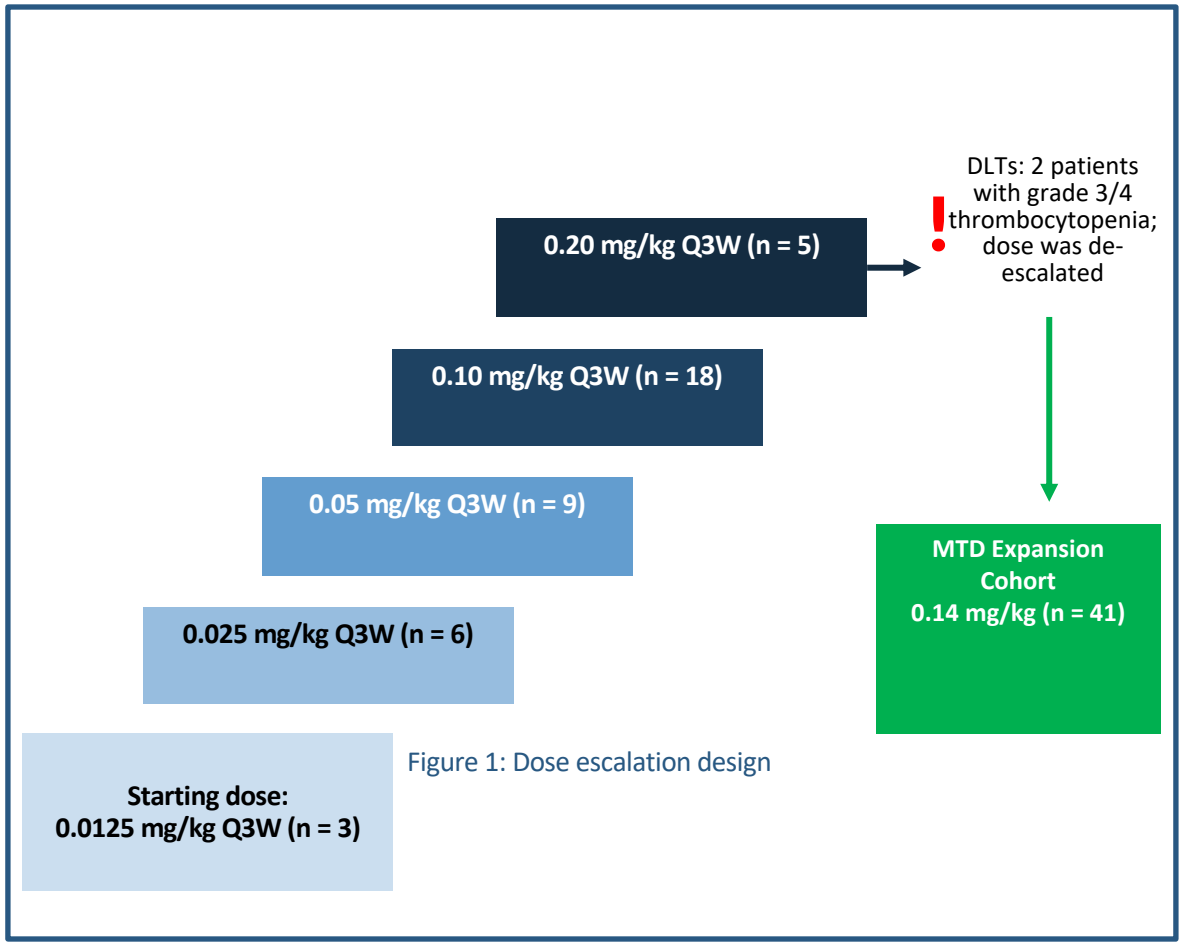


Figure 1: Dose escalation design

Kumar. ASH 2020. Abstr 179.
NCT03489525

Phase I MEDI2228: Efficacy

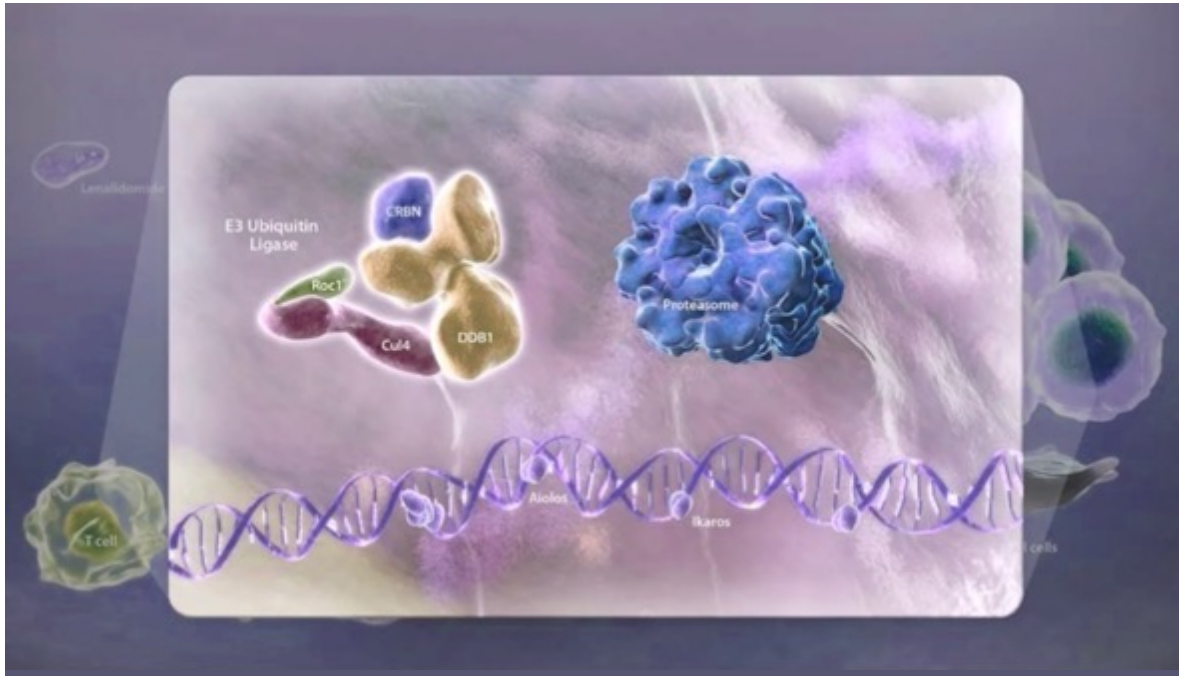
Parameter	0.0125 mg/kg (n = 3)	0.025 mg/kg (n = 6)	0.05 mg/kg (n = 9)	0.10 mg/kg (n = 18)	0.14 mg/kg (n = 41)	0.20 mg/kg (n = 5)
ORR, n (%) [95% CI]	1 (33.1) [0.8-90.6]	1 (16.7) [0.4-64.1]	3 (33.3) [7.5-70.1]	5 (27.8) [9.7-53.5]	27 (65.9) [49.4-79.9]	2 (40) [5.3-85.3]
▪ CR/sCR	0	0	0	0	1 (2.4)	0
▪ VGPR	1 (33.3)	0	2 (22.2)	4 (22.2)	10 (24.4)	0
▪ PR	0	1 (16.7)	1 (11.1)	1 (5.6)	16 (39.0)	2 (40.0)
▪ Minimal response	0	0	0	4 (22.2)	2 (4.9)	0
▪ SD	1 (33.3)	1 (16.7)	1 (11.1)	3 (16.7)	5 (12.2)	2 (40.0)
▪ PD	1 (33.3)	3 (50.0)	5 (55.6)	5 (27.8)	6 (14.6)	1 (20.0)
Median TTR, mos (95% CI)	2.1 (NA-NA)	3.5 (NA-NA)	2.8 (1.6-5.8)	2.1 (0.7-2.1)	2.1 (0.7-2.8)	0.7 (0.7-0.7)
Median cycles, n (range)	2.0 (2.0-18.0)	2.0 (1.0-12.0)	2.0 (2.0-7.0)	3.5 (1.0-17.0)	3.0 (1.0-6.0)	3.0 (2.0-3.0)

- Responses were observed at all dose levels of MEDI2228.
- Overall response rate (complete response plus partial response) was highest in the MTD expansion cohort (65.9%; 95% CI, 49.4–79.9)

Kumar. ASH 2020. Abstr 179.

CRBN E3 Ligase Modulators

- CELMoD agents are hypothesized to promote the degradation of target proteins that are important for the biology of multiple diseases
- This therapeutic approach has been demonstrated in preclinical studies.
- Proteins targeted by CELMoD agents play an important role in:
  - cell apoptosis, differentiation, and proliferation
  - are deregulated in hematologic malignancies including multiple myeloma



CELMoD agents can confer differentiated activity against target proteins. Two **CELMoD agents**, iberdomide and CC-92480, have demonstrated higher affinity for CRBN and higher potency for CRBN modulation than IMiD **agents** in multiple **myeloma** cells.

1. Chaberlain PP, Cathers BE. Drug Discov Today Technol. 2019;31:29-34.
2. https://www.bolderscience.com

Emerging Data on CRBN E3 Ligase Modulators in R/R MM

Agent	Trial	Prior Tx	N	Efficacy	Safety
CC-92480[1,2]	Phase 1	Median 6 (Range 2-13), 50% triple refractory	76	▪ ORR: 21.1% ▪ 54.5% at RP2D 1.0 mg QD 21/28 days	▪ Grade 3–4 TEAEs: Neutropenia (53%), infections (30%), anemia (29%), thrombocytopenia (17%), with 9% grade 3 fatigue
Iberdomide (CC-220)[3]	Phase Ib/IIa	≥ 2 prior regimens, including len/pom and PI) who progressed within 60 days of last therapy	50	▪ ORR (n=27) Iber + Dd: 42.3% ▪ ORR (n=23) Iber + Vd: 60.9%	▪ Grade 3–4 TEAEs Iber + Dd: Neutropenia, Febrile neutropenia, Thrombocytopenia, Anemia, Rash ▪ Grade 3–4 TEAEs Iber + Vd: Neutropenia, Febrile neutropenia, Thrombocytopenia, Anemia, Diarrhea, Rash

1. Richardson. ASCO 2020. Abstr 8500
2. Richardson. EHA 2020 Abstr S208
3. Lonial S. et al.J Clin Onc 37, no. 15_suppl (May 20, 2019) 8006-8006.
3. Van De Donk. ASH 2020. Abstr 724

Other Agents for RRMM Patients

Repurposing approved drugs

- JAK inhibitor
  - Ruxolitinib approved for polycythemia, myelofibrosis and GVHD
- BCL-2 Inhibitor
  - Venetoclax approved for lymphoma and leukemia
  - Active for myeloma patients with t(11;14)
- Immune checkpoint inhibitors (PD-1/PD-L1)
  - Approved for multiple solid tumors and select lymphomas
  - Early clinical data suggested that the inhibitors alone were not effective
  - Ongoing clinical trials are further investigating immune checkpoint inhibitors in combination approaches

Vaccines

- Most studies did not observe a significantly improved clinical outcome
- A multi-center, randomized clinical trial is underway

JAK Inhibitors in Multiple Myeloma

- Phase 1 Efficacy and Safety of Ruxolitinib and Steroids for Treating Patients with Relapsed or Refractory Multiple Myeloma (RRMM)

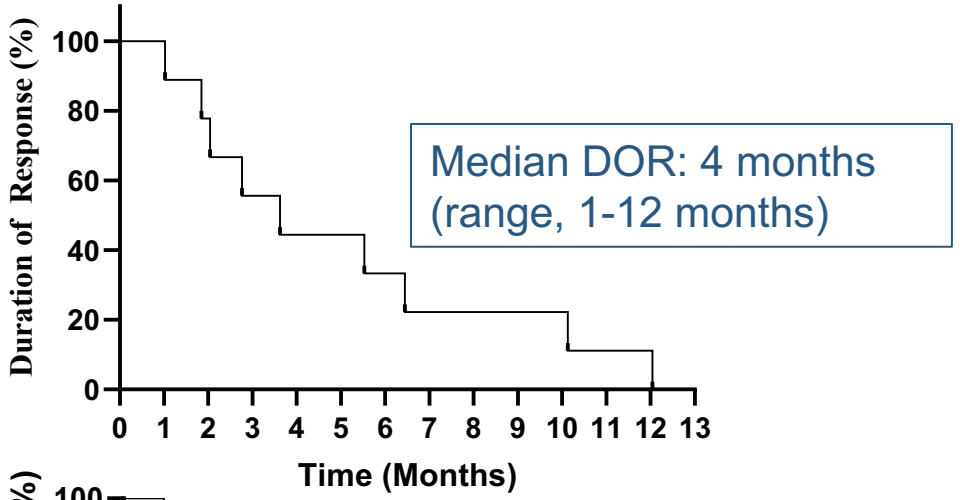
Dose Level	Ruxolitinib Days 1-28	Lenalidomide Days 1-21	Methylprednisolone Days 1-28
Part 1: Dose Level 0	15 mg BID	-	40 mg QOD
Following Disease Progression (PD), Patients enrolled in Part 2			
Part 2: Dose Level 0	15 mg BID	10 mg QD	40 mg QOD

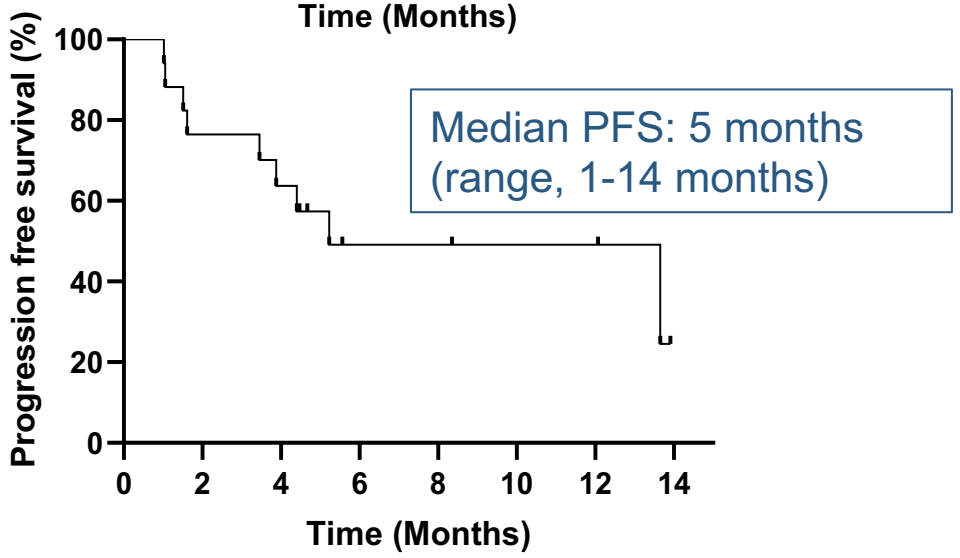
Berenson J. et al. ASH 2020 Abstract 3232

Efficacy: ORR, CBR, DOR (Duration of Response), and PFS

Best Response*	Number of Patients	%
CR	0	0
VGPR	1	6
PR	7	41
MR	1	6
SD	6	35
PD	2	12
Overall Response Rate (ORR [VGPR+PR])	8	47
Clinical Benefit Rate (CBR [VGPR+PR+MR])	9*	53

*All 9 responding patients were refractory to lenalidomide (progressed while on or within 8 weeks of the last dose)

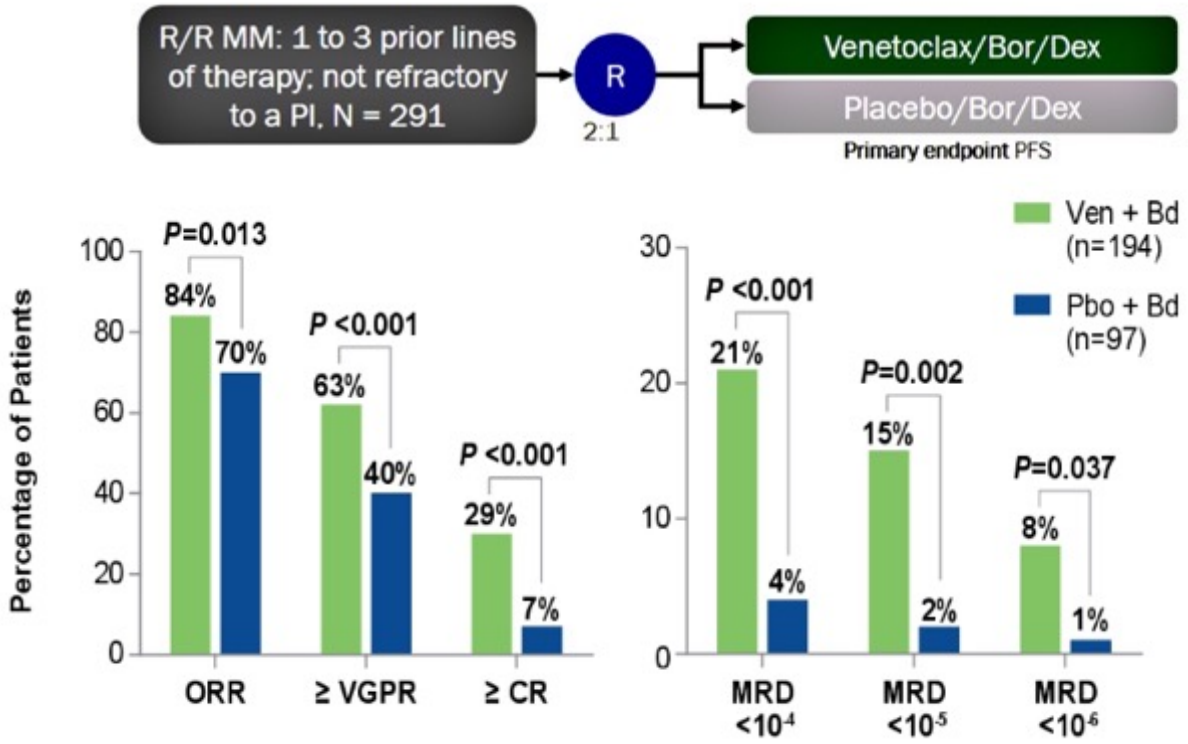


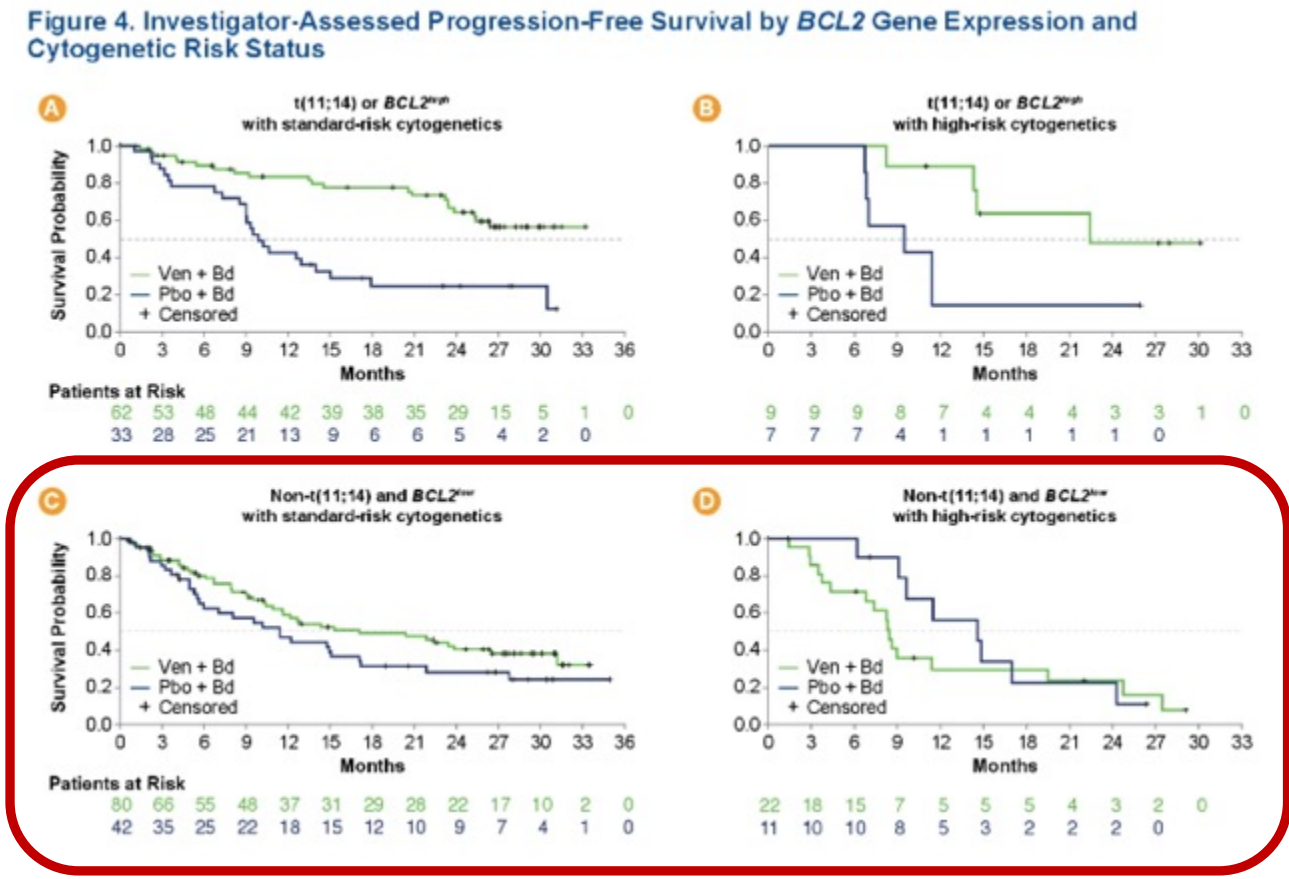


Five patients (29%) experienced SAEs including sepsis (12%), neutropenic fever and nausea (6%), pneumonia and pneumothorax (6%), thrombocytopenia (6%), anemia (6%) and hyperglycemia (6%).

Berenson J. et al. ASH 2020 Abstract 3232

BCL-2 Inhibitor: Venetoclax





- Grade 3/4 AEs: neutropenia, thrombocytopenia, anemia, diarrhea and pneumonia
- Serious adverse events occurred in 54% venetoclax and 52% placebo patients.
- 24% discontinued venetoclax due to adverse events vs 12% placebo.
- There were 14 treatment-emergent deaths in the venetoclax arm and 1 in placebo.

Kumar SK. Et al. J Clin Oncol. 2020 38(Suppl.15):Abstr. 8509

RRMM Patients Treated with Lower Doses of Venetoclax and Bortezomib in Combination with Daratumumab and Dexamethasone

(DDVV; N = 21)
28-Day Cycle

1. Daratumumab 16mg/kg IV once weekly for 8 weeks, then once every other week for 16 weeks, then once monthly thereafter.

2. Dexamethasone 40mg IV once weekly on days 1, 8, 15, and 22.

3. Bortezomib 1.0mg/m2 SQ once weekly on days 1, 8, 15, and 22.

4. Venetoclax 100mg orally once daily continuously. If well-tolerated after one week, then increase to 200mg orally once daily continuously.

Berenson J. et al. in Peer Review 2021

RRMM Patients Treated with Lower Doses of Venetoclax and Bortezomib in Combination with Daratumumab and Dexamethasone (DDVV; N = 21)

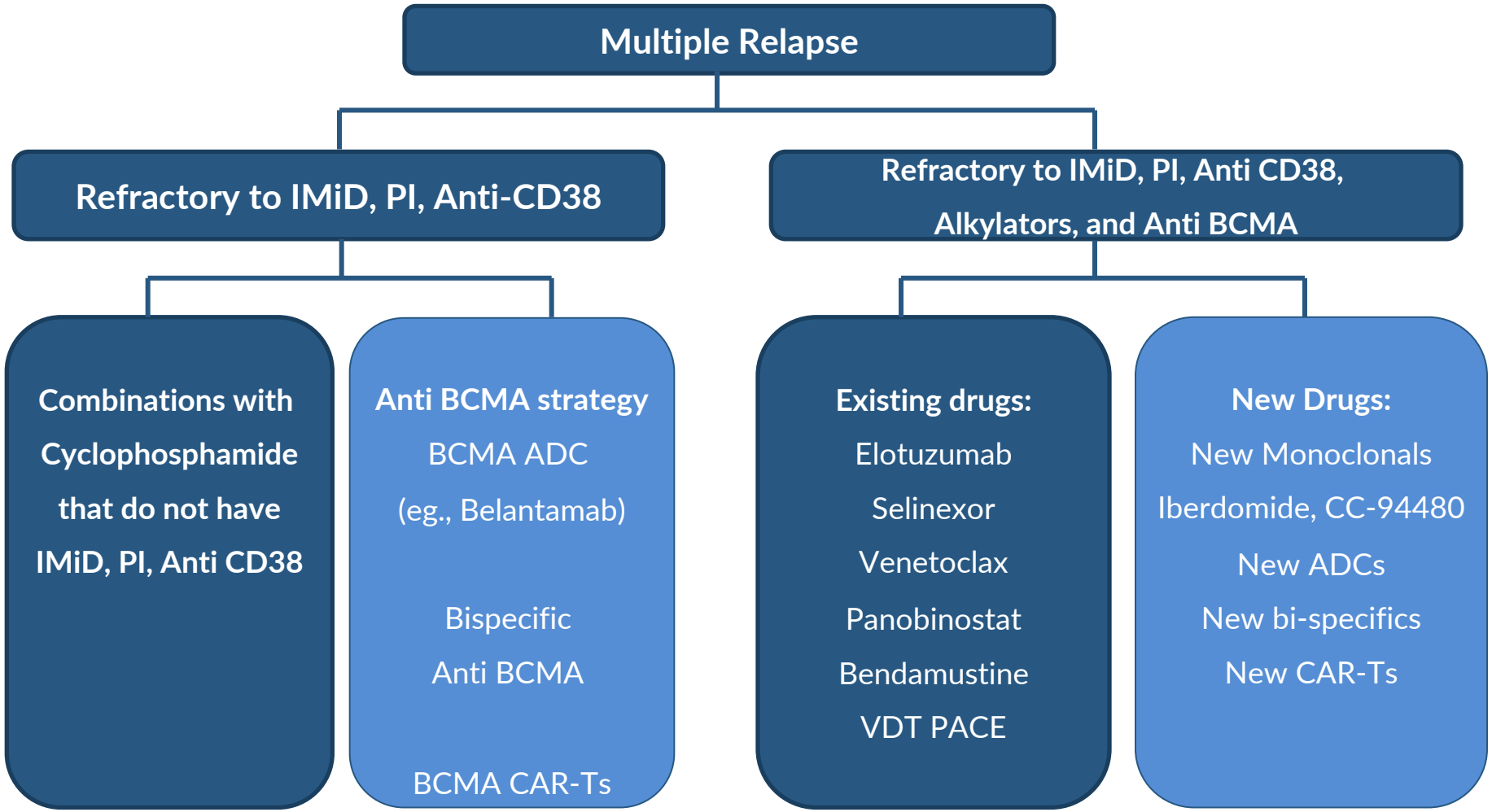
Cytogenetics	Number of Patients (n)	%
Positive for translocation t(11;14)	7	32%
ORR	5	71%
CB	5	71%
Negative for translocation t(11;14)	14	68%
ORR	4	29%
CBR	6	43%

Duration of response: 8.9 months

Well tolerated with few side effects

Berenson J. et al. in Peer Review 2021

Myeloma: Future State



Conclusions: Emerging Agents and Approaches to Treating RRMM Patients

- Increasing understanding of the mechanisms underlying MM and resistance mechanisms resulting in
  - Novel agents
  - Combinations of existing drugs
  - Adding agents to overcome resistance
- Lower doses and alternative scheduling can be highly effective and better tolerated
- Repurposing already effective drugs for other cancers including ruxolitinib and venetoclax
- Immunotherapies including checkpoint inhibitors, vaccine, BiTEs, and CAR-T cells demonstrated promising efficacy

Needs:

- Optimal sequence of treatments
- How to choose best treatment when disease progresses

Q&A

Expert Recommendations & Patient Perspectives for Treating Relapsed/Refractory Multiple Myeloma

April 16, 2021

3 PM ET | 12 PM PT

LIVE WEBINAR

MYELOMA360
Changing the global paradigm